TINTINALLI'S

Emergency Medicine

A COMPREHENSIVE STUDY GUIDE

NINTH EDITION

Judith E. Tintinalli, *Editor-in-Chief*

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ADVANCING EMERGENCY CARE

Tintinalli's Emergency Medicine

A Comprehensive Study Guide

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A Comprehensive Study Guide

Ninth Edition

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To my keenest supporters, my husband, Burton Fox, and my emergency medicine physician daughter, Anne Tintinalli, MD.

Judith E. Tintinalli, MD, MS

For Elizabeth, the love of my life.

O. John Ma, MD

I thank the people who trusted me with their care needs; the people who taught me how to think and to be a physician and scientist; the partners over the years who made me better; and to my family, who always supported and cared for me.

Donald M. Yealy, MD

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Garth D. Meckler, MD, MSHS

I dedicate this edition to my grandson, Charlie. In his eyes, I am just "Grandpa." And that means the world to me.

Joseph Stephan Stapczynski, MD

To my family, mentors, fellow clinicians, residents, students, and patients who give meaning to this work.

David M. Cline, MD

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Stephen H. Thomas, MD, MPH


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Preface

This marks the 41st year of publication of our textbook, which began as a compendium of "answers" to a massive set of questions developed by members of the American College of Emergency Physicians (ACEP) and the American Board of Emergency Medicine (ABEM) for the Emergency Medicine Board Certification Examination. The first ACEP edition was developed in 1978 as "The Study Guide," and in 1985, it matured into the first of 34 years of McGraw-Hill editions. This ninth edition continues to expand in a scope and depth that we could not foretell 41 years ago. We continue to provide clinically focused information for all emergency medicine learners and practitioners, from students and residents, to emergency medicine physicians, advanced practice providers, emergency medical technicians, and paramedics. We believe each subsequent edition demonstrates the vital contemporary role of emergency medical care for individual patients as well as for the health of the public.

This is much more than a book of emergency medicine content. It is the result of contributions over the years by over 2000 authors committed to the education and practice of emergency medicine. I give special thanks to *Howard Werman, MD*, Professor of Emergency Medicine at Ohio State University, *James Niemann, MD,* Professor of Emergency Medicine at David Geffen School of Medicine, and *Joseph Stephen Stapczynski, MD,* Professor of Emergency Medicine at the University of Arizona – Phoenix, for being the only authors who have contributed to every single McGraw-Hill edition over its 41-year history!

The ninth edition is a component of a larger work, AccessEmergencyMedicine.com, which blends the advantages of the web version of the ninth edition of *Tintinalli's Emergency Medicine*, with the leading web-based clinical texts including *Ma & Mateer's Emergency Ultrasound*; Shah & Lucchesi's *Atlas of Pediatric Emergency Medicine*; *Goldfrank's Toxicologic Emergencies*; Iserson's *Improvised Medicine*; and Knoop, Stack, and Storrow's *Atlas of Emergency Medicine*. Audio posts of each chapter are available as TNT (Tintinalli's Necessary Takeaways, by E. Paul DeKoning, Christina Shenvi, Timothy Buff, and Collyn Murray), and monthly blogs are available as BoB (Best of the Blogs, by Alex Koyfman and Brit Long). Procedure videos using traditional and ultrasound techniques are available through Multimedia. Videos are hyperlinked in the web version of the ninth edition and are continually developed at emergency medicine academic sites. Our goal is to continue to develop a set of exemplary educational tools to meet the needs of today's and tomorrow's emergency physicians.

Judith E. Tintinalli, MD, MS
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SECTION 1

Prehospital Care

CHAPTER 1

Emergency Medical Services

C. Crawford Mechem

INTRODUCTION

EMS is the extension of emergency medical care into the prehospital setting. Today's EMS systems have their roots in legislative and clinical developments of the 1960s and 1970s. The 1966 report "Accidental Death and Disability—The Neglected Disease of Modern Society" highlighted the deficiencies of prehospital care of trauma victims, attributable to inadequate equipment and training. Until that time, more than half of ambulance services were run by funeral homes because hearses were among the few vehicles able to transport a stretcher. The National Highway Safety Act of 1966 established the Department of Transportation and made it the lead agency responsible for upgrading EMS systems nationwide.[1]

In 1967, J. F. Pantridge began using a physician-staffed mobile coronary care unit in Belfast, Northern Ireland, to provide prehospital cardiac care.[2] Physician staffing of ambulances never gained popularity in the United States. However, in the late 1960s and 1970s, nonphysician personnel began learning advanced skills, including IV administration of medications, cardiac rhythm interpretation, and defibrillation.[3]

The U.S. EMS Systems Act of 1973 made available federal grants to develop regional EMS systems. Approximately 300 EMS regions were established. To receive funding, the Act required that EMS systems address 15 key elements (**Table 1-1**). These elements form the foundation of many EMS systems today.[4]

The 1970s became a Golden Age for EMS. The U.S. Department of Transportation developed curricula for emergency medical technicians, paramedics, and first responders. EMS communications systems were formalized. In 1972, the Federal Communications Commission recommended 9-1-1 be adopted as the emergency telephone number nationwide. In addition, the concept of designated trauma centers was introduced, with the idea being that EMS personnel would transport injured patients preferentially to these facilities.

The Omnibus Budget Reconciliation Act of 1981 eliminated direct federal funding for EMS. Instead, federal funds were distributed as block grants. The result was a decrease in both EMS funding and coordination. EMS systems took on a decidedly local flavor, with great variation between systems. This trend has had long-term consequences for the field.[1]

In 2011, the American Board of Emergency Medicine recognized EMS as its seventh subspecialty. The certification examination is based on the Core Content of EMS Medicine with four major content areas: Clinical Aspects of EMS Medicine, Medical Oversight of EMS, Quality Management and Research, and Special Operations.[5]

EMS SYSTEM OVERVIEW

A review of the 15 elements of EMS systems identified by the EMS Systems Act of 1973 (Table 1-1) provides insight into the structure of EMS systems and the challenges they face.

MANPOWER

In most urban areas, paid public safety and ambulance personnel provide prehospital care. In contrast, suburban, rural, or wilderness EMS systems commonly use volunteers. Personnel fall into one of four licensure levels in accordance with the National EMS Scope of Practice Model, set forth by the National Highway Traffic Safety Administration. These are emergency medical responder, emergency medical technician, advanced emergency medical technician, and paramedic. Each type of provider must master a minimum set of skills. Emergency medical responders are often first on the scene of an emergency. They are trained to perform CPR, spine immobilization, and hemorrhage control and to use auto-injectors, automated external defibrillators, and other basic interventions while awaiting an ambulance. Emergency medical technicians function as part of an ambulance crew. Their training includes oxygen administration, CPR, hemorrhage control, and patient extrication, immobilization, and transportation. They assist patients in using some of their own medications and can administer certain over-the-counter medications. Advanced emergency medical technician training includes additional assessment skills plus placement of IVs and supraglottic airway devices and administration of some medications. Paramedics have the highest skill level. Because of their advanced level of training, paramedics function under a designated physician's supervision.[6]

TRAINING

Training includes initial provider training and continuing education. As EMS call volume increases, providers often care for a disproportionate number of patients with minor medical issues. Maintaining proficiency in skills to manage critically ill patients may be difficult. Innovative training methods to ensure skills retention must be sought. Use of computerized human patient simulators is one option, both for reviewing skills and learning new ones.

COMMUNICATIONS

The adoption of 9-1-1 as a nationwide emergency number has greatly facilitated public access to emergency care. In many systems, the local public safety answering point has software that provides the number and location of a caller (enhanced 9-1-1). Widespread use of cellular telephones has prompted the development of technology to identify and locate these callers as well, in accordance with Federal Communications Commission regulations. Emergency call takers are trained to collect necessary information, dispatch appropriate resources, and offer first aid or prearrival instructions while the ambulance is en route. Ambulance personnel should also be able to communicate with the destination hospital. Most EMS personnel operate under standing orders and protocols. However, there are times when providers may require online medical control, talking directly with a physician for direction.[7] Historically, communications represent the weakest link in disasters. It is important that EMS communication systems have built-in redundancy to ensure uninterrupted service.

TRANSPORTATION

Ambulance design must enable EMS personnel to provide care such as airway and ventilatory support while transporting the patient safely. Basic life support ambulances carry equipment appropriate for personnel trained at the emergency medical technician level, such as automated external defibrillators, oxygen, bag-mask ventilation devices, immobilization and splinting devices, and wound dressings. They carry few medications and cannot transport patients requiring IVs or cardiac monitoring. Advanced life support ambulances are equipped for advanced emergency medical technicians or paramedics, including IV

TABLE 1-1 Fifteen Key Elements of EMS Systems Defined by U.S. EMS Systems Act of 1973

- Manpower
- Training
- Communications
- Transportation
- Facilities
- Critical care units
- Public safety agencies
- Consumer participation
- Access to care
- Patient transfer
- Coordinated patient record keeping
- Public information and education
- Review and evaluation
- Disaster plan
- Mutual aid

fluids and medications, intubation equipment, cardiac monitors, and pulse oximeters. Ground transportation is appropriate for the majority of patients, especially in urban and suburban areas. However, air transport, generally by helicopter, should be considered for critically ill patients when ground transport time would be long or if the terrain is difficult to navigate.[4]

FACILITIES AND CRITICAL CARE UNITS

Patients are often transported to the closest appropriate hospital. In recent years, the number of specialty hospitals has increased, including pediatric hospitals, trauma centers, burn centers, stroke centers, and centers with advanced cardiac or resuscitation capabilities.[8] Tertiary care centers provide many of these services and may also have a large number of critical care unit beds. The decision to bypass hospitals to go directly to a specialty center, often at a greater distance, is not a simple one. Although specialty hospitals often have more resources, transporting an unstable patient past an ED to get to the specialty hospital is not without risks. Furthermore, bypassing hospitals may have negative financial consequences for bypassed facilities.[1] It is wise to solicit input from the local medical community before developing destination policies involving specialty centers.

Due to ED overcrowding, even the largest hospitals may not always have adequate resources to care for EMS patients. This may result in prolonged offload times of ambulance patients, long wait times for patients to be seen, and ED boarding of admitted patients. Furthermore, some EDs may request EMS divert elsewhere.[9] Because of these issues, regional EMS systems should develop methods to monitor available resources of their receiving hospitals. A secure, Internet-based website of hospital resources, including ED and inpatient bed availability, is one option.

PUBLIC SAFETY AGENCIES

EMS systems should have strong ties with police and fire departments. Many large EMS systems are run by fire departments. In addition to providing scene security, public safety agencies can provide first responder services because they are often first on the scene. Fire and police automated external defibrillator programs are common.[10,11] Police administration of naloxone to opioid overdose victims is also a growing trend.[12] Such practices have been shown to improve patient outcomes. Finally, EMS personnel often provide medical support to police and fire departments in hazardous circumstances.

CONSUMER PARTICIPATION

Public support, both political and financial, is necessary for a good EMS system. It is important that laypersons contribute to policymaking. One way to accomplish this is to encourage representation of the public on regional EMS councils. The public can also participate by volunteering for local EMS agencies.

ACCESS TO CARE

Successful EMS systems ensure all individuals have access to care regardless of ability to pay. The EMS system is often a patient's primary entry point into the healthcare system. There should be no barriers preventing access. A more difficult problem exists when terrain or low population densities result in longer response times for some citizens, as in rural or wilderness areas. EMS telemedicine programs may be one way to bring high-level medical expertise to patients in remote areas.[13]

PATIENT TRANSFER

Patients are often transferred from one medical facility to another for a higher level of care. Safe and seamless transfer is an important concept and may be facilitated if transferring and receiving facilities develop transfer agreements in advance. The Emergency Medical Treatment and Active Labor Act of 1986 sets forth rules hospitals participating in the Medicare program must follow. Under the Emergency Medical Treatment and Active Labor Act, all patients must receive a medical screening exam and be stabilized before transfer. There must also be explicit acceptance of the transfer by the receiving hospital.[14]

COORDINATED PATIENT RECORD KEEPING

Maintaining good medical records is important to any patient encounter. Prehospital medical records must be legible and readily accessible to hospital providers. Standardization of EMS records among different agencies within a region helps streamline transfer of information between prehospital and hospital providers. The adoption of electronic charting and cloud-based electronic medical record keeping by EMS systems is a step toward this goal. Electronic charts can be printed out in the receiving ED or downloaded from a secure Internet website. Regardless of the system used, EMS agencies must comply with the Health Insurance Portability and Accountability Act of 1996, designed to protect the privacy of patient health information.[15]

PUBLIC INFORMATION AND EDUCATION

EMS systems have a responsibility to train the public on how to access EMS and use it appropriately. As EMS call volumes rise and available resources decline, educating the public to use 9-1-1 for true emergencies is an appropriate goal. However, given the obstacles that many patients encounter in accessing office- or hospital-based care, conveying this message is not simple. The public needs to know that EMS will always be there when needed.

Another important message EMS can convey to the public is the importance of learning CPR, first aid, and basic disaster preparedness. Recent disasters have illustrated that, at times, the emergency response infrastructure may be so seriously disrupted that it may take hours or longer for help to arrive. A public that is adequately prepared and trained will be in a better position to safely await help.[16]

REVIEW AND EVALUATION

To ensure proper functioning of an EMS system and high-quality care, there must be a process for ongoing review and evaluation. This requires input from EMS providers and active involvement of a physician medical director. A continuous quality improvement program should be established to assess system performance and formulate improvements.[17] Routine audits of communications, response and scene times, and patient care records should be performed. Focused audits of conditions such as cardiac arrest and trauma are valuable. However, obtaining patient outcomes may be problematic. An unforeseen consequence of the Health Insurance Portability and Accountability Act is that hospitals are often hesitant to release patient information, even to EMS services, for fear of liability.

EMS research is invaluable in advancing prehospital care. It should not be assumed that what works in the hospital will work in the

prehospital setting. Issues such as limited funding, barriers to getting patient outcomes, and obtaining informed consent from critically ill patients, or waivers of consent, can make prehospital research daunting. However, these barriers must be overcome if patients are to receive quality care.[18]

DISASTER PLAN

The EMS system is an integral part of disaster preparedness and should be involved in planning with other agencies and the medical community. The Omnibus Budget Reconciliation Act legislation of 1981 ended direct federal block grants to EMS. Because EMS is often not considered to be a public safety entity, emergency preparedness funding for EMS has fallen behind that of police and fire services.[1] Despite this, EMS agencies must maintain a high level of disaster preparedness. This involves written policies and procedures, stockpiling supplies that may be depleted in multicasualty situations, and participating in regional disaster drills with other emergency response agencies and hospitals.[19]

MUTUAL AID

EMS services should develop mutual aid agreements with neighboring jurisdictions so care is available when local agencies are unable to respond.[20] Depending on the size and resources of the system, mutual aid may be required frequently or only under extreme circumstances. Addressing in advance details such as reimbursement, credentialing, liability, and chain of command at incident scenes will streamline the process.

CHALLENGES AND FUTURE TRENDS

The 2006 Institute of Medicine publication *Emergency Medical Services at the Crossroads*[1] detailed many of the challenges facing EMS. These include fragmentation and lack of interoperability between EMS systems, between EMS and other public safety agencies, and between EMS and the rest of the healthcare infrastructure. These limit the efficiency of EMS systems and may have serious consequences in disaster response. In addition, the fallout from the Omnibus Budget Reconciliation Act legislation of 1981 is still being felt. Funding for EMS continues to fall behind other public safety agencies. Restructuring of Medicare payment for advanced life support and basic life support services has impacted reimbursement. The effect of the Affordable Care Act on EMS is unclear. It has resulted in an increased number of individuals covered by Medicaid and a proliferation of high-deductible insurance plans, factors that may affect EMS revenues. In the face of these uncertainties, many EMS agencies may have to find other funding sources or cut services. This is occurring at a time when call volumes are rising in many areas, in part due to the aging of the population and limited access to health care.[1]

While demand for EMS steadily grows, in many parts of the country, EMS staffing is not keeping pace. Many EMS systems are currently experiencing paramedic shortages. Low pay, high stress, increased length of training, and limited advancement opportunities may make alternative careers in health care more appealing.[21]

As a consequence of funding and staffing constraints, many EMS systems routinely operate at full capacity. As a result, their surge capacity, or ability to accommodate a sudden, large increase in demand for services, is limited. To enhance surge capacity, EMS systems need additional funding for personnel, vehicles, and supplies. They must also participate in mutual aid programs and frequent training based on threats they are most likely to encounter.[22-25]

Despite the many challenges EMS faces, the quality of care continues to improve, driven in part by EMS research. Some of the advances involve regionalization of care, resuscitation of cardiac arrest victims, and management of ST-segment elevation myocardial infarction (STEMI) patients. The quality of cardiac arrest studies has been enhanced by adoption of the **Utstein template** for data reporting. The Utstein style presents a systematic and standardized format for reporting cardiac arrest data, facilitating comparison of results of studies from different EMS systems.[26] The importance of basic life support skills in cardiac arrest and other emergencies is being rediscovered. Basic interventions in some cases can have a greater impact on outcome than advanced life support skills. More widespread use of automated external defibrillators by first responders and the public has the potential to increase cardiac arrest resuscitation rates. The emphasis on high-quality, uninterrupted CPR, as set forth by the 2015 Guidelines for CPR and Emergency Cardiovascular Care,[27,28] is widely reflected in EMS protocols.[29,30] Devices that provide instant feedback on the quality of CPR are in use by many EMS services.[31] Prehospital use of 12-lead electrocardiograms on patients with chest pain is now common.[32-35] Some systems transmit electrocardiograms to receiving EDs. Others activate cardiac catheterization labs directly when a patient with STEMI is identified on electrocardiogram.

EMS is maturing as an important subspecialty of emergency medicine. Growing populations and increased urbanization are driving the development of EMS systems worldwide.[36,37] The aftermath of the 2004 Asian tsunami emphasized the need for organized and effective prehospital care in developing countries, as well as for international cooperation among EMS agencies.[38,39] Although EMS systems in some countries are similar to those in the United States, in other countries, differences in geography, healthcare system design, funding, and political structure present unique challenges and the potential for novel solutions. These developing systems have the advantage of not being encumbered by decades of tradition and thus can take advantage of lessons learned elsewhere. They also present the opportunity for collaboration on international research initiatives that can lead to improved patient outcomes.[40]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 2

Prehospital Equipment

Brett Boggust
Andy Boggust

INTRODUCTION

To a large extent, early EMS equipment began as hospital equipment that was extrapolated to the field; it was assumed that if something worked in the hospital, then it would work in the field. It soon became apparent that hospital equipment did not always perform under the more rigorous conditions of the prehospital environment. Over the past 30 years, equipment has evolved specifically for EMS that is better adapted to field use in terms of size, weight, and durability. This equipment is directed at resuscitating and sustaining the patient during emergency or interfacility transport. As the science of EMS continues to mature, more equipment will be scrutinized for effectiveness.[1] The four basic questions regarding efficacy of EMS equipment are:

1. Does it do the job?
2. Is it safe?
3. Can it be applied to the field environment?
4. Can it be used effectively by prehospital personnel?

The nature of EMS equipment is changing due to the expanded scope of practice by paramedics and the blurring of care levels between basic life support (BLS) and advanced life support (ALS) personnel. Equipment once considered only for ALS care is now being carried on some BLS ambulances (e.g., defibrillators, vascular access adjuncts, and airway adjuncts).

VEHICLES

The vehicles may be ground ambulances, helicopters, fixed-wing aircraft, or a variety of first-response vehicles (fire engines, police cruisers,

or sport utility vehicles). The most common vehicle used is the ground ambulance, categorized into three common varieties:

Type I: A standard truck (e.g., pick-up) chassis with a separate modular box to carry personnel, patient, and equipment

Type II: An enlarged van-type vehicle

Type III: A van chassis with an integrated modular box on the back for medical care and equipment

In types II and III, there is physical access between the driver's and patient care compartments, as opposed to type I, in which these spaces are separate.

Ground vehicles typically have warning devices (lights and siren) as part of their equipment. Unwarranted use of red lights and sirens is dangerous for the EMS crew, the patient onboard (if present), and the general public on the streets.[2,3] Protocols or guidelines to limit the use of these devices only to times when they are medically indicated are important.

COMMUNICATIONS

The two-way radio is an important piece of equipment carried by prehospital providers. As the arena of wireless communication changes, EMS systems will need to adapt their communications system to best fit their needs. The spectrum of frequencies available for emergency services is limited and shared with other industries that require wireless communications. In the United States, EMS services may use specific frequencies (*channels*) in the very-high-frequency (around 170 MHz), ultra-high-frequency (around 460 MHz), and public safety (around 800 MHz) bands. In an attempt to create more channels for users, the Federal Communications Commission (FCC) has decreased channel spacing from 25 to 12.5 kHz, and there is an FCC mandate to continue spacing down to 6.25 kHz. Although newer radio equipment can be reprogrammed to allow for the change in channel spacing, older equipment may not function correctly with this spacing.

Historically, EMS systems in rural or suburban settings have had broad control over their communications systems; however, as they transport patients into urban settings and attempt to communicate with urban providers, the problems of compatible frequencies and channel congestion may develop. Trunked systems (typically used by urban EMS systems) may be analog, very-high-frequency/ultra-high-frequency digital radio, or 800-MHz digital radio. An 800-MHz digital trunked system is popular because of the advantages of shared equipment between different providers (EMS, police, and fire), enhanced radio coverage, shared or lowered cost, and wide-area communications. The main disadvantage with all trunked systems is the cost necessary to upgrade the current system.[4]

The First Responder Network Authority (FirstNet) was created under the Middle Class Tax Relief and Job Creation Act of 2012 as an independent authority within the United States. FirstNet is charged with establishing, operating, and maintaining an interoperable public safety broadband network. To do this, Congress allotted $7 billion and 20 MHz of radio spectrum to build the network. FirstNet requires each state to have a Radio Access Network connecting to FirstNet's network core. FirstNet is responsible for consulting with states, local communities, and tribal governments to develop the requirements for its Radio Access Network deployment plan.[5] FirstNet is creating the first nationwide high-speed broadband network providing a single interoperable platform for law enforcement, firefighters, paramedics, and other public safety officials in every state, county, locality, and tribal area.[6]

ELECTRONIC MEDICAL RECORD

Use of the prehospital electronic medical record has increased substantially over the past 10 years. As usage of these electronic systems increases, bio-surveillance, research, and system quality assurance analysis have become easier because of better data access.[7-11]

Large systems with enough resources often have their own software specifically written for that system. Smaller EMS systems often use off-the-shelf alternatives. Using one of the latter products may require either modification of a vendor's product or modification of the EMS system workflow to make the software fully functional. Many states are in the process of generating or have already generated a common data set and are collecting statewide data, which are submitted to the state EMS agency.

One common difficulty with the prehospital electronic medical record is incompatibility with the hospital electronic medical record. This means that the ambulance record cannot be expeditiously transferred to the hospital database. Long-term solutions need to be devised to ensure that all of these record systems are compatible.[12]

PERSONAL PROTECTIVE EQUIPMENT

Every EMS provider must be educated about the risks of occupational exposure and protected against exposure to blood and other body fluids from patients. Equipment such as masks, goggles, and gloves for routine use should be carried on every EMS vehicle. On occasion, gowns or sturdy gloves may be needed.[13]

Exposure to hazardous material or biologic or chemical weapons of mass destruction requires more protective equipment. **Minimum personal protective equipment for such exposure should include a high-efficiency particulate air filter mask that filters 99.97% of airborne particles 0.3 μm in diameter (or an acceptable alternative for the purpose, such as an M95 military gas mask), goggles, gloves, and protective clothing.** Protective clothing should be nonabsorbent and puncture resistant (**Figure 2-1**).[14]

Some urban EMS providers wear soft body armor as a standard part of the uniform. Suburban and rural providers can be placed in situations that necessitate similar protection. With advances in soft-armor technology, there are now a variety of styles and levels of protection from which to choose. Although each service must consider such variables as comfort, heat, weight, and cost, for EMS providers, a combination of ballistic/stab protection is optimal.[15]

EQUIPMENT FOR STABILIZATION, RESUSCITATION, AND TREATMENT

This section reviews defibrillators, ECGs, airway and ventilation adjuncts, vascular access devices, spinal immobilization, and extremity immobilization.

DEFIBRILLATORS

Defibrillators have been an essential part of prehospital care since Pantridge showed that defibrillation could be done in the field on the streets of Belfast in 1965. **Because early defibrillation is the most important factor in surviving a cardiac arrest,**[16] defibrillators have become smaller, less costly devices that are more appropriate for the prehospital setting.



FIGURE 2-1. Personal protective equipment: filtered (high-efficiency particulate air, M95, N95, or chemical-specific) mask, goggles, gloves, and protective clothing. [From Professional Paramedic Association of Ottawa, http://www.ottawaparamedics.ca/special-ops/]

An increasing percentage of BLS services carry automated external defibrillators. These devices are shock advisory defibrillators. Automated external defibrillators analyze the patient's rhythm by computer algorithm, determine if the rhythm meets defibrillation criteria, inform the operator that a shock is advised, charge the capacitor, and deliver a defibrillation when the operator pushes the appropriate button. Automated external defibrillators are designed only to shock ventricular fibrillation and very fast ventricular or supraventricular tachycardias (usually >180 beats/min). Automated external defibrillators have become so easy to use and are so effective that many health and medical organizations are promoting these devices for first responder public safety personnel and for public access defibrillation by laypersons.[17-19]

Automated external defibrillators are basic and relatively inexpensive. They often do not have monitor screens that display the patient's rhythm. This actually may be better because a rhythm on the screen may serve only to distract a non-ALS operator.[20] The device should have recording capabilities so that the cardiac arrest can later be reviewed for medical oversight and quality assurance reasons.[21] The medical director should be involved in choosing such devices, training in their use, establishing protocols for their use, and reviewing their use afterward for quality assurance.[17]

Defibrillators used by ALS personnel are typically more sophisticated devices, usually with additional functions. Defibrillation is facilitated using hands-off combination monitoring/defibrillation adhesive pads rather than with handheld paddles. Pads give better contact with the skin and decrease skin resistance to allow for a higher success rate of rhythm conversion. It is also safer for the operator who does not have direct contact with the patient when the shock is delivered. The ALS defibrillator has a screen for interpreting rhythms and so is also used for ongoing monitoring of patients' rhythms. It may be used for cardioversion of nonlethal rhythms or pacing bradyasystolic rhythms. Additional critical care patient monitoring can be incorporated into an ALS defibrillator, including noninvasive blood pressure, pulse oximetry, end-tidal partial pressure of carbon dioxide in intubated patients, and other physiologic parameters. ALS personnel can use these machines for closely monitoring very ill patients during emergent calls or interfacility transfers.

Modern defibrillators use biphasic waveforms for shock delivery (as opposed to the traditional monophasic waveform). Biphasic defibrillators defibrillate and cardiovert at lower energy levels and thus decrease myocardial injury.[22]

Prehospital 12-lead ECGs have become increasingly important in the management of ST-segment elevation myocardial infarctions. Both BLS and ALS ambulance services can perform ECGs in the prehospital setting.[23,24] Analysis of ECGs provided immediately by the electrocardiograph has demonstrated limited sensitivity for detecting ST-segment elevation myocardial infarction.[25] However, sensitivity can be increased using serial prehospital ECGs, training paramedics to interpret ECGs, and providing computer-assisted interpretation or remote physician overread of the ECG.[26-29] Irrespective of the method of interpretation, patients with a prehospital 12-lead ECG showing ST-segment elevation myocardial infarction arriving at a hospital with a dedicated percutaneous coronary intervention team in place have reduced door-to-balloon time and reduced mortality when compared with similar patients arriving without a prehospital 12-lead ECG.[30-33]

AIRWAY AND VENTILATION ADJUNCTS

In a patient with acute respiratory failure or arrest, these devices maintain a patent airway that otherwise would have to be maintained by the paramedic. In addition, some airway adjuncts aid in preventing complications of airway management, such as gastric distention or aspiration. See Chapter 28, "Noninvasive Airway Management and Supraglottic Airways," and Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation," for detailed discussions of these topics.

Oral and Nasal Airways The simplest devices for airway management after manual airway maneuvers are the oropharyngeal and nasopharyngeal airways. These basic airway adjuncts usually are paired in the field with a simple bag-valve mask device for ventilation and will work quite well together.[34] Ventilation with the bag-valve mask can be difficult for a single person to both attain a good seal with the mask and compress the bag to produce an adequate tidal volume for the patient. It is probably more effective (especially for first responder and ambulance personnel who do not perform the skill often) to make this a two-person task (one person to maintain the seal and one person to compress the bag to maintain tidal volume). Along with these adjuncts, effective portable suction devices are available to be carried to the patient's side to help clear the airway.

TABLE 2-1 Comparison of Combitube®, LMA®, and King LTS-D®

Device	Use	Comments
Combitube®	Adults Adolescents >48 in. tall or age >14 y	Prevents/minimizes aspiration If inadvertently placed in trachea, will still ventilate Cannot use if gag reflex present Sturdy balloon
LMA®	Sizes for adults and children	May not prevent aspiration Can cause respiratory obstruction if incorrectly placed Cannot use if gag reflex present
King LTS-D®	Sizes for adults and children	Prevents/minimizes aspiration If inadvertently placed in trachea, will still ventilate Cannot use if gag reflex present Sturdy balloon Port for gastric decompression tube

Abbreviation: LMA® = laryngeal mask airway.

Supraglottic Airways More advanced airway devices are used if the patient appears to need more prolonged airway management or is at greater risk for aspiration.[35,36] At the BLS level, these airways include, most commonly, the **esophagotracheal Combitube® or King LTS-D® airway** or the **laryngeal mask airway (LMA®) (Table 2-1).** Each of these is used in conjunction with a bag-valve mask for ventilation. Supraglottic devices improve the airway seal to promote better ventilation than the bag-valve mask with the oral airway and seal the airway off with a balloon to reduce the risk of aspiration. Supraglottic airways may decrease hands-off time during resuscitation, but there is limited prehospital evidence to suggest that any advanced airway offers a neurologic survival benefit compared to simple bag-valve mask use.[37] Previous in-hospital evaluations of supraglottic devices have reported safety and efficacy. Future prehospital evaluations of supraglottic devices will need to address benefit, harm, and neurologic outcomes.

Although supraglottic devices are available for the pediatric population, a review of pediatric alternative airway devices used in prehospital care demonstrates the problems encountered in the field with airway management of children.[38] No clear benefit exists for endotracheal intubation over simple bag-valve mask, and evidence of benefit for prehospital supraglottic device use is very limited.[39,40]

Endotracheal Intubation Endotracheal intubation is the "gold standard" for airway management in all patients and is especially useful in patients in whom the other airway adjuncts are not satisfactory.[28] The majority of ALS systems use endotracheal intubation as the airway of choice for patients in respiratory failure or with an unprotected airway. Numerous adjuncts to assist with endotracheal intubation can be found in the ED as well as the prehospital setting. However, provider procedural experience is a primary determinant for successful placement. For further discussion, see Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation."

The basic emergency medical technician curriculum has an optional module for endotracheal intubation training. Therefore, intubation equipment may be found on some BLS ambulances. Increasing the number of ambulance personnel in need of endotracheal intubation training in an EMS system may cause logistic problems for the medical director. It is sometimes difficult to obtain adequate live intubation opportunities for the personnel in an EMS system to maintain skills. Some studies have shown that basic emergency medical technicians do not maintain endotracheal intubation skills and have low rates of

successful completion.[41,42] This might suggest that intubation should remain an ALS skill.[43,44]

Rapid-Sequence Intubation Another intubation-related modality that has bearing on the equipment carried on an ambulance is **rapid-sequence intubation**. Critical care transport services have been performing rapid-sequence intubation for more than a decade, and now this same level of care is provided in ALS systems as well. Rapid-sequence intubation raises the level of training, judgment, and psychomotor skills needed by the paramedic, but has the advantage of being able to secure more difficult airways. In addition to the usual equipment required for intubation, rapid-sequence intubation requires ALS services to carry the medications needed for sedation and paralysis.[39] The technique increases the need for oversight and vigilance by the medical director. Numerous large EMS systems have all indicated difficulties with ALS prehospital intubation, with or without the assistance of neuromuscular junction blockade or sedation.[45-47] Intubation, especially rapid-sequence intubation, is a training-intensive modality. Large systems with many paramedics may have difficulties with training type and intensity.[44] Smaller services, such as air medical services, which have a smaller group to train, a smaller span of medical control, and more intubation experience per provider, may be able to attain and maintain the complex skills needed for rapid-sequence intubation.[48]

CONTINUOUS POSITIVE AIRWAY PRESSURE AND BILEVEL POSITIVE AIRWAY PRESSURE

Continuous positive airway pressure maintains a continuous level of positive airway pressure throughout the respiratory cycle. Similarly, bilevel positive airway pressure delivers continuous positive airway pressure in a preset or measured inspiratory positive airway pressure phase and expiratory positive airway pressure phase. BLS and ALS services become competent in the use of this adjunct with additional training and a broadened understanding of respiratory physiology.[49-51] Use of either modality in the ED and prehospital setting is lifesaving and cost-effective in the treatment of the severely dyspneic patient.[52,53]

VASCULAR ACCESS EQUIPMENT

The equipment used to establish IV access is the same as at hospital: tourniquets, cleaning agent, IV catheters, IV fluid bags, and IV tubing. ALS ambulances need IV access for fluid resuscitation and for administration of medications. In general, vascular access for medication administration is completed as soon as possible after the patient is assessed and it is determined that pharmacologic intervention is needed. For fluid resuscitation, usually in trauma patients, vascular access usually is started en route to the hospital after the patient is immobilized, unless there is prolonged scene time due to extrication. This is to avoid prolonged scene times that may be detrimental to a trauma patient who may need intervention in the operating room. In any event, the amount of fluid that can be administered during transport is modest and may not be physiologically significant. Some data show that aggressive fluid resuscitation of hypovolemic trauma patients is detrimental, in that it may increase morbidity and mortality by enhancing exsanguination from vascular or organ injury requiring operative intervention.[54,55] The difference between hospital and EMS usage of IV equipment is that the medical director must provide guidelines for when and how to institute vascular access to allow appropriate interventions at the appropriate time. Use of vascular access should be examined in the quality assurance process in an ongoing manner.

IO access devices are important adjuncts for rapid vascular access in the critically ill patient.[56] Multiple recent works document the ability of ALS providers to quickly establish functional IO access.[57,58] Guidance is provided in a position paper from the National Association of EMS Physicians (http://www.naemsp.org).[59,60]

PREHOSPITAL ULTRASOUND

US is an important diagnostic tool in the practice of emergency medicine. New diagnostic applications for bedside US in the ED are reported in emergency medicine literature almost monthly. Moving US into the prehospital setting would seem like a logical next step. Multiple investigations demonstrate the feasibility of prehospital US in the United States and Europe. Some prospective observational data on prehospital US in EMS systems is available.[61-64]

TABLE 2-2 Guidelines for Cervical Spine Clearance in the Field

- Absence of neck pain, tenderness, or discomfort
- Age between 11 and 65 y
- No altered sensorium
- No intoxication
- No distracting injuries

Source: Data from Tatum JM, et al. Validation of a field spinal motion restriction protocol in a level I trauma center. *J Surg Res*, 2017. 211: p. 223-227.

SPINAL IMMOBILIZATION

Preservation of the integrity of the spinal column and spinal cord is of paramount importance in the prehospital setting. The first person to assess the patient should immobilize the cervical spine immediately and, if necessary, simultaneously perform a modified jaw thrust to open the airway. Manual stabilization of the neck is not released until the patient has been transferred and securely strapped to a board. Short or long boards, either alone or in combination, are used to immobilize the spine depending on the initial position in which the patient is found by the emergency medical technician or first responder.

Carrying boarded patients takes a physical toll on emergency medical technicians and paramedics. Evaluation of the boarded patient is more expensive and time consuming in the ED because of the need to clear the cervical spine.[65] A reasonable approach is for the medical director to develop protocols and guidelines for clearance of the spine in the field.[66] A patient with no neck pain, tenderness, or discomfort (neck pain must be defined liberally and include stiffness or "feels funny"); not in the extremes of age (<10 years or >65 years); with no altered sensorium (no drugs or alcohol present, no head injury); and with no distracting injuries (long-bone fracture, abdominal or chest injury) may be cleared in the field because there is an extraordinarily low probability of neck injury (**Table 2-2**).[67]

SPINAL BOARDS AND CERVICAL COLLARS

Long or short spinal boards are made from plastic or wood and provide a rigid surface to minimize movement of the cervical, thoracic, or lumbar spine. Straps secure the patient to the board for transport. Some boards are provided with firm rubber blocks on either side of the head with straps to go across the blocks to keep the head steady. Blanket rolls or sandbags secured to the board with tape are also effective head blocks. A popular and effective variation of the short board is the Kendrick Extrication Device® (KED®) (**Figure 2-2**), which consists of slats of rigid material bound together by heavy cloth.

This board immobilizes the cervical spine, wraps partly around the patient, and is then strapped the rest of the way around the thorax and around the thighs for secure immobilization. If necessary, the patient can be lifted by the straps, allowing for easier and safer upward extrication from the vehicle.[68]

Rigid cervical collars are more accurately called cervical extrication devices. Multiple types are used in the field, such as the Philadelphia® collar, the Miami J® collar (**Figure 2-3**), the Stifneck® (Laerdal Medical, Wappingers Falls, NY), and the Nec Loc® (Junkin Safety Appliance Co., Louisville, KY).

The collars come in two asymmetric pieces, which are used and marked for back and front, or as a single piece that is folded into the correct shape. By themselves, collars are not adequate for cervical immobilization but require additional lateral support to avoid movement in that direction. For adequate immobilization, the patient needs to be strapped on the backboard and secured with head blocks and head straps. Once the patient is well secured to the board, the collar does not add a significant amount of stabilization and actually can



FIGURE 2-2. Kendrick Extrication Device® (KED®) (Armstrong Medical Industries, Lincolnshire, IL). [Reproduced with permission from Armstrong Medical Industries, Inc.]

be removed without compromise of the spine; however, it is often left in place for added protection. Patients with mandible or soft tissue neck injuries probably should not have a collar applied because of the potential for airway compromise, which could be masked by the collar. Newer collars have openings in the front to allow observation of the trachea and jugular veins, but this may not be adequate for observing other neck areas. Soft cervical collars are not adequate or appropriate for prehospital care.



FIGURE 2-3. Miami J® collar. [Reproduced with permission from Ossur Americas, Foot Hill Ranch, CO.]

SEQUENCE OF SPINAL IMMOBILIZATION

Prehospital personnel are taught to have a high index of suspicion for spine trauma. **If the patient is sitting in a car after an accident and is stable from respiratory and circulatory standpoints, a short spine board and rigid cervical collar or Kendrick Extrication Device® are first used to get the patient out of the vehicle safely and onto a long spine board.** If the situation at hand is a critical one because of the patient's condition or the threat of hazards, such as chemicals, fire, or water, the patient can be extricated more rapidly using only the cervical collar. After applying the cervical collar, the patient is carefully rotated out and slid onto the waiting long board.

At a noncritical scene, when the patient is still sitting in the vehicle, one emergency medical technician secures the neck with his or her hands and applies the necessary airway maneuvers, while the second emergency medical technician applies the rigid cervical collar. The short board is then slid in behind the patient, and the patient is strapped to the short spine board. (Short boards are not used if the patient is not seated in a vehicle.) The first emergency medical technician maintains manual stabilization of the neck until the patient is secured to the short board. The patient's head and trunk can then be rotated around as one unit and slid directly onto the long board positioned on the car seat or on the ambulance cot. The patient is then strapped to the long board and then to the cot. A properly boarded patient can be turned on the board or even stood on end if necessary to move the patient to the ambulance. If the patient vomits, for instance, the board can be partly log-rolled up to prevent aspiration.

Because of the difference in relative size and positions of head and body, adults and children need slightly different positioning on a backboard. **An adult needs more padding under the head, whereas a child needs more padding under the body to maintain neutral neck position.**

If a patient is walking at the scene when the paramedical personnel arrive but complains of neck pain, the patient can be boarded from a standing position. If the patient is lying on the ground when the emergency medical technicians arrive, the patient can be carefully log-rolled by several attendants onto a long backboard.

Immobilization on a rigid board produces midline cervical pain and tenderness, so examination and radiographs should be performed promptly on arrival. Radiographs can be done without difficulty through short and long boards. In general, patients should not be removed from immobilization until the spine has been cleared clinically and radiographically. Transfer from the hard prehospital board to a padded board at the hospital is desirable if the patient may spend prolonged time immobilized.[69,70]

FOOTBALL HELMET REMOVAL

The National Athletic Trainers' Association and the Inter-Association Task Force for the Appropriate Care of the Spine-Injured Athlete developed guidelines for the prehospital care of athletes with potential spine injury. **These guidelines had recommended that the face mask of a football helmet be removed at the earliest opportunity, before transportation and regardless of respiratory status.**[71] However, because a properly fitted football helmet with shoulder pads holds the head in a position of neutral spinal alignment, field removal of these devices is no longer recommended by these guidelines, a tenet held in many EMS systems. It is recommended that the helmet and shoulder pads remain on as the athlete is immobilized and transported on a rigid backboard.[72-74] Simultaneous removal of the helmet and shoulder pads should be done after clinical assessment and radiographs at the hospital, although radiographs may have to be repeated after equipment removal.

Removal of football shoulder pads and helmet requires several individuals to maintain spinal alignment (**Figure 2-4**). One individual stands at the head of the bed to stabilize the patient's head, neck, and helmet, while others stabilize the spine and body. All straps and laces that secure the pads to the torso and arms are cut, not unbuckled or unsnapped. The laces or straps over the sternum are cut, allowing the right and left anterior portions to be spread open, exposing the chest. The posterior portion of the shoulder pads is kept in place to maintain spinal alignment with the helmet. Another individual cuts the chin

Helmet Removal

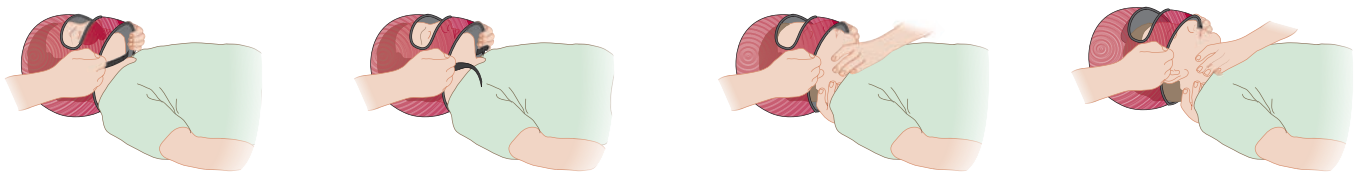
The varying sizes, shapes, and configurations of motorcycle and sports helmets necessitate some understanding of their proper removal from victims of motorcycle crashes. The rescuer who removes a helmet improperly may unintentionally aggravate cervical spine injuries.

The Committee on Trauma believes that physicians who treat the injured should be aware of helmet removal techniques. A gradual increase in the use of helmets is anticipated, because many organizations are urging voluntary wearing of helmets, and some states are reinstating their laws requiring the wearing of helmets.

Types of Helmets



Full face coverage—motorcycle, auto racer | Full face coverage—motocross | Partial face coverage—motorcycle, auto racer | Light head protection—bicycle, kayak | Football



1. One rescuer maintains inline immoblization by placing the hands on each side of the helmet with the fingers on the victim's mandible. This position prevents slippage if the strap is loose.

2. A second rescuer cuts or loosens the strap at the D-rings.

3. The second rescuer places one hand on the mandible at the angle, the thumb on one side, the long and index fingers on the other. With the other hand, pressure is applied from the occipital region. This maneuver transfers the inline immobilization responsibility to the second rescuer.

4. The rescuer at the top moves the helmet. Three factors should be kept in mind:
- The helmet is egg shaped and therefore must be expanded laterally to clear the ears.
- If the helmet provides full facial coverage, glasses must be removed first.
- If the helmet provides full facial coverage, the nose may impede removal. To clear the nose, the helmet must be tilted backward and raised over it.



5. Throughout the removal process, the second rescuer maintains inline immobilization from below to prevent unnecessary neck motion.

6. After the helmet has been removed, the rescuer at the top replaces the hands on either side of the victim's head with the palms over the ears.

7. Inline immobilization is maintained from above until a backboard is in place and a cervical immobilization device (collar) is applied.

Summary

The helmet must be maneuvered over the nose and ears while the head and neck are held rigid.
- Inline immobilization is first applied from above.
- Inline immobilization is applied from below by a second rescuer with pressure on the jaw and occiput.
- The helmet is removed.
- Inline immobilization is reestablished from above.

FIGURE 2-4. Helmet removal technique. [Reproduced with permission from American College of Surgeons, Committee on Trauma Brochure, April 1997.]

strap from below while standing beside the patient's chest. Accessible internal padding should be removed from inside the helmet and any air bladders deflated. The individual standing alongside the patient's chest then reaches up into the helmet to stabilize the head by placing a hand with fingers and thumbs spread alongside the jaw, mastoid region, and occiput. (See Video: Football Helmet Removal.)

Two additional individuals stand alongside the patient's chest and place their hands directly on the skin in the thoracic region. On command, the patient is lifted slightly, with all four individuals maintaining spinal alignment. The individual standing at the head of the bed can remove the helmet by a slight forward rotation to slide it off the occiput. Slight traction or anteroposterior motion may be necessary, but care should be taken not to move the head and neck unit. Attempting to assist removal by pulling on the ear holes tightens the helmet in the forehead and occipital regions and does not help. The posterior portion of the shoulder pads is removed, and the patient is lowered. A rigid cervical collar can then be placed.

TRACTION SPLINTS

Pelvic fractures and lower extremity fractures are potentially life and limb threatening. Fractures of the femur can damage vessels and nerves when bony fragments move. Stabilization in the field is important to minimize blood loss and soft tissue damage. The femoral traction splint is the preferred device for femur fractures.

Several leg traction splint variations are available for use. The two most commonly used types are the Hare® splint (Dynamed, Westbury, Tasmania) and the Sager® splint (Minto Research and Development, Inc., Redding, CA). The underlying technique is the application of traction by a hitch on the ankle against resistance when the splint impinges

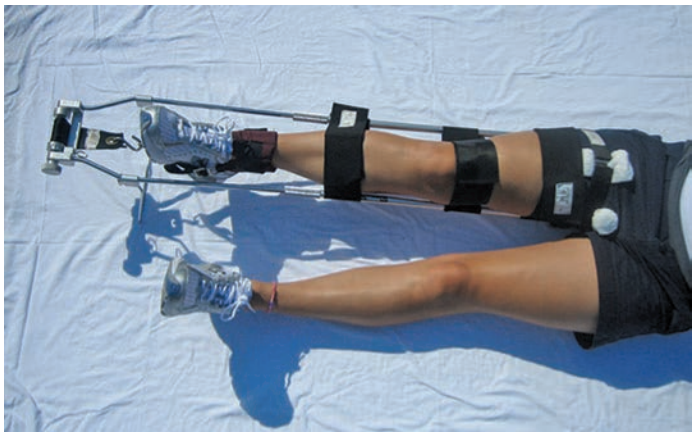


FIGURE 2-5. Hare® traction splint. (Courtesy of Jan Smith, RN, MPH, NREMT-P; acknowledgments to Kara Smith and Lucky Bruton, EMT-P.)

proximally on the pelvis. The padded proximal end of the Hare® splint abuts the ischial tuberosity (**Figure 2-5**). The proximal end of the Sager® splint rests against the pubic symphysis (**Figure 2-6**). **These splints cannot be used if a pelvic fracture is suspected because the pressure on the pelvis may further displace a fracture and cause more bleeding. Also, do not apply a traction splint if there is open fracture, hip dislocation, suspicion for neurovascular injury to the extremity, or injury about the knee, because a traction splint may exacerbate neurovascular or knee injury.** (See Video: Hare Traction Splint.)

Leg traction splints also may be used for tibial shaft fractures. Traction splints should not be used for fractures near the knee because longitudinal traction may damage neurovascular structures in the popliteal region. Traction splints for the tibia should be reserved for angulated or displaced fractures; otherwise, an air splint or a pillow splint would suffice.

At the scene, clothing should be removed and the extremity assessed for injury and distal neurovascular function. If the Hare® splint is used, the proximal half ring is placed in the crease of the buttocks against the ischial tuberosity. Traction is placed on the ankle with the padded ankle strap by one rescuer while the splint is strapped to the leg. The ankle strap is then attached to a ratcheting mechanism, and traction is tightened. If a Sager® splint is used, the splint is placed on the medial side of the limb up against the groin. The padded ankle hitch is applied, and traction is applied until malalignment is reduced and pain is relieved. Elastic straps are then applied to hold the splint to the leg.

The Hare® splint can be longer than an ambulance cot when fully extended, and care needs to be taken when closing the rear door of the ambulance. The Sager® splint is shorter than the Hare® splint, and one Sager® splint can be used to splint both legs simultaneously. The Sager® splint is less bulky and therefore takes up less room in an ambulance or a helicopter.



FIGURE 2-6. Sager Emergency Traction Splint; Model S304, Form III Bilateral, Application step 3 "Secure." [Used with permission from: Minto Research & Development, Inc., Redding, CA.]

PELVIC STABILIZERS

Unstable pelvic fractures can be immobilized to minimize the risk of bleeding from patient movement and during transport.[75] A sheet wrap, applied around the patient at the level of the trochanter and fastened with a clamp or hemostat, is the simplest stabilization method. Commercial devices, such as the SAM Pelvic Sling®, are also available.

PHARMACEUTICAL SUPPLIES

The basic emergency medical technician curriculum has modules that teach emergency medical technicians to administer a patient's personal medication in specific circumstances. For example, modules are provided for administering nitroglycerin for chest pain, inhaled β-agonists for bronchospasm, glucagon for hypoglycemia, and epinephrine-preloaded injections for anaphylaxis. Some states have gone beyond this and allow BLS services to stock and provide the medications covered in these modules.

The medications carried by ALS services are more extensive, but prehospital pharmaceutical interventions are limited to the few that make a real difference before or during transport.[76,77] These include oxygen, glucose, nitroglycerin, inhaled β-agonists, naloxone, parenteral narcotic and nonsteroidal analgesics, benzodiazepines, furosemide, epinephrine, lidocaine, magnesium, amiodarone, adenosine, diltiazem, calcium, and sodium bicarbonate. In the system that provides rapid-sequence intubation, neuromuscular junction–blocking agents (succinylcholine, vecuronium) are also provided.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 3

Air Medical Transport

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INTRODUCTION

Air medical transport consists of helicopter (or rotor-wing) and airplane (or fixed-wing) transport and is an important component of EMS systems for prehospital care and interfacility transport. These specialized vehicles offer fast speeds, ranging from 100 to 200 miles per hour for helicopters to >500 miles per hour for airplanes. Although many ill and injured patients can be transported safely by ground, air medical transport provides added medical assessment and care capabilities beyond those of the paramedic-staffed ground ambulance. Guidelines for the use of air medical transport exist, but field EMS personnel and physicians involved in transfer decision making should be able to consider situational circumstances to determine the appropriate transportation mode.

Weather can be an operational limitation, particularly for helicopters. The radius of service differs between helicopters and fixed-wing craft, but, as a general rule, fixed-wing transport is considered when weather conditions are poor or when transport distances exceed 150 to 200 miles.

The complexity of air transport far exceeds the simple act of loading a patient on an airborne vehicle. National organizations such as the Air Medical Physician Association, the Committee on Accreditation of Medical Transport Systems, and the National Association of EMS Physicians have published texts, position statements, and guidelines covering aspects of air medical transport. The Air Medical Physician Association

(http://www.ampa.org) *Air Medical Physician Handbook* is a particularly helpful resource for medical issues. The Committee on Accreditation of Medical Transport Systems (http://www.camts.org) accreditation standards address medical, aviation, organizational, and operational issues. The National Association of EMS Physicians (http://www.naemsp.org) has created detailed position statements and guidelines addressing helicopter EMS trauma and nontrauma triage criteria, as well as training of physicians involved as air medical crew or medical directors.

Rigorous training programs, covering both cognitive and procedural skills, enable flight crews to provide a high level of intratransport care. In-flight communications capabilities should include the ability of the air medical crew to speak with medical control physicians, as well as arrange for any change of plan (e.g., direct transport to the operating suite) necessitated by patient condition.

HELICOPTER TRANSPORT

AVIATION ISSUES

Individual hospitals, hospital systems, or private for-profit enterprises run most U.S. civilian air transport programs. Because helicopters are expensive (ranging from $750,000 to more than $5 million each) and other aviation needs (e.g., maintenance, pilot training) are also resource intensive, most hospital-based programs lease their helicopters from vendors. The air medical program typically provides and equips communications and medical personnel, whereas the aircraft vendor supplies the helicopters, pilots, and maintenance personnel. Although costs vary depending on geographic region, patient case mix, equipment and aircraft used, and even the methods used for their calculation, annual operating costs for a rotor-wing service typically exceed $2 million.

Safety is an overriding consideration for air transport. Optimization of safety begins well before an actual air transport, with training of the flight crew and of those who interact with them at scenes and hospitals. Training is especially important for scene responses, in which the helicopter may be landing in an unknown area with more nearby obstacles (e.g., wires, trees) than the hospital helipad. In addition to providing training for referring agencies, helicopter EMS pilots and medical crew should undergo both initial and recurrent safety training. For added protection, most helicopter EMS programs have followed the lessons of the military experience and adopted injury-prevention maneuvers such as the use of helmets and fire-resistant clothing. As another safety issue, the pilot should be "blinded" to the nature of the call during mission planning; this eliminates the introduction of acuity-related subjectivity as the pilot considers whether the mission should be accepted.

Safety is partially behind the transition of helicopter EMS programs from single-engine helicopters with visual flight rules capability to twin-engine helicopters that can fly under instrument flight rules conditions. The latter aircraft have greater lifting capacity, range, and speed and usually can execute controlled landings in the event of failure of one engine. A visual flight rules aircraft can fly only during good visibility, whereas instrument flight rules aircraft operate safely in poorer conditions; both comply with visibility limitations imposed by the Federal Aviation Administration, but the instrument flight rules helicopter has fewer restrictions. If the pilot unexpectedly encounters bad weather during a flight, an instrument flight rules helicopter (as compared with a visual flight rules aircraft) has a better chance of completing the mission successfully and safely. Due to the complexity of instrument flight rules operations, some programs (especially those with frequent bad weather periods) have elected to use two-pilot instrument flight rules.

Air medical programs operate under rules established by the national aviation authority—in the United States, the Federal Aviation Administration. Additionally, the industry itself has set forth stringent standards under the auspices of the Committee on Accreditation of Medical Transport Systems. On request, the Committee on Accreditation of Medical Transport Systems performs site visits of air medical programs to certify that they comply with strict safety and operational (as well as clinical) standards. As of September 2016, 183 U.S. transport programs were accredited by the Committee on Accreditation of Medical Transport Systems.

AIR MEDICAL CREW

The primary considerations regarding medical members of the flight crew are crew configuration and training. Although there are few absolutes with regard to optimal configuration, initial and recurrent training is at least as important as the credentials of the flight team members.

The air medical team can have multiple compositions: nurse–paramedic, nurse–nurse, nurse–physician, or nurse–respiratory therapist. These differences may be one reason that the literature has failed to answer definitively the seemingly simple question of whether a physician should be on board the helicopter. Most U.S. programs agree that physicians are not a necessary component of helicopter EMS crews, and a recent survey showed that 92% of programs use nurse–paramedic crews.[1]

The capabilities of most U.S. nonphysician crews represent an *extended scope of practice*. For instance, flight paramedics and/or nurses frequently are credentialed to perform such procedures as neuromuscular blockade–assisted endotracheal intubation and cricothyrotomy. This example of extended practice scope is important, given the importance of prehospital airway considerations and the fact that flight crews represent a highly trained group with particular expertise in this area. Reported success rates for nonphysicians are as high as 94.6% for drug-assisted and 97.7% for rapid sequence intubation–assisted endotracheal intubation and 90.9% for surgical cricothyrotomy.[2]

At this time, the best recommendation with regard to crew configuration is for programs to continue to do what works for them, as the literature does not report the superiority of a particular model. Most U.S. programs perform a variety of scene and interfacility missions for trauma and nontrauma indications, so the nurse–paramedic configuration, combining the complementary skills of prehospital and hospital-based practitioners, meets their needs. Some transport population heterogeneity can be addressed by the accommodation of extra crew members (e.g., neonatal nurses, intra-aortic balloon pump technicians) when logistics allow. Regardless of the background of the air medical crew, initial and recurrent training in both cognitive and procedural skills is necessary to ensure an optimal level of care.

ENVIRONMENTAL FACTORS OF AIR TRANSPORT

Patient care in any transport vehicle differs from that provided while the patient is on a hospital stretcher. Vehicle vibrations, bumpy rides, noise, physiologic stress, ergonomic constraints (**Figure 3-1**), and motion sickness are among the factors that can affect monitoring and interventions.

The impact of most vehicle-related issues in helicopter EMS can be eliminated, or at least reduced. Some solutions are easy (e.g., visual rather than aural alarms on ventilators), but flight crews must learn to "work around" other limitations (e.g., perform preflight intubation



FIGURE 3-1. The patient care compartment in a Dauphin II helicopter.

on patients who appear likely to deteriorate). Some problems will be specific to a service's particular aircraft, mission profile, or crew background. Individual program patient care protocols should take into account the service's equipment and personnel-related capabilities and limitations.

One transport-related issue that cannot be avoided is the question of **altitude and its potential effects on the patient and the crew**. In fact, altitude considerations vary with location—a Denver-based program has concerns that are different from those of a Miami service. Environmental conditions also have an impact on altitude considerations, because aircraft operating under instrument flight rules frequently fly at higher altitudes than those operating under visual flight rules. Of course, fixed-wing transports have more pronounced altitude considerations.

Helicopter (or fixed-wing) altitude and environment have potential effects on patient pathology as well as the crew's ability to monitor and care for the patient. Helicopters generally transport patients at about 1000 to 3500 ft above ground level (not necessarily sea level), although sometimes these altitudes are increased for instrument flight rules flights or for clearing of obstacles or terrain. Therefore, altitude-related problems such as hypoxemia, dehydration, and low temperature tend to be mild or relatively easily to overcome. However, geographic differences are important. Some western U.S. programs fly with supplemental oxygen for the medical crews.

Pressure-related problems related to Boyle's law (the volume of a gas increases when the pressure decreases at a constant temperature) may represent the most important consideration for helicopter-transported patients. For example, even the relatively low transport altitude range for helicopter EMS may affect patients with certain diagnoses (e.g., decompression sickness, cerebral arterial gas embolism) or instrumentation (e.g., tamponading devices for esophageal variceal hemorrhage). Endotracheal intracuff pressures increase an average of 33.9 cm of water at a mean altitude of 2260 ft.[3] This could raise the cuff pressure above the perfusion pressure of the tracheal mucosa, leading to injury. Hand-held commercially available devices can be used to keep cuff pressure within the target range of 20 to 30 cm of water. The devices are held in one hand and connected to the cuff inflation port. An inflation bulb can be used to further inflate the cuff, or an air-release button can be used to remove air while the cuff pressure is simultaneously measured by the device.

In some cases, an understanding of altitude issues is important in preventing complications. To minimize aspiration risk, gastric intubation should be performed for unconscious patients transported by air. Alternatively, understanding of the relevant science can be used to prevent overreaction to potential barometric risks. For example, not all patients with small pneumothoraces who do not otherwise require tube thoracostomy require pretransport chest decompression simply because they are to be transported by air.

CLINICAL USE OF HELICOPTERS

While trauma still constitutes the majority of helicopter transports for most programs, as more time-critical treatments develop, **more transports will be arranged for noninjured patients**. There are many schemes (age group, scene/interfacility mission type) for categorization of helicopter EMS transports, but the simplest categorization is into trauma and nontrauma. Logistical issues are important to both categories. Therefore, these are considered first.

LOGISTICS AND HELICOPTER EMS USE

Some logistic prompts for helicopter consideration include **(1) lengthy transport time for ground ambulances to reach the tertiary center, (2) ground vehicle transport time to the local hospital exceeds the time required for helicopter transport to the tertiary center, and (3) for entrapped trauma patients, extrication time is expected to exceed 20 minutes**. In some cases, helicopter EMS is used because local ground EMS personnel lack the expertise to provide the indicated level of intratransport care. Another important consideration is whether a region's ground EMS system can provide transport to the receiving tertiary center while maintaining the ability to cover its base area with appropriate advanced life support care. Questions that can assist healthcare providers in determining the appropriate transport modality for an individual patient are listed in **Table 3-1**.

TABLE 3-1 Questions to Aid in Determining Need for Helicopter Transport

- Is minimization of time spent out of hospital important?
- Is time-sensitive evaluation and treatment involved, and is it available at the referring facility?
- Is the patient inaccessible to ground transport?
- What are the transport route weather conditions?
- Does the weight of the patient preclude air medical transport?
- Are aircraft landing facilities available at or near the referring hospital?
- Is critical-care life support required that is not available with ground transport?
- Would ground transport leave the local area without adequate EMS coverage?
- If local ground transport is not an option, are regional ground critical-care transport services available?

HELICOPTER EMS FOR TRAUMA PATIENTS

There is one group of trauma patients—those in **traumatic cardiac arrest**—for whom air medical scene response has shown a very low rate of resuscitation and essentially zero survival.[4] Most helicopter EMS programs have their crews accompany traumatic arrest patients by ground to the nearest facility.

After the initial triage response decision, **the larger issue is whether helicopter EMS actually improves outcome for *any* injured patients**. There is disagreement over this question, but multiple studies have shown improved outcomes.[5-8]

The recent largest study to demonstrate improved outcomes after traumatic injury related to helicopter transport analyzed 223,475 patients from the National Trauma Data Bank transported by helicopter (28%) or ground EMS (72%). For trauma patients who were admitted to level I or level II centers, patients transported by helicopter had a significantly improved survival to hospital discharge compared with patients transported by ground transport.[5] Another recent study of 14,440 trauma patients taken to a level I trauma center demonstrated that patients transported by helicopter had a reduced overall mortality and that patients transported by all other means were more likely to die in the ED.[8]

The outcomes of rural trauma patients are thought to be worse than those of urban trauma victims. After controlling for age, gender, and Injury Severity Score, a Utah study[9] of helicopter transports from rural and urban trauma scenes found no difference in mortality. This study demonstrated that the helicopter scene transport of rural trauma victims appears to be a mortality equalizer.

A shortcoming of the literature is that studies generally address only the hard end point of mortality, with little emphasis on either mechanisms for survival improvement or nonmortality end points. Regardless of these shortcomings, the primary issue for trauma helicopter EMS is not whether some patients benefit, but rather how well those patients most likely to benefit from helicopter use can be identified by improved triage criteria. Although definitive criteria are lacking, the National Association of EMS Physicians has published guidelines for clinical situations that are appropriate for air transport (**Table 3-2**).

HELICOPTER EMS FOR NONTRAUMA PATIENTS

The reason that helicopter EMS trauma literature is (relatively) abundant is that there are ready means for controlling for the differing acuities of air- and ground-transported patients. Unfortunately, there is no such easy methodology for patients with nontrauma diagnoses, and acuity scales for nontrauma patients generally have not been accepted for use in assessing the association between transport mode and outcome.

Some general guidelines are available (**Table 3-3**), and the logistic considerations noted previously apply to nontrauma flights. **In most helicopter EMS programs, the largest single nontrauma diagnostic category is cardiac**. Patients in cardiac arrest should be transported to the nearest hospital rather than loaded on an aircraft. Transport for

TABLE 3-2 Air Transport Indications for Scene Trauma

General and mechanism of injury
- Trauma score <12
- Unstable vital signs
- Significant trauma in patients age <12 or >55 y and pregnant patients
- Multisystem injuries
- Ejection from vehicle
- Pedestrian or cyclist struck
- Death in same passenger compartment
- Penetrating trauma of the head, neck, chest, abdomen, or pelvis
- Crush injury of the head, chest, or abdomen
- Fall from height
- Near drowning

Neurologic injuries
- Glasgow Coma Scale score <10
- Mental status deterioration
- Obvious skull fracture
- Spinal cord injury

Thoracic injury
- Major chest wall injury (e.g., flail chest)
- Pneumothorax
- Hemothorax
- Suspected cardiac injury

Abdominal/pelvic injuries
- Significant abdominal pain after injury
- Seatbelt sign or abdominal contusion
- Rib fractures below the nipple line
- Unstable pelvis
- Open pelvic fracture
- Pelvic fracture with hypotension

Orthopedic injuries
- Amputation of limb (partial or complete)
- Finger or thumb amputation when replantation is available
- Fracture/dislocation with associated vascular compromise
- Limb ischemia
- Open long-bone fractures
- Two or more long-bone fractures

Thermal injury
- Burns of >20% body surface area
- Burns of face, head, hands, feet, or genitalia
- Inhalation injury
- Chemical or electrical burns
- Burns associated with other traumatic injuries

TABLE 3-3 Air Transport Indications for Nontrauma Conditions

Cardiac
- Acute coronary syndromes
- Cardiogenic shock
- Cardiac tamponade
- Mechanical cardiac disease (cardiac rupture)

Critically ill medical or surgical patients
- Pretransport cardiac arrest
- Pretransport respiratory arrest
- Mechanical ventricular assist
- Continuous vasoactive medications
- Risk of airway deterioration
- Severe poisoning
- Need for hyperbaric oxygen treatment
- Emergent dialysis
- Unstable GI bleeding
- Surgical emergencies (e.g., aortic dissection)

Obstetric
- Delivery will require obstetric or neonatal care beyond the capabilities of the referring facility
- Active premature labor <34 wk or estimated fetal weight <2000 grams
- Acute abdominal emergencies <34 wk or estimated fetal weight <2000 grams
- Preeclampsia or eclampsia
- Third-trimester hemorrhage
- Fetal hydrops
- Complicated maternal medical conditions
- Predicted severe fetal heart disease

Neurologic
- CNS hemorrhage
- Spinal cord compression
- Status epilepticus

Neonatal
- Gestational age <30 wk or fetal weight <2000 grams
- Supplemental oxygen exceeding 60%, continuous positive airway pressure, or mechanical ventilation
- Extrapulmonary air leak, interstitial emphysema, or pneumothorax
- Medical emergencies (e.g., congestive heart failure, disseminated intravascular coagulation)
- Surgical emergencies (e.g., diaphragmatic hernia, necrotizing enterocolitis)

primary or rescue coronary intervention for ST-segment elevation myocardial infarction is a frequent indication for helicopter use and can be done rapidly and safely.[10,11] Cardiac patients with pacemakers or those who have received thrombolytic therapy can be transported safely and effectively by helicopter EMS.

Another growing indication is the provision of lytic therapy or vascular intervention for ischemic stroke.[12] The American Stroke Association (http://www.strokeassociation.org) Task Force on Development of Stroke Systems[13] identified helicopter EMS as an important part of stroke systems. However, a study of 122 patients transported to a stroke center after receiving recombinant tissue plasminogen activator at the referring hospital demonstrated no benefit in patient outcomes in air-transported patients.[14]

Obstetric transports are a special consideration for air transport because many high-risk patients are best delivered at tertiary care centers. The question for this population is primarily one of safety during transport. In-flight deliveries are a major resuscitation problem for both mother and infant. Experience has provided some reassurance that the use of helicopter EMS to transport high-risk obstetric patients did not result in deliveries in the back of the helicopter, and **neonatal outcomes are not adversely impacted by transport**.

FIXED-WING AIR MEDICAL TRANSPORT

Fixed-wing aircraft can serve a wide variety of missions, from urgent to routine, over great distances. Because airplanes land only at airports, they cannot respond to the scene, and fixed-wing transports need ground ambulance connections at both ends of the flight to transport the patient between the hospital and airport. Because of these factors, fixed-wing flights generally take longer to arrange and are uncommonly used for truly emergent patients.

Helicopters are virtually always dedicated as air medical transport vehicles when used by U.S. EMS services, but fixed-wing airplanes used for medical transport may have other roles. When fixed-wing aircraft are used for air medical transport, cabins must be reconfigured. Vendors have developed removable medical equipment modules that can be placed relatively quickly in the aircraft cabin.

On a per-mile basis, fixed-wing transports are less expensive than helicopter EMS transports. However, the optimal transport radius for fixed-wing triage varies with regional and patient-specific considerations. The appropriate aircraft to use for any one mission depends on many factors: distance, the nature of the airport at the patient's pickup point, the condition of the patient, the amount of equipment, and the crew required in transport. A larger plane that can be pressurized can fly above 3000 m (10,000 ft), which means that the aircraft can travel faster, farther, and more comfortably. At these higher altitudes, flight crews must have a deeper understanding of altitude physiology issues. Cabin pressure (i.e., indicated altitude above sea level) should be recorded on medical records because of the importance of pressure issues to physiology, and crew safety training should include measures to take in case of inadvertent cabin depressurization.

All fixed-wing services must comply with civil aviation authority rules for airplanes. The Commission on Accreditation of Medical Transport Systems has developed standards for air medical fixed-wing transport. These standards, which are also a useful primer for more detailed information about fixed-wing air medical transport, deal with aircraft configuration, medical equipment requirements, medical crew configuration and training, and medical director qualifications.

MEDICAL DIRECTION OF AIR MEDICAL SERVICES

Medical direction may be even more important with rotor- and fixed-wing services than with ground services; it is certainly more complicated because it involves most aspects of ground EMS in addition to vehicle-specific and altitude- and acuity-related issues. The medical director should be familiar with the physiology and stress of flight on patients and should oversee the teaching of these and other applicable principles to the air medical crew. Overall, **a flight crew requires more initial and ongoing training than do most ground EMS personnel due to the higher patient acuity and extended practice scope**. Because flight crews are often far from their base of operations and may be out of voice contact, they must be sufficiently trained so that they can act independently when necessary. For nonphysician crew, standing orders or protocols (especially for advanced procedures such as cricothyrotomy) are needed. Periodic review and updating of these protocols, as well as close inspection of every transport record, are among the many responsibilities of the medical director. The Air Medical Physician Association and the National Association of EMS Physicians have published information on the responsibilities and function of the air medical program physician director.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 4

Mass Gatherings

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INTRODUCTION

Mass gathering medical care refers to the provision of medical services to organized events or venues with relatively large numbers of people in a defined geographic area. Typically, mass gatherings are considered to be events that have at least 1000 people; however, this does not have to be the case.[1,2] In fact, large organizations including the World Health Organization and the U.S. Federal Emergency Management Administration do not focus on the number of attendees when defining mass gatherings; rather, they recognize the impact on the surrounding resources.

There are several variables in event and crowd characteristics that may affect patient presentation rates, thus resulting in demands on the event medical staff and larger surrounding system that bear little direct relationship to the number in attendance. Some of these variables include weather conditions, presence of alcohol and/or illicit substances, type of event, violent spectator behavior, and presence of potable water. Further, events that are considered "bounded/focused" (stadium sporting events) are associated with higher patient presentation rates than those considered "unbounded/extended" (parades), likely due to the leakage of patients in the unbounded events into the surrounding healthcare system.[3] Event medical directors should also consider the transport to hospital rate from the same or similar previous events when planning their event. In conjunction with the patient presentation rate, the transport to hospital rate can assist in estimating resources needed.[4]

TABLE 4-1 Factors Affecting Planning for a Mass Gathering Event

- Venue entry and exit
- Communication
- Environment
- Potential public health threats

Table 4-1 lists some of the major factors affecting planning for a mass gathering event. Physical barriers may inhibit easy entry and exit from the site. These barriers can make it difficult to get medical resources into, and to get patients out of, the event location. **Reliable communication between medical personnel, event organizers, and outside medical resources is key to a successful medical response.** Finally, event planners should consider possible public health threats of widespread communicable disease and the potential for a terrorist attack with explosive or other devices.

EPIDEMIOLOGY AND TYPES OF MASS GATHERINGS

The need for mass gathering medical care was first described after two spectators collapsed and died during a University of Nebraska football game in 1965.[5] The event organizers were not prepared to manage medical emergencies in the midst of the event, and consequently, when these two patients needed medical care, the organizers were not able to meet the need. Medical directors have become experienced in mass gathering medicine, and case reports are described for sporting events, concerts, expositions, and other large congregations of people.[2]

One of the largest global gatherings, the Islamic Hajj pilgrimage to Mecca, Saudi Arabia, has required officials to manage threats to public safety from outbreaks of infectious disease to major traumatic injuries from stampedes. Other notable global mass gatherings include the 2010 World Expo in Shanghai, China, which attracted approximately 70 million visitors,[6] and the Olympic and Paralympic Games in Rio de Janeiro, Brazil, in 2016. More recently, music festivals, including electronic dance events, are increasingly common. These events have predictable risks and patient presentations. Studies suggest that appropriate on-site healthcare resources may reduce significantly the impact on the prehospital and emergency health resources in the surrounding community.[7] As mass gathering events become more common, there is a need to develop the science of mass gathering medicine. The growing field of mass gathering medicine continues to be instrumental in exploring the health risks of mass gatherings and providing strategies that contribute positively to delivering care during these events.

Interestingly, despite the fact that mass gatherings are generally attended by individuals in good health, these events tend to have a higher incidence of illness and injury than that which would be found in the general population.[8] The incidence of usage of medical care at mass gatherings has been reported to range from 4 to 440 patients per 10,000.[2] The wide variance in medical usage rate is a function of the variables previously discussed.

COMPONENTS OF A MEDICAL ACTION PLAN

In preparing for a mass gathering event, medical directors should develop an organized approach through the development of a medical action plan.[9]

PHYSICIAN MEDICAL OVERSIGHT

All mass gathering events should have an identified physician medical director who is responsible for developing the medical action plan. The objective of this plan, which should be a component of the overall incident action plan, is to describe the details about the organization and delivery of medical care. The medical director is also responsible for providing medical oversight before and during the event. This person should be board certified in emergency medicine and have a current medical license from the state(s) where the event will be located. The medical director should also have experience in the medical direction of EMS and the provision of medical care at mass gathering events. It is becoming more common for the event medical director to be board certified in EMS. Experience and training in EMS provide an event medical director with skills in field medicine, including creative thinking, the ability to make diagnostic and treatment decisions purely on clinical grounds, and an awareness of operational environments that are very different from a typical ED.

The medical director is responsible for developing plans for indirect medical oversight and ensuring a coordinated system of direct medical oversight. Indirect oversight describes a system of written protocols that provide the medical personnel with a standardized set of directions for the care of a variety of traumatic and medical conditions that may be encountered during the event. **These protocols should always be at least commensurate with local EMS protocols unless the medical director has prior approval from the local jurisdictional EMS medical director to deviate from them.** Direct medical oversight describes a method of direct communication with medical providers during the event to answer questions and provide medical direction in real time during the event. Although direct oversight can be delegated to a team of physicians for an event of long duration, ideally, the medical director should plan to be on site during the event as much as possible.

COMMAND AND CONTROL

In addition to an event medical director, mass gathering plans should have an organized system of command and control. Although many systems exist for the command and control of resources at emergency incidents or mass gatherings, one of the most well-tested and efficient methods is the Incident Command System. The system can be used for any type or size of emergency, disaster, or mass gathering, with the purpose of allowing either a single agency or multiple agencies to communicate using common terminology and operating procedures.[10]

The purpose of establishing a command and control system like the Incident Command System is to define clear lines of reporting and communication among all major functioning components that may coexist during an incident. The organizational structure develops in a modular fashion from the top down. While the Command function is always established, the other divisions, which include Operations, Logistics, Planning, and Finance, form as needed (**Figure 4-1**).[11] As will be discussed later, the physician's role within the Incident Command System structure should be focused on direct oversight of patient care and not involve the global issues that are the concern of the incident commander.

Within a typical Incident Command System, the provision of medical care to the public occurs within the Operations Section. Often referred to as the "doers," it is the function of the Operations Section to complete the primary tasks of the mission. Members of the medical branch in Operations include, but are not limited to, emergency medical technicians, paramedics, nurses, physician assistants, and physicians. It is not required that the physician take the lead role of each medical team. In fact, it may be more beneficial to have the individual with EMS or fire service experience in the role of team lead, which ideally may be an EMS physician. An agency's medical director should be available for direct medical oversight as needed and should ideally be on site as much as possible. The medical director(s) should function as a commander within the Operations Section and report back to the section head of Operations who ultimately reports to the incident commander. Key to the success of the Incident Command System is that every individual abides by the established hierarchical ranks of command.

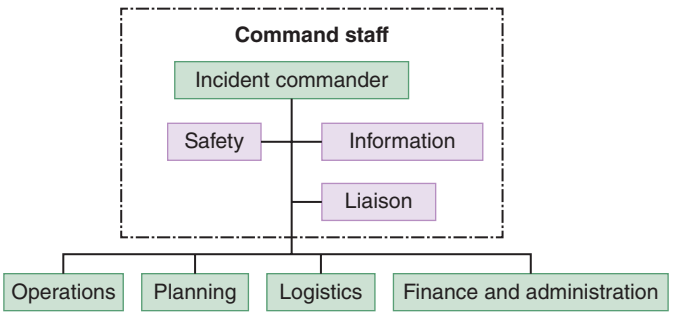


FIGURE 4-1. Incident Command System organizational chart.[11]

FORCE PROTECTION MEDICAL SUPPORT

It is well known that if a medical provider becomes sick or injured, the provider will use resources intended for the public and distract other providers from the ability to perform their duties. As such, a sick or injured medical provider has the potential to dramatically disrupt the overall medical mission for the event. While medical personnel are always responsible for assessing and ensuring their own safety and those with whom they work, it is imperative to have a well-designed plan for the overall medical care and protection of the medical providers at the event. The provision of dedicated force protection medical support can be a critical factor toward enhancing individual law enforcement and EMS/fire personnel health sufficient to maintaining effectiveness for the duration of the event.[12]

One of the duties of the event medical director is to be prepared to provide care to the other medical and law enforcement providers should the need arise. In addition, communication with law enforcement personnel will help to ensure the overall protection of the medical providers. Their support should be readily available and have the means to immediately respond to any location should the situation become unsafe. Depending on the type of event, threats could range from those that are readily seen (e.g., crowds at a concert) to those that are hidden (e.g., explosives and other weapons carried by an individual with the goal of using mass gathering events to kill and injure).

EVENT RECONNAISSANCE

In the beginning stages of preparation, the medical director and assistants need to assess the site to identify potential risks for morbidity during the event. This should ideally be done with the dates and duration of the event in mind and should also account for the geographic variants that will affect their ability to provide medical care to the public. Adequacy of exits should be addressed, routes of ingress and egress should be reviewed, and the geographic area the medical care sector is responsible for should be identified. Backup plans should also be developed. Planners should determine ideal locations for setting up a base of operations, fixed medical care sites, and staging areas for mobile units. Decisions should take into account the effects of predicted traffic flow, predicted sites of high-volume medical need, natural geographic barriers, and location of receiving medical facilities. Ideally, the event medical director should meet with the jurisdictional 9-1-1 EMS medical director(s) to discuss planning and response should a mass casualty response be required.

EVENT NEGOTIATIONS

The process of developing a medical plan for a mass gathering event requires a cohesive teamwork approach with multiple interest groups. First and foremost, the medical planners should develop a plan that meets the needs of the public and the event planners. This first step may require some negotiations with event planners in determining locations for fixed and mobile medical units, level of care to be provided, and resources provided to the medical units. Negotiations will determine if the medical units will be paid under contractual terms by the event planners or if they will volunteer their services to the event. This negotiation stage should also resolve who will finance the purchase of needed

supplies and pay for other needed resources, such as costs of transportation and liability coverage.

Regardless of who pays for supplies, it is important that the medical teams coordinate to ensure that equipment and supplies are readily available when needed. Similarly, regardless of who is responsible for acquiring supplies, there is value to the event medical director having ultimate control over the acquisition and maintenance of critical medical supplies, as this will ensure that the medical needs of the public are met.

Medical planners should also establish communication and agreements with other outside agencies that have a potential need to interact with the medical response team for the event. Medical teams that are formed outside the local jurisdictional EMS system should have an agreement with local EMS that addresses transportation of patients out of the event to local resource hospitals. Transfer and acceptance agreements should be developed with the hospitals. Local law enforcement should be contacted for assistance with traffic flow and security. Events that have the potential to be affected by security issues on a national scale may also require agreements with the U.S. Department of Homeland Security for disaster and security response.

HUMAN RESOURCES, LEVEL OF CARE, AND TRAINING

The event medical director should determine the desired level of care for the event based on the predicted medical need and available resources. While there is no universally acceptable formula that can accurately predict staffing requirement, the number of medical providers should be a balance between the number determined to be optimal based on reconnaissance, statistical estimates, and review of previous similar events. Emergency medical technician should be the minimum acceptable level of care. However, depending on the event type and size and the number of medical providers available to staff the event, there may also be a role for the emergency medical responder to provide operational medical support. Once the desired level of care and the predicted patient volume are determined, the medical director will be able to develop a plan for human resource needs. These resources may be acquired through the local EMS system, area hospitals, medical training programs, or other sources such as ski patrols and medical reserve corps.

Medical personnel should be licensed to practice at their level of training in the local jurisdiction. Although the medical personnel should be trained for their established level of care, the medical director may want to have additional training sessions to address specific injuries and medical conditions that are predicted to be encountered by the medical personnel during the event. Using new or modified protocols should be preceded by pre-event education of all relevant personnel and close medical oversight. Regardless, it is important that the providers work within a defined scope of practice as determined by level of training and any operational-specific protocols that may be authorized by local authorities for mass gathering events.

EQUIPMENT

When considering equipment for a mass gathering event, planners and medical directors should take into account the type of event, the weather, and the skill level of the medical staff. Units with physicians may elect to have on hand supplies to do simple suturing and advanced resuscitation. However, thought should be given to the available time needed to suture a wound in balance to the patient volume and the availability of the fixed standing acute care centers. If available, it may be more advantageous to refer patients needing procedures to acute care hospitals. The appropriate way to manage the need for procedures is dependent on the available resources and the overall mission of the medical care at the event.

Often, a large proportion of time spent planning out supplies is focused on generating a broad list and subsequently obtaining supplies that would be necessary to provide medical care for a critical patient. As discussed earlier, it is important to consider that rapid transport of this patient away from the incident to the controlled environment of an acute care hospital may be more beneficial for the patient and free up the provider to care for other patients who would likely not receive evaluation given the time-consuming nature of the critical patient. In addition, proportionally fewer critical patients are seen at a given event compared with the vast majority who seek aid for minor complaints such as scrapes, blisters, headaches, and sprains. Therefore, more effort should be placed on obtaining supplies in highest demand. As suggested by the number and type of complaints seen, those supplies in highest demand typically include bandages, foam padding for blisters, ice for sprains, fluids for oral rehydration, acetaminophen, and ibuprofen.

Data have demonstrated the incidence of cardiopulmonary arrest and the need for major resuscitation at mass gathering events is low.[13] However, **medical units should, at the very least, have access to an automated external defibrillator**.

Event-specific protocols should address the use of advanced airway equipment, including the possible use of medications for rapid-sequence intubation. Plans for other resuscitation needs should also be addressed prior to the event so that all providers manage these small numbers of cases in a standard format (e.g., fluids for sepsis, postresuscitation care, management of cardiac arrhythmia, status asthmaticus). Although it is rare that there is a need for major resuscitation, there may be value to having supraglottic airways and intraosseous needles.

In addition to the level of training of the medical staff, equipment needs will be determined by the mobility of the unit. Some events may need mobile medical units that are able to reach patients in difficult locations or easily move through large crowds. Units on foot and other nonmotorized means of travel will be able to carry fewer supplies than those using motorized vehicles such as golf carts. For events using nonmotorized mobile units, it will be important to design a means to bring heavier supplies to a patient should the need arise. Units in fixed locations will be able to stock a greater quantity of materials, possibly including cots, shelter, and additional medical supplies.

Although the equipment needs are unique for each event, there are some things that are universal. **Tables 4-2** and **4-3** show suggested items for both mobile and fixed units as well as suggested equipment based on the skill level of medical personnel.

TREATMENT FACILITIES

Medical directors will need to determine if the scope of the event will require fixed treatment facilities or if mobile units will be sufficient. Factors that contribute to this decision include, but are not limited to, the predicted number of patients expected to seek medical care, length of the event, distance to off-site medical care, and environmental factors. Fixed treatment facilities can be set up in mobile tents or within a permanent structure. Regardless, fixed treatment facilities should be set up in such a way as to be able to withstand the predictable weather conditions that may be encountered during the duration of the event. The location of the facility should also be easily accessible and have a secure path for ingress and egress. From a patient care perspective, it is important to have a facility that has environmental control to manage heat-related illness in warm weather and cold-related illness in cold/wet weather. Off-site treatment facilities should be arranged with local hospitals.

Staffing of both fixed treatment facilities and mobile units contributes to the success of the overall event's medical response plan. Appropriately placed physicians can expand on-site definitive treatment, including the use of chemical sedation, advanced wound care, and disposition of high-risk cases who wish to sign out against medical advice. Further, physicians on site have been able to affect ambulance transport rates, thereby helping to preserve EMS and resources for the surrounding community.[14]

TRANSPORTATION

Nonmedical and medical transportation is necessary, taking into account the number, capacity, and staging location for transport units. Nonmedical transportation units move personnel and resources throughout the site. Medical transportation moves patients within the event location and out to area hospitals. Ambulances are the mainstay of ground transport from the venue to outlying medical facilities. They should be dedicated to the event and prepositioned in an easily accessible and known location. If the supply of event-dedicated ambulances becomes depleted, there should be a plan in place to support emergency medical transportation.

TABLE 4-2 Equipment List for Mobile Units

	Item
Basic (BLS-level EMS provider and above)	Automatic external defibrillator
	(*May alternatively place in a strategic location in the site venue*)
	Cervical collar
	(*May strategically place in the site venue a method for transport of a patient requiring in-line spinal immobilization*)
	Airway adjuncts
	Oxygen delivery devices (nasal cannula, nonrebreather mask, bag-valve mask)
	Oxygen and suction
	(*May be strategically placed in site venue*)
	Bandages (4×4, roller gauze)
	Triangular cravats
	Adhesive bandages
	Nonlatex gloves
	Splints
	Stethoscope
	Sphygmomanometer
	Tape
	Shears
	Flashlight
	Documentation forms
	Hazardous waste bags
	Compact foil space blankets
	Petroleum jelly (used to prevent chaffing by marathon runners)
	Oral fluids for hydration (water, sports drinks)
Advanced (ALS-level EMS provider and above)	Advanced airway equipment including laryngoscope with assorted blades, endotracheal tubes, and cricothyrotomy kit
	(*May alternatively use a supraglottic airway device*)
	IV access devices and tubing
	(*May choose to carry an adult intraosseous set*)
	Normal saline in 1-L bags
	Glucometer
	Dextrose for IV administration
	Advanced cardiovascular life support medications: epinephrine, atropine, amiodarone, adenosine
	Aspirin
	Nitroglycerin
	IV diphenhydramine
	Parenteral benzodiazepine
	Multidose inhaler albuterol
	Epinephrine in 1:1000 concentration
	Morphine
	Airway medications: induction agent, paralytic

Abbreviations: ALS = advanced life support; BLS = basic life support.

Planners may also need to address nontraditional modes of transportation, such as golf carts, all-terrain vehicles, boats, bicycles, horses, snowmobiles, and toboggans.[15] Operators must have experience in their handling, and these resources should be dedicated for use throughout the duration of the event. Protocols should also be developed that address the appropriate use of air medical transportation, including location and setup of a safe landing zone.

PUBLIC HEALTH

Public health concerns during a mass gathering event may be addressed by the event managers or delegated to the local public health authority or the medical director and EMS system. Even if these concerns are not delegated to the medical response team, public health concerns can affect patient care, and therefore, the medical director should be aware of these issues. **Table 4-4** lists some potential public health concerns.

TABLE 4-3 Equipment List for Fixed Units

	Item
Physician-level care (some of these skills and/or medications may be available for use by EMS providers with authorized operational-specific scope of practice for mass gathering events)	Suture kits with absorbable and nonabsorbable sutures
	Needles and syringes
	Forceps
	Scalpel
	Normal saline for irrigation
	Local anesthetics
	Otoscope
	Analgesics: acetaminophen, ibuprofen, morphine
	Antacids
	Antiemetics
	Prednisone
	Antibiotics: ointment, oral
	Activated charcoal
	Airway management: induction agent, paralytic
Nonmedical equipment	Cots
	Shelter
	Blankets
	Chairs
	Hazardous waste receptacle
	Sharps box

ACCESS TO CARE

The event managers and medical director should develop plans to ensure that the public will be able to access emergency care, if needed. These plans should ensure that the locations of fixed treatment facilities are well marked with signs and other visual aids and that there are limited barriers to access these facilities. Fixed treatment facilities should be accessible to all members of the public, regardless of their ability to actively seek care, and comply with guidelines that are in accordance with the Americans with Disabilities Act. Mobile medical personnel should also wear vests or other high-visibility clothing easily identified by the public. Pamphlets or signage can alert the public about methods for accessing emergency care.

COMMUNICATIONS

Successful management of any mass gathering event is contingent upon an effective communication system. To maintain coordination and control, the system must be tailored to the unique needs of the scenario. The design is dictated by a variety of factors, including geography and size of venue, number of participants, budget, and the systems of those with whom providers will be interfacing. Consideration should also be given to environmental factors including temperature extremes, water,

TABLE 4-4 Public Health Concerns to Be Considered for a Mass Gathering Event

- Access to potable water
- Proper waste management for human waste
- Waste management for nonhuman waste
- Proper management of food service to prevent spread of foodborne illness
- Proper road/traffic management to prevent traffic-related injuries
- Other considerations for injury prevention
- Large-scale natural or man-made disaster

and noise. Venues at music concerts and motor sports may require special communication devices to allow for providers to communicate with each other while in the presence of loud background noise.

Modalities can range from simple flag signals to sophisticated radio networks and may include consumer Family Radio Service devices (walkie-talkies), cellular systems, and landline phones. Each has their strengths and weaknesses. Walkie-talkies have a multitude of channel options but are typically limited to a 1- to 2-mile range. Cellular and other phone systems may provide an inexpensive option but are easily overwhelmed by large numbers of users during a crisis. Two-way radios with more power and range than Family Radio Service systems may be analog or digital, using very high frequency, ultra-high frequency, or 800-MHz frequencies. Systems using a repeater antenna allow for communication over greater distances and across rugged terrain. Large-scale, trunked radio systems provide central control of end-user access to selected channels, allowing a greater number of people to function within a limited spectrum. These systems also allow for discrete groups of responders to communicate among themselves without disturbing other groups.

The communication center should be located in an area that affords the greatest coverage for the event and is fully accessible to the medical director. If situationally appropriate, it may be advantageous to have it co-located in the event command center. This communications network should be separate from the surrounding EMS jurisdiction and should be solely dedicated to the event. Ideally, the communications center should be linked by cell phone, landline, or radio to surrounding jurisdictional services, which include, but are not limited to, public safety answering point (PSAP), local emergency management, EDs, and public health departments.

If the communications network is not linked to surrounding resources, a protocol must be in place for making contact and for relaying information as needed. In an urban environment, this may be in the form of an on-site representative from the local EMS system or an identified phone number or frequency designated for the activation of additional resources. In a remote area, one or more people may be tasked with relaying messages via radio or traveling to the nearest telephone or area of cellular service to contact local authorities, or a specific "communications tent" may be organized.

DOCUMENTATION

The medical director should develop a system for documentation of patient encounters during the event. This system need not be as extensive as that which would be found in the typical ED setting and, instead, should be focused on the event to address specific components of the patient encounter as outlined in **Table 4-5**. Medical documentation should be easy to complete and not exhaustive, such that it can be quickly completed if large numbers of patients seek medical care at the same time. Medical directors may want to consider a method of electronic documentation. Paper documentation should ideally be on a single sheet that can be used by all providers involved in the patient's care (**Figure 4-2**).

TABLE 4-5 Documentation

Purposes of medical documentation for a mass gathering event

- Assist in transfer of care from the event site to off-site medical facilities
- Record medical interactions for the purposes of liability control
- Establish a means of data capture for continuous quality oversight and research

Essential components of medical documentation for a mass gathering event

- Patient's name, contact information, sex, and age
- Vital signs
- Chief complaint
- Focused physical examination
- Suspected diagnosis
- Medical care rendered
- Disposition

LIABILITY

All members of the medical response team for a mass gathering event should have medical liability coverage. Depending on the restrictions of the carrier, liability coverage may be provided by the policy of one's primary employment or may need to be purchased as additional coverage. The medical director may want to arrange coverage for all members of the medical response team as a group. This should be factored into the cost of providing medical care for the event and should be discussed with planners during the negotiation stage before the event. It is important to note that, if the medical personnel will be reimbursed for services in the form of legal tender or payment in kind (even in the form of a free meal at the event), they may not be protected from liability through Good Samaritan laws, depending on the state. In addition, if the medical providers are advertising their medical services to the public at an event even by setting up an established medical tent, the providers have established a duty to act and are liable to the public to provide care at an established standard. To mitigate untoward risk, the medical director should review the laws that pertain to the local area before the event.

CONTINUOUS QUALITY IMPROVEMENT

Unless an event is anticipated to be a one-time occurrence of a short duration, the medical director should establish a method of continuous quality improvement. The continuous quality improvement program should begin with a review of the documentation for patient encounters to identify elements of the system that are performing well and elements that need improvement. The results of continuous quality improvement review should then be used to improve upon the system of delivery of care. The medical director may also consider having regular case reviews with the medical personnel at the event to improve the care being delivered. In addition, an after-action report, which includes all aspects of the event from planning through execution, can identify areas of improvement for future events.

SPECIAL SITUATIONS

CARDIAC ARREST

In general, the incidence of cardiopulmonary arrest and the need for major resuscitation at mass gathering events is low. However, cardiac arrest has been shown to be particularly susceptible to successful intervention in this type of setting.[16] The foundational components of successful resuscitation, CPR and early defibrillation, should be delivered to a patient within 3 minutes of notification of collapse.[17] Thus, staging of medical personnel within an appropriate response radius and equipping medical units with an automated external defibrillator should be a priority. Planners should also consider the placement of ambulances within a location at the event for easy egress and the provision of advance life support care.

MASS CASUALTY INCIDENT

In preparing for a mass gathering event, the event medical director should contribute to and have full working knowledge of the action plan in response to a mass casualty incident. Plans should include methods of triage, coordination of the mass casualty with local EMS, and distribution of large numbers of patients as needed to area acute care facilities. There should be predesignated communication channels so incoming responders can communicate with the scene of the incident. The medical teams should function seamlessly in the Incident Command System structure. Success is partly predicated on predetermined roles of the personnel at the event, which allows for immediate implementation of the Incident Command System. History has demonstrated that mass gathering events can be targets for intentional acts of harm. Given this possibility, the medical director should be involved, along with the director of event security, in formulating an action plan should such an event occur. This plan should include a contingent causality collection area able to manage an influx of patients.

Patient Encounter Form

Event: _____

DATE & TIME (24hr) _____
Last Name: _____
First Name: _____
Phone #: _____
Age: _____ ☐Female ☐Male ☐Transgender
DOB*: _____ PHN*: _____
Family Physician*: _____

PATIENT CATEGORY _____
(A=Athlete, E=Event Staff, P=Performer, S=Spectator, U=Unknown)
PARTICIPANT ID _____
(Race/Bib Number)
TRIAGE ACUITY SCALE**
☐Black ☐Red ☐Yellow ☐Green ☐White

PRESENTING COMPLAINT _____

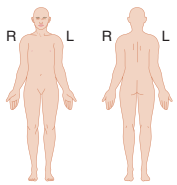
HISTORY _____

Past history _____

Medications _____

Allergies _____

Level of Consciousness (AVPU) _____



VITAL SIGNS

	#1	#2	#3
Time			
Temp.			
Pulse			
B.P.			
R.R.			
SaO2			
Glucose			
GCS			

PHYSICAL FINDINGS _____

*__DOB, PHN, Family Physician__ (Optional)

MGM Pt. ID: _____

**__Triage/Discharge Acuity Scale Level__
Black/Deceased – obvious non-survivable injury
Red/Emergent – critical, resuscitation, chest pain, collapse
Yellow/Urgent – overdose no ABC compromise, SOB
Green/Minor – assessment required, wound care, prescriptions
White/Dispensary – product requests, customer service

RA ID: _____

**__Level of Training of Care Provider__
PCP, SFA, OFA #, EMR, LPN, RN, NP, MD, Chiro, Physio, etc. _____

CLINICAL IMPRESSION OF CARE PROVIDER
☐Abrasion ☐Dental ☐Hypothermia
☐Blister ☐Dislocation ☐Intoxication
☐Chest Pain ☐Dizziness ☐Laceration
☐Concussion ☐Fracture ☐Sprain/Strain
☐Contusion ☐Hyperthermia
☐Other _____

MEDICATION or IV GIVEN

Time:	Medication/IV	Provider Name:

TREATMENT & SERVICES PROVIDED
☐Antacid ☐Splint/Taping/Tensor
☐Counselling ☐Stretching
☐Ibuprofen ☐Tylenol
☐Immobilization ☐Vaseline
☐R.I.C.E. ☐Wound Management
☐Sling ☐Other _____
☐Other _____ ☐Other _____

DISCHARGE ACUITY SCALE**
☐Black ☐Red ☐Yellow ☐Green ☐White

FOLLOW-UP
☐Event Medical Team
☐ER
☐Family Physician/Clinic
☐Other _____

DISPOSITION
☐Returned to Event/work
☐Left Event (private vehicle)
☐Left Event (taxi)
☐Left Event (event staff)
☐Ambulance Transport
☐Air Evacuation
☐AMA
☐Other _____

DISCHARGE INSTRUCTIONS _____

ADDITIONAL NOTES _____

Did the care provided on site prevent a visit to another medical facility (i.e. hospital, clinic, family doctor)? ☐Yes ☐No

LEVEL OF TRAINING OF CARE PROVIDER** _____

LOCATION CARE WAS PROVIDED _____

DISCHARGE TIME _____

Name of Attendant (please PRINT) _____

Signature of Attendant _____

2011

FIGURE 4-2. Patient encounter form. (Used with permission from the Mass Gathering Medicine On-Line Registry, accessed at http://ubcmgm.ca/registry/.)

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 2

Disaster Management

CHAPTER 5

Disaster Preparedness

Robert G. Hendrickson
B. Zane Horowitz

INTRODUCTION

Disasters have claimed millions of lives and cost billions of dollars worldwide in the past few decades. Examples of large-scale disasters include the terrorist attacks of September 11, 2001; the 2004 Pacific Ocean tsunami; the 2010 earthquake in Haiti; the 2011 earthquake and tsunami in Japan; the 2015 earthquake in Nepal; Superstorm Sandy of 2012; and the refugee and civil war crises in Africa. Emergency physicians frequently have extensive responsibilities for community and hospital-level disaster preparedness and response. Planning for these may include smaller-scale disasters such as active shooters, explosions, building fires, or transportation accidents, and increased patient volume from predictable events (e.g., storms, blizzards, floods, large gatherings for major sporting events or music festivals, or protests of large scale with anticipated violence). This chapter discusses the definition of a disaster, disaster preparedness and planning, the hospital emergency operations plan, field disaster response, and the ED disaster response.

DISASTER DEFINITION

The World Health Organization defines a disaster as a sudden ecologic phenomenon of sufficient magnitude to require external assistance. A disaster is an event that overwhelms the resources of the region or location in which it occurs. Furthermore, a hospital disaster may similarly be defined as an event that overwhelms the resources of the receiving hospital. A hospital disaster may be of any size and is not limited to mass casualty incidents. A single patient who ingested an organic phosphorous pesticide may overwhelm the resources of a hospital if that hospital is not prepared to decontaminate external to the ED. A single patient with suspected smallpox or a single influential patient (e.g., world leader or a celebrity) may use so many ED resources that it affects the care of other patients.

Whether an event is a disaster further depends on the time of day, nature of the injuries, type of event, and the amount of preparation time before the arrival of patients. The ED "surge capacity" (ability of the ED to care for more patients than is typical) may be severely limited by hospital overcrowding.

When it appears that the normal procedures of an ED may be interrupted by an event, there must be policies and procedures in place to activate a disaster response, direct the mobilization of personnel and equipment, and permit the rapid triage, assessment, stabilization, and definitive care of victims.

TYPES OF DISASTERS

Disasters are subdivided into several categories (**Table 5-1**). **External disasters occur at locations that are physically separate from the hospital (e.g., transportation accident, industrial accident). An internal disaster is an event that occurs within the confines of the hospital (e.g., bomb scare, laboratory accident involving radiologic agents, power failure).** Disasters can be both internal and external (e.g., earthquake with mass casualties as well as damage to the internal hospital). Further discussions of disasters are provided in the following chapters: Chapter 6, "Natural Disasters"; Chapter 8, "Chemical Disasters"; and Chapter 9, "Bioterrorism."

DISASTER CHARACTERISTICS

Regardless of the cause, most disasters have common characteristics that are important for disaster preparedness and planning. In an acute disaster, or a disaster with an identifiable time of onset that produces casualties (e.g., explosion, chemical release, fire, earthquake), the event is followed by a large number of minimally injured patients presenting to the nearest hospitals, usually without prehospital triage or evaluation.[1,2] This is typically followed by prehospital transport of the most affected patients to the same hospitals.[3] Initial patients can be expected within minutes, and peak volumes can be expected at 2 to 3 hours after the event.[2,3] The vast majority (~80%) of patients are not transported by prehospital agencies, but instead self-transport by car, van, police vehicle, cabs, foot, or any means available to the nearest ED.[2-4] Even in acute events, ED volumes tend to remain elevated for days to weeks after events.[3] In nonacute events, such as a pandemic of an infectious disease, ED volumes have a slower onset of surge, but ED and hospital volumes remain elevated for extended periods.

Based on previous events, common factors that may hinder ED response are listed in **Table 5-2**.

DISASTER PREPAREDNESS AND PLANNING

Planning for any type of disaster consists of common elements. A hospital disaster planning group is responsible for generating the hospital's emergency operations plan. Include a diverse membership of hospital employees and decision makers. **Table 5-3** lists some potential members and their roles. The group should meet on a regular basis to assess hazards, develop and update short- and long-term disaster plans, plan exercises and training, and redesign the disaster plan based on evaluations of exercises and real events.

The general components of the disaster plan include hazard vulnerability analysis, hospital–community coordination, integration with national response assets, and training and disaster exercises. Develop specific plans (for radiation, explosions, mass casualties, decontamination) based on an assessment of the potential disasters in the area as well as study of the events that would cause the most disruption to the ED and hospital.

HAZARD VULNERABILITY ANALYSIS

The hospital planning group should address those disasters that are most likely to occur in their community and geographic area. For example, planners on the West Coast of the United States may make earthquake planning a priority and those on the Gulf and Atlantic coasts may prioritize hurricane planning. Give consideration to the proximity of population centers to chemical release threats (military chemical weapons depots, large industrial sites, or transportation hubs).[5] Industrial sites that store large volumes of potentially harmful chemicals are required by Title III of the Superfund Amendments and Reauthorization Act to participate in local emergency planning committees. Industries are required to report spills of potentially harmful chemicals, and the approximate location of these sites may be found at http://toxmap.nlm.nih.gov. Terrorist-related disasters may be prioritized in hospitals that are in proximity to sites that may be significant terrorist targets. Include factors such as proximity to transportation facilities (e.g., ports, airports) as well as locations where large numbers of people collect (e.g., festivals, stadiums, arenas) with the risk assessment.

TABLE 5-1 Types of Disasters

Disaster Type	Definition	Examples
Natural disaster	Disaster caused by a naturally occurring event	Earthquakes, tsunamis, tornadoes, hurricanes/typhoons, volcanic eruption, pandemic influenza
Man-made disaster	Nonnatural events that are not purposefully produced	Vehicle crashes (e.g., car, plane, bus), mass casualty events, explosions, fires, industrial accident/chemical release
Terrorist-related disaster	Events that are purposefully produced in an effort to cause terror	Events of September 11, 2001, as well as intentional chemical, biological, radiologic, or toxin releases
Internal disaster	An event that occurs within the hospital	Hazardous materials spill in hospital laboratory, fire or explosion within hospital, power failure
External disaster	An event that occurs external to the hospital	Transportation accident, industrial accident
Acute disaster	Disaster that occurs in a narrow and well-defined time frame	Explosion, industrial release, earthquake
Nonacute disaster	Disaster with no well-defined start point or continuous production of casualties over a broad time frame	Pandemic infectious disease, incremental release of a biological or toxin (e.g., anthrax sent through mail)

The hazard vulnerability analysis can prioritize planning efforts because different disasters are characterized by different morbidity and mortality patterns and different challenges to the ED and hospital. For example, earthquakes may cause severe traumatic injuries requiring a concentration on surge capacity of the critically ill patient. Rescue operations may last several days. Unique needs, such as dialysis for renal failure for multiple crush injury victims, may need to be considered. Natural disasters often cause large numbers of homeless or displaced persons whose everyday medical needs are exacerbated by limited access to usual health care, as occurred after Hurricane Katrina. Chemical releases may require mass decontamination as well as large numbers of ventilators, oxygen, and specific antidotes that are not typically available in large quantities.

HOSPITAL–COMMUNITY COORDINATION

Every hospital should integrate its emergency operations plan with those of community disaster management agencies. This is especially important regarding disaster notification and communications, transportation of casualties, and provisions for dispatch of hospital medical teams to a disaster site. Strong relationships with community agencies (e.g., fire department, regional EMS system, local emergency management, or public health agency) are important to ensure a coordinated disaster response. There are a large number of community agencies that have some responsibility for disaster planning and response (**Table 5-4**).

Other organizations that a hospital may interact with during the disaster planning process include the military, local chapters of the American Red Cross, local emergency planning committees, Citizen Corps Councils, and other volunteer agencies, along with state and federal agencies (e.g., National Disaster Medical System, Metropolitan Medical Response System, Centers for Disease Control and Prevention). Medical planning in a community is usually the responsibility of local and state health departments and EMS councils.

TABLE 5-2 Factors That May Hinder ED Response to Disasters

- Poor communication between ED and disaster scene
- Poor communication within the hospital (e.g., ED to emergency operations center, emergency operations center to patient care areas)
- Inability to control volunteer healthcare personnel who are unfamiliar with the ED function and their roles in disaster response
- Inability to engage and control convergence of media to the ED
- Inability to engage, control, and direct visitors who are searching for loved ones
- Inability to control large numbers of patients (i.e., crowd control)
- Difficulty maintaining high staffing needs for extended periods

TABLE 5-3 Hospital Planning Group

Hospital Planner	Role in Disaster Planning and Response
Public safety	Crowd control, hospital lockdown, and hospital access control
Facilities/engineering	Evaluate structural damage and advise on stability of facilities
Logistics/equipment supply	Provide supplies/equipment; arrange for rapid ordering of additional supplies
Pharmacy	Provide pharmaceuticals, antidotes, and antibiotics; arrange for rapid ordering of additional pharmaceuticals
Transportation	Assist with patient transport
Clinical fields	A wide array of clinical fields should be represented, including representatives from the ED, primary specialties (internal medicine, family medicine, pediatrics), and surgical specialties
Media/public relations	Act as single point of contact for media; liaise between media and clinical areas, emergency operations center, and other hospital resources
Communications officer	Coordinate communication to employees during a disaster through e-mail, website, paging groups, phone, or social media
Nonclinical patient care	Housekeeping and food services
Safety officer	Determine and ensure safe practices for employees (e.g., appropriate personal protective equipment for decontamination)
Radiation safety officer	Prepare plan for and respond to radiologic emergencies
Infection control officer	Prepare for and respond to infectious disease emergencies

INTEGRATION WITH NATIONAL RESPONSE ASSETS

Some of the important federal response resources are listed in **Table 5-5**. During a response, these agencies may play pivotal roles and may interface and coordinate with hospitals and emergency physicians.

TABLE 5-4 Community Agencies Involved in Disaster Planning

Community Agency	Responsibilities
Federal Bureau of Investigation	Incident command if a federal crime may be involved
FEMA	Incident command in public health disaster
State governor	Authority to declare health emergency; requests federal assistance (e.g., FEMA); responsible for public safety
State health department	Authorized by governor to coordinate disaster response
State emergency management association	State-level equivalent of FEMA
City/county health department	May have jurisdiction for local disasters (variable); may be initial incident command for local health disasters
EMS	Patient triage in field; decontamination in field (if necessary); stabilization and transfer to definitive care facility
Fire service	Overall scene command in an acute disaster; victim rescue and hazard control
Police service	Traffic management and scene security in an acute disaster
Public works	Support equipment and personnel; structural safety expertise
Hazardous materials (HAZMAT) teams	Initial incident command at scene of hazardous materials spill/exposure

Abbreviation: FEMA = Federal Emergency Management Agency.

TABLE 5-5 Federal Response Resources

Agency	Role
U.S. Public Health Service/Office of Emergency Response; http://www.phe.gov/preparedness/pages/default.aspx	Office within DHHS. Management and coordination of federal health and medical activities related to preparation, response, and recovery from major emergencies or presidentially declared disasters.
Metropolitan Medical Response System For more information: www.ncbi.nlm.nih.gov/books/NBK220762/	Enhance local emergency preparedness systems by promoting coordination between local responders (e.g., police, fire, hazardous materials agencies, EMS, hospitals).
National Disaster Medical System; https://www.phe.gov/Preparedness/responders/ndms/Pages/default.aspx	Asset-sharing program between DHHS, Federal Emergency Management Agency, U.S. Department of Defense, U.S. Department of Veterans Affairs, and public/private organizations—developed to provide surge capacity for natural disasters, wartime military casualties, and large-scale bioterrorism events.
DMAT; https://www.phe.gov/preparedness/responders/pages/default.aspx	Multidisciplinary teams that deploy in response to federally declared disasters and emergencies to support a local jurisdiction's response. Teams include physicians, nurses, medics, pharmacists, and logisticians.
National Disaster Medical System Response Teams; https://www.phe.gov/preparedness/responders/pages/default.aspx	Specialty teams, based on the DMAT concept, developed to respond to chemical, biological, and radiologic events.
Disaster Mortuary Operational Response Teams; https://www.phe.gov/preparedness/responders/pages/default.aspx	Teams that respond to federally declared disasters and emergencies to support a local jurisdiction's ability to process large volumes of deceased patients.
Centers for Disease Control and Prevention; http://www.cdc.gov	Centers within DHHS. Lead federal agency in developing and applying disease prevention and control. Advisory agency in bioterrorism response.
CDC Outbreak Response Teams	Teams of CDC epidemiologists to assist with local efforts in investigating potential outbreaks, confirmation of cases and exposures, and environmental clean-up.
Laboratory Response Network; https://emergency.cdc.gov/lrn/index.asp	Network that links local and state public health laboratories to advanced-capacity laboratories, including military, chemical, veterinarian, agricultural, water, and food testing labs.
National Notifiable Diseases Surveillance System; http://wwwn.cdc.gov/nndss/script/nedss.aspx	National public health surveillance system.
Health Alert Network; http://emergency.cdc.gov/han/	System that allows for rapid early warning broadcast alerts to health departments for potential emerging infectious diseases or outbreaks.
Strategic National Stockpile; http://www.cdc.gov/phpr/stockpile/stockpile.htm	Two-part system designed to provide local jurisdictions with medications, vaccines, and equipment during a disaster. Prepackaged cache—delivered within 12 h in the U.S. Situation-specific cache—delivered within 36 h in the U.S.
Federal Bureau of Investigation	Lead federal agency for crisis management. Has authority to conduct law enforcement investigations into acts of terrorism.

Abbreviations: CDC = Centers for Disease Control and Prevention; DHHS = Department of Health and Human Services; DMAT = Disaster Medical Assistance Teams.

TRAINING AND DISASTER EXERCISES

Regular training and exercises familiarize staff with their disaster roles and responsibilities and identify weaknesses or omissions in the plans that require additions or revisions. Exercises can range from full-scale, community-wide simulations, with moulage (use of makeup or theater techniques to represent injuries) victims, to tabletop triage scenarios, mini-exercises that test only certain components of the disaster plan (such as call-up of personnel), and tests of communications. The Joint Commission requires two annual exercises at least one of which involves the movement of patients. The scenarios should reflect incidents that are likely to occur in the community as determined by the hazard vulnerability analysis.

HOSPITAL EMERGENCY OPERATIONS PLAN

The hospital emergency operations plan provides for an organized response of the hospital from the time of notification of a disaster until the situation normalizes (**Table 5-6**).

Functions include activation of the emergency operations plan, establishment of an emergency operations center, assessment of hospital capacity, surge capacity planning, communications, supply and resupply, triage and treatment of casualties, establishment of support areas, and termination of the disaster state to allow for recovery and the return to normal activities.

ACTIVATE THE EMERGENCY OPERATIONS PLAN

Clearly delineate the roles and responsibilities of all employees in the ED and any employees who may respond to the ED in the planning process; those roles must be clearly listed and easily accessed in the event of a disaster. Clarify the reasons for activation of the emergency operations plan. Activation of the emergency operations plan should provide for the immediate mobilization of supplies, equipment, and personnel.

ESTABLISH EMERGENCY OPERATIONS CENTER

The Incident Command System is a standard emergency management system used throughout the United States to provide a flexible command and control structure upon which to organize a response.[6] The Incident Command System is generally used when there is an identifiable single scene for a disaster event, such as the site of a plane crash. By standardizing an organizational structure and using common terminology, the Incident Command System provides a management system that

TABLE 5-6 Components of the Hospital Emergency Operations Plan

Component	Function
Activate emergency operations plan	Notify and mobilize personnel and equipment
Set up emergency operations center	Nerve center for hospital response and communication with outside agencies
Assess hospital capacity	Determine safety of hospital itself; determine capabilities of hospital in all units
Create surge capacity	Determine ways to handle the maximum number of patients
Establish communication systems	Develop multiple and redundant systems, including cellular phones, satellite phones, two-way radios, runners
Provide supplies and equipment	Deliver available supplies to proper areas and plan for resupplying or obtaining other needed materials
Establish support areas	Volunteer, media, and family information centers
Establish decontamination, triage, and treatment areas	Decontamination, triage, resuscitation, acute care, and minor care areas; surgical triage and holding; psychiatric area; morgue
Terminate disaster response and provide for remediation	Return personnel and supplies to normal activity; provide emotional support for caregivers; improve emergency operations plan for future incidents

is adaptable to incidents involving a multiagency or multijurisdictional response. At the most basic level, there are five main components to the organizational structure: (1) incident command, (2) operations, (3) planning, (4) logistics, and (5) finance. With this type of organizational infrastructure and the flexibility to expand and collapse as needed, an orderly and efficient response to any incident can theoretically be implemented.

The Hospital Emergency Incident Command System is modeled after the Incident Command System. Upon declaration of a disaster, an emergency operations center within the hospital should be established in a predesignated area. This center should be able to communicate with the ED and triage area and with external authorities (regional EMS, police, fire, and public health agencies). There should be a primary emergency operations center as well as a secondary site to be used in the event that the primary site is damaged or inaccessible. Provisions for multiple redundant modes of communication should be made. Other responsibilities of the emergency operations center include opening up additional hospital wards or clinics, obtaining outside assistance, evacuating endangered patients, assigning staff to treatment areas, and terminating the disaster mode of operation.

ASSESS HOSPITAL CAPACITY

Before the hospital can receive casualties, it must be determined if the hospital itself has sustained any structural damage or loss of use as a result of a disaster. These include blocked passageways or inoperable elevators; potential for fire, explosion, or building collapse; failure of utilities; loss of equipment or supplies; contamination of water; and outside access problems. This damage assessment is usually the responsibility of the hospital safety officer or engineer. If the hospital's structural integrity has been compromised, it may be necessary to initiate the evacuation plan to evacuate staff and patients.

Once it is determined that the hospital itself is safe, the hospital should determine how many casualties from the disaster site it can safely manage. This may be limited by available personnel, beds, operating room and intensive care unit capacity, and supplies, as well as by the type of disaster and the availability of other community resources. At the time of disaster notification, it is necessary to know the status of many of the hospital's capabilities: how many beds are available, how much critical supplies and medications are available, how many personnel are on duty, what structural damage has occurred, how many operating rooms are in use, which clinicians are present in the hospital, and so forth.

CREATE SURGE CAPACITY

Surge capacity is the ability to increase hospital bed capacity over normal limits. Intrahospital surge may include doubling patients in rooms, converting an acute care ward to an intensive care level unit, opening previously closed wards, or caring for patients in typically nonclinical locations, such as the hallway or cafeteria. Interhospital or regional surge may include discharging hospitalized patients to an external low acuity unit, either mobile or fixed, and altering standards of care (typically a role of the state governor and legislature and only during governor-declared disasters).[7,8] The standards of care should be altered only in the most extreme circumstances, as patient surge has been linked to somewhat worse outcomes for individual patients.[9]

ESTABLISH COMMUNICATIONS SYSTEMS

Establishment of good communications is critical in any disaster or mass casualty situation. Even the best disaster plans fail without well-established communications systems. Unfortunately, experience shows that this essential function is difficult to achieve for a variety of reasons. Many communication modes become inoperative during a disaster. Cellular telephones, in particular, are often overwhelmed in disasters. Disaster planning must include a multitiered plan for intrahospital (blackboard, two-way radios, messengers/couriers) and interhospital (citizen band groups, cellular telephones, satellite telephones, two-way radios) communication.

SUPPLIES

During a disaster, necessary supplies and equipment must be ready for immediate distribution to appropriate locations in the hospital. Each hospital will need to estimate the amount of supplies that will be needed in stock over and above their regular hospital supply. Unfortunately, due to "just in time" stocking, most U.S. hospitals do not have a surge of supplies that may be used in a disaster. The Centers for Disease Control and Prevention has arranged a series of medication push-packs throughout the United States that can be delivered to any area of disaster within 12 hours (https://www.cdc.gov/phpr/stockpile/index.htm). Once delivered, additional time is necessary to unpack the supplies and deliver the supplies to individual hospitals. The regional/local disaster plan must include a mechanism to unpack the push-packs, determine the hospitals in greatest need of individual items, divide the push-pack contents, and deliver the supplies to the hospital. This logistical issue makes it necessary for most hospitals to rely on their own supplies for a period of at least 96 hours.

ESTABLISH SUPPORT AREAS

Family Information Center During a disaster, families and friends will arrive at the hospital seeking information about victims. This convergence can seriously interfere with efforts of the hospital to respond effectively to the situation. For this reason, predesignate a separate area for family members seeking information. This area may also be used to discharge in-hospital patients and treated disaster victims.

Volunteer Coordination Center In major disasters, anticipate the potential for large numbers of volunteers, including those wishing to donate blood. Although some of these people may have appropriate clinical skills, they are unlikely to be familiar with the hospital functions and could be more hindrance than help. A separate place should be identified to handle these volunteers and, if appropriate, credential and decide how they may best be used. This area should include all equipment and personnel that are required to perform emergency credentialing (if appropriate and necessary).

Media Center Identify a single hospital spokesperson to relay information to the media. This public information officer ideally should have some training in handling media questions and making clear statements to the press and public. Similar to the family information center, the media briefing room should be set up away from clinical care areas so that the press does not negatively impact on medical care while seeking a story. Direct members of the media to this area, and closely supervise their access to any treatment area by utilizing security personnel and either the hospital administrator or public information officer.

DECONTAMINATION, TRIAGE, AND TREATMENT

Certain areas of the hospital must be designated for specific functions, including decontamination, triage, care of major and minor casualties, presurgical holding and surgical triage, psychiatric care, and morgue facilities. The plan should be quite specific as to the function of these areas, staffing requirements, and basic supplies to be used.

Decontamination **Perform decontamination in an area that is outside of the clinical care area of the ED.**[4] Typically, this area is located external to the ED, but may be in internal locations. Use the decontamination facility to remove clothing and cleanse the skin and hair of patients exposed to a chemical or radioisotope (**Table 5-7**).[10] Provide patient coverage and protection from the environment. Make sufficient personal protective equipment available for hospital staff assisting with decontamination.

Triage **Restrict patient entry to only one location—the triage area.** The primary functions of a disaster triage area are rapid assessment of all incoming casualties or ill patients, patient registration and identification, the assignment of priorities for management, and distribution of patients to appropriate treatment areas in the ED and hospital.

Treatment Patient care in disasters requires alteration of scale and sometimes location of clinical care, but staff should perform the clinical roles that are familiar to them. Several exceptions to this rule may

TABLE 5-7 Decontamination Guidelines

- **Decontaminate patients exposed to solids, liquids, vapors, or mists.**
- **Patients exposed only to a fully dispersed gas need to be assessed for pulmonary symptoms and systemic toxicity and do not require decontamination.** When uncertain if a substance is a gas or actually a vapor or mist, decontamination should occur.
- Hospital personnel should have the **initial ability to decontaminate one patient at a time with a shower or hose system** while setting up a larger tent or a multiple-person decontamination system.
- **Perform decontamination outside of the ED** in a way that prevents patients from entering the ED before decontamination.
- Hospital personnel require level C personal protective equipment while performing decontamination. Higher levels of protection are not necessary and should only be used by hospitals that follow stringent training protocols and criteria, and use only personnel who have been specifically trained to use the equipment. **Sufficient equipment for multiple personnel and rotations of personnel in and out of the decontamination zone every 30 min are suggested.**
- **The first and a very effective method for decontamination is to disrobe, brush off solid dusts or powders, and wash and dry the face.** Patient clothing and belongings should be individually bagged and labeled. Watches, earrings, body piercings, jewelry, and contact lenses should be removed. Hearing aids should be wiped with a moistened cloth and may be returned to patients after the decontamination procedure because the need to hear instructions outweighs any risk of wearing the hearing aid.
- Warm water is the universal decontamination fluid. Hosing a patient from head to toe (or showering) for 5 min will decontaminate most ambulatory patients.
- Patients with adherent materials will need additional scrubbing of hair and affected body parts with soap to remove these; medical assistance will be necessary in some circumstances. An additional check to ensure the removal of all earrings and body piercings should be done.
- Young children need assistance and reassurance and should be decontaminated with the aid of a parent or guardian who can hold and reassure the child while medical personnel perform the decontamination.
- After the decontamination procedure, provide hospital clothing (cloth or paper gowns) and triage patients to an area to await further assessment. Retriage patients with eye pain after whole-body decontamination for individual irrigation of their eyes with sterile normal saline. Patients with contaminated wounds will likely need additional irrigation of debris in wounds.
- Contain runoff water from the decontamination to prevent environmental contamination.
- Critical medical devices (infusion pumps, hearing aids, ostomy bags, etc.) may remain with the patient unless a high-risk chemical has been identified. Wash canes and walkers with soap and water or diluted household bleach and return to patients to ensure their mobility.
- At least one radiation survey meter (e.g., Geiger-Müller counter) and staff that are trained in its use are necessary for events that potentially involve radioisotopes. Patients may need a radiation survey sweep before and after decontamination, and further decontamination may be needed until levels reach background radiation levels.
- Staff involved in the decontamination process and systems need annual training and practice drills. Share an assessment of strengths and weakness learned from each drill with hospital personnel to improve preparedness and performance.

exist (decontamination); however, in general, staff are more efficient at performing typical tasks quickly than learning new tasks in real time.

Organize patient care stations so that clinicians who are familiar with the assessment and treatment of the clinical problems may staff them. One suggested method of organizing patient care stations includes "resuscitation" and "minor treatment" areas.

RESUSCITATION

From the triage location, most, if not all, of the **seriously injured patients will be sent to the resuscitation area** (trauma and cardiac resuscitation, treatment of hypovolemic or septic shock, severe respiratory distress). This is usually physically located in the ED and staffed by emergency physicians. Other areas that may be used include direct to operating room or postoperative recovery room triage.

PRESURGICAL HOLDING AREA AND SURGICAL TRIAGE

Send trauma patients who are initially stabilized in the ED to the presurgical holding area for preoperative preparation and observation. **The number of operating rooms that can be staffed is the main limiting factor in the provision of definitive care for a large number of severely injured casualties.** The most experienced surgeon available should take the responsibility to prioritize cases and to rapidly assign surgeons to individual cases.

MINOR TREATMENT AREA

In most disaster situations, the majority of patients are not very seriously injured. **These low-acuity patients can be sent to an "urgent care" area for definitive care**, including splinting of fractures, primary closure of lacerations, tetanus prophylaxis, and observation for delayed symptoms. This minor treatment area can be established in the hospital's outpatient clinics and staffed by the clinic physicians.

MENTAL HEALTH

In the event of a disaster involving mass casualties, and even property damage with loss of possessions, it is common for patients to present with episodes of anxiety and depression, or exacerbations of their psychiatric disorders.[11] Agitated patients, visitors, or staff can be extremely disruptive to hospital disaster operations. Consider a separate isolated area to receive individuals in need of psychological intervention. Include consideration for assessing patients and hospital staff who are psychologically affected by the disaster. Consider providing a critical stress response team, including social workers and psychiatrists, to provide support and critical stress debriefing.

MORGUE FACILITIES

Disasters can result in a large number of fatalities. Morgue capacities may need to be expanded to other areas of the hospital (medical school anatomy area, auditorium), enhanced by mobilization of local freezer trucks (this must be prearranged during the planning stage), or enhanced by federal assets (Disaster Mortuary Operational Response Teams). Viewing of deceased patients should take place here, not in treatment areas.

TERMINATING DISASTER RESPONSE (RECOVERY)

As soon as appropriate, direct efforts toward returning the hospital to normal operations. Besides restocking and cleaning, give consideration to the emotional stress experienced by both the EMS and hospital staff. *Critical incident stress debriefing* can reduce the psychological impact of these events on medical responders and offer immediate emotional support to healthcare workers. Data from previous experiences suggest that such intervention can assist providers in maintaining job performance and satisfaction, resulting in improved patient care.[12] Provide all members who participated in the disaster, not just medical personnel, the opportunity to participate in critical incident stress debriefing.

Carefully record and review deficiencies in a hospital's disaster plan that are revealed during a disaster, and write an after-action report. Take immediate steps to correct these flaws in the plan.

FIELD DISASTER RESPONSE

Elements of field disaster response are field triage and medical care, communications, distribution of casualties, and management of on-site disaster medical teams.

FIELD TRIAGE AND MEDICAL CARE

In the field, rescue personnel often use a simple triage and rapid treatment technique that depends on a rapid assessment of respiratory status, perfusion, hemorrhage control, and mental status. Patients are then triaged to immediate care, delayed care, or dead/dying.[13,14] Subsequently, determining

how much and what type of care to administer at the disaster site depends on several factors. If the number of patients is small and there are sufficient prehospital personnel and transportation resources available, on-site medical care can proceed in a fairly normal manner, with rapid stabilization and transportation to nearby hospitals. When extrication will be prolonged, interventions such as fluid resuscitation and pain control should be instituted in the field. On the other hand, early, rapid transportation with a minimum of treatment should be practiced when there is danger to rescuers and casualties from fire, explosion, falling buildings, hazardous materials, and extreme weather conditions.

When patients are likely to have significantly delayed transport from a scene (e.g., number of casualties exceeds transportation capacity or damage to hospital infrastructure), the "Secondary Assessment of Victim Endpoint" triage system may be helpful to identify patients who are most likely to benefit from the care available under austere field conditions.[15] The Secondary Assessment of Victim Endpoint triage system is intended to triage patients into categories that reflect a balance between resource use and probability of survival. Category 1 includes patients who will die regardless of how much care they receive. Category 2 includes patients who will survive whether or not they receive care. Category 3 includes patients who will benefit significantly from austere field interventions.[15]

COMMUNICATION—DISASTER SITE TO HOSPITALS

The local emergency communications or emergency operations center should alert hospitals in the affected area of possible mass/multiple casualty situations or disasters. This report should include the total number of injured, the number of seriously injured (who may need intensive care unit capability), and the number for whom ambulatory treatment is sufficient. Hospitals should report to the local emergency communications center the following information: bed availability, number of casualties received thus far, number of additional casualties that the hospital is prepared to accept, and specific items in short supply.

DISTRIBUTION OF CASUALTIES TO RECEIVING HOSPITALS

Maintain good communication between hospitals and on-site EMS command in order to minimize unequal distribution of victims. **Alert the on-scene incident commander immediately of a potentially overloaded hospital.** In this situation, the less injured and more stable can be sent a farther distance to outlying hospitals.

Casualties with special problems, such as major burns, carbon monoxide poisoning, spinal cord injuries, or victims of chemical or biological terrorism, may need to be transferred directly to specialized units, although it may not be possible for these units to accept a large number of ill or injured. For that reason, develop regional plans to allow for the care of specialty patients in nonspecialty hospitals.

MANAGEMENT OF ON-SITE DISASTER MEDICAL TEAMS FROM HOSPITALS

On-site disaster medical teams dispatched from local hospitals may be of value in situations in which victims require prolonged extrication; transportation routes are blocked, preventing easy evacuation to hospitals; or the number of casualties is of such magnitude that they exceed transportation capacities. Dispatch such a team with great caution. Physicians and nurses function optimally in an in-hospital setting. Few, however, are prepared to work under austere field conditions. Such hospital-based teams should probably not come from the ED staff until back-up staff has arrived to care for patients arriving from the disaster site or who are already present. Explicitly describe how such personnel are placed in action in the hospital emergency operations plan and coordinate with state and local agencies through memoranda of understanding.

Carefully map out the resources for such field response teams on a regional basis. At least one institution from each region should maintain an on-site triage team of physicians and nurses. The designated hospital should store disaster triage kits containing essential resuscitation and stabilization equipment for field use.

ED DISASTER RESPONSE

INITIAL RESPONSE

When a call is made to the hospital indicating the occurrence of a disaster or potential mass casualty–producing event, the incident must be verified by the appropriate predesignated official, who then puts the emergency operations plan into effect. In some events, the first sign of a disaster may be patients arriving at the hospital. In this case, contact the regional emergency communications center to notify the regional hospitals of the impending disaster and initiate the emergency operations plan.

This sets a series of activities into motion. The information obtained from the call is given to the charge nurse; the nursing and medical personnel in the ED are notified of the impending arrival of casualties; and the ED's plan for calling additional staff is activated. If hospital telephone communications have been completely disrupted, ED personnel may have to be reached by radio, cellular phone, e-mail, or television announcement. In many disasters, cellular phone and text messaging systems are quickly overwhelmed. Alternatively, a calling station remote from the hospital, such as at the residence of an administrator, physician, or nurse, may be able to handle this extensive calling job without taxing the hospital's phone system.

An initial needs assessment is conducted by the nurse and/or physician in charge, given the information available. They should evaluate the current status of the patients in the ED and make the appropriate disposition decisions. The ED physician or charge nurse becomes the on-site incident commander until the plan-designated incident commander arrives. **Among the decisions to be made are those related to the admission, discharge, or transfer of patients, and decisions about the priority of patient care.** Discharge all nonemergency patients from the ED with responsible individuals.

Based on the initial assessment, the number of patients that the department can receive is determined and communicated to the prehospital disaster communications center. The nurse and the physician in charge then assign staff to those areas in the department to be used during the disaster.

Take all available litters and wheelchairs to the ambulance entrance immediately on announcement of the disaster status. Patients from the disaster site are met at the receiving area by hospital escorts who assist the emergency medical technicians in transferring patients to wheelchairs or stretchers.

Place essential equipment, such as endotracheal tubes, IV fluids, cervical collars, splints, and bandages, near the ambulance entrance to permit convenient restocking of the ambulance (when plans call for ambulance restocking from hospitals) and rapid return to the disaster site.

SECURITY

Hospital security diverts nonessential vehicles and ensures a smooth, one-way flow of traffic to the ambulance entrance. Once patients, family, and media arrive, security is also responsible for protecting the treatment areas and inhibiting unplanned entry into the hospital.[4]

TRIAGE

Triage establishes priorities for care and determines the clinical area of treatment. Many seeking help will arrive independent of the EMS system.[3,4] **Triage will need to be performed at the ED entrance even if it was done at the scene.**

Triage category is identified by use of a colored band or trauma/disaster tag that is placed on the patient to document that triage has been done.

The approach to patient evaluation and treatment is quite different when dealing with disaster situations that result in high casualties.[16] To accomplish the most good for the most number of patients, the triage team should evaluate all patients arriving at the ED and classify their condition with regard to severity of injury and need for treatment. Some principles of medical care must be altered to achieve the best overall result. Patient care at triage should be limited to manually opening airways and controlling external hemorrhage.

TABLE 5-8 Triage Categories

Red
- First priority
- Most urgent
- Life-threatening shock or hypoxia is present or imminent, but the patient can likely be stabilized and, if given immediate care, will probably survive.

Yellow
- Second priority
- Urgent
- The injuries have systemic implications or effects, but patients are not yet in life-threatening shock or hypoxia; although systemic decline may ensue, given appropriate care, patients can likely withstand a 45- to 60-min wait without immediate risk.

Green
- Third priority
- Nonurgent
- Injuries are localized without immediate systemic implications; with a minimum of care, these patients generally are unlikely to deteriorate for several hours, if at all.

Black
- Dead
- No distinction can be made between clinical and biological death in a mass casualty incident, and any unresponsive patient who has no spontaneous ventilation or circulation is classified as dead. Some place catastrophically injured patients who have a slim chance for survival regardless of care in this triage category.

The most common triage classification in the United States still involves assigning patients to one of four color-coded categories (red, yellow, green, or black), depending on injury severity and prognosis (Table 5-8). In addition to the nature and urgency of the patient's systemic condition, triage decisions should be sensitive to factors affecting prognosis, such as age, general health, and prior physical condition of the patient, as well as the qualifications of the responders and the availability of key supplies and equipment.

Catastrophically injured patients who have a minimal chance for survival despite optimal medical care should be classified as "expectant" ("black": to include patients with burns involving 95% body surface area, and patients in full cardiac arrest or septic shock). Devoting time and resources to patients who are not likely to live jeopardizes other patients who are truly salvageable. The goal with these "expectant" patients should be adequate pain control and the opportunity to be with friends and family.

TRIAGE TEAM

A team consisting of an emergency physician, an ED nurse, and medical records or admitting clerks should receive every patient. In extraordinary situations, several triage teams may be required to handle the casualty load. Acknowledge the physician performing hospital triage as being in command of the triage area (clearly identified by a specially colored vest or other garment) and understanding all triage options.

Assign one member of the triage team (admitting or medical records clerk) the job of recording the victim's name on the disaster tag along with the triage destination within the hospital. If identification of the patient is not available, ethnicity, gender, and approximate age should be noted on the tag. An initial diagnostic impression should also be registered on the tag. This information is entered into a department log or into the electronic medical record, if possible. In some patient tracking systems, a scan of the bar code on the disaster tag may allow for immediate registration by disaster tag number and open an electronic medical record. Additional care can be recorded in the electronic medical record or in a paper disaster chart and kept with the patient at all times and later scanned into the electronic medical record.

ED DISASTER PATIENT CARE

Disaster care concepts often vary from the typical ED routine. Care that is not immediately time sensitive can be provided the next day. For example, wounds may benefit from delayed closure after copious irrigation due to delayed presentations or gross contamination. In the event of prolonged extrication from rubble, assess for delayed signs and symptoms, including cardiac dysrhythmias, hyperkalemia from crush injury, renal failure, and pulmonary blast injury.

Terrorist-related or industrial explosive events may lead to medical conditions or exposure to chemicals that are not familiar to clinicians.[4] Patients may require prolonged observation (e.g., exposure to phosgene or ricin) or unique testing. For infectious exposures, the Centers for Disease Control and Prevention and local/state public health agencies can guide testing, observation time, and treatment. Immediately contact the local public health agency if a biological terrorist agent or a rare and potentially fatal infectious disease is seen or suspected in the ED. In the event of a chemical agent, the regional Poison Center (1-800-222-1222) can provide information and guidance on whether decontamination is necessary, as well as testing, observation time, and antidotal or supportive treatment. Fact sheets on biological, chemical, and radiologic agents are available at http://www.cdc.gov.[4,17]

Use radiographic and laboratory studies sparingly, if at all, in a mass casualty situation, and only if the results of such tests will change treatment. For example, possible closed, nonangulated fractures can be splinted, and radiographs can be safely delayed for 24 to 48 hours. A chest radiograph may be appropriate in patients complaining of chest pain, dyspnea, or abnormal chest wall motion, or who were potentially exposed to blast waves secondary to bombs. CT imaging may be quicker than plain radiographs in some injuries, and prioritization to CT may be required. Ultrasonography to detect free intraperitoneal fluid, pericardial fluid, and pneumothorax is time- and cost-effective and has been used in earthquakes to triage operative care.[18]

With the exception of identification of biological and chemical agents, there are few indications for laboratory testing in disaster medicine. If testing will change management, use point-of-care testing to expedite care. For example, obtain a baseline hematocrit and type and cross-matching for blood in cases of hemorrhagic shock. Pulse oximetry monitors may need to be used as spot assessments, rather than continuous bedside monitoring of a single patient. Consider laboratory studies to be accessory and ordered only in specific circumstances (carboxyhemoglobin in cases of smoke inhalation).

In a disaster situation involving many casualties, the blood bank should have up to 50 units of blood available and should have access to volunteer donors who can be rapidly mobilized. Potential donors include friends and family members of patients, as well as mildly injured patients.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 6

Natural Disasters

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INTRODUCTION AND EPIDEMIOLOGY

Natural disasters continue to be an unpredictable source of worldwide morbidity and mortality and present unique challenges for practitioners of emergency care. The 2005 to 2014 annual average worldwide mortality rate was 76,416 deaths per year from natural disasters, with an average of 199.2 million worldwide victims per year during the same time period and an economic cost of $70.3 billion in 2015.[1] With the increase in rapidly mobilized recovery teams, emergency physicians are at the forefront of patient care after a natural disaster. It is here that we can have the greatest impact in treating survivors and minimizing secondary

TABLE 6-1 Timing of Disease Presentation

Timing of Onset	Presentation						
Acute phase	Trauma	Stress reactions	Drowning	Inhalational injury	Burns		
Immediate postevent phase	Infectious complications of trauma	Exacerbation of chronic disease	Acute stress disorder	Burns	Inhalational injury		
Recovery phase	Trauma	Communicable disease	Infectious complications of trauma	Soft tissue infections	Exacerbation of chronic disease	Vectorborne disease	Posttraumatic stress disorder

morbidity and mortality, often in the setting of a significantly impaired healthcare system. Research suggests that the burden of natural disasters is likely to rise in the coming years, due to increasing population density in high-risk areas and risks associated with expanding technology (e.g., fires or earthquakes in larger and taller buildings or critical infrastructure).[2]

Although the mechanics, warning period, and impact vary widely between types of natural disasters, there is a predictable pattern of events that occur and may be used to maximize the subsequent response. Natural disasters result in a combined loss of resources—infrastructure, economic, social, and health. Although this may be tempered by pre-event preparedness and infrastructure strength, this combination of resource loss has a synergistic impact on the health of and the delivery of health care to the affected population. Another commonality is the predictable pattern of pathology, seen in the progression from the impact of the event itself, through the acute aftermath, to the immediate postdisaster phase, and into the recovery phase (**Table 6-1**). Perhaps most salient for emergency practitioners, relief efforts can be implemented based on data from previous disaster experience, while simultaneously being tailored to the type of disaster (e.g., hurricane, earthquake, tornado, flood, tsunami, or snow) and region affected. Finally, disaster responders should be prepared to face the duty of management of dead bodies, on a scale otherwise seen only in the setting of combat.

LOSS OF RESOURCES

Most natural disasters—whether by water, wind, fire, or snow—cause some disruption of power, communication, and transportation systems. In developed and developing nations, entire cities can be destroyed instantly, overwhelming nearby healthcare facilities and personnel. In such cases, the traditional triage system may not be effective.[3] A Centers for Disease Control and Prevention posthurricane assessment in 2012 determined that most of the resulting public health emergencies were directly due to loss of public health infrastructure and related to clean-up and repair activities.[4] Because standard amenities, such as power, running water, and sanitation methods, may be unavailable for extended periods of time, all medical disaster planning must include practical, simple alternatives to technologies that are likely to fail during a disaster.

Lack of communication is a common feature of both the impact and delayed phases of a disaster. Even the most sophisticated equipment may fail due to regionwide outages or loss of electricity for charging devices. In our experience during the active phase of Hurricane Katrina, the only working means of communication within Charity Hospital was a single landline telephone. Difficulty in communication has led to recent innovation with proposals for disaster-specific electronic medical records.[5]

Evidence suggests that the predisaster level of preparedness and resources in a community has a significant impact on its response to a catastrophic event. Analysis of four earthquakes in different regions (developed and developing countries) found that regions with the least preparedness and weakest preexisting medical infrastructure had the highest number of deaths per patients injured.[6] Investment in targeted disaster preparedness efforts before an event occurs, particularly for the most vulnerable populations, is crucial in mitigating the effects of an inevitable disruption in resources during a disaster.[7]

DISEASE BURDEN

Understanding of the likely health emergencies to be encountered in the acute and postdisaster phases is crucial to any emergency response. Although it is widely thought that outbreaks of rare and/or severe disease inevitably follow many types of natural catastrophe, evidence does not support this belief.[8,9] Common medical problems after natural disasters include traumatic injury, infectious disease, exacerbations of chronic medical conditions, and a surge in mental health issues (**Table 6-2**). In addition to the common medical problems previously listed, the handling of bodies has an additional unique impact on the health of the affected population.

TRAUMA

Traumatic injuries frequently occur in the acute phase of a natural disaster, commonly from direct trauma from collapsing structures or flying debris. A second spike in trauma is seen during the recovery/clean-up phase, mainly due to unsafe infrastructure. However, this secondary spike in trauma may also include violent injuries, depending on the level of civil unrest.[10] Although most trauma is minor, management of severe injuries by healthcare professionals can prove especially challenging when resources are lacking, as they often require coordinated surgical care. **This necessitates adequate resources of anesthesia, blood products, surgical equipment and the ability to sterilize it, intensive care capacity, and operating theaters.** When these resources are unavailable, limb amputation, nonunion, and missed injury rates are high, and lack of safe blood products hampers surgical capability.[11,12] Recommendations for adequate surgical capability include mobile blood banks with adequate supply and well-trained staff, at least two units of blood available per operation, adequate supplies of appropriate anesthesia, strict adherence to national or international quality and safety standards, and functioning critical care units.[3,12,13]

TABLE 6-2 Common Disease Patterns

Trauma	Communicable Disease	Chronic Medical Conditions	Infectious Disease	Mental Health
Strains and sprains	Respiratory infections	Hypertension	Soft tissue infections	Stress reactions
Falls	GI infections	Diabetes	Open fractures	Depression
Lacerations		Renal failure	Vectorborne disease	Exacerbation of chronic condition
Burns		Chronic obstructive pulmonary disease	Local diseases	
Fractures				

INFECTIOUS DISEASE

Infectious diseases are commonly feared and should be anticipated after natural disasters. Although popular media often focuses on the possibility of rare disease epidemics, most postdisaster infections are directly related to the usual pathogens of that region.[9,14] One exception to this was the outbreak of cholera after the 2010 earthquake in Haiti, which is believed to have been brought in by United Nations relief workers.[15] Evidence indicates that the combination of communicable disease and population malnutrition is the major cause of morbidity and mortality in most disasters. Infectious disease predominantly occurs in the extended postevent phase.[16] Infectious disease risks are heightened by certain characteristics common to natural disasters: mass population movement and resettlement; overcrowding; poverty; sanitation and waste issues, including water contamination; absence of shelter, food, and healthcare access; and disruption of public health programs. Respiratory, GI, skin/soft tissue, and vectorborne infectious diseases are most commonly analyzed in disasters.

Respiratory illnesses range from direct aspiration of contaminated water (floods and tsunamis) to airborne droplet transmission to inhalation injuries caused by excess dust, allergens, or debris. In both the acute and postdisaster phases, reactive airway disease may be exacerbated. After one thunderstorm in 2016, nine patients died and the EMS system was overwhelmed in Melbourne, Australia, due to acute asthma exacerbations.

While infectious respiratory infections are mild, respiratory illness may account for 20% of all natural disaster deaths in children <5 years old.[13] In the acute phase of a flood or tsunami, inhalation of water with polymicrobial contamination may cause aspiration pneumonia.[17] Most respiratory infections emerge several weeks after disaster as disease spreads through shelters and settlement camps. **Both disaster victims and rescue workers are at risk for respiratory illness due to crowded conditions and compromised sanitation.**[18,19] Some respiratory illnesses (pertussis and measles) are preventable with adequate vaccination; thus, knowledge of the predisaster vaccination status of a population and sufficient vaccine stores may prevent severe outbreaks. Tuberculosis presents a special challenge for public health officials. To prevent outbreaks, adequate stores of antimicrobials must be on hand, and strict adherence to surveillance of known infectious cases is essential.[9]

GI illness—primarily diarrheal—is another common feature of postdisaster health care. Approximately 40% of deaths in the acute postevent phase (with 80% of these being children) can be attributed to diarrhea. These diseases are mainly due to issues of water quality and availability, sanitation, and cleaning materials; in one study, the mere presence of soap decreased diarrhea by 27% in a refugee camp.[16] As with respiratory illness, the incidence of GI disease often peaks several weeks after the disaster, and the infections are generally mild. With good health surveillance and attention to typical endemic disease patterns, severe GI illness outbreaks requiring extraordinary public health resources are rare.

Skin and soft tissue infections are seen in a variety of natural disasters. Falling debris from wind, fire, or earthquake can cause traumatic abrasions or lacerations. With a disrupted healthcare system or contaminated water exposure to the wound, the incidence of infection is likely to increase. Although wounds are frequently seen in the acute phase of a disaster, they are also often encountered during the clean-up phase several weeks to months after an event.[20,21] Severe infections are not prevalent; however, organisms such as *Vibrio vulnificus* in water-based disasters and gram-negative bacteria due to soil contamination of wounds in tornadoes and earthquakes have the potential for severe threats to life and limb.[9,22]

Vectorborne illnesses, such as yellow fever, malaria, and dengue fever, generally have a higher incidence during water-based disasters but can occur after any event in a vulnerable population. Although rare, the outbreak can occur up to 8 weeks after disaster.[13] Regions without predisaster populations of vectors or disease are not likely to suddenly acquire such infections; thus, although there was intense media speculation of the perceived risk of malaria, yellow fever, and other vectorborne illnesses after Hurricane Katrina, these illnesses were not seen in the Gulf Coast.[9] In regions where these illnesses are endemic, vector control is key, and initial postdisaster public health efforts should direct resources toward appropriate programs.

CHRONIC MEDICAL CONDITIONS

Management of the chronic health conditions of a displaced population is a significant contributor to postdisaster morbidity. Separation from medications or health technology products, removal from the usual sources of care, and disruption of the healthcare infrastructure after a catastrophic event can all contribute to exacerbations of patients' chronic disease. In an analysis of patients presenting to one of the few healthcare facilities available in the 2 months after Hurricane Katrina, 51% of all native patients had at least one preexisting medical condition, and half took at least one regular medication.[20] Other studies have shown that >25% of patients presenting after a variety of natural disasters have chronic medical conditions, and "medication refill" or "chronic medical problem" is frequently among the top five diagnoses made in disaster relief health clinics.[21,23]

Inability to properly control chronic diseases, such as hypertension, diabetes, asthma, or coronary artery disease, may well be the biggest unanticipated health threat to a postdisaster population (Table 6-3).[7] Understanding of the common chronic diseases of a region is essential for health relief efforts. In our experience, well-meaning donations of medications for conditions not normally experienced by our population (e.g., outdated psychiatric medications, older generation antiarrhythmics) went unused. Conversely, we were unable to keep enough antihypertensives or diabetic medications to supply the vast demand.

MENTAL HEALTH

An often-overlooked consequence of natural disasters is the psychological burden inflicted on survivors. Destruction of communities and property, witnessing terrifying and often fatal events, and disruption of normal life for days to years after the disaster can cause severe mental health consequences in survivors. In one study of post–Hurricane Katrina survivors, rates of posttraumatic stress disorder were 10 times the expected population incidence and on par with rates in returning Vietnam War veterans.[24] Psychological disorders may be exacerbated by lack of housing and illness or death of a close family member due to the disaster.[25] Disaster-related physical injury or illness may also contribute to mental health comorbidity. The number of emergency amputations due to the 2004 tsunami in an Indonesian surgical clinic quickly overwhelmed the ability of the healthcare system to provide the necessary psychological counseling for patients.[26] Conversely, mental health conditions, such as major depression, may exacerbate acute or chronic physical ailments due to weakened immune systems, disconnection with the larger community and healthcare systems, or attempts to cope by using drugs or alcohol. Suicide rates may also be elevated years after a significant disaster. Any appropriate healthcare response to disasters must include sufficient resources to deal with the degree and severity of psychological disorders suffered by survivors, including children, first responders, and those who have endured severe trauma or loss.

HANDLING OF BODIES

Any natural disaster with a significant number of casualties requires efficient and sanitary removal and proper burial of dead bodies. Although the fear of disease outbreak from survivor or rescue worker exposure to corpses is prevalent, such exposures are rare. Most initial victims of

TABLE 6-3 Commonly Neglected Disaster Response Medications and Supplies

- Antihypertensives
- Tetanus prophylaxis
- Soap
- Analgesics—oral and parenteral
- Insulin
- Oral hypoglycemics and sulfonylureas
- Antibiotics, especially for soft tissue infections
- Albuterol and ipratropium inhalers

natural disasters die of traumatic injuries; few are likely to have acute, communicable diseases, although the standard transmission risks of chronic infectious diseases, such as human immunodeficiency virus, tuberculosis, or hepatitis, to body-handling rescue workers are present.[27] Universal precautions for protective coverings, hand washing, disposal bags, and vaccinations should be followed by anyone working with dead bodies; this includes having sufficient refrigerated trucks on standby should morgue capabilities be overwhelmed.

HURRICANES

Hurricanes are among the most destructive natural disasters, particularly in coastal areas. Morbidity in the acute phase may be due to wind forces (collapsing buildings or flying debris) or water (storm surge or rapid flooding). Hurricanes tend to cause more structural damage than floods and therefore can disrupt infrastructure and population resettlement more severely.[28] Hospitals themselves are frequently damaged, but even if structurally intact, they may be affected by loss of power.[29] With catastrophic destruction of a densely populated region, such as in Hurricanes Katrina, Sandy, and Maria, temporary medical facilities may be needed months after a disaster. **Indeed, hurricanes may be the only natural disaster where more injury and death occur during the recovery period than in the acute phase.**[30]

Most posthurricane illness and injury falls into predictable categories. Studies from eight different hurricanes over the past 15 years all list a handful of patient diagnoses that compose the vast majority (up to 75%) of visits to healthcare centers: infections (specifically respiratory, GI, and skin); treatment of chronic medical conditions; wounds and lacerations; musculoskeletal injury and trauma; and rashes.[19,20,28-34] In functioning healthcare facilities, ED visits peak several days to weeks after the hurricane as citizens are allowed reentry into the area; there may be an acute, brief influx of several times the normal patient volume or a steady rise in visits over time.[5,20,31]

Initial traumatic injury directly due to hurricanes is relatively uncommon, and simple supplies for minor sprain, strain, and fracture care are recommended. Although surgical units and personnel are an important adjunct, basic supplies and some radiographic capability may provide the best investment of limited resources.[28,30] Unintentional injuries predominate; a post–Hurricane Katrina evaluation of injuries found that only 2% were due to intentional trauma.[18] Causes of traumatic death in the acute period include falling objects, motor vehicle crashes, and electrocution. In the recovery period (weeks to months after the hurricane), clean-up–associated trauma predominates. One study after Hurricane Hugo found that one-third of all wounds evaluated in an ED were caused by chainsaw accidents.[32]

As with other disasters, infections are generally mild, are reflective of the typical local disease burden, and occur several weeks to months after the hurricane. Scattered outbreaks of mild respiratory and GI illness have been described, with overcrowding in shelters and sanitation issues the main predictors of disease. Unless hurricanes are associated with concomitant prolonged flooding in endemic areas, the risks of waterborne disease are minor. Post–Hurricane Katrina incidence of *V. vulnificus* skin infection was consistent with typical nondisaster rates.[9]

Individuals without transportation or with tenuous connection to community resources are potentially more likely to be negatively impacted by the effects of a severe hurricane. These individuals may not be able to evacuate in advance of a storm and thus suffer greater risks of direct trauma and water- or wind-related morbidity during the initial impact. Effects may persist beyond the acute phase. A study of Hurricane Mitch survivors noted that GI illness and emotional distress were more likely months after the storm in those without access to housing, food, or medical care.[25] Other population concerns often seen in hurricanes include the healthcare burden of relief workers (civilian and military). Recovery efforts often require massive numbers of workers whose living conditions are often on par with storm victims. In one study, relief workers were nearly six times more likely than natives to use nonhospital healthcare facilities, and a spike in respiratory illness was attributed to transmission through a military battalion.[18] Our experience found that although younger than the native population, nearly half of relief workers seeking care had significant comorbidities that further burdened the struggling medical system after Hurricane Katrina.[20] Disaster planning should account for the needs of disenfranchised citizens as well as the expected influx of relief workers, many of whom may have chronic medical conditions.

EARTHQUAKES

Earthquakes are a unique disaster phenomenon in that there is no technology to detect a pending earthquake and thus no opportunity to provide a warning. Due to the lack of warning, supplies and a response plan must be continuously available. As was evidenced by the Haiti experience in January 2010, earthquakes can destroy water, electric, communication, gas, and sewage lines and cause structural instability. With no opportunity to evacuate before an earthquake, there is increased potential for casualties. People are at increased risk for being trapped in rubble or stranded. The first 1 to 14 days of response to an earthquake are dedicated to recovery of the injured. After an earthquake, the majority of fatalities occur within the first 3 hours.[35]

Injuries after earthquakes are the result of falling structures and debris. The most common injuries are fractures and crush injuries.[36,37] One hospital that registered 2892 patients after an earthquake reported that 37% of patients had musculoskeletal injuries. This hospital also reported the frequent occurrence of scalp injuries with large tissue defects.[36] Another hospital that registered 1500 patients in the first 72 hours after an earthquake reported that 78.4% of patients had extremity injuries; 50.4% of injuries were fractures, primarily closed. This same study reported that 37% of injuries required extensive debridement.[12] After the Mansehra earthquake in Pakistan in 2005, the medical equipment that the response teams found most useful was "external fixators that are easily applied."[36]

As with all disaster areas, the most common "illnesses" are the "regular medical needs of the people living in the earthquake zone."[36] In undeveloped regions recovering from large earthquakes, "preventable diseases, such as measles, are on the rise."[37] With proper sanitary and sewage techniques and adequate supplies of potable water, GI disease remains uncommon.

People with compromised mobility, including some geriatric patients, people with paralysis, amputees, people on ventilators, and people in wheelchairs and walkers, will be less likely to evacuate before the disaster and will have increased difficulty extracting themselves from the ruins. These people are more likely to be stranded in debris and to sustain crush injuries (see also Chapter 7, "Bomb, Blast, and Crush Injuries") by collapsing buildings. These populations are especially at risk after earthquakes, because there will be no opportunity to evacuate before the disaster. Rescue and health services coordinators should make provisions for larger numbers of patients with increased needs after earthquakes. One study analyzed a metropolitan area in the United States and found that 31.6% of people >65 years old had a disability and 16.6% of people >65 years required assistance to evacuate. Planning for and responding to earthquakes requires an estimate of the number of citizens with special needs.[38]

TORNADOES

The continent of North America sustains more tornadoes than any other location in the world.[39] Nationally, 800 tornadoes are sighted annually. The annual human toll is estimated to be 80 deaths and 1500 injuries.[40] Tornadoes cause focal damage to buildings and lines above ground. It is unusual for entire regions to lose power and communications capacity. It is unusual for multiple hospitals to be disabled by a single tornado.[41,42] As a result, medical infrastructure in developed countries remains functional. Surge capacity may be tested in the immediate aftermath, but the provision of adequate chronic medical care is usually unhampered.

Most commonly, injuries from tornadoes result from being struck by flying debris or being thrown by the force of the tornado. Patients who were thrown or airborne as a result of the tornado sustain more severe injuries than patients who are struck by debris.[43,44] Additional risk factors for hospitalization or death include being struck by broken glass or falling objects, having one's home lifted off of its foundation, collapsed

ceiling or floor, or loss of walls of the shelter structure.[44,45] Injuries are commonly multisystem. Fractures and soft tissue trauma are the most common injuries reported.[39,46-48] In one study, most patients (91%) sustained injuries to the extremities. Head, chest, and abdominal injuries were also common, occurring in 45%, 45%, and 27% of patients, respectively.[43] Head injuries are the more common cause of death.[39,47,48] Death from the impact after being thrown by the tornado is thought to most often occur at the scene, rather than en route to or at the hospital.[49-51]

Wound contamination is common among patients who are thrown by the tornado. Polymicrobial contamination is common.[39,46] Gram-negative organisms commonly infect the wounds of those injured by tornadoes.[43] Studies that report low infection rates attribute this to meticulous attention to open wounds.[52]

Where functioning tornado warning systems exist, injury and loss of life are dramatically reduced.[40,53] People in mobile homes or outdoors without cover are more likely to sustain severe and fatal injuries during a tornado.[45,53,54] Deaths are more common in patients who are in mobile homes or in rooms above ground with windows, who are "older," or who have less warning regarding the approaching tornado.[43,44,48,49,55] Use of a tornado shelter is associated with a significant reduction in tornado-associated injuries.[54]

FLOODS AND TSUNAMIS

Water-based natural disasters, such as floods and tsunamis, can be extremely destructive. Although floods can occur from a storm or flowing body of water, tsunamis are formed when a massive force (e.g., an underwater earthquake, volcanic eruption, meteorite impact, or landslide) displaces a large amount of water in a rapid period of time. A spring flood of the Yangtze River in China in 1931 caused >3 million deaths, and more recently, deaths from the Indian Ocean tsunami in 2004 approached 300,000. Factors that contribute to the catastrophic nature of these events include the short (if any) warning period to vulnerable populations and their association with other natural events, such as an oceanic earthquake resulting in a tsunami. Key challenges faced by healthcare providers include severe and prolonged incapacitation of physical buildings due to structural damage or persistent standing water; handling and identification of large numbers of dead bodies; and the chronic needs of a large, displaced population in temporary shelter.[26,56,57]

Acute injuries may be caused by sheer force of water, drowning, and trauma from falling objects. A review of flood deaths from 1989 to 2003 found that morbidity and mortality after flood were related not only to direct physical impact but also the socioeconomic conditions of the affected area. Two thirds of fatalities were from drowning, mostly associated with motor vehicles in the acute phase (e.g., when floodwaters are still high); low crossings and bridges were most dangerous. Only 12% of deaths were from trauma, and the vast majority of cases occurred in the initial impact phase of the disaster.[58]

Illnesses from water-based disasters generally occur after the acute phase and are dominated by infectious disease. True epidemics are rare, and respiratory illnesses predominate. These are generally minor and self-limited, although uncommonly, severe pulmonary infections or pneumonitis directly related to aspiration of floodwaters (e.g., "tsunami lung") may occur. As long as clean, safe, adequate supplies of potable water are available, acute gastroenteritis and diarrheal illnesses are relatively rare; a Sri Lankan refugee camp after the 2004 tsunami diagnosed GI complaints in <1% of patients.[23] Minor skin trauma is common and has the potential to progress to infected wounds if prolonged exposure to floodwaters and delayed access to care are present.

Certain population groups have been shown to have higher risks of morbidity and mortality after floods and tsunamis. Women had three times the risk of death compared with men after the 2004 tsunami due to heavier clothes impeding escape, risking lives to save their children, lack of swimming ability, and increased dangers in settlement camps.[26] In a comprehensive study of flood deaths, however, men had more than twice the mortality rate of women, which the authors surmised was due to increased risk-taking behavior during the storm (attempting to drive through flooded passages, traveling to unsafe areas in an attempt to retrieve belongings).[58] Public awareness of the rapidity and danger of water, simple swimming instruction, and clear warnings of the dangers of driving during floods may prevent at-risk populations in flood-prone areas from loss of life in future disasters.

BLIZZARDS AND SNOW DISASTERS

A blizzard is a winter storm with wind speeds of 35 miles per hour or higher accompanied by significant falling or blowing snow. The Mid-Atlantic, New England, Midwest, Plains, Rocky Mountain states, and Alaska are affected by blizzards and snow disasters. Above-ground power and communication lines are the primary resources lost during winter storms. Traditionally, these are restored relatively quickly as compared with the duration without resources after other natural disasters.[59]

Generally, ED volumes do not significantly increase after blizzards and snow disasters. However, there is a shift in the presenting complaints.[59-61] Injuries after winter weather disasters most commonly result from slipping on the ice, falling from trees while clearing branches, and injuries from clearing snow. The most common injuries are back injuries and fractures.[62,63] In one study, the incidence of fractures increased until the sixth day after the storm.[64]

Carbon monoxide poisoning increases dramatically during and following winter weather disasters.[60,62,65-68] Most people presenting with carbon monoxide poisoning report using a portable generator.[69] A smaller group reported burning charcoal in the house to generate heat.[65] In one study after a blizzard, the local hyperbarics services were overwhelmed and unable to respond to the sudden surge in carbon monoxide poisonings.[62]

One study documented an increase in the number of myocardial infarctions and angina after a blizzard. This was primarily in association with shoveling snow. The majority of these cases were in people who did not have previously diagnosed coronary artery disease. One fourth of these patients were women.[70]

RELIEF EFFORTS

Of particular importance to the emergency medical practitioner is the experience and effect of postdisaster volunteer relief efforts. Although well meaning, the literature is filled with examples of emergency personnel who ended up burdening rather than assisting a fractured community. Any emergency practitioner who truly wishes to provide meaningful health care to a displaced and disenfranchised patient population should be mindful of the lessons learned from a variety of natural disasters.

Medical relief volunteers are often the first outside help to arrive in the aftermath of a disaster, and although some are well coordinated, many are not. Volunteers are often exuberant, expecting dramatic rescues and emergency interventions. They may be unwilling to provide much-needed routine medical care, unfamiliar with the region or local disease patterns, and unable to fully comprehend the loss of resources.[71] Furthermore, the needs of rescue personnel often strain a fragile infrastructure, with demands on housing, food, health care, and essential resources; one analysis of relief efforts after the 2004 tsunami concluded that "personnel who do not bring essential skills are often a burden—much more should also be done to ensure that the right type of people are sent on relief missions."[26]

Embedding locals familiar with the language, culture, and healthcare patterns of the affected region can significantly enhance the effectiveness of relief efforts and promote cooperation between disparate volunteer groups. Furthermore, appropriate anticipation by relief groups of the true population needs can be crucial: reproductive hygiene kits were distributed to women in a postflood refugee camp after an initial spike in sexual assaults and were widely credited with improving patient morale and health.[26]

The National Disaster Medical System, a government agency responsible for sending highly organized and often experienced teams to disaster areas, recommends the following for disaster response: teams with well-trained and organized support staff; the ability to be self-sufficient for at least 72 hours; clear communication with area hospitals and medical resources; individuals dedicated to transportation issues; a designated coordinator of walk-in volunteers; and professional methods

of record keeping, forms, and copy-making capability.[30] Our experience during Hurricane Katrina also suggests that strong, coordinated partnerships between local emergency personnel and formal military medical units have great promise for sophisticated, expanded acute and delayed postdisaster medical relief as well as continuance of medical education and resident training programs in a devastated community.[20]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 7

Bomb, Blast, and Crush Injuries

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BOMB AND BLAST INJURIES

EPIDEMIOLOGY

Blast injuries using conventional weapons have emerged as the terrorist weapon of choice. In 2016, the National Counterterrorism Center reported 11,072 terrorist attacks worldwide, with 33,800 people injured and more than 25,600 deaths.[1] Total terrorist attacks decreased by 9% and total deaths decreased by 13% compared to 2015. As a comparison, in 2007, there were 14,000 terrorist attacks, with 44,000 injuries and 22,000 deaths, which was a 20% to 30% increase over 2006.[1] Explosive devices in military conflicts killed or injured more than 25,000 U.S. and Coalition forces and more than 100,000 Iraqis.[2] Blast injuries are increasing in the civilian setting, particularly suicide bombings, and emergency personnel must be familiar with the management and treatment of blast injuries and potential mass casualty incidents.[3-10] The United States is not immune from intentional bombings, with about 36,000 bombing incidents reported from 1983 to 2002 including explosive, incendiary, premature, and attempted bombings.[7] There were 281 people injured in the 2013 Boston Marathon bombing, with most injuries involving the lower extremities and soft tissue.[9] Blast injury is not a modern phenomenon, and there are reports of flammable gases causing blast injuries from volcanic eruptions and mining accidents dating back to 1316.[11] Death, survival, and hospitalization rates vary greatly, depending on the type of explosive, distance from the explosion, and whether the explosion occurred in an open or closed space. Although some victims die immediately at the scene, the majority of injuries suffered by the immediate survivors of bombings are potentially survivable. Blast injuries commonly occur not as isolated incidents, but as part of multiple-casualty incidents of varying sizes. This pattern, combined with the fact that most emergency physicians have never encountered a blast injury victim or a true mass casualty incident, makes the care of often eminently salvageable victims contingent upon appropriate training and skill retention by the individual emergency physician, along with appropriate institutional leadership, planning, and preparation.

Terrorist bombings result in high injury scores for victims as well as higher hospital resource use by victims than by victims of other trauma. Blast victims have increased immediate scene mortality, greater hospital mortality, more frequent need for surgical intervention, longer hospital stays, and greater use of critical care.

PATHOPHYSIOLOGY

An explosion is the instantaneous transformation of a solid or liquid into a gas, releasing tremendous kinetic and heat energy. Detonation of a conventional high explosive generates a blast wave that spreads out from the detonation point and displaces air, water, or anything in its path. The blast wave consists of two parts: a shock wave of high pressure followed closely by a blast wind, which is air mass in motion. The blast wave loses its energy over distance and time.



FIGURE 7-1. Secondary blast injury to the chest and abdomen due to flying debris. It is difficult to assess the degree of underlying internal organ injury without imaging and careful clinical follow-up, especially if the patient is unconscious. [Image used with permission of Tel Aviv Medical Center.]

There are four main types of blast effects. A primary injury is caused by a direct effect of blast wave overpressure on tissue. Primary blast injury mostly (but not exclusively) affects air-filled structures such as the lungs, ears, and GI tract, by the following mechanisms: spalling, shearing, and implosion. **Spalling** is displacement and fragmentation of a dense medium into a less dense medium.[12] An example of spalling is a blast wave causing the lung parenchyma to explode into the alveolar space like a geyser. **Shearing**, sometimes called inertia, is a stress caused by the blast wave traveling through different tissue densities at different velocities. An example of shearing is the blast wave traveling through the pulmonary vessels and air spaces, resulting in ruptured vascular and bronchial pedicles. **Implosion** is the opposite of spalling, where the less dense material is displaced into denser material. An example of implosion is the blast wave causing the flexible air spaces to rebound to greater than original size, sometimes causing air embolism from the alveoli into the pulmonary vessels.[12] A secondary blast injury is due to collateral damage from flying objects and shrapnel (**Figures 7-1 and 7-2**). Tertiary blast injury results from the victim being propelled through the air and striking stationary objects. A quaternary blast injury is a result of burns, smoke inhalation, or chemical agent release.

FACTORS AFFECTING BLAST INJURY

The effects of a bomb blast are difficult to predict in the individual victim, as well as in the group. However, a number of important principles are known:

Distance of victim from explosion: The intensity of an explosion pressure wave declines with the cubed root of the distance from the explosion. A person 3 m (10 ft) from an explosion experiences eight times more overpressure than a person 6 m (20 ft) away. Proximity of the victim to the explosion is an important factor in a primary blast injury.

Enclosed versus open space: The effects of an explosion in a closed space, such as a room, bus, or train, are much greater than in an open space. Injuries are more severe, and mortality is greater.

Surrounding environment: Blast waves are reflected by solid surfaces; thus, a person standing next to a wall may suffer increased primary blast injury.

Quantity of explosive: A greater quantity of explosive produces greater potential for damage at any distance.

Type of explosive: Explosives are commonly classified as either low-order or high-order. Low-order explosives burn rapidly and produce

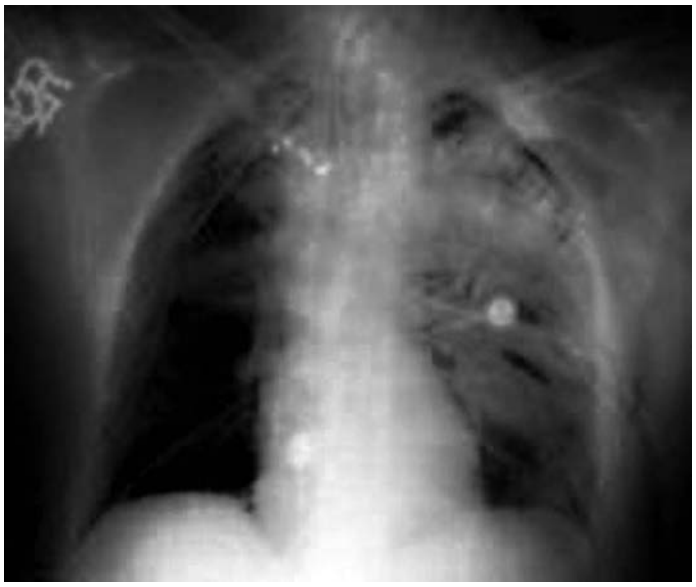


FIGURE 7-2. This young patient came in fully conscious and hemodynamically stable. Multiple externally visible shrapnel wounds required imaging. This radiograph image shows severe lung injury due to shrapnel. She also suffered multiple abdominal injuries, including major liver lacerations and bowel perforations, and required extensive surgery. [Image used with permission of Tel Aviv Medical Center.]

a blast wave of less than 1000 m/s.[13] Black powder is an example of a low-order explosive. High-order explosives detonate when a shock wave passes through them, causing an almost instantaneous transformation of the original explosive material into gases occupying the same volume of space under extremely high pressure. These high-pressure gases expand rapidly, compress the surrounding medium, and produce a supersonic, overpressure blast wave, moving at greater than 4500 m/s, followed closely by a negative pressure wave.

Embedded shrapnel: Many terrorists purposefully embed multiple pieces of metal and plastic in the explosive, maximizing the number and severity of secondary injuries.

CLINICAL FEATURES

The nature of the injury may produce a multiplicity of external signs (**Figure 7-3**), making detection of important internal injuries challenging. Insufficient or suboptimal resources need to be prioritized in a mass casualty incident. High-grade clinical expertise is even more in demand to allow optimal use of resources.[3-10]



FIGURE 7-3. The severe external injuries often seen with explosive blast may or may not indicate associated severe internal injury. Clinical examination is difficult and requires a high degree of experience and suspicion as well as early use of imaging. [Image used with permission of Tel Aviv Medical Center.]

CARDIOPULMONARY SYSTEM

The lung is very susceptible to primary blast injury. **Pulmonary barotrauma is the most common fatal primary blast injury** and the most common critical injury in people close to the blast center. Pressure differentials across the alveolar–capillary interface can cause disruption, hemorrhage, pulmonary contusion, pneumothorax, hemothorax, pneumomediastinum, and subcutaneous emphysema. Air embolism is another well-recognized consequence of blast lung injury and is probably one of the major factors leading to cardiac dysfunction and immediate death after blast wave exposure, although it is usually difficult to diagnose specifically. The resulting neurologic symptoms caused by air embolism must be differentiated from the direct effects of CNS trauma. Pulmonary fat embolism is a finding of clinical importance in survivors of blast trauma because it can lead to the development of acute respiratory distress syndrome and significantly affects clinical outcomes.

In general, managing blast lung injury is similar to caring for pulmonary contusion and acute respiratory distress syndrome, except that early recognition of the syndrome may be complicated by initially benign symptoms, especially in the context of hectic mass casualty incident situations. Hypoxia is an almost universal finding.[14] Monitoring of respiratory rate and room-air pulse oximetry, as well as serial chest radiographs, may be needed. Fluid administration should ensure tissue perfusion without volume overload. The decision to institute mechanical ventilation must be made carefully because it entails the assignment of what may be scarce critical care unit beds and ventilators and also exposes the patient to the potential complications of pulmonary barotrauma, commonly seen with the friable lungs associated with blast lung syndrome. **Keep tidal volume to 6 to 7 mL/kg ideal body weight to limit the peak inspiratory pressure and to minimize ventilator-induced lung barotrauma.** Often, neuromuscular paralysis and early institution of pressure-limited ventilation (plateau pressures <30 cm H_2O),[15] with the lowest pressures compatible with adequate ventilation, may be the best strategy. Inverse inspiratory-to-expiratory ratio ventilation may be useful. Permissive hypercapnia is acceptable depending on cerebral perfusion pressure or increased intracranial pressure.[15] Aggressive methods of oxygenation, such as extracorporeal membrane oxygenation or intravascular oxygenation, may become necessary within hours of the injury.

There are no definitive guidelines for observation, admission, or discharge of patients with possible blast lung injury. Admit patients requiring complex management to an intensive care unit. In general, asymptomatic patients with normal chest radiographs and normal room-air pulse oximetry may be considered for discharge after 4 to 6 hours of observation as long as there is no clinical deterioration. Survivors of this type of injury typically have no long-term pulmonary complaints, and most have normal physical examinations, chest radiographs, and normal lung function tests.

EARS

The tympanic membrane ruptures at 1 to 8 psi of dynamic overpressure. Dislodgement of ossicles may also occur. Patients with an isolated tympanic membrane perforation and no other immediately identified injuries should have a chest radiograph ordered but do not automatically require an extended period of observation. Conversely, intact tympanic membranes do not imply the absence of serious injury, and the use of the perforation of tympanic membrane as an indicator of primary blast injury missed up to 50% of those suffering a primary blast injury to the lung.[16] Clinical judgment is necessary, and limited observation is reasonable for patients with intact tympanic membranes. Experience from the Boston Marathon bombings suggests that blast-related otologic injuries were a major source of continued morbidity and required extended follow-up.[17]

ABDOMEN

Abdominal injuries from explosions may be occult. Reported injury rates are low, but missed injuries may carry significant morbidity due to delayed intestinal perforation and necrosis. A review of the literature

on abdominal trauma from primary blast injury reveals an incidence of 1.3% to 33%, and the terminal ileum and cecum were the most commonly injured areas.[18] Serial clinical examinations, serial imaging as needed, and 24- to 48-hour observation are indicated whenever the suspicion arises. **Air is a poor conductor of blast-wave energy; thus, patients who were subjected to enough energy to damage abdominal organs probably were situated near the explosive device.** There have been case reports of pneumoperitoneum without visceral trauma, so if the patient is suspected to have been near the explosive device, CT scan of the abdomen and pelvis might be considered.[19]

BRAIN INJURY

The conflicts of the Global War on Terror in Iraq and Afghanistan have resulted in over a quarter of a million diagnosed cases of traumatic brain injury.[20] Mild traumatic brain injury has been labeled the "signature injury of the war in Iraq."[2,21-26] Penetrating shrapnel is the most common cause of brain injury, but there may be a component of blast overpressure–induced compromise of the blood–brain barrier and cerebral blood vessels.[27] The clinical examination may be misleading for penetrating injuries. Shrapnel are low-velocity missiles, often producing small entry wounds in survivors. Small entry wounds may be missed under the hair, and evidence for traumatic brain injury may initially be benign or masked by anesthesia as the patient undergoes treatment for other life-threatening injuries. Neuroimaging is an important early diagnostic tool (**Figure 7-4**).

VASCULAR INJURY

Small entry wounds from shrapnel may mask severe vascular injuries. Compartment syndrome (see "Crush Injury and the Crush Syndrome," below) may develop and is difficult to diagnose, especially in patients receiving anesthesia. Carefully assess and document pulses and perfusion in affected limbs. **Observe for delayed presentation of compartment syndrome, and measure compartment pressure if any signs or symptoms develop.** Early angiography and intervention are indicated if pulses are lost.

EXTERNAL HEMORRHAGE

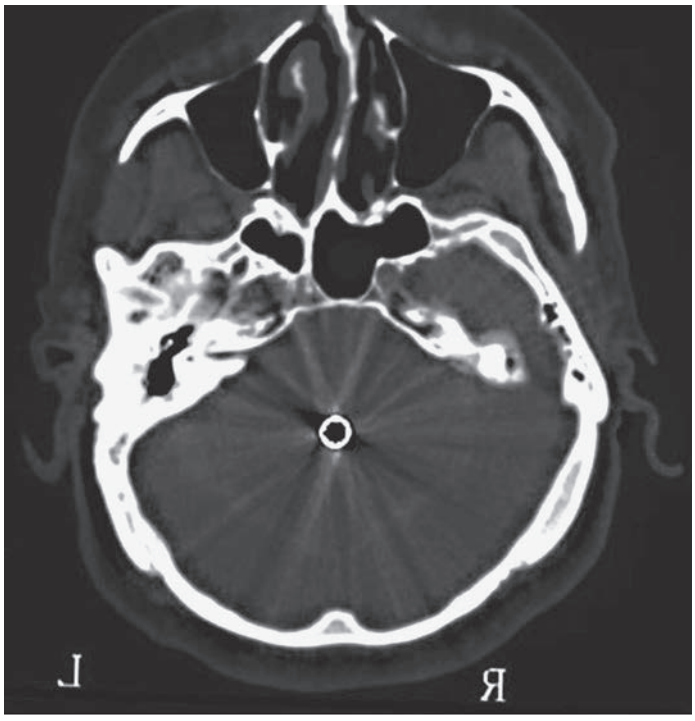
Exsanguination from wounds is likely to be the most commonly encountered life-threatening finding. Military experience has shown that hemorrhage is the most common cause of preventable death in penetrating trauma.[10] Whether venous or arterial, blood loss from multiple wounds (internal and external) may cause hypovolemic shock. Quickly control external bleeding with direct pressure. Apply tourniquets for extremity hemorrhage whenever blood loss cannot be controlled with direct pressure or if the resources required to maintain direct pressure are insufficient during treatment or transportation. Tourniquets have been successfully used for up to 6 hours in battlefield situations.[28] Angiographic vascular occlusion is an attractive treatment option if the time and staff are available. Victims of blast mass casualty incidents may require massive amounts of blood and blood products.[29]

OCULAR INJURIES

Eye injuries from a blast wave may cause shearing damage to the orbit, but ocular injuries are from a combination of primary and secondary processes.[30] Ocular injuries include lid or brow lacerations, conjunctival lacerations, open globe injuries, orbital fractures, retinal detachment, retained intraocular foreign body, lens dislocation, vitreous hemorrhage, retinal tears, and retinal detachment.[30] Eye examination is needed for all moderately to severely injured blast victims, and a poor initial visual acuity is not a guarantee of a poor final result.

DIAGNOSIS

In the ED, order diagnostic imaging judiciously in a mass casualty incident. Priorities for care are airway management, treatment of tension pneumothorax, and fluid and blood resuscitation. Visualization of a metallic object on a single-plane radiograph is often inadequate for thorough evaluation, but it can direct the treatment team on the need for urgent surgery or for additional imaging. Plain chest radiographs or ultrasonography and the FAST examination are the most rapid studies



A



B

FIGURE 7-4. **A.** CT scan image of a 17-year-old female patient injured in a terrorist bomb blast in Israel. This girl walked into the ED unassisted, was triaged "green," but deteriorated after 30 minutes. Fortunately the clinical deterioration was noted, she underwent emergent CT, and then extensive neurosurgical intervention. **B.** A 1-cm metal ball bearing was extracted. Prolonged rehabilitation was later required for residual brain damage. [Image used with permission of Tel Aviv Medical Center.]

used to evaluate for life-threatening injuries. Order laboratory tests sparingly.

TREATMENT

When blast injuries occur, they tend to be unexpected, occur outside of regular working hours, and often produce moderate to large numbers of simultaneously arriving casualties. Drills and checklists are critical for successful implementation of rarely used protocols. Checklists should be concise, never more than one to two pages, and available in a location known to everyone. Implement the hospital plan for management of mass casualty incidents.

Obtain details about the explosion from patients and rescue teams. **The nature and location of the blast, including size and type of charge, location in open or closed space, structural collapse, associated fire or smoke, and toxic agent release, will be helpful in making informed clinical decisions, especially with regard to disposition of moderately to severely injured casualties.**

Initiate triage as multiple patients arrive. Station an experienced emergency physician or surgeon at the ED entrance to triage patients to appropriate, predetermined locations in the ED or elsewhere in the hospital. Triage to categories of urgency using criteria such as those listed in **Table 7-1**. Many triage methods have been in use in various parts of the world, with varying success and scientific foundation.[3-8]

Apply the basic advanced trauma life support principles of primary and secondary surveys within the logistic limitations that may occur temporarily or permanently. Administer IV fluids and blood products judiciously. Preventing fluid overload is important for lung- and brain-injured patients. Consider tranexamic acid for uncontrollable bleeding.

Copiously irrigate and disinfect wounds urgently, but definitive debridement and closure may wait a few hours. Temporary splinting, traction, and dressings are generally sufficient for initial management of musculoskeletal injuries. Consider prophylactic antibiotics for severely soiled wounds, penetrating abdominal and thoracic wounds, and open fractures, and in patients with diabetes or who are immunocompromised.

Address pain management after life-threatening emergencies have been evaluated. Reserve opiates for patients with severe pain because opiate supplies may become limited.

Patients exposed to open-space explosions and who have no apparent significant injury, normal vital signs, and an unremarkable physical examination generally can be discharged after 4 to 6 hours of observation. Perform secondary assessments of all casualties before discharge. Admit all patients with significant burns, suspected air embolism, radiation or chemical contamination, abnormal vital signs, abnormal lung examination findings, clinical or radiographic evidence of pulmonary contusion or pneumothorax, abdominal pain, vomiting, hypoxia, or penetrating injuries to the thorax, abdomen, neck, or head to the hospital.

Patients appropriate for discharge need proper follow-up instructions, due to the austerity of initial care and the propensity to miss injuries in a mass casualty incident. Because symptoms of pulmonary contusion and intestinal hematoma may take 12 to 48 hours to develop, instruct all discharged patients to return for reevaluation if they develop breathing problems, abdominal pain, or vomiting. Provide relevant follow-up instructions in writing, including audiologic and ear, nose, and throat follow-up, wound care, immunization schedules, medications, psychological support, and social services.

TABLE 7-1 Criteria for Triage in Bomb Injuries

Severely Injured	Lightly Injured
Airway compromise	Minor wounds
Breathing difficulty	Burns, first or second degree
Hemodynamic instability	Isolated trauma to a limb
Altered level of consciousness	Anxiety states
Vascular trauma	Most walking patients
Extensive second- to third-degree burns	

SPECIAL CONSIDERATIONS

PREGNANT WOMEN AND CHILDREN

Because the fetus is surrounded by amniotic fluid, direct injury to the fetus is uncommon. **Injuries to the placenta, however, are more common.** After life-threatening conditions have been stabilized, admit patients in the second or third trimester of pregnancy who have been exposed to blast injury to the labor and delivery area for continuous fetal monitoring and further testing and evaluation. Pelvic US, fetal nonstress test monitoring, and obstetrics consultation should always be obtained. Consider Rh immune globulin administration if the mother's blood type is Rh negative.

Children may suffer significant tertiary blast injury because their lighter bodies are more easily hurled by the blast wind. Imaging, such as total-body CT, may be difficult to perform in anxious and frightened children, and typically requires sedation.

STAFF SAFETY

Issues that may affect staff safety include: (1) possible infiltration of the ED by perpetrators intent on causing second explosions or attacks in the hospital; (2) unexploded explosives inadvertently brought into the ED; (3) transmissible disease in the setting of body fluid exposure or needle sticks during stressful, rapid work; and (4) contamination of victims by chemical, radiologic, and biologic hazards, either accidental or intentionally caused by the perpetrators. Preplan for such situations.

FORENSIC ISSUES

Police and crime scene investigators, as well as counterterrorism and other security services, have legitimate interests in securing forensic and other information. Efforts should be made to accommodate them, but never at the expense of medical care. Prior coordination with all relevant authorities should establish protocols, such as who and how many persons from these agencies are allowed in, when, into which parts of the ED, who controls them, and who is empowered to limit their entry and work. As a rule, however, although a terrorist event is a crime, forensics in the hospital are of minor relevance compared with the actual crime scene. Investigators may wish to interrogate victims with minor injuries regarding the event and obtain shrapnel or clothing from patients for forensic analysis.

INFORMATION MANAGEMENT

Because blast injury is often part of a large event, information becomes a critical component of appropriate management. Such information concerns include: (1) clinical charting and other patient care–centered information, such as imaging; (2) command and control information, such as casualty flow data, resource management data, and interface with other agencies; (3) information provided to relatives; (4) information provided to the media; and (5) information recorded for quality improvement and research. An information center is an indispensable component of such events, providing relief for the relatives and also preventing them from crowding patient care spaces and impeding caregiver workflow.

CRUSH INJURY AND THE CRUSH SYNDROME

INTRODUCTION AND EPIDEMIOLOGY

A crush injury occurs when a body part is subjected to a high degree of force or pressure, usually after being squeezed between two heavy or immobile objects. **Crush injury that produces ongoing ischemia of a fascial muscle compartment is termed *compartment syndrome*, defined as increased pressure within a confined space that leads to microvascular compromise and ultimately to cell death as a result of oxygen starvation.** Crush syndrome is the systemic manifestation of

muscle cell damage resulting from pressure or crushing with or without subsequent compartment syndrome. This chapter discusses crush injury and treatment measures specifically in the context of mass natural disasters. Specific discussion of detailed physiology, compartment anatomy, and compartment pressure measurement is found in Chapter 278, "Compartment Syndrome."

Crush injuries may be seen in two different scenarios: in single-patient situations and in disasters of varying magnitude, such as earthquakes or tsunamis. Catastrophes have occurred throughout history, but the recognition of crush syndrome in the 20th century and the advent of effective treatment for some of the components of the systemic and local injury have made it one of the important aspects of the medical care of natural disaster victims. The increasing number of vehicular and workplace accidents has also led to a rise in the incidence of crush syndrome and in the importance of its timely recognition and treatment. In various reports, the incidence of crush syndrome and subsequent renal failure varies from 1% to 25%, probably resulting from reporting differences, the nature of the disaster, and the timeliness and effectiveness of the rescue efforts and medical care.[31]

Crush injuries are most commonly seen in the extremities, because crush of the trunk or head and neck is quickly lethal. There is a high incidence of associated injuries such as fractures, lacerations, and degloving injury.

Care of crush injury patients in the setting of mass casualty incidents is radically different than that of the individual victim. Extrication may be delayed, medical treatment during extrication may be unavailable, initial management may occur in makeshift or suboptimal conditions, and medical personnel may have little experience working under such conditions. Transportation to definitive care may be prolonged; critical equipment, such as dialysis machines, may be in short supply; and laboratory, monitoring, and intensive care facilities may be insufficient for the volume demands. Healthcare workers should anticipate these obstacles and develop flexible treatment protocols.

PATHOPHYSIOLOGY

Injury to muscles, including crush and ischemia, causes rupture of the sarcolemma and the release of the intracellular contents of the myocytes into the surrounding tissues. Calcium ion is one of the most destructive components released from the myocytes, because calcium stimulates proteolytic enzymes and oxygen free radicals are released. This causes more myocyte destruction, and potassium, phosphate, myoglobin, creatine kinase, and uric acid leak into the bloodstream. Serum haptoglobin binds some of the myoglobin, but its binding capacity is quickly overwhelmed, and myoglobin causes direct kidney injury. Membrane damage to the myocytes and to the systemic capillary endothelium causes vascular volume loss and hypovolemia. Hyperkalemia and hypocalcemia may cause arrhythmias and cardiac arrest. Metabolic acidosis caused by hypovolemia and shock aggravates arrhythmogenicity. **Renal failure is the most serious complication of crush syndrome.** The pathogenesis of renal failure is multifactorial, including systemic hypoperfusion, renal vasoconstriction, nephrotoxicity from myoglobin, and uric acid and phosphate precipitation in the distal tubules. Low urine pH and renal vasoconstriction promote precipitation of nephrotoxins. Myoglobin is indirectly nephrotoxic through the formation of ferrihemate, which produces free hydroxyl radicals and, combined with lipid peroxidation, damages the kidney.[32]

Reperfusion syndrome is a paradoxical phenomenon of exacerbation of cellular dysfunction after restoration of blood flow to previously ischemic tissues. It involves biochemical and cellular changes causing oxidant production and complement activation, which culminates in an inflammatory response, mediated by neutrophils and platelets interacting with the endothelium. The inflammatory response has both local and systemic manifestations.[33] Systemic manifestations include hypotension, vasodilatation, hypovolemia, myocardial depression, hyperkalemia, and acidosis.

Normal muscle compartment pressure is <10 mm Hg. After crush injury, trauma to the microcirculation leads to edema formation, interstitial bleeding, stasis, and obstruction, and the myocytes are no longer able to retain intracellular water. Edema in a closed space causes increased pressure, which further collapses the microcirculation and potentiates the problem.[34] **Pressures >30 mm Hg produce muscle ischemia; irreversible nerve and muscle damage occurs after 4 to 6 hours.**

CLINICAL FEATURES

Obvious external signs of crush injury are usually evident, as is a suggestive history. Lacerations, degloving, deformity, pain, and ischemia may occur in varying degrees.

Compartment syndrome often presents with the five "P's": **pain, paresthesias, passive stretch, pressure, and pulselessness.** Pain is the most common and consistent symptom, described as diffuse and intense; exacerbated with movement, touch, or pressure; and out of proportion to physical examination findings.

Paresthesias are numbness, tingling, or burning sensations in the affected area. Severe pain results when muscles in the affected compartment are stretched.

The affected compartment is very tight to the examiner's touch and sometimes warm, and there are measurable increases in tissue pressure. Pulselessness occurs only in the late stages. Examining for a pulse, or its lack, is the least reliable because compartment syndrome is a disorder of the microvasculature; the major vessels are frequently unaffected.

Crush syndrome is due to the manifestations of muscle toxin release and hypovolemia. Hypovolemic shock may occur, aggravated by hyperkalemic, hypocalcemic, or acidemic cardiotoxicity. Thromboplastin release may cause disseminated intravascular coagulation, which is especially critical in the face of tissue damage, open wounds, or the need for surgery. Renal failure may ensue quickly and is the primary cause of delayed death.[31]

DIAGNOSIS

Testing of the compartment pressure will confirm the diagnosis. A compartment pressure of >30 mm Hg is considered to be a positive test. Measurement is best accomplished with a dedicated device (Stryker STIC®; Stryker Co., Kalamazoo, MI) or by inserting a saline-filled needle connected to an intravascular pressure measurement system (arterial or central venous pressure gauges) into each compartment and recording the pressures.[31] See Chapter 278 for detailed description of compartment pressure measurement.

Crush syndrome is characterized by protean and rapid metabolic changes. Laboratory tests are crucial to help direct management. Serum creatine kinase levels may not necessarily predict disease severity and risk of renal failure, but they are a useful initial triage and subsequent follow-up tool. Pay close attention to serum potassium, calcium, phosphorus, pH, creatinine, hemoglobin, coagulation indices, and urine pH and electrolytes. A preplanned sequence of laboratory tests every 2 to 4 hours is useful, rather than sporadic checks. Urine collection for total electrolyte excretion and creatinine clearance calculations may be considered.[31]

TREATMENT

Establish two large-bore IV lines and administer normal saline with a 1- to 2-L bolus. Avoid Ringer's lactate and other potassium-containing fluids, because fatal hyperkalemia may occur, even in the absence of renal failure.[31] Initiate IV fluid rate at 1000 mL/h, and then reduce to 500 mL/h after 2 hours. Urine output should be approximately 200 to 300 mL/h (5 to 7 L every 24 hours) for an adult. Monitor serial serum potassium levels. Admit the patient to an intensive care unit setting to monitor fluid administration and electrolyte status.

FASCIOTOMY

In reports of mass casualties from earthquakes, most of the fasciotomy procedures were performed >12 hours after the time of trauma. Reviews of these cases showed high infection rates with increased mortality and amputations and poor long-term outcomes. Fasciotomy creates open wounds, which increases the risk for sepsis, amputation, hemodynamic

instability, chronic nerve dysfunction, and death.[31] Most recommendations discourage the use of routine fasciotomy, particularly for crush wounds, and fasciotomy is only indicated for absence of distal pulses, a requirement for debridement of necrotic muscle, compartment pressures >30 mm Hg (measured within 6 hours of injury), and differences between compartmental pressure and diastolic blood pressure of >30 mm Hg.[31] If initial compartment pressures are normal and delayed compartment syndrome develops, fasciotomy may be needed, but infection rates have been reported to be high and prolonged, and profuse local bleeding may develop.

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy is a useful adjunct in the treatment of crush injury and compartment syndrome because it supplements oxygen availability to the hypoxic tissues in the early postinjury period.[34] With hyperbaric oxygen therapy at 2 atm, the blood oxygen content (oxygen carried by hemoglobin and plasma) is increased by 125% (by increasing plasma oxygen content), and the oxygen tension in plasma and tissue fluid is increased 10-fold compared to room air breathing.[34] Edema reduction secondary to oxygen-induced vasoconstriction is another beneficial effect of hyperbaric oxygenation. Hyperbaric oxygenation reduces blood flow by 10% to 20%, thereby reducing tissue edema caused by blood flow, but oxygen delivery to the tissues is increased because of higher tissue oxygen tensions.[34] The immediate effects of hyperbaric oxygen therapy are threefold: enhanced oxygen at the tissue level, increased oxygen delivery per unit of blood flow, and edema reduction. Long-term effects may include improved wound repair after fasciotomy, diminished infection rates, and improved outcome of skin grafts.[34]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 8

Chemical Disasters

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INTRODUCTION AND EPIDEMIOLOGY

Although the term "agents of mass destruction" is often used in planning for terrorist events, in reality, few chemicals can be delivered by terrorists in the appropriate fashion to create large numbers of deaths.[1] However, chemical mass casualty events do occur. The setting may involve the release of industrial chemicals, such as the 1984 industrial accident in Bhopal, India, that caused more than 2500 deaths and 200,000 injuries from a methyl isocyanate release,[2] or a natural chemical incident, such as the emission of carbon dioxide in Lake Nyos, Cameroon, that was responsible for 1700 chemical asphyxiant deaths. Chemical terrorism may also occur through acts of willful deployment, as with the sarin release in the Tokyo subway in 1995 in which 12 people died and 5500 sought medical attention.

The emergency physician is most likely to encounter the accidental release of a chemical from a fixed industrial site or transportation accident. In 2005, a freight train collision in Graniteville, South Carolina, caused the release of chlorine gas that resulted in nine deaths and 511 ED visits.[2,3] Environmental contamination, even without injuries, may affect an entire community, including local EDs. In 2014, a previously little-known chemical named 4-methylcyclohexane methanol that was used in coal washing leaked into the Elk River in West Virginia, in proximity to the intake area for the water supply for nine counties that served 300,000 people. Although there were no injuries, emergency planners needed to supply clean water to the affected population. Providing risk management advice based on limited data on this chemical and the chemical's strong black licorice odor despite levels below the toxic concentration made it challenging to convince the citizens that the water was safe to use again.[4]

What has been learned from these incidents is that when chemicals are released, the agents create a penumbra effect, in which true chemical emergencies occur in the epicenter and a larger surrounding area of fear and panic arises in individuals with lower, usually nontoxic levels of exposure. **Planning for chemical disasters must take into account both the chemical emergency occurring near the center of any chemical release and the chaos that can ensue through fear of exposure.**[2,3] What makes these events overwhelming for an individual ED is the larger number of victims who are ambulatory, frightened, and make their own way to the hospital, bypassing any scene triage or decontamination.[5] Appropriate planning for management of this large, self-extricated population is paramount to the concept of disaster preparedness for chemical emergencies and perhaps even more important than specific antidotes for rare agents that might be encountered.

PRINCIPLES OF PHYSICS: SOLIDS, LIQUIDS, AND GASES

Solids have a fixed volume and shape and can be bulk solids, powders, dusts, or fumes.[6] Dust particles are visible if they are >100 μm in diameter; particles smaller than this size are imperceptible to the naked eye.[7] Most dust particles settle with time as the result of gravity; however, in a wind-blown environment or an explosion, they can be blown through the air and contaminate mucous membranes or be inhaled. Dust particles between 2.5 and 6.0 μm in diameter deposit in the bronchial mucosa, whereas particles smaller than 2.5 μm can reach the alveoli. Fumes are fine, solid particles created by either combustion or condensation and are smaller than 1 μm in diameter. Chemicals may adhere to fumes or dusts and be deposited in the lungs through inhalation.

Liquids have a fixed volume, but their shape conforms to both gravitation and container shape. They will flow downhill and can accumulate in clothing and shoes. A liquid forced through a small orifice under pressure can be aerosolized into fine liquid droplets (i.e., aerosols). Aerosols, like dust, will settle with gravity over time. A vapor may be a dispersion of a liquid or a volatile solid, like mercury. Vapors and aerosols may penetrate clothing, causing contact injury by soaking the underlying skin or reacting with moisture in mucous membranes.

A gas has a variable shape and volume and will diffuse to fill an enclosed space once released. Many compressed gases are stored as liquids in cylinders and are converted to a gas upon their release. Hazardous risk analysis should take into consideration misuse or theft of these compressed gas cylinders. An endothermic reaction may occur during release of a compressed gas, causing hypothermic skin injury. Gases can be inhaled into the lungs and cause local reaction, systemic toxicity, or, in some cases, delayed reactions deep in the pulmonary tree.

How deeply in the lungs a gas or vapor exerts its effects depends on its degree of water solubility. Highly water-soluble compounds react with water in mucous membranes and can irritate the eyes and upper airway.[6] Examples of agents with this property includes ammonia and hydrogen chloride. These agents have good warning properties, allowing an awake and ambulatory individual to leave the area of exposure. Low water-soluble compounds may be less irritating, allowing greater duration of exposure and, therefore, greater pulmonary penetration. Phosgene is an example of a low-solubility gas; it has a pleasant smell like new-mown hay and penetrates deep into the alveoli where it slowly is converted to hydrochloric acid.

HAZARDOUS MATERIALS EXPOSURE-LIMIT GUIDELINES

Several agencies have created exposure guidelines used for different purposes, of which a few may be useful in assessing health risks during an exposure. The American Conference of Governmental Industrial Hygienists has created threshold limit values for many substances.[8] This value is the maximum allowable airborne concentration of a substance

TABLE 8-1 Scene HAZMAT Planning Guidelines

- Community risk assessment
- Recognition of an event
- Identification of the substances involved
- Isolation and scene control
- Decontamination
- Stabilization and triage

Abbreviation: HAZMAT = hazardous materials.

that a worker can be exposed to for an 8-hour workday. Concentrations below this should be regarded as acceptable and safe.[6,8] The American Conference of Governmental Industrial Hygienists has also established a short-term exposure limit for substances to which an individual should not be exposed for >15 minutes.[8] The National Institute for Occupational Safety and Health has established an acute exposure limit called the immediately dangerous to life or health limit. This is the maximum environmental air concentration of a substance from which a person without protective equipment could escape within 30 minutes and not sustain irreversible health effects.[6] This applies only to acute health effects and does not take into account chronic health effects or carcinogenicity. The immediately dangerous to life or health level is meant to apply to the work environment and not a chemical accident, where the level of a substance measured in an environment is usually unavailable during an actual disaster and may change over time.

SCENE HAZARDOUS MATERIALS RESPONSE

Each year, there are 15,000 to 19,000 hazardous materials events in the United States. Planning for chemical exposure events, whether terrorist or accidental, builds on our existing principles of hazardous materials response. Core concepts of planning are listed in **Table 8-1**.

COMMUNITY RISK ASSESSMENT

The Superfund Amendments and Reauthorization Act, also called the Emergency Planning and Community Right-to-Know Act, requires states to create state-level emergency response commissions and communities to form local emergency planning committees to prepare emergency response plans for chemical accidents. Chemical facilities are required to provide local emergency management agencies and local fire departments with annual inventory reports and information about hazardous chemicals. The Environmental Protection Agency maintains a national database containing a Toxics Release Inventory that mandates certain facilities to annually report the quantities of their emissions of toxic chemicals (https://www.epa.gov/toxics-release-inventory-tri-program and http://www.epa.gov/triexplorer/maps.htm). This information includes the chemical name, an estimate of the maximum amount of the hazardous chemical present at the facility at any time during the preceding calendar year, an estimate of the average daily amount of the hazardous chemical present at the facility during the preceding calendar year, a brief description of the manner of storage of the hazardous chemical, and the location within the facility of the hazardous chemical. **Table 8-2** lists the most common chemicals stored in the United States. Appropriate emergency planning would require a laborious review of these databases at each local level and is not often done with any assessment of vulnerability to release. Rather than expect an accurate accounting of local risk, each ED must be knowledgeable in the general principles of hazardous materials decontamination. An awareness of the clinical manifestations of the most common stored chemicals and the availability of just-in-time information sheets can supplement risk assessment in the real world.[9]

TABLE 8-2 Most Common Chemicals Stored in the United States

- Anhydrous ammonia
- Chlorine
- Flammable mixtures
- Propane
- Sulfur dioxide

RECOGNITION OF AN EVENT

Most chemical releases are recognized early because many chemicals have early warning properties, including a noxious or unusual odor, or cause eye or upper airway irritation. Toxic exposures may produce rapid death at the site of the release. Sometimes, more subtle clues are present, such as large numbers of dead animals in an outdoor environment.

Most hazardous material events occur in fixed industrial facilities, and many industries have monitors for leaks of chemicals at nontoxic threshold levels that have no warning properties. For example, the semiconductor manufacturing industry has monitoring sensors for many toxic semiconductor gases, such as arsine, and these are triggered at very low levels.

IDENTIFICATION OF THE SUBSTANCES INVOLVED

The most common agents released in the United States are the pulmonary irritants ammonia and chlorine. There are numerous resources for the identification of which substances are involved in a spill by a transportation accident or industrial site (**Table 8-3**).

Few of these resources will identify the amount, and none will have treatment recommendations. **Although it may be intuitive that an exact identification of a substance is critical to the disaster or hazardous material process, in reality, it is more important to recognize the clinical syndromic manifestations of the victims.** It is not necessary at the scene to know which organophosphate is involved; it is more important to identify that the symptom complex of a cholinergic crisis is occurring. Similarly, early recognition of the pulmonary irritant effects of a highly water-soluble acid is usually more important than the concentration or the specific chemical identified. Ultimately, identification of the exact agent involved will need to be made. Hazardous materials teams have several techniques to identify substances and usually have a standard procedure to enter and evaluate a building where an odor is detected. The treating physician should evaluate all presumptive initial identifications of substances with some caution.[3] **If the symptoms of the patient do not fit the initial chemical identification, then the accuracy of the identification should be called into question.** Experience with chemical events has sometimes revealed that the initial determination of the chemical involved in the release is wrong.

ISOLATION AND SCENE CONTROL

Once a suspected chemical release occurs, the EMS response team must establish an incident command system; designation of hot, warm, and cold zones; and an isolation process. The immediate area where the suspected chemicals and victims of exposure are located is designated the hot zone. Only trained personnel in fully encapsulated protective gear should be allowed to enter. **Their primary role is rescue of victims by removing them from further exposure.** There is substantial risk of secondary contamination and, therefore, toxic effects for any rescuer or bystander who enters the hot zone without the proper protective gear.[10]

TABLE 8-3 Chemical Identification Aids

- U.S. Department of Transportation placards with Department of Transportation Emergency Response Guidebook
- Container National Fire Protection Association markings (NFPA 704 system)
- Chemical Abstracts Service (CAS) number
- Material Safety Data Sheets (MSDS)/Safety Data Sheets (SDS)
- Bill of lading
- Shipping documents
- CHEMical TRansportation Emergency Center (CHEMTREC): 1-800-424-9300

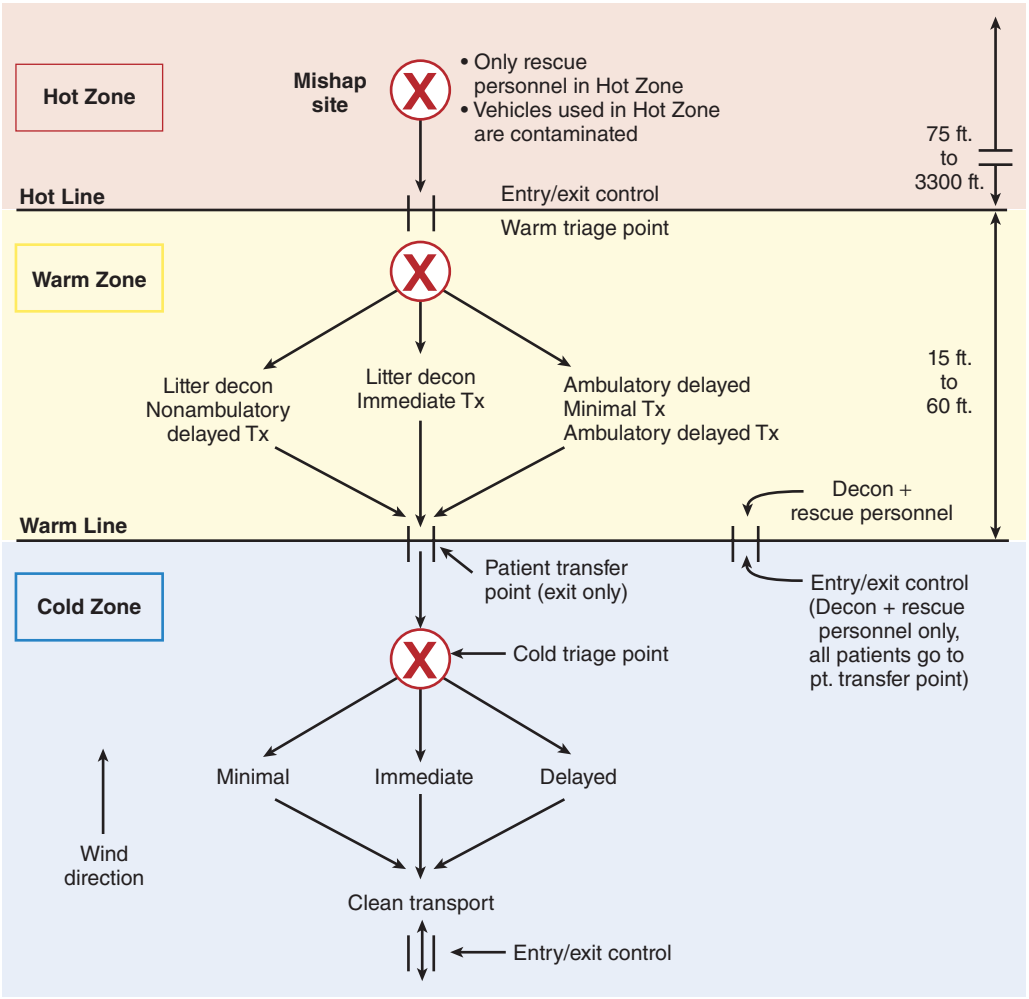

FIGURE 8-1. Control zones of a chemical event. decon = decontamination; pt. = patient; Tx = treatment.

A surrounding corridor through which each victim is washed off and decontaminated is created outside the hot zone and is designated the warm zone (**Figure 8-1**). Basic treatment, such as opening obstructed airways, may occur simultaneously with decontamination. Once appropriately decontaminated, the patient can be transferred to the cold zone where a lower level of protective equipment is necessary and a very low risk of secondary contamination exists. With less cumbersome protective gear, reevaluation in the cold zone, triage, and initiation of treatment can occur (**Figure 8-2**).

DECONTAMINATION IN THE WARM ZONE

Primary contamination is caused by direct contact with the released substance. Both people and the environment may suffer primary contamination. Secondary contamination is the inadvertent contamination of rescue personnel through contact with a contaminated patient or environment. **Secondary contamination can be avoided by proper use of personnel protective equipment and adequate decontamination of adherent solids and liquids.** Some rare substances are excreted in sweat and exhaled. Close unprotected contact with wet skin, mouth-to-mouth ventilation, or mouth-to-mask ventilation could be a source of secondary contamination. Equipment can become secondarily contaminated and may be required to be taken out of service until appropriate decontamination is done. This equipment contamination can be something as simple as a stethoscope or as large as a fire truck. Organophosphates can be excreted in sweat and may adhere to leather. Care must be taken with first responders who may not have protective gear; their shoes, belts, and holsters need to be discarded because they cannot be effectively decontaminated and could potentially pose a risk to coworkers or their families at home.

After the victim is removed from the hot zone to the warm zone, the critical management issue is adequate decontamination. The first and most effective method of decontamination is removing clothing, brushing off solid particles, and washing and toweling the face.[10-12] **Water is the universal decontamination agent.** Some guidelines recommend decontamination for nerve agents and vesicants with dilute household bleach, but there is little evidence of superiority over plain water, and bleach is likely to be unavailable in sufficient quantities at the scene. In general, 5 minutes of decontamination with warm water in the warm zone is adequate for most ambulatory patients.[12] Warm water is used to prevent shivering. If the patient has had direct contact with either liquid or vapor, he or she must be hosed off with water, paying critical attention to occult areas where fluids can hide, such as the hair, skin folds, axilla, groin, toes, and eyes. Patients with severe symptoms may require rapid decontamination and simultaneous treatment in the warm zone.

STABILIZATION AND TRIAGE IN THE COLD ZONE

Triage patients in the cold zone. Safety requires the cold zone to be upwind and, if needed, uphill from the hot zone. Once decontaminated, stabilize patients and evaluate for syndromic symptoms and the need for antidotes. **Primary stabilization includes the establishment of airway, applying oxygen, and administering bronchodilators for bronchospasm.** The establishment of IV lines in a disaster or multiple-casualty incidents requires judgment of the need for fluid resuscitation and critical IV medications. Give priority for IV line placement to patients requiring benzodiazepines for stopping seizure activity, treating cardiac dysrhythmias with usual advanced cardiac life support medications, and volume resuscitation for hypotension. Only a few antidotes may truly be

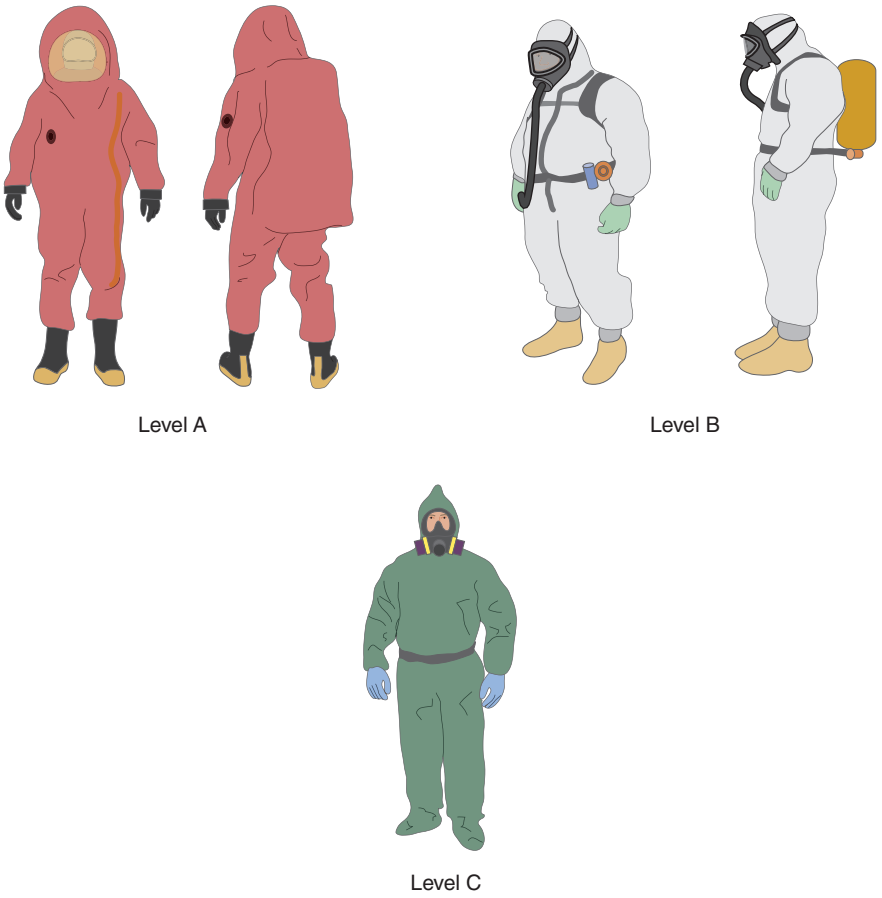

FIGURE 8-2. Personal protective equipment. Level A: Completely encapsulated protection. Requires use of self-contained breathing apparatus (SCBA) inside a chemical-resistant suit sealed at the face. Taped or suit-incorporated gloves and boots make this a completely sealed environment. Level B: Provides either an SCBA or a supplied air respirator and splash protection. The SCBA is worn outside the protective clothing and could expose this equipment to secondary contamination. There may be areas of the skin around the face mask of the SCBA where gas or vapor may penetrate. Level C: Either a gas-mask or air-purifying respirator and skin slash protection. This is the highest level of protection most hospital-based personnel should be trained to use.[11,12] (From U.S. Army Center for Health Promotion and Preventive Medicine Fact Sheet for Acute Exposure Guideline Levels. http://chppm-www.apgea.army.mil.)

beneficial if given early, such as the cyanide antidote, hydroxocobalamin, or atropine for muscarinic effects of organophosphate exposure. The need for additional antidotes in the prehospital phase is unusual unless prolonged on-scene triage is likely to occur.

ED HAZARDOUS MATERIAL RESPONSE

Despite the best planned and drilled chemical emergency response plan, most individuals will self-rescue and make their way in an uncoordinated fashion to a healthcare facility, so potentially contaminated patients will find their way by private transportation to the ED.[3] In the Tokyo subway release of sarin, 85% of patients who presented to St. Luke's Hospital, the facility closest to the scene, arrived under their own accord.[13-15] Therefore, EDs cannot rely solely on the prehospital system to completely decontaminate and triage every patient. Each facility must consider their physical space and patient flow, create a hospital-based plan for chemical emergencies, and have a policy and training that allow for the identification of chemically exposed patients. There should be an organized plan to perform decontamination and mobilize a system for decontamination of multiple patients, and the plan with deployment of equipment must be practiced on a regular basis. Regardless of the specific type of equipment, EDs should have the ability to decontaminate large numbers of patients external to the ED with warm water and proper personal protective equipment. ED decontamination is performed far from the release of the chemical, is not in a warm zone, and does not require fully encapsulated supplied air gear. However, ED personnel involved in the decontamination process should wear chemical-resistant covers for all body surfaces (e.g., chemical-resistant gloves, coveralls, and boots) and air-purifying respirator masks with filters that are designed for chemical threats.[10,12]

HIGH-RISK CHEMICALS

High-risk chemicals are detailed in **Table 8-4**.

TOXIC INHALANTS

Toxic inhalants tend to interfere with one or more of the four phases of oxygen delivery. Gases that interfere with oxygen uptake by displacement of oxygen from air are **simple asphyxiants**. Interruption of pulmonary diffusion may occur with some of the less soluble irritant agents such as phosgene. Agents that may interrupt oxygen transport include carbon monoxide and the methemoglobin-forming agents. Agents that interfere with oxygen utilization at the cellular level, such as cyanide, azide, and sulfides, produce severe lactic acidosis.

DISPLACEMENT OF OXYGEN FROM AIR: SIMPLE ASPHYXIANTS

Simple asphyxiants create an oxygen-poor environment by displacing oxygen from air. Many inert gases fall into this category, such as carbon dioxide, hydrogen, nitrogen, the noble gases (helium, neon, argon, krypton, xenon, radon), and simple hydrocarbons such as methane, butane, and propane. An occupant confined in a closed unventilated space may die as the concentration of an asphyxiant gas builds up silently. For example, deaths have been reported in persons transporting dry ice in the back seat of an automobile with the windows closed. As the solid carbon dioxide sublimes from solid to gas, oxygen concentration drops, and the

TABLE 8-4 High-Risk Chemicals

	Simple Asphyxiants	Irritant Gases or Droplets	Agents That Interrupt Delivery of Oxygen to Tissues	Agents That Interfere With Oxygen Utilization in Mitochondria	Nerve Agents	Incapacitating Agents	Vesicants
Mechanism	Displace oxygen from air	React with H_2O in upper respiratory tract	Alter hemoglobin so it cannot transport O_2; or produce methemoglobin	Bind to cytochrome oxidase	Organophosphates, which bind to acetylcholinesterase	Immobilize victims in a variety of ways	Blistering to eyes, skin, mucous membranes, lungs
Agents	CO, H, N, methane, butane, propane	Ammonia, chloramine, SO_2, HCl, HFl, chlorine, phosgene	CO, methylene chloride, nitrites, benzocaine, phenazopyridine	Cyanide, HS, phosphine, sodium azide, CO	GA, GB (sarin), GD, VX, GF	Mace, narcotic vapors, LSD, BZ	Sulfur mustard, phosgene oxime, lewisite
Treatment	Remove from source, give O_2	Remove from source, give O_2, monitor pulmonary status; for HFl, monitor serum Ca	O_2, methylene blue	Hydroxocobalamin	Identify DUMBELS syndrome; atropine for muscarinic effects; 2-PAM for nicotinic effects; benzodiazepines for seizures; ipratropium bromide (Atrovent®) for wheezing; never give succinylcholine	Individualize for agent	Irrigate with water, supportive care; mustard agents can cause marrow suppression

Abbreviations: BZ = 3-quinuclidinyl benzilate; DUMBELS = defecation, urination, miosis, bradycardia/bronchospasm/bronchorrhea, emesis, lacrimation, and salivation; LSD = lysergic acid diethylamide; 2-PAM = pralidoxime.

driver asphyxiates. When the concentration of any of these nonreactive gases increases, the fraction of inspired oxygen (FIO_2) decreases. At an FIO_2 of <16%, air hunger, tachypnea, and changes in level of consciousness occur. At FIO_2 <10%, loss of consciousness, seizures, or vomiting may occur. Treatment is restoration of a higher FIO_2 with supplemental oxygen and correction of the problem that led to the exposure.[16]

IRRITANT AGENTS THAT INTERRUPT PULMONARY DIFFUSION

Irritant agents are classified according to their water solubility as high-, intermediate-, or low-solubility agents. Despite being often referred to as "irritant gases," many of these agents are actually liquid droplets suspended in the air. **Highly water-soluble agents react with water in the upper respiratory tract and produce immediate irritation and discomfort. The most common agent released in chemical events is the highly soluble pulmonary irritant ammonia.** Ammonia, used as an industrial refrigerant, is prototypical of a highly water-soluble vapor. The gas chloramine is created accidentally when bleach and ammonia cleaners are mixed together. Other chemicals with high water solubility include sulfur dioxide and hydrogen chloride. Hydrogen fluoride, in addition to being a highly water-soluble irritant vapor, also reacts with intercellular calcium, causing life-threatening calcium depletion and cardiac dysrhythmias. Because of the immediate discomfort caused by these agents, they have excellent warning properties to those exposed. These agents cause significant eye irritation and edema, burning in the throat, and, at higher concentrations, constriction of the upper airway.[6,16] Treatment is removal from the source, providing supplemental humidified oxygen, and monitoring pulmonary status. Hydrogen fluoride exposure also requires close monitoring of the serum ionized calcium level and administration of supplemental calcium IV.

The only agents classified as intermediate in solubility are chlorine and hydrogen sulfide. Chlorine was the first gas used in chemical warfare in the trenches during the First World War.[16,17] Chlorine is used for chlorinating water in swimming pools and as a disinfectant, making **chlorine the second most common hazardous material released. Chlorine reacts with water in the upper airways to produce hydrochloric and hydrochlorous acids.** Symptoms include burning of the conjunctiva, throat, and the bronchial tree. Because of its acrid odor, chlorine has good warning properties. Higher concentrations can produce bronchospasm, lower pulmonary injury, and delayed pulmonary edema.

Phosgene, another chemical warfare agent used extensively in World War I, is prototypical of the minimally soluble agents.[16] At concentrations as low as 25 parts per million, it can be fatal after even brief exposures. It produces only minimal irritation to the eyes and upper airways and, in fact, has a pleasant odor of new-mown hay. However, it slowly hydrolyzes to hydrochloric acid and reacts in the alveoli to cause the delayed onset of severe acute lung injury. Treatment is directed at providing pulmonary monitoring, and the need for intubation and ventilator management is guided by clinical symptoms and radiographic findings of acute lung injury. Noncardiogenic pulmonary edema may require ventilation with positive end-expiratory pressure.

AGENTS THAT INTERRUPT OXYGEN TRANSPORT

Chemicals that react in the body to interrupt the delivery of oxygen do so by altering hemoglobin so that it is no longer capable of binding and transporting oxygen. Examples are carbon monoxide and methylene chloride, which is metabolized to carbon monoxide to generate carboxyhemoglobin. Certain other chemicals, including the nitrites, and some pharmaceuticals, such as benzocaine and phenazopyridine (Pyridium®), may cause the iron moiety in hemoglobin to convert from divalent Fe^{2+} to trivalent Fe^{3+}. Hemoglobin with trivalent iron is called *methemoglobin*, and it is incapable of binding and transporting oxygen.[18] Symptoms of either exposure include those consistent with declining oxygenation. Headache, nausea, and fatigue occur at low levels; however, in those with critical fixed coronary artery lesions, angina may occur. Both carboxyhemoglobin and methemoglobin can be measured by co-oximetry on an arterial blood gas analyzer. Pulse co-oximeters are also available that detect both carboxyhemoglobin and methemoglobin and may be used by either prehospital agencies or in hospitals. Both toxic hemoglobinopathies may be treated initially with high concentrations of oxygen. Methemoglobinemia may be treated with methylene blue, which acts as an electron donor and converts trivalent iron back to divalent iron.[18]

AGENTS THAT INTERFERE WITH CELLULAR OXYGEN UTILIZATION (CHEMICAL ASPHYXIANTS)

Chemical asphyxiants are agents that interfere with oxygen utilization at the electron transport chain in the mitochondria. **These agents include cyanide, hydrogen sulfide, phosphine, and sodium azide.**[19,20] Carbon

monoxide also interferes with oxygen utilization, in addition to its effect on oxygen delivery. By binding to cytochrome oxidase a_3, these agents disrupt aerobic metabolism and create intracellular acidosis. Cyanogens have been developed for use in chemical warfare, and nitriles used in industry release cyanide.[20,21] Symptoms include headache, alteration of consciousness, seizures, and severe acidosis. Hydroxocobalamin was approved for use in the United States in 2006 for cyanide toxicity and for smoke inhalation and is administered as a 5-gram infusion.[21]

NERVE AGENTS

During World War II, scientists in Germany discovered and manufactured three nerve agents, classified as GA (tabun), GB (sarin), and GD (soman). In 1952, chemists in Great Britain and America manufactured the agents VX and GF.[22,23] Although the preferred terminology for these chemicals is organic phosphorus compounds, they are still referred to as organophosphates in most publications. These agents were chosen as chemical warfare agents over existing insecticides because they had greater CNS activity and higher lethality than many of the organophosphates and carbamates used for insect control.[22-26] With the advent of the Cold War, organophosphate production accelerated, with both the United States and Soviet Union developing large stockpiles of these agents.[23] Occasional accidents occurred, sickening soldiers handling these agents, and one chemical release of VX in Skull Valley, Utah, killed 6000 sheep.[27,28] The Kuala Lumpur airport assassination in 2017 of Kim Jong-nam was carried out using VX.

In the 1980s, Iraq developed an extensive capability to manufacture and weaponize these agents and used both sarin and GF against both its own Kurdish people and the Iranians with whom it was engaged in a prolonged border war.[23] During the Syrian civil war in 2013, nerve agents were confirmed to be used as well, with over 800 civilian casualties.[29,30] Today, not only do many countries have the capability to manufacture these or similar agents, but terrorist groups have used them also. The Aum Shinrikyo cult used sarin in two separate attacks, one in Matsumoto in 1984, which killed seven people, and in a larger release in the Tokyo subway a year later that killed 12 people and sickened 5500 individuals.[13,15]

The organophosphate compounds inhibit several key enzymes by binding to them. They bind to acetylcholinesterase in a two-stage process. The first stage is reversible if the antidote pralidoxime (Protopam®) is given.[25] The second stage (aging process) makes the enzyme unavailable to be regenerated by pralidoxime. Acetylcholinesterase breaks down the neurotransmitter acetylcholine. With this enzyme inhibited, acetylcholine remains at its postsynaptic receptor sites, causing excessive cholinergic stimulation. Within the parasympathetic nervous system, there are cholinergic receptors at muscarinic sites, such as tear glands, sweat glands, bronchial secretion glands, and the sinoatrial and atrioventricular nodes of the heart. **Overstimulation of these leads to the "DUMBELS" syndrome, a mnemonic for the following symptom complex: *d*efecation, *u*rination, *m*iosis, *b*radycardia/*b*ronchospasm/*b*ronchorrhea, *e*mesis, *l*acrimation, and *s*alivation.**[6]

The second location within the peripheral nervous system where cholinergic transmission is affected is the neuromuscular junction, or nicotinic receptor. **Excess cholinergic stimulation here causes the progression from muscular fasciculation to profound muscular weakness to complete paralysis in a dose-dependent fashion.** Early in the course of an exposure, there can also be paradoxical hypertension and tachycardia, but these both subside as the bradycardia from muscarinic receptors predominates in the clinical presentation.

The last location of importance for cholinergic stimulation is the brain, where excessive stimulation produces coma and seizures. Many organophosphates cross the blood–brain barrier freely, and the nerve agents in particular have potent CNS effects.

The treatment strategy for nerve agents must counteract cholinergic excess at all three of these receptor sites. **Atropine counteracts only the muscarinic effects. Pralidoxime counteracts the nicotinic effects. Benzodiazepines treat seizures.**[23,25] The indication for each of these agents varies with the clinical manifestations. For the patient with exposure in low concentrations, such as with vapor releases, only eye findings may develop. Pinpoint pupils, frequently with local pain, may be treated with any of the anticholinergic eye drops, scopolamine, or homatropine. If pulmonary symptoms are isolated to bronchospasm in the reactive airway disease–prone patient, ipratropium bromide (Atrovent®) may be adequate. **Administer IV atropine to anyone experiencing hypersalivation, bronchial secretions, or bradycardia.**[24,25] Large doses of IV atropine, sometimes as much as 20 milligrams, may be needed.[25] This has been reported typically in ingestions but could be needed in liquid exposure to the nerve agents. High doses of atropine were not needed in the lower concentration exposures that occurred in the Tokyo subway incident.[13-15] **Titrate atropine administration to clearing of the excess secretions.** Pupil size and heart rate response are poor indicators of adequate atropinization in organophosphate exposure.

Pralidoxime reactivates the enzyme acetylcholinesterase at the neuromuscular junction. It can reactivate the enzyme only if the aging process has not occurred. How rapidly an agent ages varies from agent to agent; VX takes 24 hours, whereas soman takes only 5 to 8 minutes to age and create an irreversible bond.[25] The recommended initial dosage of pralidoxime is 1 to 2 grams IV slowly over 20 to 30 minutes.[23-25] **In a large event with multiple casualties, half this may be given to spread the antidote to the maximal number of patients.** Many patients with neuromuscular weakness will eventually require intubation and mechanical ventilation. Succinylcholine should not be used, if at all possible, because the same enzymes inhibited by the organophosphates metabolize it. **The onset of action of succinylcholine will be the same (usually <90 seconds), but the duration of action of this drug will be prolonged to several hours.**[31] Seizures, when they occur, may be refractory and, in combination with diaphragmatic paralysis, will lead to respiratory arrest. Use any of the IV benzodiazepines to treat seizures. Phenytoin and fosphenytoin are not effective for seizure control.

Patients with minor symptoms, such as eye findings only, may be observed for a 6- to 8-hour period and released if no further symptoms occur.[14] Admit any patient who received pralidoxime to an intensive care unit and give either a continuous infusion of pralidoxime at 500 milligrams/h or intermittent bolus dosages of 1 to 2 grams every 6 hours.[13,23]

INCAPACITATING AGENTS

The incapacitating agents are a diverse group of chemicals that immobilize victims.[12] Although riot control agents, such as Mace (Mace Security International, Horsham, PA) and tear gas, are not classically defined in this category, they can be considered incapacitating and are generally nonlethal. Narcotic vapors have also been used, such as the fentanyl derivatives used by Russia when they stormed the Moscow theater in 2002 where terrorists were holding hostages. The potent fentanyl derivatives, carfentanil and remifentanil, may have been mixed with a halothane-like anesthetic agent.[32] Despite the intent of this mixture to immobilize those inside the theater, lack of coordinated rescue efforts and late use of the antidote naloxone led to >100 casualties.

3-Quinuclidinyl benzilate is a long-acting potent anticholinergic agent. The U.S. Army developed it in the 1960s; exact information on how it was used is difficult to substantiate.[23] 3-Quinuclidinyl benzilate causes a severe and prolonged anticholinergic delirium similar to diphenhydramine. Other agents intended to immobilize victims have been experimented with, such as lysergic acid diethylamide, benzodiazepines, α_2-agonists, vomiting agents, and other exotic agents.

VESICANTS

Sulfur mustard was first deployed by Germany in 1917 near Ypres, Belgium, the site of their release of chlorine as a chemical weapon 2 years earlier.[33,34] Vesicant agents were used extensively as military weapons by both sides in World War I and in a variety of regional wars leading up to and during World War II (Ethiopia, Manchuria).[23] The largest number of casualties from sulfur mustard came with the explosion of the Liberty ship *John Harvey*, during World War II in Bari, Italy, where 617 sailors sustained burns from sulfur mustard.[35,36] During the 1980s, sulfur mustard was used in the Middle East (Iraq against Iran and the Kurds, Egypt against Yemen); 12 of these patients were transported to Germany, and their therapy was described in detail.[34] A small number of spills have occurred since in the United States at chemical weapons

TABLE 8-5 Indications of a Possible Biotoxin Exposure

- Occurrence of a disease or syndrome that rarely occurs naturally
- Multiple victims of a similar disease with no classic risk factors
- Epidemiology suggesting a point source or localized exposure
- Possible animal and human morbidity in the same area
- High mortality in an otherwise healthy population

storage facilities.[35] **Vesicants cause damage to eyes, skin, mucous membranes, and potentially the lungs if exposed to high concentrations.** Sulfur mustards [bis(2-chloroethyl) sulfide] make up the most common vesicants used, although the nitrogen mustards were also produced, but never used militarily.[33] Other vesicant agents are phosgene oxime, a solid that liquefies at 35°C (95°F); this agent does not cause blisters but produces severe skin erythema.[23,35] Lewisite, an arsenical compound that smells like geraniums and that was developed in 1918, too late for use in World War I and thus never deployed, is also included in this category.[35] **Both lewisite and phosgene oxime produce symptoms on immediate contact.[34-36] Sulfur mustard skin symptoms are delayed in onset for 4 to 8 hours, leading to blistering similar to second-degree burns within 2 to 18 hours of initial exposure.**[33] Ocular damage from vapor exposure to all these agents is common, leading to incapacitation of the victims exposed. Corneal vesicle formation and sloughing of epithelium occur. The primary goal of therapy is copious irrigation with water to dilute and remove the chemical, and then monitoring the patient with serial eye examinations, pulmonary monitoring, and careful attention to skin care. The mustard agents may produce a systemic toxicity, with marrow suppression as a delayed component presenting with a falling white blood cell count and increased risk of infection 3 to 5 days after exposure.[34]

BIOTOXINS

The biotoxins differ from biologic agents in that the toxins do not replicate in the body and a sufficient dose needed to cause disease must be delivered. These agents produce unusual symptoms, some with delayed onset. Clues to biotoxin exposure are presented in **Table 8-5**.

With many biotoxins, the lethal dose in 50% of exposed subjects is quite low (**Table 8-6**), allowing small amounts to potentially be made into a high-risk weaponized aerosol and dispersed intentionally.[23]

BOTULINUM TOXIN

Inhalational botulism has been described in humans only after an accidental laboratory exposure. It is estimated that the lethal dose in 50% of exposed subjects for inhalation botulism is 1 to 3 nanograms/kg.[23] Three days after performing an autopsy on a lab animal that died of botulism, three technicians developed tightness in the throat, difficulty swallowing, and symptoms characterized as a cold without a fever. They developed ocular paresis, rotatory nystagmus, dilated pupils, dysarthria, ataxia, and generalized weakness. All recovered within 2 weeks with antitoxin treatment.[23] Diagnosis requires the recognition of the clinical presentation, with early subtle cranial nerve palsies, typically presenting with difficulty swallowing, palsies of extraocular muscles, and trouble speaking.[37] **Treatment with antitoxin will prevent progression of the disease but will not reverse paralysis once it occurs. Administer the antitoxin based on clinical suspicion as early as possible; do not wait for the results of laboratory tests.** The heptavalent antitoxin against all subtypes of botulism is available by contacting the Centers for Disease Control and Prevention.[37] Give one vial of antitoxin IV in suspected cases of botulism. Supportive care, including mechanical ventilation, is frequently needed and may be required for 90 days or more in cases presenting with diaphragmatic paralysis before receiving the antitoxin.[37] Antibiotics only have a role in wound botulism and are not indicated in inhalational botulism.

TABLE 8-6 Lethality of Biotoxins

Agent	LD_{50} (micrograms/kg)
Botulinum toxin	0.001
Tetanus toxin	0.002
Staphylococcal enterotoxin B	0.02
Diphtheria toxin	0.10
Ciguatoxin	0.4
Ricin	3.0
Tetrodotoxin	8.0
Saxitoxin	10.0
Trichothecene toxin	1200

Abbreviation: LD_{50} = lethal dose in 50% of exposed subjects.

RICIN

Ricin toxin gained notoriety when it was used as the agent to assassinate Bulgarian activist Georgi Markov. At autopsy, a pellet containing ricin was removed from a small wound in the back of his leg. The pellet was fired from a specially designed umbrella into his leg while he waited at a London bus stop.[23] Ricin is a toxin derived from the castor bean, *Ricinus communis*.[38] Ricin is not toxic by ingestion and must either be injected or inhaled as an aerosolized powder to produce disease. Ricin is taken up by cells in many tissues and causes destruction of RNA, leading to cell death. With inhalation exposure, pulmonary symptoms occur after about an 8-hour postexposure delay. Inflammation, exudates, and pulmonary edema occur, producing a necrotizing pneumonitis. After parenteral administration, local pain occurs, followed in a few hours by weakness and flu-like symptoms. Fifteen to 24 hours later, nausea, vomiting, fever, and localized lymphadenopathy proximal to the injection site may occur. After 48 hours, a sepsis-like syndrome occurs with hypotension, leukocytosis, disseminated intravascular coagulation, and multiorgan system failure (involving the liver, kidneys, heart, lungs, and GI hemorrhage). In Georgi Markov's case, death occurred by deterioration to complete atrioventricular dissociation.[23] The differential diagnosis includes other causes of sepsis, but in the setting of an intentional attack, staphylococcal enterotoxin B must also be considered. Aggressive supportive care in an intensive care unit is warranted for all cases.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 9

Bioterrorism

Joe Suyama

INTRODUCTION AND EPIDEMIOLOGY

Bioterrorism is the release, or the threat of a release, of a biologic agent among a civilian population for the purpose of causing illness or death in humans, animals, or agriculture that results in the spread of fear and disruption of daily life. Such an occurrence is a low-probability but high-impact event. In the past century, the specter of bioterrorism was largely monitored by concerned government and military leaders, but in 2001, civilian emergency responders and healthcare institutions in the United States were thrust into the medical, psychological, and public health response to a real bioterrorist incident with very little training or preparation. In 2001, the U.S. Postal Service was used to deliver letters containing spores of *Bacillus anthracis*. The ensuing environmental contamination and health impact was widespread, resulting in

22 diagnosed cases of anthrax infections: 11 cases of inhalational and 11 cases of cutaneous anthrax.[1] Five patients died as a direct result of this intentional release of anthrax spores that was determined to have unnatural particle size characteristics.[2] Communities on the eastern seaboard of the United States were severely affected, with thousands of people receiving prophylaxis for anthrax.[3] Fear then spread across the nation, as concern increased for a wider delivery of anthrax. In this century, there is growing angst in the scientific and medical communities regarding the potential for biologic agents to be modified using now common gene-editing tools such as CRISPR, resulting in the creation of organisms with an even greater potential to cause harm and spread fear.[4]

Preparedness efforts against emerging or resurging infectious diseases, including the pandemic H1N1 influenza response in 2009 and the international Ebola campaign in 2014, have enhanced our individual and systemic ability to effectively care for patients with austere infectious diseases. However, the intentional aspect of bioterrorism and the specter of directed harm to the public and to healthcare providers creates a different playing field that may hinder detection and response efforts, create a greater psychological burden to the public and responders, and possibly confound the treatment of patients due to organism enhancements or atypical presentation of naturally occurring infections.[5]

Biological agents with the potential to be used for bioterrorism are classified into two groups: biologically produced toxins and infectious organisms. Biologic toxins generally have properties similar to chemical agents. The health impact does not depend upon an incubation period to manifest disease in humans. Infectious organisms are further subdivided into two categories: contagious (propagating person to person) and noncontagious. Contagious agents have additional ramifications, both for protection of the healthcare workforce as well as propagation of the disease beyond the initially exposed population. The contagious agents of greatest concern, such as smallpox, plague (pneumonic), and certain viral hemorrhagic fevers, are infectious from person-to-person through airborne or droplet transmission. Until proven otherwise, however, the primary response to a suspected biological agent release should consider the agent to be both highly infectious and contagious. This will allow for the highest level of environmental, administrative, and personal protection to be deployed to ensure the safety of first responder and the healthcare teams.

AGENTS OF CONCERN

The Federal Select Agent Program has compiled a list of agents that have been determined to have the "potential to pose a severe threat to the public, animal, or plant health."[6] Certain characteristics make individual organisms on this list particularly attractive as weapons for generating widespread fear, illness, or death among civilian populations. Thus, the Centers for Disease Control and Prevention has further characterized certain select agents based on four general criteria[7]:

1. Potential for public health impact
2. Delivery potential (an estimation of the ease for development and dissemination, including the potential for person-to-person transmission of infection)
3. Public perception (fear) of the agent
4. Special requirements for public health preparedness (diagnostic, logistic, etc.)

Using the above criteria, organisms can be broken down into three categories based on their overall potential to cause harm[8] (**Table 9-1; Figures 9-1 to 9-3**). **Class A agents have the most severe potential and include viruses and bacteria such as variola major (smallpox), *B. anthracis* (anthrax), and *Yersinia pestis* (plague). Class B agents are considered to have less potential for causing widespread illness and death or are more difficult to disseminate, and Class C agents are those that, as technology improves, could emerge as future threats.**

Many other common or emerging pathogens could be used to cause intentional injury and death. This chapter focuses on Class A agents, but applies also to a wide range of additional bacteria and viruses that could have a similar human impact if used in a nefarious manner (e.g., hanta virus). The intentional etiology of future outbreaks may be apparent only through real-time epidemiologic cohort evaluation. Thus, this chapter will also emphasize the need for public health, ED, and emergency management coordination, which is critical for:

1. Recognizing an event that is happening
2. Responding to the event by protecting healthcare assets from harm and managing illness
3. Scaling up internal and external resources (medical surge)
4. Integrating with other assets to meet the needs of the event

RECOGNITION

PUBLIC HEALTH SURVEILLANCE

Methods for potentially detecting a biologic event include the recognition of unusual epidemiologic phenomena, such as a high incidence of nonspecific illness, clusters or large numbers of rapidly fatal cases, or steep infection curves identified through public health surveillance systems.[9] For this reason, it is imperative to foster relationships with local public health entities through preparedness activities, drills, and real-time communication. Since 2001, preparedness efforts have included Joint Commission–mandated community-wide drills.[10] In addition, through Emergency Management coordination between public and private entities, front-line ED staff are now able to receive routine and urgent communication through robust public health–based Health Alert Network systems.[11]

From a surveillance perspective, information shared through networks between public health, ED, and emergency management coordinators, can include relevant data from:

1. Public health surveillance systems that can detect unusual patterns of signs, symptoms, or disease in the community
2. Sampling technologies (of which there are numerous types related to different jurisdictions and agencies) that detect the actual release of an agent of concern in the community

The surveillance systems currently in use are based on collecting and analyzing public health information and/or patient diagnostic information in specific communities. It is intuitive that this has been enhanced by the widespread adoption of electronic health records. Information is sought from many disparate sources, including hospitals, clinics, nursing homes, pharmacies, emergency medical service systems, independent laboratories, medical examiners, and general businesses (e.g., absenteeism rates). Information collected from EDs often is based on symptom complexes (syndromic surveillance).[12]

Other surveillance and risk assessment tools have been developed but must be further developed to improve their worth to the emergency medical and public health responders. Air sampling systems to detect inhalation agents have been implemented in some communities and for specific agencies, events, or facilities across the United States. The most well known is the BioWatch program,[13] which uses strategically placed sensors in specific communities. These sensors operate on the principle of drawing air samples across filters that are subsequently analyzed for some agents of concern.[14,15]

ED SCENARIOS

Based on historical cases, the following scenarios are the most likely ways in which a bioterrorist event would be detected clinically in the ED:

1. A patient presents with signs, symptoms, or real-time diagnostic results that obviously indicate a suspect disease process (e.g., smallpox rash).
2. A patient presents with protean symptoms, but an astute clinician establishes enough criteria through the history, physical exam, short-turnaround laboratory results, and public health corroborative information to designate the patient as a presumptive case until diagnostic confirmation can be accomplished (e.g., Ebola infection).

TABLE 9-1 Infectious Agents of Concern* as Defined by the Centers for Disease Control and Prevention (adapted from https://emergency.cdc.gov/bioterrorism/index.asp)

Biologic Agent	Disease Caused	Incubation Period	Signs and Symptoms
Class A agents			
Variola major	Smallpox (Figure 9-1)	7–19 d, usually 12 d	Initially fever, severe myalgias, delirium, prostration; followed within 2 d by papular rash on the face spreading to extremities (affecting palms and soles) and then to trunk (lesser extent than chickenpox); lesions progress at same rate, becoming vesicular and then pustular with subsequent scab formation
Bacillus anthracis	Cutaneous anthrax (Figure 9-2)	1–12 d, usually <5 d	Small painless or pruritic papule enlarging into eschar with surrounding vesicles and edema; sepsis possible, less common
	Oropharyngeal/GI anthrax	1–6 d	Sore throat, ulcers on base of tongue, marked unilateral neck swelling, dysphagia, abdominal pain, vomiting, GI bleeding progressing to sepsis if untreated; mesenteric adenopathy on CT
	Injection anthrax	Usually <5 d	Fever and chills, groups of small blisters or papules that may itch at the injection site, followed by a painless skin sore with black center and subsequent deep abscess formation
	Inhalational anthrax (Figure 9-3)	Usually <1 wk	First stage is nonspecific (fever, cough, headache, malaise, fatigue); second stage (severe dyspnea, chest pain, shock) with rapid progression to death within 24 h after respiratory symptoms develop; hemorrhagic mediastinitis with widened mediastinum on radiograph. Progression to CNS involvement can occur after systemic spread. If suspected as a diagnosis, consider threat of intentional release of anthrax spores.
Yersinia pestis	Bubonic plague	2–7 d	Initially fever, chills, painful swollen lymph node(s); node progresses to bubo (sometimes suppurative)
	Pneumonic plague	1–4 d	Fever, chills, cough, dyspnea, nausea, vomiting, abdominal pain; clinical condition consistent with gram-negative sepsis
	Primary septicemic plague	2–7 d	The clinical condition is consistent with gram-negative sepsis, disseminated intravascular coagulation (secondary septicemic plague may occur after bubo formation)
Clostridium botulinum	Foodborne botulism	12–36 h, as early as 2 h	GI symptoms followed by symmetric cranial neuropathies, blurred vision, progressing to descending paralysis and respiratory dysfunction
	Inhalational botulism†	6–72 h, usually 5 d	Symmetric cranial nerve palsies followed by descending paralysis; death occurs from upper airway obstruction and diaphragmatic respiratory failure
Francisella tularensis	Tularemia	1–21 d based on type of infection	Depends on route of exposure: all usually involve abrupt nonspecific febrile illness; inhalation exposure progressing to pleuropneumonitis; cutaneous exposure developing glandular or ulceroglandular lesions; ingestion developing oropharyngeal lesions/tonsillitis
Filoviruses and arenaviruses (Ebola virus)	Viral hemorrhagic fevers	2 d–3 wk, depending on virus	Initial nonspecific febrile illness, sometimes with rash; progresses to bloody vomiting, diarrhea, shock
Class B agents			
Coxiella burnetii	Q fever	2–3 wk	Fever, myalgias, headache, 30% develop pneumonia, rarely lethal (2%)
Brucella species	Brucellosis	2–4 wk	Fever, myalgias, back pain; CNS infections and endocarditis possible
Burkholderia mallei	Glanders	10–14 d	Local infection: ulcers, suppurative; pneumonia, pulmonic abscesses, sepsis possible
Burkholderia pseudomallei	Melioidosis	2 d to years reported	Local infection: nodule; pneumonia, pulmonic abscesses, sepsis
Alpha viruses (Venezuelan equine encephalitis, Eastern equine encephalitis, Western equine encephalitis)	Encephalitis	Variable	Fever, headache, aseptic meningitis, encephalitis, focal paralysis, seizures
Rickettsia prowazekii	Typhus fever	7–14 d	Fever, headache, rash
Toxins (ricin, *Staphylococcus*, enterotoxin B)	Toxic syndromes	—	—
Chlamydia psittaci	Psittacosis	6–19 d	Fever, headache, dry cough, pneumonia, endocarditis
Food safety threats (*Salmonella* species, *Escherichia coli* O157:H7)	—	—	—
Water safety threats (*Vibrio cholera, Cryptosporidium parvum*)	—	—	—
Class C threats			
Emerging threat agents (Nipah virus, hantavirus)	—	—	—

Note: Incubation periods should be interpreted with some caution. Data in some instances are limited and in others may be based on natural outbreaks. Intentional releases or engineered organisms could cause variations in expected disease parameters.

*Narayanan N, Lacy CR, Cruz JE, et al: Disaster preparedness: biological threats and treatment options. *Pharmacotherapy* 38: 217, 2018.

†Inhalational botulism may not be preceded by GI symptoms. Inhalational and foodborne botulisms are caused by botulinum toxin, not the bacteria itself.



FIGURE 9-1. Smallpox.

3. After evaluation, a patient is admitted or released, but not suspected as being a victim of bioterrorism. That patient's course then unexpectedly worsens, and diagnostic test results (blood cultures, immunoassays) or postmortem findings subsequently establish a diagnosis.
4. Multiple patients present over a defined period with similar symptoms or historical characteristics in the same geographical area. Further investigation, through public health or diagnostic testing, establishes concern for an intentional outbreak.

Scenario 3 is how the inhalational anthrax index case was diagnosed in Florida during the fall of 2001.[16] The initial inhalational anthrax infection in a postal worker was recognized as in scenario 2. Emergency physicians should have an operational knowledge of the biologic agents of concern or understand where to readily access this information. This knowledge should include basic pathologic principles for each agent, modes of dissemination and transmission, disease signs and symptoms, diagnostic testing, treatment (medications, immunizations, or prophylaxis), and infection control practices (Table 9-1 and **Table 9-2**).[17]

CLINICAL FEATURES

Unless the release of an agent is openly announced or the terrorist is caught in the process of delivering the agent, initial indications of an event may be subtle. **Early symptoms of most agents of concern are not readily distinguished from more common, less threatening infectious diseases.** Fever, myalgias, and malaise could be the initial presenting symptoms of a victim of bioterrorism (anthrax and others) or of influenza, parainfluenza, or many other common illnesses.[18] During the anthrax dissemination incident in 2001, several anthrax-infected postal workers were evaluated by physicians early in their illness. Their relatively nonspecific symptoms were



FIGURE 9-2. Ulcer and eschar of cutaneous anthrax.

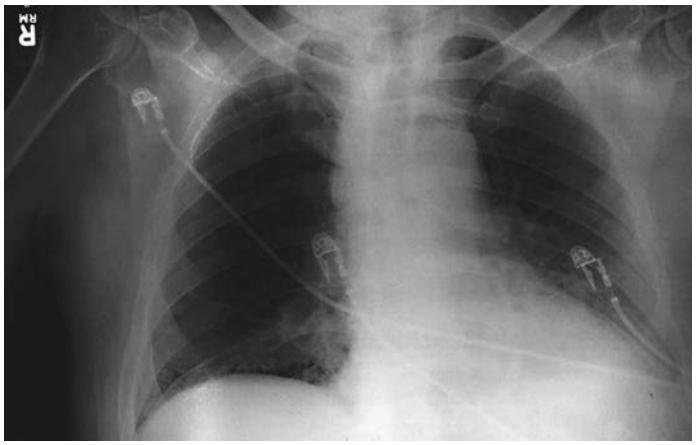

FIGURE 9-3. Chest radiograph with widened mediastinum characteristic of inhalational anthrax.

attributed to other causes, and they were discharged home without appropriate antibiotic therapy.[19] Two postal workers in this cohort died from inhalational anthrax. The similarity in early symptoms also creates another response issue: Once an attack becomes public, patients with any of those common symptoms or concerns without true risk or exposure may seek rapid evaluation in EDs, clinics, or private offices. Extreme patient volumes with diagnostic and triage challenges should be anticipated.

Real-time diagnostic studies to reliably confirm or exclude the presence of potential agents of concern are not available for all Centers for Disease Control and Prevention–designated agents; this actually does not differ from most common infectious processes. In some cases, specialized confirmatory testing by state or federal laboratories may be required,[20] and diagnostic methodologies continue to evolve. Therefore, clinicians should command sufficient knowledge to initiate available and appropriate test ordering, medical interventions, and reporting when they are suspicious of a patient's clinical presentation. Public health authorities with jurisdiction over the involved communities should be consulted early for current diagnostic recommendations and further testing (both patient and environmental).

Be prepared to appropriately respond to notification of a potential disease by another health or medical professional. Carefully query the reporting source for specific information before considering further actions. Questions to be asked include the methodology of the testing that produced the concern (specimen collection technique and the sensitivity and specificity of the test procedure) and the turnaround time of available confirmatory testing.

RESPONSE TO A BIOTERRORISM INCIDENT

An adequate response to a bioterrorist event of any magnitude requires effective coordination of many disparate health and medical entities beyond the ED. Although emergency physicians play a critical role in these types of events, many other essential functions must be addressed by individuals and organizations representing public health, mental health, law enforcement, emergency management, and others.

Every receiving facility and ED should have standard operating procedures to manage a bioterrorism threat or actual incident. These should be incorporated into the all-hazards emergency operations plan, with bioterrorism-specific procedures in an attached incident-specific annex. Initial actions taken by the emergency physician can be pivotal to the success of the hospital performance and the overall community response.

When bioterrorism is confirmed or suspected, prompt emergency operations plan activation should initiate the following:

1. Activation of processes and procedures (including preplanned surge capacity configuration) as appropriate and as listed in incident-specific annexes to the emergency operations plan.
2. Implementation of appropriate infection control procedures, which may extend to how patients are received in the ED, with provision of appropriate protective equipment and requisite training for healthcare workers.[21]

TABLE 9-2 Class A Agents: Treatment, Prophylaxis, and Vaccination* (adapted from https://emergency.cdc.gov/bioterrorism/index.asp)

Biologic Agent	Vaccination	Prophylaxis	Treatment
Variola major	Vaccinia vaccination: currently not recommended for general public use because of its association with limited numbers of deaths and complications in immunocompromised individuals and those with eczema; useful in preventing disease if given within 4 d of exposure	Vaccinia immune globulin: best given within 2–3 d of exposure; limited supplies are available, and it is available through the CDC as an IND; consider giving to those exposed who have contraindications to vaccine. Cidofovir and brincidofovir are available for postexposure prophylaxis.	Supportive. In vitro studies have shown cidofovir has antiviral properties against variola. Although not FDA approved, brincidofovir and tecovirimat have shown promise in animal models. Tecovirimat is only available through the CDC via the SNS.
Bacillus anthracis	Anthrax vaccination: Three-part series vaccination at 0, 2 wk, and 4 wk. Annual boosters may be required	Ciprofloxacin or doxycycline for 60 d is preferred, but alternatives exist. In addition, amoxicillin and penicillin V potassium for penicillin-susceptible strains; anthrax vaccine adsorbed BioThrax is now approved for both preexposure prophylaxis and postexposure prophylaxis.	Combination-drug IV regimen with protein synthesis inhibitors (e.g., linezolid) and bactericidal agents (e.g., ciprofloxacin and meropenem) for presumed or proven meningitis concurrent with illness. Two-drug regimen for illness when meningitis ruled out. Consider antitoxin administration for systemic anthrax infection (raxibacumab, obiltoxaximab, or anthrax immune globulin). Uncomplicated cutaneous infection can be treated using single-drug therapy.
Yersinia pestis	No current vaccine is available	Ciprofloxacin or doxycycline; alternative: chloramphenicol; prophylaxis for 10 d. Recommended for close contacts within 2 m.	Streptomycin or gentamicin preferred choices; alternatives: doxycycline, ciprofloxacin, chloramphenicol.
Clostridium botulinum	No current vaccine is available	Not applicable.	Heptavalent botulinum antitoxin is available (must coordinate with CDC) and should be provided within 24 h of symptom onset; antitoxin may preserve remaining neurologic function but does not reverse paralysis; may require prolonged, assisted mechanical ventilation and supportive care.
Francisella tularensis	No current vaccine is available	Ciprofloxacin or doxycycline for 14 d.	Streptomycin or gentamicin preferred choices; alternatives: doxycycline, ciprofloxacin, chloramphenicol.
Filoviruses (e.g., Ebola virus) and arenaviruses	Ebola trials with rVSV-ZEBOV	Not applicable.	Supportive therapy; ribavirin may have applicability in arenaviruses. Favipiravir, ZMapp, and brincidofovir are currently under investigation.

Note: Due to multiple ongoing efforts, some new or adjusted therapies may be available in the near future. Readers are encouraged to check peer-reviewed literature because this is a dynamic field. Specific recommendations exist for some agents and may entail use of therapies traditionally reserved for nonpregnant adults. In some cases, these entail use under Emergency Use Authorization, which is beyond the scope of this chapter.

Abbreviations: CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; IND = investigational new drug; rVSV-ZEBOV = recombinant vesicular stomatitis virus–Zaire Ebola virus; SNS = Strategic National Stockpile.

*Narayanan N, Lacy CR, Cruz JE, et al: Disaster preparedness: biological threats and treatment options. *Pharmacotherapy* 38: 217, 2018.

3. Notification of key departments, including hospital administration, infection control and infectious diseases, security, environmental services, and the hospital laboratory.
4. Information flow to all hospital personnel regarding the suspected agent, its characteristics (including potential for person-to-person transmission), and actions to protect the patients and staff.
5. Coordination of hospital media messages to internal and external entities (other hospitals, public health, emergency management) to avoid dissemination of conflicting information.
6. Notification to the local public health agency, with confirmation that law enforcement was notified by them.

The local public health agency has the responsibility to notify regional or state public health departments and the Centers for Disease Control and Prevention. With some agents and/or situations, the U.S. Department of Health and Human Services would notify the World Health Organization, because the potential impact could be global, and this reporting is mandatory under International Health Regulations administrated by the World Health Organization.[22]

INFECTION CONTROL AND DECONTAMINATION

Initiate infection control guidelines for the diagnosed or suspected agent (**Table 9-3**). This is essential to protect clinicians, hospital staff, visitors, and other patients. It is also critical in maintaining the ability of the

TABLE 9-3 Class A Agents: Guidelines for Personal Protective Equipment for Clinical Care in the ED (adapted from https://www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines.pdf)

- Unknown biological hazard: During a bioterrorism event, until the pathogen is understood and its transmission pattern defined, employ standard, contact, and airborne precautions.
- Anthrax: Cutaneous infection: standard precautions. However, contact precautions are recommended for uncontained copious drainage. Respiratory tract and GI tract infections: standard precautions.
- Ebola: If the epidemiology of transmission is consistent with natural disease, droplet precautions can be substituted for airborne precautions. Otherwise, consider Ebola a potential airborne pathogen during a bioterrorism event.
- Smallpox: Combined use of standard, contact, and airborne precautions for initial care and for up to 3–4 wk until scabs heal over. Airborne precautions are recommended when possible, but in the event of mass exposures, barrier precautions and containment within a designated area are paramount. When possible, only immune healthcare workers should care for smallpox patients.
- Pneumonic plague: Standard precautions. However, droplet precautions are needed until patients have received 48 h of antibiotic therapy.
- Botulinum toxin: Standard precaution.
- Tularemia: Standard precautions. Although person-to-person spread is rare, laboratory workers are at high risk of infection if exposed during specimen handling.

hospital to continue its regular medical commitment to the community. The Association for Professionals in Infection Control and Epidemiology has published guidelines for hospital infection control in response to a bioterrorism event.[23] Most agents of concern require only standard precautions (gloves, mucous membrane protection when potential for splashing exists, and a gown when the potential exists for soiling), but meticulous attention to detail is required. The more troubling agents are those that are contagious through airborne or droplet transmission. Disease containment for a case of pneumonic plague requires droplet protection and patient isolation. Smallpox requires airborne and contact precautions and, therefore, full patient isolation.

If a contagious disease is spreading within the community, procedures must be instituted to screen everyone entering the healthcare facility for active disease. This screening should ideally take place in an appropriately established "screening facility" before entering or immediately upon entry into the hospital building.

Administratively, isolation of large numbers of infectious patients may be necessary. Current hospital configurations often prohibit large-scale containment of patients in official isolation rooms, but entire wings could be adapted (using fire doors and manipulation of ventilation/air pressure within hospital smoke compartments) to serve as isolation wards. Plans to provide adequate separation from other, noninfected patients, to designate and train specific staff to care for these patients, and to furnish proper personal protective equipment should be developed in the emergency operations plan annex.

Another important initial consideration for ED personnel is whether patient decontamination is indicated. **Decontamination is a consideration only if a patient presents shortly after acute exposure to a substance (toxin or organism) suspected or confirmed as a biologic agent, in contrast to the presentation of the patient who has already developed symptoms of an infectious disease.** If a realistic concern exists, simply disrobing the patient and showering with soap and warm water should be adequate decontamination, but this must be accomplished in a controlled environment before patient entry into the healthcare facility. Clothing and personal belongings should be secured to assist with the public health and law enforcement investigations. Avoid using decontamination agents, such as diluted bleach, due to their potential for harm.

MANAGEMENT

Specific therapies for individual Class A agents are listed in Table 9-2. From a population perspective, morbidity and mortality are primarily minimized by preventing exposure and providing prophylaxis and immunization as appropriate. Treatment of infected and symptomatic patients may involve specific pharmaceuticals or general supportive care. Depending on the agent involved, prophylaxis or immunization of the hospital staff may be warranted. **Prophylaxis, immunization, or treatment may be indicated even without obvious signs of disease or definitive information about exposure.** This makes emergency physicians heavily reliant on the public health sector to stratify patient risk based on exposure and to provide evidence-based prophylaxis and treatment. With specific agents (e.g., anthrax), large community-based efforts have been developed with federal support related to the dispensing of postexposure prophylaxis.[24]

Preexposure prophylaxis for the general public is not recommended without a contemporaneous biological attack in the community.[25] A 2003 preexposure initiative to vaccinate healthcare workers and willing civilians against smallpox was discontinued after only a minority of the target cohort actually accepted vaccinations. The risk of potential life-threatening side effects, such as generalized vaccinia and potential cardiac sequelae, complicates the recommendations for smallpox vaccination in the absence of known circulating disease.[25]

When patients present to the ED who are potentially exposed but not physically ill (worried well), the patient interaction may require sophisticated explanations as to why the individual is or is not receiving a particular therapy. Preprinted instructions indicating category of risk stratification and why the patient was placed in that category can increase efficiency and be helpful for patients being screened and immediately released. These instructions should clearly indicate how the disease is transmitted, measures that prevent spread, and early signs and symptoms of disease with appropriate steps if they should occur. Establish appropriate follow-up with a public health agency. Note any change in the epidemiology of the incident (e.g., a new site tests positive for the agent) or if new information becomes available on the etiologic agent itself (e.g., antibiotic resistance patterns). Patients may need to be rapidly recontacted to change therapy. Entering all patients into a reliable long-term surveillance database should be a task for the public health agency, but hospitals and EDs could facilitate this process.

Pharmaceuticals recommended for some bioterrorism agents are normally not approved for children or for pregnant or lactating women. In many situations, these recommendations are relaxed when the risk of infection and its consequences exceeds the risks of the medication or vaccine. In addition, some unique treatments (e.g., ciprofloxacin for anthrax prophylaxis in children) have received U.S. Food and Drug Administration approval.

MEDICAL SURGE CAPACITY AND CAPABILITY

One critical issue in providing treatment to victims of bioterrorism is the development of adequate medical surge.[26] This issue is complicated by current healthcare industry practices that minimize staff, maintain just-in-time inventory, and limit hospital bed capacity. Medical surge capacity is developed by first maximizing individual healthcare facility capacity and capabilities (through an effective emergency operations plan) and then by coordinating regional resources to address and match patient needs to available resources. State and federal assistance should also be included in planning but not relied upon to assist initially. Federal agencies distinguish *medical surge capacity* from *surge capability*, which similarly can pose challenges.[26] *Medical surge capability* refers to the ability to manage patients requiring unusual or very specialized medical evaluation and care. It is intuitively obvious, for example, that even one patient presenting with signs and symptoms of smallpox would present highly unusual challenges affecting any hospital's continuity of operations.

INTEGRATION WITH PUBLIC HEALTH AGENCIES

In any suspected or confirmed case of bioterrorism, emergency physicians can expect to interface with multiple diverse agencies in an ongoing fashion, the most critical of which is the local public health agency. In most communities, public health epidemiologists are assigned the task of defining the size and scope of an incident, the at-risk population, and other incident parameters. This type of information becomes critical to hospitals for the evaluation and treatment of patients and in anticipating medical surge and continuity of operations requirements. **The most important assistance public health can provide to all clinicians is in the development of a community-wide patient evaluation and treatment protocol.** Evaluation and treatment protocols provide criteria to stratify individual and population risk for exposure and guide steps for specific evaluation and treatment. The protocol also should include recommended testing, treatment, patient instructions, tracking of at-risk cohorts, and public education. **A single evaluation and treatment protocol provides a uniform method across a community to evaluate patients presenting with possible exposure.** This is important not only for individual practitioners but also for the public. An iterative process is critical to deploy during these events, and it should be expected that these protocols will evolve as the event progresses. For example, during the 2001 anthrax incident, the initial epidemiologic investigation in the Washington, D.C., metropolitan area used nasal swabs in suspect exposures. This practice was misunderstood by some clinicians and the public as having individual diagnostic utility, when in fact it was merely an epidemiologic surveillance tool. Anxiety and confusion resulted when individuals received nasal swabbing at some healthcare locations and were (correctly) told it was not useful for diagnosis at other medical facilities. Because no early standardized protocol was developed by the public health system, hospitals implemented their own individual protocols to limit variation between clinicians practicing within individual hospitals. The resultant variability between institutions, however, caused great consternation for patients and providers.

Public health agencies should also provide a clear and concise case definition for the particular agent in question. **A case definition imparts definitive clinical and diagnostic criteria for an individual patient.** Within the case definition, criteria should be supplied that define "presumptive" or "suspect" cases for patients awaiting confirmatory testing. This kind of tool is simple and allows practitioners to officially designate victims as "confirmed" or "presumptive/suspected" for the target illness. Similarly delineated "exposure" categories are helpful in providing criteria for stratifying risk by designating "confirmed" or "presumptive" (suspected) exposure.

Another specific bioterrorism-related challenge to ED operations occurs when patients present after having been exposed to an unidentified substance (e.g., white powder), with circumstances that raise suspicion for terrorism (e.g., threatening letter, high-profile location, a "very important person"). The source substance may not have been properly evaluated or secured, and any recommended treatment necessarily will involve coordination with outside agencies, especially public health and law enforcement. If no environmental or agent testing was performed, one may attempt to obtain confirmatory studies through the local public health authorities if the substance remains available. Otherwise, the difficult task of stratifying patient exposure risk is necessary, using arguably nonspecific factors such as patient demographics and the specific characteristics of the incident (e.g., white powder found in a local business vs. a high-level federal official's office). Consult the public health authorities with jurisdiction over the involved communities early in the process, ideally by using a preplanned notification process and decision support tools. When testing has been performed by others, request specific information on the testing methodology. For example, anthrax environmental testing may be performed with a wide range of procedures, including immune-based assays, assays based on polymerase chain reaction, and confirmatory culture testing.[27] Older immune-based assays caused numerous instances of false-positive environmental tests, which were subsequently reported in the media and created serious public concern during and after the 2001 anthrax incident. Clearer understanding of the sensitivity and specificity of these tests could have assisted in interpretation and representation of results.[28]

INTEGRATION WITH OTHER RESPONSE ASSETS: MUTUAL AID AND THE STRATEGIC NATIONAL STOCKPILE

Just-in-time inventory practices may limit the amount of vaccine, antibiotics, other pharmaceuticals, and supplies available. Requests for assistance or for resources not available within an individual hospital should be coordinated through the hospital administration to other hospitals through mutual aid mechanisms, the local department of health, and the local emergency management agency. From there, requests may be transmitted to the regional, state, or federal levels.[26]

Without this coordination, supply management during a bioterrorism event will become an issue. For example, vendors for emergency back-up supplies and equipment are commonly shared by multiple institutions, each counting the vendor's back-up cache as their own. Having a community-wide mutual aid system between all the hospitals promotes appropriate sharing of critical supplies, equipment, and staff during an emergency. If prescriptions are being written for antibiotics, the local pharmacies' on-hand supply should be considered. Writing short-course prescriptions with procedures to provide completion of the medication regimen may be indicated until adequate supplies are available, but this strategy should be implemented on a region-wide basis to not place an individual practitioner's patients at increased risk. Integration of Strategic National Stockpile supplies into a medical community has specific requirements that are available for review through the Centers for Disease Control and Prevention and requires specific planning by the community emergency management and public health agencies.[26]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 10

Radiation Injuries

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INTRODUCTION

Radiation exposures encountered in the ED setting may either be accidental or intentional. Accidental exposures can occur during transport, storage, or working with radioactive materials or with errors in dosing radiotherapy. Most civilian incidents involve industrial exposures from sealed radiation sources.[1]

Historically, there have been multiple events that have resulted in radiation injuries. In August 1945, nuclear weapons were detonated over Hiroshima and Nagasaki, resulting in nearly 200,000 acute deaths and untold numbers of resulting injuries. The 2011 Fukushima Daiichi nuclear plant disaster involved about 1000 disaster-related deaths, although no deaths have yet been attributed to radiation injuries.[2] The largest reported civilian accidental exposure took place in 1987 after a radiosource was left at an abandoned radiotherapy institute in Goiania, Brazil. Due to the source's ability to glow in the dark, its contents were widely distributed, resulting in 112,000 individuals requiring evaluation, 249 contaminations, 20 individuals requiring hospital admissions, and four deaths.[3,4] In 2006, Alexander Litvenko, a defected former KGB agent, suffered a protracted gastrointestinal illness associated with leukopenia after meeting with former colleagues. His death was ruled a murder after elevated levels of polonium-210 were identified. Investigations into his murder revealed multiple rehearsals throughout England, leading to the contamination of multiple sites with potential exposures to 1693 local and international individuals.[5-7]

A potential intentional exposure involves the use of radiologic dispersal devices, or "dirty bombs," that combine radioactive materials with conventional explosives. They are meant to cause injuries to those nearby, while generating massive panic and hysteria, overwhelming the local resources, damaging the local economy, and causing prolonged clean-up efforts.[4]

FUNDAMENTALS OF RADIATION PHYSICS

Radiation energy includes the entire electromagnetic spectrum. Ionizing radiation contains enough energy to remove electrons from an atom, generating charged particles. Sources of ionizing radiation include alpha particles, beta particles, neutrons, and energy waves, including radiographs and gamma rays.[8] **Table 10-1** reviews the types of radiation.

ALPHA PARTICLES

Alpha particles are relatively large in size (two protons and two neutrons), resulting in a limited travel potential and thus preventing penetration of the skin. Shielding is easily accomplished with a piece of paper. Pathology only develops through inhalation, ingestion, or absorption. Its detection can be challenging since a special Geiger counter attachment is needed.[8]

BETA PARTICLES

Beta particles are much smaller (a single electron); thus, they have greater ability to travel and penetrate tissues. It is a significant hazard if internally deposited. It is a common exposure since most radioisotopes decay by beta radiation followed by gamma emission.[8]

POSITRONS

Positrons are positively charged beta particles emitted from atomic nuclei. They are the antiparticles to an electron, and interactions with electrons lead to the generation of highly energetic photons requiring shielding with lead, steel, or concrete. Positron sources are commonly used in medicine.[8]

TABLE 10-1 Types of Radiation

Type (Symbol)	Charge	Penetration	Shield	Hazard	Source
Alpha	+2	Few centimeters in air	Paper, keratin layer of skin	Internal contamination only; requires special detection devices	Heavy radioisotopes (e.g., plutonium, uranium, radon)
Beta	−1	~8 mm into skin	Clothing	External (skin) and internal contamination	Most radioisotopes decay by beta followed by gamma emission
Positron	+1	~8 mm into skin	Lead, steel, or concrete	Interacts with electrons and releases photons of energy	Medical tracers
Neutron	0	Variable	Material with high hydrogen content	Whole-body irradiation	Nuclear power plants, particle accelerators, weapons assembly plants
Gamma and radiograph	0	Several centimeters in tissue	Concrete, lead	Whole-body irradiation	Most radioisotopes decay by beta followed by gamma emission

NEUTRONS

Neutrons are uncharged particles that are able to generate radiation by altering the atomic nuclear proton-to-electron ratio. These particles are capable of traveling large distances; thus, shielding requires the use of helium, water, or paraffin. Exposures are rare and usually limited to nuclear fallout, research, industry, and weapons manufacturing.[8]

GAMMA RAYS AND RADIOGRAPHS

Gamma rays and radiographs are able to travel meters in the air and can penetrate centimeters into human tissue. Shielding materials must be very dense (concrete or lead). Individuals exposed to high doses are at risk of developing acute radiation syndrome.[8]

BIOLOGIC EFFECTS OF IONIZING RADIATION

Ionizing radiation leads to cellular effects at various levels of exposure. At high doses, ionizing radiation causes cell death, whereas at lower doses, it interrupts cellular reproduction through inhibition of mitosis, resulting in cellular injury with delayed onset of effects.[9] Rapidly dividing cells with short life spans are the cells most vulnerable to radiation injury, because they are quickly depleted and new cells are unable to replete the population.[4]

MEASURING RADIATION

There are many ways in which radiation can be measured: dose given, exposure received, absorbed dose, or activity generated. Each form of measurement generates its own unit, generating confusion between the units (**Table 10-2**).

TABLE 10-2 Radiation Units of Measure

Description	Conventional Units	SI Unit	Conversion
Activity	Curie	Becquerel	1 Bq = ~2.7×10^{11} Ci
Units of activity describe the amount of radioactivity present.			1 Ci = ~3.7×10^{10} Bq
Exposure	Roentgen	Coulomb per kilogram	1 R = 2.58×10^{4} cP/kg
Units of exposure measure the amount of radiographs or gamma radiation that produces a given number of ionizations in air.			
Absorbed dose	rad	Gray	1 rad = 0.01 Gy
Units of absorbed dose can be applied to any type of radiation and reflect the energy imparted to matter.			1 Gy = 100 rad
Dose equivalent	Roentgen equivalents man	Sievert	1 rem = 0.01 Sv
Units that provide a common scale of measure for the different types of radiation.			1 Sv = 100 rem

Abbreviation: SI = International System of Units.

RADIATION MONITORING EQUIPMENT

Commonly used equipment includes dosimeters and survey meters (**Table 10-3**). During radiation emergencies, both of these devices should be used. Staff should wear dosimeters due to their small size and ability to measure and record cumulative exposure doses. In contrast, rate meters record the amount of radiation in an area over a particular time course and are suited to monitor environmental contamination.

TABLE 10-3 Radiation Monitoring Equipment

Equipment Type	Device	Common Type of Measurement	Units Commonly Recorded
Dosimeter	Thermoluminescent dosimeter or film badge	Cumulative dose of beta, radiograph, and gamma	Roentgen equivalents man or sieverts
Dosimeter	Pocket dosimeter	Cumulative exposure to radiogrpah and gamma	Milliroentgen
Survey meter	Geiger-Müller tube	Low exposure rates of radiograph, gamma, and beta*	Counts per minute†
Survey meter	Ion chamber	Higher exposure rates of radiograph and gamma	Milliroentgen per hour

*With special instrument probes, alpha radiation can also be detected.

†2500 counts per minute equal approximately 1 mR/h.

ALLOWED ANNUAL DOSE OF RADIATION

Radiation exposures are an unavoidable hazard of living on our planet. The background radiation dose of individuals living in the United States is approximately 6.2 mSv (620 mrem).[10] The U.S. Nuclear Regulatory Commission as well as other international regulatory agencies have accepted an annual radiation dose limit for the general public at 1 mSv per year (100 mrem) over natural background radiation. See **Table 10-4** for selected approximate levels of radiation exposure.

LETHAL DOSE OF RADIATION

The $LD_{50/60}$ from exposure to ionizing radiation is defined as the dose of penetrating ionizing radiation that will result in the deaths (lethal dose)

TABLE 10-4 Selected Approximate Levels of Radiation Exposure

Natural background radiation	620 mrem/y (U.S. average)
Chest radiograph (effective dose)	10 mrem
Abdominal radiograph	120 mrem
Lumbar spine radiograph	70 mrem
CT head	200 mrem
CT chest	700 mrem
CT abdomen or pelvis	1000 mrem
Jet travel	1 mrem per 1000 miles traveled
Annual radiation dose limit (public)	100 mrem/y*
Occupational exposure limit	5000 mrem/y
Lethal dose in 50% of exposed subjects within 60 d (3.5–4.5 Gy)	350,000–450,000 mrem (350–450 rad†)

*Over natural background radiation.

†1 rem (dose equivalent) = 1 rad (absorbed dose or exposure).

TABLE 10-5 Acute Radiation Syndrome

Approximate Dose	Onset of Prodrome	Duration of Latent Phase	Manifest Illness
>2 Gy (200 rad)	Within 2 d	1–3 wk	Hematopoietic syndrome with pancytopenia, infection, and hemorrhage; survival possible
>6 Gy (600 rad)	Within hours	<1 wk	GI syndrome with dehydration, electrolyte abnormalities, GI bleeding, and fulminant enterocolitis; death likely
>20–30 Gy (2000–3000 rad)	Within minutes	None	Cardiovascular/CNS syndrome with refractory hypotension and circulatory collapse; fatal within 24–72 h

of 50% of the exposed population within 60 days without medical treatment. The most commonly cited human value is an $LD_{50/60}$ of approximately 3.5 to 4.5 Gy (350 to 450 rad).[8] The use of supportive medical therapy increases the value to 4.8 to 5.4 Gy (480 to 540 rad). During mass exposures, where resources may be limited, the $LD_{50/60}$ falls to approximately 3.4 Gy (340 rad). Stem cell transplantation and the use of hematopoietic growth factors theoretically increases the $LD_{50/60}$ to 11 Gy (1100 rad).[11]

CLINICAL EFFECTS OF RADIATION

LOCAL RADIATION INJURY

Most radiation accidents are due to local radiation injury from partial-body exposure. This irradiation rarely causes systemic manifestations; rather, a dose-dependent *cutaneous* involvement is seen. Typically, these injuries tend to be asymptomatic in the first week, although, there may be transient erythema (6 Gy), hyperesthesia, and itching. Within the second week, erythema progresses to hair loss (3 Gy). Skin tenderness, swelling, and pruritus occur in the third week after exposure. Within the fourth week, the wound will develop dry (10 to 15 Gy) or wet (20 to 50 Gy) desquamation and radionecrosis with ulceration (>50 Gy).[12]

These skin findings may be indistinguishable from thermal burns, except for the delayed onset of prolonged and severe pain. In exposures less than 50 Gy (5000 rad), these injuries develop over a longer time period than thermal burns. At doses greater than 50 Gy, the onset of pain will occur immediately, and wounds will be indistinguishable from thermal burns. Surgical intervention, such as resection and grafting, may be required.[12]

ACUTE RADIATION SYNDROME

Acute radiation syndrome occurs after a significant exposure (whole-body gamma dose exceeds 2 Gy) within a 24-hour time period (**Table 10-5**). It can also occur in the setting of neutron source exposure or internal contamination with alpha and/or beta radiation.

Acute radiation syndrome develops in four distinct phases: prodrome, latent phase, manifest-illness, and recovery.

The **prodrome** involves a transient autonomic nervous system response to the exposure characterized by nausea, vomiting, anorexia, and diarrhea accompanied by hypotension, pyrexia, diaphoresis, cephalgia, and fatigue. It is directly related to the dose received: high doses cause acute and severe symptoms, whereas lower doses lead to milder symptoms and prolonged onset.

The **latent phase** follows and involves a symptom-free interval the duration of which depends on the received dose, with larger doses resulting in a shorter duration. Doses less than 4 Gy are associated with a period that may last 1 to 3 weeks, whereas with doses greater than 15 Gy, this phase may last only a few hours.

The **manifest-illness** phase is subdivided into three dose-dependent syndromes that are hallmarked by the affected organ system. They are not independent of one another and may overlap in clinical manifestations.

Hematopoietic Syndrome With doses greater than 2 Gy, the hematopoietic system is the first affected organ system. The prodrome of this syndrome occurs within hours to a few days from the exposure, resolves within 48 hours, and is followed by a latent phase lasting 1 to 3 weeks.[12]

Radiation damages the bone marrow stem cells, resulting in destruction of the circulating hematopoietic cells (**Figure 10-1**). Lymphocytes are preferentially destroyed. The peripheral lymphocyte count is the most readily available marker to grade the extent of the injury. Other cells lines are also affected. Since granulocytes and platelets are markers of inflammation, their counts initially rise following exposure, but reach a nadir within 30 days of the injury. Morbidity and mortality are dependent on the resulting pancytopenia, immunosuppression, and hemorrhage. Aggressive medical management with blood products and growth factors may increase survival.[12]

GI Syndrome Doses greater than 6 Gy (>600 rad) are characterized by nausea, vomiting, and diarrhea within hours of exposure. A short latent phase lasting up to 1 week follows. A recrudescence of severe nausea, vomiting, diarrhea, and abdominal pain indicates the manifest illness phase that occurs after the failure to replenish the lost intestinal mucosa. Massive fluid and electrolyte shifts occur, as well as the translocation of enteric flora into the bloodstream, leading to the development of fulminant enterocolitis.[12]

Neurovascular Syndrome This occurs when doses exceed 12 Gy. It involves immediate persistent and intractable hypotension, prostration, nausea, vomiting, and explosive bloody diarrhea. CNS symptoms develop within hours and include seizures, lethargy, disorientation, ataxia, and tremors. The lymphocyte count quickly falls to near-zero levels, and death from circulatory collapse ensues within 24 to 48 hours.[12]

If reached, the final stage of acute radiation syndrome is **recovery**.

EMERGENCY RESPONSE PLANNING

Emergency response plans should involve multiple community-wide organizations, including hospitals, EDs, and public safety, public health, and emergency management officials. Every EMS system should have a prehospital plan for the evacuation of victims from a radiation disaster. Every hospital is required by The Joint Commission to have a written protocol detailing instructions for receiving and treating radiation victims. Hospitals should stage regular disaster drills and train personnel in decontamination procedures, use of personal protective equipment, and radiologic monitoring. Planning templates exist to assist hospitals in developing appropriate radiation emergency response plans.[13,14]

PREHOSPITAL EMERGENCY MEDICAL MANAGEMENT

Emergency responders should rapidly establish incident command in a situation involving radioactive materials. Personal protective equipment and respiratory protection should be used as the situation dictates. Care and transportation of seriously injured victims should not be delayed,

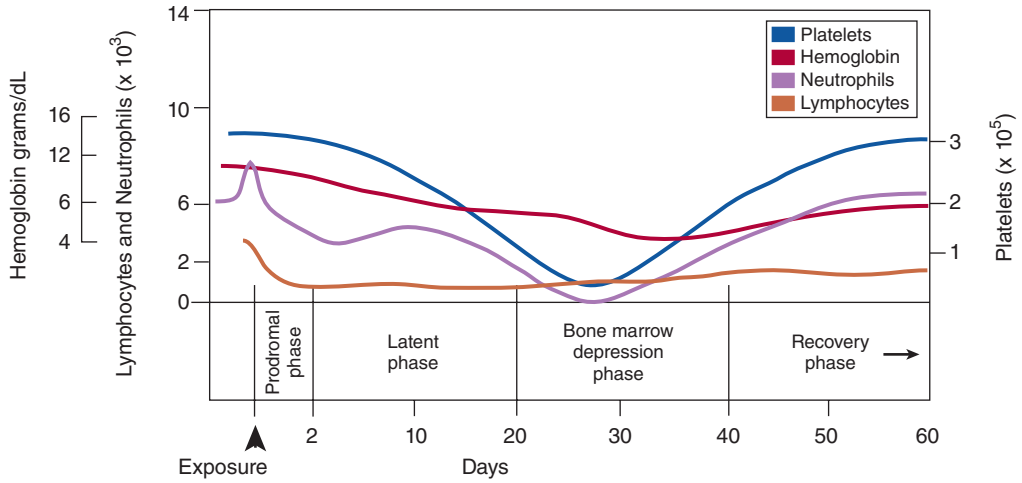

FIGURE 10-1. Typical hematologic course and clinical stages after sublethal (~3 Gy/300 rad) exposure to total-body irradiation.

even if the patient is contaminated. In medically stable patients, perform radiation monitoring and decontamination at the scene.

ED NOTIFICATION AND PREPARATION

First responders must communicate with hospitals prior to arrival to allow adequate preparation and provide incident information such as circumstances of the event, number of victims, traumatic injuries, type of radiologic insult, and identification of radioactive material. Extent of completed patient decontamination should also be relayed. The hospital disaster plan should include steps that need to be initiated by the ED upon notification to prepare for a radiologic event (**Table 10-6**).

The hospital protocol should instruct ED personnel on how to contact predetermined local radiation specialists and health physics professionals. These specialists may assist by monitoring radiation doses of personnel, surveying personnel and areas for contamination, directing contamination control and decontamination efforts, and disposing of contaminated wastes. If radiation monitors are not available, patients should undergo decontamination and then be surveyed for residual contamination when monitoring equipment is available.

TABLE 10-6 ED Preparation

Initiate hospital disaster plan

- Mobilize hospital radiation experts (radiation safety officer, nuclear medicine and radiation oncology experts and staff).
- Request dosimeters for staff and radiation monitoring and survey instruments.

Prepare the ED

- Establish an ad hoc triage area based on the location designated in the hospital disaster plan.
- Establish a "contaminated" area and "clean" area separated by a buffer zone using ropes, tape, and signs to designate areas.
- Remove contaminated outer garments when leaving contaminated area and have your body surveyed with a radiation meter prior to leaving the area.
- Cover floors with plastic or paper secured with heavy tape.
- Remove pregnant women, nonessential personnel, and nonessential equipment.
- Request extra gloves, other medical supplies, and extra large plastic bags for disposal.

Use standard precautions to protect staff

- Staff should wear a water-resistant gown, cap, and shoe covers to keep contaminants off skin and clothes.
- Double-glove with inner glove taped in place, changing the top pair after handling contaminated items and between patients.
- N95 masks, if available, are recommended, but surgical masks should be adequate.
- Survey hands and clothing at frequent intervals with a radiation meter.
- Dosimeters, if available, should be worn at the collar, under protective clothing.

TRIAGE PRINCIPLES

When there are multiple victims, field triage protocols will designate patients as minor, delayed, immediate, or deceased depending on physical trauma or burns. Do not alter triage principles based solely on radiation exposure. **Because radioactive contamination is never immediately life-threatening, do not delay treatment of life-threatening injuries for radiologic surveying.** Morbidity and mortality from ionizing radiation injuries increase dramatically in the face of physical trauma, thermal burns, and other significant medical conditions. In a mass-casualty event that could include blast injuries in addition to radiologic insult, resources may be limited and will require a coordinated approach to develop the best management plan.[15]

TREATMENT

Because most radiation injuries are not immediately life-threatening, there is usually time to determine whether the patient was irradiated, externally contaminated, or internally contaminated. Early treatment decisions are based on biologic dosimetry, including the signs and symptoms evident in the first 24 to 48 hours and corresponding laboratory test results.[14,16]

DECONTAMINATION OF EXTERNALLY CONTAMINATED PATIENTS

It is highly unlikely that the radioactivity from a contaminated patient would pose a significant risk to healthcare personnel. However, the goal of decontamination measures is to decrease total exposure of the patient and staff, by minimizing radiation exposure from a source external to the body to a level that is as low as reasonably achievable (**Table 10-7**). This is accomplished by minimizing time of exposure and the quantity of radioactive materials in the area, as well as maximizing distance and shielding from the source.[14,16]

ACUTE RADIATION SYNDROME

Patients exposed to ionizing radiation but who are not internally or externally contaminated pose no risk to healthcare workers, and decontamination is not needed. Immediate treatment of the irradiated patient is directed toward alleviating the symptoms of the prodromal phase. Pain can be managed with acetaminophen and opioids. Because the patient may be at risk for significant GI bleeding if the exposure dose is more than 5 to 6 Gy, avoid using NSAIDs.[8] Administer antiemetics for nausea and vomiting. Ondansetron or other 5-hydroxytryptamine-3 antagonists are effective.[17] Use antidiarrheal agents such as loperamide as needed. Management of GI syndrome also includes use of a fluoroquinolone for 2 to 4 days after an acute exposure.[14]

Perform a targeted history and physical exam. Note time of onset of all symptoms, especially vomiting and diarrhea, which are important in biologic dosimetry. Observe for abnormal vital signs suggestive of acute

TABLE 10-7 Steps of Patient Decontamination

Assess external contamination

- Contact radiation safety officer.
- Assess contamination with radiation survey meter (Geiger counter).
- Evaluate for radioactive shrapnel. Easily accessible pieces should be removed with a forceps and placed in a lead container.
- Document contamination pattern on a body diagram.
- Swab each nostril separately to estimate level of internal contamination of the lungs.

Decontaminate whole body

- Carefully cut and roll clothing away from the face to contain contamination.
- Double bag clothing and label as hazardous waste.
- Wash wounds first with saline or water.
- If facial contamination is present, rinse as appropriate.
- Gently cleanse intact skin and avoid scrubbing.
- Repeat patient scan with radiation survey meter. Repeat washing until radiation is <2 times background. Avoid scrubbing.
- Cover wounds with waterproof dressing.

radiation syndrome, including fever, hypotension, tachycardia, and tachypnea. Monitor for impaired level of consciousness, ataxia, motor or sensory deficits, reflex abnormalities or papilledema, abdominal tenderness, and GI bleeding.

Complete laboratory testing as soon as possible. Biologic dosimetry uses laboratory analyses (e.g., rate and nadir of lymphocyte depletion) and clinical signs to estimate absorbed dose. Cytogenetic analysis for chromosomal aberrations (dicentrics) is the gold standard for biodosimetry. Contact the Radiation Emergency Assistance Center/Training Site for assistance with obtaining chromosomal testing.[14]

Obtain a baseline CBC with differential and absolute lymphocyte count in the ED and check a CBC every 6 hours for 24 to 48 hours, monitoring for lymphocyte depletion. Also obtain a baseline serum amylase and C-reactive protein, because dose-dependent increases are expected after 24 hours in a significant exposure. If vomiting and diarrhea occur in the first 2 to 3 hours (dose estimated to >2 Gy), consider the need for human leukocyte antigen typing in anticipation of pancytopenia requiring further management. This could include administration of blood products, cytokines, colony-stimulating factors, bone marrow cells, or stem cell transplant.[18] Consultation with a hematologist/oncologist is recommended.

Management of acute radiation syndrome is focused mainly on the support and recovery of the hematologic system, including bridging cytopenic gaps and managing subsequent infections. Patients may require prophylactic antibiotics, antifungals, and antivirals during their course or appropriate monotherapy for documented infections. Consultation of an infectious disease specialist is advised for management of radiation-induced neutropenia.[14]

Monitor patients with large exposures who survive the acute phase for severe infectious and metabolic complications. Treat multiorgan failure from a large radiation exposure with standard supportive measures.[19] Other management issues include maintaining strict environmental control and neutropenic precautions, minimizing invasive procedures, and early surgery and wound closure.

LOCAL RADIATION INJURY

Management of local radiation injury focuses on analgesia, meticulous wound care, and infection control. Analgesia is important in the early management of cutaneous radiation injury. Cutaneous radiation injury differs from thermal burns in that the cutaneous injury continues to evolve and may not be visible to the naked eye. The primary goal of treatment is interruption of radiation-induced inflammation in the dermis. Perform traditional burn care, including burn dressings, surgical debridement, and skin grafting, when indicated. Consider applying topical steroids such as betamethasone to control local inflammation, giving vitamin A, C, and E supplementation, and administering pentoxifylline to decrease blood viscosity and increase blood flow.[14,19] Silver-based creams such as sulfadiazine can be used. Hyperbaric oxygen may be considered. Systemic steroids are not recommended.[19] Although inpatient treatment may not always be required, close follow-up is essential given the potential for ongoing evolution of cutaneous injury.

TABLE 10-8 Specimens for Medical Assessment

Specimen/Type of Analysis	Reason	Mechanism
Suspected radiation exposure		
Check a CBC every 6 h for 24–48 h	Establish baseline and assess lymphocyte depletion as an early predictor of dose.	Venipuncture
Serum amylase and CRP, repeat daily for 3 d	Parotid glands are sensitive to radiation; amylase will rise if exposed to >0.5 Gy.	Venipuncture
Blood: chromosomal analysis (dicentrics)	Gold standard for estimating dose.	Venipuncture. Call REAC/TS for assistance.
Urine: routine urinalysis	Establish baseline kidney function, especially if internal contamination is suspected.	Clean catch
Suspected external contamination		
Swabs of body orifices and samples from dressings/wounds	Assess internal contamination and identify radionuclide.	Use separate saline or water-moistened swabs to wipe the inside of each nostril, ear, and mouth.
Suspected internal contamination		
Urine bioassay: 24-h specimen; repeat for 4 d	Radionuclide identification	Standard specimen containers
Consider feces bioassay in consult with radiation expert		

Abbreviations: CRP = C-reactive protein; REAC/TS = Radiation Emergency Assistance Center/Training Site.

INTERNALLY CONTAMINATED PATIENTS

Internal contamination generally does not produce early symptoms but should be considered if persistently high radiation survey readings are noted and with all nose or mouth contamination cases. Obtain a 24-hour urine collection for possible radionuclide identification. Collect other specimens depending on exposure with or without contamination (**Table 10-8**). Consult radiation experts for treatment with cathartics, activated charcoal, gastric lavage, and radionuclide-specific decorporation agents (**Table 10-9**). Duration of therapy is based on dose estimations from radiochemical measurements of urine and fecal samples.

TABLE 10-9 Internal Contamination Treatment

Radionuclide	Ionizing Radiation	Treatment	Mechanism of Action	Usual Administration
Iodine (I-131)	β, γ	Potassium iodide	Block thyroid uptake	130 milligrams PO for adults
Plutonium (Pu-239)	α	Ca-DTPA or Zn-DTPA	Chelation	1 gram in 250 mL NS or 5% dextrose in water over 60 min
Tritium (H-3)	β	Water	Dilution	Oral: 3–4 L a day for 2 wk
Cesium (Cs-137)	β, γ	Prussian blue	Decrease GI uptake	1 gram in 100–200 mL water three times a day for several days
Uranium (U-235)	α	Bicarbonate	Urine alkalinization	2 ampules in 1 L NS at 125 mL/h

Abbreviations: DTPA = diethylenetriamine pentaacetate; NS = normal saline.

PRENATAL EXPOSURES

Fetal sensitivity to radiation depends on a number of factors, including radiation dose and gestational age. The radiation dose to the fetus may not be the same as the dose to the mother, because the fetus is shielded in part by the uterus and surrounding tissues. External exposure of alpha and beta particles is unlikely to reach the fetus, but gamma and radiographs directed toward a pregnant woman's abdomen could harm the fetus. In addition, internal contamination could expose the fetus to higher radiation, as the radioactive material could accumulate in the bladder of the pregnant woman.

The health effects of radiation on the fetus are dependent on the gestational age. Before about 2 weeks of gestation, there is an all-or-none phenomenon, and if the exposure does not result in death of the embryo, no observable effects are expected. An exposure of greater than 0.1 Gy is expected to be lethal, resulting in resorption of the conceptus. From 2 to 8 weeks, organogenesis occurs. During this time, the embryo is at risk for congenital malformations and growth retardation. In cases of substantial exposures, there is a significant risk of major malformations of the neurologic and motor systems. After 8 weeks of gestation, exposures are associated with an increased risk of mental retardation and miscarriage. Throughout gestation, an exposure of less than 0.05 Gy would not be expected to produce an increased risk of noncancer health effects.[20] Consult with radiation medicine physicians regarding fetal dose estimation and risk assessment counseling for the expecting parents.[21] For additional discussion, see Chapter 99, "Comorbid Disorders in Pregnancy."

SOURCES OF ASSISTANCE

Two organizations provide medical advice for the treatment of radiation casualties. The Radiation Emergency Assistance Center/Training Site, sponsored by the Department of Energy and managed by the Oak Ridge Institute for Science and Education, provides training programs, consultation assistance, and treatment capabilities, and can dispatch an emergency response team of health professionals to assist at an accident site. After initial treatment and decontamination actions are complete, REAC/TS may also accept severely contaminated or irradiated patients for transfer to its facilities for more definitive care.

Radiation Emergency Assistance Center/Training Site (REAC/TS)
Oak Ridge Institute for Science and Education
P.O. Box 117, MS 39, Oak Ridge, TN 37831-0117
865-576-3131 (daytime phone; ask for REAC/TS)
865-576-1005 (24-hour emergency number)

Another organization available for consultation is the Medical Radiobiology Advisory Team, sponsored by the Department of Defense and managed by the Armed Forces Radiobiology Research Institute.

Medical Radiobiology Advisory Team
Armed Forces Radiobiology Research Institute
National Naval Medical Center
8901 Wisconsin Avenue, Building 42
Bethesda, MD 20889-5603
301-295-0316
301-295-0530 (24-hour emergency number)

The U.S. Department of Health and Human Services sponsors the Radiation Emergency Medical Management Guidance on Diagnosis and Treatment for Health Care Providers. Information can be found at http://www.remm.nlm.gov.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 3

Resuscitation

CHAPTER 11

Sudden Cardiac Death

Joseph P. Ornato

INTRODUCTION AND EPIDEMIOLOGY

This chapter focuses on the epidemiology and pathophysiology of sudden cardiac death in adults and strategies for prevention and treatment. See Chapters 18 ("Cardiac Rhythm Arrhythmias"), 22 ("Basic Cardiopulmonary Resuscitation"), 23 ("Defibrillation and Electrical Cardioversion"), and 24 ("Cardiac Resuscitation") for detailed discussion of resuscitation pharmacotherapy.

Sudden, unexpected, out-of-hospital cardiac arrest occurs in approximately 341,397 adult Americans each year.[1] Estimated national survival of EMS-treated out-of-hospital cardiac arrest cases is 10.8%, yielding an estimated overall out-of-hospital cardiac arrest survival rate of 5.4% (EMS-treated plus deceased-on-EMS-arrival cases).[1] There is substantial variability in the odds for survival across various geographic locations.[2]

Most episodes of sudden cardiac death occur in the home, although victims who experience cardiac arrest in a public place have a much better chance of survival.[3] The initial recorded cardiac arrest rhythm is more likely to be ventricular fibrillation when cardiac arrest occurs in a public location rather than in the home, likely because patients who experience cardiac arrest in the home are typically older and more likely to have one or more chronic diseases that limit or exclude participation in activities outside the home.[3] Sudden cardiac death is 30% to 80% higher among residents in the lowest compared with the highest socioeconomic quartile.[4] This association is likely due to lifestyle and healthcare disparity issues.

There is a circadian pattern of sudden cardiac death and acute myocardial infarction,[5,6] and both are most likely to occur within the first few hours after awakening from sleep, when there is increased sympathetic stimulation. β-Blockade provides some protection from sudden cardiac death, particularly in patients with known coronary artery disease who have had myocardial infarction and have a low ejection fraction.[7]

Prevalence of sudden cardiac death in adults is greatest in the age group older than 45 to 50 years, with 60% occurring in males.[4] There are multiple known factors contributing to the likelihood of sudden cardiac death (**Table 11-1**).

Coronary artery disease (which is often undiagnosed before the event) is the major cause of sudden cardiac death in adults and is present in 80% of cases, followed by cardiomyopathy (10% to 15%) and other miscellaneous conditions (e.g., hereditary channelopathies, valvular disease, congenital anomalies), which account for most of the remaining 5% to 10% of cases.[4]

PATHOPHYSIOLOGY

CORONARY ARTERY DISEASE

Coronary atherosclerosis is present on autopsy in 80% of sudden cardiac death victims.[8] Coronary artery disease is also found in 70% to 80% of cardiac arrest victims who survive and undergo coronary angiography.[9-12] Approximately one third have evidence of acute plaque rupture in areas of long-segment coronary stenosis.[10,11] A documented initial cardiac arrest rhythm of ventricular fibrillation (or shockable rhythm if an automated external defibrillator was applied) suggests that an acute coronary syndrome is the cause, since ventricular fibrillation is noted in the majority of cases in which a coronary occlusion is found on angiography.[9-12] However, ventricular fibrillation is present in only 23% of all cardiac arrests.[13]

SEVERE LEFT VENTRICULAR DYSFUNCTION

Severe left ventricular dysfunction with a reduced ejection fraction is currently the best available predictor of sudden death risk.[4] Patients with an ejection fraction ≤35% are the primary candidates for an implantable cardioverter-defibrillator. However, almost half of sudden deaths occur in individuals with normal left ventricular function.

CARDIOMYOPATHY

Cardiomyopathy with reduced left ventricular function, regardless of cause or presence of decompensated heart failure, is another predictor of sudden cardiac death. Dilated ventricles promote dispersion of ventricular depolarization and/or repolarization, allowing "islands" of ventricular tissue to depolarize and repolarize at different rates. The lack of homogeneity in electrical activation and recovery fosters the development of circus movement reentry, which can initiate and sustain ventricular tachyarrhythmias. Myocardial ischemia and/or infarction can also transiently diminish the homogeneity of left ventricular depolarization and repolarization. Left ventricular hypertrophy (often a result of hypertension and/or valvular heart disease) or conduction disturbances (left or right bundle branch block or a nonspecific intraventricular conduction disturbance) can create similar functional disturbances.

In-hospital cardiac arrest patients with heart failure are more likely to have ventricular fibrillation as the initial documented cardiac arrest rhythm compared with non–heart failure patients.[14] New York Heart Association functional class II (symptoms with moderate exertion) and III (symptoms with mild exertion) patients are at higher risk of sudden cardiac death than death from pump failure, whereas class IV patients (symptoms at rest) are more likely to die of pump failure than sudden cardiac death.[5,15]

Hypertrophic cardiomyopathy is characterized by unexplained left ventricular hypertrophy associated with nondilated ventricular chambers.[16] The disorder can cluster in families, and the risk of sudden cardiac death increases at a rate of approximately 1% per year.[16] **Hypertrophic cardiomyopathy is the most common cardiovascular cause of sudden cardiac death in young athletes, accounting for one third of such events,** and its presence disqualifies affected individuals from competitive sports.[16] Implantable cardioverter-defibrillator placement is recommended for individuals with prior documented cardiac arrest; ventricular fibrillation; hemodynamically significant or nonsustained ventricular tachycardia; a first-degree relative who has had sudden cardiac death; one or more recent, unexplained episodes of **syncope**; a maximum left ventricular wall thickness ≥30 mm; or an abnormal blood pressure response to exercise in the presence of other sudden death risk factors or modifiers; and in high-risk children with unexplained syncope, massive left ventricular hypertrophy, or family history of sudden cardiac death.[16]

Arrhythmogenic right ventricular cardiomyopathy is a hereditary form of cardiac muscle disease that is characterized by right-sided heart failure, ventricular arrhythmias of right ventricular origin (i.e., ventricular tachycardia with a left bundle branch block morphology), syncope, and sudden cardiac death.[17,18] **The ECG typically shows**

TABLE 11-1 Known Factors Contributing to the Likelihood of Sudden Cardiac Death

Cardiovascular pathology
- Coronary artery disease
- Severe left ventricular dysfunction
- Cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Arrhythmogenic right ventricular cardiomyopathy
- Congenital heart disease, especially coronary artery anomalies
- Valvular heart disease
- Cardiac pacemaker and conducting system disease

Hereditary channelopathies
- Brugada syndrome
- Early repolarization syndrome (ERS)
- Long QT syndrome (LQTS)
- Short QT syndrome (SQTS)
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Risk factors and triggers
- Long-term risk factor management
  - Hypertension
  - Hyperlipidemia
  - Smoking
  - Diabetes mellitus
  - Socioeconomic status
- Unstable atherosclerotic plaque
  - Psychological stress
  - Physical activity

T-wave inversion in the right precordial leads (V_{1-3}). Severe right heart failure develops in the majority of cases. Patients suspected of having this disorder should be referred for cardiology evaluation. Implantable cardioverter-defibrillator placement is often the treatment of choice since β-blockers and other antiarrhythmics do not usually prevent symptomatic ventricular arrhythmias in these patients.[17]

CONGENITAL HEART DISEASE

Congenital heart disease occurs in approximately 0.8% of all live births.[19] Because many children with congenital heart disease survive to adulthood as a result of improvements in cardiac surgery, sudden cardiac death is a frequent cause of later morbidity and mortality. Congenital heart defects commonly associated with sudden cardiac death in children and adults are listed in **Table 11-2**.[19]

The most frequent coronary artery anomaly associated with sudden cardiac death is anomalous origin of the left coronary artery from the pulmonary artery syndrome, which results in the left coronary artery traversing between the aorta and main pulmonary artery. This disorder is being diagnosed more frequently in adults by cardiac CT and MRI.[20] Ischemic symptoms, ventricular arrhythmias, and sudden death can be triggered during exercise as a result of increasing venous return, which dilates the main pulmonary artery and compresses the anomalous coronary artery in the space between the aorta and main pulmonary artery. Treatment is surgical correction.

TABLE 11-2 Congenital Heart Defects Commonly Associated with Sudden Cardiac Death[19]
- Coronary artery anomalies (anomalous left coronary artery from the pulmonary artery [ALCAPA] syndrome)
- Aortic stenosis
- Aortic coarctation
- Tetralogy of Fallot
- Transposition of the great arteries
- Ebstein's anomaly
- Single ventricle

The greatest risk of sudden cardiac death in children and adults with congenital heart disease exists in those with left heart obstructive lesions (e.g., aortic stenosis, aortic coarctation) and cyanotic defects (e.g., Ebstein's anomaly, corrected transposition of the great vessels, tetralogy of Fallot).[19] Most sudden death events in this population occur during exercise, with half of cases resulting from ventricular fibrillation.[19] Nonventricular arrhythmias (e.g., sinus node dysfunction, atrioventricular block, supraventricular tachyarrhythmias) are also common, even after surgical correction.[19]

VALVULAR HEART DISEASE

Hemodynamically severe aortic stenosis can cause effort-induced dyspnea, myocardial ischemia, and ventricular arrhythmias, which can trigger syncope and sudden cardiac death. The most common causes of aortic stenosis are a congenitally bicuspid aortic valve that typically calcifies and narrows its orifice in mid-adulthood or sclerosis/calcification of a tricuspid aortic valve, which can occur in individuals who are older than 70 or 80 years of age. **A harsh, late-peaking systolic murmur at the upper-right sternal border with radiation to the neck is a typical finding in hemodynamically significant aortic stenosis.**

CARDIAC PACEMAKER AND CONDUCTING SYSTEM DISEASE

Sick sinus syndrome affects the heart's primary pacemaker and can cause intermittent lightheadedness, syncope, or sudden cardiac death. Although it is more common with advancing age, primary electrical failure of the heart can occur in infants and children. The cause is unknown, but pathologic studies reveal histologic degeneration of the sinoatrial node. In addition, the disorder often involves the atrioventricular node and the conduction tissue between the sinoatrial and atrioventricular nodes. Therefore, sick sinus syndrome should be thought of as a diffuse degenerative disease of the heart's electrical generation and conduction system. Idiopathic sclerodegeneration of the atrioventricular node and the bundle branches (Lenègre's disease) or invasion of the conduction system by fibrosis or calcification spreading from adjacent cardiac structures (Lev's disease) can lead to bradyasystolic heart block with or without cardiac arrest. In rare cases, a clinical presentation resembling the sick sinus syndrome can occur when the heart's electrical system is affected by systemic disease, vascular compromise, or tumor. Symptomatic bradycardia is treated with pacemaker placement.

HEREDITARY CHANNELOPATHIES

Sudden Arrhythmic Death Syndrome **The sudden arrhythmic death syndrome is characterized by sudden cardiac death occurring out of hospital in relatively young adults (mostly men), often during sleep or at rest, usually without any premonitory symptoms (including syncope) and with no anatomic abnormality identified at autopsy.[18,19]** Genetic disorders are associated with sudden arrhythmic death syndrome, and many cases can be identified clinically based on their characteristic ECG patterns.

Ion Channel Disease **Cardiovascular and genetic examination of first-degree relatives can identify an inherited form of heart disease known as a "channelopathy" or "ion channel disease" in almost half of cases.** Ion channel flux is responsible for the initiation, propagation, and repolarization of the cardiac action potential. Ion channel disease is caused by mutations in the genes that encode the proteins responsible for forming and interacting with the specialized sodium, potassium, and calcium ion channels within the heart.[21] There are many known ion channelopathies, modulated by a variety of causative gene defects that can have variable phenotype penetration in a given family. Genetic testing is used to screen family members for a known mutation. Common subtypes are listed in Table 11-1.

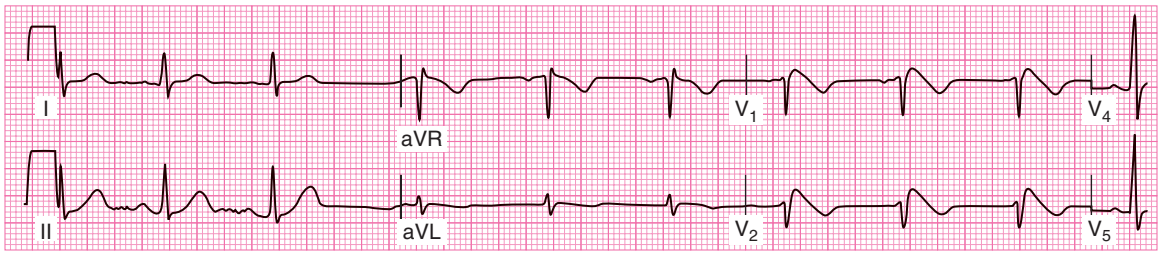

FIGURE 11-1. Brugada syndrome. Twelve-lead ECG typical of Brugada syndrome shows characteristic downsloping ST-segment elevation in leads V_1 and V_2 and QRS morphology resembling a right bundle branch block.

Brugada Syndrome **Brugada syndrome most commonly affects men and consists of a prominent J-wave with a characteristic downsloping ST-segment elevation in ECG leads $V_{1–3}$ (Figure 11-1).** This ECG pattern resembles a right bundle branch block and is associated with a 40% to 60% incidence of life-threatening ventricular arrhythmias (particularly polymorphic ventricular tachycardia that degenerates into ventricular fibrillation) and sudden cardiac death. The syndrome exhibits an autosomal dominant inheritance that results in total loss of function of the sodium channel or in acceleration of recovery from sodium channel activation.[22] **Brugada syndrome is common in Southeast Asia (where it is called sudden unexplained nocturnal death syndrome), in the Philippines (*bangungut*, "to rise and moan in sleep"), in Japan (*pokkuri*, "sudden and unexpectedly ceased phenomena"), and in Thailand (*lai tai*, "death during sleep"). It is crucial for emergency physicians to identify this condition from its characteristic ECG pattern, because the risk of sudden cardiac death is high and can be prevented by internal cardioverter-defibrillator placement.[23]**

Early Repolarization Syndrome **Early repolarization syndrome** is present in 1% to 2% of adults (mostly males) and has long been considered to be a benign variant of normal ventricular repolarization.[24] Its prevalence is higher (10%) in general athletes and reaches as high as 100% in top-performing, endurance-trained individuals.[25] Classic ECG diagnostic criteria are a prominent, notch-like J wave on the QRS downslope, followed by upsloping ST-segment elevation (**Figure 11-2**). These changes are seen most prominently in the mid to lateral precordium but can also occur just laterally or inferiorly. There is commonly reciprocal ST-segment depression in aVR. Rapid ventricular pacing or exercise usually normalizes these changes.

There may be similarity or overlap between Brugada and early repolarization syndromes, but the clinical significance of early repolarization syndrome has not been established.[24] Both syndromes are often familial and more prominent in males, and drugs alter their characteristic ECG patterns (sodium channel blockers and β-blockers increase the ST-segment elevation, whereas isoproterenol or mild exercise decreases the ST-segment elevation).[26,27] Referral for an outpatient cardiology evaluation might only be warranted in the case of a teenager or young adult with syncope of unknown origin and/or with a family history of sudden cardiac death at an early age and with an ECG pattern of early repolarization.

Long QT Syndrome **The long QT syndrome is characterized by prolongation of the corrected QT interval, syncope, and sudden death caused by torsades de pointes and ventricular fibrillation.[21]** The corrected QT interval can be calculated using Bazett's equation:

$$QT_c = \frac{QT_m}{\sqrt{R - R}}$$

where QT_c is the corrected QT interval in seconds, QT_m is the measured QT interval in seconds, and R-R is the interval between any two consecutive R waves on the ECG in seconds. Because the QT interval is heart rate dependent, the formula "corrects" the measured QT interval to a heart rate of 60 beats/min (at which the R-R interval is 1 second). Because the square root of 1 = 1, the QT_c equals the QT_m at a heart rate of 60 beats/min (at which the normal QT interval limits are 0.35 to 0.44 second).

Prolongation of the corrected QT interval represents dispersion in ventricular repolarization and can be hereditary or acquired (e.g., hypokalemia, hypomagnesemia, hypocalcemia, anorexia, ischemia, CNS pathology, levofloxacin, terfenadine-ketoconazole combinations, or certain antipsychotic or antiarrhythmic drugs).[21,28] Hereditary long QT syndrome can have an autosomal recessive (Jervell and Lange-Nielsen syndrome with nerve deafness) or dominant (Romano-Ward syndrome without nerve deafness) mode of inheritance.[21] **Management of patients with long QT syndrome involves avoidance of QT-prolonging drugs (an up-to-date list maintained by AzCERT can be found at http://www.QTdrugs.org) and high-intensity sports, as well as cardiology/electrophysiology referral.[21]** A β-blocker is typically prescribed as prophylaxis against sudden cardiac death. Long QT syndrome patients who have syncope, torsades de pointes, or ventricular fibrillation despite β-blocker therapy are candidates for implantable cardioverter-defibrillator placement.[29]

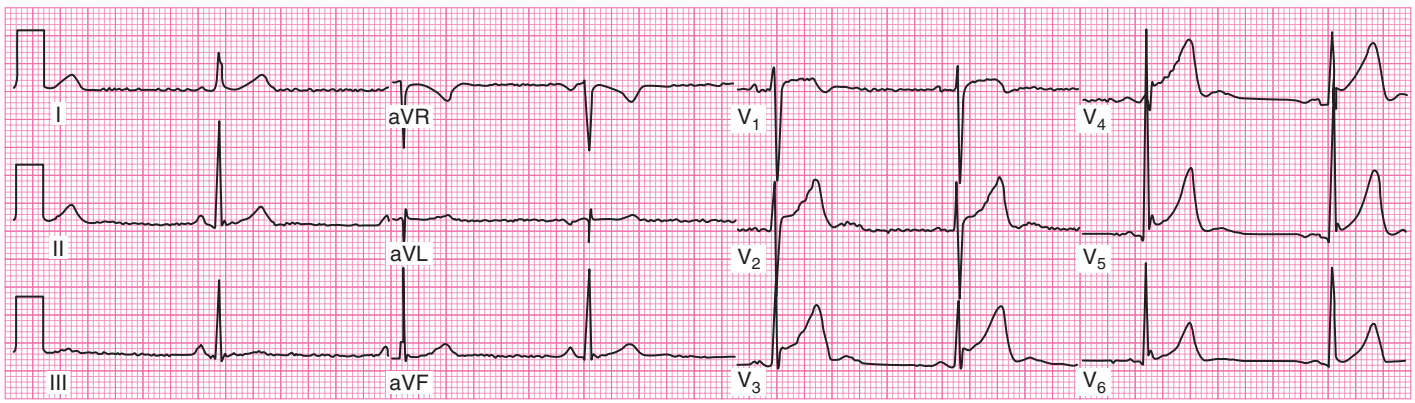

FIGURE 11-2. Early repolarization syndrome. Note in V_5 the prominent notch-like J wave on the QRS downslope and the upsloping ST segment.

Short QT Syndrome **An abnormally short corrected QT interval (i.e., <0.34 second) can be secondary to hypercalcemia, hyperkalemia, acidosis, systemic inflammatory syndrome, myocardial ischemia, or increased vagal tone or can be inherited in an autosomal dominant genetic pattern.**[30] The genetic variety, dubbed the "short QT syndrome," is associated with atrial arrhythmia, including atrial fibrillation, syncope, polymorphic ventricular tachycardia, ventricular fibrillation, and sudden cardiac death.[30] Early repolarization, especially in the inferolateral leads, is noted in 65% of patients.[31] These individuals should also be referred for cardiology/electrophysiology evaluation and are candidates for cardioverter-defibrillator placement if syncope or life-threatening ventricular arrhythmias are documented.[30]

Catecholaminergic Polymorphic Ventricular Tachycardia Catecholaminergic polymorphic ventricular tachycardia is another genetically determined disorder involving defective myocardial cellular calcium handling. Affected individuals have exercise- and stress-related ventricular tachycardia, syncope, and sudden cardiac death, usually in childhood or early adulthood. Although there are no characteristic abnormalities in the ECG pattern, a significant number of affected individuals have sinus bradycardia that is not otherwise explainable. Almost half of these individuals carry a diagnosis of epilepsy as the cause of their recurrent syncope before the true cause (i.e., catecholaminergic polymorphic ventricular tachycardia) is identified.[32] β-Blockers are the mainstay of prophylaxis, with implantable cardioverter-defibrillator placement as the next step if syncope recurs.[32]

PREVENTION OF SUDDEN CARDIAC DEATH

Unfortunately, the majority of sudden cardiac death victims cannot be identified in advance. Prodromal symptoms in the days to weeks preceding cardiac arrest are common but are usually too nonspecific to be of important predictive value.[33] The most common premonitory symptoms reported by sudden cardiac death survivors or family members of victims are chest discomfort, dyspnea, and "not feeling well."

Various tests have been used to try to "risk stratify" potential sudden cardiac death patients, but none are sensitive or specific enough to be useful. Tests include invasive and noninvasive assessment of left ventricular ejection fraction, coronary angiography, ambulatory ECG monitoring, exercise testing, detection of ventricular late potentials by using signal averaging, programmed ventricular stimulation of the heart to test the inducibility of ventricular tachyarrhythmias, assessment of heart rate variability, and T-wave alternans (alternating T-wave amplitude from beat to beat on the ECG, which is visible only with special recording equipment).[34] **The best opportunity for prevention is to recognize signs and symptoms of the syndromes that place a patient at higher risk of sudden cardiac death and to admit or refer such patients for proper evaluation and prophylaxis.**

ANTIARRHYTHMIC DRUG AND DEVICE THERAPY

The Cardiac Arrhythmia Suppression Trial showed that potent class I sodium channel–blocking antiarrhythmic drugs (encainide, flecainide, and moricizine) are proarrhythmic and paradoxically increase the odds of developing sudden cardiac death, as compared with placebo, in patients at relatively low risk for death.[35] The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society have developed an up-to-date comprehensive guide to the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[36] In general, the benefits of antiarrhythmic medications such as β-blockers, sotalol, and amiodarone in decreasing mortality from sudden cardiac death pale in comparison with the protective effects of the implantable cardioverter-defibrillator in high-risk patients,[37] including those who have been resuscitated from ventricular fibrillation or cardioverted out of sustained ventricular tachycardia.[38] Although these devices are expensive to insert, their effectiveness over conventional therapy results in a cost of less than $30,000 per year of life saved, which makes them relatively cost-effective for implantation in high-risk individuals. The Centers for Medicare and Medicaid Services is reevaluation whether to broaden its indications for implantable cardioverter-defibrillator insertion due to the efficacy and effectiveness of these devices for secondary and primary sudden cardiac death prevention in many patient populations, including patients ≥65 years.[39]

SUDDEN CARDIAC DEATH RESCUE

The outcome of resuscitation is influenced strongly by the patient's initial cardiac rhythm. In most cases in which the event has been captured during monitoring, the initiating event is either pulseless ventricular tachycardia that degenerates rapidly to ventricular fibrillation or "primary" ventricular fibrillation.[40]

EMS and in-hospital resuscitation systems are the most effective means currently known to rescue patients from sudden cardiac death. Survival from pulseless ventricular tachycardia or ventricular fibrillation is inversely related to the time interval between its onset and termination. Survival is optimal when both CPR and advanced cardiac life support, including defibrillation and drug therapy, are provided early. Community resuscitation strategies should include provision of early CPR, early activation of the EMS system, early defibrillation (including public access defibrillation), early advanced cardiac life support, and regionalized systems of postresuscitation care.[41,42] The Public Access Defibrillation randomized clinical trial showed that laypersons trained and equipped to use automated external defibrillators in public places can double survival to hospital discharge compared with layperson rescuers who can only perform CPR while awaiting EMS arrival.[43] These results have been confirmed in an analysis of 13,769 out-of-hospital cardiac arrest registry cases.[44]

PULSELESS VENTRICULAR TACHYCARDIA/VENTRICULAR FIBRILLATION

The likelihood of survival is relatively high if the initial rhythm is ventricular tachycardia or ventricular fibrillation (particularly if the ventricular fibrillation is "coarse," the arrest is witnessed, and prompt CPR and defibrillation are provided). If the initial rhythm is not ventricular tachycardia or ventricular fibrillation, survival is typically <5% in most reported series. Asystolic patients whose cardiac arrest is unwitnessed rarely survive to hospital discharge neurologically intact. The only common exceptions are witnessed cardiac arrest patients whose initial asystole is a result of increased vagal tone or other relatively easily correctible factors, such as hypoxia of brief duration.

PULSELESS ELECTRICAL ACTIVITY

Some sudden cardiac death events begin with a bradyarrhythmia or an organized rhythm without a pulse (e.g., pulseless electrical activity). *Bradyasystole* in adults is defined as a ventricular rate <60 beats/min or periods of absent heart rhythm (asystole). Bradyasystolic rhythms other than asystole can be accompanied by a pulse, or there can be no discernible pulse with each QRS (i.e., pulseless electrical activity). Bradyasystole *with* a pulse is often accompanied by a significant decrease in cardiac output, leading to hypotension and/or syncope. Bradycardia *with or without* a pulse occurs frequently during cardiac arrest, either as the initial rhythm, during the course of resuscitation, or after electrical defibrillation. Obviously, asystole occurs eventually in all dying patients. **To ensure that ventricular fibrillation is not masquerading as asystole, rescuers can switch to another lead whenever a "flat line" is recorded on the ECG during resuscitation or use US if available.**

Primary bradyasystole occurs when the heart's electrical system fails to generate and/or propagate an adequate number of ventricular depolarizations per minute to sustain consciousness and other vital functions. Secondary bradyasystole is present when factors external to the heart's electrical system cause it to fail (e.g., hypoxia). Common causes of bradyasystolic arrest are listed in **Table 11-3.**

TABLE 11-3 Common Causes of Bradyasystolic Arrest

- Myocardial ischemia or infarction
- Sick sinus syndrome
- Asphyxiation (including near-drowning)
- Hypoxia
- Hypercarbia
- Stroke
- Opiates, β-blockers, calcium channel blockers, adenosine, or parasympathetics

One of the most baffling mysteries of bradyasystolic cardiac arrest relates to myocardial mechanics. Bradyasystole, unlike ventricular fibrillation, is accompanied by very little myocardial oxygen consumption in animal models. Because of this, myocardial high-energy phosphate stores should decay relatively slowly during bradyasystole. This should theoretically result in a high incidence of return of spontaneous circulation after restoration of a more normal rhythm (e.g., with the early use of electrical pacing). It is unclear why conventional treatment of bradyasystolic cardiac arrest with atropine, epinephrine, or electrical pacemakers rarely results in survival to hospital discharge. Return of spontaneous circulation is infrequent, and long-term neurologically intact survival is rare in bradyasystolic cardiac arrest.

Other factors must play a determining role in the pathophysiology and subsequent outcome of bradyasystolic cardiac arrest. Bradyasystolic arrest is not just a disorder of rhythm generation or propagation; it is a perplexing syndrome characterized by such rhythm disturbances accompanied, in many cases, by profound depression of myocardial and vascular function. Suspected causes include endogenous myocardial depressants (including downregulation of catecholamine receptors and/or toxic influences of intense sympathetic stimulation), neurogenic influences, postischemic myocardial stunning, and/or free radical injury.

It is important to differentiate pulseless electrical activity from conditions in which the rescuer is unable to detect a pulse, but there is unmistakable evidence that there is adequate blood pressure and cardiac output to maintain vital organ perfusion (e.g., a conscious patient with profound vasoconstriction caused by hypothermia, or "pseudo pulseless electrical activity").[45]

The underlying physiologic cause of pulseless electrical activity is a marked reduction in cardiac output due to either profound myocardial depression or mechanical factors that reduce venous return or impede the flow of blood through the cardiovascular system. Common conditions that can cause pulseless electrical activity are shown in **Table 11-4**. The management of patients with pulseless electrical activity is directed at identifying and treating the underlying cause or causes.

TABLE 11-4 Conditions That Cause Pulseless Electrical Activity

- Hypovolemia
- Tension pneumothorax
- Pericardial tamponade
- Pulmonary embolism
- Massive myocardial dysfunction due to ischemia or infarction, myocarditis, cardiotoxins, etc.
- Drug toxicity (e.g., β-blockers, calcium channel blockers, tricyclic antidepressants)
- Profound shock
- Hypoxia
- Acidosis
- Severe hypercarbia
- Auto positive end-expiratory pressure
- Hypothermia
- Hyperkalemia
- Pseudo pulseless electrical activity

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 12

Approach to Nontraumatic Shock

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EPIDEMIOLOGY

Using a systolic blood pressure <90 mm Hg as criteria, 0.4% to 1.3% of patients presenting to EDs are in shock.[1] Mortality depends on the inciting event. Septic shock has an estimated hospital mortality of 26%.[2] Cardiogenic shock has an estimated hospital mortality of 39% to 48%.[3,4] Neurogenic shock occurs in <20% of spinal cord injuries (cervical, 19.3%; thoracic, 7%; lumbar, 3%).[5] The definition of and treatment approach to shock continue to evolve, but the initial approach to a patient in shock follows similar principles, regardless of the inciting factors or cause.

Patients present to the ED in varying stages of critical illness and shock. These stages are confounded by age, comorbidities, and delays in presentation. A focus on early recognition, rapid diagnosis, and empiric resuscitation is essential. Therapy and patient stabilization may need to occur simultaneously with evaluation.

PATHOPHYSIOLOGY

Shock is a state of circulatory insufficiency that creates an imbalance between tissue oxygen supply (delivery) and demand (consumption), resulting in end-organ dysfunction. Reduction in effective perfusion may be due to a local or global delivery deficiency or utilization deficiency with suboptimal substrate at the cellular or subcellular level.[6-8] The mechanisms that can result in shock are frequently divided into four categories: (1) hypovolemic, (2) distributive, (3) cardiogenic, and (4) obstructive.

CATEGORIES OF SHOCK

The four categories of shock can be described in terms of their respective physiologic changes and common causes, recognizing that a single etiology may manifest the clinical findings of more than one shock type (**Table 12-1**).[9,10] **Hypovolemic shock** occurs when decreased intravascular fluid or decreased blood volume causes decreased preload, stroke volume, and cardiac output (CO). Severe blood loss (hemorrhage) can cause decreased myocardial oxygenation, which decreases contractility and CO. This action may lead to an autonomic increase in the systemic vascular resistance (SVR). Hypovolemic shock can also occur due to volume loss from other etiologies. In **distributive shock**, there is relative intravascular volume depletion due to marked systemic vasodilatation. This is most commonly seen in septic shock.[6] Compensatory responses to decreased SVR may include increased CO (increased contractility and heart rate) and tachycardia. The concurrent decreased SVR results in a decreased preload and may hinder CO overall. In sepsis, up to 40% of patients may have a transient cardiomyopathy characterized by decreased contractility and increased mortality.[6] Anaphylaxis, adrenal insufficiency, and neurogenic shock are additional causes of distributive shock. In **cardiogenic shock**, the left ventricle fails to deliver oxygenated blood to peripheral tissues due to variances in contractility, as well as preload, afterload, and right ventricular function.[8] Myocardial infarction is the most common cause of cardiogenic shock. Dysrhythmias

TABLE 12-1 Categories of Shock

Type	Percentage*	Hemodynamic Changes	Etiologies†
Distributive	33%–50%	Decreased preload, decreased SVR, mixed CO	Sepsis, neurogenic shock, anaphylaxis
Hypovolemic	31%–36%	Decreased preload, increased SVR, decreased CO	Hemorrhage, capillary leak, GI losses, burns
Cardiogenic	14%–29%	Increased preload, increased afterload, increased SVR, decreased CO	MI, dysrhythmias, heart failure, valvular disease
Obstructive	1%	Decreased preload, increased SVR, decreased CO	PE, pericardial tamponade, tension PTX

*Percentage of patients presenting to the ED; percentages will vary depending on hospital type and population.

†Etiologies may demonstrate findings of more than one type of shock.

Abbreviations: CO = cardiac output; MI = myocardial infarction; PE = pulmonary embolism; PTX = pneumothorax; SVR = systemic vascular resistance.

are another common cause because they can lead to a decreased CO. Bradyarrhythmias result in low CO, and tachyarrhythmias can result in decreased preload and stroke volume. Patients with cardiogenic shock may soon develop clinically evident infection (up to 46%) and/or demonstrate an inflammatory response similar to but less pronounced than with septic shock.[9] **Obstructive shock** is uncommon (1%) and is due to a decrease in venous return or cardiac compliance due to an increased left ventricular outflow obstruction or marked preload decrease. Cardiac tamponade, pulmonary embolism, and tension pneumothorax are causes of obstructive shock.

FACTORS AFFECTING CARDIAC OUTPUT

CO is determined by heart rate and stroke volume. Stroke volume is dependent on preload, afterload, and contractility. The mean arterial pressure is dependent on CO and the SVR. This is important because there is a mean arterial pressure threshold below which oxygen delivery is decreased. SVR directly impacts mean arterial pressure, but also impacts afterload and thus CO. Patients in shock may initially have normal blood pressures (cryptic shock), yet have other objective signs of shock (see later section "Clinical Features"). Tissue oxygenation is predicated on CO being sufficient enough to deliver oxygenated hemoglobin to the tissues. CO is dependent on the interplay of cardiac inotropy (speed and shortening capacity of myocardium), chronotropy (heart contraction rate), and lusitropy (ability of heart muscle to relax and heart chambers to fill). Determinants of inotropy include autonomic input from sympathetic activation, parasympathetic inhibition, circulating catecholamines, and short-lived responses to an increase in afterload (Anrep effect) or heart rate (Bowditch effect). Increases in the inotropic state help to maintain stroke volume at high heart rates.[11] During shock states, higher levels of epinephrine will be produced and reinforce adrenergic tone. Epinephrine levels are significantly elevated during induced hemorrhagic shock, but these levels subsequently reduce to almost normal levels after adequate blood pressure is restored.[12] An acidotic milieu, which is common in shock, further compromises ventricular contractile force and blood pressure.[13] Chronotropy and lusitropy are both influenced by sympathetic input. Norepinephrine interacts with cardiac β_1-receptors, resulting in increased cyclic adenosine monophosphate. This leads to a process of intracellular signaling with an increased chronotropy and sequestration of calcium, leading to myocardial relaxation.[11]

LACTIC ACID

When compensatory mechanisms fail to correct the imbalance between tissue supply and demand, anaerobic metabolism occurs and results in the formation of lactic acid. Lactic acid is rapidly buffered, resulting in the formation of measured serum lactate. Normal venous lactate levels are <2.0 mmol/L. Most cases of lactic acidosis are a result of inadequate oxygen delivery, but lactic acidosis occasionally can develop from an excessively high oxygen demand (e.g., status epilepticus). In other cases, lactic acidosis occurs because of impaired tissue oxygen utilization (e.g., septic shock or the postresuscitation phase of cardiac arrest). Elevated lactate is a marker of impaired oxygen delivery or utilization and correlates with short-term prognosis of critically ill patients in the ED.[12] Serial lactate assessments may be indicated because lactate clearance is associated with improved outcomes in septic shock and may assist with resuscitation.[14]

COMPENSATORY MECHANISMS AND THEIR FAILURE

Shock provokes a myriad of autonomic responses to maintain perfusion pressure to vital organs. Stimulation of the carotid baroreceptor stretch reflex activates the sympathetic nervous system, triggering (1) arteriolar vasoconstriction, resulting in redistribution of blood flow from the skin, skeletal muscle, kidneys, and splanchnic viscera; (2) an increase in heart rate and contractility that increases CO; (3) constriction of venous capacitance vessels, which augments venous return; (4) release of the vasoactive hormones epinephrine, norepinephrine, dopamine, and cortisol to increase arteriolar and venous tone; and (5) release of antidiuretic hormone and activation of the renin-angiotensin axis to enhance water and sodium conservation to maintain intravascular volume.[13]

These compensatory mechanisms attempt to maintain oxygen delivery to the most critical organs (heart and brain), but blood flow to other organs, such as the kidneys and GI tract, may be compromised. The cellular response to decreased oxygen delivery (adenosine triphosphate depletion) leads to ion-pump dysfunction, influx of sodium, efflux of potassium, and reduction in membrane resting potential. As shock progresses, the loss of cellular integrity and the breakdown in cellular homeostasis result in cellular death. These pathologic events give rise to a cascade of metabolic features including hyperkalemia, hyponatremia, azotemia, hyper- or hypoglycemia, and lactic acidosis.

Inflammation plays an important role in several different types of shock, especially in septic shock, but also in shock associated with anaphylaxis, burns, trauma, and cardiogenic causes.[15] Previously, the systemic inflammatory response syndrome was part of the definition of sepsis, but that changed with a revised definition of sepsis, Sepsis-3, in 2016.[16] See Chapter 151, "Sepsis," for detailed discussion.

As global tissue hypoxia progresses, shock ensues, followed by the multiorgan dysfunction syndrome, which is manifested by renal failure, respiratory failure, myocardial depression, liver failure, and then disseminated intravascular coagulation. The fulminant progression from global tissue hypoxia to multiorgan dysfunction syndrome is determined by the severity of inadequate tissue perfusion and the balance of anti-inflammatory and proinflammatory mediators (**Figure 12-1**).

CLINICAL FEATURES

HISTORY AND COMORBIDITIES

Although the clinical presentation of a patient in shock and the underlying cause may be quite apparent (e.g., acute myocardial infarction, anaphylaxis, or hemorrhage), it may be difficult to obtain a history from patients in shock. Assistance with medical history from EMS, family, or other sources may help determine the cause of shock. Some patients in shock may have few symptoms other than generalized weakness, lethargy, or altered mental status. If the patient is unresponsive, consider trauma as a primary or secondary complication.

PHYSICAL EXAMINATION

Shock is usually associated with systemic arterial hypotension—systolic blood pressure <90 mm Hg. Blood pressure may not drop if there is an increase in peripheral vascular resistance in the presence of decreased CO with inadequate tissue hypoperfusion. For this reason, blood pressure is an insensitive marker for global tissue hypoperfusion. **Shock may occur with a normal blood pressure, and hypotension may occur without shock.** No single vital sign is diagnostic of shock, and blood

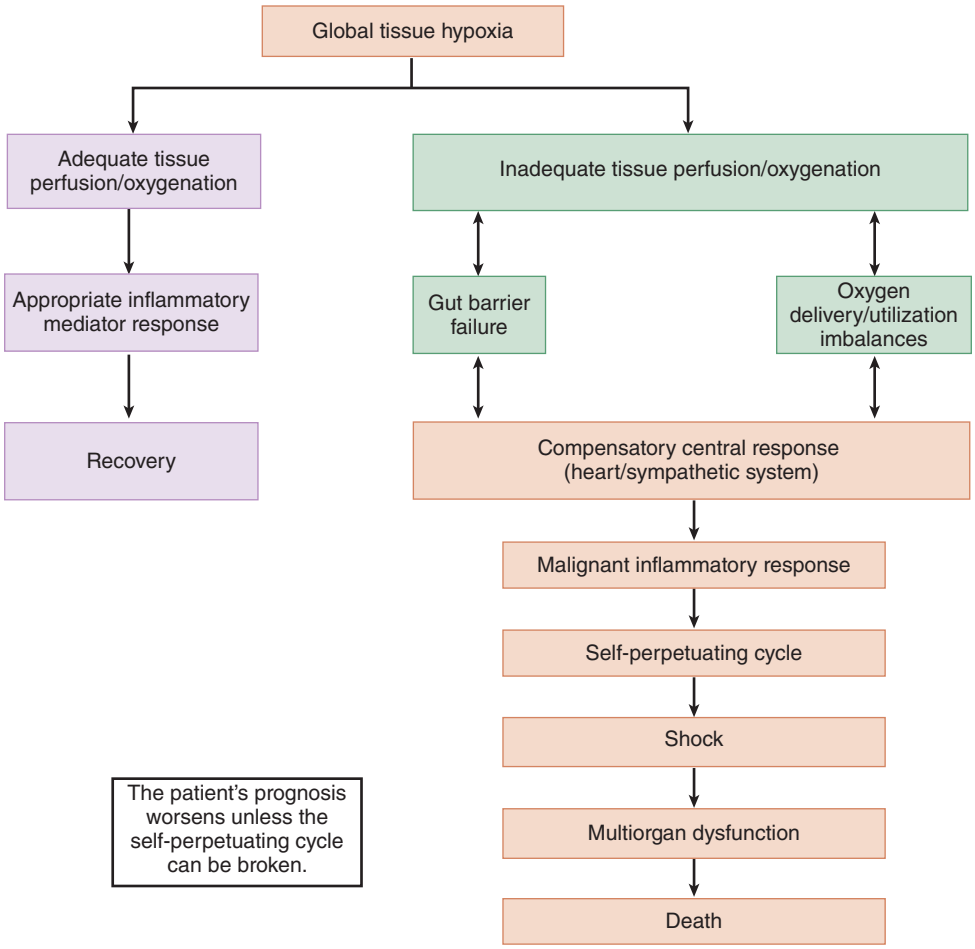

FIGURE 12-1. The pathophysiology of shock, the inflammatory response, and multiorgan dysfunction.

pressure is particularly insensitive in the presence of peripheral vascular disease, tachycardia with a small pulse pressure, or cardiac dysrhythmias. Composite physical findings are useful in the assessment of shock (**Table 12-2**).

DIAGNOSIS

LABORATORY EVALUATION

No single laboratory value is sensitive or specific for shock. Laboratory studies are driven by the clinical presentation and the presumptive cause. Common studies are listed in **Table 12-3**. Arterial blood gases are useful to assess acid-base status and ventilation and oxygenation concerns, whereas a venous blood gas is limited to acid-base information. A rise in serum lactate correlates with mortality in many shock states[12]; typically this is due to anaerobic metabolism, but nonhypoxic causes of lactic acidosis due to cellular dysfunction occur in shock states. A wide range of laboratory abnormalities may be encountered in shock. The incidence of adrenal dysfunction can be as high as 30% in this subset of patients. Most abnormal values merely point to the particular organ system that is contributing to, or being affected by, the shock state.

IMAGING

Chest Radiograph The portable anteroposterior view chest radiograph is often used in the evaluation of unstable patients to avoid transporting the patient during resuscitation. While limitations exist, evaluation of the heart size, presence of pulmonary edema, free air under the diaphragm, pneumothorax, infiltrates, or effusions may provide useful clinical information.

US Bedside US assessment is an important tool for developing a differential diagnosis, assessing volume status, defining cardiac function, and assisting with procedures. Various US methods are described to determine overall volume status by assessing right-sided filling pressures, including measuring inferior vena cava respiratory variation or end-expiratory vena cava respiratory variation, and other methods.

Bedside cardiac US to assess left ventricular ejection fraction can assist with determining the cause of shock. Emergency physicians trained in focused bedside cardiac US can provide an estimated ejection fraction with high relative correlation to cardiologists.[17]

US may also be used to assess for vascular emergencies. Identifying an abdominal aortic aneurysm on US may lead to further evaluation. Findings of a deep vein thrombosis may increase the suspicion for a pulmonary embolism.

Additional US protocols, such as the Abdominal and Cardiac Evaluation with Sonography in Shock protocol and the Rapid Ultrasound in Shock protocol, have been formulated using many of the aforementioned concepts.[17-20] The Abdominal and Cardiac Evaluation with Sonography in Shock protocol looks at cardiac function, inferior vena cava dynamics, pulmonary congestion, lung sliding and consolidation, abdominal free fluid, abdominal aortic aneurysm, and leg venous thrombosis to assist in differential diagnosis generation or narrowing.[17,18] The Rapid Ultrasound in Shock exam involves a three-part bedside physiologic assessment simplified as the pump (cardiac), the tank (volume status), and the pipes (arterial and venous).[19-21] However, as with any US intervention, operator competency is essential.

CT Although CT is an accurate and noninvasive approach for detecting internal pathology, patients must travel from the ED to the radiology suite, which may be unadvisable in unstable shock. The potential benefits of CT must be weighed against the associated risks, including

TABLE 12-2 Composite Physical Examination Findings in Shock

Temperature	Hyperthermia or hypothermia may be present. Endogenous hypothermia (hypometabolic shock) must be distinguished from exogenous environmental hypothermia.
Heart rate	Usually elevated; however, paradoxical bradycardia can be seen in shock states due to hypoglycemia, β-blocker use, and preexisting cardiac disease.
Systolic blood pressure	May actually increase slightly when cardiac contractility increases in early shock and then fall as shock advances.
Diastolic blood pressure	Correlates with arteriolar vasoconstriction and may rise early in shock and then fall when cardiovascular compensation fails.
Pulse pressure	Increases early in shock and decreases before systolic pressure begins to drop.
Mean arterial blood pressure	Often low, <65 mm Hg.
CNS	Acute delirium, restlessness, disorientation, confusion, and coma secondary to a decrease in cerebral perfusion pressure.
Skin/capillary refill	Pallor, pale, dusky, clammy, cyanosis, sweating, cool, and capillary refill time >2–3 s.
Cardiovascular	Neck vein distention or flattening depending on the type of shock. Tachycardia and arrhythmias. An S_3 may result from high-output states. Decreased coronary perfusion pressures can lead to ischemia, decreased ventricular compliance, increased left ventricular diastolic pressure, and pulmonary edema.
Respiratory	Tachypnea, increased minute ventilation, increased dead space, bronchospasm, and hyper- or hypocapnia with progression to respiratory failure.
Splanchnic organs	Ileus, GI bleeding, pancreatitis, and mesenteric ischemia can occur due to low-flow states.
Renal	Reduced glomerular filtration rate. Renal blood flow redistributes from the renal cortex toward the renal medulla leading to oliguria.
Metabolic	Lactic acidosis, hyperglycemia, hypoglycemia, and hyperkalemia. As shock progresses, metabolic acidosis occurs with concurrent respiratory compensation.

concerns about renal function due to hypovolemia and contrast-induced nephropathy. CT scans without IV contrast will add some information to the clinical picture, although not to the degree of a scan with IV contrast.

TABLE 12-3 Initial Diagnostic Studies to Evaluate a Patient in Shock*

- CBC with differential
- Electrolytes, glucose, calcium, magnesium, phosphorus
- BUN, creatinine
- Serum lactate
- ECG
- Urinalysis
- Chest radiograph
- Coagulation studies: prothrombin time, PTT, INR
- Arterial blood gas (pH, carbon dioxide and oxygen levels, base deficit)
- Hepatic function panel
- Cultures: blood, urine, suspicious wounds, quantitative sputum culture
- Cortisol level
- Pregnancy test
- CT of chest/abdomen/pelvis as indicated by history, physical exam

*Ordering of tests should be individualized by patient presentation and history (see also Chapter 151, "Sepsis").

HEMODYNAMIC MONITORING

Hemodynamic monitoring helps assess the severity of shock and the response to treatment. Monitoring capabilities should initially include pulse oximetry, ECG monitoring, and noninvasive blood pressure monitoring. In the critical care arena, intra-arterial blood pressure monitoring, end-tidal carbon dioxide monitoring, central venous pressure, and central venous oxygen saturation from the superior vena cava ($Scvo_2$) monitoring are frequently used. When obtaining central access, the average access time, number of attempts, and mechanical complications are reduced when a US-assisted approach is used.[22]

TREATMENT

See Chapter 151, "Sepsis," for treatment of sepsis. Comprehensive and timely ED care can significantly decrease the predicted mortality of critically ill patients in as little as 6 hours of treatment.[23] Application of an algorithmic approach to optimize hemodynamic end points with early goal-directed therapy in the ED reduced mortality by 16% in patients with severe sepsis or septic shock in 2001.[24] That original study, the Surviving Sepsis Campaign that followed,[25] and other algorithmic efforts[26] have changed the approach to sepsis and shock care on a worldwide basis. Two large, multicenter, randomized controlled trials published in 2014 failed to show additional benefits to a rigid algorithmic approach.[27,28] However, we attempt to present below the most beneficial aspects of shock care demonstrated by the medical progress of the past 15 years. **The *ABCDE* tenets of shock resuscitation are establishing *a*irway, controlling the work of *b*reathing, optimizing the *c*irculation, ensuring adequate oxygen *d*elivery, and achieving *e*nd points of resuscitation.[29]**

ESTABLISHING THE AIRWAY

Airway control is best obtained through endotracheal intubation. Sedatives used to facilitate intubation may cause arterial vasodilatation, venodilation, or myocardial suppression and may result in hypotension. Positive-pressure ventilation reduces preload and CO. The combination of sedative agents and positive-pressure ventilation will often lead to hemodynamic collapse. To avoid this unwanted situation, initiate volume resuscitation and vasoactive agents before intubation and positive-pressure ventilation.

CONTROLLING THE WORK OF BREATHING

Control of breathing is required when significant work of breathing accompanies shock. Respiratory muscles are significant consumers of oxygen during shock and contribute to lactate production. Mechanical ventilation and sedation allow for adequate oxygenation, improvement of hypercapnia, and assisted, controlled, synchronized ventilation. All of these treatments decrease the work of breathing and improve survival. When starting mechanical ventilation on a patient, it is essential to consider the patient's compensatory minute ventilation prior to intubation to ensure appropriate initial settings are selected. After a patient is placed on mechanical ventilation, obtain an arterial blood gas to evaluate acid-base status, oxygenation, and ventilation. Neuromuscular blocking agents should be considered to further decrease respiratory muscle oxygen consumption and preserve oxygen delivery to vital organs, especially if patients are severely hypoxemic due to acute respiratory distress syndrome.[30]

OPTIMIZING THE CIRCULATION

Fluids Circulatory or hemodynamic stabilization begins with intravascular access through large-bore peripheral venous lines. The Trendelenburg position does not improve cardiopulmonary performance compared with the supine position. It may worsen pulmonary gas exchange and predispose to aspiration. Passive leg raising above the level of the heart with the patient supine may be effective. If passive leg raising results in an increase in blood pressure or CO, fluid resuscitation is indicated.[31]

Fluid resuscitation should begin with isotonic crystalloid.[32] Balanced crystalloids, such as lactated Ringer's solution, may offer a small mortality advantage over normal saline solution (14.3% vs. 15.4% in a large trial of 15,802 critically ill patients).[33] The amount and rate of infusion are determined by an estimate of the hemodynamic abnormality. Most patients in shock have either an absolute or relative volume deficit. The exception is the patient in cardiogenic shock with pulmonary edema. Administer fluid rapidly (over 5 to 20 minutes), in set quantities of 500 or 1000 mL of normal saline, and reassess the patient after each bolus. Patients with a modest degree of hypovolemia usually require an initial 20 to 30 mL/kg of isotonic crystalloid, and current Centers for Medicare and Medicaid Services sepsis guidelines require 30 mL/kg; however, there are few data to support this uniform recommendation.[34] More fluids may be needed for profound volume deficits. It is common for patients in septic shock to receive 6 L of crystalloid in the first 24 hours of hospital care. For large fluid volumes, consider using lactated Ringer's or Plasma-Lyte® to avoid hyperchloremic metabolic acidosis associated with 0.9% sodium chloride solution[35,36] (see later section "Controversies of Treatment"). In clinical situations where hypochloremia can be predicted, such as from GI losses due to vomiting or from urinary excretion due to diuretics, there may be an advantage to 0.9% sodium chloride rehydration.

Central venous access may aid in assessing volume status (preload) and monitoring $Scvo_2$. It is also the preferred route for the long-term administration of certain vasopressor therapy. However, there is no need for universal central access in patients with septic shock, and the need for central access should be individually determined.[26]

Vasopressors Vasopressors are used when there has been an inadequate response to volume resuscitation or if there are contraindications to volume infusion.[33] Vasopressors are most effective when the vascular space is "full" and least effective when the vascular space is depleted. Patients with chronic hypertension may be at greater risk of renal injury at lower blood pressures; however, in others, there appears to be no mortality benefit in raising mean arterial pressure above the 65 to 70 mm Hg range.[37,38]

Vasopressor agents have variable effects on the α-adrenergic, β-adrenergic, vasopressin, and dopaminergic receptors (**Table 12-4**). Although vasopressors improve perfusion pressure in the large vessels, they may decrease capillary blood flow in certain tissue beds, especially the GI tract and peripheral vasculature. If multiple vasopressors are used, they should be simplified as soon as the best therapeutic agent is identified. In addition to a vasopressor, an inotrope may be needed to directly increase CO by increasing contractility and stroke volume. Careful vasopressor infusion initially through a peripheral IV is unlikely to result in tissue injury and will improve the time to achieve hemodynamic stability.[39,40]

ENSURING ADEQUATE OXYGEN DELIVERY

Control of oxygen consumption is important in restoring the balance of oxygen supply and demand to the tissue (oxygen consumption equation). A hyperadrenergic state results from the compensatory response to shock, physiologic stress, pain, cold treatment rooms, and anxiety. Pain further suppresses myocardial function, impairing oxygen delivery and increasing consumption. Providing analgesia, muscle relaxation, warm covering, anxiolytics, and even paralytic agents, when appropriate, decreases this inappropriate systemic oxygen consumption.

Once blood pressure is stabilized through optimization of preload and afterload, oxygen delivery can be assessed and further manipulated. Restore arterial oxygen saturation to ≥91%. In shock states, consider a transfusion of packed red blood cells to maintain hemoglobin ≥7 grams/dL.[34] If CO can be assessed, it should be increased using volume infusion or inotropic agents in incremental amounts until venous oxygen saturation (mixed venous oxygen saturation [Svo_2] or $Scvo_2$) and lactate are normalized.

TABLE 12-4 Commonly Used Vasoactive Agents (all vasopressors increase myocardial oxygen demand; most should be titrated to desired effect)

Drug	Dose	Action	Cardiac Contractility	Vasoconstriction	Vasodilation	Cardiac Output
Dobutamine	2.0–20.0 micrograms/kg/min	β_1, some β_2 and α_1 in large dosages	++++	+	++	Increases
Side effects and comments	Inotrope only; causes tachydysrhythmias, GI distress, hypotension in volume-depleted patients; less peripheral vasoconstriction than dopamine; fewer arrhythmias than isoproterenol					
Dopamine	0.5–20 micrograms/kg/min	α, β, and dopaminergic	++ at 2.5–5 micrograms/kg/min	++ at 5–20 micrograms/kg/min	+ at 0.5–2.0 micrograms/kg/min	Usually increases
Side effects and comments	Tachydysrhythmias; a cerebral, mesenteric, coronary, and renal vasodilator at low doses; Surviving Sepsis Campaign second line, lot of overlap with α/β/dopaminergic receptors and dose					
Epinephrine	2–10 micrograms/min	α and β	++++ at 0.5–8 micrograms/kg/min	++++ at >8 micrograms/kg/min	+++	Increases
Side effects and comments	Causes tachydysrhythmia, leukocytosis; increases myocardial oxygen consumption; may increase lactate; no real maximum dose					
Isoproterenol	0.01–0.1 microgram/kg/min	β_1 and some β_2	++++	0	++++	Increases
Side effects and comments	Inotrope; causes tachydysrhythmia, facial flushing, hypotension in hypovolemic patients; increases myocardial oxygen consumption					
Norepinephrine	0.5–50 micrograms/min	Primarily α_1, some β_1	++	++++	0	Slightly increases
Side effects and comments	Useful when loss of venous tone predominates; first-line agent for most situations					
Phenylephrine	10–200 micrograms/min	Pure α	0	++++	0	Decreases
Side effects and comments	Reflex bradycardia, headache, restlessness, excitability, rarely arrhythmias; used on patients in shock with tachycardia or supraventricular arrhythmias; not good comparatively for septic shock					
Vasopressin	0.01–0.04 units/min	Directly stimulates V_1 receptor on smooth muscle	0	++++	0	0
Side effects and comments	Primarily vasoconstriction; usually started at max dose and not titrated, typically added to norepinephrine					

Note: 0 = no effect; + = mild effect; ++ = moderate effect; +++ = marked effect; ++++ = very marked effect.

Sequential examination of lactate and Svo_2 or $Scvo_2$ is a method to assess adequacy of a patient's resuscitation. Continuous measurement of Svo_2 or $Scvo_2$ can be used in the ED, although results from the ProCESS trial question the need for this in resuscitation management.[28] A variety of technologic tools may be used to assess tissue perfusion during resuscitation.[41-47] These technologies may be available in some EDs, but are more often found in intensive care units. Transfer of the patient to the intensive care unit should not be delayed so that monitoring devices can be placed in the ED.[23,47]

END POINTS OF RESUSCITATION

The goal of resuscitation is to use hemodynamic and physiologic values to guide therapy in order to maximize survival and minimize morbidity. No therapeutic end point is universally effective, and only a few have been tested in prospective trials, with mixed results.[28,37,38] Hypotension at ED presentation is associated with poor outcomes.[48] Noninvasive parameters, such as blood pressure, heart rate, and urine output, may underestimate the degree of remaining hypoperfusion and oxygen debt, so the use of additional physiologic end points may be informative.[28,37,38,48] A goal-directed approach of mean arterial pressure >65 mm Hg, central venous pressure of 8 to 12 mm Hg, $Scvo_2$ >70%, and urine output >0.5 mL/kg/h during ED resuscitation of septic shock has been shown to decrease mortality, but which of the metrics accounts for the mortality decrease remains in question.[24,27,28,34] Source control, whether with infection, hemorrhage, or other state of shock, is essential in the initial stages of management. If shock or hypotension persists, reassessment at the patient's bedside is essential while considering the important issues in **Table 12-5**.

CONTROVERSIES OF TREATMENT

Fluid Therapy Rapid restoration of fluid deficits modulates inflammation and, if the condition progresses to shock, decreases the need for subsequent vasopressor therapy, steroid administration, and invasive monitoring (e.g., pulmonary artery catheterization and arterial line placement).[33,46] Although there is general agreement that volume therapy is an integral component of early resuscitation, there is a lack of consensus for the type of fluid, standards of volume assessment, and end points despite care mandates that dictate otherwise.[49] **Table 12-6** compares the most commonly used fluid therapies.[50-54]

Colloids are high-molecular-weight solutions that increase plasma oncotic pressure. Colloids can be classified as either natural (albumin) or artificial (starches, dextrans, and gelatins). Due to their higher molecular weight, colloids stay in the intravascular space significantly longer than crystalloids. The intravascular half-life of albumin is 16 hours versus 30 to 60 minutes for normal saline and lactated Ringer's solution.[32,50-54]

Resuscitation with **crystalloids** requires two to four times more volume than colloids.[32,49,50] The outcome advantage between crystalloid and colloids continues to remain unresolved in sepsis, despite multiple studies.[32,49-52] Due to the equivalency and the higher cost of colloids, crystalloids would seem to be a better choice for resuscitation in the ED.

Crystalloid type affects acid-base status and may have an effect on mortality, acute kidney injury, and the need for renal replacement therapy.[35,36,55-58] Two large, single-center, randomized controlled trials compared normal saline to balanced salt solutions (lactated Ringer's or Plasma-Lyte®) in the resuscitation of patients in the ED prior to admission and found fewer major adverse events (persistent renal dysfunction, new renal replacement therapy, or mortality) in the balanced salt group.[55,56] The difference favoring fewer adverse effects in the balance salt group was small (10.3% vs. 11.1% in those admitted to the intensive care unit and 4.7% vs. 5.6% in those admitted to the floor).[55,56] Since then, a meta-analysis including those two studies, plus four prior randomized controlled trials, totaling 19,332 patients, found no significant differences in the outcome measures of intensive care unit mortality, acute kidney injury, and new renal replacement therapy when comparing 0.9% normal saline to balanced salt solutions.[59] Several ongoing randomized controlled trials comparing IV resuscitation fluids are pending completion.[57,60,61] A randomized controlled trial of 157 patients receiving IV hydration with 2 L of 0.9% normal saline versus lactated Ringer's solution before presumed discharge from ED found no difference in outcomes.[62] The majority of the patients were healthy, with hypovolemia from vomiting or diarrhea.[62] Most consistent in all the cited trials is a hyperchloremic acidosis associated with large-volume resuscitation with normal saline and, as of yet, no measured adverse effects of resuscitation with balanced salt solutions, despite a theoretical potential for metabolic

TABLE 12-5 Questions to Answer If There Is Persistent Shock or Hypotension

Equipment and monitoring

- Is the patient appropriately monitored?
- Is there an equipment malfunction, such as dampening of the arterial line or disconnection from the transducer?
- Is the IV tubing into which the vasopressors are running connected appropriately?
- Are the vasopressor infusion pumps working?
- Are the vasopressors mixed adequately and in the correct dose?

Patient assessment

- Do mentation and clinical appearance match the degree of hypotension?
- Is the patient adequately volume resuscitated?
- Does the patient have a pneumothorax after placement of central venous access?
- Has the patient been adequately assessed for an occult penetrating injury?
- Is there hidden bleeding from a ruptured spleen, large-vessel aneurysm, or ectopic pregnancy?
- Does the patient have adrenal insufficiency?
- Is the patient allergic to the medication just given or taken before arrival?
- Is there cardiac tamponade in the dialysis patient or cancer patient?
- Is there associated acute myocardial infarction, aortic dissection, or pulmonary embolus?

TABLE 12-6 Fluid Therapy

Crystalloids	
Normal saline (NS)	Slightly hyperosmolar containing 154 mEq/L of both sodium and chloride. Risk of inducing hyperchloremic metabolic acidosis when given in large amounts due to relatively high chloride concentration.
Lactated Ringer's (LR)	Sodium 130 mEq/L, potassium 4 mEq/L, calcium 3 mEq/L, chloride 109 mEq/L, lactate 28 mEq/L. Lactate can accept a proton and subsequently be metabolized to carbon dioxide and water by the liver, leading to release of carbon dioxide in the lungs and excretion of water by the kidneys. LR results in a buffering of the acidemia that is advantageous over NS. Theoretical risk of inducing hyperkalemia in patients with renal insufficiency or renal failure due to small potassium content (very small amount).
Plasma-Lyte®	Balanced pH 7.4, sodium 140 mEq/L, chloride 98 mEq/L, potassium 5 mEq/L, magnesium 3 mEq/L, gluconate 23 mEq/L, acetate 27 mEq/L.
Colloids	
Albumin	Derived from human plasma. Available in varying strengths from 4% to 25%. Multiple studies have shown that there is no outcome difference whether colloids or crystalloids are used. Colloids cost significantly more than crystalloids. One study actually showed an increase in mortality in trauma patients with head injury.
Hydroxyethyl starch	Synthetic colloid derived from hydrolyzed amylopectin. **These agents should be avoided in sepsis.** Many harmful effects: renal impairment at recommended doses and impairment of long-term survival at high doses, coagulopathy and bleeding complications from reduced factor VIII and von Willebrand factor levels, impaired platelet function.

alkalosis, hypotonicity from fluids with lactate, and cardiotoxicity from fluids with acetate.[63]

Sodium Bicarbonate Bicarbonate administration shifts the oxygen-hemoglobin dissociation curve to the left, impairs tissue unloading of hemoglobin-bound oxygen, and may worsen intracellular acidosis. However, despite no definitive clinical trials supporting benefit but perhaps harm, many clinicians remain uncomfortable withholding bicarbonate if the pH is <7.00.[64,65] Animal studies of profound acidosis demonstrate decreased ventricular contractility and systolic blood pressure.[13] If bicarbonate is given, recognize the risk of paradoxical intracerebral intracellular acidosis in the process. Consider situations, such as end-stage renal disease and renal tubular acidosis, that cannot reclaim bicarbonate through normal renal processes and whether bicarbonate may be indicated.

DISPOSITION

TRANSITION TO THE INTENSIVE CARE UNIT

Early recognition, treatment, and subsequent transfer of critically ill patients to the intensive care unit improves patient outcomes and improves ED throughput.[23,47] Communicate and document all ED resuscitative efforts to the critical care team. Even when resuscitation is systematic and thoughtful, miscommunication can undo the benefits of initial ED treatment. Ideally, before transfer, verbally communicate and document a system-oriented problem list with an assessment and plan, including all procedures and complications. For prolonged or "boarded" ED stays, constantly reassess the critically ill patient, ensure that care plans are continuing, and consider creating a critical care patient checklist. Often, this will entail ordering tests that are not commonly performed on ED patients or ordering subsequent doses of medicines, particularly antibiotics.

PROGNOSIS

Some clinical variables are associated with poor outcome, such as severity of shock, temporal duration, underlying cause, preexisting vital organ dysfunction, and reversibility. Early recognition, intervention, source control, and smooth care transitions optimize outcomes. While associated morbidity and mortality remain high for patients with shock, integration of protocol-based care pathways with ongoing refinement in response to new information may lead to continued reductions over time.[23,28,34,47] Additional outcome predictions related to physiologic scoring systems, ED-based shock interventions, and the balance between invasive and noninvasive or minimally invasive strategies are still being studied.[23,66,67]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 13

Approach to Traumatic Shock

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INTRODUCTION

Severe hemorrhage after injury carries a mortality rate of 30% to 40% and is responsible for almost 50% of deaths occurring within 24 hours of injury. Hemorrhagic shock is an important contributor to postresuscitation organ failure and late mortality.[1] Resuscitation of traumatic shock, starting in the prehospital setting and continuing throughout the victim's care in the ED and on into the hospital, has the goal of restoring the necessary level of tissue perfusion and oxygenation for survival while simultaneously limiting further volume loss.

This chapter focuses on the issues related to fluid and blood resuscitation in traumatic shock, with an emphasis on hemorrhagic shock. Processes that cause loss of plasma fluid and electrolytes (e.g., burns, sepsis), often requiring aggressive fluid therapy, are discussed in other chapters (see Chapter 151, "Sepsis," and Chapter 217, "Thermal Burns").

The principal objectives of fluid and blood resuscitation in traumatic shock are (1) to restore intravascular volume sufficient to maintain oxygen-carrying capacity and tissue perfusion for adequate cellular oxygen delivery and (2) to prevent or correct derangements in coagulation.

PATHOPHYSIOLOGY

Hemorrhagic shock creates a state of impaired oxidative metabolism and homeostasis, due to inadequate oxygen delivery to meet metabolic demand, and hypoperfusion leading to inadequate cellular waste removal. Hemorrhagic shock triggers a complex range of physiologic responses that may temporarily compensate for intravascular volume loss and maintain perfusion to the most important vascular beds. Shock also produces a global insult to the vascular endothelium that activates the coagulation and inflammatory systems (**Figure 13-1**). When uncorrected, coagulopathy, additional inflammation, and organ system damage will result.

While moderate transient hypoperfusion may be well tolerated, prolonged or severe hypoperfusion leads to accumulation of oxygen debt and progressive cellular and organ dysfunction. If rapid and severe, sudden cardiovascular collapse and death may occur.

Coagulopathy observed in trauma victims, termed *trauma-induced coagulopathy*, is ascribed to a combination of factors beginning with tissue hypoxia, loss of coagulation factors from hemorrhage followed by hemodilution from crystalloid resuscitation, and then exacerbated by acidosis (evidenced by a base deficit) and hypothermia that occur during the course of ongoing hemorrhage and resuscitation.[2,3] However, acidosis does not, by itself, have a significant effect on coagulation until the pH decreases below 7.0.[4]

The normal total circulating volume of an adult is approximately 7% of ideal body weight or about 5 L for an average 70-kg adult patient divided into about 3 L of plasma and 2 L of red blood cell volume (**Table 13-1**). Replacement of lost blood with room temperature isotonic unbuffered crystalloid contributes to hypothermia, hemodilution, and acidosis.

Early trauma-induced coagulopathy is characterized by anticoagulation and hyperfibrinolysis modulated through the protein C pathway.[5] Endothelial damage associated with trauma stimulates an increase in thrombomodulin expression on the endothelium that complexes with thrombin and in turn activates protein C (**Figure 13-2**). Complexed thrombin is now no longer available for its usual hemostatic role of cleaving fibrinogen to form fibrin. Subsequent consumption of plasminogen activator inhibitor-1 by activated protein C contributes to hyperfibrinolysis (Figure 13-2).[6]

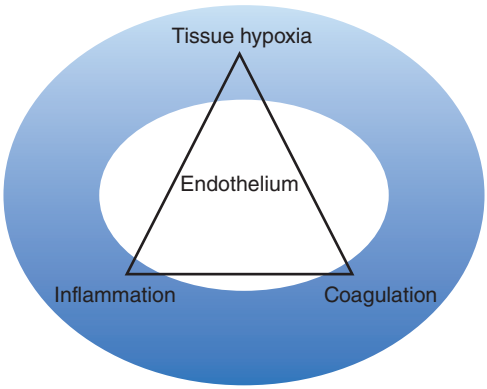

FIGURE 13-1. Endothelium-mediated activation of the triad of hypoxia, inflammation, and coagulation. [©Kevin R. Ward, MD.]

TABLE 13-1 Adult Fluid Spaces

Fluid Compartment	% Body Weight*	% Body Water*	Volume* (70 kg)
Total body water	60	100	42 L
Intracellular	40	67	28 L
Extracellular	20	33	14 L
Interstitial	15	25	10 L
Intravascular	~7–8	~11–13	~5.0–5.5 L
Plasma	~4.0–4.5	~7	~3.0–3.5 L
Red blood cells†	~3.0–3.5	~5	~2.0–2.5 L

*Approximate percentage and amount.

†Percentages do not add up to 100% because fluid contained within intravascular red blood cells is included within the intracellular fluid compartment.

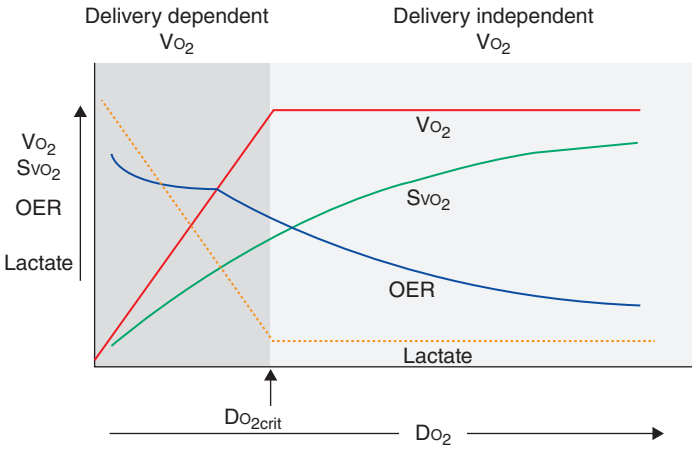

FIGURE 13-3. The biphasic relationship of oxygen delivery (Do_2) and oxygen consumption (Vo_2). As Do_2 decreases, Vo_2 may remain constant due to an increase in the ratio of extracted oxygen (OER) at the tissue level. This is mirrored by a decrease in venous hemoglobin oxygen saturation (Svo_2). However, at some point, OER will not meet the Vo_2 demands of the tissues, resulting in a state of Do_2 dependent Vo_2 whereby aerobic Vo_2 transitions to anaerobic Vo_2. At this point of critical Do_2, oxygen debt begins to accumulate along with metabolic by-products of anaerobiosis such as lactate. While this relationship exists for the body as a whole, it also exists for each individual organ system and is largely mediated by the microcirculation. [© Kevin R. Ward, MD.]

Thrombomodulin normally found in the endothelium may be viewed as locally protective because it is able to sequester thrombin and thus allow for generation of adequate levels of protein C to prevent thrombosis caused by local low-flow states. However, on a systemic level, this appropriate local response may become pathologic, resulting in clotting inhibition.

CLINICAL FEATURES

The clinical appearance of acute traumatic shock is variable and depends on the cause, rate, volume, and duration of volume loss or bleeding; the presence of other acute disorders; the effects of current medications; and the patient's baseline physiologic status.

The hemodynamic response to acute severe hemorrhage-induced hypovolemia traditionally includes tachycardia, hypotension, and signs of poor peripheral perfusion (cool, pale, clammy extremities with weak peripheral pulses and prolonged capillary refill). Arterial and venous vasoconstriction leads to a narrowing of the pulse pressure. Cerebral hypoperfusion causes alterations in mental status. With increasing blood loss, signs and symptoms become more pronounced. **Classification of hemorrhage severity as a percentage of blood volume loss estimated based on systolic blood pressure, heart rate, and Glasgow Coma Scale is not reliable and should not be used to guide ED resuscitation.**[7]

Patients with excellent baseline physiologic status (e.g., young athletes) may have such a robust compensatory response to hemorrhage that they appear stable and do not manifest tachycardia or hypotension, even with large blood volume loss. Signs of peripheral hypoperfusion and subtle mental status alterations may be the only clues that the severity of hemorrhage is greater than predicted based on hemodynamic parameters. Elderly patients may not develop tachycardia due to underlying heart disease or medications such as β-adrenergic blockers. Bradycardia or lack of tachycardia may occur in about 30% of patients with intra-abdominal hemorrhage from increased vagal tone in response to hemoperitoneum. In a pregnant trauma patient, compression of the inferior vena cava by the gravid uterus can decrease central venous return and worsen hypotension and tachycardia in the setting of less severe hemorrhage.

DIAGNOSIS

Vital signs offer little value unless they are in extreme low ranges. Arterial blood pressure does not adequately reflect cardiac output or regional perfusion. Clinical evidence of peripheral hypoperfusion is useful but is not a quantitative measurement. Metabolic information (discussed later), assessment of mechanisms of injury, and appropriate imaging studies offer the best chance for early recognition of severe hemorrhage and for guiding an appropriate response to treatment.

There is a biphasic relationship between oxygen consumption and oxygen delivery (**Figure 13-3**). This relationship exists for the body as a whole, but also is present in each individual organ system largely mediated by the microcirculation. Oxygen debt develops in tissues or organs when oxygen delivery does not meet the metabolic demands and represents the amount of extra oxygen that is needed to metabolize the accumulated

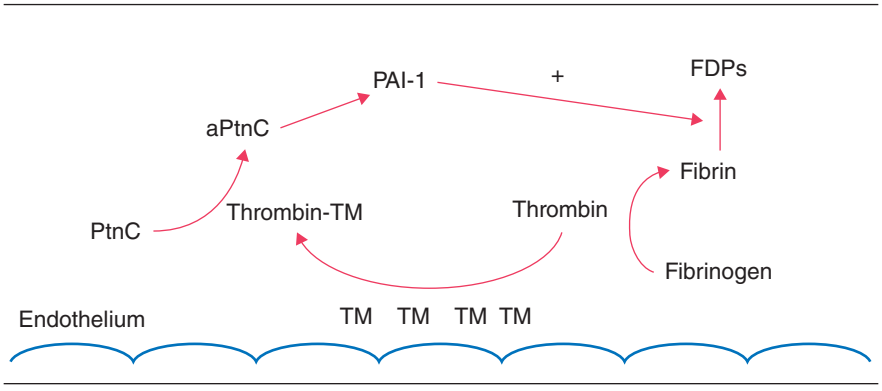

FIGURE 13-2. Endothelial damage results in increased thrombomodulin (TM) expression. TM can complex with thrombin (thrombin-TM complex), leading to activation of the protein C (PtnC to aPtnC) pathway. Modulated through a multistep pathway leading to plasminogen activator inhibitor-1 (PAI-1), fibrinolysis is encouraged, resulting in increased fibrin degradation products (FDPs). In addition, the complexed thrombin is no longer able to perform its usual role in cleaving fibrinogen to fibrin to form clots.

products of anaerobic metabolism once perfusion is restored. Total oxygen debt is the accumulation of multiple oxygen deficits over time and is a measure of whole-body ischemia. Oxygen debt is the only physiologic measure that has clearly been linked to both mortality and morbidity in the form of multiple organ failure after shock. The degree of oxygen debt incurred after injury has also been clearly linked to inflammation.[8]

Measurements of lactate and base deficit are commonly used in trauma centers and EDs to detect occult shock. Using lactate and/or base deficit as a resuscitation trigger and its clearance/normalization as an endpoint is associated with improvements in survival. However, elevated lactate and base deficit are late findings. An earlier finding is an increase in oxygen extraction, indicated by a decrease in indicators of oxygen consumption such as mixed or central venous hemoglobin oxygen saturation (Figure 13-2). Furthermore, improvements in oxygen delivery resulting in lactate clearance do not indicate that oxygen extraction is normal. Although lactate is also a measure of oxygen debt, its resolution during resuscitation does not ensure the important repayment and resolution of oxygen debt.

To overcome the limitations with intermittent lactate or base deficit measurement, continuous measures of oxygen consumption surrogates are available in the form of invasive oximetric catheters measuring central venous oxygen saturation ($ScvO_2$) and tissue oxygen saturation (StO_2) noninvasively from target tissues such as skeletal muscle using near-infrared spectroscopy. StO_2 measurements with infrared spectroscopy are based on the fact that tissue blood volume is 70% to 80% venous blood with the remaining 10% to 20% a combination of arterial and capillary blood. Thus, aggregate measures of hemoglobin oxygenation in the tissue are heavily dominated by the venous blood and thus the postextraction compartment. Although not an exact mirror of $ScvO_2$, ensuring StO_2 values above 50% appears to be reasonable from both a diagnostic and treatment standpoint to begin and sustain hemostatic resuscitation. A target StO_2 or $ScvO_2$ between 60% and 70% should be maintained to help ensure resolution of tissue hypoxia.

TREATMENT

Resuscitation begins in the prehospital setting and continues in the ED. The priority for prehospital care is treatment of life-threatening conditions and rapid transport to an appropriate facility. For the hemorrhaging patient, this entails ensuring adequate ventilation and oxygenation (including securing an airway if necessary), controlling external bleeding (if present), and protecting the spinal cord (if potentially vulnerable).

In the ED, priorities are to **restore intravascular volume** to reverse or limit systemic and regional hypoperfusion, **maintain oxygen-carrying capacity** so that tissue oxygen delivery meets demand, **limit ongoing blood loss**, and **prevent the development of coagulopathy**. From the moment resuscitation begins, prevent the development of **hypothermia** by keeping the patient warm and administering warmed IV fluids and blood products.[9] Endogenous hypothermia occurs when heat production from cellular respiration is decreased by hypoperfusion and inadequate tissue oxygen delivery. Major causes of exogenous hypothermia are exposure and the use of below-body-temperature fluid and blood resuscitation. Apply external warming devices early to prevent external heat escape. Warming devices that allow for the rapid warming of infused fluid and blood should be used for all patients in whom large-volume resuscitation is undertaken.[9]

AIRWAY CONTROL, VENTILATION, AND OXYGENATION

If spontaneous ventilation is not adequate, intubate and ventilate to achieve an arterial hemoglobin oxygen saturation of ≥94%. Identify and treat potential respiratory conditions such as pneumothorax, tension pneumothorax, hemothorax, or upper airway obstruction.

VASCULAR ACCESS AND MONITORING

Establish adequate IV access concurrent with airway management. Large-bore (14- to 16-gauge in adults) peripheral lines may be adequate if two or more can be secured. Intraosseous lines are suitable for resuscitation when peripheral IV access is problematic.

Institute continuous ECG heart rate monitoring, continuous pulse oximetry, and, if possible, continuous end-tidal carbon dioxide monitoring. Monitor arterial blood pressure, mental status, and peripheral perfusion frequently. Bedside FAST and POCUS are useful to identify intraperitoneal bleeding, assess cardiac function and volume status, and assist in central venous cannulation.

HEMOSTATIC-HYPOTENSIVE RESUSCITATION

A principle of hemostatic resuscitation is to limit intravascular volume expansion and avoid normalization of blood pressure. Complete normalization of blood pressure will raise hydrostatic pressure and can increase hemorrhage, which is particularly evident in noncompressible hemorrhage where raising blood pressure could potentially "pop the clot" and reestablish active hemorrhage.

Hypotensive resuscitation limits initial fluid resuscitation to an acceptable systolic blood pressure goal until surgical control of the bleeding is obtained, usually in the operating room.[10] The acceptable value has sometimes been defined as 90 mm Hg (12.0 kPa), although there is no supporting data for this value. Alternatively, the specific value for acceptable systolic blood pressure can be pragmatically chosen as the initial value below which adverse physiologic outcomes increase. This occurs at about a systolic blood pressure of 110 mm Hg (14.7 kPa) for civilian trauma patients[11] and 100 mm Hg (13.3 kPa) for combat casualties.[12] The overall benefit of low-volume hypotensive resuscitation is supported by civilian studies.[13]

Hypotensive resuscitation may be harmful to some patients, such as those with head injury, hypertension, coronary artery disease, or cerebral vascular disease where a low systolic pressure exacerbates end-organ hypoperfusion. **Hypotensive resuscitation should not be used in patients with myocardial disease, cerebral ischemia, or traumatic brain injury.**[14] Obviously, there is not an unlimited time span that patients can tolerate hypotensive resuscitation. From a cellular standpoint, patients will at some time incur irreversible damage from prolonged tissue hypoxia if adequate tissue oxygenation is not restored.

ISOTONIC CRYSTALLOID SOLUTIONS

Isotonic crystalloids—normal saline and lactated Ringer's solution—are the most commonly used resuscitation fluids in the United States. Concerns about each fluid are as follows: (1) infusion of large volumes of either normal saline or lactated Ringer's solution can cause increased neutrophil activation; (2) lactated Ringer's solution can increase cytokine release and may increase lactic acidosis when given in large volumes; and (3) normal saline can exacerbate intracellular potassium depletion and cause hyperchloremic acidosis.[15]

Crystalloid solutions are isotonic but hypo-oncotic, because they lack the large protein molecules present in the plasma. Low oncotic pressure results in substantial shifts of crystalloid to the extravascular space corresponding to the relative size of the intravascular and interstitial fluid compartments (**Table 13-2**). This was the physiologic basis for the 3:1 ratio for crystalloid to blood; for every amount of blood lost, three times that amount of isotonic crystalloid is required to restore intravascular volume because, at best, about 30% of the infused fluid stays intravascular. Based on this rule, a loss of 1 L of blood (about 15% to 20% of total circulating blood volume) would require about 3 L of isotonic crystalloid to restore normovolemia, assuming no ongoing blood loss.

TABLE 13-2 Theoretical Volemic Effect of 1 L of Fluid Administration on Fluid Compartments

	Intracellular (mL)	Interstitial (mL)	Plasma (mL)
5% dextrose in water	660	255	85
Normal saline or Ringer's lactate	−100	825	275
7.5% saline	−2950	2960	990
5% albumin	0	500	500
Whole blood	0	0	1000

TABLE 13-3 Isotonic Fluid Composition*

Fluid	Na^+ (mmol/L)	K^+ (mmol/L)	Ca^{++} (mmol/L)	Mg^{++} (mmol/L)	CL^- (mmol/L)	Buffer (mmol/L)	Osmolarity (mOsm/L)
Normal saline	154	0	0	0	154	None	308
Ringer's lactate	130	4	1.4	0	109	28 lactate	273
Ringer's acetate	130	5	1	1	112	27 acetate	276
Hartmann's	131	5	2	0	111	29 lactate	278
Plasma-Lyte A®	140	5	0	1.5	98	27 acetate 23 gluconate	294

*Minor variations may exist between different commercial manufacturers.

Common modifications of isotonic fluids include use of acetate instead of lactate in Ringer's solution, Hartmann's solution, and Plasma-Lyte® (**Table 13-3**). Plasma-Lyte is the shared name for a family of isotonic crystalloid solutions available worldwide, marketed with variation in composition according to regional preferences. Solutions containing lactate or acetate are considered **balanced crystalloids** because they are buffered and have a lower chloride concentration compared to normal saline. Balanced crystalloids yield better clinical outcomes compared to normal saline in both critically ill and non–critically ill patients from all causes, although the effect is small (number needed to treat is approximately 90).[16,17] Ringer's lactate is compatible with current red blood cell preservatives.

COLLOIDS

Despite theoretical and animal model benefits, clinical trials of colloid resuscitation for traumatic shock have not demonstrated a clear survival benefit or reduction in morbidity.[18] The one advantage of colloids is that achievement of hemodynamic goals requires less volume to be infused. However, initiating resuscitation with plasma—a colloid solution—instead of crystalloids as part of a hemostatic resuscitation along with red cells as needed conferred a survival advantage in hypotensive predominantly blunt trauma patients transported by air medical services[19], but this effect was not seen in an urban ground EMS system with equal number of blunt and penetrating trauma victims.[20] In light of these studies, serious consideration should be given to severely restricting the use of crystalloids and instead beginning the early use of blood products in blunt trauma victims, especially if ongoing hemorrhage is expected or operative repair is going to be delayed.[21]

PACKED RED BLOOD CELLS

Packed red blood cells (PRBCs) are the most commonly transfused blood product (see Chapter 238, "Transfusion Therapy"). Using only PRBCs in the patient with traumatic shock and ongoing bleeding (without plasma and platelets) will do little to promote hemostasis and may not fully restore tissue oxygenation. If hemorrhage is definitively controlled, do not transfuse if the hemoglobin concentration is >7 grams/dL (>70 grams/L) for those without cardiopulmonary, cerebral, or peripheral vascular disease.[21,22] For those with comorbidities such as coronary artery or cerebrovascular disease, clinical judgment should be used for achieving and maintaining minimum hemoglobin levels, with the general principle that there is no benefit to transfusion when the hemoglobin concentration is >10 grams/dL (>100 grams/L).[21,22]

When possible, typed and cross-matched blood is preferable. However, if time and the patient's clinical status do not permit full cross-matching, type-specific blood is the next option, followed by low-titer O-negative blood. In U.S. blood banks, whole blood is not routinely stocked, and only PRBCs are available. See Chapter 302, "Military Medicine," for discussion of whole-blood transfusion in trauma combat casualty care.

PRBC transfusion obviously restores lost hemoglobin. Using current preservatives, PRBCs can be stored for up to 45 days, and the average age of a unit of blood administered in the United States is about 21 days. Stored red blood cells can lose deformability (storage lesion), limiting their ability to pass normally through capillary beds or even resulting in capillary plugging. The oxygen dissociation curve is altered by loss of 2,3-diphosphoglycerate in the erythrocytes of stored PRBCs, impeding the off-loading of oxygen at the tissue level. Despite these changes, no consistent harm has been identified with use of "older" stored blood.[23]

PLASMA

Fresh frozen plasma (FFP) is plasma obtained after the separation of whole blood from red blood cells and platelets and then frozen within 8 hours. A unit of FFP has a volume of 200 to 250 mL and contains all the coagulation factors present in fresh blood. Kept frozen, FFP can be stored for up to a year after the unit was collected. It takes between 15 and 20 minutes to thaw a unit of FFP in a 37°C water bath, which can limit availability in a massive transfusion situation. However, some major trauma centers and their respective blood banks keep thawed FFP (kept at 1°C to 6°C) available for immediate use. When transfusing FFP, ABO compatibility is required, but because there are no red cells in FFP, Rh compatibility is less important; universal donor FFP is typically AB+ (see Chapter 238) and does not require cross-matching for emergency use.

Dried plasma is currently used by combat medical personal in European and Israeli military forces.[24] When reconstituted, this product both restores volume and hemostatic factors. There is no currently available U.S. Food and Drug Administration–approved dried plasma product.

PLATELETS

Platelets are collected from whole-blood donations or from single donors using apheresis techniques and can be stored for up to only 5 days. Six units of pooled random-donor platelet concentrate or one apheresis-collected single-donor platelet concentrate in an adult will increase platelet count up to 50,000/mm^3 (50×10^9/L).

MASSIVE TRANSFUSION PROTOCOLS

CONCEPT

Massive transfusion is generally defined as the requirement for >10 units of PRBCs within the first 24 hours of injury. An estimated 10% of military trauma patients and 3% to 5% of civilian trauma patients receive massive transfusion. Massive transfusion is not a substitute for definitive surgical hemostasis but enhances the ability to achieve surgical hemostasis and to limit complications.[25] Several accurate and validated tools exist to predict the need for massive transfusion in trauma.[26] The Assessment of Blood Consumption score uses four values available on patient arrival: penetrating mechanism of injury, positive FAST examination, blood pressure <90 mm Hg (<12.0 kPa), and pulse rate >120 beats/min. The presence of two or more variables has a sensitivity for massive transfusion of 76% to 90%, with a specificity of 67% to 87%.[27] If hemorrhage is clinically significant and immediate hemostasis is not achievable, transition from crystalloid-based resuscitation to a plasma-based massive transfusion protocol.

Draw sufficient specimens from the patient early in anticipated massive transfusion because once the patient has received close to one blood volume of transfused products, new blood specimens will contain so

much donor blood that cross-matching of subsequent units is difficult. Initially use isotonic solutions to begin resuscitation in predetermined aliquots (250 to 500 mL) while assessing the likelihood of ongoing active hemorrhage and the need for further resuscitation.[28]

PROTOCOL

Soldiers receiving high ratios of plasma to PRBC (a plasma:PRBC ratio of approximately 1:1.4) have significantly improved survival rates compared with those receiving lower ratios (between 1:1.8 and 1:2.5). Additional evidence supporting this also comes from combat casualty care data suggesting that early administration of fresh whole blood (something not currently practical in civilian trauma) offers survival advantages.[29] These survival observations using high plasma-to-PRBC ratios were confirmed by civilian studies.[30,31]

High plasma-to-PRBC ratio resuscitation appears to also offer survival benefit independent of coagulopathy, and plasma may enhance cell survival by endothelial repair and reducing vascular permeability. It may also be that plasma is simply a superior fluid for perfusion and tissue oxygenation restoration.

In addition, many trauma centers now include early platelet administration in predetermined ratios to plasma and PRBC in their resuscitation protocols based on findings that platelet function can rapidly decrease soon after trauma. Studies using platelets during massive transfusion have shown improved clinical outcomes in mortality and blood loss.[31-33] Some experts advocate a 1:1:1 ratio of PRBCs to platelets to FFP during massive transfusion, but the optimal ratio is unknown.[32] Likewise, the benefits with adjunctive agents such as prothrombin complex concentrates and fibrinogen concentrate included in some protocols are unknown.[32,33]

An institution-specific massive transfusion protocol is recommended to guide the clinician when ordering blood components and to facilitate release from the blood bank (**Figure 13-4**).

ADJUNCTS

Tranexamic Acid Currently, tranexamic acid (an antifibrinolytic) is advocated early in the resuscitation of major trauma victims based on the early fibrinolytic phase of trauma-induced coagulopathy and on clinical studies suggesting improved survival. Military and civilian studies have shown that the administration of tranexamic acid to bleeding trauma patients reduces overall mortality.[34-36] Ongoing studies are seeking to define which specific patient group most benefits from the administration of tranexamic acid (see Chapter 254, "Trauma in Adults").

Calcium PRBCs and FFP contain citrate that can complex calcium, producing life-threatening hypocalcemia.[37] Most massive transfusion protocols include the administration of calcium and/or monitoring of ionized calcium. Calcium chloride is preferred over calcium gluconate because a well-perfused liver is required to liberate more free calcium from calcium gluconate. Maintain ionized calcium levels at or above 0.9 mmol/L.[38]

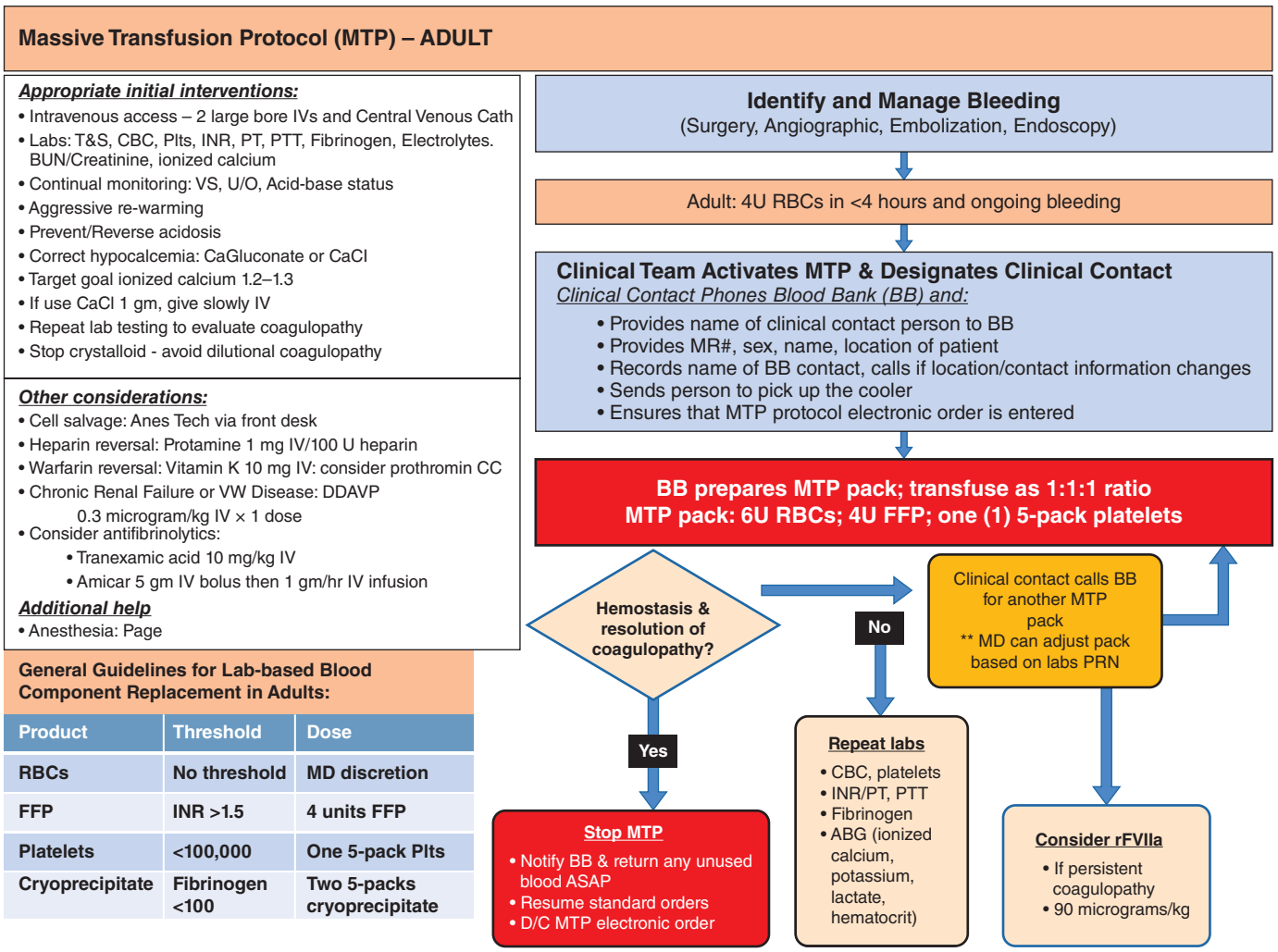

FIGURE 13-4. Massive transfusion protocol (MTP) from the University of Michigan's Level I Trauma Center. ABG = arterial blood gas; D/C = discontinue; DDAVP = desmopressin; FFP = fresh frozen plasma; MD = physician; Plts = platelets; PT = prothrombin time; RBCs = red blood cells; T&S = type and screen; U/O = urine output; VS = vital signs; VW = von Willebrand's.

Viscoelastic Hemostatic Assays The blood coagulation system consists of nearly 80 very tightly coupled biochemical reactions. Conventional coagulation testing such as the prothrombin time and activated partial thromboplastin time does not account for the cellular components of the clot such as red cells and platelets. Because the blood clot itself consists of a complex three-dimensional network of cross-linked fibers made of fibrin, platelets, and red cells entrapped within this mesh, newer viscoelastic hemostatic assays, namely **thromboelastography** and rotational **thromboelastometry**, measure the physical and dynamic characteristics of clotting. Thromboelastography and thromboelastometry can detect trauma-induced coagulopathy and can be used to guide massive transfusion protocols better than traditional prothrombin time and activated partial thromboplastin time assays.[39] Recent studies indicate trauma resuscitations guided by such viscoelastic hemostatic assays improve survival and reduce total blood product use.[40]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

TABLE 14-2 Common Causes for Anaphylaxis, Anaphylactoid, and Allergic Reactions

Drugs	Foods and Additives
• β-Lactam antibiotics	• Shellfish
• Acetylsalicylic acid (ASA)	• Soybeans
• Trimethoprim-sulfamethoxazole	• Nuts (peanuts and tree nuts)
• Vancomycin	• Wheat
• NSAIDs	• Milk
• Virtually any drug	• Eggs
Others	• Salicylates
• Hymenoptera stings	• Seeds
• Insect parts	• Sulfites
• Molds	• Mammalian meat (galactose-alpha-1,3-galactose [alpha-gal])
• Radiographic contrast material	
• Vaccines	
• Latex	
• Blood products	

CHAPTER 14

Allergy and Anaphylaxis

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Brian Grunau

ANAPHYLAXIS

INTRODUCTION

Anaphylaxis is a serious allergic reaction, with a rapid onset; it may cause death and requires emergent diagnosis and treatment. Consensus clinical criteria provide consistency for diagnosis (**Table 14-1**).[1-3]

The terms *anaphylactic* and *anaphylactoid* were previously applied to immunoglobulin E (IgE)-dependent and IgE-independent events, respectively. Because the final pathway in both events is identical, *anaphylaxis* is the term now used to refer to both.[4] Hypersensitivity is an inappropriate immune response to generally harmless antigens, representing a continuum from minor to severe manifestations. Anaphylaxis represents the most dramatic and severe form of immediate hypersensitivity.

Foods, medications, insect stings, and allergen immunotherapy injections are the most common provoking factors for anaphylaxis, but any agent capable of producing a sudden degranulation of mast cells or basophils can induce anaphylaxis (**Table 14-2**).[5,6] Latex hypersensitivity is increasing in prevalence in the general population, with a resultant risk for anaphylaxis. In addition, a significant number of anaphylaxis cases have no identified cause, termed *idiopathic anaphylaxis*.[7] The lifetime individual risk of anaphylaxis is estimated to be 1% to 3%, but the prevalence of anaphylaxis may be increasing.[8] Although allergic reactions are a common cause for ED visits,[9] anaphylaxis is likely underdiagnosed.[10,11]

TABLE 14-1 Clinical Criteria for Anaphylaxis

- Urticaria, generalized itching or flushing, or edema of lips, tongue, uvula, or skin developing over minutes to hours and associated with at least 1 of the following:
  - Respiratory distress or hypoxia
    or
  - Hypotension or cardiovascular collapse
    or
  - Associated symptoms of organ dysfunction (e.g., hypotonia, syncope, incontinence)
- Two or more signs or symptoms that occur minutes to hours after allergen exposure:
  - Skin and/or mucosal involvement
  - Respiratory compromise
  - Hypotension or associated symptoms
  - Persistent GI cramps or vomiting
- Consider anaphylaxis when patients are exposed to a known allergen and develop hypotension

PATHOPHYSIOLOGY

Anaphylaxis, for the most part, arises from the activation of mast cells and basophils through a mechanism involving crosslinking of IgE and aggregation of the high-affinity receptors for IgE.[6] Upon activation, mast cells and/or basophils quickly release preformed mediators from secretory granules that include histamine, tryptase, carboxypeptidase A, and proteoglycans. Downstream activation of phospholipase A_2, followed by cyclooxygenases and lipoxygenases, produces arachidonic acid metabolites, including prostaglandins, leukotrienes, and platelet-activating factor. The inflammatory cytokine, tumor necrosis factor-α, is released as a preformed mediator and also as a late-phase mediator with other cytokines and chemokines.

These mediators are responsible for the pathophysiology of anaphylaxis. Histamine stimulates vasodilation and increases vascular permeability, heart rate, cardiac contraction, and glandular secretion. Prostaglandin D_2 is a bronchoconstrictor, pulmonary and coronary vasoconstrictor, and peripheral vasodilator. Leukotrienes produce bronchoconstriction, increase vascular permeability, and promote airway remodeling. Platelet-activating factor is also a potent bronchoconstrictor and increases vascular permeability. Tumor necrosis factor-α activates neutrophils, recruits other effector cells, and enhances chemokine synthesis. These overlapping and synergistic physiologic effects contribute to the overall pathophysiology of anaphylaxis.[6]

CLINICAL FEATURES

The classic presentation of anaphylaxis begins with pruritus, cutaneous flushing, and urticaria. These symptoms are followed by a sense of fullness in the throat, anxiety, a sensation of chest tightness, shortness of breath, and lightheadedness. A complaint of a "lump in the throat" and hoarseness heralds life-threatening laryngeal edema in a patient with symptoms of anaphylaxis. These major symptoms may be accompanied by abdominal pain or cramping, nausea, vomiting, diarrhea, bronchospasm, rhinorrhea, conjunctivitis, and/or hypotension. As the cascade progresses, respiratory distress, decreased level of consciousness, and

circulatory collapse may ensue. In severe cases, loss of consciousness and cardiorespiratory arrest may result.

In most patients, signs and symptoms begin suddenly, often immediately and usually within 60 minutes of exposure. In general, the faster the onset of symptoms, the more severe the reaction—**one half of anaphylactic fatalities occur within the first hour**. After the initial signs and symptoms abate, patients are at a small risk for a recurrence of symptoms caused by a second phase of mediator release, peaking 8 to 11 hours after the initial exposure and manifesting symptoms and signs 3 to 4 hours after the initial clinical manifestations have cleared. The late-phase allergic reaction is primarily mediated by the release of newly generated cysteinyl leukotrienes, the former slow-reacting substance of anaphylaxis. The incidence of this biphasic phenomenon has been reported to vary widely up to 20%; however, prospective studies specifically searching for clinically important biphasic events report a much lower incidence (4% to 5%).[12,13]

DIAGNOSIS

The diagnosis of anaphylaxis is clinical. Consider anaphylaxis when involvement of any two or more body systems is observed, with or without hypotension or airway compromise (**Table 14-3**).[1,15] The diagnosis is easily made if there is a clear history of exposure, such as a bee sting, shortly followed by the multisystem signs and symptoms described earlier. Unfortunately, the diagnosis is not always easy or clear, because symptom onset may be delayed, symptoms may mimic other presentations (e.g., syncope, gastroenteritis, anxiety), or anaphylaxis may be a component of other diseases (e.g., asthma).

The differential diagnosis of anaphylactic reactions is extensive, including vasovagal reactions, myocardial ischemia, dysrhythmias, severe acute asthma, seizure, epiglottitis, hereditary angioedema, foreign body airway obstruction, carcinoid, mastocytosis, vocal cord dysfunction, and non–IgE-mediated drug reactions. The most common anaphylaxis imitator is a vasovagal reaction, which is characterized by hypotension, pallor, bradycardia, diaphoresis, and weakness, and sometimes by loss of consciousness.

Laboratory investigations are of minimal utility and should be limited in the ED setting.[16] Serum histamine levels, elevated for 5 to 30 minutes after reaction, are unhelpful because they are typically normal upon ED presentation. Tryptase is a neutral protease of unknown function in anaphylaxis that is found only in mast cell granules and is released with degranulation. Serum tryptase levels are elevated for several hours and have been proposed for later confirmation of a suspected anaphylactic episode. This test, however, has poor sensitivity; about one third of patients with an acute anaphylaxis episode have a normal serum tryptase level upon ED arrival,[17] and some patients experience severe anaphylaxis without elevated tryptase levels.[18]

TABLE 14-3 Clinical Manifestations of Anaphylaxis

System	Signs and Symptoms (approximate incidence)
ENT	Oropharyngeal or throat fullness (50%) Tongue swelling (1%–2%) Uvular edema/hydrops (1%–5%)
Respiratory	Shortness of breath and/or wheezing (45%–50%) Pharyngeal or laryngeal edema (50%–60%) Stridor (rare) Rhinitis (30%–35%)
Cardiovascular	Hypotension (30%–35%) Chest pain (4%–5%)
Skin	Urticaria and/or angioedema (60%–90%) Flushing (45%–55%) Pruritus only (2%–5%)
GI	Nausea, emesis, cramps, or diarrhea (25%–30%)
Neurologic	Headache (5%–8%) Seizure (1%–2%)

Abbreviation: ENT = ear, nose, and throat; GI = gastrointestinal.

TREATMENT

Triage for all acute allergic reactions should be at the highest level of urgency because of the possibility of sudden deterioration.[10] Current treatment recommendations are derived from the clinical experience of experts as professed in consensus statements and guidelines.[16,19-21]

FIRST-LINE THERAPY

Emergency management starts with assessment of airway, breathing, and circulation. Assess vital signs and pulse oximetry. Initiate IV access, oxygen administration, and cardiac rhythm monitoring in patients with severe symptoms. The first-line therapies for anaphylaxis (airway protection, oxygen, decontamination, epinephrine, IV crystalloids) have immediate effect during the acute stage.[20-23]

Airway and Oxygenation **In severe anaphylaxis, securing the airway is the first priority.** Examine the mouth, pharynx, and neck for signs and symptoms of angioedema: uvula edema or hydrops, audible stridor, respiratory distress, or hypoxia. If angioedema is producing respiratory distress, intubate early, since any delay may result in complete airway obstruction secondary to progression of angioedema. Provide supplemental oxygen to maintain arterial oxygen saturation >90%.

Decontamination If the causative agent can be identified, termination of exposure should be attempted. Gastric lavage is **not recommended** for foodborne allergens and may be associated with complications (i.e., aspiration) and delays in the administration of more effective treatments (e.g., epinephrine). In insect stings, remove any remaining stinging remnants because the stinger continues to inject venom even if it is detached from the insect (see Chapter 211, "Bites and Stings").

Epinephrine Epinephrine (adrenaline) is a mixed α_1- and β-receptor agent. The α_1-receptor activation reduces mucosal edema and treats hypotension, β_1-receptor stimulation increases heart rate and myocardial contractility, and β_2-receptor stimulation provides bronchodilation and limits further mediator release.[16] **Epinephrine is the treatment of choice for anaphylaxis.[16,19,24,25] However, observational studies indicate that it is underused, often dosed suboptimally, and underprescribed upon discharge for potential future self-administration.[9,11]** Most of the reasons proposed to withhold epinephrine are flawed, and the therapeutic benefits of epinephrine exceed the risk when given in appropriate routes and doses, even in elderly patients.[24]

In patients without signs of cardiovascular compromise or collapse, administer epinephrine IM (**Table 14-4**).[26] **Repeat every 5 to 10 minutes according to response or if relapse occurs.** Injections into the thigh are more effective at achieving peak blood levels than injections into the deltoid area.[26] Intramuscular dosing is recommended because it provides higher, more consistent, and more rapid peak blood epinephrine levels than SC administration.[26,27] For convenience and accurate dosing, many EDs have adopted the use of epinephrine autoinjectors, such as EpiPen® (0.3 milligrams of epinephrine for adults; Dey, L.P., Napa, CA) and EpiPen Junior® (0.15 milligrams of epinephrine for children <30 kg; Dey, L.P.); however, recent shortages in production have demonstrated the need for multiple sources of the drug. Some evidence suggests that expired epinephrine autoinjectors retain potency many months to years after their expiration date.[28] While retaining an expired EpiPen® may be a reasonable safety strategy for patients, it does not negate the need for a new prescription.

Most patients with anaphylaxis need only a single dose of epinephrine IM. Blood pressure should be checked in patients taking β-blockers, because epinephrine use may result in severe hypertension secondary to unopposed α-adrenergic stimulation. Age is not a barrier to epinephrine IM injections in patients with anaphylaxis.

If the patient is refractory to treatment despite repeated doses of epinephrine IM or has signs of cardiovascular compromise or collapse, then an epinephrine IV bolus and/or infusion should be instituted.

TABLE 14-4 Drug Treatment of Anaphylaxis and Allergic Reactions

Drug	Adult Dose	Pediatric Dose
First-Line Therapy		
Epinephrine	IM: 0.3–0.5 milligram (0.3–0.5 mL of 1:1000 dilution); *or* EpiPen® 0.3 milligram epinephrine (or equivalent preformulated product)	IM: 0.01 milligram/kg (0.01 mL/kg of 1:1000 dilution) *or* EpiPen Junior® 0.15 milligram of epinephrine (or equivalent preformulated product)
	IV bolus: 100 micrograms over 5–10 min; mix 0.1 milligram (0.1 mL of 1:1000 dilution) in 10 mL NS and infuse over 5–10 min	
	IV infusion: start at 1 microgram/min; mix 1 milligram (1 mL of 1:1000 dilution) in 500 mL NS and infuse at 0.5 mL/min; titrate dose as needed	IV infusion: 0.1–0.3 microgram/kg per min; titrate dose as needed; maximum, 1.5 micrograms/kg per min
Oxygen	Titrate to Sa_{O_2} ≥90%	Titrate to Sa_{O_2} ≥90%
IV fluids: NS or LR	1–2 L bolus	10–20 mL/kg bolus
Second-Line Therapy		
H_1 Blockers		
Diphenhydramine	25–50 milligrams IV, IM, or PO every 6 h	1 milligram/kg IV, IM, or PO every 6 h
H_2 Blockers		
Ranitidine	50 milligrams IV over 5 min	0.5 milligram/kg IV over 5 min
Cimetidine	300 milligrams IV	4–8 milligrams/kg IV
Corticosteroids		
Hydrocortisone	250–500 milligrams IV	5–10 milligrams/kg IV (maximum, 500 milligrams)
Methylprednisolone	80–125 milligrams IV	1–2 milligrams/kg IV (maximum, 125 milligrams)
Prednisone	40–60 milligrams PO daily or 20–30 milligrams PO twice daily	1–2 milligrams/d PO divided twice a day or daily
	To be used after initial IV dose (for outpatients: 3–5 d; tapering not required)	To be used after initial IV dose (for outpatients: 3–5 d; tapering not required)
Treatment of Bronchospasm, Add:		
Albuterol (salbutamol)	Single treatment: 2.5–5.0 milligrams nebulized (0.5–1.0 mL of 0.5% solution)	Single treatment: 1.25–2.5 milligrams nebulized (0.25–0.5 mL of 0.5% solution)
	4–6 puffs from MDI with holding chamber	4–6 puffs from MDI with holding chamber
	Both repeated every 20 min as needed	Both repeated every 20 min as needed
	Continuous nebulization: 5–10 milligrams/h	Continuous nebulization: 3–5 milligrams/h
Ipratropium bromide	Single treatment: 250–500 micrograms nebulized	Single treatment: 125–250 micrograms nebulized
	4–6 puffs from MDI with holding chamber	4–6 puffs from MDI with holding chamber
	Both repeated every 20 min as needed	Both repeated every 20 min as needed
Magnesium sulfate	2 grams IV over 20 min	25–50 milligrams/kg IV over 20 min
Treatment for Patients on β-Blockers with Refractory Hypotension, Add:		
Glucagon	1 milligram IV every 5 min until hypotension resolves, followed by 5–15 micrograms/min infusion	50 micrograms/kg IV every 5 min

Abbreviations: H_1 = histamine-1; H_2 = histamine-2; LR = lactated Ringer's; MDI = metered-dose inhaler; NS = normal saline; Sa_{O_2} = arterial oxygen saturation.

The initial epinephrine IV bolus is a dilute solution of 100 micrograms (0.1 milligram) IV, given over 5 to 10 minutes.

If the patient is refractory to the initial bolus, institute an epinephrine IV infusion, starting at 1 microgram/min and titrating to effect. There is a higher risk of cardiovascular complications when epinephrine IV is used to treat anaphylaxis.[29] It should be stressed that the initial IV bolus dose is very dilute, is given over 5 to 10 minutes, and should be stopped immediately if dysrhythmias or chest pain occur.

IV Crystalloids Hypotension is generally the result of distributive shock and responds well to fluid resuscitation.[16] A bolus of 1 to 2 L (10 to 20 mL/kg in children) of isotonic crystalloid solution should be administered concurrently with epinephrine. There is no evidence that albumin or hypertonic saline should replace crystalloids.[30]

SECOND-LINE THERAPY

The second-line anaphylaxis treatments include corticosteroids, antihistamines, inhaled bronchodilators, vasopressors, and glucagon.[16,19-21] These drugs are used to treat anaphylaxis refractory to the first-line treatments or associated with complications and also to prevent recurrences.[23]

Corticosteroids Patients with anaphylaxis often receive corticosteroids to prevent protracted and biphasic reactions, although evidence for clinical benefit is scant and primarily derived from acute asthma studies.[19-21,23,31-33] Methylprednisolone, 80 to 125 milligrams IV (2 milligrams/kg in children; up to 125 milligrams), and hydrocortisone, 250 to 500 milligrams IV (5 to 10 milligrams/kg in children; up to 500 milligrams), are equally effective. The mineralocorticoid effects of corticosteroids are ranked in declining order. Hydrocortisone and cortisone have the strongest effects, followed by prednisone. Methylprednisolone and dexamethasone have the lowest mineralocorticoid effect and produce less fluid retention than hydrocortisone and cortisone and thus are preferred for the elderly and for those in whom fluid retention would be problematic.

Antihistamines Consensus guidelines recommend that most patients with anaphylaxis should receive an H_1 antihistamine, such as diphenhydramine, 25 to 50 milligrams IV by slow infusion or via IM injection,[16,19-21,23] although clinical benefit is unproven.[34] In severe cases, especially with circulatory shock, guidelines recommend H_2 antihistamines, such as ranitidine or cimetidine,[19-21,23] although evidence for benefit is lacking.[35] Cimetidine should not be used for patients who are elderly (side effects), have multiple comorbidities (interference with metabolism of many drugs), have renal or hepatic impairment, or whose anaphylaxis is complicated by β-blocker use (cimetidine prolongs metabolism of β-blockers and may prolong anaphylactic state). After the initial IV dose of corticosteroids and antihistamines, the patient may be switched to oral administration (Table 14-4).

Vasopressors In patients with anaphylaxis and shock resistant to initial treatment, including repeated doses of IM epinephrine, oxygen, and IV crystalloids, initiate IV epinephrine infusion. If dangerous dysrhythmias or tachycardia result from epinephrine, other agents (e.g., dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, or vasopressin) may be effective, and superiority from a specific agent has not been demonstrated.[16,19-21] Clinicians should use the agent they feel most comfortable with and titrate according to the clinical response.

AGENTS FOR ALLERGIC BRONCHOSPASM

A β_2 bronchodilator, such as intermittent or continuous nebulized albuterol/salbutamol, should be instituted if wheezing is present. Asthmatics are often more refractory to the treatment of allergic bronchospasm. For severe bronchospasm refractory to inhaled albuterol/salbutamol, inhaled anticholinergics and IV magnesium sulfate can be added (Table 14-4).[31,36] Bronchodilators should be given at a lower dose and at a slower rate in elderly patients. IV aminophylline is not recommended. Leukotriene receptor antagonists are not effective for the treatment of anaphylaxis.

GLUCAGON

Concurrent use of β-blockers is a risk factor for severe prolonged anaphylaxis. For patients taking β-blockers with hypotension refractory to fluids and epinephrine, glucagon IV should be used every 5 minutes until hypotension resolves, followed by an infusion (Table 14-4).[16,19-21] The side effects of glucagon include nausea, vomiting, hypokalemia, dizziness, and hyperglycemia.

DISPOSITION AND FOLLOW-UP

With appropriate initial treatment, admission to hospital is rare, only required in about 1% to 4% of acute allergic reactions treated in the ED.[9,13] All unstable patients with anaphylaxis refractory to treatment or in whom airway interventions were required should be admitted to the intensive care unit. While patients who receive epinephrine IM should be observed in the ED, the precise duration of observation is unclear.[12,13] Otherwise healthy patients who remain symptom free for one or 6 hours after appropriate treatment can be discharged home with less than 5% or 3% incidence, respectively of a biphasic reaction.[14]

Consider prolonged observation in patients with a past history of severe reaction and those using β-blockers. Although the risk of important biphasic reactions after ED discharge is low,[13] patients who live alone, reside long distances from medical care, have significant comorbidity (including but not limited to asthma), or are elderly should be observed longer before discharge.

Patients with severe allergic reactions or anaphylaxis are usually discharged with prescriptions for antihistamines and corticosteroids for 3 to 5 days and a prescription for an epinephrine autoinjector. Although prolonged corticosteroid treatment should not be required for most patients, an aggressive longer-term approach (1 to 2 weeks or until symptoms are controlled) appears to reduce the frequency of relapses in patients with idiopathic anaphylaxis.[7]

Discharge instructions should provide recommendations to prevent future episodes (**Table 14-5**).[37] For all allergic reactions, instruct the patient on how to avoid future exposure to the causative agent (if the agent is known). Prescribe an epinephrine autoinjector to patients with serious allergic reactions or anaphylaxis with clear instructions on the use of the autoinjector. Overall, less than one third of patients and parents of children with anaphylaxis can demonstrate the effective use of an epinephrine autoinjector device, so education is a key component of discharge instructions. If delay in filling a prescription is anticipated, patients can be discharged from the ED with an epinephrine autoinjector (EpiPen®). Reinforce this prescription with documentation in the ED discharge instructions. Because allergic occurrences are unpredictable, prescriptions should include sufficient samples for multiple locations (e.g., home, vehicle, work), and patients should be advised to carry epinephrine with them at all times. Unfortunately, research in the United States suggests that fewer than half of children, adolescents, and adults carry their epinephrine autoinjector devices with them.[38]

TABLE 14-5 Discharge Planning for Patients With Anaphylaxis

- Education
- Identification of inciting allergen, if possible
- Instructions on use of medications and epinephrine autoinjector
- Advice about personal identification/allergy alert tag
- Prescriptions for current reaction
  - Antihistamines: Diphenhydramine, 25–50 milligrams PO every 6–8 h for 3–5 d
  - Corticosteroids: Prednisone, 40–60 milligrams PO daily or 20–30 milligrams PO twice daily for 3–5 d
- Prevention
  - Instructions on avoiding future exposure
- Prescription for future reactions
  - Epinephrine autoinjector (at least 2)
- Referral of selected patients to allergist

Refer patients with severe or frequent allergic reactions to an allergist for in-depth preventive management and attempts at allergen identification.[39] Offer patients information about this syndrome (e.g., from websites), advice on advocacy groups, and education regarding food contamination for food allergies, and encourage wearing of personal identification alerts about this condition (e.g., MedicAlert® bracelets). Because of the potential for severe and prolonged future reactions, patients with anaphylaxis on β-blockers should be switched to an agent from a different therapeutic class.

ALLERGIES AND ANGIOEDEMA

URTICARIA

Urticaria, or hives, is a cutaneous reaction marked by acute onset of pruritic, erythemic wheals of varying size that generally are described as "fleeting."[40] Erythema multiforme is a more pronounced variation of urticaria, characterized by typical "target" skin lesions. Although these manifestations may accompany many allergic reactions, they also may be nonallergic; many acute urticarial reactions are due to viruses, especially in children, and present as hives persisting or recurring for more than 24 hours. Obtain a detailed history; if an etiologic agent can be identified (e.g., cold, exercise, food), future reactions may be avoided.

Treatment of urticarial reactions is generally supportive and symptomatic, with attempts to identify and remove the offending agent. H_1 antihistamines, with or without corticosteroids,[41-43] are usually prescribed; however, some evidence suggests the addition of corticosteroids to nonsedating antihistamines is no better than antihistamines alone in preventing relapse or reducing itch.[41] Epinephrine can be considered in severe or refractory cases. The addition of an H_2 antihistamine, such as ranitidine, may also be useful in more severe, chronic, or unresponsive cases. Cold compresses may be soothing to affected areas. Referral to an allergy specialist is indicated in severe, recurrent, or refractory cases.

ANGIOEDEMA

Angioedema is a similar reaction as urticaria, but with deeper involvement characterized by edema formation in the dermis, generally involving the face and neck and distal extremities. Angioedema of the tongue, lips, and face has the potential for airway obstruction.[44] Although angioedema is caused by a variety of agents, an angiotensin-converting enzyme inhibitor is a common trigger, with angioedema occurring in 0.1% to 0.7% of patients taking angiotensin-converting enzyme inhibitors.[45,46] The pathophysiology of **angiotensin-converting enzyme inhibitor–induced angioedema** is complex, involving both bradykinin and substance P.[45,46]

Management of angiotensin-converting enzyme inhibitor–induced angioedema is supportive, with special attention to the airway,[47] which can become occluded rapidly and unpredictably. Drugs used to treat allergic reactions, such as epinephrine, antihistamines, and corticosteroids, are

TABLE 14-6 Pharmacologic Treatment of Angioedema in Adults

Agent*	Recommended Adult Dose	Comments
C1 esterase inhibitor [human] (Berinert®)	20 U/kg IV for HAE 1000 U IV for ACEI-induced angioedema	Effective in HAE and ACEI-induced angioedema† Adverse side effects include headache, abdominal pain, nausea, diarrhea, and vomiting
C1 esterase inhibitor [recombinant] (Ruconest®)	50 U/kg IV (maximum dose, 4200 U)	Effective in HAE, but effectiveness in laryngeal attacks not established No data for ACEI-induced angioedema Adverse side effects include headache and vertigo
Icatibant (Firazyr®)	30 milligrams SC	Effective in HAE and ACEI-induced angioedema† Bradykin-2 receptor antagonist Single dose highly effective: about 10% require second dose 90% experience mild local reactions: pain, swelling, erythema
Ecallantide (Kalbitor®)	30 milligrams SC (in 3 separate 10-milligram or 1-mL injections)	Effective in HAE, but not ACEI-induced angioedema Kallikrein inhibitor Risk of anaphylaxis in up to 4% May repeat 30-milligram dose within 24 h if reaction persists Adverse side effects include headache, nausea, fatigue, diarrhea, nasopharyngitis, injection site reactions, and vomiting

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; FDA = U.S. Food and Drug Administration; HAE = hereditary angioedema.

*Proprietary names provided to aid in recognition

†Not FDA approved for ACEI-induced angioedema

not beneficial because angiotensin-converting enzyme inhibitor–induced angioedema is not mediated by IgE.[45,46] **Icatibant,** a bradykinin-2 antagonist, is an effective agent to reduce swelling and shorten time to complete resolution (**Table 14-6**).[48] C1 esterase inhibitor (human) at a dose of 1000 U IV also appears effective based on a case series compared to historical controls.[49] Ecallantide, a kallikrein inhibitor, is not effective in angiotensin-converting enzyme inhibitor–induced angioedema.[50]

Immediate withdrawal from the angiotensin-converting enzyme inhibitor is indicated, and another antihypertensive should be prescribed, with the important exception that angiotensin II receptor–blocking agents should not be used. Most cases resolve in a few hours to days, so patients with mild swelling and no evidence of airway obstruction should be observed for 12 to 24 hours and discharged if swelling diminishes. Rebound or recurrent swelling will not occur unless the patient takes an angiotensin-converting enzyme inhibitor again.

Hereditary angioedema is a rare autosomal dominant disorder due to deficiency in C1 esterase inhibitor, either low levels (type I) or a dysfunctional enzyme (type II).[51,52] About 25% of cases are due to new mutations.[53] The disorder is characterized by acute edematous reactions involving the upper respiratory system, soft tissue of extremities or trunk, or gastrointestinal tract. Attacks can last from a few hours to 1 to 2 days. Minor trauma often precipitates an acute episode; however, triggers are often elusive. Typical treatments for allergic reactions, such as epinephrine, corticosteroids, and antihistamines, are ineffective. The best screening test is the C4 level. A C4 level <30% of normal suggests hereditary angioedema.

Acute attacks can be shortened by a C1 esterase inhibitor (either human plasma derived or recombinant), the bradykinin-2 receptor antagonist icatibant, or the kallikrein inhibitor ecallantide (Table 14-6).[54,55] Fresh frozen plasma may be used if C1 esterase inhibitor is not available, although the dosing is not standardized, with 2 to 3 units described in most case reports.[56] Prophylaxis of acute attacks is possible with attenuated androgens, such as stanozolol 2 milligrams PO TID or danazol 200 milligrams PO TID. Treatment of patients is complex and best done in coordination with the appropriate specialist.

FOOD ALLERGY REACTIONS

Hypersensitivity reactions to ingested foods are generally caused by IgE-coated mast cells lining the GI tract reacting to ingested food proteins and, rarely, to additives. Their frequency is rising for unknown reasons and varies based on age (more common in children), country of origin, and definitions and confirmatory tests used.[52] Dairy products, eggs, nuts, and shellfish are the most commonly implicated foods.[57,58]

A detailed dietary history within the 24 hours of allergic symptoms may provide the best clues to food allergy, with particular attention to other allergic history and prior reactions. Diagnosis is often difficult, however, and it may require multiple episodes before an offending agent is identified.[58] Symptoms of food allergy include swelling and itching of the lips, mouth, and pharynx; nausea; abdominal cramps; vomiting; and diarrhea. Cutaneous manifestations, such as angioedema and urticaria, as well as anaphylaxis, can occur. Treatment for mild reactions is supportive, with the administration of antihistamines to lessen symptoms. More severe reactions and anaphylaxis are managed as described earlier.

Mammalian meat allergy or galactose-alpha-1,3-galactose (alpha-gal) allergy is an IgE-mediated allergic reaction to ingestion of red meat containing the mammalian oligosaccharide epitope alpha-gal.[59] Alpha-gal is found in all mammals except Old World monkeys, apes, and humans. Bites (often unrecognized) from certain ticks, such as the Lone Star tick in the United States, can transfer this carbohydrate to humans, stimulating the production of the antibody implicated in a delayed allergic response triggered by the consumption of mammalian meat products. The onset is usually about 4 hours (range, 3 to 8 hours) after eating meat, manifested by urticaria, angioedema, gastroenteritis, or anaphylaxis.[60,61] Treatment is the same as for urticaria or anaphylaxis of any cause, and control is maintained by avoidance of eating any mammalian meat. Duration of allergy is unknown. Alpha-gal allergy is an increasing cause of allergic and anaphylactic reactions, reported most commonly in the middle United States and the north, central, and southern Atlantic states, where the Lone Star tick is prevalent.[62]

To identify this syndrome, ask the patient about recent meat ingestion within 8 hours prior to the onset of symptoms, as well as prior episodes. Diagnosis is confirmed by blood testing with a positive reaction to specific IgE alpha-gal antibodies.[59] The results of testing are not immediately available to the ED; however, it is definitely worthwhile obtaining the assay and ensure diagnostic follow-up along with epinephrine autoinjector prescription because repeated anaphylactic reactions can be life threatening.

ALLERGIC DRUG REACTIONS

Adverse reactions to drugs are common; however, true hypersensitivity reactions probably account for <10% of these occurrences, with the majority anaphylaxis from IgE-mediated drug reactions.[63] Although

most drugs are small organic molecules, generally unable to stimulate an immune response alone, when a drug or metabolite becomes protein bound, either in serum or on cell surfaces, the drug–protein complex can become an allergen and stimulate immune system responses. Thus, the ability of a drug or its metabolites to sensitize the immune system depends largely on the ability to bind to tissue proteins. Many different drugs and treatments can cause allergic reactions and anaphylaxis.

Penicillin is the drug most commonly implicated in eliciting true allergic reactions and accounts for approximately 90% of all reported allergic drug reactions and about 75% of fatal anaphylactic drug reactions.[64] **Fatal reactions can occur without a prior allergic history; <25% of patients who die of penicillin-induced anaphylaxis exhibited allergic reactions during previous treatment with the drug.** Parenteral penicillin administration is more than twice as likely to produce fatal allergic reactions as is oral administration. The cross-reactivity of penicillin allergy with cephalosporins is about 10%, so patients with a previous life-threatening or anaphylactic reaction to penicillin should not be given cephalosporins.

The clinical manifestations of drug allergy vary widely. A generalized reaction similar to immune-complex or serum sickness reactions is very common, especially with trimethoprim-sulfamethoxazole and certain cephalosporins (cefaclor being the most frequent). While sulfa moieties are contained in many drugs, sulfa allergic reactions upon exposure to the nonantibiotic sulfas are uncommon. See Chapter 206, "Antimicrobials," for more discussion of drug allergies.

Serum sickness usually begins in the first or second week after initiation of the drug and can take many weeks to subside after drug withdrawal. Generalized malaise, arthralgias, arthritis, pruritus, urticarial eruptions, fever, adenopathy, and hepatosplenomegaly are common signs and symptoms. Drug fever may occur without other associated clinical findings and may also occur without an immunologic basis. Circulating immune complexes are probably responsible for the lupus-like reactions caused by some drugs.

Other reactions are possible. Cytotoxic reactions include penicillin-induced hemolytic anemia. Skin eruptions include erythema, pruritus, urticaria, angioedema, erythema multiforme, and photosensitivity. Severe reactions, such as those seen in Stevens-Johnson syndrome and toxic epidermal necrolysis, may also occur. Delayed hypersensitivity reactions may manifest as contact dermatitis from drugs applied topically.

Diagnosis is determined by a careful history. Treatment is supportive, with oral or parenteral antihistamines and corticosteroids. Drug cessation is important, but reactions can continue. Referral to an allergy specialist is indicated for severe reactions.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 15

Acid-Base Disorders

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INTRODUCTION

This chapter describes a practical approach to the clinical evaluation and treatment of acid-base disorders. We discuss the traditional approach recognizing that acid-base homeostasis is maintained by respiratory control of the partial pressure of carbon dioxide (P_{CO_2}) through changes in alveolar ventilation and control of HCO_3^- reabsorption and H^+ excretion by the kidneys.[1,2] The traditional bicarbonate-centered model continues to be the most commonly used at the bedside.[3]

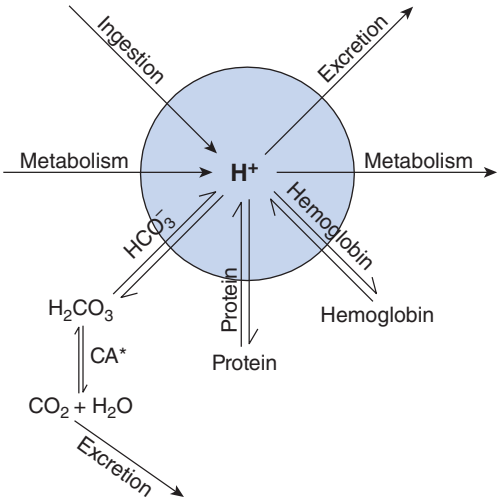

FIGURE 15-1. Schematic representation of hydrogen ion homeostasis.

PATHOPHYSIOLOGY

Plasma $[H^+]^*$ is influenced by the rate of endogenous production, the rate of excretion, exogenous addition (e.g., acetylsalicylic acid ingestion), and the buffering capacity of the body.[1] Buffers mitigate the impact of large changes in available hydrogen ion on plasma pH.

Buffer systems that are effective at physiologic pH include hemoglobin, phosphate, proteins such as albumin, and bicarbonate (**Figure 15-1**). One can consider the $[H^+]$ to be the result of all physiologic buffers acting on the common pool of hydrogen ions.

The quantity of $[HCO_3^-]$ in relation to carbonic acid buffer in the system is not fixed, but varies according to physiologic need. This flexibility is largely provided by pulmonary exhalation of carbon dioxide (CO_2), which can vary significantly and change rapidly as required by alterations in the underlying acid-base status.

The kidney regulates HCO_3^- excretion and the formation of new HCO_3^-. The rate of these processes is dependent on the underlying acid-base status. The renal response to pulmonary acid-base disturbances begins within 30 minutes of onset, but requires hours to days to achieve equilibrium.[4]

Any condition that acts to increase $[H^+]$—whether through endogenous production, decreased buffering capacity, decreased excretion, or exogenous addition—is known as *acidosis*. Similarly, any condition that acts to decrease $[H^+]$ is termed *alkalosis*. The terms *acidemia* and *alkalemia* refer to the net imbalance of $[H^+]$ in the blood.

Acid-base disturbances are further classified as respiratory or metabolic. Respiratory acid-base disorders are due to primary changes in P_{CO_2}, and metabolic acid-base disorders reflect primary changes in $[HCO_3^-]$. Compensatory mechanisms are, by definition, not "disorders," but rather normal physiologic responses to acid-base derangements. Failure of appropriate compensatory response implies the presence of another primary acid-base disturbance.

THE ANION GAP

The principle of electrical neutrality requires that plasma have no net charge. The charge of the predominant plasma cation, Na^+, must therefore be "balanced" by the charge of plasma anions.[5] Although HCO_3^- and Cl^- constitute a significant fraction of plasma anions, the sum of their concentrations does not equal that of sodium. Therefore, there must be other anions present in the serum to maintain electrical neutrality. These

*Standard nomenclature is used in this chapter. The presence of brackets, [ ], surrounding an element or molecule implies the term concentration. Without the brackets, the chemical expressions simply refer to the element or molecule.

TABLE 15-1 Unmeasured Anions Associated With an Elevated Anion Gap Metabolic Acidosis

Diagnostic Category	Anion Species	Origin	Diagnostic Adjuncts
Renal failure (uremia)	$[PO_4^{2-}]$, $[SO_4^{2-}]$	Protein metabolism	BUN/creatinine
Ketoacidosis	Ketoacids, lactate	Fatty acid metabolism	Serum/urine ketones
Diabetic	β-hydroxybutyrate, lactate	Fatty acid metabolism	Specific test now available (older nitroprusside test yields false-negative result for β-hydroxybutyrate)
Alcoholic	Acetoacetate, lactate	Fatty acid metabolism	
Starvation	β-hydroxybutyrate		Consider coexistent volume depletion
Lactic acidosis*	Lactate	Metabolism	Lactate level for subtypes
Sepsis	Lactate	Hypoperfusion, anaerobic metabolism	Culture/organism-specific tests
Cardiac arrest	Lactate	Hypoperfusion/reperfusion injury	Consider other acidosis
Liver failure	Lactate	Decreased lactate clearance	Liver function tests
Iron	Lactate	Disruption of cellular metabolism	Serum iron level
Metformin	Lactate	Inhibition of gluconeogenesis	
Cyanide	Lactate	Mitochondrial dysfunction, histotoxic hypoxia	
Carbon monoxide	Lactate	Hypoxia, anaerobic metabolism	Carbon monoxide level
Thiamine deficiency	Lactate	Aerobic metabolism interrupted, lactate accumulates	Assess peripheral sensory and motor function for neuropathy
Exogenous poisoning*			
Methanol	Formate	Methanol metabolism	Osmolal gap
Ethylene glycol (EG)	Oxalate and organic anions	EG metabolism favors pyruvate conversion to lactate	Osmolal gap Oxalate crystals (urine)
Salicylate	Salicylate	Salicylate, lactate, ketoacids	Concomitant respiratory alkalosis and metabolic acidosis
Isoniazid	Lactate	Anaerobic metabolism, lactate accumulation	

*This is not an exhaustive list; several other causes exist.

anions are primarily albumin, phosphate, sulfate, organic anions such as lactate, and the conjugate bases of ketoacids. Because these substances are not commonly measured, they are termed unmeasured anions. Unmeasured cations also exist, largely in the form of Ca^{2+} and Mg^{2+}. The unmeasured anion concentration, the anion gap (AG), that is, the difference between the serum $[Na^+]$ and the sum of serum $[Cl^-]$ and $[HCO_3^-]$, equals the concentration of the unmeasured anions. There are other cations that could be considered in the equation, such as $[Ca^{2+}]$, $[Mg^{2+}]$, and $[K^+]$; however, typically they are not included. Most laboratories now provide a calculated AG in their reports of blood chemistries; readers should check with their own laboratories for information on their institutional methods. As with other acid-base concepts, the accepted "normal" range for the AG is less important than whether it has changed in relation to the patient's steady-state baseline value. Thus, a relative change in the AG, referred to as the delta gap, may be more important than the actual AG value. Virtually all AG values above 15 mEq/L can be considered abnormal, even when there are no previous comparison values available. The common laboratory threshold is 12 mEq/L.

Elevations of the AG are most commonly associated with metabolic acidosis (**Table 15-1**).

Albumin is a major component of the AG. Critically ill patients are frequently hypoalbuminemic, which may decrease the AG into the normal range, effectively masking the presence of a wide AG acidosis.[6] If the albumin is significantly low, then the normal range for the AG should be lower. **For every drop in the albumin level by 1 gram/dL, the normal AG range should be lowered by approximately 2.5.[6]**

PARAMETERS REQUIRED FOR CLINICAL ACID-BASE EVALUATION

When taking a medical history, ask about events that may result in the gain or loss of acid or base, such as vomiting, diarrhea, medications, or ingestions of toxins, and seek evidence of dysfunction of the organs of acid-base homeostasis—the liver, kidneys, and lungs.

Obtain blood gases (pH, P_{CO_2}, and $[HCO_3^-]$), electrolytes ($[Na^+]$, $[K^+]$, $[Cl^-]$, and $[HCO_3^-]$), and other tests that affect the patient's acid-base status (albumin, lactic acid, creatinine, BUN, drug levels of suspected ingestions such as salicylate). Based on current history and physical and past medical history, consider the need to obtain calcium, magnesium, phosphate, serum ketones, glucose, lactate, serum osmolality, and urine electrolytes and osmolality. Most clinical laboratories measure two of the parameters reported in blood gas results (most commonly the pH and P_{CO_2}) and use the Henderson-Hasselbalch equation to calculate the third ($[HCO_3^-]$).

Venous or capillary blood gases, rather than arterial samples, may be satisfactory for many clinical situations.[7] Venous P_{CO_2} may be a sensitive screen for hypercarbia (cutoff 45 mm Hg), but the venous and arterial P_{CO_2} values exhibit wide variation and are not interchangeable.[8] Confirming an elevated venous lactate with an arterial sample[9] is not necessary.[8,10] See the Box, "Clinical Approach to Acid-Base Disorders," for one method of assessing acid-base disorders.

METABOLIC ACIDOSIS

Metabolic acidosis may result from HCO_3^- loss, administration of acid (parenteral nutrition), or endogenous production and accumulation of acid. Loss of HCO_3^- occurs by externalization of intestinal contents (e.g., vomiting, enterocutaneous fistulae) and renal wasting of bicarbonate (e.g., renal tubular acidosis, carbonic anhydrase inhibitor therapy). Endogenous acids accumulate in renal tubular acidosis, ketoacidosis, and lactic acidosis.

Unopposed metabolic acidosis results in a decreased serum $[HCO_3^-]$ and an increase in serum $[H^+]$. The increased $[H^+]$ stimulates the respiratory center, resulting in increased minute ventilation. The physiologically based "respiratory compensation" is an attempt to lower the $[H^+]$ by a reduction in P_{CO_2} through increased ventilation.

With normal respiratory compensation, P_{CO_2} decreases by 1 mm Hg for every 1 mEq/L net decrease in $[HCO_3^-]$. Using these relationships

Clinical Approach to Acid-Base Disorders

Following is one method that has worked well for the authors. You will need results of a blood gas and serum sodium, chloride, and bicarbonate to apply this method. This method requires methodical interpretation of laboratory results and correlation with clinical findings.

1. **Look at the pH.** If it is decreased below 7.35, the primary (or predominant) disturbance is acidemia; go to step 2. If the pH is increased above 7.45, the predominant disturbance is alkalemia; go to step 5. If the pH is in the normal range, but the $[HCO_3^-]$ or the P_{CO_2} is abnormal, consider a mixed acid-base disorder.
2. **Acidemia.** If the pH indicates acidemia, the acidemia type can be ascertained by examining the $[HCO_3^-]$ and P_{CO_2}. If the $[HCO_3^-]$ decreased, go first to step 3; if the P_{CO_2} is elevated, but the $[HCO_3^-]$ is normal, go to step 4.
3. **Metabolic Acidosis**
   a. If the $[HCO_3^-]$ is lower than the laboratory normal range (implying a primary metabolic acidosis), then the anion gap (AG) should be examined and, if possible, compared with a known steady-state value.[2]
   b. Calculate the AG: $AG = [Na^+] - ([HCO_3^-] + [Cl^-])$
      - If the AG is increased compared with the known steady-state value or is >12 (or above institutional threshold), then by definition, a wide AG metabolic acidosis is present, and the absolute change in the AG should be compared with the absolute change in the $[HCO_3^-]$ from normal to detect other disturbances.
      - If the AG is unchanged (or in the normal range), then the disturbance is nonwidened or *normal AG* metabolic acidosis, typically associated with hyperchloremia.
      - If the change in the AG (increase) is equal to the change in the $[HCO_3^-]$ (decrease), then the wide AG acidosis is termed *pure*.[2] If the AG has risen more than the $[HCO_3^-]$ has decreased, then there is also likely to be a concomitant metabolic alkalosis. If the change in the AG is less than the change in the $[HCO_3^-]$, then a normal AG acidosis is also present. (This is a difficult concept, but two separate physiologic mechanisms resulting in increased $[H^+]$ can occur simultaneously.)
   c. Next examine whether the ventilatory response is as expected.
      - The expected respiratory compensation is 1:1, the P_{CO_2} decreases by 1 mm Hg for every 1 mEq/L decrease in $[HCO_3^-]$.
        (1) If the measured P_{CO_2} from the blood gas equals the expected value based on the calculated P_{CO_2} (which is determined by the decrease in the $[HCO_3^-]$), there is appropriate respiratory compensation. Note that the pH will not return to normal.
        (2) If the measured P_{CO_2} from the blood gas is higher than the expected value based on the calculated P_{CO_2} (which is determined by the decrease in the $[HCO_3^-]$), there is a concomitant respiratory acidosis. With higher than expected P_{CO_2}, think respiratory acidosis.
        (3) If the measured P_{CO_2} from the blood gas is lower than the calculated P_{CO_2} (which is determined by the decrease in the $[HCO_3^-]$), there is also a concomitant primary respiratory alkalosis.
4. **Respiratory Acidosis**
   a. If the P_{CO_2} is elevated from normal (rather than the $[HCO_3^-]$ being decreased), the primary disturbance is respiratory acidosis.
   b. The next step is to determine if the respiratory acidosis is acute or chronic by examining the ratio of the downward change in pH (from normal) to the upward change in P_{CO_2} (from normal). By determining the drop in pH, you are examining the rise in $[H^+]$. Subtract the measured pH on the blood gas from the institution's lower limit of normal; use the number of hundredths (to the right of the decimal point). Divide this number by the elevation in P_{CO_2} in mm Hg (above normal range).
      - If the ratio is 0.8, it is considered acute.[4]
      - If the ratio is 0.33, it is considered chronic.
      - If the ratio is between 0.8 and 0.33, it is probably an acute exacerbation of the chronic condition. An alternate explanation is that a metabolic acidosis is also present as evidenced by a decreased $[HCO_3^-]$.
      - If the ratio is >0.8, there must be a metabolic acidosis as an explanation for the excess $[H^+]$.
      - If the ratio is <0.33, a metabolic alkalosis must also be present.
5. **Alkalemia.** If the pH is >7.45, the alkalemia type can be determined by examining the $[HCO_3^-]$ and P_{CO_2}. If the $[HCO_3^-]$ is increased, go to step 6 first; if the P_{CO_2} is decreased, go to step 7.
6. **Metabolic Alkalosis.** If $[HCO_3^-]$ is elevated, there is a primary metabolic alkalosis.
   a. There is an expected ventilatory response, although it is quite varied.
   b. The ratio of the change upward in P_{CO_2} (mm Hg) to the change upward in $[HCO_3^-]$ (mEq/L), each from the institutional norms, can be examined. If the ratio is much less than 0.7, there is also a respiratory alkalosis (in addition to the metabolic alkalosis). If the ratio is close to 0.7, this is likely to be a compensatory ventilatory response. If the ratio is well above 0.7, respiratory acidosis is concomitantly present.
7. **Respiratory Alkalosis.** If the P_{CO_2} is lower than normal, there is a primary respiratory alkalosis.
   a. The ratio of the change in $[H^+]$ to the change in P_{CO_2} should be examined. Subtract the institution's upper limit of normal pH from the measured pH on the blood gas; use the number of hundredths (to the right of the decimal point). Divide this number by the decrease in P_{CO_2} in mm Hg (below normal range).
      - Acute respiratory alkalosis has a ratio of about 0.75. If the ratio is well above 0.75, there is probably also a concomitant metabolic alkalosis to explain the greater than expected decline in $[H^+]$. If the ratio is smaller, the condition is chronic or there may also be a metabolic acidosis component.
8. **Mixed Acid-Base Disorder.** Every arterial blood gas that shows no or minimal pH derangement should still call for examination of the P_{CO_2}, $[HCO_3^-]$, and AG, because there may well be a mixed acid-base disturbance. It is quite possible for the pH, $[HCO_3^-]$, and P_{CO_2} to be normal and yet have significant acid-base disturbances. The only evident abnormality may be the AG. Take the example of an $[Na^+]$ of 145, $[Cl^-]$ of 97, $[K^+]$ of 4.5, and $[HCO_3^-]$ of 25 and a normal arterial blood gas. All the numbers look reasonably normal. However, the AG is 23, so by definition, there must be a wide AG metabolic acidosis. The explanation for the normal numbers is a concomitant metabolic alkalosis.

allows the clinician to calculate the expected P_{CO_2} from the measured $[HCO_3^-]$, assuming respiratory compensation is normal. If the expected P_{CO_2} value differs from the measured value in steady-state metabolic acidosis, then respiratory compensation is compromised, and a primary respiratory disorder exists in conjunction with the metabolic acidosis.

There are limits to the adequacy of respiratory compensation for metabolic acidosis. Respiratory minute volume actually declines when pH decreases below 7.10. It is particularly important to appreciate any contribution to the acidosis from an inadequate respiratory response. Administration of HCO_3^- in the presence of hypoventilation may exacerbate the respiratory acidosis, because the HCO_3^- converts to CO_2 and water (H_2O).

The development of metabolic acidosis that drives the pH below 7.10 is likely associated with a very high risk of inadequate ventilation response, since there is a limit to respiratory compensation. The lowest P_{CO_2} level achievable is approximately 12 mm Hg. This lower limit in obtainable P_{CO_2} is due to resistance in airflow and increased CO_2 generated by the exertion required for rapid ventilation, both offsetting the ventilator exhalation of CO_2. The superimposition of respiratory acidosis on a patient in such a condition will result in a rapid decline of pH to levels at which organ function drops and pharmacotherapy will fail. Noninvasive or mechanical ventilation usually should be instituted in such situations to ensure the ventilatory rate and volume are sufficient to prevent an increase in P_{CO_2} at this critical time.

Symptoms of metabolic acidosis can result from acidosis itself or the underlying disease itself. Patients may complain of abdominal pain, headache, nausea with or without vomiting, and generalized weakness, and because acidosis stimulates the respiratory center, the patient may complain of dyspnea. Acute metabolic acidosis depresses cardiovascular

function, can facilitate cardiac dysrhythmias, stimulates inflammation, and suppresses the immune response.[11]

CAUSES OF METABOLIC ACIDOSIS

The causes of elevated AG metabolic acidosis are listed in Table 15-1. A comparison with the patient's steady-state AG should be made whenever possible. Measurement and detection of specific anions may be indicated.

Differential Diagnosis of Wide AG Acidosis The differential diagnoses to be considered in emergency practice fall into four broad categories: renal failure (uremia), ketoacidosis (diabetic ketoacidosis, alcoholic ketoacidosis, starvation ketoacidosis), lactic acidosis, and ingestions (methanol, ethylene glycol, salicylates, and many others).

Renal failure should be evident from the serum chemistries. Acidosis seen in initial stages of renal failure may be severe but tends to be stable, with [HCO_3^-] approximately 15 mEq/L in cases of chronic renal failure.

Positive serum ketones point to one of the ketoacidoses. In instances of known insulin-dependent diabetes mellitus, diabetic ketoacidosis is likely, although there is usually a component of lactic acidosis. In alcoholics who have recently stopped heavy drinking, alcoholic ketoacidosis should be considered; ketoacids contribute far less to the acidosis in ketoacidosis than lactate. Starvation ketosis will be found in patients with recent oral intake that is inadequate, such as in cases of fasting, dieting, or protracted vomiting, although the magnitude of acid-base disturbance in starvation ketosis should be small. The major ketone present in the serum of a patient with untreated diabetic or alcoholic ketoacidosis may be β-hydroxybutyrate. See Chapter 223, "Type 1 Diabetes Mellitus," for a detailed discussion.

Lactic acidosis occurs whenever lactate production exceeds lactate metabolism and is classified into two types. The first, in which tissue hypoxia is present and lactate production is elevated, is referred to as **type A**. Normal tissue oxygenation and impairment of lactate metabolism define the second, called **type B**. Severe acidosis that is resistant to treatment is seen in various type B lactic acidoses and ingestions. **Lactic acidosis is not a diagnosis, but a syndrome with its own differential diagnosis**. Causes of lactic acidosis are listed in Table 15-1.

Lactate levels should be measured and accounted for in an adjustment of the AG. Ethanol is frequently cited as a cause of wide AG acidosis, but **ethanol should never be considered the cause of any significant metabolic acidosis**; look for other causes. Although ethyl alcohol metabolism may lead indirectly to very mild lactic acidosis, usually due to the same mechanism as alcoholic ketoacidosis, in which lactic acidosis is more substantial, neither the alcohol nor its metabolites directly contribute to the acidosis.

The relation of [HCO_3^-] to the AG and the [HCO_3^-] to the expected P_{CO_2} compensation must be examined in every patient with wide AG acidosis to determine whether other acid-base disturbances, metabolic or respiratory, exist. For example, the triple acid-base disturbance of wide AG metabolic acidosis, metabolic alkalosis, and respiratory alkalosis is seen with sepsis (lactic acidosis) and salicylate poisoning.

Osmolal Gap Determination of the osmolal gap will help identify methanol and ethylene glycol from other etiologies. The interpretation of serum osmolality requires the measured (laboratory measurement) and calculated osmolality.[12] The common formula is (2 × [NA^+]) + [glucose] + [urea], but recently, a study of several methods determined that the most accurate equation to identify true osmolal gap is as follows: (2 × [NA^+]) + (1.4 × [glucose]) + (1.2 × [urea]) + (1.2 × [ETOH]).[13] Increased osmolal gap can also be associated with an increased AG acidosis in the setting of acute kidney injury, lactic acidosis, and diabetic or alcoholic ketoacidosis.[12]

Differential Diagnosis of Unchanged (Normal) AG Acidosis The non-AG type of acidosis is often referred to as "normal" AG acidosis.[3] Some texts refer to this as **hyperchloremic metabolic acidosis**, but not all cases of normal AG acidosis are associated with hyperchloremia. If the patient has hyponatremia with a normal AG acidosis, the chloride may be in the normal range. Abnormal chloride levels alone usually signify a more serious underlying metabolic disorder, such as metabolic acidosis (elevated chloride) or metabolic alkalosis (low chloride).[14]

TABLE 15-2 Causes of Normal Anion Gap Metabolic Acidosis

With a Tendency to Hyperkalemia	With a Tendency to Hypokalemia
Subsiding diabetic ketoacidosis	Renal tubular acidosis, type I (classical distal acidosis)
Early uremic acidosis	Renal tubular acidosis, type II (proximal acidosis)
Early obstructive uropathy	Acetazolamide; carbonic anhydrase inhibitor, causing functional renal tubular acidosis
Renal tubular acidosis, type IV	Acute diarrhea with losses of HCO_3^- and K^+
Hypoaldosteronism (Addison's disease)	Ureterosigmoidostomy with increased resorption of [H^+] and [Cl^-] and losses of HCO_3^- and K^+
Infusion or ingestion of HCl, NH_4Cl, lysine-HCl, or arginine-HCl	Obstruction of artificial ileal bladder
Potassium-sparing diuretics	Fluid resuscitation with unbalanced, high chloride content crystalloids (dilution acidosis)

The causes of hyperkalemic and hypokalemic normal AG metabolic acidosis are listed in **Table 15-2**.

One should be wary of traditional classification based on [K^+], because serum [K^+] itself is dependent on the actual pH. Thus, in severe acidosis, a normal range [K^+] value may not represent true potassium levels. As acidosis is corrected and acidemia resolves, the [K^+] will concordantly fall.

Because all diuretics may cause a contraction alkalosis, the metabolic acidosis that occurs simultaneously with potassium-sparing diuretics may not be evident, as the two may simply cancel each other out. Because the AG is unchanged, there is no indication that two distinct opposing processes may be occurring. As with wide AG–type acidosis, the expected P_{CO_2} compensation must be examined in every patient with normal AG acidosis to determine whether other respiratory acid-base disturbances exist.

Acidosis with Large-Volume Normal Saline Resuscitation It has been known for some time that large-volume fluid resuscitation with normal saline is associated with hyperchloremic acidosis (formerly called dilution acidosis). Two large, single-center, randomized controlled trials compared normal saline to balanced salt solutions (lactated Ringer's or Plasma-Lyte®) in the resuscitation of patients in the ED prior to admission and found fewer major adverse events (persistent renal dysfunction, new renal replacement therapy, or mortality) in the balanced salt group.[15,16] Since then, a meta-analysis including those two studies plus four prior randomized controlled trials, totaling 19,332 patients, found no significant differences in the outcome measures of intensive care unit mortality, acute kidney injury, and new renal replacement therapy when comparing 0.9 normal saline to balanced salt solutions.[17] Most consistent in all the cited trials is the frequent development of hyperchloremic metabolic acidosis associated with large-volume resuscitation using normal saline.

TREATMENT

The treatment of acidosis reflects the treatment of the underlying disorder and the restoration of normal tissue perfusion and oxygenation. The most important step is to determine whether there is a respiratory component to the acidosis (i.e., a primary respiratory acidosis), because the treatment approach differs. If there is inadequate respiratory compensation, the most appropriate treatment will be to first correct the respiratory problem. Address electrolyte disturbances, administer antidotes for toxins as appropriate, and initiate treatment for underlying causes such as sepsis (see Chapter 151, "Sepsis") or diabetic ketoacidosis (see Chapter 225, "Diabetic Ketoacidosis").

Bicarbonate Therapy in Acidosis Bicarbonate therapy results in the generation of significant quantities of CO_2, which diffuses readily into

TABLE 15-3 Potential Indications for Bicarbonate Therapy in Metabolic Acidosis

Indication	Rationale
Severe hypobicarbonatemia (<4 mEq/L)	Insufficient buffer concentrations may lead to extreme increases in acidemia with small increases in acidosis.
Severe acidemia (pH <7.00 to 7.15)* in cases of wide anion gap acidosis, with signs of shock or myocardial irritability that has not responded to supportive measures including adequate ventilation and fluid resuscitation as indicated by the patient's clinical characteristics	Therapy for the underlying cause of acidosis depends on adequate organ perfusion.
Severe hyperchloremic acidemia†	Lost bicarbonate must be regenerated by kidneys and liver, which may require days.

*Presented as a range because recommendations differ among authors; data do not support a specific threshold for treatment.

†No specific threshold indication by pH exists. The presence of serious hemodynamic insufficiency despite supportive care should guide the use of bicarbonate therapy for this indication.

cells, in particular those of the CNS, which may cause paradoxical worsening of intracellular acidosis.[18] An abrupt CO_2 increase may exceed the ventilatory capacity of a patient already at maximum minute ventilation, thereby producing abrupt and worsening respiratory acidosis. After successful treatment with bicarbonate, "overshoot" alkalosis may result.[18] Bicarbonate therapy imposes an osmotic and sodium load (1000 mEq/L of typical 1 N solution).

Bicarbonate therapy may be appropriate for limited indications (**Table 15-3**).[11,19-25]

When given, HCO_3^- can be dosed at 0.5 mEq/kg for each milliequivalent per liter rise in $[HCO_3^-]$ desired.[11] The goal is to restore adequate buffer capacity ($[HCO_3^-]$ >8 mEq/L) or to achieve clinical improvement in shock or dysrhythmias. Bicarbonate should be given as slowly as the clinical situation permits. Seventy-five milliliters of 8.4% sodium bicarbonate in 500 mL of dextrose 5% in water produces a nearly isotonic solution for infusion. Adequate time should be allowed for the desired effect to be achieved, with monitoring of acid-base balance.

METABOLIC ALKALOSIS

Metabolic alkalosis is typically classified as chloride sensitive or chloride insensitive, thus indicating the treatment approach. Metabolic alkalosis results from gain of bicarbonate or loss of acid. The physiologic effects of alkalemia are substantial. Neurologic abnormalities, especially tetany, neuromuscular instability, and seizures, are common. Reduction in $[H^+]$ results in reductions in ionized calcium, potassium, magnesium, and phosphate levels. Serum proteins, largely polyanionic, buffer H^+; with rapid acid loss, such as that which occurs in respiratory alkalosis, the newly available buffer capacity of those proteins binds calcium and other cations instead.[26] Alkalemia may be of particular concern in patients with chronic obstructive pulmonary disease, because of the shift of the oxygen–hemoglobin dissociation curve to the left, which makes O_2 less available to the tissues. Alkalemia depresses respiration, a serious effect in patients with compromised ventilation. Many patients with chronic obstructive pulmonary disease also take diuretics, leading to a contraction alkalosis.

Bicarbonate and chloride homeostasis is closely intertwined. Conditions that result in chloride loss, such as vomiting (which also causes acid loss), diarrhea, diuretic therapy, and chloride-wasting diseases (e.g., cystic fibrosis and chloride-wasting enteropathy), tend to reduce serum chloride concentration and extracellular volume. The reduction in extracellular volume increases mineralocorticoid activity, which enhances sodium reabsorption and potassium and hydrogen ion secretion in the distal tubule, which in turn enhance bicarbonate generation. The resulting increase in serum $[HCO_3^-]$ eventually exceeds the tubule's maximum ability to reabsorb filtered bicarbonate. The resulting urine is alkaline, and because its anionic content is mostly bicarbonate, it is largely free of chloride (<10 mEq/L). (Nevertheless, the urine chloride may be normal when diuretics are administered.) The result is hypokalemic, hypochloremic alkalosis that responds to normal saline (chloride-responsive alkalosis).

Other diseases that cause metabolic alkalosis are usually associated with normovolemia or hypervolemia and often include hypertension. These diseases usually cause excess mineralocorticoid activity, resulting in the same pathophysiologic cascade described earlier. However, the excess mineralocorticoid activity is not associated with hypovolemia, so the urine chloride is generally normal or elevated (>10 mEq/L) and the alkalosis cannot be reversed with normal saline. Conditions producing "chloride-unresponsive alkalosis" and hypertension include renal artery stenosis, renin-secreting tumors, adrenal hyperplasia, hyperaldosteronism, Cushing's syndrome, and exogenous mineralocorticoids (e.g., licorice, fludrocortisone).

The compensation for metabolic alkalosis involves reduction in alveolar ventilation, but the exact relationship between P_{CO_2} and $[H^+]$ is not well established. Most studies to date have been conducted in dialysis patients or patients with conditions that predispose to alveolar hyperventilation (e.g., sepsis, pneumonia). **As a guideline, P_{CO_2} in patients with significant metabolic alkalosis should rise by 0.7 mm Hg for each milliequivalent increase in $[HCO_3^-]$. The P_{CO_2} also rarely rises above 55 mm Hg in compensation for metabolic alkalosis.**

TREATMENT

In the emergency setting, metabolic alkalosis rarely requires active management. Treat the underlying cause. Hydrate, and replace volume with sodium chloride and potassium. Aggressive therapy, such as IV hydrochloric acid, requires intensive care unit admission and monitoring.[27]

RESPIRATORY ACIDOSIS

Respiratory acidosis is defined by alveolar hypoventilation and is diagnosed when the P_{CO_2} is greater than the expected value. Regardless of underlying cause, the final common path is inadequate ventilation.

Inadequate minute ventilation most frequently results from head trauma, chest trauma, lung disease, or excess sedation. The chronic hypoventilation seen in extremely obese patients is often referred to as the **Pickwickian syndrome or obesity hypoventilation syndrome.** Patients with severe chronic obstructive pulmonary disease have increased dead space and frequently also have decreased minute ventilation.

In general, a rise in the P_{CO_2} stimulates the respiratory center to increase respiratory rate and minute ventilation. However, if the arterial P_{CO_2} chronically exceeds 60 to 70 mm Hg, as may occur in 5% to 10% of patients with severe emphysema, respiratory acidosis may depress the respiratory center. Under such circumstances, the stimulus for ventilation is provided primarily by hypoxemia acting on chemoreceptors in the carotid and aortic bodies. Giving oxygen could remove the main stimulus to breathe, causing the P_{CO_2} to rise abruptly to extremely dangerous levels. Consequently, when administering oxygen to patients with chronic obstructive pulmonary disease, carefully monitor for apnea or hypoventilation; however, do not withhold oxygen in the case of severe hypoxemia. Evaluation of ventilation requires attention to several important clinical issues. First, the ventilation that would be expected based on assessment of the respiratory rate and depth should be compared with the actual ventilation of the patient (i.e., P_{CO_2}). A "normal" P_{CO_2} of 40 mm Hg in a tachypneic, dyspneic patient likely reflects significant ventilatory insufficiency. Second, the impact of respiratory acidosis on partial pressure of oxygen in the alveoli (P_{AO_2}) in such a patient may be considerable. The alveolar gas equation suggests that if inspired oxygen concentration and respiratory quotient do not change, increases in P_{CO_2} will result in reductions in P_{AO_2}.

Each 1-mm Hg increase in P_{CO_2} results in a 1-mmol increase in $[H^+]$. Across the linear portion of the pH–hydrogen ion concentration relationship, each 1-mm Hg increase in P_{CO_2} should theoretically produce a decrease in pH of 0.01. The actual relationship between changes in P_{CO_2} (up to values of 90 mm Hg) and changes in $[H^+]$ determined in normal humans is about 8 to 10. Thus, **a 10-mm Hg increment in P_{CO_2}**

TABLE 15-4 Evaluation of Acid-Base Status in Respiratory Acidosis

*Ratio = $\Delta[H^+]/\Delta P_{CO_2}$				
Ratio < 0.3	Ratio = 0.3	0.3 < Ratio < 0.8	Ratio = 0.8	Ratio > 0.8
Change in hydrogen ion concentration is less than accounted for by chronic change in P_{CO_2}. Metabolic alkalosis is also present.	Change in hydrogen ion concentration matches chronic change in P_{CO_2}. Chronic respiratory acidosis is present.	Change in hydrogen ion concentration is larger than accounted for by chronic change in P_{CO_2}. Chronic respiratory acidosis plus either acute respiratory acidosis or metabolic acidosis is present; examine pH.	Change in hydrogen ion concentration matches acute change in P_{CO_2}. Acute respiratory acidosis is present.	Change in hydrogen ion concentration is larger than accounted for by acute or chronic change in P_{CO_2}. Metabolic acidosis is also present.

Abbreviation: P_{CO_2} = partial pressure of carbon dioxide.

*See method of calculation in the Box, "Clinical Approach to Acid-Base Disorders," in this chapter.

produces an 8-mmol increase in $[H^+]$, with little change in bicarbonate concentration (usually 1 mEq/L) or urinary acid excretion. If the $[H^+]$ is higher or lower than that suggested by the change in the P_{CO_2}, a mixed disorder is present.

The adaptation to chronic respiratory acidosis is complex. Over time, chronic elevation of P_{CO_2} reduces carotid sinus sensitivity to hypercapnia, and ventilatory drive is then controlled by P_{aO_2}. The acidosis results in significant increases in renal HCO_3^- generation and avid reclamation of filtered HCO_3^-.

It is frequently uncertain whether a patient has an acute respiratory acidosis, a chronic respiratory acidosis, or a mixed disorder. Evaluation of the acid-base status in such circumstances does not require "baseline" arterial blood gas values. Instead, the change in $[H^+]$ is compared with the change in P_{CO_2}. If this ratio is 0.3, the patient has a chronic respiratory acidosis; if it is 0.8, the patient has an acute respiratory acidosis. Other ratios suggest a mixed acid-base disturbance, as shown in **Table 15-4**.

TREATMENT

Treatment of respiratory acidosis is the improvement of alveolar ventilation. In general, if the minute ventilation is doubled, the P_{CO_2} will be reduced by 50%. Treat chronic obstructive pulmonary disease, and provide noninvasive ventilatory support or tracheal intubation as needed. See Chapter 29B, "Mechanical Ventilation," for further discussion.

In patients with chronic respiratory acidosis, the arterial P_{CO_2} should not be reduced by more than 5.0 mm Hg/h. Rapid correction of a chronic respiratory acidosis can cause sudden development of a severe metabolic alkalosis, with resulting dysrhythmias. A rapid rise in pH can cause an abrupt decrease in ionized calcium levels and hypokalemia.

RESPIRATORY ALKALOSIS

Respiratory alkalosis is alveolar hyperventilation and exists when P_{CO_2} is less than expected. It is caused by conditions that stimulate respiratory centers, including CNS tumors or stroke, infections, pregnancy, hypoxia, and toxins (e.g., salicylates). Anxiety, pain, and iatrogenic overventilation of patients on mechanical ventilators also cause respiratory alkalosis.

The clinical symptoms of acute respiratory alkalosis are predictable from its physiologic effects. Acute reduction in P_{CO_2} produces a reduction in $[H^+]$, resulting in an increase in negative charge on anionic buffers. The now negatively charged proteins instead bind calcium, and if the effect is sufficiently large, the reduction in ionized calcium produces tetany (e.g., carpopedal spasm) and paresthesias.[26] Hypocapnia also produces substantial reductions in cerebral blood flow and results in reduced tissue oxygen delivery due to a leftward shift in the oxygen–hemoglobin dissociation curve (i.e., increased hemoglobin-oxygen binding).

The predicted relationship of $[H^+]$ and P_{CO_2} is that a 1-mmol decrease in $[H^+]$ results from each 1-mm Hg reduction in P_{CO_2}.

Chronic respiratory alkalosis is unique among the acid-base disorders in that its compensation may be complete. Compensatory events include bicarbonaturia and a reduction in acid excretion, requiring 6 to 72 hours to develop fully and at least 1 week to normalize pH. The steady-state relationship between $[H^+]$ and P_{CO_2} in chronic respiratory alkalosis observed in normal human subjects at high altitude is roughly half that expected at sea level. Each 1-mm Hg reduction in P_{CO_2} results in a 0.4-mmol reduction in $[H^+]$.

TREATMENT

Treat the underlying cause. For patients with anxiety and hyperventilation, do not use "paper-bag" rebreathing because it may lead to hypoxia. Chronic respiratory alkalosis is seen at high altitudes, in particular among mountaineers climbing over 3700 m (12,000 ft), where the partial pressure of oxygen is significantly diminished. Acetazolamide is frequently prescribed to counter the physiologic respiratory effects of such ascents.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 16

Blood Gases, Pulse Oximetry, and Capnography

Casey M. Glass

INTRODUCTION

Blood gases provide important clinical information for patients with respiratory disorders, compromised circulation, or abnormal metabolism. This chapter briefly reviews respiratory physiology to aid selection of assessment options and discusses appropriate use of arterial and venous blood gases and the advantages and limitations of noninvasive monitoring methods. The material focuses on the evaluation of oxygen and carbon dioxide levels; for information on carbon monoxide, please refer to Chapter 222, "Carbon Monoxide."

RESPIRATORY PHYSIOLOGY

Several factors contribute to overall gas exchange in the lungs.

Each breath (*tidal volume*) moves air in and out of the alveolus for gas exchange but also moves air through large airways and nonperfused areas of lung, the *physiologic dead space*. The physiologic dead space is approximately 30% of the tidal volume. The air remaining in the chest at the end of exhalation is the *functional residual capacity*. Dead space and the functional residual capacity do not contribute to gas exchange. *Minute ventilation* is a product of the respiratory rate and tidal volume. Relatively small changes in the usable alveolar space require

large increases in the minute ventilation to maintain the same rate of gas exchange. Raising the fraction of inspired oxygen (F_{IO_2}) or increasing the surface area or functional residual capacity of the lung can increase total alveolar oxygen content. Positive-pressure ventilation increases the functional residual capacity through recruitment of collapsed nonventilated alveolar space.

ESTIMATING OXYGEN DELIVERY

The F_{IO_2} is the percentage of oxygen in each breath. At sea level, room air is 21% oxygen. As F_{IO_2} increases, so does the alveolar concentration of oxygen (P_{AO_2}). Each liter per minute of oxygen flow delivered via nasal cannula increases the F_{IO_2} by about 4%. Flow rates >4 L/min through a nasal cannula are poorly tolerated because of upper airway irritation, although some noninvasive devices can supply a higher F_{IO_2} via nasal cannula. A simple mask provides an F_{IO_2} of 35% to 60% at flows of 10 to 15 L/min. A nonrebreather mask with a reservoir can deliver 95% F_{IO_2} with a supply flow rate of 10 to 12 L/min.

The nature and severity of respiratory disorders can be estimated by comparing the measured arterial concentration of oxygen to the expected concentration of oxygen. The approximate arterial oxygen concentration (Pao_2) values that are expected in normal persons who are inhaling various concentrations of oxygen are listed in **Table 16-1**.

The expected Pao_2 from supplemental oxygen can be roughly estimated by multiplying the actual F_{IO_2} by 5, the **Five Times Rule**. Thus, a patient getting 60% O_2 would be expected to have a Pao_2 of about 60 × 5, or 300 mm Hg. For every 1000-ft (305-m) rise in altitude, the atmospheric partial pressure of oxygen (Po_2) drops about 5 mm Hg, and the arterial oxygen estimate would therefore be reduced by that value. The total alveolar oxygen pressure cannot be greater than atmospheric pressure. See Chapter 214, "Diving Disorders," and Chapter 216, "High-Altitude Disorders," for further discussion of oxygenation and ventilation at altitude and depth.

Cardiac output and the patient's hemoglobin level are the biggest determinants of oxygen delivery to the tissues. Relatively little oxygen is dissolved in the plasma itself. Both hypoxia and anemia stimulate intrinsic mechanisms to increase cardiac output. If this is insufficient, increasing the hemoglobin level or oxygen saturation will improve the systemic delivery of oxygen. Based on survival data and the known complications of transfusions, the recommended threshold for transfusion in the absence of acute bleeding is 7.0 grams/dL (70 grams/L).[1] See Chapter 13, "Approach to Traumatic Shock," and Chapter 238, "Transfusion Therapy," for further discussion of transfusion indications. Therefore, in most clinical situations, increasing the oxygen saturation of existing hemoglobin is the fastest method to increase oxygen delivery.

ALVEOLAR GAS EXCHANGE

Once oxygen and carbon dioxide reach the lung, the gases diffuse across the interstitial space to either the red blood cell or alveolar space, respectively. The efficiency of diffusion depends on the distance across the alveolar-capillary membrane (interstitial space), the partial pressure of the gas in the alveolar space, and the solubility of the gas. Both oxygen and carbon dioxide are highly soluble, and carbon dioxide is 20 times more soluble than oxygen. As a result, increases in the distance across the interstitial space (as in pulmonary edema, for example) have a greater effect on oxygen diffusion than carbon dioxide diffusion. Gas diffusion requires functioning alveolar space, and conditions that damage the alveoli prevent effective oxygen and carbon dioxide transport.

TABLE 16-1 Expected Pao_2 in Patients Inhaling Various Concentrations of Oxygen (mm Hg)

Fraction of inspired oxygen	0.21 (room air)	0.4	0.6	0.8	1.0
Expected Pao_2* (approximate)	105†	200	300	400	500

Abbreviation: Pao_2 = partial pressure of arterial oxygen.

*Assuming a patient with normal lung function at sea level and a partial pressure of carbon dioxide (Pco_2) of 40 mm Hg.

†Calculation demonstrates small overestimation using this technique.

TABLE 16-2 Interpretation of Pao_2/F_{IO_2}

Pao_2 (mm Hg)	F_{IO_2} (mm Hg)	Ratio	QS/QT (%)	Impairment of Oxygenation
240	0.4	600	5	None
120	0.4	300	10	Minimal
100	0.4	250	15	Mild
80	0.4	200	20	Moderate
60	0.4	150	30	Severe*
40	0.4	100	40	Very severe*

Abbreviations: F_{IO_2} = fraction of inspired oxygen; Pao_2 = partial pressure of arterial oxygen; QS/QT = venous-arterial admixture (shunt).

*Ventilatory support and positive end-expiratory pressure to increase functional residual capacity and reduce the QS/QT to 15% should be considered.

Additionally, the alveolar space must be perfused by the pulmonary circulation. When portions of lung are perfused but not ventilated (as in pneumonia) or ventilated but not perfused (as in pulmonary embolism), there is a *ventilation-perfusion mismatch*. Either scenario may lead to hypoxemia, the first as deoxygenated blood passes through the nonfunctional lung and mixes with oxygenated blood in the left atrium, and the second when too little perfused lung is available for adequate oxygen loading.

The alveolar-arterial gradient or the P_{AO_2}/F_{IO_2} ratio can estimate the effectiveness of alveolar oxygenation. The alveolar-arterial gradient is the difference between the partial pressure of oxygen in the alveolar space (estimated from F_{IO_2} at atmospheric pressure) and the measured partial pressure of the gas in an arterial blood gas sample. The following formula estimates the alveolar-arterial gradient [the $P_{(A\text{-}a)O2}$]:

$$P_{(A\text{-}a)O2} = [F_{IO_2}(P_{atm} - P_{H2O}) - (Pa_{CO2} \times 1.25)] - Pao_2$$

F_{IO_2} is the fraction of oxygen in the inspired air (21% if room air), P_{atm} is the atmospheric pressure (760 mm Hg at sea level), P_{H2O} is the vapor pressure at body temperature (47 mm Hg), and Pa_{CO2} and Pao_2 are the partial pressures of carbon dioxide and oxygen (respectively) from the patient's blood gas. A normal gradient for young adults is <15 mm Hg. The gradient increases with age and is estimated with the following formula: age/4 + 4. The Pao_2/F_{IO_2} ratio correlates with the relative venous shunt across the pulmonary circulation and is calculated as the measured Pao_2 divided by the F_{IO_2} in decimal form. A healthy person on 40% oxygen would be expected to have a ratio of approximately 600, representing a normal physiologic shunt of approximately 5%. As the shunt increases, the ratio decreases. **Table 16-2** illustrates the decrease in the Pao_2/F_{IO_2} ratio with increasing physiologic shunt in hypothetical patients all receiving oxygen with an F_{IO_2} of 40%.

The Pao_2/F_{IO_2} ratio is the most frequently used parameter for evaluating the severity of lung failure and is included in the current definition for acute lung injury/acute respiratory distress syndrome.[2,3] Carbon dioxide is transported by the red blood cells bound to hemoglobin and other proteins and dissolved in the plasma. Most carbon dioxide (60% to 70%) combines with plasma water to form carbonic acid, which dissociates into bicarbonate and hydrogen ions. Carbonic anhydrase in the erythrocyte catalyzes this near-instantaneous reaction. The deoxygenated hemoglobin is a willing receptor for released hydrogen ions. As hemoglobin is oxygenated in the lung, hydrogen ions are returned to the plasma, driving the reaction back toward the production of carbon dioxide.

ARTERIAL BLOOD GAS ANALYSIS

The amount of oxygen and carbon dioxide in the blood can be sampled and reported as the partial pressure of the gas. Blood gas analysis also typically includes a direct measurement of the serum pH and estimates of serum bicarbonate derived from the measured partial pressure of carbon dioxide (Pco_2) and pH (see Chapter 15, "Acid-Base Disorders"). Current tests often include other useful information such as direct measurement of lactic acid as lactate, total hemoglobin, and serum electrolytes.

An arterial blood sample is the reference standard for pH, oxygen, carbon dioxide, and lactate content providing a description of the oxygen and carbon dioxide content of the blood after leaving the pulmonary circulation and before any gas exchange in the peripheral tissues has occurred. In scenarios that require precise determination of these variables, an arterial sample is necessary.

Arterial blood gas samples are sometimes used for evaluation of serum hemoglobin and electrolytes. Blood gas analyzers typically have good concordance with the reference laboratory autoanalyzer; however, there may be clinically significant variances depending on the equipment involved, especially for sodium, hemoglobin, and chloride. Results should be interpreted with caution when they are significantly abnormal.[4-8]

VENOUS BLOOD GAS ANALYSIS

Venous samples may be either centrally or peripherally obtained. Mixed venous blood samples from the central circulation provide a source of information regarding the systemic uptake of oxygen and can be used to calculate cardiac output. The ideal sampling site for a systemic venous sample is at the pulmonary artery because blood from all body sites is equally represented, but such a sample is rarely practical. More commonly, blood is sampled from the superior vena cava or right atrium after placement of a central venous catheter. Blood from the superior vena cava disproportionally represents cerebral and upper body blood flow, but is generally useful for determining systemic oxygen uptake and lactic acid production. Peripherally obtained venous samples are widely used in emergency medicine, and they correlate with arterial values closely enough to be clinically useful. Significantly abnormal values should be confirmed with an arterial sample.[9-11]

Venous blood gases are commonly used to monitor serum pH and, in certain situations, may be an appropriate substitute to monitor Pco_2 and serum lactate. When compared to arterial blood gases, the venous pH correlates closely such that most differences are not clinically significant (+/– 0.05 pH units).[4-6,12,13] Venous carbon dioxide values trend along with arterial carbon dioxide, although they vary somewhat (up to +/– 20 mm Hg). Normal venous carbon dioxide is predictive of normal $Paco_2$; however, the clinical outcomes of substituting venous carbon dioxide for evaluation of hypercarbia have not been described in the literature.[11,14] Venous Pao_2 values do not correlate with arterial oxygen content and cannot be used for evaluation of oxygenation.

Regular monitoring of the venous oxygen saturation at the superior vena cava ($S_{cv}o_2$) or right atrium ($S_{ra}o_2$) had been recommended as part of the Surviving Sepsis Campaign, but a failure to demonstrate a benefit from this approach led to a removal of that recommendation in the 2016 guidelines.[15,16] Measurement of the oxygen saturation from the superior vena cava may not accurately reflect the $S_{ra}o_2$, and neither the $S_{cv}o_2$ nor the $S_{ra}o_2$ may accurately reflect the mixed venous oxygen saturation at the pulmonary artery (S_vo_2) for critically ill patients.[17]

Venous measurements of serum lactate are widely used for patient care, but most studies describing the clinical utility of serum lactate reference an arterial sample. Normal and markedly abnormal venous lactate values correlate with the arterial lactate, but mildly elevated venous lactate may not correlate. In the latter case, if necessary, it may be wise to confirm the result with an arterial sample.[18-22]

PULSE OXIMETRY

It is not possible to directly measure the arterial oxygen concentration by noninvasive means, and the standard bedside tool for estimating arterial oxygen saturation is the photometric pulse oximeter.

Pulse oximetry measures the relative absorption of oxygenated hemoglobin and deoxygenated hemoglobin and reports the percentage of oxygenated hemoglobin compared to the total. Pulse oximetry is fairly accurate, typically within 2% to 5% of the directly measured value performed at blood gas analysis. Importantly, the discrepancy between peripheral pulse oxygenation results and arterial gas saturation increases with hypoxia and poor circulation. Pulse oxygenation values greater than 92% are highly predictive of arterial saturations greater than 90%. Borderline normal pulse oxygenation values (between 88% and 92%) do not necessarily reflect normal arterial saturations and may overestimate arterial oxygen saturation.[23] The pulse oximeter becomes more inaccurate when arterial saturations range between 80% and 90%.[23-25] Carbon monoxide also causes hemoglobin to conform to the saturated state and will cause a false elevation in measured saturation (see Chapter 222).

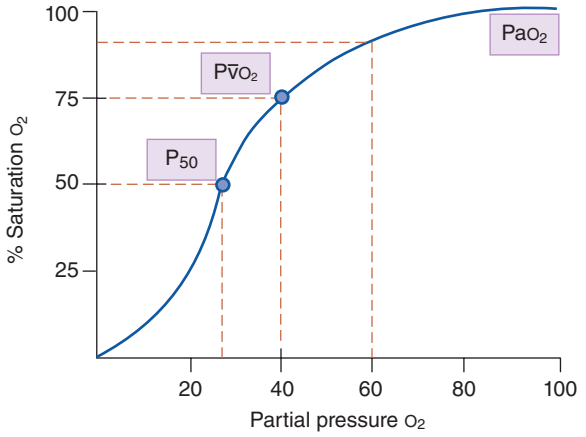

FIGURE 16-1. The oxyhemoglobin dissociation curve. This curve demonstrates the relationship of the partial pressure of oxygen (Po_2) in the plasma to the saturation of hemoglobin molecules with oxygen (O_2). The P_{50} is the Po_2 at which hemoglobin is 50% saturated and correlates with Po_2 of 27 mm Hg normally. Normal mixed venous blood has an oxygen partial pressure ($Pmvo_2$) of 40 mm Hg and an oxyhemoglobin saturation of 75%. A partial pressure of arterial oxygen (Pao_2) of 60 mm Hg normally results in approximately 90% saturation of hemoglobin.

Pulse oximetry does not allow for determination of the partial pressure of oxygen in the arterial blood, which, in combination with total hemoglobin content, is the primary determinant of peripheral oxygen delivery. A basic understanding of the oxygen saturation/dissociation curve is essential for practicing clinicians when using pulse oximetry to guide clinical therapy (**Figure 16-1**). Most notably, arterial oxygen content declines precipitously when the oxygen saturation falls below 92%.

Studies of pulse oximetry typically use a finger-applied probe as the measurement site. Alternative locations such as the ear or forehead are used when it is difficult to obtain a reliable tracing from the patient's finger. To date there is no definitive literature describing the accuracy of such measurements, although limited results suggest that probe locations on the head may be preferable to the extremities for patients with compromised perfusion.[26]

CAPNOGRAPHY

Noninvasive techniques, direct transcutaneous measurement, cutaneous photometric measurement, or sampling of expired gases can easily estimate the carbon dioxide content of arterial blood. Of these, only sampling of expired gases is in common in the ED.

The carbon dioxide content of expired gases at the end of the expiration phase of respiration ($Etco_2$) proportionally approximates the $Paco_2$ content in healthy individuals, because carbon dioxide rapidly diffuses into the alveolar space, and arterial levels are typically only about 5 mm Hg higher than alveolar samples when pulmonary ventilation and perfusion are normal. The carbon dioxide content of the entire volume of expired gas can be photometrically assessed by means of a **mainstream** detector, or a sample of the expired gases can be aspirated from the airway via a **side stream** detector. Mainstream detectors are larger and must be inserted into the breathing circuit, either in a ventilator circuit or with the patient breathing through an occlusive mask or other tube. Side stream detectors are smaller and have the advantage of ease of use in nonintubated patients. Interpretation of the capnogram is not necessarily intuitive. A summary of typical capnogram waveforms is described in **Figure 16-2**.

End-tidal carbon dioxide measurements ($Petco_2$) do not accurately represent $Paco_2$. Mainstream and side stream sampling may each include air that has not been involved in the gas exchange process, either from physiologic dead space or from environmental air that enters the sample.

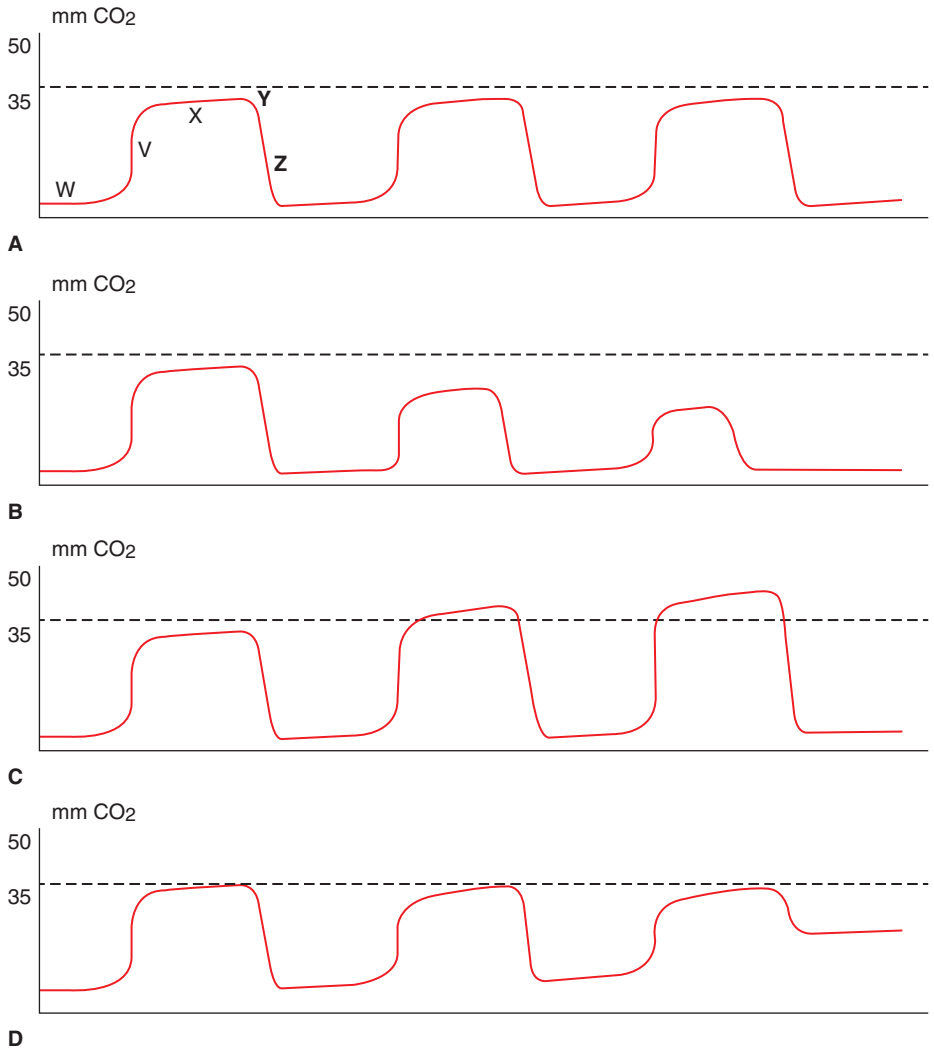

FIGURE 16-2. End-tidal capnogram. Capnogram **A** depicts a normal capnogram with inspiratory baseline (V), expiratory upstroke (W), expiratory plateau (X), end-tidal concentration (Y), and inspiratory downstroke (Z). Capnogram **B** represents apnea, which appears as serially decreasing end-tidal concentrations as little gas is expired. Capnogram **C** represents hypoventilation, which appears as an upward trend in the plateau and end-tidal concentration. Capnogram **D** represents rebreathing or air trapping, which appears as an increase in the baseline phase of the capnogram.

In either case, the $Petco_2$ value will be lower than the arterial value. These errors may be exacerbated in the setting of obstructive pulmonary disease due to incomplete expiration of gases secondary to air trapping. In a study of ED patients with chronic obstructive pulmonary disease, end-tidal measurements did not significantly vary from presentation to admission and were not clinically different for patients discharged home as compared to those requiring admission.[27] Studies assessing the accuracy of $Etco_2$ measurements compared to arterial sampling are mixed. In one study of patients presenting to the ED with undifferentiated dyspnea, mainstream $Petco_2$ did correlate closely with $Paco_2$.[28] In a comparison of healthy individuals, neither mainstream nor side stream sampling accurately predicted the arterial Pco_2.[29] A convenience sample of ED patients with an indication for arterial blood gas did not have a close correlation of side stream $Etco_2$ with the $Paco_2$.[30] Notwithstanding these specific limitations, capnography enjoys a multitude of well-described applications in the emergency setting.[31] It is most useful for identifying respiratory compromise in patients undergoing sedation, as hypoventilation appears in the capnogram long before the patient develops hypoxia.[32] Colorimetric carbon dioxide detectors have been used for over a decade to help identify tracheal intubation. End-tidal capnography has also been studied extensively for identification of the return of spontaneous circulation in patients suffering cardiac arrest.[33] Numerous other applications are described in the literature, and further discussion of them is beyond the scope of this chapter.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 17

Fluids and Electrolytes

Roberta Petrino
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FLUIDS AND SODIUM

PATHOPHYSIOLOGY

Total body water (TBW), which accounts for approximately 60% of total body weight, can be divided into intracellular fluid (ICF) and extracellular fluid (ECF) compartments. The ECF is composed of intravascular fluid and extravascular, or interstitial, fluid. Three fundamental homeostatic equilibriums govern the behavior of fluids: the osmotic equilibrium, the electric equilibrium, and the acid-base equilibrium.

TABLE 17-1 Electrolyte Concentrations of Fluids

Solution	Plasma	Interstitial	Intracellular	Normal Saline	Lactated Ringer's Solution	Multiple Electrolyte Injection*
Cations						
Sodium, mEq/L	142	144	10	154	130	140
Potassium, mEq/L	4	4.5	150	—	4	5
Magnesium, mEq/L†	2	1	40	—	—	3
Calcium, mEq/L‡	5	2.5	—	—	3	—
Total cations, mEq/L	153	152	200	154	137	148
Anions						
Chloride, mEq/L	104	113	—	154	109	98
Lactate, mEq/L#	—	—	—	—	28	
Acetate, mEq/L	—	—	—	—	—	27
Gluconate, mEq/L	—	—	—	—	—	23
Phosphates, mEq/L	2	2	120	—	—	—
Sulfates, mEq/L	1	1	30	—	—	—
Bicarbonate, mEq/L	27	30	10	—	—	—
Proteins, mEq/L	13	1	40	—	—	—
Organic acids, mEq/L	6	5	—	—	—	—
Total anions	153	152	200	154	137	148
Osmolality, mOsm	285–295	285–295	285–295	286	254	

*Multiple electrolyte injection, type 1, is the generic name for Plasma-Lyte 148®, Normosol®, and Isolyte®

†Multiply by 0.411 to convert to International System of Units (SI) units in mmol/L.

‡Multiply by 0.25 to convert to SI units in mmol/L.

#Multiply by 0.323 to convert to SI units in mmol/L.

The key point is that sodium is much more concentrated in the ECF (approximately 140 mEq/L) than in the ICF (approximately 10 mEq/L), but is equal in both compartments of the ECF because the capillary membrane between intravascular fluid and interstitial fluid is permeable to water and electrolytes. In contrast, the cell membrane is permeable to water but not to electrolytes, which are moved through ionic pumps against gradient to keep the intracellular sodium concentration constant around 10 mEq/L and potassium at 150 mEq/L. **Table 17-1** lists the electrolyte concentration of body fluids and the most commonly used therapeutic solutions. **Table 17-2** defines commonly used terms that describe measures or characteristics of electrolytes and/or disorders.[1]

TABLE 17-2 Definition of Terms

Term	Definition	Comments
Mole	6.02×10^{23} molecules of a substance	Unit measure used in International System of Units format.
Equivalent	Mass (in grams) of a mole of a substance divided by charge of substance	Unit of measure used in conventional lab values.
Osmole	Amount of a substance (in moles) that dissociates to form 1 mole of osmotically active particles	
Osmolarity	Measure of solute concentration per unit volume of solvent	Osmolarity varies with changing temperature, because water changes its volume according to temperature.
Osmolality	Measure of solute concentration per unit mass of solvent	Osmolality is the preferred measure because it remains constant with changes in temperature.
Tonicity or effective osmolality	Measure of the osmotic pressure gradient between two solutions, across a semipermeable membrane	Tonicity is affected only by solutes that cannot cross a semipermeable membrane. For example, tonicity is not affected by urea or glucose as they cross semipermeable membranes.

When two solutions are separated by a membrane that is permeable only to water, water crosses into the compartment with the more concentrated solution to equalize the ion concentration in each. The force driving this movement is "osmotic pressure."[1] In human fluids, the substances that contribute the most to osmotic pressure in ECF are sodium (Na^+) and the anions HCO_3^- and Cl^-, plus glucose. In physiology, this force is called effective osmolality or tonicity. The formula to calculate **effective osmolality** or **tonicity** is

$2 \times [Na^+]$ + glucose/18 (normal range, 275 to 290 mOsm/L)

When 1 L of free water is added to the ECF, it crosses the cell membrane into the ICF to equalize ECF osmolality. The result is TBW expansion and slight reduction in osmolality (**Figure 17-1**). When 1 L of isotonic saline solution 0.9% is added to the ECF, there is no movement of water into the cells, and the final result is ECF expansion only.[2]

In contrast, when there is a fluid loss and a consequent increase in osmolality, osmoreceptors in the hypothalamus stimulate thirst and the release of antidiuretic hormone (ADH, known also as vasopressin) from the pituitary gland. With a decrease in circulating blood volume, low-pressure baroreceptors in the great veins and the right atrium augment the effect on the osmoreceptors, with a consequent urine water reabsorption and vasoconstriction.[1-5]

The plasma sodium concentration, or tonicity, leads to changes in cell volume. Hypertonic plasma draws water out of the cell into the vasculature, causing cell shrinkage. In the setting of hypotonic plasma, cells swell with water.[4]

DEHYDRATION

Dehydration is a loss in TBW caused by either water loss (hyperosmolality) or salt loss (hypo-osmolality).[6] Water loss may be caused by inadequate fluid intake to replace insensible loss or excessive diuresis,

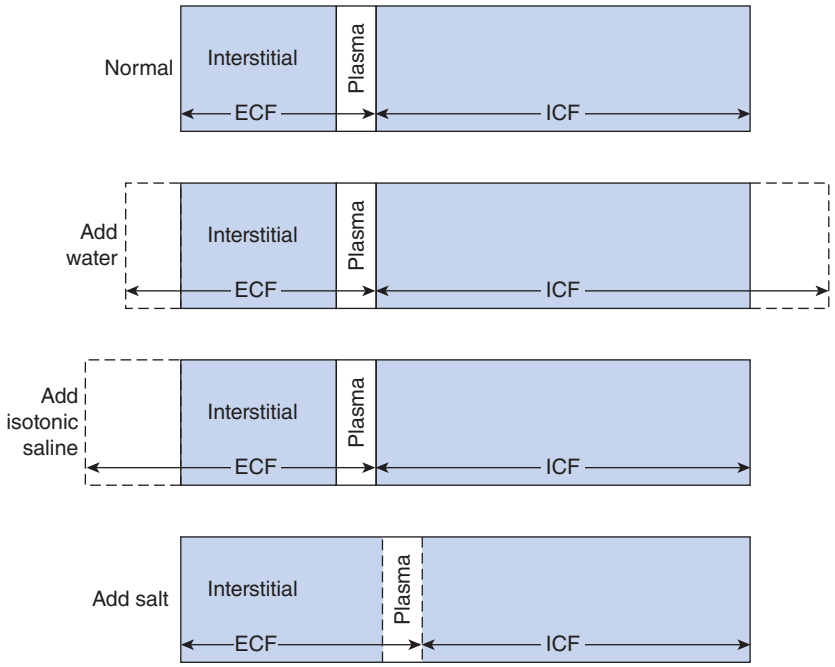

FIGURE 17-1. Distribution of total body water into the intracellular fluid (ICF) and extracellular fluid (ECF) compartments. Addition of water expands both compartments. Addition of isotonic saline expands only the ECF, whereas addition of salt without water expands the ECF at the expense of the ICF. [Reproduced with permission from Eaton DC, Poole JP (eds): *Vander's Renal Physiology*, 8th ed. New York: McGraw-Hill, Inc.; 2013. Fig 6-1.]

due to hyperglycemia for example. Salt loss can be caused by vomiting, diarrhea, sweating, bleeding, or chronic kidney failure.[7]

Symptoms of dehydration include thirst, fatigue, dizziness, and ultimately confusion; signs include sunken eyes, dry mouth and tongue, and tenting of the skin. In elderly patients, dehydration is a cause of delirium, cognitive deterioration, agitation, hallucinations, and delusions. In these patients, rapid weight loss, dark (concentrated) urine, and behavioral change suggest a diagnosis of dehydration.[8] A combination of factors may precipitate an episode of dehydration, such as chronic antihypertensive medication or diuretic use combined with exposure to high outdoor temperature, an episode of fever, or an acute illness when water intake is insufficient.[9]

Table 17-3 lists the screening suggested by the Dehydration Council to evaluate the risk of dehydration.[6]

HYPONATREMIA

Hyponatremia is defined as a serum [Na^+] <138 mEq/L. However, symptomatic hyponatremia rarely occurs until [Na^+] falls to ≤135 mEq/L. In the setting of normal water intake, high circulating levels of ADH with subsequent water retention are a prerequisite for the development of hyponatremia.[3,10,11] Urine osmolality is always >100 mOsm/L H_2O with the exception of samples from patients with psychogenic polydipsia, which drives down urine osmolality below the typical minimum.

Mild hyponatremia is common, with an incidence of 15% to 30% in hospitalized patients; 1% to 4.5% of patients have sodium levels below 126 mEq/L.[10,12] Hyponatremia affects approximately 20% of patients with heart failure, whereas at least 50% of nursing home patients have had one or more episodes of hyponatremia.[8,11]

The concentration of Na^+ does not give information regarding volume status. **Therefore, the first step in the evaluation should include a clinical evaluation of ECF volume status plus comparing measured and calculated plasma osmolalities.**

TABLE 17-3 Checklist for Evaluation of Dehydration Risk

- Diuretics
- End of life
- High fever
- Yellow urine turns dark
- Dizziness (orthostasis)
- Reduced oral intake
- Axilla dry
- Tachycardia
- Incontinence (fear of, reducing oral intake)
- Oral problems
- Neurologic impairment
- Sunken eyes

HYPEROSMOLAR HYPONATREMIA (PLASMA OSMOLALITY [P_{OSM}] >295 mOsm/kg H_2O)

Hyperosmolar hyponatremia occurs when large quantities of osmotically active solutes accumulate in the ECF space. In this setting, there is a net movement of water from the ICF to the ECF, thereby effectively diluting the ECF [Na^+]. **This happens commonly with severe hyperglycemia.** Each 100 milligram/dL increase in plasma glucose above the normal level of 100 milligrams/dL decreases the serum [Na^+] by 1.6 mEq/L.[1] Other causes of hypertonic hyponatremia are administration of osmotic agents such as mannitol, glycerol, and maltose, causing an osmolar gap and hyponatremia. The osmolar gap is the difference between measured osmolality and calculated osmolality. Normally the difference is around 10 mOsm/L; if it is >15 mOsm/L, it means that a nondetectable agent with osmotic activity is present, causing an osmolar gap. A consequent osmotic diuresis will cause [Na^+] deficit with volume depletion that should be treated with saline solution.

ISO-OSMOLAR HYPONATREMIA (P_{OSM} 275 TO 295 mOsm/kg H_2O)

Pseudohyponatremia is a factitiously low value of [Na^+] that occurs in the setting of severe hyperproteinemia or hyperlipidemia yielding a measurement error. High concentrations of lipids or protein can displace serum water, which causes laboratory misinterpretation of normal [Na^+]; some laboratories use instruments that avoid this laboratory

TABLE 17-4 Classification, Differential Diagnosis, and Features of Hyponatremia According to Volume Status

	Clinical Conditions	Orthostatic Hypotension	Edema	$U_{[Na+]}$, mEq/L	U_{OSM}, mOsm/L
Hypervolemic hypernatremia	CHF Cirrhosis Nephrotic syndrome Acute and chronic kidney disease	Absent	Yes	Compensated: >20 Decompensated: <10	Compensated: <100 Decompensated: >100
Normovolemic hyponatremia	Psychogenic polydipsia Glucocorticoid deficit Hypokalemia Drugs SIADH	Absent	No	>20	>100
Renal hypovolemic hyponatremia	Diuretics Mineralocorticoid deficit Salt-losing nephropathy	Normally present	No	>20	>100
Extrarenal hypovolemic hyponatremia	Vomiting Diarrhea	Normally present	No	<10	>100

Abbreviations: CHF = congestive heart failure; SIADH = syndrome of inappropriate antidiuretic hormone excretion; $U_{[Na+]}$ = urine sodium; U_{OSM} = urine osmolality.

error; check with your laboratory administrator. Patients are asymptomatic; treatment is not needed.

HYPO-OSMOLAR HYPONATREMIA (P_{OSM} <275 mOsm/kg H_2O)

The different causes of hypo-osmolar (hypotonic) hyponatremia according to volume status are listed in **Table 17-4**.[2,3] Osmol receptors in the hypothalamus react to low osmolality by secreting ADH, which limits water excretion and increases water reabsorption. In situations such as heart failure,[13,14] cirrhosis,[15] and nephrotic syndrome, the effective arterial blood volume is decreased because water is mainly distributed to the interstitial space. Thus, Na^+ and water reabsorption are increased, and water excretion is reduced.

Two important hyponatremic disorders are the **syndrome of inappropriate ADH secretion** and the less common **cerebral salt-wasting syndrome**.[1,2,11] Both conditions are diagnoses of exclusion after dismissing other causes of hyponatremia. The onset of both syndromes is linked to chronic cerebral disease, but syndrome of inappropriate ADH secretion may also be caused by noncerebral diseases and conditions as described in **Table 17-5**. In syndrome of inappropriate ADH secretion, volume status is normal, whereas in cerebral salt-wasting syndrome, there is hypovolemia; therefore, these two disorders are treated differently (see treatment section later in this chapter).

Methylenedioxymethamphetamine (MDMA or Ecstasy) intoxication is an uncommon but important cause of hyponatremia that may be profound (see also Chapter 188, "Hallucinogens").

CLINICAL FEATURES

The most important symptoms of hyponatremia are due to its effects on the brain; symptoms can be divided into moderately severe and severe, according to a European clinical practice guideline.[3,4] Moderately severe symptoms often start when a plasma $[Na^+]$ is <130 mEq/L and consist of headache, nausea, disorientation, confusion, agitation, ataxia, and areflexia. When $[Na^+]$ reaches levels <120 mEq/L, severe symptoms may develop including intractable vomiting, seizures, coma, and ultimately respiratory arrest due to brainstem herniation. Brain injury may become irreversible. The symptoms of hyponatremia can be due to many other conditions, and clinicians are cautioned to consider other etiologies before making treatment decisions.[4] The presence of hyponatremia-related symptoms is directly related to the rapidity of onset. After a certain period, brain cells begin to adapt to hyponatremia. Initially the hypo-osmolality drives water into the brain cells, yielding swelling.[2,3] Due to the rigid skull, intracranial hypertension occurs and the described symptoms begin. After 48 hours, the brain cells start to adapt by extruding Na^+, K^+, Cl^-, and organic osmolytes such as glycine and taurine from the cells, reducing cell osmolality and preventing further water uptake. In several clinical or physiologic conditions, this adaptation mechanism is impaired, as in the syndrome of inappropriate ADH secretion, in children, in menstruating women, and in hypoxia. In such cases, symptoms are more severe and persistent.

DIAGNOSIS

The diagnosis of hyponatremia and its subtypes is based on the clinical findings of volume status in association with specific laboratory values

TABLE 17-5 Causes of Syndrome of Inappropriate Antidiuretic Hormone Secretion

Neurologic and psychiatric disorders
- Infections: meningitis, encephalitis, brain abscess
- Vascular: hemorrhagic or ischemic stroke, subdural hemorrhage, temporal arteritis, cavernous sinus thrombosis
- Malignancy: primary or metastatic
- Traumatic brain injury
- Psychosis, delirium tremens
- Other: Guillain-Barré syndrome, neurosurgery

Drugs
- Cyclophosphamide
- Carbamazepine
- Vinca alkaloids (chemotherapy agents)
- Thioridazine, other phenothiazines, haloperidol
- Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
- Bromocriptine
- Narcotics, opiate derivatives
- Amiodarone
- Desmopressin overtreatment of diabetes insipidus or enuresis

Lung diseases
- Tuberculosis
- Lung abscess, empyema
- Acute respiratory failure

Non-CNS tumors with ectopic production of vasopressin
- Carcinoma of lung (small cell, bronchogenic), duodenum, pancreas, thymus, bladder, prostate, uterus; olfactory neuroblastoma
- Lymphoma, leukemia
- Sarcoma

TABLE 17-6 Syndrome of Inappropriate Secretion of Antidiuretic Hormone Diagnostic Criteria

Diagnostic Criteria
• Hypotonic hyponatremia with (P_{OSM} <275 mOsm/kg H_2O)
• Inappropriately elevated urinary osmolality (usually >200 mOsm/kg)
• Elevated urinary [Na^+] (typically >20 mEq/L)
• Clinical euvolemia
• Normal adrenal, renal, cardiac, hepatic, and thyroid functions

Abbreviation: P_{OSM} = plasma osmolality.

including serum [Na^+], serum osmolality, volume status, urinary sodium (U_{Na+}), and urine osmolality (U_{OSM}). Acute and chronic hyponatremia are defined by an onset time of less than (acute) or greater than (chronic) 24 to 48 hours. Experts recommend that when duration is unknown, the hyponatremia should be assumed to be chronic and treated as chronic with a longer correction time. If U_{OSM} is not readily available from the laboratory, it can be estimated using urinary specific gravity (π). Consider the numerals in the hundredths and thousandths decimal places of the π as whole numbers and multiply them by 35 to obtain U_{OSM}. As an example, for a π of 1.005, U_{OSM} = 05 × 35 = 175 mOsm/L.[1] Table 17-4 lists the values of U_{Na+} and U_{OSM} in different classifications of hyponatremia according to volume status and the differential diagnosis for each classification. As a rule, only in patients with edematous syndromes and in patients with vomiting and diarrhea will U_{Na+} be found to be <10 mEq/L.[16] The diagnostic criteria for syndrome of inappropriate ADH secretion are listed in **Table 17-6**.

Use care when assessing patients with potential exercise-associated hyponatremia. Since the worldwide effort to encourage consuming fluids during endurance exercise beginning in the early 1980s, overhydration with hypotonic fluids is now being seen. If a postexercise athlete presents with bloating, nausea, vomiting, and edema (check wrists and fingers), consider hyponatremia. In contrast, dehydration presents with excessive thirst, sunken eyes, poor skin turgor, and postural hypotension.

TREATMENT

Treatment of hyponatremia is guided by four variables: severity of symptoms, rate of onset, volume status, and the current serum [Na^+]. Nevertheless, the most important guides for therapy are symptoms (defined also as hyponatremic encephalopathy) rather than the serum [Na^+]. **When the patient presents with severe neurologic symptoms (vomiting, seizures, reduced consciousness, cardiorespiratory arrest), the initial treatment includes infusion of 3% hypertonic saline** as recommended by European guidelines[4,17] and U.S. experts[10,18] (**Table 17-7**).

Raising serum sodium by 5 mEq/L is typically all that is required to see an improvement in severe neurologic symptoms.[10,17,19] When symptoms are mild or moderate (nausea, confusion, headache) or in **chronic hyponatremia, the [Na^+] correction should be slower than for acute hyponatremia**. Rapid correction increases risk for the most dangerous complication of treatment, the osmotic demyelination syndrome. For **chronic hyponatremia [Na^+], the correction rate should not exceed 6 mEq/24 h** in high-risk patients and 12 mEq/24 h in low-risk patients (see "Osmotic Demyelination Syndrome" section later in this chapter for risks).[10] Hypertonic (3%) saline can be given at a low infusion rate, 0.5 to 1 mL/kg/h, with frequent [Na^+] checks. Isotonic (0.9%) saline is frequently used (sometimes before the [Na^+] is known), especially for the treatment of mild hyponatremia; however, the additional fluid load must be accounted for in treatment calculations. Loop diuretics (primarily furosemide, starting with a small dose of 20 milligrams IV) may be used in addition to treatment with saline infusions. Urine volume and [Na^+] should be strictly measured. Specific recommendations for hyponatremia treatment are summarized in **Table 17-8**.[2,7] There is no definitive consensus regarding the role of vaptans for patients with hyponatremia, their safety, or their tolerability. The major concerns remain the risk of overcorrection, the risk of precipitating osmotic demyelination syndrome, and the high cost.[20]

TABLE 17-7 Treatment of Hyponatremia Symptomatic With Seizures or Coma

Step 1	Assess for indication for 3% hypertonic saline: severe symptoms of hyponatremia such as seizures or coma with suspected impending brainstem herniation in setting of acute* or chronic† hyponatremia.
Step 2	Infuse 100–150 mL of 3% hypertonic saline IV over 15–20 min.‡
Step 3	Measure serum sodium level after each 3% hypertonic saline infusion.
Step 4	Stop infusion when symptoms improve or a target of a 5 mEq/L (range, 4–6 mEq/L) increase in serum sodium concentration is achieved.
Step 5	May repeat 150 mL of 3% hypertonic saline up to 3 total doses, or a total of 450 mL IV of 3% hypertonic saline.
Step 6	Keep the IV line open with minimal volume of 0.9% normal saline until cause-specific treatment is started. Limit increase in sodium level to no more than 8–12 mEq/L during the first 24 h or 18 mEq/L over 48 h.

*Both European guidelines and U.S. expert panel recommend 3% hypertonic saline infusion for acute life-threatening hyponatremia, which is most commonly due to self-induced water intoxication during endurance exercise, psychiatric illness, in association with methylenedioxymethamphetamine intoxication, or intracranial pathology or increased intracranial pressure.

†European guidelines state that regardless of onset of acute or chronic hyponatremia, presence of seizures or coma is an indication for brief infusion of hypertonic saline to improve symptoms.

‡European guidelines recommend a prompt 150-mL 3% hypertonic saline infusion over 20 minutes, then checking the serum sodium concentration after 20 minutes while repeating an infusion of 150 mL 3% hypertonic saline for the next 20 minutes, repeating this sequence up to twice more, and stopping with clinical improvement or when target sodium level is reached.

COMPLICATIONS OF TREATMENT

Osmotic Demyelination Syndrome Osmotic demyelination syndrome is caused by rapid correction of hyponatremia (>12 mEq/L/24 h) as water moves from cells to ECF yielding intracellular dehydration (**Figure 17-2**). Risk factors for osmotic demyelination syndrome include [Na^+] <120 mEq/L, chronic heart failure, alcoholism, cirrhosis, hypokalemia, malnutrition, and treatment with vasopressin antagonists such as tolvaptan. Main symptoms are dysarthria, dysphagia, lethargy, paraparesis or quadriparesis, seizures, and coma. The treatment of [Na^+] overcorrection is rarely done in the ED, but consists of giving 5% dextrose in water at 3 mL/kg/h, loop diuretics, and desmopressin.[3,10]

HYPERNATREMIA

Hypernatremia is defined as serum or plasma **[Na^+] >145 mEq/L and hyperosmolality** (serum osmolality >295 mOsm/L).

Hypernatremia results from a deficit in TBW and/or a net gain of Na^+ (less common). When [Na^+] and osmolality increase, normal subjects become thirsty and drink free water, and the Na^+ level returns toward normal. Any clinical situation that impairs the patient's sense of thirst, limits the availability of water, limits the kidney's ability to concentrate urine, or results in increased salt intake predisposes the patient to hypernatremia. Elderly patients, decompensated diabetics, infants, and hospitalized patients are at particular risk of developing hypernatremia. In addition, hypernatremia may be the result of loss of free water in diarrheal stools or in the urine.[21,22]

As in hyponatremia, symptoms will be more severe and evident when the onset is rapid; after the first 48 hours, there is an adaptation of brain cells with an increase in electrolytes and organic osmolytes and thus increased intracellular water partly correcting the initial cell shrinking (**Figure 17-3**).

If severe hypernatremia develops in the course of minutes to hours, such as from a massive salt overdose in a suicide attempt, a suddenly shrinking brain may prompt intracranial hemorrhage.

Based on volume status, hypernatremia may be classified as hypovolemic hypernatremia (decreased TBW and total body Na^+ with a relatively greater decrease in TBW), hypervolemic hypernatremia (increased total body Na^+ with normal or increased TBW), or normovolemic hypernatremia (near normal total body sodium and decreased TBW)[1,2] (**Table 17-9**).

TABLE 17-8 Cause-Specific Treatment for Hyponatremia

Clinical Condition	Therapy	Cautions/Comments
Chronic heart failure and cirrhosis	Loop diuretics, water restriction. Consider vasopressin antagonists* if the above therapies fail for patients with chronic heart failure.	When vasopressin antagonists* are used, serum [Na^+] should be frequently measured to avoid hypernatremia. FDA recommends against vasopressin antagonists in patients with liver disease.
Nephrotic syndrome	Water restriction.	
Acute or chronic kidney disease	Water restriction.	Frequent assessment of creatinine.
Psychogenic polydipsia	Water restriction.	Treat the underlying psychiatric disease.
Hypothyroidism	Levothyroxine.	Several days of therapy are typically required to correct hyponatremia.
Glucocorticoid deficiency	Hydrocortisone. If neurologic symptoms, consider vasopressin antagonists* if resistant to hydrocortisone.	When vasopressin antagonists* are used, [Na^+] should be frequently measured.
SIADH	Water restriction. Enhanced Na^+ and protein intake + furosemide. Vasopressin antagonists* can be used for [Na^+] <125 mEq/L. Demeclocycline. Lithium.	Isotonic (0.9%) NaCl may worsen hyponatremia; when vasopressin antagonists* are used, [Na^+] should be frequently measured.
Diarrhea and vomiting	Isotonic (0.9%) NaCl. Add KCl if hypokalemia is present.	Treat the cause, monitor hemodynamic status.
Diuretics (most commonly thiazides)	Stop diuretic. KCl may be sufficient in patients with coexistent potassium depletion and normal dietary sodium intake. NaCl can be given orally.	Slow correction is recommended. Do not overcorrect K^+ deficit.
Mineralocorticoid deficiency	Replace volume deficit. Fludrocortisone therapy is indicated once diagnosis is confirmed.	Mechanism: volume depletion $\rightarrow\uparrow$ ADH $\rightarrow$ decreases water excretion, $\uparrow$ Na loss.
Salt-losing nephropathies	Isotonic (0.9%) NaCl.	
Cerebral salt wasting	Isotonic (0.9%) NaCl. Fludrocortisone may be considered after the diagnosis is confirmed.	NaCl orally at home.

Abbreviations: ADH = antidiuretic hormone; FDA = Food and Drug Administration; KCl = potassium chloride; NaCl = sodium chloride; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

*Vasopressin antagonists or vaptans are rarely started in the ED; they are not indicated unless [Na^+] <125 mEq/L; starting doses are tolvaptan, 15 milligrams PO daily; and conivaptan, 20 milligrams loading dose IV over 30 minutes, then continuous infusion of 20 milligrams over 24 hours for 2 to 4 days.

CLINICAL FEATURES

History depends on hypernatremia type and may reveal nausea and vomiting, lethargy, weakness, increased thirst, low water intake, salt intake, polyuria (>3000 mL of urine/24 h), diabetes, hypercalcemia, hypokalemia, medications such as lactulose, loop diuretics, lithium, demeclocycline (may cause nephrogenic diabetes insipidus), or NSAIDs (may cause interstitial nephritis). Physical exam may reveal hypotension, tachycardia, orthostatic blood pressures, sunken eyes, dry mucous membranes (symptoms of hypovolemia), altered mental status (may be

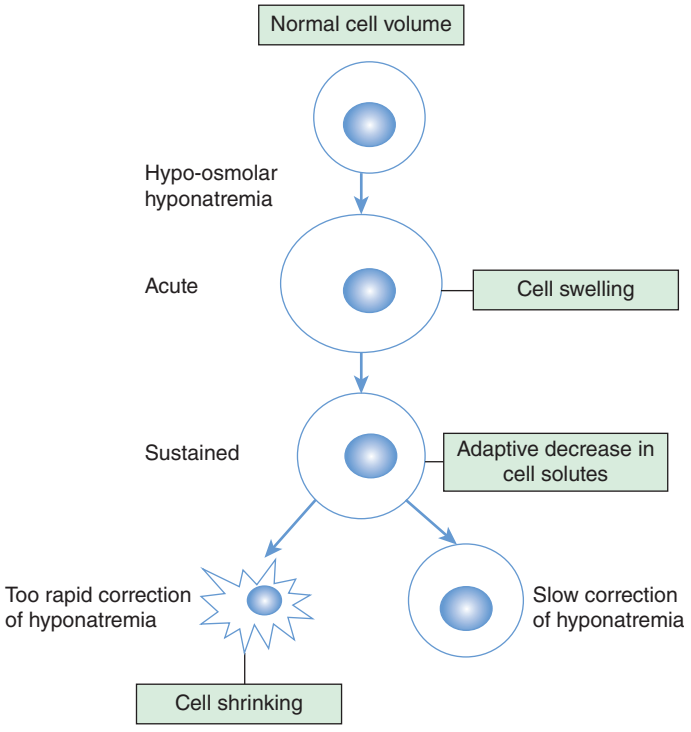

FIGURE 17-2. Adaptation of brain volume to hyponatremia and effect of correction.

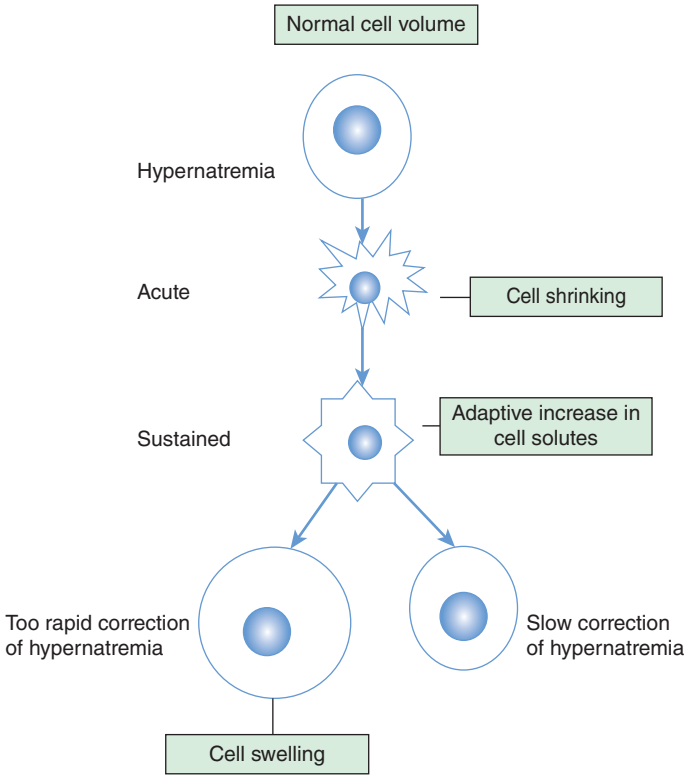

FIGURE 17-3. Adaptation of brain volume to hypernatremia and effect of correction.

TABLE 17-9 Hypernatremia Classification and Features According to Volume Status

Volume Status	Clinical Conditions	Diagnosis	U_{OSM}, mOsm/kg H_2O	$U_{[Na+]}$, mEq/L
Hypervolemic hypernatremia	Cushing's syndrome	Cortisol test	>100	>20
	Primary hyperaldosteronism	History of hypertension and hypokalemia		
	Salt water intake	Psychiatric disorder		
	Iatrogenic	Hypertonic saline, enteral feeding, bicarbonate infusion		
	Hemodialysis	Clinical history		
Normovolemic hypernatremia	Central DI	History of CNS lesion, urinary concentration after desmopressin	Central DI <300	>20
	Partial DI		Partial DI >300 but <800	
	Nephrogenic DI	History of nephrotoxic drugs, no response to desmopressin	<200	
	Hypodipsia	History of poor oral intake	>100	
	Medications	Amphotericin, aminoglycosides, lithium, phenytoin	<200	
Renal hypovolemic hypernatremia	Osmotic diuretics	Hyperglycemia. High sodium level after correction	>100	>20
	Loop diuretics	Clinical history		
	Postobstructive diuresis	Clinical history		
Extrarenal hypovolemic hypernatremia	Vomiting	Clinical history	>800	<10
	Diarrhea			
	GI fistulas			
	Sweating			
	Burns			

Abbreviations: DI = diabetes insipidus; $U_{[Na+]}$ = urine sodium; U_{OSM} = urine osmolality.

present in any of the hypernatremia classifications), poor skin turgor, or edema in hypervolemic hypernatremia. Without intervention, coma, seizures, and shock may occur. Signs of Cushing's syndrome may be present, including moon facies, fatty deposits between the shoulders and upper back, and thinning of the skin. Severe hypernatremia (i.e., a $[Na^+]$ >150 to 160 mEq/L) yields a mortality of 75%.[23]

DIAGNOSIS

The diagnosis of hypernatremia and its classification are based on the clinical evaluation including volume status and specific laboratory tests, such as serum electrolytes and osmolality, urine osmolality, urea/creatinine ratio, and free water deficit. A BUN/creatinine ratio >40 is indicative of hyperosmolar dehydration. Urine osmolality can be used to suggest the type of hypernatremia (**Table 17-10**). A patient's free water deficit can be calculated with the aid of a phone application or Internet calculator.

TREATMENT

First, shock, hypoperfusion, or volume deficits should be treated with isotonic (0.9%) saline. Second, treat any existing underlying cause, such as diabetes insipidus (see "Diabetes Insipidus" section later in this chapter), vomiting, diarrhea, or fever. Third, correct the patient's free water deficit at a rate reflecting the acuity or duration time of the hypernatremia onset (**Table 17-11**).[15,24] In cases of a lethal sodium chloride ingestion/load (0.75 to 3.0 grams/kg) less than 6 hours prior to presentation, the free water deficit may be replaced rapidly with no reported adverse events.[11,25] When the adaptation of brain cells is incomplete (onset over <48 hours), the correction rate of acute hypernatremia can be performed at a rate of 1 mEq/L/h. In an alert patient capable of safely drinking water, the route of administration should be two-thirds free water orally and one-third IV. If hypernatremia is chronic (onset over >48 hours), the rate of correction should be slower to avoid the risk of cerebral edema, at no more than 0.5 mEq/L/h or 10 to 12 mEq/24 h.[26]

TABLE 17-10 Urine Osmolality Findings in Selected Hypernatremic States

Urine Osmolality (U_{OSM})	Potential Hypernatremic State
U_{OSM} <300 mOsm/kg H_2O	Central or nephrogenic diabetes insipidus
U_{OSM} >300, <800 mOsm/kg H_2O	Partial diabetes insipidus or osmotic diuresis
U_{OSM} >800 mOsm/kg H_2O	Hypertonic dehydration

DIABETES INSIPIDUS

Diabetes insipidus is a disease where the ability of the kidney to reabsorb free water is compromised.[2,27] The disorder is characterized by polyuria, polydipsia, and an increased volume of hypo-osmolar urine.

TABLE 17-11 Treatment of Hypernatremia

Treatment	Indication and Comments
Isotonic (0.9%) saline	Use for correction of volume deficits.
Etiology-specific therapy	Treat fever with antipyretics, vomiting with antiemetics, and diabetes insipidus with desmopressin (see "Diabetes Insipidus" section).
D_5W or oral free water to replace free water deficit over 2–3 d	In cases of chronic hypernatremia, it is suggested that correcting (lowering) the sodium level should occur at a rate of no more than 0.5 mEq/L/h or 10–12 mEq/24 h.
0.45% normal saline at 100 mL/h	Correct volume deficits first. A commonly used infusion for mild to moderate hypernatremia, but this therapy adds sodium to total body.
D_5W to replace free water deficit over 1–2 h	Reserved only for those cases where acuity is known to be <6 h and the salt load is known to be lethal (0.75–3.0 grams/kg of body weight).
Hemodialysis	An alternative or as a supplement to D_5W to replace free water deficit in life-threatening acute cases of salt ingestion.

Abbreviation: D_5W = 5% dextrose in water.

TABLE 17-12 Classification of Diabetes Insipidus

Class	Acquisition	Pathophysiology
Central or neurogenic diabetes insipidus	Congenital	Structural malformations affecting the hypothalamus or pituitary Autosomal dominant (or rarely recessive) mutations in the gene encoding AVP-NPII precursor protein
	Acquired	Primary tumors (craniopharyngioma) or metastases Infection (e.g., meningitis, encephalitis) Histiocytosis and granulomatous diseases Trauma Surgery Idiopathic
Nephrogenic diabetes insipidus	Congenital	X-linked: inactivating mutations in *AVPR2* gene Autosomal: recessive or dominant mutations in *AQP-2* gene
	Acquired	Primary renal disease Obstructive uropathy Metabolic causes (e.g., hypokalemia, hypercalcemia) Sickle cell disease Drugs (e.g., lithium, demeclocycline)
Primary polydipsia or dipsogenic diabetes insipidus	Acquired	Psychogenic illness characterized by excessive fluid intake. Treatment is aimed at the psychiatric disease.

Hypernatremia is present only when the thirst center is impaired or water intake is reduced. Diabetes insipidus can be central (also called neurogenic), due to inadequate ADH secretion, or renal (also called nephrogenic), when ADH secretion is normal or increased but the v2R receptors of the kidney's collecting duct cells do not respond appropriately to ADH. Diabetes insipidus may be congenital or acquired. In **Table 17-12**, the main causes of diabetes insipidus are listed. Congenital forms of diabetes insipidus present during infancy. Eventually, recurrent cellular dehydration causes cerebral calcifications that manifest as delayed intellectual advancement.

Central diabetes insipidus is acquired in most cases, associated with various disorders that cause destruction of ADH-secreting neurons. When a diagnosis is not possible, despite imaging and other diagnostic tests, diabetes insipidus will be defined as idiopathic diabetes insipidus.

The most common clinical symptoms and signs are excessive thirst, polydipsia, and polyuria plus several nonspecific symptoms including weakness, lethargy, myalgias, and irritability. In infancy, congenital forms of diabetes insipidus present with fatigue and weakness often manifested by less activity or tiring with feeding, vomiting, polyuria, and sometimes fever. Diagnosis can be suspected in the ED by clinical presentation, but the diagnosis requires a prolonged test, requiring 4 to 18 hours. Urine osmolality is assessed after water deprivation; many cases require another assessment after a dose of desmopressin, the "water deprivation test." A spot check in the ED without water deprivation will typically reveal a U_{OSM} of <300 mOsm/L. In central diabetes insipidus, a cerebral MRI is indicated (on a nonurgent outpatient basis) to evaluate the hypothalamic–pituitary area.

Central diabetes insipidus is treated with the synthetic hormone desmopressin, as a nasal spray, 10 micrograms (0.1 mL) every 12 hours, or PO, 0.05 milligrams every 12 hours, as starting doses. Therapy of nephrogenic diabetes insipidus includes a low-salt, low-protein diet, adequate hydration, and the careful use of one to three agents that act together to concentrate urine in these patients: a thiazide diuretic, the potassium-sparing diuretic amiloride, and indomethacin. Exogenous ADH, 5 to 10 micrograms SC, two to four times daily, is also used in noncongenital nephrogenic diabetes insipidus, as these patients have a partial response to ADH. Patients with significant electrolyte abnormalities should be admitted to the hospital, whereas stable patients suspected of having diabetes insipidus should be referred for testing.

POTASSIUM

PATHOPHYSIOLOGY

Potassium (K^+) is the major intracellular cation of the body: 98% of total body K^+ in healthy subjects is intracellular, and 70% to 75% of total K^+ is in muscle tissues. The normal intracellular concentration averages 150 mEq/L, and the normal extracellular concentration is 3.5 to 5.0 mEq/L. K^+ is excreted predominantly by the kidneys (80% to 90%) and is filtered freely through the renal glomerulus and then reabsorbed in the proximal and ascending tubules. It is secreted in the distal tubule in exchange for Na^+. In healthy individuals, the kidneys are able to excrete up to 6 mEq/kg/d. The several mechanisms of K^+ handling along the nephron are the targets of diuretic therapy.

Being mostly intracellular, an accurate calculation of total body K^+ is difficult, but an estimation of the K^+ deficit can be determined using the following equation: **estimated K^+ deficit in mEq/L = (expected serum [K^+] in mEq/L – measured serum [K^+] in mEq/L) × ICF** (calculated as 40% of total body weight).[1]

However, this equation is reliable only for healthy subjects, because critical patients sustain significant and rapid intracellular to extracellular shifting in response to severe injury (e.g., surgical stress, trauma, or burns), acid-base imbalance, catabolic states, increased extracellular osmolality, or insulin deficiency. So it is possible to have hyperkalemia in patients with a total body K^+ deficit (e.g., diabetic ketoacidosis) and hypokalemia with total body K^+ surplus.[2] These shifts are crucial considering the role of K^+ in maintaining the resting membrane potential, as the ratio of intracellular to extracellular K^+ is the most important determinant of neuromuscular and cardiovascular excitability.[28,29]

Acid-base imbalance plays an important role in critically ill patients: there is an inverse proportionality between serum pH and [K^+], with [K^+] rising about 0.6 mEq/L for every 0.1 decrease in pH and vice versa, through an exchange between H^+ and K^+.[1,30]

In addition, the duration of both hypo- and hyperkalemia influences the clinical response: chronic potassium depletion or surplus allows adaptation through shifts in intra-/extracellular K^+ concentration to maintain the resting membrane potential, thus mitigating neuromuscular and cardiac electrophysiologic effects.

Potassium derangements are becoming more and more frequent in the ED (up to 11%)[31] and should be promptly and correctly addressed.[32]

HYPOKALEMIA

Hypokalemia is defined as a serum [K^+] of <3.5 mEq/L. The most frequent causes of hypokalemia are insufficient dietary intake (e.g., fasting, eating disorders, alcoholism), intracellular shifts (e.g., alkalosis, insulin, β_2-agonists, hypokalemic periodic paralysis), and increased losses, mainly GI (vomiting, nasogastric suction, diarrhea) or renal (diuretics,[33] hyperaldosteronism, osmotic diuresis, toxins)[34] (**Table 17-13**).

The clinical manifestations result from abnormalities in membrane polarization and affect almost every body system but are particularly dangerous in the excitable myocardium. Hypokalemia makes the resting potential more electronegative, thus enhancing depolarization; the reduction in [K^+] conduction delays repolarization, causing prolonged QT_c, flattened T waves, and the appearance of U waves in the ECG (**Figure 17-4**).

CLINICAL FEATURES

Symptoms of hypokalemia (**Table 17-14**) usually start when serum concentrations reach 2.5 mEq/L, although they may appear sooner with rapid decreases in concentration or appear later (i.e., at even lower [K^+]) for chronic depletion.

Particular attention must be paid to cardiac arrhythmias, usually tachyarrhythmias (atrial fibrillation,[35] torsadess de pointes, ventricular tachycardia, and ventricular fibrillation), which can be life threatening.

TABLE 17-13 Causes of Hypokalemia

Transcellular shifts	Alkalosis*
	Increased plasma insulin (treatment of diabetic ketoacidosis)
	β-Adrenergic agonists
	Hypokalemic periodic paralysis (congenital)
	Thyrotoxic hypokalemic periodic paralysis
Decreased intake	Fasting
	Alcoholism (worsened by hypomagnesemia)
	Eating disorders
GI loss	Vomiting*, nasogastric suction
	Diarrhea* (including laxative, enema abuse)
	Malabsorption
	Ureterosigmoidostomy
	Enteric fistula
	Villous adenoma
Renal loss	Diuretics (carbonic anhydrase inhibitors, loop diuretics, and thiazide-like diuretics)*
	Primary hyperaldosteronism
	Secondary hyperaldosteronism
	Licorice ingestion
	Excessive use of chewing tobacco
	Renal tubular acidosis
	Postobstructive diuresis
	Osmotic diuresis
	Bartter's syndrome (mimics loop diuretic use)
	Gitelman's syndrome (mimics thiazide diuretic use)
	Apparent mineralocorticoid excess and related syndromes (Conn's, Liddle's)
	Drugs and toxins (aminoglycosides, echinocandins, carbenicillin, penicillins, amphotericin B, levodopa, lithium, thallium, cesium, barium, toluene, theophylline, chloroquine, steroids, etc.)
Sweat loss	Heavy exercise
	Heatstroke
	Fever
Other	Hypomagnesemia
	Acute leukemia and lymphomas
	IV hyperalimentation
	Recovery from megaloblastic anemia
	Hypothermia (accidental or induced)

*Frequently encountered etiologies in the ED.

DIAGNOSIS

Diagnosis of hypokalemia is made with serum chemistry measurement; the etiology is investigated with additional testing. An ECG should be obtained from hypokalemic patients in the ED (Figure 17-4). Obtain blood gas analysis when alkalosis is suspected. If the cause of hypokalemia is not apparent from history, spot urinary electrolytes can be obtained before starting K^+ replacement (see **Table 17-15** for interpretation of urine K^+ values[1]); also U_{Na+}, U_{OSM}, and P_{OSM} should be measured, because a U_{Na+} value <30 mEq/L and a U_{OSM} value less than P_{OSM} suggest polyuria. Polyuria can increase K^+ excretion even if total body K^+ is depleted; thus urinary K^+ may be misleading for diagnosis in the setting of polyuria.[2]

Another useful tool for differential diagnosis is **transtubular K^+ gradient = (Urinary K^+ × P_{OSM})/(U_{OSM} × Plasma K^+),** with normal values of 8 to 9 mEq/L. Values <5 mEq/L suggest hyperaldosteronism; if paralysis is present, values <3 mEq/L suggest hypokalemic periodic paralysis. A calcium/phosphate ratio >1.7 on a spot urine is 100% sensitive and 96% specific for thyrotoxic hypokalemic periodic paralysis.[36,37]

TREATMENT

The treatment of hypokalemia is replacement of K^+. This should be done orally in stable patients with mild hypokalemia (>3.0 mEq/L) who are able to tolerate oral intake.[2] Foods rich in K^+ (fruits, dried fruits, nuts, vegetables, and meat) can be suggested at discharge from ED, as well as salt substitutes or K^+ supplements that should be prescribed with abundant fluids and/or food to prevent gastric irritation. Additional treatment targeted to the underlying cause should be considered. For example, it is possible to treat (and prevent) chronic hypokalemia induced by loop or thiazide diuretics by adding an adequate amount of spironolactone to the patient's chronic therapy[38]; however, the primary care physician should be aware of or guide such a change in medication. Whenever modifying diuretics or other drugs at ED discharge, recommend follow-up within 1 week for repeat assessment of renal function and [K^+]. In hypokalemia secondary to respiratory alkalosis (as caused by an acute anxiety disorder), the simple correction of the acid-base imbalance (through reassurance or anxiolytics) can correct [K^+] without administering exogenous potassium.

IV replacement is indicated in patients with severe (<2.5 mEq/L) hypokalemia and in symptomatic patients with moderate (2.5 to 3 mEq/L) hypokalemia. Treat patients with cardiac arrhythmias or prolonged QT_c or when oral replacement is not tolerated or not feasible (see **Table 17-16** for common medications known to prolong QT_c). Monitor the patient's rhythm when treating with IV K^+.

Monitor closely those patients who sustain rapid [K^+] changes due to their illness (e.g., postobstructive polyuria) or IV treatment. An example is diabetic ketoacidosis treatment, where rapid hypokalemia (including life-threatening arrhythmias) should be prevented by adequate IV K^+ administration prior to the detection of a rapid fall in serum potassium.

The following are **general principles in hypokalemia correction:**

1. Use potassium chloride and avoid administering K^+ in glucose solutions, to reduce insulin-induced K^+ transfer into cells.
2. Potassium is irritating to the endothelium; adequate dilution is mandatory to prevent pain and phlebitis (maximum recommended [K^+] in 500 mL of a saline solution is 40 mEq, to be infused in 4 to 6 hours in a peripheral line). If a more aggressive correction is needed, an identical solution can be administered in a second peripheral line. Higher concentrations can be administered through a central line, but infusion rates should never exceed 20 mEq/h.
3. Reassessing serum [K^+] should be adjusted to infusion rate and coexisting factors (e.g., concomitant acid-base imbalance, volume depletion, cardiac arrhythmias).
4. ECG monitoring is recommended.
5. In most cases, hypokalemic patients are also hypomagnesemic. Thus, magnesium (20 to 60 mEq/24 h) may be added to the infusion both to optimize tubular reuptake of potassium and to contrast proarrhythmic effect of hypokalemia.[1]

HYPERKALEMIA

PATHOPHYSIOLOGY

Hyperkalemia is defined as measured serum [K^+] of >5.5 mEq/L. The most common cause is factitious hyperkalemia due to release of intracellular potassium caused by hemolysis during phlebotomy. Other causes are listed in **Table 17-17**.

Clinical manifestations of hyperkalemia result from disordered membrane polarization (**Figure 17-5**). Cardiac manifestations are the most serious. In hyperkalemia, the resting potential of the excitable myocardium becomes less electronegative, with a consequent partial depolarization that reduces the activation of voltage-dependent sodium channels; this results in a slower and reduced amplitude of action potential. **Table 17-18** summarizes the ECG effects that may lead to arrhythmic complications, such as sinoatrial and atrioventricular blocks and atrial paralysis (Figure 17-5). Calcium administration does not affect potassium levels; rather, calcium antagonizes the effects of hyperkalemia

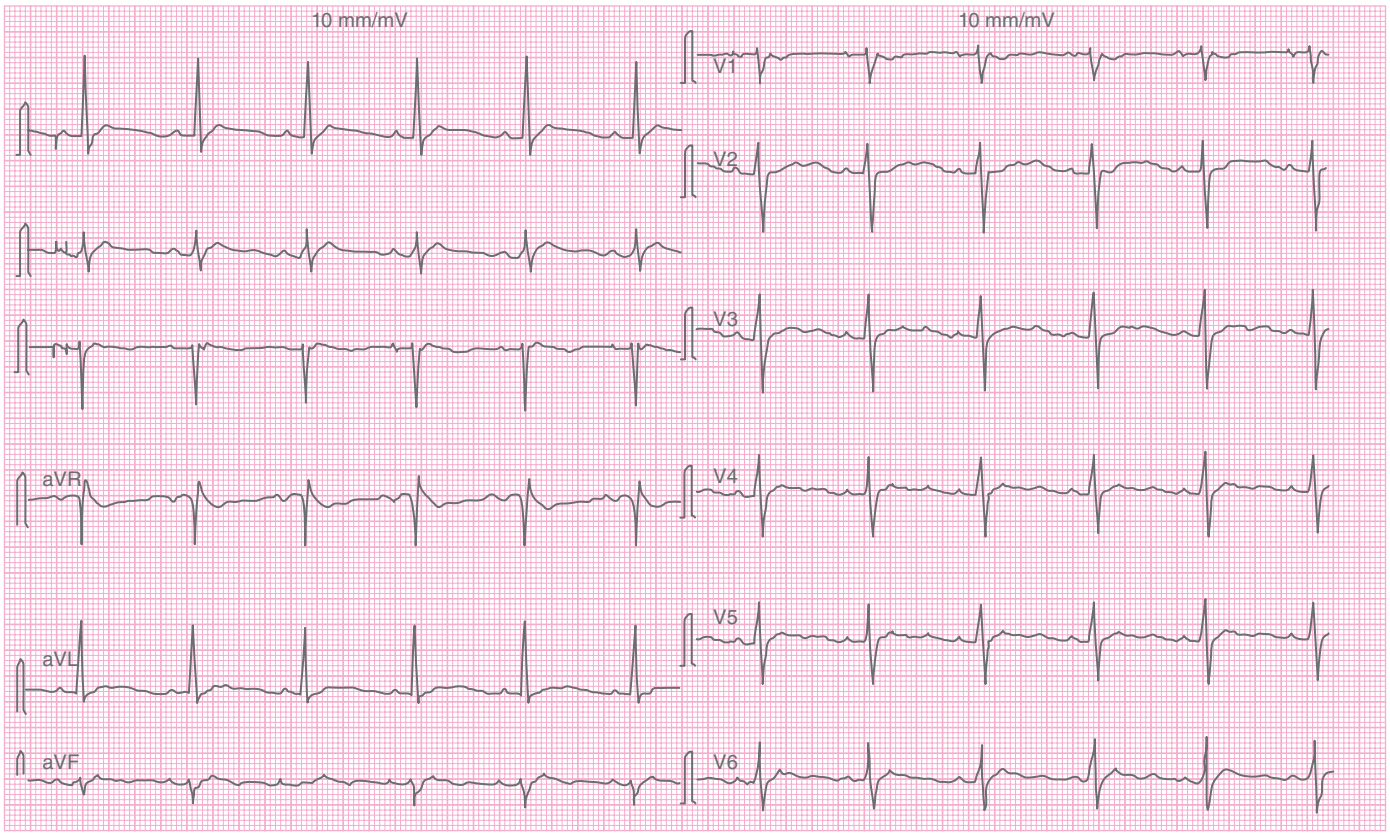

FIGURE 17-4. ECG of a patient with potassium of 1.4 mEq/L, with leg paralysis and deep fatigue. The patient had been taking a thiazide-like diuretic for hypertension. Notice the prolonged QT_c and a flattened T wave with a U wave visible in V_2 to V_5.

at the level of the cell membrane, raising the threshold potential, thus restoring the membrane potential and myocyte excitability close to normal (**Figure 17-6**).

CLINICAL FEATURES

Cardiac dysrhythmias, such as ventricular fibrillation, sinoatrial and atrioventricular blocks until complete heart block, and asystole, may occur. Death from hyperkalemia is usually the result of diastolic arrest or ventricular fibrillation. Other common symptoms include neuromuscular dysfunctional weakness, paresthesias, areflexia, ascending paralysis, and GI effects (nausea, vomiting, and diarrhea).[39]

TABLE 17-14 Symptoms and Signs of Hypokalemia

Cardiovascular	Hypertension
	Orthostatic hypotension
	Potentiation of digitalis toxicity
	Dysrhythmias (usually tachyarrhythmias)
	T-wave flattening, QT prolongation, U waves, ST depression
Neuromuscular	Malaise, weakness, fatigue
	Hyporeflexia
	Cramps
	Paresthesias
	Paralysis
	Rhabdomyolysis
GI	Nausea, vomiting
	Abdominal distention
	Ileus
Renal	Increased ammonia production
	Urinary concentrating defects
	Metabolic alkalemia, paradoxical aciduria
	Nephrogenic diabetes insipidus
Endocrine	Glucose intolerance

DIAGNOSIS

A stat ECG is essential in all hyperkalemic patients (Table 17-18); **if ECG changes are present, emergency treatment of hyperkalemia should start immediately.** In addition, if ECG changes are detected in a patient whose electrolyte levels are not yet known (e.g., a dialysis patient), hyperkalemia should be suspected and treated. A symptomatic

TABLE 17-15 Interpretation of Urinary Potassium

Spot Urinary Potassium	Possible Mechanism
U_{K+} <10 mEq/L	Decreased K^+ intake, nonrenal losses
	GI losses
	Sweat losses
	Nasogastric suction ($\downarrow U_{Cl-}$)
	Transcellular shift
	Alkalosis ($\downarrow U_{Cl-}$)
	Hypomagnesemia ($\uparrow U_{Cl-}$)
	Hypokalemic periodic paralysis
	Thyrotoxic hypokalemic periodic paralysis (calculate TTKG)
U_{K+} >20 mEq/L	Renal losses
	If hypernatremia coexists consider:
	hyperaldosteronism (calculate TTKG)
	Massive GI losses (secondary to metabolic alkalosis)

Abbreviations: TTKG = transtubular K^+ gradient; U_{Cl-} = urinary chloride; U_{K+} = urinary potassium.

TABLE 17-16 Common Medications Known to Prolong QT_c

Antiarrhythmics	Amiodarone, sotalol, flecainide, quinidine, dronedarone, dofetilide
Vasopressors/inotropes	Epinephrine, norepinephrine, dopamine, dobutamine
Neuroleptics	Haloperidol, droperidol, chlorpromazine, olanzapine, quetiapine, risperidone, paliperidone, clozapine, aripiprazole
Antidepressants	Amitriptyline, nortriptyline citalopram, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine
Antibiotics	Macrolides, quinolones, metronidazole, cotrimoxazole
GI prokinetics	Domperidone, cisapride, metoclopramide
Antiemetics	Ondansetron, granisetron, dolasetron, promethazine
Antifungals	Fluconazole, itraconazole, voriconazole, ketoconazole, posaconazole
Antivirals	Foscarnet, amantadine, atazanavir, nelfinavir, rilpivirine, ritonavir, saquinavir, telaprevir
Antiparasitics	Chloroquine, mefloquine, quinine, hydroxychloroquine, pentamidine
Antihistamines	Terfenadine, hydroxyzine, diphenhydramine
Others	Cocaine, lithium, methadone, tamoxifen, vardenafil, tacrolimus, pseudoephedrine

patient with a relatively small elevation of [K^+] (5.0 to 6.0 mEq/L) requires identification and treatment of the underlying cause. A spot urine K^+ may identify the diagnosis. An elevated spot urine K^+ (>20 mEq/L) suggests an extrarenal cause (and will more likely be responsive to therapy). A low urine K^+ output (<10 mEq/L) suggests oliguric kidney failure or drug effect, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

TABLE 17-17 Causes of Hyperkalemia

Pseudohyperkalemia	Tourniquet use Hemolysis (in vitro)* Leukocytosis Thrombocytosis
Intracellular to extracellular potassium shift	Acidosis* Heavy exercise β-Blockade Insulin deficiency Digitalis intoxication Hyperkalemic periodic paralysis
Potassium load	Potassium supplements Potassium-rich foods IV potassium Potassium-containing drugs Transfusion of aged blood Hemolysis (in vivo) GI bleeding Cell destruction after chemotherapy Rhabdomyolysis/crush injury* Extensive tissue necrosis
Decreased potassium excretion	Renal failure* Drugs—potassium-sparing diuretics,* β-blockade, NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, cyclosporine, tacrolimus Aldosterone deficiency* Selective defect in renal potassium excretion (pseudohypoaldosteronism, systemic lupus erythematosus, sickle cell disease, obstructive uropathy, renal transplantation, type IV renal tubular acidosis)

*Frequent or important ED diagnostic considerations.

TREATMENT

Emergency treatment includes continuous ECG monitoring and immediate intervention with several therapeutic medications, which based on the action mechanism can be divided into three modalities: membrane stabilization (crucial for cardiac tissue, must be done immediately), intracellular shift of K^+, and removal/excretion of K^+ from the body. All three modalities should be administered sequentially in rapid succession. Each mode has a different onset time and duration[40] (**Table 17-19**).

A blood gas is essential to identify metabolic acidosis. A 2015 Cochrane review does not recommend the routine administration of sodium bicarbonate for hyperkalemia unless there is concomitant metabolic acidosis.[41] In this Cochrane review, the effectiveness of sodium bicarbonate alone, or in combination with other therapies listed in Table 17-19, could not be clearly demonstrated, even at a variety of time points. Treatment should correct the underlying cause of the acid-base imbalance. If pH is normal or alkaline, the therapeutic measures that act to promote an intracellular to extracellular shift of [K^+] will be less effective, and treatment should be aimed at improving renal excretion.

Until recently, sodium polystyrene sulfonate was the only oral agent that lowered potassium levels by enhancing excretion (rather than shifting K^+ into cells). This agent has recently been associated with intestinal necrosis.[43] Two new oral binding agents, **patiromer** and **sodium zirconium cyclosilicate**, have proven useful to lower potassium levels for patients with mild hyperkalemia in a few randomized controlled trials (some still ongoing); however, although the onset of action for patiromer is too slow to be of benefit in life-threatening hyperkalemia, sodium zirconium cyclosilicate, which is still in development, seems to provide an effective reduction in [K^+] in a few hours, thus making it valuable for ED use.[44]

The following are **general principles in treatment of hyperkalemia:**

1. Immediate cessation of further K^+ administration, reduction of dietary intake, and suspension of drugs impairing K^+ renal excretion directly (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, K^+-sparing diuretics) or indirectly through worsening of renal function (e.g., NSAIDs, iodine contrast, antibiotics).
2. Fluid administration enhances K^+ renal excretion through increasing urine output.
3. If a patient is on digitalis,[45] hypercalcemia enhances the toxic cardiac effects of digitalis. However, in severe hyperkalemia secondary to digitalis intoxication with advanced intraventricular conduction impairment (wide, low-voltage QRS complexes), calcium administration must be considered, in association with antidigoxin antibodies.[46]
4. ECG continuous monitoring should be used to confirm the effects of therapy, thus reducing the frequency of rechecking [K^+].

MAGNESIUM

The total body content of magnesium (Mg^{2+}) is 24 grams, or 2000 mEq, 50% to 70% of which is fixed in bone and only slowly exchangeable. Most of the remaining Mg^{2+} is found in the ICF space, with a concentration of approximately 40 mEq/L. The distribution of Mg^{2+} is similar to that of K^+, with the major portion being intracellular. It is the second most abundant intracellular cation. Normal serum [Mg^{2+}] ranges between 1.5 and 2.5 mEq/L (0.7 to 1.1 mmol/L or 1.7 to 2.7 milligrams/dL). Circulating Mg^{2+} is 25% to 35% bound to proteins (mainly albumin), 10% to 15% complexed, and 50% to 60% ionized, which is the active portion. The normal dietary intake of Mg^{2+} is approximately 240 to 336 milligrams/d and is found in vegetables such as dry beans and leafy greens, meat, and cereals. Sixty percent of excreted Mg^{2+} is through stool, with the remainder via the urine.

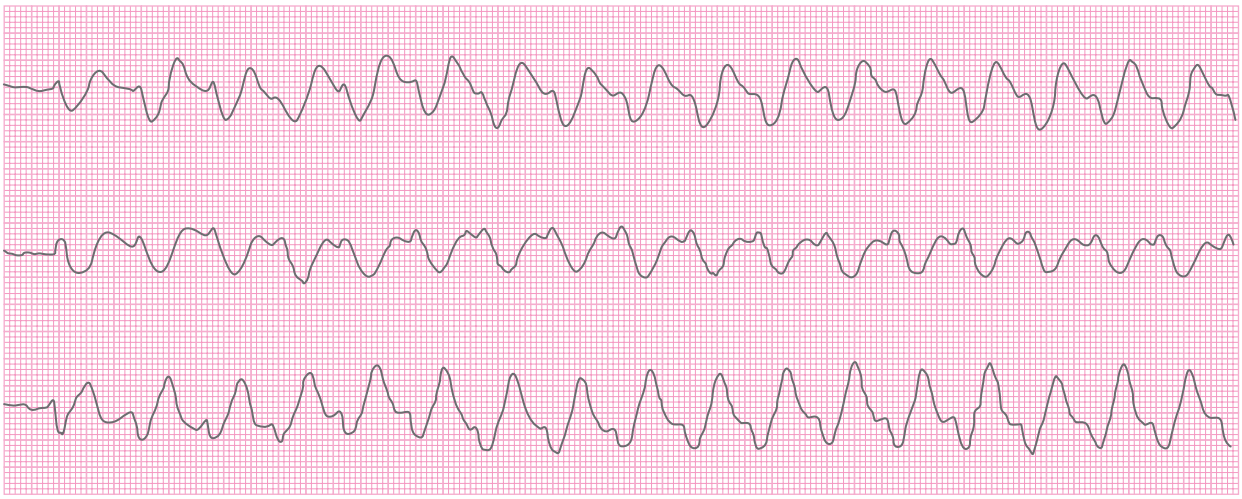

FIGURE 17-5. Monitor strip (V_1–V_3) of a 35-year-old patient in critical condition, who was hypotensive and fatigued and rapidly deteriorated into cardiac arrest. Potassium level was 9.1 mEq/L. She was on spironolactone and steroid therapy.

TABLE 17-18 ECG Changes Associated with Hyperkalemia

$[K^+]$ (mEq/L)	ECG Changes*
6.5–7.5	Prolonged PR interval, tall peaked T waves, short QT interval
7.5–8.0	Flattening of the P wave, QRS widening
10–12	QRS complex degradation into a sinusoidal pattern

*In chronic or slowly developing hyperkalemia, ECG changes may not occur until higher $[K^+]$ levels are reached.



FIGURE 17-6. The same patient as in Figure 17-5 during calcium chloride infusion. She regained a pulse and became conscious. The QRS and T wave narrowed, as compared with Figure 17-5.

TABLE 17-19 Emergency Therapy of Hyperkalemia

Therapy	Dose and Route	Onset of Action	Duration of Effect	Mechanism
Calcium chloride (10%)*	5–10 mL IV	1–3 min	30–50 min	Membrane stabilization
Calcium gluconate (10%)*	10–20 mL IV	1–3 min	30–50 min	Membrane stabilization
$NaHCO_3$†	50–150 mEq IV if accompanying metabolic acidosis	5–10 min	1–2 h	Shifts $[K^+]$ into cell
Albuterol (nebulized)	10–20 milligrams in 4 mL of normal saline, nebulized over 10 min	15–30 min	2–4 h	Upregulates cyclic adenosine monophosphate, shifts $[K^+]$ into cell
Insulin‡ and glucose#	5–10 units regular insulin IV Glucose 25 grams (50% solution) IV	30 min	4–6 h	Shifts $[K^+]$ into cell
Furosemide	40–80 milligrams IV	Varies	Varies	Renal $[K^+]$ excretion
Sodium polystyrene sulfonate	25–50 grams PO or PR	1–2 h	4–6 h	GI $[K^+]$ excretion
Hemodialysis	—	Minutes	Varies	Removes $[K^+]$

*Calcium chloride has three times the elemental calcium when compared to calcium gluconate. 10% calcium chloride = 27.2 milligrams $[Ca^{2+}]$/mL; 10% calcium gluconate = 9 milligrams $[Ca^{2+}]$/mL. Due to its short duration, calcium administration (both chloride and gluconate) can be repeated up to four times per hour.

†May be institutional variations in treatment with sodium bicarbonate; refer to Batterink et al[41] and Rossignol et al[42] for full discussion.

‡Reduce dose of insulin in patients with renal failure.

#Glucose infusion should be administered after initial bolus to prevent hypoglycemia. Glucose should not be administered in hyperglycemic patients.

Renal reabsorption is carried out with sodium and water and is unidirectional; that means that it is impaired by volume overload, osmotic diuresis, and diuretics. About 300 enzymes have their activities regulated by Mg^{2+}; it assists the production of adenosine triphosphate, participates in nucleic acid and protein synthesis, and is involved in coagulation, platelet aggregation, and neuromuscular activity, as well as in cardiac action potential.[1,2,47]

Mg^{2+} homeostasis is very complex and finely regulated by many factors, such as parathyroid hormone, calcitonin, ADH, glucose, insulin, glucagon, catecholamines, sodium, potassium, calcium, and phosphorus levels. Mg^{2+} is effective therapy in severe asthma when added to standard therapy[48] (see Chapter 69, "Acute Asthma and Status Asthmaticus").

HYPOMAGNESEMIA

Table 17-20 lists the different causes of hypomagnesemia.

IV hyperalimentation or treatment of diabetic ketoacidosis without adequate provision of Mg^{2+}, especially in a previously malnourished patient, can cause an abrupt fall in plasma Mg^{2+} levels. Acid-base imbalance affects the levels of ionized Mg^{2+}; a typical example is respiratory alkalosis that enhances neuromuscular activity (thus provoking tremors and cramps) by rapidly decreasing ionized $[Mg^{2+}]$ and $[Ca^{2+}]$ at the same time.

Among the iatrogenic causes, **proton pump inhibitors** may cause hypomagnesemia,[49] especially in association with **diuretic therapy**, probably through the inhibition of intestinal absorption. Concomitant hypomagnesemia and hypokalemia may coexist.

CLINICAL FEATURES

Due to the essential role of Mg^{2+} in enzyme regulation in multiple body systems, hypomagnesemia may result in a wide variety of neuromuscular, GI, and cardiovascular effects (**Table 17-21**).

DIAGNOSIS

Hypomagnesemia is common in acute illness; it has been found in 12% of hospitalized patients and in up to 65% of medical intensive care patients.[50] It is likely underdiagnosed because few hospitalized patients have levels drawn.[51]

The diagnosis of hypomagnesemia in the presence of normal serum calcium levels is suggested by increased neuromuscular irritability, shown by hyperreflexia tremor, tetany, or even convulsions. Chvostek sign and Trousseau sign, findings traditionally associated with hypocalcemia, may be elicited in hypomagnesemic patients. Hypomagnesemia

TABLE 17-20 Causes of Hypomagnesemia

Redistribution	IV glucose Correction of diabetic ketoacidosis IV hyperalimentation Refeeding after starvation Acute pancreatitis Postparathyroidectomy (hungry bone syndrome) Osteoblastic metastasis (hungry bone syndrome)
Extrarenal loss	Nasogastric suction (infrequent) Lactation Profuse sweating, burns, sepsis Intestinal or biliary fistula Diarrhea
Decreased intake	Alcoholism (cirrhosis) Malnutrition, poor intake Small bowel resection Malabsorption (steatorrhea)
Renal loss	Ketoacidosis Saline or osmotic diuresis Potassium depletion Phosphorus depletion Familial hypophosphatemia Tubulointerstitial renal disease
Drugs	Loop diuretics Aminoglycosides Amphotericin B Vitamin D intoxication Alcohol Cisplatin Theophylline Proton pump inhibitors Calcineurin inhibitors (cyclosporine, tacrolimus)
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion Hyperthyroidism Hyperparathyroidism Hypercalcemic states Primary or secondary aldosteronism

TABLE 17-21 Symptoms and Signs of Hypomagnesemia

Neuromuscular	Tetany
	Muscle weakness
	Chvostek and Trousseau signs
	Cerebellar (ataxia, nystagmus, vertigo)
	Confusion, obtundation, coma
	Seizures
	Apathy, depression
	Irritability
	Paresthesias
GI	Dysphagia
	Anorexia, nausea
Cardiovascular	Heart failure
	Dysrhythmias
	Hypotension
Miscellaneous	Hypokalemia
	Hypocalcemia
	Anemia

should be suspected in patients with alcoholism or cirrhosis or those requiring IV fluids or hyperalimentation for prolonged periods. Low total [Mg^{2+}] can also be secondary to hypoalbuminemia.

The ECG changes may be similar to those caused by hypokalemia and/or hypocalcemia because they may be due to Mg^{2+} deficiency altering cardiac intracellular potassium content. As for hypokalemia, low [Mg^{2+}] levels enhance digitalis toxicity, so hypomagnesemia should be searched in ECG disturbances associated with digoxin intake, especially when both digoxin and K^+ levels are normal.[52]

TREATMENT

Hypokalemia, hypocalcemia, and hypophosphatemia are often present with severe hypomagnesemia and must be monitored carefully. Hypocalcemia does not develop until [Mg^{2+}] falls below 1.2 milligrams/dL.

The following are **general principles in treatment of hypomagnesemia:**

1. Treat or stop the cause of hypomagnesemia.
2. For asymptomatic patients (including ECG changes), magnesium supplements should be administered orally, in multiple low doses during the day, to avoid diarrhea. Magnesium lactate, chloride, gluconate, and proteinate are the formulations with minimum effect on intestinal motility.
3. For severe and symptomatic hypomagnesemia, urgent IV replacement is mandatory. The formulation most commonly used is magnesium sulfate ($MgSO_4$). In life-threatening conditions (torsades de pointes, eclampsia), 1 to 4 grams or 8 to 32 mEq diluted in at least 100 mL of 5% dextrose or normal saline (0.9%) solution can be administered in 10 to 60 minutes under continuous monitoring: ECG (risk of hypokinetic arrhythmias), noninvasive blood pressure (risk of hypotension), and ventilatory pattern (risk of respiratory depression, usually preceded by areflexia, that can be monitored as an alarm sign). As a minor side effect, flushing due to vasodilatation is common.
4. Patients with chronic Mg^{2+} deficiency may require >50 mEq of oral Mg^{2+} (6 grams of $MgSO_4$ per day). In chronic alcoholics with delirium tremens and in patients with severe hypomagnesemia, up to 8 to 12 grams of $MgSO_4$ may be given IM (possible, but very painful) or IV the first day. The first 10 to 15 mEq (1.5 to 2.0 grams) of IV $MgSO_4$ can be given over 1 to 2 hours. This may be followed by up to 4 to 6 grams/d. Approximately half of the administered Mg^{2+} will be lost in the urine.
5. Spironolactone is effective in maintaining [Mg^{2+}] homeostasis as well as in reducing the incidence of arrhythmias in congestive heart failure patients.[53]

TABLE 17-22 Causes of Hypermagnesemia

Renal Failure	Acute or Chronic
Increased magnesium load	Magnesium-containing laxatives, antacids, or enemas*
	Treatment of preeclampsia/eclampsia (mothers and neonates)
	Diabetic ketoacidosis (untreated)*
	Tumor lysis
	Rhabdomyolysis*
Increased renal magnesium absorption	Hyperparathyroidism
	Familial hypocalciuric hypercalcemia
	Hypothyroidism
	Mineralocorticoid deficiency, adrenal insufficiency (Addison's disease)

*Most likely presentations relevant to the ED.

HYPERMAGNESEMIA

Hypermagnesemia is rarely encountered in emergency medicine practice, because the kidney can increase the fractional excretion of Mg^{2+} up to nearly 100%. A small elevation in serum concentration has little clinical significance. The most common cause for hypermagnesemia can be found in patients with renal insufficiency or renal failure who ingest Mg^{2+}-containing drugs.[54] Hypermagnesemia is more commonly seen in the perinatal setting secondary to the treatment of preeclampsia or eclampsia. It has been described as a serious, life-threatening consequence of Mg^{2+}-containing laxative abuse in patients with normal renal function.[55] Other causes of hypermagnesemia include lithium ingestion, volume depletion, or familial hypocalciuric hypercalcemia (**Table 17-22**).

CLINICAL FEATURES

Hypermagnesemia rarely produces symptoms. Mg^{2+} decreases the transmission of neuromuscular messages and thus acts as a CNS depressant and decreases neuromuscular activity. Signs and symptoms related to [Mg^{2+}] can be found in **Table 17-23**.

DIAGNOSIS

Serum [Mg^{2+}] is usually diagnostic. **The possibility of hypermagnesemia should be considered in patients with hyperkalemia or hypercalcemia.** Hypermagnesemia also should be suspected in patients with renal failure, particularly in those who are taking magnesium-containing antacids or laxatives.

TREATMENT

Immediate cessation of Mg^{2+} administration is required. If renal failure is not evident, dilution by IV fluids followed by furosemide (40 to 80 milligrams IV) may be indicated. Calcium directly antagonizes the cardiac effects of magnesium because it reverts the calcium channel blockade provoked by elevated [Mg^{2+}]. Severe symptomatic hypermagnesemia can be treated with 10 mL of 10% calcium chloride IV over 2 to 3 minutes. Further infusion of 40 to 60 mL during the next 24 hours can be administered. Patients with renal failure may benefit from dialysis using a decreased [Mg^{2+}] bath that lowers serum [Mg^{2+}].

TABLE 17-23 Symptoms and Signs of Hypermagnesemia

Magnesium Level (mEq/L)	Clinical Manifestations
2.0–3.0	Nausea
3.0–4.0	Somnolence
4.0–8.0	Loss of deep tendon reflexes
8.0–12.0	Respiratory depression
12.0–15.0	Hypotension, heart block, cardiac arrest

CALCIUM

PATHOPHYSIOLOGY

Calcium (Ca^{2+}) is the most abundant mineral in the body. The total body [Ca^{2+}] is 15 grams/kg of body weight, or about 1 kg in an average-sized adult. Ca^{2+} is 99% bound in bone as phosphate and carbonate (mineral apatite), with the remainder in the teeth, soft tissues, plasma, and cells. The normal daily intake of Ca^{2+} is 800 to 3000 milligrams, one third of which is absorbed primarily in the small bowel by active (vitamin D–dependent) and passive (concentration-dependent) absorption. Excretion of Ca^{2+} is primarily via the stool.

The cell content of Ca^{2+} is 10,000 times lower than the plasma content, and this gradient is maintained by Ca-ATPase, Ca^{2+}-specific channels, and Na/Ca exchangers.

Plasma [Ca^{2+}] is between 8.5 and 10.5 milligrams/dL (4.3 to 5.3 mEq/L or 2.2 to 2.7 mmol/L) and is present in three different forms: ionized calcium, 50% of total (4.5 to 5.6 milligrams/dL; 1.1 to 1.4 mmol/L), which is the only active fraction; protein-bound calcium, 40% of total, which is inactive and not filtered by glomerulus; and complexed calcium, 10% of total, which is bound to anions such as phosphate, carbonate, and citrate.

It is necessary to be aware of **standard units** used by different laboratories to express Ca^{2+} value: **1 mEq/L = 2 milligrams/dL = 0.5 mmol/L**. The ionized fraction is the only biologically active fraction; a decrease in albumin decreases the total [Ca^{2+}] but does not change the ionized fraction. On average, 0.8 milligram of Ca^{2+} binds to 1 gram of protein. Therefore, total serum [Ca^{2+}] is equal to ionized [Ca^{2+}] plus the product of 0.8 and total protein. Alkalosis produces a decrease in ionized fraction with no change in the total serum [Ca^{2+}]. Each 0.1 rise in pH lowers ionized [Ca^{2+}] by about 3% to 8%. The opposite effect is produced by acidosis.

The role of Ca^{2+} is crucial for muscle and cardiac contraction, nerve conduction, cell growth, enzyme activation, and coagulation, and consequently, any hypo- or hypercalcemia leads to severe dysfunctions.

HOMEOSTASIS OF CALCIUM

The organs involved in the homeostasis of calcium are bones, kidneys, and the intestines, whereas the major determinants are three hormones and one receptor.[1,2,56,57]

1. **1,25-Dihydroxycholecalciferol (active vitamin D_3)**[57] is formed in the distal tubule. It promotes Ca^{2+} absorption from intestine, but this activity is modulated by physiologic conditions that may enhance it (pregnancy and growth) or reduce it (oxalates and phytates in food and aging).
2. **Parathyroid hormone (PTH)** is secreted by parathyroid glands when [Ca^{2+}] is low and is regulated by Ca^{2+}-sensing receptor, vitamin D_3, and Mg^{2+} (hypomagnesemia inhibits PTH secretion). PTH stimulates bone demineralization by activating osteoclasts and by increasing the synthesis of vitamin D_3 and increasing Ca^{2+} reabsorption from kidney.[58]
3. **Calcitonin** is a peptide secreted by C-cells of the thyroid gland when [Ca^{2+}] is high. It inhibits the activity of osteoclasts and thus bone resorption.
4. **Ca^{2+}-sensing receptor**[58,59] is mainly present on plasma membranes of parathyroids, kidney, bones, and thyroid. It becomes active in case of hypercalcemia and inhibits the production of PTH. In the kidney, activated Ca^{2+}-sensing receptor provokes hypercalciuria and polyuria, preventing nephrocalcinosis. The activation of the receptor also stimulates the secretion of calcitonin and inhibits osteoclast formation.

Urinary secretion of Ca^{2+} is variable and influenced by many different factors. Hypercalcemia, metabolic acidosis, hypervolemia, and loop diuretics increase urinary secretion of [Ca^{2+}]. PTH, vitamin D_3, metabolic alkalosis, hypovolemia, and the chronic use of thiazides reduce secretion.

TABLE 17-24 Selected Causes of Hypocalcemia

Cause	Mechanism(s)
Decreased calcium absorption	
Vitamin D deficiency	
Decreased oral intake	Malnutrition
Decreased intestinal absorption	Intestinal bypass, gastrectomy
Decreased production of $25(OH)D_3$	Liver failure
Decreased synthesis of $1,25(OH2)D_3$	Renal failure, hyperphosphatemia
Malabsorption syndromes	Malabsorption
Increased calcium excretion/reduced bone resorption	
Alcoholism	Hypomagnesemia causing inhibition of PTH secretion, PTH resistance to bone resorption
Hypoparathyroidism	Genetic, autoimmune, surgical, tumoral
Pseudohypoparathyroidism	Resistance to PTH action
Hypomagnesemia	Inhibition of PTH secretion, PTH resistance to bone resorption
Drugs (Table 17-25)	
Malignancy	Pseudohypocalcemia, hyperphosphatemia, hypomagnesemia, vitamin D or PTH deficiency, osteoblastic metastasis
Sepsis	
Acute pancreatitis	Fatty acids combine with [Ca^{2+}] to form insoluble Ca^{2+} soaps and lead to a reduction of serum [Ca^{2+}]
Massive transfusions	
Rhabdomyolysis	

Abbreviations: $25(OH)D_3$ = 25-hydroxyvitamin D_3; $1,25(OH2)D_3$ = 1,25-dihydroxyvitamin D_3; PTH = parathyroid hormone.

HYPOCALCEMIA

Hypocalcemia is defined by an ionized [Ca^{2+}] level <2.0 mEq/L (<4 milligrams/dL or <1.1 mmol/L). Homeostasis is regulated by the maintenance of the gradient between cells and ECF, is controlled by the previously described mechanism, and is mediated intracellularly by phosphates, cyclic adenosine monophosphate, and ion pumps.[56] Any process that interferes with cell metabolism, such as shock or sepsis, will tend to reduce ionized [Ca^{2+}] by allowing increased net movement of Ca^{2+} across the cell membrane into the cytoplasm of the poorly functioning cells.

Table 17-24[59-61] lists the most common causes of hypocalcemia and the primary mechanism of each. **Table 17-25** lists the principal drugs that cause hypocalcemia.[2]

CLINICAL FEATURES

The severity of signs and symptoms depends greatly on the rapidity of the decrease in [Ca^{2+}]. **Table 17-26** lists the different signs and symptoms that can be seen in the course of hypocalcemia.[1,2,62]

TABLE 17-25 Drugs That Can Cause Hypocalcemia

- Phosphates (e.g., enemas, laxatives)
- Phenytoin, phenobarbital
- Gentamicin, tobramycin, dactinomycin, foscarnet
- Cisplatin
- Citrate
- Loop diuretics
- Glucocorticoids
- Magnesium sulfate
- Bisphosphonates, calcitonin, denosumab
- Cinacalcet

TABLE 17-26 Symptoms and Signs of Hypocalcemia

Muscular	Weakness, fatigue
	Spasms, cramps
Neurologic	Seizures
	Tetany
	Chvostek sign, Trousseau sign
	Circumoral and digital paresthesias
	Impaired memory, confusion
	Hallucinations, dementia
	Extrapyramidal disorders
Dermatologic	Hyperpigmentation
	Coarse, brittle hair
	Dry, scaly skin
Cardiovascular	Heart failure
	Ventricular arrhythmias, QT_c prolongation leading to torsades de pointes
	Vasoconstriction
Skeletal	Osteodystrophy
	Rickets
	Osteomalacia
Miscellaneous	Dental hypoplasia
	Cataracts
	Decreased insulin secretion

Neuromuscular and cardiovascular signs and symptoms predominate. As serum [Ca^{2+}] falls, neuronal membranes become increasingly more permeable to sodium, thereby enhancing excitation and causing smooth and skeletal muscle contractions. Irritability, confusion, dementia, extrapyramidal symptoms, seizures, and hallucination may occur.

Decreased ionized [Ca^{2+}] reduces the strength of myocardial contraction primarily by inhibiting relaxation. The most characteristic ECG finding in hypocalcemia is a prolonged QT_c interval.[28,29] The T wave may be of normal width, and it is the ST segment that is actually prolonged. In very severe hypocalcemia, T waves may present abnormalities that may mimic ischemia (**Figure 17-7**). This finding is usually seen with total serum calcium levels <6.0 milligrams/dL.

A positive Chvostek sign (twitch at the corner of the mouth when the examiner taps over the facial nerve just in front of the ear) and Trousseau sign (carpal spasm produced when the examiner applies a blood pressure cuff to the upper arm and maintains a pressure above systolic for 2 to 3 minutes; the fingers are spastically extended at the interphalangeal joints and flexed at the metacarpophalangeal joints with wrist flexion and forearm pronation) are classically associated with hypocalcemia (but also may occur in respiratory alkalosis, which shifts ionized Ca^{2+} to the protein-bound form). These diagnostic signs have not been subjected to rigorous assessment, and there is no agreement on sensitivity or specificity.[63,64]

DIAGNOSIS

In addition to total serum [Ca^{2+}], a full electrolyte panel, renal function tests, ionized [Ca^{2+}], and magnesium levels aid in the diagnosis. An albumin level should be obtained because hypoalbuminemia may falsify the diagnosis.

In cases where acid-base abnormalities are suspected, a blood gas analysis to evaluate pH should be obtained. Also consider a phosphate level. Blood samples for PTH and vitamin D_3 levels should be drawn (but results are not required) before starting therapy.

TREATMENT

Treatment of hypocalcemia is tailored to the individual patient and directed toward the underlying cause. If a patient is asymptomatic or if the hypocalcemia is not severe or prolonged for >10 to 14 days, oral Ca^{2+} therapy with or without vitamin D may be sufficient. Ca^{2+} lactate,

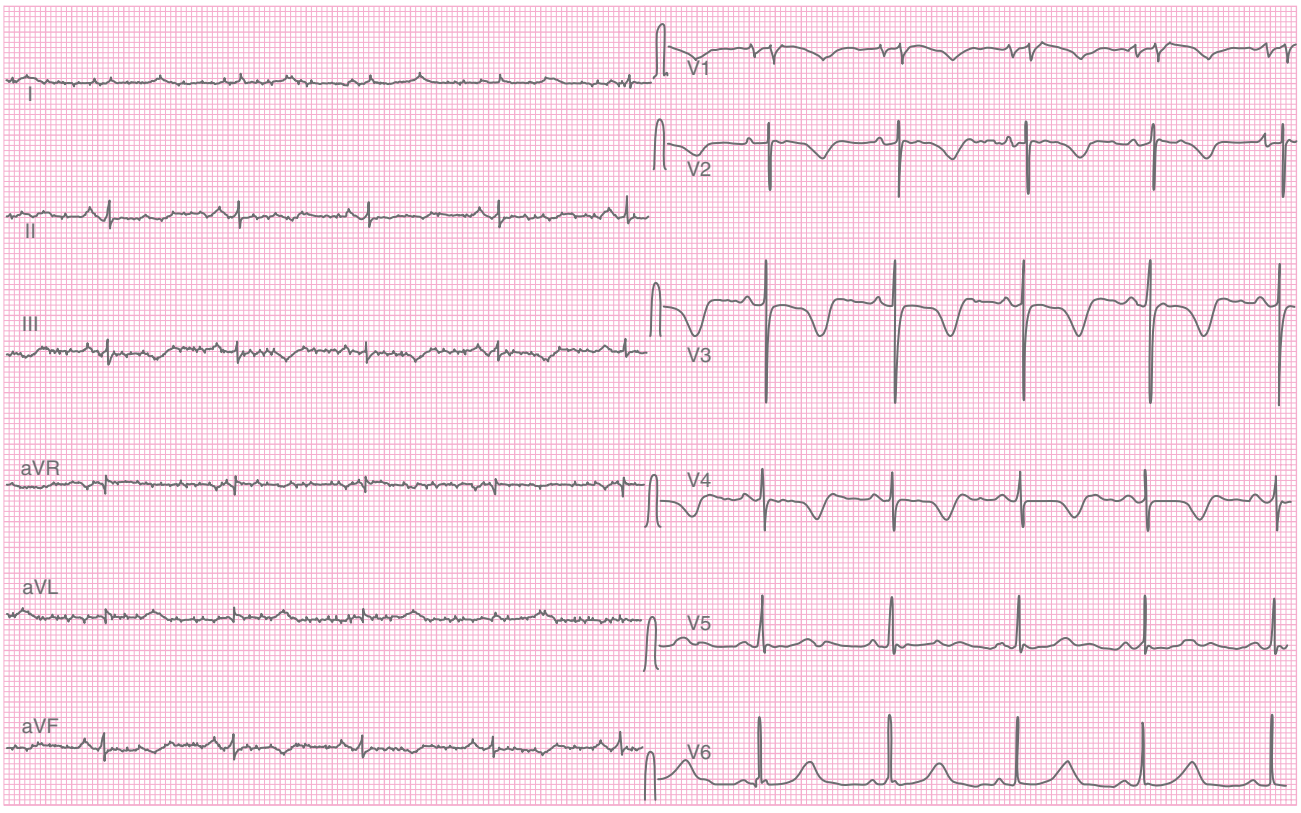

FIGURE 17-7. ECG of a patient with severe hypocalcemia (Ca^{2+} 4.5 milligrams/dL) who was complaining of chest and abdominal pain, pain in the legs, and Trousseau sign. A very long QT_c and T-wave abnormalities mimicking ischemia are evident.

ascorbate, carbonate, and gluconate are available in oral preparations and contain variable percentages of elemental Ca^{2+}; 1 mEq of elemental Ca^{2+} is equal to 20 milligrams of elemental Ca^{2+}. **Regimens can be 500 to 3000 milligrams of elemental Ca^{2+} by mouth daily, in one dose or up to three divided doses. The dose must be individualized for each patient, according to the cause and severity of hypocalcemia.**

IV Ca^{2+} is recommended only in cases of symptomatic or severe hypocalcemia[2] (ionized [Ca^{2+}] <1.9 mEq/L or <0.95 mmol/L), because IV Ca^{2+} administration causes vasoconstriction and possible ischemia, especially in patients with low cardiac output who already have significant peripheral vasoconstriction. **IV Ca^{2+} gluconate is preferred over IV calcium chloride ($CaCl_2$)** in nonemergency settings due to the dangers of extravasation with **$CaCl_2$** (calcinosis cutis). **With severe acute hypocalcemia, 10 mL of 10% $CaCl_2$ (or 10 to 30 mL of 10% Ca^{2+} gluconate) may be given IV over 10 to 20 minutes and repeated every 60 minutes until symptoms resolve or followed by a continuous IV infusion of 10% $CaCl_2$ at 0.02 to 0.08 mL/kg/h (1.4 to 5.6 mL/h in a 70-kg patient).**[65] The serum [Ca^{2+}] should then be rechecked before continuing parenteral Ca^{2+}. **IV Ca^{2+} should be used with caution in patients taking digitalis because hypercalcemia can potentiate digitalis toxicity.**[66] Symptomatic patients after thyroid or parathyroid surgery are often treated with parenteral Ca^{2+}.

During massive transfusions, if the blood is being given faster than 1 unit every 5 minutes, 10 mL of 10% $CaCl_2$ can be given after every 4 to 6 units of blood if a patient is in shock or has heart failure despite adequate volume replacement therapy.

Hypocalcemia is difficult to correct if hypomagnesemia is also present because of reduction of PTH and Ca^{2+} releases from bone. Therefore, magnesium should be replaced before, or in conjunction with, Ca^{2+} replacement.[56,57]

HYPERCALCEMIA

Hypercalcemia is relatively common. It is defined as a total [Ca^{2+}] >10.5 milligrams/dL or an ionized [Ca^{2+}] level >2.7 mEq/L.

Because Ca^{2+} is necessary for cellular functions, every organ and system is affected by hypercalcemia, and clinical manifestations are dependent on the level of [Ca2+]: mild hypercalcemia, 10.5 to 11.9 milligrams/dL; moderate, 12 to 13.9 milligrams/dL; severe, >14 milligrams/dL.[2,67]

Neuromuscular changes include decreased sensitivity, responsiveness, and strength of muscular contraction and nerve conduction. The conduction of the heart is slowed and automaticity is decreased with a shortening of the refractory period. Increased sensitivity to cardiac glycosides may be seen.

Loss of concentrating ability is the most frequent renal effect of hypercalcemia. This is a reversible tubular defect, which results in polyuria and volume depletion even in the presence of thirst. Potassium wasting resulting in hypokalemia may occur in up to one third of patients. Nephrocalcinosis and nephrolithiasis may result from hypercalcemia and can be exacerbated by volume depletion. As the hypercalcemia persists, increasing microscopic Ca^{2+} deposits in the kidney can lead to progressive renal insufficiency.

More than 90% of occurrences are associated with hyperparathyroidism[2,68] or malignancy, the latter being the most likely presentation in the ED. A list of potential causes of hypercalcemia and the relative mechanism of onset are provided in **Table 17-27**.

CLINICAL FEATURES

Hypercalcemic patients with plasma total [Ca^{2+}] below 12.0 milligrams/dL are usually asymptomatic, but higher levels can cause a wide variety of symptoms (**Table 17-28**).

Patients with total [Ca^{2+}] >14 to 16 milligrams/dL are usually very weak, lethargic, and confused. Polyuria and polydipsia are due to impaired renal tubular reabsorption of water and result in volume depletion. Total [Ca^{2+}] >15.0 milligrams/dL may cause somnolence, stupor, and even coma. A mnemonic sometimes used for the signs and symptoms of hypercalcemia is *stones* (renal calculi), *bones* (osteolysis), *moans* (psychiatric disorders), and *groans* (peptic ulcer disease, pancreatitis, and constipation).

TABLE 17-27 Causes of Hypercalcemia

Cause	Mechanism
Hypercalcemia due to increased bone Ca^{2+} resorption	
Primary hyperparathyroidism	↑ PTH
Malignancy	Osteolysis, PTH-related protein (PTHrP) production
Pseudohyperparathyroidism	PTH from non–parathyroid tissue source
Renal failure	Secondary and tertiary hyper-PTH due to chronic hypocalcemia
Addison's disease	↑ Albumin, bone resorption
Hyperthyroidism	Increased bone resorption
Immobilization	Osteoclast activation
Hypercalcemia due to decreased urinary Ca^{2+} excretion	
Familial hypercalcemic hypocalciuria	Mutation of CaSR
Thiazides	Increased kidney Ca^{2+} reabsorption in proximal tubule
Hypercalcemia due to increased GI Ca^{2+} absorption	
Granulomatous diseases (sarcoidosis, tuberculosis, coccidioidomycosis, histoplasmosis)	1α-Hydroxylase activity
Milk (calcium)-alkali syndrome	↑Ca^{2+} intake (calcium carbonate) and absorption
Vitamin D intoxication	Increased calcium absorption and bone resorption

Abbreviations: CaSR = Ca^{2+}-sensing receptor; PTH = parathyroid hormone.

Hypercalcemia should be investigated in patients with extensive metastatic bone disease, particularly if the primary site involves the breast, lungs, or kidneys, and in individuals with combinations of clinical problems, such as renal calculi, pancreatitis, or ulcer disease.

On ECG, hypercalcemia may be associated with depressed ST segments, widened T waves, and shortened ST segments and QT intervals. In severe hypercalcemia, ST-segment elevation mimicking myocardial infarction may be seen.[69] Bradyarrhythmias may occur, with bundle branch patterns

TABLE 17-28 Signs and Symptoms of Hypercalcemia

General	Cardiovascular
Malaise, weakness	Hypertension
Polydipsia, dehydration	Dysrhythmias
Neurologic	Vascular calcifications
Confusion	ECG abnormalities
Apathy, depression, stupor	QT shortening
Decreased memory	Coving of ST-T wave
Irritability	Widening of T wave
Hallucinations	Digitalis sensitivity
Headache	GI
Ataxia	Anorexia, weight loss
Hyporeflexia, hypotonia	Nausea, vomiting
Mental retardation (infants)	Constipation
Metastatic calcification	Abdominal pain
Band keratopathy	Peptic ulcer disease
Conjunctivitis	Pancreatitis
Pruritus	Urologic
Skeletal	Polyuria, nocturia
Fractures	Renal insufficiency
Bone pain	Nephrolithiasis
Deformities	

that may progress to second-degree block or complete heart block. Levels of [Ca^{2+}] above 20 milligrams/dL may cause cardiac arrest.

DIAGNOSIS

True hypercalcemia must be confirmed by measuring ionized [Ca^{2+}][70]; then electrolytes, CBC, phosphate, magnesium, BUN, creatinine, and alkaline phosphatase will help determine the cause. The acuity of hypercalcemia can be determined or suggested using the medical history together with an ECG, chest radiograph, and laboratory investigation. Normally, acute, severe hypercalcemia is not caused by hyperparathyroidism. Malignancies, in particular lymphoma, leukemia, and metastatic bone cancer, are common causes of severe, acute hypercalcemia. A corrected Ca^{2+} level should be calculated if albumin is not in the normal range: corrected Ca^{2+} (milligrams/dL) = measured total Ca^{2+} (milligrams/dL) + 0.8 (4.0 – serum albumin [grams/dL]), where 4.0 represents the average albumin level in grams/dL. If the reference lab reports values in mmol/L, use the following formula: corrected Ca^{2+} (mmol/L) = measured total Ca^{2+} (mmol/L) + 0.02 (40 – serum albumin [grams/L]), where 40 represents the average albumin level in grams/L. If the values listed in the corrected Ca^{2+} formulas for normal albumin do not match your institution's lab, adjust this value accordingly.

TREATMENT

Symptomatic patients or asymptomatic patients with [Ca^{2+}] levels >14 milligrams/dL should receive treatment starting with volume repletion. Administer **0.9% normal saline at 500 to 1000 mL/h for 2 to 4 hours** as tolerated by the patient. In general, 3 to 4 L should be given over the first 24 hours, then 2 to 3 L per 24 hours until a urine output of 2 L/d is achieved.[71] Furosemide is recommended to promote a diuresis of 150 to 200 mL/h, which increases the calciuric effect,[1,71] with an initial dose of 20 to 40 milligrams. Caution should be used for possible paradoxical hypercalcemia due to bone resorption, and for hypokalemia and/or hypomagnesemia occurrence, when furosemide is being used.[72]

Decreased mobilization of [Ca^{2+}] from bone through reduction of osteoclastic activity can be obtained with **corticosteroids,** such as prednisone, 1 to 2 milligrams/kg PO, or hydrocortisone, 200 to 300 milligrams IV initial dose, in Addison's disease or in steroid-responsive malignancies.

In very severe cases, it will be necessary to receive **hemodialysis** to quickly remove Ca^{2+} from blood.[67,72] In the ED, initiating bisphosphonates or calcitonin is not mandatory. However, for hypercalcemia associated with malignancy, IV bisphosphonates are now considered first-line therapy[71]; examples are pamidronate or zoledronate (zoledronic acid). Zoledronic acid is recommended; for a corrected [Ca^{2+}] level of 12 milligrams/dL or higher, 4 milligrams as a single dose can be given IV over 15 minutes. Calcitonin works more rapidly than bisphosphonates and can be given at a dose of 4 units/kg SC or IM.

PHOSPHORUS

As phosphorus is a highly reactive mineral, it is found as phosphate (PO_4^{3-}) existing mainly as hydroxyapatite (85%) or as an intracellular constituent (10% to 15%). Only about 1% is in the ECF, so serum measurements may not accurately reflect total body stores. It is involved in oxidative phosphorylation and mitochondrial respiration, and it is the essential component of adenosine triphosphate, a requirement for cellular energy metabolism.[2,73] Serum [PO_4^{3-}] decreases with age from a range of 4.0 to 7.0 milligrams/dL in newborns to 2.5 to 5.0 milligrams/dL in adults. The total body phosphorus store in a normal man is approximately 700 grams (10 to 15 grams/kg). Metabolism of phosphorus is strictly linked to that of calcium. The only active status of PO_4^{3-} is in biological fluids. Homeostasis of PO_4^{3-} is mainly regulated by gut absorption and urine excretion. Gut absorption is localized in two different sites. The first is the duodenum, which is inhibited by calcitonin and is stimulated by vitamin D_3 and low phosphate intake. The second is the jejunum and ileum, where absorption is passive and dependent on PO_4^{3-} concentration in the gut.

Excretion is predominantly in the urine by the glomerulus, with the majority reabsorbed in the proximal tubules. Excretion is regulated by PTH, which lowers serum phosphate by increasing renal excretion, and by a hormone secreted by osteoclasts and osteoblasts, the fibroblast growth factor-23, which increases PO_4^{3-} excretion and inhibits intestinal absorption. Proximal tubule absorption increases when serum [PO_4^{3-}] levels drop and with hypoparathyroidism, volume depletion, hypocalcemia, or the presence of growth hormone. Excretion increases in the presence of volume expansion, hypercalcemia, acidosis, hypomagnesemia, hypokalemia, glucocorticoids, diuretics, calcitonin, or PTH.[59]

HYPOPHOSPHATEMIA

Hypophosphatemia is defined as serum [PO_4^{3-}] <2.5 milligrams/dL, but severe symptoms may not occur until the [PO_4^{3-}] level drops to <1 milligram/dL. Because phosphorus is abundant in many foods and readily absorbed, hypophosphatemia is relatively unusual. Mechanisms include a shift of phosphate into cells, increased renal excretion, and decreased GI absorption (**Table 17-29**). Only when depletion is present will clinical manifestations occur and require treatment. It is important to understand pseudohypophosphatemia, which occurs when a patient is treated with mannitol, which binds to molybdate in the serum, causing an artificially low value when [PO_4^{3-}] is measured by the laboratory.

Severe hypophosphatemia can occur in patients with prolonged use of antacids, such as aluminum hydroxide, magnesium hydroxide, or calcium carbonate. Several other drugs may cause hypophosphatemia with different mechanisms (**Table 17-30**).

Critically ill patients are particularly at risk for hypophosphatemia, which occurs in up to 30% of those admitted to the intensive care unit with sepsis, trauma, and pulmonary diseases. It has also been associated with cardiac surgery.[74,75] The mechanism is glucose infusions, starvation, refeeding, shock, acidosis, alkalosis, diuretics, and catecholamine treatment.

CLINICAL FEATURES

Symptoms are due to the depletion of adenosine triphosphate and the reduction of erythrocyte 2,3-diphosphoglycerate. The final outcome will

TABLE 17-29 Causes of Hypophosphatemia

Shift from ECF to ICF without depletion of PO_4^{3-}	Glucose Insulin Catecholamines Respiratory alkalosis
Shift from ECF to ICF with depletion of PO_4^{3-}	Hyperalimentation Refeeding syndrome
Decreased intestinal absorption	Low intake Malabsorption Chronic use of calcium acetate or bicarbonate, aluminum hydroxide Vitamin D deficiency
Increased renal loss	Hyperparathyroidism Increased fibroblast growth factor-23 (FGF-23) Genetic hypophosphatemia mutations Tubular acidosis Fanconi's syndrome Hypokalemia Hypomagnesemia Polyuria Acidosis
Miscellaneous causes	Alcoholism (poor intake, vitamin D deficiency) Diabetic ketoacidosis (osmotic diuresis) Toxic shock syndrome
Drugs	See Table 17-30

Abbreviations: ECF = extracellular fluid; ICF = intracellular fluid.

TABLE 17-30 Drugs That Cause Hypophosphatemia and Underlying Mechanism

Osmotic diuretics, loop diuretics, carbonic anhydrase inhibitor	↓ Renal reabsorption and phosphaturia
Acyclovir	Inhibition of Na/Pi-IIa cotransporter
Acetaminophen	↓ Renal reabsorption and phosphaturia
Tyrosine kinase inhibitors	Ca^{2+} and phosphate reabsorption and secondary hyperparathyroidism
Bisphosphonates	Inhibits bone resorption
Aminoglycosides, tetracyclines, valproic acid	Induction of Fanconi's syndrome
Cyclophosphamide, cisplatin	↑ Phosphaturia
Corticosteroids	↓ Intestinal phosphate absorption and phosphaturia

be cellular dysfunction and hypoxia. The main symptoms of hypophosphatemia are listed in **Table 17-31**.[76]

TREATMENT

When symptomatic, hypophosphatemia can be corrected both PO and IV. Possible adverse effects of IV therapy include hypocalcemia with consequent myocardial depression, arrhythmias (especially ventricular fibrillation),[75] acute kidney injury, and calcifications. The suggested doses for PO_4^{3-} replacement are listed in **Table 17-32**, and the commonly used preparations are described in **Table 17-33**.[2,76]

In asymptomatic or mildly symptomatic patients, hypophosphatemia may be treated orally with skim milk ([PO_4^{3-}] 1 gram/L) or oral preparations such as Neutra-Phos®, one to two tabs PO four times daily, or K-Phos®, one tab PO four times daily, which contain 150 to 250 milligrams per tablet (PO_4^{3-}: 1 mmol/L = 3.1 milligrams/dL). A treatment regimen of 50 mmol/d for 7 to 10 days is sufficient to replace deficits, but in severe hypophosphatemia, higher doses may be necessary.

HYPERPHOSPHATEMIA

Hyperphosphatemia is defined as serum [PO_4^{3-}] >4.5 milligrams/dL and is rarely encountered in emergency medicine practice. The causes can be divided into three groups according to mechanism: decrease in renal excretion of PO_4^{3-}, addition or movement of PO_4^{3-} from ICF to ECF, and drugs (**Table 17-34**).[73] In clinical practice, the most important cause of hyperphosphatemia is acute or chronic renal failure.[76]

Hyperphosphatemia worsens renal tubulointerstitial disease, renal osteodystrophies, and cardiovascular disease. The acute symptoms are due to renal failure, hypocalcemia, and hypomagnesemia.

It is important to lower phosphorus intake with a careful protein-containing diet and to avoid excessive vitamin D intake to limit intestinal absorption. In very high PO_4^{3-} levels, it is necessary to remove it with hemodialysis. Phosphate binders like calcium carbonate or calcium acetate bind intestinal phosphate, decreasing its absorption.[77]

TABLE 17-31 Symptoms and Signs of Hypophosphatemia

Hematologic
- Reduced survival and function of platelets and red and white blood cells
- Impaired macrophage function

Neuromuscular
- Weakness, tremors, circumoral and fingertip paresthesias, decreased deep tendon reflexes, decreased mental status, anorexia

Cardiac
- Impaired myocardial function

Metabolic
- Insulin resistance

TABLE 17-32 IV PO_4^{3-} Replacement Dose (6–72 h)

Serum [PO_4^{3-}] (milligrams/dL)	Dose (mmol/kg)	Duration (h)
<1	0.6	6–72
1–1.7	0.3–0.4	6–72
1.8–2.2	0.15–0.2	6–72

TABLE 17-33 PO_4^{3-} Preparations

Preparation	PO_4^{3-} Content	Na^+ Content	K^+ Content
Neutral Na/K PO_4 (PO)	8 mmol	7.1 mEq	7.1 mEq
Sodium PO_4^{3-} (IV)	3 mmol/mL	4 mEq/mL	0
Potassium PO_4^{3-} (IV)	3 mmol/mL	0	4.4 mEq/mL

TABLE 17-34 Causes of Hyperphosphatemia

Decrease in renal excretion of PO_4^{3-}	Acute and chronic renal failure* Hypoparathyroidism, pseudohypoparathyroidism
Shift of PO_4^{3-} from ICF to ECF	Hemolysis* Rhabdomyolysis* Tumor lysis syndrome Respiratory acidosis Diabetic ketoacidosis
Addition of PO_4^{3-} exogenous to the ECF	PO or IV treatment of hypophosphatemia Phosphate-containing laxatives, antacids*
Drugs	Excess of vitamin D Growth hormone Bisphosphonates

Abbreviations: ECF = extracellular fluid; ICF = intracellular fluid.

*Most likely presentation relevant to the ED.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 18

Cardiac Rhythm Disturbances

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GENERAL CONSIDERATIONS

INITIAL APPROACH TO THE STABLE PATIENT

The focused evaluation of the patient includes determining the presenting complaint(s), obtaining the medical history, identifying medication use, performing a physical examination, initiating continuous cardiac rhythm monitoring, reviewing the 12-lead ECG, and analyzing the cardiac rhythm on the rhythm monitor, a printed strip, or the ECG.

Presenting symptoms may include palpitations, lightheadedness, fatigue, or weakness. Ischemic symptoms, such as chest pain, nausea, dyspnea, or lightheadedness, may be due to dysrhythmia-induced ischemia.

The medication history includes prescribed medications, herbals, recreational drugs, and caffeine-containing beverages. Especially

TABLE 18-1 Instability Indicators in the Patient With Cardiac Dysrhythmias

- Hypotension: e.g., systolic blood pressure <90 mm Hg (<12 kPa)
- Systemic hypoperfusion
  - Altered mentation
  - Chest pain (due to coronary ischemia)
  - Dyspnea (due to pulmonary edema)
- Extremely rapid ventricular rate: e.g., rate over 220–240 beats/min in adult

note recently started new medications or increased medication doses. Symptoms of hyperthyroidism should be sought. Patients with a family history of sudden death or syncope and those with organic heart disease have a higher risk of cardiac dysrhythmias and complications. Panic or anxiety is a diagnosis of exclusion in tachycardic ED patients.

INITIAL APPROACH TO THE UNSTABLE PATIENT

An unstable patient requires rapid assessment and treatment to prevent cardiovascular collapse. Instability as related to cardiac rhythm disturbances means that the dysrhythmia is (1) impairing perfusion and threatening vital organ function or (2) has the potential to deteriorate into cardiac arrest (**Table 18-1**).[1] Establish an IV line, initiate cardiac rhythm monitoring, obtain an ECG, and be prepared for drug or electrical therapy.

Dysrhythmia-induced chest pain results from coronary hypoperfusion, and dyspnea results from pulmonary edema, usually with objective evidence: ST-segment abnormalities, rales on examination, or low oxygen saturation. As the ventricular rate exceeds 220 beats/min, severe systemic hypoperfusion often results, increasing the opportunity for malignant ventricular dysrhythmias.

GENERAL APPROACH TO BRADYDYSRHYTHMIAS

Bradydysrhythmia describes rhythms with a ventricular rate slower than 60 beats/min in the adults and slower than age-appropriate heart rates in children. Bradydysrhythmias can be broadly categorized as bradycardias (atria and ventricles beat at the same slow rate) and atrioventricular (AV) blocks (ventricles beat slower than the atria).[1] The bradycardias include sinus bradycardia, junctional rhythm, idioventricular rhythm, atrial fibrillation/flutter with a slow ventricular response, and hyperkalemia-related sinoventricular rhythm. Bradydysrhythmias due to AV blocks include second-degree (usually type II) and third-degree AV block.

The most common bradycardia is sinus bradycardia, followed by junctional rhythm and, less commonly, idioventricular rhythm. These rhythms are found in both stable and unstable patients. Atrial fibrillation or flutter with slow ventricular response are uncommon; these rhythms are usually seen in patients experiencing significant conduction system disease, such as sick sinus syndrome, or suffering from excessive AV node blocking medications. If the patient is unstable, the vast majority of AV blocks are third-degree heart block followed much less frequently by second-degree AV block. If the patient is stable, second-degree type I AV block is most frequently seen, third-degree AV block is less common, and second-degree type II AV block is quite rare.[2-4]

Bradydysrhythmias result from conditions that affect the automaticity and refractoriness of cardiac cells as well as the conduction of impulses within the cardiac electrical system.[1,4] About 80% of bradydysrhythmias are caused by factors external to the cardiac electrical system including acute coronary syndrome, drug effects or overdose, and hypoxia with cardiac hypoperfusion.[2,3]

Emergent treatment of bradydysrhythmia is not required unless (1) the heart rate is slower than 50 to 60 beats/min accompanied by hypotension or hypoperfusion and/or (2) the bradydysrhythmia is due to structural disease of the infranodal conduction system. This first group requires resuscitative treatment while evaluating the cause. The second group of patients does not require immediate treatment but should be closely monitored, with cardiac pacing readily available while arranging definitive care. Of course, patients with "low normal" heart rates (i.e., pulse of approximately 65 beats/min in an adult) who are simultaneously in shock are experiencing a relative bradycardia—the relative nature of the bradycardia is noted in that the appropriate or anticipated heart rate in this situation is rapid, with a markedly accelerated sinus rhythm or sinus tachycardia; selected patients in this setting may require rhythm-focused therapy as well.

Medications used to increase heart rate in symptomatic bradycardias include atropine, β-adrenergic agonists, and glucagon (**Table 18-2**; see Chapter 19, "Pharmacology of Antiarrhythmics and Antihypertensives").[1,4] Atropine enhances the automaticity of the sinoatrial (SA) node and potentiates conduction through the AV node by direct vagolytic activity. Atropine is usually effective for sinus bradycardia and junctional rhythms but is not useful (nor particularly harmful) in idioventricular rhythms and second-degree type II and third-degree AV block.[2,3] β-Adrenergic agents stimulate both chronotropic and inotropic cardiac activity, as well as enhancing electrical conduction within the AV node and infranodal system, thus their potential to produce ischemia and ectopy. Glucagon stimulates inotropic and chronotropic cardiac activity independent of the β-adrenergic receptors. Glucagon is primarily used for bradycardias due to cardiotoxicity from β-blocker or calcium channel–blocker overdose. Effectiveness of drug treatment for bradycardia varies, and in general, these agents are best used as a temporary bridge to cardiac pacing unless a sustained, near-complete to complete response occurs in response to these medications and the cause of the bradycardia is temporary.

Transcutaneous pacing is the most appropriate pacing method for the acutely symptomatic patient (see Chapter 33, "Cardiac Pacing and Implanted Defibrillation"). Transvenous pacing requires physician expertise, time, and specialized equipment for insertion and proper placement. With any form of cardiac pacing, (1) establish electrical capture (pacer spike is associated with appropriate ECG response, such as QRS complex); (2) once electrical capture occurs, determine mechanical capture by demonstrating a palpable pulse occurring in association with the paced beat as well as a sustained improvement in perfusion; (3) adjust the paced rate (the rate at which the pacer spikes are delivered by the machine); and (4) establish the energy required to achieve sustained electrical pacing (capture). Disease-specific therapies can also be effective in reversing a toxin-induced bradycardia (e.g., treatment of hyperkalemia or toxicity from calcium channel blockers, β-blockers, or digitalis).

GENERAL APPROACH TO TACHYDYSRHYTHMIAS

Tachycardia describes rhythms with a ventricular rate greater than 100 beats/min in an adult, with age-appropriate values in children. Tachycardias are categorized as supraventricular or ventricular (**Figure 18-1**). Supraventricular tachycardias originate from a focus within or above the AV node and most often present with a narrow QRS complex; thus, they are termed *narrow-complex tachycardias*. Ventricular tachycardias, resulting from a focus below the AV node in the ventricular myocardium, usually demonstrate a widened QRS complex and are referred to as *wide-complex tachycardias*. This classification scheme does have limitations; a supraventricular rhythm can present with a widened QRS complex due to aberrant ventricular conduction, the widened QRS complex resulting from a fixed (i.e., preexisting) bundle branch block, rate-related conduction block, ventricular preexcitation syndrome (i.e., Wolff-Parkinson-White [WPW] syndrome), or toxic-metabolic condition.[5] The normal QRS complex duration is less than 100 milliseconds for older children and adults; therefore, a wide-complex tachycardia possesses a QRS complex width greater than 100 milliseconds.

Common narrow-complex tachycardias include sinus tachycardia, atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia; less common narrow-complex tachycardias include multifocal atrial tachycardia, atrial tachycardias, and preexcited tachycardias seen in accessory pathway syndromes such as the WPW syndrome.[6] Wide-complex tachycardias include ventricular tachycardia and supraventricular tachycardia with aberrant conduction.[5,7] Ventricular tachycardia is further subdivided into monomorphic and polymorphic forms; the

TABLE 18-2 Drug Treatment for Cardiac Dysrhythmias in Adults

Drugs for Bradydysrhythmias		
Atropine	0.5- to 1.0-milligram IV push; may repeat every 3–5 min until desired heart rate is achieved or to total dose of 3 milligrams	Most effective for bradydysrhythmias due to sinus and higher AV nodal disease
Dopamine	IV infusion at rate 2–20 micrograms/kg/min; titrate to desired heart rate	May precipitate myocardial ischemia and ectopy
Epinephrine	IV infusion at rate 2–10 micrograms/min; titrate to desired heart rate	May precipitate myocardial ischemia and ectopy
Glucagon	3–10 milligrams IV infused over 1–2 min, followed by an IV continuous infusion of 1–5 milligrams/h	Used for cardiotoxicity associated with β-blocker and calcium channel–blocker overdose Limited human data are available supporting its use Nausea and vomiting are often limiting side effects Tachyphylaxis may develop during infusion
Drugs to Block AV Nodal Conduction		
Adenosine	6-milligram rapid IV push; if after 1–2 min the dysrhythmia persists, repeat rapid IV push with 12 milligrams; may repeat once more if dysrhythmia persists	Effective in terminating narrow QRS complex reentrant tachydysrhythmias involving the AV node
Verapamil	5–10 milligrams IV bolus over 2–3 min; if after 15 min the dysrhythmia persists, may repeat with dose of 10 milligrams	Effective in terminating narrow QRS complex reentrant tachydysrhythmias involving the AV node and reducing ventricular rate in atrial fibrillation or flutter
Diltiazem	15–20 milligrams IV bolus over 2 min, followed by IV infusion at 5–10 milligrams/h; a repeat bolus of 20–30 milligrams may be given after 15 min if inadequate response to initial bolus	
Esmolol	500 micrograms/kg IV bolus over 1 min, followed by IV infusion starting at 50 micrograms/kg/min; titrate infusion to desired heart rate	
Metoprolol	2.5–5 milligrams IV every 2–5 min; maximum total dose 15 milligrams IV over 10–15 min	
Propranolol	1–3 milligrams IV over 1 min; may repeat every 2–5 min up to a total of 5 milligrams	
Drugs to Terminate Tachydysrhythmias		
Procainamide	Initial: 20–50 milligrams/min ***OR*** 100 milligrams every 5 min until arrhythmia is suppressed, hypotension occurs, or the QRS complex is prolonged by 50% from its original duration (maximum dose: 17 milligrams/kg) Maintenance infusion rate: 1–4 milligrams/min	Used in wide-complex tachydysrhythmias and new-onset atrial fibrillation Median time to conversion of new-onset atrial fibrillation about 1 h Caution in patients with AMI and LV dysfunction Infuse initial dose at rate of 20 milligrams/min to reduce adverse effects
Amiodarone	Stable patient: 150 milligrams in 100 mL of D5W over 10 min, followed by infusion at 1 milligram/min for 6 h If breakthrough arrhythmia occurs, may give repeat 150-milligram boluses over 10 min Maximum total daily dose is 2.2 grams Ventricular fibrillation or pulseless ventricular tachycardia: 300 milligrams IV bolus; may repeat with additional dose of 150 milligrams IV bolus	Used in wide-complex tachydysrhythmias and new-onset atrial fibrillation Preferred in setting of AMI or LV dysfunction Contraindicated in pregnancy
Lidocaine	Loading dose: 50–100 milligrams over 2–3 min. May repeat in 5 min (up to 300 milligrams in any 1-h period) Maintenance: 1–4 milligrams/min (start low in patients with liver dysfunction or CHF)	Third-line agent for ventricular tachycardia and ventricular fibrillation
Magnesium sulfate	2 grams IV over 2 min, followed by infusion of 1–2 grams/h	Used in torsades de pointes with long QT interval
Ibutilide	Weight <60 kg: 10 micrograms/kg IV over 10 min Weight >60 kg: 1 milligram IV over 10 min	Used for conversion of new-onset atrial fibrillation or flutter Median time to conversion 20–30 min
Flecainide	Weight <70 kg: 200 milligrams PO Weight >70 kg: 300 milligrams PO OR 2 milligrams/kg IV over 10 min*	Used for conversion of new-onset atrial fibrillation or flutter Median time to conversion up to 4 h Avoid in patients with ACS or cardiomyopathy
Propafenone	Weight <70 kg: 450 milligrams PO Weight >70 kg: 600 milligrams PO OR 2 milligrams/kg IV over 10 min*	Used for conversion of new-onset atrial fibrillation or flutter Median time to conversion 2 h Avoid in patients with ACS, cardiomyopathy, or severe COPD
Vernakalant*	3 milligrams/kg IV infusion over 10 min; if dysrhythmia persists after 15 min, a second infusion of 2 milligrams/kg IV over 10 min can be given	Used for conversion of new-onset atrial fibrillation or flutter Median time to conversion 8–11 min Avoid in patients with hypotension, ACS within 30 days, severe aortic stenosis, and prolonged QT interval

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; AV = atrioventricular; COPD = chronic obstructive pulmonary disease; LV = left ventricle.

*IV preparations of flecainide, propafenone, and vernakalant not available in the United States.

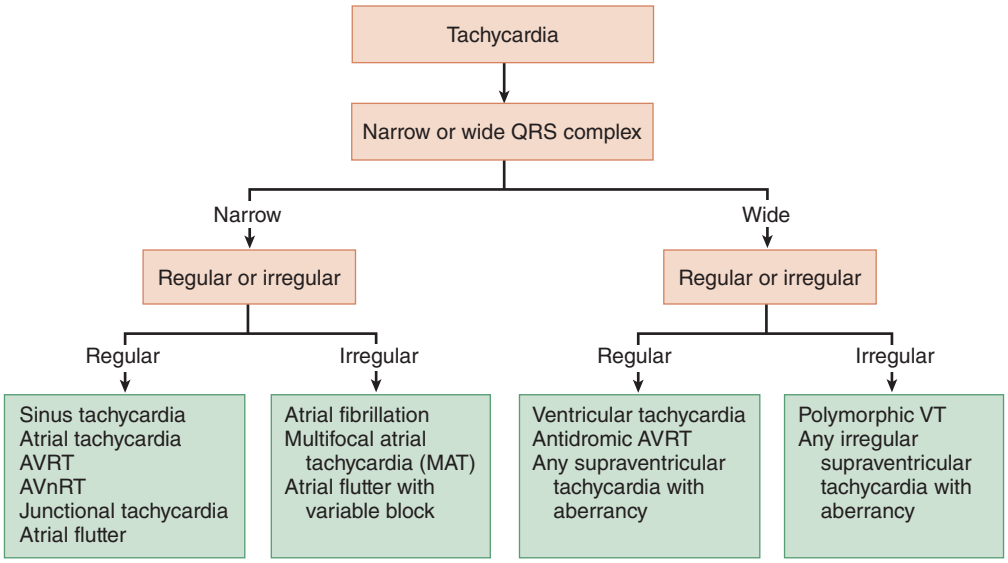


FIGURE 18-1. Tachycardia classification. AVnRT = atrioventricular nodal reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; VT = ventricular tachycardia.

polymorphic category includes the subtype called *torsades de pointes,* a form of polymorphic ventricular tachycardia diagnosed when the specific QRS complex pattern (sequential and recurring QRS complex amplitude increase and decrease) and QTc interval prolongation (>450 milliseconds) are noted.[8]

Treatment for symptomatic tachycardia is primarily IV medications for the stable patient and electrical therapy for the unstable patient (see Chapter 23, "Defibrillation and Cardioversion"). In certain situations, treatment of the underlying event is the most appropriate, rather than therapy aimed at the dysrhythmia; in other situations, direct attention to both the dysrhythmia and the underlying medical situation is required. The QRS width, often indicating the portion of the heart where the dysrhythmia originates, guides therapeutic choices.

NARROW-COMPLEX TACHYCARDIA

Sinus tachycardia and multifocal atrial tachycardia are best managed by treating the underlying cause rather than the dysrhythmia specifically. Other narrow-complex tachycardias, such as atrial fibrillation/flutter, AV nodal reentrant tachycardia, and AV reentrant tachycardia, require specific antiarrhythmic treatment by a combination of vagal maneuvers (**Table 18-3**), medications (Table 18-2), and electrical cardioversion (**Figure 18-2**).[9] Basic supportive therapy in most patients involves an IV fluid bolus to expand the circulating intravascular volume and supplemental oxygen as needed. (See Video: Narrow Complex Tachycardia.)

Vagal maneuvers heighten parasympathetic tone and may slow electrical conduction in the heart to a degree that abolishes sustained reentry (Table 18-3). If applied early, vagal maneuvers can convert many patients presenting with reentrant tachycardias, such as paroxysmal supraventricular tachycardia and narrow-complex tachycardia associated with WPW syndrome. Effective vagal maneuvers include carotid sinus massage, the release phase of the Valsalva maneuver, and the diving reflex; the response to these vagal maneuvers is enhanced by placing the patient supine during the release phase.[10-12] A recently described modification of the Valsalva maneuver (Table 18-3) is more effective than the standard technique in terminating reentrant supraventricular tachycardias.[13,14]

Adenosine is a very-short-acting agent that blocks conduction through the AV node and can interrupt sustained reentry when the AV node is part of the circuit (Table 18-2). The AV nodal blocking effect of adenosine is very transient, although quite profound, so a brief period of AV nodal blockade with near-immediate recurrence of the reentrant supraventricular tachycardia is not a treatment failure but a consequence of the medication's short duration of effect. In such situations, repeat adenosine with a higher dose (12 milligrams).[15]

β-Blockers and calcium channel blockers slow conduction through the AV node and can convert some supraventricular tachycardias, such as reentrant supraventricular tachycardias, and slow the ventricular response in others, such as atrial fibrillation or flutter. Esmolol, an IV β-blocker with a short duration of effect, can be used when temporary AV nodal blockade is desired and a longer period of action is not anticipated (as in conversion of paroxysmal supraventricular tachycardia) or when the patient is unstable and the ability to titrate the degree of drug effect is important. Metoprolol is a longer-acting β-blocker used in more stable patients, typically for ventricular rate control in patients with atrial fibrillation. Verapamil is a calcium channel blocker used for conversion of reentrant supraventricular tachycardias, and although it can be used for ventricular rate control, there is a greater potential for hypotension, so diltiazem, which does not have as much potential to induce hypotension, is the calcium channel blocker recommended for ventricular rate control.

Synchronized electrical cardioversion can be used in narrow-complex tachycardias when patients are unstable or do not respond to pharmacologic measures (see Chapter 23).

TABLE 18-3 Vagal Maneuvers

Carotid sinus massage	Listen for bruit first; do not massage an artery with a bruit Massage only one side at a time Massage for 20 s or less
Valsalva maneuver	Patient lying flat or with head and chest elevated to 45 degrees Have patient hold breath and strain against closed glottis while tightening abdominal wall muscles Hold for as long as practical, ideally >10–20 s Increased vagal tone seen during release phase after breath hold
Modified Valsalva maneuver[13]	Patient lying on stretcher with head and chest elevated to 45 degrees Patient instructed to blow into 10-mL syringe with enough force to move plunger for 15 s Patient then laid flat and legs passively elevated to 45 degrees for 15 s Legs then lowered and patient lies flat for an additional 45 s
Diving reflex	More effective in infants than adults Place bag of ice and water on face for 15–30 s

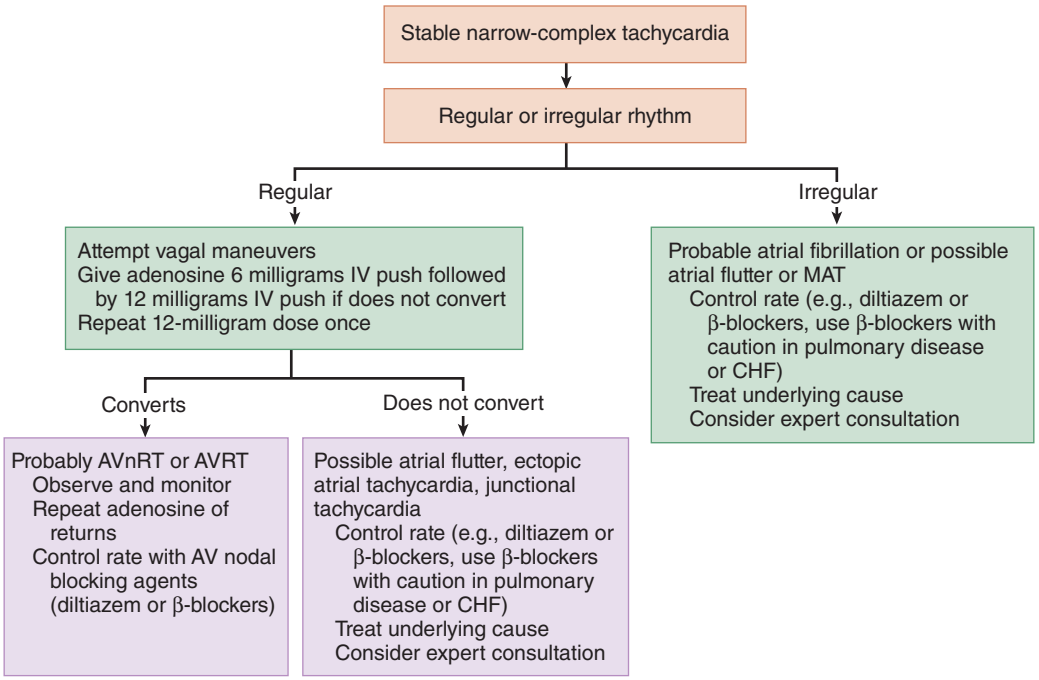


FIGURE 18-2. Treatment of narrow-complex tachycardia. AV = atrioventricular; AVnRT = atrioventricular nodal reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; CHF = congestive heart failure; MAT = multifocal atrial tachycardia; VT = ventricular tachycardia.

WIDE-COMPLEX TACHYCARDIA

Wide-complex tachycardia includes ventricular tachycardia and supraventricular tachycardia with aberrant conduction, manifested by widened QRS complex.

In the stable patient, pharmacologic agents used to terminate a wide-complex tachycardia include procainamide, amiodarone, lidocaine, and magnesium (Table 18-2 and **Figure 18-3**). **Procainamide is the antiarrhythmic of choice for the stable patient.**[16,17] Amiodarone and lidocaine are less effective.[16-18] Magnesium is used for tachydysrhythmias associated with QT interval prolongation, such as torsades de pointes.

Electrical cardioversion is the preferred treatment for wide-complex tachycardia (including ventricular tachycardia and certain types of supraventricular tachycardia with aberrant conduction [atrial fibrillation/flutter, AV nodal reentrant tachycardia, and AV reentrant tachycardia]) with hemodynamic instability, myocardial ischemia, or failure of pharmacologic treatment (see Chapter 23).[7,8]

ECTOPIC BEATS

Ectopic beats originate from atrial, AV nodal, and/or ventricular tissues. These beats are frequently benign but can cause symptoms, with patients noting palpitations or an irregular heartbeat.[19] Uncommonly, premature ventricular contractions can trigger serious reentrant dysrhythmias and may require therapy.

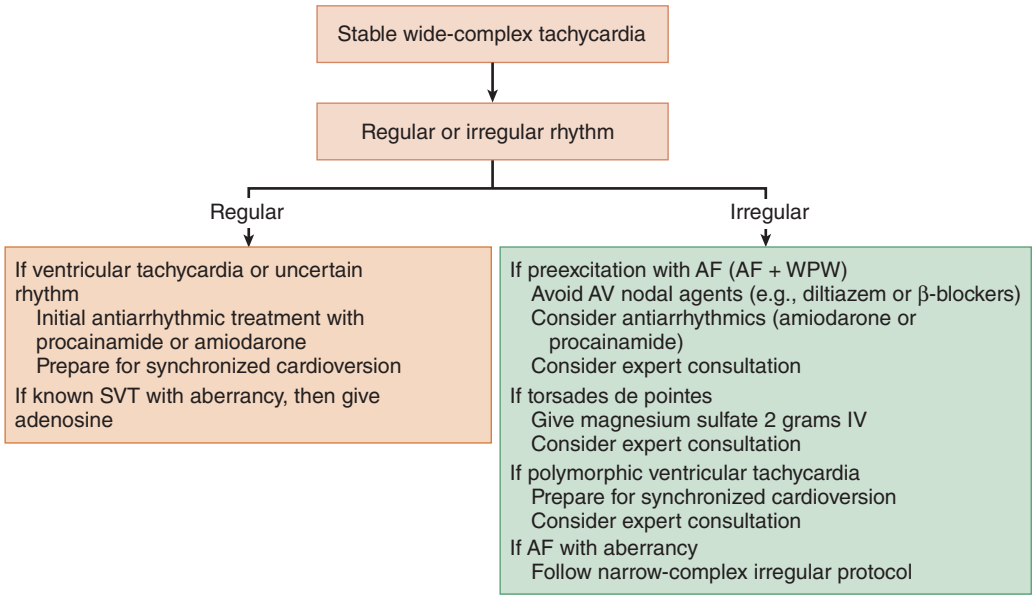


FIGURE 18-3. Treatment of wide-complex tachycardia. AF = atrial fibrillation; AV = atrioventricular; SVT = supraventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.



FIGURE 18-4. Premature atrial contractions in an atrial trigeminal pattern.

PREMATURE ATRIAL CONTRACTIONS

DESCRIPTION

Premature atrial contractions originate from ectopic pacemakers anywhere in the atrium other than the SA node (**Figure 18-4**); they are identified by characteristic ECG features (**Table 18-4**).[19] The ectopic P wave may not be conducted through the AV node if the premature atrial contraction reaches the AV node during the absolute refractory period. When a premature atrial contraction reaches the AV node during the relative refractory period, it may be conducted with a delay, as demonstrated on the ECG by a longer PR interval than seen with a sinus beat. Nonconducted premature atrial contractions are the most common cause of pauses in cardiac rhythm. Premature atrial contractions may occur in a pattern, such as every other beat (atrial bigeminy), every third beat (atrial trigeminy), and so on.

Most premature atrial contractions are conducted with baseline QRS complexes, but some may be conducted aberrantly through the infranodal system, particularly if they reach a bundle branch during the refractory period. The premature atrial contraction will often depolarize the SA node ("reset"), so the interval between normal P waves encompassing the premature atrial contraction will not be twice the existing P to P interval, creating a shorter pause than the fully compensatory pauses seen after most premature ventricular contractions.

CLINICAL SIGNIFICANCE

Premature atrial contractions are common at all ages and usually do not indicate underlying heart disease. Increased rates of premature atrial contractions are seen in patients with chronic heart or lung disease. Chemical agents that enhance either sympathetic tone (e.g., cocaine, amphetamines, caffeine, nicotine) or parasympathetic tone (e.g., digoxin) may lead to a higher frequency of premature atrial contractions. Premature atrial contractions can precipitate sustained atrial tachycardia, flutter, or fibrillation under certain circumstances. Frequent premature atrial contractions are associated with an increased risk for stroke and sudden death,[20] although there is no evidence that attempts to suppress reduce that risk. Symptomatic patients are managed by discontinuing any precipitating toxins and treating any underlying disorder that is contributing to premature atrial contraction generation.

PREMATURE VENTRICULAR CONTRACTIONS

DESCRIPTION

Premature ventricular contractions (PVCs) occur when electrical impulses originate from single or multiple areas in the ventricles (**Figure 18-5**) and are identified by characteristic ECG features (**Table 18-5**).[19]

Most PVCs do not affect the spontaneous discharge of the SA node, so the interval between normal sinus P waves encompassing the PVC is twice the previous P to P interval—an interval termed a fully compensatory postectopic pause. This fully compensatory pause occurs because the SA node discharges during the refractory period of either the AV node or His bundles induced by the PVC. Less commonly, a PVC may be interpolated between two sinus beats. Many PVCs occurring in a bigeminal or trigeminal pattern have a fixed coupling interval (within 40 milliseconds) from the preceding sinus beat (**Figure 18-6**). Occasionally, a **ventricular fusion beat** occurs when both supraventricular and ventricular impulses depolarize the ventricular myocardium almost simultaneously. The QRS configuration of a fusion beat has characteristics of both the normally conducted beat and the ectopic one.

The degree (quantity and quality) of the PVCs is categorized as follows: (1) an occasional PVC seen on the rhythm strip is categorized as isolated (Figure 18-5A), (2) multiple PVCs of similar morphology are called unifocal (Figure 18-5B), and (3) multiple PVCs with different morphology are called multifocal (Figure 18-5C), implying more than one ventricular focus is producing ectopy.

CLINICAL SIGNIFICANCE

PVCs are very common and related to factors that alter the electrophysiology of cardiac tissue or to pathologic conditions of the myocardium itself. Sometimes, infrequent or rare PVCs may be observed in patients without any evidence of heart disease. PVCs may trigger sustained runs of ventricular tachycardia (**Figure 18-7**).[14,21]

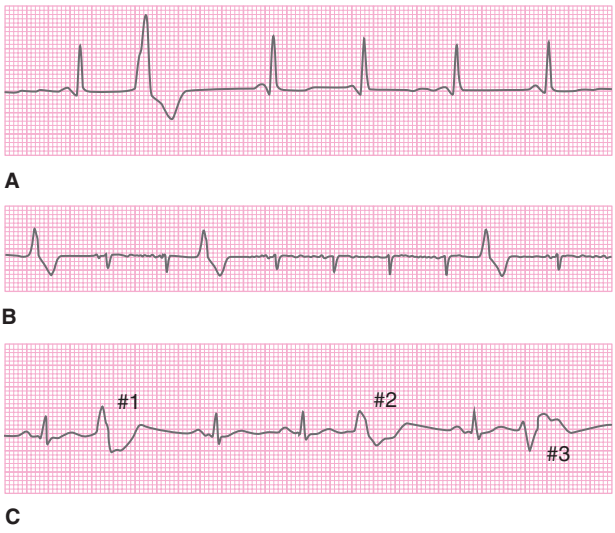


FIGURE 18-5. Sinus rhythm with premature ventricular contractions (PVCs). **A.** Sinus rhythm with a single PVC. **B.** Sinus rhythm with multiple, unifocal PVCs. **C.** Sinus rhythm with multifocal PVCs (in this example, three different PVC morphologies in this single lead, indicated by #1, #2, and #3).

TABLE 18-4 ECG Features of Premature Atrial Contractions

- P waves that appear sooner (prematurely) than expected sinus beat
- Ectopic P waves
  - With different shape and axis than the SA node–initiated P wave
  - That may or may not be conducted through the AV node
- Interval between normal P waves encompassing the premature atrial contraction is less than twice the existing P to P cycle length (a noncompensatory pause)

Abbreviations: AV = atrioventricular; SA = sinoatrial.

TABLE 18-5 ECG Features of Premature Ventricular Contractions

- Absence of P wave prior to the QRS complex
- Occasional retrograde P wave following QRS complex
- Abnormally widened QRS complex with different morphology from SA node–initiated QRS complex
- Commonly a compensatory postectopic pause following the PVC to next SA node–initiated beat
- ST segments and T waves that are directed opposite the major QRS complex deflection

Abbreviations: PVC = premature ventricular contraction; SA = sinoatrial.

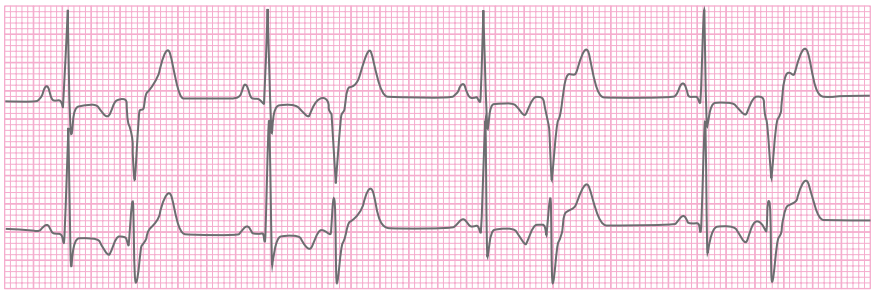


FIGURE 18-6. Premature ventricular contractions producing ventricular bigeminy.

There is a correlation between the severity of underlying coronary artery disease and the degree of ventricular ectopy, and in addition, ventricular ectopy is an independent risk factor for sudden cardiac death.[22,23] In acute coronary syndrome, PVCs indicate the underlying electrical instability of the heart, but patterns of ventricular ectopy ("warning dysrhythmias") are not reliable predictors of subsequent ventricular fibrillation.

Frequent PVCs present over a long duration (>30 months) can induce a reversible impairment in ventricular function, termed **PVC-induced cardiomyopathy**.[26] Such patients typically have >15% to 20% of their heartbeats due to PVCs (PVC burden), noting palpitations along with symptoms of heart failure.

TREATMENT

Review the ECG for evidence of ischemia or infarction, chamber enlargement, QT interval prolongation, or Brugada syndrome. Assess for potentially reversible conditions such as hypoxia, drug effect, or electrolyte abnormalities and treat appropriately.[24,25] Typical recommendations for stress reduction and elimination of stimulants such as caffeine or nicotine are not consistently effective.[25] Patients with greater than three PVCs in a row are considered to have nonsustained ventricular tachycardia, which can be a marker for sustained tachydysrhythmias and sudden cardiac death. If this is a new dysrhythmia, initiate emergency cardiac investigation.

Pharmacologic suppression of isolated PVCs with IV antiarrhythmic medications in the acute setting does not improve survival for the acute condition, and attempts to suppress PVCs with long-term oral antiarrhythmics increase mortality due to the dangerous prodysrhythmic properties of the medications themselves.[24,25] Implantable cardioverter-defibrillators are used in patients with PVCs that have potential to trigger malignant ventricular dysrhythmias or cardiac arrest. Patients with PVC-induced cardiomyopathy can be successfully treated with ablation of the ectopic focus, reducing PVC burden with recovery of impaired ventricular function over time.[26]

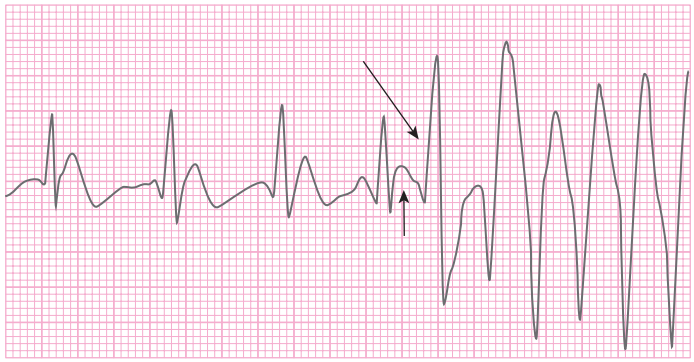


FIGURE 18-7. Sinus rhythm in an ST-segment elevation myocardial infarction patient with a premature ventricular contraction (PVC) initiating ventricular tachycardia. Note the R wave (*large arrow*) of a PVC falling on the T wave (*small arrow*) of the last sinus beat. This R-on-T event produces ventricular tachycardia.

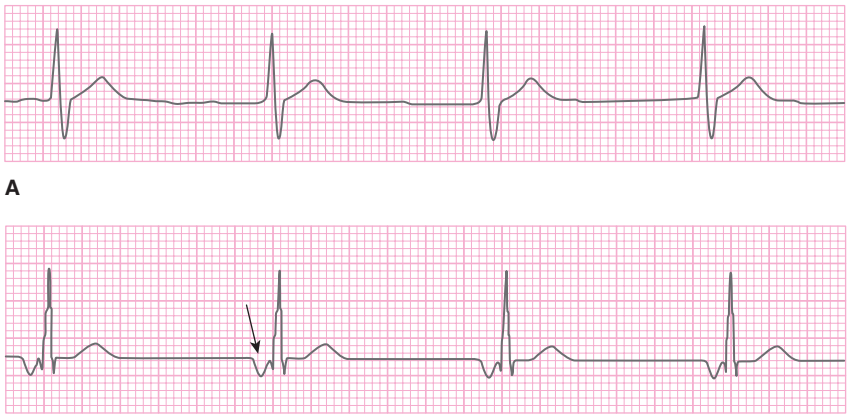
BRADYDYSRHYTHMIAS

Junctional and idioventricular rhythms may present with lightheadedness, syncope, or hypotension requiring therapy.

JUNCTIONAL RHYTHM

DESCRIPTION

Under normal circumstances, the SA node discharges at a faster rate than the AV node, so the pacemaker function of the AV node and all other slower pacemakers are suppressed. If SA node discharges are slow or fail to reach the AV node, junctional escape beats will produce a rhythm (**Figure 18-8**) usually at a rate between 40 and 60 beats/min. If the junctional beats continue in sequence, then a junctional rhythm is present. In most cases, junctional escape beats do not conduct retrograde into the atria, so a QRS complex without a P wave is usually seen (Figure 18-8A); rarely, the junctional escape beat conducts back



A

B

FIGURE 18-8. Junctional rhythm. **A.** Junctional rhythm. **B.** Junctional rhythm with retrograde P waves (*arrow*).

TABLE 18-6 ECG Features of Junctional Rhythm

- Absence of normal (sinus-mediated) P waves with normal PR interval
- Rare retrograde P wave (usually an inverted P wave and immediately adjacent to QRS complex, before or after)
- Narrow QRS complex
- Ventricular rate
  - Between 40 and 60 beats/min for junctional rhythm
  - Between 60 and 100 beats/min for accelerated junctional rhythm
  - >100 beats/min for junctional tachycardia

into the atria, producing the retrograde P wave, which is an inverted P wave found immediately prior to or following the QRS complex (Figure 18-8B).

At times, enhanced AV nodal automaticity overrides the sinus node and produces an accelerated junctional rhythm with a rate of 60 to 100 beats/min or junctional tachycardia with a rate greater than 100 beats/min (**Table 18-6**). Usually, the enhanced junctional pacemaker captures both the atria and ventricles.

CLINICAL SIGNIFICANCE

Junctional escape beats may occur whenever there is a long enough pause in the impulses reaching the AV node, as with sinus bradycardia, slow phase of sinus dysrhythmia, or during the pause after premature beats.[27] Sustained junctional escape rhythms may be seen with heart failure, myocarditis, hypokalemia, or digitalis toxicity.

Accelerated junctional rhythm, including junctional tachycardia, may occur from medication toxicity, acute rheumatic fever, or inferior myocardial ischemia.[27] With medication toxicity (particularly digitalis compounds) in a patient being treated for atrial fibrillation, the rate is usually between 70 and 130 beats/min, and the ECG is characterized by regular QRS complexes superimposed on atrial fibrillatory waves.

TREATMENT

Isolated, infrequent junctional escape beats usually do not require specific treatment. If sustained junctional escape rhythms are producing symptoms, the underlying cause should be treated. Atropine can be used to accelerate the SA node discharge rate and enhance AV nodal conduction. Accelerated junctional rhythm and junctional tachycardia are managed by treating the underlying cause.

IDIOVENTRICULAR RHYTHM

DESCRIPTION

Idioventricular rhythms originate from the ventricles (**Figure 18-9**), manifesting as regular widened QRS complexes without evidence of atrial activity (**Table 18-7**). An idioventricular rhythm has a ventricular rate of 30 to 50 beats/min, and an accelerated idioventricular rhythm has a ventricular rate of 50 to 110 beats/min.[28] Idioventricular rhythm tends to appear in nonsustained fashion with runs of short duration, ranging from 3 to 30 consecutive beats, and will typically begin with a fusion beat. Accelerated idioventricular rhythms are more sustained and tend to have a gradual onset and termination.

TABLE 18-7 ECG Features of Idioventricular Rhythm

- Widened QRS complex
- QRS complexes occurring regularly
- No evidence of atrial activity: no P waves
- Ventricular rate
  - 30–50 beats/min for idioventricular rhythm
  - 50–110 beats/min for accelerated idioventricular rhythm
- Often in nonsustained fashion with runs of short duration: 3–30 consecutive beats

CLINICAL SIGNIFICANCE

Idioventricular rhythm is seen most commonly in the setting of an ST-segment elevation myocardial infarction. Accelerated idioventricular rhythms have been seen in drug toxicity (cocaine and digitalis), electrolyte abnormalities (hyperkalemia), and cardiomyopathies, and during fibrinolysis of an occluded coronary artery, termed a *reperfusion dysrhythmia*, although the appearance of this dysrhythmia does not distinguish between complete and incomplete reperfusion.[29] Although there is some association with ventricular tachycardia, there is no apparent association with ventricular fibrillation. Idioventricular rhythms, particularly the slower versions, can produce dizziness, weakness, syncope, chest pain, and dyspnea; profound hypoperfusion may occur. Accelerated idioventricular rhythm itself usually produces no symptoms, but the loss of atrial contraction and subsequent fall in cardiac output can produce hemodynamic deterioration.

TREATMENT

With idioventricular rhythm producing hypoperfusion, drugs to increase the heart rate are appropriate. Atropine can be tried, although the likelihood of successful treatment is low. Cardiac pacing is often needed, starting via the transcutaneous route. In most cases of accelerated idioventricular rhythm, treatment is not necessary. If accelerated idioventricular rhythm is the only functioning pacemaker, **suppression with antiarrhythmic agents may lead to asystole**. If sustained accelerated idioventricular rhythm produces symptoms secondary to a decrease in cardiac output, sequential AV pacing is recommended.

SUPRAVENTRICULAR TACHYDYSRHYTHMIAS

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

DESCRIPTION

After sinus tachycardia, atrial fibrillation is the next most frequent narrow-complex tachycardia encountered in the ED; atrial flutter is a less common dysrhythmia. Atrial fibrillation occurs when there are multiple, small areas of atrial myocardium continuously discharging and contracting.[30] There is no uniform atrial depolarization and contraction but, rather, only a quivering of the atrial chamber walls, resulting in less than effective ventricular filling and diminished cardiac output.

The ECG hallmarks of atrial fibrillation (**Figure 18-10** and **Table 18-8**) include the absence of discernible P waves and an irregularly irregular ventricular rhythm. With the chaotic atrial activity, distinct P waves are not noted; rather, either a flat or chaotic baseline is seen, most prominent

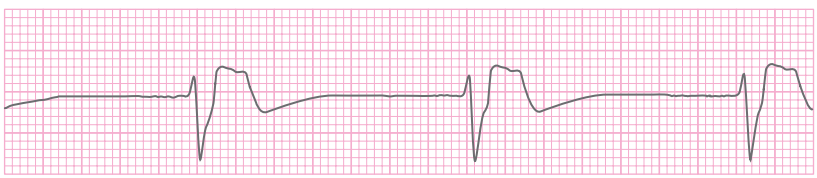


FIGURE 18-9. Idioventricular rhythm with a ventricular rate of approximately 30 beats/min.

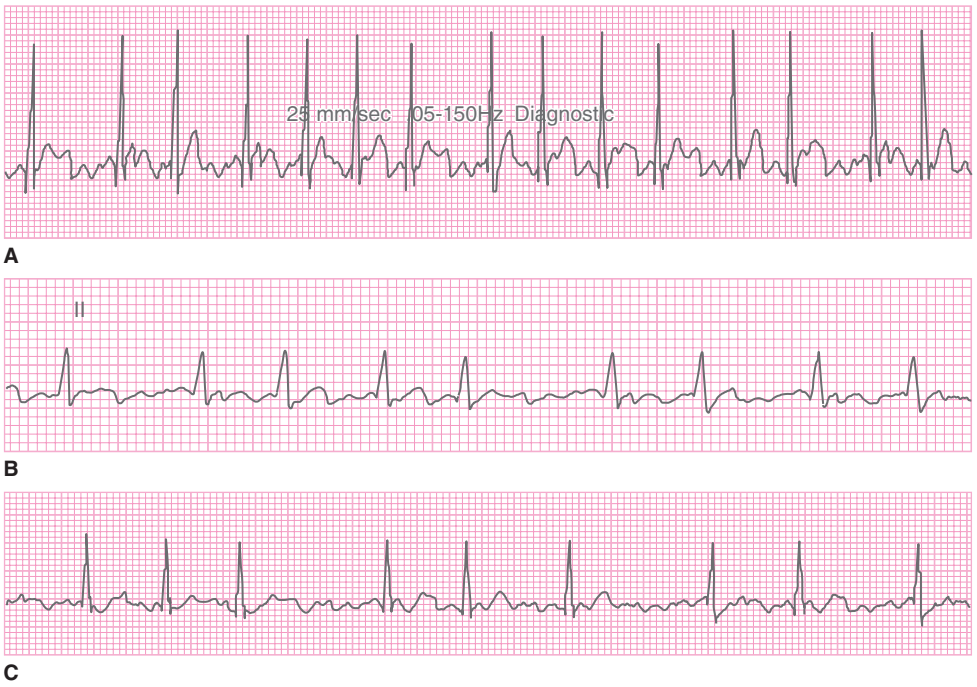


FIGURE 18-10. Three examples of atrial fibrillation with irregular ventricular response.

in lead V_1. The irregularly irregular ventricular rhythm results from the atrial chaos and the variable conduction of impulses through the AV node to the ventricle. The atrial rate in atrial fibrillation is often greater than 600 beats/min, whereas the ventricular rate is markedly lower due to the refractory period of the AV node; in atrial fibrillation where the AV node is unaffected by disease or medications, the ventricular rate is typically 120 to 170 beats/min. Illnesses or medications may reduce AV node conduction and markedly slow ventricular response. A very rapid ventricular response (>200 beats/min) may be seen in patients with accessory or bypass tracts (discussed later in this chapter).

In contrast to atrial fibrillation, atrial flutter most often is a regular rhythm (**Figure 18-11** and **Table 18-9**); in rare cases, it can be irregular due to variable AV nodal block. P waves are present and of a single morphology, typically a downward deflection, called *flutter waves* resembling a saw blade with a "sawtooth" pattern, best seen in the inferior ECG leads and lead V_1. Most commonly, the atrial rate is regular, classically around 300 beats/min, varying between 250 and 350 beats/min. The ventricular rhythm is frequently regular and is a function of the AV block. AV ratios of 2:1 are common and produce a ventricular rate around 150 beats/min, whereas a 3:1 AV ratio will result in a ventricular rate of 100 beats/min. Although the degree of AV conduction is often fixed, it may also be variable and create an irregular ventricular response. **A regular narrow-complex tachycardia at an approximate rate of 150 beats/min (+/– 5 beats/min) strongly suggests atrial flutter with 2:1 conduction**.

CLINICAL SIGNIFICANCE

Atrial fibrillation is usually associated with ischemic or valvular heart disease; less common causes include congestive cardiomyopathy, myocarditis, alcohol binge ("holiday heart"), thyrotoxicosis, and blunt chest trauma.[30,31] Left atrial enlargement is a common feature of patients with chronic atrial fibrillation. Atrial fibrillation can be paroxysmal (lasting less than 7 days, terminating either spontaneously or with treatment), persistent (sustained longer than 7 days or requiring treatment to terminate), long-standing persistent (lasting continuously longer than 1 year), or permanent (long-standing where a decision has been made not to try to restore normal sinus rhythm).[30] New or recent onset is applied to symptomatic patients presenting to the ED without a prior history of atrial fibrillation.

TABLE 18-8 ECG Features of Atrial Fibrillation

- Absence of discernible P waves with flat or chaotic isoelectric baseline
- QRS complexes narrow unless preexisting bundle branch block or preexcitation syndrome
- Irregularly irregular ventricular rhythm

The clinical consequences of atrial fibrillation include loss of atrial contraction, potential for rapid ventricular rates, and risk of thromboembolism. In patients with compromised cardiac function, left atrial contraction contributes significantly to left ventricular filling, so the loss of effective atrial contraction, as in atrial fibrillation, may produce heart failure in these patients. A rapid ventricular rate can impact ventricular filling as well as coronary and systemic perfusion. Atrial fibrillation increases the risk of venous and atrial thrombosis, with potential for pulmonary and systemic arterial embolism.[32]

If an atrial thrombus has formed, conversion from atrial fibrillation to sinus rhythm can propel a portion of the thrombosis out into the systemic circulation, and this risk increases with duration of the dysrhythmia. Observational studies note that conversion from new-onset atrial fibrillation that has been present for 12 hours or less carries a 0.3% risk of arterial embolism, whereas that risk is about 1% for durations of 12 to 48 hours before conversion.[33] For patients with heart failure and diabetes mellitus, conversion from new-onset (duration <48 hours) atrial fibrillation carries a risk of thromboembolic events as high as 9.8%.[34] After a duration of >48 hours, the risk of conversion-induced thromboembolic events is increased across all patient groups, so a 3- to 4-week period of anticoagulation is recommended prior to conversion.[30,35]

TREATMENT

Treatment of atrial fibrillation in the ED involves three issues: ventricular rate control, rhythm conversion, and anticoagulation to prevent arterial embolism.[35-40] Treatment varies according to patient stability, duration of symptoms, and chronicity of atrial fibrillation (paroxysmal, persistent, or permanent). Review prior records to identify past episodes or treatment for atrial fibrillation. For new-onset atrial fibrillation, consider checking thyroid function.[41] For patients on warfarin, check the prothrombin time and INR. Calculate either the $CHADS_2$ or

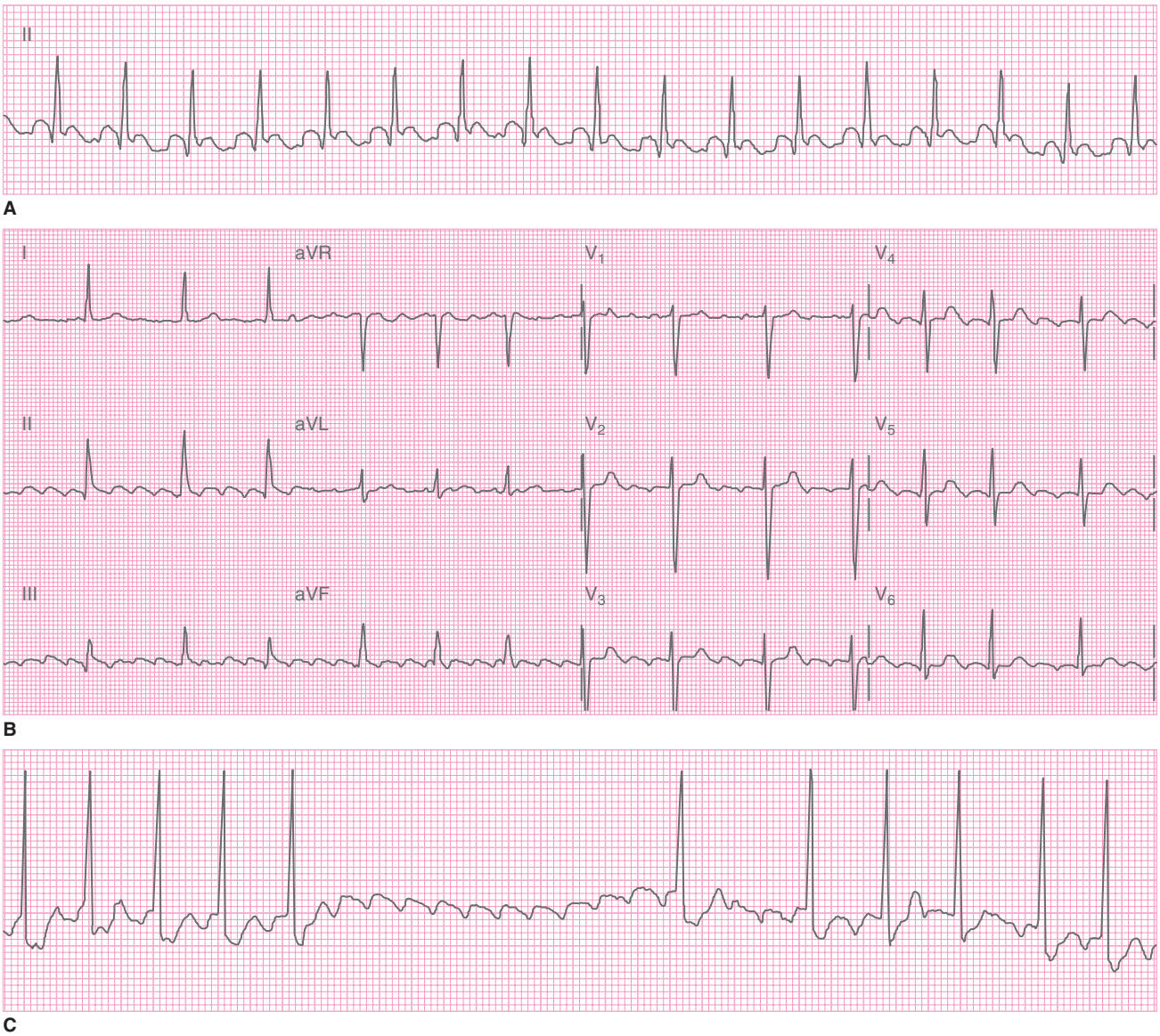


FIGURE 18-11. Atrial flutter. **A.** Regular, narrow-complex tachycardia at a ventricular rate of 155 beats/min. **B.** Atrial flutter with flutter waves most visible in leads 2, 3, and aVF. **C.** Atrial flutter response to carotid sinus massage inducing transient AV block and unmasking flutter waves.

CHA_2DS_2-VASc score to risk-stratify the potential for future arterial embolic complications; a $CHADS_2$ score of 0 or a CHA_2DS_2-VASc score of 0 or 1 identifies low-risk patients (**Table 18-10**).[30,31]

For patients with paroxysmal atrial fibrillation or acute medical conditions producing atrial fibrillation, a period of observation and treatment in the ED is appropriate as the atrial fibrillation may spontaneously convert.[12,42] Up to 70% of otherwise healthy ED patients evaluated for acute-onset atrial fibrillation will spontaneously convert within 48 to 72 hours.[43] Ventricular rate control may help control symptoms until conversion. Also, it is significantly more difficult to achieve rate or rhythm control of atrial fibrillation in patients with acute underlying medical illness, and such attempts are associated with an increased incidence of adverse events.[44] In situations involving atrial fibrillation with rapid ventricular response and an active, significant underlying acute medical issue (e.g., sepsis, severe hypovolemia, pulmonary embolus, alcohol withdrawal), the presentation can be described as complex atrial fibrillation.[44] In these presentations, management priority is focused on treating the underlying medical issue while not employing standard rate and rhythm control therapies in the early stages of care.

For patients with recent-onset atrial fibrillation and a rapid ventricular response that is producing hypotension, myocardial ischemia, or pulmonary edema, treat with urgent electrical cardioversion.[30,35,36,45] For unstable patients with long-standing atrial fibrillation, electrical cardioversion is not likely to succeed, and instead, initiate hemodynamic resuscitation and ventricular rate control treatment. If the unstable patient is at increased risk for embolic complications related to cardioversion, administer an initial dose of a direct-acting oral anticoagulant for nonvalvular atrial fibrillation or low-molecular-weight heparin for patient with mechanical prosthetic valve, rheumatic mitral stenosis, or serious renal impairment before or immediately after electrical

TABLE 18-9 ECG Features of Atrial Flutter

- Identifiable P waves
  - Single morphology
  - Negative amplitude ("flutter waves" in "sawtooth pattern") best seen in inferior ECG leads and V_1
  - Atrial rate is regular, usually at 300 beats/min (250–350 beats/min)
- QRS complexes narrow unless preexisting bundle branch block
- Ventricular rate regular, although occasional irregularity can be seen
- Ventricular rate often 150 beats/min due to 2:1 atrioventricular nodal block

TABLE 18-10 $CHADS_2$ and CHA_2DS_2-VASc Scores

Criteria	$CHADS_2$	CHA_2DS_2-VASc
Congestive heart failure	1	1
Hypertension	1	1
Age ≥75 y	1	2
Diabetes mellitus	1	1
Stroke, TIA, or thromboembolism	2	2
Vascular disease (CAD, PAD)	–	1
Age 65–74 y	–	1
Sex (female)	–	1
Range	0–6	0–9

Abbreviations: CAD = coronary artery disease; PAD = peripheral artery disease; TIA = transient ischemic attack.

cardioversion (**Table 18-11**).[45] For patients treated with heparin, transition to warfarin is begun on discharge with continued heparin treatment until the INR is in the therapeutic range, typically 2.5 to 3.5 for mechanical prosthetic valves or mitral stenosis. Patients are continued on anticoagulant therapy until early follow-up to review whether long-term anticoagulation is needed.[45]

For stable low-risk patients in the ED with new-onset atrial fibrillation, either rate-control or rhythm-conversion strategies are appropriate (**Table 18-12**).[30,35,36] The rate-control approach consists of initiating medications that block the AV node to control the ventricular response, initiating oral anticoagulants to prevent thromboembolism (if appropriate), and reevaluation after 3 to 4 weeks for elective cardioversion. The rhythm-conversion approach uses electrical or pharmacologic methods to convert the patient back into sinus rhythm while in the ED.

Control of the ventricular response is done using a calcium channel blocker (diltiazem) or β-blockers (metoprolol or esmolol) with evidence of more effective acute rate control with diltiazem.[46] If diltiazem or β-blockers are ineffective, IV procainamide or amiodarone is an option to slow the ventricular response. The goal for rate control is a ventricular rate of <100 beats/min at rest.[36]

Electrical cardioversion using 150 to 200 J can terminate atrial fibrillation allowing for sinus rhythm to resume.[35,45] Conversion to and retention of sinus rhythm is more likely when atrial fibrillation is of short duration (<48 hours) and the atria are not greatly dilated. Observational analysis also notes that administration of rate control or rhythm conversion medications prior to electrical cardioversion attempts is associated with a reduced rate of successful conversion to sinus rhythm.[47] Although ED electrical cardioversion is effective in many atrial fibrillation patients[48] and observational studies indicate shorter ED length of stay,[37] there has been mixed acceptance of this approach.[49-51] As noted earlier, a significant portion of patients with new-onset atrial fibrillation will spontaneously convert to sinus rhythm within 24 hours of onset and evaluation.[12,42,43,52,53]

TABLE 18-11 Pericardioversion Anticoagulation for Unstable Patients

Nonvalvular atrial fibrillation: Onset >48 h or unknown *or* Stroke or TIA <6 mo *or* CHA_2DS_2-VASc scores ≥2	Dabigatran etexilate mesylate 150 milligrams PO (75 milligrams if CrCl is 15–30 mL/min) *or* Rivaroxaban 20 milligrams PO (15 milligrams if CrCl is 15–50 mL/min) *or* Apixaban 5 milligrams PO (2.5 milligrams PO in patients with at least 2 of the following characteristics: age ≥80 y, body weight ≤60 kg, or serum creatinine ≥1.5 milligrams/dL)
Mechanical prosthetic valve, rheumatic mitral stenosis, or CrCl <15 mL/min	Enoxaparin 1 milligram/kg SC

Abbreviations: CrCl = creatinine clearance; TIA = transient ischemic attack.

TABLE 18-12 ED Management of Atrial Fibrillation/Flutter in Stable Patients*

Ventricular Rate Control	
Diltiazem	• 15–20 milligrams IV bolus over 2 min; may repeat bolus if inadequate rate response • Once satisfactory rate response, begin IV infusion 5–10 milligrams/h, titrate to ventricular rate <90–100 beats/min • Begin transition to oral diltiazem, 60 or 90 milligrams PO at 5- or 10-milligram infusion rate, respectively • Stop IV infusion 2 h after oral dose
Metoprolol	• 5 milligrams IV; may repeat every 5 min to total of 15 milligrams • Once satisfactory rate response, give metoprolol PO (12.5 milligrams PO for every 5 milligrams given IV)
Rhythm Conversion: Synchronized Cardioversion	
Atrial flutter	May require as little as 25–50 J
Atrial fibrillation	150–200 J
Rhythm Conversion: Pharmacologic	
Ibutilide	Weight <60 kg: 10 micrograms/kg IV over 10 min Weight >60 kg: 1 milligram IV over 10 min
Procainamide	15–17 milligrams/kg IV over 30 min, followed by IV infusion at 1–4 milligrams/min
Flecainide	2 milligrams/kg IV over 10 min†
Vernakalant†	3 milligrams/kg IV infusion over 10 min; if dysrhythmia persists after 15 min, a second infusion of 2 milligrams/kg IV over 10 min can be given

*See Chapter 19, Tables 19-6, 19-7, and 19-19, for detailed discussion.

†Not available in the United States

This rate of spontaneous conversion coupled with the results of atrial fibrillation trials demonstrating that rate control is similar to rhythm control in terms of several key end points indicates no proven benefit for conversion of all new atrial fibrillation patients to sinus rhythm while in the ED.[35,52-54] The patient with new-onset atrial fibrillation who is stable can certainly be managed with rate control alone, either as an inpatient or outpatient depending on overall clinical condition.

The antiarrhythmics procainamide, ibutilide, flecainide, propafenone, and vernakalant can chemically convert atrial fibrillation to sinus rhythm.[35,55-58] Of the five, ibutilide has the highest consistent success rate for conversion. Ibutilide should not be given in the presence of hypokalemia, prolonged QT interval, or history of heart failure, as torsades de pointes may be initiated. This risk of torsades de pointes persists for 4 to 6 hours after the ibutilide is given. Pharmacologic conversion therapy is best avoided if duration is unknown or greater than 48 hours, allowing for heart clot detection and anticoagulation prior to any attempt.

Patients with recurrent paroxysmal atrial fibrillation are sometimes given oral medications (usually flecainide or propafenone) to be taken at the onset of the dysrhythmia; this "pill in a pocket" approach is successful in selected outpatients.[35] This approach should only be used in patients with paroxysmal episodes after SA or AV node dysfunction, conduction disturbance (bundle branch block, Brugada syndrome), and structural heart disease have been excluded.[2]

Atrial flutter is managed in the same fashion as atrial fibrillation: either rhythm conversion or ventricular rate control with β-blockers or calcium channel blockers.[35] Atrial flutter is very responsive to electrical cardioversion; as little as 25 to 50 J is often effective. In general, patients in atrial flutter tend to better tolerate the dysrhythmia hemodynamically than patients with atrial fibrillation. This "hemodynamic toleration" results from the organized atrial contraction seen with atrial flutter, as opposed to the lack of organized atrial contraction with atrial fibrillation. Despite organized atrial activity, there is a risk of arterial embolism with atrial flutter,[59] and corresponding recommendations for anticoagulation are based on the same criteria used for atrial fibrillation.[36]

Patients with chronic atrial fibrillation and planned cardioversion should be anticoagulated for 3 to 4 weeks, assuming clinical stability

allows such an approach.[30] Patients with permanent atrial fibrillation are at increased risk for embolic stroke, and oral anticoagulation can reduce that occurrence. The benefits of oral anticoagulation are counterbalanced by the potential adverse effects, usually hemorrhagic events. Clinical scoring tools, such as the CHA_2DS_2-VASc, are used to estimate risk of stroke and guide the decision to initiate long-term oral anticoagulation therapy in atrial fibrillation patients.[30,31]

DISPOSITION

Significant regional variation for hospitalization after an ED visit for atrial fibrillation has been reported, reflecting the interplay between patient clinical, socioeconomic, and hospital characteristics.[60] Admission is indicated when the patient's clinical status identifies distress with the need for continued therapy, such as heart failure with pulmonary congestion and continued respiratory distress, or ongoing myocardial ischemia.[36] Admission is advised when ventricular rate control cannot be achieved and the patient has persistent symptoms.[36] Patients with longer duration of dysrhythmia onset to presentation, previous stroke or transient ischemic attack, or pulmonary congestion on chest radiography are at higher risk for adverse 30-day outcomes[61]; these issues as well as other clinical factors should be considered when selecting disposition. Nonetheless, many patients can be safely discharged from the ED with short-term cardiology follow-up. Eighty percent or more of patients with atrial fibrillation can be discharged from the ED after rate or rhythm control with low risk for stroke or death within 30 days.[42] For patients with atrial flutter converted to sinus rhythm with electrical cardioversion, about 90% can be discharged with a very low incidence of stroke within the following year.[61,62] A site-specific protocol is useful to ensure that the patient with persistent dysrhythmia is discharged with appropriate medications and a plan for follow-up (**Tables 18-13** and **18-14**).[45]

Oral anticoagulation is used to reduce the incidence of embolic stroke in patients with atrial fibrillation or flutter.[63] Practical factors such as comorbidities, convenience, and cost should be considered when selecting the specific oral anticoagulant. It is appropriate to consult with the specialist who will be following the patient after ED discharge to discuss the specific agent to be used.

TABLE 18-13 Example Protocol for Discharge of Patient With Persistent Atrial Fibrillation or Flutter

- Patient is breathing comfortably on room air with oxygen saturation by pulse oximetry >95% and blood pressure is at baseline
- Ventricular rate has been controlled to a rate <100 beats/min at rest
- For nonvalvular atrial fibrillation patients not converted to sinus rhythm, determine risk for embolic stroke by calculating the CHA_2DS_2-VASc score:
  - CHA_2DS_2-VASc = 0: oral anticoagulation not recommended
  - CHA_2DS_2-VASc = 1: either no anticoagulation or antiplatelet or oral anticoagulant is acceptable
  - CHA_2DS_2-VASc ≥ 2: oral anticoagulation recommended; consult follow-up specialist for specific agent
- Consult with internist or cardiologist to arrange early follow-up (within 7 d) and choose medications for rate and/or rhythm control and oral anticoagulants upon discharge (see Table 18-14)
- Arrange outpatient echocardiography for patients with new-onset atrial fibrillation or flutter
- Discharge patient with prescriptions for rate and/or rhythm control, and oral anticoagulant if indicated, in quantity only sufficient to last until follow-up appointment

TABLE 18-14 Rate Control and Oral Anticoagulation Medications Used Upon Discharge of Patients With Persistent Atrial Fibrillation or Flutter

	Typical Initial Dose	Comments
Rate Control Medications		
Diltiazem	60 to 90 milligrams PO four times a day (immediate release); adjust dose as needed for ventricular rate control	More effective than metoprolol in controlling heart rate and reducing dysrhythmia-related symptoms Avoid in patients with heart failure with reduced ejection fraction Transition to extended-release form when rate control dose established
Metoprolol	25 to 50 milligrams twice a day (immediate-release form); adjust dose as needed for ventricular rate control	Transition to extended-release form when rate control dose established
Anticoagulants		
Warfarin	5 milligrams PO daily	Half-life 20–60 h; mean 40 h Preferred regimen if CrCl <15 mL/min
Enoxaparin	1 milligram/kg SC every 12 h Reduce dose if CrCl <30 mL/min	See text comments about bridging parenteral anticoagulation
Dabigatran etexilate mesylate	150 milligrams PO twice a day (if CrCl >30 mL/min) 75 milligrams PO twice a day (if CrCl 15–30 mL/min)	Half-life 12–17 h
Rivaroxaban	20 milligrams PO daily with evening meal (if CrCl >50 mL/min) 15 milligrams PO daily with evening meal (if CrCl 15–50 mL/min)	Half-life 5–9 h
Apixaban	5 milligrams PO twice a day 2.5 milligrams PO twice a day in patients with at least 2 of the following characteristics: age ≥80 y, body weight ≤60 kg, or serum creatinine ≥1.5 milligrams/dL	Half-life during repeat oral dosing 12 h

Abbreviation: CrCl = creatinine clearance.

MULTIFOCAL ATRIAL TACHYCARDIA

DESCRIPTION

Multifocal atrial tachycardia is an irregular rhythm resulting from at least three different atrial foci competing to pace the heart, resulting in distinct P-wave morphologies on the ECG (**Figure 18-12** and **Table 18-15**).[64] **Due to irregularity and the chaotic appearance of atrial depolarization, multifocal atrial tachycardia is often confused with atrial fibrillation or atrial flutter.**

CLINICAL SIGNIFICANCE

Multifocal atrial tachycardia is found most often in elderly patients with decompensated chronic lung disease, but may also complicate heart failure or sepsis. Treatment is directed toward the underlying disorder. With decompensated lung disease, oxygen and bronchodilators improve pulmonary function and arterial oxygenation and decrease atrial ectopy. Antiarrhythmic treatment is not indicated, and cardioversion has no effect.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA)

DESCRIPTION

Eighty percent or more of cases of paroxysmal supraventricular tachycardia are AV nodal reentrant tachycardia, resulting from sustained reentry occurring within the AV node, with an ectopic atrial focus



FIGURE 18-12. Multifocal atrial tachycardia. Note multiple P-wave morphologies with irregular tachycardia rhythm.

TABLE 18-15 ECG Features of Multifocal Atrial Tachycardia

- At least 3 distinct P-wave morphologies in a single ECG lead
- No consistent P to P, PR, or R to R intervals
- Irregularly irregular rhythm with rates usually 100–180 beats/min
- Normal QRS complex unless preexisting bundle branch blocks
- Frequently confused with atrial fibrillation or flutter

TABLE 18-16 ECG Features of Paroxysmal Supraventricular Tachycardia

- Absence of normal (sinus-mediated) P waves with normal PR interval
- Rare retrograde P wave (usually inverted P wave and immediately adjacent to QRS complex, before or after)
- Narrow QRS complex, usually <100 ms in duration
- Ventricular rate usually 170–180 beats/min; the rate can range from as low as 130 beats/min to as high as 300 beats/min

accounting for the remaining 15% to 20%. In paroxysmal supraventricular tachycardia (**Figure 18-13** and **Table 18-16**), the QRS complex is of normal width, rapid, and regular. P waves are "buried" within the QRS complex in about 70% of cases. In the other 30%, a P wave (so-called "retrograde" P wave) is found immediately adjacent before, during, or after the QRS complex without a measurable PR interval.

CLINICAL SIGNIFICANCE

Paroxysmal supraventricular tachycardia is seen more frequently in females, with a peak in the late teenage and young adult years. The majority of patients are without active cardiovascular disease.[65] Patients may be able to describe the abrupt onset of this reentrant dysrhythmia and also note when it self-terminates. Palpitations, lightheadedness, and dyspnea are common symptoms.

TREATMENT

If applied early in the dysrhythmia course, vagal maneuvers are often effective (Table 18-3).[10,11,13,14] Attention to technique is important to maximize success rate. If there is no response to vagal maneuvers, IV adenosine is recommended to convert to sinus rhythm.[9] It is the rare patient who requires β-blocker or calcium channel blocker. In patients with recalcitrant paroxysmal supraventricular tachycardia or who are unstable, use electrical cardioversion to convert the dysrhythmia.

ATRIOVENTRICULAR BLOCKS

First-degree AV block is characterized by a delay in AV conduction manifested by a prolonged PR interval. Second-degree AV block is characterized by intermittent AV conduction: some atrial impulses reach the ventricles, and others are blocked. Third-degree AV block is characterized by the complete blockage of atrial impulses to the ventricles.

First-degree and second-degree Mobitz type I AV blocks are usually not compromising. These two AV blocks can occur in asymptomatic healthy individuals without any implication for subsequent problems, but if newly noted or occurring in the setting of an acute presentation, such as acute coronary syndrome or ingestion, then these two forms of AV block should be considered as potential warning of the development of more serious forms of AV block. Second-degree Mobitz type II and third-degree AV blocks are always abnormal with frequent hemodynamic compromise.

AV blocks are divided into nodal and infranodal blocks because of the clinical significance and prognostic differences.[1] Nodal AV block (block within the AV node) is usually due to reversible depression of conduction, is often self-limited, and generally has a stable infranodal escape pacemaker pacing the ventricles. Infranodal blocks (block below the AV node) usually are due to organic disease of the His bundle or bundle branches; often the damage is irreversible. They generally have a slow and unstable ventricular escape rhythm pacing the ventricles, and they frequently have a bad prognosis.

FIRST-DEGREE ATRIOVENTRICULAR BLOCK

DESCRIPTION

In first-degree AV block, each atrial impulse is conducted to the ventricles but less rapidly than normal, as noted by a prolonged PR interval, greater than 200 milliseconds. There is a P wave for each QRS complex; this association is consistent from one beat to the next (**Figure 18-14** and **Table 18-17**). The AV node is usually the site of conduction delay, although this block may occur at an infranodal level.



FIGURE 18-13. Paroxysmal supraventricular tachycardia.



FIGURE 18-14. Sinus rhythm with first-degree atrioventricular block (PR interval, 300 milliseconds).

TABLE 18-17 ECG Features of First-Degree Atrioventricular Block

- Consistent P wave to QRS complex relationship
- Prolongation of PR interval >200 ms

CLINICAL SIGNIFICANCE

First-degree AV block occasionally is found in normal hearts. Other common causes include increased vagal tone of any cause, medication toxicity, inferior myocardial infarction, and myocarditis. Patients with first-degree AV block without evidence of organic heart disease appear to have no difference in mortality compared with matched controls. In the setting of an acute coronary syndrome event, its appearance can indicate an increased chance of progression to complete heart block.

SECOND-DEGREE MOBITZ TYPE I (WENCKEBACH'S) ATRIOVENTRICULAR BLOCK

DESCRIPTION

In second-degree Mobitz type I (Wenckebach's) block, there is progressive prolongation of AV conduction (and the PR interval) until an atrial impulse is completely blocked; when an atrial impulse is blocked, no accompanying QRS complex is seen (**Figure 18-15** and **Table 18-18**). Conduction ratios indicate the ratio of atrial to ventricular depolarizations; for instance, a 4:3 ratio indicates that three of four atrial impulses are conducted into the ventricles. Usually, only one atrial impulse is blocked. After the dropped beat, the AV conduction returns to normal, and the cycle usually repeats itself with the same conduction ratio (fixed ratio) or a different conduction ratio (variable ratio). This type of block almost always occurs at the level of the AV node and is often due to reversible depression of AV nodal conduction.

Second-degree type I, or Wenckebach's, block occurs because each successive depolarization produces prolongation of the refractory period of the AV node. When the next atrial impulse comes upon the node, it is earlier in the relative refractory period, and conduction occurs more slowly relative to the previous stimulus. This process is progressive until an atrial impulse reaches the AV node during the absolute refractory period, and conduction is blocked altogether (**Figure 18-16A**). The pause allows the AV node to recover, and the cycle repeats. This cyclic occurrence produces a pattern of "grouped beating" and is apparent over successive cycles (**Figure 18-16B**).

TABLE 18-18 ECG Features of Second-Degree Mobitz Type I (Wenckebach's) Atrioventricular Block

- Progressive prolongation of PR interval until an atrial impulse is completely blocked: a P wave without accompanying QRS complex
- After the nonconducted beat, cycle repeats
- Grouped beating

CLINICAL SIGNIFICANCE

This block is often transient and usually associated with inferior myocardial ischemia, medication toxicity, or myocarditis, or after cardiac surgery. It may occur when a normal AV node is exposed to very rapid atrial rates. This block can also be a normal variant, not indicative of acute or chronic heart disease. Specific treatment is usually not necessary unless very slow ventricular rates produce signs of hypoperfusion, where most patients will respond to atropine.

SECOND-DEGREE MOBITZ TYPE II ATRIOVENTRICULAR BLOCK

DESCRIPTION

In second-degree Mobitz type II block, the PR interval remains constant across the rhythm strip, both before and after the nonconducted atrial beats (**Figure 18-17** and **Table 18-19**). Each P wave is associated with a QRS complex until a nonconducted atrial depolarization (i.e., P wave) is noted without accompanying QRS complex. Mobitz II blocks usually occur in the infranodal conducting system, often with coexistent fascicular or bundle branch blocks, and the QRS complexes therefore are usually wide. High-grade AV block is noted when more than one consecutive P wave is not conducted (Figure 18-17C).

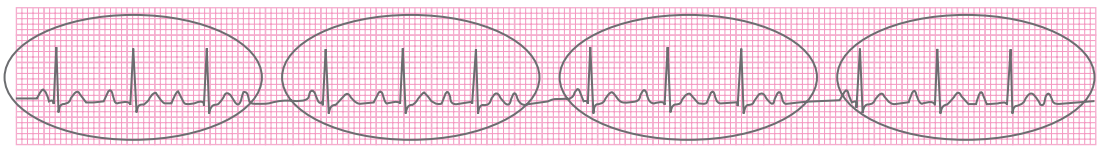
When second-degree AV block occurs with a fixed conduction ratio of 2:1, it is not possible to differentiate between type I (Wenckebach's) and type II block. If the QRS complex is wide, the block is more likely to be in the infranodal system. If the QRS complex is narrow, then the block is in the AV node or infranodal system with about equal incidence; it is



FIGURE 18-15. Second-degree, type I atrioventricular block. Note the nonconducted P waves (*arrows*).



A

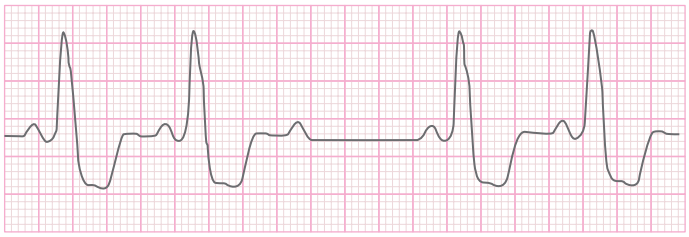


B

FIGURE 18-16. **A.** Second-degree, type I atrioventricular block. **B.** The cardiac rhythm strip illustrates the concept of grouped beating, or clustering of QRS complexes indicated by the ovals in the rhythm strip.



A



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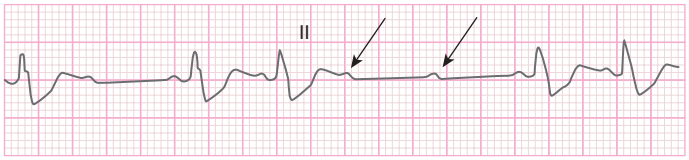


C

FIGURE 18-17. Three examples of second-degree, type II atrioventricular (AV) block: (**A**) with narrow QRS complex rhythm; (**B**) with wide QRS complex rhythm; and (**C**) with wide QRS complex rhythm and high-grade AV block indicated by two or more consecutive nonconducted P waves (*arrows*).

TABLE 18-19 ECG Features of Second-Degree Mobitz Type II Atrioventricular Block (AVB)

- PR interval remains constant.
- Each P wave is associated with a QRS complex until a nonconducted atrial depolarization (i.e., P wave) is noted without accompanying QRS complex.
- QRS complexes are usually widened, although a narrow complex is occasionally seen.
- High-grade AVB is noted when more than one consecutive P wave is not conducted.

recommended that the "worst case scenario" be assumed in such presentations and to consider the "untypeable" second-degree AV block a type II blockage.

CLINICAL SIGNIFICANCE

Type II blocks imply structural damage to the infranodal conducting system, are usually permanent, and may progress suddenly to complete heart block, notably with concomitant acute myocardial ischemia. Patients should have transcutaneous cardiac pacing pads applied in the ED in anticipation of possible need. Start emergent pacing when slow ventricular rates produce symptoms of hypoperfusion. Atropine can be tried, but the effect is inconsistent.[2,3] Most patients, especially in the setting of acute myocardial ischemia, will require eventual transvenous cardiac pacing.

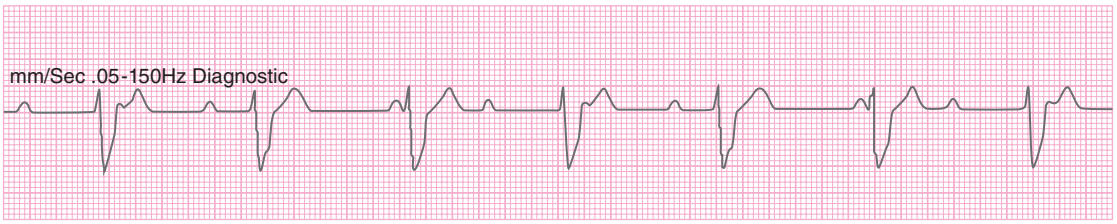
THIRD-DEGREE ATRIOVENTRICULAR BLOCK (COMPLETE HEART BLOCK)

DESCRIPTION

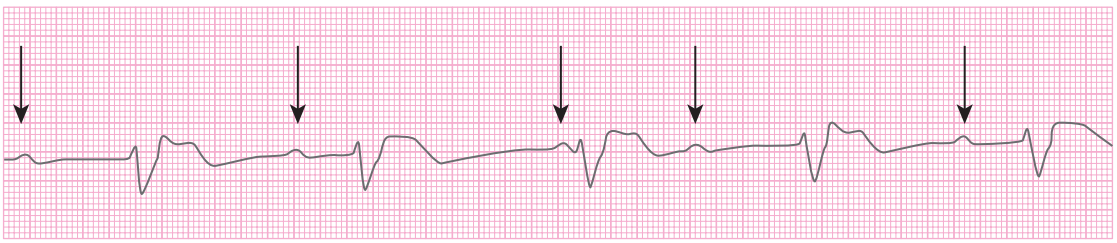
In third-degree AV block, there is no AV conduction (**Figure 18-18** and **Table 18-20**). An escape pacemaker (manifested by the QRS complex) paces the ventricles at a rate slower than the atrial rate manifested by the P wave. When third-degree AV block occurs in the AV node, a junctional escape pacemaker takes over with a ventricular rate of 40 to 60 beats/min. The QRS complexes are narrow because the rhythm originates above the bifurcation of the bundle of His. When third-degree AV block occurs at the infranodal level, the ventricles are driven by a ventricular escape rhythm at a rate slower than 40 beats/min. Third-degree AV blocks at the His bundle level can have a narrow or wide QRS complex, whereas blocks in the bundle branches or elsewhere in the Purkinje system invariably have escape rhythms with wide QRS complexes.

CLINICAL SIGNIFICANCE

Nodal third-degree AV block (i.e., with a narrow QRS complex) develops in up to 8% of inferior acute myocardial infarction patients and may last for several days. Infranodal third-degree AV blocks (i.e., with a wide QRS complex) indicate structural damage to the infranodal conducting system, as seen with an extensive anterior acute myocardial infarction. The ventricular escape pacemaker is usually inadequate to maintain cardiac output and the patient is unstable, with periods of ventricular asystole. When third-degree block is seen in acute myocardial infarction, mortality is increased, even with pacing.



A



B

FIGURE 18-18. Two examples of third-degree atrioventricular block. Both have an atrial rate of 83 with ventricular escape rate of 50. Not all P waves are visible; some are hidden by the QRS complex or T wave.

TABLE 18-20 ECG Features of Third-Degree Atrioventricular Block (Complete Heart Block)

- No association of P wave with QRS complexes
- Atrial rate greater than ventricular rate
- QRS complexes are usually widened; occasional narrow QRS complexes are seen
- Ventricular rate is regular

Infrequently, patients with complete heart block will present with minimal to no symptomatology; these patients require monitoring and admission. Manage the symptomatic patient with either medication and/or pacing. Nodal blocks may respond to atropine; infranodal blocks are unlikely to respond to atropine or other medications that can enhance AV nodal conduction. Patients should have transcutaneous cardiac pacer pads applied in the ED. If there is no or incomplete response to atropine, use transcutaneous cardiac pacing, recognizing that transvenous pacing is eventually necessary in most patients.

WIDE-COMPLEX TACHYCARDIAS

Wide-complex tachycardias are defined as a rhythm with a QRS complex duration greater than 100 milliseconds and a rate over 100 beats/min. Both ventricular tachycardia and supraventricular tachycardia with aberrant ventricular conduction present with wide QRS complexes (**Figure 18-19**).[5]

Traditional teaching, derived largely from coronary care units and electrophysiology laboratories, presents that 80% of wide-complex tachycardias are ventricular tachycardia.[66] However, in the ED, there is a range of pathophysiologic conditions that can produce delayed ventricular depolarization that, when combined with a sinus tachycardia induced by acute illness, results in a wide-complex tachycardia.[7] The conduction abnormality can be the result of a bundle branch block (new-onset, preexisting, or rate-related), metabolic abnormality (e.g., hyperkalemia), adverse medication effect (e.g., sodium channel blockade), or ventricular preexcitation syndrome. All supraventricular tachycardias can present as a wide-complex rhythms if intraventricular conduction is abnormal. In addition, two tachycardias seen in WPW syndrome will present with a widened QRS complex: the antidromic version of the AV nodal reentrant tachycardia and atrial fibrillation or flutter with ventricular depolarization predominantly or exclusively via the accessory tract.

VENTRICULAR TACHYCARDIA

DESCRIPTION

Ventricular tachycardia is the occurrence of three or more consecutive depolarizations from a ventricular ectopic pacemaker at a rate faster than 100 beats/min.[8] Ventricular tachycardia can occur in a nonsustained manner,[67] with short episodes, lasting several beats, with spontaneous termination, or it can occur in a sustained fashion, with longer episodes that typically require treatment.[8] Ventricular tachycardia can be further characterized according to hemodynamic effect (stable vs. unstable), morphology (monomorphic vs. polymorphic), or clinical presentation (perfusing vs. pulseless as during cardiac arrest).

The ECG features (**Figure 18-20** and **Table 18-21**) vary between the monomorphic and polymorphic varieties. Monomorphic ventricular tachycardia is the most commonly encountered form of ventricular tachycardia, accounting for about 70% of cases, and is usually very

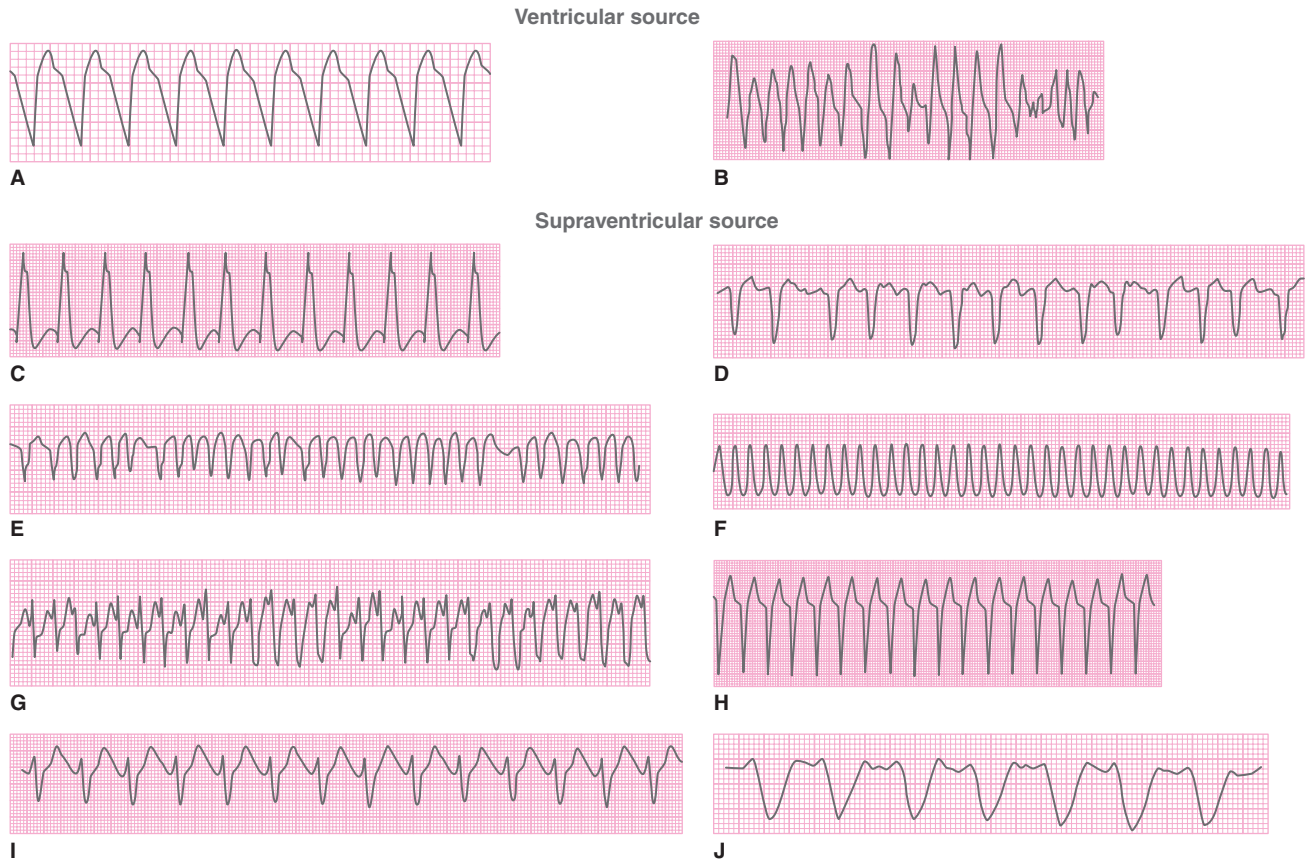


FIGURE 18-19. Wide-complex tachycardias. **A.** Ventricular tachycardia (monomorphic). **B.** Ventricular tachycardia (polymorphic). **C.** Sinus tachycardia with bundle branch block. **D.** Atrial fibrillation with preexisting bundle branch block. **E.** Preexcited atrial fibrillation in the Wolff-Parkinson-White syndrome. **F.** Atrioventricular reentrant tachycardia in the Wolff-Parkinson-White syndrome. **G.** Paroxysmal supraventricular tachycardia with rate-related bundle branch block in an infant. **H.** Paroxysmal supraventricular tachycardia with fixed (preexisting) bundle branch block. **I.** Sodium channel–blocker toxicity with wide-complex tachycardia. **J.** Wide-complex tachycardia in patient with severe hyperkalemia.

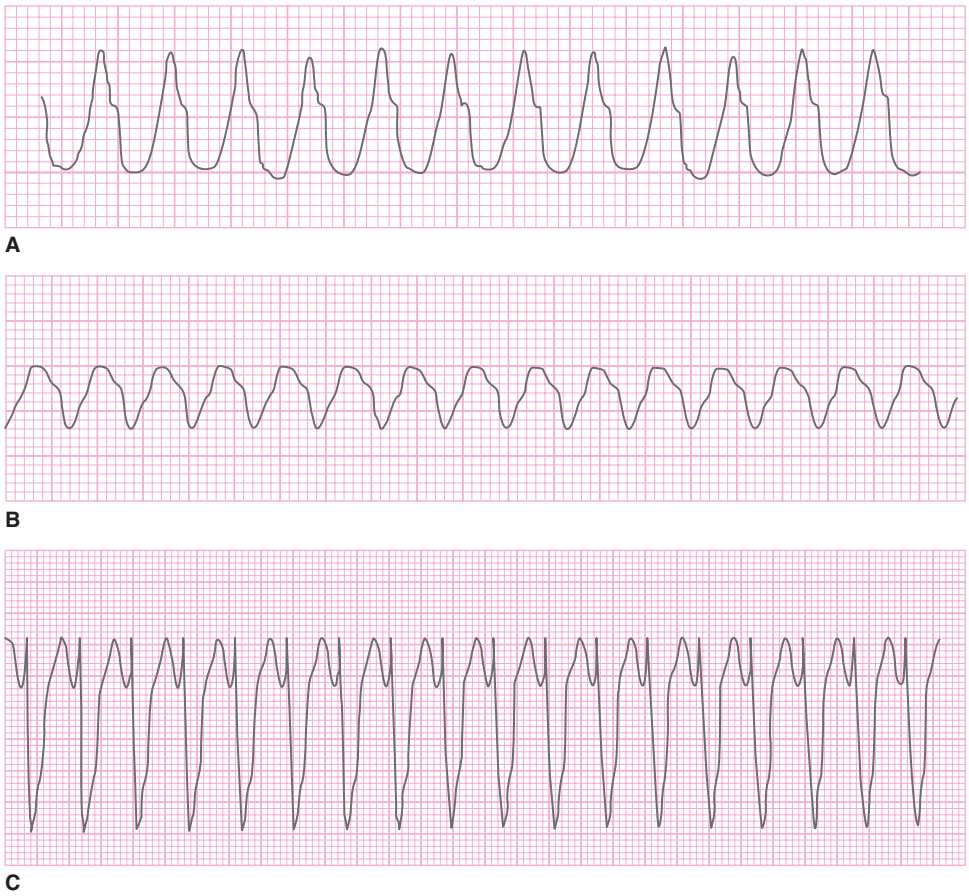


FIGURE 18-20. Three examples of monomorphic ventricular tachycardia. **A.** Ventricular tachycardia with a rate of 270 beats/min. **B.** Ventricular tachycardia with a rate of 220 beats/min. **C.** Ventricular tachycardia with a rate of 180 beats/min.

regular with rates most often in the 140 to 180 beats/min range. Medications, such as amiodarone, may slow the rate of ventricular tachycardia; such patients may present with ventricular rates of 110 to 130 beats/min. On rare occasions, monomorphic ventricular tachycardia may present with an irregular rhythm, but only minimally irregular as compared to an aberrantly conducted atrial fibrillation, which ordinarily manifests marked irregularity.

Polymorphic ventricular tachycardia has varying QRS morphology in any single ECG lead (**Figure 18-21** and Table 18-21). Variations in both the RR interval and electrical axis are also features of this form of ventricular tachycardia. Torsades de pointes, a specific subtype of polymorphic ventricular tachycardia, occurs in the setting of delayed myocardial repolarization manifested on the sinus rhythm ECG by a prolongation of the QT interval.[68] The French term *torsades de pointes* means "twisting of the points" and describes the appearance of the QRS complex as it varies in appearance (Figure 18-21B).

TABLE 18-21 ECG Features of Monomorphic and Polymorphic Ventricular Tachycardia

Monomorphic
- No P waves associated with QRS complex, occasional dissociated P wave
- Rapid and regular rhythm
- Rate usually 140–180 beats/min (range, 120–300 beats/min)
- Widened QRS complex >100–120 ms with consistent beat-to-beat morphology

Polymorphic
- No P waves associated with QRS complex; may have occasional dissociated P wave
- Rapid and irregular rhythm
- Rate 140–180 beats/min (range, 120–300 beats/min)
- Widened QRS complex >100–120 ms with inconsistent beat-to-beat morphology

CLINICAL SIGNIFICANCE

Ventricular tachycardia is rare in patients without underlying heart disease.[5] The most common causes of ventricular tachycardia are chronic ischemic heart disease and acute myocardial infarction, composing about 50% of all cases of symptomatic ventricular tachycardia. Less common causes of ventricular tachycardia include dilated or hypertrophic cardiomyopathy, valvular heart disease (including mitral valve prolapse), inherited ion channel abnormalities, and drug toxicity. Hypoxia, alkalosis, and electrolyte abnormalities, especially hyperkalemia, exacerbate the propensity for ventricular ectopy and tachycardia.

Torsades de pointes occurs when repolarization is delayed, and cardiac afterpotentials can initiate this form of polymorphic ventricular tachycardia. Delayed repolarization is seen in inherited (congenital long QT syndrome) and acquired (primarily drug toxicity) circumstances.[68] Torsades de pointes often occurs in bursts of up to 30 cycles before spontaneously stopping. Sustained torsades de pointes is uncommon and can potentially degenerate into ventricular fibrillation.

It is a misconception that patients with ventricular tachycardia are clinically unstable. Ventricular tachycardia cannot be reliably differentiated from supraventricular tachycardia with aberrant conduction on the basis of clinical symptoms or vital signs. Differentiation using the 12-lead ECG can be challenging and, at times, impossible (see discussion in next section).

TREATMENT

The management of ventricular tachycardia is based on the patient's clinical stability. The most extreme form of instability is cardiac arrest; these patients should receive prompt electrical defibrillation, chest compressions, and other advanced life support measures. Patients with a pulse but compromised by the ventricular tachycardia should undergo



FIGURE 18-21. Two examples of polymorphic ventricular tachycardia. **A.** Polymorphic ventricular tachycardia. **B.** Polymorphic ventricular tachycardia of the torsades de pointes subtype, with the characteristic pattern of progressively changing QRS complex amplitude and direction.

electrical cardioversion, coupled with administration of a procedural analgesia and sedation if clinical status allows. In the stable patient, pharmacologic agents are first-line therapy.[69]

Hemodynamically stable patients with ventricular tachycardia are treated with procainamide, amiodarone, lidocaine, or magnesium.[18] Procainamide is superior to amiodarone or lidocaine for converting patients with stable ventricular tachycardia.[16,17] The primary disadvantage of procainamide is the relatively slow dosing because rapid infusions can cause hypotension. If the patient deteriorates during pharmacologic treatment, proceed to electrical synchronized cardioversion, airway management, and sedation, if possible. Obtain a cardiology consult in stable patients with ventricular tachycardia refractory to standard pharmacologic therapy because unusual forms of this dysrhythmia may require electrophysiologic evaluation and treatment.[18]

Magnesium is primarily used as an antiarrhythmic agent in patients with known hypomagnesemia, QT interval prolongation, polymorphic ventricular tachycardia, or torsades de pointes.[70] Case reports describe the benefits of isoproterenol or phenytoin in torsades de pointes, but controlled studies are lacking.[71-73] Definitive treatment of torsades de pointes is ventricular pacing at a rate necessary to prevent the bursts of polymorphous ventricular tachycardia. Pacing is continued until the cause of QT prolongation (drug toxicity, electrolyte abnormality) is ameliorated.

UNDIFFERENTIATED WIDE-COMPLEX TACHYCARDIA

DESCRIPTION

A regular, wide-complex tachycardia can be either of ventricular origin (ventricular tachycardia) or due to a supraventricular tachycardia with aberrant conduction of the electrical impulse through the ventricles.[7] While the differentiation between ectopic beats of ventricular origin and those of aberrantly conducted supraventricular origin can be difficult, it is more so in sustained tachycardias with wide QRS complexes.

CLINICAL FEATURES

Traditional teaching emphasizes five ECG features as helpful in differentiating ventricular tachycardia from supraventricular tachycardia with aberrant conduction: irregularity, AV dissociation, fusion and capture beats, QRS duration, and QRS complex concordance, both negative and positive (**Figure 18-22**).[5,7] Ventricular tachycardia is usually very regular; and if irregular, the degree of irregularity is minimal (see Figures 18-20B and 18-22C). Marked irregularity is strongly suggestive of atrial fibrillation with bundle branch block; of course, torsades de pointes is also irregular, but the changing polarity of the QRS complex is usually quite apparent.

AV dissociation, where the atria and ventricles have separate independent pacemakers (Figure 18-22C), if noted, is strongly suggestive of ventricular tachycardia. In cases of ventricular tachycardia without retrograde conduction to the atria, the SA node continues to initiate atrial depolarization. Because atrial depolarization is completely independent of ventricular activity, the resulting P waves will be dissociated from the QRS complexes. AV dissociation is not common; it is noted in only approximately 10% of ventricular tachycardia patients.

Capture and fusion beats (Figure 18-22D) are potentially useful and suggest ventricular tachycardia. In the patient with ventricular tachycardia, an independent atrial impulse may occasionally cause ventricular depolarization via the normal conducting system; such a supraventricular impulse, if conducted and able to trigger a depolarization within the ventricle, will result in a different QRS complex morphology—different

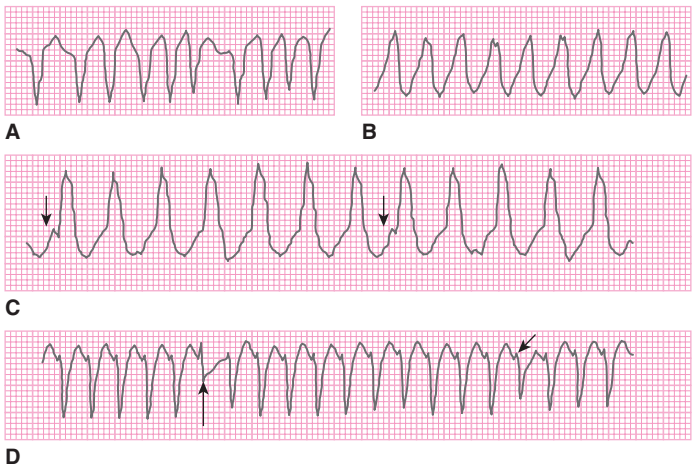


FIGURE 18-22. ECG considerations in the distinction of supraventricular tachycardia with aberrant ventricular conduction from ventricular tachycardia. **A.** Irregular rhythm in Wolff-Parkinson-White–related atrial fibrillation. **B.** Regular rhythm in ventricular tachycardia. **C.** Atrioventricular dissociation in ventricular tachycardia. The *arrows* indicate P waves, indicative of atrioventricular dissociation, which is strongly suggestive of ventricular tachycardia. **D.** Capture (*large arrow*) and fusion (*small arrow*) beats that are indicative of ventricular tachycardia.

TABLE 18-22 Methods for Wide-Complex Tachycardia Differentiation

Author and Year	Favors Ventricular Tachycardia (VT)	Favors Supraventricular Tachycardia with Aberrant Conduction (SVTAC)
Brugada, 1991[74]	VT diagnosed if, analyzed in sequence, any 1 of these 4 criteria is present: • Absence of RS complexes in all precordial leads • R to S interval >100 ms in one or more precordial leads • AV dissociation • Morphologic criteria for VT in leads V_1 and V_6 (V_1: monophasic R, qR, QS, or RS; and V_6: rS, QS, qR, or S > R)	SVTAC diagnosed if no to all 4 criteria for VT
Griffith, 1994[75]	VT diagnosed if no to either criteria for SVTAC	SVTAC diagnosed if both criteria are present: • QRS morphology classic for bundle branch block: LBBB (rS or QS in leads V_1 and V_2; time to S wave nadir in lead V_1 or V_2 >70 ms; R wave and no Q wave in V_6) *or* RBBB (rSR′ in lead V_1; RS in lead V_6; R wave larger than S wave in V_6) • No atrioventricular dissociation is seen
Lau, 2000[76]	Bayesian analysis starting with pretest odds for VT then multiply by likelihood ratio for VT associated with each of these factors: • QRS duration • QRS frontal plane axis • V_1 morphology with a RBBB pattern • V_1 and V_2 morphology with an LBBB pattern • Interval of initial R-wave deflection in V_6 • V_6 morphology VT diagnosed if posttest odds >3	SVTAC diagnosed if posttest odds <0.33
Vereckei, 2008[77]	VT diagnosed if, analyzed in sequence, any of these 4 criteria are present in lead aVR: • Initial R wave • Initial r or q wave >40 ms • Notch present on the initial descending limb of a predominantly negative QRS • Slow conduction at beginning of QRS: ratio of vertical distance traveled in voltage during the initial 40 ms (v_i) and terminal 40 ms (v_t); ratio of v_i/v_t <1	SVTAC diagnosed if none of the 4 criteria for VT are present
Pava, 2010[78]	VT diagnosed if time from isoelectric to peak of R wave in lead II is >50 ms	SVTAC diagnosed if not

Abbreviations: LBBB = left bundle branch block; RBBB = right bundle branch block.

than the other wide QRS complex beats. If the resulting QRS complex occurs earlier than expected and is narrow, the complex is called a **capture beat**; the supraventricular impulse electrically captures the ventricle, producing a narrow complex. The presence of capture beats strongly supports a diagnosis of ventricular tachycardia. **Fusion beats** occur when a sinus beat conducts to the ventricles via the AV node and joins, or fuses, with a ventricular beat originating from the abnormal ectopic focus. These two electrical "beats" combine, resulting in a QRS complex of intermediate width and differing morphology when compared to the other beats of ventricular tachycardia. As with capture beats, the presence of fusion beats is strongly suggestive of ventricular tachycardia. Fusion and capture beats occur infrequently and are seen in fewer than 10% of patients with ventricular tachycardia.

Ventricular tachycardia usually has a wider QRS complex than does supraventricular tachycardia with aberrancy, so extreme QRS durations >160 milliseconds argue in favor of ventricular tachycardia. Concordance describes that the polarity of the QRS complexes is consistent across the precordium, either all negative or positive from leads V_1 to V_6. Negative concordance, with all the precordial QRS complexes having a negative or downward deflection, suggests ventricular tachycardia.

In addition to these traditional characteristics, algorithms using ECG features have been created to assist in the differentiation of ventricular tachycardia versus supraventricular tachycardia with aberrancy (**Table 18-22**).[74-78] The algorithmic approach varies: the Brugada, Griffith, and Lau approaches use multiple leads and criteria; the Vereckei algorithm uses only lead aVR, although with four criteria; and the Pava algorithm uses only lead II and only one criterion. The Griffith approach is reversed from the other four; it assumes that the wide-complex tachycardia is ventricular in origin and then looks for evidence that favors supraventricular with aberrancy. Published comparisons are mixed regarding the sensitivity and specificity of these different algorithms, and neither has proven consistently superior.[79-83] Simplicity favors the Vereckei or Pava approaches.

TREATMENT

Before treating the patient, consider if the undifferentiated wide-complex tachycardia is due to either hyperkalemia or sodium channel blockade producing the widened QRS complex; both situations require specific therapy.

If the patient is hemodynamically unstable, assume the symptomatic wide-complex tachycardia is ventricular in origin and treat accordingly. In stable patients, response to adenosine has been described as helpful in differentiating ventricular from supraventricular wide-complex tachycardias, but rare forms of ventricular tachycardia can be responsive to adenosine, potentially missing the diagnosis because of conversion to sinus rhythm.[84] Not all wide-complex tachycardias require antiarrhythmic agents or urgent electrical therapy; consultation with a cardiologist for stable patients with unclear diagnosis is recommended.

VENTRICULAR FIBRILLATION

DESCRIPTION

Ventricular fibrillation is disorganized depolarization and chaotic contraction of small areas of ventricular myocardium absent any effective mechanical cardiac activity; there is no cardiac output. The ECG of ventricular fibrillation shows a fine, irregular pattern without discernible

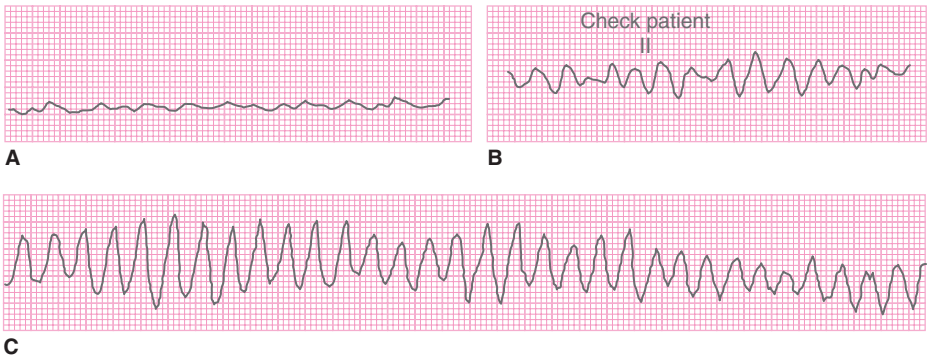


FIGURE 18-23. Three examples of ventricular fibrillation. **A.** Fine amplitude. **B.** Coarse amplitude. **C.** Coarse amplitude mimicking ventricular tachycardia.

P waves or organized QRS complexes. The irregular pattern itself can be coarse, intermediate, or fine in amplitude (**Figure 18-23**).

CLINICAL SIGNIFICANCE

Ventricular fibrillation is seen most commonly in patients with severe ischemic heart disease, with or without an acute myocardial infarction. Primary ventricular fibrillation occurs suddenly and without preceding hemodynamic deterioration, whereas secondary ventricular fibrillation occurs after a prolonged period of left ventricular failure and/or circulatory shock. In addition, direct stimulation of the myocardium by catheters or other instruments, electrocution, and direct blunt chest trauma (also known as *commotio cordis*) can induce ventricular fibrillation.

Treatment of pulseless ventricular tachycardia or fibrillation is with electrical defibrillation along with chest compressions and other advanced life support measures. If resuscitation is successful at restoring spontaneous circulation, address any dysrhythmic triggers including acute ischemia, metabolic derangements, or toxicologic insult.[18]

CONDUCTION AND REPOLARIZATION ABNORMALITIES

Inherited or acquired abnormalities in myocardial conduction or repolarization can provide the substrate for cardiac dysrhythmias.

WOLFF-PARKINSON-WHITE SYNDROME

DESCRIPTION

WPW syndrome is a form of ventricular preexcitation involving an accessory conduction pathway that bypasses the AV node and creates a direct electrical connection between the atria and ventricles.[85,86] WPW patients are prone to a variety of supraventricular tachydysrhythmias (**Table 18-23**). Ventricular fibrillation is rare in the WPW patient and often the result of therapeutic misadventure.

CLINICAL FEATURES

The classic triad of ECG findings (**Table 18-24** and **Figure 18-24**) seen in WPW is visible during sinus rhythm and is usually not detectable during tachydysrhythmias. The PR interval is shortened in sinus rhythm because the impulse moving through the accessory pathway is not subject to the physiologic slowing within the AV node. The ventricle is activated by two separate pathways, resulting in a fused, or slightly widened, QRS complex. The initial part of the complex, the delta wave, represents aberrant activation through the accessory pathway, while the terminal portion of the QRS complex represents normal activation through the His-Purkinje system from impulses traveling through the AV node. Due to altered ventricular depolarization, secondary repolarization changes are reflected in altered ST segments and T waves that are generally directed opposite (discordant) to the major delta wave and QRS complex. The delta wave may create Q waves that can mimic ECG changes associated with ischemic heart disease.

An incidental ECG may identify WPW in an otherwise asymptomatic individual. While such asymptomatic individuals will never develop tachydysrhythmias, a portion of patients do, and some rare patients experience ventricular fibrillation and cardiac arrest.[87] Electrophysiologic studies can identify patients with multiple accessory tracts and short refractory periods in those tracts and, thus, who are at increased risk for ventricular fibrillation and cardiac arrest.[88]

The most frequent dysrhythmia seen in the WPW patient is a reentrant tachycardia termed AV reciprocating tachycardia. In AV reciprocating tachycardia, the reentry circuit involves the AV node and the accessory pathway. AV reciprocating tachycardia is either orthodromic (anterograde conduction through the AV node with narrow QRS complex) or antidromic (retrograde conduction through the AV node with widened QRS complex). During orthodromic or anterograde AV reciprocating tachycardia (Table 18-23 and **Figure 18-25**), the atrial stimulus is conducted to the ventricle through the AV node with a return of the impulse back to the atria through the accessory pathway. Since the ventricles are stimulated solely via the normal His-Purkinje system, the QRS complexes are narrow and there is no delta wave. Orthodromic

TABLE 18-23 Dysrhythmias Seen in Symptomatic Wolff-Parkinson-White Syndrome

Atrioventricular reciprocating tachycardia (AVRT)

- **Narrow QRS complex tachycardia (orthodromic AVRT)—65%**
  - No P wave
  - Narrow QRS complexes
  - No delta wave
  - Rapid and regular
  - Ventricular rates ranging from 160–220 beats/min
  - Difficult to distinguish from paroxysmal supraventricular tachycardia
- **Wide QRS complex tachycardia (antidromic AVRT)—5%–10%**
  - No P wave
  - Widened QRS complexes with consistent QRS complex morphology
  - Rapid and regular
  - Ventricular rates ranging from 160–220 beats/min
  - Difficult to distinguish from ventricular tachycardia
- **Atrial fibrillation—25%**
  - No P wave
  - Widened QRS complexes with varying, bizarre QRS complex morphologies
  - Delta wave
  - Rapid and irregular
  - Ventricular rates usually >200 beats/min

TABLE 18-24 The ECG Triad of Wolff-Parkinson-White Syndrome During Sinus Rhythm

- PR interval <120 ms
- Slurring of the initial QRS complex, known as a delta wave
- Slightly widened QRS complex

AV reciprocating tachycardia accounts for approximately 65% of dysrhythmias seen in WPW patients and is difficult to distinguish from AV nodal reentrant tachycardia (i.e., typical paroxysmal supraventricular tachycardia).

In approximately 5% to 10% of symptomatic WPW patients, an antidromic (retrograde) AV reciprocating tachycardia occurs (Table 18-23 and **Figure 18-26**). In antidromic AV reciprocating tachycardia, the reentrant circuit conducts in the opposite direction, with anterograde conduction down the accessory pathway and return of the impulse retrograde to the atria via the AV node. With this pathway, the QRS complexes are wide; the ECG displays a very rapid, wide-complex tachycardia that looks like ventricular tachycardia.

Atrial fibrillation occurs in up to 25% of WPW patients with symptomatic dysrhythmias. The ECG features (Table 18-23 and **Figure 18-27**) of atrial fibrillation with WPW syndrome are a very fast ventricular rate due to the ability of the accessory pathway to conduct impulses into the ventricle faster than through the AV node and significant beat-to-beat variation in the QRS complex morphology resulting from a combination of the two impulses arriving at the ventricle and fusing to form a composite depolarization. This wide-complex dysrhythmia may appear relatively regular and can be misdiagnosed as ventricular tachycardia.[89]

TREATMENT

Treat all three tachydysrhythmias in the WPW patient according to the patient's clinical stability and the ECG features of the dysrhythmia. Use electrical cardioversion in patients with hemodynamic instability.

In the stable patient, therapy is guided by the QRS complex width and the regularity of the rhythm. In patients with a regular, narrow QRS complex tachycardia (i.e., orthodromic AV reciprocating tachycardia), the first intervention is vagal maneuver (Table 18-3). If this intervention fails, the next step would be IV adenosine (Table 18-2). If adenosine fails, then longer-acting AV nodal blocking agents, such as β-blockers and calcium channel blockers, are indicated. In refractory cases, procainamide is an effective agent that blocks conduction in the accessory conduction pathway and can terminate this reentrant tachycardia. If all medications are unsuccessful, the patient can be electrically cardioverted with appropriate sedation.

In stable patients with a wide QRS complex tachycardia, either regular (i.e., orthodromic AV reciprocating tachycardia) or irregular (atrial fibrillation), procainamide should be administered.[90] If unsuccessful, electrical cardioversion with appropriate sedation should be considered. Some antiarrhythmic medications can paradoxically enhance condition via the accessory tract, potentially enabling excessively rapid atrial activity to trigger ventricular fibrillation. Also, by blocking conduction through the AV node in WPW patients with atrial fibrillation, more of the rapid atrial depolarizations are able to initiate ventricular depolarization because competition from the normal conducting pathway is impaired, although evidence of adverse clinical outcome by such action is weak.[91] **Agents that can enhance conduction in the accessory tract and/or block conduction in the AV node should be avoided in WPW patients with wide-complex, both regular and irregular tachycardias; these include adenosine, amiodarone, β-blockers, and calcium channel blockers.[30]**

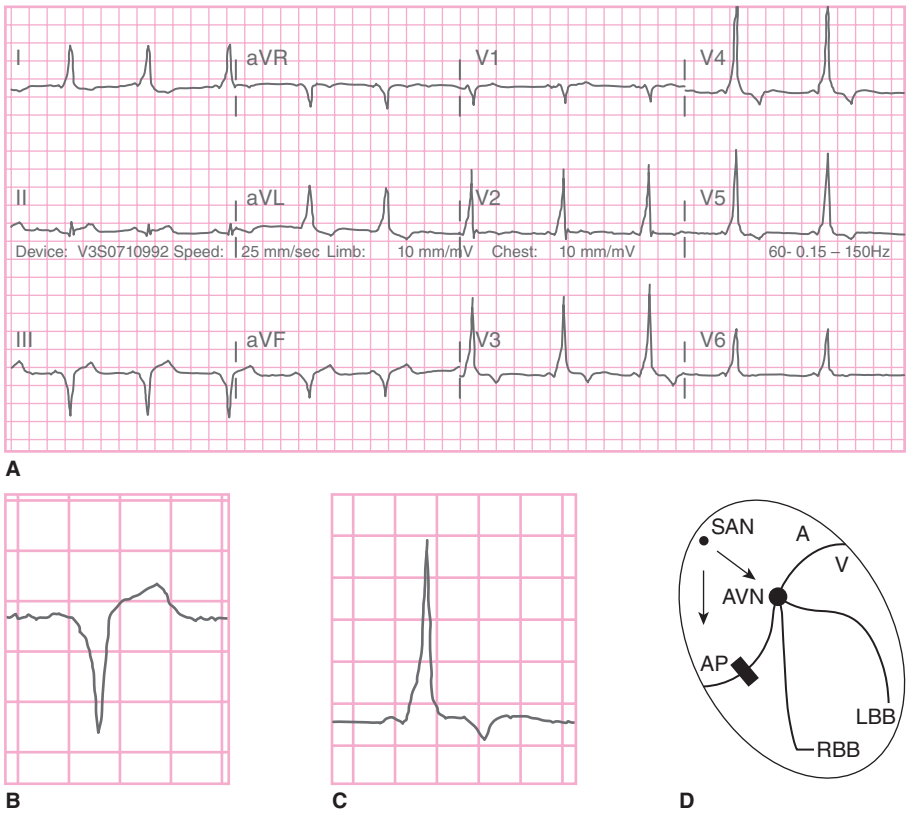


FIGURE 18-24. **A.** A 12-lead ECG of a patient with the Wolff-Parkinson-White (WPW) syndrome in sinus rhythm. **B** and **C.** Single P-QRS-T complex; note the shortened PR interval, delta wave, and widened QRS complex. **D.** The direction of cardiac impulse conduction in the WPW syndrome patient in sinus rhythm. The *two arrows* indicate the direction of the impulse, moving from atrial (A) tissues to ventricular (V) tissues via the accessory pathway (AP) and atrioventricular node (AVN). The impulse arrives at the ventricular tissues via the AVN and moves through ventricular tissues via the right bundle branch (RBB) and left bundle branch (LBB); the impulse also arrives at ventricular tissues via the AP and moves through ventricular tissues using cell-to-cell conduction. SAN = sinoatrial node.

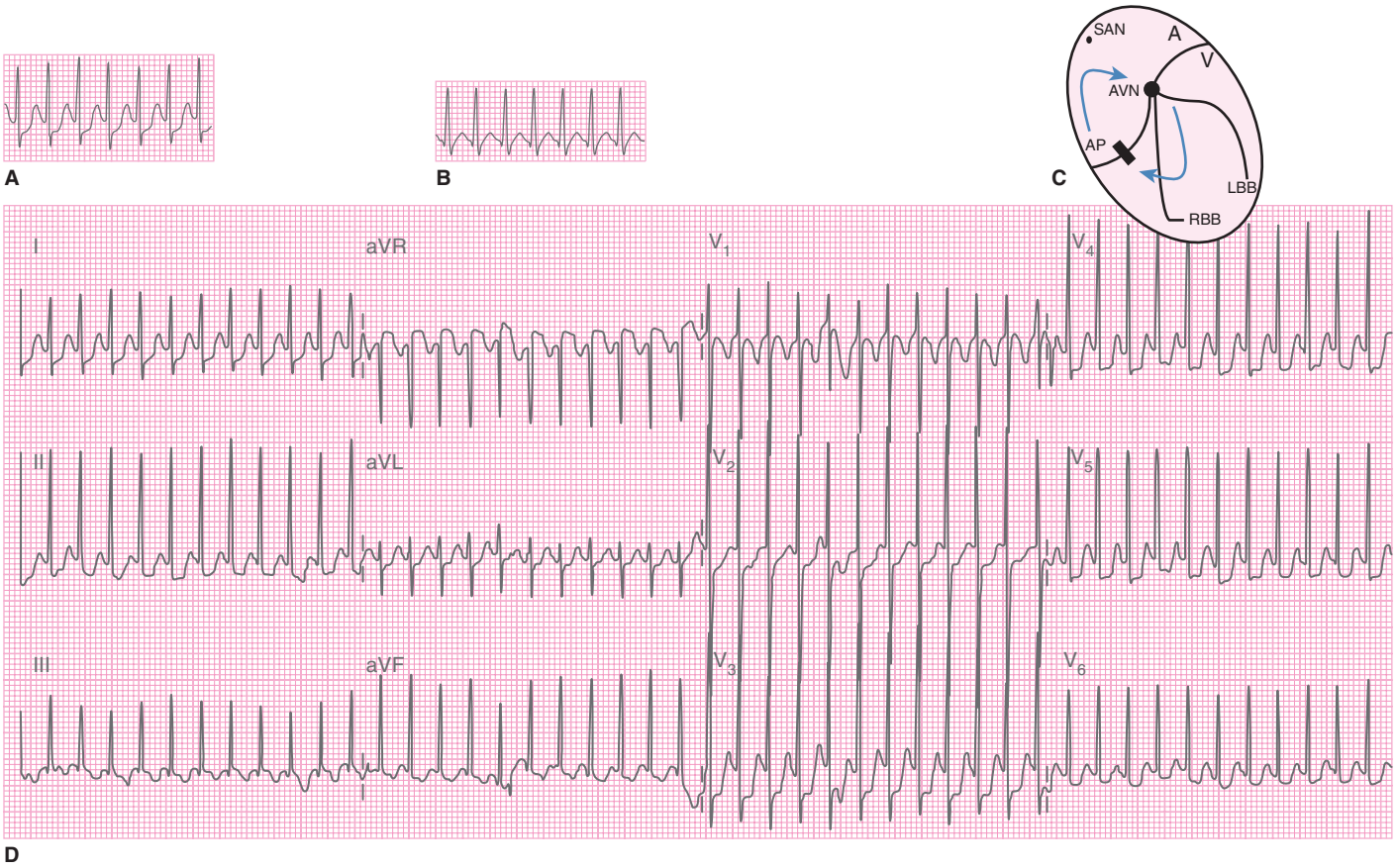


FIGURE 18-25. Narrow-complex tachycardia (orthodromic atrioventricular [AV] reciprocating tachycardia [AVRT]), the most common dysrhythmia of the Wolff-Parkinson-White syndrome. **A** and **B.** Rapid, regular, narrow QRS complexes without delta waves. **C.** The direction of cardiac impulse conduction in orthodromic AVRT; anterograde from atrial (A) tissues to ventricular (V) tissues through the AV node (AVN) and returning to the atrial tissues from ventricular tissues via the accessory pathway (AP). **D.** A 12-lead ECG demonstrating orthodromic AVRT. AP = accessory pathway; LBB = left bundle branch; RBB = right bundle branch; SAN = sinoatrial node.

After conversion, observe the patient with continuous cardiac rhythm monitoring and a repeat ECG. In general, patients who have rare episodes of tachydysrhythmias and who are stable after conversion can be discharged home with routine follow-up. Patients with frequent tachydysrhythmia episodes or who have an episode of atrial fibrillation with a very rapid ventricular response should be promptly referred for ablation of the accessory pathway. Patients who experience loss of consciousness during a known or possible tachydysrhythmia should be kept for observation due to the potential for repeat episode or cardiac arrest. Asymptomatic patients in whom WPW appears as an incidental finding should be referred to a cardiologist for further evaluation.[92]

BRUGADA SYNDROME

DESCRIPTION

Brugada syndrome is an inherited disorder of myocardial depolarization that predisposes young individuals to malignant ventricular

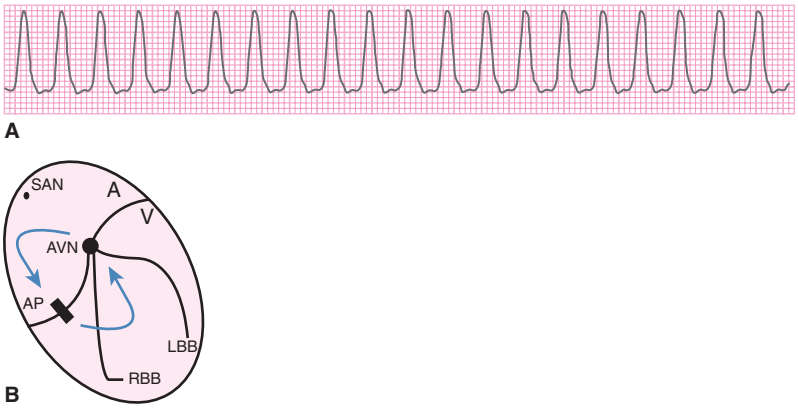


FIGURE 18-26. Antidromic atrioventricular (AV) reciprocating tachycardia (AVRT; wide-complex tachycardia). **A.** Wide-complex tachycardia that mimics ventricular tachycardia. **B.** The direction of cardiac impulse conduction in a Wolff-Parkinson-White syndrome patient during antidromic AVRT. The *two arrows* indicate the direction of the impulse movement, anterograde from atrial (A) tissues to ventricular (V) tissues through the accessory pathway (AP) and returning to the atrial tissues from ventricular tissues via the AV node (AVN). LBB = left bundle branch; RBB = right bundle branch; SAN = sinoatrial node.

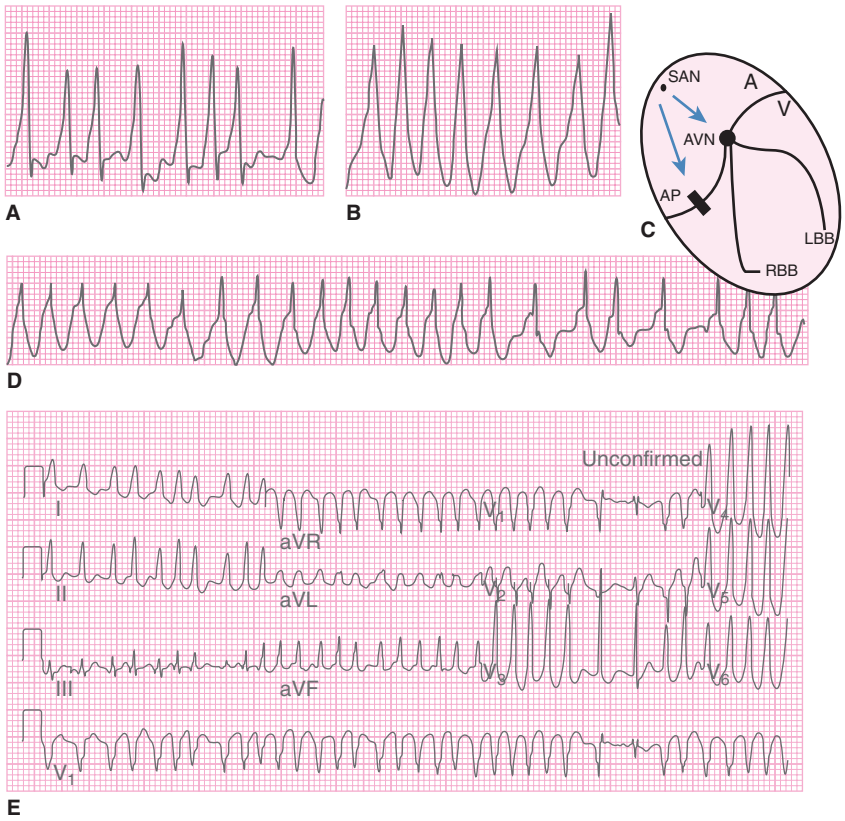


FIGURE 18-27. Atrial fibrillation in Wolff-Parkinson-White (WPW) syndrome. **A, B,** and **D.** Rapid, wide, irregular QRS complex tachycardia with varying QRS complex morphologies. **C.** The direction of cardiac impulse conduction in a WPW syndrome patient during atrial fibrillation. The *two arrows* indicate the direction of the impulse movement, both anterograde from atrial (A) tissues to ventricular (V) tissues through both the accessory pathway (AP) and the atrioventricular node (AVN). The larger of the two arrows indicates that the majority of impulses travel to the ventricular via the AP. **E.** A 12-lead ECG demonstrating a rapid, wide, irregular QRS complex tachycardia with varying QRS complex morphologies. LBB = left bundle branch; RBB = right bundle branch; SAN = sinoatrial node.

dysrhythmias and sudden death.[93-96] Congenital Brugada syndrome is due to mutations in the genes responsible for transmembrane sodium, calcium, or potassium ion channels in the heart.[97] Eight genetic mutations have been identified as producing a *channelopathy* that results in the Brugada syndrome.[98] Brugada syndrome occurs predominantly in males, and its prevalence varies dramatically among different ethnic groups; it is highest in East and Southeast Asian populations, relatively lower in groups originating from Western Europe, and less common in the Americas.

CLINICAL FEATURES

The majority of patients with Brugada syndrome are asymptomatic and are only found via an incidental ECG. Symptomatic patients present with palpitations, near to complete syncope, or seizures due to cerebral ischemia resulting from ventricular tachydysrhythmias.[96] Characteristic ECG changes are necessary for the diagnosis, but such changes are variable and not always evident (**Table 18-25** and **Figure 18-28**).[99] Fever and provocative testing with a sodium channel blocker (e.g., flecainide) may provoke surface ECG abnormalities associated with Brugada syndrome.

TABLE 18-25 ECG Patterns Associated With Brugada Syndrome in ECG Leads V_1 to V_3

Type 1	• Coved-shaped ST-segment elevation >2 mm • Followed by an inverted T wave
Type 2	• ST-segment elevation >2 mm • With a trough in the ST segment at least 1 mm deep • Followed by a positive or biphasic T wave • Producing a "saddleback" pattern

The type 1 pattern is considered diagnostic when combined with appropriate clinical or family history (**Table 18-26**). Type 2 is considered suggestive but not diagnostic of Brugada syndrome. Because type 2 may convert to type 1, either spontaneously or with provocative testing, further evaluation is recommended if there is an appropriate history.

Risk stratification is done to identify patients with Brugada syndrome at significant risk for malignant ventricular tachydysrhythmias.[100,101] In patients with aborted sudden cardiac death, the risk of recurrence of ventricular fibrillation is over 50% within 5 years.

TREATMENT

An important role for the emergency provider is to recognize this ECG pattern, especially in patients who present with symptoms, and to refer for appropriate follow-up.[102] Avoid exacerbating the underlying pathophysiology; do not use medications that possess sodium channel–blockade effects (http://www.brugadadrugs.org). Educate the patient on the importance of treating fever, with even minor infections. The only proven therapy to terminate malignant ventricular dysrhythmias and prevent

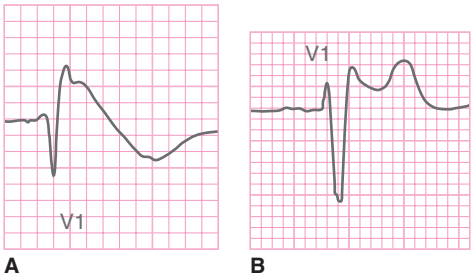


FIGURE 18-28. Brugada ECG pattern. **A.** Type 1. **B.** Type 2.

TABLE 18-26 Risk Stratification in Brugada Syndrome

Personal history	• Near or complete syncope • Seizure • Nocturnal agonal respiration
Aborted sudden cardiac death	• Polymorphous ventricular tachycardia • Ventricular fibrillation
Family history	• Family history of unexplained sudden cardiac death • Family history of coved-shaped ST segment (type 1) ECG pattern
Electrophysiologic study	• Inducibility of ventricular tachycardia or fibrillation with programmed stimulation

sudden death is implantable cardioverter-defibrillator placement.[96] Quinidine, a class Ia antiarrhythmic, is sometimes used as an adjunct with implantable cardioverter-defibrillator placement to reduce the incidence of dysrhythmias. Side effects (hepatitis, thrombocytopenia, and diarrhea) and the potential to induce torsades de pointes are cautions to quinidine's routine use.

LONG QT SYNDROME

DESCRIPTION

The long QT syndromes are characterized by prolongation of the QT interval (**Figure 18-29**) and a predisposition to ventricular tachydysrhythmias, including torsades de pointes and sudden cardiac death.[103-106] Congenital long QT syndrome is an inherited disorder due to mutations in cation channel genes (*channelopathies*).[98] Of the 13 described variants of congenital long QT syndrome, the three most common, accounting for about 90% of all cases, are mutations in a cardiac potassium channel for long QT syndrome types 1 and 2 and the sodium ion channel for long QT syndrome type 3.[105] With increased awareness and identification, the prevalence of congenital long QT syndrome is estimated to be 1 in 2000 live births. Acquired long QT syndrome can occur from electrolyte abnormalities (hypokalemia, hypomagnesemia), medication effects, and other disease states, such as acute coronary syndrome and severe left ventricular dysfunction.[107,108]

CLINICAL FEATURES

The normal QT interval corrected for heart rate (QTc) is up to 440 milliseconds in adult males and 460 milliseconds in adult females. The risk of dysrhythmias associated with long QT syndrome increases as the QTc prolongs, with moderate risk between 480 and 499 milliseconds and significantly higher risk when the QTc is greater than 500 milliseconds.[41] Syncope is the most common clinical feature and torsades de pointes is the most common dysrhythmia in symptomatic patients. A diagnostic scoring system has been created to assist in identifying patients with congenital long QT syndrome (**Table 18-27**).[109]

TREATMENT

An important role for the emergency provider is to recognize this ECG pattern, especially in patients who present with syncope, and to refer for appropriate follow-up.[102,110] Avoid exacerbating the underlying pathophysiology; do not use medications that possess channel blockade effects, impair cardiac repolarization, prolong the QT interval, and provoke tachydysrhythmias (https://crediblemeds.org/healthcare-providers/).[111] Correct underlying electrolyte abnormalities, especially



FIGURE 18-29. Long QT interval; QTc is 550 milliseconds.

TABLE 18-27 Diagnostic Score for Congenital Long QT Syndrome

Feature		Points
ECG*		
QTc	≥480 ms	3
	460–479 ms	2
	450–459 (male) ms	1
QTc ≥480 ms at 4th min of recovery from exercise stress test		1
T-wave alternans		1
Notched T waves in three ECG leads		1
Heart rate < second percentile for age (<50 in adults age 20–60)		0.5
Clinical History		
Syncope *or* episode of torsades de pointes (not both)	Torsades de pointes	2
	Syncope provoked by stress	2
	Syncope not provoked by stress	1
Congenital deafness		0.5
Family History		
Family members with definite long QT syndrome		1
Immediate family member <30 y old with unexplained sudden cardiac death		0.5
Scoring: Range, 0 to 10; 1.5 to 3 points = intermediate probability; ≥3.5 points = high probability		

*In absence of medications or conditions known to affect QT interval or T wave.

those of potassium and magnesium. β-Blockers are the initial treatment for symptomatic patients with congenital long QT syndrome.[112] Propranolol and nadolol are the most effective β-blockers, and patients with congenital long QT syndrome type 1 are the most responsive.

Lifestyle modifications are beneficial in congenital long QT syndrome.[113] Exercise is a trigger for lethal dysrhythmic events, especially in patients with congenital long QT syndrome type 1, where swimming is notably dangerous. Patients with congenital long QT syndrome type 2 are sensitive to decreased serum potassium and are at risk for lethal cardiac events triggered by emotions or being startled, such as being roughly aroused from rest or sleep.

SHORT QT SYNDROME

DESCRIPTION

Short QT syndrome is a rare but highly lethal entity associated with an increased risk of ventricular tachydysrhythmias.[114,115] As with long QT syndrome, short QT syndrome is an inheritable illness with demonstrated autosomal dominant pattern. The syndrome is primarily recognized by a shortened QT interval without any need to adjust for heart rate. Afflicted patients have otherwise structurally and functionally normal hearts.

CLINICAL FEATURES

Patients can be asymptomatic or present with palpitations, lightheadedness, syncope, or cardiac arrest due to ventricular dysrhythmias. The primary ECG feature is a shortened QT interval (<360 milliseconds), with QT intervals <340 milliseconds associated with increased risk of sudden death.[114,115] Other ECG features include tall, peaked T waves and a shortened J-point to T-wave apex less than 120 ms (the time interval from the J point to the top of the T wave).

A risk stratification tool is available using the following features: QT interval, J-point to T-wave peak, patient history of cardiac events (atrial fibrillation, unexplained syncope, known polymorphic ventricular

tachycardia or ventricular fibrillation, and/or sudden cardiac death), family history (close relative with sudden cardiac death, diagnosed syndrome, or sudden infant death syndrome), and identified mutations in one of eight known genes.[98,114,115]

TREATMENT

Asymptomatic, incidental discovery should result in cardiology referral. Symptomatic presentation with concerning findings should include cardiology evaluation and/or admission. Current recommendations are that an implanted defibrillator be placed in patients who have had episodes of ventricular tachycardia or fibrillation and be considered in those with a strong family history of sudden cardiac death.[115] Pharmacologic therapy with quinidine is recommended in symptomatic individuals and in asymptomatic patients with a strong family history of sudden cardiac death.[114,115]

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

DESCRIPTION

Arrhythmogenic right ventricular cardiomyopathy, also known as arrhythmogenic right ventricular dysplasia, is an inherited myocardial disease associated with sudden cardiac death.[116-118] The pathogenesis includes a fibrofatty replacement of right ventricular myocardium. The prevalence of arrhythmogenic right ventricular cardiomyopathy is 1 in 5000 to 10,000 persons; it is more common in men (3:1 male:female ratio) and those with a Mediterranean heritage. As with the other inherited arrhythmogenic disorders, a family history of unexplained (or explained) sudden cardiac death is present. Patients may also develop subacute to acute right ventricular heart failure, eventually progressing to biventricular failure.

CLINICAL FEATURES

Patients typically present with palpitations and syncope due to ventricular tachycardia, which may be transient or sustained. Other manifestations include circulatory shock, cardiac arrest, and right ventricular failure. ECG features suggestive of arrhythmogenic right ventricular cardiomyopathy include the following: epsilon wave (seen in 30% of patients); T-wave inversions in leads V_1 to V_3 (85% of patients); a prolonged S-wave upstroke (55 milliseconds) in leads V_1 to V_3 (95% of patients); QRS complex widening (110 milliseconds) seen in leads V_1 to V_3; and in patients with ventricular dysrhythmia, paroxysmal episodes of ventricular tachycardia with left bundle branch block morphology.[116,117]

The epsilon wave—a terminal irregularity of the QRS complex occurring at the J point—is the most specific finding of arrhythmogenic right ventricular cardiomyopathy yet is seen in only 30% of afflicted patients. A prolonged upstroke of the S wave of 55 milliseconds in the anterior leads is also suggestive of arrhythmogenic right ventricular cardiomyopathy.

The diagnosis of arrhythmogenic right ventricular cardiomyopathy is complex and based on a combination of clinical, ECG, biopsy, and echocardiographic features, with little application in the ED.[116,117] For the emergency provider, when the ECG demonstrates the combination of an epsilon wave and anterior ECG lead findings (deep S-wave upstroke and T-wave inversion), the diagnosis can be considered, particularly in a patient with palpitations, syncope, family history of sudden death, and/or resuscitation from cardiac arrest.[116]

TREATMENT

Asymptomatic discovery of an epsilon wave should prompt a referral to a cardiologist. Symptomatic patients with suggestive clinical features should be admitted for cardiology evaluation. Active dysrhythmias, most often a malignant ventricular dysrhythmia, are managed in standard manner.

Patients with high-risk features (e.g., prior history of cardiac arrest, ventricular tachydysrhythmias, or strong family history of sudden cardiac death) likely require insertion of an implantable cardiac defibrillator. Patients lacking high-risk features can be managed with β-blockers (e.g., sotalol) or amiodarone, as prescribed by a cardiologist. Persistent malignant dysrhythmias can be managed with ablation. Heart failure, whether right or biventricular, is managed in standard fashion.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 19

Pharmacology of Antiarrhythmics and Antihypertensives

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Benjamin Small

This chapter reviews common antiarrhythmic and antihypertensive medications administered in the ED. Acute medical conditions presenting with systemic hypertension and the specific recommended antihypertensive agents are presented in Chapter 57, "Systemic Hypertension." Antiarrhythmic medications treat cardiac rhythm abnormalities by modifying autonomic function or myocardial ion channels, leading to changes in conduction velocity or duration of the effective refractory period.[1] Long-term use of these agents to prevent arrhythmias has not been proven to reduce mortality[2-5]; however, this chapter focuses on medications used for acute pharmacologic conversion or rate control of common arrhythmias. In general, electrical cardioversion is preferable to pharmacologic conversion in patients who are hemodynamically unstable. The majority of antiarrhythmics are organized based on the Vaughan-Williams classification system (classes I to IV) (**Table 19-1**). This chapter also discusses the emergency applications of atropine, adenosine, magnesium, and isoproterenol.

CLASS I ANTIARRHYTHMICS: FAST SODIUM CHANNEL BLOCKERS

Class I agents block fast sodium channels and are further categorized based on their degree of blockade into classes Ia (moderate blockade), Ib (weak blockade), and Ic (strong blockade). They increase the excitability threshold, requiring more sodium channels to open in order to overcome the potassium current and generate an action potential. This effect

TABLE 19-1 Vaughan-Williams Classification of Antiarrhythmic Medications

Action	Class	Selected Example Medications
Sodium channel blockers	Class Ia	Procainamide
	Class Ib	Lidocaine
	Class Ic	Flecainide, propafenone
β-Blockers	Class II	Esmolol, labetalol, metoprolol, propranolol
Potassium channel blockers	Class III	Amiodarone, dronedarone, dofetilide, ibutilide, sotalol*, vernakalant†
Calcium channel blockers	Class IV	Diltiazem, verapamil, nicardipine

*Also a β-blocker.

†Not available in the United States; available in Canada and Europe.

TABLE 19-2 Procainamide Pharmacokinetics (Adults)

Distribution	Metabolism	Excretion	Half-Life	Onset/ Duration of Action
2 L/kg	Hepatic and renal Active metabolite: NAPA (renal elimination)	Urine, feces	Procainamide: 2.5–4.7 h NAPA: 6–8 h (prolonged with renal impairment)	Onset (IV): immediate Duration: 3–6 h

Abbreviation: NAPA = *N*-acetylprocainamide.

TABLE 19-4 Lidocaine Pharmacokinetics (Adults)

Distribution	Metabolism	Excretion	Half-Life	Onset/ Duration of Action
0.9–2.1 L/kg	Hepatic Active metabolites	Urine	Initial: 7–30 min Terminal: 1.5–2 h (prolonged in congestive heart failure, liver disease, and severe renal impairment)	Onset: 45–90 s Duration: 10–20 min

increases the refractory period and can be useful in terminating reentry currents. In addition, some class I agents block potassium channels and exhibit antimuscarinic effects.

PROCAINAMIDE

Actions Procainamide increases the refractory period, decreases automaticity and conduction, and prolongs cardiac action potentials through intermediate blockade of open sodium and potassium channels. *N*-Acetylprocainamide, the active metabolite of procainamide, lacks sodium channel effects but does block potassium channels, which can lead to QT prolongation.

Pharmacokinetics See **Table 19-2**.[6]

Indications Procainamide is indicated for life-threatening ventricular arrhythmias and supraventricular arrhythmias. Although it can be used to treat supraventricular tachycardia, the proarrhythmic nature of this agent (including torsades de pointes) and the risk of toxicity make procainamide less desirable for this indication. For hemodynamically stable ventricular tachycardias, procainamide, at a dose of 10 milligrams/kg, was shown in the PROCAMIO trial to be more effective than amiodarone, 5 milligrams/kg, for conversion to sinus rhythm (68% vs. 48%) with fewer adverse events (24% vs. 48%).[7] Procainamide should be avoided in patients with prolonged QT intervals or symptomatic congestive heart failure (CHF).[8,9] Procainamide is reported as an effective agent for rhythm control in atrial fibrillation of onset <48 hours.[10] The dose is not standardized, but one method is administering 1 gram of procainamide in 250 mL of 5% dextrose in water over 60 to 120 minutes with continuous cardiac and blood pressure monitoring. Stop the infusion for blood pressure <100 mm Hg or heart rate <60 beats/min or rate conversion.

Dosing and Administration See **Table 19-3**.[6]

Adverse Effects The most common adverse effects associated with procainamide are hypotension, cardiac conduction abnormalities, and rash. Serious adverse effects include prolonged QT interval, torsades de pointes, ventricular fibrillation, paradoxical increase in ventricular rate in atrial fibrillation/flutter, hepatotoxicity, and CHF.

LIDOCAINE

Actions Lidocaine is a class Ib agent with weak sodium channel–blocker properties that preferentially acts on ischemic myocardial tissue to decrease conduction; in addition, it has local anesthetic properties. Effects exerted on the cardiac action potential are negligible, with very minimal decrease to no effect on the QT interval and the refractory period.

Pharmacokinetics See **Table 19-4**.[6]

Indications Lidocaine is indicated in the acute management of ventricular arrhythmias. Consider lidocaine for patients with pulseless ventricular tachycardia or ventricular fibrillation as an alternative agent to amiodarone in patients unresponsive to CPR, defibrillation, and vasopressors. Also, consider lidocaine maintenance in the event of return of spontaneous circulation after lidocaine is used in the treatment of pulseless ventricular tachycardia/ventricular fibrillation.[8]

Dosing and Administration See **Table 19-5**.[6]

Adverse Effects Adverse effects of lidocaine are typically dose dependent or due to rapid bolus infusion rates. Lower infusion rates reduce adverse hemodynamic effects. Patients should be monitored for CNS effects, including numbness, speech impairment, somnolence, dizziness, and seizures.

PROPAFENONE AND FLECAINIDE

Class Ic agents, propafenone and flecainide, evoke strong blockade of fast sodium channels. They are most commonly used for supraventricular tachycardia because they slow conduction and frequently restore sinus rhythm. Propafenone has additional β-adrenergic–blocking properties; therefore, it can cause bradycardia and bronchospasm. It is more selective for cells with high rates of conduction. Flecainide reduces excitability primarily in the His-Purkinje system and ventricular myocardium. Both agents are indicated for the conversion of recent-onset atrial fibrillation (<7 days) to sinus rhythm.[11] They also carry indications for paroxysmal supraventricular ventricular tachycardia and ventricular tachycardia but are rarely used for these indications in the ED. Propafenone is given as a one-time oral dose of 450 milligrams (weight <70 kg) or 600 milligrams (weight ≥70 kg). Adverse effects include hypotension, bradycardia, bronchospasm, atrial flutter, and ventricular arrhythmias. Propafenone should be avoided in patients with CHF, coronary artery disease, structural heart disease, bronchospasm, or hepatic dysfunction. Flecainide is given as a one-time oral dose of 200 milligrams (weight <70 kg) or 300 milligrams (weight ≥70 kg). Adverse effects are similar to propafenone with the exception of bradycardia and bronchospasm. Flecainide should be avoided in patients with hypokalemia, atrioventricular block, coronary artery disease, significant structural heart disease, or CHF. Long-term use of these agents for arrhythmia prevention

TABLE 19-3 Procainamide IV Dosing and Administration (Adults) for Regular Wide-Complex Tachycardia*

- Initial: 20–50† milligrams/min ***OR*** 100 milligrams every 5 min until arrhythmia is suppressed, hypotension occurs, or the QRS complex is prolonged by 50% from its original duration (maximum dose: 17 milligrams/kg)
- Maintenance infusion rate: 1–4 milligrams/min

*Not recommended in patients with pulseless ventricular arrhythmias due to prolonged administration rate and unclear efficacy.

†Slower administration preferred if patient is stable.

TABLE 19-5 Lidocaine IV Dosing and Administration (Adults)

Ventricular Arrhythmia	Ventricular Fibrillation
Loading dose: 50–100 milligrams over 2–3 min. May repeat in 5 min (up to 300 milligrams in any 1-h period) Maintenance: 1–4 milligrams/min (start low in patients with liver dysfunction or CHF)	Initial dose: 1–1.5 milligrams/kg If refractory VF/pulseless VT, repeat 0.5–0.75 milligram/kg every 5–10 min (maximum total dose: 3 milligrams/kg)

Abbreviations: CHF = congestive heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.

in patients with cardiovascular disease, particularly after myocardial infarction, is associated with increased mortality.[3,12]

CLASS II ANTIARRHYTHMICS: β-BLOCKERS

β-Blockers have various indications, including hypertension, supraventricular ventricular tachycardia and ventricular arrhythmias, rate control in recurrent atrial fibrillation, and symptom control in thyrotoxicosis. Although these medications share the principal characteristic of blocking catecholamine effects on β-receptors, individual agents differ with respect to their cardioselectivity, α-adrenergic–blocking activity, intrinsic sympathomimetic activity, membrane-stabilizing effect, and pharmacokinetic properties (**Table 19-6**). β-Receptors are divided into two subtypes. β_1-Receptors are found in heart muscle, and β_2-receptors are found in bronchial and vascular smooth muscle. Nonselective β-blockers target all β-receptors, thereby affecting heart rate, conduction, and contractility, as well as smooth muscle contraction, thus increasing the risk of bronchospasm. In contrast, cardioselective agents have relative selectivity for β_1-receptors and decrease heart rate and blood pressure. These agents may be a better option for patients with a history of asthma, chronic obstructive pulmonary disease, or insulin-dependent diabetes because they are less likely to act on β_2-receptors. Because cardioselectivity is dose dependent, it decreases or is lost at higher doses. This is variable between agents, and the dose at which this occurs has not been clearly established.

With the exception of sotalol (discussed below), all listed β-blockers are indicated for the treatment of hypertension. These agents are also used for ventricular rate control in atrial fibrillation because they slow atrioventricular nodal conduction by decreasing sympathetic tone.

PROPRANOLOL

Actions Propranolol, a nonselective β-blocking agent, decreases heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand.

TABLE 19-6 Class II Antiarrhythmics: β-Blockers (Selected)

Generic Name	Onset of Action	Duration of Action	Metabolism	Half-Life	Indications	Adverse Effects
Noncardioselective						
Propranolol	Oral: 1–2 h IV: ≤1 min	Oral: IR: 6–12 h ER: 24–27 h IV: 4–6 h	Hepatic, extensive first-pass elimination	IR: 3–6 h ER: 8–10 h	HTN, supraventricular arrhythmias, ventricular tachycardias	Bradycardia, heart block, hypotension, worsening heart failure, bronchospasm
Propranolol dose	**Tachyarrhythmias:** 1–3 milligrams/dose slow IVP; may repeat every 2–5 min up to a total of 5 milligrams ***OR*** 0.5–1 milligram IV over 1 min; may repeat, if necessary, up to a total maximum dose of 0.1 milligram/kg ***OR*** 1 milligram IV over 1 min; may be repeated every 2 min up to 3 doses for rate control in patients with AFib **Oral**: 10–30 milligrams every 6–8 h for tachyarrhythmias					
Cardioselective						
Esmolol	IV: 2–10 min	IV: 10–30 min	In blood by RBC esterases	9 min	HTN, SVT, AFib/AFL (rate control)	Hypotension, bradycardia, heart block, injection site reaction, nausea, bronchospasm, pulmonary edema; abrupt discontinuation may cause rebound HTN or angina
Esmolol dose	500 micrograms/kg bolus (optional) over 1 min followed by an infusion starting at 50 micrograms/kg/min titrated to therapeutic effect in 50 micrograms/kg/min increments every 4 min to a maximum of 200 micrograms/kg/min. To achieve more rapid response, two additional 500 micrograms/kg bolus doses may be given prior to increasing the infusion rate to 100 micrograms/kg/min (after second bolus) and 150 micrograms/kg/min (after third bolus), as required. After 4 min at the rate of 150 micrograms/kg/min, the infusion rate may be increased to a maximum rate of 200 micrograms/kg/min (without an additional bolus dose).					
Metoprolol	Oral (IR): ≤1 h IV: 20 min	Oral: IR: variable ER: ~24 h IV: 5–8 h	Hepatic, extensive first-pass elimination	3–4 h	HTN, acute MI, angina	Bradycardia, heart block, hypotension, bronchospasm
Metoprolol dose	**AFib/AFL** (rate control): 2.5–5 milligrams IV every 2–5 min (maximum total dose: 15 milligrams IV over 10–15 min) **SVT**: 2.5–5 milligrams IV bolus over 2 min; may repeat within a 10-min period, up to 3 doses **HTN**: 1.25–5 milligrams IV every 6–12 h; titrate to response **Oral**: start 50 milligrams immediate release twice daily; maximum 200 milligrams twice daily					
Vasodilatory, Noncardioselective						
Labetalol	Oral: 20 min–2 h IV: ≤5 min	Oral: 8–12 h* IV: 16–18 h*	Hepatic, extensive first-pass elimination	Oral: 6–8 h IV: ~5.5 h	HTN	Orthostatic hypotension, heart failure, hyperkalemia, hepatotoxicity, bronchospasm, nausea, dizziness, fatigue
Labetalol dose	**Initial:** 10–20 milligrams IVP over 2 min; may administer additional injections using double the dose (maximum: 80 milligrams/dose) at 10-min intervals until target SBP is reached (up to 300 milligrams total cumulative dose) **Continuous infusion:** Initial: 0.5–2 milligrams/min; titrate to response (range: 2–10 milligrams/min) **Oral**: start 100 milligrams twice daily, maximum 400 milligrams twice daily					
Carvedilol	30–60 min	IR 14–20 h	Hepatic	IR 7–10 h	HTN	Hypotension, bradycardia, syncope, dizziness, hyperglycemia, weight gain
Carvedilol dose	6.25 milligrams orally twice daily, reduce dose if heart rate drops to <55 beats/min; if tolerated, may double dose in 2 wk as needed					

Abbreviations: AFib = atrial fibrillation; AFL = atrial flutter; ER = extended release; HTN = hypertension; IR = immediate release; IVP = IV push; MI = myocardial infarction; RBC = red blood cell; SBP = systolic blood pressure; SVT = supraventricular tachycardia.

*Dose dependent.

TABLE 19-7 IV to Oral Conversion of Metoprolol

Medication	IV to Oral Conversion
Metoprolol	5 milligrams IV = 12.5 milligrams oral

TABLE 19-8 IV to Oral Conversion of Labetalol

Medication	IV to Oral Conversion
Labetalol	Upon discontinuation of IV infusion, initiate 200 milligrams orally, followed in 6–12 h with an additional dose of 200–400 milligrams. Thereafter, dose patients with 400–2400 milligrams/d in divided doses depending on blood pressure response

For pharmacokinetics, indications, dosing and administration, and adverse effects, see Table 19-6.[6]

ESMOLOL

Actions Esmolol is a short-acting, selective β_1-antagonist that exhibits negative inotropic and chronotropic effects. By blocking β_1-receptors, esmolol prevents excessive adrenergic stimulation of the myocardium, thus causing an increase in sinus cycle length, prolongation of sinoatrial nodal recovery time, and a decrease in conduction through the atrioventricular node.

For pharmacokinetics, indications, dosing, administration, and adverse effects, see Table 19-6.

METOPROLOL

Actions Metoprolol is a selective antagonist of β_1-receptors and exerts its antihypertensive effects by decreasing cardiac output, reducing sympathetic outflow, and suppressing renin activity.

For pharmacokinetics, indications, and adverse effects, see Table 19-6. For dosing and administration, see Table 19-6 and **Table 19-7**.

LABETALOL

Actions Labetalol is a combined selective α_1-blocking and nonselective β-blocking agent with direct vasodilatory action. The β-blocking effects of labetalol are greater than the α_1-blocking effects, with ratios of 3:1 in the oral and 7:1 in the parenteral formulation. Labetalol is useful as an antihypertensive agent because it decreases heart rate, contractility, cardiac output, and total peripheral vascular resistance.

For pharmacokinetics, see Table 19-6.

Indications Labetalol is used primarily for its antihypertensive effects. It is used in patients with acute hypertensive emergencies where rapid blood pressure reduction is indicated (see Chapter 57, "Systemic Hypertension") and is considered safe for use in the treatment of hypertension in pregnancy (see Chapter 99, "Comorbid Disorders in Pregnancy," and Chapter 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period").

Dosing and Administration See Table 19-6 and **Table 19-8**. Once control of blood pressure has been established with IV labetalol, patients may transition to PO labetalol (Table 19-8).[6]

Adverse Effects See Table 19-6.

CARVEDILOL

Actions Carvedilol is a nonselective β-blocker and α-adrenergic blocker. Carvedilol reduces cardiac output, reduces exercise-induced tachycardia, reduces reflex orthostatic tachycardia, and prompts vasodilation and decreased peripheral vascular resistance, thereby reducing blood pressure. For patients with CHF, carvedilol lowers heart rate, increases stroke volume index, and decreases right atrial pressure.[6]

Indications Carvedilol is indicated for hypertension. Carvedilol is recommended for patients with compensated heart failure with reduced ejection fraction as an alternative or in addition to an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, which are considered first line.[13]

For pharmacokinetics, dosing and administration, and adverse effects, see Table 19-6.[6]

CLASS III ANTIARRHYTHMICS: INHIBIT POTASSIUM CURRENTS

Class III antiarrhythmic medications inhibit inward potassium currents (**Table 19-9**),[6] leading to a significantly longer refractory period. Myocardial tissue in a refractory state is resistant to reentrant conduction circuits that may produce arrhythmia. These agents prolong the QT interval, which is associated with significant risk for torsades de pointes. Clinical indications for class III antiarrhythmics are contrasted in **Table 19-10**.

AMIODARONE

Amiodarone is a "broad-spectrum" antiarrhythmic indicated in the acute management and chronic suppression of supraventricular ventricular tachycardia and ventricular arrhythmias. Potential benefits of amiodarone must be weighed against an array of potentially serious adverse effects, and clinical use is further complicated by distinctive pharmacokinetics and significant drug interactions.

Actions Amiodarone possesses properties of all four classes of antiarrhythmics (**Table 19-11**).[6,14]

Pharmacokinetics See **Table 19-12**.[6] Amiodarone is highly lipophilic and extensively distributed to bodily tissues.[15] Although IV amiodarone produces a rapid antiarrhythmic effect, it quickly redistributes from the serum into tissue, causing a precipitous drop in serum concentration.[16] Therefore, large oral or IV loading doses, generally given over a week or more, are needed to fill this large tissue reservoir and achieve sustained serum concentrations. As tissue stores become saturated after long-term oral therapy, terminal-phase elimination dominates and is characterized by a long half-life and duration of action.

Indications See **Table 19-13**.[8,11,17-19]

TABLE 19-9 Pharmacology of Class III Antiarrhythmic Agents

	Ion Channels and Receptors Antagonized				
	K^+ Channels	Na^+ Channels	Ca^{2+} Channels	β-Adrenergic	α-Adrenergic
Amiodarone	+	+	+	+	+
Dronedarone	+	+	+	+	+
Sotalol	+			+	
Dofetilide	+				
Ibutilide	+*	Activates a slow inward Na^+ current			
Vernakalant	+†	+†			

*Lesser effect.

†Ultrarapid and acetylcholine K^+ currents.

TABLE 19-10 Class III Antiarrhythmic Indications

	Clinical Indications	
	Supraventricular Arrhythmias	Ventricular Arrhythmias
Amiodarone	Acute rate control or cardioversion and maintenance of sinus rhythm*	Acute management of life-threatening arrhythmias; chronic suppression
Dronedarone	AFib (history of paroxysmal or persistent, but currently in sinus rhythm) to reduce risk of hospitalization	No
Sotalol	AFib or AFL	Monomorphic VT†
Dofetilide	AFib or AFL; conversion to and maintenance of sinus rhythm	No
Ibutilide	Acute cardioversion of AFib or AFL	No
Vernakalant	Acute cardioversion of AFib‡	No

Abbreviations: AFib = atrial fibrillation; AFL = atrial flutter; VT = ventricular tachycardia.

*Off-label.

†Off-label in United States, but guideline recommended with IV formulation if available.

‡Approved in Europe but not available in United States.

TABLE 19-11 Electrophysiologic and Electrocardiographic Effects of Amiodarone

Ion Channels and Receptors	Effects on Cardiac Electrophysiology	Effects on the ECG
Blocks inactivated Na^+ channels Noncompetitive blockade of α- and β-adrenergic receptors Blocks inward K^+ channel rectifier Blocks myocardial Ca^+ channels	Prolongs the refractory period Decreases sinoatrial node function Slows atrioventricular node conduction Modifies automaticity of Purkinje fibers	Decreases heart rate and may cause sinus bradycardia Prolongs: PR interval QRS interval* QT interval*

*More common with chronic oral administration than with acute IV use.

Dosing and Administration See **Table 19-14**.[6] IV amiodarone is associated with bradycardia, hypotension, and phlebitis. Hypotension may be dose and infusion rate dependent; therefore, infusion rates should not exceed 30 milligrams/min, and total daily doses should not exceed 2.2 grams. Preparations of IV amiodarone should be mixed in 5% dextrose in water, as amiodarone has precipitated in compatibility studies with normal saline.[20] Dose adjustments are not required for renal insufficiency but should be considered for severe hepatic dysfunction.

Adverse Effects See **Table 19-15**.[6,21] Long-term amiodarone has many common, serious, and potentially fatal adverse effects that limit

TABLE 19-13 Acute Intravenous Amiodarone Clinical Indications

Indications	Comments
Atrial fibrillation Ventricular rate control	Consider the potential risks of cardioversion (thromboembolic complications)* Consider when other measures are ineffective or contraindicated† Considered a first-line option in patients with HF† Avoid IV amiodarone in patients with WPW syndrome who have preexcited atrial fibrillation as it is potentially harmful and can accelerate the ventricular rate†
Atrial fibrillation Pharmacologic Cardioversion	Not first line; considered a reasonable option for pharmacologic cardioversion† Acceptable option in patients with structural heart disease† Slow onset; average time to cardioversion is 24 h
VT Monomorphic, sustained	A first-line agent for hemodynamically stable VT*
VT Polymorphic, not associated with long QT interval	If not associated with long QT interval (i.e., TdP)* Polymorphic VT with normal QT interval may be associated with myocardial ischemia, and amiodarone may be effective in arrhythmia suppression*
Pulseless VT or VF	Antiarrhythmic of choice in ACLS algorithm*

Abbreviations: ACLS = advanced cardiovascular life support; HF = heart failure; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

*2015 ACLS guideline recommendation.

†2014 American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society atrial fibrillation management guideline recommendation.

TABLE 19-14 Amiodarone IV Dosing and Administration by Indication

Indications	Dosing and Administration
Cardiac Arrest (refractory to defibrillation) Pulseless ventricular tachycardia Ventricular fibrillation	300 milligrams rapid bolus (may give undiluted) May give a single repeat 150 milligrams bolus if needed
Ventricular tachycardia with pulses Stable monomorphic Polymorphic with normal QT interval	150 milligrams in 100 mL of D5W over 10 min, followed by infusion at 1 milligram/min for 6 h, then 0.5 milligram/min for the next 18 h If breakthrough arrhythmia occurs, may give repeat 150-milligram boluses over 10 min Maximum total daily dose is 2.2 grams
Atrial fibrillation/atrial flutter Conversion to sinus rhythm To control rapid ventricular rate due to accessory pathway conduction in preexcited atrial arrhythmias	

Abbreviation: D5W = dextrose 5% in water.

TABLE 19-12 Amiodarone Pharmacokinetics

Absorption	Distribution	Metabolism	Excretion	Half-Life	Onset/Peak/Duration of Action
Oral BA: 35%–65% Slow and variable GI absorption	Oral: V_d: 66 L/kg (range: 18–148 L/kg) Plasma protein binding: >96%	Hepatic via CYP450 3A4 and 2C8 Active metabolite	Feces; urine (<1% as unchanged drug)	IV single dose: 9–36 d Oral chronic therapy: 40–55 d	Onset Oral: 2 d–3 wk IV: initial effects rapid Peak 1 wk–5 mo Duration (variable) 2 wk to several mo

Abbreviations: BA = bioavailability; V_d = volume of distribution.

TABLE 19-15 Amiodarone Adverse Effects*

Cardiovascular	Sinus bradycardia (5% with oral) Ventricular arrhythmias Torsades de pointes (<1%) Increased risk with: Concomitant QT_c-prolonging agent Hypokalemia, hypomagnesemia Female gender Thrombophlebitis (consider in-line IV filter if given via peripheral IV) Atrioventricular nodal block Hypotension (16% with IV); may be related to infusion rate or the IV solution emulsifier polysorbate 80
CNS	Paresthesias and peripheral neuropathy Dizziness
GI	Nausea/vomiting, anorexia, constipation (10%–33% with oral) Usually responds to a dose reduction or divided doses
Hepatic	Increased liver enzymes (15%–50%) Hepatic injury is typically mild and reversible, but liver failure and death have been reported Monitor baseline LFTs and every 6 mo thereafter
Pulmonary	Pulmonary toxicity (2%–7%, as high as 17%) May be most serious adverse effect other than cardiac. Often reversible, but fatalities have been reported after only 8–14 d of treatment Various manifestations Pulmonary fibrosis, eosinophilia, interstitial pneumonia, allergic alveolitis Monitor baseline PFTs and chest radiograph; repeat chest radiograph annually
Thyroid	Hypothyroidism, more common (4%–22% in some studies) Hyperthyroidism (3%–10%) Hyperthyroidism may diminish antiarrhythmic effect Monitor thyroid function at baseline and every 3–6 mo thereafter
Pregnancy	Contraindicated in pregnancy

Abbreviations: LFTs = liver function tests; PFTs = pulmonary function tests.

*Incomplete listing: excludes nonacute/non–life-threatening dermatologic, ocular, and other effects.

widespread clinical use and require regular monitoring of liver, pulmonary, thyroid, and ocular function. Although amiodarone prolongs the QT interval, it has a relatively low incidence of torsades de pointes even in patients with structural heart disease.[22]

Amiodarone is responsible for many clinically significant drug interactions. As a strong inhibitor of hepatic enzymes, amiodarone can increase serum concentrations of many other medications. Amiodarone may also augment the effects of medications that concomitantly prolong the QT_c interval or cause bradycardia. Specific dose reductions are recommended for colchicine, digoxin, warfarin, procainamide, quinidine, simvastatin, and lovastatin when used concomitantly with amiodarone. Given the extremely long half-life of amiodarone, drug interactions may persist for months after discontinuation of therapy.

DRONEDARONE

Actions Dronedarone is a noniodinated, less lipophilic derivative of amiodarone, designed to have fewer adverse effects. It is categorized as a class III antiarrhythmic, but has all four antiarrhythmic class effects and also blocks α-adrenergic receptors. Electrophysiologic action is primarily mediated through class III antiarrhythmic effects by prolonging the refractory period.[6]

Pharmacokinetics See **Table 19-16**.

TABLE 19-16 Dronedarone Pharmacokinetics

Absorption	Distribution	Metabolism	Excretion	Half-Life
Bioavailability Fasting: 4% High-fat meal: 15%	V_d: ~1400 L Plasma protein binding: >98%	Hepatic via CYP450 3A4 Active metabolite	Primarily as metabolites Feces: 84% Urine: ~6%	13–19 h

Abbreviation: V_d = volume of distribution.

Indications Dronedarone is indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation.

Dosing and Administration The dose of dronedarone is 400 milligrams orally twice daily, and it should be administered with food to increase bioavailability. Coadministration with grapefruit or grapefruit juice is contraindicated, as this may increase serum concentrations.

Contraindications and Adverse Effects See **Table 19-17**. Compared to amiodarone, dronedarone has lower rates of pulmonary toxicity and has not demonstrated adverse effects on thyroid function. Two clinical trials with dronedarone were prematurely discontinued due to significantly higher rates of serious adverse events in the dronedarone treatment groups, prompting black box warnings that dronedarone is contraindicated in severe or decompensated heart failure and in patients with permanent atrial fibrillation.[5,23] It is also contraindicated in pregnancy. ECGs should be monitored every 3 months while on dronedarone. If the patient is found to be in atrial fibrillation, he or she should be cardioverted (if clinically indicated) or dronedarone should be discontinued. Liver function should also be monitored periodically, especially during the first 6 months of therapy.

SOTALOL

Actions Sotalol is a noncardioselective β-blocker that exhibits electrophysiologic characteristics of class III antiarrhythmics, thus prolonging repolarization and refractoriness without affecting conduction.

Pharmacokinetics The onset of action of sotalol is 1 to 2 hours for the oral formulation and 5 to 10 minutes after IV administration. The

TABLE 19-17 Contraindications and Significant Adverse Effects of Dronedarone

Contraindications	Patients with NYHA class IV HF or NYHA class II–III HF with recent decompensation requiring referral to a specialized HF clinic Permanent AFib (in patients in whom sinus rhythm will not or cannot be restored) Severe hepatic impairment or previous liver or lung toxicity with amiodarone Bradycardia <50 beats/min, QT_c ≥500 ms or PR interval >280 ms, second-degree or third-degree AV block or sick sinus syndrome (except when used with a pacemaker) Drug–drug interactions with strong CYP450 inhibitors and QT_c-prolonging medications Pregnancy
Significant adverse effects	Cardiovascular New-onset or worsening HF; QT_c prolongation Hepatic Severe liver injury, including acute liver failure Renal Upon initiation, serum creatinine may increase ~0.1 milligram/dL Respiratory Interstitial lung disease; pulmonary fibrosis and pneumonitis

Abbreviations: AFib = atrial fibrillation; AV = atrioventricular; HF = heart failure; ms = milliseconds; NYHA = New York Heart Association.

elimination half-life is 12 hours and increases with renal dysfunction. Sotalol is eliminated unchanged in the urine.

Indications Sotalol is an effective agent for the suppression of life-threatening ventricular arrhythmias refractory to other antiarrhythmic drugs. It can suppress supraventricular ventricular tachycardia and atrial fibrillation, but is not indicated for cardioversion of atrial fibrillation.[11]

Dosing and Administration The recommended dose of IV sotalol for hemodynamically stable monomorphic ventricular tachycardia is 1.5 milligrams/kg infused over 5 minutes. The usual oral starting dose is 80 milligrams twice daily, titrated to a typical maintenance dose of 160 to 320 milligrams per day. Patients with renal insufficiency (creatinine clearance of 40 to 60 mL/min) require a dose frequency reduction of 50%, and sotalol should not be used (except in special cases) if creatinine clearance is <40 mL/min. During initiation of sotalol therapy, pretreatment QT_c should be <450 milliseconds, QT_c intervals should be monitored after each dosage administration, and therapy should be discontinued or the dosage reduced if QT_c measures ≥500 milliseconds. Hypokalemia and hypomagnesemia should be corrected prior to initiation to minimize the risk of torsades de pointes.

Adverse Effects The most common adverse effects of sotalol are bradycardia and hypotension. Sotalol does possess a significant proarrhythmic effect with a 4.3% rate of new or worsened ventricular arrhythmias and a 2.4% rate of torsades de pointes.[24]

DOFETILIDE

Actions and Indications Dofetilide is a pure class III antiarrhythmic and is indicated for the conversion to, and maintenance of, normal sinus rhythm in patients with atrial fibrillation or atrial flutter. Because dofetilide has a significant proarrhythmic effect, it is reserved for patients in whom atrial fibrillation or atrial flutter is highly symptomatic and alternative safer agents are contraindicated or otherwise not desired.[11] Hospitalization is required for 3 days upon initiation of therapy to allow for monitoring of QT_c interval, continuous ECG, and creatinine clearance. The U.S. Food and Drug Administration announced the elimination of the Risk Evaluation and Mitigation Strategy for dofetilide (Tikosyn®) on March 9, 2016.[25]

Adverse Effects Serious adverse effects of dofetilide are ventricular tachycardia and QT_c interval prolongation, which can result in torsades de pointes.

Drug Interactions **Dofetilide therapy is contraindicated with concomitant verapamil**, hydrochlorothiazide, cimetidine, ketoconazole, trimethoprim, prochlorperazine, megestrol, and dolutegravir because these medications may cause an increase in dofetilide plasma concentration.

IBUTILIDE

Actions and Pharmacokinetics Ibutilide prolongs the refractory period in atrial and ventricular cardiac tissues. This action is caused by activation of a slow inward sodium current. Blockade of the delayed rectifier potassium current, which slows repolarization, may also contribute to its clinical effects. The onset of action of ibutilide is ≤90 minutes after starting the infusion. Ibutilide is metabolized in the liver, is excreted in the urine and feces, and has a half-life of approximately 6 hours after IV administration.

Indications, Dosing and Administration, and Adverse Effects Ibutilide is indicated for the rapid conversion of recent-onset atrial fibrillation or atrial flutter to sinus rhythm.[11] If effective, cardioversion is expected to occur within 1 hour of administration. Ibutilide is also recommended to restore sinus rhythm or slow ventricular rate for patients with preexcited atrial fibrillation and rapid ventricular rate who are not hemodynamically compromised.[11] For patients with atrial fibrillation and an accessory pathway, ibutilide is considered a reasonable option for pharmacologic cardioversion.[19] A 2018 ED trial reported a 50.5% conversion rate for atrial fibrillation and a 75% conversion rate for atrial flutter.[26] The loading dose is 1 milligram IV (weight ≥60 kg) or 0.01 milligram/kg IV (weight <60 kg) over 10 minutes and may be repeated once every 10 minutes after completion of the first dose. ECG monitoring is continued for at least 4 hours or until the QT_c interval returns to baseline. Cardiovascular adverse effects of ibutilide include hypotension, hypertension, bradycardia, sinus arrest, syncope, QT_c interval prolongation, CHF, and torsades de pointes. Hypokalemia and hypomagnesemia should be corrected prior to initiation to minimize the risk of torsades de pointes.

VERNAKALANT

Vernakalant is a class III antiarrhythmic that inhibits sodium and potassium currents. The atria are more susceptible to vernakalant-induced refractory period prolongation. Vernakalant is not U.S. Food and Drug Administration approved for use in the United States due to concerns over safety.[27] In Europe and Canada, vernakalant is indicated for rapid conversion of recent-onset atrial fibrillation in adults at a dose of 3 milligrams/kg over 3 minutes.[28] Compared to other agents, vernakalant has the shortest median time to conversion (8 to 11 minutes).[29]

CLASS IV ANTIARRHYTHMICS: CALCIUM CHANNEL BLOCKERS

Calcium channel blockers inhibit L-type calcium channels, resulting in slowing of atrioventricular nodal conduction and an increase in the refractory period of nodal tissue. In the myocardium, calcium channels primarily affect the action potential plateau and modulate the strength of muscle contraction. Calcium channel blockers are divided into two categories, dihydropyridine and nondihydropyridine. Nondihydropyridine calcium channel blockers have greater cardioselectivity and are generally used for paroxysmal supraventricular tachycardias and rate control in atrial fibrillation, whereas dihydropyridine calcium channel blockers are more selective for the vasculature at therapeutic doses and are used to treat hypertension.

DILTIAZEM/VERAPAMIL

Actions Diltiazem and verapamil are nondihydropyridine calcium channel blockers that slow atrioventricular nodal conduction, increase the atrioventricular node's refractory period, decrease automaticity, and prolong the PR interval. Verapamil is more potent than diltiazem, resulting in greater atrioventricular nodal depression.

Pharmacokinetics See **Table 19-18**. Immediate-release oral diltiazem has a relatively rapid onset of action; therefore, transitioning from an IV infusion to an oral preparation can be accomplished with relative ease. In addition, IV diltiazem has a short duration of action, necessitating either a continuous infusion or repeat bolus doses.

Indications Diltiazem and verapamil are indicated for paroxysmal supraventricular ventricular tachycardia as well as for rate control in atrial fibrillation[11]; however, verapamil is used more commonly to abort supraventricular ventricular tachycardia with a conversion rate to sinus rhythm similar to adenosine (90%),[30] whereas diltiazem is used more commonly to control rapid ventricular rate in atrial fibrillation.[11] Both agents are contraindicated for wide-complex tachyarrhythmias, which may be a result of Wolff-Parkinson-White syndrome due to the high risk of life-threatening ventricular arrhythmia when given to these patients. Other contraindications include sick sinus syndrome, second- or third-degree AV block, severe hypotension, cardiogenic shock, administration concomitantly or within a few hours of IV β-blockers, and ventricular tachycardia.

Diltiazem Dosing and Administration When initiating diltiazem, an IV bolus of 0.25 milligram/kg over 2 minutes is administered, and a continuous infusion is started at 5 to 10 milligrams/h (if bolus is effective). A repeat bolus of 0.35 milligram/kg over 2 minutes may be given if there is inadequate response to initial bolus. The continuous infusion may be increased in increments of 5 milligrams/h until rate control is achieved to a maximum rate of 15 milligrams/h. Once rate control is achieved, patients may be transitioned to oral diltiazem (**Table 19-19**).

Immediate-release formulations should be used when initially starting a patient on oral diltiazem. Once stable on immediate-release

TABLE 19-18 Diltiazem and Verapamil Pharmacokinetics

	Absorption	Distribution	Metabolism	Excretion	Half-Life	Onset/Peak/Duration of Action
Diltiazem	IR: ~98% ER capsule: ~93% to >95% Oral BA: ~40% (undergoes extensive first-pass metabolism)	V_d: 3–13 L/kg Plasma protein binding: 70%–80%	Hepatic via CYP450 and conjugation Active metabolites	Urine (2%–4% as unchanged drug); feces	IR: 3–4.5 h ER tablet: 6–9 h ER capsule: 4–9.5 h IV bolus: ~3.4 h Continuous infusion: 4–5 h	Onset IV: 3 min Oral, IR: 30–60 min Peak Oral, IR: 2–4 h Oral, ER tablet: 11–18 h Oral, ER capsule: 10–14 h Duration IV bolus: 1–3 h Continuous infusion (after discontinuation): 0.5–10 h
Verapamil	Oral: >90% Oral BA: 20%–35% (undergoes extensive first-pass metabolism)	V_d: 3.89 L/kg Plasma protein binding: ~90%	Hepatic via CYP450 Active metabolites	Urine (~70% as metabolites, 3%–4% as unchanged drug); feces (≥16%)	Injection (terminal): 2–5 h Oral, IR: 2.8–7.4 h (single dose); 4.5–12 h (multiple doses) Oral, ER: ~12 h	Onset/peak IV: 3–5 min Oral, IR: 1–2 h Duration IV: 0.5–6 h Oral, IR: 6–8 h

Abbreviations: BA = bioavailability; ER = extended release; IR = immediate release; V_d = volume of distribution.

diltiazem, patients can be transitioned to an extended-release formulation by giving an equivalent daily dose.

Verapamil Dosing and Administration For acute treatment of supraventricular ventricular tachycardia and atrial fibrillation (rate control), administer 5 to 10 milligrams (0.075 to 0.15 milligram/kg) IV over 2 minutes. If no response, a second dose of 10 milligrams (0.15 milligram/kg) may be given 15 to 30 minutes after the initial dose. If the patient responds to the initial or repeat bolus dose, a continuous infusion may be initiated.[6]

Adverse Effects Diltiazem is generally well tolerated by patients and has a favorable safety profile when compared to other antiarrhythmic agents. Adverse effects associated with diltiazem and verapamil administration are bradyarrhythmia, asystole, fatigue, headache, hypotension, atrioventricular block, peripheral edema, syncope, and dizziness.

NICARDIPINE

Actions Nicardipine is a dihydropyridine calcium channel blocker that causes relaxation of smooth muscle, thereby lowering blood pressure. It has no antiarrhythmic properties and little to no effect on the myocardium at therapeutic doses.

TABLE 19-19 Conversion From IV to Oral Diltiazem

Medication	IV to Oral Conversion	
Diltiazem	After continuous infusion at typical rate of 5–15 milligrams/h has heart rate controlled, may convert to oral. Oral dose (milligrams daily) is approximately equal to [rate (milligrams/h) × 3 + 3] × 10. Discontinue infusion 2–3 h after oral dose is given.	
	Diltiazem Infusion Rate	**Equivalent Oral Dose (Immediate Release)**
	3 milligrams/h	120 milligrams daily
	5 milligrams/h	180 milligrams daily
	7 milligrams/h	240 milligrams daily
	11 milligrams/h	360 milligrams daily

Pharmacokinetics See **Table 19-20**.[6]

Indications Nicardipine is primarily used for the treatment of hypertension and is contraindicated in patients with aortic stenosis. It is especially useful in patients with acute neurologic emergencies where progressive rapid blood pressure reduction over 15 to 30 minutes is indicated.

Dosing and Administration Nicardipine is administered as an IV infusion with an initial rate of 5 milligrams/h. The infusion may be titrated in increments of 2.5 milligrams/h every 5 to 15 minutes based on blood pressure response, with a maximum infusion rate of 15 milligrams/h.

Adverse Effect Profile Nicardipine is generally well tolerated by patients. Common side effects include hypotension/orthostatic hypotension, edema, flushing, tachycardia, palpitations, and nausea.

CLEVIDIPINE

Actions Clevidipine is a fourth-generation dihydropyridine calcium channel blocker with potent vasodilating activity that reduces blood pressure by decreasing systemic vascular resistance.

Pharmacokinetics The onset of action after initiating a clevidipine infusion is 2 to 4 minutes, and the duration of action is 5 to 15 minutes. Clevidipine undergoes rapid metabolism via hydrolysis by esterases in the blood and has a half-life of 1 minute. Clevidipine is delivered in a lipid emulsion.

Indications Clevidipine is indicated for the management of acute hypertension when oral therapy is not deemed desirable. It has been studied in the ED and found to be safe and effective in reducing blood pressure in the treatment of various hypertensive emergencies, stroke, heart failure, and aortic dissection (adjunct to esmolol).

Dosing and Administration Clevidipine should be initiated as an IV infusion, starting at 1 to 2 milligrams/h; the dose may be doubled at 2-minute intervals. The usual dose is 4 to 6 milligrams/h, with a maximum infusion rate of 21 milligrams/h. When the treatment goal is near, slow the rate of rise in stepped increases in therapy to stabilize blood pressure and avoid unwanted hypotension.

Adverse Effects Adverse effects of clevidipine include atrial fibrillation, nausea, vomiting, hypotension, and elevation in serum creatinine.

TABLE 19-20 Nicardipine Pharmacokinetics (IV)

Distribution	Metabolism	Excretion	Half-Life	Onset/Peak/Duration of Action
V_d: 8.3 L/kg Plasma protein binding: >95%	Hepatic via CYP450 3A4, 2C8, 2D6; extensive first-pass effect (saturable)	Urine (49% as metabolites, <1% as unchanged drug); feces (43%)	Follows dose-dependent (nonlinear) pharmacokinetics; half-life dependent on serum concentrations After IV infusion, serum concentrations decrease tri-exponentially α half-life: 3 min β half-life: 45 min Terminal half-life: 14 h (seen only after long-term infusions)	Continuous infusion Onset: within minutes Peak: 50% of maximum effect seen by 45 min Duration: upon discontinuation, 50% decrease in effect seen in ~30 min with gradual discontinuing antihypertensive effects for ~50 h

Abbreviation: V_d = volume of distribution.

OTHER ANTIARRHYTHMIC MEDICATIONS

ATROPINE

Actions Atropine blocks the effects of acetylcholine at parasympathetic sites in smooth muscle thus increasing cardiac output.[6]

Pharmacokinetics See **Table 19-21**.

Indications Atropine is considered first-line therapy for the treatment of symptomatic bradycardia. Atropine is no longer recommended for the treatment of asystole or pulseless electrical activity.[8] Atropine may precipitate or worsen myocardial ischemia in patients with coronary artery disease, acute coronary syndrome, CHF, tachycardia, and hypertension.[6]

Dosing and Administration See Table 19-21.[6,8] IV doses <0.5 milligram and slow injection have been associated with paradoxical bradycardia.

Adverse Effects The most common adverse effects of atropine include tachyarrhythmia, constipation, xerostomia, blurred vision, and photophobia.

ADENOSINE

Actions Adenosine, an endogenous nucleoside, slows conduction time through the atrioventricular node, interrupts reentry pathways through the atrioventricular node, and restores normal sinus rhythm for patients in supraventricular tachycardia.[6]

Pharmacokinetics See **Table 19-22**.[6]

Indications Adenosine is used for the treatment of paroxysmal supraventricular ventricular tachycardia with or without reentry pathways, after failure of vagal maneuvers. It is ineffective for conversion of atrial fibrillation, atrial flutter, or ventricular tachycardia.[6,30]

Dosing and Administration See **Table 19-23**.[6]

Adverse Effects Common adverse effects include chest discomfort/pressure, headache, flushing, and nausea and are usually temporary due to the short half-life of the drug. Bronchospasm and atrial fibrillation can also occur, but the incidence is rare. Severe adverse effects, including cardiac conduction abnormalities and hypotension, are more common with continuous infusion adenosine used in stress testing.

TABLE 19-21 Atropine Drug Information

Onset of Action	Metabolism	Half-Life	IV Dose (Adult)	Indications
IM: ≤15–30 min IV: immediate	Hepatic	Adults: 2.1–3.9 h	0.5 milligram every 3–5 min (maximum total dose: 3 milligrams or 0.04 milligram/kg)	Symptomatic sinus bradycardia

MAGNESIUM SULFATE

Actions, Indications, and Dosing and Administration The antiarrhythmic activity of IV magnesium sulfate is mediated by inhibiting calcium currents that cause pathologic early afterdepolarizations and thereby cardiac dyssynchrony. Magnesium slows sinoatrial node activity, prolongs myocardial conduction time, stabilizes excitable membranes, and is a cofactor in ion movement.[31] IV magnesium sulfate has a rapid onset of action and is indicated in the treatment of torsades de pointes, polymorphic ventricular tachycardia associated with a prolonged QT interval, and cardiac arrest when ventricular fibrillation/pulseless ventricular tachycardia is associated with torsades de pointes. In patients with a pulse, 1 to 2 grams IV are diluted in normal saline or 5% dextrose in water and administered as a rapid bolus. Rapid IV administration is associated with vasodilation, flushing, and hypotension.

ISOPROTERENOL

Actions, Pharmacokinetics, and Indications Isoproterenol exerts antiarrhythmic effects by stimulating β_1- and β_2-receptors. The β_1-receptor interaction results in increased chronotropic and inotropic activities in the myocardium and vasodilation by β_2-receptor–mediated relaxation of smooth muscle. IV isoproterenol has an immediate onset of action, a half-life of 2.5 to 5 minutes, and a duration of 10 to 15 minutes. It is indicated for refractory bradyarrhythmias, atrioventricular nodal block, and refractory torsades de pointes; however, it is rarely used in the ED. Isoproterenol is contraindicated in patients with angina, preexisting ventricular arrhythmias, tachyarrhythmias, or digoxin toxicity.[6]

Dosing and Administration A continuous IV infusion should be initiated at 2 micrograms/min and titrated every 5 to 10 minutes based on patient response (usual range, 2 to 10 micrograms/min).

Adverse Effects Serious adverse effects of isoproterenol include hypotension, premature ventricular contractions, tachyarrhythmia, ventricular arrhythmia, dyspnea, and pulmonary edema.

DIGOXIN

Actions Digoxin, a cardiac glycoside, has positive inotropic, negative chronotropic, and negative dromotropic effects on the myocardium due to inhibition of the sodium-potassium ATPase. It also causes direct suppression of the atrioventricular node, leading to an increased refractory period and decreased conduction velocity.[6]

Pharmacokinetics See **Table 19-24**.[6] Many disease states such as CHF, hypokalemia, renal failure, and thyroid disease can have a substantial

TABLE 19-22 Adenosine Pharmacokinetics

Metabolism	Half-Life	Onset/Duration of Action
Systemic Active metabolites	<10 s	Onset: rapid Duration: very brief

TABLE 19-23 Adenosine Dosing and Administration

Indication	Dosing and Administration
Paroxysmal supraventricular tachycardia	Initial dose: 6 milligrams IV If ineffective after 1–2 min, may give second dose of 12 milligrams IV May repeat 12 milligrams IV if needed

Note. Rapid IV push over 1–2 seconds via peripheral line. Flush line after each dose with 20 mL of normal saline. Patients usually experience transient asystole (<5 seconds). Initial dose should be reduced to 3 milligrams in heart transplant patients, in patients taking dipyridamole or carbamazepine, and when administered via central line. Patients taking caffeine or theophylline may require larger doses.

effect on the pharmacokinetics of digoxin. It has a narrow therapeutic index (therapeutic range, 0.5 to 2 nanograms/mL), and toxicity can develop at levels >2 nanograms/mL. In addition, digoxin has numerous drug interactions that can be clinically significant.

Indications Digoxin is indicated for rate control in atrial fibrillation (not first line)[11] and for symptom reduction in CHF unrelieved by diuretics and angiotensin-converting enzyme inhibitors. Although digoxin is only contraindicated in patients with ventricular arrhythmias, its use should be avoided in patients with Wolff-Parkinson-White syndrome (increased risk of ventricular fibrillation), acute myocardial infarction, untreated beriberi heart disease, electrolyte imbalances, sinus node disease, atrioventricular block, and renal impairment. Studies on mortality associated with long-term digoxin use report conflicting results.[32-36]

Dosing and Administration There are several dosing strategies for digoxin initiation. For atrial fibrillation (rate control) in adults, current guidelines recommend 0.25 milligram IV with repeat dosing to a maximum of 1.5 milligrams over 24 hours, followed by an oral maintenance regimen (0.125 to 0.25 milligram once daily).[6,11] Dose adjustments are often necessary based on age, comorbidities, concomitant medications, and renal dysfunction. Digoxin levels should be monitored for safety and efficacy.

Adverse Effects Adverse effects of digoxin are generally GI, including nausea, vomiting, and diarrhea. Other rarer adverse effects may include gynecomastia, skin rash, eosinophilia, and thrombocytopenia. Digoxin can also cause cardiac arrhythmias, such as sinus bradycardia, atrioventricular or sinoatrial nodal block, and ventricular arrhythmias.

Symptoms of digoxin toxicity include mental status changes, visual disturbances, delirium, hyperkalemia, and seizures. Many types of arrhythmias can occur as a result of digoxin toxicity, and clinicians must be able to recognize the signs and symptoms associated with toxicity and treat accordingly.

SELECTED ANTIHYPERTENSIVE MEDICATIONS

See earlier sections for discussion of β-blockers, nicardipine, and clevidipine. Eleven of the most commonly prescribed oral antihypertensive agents are listed in **Table 19-25**.

Actions of Selected Antihypertensive Classes Lisinopril, captopril, and benazepril are **angiotensin-converting enzyme inhibitors**, which act by preventing the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor), ultimately reducing aldosterone secretion and blood pressure.[6] Valsartan and losartan are **angiotensin receptor blockers**, which reduce blood pressure by blocking the vasoconstrictor effects and aldosterone-secreting stimulus of angiotensin II.[6] Amlodipine and nifedipine are dihydropyridine **calcium channel blockers**, which lower blood pressure by relaxing vascular smooth muscle to produce arterial vasodilation and decreased systemic vascular resistance.[6] Amlodipine and nifedipine have very few chronotropic effects. Chlorthalidone, a thiazide-related **diuretic**, inhibits sodium and chloride reabsorption in the cortical-diluting segment of the ascending loop of Henle; hydrochlorothiazide, a thiazide diuretic, inhibits sodium reabsorption in the distal tubules, causing increased excretion of sodium and water as well as potassium and hydrogen ions.[6] Clonidine stimulates α_2-adrenoceptors in the brainstem, decreasing sympathetic outflow and thereby reducing peripheral resistance, heart rate, and blood pressure.[6] Hydralazine is a smooth muscle relaxant that decreases tone in arterial walls, yielding vasodilation and a decrease in peripheral vascular resistance.[6]

Indications Medications from the antihypertensive classes of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are considered preferred initial drugs for the initiation of antihypertensive therapy (Table 19-25), with a few important exceptions.[37] For patients with chronic kidney disease being started on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, there is a risk of hyperkalemia. Also, with these two drug classes, there is a risk of acute kidney injury in the setting of severe bilateral renal artery stenosis, a condition that affects up to 1.4% of the hypertensive population.[38] Nifedipine and labetalol (discussed earlier) are preferred agents in hypertensive women who are pregnant or planning to become pregnant.[37] Calcium channel blockers should be avoided in patients with a history of heart failure with reduced ejection fraction; the initial antihypertensive drug for these patients should be an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.[13] Of the diuretics, chlorthalidone is the preferred agent because of its long duration of action (40 hours) and trial-proven reduction of cardiovascular disease.[37] Thiazide diuretics should be avoided in patients with a history of gout. Clonidine and hydralazine are frequently used in cases of hypertensive urgency (see Chapter 57, "Systemic Hypertension"). Hydralazine is not recommended as an initial drug for hypertension.[37] Hydralazine is not recommended for hypertensive emergencies,[6] except when associated with pregnancy[39] (see Chapter 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period"). With abrupt discontinuation, clonidine is associated with rebound hypertension.

Most patients taking medication to control their hypertension will require at least two medications. While the dose of one medicine may be increased to its maximum recommended daily dose (Table 19-25),[6,37] when lower doses do not sufficiently reduce blood pressure, two drugs of the same class should not be used simultaneously. Also, an angiotensin receptor blocker should not be combined with an angiotensin-converting enzyme inhibitor. The most commonly prescribed two-drug antihypertensive combinations are a diuretic added to an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. See Table 19-25 for dosing information and adverse effects.

TABLE 19-24 Digoxin Pharmacokinetics

Distribution	Metabolism	Excretion	Half-Life	Onset/Peak/Duration of Action
Normal renal function: 6–7 L/kg Plasma protein binding: ~25%	GI tract Hepatic Active metabolites	Urine (50%–70% as unchanged drug)	Age, renal, and cardiac function dependent Parent drug: 38 h Metabolites: digoxigenin (4 h); monodigitoxoside (3–12 h)	Onset Oral: 1–2 h IV: 5–60 min Peak Oral: 2–8 h IV: 1–6 h Duration: 3–4 d

TABLE 19-25 Selected Oral Antihypertensive Medications

Drug	Dose*	Frequency	Onset	Metabolism/Excretion	Side Effects/Comments
Angiotensin receptor blockers					
Valsartan	Start 80 milligrams Max 320 milligrams/d	Daily, or divided twice daily	2 h; peak 4 h	To inactive metabolite/feces	Hyperkalemia, renal impairment, angioedema
Losartan	Start 50 milligrams Max 100 milligrams/d	Daily	2 h; peak 6 h	Hepatic/feces	Hyperkalemia, renal impairment, angioedema
Angiotensin-converting enzyme inhibitors					
Lisinopril	Start 5 milligrams Max 40 milligrams/d	Daily	1 h; peak 6 h	Not metabolized/ unchanged in urine	Angioedema, hyperkalemia, renal impairment, cough
Captopril	Start 25 milligrams Max 450 milligrams/d	3 times daily	15 min; peak 90 min	Hepatic/urine	Angioedema, hyperkalemia, renal impairment, cough
Benazepril	Start 5 milligrams Max 40 milligrams/d	Daily, or divided twice daily	1 h; peak 2 h	Hepatic/urine	Angioedema, hyperkalemia, renal impairment, cough
Calcium channel blockers					
Amlodipine	Start 2.5 milligrams Max 10 milligrams	Daily	10 h; peak 24–48 h	Hepatic/urine	Peripheral edema, headache, palpitations
Nifedipine	IR: Start 10 milligrams Max 120 milligrams/d ER: Start 30 milligrams Max 120 milligrams/d	IR: 3 times daily ER: daily	20 min; peak 1 h	Hepatic/urine	Hypotension, peripheral edema, headache, palpitations, flushing
Diuretics					
Chlorthalidone	Start 12.5 milligrams Max 50 milligrams/d	Daily	2 h; peak 4–6 h	Hepatic/urine	Dizziness, headache, electrolyte imbalance, hypokalemia
Hydrochlorothiazide	Start 12.5–25 milligrams Max 50 milligrams/d	Daily	2 h; peak 2–6 h	Not metabolized/ unchanged in urine	Dizziness, headache, electrolyte imbalance, hypokalemia
Smooth muscle relaxant, vasodilator					
Hydralazine	IV: 10–20 milligrams Oral: Start 10–25 milligrams per dose Max 300 milligrams/d	IV: every 4–6 h Oral: divided 2–4 times daily	IV: 10–80 min Oral: 1–2 h	Hepatic/urine	Tachycardia, dizziness, lupus-like syndrome at higher doses, fever
Centrally acting α_2-adrenergic agonist					
Clonidine	IR: Start 0.1 milligram Max 2.4 milligrams/d	Twice daily	30–60 min; peak 1–3 h	Hepatic/urine, 40%–60% unchanged	Sedation, bradycardia, headache, dizziness, irritability

Abbreviations: ER = extended release; IR = immediate release.

*Dose is oral unless otherwise stated.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 20

Pharmacology of Vasopressors and Inotropes

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INTRODUCTION

Vasopressors are potent pharmacologic agents that are used to increase blood pressure and mean arterial pressure by vasoconstriction, thus increasing systemic vascular resistance. They should be reserved for cases of persistent hypotension and tissue hypoperfusion after volume resuscitation has failed. Most vasopressors have proarrhythmic potential and exert effects on both the heart and vasculature. Some agents also have inotropic properties and are used to improve cardiac output, particularly in patients with left ventricular pump failure or cardiogenic shock. In patients with septic shock, the cumulative vasopressor dose to maintain blood pressure is a predictor for early death.[1] **Table 20-1**[2-8] provides a summary of vasopressors and inotropic agents.

ADMINISTRATION RECOMMENDATIONS AND COMPLICATIONS

In general, vasopressors should be given via a central venous catheter to reduce the incidence of complications.[9,10] Most complications resulting in tissue loss due to necrosis result from vasopressor infusions below the antecubital or popliteal sites.[11] Short-term use, using an antecubital or more proximal site, has a complication rate of 2%.[12] Treatment with

TABLE 20-1 Summary of Common Vasopressors, Doses, Effects, and Contraindications

Medication	Dosing	Cardiovascular Effects	Contraindications
Dopamine	**Hemodynamic support** IV infusion: 2–20 micrograms/kg/min; titrate by increments of 5–10 micrograms/kg/min to desired response (maximum, 50 micrograms/kg/min)	↑ HR, BP, CO, SVR (dose dependent)	Hypersensitivity to sulfites Pheochromocytoma Uncorrected tachyarrhythmias VF
Epinephrine	**Asystole/pulseless arrest, pulseless VT/VF** 1 milligram IV/IO every 3–5 min until ROSC; 2–2.5 milligrams ET every 3–5 min until IV/IO access established or ROSC (dilute in 5–10 mL NS or SW) **Bradycardia** IV infusion: 2–10 micrograms/min; titrate to desired response **Septic shock** IV infusion (initial): 0.05–2 micrograms/kg/min; titrate every 10-15 min by increments of 0.02–0.05 microgram/kg/min to desired MAP **Hypotension after intubation or sedation** 5–20 micrograms/bolus dose over 20–30 s every 2–5 min as needed **Anaphylaxis 0.3–0.5 milligram IM by epinephrine autoinjector or equivalent; IV infusion, mix 1 milligram in 500 mL D5W and infuse at 0.5 mL/min and titrate dose as needed**	↑ HR, BP, MAP, SV, SVR, CO	No absolute contraindications in a life-threatening situation
Norepinephrine	**Hypotension/shock** IV infusion (initial): 8–12 micrograms/min; titrate to desired response; usual maintenance range: 2–4 micrograms/min **Post–cardiac arrest care** Initial: 0.1–0.5 microgram/kg/min; titrate to desired response **Sepsis/septic shock*** Start 0.02–0.04 microgram/kg/min; typical range, 0.02–1.0 microgram/kg/min; titrate every 5–10 min by 0.02–0.04 microgram/kg/min; wean at rate 0.01–0.03 microgram/kg/min	↑ BP, MAP, SVR, CO	Hypotension from hypovolemia except as an emergency measure to maintain coronary and cerebral perfusion until volume can be replaced
Phenylephrine	**Hypotension/shock** IV infusion (initial): 100–180 micrograms/min *or* 0.5 microgram/kg/min; titrate to desired response **Hypotension after intubation or sedation** IV bolus: 40–100 micrograms/bolus dose over 20–30 s every 2–5 min as needed	↑ BP, MAP, SVR	Severe hypertension VT
Vasopressin	**Septic shock (SSC recommendations)** ≤0.03 unit/min with concomitant norepinephrine to raise MAP to target or to decrease norepinephrine dose	↑ BP, SVR	Hypersensitivity to vasopressin or chlorobutanol†
Angiotensin II	**Septic shock (not first line)** Initial dose 10–20 nanograms/kg/min, titrate in increments of 5–10 nanograms/kg/min every 5 min; maximum initial dose, 80 nanograms/kg/min during initial 3 h After improvement in blood pressure, down-titrate to 15 nanograms/kg/min every 5–15 min to minimum effective dose; maximum maintenance dose (after first 3 h), 40 nanograms/kg/min	↑ BP, MAP	No absolute contraindications; manufacturer warning: because of the risk of thromboembolic events, angiotensin II should be used in combination with venous thromboembolism prophylaxis
Dobutamine	**Decreased CO** IV infusion (initial): 1–3 micrograms/kg/min; maintenance: 2–40 micrograms/kg/min; titrate to desired response **ACLS (immediately after cardiac arrest)** IV infusion (initial): 5–10 micrograms/kg/min; titrate to desired response	↑ BP, CO ↔/↑ HR ↔ MAP ↓ SVR	Hypertrophic cardiomyopathy with outflow tract obstruction
Milrinone	**Congestive heart failure, acute bridge to definitive treatment** Loading dose (optional): 50 micrograms/kg over 10 min Maintenance (continuous IV infusion): 0.375–0.75 microgram/kg/min‡; titrate to desired response	↑ CO ↔/↑ HR ↓ SVR, BP ↔/↓ MAP	Hypersensitivity to milrinone

Abbreviations: ACLS = advanced cardiovascular life support; BP = blood pressure; CO = cardiac output; D5W = dextrose 5% in water; ET = endotracheal; HR = heart rate; HTN = hypertension; MAP = mean arterial pressure; NS = 0.9% normal saline; ROSC = return of spontaneous circulation; SSC = Surviving Sepsis Campaign; SV = stroke volume; SVR = systemic vascular resistance; SW = sterile water; VF = ventricular fibrillation; VT = ventricular tachycardia.

*There is no defined maximum norepinephrine dose for refractory shock, but doses above 0.5-1.0 micrograms/kg/min are considered high, and may be associated with worse outcomes. SSC recommends adding vasopressin to reduce the dose of norepinephrine.

†Not available in the United States.

‡Dose adjustment in renal impairment.

phentolamine injection locally using a fine needle and nitroglycerin ointment topically can reduce tissue loss.[12]

BOLUS-DOSE ADMINISTRATION OF VASOPRESSORS

Bolus-dose vasopressors, also called push-dose pressors, have been used by anesthesiologists for the treatment of sudden hypotension during surgical procedures for many years. Only recently has bolus-dose vasopressor use for ED patients received attention in the emergency medicine literature.[8,13-18] Authors urged caution because safety is questioned.[8,15-17] Phenylephrine is the most commonly used vasopressor in the setting of acute onset of hypotension; epinephrine is used when the patient could benefit from an increase in pulse rate as well as cardiac output.[8] Dose errors are common, highlighting the importance of careful dose calculations (Table 20-1).[8,15-17] A systems approach to standardize vasopressor concentration across an institution is recommended to prevent dose errors.[8,16] Assistance from an on-site pharmacist to prepare and clearly label drug concentration on a bolus syringe or IV bag is recommended if available.[8,15,16]

VASOPRESSORS

DOPAMINE

Actions Dopamine is an endogenous catecholamine and a metabolic precursor of norepinephrine and epinephrine that acts on dopaminergic α_1-, β_1-, and β_2-receptors in a dose-dependent fashion. At intermediate doses (5 to 10 micrograms/kg/min), dopamine increases renal blood flow, heart rate, cardiac contractility, and cardiac output. At high doses (>10 micrograms/kg/min), the α-adrenergic effects of dopamine dominate, leading to vasoconstriction and increased blood pressure. Low-dose (1 to 5 micrograms/kg/min) dopamine is no longer recommended for renal protection due to lack of patient outcome evidence.[5]

Pharmacokinetics See **Table 20-2**.[4]

Indications Dopamine increases cardiac output, blood pressure, and peripheral perfusion and is indicated for reversing hemodynamically significant hypotension caused by myocardial infarction, trauma, heart failure, and renal failure, when fluid resuscitation is unsuccessful or inappropriate. Surviving Sepsis Campaign guidelines no longer recommend dopamine as an initial vasopressor for septic shock, based on data showing lower short-term mortality and decreased incidence of tachyarrhythmias in patients receiving norepinephrine versus dopamine.[5] Dopamine can be considered as an alternative vasopressor agent to norepinephrine only in highly selected patients (i.e., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).[5] Although not considered a first-line agent, dopamine can also be used for the treatment of symptomatic bradycardia that is unresponsive to atropine.[19]

Dosing and Administration See Table 20-1.

Adverse Effects Adverse effects include chest pain, hypotension (low doses), hypertension (high doses), ectopic beats, palpitations, nausea, vomiting, headache, tissue ischemia, and tachycardia.

EPINEPHRINE

Actions Epinephrine, an endogenous catecholamine, is an α_1- and nonselective β-adrenergic agonist that increases systemic vascular resistance, heart rate, cardiac output, and blood pressure.

TABLE 20-2 Dopamine Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset/Duration of Action
Renal, hepatic, plasma; 75% to inactive metabolites by monoamine oxidase (MAO) and 25% to norepinephrine (active)	Urine (as metabolites)	~2 min	Onset: ≤5 min Duration: <10 min

TABLE 20-3 Epinephrine Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset/Duration of Action
Hepatic, other tissues: rapidly inactivated and degraded by enzymes Hepatic: metabolized by monoamine oxidase and catechol-*O*-methyl transferase	Urine (mostly as inactive metabolites)	<5 min	Onset: 1–2 min Duration: 2–10 min

Pharmacokinetics See **Table 20-3**.[4,6]

Indications Epinephrine is indicated in the treatment of cardiac arrest and can also be used for symptomatic bradycardia unresponsive to atropine or transcutaneous pacing. Sepsis guidelines recommend epinephrine when an additional agent is needed to maintain adequate blood pressure in patients with severe sepsis or septic shock.[5] It is an essential agent for the treatment of anaphylaxis.

Dosing and Administration See Table 20-1 and **Figure 20-1**. Epinephrine concentration varies depending on the formulation, and dosing is described both as milligrams and as micrograms. Microgram doses are described primarily for IV infusions. Epinephrine is pre-prepared for cardiac arrest treatment (0.1 mg/mL, 10 mL in 1:10,000 dilution) because the 1:10,000 solution is specifically used for bolus IV administration. Epinephrine in vials or autoinjectors is typically supplied as 1 mg/mL in the 1:1000 dilution specifically for IM injection, with doses of 0.15 milligram for children and 0.3 milligram for adults. To avoid errors in dosing, be familiar with the formulations of epinephrine used in your ED.

Adverse Effects Adverse effects include angina, palpitations, arrhythmias, hypertension, tachycardia, nausea, vomiting, headache, anxiety, and pulmonary edema.

NOREPINEPHRINE

Actions Norepinephrine is an endogenous catecholamine that stimulates α-adrenergic receptors, resulting in peripheral vasoconstriction and increased blood pressure. Norepinephrine also activates β-adrenergic receptors ($\beta_1 > \beta_2$), leading to inotropic stimulation of the heart and coronary artery vasodilation.

Pharmacokinetics See **Table 20-4**.[4,6]

Indications Norepinephrine is indicated for the treatment of acute hypotension and shock. It is recommended as the initial vasopressor of choice for the treatment of severe sepsis and septic shock refractory to adequate fluid resuscitation based on the sepsis guidelines.[5]

Dosing and Administration See Table 20-1.

Adverse Effects Adverse effects include bradycardia, arrhythmias, peripheral ischemia, hypertension, nausea, vomiting, headache, anxiety, and cardiac arrest.

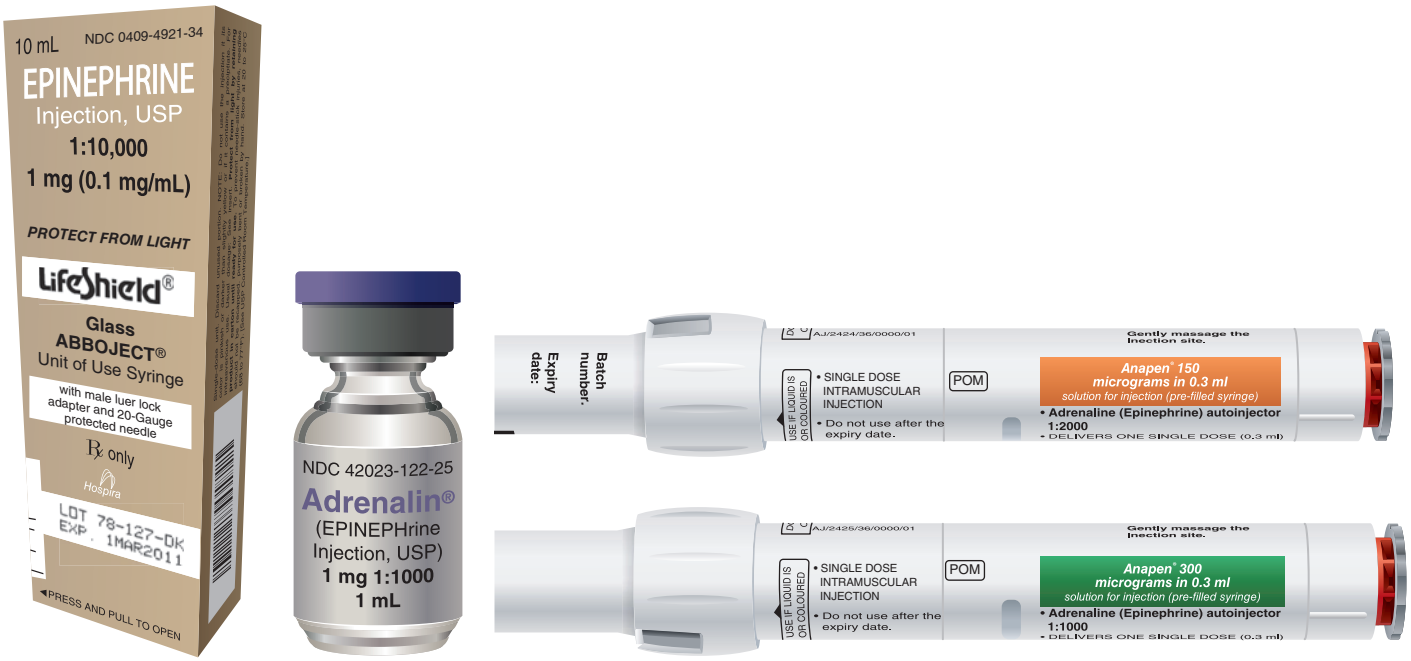
PHENYLEPHRINE

Actions Phenylephrine is a selective α_1-adrenergic agonist that increases systemic vascular resistance and elevates systolic and diastolic blood pressure through systemic arterial vasoconstriction. Phenylephrine has no direct effects on heart rate; however, reflex bradycardia and reduced cardiac output may occur, especially in patients with heart failure or cardiogenic shock.[5,6]

Pharmacokinetics See **Table 20-5**.[4]

Indications Phenylephrine is indicated for the treatment of hypotension and vascular failure in shock, but is not recommended in the treatment of septic shock.[5,6]

Dosing and Administration See Table 20-1. The dose of phenylephrine in the setting of anesthesia or after intubation or rapid sequence



A B C

FIGURE 20-1. Examples of epinephrine (adrenalin) formulations. **A.** Epinephrine for cardiac arrest, 1:10,000. **B.** Epinephrine in vials, 1:1000. **C.** Epinephrine autoinjectors. Dosing may be described in micrograms or milligrams.

induction is an IV bolus of 40 to 100 micrograms per dose over 20 to 30 seconds every 2 to 5 minutes as needed.[8]

Adverse Effects Adverse effects include hypertension, low cardiac output, reflex bradycardia, and arrhythmias. Phenylephrine can also lead to renal, mesenteric, myocardial, and peripheral ischemia.

VASOPRESSIN

Actions Vasopressin, an endogenous nonadrenergic vasopressor, stimulates V_1 receptors in vascular smooth muscle, causing direct peripheral vasoconstriction, increases in systemic vascular resistance and blood pressure, and improved cerebral and cardiac perfusion. It does not exhibit inotropic or chronotropic effects on the heart and can cause a decrease in heart rate and cardiac output. Vasopressin also acts on V_2 receptors in the kidneys, causing an antidiuretic effect.

Pharmacokinetics See **Table 20-6**.[4,6]

Indications Vasopressin is no longer recommended in the advanced cardiovascular life support cardiac arrest algorithm.[19] According to sepsis guidelines, vasopressin (up to 0.03 unit/min) may be added to norepinephrine either to raise mean arterial pressure to target or to decrease norepinephrine dose, but should not be used as the single initial vasopressor for treatment of sepsis-induced hypotension (weak recommendation; moderate quality evidence).[5]

Dosing and Administration See Table 20-1.

Adverse Effects Adverse effects include diaphoresis, nausea, vomiting, headache, urticaria, arrhythmias, mesenteric and peripheral ischemia, chest pain, myocardial infarction, bronchoconstriction, and cardiac arrest.

TABLE 20-4 Norepinephrine Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset/Duration of Action
Via monoamine oxidase and catechol-*O*-methyl transferase	Urine (as inactive metabolites)	1–2 min	Onset: very rapid Duration: 1–2 min

TABLE 20-5 Phenylephrine Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset/Duration of Action
IV: hepatic via oxidative deamination (50%); undergoes sulfation (8%) and some glucuronidation; forms inactive metabolites	Urine (mostly as inactive metabolites)	Alpha phase: ~5 min Terminal phase: 2–3 h	Onset: immediate Duration: ~15–20 min

ANGIOTENSIN II

Actions Angiotensin II is an octapeptide hormone component of the renin-angiotensin-aldosterone system that raises blood pressure by stimulating vasoconstriction and release of aldosterone.[4,20] The U.S. Food and Drug Administration approved angiotensin II for use in the United States in 2017.[20] ATHOS-3, a randomized trial, demonstrated that angiotensin II increases blood pressure when given to patients in septic or distributive shock who remain hypotensive despite fluid resuscitation and norepinephrine.[21] Seventy percent of the angiotensin group compared to 23% of the placebo group reached target blood pressure over 3 hours; however, there was no mortality benefit.[21]

Pharmacokinetics See **Table 20-7**.[4,20]

TABLE 20-6 Vasopressin Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset/Duration of Action
Hepatic, renal (inactive metabolites)	Urine (~6% as unchanged drug)	10–20 min	Onset: rapid Duration: ≤20 min

TABLE 20-7 Angiotensin II Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset/Duration of Action
Enzymes found in the plasma, red blood cells, kidney, liver, and lungs	Not reported by manufacturer	<1 min	Onset 5 min with infusion (median); duration up to 3 h

Indications Angiotension II is indicated for septic or other distributive shock when other drugs such as norepinephrine have failed to increase mean arterial pressure to target levels.[4,20,21]

Dosing and Administration See Table 20-1.

Adverse Effects Adverse effects include thromboembolic events (12.9%), thrombocytopenia (9.8%), tachycardia (8.6%), fungal infection (6.1%), delirium (5.5%), and acidosis (5.5%).[21,22]

INOTROPES

DOBUTAMINE

Actions Dobutamine is a synthetic dopamine analogue with potent inotropic and mild vasodilatory and chronotropic effects. It competitively binds and stimulates α- and β-receptors ($\beta_1 > \beta_2 > \alpha_1$), resulting in increased contractility and heart rate with neutral effect or possible decrease in blood pressure.[23]

Pharmacokinetics See **Table 20-8**.[4]

Indications Dobutamine is indicated for the short-term management of patients with acute cardiac decompensation, particularly in patients presenting with cardiogenic shock. Dobutamine can also be used for patients with persistent hypoperfusion despite adequate fluid resuscitation and the use of vasopressor agents.[5]

Dosing and Administration See Table 20-1.

Adverse Effects Adverse effects include hypertension, tachyarrhythmia, headache, angina, and hypokalemia.

MILRINONE

Actions Milrinone is an inotrope with vasodilator properties (inodilator) that selectively inhibits the phosphodiesterase type III enzyme, resulting in the inhibition of cyclic adenosine monophosphate breakdown in myocardial and vascular smooth muscle cells. Increased cyclic adenosine monophosphate levels result in increased cardiac contractility, peripheral arterial and venous vasodilation, increased cardiac output, and reduced systemic vascular resistance.[7]

Pharmacokinetics See **Table 20-9**.[4]

Indications Milrinone is used for the short-term treatment of acute decompensated heart failure. It is typically encountered in the ED when used as a short-term bridge to heart transplant or left ventricular assist device placement or as a continuous pump infusion for patients at home. In the ED, it is most commonly ordered in conjunction with cardiology or the heart failure service.[24]

Dosing and Administration See Table 20-1.

Adverse Effects Adverse effects include ventricular and supraventricular arrhythmias, hypotension, angina, and headache.

TABLE 20-8 Dobutamine Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset of Action/ Peak Effect
In tissues and hepatically to inactive metabolites	Urine (as metabolites)	2 min	Onset: 1–10 min Peak: 10–20 min

TABLE 20-9 Milrinone Pharmacokinetics

Metabolism	Excretion	Half-Life	Onset of Action
Hepatic (minor); majority is not metabolized	Urine (83% as unchanged drug; 12% as metabolites)	2.3–2.4 h	Onset: 5–15 min

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 21

Hyperbaric Oxygen Therapy

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INTRODUCTION

Hyperbaric oxygen (HBO) therapy is a medical intervention in which a patient breathes continuous or intermittent 100% oxygen while inside a hyperbaric chamber that is pressurized to an ambient pressure greater than sea level.[1] HBO therapy results in the systemic delivery of oxygen that produces supraphysiologic oxygen tension in perfused tissues. The effects of HBO therapy are due to the combined effects of both increased ambient pressure and increased oxygen tension.[2]

Monoplace chambers accommodate a single occupant. An attendant monitors the patient from the outside and communicates via intercom. Specially designed cardiopulmonary monitoring devices, IV infusion pumps, and ventilators enable critically ill patients to be treated in monoplace chambers. Multiplace chambers (**Figure 21-1**) can simultaneously treat multiple patients and will accommodate medical personnel inside the chamber to perform hands-on patient assessment and care. Monoplace chambers generally use 100% oxygen for pressurization, whereas multiplace units are pressurized with air and patients breathe oxygen using a tight-fitting facemask, a hood, or an endotracheal tube while inside.

Ambient pressure is an important concept in HBO therapy. At sea level, the pressure exerted by the air column (the atmosphere) above is quantified as 1 atmosphere absolute of pressure (ATA), 760 mm Hg, 760 torr, or 101 kPa. Once a patient is placed inside a chamber, the ambient pressure is increased by the gradual inflow of compressed gas, either oxygen or air. Most HBO therapy uses pressures between 2.0 and 3.0 ATA (202 to 303 kPa). A typical HBO treatment lasts 90 to 120 minutes. HBO therapies are performed using preset protocols that define pressurization level, treatment duration, use of air breaks, and the number of HBO sessions in a course of therapy.

The oxygen content of the blood is the sum of the oxygen carried by hemoglobin and oxygen dissolved in the plasma. Hemoglobin becomes fully saturated around a Po_2 of 100 mm Hg (13.3 kPa); fully saturated hemoglobin carries approximately 20 mL of oxygen per 100 mL of blood, which is expressed as 20 vol%. At 1 ATA breathing room air, dissolved oxygen in the plasma is typically only 0.3 vol%. At a pressure of 3 ATA inside an HBO chamber pressurized with 100% oxygen, the arterial oxygen tension (Pao_2) will approach 2200 mm Hg (293 kPa), which will bring the dissolved oxygen content up to about 5.4 vol%.[2] This amount of dissolved oxygen can sustain basal metabolic functions in the complete absence of hemoglobin.

PHYSIOLOGIC EFFECTS

HBO therapy should be viewed as a drug and the hyperbaric chamber as a delivery device. HBO affects tissues in two ways: there are effects related to mechanical forces of increased pressure and effects due to



FIGURE 21-1. The outer and inner configurations of a multiplace hyperbaric chamber at the University of Pennsylvania Department of Hyperbaric Medicine, Philadelphia, Pennsylvania.

hyperoxygenation. Of the two, elevated tissue oxygen tension is thought to be the primary effect. Hyperoxygenation reverses tissue ischemia, but also induces the formation of reactive oxygen species, including superoxide, hydrogen peroxide, hypochlorous acid, hydroxyl, and reactive nitrogen species (primarily nitric oxide). This stimulates the body's natural antioxidant defenses, strongly mobilizing the antioxidant enzyme system and thus improving defense from oxidative damage.[3] Highly elevated oxygen levels generated during HBO therapy have therapeutic beneficial effects seen after tissue oxygen levels return to normal (**Table 21-1**).[4] Reactive oxygen species are natural by-products of metabolism that can oxidize proteins and membrane lipids, damage DNA, and mediate tissue and organ damage seen in oxygen toxicity. The body has scavenger antioxidant systems to reverse the oxidative damage caused by reactive oxygen species generated during HBO therapy (making oxygen toxicity rare) and that continue to protect the body against oxidative stress upon completion of HBO therapy.[4,5]

TABLE 21-1 Beneficial Effects of Hyperbaric Oxygen Therapy

- **Provides hyperoxygenation:** reverses tissue ischemia
- **Limits toxin production:** inhibits microbial endotoxin and exotoxin production
- **Bacteriostatic and bactericidal:** to obligate anaerobic microorganisms
- **Reduces tissue edema:** induces vasoconstriction-mediated reductions of inflow without reducing outflow in posttraumatic tissue beds
- **Stimulates angiogenesis:** promotes production of oxygen-dependent collagen matrix, increases wound growth factors synthesis, and mobilizes stem/progenitor cells from bone marrow
- **Promotes osteogenesis:** in hypoxic bone by providing osteoblast simulation and bone tissue regeneration
- **Promotes wound healing:** by impairing B2 integrin function and the amplifying oxygen gradients surrounding ischemic wounds
- **Diminishes inflammatory responses:** by lowering monocyte chemokine synthesis and ischemic preconditioning changes in heme oxygenase-1, heat shock proteins, and hypoxia-inducible factor
- **Augments fibroblast replication:** increasing collagen formation
- **Blunts ischemia-reperfusion injury:** to endothelial tissue
- **Increases red blood cell flexibility:** facilitating increases in elastic deformation
- **Enhances leukocyte bactericidal activity:** improves neutrophil oxygen-dependent peroxidase bactericidal activity
- **Enhances antibiotic transport:** increases antibiotic penetration into target bacteria
- **Preserves intracellular adenosine triphosphate:** supporting intracellular functions
- **Terminates lipid peroxidation:** obviating tissue destruction

INDICATIONS

The Undersea and Hyperbaric Medical Society has defined clinical indications for HBO therapy, some of which are within the scope of emergency medicine practice (**Table 21-2**).[5]

AIR OR GAS EMBOLISM

Air or gas embolism can occur as a consequence of a deep-sea dive–related accident[6] or as the result of a medical procedure (**Table 21-3**),[7-10] including emergent or urgent procedures performed within the ED. Diving accidents are discussed in Chapter 214, "Diving Disorders," and this chapter will focus primarily on iatrogenic embolism. Air or gas embolism can occur either on the venous or arterial side of the circulatory system.

Venous gas embolism can occur after surgical procedures.[8,10] The amount of gas is typically small, and the air bubbles trapped in the pulmonary capillaries are resorbed without symptoms. Large quantities of gas in the pulmonary vasculature can stimulate cough, dyspnea, and pulmonary edema and, in severe cases, cause vapor lock. A paradoxical arterial gas embolism may develop when a venous gas embolism travels to the arterial system (right to left shunt) by way of an intrapulmonary shunt or through an atrial septal defect or a patent foramen ovale.[10]

The consequences of an arterial gas embolism depend on location and magnitude of arterial occlusion. Arterial gas embolism is a potentially catastrophic event with a reported mortality rate of 20%.[11] Skeletal muscle, connective tissue, and skin can often tolerate small emboli, but air entering the coronary, cerebral, or spinal circulation can precipitate

TABLE 21-2 Indications for Hyperbaric Oxygen Therapy

Acute ischemic events	**Gas toxicities**
Arterial gas embolism	Carbon monoxide poisoning
Decompression sickness	Cyanide poisoning
Central retinal artery occlusion	**Infections**
Sensorineural hearing loss	Clostridial myonecrosis (gas gangrene)
Select problem wounds*	Necrotizing soft tissue infections
Exceptional blood loss anemia	Intracranial abscess*
Traumatic injuries	Refractory osteomyelitis*
Crush injury and compartment syndrome	**Radiation injuries***
Other acute ischemias	Osteoradionecrosis
Acute thermal burns	Soft tissue radionecrosis
Compromised grafts and flaps*	

*These usual nonemergent indications for hyperbaric oxygen therapy are not discussed in detail.

TABLE 21-3 Iatrogenic Air or Gas Embolism

Emergency Department Procedures	Surgical Procedures	
Mechanical ventilation	Cardiac surgery	Hip replacement
Chest tube placement	Bronchoscopy	Arthroscopy
Cardiopulmonary resuscitation	GI endoscopy	Spine surgery
Lumbar puncture	Laparoscopy	Neurosurgery in sitting position
Arterial or central line insertion/removal	Hysteroscopy	Endoscopic vein harvesting
Penetrating chest trauma	Cesarean section	Vitrectomy
Contrast mechanical injection	Prostatectomy	Liver resection or transplantation
Hemodialysis/dialysis catheter placement	Transurethral surgery	Percutaneous organ puncture

acute coronary syndrome, stroke, or paralysis, respectively. The introduction of intravascular sheaths, such as at the start of an interventional radiologic procedure, accounts for the greatest proportion of iatrogenic gas embolism.[11]

When suspected, administer supplemental oxygen to support arterial oxygenation and hasten bubble resorption. Place the patient in the supine position; there is no proven benefit to a head-down position to lower the risk of additional cerebral air embolization or a left lateral decubitus position to trap gas within the apex of the right ventricle and minimize migration. Catheter aspiration of trapped air may be attempted in those rare instances when it is visualized and a preexisting catheter is in place; de novo placement of a vascular catheter to attempt air aspiration is controversial.[12]

HBO is definitive treatment for arterial gas embolism and is recommended when there is neurologic or cardiovascular impairment.[10] Start treatment as soon as possible, but there is evidence of improved outcomes out to 60 hours or longer.[13-15] The most common protocol used is the U.S. Navy Treatment Table 6, which begins at 2.8 ATA, with a subsequent decompression to 1.8 ATA (total treatment time of 285 minutes). For patients whose symptoms are not improved or worsen, the U.S. Navy Treatment Table 6A (initial pressurization up to 6 ATA in a multiplace chamber) may be considered. For patients with residual symptoms after the initial HBO treatment, additional treatments are recommended until there is no further neurologic improvement.[10]

DECOMPRESSION SICKNESS

Decompression sickness is due to the formation of nitrogen bubbles in body tissue and circulation during decompression (see Chapter 214, "Diving Disorders"). These bubbles cause direct mechanical disruption of tissue, occlusion of blood flow, platelet deposition and activation of the coagulation cascade, endothelial dysfunction, capillary leakage, endothelial cell death, complement activation, and leukocyte-endothelial interaction.[16]

HBO treatment is the definitive treatment for decompression sickness and recommended in all cases of diving decompression sickness. If HBO therapy is not available, patients with mild symptoms who are stable for longer than 24 hours may be treated with supplemental oxygen alone. If a patient must be transported by air to a hyperbaric facility, use pressurized aircraft to maintain sea-level pressure or transport at the lowest possible altitude in a nonpressurized craft, such as a helicopter.

A variety of HBO regimens are used to treat decompression sickness,[17] but most centers use the U.S. Navy Treatment Table 6 and most patients with decompression sickness who receive rapid HBO therapy will respond to a single treatment. The U.S. Navy Treatment Table 9 may be used in patients with residual symptoms.

CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion is rare, usually presenting as painless vision loss in one eye; without treatment, vision loss can be permanent. Poor outcomes occur because the occlusion is often the result of a cholesterol embolus that is not treatable with thrombolysis. HBO therapy produces a clinically significant visual improvement especially when instituted within 24 hours of onset.[18] There are no other central retinal artery occlusion therapies with similar outcomes.[19,20]

Adjunctive therapies (i.e., supplemental oxygen and lowering intraocular pressure) are recommended until HBO can be initiated. The HBO central retinal artery occlusion protocol is 2.0 ATA for 30 minutes. If vision improves, the patient is treated for a total of 90 minutes. Treatments are done twice daily and continued until there is no visual improvement for 3 consecutive days. If vision does not improve at 2.0 ATA for 30 minutes, the pressure is raised to 2.4 to 2.8 ATA (titrating to effect with at-depth visual acuities) for a total of 90 minutes with air breaks.[20] If there is no improvement after eight treatments, visual recovery is unlikely.

SUDDEN SENSORINEURAL HEARING LOSS

Sudden sensorineural hearing loss is hearing loss of at least 30 dB occurring over 3 days involving at least three contiguous auditory frequencies.[21] The usual presentation is of a patient awaking from sleep with a sudden unilateral hearing loss, aural fullness, and at times tinnitus and vertigo. The cause is unclear, and many mechanisms have been described, including ischemia, trauma, toxins, vascular occlusion, viral infections, immune-associated disease, abnormal tissue growth, and labyrinthine and/or cochlear membrane damage.[22]

HBO therapy is effective primarily by achieving extremely high arterial perilymphatic oxygen concentrations. In combination with steroids, HBO therapy produces hearing gains over all frequencies.[22,23]

HBO therapy is indicated for profound sudden sensorineural hearing loss (>40 dB) within 14 days of symptom onset.[24] Patients with longer delays in presentation may benefit; the American Academy of Otolaryngology–Head and Neck Surgery advocates HBO therapy for up to 3 months after symptom onset.[25] It is essential that both corticosteroids (e.g., prednisone, 60 milligrams, orally, daily for 7 to 14 days and then tapered over 1 to 2 weeks) and HBO therapy (e.g., 100% oxygen at 2.0 to 2.5 ATA for 90 minutes daily for 10 to 20 sessions) be used together.[24]

EXCEPTIONAL BLOOD LOSS ANEMIA

In cases of acute severe anemia where transfusion cannot be used to improve oxygen content to sustainable levels (e.g., Jehovah's Witness, Rh incompatibility/transfusion reactions, patient refusal), HBO aids in sustaining life.[26] The benefits of HBO include rectifying the oxygen debt, providing a bridge that corrects end-organ damage, and allowing time for the patient's endogenous erythropoietin levels and baseline hemoglobin to rise. The HBO treatment protocol is 100% oxygen at 2.5 to 3.0 ATA for 3 to 4 hours (with air breaks) up to four times daily to raise Pao_2 in plasma to meet metabolic needs until red blood cell concentration improves.[27-30] Both animal studies and human clinical experience support the use of HBO for severe blood loss anemia.[31]

CRUSH INJURIES

Crush injuries damage multiple tissues, creating a cycle of edema and ischemia. Approximately half of patients with severe injuries develop complications such as osteomyelitis, fracture nonunions, amputations, and failed flaps despite optimal surgical and medical care. HBO treatment is effective in reducing complications and promoting healing in such patients.[32] The HBO protocol for crush injuries is 2.4 ATA for 100 minutes three times daily for 2 days, and then twice daily for 2 days, followed by once-daily sessions for 2 days.[33]

COMPARTMENT SYNDROME

Standard therapy for **compartment syndrome** is a fasciotomy to decompress the compartment and reverse ischemia of enclosed muscles and nerves. Fasciotomy itself has associated complications, and in the situation of impending compartment syndrome, HBO can improve oxygenation to hypoperfused tissues, promote arterial hyperoxia, decease vasoconstriction and edema, and prevent progression requiring

fasciotomy.[34-36] After fasciotomy for established compartment syndrome, HBO can prevent wound healing complications and accelerate recovery. Approximately three to five HBO treatments are usually required.[33]

OTHER ACUTE TRAUMATIC ISCHEMIAS

HBO therapy has been reported to be beneficial in other acute traumas that involve a self-perpetuating cycle of accelerating tissue damage from edema and ischemia, such as frostbite injuries[37,38]; threatened grafts and flaps[39]; in-jeopardy digit amputations or replantations[33,40]; ear amputations[41-43]; nose amputations[44,45]; penis injuries and amputations and postsurgical penile gangrene[46-49]; snake envenomation[50]; high-pressure water gun injection[51]; and electrical injury complications.[52] HBO therapy is a noninvasive, economically advantageous, and clinically efficacious adjunctive therapy to consider when complications or poor outcomes are likely despite appropriate surgical and medical care.

ACUTE THERMAL BURN INJURY

Animal models have shown significant benefits of HBO for thermal burns, including reducing partial- and full-thickness skin loss, hastening epithelialization, and lowering mortality.[53] Although some uncontrolled series have reported mixed results,[54-56] many clinical trials have reported significant improvement in healing,[57,58] decreased length of stay,[59-61] decreased mortality,[58,59,62] reduced cost of care,[59,60,62] improved morbidity,[58,59] decreased fluid requirements (30% to 35%),[58,62,63] and decreased surgical procedures.[60,63,65] Overall, in clinical trials, HBO showed benefit in 20 or 22 studies.[66] The HBO protocol for the treatment of thermal burns is 2.4 ATA for 100 minutes with two air breaks. Treatments begin three times daily and then decrease to twice daily and then once daily as healing occurs.[66]

CARBON MONOXIDE POISONING

Carbon monoxide toxicity develops from impairment of hemoglobin function and direct carbon monoxide–mediated cellular damage that poisons the electron transport chain and inhibits adenosine triphosphate formation (see Chapter 222, "Carbon Monoxide"). After removal from continued carbon monoxide exposure, the carbon monoxide slowly dissociates from the hemoglobin and the electron transport chain and is metabolized or exhaled. Treatment with HBO enhances elimination of carbon monoxide from the body.

Professional hyperbaric medicine organizations[66,67] recommend HBO treatment for appropriate carbon monoxide–poisoned patients. Two HBO protocols have been studied for carbon monoxide poisoning. The Salt Lake City protocol uses 3 ATA for 60 minutes, with two air breaks, followed by a reduction to 2 ATA for 65 minutes with one air break.[68] Two additional treatments are given in 6- to 12-hour intervals.[68] The Philadelphia protocol uses a single treatment at 2.8 ATA for 30 minutes followed by 2.0 ATA for 90 minutes.[69]

CYANIDE POISONING

Concomitant cyanide and carbon monoxide poisoning may be seen in patients rescued from closed-space fires in which synthetic materials are burned. Experimental evidence suggests that cyanide and carbon monoxide can produce synergistic toxicity.[70-72] HBO may directly reduce cyanide toxicity[73,74] and/or augment other antidote treatments.[75] However, clinical experience with HBO for pure cyanide toxicity is sparse, and there are no controlled trials.[75-80] Cyanide is among the most lethal poisons, and toxicity is rapid, so standard antidotal therapy for isolated cyanide poisoning is of primary importance (see Chapter 204, "Industrial Toxins"). HBO can be considered in case of dual carbon monoxide and cyanide poisoning and in cyanide poisoning when vital signs and mental status do not improve with antidote treatment.

NECROTIZING SOFT TISSUE INFECTIONS

Necrotizing soft tissue infections, including **necrotizing fasciitis** and **Fournier's gangrene**, are rapidly spreading, deep, typically mixed infections that result in profound morbidity and mortality (see Chapter 152, "Soft Tissue Infections"). Over the past 10 years, advances in surgical technique and antibiotic therapy and a higher index of suspicion regarding presentations and at-risk populations have improved survival.

HBO is a valuable adjunct to surgical debridement and antibiotic therapy in necrotizing soft tissue infections, reducing mortality, improving recovery rates, and decreasing both amputation rates and the number of required surgical interventions.[81-90] HBO is beneficial due to its ability to suppress growth of anaerobic microorganisms, improve bactericidal action of leukocytes that function poorly in hypoxic conditions, and enhance antibiotic penetration into target bacteria.[91-94] The HBO protocol for necrotizing soft tissue infections is twice-daily treatments at 2.0 to 2.5 ATA for 90 minutes with two air breaks until the extension of the necrosis is halted, and then daily until the infection is well controlled, for up to 30 sessions.[90]

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Gas gangrene is an acute, rapidly progressing clostridial infection of muscle tissue characterized by profound toxemia, edema, tissue death, and variable gas production.[95] The induction of gas gangrene requires only the presence of clostridial spores and a region of lowered oxidation reduction potential caused by local circulatory failure or extensive soft tissue damage and muscle necrosis.[96] Under the conditions of low oxygen tension, the clostridial spores can develop into the vegetative form.[96]

The pathogenesis of gas gangrene involves the production of clostridial exotoxins, of which more than 20 have been identified.[97-99] Alpha toxin is the most prevalent exotoxin and causes platelet and leukocyte destruction, widespread capillary damage, hemolysis, tissue necrosis, and often death.[99] Alpha toxin can be detoxified within hours after its elaboration, with natural host defenses conferring active immunity with production of a specific antitoxin.[98,100] However, death often occurs because the infection is so rapidly progressive that the patient dies before immunity can develop.[96]

The primary benefit of HBO therapy for gas gangrene is that inducing an oxygen tension of 250 to 300 mm Hg (33.3 to 40 kPa), achieved at 3.0 ATA,[101-103] halts alpha-toxin production, inhibits clostridial growth,[104] and allows normal host factors to swiftly detoxify the patient so that a moribund patient can rapidly be made nontoxic.[97,104-110]

The addition of HBO to standard treatment for gas gangrene shows consistently beneficial results, with survival rates between 72.9% and 81%[111-113] and limb salvage rates between 80% and 82% (compared to 40% to 50% with primary surgery).[111,114-117] Results decline progressively when HBO is delayed.

Treatment begins with an index of suspicion and a positive gram-stained smear of the wound fluid revealing gram-positive rods and a paucity of leukocytes. Although treatment with gas gangrene involves a three-pronged approach—antibiotics, surgery, and HBO—the initial surgery can be restricted to opening of the wound or an initial fasciotomy, followed by immediate HBO therapy. Lengthy and extensive procedures in gravely ill patients may be deferred, with necrotic tissue debridement performed between HBO sessions when a clear demarcation between dead and viable tissues is appreciated.[96] The HBO protocol for treatment of gas gangrene is 3.0 ATA for 90 minutes three times a day in the first 24 hours and then twice daily for the next 2 to 5 days. In several series, no mortality has been shown after the third HBO session (end of day 1).[115,118]

COMPLICATIONS OF HBO THERAPY

BAROTRAUMA

Middle ear barotrauma is the most common adverse effect of HBO treatment.[119] As the ambient pressure within the hyperbaric chamber increases, a patient must be able to equalize the pressure within the middle ear by autoinsufflation or else ear pain, tympanic hemorrhage, serous effusion, or rupture will develop. Standard protocols include instruction on autoinsufflation techniques and medical therapy when needed. When these interventions fail, tympanostomy tubes must be placed in order for HBO therapy to continue. The reported overall

incidence of aural barotrauma is between 1.2% and 7% of patients who undergo HBO therapy.[120,121] One series reported a 4% incidence of tympanostomy tube placement.[122]

Pulmonary barotrauma during HBO treatment is extremely rare but should be suspected when significant chest or hemodynamic symptoms occur during, or shortly after, decompression. If symptoms develop and the patient is in a multiplace chamber, stop decompression and evaluate for pneumothorax. If the patient is in a monoplace chamber, slowly decompress and provide supplemental oxygen upon returning to ambient pressure.

OXYGEN TOXICITY

Biochemical **oxygen toxicity** can injure the brain, lungs, and eyes. Acute oxygen toxicity manifests as a grand mal seizure, reported to occur approximately one to four times per 10,000 patient treatments.[120,123-125] The risk of seizure is higher in hypercapnic patients and possibly those who are acidotic or septic. Seizures are managed by reducing the inspired oxygen tension while leaving the patient at the same pressure (to avoid pulmonary overexpansion injury when a patient is in tonic convulsion phase). Chronic oxygen toxicity can impair lung mechanics (elasticity), vital capacity, and gas exchange.[126] These changes are typically observed only when treatment duration and pressures exceed typical HBO protocols.[127-129] Progressive myopia has been reported in patients who undergo prolonged daily therapy and typically reverses within 6 weeks after stopping HBO therapy.[130] There is a risk for nuclear cataract development, typically when treatments exceed a total of 150 to 200 hours, but they may arise with less provocative exposures.[131,132] Current evidence does not indicate that typical HBO protocols have detrimental effects on neonates or the unborn fetus.[133]

MISCELLANEOUS COMPLICATIONS

Confinement anxiety may occur and is typically managed with sedating agents. Any environment with an elevated concentration of oxygen presents a risk for fire. Scrupulous avoidance of an ignition source is standard in HBO therapy programs.[134]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 4

Resuscitative Procedures

CHAPTER 22

Basic Cardiopulmonary Resuscitation

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Jon Mark Hirshon

INTRODUCTION

The time sensitivity of CPR in sudden cardiac death is emphasized in the American Heart Association **Chain of Survival** (**Table 22-1**).[1,2] This chapter reviews basic CPR for adults and children ≥8 years old, including the approach to an unresponsive patient; the physiology and mechanics of closed chest compression techniques; and basic airway opening procedures, including initial management of an obstructed airway. This chapter is specifically directed toward healthcare providers, although key updates for lay rescuers are noted, given the healthcare provider's role in layperson education. **Table 22-2** outlines the sequence of steps to be taken when someone is found unresponsive.

SEQUENCE OF STEPS FOR BASIC CPR

1. C-A-B (chest compressions, airway, breathing) is the recommended sequence for a single rescuer. Provide chest compressions before giving rescue breaths.
2. Compression rate should be 100 to 120 per minute.
3. Compression depth should be 2 to 2.5 in. (5 to 6 cm).
4. Do not lean hands on the chest between compressions to allow complete recoil between compressions.
5. Continue compression-only CPR until arrival of automated external defibrillator or rescuers with additional training.
6. If trained in rescue breathing, add rescue breaths after 30 compressions, using two breaths then and every 30 compressions until skilled help arrives.
7. Naloxone may be given for suspected life-threatening opioid-associated emergencies.
8. Assessment of breathing and pulse checks may be done first by basic life support healthcare providers, but must be done in <10 seconds.

STEPS OF BASIC CPR

STEP 1 AND STEP 2 IN BASIC CPR: RECOGNITION AND CALL FOR HELP

Before approaching a collapsed individual, assess the scene for risks to healthcare providers. Potential risks include the presence of hazardous materials, an unstable physical environment, or personal violence. Once the patient is reached, determine the patient's level of responsiveness to noxious stimuli. If the patient is without normal breathing, get help first before starting chest compressions. In a hospital, this may mean calling for the arrest team and requesting the arrest cart. Outside the hospital, this is likely to mean asking a bystander to activate the local EMS system. Look around to see if an automatic external defibrillator (AED) is nearby. Rapid application of defibrillation for unstable ventricular tachycardia or ventricular fibrillation is critical for patient survival.

STEP 3 IN BASIC CPR (HEALTHCARE PROVIDER ONLY): ASSESS CIRCULATION

The carotid artery is generally the most reliable and accessible location to palpate a pulse. The artery is located by placing two fingers on the trachea and then sliding them down to the groove between the trachea and the sternocleidomastoid muscle. Simultaneous palpation of both carotid arteries should not be performed because, in low-pressure states, this could obstruct cerebral blood flow and may interfere with the ability to detect a pulse. The femoral artery may be used as an alternative site to palpate a pulse. This can be found just below the inguinal ligament approximately halfway between the anterior superior iliac spine and the pubic tubercle. If no definite pulse is felt within 10 seconds, chest compression should begin.

STEP 4 IN BASIC CPR: BEGIN CARDIAC COMPRESSIONS

Physiology of Closed Chest Compressions There has been an active debate as to the exact mechanism that causes blood flow since the technique of closed chest compressions was put forth in the 1960s.[5,6] In a closed system, liquid flows when pressure gradients develop. There are three basic theories for how pressure gradients and flow are produced during **closed chest cardiac massage**.[7,8] The conventional theory of blood flow during compressions is called the **cardiac pump theory**. The pump theory postulates that direct compression of the heart between the spine and the sternum leads to increased pressure in the ventricles. This causes closure of the mitral and tricuspid valves, leading to blood flow into the aorta and the pulmonary arteries. The **thoracic pump theory** postulates that compressions lead to an increase in pressure throughout the thoracic cavity, leading to a pressure gradient from intrathoracic to extrathoracic arteries. The third mechanism described is the **abdominal pump theory**, which has both an arterial and a venous component. The arterial component postulates blood flow into the peripheral arterial system from increased arterial pressure caused by abdominal compressions that forces blood from the abdominal aorta against the closed aortic valve. The venous component leads to blood return via the inferior vena cava from abdominal pressure. However, regardless of the mechanism, conventional chest compressions generate one fourth to one third of physiologic cardiac output. Lower ratios can be expected with delays in initiating compressions.

Technique of Closed Chest Compression When the lack of a pulse is confirmed, begin serial rhythmic closed chest compressions (**Table 22-3**). Place the victim supine on a firm surface, with the rescuer at the victim's side. Place the heel of one hand midline on the lower half of the sternum, 4 to 5 cm (~2 in.) cephalad of the xiphoid process (**Figure 22–1**). The heel of the hand should be parallel with the long axis of the patient's body. Then place the second hand on top of the first hand, so the hands are parallel with each other. The fingers of the two hands may be interlaced if desired, but they should not be touching the chest. Keep the arms straight and the elbows locked. The vector of the compression force should start from the rescuer's shoulders and be directed downward. Lateral compressive forces will decrease the efficiency of the compressions and increase the likelihood of complications. **Depress the sternum 2 to 2.5 in. (5 to 6 cm) in an adult at a rate of 100 to 120 compressions per minute.** Rates lower than this are inadequate. The compression-release phases should be roughly equal in length. **With a single rescuer or with two rescuers if the patient is not intubated, give two ventilations after every 30 compressions. With two rescuers assisting an intubated patient, ventilate at a rate of 8 to 10 per minute, without interrupting chest**

TABLE 22-1 American Heart Association Chain of Survival[1-4]

Links in Chain	Comment
Recognition and activation of the emergency response system (EMS)	Early recognition of the emergency and activation of the EMS or local emergency response system are vital. Phone the local emergency medical telephone number.*
Immediate high-quality CPR	Immediate bystander CPR can double or triple the victim's chance of survival.
Rapid defibrillation	CPR plus defibrillation within 3 to 5 min of collapse can produce improved survival rates.
Basic and advanced emergency medical services	High-quality resuscitative care is provided by EMS personnel.
Advanced life support and postarrest care	High-quality, integrated post–cardiac arrest clinical care by healthcare providers.

*For a global list of emergency numbers and mobile phone use, see https://en.wikipedia.org/wiki/List_of_emergency_telephone_numbers.

TABLE 22-2 Systematic Approach to CPR

CPR Steps	Comments
Step 1: Recognition	Assess for responsiveness, lack of breathing, or presence of abnormal breathing/gasping.
Step 2: Activate the emergency medical response system and get an automatic external defibrillator (AED)	If possible, call for an assistant to activate EMS and obtain an AED. It is recommended that dispatchers help determine if there is presence of a cardiac arrest and help initiate dispatcher-guided CPR if indicated.
Step 3: Assess circulation (*healthcare provider only*)	If no pulse after 10-second maximum check, go to step 4. (*Pulse checks are for healthcare providers only.*)
Step 4: Begin cycle of 30 closed chest compressions	Compressions: "Push hard and fast." 100–120 compressions/min. Compress 2–2.5 in. (5–6 cm). Allow for complete chest recoil, <10-second compression interruption. Ratio of 30 compressions to 2 breaths. Alternate compressors every 2 minutes or when the compressor becomes fatigued if an assistant is available.
Step 5: Use the defibrillator when available and indicated	A defibrillator should be used as soon as available. It is recommended that while the AED is being retrieved and applied CPR is initiated and continued until the device is ready for use.
Step 6: Continue high-quality CPR	Continue CPR between rhythm checks, while the defibrillator is being applied and immediately restart compressions after defibrillation. This is to maximize compression times and decrease interruptions.
Step 7: Rescue breathing	Rescue breaths are to be initiated only by a trained lay rescuer that is able to perform rescue breaths or by a healthcare provider. Untrained lay rescuers and trained lay rescuers unable to provide rescue breaths should perform compression-only CPR. Administer 2 breaths following a cycle of 30 chest compressions. Deliver each breath over 1 second with sufficient tidal volume to see a visible chest rise. Continue cycles of 30 closed chest compressions and 2 breaths, minimizing interruptions.

*For a global list of emergency numbers and mobile phone use, see https://en.wikipedia.org/wiki/List_of_emergency_telephone_numbers.

TABLE 22-3 Techniques of Closed Chest Compression

Closed chest compressions	Depth: 2–2.5 in. (5–6 cm). Rate: 100–120/min. Allow complete recoil of the chest between compressions, with approximately equal compression and relaxation times. Minimize interruptions.
Ventilations	Single rescuer or 2 rescuers, nonintubated patient: give 2 breaths after every 30 compressions. Two rescuers, intubated patient: give breaths at a rate of 8–10 breaths/min. Do not pause chest compressions during ventilations.

compressions. Of note, although assisting ventilation is important, not everyone is willing to perform mouth-to-mouth breathing due to concerns over infectious disease transmission. **Chest compressions alone can be effective and should be provided even if rescue breathing is not being performed.**[1,2,9,10]

Open Chest Cardiac Compressions Open chest cardiac massage is an alternative to standard CPR and improves blood flow in animal models. This technique may be considered in a number of situations, including (1) after penetrating chest trauma; (2) in the perioperative period before or after cardiothoracic surgery; (3) during cardiac arrest caused by hypothermia, pulmonary embolism, pericardial tamponade, or abdominal hemorrhage; (4) in cases of chest deformity in which closed chest CPR is ineffective; (5) in penetrating abdominal trauma with deterioration and cardiac arrest; and (6) in blunt trauma with cardiac arrest.[11] However, opening the chest solely to perform open cardiac massage does not provide benefit over closed chest compressions.[12] Moreover, the use of this technique requires a well-coordinated multidisciplinary team (see Chapter 262, "Cardiac Trauma").

STEP 5 IN BASIC CPR: DEFIBRILLATE

Defibrillation is discussed in Chapter 23, "Defibrillation and Electrical Cardioversion."

STEP 6 IN BASIC CPR: CONTINUE HIGH-QUALITY CARDIAC COMPRESSIONS

Continuing high-quality compressions as much as possible while minimizing interruptions is critical to increase the chances of achieving return of spontaneous circulation and optimizing the chance of survival to hospital discharge.[13] Chest compressions fraction refers to the proportion of time spent performing compressions. Current guidelines recommend a chest compression fraction of at least 60%.[14] Interruptions can be minimized by continuing compressions between pulse checks, while applying the AED, and immediately restarting CPR after defibrillation. When performing US in cardiac arrest, minimize the time spent on the chest by the US probe. Techniques to minimize the time on the chest include loading the probe with gel and having it ready at the bedside, counting the time on the chest, and having a towel ready to wipe off the gel so as to not create a slippery surface for the compressor.

STEP 7 IN BASIC CPR: OPEN THE AIRWAY AND RESCUE BREATHING

The seventh step is to **assess the upper airway of the victim**. This usually requires positioning the individual supine on a flat, firm surface with the arms along the sides of the body. Unless trauma can be definitely excluded, any movement of the victim should consider the possibility of a spine injury. As the patient is placed supine, stabilize the cervical spine by maintaining the head, neck, and trunk in a straight line. If the neck is not already straight, then it should be moved as little as possible to establish the airway. If the patient cannot be placed supine, the jaw thrust maneuver (see "Jaw Thrust Maneuver" section) can be applied with the rescuer at the victim's side. **Common causes of airway obstruction in an unconscious patient are occlusion of the oropharynx by the tongue and laxity of the epiglottis.** With loss of muscle tone, the tongue or the

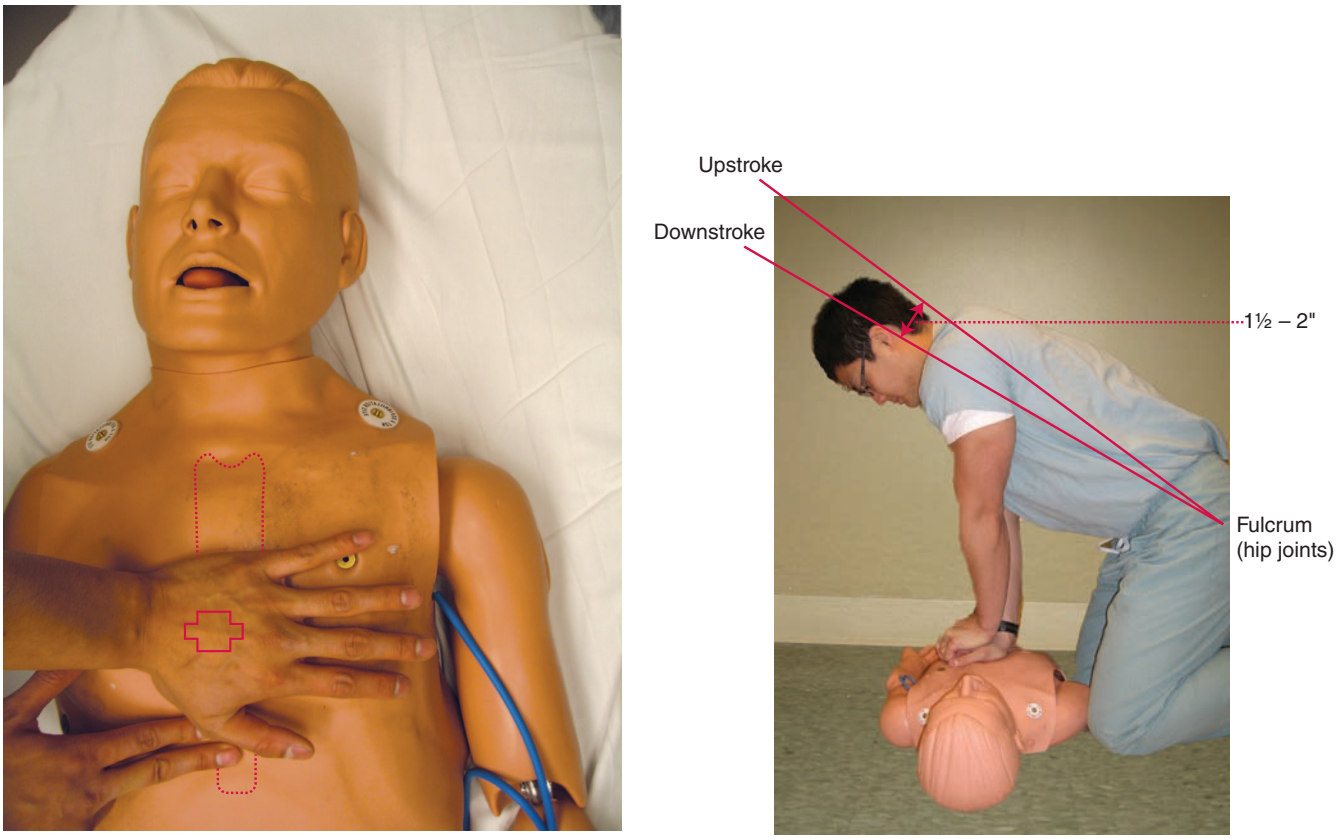

FIGURE 22-1. Proper hand (A) and rescuer (B) positioning for chest compression. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

epiglottis can be forced back into the oropharynx upon inspiration. This can create the effect of a one-way valve at the entrance to the trachea, leading to airway obstruction. After positioning the patient, inspect the mouth and oropharynx for secretions, foreign objects, loose (floppy) dentures, partial dentures, or broken teeth. If dentures fit properly, keep them in place if possible, as they will allow for a better seal. If secretions are present, they can be removed with the use of oropharyngeal suction if available; a visualized foreign body may be dislodged by use of a finger sweep and then manually removed. **In contrast to earlier recommendations, a blind finger sweep should never be performed as there is a risk of worsening airway obstruction** (see "Finger Sweep" section).

Once the oropharynx has been cleared, two basic maneuvers for opening the airway may be tried. These are the head tilt–chin lift and the jaw thrust. These maneuvers help to open the airway by mechanically displacing the mandible and the attached tongue out of the oropharynx.

Head Tilt–Chin Lift Maneuver To perform the **head tilt–chin lift maneuver**, gently extend the patient's neck by placing one hand under the patient's neck and the other on the forehead and extending the head in relation to the neck. This maneuver should place the patient's head in the sniffing position, with the nose pointing up. In conjunction with the head tilt, perform the chin lift. The chin lift is done by carefully placing the hand that had been supporting the neck for the head tilt under the symphysis of the mandible, taking care not to compress the soft tissues of the submental triangle and the base of the tongue. Then lift the mandible forward and up, until the teeth barely touch. This supports the jaw and helps tilt the head back.

Jaw Thrust Maneuver The **jaw thrust** is the safest method for opening the airway if there is the possibility of cervical spine injury. This maneuver helps to maintain the cervical spine in a neutral position. The rescuer, who is positioned at the head of the patient, places the hands at the sides of the victim's face, grasps the mandible at its angle, and lifts the mandible forward (**Figure 22-2**). This lifts the jaw and opens the airway with minimal head movement.

Suspected Opioid Overdose In the setting of the opioid epidemic, including the demographic data showing a rise in opioid-related deaths, the use of prehospital naloxone has become more prevalent. Laypersons and healthcare providers are encouraged to administer intranasal or intramuscular naloxone using an autoinjector in patients with a pulse but no effective breathing in the setting of a known or suspected opioid overdose.[1] Medication administration to patients in cardiac arrest is ineffective without high-quality chest compressions. Hence, administration of naloxone in patients in cardiac arrest should be considered only after CPR has been initiated.[1]



FIGURE 22-2. Jaw thrust maneuver. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

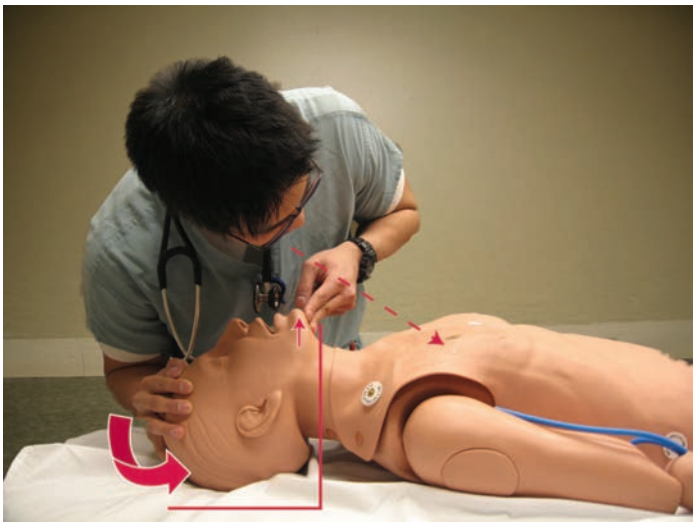

FIGURE 22-3. Determine breathlessness. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]



FIGURE 22-4. Mouth-to-mouth rescue breathing. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

Rescue Breathing After opening the airway, assess respiratory effort and air movement. Look for chest expansion, and listen and feel for airflow. The simple act of opening the airway may be adequate for the return of spontaneous respirations. However, if the victim remains without adequate respiratory effort, then further intervention is required. **If rescuers are reluctant to perform mouth-to-mouth ventilation and the patient is in cardiac arrest, chest compressions alone can be effective** (Table 22-3).

Two breaths over 1 second each should be given with sufficient volume to cause visible chest rise. At this point, if a foreign body obstruction is noted, as indicated by a lack of chest rise or airflow on ventilation, the obstruction requires removal (**Figure 22-3**). Agonal respirations in an individual who has just suffered a cardiac arrest are not considered adequate for ventilation. Intermittent positive-pressure ventilation, with oxygen-enriched air if possible, should be initiated.

Table 22-4 outlines the recommendations for delivery of rescue breaths during cardiac arrest.[1,2] When an advanced airway (e.g., endotracheal tube, Combitube, or laryngeal mask airway) is in place during two-person CPR, ventilate at a rate of 8 to 10 breaths per minute without attempting to synchronize breaths between compressions. There should be no pause in chest compressions for delivery of ventilations.[1,2]

In an adult with normal perfusion, 8 to 10 mL/kg tidal volume is required for adequate oxygenation and ventilation. However, in the setting of CPR, where cardiac output is only 25% to 33% of normal, a lower minute ventilation, and thus tidal volume, can be satisfactory. **Approximately 6 to 7 mL/kg will suffice.** Use an appropriately sized bag for bag-valve-mask ventilation. A pediatric bag will provide inadequate tidal volumes for an adult.

There are a number of techniques for ventilating an individual, including mouth to mouth, mouth to nose, mouth to stoma, and mouth to mask. **Rescue breaths with an inspiratory time of 1 second each should be given at a rate of 8 to 10 per minute, with a volume adequate to make the chest rise visibly (approximately 6 to 7 mL/kg; 500 to 600 mL in adults). Supplemental oxygen should be delivered as soon as possible.** Expired air has a fraction of expired oxygen of 16% to 17%. Too large a volume or too rapid an inspiratory flow rate can cause gastric distention, which can lead to regurgitation and aspiration.

TABLE 22-4 Delivery of Rescue Breaths During CPR

- Deliver each rescue breath over 1 second.
- Give a sufficient tidal volume (by mouth to mouth/mask or bag mask with or without supplementary oxygen) to produce visible chest rise.
- Avoid rapid or forceful breaths.
- Avoid hyperventilation.

Mouth-to-Mouth Ventilation With the airway open, gently pinch the patient's nose shut with the thumb and index finger (**Figure 22-4**). This prevents air escape. After taking a deep breath, place the lips around the patient's mouth, forming an airtight seal. Slowly exhale. Release the seal and allow adequate time for passive exhalation by the victim, and then repeat the procedure. Protective devices such as face shields decrease the risks to the provider of contracting an infectious disease and can be purchased from most medical equipment stores.

Mouth-to-Nose Ventilation In some cases, as with severe maxillofacial trauma, mouth-to-nose ventilation may be effective. With the airway open, lift the patient's jaw, closing the patient's mouth. After a deep breath, place the lips around the patient's nose, forming an airtight seal. Slowly exhale.

Mouth-to-Stoma or Tracheostomy Ventilation After laryngectomy or tracheotomy, the stoma or tracheostomy becomes the patient's airway. As with the other techniques, a seal is made around the stoma or tracheostomy tube, and the rescuer slowly exhales.

Mouth-to-Mask Ventilation Proper and secure placement of the mask on a victim's face is important when using a mask for ventilation, either with a bag or via mouth to mask. Place the mask over the bridge of the patient's nose and around the mouth. Place the thumb on the part of the mask that is sitting on the patient's nose and place the index finger of the same hand on the part of the mask sitting on the patient's chin (**Figure 22-5**). The three other fingers of the same hand are then placed along the bony margin of the jaw. The mask can then be firmly sealed to the patient's face. Two hands may be used for this technique if a second rescuer is available. Ventilations are then performed through the mask. Some masks also allow for supplemental oxygenation.

FOREIGN BODY OBSTRUCTION

It is important to recognize and be able to assist someone with an airway obstruction due to a foreign body.[15] An individual in distress from a compromised airway is likely to use the **universal sign for an airway obstruction**, which is for the individual to grab his or her neck with both hands. Foreign bodies can cause partial or complete obstruction. With a partial airway obstruction, air exchange may be adequate or inadequate. If the victim is able to speak, cough, and exchange air, then he or she should be encouraged to continue spontaneous efforts. Obtain assistance, such as activation of the local EMS system. Do not interfere with the patient's attempts to cough or expel the foreign body **and do not perform a blind finger sweep**. If air exchange becomes inadequate,



FIGURE 22-5. Mouth-to-mask rescue breathing with proper mask placement. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

as indicated by an inability to speak, increased difficulty breathing, weak and ineffective cough, worsening stridor, or cyanosis, immediate medical intervention is needed (see next section, "Obstructed Airway (Heimlich) Maneuver"). Inadequate air exchange from a severe partial or a complete airway obstruction should be managed the same way. In an unconscious person, the presence of airway obstruction may be ascertained by noting inadequate airflow and poor chest rise with efforts to ventilate.

Maneuvers used to relieve foreign body obstructions include the **Heimlich maneuver** (subdiaphragmatic abdominal thrusts), **chest thrusts**, and the finger sweep. In a conscious individual, the obstructed airway (Heimlich) maneuver is the recommended maneuver in most adults for relieving airway obstruction due to a solid object. It is not useful for liquids. In an unconscious individual suspected of having an aspirated foreign body and in whom the foreign body is visualized, the recommended first step is the finger sweep. **A blind finger sweep is no longer recommended** as it may worsen airway obstruction by pushing an unseen object into an even less favorable position. Otherwise, in an unconscious patient, the recommended sequence is to perform the obstructed airway maneuver up to five times, open the mouth and perform a finger sweep if a foreign body has become visible, and then attempt to ventilate. This sequence may be repeated as often as needed until the patient recovers or additional assistance arrives.

OBSTRUCTED AIRWAY (HEIMLICH) MANEUVER

The **Heimlich maneuver** creates an artificial cough by forcefully elevating the diaphragm and forcing air from the lungs.[16] It may be repeated multiple times. Each individual thrust should be performed aggressively, with the intention of removing the obstruction. The maneuver can be performed with the victim standing, sitting, or lying down, or it can be self-administered (**Figure 22-6**). To perform the maneuver with the patient standing or sitting, stand behind the patient and place the thumb side of a fist against the victim's abdomen midline just above the umbilicus and well below the xiphoid process (Figure 22-6). Grasp the fist with the other hand, and forcefully push the fist into the victim's abdomen with a quick upward thrust. Repeat until the item is dislodged or the patient becomes unconscious. For an unconscious patient, place the victim supine on a firm surface and sit astride the victim's thighs (**Figure 22-7**). Place the heel of the dominant hand midline just above the patient's umbilicus, and the other hand directly on top of the first. Then deliver quick upward thrusts. To self-administer thrusts, the individual can either use his or her own fist to deliver the thrusts or lean forcibly against a firm object, such as a porch rail or the back of a chair. Potential complications of the Heimlich maneuver include injury or rupture of abdominal or thoracic viscera and regurgitation of stomach contents.



FIGURE 22-6. Standing Heimlich maneuver administered to conscious victim of foreign body airway obstruction. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

CHEST THRUSTS

The **chest thrust** maneuver is used primarily if someone is morbidly obese or in the late stages of pregnancy and the rescuer cannot reach around the patient's abdomen to perform abdominal thrusts (**Figure 22-8**). To perform chest thrusts with the patient standing or sitting, stand behind the patient



FIGURE 22-7. Prone Heimlich maneuver administered to unconscious victim of foreign body airway obstruction. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]



FIGURE 22-8. Standing chest thrust maneuver administered to conscious victim of foreign body airway obstruction.

and place the thumb side of a fist against the victim's sternum, avoiding the costal margins and the xiphoid process. Grasp the fist with the other hand, and press the fist into the victim's chest with a quick backward thrust. Repeat until the item is dislodged or the patient becomes unconscious. For an unconscious patient, place the victim supine on a firm surface and kneel close to the victim's side. Place the hands in the same position as for chest compression (i.e., the lower sternum), and deliver quick thrusts.

FINGER SWEEP

The **finger sweep** maneuver is used only in unconscious patients (**Figure 22-9**). Using the thumb and fingers of one hand, grasp both the tongue and the mandible and lift them. This may partially relieve the obstruction by lifting the tongue away from the back of the throat. With the other hand, insert the index finger into the back of the throat, and use a hooking action in an attempt to dislodge the foreign body to move it into the mouth for manual removal. Use care so the foreign object is not pushed deeper into the throat.

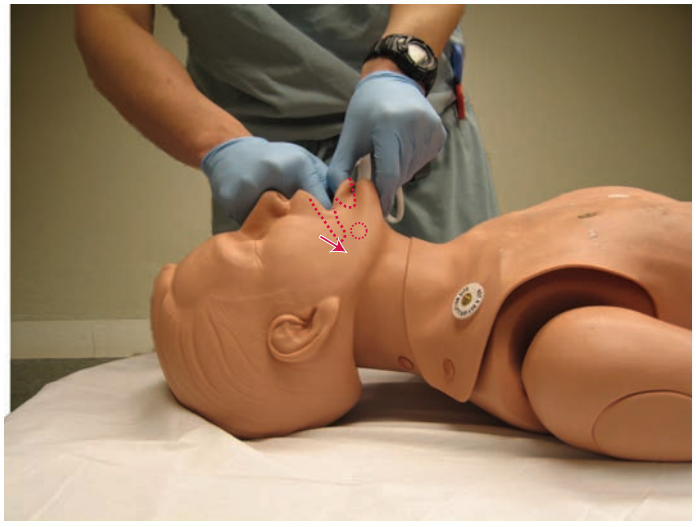

FIGURE 22-9. Finger sweep maneuver administered to unconscious victim of foreign body airway obstruction. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

MECHANICAL DEVICES FOR CHEST COMPRESSIONS

Mechanical piston devices are designed to deliver chest compressions in place of manual chest compressions. They consist of an automated compressed gas- or electric-powered plunger that is placed over the sternum and delivers compressions to the chest at a set rate. Certain devices have a suction cup at the end of the piston to actively decompress the chest following a chest compression. The Lund University Cardiac Arrest System is the most widely used and studied mechanical piston device, but other devices are available as well. A load-distributing band is a circumferential chest compression device composed of a pneumatically or electronically constricting band and backboard. The AutoPulse is an example of a load-distributing device.

Thus far, studies have not shown that the use of a Lund University Cardiac Arrest System device improves either early (4-hour) or late (1- and 6-month) survival.[17,18] Literature has shown possible negative effects on outcomes with use of the AutoPulse.[19,20] Therefore, the American College of Cardiology/American Heart Association guidelines recommend manual chest compressions as the preferred compression method.[21] The guidelines only recommend the use of a mechanical device by properly trained personnel in specific settings. These settings would include scenarios where compressions are difficult or dangerous for the provider, such as limited provider availability, prolonged CPR, during hypothermic arrest, in a moving ambulance, in an angiography suite, or during preparation for extracorporeal CPR. When using a mechanical device, interruptions should be strictly limited to placement and removal of the device.

COMPLICATIONS OF CPR

Ventilations can cause insufflation of the stomach, leading to regurgitation and aspiration and possibly to gastric rupture. Closed chest compressions can lead to fractures of the sternum or the ribs, separation of the ribs from the sternum, pulmonary contusion, pneumothorax, myocardial contusion, hemorrhagic pericardial effusions, splenic laceration, or liver laceration. Proper techniques can minimize these complications but cannot totally prevent them. Late complications include pulmonary edema, GI hemorrhage, pneumonia, and recurrent cardiopulmonary arrest. Anoxic brain injury can occur in a resuscitated individual subjected to prolonged hypoxia; it is the most common cause of death in resuscitated patients.

TERMINATING RESUSCITATION

Efforts at resuscitation should be continued until the patient recovers spontaneous respirations and cardiac output, the rescuer becomes exhausted, or the patient is pronounced dead. An atraumatic individual who recovers spontaneous respirations and circulation should be placed on his or her side—the **recovery position**. Recovery from cardiac arrest depends on time to CPR and rhythm-specific intervention. Resuscitation and long-term outcome in normothermic patients with arrest times of 20 minutes or more are very poor.

ETHICAL CONSIDERATIONS IN RESUSCITATION

During the initiation of resuscitation attempts, try to discover whether or not the victim has advance directives that prohibit CPR.[22] Family members may wish to be present during resuscitation attempts,[22] and support from social services and clergy should be sought early (see Chapter 27, "Ethical Issues of Resuscitation").

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 23

Defibrillation and Electrical Cardioversion

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PURPOSE OF PROCEDURE

Defibrillation is the therapeutic use of electricity in cardiac arrest to depolarize the entire myocardium to eliminate ventricular fibrillation or nonperfusing ventricular tachycardia so that coordinated contractions can resume. It should be performed in close coordination with CPR of the cardiac arrest patient.

Electrical cardioversion is the application of a synchronized electrical impulse to convert a still-perfusing tachydysrhythmia back to a normal sinus rhythm. Cardioversion may also be performed pharmacologically or nonpharmacologically for the stable patient.

PATIENT SELECTION

The indications for defibrillation include ventricular fibrillation (**Figure 23-1**) and pulseless ventricular tachycardia (**Figure 23-2**). Defibrillation is not "jumpstarting the heart" and is thus not indicated for asystole or pulseless electrical activity. It is contraindicated for sinus rhythm, conscious patients with a pulse, or when there is danger to the operator or others (e.g., from a wet patient or wet surroundings).

Electrical cardioversion is indicated for patients with ventricular tachycardia, supraventricular tachycardia, atrial flutter, or atrial fibrillation, who are hemodynamically unstable as a consequence of the rhythm. It may also be considered after unsuccessful pharmacologic therapy for the previously mentioned arrhythmias, even if the patient remains hemodynamically stable. Electrical cardioversion should be synchronized, which means the electric impulse will be timed with the patient's intrinsic QRS complexes, to minimize the risk of inducing ventricular fibrillation.

EQUIPMENT

The energy used for defibrillation or electrical cardioversion is delivered as a wave and may be **monophasic** or **biphasic**. Monophasic waveforms are found in older defibrillators and deliver the energy in a single direction, while biphasic waveforms deliver the energy forward and back in two phases within the same amount of time. The amount of energy required for successful defibrillation is typically lower with biphasic waveforms. Most current defibrillators employ biphasic waveforms, with some manufacturers using their own proprietary waveforms.

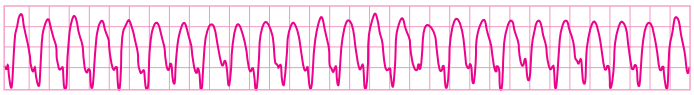


FIGURE 23-2. Ventricular tachycardia.

Manual defibrillators require a manual analysis of the patient's cardiac rhythm, as well as manual delivery of the shock through paddles or self-adhesive pads (see below) by the operator.

Automated external defibrillators may be fully or semi-automated. Fully automated external defibrillators will analyze the rhythm automatically, and if indicated, charge and deliver the shock, whereas semi-automated external defibrillators will require an operator to manually deliver the shock after analysis and charging.

Manual shocks may be delivered using paddles or self-adhesive defibrillator pads. **Manual paddles** are docked in **cradles** on the defibrillator and need to be removed and applied onto the patient's chest, with minimal time in transit from one position to the other. To prevent inadvertent discharges, always point the paddles downward (**Figure 23-3A**), and never wave the paddles around, face them toward each other, or hold both paddles in one hand (**Figure 23-3B**), especially when charged. **Safety** must be ensured. When using paddles, apply **conductive gel** or **gel pads** and firmly press the paddles against the chest wall (25 pounds per square inch of pressure). If conducting gel is used, ensure that the gel does not smear across the chest between the two paddles. Similarly, if gel pads are used, ensure that the two pieces do not overlap (**Figure 23-4, A and B**).



A



B



FIGURE 23-1. Ventricular fibrillation.

FIGURE 23-3. **A.** Correct paddle handling. **B.** Improper paddle handling.



A B

FIGURE 23-4. **A.** Anteroapical positioning of defibrillation paddles in an adult using gel pads. **B.** Do not overlap gel pads.

Adhesive pads are single-use and come in disposable packaging. When applying the pads, ensure that they do not overlap and there are no air pockets between the pads and the skin. Good contact ensures maximal shock efficacy. In automated external defibrillators, if contact is insufficient for the defibrillator to operate, a "Check Electrodes" message may also be heard.

Pads are considered advantageous over paddles because of ease of placement, self-retaining nature, improved transmission of current, safety, and hygiene. In addition, they may be used as electrical leads for monitoring of the rhythm or in cardiac pacing. Due to their thinner profile, they can be easily placed in anteroapical, anteroposterior, or anterior-posterior positions (see below) with greater ease. They are preferrred, if available. However, because the pads are only single-use and have expiration dates, paddles may be kept as a backup for situations when pads are unavailable, expired, or malfunction.

Defibrillators and their accessories should be properly maintained and kept in a constant state of readiness. We recommend the use of checklists[1] to identify defibrillator malfunctions and ensure proper maintenance of batteries. Users should be trained in the proper use of checklists and checks should be performed regularly (such as daily or every shift).

PATIENT POSITIONING AND SKIN PREPARATION

Ensure that the **scene is safe** for performing defibrillation, including water and environmental scene dangers such as traffic. The patient should be in the supine position with ongoing CPR. Expose the chest to apply the pads or paddles. To avoid skin burns, remove all **metallic objects, jewelry,** or **medication patches** (wipe off any residue). If there is excessive **chest hair** over the areas where the pads or paddles are to be placed, quickly shave the hair off to ensure a good contact with the skin. If the patient is on a **wet or conducting surface**, move the patient to a safe area and dry the body before delivering any shocks. Sweat or moisture on the chest will conduct the current and may reduce the adhesion of pads. Remove all **direct sources of oxygen** to avoid fire.[2,3]

PLACEMENT OF PADS/PADDLES

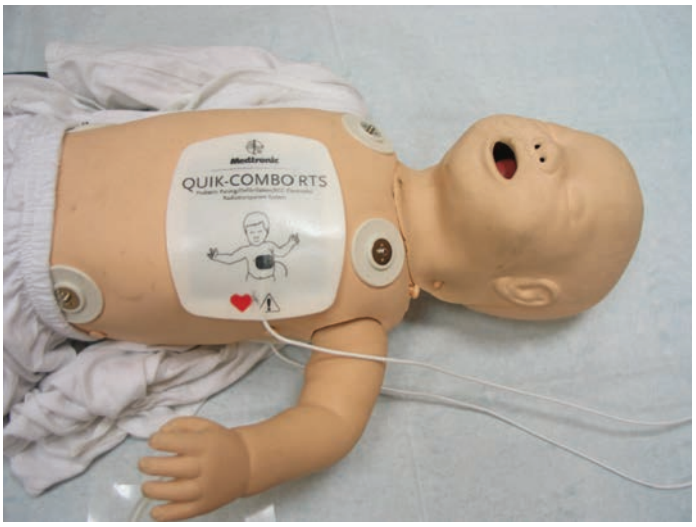
There are several possible positions for the placement of the pads or paddles:

1. **Anteroapical position:** Place one paddle/pad to the right of the upper half of the sternum, just below the patient's right clavicle, and place the other pad just below and to the left of the left nipple. With a female patient, place the paddle/pad just below and to the left side of the breast. Do not place it over the breast (**Figure 23-5**).

   This is the preferred position for a supine patient, such as in cardiac arrest, and when using defibrillation paddles. The idea is to maximize current flow across the cardiac chambers rather than along the chest wall.
2. **Anteroposterior position:** Place one pad/paddle at the left lower sternal border and the posterior pad/paddle below the left scapula (**Figure 23-6, A and B**).
3. Pacemakers, automated implantable cardiac defibrillators, and other implants: such devices are implanted under the skin and palpable on examination. Ensure that the placement of the pads is at least four fingerbreadths away from such devices.



FIGURE 23-5. Anteroapical positioning of defibrillation pads. [Image used with permission of Medical Simulation & Education.]



A



B

FIGURE 23-6. Anteroposterior positioning of defibrillation pads in an infant. [Reproduced, with permission, from Children's Emergency, KK Women's and Children's Hospital, Singapore.]

ANESTHESIA AND PROCEDURAL MONITORING

For patients in cardiac arrest, defibrillation is part of the immediate resuscitation process, and anesthesia is unnecessary. However, for emergency or elective **electrical cardioversion**, good preparation, procedural sedation, and monitoring—before, during, and after the procedure—are essential.

Obtain informed consent whenever possible. Place an IV line and a crystalloid fluid drip to ensure that the vein is open for drug delivery. Ensure airway equipment, suction apparatus, oxygen, and resuscitation drugs are immediately available. Procedural sedation may be provided by using a combination of sedation agents (e.g., etomidate, propofol, midazolam, or ketamine) and analgesic agents (e.g., fentanyl or morphine). Drugs should be selected based on familiarity with the pharmacologic profile as well as the patient comorbidity profile. Ensure cardiac, hemodynamic, and pulse oximetry monitoring before, during, and after the procedure, watching out for adverse effects of the drugs or deterioration of the rhythm.

STEP-BY-STEP TECHNIQUE

MANUAL DEFIBRILLATION

1. Prepare the patient and equipment as described earlier. **CPR should be ongoing.**
2. If using paddles, attach the **rhythm monitoring electrodes**. Alternatively, the paddles may be applied to the chest directly in "quick look" mode to read the rhythm.
3. If pads are used, the rhythm will be read by the pads, and additional rhythm electrodes are not necessary.
4. Interrupt chest compressions only briefly (<10 seconds) to **analyze the rhythm** manually.
5. Confirm that the rhythm is ventricular fibrillation or pulseless ventricular tachycardia, then **resume CPR immediately**.
6. Select the appropriate **energy level**. For biphasic defibrillators, select according to the manufacturer's recommendation (150 to 200 J for biphasic truncated exponential waveforms and 120 to 200 J for rectilinear biphasic waveforms). If the recommendation is unknown, use the maximum energy available. For monophasic defibrillators, begin with an initial 360-J shock. If starting with less than the maximum energy, consider escalation of shock energy for failed shocks or recurrence of fibrillation.
7. Ensure that the defibrillator is in **unsynchronized** mode.
8. If using paddles, apply the paddles and **charge**. CPR should NOT be interrupted during charging. All other personnel may begin to stand clear at this point.
9. Call out, "**Stand clear,**" and ensure that no one is in contact with the patient or trolley. CPR is interrupted only *briefly* (<10 seconds) at this point.
10. With the CPR interrupted, quickly confirm the rhythm remains shockable, then **deliver the shock**. The operator's eyes should be back on the patient at the time of shock delivery, to ensure safety.
11. Resume CPR *immediately* once the shock has been delivered. Do NOT pause to check the pulse or reanalyze the rhythm at this time.
12. Continue management according to the local resuscitation protocol.

AUTOMATED EXTERNAL DEFIBRILLATION

1. Prepare the patient and equipment as described earlier. **CPR should be ongoing.**
2. **Turn on** the automated external defibrillator (follow the voice prompts according to your device).
3. Open the package containing the **defibrillation pads** with the attached cable and connector. With the chest prepared, carefully pull off the protective backing from the pads and apply the pads to the chest, taking care to avoid air pockets. The pads should be placed at least 2 inches away from any automated implantable cardiac defibrillators.
4. Initiate **analysis** of the rhythm. This may be automatic or require pressing a button to activate analysis. Ensure that there is no movement of the patient during analysis, including a brief interruption of CPR.
5. If a shock is advised, the device will **automatically charge** to a preset energy level. If a semi-automated external defibrillator is used, CPR should *immediately* resume while charging. All other personnel may begin to stand clear at this point. Note that fully automated defibrillators do not require the operator's input to discharge a shock, and all rescuers should stay clear at the time of charging. Follow the voice prompts of the device.
6. Call out, "**Stand clear,**" and ensure that no one is in contact with the patient or trolley. CPR is interrupted only *briefly* (<10 seconds) at this point.
7. **Deliver the shock**.
8. Resume CPR *immediately* once the shock has been delivered. Do NOT pause to check the pulse or reanalyze the rhythm at this time.
9. Continue management according to the local resuscitation protocol.

10. There are increasing numbers of automated external defibrillators that provide CPR "guidance" in the form of metronome beats or active feedback on the correct rate and depth of chest compressions in real time. Achieving optimal CPR quality increases the likelihood of successful defibrillation.

ELECTRICAL (SYNCHRONIZED) CARDIOVERSION

1. Prepare the patient and equipment as described earlier. Ensure the patient has adequate monitoring and that there is resuscitation equipment on standby.
2. Explain the procedure to the patient and provide adequate sedation and analgesia when ready.
3. Reassess the patient and the rhythm.
4. Ensure that the defibrillator is in **synchronized** mode.
5. Select the appropriate energy level. Narrow regular rhythms should start at 50 to 100 J (biphasic/monophasic), whereas narrow irregular rhythms should start at 120 to 200 J for biphasic and 200 J for monophasic defibrillators. Wide-complex regular rhythms should start at 100 J (biphasic/monophasic). Synchronized shocks should not be attempted for **wide irregular** rhythms; use unsynchronized defibrillation instead.
6. Apply the pads or paddles as described above and charge.
7. Call out, "**Stand clear,**" and ensure that no one is in contact with the patient or trolley.
8. Visually confirm that the rhythm remains shockable, and then **deliver the shock**. The operator's eyes should be back on the patient at the time of shock delivery to ensure safety.
9. **Reassess** the patient and the rhythm.
10. If the rhythm has **successfully** been converted to sinus, continue to monitor and manage according to local protocols.
11. If the rhythm remains unconverted, **increase the energy level** and repeat from step 5. If maximal energy levels have been reached and the rhythm remains unconverted, consult cardiology for consideration of **overdrive pacing**.
12. If the patient develops **cardiac arrest** after a cardioversion shock, immediately switch the defibrillator to **unsynchronized** mode, set the energy level for defibrillation, and charge and deliver shock as described above. If there is any delay during this process, **begin CPR immediately** while the device is being set and charged. After the defibrillation shock is delivered, **resume CPR immediately**.

RISKS AND PRECAUTIONS

Electrical energy can terminate an abnormal rhythm, but if inappropriately delivered, it may also induce ventricular fibrillation. This can happen if the electric shock is delivered during the relative refractory period of the cardiac electrical cycle.[4] Fine ventricular fibrillation may resemble asystole, and the size of the rhythm waveform should be magnified to reveal this. Movement artifacts or loose leads may resemble ventricular fibrillation and result in an inappropriate shock. New defibrillator technology is available that can filter compression or movement artifacts to "see through" the artifacts to reveal underlying rhythm. However, when using automated external defibrillators, all manufacturers currently still recommend stopping all compressions and patient movement (e.g., during transport) before initiating rhythm analysis.

SPECIAL SITUATIONS

INTERNAL DEFIBRILLATION

Internal defibrillation is indicated in a patient with ventricular fibrillation or pulseless ventricular tachycardia with an open thoracotomy. This could be in a patient with traumatic cardiac arrest, for example, or during open heart surgery. The procedure requires a special set of internal defibrillator paddles (**Figure 23-7**).

Moisten the internal defibrillator paddles with saline, and then place one paddle posteriorly over the left ventricle and the other anteriorly over the right ventricle. Hold the paddles firmly against the myocardium to ensure good contact. Begin with 10 J for defibrillation and increase as needed. Open-chest cardiac massage is performed between shocks in this situation.



FIGURE 23-7. Internal defibrillation paddles.

PEDIATRIC DEFIBRILLATION

Ventricular fibrillation and pulseless ventricular tachycardia in children are relatively uncommon, with the most frequent causes of cardiac arrest being typically respiratory in nature. Thus, treatment should be directed toward preventing cardiac arrest by supporting oxygenation and ventilation. In the event of ventricular fibrillation, use a weight-based energy dose of 2 to 4 J/kg body weight for monophasic or biphasic devices. For refractory ventricular fibrillation, consider increasing the dose to 4 J/kg. For ventricular tachycardia with a pulse, perform electrical cardioversion with 1 J/kg. This can be progressively increased up to 4 J/kg subsequently if needed. Some defibrillator paddles may have integrated child paddles built in, but special pediatric paddles (**Figure 23-8, A and B**) or pads are also separately available. Adult automated external defibrillators may be used down to 8 years of age, and some automated external defibrillators also come with pediatric attenuator pads or keys, allowing the device to be used down to 1 year of age. In an infant, it is possible to defibrillate with the patient propped on the side using the anteroposterior paddle placement. The appropriate compression and ventilation techniques for child or infant CPR will apply accordingly.

DEFIBRILLATION IN HIGH-PERFORMANCE CPR

The concept of high-performance CPR was first promoted by Eisenberg and colleagues and focuses on optimizing the quality of CPR and minimizing pauses in compressions associated with defibrillation in team-based resuscitation.[5] It is still important to "stand clear" during defibrillation and to emphasize safety during training. However, it is also important to emphasize attention to high-quality CPR and minimizing rather than eliminating the pause in compressions for defibrillation.

Avoid prolonged pauses beyond 5 to 10 seconds, as pauses reduce the chance of defibrillation success.[6] Some strategies adopted by high-performance resuscitation teams include the practice of precharging a defibrillator 15 seconds before the 2-minute cycle or providing chest compressions while charging and resuming chest compression immediately after a shock. Another strategy is practicing having a second rescuer hovering, ready to commence compressions immediately after defibrillation. In addition, if a mechanical CPR device is being used, defibrillation can be safely performed without stopping ongoing mechanical compressions to reduce unnecessary pauses.[7]

HANDS-ON DEFIBRILLATION

This is the practice of defibrillating a patient while providing ongoing manual chest compressions with gloved hands, with the aim of



A



B

FIGURE 23-8. **A.** Pediatric defibrillation paddles. **B.** Anteroapical positioning of defibrillation paddles in an infant. [Reproduced, with permission, from Children's Emergency, KK Women's and Children's Hospital, Singapore.]

eliminating hands-off time.[8] Although inadvertent shocks have been reported in medical literature, inadvertent *electrocution* during actual resuscitation leading to ventricular fibrillation or death of a rescuer has not been reported. The risk of electrocution is low with proper precautions (e.g., donning of double gloves or electrical safe gloves), but the risk implications must be carefully considered.

DOUBLE SEQUENTIAL DEFIBRILLATION

Double sequential defibrillation (also called dual sequential defibrillation) is a recent practice employing the use of two sets of manual defibrillators simultaneously to attempt to double the defibrillation energy in refractory ventricular fibrillation patients who do not respond to multiple shocks and antiarrhythmic drugs.[9] There are anecdotal reports of success with the technique, but lack of evidence from clinical trials. There are manufacturer concerns of electrical damage to the defibrillators.[10]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 24

Cardiac Resuscitation

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INTRODUCTION

Cardiac resuscitation is a rapidly changing clinical science. Recommendations of the 2015 American Heart Association Advanced Cardiac Life Support updates[1] are provided in this chapter and are augmented by the most current resuscitation research literature. These recommendations are similar to the recent 2017 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary.[2] The guidelines are summarized as follows.

CHEST COMPRESSIONS

- The recommended chest compression rate is 100 to 120 per minute, updated from 100 per minute.
- Chest compression depth should be 5 to 6 cm, not >6 cm. Chest compression ratio should be >60 and as close to 90 as possible.
- There does not appear to be an advantage to asynchronous or interpolated breaths as long as the highest possible compression ratio is maintained.
- The compression-to-breath ratio is 30:2. If an adjunctive or definitive airway is in place, provide 10 breaths per minute.

DEFIBRILLATION

- Early defibrillation is the most effective modality for return of spontaneous circulation (ROSC).

DRUGS

- Amiodarone or lidocaine (lignocaine) may not provide added benefit to defibrillation.
- Vasopressin has been removed from the Advanced Cardiac Life Support algorithm.
- Routine use of β-blockers after cardiac arrest is not recommended, with benefits for ROSC only demonstrated through animal studies and case reports.
- Steroids may provide some benefit when bundled with vasopressin and epinephrine in in-hospital cardiac arrest, although routine use is not recommended.

OXYGENATION AND CAPNOGRAPHY

- Provide 100% fraction of inspired oxygen (FIO_2) during cardiac arrest, with oxygen saturation titrated to >94% after ROSC.

- End-tidal carbon dioxide (CO_2) can be used to monitor for ROSC. Low end-tidal CO_2 (<10 mm Hg) after 20 minutes is associated with low likelihood of survival.

EXTRACORPOREAL MEMBRANE OXYGENATION

- Extracorporeal membrane oxygenation (ECMO) or extracorporeal CPR can be considered in patients with refractory cardiac arrest who have not responded to conventional CPR, where it can be rapidly implemented with suspicion of reversible cause of cardiac arrest.

POST-ROSC CARE

- Emergency percutaneous coronary intervention is recommended for patients with ST-segment elevation on ECG and for hemodynamically or electrically unstable patients with no ST-segment elevation but suspected cardiovascular cause.
- Targeted temperature management between 32°C and 36°C for comatose patients with ROSC for at least 24 hours is recommended.

SOCIAL MEDIA AND EDUCATION

- Use of social media technologies that summon rescuers in close proximity to a victim of out-of-hospital cardiac arrest may be reasonable. Audiovisual devices can be used to educate providers and improve CPR quality.

EPIDEMIOLOGY

Every year, approximately 6.8 to 8.5 million persons throughout the world[3] sustain cardiac arrest. About 70% of cardiac arrests occur out of hospital. The proportion of cardiac arrest patients who are treated varies from 54.6% (United States) to 28.3% (Asia). The proportions with ventricular fibrillation (VF) and survival vary from 11% and 2%, respectively, in Asia, to 28% and 6% in North America, 35% and 9% in Europe, and 40% and 11% in Australia.[4] Approximately half of cardiac arrest victims are <65 years old.

Ventricular tachydysrhythmias are the initiating event in approximately 80% of patients with out-of-hospital primary cardiac arrest. During ambulatory ECG monitoring of 157 witnessed cardiac arrests, Bayés de Luna et al[5] documented 70% with ventricular tachycardia (VT) and VF, 13% with torsades de pointes, and 17% with bradydysrhythmias. Untreated VF deteriorates to asystole in approximately 15 minutes.[6] For patients with sudden cardiac arrest, the rate of survival declines rapidly by 7% to 10% for each minute without defibrillation.[7] If delay to defibrillation exceeds 12 minutes,[8] survival approaches 0% to 5%.

THE CHAIN OF SURVIVAL

The structured emergency care system concept for treatment of cardiac arrest is called the **Chain of Survival and includes five components: recognition and activation of the emergency response system, immediate high-quality CPR, rapid defibrillation, basic and advanced EMS, and advanced life support and postarrest care for out-of-hospital cardiac arrest (OHCA).** If a community's prehospital EMS can be activated promptly, reach the patient within 5 minutes of collapse, and deliver the first shock shortly thereafter, survival in excess of 15% to 20% can be expected, with recent reports of >30% survival.[9,10] With delayed initiation of CPR, defibrillation, and access to the patient by EMS, the impact of advanced life support measures is small (**Figure 24-1**). Improved survival can only occur if structured emergency care systems allow trained providers to access the patient rapidly and deliver the appropriate treatment in a timely fashion. Delays in initiating the various links weaken the chain

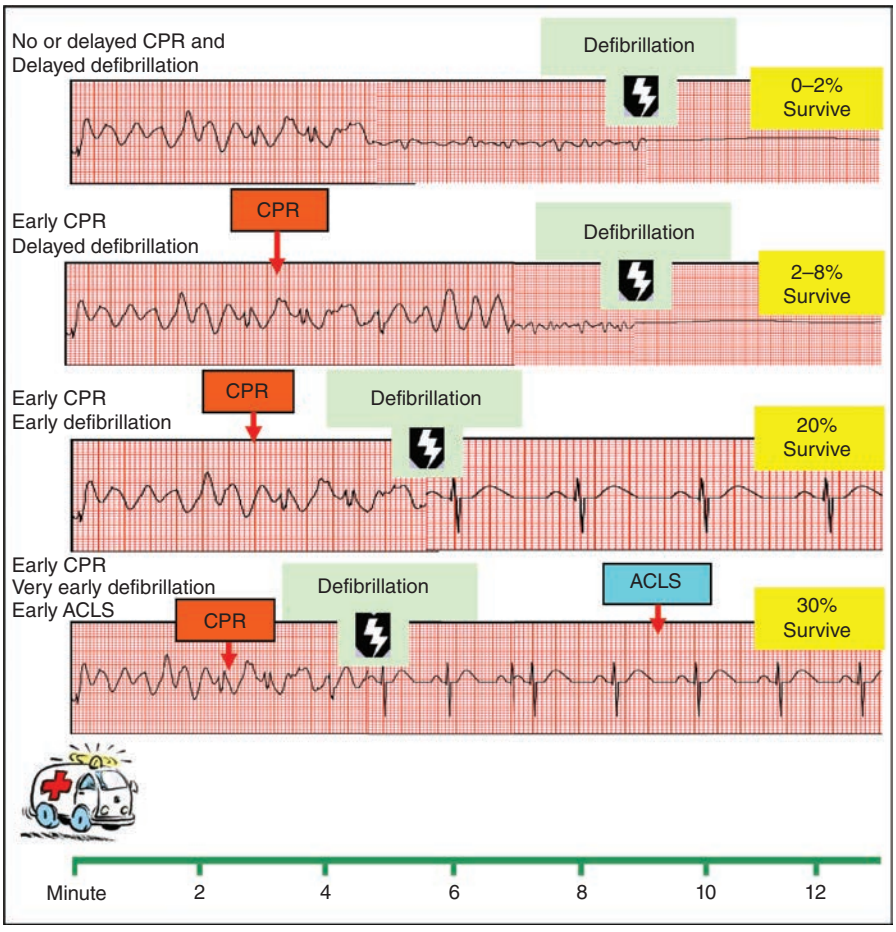


FIGURE 24-1. Incremental survival benefits by the links in the Chain of Survival. ACLS = Advanced Cardiac Life Support. [Reproduced, with permission, from the National Resuscitation Council, Singapore.]

and adversely affect the next link, resulting in a decreased chance of a good outcome for the patient.

Based on the Chain of Survival, cardiac arrest can be divided into three separate time-sensitive phases: the electrical, circulatory, and metabolic phases.[11,12] These phases affect treatment efficacy. The electrical phase is present in the first 5 minutes of arrest, where the cardiac system is most amenable to defibrillation if a shockable rhythm is present. The circulatory system consists of the next 15 minutes after arrest, when high-quality chest compressions and epinephrine provide the greatest benefit. The metabolic phase is >20 minutes after arrest and is marked by electrolyte and acid-base disorders; epinephrine delivered >20 minutes after arrest is associated with decreased cerebral blood flow, worse neurologic outcome, and increased cardiac ischemia.

ADVANCED CARDIAC LIFE SUPPORT (ACLS)

The basic life support assessments and interventions include the **Primary Survey**, and the advanced life support assessments and interventions include the **Secondary Survey**.

An organized approach to resuscitation begins with the Primary Survey and blends smoothly with the Secondary Survey. These are summarized in the **Universal Advanced Cardiac Life Support Algorithm** (**Figure 24-2**). This method helps any Advanced Cardiac Life Support provider remember the sequence of resuscitation actions and be less likely to miss any of the vital steps in the care of the patient.

PRIMARY SURVEY

The **Primary Survey** addresses the identification of cardiac arrest and performance of good-quality CPR (including ventilation) and defibrillation. Procedures for the Primary Survey are described in Chapters 22 and 23. The 2015 Advanced Cardiac Life Support guidelines and 2017 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary emphasize chest compressions, starting with circulation-airway-breathing as opposed to airway-breathing-circulation. Maximize chest compression fraction to >60% with minimal pauses in compressions.

Defibrillate as soon as possible for VF or pulseless VT. Start at 200 J biphasic or at maximum energy. Make sure CPR interruptions are as brief as possible when defibrillating. Maintain continuous compressions

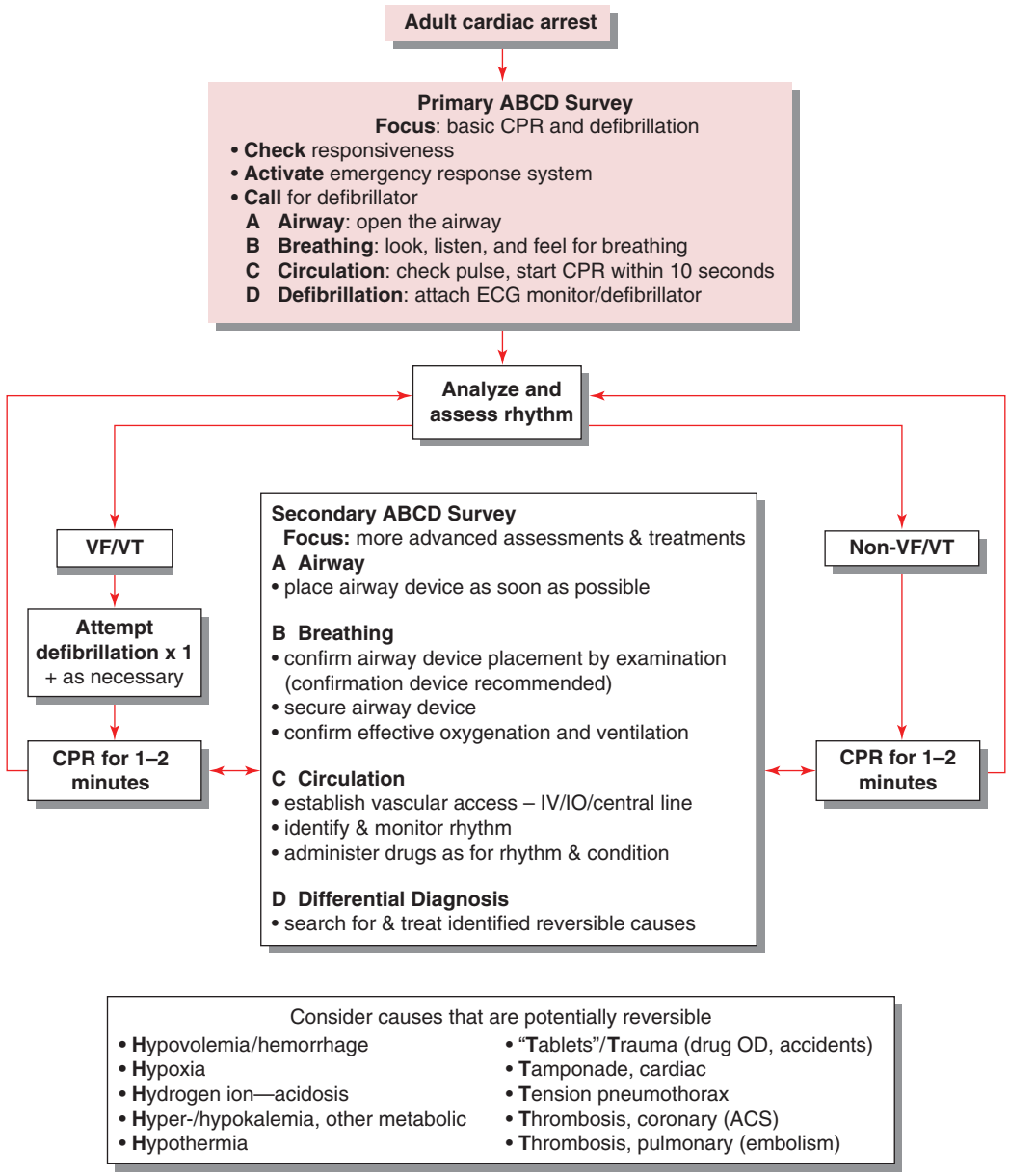


FIGURE 24-2. Universal Advanced Cardiac Life Support Algorithm. ACS = acute coronary syndrome; OD = overdose; VF = ventricular fibrillation; VT = ventricular tachycardia.

during rhythm analysis and defibrillator recharging. Resume one cycle of CPR immediately after defibrillation even with ROSC.

For ventilation, bag-valve masks (BVMs) deliver 21% oxygen if using room air, 60% oxygen when connected to an oxygen source with flow at 12 L/min, and 90% to 95% with a reservoir bag. Chest compressions should not be stopped to initiate or continue ventilation.

During cardiac arrest, 100% F_{IO_2} during compressions is recommended due to unreliable measurement of oxygen saturation. The time required to perform endotracheal intubation may decrease compression fraction.[13] Any airway device may be used during CPR, including BVM, supraglottic airway, or endotracheal intubation, with literature suggesting similar patient outcomes.[14,15]

The 2015 updates and 2017 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary recommend a 30:2 compression-to-breath ratio, maximizing compression time, with no pauses longer than 10 seconds.[1,16] The target compression rate is 100 to 120 per minute, rather than at least 100 per minute. The maximum compression rate is 120 per minute because quality decreases with rates greater than this. The maximum depth of compressions is 6 cm, with a target of 5 to 6 cm, rather than at least 5 cm in the 2010 guidelines. Audiovisual devices may be used to optimize CPR quality.

For one- and two-rescuer CPR, the 2015 Advanced Cardiac Life Support guidelines recommend 30 compressions followed by two breaths (30:2 ratio) in patients without an advanced airway, similar to the 2017 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary.[2] During breaths, compressions may be withheld. If an advanced airway is in place, the 2015 updates recommend a breath rate of 10 per minute, or one breath every 6 seconds, asynchronous from compressions. A 2015 study by the Resuscitation Outcomes Consortium compared continuous chest compressions with asynchronous BVM ventilation versus CPR with compression pauses for breaths in patients without an advanced airway in place. This study found no significant difference between the two ventilation techniques with regard to survival to hospital discharge, as long as the chest compression fraction was >75%. A 2017 study suggests that endotracheal intubation within the first 15 minutes of arrest with a shockable rhythm may be associated with lower survival due to interruptions in chest compressions.[17] The key point is to provide meticulous CPR, maximizing compressions, with the briefest of pauses (<10 seconds).[18]

Mechanical CPR devices may also be used to provide cardiac compression. The two most common types of mechanical CPR devices used in clinical practice are the LUCAS-2®, with a piston attached to an active compression-decompression cup (**Figure 24-3**), and the load-distributing band AutoPulse® (**Figure 24-4**). These devices allow provision of either 30:2 CPR or continuous chest compressions with interposed manual ventilations. Apply defibrillator pads to the bare chest before placing a mechanical CPR device.



FIGURE 24-3. The LUCAS-2® chest compression gadget with its attached active compression-decompression device.



FIGURE 24-4. The AutoPulse® mechanical CPR device with its load-distributing band.

The evidence to date does not suggest benefit from mechanical versus high-quality manual chest compressions from trained individuals based on several meta-analyses and Cochrane reviews.[19-21] However, mechanical compressions are reasonable if sustained high-quality compressions compromise provider safety or are impractical. There is little evidence to support the use of impedance threshold devices.

The critical rhythms associated with cardiac arrest are **VF** (**Figure 24-5**), pulseless **VT** (**Figure 24-6**), **asystole** (**Figure 24-7**), and **pulseless electrical activity (PEA)** (**Figure 24-8**).

Defibrillation may be done with either an automated external defibrillator or a manual defibrillator (see Chapter 23, "Defibrillation and Electrical Cardioversion"). **Deliver shocks for VF or pulseless VT with minimal interruption of chest compressions only during actual shock delivery**. Make sure that the position of the defibrillator pads (**Figure 24-9**) does not interfere with monitoring leads.

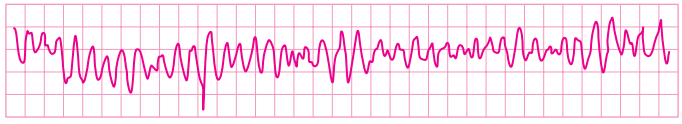


FIGURE 24-5. Ventricular fibrillation.

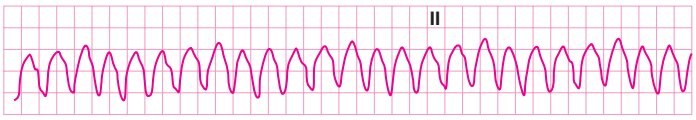


FIGURE 24-6. Pulseless ventricular tachycardia.

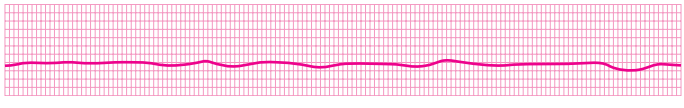


FIGURE 24-7. Asystole.

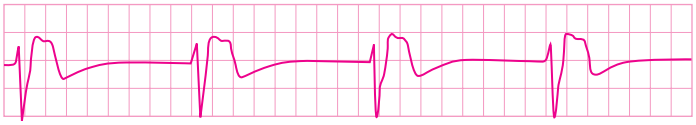


FIGURE 24-8. Pulseless electrical activity.



FIGURE 24-9. Placement of defibrillator pads.

TABLE 24-1 Components of the Secondary Survey

Component and Function	Detailed Components
A: Securing the Airway	Endotracheal intubation or other supraglottic airway, e.g., laryngeal mask airway, although BVM may be used
B: Breathing (ventilation)	1. Ventilation with BVM 2. Oxygen 3. Mechanical ventilation
C: Maintaining the Circulation	1. Continue CPR 2. Provide defibrillation and cardioversion to correct life-threatening "shockable" rhythms 3. Continuous ECG monitoring to monitor the circulation's rhythm and identify dysrhythmias that need to be corrected 4. Gain vascular access through IV/IO line 5. Provide drugs to help maintain circulation 6. Consider use of ECMO
D: Differential Diagnosis	1. Determine why the patient is not responding to the resuscitative efforts 2. Look for correctible causes of collapse and provide necessary interventions
Specialized Care after ROSC	Targeted temperature management, glycemic control, early goal-directed therapy, percutaneous coronary interventions

Abbreviations: BVM = bag-valve mask; ECMO = extracorporeal membrane oxygenation; ROSC = return of spontaneous circulation.

After delivery of the first shock, resume CPR (**Figure 24-10**) immediately for 2 minutes before reviewing the ECG monitor for a rhythm diagnosis. If a viable rhythm has returned, check for pulse and breathing. If breathing and pulse have returned, begin care for post-**ROSC** management. If breathing is absent, continue rescue breathing with a BVM at the rate of about 10 breaths per minute; if pulse is not present, continue CPR and move to the **Secondary Survey**.

SECONDARY SURVEY

Components of the Secondary Survey are listed in **Table 24-1**.



FIGURE 24-10. Continuing CPR after shock using an automated external defibrillator.

The **Secondary Survey** includes endotracheal intubation or the placement of another airway adjunct, assessment of ventilatory status, gaining IV access, identifying ECG rhythms, delivering drugs to enhance circulation, and addressing the reasons for the occurrence or persistence of cardiac arrest.

ECG and POCUS may assist in determining etiology of arrest, particularly in PEA.[22] PEA with narrow QRS is generally due to mechanical problems caused by right ventricular inflow or outflow obstruction. PEA with wide-complex QRS is associated with metabolic pathology or myocardial ischemia with left ventricular failure. The use of US to assess cardiac contractility and arrest etiology may provide benefit, but make sure US assessment does not compromise compressions. US may also be used to confirm ROSC and endotracheal tube placement.

While the Secondary Survey is in progress, continue the basic resuscitative actions of the Primary Survey. Usually, defibrillation pads placed carefully left of the apex and to the right of the sternum just below the right clavicle (Figure 24-9) can also act as monitoring leads. Otherwise, true monitoring leads may be placed at the front of the right and left shoulders and over the left iliac crest. Such placement does not interfere with defibrillation or cardiac pacing procedures. Further management is based on the cardiac rhythm.

VASCULAR ACCESS

Vascular access techniques are discussed in Chapter 31, "Vascular Access." A large peripheral vein allows a rapid rate of fluid administration, if needed. If unable to cannulate a peripheral vein, establish IO access. Central venous lines take time to establish and, because of the length of the cannula, cannot deliver fluids as rapidly as a peripheral line; in addition, every bolus dose of drugs requires flushing with at least 20 mL of normal saline. Central lines are useful for central venous pressure monitoring to guide fluid resuscitation and circulatory management. The key is to provide high-quality compressions and defibrillate if necessary while obtaining rapid access (IV, IO, or central access).

In cardiac arrest, circulation of blood grinds to a halt. With good-quality CPR, one can expect to generate up to 30% of normal cardiac output, which is required to supply vital organs such as the heart, brain, and kidneys. The reduced circulation is associated with a slower

circulation time. Therefore, drugs given during cardiac resuscitation are best administered through a proximal peripheral vein. Once drugs are given, flush the line with normal saline, and continue CPR for at least 30 to 60 seconds before repeat external defibrillation so that the heart is optimally primed to respond.

The optimal infusion fluid is normal saline and not dextrose, Ringer's lactate, or sodium bicarbonate. However, unless hypovolemia is a contributing factor to cardiac arrest, fluid infusion is typically not necessary, but if provided, it should be slow. Drug dosages are the same whether given by the IO, IV, or central line routes. The endotracheal tube route is no longer recommended for drug administration because drug absorption is limited in the setting of pulmonary edema.

CAPNOGRAPHY

Waveform capnography is the most reliable means of confirming and continuously monitoring tracheal tube placement, as well as monitoring resuscitation and ROSC.[23-25] An end-tidal reading <10 mm Hg CO_2 after 20 minutes of resuscitation is associated with low chance of survival. However, this should not be used alone when deciding to cease resuscitation efforts. Capnography may also be used to monitor ventilation rate and CPR quality because high-quality compressions should produce an end-tidal CO_2 of at least 12 to 15 mm Hg, if not greater. End-tidal CO_2 readings >20 mm Hg at 20 minutes predict a higher chance of ROSC, whereas readings <10 mm Hg at 20 minutes predict almost no chance of ROSC.[23-25] A sudden rise in end-tidal CO_2 is an early indication of ROSC.

DRUGS USED FOR ROSC FROM CARDIAC ARREST

Drugs available for cardiac resuscitation and cardiac dysrhythmia management are also described in Chapters 19 and 20. This section will cover those drugs specifically used for resuscitation from cardiac arrest to ROSC. Drugs are an adjunct in the management of cardiac arrest patients. Good CPR, ventilation, and early defibrillation are the cornerstones of management of cardiac arrest. The effectiveness of standard resuscitative drugs on ROSC and survival to hospital discharge has not been well demonstrated.[26-28] Antidysrhythmic drugs for shockable cardiac arrest show no benefit versus placebo for survival to hospital discharge, survival with favorable neurologic function, and long-term survival.[29] However, consensus documents recommend the standard resuscitative drugs described below with the presumptive rationale that drugs help "restart" the heart and preserve coronary and cerebral circulation.

EPINEPHRINE

Epinephrine (adrenaline) is an endogenous catecholamine. It has an important role in cardiac arrest, although the evidence base for improved outcomes in humans is weak.[30] Epinephrine seems to improve ROSC and short-term survival[31] but does not appear to improve survival to hospital discharge or neurologic outcome.[32,33] A 2018 study suggested improved ROSC with epinephrine, but survivors demonstrated a higher rate of severe neurologic disabilities.[34] Epinephrine may provide the most benefit within the first 15 to 20 minutes of cardiac arrest during the circulatory phase, based on its alpha effects of increasing peripheral vasoconstriction and coronary and cerebral blood flow.[11] Potential adverse effects include an increase in myocardial oxygen consumption and an increase in pulmonary shunting. The most common adverse reaction is tachycardia. Epinephrine may worsen myocardial ischemia and induce ventricular ectopy and VT, especially when provided beyond 20 minutes after arrest. **Epinephrine is used mainly to treat cardiac arrest from VF or pulseless VT unresponsive to the initial shock, asystole, PEA, and profoundly symptomatic bradycardia.** The 2015 updates provide a class IIb recommendation, stating that standard-dose epinephrine may be reasonable for patients with cardiac arrest. The standard dose in cardiac arrest is 1.0 milligram diluted to 10 mL (10 mL of 1:10,000) given IV or IO. Repeat if needed at 3- to 5-minute intervals. There is no maximum dose. Escalating doses to 2 to 5 milligrams IV every 3 to 5 minutes (high-dose epinephrine) has not resulted in increased long-term survival.[30] For IV infusion in patients with cardiogenic shock or symptomatic bradycardia, the dose is 1 milligram in 500 mL of normal saline beginning at 2 to 10 micrograms/min and escalating as needed at 3- to 5-minute intervals. Do not add epinephrine to infusions that contain alkaline solutions because epinephrine has ineffective clinical activity in alkaline solutions.

AMIODARONE

Amiodarone is considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan-Williams classes. It causes coronary and peripheral artery vasodilation. **Its main use in cardiac arrest is for persistent VT or VF after defibrillation and epinephrine.** Although the 2015 Advanced Cardiac Life Support guidelines recommend amiodarone for refractory VF, in 2016 a large multicenter trial failed to demonstrate a difference in survival to hospital discharge for shock-refractory VF or pulseless VT with amiodarone or lidocaine compared to placebo.[35]

Amiodarone can also be used for hemodynamically stable VT, hemodynamically stable polymorphic VT, and hemodynamically stable wide-complex tachycardia of uncertain origin. It is also used for the pharmacologic conversion of atrial fibrillation, control of rapid ventricular rate in preexcitation supraventricular dysrhythmias, and as an adjunct to electrical cardioversion of refractory paroxysmal supraventricular tachycardia/atrial tachycardia. For pulseless VT or VF, the dose is a bolus of 300 milligrams IV followed by a 20-mL flush with 5% dextrose in water or saline. Give another 150-milligram bolus if there is no response to the first dose. For stable ventricular and supraventricular dysrhythmias, administer amiodarone IV 150 milligrams over 10 to 15 minutes (not to exceed 30 milligrams/min), followed by a maintenance infusion of 1 milligram/min for 6 hours and then 0.5 milligram/min for the next 18 hours. Infusions exceeding 2 hours should be administered in glass or polyolefin bottles because the drug precipitates in plastic tubing. Hypotension and bradycardia are the most common unwanted effects. These may be addressed by slowing the infusion rate, giving an IV fluid challenge, or using pressors or positive chronotropic agents. Occasionally, temporary pacing for refractory bradycardia from amiodarone may be required, especially if other measures are ineffective.

Recent literature suggests no improvement in survival or favorable neurologic outcome in patients with OHCA due to initial shock-refractory VF or pulseless VT with antidysrhythmic medications such as amiodarone or lidocaine.[35] A meta-analysis published in 2016[36] found that amiodarone improves survival to hospital admission for OHCA, but it does not improve survival to discharge or neurologic outcomes compared to placebo or other antidysrhythmics. Patients with in-hospital cardiac arrest may receive some benefit when given steroids, vasopressin, and epinephrine as a bundle, although routine use is not recommended.[37]

LIDOCAINE (LIGNOCAINE)

Lidocaine (lignocaine) (see also Chapter 12, "Approach to Nontraumatic Shock") is a class I antidysrhythmic drug. It reduces automaticity, suppresses ventricular ectopy, and may be used for hemodynamically stable VT and refractory VF/pulseless VT. In the 2010 recommendations, lidocaine was the second-choice drug after amiodarone or was used if amiodarone was not available. However, a 2016 multicenter study suggests no improvement in survival or neurologic outcome with use of lidocaine (or amiodarone or placebo) for OHCA from VF or pulseless VT.[35] In the 2010 guidelines for cardiac arrest, the dose was an IV bolus of 1 to 1.5 milligrams/kg body weight. A second bolus of 0.5 to 0.75 milligram/kg was provided if the rhythm persisted. The 2015 algorithm no longer contains lidocaine, and guidelines state that the routine use of lidocaine after ROSC is not recommended, although it may be considered in patients with ROSC after VF or pulseless VT. Upon ROSC, lidocaine may be given as an infusion at a rate of 1 to 4 milligrams/min.

If dysrhythmia reappears during the infusion of lidocaine, give a bolus of 0.5 milligram/kg and increase the infusion rate to 4 milligrams/min. Toxicity may occur with doses exceeding 3 milligrams/kg body weight bolus or in patients with liver disease, since the drug is hepatically metabolized. Symptoms include neurologic changes such as drowsiness, disorientation, reduced hearing ability, perioral paresthesia, muscle

tremors, and seizures. Myocardial depression and circulatory depression are also features of toxicity, and these may be illustrated by widening QRS complexes and falling blood pressures. In patients with known impaired liver function or patients >70 years old, give the same recommended bolus doses but decrease the normal infusion rate by 50%.

β-BLOCKERS

In animal studies, β-blockers can reduce myocardial oxygen requirements, decrease the number of shocks needed for defibrillation, and prolong survival from VF/pulseless VT. Successful use in humans is based primarily upon case reports. β-Blockade in cardiac arrest demonstrates the most benefit in patients with refractory VF or VT, known as electrical storm, which is defined by three or more sustained episodes of VF or VT in a 24-hour period.[38-40] Esmolol, metoprolol, and propranolol can be used in refractory VF or VT.[38,41] One retrospective series of patients with refractory VF or VT who received at least three defibrillations, 300 milligrams of amiodarone, and 3 milligrams of adrenalin, without success, reported that esmolol given during resuscitation improved rate of ROSC, intensive care unit admission, survival to hospital discharge, and favorable neurologic outcome.[38,41] Further study is required.

MAGNESIUM

Magnesium is a cofactor in numerous enzymatic reactions. It is essential for the function of the Na^+-K^+-ATPase pump. Magnesium deficiency may be associated with cardiac dysrhythmias, sudden death, and precipitation of VF. Magnesium is used to treat hypomagnesemia, with or without dysrhythmias.

Magnesium is initial treatment for torsades de pointes and dysrhythmias secondary to hypomagnesemia, cardiac arrest from QT_c prolongation, or cardiac glycoside toxicity.[26,42] For patients in VF or pulseless VT due to the above conditions, give 1 to 2 grams in 10 mL 5% dextrose in water IV over 1 minute. Magnesium provides no benefit for routine use in cardiac arrest. For patients with a pulse, the dose is 1 to 4 grams in 50 mL of 5% dextrose in water over 60 minutes. Adverse reactions include flushing, sweating, mild bradycardia, hypotension, asystole with circulatory collapse (with too rapid administration), and respiratory depression. Hypermagnesemia may produce depressed reflexes, flaccid paralysis, diarrhea, respiratory depression, and circulatory collapse.

OTHER DRUGS IN CARDIAC ARREST

Atropine **Atropine** is a parasympatholytic agent that enhances sinus node automaticity and atrioventricular conduction by direct vagolytic action. **It is not recommended for PEA or for treatment of cardiac arrest**. It is indicated for symptomatic bradycardia. The dose is 0.5 or 0.6 milligram IV (dose depends on formulation in country of use) and may be repeated at 5- to 10-minute intervals up to a maximum of 0.04 milligram/kg body weight. Atropine may induce tachycardia or premature ventricular contractions and cause worsening of myocardial ischemia. Symptoms of overdosage include tachycardia, delirium, coma, flushed and hot skin, ataxia, and blurred vision. Administration of low doses <0.5 milligram IV may produce paradoxical bradycardia and precipitate VF.

Calcium **Calcium is given during resuscitation only for cardiac arrest from hyperkalemia, hypocalcemia, or β-blocker/calcium channel–blocker overdose**. Calcium is not recommended for routine administration for VF/pulseless VT or PEA.[26,43] The dose of calcium chloride is 0.2 mL/kg of 10% calcium chloride, given as a slow IV bolus.

Sodium Bicarbonate The use of sodium bicarbonate during cardiac arrest was advocated in the past to treat presumptive acidosis, because severe acidosis decreases myocardial contractility.[44] However, **routine use during cardiac arrest is no longer recommended** due to a number of potential adverse effects. Sodium bicarbonate causes hypernatremia, hyperosmolality, and alkalosis (which in turn induces a left shift of the oxyhemoglobin dissociation curve), and IV sodium bicarbonate produces carbon dioxide, resulting in hypercarbia unless ventilation is increased. It does not appear to improve defibrillation success. **It may be given in cardiac arrest from hyperkalemia or cyclic antidepressant overdose or other agents that result in sodium channel blockade (cocaine toxicity)**. It is acceptable for intubated patients with a long arrest interval until ROSC and with persistent severe metabolic acidosis. However, a pilot study evaluating the use of sodium bicarbonate in patients with prolonged cardiac arrest with pH <7.1 or bicarbonate <10 mEq/L found sodium bicarbonate did not improve rate of ROSC or neurologic survival, but further study is required in this population.[45] In undifferentiated cardiac arrest, sodium bicarbonate does not benefit and may be harmful based on several randomized trials and retrospective observation studies.[46-48] The 2015 AHA guidelines recommend against routine use in cardiac arrest. If provided, the dose is 1 to 1.5 mEq/kg IV bolus, followed by 0.75 mEq/kg every 10 to 15 minutes as needed. If continuous infusion of sodium bicarbonate is used, check pH to guide therapy. Increased ventilatory rate is recommended to remove excess CO_2 produced by sodium bicarbonate infusion.

Vasopressin Vasopressin, also called antidiuretic hormone, is a naturally occurring neurohypophysial peptide hormone synthesized in the hypothalamus and stored in the pituitary gland. It increases water absorption in the nephron and increases peripheral vascular resistance. Vasopressin levels elevate during cardiac arrest, and this observation led to investigation of its role in resuscitation. Vasopressin has a longer duration of action and, in laboratory studies, maintains coronary perfusion pressure, myocardial blood flow, and cerebral blood flow better than epinephrine. However, most studies do not show superiority of vasopressin over epinephrine.[30,43] Vasopressin as a first-line agent in cardiac arrest (40-unit dose) does not improve long-term survival when compared to epinephrine,[49] although vasopressin might improve short-term survival in patients with prolonged cardiac arrest.[49] Combining vasopressin (40 units) with epinephrine does not appear to improve outcomes.[50] The 2015 updates remove vasopressin from all algorithms. A combination of vasopressin, epinephrine, and steroids is not recommended at this time for routine use, due to low quality of evidence.

COMMON CARDIAC ARREST ALGORITHMS

The algorithmic approach to cardiac arrest management allows a structured decision-making process when managing cardiac arrest victims. The cardiac arrest rhythms discussed here are pulseless VT/VF, asystole, and PEA. The use of US to assess contractility and ECG for length of the QRS interval (narrow vs. wide) has been evaluated and may provide benefit in determining etiology of arrest, although it is currently unclear if the use of US affects clinical outcomes. Periarrest US should *not* compromise compressions. Be meticulous with compressions because the literature suggests that US used in cardiac arrest is associated with delays in compressions.[51,52] Pauses in compressions should be no longer than 10 seconds. US may assist in identifying reversible causes of arrest, and several dedicated US protocols are available.[22,53] A relatively new US protocol, the **Cardiac Arrest Sonographic Assessment**,[54] assesses for cardiac tamponade (first pause in compressions), pulmonary embolism (second pause), and cardiac activity (third pause) during CPR pauses to minimize interruptions in compressions. During CPR, the ultrasonographer assesses for hypovolemia and pneumothorax. This protocol was associated with reduced interruptions in high-quality compressions.[22,53]

VENTRICULAR FIBRILLATION/PULSELESS VENTRICULAR TACHYCARDIA

Once VF or pulseless VT is diagnosed, prepare for electrical conversion while CPR is in progress. If ROSC does not occur after the first shock, move to the mega-VF approach (**Figure 24-11**). Continue CPR for 1 to 2 minutes followed by rhythm analysis, and if VF persists or recurs, deliver electrical shocks, usually biphasic, beginning usually at 200 J and escalating, if needed, to 360 J. For monophasic defibrillators, begin at 360 J. After delivery of shock, follow with CPR again for 1 to 2 minutes before rhythm analysis. Maintain good-quality CPR for optimal coronary and vital organ perfusion. Parallel to the CPR-analysis-shock-CPR-analysis-shock-CPR cycle, begin secondary ABCDs (airway,

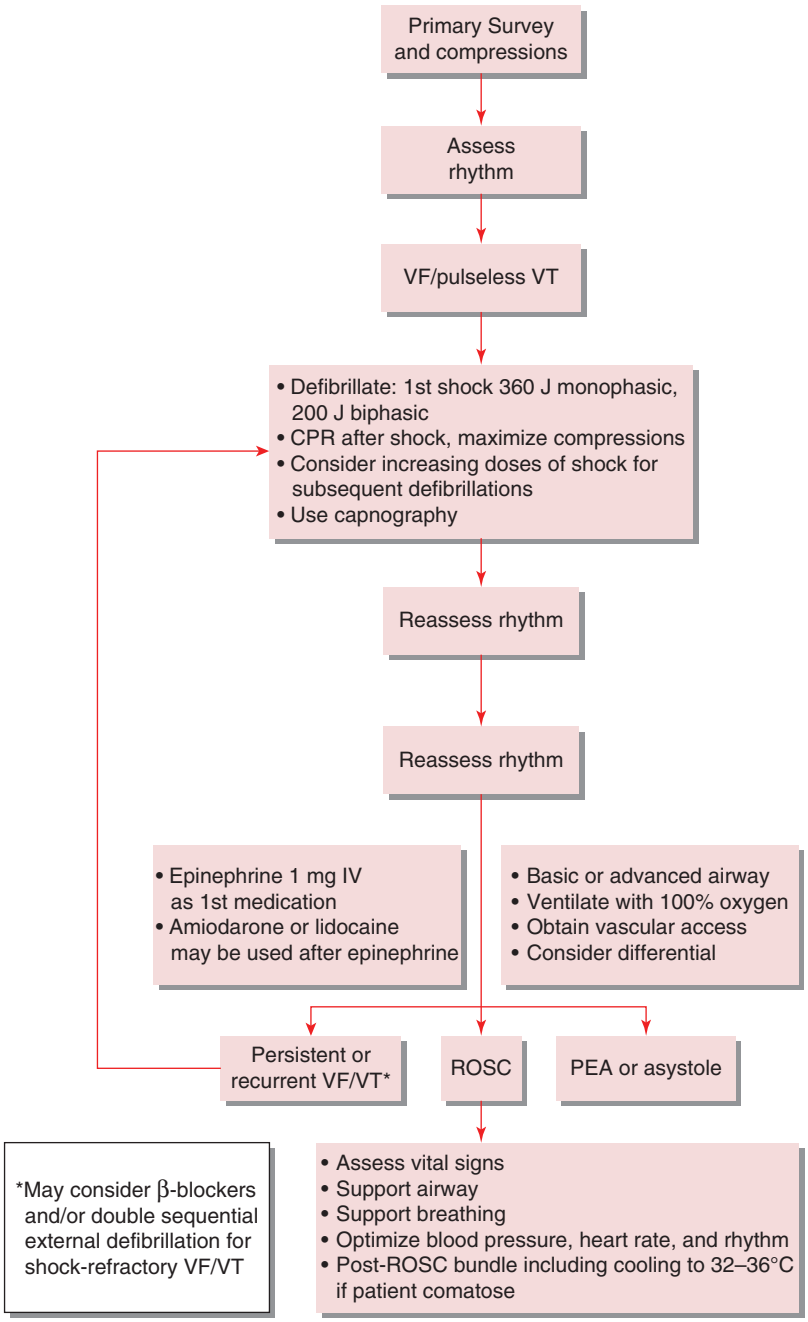


FIGURE 24-11. Management of ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT). PEA = pulseless electrical activity; ROSC = return of spontaneous circulation.

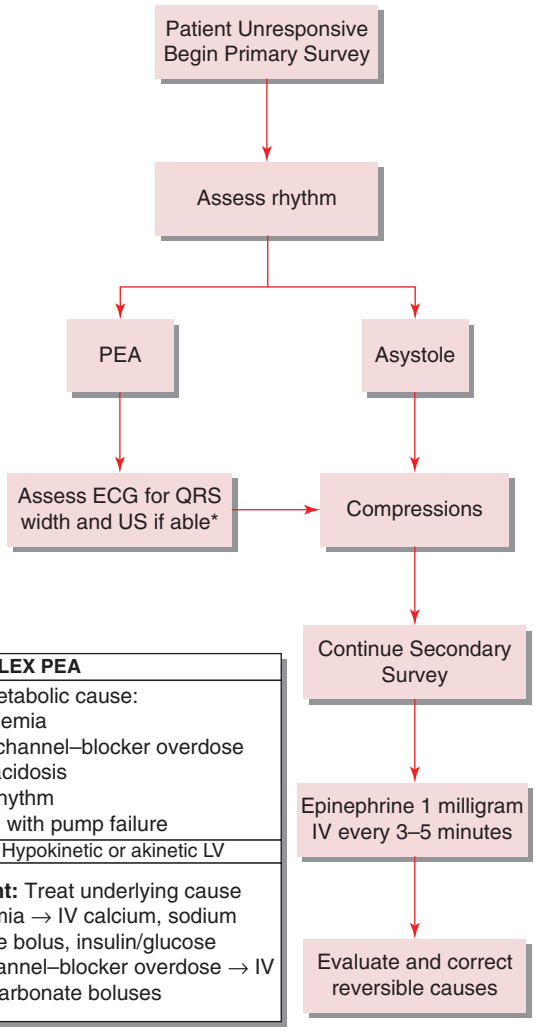
breathing, circulation, defibrillation) and give drugs that may help to lower defibrillation thresholds, such as epinephrine (adrenaline) and/or amiodarone, or perhaps lidocaine. Any or all of these drugs may be administered in any combination and repeated at roughly 3- to 5-minute intervals. After administration of any of these drugs, provide at least 30 to 60 seconds of effective CPR to allow the injected drug to reach the central circulation before the next shock. Continue the resuscitation cycle for as long as the rhythm remains as VF or pulseless VT.

DOUBLE SEQUENTIAL EXTERNAL DEFIBRILLATION

Double sequential external defibrillation may be appropriate for patients with shock-refractory VF, defined as three or more sustained episodes of VT, VF, or implantable cardioverter-defibrillator shocks within 24 hours.[39,40] This was initially described in the 1980s, with several current descriptions of success in patients with refractory VF.[50,55,56] It is theorized that double sequential defibrillation reduces the VF threshold and overrides the relative refractory period of cardiac tissue. To complete this, a second set of defibrillator pads is placed in the anterior-posterior positions (if the first set is placed in the standard apex-sternum orientation), for a total of two sets (four separate pads). Both sets are charged to maximal settings, with simultaneous shock delivery, which requires coordination. This may be appropriate for patients in refractory VF after quality CPR and several attempts at defibrillation.

ASYSTOLE/PULSELESS ELECTRICAL ACTIVITY

For asystole or PEA (a condition in which cardiac contractions are absent in the presence of coordinated electrical activity), continue CPR and institute the secondary ABCDs. Give drugs to enhance the chances of ROSC (**Figure 24-12**). Epinephrine (adrenaline) 1.0 milligram as



*PEA Evaluation

NARROW-COMPLEX PEA	WIDE-COMPLEX PEA
Consider mechanical cause: • Tamponade • PE • Hypovolemia/bleeding (IVC) • Tension PTX • Acute MI with cardiac rupture	Consider metabolic cause: • Hyperkalemia • Sodium channel–blocker overdose • Severe acidosis • Agonal rhythm • Acute MI with pump failure
Bedside US: Hyperdynamic LV	**Bedside US:** Hypokinetic or akinetic LV
Management: IV fluid bolus and treat underlying condition • Tamponade → Pericardiocentesis • PE → Thrombolysis • Hypovolemia/bleeding → Resuscitation • Tension PTX → Decompression	**Management:** Treat underlying cause • Hyperkalemia → IV calcium, sodium bicarbonate bolus, insulin/glucose • Sodium channel–blocker overdose → IV sodium bicarbonate boluses

FIGURE 24-12. Asystole/pulseless electrical activity (PEA) management algorithm. IVC = inferior vena cava; LV = left ventricle; MI = myocardial infarction; PE = pulmonary embolism; PTX = pneumothorax.

a bolus dose in 10 mL is the drug of choice. Vasopressin alone or in combination with epinephrine is no more effective than epinephrine alone. Repeat epinephrine as needed in 3- to 5-minute intervals. Consider other possible causes of asystole or PEA, and identify and correct them. It is currently assumed that narrow-complex PEA[57] could be the result of mechanical problems such as cardiac tamponade, pneumothorax, mechanical hyperinflation, pulmonary embolism, or myocardial rupture. Bedside ultrasound and assessment of the clinical scenario can direct specific treatment. Wide-complex PEA, on the other hand, can result from a metabolic problem (e.g., hyperkalemia), drug toxicity (e.g., sodium channel–blocker toxicity), cardiac ischemia, or left ventricular failure and should be treated as appropriate.[22] Survival is low if patients in asystole do not achieve ROSC in the field or convert to a shockable rhythm.[58-60]

DIFFERENTIAL DIAGNOSES OF CARDIAC ARREST

In every resuscitation, it is useful to identify important causes of cardiac arrest and reasons for lack of response to standard resuscitation algorithms. Causes can be grouped as the **5 H's—hypovolemia or hemorrhage, hypoxia, hydrogen ion (acidosis), hypo- or hyperkalemia, and hypothermia**—and the **5 T's—trauma and tablets (overdose), cardiac tamponade, coronary thrombosis, tension pneumothorax, and thrombosis (pulmonary embolism)**. The use of US to assess contractility and ECG to assess for length of the QRS interval (narrow versus wide) has been evaluated and may benefit in determining etiology of arrest. Periarrest US should not compromise compressions, but it may assist in identifying reversible causes of arrest. It is currently unclear whether the use of US affects clinical outcomes. However, use of US in PEA may affect clinical decision making through identification of pathologies requiring emergent intervention.[61]

H: HYPOVOLEMIA OR HEMORRHAGE

History of fluid or blood loss may be available. Rectal examination can identify massive lower GI bleeding; nasogastric intubation can identify massive upper GI bleeding; and bedside FAST can diagnose massive intraperitoneal bleeding. Treat with fluids and blood products.

H: HYPOXIA

Hypoxia occurs with lack of oxygen and alveolar ventilation. Make sure that the airway adjunct is placed correctly. Check breath sounds at intervals to ensure that the endotracheal tube has not slipped out of the trachea or to identify pneumothorax. Verify the source of oxygen—an oxygen cylinder or the piped oxygen supply.

H: HYDROGEN ION (ACIDOSIS)

The acidosis of cardiac arrest is a combination of respiratory and metabolic acidosis. Respiratory acidosis is addressed by early endotracheal

intubation and alveolar ventilation. Metabolic acidosis can be somewhat addressed by good-quality CPR. Sodium bicarbonate can be administered for severe metabolic acidosis from prolonged or poor initial resuscitation, at a dose of 1 to 1.5 mEq/kg. Half the initial dose can be readministered after 10 to 15 minutes, depending on pH. However, data currently do not support routine administration of sodium bicarbonate for acidosis, with no controlled studies demonstrating improved hemodynamics with sodium bicarbonate.[62] If administered, ventilatory rate should be increased to counteract the increased CO_2 produced by sodium bicarbonate. Continuous venovenous hemodialysis may be required for severe acidosis.[62]

H: HYPER- OR HYPOKALEMIA, OTHER METABOLIC DISORDERS

Suspect hyperkalemia in patients on hemodialysis or peritoneal dialysis (look for presence of arteriovenous fistula or dialysis catheter). Other metabolic disorders are extremely difficult to confidently identify in cardiac arrest. If hyperkalemia is suspected, administer calcium chloride, sodium bicarbonate, insulin, and glucose. Treat hyperkalemia from suspected digitalis toxicity with IV magnesium sulfate or digoxin-specific Fab fragments (Digibind®).

H: HYPOTHERMIA

Treat hypothermia with gradual rewarming with blankets and warm IV fluids. If there is no recovery of consciousness in the hypothermic patient following ROSC, maintain a body core temperature of 33°C until further assessment and decisions can be made.

T: "TABLETS" (DRUG OVERDOSE)

Drug overdose is rarely identified as a cause of cardiac arrest during the resuscitation process. In the event of antidepressant overdose, administer IV sodium bicarbonate. Lipid emulsion infusion may be useful in cardiac arrest associated with cyclic antidepressants or local anesthetics. β-Blocker or calcium channel–blocker overdose may require high-dose insulin therapy and lipid emulsion infusion.

T: CARDIAC TAMPONADE

Cardiac tamponade is best identified during resuscitation by bedside transthoracic US. This requires brief interruption of chest compressions. Treatment of tamponade causing cardiac arrest is bedside pericardiocentesis.

T: TENSION PNEUMOTHORAX

Suspect tension pneumothorax during cardiac resuscitation if breath sounds are unequal on chest auscultation after verifying correct endotracheal tube placement. Treatment is immediate needle decompression.

T: CORONARY THROMBOSIS

Acute coronary thrombosis or acute myocardial infarction is one of the most common causes of cardiac arrest. Risk factors are a history of coronary artery disease and initial rhythm of VF/VT.[63-67] Cardiac catheterization after resuscitation is an underused procedure.[67] A 12-lead ECG in the immediate post–cardiac arrest state can identify an ST-segment elevation acute myocardial infarction and allow arrangements for immediate coronary angiography. Myocardial and neurologic function can improve after percutaneous coronary intervention following cardiac arrest.[68] The 2015 American Heart Association/American College of Cardiology guidelines[1] provide a class I recommendation to activate the cardiac catheterization laboratory in patients with OHCA with ST-segment elevation acute myocardial infarction on ECG. Thus, after ROSC, especially in the face of post-ROSC ECG evidence of acute myocardial infarction, advocate for cardiac catheterization and percutaneous coronary revascularization if available and appropriate. A few case reports describe fibrinolysis during CPR with resultant ROSC and good neurologic outcome.[69] Coronary angiography is reasonable in select patients with suspected cardiac origin of arrest but without ST elevation or in those electrically unstable patients without ST-segment elevation with suspected cardiovascular lesions. The absence of ST-segment elevation on postarrest ECG does not exclude acute coronary thrombus, as approximately one third of patients without ST-segment elevation myocardial infarction on postarrest ECG demonstrate a culprit lesion on angiography.[70] Reports are too few to determine whether thrombolysis together with CPR results in more severe bleeding than thrombolysis without CPR.[71]

T: THROMBOSIS (PULMONARY EMBOLISM)

Pulmonary embolism causing cardiac arrest requires fibrinolysis or embolectomy. However, the diagnosis is rarely made at time of collapse, and even then, most systems are not geared to make such prompt diagnosis and initiate the necessary procedures for embolectomy. Fibrinolytic agents could be considered during cardiac arrest from suspected pulmonary embolism on a case-by-case basis.[72] A single-center case series of patients with diagnosed pulmonary embolism suffering PEA arrest found that rapid administration of alteplase 50 milligrams IV to be safe and effective, with 20 of 23 patients demonstrating ROSC.[73-75] High-quality compressions should be continued after thrombolytic therapy is administered, with several studies recommending 60 to 90 seconds of compression after the drug is given. Factors suggestive of pulmonary embolism causing cardiac arrest include two of three signs or symptoms (prearrest respiratory distress, altered mental status, or shock); arrest witnessed by a physician or emergency medical technician; and PEA as the first or primary arrest rhythm.

POST-ROSC COMPLICATIONS

After return of spontaneous circulation (ROSC), many factors affect survival, including anoxic brain injury, post–cardiac arrest myocardial dysfunction, the systemic reperfusion response, and the cause of cardiac arrest. Ischemic-reperfusion injury is discussed in Chapter 26, "Post–Cardiac Arrest Syndrome." Anoxic brain injury results in disturbance of cerebral microvascular hemostasis and manifests as coma, seizures, myoclonus, and varying degrees of neurocognitive dysfunction, including brain death. Post–cardiac arrest myocardial dysfunction results from myocardial stunning with cardiac hypokinesis and a low left ventricular ejection fraction. Clinical manifestations include tachycardia and elevated left ventricular end-diastolic pressures, progressing to hypotension and reduced cardiac output. The systemic ischemia-reperfusion response consists of inflammation, endothelial activation, and disturbed vasoregulation with generalized activation of immunologic and coagulation pathways, causing increased risk of multiple organ failure and infection. Clinical manifestations of the systemic ischemia-reperfusion response include impaired oxygen delivery and utilization and increased susceptibility to infection.

OXYGENATION AND VENTILATION

Hyperoxia during the early phase of reperfusion after ROSC harms postischemic neurons and increases brain lipid peroxidation.[76-78] After ROSC, adjust the rate of ventilation and tidal volume to maintain arterial oxyhemoglobin saturation at 94% to 98%.[79] Hyperventilation is not recommended because it can increase intrathoracic pressures and decrease venous return and cardiac output. In addition, hypocarbia resulting from hyperventilation decreases cerebral blood flow and aggravates anoxic brain damage. The suggested ventilator parameters during the post-ROSC phase[77-79] are as follows: $Paco_2$, 35 to 45 mm Hg (5 to 6 kPa); Sao_2, 94% to 98%; tidal volume, 6 to 8 mL/kg ideal body weight; $Petco_2$, 35 to 40 mm Hg, and 10 to 12 ventilations per minute.

HEMODYNAMIC MANAGEMENT

Obtain 12-lead ECG after ROSC and repeat at 8 hours or as needed. Administer IV fluids and drugs to optimize blood pressure, cardiac output, and urine output. The target for blood pressure is a mean arterial

pressure of 65 to 100 mm Hg, and the target for blood oxygenation is an $Scvo_2$ of ≥70%.[79] Pharmaceutical agents to support the circulation include epinephrine, norepinephrine, dopamine, dobutamine, nitroglycerine, and esmolol. Routine use of lidocaine after ROSC is not recommended. Obtain an echocardiogram at 24 hours after ROSC to detect regional wall motion abnormalities and determine ejection fractions.

TARGETED TEMPERATURE MANAGEMENT (THERAPEUTIC HYPOTHERMIA)

Cooling of the CNS decreases cerebral oxygen demand, reduces cellular effects of reperfusion, and decreases the production of reactive oxide radicals. Targeted temperature management (cooling to 32°C to 36°C; temperature goal is controversial) during the first 24 hours after ROSC improves survival and neurologic recovery[80-82] in patients who remain comatose soon after ROSC. The phases of temperature management are induction, maintenance, and rewarming. The most recent evidence suggests cooling for 48 hours is not associated with improved neurologic outcomes,[83] and a greater degree of cooling (32°C vs. 36°C) is not associated with improved patient outcomes.[84] Hyperpyrexia in the first 48 hours is associated with a lowered chance of optimal neurologic recovery, and avoiding hyperpyrexia is paramount. See Chapter 26, for detailed discussion.

GLYCEMIC CONTROL

Post-ROSC hyperglycemia is associated with increased mortality and worse neurologic outcomes.[85] Hypoglycemia, similarly, is also associated with poor outcomes in critically ill patients. Maintain blood sugar levels between 100 and 180 milligrams/dL (6 and 10 mmol/L).

NEUROLOGIC ASSESSMENT

Features of brain injury after ROSC include coma, seizures, myoclonus, and various degrees of neurocognitive dysfunction ranging from memory deficits to a persistent vegetative state and finally brain death. Treat seizures promptly. The neurologic prognosis in the majority of comatose cardiac arrest survivors undergoing therapeutic hypothermia is challenging and typically cannot be reliably predicted in the ED.[86] Cerebral imaging for prognostication has been studied, including MRI and CT in association with scoring systems or biomarkers, but requires further study.[87,88]

ADVANCED RESUSCITATION TECHNIQUES

ECMO (Box 1) and SAAP (Box 2) are advanced resuscitation techniques available or practiced in some settings.

BOX 1 Extracorporeal CPR (ECMO) in Cardiac Arrest

ECMO, also known as extracorporeal life support, is a recent introduction in the management of cardiac arrest. Its use is well documented in the neonatal and pediatric population and in adults for refractory respiratory failure and cardiogenic shock. Use in refractory cardiac arrest is also known as extracorporeal CPR (Table 1). Extracorporeal CPR is a bridging therapy to definitive treatments, such as percutaneous coronary interventions, cardiac bypass surgery, or heart transplant. Current published results on effectiveness are inconclusive.[89]

The ECMO equipment consists of a blood pump, a venous reservoir, an oxygenator for exchanging both oxygen and CO_2, and a heat exchanger to warm the blood used (Figure 1). The whole system is monitored through pressure, oxygen saturation, and temperature monitors. Three types of ECMO circuits are available:

1. Venoarterial ECMO pumps blood from the venous side to the arterial side to facilitate gas exchange and provide hemodynamic support. The blood is pumped from the venous circulation through a cannula inserted in either the inferior vena cava or right atrium and through the oxygenator where gas exchange occurs, and then is warmed and returned to the patient through a cannula placed in either the aortic arch or femoral artery into the arterial circulation. This is the modality that is used to support cardiac arrest patients.
2. Venovenous ECMO removes blood from the right atrium, passes it through the gas exchanger, and returns it across the tricuspid valve into the right ventricle. It does not provide hemodynamic support. This modality is used primarily for refractory respiratory failure.
3. Arteriovenous ECMO uses the patient's own arterial pressure to pump the blood from the arterial to the venous side and facilitates gas exchange in the process. This does not require the use of a separate blood pump.

The ECMO circuit is initially primed with fresh blood, which is then pumped through the circuit. During maintenance of ECMO, hemodynamic parameters, urinary output, hematologic indices, fluids, and electrolytes are monitored.

Extracorporeal CPR complications can be mechanical, medical, or both. Mechanical complications consist of clots in the circuit; mediastinal bleeding from tears to the great vessels; oxygenator failure; and malfunction of the blood pump, oxygenator, heat exchanger, and sensors. Medical complications include intracranial and systemic hemorrhage, initial cardiac stunning that may occur soon after initiation of ECMO, pneumothorax, acute kidney injury, GI bleeding, sepsis, and metabolic derangement.

Extracorporeal CPR must also be accompanied by appropriate post–cardiac arrest management, including targeted temperature and hemodynamic management and early coronary angiography for definitive treatment. At present, survival rates are low, but can be improved with EMS and ED training, appropriate patient selection, and more widespread application of the technique.



FIGURE 1. Extracorporeal CPR in the ED of Singapore General Hospital.

TABLE 1 General Indications and Contraindications for Extracorporeal CPR (Extracorporeal Membrane Oxygenation in Cardiac Arrest)

Indications	Contraindications
Good premorbid status before cardiac arrest	Advanced age; advanced malignancy; poor baseline neurologic function; baseline inability to perform activities of daily living; preexisting "do not resuscitate" order
Intervention to be curative, not palliative	Suspect aortic dissection or severe aortic regurgitation; traumatic cardiac arrest
Reversible trigger event for cardiac arrest (dysrhythmia, ST-segment elevation myocardial infarction, etc.)	Unwitnessed cardiac arrest and no bystander CPR Long prehospital transport time Prolonged cardiac arrest unless good perfusion and metabolic support is documented

BOX 2 Selective Aortic Arch Perfusion

- Selective aortic arch perfusion (SAAP) (Figure 2) is an extracorporeal perfusion therapy providing effective blood flow during cardiac arrest, improving chance of ROSC and limiting time-critical ischemic injury, and reducing cardiac and CNS damage.[90-92]
- SAAP can be used for cardiac arrest and hemorrhage-induced traumatic cardiac arrest (similar to resuscitative endovascular balloon occlusion of the aorta).
- The procedure involves insertion of a femoral artery large-lumen balloon occlusion catheter advanced to the descending thoracic aorta. Balloon inflation isolates the aortic arch vessels, perfusing the coronary, carotid, and vertebral arteries.
- If the limit of the exogenous oxygen carrier is reached, oxygenated autologous blood can be provided with a closed-loop circuit.
- Full ECMO can follow SAAP if prolonged extracorporeal perfusion is required.

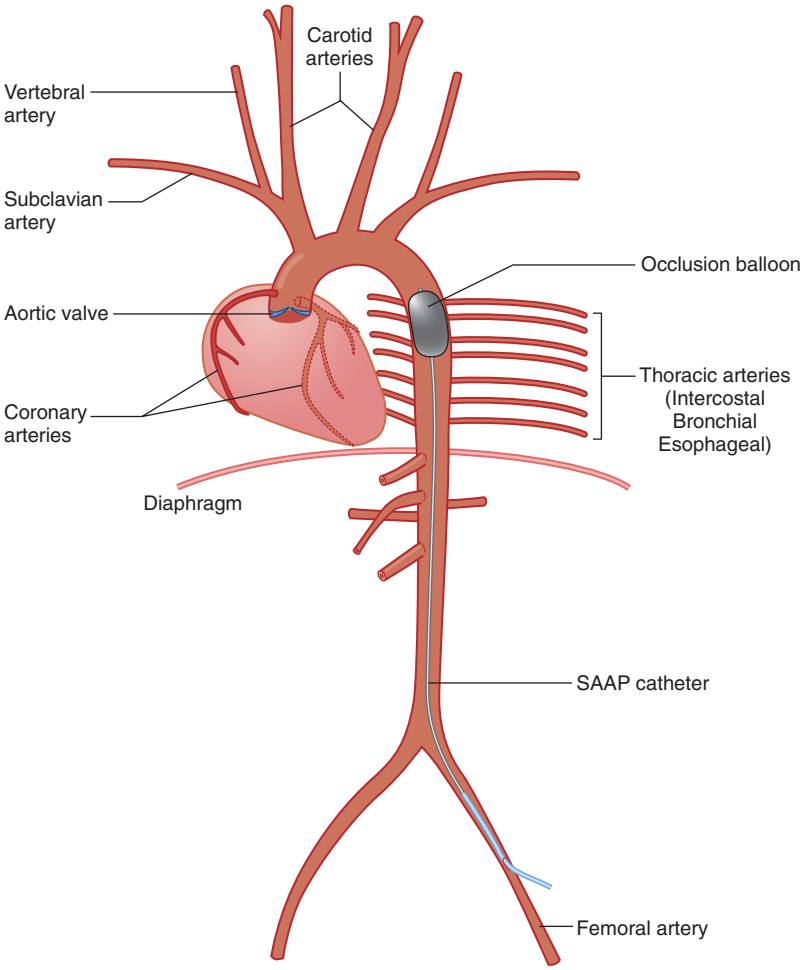


FIGURE 2. Illustration of fluoroscopic image of selective aortic arch perfusion with descending thoracic aortic occlusions, competent aortic valve closure, and coronary artery perfusion. [Figure used with permission of James Manning, MD.]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 25

Resuscitation in Pregnancy

Boyd D. Burns
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INTRODUCTION AND EPIDEMIOLOGY

Cardiac arrest in pregnancy is rare, and resuscitation of a pregnant woman is typically an unexpected and chaotic event, which ideally involves multiple consultants from different specialties with different levels and types of skills. Emergency care and lifesaving procedures for resuscitation and cardiac arrest should not be delayed if specialists are not available. Contact the closest center providing neonatal and maternal services as soon as possible to facilitate rapid transport and continued care of the newly delivered infant and the mother.

The World Health Organization defines maternal deaths as deaths while pregnant or within 42 days of the end of pregnancy, related to or aggravated by pregnancy or pregnancy management, regardless of the duration or site of the pregnancy and irrespective of the cause of death.[1] Factors associated with pregnancy-related deaths in the United States include advanced maternal age, African-American race, increasing live birth order, and lack of prenatal care.[2]

Recent U.S. data demonstrate that cardiac arrest, in the inpatient setting, occurs in 1:12,000 admissions.[3] The trend in maternal mortality

TABLE 25-1 Physiologic Changes in Pregnancy Affecting Resuscitation

System	Parameters	Comment
Cardiovascular	Cardiac output	Increases 30%–50%
	Peripheral resistance	Decreases 20%
	Blood pressure	Decreases 10–15 mm Hg systolic in first half of pregnancy; then back to baseline
	Blood volume	100 mL/kg or 6–7 L
	Central venous pressure	May be increased up to 10 mm Hg
	Central venous oxygen saturation	Increases as high as 80%[5]
	Plasma volume	Increases 30%–50%
Hematologic	Fibrinogen, factors V, VII, VIII, X, von Willebrand factor	Increase, with heightened risk for venous thromboembolism in second half of pregnancy
Respiratory and pulmonary	Upper airway edema, hyperemia, and friability	Estrogen and volume effects; can result in difficult airway
	Diaphragm elevation	Higher thoracostomy tube insertion site during pregnancy
	Hemoglobin F has greater affinity for oxygen than maternal hemoglobin	Fetal oxygen maintained at expense of maternal oxygenation; maintain maternal oxygen saturation >95%
	Respiratory rate	No change
	Tidal volume, minute ventilation	Increase
Renal and urinary	Progesterone dilates renal collecting system; ureteral peristalsis decreases	Renal US may show mild hydronephrosis; increased risk for ascending infection
GI	Alkaline phosphatase rises from placental production; bile is more lithogenic	Increased risk of cholecystitis/cholelithiasis
	Decreased lower esophageal tone; decreased gastric emptying	Increased likelihood of aspiration of gastric contents
Uteroplacental unit	25% of blood flow directed to uteroplacental unit; no autoregulation of blood flow; enlarging uterus can compress vena cava and vessels below the diaphragm; supine hypotension syndrome can occur after 30 min of supine position	Place patient in left lateral tilt position during third trimester; replace volume adequately to account for increased blood and plasma volume in pregnancy; avoid femoral and lower extremity site for blood and volume delivery in second half of pregnancy

in the United States, according to the Centers for Disease Control and Prevention, has seen a steady increase from 7.2 deaths per 100,000 live births in 1987 to 17.8 deaths per 100,000 live births in 2009.[4]

Management of emergencies during labor and delivery is discussed in Chapter 101, "Emergency Delivery."

PHYSIOLOGY OF PREGNANCY

Beginning early in pregnancy, virtually all major organ systems undergo changes (**Table 25-1**) that affect patient management.

CARDIOVASCULAR CHANGES

Uterine blood flow is not autoregulated but is directly proportional to the maternal mean arterial pressure and inversely proportional to the resistance of the uterine vasculature. Conditions that decrease uterine blood flow during pregnancy include maternal hypovolemia, hypotension, uterine vasoconstriction, tetanic uterine contractions, and aortocaval compression.

As the uterus enlarges throughout pregnancy, compression of the pelvic and abdominal vasculature can occur, especially when the patient is supine. Compression of the inferior vena cava can decrease maternal venous return and reduce cardiac output from 10% to 30% (**Figure 25-1**).[6] This can contribute to supine hypotension syndrome, which is a constellation of findings including hypotension, tachycardia, dizziness, pallor, and nausea. It is reported to occur after 30 minutes in the supine position.[6] Therefore, place any patient in the third trimester of pregnancy in the full left lateral tilt position when in hemodynamic distress or exhibiting hypotension.[7] Left lateral tilt can be achieved by placing a roll under the patient's right hip, inserting a Cardiff wedge, or placing the patient in full left lateral tilt while on a backboard (**Figure 25-2**). The Cardiff wedge provides a tilt of 27 degrees from the horizontal. Foam or hard wedges are better for maintaining the left lateral tilt position than are pillows or manual tilting.[8] Because compression of the abdominal vasculature can compromise intravascular delivery of medications through sites below the diaphragm, avoid femoral or saphenous venous sites for IV access during the resuscitation of a pregnant woman at >20 weeks of gestation. The negative effects of great

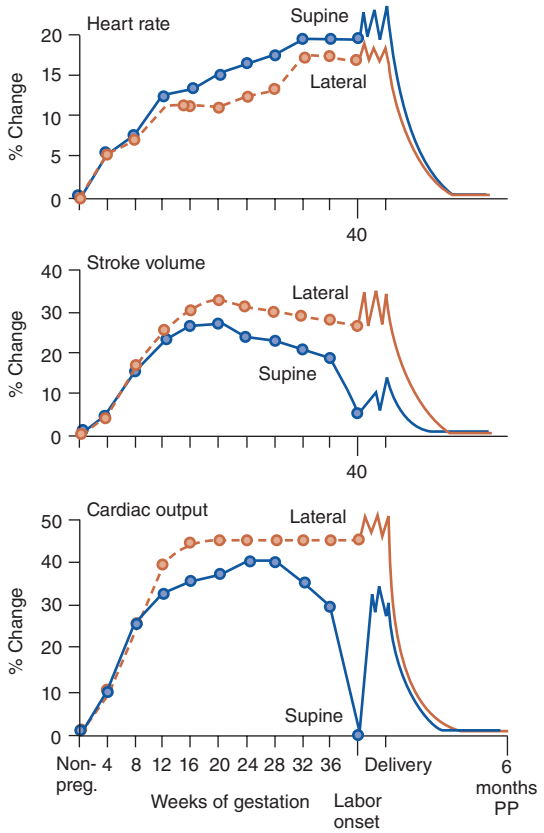

FIGURE 25-1. Changes in maternal heart rate, stroke volume, and cardiac output during pregnancy (preg.), with the gravida in the supine and lateral positions. PP = postpartum. [Reproduced with permission from Barclay ML: Critical physiologic alterations in pregnancy, in Pearlman MD, Tintinalli JE (eds): *Emergency Care of the Woman.* New York, The McGraw-Hill Companies, Inc., 1998, Chapter 2, Figure 2-3, p. 14. Copyright © 1998 by The McGraw-Hill Companies, Inc. All rights reserved.]



FIGURE 25-2. Left lateral tilt position.

vessel compression on uteroplacental blood flow increase in the presence of maternal hypotension and uterine contractions.

RESPIRATORY AND PULMONARY CHANGES

Respiratory changes occur early to help optimize fetal oxygenation. Progesterone drives an increase in resting minute ventilation and tidal volume. The respiratory rate, however, remains relatively unchanged, so **do not dismiss tachypnea as a normal part of pregnancy**. As pregnancy progresses, the diaphragm elevates approximately 4 cm with an increase of the transverse diameter of the thoracic cage by 2 cm.[9] Changes in pulmonary physiology and increased metabolic oxygen consumption can result in the rapid development of hypoxia during respiratory illnesses or as a result of respiratory arrest.

Because the fetal oxyhemoglobin dissociation curve is shifted to the left relative to the maternal oxyhemoglobin dissociation curve, the bond of fetal hemoglobin to oxygen is stronger than maternal hemoglobin, which results in preservation and optimization of fetal oxygen delivery at any given partial pressure of oxygen. Strive to maintain maternal pulse oximetry readings >95% to maintain a partial pressure of oxygen in arterial blood of >70 mm Hg to optimize maternal oxygenation and oxygen delivery to the placenta.[9]

The fetus exists in a physiologically acidemic state relative to the mother, which allows preferential oxygen transfer at the fetal tissue level.[10] Acidemia favors a rightward shift of the oxyhemoglobin dissociation curve, resulting in a greater amount of oxygen supplied to fetal tissues. Fetal cardiac output protects against brief periods of hypoxia, with increases in umbilical blood flow and placental gas exchange and preferential redistribution to vital tissues.

RESUSCITATION STEPS

The most common causes of pregnancy-related deaths in the United States are cardiovascular disease, cardiomyopathy, hemorrhage, infection/sepsis, hypertensive disorders of pregnancy, and thrombotic pulmonary embolism.[2,11] Major trauma is the greatest risk for nonobstetric cause of death. Motor vehicle collisions account for almost half of trauma, followed by falls and assaults.[12]

The best maternal care provides the best fetal care, so follow general principles of resuscitation when treating pregnant women. **To accommodate the increase in blood and plasma volume that develops during pregnancy, make sure that the volume of resuscitative fluids increases by 50% above that required by the nonpregnant patient**. Place two large-bore IVs above the level of the diaphragm, and provide rapid infusions of isotonic saline. Volume must be adequately replaced before considering vasopressors, especially in pregnancy, because the uterine arteries are maximally dilated and blood flow is pressure dependent.

The gravid uterus can cause aortocaval compression, leading to increased afterload and decreased cardiac return as early as 12 to 14 weeks of gestation.[13] Place pregnant patients in the left lateral decubitus position to improve both ejection fraction and stroke volume whenever feasible from a resuscitation standpoint.

Select a vasopressor by the desired effects in the mother and the least harmful effects on the fetus (see Table 25-4). Vasopressors have variable effects on fetomaternal circulation, so if time allows, critical care or obstetrical consultation may be helpful before selecting vasopressors.

Studies of vasopressors in pregnancy are limited to either animal models or focus on the short-term use of pseudoephedrine or ephedrine for spinal anesthesia–induced hypotension during cesarean section. This makes available data difficult to extrapolate to other human hypotensive situations. **Phenylephrine** (pregnancy category C) is an α_1-selective agent without any β activity, so it raises blood pressure through vasoconstriction but can cause reflex bradycardia in some cases. It crosses the placenta, and effects on lactation are unclear. It appears to have a favorable fetal acid-base profile. **Ephedrine** (pregnancy category C) is a mixed α and β stimulator. It crosses the placenta and can induce fetal acidosis.[14,15] Standard vasoactive agents such as norepinephrine, dopamine, and vasopressin are all pregnancy category C with limited data available on use in pregnancy. There is concern that use of these medications may decrease uterine blood flow as a result of vasoconstriction. However, the benefits of correcting maternal hemodynamic instability secondary to shock generally outweigh the risk to the fetus.

SEPSIS

Sepsis is a systemic inflammatory response to infection leading to acute organ dysfunction. Currently there are no sepsis guidelines specifically for pregnant women because this population has been excluded from early landmark sepsis studies. Pregnant women, when compared with nongravid women, are more likely to develop complications from serious infections. Maintain a high index of suspicion for sepsis in pregnant women because signs and symptoms of sepsis may not be as apparent when compared to the nonpregnant population.[16] The clinical features of sepsis in pregnancy include fever or rigors, diarrhea or vomiting, rash, abdominal or pelvic pain, vaginal discharge, productive cough, or urinary symptoms.[17]

The determination of the severity of sepsis in pregnancy can be challenging due to normal physiologic changes in pregnancy that mimic the changes in sepsis. These changes include a decrease in diastolic blood pressure during the second trimester, increase in heart rate, and increase in leukocyte count.[18]

Septic shock in pregnancy is rare, occurring in a small number (0.002% to 0.01%) of deliveries and in only 0.3% to 0.6% of pregnant women (**Table 25-2**). However, sepsis as a cause of mortality can vary between 2.7% in developed countries to 11.6% in developing countries.[19] The most common causes of peripartum sepsis are pyelonephritis and pelvic infections such as chorioamnionitis. Less common causes include pneumonia and septic abortion.[20,21] Malaria, human immunodeficiency virus, and tuberculosis are more common in developing countries.[22]

Prompt antibiotic therapy is key and should target suspected pathogens based on site of infection, likely causative organisms, and local resistance patterns. In general, β-lactams, aminoglycosides, and macrolides are preferred during pregnancy, if appropriate, due to their safety profile for the fetus.

Pyelonephritis is the most common cause of septic shock in pregnancy.[23] Progesterone produces dilatation of the ureters, and

TABLE 25-2 Some Causes of Maternal Sepsis

- Pyelonephritis
- Chorioamnionitis
- Endometritis
- Septic abortion
- Pelvic abscess
- Pneumonia
- Influenza
- Herpes
- Varicella
- Wound infection/abscess
- Necrotizing cellulitis/fasciitis
- Appendicitis
- Cholecystitis
- Pancreatitis
- Malaria or HIV in developing countries

mechanical compression of the urinary system by the enlarging uterus results in relative obstruction of the urinary tract. The most common causative agent is *Escherichia coli,* with *Klebsiella*, *Proteus*, and *Enterobacter* responsible for most other cases. Consider renal US to assess for renal/ureteral stones and to assess for renal complications.[24] Hospitalize pregnant women with pyelonephritis, because bacteremia is likely and the physiologic changes of pregnancy can rapidly cause hypoxia.[25,26] Begin empiric antibiotics. Treatment needs to consider local resistance patterns. In general, for mild to moderate disease, standard regimens are amoxicillin/clavulanate, ampicillin plus gentamicin, ceftriaxone, or cefepime. For severe disease with immunocompromise, consider ticarcillin/clavulanate or piperacillin/tazobactam.

Pneumonia in pregnancy has a similar prevalence as in nonpregnant women, but can be particularly severe because a rapid decline in oxygen saturation can complicate the course whether or not sepsis is present.[25,26] Follow standard community-acquired pneumonia protocols for pneumonia treatment[27] (see Chapter 65, "Community-Acquired Pneumonia, Aspiration Pneumonia, and Noninfectious Pulmonary Infiltrates" for further discussion). All antibiotics cross the placenta. Select pregnancy risk category B agents for treatment.

Influenza infection in pregnancy carries higher morbidity and mortality than in nonpregnant patients due to an altered immune response to the virus involving increased proinflammatory cytokines.[28] Pregnant patients with influenza have an increased risk for severe disease, resulting in higher rates of hospitalization, intensive care unit admission, and death compared with nonpregnant patients, in addition to an increased risk of miscarriage, preterm birth, and stillbirth.[29,30] Lower disease severity is associated with women who receive influenza vaccination and those treated with antivirals within 2 days of symptom onset.[31] Both vaccination and antivirals have been shown to be safe and efficacious in pregnancy.

AIRWAY IN PREGNANCY

ANATOMIC CHANGES AFFECTING INTUBATION

Fluid retention causes edema within the structures of the upper airway,[32,33] and weight gain with adipose deposition can contribute to landmark distortion. Anticipate difficulty with mask ventilation, laryngoscopy, glottic visualization, and endotracheal intubation. Desaturation occurs quickly as a result of maternal increased oxygen consumption and decreased functional residual capacity.

During pregnancy, the incidence of **Mallampati class III** airways increases (only the soft palate and base of the uvula are seen when the mouth is open and the tongue is protruding), making intubation more difficult (see Figure 29A-8 in Chapter 29A, "Tracheal Intubation"). Increased Mallampati scores correlate with gains in body weight,[34] and because obesity in pregnancy is more common than in the nonpregnant state, this contributes to the likelihood of a difficult airway.[35]

Mucosal engorgement and increased capillary friability make airway bleeding and swelling likely. Due to the engorgement and friability of the nasal mucosa, avoid blind nasotracheal intubation if possible. Pregnant women are likely to have full and intact dentition, and there may be little interdental distance in which to maneuver a laryngoscope. In addition, there are often redundant pharyngeal and palatal folds in the airways of obese gravid women. The rates of difficult intubation are reported to range from 1% to 6% and the incidence of failed intubation from 0.1% to 0.6%.[35,36] Decreased lower esophageal tone, increased intra-abdominal pressure, decreased gastric emptying, and a full stomach increase the likelihood of gastric aspiration.

Supplemental oxygen via nasal cannula and facemasks often is insufficient for patients in severe respiratory distress and significant hypoxia. As in most cases, these patients will require positive pressure in addition to supplemental oxygen alone to optimize delivery and oxygenation. Oxygen delivered through a high-flow nasal cannula provides humidified, heated oxygen at flow rates up to 60 L/min,[37] providing positive pressure and decreasing the work of breathing.[38,39] High-flow nasal cannula helps in patients with hypoxemia and an intact respiratory drive, often as an alternative to intubation or noninvasive positive-pressure ventilation. It is best avoided in those not breathing or with bullous lung disease and pneumothoraces.[40] Another option is flush rate oxygenation, where the wall oxygen unit is turned past 15 L/min to maximum flow rates of 40 to 60 L/min.[41,42] The latter helps avoid desaturation during rapid-intubation techniques in addition to other respiratory distress events. Both high-flow nasal cannula and flush rate oxygenation are best seen as bridges to awaiting clinical improvement or other ventilation methods.

INTUBATION

The most experienced physician should undertake the intubation with adjunctive airway equipment, smaller-sized endotracheal tubes, a gum elastic bougie, short laryngoscope handles, and stylets readily available. A video laryngoscope system facilitates first-pass success and direct visualization and decreases complications and prolonged hypoxia.[43-45]

Preoxygenate to 95% oxygen saturation to prevent hypoxia during intubation. Provide supplemental oxygenation by nasal cannula set to deliver 15 L/min during the procedure, even after paralysis, to continue oxygen delivery to the alveoli (passive apneic oxygenation).[46]

Place the patient in the supine position; manually displace the uterus to the left. Elevate the head and shoulders with a pillow or folded sheets to achieve the sniffing position. This maneuver is particularly important in obese patients.

For rapid-sequence induction, use standard doses of induction agents and paralytics (see Chapter 29). The laryngeal mask airway was described as safe and effective in healthy selected patients undergoing elective cesarean section[47] and has been used as a rescue device after failed intubation.[48]

The determination of the initial ventilator settings should be the same as in the nonpregnant patient, with a Pco_2 goal of 28 to 35 mm Hg. Avoid respiratory alkalosis because, in animal models, this decreases uteroplacental flow.[49]

CARDIAC ARREST IN PREGNANCY

Pregnant women are typically younger than the traditional cardiac arrest patient but often have poor outcomes, with survival rates reported as low as 6.9%.[2,11] The causes of cardiac arrest in pregnancy are listed in **Table 25-3**.[50,51]

Cardiopulmonary arrest in pregnancy is broken down into two categories: before and after fetal viability. Typically, the onset of fetal viability varies between 22 and 26 weeks, with some institutional variation considering backup and available resources. By 20 weeks, the uterine fundus is palpable at the umbilicus; then from 20 to 32 weeks, the fundal height (in centimeters) approximates the gestational age (for singleton pregnancies). If the fundal height is at or below the umbilicus, resuscitative effort should focus on the mother with no modifications of CPR. If the uterus is palpable above the umbilicus, one person should provide manual left lateral displacement of the uterus while another is performing CPR.[7,51]

TABLE 25-3 Pregnancy-Related Causes of Maternal Cardiopulmonary Arrest

Obstetric complications
- Hemorrhage (17.2%)
  - Uterine atony
  - Placental abruption
  - Placenta previa, accreta, increta, or percreta
  - Disseminated intravascular coagulopathy
- Severe pregnancy-induced hypertension (15.7%)
- Amniotic fluid embolism
- Idiopathic peripartum cardiomyopathy (8.3%)
- Iatrogenic events
- Failed intubation
- Pulmonary aspiration
- Intravascular local anesthetic overdose (1.6%)
- Drug error, overdose, or allergy
- Hypermagnesemia

Pulmonary embolism (19.6%)
- Thrombus
- Air
- Fat

Stroke (5%)

Trauma
- Homicide
- Suicide
- Motor vehicle accident

Infection or sepsis (12.6%)

Other (19.2%) (cardiovascular, pulmonary, and neurologic comorbidities)

Source: Reproduced with permission from Chang J, Elam-Evans LD, Berg CJ, et al: Pregnancy-related mortality surveillance—United States, 1991–1999. *MMWR Surveill Summ* 52: 1, 2003.



FIGURE 25-3. Manual left uterine displacement by the one-handed technique from the right of the patient during adult resuscitation. [Reproduced with permission from Zelop CM, Einav S, Mhyre JM, et al: Cardiac arrest during pregnancy: ongoing clinical conundrum, *Am J Obstet Gynecol*. 2018 Jan 2. pii: S0002-9378(17)32806-5. Copyright Elsevier.]

DEFIBRILLATION AND VASOACTIVE MEDICATIONS

When left lateral decubitus positioning is not feasible due to ongoing CPR or intubation, maintain leftward uterine displacement with one team member manually and continuously displacing the gravid uterus toward the patient's left.[52] Chest compressions with the patient tilted to the side are less effective than those performed in the usual supine position[53] (**Figure 25-3**).

Treat pregnant women in cardiac arrest according to current Advanced Cardiac Life Support guidelines (**Table 25-4**). Perform defibrillation at

TABLE 25–4 Medications Used During Resuscitation: Considerations in Pregnancy

Drug	Indications	Pregnancy Risk Category
Epinephrine	Potentially beneficial in all forms of cardiac arrest	Category C. Teratogenic in animals in large doses; may induce uteroplacental vasoconstriction and fetal anoxia.
Lidocaine	Ventricular ectopy, tachycardia, and fibrillation	Category B. Use during pregnancy is not well studied; crosses the placenta, but in therapeutic doses has no teratogenic effect on the fetus; may cause fetal bradycardia.
Atropine	Symptomatic bradycardia	Category C. Crosses placenta but results in no fetal abnormalities; can cause fetal tachycardia.
Sodium bicarbonate	Cardiac arrest unresponsive to other measures; documented preexisting metabolic acidosis	Category C. No studies of risk. Use for hyperkalemia and selected toxic overdoses.
Calcium chloride or gluconate	Cardiac arrest due to hyperkalemia, or as antidote to magnesium toxicity (a potential complication when giving high doses of magnesium for eclampsia)	
Dopamine	Hemodynamically significant hypotension in the absence of hypovolemia	Category C. No teratogenic effects in animals, but sufficient studies in humans are lacking; use only when clearly indicated.
Dobutamine	Short-term inotropic support of patients with depressed myocardial contractility	Category B. Not teratogenic in animal studies.
Norepinephrine	Vasopressor for septic shock after adequate volume replacement	Category C. No animal reproductive studies done. Crosses the placenta.
Amiodarone	Ventricular fibrillation, tachycardia, and supraventricular tachycardia	Category D. Is part of Advanced Cardiac Life Support algorithm in pregnancy; use if benefit outweighs risk; serious fetal adverse effects of congenital goiter and hypothyroidism.
Adenosine	Supraventricular tachycardia	Class C. Multiple case reports of the safe use of adenosine to treat maternal and fetal supraventricular tachycardia.
Magnesium sulfate	Torsades de pointes; prevention or treatment of seizures in severe preeclampsia or eclampsia	Class D. Crosses the placenta, and levels in fetus are similar to the mother. Neonatal neurologic depression may occur with respiratory depression, muscle weakness, and loss of reflexes. Continuous maternal use for >5 days may cause fetal hypocalcemia or bone abnormalities.
Ephedrine	Hypotension related to spinal anesthesia or unresponsive to fluids	Class C. Multiple reports of use during anesthesia-related hypotension in pregnancy. Maintains uterine blood flow. May cause dose-dependent increase in fetal acidosis, tachycardia, and abnormal variability in fetal heart rate (indicative of fetal stress), or an increase in metabolic activity.
Phenylephrine	Hypotension related to spinal anesthesia or unresponsive to fluids	Class C. Superior to ephedrine for management of hypotension after spinal anesthesia with a decrease in fetal acidosis.[14]
Vasopressin	No longer recommended for cardiac arrest	Class C. There are no controlled data in human pregnancy.

recommended adult doses. Despite an increase in plasma volume and glomerular filtration rate, there is no evidence that the standard doses of Advanced Cardiovascular Life Support medications should be altered. Place IV sites above the diaphragm secondary to aortocaval compression. Vasopressin is no longer part of the 2015 Advanced Cardiac Life Support algorithms, and vasopressin can lead to uterine contractions.[54] Amiodarone can be given at its usual doses as appropriate for management of refractory ventricular fibrillation or tachycardia. Defibrillate with the usual settings and paddle positioning. Pregnant patients have limited oxygen reserve, so provide airway management early in the resuscitation to rule out maternal hypoxia as a source of the patient's deterioration.[52] Perform perimortem cesarean section early in the management of any arresting patient with a uterus at or above the level of the umbilicus to improve both maternal and fetal outcomes.

POST–CARDIAC ARREST HYPOTHERMIA AND EXTRACORPOREAL MEMBRANE OXYGENATION

Case reports describe successful use of post–cardiac arrest hypothermia during pregnancy. The 2010 American Heart Association guidelines, Cardiac Arrest in Special Situations, recommend hypothermia in early pregnancy without emergency cesarean section (with fetal heart monitoring). Hypothermia should be considered on a case-by-case basis based on the current recommendations for the nonpregnant patient.[55-57] As the use of extracorporeal membrane oxygenation continues to increase, this modality may be considered in the appropriate facility setting (dedicated extracorporeal membrane oxygenation center).[58]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 26

Post–Cardiac Arrest Syndrome

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INTRODUCTION AND EPIDEMIOLOGY

Sudden cardiac arrest represents one of the most time-sensitive diseases in the practice of emergency medicine, requiring prompt recognition and rapid delivery of resuscitative care, including high-quality CPR, early defibrillation when appropriate, and appropriate airway management.[1] Even with these interventions, aggregate survival to hospital discharge is less than 20% in most communities and hospital systems.[2,3] Among survivors, neurologic injury is common (present in up to 50% of survivors) and widely varied, ranging from subtle memory deficits to persistent vegetative state.[4,5] This chapter focuses on the pathophysiology of ischemia-reperfusion injury and the provision of targeted temperature management, also called therapeutic hypothermia.[6]

PATHOPHYSIOLOGY OF ISCHEMIA-REPERFUSION INJURY

The brain is exquisitely sensitive to ischemia, such that disruption of blood flow for several minutes is sufficient to initiate a set of injury mechanisms that may lead to irreversible disabilities.[7,8] The complete loss of blood flow, followed by the abrupt **return of spontaneous circulation**, rapidly leads to a complex pathophysiologic process known as ischemia-reperfusion injury, also known specifically in the sudden cardiac arrest setting as postresuscitation syndrome.[8,9]

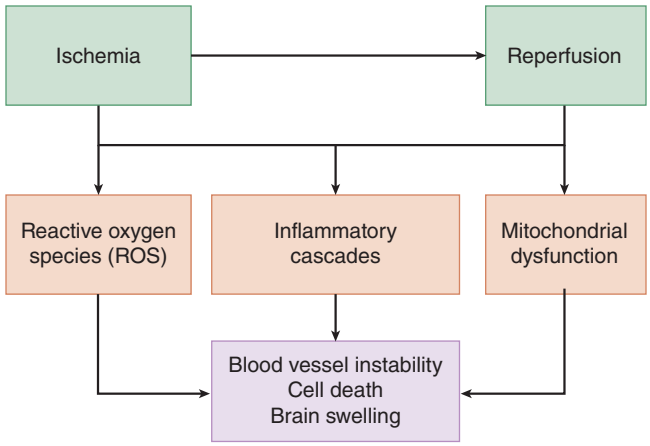

FIGURE 26-1. Schematic of postarrest pathophysiology, also called ischemia-reperfusion injury. The concepts shown here represent processes that occur at the subcellular, cellular, tissue, and organismal levels. The kinetics of these processes following cardiac arrest and the extent to which they affect clinical outcomes are still unclear.

When blood flow is abruptly stopped and then restored, a number of overlapping mechanisms lead to clinical injury (**Figure 26-1**).

CELLULAR RESPONSES TO RETURN OF SPONTANEOUS CIRCULATION

At the cellular level, mitochondrial integrity and function become damaged, with release of crucial enzymatic machinery such as cytochrome c and disruption of oxidative phosphorylation.[9,10] Mitochondrial injury is implicated in the increased concentration of oxygen free radicals and downstream activation of programmed cell death pathways.[10,11] At the humoral level, reperfusion triggers a broad array of immune activation, including increased blood levels of cytokines such as interleukin-6 and tumor necrosis factor-α.[12] In addition, aberrant neutrophil and platelet activation can occur. These immune phenomena have led Adrie et al[13] to describe the postresuscitation condition as a "sepsis-like syndrome," in which inflammation plays a crucial role in injury. Immune activation, in turn, can lead to additional production of oxygen free radicals such as superoxide and hydrogen peroxide. These molecules, produced in small quantities during normal cellular function, are usually converted to oxygen and water by the enzymes catalase and superoxide dismutase. However, enzyme systems become overwhelmed with the dramatic increase of free radical species generated during postresuscitation syndrome. Different tissues exhibit varying sensitivity to ischemia-reperfusion processes, with brain tissue and vascular endothelium appearing to be particularly vulnerable.[8,9]

ORGAN SYSTEM EFFECTS OF RETURN OF SPONTANEOUS CIRCULATION

The biochemical and cellular phenomena described earlier lead to diverse clinical manifestations of injury in the minutes to hours following resuscitation. Inflammatory changes and immune cellular activation can lead to vascular leak and a drop in peripheral vascular resistance, with concomitant loss of fluid from the intravascular compartment and hypotension.[14] Cellular injury in the brain, combined with endothelial damage, can trigger cerebral edema, a common and dangerous component of postresuscitation syndrome.[15] Cerebral edema and increased intracranial pressure can cause cerebral herniation and serve as the cause of death, often in the initial 72 hours following resuscitation. Myocardial stunning is clinically evident on echocardiography as global hypokinesis and markedly reduced ejection fraction.[16,17] Myocardial depression is usually transient and typically resolves over the first few days following resuscitation with appropriate hemodynamic support.[17,18] Postresuscitation infection may be related to bacterial translocation into the bloodstream from loss of intestinal tissue integrity.[19] Adrenal

injury from ischemia may cause adrenal insufficiency furthering clinical deterioration.[20]

CLINICAL FEATURES AFTER RETURN OF SPONTANEOUS CIRCULATION

Following initial resuscitation, the clinical condition of patients varies considerably. Some patients with prompt recovery after only brief periods of CPR can be awake and responsive; however, most patients are initially comatose or markedly obtunded following resuscitation. Neurologic assessment is limited in most cases because, in the course of clinical resuscitation care, patients are intubated and sedated and/or pharmacologically paralyzed.

Physical examination is limited in the immediate postresuscitation period as well. Most patients exhibit absent or abnormal papillary responses and absent gag reflex or doll's eyes responses. **Clinical neurologic reflexes are not predictive of cardiac arrest outcomes.**[21] Internation resuscitation guidelines strongly recommend that **bedside neurologic examination should not influence decisions for continued care in the first 72 hours following successful resuscitation.**[22] Focus the physical examination after resuscitation on identifying clues to determine the possible cause of cardiac arrest, such as asymmetric lower extremity edema, which might suggest thromboembolic disease; absent or decreased lung sounds, which might implicate pneumothorax; or jugular venous distention and muted heart sounds, which might suggest cardiac tamponade. Promptly obtain an ECG because myocardial ischemia is the most common cause of sudden cardiac arrest.

DIAGNOSIS OF ANOXIC BRAIN INJURY AFTER RETURN OF SPONTANEOUS CIRCULATION

Neuroprognostication after sudden cardiac arrest is a challenging and inexact process. A variety of radiographic, biochemical, and neurophysiologic tools are available to assess brain injury following sudden cardiac arrest, but most are poorly validated and require additional research to determine clinical utility.

In the ED, perform head CT in survivors as soon as feasible. Head CT can identify subarachnoid hemorrhage[21,23] or epidural and subdural hematomas. The degree of cerebral edema can also be assessed by head CT.[23-25] Because cerebral edema often peaks several days after resuscitation, swelling that is radiographically apparent on initial CT is a worrisome sign. Brain MRI is generally neither practical nor useful during initial ED management.[26]

Many protocols for postarrest care involve the early institution of continuous electroencephalogram monitoring to assess for electrical convulsive activity, which is present in up to 25% of patients after resuscitation.[27] The presence of seizures generally augurs a poor prognosis, but not all patients with electrical seizure activity sustain severe long-term injury. Bispectral index monitoring, a simple approach to electrical brain monitoring relative to electroencephalography, can be useful to predict neurologic outcome.[28,29] Measurement of somatosensory evoked potentials, a bedside test of neuronal connectivity and function, can be performed several days following cardiac arrest and may also be useful to predict outcome.[30]

TARGETED TEMPERATURE MANAGEMENT (OR THERAPEUTIC HYPOTHERMIA)

The key ED intervention for postresuscitation syndrome is the prompt delivery of systemic cooling therapy, also called therapeutic hypothermia or **targeted temperature management**. Systemic cooling of resuscitated adult cardiac arrest for 24 hours following arrest and return of spontaneous circulation can dramatically improve survival and neurologic outcomes.[31-34]

A multicenter, randomized, European study demonstrated that therapeutic hypothermia instituted for 24 hours following cardiac arrest and return of spontaneous circulation resulted in a Cerebral Performance Score of 1 or 2 (awake, alert, can work or perform independent daily activities) in 55% of hypothermia-treated patients, whereas only 39% of patients in the control group achieved a score of 1 or 2 (absolute difference, 16%; number needed to treat, about 8).[32] Six-month mortality was 41% in the hypothermia group and 55% in controls. This trial only enrolled out-of-hospital cardiac arrest patients with ventricular fibrillation/ventricular tachycardia as an initial rhythm; no definitive trial has been performed for patients specifically with either pulseless electrical activity or asystole as the initial arrest rhythm. However, a body of clinical evidence suggests that targeted temperature management also improves outcomes for patients with pulseless electrical activity or asystole.[35-38]

Some controversy exists regarding the appropriate "target temperature" for postarrest care; most hospital protocols aim for a core temperature of 32°C to 34°C (89.6°F to 93.2°F). Modest cooling to 36°C (96.8°F) produces similar outcomes as cooling to 33°C (91.4°F),[39] but there is still considerable debate about the best goal temperature for postarrest targeted temperature management.[40]

INCLUSION AND EXCLUSION CRITERIA

Patients who are awake and appropriately alert following return of spontaneous circulation are excluded from consideration (**Table 26-1**). Patients with very poor neurologic status before arrest and resuscitation are often not considered for target temperature management, as treatment can at best only restore patients to their prearrest clinical state. Other inclusion and exclusion criteria are less well defined. For example, many hospital protocols for postarrest care exclude pregnant patients; however, several case reports have demonstrated good outcomes for postarrest pregnant patients.[41,42] Because coagulopathy and bleeding can result from lowering of core body temperature, patients with clinically significant bleeding at the time of arrest or who have arrested from penetrating trauma are generally excluded from targeted temperature management, although therapeutic anticoagulation is not a contraindication. Target temperature management may benefit patients resuscitated from hanging-related asphyxial arrest.[43]

PRACTICAL CONSIDERATIONS

The techniques of targeted temperature management require coordination of care between the ED, critical care units, and cardiology intensive

TABLE 26-1 Suggested Inclusion and Exclusion Criteria for Postarrest Targeted Temperature Management[41]

Inclusion criteria	Postresuscitation ROSC and GCS motor score <6
	No other reason for coma
	No DNR or DNI status
	Adult (age >17 y)*
Exclusion criteria	Awake/alert after cardiac arrest
	Arrest of traumatic etiology
	Arrest associated with significant bleeding
	Coma or vegetative state prior to arrest
	Pregnancy*
	DNR/DNI status
Not an exclusion criterion	Patient on warfarin or heparin
	Initial arrest rhythm was nonshockable
	Long QT syndrome

Note the inclusion of a category of clinical items that would *not* preclude the use of therapeutic hypothermia. These represent issues commonly asked about by practitioners but should not represent exclusion criteria.

Abbreviations: DNI = do not intubate; DNR = do not resuscitate; GCS = Glasgow Coma Scale; ROSC = return of spontaneous circulation.

*Criteria that are controversial and may vary from hospital to hospital.

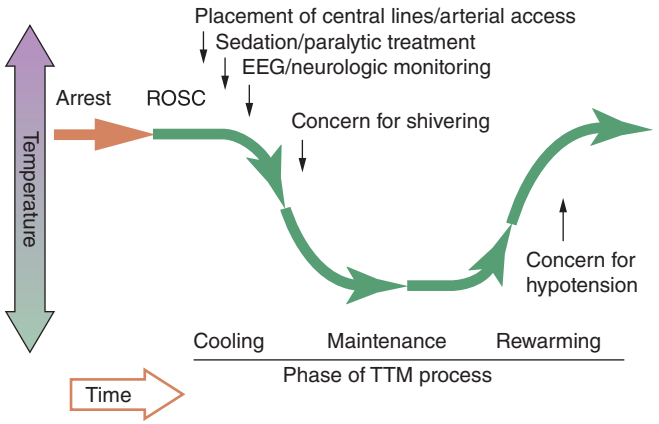

FIGURE 26-2. Timeline of postarrest therapeutic hypothermia induction, maintenance, and rewarming. Relevant clinical actions are shown in relation to these three phases of the treatment process. EEG = electroencephalographic; ROSC = return of spontaneous circulation; TTM = targeted temperature management.

care units. A standing hospital protocol is a crucial step for hospital systems; sample protocols are available on the internet.[44] Protocols should delineate processes for hypothermia induction, maintenance, and rewarming; adjunctive pharmacologic interventions (sedation, paralysis) and monitoring; and goals for the time intervals of treatment (**Figure 26-2**). Incorporation of these protocols into electronic order sets for postarrest care encourages uniformity of treatment.

Cooling and Supportive Care An organized approach is desirable to safely cool and provide supportive care (**Table 26-2**). To lower core body temperature to 32°C to 36°C (89.6°F to 96.8°F), apply commercially available clinical cooling systems (both surface-wrap or catheter-based cooling solutions exist), or apply chilled saline or ice packs to the axillae and groin. The aim is to reach goal temperature within several hours of resuscitation, so a combination of these approaches is often employed.

Maintain hypothermia for 12 to 24 hours following lowering of core temperature. It is difficult to maintain a steady temperature with chilled saline or ice packs alone.[50] Commercial cooling devices take input from temperature probes to modify cooling power and carefully hold core temperature steady.[51] During hypothermia maintenance, check serum electrolytes frequently (every 4 h) as hypokalemia can result from cold-mediated diuresis.[52] Monitor hemodynamic parameters carefully to maintain a mean arterial pressure sufficient to enable cerebral perfusion; often a mean arterial pressure >60 mm Hg (>8 kPa) is considered minimum.[53] After the maintenance phase, rewarm over 12 to 24 hours. More rapid rewarming can induce hypotension from vasodilation as well as electrolyte shifts.

TABLE 26-2 Components of Cooling and Supportive Care

- Lower core body temperature to 32°C–36°C (89.6°F–96.8°F) as soon as possible but within 4–6 h after return of spontaneous circulation
- Surface cooling
  - Chilled saline or ice packs to the axillae, neck, and groin
  - Cooling blankets, vests, and leg wraps[45]
  - Cooling helmet[46,47]
- Intravascular cooling[48]
  - IV 30 mL/kg normal saline at 4°C over 30 min[48,49]
- Intubation and mechanical ventilation
- Obtain ECG and provide continuous cardiac monitoring, pulse oximetry, and capnometry
- Sedation and neuromuscular blockade
- Central venous and arterial access
- Continuous core temperature monitoring; use bladder catheter, central venous catheter, or esophageal probe
- Maintain mean arterial pressure >60 mm Hg (>8 kPa)
- Check electrolytes every 4 h
- Maintain hypothermia for 12–24 h
- Do not let core temperature drop to <32°C (89.6°F); avoid fever

TABLE 26-3 Potential Adverse Effects of Targeted Temperature Management (Therapeutic Hypothermia)

More Common	Less Common
Bradycardia	Nonsustained ventricular tachycardia
Prolongation of QT interval	Significant bleeding
Coagulopathy with PTT prolongation	Skin injury/ulceration from surface cooling
Hypokalemia during cooling	
Hyperkalemia during rewarming	
Shivering	

Complications Adverse effects are associated with temperature-targeted hypothermia (**Table 26-3**). Bradycardia is very common and often pronounced (heart rate <50 beats/min) with induction, but usually is of little clinical consequence and requires no treatment.[31] Tachyarrhythmias, atrial fibrillation, and nonsustained ventricular tachycardia are uncommon unless core body temperature is <32°C (89.6°F). QT_c prolongation has been observed, so continuous cardiac monitoring and interval ECGs are necessary.[54]

Shivering can impede the lowering of body temperature. A variety of treatment approaches to shivering exist, the most definitive being neuromuscular blockade. Bleeding can be exacerbated by lowered core temperature but occurs in <5% of cases.[31,55] Hypokalemia and hypomagnesemia can result from intracellular shifts and diuresis mediated by lowered core temperature.

SPECIAL CONSIDERATIONS FOR TARGETED TEMPERATURE MANAGEMENT

Children The indications for targeted temperature management after cardiac arrest in children are not well established. Although hypothermia improves outcomes after neonatal hypoxic-ischemic encephalopathy,[56] a recent multicenter trial found that no significant outcomes benefit from lowering postarrest temperature in children, although a trend toward improved survival was present with cooling.[57] A criticism could be that this multicenter study was underpowered, and postarrest temperature management is likely of benefit for pediatric patients. At the very least, careful avoidance of postarrest fever in children is likely important.

Prehospital Application Some EMS systems have implemented protocols to initiate cooling prior to hospital arrival.[58] Although this strategy has logical validity, recent randomized trials found no improvement in outcomes and possibly a higher frequency of rearrest with prehospital cold saline infusion.[59-61] **Current resuscitation guidelines do not recommend prehospital induction of targeted temperature management.**

Temperature Management in the Cardiac Catheterization Laboratory Many postarrest patients should be considered for prompt cardiac catheterization given the likelihood of coronary occlusion, especially in the setting of ventricular fibrillation arrest in patients with coronary risk factors.[62] Targeted temperature management started in the ED can be continued safely in the catheterization laboratory without untoward effects.[63]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 27

Ethical Issues of Resuscitation

Catherine A. Marco

GENERAL PRINCIPLES OF MEDICAL ETHICS

The study of ethics is an effort to *understand and examine the moral life.*[1] The Hippocratic Oath is revered as one of the oldest codes of medical ethics. More recently, the American Medical Association Code of Ethics (earliest version in 1847)[2] and the American College of Emergency Physicians Code of Ethics (2016 and 2017)[3,4] have provided guidance to emergency physicians in the application of ethical principles to clinical practice. Principles of bioethics include *beneficence* (doing good); *nonmaleficence* (*primum non nocere,* or "do no harm"); respect for patient *autonomy*, *confidentiality*, *and honesty*; *distributive justice*; and *respect for the law.* Ethical dilemmas arise when there is a potential conflict between two principles, values, or individuals. Physicians resolve these dilemmas by gathering additional information; assessing patient capacity; conducting meetings with other healthcare professionals, patients, and families; and applying an informed judgment in individual situations. In some circumstances, physicians may seek the involvement of the institutional ethics committee or the judicial system.

CARDIAC RESUSCITATION AND OUTCOMES

There are approximately 300,000 sudden deaths in the United States annually.[5] The outcome of resuscitative efforts for victims of cardiac arrest is uniformly poor but varies depending on a variety of factors, including time elapsed since arrest (down time), presenting rhythm, bystander CPR, and response to prehospital advanced cardiac life support protocols. Reported estimates of survival of out-of-hospital arrest vary significantly. Recent data suggest improved survival after cardiac arrest. Overall survival after out-of-hospital cardiac arrest was 5.6% in 2005 to 2006 and improved to 8.3% in 2012.[6]

Several variables are associated with improved outcome after out-of-hospital cardiac arrest, including witnessed arrest, shockable rhythm, lower age, lack of significant comorbidities, bystander CPR, early advanced cardiac life support early defibrillation, and targeted temperature management.[7-19]

FUTILITY AND NONBENEFICIAL INTERVENTIONS

An **advance directive** is any proactive document stating the patient's wishes in various situations should the patient be unable to do so, yet most Americans do not have an advance directive, complicating the application of resuscitative interventions.[20-25] See Chapter 301, "Death Notification and Advance Directives," for further information; see also Chapter 303, "Legal Issues in Emergency Medicine."

The term *futility* is subject to interpretation. Healthcare professionals may determine futile interventions to be those that carry an absolute impossibility of successful outcome, a low likelihood of return to spontaneous circulation, a low likelihood of survival to discharge from the hospital, or a low likelihood of restoration of meaningful quality of life. *Futility* can be defined as "any effort to achieve a result that is possible, but that reasoning, or experience suggests is highly improbable and that cannot be systematically produced."[26] There is no consensus among physicians about the meaning of the term. It is probably more accurate to use terminology such as *nonbeneficial*, *ineffectual*, or *low likelihood of success* when discussing resuscitation with patients or families.

The American Medical Association Council on Ethical and Judicial Affairs stated that CPR may be withheld, even if requested by the patient, "when efforts to resuscitate a patient are judged by the treating physician to be futile."[27] Dilemmas regarding nonbeneficial interventions often arise due to inadequate or ineffective communication between the physician, patient, and family. This is of concern in emergency medicine, in which previous relationships with patients and family rarely exist and time is often inadequate to establish effective relationships. Thus, initial efforts should be directed to improve communication, education, and joint decision making.

Emergency physicians' judgments should be unbiased, based on available scientific evidence, mindful of societal and professional standards, and sensitive to differences of opinion regarding the value of medical intervention in various situations.

Ultimately, the decision regarding CPR and its likelihood of benefit to the patient and decisions to provide, limit, or withhold resuscitative efforts are to be made by the emergency physician in the context of well-accepted research results, patient and family wishes, and professional judgment. Individual bias regarding quality of life or other related issues should be avoided. There are many situations in which dying can be accepted as a natural process, even in an emergency setting.

TABLE 27-1 National Association of EMS Physicians Standards for Termination of Resuscitation in Nontraumatic Cardiopulmonary Arrest

Termination of resuscitation may be considered when, at the time of decision of termination, all of the following conditions have been met:

- The arrest was not witnessed by an EMS provider.
- There is no shockable rhythm identified by an automated external defibrillator (AED) or other electronic monitor.
- There is no return of spontaneous circulation prior to EMS transport.

TERMINATION OF RESUSCITATIVE EFFORTS

Several organizations have proposed criteria for withholding resuscitative efforts for patients with a very low likelihood of successful resuscitation. Several validated decision rules incorporate related factors predictive of dismal outcome.[28-32] Prehospital resuscitative efforts may be terminated under circumstances delineated by the Basic Life Support Termination of Resuscitation Rule.[33] This rule is recognized by the American Heart Association[34]; the National Association of EMS Physicians has adopted these criteria, which are listed in **Table 27-1**.[35]

In accordance, American College of Emergency Physicians policy states, "Resuscitative efforts may be appropriately withheld, withdrawn, or limited in circumstances such as the lack of immediately available resuscitation resources, or when there is no realistic likelihood of benefit to the patient based on existing scientific evidence and reasonable medical judgment."[36]

FAMILY PRESENCE DURING RESUSCITATION

Family presence during resuscitation may improve understanding and relieve family member guilt or disappointment and may be a helpful part of the grieving process.[37-44] Physicians should be sensitive to the possibility that this option may be difficult for certain family members or staff. If family members are invited to be present, provide a liaison to assist with communication and education about procedures and other medical issues.

SPECIAL SITUATIONS

RESUSCITATION AFTER SUICIDE ATTEMPTS

Following a suicide attempt, assessment of mental capacity is difficult or impossible. Because resuscitative efforts may be lifesaving, efforts should be undertaken in this setting. Potential issues regarding capacity, patient autonomy, and shared decision making can be addressed following successful resuscitative efforts.[45]

PROCEDURES ON RECENTLY DECEASED PATIENTS

The practices of teaching and performing procedures on recently deceased patients are controversial. The most important benefit of these practices is the opportunity for hands-on practice for students,

house staff, and even experienced physicians.[46] However, some consider performing procedures without informed consent to be disrespectful, deceptive, or unethical.[47] Obtaining consent from families or surrogates is recommended before such practice.[48,49]

RESUSCITATION RESEARCH

Research on resuscitation techniques and pharmaceuticals has been problematic due to the frequent inability to obtain informed consent and the constraints of the decision-making process. Ordinarily, the informed consent procedure for human subject research is designed to ensure protection and autonomy of the subject. However, this process is time-consuming and requires decisional capacity in the subject. Because of these difficulties, the U.S. Food and Drug Administration issued guidelines under which resuscitation research may be performed, with a waiver of informed consent under certain conditions.[50] When designing such research protocols, relevant factors include the patient's wishes (if known), expected safety of the study protocol, expected benefit of the therapeutic intervention, overall predicted benefit to society by improved knowledge regarding resuscitation, related animal data, feasibility of surrogate consent, local institutional review board opinion, and local general public opinion, if available. Waiver of consent is available through application with the Food and Drug Administration with local institutional review board approval.

COMMUNICATION AND COUNSELING FOR SURVIVORS

Counseling should be available for families and friends of those patients who have died in the ED. See Chapter 301, "Death Notification and Advance Directives," for detailed discussion on communication strategies. **Table 27-2** summarizes the American College of Emergency Physicians Policy on Ethical Issues at the End of Life.[51] **Table 27-3** provides a summary of practical advice for resuscitation scenarios. See also Chapter 300, "Palliative Care," for guidance in situations where de-escalation of care is appropriate.

TABLE 27-2 Ethical Issues at the End of Life: The American College of Emergency Physicians Policy

The American College of Emergency Physicians believes that:

- Emergency physicians play an important role in providing care at the end of life (EOL).
- Helping patients and their families achieve greater control over the dying process will improve EOL care.
- Advance care planning can help patients formulate and express individual wishes for EOL care and communicate those wishes to their healthcare providers by means of advance directives (including state-approved advance directives, Do Not Attempt Resuscitation orders, living wills, and durable powers of attorney for health care).

To enhance EOL care in the emergency department, the American College of Emergency Physicians believes that emergency physicians should:

- Respect the dying patient's needs for care, comfort, and compassion.
- Communicate promptly and appropriately with patients and their families about EOL care choices, avoiding medical jargon.
- Elicit the patient's goals for care before initiating treatment, recognizing that EOL care includes a broad range of therapeutic and palliative options.
- Respect the wishes of dying patients including those expressed in advance directives. Assist surrogates to make EOL care choices for patients who lack decision-making capacity, based on the patient's own preferences, values, and goals.
- Encourage the presence of family and friends at the patient's bedside near the end of life, if desired by the patient.
- Protect the privacy of patients and families near the end of life.
- Promote liaisons with individuals and organizations to help patients and families honor EOL cultural and religious traditions.
- Develop skill at communicating sensitive information, including poor prognoses and the death of a loved one.
- Comply with institutional policies regarding recovery of organs for transplantation.
- Obtain informed consent from surrogates for postmortem procedures.

TABLE 27-3 Practical Advice for Resuscitation Scenarios

- Identify patient wishes (advance directive, prior communications).
- Communicate with family and loved ones during and following resuscitative efforts.
- Allow family to be present during resuscitative efforts, if appropriate.
- Assess prognosis, based on scientific evidence.
- Enroll patient in research trials, with surrogate consent, or using U.S. Food and Drug Administration waiver of consent rule, as appropriate.
- Provide spiritual, psychosocial, and educational support to family and loved ones throughout and after termination of resuscitative efforts.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 28

Noninvasive Airway Management and Supraglottic Airways

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INTRODUCTION

Airway support is necessary in many acutely ill and injured patients. Optimal strategies assist with airway patency, oxygen delivery, and carbon dioxide excretion. Many classify airway management techniques into two categories: noninvasive (passive oxygenation, bag-valve-mask ventilation, and noninvasive positive-pressure ventilation) and invasive (supraglottic airways, endotracheal intubation, cricothyroidotomy, transcutaneous needle jet ventilation, and tracheostomy). This chapter discusses noninvasive airway management strategies and supraglottic airways. Detailed discussion of invasive airway management strategies is found in Chapter 29A ("Tracheal Intubation"), Chapter 30 ("Surgical Airways"), and Chapter 113 ("Intubation and Ventilation in Infants and Children").

Patients may require airway management for a variety of conditions relating to hypoventilation (inadequate carbon dioxide excretion) and hypoxia (inadequate alveolar oxygen content). Management of these conditions can incorporate multiple airway strategies ranging from passive oxygenation to endotracheal intubation, and the interventions best used may vary over time in the same patient and between patients.

Patients with hypoventilation and hypoxia may have varying symptoms including weakness, fatigue, chest pain, or shortness of breath. Inadequate oxygenation and ventilation can lead to altered mentation, including anxiety, confusion, obtundation, or coma. Patients with respiratory distress may have wheezing, stridor, or a silent chest. A subjective gauge of respiratory distress is the patient's respiratory effort or "work of breathing."[1] Dyspnea, tachypnea, hyperpnea, or hypopnea; accessory muscle use; and cyanosis are signs of increased work of breathing.

There are two types of respiratory failure. **Type 1 respiratory failure** has hypoxia *without* hypercapnia. Type 1 respiratory failure may be the result of conditions that affect oxygenation but not necessarily ventilation (e.g., pneumonia, pulmonary embolism). Patients with type 1 respiratory failure require actions that optimize oxygenation. **Type 2 respiratory failure** has hypoxia *with* hypercapnia. Type 2 respiratory failure is often the result of conditions that affect ventilation (e.g., chronic obstructive pulmonary disease). Treatment of type 2 failure requires not only optimizing oxygenation but also supporting ventilation.

TABLE 28-1 Causes of Upper Airway Obstruction

Congenital/ Genetic	Infectious	Medical	Trauma/Tumor
Large tonsils	Tonsillitis	Cystic fibrosis	Laryngeal trauma
Macroglossia	Peritonsillar abscess	Angioedema	Hematoma/masses
Micrognathia	Pretracheal abscess	Laryngospasm	Smoke inhalation
Neck masses	Epiglottitis	Inflammatory	Thermal injuries
Large adenoids	Laryngitis/respiratory syncytial virus Ludwig angina Retropharyngeal abscess	Airway muscle relaxation	Foreign body/ hemorrhage

ASSESSMENT OF THE AIRWAY AND VENTILATORY EFFORT

The decision to initiate airway support is often based on the patient's clinical condition. Do not delay management efforts for laboratory testing or other studies, although these can help guide treatment.

First, assess every patient for airway obstruction, which can be functional (e.g., unconscious patient) or mechanical (e.g., foreign body). The ability to spontaneously swallow and speak provides a basic indication of airway patency, and the absence of this ability is a potential sign of obstruction. Other potential signs of airway obstruction include anxiety, wheezing or stridor, and coughing. Many conditions can cause airway obstruction (**Table 28-1**).

Some obstructions, such as foreign bodies or masses, are subglottic (below the vocal cords).

Laryngospasm is obstructive closure of the glottis by constriction of laryngeal muscles. Laryngospasm may result from stimulation of the upper airway receptors on the tongue, palate, and oropharynx. Other causes include chemical irritation; secretions; blood, water, and vomitus in the upper airway; and traction on the pelvic/abdominal viscera. Laryngospasm can persist after the causative stimulus departs.

PREDICTING THE DIFFICULT AIRWAY AND PREPARATION FOR AIRWAY MANAGEMENT

Assess and anticipate challenges with airway management before any attempts to intervene. **Table 28-2** lists some factors that may complicate noninvasive airway management.[2]

PATIENT POSITIONING

The first step in airway management is to optimize patient positioning to facilitate airway patency and subsequent airway management efforts.

TABLE 28-2 Predictors of Difficult Noninvasive Airway Management Techniques[2]

BVM ventilation			
	M	Mask seal	Beard, trauma, or other situations that may cause BVM to not seal
	O	Obesity or Obstruction	
	A	Age	Age >55 y
	N	No teeth	
	S	Stiff lungs or chest wall	
Supraglottic airway			
	R	Restricted mouth opening	
	O	Obesity or Obstruction	
	D	Disrupted or Distorted airway	
	S	Stiff lungs or cervical spine	

Abbreviation: BVM = bag-valve-mask ventilation.

TABLE 28-3 Oxygen Delivery Methods

	Oxygen Flow	F_{IO_2} Delivered
Nasal cannulae	2–5 L/min	20%–40%
Simple facemask	6–10 L/min	40%–60%
Non-rebreather mask	10–15 L/min	Near 100%

Abbreviation: F_{IO_2} = fraction of inspired oxygen.

Upper airway obstruction occurs in the unconscious patient as the intrinsic muscles of the neck and upper airway relax, causing the epiglottis to obstruct the laryngeal inlet. Although the tongue displaces posteriorly during anesthesia in supine patients, it may not always occlude the pharynx.[3]

The first relief step in upper airway obstructions is extension of the neck with anterior displacement of the mandible. This maneuver moves the hyoid bone anteriorly and lifts the epiglottis away from the laryngeal inlet. Forward flexion of the neck in addition to extension ("sniffing" position) may relieve upper airway obstructions and requires less neck extension. To achieve, place a *folded* towel (not rolled) or foam rubber device underneath the patient's occiput. Do not attempt neck extension or sniffing positioning in patients when there is concern for cervical spine injury.

OXYGENATION

Provide supplemental oxygen to all critically ill patients requiring airway management. The method of oxygenation used depends on the patient's clinical condition and oxygen requirement (**Table 28-3**). Even if the patient is apneic, providing supplemental oxygenation with nasal cannulae can extend the time to hypoxia and hypoxemia, allowing providers additional time to prepare for or attempt airway maneuvers.[4]

AIRWAY EQUIPMENT

Having key equipment at the bedside is a fundamental requirement for optimal airway management. **Table 28-4** provides a model list of equipment.

Oropharyngeal (Oral) Airway An oropharyngeal or oral airway (**Figure 28-1**) is a curved, rigid instrument used to prevent the base of

TABLE 28-4 Sample List of Equipment for Noninvasive Airway Management

- Oxygen source and tubing
- Tongue blade
- Bag-valve-mask device
- Clear facemasks—various sizes and shapes
- Oropharyngeal airways—small, medium, large
- Nasopharyngeal airways—small, medium, large
- Suction catheter
- Suction source
- Pulse oximetry
- End-tidal carbon dioxide detector
- Syringes
- Magill forceps
- Water-soluble lubricant or anesthetic jelly
- CPAP/BiPAP mask and machine
- Supraglottic airways: laryngeal mask airway, intubating laryngeal mask airway, i-gel® (Intersurgical Inc., Liverpool, NY), King LT® (King Systems, Noblesville, IN)
- Backup equipment in the case of unsuccessful NIPPV*†

*See Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation."

†See Chapter 30, "Surgical Airways."

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; NIPPV = noninvasive positive-pressure ventilation.



FIGURE 28-1. An oral airway.

the tongue from occluding the hypopharynx. Use only in a comatose or deeply obtunded patient without a gag reflex. Properly sized oral airways should reach from the corner of the mouth to the angle of the mandible. Place an oral airway with the concave portion of the airway cephalad and rotate 180 degrees after passing the tongue. Alternatively, orient the concaved portion horizontal and rotate 90 degrees, following the curvature of the tongue, after insertion.

Nasopharyngeal (Nasal) Airway A nasopharyngeal or nasal airway (**Figure 28-2**) is pliable and inserted into the nostril, displacing the soft palate and posterior tongue. Nasal airways are helpful in patients with an intact gag reflex absent any midface trauma. Properly sized nasal airways reach from the corner of the mouth to the angle of the mandible. After lubrication, insert the nasopharyngeal airway in the most patent nostril and horizontal to the palate with the bevel oriented toward the nasal septum; insert parallel to the nasal floor, not pointing cephalad.

Many techniques augment oxygen delivery. Traditional approaches include nasal cannula and simple facemasks. Table 28-3 summarizes the oxygen delivery rates for various methods.

Traditional oxygen delivery methods such as nasal cannula and simple facemasks deliver variable and lower inspired oxygen amounts, which may not be adequate for select patients in severe respiratory distress. High-flow oxygenation delivered through a high-flow nasal cannula provides humidified, heated oxygen at flow rates up to 60 L/min,[5] providing positive pressure while decreasing the work of breathing.[6,7] High-flow nasal cannula is best used in patients with hypoxia and an intact respiratory drive; it is an alternative to invasive ventilation in ED patients with hypoxia (oxygen saturation <92%) and respiratory rates >22 breaths/min, while excluding patients with bullous lung disease and pneumothoraces.[8] Another option is flush rate oxygenation, where the wall oxygen unit is turned past 15 L/min to maximum flow rates of 40 to 60 L/min.[9,10] Both high-flow nasal cannula and flush rate oxygenation can bridge to other ventilation methods. High-flow nasal cannula may improve mortality rates in patients with nonhypercapnic, acute hypoxemic respiratory failure compared to noninvasive positive-pressure ventilation and conventional supplemental oxygen.[11]



FIGURE 28-2. A nasal airway.



FIGURE 28-3. Bag-valve mask.

BAG-VALVE MASK

Bag-valve masks (**Figure 28-3**) contain a self-inflating insufflation device coupled with a facemask and a valve to prevent reinhalation of exhaled air. Although typically used with supplemental oxygen, the bag-valve mask can aid even when used with room air. Most bag-valve-mask systems deliver approximately 75% oxygen with optimal use. A demand valve attached to the reservoir port of the ventilation bag may help to deliver a higher concentration of oxygen.[12] Adequate oxygenation and ventilation with a bag-valve mask requires upper airway patency and a good facemask seal, which may be difficult in patients with facial trauma, facial hair, or anatomic anomalies or in those who are edentulous.

Bag-valve-mask ventilation can be done using one- or two-person techniques. Two-person techniques deliver greater tidal volumes than one-person techniques and are preferred.[13]

With the one-person approach, the rescuer uses one hand to grasp and seal the mask and the other hand to squeeze the bag-valve-mask reservoir bag. A common mask-sealing technique is to grasp the mask with the thumb and index finger in a "C" shape while placing the third, fourth, and fifth digits in an "E" shape to lift the mandible. During mask ventilation, be careful to keep the fingers *on* the mandible, not compressing the soft tissue beneath (and hence compressing the airway) (**Figure 28-4A**).

In the two-operator approach, one rescuer seals the facemask using both hands, while the other squeezes the reservoir bag. The rescuer sealing the mask may use the same "E-C" approach, but with both hands applied to the mask (**Figure 28-4B**). In an alternate modified two-handed technique, the practitioner places the thenar eminence and thumb of each hand on the mask while the remaining digits grasp the mandible (**Figure 28-4C**). Both two-handed techniques provide similar tidal volumes.[13]

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Noninvasive positive-pressure ventilation (NIPPV) provides positive-pressure airway support through a face or nasal mask without the use of an endotracheal tube or other airway device. In adults, NIPPV includes continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP).

NIPPV helps to augment spontaneous respirations. Ideal patients for NIPPV are cooperative, have protective airway reflexes, and have intact ventilatory efforts. NIPPV is not appropriate in patients who have absent or agonal respiratory effort, impaired or absent gag reflex, altered mental status, severe maxillofacial trauma, potential basilar skull fracture, life-threatening epistaxis, or bullous lung disease. Use NIPPV with caution in hypotensive patients because any volume depletion effect on cardiac output can be worsened from the positive pressure, triggering more hypotension (**Table 28-5**).

NIPPV reduces work of breathing through multiple mechanisms.[14,15] NIPPV improves pulmonary compliance and recruits and stabilizes



A



B



C

FIGURE 28-4. **A.** One-person bag-valve-mask ventilation. **B.** Two-handed mask seal. **C.** Modified two-handed mask seal.

TABLE 28-5 Advantages and Adverse Effects of Noninvasive Positive-Pressure Ventilation

Advantages	Disadvantages
Reduces work of breathing	Air trapping
Improves pulmonary compliance	Increased intrathoracic pressure leading to decreased venous return, afterload, and cardiac output, and hypotension
Recruits atelectatic alveoli	Pulmonary barotrauma leading to pneumothorax
Less sedation	Respiratory alkalosis
Shorter hospital stay	Abdominal compartment syndrome
Decreased rate of intubation without risks of endotracheal intubation	

collapsed alveoli, improving alveoli aeration and ventilation-perfusion mismatches.[1] NIPPV increases both intrathoracic and hydrostatic pressure, shifting pulmonary edema into the vasculature. Increased intrathoracic pressure can also decrease venous return, transmural pressure, and afterload, leading to improved cardiac function. NIPPV also increases tidal volume and minute ventilation, leading to increased Pao_2 and reduction in $Paco_2$. NIPPV reduces work of breathing by 60% and dyspnea scores by 29% to 67%, while improving inspiratory muscle endurance by 14% to 95% over spontaneous respirations.[1] The effect of NIPPV on forced expiratory volume and forced vital capacity is unclear.[16-18]

CPAP delivers a constant positive pressure throughout the respiratory cycle. **BiPAP** provides different levels of positive airway pressure during inspiration (inspiratory positive airway pressure [IPAP]) and expiration (expiratory positive airway pressure). Although the terms *expiratory positive airway pressure* and *positive end-expiratory pressure* are often used interchangeably, positive end-expiratory pressure is specific to the end of the respiratory cycle, whereas expiratory positive airway pressure refers to the pressure administered via the BiPAP machine during the entire expiratory phase. Both CPAP and BiPAP are options in a variety of patient populations, with limited data directly comparing the two methods.

Be aware that different NIPPV devices exist with differing operating mechanisms. Many standard ventilators can provide NIPPV, although in these devices, the inspiratory and expiratory pressures are additive. For example, if the IPAP is set at 5 cm H_2O and the IPAP is set at 15 cm H_2O, the total delivered IPAP may be 20 cm H_2O (5 + 15). There are standalone NIPPV units that can provide both CPAP and BiPAP, allowing for independent setting of inspiratory and expiratory pressures. In this example, if the IPAP is set at 5 cm H_2O and the IPAP is set at 15 cm H_2O, the total delivered IPAP will be 15 cm H_2O. Specialized adapters that connect directly to oxygen tanks and wall-mounted oxygen units may provide CPAP for a brief period of time. These devices have a limited range of settings and are best used on a temporary basis.

INITIATING AND TITRATING NIPPV

Select the mask for NIPPV to create a tight seal while preserving patient comfort. Base the initial settings on the patient's condition and type of respiratory failure. Typical starting settings for CPAP are 5 to 15 cm H_2O. Typical starting settings for BiPAP include "spontaneous" mode with IPAP set to 8 to 10 cm H_2O and expiratory positive airway pressure set to 3 to 5 cm H_2O. Be cautious when using NIPPV at pressures >15 cm H_2O because this may increase the intrathoracic pressure, leading to barotrauma along with decreased venous return, decreased preload and afterload, and eventually decreased cardiac output.

NIPPV requires frequent assessment for work of breathing, heart rate, respiratory rate, oxygen saturation, and blood pressure. Arterial blood gas analysis aids NIPPV titration but is not mandatory. Expiratory positive airway pressure can help open and stabilize collapsed alveoli and reverse hypoxemia. In patients in whom ventilation is an issue, adjust the IPAP settings to help decrease the work of breathing and improve ventilation.

If the patient is not tolerating NIPPV, look first for an air leak. NIPPV is a flow-limited, pressure support system, and therefore, leaks prevent

the machine from reaching the preprogrammed flow rate for a set pressure. As a result, the inspiratory time may be prolonged, making each breath cycle less comfortable for the patient. Potential solutions for air leaks include programming the machine to limit the inspiratory time or selecting alternative modes of ventilation including proportional assist ventilation.[1] Proportional assist ventilation is a form of synchronized ventilatory support where the NIPPV machine generates pressure in proportion to the patient's instantaneous effort such that as the patient generates a greater inspiratory effort, the machine generates greater IPAP. This allows the machine to adjust to air leaks that may impair ventilation and oxygenation with other modes (CPAP and BiPAP) and is better tolerated by some patients.[19] If the patient is not improving with NIPPV, consider endotracheal intubation and mechanical ventilation.

NIPPV Applications The most common use of NIPPV is for **cardiogenic pulmonary edema;** NIPPV may reduce rates of endotracheal intubation, hospital length of stay, and mortality.[20-27] In patients with **chronic obstructive pulmonary disease,** NIPPV is helpful in those with respiratory acidosis.[28] NIPPV may benefit patients with moderate to severe **asthma** exacerbations, although data on effectiveness are limited.[29] Because of the bronchospastic nature of chronic obstructive pulmonary disease and asthma, be vigilant for air trapping and subsequent barotrauma when using NIPPV.

NIPPV may reduce the rate of intubation and in-hospital death in patients with **pneumonia**.[30-32] Exercise caution in this patient group because hypovolemia may coexist, with resultant NIPPV-induced hypotension.

There are reports of NIPPV use in **blunt chest wall trauma,** including **flail chest**.[33-35] NIPPV is also reported in burn patients. Do not use NIPPV in patients with suspected or confirmed high esophageal or tracheal injuries, maxillofacial or basilar skull fractures, or severe facial burns.[36,37]

Prehospital NIPPV Prehospital NIPPV in patients with cardiogenic pulmonary edema and chronic obstructive pulmonary disease decreases the rate of subsequent intubation and mortality.[38-41] When such patients arrive in the ED, assess the response to NIPPV and determine whether to discontinue NIPPV, adjust the NIPPV settings, or change to invasive airway strategies.

NIPPV Complications Complications of NIPPV include difficulty with mask seal, patient discomfort, aspiration (rare), air trapping, pulmonary barotrauma including pneumothorax, and increased intrathoracic pressure leading to decreased cardiac output and hypotension. Monitor patients carefully to determine NIPPV effectiveness and to identify the need to further secure the airway with intubation. Minimize aspiration risk by proper patient selection[42]; make sure selected NIPPV patients have a gag reflex and do not have altered mental status. Gastric distention and increased intragastric pressure can lead to *abdominal compartment syndrome*, resulting in oliguria, hypoxia, hypercarbia, high peak inspiratory pressures, and even renal failure. A nasogastric tube can decompress the stomach and relieve this syndrome.[43] Although uncommon, evaluate patients frequently to identify any of these complications early.

Occasionally, patients develop anxiety and agitation during NIPPV treatment due to the claustrophobic feeling of the mask or the discomfort of positive-pressure ventilation. Anxiety and agitation can increase the work of breathing and result in NIPPV asynchrony. Although often relieved with encouragement and verbal support, this may require sedatives or anxiolytics. There are limited data examining sedation during NIPPV, and choices are typically based on physician preference.[42,44] Avoid agents or doses that cause excess sedation or respiratory depression. Dexmedetomidine, a centrally acting α_2 agent, can provide sedation without decreasing respiratory drive, but its expense and availability limit general use.[45] Benzodiazepines and opiates are commonly used but can be difficult to titrate and may cause respiratory depression.[42,44,45] Haloperidol in low doses may aid anxiolysis with less respiratory depression than opioids or benzodiazepines.[44] Ketamine decreases airway resistance and improves pulmonary function without respiratory depression.[46] Patients should be closely monitored as ketamine can cause hypersalivation.

SUPRAGLOTTIC AIRWAYS

Supraglottic airways (SGAs) are devices placed in the oropharynx, allowing for oxygenation and ventilation without the visualized or surgical insertion of a tube into the trachea. SGAs are often a bridge to endotracheal intubation or a rescue device after unsuccessful intubation efforts. Although SGAs provide adequate oxygenation and ventilation for short periods of time, they are not used for prolonged ventilation. SGA should not be used in any patient needing high inspiratory pressures (e.g., chronic obstructive pulmonary disease) given seal issues and the potential for leaks to occur.[47] In the out-of-hospital setting, these devices improve survival after cardiac arrest compared to endotracheal intubation, although their impact in the ED is less clear.[48]

SGAs are most often placed in apneic, unconscious patients; their large cuffs can cause gagging and discomfort in awake patients. Another option is use after deploying a rapid-sequence induction medication regimen.[49] After inserting, confirm proper position of any SGA with end-tidal carbon dioxide and secure it with tape or commercial holders.[50-52] A number of SGAs are commercially available (**Figure 28-5A–D**).

I-GEL

The i-gel® (Intersurgical Inc., Liverpool, NY) (Figure 28-5A) has a soft, gel-like cuff that seals the perilaryngeal structures without inflation. This limits tissue compression caused by devices with large cuffs. Lubricate the gel-like cuff prior to insertion, and then advance the device into the posterior pharynx until resistance is met and the lips align with the lip line on the i-gel. Data from operating room use suggest that complications of i-gel use are infrequent but most commonly include laryngospasm and sore throat; there are rare reports of vasovagal asystole and glottic hematoma.[53] The i-gel is available in various sizes for patients from 2 to >90 kg.

KING LARYNGEAL TUBE (KING LT®)

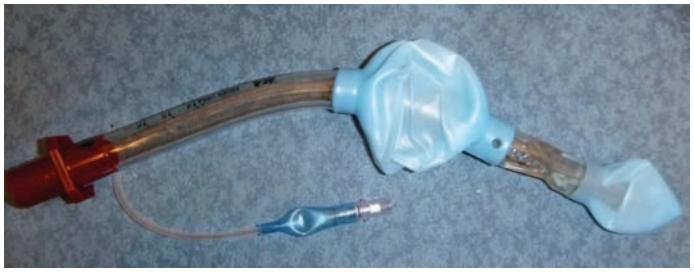
The King LT® (King Systems, Noblesville, IN) (Figure 28-5B) is a *single* lumen tube with a proximal cuff that seals the posterior oropharynx while a distal cuff occludes the esophagus. The King LT is placed blindly (that is, without seeing beyond the mouth opening) into the oropharynx until the lip aligns with the device lip line. The balloon is then inflated to a pressure of 60 cm H_2O. After placement, the provider may need to withdraw the King LT slightly to allow it to fully occlude the oropharynx. The King LT resides in the esophagus >95% of the time, allowing ventilation of the trachea through the multiple fenestrations between the proximal pharyngeal and distal esophageal cuffs.[54] Complications with the King LT include tongue engorgement whereby the proximal balloon can impair venous drainage of the tongue.[55] Removing the King LT will relieve this condition. The King LT is available in several sizes depending on the patient's height: 4 to 5 feet, size 3 (yellow); 5 to 6 feet, size 4 (red); and >6 feet, size 5 (purple).

LARYNGEAL MASK AIRWAY (LMA®)

The Laryngeal Mask Airway (LMA®; Teleflex, Research Triangle Park, NC; Figure 28-5C) is another SGA placed blindly through the mouth; it occludes the structures around the larynx. The LMA consists of a single cuff inflated with 20 to 30 mL of air. To insert the LMA, place a gloved index finger into the oropharynx to guide the device into the oropharynx and position the cuff around the larynx. The LMA may be especially useful when the vocal cords cannot be visualized during intubation attempts and is successfully placed 88% to 100% of the time.[56,57] There are various models, including an intubating LMA, that allow an endotracheal tube to be passed through the lumen. This permits conversion from an SGA to an endotracheal tube without visualizing the glottis. Complications of the LMA include partial or complete airway obstruction and aspiration of gastric contents, although animal data suggest the LMA may prevent aspiration.[58] The LMA is available in several sizes based on the patient's estimated body weight: 50 to 70 kg, size 4; 70 to 100 kg, size 5; and >100 kg, size 6.



A



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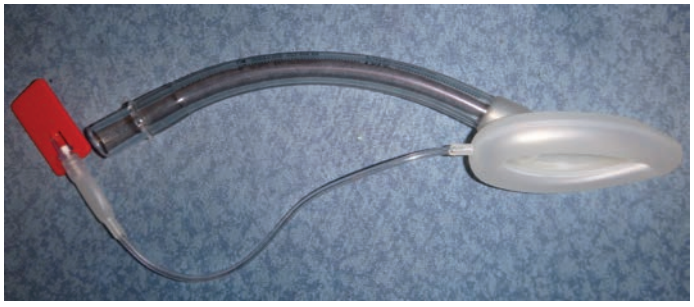


C



D



FIGURE 28-5. Esophageal airways. **A.** i-gel. **B.** King LT. **C.** Laryngeal Mask Airway. **D.** Shiley® esophageal tracheal airway. [Copyright ©2014 Covidien. All rights reserved. Used with permission of Covidien, Boulder, CO.]

OTHER SUPRAGLOTTIC AIRWAYS

The Shiley® esophageal tracheal airway (Covidien, Boulder, CO; Figure 28-5D) is a plastic double-lumen tube that is inserted blindly. It is a predecessor to the King LT and is still used by some EMS agencies. It has a proximal low-pressure cuff that seals the pharyngeal area and a distal cuff that seals the esophagus. After placement, the proximal balloon is inflated with 80 mL of air while the distal balloon is inflated with 10 mL of air. During insertion, the device may rest in the esophagus or trachea. To determine the location of the device, first ventilate through the longer blue port; this allows oxygen to be delivered through fenestrations between the proximal and distal balloons. If chest rise is absent, the endotracheal tube cuff is in the trachea; switch to ventilation through the shorter, clear/white port.

The CobraPLA® (Engineered Medical Systems, Indianapolis, IN) is a cuffed SGA that is inserted blindly similarly to the King LT. The potential advantage of the CobraPLA is that providers can pass an endotracheal tube through the lumen of the device, easing conversion to an endotracheal tube. The CobraPLA is available in various sizes for patients from 2.5 to >130 kg.

CONVERTING A SUPRAGLOTTIC AIRWAY TO AN ENDOTRACHEAL TUBE

In general, SGAs have a higher risk of aspiration than cuffed endotracheal tubes, and the large cuffs may cause hypopharyngeal mucosal damage. Thus, endotracheal tubes are better suited for long-term ventilation. **SGAs do not need to be *immediately* changed to an endotracheal tube.** The urgency for conversion depends on the condition of the patient, the adequacy of oxygenation and ventilation through the SGA, and the reasons for SGA insertion. Strategies for converting an SGA to an endotracheal tube include the following:

- **Remove the supraglottic device and perform direct laryngoscopy.** If the SGA placement was because of intubation difficulty, removing the SGA and attempting direct laryngoscopy is risky; it is better to choose an alternative technique. If attempting direct visualization to intubate the trachea after SGA removal, use airway adjuncts (e.g., gum elastic bougie, video laryngoscopy) to help make laryngoscopy efforts successful.

- **Convert the SGA (King LT or i-gel) with a gum elastic bougie.** Insert the gum elastic bougie though the King LT into the trachea and then remove the King LT, leaving the gum elastic bougie in place. Then pass a standard endotracheal tube over the bougie. This is a "blind" exchange, meaning that the operator does not visualize the glottis during the conversion. While this maneuver can be attempted with the standard LMA, it often fails.[59] Limited data describe this technique with the i-gel.
- **Convert the SGA (i-gel, King LT, or LMA) with a fiberoptic bronchoscope.** Use an intubating catheter (Aintree; Cook Medical, Inc., Bloomington, IN), which is similar to a bougie but is hollow, allowing placement over a fiberoptic bronchoscope. First, place the catheter over the fiberoptic scope, and then direct the scope into the trachea. Next, remove the fiberoptic scope and SGA, leaving the catheter in the trachea. Finally, direct a standard endotracheal tube over the catheter into the trachea. This technique allows for visualization of the glottis but requires expertise in the use of a fiberoptic bronchoscope. This technique is not possible with the Shiley®.
- **Leave the SGA in place and perform a surgical airway (cricothyroidotomy or tracheostomy).** This is often chosen after an SGA insertion followed difficulties with standard intubation and if the patient requires prolonged mechanical ventilation. This can be done either in the operating room or in the ED if needed, depending on the patient's condition, available resources, and skills of the provider.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

TABLE 29A-1 Equipment Needed for Airway Management

- Oxygen source and tubing
- Ambu bag
- Mask with valve, various sizes and shapes
- Oropharyngeal airways—small, medium, large
- Nasopharyngeal airways—small, medium, large
- Suction catheters: Yankauer, tracheal suction catheters, nasogastric suction connection tubing for particulate and large amounts of vomitus
- Suction source
- Pulse oximetry
- Carbon dioxide detector
- Endotracheal tubes—various sizes
- Laryngoscope blades and handles
- Syringes
- Magill forceps
- Stylets, assorted
- Tongue blade
- Intubating stylet (gum elastic bougie)
- Water-soluble lubricant or anesthetic jelly
- Rescue devices: video laryngoscopes, laryngeal mask airway, intubating laryngeal mask airway, i-gel® (Intersurgical Inc., Liverpool, NY), King LT® (King Systems, Noblesville, IN)
- Surgical cricothyroidotomy kit
- Medications for topical airway anesthesia, sedation, and rapid-sequence intubation

CHAPTER 29A

Tracheal Intubation

Henry E. Wang
Jestin N. Carlson

INTRODUCTION

Tracheal intubation is a cornerstone of emergency airway management, creating a direct conduit to the trachea, allowing airway patency, aiding oxygenation and ventilation, and preventing aspiration. Intubation may also be needed to safely allow sedation or paralysis needed in critically ill patients requiring diagnostic or therapeutic interventions. Intubation is one component of the spectrum of emergency airway interventions. Supraglottic airways and the conversion of a supraglottic airway to an endotracheal tube (ETT) are discussed in Chapter 28, "Noninvasive Airway Management and Supraglottic Airways."

PREPARATION

Proper preparation is key to successful intubation. **Table 29A-1** lists emergency airway equipment needed at the bedside ***before*** beginning intubation. Have basic airway, intubation, rescue, and surgical airway equipment immediately accessible, ideally in the same cart with other airway management equipment. If treating a child, have enough and appropriately sized pediatric airway devices accessible (see Chapter 113, "Intubation and Ventilation in Infants and Children").

Key starting tasks are imperative: Ensure ongoing cardiac rhythm monitoring with continuous displays of the heart rate, blood pressure, oxygen saturation, and end-tidal capnography. Establish IV access and appropriate fluids.

Raise the patient to the level of the operator's xiphoid (**Figure 29A-1**). Although ventilation and intubation are typically performed with the patient fully supine, positioning the patient so that the external ear is aligned with the sternal notch may improve glottis visualization (**Figure 29A-2**). Refrain from applying padding under the shoulders or neck as this position is suboptimal for facilitating emergency intubation. A more upright position for intubation may be necessary if the patient cannot lay supine—for example, the patient with severe pulmonary edema or morbid obesity (**Figure 29A-3**).

Ensure that the oxygen source and regulator are functional. Have a bag-valve-mask ventilator and oral and nasal airways at the bedside, and make sure that a large-diameter suction catheter and functional suction unit are ready. For potential uncontrolled emesis, use an assistant to place a Yankauer catheter or the suction tubing itself in the side of the mouth, so suctioning can be done throughout the intubation process. Another option for large-volume suction or in instances where suction is required to remove large particles of material (e.g., food debris) is to use another ETT attached to suction tubing, placing it to the left oropharynx to allow continuous large-volume suction (suction-assisted laryngoscopy airway decontamination)[1,2] (**Figure 29A-4**).

Verify the function of primary and backup intubation equipment, including laryngoscope blade, bulbs, and video laryngoscope screens. Test the cuffs of selected ETTs, usually the size you think is best and one smaller. Verify the availability of rescue supraglottic airways and surgical airway kits. Confirm that a mechanical ventilator is available for application immediately after intubation. Estimate the patient's body mass and calculate appropriate doses of any adjunctive intubation medications.

Before proceeding with intubation, assess all available clinical information, including the patient's suspected condition, history, anatomy, physiology, and goals of care. Develop an emergency airway management plan—one that anticipates failure and has alternative options—and review this plan with the entire care team. Discuss the plan for preparation, medications, intubation, postintubation sedation, and rescue airway management. A checklist may facilitate decision making and reduce errors.[3]

Try to normalize patient heart rate and blood pressure, and try to optimize oxygen saturation prior to drug administration and laryngoscopy; peri-intubation cardiac arrest is likely if any of these parameters is abnormal. Anticipate airway difficulty; if anatomic abnormalities will impede basic airway techniques or will not improve with rapid-sequence intubation, consider awake intubation.



A B

FIGURE 29A-1. Correct patient-stretcher height, so that the patient's head is just below the intubator's xiphoid. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 4th ed. © 2016, McGraw-Hill, Inc., New York. Figure 22.14. Photo contributor: Lawrence B. Stack, MD.]

AIRWAY ASSESSMENT

Approximately up to 15% of initial emergency airway attempts and 1% to 3% of overall attempts at tracheal intubation fail with standard techniques.[4] It is best to expect difficulty with all emergency airway cases, applying a uniform approach to all patients. While the terms *difficult intubation* and *difficult laryngoscopy* are often used interchangeably, there are important distinctions. *Difficult intubation* refers to a situation where multiple attempts are made at intubation, whereas *difficult laryngoscopy* refers to challenges with or inability to visualize the glottis.



FIGURE 29A-2. Patient positioning for optimal laryngoscopy. Align the external auditory canal and the sternal notch. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 4th ed. © 2016, McGraw-Hill, Inc., New York. Figure 22.10 Part C. Photo contributor: Lawrence B. Stack, MD.]

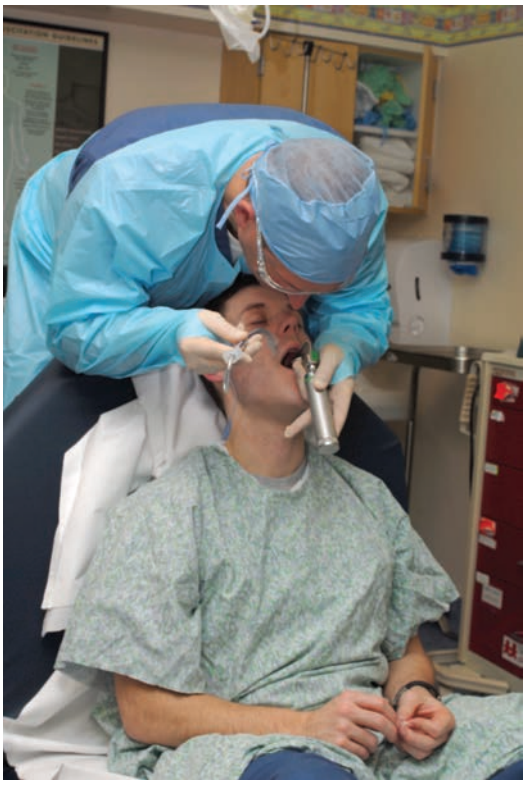


FIGURE 29A-3. An upright position may be necessary for intubation of select patients. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 4th ed. © 2016, McGraw-Hill, Inc., New York. Figure 22.6. Photo contributor: Lawrence B. Stack, MD.]



A



B

FIGURE 29A-4. Suction-assisted laryngoscopy airway decontamination (SALAD) approach for suctioning. **A.** SALAD set up. **B.** View of suction in the esophagus.

Factors associated with airway management and intubation difficulty are listed in **Table 29A-2**.

Obesity or the lack of neck flexibility may make it difficult to align the oral, pharyngeal, and tracheal axes needed for intubation. Physical airway obstruction (foreign body, tumor, angioedema, epiglottitis) may limit the physician to nasal techniques or a surgical airway (see Chapter 30, "Surgical Airways"). Some anesthesia scales associate anatomical features with intubation difficulty; for example, **Mallampati criteria** relate the degree of posterior pharyngeal obstruction by the tongue with intubation difficulty[5] (**Figure 29A-5**). Although potentially applicable to some ED patients, in select situations, formal airway assessment may be impractical or impossible.

TABLE 29A-2 Factors Associated With Airway Management Difficulty

- Obesity
- Facial hair
- Edentulous anatomy
- History of snoring/sleep apnea
- Short neck
- Limited neck mobility
- Small or large chin
- Prominent incisors
- High arched palate
- Facial or airway trauma
- Head and neck tumors
- Angioedema
- Ludwig's angina
- Inflammation of the airway (e.g., airway burns)

OROTRACHEAL INTUBATION

PREOXYGENATION

Oxygen desaturation to <70% is associated with increased risk of dysrhythmias, decompensation, and cardiac arrest.[6] Preoxygenation displaces nitrogen from the alveoli, creating a potential oxygen reservoir that may prevent hypoxia and hypoxemia during apnea. In the healthy operating room patient, preoxygenation increases safe apnea time (time to desaturation to <90%) from 1 to 8 minutes. However, in critically ill patients such as those with chest injuries or shock states, safe apnea time is shorter.

Begin preoxygenation as soon as possible before intubation, even for patients with no apparent hypoxia or hypoxemia. Administer 100% oxygen for at least 3 minutes using a non-rebreather mask supplied with at least 15 L/min of oxygen. Non-rebreather masks typically deliver 60% to 70% oxygen. Higher oxygen delivery is possible by increasing the oxygen regulator to its maximum "flush" rate, which will provide 90% to 97% oxygen, between 40 and 60 L/min.[7] Preoxygenation must occur with tidal volume breathing and/or a good mask seal. If unable to achieve oxygen saturation >95% with spontaneous breathing, consider the use of bag-valve-mask ventilation, application of a positive end-expiratory pressure valve, or the use of continuous positive airway pressure or bilevel positive airway pressure. Elevating the head of the patient 20 to 30 degrees may improve preoxygenation. With agitated patients, some clinicians selectively use sedation with induction agents to facilitate preoxygenation.[8]

Nasal cannulas with low flow alone do not provide optimal preoxygenation. However, some clinicians use **apneic oxygenation**—oxygen at ≥15 L/min via nasal cannula—concurrently with bag-valve-mask (or bilevel positive airway pressure) ventilation and subsequent laryngoscopy.[9] During laryngoscopy, the continued high oxygen flow creates a pressure gradient, facilitating airflow from the pharynx to the lungs.

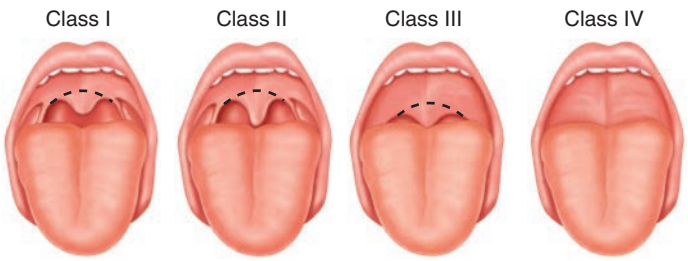


FIGURE 29A-5. The Mallampati score. [Reproduced with permission from Samsoon Y: Difficult tracheal intubation: a retrospective study. *Anaesthesia* 42: 487-490, 1987.]

TABLE 29A-3 Steps of Tracheal Intubation

Step	Comments
1. Clear the oropharynx.	Remove dentures and any obscuring blood, secretions, or vomitus. Suction airway clear.
2. Hold laryngoscope in left hand.	Hold the laryngoscope at the base, where the blade inserts to the handle.
3. Use right hand to: Open the mouth. Operate suction catheter. Manipulate larynx to enhance visualization. Insert the ETT.	Use a scissor motion to open the mouth and facilitate laryngoscope passage by pressing caudally on the patient's lower incisors with the operator's thumb and cranially on the patient's upper incisors with the operator's index finger. Use a properly sized stylet to assist with tube placement. The tip of the stylet must not extend beyond the end of the ETT or exit the Murphy eye.
4. Insert blade into the right corner of the patient's mouth. Carefully advance blade into oropharynx. Lift and hyperextend the head.	Use the vertical flange of the curved Macintosh blade to push the tongue toward the left side of the oropharynx.
5. Visualize and lift the epiglottis.	Lift the epiglottis directly with the straight blade (Miller) or indirectly with the curved blade (Macintosh).
6. Visualize vocal cords (arytenoids).	Look for the arytenoid cartilages to avoid overly deep insertion of the blade, which is a common error. BURP maneuver may improve visualization.
7. Advance ETT.	Visualize tube *and* cuff passing through vocal cords. Correct tube placement is a minimum of 2 cm above the carina (approximately 23 cm at the incisors in men and 21 cm in women).
8. Inflate balloon.	Use 5–7 mL of air. Check cuff pressure to avoid tracheal injury from pressure (target 25–40 cm H_2O).
9. Confirm ETT placement.	Listen for bilateral breath sounds and the absence of epigastric sounds. Confirm placement with capnography or colorimetric carbon dioxide detector.
10. Secure ETT.	Use commercial tube holder, adhesive tape, or umbilical tape.

Abbreviations: BURP = backward-upward-rightward pressure; ETT = endotracheal tube.

PROCEDURE

Table 29A-3 summarizes the steps of tracheal intubation. The objective of laryngoscopy is to align the oral, pharyngeal, and laryngeal axes to provide an unobstructed direct view of the glottis and allow passage of the ETT between the vocal cords (**Figure 29A-6**). (See Video: Orotracheal Intubation.)

Select the appropriate-size ETT: 8.0- to 8.5-mm inner diameter for an average adult male and 7.5- to 8.0-mm inner diameter for an adult female. Check the cuffs for air leaks with a 10-mL syringe. Choose an ETT with a high-volume, low-pressure cuff. The second hole at the end of the ETT (Murphy eye) permits some uninterrupted airflow if the tip is occluded. Insert a lightly lubricated stylet to aid ETT direction and placement.

The Macintosh and Miller blades are most commonly used in direct laryngoscopy. The curved **Macintosh blade** tip is placed in the vallecula to indirectly lift the epiglottis off the larynx. The straight **Miller blade** physically lifts the epiglottis to visualize the larynx. Blade selection is a matter of personal preference. Be sure to test the light on the laryngoscope after attaching the appropriate-size blade (**Figure 29A-7**).

With the curved Macintosh blade, choose a #3 for most adults or a #4 for larger patients. Holding the laryngoscope with the left hand, insert the curved blade deeply into the far right side of the patient's mouth. Use the broad vertical flange to sweep the tongue to the left while

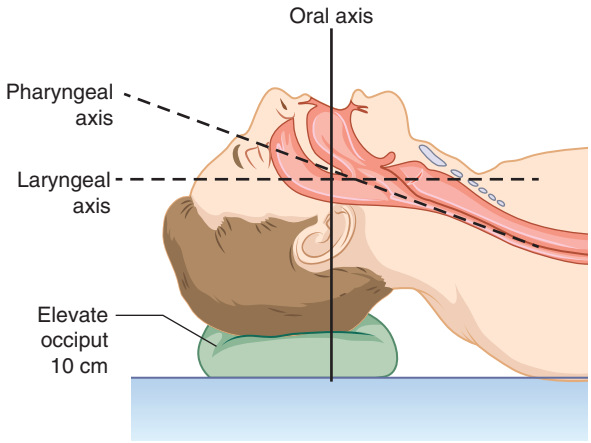


FIGURE 29A-6. Alignment of oral, pharyngeal, and laryngeal axes during intubation.

simultaneously placing the blade tip in the vallecula. Apply pressure upon the vallecula via the hyoepiglottic ligament to facilitate elevation of the epiglottis and exposure of the vocal cords. Lift upward to flex the lower neck and extend at the atlanto-occipital joint. The goal is to align the oral, pharyngeal, and laryngeal axes, facilitating a direct view of the glottis. Laryngoscopy should be performed in a single fluid motion.

With the straight Miller blade, choose a #3 for most adults. Insert the straight blade at the far right side of the mouth at an angle, aiming to expose and lift the glottis in a single motion. Bring the handle to midline, using the broad part of the blade to lift the tongue.

Optimal intubation occurs with a full, unobstructed view of the glottis. Often, no matter what blade chosen, the glottis is not seen; a common error is inserting the tip of a blade too deep. Withdraw the blade slowly and slightly; the glottis often "drops" into view. If the glottis and vocal cords are not seen clearly, esophageal tube placement is more likely. Anesthesiologists characterize glottic exposure using the Cormack-Lehane system; grade 1 reflects a fully exposed glottic view, and grade 4 reflects the inability to visualize any of the vocal cord[10] (**Figure 29A-8**). The percentage of glottic opening provides an alternate glottic visualization rating from 0% to 100%.[11] Abort the attempt if you cannot visualize the larynx.

Glottic exposure may be aided by backward-upward-rightward pressure (**BURP maneuver**) applied to the thyroid cartilage.[12] Another effective technique is bimanual laryngoscopy, where the intubator manipulates the larynx with the right hand until ideal visualization and then an assistant maintains this position.[13] The **Sellick or cricoid maneuver** (application of direct pressure on the cricoid ring) can hamper bag-valve-mask ventilation, laryngoscopic view, and ETT insertion.[14]

Where there is concern for cervical spine fracture or injury, use **in-line stabilization of the cervical spine** without extension of the head or neck during laryngoscopy. This stabilization may make laryngoscopy and glottic exposure more difficult; because of this, some experts question the utility of manual inline stabilization and wonder if it really affords adequate spinal cord protection.[15]

Gently insert the ETT through the glottis, inflate the cuff, and remove the stylet. **The typical correct tube insertion depth is 22 cm**, measured at the patient's incisors. Difficulties in passing the ETT may result from the failure to maintain optimal laryngoscopic view, selecting too large a tube, applying cricoid pressure, or suboptimal shaping of the ETT stylet. Switching to a smaller tube, altering the curve of the stylet, and rotating the tube 90 degrees to align the bevel with the glottic opening are other techniques for facilitating ETT insertion.

Multiple intubation attempts are associated with adverse events including cardiac arrest.[4,16] To minimize oxygen desaturation, limit each intubation attempt (insertion of blade) to no more than 30 seconds. Between intubation attempts, use a bag-valve mask to reoxygenate the patient to 100% oxygen saturation. For anyone in extremis or with anticipated difficulty, first-pass success is more vital; have the most experienced person perform intubation in these situations.

The **gum elastic bougie** (**"bougie"**) introducer aids orotracheal intubation, especially when the glottis cannot be fully visualized



A



B

FIGURE 29A-7. **A.** Curved or Macintosh blade. **B.** Straight or Miller blade.



FIGURE 29A-9. Gum elastic bougie.

(**Figure 29A-9**). After laryngoscopy and best exposure of the vocal cords, insert the angled tip of the bougie through the glottis. When correctly inserted, you may feel the bougie tip moving over the tracheal rings. Thread the ETT over the introducer into the trachea, inflate the ETT cuff, and then remove the introducer. First-pass success is higher with bougie-assisted intubation.[17] Never force the tube through the vocal cords, which can avulse the arytenoid cartilages or lacerate the vocal cords.

CONFIRM ENDOTRACHEAL TUBE LOCATION

Mainstem bronchial or esophageal intubation may cause hypoxia, hypoxemia, hypercarbia, bradycardia, and cardiac arrest. **Confirm intratracheal tube positioning with multiple methods; no single technique is infallible.** Although directly visualizing the tube between the vocal cords is the best method for confirming successful placement, trauma or a small oropharynx may limit visual assessment. Other clinical assessments include chest and epigastric auscultation and observation for tube condensation or symmetric chest wall expansion.

Capnometers and capnographs measure carbon dioxide in expired air of the ETT (**Figure 29A-10**). The presence of carbon dioxide suggests intratracheal tube placement. The absence of carbon dioxide

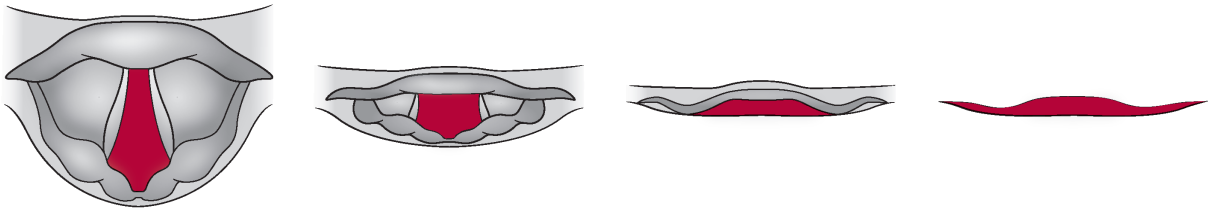
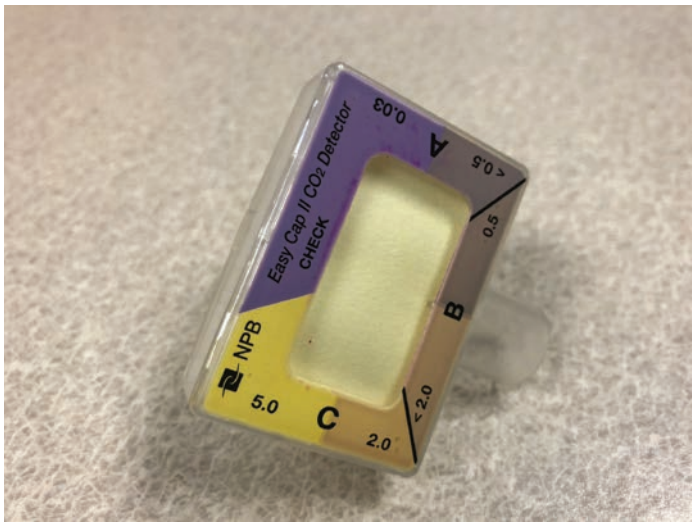


FIGURE 29A-8. Cormack-Lehane scale for rating glottic exposure. [Reproduced with permission from Stone CK, Humphries RL, Drigalla D, Stephan M (eds): *Current Diagnosis & Treatment: Pediatric Emergency Medicine*. McGraw-Hill Education, Inc. © 2015. Figure 9-6.]



A



B

FIGURE 29A-10. End-tidal carbon dioxide detectors. **A.** Colorimetric. **B.** Combined digital and waveform.

suggests ETT misplacement. Colorimetric end-tidal carbon dioxide detectors have a pH-sensitive filter paper that changes color from yellow to purple with carbon dioxide exposure. Capnography measures expired carbon dioxide in real time, displaying either the peak value with each breath or continuous graphical waveforms. Clear, regular waveforms or carbon dioxide measurements >30 mm Hg correlating with exhalations suggest proper ETT placement. Rarely, a misplaced hypopharyngeal glottic tube tip may result in normal oximetry and capnography in a spontaneously breathing patient. In cardiac arrest states, expired carbon dioxide will be low due to poor perfusion; continuous capnography waveforms may still be detectable in these cases. **Table 29A-4** notes conditions associated with false colorimetric or capnographic carbon dioxide readings.

The esophageal detection device may also indicate ETT placement. When the ETT is in the esophagus, the soft, noncartilaginous walls will collapse, and air cannot be easily aspirated with an esophageal detector. Esophageal detection devices use either syringe aspiration or a compressible bulb technique. If the ETT tube is in the esophagus, the vacuum causes the esophagus to collapse around the tube, creating resistance to aspiration or preventing the bulb from refilling. Conversely, syringe aspiration or bulb refilling is rapid when the ETT is in the trachea.

Recent studies suggest ultrasonography as an alternate technique for confirmation of intratracheal ETT placement.[18,19] Position the US probe cephalad to the cricoid membrane, just above the sternal notch (**Figures 29A-11** and **29A-12**). The ETT should be visualized within the lumen of the trachea. The visualization of two separate structures ("double track sign") likely indicates esophageal intubation. Some operators inflate the ETT cuff with water to improve its visualization on ultrasonography.

TABLE 29A-4 Conditions Associated With False Colorimetric or False Capnographic Carbon Dioxide Readings

False-Negative Reading

- Low pulmonary perfusion—cardiac arrest, inadequate chest compressions, massive pulmonary embolism, shock
- Massive obesity
- Tube obstruction (secretions, blood, foreign body)

False-Positive Reading

- Recent ingestion of carbonated beverage (should not persist beyond 6 breaths)
- Heated humidifier, nebulizer, or endotracheal epinephrine (transient false readings)

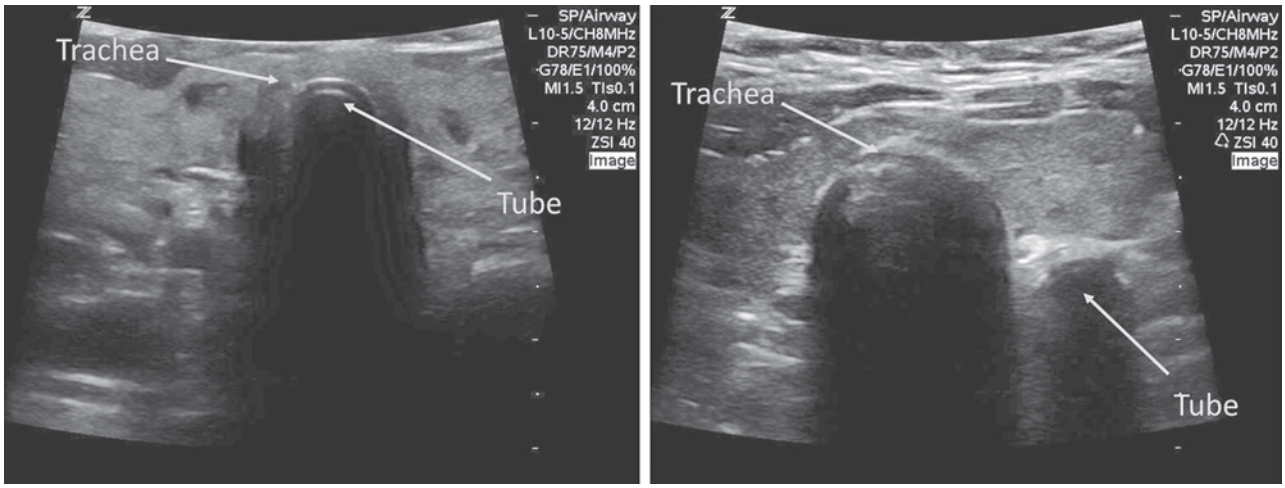
A chest radiograph is customarily obtained after intubation to verify correct *vertical* positioning of the ETT. However, **a chest radiograph does not reliably distinguish ETT placement in the trachea from the esophagus.** Other important postintubation radiograph findings include the presence of a pneumothorax and consolidations suggestive of pneumonitis (due to aspiration or infection).

Never assume correct ETT positioning and patency if the patient is deteriorating after intubation. Suctioning may help to clear secretions from obstructing the tube. If the ETT cuff leaks after the intubation, check the inflation valve. If the tube needs to be replaced, use a tube changer or bougie; insert the changer into the ETT, withdraw the ETT, and then insert a new ETT over the catheter and reconfirm placement. If in doubt about its position, withdraw and replace the ETT or restart bag-valve-mask assistance.

After successful intubation, secure the ETT to prevent device dislodgement during subsequent patient care. **Tube displacement can occur during patient movement or any care if not properly secured.** During EMS transfer of the patient into the stretcher, have an assistant hold the ETT in place during the transfer. Once the patient is stabilized, the most common approach to securing the ETT is wrapping adhesive tape around the neck and the ETT (Lillehei method).[20] Flat umbilical "twill" cloth tape may also be used to tie the tube in place. Commercial tube holders consist of a plastic bite block strapped to the patient's face using Velcro tape and a plastic strap or screw clamp to hold



FIGURE 29A-11. Use of ultrasonography for confirmation of tracheal tube placement. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd ed. © 2019, McGraw-Hill, Inc., New York. Figure 19-7.]



A B

FIGURE 29A-12. **A** and **B.** Ultrasonographic view of intratracheal (left) and esophageal (right) endotracheal tube placement. [Images used with permission of Jordan Chenkin, MD.]

the ETT in place. One cadaver study found that conventional adhesive taping surpassed most commercial ETT holders.[20] Finally, if not already done, place an orogastric tube and connect it to suction.

COMPLICATIONS OF ENDOTRACHEAL INTUBATION

Many complications can be avoided with preparation (**Table 29A-5**). Although some events are directly associated with the procedure (e.g., ETT misplacement), other indirect events are also important (e.g., hyperventilation and CPR interruption). **Be especially vigilant for peri-intubation hypotension** and cardiac arrest, which occur after 23% and 4% of ED intubations, respectively.[21-23] Some advocate for bolus-dose or 'push-dose' vasopressors to mitigate hypotension. However the ideal pressor and dose is not yet evidence-based. See Chapter 20, Pharmacology of Vasopressors and Inotropes, 'Bolus-Dose Administration of Vasopressors' and Table 20-1 for further discussion.

RAPID-SEQUENCE INTUBATION

Rapid-sequence intubation (RSI) is the sequential administration of an induction agent and neuromuscular blocking agent to facilitate endotracheal intubation (**Table 29A-6**). The goal of RSI is to facilitate rapid insertion of the ETT while minimizing physiologic perturbations. RSI is superior to sedation alone, allows the highest intubation success rate in properly selected emergency airway cases, and is the method of choice for emergency airway management.

Not all patients are best managed with RSI. Patients who are deeply comatose or in cardiac or respiratory arrest may be intubated without

TABLE 29A-5 Complications of Endotracheal Intubation, Preventive Strategies, and Potential Corrective Actions

Complication	Preventive Strategies	Corrective Action
ETT misplacement	View ETT entry through glottis	Quick recognition. Remove and replace ETT.
ETT dislodgement	Secure ETT, minimize patient movement, use continuous capnography	Quick recognition. Remove and replace ETT.
Mainstem intubation	View ETT entry through glottis, know appropriate ETT depth	Quick recognition. Adjust ETT position.
Oxygen desaturation	Preoxygenate patient prior to intubation	Verify ETT position. Clear ETT. Hyperventilate.
Hypotension	Ensure adequate blood pressure before intubation efforts, minimize use of medications known to induce hypotension	Place patient in Trendelenburg position. Give IV fluids. Give pressors. Avoid hyperventilation.
Bradycardia	Ensure adequate heart rate before intubation efforts	Hyperventilate. Give atropine or epinephrine.
Cardiac arrest	Ensure adequate heart rate, blood pressure, oxygen saturation before intubation efforts	Initiate CPR.
Aspiration	Avoid aggressive BVM ventilation, keep patient upright before intubation	Large-bore suction or oropharynx and ETT.
Injury to oropharynx or hypopharynx	Careful laryngoscopy	
Pneumothorax	Careful laryngoscopy, avoid aggressive BVM ventilation	Insert chest tube or pigtail.
Gastric/visceral perforation	Careful laryngoscopy, avoid aggressive BVM ventilation	
Vocal cord injury	Careful laryngoscopy, careful ETT placement	
ETT cuff leak	Check cuff before intubation, avoid rubbing cuff against teeth	Remove and replace ETT.
ETT obstruction (secretions, vomitus, foreign body)	Suction oropharynx before intubation efforts	Suction ETT. Clear obstruction.
Hyperventilation	Judicious control of manual ventilations	
Interruptions in CPR chest compressions	Minimize CPR interruptions during intubation, use a supraglottic airway instead of ETT	
Failed intubation/Inability to intubate	Anticipate and plan for intubation difficulty	Immediate rescue with supraglottic or other airway.

Abbreviations: BVM = bag-valve mask; ETT = endotracheal tube.

TABLE 29A-6 Rapid-Sequence Intubation Steps

- Discuss airway management strategy with the team.
- Set up IV access, cardiac monitor, oximetry, and capnography/capnometry.
- Plan procedure. Assess physiologic status and airway difficulty.
- Prepare equipment, suction, and potential rescue devices.
- Preoxygenate.
- Consider pretreatment agents.
- Give sedative agent immediately followed by neuromuscular blocking agent.
- Intubate trachea.
- Confirm tube placement.
- Secure tube.
- Adjust mechanical ventilation and provide postintubation sedation.

pharmacologic assistance. Relative contraindications to RSI include anticipated airway management difficulty and clinical scenarios where muscle relaxation will not improve laryngeal exposure (e.g., massive edema, immobile jaw from injury or infection, oral tumors or obstruction). Always be prepared for failure and have rescue airway plan and equipment ready.

PRETREATMENT AGENTS

Sympathetic responses to laryngoscopy and intubation include increases in heart rate, blood pressure, and intracranial pressure. These effects may be particularly important in select clinical settings such as traumatic brain injury, hemorrhagic stroke, myocardial ischemia, or aortic dissection. Laryngeal stimulation may cause laryngospasm, cough, and bronchospasm. Pretreatment medications may help to mitigate these responses prior to RSI (**Table 29A-7**). However, since the effectiveness of these measures is unclear, many clinicians omit this step. If used, administer pretreatment agents 3 to 5 minutes before initiation of RSI.

TABLE 29A-7 Rapid-Sequence Intubation Pretreatment Agents

Agent	Dose	Indications	Precautions
Lidocaine	1.5 milligrams/kg IV/topically	Elevated ICP Bronchospasm, asthma	Lack of evidence-based studies on effectiveness in ICP No evidence of improved outcome and may not be better than inhaled albuterol
Fentanyl	3 micrograms/kg IV	Elevated ICP Cardiac ischemia Aortic dissection	Respiratory depression Hypotension Chest wall rigidity

Abbreviations: ICP = intracranial pressure.

INDUCTION AGENTS

The ideal RSI induction agent achieves rapid, deep sedation of limited duration, avoids hypotension, and mitigates the physiologic response to laryngoscopy and intubation. There is no single induction agent of choice. Commonly used agents offer advantages and risks in specific clinical conditions (**Table 29A-8**).

Etomidate, a nonbarbiturate hypnotic, has a short duration of action, protects from myocardial and cerebral ischemia, causes minimal histamine release, and causes little hemodynamic depression in most patients. Myoclonus, nausea, and vomiting can occur in awake patients, but these effects are less important in the setting of RSI. Etomidate is not an analgesic, and it does not blunt the sympathetic response to intubation. Single-dose etomidate given for ED RSI can cause cortisol inhibition, but the clinical significance of this association is unclear.[24]

Propofol is a highly lipophilic, rapid-acting sedative. Propofol has a more rapid onset of action and shorter duration of action than etomidate. It has anticonvulsant and antiemetic properties, and it may lower intracranial pressure without triggering histamine release. Important side effects of propofol include hypotension through myocardial depression and vasodilation, making it less appealing for trauma patients or shock states.

Ketamine, a phencyclidine derivative, is a dissociative agent that provides analgesia and amnesia. Ketamine preserves the respiratory drive, an ideal feature for sedation during awake intubation. Ketamine increases blood pressure and heart rate through catecholamine release, which may be useful in hypovolemic or hypotensive states. Ketamine causes direct smooth muscle relaxation and bronchodilation and is often used in those with refractory status asthmaticus. Despite theoretic concerns about γ-aminobutyric acid–altering effects that could worsen CNS function, ketamine is a good option in patients with head injury and hypotension. Ketamine does not cause consistent increased intracranial pressure in sedated and ventilated patients, and some studies suggest that the drug has possible cerebroprotective effects. Avoid ketamine in the elderly or for patients with suspected acute cardiac ischemia because of the potential for associated tachycardia and hypertension.

Other Agents **Barbiturates** commonly cause hypotension from myocardial depression and venous dilatation; they have been largely replaced with etomidate or propofol. Benzodiazepines such as **midazolam** may be used when other agents are contraindicated or unavailable, but their depth and speed of onset are less reliable.

PARALYTIC (NEUROMUSCULAR BLOCKING) AGENTS

Neuromuscular blockade eliminates protective airway reflexes (**Table 29A-9**). Neuromuscular blockade can facilitate tracheal intubation, improve mechanical ventilation, and help control intracranial hypertension. Neuromuscular blockade limits assessments of neurologic status, and long-term use increases the risks of polyneuropathy and posttraumatic stress disorder. Neuromuscular blockers are neither anxiolytics nor analgesics, so delivering concurrent sedation is mandatory. Neuromuscular blockers include **depolarizing** and **nondepolarizing** agents. **Depolarizing** neuromuscular blocking agents have high affinity for cholinergic receptors of the motor end plate and are resistant to

TABLE 29A-8 Rapid-Sequence Intubation Induction Agents

Agent	Dose	Onset	Duration	Benefits	Caveats
Etomidate	0.3–0.5 milligram/kg IV	<1 min	10–20 min	↓ ICP	Myoclonic jerking or seizures and vomiting in awake patients
				↓ Intraocular pressure	No analgesia
				Neutral BP	↓ Cortisol
Propofol	0.5–1.5 milligrams/kg IV	20–40 s	8–15 min	Antiemetic	Apnea
				Anticonvulsant	↓ BP
				↓ ICP	No analgesia
Ketamine	1–2 milligrams/kg IV	1 min	10–20 min	Bronchodilator	↑ Secretions
				"Dissociative" amnesia	↑ BP
				Analgesia	Emergence phenomenon

Abbreviations: BP = blood pressure; ICP = intracranial pressure.

TABLE 29A-9 Rapid-Sequence Intubation Paralytic (Neuromuscular Blocking) Agents

Agent	Adult Intubating IV Dose	Onset	Duration	Comments
Rocuronium (intermediate/long)	1 milligram/kg	1–3 min	30–45 min	Tachycardia. Longer duration of action and onset compared to succinylcholine. Most common alternative to succinylcholine.
Vecuronium (intermediate/long)	0.08–0.15 milligram/kg 0.15–0.28 milligram/kg (high-dose protocol)	2–4 min	25–40 min 60–120 min	Prolonged recovery time in obese or elderly, or if there is hepatorenal dysfunction.
Succinylcholine	1.5 milligrams/kg	45–60 s	5–9 min	Provides optimal intubating conditions most rapidly. There are several rare but important contraindications (see Table 29A-10).

acetylcholinesterase. Depolarizing blockade is not antagonized and may be enhanced by anticholinesterase agents. **Nondepolarizing** neuromuscular blocking agents compete with acetylcholine for the cholinergic receptors and usually can be antagonized by anticholinesterase agents.

Succinylcholine is the most commonly used agent for neuromuscular blockade in ED RSI. A depolarizing agent, succinylcholine is two joined acetylcholine molecules and is rapidly hydrolyzed by plasma cholinesterase. It has a rapid onset after IV dosing and a shorter duration of action than nondepolarizing agents. After brief fasciculation, complete relaxation occurs at 60 seconds, with maximal paralysis at 2 to 3 minutes. Effective respirations resume in 8 to 12 minutes. IM succinylcholine (4 milligrams/kg) acts more slowly and lasts longer; this is best reserved for the rare setting where paralysis is required absent IV access.

If choosing succinylcholine, know its side effects (**Table 29A-10**). Serum potassium will transiently rise in all patients by an average of 0.5 mEq/L with succinylcholine, usually without any clinical impact. Due to acetylcholine receptor upregulation at the neuromuscular junction, an exaggerated hyperkalemic response may occur 5 or more days after a burn, denervation, or crush injury, or in patients with preexisting myopathies. **Do not use succinylcholine in patients with suspected preexisting significant hyperkalemia (especially renal failure), myopathies, or myasthenia gravis.** Repeated doses can cause cardiac dysrhythmias including bradycardia and asystole.

Genetically susceptible individuals may develop malignant hyperthermia after succinylcholine. Suspect malignant hyperthermia if unexplained rapid fever with muscle rigidity, acidosis, or hyperkalemia occurs after succinylcholine. Treat with IV dantrolene sodium (2.5 milligrams/kg) and temperature control. Patients with acquired or genetic atypical or low plasma cholinesterase may have prolonged paralysis. Cocaine is metabolized by plasma cholinesterase, which reduces the amount of enzyme available for succinylcholine metabolism. If known plasma cholinesterase deficiency is suspected, use a nondepolarizing agent (usually rocuronium) instead of succinylcholine.

Rocuronium is an intermediate-duration nondepolarizing agent that is an excellent alternative to succinylcholine for RSI due to its shorter duration of action. By increasing the dose of rocuronium to 0.9 to 1.2 milligrams/kg, the onset of action approximates that of succinylcholine, but the duration of action is prolonged.

Vecuronium bromide is an intermediate- to long-acting nondepolarizing agent. Vecuronium has no cardiac effects. Hypersensitivity reactions are rare, doses are only minimally cumulative, and excretion is biliary. Despite the lack of histamine release, hypotension may occur through other mechanisms that include sympathetic ganglia block and less venous return from altered or absent muscle tone and positive-pressure ventilation.

Sugammadex is a reversal agent that reverses blockade from rocuronium or vecuronium by encapsulating the molecules of the nondepolarizing agents circulating in plasma.[25] The dose is 2 to 4 milligrams/kg, depending on the intensity of neuromuscular paralysis, and the drug takes effect within minutes. Neostigmine, a cholinesterase inhibitor, may be used to reverse neuromuscular blockade, but it has undesirable cardiac and cholinergic side effects.

TABLE 29A-10 Succinylcholine Complications and Contraindications

Complications
- Fasciculations
- Transient increased intragastric, intraocular, and intracranial pressure
- Bradycardia
- Masseter spasm
- Malignant hyperthermia
- Prolonged apnea with pseudocholinesterase deficiency or myasthenia gravis

Contraindications
- Preexisting hyperkalemia
- Burns >5 d old
- Denervation injury >5 d old
- Significant crush injuries >5 d old
- Severe infection >5 d old

Preexisting myopathies

VIDEO LARYNGOSCOPY

Video laryngoscopes (VLs) use an integrated high-resolution camera and video monitor to facilitate indirect glottic visualization and ETT placement. VL creates a magnified view that cannot be obtained through direct laryngoscopy. VL also allows shared visualization and video recording useful for quality review, education, and training. VL may be used as the primary or rescue intubation technique. While first-pass and overall intubation success rates are similar between direct laryngoscopy and VL, VL improves glottic visualization and reduces intubation complications, including rates of esophageal intubation.[26-28] However, compared with conventional direct laryngoscopy, the glottic view with VL may be inferior in a small subset of patients.[29] VL may be most useful in patients with difficult airway anatomy, including obese patients and those with limited mouth opening or neck mobility. Avoid VL and use direct laryngoscopy if the camera may be obscured by emesis.

Laryngoscopic technique is slightly different with VL than conventional laryngoscopy. First, the operator performs the intubation watching a video screen rather than looking directly into the oropharynx. Second, VL often uses a hyperangulated blade. The combination of these two features allows visualization of the glottis with only limited extension of the head and neck. A specially designed stylet is required when VL is used in this manner.

In contrast to traditional laryngoscopy, a midline insertion approach is preferred and a tongue sweep is not needed with VL. Once past the teeth, the operator identifies the midline by finding the uvula. The blade is then slowly advanced down the tongue until the epiglottis is seen. The ideal view is usually obtained by insertion into the vallecula, much like a Macintosh blade. The handle is then gently tilted forward until visualization of the glottic opening is obtained.

The two most studied VLs are the **GlideScope Video Laryngoscope®** (Verathon, Bothell, WA) and the **C-MAC Video Laryngoscope®** (Karl Storz, Tuttlingen, Germany) (**Figure 29A-13**). Both brands also have conventionally curved blades available, allowing the device to function much like a conventional laryngoscope; this feature allows for supervision of novice intubators during the traditional intubation technique. (See Video: Intubation: C-MAC Video Laryngoscope.)



A

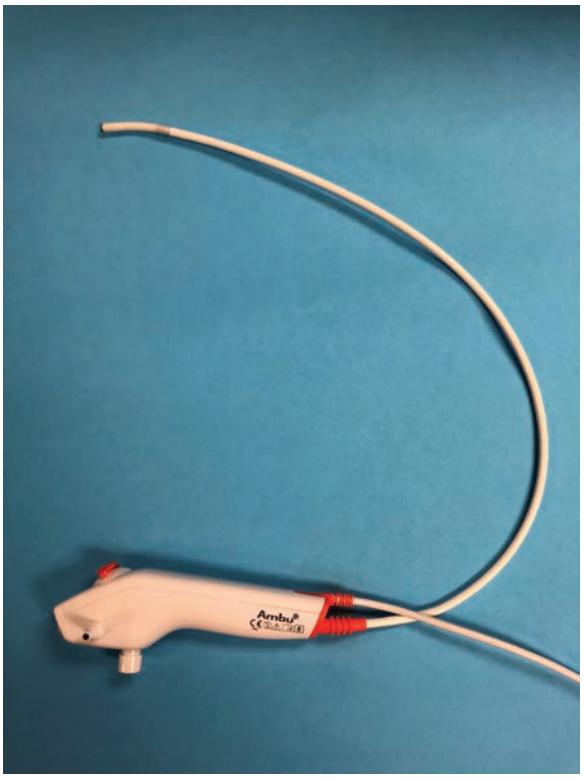


B

FIGURE 29A-13. Video laryngoscopes. **A.** GlideScope®. **B.** C-MAC®.

FLEXIBLE FIBEROPTIC LARYNGOSCOPY

The flexible fiberoptic laryngoscope (FFL) uses fiberoptic technology embedded in a flexible tube to facilitate visualization of and access to the airway (**Figure 29A-14**). Newer flexible scopes use video technology,



A



B

FIGURE 29A-14. Flexible fiberoptic intubation (Ambu Airscope; Ambu, Ballerup Denmark). **A.** Flexible fiberoptic scope **B.** Flexible fiberoptic scope with screen.

not fiberoptics, and interface directly with VL monitors. FFL aids when anatomic limitations, such as angioedema, epiglottitis, Ludwig's angina, congenital anatomic abnormalities, and cervical spine immobility, prevent traditional laryngoscopy. Growing numbers of ED practitioners are becoming skilled with FFL.[30] FFL requires proper equipment as well as appropriate training. If equipment or expertise is not available in the ED, consult an expert with fiberoptic skills and tools.

FFL requires setup time as well as a compliant, spontaneously breathing patient. Patients needing an immediate airway, with near-complete obstruction, with large bleeding or vomitus, and who cannot be ventilated to maintain saturation are poor FFL candidates.

Topical anesthesia is essential for FFL intubation success. Use atomized or nebulized topical anesthetics, such as 4% lidocaine. An

antisialagogue, such as glycopyrrolate 0.01 milligram/kg, or homatropine reduces secretions and enhances topical anesthesia, but should be given 20 minutes prior to intubation for best effect. If sedation is necessary to facilitate FFL, ketamine is a good choice as it will preserve spontaneous breathing. If using the nasal route, instill a topical vasoconstrictor such as phenylephrine or oxymetazoline. Nasal viscous lidocaine followed by a nasal airway allows topical anesthesia and enhanced passage of the scope through the airway; remember to remove the nasal tube prior to the passage of an ETT.

Focus the eyepiece if needed and lubricate the flexible shaft. Immerse the lens at the tip of the laryngoscope in warm water or apply antifogging solution. Intermittent insufflation of oxygen at 10 to 15 L/min through the suction port will keep the optic tip clear. If possible, use a #7.5 ETT. Remove the adapter from the ETT and slip the lubricated tube over the FFL up to the handle. If the distal end of the FFL does not extend beyond the end of the ETT, the scope is too small and should not be used for intubation.

FFL is often easiest through the nasal route, allowing easier midline airway positioning and entry of the glottis at a less acute angle. If using the oral route, tongue extrusion, anterior mandibular displacement, or the use of a specially designed oral airway or bite block may help (**Figure 29A-15**). Advance the scope through the hypopharynx. Hold the laryngoscope in the opposite hand to control tip deflection while advancing it through the vocal cords. Spraying 4% lidocaine through the working channel when the scope is over the glottic opening may help to suppress the gag or cough reflex. Once the scope is through the cords, pass the ETT over the scope in Seldinger fashion and remove the scope. Resistance at the cords is best overcome with tube rotation rather than forceful insertion.

A valuable adjunct to FFL is the Aintree catheter (Cook Medical, Bloomington, IN), a hollow stylet that can be inserted over an FFL. After intratracheal placement of the Aintree catheter, the FFL may be removed and a standard ETT inserted over the Aintree much like a bougie. The Aintree may be inserted via FFL through a properly placed supraglottic airway (e.g., laryngeal mask airway), allowing for conversion to an ETT.



FIGURE 29A-15. Bite block for oral passage of flexible fiberoptic laryngoscope (ConMed, Utica, NY).

BLIND NASOTRACHEAL INTUBATION

Blind nasotracheal intubation may be helpful where laryngoscopy may be difficult, RSI is contraindicated, and FFL is not available. Nasotracheal intubation is less common given other available options. Severe traumatic nasal or pharyngeal hemorrhages are relative contraindications to nasotracheal intubation.

Position the patient upright with the head in a neutral or slightly extended position ("sniffing position"). Stand to the side of the patient with one hand on the tube and with the thumb and index finger of the other hand straddling the larynx. Insert and advance the lubricated tube along the nasal floor; the right naris is often larger. Pass the ETT *straight back toward the occiput* (not upward), and then advance it while rotating it medially 15 to 30 degrees until maximal airflow is heard through the tube. Steady, gentle pressure or slow rotation of the tube usually bypasses small obstructions. Gently but swiftly advance the tube at the *initiation (upswing) of inspiration*. The typical optimal depth of nasotracheal tube placement is 28 cm at the nares in men and 26 cm at the nares in women. Confirm tracheal placement using multiple methods.

MANAGING INTUBATION DIFFICULTY

ANTICIPATED INTUBATION DIFFICULTY

Several factors can help identify a potentially difficult intubation (Table 29A-2).[31] Assess the patient's clinical condition and identify factors that will impede successful intubation. Weigh these observations against the urgency of the patient's condition. If patient consciousness or agitation is the sole anticipated obstruction, proceed with sedation and paralysis. In the presence of major anatomic barriers (tumor, trauma, obesity, difficult anatomy), consider deferring RSI, preserving the patient's natural respiratory drive and protective airway reflexes. In these situations, strategies of awake intubation using FFL or (for those skilled with the technique) blind nasotracheal intubation are options. In the case of severe facial trauma, immediate or urgent surgical airway placement (cricothyroidotomy or tracheostomy) is always an option. Awake orotracheal intubation with topical anesthetic is theoretically possible but rarely achievable in the emergency setting.

Where immediately available, emergent assistance from anesthesiologists, surgeons, or otolaryngologists may aid. The use of bilevel positive airway pressure, continuous positive airway pressure, or high-flow nasal cannula oxygen may mitigate the patient's deterioration, affording additional time to assemble resources.

UNANTICIPATED INTUBATION DIFFICULTY

The more challenging clinical scenario is the case of unanticipated intubation difficulty occurring after the administration of sedative and paralytic medications. A single failed laryngoscopy attempt should signal potential airway difficulty and prompt corrective action. Although there is no single pathway or approach to unanticipated intubation difficulty, operators should consider several guiding principles.

Stay calm. Think clearly. Communicate directly and clearly. Use available team members (nurses, respiratory therapists, technicians, and other physicians) to assist with care and mobilize needed equipment, medications, and personnel. Use of cognitive aids (e.g., checklists and difficult airway algorithms) can help to minimize the stress while providing cognitive offloading. **Call for help.** Where readily available, assistance from anesthesiologists, surgeons, otolaryngologists, intensivists, or fellow emergency physicians may be helpful but often requires time to mobilize. If you anticipate the need for assistance, call for help early. **Plan and communicate the next two steps.** Plan not only the next therapeutic intervention but also the subsequent intervention in the event of failure. For example, "I will switch to a Miller blade with bougie insertion. If unsuccessful, I will insert a laryngeal mask airway." Engage team members so that they are aware of your planned actions. **Alter airway techniques with each attempt.** Modify intubation blade type, blade size, approach, or operator with each attempt. Do not repeat the same unsuccessful methods with successive attempts. **Let RSI medications wear off.** Recovery of even a minimal degree of protective airway reflexes and spontaneous respirations may facilitate critically needed

airway patency. **Use noninvasive airway measures**. Bag-valve mask with an oral or nasal airway or insertion of a supraglottic airway may be helpful, mitigating clinical deterioration. Bag-valve mask or supraglottic airway insertion may allow additional time for surgical airway execution.

HYPOTENSION ASSICIATED WITH INTUBATION

Physiologic changes triggered by laryngscopy or the medications used during RSI can induce hypotension. While some advocate for empiric isotonic crystalloid infusion just prior to RSI, others believe dilute low-dose boluses or 'push-dose' pressors prior to ETI help mitigate hypotension. The ideal fluid volume and timing, and the optimal vasopressor choice and dose, are unknown. Table 20-1 notes common vasopressor preparations used in this manner, commonly epinephrine or phenylephrine ready ahead of time in syringes (rather than quickly drawn at the time of perceived need).

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

TABLE 29B-1 Acute Respiratory Distress Syndrome Definition (Berlin Definition)[8]

- Onset within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Bilateral opacities on chest imaging not fully explained by lobar/lung collapse or nodules
- Respiratory failure not fully explained by cardiac failure or volume overload
- Pao_2/Fio_2 ratio ≤300 mm Hg with PEEP ≥5 cm H_2O
  - Mild Pao_2/Fio_2 200–300 mm Hg
  - Moderate Pao_2/Fio_2 100–200 mm Hg
  - Severe Pao_2/Fio_2 ≤100 mm Hg

Abbreviations: Fio_2 = fraction of inspired oxygen; Pao_2 = partial pressure of arterial oxygen; PEEP = positive end-expiratory pressure.

Source: Data from The ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307(23):2526-2533.

CHAPTER 29B

Mechanical Ventilation

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MANAGING VENTILATORS SETTINGS

The primary function of mechanical ventilation is to provide respiratory support while treating the underlying process that caused respiratory failure. Safe oxygenation and ventilation can be accomplished in either a volume- or pressure-targeted mode. The chosen mode is often based on provider preference and experience. Patient outcomes are unlikely to be changed by the mode of ventilation.[1,2]

VOLUME TARGETED

In a volume-targeted mode (e.g., volume control; **Figure 29B-1**), the ventilator provides an inspiratory flow over time to target a set volume. To avoid ventilator-induced injury, multiple trials have shown that limiting the tidal volume improves patient outcomes compared to using the larger volumes more common in the past (often ≥10 mL/kg to start).[3-6] One approach is to start volume-targeted ventilation at 6 mL/kg ideal body weight for patients with or at risk for acute respiratory distress syndrome and 6 to 8 mL/kg ideal body weight for other patients. The definition of acute respiratory distress syndrome is provided in **Table 29B-1**. Those at risk for acute respiratory distress syndrome have pneumonia, sepsis, trauma, pancreatitis, or any shock state.[7] To choose ventilation settings, calculate ideal body weight using the patient's height, an important caveat in obese patients in whom harm is risked if tidal volumes choice is based on actual body weight.

In volume control mode, the airway pressures depend on the tidal volume plus the size and compliance of the respiratory system. Peak pressures are the highest pressures seen by the respiratory system and are measured every breath by the ventilator. They are a combination of airway resistance and alveolar and thoracic pressures. Peak pressures often reflect proximal airway resistance either in the endotracheal tube (as with mucous plugging or tube obstruction) or conducting airways (as with bronchospasm), but do not represent the pressure applied to the alveoli (**Figure 29B-2**). To approximate alveolar pressure, measure a plateau pressure with an end inspiratory pause in a passively breathing or paralyzed patient. The end inspiratory pause means flow in the respiratory circuit is zero and the pressure measured at the ventilator is the same at the alveolus[9] (**Figure 29B-3**). Target a plateau pressure of <30 cm H_2O.[3,4]

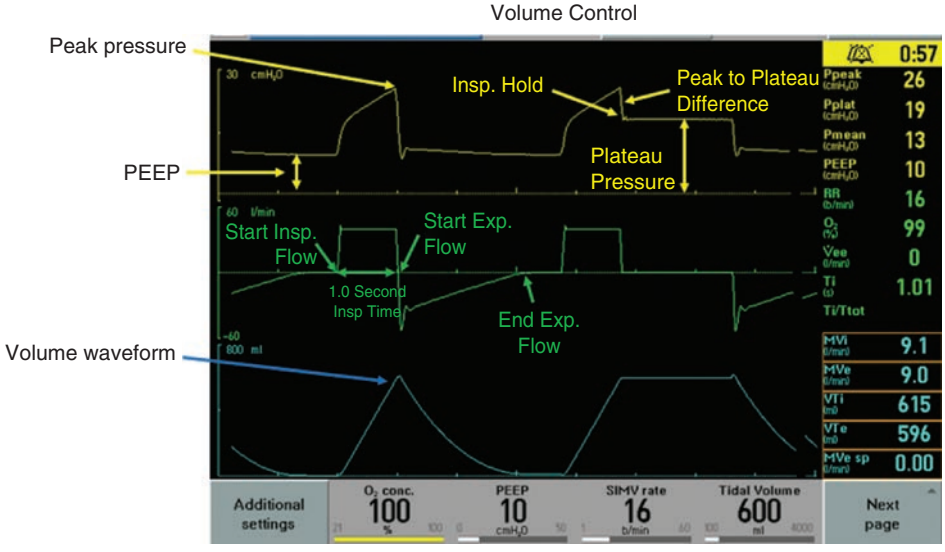

FIGURE 29B-1. Normal ventilator waveforms for volume control with a square inspiratory waveform flow. Yellow is the pressure waveform, green is the flow waveform, and blue is the volume waveform. This figure is an example of volume control with a square inspiratory waveform where the tidal volume of 600 mL is delivered over 1 second. PEEP = positive end-expiratory pressure.

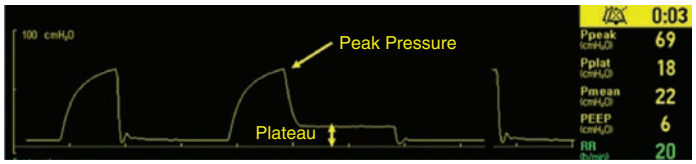

FIGURE 29B-2. Pressure waveform of a patient with high airway resistance from obstructed airways (e.g., chronic obstructive pulmonary disease or asthma). The high peak pressure and low plateau pressure indicate the problem is in the proximal airways. It also illustrates that the high peak pressure (69 cm H_2O) is not being transmitted to the alveoli.

PRESSURE TARGETED

In a pressure-targeted mode (e.g., pressure control), the ventilator will raise the airway pressures a prescribed amount over the positive end-expiratory pressure (PEEP) for a set amount of time (inspiratory time). The tidal volume depends on the resistance and compliance of the respiratory system. In pressure-control ventilation, follow tidal volumes and minute ventilation to ensure adequate ventilation. Start with a pressure control of 10 cm H_2O above PEEP and adjust the pressure up or down to target tidal volumes of 6 to 8 mL/kg ideal body weight. In a spontaneously breathing patient who is not intubated for severe hypoxemia or obstructive lung disease, consider transitioning to pressure support after a volume-targeted mode because the former may be more comfortable for the patient.

SYNCHRONOUS INTERMITTENT MANDATORY VENTILATION

Synchronous intermittent mandatory ventilation allows the patient to spontaneously breath between mandatory volume or pressure-targeted breaths. In this mode, the provider prescribes the mandatory breath type (volume or pressure targeted) and the amount of pressure support for spontaneous breaths. The set mandatory respiratory rate ensures a minimal minute ventilation. In heavily sedated or paralyzed patients not spontaneously breathing, synchronous intermittent mandatory ventilation is no different than pressure- or volume-targeted control modes (i.e., volume control–assist control). Similarly, if the mandatory rate is set close to zero, almost all breaths will be spontaneous and appear more similar to pressure support. The type of breath delivered to spontaneously breathing patients depends on the timing of the triggered breath. If the breath is triggered near a mandatory breath time, the patient will receive a controlled breath. If the breath is triggered outside of the set timing of the mandatory breath, ventilator support will depend on the set pressure support.[10] When using synchronous intermittent mandatory ventilation in critically ill patients, be sure to guarantee safe tidal volumes during spontaneous breaths.

RESPIRATORY RATE

The ideal respiratory rate depends on many factors. Most adult patients with normal respiratory physiology have adequate ventilation at a respiratory rate of 10 to 20 breaths/min. In sedated or paralyzed patients, the prescribed machine rate will be the actual respiratory rate. In patients who are triggering their own breaths, patients may determine their respiratory rate above the set rate. When deciding on a rate, anticipate demands; for example, in severe metabolic acidosis (e.g., diabetic ketoacidosis), set a high respiratory rate to maintain an adequate minute ventilation.

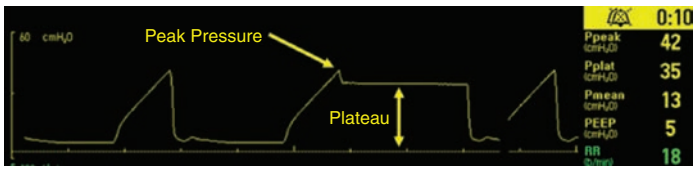

FIGURE 29B-3. Pressure waveform of a patient with low lung compliance (i.e., acute respiratory distress syndrome). The plateau is 35 cm H_2O in this example. A high plateau pressure in relation to the peak pressure indicates that there is reduced pulmonary compliance and not proximal airway resistance.

TABLE 29B-2 Positive End-Expiratory Pressure (PEEP) Tables

Lower PEEP/higher F_{IO_2}								
F_{IO_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
F_{IO_2}	0.7	0.8	0.9	0.9	0.9	1.0		
PEEP	14	14	14	16	18	18–24		
Higher PEEP/lower F_{IO_2}								
F_{IO_2}	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16
F_{IO_2}	0.5	0.5–0.8	0.8	0.9	1.0	1.0		
PEEP	18	20	22	22	22	24		

Abbreviation: F_{IO_2} = fraction of inspired oxygen.

Source: Adapted from http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf (ARDSNet: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary). Accessed January 22, 2019.

POSITIVE END-EXPIRATORY PRESSURE

Oxygenation can improve with mechanical ventilation by increasing the fraction of inspired oxygen (F_{IO_2}) or increasing the mean airway pressure with PEEP.[9] PEEP improves oxygenation by recruiting additional lung units, increasing the surface area for gas exchange, and redistributing lung water. Set initial PEEP at 5 cm H_2O in most patients. Obese patients or those with a tense abdomen require a higher PEEP; for these patients, start PEEP at 8 to 10 cm H_2O.[4] When you encounter a patient who is difficult to oxygenate despite using these initial PEEP and F_{IO_2} settings, titrate using a table (**Table 29B-2**) to incrementally increase your PEEP until the desired oxygenation is achieved. Improvements through increased PEEP are not immediate, so use incremental changes in PEEP of 2 cm H_2O every 10 to 20 minutes rather than rapidly increasing or decreasing because there is potential for unanticipated hemodynamic, intrathoracic, or intrapulmonary changes.

HYPEROXIA

Hyperoxia (too much supplemental oxygen) increases patient mortality in a dose-dependent relationship.[11-13] Many recommend titrating the F_{IO_2} to target an oxygen saturation of **no greater than 96%** as soon as the patient recovers from the apneic induction period (**Table 29B-3**).

SEDATION OF THE INTUBATED PATIENT

Sedation decisions during mechanical ventilation center on a fundamental question: *Does the ventilator need to be adjusted to accommodate the patient, or does the patient need to be sedated to accommodate the ventilator?* Next, decide how much sedation is needed; not all patients require the same depth. Patients intubated for severe hypoxic/hypoxemic or hypercapnic respiratory failure often need to be more

TABLE 29B-3 Initial Ventilator Settings

Mode	Volume control	Pressure control
Control variable	Tidal volume 6–8 mL/kg ideal body weight	10 cm H_2O
Measure-dependent variable	Peak and plateau pressures	Tidal volume
Respiratory rate	10–20 breaths/min	
PEEP	5–8 cm H_2O	
F_{IO_2}	Titrate to saturation of <96%	

Abbreviations: F_{IO_2} = fraction of inspired oxygen; PEEP = positive end-expiratory pressure.

deeply sedated to accommodate lung protective ventilation. Patients who are intubated for airway protection do not often require the same level of sedation as others being mechanically ventilated. Finally, although often not an ED issue, ending sedation or using sedation holidays allows for more prompt return to spontaneous ventilation.

Target adequate analgesia before targeting sedation because pain can be a major source of agitation and dyssynchrony (i.e., discoordinated breathing—an injury mechanism along with volume-induced lung injury). Use a standardized scale to assess pain and agitation, such as the Richmond Agitation-Sedation Scale. In the ED, target a Richmond Agitation-Sedation Scale score of –2 (awakens and makes eye contact to voice) to 0 (awake, alert, and calm).[14,15] If possible, avoid continuous benzodiazepine infusions as they have been associated with higher mortality, increased delirium, and increased sedation duration.[15,16]

OBSTRUCTIVE LUNG DISEASE

Acutely decompensated asthma and chronic obstructive lung disease patients are difficult to manage on the ventilator because the primary pathology is not improved by intubation (**Table 29B-4**). The problems encountered are increased airway resistance (with resultant high peak pressures; Figure 29B-2), pulmonary hyperinflation, and increased dead space causing hypercapnia.[10] The obstructive nature of these diseases leads to an effort-independent prolonged exhalation time.[17,18] Arterial hypercapnia tempts the treating physician to increase the respiratory rate to exhale more carbon dioxide; however, increasing the respiratory rate is counterproductive because it shortens the exhalation time, leading to an additional breath prior to the lungs completely emptying. This latter event is called *dynamic hyperinflation*.[10,19] As dynamic hyperinflation worsens, lung volumes increase, and the risk of barotrauma, pneumothorax, and hypotension also increases.[20] Incomplete emptying can be detected by monitoring the expiratory flow limb on the ventilator (**Figure 29B-4**) in a passively breathing patient. Measure the intrathoracic pressure from dynamic hyperinflation during an end-expiratory hold (Figure 29B-4). The difference between the total PEEP (from end-expiratory hold) and set PEEP is called auto-PEEP or intrinsic PEEP, signifying trapped air.

SEVERE HYPOXIA/HYPOXEMIA, ACUTE RESPIRATORY DISTRESS SYNDROME, AND TRAUMA

Determining the etiology of hypoxia (depressed alveolar oxygen) or hypoxemia (depressed arterial oxygen) starts with determining if there is unilateral or bilateral lung disease; this strategy guides potential therapies or interventions. In patients with bilateral lung disease at risk for acute respiratory distress syndrome, use lung-protective ventilator

TABLE 29B-4 Ventilator Management for Obstructive Lung Disease

Slow respiratory rate	**Start with a rate of 10–14 breaths/min.** A slow respiratory rate is the best way to increase emptying time compared with a decrease in inspiratory time.
Tolerate hypercapnia	**Tolerate a pH of ≥7.20.** A respiratory acidosis with a pH >7.20 is safe assuming there is not concomitant pulmonary hypertension.[19,21] If a respiratory acidosis is causing systemic effects, increase the tidal volume >8 mL/kg while keeping a low respiratory rate to maximize alveolar ventilation.
Check for gas trapping	**Check for auto-PEEP.** Ensure the expiratory flow limb of the flow curve reaches zero before the next breath (in a passively breathing patient). Perform an end-expiratory hold to calculate auto-PEEP. If hypotension occurs, disconnect the patient from the ventilator for 15–20 seconds and decrease the respiratory rate after reconnection.

Abbreviation: PEEP = positive end-expiratory pressure.

Source: PEEP Table Adapted from ARDSNet NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary. http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf

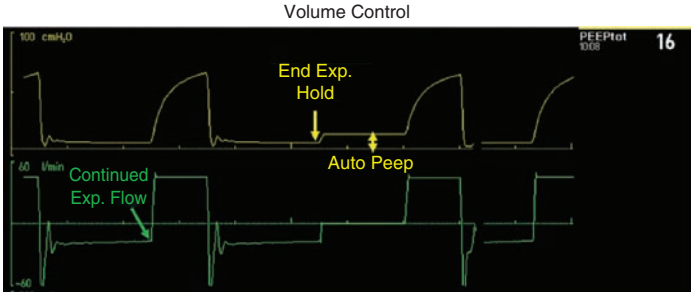

FIGURE 29B-4. Pressure waveform demonstrating auto–positive end-expiratory pressure (PEEP) with an end-expiratory hold. The total PEEP is 16 cm H_2O, and the set PEEP is 5 cm H_2O, which means the auto-PEEP is 11 cm H_2O. In the green flow waveform, inspiration is positive (above the baseline flow of zero) and expiration is negative (below the baseline flow of zero). The expiratory flow limb not returning to zero (baseline) means there is continued expiration when the next breath is delivered. This leads to dynamic hyperinflation and air trapping.

settings discussed earlier. Although it is often difficult to completely exclude a cardiogenic source of bilateral infiltrates and all patients at risk will not develop acute respiratory distress syndrome, this approach of limiting tidal volume can provide benefit.[6]

The mainstays of suspected acute respiratory distress syndrome treatment are low tidal volume ventilation, adequate PEEP, and treatment of the underlying condition (**Figure 29B-5**). If the plateau pressure is above 30 cm H_2O, the tidal volume should be incrementally decreased by 1 mL/kg to as low as 4 mL/kg. These protective lower tidal volumes may lead to hypercapnia and acidemia, although a pH of >7.20 is usually well tolerated. Most patients with restrictive lung physiology tolerate a respiratory rate of 30 to 35 breaths/min without air trapping.[5] As noted earlier, avoid hyperoxia; do not routinely seek a saturation of 98% to 100% in most patients.[11,12] In acute respiratory distress syndrome, many seek an oxygen saturation of 88% to 95% or partial pressure of arterial oxygen of 55 to 80 mm Hg.[3]

Setting appropriate PEEP aids by improving oxygenation through recruiting additional lung, increasing the surface area for gas exchange, and preventing atelectrauma. Titrate PEEP based on the PEEP/F_{IO_2} tables in Table 29B-2.[3]

In those with refractory hypoxemia and criteria for severe ARDS, other options include neuromuscular blockade, prone positioning, pulmonary vasodilators, or transfer to an extracorporeal membrane oxygenation–capable center.[22-25]

Trauma patients are at risk for either lung injury by direct trauma to the chest or secondary lung injury from systemic inflammation. Use the same principles noted earlier, targeting normoxia and maintaining plateau pressure <30 cm H_2O and adequate PEEP.[26] In traumatic brain injury, the current goal is normoxia and normocapnia with a goal partial pressure of carbon dioxide of 35 to 45 mm Hg while reserving hyperventilation for a temporizing therapy in those with an increased intracranial pressure.[27]

VENTILATOR CARE BUNDLE

Implement a ventilator care bundle in every intubated patient as soon as possible. This includes routine measurement of patient height to determine appropriate tidal volume for ventilation, elevating the head of bed to at least 30 degrees, decompressing the GI tract, and oral care with a chlorhexidine solution every 2 hours (**Figure 29B-6**).[4,28] Although many recommend stress ulcer prophylaxis with a proton pump inhibitor or a H_2 blocker, the overall effect on mortality and morbidity, including ventilator-associated pneumonia, gut infection, and bleeding, is uncertain.[29]

Reassess intubated patients after initial neuromuscular blockade has worn off to assess adequacy of sedation, decrease the F_{IO_2} quickly to avoid hyperoxia, check an arterial blood gas, and adjust ventilatory strategy to meet the patient's needs. Start a venous thromboembolism prophylaxis approach, and think early about sedation holidays and spontaneous breathing trials in patients expected to be housed in the ED for ≥24 hours.

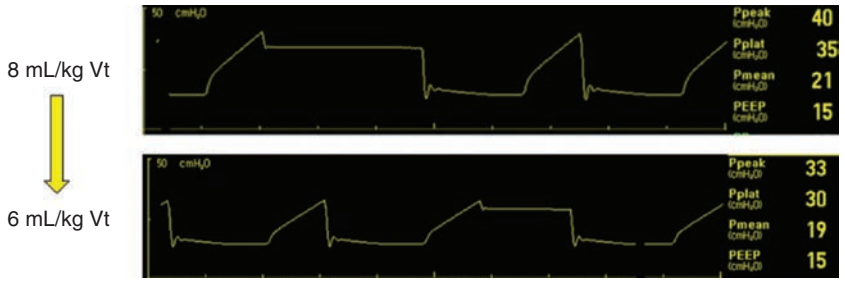

FIGURE 29B-5. Pressure waveform of a patient with low lung compliance (i.e., acute respiratory distress syndrome). Decreasing the tidal volume is one method to decrease the plateau pressure. In the top waveform, the tidal volume is 8 mL/kg ideal body weight and the plateau is 35 cm H_2O. In the bottom waveform, the tidal volume is 6 mL/kg ideal body weight and the plateau is 30 cm H_2O.

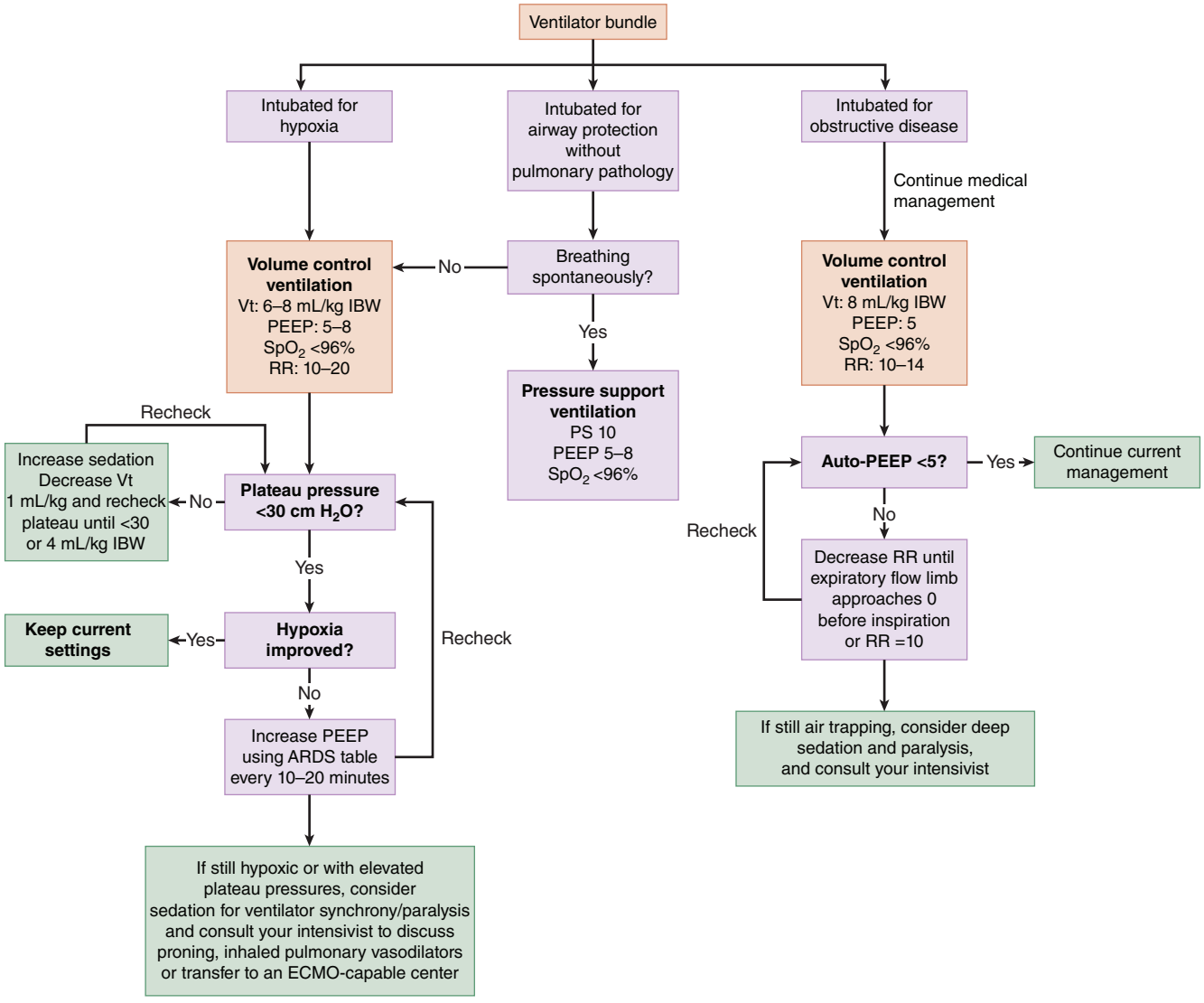

FIGURE 29B-6.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 30

Surgical Airways

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INTRODUCTION

Establishing a surgical airway by front-of-neck access is an indicated intervention in patients who cannot be intubated via the oral or nasal routes and also when faced with a cannot intubate–cannot oxygenate scenario. With the many devices available to improve laryngoscopy, offer oxygenation, or allow a supraglottic path for respiration, emergent surgical airways are rarely performed. When needed, absence of knowledge or preparation can lead to delays in performing this lifesaving procedure. The key is preparation and repetition through use or training in a laboratory setting.[1,2]

Surgical cricothyrotomy uses the cricothyroid membrane (CTM) as an insertion route, inserting a tracheal tube either directly through an incision or by using the Seldinger technique after puncture. Percutaneous transtracheal jet ventilation/oxygenation is an alternative to surgical airway establishment whereby a 12- to 16-gauge catheter is inserted into the trachea through the CTM and connected to a high-pressure (35 to 50 psi) oxygen source for both oxygenation and ventilation.

PATIENT SELECTION

The primary indication for surgical airway placement is a cannot intubate–cannot oxygenate scenario, often following failed attempts to establish an oral/nasal endotracheal airway. Cricothyrotomy and jet ventilation can be used before laryngoscopy and direct glottic intubation if the latter is likely to fail because of anatomic distortion or any other cause that impedes visualization, notably blood, secretions, vomitus, swelling, or foreign matter. Attempting tracheal intubation prior to cricothyrotomy may increase the risk of harm to the patient by delaying oxygenation or increasing the risk of failure of a surgical airway. If standard intubation seems unlikely to succeed, it is not always necessary to attempt it prior to establishing a surgical airway.

Many things, often combined, add to difficulty of establishing a traditional endotracheal airway; the **LEMON** acronym helps organize those factors (**Table 30-1**). In addition, trauma can distort the neck anatomy by hematoma (e.g., cervical fracture, major vessel injury), create aspiration of blood or active oropharyngeal bleeding (facial trauma), or lessen the integrity of supporting structures (e.g., mandible fracture, LeForte fractures). Look for these features and have a preplanned difficult airway algorithm to include surgical airway to mitigate impending or actual respiratory failure. Often, predicting difficult laryngoscopy in the emergency setting is unreliable.[3,4] Clinical signs and symptoms of airway obstruction—one common reason to perform a surgical airway—are listed in **Table 30-2**.

Pregnant patients, specifically at or near term, are at increased risk of regurgitating gastric contents secondary to reduced lower esophageal sphincter tone, will desaturate faster by virtue of having a decreased functional reserve capacity (reduced by 20% near term), will have edematous tissues secondary to increased total body water and decreased oncotic pressure, and may be malpositioned for ideal intubation if lying in a lateral tilt.[5] Children are another special population with limited surgical options, especially when younger than 12 years old.

TABLE 30-1 LEMON Airway Assessment Method

L	Look externally (facial trauma, large incisors, beard, large tongue)
E	Evaluate the 3-3-2 rule • Incisor opening distance: 3 fingerbreadths • Hyoid-mental distance: 3 fingerbreadths • Thyroid-to-mouth distance: 2 fingerbreadths
M	Mallampati score ≥3
O	Obstruction: Presence of condition such as epiglottitis, peritonsillar abscess, or trauma
N	Neck mobility (limited neck mobility)

TABLE 30-2 Clinical Manifestations Associated With Acute Airway Obstruction

Etiology	Manifestation
Vascular	Hematoma External hemorrhage Hypotension Hemoptysis
Laryngotracheal	Stridor Subcutaneous air (massive) Hoarseness Dysphonia Hemoptysis
Pharyngeal and/or hypopharyngeal	Subcutaneous air Hematemesis Dysphagia Sucking wound

PATIENT AGE

Inserting any airway into the trachea in children under age 12 years has specific challenges, including a shorter neck, more relative soft tissue, more compressible proximal airway structures, and less distinctive thyroid and cricoid cartilages. Hyperextension of the neck to increase the sagittal length of the CTM may mitigate some of these factors. Cricothyrotomy is more challenging in children, leading to increased risk of laryngeal and tracheal injuries.[6-8] **Due to these complications, tracheotomy is preferred in children under 12 years old, particularly those under age 8.** Because few emergency physicians are skilled in this technique due to the uncommon need for an emergency physician to perform the procedure in a pediatric patient, we will discuss alternatives for when an experienced pediatric airway surgeon is not available to assist.

The American Heart Association and others recommend attempting percutaneous transtracheal jet ventilation first, with surgical cricothyrotomy as a second-line option.[6-9] Despite this recommendation, data supporting any one approach in children over another are limited and conflicting.[7-10] We believe **the key to successful rescue airway placement in children is advance planning and training for this specific scenario.**

INJURIES REQUIRING CRICOTHYROTOMY

Trauma is a common reason to consider a surgical airway. Penetrating trauma to the neck affecting a major artery (carotid, vertebral, or thyroid) may create an expanding hematoma and obstruct the airway. If free blood spills into the oro- or hypopharynx, direct visualization for intubation is often not possible. Placing a cuffed tracheostomy tube after cricothyrotomy is the best option to restore gas exchange and limit aspiration. Difficulty in establishing an airway occurs in approximately 10% of patients with penetrating cervical trauma.[11]

Blunt trauma to the neck or face may cause hemorrhage of the soft tissues or injury to the trachea/larynx, including rupture. **If the trachea or larynx is disrupted, *do not* attempt cricothyrotomy**; in this rare setting, an emergency tracheostomy is needed. In blunt facial trauma, the principal cause of death is airway obstruction from bleeding (often from fractures) or soft tissue swelling; a surgical airway can prevent death and harm if deployed quickly and with skill.



FIGURE 30-1. Tracheostomy tube with obturator. [Photo used with permission of David Effron, MD.]

TYPE OF EMERGENCY AIRWAY AND TUBE SELECTION

Cricothyrotomy is preferred over percutaneous approaches (except for children <12 years old). The most skilled provider should perform this procedure to optimize success and limit harm.

Although any large-bore tube is adequate, we suggest using a **tracheostomy tube** because it has an obturator to ease insertion, is shorter and easier to suction, and is easier to secure (**Figure 30-1**). Endotracheal tubes placed during cricothyrotomy may be inadvertently directed cephalad or advanced too deeply and are more difficult to secure. To avoid endotracheal tube malposition, many use a gum elastic bougie to ensure tracheal placement and the correct tube direction.[12] If a standard endotracheal tube is used, many prefer to change later to a tracheostomy tube. Use a gum bougie or endotracheal tube stylet as an obturator for endotracheal tube removal and tracheostomy tube insertion.

The diameter of the tube inserted is crucial. A common choice for an adult is a **6-mm tracheostomy or 5- to 6-mm endotracheal tube**. **Do not choose a larger (≥7 mm) tube or one smaller than 4 mm, the latter excepted in pediatric patients.** Larger tubes are difficult to insert in the narrow space between the cricoid and thyroid cartilages. If airway pressures are high with the small-diameter tube or if ventilation is inadequate, consider changing to a larger diameter tube using a tube exchange device or bougie. Ventilation problems in adults may occur when a smaller tube is used (3-mm internal diameter or less). Any tube with a 4- or 5-mm or larger internal diameter will allow adequate volume ventilation in most patients, although at 4 mm, there is limited area for suctioning and aggressive minute ventilation. For these reasons, select a 4- to 5-mm size only if a 6-mm tube is unavailable or cannot be placed.

SURGICAL (OPEN) CRICOTHYROTOMY

ANATOMY

The CTM is located between the thyroid and cricoid cartilages (**Figure 30-2A**). Both structures are easily palpated but are not directly seen because they are covered with the pretracheal fascia. In men, the thyroid cartilage is prominent and creates the "Adam's apple"; in women and children, the thyroid and cricoid cartilages can be hard to distinguish from each other.

The CTM is found approximately one third of the distance from the manubrium to the chin in the midline in patients with normal habitus

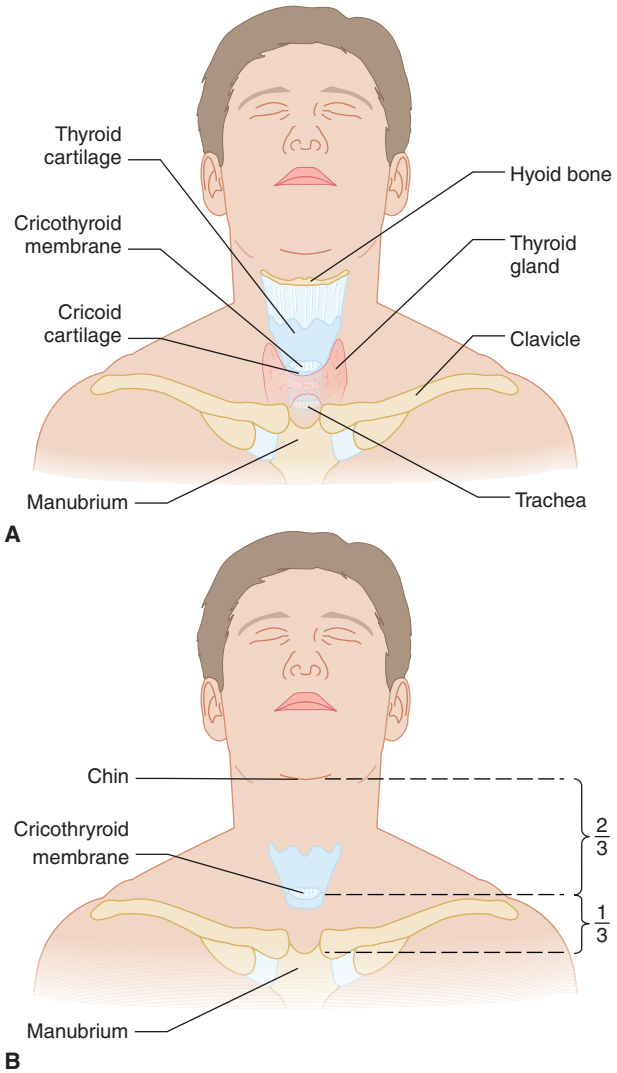


FIGURE 30-2. **A.** Neck anatomy. **B.** Location of the cricothyroid membrane.

(**Figure 30-2B**). In a patient with a short, obese neck, the membrane may be hidden at the level of the manubrium. In a patient with a thin, long neck, it may be midway between the chin and the manubrium. The thyroid gland overlies the trachea; both structures are difficult to palpate. One easy way to find the cricoid membrane is to slowly palpate the trachea as you move up toward the head from the sternal notch; when your fingers "fall off" after a firm structure, you have palpated the thyroid cartilage. Next, slowly palpate back toward the feet, and the first "soft spot" after that thyroid cartilage is the cricoid membrane. Additionally, a very rough approximation of where to find the CTM should landmarks be skewed is to take your outstretched four fingers held together and place your fifth finger on the superior aspect of the manubrium. With the rest of your fingers directed cephalad, the most superior aspect of the index finger is roughly juxtaposed to the CTM.

The vascular structure often injured during cricothyrotomy is the thyroidea ima artery, a branch of the aorta running up to the thyroid gland in the midline. This vessel infrequently reaches the level of the CTM. A carotid injury usually results from attempts using poor landmarks (either indistinct or not carefully sought) or when technique is poor. The first step after recognizing any vascular injury during cricothyrotomy is immediate direct pressure to stop the bleeding and avoid catastrophe.

EQUIPMENT

The equipment needed to perform a surgical cricothyrotomy is listed in **Table 30-3**.

TABLE 30-3 Equipment Needed to Perform a Surgical Cricothyrotomy

- Personal protective equipment
- Scalpel with a #10 (preferable because of its greater width) or #11 blade
- A 6-mm endotracheal tube or tracheostomy tube (latter preferred), plus a smaller one available
- Tape to secure the tube in place
- Cloth ribbon and sutures to secure tracheostomy tube in place
- Bag-valve-mask device and oxygen source
- Gum elastic bougie for guiding tube
- Suction devices

PATIENT PREPARATION AND POSITIONING

Place the patient supine, with the neck slightly hyperextended if no cervical trauma is present (neutral if there is suspected trauma); this optimizes neck structure palpation and recognition. If time permits, apply antiseptic solution to the skin. Ventilate with a bag-valve mask connected to 100% oxygen while preparing. For the patient in extremis, do not delay initiating the procedure to achieve any of these preparations.

PROCEDURE

The procedure summary for performing a surgical cricothyrotomy is provided in **Table 30-4**. (See Video: Cricothyrotomy.)

TABLE 30-4 Performing a Surgical Cricothyrotomy

Step	Comment
1. Stand to one side of the patient at the level of the neck.	Right-handed practitioner—stand on the patient's right side. Left-handed practitioner—stand on the patient's left side.
2. Locate the cricothyroid membrane.	Locate the cricoid ring. Place the index finger at the sternal notch and palpate cephalad until the first rigid structure is felt (cricoid ring). Roll the index finger one fingerbreadth above to locate the membrane between the cricoid and thyroid cartilages (**Figure 30-3**).
3. Using the thumb and middle finger of the nondominant hand, stabilize the two cartilages.	Once the two cartilages are secured in between the thumb and middle finger, this hand should not move until the entire procedure is finished.
4. Use the scalpel to make a vertical incision in the midline between the two cartilages, extending if needed.	Incise through the skin and subcutaneous tissues. The structures are superficial, so do not incise deep to avoid damage to the cricoid or thyroid cartilage or vascular structures (**Figure 30-4**). The membrane is felt, not directly seen, after incision.
5. With the scalpel blade positioned horizontally, perforate the cricothyroid membrane so that the blade goes in approximately half its length.	The horizontal orientation is in anatomic alignment with the membranes to avoid vascular injury (**Figure 30-5**). **Once the membrane is perforated, do not leave it empty**; slide forceps, dilator, or tracheal hook around the blade or place a bougie before removing the scalpel. In addition, the index finger of the securing hand can be inserted into the space to mark position.
6. Widen the incision opening.	A dilator or mosquito or Kelly clamp may be used (**Figure 30-6**).
7. Place the tube in the opening.	Although instinct may guide you to direct the tracheostomy tube posterior, remember that the trachea is superficial and the tube should follow the tracheal axis (**Figure 30-7**).
8. Connect to a bag-valve-mask device for ventilation. Check for breath sounds with ventilation.	If no ventilation is heard bilaterally, pull the tube out and reinsert it. Recheck for breath sounds to ensure that the endotracheal tube is correctly positioned after any manipulation. When inserting a standard endotracheal tube, listen for asymmetry of breath sounds. If breath sounds are absent on the left side, then the tube has been inserted down the right mainstem bronchus and needs to be pulled back a few centimeters. If using an endotracheal tube, insert no more than 2–3 cm to avoid mainstem bronchus placement.
9. Secure the tube carefully with a ribbon and/or adhesive tape.	More challenging with a standard endotracheal tube.
10. Apply dressing and further secure the tube.	If a tracheostomy tube has been used, fashion a simple dressing by cutting a slit halfway down the middle of a 4×4 gauze dressing and placing it under the tracheostomy tube. Secure the tube with a ribbon placed through the flanges of the tracheostomy tube. For added security, use 2-0 nylon sutures to fix the tube to the skin. Consider changing endotracheal tubes to tracheostomy tubes whenever possible.



FIGURE 30-3. Locate the cricothyroid membrane. [Photo used with permission of Jennifer McBride, PhD, and Michael D. Smith, MD.]



FIGURE 30-6. Widen the opening. [Photo used with permission of Jennifer McBride, PhD, and Michael Phelan, MD.]



FIGURE 30-4. Make a midline vertical incision. The pretracheal fascia is seen through the incision. Bleeding is less likely with a vertical incision. [Photo used with permission of Jennifer McBride, PhD, and Michael Phelan, MD.]

SURGICAL CRICOTHYROTOMY USING SELDINGER TECHNIQUE

This method (**Figure 30-8**) uses a kit most often and starts with a small vertical incision through the skin at the CTM. Next, insert the needle at a 30- to 45-degree angle pointing to the feet and aspirate air to make sure the needle is in the trachea. Once air aspiration is free, pass the guidewire through the needle, directing the guidewire caudally (toward the feet). Place a tracheostomy tube over the dilator, and make another "nick" in the skin to ease penetration. Pass the dilator, with the tracheostomy tube, over the guidewire into the trachea. Once the dilator is in the trachea, remove the guidewire, direct the tracheostomy tube into the trachea, and verify correct placement. Indications and complications are similar to the open method. Multiple different commercial kits exist, but proper use depends more on deliberate, repetitive training. (See Video: Needle Cricothyrotomy.)

COMPLICATIONS

Acute complications after emergency cricothyrotomy occur in up to 15% of cases.[13] Venous bleeding usually occurs from small veins and stops spontaneously. Arterial bleeding can be from the thyroidea ima



FIGURE 30-5. Perforate the cricoid membrane with a horizontal incision. [Photo used with permission of Jennifer McBride, PhD, and Michael Phelan, MD.]



FIGURE 30-7. Insert a tracheostomy tube with obturator. [Photo used with permission of Jennifer McBride, PhD, and Michael Phelan, MD.]



FIGURE 30-8. Placement of a percutaneous cricothyrotomy with a commercial kit and the Seldinger technique. [Photo used with permission of David Effron, MD.]

artery or from a small artery at the base of the CTM. The first step in controlling ongoing bleeding is to apply pressure. If bleeding persists, topical hemostatic agents or ligation may help stop it. A small amount of bleeding usually creates no hemodynamic concerns, but it can make the procedure more challenging.

In an obese patient, it is possible to place the tube anterior to the larynx and trachea into the mediastinum (false passage), making ventilation impossible. Signs of an incorrectly positioned tube are high airway pressures, absent breath sounds, and massive subcutaneous emphysema. If suspected, remove the tube and make a second attempt at insertion. Surgical consultation is recommended quickly as revision can be even more challenging than the initial approach.[12]

Laceration of the trachea, esophagus, or recurrent laryngeal nerves is rare and often occurs when the procedure is performed by someone unfamiliar with the neck anatomy. Pneumothorax is usually secondary to barotrauma caused by ventilation initiated immediately after tube placement.

A tube left in the narrow space between the cricoid and thyroid cartilages can erode both cartilages over time, and bacterial chondritis may occur. The cartilages degrade and scar, leading to stenosis and loss of the function of the larynx. Because cricothyrotomy has a high incidence of airway stenosis,[13] a change to tracheotomy is common after 2 to 3 days. In addition, if using an endotracheal tube, right mainstem intubation is common after a surgical airway given the relatively longer tube length. The key when using a standard endotracheal tube is to only insert deep enough to inflate the balloon within the trachea and achieve a seal; then, careful auscultation of breath sounds, assessment of carbon dioxide in expelled gas, and confirmation of placement above the carina follow.

PERCUTANEOUS CRICOTHYROTOMY AND TRANSTRACHEAL JET INSUFFLATION

If percutaneous access is pursued by "needle cricothyrotomy"—a poor but common term that is defined as a 12- to 16-gauge needle catheter inserted into the trachea—the catheter must be attached to a higher-pressure oxygen source (≥35 psi); it cannot simply be attached to a standard wall oxygen outlet and be turned up or to wide open. Attachment of a 12- to 16-gauge catheter directly to a wall oxygen source or bag-valve mask **will not** reverse ventilation gaps and may only modestly aid oxygen delivery.[14-16]

The proper equipment for jet ventilation must exist and be maintained, and the procedure requires practice, just like other surgical interventions.[9] **Do not perform jet ventilation without the correct equipment ready in advance and without antecedent practice;** one cannot simply "put this together" at the time of critical need.

Jet ventilation uses a small catheter attached to either a pressure regulator attached directly to a wall oxygen source or cylinder via pressure tubing. Jet ventilation can also be done using the VBM Manujet III or a commercial oxygen insufflator attached to high-flow oxygen (≥15 L or greater), such as the ENK® Oxygen Flow Modulator or the Rapid O_2 Insufflator® (**Figure 30-9**).[9] Set the oxygen pressure at 35 to 50 psi; if setting pressure for a small adult or child, use 0.5 psi/kg body mass and observe. In jet ventilation, the catheter and high-pressure gas provide volume for inhalation, and the native airway is the *passive* exhalation route. **With proper jet ventilation, adequate oxygenation and ventilation occur.**[10] Duration is limited only by airway desiccation from nonhumidified gas, an effect that takes hours to a day to occur. **Properly performed jet ventilation does not create hypercarbia** or the need for rapid reestablishment of another airway; only poorly performed or "needle cricothyrotomy" low-pressure techniques create those situations.

ANATOMY, INDICATIONS, AND CONTRAINDICATIONS

Anatomy and general indications were described earlier in this chapter. The only absolute contraindication is complete airway obstruction (i.e., expiration is blocked); this is exceptionally rare because most upper airway obstruction is inspiratory, including obstruction from masses. Relative contraindications are unfamiliarity, not having the equipment ready, and local infection at puncture site.

EQUIPMENT NEEDED

Equipment needed for transtracheal jet ventilation is listed in **Table 30-5**. **Do not try to use standard oxygen tubing, three-way stopcocks, or bag-valve devices or attach to wall outlets turned to highest liter flow**.

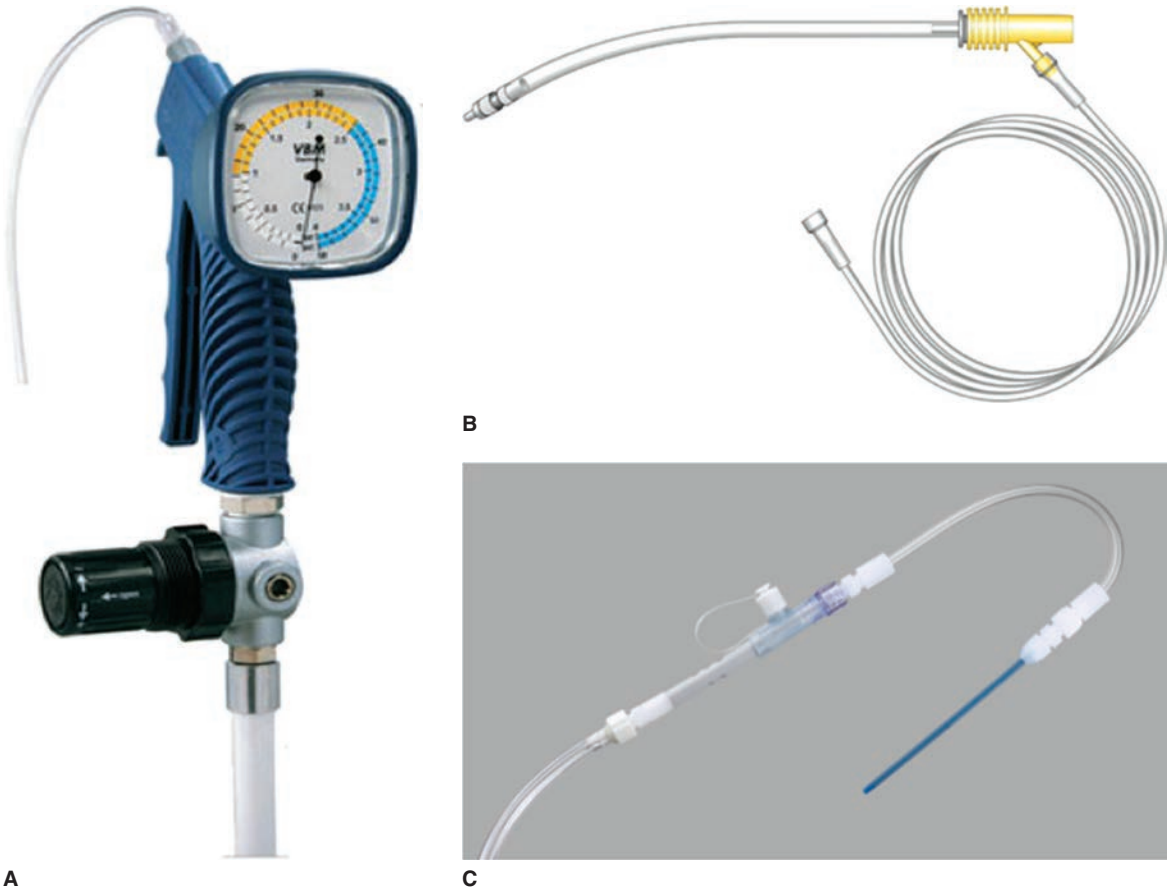


FIGURE 30-9. **A.** VBM Manujet III. [Photo cropped from https://www.vbm-medical.com/products/airway-management/manujet-iii-jet-ventilation-catheters/. Used with permission from VBM Medical, Inc., Noblesville, IN.] **B.** Meditech Rapid-02. [Photo from http://www.diathermy.net/index.php/product/rapid-02/. Meditech Systems Limited, unit 3 Shrublands, shearstock, Shaftesbury Dorset SP79PT UK.] **C.** Cook Medical ENK Oxygen Flow Modulator Set. [Photo from https://www.cookmedical.com/products/cc_efms_webds/. Permission for use granted by Cook Medical, Bloomington, Indiana, not available in U.S.]

PROCEDURE

The steps of performing jet ventilation are listed in **Table 30-6**. Optimize preprocedural oxygenation and ventilation when possible (although often failure is the reason for the procedure).

COMPLICATIONS

Damage to the trachea during insertion may occur, including perforation of the lateral or posterior wall, particularly in children.[8,17] Failure to secure the catheter can lead to displacement. Bleeding at the puncture site and infection may occur. Massive subcutaneous emphysema can develop during ventilation, especially if the catheter is improperly inserted or misplaced in the soft tissues of the neck. Finally, delivery of excessive ventilatory force is associated with barotrauma, and equipment used in jet ventilation requires constant surveillance of chest rise and appropriate exhalation.[16] Even if the cricoid membrane is not used (from misidentification), jet punctures rarely cause long-term airway complications, which is an advantage over cricothyrotomy.

DEVICE REMOVAL

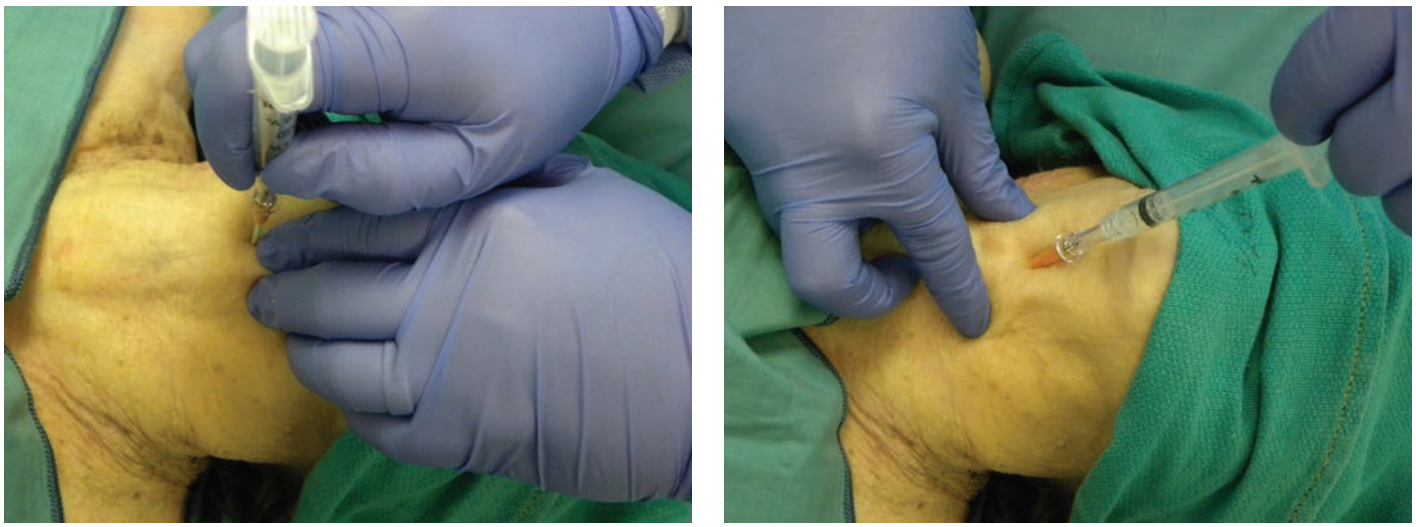
Jet ventilation allows a more controlled approach to airway management; one can plan the next step(s) carefully and without fear of ventilation failure if done properly, avoiding any rush to another procedure. Often, a better laryngoscopic attempt or a formal tracheostomy can occur once time pressures are abated with jet ventilation.

TABLE 30-5 Equipment Needed to Perform Jet Ventilation

- Personal protective equipment
- A 16-gauge or larger sheathed needle catheter or a commercial jet catheter
- A 3-mL syringe
- Connective tubing and connectors designed for high pressure (not standard oxygen tubing/securing attachments; these will not allow jet ventilation)
- High-flow regulator with insufflation control
- A high-pressure oxygen source; your respiratory technician can have the jet insufflator attached to an E cylinder or wall unit before downregulation to ensure high-pressure (35–50 psi) gas

TABLE 30-6 Performing Jet Ventilation

Step	Comment
1. Stand to one side of the patient at the level of the neck.	Right-handed practitioner—stand on the patient's right side. Left-handed practitioner—stand on the patient's left side.
2. Locate the cricothyroid membrane.	Locate the cricoid ring. Place the index finger at the sternal notch and palpate cephalad until the first rigid structure is felt (cricoid ring). Roll the index finger one fingerbreadth above to locate the "hollow" between the cricoid and thyroid cartilages, locating the cricothyroid membrane (Figure 30-3).
3. Attach a 3-mL syringe to the catheter.	Smaller catheters tend to kink easily, as noted in photos, and limit gas flow. Use of a 16-gauge or larger commercial catheter is preferred (commonly a 13-gauge device).
4. Introduce the catheter into the subcutaneous tissue at a 45-degree angle to the skin, aiming toward the patient's feet.	**Figure 30-10.**
5. Aspirate gently while advancing the catheter over the needle.	
6. When air suddenly returns (indicating entry into the airway), advance the catheter over the needle into the larynx.	Free air aspiration = intratracheal placement; any resistance means not clearly in trachea.
7. Once fully inserted, remove the needle and reaspirate to ensure ongoing free air aspiration.	If resistance to air aspiration occurs after advancement, remove catheter and retry. **Once the catheter is fully inserted, a stabilizing hand *must* always be present**; do not ever let the proximal end be unsecured.
8. Attach the high-flow regulator via connective tubing to the catheter and start ventilation with a 100% oxygen source. If a child, use 0.5 psi/kg to start and a 16-gauge catheter.	Connect to a high-pressure source (35–50 psi); bag-valve devices and **standard wall oxygen valves opened to 15 L/min do *not* deliver 35–50 psi**. The jet device is attached directly to wall unit before standard regulators or directly to E cylinder (latter will allow >30 min of ventilation if full). Insufflate by holding valve down (open) for maximum of 1 s, and then release the occlusion for 4 s. Listen for symmetric breath sounds, watch the chest rise and fall, and measure exhaled carbon dioxide if desired.
9. Hold the catheter securely to avoid dislodgement. The catheter tends to kink easily, so maintain care with positioning.	An inspiration:expiration ratio of 1:4 allows passive exhalation and avoids overventilation. Monitor like any volume ventilation technique.
10. Stabilization is similar to cricothyrotomy, and plan for next airway; gas exchange will be adequate for a prolonged interval, allowing a careful and controlled approach.	Dressings are not necessary, and commercial kits have straps like tracheostomy tubes. The exhaled gas offers some aspiration protection.



A B

FIGURE 30-10. Introduce the catheter into the larynx. **A.** Introduce the catheter into the larynx skin at a 90-degree angle to the skin. **B.** When air returns, change the angle to 45 degrees. [Photo used with permission of Jennifer McBride, PhD, and Michael D. Smith, MD.]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 31

Vascular Access

Chris Wyatt

INTRODUCTION

Multiple factors determine the route and site for vascular access, and knowing the basic anatomy, techniques, indications, and contraindications is essential.

Infusion rate is key in the resuscitation of those with severe hypovolemia or hemorrhage.[1] Flow rates increase with larger catheter radius, use of more pressure (gravity, manual push-pull devices, pressure bag application, or commercial rapid infusing devices), decreasing viscosity (coadministration of crystalloid with viscous blood products), or decreasing catheter length (peripheral angiocatheter vs. triple-lumen catheter). **Maximal flow rates occur from shorter and wide catheters, although both may be hard to achieve.**

PERIPHERAL VENOUS ACCESS AND ANATOMY

The most commonly accessed veins for peripheral catheterization of the upper extremity are in the dorsal hand and the antecubital fossa (**Figure 31-1**).

Peripheral catheterization of the superficial veins of the lower extremity is possible, sometimes overlooked, and occasionally more difficult. Avoid IV access of the lower extremity in adults, especially diabetics, due to an increased risk of infection and phlebitis. See discussion below of venous cutdown of the saphenous vein at the medial malleolus.

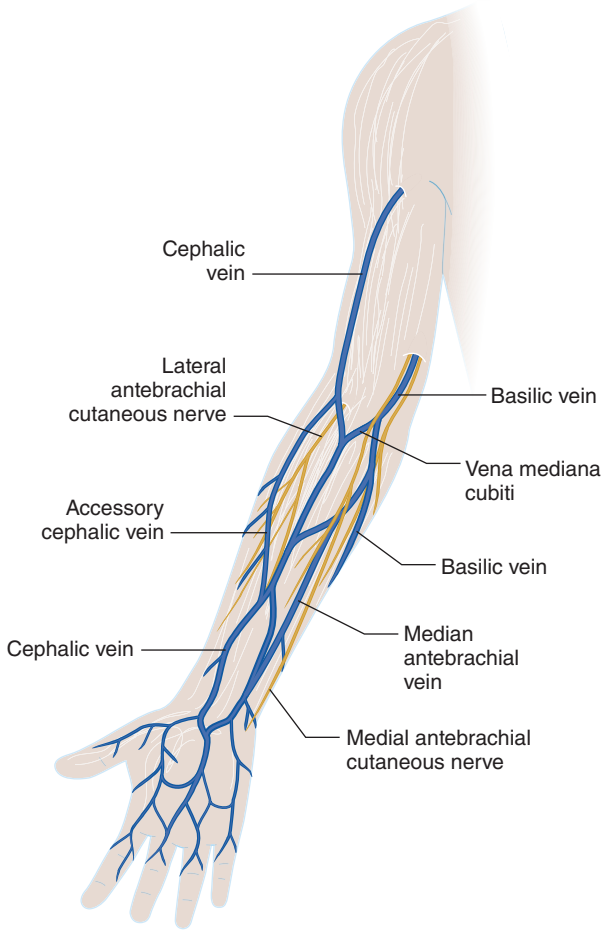


FIGURE 31-1. Venous anatomy of the upper extremity.

TABLE 31-1 Materials for Peripheral IV Line Placement

- Personal protective equipment (gloves, face shield)
- Tourniquet
- Alcohol swabs or povidone-iodine
- Appropriate-sized venous catheter
- IV solution and tubing (if indicated)
- 2 ×2 gauze
- Tape
- Sterile transparent dressing

TECHNIQUE FOR PERIPHERAL VENOUS ACCESS

Gather all equipment before beginning the procedure (**Table 31-1**). Observe universal precautions. The procedure for peripheral IV line insertion is in **Table 31-2**.

Avoid venous access through or distal to areas of infection, injuries, or sites of potential vascular disruption (e.g., injury to the inferior vena cava from abdominal trauma). Also avoid using extremities with arteriovenous fistulas or grafts and those in which there have been previous lymph node dissections. **If using peripheral access for vasopressors, make sure it is not distal and it is well secured**; otherwise, this is safe and effective for the first minutes to hours. Do not use peripheral venous access to administer infusing sclerosing solutions, concentrated electrolyte or glucose solutions, or cytotoxic chemotherapeutic agents.

TABLE 31-2 Peripheral IV Line Insertion

Step	Comment
1. Apply tourniquet.	Apply tourniquet tightly enough to facilitate adequate venous filling and distention without causing patient discomfort or ischemia.
2. Locate vein.	Inspect and palpate the vein. Warm the skin, tap the vein, or apply topical nitroglycerin ointment to ease identification.
3. Clean area with either an alcohol swab or povidone-iodine solution.	—
4. Apply gentle traction with the nondominant hand to anchor the vein.	—
5. Insert catheter needle into skin and vessel at a 15- to 30-degree angle with dominant hand.	Peripheral veins are easiest to access at the apex of the "Y" formed by merging veins or where veins are straight for several centimeters. Use a more obtuse (60-degree) angle for deeper veins.
6. Observe for blood flash in catheter hub.	This indicates successful vessel penetration.
7. Gently advance catheter into vessel lumen until the hub is flush against the skin.	See **Figure 31-2**. If you meet resistance, withdraw the catheter slightly, as it may have penetrated the posterior vessel wall.
8. Remove tourniquet.	—
9. Attach IV tubing and monitor for flow.	—
10. Secure catheter with tape and a sterile transparent dressing.	—

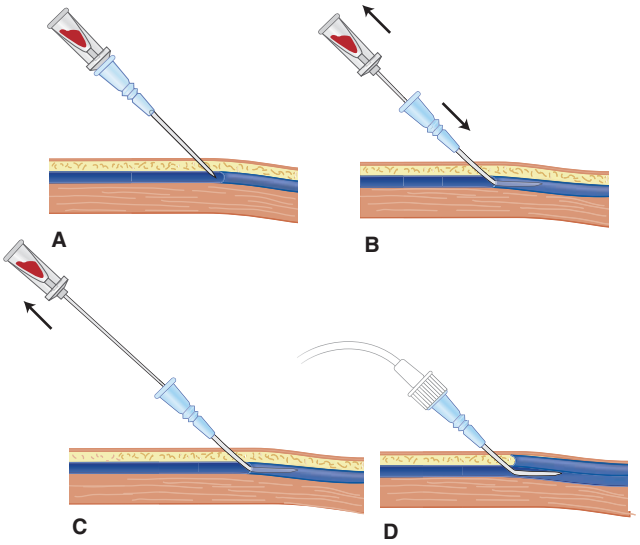


FIGURE 31-2. Catheter-over-needle technique for venous access. **A.** Catheter needle is inserted into skin and vessel until blood flash. **B.** Catheter is advanced. **C.** Needle is withdrawn. **D.** Catheter is attached to IV tubing and secured.

Flush peripheral catheters with normal saline every 8 hours, change dressings that are damp or soiled, and change the catheter site every 72 to 96 hours.[2] Risk of infection and thrombophlebitis increases with time. Assess the skin for signs of infection (erythema) or infiltration (induration, edema). Reassess catheter function and neurovascular status of the distal extremity frequently.

The complications of peripheral venous access are listed in **Table 31-3**. **The first step in treating complications is catheter removal.**

US-GUIDED PERIPHERAL ACCESS

US can localize veins with inconsistent anatomic relationships or those too deep to palpate. US-guided peripheral IV placement results in high success rates, fewer complications, and a decreased need for central vein cannulation.[5,6] The cephalic, basilic, and brachial veins, which are not readily palpable, are easily located and cannulated using US guidance. (See Video: Basilic Vein Cannulation.)

When inserting an IV using US guidance, use a high-frequency linear transducer. Vascular structures are anechoic (black) in US imaging. Key sonographic characteristics help distinguish veins from arteries: Veins are more easily compressed, have thinner walls, and have no arterial pulsation. Color flow also helps differentiate between the two types of vessels. A centimeter scale on the US monitor indicates the depth of the vessel.

To locate a vessel, view it in short axis (transverse plane) and long axis (sagittal plane), and then center the vessel on the screen. The midpoint of the screen correlates with the midpoint of the transducer. Introduce the catheter into the skin at the transducer's midpoint and direct it toward the vessel lumen. Use a longer catheter (2.5 inches or 6.4 cm) for deeper vessels. Watch the screen as the catheter enters the vessel lumen; it is best to save an image of the catheter inside the vein. Secure the catheter and apply a sterile dressing to the IV line.

TABLE 31-3 Complications of Peripheral Venous Access

Complication	Comment
Hematoma formation and pain	Prevent hematomas by removing the tourniquet before needle removal and applying direct pressure to site after removal.
Extravasation of fluids	Apply cool or warm compresses and elevate extremity. Monitor site for tissue damage and necrosis.
Phlebitis (vein inflammation)	Occurs in 2%–13% of catheterized veins.[3,4] Presents as discomfort or pain at the catheter site with warmth, erythema, and tenderness along the vein. A palpable cord may also be present. Give anti-inflammatory medications. Apply warm compresses.
Cellulitis	Infection rates with peripheral IVs are relatively low. Typical organisms include *Staphylococcus epidermidis, Staphylococcus aureus,* and *Candida.* Treat with antibiotics effective against suspected pathogens. Infection can be reduced by using sterile technique during IV placement and routine handling.
Neurovascular injury	—
Bacteremia/sepsis	—
Deep vein thrombosis	—
Tissue necrosis	—

TABLE 31-4 Indications for Central Venous Catheterization

- Inability to obtain peripheral access
- Access to central circulation needed for procedures (pulmonary artery catheter placement, transvenous pacemaker placement, or urgent hemodialysis)
- Measurement of central venous pressure (sepsis, congestive heart failure, pericardial effusion)
- Administration of sclerosing medications, continuous vasopressors, concentrated ionic solutions, or cytotoxic chemotherapeutic agents

CENTRAL VENOUS ACCESS AND ANATOMY

The indications for central venous catheterization are listed in **Table 31-4**. In cardiac arrest, the time to insert a central venous catheter creates a tradeoff in drug effectiveness if peripheral venous or intraosseous access exists.

The most frequent sites used for central venous access are the internal jugular, subclavian, and femoral veins (**Figures 31-3** and **31-4**). The external jugular vein, a superficial structure, also provides a route to the central circulation but is technically a peripheral site. Femoral vein cannulation is discussed separately below.

The clavicles, first ribs, sternum, sternocleidomastoid, platysma, and other strap muscles of the neck overlie the internal jugular and subclavian veins (Figure 31-3). The internal jugular vein lies lateral to the

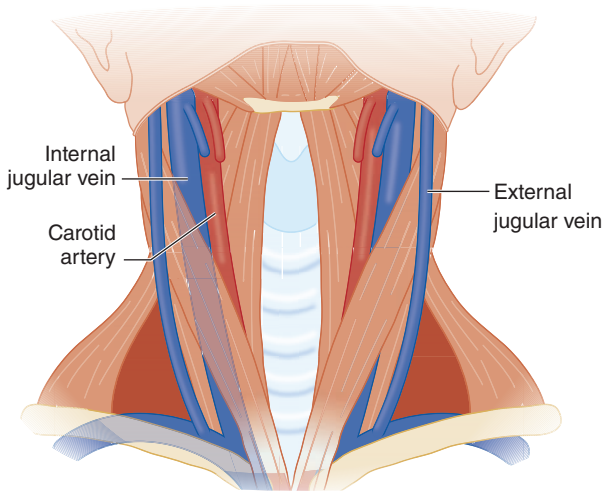


FIGURE 31-3. Vascular anatomy of the neck.

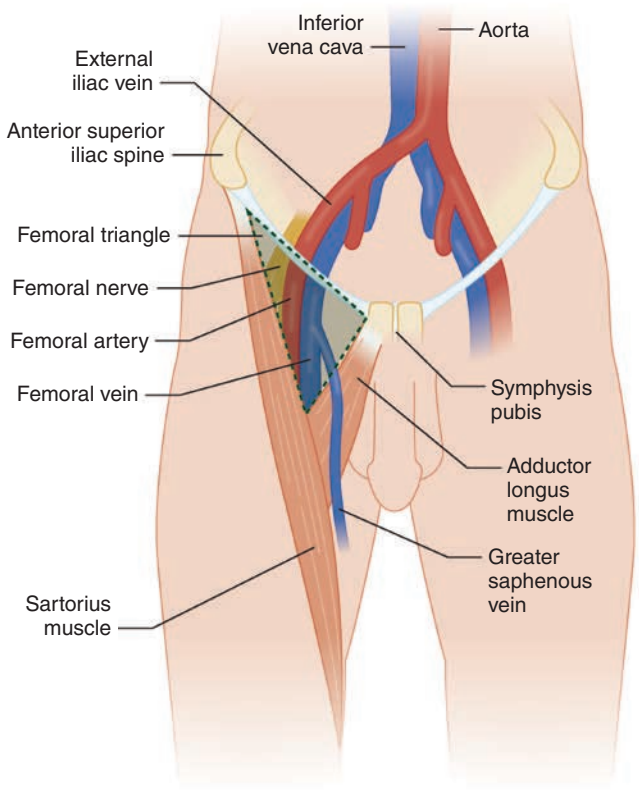


FIGURE 31-4. Vascular anatomy of the torso and lower extremities.

internal carotid artery inside the carotid sheath. The internal jugular vein joins the subclavian vein to form the brachiocephalic vein.

The subclavian vein crosses under the clavicle at the medial to proximal third of the clavicle. The subclavian artery lies posterior and superior to the brachiocephalic vein. The thoracic duct joins the left subclavian vein at its junction with the left internal jugular vein. The domes of the pleura lie posterior and inferior to the subclavian veins and medial to the anterior scalene muscles.

US TECHNIQUE FOR CENTRAL VENOUS ACCESS

US-guided central venous access increases first attempt success rates and decreases the number of attempts needed for success when compared to the unassisted standard method. The technique of US-guided central venous access is similar to peripheral venous access described previously.

Complications of central venous catheterization are listed in **Table 31-5.**

Complication rates increase with each additional attempt or percutaneous puncture. Femoral lines have the highest rate of infection, and they thrombose (nearly 20% each in some studies); for these reasons, many avoid this site for longer use. Do not use the subclavian approach in patients with coagulopathy because accidental arterial puncture or injury is not amenable to direct vascular compression.

TABLE 31-5 Complications of Central Venous Catheterization

- Pneumothorax
- Arterial puncture
- Malpositioning
- Catheter-associated infection
- Thrombosis
- Chylothorax (injury to the thoracic duct on left-sided attempts)
- Hydrothorax/hydromediastinum (infusion into the pleural space)
- Air emboli
- Great vessel or right atrial perforation (hemothorax, tamponade)
- Airway compromise (tracheal injury, hematoma with airway compression)

TABLE 31-6 Materials for Central Venous Catheterization

- Sterile personal protective gear (gloves, gown, mask, hair cover)
- Sterile drape and towels
- Sterile prep solution (povidone-iodine or chlorhexidine)
- 3 × 10-mL syringes containing sterile normal saline flush
- Central venous catheter set containing:
  - 1% lidocaine, small-gauge needle, and syringe
  - 18-gauge introducer needle
  - Guidewire
  - #11 blade scalpel
  - Venodilator
  - Single- or multilumen catheter
  - 4 × 4 gauze pads
  - 3-0 or 4-0 silk suture with straight needle or with needle driver
  - Sterile transparent dressing

After gaining consent when possible, identify the access site and approach and position the patient. Prepare all materials before the procedure (**Table 31-6**). Use a procedure checklist to optimize infection prevention practices. The techniques for all approaches are summarized in **Table 31-7** and **Table 31-8** and depicted in **Figure 31-5**.

EXTERNAL JUGULAR VEIN

The external jugular vein is readily available due to its superficial location in the subcutaneous tissue overlying the sternocleidomastoid muscle. Place the patient in the head-down position or use Valsalva maneuvers to distend the vein and improve visualization. Puncture the skin at a 10-degree angle. Placement is aided by tilting the head to the contralateral side and applying skin traction to "straighten" the course of the vein.

INTERNAL JUGULAR VEIN

The internal jugular vein is easily located with US guidance. The three approaches to internal jugular vein catheterization are central, posterior, and anterior. The right internal jugular vein has a shorter, straighter course to the superior vena cava and avoids injury to the thoracic duct on the left; use this site unless contraindications exist. See **Table 31-9** for a summary of approaches to internal jugular vein catheterization. (See Video: Internal Jugular Vein Cannulation.)

TABLE 31-7 Preprocedure Checklist for Central Line Access

Before the procedure, did the provider:

- Perform a time out to ensure right patient, right location/side?
- Cleanse hands immediately prior?
- Sterilize procedure site and allow site to dry?
  - 30 s for dry site
  - 2 min for moist site (femoral)
  - Drape the patient from head to toe with a large sterile drape?

During the procedure:

- Did the provider wear sterile gloves, cap, mask, and gown?
- Did assisting physician(s) follow the above precautions?
- Did the provider maintain sterility of tray, site, field, and gloves at all times?
- Did ALL staff in room wear a mask?
- Was unnecessary traffic in and out of the room prevented during the procedure (did the door remain closed)?

After the procedure, did the provider:

- Apply a dated sterile dressing?

TABLE 31-8 Seldinger Technique for Insertion of Central Venous Line

Step	Comments
1. Gown in sterile fashion.	Use sterile gloves and gown. Wear mask and hair covering.
2. Identify vessel—US guidance preferred over landmarks.	—
3. Prep and drape patient using standard sterile procedure.	Prep a wide area so an alternate site can be used if initial attempts fail. Prep the entire ipsilateral neck and upper chest when preparing to insert an internal jugular or subclavian catheter.
4. Open the central catheter kit. Inspect for content in a sterile fashion. Place kit close to bedside and operator. Maintain sterile conditions.	—
5. Anesthetize area in all conscious patients.	Inject area with 1%–2% lidocaine. Anesthetize the periosteum of the clavicle if using the subclavian approach. Reorient to landmarks after injection.
6. Hold the 18-gauge introducer needle on a 10-mL syringe in the dominant hand and align the needle to the target.	—
7. Advance the needle slowly through the skin and subcutaneous tissue until a flash of dark venous blood appears.	Maintain steady constant aspiration of syringe.
8. Stabilize the needle with the nondominant hand.	—
9. Check for continued free venous flow with aspiration.	If no flow is noted, withdraw the needle slightly, as the needle may have breached the posterior vessel wall.
10. Remove the syringe attached to the needle and immediately occlude the catheter with a finger.	This maneuver helps to prevent introducing air in the catheter and subsequent central system air embolism.
11. Insert the guidewire gently through the needle. Always maintain a firm grip on the wire—do not let go of the wire for any reason.	The wire should advance with minimal resistance. Do not force the wire for any reason. If the wire does not pass easily, reattach the syringe and aspirate to confirm continued venous flow. Reposition the needle as needed. Premature ventricular contractions or dysrhythmias during wire advancement may indicate that the wire is in the right atrium or beyond.
12. Remove the needle over the wire when the guidewire is inserted at least 10 cm into the vessel.	—
13. Incise the skin with a #11 blade scalpel at the entry site to accommodate the venodilator or catheter.	Do not cut the guidewire.
14. Advance the dilator or catheter over the guidewire into the vessel lumen with a gentle twisting motion.	—
15. Remove the dilator (if used), and advance the catheter over the wire until the wire is advanced through the distal port.	Maintain a grip on the guidewire during this procedure.
16. Grab the end of the guidewire.	—
17. Advance the catheter to the appropriate depth.	—
18. Remove the guidewire.	It is easy to "lose" the wire; if you cannot find it after a procedure, immediately obtain a radiograph to seek retention.
19. Aspirate and flush all ports to confirm catheter function.	—
20. Secure catheter with suture and apply a sterile transparent dressing.	—
21. Confirm catheter placement in the superior vena cava with chest radiograph.	A catheter tip in the right atrium can perforate the right atrium and cause hemothorax or hemomediastinum with pericardial tamponade. Examine the chest radiograph for signs of complications.

For the first step, place the probe on the sternocleidomastoid muscle (**Figure 31-6**). Identify the thyroid gland and carotid artery in addition to the internal jugular vein. Do not attempt needle insertion before visualizing all three structures.

CENTRAL APPROACH

Place the patient in the Trendelenburg position, with head slightly tilted to the contralateral side. The landmark for the central approach is the triangle created by the clavicle and the sternal and clavicular heads of the sternocleidomastoid. The internal jugular vein lies just deep to this triangle. Insert the needle at a 30- to 45-degree angle to the skin, 1 cm below the apex of the triangle, parallel to the carotid artery located medially, and directed toward the ipsilateral nipple (**Figure 31-7**). Successful venous return typically occurs within 1 to 3 cm of needle advancement.

POSTERIOR APPROACH

The landmark for the posterior approach is the lateral aspect of the clavicular portion of the sternocleidomastoid, one third of the distance from the clavicle to the mastoid process. Direct the needle toward the sternal notch (**Figure 31-8**). Successful venous return typically occurs within 3 to 5 cm of needle advancement.

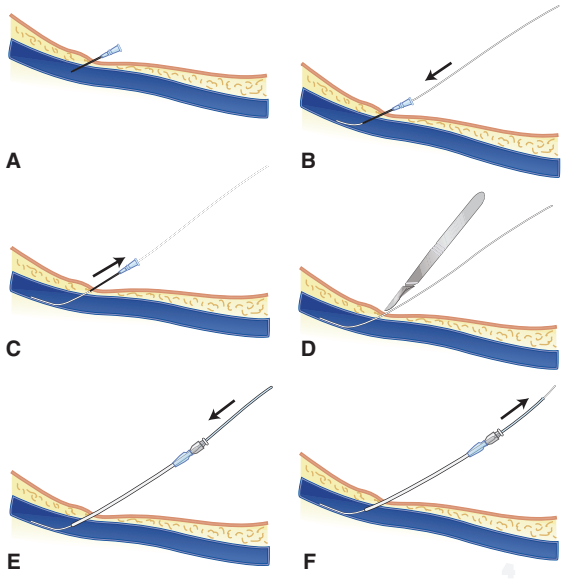


FIGURE 31-5. Seldinger technique. **A.** Needle is inserted through skin and vessel until venous blood is aspirated. **B.** Guidewire is inserted gently through the needle and advanced. **C.** Needle is removed over guidewire. **D.** The skin is incised. **E.** Dilator or catheter is inserted over the guidewire. **F.** The guidewire is removed.

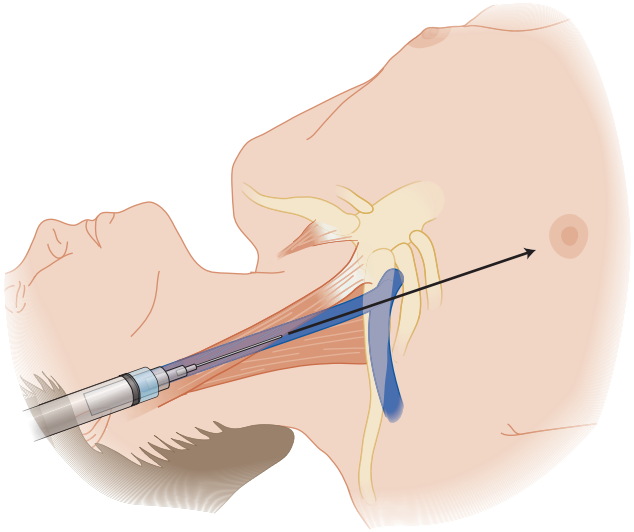


FIGURE 31-7. Central approach to the internal jugular vein.

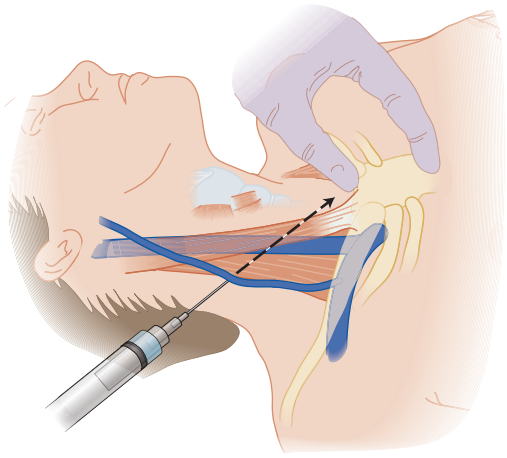
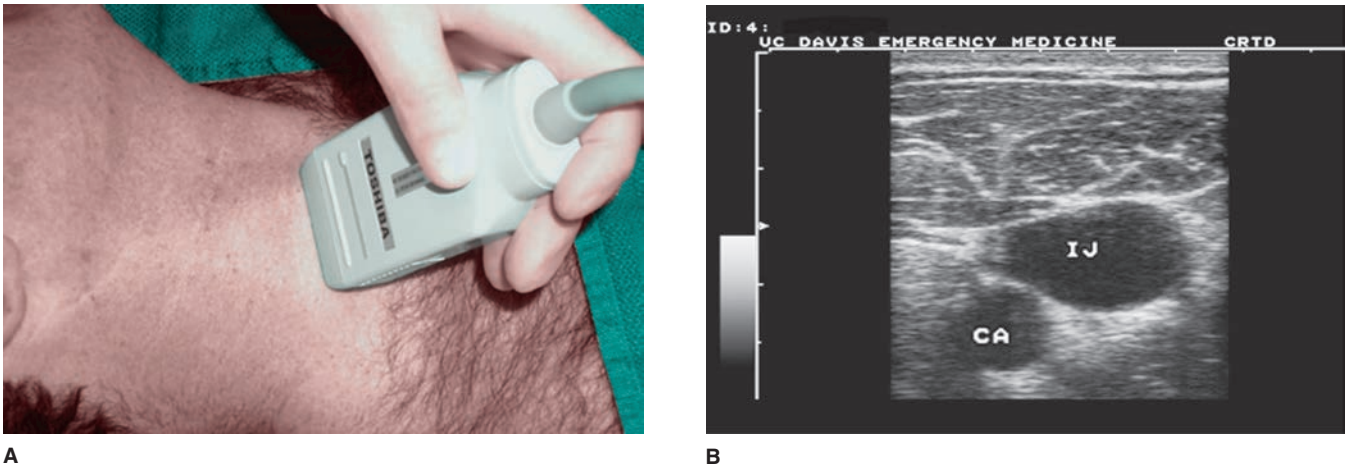


FIGURE 31-8. Posterior approach to the internal jugular vein.

TABLE 31-9 Summary of Approaches to Internal Jugular Vein Catheterization

	Landmarks	Direction of Aim	Depth of Vein (cm)
Central	Apex of triangle formed by the clavicle and sternal and clavicular components of the sternocleidomastoid muscle	Ipsilateral nipple	1–3
Posterior	Lateral aspect of the clavicular portion of the sternocleidomastoid, one third of the distance from the clavicle to the mastoid process	Sternal notch	3–5
Anterior	Midpoint of the medial aspect of the sternal portion of the sternocleidomastoid, lateral to the carotid artery	Ipsilateral nipple	3–5



A B

FIGURE 31-6. US-guided localization of the internal jugular vein. US image of the large internal jugular vein and deeper carotid artery. Probe position (**A**) and corresponding US image (**B**). CA = carotid artery; IJ = internal jugular vein.

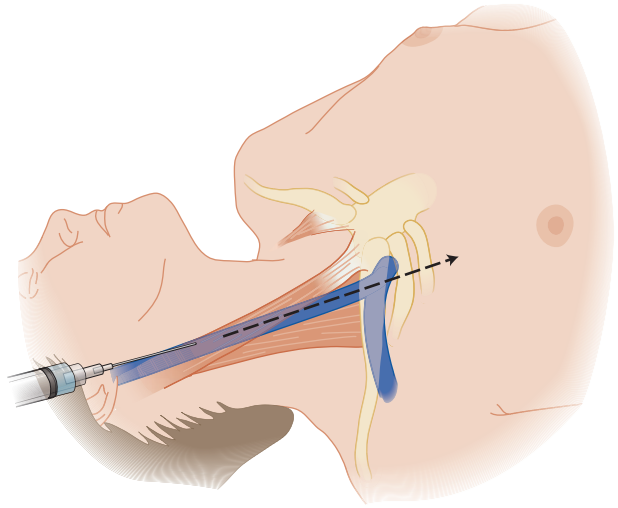


FIGURE 31-9. Anterior approach to the internal jugular vein.

ANTERIOR APPROACH

Identify the pulse and course of the carotid artery, which lies just medial to the site of entry for the anterior approach. Hold the carotid artery with fingers of the nondominant hand. Hold the needle and syringe in the dominant hand at an angle of 30 to 45 degrees and enter at the midpoint of the medial aspect of the sternal portion of the sternocleidomastoid muscle. Aim the needle toward the ipsilateral nipple (**Figure 31-9**). Successful venous return typically occurs within 3 to 5 cm of needle advancement.

SUBCLAVIAN VEIN

The location of the subclavian vein allows patient mobility and is an excellent choice for longer-term use. The two traditional approaches to the catheterization of the subclavian vein are the infraclavicular and supraclavicular approaches (**Figure 31-10**). The infraclavicular approach to US-guided subclavian vein catheter placement is limited by the large acoustic shadow created by the clavicle (**Figure 31-11**), so surface anatomy is used as the guide. The supraclavicular approach allows good sonographic visualization of the proximal subclavian vein anatomy. Subclavian vein cannulation by any approach carries the risk of pneumothorax. If attempts at subclavian venous access fail on one side, assess for pneumothorax using a chest radiograph or US before attempting cannulation on the contralateral side. (See Video: Central Venous Catheter via the Subclavian Vein (now Entitled Subclavian Cannulation.))

INFRACLAVICULAR APPROACH

Place the patient head down and in a neutral position with a small towel under the thoracic spine to help identify the clavicle. The landmark for the site of entry is the junction of the middle and medial thirds of the clavicle. Orient the bevel of the needle inferomedially to direct the guidewire to the brachiocephalic trunk rather than the internal jugular vein. Align the numbered markings on the syringe with the bevel of the needle to guide the orientation of the bevel once the needle has breached the skin. Place the index finger of the nondominant hand at the suprasternal notch and the thumb at the midpoint of the clavicle. Direct the needle toward the suprasternal notch at a 10-degree angle parallel to the surface of the chest (**Figure 31-12**). If you hit bone, "walk" the needle down the clavicle until the needle is posterior to it. Successful venous return occurs typically at a depth of 3 to 5 cm.

SUPRACLAVICULAR APPROACH

The supraclavicular approach is often referred to as the "pocket shot." The supraclavicular approach has fewer failures, fewer catheter malpositions, and less interference with CPR than the infraclavicular approach. It is possible in the upright position in patients unable to lay supine in the setting of severe orthopnea.

The landmark for entry is 1 cm lateral to the clavicular head of the sternocleidomastoid and 1 cm posterior to the clavicle. Enter at an angle of 10 degrees above horizontal. Orient the bevel of the needle medially, bisecting the angle formed by the clavicle and sternocleidomastoid

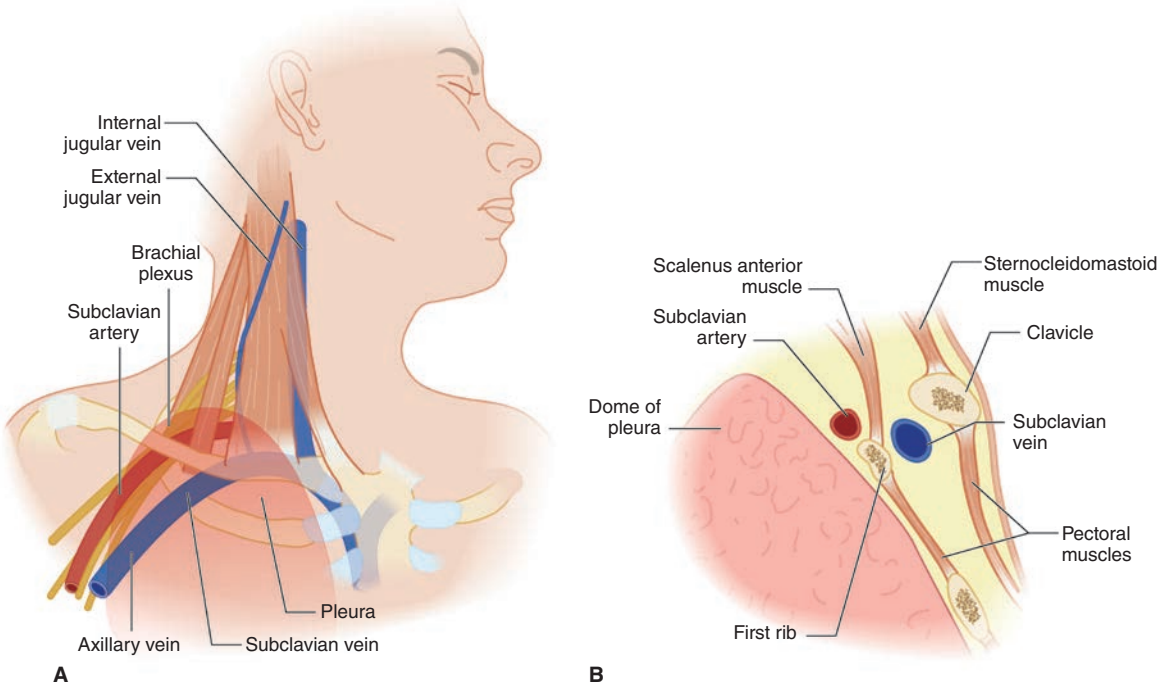
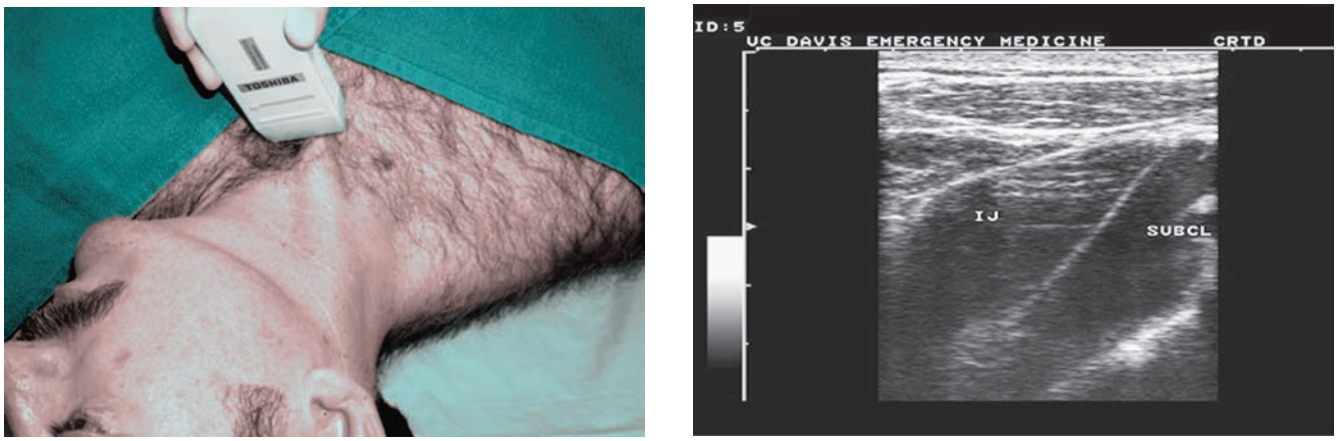


FIGURE 31-10. **A.** Anatomy of the subclavian vein. **B.** Cross-section of the subclavian vein with its relation to the clavicle.



A B

FIGURE 31-11. US-guided localization of the subclavian vein. **A.** Placement of the transducer to facilitate visualization of the internal jugular/subclavian vein junction using a supraclavicular approach. In some patients, a more lateral probe position is required. **B.** Transverse view of the "venous lake" created by the combined subclavian (SUBCL) vein and internal jugular (IJ) vein.

toward the contralateral nipple. Successful venous return typically occurs at a depth of 2 to 3 cm (**Figure 31-13**).

FEMORAL VEIN

The femoral vein is the most accessible central access site during critical illness, notably cardiac arrest or trauma. It travels in the femoral sheath with the femoral artery, nerve, and lymphatics deep to the medial third of the inguinal ligament. A mnemonic for the anatomy of the femoral structures from lateral to medial is **NAVEL**: nerve, artery, vein, empty space, and lymphatics.

The femoral vein can be cannulated with the traditional approach, using surface anatomy and palpation as a guide, or by US.

SURFACE ANATOMY APPROACH

Place the patient supine in reverse Trendelenburg position with the hip slightly abducted and leg slightly externally rotated.[7,8] Palpate the femoral artery, if possible. Classically, the femoral vein is just medial to the femoral artery and 1 to 2 cm below the inguinal ligament, although US often demonstrates an anomalous position, which is one reason why landmark-based insertions are less successful (**Figure 31-14**). Use a 45-degree angle of approach.

In pulseless arrest, locate the femoral vein using the "V" technique. Place the thumb on the pubic tubercle and the index finger on the anterior superior iliac spine. The femoral vein is typically located at the interdigital space (the "V" of the finger and thumb) just inferior to the inguinal ligament.

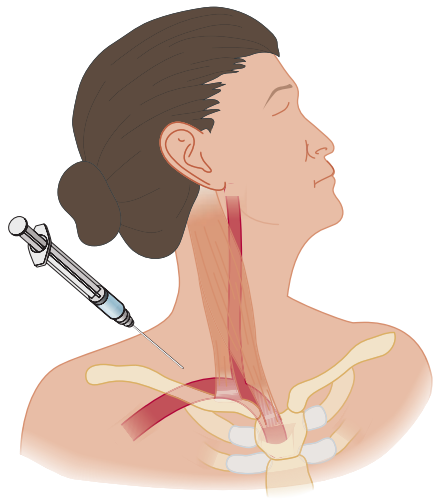


FIGURE 31-13. Supraclavicular approach to the subclavian vein.

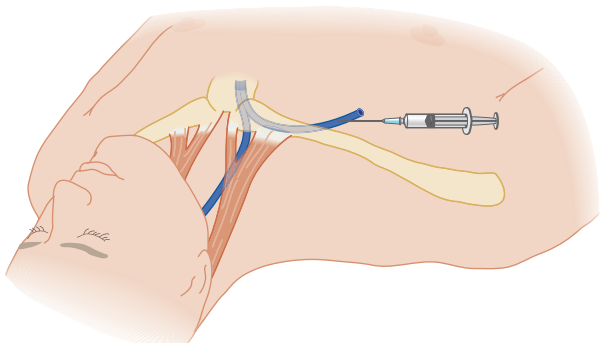


FIGURE 31-12. Infraclavicular approach to the subclavian vein.

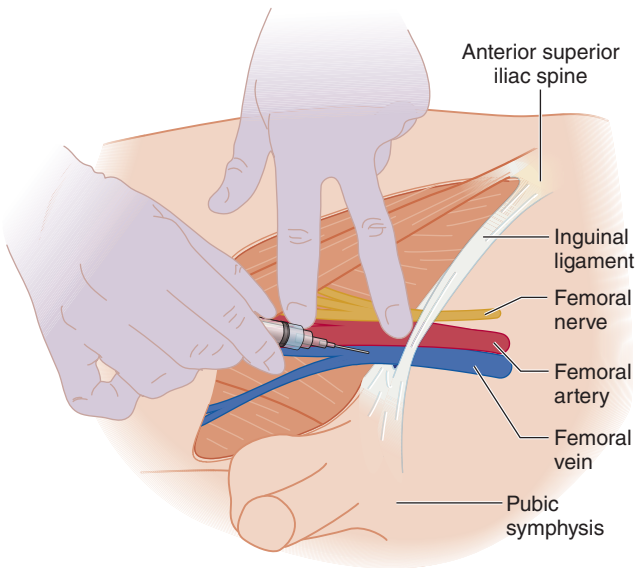


FIGURE 31-14. Technique for femoral vein access.

Always insert the needle below the inguinal ligament, because vascular injury above the inguinal ligament may cause hemorrhage into the retroperitoneal space.

Limit femoral vein cannulation because of the higher complication rates (notably infection and thrombosis) and the limits it places on patient mobility.

US-GUIDED APPROACH

Place the transducer in a transverse position just below the midportion of the inguinal ligament. Identify the femoral vein just below the inguinal ligament and medial to the femoral arterial pulsation. The vein is more easily compressed than the artery. The relationship among the vessels varies depending on limb position (**Figure 31-15**; See Video: Femoral Vein Cannulation).

VENOUS CUTDOWN

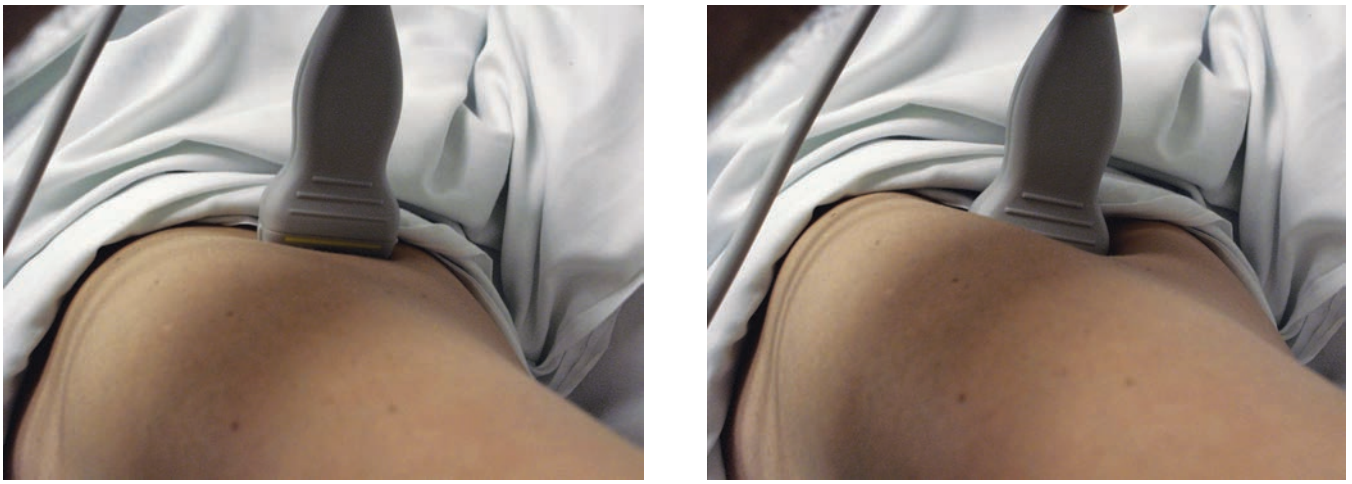
Venous cutdown is typically performed on the saphenous vein, anterior and superior to the medial malleolus. It is rarely used due to widespread use of IO techniques and US for peripheral vein cannulation of the upper extremities. To perform a venous cutdown, expose the vein surgically just above the medial malleolus. The vein's location is predictable after careful dissection through the skin only, and there are no other nearby structures that can be injured. Free 2 to 4 cm of the vein, tie the distal portion, and cannulate the proximal portion and connect to an IV line. Place a secure suture around the cannula and proximal portion of the vein. (See Video: Venous Cutdown.)

IO VASCULAR ACCESS

IO vascular access is possible in patients of all ages when venous access cannot be quickly and reliably established during circulatory collapse.[8] The commercial EZ-IO® (Vidacare Corp., San Antonio, TX) eases procedure performance (**Figure 31-16**). Contraindications to IO access include proximal ipsilateral fracture, ipsilateral vascular injury, and severe osteoporosis or osteogenesis imperfecta. Complications of IO access include cellulitis, osteomyelitis, iatrogenic fracture or physeal plate injury, and fat embolism (rare). (See Videos: Intraosseous Line Placement and Intraosseous Line Placement EZ-IO.)

TECHNIQUE FOR IO ACCESS

Use either a standard bone marrow aspiration needle or specialized IO infusion needle. In children, the site of entry is two finger-widths (2 cm) below the tibial tuberosity on the medial, flat surface of the proximal



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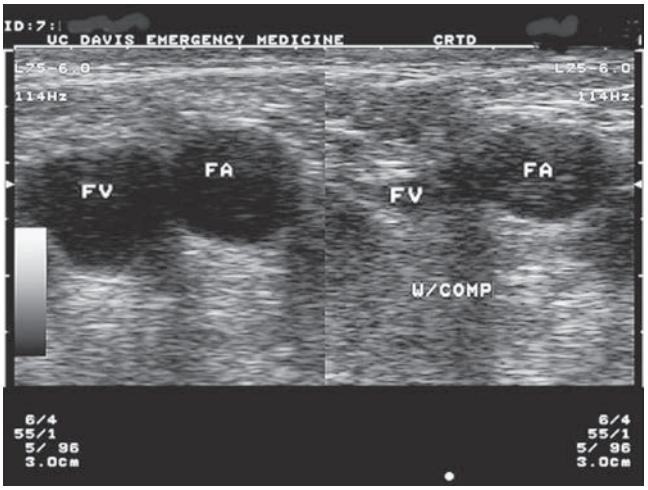

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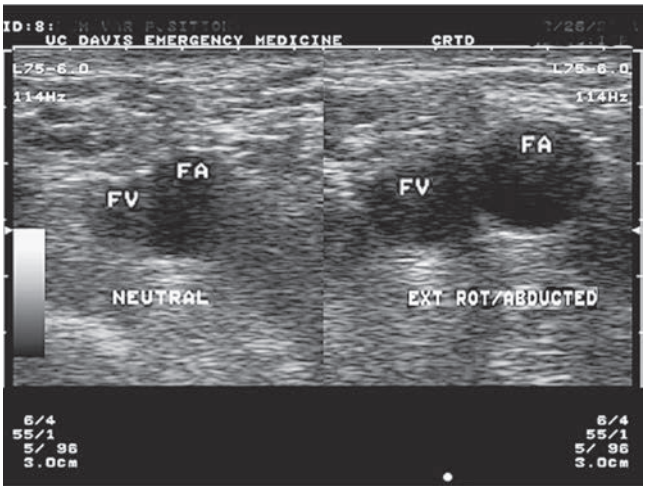


C

FIGURE 31-15. US-guided localization of the femoral vein. **A.** Gentle pressure is applied to the transducer to identify venous structures by their easy compressibility. **B.** Femoral vein (FV) collapses with compression, and the femoral artery (FA) retains its shape even with compression. **C.** FV position is seen to vary with hip abduction and external rotation. In neutral position (*left frame*), the vein is closely opposed to the FA; however, when the hip is abducted and rotated, the vein is displaced from the artery (*right frame*). [Part A used with permission of Michael Blaivas, MD.]



FIGURE 31-16. IO drill device.

tibia (**Figure 31-17**). Use other sites, such as the medial malleolus, distal femur, sternum, humerus, and ileum, in adults because the tibia is thick and difficult to penetrate.

The procedure for manual insertion of IO venous needles is described in **Table 31-10** and **Figure 31-18**.

TABLE 31-10 Procedure for Manual IO Venous Access

- Prepare site using routine sterile fashion.
- Infiltrate area with 1%–2% lidocaine to anesthetize the skin and periosteum if the patient is conscious.
- Support and stabilize the leg with the nondominant hand.
- Grasp the needle in the palm of the dominant hand.
- Direct the needle perpendicular to the bone and away from the joint space (to avoid injury to the physeal plate in pediatric patients).
- Twist and apply constant pressure until resistance is abruptly decreased and the marrow cavity is breached.
- Remove the stylet.
- Confirm placement by either aspiration or continuous infusion.
- Observe for signs of extravasation (Figure 31-18).
- Secure the IO needle with gauze and a bulky dressing.
- Confirm placement and exclude iatrogenic fracture with radiograph after stabilizing the patient.

ARTERIAL ACCESS

The indications for arterial line placement are provided in **Table 31-11**.

RADIAL ARTERY ANATOMY

The most common site for arterial line placement is the radial artery due to the ease of identifying its location and accessibility at the wrist. The collateral artery blood supply provided by the ulnar artery lowers the risk of complications (**Figure 31-19**). The anatomic landmarks for the radial artery are medial to the radial styloid process and lateral to the flexor carpi radialis tendon at the proximal flexor crease of the wrist. **Palpate the radial pulse; many do a radial and ulnar artery compression test (release of latter to assess collateral circulation, looking for hand to "pink up" rapidly—called the Allen test) prior to any puncture**, although these do not reliably predict later ischemic complications.

ALTERNATIVE ARTERIAL SITES

Other sites for arterial catheter placement include the dorsalis pedis artery and the brachial artery. Similar to the radial artery, the dorsalis pedis artery is superficial and easy to identify, and the foot has collateral circulation similar to the hand. The brachial artery is just medial to the biceps brachii muscle in the antecubital fossa adjacent to the medial nerve. Unless absolutely needed, avoid the brachial artery because the lack of collateral blood flow increases the risk of upper extremity ischemia.

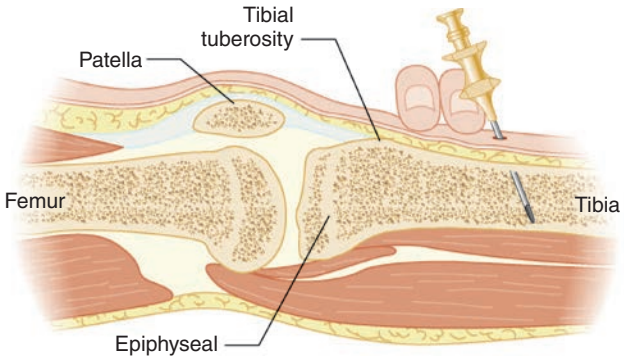


FIGURE 31-17. Location for IO placement in the proximal tibia.

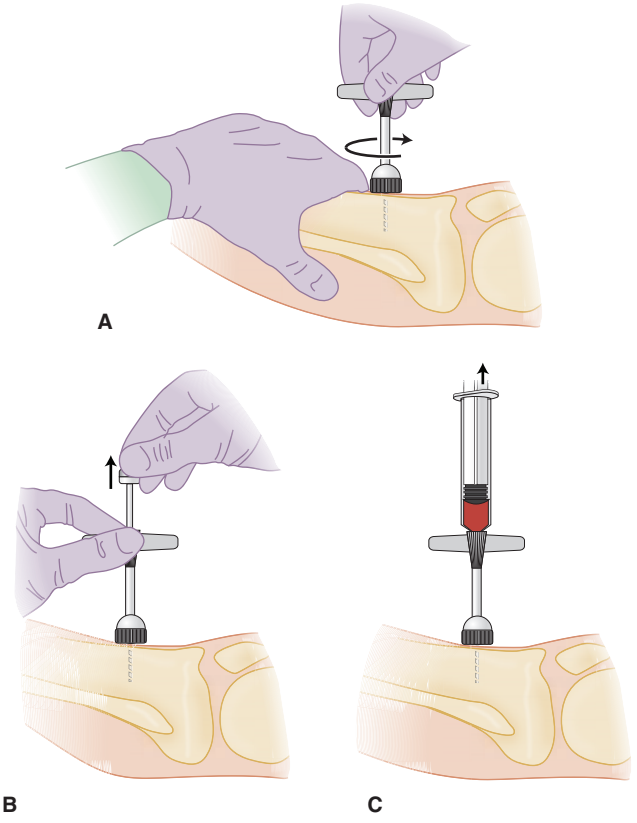


FIGURE 31-18. Technique for IO placement. **A.** Needle is directed perpendicular to the bone with constant pressure and a twisting motion. **B.** Stylet is removed. **C.** Placement is confirmed with successful aspiration.

TABLE 31-11 Indications for Arterial Catheter Placement

- Frequent laboratory testing, including arterial blood gas sampling for acid-base status or monitoring of oxygen saturations and carbon dioxide levels in patients with respiratory failure
- Need for accurate, moment-to-moment blood pressure monitoring in hypotensive patients, patients on vasopressors, or hypertensive patients with intracranial hemorrhages or vascular catastrophes (i.e., aortic dissections, abdominal aortic aneurysms)

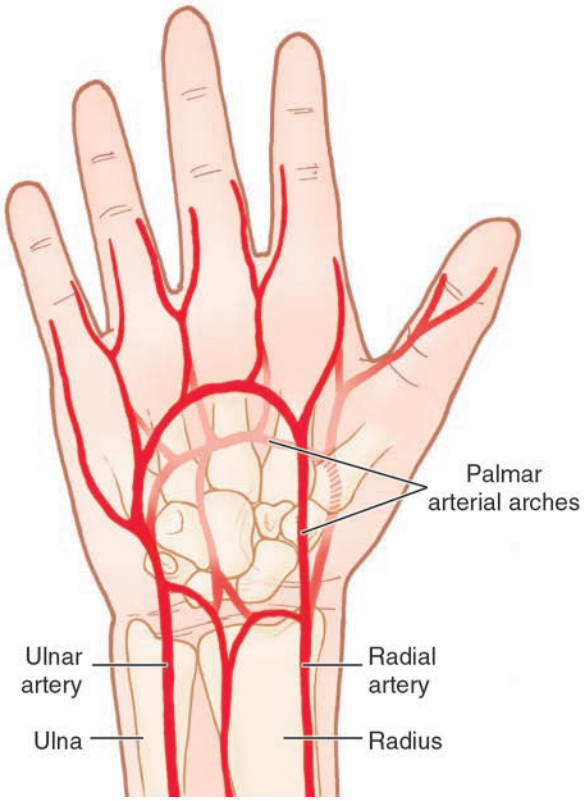


FIGURE 31-19. Arterial anatomy of the wrist and hand. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures*, 2nd ed. Chapter 57. Arterial Puncture and Cannulation. McGraw-Hill, Inc., 2013, Figure 57-1.]

TECHNIQUE FOR ARTERIAL ACCESS

After explaining the procedure and gaining consent, identify the access site and approach and position the patient with all materials at the bedside (**Table 31-12**).

The technique for all approaches is provided in **Table 31-13** and **Figures 31-20, 31-21,** and **31-22**. The direct puncture approach is less often successful, takes longer, and requires more puncture attempts than the integral wire approach.

Secure the arterial catheter to the skin either by suture or adhesive catheter locking device with a sterile transparent protective dressing placed over the site. An arm board or wrist splint may aid securing a radial artery line. Monitor the site regularly for dislodgment, hematoma, bleeding, infection, or distal ischemia. Change the dressing regularly, and check for complications (**Table 31-14**).

Air embolization from an arterial catheter is more likely to have adverse sequelae to whatever tissue is downstream compared to similar area venous catheterization because of no pulmonary filtration. Infection rates increase with poor aseptic technique and duration of catheter use.

TABLE 31-12 Materials for Arterial Access

- Sterile personal protective gear (gloves, gown, mask, hair covering)
- Sterile towels
- Povidone-iodine or chlorhexidine cleaning solution
- 1% lidocaine, small-gauge needle, and syringe (e.g., a 1-mL tuberculin syringe)
- 20-gauge angiocatheter or integral-guidewire arterial catheter
- 4 × 4 gauze
- 3-0 or 4-0 nylon suture with straight needle or needle driver
- Sterile transparent dressing
- Arterial line setup (pressure bag, saline, tubing, transducer, and flushing system)

TABLE 31-13 Technique for Artery Cannulation

Step	Comments
1. Position the patient for the procedure.	For radial artery approach, the wrist is extended. A towel roll under the dorsal wrist can maintain this position. See Figure 31-20. For femoral artery approach, the hip is slightly abducted and leg slightly externally rotated.
2. Gown in standard sterile fashion.	Use sterile gloves and gown. Wear mask and hair covering. **Do not stand in direct line of the catheter.**
3. Identify artery using either landmarks or US guidance.	A palpable pulse is a must for landmark approach. Palpate pulse with 2 fingers of nondominant hand.
4. Prep and drape patient using standard sterile procedure.	Improper sterile technique increases risk of infection.
5. Anesthetize area in all conscious patients.	Inject 1% lidocaine with 1-mL tuberculin syringe.
6. Hold the 20-gauge angiocatheter or integral-guidewire catheter in the dominant hand at a 30- to 45-degree angle to the skin surface.	For direct angiocatheter cannulation, see Figure 31-21. For use of an integral-guidewire catheter, see Figure 31-22.
7. Advance the needle slowly through the skin and subcutaneous tissue until pulsatile red blood return is obtained.	—
8. Stabilize the needle with the nondominant hand.	—
9. If an integral-guidewire catheter is used, advance the wire with the dominant hand.	If resistance is encountered, STOP advancing the guidewire immediately, withdraw the entire unit, and apply pressure to the puncture site.
10. Advance the catheter over the needle (or needle and guidewire if used).	A gentle rotating motion of the catheter may be helpful.
11. Remove the needle or needle-guidewire unit and *immediately occlude the catheter with a finger.*	Occlusion prevents arterial blood loss and air embolism.
12. Attach arterial line setup/IV tubing to the catheter.	Be sure to have arterial line setup prepared prior to start of the procedure.
13. Secure catheter with suture and apply a sterile transparent dressing.	—
14. "Zero" the transducer.	Align the stopcock to the level of the heart. Turn the stopcock off to the patient and open to air. Adjust the monitor display to zero.
15. Monitor for signs of bleeding, hematoma, or infection.	Assess the continued need for the arterial line daily.

Thrombosis occurs in up to 25% of patients with an arterial catheter, although clinical morbidity occurs in less than 1%. Neuropathies can occur from direct nerve injury from cannulation attempts or hematoma formation causing nerve compression. **The first step in treating all complications is catheter removal. Apply direct pressure for a minimum of 3 to 5 minutes after removal at all peripheral sites and 10 minutes for a femoral site.**

US-GUIDED ARTERIAL ACCESS

US-guided arterial puncture aids cannulation, especially when a palpable pulse is difficult to identify.[9] Key sonographic characteristics to identify arteries include round, pulsatile, thick-walled vessels that are difficult to compress. (See Video: Radial Artery Cannulation.)

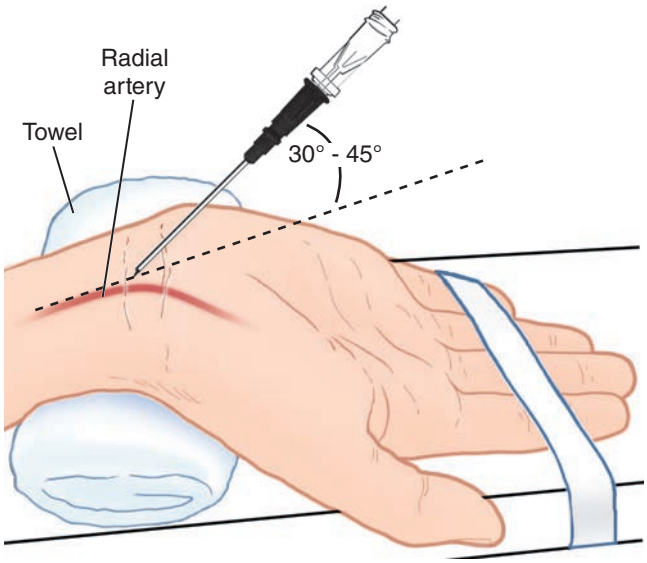
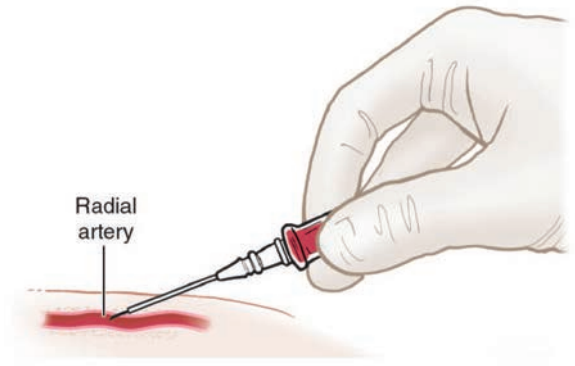


FIGURE 31-20. Correct positioning for radial artery cannulation. Flexion of the wrist is supported by a dorsal towel roll. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures*, 2nd ed. Chapter 57. Arterial Puncture and Cannulation. McGraw-Hill, Inc., 2013, Figure 57-5.]



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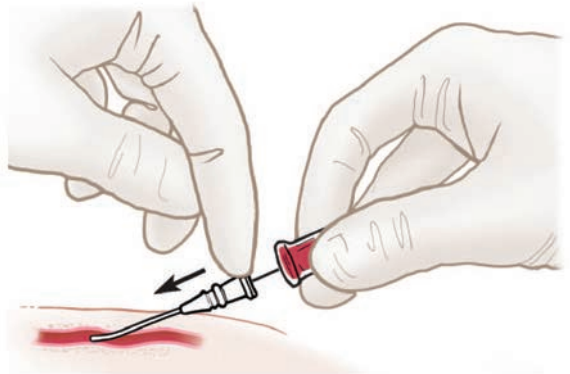

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FIGURE 31-21. Direct angiocatheter technique for arterial cannulation. **A.** The angiocatheter and needle are held at a 30- to 45-degree angle to the skin with the dominant hand and advanced into the artery. **B.** The catheter is advanced over the needle and into the artery with the nondominant hand. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures*, 2nd ed. Chapter 57. Arterial Puncture and Cannulation. McGraw-Hill, Inc., 2013, Figure 57-7.]

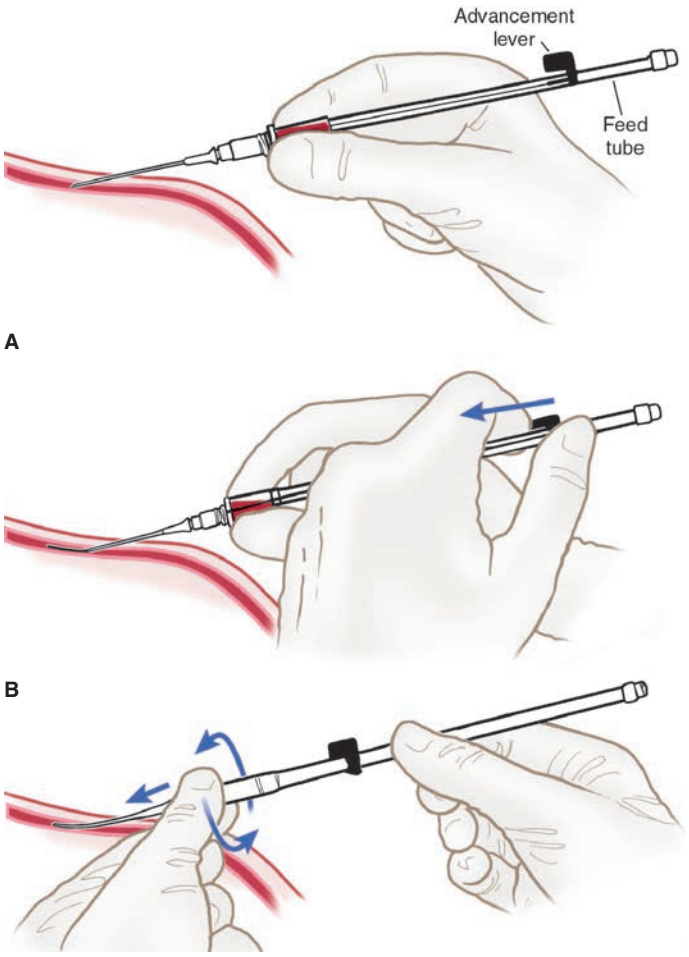

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FIGURE 31-22. Integral-guidewire technique for arterial cannulation. **A.** The integral-catheter unit is held at a 30- to 45-degree angle to the skin and slowly advanced into the artery. **B.** The guidewire is advanced through the needle and into the artery with the nondominant hand. **C.** The catheter is advanced over the guidewire and into the artery with a gentle twisting motion. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures*, 2nd ed. Chapter 57. Arterial Puncture and Cannulation. McGraw-Hill, Inc., 2013, Figure 57-8.]

TABLE 31-14 Complications of Arterial Access and Cannulation

- Pain at site
- Hematoma formation
- Hemorrhage
- Artery laceration/injury
- Arterial vasospasm
- Pseudoaneurysm formation
- Arteriovenous fistula
- Infection
- Limb ischemia
- Thrombosis/embolization
- Nerve damage/neuropathy

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 32

Hemodynamic Monitoring

Bachar Hamade
David T. Huang

INTRODUCTION

Hemodynamic monitoring can identify cardiovascular insufficiency and facilitate optimal treatment of the critically ill. Advanced techniques help sort through various causes of hemodynamic instability and enable tailored interventions.

We focus on techniques applicable in the ED: blood pressure monitoring, central venous pressure (CVP) monitoring, cardiac output (CO) monitoring, and blood oxygenation and lactate monitoring (**Table 32-1**). In practice, it is best to use more than one approach and monitor therapeutic responses.[1]

ARTERIAL BLOOD PRESSURE

Blood pressure is the force exerted by circulating blood through a blood vessel. Assessing arterial pressure is important, as hypotension implies tissue hypoperfusion. Hypotension is always pathologic and reflects a failure of normal circulatory homeostatic mechanisms. Shock is a state of organ hypoperfusion; while often present with hypotension, it can occur in the setting of normotension. For example, a patient in cardiogenic or hypovolemic shock may remain normotensive because of a marked increase in vascular resistance.

OPTIMAL BLOOD PRESSURE

Arterial pressure is the input pressure for organ perfusion and is a function of peripheral vascular resistance and blood flow. Mean arterial pressure (MAP) is measured directly by indwelling catheter or estimated (see below). Organ perfusion pressure often becomes compromised as MAP decreases below 65 mm Hg.[2,3]

Optimal MAP varies depending on the underlying cause of hemodynamic instability. In septic shock, many target a minimum MAP of 65 mm Hg,[4] and increasing MAP beyond 65 mm Hg with fluids and vasopressors increases oxygen delivery but does not improve mortality.[5] However, aiming for a higher MAP (75 to 85 mm Hg) may reduce kidney injury in patients with chronic hypertension.[3,6]

Debate exists regarding whether MAP or systolic blood pressure is a better target in trauma patients. In patients with hemorrhagic shock, recommendations seek a systolic blood pressure of 80 to 90 mm Hg until major bleeding stops. This concept, called permissive hypotension, decreases complications and improves outcomes in trauma patients in the preoperative period.[7-9] The Brain Trauma Foundation recommends maintaining a systolic blood pressure greater than 110 mm Hg for patients with traumatic brain injury, with a minimum systolic blood pressure of 100 mm Hg for patients between the ages of 50 to 69 years.[10] For patients in hemorrhagic shock with concomitant severe traumatic brain injury, maintain a MAP greater than 80 mm Hg.[11]

TABLE 32-1 Hemodynamic Variables Obtainable in the ED

Hemodynamic Variable	Method of Measurement
Blood pressure, mm Hg	Sphygmomanometry, oscillometry, intra-arterial catheterization
Central venous pressure, mm Hg	Jugular venous pulsation, ultrasonography
Cardiac output, L/min	Transthoracic echocardiography, pulse contour analysis
Central venous oxygen saturation, %	Central venous catheterization for venous blood sampling
Lactate, mmol/L	Blood sampling

NONINVASIVE BLOOD PRESSURE MEASUREMENT

Blood pressure varies with each heartbeat. The *systolic pressure* is the maximum pressure during ventricular ejection, and the *diastolic pressure* is the lowest pressure in the blood vessels between heartbeats during ventricular filling. The difference between systolic and diastolic pressures is the pulse pressure. Because the vascular circuit is elastic, both systolic and diastolic pressures vary throughout the vascular system. Systolic pressure can increase by up to 20 mm Hg, whereas the diastolic pressure similarly decreases as the pressure wave moves peripherally from the aorta. However, MAP (**Formula 1**) varies by only 1 to 2 mm Hg, whether measured centrally or peripherally; in practice, estimate MAP using the sum of the diastolic pressure and one third of the pulse pressure (Formula 1).[12]

Formula 1:

Mean arterial blood pressure = Diastolic blood pressure + [Pulse pressure/3]

PALPATION

Traditional teaching is that the ability to palpate the radial, femoral, or carotid pulse represents a minimum systolic pressure of 80, 70, or 60 mm Hg, respectively. However, two small studies showed that these values generally overestimate the patient's systolic blood pressure[13,14] and are not included in the current ninth edition of the Advanced Trauma Life Support guidelines.[15]

SPHYGMOMANOMETRY

Auscultation for blood pressure began with the invention of the sphygmomanometer by Scipione Riva-Rocci in 1896 and later refined by Nicolai Korotkoff in 1905. The cuff is placed around the upper arm, and the bell is held over the brachial artery as the cuff is gradually inflated to at least 30 mm Hg above the point where the radial artery sound disappears. During cuff deflation, the first tapping sound (Korotkoff sound) corresponds to the systolic pressure, while the disappearance of these sounds corresponds to the diastolic pressure. An inappropriately small cuff results in falsely elevated blood pressure measurements, and an inappropriately large cuff results in falsely low measurements.

Sphygmomanometric measurements of blood pressure often report slightly higher systolic pressure and lower diastolic pressure than those reported from simultaneous direct measurement using an intra-arterial catheter. This is because the reflected pressure waves summate with cuff inflation and increase systolic pressure, whereas the ischemic vasodilation downstream from the occluded cuff decreases cuff opening diastolic pressure. In normotensive patients, use the arm or leg for noninvasive blood pressure measurements; in critically ill and hypotensive patients, noninvasive arm measurements are usually temporizing while establishing arterial line access.[16]

OSCILLOMETRY

Most automated blood pressure monitors use oscillometry. The device analyzes the amplitude of the fluctuations (or oscillations) in blood pressure in a sphygmomanometer cuff and converts it to a pressure measurement without the need for auscultation. With gradual deflation of the cuff, oscillations begin above systolic pressure. The point of maximum oscillation corresponds to MAP. Noninvasive measurements overestimate the systolic blood pressure compared to invasive arterial monitoring, but the calculated MAP shows better correlation and thus is more reliable in the critically ill patient.[17]

INVASIVE BLOOD PRESSURE MEASUREMENT

The arterial catheter measures MAP and pulse pressure, estimates CO, and enables repeated blood sampling. The International Consensus Conference for Hemodynamic Monitoring in Shock recommends invasive blood pressure monitoring for patients with refractory shock receiving vasoactive agents[18]; however, the use of arterial catheters in the intensive care unit alone does not improve mortality.[19] Some argue that

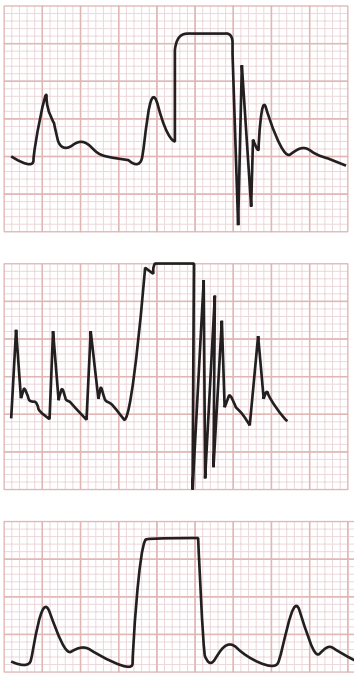

FIGURE 32-1. Square wave flush test with intra-arterial blood pressure measurement. During a flush bolus of the catheter tubing, a square wave is observed. The number of oscillations after the square wave at the end of the bolus and prior to returning of the blood pressure tracing may result in an overestimation or underestimation of blood pressure.

TABLE 32-2 Contributors to Central Venous Pressure Values

Central venous blood volume
- Venous return
- Cardiac output
- Total blood volume

Compliance of the central compartment
- Vascular tone
- Right ventricular compliance
- Myocardial disease
- Pericardial disease

Tamponade
- Tricuspid valve disease
- Stenosis
- Regurgitation

Dysrhythmia
- Junctional rhythm
- Atrial fibrillation
- Atrioventricular dissociation

Reference level of transducer
- Positioning of patient

Intrathoracic pressure
- Respiratory changes
- Intermittent positive-pressure ventilation
- Positive end-expiratory pressure
- Tension pneumothorax

noninvasive measurements are sufficient even in patients with dysrhythmias or receiving vasopressors, deferring arterial catheter placement.[20] Large randomized trials validating these postulations do not exist, and it is reasonable to avoid placing an arterial line in cases where hypotension is expected to be short term.

Placement of an intra-arterial catheter requires knowledge of the anatomic landmarks of the selected site. US guidance aids placement. The catheter insertion is either directly over a needle or over a guidewire (called the Seldinger technique). The Allen test, compression of both the ulnar and radial arteries with subsequent release of the ulnar artery pressure to see if "pink" returns, confirms collateral blood flow before radial artery catheterization; however, the test does not predict postcatheterization hand ischemia reliably. In patients with profound hypotension, a cutdown aids cannulation. After successful arterial catheterization, connect the catheter to the pressure transducer and look for an arterial waveform. The square wave flush test is applied to determine if artifacts in the tubing and recording system are damping the pressure measurements. See **Figure 32-1** for the square wave flush test with intra-arterial blood pressure measurement.

An overdamped system suggests that air bubbles in the tubing are falsely lowering pressure measurements. An underdamped system will overestimate systolic pressure and underestimate diastolic pressure. Flushing the system should remove the air bubbles. If this does not fix the problem, replace the tubing.

CENTRAL VENOUS PRESSURE MONITORING

CVP is the back pressure to systemic venous return. Multiple factors contribute to the CVP value (**Table 32-2**).

OPTIMAL CENTRAL VENOUS PRESSURE

CVP measurements range from 2 to 8 mm Hg in normal healthy individuals but are affected by multiple factors (Table 32-2).[21] A single absolute CVP value helps most when it is very low (such as to exclude right heart failure in a patient with a normal MAP) or very high (such as to suggest right heart failure and/or volume overload). In general, a CVP less than 4 mm Hg in the hypotensive patient prompts fluid resuscitation with careful monitoring.[18] However, CVP measurements do not correlate with circulating blood volume or changes in blood volume.

Volume expansion in a healthy volunteer with normal diastolic compliance will immediately increase blood volume, whereas the CVP remains relatively normal. On the contrary, the same volume expansion in an elderly patient with cardiomyopathy, decreased diastolic compliance, and low circulating volume will elevate CVP (**Figure 32-2**).

Always measure CVP at end-expiration for both spontaneously breathing and mechanically ventilated patients. During spontaneous inspiration, the decreased intrathoracic pressure decreases transmural pressure in the heart, resulting in a decreased CVP. Conversely, intrathoracic pressure increases during an inspiratory breath of mechanical ventilation, resulting in an increase in CVP. Significant variation in inspiratory and expiratory CVP measurements suggests a compliant

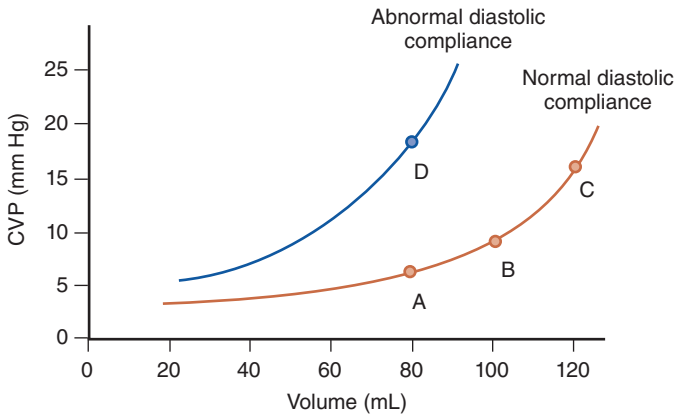

FIGURE 32-2. Right ventricular end-diastolic volume versus central venous pressure (CVP) varies with cardiac compliance. The same volume (80 mL) may result in different CVP measurements depending on diastolic compliance. The letters A to D designate response after a small fluid bolus of same size in these groups.

heart wall that will most likely respond to volume infusion. Conversely, the lack of respiratory variation in CVP may indicate that the heart is on the flat part of the cardiac function curve and will no longer respond to fluids.

NONINVASIVE CVP MEASUREMENT

JUGULAR VENOUS PULSATION

Observing internal jugular venous pulsation can estimate right atrial pressure. The sternal angle is roughly 5 cm above the center of the right atrium regardless of the patient's position. With the patient sitting at a 45-degree angle, add 5 cm (distance from the sternal angle to the right atrium) to the vertical distance between the jugular pulsation and the sternal angle to estimate CVP in centimeters of water (cm H_2O). A pulsation greater than 4.5 cm vertically above the sternal angle when the patient is sitting at 45 degrees indicates a CVP of greater than 9.5 cm H_2O (**Figure 32-3**). In patients with heart failure, an elevated jugular venous pressure is independently associated with adverse outcomes, such as hospitalization and death.[22] Visualization of internal jugular vein pulsation is not always possible in obese or uncooperative patients.

ULTRASONOGRAPHY

Ultrasonography is a valuable tool to visualize the neck veins for central venous catheterization. It can also be used to determine elevated jugular venous pressure and provide a noninvasive method for measuring CVP. Examine the right jugular vein using a high-frequency linear transducer (7 to 9 MHz), looking for the site where the vein tapers, resembling the neck of a wine bottle. Measure the vertical distance in centimeters between this point of vein collapse and the sternal angle and add 5 cm to obtain a CVP measurement in cm H_2O.

When a distended jugular vein that is larger than the adjacent common carotid artery is seen in the transverse plane with the patient in a semi-upright position, then the estimated CVP is greater than 10 cm H_2O. A nearly collapsed internal jugular vein on the transverse view in the supine position indicates a very low CVP.

Similarly, CVP estimation using ultrasonography of the inferior vena cava (IVC) throughout the respiratory cycle is possible. An IVC that is small and measures less than 2 cm in diameter that has greater than 50% collapsibility with inspiration correlates to a CVP of less than 10 cm H_2O.[23]

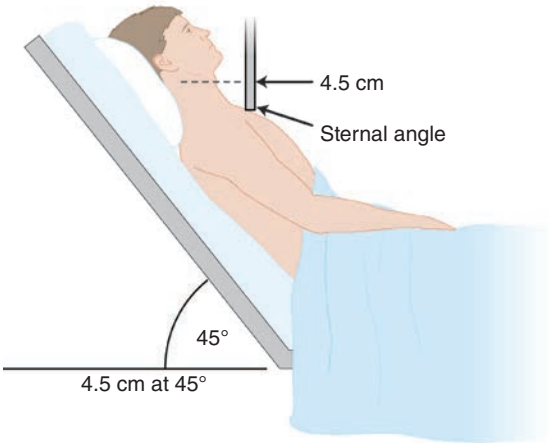

FIGURE 32-3. Internal jugular venous pulsation as an estimate of central venous pressure (CVP; or right atrial pressure). With the patient's head slightly turned to the left, shine a light tangentially in front of the neck to obtain a jugular shadow. The oscillations observed reflect the changing pressures within the right atrium and the various wave components of the CVP. The first elevation in the jugular pulse indicates the a-wave, or atrial contraction. The venous pressure is more accurately seen on the right side than the left because the right internal jugular vein has a more direct path to the right atrium. If the jugular pulse is higher than 4.5 cm at a 45-degree angle, it indicates an elevated CVP.

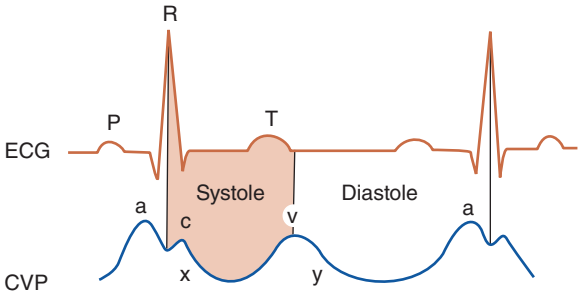

FIGURE 32-4. Central venous pressure (CVP) waveform and its relationship to the ECG. a = a-wave due to atrial contraction during diastole, which is absent in atrial fibrillation, but enlarged in tricuspid stenosis, pulmonary stenosis, and pulmonary hypertension; c = c-wave due to bulging of tricuspid valve back into the right atrium at the onset of systole; v = v-wave due to rise in atrial pressure from venous return through the vena cavae during systole and before the tricuspid valve opens at the onset of diastole, which is enlarged in tricuspid regurgitation; x = x-descent due to atrial relaxation; y = y-descent due to atrial emptying into the ventricle during diastole.

INVASIVE CENTRAL VENOUS PRESSURE MEASUREMENT

CVP monitoring uses a fluid-filled catheter inserted in the internal jugular or subclavian vein proximal to the right atrium. The distal tip sits in the superior vena cava. Indications for central venous catheterization include fluid and vasopressor administration, unsuccessful or inadequate peripheral venous access, central venous oxygenation ($ScvO_2$) measurement, pulmonary artery catheterization, and transvenous pacemaker placement. Further details regarding central venous cannulation are provided in Chapter 31, "Vascular Access."

After successful catheter insertion, connect the catheter to a manometer or a pressure transducer of a monitor for continuous CVP waveform display. Place the transducer at the level of the right atrium, approximately 5 cm below the sternal angle. An acceptable CVP waveform allows accurate measured values (**Figure 32-4**). The c-wave represents bulging of the tricuspid valve into the right atrium and occurs at the onset of systole. The base of the c-wave determines a CVP value because it is the final pressure in the ventricle before the onset of contraction, reflecting preload.

CARDIAC OUTPUT MONITORING

Oxygen delivery is a function of arterial oxygen content and CO. Perfusion pressure is the most important driving force determining regional blood flow, which in the aggregate defines CO. Because the primary goal of resuscitation from shock is to reverse tissue hypoperfusion, CO is an ideal indicator of perfusion and oxygen delivery. There is no absolute level of normal CO in the unstable, metabolically active patient because CO is proportional to metabolic demand.

OPTIMAL CARDIAC OUTPUT AND DETERMINING FLUID RESPONSIVENESS

CO is the product of heart rate and stroke volume. Fluid, or volume responsiveness, is the response of stroke volume to fluid loading.[24] Traditionally, Starling's law (**Figure 32-5**) guided resuscitation care, with an increase in CO of greater than 15% after a fluid challenge identifying fluid responsiveness.[25]

VOLUME RESPONSIVENESS IN SPONTANEOUSLY BREATHING PATIENTS

Volume responsiveness in spontaneously breathing patients may be assessed by passive leg raising. Postural changes transiently increase venous return when the legs are raised to 30 degrees above the chest and held for 1 minute. This maneuver approximates giving a 300-mL blood bolus to a 70-kg patient. Changes in heart rate, blood pressure, CVP, or

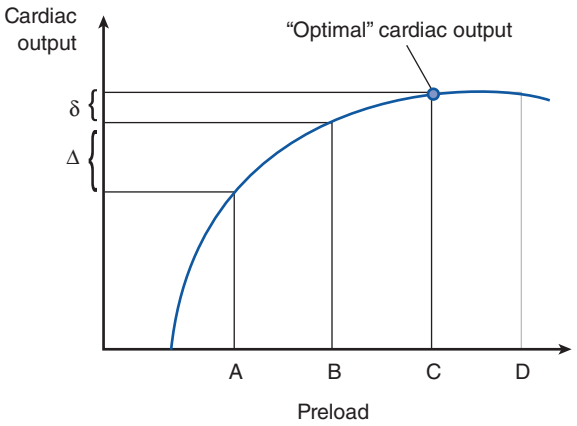

FIGURE 32-5. Starling cardiac function curve illustrating the effects of increased preload on cardiac output. As illustrated in the Starling cardiac function curve, the first increase in preload (from A to B) results in a large increase in cardiac output (Δ) as the cardiovascular system operates in the "preload-dependent" portion of the curve. The second increase in preload (from B to C) only results in a small increase in cardiac output (δ), and further increase in preload (from C to D) does not yield any increase in cardiac output as the cardiovascular system is now considered "volume resuscitated" or preload independent.

CO persist for approximately 2 to 3 minutes after passive leg raising. The dynamic increases in CO induced by passive leg raising are as sensitive and specific to predicting volume responsiveness as pulse pressure variation during positive-pressure mechanical ventilation.[26]

US also assesses volume responsiveness in the spontaneously breathing patient. As described in the earlier section on CVP, a small-caliber (<2 cm diameter) IVC with low minimal respiratory variation correlates with a low CVP and potentially a hypovolemic state. Assess IVC diameter before and after fluid bolus, or look for little IVC changes with respiratory variation to identify fluid responsiveness.[23]

VOLUME RESPONSIVENESS IN MECHANICALLY VENTILATED PATIENTS

Respiratory variations in blood pressure may aid in assessing volume status in the mechanically ventilated patient. Positive-pressure mechanical ventilation alters venous return and induces several predictable cyclic changes in vena caval diameters, pulmonary blood flow, and left ventricular output (**Figure 32-6**).[27] This phasic variation in stroke volume results in arterial pressure variation, defined as the cyclic fluctuation in arterial pressure with a phase length equal to the respiratory rate. This variation in arterial pressure is a variation in the pulse pressure, defined by the difference between maximal and minimal pulse pressure values divided by the mean pulse pressure over one respiratory cycle.[28] In the volume-responsive patient, increasing intrathoracic pressure during positive-pressure inspiration decreases venous return, and thus preload. A pulse pressure variation greater than 13% predicts a greater than 15% increase in CO in response to a 500-mL crystalloid bolus.[29]

Fluid administration continued until the pulse pressure variation between inspiration and expiration decreases to less than 10% may improve outcomes.[30,31] Because arterial pressure is directly proportional to stroke volume, stroke volume variation strongly predicts fluid responsiveness.[32] However, the patient must be breathing in synchrony with the positive-pressure mechanical breaths and without vigorous spontaneous breathing or dysrhythmia for stroke volume variation to be accurate. This technique aids assessing volume responsiveness in the sedated and ventilated patient.

Similar to the spontaneously breathing patient, US helps assess volume responsiveness in the mechanically ventilated patient with a few caveats. In mechanically ventilated patients, the IVC is less compliant and more distended throughout the respiratory cycle, and the dynamics reverse in comparison to spontaneous ventilation: the IVC expands on inspiration and collapses on expiration. Despite these limitations, an increase in IVC diameter with fluid administration seen with US over time reflects fluid responsiveness.[23]

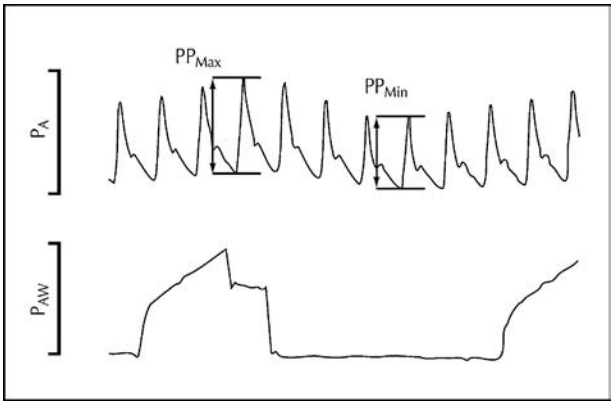

FIGURE 32-6. Pulse pressure variation (PPV) on positive-pressure mechanical ventilation. PPV is defined as the maximal pulse pressure (PP_{Max}) during inspiration minus the minimum pulse pressure (PP_{Min}) during expiration, divided by the average of these two pressures. P_A = arterial pressure; P_{AW} = airway pressure. [Reproduced with permission from Gunn SR, Pinsky MR: Implications of arterial pressure variation in patients in the intensive care unit. *Curr Opin Crit Care* 7: 212, 2001. Lippincott Williams & Wilkins, Inc. Copyright Wolters Kluwer Health.]

NONINVASIVE CARDIAC OUTPUT MEASUREMENT

Minimally invasive or noninvasive hemodynamic monitoring techniques to measure CO in the ED setting include transthoracic echocardiography and pulse contour waveform analysis.

TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography is an accurate tool to estimate CO in the critically ill patient[23,33-35] recommended by the American Society of Echocardiography.[36] Using the parasternal long axis to measure the left ventricular outflow tract diameter and pulse wave Doppler in the apical four-chamber view to measure stroke volume from the left ventricular outflow tract, one can reliably estimate CO.[36]

PULSE CONTOUR ANALYSIS

Several minimally invasive hemodynamic monitoring devices can be easily used in the ED. Most common are devices using pulse contour analysis that quantify CO, stroke volume, and stroke volume or pulse pressure variation to help guide resuscitation. The devices require placement of an indwelling arterial catheter and a central venous catheter to obtain CVP measurement and derive systemic vascular resistance. These devices require a mechanically ventilated patient with a set tidal volume of 8 mL/kg. Also, because these devices rely on pulse contour analysis as the primary means of CO measurement, they cannot be used in the presence of cardiac dysrhythmias (e.g., atrial fibrillation) or mechanical circulatory devices.[37]

INVASIVE CO MEASUREMENT

CO is measured invasively with pulmonary artery catheterization and the thermodilution method. The benefit of using the pulmonary artery catheter for hemodynamic monitoring in the ED setting is understudied. Current expert consensus does not recommend the routine use of the pulmonary artery catheter in the management of the critically ill patient.[18,38] For this reason, pulmonary artery catheterization is usually avoided in the ED.

ORGAN OXYGENATION AND PERFUSION MONITORING

Blood pressure, CVP, and CO serve as macrohemodynamic parameters. Venous oxygen saturation and blood lactate level help to indirectly assess tissue oxygenation or perfusion.

TABLE 32-3 Contributors to Abnormal Central Venous Oxygen Saturation ($Scvo_2$)

Low $Scvo_2$ (<70%)		High $Scvo_2$ (>70%)	
Low Do_2	High $\dot{V}o_2$	High Do_2	Low $\dot{V}o_2$
Hypoxia, suctioning (low Sao_2)	Exercise	Hyperoxia (high Fio_2)	Hypothermia
Anemia, hemorrhage (low Hgb)	Pain	Erythrocytosis (high Hgb)	Anesthesia, pharmacologic paralysis
Cardiac dysfunction, hypovolemia, shock, arrhythmia (low CO)	Hyperthermia, shivering, seizure	Hyperdynamic state (high CO)	Arteriovenous shunting, mitochondria defect, terminal shock

Note: Determining the causes of and treating a low or high $Scvo_2$ clinical state involves troubleshooting for conditions resulting in abnormal oxygen delivery (Do_2) and oxygen consumption ($\dot{V}o_2$).

Abbreviations: CO = cardiac output; Fio_2 = fraction of inspired oxygen; Hgb = hemoglobin; Sao_2 = arterial oxygen saturation.

CENTRAL VENOUS OXYGEN SATURATION

Venous oxygen saturation monitoring assesses the relationship between tissue oxygen extraction, oxygen delivery, and oxygen consumption, with low values reflecting inadequate delivery and/or excessive consumption. It is ideally measured in the pulmonary artery as a mixed venous sample ($Smvo_2$); however, this is impractical in the ED, and central venous oxygen saturation ($Scvo_2$) measured from the internal jugular or subclavian veins acts as a surrogate. A normal oxygen extraction ratio of 25% to 35% results in a *venous* oxygen delivery (reflected in venous oxygen saturation) of approximately 70% of arterial oxygen delivery.

In healthy individuals, $Scvo_2$ is 2% to 3% less than $Smvo_2$; in shock states, $Scvo_2$ is typically 5% to 10% *higher* than $Smvo_2$ as blood flow is redistributed from the abdominal vascular beds to the cerebral and coronary circulation.[39] Although absolute values of $Scvo_2$ and $Smvo_2$ may be different, low values of either measurement reflect an imbalance in oxygen transport and portend worse outcomes. Most important, the two measures typically change in parallel and thus *trends* in $Scvo_2$ closely reflect trends in $Smvo_2$.[40]

Clinical Use of Central Venous Oxygen Saturation The principal value of $Scvo_2$ is to detect occult inadequate oxygen delivery. Regardless of the underlying pathophysiologic state (e.g., heart failure, septic shock, trauma), a low $Scvo_2$ value represents inadequate oxygen delivery relative to oxygen consumption, which can be due to inadequate delivery due to hypoxemia, anemia, or impaired CO (low contractility, hypovolemia, or tamponade) and/or increased oxygen consumption due to increased metabolic demand (**Table 32-3**).

Normal (approximately 70%) or high $Scvo_2$ values do not necessarily mean that the patient is well. $Scvo_2$ is a global measure of oxygen transport, and regional areas of tissue hypoperfusion can exist with normal $Scvo_2$ values, particularly in the lower half of the body. In several disease states (e.g., hypothermia, terminal shock, cyanide poisoning), tissues oxygen extraction from the blood is impaired, leading to "arterialization" of the venous blood with high $Scvo_2$. Routine measuring of $Scvo_2$ in sepsis is not recommended, but if a central venous catheter is in place, obtaining a single $Scvo_2$ measurement is reasonable. A low $Scvo_2$ is always abnormal.

LACTATE

In critical illness, an oxygen debt develops when oxygen delivery is inadequate to meet tissue demand and compensatory mechanisms are exhausted. This results in global tissue hypoxia, anaerobic metabolism, and lactate production. High lactate is a prognostic marker in critically ill patients with various forms of shock, known since the 1800s.[41] This type of acidosis due to anaerobic metabolism is called type A lactic acidosis.

In addition to shock, other causes of elevated lactate include seizure, diabetic ketoacidosis, malignancy, thiamine deficiency, malaria, human immunodeficiency virus infection, carbon monoxide or cyanide poisoning, and mitochondrial myopathies. Commonly used drugs, such as albuterol, propofol, metformin, simvastatin, lactulose, antiretrovirals, niacin, isoniazid, and linezolid, can also cause a lactate elevation.[42] This type of acidosis is called type B lactic acidosis and is not due to hypoperfusion.[37] However, **all lactic acidosis is associated with poor outcome,** and types A and B lactic acidosis can both be present. It is key to understand that not all lactic acidosis is due to hypoperfusion, and fluid administration is based on the global assessment, not just lactate value.

Blood lactate concentrations also reflect the interaction between its production and elimination. During critical illness, a patient with hepatic dysfunction may have a higher lactate level compared with another patient without liver disease due to impaired hepatic clearance. Lactate elevation in a patient with chronic liver disease still portends a poor prognosis, because patients with liver disease do not have a high lactate level in the absence of shock.[43]

Hyperlactatemia is not always accompanied by hypotension or a low bicarbonate level and/or elevated anion gap. Most recently, a blood lactate level ≥2 mmol/L became part of the new definition of septic shock,[44] and an elevated lactate level in a normotensive patient requires further attention because a continued increase in lactate levels is associated with increased mortality.[45] Lactate clearance (a drop of at least 25% within 6 hours of an initial elevated level) in patients with septic shock is associated with increased 60-day survival.[46] When lactic acidosis accompanies low-flow disease states such as sepsis, mortality increases by almost threefold;[47] thus, **all lactic acidosis should be alarming to the emergency physician**.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 33

Cardiac Pacing and Implanted Defibrillation

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Wee Siong Teo
Venkataraman Anantharaman

PURPOSE OF PROCEDURE

Cardiac pacing serves to maintain or restore myocardial depolarization and thus ensure adequate cardiac output. In the ED, pacing corrects rhythm disturbances or starts in anticipation of a conduction problem with hemodynamic impact.[1]

Indications for emergency pacing are provided in **Table 33-1**.

GENERAL EQUIPMENT

Cardiac pacemakers deliver an electrical stimulus to the heart through electrodes, causing depolarization and subsequent cardiac contraction.[2] The modern implanted pacemaker only stimulates the heart chamber if it does not recognize (sense) intrinsic electrical activity from that chamber after a selected time interval. Impulses go to the atria, ventricles, or both.

TABLE 33-1 Indications for Emergency Pacing

Indication	Comments
Symptomatic or hemodynamically unstable bradycardia/AV block	Symptoms include hypotension, change in mental status, angina, and pulmonary edema. Pharmacologic therapy may be used to temporize while preparing to pace.
Severe sick sinus syndrome with prolonged asystole (generally >3 s) and syncope	—
Ventricular standstill due to complete heart block or Mobitz type II AV block	—
Torsades de pointes	Overdrive pacing.
Recurrent monomorphic ventricular tachycardia	Overdrive pacing. The technique is limited by: Maximum pacing rate of the pacing device (usually 180 beats/min). Potential of accelerating the ventricular tachycardia and inducing ventricular fibrillation.
Unstable supraventricular tachycardia	Overdrive pacing should be used only after pharmacologic intervention and cardioversion have failed.

Abbreviation: AV = atrioventricular.

Components of a cardiac pacemaker include:

- Pulse generator
- Electronic circuitry for sensing and pacing
- Lead system that connects the pulse generator to the electrode(s) and stimulates the myocardium

Relevant clinical details of these components are provided in **Table 33-2**.

TRANSCUTANEOUS PACING

Transcutaneous pacing is an emergency technique frequently chosen in patients presenting with hemodynamically significant bradycardia because of its easy application. It uses externally (chest wall) applied electrodes to deliver an electric impulse to stimulate the myocardium. Transcutaneous pacers differ from standard pulse generators: The pulse duration of the externally stimulating impulse is longer and the current output higher than in internal pacing. Muscle contraction (usually the chest wall or diaphragm) is notable during external pacing, especially at high outputs, and may be painful. The muscle twitching makes palpation of the radial, carotid, or femoral pulse difficult. Finally, cardiac monitoring with standard ECG monitors is difficult during external pacing due to interference from the large current outputs that create large-amplitude pacing spikes. Most of the newer transcutaneous pacing units have a monitor that filters pacing spikes, allowing simultaneous monitoring.

TABLE 33-2 Pacemaker Component Details

Pacemaker Type	Pulse Generator Location	Electrode Location
Transcutaneous	External	Skin of anterior chest wall and back or Anterior chest wall below right clavicle and apex
Transvenous	External	Venous catheter with tip in right ventricle and/or right atrium
Transesophageal	External	Esophagus
Epicardial	External or Internal	Epicardium Electrodes are usually placed on heart's surface during surgery
Permanent	Internal (subcutaneous in the prepectoral region)	Venous or epicardial

TABLE 33-3 Transcutaneous Pacing Equipment

- Pulse generator and monitor (usually a combination defibrillator/cardioversion/pacemaker unit)
- Pacemaker pads with pacing cables
- ECG monitor and cables with ECG electrode pads

RISKS AND PRECAUTIONS

There is little risk of electrical injury to healthcare providers during transcutaneous pacing. The electrode insulation allows contact with the patient, including closed chest compressions, while pacing.

EQUIPMENT

Table 33-3 lists the equipment needed to perform transcutaneous pacing.

TECHNIQUE

If time and conditions allow, explain the procedure to the patient and administer IV sedation and analgesia before pacing. Vital signs and ECG monitoring are mandatory during the procedure.

Place the pacing pads on the patient's chest either in the anterolateral or anterior-posterior position (**Figure 33-1**). The anterior-posterior position minimizes transthoracic electrical impedance by sandwiching the heart between the two pads. The same pads and electrodes allow pacing, cardioversion, and defibrillation in most of the newer defibrillator units.

In bradyasystolic arrest or with depressed sensorium, turn the stimulating current to maximum output; after restoring pulses, you may titrate energy downward to a level just above loss of capture. In a still-conscious patient with a hemodynamically compromising bradycardia, slowly increase the output from the minimum setting until capture—usually between 50 and 100 mA. Continue pacing at about 1.25 times the threshold of initial electrical capture.

Transcutaneous pacing may be fixed rate (asynchronous) or demand (synchronous). **Asynchronous pacing** delivers an electrical impulse at a regular interval without regard to intrinsic cardiac pacemaker activity. This creates the potential risk of precipitating a dysrhythmia if the pacing stimulus occurs during the vulnerable period of ventricular repolarization. Although many state a preference for synchronous pacing, there are little outcome or safety data to support that preference.

OUTCOMES ASSESSMENT

Assess capture using the ECG on the filtered monitor of the pacing unit. Look for the presence of a consistent ST segment and T wave after each pacer spike. Palpate for carotid and femoral pulses with each such waveform. Bedside cardiac US can assess external pacer mechanical contraction, identifying capture. If these appear favorable, assess blood pressure by cuff or arterial catheter.

Failure to capture with transcutaneous pacing may be related to faulty electrical contact, inadequate current, poor pacing pad placement, or the underlying pathology. Recheck the lead connections, skin–electrode contact, and electrode placement. On occasion, pneumothorax, pericardial effusion or tamponade, severe myocardial ischemia, and metabolic derangements limit capture. Unless an easily resolved trigger exists, arrange for transvenous pacing as soon as possible.

TRANSVENOUS PACING

The indications for transvenous pacing are the same as for other methods of cardiac pacing. Transvenous pacing is an urgent rather than emergent intervention, with transcutaneous pacing serving as the bridge.

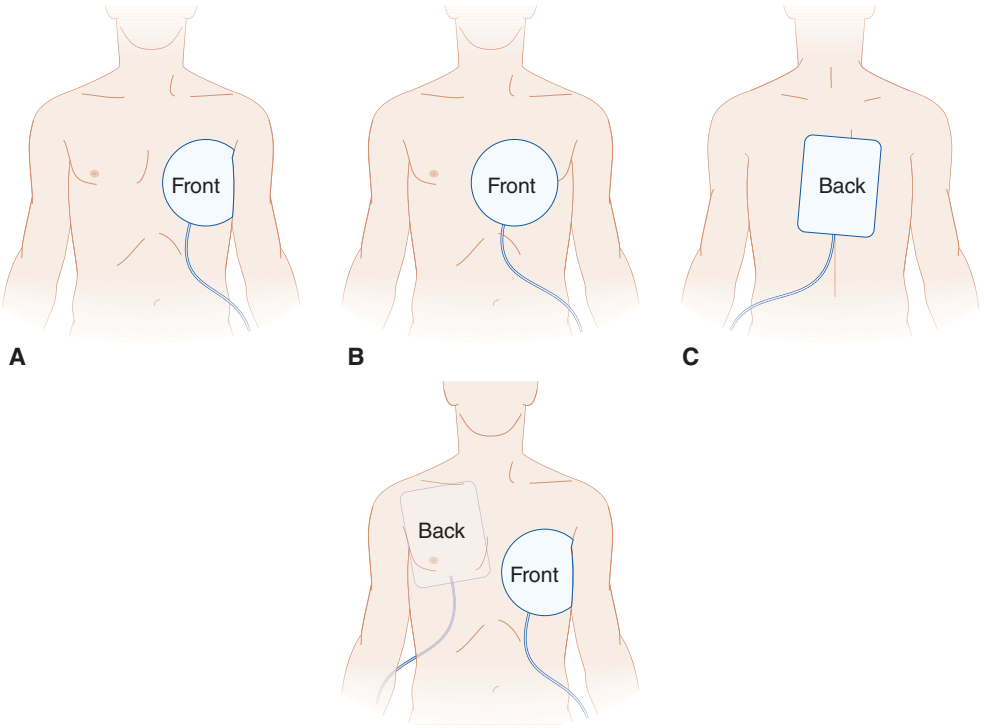

FIGURE 33-1. Placement of the transcutaneous pacing electrodes. **A.** Anterior (negative) electrode position centered over the cardiac apex. **B.** Anterior (negative) electrode position centered over the V_3 lead position. **C.** Posterior (positive) electrode position. [Reproduced with permission from Doukky R, Rajanahally RS: Transcutaneous cardiac pacing, in Reichman EF, Simon RR (eds): *Emergency Medicine Procedures*. Figures 20-2 and 20-3. Copyright © 2004. The McGraw-Hill Companies, Inc. All rights reserved.]

Gather all equipment needed, including that to insert a central venous catheter (see Chapter 31, "Vascular Access"). Resuscitation equipment and drugs and the pacing needs are listed in **Table 33-4**.

TECHNIQUE

You should know the equipment and have practiced or done the procedure before starting. If conditions permit, explain the procedure to the patient and obtain informed consent. Next, identify the access site and approach and position the patient. The primary **sites of catheter insertion in the ED are the right internal jugular vein (preferred)** and the left subclavian vein. The right internal jugular vein allows a relatively straight line of access through the superior vena cava and right atrium into the right ventricle.

The steps for transvenous pacemaker insertion are listed in **Table 33-5**.

The most commonly encountered difficulties with transvenous pacing are securing venous access and obtaining proper placement of the stimulating electrode in the right ventricle, both of which can be time-consuming. When patients have decreased or no forward blood flow, positioning of the pacer tip within the right ventricle is difficult. Balloon-tipped catheters do not aid during low- or no-flow states. In an emergency, connect the pacemaker electrodes to the power source and advance the catheter until the tip encounters the endocardium of the right ventricle and creates capture.

Set the initial rate between 80 and 100 beats/min, using the asynchronous mode (sensitivity off) initially in patients requiring emergency pacing for hemodynamically unstable bradycardias. Follow the ECG to determine the presence or absence of capture (**Figure 33-2**). Adjust subsequent rate and sensitivity settings as clinically indicated by the response and underlying rhythm disturbance.

TABLE 33-4 Equipment Needed for Transvenous Pacing

- Central catheter kit—introducer sheath must be one size larger than the pacer catheter
- Flexible transvenous cardiac pacing catheter
- Pacemaker generator and battery (and spare battery)
- Cardiac monitor
- Insulated connecting wire with alligator clamps at both ends

COMPLICATIONS

Complications include perforation of the myocardium, cardiac dysrhythmias, air embolism, failure of the circuit, catheter dislodgement, and delayed infection, plus any complications possible with central venous access (see Chapter 31).

PERMANENT PACING

Permanent pacing is not performed in the ED.[1] Permanent pacemaker pulse generator (battery) placement is usually on the side of the patient's nondominant hand (thus, usually in the left prepectoral region below the left clavicle). The endocardial transvenous leads insert into the right ventricle at the apex, septum, right ventricular outflow tract, or His Bundle region and, in the case of a dual-chamber device, also in the right atrium. A subclavian or cephalic vein approach is common. An epicardial lead may be implanted during open heart surgery. Patients with heart failure may have a cardiac resynchronization therapy device and will have three wires, with one in the atrium, one in the right ventricle, and one in the coronary sinus pacing the left ventricle.

Pacemaker leads are either bipolar or unipolar in configuration; unipolar leads are prone to oversensing myopotential and electromagnetic interference.

A new form of pacing is the leadless pacemaker where insertion of a miniature device transvenously for right ventricle implantation occurs.[3] There is no device noted externally.

PACEMAKER NOMENCLATURE

A five-letter code describes the features of the pacemaker.[4] The first three code letters are most commonly used. The first letter refers to the chamber or chambers in which the pacing occurs: **A** = **atrium, V** = **ventricle**, and **D** = **dual chamber** or both A and V. The second letter

TABLE 33-5 Transvenous Pacemaker Insertion

Step	Comments
1. Gown in standard sterile fashion.	Use sterile gloves and gown. Wear mask and hair covering.
2. Identify vessel using US guidance.	—
3. Prep and drape patient using standard sterile procedure.	Prep a wide area in case initial attempts fail and an alternate site is needed. Prep the entire ipsilateral neck and upper chest when preparing to insert an internal jugular or subclavian catheter.
4. Open a central catheter kit that contains an introducer catheter. Inspect for content in a sterile fashion. Place kit close to bedside and operator. Maintain sterile conditions.	The introducer catheter should be one size larger than the pacing catheter.
5. Open pacing catheter and pacing kit (if available).	Pulmonary artery catheters with dedicated atrial and ventricular ports may also be used. Assess integrity of the pacing catheter balloon by inflating it with 1.5 mL of air and immersing it in sterile saline. Air bubbles indicate a leaky balloon.
6. Attach the pacemaker to any of the V leads and ensure it is recording.	—
7. Anesthetize area in all conscious patients.	Inject area with 1%–2% lidocaine. Anesthetize the periosteum of the clavicle if using the subclavian approach. Reorient to landmarks after injection.
8. Hold the 18-gauge introducer needle on a 10-mL syringe in the dominant hand and align the needle to the target.	—
9. Advance the needle slowly though the skin and subcutaneous tissue until a flash of dark venous blood appears.	Maintain steady constant aspiration of syringe.
10. Stabilize the needle with the nondominant hand.	—
11. Check for continued free venous flow with aspiration.	If no flow is noted, withdraw the needle slightly, as the needle may have breached the posterior vessel wall.
12. Remove the syringe attached to the needle, and immediately occlude the catheter with a finger.	This maneuver helps to prevent introducing air in the catheter and subsequent central system air embolism.
13. Insert the guidewire gently through the needle. Always maintain a firm grip on the wire—do not let go of the wire for any reason.	The wire should advance with minimal resistance. Do not force the wire for any reason. If the wire does not pass easily, reattach the syringe and aspirate to confirm continued venous flow. Reposition the needle as needed. Premature ventricular contractions (PVCs) or dysrhythmias during wire advancement may indicate that the wire is in the right atrium or beyond.
14. Remove the needle over the wire when the guidewire is inserted at least 10 cm into the vessel.	—
15. Incise the skin with a #11 blade scalpel at the entry site to accommodate the introducer.	Do not cut the guidewire.
16. Advance the introducer over the guidewire into the vessel lumen with a gentle twisting motion.	Maintain a grip on the guidewire during this procedure.
17. Remove the guidewire.	—
18. Insert and advance the pacing catheter approximately 10 cm.	This ensures that the balloon is past the introducer catheter and within the vascular system. Inflate the balloon with 1.5 mL of sterile saline.
19. Slowly advance the catheter into the right ventricle.	Use fluoroscopy or bedside US to guide placement. The ECG tracing recorded from the electrode also helps localize the position of the catheter tip. Inflate the balloon after the catheter enters the superior vena cava. Stop advancing when the pacing catheter is in the apex of the right ventricle.
20. Reassess balloon integrity.	—
21. Connect the pacemaker generator to the catheter.	—
22. Disconnect the negative terminal of the pacemaker catheter from the ECG lead.	—
23. Connect the proximal pacemaker catheter terminals to the terminals of the pacemaker generator.	—
24. Set the pacemaker generator on demand mode with a rate of 80–100 beats/min.	Start with 5 mA of energy on the output dial.
25. Turn on the pacemaker.	With optimal tip position, capture should occur at <2 mA. Pacing spikes and a wide QRS complex in lead V_1 reflect capture.
26. After capture, decrease the pacemaker generator output to just below where pacing stops.	Continue pacing at 1.5–2.0 times the threshold output required for capture.
27. Examine the chest radiograph for catheter tip placement and signs of complications.	—
28. Secure catheter and apply a sterile transparent dressing.	—

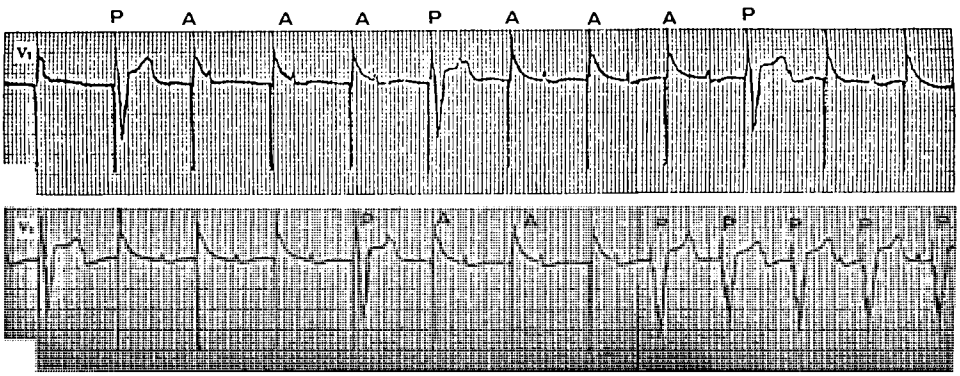

FIGURE 33-2. Pacing with intermittent capture. "P" indicates paced beats, and "A" indicates pacer artifact without capture.

refers to the chamber or chambers in which sensing occurs. The letters are the same as those for the first letter code. "**I**" indicates that a sense event inhibits the output pulse and causes the pacemaker to recycle the timing cycles, "**T**" means that an output pulse is triggered in response to a sensed event. "**D**" means that both "**T**" and "**I**" responses can occur. The most common pacemakers are **VVI** and **DDD**. The fourth letter is used to indicate the presence or absence of an adaptive-rate mechanism (rate modulation). Pacemaker designations may be VVIR or DDDR. The fifth letter indicates whether multisite pacing is present and is rarely used. See **Figures 33-3 and 33-4** for examples of ECGs with pacemaker spikes.

RESUSCITATION IN PATIENTS WITH A PERMANENT PACEMAKER

If a patient who has a permanent pacemaker requires countershock, place the pads or paddles at least 8 cm from the pulse generator. The current normal positioning of the paddles—below the right clavicle and apex of the heart—is safe because most pulse generators are below the left clavicle. Alternatively, place adhesive electrodes in an anteroposterior configuration. After countershock, interrogate the pacemaker to ensure that it is still functioning normally.

Potential problems after defibrillation include:

- Pacemaker inhibition due to reversion to noise mode
- Deletion (reprogramming)
- Circuit damage
- Myocardial damage adjacent to the lead tip caused by current transmission via the electrode to the myocardial interface

Another reason that immediate return of pacing (capture) fails after defibrillation is that global myocardial ischemia increases pacing threshold. If this occurs, try transcutaneous pacing at higher delivered energy settings.

PACEMAKER COMPLICATIONS

Complications for which a patient may seek care in the ED early after pacemaker insertion are listed in **Table 33-6**.

Pacemaker Syndrome Atrioventricular synchrony and the presence of ventriculoatrial conduction are most common in the setting of VVI pacing but may occur with the DDI mode. With VVI pacing, the ventricle stimulation results in ventricular contraction. If sinus node functions are intact, the native sinus impulse causes contraction with closed tricuspid and mitral valves. This results in an increase in jugular and pulmonary venous pressures and may produce symptoms of congestive heart failure. Atrial distention can result in reflex vasodepressor effects mediated by the CNS. If the contribution of atrial contraction to late diastolic ventricular filling is important in maintaining an adequate cardiac output, orthostatic hypotension may occur. DDI pacing in a patient with atrioventricular block can result in pacemaker syndrome if the sinus node discharge rate exceeds the programmed rate of the pacemaker.

In most instances, symptoms are mild and patients adapt to them. In about one third of these patients, symptoms are severe. Treatment usually requires upgrading a VVI pacemaker to a dual-chamber pacemaker or lowering the pacing rate of the VVI unit so that ventricular pacing does not occur provided intrinsic conduction occurs. If symptoms occur



FIGURE 33-3. Single-lead pacemaker. Only the ventricle is paced.

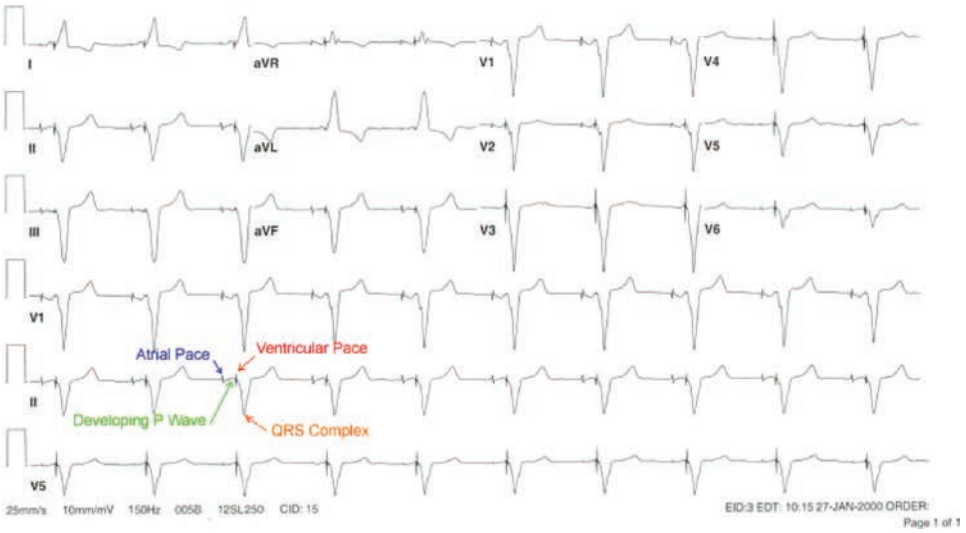

FIGURE 33-4. Atrioventricular pacer spikes seen best in leads II and aVF.

TABLE 33-6 Complications Seen After Pacemaker Insertion

Complication	Comment
Infection	Infection rate is <1%. Infections are more common in patients after pacemaker replacement or prolonged procedure. Early infections are most commonly caused by *Staphylococcus aureus or Staphylococcus epidermidis.* Pacemaker infection presents as: Local inflammation or abscess formation in the pacemaker pocket, as evidenced by pain, tenderness, or redness at the site. Skin adherence to the device, especially with discoloration of the skin over it, is highly indicative of localized infection. Do not aspirate the pocket because this can worsen the infection. If only a superficial infection is suspected, antibiotics and analgesics may be given with an early referral to the device implanter to review. Erosion of the device or lead through the skin resulting in the leads or pulse generator being exposed. Complete device and lead removal is almost always required. Cardiac device–related infective endocarditis involving the lead or valves. Patient may present with sepsis and positive blood culture without sign of local inflammation.
Thrombophlebitis and venous obstruction	Symptomatic thrombosis of the upper extremities and central veins is uncommon, possibly because of extensive venous collaterals (0.3%–3.0% of patients). Site of insertion does affect incidence. Symptoms include edema, pain, or venous engorgement of the arm ipsilateral to lead insertion. Treatment includes IV heparin therapy followed by long-term warfarin administration.
Pneumothorax	1% of patients. More common with subclavian introducer technique. Hemothorax and pneumomediastinum are rare.
Pacemaker syndrome	20% of patients. New or worsening of symptoms such as syncope or near-syncope, orthostatic dizziness, exercise intolerance, dizziness, uncomfortable pulsation over the neck and abdomen, right upper quadrant pain, etc.

in a patient paced in the DDI mode, optimizing the timing of atrial and ventricular pacing is best done by a consulting cardiologist.

PACEMAKER MALFUNCTION

Pacemaker malfunction occurs in four ways: failure to sense, failure to pace, failure to capture, or overpacing or pacemaker-associated tachycardia.[5]

Failure to Sense (Undersensing) Undersensing occurs when the pacemaker cannot detect the intrinsic electrical cardiac activity. This results from lead placement in an area of the heart with poor or variable conductivity, or if a lead is loose, dislodged, or physically broken. Sensing failure can occur if the programmed sensing threshold is set too high. With undersensing, if the pacer is set in an inhibit mode, it will fire at a set rate that is uncoordinated with the patient's underlying cardiac cycle (**Figure 33-5A**).

Failure to Pace (Oversensing) Oversensing occurs when the pacemaker experiences interference from electrical signals within the body (i.e., skeletal or smooth muscle myopotentials) that are not related to the normal cardiac cycle. Sources of interference may include skeletal muscle, the diaphragm, nerve stimulators, broken pacer leads, and uncommonly, coarse atrial fibrillation. When oversensing, the pacemaker erroneously inhibits the pulse generator, and the patient may develop bradycardic rhythms (**Figure 33-5B**).

Failure to Capture Failure to capture occurs when the pulse generator fires but the current delivered to the endocardium is too low to initiate depolarization and wavefront propagation. Dislodged or broken leads, poor cardiac conductivity due to myocardial disease (e.g., ischemia, acidosis, fibrosis), and programming problems are the most common reasons for this malfunction. Failure to capture can be intermittent (**Figure 33-5C**).

PACEMAKER-ASSOCIATED TACHYCARDIA

Occasionally the patient with an implanted device may present with a rapid paced rhythm. This may be due to:

- Rapid atrial arrhythmia triggering an upper rate response in a patient with complete heart block
- Pacemaker-mediated tachycardia
- Runaway pacemaker

Unless preprogrammed to mode switch, pacemakers detect rapid atrial rhythms and track them, resulting in pacing at the upper rate limit. Pacemaker-mediated tachycardia can occur in a *dual-chamber*

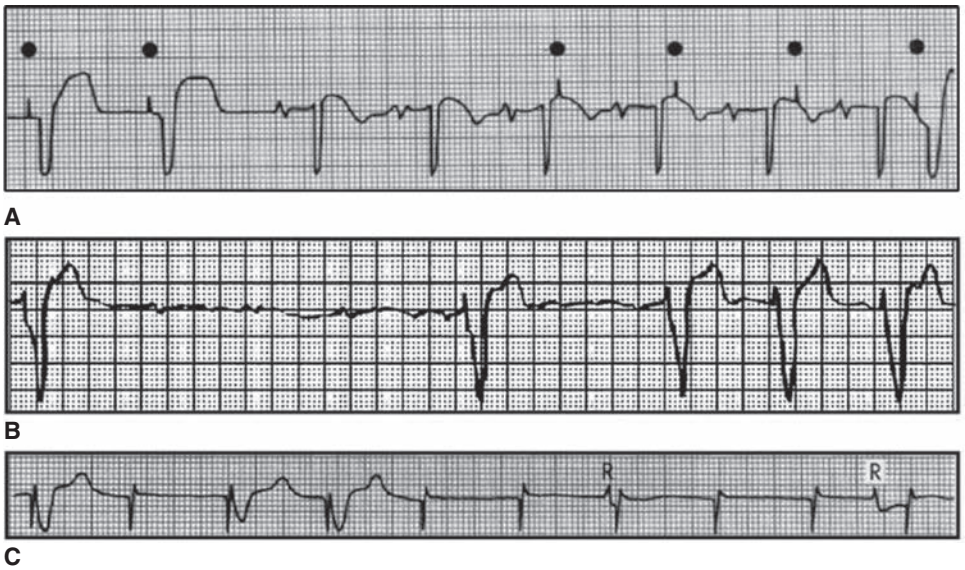

FIGURE 33-5. Various pacemaker malfunctions. **A.** Undersensing. **B.** Oversensing. **C.** Failure to capture.

pacemaker when a premature ventricular ectopic beat triggers a retrogradely conducted atrial depolarization outside the atrial refractory period, then sensed by the pacemaker, initiating ventricular pacing. If this continues, it can cause an endless loop tachycardia. Rarely the pacemaker may malfunction with acceleration of pacing (runaway pacemaker). This occurs when the pulse generator discharges at a rapid rate above its preset upper limit and is most commonly associated with a battery failure or damage from external interference. Placing a magnet over the pacemaker may help in the pacemaker-mediated tachycardia or runaway pacemaker. However, interrogation of the device is usually required, and the device must be replaced if programming is not successful.

PACEMAKER PROGRAMMING ERRORS

Pacemakers are computer-controlled devices with complex software that requires adjustment and maintenance. Reprogramming is noninvasive through radio frequencies. Occasionally, settings are inadvertently altered, or software can fail. Software changes may occur in set rates, sensing thresholds, and current outputs.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Implantable cardioverter-defibrillators are the treatment of choice for sudden cardiac death, reducing mortality from approximately 30% to 45% per year to <2% per year.[5] This remarkable impact, coupled with the failure (and potentially prodysrhythmic effects) of pharmacologic therapy and the increasing sophistication and miniaturization of the devices, all add to implantable cardioverter-defibrillator use. The most common cause of death in patients with an implantable cardioverter-defibrillators is congestive heart failure.

An implantable cardioverter-defibrillator consists of a pulse generator, a lead system with both sensing and shocking electrodes, circuitry to analyze the cardiac rhythm and trigger defibrillation, and a power supply.

In the past, insertion of these devices generally was by thoracotomy or sternotomy, and defibrillation occurred through electrodes positioned inside or outside the pericardium. In newer implantable cardioverter-defibrillators, sensing-pacing-defibrillation electrodes are inserted transvenously, and the control device is placed subcutaneously in the subpectoral region or in an abdominal pocket. Newer implantable cardioverter-defibrillators are better at discriminating supraventricular tachycardia and are capable of a variety of responses to ventricular tachycardia and fibrillation. Most device programs follow a tiered approach to ventricular dysrhythmias: antitachycardia pacing, low-energy cardioversion, and finally defibrillation. Depending on the frequency of discharge and whether the pacemaker function is used, the latest implantable cardioverter-defibrillators have a projected life span of approximately 6 to 9 years, depending on whether they are single- or dual-chamber devices.

Some newer devices may be implanted subcutaneously. These devices do not have pacing function and reside in the left axillary region, with the lead tunneled to the left sternal region. In such patients, place the defibrillation pad in the anterior-posterior region.

ED EVALUATION

The most common reason a patient with an implantable cardioverter-defibrillator comes to the ED is evaluation after a delivered shock. Causes of inappropriate shock delivery are listed in **Table 33-7**. Determine the number of shocks delivered, the activity of the patient at the time of shock, and any prodromal symptoms or postshock trauma. Ask about any recent changes in rhythm-directed drug therapy. Focus the physical examination on the vital signs, the cardiovascular status, the generator pocket, and evidence of incidental trauma. Place each patient on a continuous ECG monitor, and **obtain a 12-lead ECG; any shock-related ST-segment elevations or depressions should resolve within 15 minutes; ongoing changes suggest new ischemia.** Examine a chest radiograph for electrode migration, displacement, or fracture. Obtain rhythm-related drug levels and serum electrolyte levels.[6,7]

If the patient is receiving repeated inappropriate shocks for a nonlethal rhythm, temporarily deactivate the implantable cardioverter-defibrillator by placing a magnet over the device. Defibrillation can be reenabled by removing the magnet. Have a cardiologist evaluate all patients with implantable cardioverter-defibrillators after exposure to a magnet.

TABLE 33-7 Potential Causes of Inappropriate Implantable Cardioverter-Defibrillator (ICD) Shock Delivery

- False sensing
- Supraventricular tachycardia with rapid ventricular response
- Muscular activity (shivering, diaphragmatic contraction)
- Extraneous source (tapping of chest wall, vibrations, pacer spikes)
- Sensing T waves as QRS complex (double counting)
- Sensing lead fracture or migration
- Unsustained tachyarrhythmia
- ICD–pacemaker interactions
- Component failure

For a patient with an implantable cardioverter-defibrillator in cardiac arrest, follow standard resuscitation measures. **If defibrillation is necessary, do not place either the paddle or pad directly over the implantable cardioverter-defibrillator pulse generator.** Perform CPR in the usual fashion. If the implantable cardioverter-defibrillator discharges, the CPR provider may perceive a small electrical shock, but the shock is neither uncomfortable nor dangerous.

DISPOSITION AND FOLLOW-UP

Admission criteria depend on the reason for shock delivery. Consultation with the treating cardiologist is key with implantable cardioverter-defibrillator interrogation, which is manufacturer and model specific. Admit those with any sign of cardiovascular instability, a history of two or more new shocks in a 1-week period, correctable causes of dysrhythmia, and any sign of infection or mechanical disruption of the implantable cardioverter-defibrillator or lead system.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 34

Pericardiocentesis

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Eric J. Brown

INTRODUCTION AND EPIDEMIOLOGY

Cardiac tamponade is a rare condition in daily ED practice but in need of recognition. **If a pericardial effusion compromises hemodynamics, pericardiocentesis is lifesaving.** Blood or fluid filling the pericardial space can cause tamponade, with the latter dictated by the pace and volume of either material accruing. The cause of cardiac tamponade may be determined by fluid analysis after pericardiocentesis (**Table 34-1**).[1-4] In oncology patients, look carefully for this as a cause of weakness, breathing difficulty, syncope, or chest pain.

In a small study of medical cardiac tamponade, the mean volume drained was 593 ± 313 mL; traumatic acute tamponade typically has much smaller volumes of pericardial fluid. When the primary cause was malignancy, the 1-year mortality was almost 80%.[5] In Africa, up to 70% of pericardial effusions in patients with human immunodeficiency virus are caused by tuberculosis.[6]

Blunt cardiac rupture is rare, occurring approximately in 1 in 2400 blunt trauma patients. Of this subgroup, 89% arrive alive to the ED.[7] Those who arrive alive may benefit from a bedside US examination to detect a traumatic effusion. **Tamponade from trauma is best treated with a subxiphoid window procedure, though a temporizing pericardiocentesis can aid while preparing for this or definitive surgical repair.**

In a South African study, the mortality rates from chest gunshot wounds and stab wounds were 81% and 15.6%, respectively.[8] This comparison underlines the probability that patients with stab wounds to the heart are more likely to survive to the ED and may benefit from pericardiocentesis.

PATHOPHYSIOLOGY

The pericardium is a fibrocollagenous sac covering the heart that contains a small amount of physiologic serous fluid. The fibrocollagenous pericardium has elastic properties and will stretch in response to increases in intrapericardial fluid. Accumulation of fluid that exceeds the stretch capacity of the pericardium precipitates hemodynamic compromise and results in pericardial tamponade.

The initial portion of the pericardial volume–pressure curve is flat, so early on, relatively large increases in volume result in comparatively small changes in intrapericardial pressure. The pericardium becomes less elastic as the slope of the curve marches upward. As fluid continues to accumulate, intrapericardial pressure rises to a level greater than that of the filling pressures of the right atrium and ventricle. When this occurs, restricted ventricular outflow results in symptoms and cardiac tamponade.[9]

TABLE 34-1 Causes of Pericardial Effusions

Cause	Sagrista-Sauleda et al[1] (n = 322) (%)	Corey et al[2] (n = 75) (%)	Levy et al[3] (n = 204) (%)	Kil et al[4] (n = 116) (%)
Acute idiopathic	20	7	48	—
Idiopathic	16	7	—	4
Malignancy	13	23	15	52
Chronic	9	—	—	—
Post–myocardial infarction	8	—	—	—
Uremia	6	12	2	7
Autoimmune	5	12	10	5
Radiation	—	14	—	—
Infection	—	27	16	4
Hypothyroidism	—	—	10	3
Tuberculosis	—	—	—	14

Pulsus paradoxus is common in those with cardiac tamponade, defined as an abnormal decrease in systolic blood pressure and pulse wave amplitude. During normal respirations, systolic blood pressure drops less than 10 mm Hg. In pulsus paradoxus, systolic blood pressure drops >10 mm Hg, resulting in a cardiac contraction that does not result in a normal radial pulse. This causes a paradoxical pulse.[10]

In blunt trauma, forces within the thorax can compress the right atrium, resulting in rupture of the atrium or the right atrial appendage. This occurs when blood continues to fill the relatively inelastic pericardial sac. Deceleration injuries can lead to a cardiac or pericardial rupture, herniation, or a myocardial contusion with intrapericardial hemorrhage. Blast injuries can cause acute cardiac tamponade.[11] **During an acute rapidly expanding pericardial effusion, stroke volume will increase with removal of even a small amount of fluid (as little as 50 mL) from the pericardial sac (Figure 34-1).**

CLINICAL FEATURES

HISTORY

Trauma as a cause of pericardial tamponade is generally evident from history and clinical presentation. Postoperative or penetrating trauma

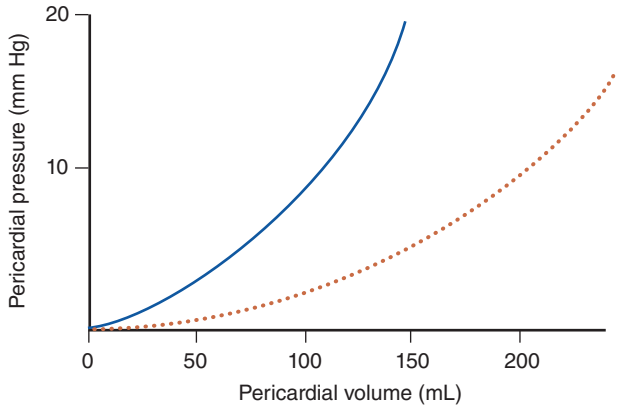


FIGURE 34-1. Acute versus chronic pericardial effusion. Pericardial volume–pressure curve with acute (*solid line*) versus chronic effusion (*dotted line*). [Reproduced with permission from Reardon RF, Joing SA: Cardiac, in Ma OJ, Mateer J, Reardon R, Joing SA(eds): *Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill, Inc.; 2013.]

patients may develop tamponade 2 weeks or more after surgery.[7] Oncology patients are the largest group with pericardial effusions leading to hemodynamic compromise. Other conditions that may predispose a patient to pericardial effusion and tamponade include renal failure, acute infection (viral, bacterial, mycoplasma, fungal, parasitic, or endocarditis), or radiation exposure. Other chronic conditions in which this diagnosis may be considered include tuberculosis, autoimmune diseases, drugs that induce a lupus-like syndrome, hypothyroidism, or ovarian hyperstimulation syndrome.[12] Many cases are idiopathic.

The **key symptoms of tamponade are dyspnea and chest pain.** Trauma patients may or may not exhibit pleuritic pain, tachypnea, and dyspnea before becoming confused, losing consciousness, or developing shock.[13] Other symptoms include chest fullness, nausea, esophageal pain, or abdominal pain from hepatic and visceral congestion. Other nonspecific symptoms include lethargy, fever, weakness, fatigue, anorexia, palpitations, and shock. Be aware of these symptoms and focus the examination to exclude life-threatening conditions such as cardiac tamponade.

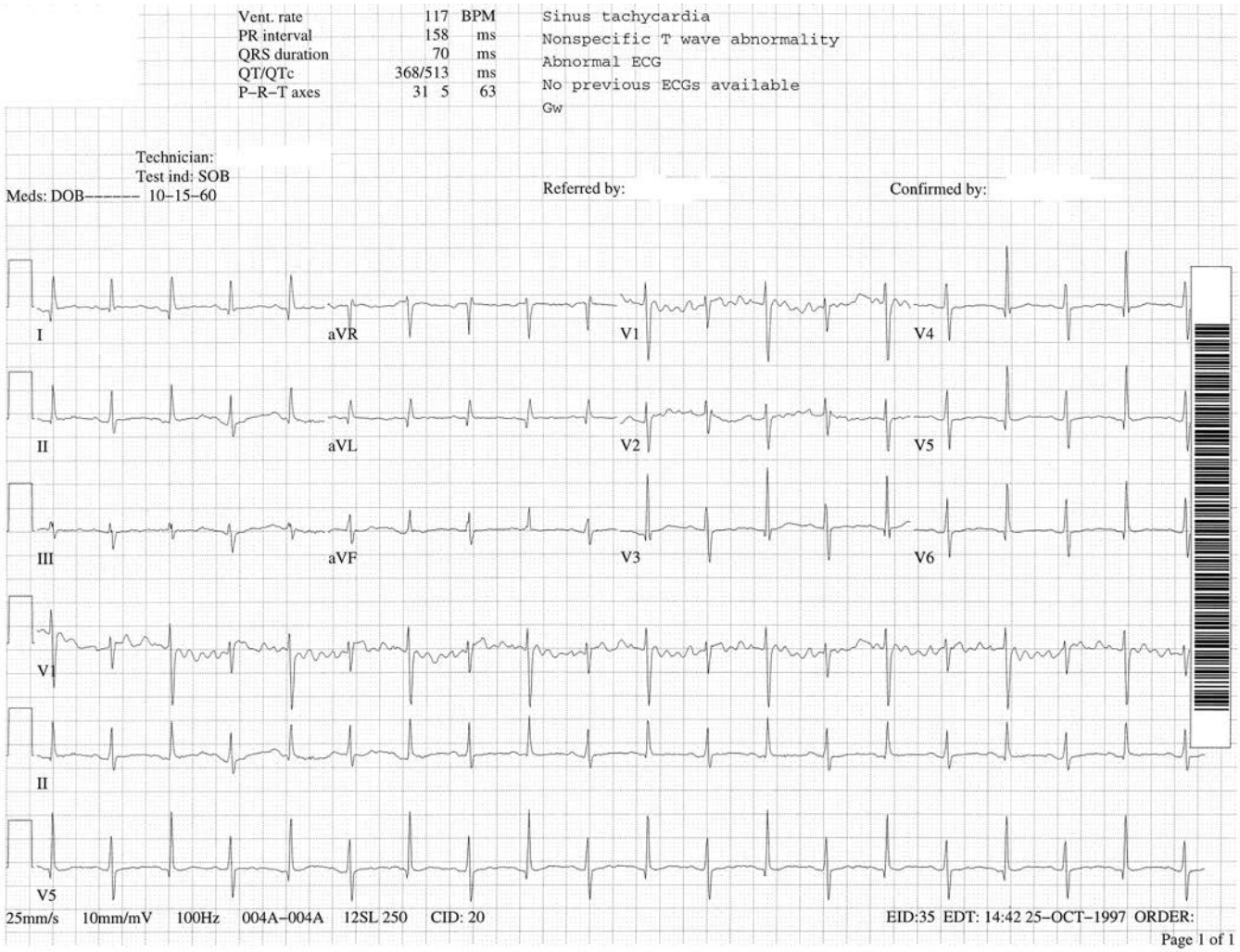
PHYSICAL EXAMINATION

Common clinical signs of cardiac tamponade resemble other severe cardiopulmonary disease processes such as tension pneumothorax or decompensated congestive heart failure. The sensitivities of examination findings are 82% for pulsus paradoxus >10 mm Hg, 77% for tachycardia, 76% for jugular venous distention, 28% for diminished heart sounds, and 26% for hypotension. The classic (but not common) **Beck's triad** includes low blood pressure, elevated jugular venous distention, and decreased heart sounds.[10] Detection of jugular distention may be difficult to appreciate in patients with a short, thick neck or if working under levels of low lighting. **The combination of pulsus paradoxus and elements of the Beck's triad should prompt imaging with bedside US to search for a pericardial effusion.** Any disorder that increases intrathoracic pressure may result in pulsus paradoxus, including chronic obstructive pulmonary disease, obesity, tense ascites, severe asthma, congestive heart failure, mitral stenosis, and massive pulmonary embolism.

DIAGNOSIS

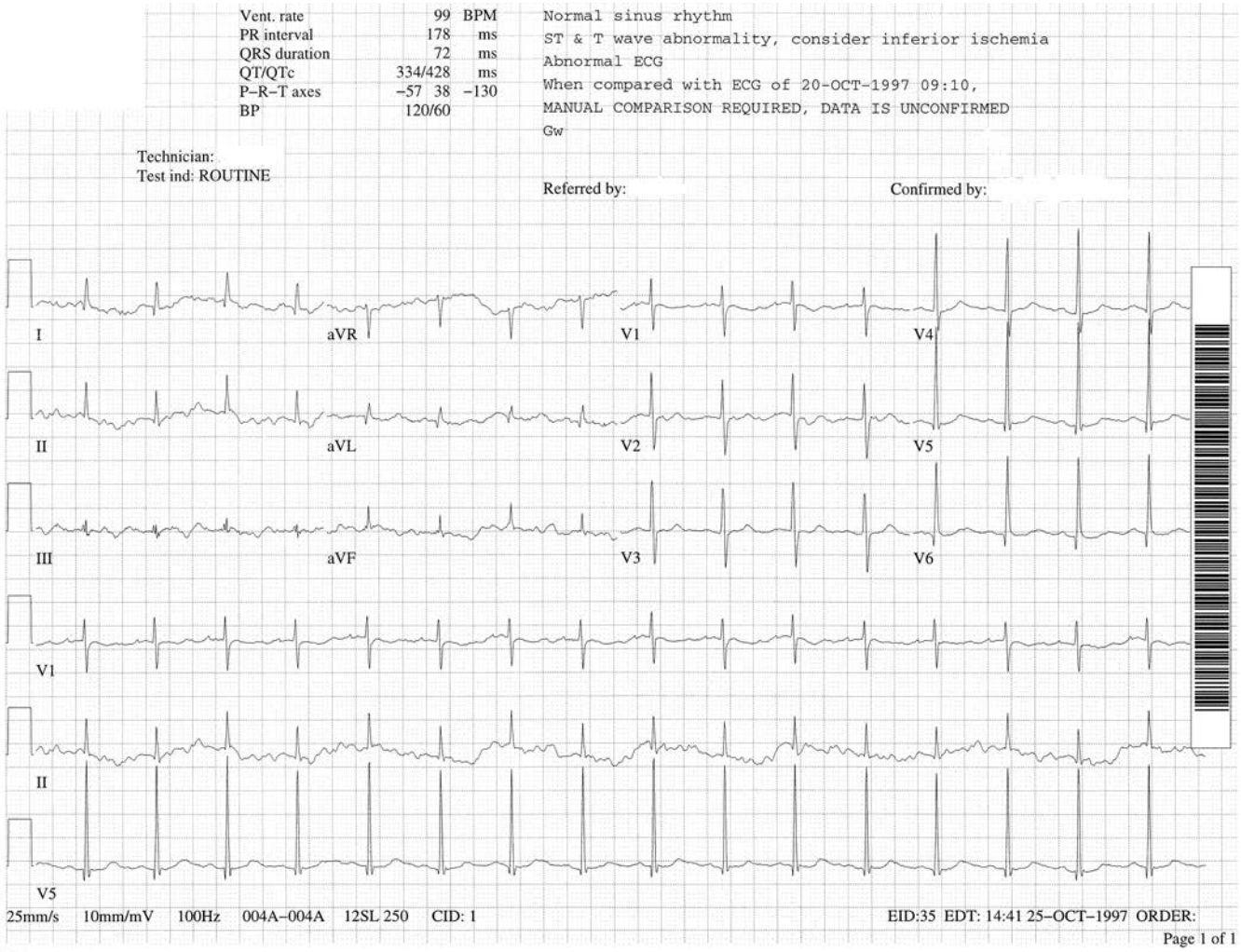
The diagnosis relies on considering this cause by recognizing the signs and symptoms of cardiac tamponade and then confirmation using bedside US.

The ECG is often normal or nondiagnostic; the classic ECG finding is electrical alternans, alternating high- and low-voltage QRS complexes as the heart swings toward and then away from the ECG leads on the chest wall with each contraction (**Figure 34-2**). Other findings include nonspecific ST-T–wave changes or bradycardia, which can be seen in the late stages of cardiac tamponade progressing to pulseless electrical activity. In the absence of hypotension and tension pneumothorax in a



A

FIGURE 34-2. ECG of electrical alternans, with alternating higher- and lower-voltage QRS complexes. **A.** Initial ECG in the ED. Bedside echocardiography revealed a large pericardial effusion with right ventricular diastolic collapse. **B.** Resolution of electrical alternans after pericardiocentesis. [Reproduced with permission from Smith RF: Pericardiocentesis, in Reichman EF (ed): *Emergency Medicine Procedures,* 2nd ed. New York: McGraw-Hill, Inc.; 2013.]



B

FIGURE 34-2. (*Continued*)

patient with pulseless electrical activity, consider the diagnosis of cardiac tamponade.

IMAGING

Chest radiographs may show a normal or enlarged cardiac silhouette with clear lungs, as demonstrated in **Figure 34-3**. On lateral chest radiographs, a double lucency sign demonstrates the epicardial fat pad.

Echocardiography Cardiac tamponade is best detected at the bedside with two-dimensional echocardiography and Doppler echocardiography. This allows for visualization of a pericardial effusion and the compression of the ventricles. The most characteristic sign on echocardiogram is right-sided heart collapse. During diastole, the right ventricle presses inward (**Figure 34-4**), and during systole, the right atrium presses inward. Right-sided collapse portends rapid development of cardiac tamponade. Right atrial collapse during at least 30% of the cardiac cycle is more sensitive than the finding of right ventricular collapse for cardiac tamponade. In 25% of patients with tamponade, a late finding is left atrium collapse. Doppler US can monitor the respiratory changes in flow between ventricle and atrium.[9]

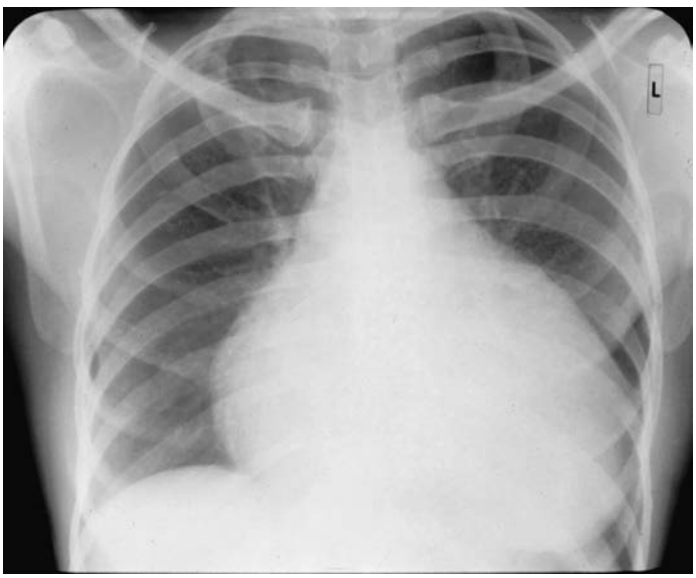


FIGURE 34-3. Pericardial effusion on posteroanterior chest film. Note how the cardiac silhouette is rounded in its lower portion and tapers at the base of the heart, resembling a plastic bag filled with water sitting on a table. [Reproduced with permission from Sorajja P: Pericardial disease, in Hall JB, Schmidt GA, Kress JP (eds): *Principles of Critical Care*, 4th ed. New York: McGraw-Hill, Inc.; 2015.]

PROCEDURE: EMERGENCY PERICARDIOCENTESIS

When hemodynamic compromise is present, infusion of a crystalloid fluid bolus enhances right ventricular volume while preparing for emergency pericardiocentesis.[1]

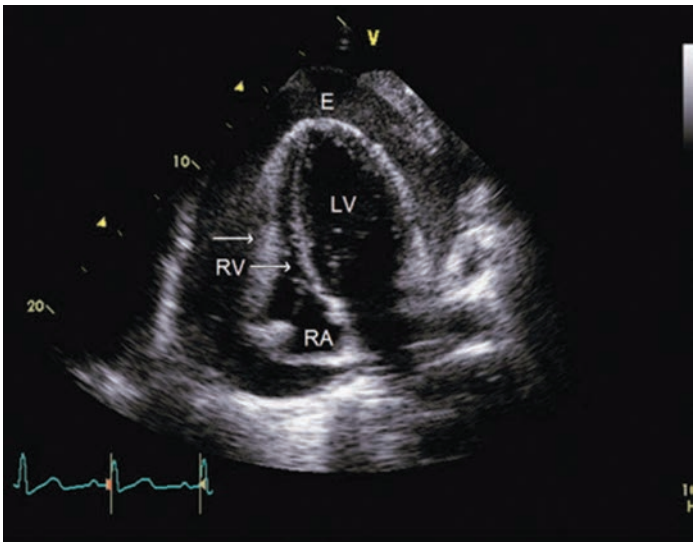


FIGURE 34-4. RV compression (*arrow*) in cardiac tamponade (apical four-chamber plane). E = effusion; LV = left ventricle; RA = right atrium; RV = right ventricle. [Reproduced with permission from Fuster V, Harrington RA, Narula J, Eapen ZP: *Hurst's the Heart*, 14th ed. New York: McGraw-Hill, Inc.; 2017. Figure 15-135B.]

PURPOSE AND INDICATIONS

Emergency pericardiocentesis relieves hemodynamic compromise from cardiac tamponade. Emergency pericardiocentesis is also indicated during resuscitation from pulseless electrical activity after excluding other causes.

In one study of traumatic tamponade, the most common indication for pericardiocentesis was clinical tamponade (83%), with echocardiographic findings of ventricular diastolic collapse (69%) and right atrial collapse (33%).[14] Pericardiocentesis for a traumatic effusion from penetrating cardiac trauma is done during resuscitation to stabilize a patient until surgery for definitive repair is available, but surgical drainage is preferred in traumatic effusions and purulent pericarditis.[15] **If the patient is hemodynamically compromised or close to or in cardiac arrest, perform emergency pericardiocentesis in the ED rather than delaying treatment by transporting to the operating room.**

BEDSIDE US

Use two-dimensional echocardiographic imaging to guide pericardiocentesis[16-22] and evaluate the size of the effusion and its effect on cardiac output. The 2010 Focused Cardiac Ultrasound in the Emergent Setting guidelines state: "When emergency pericardiocentesis is indicated ultrasound can provide guidance by first imaging the fluid collection from the subxiphoid/subcostal or other transthoracic windows to define the best trajectory for needle insertion"[20] (**Table 34-2**). Bedside US pericardiocentesis guidance results in fewer complications and greater success.[20] The European Society of Cardiology's 2015 Guidelines on the Diagnosis and Management of Pericardial Disease note that this procedure is lifesaving in cardiac tamponade and is indicated in effusions >20 mm by echocardiography, but also in smaller effusions for diagnostic purposes (pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy). The society also recommends the use of US guidance rather than blind approaches or the ECG-alone guided approach for pericardiocentesis.[21]

RISKS AND PRECAUTIONS

Some consider aortic dissection as an absolute contraindication. Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia, and small posterior loculated effusions.

Traditional blind subxiphoid approaches increase the risk of damage to adjacent structures, such as the liver, lung, diaphragm, and GI tract. Other potential cardiac injuries are chamber puncture, myocardial damage, and laceration of coronary arteries/veins. Resultant dysrhythmias may develop secondary to myocardial damage. Using US to guide reduces injury risks from the procedure. If bedside US is not available and the patient has cardiac or hemodynamic compromise, the blind subxiphoid approach for cardiac tamponade for acute hemopericardium is used.[22] See **Table 34-3** for a list of equipment needed.

PATIENT PREPARATION AND POSITIONING

If time and conditions permit, obtain and review a stat portable chest radiograph to assess for other causes or complicating features such as mediastinal shift or pneumothorax. Traditional positioning for pericardiocentesis is with the head of the bed elevated to approximately 30 to 45 degrees, but in cardiac arrest or near-arrest, this may not be feasible and the patient may need to be supine. Before choosing the needle insertion site, any mediastinal shift will displace structures and alter normal anatomic locations. In some instances, very small effusion volumes (50 to 100 mL) precipitate cardiac tamponade, with fluid collecting in dependent portions of the pericardial space. If the size of the effusion is small, rolling a patient to the left lateral decubitus position allows fluid to collect around the apex and provides easier access. This positioning also allows the left lung to move laterally, thereby increasing cardiac exposure.

ANESTHESIA AND MONITORING

Patients undergoing emergency pericardiocentesis in the ED are often in distress and are being resuscitated. They may already be sedated or paralyzed; if not, use local anesthesia, 1% to 2% lidocaine injected subdermal

TABLE 34-2 Characteristics of the Different Pericardiocentesis Approaches

Place of Puncture	Description	Disadvantages	Advantages
Apical	The needle insertion site is 1–2 cm lateral to the apex beat within the fifth, sixth, or seventh intercostal space. Advance the needle over the superior border of the rib to avoid intercostal nerves and vessels.	Risk of ventricular puncture, due to the proximity to the left ventricle. Increased risk for pneumothorax for the proximity to the left pleural space.	The thicker left ventricle wall is more likely to self-seal after puncture. Using US ensures avoiding the lung. The path to reach the pericardium is shorter.
Parasternal	The needle insertion site is in the fifth left intercostal space, close to the sternal margin. Advance the needle perpendicular to the skin (at the level of the cardiac notch of the left lung).	Risk of pneumothorax and puncture of the internal thoracic vessels (if the needle is inserted more than 1 cm laterally).	US with phased array probe, provides a good visualization of pericardial structures.
Subxiphoid	The needle insertion site is between the xiphisternum and left costal margin. Once beneath the cartilage cage, lower the needle to a 15- to 30-degree angle with the abdominal wall directed toward the left shoulder.	A steeper angle may enter the peritoneal cavity and a medial direction increases the risk of right atrial puncture. In some cases, the left liver lobe may be transversed intentionally if an alternative site is not available. The path to reach the fluid is longer.	Lower risk of pneumothorax.

Source: Reproduced with permission from Chiara De Carlini C, Maggiolini S: Pericardiocentesis in cardiac tamponade: indications and practical aspects. *E-J Cardiol Pract* 15: 19, 2017. Available at: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Pericardiocentesis-in-cardiac-tamponade-indications-and-practical-aspects.

TABLE 34-3 Equipment for Emergency Pericardiocentesis

- Antiseptic (e.g., povidone-iodine, ChloraPrep®)
- Local anesthetic (1%–2% lidocaine)
- 25-gauge needle, $^5/_8$ in. long
- 18-gauge catheter-type needle, $1^1/_2$ in. long (for parasternal or apical approaches)
- Syringes (10, 20, and 60 mL)
- 4 × 4 gauze squares
- Plastic tubing
- Collection system or basin
- US machine
- Sterile US probe cover (can be sterile glove)
- Sterile drapes
- Yankauer suction catheter
- Suction tubing
- Cardiac monitoring
- Optional
- 18-gauge spinal needle, $3^1/_2$ in. long (if needed for subxiphoid blind approach)
- Alligator clips connected by wire (for ECG approach)
- Bedside ECG
- Nasogastric tube
- Variable angle needle guide attachment for US
- Towel clips
- #11 scalpel blade
- J-tipped guidewire 0.035 mm diameter
- 6F–8F pigtail catheter
- Three-way stopcock

and deeper along the plane of expected needle insertion. Aspirate during infiltration to avoid injection of lidocaine directly into vascular structures.

Use ongoing cardiac monitoring and pulse oximetry, and provide supplemental oxygen. Ask an aide to help monitor the pulse amplitude.

STEP-BY-STEP TECHNIQUE (SEE VIDEO: PERICARDIOCENTESIS)

1. Use universal precautions.
2. Organize needed materials.
3. Position patient as needed.
4. Identify point of maximal effusion with US (i.e., closest to transducer/skin and where accumulation is maximal). Pericardial effusions are dark, or anechoic, areas surrounding the heart. Usually the pericardium can be seen overlying the effusion. In addition, paradoxical motion of the right ventricular wall with collapse during diastole is noted in states of tamponade. Distance from the skin surface to the effusion border can be measured with most US models to better assess expected needle depth.
5. Choose needle trajectory. Trajectory should coincide with the plane of the US beam. Identify any anatomic structure between the skin and pericardial space that lies within the expected needle path. The best approach should aim for the point of maximal effusion with the fewest intervening structures. For most patients, the optimal approach is the left chest wall. Most common is the left parasternal approach or the apical approach, both at the fifth intercostal space (**Figure 34-5**), or the subxiphoid approach. If using the left parasternal approach, select a site approximately 3 to 5 cm from the sternal edge to avoid the left internal mammary artery. Direct the needle over the superior margin of the rib to avoid injuring the neurovascular bundle on the inferior margin of each rib. Mark any site with a surgical pen for easier location after sterile preparation.
6. Sterile preparation. Prepare area with an antiseptic. Drape the surrounding area with sterile towels or a premade drape.

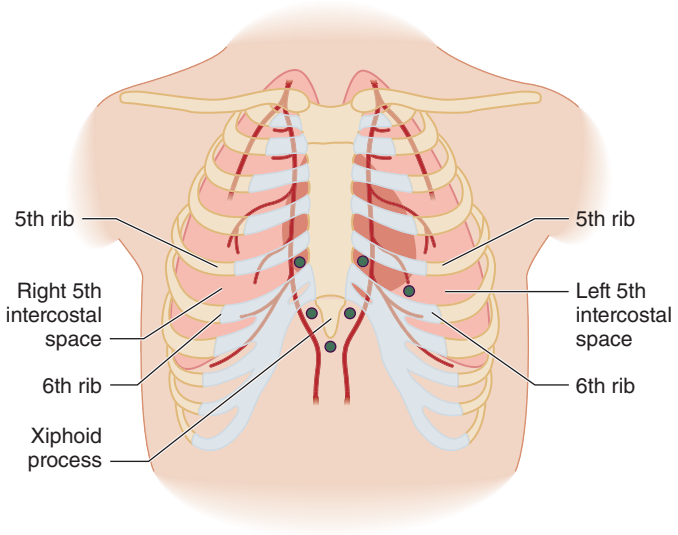


FIGURE 34-5. Potential sites to perform a pericardiocentesis. [Adapted with permission from Smith RF: Pericardiocentesis, in Reichman EF (ed): *Emergency Medicine Procedures*, 2nd ed. New York: McGraw-Hill, Inc.; 2013.]

7. Inject local anesthetic. Inject 1% to 2% lidocaine with a 25-gauge, $^5/_8$-inch needle at the selected site before the procedure. Produce a subdermal wheal, and then inject into deeper tissues while avoiding entry into the chest cavity. Aspirate before injection to avoid injection of anesthetic into vascular structures.
8. Preparation of US. Using the cardiac probe, place a sterile cover over the probe (may use sterile glove) after placing US gel on the probe tip. Place sterile US gel over the planned site of entry. Using the nondominant hand, hold the US probe in the plane of planned needle insertion. A second operator technique may be used.
9. Pericardial needle insertion. Under direct US guidance, insert an adequately long needle at the predetermined site at an approximately 45-degree angle to the skin at the transducer. Visualize the needle "tenting" the pericardium. Upon entry into the pericardial sac, a return of blood, serous fluid, or pus indicates the entry. Clotted blood may prevent aspiration, although this may be seen on US as echogenic material. If you suspect needle obstruction, attempt flushing the needle with 1 to 2 mL of normal saline to cleanse the needle. If aspiration of free blood is too easy, suspect ventricular puncture. To decrease complications of needle insertion, do not redirect the needle within the pericardium while aspirating. This may reduce the number of occurrences of inadvertent coronary artery lacerations or penetration of the pericardium.
10. Collect fluid for diagnostic testing outside of trauma to assess for protein or albumin, cell types and counts, Gram stain, and cultures.
11. Catheter removal. Once adequate fluid has been withdrawn from the pericardial space and hemodynamic equilibrium returns, you may remove the catheter. Dress the site after removal. Alternatively, you may place an optional indwelling flexible J-tip catheter (see step 2). Although recurrence rates decrease with indwelling or extended catheter drainage, this is not routinely performed in the ED secondary to patient acuity and ongoing resuscitative measures. Once stabilized, a cardiologist or cardiac surgeon may evaluate for other care and possible indwelling catheter placement.

OPTIONAL STEPS

1. Saline echo-contrast technique. When confirmation of the needle tip is necessary, use an agitated saline solution. Using a three-way stopcock, attach one end to the catheter. Attach one syringe with 3 mL of normal saline and one syringe with an equivalent amount of air to the remaining two ports. Quickly mix the saline and air together and then inject into the pericardial sac under US visualization.

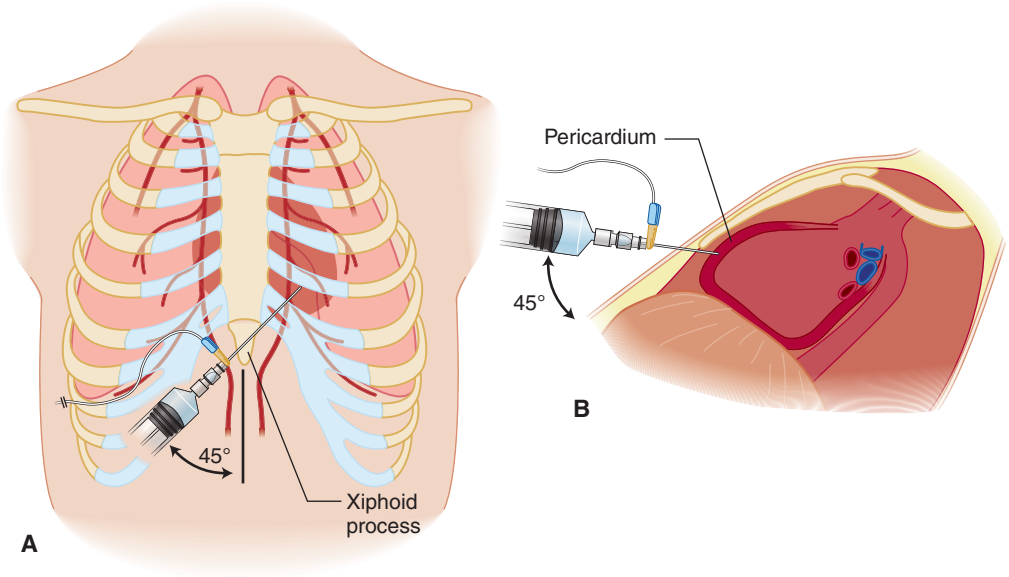


FIGURE 34-6. The subxiphoid approach. The needle is inserted at a 45-degree angle to the midsagittal plane **(A)** and at a 45-degree angle to the abdominal wall **(B)**. [Adapted with permission from Smith RF: Pericardiocentesis, in Reichman EF (ed): *Emergency Medicine Procedures*, 2nd ed. New York: McGraw-Hill, Inc.; 2013.]

Alternatively, the saline is agitated by simply shaking a 10-mL syringe filled with 3 to 5 mL of normal saline and then injecting this into the pericardial space. An echo-contrasted medium should appear in the pericardial space. If the contrast disappears quickly after injection, suspect tip placement in ventricle. Rather than attempting to reinsert needle into the catheter, it is best to start again with a new needle should this complication arise.

2. Catheter placement. Using the standard Seldinger technique, introduce a flexible J-tip guidewire through the catheter. Remove the catheter, and then make a small "stab" incision at the needle entry site. Introduce a 6F to 8F dilator over the guidewire, remove it, and then introduce a 6F to 8F pigtail catheter over the guidewire. Finally, remove the guidewire and confirm placement by saline echo-contrast as in step 1 above. Once confirmed, place the catheter on suction.
3. Dressing. Secure the catheter to the chest wall with suture, dressing, or both.
4. Aspirate pericardial fluid every 4 to 6 hours, avoiding continuous drainage. Flushing the catheter with saline after drainage will ensure patency.

BLIND SUBXIPHOID APPROACH

The blind subxiphoid approach starts with similar preparation and anesthetic. The point of needle insertion starts either directly below or adjacent to the xiphoid process. Insert a longer 18-gauge needle at a 45-degree angle to the patient's skin, and direct the needle tip to *either* the left or right shoulder (**Figure 34-6**). Some authors advocate using the right shoulder as the direction of choice because this direction is parallel to the ventricular wall (in contrast to perpendicular for left shoulder direction), theoretically reducing the chance of myocardial injury. In either approach, aim the needle toward the heart and use continuous aspiration of the syringe until return of pericardial fluid.

ECG MONITORING TECHNIQUE

This technique uses ECG monitoring to detect myocardial injury patterns and localize needle location. However, ECG injury monitoring alone is not an adequate safeguard.[17] The approach is similar to the blind approach in orientation. Attach the V_1 monitor lead to the needle. Watch the monitor while introducing the needle. ST elevation on the monitor indicates that the needle tip has contacted the myocardium. Withdraw the needle slightly and aspirate. This technique is rarely used currently due to complexity in the emergent setting and advances in US allowing for safer alternatives.

OUTCOME ASSESSMENT AND COMPLICATIONS

A favorable outcome is the restoration of hemodynamic stability as indicated by blood pressure and heart rate. Two-dimensional echocardiography should also show decreased effusion, increased cardiac contractility, and increased cardiac output.

Complications depend on approach and the underlying cause of tamponade. Traditional blind techniques have an associated morbidity of 20%, with mortality as high as 6%. The overall complication rate of US-guided approaches is <5%.[16]

Major complications include chamber lacerations requiring surgery, intercostal vessel injury requiring surgery, pneumothorax requiring chest tube placement, ventricular tachycardia, and bacteremia. Minor complications include transient chamber entries, small pneumothorax not requiring intervention, hypotension secondary to vasovagal response, sinus tachycardia, pericardial catheter occlusion, and possible pleuropericardial fistulas.[16] Cardiac dysrhythmias, such as atrial fibrillation, ventricular tachycardia, or asystole, may occur when the needle penetrates the pericardium. Monitor the patient closely for reaccumulation of pericardial fluid after pericardiocentesis.

DISPOSITION AND FOLLOW-UP

All patients undergoing ED pericardiocentesis require admission to the intensive care unit. Consult the trauma surgeon, cardiologist, or cardiothoracic surgeon early in patient evaluation.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 5

Analgesia, Anesthesia, and Procedural Sedation

CHAPTER 35

Acute Pain Management

James Ducharme

INTRODUCTION

Pain is the most common presenting symptom for patients coming to the ED, with 70% to 80% of all patients having pain as their primary complaint.[1,2] Despite increasing research and information about pain management, oligoanalgesia, or the undertreatment of pain, persists.[3] While all patients are susceptible to oligoanalgesia, certain subgroups, such as ethnic minorities, the aged, the very young, and those with diminished cognitive function, are more at risk (**Table 35-1**).[4-7] Pain management can also be negatively influenced by concerns of prescription opioid misuse, a situation declared to be a public health epidemic in North America.[8] An initial prescription of opioids, such as upon ED discharge, has been associated with persistence of opioid use months after the original visit.[9] Nevertheless, appropriate treatment of acute severe pain should not be withheld for fear of facilitating drug misuse; rather, opioid use should be but one of many options considered in pain management.[10] Pain and addiction are not mutually exclusive.

Specific measures to treat pain should occur *in addition* to, and at the same time as, treatment of the underlying illness or injury. **It is not possible to generalize the extent and quality of pain control needed for a specific patient.** For example, pain is an indicator of ongoing cardiac ischemia, and the goal should be to eliminate all pain. On the other hand, a patient with a traumatic injury may choose to endure more pain out of personal or cultural beliefs. Whenever possible, medications that act on specific sites that initiate the pain signal—a mechanistic approach—are preferred to agents such as opioids that mask pain, which is more a symptomatic approach. Current migraine treatment is an excellent example of the mechanistic approach; preferred treatment includes a serotonin agonist (triptan) or a dopamine antagonist (phenothiazine or metoclopramide), rather than opiates.[11]

PATHOPHYSIOLOGY

Pain is the physiologic response to a noxious stimulus, whereas suffering—the expression of pain—is modified by the complex interaction of cognitive, behavioral, and sociocultural dimensions. Individual pain experience is therefore not static, but varies depending on current and past medical history, physical and emotional maturity, cognitive state, meaning of pain, family attitudes, culture, and environment. Emotions can modify pain either negatively or positively: fear and anxiety may accentuate pain, or pain can be suppressed completely if an essential task must be performed or if there is acute concern about a loved one. It is difficult for another to assess the severity of pain a patient is feeling as they cannot understand the impact of these modifying variables on any given patient. It is why **self-reporting is considered the gold standard for quantifying the severity of a patient's pain.** Since pain and suffering are so intertwined, it must be recognized that a pain score using a standardized rating scale does not have more than a moderate relationship to the amount or type of analgesia required.

The peripheral nervous system (e.g., nociceptors, C fibers, A-δ fibers, and free nerve endings) initiates the sensation of somatic pain by responding to a noxious stimulus and sending a neuronal discharge to the dorsal horn of the spinal cord. Neurons in the dorsal horn of the spinal cord integrate and modulate input from multiple peripheral nerves and other sensory stimuli. Transmission then proceeds up the spinal cord to the CNS (e.g., hypothalamus, thalamic nuclei, limbic system, and reticular activating system) where further integration and processing generate the perception of pain. Identification and localization of pain, cognitive interpretation, and triggering of emotional and physiologic reactions also occur at these central sites. Unlike somatic pain, which is easily localized, visceral pain pathways are more complex and differ in structure from somatic pain pathways, which may explain the poor localization of visceral pain.

Opioid analgesics work by binding to receptors in the spinal cord and brain. There are four types of **opioid receptors**: three classic ones (**delta, kappa,** and **mu**, each with identified subtypes) and nociceptin, a receptor with significant structural homology. These receptors are found in the brain, spinal cord, and GI tract where their physiologic function is to interact with endogenous dynorphins, enkephalins, endomorphins, endorphins, and nociceptin. Opioid analgesics interact with these receptors in varying degrees, accounting for the difference in desired and adverse effects among the drugs in this class. Stimulation of the mu-1 (μ_1) receptor produces supraspinal analgesia. Stimulation of the mu-2 (μ_2) receptor results in euphoria, miosis, respiratory depression, and depressed GI motility. Stimulation of the delta (δ) receptor produces analgesia, but less than the μ_1 receptor, and also exerts an antidepressant effect. Stimulation of the kappa (κ) receptor produces dysphoria, along with dissociation, delirium, and diuresis by inhibiting antidiuretic hormone release. Opioid receptors, surprisingly, are not linked to addiction, which is much more closely linked to the cannabinoid-1 receptor.

EVALUATION

Document the degree of pain on initial assessment. This process serves to identify patients with severe pain and facilitate pain treatment. ED pain assessment should determine duration, location, quality, severity, and exacerbating and relieving factors. **The patient's subjective reporting of pain, not the healthcare provider's impression, is the basis for pain assessment and treatment.** There is a weak correlation between nonverbal signs, such as tachycardia, tachypnea, and changes in patient expression and movements, and the patient's report of pain, so do **not** rely on these to determine the severity of a patient's pain[12,13] or their response to treatment.[14] Because pain is dynamic and changes with time, periodic pain reassessment is needed.

PAIN SCALES

Although standardized scales for measuring reported pain are commonly used, their impact on effective pain control is uncertain.[15,16] **The primary purpose of pain scales is to quantitate pain severity, guide the selection and administration of an analgesic agent, and reassess the pain response to determine the need for repeated doses or alternative analgesics.** Pain scales are also essential in pain management research, enabling reproducible comparisons of interventions. Some studies have suggested that the use of pain scales may actually *decrease* the provision of analgesics. Given the subjectivity both of pain reporting and the provider's interpretation of such reporting, the use of simple descriptors such as "a little" or "an awful lot" is equally valid in the clinical setting. What **is** important is that the patient's subjective reporting should be the basis for assessment and management. For most, but not all, painful conditions, the goal is to control pain to the level the patient desires. Once it is determined a patient requires pain management, **asking if the**

TABLE 35-1 Barriers to Adequate ED Pain Control

Patient Related	Provider Related	System Related
Ethnicity, gender, age (very young, very old)	Inadequate education	Lack of clearly articulated standards
Diminished cognitive function	No objective measuring tool for pain	Paucity of treatment guidelines
Fear of medications: addiction, side effects	Accepting only pain reports that conform to expectations	Fear of regulatory sanctions
Acceptance of pain as being inevitable	Concerns of opioid addiction and drug-seeking behavior	Lack of healthcare provider accountability
Unwillingness to bother healthcare providers		

patient requires more analgesic may even be simpler and accomplish more than using any standardized pain evaluation tool.[17,18]

Several self-report instruments are valid in patients with acute pain, with some requiring only a verbal response (**Table 35-2**). Each tool has advantages and specific limitations. ED personnel in any one location should use the same tool so information collected is standardized. **A value assigned by a patient is not an absolute value but rather a reference point based on past personal experience.**[19]

PAIN SCALE PERFORMANCE IN SPECIAL PATIENT POPULATIONS

The elderly often report pain differently from younger patients because of physiologic, psychological, and cultural changes associated with aging. Visual, hearing, motor, and cognitive impairments can be barriers to effective pain assessment. Using a numerical pain scale, the elderly may also experience a decrease in the minimum clinically significant noticeable difference in acute pain over time, making it difficult to assess response to successive doses of analgesics.[21,22] Family members and caregivers are often able to judge nonverbal actions of the patient as representing pain or distress, so they should be used if available to help with pain assessment in the noncommunicating elderly patient.[23]

Trauma patients and those with acute intoxication do not perform as well on pain scales.[24] Women are more likely to express pain and to actively seek treatment for pain,[25,26] yet there is a tendency to underestimate and undertreat pain in women. Ethnicity of both the patient and the physician has a bearing on different cultural concepts of pain and on the characteristics of culturally appropriate pain-related behaviors.[5] Translators and family members should be asked to provide assistance.

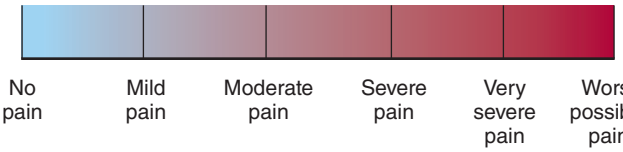


FIGURE 35-1. Pain scale: Adjective rating scale.

There is also interplay between the ethnicity of the patient and that of the physician.[5] **When there are language difficulties or cross-cultural differences, the visual analog scale is the preferred pain assessment tool because it is the least affected by these factors.**

PHARMACOLOGIC ACUTE PAIN TREATMENT

The administration of pharmacologic agents is the mainstay of acute pain management. **The key to effective pharmacologic pain management in the ED is selection of an agent appropriate for the intensity of pain, time to onset of analgesic activity, ease of administration, safety, and efficacy.**[27] Acute pain is usually accompanied by anxiety and feelings of loss of control. Management of the *suffering* component of acute pain may be best managed by restoring emotional control and providing information about the situation. If verbal reassurance combined with an analgesic does not suffice, an anxiolytic may be useful.

The "tiered approach" to pain management starts with an agent of low potency regardless of pain intensity, assesses the response after a clinically relevant period, and sequentially changes to agents of higher potency if pain persists. **The tiered approach to acute pain management unnecessarily subjects the patient to more prolonged suffering. It is preferable to select initial analgesics that are appropriate to treat the intensity (mild, moderate, or severe) of the patient's pain.** Agents such as NSAIDs should be considered for mild to moderate pain or when targeting severe pain originating from smooth muscle spasm such as renal or biliary colic. Systemic opioids should be reserved for severe nociceptive pain (**Table 35-3**); opioids have little if any role in managing acute neuropathic pain or acute pain flares linked to chronic pain states. In specific instances such as renal and biliary colic, although parenteral NSAIDs may control severe pain, combination therapy with an opioid is usually superior.

When possible, local or regional anesthesia can be a useful adjunct. Peripheral nerve blockade for pain control and for procedures is an excellent option, especially if guided by US (see Chapter 36, "Local and Regional Anesthesia").[28,29]

TABLE 35-2 Pain Scales[20]

Scale	Method	Comments
Adjective rating scale (**Figure 35-1**)	Patient rates pain by choosing from an ordered list of pain descriptors, ranging from *no pain* to *worst possible pain*, with allowance for marks between discrete labels.	Easy to administer.
Visual analog scale (VAS) (**Figure 35-2**)	Patient places a mark that best describes pain intensity along a 10-cm linear scale marked at one end with a term such as *no pain* and at the other end with *worst imaginable pain*.	Pain intensity measured in millimeters from the no-pain end. A difference of 13 mm is the minimum clinically significant change *noticeable* by patients, whereas an average decrease of 30 mm appears to be the minimum *acceptable* change for pain control.
Numeric rating scale (**Figure 35-3**)	The patient is asked to self-report pain on a scale of 0 to 10 with descriptors for 0, 5, and 10.	Can be used in patients with visual, speech, or manual dexterity difficulties by using upheld fingers. Not as discriminating as the VAS.
5-Point global scale	Patient rates pain as: 0 = none 1 = a little 2 = some 3 = a lot 4 = worst possible	A decrease of 1 point is a large change; scales with more choices allow monitoring of small changes in pain and may be more sensitive to changes.
Verbal quantitative scale	The patient is asked to self-report pain on a scale of 0 to 10 without descriptors.	Most commonly used scale; easy to administer.



FIGURE 35-2. Pain scale: Visual analog scale (VAS).

TABLE 35-3 Pain Severity With VAS or NRS

Pain Severity	VAS (0 to 100 mm) or NRS (0 to 10)
Mild	VAS: 0 to 30–40 mm or NRS: 0 to 3–4
Moderate	VAS: 40 to 60–70 mm or NRS: 4 to 6–7
Severe	VAS: >60–70 mm or NRS: >6–7

Abbreviations: NRS = numeric rating scale; VAS = visual analog scale.

OPIOID ANALGESICS

Opioid analgesics are the cornerstone of pharmacologic management for severe acute pain (**Table 35-4**). The term *opiate* refers to agents that are structurally related to natural alkaloids found in opium, the dried resin of the opium poppy. The term *opioid* describes any compound with pharmacologic activity similar to an opiate, regardless of chemical structure. Opioid use in the ED is often affected by concern for the precipitation of adverse events, such as respiratory depression or hypotension, or for facilitating drug-seeking behavior. Based on World Health Organization recommendations, amounts of opioids prescribed per capita are excessive in North America, but this should not preclude the use of opioids for ED patients in severe pain; **when opioids are felt to be indicated,** they should be titrated to effect based on patient feedback or with patient-controlled analgesia systems. Considerations for use of different opioids include (1) desired onset of action; (2) available routes of administration; (3) duration of action, which will determine achievable frequency of administration; (4) concurrent use of nonopioid analgesics and adjunctive agents; (5) possible incidence and severity of side effects; and (6) continuation of the agent in an inpatient or ambulatory setting.

Opioids should be titrated to effect after the initial dose as patients differ greatly in their response to opioid analgesics.[32-34] Variation in pain reduction is related to age, initial pain severity, and previous or chronic exposure to opioids, but not body mass[35,36] or gender.[37] Relative potency estimates provide a rational basis for selecting the appropriate starting dose to initiate analgesic therapy,[38,39] changing the route of administration (e.g., from parenteral to PO), or switching to another opioid (**Table 35-5**), but undue reliance on these ratios is an oversimplification with potential for over- or underdosing.[40]

Oral opioids are often manufactured in combination with acetaminophen (paracetamol), ibuprofen, or aspirin. There is evidence that such combinations possess a synergistic effect in treating chronic pain. It is possible for the patient to consume a toxic amount of the nonopioid component with frequent dosing. Patients may also consume a toxic amount by continuing to take their nonopioid analgesic in addition to the prescribed opioid combination. Avoid prescribing combinations upon patient discharge.

Opioid hypersensitivity is uncommon, and true allergic reactions are extremely rare. There is minimal evidence of clinical cross-sensitivity within opioid classes, with the possible exception that cross-sensitivity has been suggested among the phenylpiperidines (fentanyl, alfentanil, and sufentanil). **Until more is known, it would be prudent to switch to a drug from a different opioid class if a patient develops a hypersensitivity reaction.** When used in equianalgesic doses, there is no compelling evidence to recommend one opioid over another. As much as possible, avoid using multiple agents, and titrate a single drug to the desired effect.

Codeine is not a reliable analgesic, and it produces more nausea, vomiting, and dysphoria than other opioids. The analgesic effect of codeine is highly dependent on the metabolic conversion to the active metabolites codeine-6-glucuronide and morphine. Up to 10% of the U.S. population, and 30% of Asians are deficient in the relevant enzymes for this conversion and cannot obtain any analgesic response. Conversely, there are case reports of neonatal deaths as a result of breastfeeding from mothers who were hypermetabolizers of codeine. In addition, the standard PO dose of 30 to 60 milligrams produces little analgesic effect above that of acetaminophen or NSAIDs alone.[41,42]

Tramadol binds to mu receptors and weakly inhibits the reuptake of norepinephrine and serotonin, producing a central opioid analgesic effect.[43] Tramadol is extensively metabolized by cytochrome P450 enzymes into more potent opioid metabolites, with desmetramadol binding to the mu receptor at 700-fold higher affinity than the parent compound. Thus, the analgesic potency of tramadol varies according to the patient's cytochrome P450 activity. Common side effects include dizziness, nausea, constipation, and headache. Tramadol can induce serotonin syndrome. Severe toxicity can include agitation and seizures. Tramadol is one of the many substances that can produce a false-positive result on the urine phencyclidine screen.[44]

Meperidine (pethidine) was removed from the World Health Organization list of essential medications in 2003, and its use in North America has decreased because of its potential for addiction and adverse side effects.[45] Meperidine is considered to produce more elation than other opioids, prompting concern the euphoria induced will more likely lead to continued use, misuse, and addiction. Meperidine can interact with many drugs to precipitate serotonin syndrome, although this interaction is also seen with other opioids.[46,47] Compared to other opioids, meperidine is associated with an increased risk of delirium in the elderly.[48] Meperidine is metabolized to normeperidine, which has neuroexcitatory properties and a long elimination half-life (24 to 48 hours).[49] With continued use, such as duration greater than 48 hours or total daily dose greater than 600 milligrams, normeperidine can accumulate and produce toxicity, typically seizures, in the elderly and those with renal failure, although this is a rare event.[50]

Adverse effects of opioids include nausea, vomiting, constipation, pruritus, urinary retention, confusion, and respiratory depression. Pruritus, urinary retention, confusion, and respiratory depression are more common with IV, transmucosal, and epidural administrations as opposed to PO administration.

Adjuncts are sometimes used to enhance the analgesic effect, reduce the amount of opioid required, and prevent side effects (**Table 35-6**). Depending on the agent, amount, route, and setting, a beneficial effect can be seen. However, appropriate titration with opioids in the ED is highly effective, and there are few data to support the routine use of adjuncts with opioids in the ED.[51] Pretreatment with antiemetics is not necessary given the low risk of emesis,[52] but symptom-targeted therapy is sometimes necessary.

Transdermal formulations are not useful for acute pain treatment because of delayed onset and prolonged duration of action. **Transdermal fentanyl** and **transdermal buprenorphine** preparations are used for chronic pain, particularly in cancer patients. When such patients are treated for acute pain in the ED, it is best to remove the delayed-release transdermal opioid patches to better titrate the acute opioid dose and to minimize adverse reactions from the combination of agents.

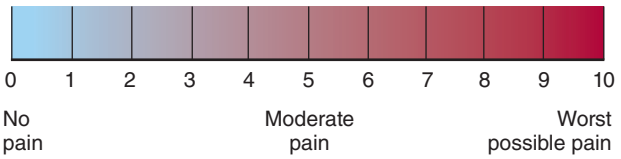


FIGURE 35-3. Pain scale: Numeric rating scale.

OPIOID AGONISTS-ANTAGONISTS

Opioid agonists-antagonists are used to minimize some of the adverse effects of pure opioid agonists (**Table 35-7**). The major benefit claimed is a ceiling on respiratory depression, with no further reduction in respiration with increasing doses past a set amount. It is not clear if there

TABLE 35-4 Pain Treatment: Initial Opioid Dosing

Drug [Origin, Class]	Typical Initial Adult Dose	Pharmacokinetics	Comments
Morphine [natural alkaloid phenanthrene]	2–6 milligrams IV 10 milligrams IM/SC 10–30 milligrams PO IR tablet	Onset: 1–2 min IV, 10–15 min IM/SC, and 30 min PO IR tablet Peak effect: 3–5 min IV, 15–30 min IM/SC, and 1 h PO IR tablet Duration: 1–2 h IV, 3–4 h IM/SC, and 3–5 h PO IR tablet	Histamine release may produce transient hypotension or nausea and emesis; neither requires routine adjunctive treatment.
Hydromorphone [semisynthetic phenanthrene]	0.5–2 milligrams IV 1–2 milligrams IM	Onset: 5–15 min IV Peak effect: 10–20 min IV Duration: 2–4 h IV	More euphoria inducing than morphine.
Fentanyl [synthetic phenylpiperidine]	50–100 micrograms IV	Onset: <1 min IV Peak effect: 2–5 min IV Duration: 30–60 min IV	Less cardiovascular depression than morphine. High doses (>5 micrograms/kg IV) can cause chest wall rigidity.
	100-microgram nasal spray in 1 nostril[30]		Used for breakthrough pain in opioid-tolerant cancer patients. Wait >2 h before treating another episode. May increase dose by 100 micrograms per episode.
	100-microgram buccal mucosa tablet[31]		Used for breakthrough pain in opioid-tolerant cancer patients. May repeat after 30 min. Wait >4 h before treating another episode. May increase dose by 100 micrograms per episode. Available transmucosal forms not bioequivalent.
Meperidine (pethidine) [synthetic phenylpiperidine]	25–50 milligrams IV 50–150 milligrams IM/SC	Onset: 5 min IV Peak effect: 5–10 min IV Duration: 2–3 h IV	Contraindicated when patient has taken a monoamine oxidase inhibitor within the past 14 d to avoid precipitating serotonin syndrome. Neurotoxicity may occur when multiple doses are given for >48 h or with a total daily dose >600 milligrams, especially in the presence of renal failure.
Oxycodone [semisynthetic phenanthrene]	5–10 milligrams PO	Onset: 10–15 min PO Duration: 3–6 h PO	Lower incidence of nausea than other opioids. Possible inadvertent acetaminophen overdose with combination agents.
Hydrocodone/acetaminophen [semisynthetic phenanthrene]	5/325–10/325 milligrams PO	Onset: 30–60 min PO Duration: 4–6 h PO	Lower incidence of nausea than other opioids. IR tablets only available as hydrocodone-acetaminophen combination; possible inadvertent acetaminophen overdose with concomitant use of nonprescription acetaminophen.
Codeine [natural alkaloid phenanthrene]	30–60 milligrams PO 30–100 milligrams IM	Onset: 30–60 min PO and 10–30 min IM Duration: 4–6 h PO and IM	High incidence of GI side effects. Some patients cannot convert to codeine-6-glucuronide and morphine. Possible inadvertent acetaminophen overdose with combination agents or with concomitant use of nonprescription acetaminophen.
Tramadol [other]	50–100 milligrams PO	Onset: 1 h PO Duration: 4–6 h PO	CNS side effects common.

Abbreviation: IR = immediate release.

TABLE 35-5 Equipotent Opioid Doses

Drug	Equipotent Parenteral Dose (milligrams)	Equipotent PO Dose (milligrams)	Morphine Milligram Equivalents (MME)* for PO Dosing
Morphine	10	60 (acute) and 30 (chronic)	1
Hydromorphone	1.5	7.5	4
Fentanyl	0.1	0.2 (transmucosal)	2.4 (transdermal in micrograms/h)
Meperidine (pethidine)	75	300	0.1
Oxycodone	—	20	1.5
Hydrocodone	—	30	1
Codeine	120	200	0.15
Tramadol	—	300	0.1

*Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs.

TABLE 35-6 Opioid Pain Management: Adjunctive Medications

Drug	Initial Dosing	Elimination Half-Life	Comments
Ondansetron	4–8 milligrams IV/PO	3–6 h	Can prolong QT interval
Prochlorperazine	5–10 milligrams IV/IM/PO	7 h	Can cause extrapyramidal reactions
Promethazine	25–50 milligrams IV/IM	7–14 h	Can cause extrapyramidal reactions
Metoclopramide	5–10 milligrams IV/IM/PO	5–6 h	Can cause extrapyramidal reactions

is a ceiling effect for analgesia. The variability in efficacy relates to each particular agent's affinity for the various central opioid receptors. **These agents may precipitate withdrawal symptoms in opioid-addicted patients due to the antagonistic effect.**

NONOPIOID AGENTS

Acetaminophen (paracetamol) is an effective analgesic for acute mild to moderate pain,[53] but is not effective for persistent or chronic pain (**Table 35-8**).[54] Acetaminophen does not affect platelet aggregation and does not have anti-inflammatory properties. No dosage change is required for renal or mild hepatic impairment. **An important precaution is to carefully monitor nonprescription acetaminophen use when concomitantly using combination opioid-acetaminophen products.**

Aspirin and the **NSAIDs** are both anti-inflammatory agents and analgesics. As anti-inflammatory agents, aspirin and NSAIDs decrease the production of prostanoids and arachidonic acid–mediated inflammatory peptides generated at the site of tissue injury, diminishing the inflammatory response seen with some noxious stimuli. As analgesics, inhibition of the cyclooxygenase-2 enzyme in the spinal cord decreases the excitability of dorsal horn neurons that produce hyperalgesia and allodynia. These agents do not cause sedation or respiratory depression or interfere with bowel or bladder function. NSAIDs have significant opioid dose-sparing effects and are more effective than acetaminophen for acute musculoskeletal pain.[53] There is no consistent evidence that the combination of acetaminophen and ibuprofen is more effective than either agent singly for acute pain in the ED.

Adverse effects of NSAIDs include platelet dysfunction, GI irritation and mucosal bleeding, nephropathy, headaches, and dizziness. All NSAIDs increase the risk of cardiac death in patients with ischemic heart disease.[55,56] NSAID-induced acute renal failure is more common in elderly patients and in those who are volume depleted, have preexisting renal or cardiac disease, or are taking loop diuretics. Alternating acetaminophen and an NSAID using standard doses every 3 to 4 hours is one approach to reducing toxic side effects when treating acute pain for several days.

OTHER PHARMACOLOGIC AGENTS

Ketamine A phencyclidine derivative, ketamine produces analgesia and/or dissociative anesthesia with the advantage of causing minimal respiratory depression at usual doses (see Chapter 37, "Procedural Sedation and Analgesia in Adults"). Low-dose (subdissociative or analgesic dose) infusions of ketamine are effective in combination with opioids for patients in severe pain.[57,58] Ketamine dosing for analgesia is typically an IV loading dose, followed by repeat doses or a continuous infusion (Table 35-8).[59] IV ketamine works best as an adjunct to opioids for patients in severe pain, reducing the amount of opioids required,[59,60] as with pain associated with sickle cell vaso-occlusive crisis.[61,62] Occasionally, ketamine can be effective on its own for acute severe pain.[63] Adverse effects such as dysphoria, hallucinations (at times frightening), and dissociative symptoms have been reported with even these low doses of ketamine.[57-59]

Lidocaine Lidocaine, a local anesthetic, has been studied as an IV systemic analgesic for perioperative and neuropathic pain. A small number of studies have been done using fixed (50 to 150 milligrams) or weight-based dose (1 to 2 milligrams/kg) IV lidocaine for ED pain management in patients with migraine, renal colic, radicular low back pain, and critical limb ischemia.[64-66] There is no consistent benefit with IV lidocaine when compared with standard therapy (morphine, fentanyl, ketorolac, dihydroergotamine, or chlorpromazine) for the appropriate condition.

Nitrous Oxide Nitrous oxide is a fast-onset, short-acting analgesic and sedative inhalational agent useful for brief, minor procedures (see Chapter 37) and for prehospital analgesia.[67,68] The primary adverse effects are nausea and vomiting. Nitrous oxide as a preblended 50% mixture with oxygen and administered to the patient by facemask provides variable results in terms of pain relief and sedation. If available, the 70/30 nitrous oxide/oxygen mixture is consistently effective. While minimally available in the United States, the latter mixture is used routinely in pediatric departments in Canada, the United Kingdom, and Australasia. Barriers to ED use of nitrous oxide seem to be related to misunderstanding of risk as well as concern of misuse by staff. An effective scavenging system is mandatory and is now standard in all available systems. Nitrous oxide is contraindicated in patients with altered mental status, head injury, suspected pneumothorax, or perforated abdominal viscus. Severe pulmonary disease also may alter the respiratory elimination of nitrous oxide.

Antidepressants and Anticonvulsants Patients with acute-onset neuropathic pain, such as postherpetic or trigeminal neuralgia, are

TABLE 35-7 Pain Management: Initial Opioid Agonist-Antagonist Dosing

Drug [Class]	Initial Dosing	Pharmacokinetics	Morphine Milligram Equivalents (MME)	Comments
Buprenorphine [synthetic phenanthrene]	0.3 milligram IV/IM every 6 h 75-microgram buccal film every 12 h	Onset: rapid Elimination half-life: 20–44 h	10 (approximate, no reliable conversion)	Sedation, dizziness, nausea
Butorphanol [synthetic morphinan]	1 milligram IV or 2 milligrams IM every 3–4 h 1 milligram nasal spray every 3-4 h	Onset: <1 min Elimination half-life: 5–6 h	7	Sedation, dizziness, nausea
Dezocine* [synthetic benzomorphan]	0.1 milligram/kg IV every 4 h	Onset: 15 min IV and 30 min IM Elimination half-life: 2 h	4–6	Dizziness, respiratory depression
Nalbuphine [synthetic phenanthrene]	10 milligrams IV/IM/SC every 3–6 h	Onset: 2–3 min IV and <15 min IM Elimination half-life: 5 h	1	Sedation, headache, dizziness
Pentazocine [synthetic benzomorphan]	30 milligrams IV/IM/SC every 3–6 h	Onset: 2–3 min IV and 15–20 min IM Elimination half-life: 2–3 h	0.37	CNS side effects

*No longer clinically used in Western countries.

TABLE 35-8 Pain Management: Nonopioid Analgesics

Drug	Adult Dosage	Comments
Acetaminophen (paracetamol)	325–1000 milligrams PO every 4–6 h 325–650 milligrams PR every 4–6 h If >50 kg: 1 gram IV every 6 h If <50 kg: 15 milligrams/kg IV every 6 h	Liver dysfunction and necrosis. Maximum oral dose is 4 grams/d under direction of physician but no more than 3 grams/d when using nonprescription product. Maximum IV dose is 4 grams/d if >50 kg body weight and 3.75 grams/d if <50 kg body weight. Not effective for chronic pain.
Aspirin (acetylsalicylic acid)	325–650 milligrams PO every 4 h 300–600 milligrams PR every 4–6 h	GI irritation and mucosal bleeding. Platelet dysfunction. Tinnitus, CNS toxicity, metabolic acidosis. Maximum dose is 4 grams/d.
Ibuprofen (NSAID)	400–800 milligrams PO every 4–6 h 400–800 milligrams IV every 6 h	GI upset, platelet dysfunction, renal dysfunction, bronchospasm. Maximum dose is 3200 milligrams/d.
Naproxen (NSAID)	250–500 milligrams PO every 8–12 h	GI upset, platelet dysfunction, renal dysfunction, bronchospasm. Maximum dose is 1250 milligrams on initial day and 1000 milligrams on subsequent days.
Indomethacin (NSAID)	25–50 milligrams PO every 8 h 25–75 milligrams PR every 6–8 h	GI upset, platelet dysfunction, renal dysfunction, bronchospasm. Maximum dose is 200 milligrams/d.
Ketorolac (NSAID)	15 milligrams IV/IM every 6 h 10 milligrams PO every 4–6 h	GI upset, platelet dysfunction, renal dysfunction, bronchospasm. Greater risk of GI bleeding than ibuprofen. Use limited to 3 d IV and 5 d PO. Maximum IV/IM dose is 120 milligrams/d, but if age >65 y or weight <50 kg, then maximum dose is 60 milligrams/d. Maximum PO dose is 40 milligrams/d.
Ketamine	0.1–0.3 milligram/kg (maximum 30 milligrams) IV over 10–15 min; can repeat in 1–15 min up to 0.5 milligram/kg; can follow by IV infusion of 0.1–0.2 milligram/kg per h	No renal or hepatic adjustment; administer slowly to reduce dystonic reactions, laryngospasm, or mental status changes; adverse effects uncommon with single doses; dizziness, agitation, and hallucinations possible with higher doses.
Lidocaine	Fixed dose: 50–150 milligrams IV Weight-based dose: 1–2 milligrams/kg IV	No consistent benefit in migraine, renal colic, or radicular low back pain. Adverse effects noted in 9% of patients. Not U.S. Food and Drug Administration approved for acute pain management.

difficult to treat with short-acting opioid analgesics. It may be difficult to identify neuropathic causes of pain in ED patients, but if suspected, **cyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or anticonvulsants can be initiated (Table 35-9).**[69,70] When initiating an agent for patients with new-onset neuropathic pain, close follow-up with the primary care physician is important so that titration to effect may continue. Patients already taking one of these agents for chronic neuropathic pain may require either titration upward of their medication or addition of a second agent; this should be discussed with the patient's regular physician.

Topical Medications Topical administration of medications at the site of injury or inflammation can provide pain relief with reduced systemic drug absorption and a lower risk of adverse drug reactions (**Table 35-10**).[71,72] This approach differs from transdermal drug administration to achieve systemic effects, typically with opioids. Topical NSAIDs are effective for treating acute soft tissue injuries such as sprains

TABLE 35-9 Pain Management: Neuropathic Pain Syndromes

Drug	Use	Initial Dosage	Titrate	Typical Effective Dosage (Maximum Daily Dose)
Amitriptyline or nortriptyline	Chronic pain	25–50 milligrams PO once in the evening	Increase over 2–3 wk	10–50 milligrams/d PO (maximum 150 milligrams/d)
Carbamazepine	Trigeminal neuralgia	100 milligrams PO twice per day	Increase 100–200 milligrams/d	200–400 milligrams PO twice per day (maximum 1200 milligrams/d)
Oxcarbazepine	Trigeminal neuralgia	300 milligrams PO daily	Increase to 300 milligrams PO twice a day after 3 d	450–1200 milligrams PO twice per day
Duloxetine	Diabetic neuropathic pain	30 milligrams PO once per day	Increase after 1 wk on initial dose	60 milligrams PO once per day (maximum 60 milligrams/d)
Gabapentin	Neuropathic pain, postherpetic neuralgia	For neuropathic pain: 300 milligrams PO 3 times a day For postherpetic neuralgia: 300 milligrams PO on day 1, followed by 300 milligrams PO twice a day on day 2, and 300 milligrams PO 3 times a day on day 3	Titrate by increasing by 300 milligrams per day up to effective dose	Neuropathic pain: 300–1200 milligrams PO 3 times per day Postherpetic neuralgia: 1800–3600 milligrams/d (maximum 3600 milligrams/d)
Pregabalin	Neuropathic pain, postherpetic neuralgia	50 milligrams PO 3 times per day or 75 milligrams PO twice per day	Increase over 1 wk	150 milligrams PO twice per day to 100 milligrams PO 3 times per day (maximum 600 milligrams/d)

TABLE 35-10 Pain Management: Topical Analgesic Agents

Agent	Preparation	Comments
Diclofenac	1% gel 1.3% topical patch	Gel: apply using dosing card—4 grams for knees, ankles, and feet, and 2 grams for elbows, wrists, and hands. Lightly rub until absorbed. Use up to 4 times a day. Maximum total daily dose is 32 grams. Patch: apply to intact skin at most painful site twice a day.
Ibuprofen	5% gel	Squeeze 50–125 milligrams (4–10 cm) of the gel from the tube and lightly rub into the affected area until absorbed. Apply up to 4 times per day.
Ketoprofen	2.5% gel	Squeeze 2–4 grams (5–10 cm) of the gel from the tube and lightly rub into the affected area until absorbed. Apply 2–4 times per day.
Lidocaine	5% gel 5% topical patch	Gel: apply a moderately thick layer to the affected area (approximately 1/8 inch thick). Allow time for numbness to develop. Best results obtained 20 min to 1 h after application. Patch: apply to intact skin to cover the most painful area. Up to 3 patches can be applied in a single application. Patch may be cut to size to fit. Use only once for up to 12 h within a 24-h period.
Capsaicin	0.025% cream 0.075% cream 0.1% gel 8% patch	Cream and gel: apply to affected area not more than 3–4 times daily. Massage into area until thoroughly absorbed. Patch: only for postherpetic neuralgia. Requires physician or healthcare professional application. Applied for 60 min. Treatment may be repeated every 3 mo.
Methyl salicylate	10% patch	Use only one patch at a time. Apply patch to the affected area and leave on for 8–12 h. Do not use more than 2 patches per day and do not use for more than 3 d in a row.

and strains and also for treating chronic joint pain from osteoarthritis. Topical lidocaine therapy is effective for patients with postherpetic neuralgia and diabetic neuropathy. Topical capsaicin has produced variable results depending on the treatment population and dose applied; regular use appears necessary for prolonged pain relief. A single 60-minute application of a high-dose preparation (8% capsaicin topical patch) is effective for postherpetic neuralgia, but requires professional application and removal to minimize side effects.

The primary adverse reaction of topical medications is local burning, particularly seen with capsaicin, which is derived from chili peppers. Rare cases of localized burns have been reported with topical muscle and joint pain relievers.[73] Most of the serious burns were associated with agents containing menthol (>3% concentration) and/or methyl salicylate (>10% concentration).

PRECAUTIONS

Safe and effective use of opioids is facilitated by choosing an appropriate initial dose and subsequently titrating additional doses toward the desired effect, thus avoiding overmedication and minimizing unwanted effects. Excessive doses of opioids given without titration and patient feedback can result in respiratory depression and decreased levels of consciousness. Hypotension is infrequent, is almost always due to histamine release with the first dose of medication, and is usually of short duration. With comorbidities, such as altered mental status, hemodynamic instability, respiratory dysfunction, or multisystem trauma, initial dosing should be decreased.

The Elderly Acute pain management for the elderly can be a challenge; these patients may have more than one source of pain and/or multiple comorbidities and are at increased risk for drug–drug and drug–disease interactions.[74] Opioid-naive elderly patients are more sensitive to the analgesic effects of opioid drugs because they experience a higher peak and longer duration of pain relief. Moreover, they are more sensitive to sedation, respiratory depression, and cognitive and neuropsychiatric dysfunction. Initial IV opioid doses in the elderly are typically half those used in younger adults, although single doses may not achieve adequate pain control for elderly patients with acute severe pain.[75]

Addiction and Dependence Addiction is the misuse of a medication or drug to the detriment of the patient's well-being. Dependence infers that abrupt cessation of a medication will result in acute withdrawal symptoms. Dependence on opioids requires regular daily usage for 4 to 6 weeks in most patients, whereas addiction may occur after one use of heroin or even a few pills of a prescribed opioid. Consider carefully risk factors for misuse, such as concomitant mental health illness or previous drug or alcohol abuse, when prescribing opioids (see Chapter 292, "Substance Use Disorders"). There is no validated assessment tool to classify ED patients for abuse risk. When uncertain, the general approach is to err on the side of acute pain control, using nonopioid options whenever possible. Management in opioid-tolerant patients can be a challenge.[76] Although EDs are not where most cases of opioid addiction originate,[77] they are perceived as a potential perpetuator of misuse.[78] Distinguishing patient requests for medications because of oligoanalgesia from addiction often requires multiple patient assessments over time; subjective assessment in the ED during a single visit is usually inaccurate for identifying addiction versus aberrant behavior due to oligoanalgesia.

Renal and Hepatic Dysfunction Because most analgesics are metabolized by the liver or kidney, care must be taken when giving opioids to patients with impaired hepatic or renal function. Renal excretion is a major route of elimination for such pharmacologically active opioid metabolites such as morphine-6-glucuronide and dihydrocodeine. Mild renal failure can impede excretion of the metabolites of many opioids, resulting in clinically significant narcosis and respiratory depression. **In patients with renal failure, hydromorphone and fentanyl are the preferred opioids.** Mild hepatic dysfunction has little effect on opioid metabolism. In patients with severe hepatic dysfunction, titration with low doses of analgesics will minimize the risk of overdose.

Respiratory Insufficiency Patients with respiratory insufficiency and those with chronic obstructive pulmonary disease, cystic fibrosis, and neuromuscular disorders affecting respiratory effort (e.g., muscular dystrophy and myasthenia gravis) are particularly vulnerable to the respiratory depressant effects of opioids and nitrous oxide. Careful dose titration and monitoring of oxygenation and ventilation are necessary. Ketamine may be a useful alternative agent in such cases.

Drug Interactions Opioids may have adverse synergistic sedative effects in patients with psychiatric illnesses taking anxiolytics or other psychoactive drugs. The cyclic antidepressants clomipramine and amitriptyline may increase morphine levels and potentiate the opioid effects. The combination of opioids with benzodiazepines carries a high risk of central sleep apnea and should be used with caution.

NONPHARMACOLOGIC MODALITIES

Traditionally, nonpharmacologic techniques of pain management in the ED have been limited to application of heat or cold and immobilization and elevation of injured extremities. Other techniques may be useful in the ED and after discharge.[79] Cognitive-behavioral techniques can be effective in reducing pain and anxiety, may control mild pain when used alone, and can enhance patient satisfaction. Such techniques include reassurance, explanation, reframing, relaxation, breathing exercises, music, psychoprophylaxis, biofeedback, guided

imagery, hypnosis, and distraction. They are a useful adjunct to pharmacologic management of moderate to severe pain. Successful application of these therapies requires a cognitively intact patient and skilled personnel, but many of the techniques require only a few minutes to teach the patient.

Physical nonpharmacologic agents are becoming increasingly relevant to acute pain management. In addition to the traditional techniques noted above, less commonly used physical modalities, such as transcutaneous electrical nerve stimulation and acupuncture, may have some potential role in the ED. Although specific technical skills and equipment are required, there is no need for IV access, and there is no systemic effect such as respiratory depression or altered mental status.

SPECIFIC SITUATIONS

ABDOMINAL PAIN

Early administration of IV opioids is safe for the treatment of acute abdominal pain in the ED and does not affect the accuracy of the evaluation, diagnosis, or management.[80] The one valid concern regarding analgesia and abdominal pain is that reduction in pain does not indicate improvement in pathophysiology. Analgesia without proper evaluation is as inappropriate as proper evaluation without analgesia.[81]

TRAUMA

Patients in shock and those with trauma, burns, and hemodynamic or respiratory instability need judicious use of opioids.[27,82] Fentanyl, first as a bolus and then as an infusion, may be the opioid of choice due to its lesser impact on hemodynamic function and shorter duration of action. Use of regional analgesia is encouraged.[27] NSAIDs should not be given to patients with major trauma due to the risks of excessive bleeding from platelet dysfunction and gastric stress ulcers and the potential for acute renal failure in a volume-depleted patient.

DISPOSITION

Although rare, intractable acute pain can be a primary reason for hospital admission. Otherwise, most patients may be safely discharged with a plan for pain management that includes instructions for use of immediate-release analgesics (i.e., those with a duration of action of up to 6 hours). Persistent pain after ED discharge is common.[83,84] Prescriptions for long-acting agents (e.g., methadone, controlled-release preparations of morphine or oxycodone) are generally avoided upon ED discharge but are sometimes used for those with cancer in whom short-acting agents are no longer effective (see Chapter 38, "Chronic Pain").

Patients should be counseled to take subsequent doses on a regular basis or when their pain begins to return, rather than when it approaches its peak. Patients with recurrence of severe pain, changes in the quality of pain, or persistence of pain longer than 48 hours should be told to return to the ED for reassessment. If opioids are prescribed to the elderly or those naive to narcotics, home observation by a responsible adult is recommended so that adverse effects can be quickly recognized. **Discharge instructions for those given opioids should include instructions to avoid making important decisions while medicated and to avoid driving, operating machinery, climbing or working from heights, and so on, and should also include instructions for treatment of constipation.** The patient should be instructed to not take acetaminophen or ibuprofen within 6 hours of an opioid combined with the same agent. Education about securing opioid prescriptions is also required because up to 85% of prescription opioids misused by adolescents come from their parents' medication cabinet.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 36

Local and Regional Anesthesia

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Teresa Wu

INTRODUCTION

Local anesthetics (**Tables 36-1** and **36-2**) are used to reduce pain from acute injury or procedures performed in the ED.[1] The most common routes of administration include topical, subdermal, and infiltrative around peripheral nerves (regional anesthesia).[2,3]

LOCAL ANESTHESIA

PHARMACOLOGY

Local anesthetics are divided into two classes—**esters** and **amides**—that work by reversibly blocking sodium channels and inhibiting the propagation of nerve impulses.[4,5] Sodium channel blockade first affects the smaller nerve fibers, causing a reduction in pain and temperature sensation, followed by loss of touch, deep pressure sensation, and, finally, motor function. Esters are hydrolyzed by cholinesterase enzymes in plasma, whereas amides are metabolized by hepatic microsomal enzymes. Onset of action, duration of anesthesia, and potential for systemic toxicity are the three primary factors in selecting a local anesthetic.

The onset of action of a local anesthetic is dependent on the pK_a (the pH at which 50% of the drug is ionized and 50% of the drug is nonionized). If the ambient pH is higher than the pK_a of the agent, a greater percentage of the drug will be in the nonionized form, which diffuses more rapidly across lipid membranes with a more rapid onset of action. Thus, drugs with a lower pK_a, such as mepivacaine, lidocaine, and prilocaine, have a more rapid onset of action. The pH of available local anesthetic solutions is acidic, varying from 3.3 to 6.8, depending on the agent, additives, and buffers, accounting for some of the initial pain upon local injection. The duration of action of the local anesthetics is a function of receptor affinity. Agents with a higher receptor affinity as measured by protein binging (e.g., bupivacaine or tetracaine) have a longer duration of action than those with lower receptor affinity (e.g., lidocaine, prilocaine).[6] Selecting agents with a longer duration of action provides superior results for long procedures or for those in which postprocedure analgesia is desired. Longer-acting agents also offer continued analgesia when providers are pulled away from the procedure. The downside of long-acting agents is the greater risk of systemic toxicity.[7] Levobupivacaine[8] and ropivacaine[9] appear to have a lower risk of systemic toxicity than bupivacaine.

LOCAL ANESTHETIC SYSTEMIC TOXICITY

Local anesthetic systemic toxicity occurs from dose-related clinical progression of sodium channel blockade in nontarget tissues, primarily the brain and heart.[10,11] Toxicity can range from subtle neurologic symptoms to refractory seizures and, ultimately, cardiovascular collapse (**Figure 36-1**).[12-14] The risk of systemic toxicity can be reduced by adherence to dose limitation and techniques to minimize systemic absorption.[15-18] Seizures due to neurologic toxicity should be treated with benzodiazepines.[19,20] Patients with cardiac depression or arrest should be treated with **intravenous 20% lipid emulsion,** especially if systemic toxicity is due to bupivacaine with its high lipid solubility.[19-28] Guidelines recommend an initial dose of 20% lipid emulsion 1.5 mL/kg infused over 1 minute followed by an infusion at 0.25 mL/kg based on lean body mass continued for 10 minutes after hemodynamic stability occurs. If hemodynamic instability persists, repeat boluses can be administered with the recommended maximum dose of approximately 10 mL/kg over the initial 30 minutes.[19,20] Cardiac arrest is treated with standard resuscitative

TABLE 36-1 Topical Anesthetic Agents

Agent	Active Ingredients	Application	Time to Effectiveness
Intact Dermis			
Eutectic mixture of local anesthetic agents (EMLA®)	Lidocaine 2.5% Prilocaine 2.5%	Apply thick layer, 5–10 grams (maximum 20 grams), to area to be anesthetized; cover with semiocclusive dressing.	60 min
Tetracaine (amethocaine) gel (Ametop®)	Tetracaine 4%	Apply 1 gram (1 tube) to area to be anesthetized; cover with occlusive dressing.	30 min
Liposome-encapsulated tetracaine	Tetracaine 5%	Apply 0.5 gram to area to be anesthetized.	60 min
Liposome-encapsulated lidocaine (LMX4® and LMX5®)	Lidocaine 4% or 5%	Apply 2.5 grams to area to be anesthetized.	30–60 min
Open Dermis			
Lidocaine, epinephrine, tetracaine (LET)	Lidocaine 4% Epinephrine 0.1% Tetracaine 0.5%	Apply 3–5 mL to gauze pad placed into wound; cover with semiocclusive dressing.	20–30 min
Mucosa			
Topical anesthetic gel (ZAP®)	Benzocaine 18% Tetracaine 2%	Apply 0.2 mL (1 dispenser application) with cotton swab to area to be anesthetized.	5 min
Benzocaine spray (Hurricaine®)	Benzocaine 20%	Apply 1 spray to area to be anesthetized; volume delivered is highly dependent on canister orientation and residual volume.	15–30 s
Viscous lidocaine	Lidocaine 2%	Apply 10 mL to area (e.g., topical anesthesia before upper airway procedures).	2–5 min

measures with the exception that small doses of epinephrine, 10 to 100 micrograms, are preferred instead of the standard adult dose of 1 milligram, and vasopressin (for use as a vasopressor) and lidocaine (for use as an antiarrhythmic) should be avoided.[20]

Prilocaine and benzocaine can cause the oxidation of the ferrous iron in normal hemoglobin to the ferric form creating methemoglobin, which results in cyanosis when methemoglobin concentrations exceed 1.5 grams/dL (see Chapter 207, "Dyshemoglobinemias").

GENERAL PRINCIPLES

When using any local anesthetic, calculate the volume and concentration of drug used, especially when treating smaller patients or tending to large wounds (Table 36-2). Aspiration before injection helps to avoid inadvertent deposit of local anesthetic in a vein or artery. When the use of a large quantity of local anesthetic seems unavoidable, procedural sedation or alternative regional blocking techniques and

TABLE 36-2 Local Anesthetic Agents

Agent	Lipid Solubility*	Protein Binding	Duration† without epinephrine (min)	Onset‡ (min)	Maximum Dose milligrams/kg without epinephrine (with epinephrine)	Concentration (subdermal use)	Concentration (regional anesthesia use)
Amides							
Bupivacaine	High	High	120–240	2–10	3 (5)	0.50%–0.75%	0.25%–0.50%
Lidocaine	Medium	Medium	30–120	<1	4 (7)	0.5%–1.0%	1%–2%
Levobupivacaine	High	High	>1000	10–20	2	0.25%	0.50%
Mepivacaine	Low	Medium	30–120	3–20	4	0.5%–1.0%	1%–2%
Prilocaine	Medium	Medium	30–120	5–6	5	4%	NA
Ropivacaine	Medium	High	120–350	10–45	3	0.5%	0.5%
Esters							
Procaine	Low	Low	15–90	5	7	0.25%–0.5%	0.5%–2.0%
Chloroprocaine	Low	Low	30–60	5–6	8	1%–2%	1%–2%
Tetracaine (amethocaine)	High	High	120–240	7	1.5	NA	0.2%–0.3%
Alternatives for patients with reactions to amides and esters							
Diphenhydramine§			25			1%	NA
Benzyl alcohol with epinephrine¶			15–25			0.9%	NA

Abbreviation: NA = not applicable.

*Lipid solubility determines the potency of the anesthetic, with the more lipophilic anesthetics having enhanced potency compared with less lipophilic agents.

†The more an anesthetic is bound to proteins, generally, the longer the duration of action.

‡The onset of action of an anesthetic is determined by the total dose of anesthetic given and the pH at which 50% of the drug is ionized and 50% of the drug is nonionized.

§Diphenhydramine 1% or 10 milligrams/mL (created by mixing 4 parts normal saline and 1 part 5% diphenhydramine).

¶Benzyl alcohol 0.9% solution (created by mixing 0.2 mL of epinephrine 1:1000 with a 20-mL vial of normal saline containing benzyl alcohol 0.9%).

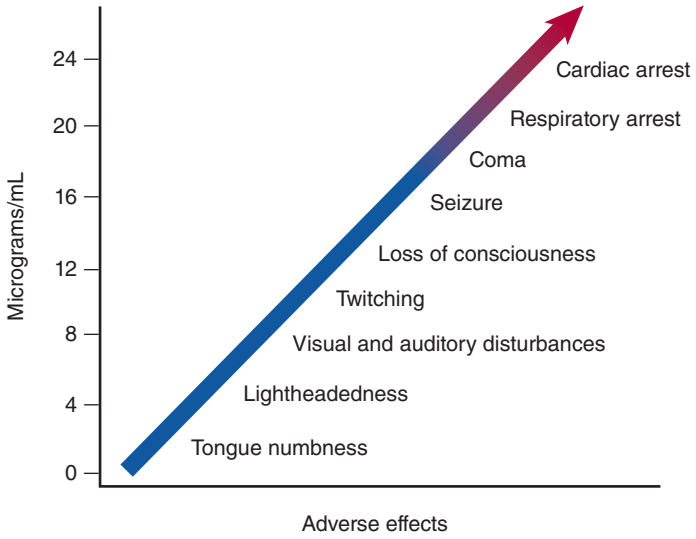


FIGURE 36-1. Adverse effects of local anesthetics. Plasma concentration of local anesthetics versus toxic effects.

supplementation with systemic analgesics or anxiolytics should be considered (see Chapter 37, "Procedural Sedation and Analgesia in Adults").

The addition of **epinephrine** to the injected local anesthetic solution increases the duration of anesthesia, helps to control wound bleeding, and slows the systemic absorption.[29] The use of local anesthetic with epinephrine is safe in end-arterial fields (e.g., fingers, toes) in healthy patients,[30-35] but probably should be avoided in suspected digital vascular injury; in patients with vascular disease, such as Raynaud's or Berger's disease; or in other conditions in which end-arterial vascular supply is problematic. An alternative to epinephrine is clonidine (U.S. Food and Drug Administration unlabeled use), an α-adrenergic agonist that can also be used in combination with a local anesthetic to prolong the duration of anesthesia.[36-38] A dose of 0.5 microgram/kg of clonidine (maximal dose, 150 micrograms) can be mixed with the anesthetic to prolong the duration of anesthesia by >50%. Do not exceed a maximum dose of 150 micrograms because sedation, hypotension, and bradycardia can result.[37,38]

The addition of **sodium bicarbonate** to local anesthetics reduces the pain of injection and slightly shortens the onset of action by raising tissue pH.[1,39-41] Lidocaine can be buffered by adding 1 mL of sodium bicarbonate 8.4% (1 mEq/mL) to 9 mL of 1% lidocaine. Bupivacaine can be buffered by adding 1 mL of sodium bicarbonate 8.4% (1 mEq/mL) to 29 mL of bupivacaine 0.25%. The addition of bicarbonate can cause precipitation of the anesthetic agent (most prominently bupivacaine) and accelerate degradation of epinephrine, but the clinical effectiveness of buffered anesthetic solutions is maintained for at least 1 week after preparation.

Adverse reactions to local anesthetics are most often local reactions to preservatives or to the epinephrine in the solution, and true allergic reactions are extremely rare.[42,43] In patients with true allergies to local anesthetics, two nontraditional agents can be used for wound repair via local injection—**diphenhydramine** and **benzyl alcohol** (Table 36-2).[44-46]

Local anesthetics can be administered topically, intradermally, subdermally, or infiltrated near peripheral nerves. Considerations in wound management include patient factors (age, anticipated pain tolerance, comorbidities), wound factors (location, depth, presence or absence of contamination, and/or neurovascular injury), and technical factors (time required, clinician experience).

TOPICAL ANESTHESIA

Topical anesthetics are used in three major situations: on *intact skin* before dermal instrumentation, applied to *intact mucosa*, and placed on *open skin* for pain control or before wound repair.[47-49] Topical anesthetics are probably as effective as local anesthetic infiltration for suturing of many dermal lacerations, although the comparison studies are of modest quality.[50]

An alkaline (pH approximately 9) cream mixture of lidocaine 2.5% and prilocaine 2.5% (eutectic mixture of local anesthetics [**EMLA®**]) was the first topical anesthetic formulated to penetrate intact skin. When applied for at least 60 minutes under a semiocclusive dressing before dermal instrumentation, this lidocaine/prilocaine mixture is as efficacious as the infiltration of local anesthetic and is ideal for venous catheter insertion and lumbar puncture. EMLA® is approved for application to intact normal skin and genital mucous membranes. Liposome-encapsulated tetracaine, liposome-encapsulated lidocaine, and tetracaine gel have all been compared to the lidocaine/prilocaine mixture and found to be equally efficacious (Table 36-1).[51-55]

A mixture of **lidocaine, epinephrine, and tetracaine** acts as a topical anesthetic when used on open dermis.[56] This mixture is used in a variety of liquid and gel formulations that are usually compounded by the hospital pharmacy in accordance with the concentration preferences of local clinicians; a common version is 4% lidocaine, 0.1% epinephrine, and 0.5% tetracaine prepared for use in 3- to 5-mL aliquots.

INTRADERMAL AND SUBDERMAL ANESTHESIA

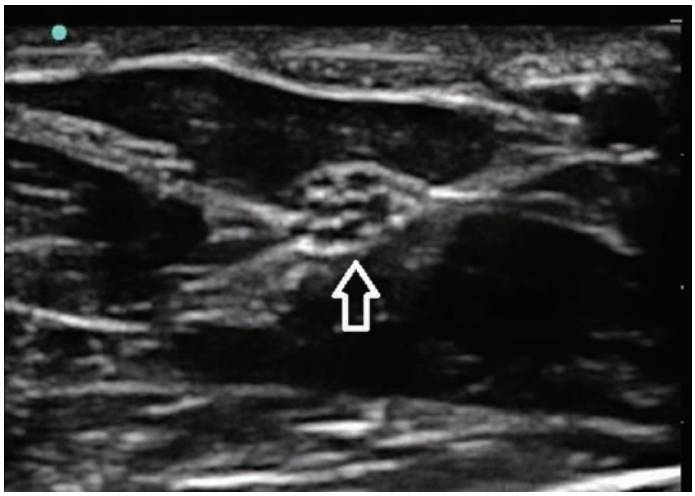
Intradermal injection produces a visible wheal, whereas subdermal injection does not. Intradermal injection produces more immediate pain upon injection due to stretching of the compact dermal structure, but can enhance the anesthetic effect by applying pressure to and numbing the cutaneous pain sensors. Intradermal injection raises the skin surface and is useful when shaving off a cutaneous lesion. Subdermal injections have a slower onset of action, are less painful, and are the most commonly used method of achieving local anesthesia in the ED and for office-based surgery.[1,57] Local anesthetics may be delivered directly into the subdermal space in most clean lacerations or as a field block for contaminated wounds.

In addition to modifying the injected solution, a variety of techniques are used to reduce the pain of needle puncture and local anesthetic injection[39-41,58]: application of a topical anesthetic prior to injection,[59,60] warming the local anesthetic agent,[61-63] stretching the skin at the puncture site, vibrating the skin adjacent to the area,[64,65] talking during the process to distract the patient, use of a small-bore needle (27 to 30 gauge),[39,66] small pulse or slow injection,[39,67] inserting the needle through enlarged pores or hair follicles, inserting the needle perpendicular to skin surface,[68] inserting the needle with bevel-up position,[69] or numbing the skin with an aerosol refrigerant.[70-74]

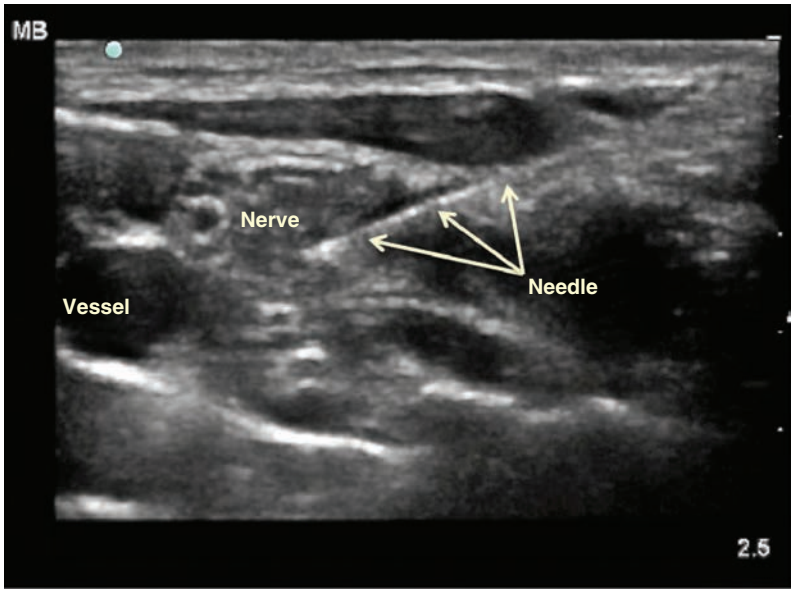
REGIONAL ANESTHESIA

Regional anesthesia is a technique that infiltrates local anesthetic agents adjacent to peripheral nerves ("nerve blocks") and is typically used for complicated lacerations, abscesses, fractures, debridement, and dislocations.[75-77] Providing adequate anesthesia quells patient anxiety, provides greater patient satisfaction, and increases the likelihood of an optimal result when treating complex injuries. With careful technique, serious complications from peripheral nerve blocks are uncommon.[78-80] Assess and document distal neurovascular status before application of a regional nerve block to prevent masking a primary traumatic neurovascular injury. Distal vascular function is assessed by noting skin color and temperature, measuring capillary refill time, and palpating pulses. Distal neurologic function is assessed by noting cutaneous sensation (pain, touch) and motor function (active movement, strength). For digital injuries, assess digital nerves by determining two-point discrimination on the volar pad before anesthetic injection. **Normal two-point discrimination is <6 mm at the fingertips and is often <2 mm. Compare the injured digit with the contralateral normal digit.**

Regional anesthesia for laceration repair eliminates wound distortion caused by large-volume subdermal injection. Regional anesthesia on the extremities provides superior pain control when compared with subdermal infiltration of anesthetic.[75] Topical anesthetic before peripheral nerve blocks can minimize the pain associated with the block.[51-55,59,60]



A



B

FIGURE 36-2. **A.** White, hyperechoic, honeycomb appearance of a nerve in cross-section on US (*arrow*). [Image used with permission of Teresa Wu, MD.] **B.** US visualization of the bright white, hyperechoic needle approaching the target nerve via long-axis approach. [Image used with permission of Teresa Wu, MD.]

When selecting a local anesthetic for regional anesthesia, consider the onset of clinical effects, duration of analgesia, and risk of toxicity.[75] Although lidocaine continues to be the most popular agent, bupivacaine, levobupivacaine, and ropivacaine offer a longer duration of action, with levobupivacaine and ropivacaine being significantly less cardiotoxic.[6,8,9] Peripheral nerve blocks require time to achieve optimal analgesia, approximately 10 to 20 minutes for lidocaine and 15 to 30 minutes for bupivacaine. Pain and temperature sensation are affected first, followed by loss of touch, deep pressure, and then motor function. Intraneural injection of anesthetic causes significant pain.[81] Thus, if excessive pain upon injection is noted, withdraw the needle a few millimeters, and after pain abates, resume the injection.

The regional nerve blocks commonly performed by emergency physicians often use the "landmark" technique to identify the site of local anesthetic injection.[75] The major disadvantage of the landmark approach is anatomic variation. Large volumes of anesthetic are typically administered in case the needle tip is not close enough to the desired nerve. There are currently two devices that are commonly used to help localize and direct the needle and to maximize the rate of successful anesthesia: a peripheral nerve stimulator using electrically insulated needles and US guidance to localize the nerve.[82-87] US guidance shortens the block performance time, reduces the number of needle passes, minimizes risk for vascular injury, and enables blocks to be performed using lower anesthetic doses.[88-91]

During a US-guided nerve block, the goal is to visualize the needle tip as it is being directed toward the target nerve.[87] Using a high-frequency linear array transducer, the nerve will appear as a white honeycomb structure in the short axis and a hyperechoic, white linear array of fibers in the long axis (**Figure 36-2A**). The needle can be visualized as a hyperechoic, bright white structure in either the short-axis or long-axis approach (**Figure 36-2B**). It is often helpful to inject anesthetic through the needle as it is slowly being advanced toward the target nerve. This hydrodissection of the adjacent tissues and infiltration of fluid allow better visualization of the needle tip and improved pain control. Once the needle is in close proximity to the nerve, US can be used guide injection of anesthetic around the nerve.

DIGITAL BLOCKS

DIGITAL NERVE BLOCK

Purpose A digital nerve block provides anesthesia to the entire digit and is an excellent block when tending to lacerations of the fingers or toes, drainage of paronychia, finger or toenail removal or repair, and

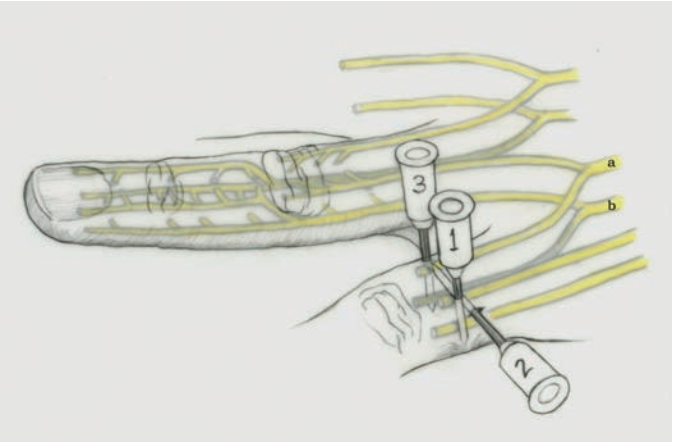


FIGURE 36-3. Digital nerve block. Anesthetic placed as shown blocks both the dorsal (*a*) and palmar (*b*) digital nerves, ensuring circumferential anesthesia of the finger. By using the sequence shown, the prior injection provides relief from the injection to follow. [Illustration used with permission of Timothy Sweeney, MD.]

reduction of fractured or dislocated fingers or toes.[92] Use of topical anesthesia before instrumentation can quell anxiety about the procedure and minimize pain. Assess distal capillary refill and two-point discrimination (normal <6 mm) on the volar pad of a finger before the block. There is less pain with injection using lidocaine 1% with epinephrine compared to bupivacaine 0.5% for digital blocks, but the duration of anesthesia is only about half as long.[93] (See Video: Digital Nerve Block.)

Patient Positioning and Anatomy The hand and wrist are placed in a prone (palm down) position. The common digital nerves are derived from the median and ulnar nerves. In the distal palm, the common digital nerve divides into paired palmar branches that travel on both sides of the flexor tendon sheath and innervate the lateral and palmar aspect of each digit. The dorsal digital nerves are smaller, derived from the radial and ulnar nerves, and travel on the dorsal lateral aspect of each finger to provide sensation to the back of the finger.

Technique Insert the needle on the dorsal surface of the proximal phalanx, advance toward the volar surface staying tangential to the phalanx, aspirate to ensure no inadvertent vascular puncture has occurred, deposit 1 mL of anesthetic solution, and inject an additional 1 mL while withdrawing the needle back to the skin surface (**Figure 36-3**). Reinsert the needle in the same location, but direct it across the dorsum of the digit to the other side, and inject a 1-mL band of anesthetic solution into the subcutaneous space across the dorsum of the digit. Repeat the initial injection process on the other side of the digit.

The digital nerves can also be blocked at their bifurcation adjacent to the metacarpal heads. This approach (metacarpal block) is particularly useful for long and ring finger anesthesia.

TRANSTHECAL OR FLEXOR TENDON SHEATH DIGITAL NERVE BLOCK

Purpose A transthecal or flexor tendon sheath digital nerve block provides anesthesia to the entire digit by using the flexor tendon sheath to guide anesthetic to the underlying digital nerves.[94,95] This procedure can be performed in addition or as an alternative to a digital nerve block. However, a **flexor tendon sheath block may not fully anesthetize the distal fingertip.**

Patient Positioning and Anatomy The hand and wrist are placed in a supine (palm up) position. The flexor tendon sheath surrounds the flexor tendon on the palmar side of the digit.

Technique Identify the distal palmar crease on the palmar aspect of the hand. Have the patient flex the finger against resistance to improve visualization of the flexor tendon. Insert the needle at the distal palmar crease directed distally at a 45-degree angle to the palmar plane with the tip pointed distally (**Figure 36-4**).

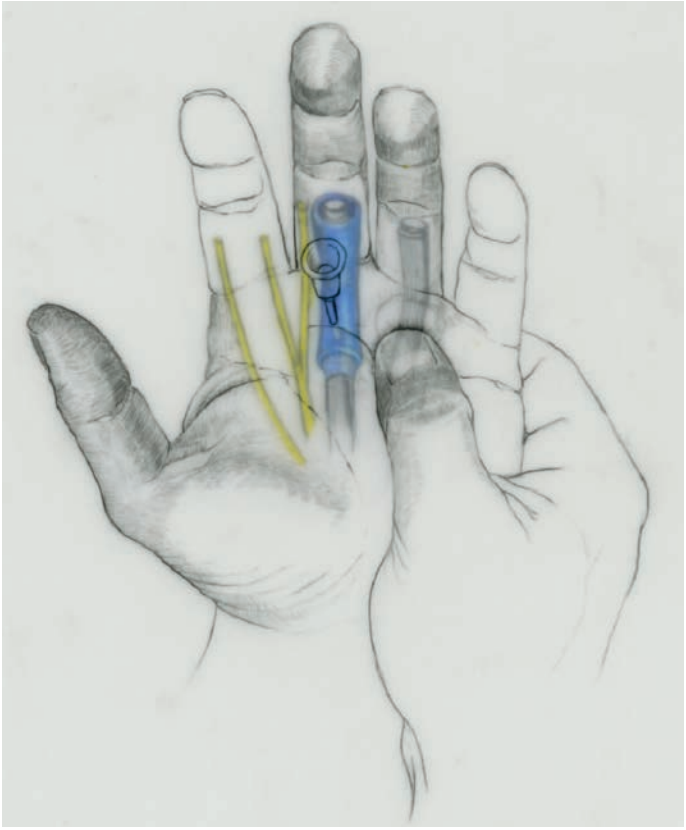


FIGURE 36-4. Transthecal (flexor tendon sheath) digital nerve block. The point of injection is in the middle of the flexor tendon sheath at the level of the distal palmar crease. A 25-gauge needle is advanced at 45 degrees, with tip directed distally until it enters the flexor tendon sheath (shown in blue) or until bone is encountered. When the needle is properly placed within the flexor tendon sheath, the anesthetic solution is injected. Diffusion out of the tendon sheath blocks adjacent palmar digital nerves. [Illustration used with permission of Timothy Sweeney, MD.]

Advance the needle until a "pop" is felt, indicating penetration of the flexor tendon sheath. Inject 2 to 3 mL of anesthetic solution. If bone is struck before the "pop" is felt, withdraw the needle 2 to 3 mm and inject the solution.

A modification of the transthecal approach is to inject into the flexor tendon sheath at the base of the digit in the metacarpal crease[96-98] or into the midportion of the proximal phalanx.[99]

HAND AND WRIST BLOCKS

The median, radial, and ulnar nerves supply the sensory innervation to the hand and can be used in part or in combination to provide anesthesia for wound repair or fracture/dislocation reductions (**Figures 36-5** and **36-6**). (See Video: Forearm Nerve Blocks.)

MEDIAN NERVE BLOCK

Purpose A median nerve block provides anesthesia to the thumb, index, long, and half of the ring finger distal to the proximal interphalangeal joint, but not the dorsum of the thumb (Figures 36-5 and 36-6).

Patient Positioning and Anatomy The hand and wrist are placed in a supine (palm up) position. The median nerve traverses between the flexor carpi radialis and the palmaris longus tendon at the proximal wrist crease. With the hand and wrist in a supine position, the flexor carpi radialis is lateral (radial direction) and the palmaris longus is medial (ulnar direction) to the nerve. When the patient makes a fist and flexes the wrist, the palmaris longus tendon is usually the more prominent of the two tendons (**Figure 36-7**, top left).



FIGURE 36-5. Hand innervation, dorsal view. Dorsal hand distribution of ulnar nerve (yellow), radial nerve (red), and median nerve (blue).

Technique Raise a wheal of anesthetic in the subcutaneous space between the palmaris longus and flexor carpi radialis at the level of the proximal palmar crease (Figure 36-7, right). Insert the needle until the "pop" of the deep fascia can be felt, and inject 3 to 5 mL of anesthetic.

If bone is contacted before the "pop" is felt, withdraw the needle 2 to 3 mm and inject the solution. To increase the probability of a successful block, withdraw the needle back to the skin and reinsert, directing the needle 30 degrees both medially and laterally, and inject an additional 1 to 2 mL of anesthetic solution. The palmar branch of the medial nerve is superficial and can be blocked by withdrawing the needle to the subcutaneous space and injecting 2 to 3 mL of anesthetic solution.

RADIAL NERVE BLOCK

Purpose A radial nerve block provides anesthesia to the dorsal lateral half of the hand and dorsal aspect of the thumb.

Patient Positioning and Anatomy The hand and wrist are placed in a supine (palm up) position. The superficial branch of the radial nerve traverses above the styloid process of the radius and provides sensation to the dorsum of the thumb, index finger, and lateral half of the middle finger (Figures 36-5 and 36-6). Other branches of the radial nerve traverse over the anatomic snuff box. The sides of the anatomic snuff box are formed by the tendons of the extensor pollicis brevis and longus and the base by the radial styloid.



FIGURE 36-6. Hand innervation, palmar view. Palmar hand distribution of ulnar nerve (yellow), radial nerve (red), and median nerve (blue).

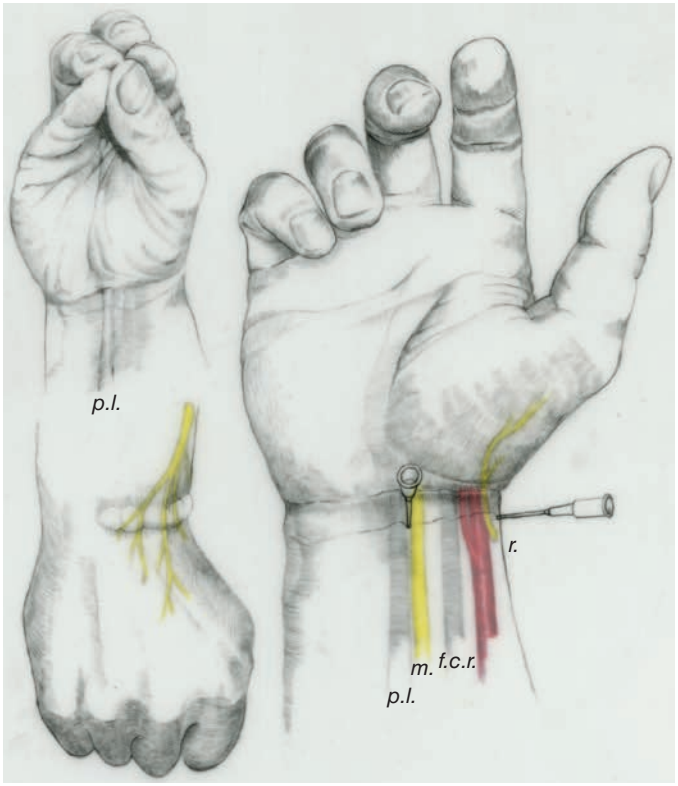


FIGURE 36-7. Median and radial nerve block. *Top left:* Technique for identification of the palmaris longus tendon (p.l.) through wrist flexion using finger and thumb opposition. *Right:* The median nerve (m.) is blocked by inserting the needle between the palmaris longus and flexor carpi radialis (f.c.r.) tendons. The radial nerve (r.) block begins with an injection over the lateral aspect of the radial styloid. *Lower left:* The radial nerve block continues dorsally as a subcutaneous field block extending to the dorsal midwrist. [Illustration used with permission of Timothy Sweeney, MD.]

Technique Raise a wheal of anesthetic in the subcutaneous space just proximal to the anatomic snuffbox. Inject 5 mL of anesthetic solution into the subcutaneous tissue overlying the radial styloid (Figure 36-7, right). (See Video: Regional Anesthesia: The Hand – Radial Nerve.)

Then, reinsert the needle and direct it through the subcutaneous space in a lateral (ulnar) direction, injecting a band of an additional 5 mL of anesthetic solution overlying the dorsum of the wrist to ensure blockage of the smaller branches of the radial nerve (Figure 36-7, lower left). The distribution of the radial nerve is less predictable; therefore, a generous amount of anesthetic solution should be injected.

ULNAR NERVE BLOCK

Purpose An ulnar nerve block provides anesthesia to the entire fifth digit, half of the fourth digit, and the medial aspect of the hand and wrist.

Patient Positioning and Anatomy The hand and wrist are placed in a supine (palm up) position. The ulnar nerve travels with the corresponding vein and nerve and can be located underneath (deep to) the flexor carpi ulnaris. To identify the flexor carpi ulnaris, have the patient make a fist and tense the wrist. The flexor carpi ulnaris is the most prominent tendon on the ulnar side at the wrist (**Figure 36-8A**).

Technique Raise a wheal of anesthetic in the subcutaneous space just proximal (1 to 2 cm) to the most distal wrist crease. Insert the needle under the flexor carpi ulnaris tendon to an additional 5 to 10 mm past

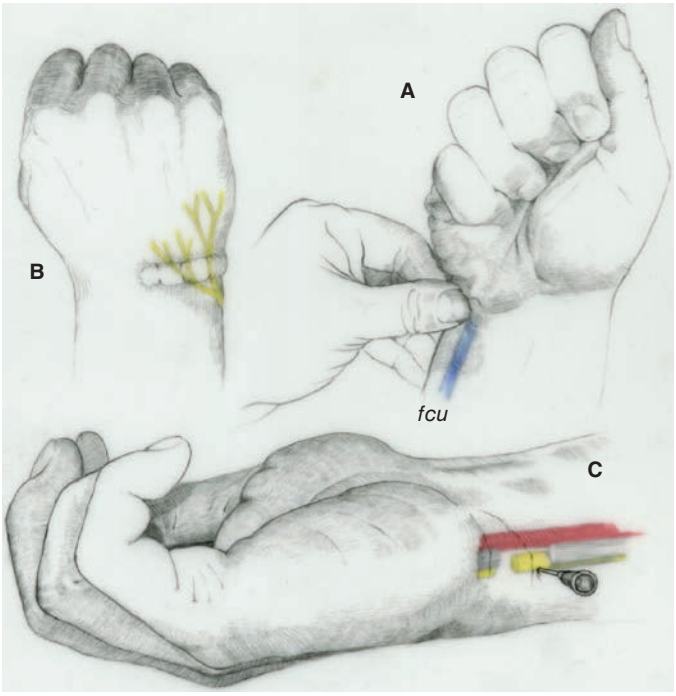


FIGURE 36-8. Ulnar nerve block. **A.** Technique for identifying the flexor carpi ulnaris tendon (fcu) by making a fist and tensing the wrist. **B.** The subcutaneous field block of the dorsal ulnar nerve branches, extending from the site of insertion of the ulnar block to the midline dorsal wrist. **C.** The needle is oriented horizontally beneath the flexor carpi ulnaris tendon and inserted to a depth of 5 to 10 mm past the tendon edge where the anesthetic solution is injected after a negative aspiration. [Illustration used with permission of Timothy Sweeney, MD.]

the edge of the tendon (**Figure 36-8C**). (See Video: Regional Anesthesia: The Hand – Ulnar Nerve.)

Aspirate before injection to ensure that inadvertent arterial/venous puncture has not occurred, and inject 3 to 5 mL of anesthetic solution. To block the dorsal branches of the ulnar nerve, inject 2 to 3 mL band of anesthetic solution in the subcutaneous space just above the tendon of the extensor carpi ulnaris (**Figure 36-8B**). US guidance can be useful when anatomic landmarks are not easy to discern.[100,101]

FOOT AND ANKLE BLOCKS

The five nerves that provide sensation to the foot are four branches of the sciatic nerve (deep and superficial peroneal, tibial, and sural nerves) and one cutaneous branch of the femoral nerve (saphenous nerve; **Figures 36-9** through **36-12**). These are excellent blocks to use alone or in combination for lacerations, fracture reductions, and exploring wounds. The deep peroneal nerve and the posterior tibial nerves are deep nerves and can be consistently found by anatomic landmarks. The superficial peroneal, sural, and saphenous nerves are superficial and located in the subcutaneous tissue encircling the ankle. Due to the anatomic variability of these three nerves, no single injection point can reliably provide adequate anesthesia, so these nerves are blocked by depositing the local anesthetic agent as a field block in the subcutaneous space in the area through which the nerve travels. The pertinent landmarks for performing all of the ankle blocks are the extensor hallucis longus, tibialis anterior tendon, Achilles tendon, and the medial and lateral malleolus (**Figure 36-13**).

When all five blocks are used for complete foot anesthesia, the deep nerves (deep peroneal and posterior tibial) should be anesthetized before the surface anatomy is distorted by the superficial field blocks of the other three. An additional tip is to prepare and clean the entire foot before starting so that the physician can change his or her body position and reposition the patient's foot as needed to avoid awkward reaches when accessing all five sites.

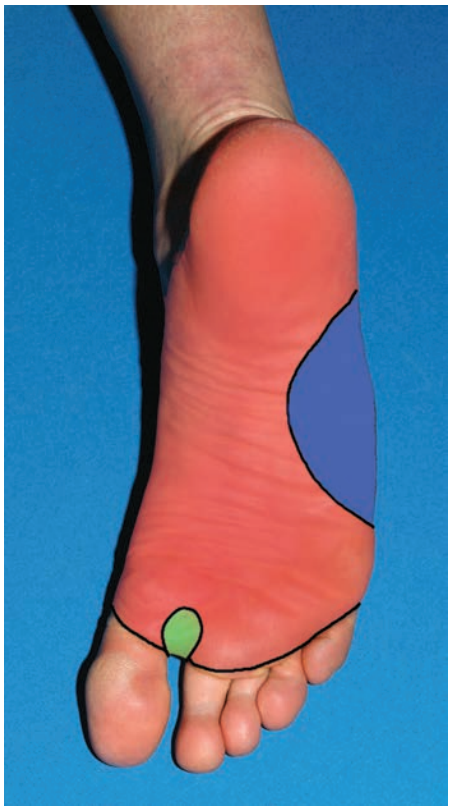


FIGURE 36-9. Foot innervation plantar view. Plantar foot distribution of deep peroneal nerve (green), posterior tibial nerve (red), and sural nerve (blue).

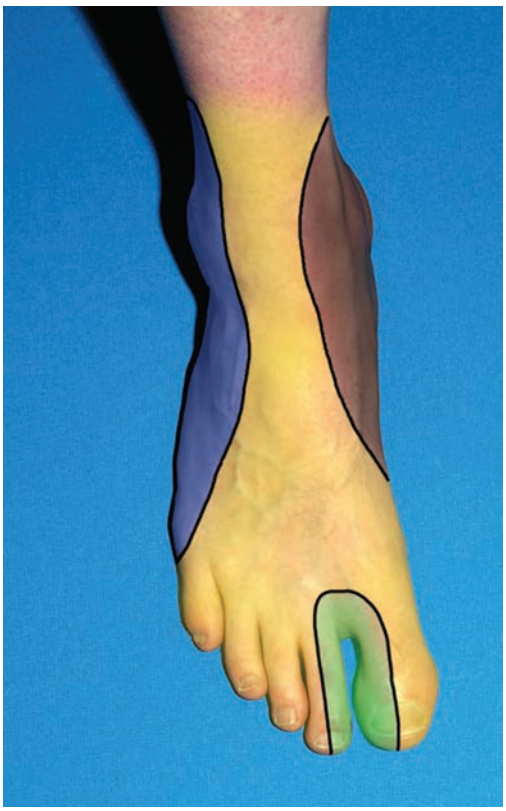


FIGURE 36-10. Foot innervation dorsal view. Dorsal foot distribution of deep peroneal nerve (green), superficial peroneal nerve (yellow), saphenous nerve (brown), and sural nerve (blue).

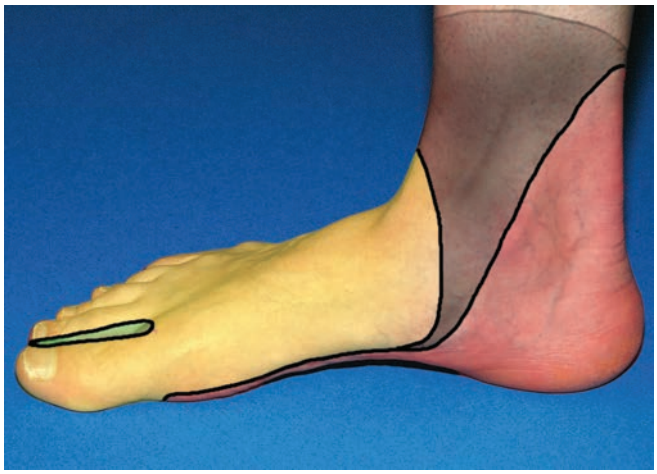


FIGURE 36-11. Foot innervation medial view. Medial foot distribution of superficial peroneal nerve (yellow), saphenous nerve (brown), and posterior tibial nerve (red).

DEEP PERONEAL NERVE BLOCK

Purpose A deep peroneal nerve block provides anesthesia to the web space between the first and second toe and a small area just proximal to the first and second toe on the plantar aspect of the foot.

Patient Positioning and Anatomy The foot is placed in a neutral position. At the level of the medial malleolus, the deep peroneal nerve can be found between the extensor hallucis longus and the tibialis anterior tendon. Extension of the big toe against resistance will help to identify the extensor hallucis longus. Dorsiflexion and inversion of the ankle will help to identify the tibialis anterior tendon.

Technique Raise a wheal of anesthesia in the subcutaneous space between the extensor hallucis longus and the tibialis anterior tendon at the level of the medial malleolus (Figure 36-13B). With the syringe perpendicular to the skin, insert the needle until the extensor retinaculum is penetrated or bone is struck. If bone is struck, withdraw the needle 2 mm. After aspirating to verify that no vascular structure has been entered, inject approximately 2 to 3 mL of anesthetic solution. To increase the chance of a successful block, withdraw the needle back to the skin and reinsert, direct the needle 30 degrees medially and laterally, and deposit an additional 2 mL of anesthetic solution on each side.

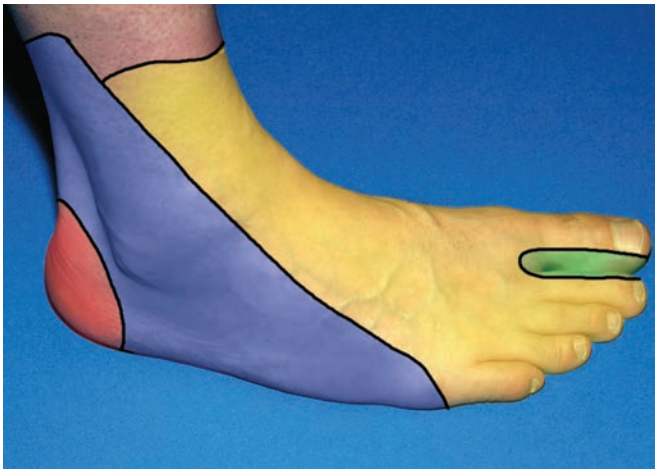


FIGURE 36-12. Foot innervation lateral view. Lateral foot distribution of deep peroneal nerve (green), superficial peroneal nerve (yellow), posterior tibial nerve (red), and sural nerve (blue).

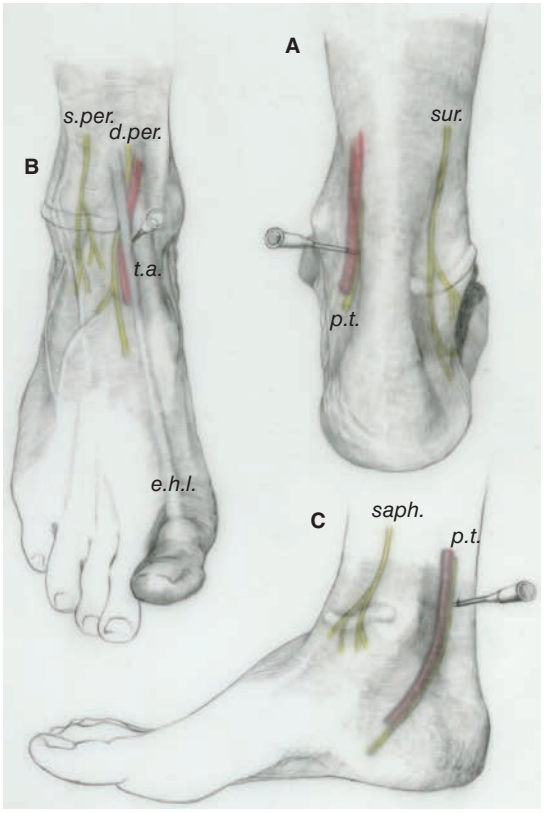


FIGURE 36-13. Ankle nerve blocks. **A.** The subcutaneous field block of the sural nerve (sur.) extends from the Achilles tendon to the lateral malleolus. The posterior tibial nerve (p.t.) is blocked just behind the posterior tibial artery. **B.** The deep peroneal nerve is blocked at the level of the medial malleolus between the anterior tibial tendon (t.a.) and extensor hallucis longus tendon (e.h.l.). The subcutaneous field block of the superficial peroneal nerve (s.per.) extends from the lateral malleolus to the anterior tibial tendon. **C.** The posterior tibial nerve is blocked posteriorly to the posterior tibial artery. The subcutaneous field block of the saphenous nerve (saph.) extends from the medial malleolus to the anterior tibial tendon. [Illustration used with permission of Timothy Sweeney, MD.]

POSTERIOR TIBIAL NERVE BLOCK

Purpose A posterior tibial nerve block provides anesthesia to the plantar aspect of the foot. This is an excellent block when repairing a laceration on the bottom of the foot.

Patient Positioning and Anatomy The patient can be either supine with the foot rotated outward or prone with the foot rotated inward. The posterior tibial nerve, artery, and vein can be found just posterior to the medial malleolus. The nerve is deep to the fascia and superficial/posterior to the artery.

Technique Raise a wheal of anesthesia posterior to the medial malleolus. Palpate the posterior tibial artery and insert the needle just posterior to the artery until it is deep to the fascia or bone is struck (Figure 36-13A and C). (See Video: Regional Anesthesia: The Foot – Posterior Tibial Nerve.)

If bone is struck, withdraw the needle 2 mm. Inject 2 to 3 mL of local anesthetic solution after aspirating to ensure that inadvertent arterial/venous puncture has not occurred. To increase the chance of a successful block, withdraw the needle back to the skin and reinsert, directing the needle 30 degrees medially and laterally, and deposit an additional 2 mL of anesthetic solution on each side. US guidance can be used to guide the needle and increase the completeness of a posterior tibial nerve block.[102]

SUPERFICIAL PERONEAL NERVE BLOCK

Purpose A superficial peroneal nerve block provides anesthesia to the dorsal lateral aspect of the foot.

Patient Positioning and Anatomy The patient is supine, and the foot is rotated inward. The superficial peroneal nerve traverses the lateral portion of the ankle in the subcutaneous space between the lateral malleolus and the tibialis anterior tendon.

Technique Prepare a sterile site between the superior border of the lateral malleolus and the tibialis anterior tendon. Dorsiflexion and inversion of the ankle will help to identify the tibialis anterior tendon. In the subcutaneous space, inject 5 mL of anesthetic, tracking from the tibialis anterior tendon to the superior portion of the lateral malleolus (Figure 36-13B). Creation of a subcutaneous wheal indicates proper anesthetic placement.

SURAL NERVE BLOCK

Purpose A sural nerve block provides anesthesia to the lateral aspect of the ankle with some extension of anesthesia to the plantar aspect of the foot.

Patient Positioning and Anatomy The patient can be either supine with the foot rotated inward or prone with the foot rotated outward. The sural nerve traverses the posterior lateral portion of the ankle in the subcutaneous space between the Achilles tendon and the lateral malleolus.

Technique Identify the space between the Achilles tendon and the superior border of the lateral malleolus. In the subcutaneous space, inject 5 to 6 mL of anesthetic solution in a band running from the superior portion of the lateral malleolus to the Achilles tendon (Figure 36-13A). (See Video: Regional Anesthesia: The Foot – Sural Nerve.)

Creation of a subcutaneous wheal indicates proper anesthetic placement. Using US guidance to inject local anesthetic around the lesser saphenous vein may facilitate a more complete block of longer duration.[103]

SAPHENOUS NERVE BLOCK

Purpose A saphenous nerve block provides anesthesia to the medial aspect of the ankle.

Patient Positioning and Anatomy The foot is in a neutral position. The saphenous nerve traverses the anterior medial portion of the ankle in the subcutaneous space between the tibialis anterior tendon and the medial malleolus.

Technique Identify the space between the tibialis anterior tendon and the superior border of the medial malleolus. In the subcutaneous space, inject 5 to 6 mL of anesthetic solution in a band from the tibialis anterior tendon to the superior portion of the medial malleolus (Figure 36-13C). (See Video: Regional Anesthesia: The Foot – Saphenous Nerve.)

Creation of a subcutaneous wheal indicates proper anesthetic placement.

FACIAL NERVE BLOCKS

Facial nerve blocks provide excellent analgesia and little to no distortion of the forehead, cheek, and chin (**Figure 36-14**).[75,104] **Topical anesthetic applied to the mucosa should be used before the intraoral approach for infraorbital and mental nerve blocks.** It is important to assess neurovascular status before application of the block to prevent masking a primary traumatic neurovascular injury.

SUPRAORBITAL AND SUPRATROCHLEAR NERVE BLOCKS

Purpose Supraorbital and supratrochlear nerve blocks provide anesthesia to the entire forehead up to the vertex of the scalp and down the bridge of the nose.

Patient Positioning and Anatomy The patient is either lying supine or sitting upright in a position of comfort. The supraorbital nerve exits the supraorbital foramen, which is in line with the pupil and above the superior orbital rim. The supratrochlear nerve exits from under the superior orbital rim 5 to 10 mm medial to the supraorbital foramen. The supraorbital nerve supplies most of the forehead, whereas the supratrochlear nerve supplies the area along the bridge of the nose (Figure 36-14).

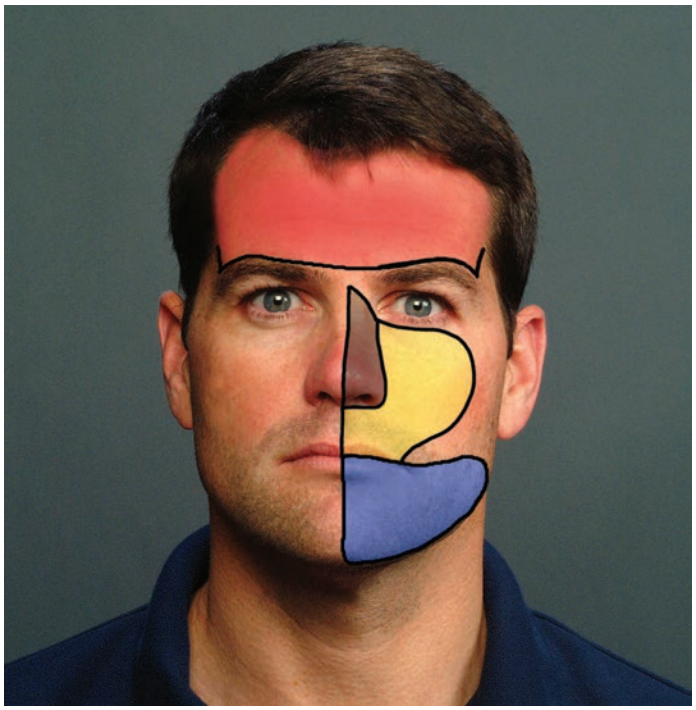


FIGURE 36-14. Face innervation frontal view. Nerve distribution to the face with supraorbital nerve (red), supratrochlear nerve (brown), infraorbital nerve (yellow), and mental nerve (blue).

Technique Raise a wheal of anesthesia in the subcutaneous space just superior to the eyebrow and in line with the pupil. Deposit 2 to 3 mL of anesthetic solution in the subcutaneous space, and then direct the needle medially to raise a horizontal wheal reaching to the medial border of the eyebrow using an additional 5 mL of anesthetic solution (**Figure 36-15**).

INFRAORBITAL NERVE BLOCK

Purpose An infraorbital nerve block provides anesthesia to the lower lid, medial cheek, ipsilateral side of the nose, and ipsilateral upper lip (Figure 36-14).

Patient Positioning and Anatomy The patient is either lying supine or sitting upright in a position of comfort. The infraorbital nerve exits the infraorbital foramen 5 to 10 mm inferior to the midportion of the orbital rim and just cranial (superior) to the maxillary canine teeth (tooth #6 on the patient's right and #11 on the patient's left).

Technique After adequately providing topical anesthetic to the mucosa superior to the maxillary canine, dry the mucosa and retract the upper lip. The recommended technique involves placing the index finger and middle finger of the noninjecting hand on the inferior optic rim and everting the upper lip with the thumb. Insert the needle at the gingival reflection above the maxillary canine, direct the needle superiorly, advance approximately half the distance from the entry site to the orbital rim, and inject 3 to 5 mL of anesthetic solution (Figure 36-15). Depending on the patient's anatomy, it may be possible for the physician's index or middle finger to palpate the infraorbital foramen through the skin and direct the needle to this site.

MENTAL NERVE BLOCK

Purpose A mental nerve block provides anesthesia to the labial mucosa, gingiva, and lower lip adjacent to the incisors and canines.

Patient Positioning and Anatomy The patient can be either lying supine or sitting upright in a position of comfort. The inferior alveolar nerve gives rise to the mental nerve, which exits the mental foramen, located inferior to the mandibular canines and first premolars

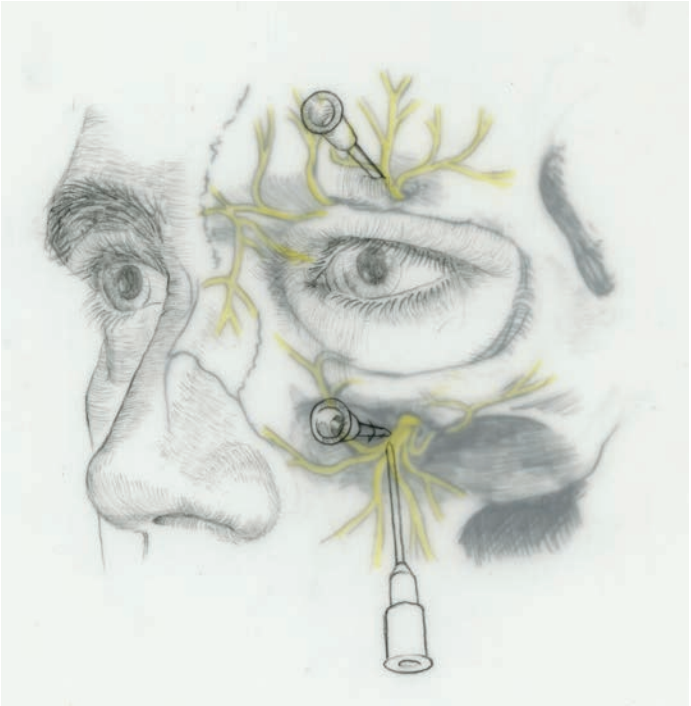


FIGURE 36-15. Supraorbital and infraorbital nerve blocks. Palpation of the subtle supraorbital foramen may be difficult, although identification is achieved when forehead paresthesias are elicited. A subcutaneous field block extending horizontally above the eyebrow is a useful addition. Palpation of the infraorbital foramen, especially via the intraoral approach, is typically easier. [Illustration used with permission of Timothy Sweeney, MD.]



FIGURE 36-16. Mental nerve block. Infiltration of anesthetic around the mental foramen from an intraoral (*right needle*) or transcutaneous (*left needle*) approach. [Illustration used with permission of Timothy Sweeney, MD.]

(teeth #21 and #22 on the patient's left, and #27 and #28 on the patient's right).

Technique After adequately providing topical anesthetic to the mucosa inferior to the canine and first premolars, dry the mucosa and evert the lower lip. Insert the needle at the gingival reflection at this site, direct the needle inferiorly, advance approximately 1 cm, and inject 3 to 5 mL of anesthetic solution (**Figure 36-16**). (See Video: Mental Nerve Block.)

Depending on the patient's anatomy, it may be possible for the physician's finger to palpate the mental foramen through the skin and direct the needle to this site.

AURICULAR BLOCK

Purpose An auricular block provides anesthesia to the external ear by blocking the auriculotemporal (anterior and superior portion), lessor occipital (posterior), and great auricular (inferior portion) nerves.[105]

Patient Positioning and Anatomy Patient can either be lying supine or sitting upright in a position of comfort. The sensation to the ear is provided anteriorly by the auriculotemporal nerve and posteriorly by the greater auricular nerve and the mastoid branch of the lesser occipital nerve.

Technique Raise a wheal in the subcutaneous space inferior to the auricle. From this site, direct the needle in the subcutaneous space anterior and superior, and inject 2 to 3 mL of anesthetic while withdrawing the needle (**Figure 36-17**). From the original injection point, redirect the needle posteriorly and superiorly and deposit 2 to 3 mL in the subcutaneous space while withdrawing the needle. Repeat this process from the superior aspect of the ear, injecting 2 to 3 mL of local anesthetic in the subcutaneous space both anterior and posterior to the ear to complete the field block around the ear.

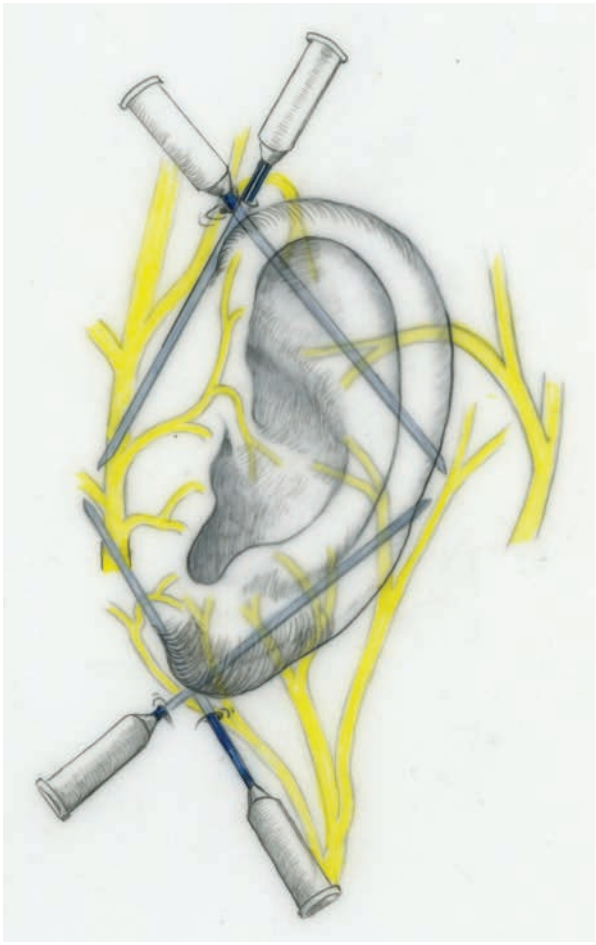


FIGURE 36-17. Auricular field block. The auricular block is a simple field block around the base of the external ear. [Illustration used with permission of Timothy Sweeney, MD.]

INTERCOSTAL NERVE BLOCK

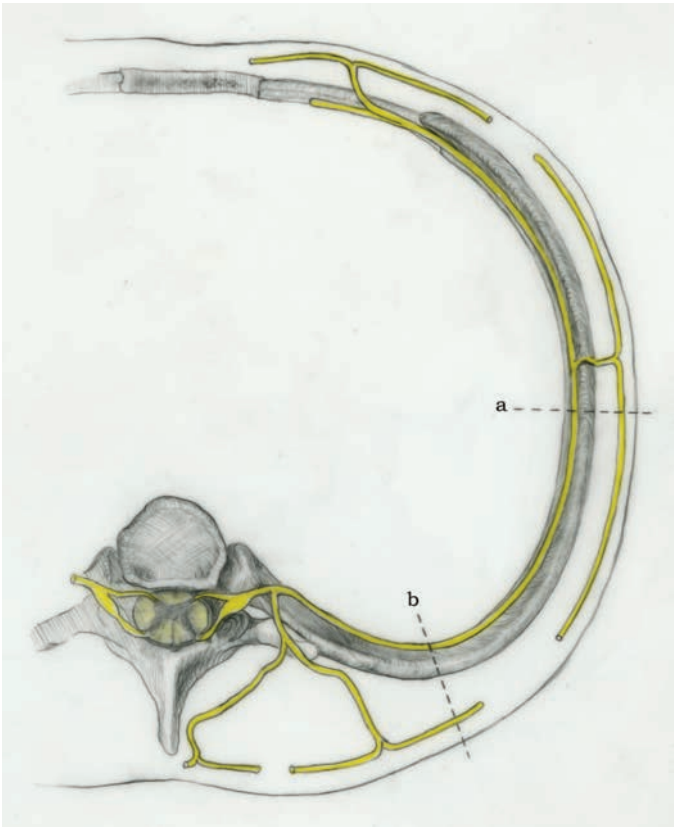
Purpose An intercostal nerve block provides analgesia to the intercostal nerve above and below the affected rib in a band-like fashion around

the chest wall. These blocks provide an alternative to parenteral analgesia for controlling pain from rib fractures,[106,107] tube thoracostomy,[108] and thoracic herpes zoster.[109] Although controlled trials comparing parenteral analgesia with intercostal nerve blocks are lacking, clinical observations suggest better pain control and increased lung function associated with intercostal blocks.[110] A good intercostal block will provide anesthesia duration between 8 and 18 hours when a long-acting local anesthetic is used.

Patient Positioning and Anatomy Patient is sitting upright, with the ipsilateral arm raised at the shoulder and the wrist rested on top of the head. Within the subcostal groove of the rib, the intercostal nerve originates from the thoracic nerve and runs inferior to the artery and vein ("vein, artery, nerve"). Ribs 1 through 6 are difficult to block due to the position of the scapula and rhomboid muscles. With both anterior and posterior rib fractures, the optimal block site is at the "rib angle," approximately 6 cm lateral to the midline, or just lateral to the paraspinous muscles. **Blocking posterior to the midaxillary line ensures analgesia to the lateral cutaneous and anterior branch of the intercostal nerve (Figure 36-18, top).**

Technique Palpate the inferior border of the rib to be blocked with the noninjecting hand, and retract the skin cephalad at a location about 6 cm from the midline. Raise a wheal in the subcutaneous space, and insert the needle bevel up with the syringe lower than the entry site. The optimal angle is approximately 10 to 15 degrees off the perpendicular with the needle tip angled cephalad (Figure 36-18, top). Continue inserting the needle until it contacts bone. The needle should be resting at the inferior border of the rib to be blocked. Release the skin being retracted with the noninjecting hand, walk the needle caudally until it drops off the inferior edge of the rib, and advance the needle approximately 3 mm. This is the subcostal groove. Aspirate before injection, and deposit 2 to 5 mL of anesthetic.

The patient should be monitored for 30 minutes after the procedure to watch for clinical signs of pneumothorax. A postprocedure chest radiograph is not routinely indicated unless clinical signs of pneumothorax, including coughing, shortness of breath, or hypoxia, occur. A bedside pulmonary US can be performed following the procedure to assess for pneumothorax. Pneumothorax occurs in 8% to 9% of patients, or at a rate of about 1.4% for each individual intercostal block.[111]



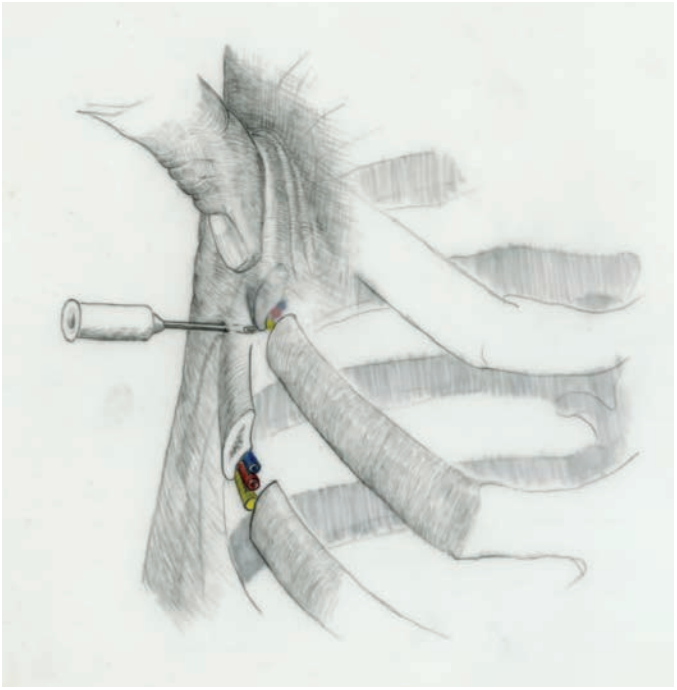


FIGURE 36-18. Intercostal block. *Top:* Cross-section of the chest shows the relevant branching of a typical intercostal nerve. Intercostal nerve blocks are commonly performed at the midaxillary line (*a*) or the posterior axillary "rib angle" line (*b*). *Bottom:* Retraction of the skin cephalad from the lower edge of the rib exposes the site of entry. The needle is inserted at a 10-degree angle off perpendicular, tip cephalad until contact is made with the lower rib edge. When the skin is released, the needle is allowed to slide caudad to the lowermost rib border. There, the needle is advanced 3 mm, aspiration is attempted, and the anesthetic solution is injected. [Illustration used with permission of Timothy Sweeney, MD.]

EXTREMITY BLOCKS

FEMORAL NERVE BLOCK

Purpose Regional anesthesia in the femoral region can result in an isolated femoral nerve block or a larger block involving the femoral, obturator, and lateral femoral cutaneous nerves. These blocks provide good to excellent pain control for patients with proximal femur and hip fractures and are especially useful in the elderly.[112-117] The "three-in-one" block uses the same injection location as a femoral nerve block but applies distal pressure to promote cephalad distribution of the anesthetic agent to block the obturator and lateral femoral cutaneous nerves.[118] It is important to assess distal neurovascular status before application of the block to prevent masking a primary traumatic neurovascular injury.

Patient Positioning and Anatomy The patient is lying in a supine position. In obese patients, placement of a pillow underneath the hip and retraction of the lower abdominal pannus superiorly and laterally will help expose the area. At the inguinal ligament and the inguinal (femoral) crease, the femoral nerve is positioned lateral to and slightly deeper than the femoral artery (**Figure 36-19**). The femoral nerve block will provide anesthesia to the anterior thigh and medial leg. The "three-in-one" block anesthetizes regions innervated by the obturator and the lateral femoral cutaneous nerves in addition to the anterior thigh and medial leg. (See Video: Femoral Nerve Block.)

Technique **A peripheral nerve stimulator or US guidance is recommended.**[82-86,88-90,119,120] Ropivacaine is an excellent long-acting anesthetic for femoral nerve blocks.[6,8,9]

Locate the femoral artery on the affected side at the level of the inguinal crease. Palpate the femoral artery with the noninjecting hand, and raise a wheal of anesthetic in the subcutaneous space at the level of the

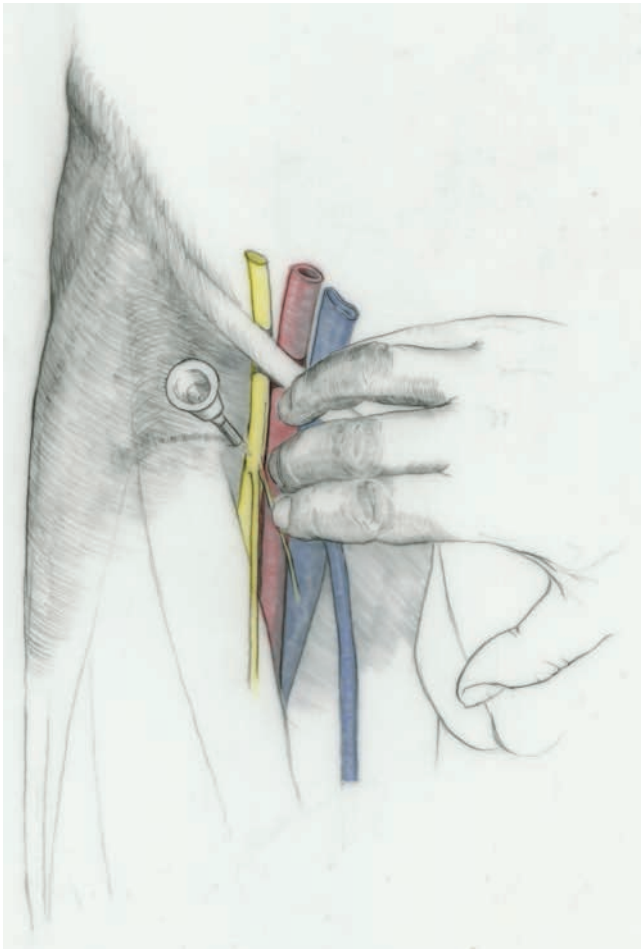


FIGURE 36-19. Femoral nerve block. The area 1 cm lateral to the femoral artery and at the level of the inguinal crease provides the point of insertion. The needle enters directly slightly cephalad and advances until paresthesia is felt. [Illustration used with permission of Timothy Sweeney, MD.]

inguinal crease and 1 cm lateral to the femoral artery. Insert the needle at this site and directed slightly cephalad (Figure 36-19). The femoral nerve is typically 2 to 3 cm below the skin.

If a peripheral nerve stimulator is being used, needle position is confirmed by contraction of the quadriceps muscle and subsequent patellar movement. If the sartorius muscle contracts, the needle should be repositioned slightly lateral and deeper. The sartorius muscle may mimic the quadriceps contractions, but the patella will only move with quadriceps contractions. US can also be used to accurately guide needle advancement and distribution of the anesthetic agent for a femoral nerve block.[120]

If a peripheral nerve stimulator is not being used, correct positioning of the needle is confirmed by the patient reporting paresthesia over the anterior thigh as the needle impacts the femoral nerve. Back the needle off slightly and inject approximately 20 mL of the anesthetic solution into the perineural space. If paresthesia over the anterior thigh cannot be elicited, the needle should be withdrawn to the skin, redirected 10 to 15 degrees laterally, and advanced as before. More lateral skin insertions may be required to locate the femoral nerve. Alternatively, a "blind" attempt can be made by injecting a larger quantity (30 to 40 mL) of anesthetic solution in and around the original site in an effort to spread the anesthetic through the region and reach the femoral nerve. Aspirate before each injection to avoid inadvertent arterial puncture, and do not inject if resistance is felt, as this indicates the possibility for intraneural injection.

To perform a "three-in-one" block, needle position should be confirmed by paresthesia or preferably by US.[119] Firm pressure distal to the injection site is then applied and held for 5 minutes as 20 to 30 mL of anesthetic solution is delivered. This distal pressure promotes cephalad distribution of the anesthetic solution.

An alternative to the femoral nerve block for pain control in patients with hip and femoral neck fractures is the fascia iliaca compartment block.[121-123] During the fascia iliaca compartment block (also known as the fascia iliaca block), 30 to 40 mL of anesthetic is injected deep to the fascia iliaca and allowed to spread medially and laterally to reach the femoral nerve and lateral femoral cutaneous nerve. The procedure can be performed under US guidance where the needle can be easily visualized as it approaches and passes through the fascia lata and fascia iliaca. If the procedure is being performed via the landmark approach alone, two "pops" will be felt as the needle is advanced through the fascia lata and the underlying fascia iliaca. Following the second "pop," aspirate to ensure that the needle tip is not within a vessel, and then inject the full amount of anesthetic to complete the fascia iliaca compartment block.

HEMATOMA BLOCK

Purpose Hematoma blocks are commonly performed for fracture reduction, using the hematoma formation around the fracture to deliver anesthetic to the fracture site, most commonly for Colles' fractures.[124-126] This block has waned in use due to the rising popularity of procedural sedation and the misconception that hematoma blocks dramatically increase the risk of infection. The hematoma block remains a staple in the armamentarium of fracture analgesia because it is simple, fast, and requires no special tools or personnel.[127,128]

Patient Positioning The patient is usually lying supine with the limb placed in a position of comfort to allow access to the fracture hematoma.

Technique Prepare a sterile block site over the bony fracture site and insert the needle directly into the hematoma (**Figure 36-20**). Positioning the needle in the hematoma can be difficult at times. Bedside US can be used to localize the dark, anechoic hematoma. Aspiration of blood aids in confirmation of needle position. Inject 5 to 20 mL of local anesthetic solution into the fracture site. The typical dose for distal radius fractures is 20 mL of 1% lidocaine or 10 mL of 2% lidocaine.[129] **When performing this block, ensure that the maximum dose of local anesthetic is not exceeded. This procedure should not be performed through a contaminated wound or an open fracture.**

INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK)

PURPOSE

The Bier block provides dense anesthesia in a limb for up to 60 minutes without the risks of general anesthesia. It is an excellent block for large complex lacerations, fracture reductions, and surgical procedures lasting <1 hour in duration on the extremities[130,131] and does not require fasting for safe performance.[132] **Although this block is relatively easy to perform, it does require a specialized pneumatic tourniquet and provides no postprocedure pain control.** Because the local anesthetic solution is directly infused into the venous system, careful attention to technique is important to prevent systemic toxicity.[133] It is important to assess neurovascular status in the involved limb before application of the block to prevent masking a primary traumatic neurovascular injury.

TECHNIQUE

Place two IV catheters: one small-gauge catheter distally in the affected extremity and the other in the unaffected extremity for fluid administration and sedation, if needed. Apply the specialized double-cuff pneumatic tourniquet to the affected upper arm or thigh. **The standard blood pressure cuff is not an acceptable alternative.** The pneumatic tourniquet should be placed proximal to the site of injury. Provide adequate padding beneath the cuff, as this is often the site of maximal discomfort during the procedure.

Exsanguinate the affected extremity by either elevating it for 3 to 4 minutes or wrapping the extremity with a compression bandage from distal to proximal. The cuffs are then inflated in the following sequence: Inflate the distal cuff first, followed by inflating the proximal cuff and,

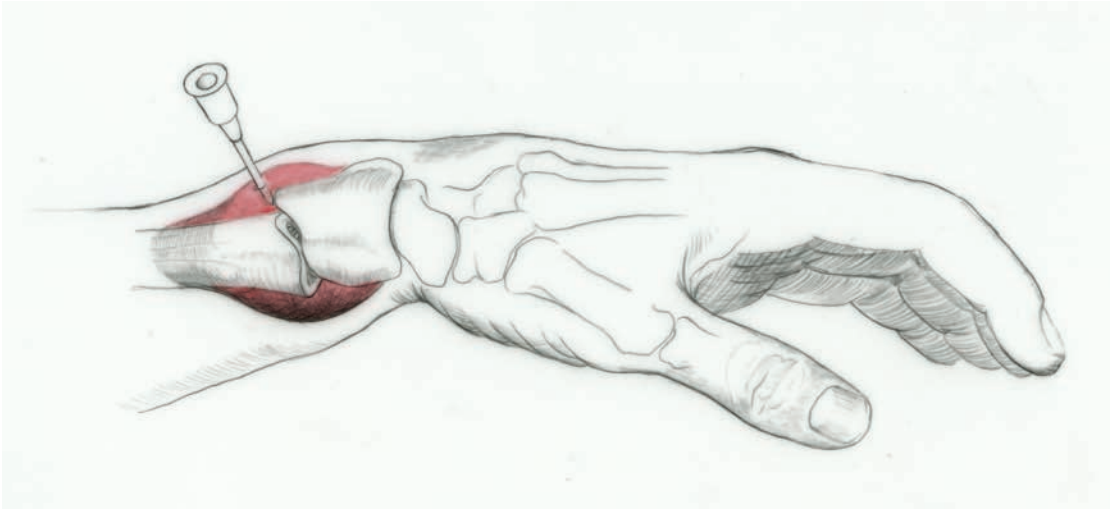


FIGURE 36-20. Hematoma block. After careful palpation for the fracture edge, the needle is inserted directly into the hematoma, with care taken to avoid regional vessels. [Illustration used with permission of Timothy Sweeney, MD.]

finally, deflating the distal cuff. In the upper extremity, inflate the pneumatic tourniquet to 250 to 300 mm Hg (30 to 45 kPa) or 100 mm Hg (15 kPa) above the patient's systolic blood pressure. In the leg, cuff inflation pressures are 350 to 400 mm Hg (45 to 55 kPa). The compression bandage should be removed if used. The limb should be pale, and pulses should not be palpable.

Infuse the anesthetic via the small catheter of the affected limb. Most authors recommend diluting standard 1% lidocaine with equal parts normal saline to create a 0.5% (5 milligrams/mL) solution. The amount infused varies according to physician preference in the range of 1.5 to 3.0 milligrams/kg (3 to 6 mL of the 0.5% lidocaine solution for every 10 kg of body weight).[130] Onset of anesthesia is usually within 5 minutes. If inadequate anesthesia occurs when using a minidose (1.5 milligrams/kg), infuse additional lidocaine up to 3 milligrams/kg. If adequate anesthesia is not obtained with the maximum dose of lidocaine, infuse additional normal saline to help circulate the anesthetic.

The patient may report a sensation of warmth or cold, and the skin will become mottled. The smaller nerve fibers are affected first, causing a reduction in pain and temperature sensation followed by loss of touch, deep pressure, and, finally, motor function. An ideal Bier block will provide complete anesthesia and muscle relaxation, but some patients may retain varying degrees of intact touch, deep pressure sensation, and motor function. Remove the IV in the affected extremity once adequate analgesia is obtained. Many patients will describe pain or pressure at the tourniquet site, usually within 30 minutes or so. This is handled by reinflating the previously deflated distal cuff. After ensuring that the distal cuff is inflated to the proper level and will hold pressure, the proximal cuff is slowly deflated. Adjuncts, such as ketorolac 30 milligrams, dexamethasone 8 milligrams, midazolam 50 micrograms/kg, ketamine 0.5 milligram/kg, or dexmedetomidine 1 microgram/kg, mixed with the local anesthetic can also be used to control the pain of tourniquet inflation and provide postprocedure analgesia.[134-136]

The cuff should not be released until a minimum of 30 minutes after the initial lidocaine infusion. Premature release of the cuff increases the chance of systemic toxicity from the anesthetic. Upon completion of the procedure, the pneumatic tourniquet should be cycled by lowering the cuff pressure for 5 to 10 seconds and then reinflating it for 1 to 2 minutes. This cycle should be repeated three to five times to prevent any possible bolus of anesthetic into the central circulation. Additional analgesia is usually required after completion of the procedure because anesthesia rapidly dissipates after release of the tourniquet. The patient should be monitored for approximately 30 minutes to ensure that no adverse reaction to the anesthetic has occurred.[130]

Acknowledgment: We acknowledge the contributions of Douglas C. Sillon to this chapter in the previous edition.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 37

Procedural Sedation and Analgesia in Adults

Justin G. Myers
Jennifer Kelly

INTRODUCTION

Procedural sedation and analgesia (PSA) for unscheduled, time-sensitive procedures is a standard practice in the ED.[1,2] **The accepted definition and goals of PSA are "the use of anxiolytic, sedative, hypnotic, analgesic, and/or dissociative medications(s) to attenuate anxiety, pain and/or motion. These agents are administered in order to facilitate amnesia or decreased awareness and/or patient comfort and safety during a diagnostic or therapeutic procedure."**[1-5] Levels of sedation are defined by the patient's level of responsiveness and cardiopulmonary function, not by the agents used (**Table 37-1**).[6] Although these are the currently accepted definitions of levels of sedation, sedation is a continuum, and responsiveness alone is not a perfect tool to judge the level of sedation.[4,7,8] By definition, patients receiving PSA do not require routine airway protection with endotracheal intubation or other airway adjuncts. This is in contrast to provision of general anesthesia, which typically requires airway protection. This chapter focuses on PSA in adults. For children, see Chapter 115, "Pain Management and Procedural Sedation in Infants and Children."

Minimal sedation is characterized by anxiolysis but with normal or slowed responses to verbal stimuli. Minimal sedation is typically used for minor procedures that require patient cooperation and for those in which pain is controlled by local or regional anesthesia. During minimal sedation, ventilatory function is usually maintained with a low risk of hypoxia or hypoventilation.

Moderate sedation is characterized by a depressed level of consciousness and a slower but purposeful motor response to simple verbal or tactile stimuli. Patients at this level generally have their eyes

TABLE 37-1 Levels of Sedation and Analgesia

	Responsiveness	Airway	Breathing	Circulation
Minimal sedation ("anxiolysis")	Normal but slowed response to verbal stimulation	Unaffected	Unaffected	Unaffected
Moderate sedation	Purposeful response to verbal or physical stimulation	Usually maintained	Usually adequate	Usually maintained
Dissociative sedation	Trance-like state with variable responsiveness	Usually maintained	Usually maintained	Usually maintained
Deep sedation	Purposeful response after repeated or painful physical stimulation	May be impaired	May be suppressed	Usually maintained
General anesthesia	Not arousable, even by painful stimulation	Usually requires assistance	Often impaired	May be impaired

closed or demonstrate ptosis and respond slowly to verbal commands. Moderate sedation can be used for procedures in which patient cooperation is not necessary and muscular relaxation is desired. During moderate sedation, the patient is usually able to maintain a patent airway with adequate respirations,[9] and cardiovascular function is usually maintained.[2]

Dissociative sedation does not easily fit into the PSA continuum outlined in Table 37-1. Dissociation is a state of detachment from immediate surroundings, in which the cortical centers are prevented from receiving sensory stimuli. It is a trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability.[10] Nonresponsiveness of dissociated patients to stimuli, even when repeated or painful, means that such patients do not fit the "moderate sedation" or "deep sedation" categories. Ketamine and nitrous oxide are the ED PSA agents characterized by dissociative sedation.

Deep sedation is characterized by a profoundly depressed level of consciousness, with a purposeful motor response elicited only after repeated or painful stimuli. Deep sedation may be required with painful procedures that require muscular relaxation and patient unresponsiveness. The risk of losing airway patency or developing hypoxia or hypoventilation is greater with deep sedation than with moderate or minimal sedation.[11] Examples of ED procedures sometimes requiring deep sedation include burn wound care and reduction of open fractures or fracture dislocations. Deep sedation generally is achieved in the ED with the same agents as moderate sedation, but with larger or more frequent doses.

General anesthesia is defined as a "drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired."[1,12,13]

PSA SEDATION POLICIES AND GUIDELINES

PSA is a multidisciplinary activity. Formation of a hospital sedation committee allows for diverse representation to create collaborative, evidence-based, institution-specific policies.[1,14] The logistics and roles for PSA at each institution should be determined in advance, allowing the ED physician the freedom to create a situationally appropriate sedation plan for each patient.[1,15]

In the emergency medicine model of PSA, clinical experience indicates that one emergency physician—providing monitoring and sedation and performing the procedure—is as effective as two physicians, one providing monitoring and the other performing the procedure.[2,16,17] Thus, one emergency physician simultaneously administering sedation and performing the procedure with a nurse or respiratory therapist monitoring the patient is an appropriate practice. However, the physician must be ready to resuscitate the patient immediately.[18] Nurses who have demonstrated the appropriate competencies can safely administer procedural medications,[19-22] even in resource-limited settings.[23] Emergency physicians and nursing leadership should conjointly develop policies regarding the scope of nursing practice in PSA sedation at their institutions.[15,20]

CLINICAL APPROACH TO PROCEDURAL SEDATION

PROCEDURAL SEDATION NEEDS ASSESSMENT

As you consider PSA for an ED procedure, consider the urgency, the depth of sedation required, and the duration needed. Is analgesia, anxiolysis, or immobility required? Do the patient's clinical condition or comorbidities place them at higher risk of adverse events? Can sedation be avoided altogether? Alternatives to PSA include systemic analgesics, regional nerve blocks, or local anesthesia. Some patients may be better served with general anesthesia.

Decisions regarding the procedural sedation plan should balance the urgency of the procedure and the likelihood of difficult complications. These decisions should be made with the patient and/or caregivers when possible, with appropriate consent.[24-26] If the situation is deemed too high-risk for ED PSA, consult anesthesiology or other specialists for assistance or sedation in the operating room.[1,27,28]

A common tool for assessing the patient's suitability for procedural sedation is the American Society of Anesthesiologists (ASA) physical status classification system (**Table 37-2**).[29] The risk of a significant complication from ED PSA in ASA class I and II is usually less than 5%.[14,30-32] The risk of an adverse PSA event increases as the ASA classification rises,[33,34] although safe ED procedural sedation for classes III and IV has also been reported.[33,35]

PRE-SEDATION PATIENT EVALUATION

Perform a focused history and physical examination[36] to identify a potentially difficult airway or cardiorespiratory problem. Ask about prior experiences with sedation or anesthesia, current medications, and allergies. A potentially difficult airway should be anticipated when the following findings or conditions are present: short neck, micrognathia, large tongue, trismus, morbid obesity, a history of difficult intubation, or anatomic anomalies of the airway and neck. The implications of these individual factors vary,[37-39] partially due to the weak interobserver reproducibility.[40] Studies on the association between these findings and

TABLE 37-2 American Society of Anesthesiologists (ASA) Classification System

ASA Class	Description	Examples
Class I	Healthy	
Class II	Mild systemic disease	Mild asthma, pregnancy, obesity, controlled diabetes
Class III	Severe systemic disease	Pneumonia, moderate to severe asthma, premature infant with postconceptional age <60 wk, end-stage renal disease
Class IV	Severe systemic disease that is a constant threat to life	Sepsis, severe cardiac dysfunction, disseminated intravascular coagulation
Class V	Moribund and not expected to survive without surgery	Massive trauma, intracranial hemorrhage with mass effect, ischemic bowel with multiple organ system dysfunction
Class VI	Declared brain dead whose organs are being harvested	

Source: asa-physical-status-classification-system.pdf (American Society of Anesthesiologists: ASA Physical Status Classification System). Retrieved May 19, 2019.

difficult intubation are usually done on patients going to the operating room for general anesthesia, and these findings may not be entirely relevant to the ED patient.[41]

Predisposing conditions affect the selection and dose of the sedative agent and also the timing of the procedure. Routine laboratory studies are not necessary in otherwise healthy patients. Directed ancillary testing may be useful in patients with comorbidities or dehydration. Ask about pregnancy in females of childbearing age, due to physiologic changes in pregnancy and the potential for fetal distress with PSA.[42]

Most sedative agents can cause vasodilatation and hypotension, particularly in patients with preexisting hypovolemia. Clinically active obstructive pulmonary disease or upper respiratory infections may predispose the patient to periprocedural hypoventilation or heightened airway reactivity. Drug or alcohol intoxication or reduced level of consciousness increases the risk of hypoxemia and hypoventilation. **If possible, delay PSA in intoxicated patients until mental status improves.** These various conditions may increase the risk of hypotension, prolonged sedation, and/or hypoxemia with PSA.

The ASA guidelines for fasting prior to general anesthesia are of limited relevance to the risk of aspiration with ED procedural sedation.[43] Pre-procedural fasting for any duration has not demonstrated a reduction in the risk of emesis or aspiration.[2,18,43-47] **It is not necessary to delay ED PSA for time-sensitive procedures in adults or children based on fasting time.**[1,2]

After pre-PSA patient evaluation, discuss general PSA risks and any specific risks attendant to the particular patient (e.g., older patient with airway disease) or selected drug regimen (e.g., delayed vomiting with ketamine) with the patient and/or family. Obtain informed consent for PSA just as for any other ED procedure and with the same caveats (e.g., intoxication and patient capacity to consent).

PREPARATION OF EQUIPMENT AND SUPPLIES

The sedation area should include ready access to necessary size-appropriate equipment for airway management and resuscitation: oxygen, a bag-mask ventilation device, suction, oral/nasal airway(s), intubation equipment, physiologic monitoring equipment, resuscitation medications, and a defibrillator.[1,14,36]

IV fluids should be initiated or readily available, particularly if the PSA regimen will include drugs (e.g., propofol) often associated with hypotension.

If using an opioid, have naloxone available. For benzodiazepines, have flumazenil on hand. Other drugs include antiemetics, agents used to treat allergic reactions, and push-dose vasopressors.[1,48,49] **(See later section "Rescue Medications and Reversal Agents.")**

The incidence of oxygen desaturation during ED procedural sedation without supplemental oxygen varies widely, depending on the patient and PSA agent, from 6% to 40%.[50-52] Supplemental oxygen reduces the incidence of hypoxemia[50-52] and has no adverse clinical effects. However, the administration of oxygen may mask hypoventilation, since oxygen saturation can be maintained despite rising carbon dioxide (a finding that would be readily identified by capnography).[50-52]

PATIENT MONITORING AND INTERVENTION

The safe practice of PSA requires both interactive and physiologic monitoring.[1] Interactive monitoring includes direct visualization of the patient's airway (mouth, face) and chest wall motion, chest auscultation, monitoring patient responsiveness, and providing appropriate maneuvers to maintain the patient's airway and ventilation.[1,8,18] Physiologic monitoring includes continual tracking of arterial oxygenation, ventilation, blood pressure, and cardiac rate/rhythm.[1,53]

Cardiac monitoring is particularly recommended for patients with preexisting cardiac disease or dysrhythmias or during procedures such as cardioversion. Monitor arterial oxygen saturation with pulse oximetry. Pulse oximetry is not a substitute for monitoring ventilation because hypoventilation or apnea develops before oxygen saturation decreases, especially in patients who receive supplemental oxygen.[50,51,54,55] Airway repositioning and bag-valve-mask ventilation are effective and usually the only interventions required.

Once PSA has begun, observe the patient until the peak effect of the initial sedative dose has been reached; with ketamine PSA, monitor until dissociation occurs. If necessary, titrate with additional medications to the desired sedation level. Once the patient has achieved the target sedation level, the actual procedure may begin. If the patient begins to regain alertness before completion of the procedure, additional sedative doses may be required. However, additional sedative doses given to extend procedural sedation are usually associated with an increased risk of respiratory depression. Depending on the agent selected, as larger cumulative doses of the drug are given, the half-life of each bolus increases. As the patient recovers from sedation, administer analgesics as needed for patient comfort.

The recommended extent of monitoring is determined by the level of sedation (**Table 37-3**). **Check patients after each dose of medication to assess the response, determine the need for further doses, and make appropriate interventions if needed.** The risk of adverse events increases with deeper levels of sedation. However, targeting moderate versus deep sedation is clinically difficult and unnecessary. Fortunately, no differences in pain, satisfaction, or recollection of procedures have been reported in patients who were sedated to a moderate versus a deep level.[9,34,56]

Capnography The interactive observation of ventilation may be improved through physiologic monitoring of ventilation with electronic capnography[54,55,57-59] (see Chapter 16, "Blood Gases, Pulse Oximetry, and Capnography"). The partial pressure of carbon dioxide detected at the nares during the respiratory cycle is represented by the carbon dioxide waveform (capnogram) that is displayed on a monitor (**Figure 37-1**). The end-tidal carbon dioxide correlates with arterial partial pressure of carbon dioxide, so that an end-tidal carbon dioxide >50 mm Hg or an increase in end-tidal carbon dioxide >10 mm Hg indicates hypoventilation. Capnography can assess the severity of ventilatory abnormalities and the response to interventions. Most importantly, capnography can detect changes in ventilation before clinical observation.[2,54,55,60]

Variations in the capnogram can identify specific conditions, such as apnea, upper airway obstruction, laryngospasm, bronchospasm, and

TABLE 37-3 Recommendations for Procedural Sedation and Analgesia Monitoring by Target Sedation Level

Target Level of Sedation	Level of Consciousness	Heart Rate	Respiratory Rate	Blood Pressure	Oxygen Saturation	Capnography End-Tidal CO_2
Minimal	Observe frequently	Record every 15 min	Record every 15 min	Record every 15 min and after sedative boluses	Monitor continuously	No recommendation
Dissociative	Observe constantly	Monitor continuously	Continuous direct observation	Record at initiation, frequent monitoring generally unnecessary	Monitor continuously	Recommend continuous monitoring
Moderate	Observe constantly	Monitor continuously	Continuous direct observation	Record every 5 min and after sedative boluses	Monitor continuously	Recommend continuous monitoring
Deep	Observe constantly	Monitor continuously	Continuous direct observation	Record every 5 min and after sedative boluses	Monitor continuously	Recommend continuous monitoring

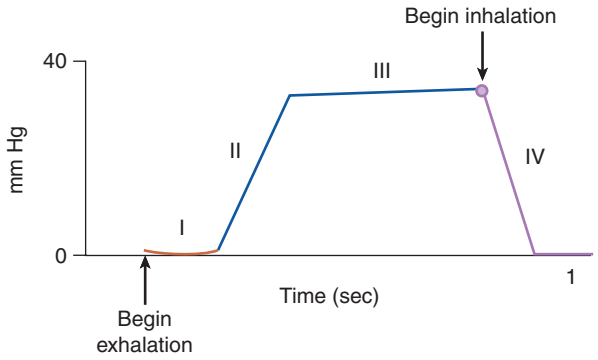


FIGURE 37-1. Normal capnogram. Phase I: At the start of exhalation, carbon dioxide concentration in the exhaled gas is essentially zero, representing gas from the anatomic dead space that does not participate in gas exchange. Phase II: As the anatomic dead space is exhaled, carbon dioxide concentration rises as alveolar gas exits the airway. Phase III: For most of exhalation, carbon dioxide concentration is constant and reflects the concentration of carbon dioxide in alveolar gas. Phase IV: During inhalation, carbon dioxide concentration decreases to zero as atmospheric air enters the airway. [Reproduced with permission from Krauss B, Hess DR: Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 50: 172, 2007 (Table 1, p. 176). Copyright Elsevier.]

respiratory failure.[54] A flat-line capnogram can be due to apnea, upper airway obstruction, complete laryngospasm, or faulty equipment. Normalization of the waveform after airway alignment maneuvers (chin lift, jaw thrust, or oral airway placement) confirms that apnea was due to upper airway obstruction. As of this writing, no cases of unexpected death or hypoxic neurologic injury from ED procedural sedation have been reported, with or without capnography.[47,61,62] There is a lack of evidence that capnography use, despite being possibly associated with increased airway intervention rates, reduces the incidence of serious adverse events such as hypoxic brain injury, aspiration, or death.[60,63] However, capnography is still recommended and may improve patient safety by reducing mild and severe oxygen desaturations as well as the need for assisted ventilation.[2,62]

DOCUMENTING PSA

Vital signs (pulse, blood pressure, and respiratory rate) and oxygen saturation should be obtained and recorded before the procedure, after each dose of medication, upon completion of the procedure, at the beginning of the recovery period, and before discharge.[32,36] For minimal sedation, intermittent measurements are sufficient. For other levels of sedation,[18] assess blood pressure every 5 minutes (unnecessary for ketamine dissociative sedation) and monitor heart rate, capnography, and pulse oximetry continuously. Predesigned documentation templates are good practice because such forms can guide providers through the procedure, improve documentation quality,[64] and facilitate quality auditing for PSA-related events.[65]

PRE-PROCEDURAL ANALGESICS

It may be necessary to give a short-acting opioid, such as fentanyl (often at doses of 1 to 2 micrograms/kg),[66] for pain control before the start of a procedure. If an opioid is to be used, it is best to initiate and titrate early to attain pain relief peak effect.[67] Delay the start of the procedure until after the peak effect of the opioid has been reached (2 to 3 minutes for IV fentanyl) to minimize the risk of respiratory depression and apnea.[18] It may be unnecessary to await pain control by opioids if analgesia will be provided by the PSA regimen. Ketamine alone or in combination with propofol (ketofol) provides analgesia while avoiding concomitant use of opioids.[18,67,68] A further review of ketamine-based regimens will be discussed later in the chapter. (See Chapter 35, "Acute Pain Management," for further discussion.)

SELECTION AND DOSING OF PROCEDURAL SEDATION AGENTS

Select the most appropriate agents for the PSA, taking into account the type and length of the procedure, the patient's age and comorbidities, the sedation target level, and potential for adverse events during sedation.[69] (See **Table 37-4** and section titled "Agents for Procedural Sedation.")

TABLE 37-4 Agents for Procedural Sedation in Adults.[68–105] Times May Vary With Different Dosing

Agent	Recommended IV Dose	Average Onset of Action	Average Effective Action	Advantages/Ideal Procedures	Disadvantages/Side Effects
Propofol	0.5–1.0 milligram/kg (elderly: 0.25–0.5 milligram/kg) Repeat dosing: 0.25–0.5 milligram/kg	10–50 s	<10 min	Rapid onset, short duration of action; good agent for orthopedic reductions	Does not provide analgesia, may cause respiratory depression (increased risk in elderly patients), may burn on injection; lidocaine added to syringe can decrease pain (see discussion below)[106]
Ketamine	1.0–1.5 milligrams/kg (give over 30–60 s) Repeat dosing: 0.5–1.0 milligram/kg **For analgesia only (subdissociative dose): 0.1–0.3 milligram/kg** (same repeat doses as initial dose)	30–40 s	5–10 min	Provides sedation, analgesia, cardiorespiratory stability; may be safer if comorbid conditions; may be useful for longer procedures; useful for patients at risk for bronchospasm	Emergence reaction, vomiting, cardiac stimulation may increase blood pressure, heart rate, and cardiac output; rare muscle hypertonicity/rigidity; avoid in psychotic or schizophrenic patients; respiratory depression with rapid IV bolus push
Etomidate	0.1–0.2 milligram/kg Repeat dosing: 0.05 milligram/kg	10–20 s	2–3 min for 0.15 milligram/kg dose min	Minimal cardiovascular and respiratory depression; ideal for shorter procedures, cardioversion	Myoclonus, adrenal suppression in critically ill
Ketamine + propofol ("single syringe" ketofol, 1:1)	Same total milligram dose for two agents together as when using single agent alone (ie, 1:1 = 0.5 milligram/kg of ketamine + 0.5 milligram/kg of propofol)	<1 min	<10 min	Ketamine adds analgesia without opioids; ketamine component blunts propofol-induced hypotension; combination good for prolonged procedures	Higher ketamine:propofol ratios lead to longer recovery; do not reduce clinically important adverse events; while not harmful, objective benefits have mixed evidence

(*Continued*)

TABLE 37-4 Agents for Procedural Sedation in Adults.[68–105] Times May Vary With Different Dosing (*Continued*)

Agent	Recommended IV Dose	Average Onset of Action	Average Effective Action	Advantages/Ideal Procedures	Disadvantages/Side Effects
Midazolam	1–2.5 milligrams; 0.5 milligram in elderly *or* 0.1 milligram/kg; 0.05 milligram/kg in elderly Repeat dosing: 0.5–2.5 milligrams; can repeat every 2–3 min (longer interval for elderly)	3–5 min	30–80 min	Preferable for longer procedures requiring deep sedation	Provides no analgesia (must be combined with analgesic if pain reduction is desired) Increased cardiovascular and respiratory depression when combined with opioids
Fentanyl	0.5–1.5 micrograms/kg; start with 0.25 microgram/kg in elderly Repeat dose: 0.5–1.5 micrograms/kg, can repeat every 1–3 min (longer between-dose intervals are recommended if larger initial doses are given)	Effect in 1–2 min	30–60 min	Given in combination with sedatives that lack analgesic properties; monotherapy may be used for minimal sedation	Monotherapy for moderate or deep sedation will not provide adequate sedation/amnestic effects Respiratory depression
Alfentanil	10 micrograms/kg; decrease dose in elderly Repeat dose: 10 micrograms/kg; decrease dose in elderly	Effect in <1 min	7–9 min	Fast onset, short duration of action Studied for moderate sedation alone or in combination with propofol	Increased risk of apnea
Remifentanil	0.16 microgram/kg/min infusion *or* 1 microgram/kg bolus; decrease dose in elderly Repeat dose (when using bolus dosing): 0.5 microgram/kg; decrease dose in elderly	Nearly immediate	3–10 min	Fast onset, short duration of action Does not rely on renal or hepatic function for metabolism or clearance Studied for moderate sedation alone or in combination with propofol	Poor muscle relaxation Increased risk of apnea
Dexmedetomidine	1 microgram/kg over 10 min, then maintenance infusion of 0.6 microgram/kg/h (range, 0.2–1.0 micrograms/kg/h)	4–5 min	45–90 min	Potentially useful when cooperation is required or in a patient experiencing respiratory depression with opioids	Hypotension (common); longer readiness to discharge; limited evidence for adults in ED setting
Nitrous oxide	50%/50% mixture with oxygen self-administered by patient through a mask Repeat dosing: when needed	Immediate	Seconds	Mild anesthetic, strong analgesic, causes euphoria, anxiolytic Nearly immediate onset and recovery Ideal procedures: dressing changes, lumbar punctures, wound closure, vein puncture, IV placement, urine catheterization, gastric tube placement	Risk for occupational exposure; should be given in well-ventilated room with scavenging system; potential for abuse by staff
Methohexital	0.75–1.5 milligrams/kg Repeat dosing: 0.5 milligram/kg every 2–5 min	<1 min	<10 min	Short procedures requiring moderate to deep sedation	Respiratory depression (common)[87]; myocardial depressant; avoid in hemodynamically unstable patients

Data adapted from Rahman, N.[70] References for table: 68–105.

COMPLETION OF PROCEDURAL SEDATION

At the completion of sedation and the procedure, patients should be monitored until they return to their baseline mental status and cardiopulmonary function. A structured assessment, such as the Aldrete Score©,[107] can be used to assess the patient's recovery and safety for discharge. Such assessment tools are typically part of procedural sedation documentation forms.

The duration of observation before terminating monitoring or discharge is variable. It depends on the quantity of sedatives given, the patient's response, the duration of the procedure, and the occurrence of any adverse events. Generally, patients who have returned to a baseline level of consciousness are unlikely to have further negative changes in level of consciousness. Most adverse events occur during procedural sedation itself, typically within a few minutes of sedative administration. The occurrence of major adverse events >5 minutes after completion of the procedure is rare (<1%).[108] The occurrence of life-threatening adverse events after discharge of an ED patient who has undergone procedural sedation has not been reported. Patients should be instructed to return if they develop respiratory complaints or nausea or repetitive vomiting. The follow-up interval required for patients who undergo ED procedural sedation is usually related to the procedure rather than the sedation.

AGENTS FOR PROCEDURAL SEDATION

PROPOFOL

Propofol is a safe and efficacious medication for providing moderate and deep procedural sedation in the ED.[2,18,34,71,109-114] Predictable, ultra-rapid

onset; short duration of action; and the combined effects of sedation, amnesia, and muscle relaxation render propofol an excellent choice for most procedures requiring moderate or deep sedation in the ED.[2,18,56,71,109,115-118]

Because the most serious adverse effects of propofol are rapidly developing respiratory depression and apnea,[44,119] have ventilatory support equipment at the bedside. Propofol can produce hypotension as a result of both negative inotropy and vasodilatation. Hypotension is more common in hypovolemic patients and those with ASA physical status scores of III or IV.[81] **Correct hypovolemia before propofol administration.**

Sedation from propofol occurs within 30 to 60 seconds after injection and lasts for about 5 to 6 minutes. Propofol is rapidly distributed into tissues, and once tissues are saturated, subsequent doses will have a greater effect than the initial bolus. The recommended dose for ED procedural sedation in healthy nonelderly adults is 0.5 to 1.0 milligram/kg IV, followed by 0.5 milligram/kg IV every 3 minutes if needed. Higher doses are associated with more respiratory depression. Exercise caution with subsequent doses, because repeat dosing can lead to variable depths of sedation and prolonged duration of action.[18] **In elderly patients, use 50% lower doses (0.25 to 0.5 milligram/kg) and titrate more slowly. (See section titled "Dosing Considerations in Special Populations").**

Propofol target-controlled infusion, an alternative to bolus dosing, is executed using a targeted plasma concentration from a loading dose (based on volume of distribution and targeted drug concentration), which is followed by a decreasing rate of infusion. Propofol target-controlled infusion may be a safer route of delivery and is undergoing further study for ED sedation.[120-122]

Propofol Safety With Soy and Egg Allergies Propofol was previously considered contraindicated for patients allergic to eggs or soy protein. The contraindication was based on case reports of possible allergy and also on theoretical risk based on propofol's formulation with soybean oil, glycerol, and egg lecithin emulsion.[123] However, during the manufacture and formulation of the soybean oil and egg lecithin in propofol, clinically significant allergy-mediating proteins are likely removed.[124] Furthermore, propofol has been administered safely to patients with soy, egg, and peanut allergies.[125-128] The American Academy of Allergy, Asthma, and Immunology supports the safety of propofol in patients with soy and egg allergies, and recent emergency medicine practice guidelines state that propofol's only true immunologic contraindication is an allergy to the drug itself.[18,129]

Pain on Injection Propofol may cause local pain at the IV site during administration. Suggested methods to reduce propofol infusion burning include pretreating the injection-site vein with lidocaine or mixing the lidocaine with the initial propofol injection. With pretreatment, a tourniquet is placed proximal to the injection-site vein and 0.5 milligram/kg of lidocaine is injected approximately 60 seconds prior to propofol infusion. When the alternative method of combining lidocaine with the initial propofol dose is used, add 0.5 to 1.0 milligram/kg of lidocaine to the first bolus of propofol.[130,131]

KETAMINE

Ketamine produces a state of dissociation, or detachment from immediate surroundings, characterized by profound analgesia, sedation, and amnesia. Unlike other agents used for procedural sedation, ketamine possesses both analgesic and anxiolytic properties.[10] Ketamine is an effective agent for ED and prehospital PSA and is safe and versatile.[10,132-136]

Ketamine is a derivative of the drug phencyclidine and is an *N*-methyl-D-aspartate glutamate receptor antagonist. It exerts its effects through a wide range of spinal and cortical pathways via dopamine, norepinephrine, serotonin, and opioid receptor antagonism.[137-139] Reported psychotropic effects of ketamine include hallucinations, synesthesia, pronounced derealization and depersonalization, a "detachment from the body," and a preoccupation with unimportant sounds.[140] At higher doses, users have described being "lost in the K-hole," a term used for the pronounced depersonalization or "out of body" experience, perceptions that can be quite frightening to patients.[139,141]

Ketamine does not have a typical dose-response continuum with progressive titration. At low doses, between 0.1 and 0.3 milligram/kg, analgesia and minimal sedation occur.[142-149] Low-dose ketamine for minimal sedation or analgesia is a reasonable choice either with or without opioids.[142-149] Side effects, such as dizziness or psychoperceptual disturbances, are seen with higher doses (see below) and may also occur during emergence.[150,151] Other side effects to be prepared for when using ketamine are increased muscle tone, clonus, or the rare case of sudden muscle rigidity, which can be alleviated with midazolam.[152]

Once a critical dosing threshold is exceeded (about 1.0 to 1.5 milligrams/kg IV or 3 to 4 milligrams/kg IM), ketamine's characteristic dissociative state abruptly appears. This dissociation has no observable levels of depth. The only value of additional ketamine is to prolong the dissociative state for extended procedures. Ketamine can be given either IV or IM. The IM route allows for approximately 40 minutes of sedation, compared with 10 minutes by the IV route.

Ketamine preserves a patient's ventilatory effort and has minimal depressant effect on blood pressure. However, ketamine can cause transient apnea (approximately 20 seconds), particularly when administered rapidly IV.[101,150,153,154]

Ketamine Emergence Reactions and Other Effects **Emergence reactions** after ketamine range from mild agitation to nightmares and hallucinations.[134,155] Midazolam or propofol can be given along with ketamine to minimize the development of emergence reactions.[155,156] In one study, coadministered IV midazolam in adults (0.03 milligram/kg IV) who were receiving IV ketamine (1.5 milligrams/kg) reduced recovery agitation by about 4% without an increase in respiratory events.[156] A single dose of propofol (30 to 40 milligrams for adults younger than age 50 years, with lower doses in older adults), given when distressing symptoms are recognized, has anecdotally been reported to reduce the incidence and severity of emergence reactions, hypertension, and muscle rigidity.[157] Further evidence of propofol's mitigation of ketamine-associated recovery agitation is supported by the finding that ketofol produces fewer emergence reactions than ketamine alone.[158] It is sufficient to give ketamine *without* midazolam or propofol and then treat patients who develop emergence reactions with midazolam as they occur. It is also reasonable to coadminister a dose of 0.03 milligram/kg of midazolam when ketamine is used in adults, both to reduce risk of emergence reactions and also to potentially reduce chances of postprocedural vomiting. Because of the possibility of emergence reactions, do not use ketamine in patients with schizophrenia and psychosis.[10]

Anorexia, nausea, and vomiting have been reported with ketamine use in approximately 5% to 15% of patients.[10] However, these effects are not normally severe, with most patients able to drink shortly after regaining consciousness.[159] Emesis typically occurs during the recovery phase when the patient is alert and can clear his or her airway.[10] Consider using an antiemetic when using ketamine for PSA.

Ketamine induces a **hypersympathetic state**, leading to hypertension and an increase in intraocular pressure. **Blood pressure elevations** begin shortly following administration, reaching peak levels in a few minutes. Blood pressure typically returns to preanesthetic levels 15 minutes following administration of the last dose.[159] Systolic and diastolic pressures typically peak at 10% to 50% above preanesthetic levels. However, elevations may be higher or last longer in individual cases. For this reason, **avoid ketamine in patients in whom a significant elevation in blood pressure would constitute a serious hazard (e.g., coronary artery disease)**.[69,159] Increases in **intraocular pressure** with ketamine are minimal,[159] but the evidence for use of ketamine in patients with acute globe injury or glaucoma is inconclusive.[10,69] There is some evidence that the hypersympathetic state resulting from ketamine administration may be more profound in patients with porphyria and thyroid disorders.[10]

Although rare, **hypersalivation and bronchorrhea** have been reported with ketamine administration through the stimulation of tracheobronchial secretions.[10,69] Be prepared to suction patients with respiratory tract concerns and those with an impaired ability to mobilize secretions.[10] Glycopyrrolate or atropine can be given to blunt this effect, but these drugs are not routinely or prophylactically recommended because they are associated with significantly more airway and respiratory events.[10,69]

It is historically stated that ketamine increases **intracranial pressure (ICP),** limiting its use in emergent situations.[160,161] The experimental data from animal studies and human observations are conflicting, depending

on the specific circumstances.[160,161] However, prospective controlled data in patients with brain injury and ICP monitoring demonstrate that ketamine does *not* increase ICP (it may actually decrease ICP), and the drug blunts adverse ICP response to stimulation.[162] At least two systematic reviews since 2014 have concluded that there is no evidence to support concerns that ketamine has an adverse ICP effect.[163,164] Experts in the use of ketamine in the ED have concluded that in the absence of hydrocephalus, there is no evidence to support concerns about ketamine and adverse ICP effect.[165] The weight of available evidence, including expert opinion, favors use of ketamine without concerns over ICP when the drug is otherwise the correct choice for PSA. Thus, there is no clear evidence that ketamine is harmful as an induction or sedation agent in patients with a potential head injury if it is the appropriate sedative choice based on other considerations.

There are growing reports of successful use of ketamine in resource-limited settings including the prehospital environment.[166-168] In austere settings, ketamine can facilitate procedures such as fracture splinting, chest tube placement, extrication, and field amputations.[169-172]

ETOMIDATE

Etomidate is a unique nonbarbiturate sedative-hypnotic agent with minimal side effects, a rapid onset, and short duration of action.[92,95,173] It is an excellent tool for clinicians and is frequently used for rapid-sequence intubation (RSI) in the ED.[69] The recommended dose for etomidate in procedural sedation is 0.1 to 0.2 milligram/kg,[69,90,92,95,100,173] with optional repeat doses of 0.05 milligram/kg administered every 3 to 5 minutes.[173] Etomidate has an onset of less than 1 minute and a duration of 4 to 15 minutes.[69,90,92,95,100,173]

When compared with propofol for procedural sedation, etomidate appears equally effective at achieving deep sedation and enabling successful procedure completion (89% with etomidate, 97% with propofol). Respiratory adverse event rates appear similar between the two drugs. Propofol results in more hypotension, whereas etomidate results in more myoclonus.[173]

When compared with midazolam use for shoulder reduction, etomidate PSA has similar rates of successful reductions. However, patients experienced faster recovery rates when receiving etomidate (10 minutes) as compared to midazolam (23 minutes).[174]

Etomidate is typically well tolerated and has a uniquely neutral cardiovascular profile when compared to other PSA sedatives. **Its minimal hemodynamic effects, combined with a short duration of action, make etomidate an excellent agent for procedures such as cardioversion.**[69] Etomidate's short duration of action makes it an unfavorable choice for procedures requiring a longer duration of sedation.[69]

Etomidate is characterized by two issues, adrenocortical suppression and myoclonus, that are not commonly seen with other PSA agents.

Etomidate's known effect of adrenocortical suppression has long been a source of controversy.[69,95,175] Even one dose of etomidate has been associated with lowering of cortisol levels after surgery, but without adverse outcomes.[176] Many surveys, emergency RSI series, and expert editorials worldwide have highlighted the high frequency with which etomidate is endorsed for use in stable or unstable patients, including patients with sepsis or trauma.[177-180] However, a 2018 survey of emergency medicine physicians and anesthesiologists identified the etomidate issue as "significant and not adequately resolved."[181] Fortunately, septic patients, the group for which there is the most support for risk due to etomidate's adrenocortical axis effects,[180] are infrequent candidates for ED PSA.

Myoclonus is sufficiently frequent (seen to some degree in up to half or more of patients receiving the drug[182]) that PSA planning with etomidate should account for the side effect. Myoclonus is likely due to subcortical disinhibition. Pretreatment with midazolam, suggested for over a decade as effectively blocking disinhibition, can reduce the incidence and severity of myoclonus.[182] Depending on situational characteristics related to the patient and procedure, PSA using etomidate may be accompanied by pretreatment with midazolam in a 1- to 2-milligram IV dose for adults.

Other etomidate side effects include emergence nausea and vomiting (up to 40% of patients), which can be severe and interfere with the procedure being performed.[2,69,90,95,173,174] Consider coadministration of an antiemetic when etomidate is being used for PSA.

KETAMINE AND PROPOFOL (KETOFOL)

The combination of ketamine and propofol for ED procedural sedation has a well-documented safety and efficacy profile.[66,73,158,183-190] Propofol is an excellent sedative, but respiratory depression and hypotension are important adverse events. In addition to providing analgesia (which propofol does not), ketamine coadministration may mitigate propofol's respiratory and hemodynamic depression. In turn, the adverse events associated with ketamine (vomiting and emergence reactions) can be mitigated by propofol's antiemetic and hypnotic properties.

The "ketofol" combination is safe and effective for ED PSA.[66,73,158,183,185,186,188-190] Published ketofol ED procedural sedation studies have used a variety of combinations, from equal mixtures of propofol and ketamine to normal doses of propofol with subdissociative doses of ketamine (used for analgesia only).

Adding ketamine to propofol promotes hemodynamic stability, which is reassuring in patients with known or potentially reduced cardiac function.[73] There is also evidence of synergism between the two drugs; data indicate that as compared to propofol alone, ketofol provides improved, less erratic sedation.[187,191,192] The analgesic properties of ketamine preclude the need for (and risks of) opioids that are administered with propofol.[66,73,193]

Most studies to date have failed to demonstrate a consistent difference in complications between ketofol (mixtures of ketamine and propofol from 1:1 to 1:4) compared with propofol alone.[189,191] However, a meta-analysis of five randomized controlled trials published between 1990 and 2017 found that, as compared to propofol alone, ketofol was associated with fewer respiratory adverse events.[193] Editorialists assessing the ketofol evidence base have also concluded that the combination agent is arguably preferable (as compared to propofol or ketamine alone) in patients with risk of hypotension; propofol alone risks hemodynamic depression, and ketamine alone risks recovery agitation.[194]

Another advantage of ketofol is that it may be able to achieve adequate sedation with lower total doses, as compared with either propofol or ketamine used alone. Ketofol prolongs the duration of sedation beyond that expected with propofol alone; this may reduce the need for repeat propofol boluses and be useful for procedures anticipated to take more time.

MIDAZOLAM

Benzodiazepines have amnestic, anxiolytic, and sedative properties. Midazolam is the preferred agent in this drug class because of its rapid onset, short duration of action, and ability to be given via multiple routes (IV, IM, intranasal, and PO).[69,96]

Midazolam is not an analgesic, so the drug is often combined with analgesics such as fentanyl or ketamine.[69,103] The combinations of midazolam/ketamine and midazolam/fentanyl have both been found to be effective for ED orthopedic procedures, although there was more hypotension seen in the midazolam/fentanyl group.[103] When compared to combination propofol/fentanyl PSA, midazolam/fentanyl combination therapy is equally efficacious (although with longer recovery time).[71,104]

Recommended dosing for midazolam in procedural sedation is 1 to 2.5 milligrams given as a slow IV push. Weight-based dosing of 0.1 milligram/kg has also been evaluated, but these larger doses (e.g., 7 milligrams in a 70-kg adult) have more adverse effects.[103,104]

Titrate midazolam slowly, with the dose repeated every 2 to 5 minutes.[69,96,105] The onset of action is 1 to 3 minutes, with peak effect seen in 3 to 5 minutes. The duration of sedation correlates linearly with the amount of drug administered, with sedation times reported to be as long as 17 to 80 minutes.[69,96,105,195] The IV route is preferred because other administration routes are subject to erratic absorption and corresponding delayed onset.[86]

Common side effects include hypotension, hypoventilation, and hypoxia. These effects are exacerbated when midazolam is combined with other medications such as opioids.[69]

SYNTHETIC OPIOIDS

Synthetic opioids, such as **fentanyl**, **alfentanil, sufentanil,** and **remifentanil**, have a role in procedural sedation as both monotherapy and in combination with sedative agents. Opioids alone may be sufficient in procedures where deep levels of sedation are not required.[74] The analgesia provided by the opioid complements the sedation and amnesia (which is not expected with opioids) provided by the sedative.[79,196]

Synthetic opioids are rapid-acting opioids and are the preferred analgesics for PSA. Their pharmacokinetic profiles make them easily titratable and offer advantages over other common opioids such as morphine. As compared to fentanyl, for instance, morphine and hydromorphone have longer times to onset, longer durations of action, and higher incidences of emesis and are associated with more hemodynamic effects.[79,196]

Fentanyl is a synthetic opioid 50 to 100 times as potent as morphine.[91] Fentanyl has become the analgesic of choice for PSA in the ED. It is highly lipophilic, which results in a very rapid onset of action (typically 1 to 2 minutes) and a short duration of action (30 to 60 minutes).[91,97] Dosing for fentanyl is recommended to start at 0.5 to 1.5 micrograms/kg in most patients (with a 0.25 microgram/kg lower dose in elderly patients) and can be repeated every 1 to 3 minutes.[79,91,97] Although typically not associated with hypotension and respiratory depression when used as monotherapy, fentanyl can cause these effects in certain patient populations; the incidence of hemodynamic or ventilatory depression is higher when fentanyl is used in combination with sedatives.[18,67,69]

Alfentanil and remifentanil are ultra-short-acting opioids that have been used for the induction of moderate sedation. As compared to fentanyl, **alfentanil** is one-fourth as potent, has one-third the duration, and exerts a more rapid onset of sedation.[93,98] The recommended dose for alfentanil in PSA is 10 micrograms/kg, with an expected duration of sedation of 7 to 9 minutes.[74] Alfentanil has been studied as both monotherapy and in combination with propofol for moderate sedation. When used for ED PSA, alfentanil and propofol have similar major airway and respiratory adverse events, but alfentanil has higher rates of reported pain and patient recall of the procedure.[74-76]

Sufentanil is more lipid soluble than either fentanyl or alfentanil. Its onset is rapid, and its half-life falls between that of fentanyl and alfentanil. Although used primarily for analgesia, sufentanil (by infusion) is useful for intensive care sedation.[197] There are few data reporting on acute care sufentanil use, and the drug's potential role in ED PSA remains to be seen.

Remifentanil offers some pharmacokinetic advantages over both alfentanil and fentanyl. Its onset of action is nearly immediate, and its recovery time is equally rapid. It is metabolized by plasma esterase in the blood and therefore does not rely on hepatic metabolism, as do fentanyl and alfentanil.[91,94,97,98,198] This allows for fast clearance and recovery, even in the setting of organ dysfunction, comorbidities, or advanced age.[199] Due to the pharmacokinetics of remifentanil, it is typically administered as a continuous infusion. A study evaluating remifentanil given as a continuous infusion in the ED found efficacy in short, painful procedures using a dose of 0.16 microgram/kg/min.[77]

Multiple trials have evaluated bolus dosing of remifentanil for procedural sedation in the ED in adult patients.[78,79,200] In one study,[78] remifentanil 1 microgram/kg was combined with propofol 0.5 milligram/kg with rescue doses of 0.5 microgram/kg and 0.25 milligram/kg, respectively. This regimen was found to have equal efficacy and a faster recovery when compared to the combination of midazolam/morphine. Another study compared monotherapy of remifentanil to the combination of propofol and fentanyl for anterior shoulder reductions.[79] In this study, the bolus dose for remifentanil was 1 microgram/kg with a 0.5 microgram/kg rescue dose. The results showed equal efficacy for pain management when compared to propofol/fentanyl for shoulder reduction. However, as compared to the other agents, remifentanil demonstrated a lower success rate in muscle relaxation as well as a significantly higher rate of apnea.[79]

Rigid Chest Syndrome A rare side effect of synthetic opioids is skeletal muscle rigidity, which primarily affects the chest and abdominal muscles. Chest wall rigidity decreases chest wall compliance and may result in the inability to effectively ventilate.[201] Although the exact mechanism is unknown, skeletal muscle rigidity is related to both the dose and rate of administration.[94,98,201]

Chest wall rigidity has been reported with low doses of synthetic opioids. However, the rigid chest syndrome is predictably seen only with high doses (exceeding 3 to 5 micrograms/kg of fentanyl, 130 micrograms/kg of alfentanil, and >1 microgram/kg of remifentanil), particularly if given by rapid IV push.[91,93,94,97,201] To prevent this complication, administer synthetic opioids in multiple low doses, each by slow IV push, rather than rapidly administering them as a single large dose.

If chest wall rigidity occurs, stop administration. The use of concurrent propofol or thiopental may attenuate the rigidity, and naloxone has been occasionally reported to be of use.[201] In rare cases, administration of a neuromuscular blocker (e.g., succinylcholine) and intubation may be required.[94,97,98]

LESS COMMONLY USED AGENTS

The medications previously discussed in this chapter demonstrate suitable pharmacodynamics and evidence for procedural sedation and have optimized the care patients receive. As with many older drugs, a gap of evidence develops over time comparing older to newer agents.[85] Despite an evidence base that may be more limited than that addressing some of the medications discussed earlier, these drugs remain plausible agents for adult procedural sedation in the ED.[69,85,86]

Dexmedetomidine Dexmedetomidine achieved U.S. Food and Drug Administration approval for procedural sedation in 2003.[202] It can provide sedation without respiratory depression.[203,204] It has not been extensively studied in the ED. Some emergency medicine investigators have found high rates of hemodynamic compromise with dexmedetomidine use in the ED, and there are insufficient data to currently support a recommendation for its routine use for ED PSA.

Dexmedetomidine is an α_2-adenoreceptor agonist and possesses sedative, anxiolytic, sympatholytic, and analgesic-sparing effects, with minimal respiratory depression.[82,202] It exerts its anxiolytic and sedative properties by reducing sympathetic tone. The sedative effects are reversible: The patient can be easily roused to a lucid state with stimulation, and then can fall back into a state similar to natural sleep when stimulation is removed. The degree of sedation is dose dependent, with effects ranging from minimal to deep sedation.[82,83]

The U.S. Food and Drug Administration approved dose for dexmedetomidine in procedural sedation is a 1 μg/kg loading dose given over 10 minutes followed by a maintenance infusion of 0.6 microgram/kg/h. It can then be titrated to clinical effect with a dosing range of 0.2 to 1 microgram/kg/h.[82,83,202] Although clinical trials have not studied bolus dosing in the setting of ED PSA, case reports have demonstrated success using bolus dosing of dexmedetomidine 1 to 2 micrograms/kg for shoulder reductions.[84] Intranasal administration may also be effective, but the long time to peak sedation (20 to 30 minutes) and long duration of sedation (45 to 90 minutes) limit intranasal dexmedetomidine use in the ED.[205]

Dexmedetomidine has moderately slow pharmacokinetics compared with other agents used for procedural sedation.[83] It is hepatically cleared, so elimination may be affected with hepatic impairment.[202] The half-life is relatively short at 6 minutes.[89,202] However, time to sedation following a bolus dose is typically longer at 4 to 5 minutes.[84] When compared to propofol (in pediatric patients), dexmedetomidine was found to have longer time to recovery.[80] Even during recovery, patients may be drowsy when not stimulated.[83]

Dexmedetomidine does not directly impair respiratory drive, but it may alter respiratory responses to hypoxia and hypercapnia. This effect can be more profound when given concomitantly with other sedatives or opioids.[82]

Hemodynamic effects include hypertension, hypotension, and bradycardia as a result of vasoconstriction, sympatholysis, and baroreflex-mediated parasympathetic activation.[82,99,202]

Nitrous Oxide Nitrous oxide (N_2O) is one of the oldest drugs still used in medicine and remains the fastest "in/out" anesthetic drug in use today.[85] It possesses mild anesthetic, dissociative, and muscle relaxant properties. N_2O works by stabilizing axonal membranes to partially inhibit action potentials, leading to sedation. Its analgesic properties are similar to morphine through its action on opiate receptor systems.[85,99]

N_2O has been used in the ED for mildly painful procedures, including dressing changes, lumbar punctures, wound closure, vein puncture, IV placement, urine catheterization, and gastric tube placement.[85] It does not work well for orthopedic procedures. It does not provide adequate analgesia or sedation for procedures of moderate to severe pain intensity.[85]

There is also an issue surrounding occupational N_2O exposure for staff administering the medication. Administer in well-ventilated areas with scavenger systems available to minimize risk to staff.[85,86] Because of the euphoria induced by N_2O, there is a high potential for abuse in healthcare workers.[86]

N_2O is typically administered as a 50%/50% mixture with oxygen through a mask. Patients can self-administer the medication through the mask provided.[85] N_2O use in adult patients in the ED has been criticized due to difficulties with administration and a lack of recent evidence. However, N_2O may see increased utilization in the prehospital setting based on evidence of efficacy in prehospital acute traumatic pain relief and improved delivery systems.[206]

Barbiturates Barbiturates have intermittently had a role in PSA. Barbiturates work by depressing the sensory cortex, decreasing motor activity, and altering cerebellar function. These actions produce drowsiness, sedation, and hypnosis. Of the barbiturates, methohexital is the best drug for adult ED procedural sedation.[69,86] Methohexital's overall risk profile renders it an unusual agent for IV ED PSA, but it remains a viable choice in selected circumstances.

Methohexital is an ultra-short-acting barbiturate that provides sedation while leaving airway protective measures intact. It does not deposit in fat tissue to the extent of other barbiturates, resulting in faster clearance.[207]

Older ED PSA trials demonstrated some potential utility for methohexital but with concerns for respiratory depression. The usual IV dose range is 0.75 to 1.5 milligrams/kg; additional doses of 0.5 milligrams/kg can be given every 2 to 5 minutes as needed.[86-88] The time to onset is less than 1 minute, and sedation typically lasts less than 10 minutes.[86,87]

One report of IV methohexital reported the drug potentially useful for adult PSA in a trial in which a mean dose of 88 milligrams was used. Apnea requiring bag-valve-mask ventilation was noted in 10.5% of cases.[88] Another older series of methohexital use for ED orthopedic procedures reported that methohexital (mean dose of 1.4 milligrams/kg) facilitated PSA in 81% of patients; 20.2% had complications, mainly respiratory depression and vomiting.[208]

Methohexital has a direct myocardial depressive effect, which can decrease blood pressure with a compensatory rise in heart rate. For this reason, it should be avoided in hemodynamically unstable patients.[86] ED PSA expert reviews caution that adding methohexital to opioids increases risk of respiratory depression.[86] As compared to propofol when used for orthopedic sedation, methohexital exhibited similar rates of recall, sedation, pain relief, satisfaction, and time to return of baseline mental status.[87]

DOSING CONSIDERATIONS IN SPECIAL POPULATIONS

OBESITY

Obesity remains a widespread problem, and clinicians should be aware that the physiologic changes associated with obesity can affect the distribution, clearance, and binding of many medications.[209] This includes many sedatives and analgesics, which are highly fat soluble, and obese patients exhibit marked changes in clearance and volume of distribution. There is no consensus or ED evidence on the optimal dosing strategy based on body habitus.

Despite an absence of data directly addressing PSA drug dosing in obese ED patients, clinical decisions may be informed by pharmacokinetic drug properties and data extrapolated from the anesthesia evidence base.[210] Standardized dosing equations used to modify dosing weight are detailed in **Table 37-5**.[211]

Propofol is highly lipophilic and distributes rapidly to the tissues from the plasma.[212] Data from morbidly obese subjects undergoing anesthesia induction have shown a similar response to doses based on lean body weight as lean control subjects who received doses based on total body weight.[213] Additionally, studies evaluating procedural sedation in children with obesity revealed that children could be successfully sedated with less propofol on a per-weight basis compared with children of normal weight, suggesting that dosing propofol by ideal body weight is an appropriate strategy.[210]

TABLE 37-5 Standardized Dosing Equations in Obesity

Total body weight (TBW)	Measured body weight (kg)
Ideal body weight (IBW)	Men (kg) = 50 + (2.3 [height (in.) – 60]) Women (kg) = 45.5 + (2.3 [height (in.) – 60])
Lean body weight (LBW)	Men (kg) = (9270 × TBW)/[6680 + (216 × BMI)] Women (kg) = (9270 × TBW)/[8780 + (244 × BMI)]
Body mass index (BMI)	Weight (kg)/height $(m)^2$

Source: Modified with permission from Willis S, Bordelon GJ, Rana MV. Perioperative pharmacologic considerations in obesity. *Anesthesiol Clin* 2017 Jun;35(2):247-257. Copyright Elsevier.

Etomidate, ketamine, and synthetic opioids such as fentanyl possess very similar pharmacodynamic properties to propofol, because they are also highly lipophilic and protein bound.[211,214] Anesthesia studies evaluating etomidate in obese patients have found that using lean body weight and ideal body weight was equally as effective as using total body weight.[211,214] Pharmacokinetic data for fentanyl in morbidly obese patients found a correlation between clearance of fentanyl and lean body weight, concluding that dosing should be based on lean body weight.[209] Ketamine has not been thoroughly investigated in obesity. However, based on its lipophilicity and large volume of distribution, ketamine is recommended (in the anesthesia literature) to be dosed based on ideal body weight.[211,215]

Benzodiazepines, while similarly lipophilic as the other sedative agents used in procedural sedation, have a volume of distribution that correlates with excess fat tissue. **When single IV boluses are given, regardless of which benzodiazepine is used, the dose should be increased in proportion with total body weight.**[195,209]

Integration of pharmacokinetic data from non-ED settings should potentially inform, but not dictate, EM PSA. Many other factors besides body habitus influence drug dosing. In balancing a common-sense approach of sound pharmacology and practice based on EM evidence, two recommendations can be made. First, scale the dose based on ideal body weight or lean body weight for propofol, fentanyl, etomidate, and ketamine in obese patients. Second, benzodiazepines should be dosed based on total body weight.[209-211,213,214]

ELDERLY, UNDERWEIGHT, AND COMORBID CONDITIONS

Patient age, weight, and comorbidities can have marked effects on the pharmacokinetics of anesthetics. Changes in cardiac output, total blood volume, and alterations of plasma protein binding can affect peak plasma concentrations, metabolism, and elimination half-life.[213] In addition, elderly patients may demonstrate a low physiologic reserve, potentially leading to increased adverse event rates.[216] It is prudent for a clinician to consider patient-specific factors when choosing the appropriate drug and dose in procedural sedation.

Elderly and underweight individuals can have a more profound response to anesthetic agents. This is largely due to a small central compartment and a lower body fat percentage.[217] Medications such as propofol, ketamine, benzodiazepines, etomidate, and fentanyl are highly lipophilic with large volumes of distribution. In situations where there is less fat mass and therefore a smaller peripheral compartment, larger quantities of drugs remain in the serum and are available to cross the blood–brain barrier.[210] This can be further exacerbated by hypoalbuminemia as many anesthetics are highly protein bound.[95,97,159,195,212]

ED studies evaluating propofol in elderly patients recommend using half the dose recommended in healthy adults (0.5 milligrams/kg with additional doses of 0.25 milligrams/kg as needed).[18,216,217] Although

guiding ED data are sparse, the lower dosing may be prudent for medications (e.g., fentanyl, ketamine) with pharmacokinetics similar to those of propofol.[97,159]

Etomidate has demonstrated higher free serum levels in the setting of cirrhosis, renal failure, and advanced age. However, a study specifically evaluating its use in elderly patients found similar efficacy and adverse event rates as seen in young, healthy patients receiving the same dose (average dose 0.14 milligram/kg for both groups).[100] Elderly patients between the age of 75 and 101 years old have been safely sedated for procedures in the ED.[216]

The volume of distribution for midazolam fluctuates in patients with advanced age, obesity, congestive heart failure, hepatic impairment, and renal failure. It also has decreased clearance in patients with cirrhosis.[96,195] It may be preferred to choose another agent over midazolam in these patient populations. If midazolam is to be used, lower initial doses of 0.5 to 1.5 milligrams should be administered, repeat doses should not exceed 1 milligram, and more time should be allowed between repeat doses (at least 3 to 5 minutes) when titrating to the desired level of sedation. Total doses in these patient populations typically do not exceed 3.5 milligrams.[96,195]

PREGNANCY

Pregnant woman present unique challenges in PSA. Maternal physiologic changes impact functional residual capacity, oxygen consumption, and ventilatory compensation. Pregnant women may develop hypotension when placed in the supine position due to aortocaval compression from a gravid uterus.[42] See Chapter 99, "Comorbid Disorders in Pregnancy," Chapter 256, "Trauma in Pregnancy," and Chapter 25, "Resuscitation in Pregnancy," for detailed discussions of the physiologic changes in pregnancy that would affect PSA in pregnancy.

Acute fracture/dislocations, sprains, and severe open wounds are examples of situations that may require PSA for effective treatment. Unfortunately, there is no specific evidence base to specifically guide PSA in pregnancy. None of the medications discussed below have been studied in well-controlled trials to evaluate their use in pregnancy. Because of this, use medications for PSA only when clearly indicated.

If possible, consult with obstetrics or obstetrical anesthesia to help determine the best PSA agent. However, such consultation may not be available in real emergencies or in rural, low-resource, or community settings. Although no specific recommendations exist for PSA in pregnancy, the following information regarding monitoring and drug selection provides a guide for how to proceed.

The adage "the best maternal care is the best fetal care" applies. Follow the general principles of patient evaluation and monitoring for PSA. Discuss risks and benefits. Maternal vital sign monitoring, including capnography; fetal tocodynamometry or, if not available, intermittent fetal heart tone auscultation; maintenance of maternal oxygenation and ventilation; and fluid resuscitation are mainstays of treatment.

Exposure to PSA medication is typically brief, and the exact effects of these medications in pregnancy are unknown. Rapid-acting, short duration of action synthetic opioids such as **remifentanil or fentanyl** are not considered to be human teratogens. They cross the placenta but should be rapidly metabolized by the fetus.[94,97] **Propofol** is not considered a teratogen and is considered safe in pregnancy, but is associated with maternal hypotension.[212] However, propofol reportedly dilates fetal placental blood vessels and maintains umbilical blood flow.[42] This likely mitigates some of the hypotensive effects on the fetus. Administer pre-PSA fluids to minimize hypotension associated with propofol. Neonatal depression may occur from propofol used close to delivery.[212] There are no human data about the teratogenicity of **ketamine,** and therefore, its use cannot be recommended.[159] Additionally, ketamine can increase blood pressure and therefore is not a good choice in hypertensive pregnant women or those with eclampsia or preeclampsia. Neonatal depression can occur if ketamine is given close to delivery. Effects on uterine contractility are reported as variable.[42] **Nitrous oxide** and **methohexital** appear to be safe in pregnancy when exposure is short, like that seen in PSA.[206,207] There is no data regarding the use of etomidate in pregnancy, so its use is not recommended at this time.[95,195] Although medications such as N_2O and methohexital have shown no teratogenic effects in animals, the results are not always predictive of human response.[206,207,212]

RESCUE MEDICATIONS AND REVERSAL AGENTS

All sedatives and analgesics used for procedural sedation carry some risk of transient hypotension.[218] Although the prevalence is highest with propofol, blood pressure drops can be seen even with drugs such as ketamine and etomidate (which are typically viewed as hemodynamically neutral).[18] For any drug reducing sympathetic outflow, hemodynamic depression will be more likely and more profound in a volume-depleted patient. For patients with a history of dehydration, blood loss, or a prolonged fasting state, the clinician should optimize volume status before sedation.[18]

Most incidents of transient hypotension associated with ED PSA can be easily reversed with an infusion of crystalloid; sequalae are rare.[18] If a fluid bolus is inadequate or contraindicated, bolus-dose vasopressors, often referred to as "push-dose pressors," can be considered. Push-dose pressors are administered in a titratable fashion, with incremental dosing by manual, intermittent, slow IV push from a syringe. Dosing can be repeated according to patient response.[48] Preferred agents for short-lived hypotension are phenylephrine and epinephrine.[48,49]

Phenylephrine is a pure vasoconstrictor through agonism of α_1-adrenergic receptors. The onset of effect is less than 1 minute. Duration of effect can be up to 20 minutes but is typically less than 5 minutes.[49,219] The recommended dose of phenylephrine is 40 to 200 micrograms (0.5 to 2 mL based on a 40 to 50 micrograms/mL concentration) given every 1 to 5 minutes.[48,49,219]

Epinephrine causes both vasoconstriction and inotropy through its effects on both α- and β-adrenergic receptors. Epinephrine's β activity may render the drug preferable to phenylephrine in patients benefiting from an increase in heart rate and cardiac output. The onset of effect is less than 1 minute, with a duration of less than 10 minutes.[49,220] The recommended dose is 5 to 20 micrograms (0.5 to 2 mL based on a 10 micrograms/mL concentration) every 1 to 5 minutes.

Push-dose pressors have a role in increasing patient safety in ED PSA. However, because some of the dosing will be less familiar to EM clinicians, meticulous attention must be paid to confirming proper drug administration. Mixing and dosing should be done carefully because high doses (such as those used in resuscitation) can lead to malignant hypertension, dysrhythmias, and cardiac arrest.[48,49]

Flumazenil and **naloxone** are the two most commonly discussed pharmacologic reversal agents with PSA applicability.[97,195] In ED PSA, both of these agents should be readily available.[102] However, routine use is not encouraged.[69] Reasons for this are based on practical considerations if the reversal agents work. A PSA patient receiving naloxone may pose pain control challenges, and flumazenil administration can precipitate seizures in patients chronically exposed to benzodiazepines.[69,195] Reversal agents should be used only when there is concern for a major complication, such as aspiration, need for intubation, or cardiovascular decompensation.[69]

If the situation allows, when reversal agents are used in the setting of PSA, use these drugs at the lower end of the effective range. Dosing for naloxone is 0.1 to 0.4 milligram IV, with peak effect seen after 2 to 3 minutes. The dosing for flumazenil is 0.2 milligram IV, and its peak effect is seen in 6 to 10 minutes. Effects of both agents should last 45 to 60 minutes, but be vigilant for possible recurrent sedation as early as 20 minutes after giving reversal drugs.[69]

COMPLICATIONS OF ED PSA

A 2016 meta-analysis evaluated 55 studies with 9652 procedural sedations.[47] Rates of adverse events with ED PSA are quite low, and there have been no known deaths reported.[16,216,218,221-223] Prior single studies reported complication rates between 2.3% and 11%.[16,216,221-223] However, pooled complication rates from 25 randomized controlled trials found rates of adverse events between 0% and 8.7%; adverse event

TABLE 37-6 Estimated Rate of Adverse Events in ED Procedural Sedation

Agent	No. of Studies/No. of Sedations	Estimate per 1000 Sedations	Approximate % of All Sedations	Agent with Most Frequent Adverse Event
Agitation	33/6631	9.8	1%	Ketamine, ketamine/propofol
Apnea	22/3264	12.4	1%	Midazolam, midazolam/opioid
Aspiration	10/2370	1.2	0.1%	Propofol and fentanyl (n = 1)
Bradycardia	5/837	6.5	0.5%	Etomidate, midazolam/opioid
Hypotension	27/5801	15.2	2%	Propofol, midazolam/opioid
Hypoxia	42/7116	40.2	4%	Propofol, midazolam/opioid
Intubation	19/3636	1.6	0.2%	
Laryngospasm	5/883	4.2	0.4%	Ketamine (n = 1)
Vomiting	25/3319	16.4	2%	Ketamine

Source: Table adapted from Bellolio et al[47] and Rezaie.[225]

rates were even lower (0% to 4%) when all 55 studies were included[47] (**Table 37-6**).

Most ED PSA complications can be categorized as minor adverse events. These include sedation to a deeper level than intended, agitation, transient hypoxia, hypotension, or emesis. Factors associated with an increased rate of complications include age >65 years,[35,221,223] level of sedation,[222,223] premedication with fentanyl,[223] use of short-acting agents, and sedation for a procedure (as compared to imaging). Analgesia performed at night may be another risk factor for adverse events; this is likely due to PSA being administered by inexperienced providers.[222]

Serious adverse events include the need for assisted ventilation, endotracheal intubation, or treatment of hypotension or cardiac dysrhythmias. In pooled analysis, serious adverse events requiring emergent intervention were rare and included one case of aspiration (out of 2370 sedations), one case of laryngospasm (out of 883 sedations), and two intubations (out of 3636 sedations).[47] Although drug-specific content (i.e., particular risks associated with the planned PSA approach in a given case) should constitute the main basis for PSA discussions with patients, the pooled-review data can inform conversations about general ED PSA risks, benefits, and alternatives. The estimated incidences of adverse events per 1000 procedural sedations are shown in Table 37-6.

Failure to successfully complete a procedure during ED procedural sedation occurs in about 5% of patients and is more common with certain joint reductions (hips, mandibles) and with increased patient body weight >100 kg.[224]

These overarching summary data for ED PSA success and complications are based on the best available data, but data are heterogenous due to variation in individual study approaches and even definition of important terms such as respiratory depression. Further research and multicenter collaboration are underway to standardize adverse event definitions and reporting, and these endeavors will improve quality monitoring and patient safety in ED PSA.[3,5,225-227]

COMMON PROCEDURAL SEDATION ERRORS IN THE ED

CHOOSING THE WRONG DRUG FOR THE PROCEDURE

All sedatives and analgesics offer different benefits and have different side effect profiles.[105] For example, propofol offers excellent muscle relaxation and may be a preferred option for a joint reduction, but etomidate's hemodynamic profile may translate into preference for this drug in a patient in whom there is significant concern for hypotension. On the other hand, etomidate's myoclonus may render the drug suboptimal for procedures (e.g., lumbar puncture, fine suturing) for which patient immobility is important (Table 37-4).

CHOOSING THE WRONG DOSE FOR THE PATIENT

A patient's age, weight, and comorbidities will impact response to medications. Account for these factors in PSA drug selection and dosing.[105] In particular, elderly patients have a lower physiologic reserve and have more profound effects to sedation; consider empirically decreasing sedation doses and titrate based on patient response. (See section titled "Dosing Considerations in Special Populations.")[18,210,216,217,228]

NOT BEING PREPARED

Prepare for procedural sedation by ensuring the right people, equipment, and drugs are in the room. ED PSA safety is enhanced when there is ready availability of airway equipment, IV fluids, and situationally indicated rescue or reversal drugs.[2,228]

NOT USING CAPNOGRAPHY

End-tidal carbon dioxide monitoring is a low-cost, minimally invasive, easily used tool allowing early recognition of hypoventilation. Capnography provides earlier indication of respiratory depression than either pulse oximetry or physical assessment. The presence of a waveform may provide more utility than pulse oximetry alone in determining respiratory status.[67,102,218,228,229]

NOT OPTIMIZING FLUIDS

Any sedative or analgesic can cause hypotension in volume-depleted patients due to decreased sympathetic outflow and blocking of compensatory mechanisms.[18] Volume status should be corrected prior to ED PSA if this is feasible. In most cases (ketamine IM sedation being a noteworthy exception), IV access is necessary for ED PSA, and crystalloids should be readily available.

AGGRESSIVE USE OF THE BAG-VALVE MASK

During PSA, hypoventilation is likely due to airway and ventilation issues. Repositioning the patient, performing a chin lift or jaw thrust, or suctioning may be adequate. Bag-valve mask may be used to facilitate ventilation while awaiting medication clearance. However, bag-valve mask carries a risk of vomiting and aspiration (in nonparalyzed, nonintubated PSA cases) and thus should be employed only when necessary for oxygenation and ventilation.[67,228]

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 38

Chronic Pain

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CHRONIC PAIN

EPIDEMIOLOGY

Chronic pain is defined as a painful condition that lasts greater than 3 months, pain that persists beyond the reasonable time for an injury to heal, or pain that persists 1 month beyond the usual course of an acute disease. Whereas acute pain is a vital biologic signal to stop the individual from a potentially injurious activity or to pursue medical care, chronic pain serves no obvious biologic function. Complete pain relief is unrealistic in cases of chronic pain. Rather, the goal of therapy is pain reduction and return to functional status. Chronic pain syndromes discussed in this chapter are divided into neuropathic and nonneuropathic conditions, with a separate discussion of abdominal and pelvic pain syndromes. Aberrant drug-related behavior is also discussed.

Chronic pain is a common problem, affecting 20% to as much as 50% of the population in developed countries.[1-3] Women (34%) are affected more than men (27%).[1] The back is the most common site for chronic pain, followed by the knee and neck.[1] The prevalence of neuropathic pain is 6.9% to 10% of the population.[4] The prevalence of chronic abdominal pain in association with irritable bowel syndrome and functional dyspepsia is 23%.[5] Risk factors for chronic pain include increasing age, female gender, higher body mass index, and chronic illness.[2] An exacerbation of chronic pain is part of the presentation of 11% to 15% of ED visits.[6] Compared to patients with acute pain, chronic pain patients are more likely to report their pain as severe and are more likely to be frequent visitors to the ED.[7]

PATHOPHYSIOLOGY

Our understanding of the pathophysiology of chronic pain is incomplete. Many chronic pain syndromes follow nerve or tissue injury, producing nerve dysfunction secondary to the mechanical injury or in response to chemical mediators released from adjacent cell injury. Peripheral sensitization or central sensitization commonly follows, where peripheral nerves or the CNS become abnormally sensitive, exhibiting pathologic spontaneous activity through upregulation of sodium channels and receptors.[8] Neuroplastic changes in the central descending pain modulatory systems, inhibitory or facilitatory, may lead to further hyperexcitability. These changes lead to **hyperalgesia** (exaggerated response to a normally painful stimulus) and **allodynia** (pain from a normally nonpainful stimulus). In several disorders, a history of injury may be lacking, such as for fibromyalgia, where central sensitization plays a key role.[9] Psychological factors frequently precede or follow the onset of chronic pain and often predispose individuals to physiologic changes through the fear-avoidance model.[10] The fear of pain may lead to disuse disability, which leads to nerve hyperexcitability and dysfunction, which may ultimately result in a chronic pain syndrome.[11]

CLINICAL FEATURES

The nonneuropathic syndromes share certain characteristics, with the most common feature being muscle-related pain (**Table 38-1**). A feature common to most neuropathic syndromes is allodynia (**Table 38-2**).

Clinical assessment should be appropriate to the circumstances and either be comprehensive for the unidentified patient or focused for the patient presenting with a typical exacerbation of well-established chronic pain. A comprehensive evaluation starts with assessing the quality and character of the patient's current pain, including initiating, exacerbating, and relieving factors. Compare and quantify prior episodes as they relate to the current episode. Determine sources, modes, and success or failure of prior treatment, including medications and dosages for physician-prescribed, over-the-counter, and alternative medications. Determine the patient's functionality across the course of the illness and treatment. Treatments that have provided pain relief yet have led to disability cannot be considered a success. Assess any history of alcohol or drug addiction, need for prior detoxification, or psychiatric illness that may impact decisions about choice of medication. A review of systems should assess for potential life- or limb-threatening conditions.

Look for findings of acute pain, such as tachypnea, tachycardia, hypertension, and less commonly, diaphoresis or muscle spasms on stimulation, although, for ED patients, there is no correlation between patient-reported pain severity and vital signs.[12] Evaluate for muscle atrophy in the distribution of pain due to disuse and skin temperature changes due to the effects of the sympathetic nervous system after disuse or secondary to nerve injury. Trigger points, another objective sign, are focal points of muscle tenderness and tension that, when stimulated with pressure, provoke referred pain, typically in the distribution of the involved muscle. **Trigger points are differentiated from simple focal tender portions of the muscle, as trigger points provoke referred pain throughout the affected muscle.** Trigger points lack a biologic basis and interexaminer agreement, yet they remain an essential feature of the diagnosis of myofascial pain syndromes.[13] Lack of objective evidence of pain does not rule out the presence of pain.

CLINICAL FEATURES OF SELECTED CHRONIC PAIN SYNDROMES

Further discussion of chronic pain, including treatment of chronic back pain, neck pain, and sciatica, is found in Chapter 279, "Neck and Back Pain." Migraine headaches and tension headaches are discussed in Chapter 165, "Headache."

Medication Overuse Headache History of migraine, depression, using combination analgesics, headache disability, and fear of pain are

TABLE 38-1 Symptoms and Signs of Nonneuropathic Pain Syndromes

Disorder	Pain Symptoms	Signs
Myofascial headache	Constant dull pain, occasionally shooting pain	Trigger points on scalp, muscle tenderness and tension
Chronic tension headache	Constant dull pain	Diffuse tenderness of the scalp and associated tension
Medication overuse headache	May be migraine like, becomes constant, dull; nausea, vomiting	Muscle tenderness and tension, normal neurologic exam
Myofascial neck pain	Constant dull pain, occasionally shooting pain, pain does not typically follow nerve distribution	Trigger points in area of pain, usually no muscle atrophy, poor ROM in involved muscle
Chronic neck pain	Constant dull pain, occasionally shooting pain, pain does not follow nerve distribution	No trigger points, poor ROM in involved muscle due to pain
Chronic back pain	Constant dull pain, occasionally shooting pain, pain does not follow nerve distribution	No trigger points, poor ROM in involved muscle due to pain
Myofascial back pain syndrome	Constant dull pain, occasionally shooting pain, pain does not typically follow nerve distribution	Trigger points in area of pain, usually no muscle atrophy, poor ROM in involved muscle

Abbreviation: ROM = range of motion.

TABLE 38-2 Symptoms and Signs of Neuropathic Pain Syndromes

Disorder	Pain Symptoms	Signs
Painful diabetic neuropathy	Symmetric numbness and burning or stabbing pain in lower extremities; allodynia may occur	Sensory loss in lower extremities
Phantom limb pain	Variable: aching, cramping, burning, squeezing, or tearing sensation	May have peri-incisional sensory loss
Trigeminal neuralgia	Paroxysmal, short bursts of sharp, electric-like pain in nerve distribution	Tearing or red eye may be present
HIV-related neuropathy	Symmetric pain and paresthesias, most prominent in toes and feet	Sensory loss in areas of greatest pain symptoms
Postherpetic neuralgia	Allodynia; shooting, lancinating pain	Sensory changes in the involved dermatome
Fibromyalgia and chronic widespread pain	Widespread muscular pain in 4 of 5 regions (right upper body, left upper body, torso, right leg, or left leg) for >3 mo, with stiffness, fatigue, sleep disturbance, and cognitive dysfunction (forgetfulness, inability to concentrate or recall simple words or numbers)	Widespread point tenderness common, but not required for diagnosis, isolated fibromyalgia does not produce joint inflammation, muscle atrophy, or sensory changes
Poststroke pain	Same side as weakness; throbbing, shooting pain; allodynia	Loss of hot and cold differentiation
Sciatica (neurogenic back pain)	Constant or intermittent, burning or aching, shooting or electric shock–like pain; may follow dermatome; leg pain > back pain	Possible muscle atrophy in area of pain, possible diminished tendon reflexes
Complex regional pain syndrome type I	Burning persistent pain, allodynia, associated with immobilization or disuse	Early: edema, warmth, local sweating
		Late: above alternates with cold, pale, cyanotic skin; eventually atrophic changes
Complex regional pain syndrome type II	Burning persistent pain, allodynia, associated with peripheral nerve injury	Early: edema, warmth, local sweating
		Late: above alternates with cold, pale, cyanotic skin; eventually atrophic changes

Abbreviation: HIV = human immunodeficiency virus.

risk factors for medication overuse headache.[14] The patient may carry the diagnosis of classic or common migraine headaches that change over time and develop into a chronic pain syndrome due to medication overuse.[14] Medications implicated in this transition are barbiturates, opioids, triptans, or less commonly, NSAIDs.[15] Patients with medication overuse headache may have more symptoms similar to tension headache with tenderness and tension of scalp musculature. Nausea and vomiting or failure of an oral antimigraine medication often prompts an ED visit. In addition to increased headache frequency, headache duration is longer in patients with medication overuse headaches.

Fibromyalgia Fibromyalgia is a clinical syndrome of widespread chronic pain associated with fatigue, unrefreshing rest, and/or cognitive symptoms. Prevalence is thought to be 5.4% of the population.[16] Diagnostic criteria for fibromyalgia were initially proposed in 1977 and most recently updated in 2016.[17] Widespread chronic pain is defined as affecting at least four of five body regions (right upper body including jaw, left upper body including jaw, torso including neck, right leg, and left leg) for more than 3 months. The nonpain component of fibromyalgia for diagnosis requires a symptom severity score ≥5, calculated from the severity of fatigue (0 to 3 scale), unrefreshed waking (0 to 3 scale), and cognitive symptoms (0 to 3 scale), plus presence of headache, abdominal pain, and depression (1 point each, if present).[17] Patients without fatigue or cognitive symptoms may carry a diagnosis of chronic widespread pain.

Painful Diabetic Neuropathy The symptoms of painful diabetic neuropathy are symmetric numbness associated with burning, electrical, or stabbing pain in lower extremities. Patients may have hyperesthesia, dysesthesias, and/or deep aching pain. Pain may be provoked with a gentle touch to the skin in the areas of abnormal sensation.

Postherpetic Neuralgia Postherpetic neuralgia may follow the course of an acute episode of herpes zoster in 5% to 30% of cases; pain lasts more than 1 year for 30% of patients.[18] Pain is characterized by allodynia and a shooting, lancinating (tearing or sharply cutting) sensation. Often, patients have hyperesthesia in the involved dermatome. Occasionally there are pigmentation changes in the distribution of the involved dermatome, but this is not unique to postherpetic neuralgia.

Trigeminal Neuralgia Typical symptoms of trigeminal neuralgia include short, paroxysmal bursts of sharp, electric shock–like pain in the nerve distribution of the trigeminal nerve. Pain is often triggered by chewing, speaking, washing, brushing teeth, or something touching the face. Tearing of the eyes or red eye may be present.

Phantom Limb Pain Phantom limb pain is quite variable in presentation but occurs more frequently in patients who had pain in the extremity before amputation. Pain may be described as aching, cramping, burning, tearing, or squeezing. Phantom limb pain occurs in 30% to 81% of amputations and changes over years, typically becoming less knife-like and more burning in character.[19]

Complex Regional Pain Syndrome There are two types of complex regional pain syndrome: type I, from prolonged immobilization or disuse, as after stroke; and type II, from a peripheral nerve injury (e.g., due to fracture or gunshot). Symptoms include allodynia and a persistent burning or shooting pain on the affected side or limb. Associated signs early in the course of the disease include edema, warmth, and localized abnormal sweating. It may be difficult to distinguish this stage from an underlying wound infection or osteomyelitis. Later signs include periods of edema and warmth that alternate with cold, pale, cyanotic skin and, eventually, atrophic changes.

Human Immunodeficiency Virus–Related Pain Patients with acquired immunodeficiency syndrome can develop distal sensory polyneuropathy characterized by shooting pain, numbness, and burning sensations, primarily on the soles, dorsum of the feet, and toes. This human immunodeficiency virus–related sensory neuropathy is associated with antiretroviral therapy but not with low CD4 counts.[20] Sensory loss is common in the areas of greatest pain symptoms. As the neuropathy progresses, walking becomes difficult, and quality of life is diminished.

CHRONIC ABDOMINAL AND PELVIC PAIN SYNDROMES

By definition, these disorders lack features to suggest impending life-threatening complications or a need for surgical intervention. However, these syndromes may present with transient tachycardia or tachypnea in response to the patient's pain experience. Furthermore, patients experiencing significant vomiting (or less commonly diarrhea) may be dehydrated on initial presentation and therefore may have hypotension due to hypovolemia. Patients with isolated exacerbations in pain will lack alarm signs, such as unintentional weight loss, palpable abdominal mass, significant fever, or positive fecal blood (see later "Diagnosis" section for discussion of laboratory testing). The patient should be asked

TABLE 38-3 Signs and Symptoms of Chronic Pain Syndromes of the Esophagus and Stomach

Disorder	Pain Symptoms	Signs
Functional heartburn	Retrosternal burning discomfort or pain present longer than 6 months that is refractory to optimal antisecretory therapy (H_2 blockers and proton pump inhibitors) in patients without endoscopic evidence of GERD, histopathologic mucosal abnormalities, GI motor disorders, or structural explanations.	Normal upper endoscopy, no correlation between symptoms and endoscopic evidence of physiologic reflux. Absence of alarm signs.*
Reflux hypersensitivity	Retrosternal heartburn or chest pain present longer than 6 months in patients who lack evidence of reflux on endoscopy or abnormal acid burden on reflux monitoring, but show triggering of symptoms by physiologic reflux (some degree of reflux is considered normal, such as postprandial reflux).	Normal upper endoscopy, positive correlation between symptoms and endoscopic evidence of physiologic reflux. Absence of alarm signs.*
Functional dyspepsia with epigastric pain syndrome	Bothersome epigastric pain or epigastric burning for ≥6 months. Symptoms severe enough to significantly limit meals or limit daily activities at least 1 day per week. Significant vomiting suggests another disorder.	No evidence of structural disease on endoscopy. Pain may be induced or relieved by a meal. Absence of alarm signs.*
Cyclic vomiting syndrome (with pain)	Stereotypical episodes of vomiting with acute onset and duration lasting a week or less; ≥3 discrete episodes in the previous year; absence of nausea and vomiting characterize symptom-free periods lasting weeks to months. Personal or family history of migraine headache supports the diagnosis.	Upper endoscopy is normal or does not reveal cause of repeated vomiting. Absence of alarm signs.*
Gastroparesis with pain	Patients with gastroparesis may have frequent visits to the ED with vomiting and abdominal pain and distention. Pain may be a primary complaint, especially for patients with recurrent symptoms.	Absence of alarm signs.* Distention may occur in the absence of small bowel obstruction. Assess for dehydration.
Cannabinoid hyperemesis syndrome	Stereotypical episodic abdominal pain and vomiting after prolonged excessive cannabis use with 3 or more episodes in the past year. Relief of vomiting episodes by hot showers, often for hours at a time.	Urine drug screen positive for cannabinoids. If performed, upper endoscopy is normal. Absence of alarm signs.*

*Alarm signs: unintentional weight loss, abdominal mass, positive fecal blood, anemia, hypoalbuminemia, abnormal liver function tests, elevated erythrocyte sedimentation rate, and elevated C-reactive protein.

Abbreviation: GERD = gastroesophageal reflux disease.

about prior episodes, and to describe any unique aspects to the current presentation. An atypical presentation suggests the need to broaden the differential diagnosis to include acute disorders.

Chronic Pain Syndromes of the Esophagus and Stomach Esophageal and gastric pain syndromes typically present with epigastric and/or chest pain, with or without vomiting (**Table 38-3**).[21-23] Upper endoscopy is necessary to differentiate these disorders from acute disorders, and therefore, a clinical diagnosis is only preliminary. Eliciting a history of cannabis use is essential in identifying **cannabinoid hyperemesis syndrome** (Table 38-3).

Chronic Pain Syndromes of the Bowel Centrally mediated abdominal pain syndrome (formerly, functional abdominal pain syndrome) requires repeated episodes to meet criteria for diagnosis (**Table 38-4**).[23-27] By the

TABLE 38-4 Signs and Symptoms of Chronic Pain Syndromes of the Bowels

Disorder	Pain Symptoms	Signs
Centrally mediated abdominal pain syndrome (formerly, functional abdominal pain syndrome)	Near-continuous abdominal pain (6 months or longer); no or only occasional relationship of pain to physiologic events (e.g., eating, defecation, or menses); pain limits daily functioning; pain is not explained by another structural or functional disorder. Patients may previously have had a disorder causing abdominal pain with a clear anatomic basis or that required prior surgery.	Absence of alarm signs*; may have voluntary guarding, frequently has had prior surgery, may have had surgery for lysis of adhesions.
Narcotic bowel syndrome	Must include all 3 of the following criteria: 1. Chronic or recurrent abdominal pain that is treated with acute high-dose or chronic narcotics. 2. The nature and intensity of the pain is not explained by a current or previous GI diagnosis. 3. Two or more of the following: a. The pain worsens or incompletely resolves with continued or escalating dosages of narcotics. b. There is marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstituted (soar and crash). c. There is a progression of the frequency, duration, and intensity of pain episodes.	Absence of alarm signs*; may have voluntary guarding. Would be expected to test positive for opioids, unless test is not specific to the opioids taken chronically.
Irritable bowel syndrome (IBS) with pain (2 types: IBS–diarrhea predominant and IBS–constipation predominant)	Recurrent abdominal pain, on average, at least 1 day per week in the past 3 months, associated with 2 or more of the following criteria: (1) related to defecation, (2) associated with a change in frequency of stool (diarrhea or constipation), or (3) associated with a change in form (appearance) of stool.	May have bloating or distention. May have had multiple imaging studies. Patients with depression and anxiety seek care for abdominal pain more frequently.
Inflammatory bowel disease, Crohn's disease, and ulcerative colitis	Recurring episodes of crampy abdominal pain, fatigue, and diarrhea, with or without fever and blood per rectum, are typical symptoms of Crohn's disease and ulcerative colitis. Twenty percent of patients with inflammatory bowel disease have chronic abdominal pain despite resolving inflammation and clinical remission; chronic opioid use is associated with exacerbations of pain in the absence of active bowel wall inflammation. Coexisting diagnosis of irritable bowel syndrome associated with chronic opioid use.	Exacerbations of chronic pain should be distinguished from exacerbations in bowel wall inflammation using both clinical and objective factors; smoking, prior outpatient opioid use, and psychiatric diagnoses are associated with exacerbations of chronic pain.

*Alarm signs: unintentional weight loss, abdominal mass, positive fecal blood, anemia, hypoalbuminemia, abnormal liver function tests, elevated erythrocyte sedimentation rate, and elevated C-reactive protein.

TABLE 38-5 Signs and Symptoms of Chronic Pelvic Pain Disorders

Disorder	Pain Symptoms	Signs
Endometriosis	Defined as the presence of endometrial glands and stroma outside of the normal location, typically over pelvic peritoneum or ovaries. Pain is constant (noncyclic) in middle to lower pelvis, but may slowly intensify. Dysmenorrhea or dyspareunia may herald worsening of pain or be the presenting complaint. Uncommonly, there is dysuria (bladder involvement) or pain with defecation (rectosigmoid involvement).	Diagnosis is usually made with laparoscopy or MRI. Patients with postcoital bleeding, postmenopausal bleeding, weight loss, pelvic mass, or hematuria should have further testing or referral.
Post–pelvic inflammatory disease (PID) chronic pelvic pain	30%–36% of patients treated for PID develop chronic pain. An exacerbation of chronic pelvic pain in a patient with prior PID is unlikely to be associated with fever, mucopurulent discharge, cervical friability, elevated C-reactive protein, or erythrocyte sedimentation rate. Patients with postcoital bleeding, postmenopausal bleeding, or weight loss should have further testing or referral.	Patients often have cervical motion tenderness, possibly with uterine and adnexal tenderness. Patients with pelvic mass or hematuria should have further testing or referral.
Interstitial cystitis/bladder pain syndrome	Suprapubic pain, occasionally radiating to groin, vagina, rectum, or sacrum, exacerbated by bladder fullness and relieved partially by voiding. Symptoms are worsened by fluid intake.	Suprapubic tenderness, negative urinalysis; cystoscopy commonly performed but controversial.

time of diagnosis, **narcotic bowel syndrome** may coexist or dominate the clinical picture.[24] It is important to differentiate these chronic syndromes from acute disorders, but this task may be difficult for both the patient and the physician. Prior records are helpful to identify the patient's typical presentation. Patient with inflammatory bowel disease my present with exacerbations of the underlying disease, chronic noninflammatory pain, or coexistent **irritable bowel syndrome**.[26,27] Differentiation of these disorders may require more than history and physical examination.

Chronic Pelvic Pain Syndromes Chronic pelvic pain be due to more than one etiology (**Table 38-5**), and consideration should be given to coexistent syndromes, such as irritable bowel syndrome, or other chronic abdominal pain syndromes (Table 38-3).[28-31] If the history suggests an atypical presentation of pain or related symptoms, a pelvic exam should be done to rule out new palpable pathology. The most common diagnosis at the time of laparoscopy for the evaluation of chronic pelvic pain in woman is **endometriosis**; however, endometriosis may exist without pain.[28] **Post–pelvic inflammatory disease pain** and **interstitial cystitis** (**bladder pain syndrome**) are common causes of chronic abdominal pain.[29,30]

DIAGNOSIS

The most important task is to distinguish an exacerbation of chronic pain from a life- or limb-threatening condition. The history and physical examination should either confirm the chronic condition or point to the need for further evaluation when unexpected signs or symptoms are elicited. Because patients with chronic pain may be frequent visitors to the ED, the entire staff may prejudge complaints as simply chronic or even factitious. Follow routine procedures, including a standard triage assessment and a complete set of vital signs.

After eliminating potential conditions that require emergent treatment, clinical judgment determines if focused management of pain is an appropriate course of action in the ED. The principles of focused management are to identify that symptoms are an exacerbation or continuation of a chronic pain pattern, provide appropriate rescue therapy for pain relief, and reinforce the need for a single provider (physician or clinic) for ongoing pain management.

Rarely is a provisional diagnosis of a chronic pain condition made for the first time in the ED. Definitive assessment for chronic pain conditions is difficult and requires expert opinion and often advanced procedures such as MRI, CT, and thermography. Furthermore, abnormal results usually do not confirm with certainty the cause of pain. For example, abnormalities on MRI of the spine and extremities are common in both asymptomatic and symptomatic patients. Therefore, referral back to the primary source of care is warranted to confirm the diagnosis.

The diagnosis of a chronic abdominal or pelvic pain syndrome is clinically based (Tables 38-3 to 38-5) but frequently requires testing to exclude other disorders. A specialist is best suited to make the diagnosis of these syndromes (specialist type will depend on the syndrome). However, emergency physicians who suspect a diagnosis should refer the patient for confirmation. When laboratory investigation is warranted by an atypical presentation or physician suspicion of an acute disorder, the presence of a new anemia, elevated white blood cell count, elevated creatinine, hypoalbuminemia, abnormal liver function tests, elevated erythrocyte sedimentation rate, or elevated C-reactive protein may warrant imaging or other additional testing. Stable patients can be discharged to follow-up for further testing. When the diagnosis cannot be determined during the ED visit, patient acuity should determine the need for admission.

TREATMENT

OPIOIDS FOR CHRONIC PAIN

Opioids are not recommended for the ED treatment of chronic pain. The use of opioids to treat chronic, noncancer pain in the United States increased rapidly from 1986 to 2010.[32,33] A similar increase in opioid prescribing was seen upon ED discharge, from 20.8% to 31.0% between 2001 and 2010.[34,35] With the growth in opioid prescribing, the age-adjusted rate for opioid-analgesic poisoning deaths nearly quadrupled from 1.4 per 100,000 in 1999 to 5.4 per 100,000 in 2011.[36] Poisoning is now the most common cause of injury-related death in the United States, surpassing motor vehicle–related death.

In response to the dramatic increase in opioid-analgesic poisoning, state agencies created statewide prescription drug monitoring programs accessible by the Internet for registered medical providers to view controlled substance prescriptions that a patient has received.[37-39] Although helpful, drug monitoring programs have not been shown to reduce opioid prescribing.[40] In contrast, individual hospital opioid-prescribing policies reduce opioid prescribing.[41] The American College of Emergency Physicians, individual states, and the Centers for Disease Control and Prevention have issued guidelines on the prescription of opioids for patients discharged from the ED (**Table 38-6**).[42-45]

CANNABIS FOR CHRONIC PAIN

Many patients with chronic pain self-medicate with cannabis.[46] Medical use of cannabis has significant health risks but may offer benefits in some patients.[47,48]

TREATMENT OF CHRONIC NONNEUROPATHIC PAIN SYNDROMES

Evidence-based treatment for chronic nonneuropathic pain syndromes is divided into primary and secondary treatment modalities (**Table 38-7**).[49-55] For management in the ED, an acute exacerbation of a chronic migraine can be treated like an exacerbation of episodic migraine (see Chapter 165, "Headache").[49]

Treatment in the ED should never be regarded as definitive, and follow-up care is essential. Many emergency providers will elect to

TABLE 38-6 Summary of Key Guideline Recommendations for Prescribing Opioids to Adult Patients in the ED[42-45]

*For the treatment of back pain, given a lack of demonstrated evidence of superior efficacy of either opioid or nonopioid analgesics, and the individual and community risks associated with opioid use, misuse, and abuse, opioids should be reserved for more severe pain or pain refractory to other analgesics rather than routinely prescribed.

†If opioids are indicated, the prescription should be for the lowest practical dose for a limited duration (e.g., 3 days), and the prescriber should consider the patient's risk for opioid misuse, abuse, or diversion.

*Emergency providers should avoid the routine prescribing of outpatient opioids for a patient with an acute exacerbation of chronic noncancer pain seen in the ED.

*The clinician should, if practicable, honor existing patient–physician pain contracts/treatment agreements.

*The clinician should, if practicable, consider past prescription patterns from information sources such as prescription drug monitoring programs.

‡The administration of IV and IM opioids in the ED for the relief of acute exacerbations of chronic pain is discouraged.

‡Emergency medical providers should not provide replacement prescriptions for controlled substances that were lost, destroyed, or stolen.

‡Long-acting or controlled-release opioids (such as OxyContin®, fentanyl patches, and methadone) should not be prescribed from the ED.

‡Prescriptions for controlled substances from the ED should state that the patient is required to provide a government-issued picture identification (ID) to the pharmacy filling the prescription.

‡Emergency medical providers should not provide replacement doses of methadone for patients in a methadone treatment program.

‡If the emergency medical provider decides to prescribe opioids to a patient with chronic pain, the provider should only prescribe enough pills to last until the office of the patient's primary opioid prescriber opens.

*2012 American College of Emergency Physicians policy.

†Centers for Disease Control and Prevention guidelines.

‡Washington State Opioid Prescribing guidelines.

prescribe short-acting nonspecific pain medications (Table 38-7) for patients with chronic pain, deferring initiating of more specific therapy for the primary care physician or pain specialist. Specialty referral may provide optimization of therapy, trigger point injections, and novel treatments, such as onabotulinumtoxinA injections.

TREATMENT OF CHRONIC NEUROPATHIC PAIN SYNDROMES

Evidence-based treatment for chronic neuropathic pain syndromes is divided into primary and secondary treatment modalities (**Table 38-8**).[56-69]

There is no convincing unbiased evidence to support the use of opioids (specifically oxycodone) in the treatment of neuropathic pain, including fibromyalgia.[70] Duloxetine is favored over pregabalin and gabapentin in the treatment of painful diabetic neuropathy.[65] Human immunodeficiency syndrome–related neuropathy is resistant to many therapies commonly used for neuropathic pain; gabapentin is recommended.[59] Topical capsaicin is effective for chronic neuropathic pain,[60] but is best directed by a specialist because pain increases at first application and pretreatment with topical lidocaine may be required. Phantom limb pain responds poorly to medication[62]; mirror therapy provides some benefit.[63] Poststroke pain responds poorly to most therapies.[64]

Tramadol reduces pain in most neuropathic pain syndromes, but is considered secondary treatment because it is less effective than the primary treatments (Table 38-8).[60,71] Complex regional pain syndrome is resistant to most therapies.[69] An IV infusion of ketamine may reduce pain for up to 12 weeks[69] but does not improve function. Corticosteroids (prednisone, 60 milligrams PO once a day) have been recommended at the time of first diagnosis when signs of inflammation are present,[69] but steroids do not affect the course of illness. Although considered second line, cyclic antidepressants are effective therapy for most patients with neuropathic pain, except spinal cord injury pain, phantom limb pain, human immunodeficiency virus–related neuropathy, and chronic regional pain syndrome. Amitriptyline can be started at 25 milligrams PO nightly and escalated by the follow-up clinician. Complete relief of pain is an unrealistic goal for patients with chronic pain, both for the ED visit and for follow-up care; patients should be informed of this limitation early in their ED course.

TREATMENT OF CHRONIC ABDOMINAL AND PELVIC PAIN SYNDROMES

Patients with chronic abdominal and pelvic pain syndromes may require acute treatment (**Table 38-9**).[21,22,28,72-87] Potent opioid analgesics are associated with narcotic bowel syndrome[81] and should be avoided, unless a single dose is required to obtain an abdominal examination to minimize voluntary guarding.[88] Antinausea medication and IV fluids may be required. Nonopioid analgesics should be provided as the individual case requires, provided that the known side effect profile of the drug would not worsen the patient's condition (e.g., NSAIDs exacerbating gastritis).

TREATMENT OF CHRONIC PAIN IN THE ELDERLY AND MENTALLY IMPAIRED

The prevalence of chronic pain increases with age.[1] Opioid analgesic alternatives, such as NSAIDs, have side effects that may limit their use in the elderly who are prone to GI and renal complications; however, when compared to opioids, NSAIDs have fewer side effects overall and are less likely to lead to premature death in the elderly.[89] GI bleeding rates are similar for patients treated with opiates or nonselective NSAIDs and lower for those treated with cyclooxygenase-2 inhibitors.[89] NSAIDs should not be given to patients with renal dysfunction. Topical analgesics (lidocaine 5% or capsaicin 8%) are effective[90] and can be given alone or as adjuncts. Topical NSAIDs provide excellent joint and tissue levels with low plasma levels and are available as diclofenac gel, patch, or topical solution.[90]

Cognitively and mentally impaired adults with chronic pain are at risk for inadequate pain control due to barriers in communicating the nature and intensity of their pain. Be alert to these potential barriers and look for nonverbal signs of pain: agitation, irregular breathing, facial expressions

TABLE 38-7 Management of Nonneuropathic Chronic Pain Syndromes

Disorder	Primary Treatment	Secondary Treatment	Possible Referral Outcome
Myofascial pain syndromes	NSAIDs orally, topical diclofenac patch for single site of pain	Amitriptyline	Trigger point injections or dry needling, US treatments, optimization of medical therapy, recommendations for exercise
Chronic migraine headache	See Chapter 165, "Headache," for treatment of acute exacerbations	Prophylaxis with sodium valproate or topiramate	Optimization of medical therapy, evaluation for use of prophylactic onabotulinumtoxinA
Medication overuse headache	Stop prior medications	Celecoxib or prednisone taper during withdrawal period	Optimization of medical therapy, withdrawal of prior medications, evaluation for use of prophylactic onabotulinumtoxinA

Medication dosing for above indications: **amitriptyline** 25 milligrams PO at bedtime; **celecoxib** 400 milligrams PO per day for the first 5 days, then decreased at a rate of 100 milligrams every 5 days; **diclofenac** 1.3% patch every 12 hours over single site of focal pain; **prednisone** 60 milligrams PO per day for the first 5 days then tapered down to a dose of 20 milligrams every 5 days; **sodium valproate** 250 milligrams PO two times daily; **topiramate** 25 milligrams PO at bedtime during first week, then 25 milligrams two times daily during second week, with further dose adjustments at follow-up.

TABLE 38-8 Management of Neuropathic Chronic Pain

Disorder	Primary Treatment	Secondary Treatment	Possible Referral Outcome
Fibromyalgia	Pregabalin	Duloxetine	Exercise program; optimization of medical therapy
Trigeminal neuralgia	Carbamazepine	Oxcarbazepine	Optimization of medical therapy; consideration for surgery or radiation
HIV-related neuropathy pain	Gabapentin	Topical capsaicin	Optimization of medical therapy including antiretroviral medications
Spinal cord pain	Pregabalin	Tramadol	Optimization of medical therapy
Painful diabetic neuropathy	Duloxetine	Gabapentin or pregabalin	Optimization of medical therapy
Postherpetic neuralgia	Pregabalin or gabapentin	Lidocaine patch	Optimization of medical therapy; regional nerve blockade
Phantom limb pain	Gabapentin	Referral for mirror therapy	Optimization of medical therapy; ketamine infusion
Poststroke pain	Pregabalin	Gabapentin	Optimization of medical therapy
Complex regional pain syndrome types I and II (reflex sympathetic dystrophy and causalgia)	Acute phase: prednisone	Chronic: intermittent ketamine, bisphosphonates, by specialist	Physical therapy, individualized therapy based on neurologic testing
Dosing for above indications can be started as follows: **capsaicin** is best started at follow-up as pain increases before it decreases; **carbamazepine** 100 milligrams PO two times daily; **duloxetine** 30 to 60 milligrams PO daily; **gabapentin** 300 milligrams PO, once on day 1, two times day 2, then three times daily, eventually increasing to 1200 milligrams per day guided by follow-up clinician; **lidocaine patch** 5%, up to three patches at a time, apply for up to 12 hours per day; **oxcarbazepine** 300 milligrams PO two times daily for 3 days, 300 milligrams at morning and 600 milligrams at evening for 3 days, then 600 milligrams two times daily; **prednisone** 60 milligrams PO daily for 7 days to be adjusted by follow-up physician; **pregabalin** 50 milligrams PO three times per day; **tramadol** 50 milligrams PO every 6 hours as needed.			

Abbreviation: HIV = human immunodeficiency virus.

TABLE 38-9 Treatment of Selected Chronic Abdominal and Pelvic Pain Syndromes

Disorder	Primary Management	Secondary Management
Functional heartburn*	Citalopram, other agents.	Behavioral modification.
Reflux hypersensitivity*	Standard-dose or double-dose proton pump inhibitor.	Citalopram, other agents.
Functional dyspepsia with epigastric pain syndrome*	Amitriptyline; frequent, small, low-fat meals; avoid NSAIDs.	Proton pump inhibitors, H_2 blockers, *Helicobacter pylori* eradication.
Cyclic vomiting syndrome (with pain)	Rehydration with 0.9% normal saline including dextrose; give ondansetron, ketorolac but opioids or lorazepam may be required for acute vomiting.	Avoidance of triggers (stress, poor sleep, infections), management of common coexisting disorders (irritable bowel syndrome, migraine headaches, gastroparesis, and anxiety).
Cannabinoid hyperemesis syndrome	Stop cannabinoids; treat with antiemetics and hydration as for cyclic vomiting; avoid opioids.	Substance abuse treatment as necessary, amitriptyline for recurrent cases.
Centrally mediated abdominal pain syndrome (formerly, functional abdominal pain syndrome)	Specialty care for chronic abdominal pain; avoid opioids; amitriptyline first line for chronic management.	Consider substituting duloxetine, add quetiapine.
Gastroparesis-related pain and vomiting*	Haloperidol reduces pain and need for hospital admission when compared to other antiemetics.	Standard antiemetics and IV fluids.
Narcotic bowel syndrome	May require admission with 15%–30% reduction in daily narcotic dose per day; give antiemetics for vomiting and benzodiazepines for anxiety as needed. Augment first day with amitriptyline and continue at discharge.	For outpatient management, consider 4- to 6-week withdrawal duration. Maintenance of antidepressant therapy and ongoing outpatient care for prevention of repeat ED visits.
Irritable bowel syndrome (IBS) with pain (2 types: IBS–diarrhea predominant and IBS–constipation predominant)	For constipation: psyllium, polyethylene glycol. For pain: dicyclomine and/or amitriptyline.	Change in diet (per specialist, after testing); for resistant symptoms, lubiprostone, linaclotide, and other medications.
Inflammatory bowel disease, Crohn's disease, and ulcerative colitis	Acute medical management discussed in Chapter 73, "Disorders Presenting Primarily With Diarrhea."	Parenteral opioids are given in 70% of hospitalizations; outpatient opioids should be limited and/or replaced with dicyclomine and amitriptyline.
Endometriosis	Progesterone orally (or long-acting injection at follow-up). NSAIDs.	Levonorgestrel-releasing intrauterine system or goserelin at follow-up.
Post–pelvic inflammatory disease chronic pelvic pain	NSAIDs are the most common treatment for pain. Empiric treatment for possible reinfection of a sexually transmitted disease should be considered.	Amitriptyline, with or without gabapentin.
Interstitial cystitis/bladder pain syndrome	Amitriptyline.	Pentosan polysulfate sodium (coating agent), hydroxyzine, gabapentin.

*Referral to specialist in chronic abdominal pain or gastroenterologist that performed the original endoscopy.

Note: Dosing for above indications can be started as follows: **amitriptyline** 10 to 25 milligrams daily at bedtime; **citalopram** 20 milligrams daily; **dicyclomine** 10 to 20 milligrams up to four times daily; **duloxetine** 30 to 60 milligrams daily; **gabapentin**, 300 milligrams PO, once on day 1, two times on day 2, then three times daily; **haloperidol** 5 milligrams IV; **ketorolac** 15 to 30 milligrams IV; **linaclotide** 290 micrograms daily; **lorazepam** 1 to 2 milligrams; **lubiprostone** 8 micrograms twice daily; **ondansetron** 4 to 8 milligrams acutely; **polyethylene glycol** 17 to 34 grams daily; **progesterone** 5 to 10 milligrams daily; **psyllium** up to 30 grams per day divided two to three times daily; **quetiapine** 25 to 100 milligrams daily; **hydroxyzine** 25 milligrams every 6 to 8 hours.

TABLE 38-10 Aberrant Drug-Related Behaviors

- Forges/alters prescriptions*
- Sells controlled substances*
- Uses aliases to receive opioids*
- Current illicit drug use*
- Factitious illness, requests opioids
- Conceals multiple physicians prescribing opioids
- Abusive when refused
- Conceals multiple ED visits for opioids

*Unlawful behaviors in many states.

of pain, stiffened body positioning, and reports of irregular sleep patterns. Undesired side effects, such as sedation, may limit the use of certain pain medications in this population.

DISPOSITION AND FOLLOW-UP

Referral to an appropriate specialist is one of the most productive means of aiding in the care of chronic pain patients who present to the ED. Chronic pain clinics have been successful in changing the lives of patients by eliminating opioid use, decreasing medication use, reducing pain levels, and increasing work hours. Patients' compliance with pain clinics may improve if these benefits are explained. Admission to the hospital is rarely indicated. However, occasionally patients may be admitted for pain control, possibly using self-controlled analgesic administration.

ABERRANT DRUG-RELATED BEHAVIOR

INTRODUCTION

The term ***drug-seeking behavior*** is imperfect, and its definition varies among clinicians. A more accurate term is ***aberrant drug-related behavior***, which raises concern for addiction and opioid misuse (**Table 38-10**).

The spectrum of people seeking controlled drugs includes those who have chronic pain and have been prescribed limited opioids, the drug addict who is trying to supplement a habit, and the "hustler" who is obtaining prescription drugs to sell on the street. However, the ability of the physician to correctly identify individuals in any of these three categories is difficult and imperfect.

The prevalence of aberrant drug-related behaviors is not known; however, there is considerable indirect evidence of the problem. A systematic review of the literature found that the only consistent predictor of aberrant drug-related behaviors in chronic pain patients is a personal history of illicit drug and alcohol abuse.[91] A separate systematic review of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy found that 20.4% of patients had negative urine tests for prescribed opioids despite filling regular prescriptions, and 14.5% tested positive for illicit drugs.[92] In 2012, 17% of the teens trying illicit drugs for the first time used prescription opioids, second only to marijuana.[93] Individuals attempting to secure opioids from emergency providers are often successful through persistence.[94]

CLINICAL FEATURES

The history given may be factual or fraudulent. Patients may be demanding, intimidating, or flattering. The most common complaints of patients who attempt to obtain opioids from the ED are (in decreasing order) back pain, headache, extremity pain, and dental pain.[94] Patients may complain of panic disorder or drug withdrawal symptoms and request benzodiazepines. In some cases, observation of vital signs and physical examination findings will help identify factitious illness, but even experienced clinicians are frequently misled.

Patients should be examined for signs of injection drug use, including needle marks, and the heart should be examined for evidence of a regurgitant murmur indicative of valve damage from prior endocarditis. Look for key characteristics of patients attempting to falsify illness (**Table 38-11**). Patients most commonly have completely normal physical examination findings. Widespread anecdotal experience of ED personnel has indicated that such patients will relate an allergy to alternative pharmacotherapy and insist that only one or two specific opioids are effective.

TABLE 38-11 Recommendations to Manage Fraudulent Techniques Used by Patients Attempting to Obtain Opioids for Illicit Use

Technique	Characteristics	Management
Lost prescription	Calls or returns stating that opioid prescription was lost before being filled.	Establish a policy: no lost opioid prescriptions refilled. Notify patients of policy at discharge as they receive prescriptions.
"Stolen" prescription or pill bottle	Police have not been called.	Inform patient this is a police issue and recommend calling police to rectify matter. Establish a policy: no stolen opioid prescriptions refilled.
Impending surgery	Wants temporizing opioids, doctor "unavailable," previous surgery, patient from out of town.	Use Internet and phone calls to check validity of information. Check medical records. Offer substitute for opioid.
Carries own records and radiographs	Suspicious or forged records, doctor's written permission to receive opioids, patient from out of town.	Use Internet and phone calls to check validity of information. Check medical records. Offer substitute for opioid.
Factitious hematuria with complaint of kidney stones	Appears comfortable or overacting, pricked finger dipped in urine, lip/cheek bitten and blood spat into urine.	Examine fingers and mouth. Obtain witnessed urinalysis. Offer nonopioid pain medicine. Obtain confirmatory test before giving opioid.
Self-mutilation	Done with dominant hand, requests opioids for pain.	Use bupivacaine for local block. Do not prescribe opioids without indications. Offer substitute for opioids.
Dental pain	Dental caries only.	Perform local nerve block with bupivacaine. Refer to dentist.
Factitious injury	Old injury, old deformity, self-massaged to produce erythema; patient from out of town.	Radiograph before treatment. Check medical records. Check for erythema that dissipates over time.

DIAGNOSIS

The diagnosis of aberrant drug-related behavior may not be possible in the ED. The medical record can provide a wealth of information about the patient, including documentation proving that the patient is supplying false information. Often the diagnosis is suspected in the ED but cannot be confirmed. In such cases, the clinical impression should be documented in the chart listing the provider's concerns, but physicians should be careful when using terms such as *drug-seeking behavior*; instead, document the concerning facts. Electronic medical records can be programmed to flag charts with alerts for patient safety; accidental overdose is always a concern in such patients.

Do not miss a true emergency in patients suspected of aberrant drug-related behaviors because the negotiation over pain medicine can distract the entire team from a subtle yet life-threatening medical or surgical illness.

Prescription drug monitoring programs[39] and other computerized tracking systems help identify patients who are abusing or overusing prescription drugs. Practitioners are encouraged to review the prescription drug monitoring program database before prescribing a discharge medication, because that information may change the intended discharge plan.[95]

TREATMENT AND DISPOSITION

The treatment of definite aberrant drug-related behavior is to refuse the controlled substance, consider the need for alternative medication or treatment, and refer for drug counseling. When confronted, patients hoping to acquire opioids may become verbally abusive, and hospital security may be required to control the situation and, if necessary, escort the patient out of the ED. Inform the patient that you are not able to prescribe or administer the medication they seek, and offer a substitute.

When aberrant drug-related behavior is confirmed or suspected in the ED, it should be documented in the chart, stating only the facts. Concerns about opioid overuse can be documented without diagnosing the patient with "drug-seeking behavior," which may not be appropriate without evidence of illegal behavior. When physicians are notified by a pharmacist of forged or altered prescriptions, law enforcement authorities should be called, and physicians should cooperate with the legal investigation. The prosecution of fraudulent behaviors, such as using aliases to obtain opioids, requires the involvement of the state bureau of investigation or a similar state agency.

SPECIAL CONSIDERATIONS: LEGAL ISSUES

The U.S. Drug Enforcement Agency (in addition to state agencies) licenses physicians to administer or dispense controlled substances. However, state law determines most prescribing regulations. Physicians should be aware of state laws regulating controlled substances prescribed in their practice setting. The prescribing of opioids to a known drug addict could result in restriction of the physician's medical license in some states, although this is rarely prosecuted for isolated incidents. If a patient refuses to acknowledge an addiction, the physician cannot be held accountable unless medical records at the facility where the patient presents document the addiction. In all states, it is illegal for patients to forge or alter prescriptions. In some states, it is illegal for patients to use aliases or factitious illness to obtain opioids. Furthermore, in some states, concealing previous or recent prescriptions for opioids when requesting opioids from a new practitioner is illegal.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 6

Wound Management

CHAPTER 39

Wound Evaluation

Adam J. Singer
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PRINCIPLES OF INITIAL EVALUATION

Evaluation of the patient with a traumatic wound begins with overall patient assessment.[1-3] Less obvious but more serious life-threatening injuries need care before directing attention to wound management. Determine the patient's past medical history and circumstances surrounding the injury.[1,2] Remove rings or other circumferential jewelry as soon as possible so they do not act as constricting bands when swelling progresses. Remove clothing over the injured area to reduce the potential for contamination.

External bleeding can usually be controlled by focal direct pressure over the bleeding site. When possible, replace skin flaps to their original position before applying pressure in order to avoid exacerbating vascular compromise. Tourniquet application may be necessary to stop life-threatening exsanguination or when needed for a short period to create a "bloodless" field for wound inspection.[4,5] Amputated fingers or extremities should be wrapped with a moist, sterile, protective dressing, placed in a waterproof bag, and then placed in a container of ice water for preservation and consideration for future reattachment. Before wound exploration, cleansing, and repair, most patients will need some form of anesthesia.[6] Systemic analgesia or procedural sedation may be required (see Chapter 35, "Acute Pain Management," and Chapter 37, "Procedural Sedation and Analgesia in Adults").

RISK ASSESSMENT

Proper wound management begins with a pertinent patient history (**Table 39-1**).[1,2] A variety of patient factors have adverse effects on wound healing and increase the rate of wound infection—extremes of age, diabetes mellitus, chronic renal failure, obesity, malnutrition, the use of immunosuppressive medications, the presence of connective tissue disorders, and protein and vitamin C deficiencies.[1] Predictive factors for infection are the wound characteristics of mechanism of injury, location, depth, length, configuration, and contamination.[7-9]

Ascertain the tendency of patients to form hypertrophic scars or keloids by both history and examination, as past experience may predict poor scar formation. Black and Asian patients are more prone to keloid formation than whites. Hypertrophic scars are due to tissue tension during wound healing, and these scars stay within the original wound boundaries and tend to undergo partial spontaneous regression within 1 to 2 years. Keloids are genetically linked variations in wound healing, resulting in the production of excess collagen beyond the original wound boundaries (**Figure 39-1**). Once formed, keloids rarely decrease in size.

Obtain a detailed history of allergies or prior adverse reactions to anesthetic agents or antibiotics. **Review any prior allergies to latex.[10] Determine the status of prior tetanus immunization and the need for further tetanus vaccination** (see Chapter 157, "Tetanus").

Review the mechanism of injury to determine the risk for potential wound contaminants and foreign bodies. Bite wounds have higher risk for infection and are generally managed differently than other lacerations (see Chapter 46, "Puncture Wounds and Bites"). Foreign bodies are more common in puncture wounds, wounds associated with broken glass, and motor vehicle collisions.[11,12] Ask about the presence of a foreign body sensation. In adults, those reporting a foreign body sensation are more likely to have a retained foreign body than those who do not.[13] This question has little utility in children.[14]

Both foreign body retention and visible contamination increase the risk of infection.[7,8] Organic and inorganic components of soil can cause infection even from very small doses of bacterial inoculum. Clay is the major inorganic soil component responsible for promoting infection. Conversely, sand grains and black dirt from roadways are relatively inert.

The likelihood of wound infection varies according to the forces applied at the time of injury.[7,8] The most common mechanism for traumatic wounds is blunt force. The skin is crushed against underlying bone and tears or splits from the subsequent tension. Conversely, sharp objects produce shear forces that cut skin cleanly. Severely crushed injuries producing extensive tissue devitalization are more susceptible to infection than wounds from shear forces. However, these distinctions may not be clinically relevant when appropriate principles of wound care are used, as was observed in a multicenter observational study that did not find higher rates of infection in blunt versus sharp injuries.[9]

Low-energy impact injuries may not result in lacerations, but instead may disrupt vessels, leading to ecchymosis or hematoma formation. Some hematomas spontaneously resorb. Those that become encapsulated may eventually require aspiration or incision and drainage.

Determine the time that the injury occurred. Although the growth of the bacterial inoculum is directly related to the time interval from injury to laceration repair, **there is no clearly defined relationship of time to closure to clinical infection[9,15-17] (Table 39-2). Therefore, time from injury until presentation is only one element to be considered, in addition to the injury mechanism, location, degree of contamination, host risk factors, and the importance of cosmetic appearance, before determining whether or not to perform primary wound closure.** The aforementioned multicenter observational study[9] confirmed that a history of diabetes, visible contamination, length greater than 5 cm, and non–head-and-neck location are associated with higher rates of infection. However, there was no association between time from injury to wound closure and the development of infection.[9] Wounds that are not closed primarily because of a high risk of infection should be considered for delayed primary closure after 4 days. The consensus of wound-care experts is that after 4 days of open wound management, the risk of infection after closure substantially decreases, although this approach has not been subjected to randomized controlled trials.[18]

Determine whether the wound was the result of an intentional, unintentional, or workplace event. Most states have regulations that require the reporting of intentional injuries, and patients with self-inflicted injuries may need psychiatric evaluation. Occupational injuries may require alternative follow-up arrangements.

The anatomic location of the injury helps predict the clinical outcome, both in terms of infection risk and cosmetic result (**Table 39-3**).[7-9,19] The risk of infection is determined largely by the interplay between baseline bacterial colonization and vascular blood supply. With respect to bacterial colonization, the density of the bacterial population is low on the upper arms, legs, and torso. Conversely, moist areas of the body, such as the axilla, perineum, toe webs, and intertriginous areas, harbor millions of bacteria per square centimeter, including anaerobes.[20] Obviously, any wounds with human or animal fecal contaminants run a high risk of infection, even with therapeutic intervention.

Wounds located on highly vascular areas, such as the face or scalp, are less likely to be infected than wounds located in less vascular areas.[7-9] The increased vascularity of the area more than offsets the high bacterial inoculum found in the scalp, and lacerations of the

TABLE 39-1 Pertinent Medical History

- Symptoms
  - Pain, swelling, paresthesias, muscle weakness
- Type of force causing injury
  - Crush (blunt) or shear (sharp)
  - Bite or puncture
- Elements of contamination
  - Time elapsed from injury until initial cleansing
  - Time elapsed from injury until presentation
  - Wound care performed prior to ED arrival
  - Object that caused injury (glass, wood, etc.)
  - Cleanliness of body and environment at time of injury and afterward
- Factors resulting in injury
  - Intentional or unintentional
  - Occupation or nonoccupation related
  - Assault or self-inflicted
- Foreign body potential
  - Did the object break or shatter?
  - Foreign body sensation
  - Removal of portion of object
- Function
  - Occupation and handedness
- Allergies
  - Anesthetics, analgesics, antibiotics, and latex
- Medications
- Chronic medical conditions that increase risk of infection
- Chronic medical conditions that increase likelihood of poor wound healing
- Previous scar formation (hypertrophic scars or keloids)

scalp and face have a very low infection rate regardless of the intensity of cleansing.[9,21] Although prophylactic oral antibiotics have traditionally been considered as warranted for intraoral lacerations, there is inconclusive evidence to support their use,[22] and practice varies considerably.[23]

WOUND EXAMINATION

Thorough wound examination should be conducted when the patient is calm and cooperative and positioned appropriately, with optimal lighting conditions, and with little or no residual bleeding. The use of magnifying lenses, such as surgical loupes (×2.5) or reading glasses, may improve visualization and reduce the likelihood of missing foreign bodies.[24]

Cursory examination under poor lighting or when the depths of the wound are obscured by blood will occasionally result in poor detection of foreign bodies and tendon, nerve, and vascular injuries. If bleeding is a problem, epinephrine-containing anesthetic solutions may be helpful, when not contraindicated. **Tourniquets may be used to obtain a bloodless field, but they should not be used for more than 30 minutes.** Lacerations over joints may have penetrated the joint capsule, and sometimes it is necessary to inject the joint with normal saline to ensure that there is no communication between the joint space and the laceration.[25] Evaluate the wound in neutral position, throughout the full range of motion, and particularly in the position present during injury. Chainsaw knee wounds, for example, are often sustained with the knee in flexed position. **Repositioning the joint or extremity in the position assumed during injury can better reconstruct the mechanism of injury and identify injured structures.** Lacerations over the metacarpophalangeal joints are suspicious for having occurred during a fight (clenched fist injury) and should be treated as though they are human bites.



FIGURE 39-1. A large keloid extending beyond the original wound margins. [Reproduced with permission from Park CW, Juliano ML, Woodhall D: Wounds and soft tissue injuries, in Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *Atlas of Emergency Medicine*, 4th ed. Figure 18-41. Copyright © 2016, by McGraw-Hill Education. All rights reserved.]

IMAGING

Although most lacerations will not require any diagnostic testing, on occasion, wound imaging for detection of foreign bodies may be necessary (see Chapter 45, "Soft Tissue Foreign Bodies"). Most foreign bodies commonly found in wounds are much denser than the surrounding tissue and are readily apparent on plain radiographs.[26] Metal, bone, teeth, pencil graphite, certain plastics, glass, gravel, sand, some fish bones, some painted wood, and most aluminum are visible on plain radiographs.

CT and MRI are useful for identifying and locating objects that have densities similar to soft tissue.[27,28] US may also be useful, particularly for wooden foreign bodies, although the sensitivity of US is inadequate to

TABLE 39-2 Risk of Wound Infection as Function of Time From Injury to Closure

Reference	Comments	Distinction Between Early and Late Closure (h)	Infection Rate/Inadequate Healing With Early Closure	Infection Rate/Inadequate Healing With Late Closure	Percent Difference (95% CI)
Berk et al, 1988[16]	All locations	19	8/97 (8.2%)	25/107 (23.4%)	15.1% (5.4% to 24.8%)
	Head	19	2/44 (5%)	1/36 (3%)	−1.8% (−9.9% to 6.4%)
	Trunk and extremities	19	6/53 (11.3%)	24/71 (33.8%)	22.5% (8.6% to 36.4%)
Baker and Lanuti, 1990[16]	Children, 59% head and neck location	6	32/2665 (1.2%)	2/147 (1.3%)	0.16% (−1.76% to 2.08%)
Van den Baar et al, 2010[17]	Adults, all locations, sutured	6	30/363 (9.1%)	3/45 (6.7%)	−1.6 (−6.2 to 9.4)
Quinn et al, 2014[9]	All locations, sutured wounds	6	5/135 (3.7%)	43/1443 (3.0%)	0.7% (−1.6% to 5.5%)

TABLE 39-3 Approximate Risk of Wound Infection After ED Closure

Location	Risk of Infection (%)
Head and neck	1–2
Upper extremity	4
Lower extremity	7

reliably exclude small (<2.5 mm) wood fragments.[29] Cone beam CT may be even more sensitive than the other modalities.[30]

PATIENT EDUCATION

Patients should be carefully educated regarding the expected cosmetic outcome. They should be informed that all lacerations result in some scarring and, if predisposed, possible keloid formation.[1] Some indication of the maximal width of the scar can be predicted based on wound location, whether the laceration is aligned parallel or perpendicular with lines of minimal tension, and how gaping the wound is while at rest (static tension) or when put through a range of motion (dynamic tension).[20,23] Lacerations over joints (which have more dynamic tension) will have wider scars than similar lacerations subject to less tension. Wounds that deviate from the lines of skin tension will also be prone to greater scar formation after suturing than wounds that are more closely aligned with skin tension.[31] The most important determinant of cosmetic outcome under control of the treating physician is meticulous wound repair with approximation of viable wound edges under little tension.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 40

Wound Preparation

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INTRODUCTION

All traumatic lacerations are contaminated to some degree; however, the level of contamination differs based on etiology, wound location, and time of injury. Wound preparation includes all of the steps required prior to wound closure (either by primary or secondary intention) aimed at reducing the risk of infection, optimizing cosmetic outcome, and minimizing patient pain and discomfort. For most wounds, adequate preparation requires some form of anesthesia, be it topical, local, or regional. For other patients (especially young children or the mentally disabled), anxiolysis using oral or intranasal midazolam or ketamine may be required. When patient cooperation is problematic and absolute immobilization is required (e.g., when repairing a laceration near the eye or in the mouth), procedural sedation or even general anesthesia should be considered.

Although the order of procedures may vary, in general, wound preparation starts with decontamination of the skin surrounding the laceration, followed by local anesthesia through the wound edges. After achieving adequate wound anesthesia, the wound is reexamined. When necessary, sharp debridement of obviously devitalized or heavily contaminated tissue should be performed. Finally, wound cleansing (e.g., scrubbing or irrigation) should be used to remove any remaining debris and bacteria. After excluding the presence of embedded foreign bodies and underlying tissue damage (e.g., tendon injuries), the wound is repaired. With heavily contaminated wounds, irrigation with soap and water under running tap water may precede local anesthesia when tolerated by patients. Early application of a topical anesthetic may make this procedure less uncomfortable.

STERILE TECHNIQUE

Although routinely practiced in other settings (e.g., the operating room), full sterile technique (mask, cap, gown, and gloves) apparently does not reduce wound infection rates after laceration repair in the ED setting.[1] Use of sterile gloves for laceration repair or outpatient surgical procedures does not reduce infection rates compared to clean, nonsterile gloves.[2] Hand washing prior to patient contact is a tenet of infection control, but there is no firm evidence that one form of hand antisepsis is better than another for reducing postprocedure wound infections.[3] Nonetheless, gloves protect the provider and should routinely be used, even if not sterile. Common sense suggests that masks should be used during wound preparation and closure when the practitioner has a respiratory infection or is otherwise potentially contagious.

SKIN DISINFECTION

Due to the presence of abundant normal microbial flora, skin disinfection is generally the first step in wound preparation. There is no evidence to support the historic practice of skin disinfection prior to ED laceration closure using povidone-iodine.[4] Chlorhexidine is likely a better agent, as noted in a meta-analysis of 13 randomized controlled trials involving 6997 patients undergoing clean or clean-contaminated surgeries; preoperative chlorhexidine antisepsis was associated with a lower incidence of surgical site infections (relative risk, 0.70; 95% confidence interval, 0.60 to 0.83).[5] Regardless of which agent is used, avoid contact of the antiseptic agent with the wound or the eyes. The antiseptic should also be allowed to dry for 2 to 3 minutes for maximal efficacy.

WOUND ANESTHESIA

Most lacerations will require some form of anesthesia to allow meticulous examination, irrigation, debridement, and repair. Short lacerations requiring few if any sutures or staples may sometimes be managed without injection of a local anesthetic, especially when topical anesthetics are applied. Shared decision making between the practitioner and patient in these cases is encouraged. The specific choice of anesthetic and route of administration (local or regional) is determined by wound size, location, and patient condition (see Chapter 36, "Local and Regional Anesthesia"). Importantly, a detailed sensory examination should be performed and documented prior to administration of any anesthetic. Consider the use of anxiolysis, procedural sedation (see Chapter 37, "Procedural Sedation and Analgesia in Adults," or Chapter 115, "Pain Management and Procedural Sedation in Infants and Children"), or even general anesthesia in noncooperative patients (e.g., infants, mentally disabled) and in sensitive or cosmetically important areas (e.g., mouth, eyes).

HAIR REMOVAL

Hair removal prior to wound repair does not reduce the incidence of infection and is not necessary before wound repair.[6] However, removal of the hair may facilitate wound evaluation and closure, especially with long hair. If hair is to be removed, trim with scissors or clip away with a disposable hair clipper. Avoid shaving of hair since it injures the hair follicles, allowing dissemination of bacteria, and increases the risk of wound infection. The hair can also be matted down with an antiseptic solution or petrolatum-based ointment to prevent it from entering the wound. The presence of hair on either side of a wound may also serve as a landmark for meticulous approximation of the wound edges. Do not trim eyebrows since they may not grow back or grow back in an abnormal pattern. Scalp hair from both sides of the wound may also sometimes be used to close a scalp laceration.[7] This method of closure also improves patient satisfaction and cosmetic outcome.

CONTROL OF BLEEDING

In addition to reducing blood loss, control of bleeding is necessary for optimal visualization of the wound. In most cases the bleeding can be controlled with local pressure with a gloved finger.

Physical means of applying pressure to bleeding include the use of **gelatin**, **cellulose**, or **collagen** sponges placed directly into the wound. Denatured gelatin (Gelfoam®; Pfizer, Inc., New York, NY) has no intrinsic hemostatic properties and works by the pressure it exerts as it expands. A cellulose derivative (Oxycel®; Becton Dickinson Infusion Therapy Systems, Inc., Sandy, UT) or a collagen (Actifoam®; MedChem Products, Inc., Woburn, MA) sponge reacts with blood, forming an artificial clot. These products are not particularly effective for actively bleeding wounds, as the blood flowing into the wound can wash them out.

Topical application of hemostatic agents is another approach to wound hemostasis. Kaolin, which initiates the closing process by activating factor XII of the coagulation cascade, is commercially available impregnated in polyester/rayon gauze pads and rolls (QuickClot®; Z-Medica, Wallingford, CT). Compressed directly onto a bleeding wound, these pads achieve hemostasis typically in 5 minutes in clinical studies.[8] **Topical tranexamic acid** can be applied directly to a bleeding wound by saturating a gauze pad with the liquid tranexamic acid (5 to 10 mL of the 100 milligrams/mL solution), or it can be applied as a powder (created by crushing tranexamic acid tablets)[9] or a paste (created by mixing about 2000 milligrams of crushed tranexamic acid tablets with 2 mL of sterile water).[10] For wound hemostasis, material is left on for 20 to 30 minutes; the paste, powder, or gauze is then removed so wound closure can proceed. Although widely used, tranexamic acid is not U.S. Food and Drug Administration approved for this indication.

A proximal tourniquet may be used as a temporizing measure when excessive bleeding is not controlled with pressure. Finger tourniquets using a rubber Penrose drain may be used when exploring and repairing finger lacerations (**Figure 40-1**). However, they should not be left on for more than 30 minutes.

When relevant, elevate the injured extremity. Infiltration of a local anesthetic containing epinephrine (in a concentration of 1:100,000 or 1:200,000) or the direct application of epinephrine (either as a single solution or as part of a topical anesthetic combination such as lidocaine-epinephrine-tetracaine) may also help control bleeding by inducing vasoconstriction.[11]

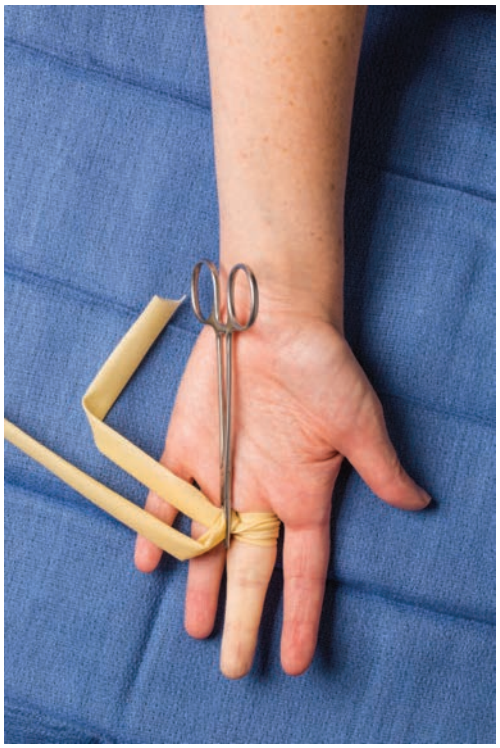


FIGURE 40-1. Construction of a finger tourniquet using a rubber Penrose drain.

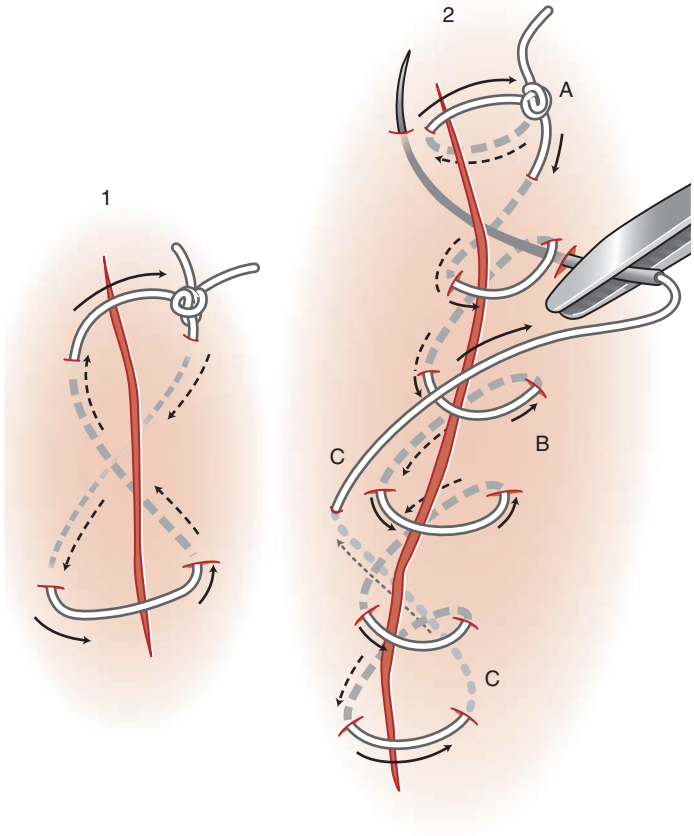


FIGURE 40-2. "Figure of 8" stitch, used for hemostasis on short lacerations (*1*). For longer lacerations (*2*), we suggest that after tying the first knot (*A*) continue with an over-and-over continuous suture (*B*). If after pulling on it the bleeding does not stop, continue with cross stitching backward over the previous stitches (*C*), tying it to the free end of the first knot.

Continued bleeding from the wound edges is best managed with sutures. Either a horizontal mattress suture or a figure-of-eight suture (**Figure 40-2**, left) may be required when simple interrupted sutures do not control the bleeding. Because tying the knot in a figure-of-eight suture will shorten the laceration line, opening it in the center, it should only be used in short lacerations (approximately 1 cm). For longer lacerations, after tying the first knot of a traditional stitch, continue with an over-and-over continuous suture. If after pulling on the suture there is still bleeding, the direction of the suturing should be reversed with cross-stitching backward over the previous stiches (Figure 40-2, right). Larger blood vessels may be tied off with an absorbable suture. If major arterial bleeding is identified or suspected, consult with a specialist.

Special clips (Raney) are available to rapidly control bleeding from scalp lacerations prior to definitive repair. Alternatively, metal binder clips can used to control bleeding from the wound edges.[12] In scalp lacerations, the sutures should include the underlying galea aponeurotica, since most bleeding vessels are within this layer. Large strong needles are best for this purpose.

WOUND IRRIGATION

Cleansing of traumatic wounds is considered an essential component of wound preparation. Irrigation is especially useful in heavily contaminated wounds.[13] It removes not only bacteria but also particles (such as soil) that increase the susceptibility to infection. High-pressure irrigation (generally defined as pressures greater than 7 pounds per square inch or 48 kPa) is more effective at removing bacteria and debris than low-pressure irrigation. However, high-pressure irrigation has the potential to cause further tissue trauma and distortion of the tissues, complicating



FIGURE 40-3. Syringe and splatter guard set up for wound irrigation.

meticulous wound closure, and exposes the provider to bloodborne splatter.[14] Thus, high-pressure irrigation should be limited to heavily contaminated wounds. Do not use high pressure when irrigating areas with loose areolar tissue such as the eyelids. A retrospective ED study of approximately 2000 patients did not find an association between high-pressure irrigation and wound infection in patients with facial and scalp lacerations.[15] Furthermore, a recent multicenter randomized controlled trial of nearly 2500 patients showed no benefit of pulsed high-pressure irrigation (8 to 10 pounds per square inch) over continuous irrigation using gravity alone in open fractures.[16] High-pressure irrigation can most easily be achieved using a large syringe (30 to 65 mL) and splatter guard (**Figure 40-3**).[17] Although the exact volume of irrigation is not clear, we suggest 50 to 100 mL/cm for contaminated wounds. Irrigation using tap water directly from the faucet achieves both high volume and high pressure.[18] Tap water is as effective as normal saline in reducing wound infection in both children and adults with traumatic lacerations.[19]

WOUND DEBRIDEMENT

The presence of devitalized, nonviable tissue increases the risk of wound infection and poor cosmesis.[20,21] Therefore, remove any nonviable tissue and any imbedded gross contaminants or foreign bodies. Debridement can reduce the bacterial burden in traumatic wounds.[22] Debridement is performed using a surgical blade or fine scissors. In areas of cosmetic importance or where excess surrounding tissue is unavailable, take extreme care to limit debridement and consider specialty consultation (e.g., plastic surgery). Simple debridement of contused wound edges (also referred as refreshing the wound margins) is generally performed. Undermining of the wound may facilitate wound closure, especially if it is under tension. For wounds that cross the relaxed skin tension lines (also known as the lines of minimal tension) at an angle greater than 30 degrees, more complex W-plasty can improve cosmetic outcome.[23] With this method, continuous W shapes are traced and later incised on both sides of the wound (**Figure 40-4**). This creates multiple triangular flaps with lengths of 4 to 7 mm and angles of 45 to 90 degrees, which are then sutured together after undermining the wound edges (**Figure 40-5**).

REMOVAL OF FOREIGN BODIES

Foreign bodies significantly increase the risk of wound infection and may also injure surrounding structures such as neurovascular bundles and tendons. Therefore, try to remove most foreign bodies at the time of wound exploration. Suspect the presence of foreign bodies with all injuries involving glass, especially in puncture wounds and after motor

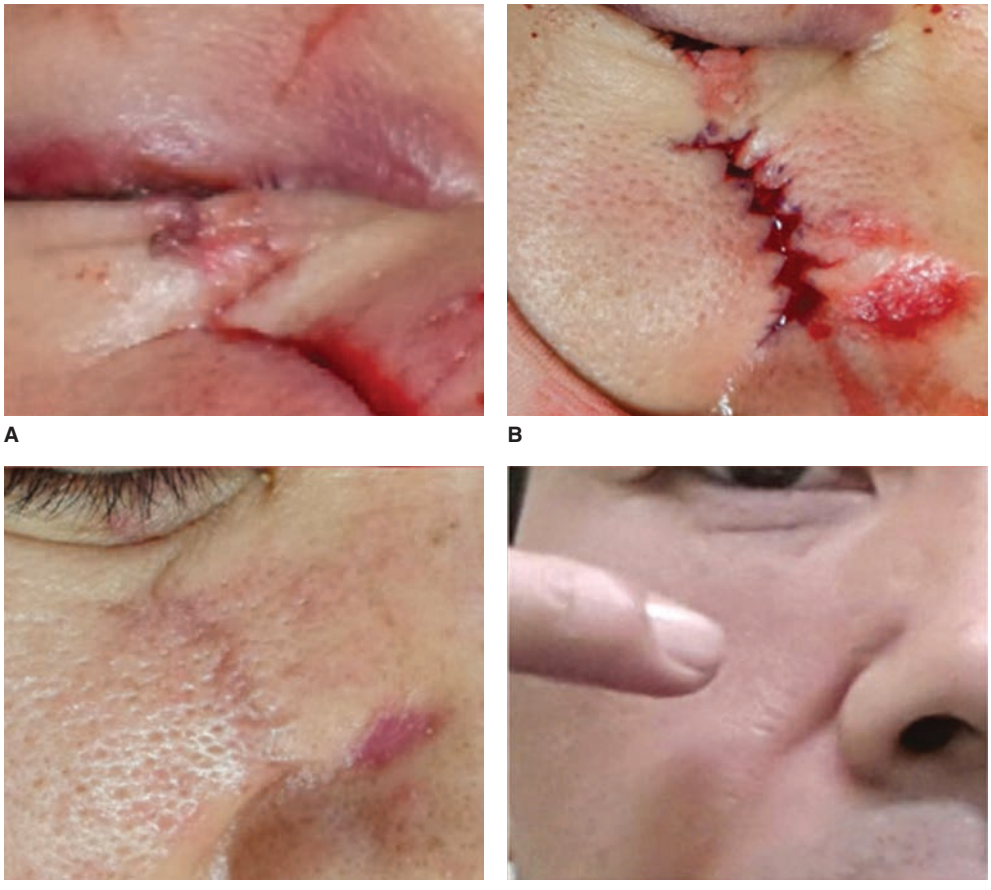
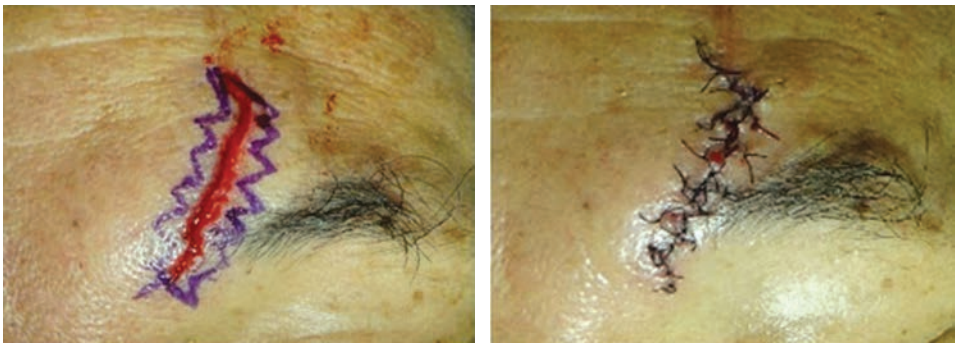


FIGURE 40-4. A case of a 51-year-old male with laceration of the right infraorbital margin to lateral margin of nasal ala. Angle to the relaxed skin tension line is nearly 80 to 90 degrees. The patient underwent W-plasty. **A.** Initial crush wound on face. **B.** W-shaped incision along the design line. **C.** State at 10 days after suture removal. **D.** State at 6 months after suture removal.



A B

FIGURE 40-5. Laceration debridement using W-plasty. The basic technique is the same as that of W-plasty for scar revision. W-shaped patterns are sketched on either side of the intact skin surface close to the wound site (**A**), and a number of triangular flaps are prepared with a length of 4 to 7 mm (normally 5.5 mm) (**B**). The angle between the two lines should be drawn at 40 to 90 degrees (normally 55 degrees). [Reproduced with permission from Min JH, Park KH, Choi HL, Park JS, Lee JH, Kim H, Lee BK, Lee DH, Lee TG (eds). Usefulness of direct W-plasty application to wound debridement for minimizing scar formation in the emergency department. *Am J Emerg Med* 2017 Dec;35(12):1804-1809. Copyright Elsevier.]

vehicle collisions. The sensation of a foreign body by the patient is reasonably specific for the actual presence of a foreign body and should be investigated. Point tenderness and increased pain with motion are also suggestive. Avoid blind probing of the wound with a finger to prevent provider injury. Close visual inspection of the entire depth and course of the wound and probing with a blunt metal instrument help exclude foreign bodies. Plain radiographs are helpful at identifying radiopaque foreign bodies such as glass fragments. However, bedside US, CT, or MRI may be required with radiolucent foreign bodies such as wood and rubber.[24,25]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 41

Wound Closure

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INTRODUCTION

The major goal of wound closure is to restore the skin's integrity in order to reduce the risk of infection, scarring, and impaired function. Closure can occur in three ways. With **primary closure**, the wound is immediately closed by approximating its edges, with the main advantage being a reduction in healing time in comparison with other closure methods. Primary wound closure also may reduce bleeding and discomfort often associated with open wounds. **Secondary wound closure**, in which the wound is left open and allowed to close on its own, is particularly well suited for highly contaminated or infected wounds as well as in patients at high risk of infection. Although this method may reduce the risk of infection, it is relatively slow and uncomfortable and leaves a larger scar than primary closure. With **delayed (or tertiary) closure**, also sometimes referred to as delayed primary closure, the wound is initially cleansed and then packed with moist sterile gauze covered by a sterile covering. The dressing is left undisturbed unless signs of infection—fever, purulent exudate, or spreading cellulitis—develop. After 4 to 5 days, the dressing is removed, and the wound edges can be closed if no infection has supervened. This approach may be useful for highly contaminated wounds and animal bites, and while commonly described and recommended, there is little evidence documenting the effectiveness for traumatic wounds seen in the ED.[1]

OVERVIEW OF WOUND CLOSURE METHODS

Lacerations may be closed by one of five commonly available methods or devices: sutures, staples, adhesive tapes, tissue adhesives, and hair apposition. Each method has advantages and disadvantages (**Table 41-1**). Choice of the wound closure method and timing should take into account both

TABLE 41-1 Advantages and Disadvantages of Wound Closure Techniques

Technique	Advantages	Disadvantages
Sutures	Time honored Meticulous closure Greatest tensile strength Lowest dehiscence rate	Requires removal (if using nonabsorbable material) Requires anesthesia Risk of needle stick to physician Greatest tissue reactivity Highest cost Slowest application
Staples	Rapid application Low tissue reactivity Low cost Low risk of needle stick	Less meticulous closure May interfere with some imaging techniques (CT, MRI) Requires removal
Tissue adhesives	Rapid application Patient comfort Resistant to bacterial growth No need for removal Low cost No risk of needle stick Microbial barrier Occlusive dressing	Lower tensile strength than 5-0 or greater sutures Dehiscence over high-tension areas (joints) Not useful on hands Cannot bathe or swim (can briefly get wet in a shower)
Adhesive tapes	Least reactive Lowest infection rates Rapid application Patient comfort Low cost No risk of needle stick	Frequently fall off Lower tensile strength than sutures or tissue adhesives Highest rate of dehiscence Often requires use of toxic adjuncts Cannot be used in areas with hair Cannot get wet
Hair apposition	Simple Low cost No foreign body placed in wound No risk of needle stick	Can be used only on the scalp Can only approximate simple non-gaping lacerations

patient and wound characteristics.[2] Cosmetic outcome is more closely related to practitioner technique and the patient's own healing characteristics than to any specific closure method or device. Many of the principles discussed in this chapter are based on experience and observation rather than on controlled trials.

One important consideration when choosing a wound closure method is the amount of tension on the wound, both *static* (at rest) and *dynamic* (with motion). *Linear lacerations subject to little tension* can usually be closed by any one of the five closure methods. For low-tension lacerations, consider patient characteristics and preferences such as compliance, the availability to return for follow-up and device removal, and overall level of patient anxiety. *With low-tension irregular lacerations,* sutures may be the best alternative, allowing the greatest degree of precision for accurate wound edge approximation. Conversely, some small lacerations where the wound edges approximate with little tension do not require primary closure. For example, simple (<2 cm) uncomplicated hand and finger lacerations, when treated with antibiotic ointment and gauze dressing, heal as fast and with no notable differences in appearance or function as those closed primarily with sutures.[3] Note that this technique is limited to small, superficial hand lacerations; it cannot be recommended for larger lacerations, and it has not been studied in other sites.

With *lacerations subject to high tension* (static and/or dynamic), relief of tension on the wound can reduce the risk of early dehiscence or gradual widening of the scar. Relief of tension is best achieved by careful undermining, placement of deep dermal sutures, and wound immobilization (when appropriate). After placement of deep, tension-relieving sutures, the superficial epidermal layer may be closed by any of the aforementioned closure methods. Reinforcement with adhesive skin tape is useful when the skin is thin, as in pretibial lacerations.[4-6]

With patients at risk of **keloid** formation, it makes logical sense to relieve tension and minimize the amount of foreign material introduced into the wound by using skin tapes or tissue adhesives, instead of sutures.

SUTURES

Sutures are the strongest of all the closure devices and allow the most accurate approximation of the wound edges, regardless of their shape or configuration. However, sutures are the most time-consuming and operator dependent of all wound closure methods and have the risk of inadvertent needle-stick injury (to the provider). Using forceps to handle the needle during suturing can reduce this risk. A needle-catcher device is reported to be useful in reducing needle-stick injury during skin suturing.[7-9]

Sutures may be classified as absorbable and nonabsorbable. ***Nonabsorbable sutures*** **retain their tensile strength for at least 60 days.** They are most often used to close the outermost layer of the skin (where they can be removed) or for repair of tendons (where prolonged strength is desired due to high tension). In general, nonabsorbable sutures are avoided in deep vascularized tissues where their presence stimulates a foreign body response with fibroblastic proliferation. Nonabsorbable sutures are differentiated by their origin and structure (**Table 41-2**). Due to their strength, handling, and relatively low tissue reactivity, synthetic monofilament material (such as nylon or polypropylene) is preferred for nonabsorbable use.[10] Polybutester sutures have the ability to elongate in response to external forces and possess elasticity to return to the original size once the load is removed. This property may be useful in wounds where swelling is anticipated. Less distensible sutures, such as nylon or polypropylene, cannot expand, and instead may lacerate the wound edges as the tissue swells.

Absorbable sutures **lose most of their tensile strength in less than 60 days**; they are well suited for closure of deep structures such as the dermis and fascia (**Table 41-3**). Poliglecaprone 25 has handling characteristics that are similar to nonabsorbable sutures (such as nylon) and is particularly useful for intradermal or subcuticular closure. Due to its rapid absorption, poliglecaprone 25 should probably be limited to relatively low-tension wounds. With high-tension wounds, a suture with more sustained tensile strength is preferred, such as polyglyconate. Absorbable sutures that incorporate the antibacterial agent triclosan are also available and may be especially indicated in contaminated wounds.[11-14] Rapidly absorbing sutures can also be used to close skin and mucosa, especially when avoidance of suture removal is desirable.[15-20]

For most ED use, the choice between absorbable and nonabsorbable material for percutaneous sutures is clinically irrelevant. The cosmetic outcomes and complications of traumatic lacerations and surgical incisions closed with absorbable or nonabsorbable sutures have similar short- (infection, dehiscence) and long-term (cosmesis) outcomes. Absorbable sutures, such as rapidly absorbing gut, are especially useful for skin closure in children who are not candidates for wound repair with skin tapes or tissue adhesives.[17,20]

Suture material is categorized by the U.S. Pharmacopeia gauge size. The larger the suture size number, the thinner is the suture (and the lower the tensile strength), so that, for example, a 6-0 suture is thinner than a 5-0 suture. **A general principle is that larger-diameter material produces more damage to the tissues and leaves larger holes in the skin, so generally thinner suture material is used whenever possible.** Because smaller-diameter material has less tensile strength, the trade-off is that more individual sutures closer together are sometimes needed to close a wound. Where cosmetic appearance is important, as on the face, smaller-diameter material is preferred (**Table 41-4**).

Improper tissue handling further traumatizes the tissues and results in an increased risk of infection and poor scarring.[21] Gentle tissue handling using either skin hooks or the open limb of fine forceps is encouraged (**Figure 41-1**). Magnifying lenses such as surgical loupes can assist in accurate placement of sutures, as well as in the identification of retained foreign bodies.[22] While there are many types of **surgical loupes** available, a version useful in the ED is a magnifying power of 2.5× with the Keplerian lens system, which will provide a bright, clear image out to a field of view of 10 cm. Alternatively, over-the-counter reading glasses with similar magnification may be used. Hemostasis is best achieved by direct pressure. Topical vasoconstrictors (e.g., epinephrine) applied to the wound edges and bed or mixed with the local anesthetic injected into the wound may help control bleeding in traumatic lacerations

TABLE 41-2 Nonabsorbable Suture Characteristics

Suture	Structure	Raw Material	Tensile Strength Retention Profile	Tissue Reactivity	Common ED Uses
Silk	Braided	Organic protein fibroin	Degradation of fiber results in loss of strength over many months	Significant inflammatory reaction	Intraoral mucosal surfaces for comfort
Nylon (Ethilon®, Dermalon®)	Braided and monofilament	Polyamide polymer	Hydrolysis results in 20% loss in strength per year	Minimal	Soft tissue and skin reapproximation
Polypropylene (Prolene®, Surgipro®)	Monofilament	Polypropylene polymer	Indefinite	Least	Soft tissue and skin reapproximation
Polyester (Mersilene®, Ti–Cron®)	Braided and monofilament	Polyethylene terephthalate polymer	Indefinite	Minimal	Tendon repair using undyed (white) color
Polybutester (Novafil®)	Monofilament	Copolymer of butylene terephthalate and polytetramethylene ether glycol	Indefinite	Minimal	Soft tissue approximation

TABLE 41-3 Absorbable Sutures

Suture	Structure	Raw Material	Tensile Strength Retention Profile	Absorption Rate	Tissue Reactivity	Common ED Uses
Surgical gut	Monofilament	Collagen derived from beef serosa or sheep submucosa	7–10 d	Absorbed by proteolytic processes in 70 d	Moderate reactivity	Intraoral wounds
Chromic gut	Monofilament with chromic salt coating	Collagen derived from beef serosa or sheep submucosa	21–28 d	Absorbed by proteolytic processes in 90 d	Moderate reactivity	Subcutaneous approximation and intraoral wounds
Fast-absorbing gut	Monofilament heat treated to facilitate absorption	Collagen derived from beef serosa or sheep submucosa	5–7 d	Absorbed by proteolytic processes in 21–42 d	Moderate reactivity	Facial wounds and skin grafts
Polyglycolic acid (Dexon®)	Braided	Glycolic acid polymer	65% at 14 d and 35% at 21 d	Absorbed by hydrolysis, complete by 60–90 d	Minimal	Subcutaneous approximation and ligation of vessels
Coated polyglactin 910 (Vicryl®)	Braided	Copolymer of lactide and glycolide, coated with polyglactin 370 and calcium stearate	75% at 14 d and 40% at 21 d	Absorbed by hydrolysis, complete by 56–70 d	Minimal	Subcutaneous approximation and ligation of vessels
Coated polyglactin 910 with triclosan (Vicryl PLUS®)	Braided	Copolymer of lactide and glycolide, coated with polyglactin 370 and calcium stearate; incorporates antibacterial agent triclosan	75% at 14 d, 50% at 21 d, and 25% at 28 d	Absorbed by hydrolysis, complete by 56–70 d	Minimal	Subcutaneous approximation and ligation of vessels, especially useful in contaminated wounds
Coated polyglactin 910 rapid absorption (Vicryl Rapide®)	Braided	Copolymer of glycolide and lactide, coated with polyglactin 370 and calcium stearate	50% by 5 d and 0% at 14 d	Absorbed by hydrolysis, complete by 42 d	Minimal to moderate	Skin approximation when absorbable sutures are used
Coated glycolide and lactide (Polysorb®)	Braided	Copolymer of glycolide and lactide, coated with mixture of caprolactone, glycolide copolymer, and calcium stearoyl lactylate	80% at 14 d and 30% at 21 d	Absorbed by hydrolysis, complete by 56–70 d	Minimal	Subcutaneous soft tissue approximation
Polydioxanone (PDS II®)	Monofilament	Polyester polymer	70% at 14 d, 50% at 28 d, and 25% at 42 d	Absorbed by hydrolysis, complete at 180–210 d	Slight	Subcutaneous soft tissue approximation where more prolonged strength is needed
Poliglecaprone 25 (Monocryl®)	Monofilament	Copolymer of glycolide and epsilon-caprolactone	50%–70% at 7 d and 20%–40% at 14 d	Absorbed by hydrolysis, complete by 91–119 d	Minimal	Subcutaneous soft tissue approximation
Poliglecaprone 25 with triclosan (Monocryl PLUS®)	Monofilament	Copolymer of glycolide and epsilon-caprolactone; incorporates antibacterial agent triclosan	50%–70% at 7 d and 20%–40% at 14 d	Absorbed by hydrolysis, complete by 91–119 d	Minimal	Subcutaneous soft tissue approximation, especially in contaminated wounds
Glycomer 631 (Biosyn®)	Monofilament	Polyester composed of glycolide, dioxanone, and trimethylene carbonate	75% at 14 d and 40% at 21 d	Absorbed by hydrolysis, complete by 90–110 d	Slight	Subcutaneous soft tissue approximation where extended strength is not needed
Polyglyconate (Maxon®)	Monofilament	Copolymer of glycolic acid and trimethylene carbonate	80% at 7 d, 75% at 14 d, 65% at 21 d, 50% at 28 d, and 25% at 42 d	Absorbed by hydrolysis, complete by 180 d	Slight	Subcutaneous soft tissue approximation where more prolonged strength is needed

treated in the ED. Careful and selective placement of a ligature tie is sometimes necessary for bleeding from vessels >2 mm in diameter.

The best cosmetic outcome is achieved by carefully matching each layer of the wound with its corresponding counterpart on the opposite side, ensuring eversion of the wound edges and minimizing the amount of tension on the wound. As the wound heals and the swelling subsides, the wound will eventually flatten, becoming flush with the surrounding skin surface. Inadvertent inversion of the wound edges may result in an unsightly depressed scar. A variety of suture techniques can be used to handle wounds of nearly all shapes, irregularities, and depths (**Table 41-5**). Studies of abdominal surgical incision closure did not consistently find that small suture bites placed close to the wound edges and close to one another reduced surgical site infections compared with larger suture bites.[23,24] Although small suture bites placed close together have not been compared to larger suture bites in the closure of traumatic wounds, there is likely no clear advantage to sutures placed close to the wound edges and each other; the number of sutures placed and bite size chosen should achieve optimal approximation of wound edges while minimizing the amount of suture

TABLE 41-4 Recommended Suture Size Based on Laceration Location

Location	Suture Size
Scalp	3-0 or 4-0
Face	6-0
Trunk	4-0
Extremities	4-0
Digits	5-0

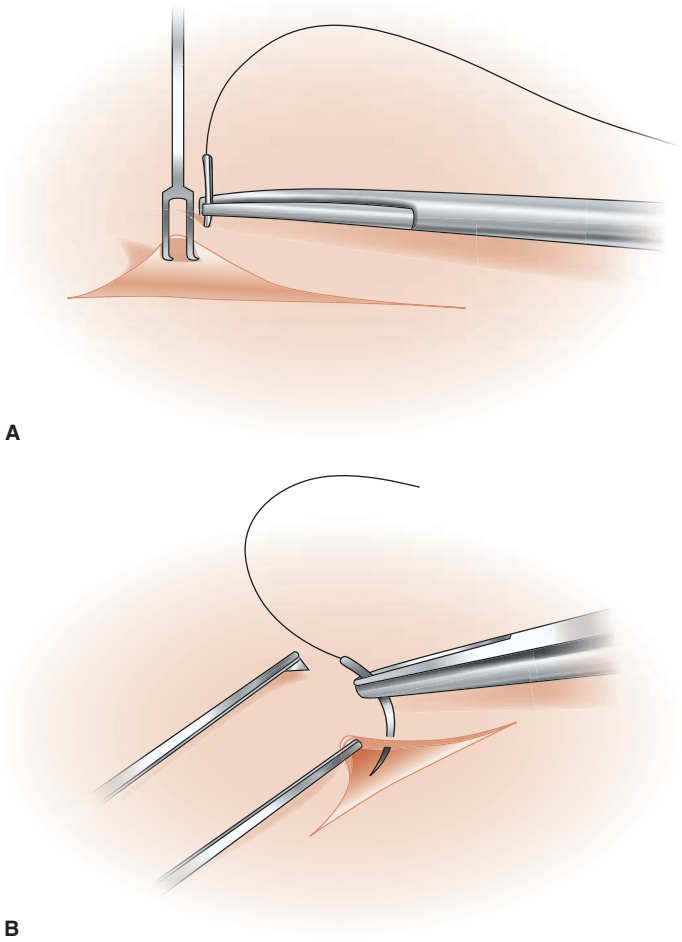

FIGURE 41-1. The skin hook (**A**) or one limb of a tissue forceps with teeth (**B**) is used to elevate the wound edge to facilitate placement of the percutaneous suture.

material used. The operator should concentrate on suture placement; minimize nonrelevant small talk during wound closure to reduce the risk of wound infection.[25]

SIMPLE INTERRUPTED PERCUTANEOUS SUTURES

Individual simple interrupted percutaneous sutures are the most basic and most commonly used approach for laceration closure. Introduce the needle through the outer layer of the skin, and exit at the level of the dermis on one side of the wound. Then, reinsert the needle through the opposite wound edge starting at the level of the dermis and exit superficially (**Figure 41-2**). To ensure proper wound edge eversion, the needle should enter and exit the skin at equal distances from the wound and at an angle of 90 degrees. Wound edge eversion is achieved by taking a larger bite through the depth of the wound than through the more superficial layers (**Figure 41-3**).

The entrance and exit of the suture should be close enough to the wound edges that they are not puckered when the knot is tied but far enough away to allow the suture material a firm hold on the tissue. **Sutures are tied using square knots, and, generally, the number of knot ties should correspond to the suture size** (i.e., four ties for a 4-0 suture, five ties for a 5-0 suture, etc.). Additional ties do not increase the strength of a properly tied square knot; they only add to its bulk. The extra ties are to increase knot security and prevent unraveling. Once the knot is completed, it should be moved to one side of the wound so as to not rest directly over the edges. For simple linear lacerations, a useful approach is to place the first suture in the middle of the wound, creating two smaller segments that are sequentially bisected into smaller segments until adequate coaptation of the edges is achieved. Sutures should not be cut so short that they may be difficult to locate through a scab or scalp hair at the time of suture removal.

CONTINUOUS (RUNNING) PERCUTANEOUS SUTURES

The major advantage of this method is its rapidity, as the entire wound is closed before any of the suture material is cut. This technique is most appropriate for long linear lacerations. Because running percutaneous

TABLE 41-5 Suture Techniques Based on Wound Type

Suture Type	Advantages	Disadvantages	Frequent Uses
Interrupted percutaneous	Excellent approximation for irregular and complex lacerations	Time-consuming May strangulate tissues	Low-tension wounds May be used with deep sutures for high-tension wounds
Continuous percutaneous	Rapid closure Accommodates edema	Less meticulous closure than interrupted sutures Wound may dehisce if a single knot unravels and no deep sutures were placed	Percutaneous closure in conjunction with deep sutures
Deep dermal	Reduces tension on wound surface Allows early removal of percutaneous sutures, avoiding hatch marking May reduce scar width	May increase infection in contaminated wounds	High-tension wounds Closure of dead space
Continuous subcuticular	Rapid closure Reduces tension on wound surface Reduces or eliminates need for percutaneous sutures May reduce scar width	Technically difficult Less accurate approximation than interrupted sutures Wound may dehisce if a single knot unravels	Cosmetically visible areas to reduce scarring
Vertical mattress	Excellent wound edge eversion Combines advantages of deep and superficial sutures	May cause tissue strangulation	Thin or lax skin with little dermal or fascial tissue High-tension areas (e.g., extremities)
Horizontal mattress	More rapid than simple interrupted sutures Avoids punctures close to wound edges that may impair perfusion Accommodates wound swelling	Requires skill to achieve wound edge eversion	Volar wounds of the hands Initial approximation of high-tension wounds
Half-buried horizontal mattress	Less compromising to flap tip perfusion and stellate lacerations	Technically difficult	Corner stitches and flaps Stellate lacerations

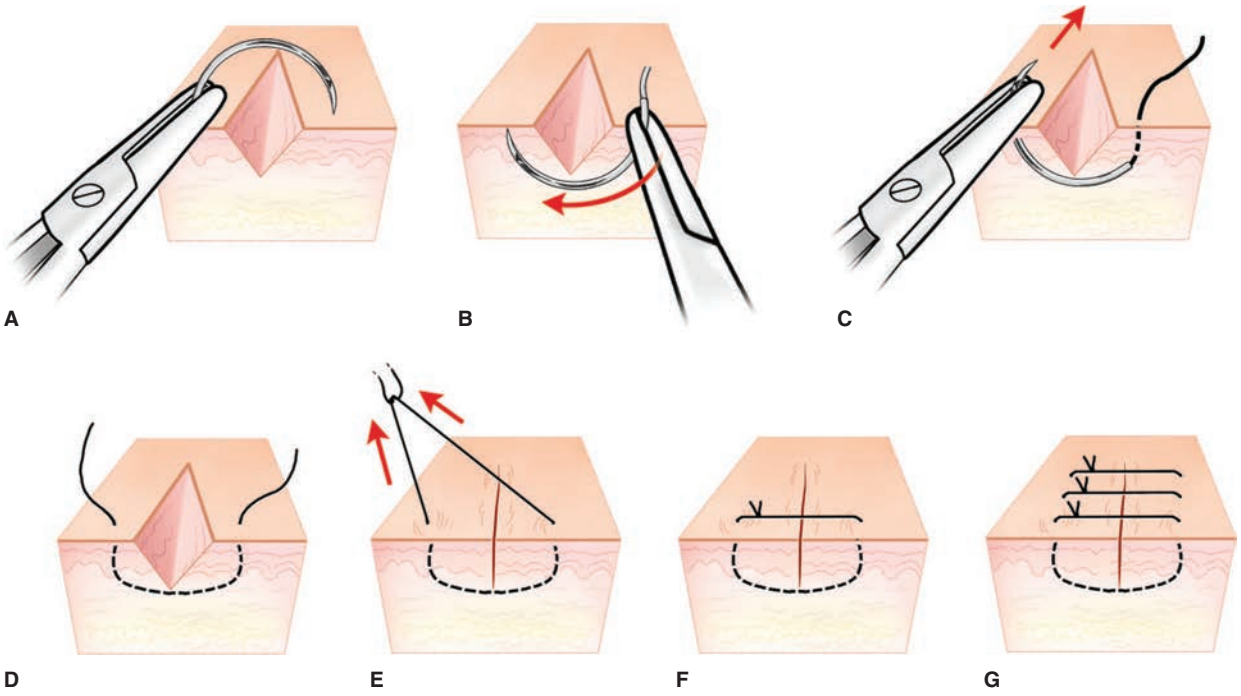

FIGURE 41-2. Placement of simple interrupted percutaneous sutures. **A.** Insert the needle at a 90-degree angle to the skin. **B.** Drive the needle through the tissue until the tip exits the skin. **C.** Grasp the needle behind the tip and pull it through the wound. **D.** The suture should enter and exit the skin equidistant from the wound edges. **E.** Pull the suture to oppose the wound edges and cinch down the knot. **F.** Complete the knot to one side of the laceration. **G.** Apply additional sutures equidistant from each other until the wound is closed. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures,* 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-6. New York, NY: McGraw-Hill, Inc.]

sutures do not enable precise wound edge apposition, it should be avoided in irregularly shaped lacerations. With this method, the first suture is placed at one end of the laceration similarly to an interrupted percutaneous suture. After the knot is tied, the suture material is not cut, and the needle is reintroduced into the skin on the opposite side, pulling the suture across the wound at a 65-degree angle (**Figure 41-4**). The needle then crosses the depth of the wound in a circular motion perpendicular to the wound, exiting on the opposite side approximately 3 to 5 mm from the wound edge. This process is repeated as needed until the entire wound is approximated and a second knot is tied.

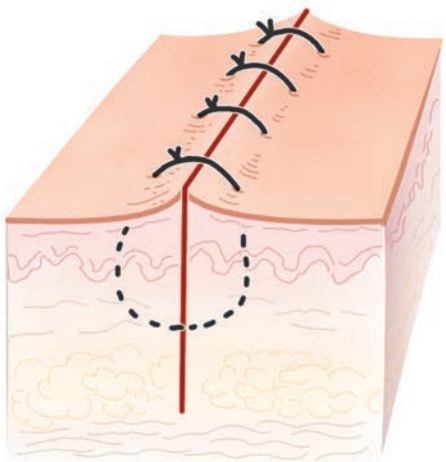

FIGURE 41-3. Wound edge eversion. The distance of the suture from the wound edge is greater at the depth of the wound than at the surface, promoting wound edge eversion when tightened. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures,* 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 114-14. New York, NY: McGraw-Hill, Inc.]

BURIED DERMAL SUTURES

Deep dermal sutures are used to reduce tension on the wound and to close dead spaces. Placement of buried dermal sutures requires judgment because the benefits for nongaping small wounds are unproven and their presence may increase the risk of infection in contaminated wounds.[26,27] Do not suture through adipose tissue to approximate wound edges; adipose tissue will not hold tension, and sutures through adipose tissue are unnecessary in clean surgical cases and only promote infection in contaminated wounds.[28]

With buried dermal sutures, the needle is first inserted at the level of the mid dermis on one side of the wound and then exits more superficially below the dermal–epidermal junction (**Figure 41-5**). The needle is then introduced below the dermal–epidermal junction on the opposite wound side and exits at the level of the mid dermis. Thus, the knot becomes buried in the depth of the tissue when tying of the suture is completed. The first suture is placed at the center of the laceration, followed by additional sutures that sequentially bisect the wound. The number of buried sutures should be limited to those necessary to enable skin closure with minimal tension. There is no difference in surgical site infections after interrupted intradermal and interrupted percutaneous suturing[29]; since placement of interrupted percutaneous sutures is easier and faster, this method is generally preferred in the ED.

CONTINUOUS SUBCUTICULAR SUTURES

The continuous subcuticular suture is one of the more complex methods of wound closure. The major advantage of this method is that it results in fairly good wound approximation, often without requiring any percutaneous sutures. For this technique, after anchoring the absorbable suture at one end of the wound, sequential, horizontally oriented "bites" are taken immediately below the dermal–epidermal junction, working toward the other end until the wound is adequately approximated (**Figure 41-6**). The second knot is tied with the tails cut short so as to remain buried.

VERTICAL MATTRESS SUTURES

Vertical mattress sutures combine some of the advantages of deep and percutaneous sutures—closure of gaping wound edges with excellent

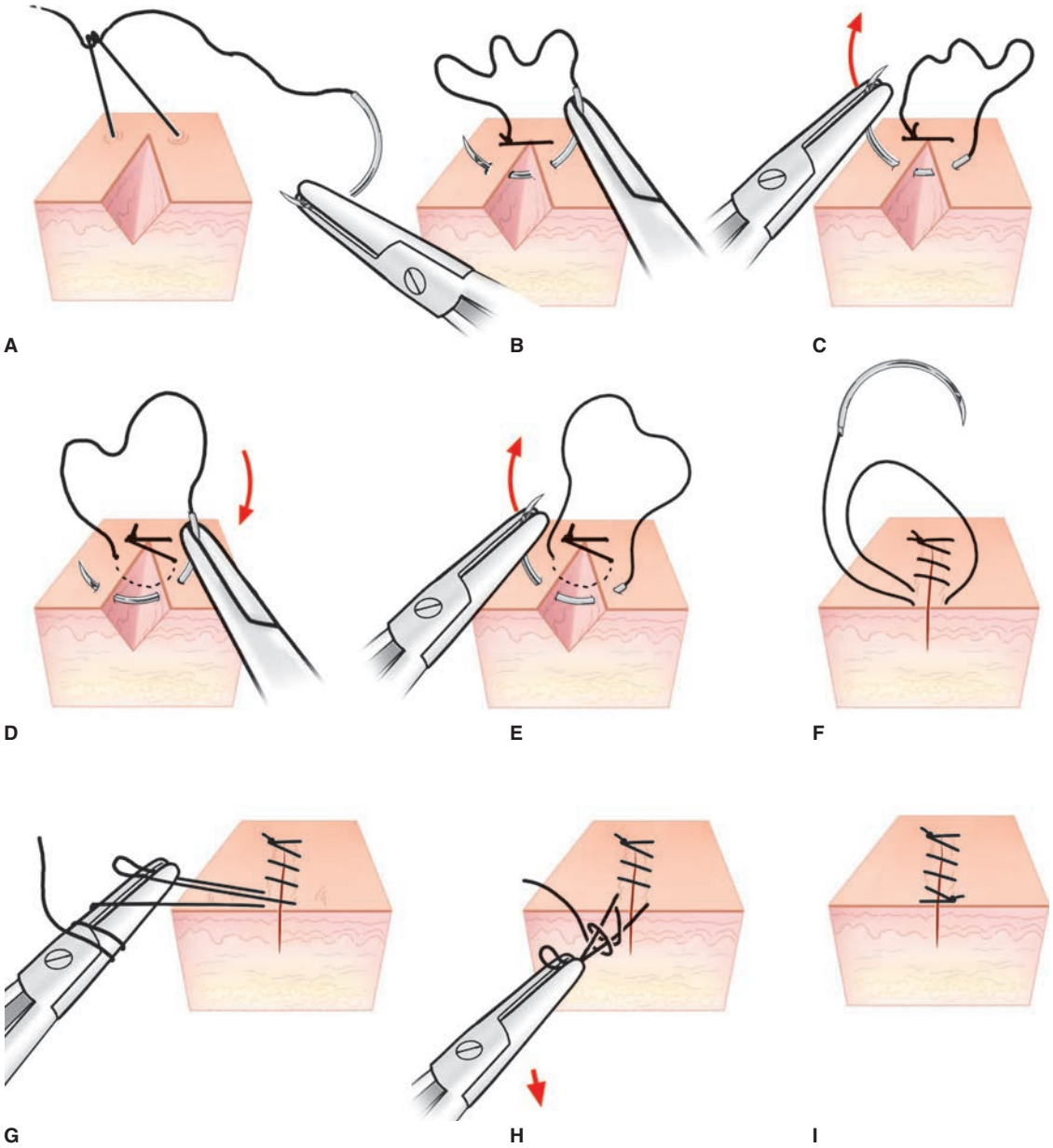

FIGURE 41-4. Continuous or running percutaneous suture. **A.** Place the initial stitch as a simple interrupted stitch, but do not cut the suture after the knot is securely tied. **B** and **C.** Place a second stitch 3 to 5 mm from the first stitch as if placing another simple interrupted stitch. **D** and **E.** Place a third stitch 3 to 5 mm from the second stitch and continue to place additional stitches until the end of the laceration is reached. **F.** Do not pull the last throw taut against the skin; the loop will act as the tail end of the suture for knot tying. **G.** Loop the needle end of the suture twice around the tip of the needle driver and grasp the last throw with the tips of the needle driver. **H.** Pull the last throw through the loops until the knot is against the skin. **I.** Perform three to five more instrument ties to secure the knot, and then cut off the excess suture. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures,* 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-9. New York, NY: McGraw-Hill, Inc.]

wound edge eversion. Vertical mattress sutures are particularly useful in very thin or lax skin and in areas where the deep subcutaneous tissues are too fragile to be used for anchoring tension-reducing sutures (e.g., over the shin). After taking a large, deep bite from both sides of the wound ("far to far"), the direction of the needle is reversed, and a smaller superficial bite is taken from both sides ("near to near") of the laceration (**Figure 41-7**). Vertical mattress sutures may result in excessive tension on the more superficial skin edges, which reduces blood supply to the skin and may result in necrosis of the wound margins.

A modification of the standard vertical mattress suture is the shorthand version. In this approach, the first stitch is close to the wound edges ("near to near"); the suture is then grasped and pulled away from the wound, elevating the wound edges while a second stitch is performed farther away from the wound ("far to far") (**Figure 41-8**).[30] This shorthand version can be performed in less time with the same outcome; however, blind placement of the larger bite may injure underlying structures.

HORIZONTAL MATTRESS SUTURES

The horizontal mattress is a good suture technique to close wounds with poor circulation to the wound edges because no percutaneous punctures that could further disrupt skin perfusion are placed close to the wound edges. This suture also reduces tension at the wound edges and reduces the potential for subsequent local necrosis. Horizontal mattress sutures can close a wound with fewer individual stitches because each stitch encases more tissue than other techniques (**Figure 41-9**). This suture is useful on the volar surfaces of the hands and fingers, because these delicate skin areas may swell but the skin edges are not easily cut due to the placement of the skin punctures far from the wound. The main disadvantage of the horizontal mattress stitch is the skill required to place the suture to achieve wound eversion.

One variation is the **locking horizontal mattress suture,** which applies additional force to approximate separated wound edges.[31,32] This

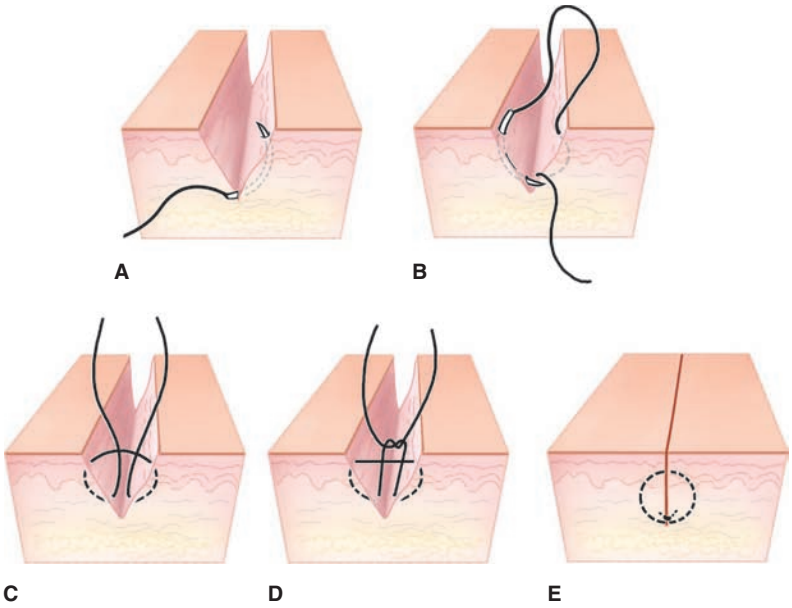

FIGURE 41-5. Buried dermal suture. **A.** Insert the needle into one side of the base of the wound, and drive the needle from deep to superficial, exiting at the dermal–epidermal junction. **B.** Insert the needle through the dermal–epidermal junction on the opposite side of the wound and drive it through the base of the wound. The suture should exit the base of the wound across from and level with the entrance site of the first throw. **C.** Pull both free ends of the suture up and out through the laceration. **D.** Tie a knot in the suture. **E.** Pull both free ends of the suture to lower the knot to the base of the wound and oppose the tissue. Tie three additional knots to secure the suture. Cut off any excess suture. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-19. New York, NY: McGraw-Hill, Inc.]

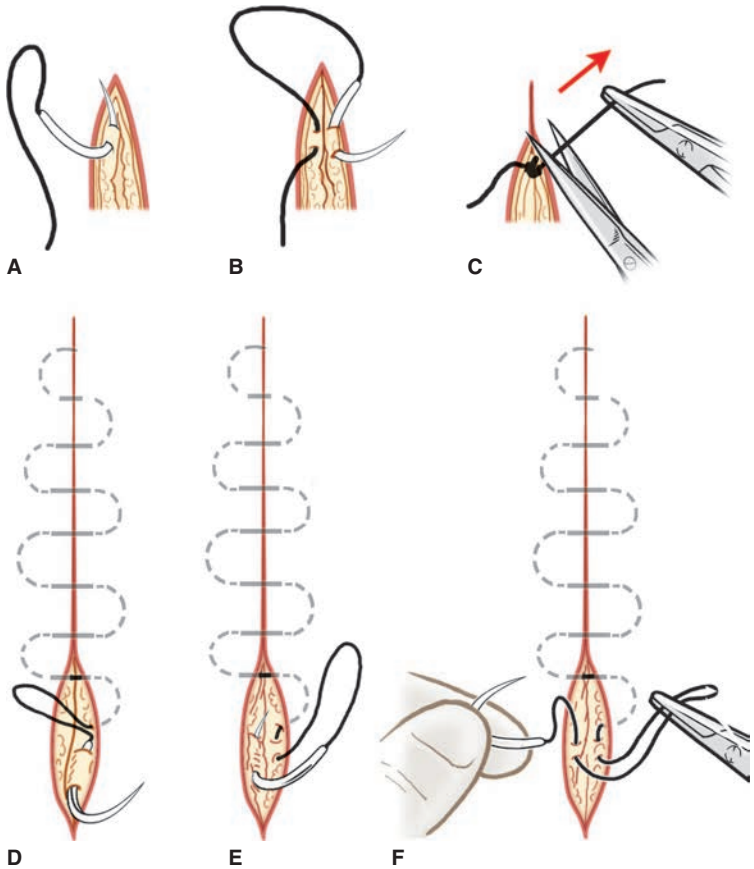

FIGURE 41-6. Continuous subcuticular sutures. **A, B,** and **C.** Place the first stitch into the dermis, just inside the laceration edge, as a buried knot. **D.** Place the continuous suture until the opposite end of the laceration is reached. **E.** The final throw should be left lax with a trailing loop of suture. **F.** The loop should be used as the "tail end" to perform an instrument tie. Tie three or four knots in the suture. Lift the free ends of the suture and cut them just above the knot. Apply adhesive tape across the laceration to help maintain the apposition of the wound. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures,* 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-18. New York, NY: McGraw-Hill, Inc.]

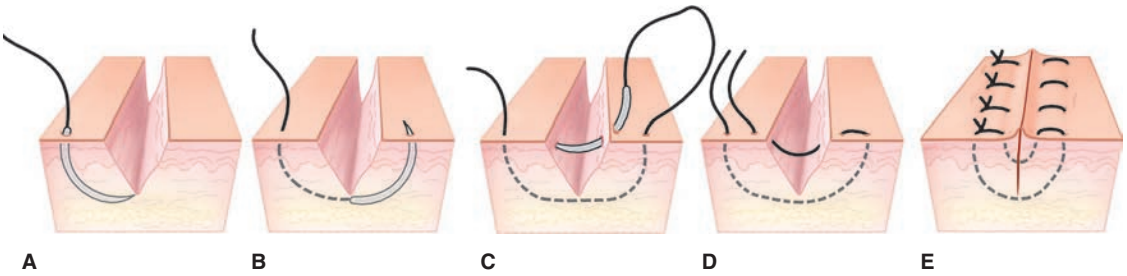

FIGURE 41-7. Vertical mattress suture. **A.** The needle should enter and exit the skin 1.0 to 1.5 cm from the wound edge. **B.** The needle should traverse the base of the wound and grasp a large amount of tissue. **C** and **D.** Reverse the needle. The second throw should enter and exit the skin approximately 2 to 3 mm from the wound edge. The first and second throws must be directly over each other and parallel. **E.** Tie the suture to approximate the wound edges. The first throw will close the wound base and relieve the tension at the skin surface. The second throw approximates and everts the skin edges. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-11. New York, NY: McGraw-Hill, Inc.]

technique passes the needle through the loop formed on the second side before typing the knot. A v-shaped pattern is created as the loop is pulled over the wound when the knot is tied on the initial side (**Figure 41-10**).[31]

A modification of this technique incorporates the loop into the knot.[32] After initial placement of the horizontal mattress suture, the end of the suture with needle attached is looped twice around the needle driver (**Figure 41-11**). The tip of the needle driver is passed through the loop to grasp the tail of suture. As the suture tail is pulled back through the loop, the suture looped around the needle driver slides off and the knot is placed over the wound, creating an x-shaped pattern (**Figure 41-12**).

The benefits of these modifications are increased pressure on the wound edges to enhance hemostasis, reduce dehiscence, promote extra wound edge eversion, and achieve precise epidermal edge apposition.

HORIZONTAL HALF-BURIED MATTRESS SUTURES

Horizontal half-buried mattress sutures are particularly well suited for closing the tip of skin flaps and stellate lacerations because they minimize strangulation of the blood supply to the tip. **The key to this stitch is that the needle and suture pass through the dermis of the tip and not the epidermis.** The needle is introduced percutaneously through one side of the wound, then horizontally through the tip at the level of the dermis. The suture is completed by exiting the skin through the other side and tying the knot (**Figure 41-13**). The stitch through the tip of the flap should be at the level of the mid dermis and close to the distal end of the tip to avoid burying of the tip beneath the adjacent wound edges. The stiches through the wound edges adjacent to the tip should exit and enter the wound at the same level of the middle of the dermis to prevent a step off between the wound edges and the tip.

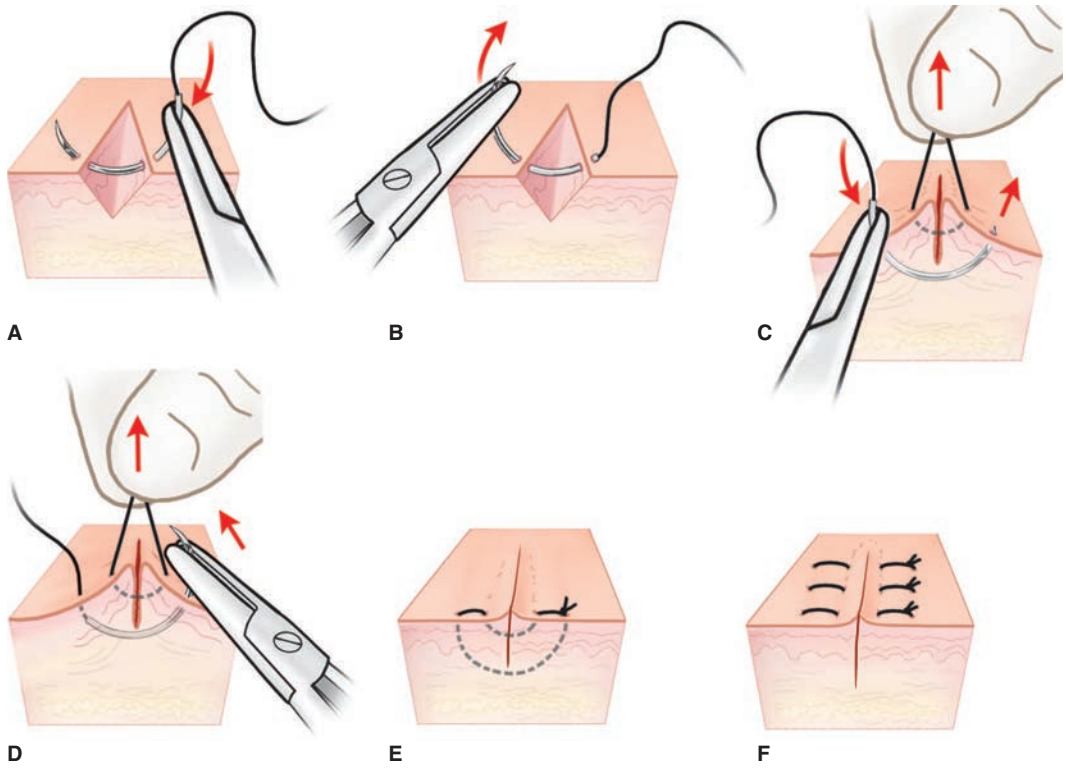

FIGURE 41-8. The "shorthand" vertical mattress suture. **A** and **B.** Place the first throw close to the lacerated wound edge to approximate the skin edges. **C.** Grasp and pull the suture to elevate the wound edges. This allows the needle to more easily take a large bite of tissue on the second throw. **D.** Place the second throw 1.0 to 1.5 cm from the wound edge. Release the suture. **E.** Tie the suture to approximate the wound edges and evert the skin surface. **F.** The final product looks exactly the same as the traditional vertical mattress suture. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-12. New York, NY: McGraw-Hill, Inc.]

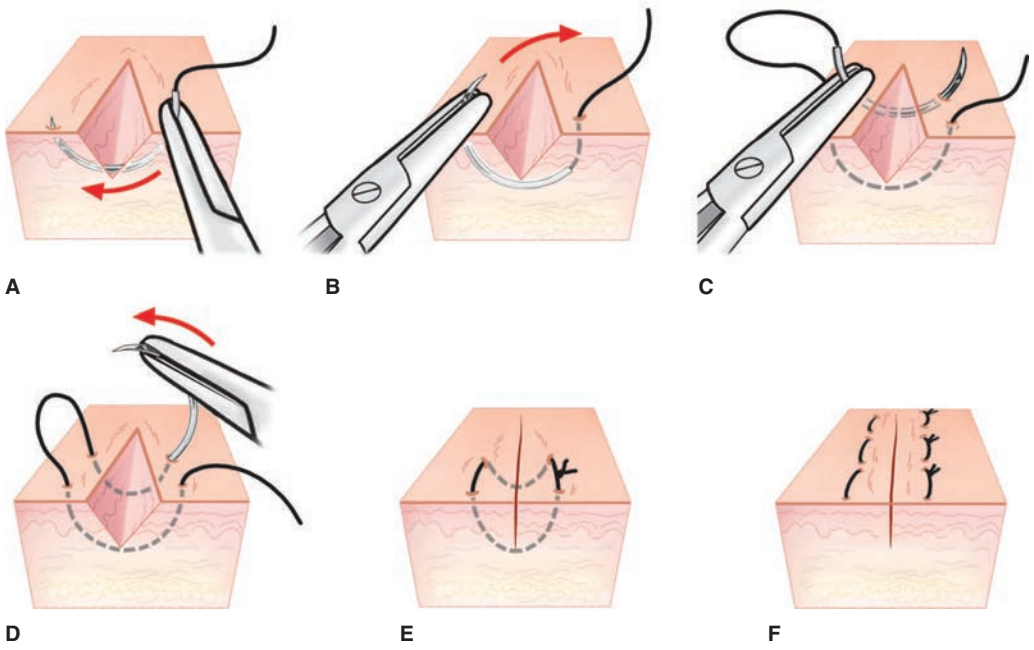

FIGURE 41-9. Horizontal mattress suture. **A.** The needle should enter and exit the skin 0.5 to 1.0 cm from the wound edge. **B.** The needle should traverse the base of the wound. **C.** Reverse the needle and make a second throw 0.5 cm from the first. **D.** The needle must enter and exit the skin and the wound edges so that the first and second throws are parallel to each other. **E.** Pull the free ends of the suture taut to oppose and evert the wound edges. **F.** The final result. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-14. New York, NY: McGraw-Hill, Inc.]

STAPLES

The major advantages of staples are their speed and relative ease of use. They are also cost-effective, especially when devices containing fewer staples are used in the ED, where most lacerations are relatively short. However, of all closure techniques, staples allow the least precision in wound approximation. As a result, **their use should be limited to linear, nonfacial lacerations**. Staples are particularly useful for scalp lacerations because the hair does not require clipping and staples are easier to locate than sutures for removal. However, deep sutures may be required to close lacerations of the galea aponeurotica, whereas percutaneous sutures are always desirable when hemostasis is difficult. In appropriate patients, staples have infection rates and cosmetic outcomes similar to sutures.[33-37] Staple removal is more painful than removal of sutures.[37]

There are few practical differences between the variety of stapling devices commercially available from the standpoint of the emergency practitioner. The key principle is to approximate the wound edges and align the centerline indicator of the stapler head so that the legs of the staple will straddle the wound an equal distance on each side (**Figure 41-14**). Touch the stapler lightly to the skin so that the staple comes out and pinches the wound edges together with eversion. **Pressing firmly downward can cause depression of the wound edges.** After

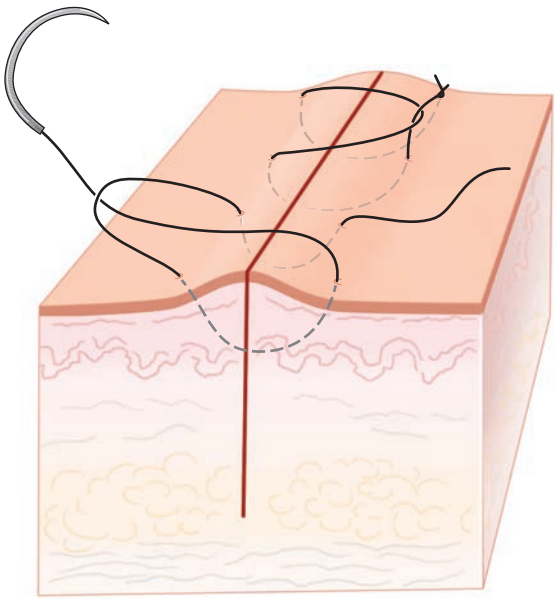

FIGURE 41-10. The standard horizontal mattress suture is placed, with 1- to 2-cm loop of suture left protruding on the second side. The suture needle is then passed through the loop before tying the knot on the initial side, thus pulling the loop across the wound creating a v-shape.

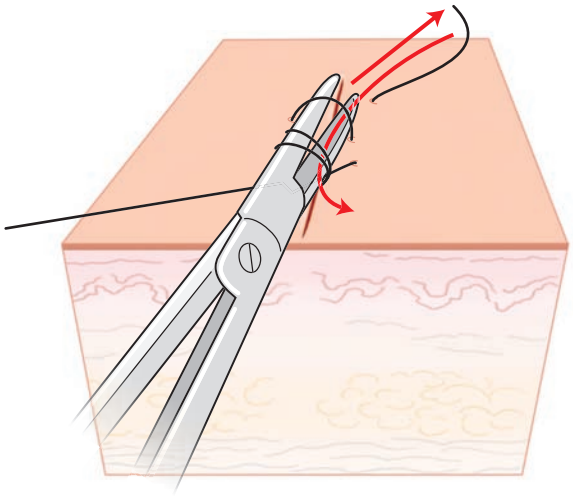

FIGURE 41-11. The standard horizontal mattress suture is placed, with 1- to 2-cm loop of suture left protruding on the second side. The end of the suture with needle attached is looped twice around the needle driver. The tip of the needle driver is passed through the loop to grasp the tail of suture and then pulled back out of the loop.

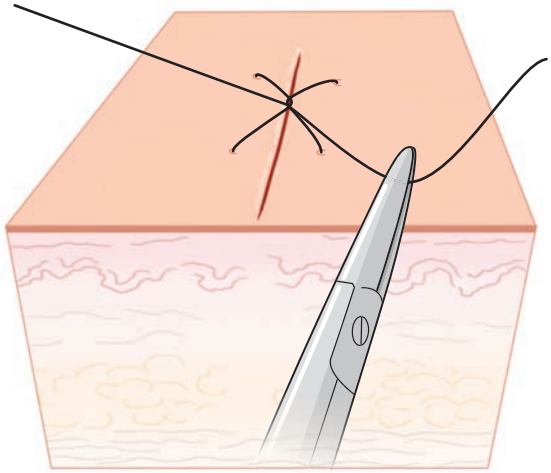

FIGURE 41-12. As the suture tail is pulled through the loop, the suture looped around the needle driver slides off and the knot is placed over the wound, creating an x-shaped pattern.

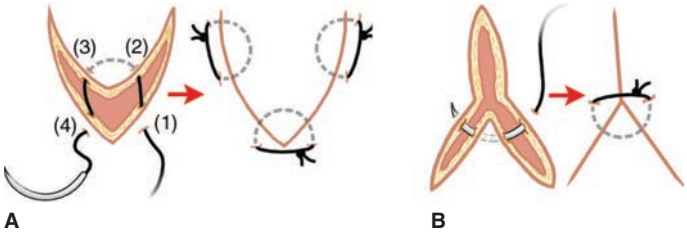

FIGURE 41-13. Half-buried horizontal mattress suture. **A.** To close a flap tip, place the first stitch percutaneously through the skin adjacent to the tip of the flap. Advance the needle horizontally through the dermal layer of the flap, the dermal layer of the skin adjacent to the tip of the flap, and out the skin adjacent to the tip of the flap opposite to where the stitch began. The needle must traverse the dermis of the flap and adjacent tissue at the same level of the dermis to properly approximate the wound edges. Gently pull on the free ends of the suture to approximate the flap against the adjacent skin edges. Tie and secure the suture in the usual manner. **B.** To close a stellate laceration, insert the needle through the skin of the largest flap. Advance the needle so that its tip exits the dermis. Continue to advance the needle through the dermis of each flap. The half-buried horizontal mattress stitch should encompass the tips of all the flaps. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-15. New York, NY: McGraw-Hill, Inc.]

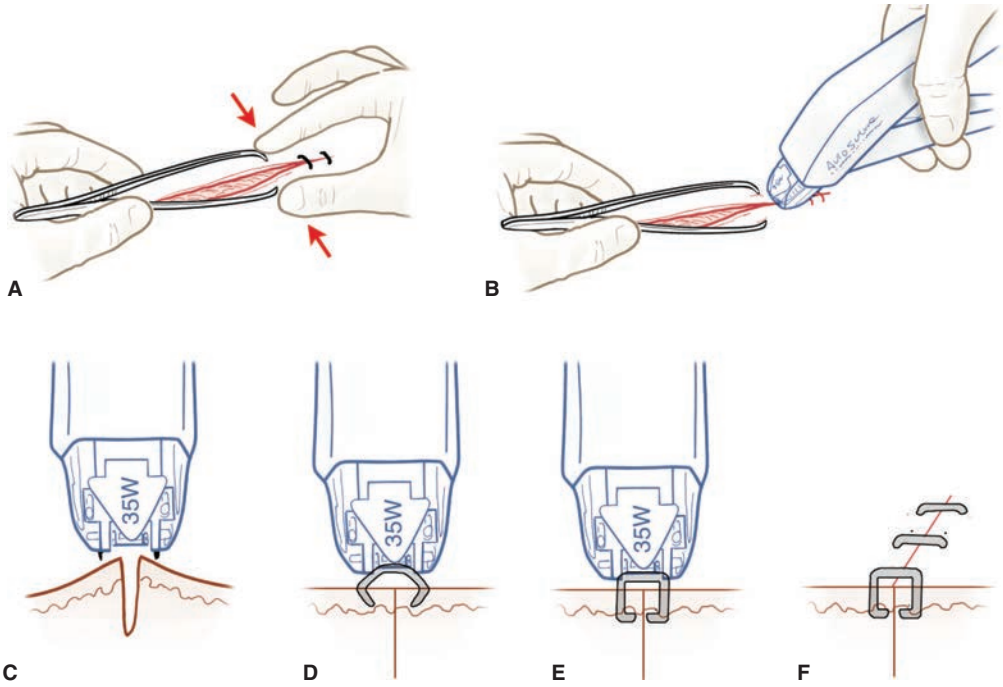

FIGURE 41-14. Laceration repair with staple closure. **A.** The wound edges are opposed and everted. **B.** The stapler is applied over the laceration. **C.** The stapler is applied over the everted wound edges. **D.** The plunger advances the staple into the wound margins. **E.** The anvil bends the staple into shape. **F.** The final result. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-26. New York, NY: McGraw-Hill, Inc.]

the staple is set, pull the stapler slightly backward to disengage. New stapling devices that allow placement of deep staples are available, but they have not been studied in the ED.

ADHESIVE TAPES

Adhesive tapes are the least reactive and most cost-effective of all wound closure devices.[38] Their application is simple, painless, and rapid, and they also do not require formal removal. However, adhesive tapes tend to slough off when exposed to any tension or moisture. As a result, their use is limited to very low-tension simple wounds or for closure of fragile skin subject to low tension, such as superficial skin tears. They are also of little use in noncompliant patients because they are so easy to remove.

To increase their adhesiveness, skin tapes should be used in conjunction with a liquid adhesive adjunct, such as tincture of benzoin or Mastisol®, that is gently painted on either side of the wound edges and allowed to dry until tacky. Because these adhesive adjuncts are toxic to wounds, avoid their introduction into the wound itself.

The tapes should be placed perpendicular to the wound edges approximately 2 to 3 mm apart. With long lacerations, the first strip of tape should be placed across the center of the wound followed by additional strips on either side of the wound center (**Figure 41-15**). To reduce the possibility of skin blistering or premature dislodgement, additional strips should be placed over the ends of the other strips, parallel to the laceration.

Simple skin tapes may also be used to reinforce lacerations after suture or staple removal. The cosmetic results and dehiscence rates after closure of small (<4 cm) and superficial facial lacerations with tapes are similar to those with cyanoacrylate tissue adhesives.[39] A version of skin tape composed of two independent parts, each with an adhesive underside and multiple interlocking filaments attached to pulling ends, is useful for simple wound closure (Steri-Strip® S Surgical Skin Closure; 3M, St. Paul, MN; **Figure 41-16**).[40,41]

CYANOACRYLATE TISSUE ADHESIVES

The cyanoacrylate tissue adhesives are liquid monomers that polymerize into a stable bond when they come into contact with moisture.[42] The adhesive is applied topically to the epidermis across the apposed wound edges, forming a strong bridge that holds the wound closed. The adhesive sloughs off in 5 to 10 days as the skin renews itself. The tissue adhesives offer many advantages over other wound closure methods. They may be applied rapidly and painlessly to any easily approximated laceration. Because they slough off spontaneously, they do not require removal. The cyanoacrylates form an occlusive dressing that serves as a barrier to microbial penetration. They have antibacterial effects in vitro and reduce infection rates in experimental contaminated wound models in animals.[43]

The cyanoacrylate tissue adhesives are similar in strength to 4-0 poliglecaprone subcuticular sutures, but weaker than staples.[44] Tissue adhesives should not be used alone for high-tension wounds nor should they be used for wounds subjected to varying dynamic tension, such as over a moving joint. However, they can be used in conjunction with deep dermal sutures and/or immobilization aimed at reducing wound tension. A variety of octyl- and butyl-based cyanoacrylate adhesives (alone or in combination) are now commercially available. The tensile strength and surface characteristics of octyl- and butyl-cyanoacrylate differ (**Table 41-6**).[45,46] Octyl-cyanoacrylate is generally stronger and more flexible than butyl-cyanoacrylate, allowing its use on irregular

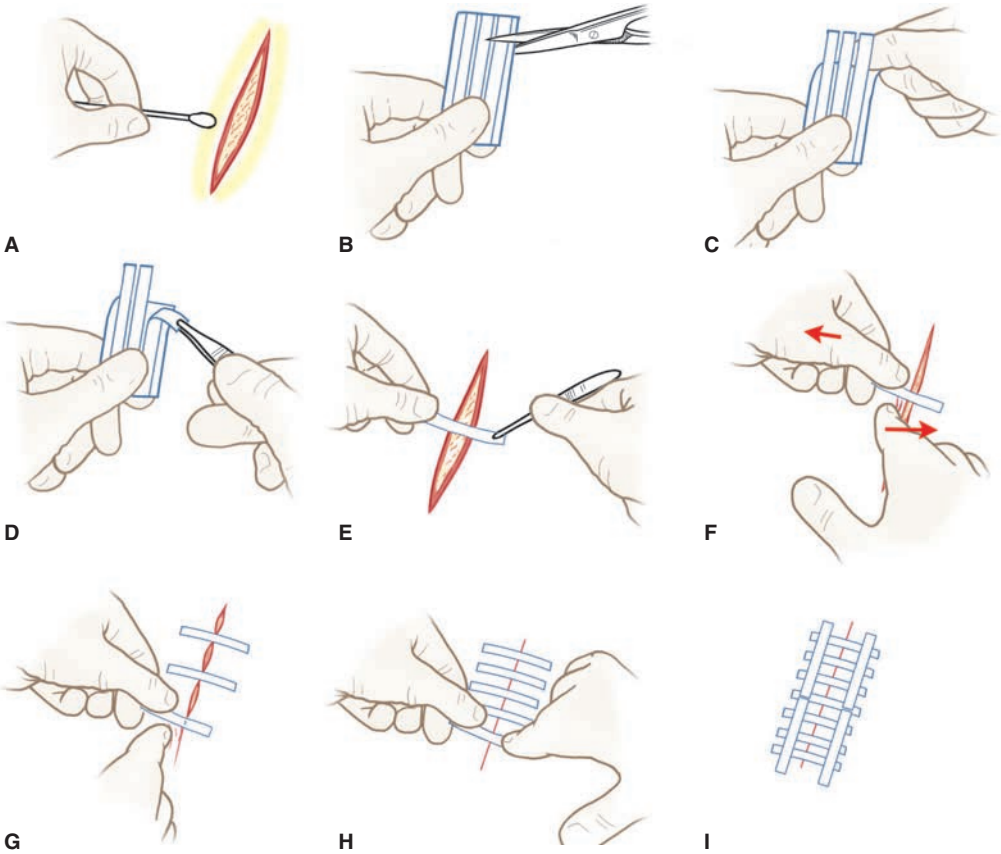

FIGURE 41-15. Laceration repair with adhesive tapes. **A.** After the initial cleansing of the skin, clean the skin surface with acetone or alcohol to remove any surface oils. Allow the skin to dry. Apply benzoin solution to the skin on both sides of the wound with a cotton applicator. **B.** Cut the skin closure tapes to the proper length. **C.** Gently tear the end-tab off the back of the card to prevent the strips from deforming. **D.** Remove a strip from the card. **E.** Firmly secure the tape to one side of the wound. **F.** Use the nondominant hand to oppose the wound edges as the tape is brought over and secured to the skin on the opposite wound edge. **G** and **H.** Place additional tapes at 2- to 3-mm intervals until the wound edges are opposed. **I.** Place pieces of tape across the tape edges to prevent premature removal and skin blistering from the tape ends. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-23. New York, NY: McGraw-Hill, Inc.]

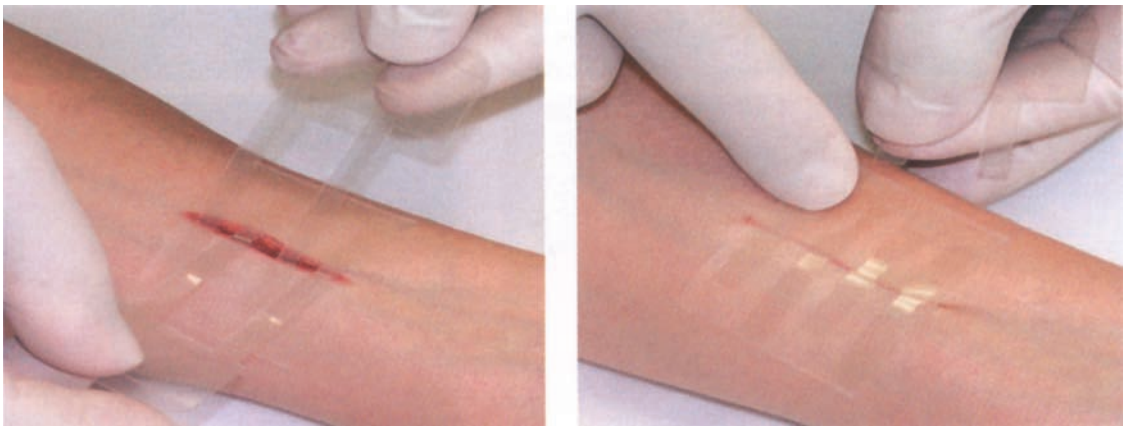

FIGURE 41-16. Application of Steri-Strip® S Surgical Skin Closure (3M, St. Paul, MN). **A.** The two adhesive pads are applied to the two sides of the wound approximately 1 to 2 mm from the wound edges. **B.** The skin edges are drawn together by pulling on the clear pulling tabs across the wound at a 45-degree angle in opposite directions approximating and aligning the wound edges.

surfaces and long lacerations. The mechanical characteristics of the adhesive are also determined by a number of additives such as chemical initiators and plasticizers.

Wound closure with the tissue adhesives is faster than with other wound closure methods, is cost-effective compared with sutures, and has comparable rates of infection and ultimate cosmetic appearance.[47-50] Patient-reported pain scores and physician-reported procedure time are lower with tissue adhesives. However, there is a small increase, about 4%, in wound dehiscence using tissue adhesives,[48] emphasizing the need to limit the use of adhesives to low-tension wounds.

Few studies have directly compared the various cyanoacrylate tissue adhesives against each other. For closure of short, simple facial lacerations in children, comparable results are seen with either type of cyanoacrylate.[51] For closure of pediatric operative wounds subject to more tension than facial lacerations, octyl-cyanoacrylate had a lower wound dehiscence rate.[52]

To ensure optimal results, tissue adhesives should be used only when laceration edges are easily approximated with the practitioner's hands, forceps, or tape. An assistant can maintain constant and meticulous wound edge apposition while the adhesive is applied. With octyl-cyanoacrylate, the adhesive is carefully expressed through the tip of the applicator and gently brushed over the wound surface parallel to the wound edges in a continuous, steady motion (**Figure 41-17A**). **The adhesive should cover the entire wound and extend 5 to 10 mm on either side of the wound edges.** A single layer is applied and allowed to dry for 30 to 45 seconds. With butyl-cyanoacrylate, the adhesive is applied from the tip of the applicator in discrete drops along the wound edges, similar to "spot welds" (**Figure 41-17B**), or as bands across the wound (**Figure 41-17C**).

TABLE 41-6 Comparison of Butyl- and Octyl-Cyanoacrylate

	Octyl-Cyanoacrylate	Butyl-Cyanoacrylate
Number of carbons in side chain	8	4
Bursting strength	High	Moderate
Plasticizers that enhance flexibility	Present	Absent
Water resistance	Moderate	Minimal
Need for refrigeration	No	Yes
Clinical experience	Short and long incisions and lacerations	Limited to incisions and lacerations up to 8 cm
Viscosity	High	Low
Cost	Moderate	Slightly less than octyl-cyanoacrylate
Polymerization time	30–45 s	5–10 s
Working time once applicator opened	2–3 min	Unlimited

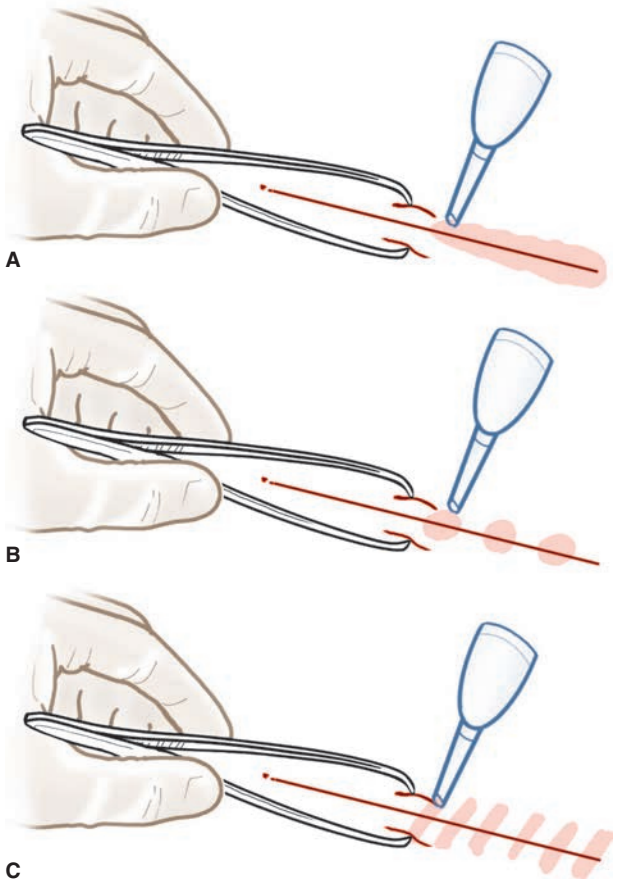

FIGURE 41-17. Laceration repair with tissue adhesives. **A.** Apply octyl-cyanoacrylate in a single layer along the wound edges, extending 5 to 10 mm on either side. With butyl-cyanoacrylate, the adhesive may also be applied (**B**) in spots over the laceration or (**C**) as bands across the laceration. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 117-8. New York, NY: McGraw-Hill, Inc.]

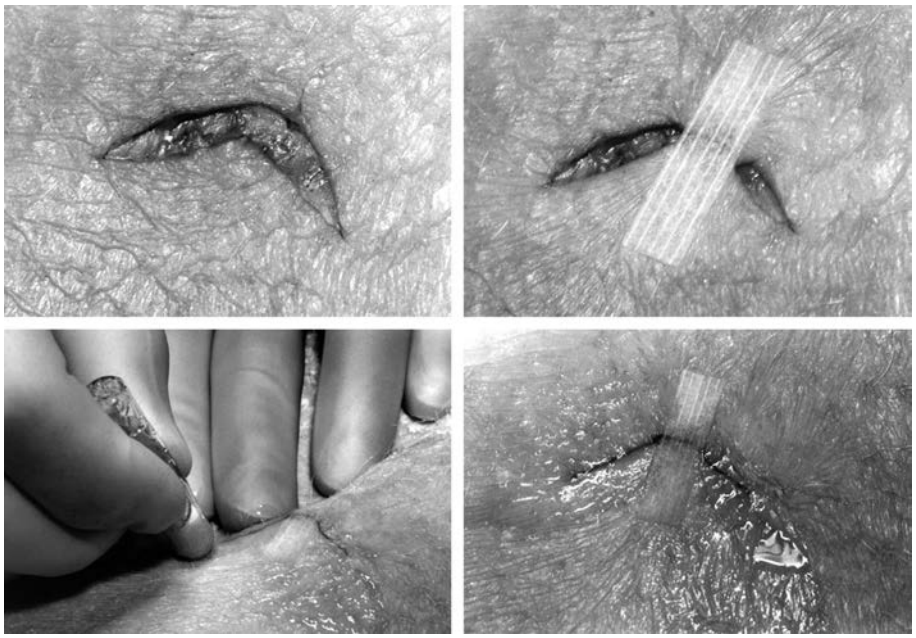

FIGURE 41-18. Closure of a long or complex laceration is achieved by applying adhesive tape to approximate the wound edges followed by application of the tissue adhesive over the approximated wound and tape.

With long or complex lacerations, adhesive tape can be used to approximate the wound edges, making closure with a tissue adhesive easier (**Figure 41-18**). Application of a tissue adhesive *on top of adhesive tape* also results in greater wound-bursting strength than either device alone.[53] A combination of a mesh tape and tissue adhesive has recently become available and may be especially useful on very long lacerations.[54] However, its cost may be prohibitive in the ED. Care in application will reduce some of the common problems associated with tissue adhesives (**Table 41-7**).

HAIR APPOSITION

Simple scalp wounds, without contamination or active bleeding, may be closed via the hair apposition technique.[55,56] This technique is an efficient alternative to more traditional methods of closure, with potentially fewer complications, less pain to the patient, and less overall cost.[57,58] Contraindications to hair apposition closure include long lacerations (e.g., >10 cm), grossly contaminated wounds, uncontrolled bleeding, wounds that gape open and cannot be closed without significant tension, and hair strands adjacent to the wound that are less than 3 cm in length.

After wound irrigation and control of bleeding, select and twist together three to seven strands of hair at least 3 cm in length that lie close to the edge on one side of the wound. Repeat this process directly opposite on the other side of the wound. Then twist these two hair bundles in a full 360-degree revolution and secure the intertwined hair bundles by applying a few drops of tissue adhesive. Repeat this process as needed to close the full length of the laceration (**Figure 41-19**). The patient will not need a routine return visit because the tissue adhesive will flake off and the hair will unravel in about a week.

TABLE 41-7 Avoiding Potential Pitfalls of Tissue Adhesives

Problem	Ways to Avoid the Problem
Runoff	Position patient with wound parallel to floor. Use high-viscosity adhesive. Apply small, controlled amount of adhesive.
Spillage into eyes	Cover eyes with moist gauze barrier. Position patient so adhesive will not run into the eye. For eyebrow and forehead lacerations, place the patient in the Trendelenburg position. For lacerations on the cheek and lower face, place the patient in the reverse Trendelenburg position. Apply petrolatum-based ointment on the eyelashes before applying adhesive.
Wound dehiscence	Avoid adhesive use for high-tension wounds. Reduce exposure to friction or moisture. Use deep sutures or immobilization for high-tension wounds. Do not introduce adhesive into wound.
Wound infection	Use adhesives only for properly selected wounds. Use proper wound preparation, including irrigation, exploration, and, when necessary, debridement. Use proper application technique.
Getting stuck to the wound	Practice expressing small amounts of adhesive and controlling runoff. Alternate the hand used to oppose wound edges prior to complete polymerization of the adhesive.

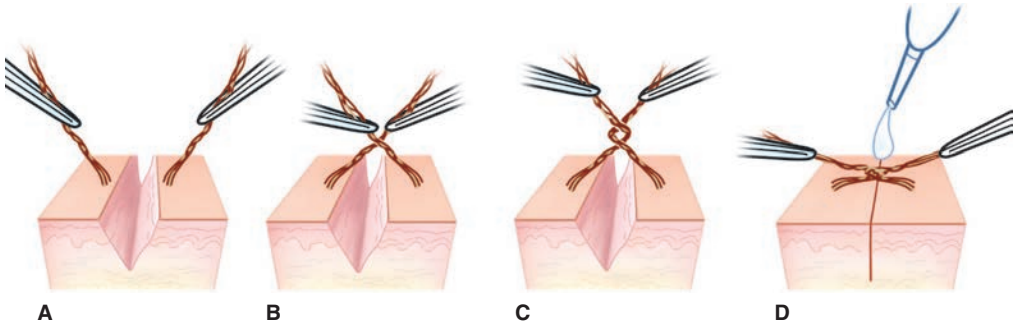

FIGURE 41-19. The hair apposition technique to close a scalp laceration. **A.** Grasp hairs on each side of the laceration. Twist the hair strands on each side of the laceration to form a single "rope." **B.** Cross the hair ropes to opposite sides of the laceration. **C.** Twist the two "ropes" of hair together to close the wound and appose the wound edges. **D.** Apply tissue adhesive to the twisted hair and apposed skin segment of the laceration. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd edition. Copyright © 2019 by Eric F. Reichman, PhD, MD, Figure 116-29. New York, NY: McGraw-Hill, Inc.]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 42

Face and Scalp Lacerations

Wendy C. Coates

INTRODUCTION

Facial wounds are the most cosmetically apparent of all wounds and therefore warrant careful evaluation and meticulous repair technique for the best possible outcome. Most facial and scalp lacerations can be closed by the emergency physician, but consult with specialists if the technical aspects of closure are complex or exceed the skill of the individual practitioner.

Three common principles guide repair of facial and scalp lacerations.[1] First, cleanse, irrigate, and remove foreign material to minimize infection. Second, limit debridement of skin edges because the excellent blood supply enables tissues to recover that may initially appear nonviable. And third, consider regional nerve blocks or topical anesthesia if local anesthetic infiltration would distort anatomy or hinder wound edge alignment (see Chapter 36, "Local and Regional Anesthesia").[2]

Use nonabsorbable monofilament suture for facial skin. Rapidly absorbable suture and tissue adhesives are alternatives in selected locations and in some patients (e.g., patients who are unlikely to return for suture removal or selected wounds in children) (**Table 42-1**).[3,4] Use absorbable suture for mucosa and fascial layers. To minimize scarring, place percutaneous sutures on the face 1 to 2 mm from the wound edges, 2 mm apart, with everted edges. Place mucosal sutures 2 to 3 mm from the wound edges, 2 to 3 mm apart, and superficial including only the mucosa and not the underlying muscle or fascia. Magnification with surgical loupes may facilitate more accurate suture placement in facial wounds.

Ask about the possibility of domestic violence in patients with facial injuries, and notify appropriate authorities if suspected (**Table 42-2**).[5-8]

TABLE 42-1 Indications for Tissue Adhesives on the Face

- Minimal tension
- Not a hair-covered area
- Epidermal closure only (no mucosa)

PATHOPHYSIOLOGY

Facial and scalp wounds are most often caused by a combination of sharp and blunt mechanisms. Lacerations caused by sharp objects likely have discrete edges, but may extend deeply and involve underlying structures, such as the muscles of facial expression, nerves, and arteries. Wounds caused by blunt forces burst the skin open, damage cells, and produce tissue edema, all of which slow the wound-healing process and increase risk for infection. Blunt forces are also more likely to cause diffuse underlying damage, such as fractures of the facial bones or skull.

In most patients with isolated facial trauma resulting in lacerations, the incidence of facial fractures is low, especially in children.[8] However, in multiply injured patients, suspect underlying fracture in facial lacerations involving the infraorbital area, zygoma, nose, lips, and intraoral mucosa; perform a careful physical examination; and consider facial CT scans.[9,10]

Facial and scalp lacerations have a low incidence of postrepair infection, so **primary closure can usually be done in wounds up to 24 hours after the injury,[11-13] including most bite wounds.**[14,15] The presence of foreign bodies, such as soil, glass, or wood fragments, complicates wound healing.[13]

SCALP AND FOREHEAD

ANATOMY

Both the scalp and forehead overlie bone with little cushioning fat and have thick skin (**Figure 42-1**). The one difference is that the scalp has abundant hair follicles and sebaceous glands. Three branches of the external carotid artery (occipital, superficial temporal, and posterior auricular) and two branches from the internal carotid artery (supraorbital and supratrochlear) provide a rich blood supply to the scalp and forehead. The fibrous dermal tissue limits vessel retraction after injury, so significant hemorrhage can result from an arterial laceration. The potential space between the pericranium (periosteum covering the external surface of the skull bones) and the galea aponeurosis that allows for easy movement of the scalp over the cranium also enables hematoma and infection to collect in this subaponeurotic space and spread to involve the entire forehead and scalp. This high degree of mobility sometimes leads to a scalping injury, in which a large segment of the scalp is torn off in one piece.

TABLE 42-2 Maxillofacial Injuries and Domestic Violence in the ED

- Most victims of domestic violence have maxillofacial injuries.
- Women are more commonly affected than men.
- Fist is most common weapon.
- Left side of face is most common site of injury (from right-hand-dominant assailants).
- Nasal bone is commonly fractured.

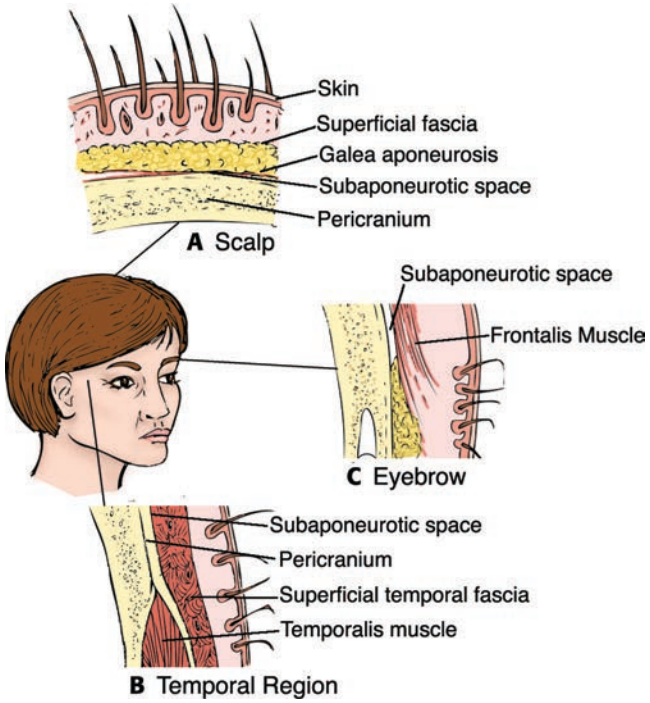

FIGURE 42-1. Layers of the scalp.

CLINICAL FEATURES

For some patients with scalp and forehead lacerations, the wound may be only a minor part of the overall injury. Perform a focused assessment looking for intracranial injury before definitive wound care. Control scalp hemorrhage by applying direct pressure, clamping the involved vessel(s) at the wound edges (e.g., using Raney clips; see Chapter 40, "Wound Preparation"), or placing a figure-of-eight suture at the bleeding wound edge.[16]

Inspect scalp lacerations, and gently palpate with a gloved finger to determine depth and to identify galeal laceration or depressed skull fracture. Evaluate palpable depressions with a CT scan. Orientation of forehead lacerations has important cosmetic implications. In general, forehead wounds that fall parallel to the lines of skin tension (and perpendicular to muscle fibers) yield the best cosmetic results. For example, the horizontal lines seen on the forehead when the brow is raised are perpendicular to the frontalis muscle underneath (**Figure 42-2**).

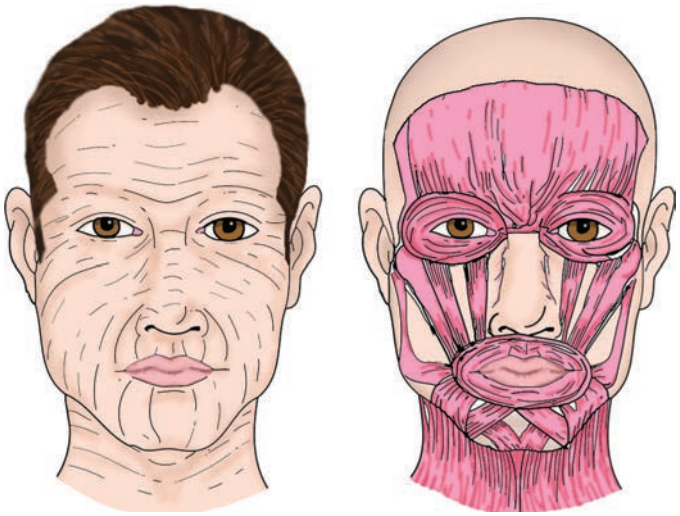

FIGURE 42-2. Skin tension lines. Skin tension lines are perpendicular to underlying muscles.

TREATMENT

Anesthesia can be provided by topical, local, or regional infiltration. Topical agents alone, such as lidocaine-epinephrine-tetracaine or lidocaine-prilocaine (EMLA®), provide adequate anesthesia in many patients and reduce the pain of supplemental local anesthetic injection.[17-22] Local anesthetics containing epinephrine are often used in highly vascular wounds to help control hemorrhage from small vessels. Children may need sedation for wound repair (see Chapter 115, "Pain Management and Procedural Sedation in Infants and Children").

Irrigate to reduce contamination and lessen the risk of wound infection. However, in resource-poor situations, because the face and scalp are highly vascular, clean-appearing wounds have been repaired using adhesive strips, without prior cleansing and irrigation.[23]

Repair of Scalp Lacerations Do not shave hair before wound closure, as shaving increases the risk of infection.[24] To visualize the injured area, brush the hair aside or matt it down with an ointment, such as bacitracin zinc or petrolatum.[25] If visualization is still difficult, trim the adjacent scalp hair with scissors. Suture accessible lacerations of the galea[26] to prevent formation of a subgaleal hematoma (**Table 42-3**).[27]

Close scalp lacerations with surgical staples or simple interrupted percutaneous sutures using nonabsorbable monofilament or rapidly absorbable material.[28-31] Leave suture tails long, and use sutures of a color different than the hair for easy suture removal.

Hair braiding is a technique combining hair apposition and tissue adhesive.[25,32,33] In this technique, bring together three to seven strands of hair from opposite sides of the wound, twist the strands once, and secure them with a drop of tissue adhesive. This technique requires the wound edges to approximate with little tension, so subcutaneous sutures are sometimes necessary before hair apposition is used to close the skin.

Consider a pressure dressing over a deep scalp laceration for the first 24 hours after repair, to prevent wound hematoma formation.

Repair of Forehead Lacerations Forehead lacerations are categorized as either superficial, meaning the **frontalis muscle** is not injured, or deep, indicating the frontalis muscle is involved. Start repair by using key stitches to align skin tension lines and the hairline (**Figure 42-3**). For superficial lacerations, close the skin with 6-0 nonabsorbable interrupted suture or tissue adhesive.[26,34,35] For deep lacerations, close the muscle layer to avoid noticeable defects, especially when the facial muscles of expression are involved. Close the muscle fascia with buried 5-0 absorbable suture. The dermis may be approximated with a buried subcuticular stitch. Close the epidermal layer with 6-0 nonabsorbable sutures in a simple, interrupted fashion; with skin closure strips; or with tissue adhesive (Table 42-3).[36] Adhesive strips or tissue adhesives are useful if the patient is at risk for keloids or hypertrophic scars.

Repair of Eyebrow Lacerations Do not clip or shave eyebrows because their delicate contour and form are valuable landmarks for wound edge reapproximation. Debridement of loose or nonviable skin in the eyebrow region should be minimal and, if necessary, done so that the remaining hairs preserve as much as possible of the original length, width, and curve of the eyebrow. Use care to align the hair margins. Use sutures that are a different color from the hair and leave long tails to facilitate removal.

EYELIDS

ANATOMY

The eyelid is composed of five layers: skin, subcutaneous tissue, orbicularis oculi muscle, tarsal plate, and conjunctiva. The muscular layer controls lid closure and forms both the medial and lateral canthus. Fibers of the orbicularis oculi wrap around the lacrimal system. Nerve supply to the eyelid arises from the temporal and zygomatic branches of the facial nerve. The tarsal plate forms the main body of the lower half of the lid and consists of elastic tissue in a dense matrix of connective tissue. Embedded in the tarsal plate are the meibomian glands, which open onto the white line just in front of the conjunctival edge of the lid margin. In the lid margin, the eyelashes are arranged in irregular rows with their follicles extending obliquely into the tarsal plate.

TABLE 42-3 Suturing Guidelines for the Face and Scalp

Area	Suture	Size	Anesthetic	Removal
Scalp				
Galea	Absorbable	4-0	Local	Not removed
Skin	Staples	Standard	Local	14 d
	Nonabsorbable monofilament	4-0	Local	14 d
	Rapidly absorbing	4-0	Local	Not removed
Forehead				
Muscle fascia	Absorbable	4-0	Local or supraorbital nerve block	Not removed
Skin	Nonabsorbable monofilament	5-0 or 6-0	Local or supraorbital nerve block	5 d
	Tissue adhesive	May need deep layer	—	Not removed
Cheek and face				
Muscle fascia	Absorbable	4-0	Local or infraorbital nerve block	Not removed
Skin	Nonabsorbable monofilament	6-0	Local or infraorbital nerve block	5 d
	Rapidly absorbing	6-0	Local or infraorbital nerve block	Not removed
	Tissue adhesive	May need facial layer closure	—	Not removed
Eyelids				
Skin	Nonabsorbable monofilament	6-0 or 7-0	Supra- or infraorbital nerve block	3 d
Nose				
Mucosa	Rapidly absorbing	4-0	Intranasal	Not removed
Cartilage	Absorbable (if necessary)	5-0	Intranasal	Not removed
Skin	Nonabsorbable monofilament	6-0	Local or intranasal	3–5 d
Ears				
Skin	Nonabsorbable monofilament	6-0	Auricular block	5 d
Perichondrium	Absorbable	5-0	Auricular block	Not removed
Lips				
Mucosa	Rapidly absorbing	5-0	Local, infraorbital, mandibular, or mental nerve block	Not removed
Muscle fascia	Absorbable	4-0 or 5-0	Local, infraorbital, submandibular, or mental nerve block	Not removed
Skin	Nonabsorbable monofilament	6-0	Local, infraorbital, or mental nerve block	3–5 d

The lacrimal system begins at the upper and lower puncta that transition into the canaliculi. The canaliculi travel medially into the lacrimal sac that extends inferiorly to the nasolacrimal duct responsible for tear drainage into the nose (**Figure 42-4**).

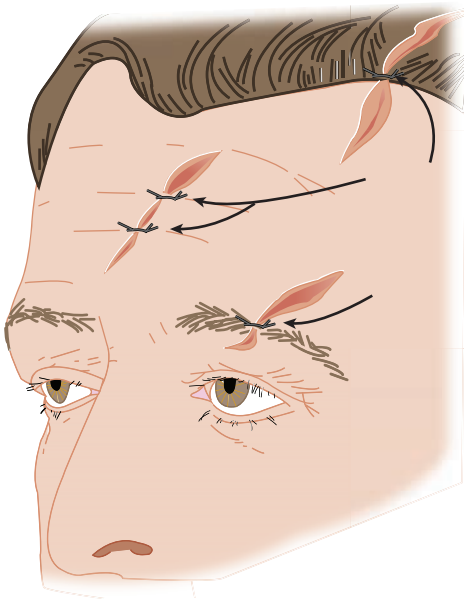

FIGURE 42-3. Key stitches in the forehead to align natural skin tension lines and cosmetically important landmarks.

CLINICAL FEATURES

The structures surrounding the eye and eyelids are delicate as well as cosmetically and functionally important. The eyelids are thin and offer limited protection from injuries to the globe, so **examine the eye's structure and function before laceration repair**. Once the integrity and function of the globe and orbital structures are verified, examine the lid for involvement of the canthi, the lacrimal system, or penetration through the tarsal plate or lid margin. **Eyelid injuries within 6 to 8 mm of the medial canthus are at risk for canalicular laceration, especially if associated with medial wall blowout fractures.**[37] Refer the following injuries to an ophthalmologist or oculoplastic specialist: (1) injuries involving the inner surface of the lid, (2) wounds across lid margins, (3) injuries to the lacrimal duct, (4) wounds associated with ptosis, or (5) injuries extending into the tarsal plate (**Figure 42-5**).

Poor repair of the inside surface of the eyelid can lead to scar formation and persistent corneal irritation. Imprecise approximation of the lid margins leads to notching. Failure to recognize and properly repair the lacrimal system can result in chronic tearing (epiphora). Wounds through the tarsal plate or with ptosis require careful closure of the orbicularis oculi to preserve normal eyelid appearance. In general, wounds that are superficial, and especially those parallel to the lid margins, may be carefully repaired by the emergency physician.

TREATMENT

After topical anesthesia, gently irrigate the wound with normal saline. For closure, use 6-0 or 7-0 nonabsorbable monofilament for simple interrupted percutaneous sutures. Avoid deep penetration of the needle through the lid and into the underlying globe. Do not use tissue

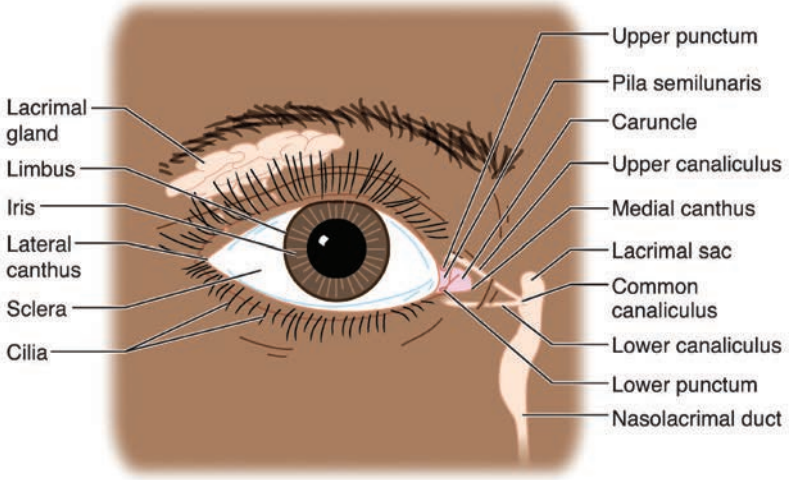

FIGURE 42-4. Periorbital anatomy.

adhesive near the eye, as adhesives may abrade the cornea or bond the lids together.[38] If tissue adhesive inadvertently finds its way onto the globe, instill topical ophthalmic anesthetic drops to numb the cornea and conjunctiva, apply ophthalmic erythromycin ointment to loosen the adhesive, and remove loose pieces of adhesive with cotton swabs.[39] If the eyelids are unintentionally bonded, do not force the eyelids open. A conservative approach appropriate in children is to wash the lids thoroughly with warm water and apply an eyepatch; the tissue adhesive will loosen in 1 to 4 days, releasing the bond. Surgical debridement with trimming of the eyelashes to remove the glue is an alternative in adults and children under sedation.[39,40]

NOSE

ANATOMY

The nose is especially vulnerable to blunt trauma, and nasal fracture is the most common fracture in victims of domestic violence and assault.[7] The nose is composed of cartilaginous and osseous structures that support the overlying skin and musculature and the underlying mucosa. It is separated into halves by the septum. Two C-shaped alar cartilages that are covered directly by skin form the tip of the nose. The interior of the nose is covered by specialized skin with mucus-producing cells and

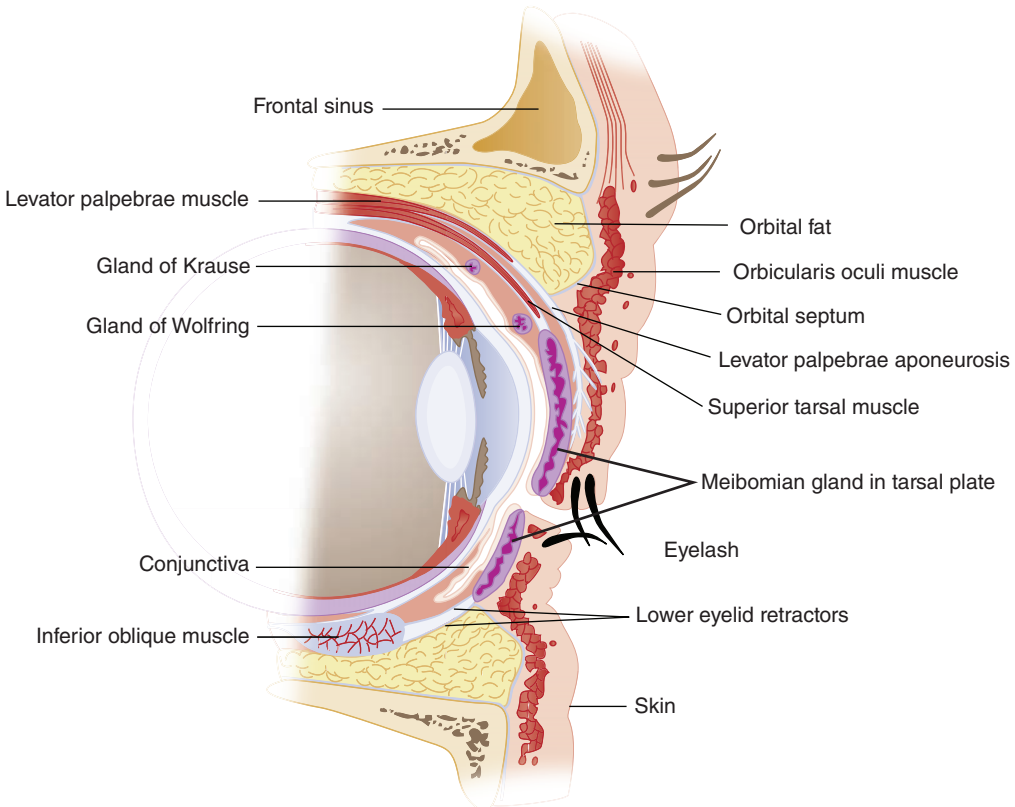

FIGURE 42-5. Cross-section of the eyelid. [Reproduced with permission from Riordan-Eva P, Augsburger JJ, eds: *Vaughn & Asbury's General Ophthalmology*, 19th ed. Figure 1-22, New York, NY: McGraw-Hill, Inc.; 2018.]

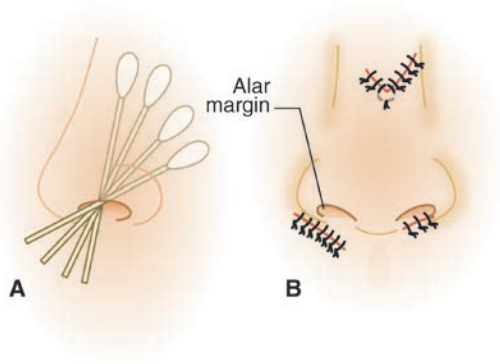

FIGURE 42-6. The nose. **A.** Nasal anesthetic technique using cotton-tipped applicators. **B.** Frontal view showing closure of skin edges.

thick, long hairs near the end, whereas the proximal portion of the nasal lining is made up of ciliated pseudostratified columnar epithelial cells.

CLINICAL FEATURES

The most important assessment of nasal lacerations is to determine their depth and the involvement of the deeper tissue layers and septum.[41] Exposed cartilage or penetration through all tissue layers increases the risk of infection. Inspect the nasal septum and look for discolored lateral bulging indicating a septal hematoma. This hematoma develops between the cartilage and its protective mucoperichondrial layer and may produce complications such as (1) permanent thickening of the septum, causing partial airway obstruction of the nasal passage; (2) necrosis and subsequent erosion of the septum, resulting in communication between the nasal passageways; or (3) septal erosion leading to a saddle-nose deformity. With direct blunt trauma to the nose, assess for a cribriform plate fracture with cerebrospinal fluid rhinorrhea.

TREATMENT

Epinephrine-containing local anesthetics are acceptable for infiltrative anesthesia on the nose.[42] Topical application of lidocaine into the nasal cavity may provide sufficient anesthesia for local wound repair. Insertion of multiple cotton-tipped swabs or plain nasal packing gauze soaked in 4% lidocaine solution is usually sufficient (**Figure 42-6A**). After several minutes in place and before repair, remove the swabs or gauze.

Close superficial lacerations to the skin layer with 6-0 nonabsorbable monofilament simple interrupted sutures. Close lacerations over exposed cartilage promptly. Preserve any small pieces of loose cartilage under the skin for use in future revision.

If the laceration extends through all tissue layers and involves the nostril, begin closure with a 5-0 nonabsorbable monofilament suture that aligns the skin surrounding the entrance to the nasal canals at the alar margin (**Figure 42-6B**). Initially, leave the ends untied and long to facilitate the closure of the deeper structures. *Gentle* traction on this suture facilitates alignment of the mucosa and cartilage layers during placement of subsequent sutures. Close the mucosal layer with 5-0 rapidly absorbable interrupted sutures, and reirrigate the area gently from the outside. Placement of sutures directly into the cartilage is rarely needed; in most cases, closure of the overlying skin is usually sufficient to align the cartilage. If necessary to align cartilage pieces, place a minimal number of 5-0 absorbable sutures through the cartilage. Reevaluate the initial stitch at the alar margin, and then tie it. Finally, suture the remainder of the skin with 6-0 nonabsorbable monofilament material close to the wound edges. With extensive wounds, consider a loose anterior nasal pack with antibiotic-impregnated gauze to prevent scar contracture.

Small unilateral septal hematomas can often be aspirated through an 18-gauge needle. Larger hematomas require an incision in the septal mucoperichondrium overlying the hematoma (**Figure 42-7**).[43] After hematoma evacuation, place an anterior nasal pack to discourage

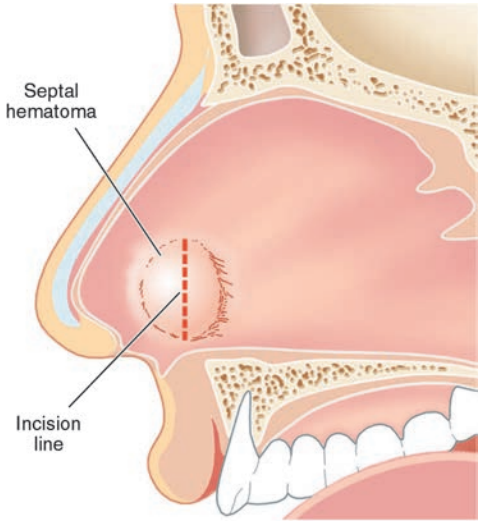

FIGURE 42-7. Incision for drainage of septal hematoma. Septal hematoma with markings for a vertical incision through the mucoperichondrium. [Reproduced with permission from Reichman EF, ed: *Reichman's Emergency Medicine Procedures*, 3rd ed. Figure 204-5. Copyright © 2019 McGraw-Hill Education. All rights reserved.]

reaccumulation of the hematoma. Bilateral hematomas are often drained in the operating room. There is no evidence to support the use of prophylactic antibiotics after nasal cartilage injury or septoplasty with anterior nasal packing.[44,45]

EARS

ANATOMY

The external ear begins with the external auditory canal and extends to the fibrocartilaginous framework of the auricle and the soft fatty tissue of the earlobe. The blood supply to the ear arises from the superficial temporal and posterior auricular arteries. The majority of the sensory innervation is from the anterior and posterior branches of the greater auricular nerve. **The auricular branches of the vagus nerve supply the posterior wall of the external auditory canal, so lacerations that involve this area cannot be anesthetized with auricular nerve blocks.**

CLINICAL FEATURES

Lacerations caused by blunt forces to the ear can rupture the tympanic membrane or produce a subchondral hematoma even in the absence of a laceration. Lacerations caused by blunt or shear forces may also involve the cartilage.[1,46] If a wound extends deep into the canal, verify the integrity of the tympanic membrane. The presence of hemotympanum, mastoid area ecchymoses, or cerebrospinal fluid otorrhea suggests a basilar skull fracture.

TREATMENT

Insert a cotton plug into the ear canal during wound preparation and irrigation. Regional anesthesia by auricular field block is ideal (see Chapter 36, "Local and Regional Anesthesia"). Hemostasis before repair of an auricular laceration is important to prevent the formation of a hematoma.

Close superficial lacerations to the skin with 6-0 nonabsorbable monofilament interrupted sutures.[47] Cover any exposed cartilage to prevent subsequent infection. Do not remove crushed or loose pieces of cartilage under the skin, as the pieces may be beneficial if reconstructive surgery is necessary. Do not debride the edges of an auricular laceration because there is very little excess skin available to cover the existing cartilage.

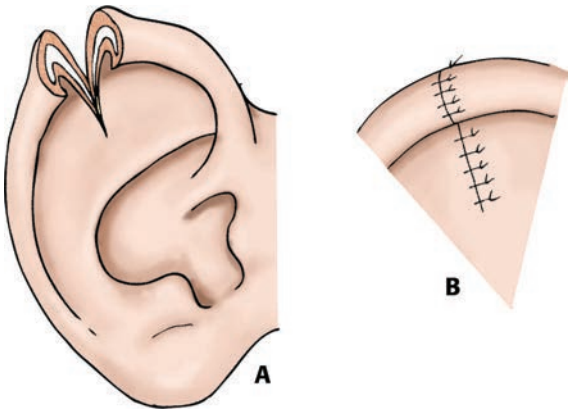

FIGURE 42-8. Repair of auricular laceration. **A.** Laceration through auricle. **B.** Interrupted 6-0 nonabsorbable sutures approximate the skin edges.

In most through-and-through lacerations of the auricle, skin and perichondrial approximation will adequately support and align the underlying cartilage (**Figure 42-8**). If the overlying skin is avulsed, refer to a specialist for repair.[1,46] Partial or complete avulsion of the auricle requires immediate consultation.

A perichondral hematoma is a potentially damaging complication after repair of auricular lacerations. The collection of blood and buildup of pressure may damage the cartilage and create a deformed external ear. A postrepair **auricular pressure dressing** can prevent hematoma formation (**Figure 42-9**). **Reevaluate the dressing and the ear in 24 hours. If there is no hematoma, discontinue the pressure dressing.**

An **auricular hematoma** may develop within the first few days after injury. The patient typically presents with pain and swelling; the ear may look purplish; and the repair site is swollen, warm, and boggy to touch, and blood often oozes when the area is squeezed. Treatment requires evacuation of the hematoma and bleeding control. If a specialist is not available, the emergency physician may choose to drain the hematoma. The initial step is to remove all the sutures, drain the blood, and thoroughly irrigate the wound.[43] Then resuture the wound and apply a pressure dressing.

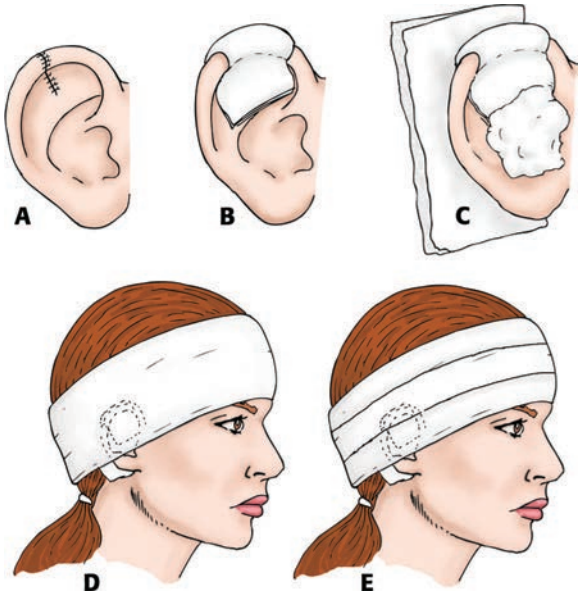

FIGURE 42-9. Auricular pressure dressing. **A.** Apply a nonadherent dressing over the repair site. **B.** Conform this dressing to the shape of the ear using gentle pressure. **C.** Place opened and fluffed gauze pads behind the ear to fill the space between the skull and pinna and in front of the ear to fill the interior contours. **D.** Wrap the head and ear with gauze wrap. **E.** Cover with a light (not tight) elastic bandage wrap. Do not enclose opposite external ear.

LIPS

ANATOMY

The external surfaces of the lips have three distinct regions: skin, vermilion, and oral mucosa. The cosmetically important junction of the skin and the red portion of the lip is the **vermilion border**. The orbicularis oris muscle surrounds the mouth. Its integrity is responsible for retaining the saliva inside the mouth, producing the bilabial sounds of speech, and providing facial expressions. The infraorbital nerve supplies the upper lip, and the submandibular nerve supplies the lower lip. Both are branches of the trigeminal nerve and can easily be blocked by regional anesthetic techniques. The lips are richly supplied by the labial arteries.

CLINICAL FEATURES

Perform both extra- and intraoral examinations to evaluate completely for injury. Fully explore lacerations, teeth, and mucosa. Identify missing, impacted, or fractured teeth (see Figure 245-2 in Chapter 245, "Oral and Dental Emergencies") or exposed bone of the maxilla or mandible. If portions of the teeth are missing, after adequate anesthesia, explore the wound fully because broken-off pieces may become embedded in the laceration or may be aspirated.[48-50] Note if lacerations cross the vermilion–skin and/or the vermilion–mucosal borders.

TREATMENT

Mucosal lip lacerations may not need to be sutured if they are isolated and the wound edges spontaneously approximate. Large or gaping wounds should be closed with a rapidly absorbable 5-0 suture. Carefully place the suture to include only mucosa with entrance 2 to 3 mm from the wound edges, and use care to evert the edges. Larger tissue bites can bunch the mucosa and pucker the outside skin.

Through-and-through lacerations that do not include the vermilion border should be closed in layers. Close the mucosal layer with a 5-0 rapidly absorbable suture as described in the previous paragraph, followed by gentle reirrigation from the outside. Next, approximate the orbicularis oris muscle fascia with 4-0 or 5-0 absorbable suture material with a simple interrupted or horizontal mattress technique. Finally, after repeat irrigation, suture the skin with 6-0 nonabsorbable monofilament sutures in a simple interrupted fashion or use tissue adhesive.

Wounds that cross the vermilion border should be repaired by placing the first stitch with 6-0 nonabsorbable monofilament suture to precisely align the edges of the vermilion border (**Figure 42-10**). Even 1 mm of step-off will be cosmetically unappealing.[51] After this first stitch, repair the vermilion and skin with the same 6-0 material, and repair the mucosa and underlying muscle with 5-0 rapidly absorbable suture. A useful technique in some cases is to leave the initial alignment suture untied and apply gentle traction on the ends to help approximate and align the underlying tissue as the skin and vermilion are closed.

INTRAORAL MUCOSAL LACERATIONS

ANATOMY

Two types of intraoral mucosal lacerations are common: those involving the buccal mucosa and those at the mucosal reflections. Buccal mucosal lacerations near the parotid duct opening, identified as a small papilla adjacent to the upper second molar, may injure that structure. Lacerations of the mucosal reflections are located at the transition from the cheek to the outside surface of the maxilla or mandible. Because of the loose attachment of the mucosa in this area, these lacerations may have great depth and extend deeper than initially suspected.

CLINICAL FEATURES

Visualize and explore intraoral lacerations to determine their depth and extent. **Lacerations of the mucosal reflections are easily missed**

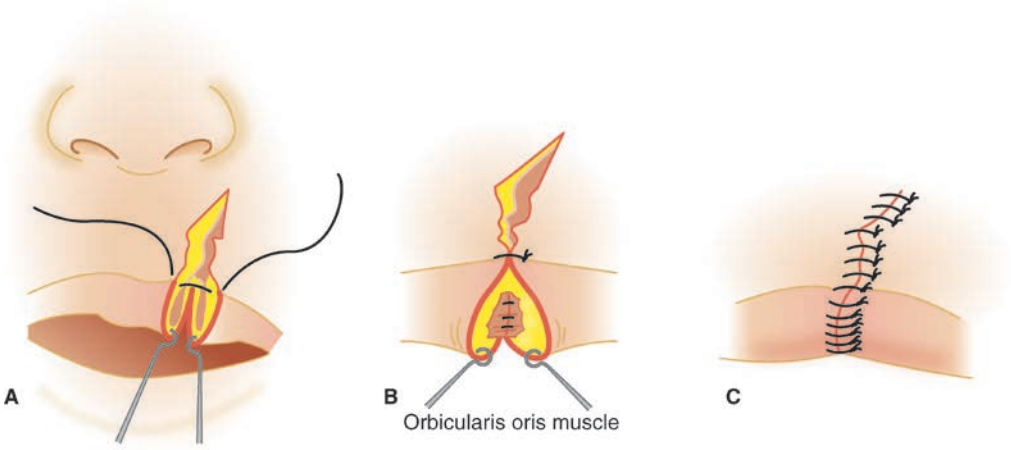

FIGURE 42-10. Lip laceration repair. **A.** The first suture is placed to align the vermilion skin junction. **B.** The orbicularis oris muscle fascia is then repaired with 5-0 absorbable sutures. **C.** The irregular edges of the skin are then approximated with 6-0 nonabsorbable sutures.

unless the lips are manipulated to see into all the recesses. Evaluate the adjacent teeth for fracture or avulsion, because missing tooth fragments may be embedded in the wound, swallowed, or aspirated into the airway.

TREATMENT

Small intraoral lacerations do not need routine repair and can be allowed to heal naturally. **Suture closure of intraoral lacerations is indicated when wounds are large enough to trap food particles or have a tissue flap that interferes with chewing.** Anesthesia may be achieved by dripping 1% lidocaine into the wound and waiting for 5 minutes before suture repair.[52] Use 4-0 rapidly absorbing suture to close the mucosa with edges everted. To avoid bunching of the mucosa as the suture knot is tied, insert the needle about 2 to 3 mm from the edge of the wound. Include only the mucosa in the suture because an external pucker may be created if the underlying muscle is ensnared in the suture loop. Typically, sutures placed 5 mm apart are adequate.

CHEEKS AND FACE

ANATOMY

The cheek area has two structures that influence wound repair: the parotid duct and branches of the facial nerve (**Figure 42-11**).[1] The opening of the parotid duct is adjacent to the second maxillary molar; wounds in this region can lacerate the parotid duct. As the facial nerve traverses the parotid gland, it divides into five major segments, the precise courses of which are difficult to predict. Therefore, lacerations or deeply placed sutures may ensnare one of these branches.

CLINICAL FEATURES

Evaluate wound depth and assess for damage to the parotid gland, parotid duct, and facial nerve. Assess the teeth for fracture, avulsion, or fragments embedded in the wound. Suspect parotid duct injury when the wound crosses a line from the tragus to the corner of the mouth and is posterior to a vertical line downward from the lateral canthus. The buccal branch of the facial nerve and a branch of the facial artery travel with the parotid duct, so facial paralysis or arterial bleeding from the wound should arouse suspicion that the parotid duct is also injured. Parotid duct laceration can be confirmed by inserting a 19-gauge silastic tube into the intraoral parotid duct papilla and seeing if the catheter is visible in the wound. Alternatively, a small amount of saline can be injected into the tube while observing for flow in the wound. These procedures require patient cooperation and are usually performed by the consulting specialist.

TREATMENT

Repair superficial lacerations that involve the cheek and surface of the face with 6-0 nonabsorbable monofilament, simple, interrupted, percutaneous sutures. Alternatives include adhesive strips, tissue adhesives, or in selected cases, subcuticular closure with rapidly absorbing suture. If there is significant skin tension, place intradermal absorbable sutures, and ensure the parotid duct is not caught in the suture (Figure 42-11). If the parotid duct is injured, operative repair is indicated.

A full-thickness cheek laceration traverses the skin and the underlying subcutaneous tissue/muscle and penetrates through the intraoral mucosa. Such wounds are repaired in layers, starting with the intraoral mucosa. Once the mucosa is closed, reirrigate the wound before closure of the subcutaneous layer with 5-0 absorbable suture and skin with 6-0 nonabsorbable suture, tissue adhesive, or adhesive strips.

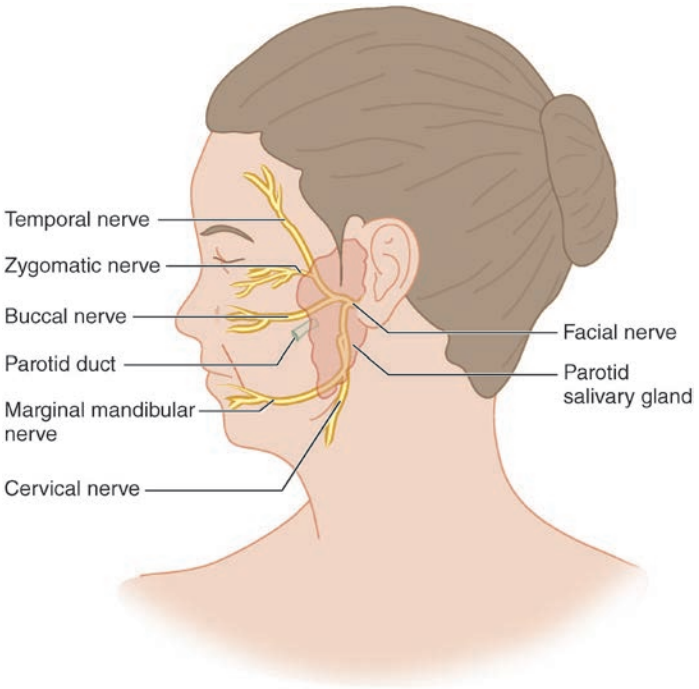

FIGURE 42-11. Cheek anatomy. The course of the parotid duct is along a line drawn from the lower border of the tragus to the corner of the mouth.[53] The five branches of the facial nerve are the temporal, zygomatic, buccal, marginal mandibular, and cervical.

DISPOSITION AND FOLLOW-UP

Where possible, the wound should be dressed with either an antibiotic ointment or nonadherent dressing material to maintain moisture and encourage wound healing.[54-56]

Patients should be discharged with routine wound-care instructions (see Chapter 47, "Postrepair Wound Care") and, if the injury resulted from a major blunt impact, closed head injury precautions. Remove scalp sutures or staples in 14 days, and remove nonabsorbable percutaneous sutures in the forehead, external ear, or lips in 5 days. Underlying absorbable sutures will maintain structural integrity for wounds that were under tension.

Percutaneous nonabsorbable sutures placed in the eyelid, nose, or face should be removed in 3 to 5 days. A thin layer of ophthalmic antibiotic ointment may be applied in place of a dressing; do not apply antibiotic ointment intended for routine use elsewhere around the eye. Remove intranasal packing in 1 to 2 days.

Auricular pressure dressings should be left undisturbed for 24 hours and then removed for inspection of the wound site. If the wound is healing without infection or hematoma, replacement of the pressure dressing is not necessary.

Patients with intraoral lacerations should practice good oral hygiene and rinse their mouth several times a day. There is no evidence to support the use of prophylactic antibiotics for intraoral lacerations and through-and-through facial wounds; their use is a matter of physician preference.[57,58]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 43

Arm, Forearm, and Hand Lacerations

Moira Davenport

GENERAL MANAGEMENT PRINCIPLES

Specific concerns relative to wounds and lacerations of the arm and hand include potential injury to the arteries, nerves, and tendons that lie close to the skin and the impact of these injuries on the use of the hands in daily and occupational life. Injuries may be classified as either isolated or combinations of closed crush, simple lacerations, open crush, partial amputation, and complete amputation.

HISTORY AND EXAMINATION

Specific considerations in the history include patient age, occupation, mechanism of injury, and hand dominance. Age is important because the potential for bony injury increases with decreasing bone density, and the likelihood for healing and functional recovery decreases with age due to loss of elasticity. Mechanism of injury identifies wounds that are more prone to infection or injury to deeper structures. Note the time from injury to repair; there is no distinct threshold for infection from time of injury to closure, but wounds sutured >12 hours after injury could be more prone to infection (see Chapter 39, "Wound Evaluation"). (See Videos: Hand Exam and Digital Nerve Block.)

Inspection Observe the position and stance of the arm, hand, and digits. Identify exposed tendon or bone and note the location of the wound relative to major arteries, nerves, and tendons. Inspect the wound carefully for possible foreign body, debris, or other visible contaminants. Note significant soft tissue avulsion or loss of length of the injured part, as these findings may be indications for operative repair. Remove rings from the affected arm. (See Video: Ring Removal.)

TABLE 43-1 Motor Testing of the Peripheral Nerves of the Upper Extremity

Nerve	Motor Exam
Radial	Dorsiflexion of wrist
Median	Thumb abduction away from the palm Thumb interphalangeal joint flexion
Ulnar	Adduction/abduction of digits

Motor Function Evaluate active motion and resistance to passive movement. Patients with a painful injury may be unwilling to move the affected extremity. After checking sensory function, local anesthesia may be required to obtain an adequate motor exam. The belief that a local anesthetic with epinephrine should not be used for digital nerve blocks is without evidence, and clinical observation studies have found agents containing epinephrine safe for digital nerve blocks.[1,2]

The most distal pure motor function of each major nerve should be tested against resistance (**Table 43-1**).

Individually assess each tendon within, and adjacent to, the injured area. For injuries to the hand and fingers, individually examine the extensor digitorum, flexor digitorum profundus, and the flexor digitorum superficialis of each digit. The flexor digitorum superficialis, which splits and inserts at the proximal interphalangeal joint, can be examined by holding all other digits in extension and flexing the proximal interphalangeal joint against resistance. The flexor digitorum profundus, which runs below the flexor digitorum superficialis past the split to attach at the distal interphalangeal joint, can be examined by holding the proximal interphalangeal joint in extension and flexing the distal interphalangeal joint against resistance. The extensor digitorum can be assessed by sequentially flexing the digit at the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints and having the patient extend the digit. Extension should be performed first against gravity and then against resistance applied by the examiner. **Weak, limited, or painful movement suggests partial involvement of a tendon.** Abnormality in motor nerve or tendon function testing warrants a more in-depth evaluation, including visual exploration of the wound after anesthesia.

Sensory Function Assess pain and touch sensation in the median, ulnar, and radial nerve distributions (**Table 43-2** and **Figure 43-1**). For injuries distal to the midpalm, assess the digital nerves by static two-point discrimination, testing longitudinally along the ulnar and radial aspect of the volar pad of the potentially involved digits. Static two-point discrimination is evaluated by using ECG calipers or a paper clip bent into a "V" shape with the two ends separated by approximately 5 to 6 mm. During testing, the two points should not cross the midline, and each stimulus should be timed 3 to 4 seconds apart. **Normal two-point discrimination is defined as <6 mm;** good is 6 to 10 mm, fair is 11 to 15 mm, and poor is >15 mm. Two-point spatial acuity of touch diminishes with age. Young (18 to 33 years) patients have a mean two-point acuity of 2 mm, whereas elderly (>66 years old) patients have a mean acuity of 5 mm.[3] The two most important areas to maintain sensation are the ulnar side of the distal thumb and the radial side of the index volar pad to preserve pinch sensation.

Vascular Supply Intact radial and ulnar pulses and capillary refill are usually adequate to exclude significant vascular injury. However, an arterial injury proximal to the wrist may not be obvious as a result of collateral circulation. Perform the **Allen test** to better assess the integrity of the radial and ulnar arteries. The test is performed by first instructing

TABLE 43-2 Sensory Testing of Peripheral Nerves in the Upper Extremity

Sensory Nerve	Area of Test
Radial	First dorsal web space
Median	Volar tip of index finger
Ulnar	Volar tip of little finger

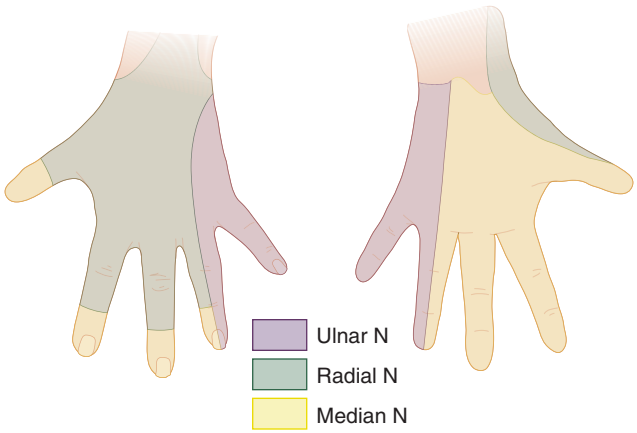

FIGURE 43-1. Sensory innervation to the hand. N = nerve.

the patient to make a fist as tightly as possible. Then, apply digital pressure to both the radial and ulnar artery at the volar aspect of the wrist. Next, while maintaining compression of the radial and ulnar artery, have the patient open the hand—a blanched palm indicates that arterial inflow is occluded. Now release the radial artery and note the time for the hand to return to normal color. Repeat the entire process, this time releasing the ulnar artery. If the patient cannot make a fist, occlusion of both arteries will still blanch the hand, but the color change will not be as evident or pronounced. **Refill times >3 seconds raise suspicion for a significant vascular injury.**

A Doppler probe is useful to detect a diminished pulse, detect flow in digital arteries, and calculate an arterial pressure index. The **arterial pressure index** is the ratio of the systolic blood pressure between the injured and the uninjured side. It is useful to assess the vascular integrity of an injured arm or leg. To obtain the index, place a blood pressure cuff proximal to the ankle or wrist of the injured limb and distal to the wound. Then use a Doppler probe to determine the systolic pressure at the radial or ulnar artery. In the absence of a diminished pulse or an arterial pressure index ratio <1.0, the likelihood of a clinically significant arterial injury is <5%.[4,5] Lack of obvious arterial bleeding does not rule out arterial injury because cleanly transected arteries may contract and prevent obvious bleeding. Abnormal findings warrant consultation with a vascular surgeon as well as with a hand surgeon.

IMAGING

Obtain radiographs with anteroposterior, oblique, and lateral views if bony injuries, foreign bodies, or joint penetration are suspected. Additional oblique views of the hand and digits are useful to visualize small areas with overlapping bones. For isolated finger injuries, dedicated anteroposterior and lateral radiographs of the involved digit(s) are preferred, as the detail on hand films alone is often not adequate for complete visualization of small, subtle fractures. **Plain radiography visualizes radiopaque objects as small as 1 mm.** When there is suspicion for a radiolucent retained foreign body, especially wood, other imaging modalities (US, CT, or MRI) may be necessary (see Chapter 45, "Soft Tissue Foreign Bodies"). US is gaining popularity as a means to evaluate for fracture, foreign body, and tendon/ligament integrity.[6] Tendon function can be evaluated using US and the water bath technique. (See Video: Waterbath for Finger Exam.)

WOUND VISUALIZATION AND TOURNIQUET APPLICATION

Because wounds and the affected structures are often small, patient positioning, bright lighting, and a bloodless field are necessary for wound evaluation. Local anesthesia or nerve blocks are needed to adequately examine the wound. Test sensation and motor function prior to anesthesia if at all possible. (See Video: Forearm Nerve Blocks.)

For some injuries, a bloodless field may require a proximal tourniquet to temporarily halt arterial inflow and allow adequate visualization of the injury.[7] Penrose (rubber) drains are typically used to tourniquet an injured finger, and pneumatic tourniquets placed around the arm are used with forearm and wrist injuries. To tourniquet a digital injury, place a 1-in. Penrose drain around the base of the finger, stretch the drain away from the hand, and secure the drain with a clamp or hemostat. **Excessively high pressures and tourniquet times >15 to 20 minutes can cause neurovascular damage and may be avoided by limiting the stretch of the drain to no more than 50% of the original length.**[8]

For more proximal injuries, especially those with brisk arterial bleeding, an inflated manual blood pressure cuff is used. **Esmarch's technique** is used to exsanguinate the limb and prevent backflow bleeding. Elevate the injured extremity and apply an elastic bandage starting distally and wrapping proximally to the area where the cuff will be applied. The cuff is applied around the upper arm and inflated to pressures above the systolic blood pressure of the patient, but not to exceed 250 mm Hg (33 kPa). The cuff tubing is clamped with a hemostat instead of closing the air release valve to prevent slow air leakage. The maximum cuff inflation time is limited to 30 minutes to avoid ischemic damage to the distal muscles and nerves.

Once adequate visualization is obtained, examine the area for foreign bodies and tendon and joint capsule injuries. **Examine the arm and hand in a variety of positions, including the position of injury and a full, passive range of motion, to avoid missing injuries that may move out of the field of view when the extremity is examined in a neutral position.** Examine lacerations near a joint carefully to identify violation of the joint capsule. If the location and depth of the injury raise the question of extension into the joint capsule, joint injection for a **saline load test** can be done, although there is minimal evidence for its sensitivity in upper extremity joints other than the elbow.[9] Inject sufficient amounts of saline to adequately stress the capsule; false-negative results may be obtained if too little fluid is injected. Fluid dripping from the joint indicates an open joint capsule and requires specialty consultation. For small joints or questionable exams, a few drops of sterile fluorescein for IV use (Ak-Fluor®) may be added to the injected saline and the joint examined with a Wood's lamp for evidence of fluorescent effluent. **There is no advantage of adding methylene blue to the injected saline, and it may affect operative management by staining the intra-articular surfaces.**

WOUND DRESSING AND POSTREPAIR CARE

After the injury is repaired, apply antibiotic ointment to the repaired incision/sutures and cover the wound with a nonadherent dressing. Wrap the area loosely with a soft dressing to allow for adequate circulation. Leave a small portion of the fingernail or volar pad visible to allow serial assessment of capillary refill in patients with digital injuries. Tubular gauze over a finger wound should not be applied in more than two layers or twisted between layers to prevent a tight bandage producing ischemic damage to the digit.[10,11] Certain injuries, especially large lacerations in close proximity to a joint and those with tendon involvement, may be splinted for protection and limitation of pain. Provide adequate analgesia and remind the patient to keep the injured extremity elevated above the level of the heart for the first 24 hours to reduce edema. A follow-up wound check is recommended within 48 to 72 hours. Sutures are usually removed 8 to 10 days after the injury. **Provide tetanus immunization or booster as needed.**

Infection of simple hand lacerations is low, between 1% and 5%.[12,13] Prophylactic antibiotics are not needed for uncomplicated hand lacerations. Uncomplicated hand lacerations are those that: (1) are not caused by a human or animal bite; (2) are not complicated by a fracture through bone or a joint; (3) do not involve tendons, bones, large vessels, or nerves; or (4) have no severe soft tissue damage or maceration.[14] Antibiotics are generally given for mammalian bite wounds (see Chapter 46, "Puncture Wounds and Bites") and are considered for injuries >12 hours old, contaminated wounds, or injuries with exposed bone.[15] There is a lack of evidence regarding the use of antibiotics following simple hand lacerations in patients with concurrent medical problems that may affect wound healing (i.e., diabetes, renal or peripheral vascular disease, immunocompromise). Antibiotics should be chosen to cover suspected contaminants and pathogens and should be given

early in the ED by a route that quickly achieves high blood and tissue concentrations.

Indications for admission to the hospital include injuries that require repair in the operating room, those that require a course of IV antibiotics for infection, or the presence of social issues such as abuse cases, homelessness, or other factors affecting the patient's ability to follow basic aftercare instructions.

INJURIES IN CHILDREN

Because of the presence of an open epiphysis in children, a fracture can be difficult to identify using plain radiographs. It is often necessary to obtain radiographs of the unaffected side for comparison. Procedural sedation may be required if the child is unable to tolerate the procedure after local anesthesia alone. The continuous high activity level of children makes keeping dressings intact a problem, rendering routine hand dressings and splints ineffective. If the dressing and immobilization are essential to wound healing, the child can be placed in a long-arm splint or bi-valved cast.

UPPER ARM AND ELBOW LACERATIONS

Lacerations of the upper arm and elbow account for about 9% and 7%, respectively, of upper extremity lacerations presenting to the ED.[16] The major issues with lacerations in these areas are potential for (1) arterial laceration, (2) nerve laceration, and (3) elbow joint penetration. After excluding such injuries, wounds in this region can be closed with absorbable monofilament (e.g., 4-0 polydioxanone) for deep layer closure and 4-0 nylon or surgical staples for skin closure.

DORSAL FOREARM, WRIST, AND HAND LACERATIONS

The forearm has six extensor compartments located dorsally, all of which are innervated by the radial nerve (**Table 43-3**).

The dorsal skin on the forearm and hand is thin and lacks underlying tissue, which allows avulsions to easily occur, making wound edge approximation sometimes difficult. For most lacerations, simple 5-0 nonabsorbable percutaneous sutures should be adequate for closure. To provide better cosmesis for injuries to the dorsum of the hand, consider subcuticular stitches with 5-0 absorbable material (see Figure 41-6). Closure of the fascial defect with 4-0 absorbable sutures for deep wounds that penetrate through the muscle fascia and lacerate the muscle belly is generally recommended. However, deep sutures increase the potential for infection in a contaminated wound.

TABLE 43-3 Extensor Compartments in the Forearm

Compartment	Muscle	Function
First compartment	Abductor pollicis longus	Abducts and extends thumb
	Extensor pollicis brevis	Extends thumb at MCP joint
Second compartment	Extensor carpi radialis longus	Extends and radially deviates wrist
	Extensor carpi radialis brevis	Extends and radially deviates wrist
Third compartment	Extensor pollicis longus	Extends thumb at interphalangeal joint
Fourth compartment	Extensor digitorum communis	Splits into four tendons at level of the wrist; extends index, long, ring, and little digits
	Extensor indicis proprius	Extends index finger
Fifth compartment	Extensor digiti minimi	Extends little finger at MCP joint
Sixth compartment	Extensor carpi ulnaris	Extends and radially deviates wrist

Abbreviation: MCP = metacarpophalangeal.

CLENCHED FIST INJURIES

Patients with lacerations to the dorsum of the hand should be questioned about the possibility of a **clenched fist injury, "fight bite," or tooth-knuckle injury,** wounds created by the patient throwing a punch, impacting the front teeth of the intended target, and producing a small laceration (3 to 5 mm) over the dorsal metacarpophalangeal joint.[17] Extension of the affected digit after the fight deeply inoculates oral bacteria into the wound with a high risk for complications.[18] *Staphylococcus aureus* is the most common bacterial species isolated from human bite wounds, followed by *Streptococcus* spp., *Corynebacterium* spp., and *Eikenella corrodens.* In clenched fist injury infections, polymicrobial involvement is the rule.[19] Human bites can also transmit herpes, actinomycosis, syphilis, tetanus, and hepatitis B and C. Bites are not the only way to inoculate the hand with human oral flora; significant hand and finger infections have been reported after toothpick injuries. Patients sustaining such puncture wounds should receive antibiotics to protect against the above-mentioned bacteria.[20]

Obtain radiographs on clenched fist injuries to evaluate for embedded teeth, air in the joint/soft tissues, and fractures. Patients who delay evaluation and develop obvious infection require exploration, open irrigation, and debridement in the operating room followed by admission for IV antibiotics and elevation. Patients presenting soon after the injury and without evident infection can undergo evaluation, exploration, and irrigation in the ED with appropriate equipment and physician expertise. It is important to visualize the full extent of the wound, evaluate the hand through full range of motion, and exclude injury to the extensor tendon and joint capsule. If no injury to these structures is seen, the wound should be copiously irrigated. **Most practitioners do not close fresh closed fist injury wounds**; instead, the wound is covered with a nonadherent dressing and allowed to heal by secondary intention or undergo delayed primary closure in 4 to 5 days or revision at a later date. Fresh, uninfected wounds may be closed, although that decision is best made by a hand surgery specialist who has adequately explored the wound.[7]

Splint the hand in a position of function (**Figure 43-2**). A 3- to 5-day course of prophylactic antibiotics should be prescribed, usually amoxicillin-clavulanic acid. Give the first antibiotic dose in the ED. Instruct the patient to elevate the extremity and return for reevaluation in 24 to 48 hours. Consult a hand surgeon if there is already evidence of infection or joint/tendon involvement, and consider an initial dose of IV antibiotics, typically ampicillin-sulbactam or cefoxitin.

EXTENSOR TENDON LACERATIONS

The dorsal skin of the hand is thin and freely mobile with the extensor tendons located very superficially. A careful examination through a full range of motion at the site of injury in a neutral position and in the position of injury is necessary to avoid missing a tendon injury. Consult

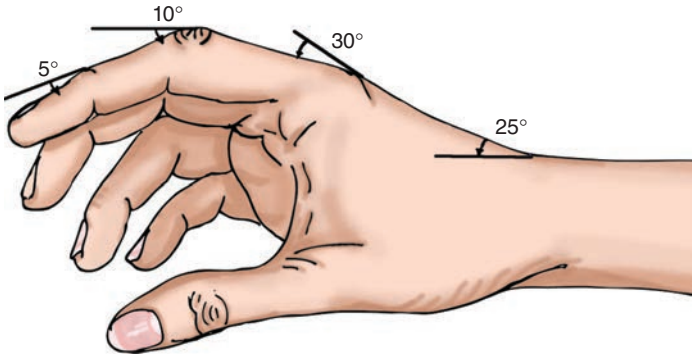

FIGURE 43-2. Wrist and hand position when splinted in "position of function." The wrist is extended 25 degrees so that the thumb metacarpal is in alignment with the forearm. The thumb is abducted away from the palm. Metacarpophalangeal joints are flexed to 30 degrees. Proximal interphalangeal joints are flexed to 10 degrees. Distal interphalangeal joints are flexed to 5 degrees.

a hand surgeon for wounds with gross contamination, that are large, or that result from crush injury; these need emergent exploration in the operating room.[21] For most other extensor tendon injuries of the digits, irrigate the wound, close the skin, splint with wrist and digit in extension, and refer the patient to a hand specialist for repair later.

Extensor tendon injuries between the distal wrist and metacarpophalangeal joints can be repaired in the ED. It is recommended to consult the hand surgeon for treatment preferences and ensure continuity of care. Small partial extensor tendon injuries (<50% transected) should be repaired with absorbable synthetic material. Larger partial tendon injuries (>50% transected) and complete extensor tendon lacerations should be sutured with 4-0 (5-0 for smaller tendons) colorless nonabsorbable material, such as polypropylene or nylon, and the skin closed with 5-0 nonabsorbable suture material. A figure-of-eight stitch with the knot placed at the edge of the tendon is recommended to repair lacerated extensors (**Figure 43-3**).

After repair of the tendon and overlying skin, **splint the hand or digit in a position of function** with instructions to maintain elevation of the extremity for 24 hours (Figure 43-2). Follow-up with a hand surgeon is recommended.

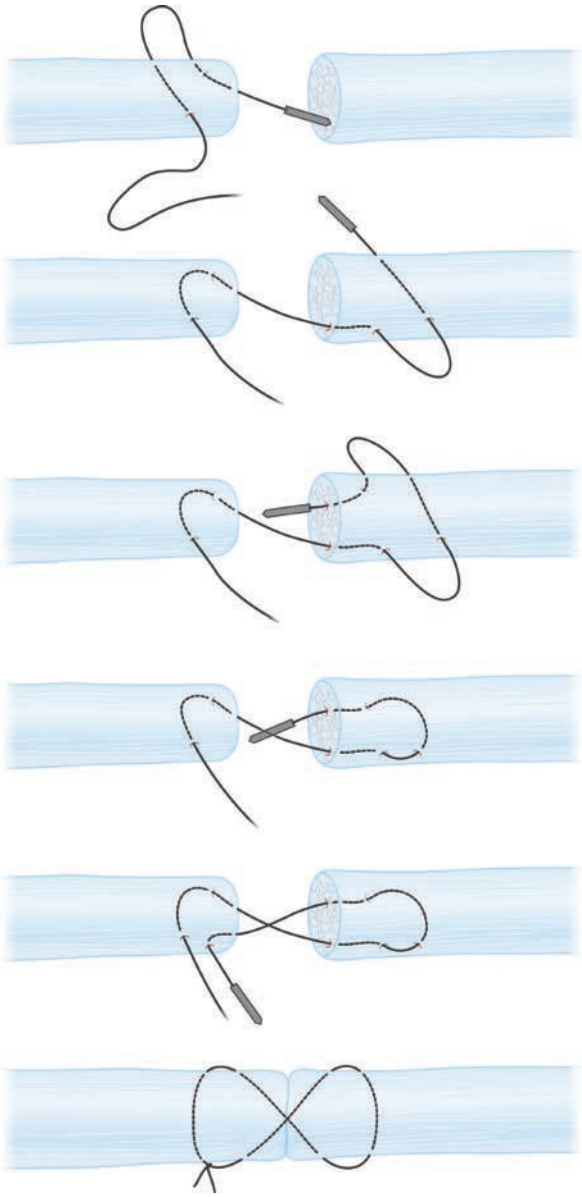

FIGURE 43-3. Extensor tendon laceration repair with a figure-of-eight stitch.

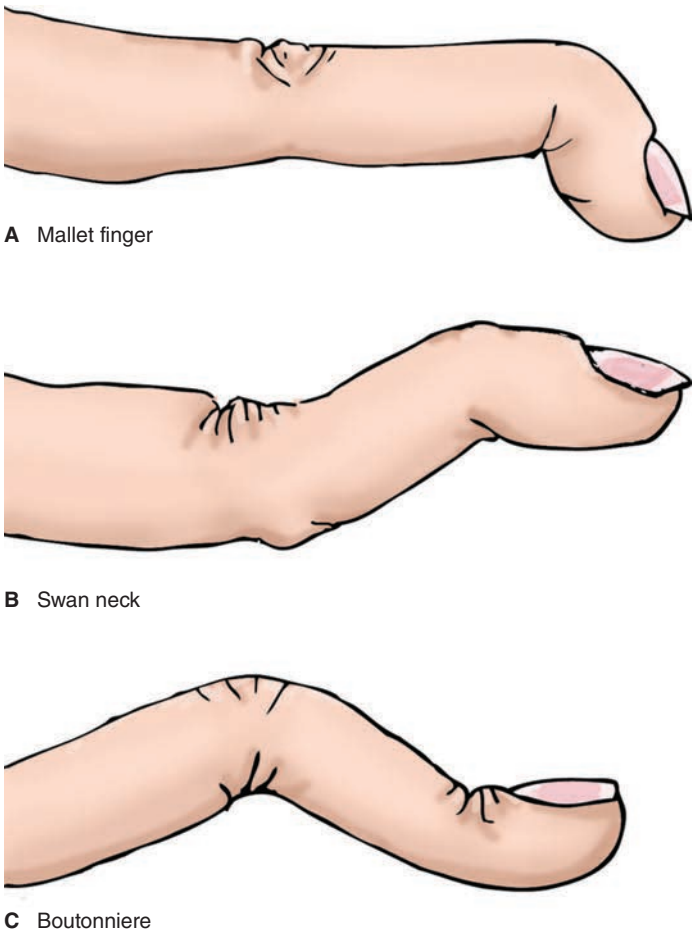

FIGURE 43-4. **A.** Mallet finger. **B.** Swan neck finger. **C.** Boutonniere deformity.

Complications can be seen with disrupted extensor mechanisms. The **mallet finger deformity** (inability to extend the distal interphalangeal joint, resulting in the joint being held in flexion) and **swan neck deformity** (hyperextension of the proximal interphalangeal joint resulting from unrepaired mallet finger deformity) are caused by the complete disruption of the terminal extensor mechanism and subsequent proximal and dorsal displacement of the lateral bands (**Figures 43-4A** and **43-4B**). A **boutonniere deformity** (hyperflexion of the proximal interphalangeal joint with hyperextension of the distal interphalangeal joint) is usually a delayed complication after injury to the proximal interphalangeal joint. The central slip of the extensor tendon is disrupted, allowing the lateral bands to move volarly and operate as flexors at the proximal interphalangeal joint while still producing extension at the distal interphalangeal joint (**Figure 43-4C**). If these injuries are open, operative repair is required. Closed injuries may be treated by splinting the digit in extension (distal interphalangeal joint for mallet finger and both proximal interphalangeal and distal interphalangeal joints for boutonniere deformity) for up to 6 weeks or until operative repair.[22,23] Patients should be referred to a hand surgeon for follow-up.

VOLAR FOREARM, WRIST, AND HAND LACERATIONS

Patients with volar wrist lacerations should be questioned about suicidal attempts, and potentially suicidal patients require psychiatric evaluation after wound repair.[24] There are 12 flexor tendons innervated by the median and ulnar nerves located on the volar surface of the forearm that cross the wrist (**Table 43-4**).

Injuries in the elbow region may affect the radial and ulnar nerves, which run in close proximity to the lateral and medial epicondyles, respectively. The radial nerve emanates from the spiral groove in the

TABLE 43-4 Flexor Tendons in the Forearm

Flexor Tendon	Function
Flexor carpi radialis	Flexes and radially deviates wrist
Flexor carpi ulnaris	Flexes and ulnarly deviates wrist
Palmaris longus	Flexes wrist
Flexor pollicis longus	Flexes thumb at MCP and interphalangeal joints
Flexor digitorum superficialis	Flexes index, long, ring, and little digits at MCP and PIP joints
Flexor digitorum profundus	Flexes index, long, ring, and little digits at MCP, PIP, and DIP joints

Abbreviations: DIP = distal interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

humerus approximately 10 cm proximal to the lateral epicondyle. The ulnar nerve travels behind the medial epicondyle as it runs between the two heads of the flexor carpi ulnaris into the forearm. The median nerve in the elbow region is more protected, as it runs in close proximity to the brachial artery and crosses anteriorly to the ulnar artery at the origin of the anterior interosseous nerve in the forearm. Although injuries to these nerves are more common with fractures and dislocations, simple soft tissue injuries at the elbow may result in nerve damage due to the superficial location and lack of overlying protective soft tissue in this area.

For most simple lacerations to the volar surface of the forearm and wrist, 4-0 or 5-0 nonabsorbable monofilament percutaneous sutures, such as nylon or polypropylene, should be used. For gaping injuries or injuries under high stress, a layer of deep sutures using 4-0 absorbable material may be required. Alternatively, mattress sutures can be used as well. For deep wounds that penetrate through the muscle fascia and lacerate the muscle belly, closure of the fascial defect with 4-0 absorbable suture is generally recommended.

Injuries that involve more than one parallel laceration, classic for suicide attempts, may require horizontal mattress sutures to cross all lacerations for closure to prevent compromising the vascular supply of the island of skin located between incisions (**Figure 43-5**). Alternatively, adhesive tapes or tissue adhesives alone or in conjunction with sutures may be used.

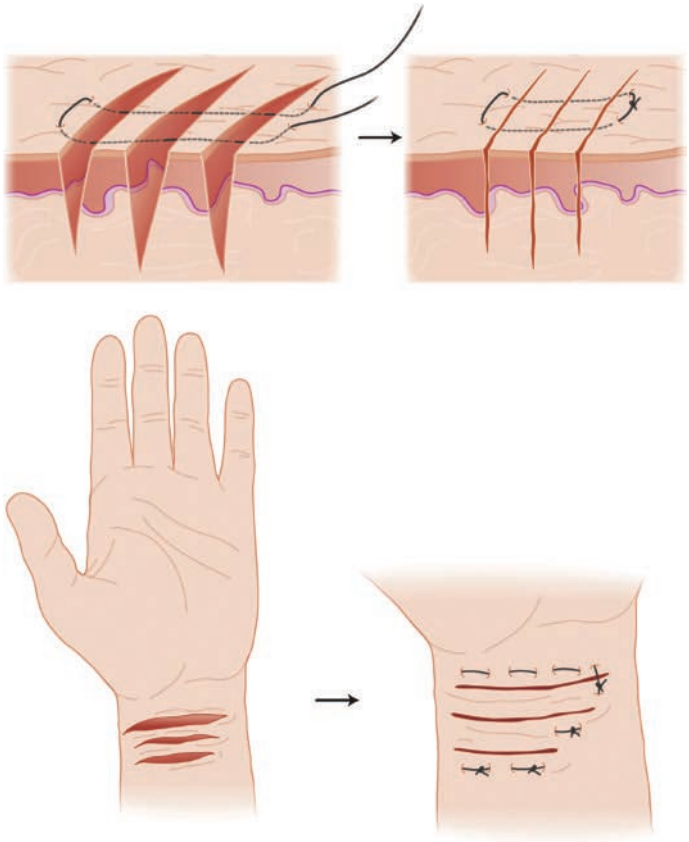

FIGURE 43-5. Horizontal mattress sutures for multiple parallel lacerations.

PALM LACERATIONS

The palmar skin surface is well adapted for contact with objects in the environment. Palmar skin is thicker than dorsal skin and has an underlying connective tissue fascial layer, making it much more adherent to bone. The thenar, palmar, and digital creases are connections between the skin and underlying fascia, and these areas have no intervening adipose tissue. Because tendons, nerves, and arteries course through this area, palm lacerations have great potential to damage these deep structures through small and innocuous-appearing lacerations.[25,26] **Carefully assess digital flexor tendon function and two-point discrimination.**

Carefully approximate creases during skin closure. The thickness of palmar skin makes eversion of the edges especially difficult. For this reason, interrupted horizontal mattress sutures with 5-0 nonabsorbable monofilament are recommended to ensure that sutures do not pull through the skin.

FLEXOR TENDON LACERATIONS

Flexor tendon injuries are usually repaired in the operating room by a hand surgeon because of the complexity of the anatomy and the reparative procedures required. Early consultation is important, as many surgeons prefer to repair complete flexor tendon lacerations within 24 hours after injury. If operative repair of the flexor tendon is going to be delayed, the wound should be appropriately cleaned and irrigated, the skin closed, and the affected extremity splinted. **Splint with the wrist and metacarpophalangeal joint flexed and the proximal interphalangeal and distal interphalangeal joints in extension to prevent contraction of the surrounding muscles.** The hand surgeon can follow up with the patient in 2 to 3 days to schedule the flexor tendon repair within 7 days of the injury. **Timely repair is important to restore vascular and synovial flow to the area and because postinjury scarring and tendon retraction make flexor tendon repairs more difficult after 10 to 14 days.** Patients with suspected partial flexor tendon lacerations should also have follow-up with a hand surgeon because unrepaired partial flexor digitorum superficialis disruption can produce a trigger finger.[27]

FINGER LACERATIONS

In general, isolated finger lacerations are straightforward injuries to examine and repair. Vascular status is checked by capillary refill, and sensory nerve status is checked by static two-point discrimination. Assess motor function of the extensor and flexor mechanisms. Careful examination and wound exploration of hand and digit lacerations are important, regardless of size. About half of patients with metacarpal or digit lacerations <2 cm in size have an associated deep structure injury, most commonly a tendon, with extensor tendon defects more common than flexor tendon injuries.[26]

Simple interrupted sutures with 5-0 nonabsorbable suture provide adequate closure for most digital lacerations. Alternatively, small, <2 cm, clean, and uncomplicated hand and digit lacerations can be treated conservatively without wound closure.[28] Although there appears to be no difference in cosmetic appearance or time to return to normal function without wound closure compared with wound closure, this practice has not been widely adopted.

DIGITAL AMPUTATIONS

Deep finger lacerations may include partial or complete amputations of the digit. Amputations should involve the consultation of a hand surgeon to discuss the possibility of replantation. Relative indications for replantation are injuries in children, injuries to the thumb, multiple digit

amputation, and single-digit amputation proximal to the insertion of the flexor digitorum superficialis.[29] The strongest contraindications to replantation are crush and avulsion injuries because neurovascular damage to the amputated digit is significant and functional outcome is poor. Other relative contraindications include multiple levels of injury to the amputated part, prolonged ischemia time (>24 hours) of the amputated part, patients in poor health, or significant comorbid factors, such as diabetes or severe pulmonary or cardiac disease that may lead to significant perioperative mortality. Patient attitudes analyzed by region show a preference for replantation to restore cosmetic appearance despite suboptimal functional outcome noted in Asia compared with Europe and North America.[30]

DIGITAL NERVE INJURIES

Suspect digital nerve injuries when static two-point discrimination is distinctly greater on one side of the volar pad than the other, or when it is >10 mm. Digital nerve injuries can be repaired using microsurgical techniques either acutely or days to weeks after the injury. Concomitant injuries and wound contamination are the most common indications for delayed repair. Prognosis depends on the specific injury and the age of the patient. Nerve contusions have variable healing, with a range of 12 days to 6 months. Nerve transection injuries do slightly better than crush injuries, but even with microsurgical repair, recovery is often incomplete.

FINGERTIP INJURIES

Fingertip injuries occur distal to the insertion of the deep flexor and extensor tendons at about the level of the lunula. This location is among the most frequently injured parts of the hand. Such injuries may involve the skin, pulp tissue, distal phalanx, and the perionychium (the nail, nail bed, and surrounding structures) (**Figure 43-6**).[31,32] The goals of healing are to maintain length and cosmetic appearance and to have the fingertip approach normal sensation and function.

DIGITAL TIP INJURIES WITH SKIN AND PULP TISSUE LOSS ONLY

Distal fingertip soft tissue (pulp) amputations that are < 1 cm^2 in size without exposed bone or nail bed involvement can be treated conservatively with serial dressing changes alone (Figure 43-7, line A).[31-33] Apply nonadherent dressing on the wound itself, avoiding the surrounding skin to prevent maceration, followed by standard gauze for additional protection. Instruct the patient to soak the injured fingertip for 10 minutes a day in warm water with added antibacterial soap, followed by tap-water irrigation and application of a new sterile nonadherent dressing. Change dressings daily for the first 10 to 15 days and every other day thereafter. Complete healing may take 4 to 8 weeks. Conservative management of fingertip injuries without bone exposure appears to be superior in terms of cosmetic appearance, improved function, and sensibility of the involved digit, especially in children.[32]

For larger avulsions, >1 cm^2, an intact amputated portion can be used as a full-thickness skin graft. The amputated tissue is cleaned and debrided of nonviable tissue, the undersurface of the skin is defatted with sharp scissors, and the graft is sutured to the defect. A split- or full-thickness skin graft harvested from a distant site can provide wound coverage when the severed skin tip is not available.

Two approaches are suggested for dermal avulsion injuries with persistent bleeding. One approach is to soak the fingertip in 10-20 mL of lidocaine 1% with epinephrine until numb and the bleeding stops. Then examine and clean the wound, apply a topical hemostatic pad, and secure with tube gauze. The other approach is to apply a tourniquet around the proximal phalanx to stop bleeding and create a dry wound. Then three to four layers of tissue adhesive are applied over the open area, allowing each layer to dry before applying the next. The tourniquet is released when the final layer is dry and the wound observed for several minutes to ensure hemostasis.

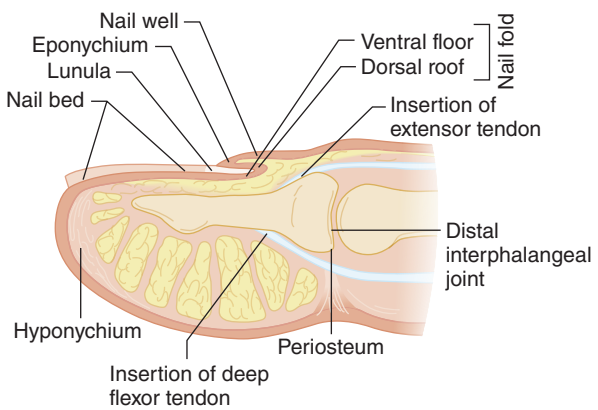

FIGURE 43-6. Anatomy of the perionychium.

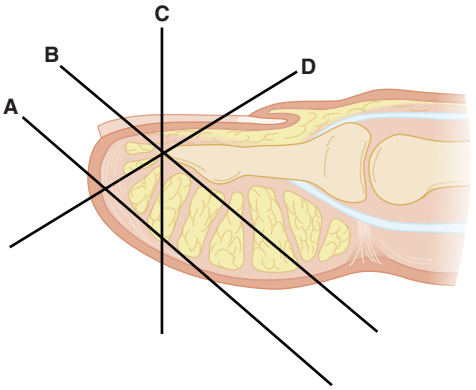

FIGURE 43-7. Fingertip amputations. (A) Volar angulation without bone exposure. (B) Volar angulation with bone exposure. (C) Transverse or perpendicular angulation with bone exposure. (D) Dorsal angulation with bone exposure.

DIGITAL TIP INJURIES WITH EXPOSED BONE

Skin grafting will be unsuccessful if a significant loss of tissue at the fingertip exposes the distal phalanx tuft, as bone does not provide adequate vascularity to support donor tissue.[33] Several treatment options exist, and the method used should be based on the best way to preserve the digit length and maintain the sensitivity and functionality of the fingertip. The size and geometry of the injury, the angle of the amputation, and the availability of the amputated tip will determine the options available for repair.[32]

If the bony protuberance is <0.5 cm in length and the soft tissue defect is <1 cm^2, the bone may be trimmed back using a rongeur and the wound left to heal by secondary intention with wound care, as described in the section "Digital Tip Injuries With Skin and Pulp Tissue Loss Only." A dorsal, obliquely angulated wound may be treated in the ED with bone shortening followed by primary closure of the wound using the adjacent volar tissue (Figure 43-7, line D). Fat from the local tissue may need to be trimmed to allow wound closure without tension. The nail should be removed, and the nail bed and surrounding structures should be repaired. Although results are comparable to those following conservative management, shortcomings include loss of length as well as tenderness of the fingertip and some degree of functional disability.

Amputations that are angled either in a transverse or volar direction have less favorable outcomes, as there is not always adequate soft tissue and skin coverage to allow for primary closure and preservation of length (Figure 43-7, lines B, C, and D). Consultation with a hand surgeon is necessary, as these injuries often require techniques beyond the scope of practice of most emergency physicians.[33]

Incomplete digital tip amputations, defined by the retention of the neurovascular bundle as well as portions of the underlying bone, require consultation with a specialist for fracture reduction, internal pin fixation, and repair of the soft tissue injury in the operating room.

Consult a hand surgeon for a complete digital tip amputation occurring proximal to the lunula, to evaluate the potential for replantation in the operating room.[33] Replantation of a complete amputation distal to the lunula is not usually advocated for adults because the procedure

is technically demanding and has a generally poor prognosis. However, specialist consultation is indicated in patients with specific occupational concerns and when the affected digit is the thumb or index finger.

Although fingertip injuries are quite common in children, most require only conservative management owing to the rapid healing ability of the young. Repairs in young children should be done using absorbable sutures to eliminate the need for suture removal, as suture removal often requires repeat procedural sedation.

INJURIES INVOLVING THE NAIL AND NAIL BED

The nail, nail bed, and surrounding soft tissue make up the perionychium (Figure 43-6). The nail bed is made up of the germinal and sterile matrices. The germinal matrix begins at the proximal base of the nail (typically 3 to 5 mm proximal to the eponychium) and extends to the lunula. From there, the sterile matrix extends distally to the hyponychium. Nail injuries can be described as simple nail bed laceration, stellate laceration, severe crush, and complete avulsion. Injury to the perionychium is most commonly due to closure of the fingertip in a door and is usually located at the distal portion of the nail bed. The mechanism of injury is a force directed to the dorsum of the nail, causing it to bend or break, and crushing the nail bed against the unyielding distal phalanx. Image the involved digit because distal tuft or phalanx fractures are associated with approximately 50% of nail bed injuries. Nail plate deformity permanently affecting nail growth is the most common complication resulting from inadequate treatment.

SUBUNGUAL HEMATOMA

Disruption of the blood vessels of the nail bed without fracture of the nail results in accumulation of blood under the nail. A subungual hematoma that covers >50% is treated with trephination of the nail plate to allow decompression and drainage of the hematoma. Various tools for this purpose include a heated paper clip, electric nail drill, hand-held electrocautery, 18-gauge needle, or #11 scalpel.[34-36] (See Video: Subungual Hematoma.)

The disadvantages of the heated paper clip include coagulation of the hematoma and introduction of carbon particles into the nail bed, which may delay healing and cause tattooing. Use of a needle, scalpel, or nail drill requires pressure to be applied to the nail and can be painful. A hand-held electrocautery device provides rapid and painless trephination. Do not apply alcohol or other flammables to the fingertip before electrocautery, because flames result when cautery is then applied. **Simple trephination produces a good to excellent outcome in most patients regardless of subungual hematoma size, injury mechanism, or the presence of fracture.**[34,35,37,38] After drainage, instruct patients to soak the affected finger in warm water containing antibacterial soap two to three times a day for 7 days and to follow basic wound-care principles.

NAIL BED INJURIES

Nail removal is recommended only if there is associated partial nail avulsion or surrounding nail fold disruption. Nail removal can be accomplished with adequate anesthesia, elevation of the nail off the nail bed using iris scissors, elevation of the eponychium off the nail, and then removal by gentle longitudinal traction with a hemostat. Digital tourniquet application to the digit may be required to adequately visualize the extent of nail bed laceration. Lacerations of the nail bed should be carefully repaired using 6-0 absorbable sutures to provide a smooth surface so the nail can grow without cosmetic deformity. Tissue adhesives can also be used to repair small nail bed lacerations by providing an additional structural anchor and minimizing venous bleeding associated with suturing the delicate nail bed tissue.[39] Crush injuries often result in stellate lacerations, which may require extensive, meticulous repair using magnifying loupes for visualization. Nail bed injuries in children can also be repaired with a good outcome.[40]

After nail bed repair, replace the removed nail by first gently cleaning it with saline, taking care to avoid damage to the germinal matrix. Once the nail is clean, trephinate the nail to prevent the development of a postrepair subungual hematoma, and secure the nail in its anatomic position. To secure the nail, place a 5-0 nonabsorbable suture through the proximal end of the nail plate, and then pass the suture underneath and through the center of the eponychial fold. Once the nail is secured in its anatomic position, tie the suture down over the nail. The replaced nail acts as a natural splint to the terminal phalanx, prevents formation of synechiae, and protects the sensitive nail bed.[41] If the nail is not available or is significantly deformed, nonbiologic stents or a sterile piece of aluminum foil (such as that used to wrap suture materials) may be fashioned to resemble the avulsed nail, inserted under the eponychium, and sutured in place similar to a replaced nail. However, use of the native nail is preferred.[41]

Once the nail is replaced, dress the fingertip with nonadherent gauze and apply a volar splint to limit distal interphalangeal joint movement. Provide postoperative wound-care instructions (e.g., regarding hand elevation as well as neurovascular checks) and adequate pain relief. Unless obvious purulence is noted, leave the dressing undisturbed for 5 to 7 days. At that time, examine the site for new hematoma formation. The suture attached to the nail can be removed after 3 weeks. The replaced nail will be dislodged by the new (growing) nail after an additional 1 to 3 months of growth.

If an associated distal phalanx or tuft fracture coexists with a nail bed laceration, it usually manifests as an avulsion of the nail out of the proximal eponychial fold. In this case, remove the nail, reduce the fracture as needed, and repair the nail bed as described previously. Once replaced in its anatomic position, the nail serves as a biologic splint to maintain fracture reduction owing to its proximity to the underlying bone. Unstable reductions require consultation with a hand surgeon for internal fixation using Kirschner wires to prevent deformity of the nail bed.

NAIL BED AVULSION INJURIES

An avulsion or crush injury may tear the nail completely away from the digit, with fragments of germinal matrix tissue left on the underside of the avulsed nail. These matrix fragments should be preserved for use as free grafts and, when possible, reattached to the nail bed using 6-0 or 7-0 absorbable sutures. When the nail or avulsed nail bed fragments are not available, or if the nail bed defect is large, a full-thickness nail bed graft can be harvested from the patient's toe and sutured into the nail bed of the affected finger. Consultation with a hand surgeon is needed, as these injuries are complex, and repair is technically challenging.

Avulsion injuries may also incompletely tear the proximal portion of the nail out from under the eponychium. Replace the nail root into its anatomic position using horizontal mattress sutures (**Figure 43-8**). The suture is placed through the eponychial fold and passed through the proximal portion of the corresponding segment of avulsed germinal matrix and then back out through the nail fold, pulling the matrix back to its anatomic position.

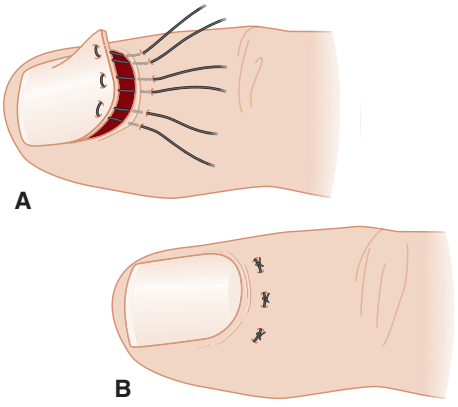

FIGURE 43-8. **A** and **B.** Technique for repair of an avulsion of the germinal matrix using three horizontal mattress sutures.

RING TOURNIQUET SYNDROME

A tight ring encircling the proximal phalanx may become entrapped as a result of distal swelling. As the digit expands, venous outflow is restricted by the tight ring, producing more swelling. This vicious cycle may lead to nerve damage, ischemia, and digital gangrene. The presence of impaired sensation (diminished static two-point discrimination) or diminished perfusion (delayed capillary refill) indicates significant constriction; rapid ring removal is then warranted, typically cutting the ring.[42] If sensation and perfusion are intact, removal can be attempted with slower techniques that preserve the ring. However, if there is an underlying phalangeal fracture, it is prudent to cut the ring. (See Video: Ring Removal.)

In all ring-preservation methods (using string, rubber bands, or surgical mask tie), the hand should be elevated to encourage venous and lymphatic drainage and thus reduce swelling.[42,43] Additionally, the finger can be circumferentially wrapped with a $^1/_2$- to 1-in. elastic band (e.g., Penrose drain), starting from the distal tip and winding the band tightly around the finger, progressing toward the proximal phalanx to reduce swelling. Leave the wrap in place for several minutes before it is unwrapped and the ring is removed. A digital nerve block or other method of regional anesthesia is often required prior to ring removal. A metacarpal or tendon sheath block produces less swelling of the finger but may not provide as much anesthesia as a digital block.[44] After ring removal, reassess sensation and perfusion.

Infants presenting to the ED for unexplained crying should be assessed for the potential of hair tourniquet syndrome. The signs are similar to that of ring tourniquet syndrome and result from a piece of hair wrapping around the affected digit. Once the hair is identified, release the constriction using chemical depilatory agents, suture removal scissors, or a small scalpel.[45]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 44

Thigh, Leg, and Foot Lacerations

Moira Davenport

ANATOMY

Lower extremity injuries most frequently involve the lower leg and ankle, followed by the foot and toes, hip, and then knee.[1]

THIGH ANATOMY

The thigh contains two fascial layers; the superficial fascia containing fat, lymphatics, cutaneous nerves, and superficial veins; and the deep fascia, containing muscles, major vessels, and nerves.

Thigh lacerations typically involve skin and superficial fascia, although deep lacerations can penetrate the deep fascia and into the underlying muscle. Lacerations in the area of the femoral triangle can injure the femoral nerve, artery, or vein (**Figure 44-1A**). Arterial injury resulting from penetrating and blast wounds most commonly affects the femoral artery or its branches: circumflex, deep femoral, popliteal, and geniculate (**Figure 44-1B**). Vascular injury is the most life- and limb-threatening concern, with arterial injuries at high risk for limb loss.[2] Suprapatellar lacerations may involve the quadriceps tendon, resulting in impaired knee extension. Compartment syndrome is a rare complication of thigh wounds (see Chapter 278, "Compartment Syndromes").

LOWER LEG ANATOMY

The muscles of the lower leg are organized into four fascial compartments (see Figure 278-1). Muscles in the anterior compartment primarily produce extension (dorsiflexion) and inversion (**Figure 44-2A**); muscles in the superficial and deep posterior compartments primarily produce flexion (plantarflexion) and inversion (**Figure 44-2B**); and muscles in the lateral compartment primarily produce flexion (plantarflexion) and eversion (**Figure 44-2C**).

Several important tendons in the lower leg are at risk for injury. The fibularis longus and fibularis brevis (also known as the peroneus longus and peroneus brevis) tendons, which contribute to foot plantar flexion and eversion, run behind the lateral malleolus and can be lacerated at this location (Figure 44-2C). Lacerations of the shin rarely involve vital nerves or tendons, but infrapatellar lacerations can transect the patellar tendon, resulting in inability to extend the leg. The common peroneal nerve can be injured in complex fractures, sharp injuries, or lacerations of the lower extremity, resulting in foot drop (**Figure 44-3**).[3]

Arterial supply to the lower leg originates from the popliteal artery (a continuation of the femoral artery) that bifurcates into the anterior and posterior tibial arteries at the inferior border of the popliteus muscle (**Figure 44-4**).

FOOT ANATOMY

With the exception of the arch, the plantar epidermis and dermis of the foot are thick, able to withstand the force produced by a moving body while remaining quite sensitive to two-point discrimination and pressure. The heel has an 18-mm-thick modified pad of fat separated into chambers by fibrous septae. There is an additional broad internal fibrous arch, called the *inner cup ligament*, which helps maintain the shape of the heel. The skin of the sole readily hypertrophies, becoming quite thickened, especially in people who walk barefoot. The dense fibrous fatty tissue of the ball of the foot and heel makes wound exploration and visualization difficult in the ED.

In contrast to the protective plantar surface, skin on the dorsal aspect of the foot and about the entire ankle provides little protection for underlying tendons, nerves, and blood vessels. The dorsum of the foot, the ankle, and the pretibial surface are particularly vulnerable to blunt-force injuries. Most lacerations on the dorsal foot and in the ankle area are easily explored, except for posterior ankle lacerations, a limitation when partial laceration of the Achilles tendon is considered. The extensor hallucis longus tendon, which extends the first toe, runs along the top of the first metatarsal and may be injured when heavy objects are dropped on the foot (**Figure 44-5**). The Achilles tendon, the primary contributor to foot plantar flexion, may be severed by penetrating injuries to the posterior ankle.

Sensory nerves predominate in the foot, with most motor control of the foot being performed by nerves and muscles in the lower leg (**Figures 44-6** and **44-7**). **The exceptions to this generalization are that the posterior tibial nerve innervates the intrinsic foot musculature, and the deep peroneal nerve innervates the extensor digitorum brevis and extensor hallucis brevis muscles; injuries to these nerves may result in toe clawing.**[4]

GENERAL MANAGEMENT PRINCIPLES

HISTORY

Obtain a description of the mechanism of injury, assessing the potential for damage to underlying tissue, the risk of a retained foreign body, and degree of potential contamination. Determine the time interval from injury to evaluation, as delayed presentations can increase the incidence of infection. Inquire about foreign body sensation, paresthesias, anesthesia, weakness, or loss of function suggesting a nerve, vascular, or tendon injury.

The patient's age influences wound healing and functional status following the injury. Ask about tetanus immunization status and conditions that increase the risk for infection or delayed wound healing such as diabetes, immunosuppression, or vascular disease. Patients who smoke, consume alcohol, or use illicit substances may be at additional

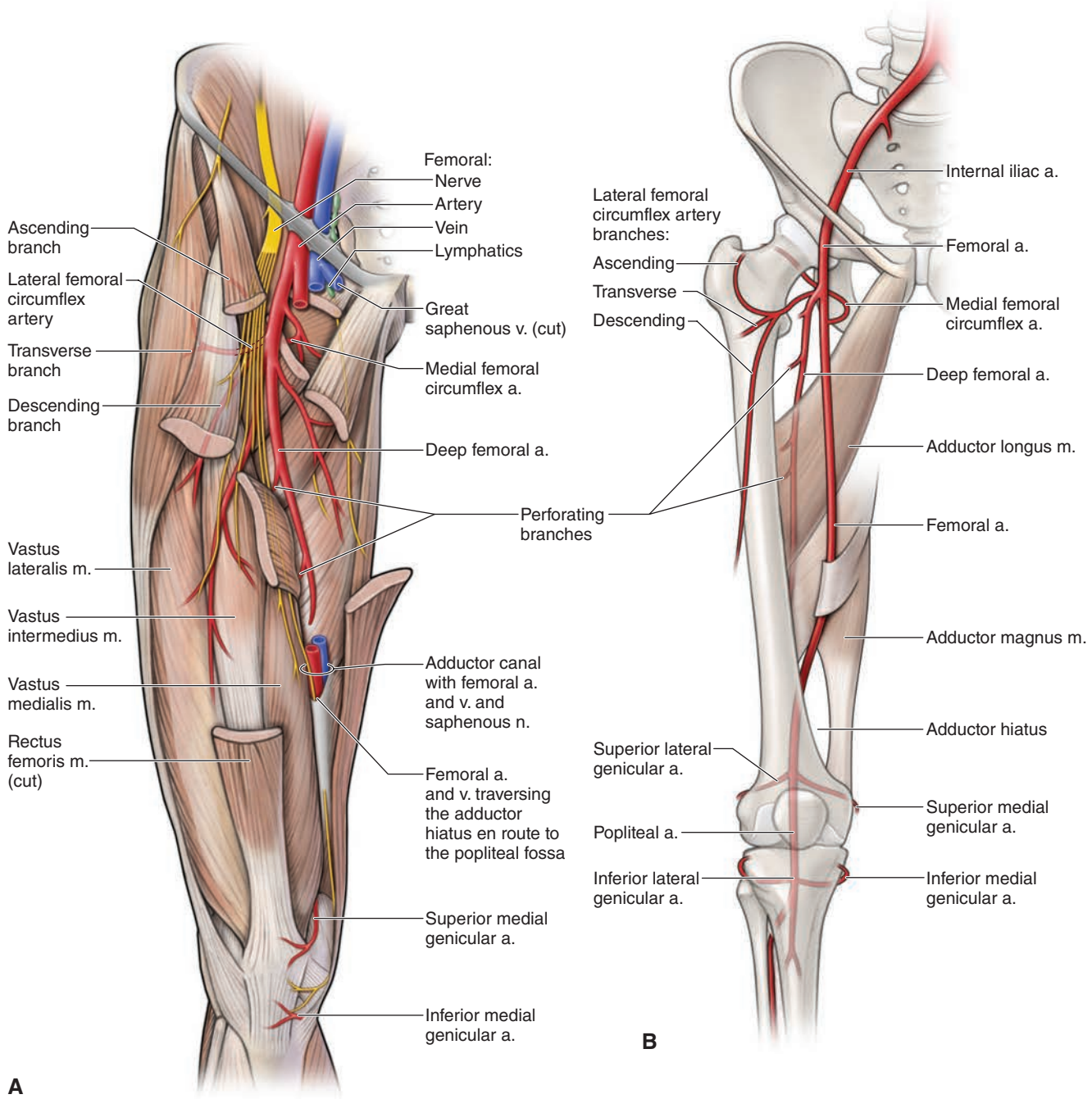

FIGURE 44-1. Thigh anatomy. **A.** Nerves, arteries, and veins in the femoral triangle. **B.** Femoral artery and its branches. a = artery; m = muscle. [Reproduced with permission from Morton DA, Foreman KB, Albertine KH: *The Big Picture: Gross Anatomy*, McGraw-Hill Education, Inc. © 2011, Figure 36-4.]

risk of poor healing secondary to vascular disease. The patient's employment should also be discussed as injuries may preclude a patient's ability to return to work during the healing process.

PHYSICAL EXAMINATION

Inspect the wound, noting its location and proximity to underlying nerves or arteries. Document the location, length, estimated depth, and general shape of the wound. General appearance, obvious injuries, or visible foreign bodies should be noted; more detailed wound exploration typically waits until after anesthesia and radiographs, if needed. Provide anesthesia, cleanse the wound, and carefully inspect the full extent of the wound for foreign bodies.

The loose, thin skin over the dorsum of the foot allows for adequate visual, digital, and instrument exploration for tendon lacerations, as well as for foreign body discovery. The dense tissue of the plantar surface of the foot limits wound visualization, and the risk of creating further injury limits exploration. An exception to this general rule of limited exploration on the weight-bearing plantar surface is in an infected wound with suspected foreign body. With significant blunt injury to the leg, like a crush injury, consider compartment syndrome and evaluate accordingly (see Chapter 278, "Compartment Syndromes").

If a nerve laceration is suspected, light touch and/or static two-point discrimination should be tested in the foot and toes and compared with the uninjured side. Two-point discrimination varies in the foot, with normal values of 1.5 cm in the hind, mid, and forefoot, and <1 cm in

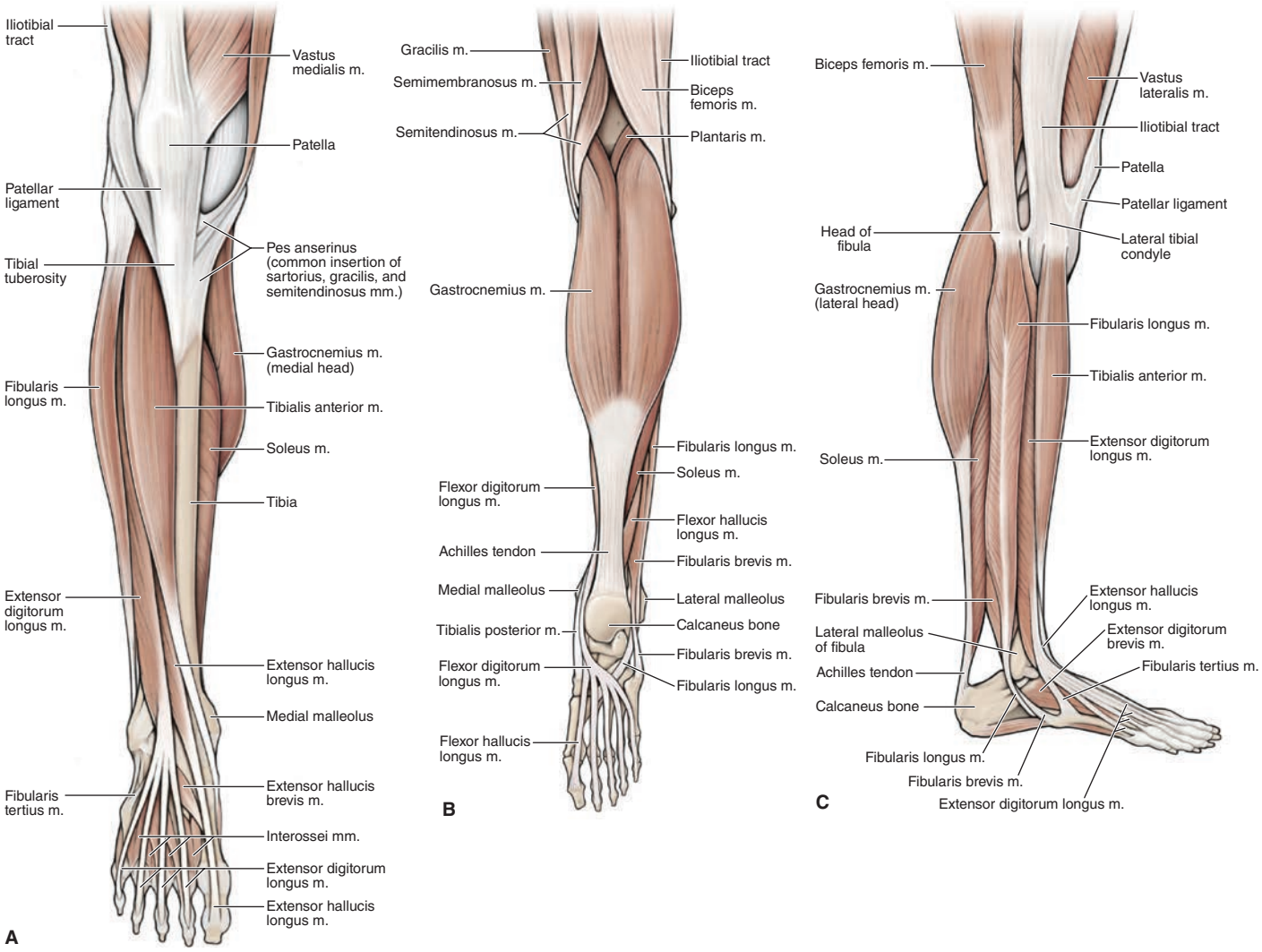

FIGURE 44-2. Muscles of the lower leg. **A.** Anterior compartment. **B.** Superficial posterior compartment. **C.** Lateral compartment. m = muscle; mm = muscles. [Reproduced with permission from Morton DA, Foreman KB, Albertine KH: *The Big Picture: Gross Anatomy*, McGraw-Hill Education, Inc. © 2011, Figures 37-1C, 37-3A, and 37-2, respectively.]

the big toe, but these measures are not reliable in patients with diabetes or peripheral vascular disease.[5] Sensory deficits to the foot can result in significant long-term morbidity. Motor function may be easier to assess after anesthesia or reduction of an associated fracture or dislocation. Obtain prompt surgical consultation if motor nerve or major sensory nerve injury is identified as primary repair may be indicated.[4] Nerve injuries caused by open blunt injuries are not typically repaired at the time of injury, partly due to the risk of infection and partly due to the possibility that a contused nerve will regain function without surgical intervention.

Assess motor function, palpate the tendon, and observe the tendon through its entire range of motion to evaluate for tendon injuries. A partially injured tendon may be noted to "catch" on the synovial sheath during range of motion. The superficial location of the Achilles tendon facilitates evaluation of an injury to this structure; US can be used to augment manual palpation. Sometimes an Achilles tendon laceration may not be visible or palpable, and presence of active plantar flexion of the foot cannot be used to exclude the injury as the tibialis posterior muscle also flexes the foot at the ankle. The Thompson test can assist in detecting an Achilles tendon rupture. The patient lies prone on the examination cart with the feet hanging over the edge of the bed, and the examiner places one hand on each mid-calf (**Figure 44-8**). If the Achilles tendon is intact, the foot plantar flexes when the calf is squeezed. Comparison with the unaffected side is helpful to detect subtle movement. A positive Thompson test is when the affected foot does not flex, indicative of an Achilles tendon rupture.[6]

If the patient has a laceration about the knee, quadriceps and patellar tendon disruption may be directly visualized. Tendon integrity is also assessed by having the patient lay supine on the stretcher with the hip partially flexed and the heel in contact with the stretcher pad. Ask the patient to lift the foot; inability to raise the foot off the stretcher suggests quadriceps or patellar tendon disruption.

ANCILLARY STUDIES

Obtain radiographs when a fracture, radiopaque foreign body, or joint penetration is suspected. Forgoing radiographs and using wound exploration alone to exclude a foreign body is a reasonable approach, but carries a small risk of missing a retained object.[7-9] CT or MRI can detect retained organic material. Bedside US may identify retained foreign bodies and detect tendon lacerations and fractures (see Chapter 45, "Soft Tissue Foreign Bodies"). Fluoroscopy is a useful dynamic imaging modality that may assist in identifying and removing foreign bodies. No single imaging modality or wound exploration will identify every foreign body; emphasize close follow-up if the mechanism of injury suggests a potential for a foreign body but none was identified on imaging or wound exploration.

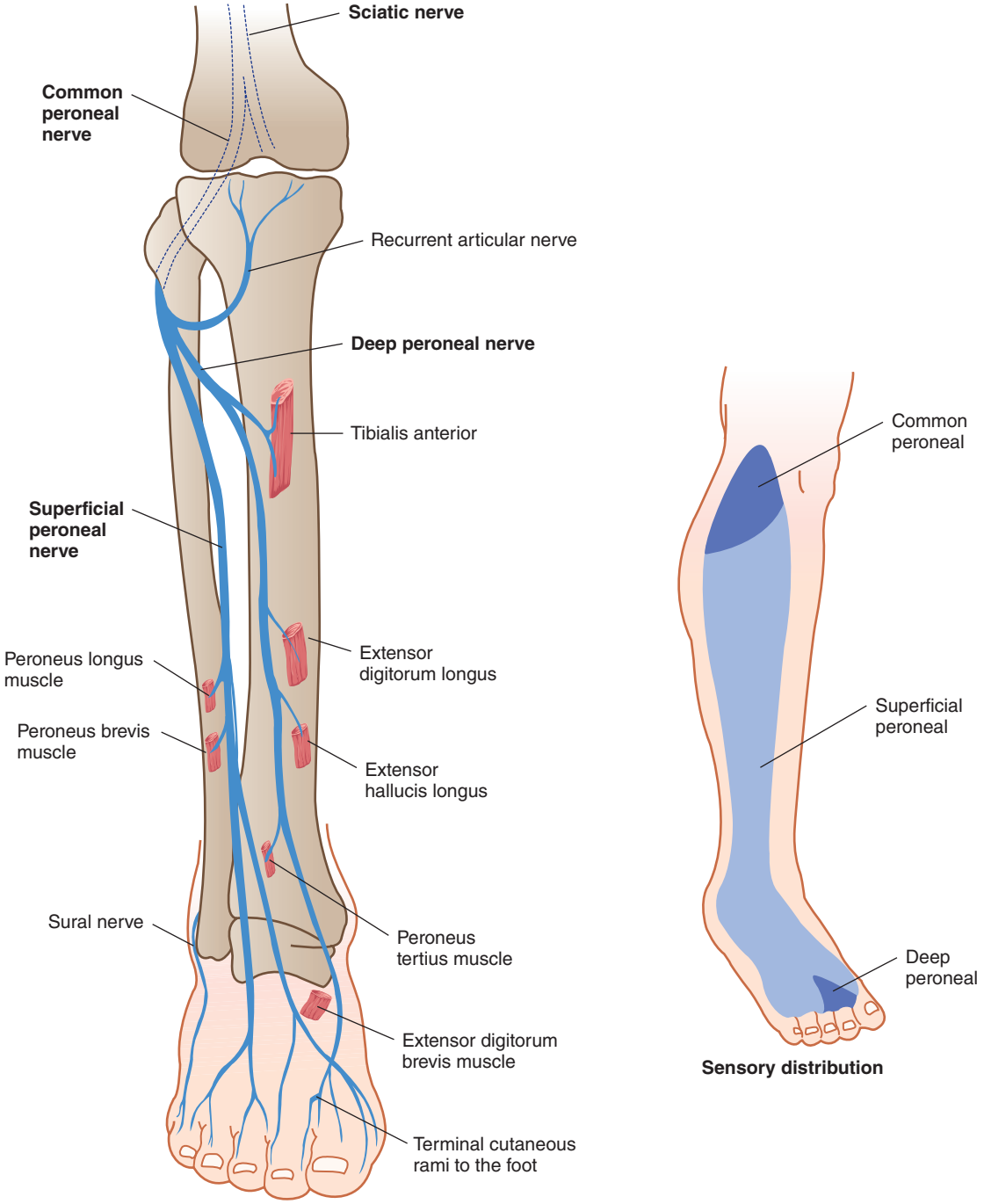

FIGURE 44-3. Common peroneal nerve. [Reproduced with permission from: Waxman SG: Appendix C. Spinal nerves and plexuses. In: Waxman SG (ed): *Clinical Neuroanatomy*, 27th ed. New York, NY: McGraw-Hill, Inc.; 2013. Figure C-16.]

Lacerations in proximity to a joint may penetrate the articular capsule, but detecting joint penetration by examination alone is often difficult. Intra-articular gas on plain radiograph is a definite sign of joint penetration. **If the radiograph does not display intra-articular gas, the saline load test can be used to determine joint integrity, especially in the knee and ankle.**[10] Inject sufficient amounts of saline to adequately stress the capsule, because false-negative results may be obtained if too little fluid is injected. Volumes of 74 to 194 mL into the knee and 30 to 55 mL into the ankle yield sensitivities of ≥95% in detecting joint penetration by observing fluid leaking from the wound.[10,11] The addition of **methylene blue** to the injected saline does not increase diagnostic accuracy.[12] CT detection of intra-articular gas can also be used to identify joint penetration in periarticular knee wounds with high sensitivity.[13]

TREATMENT

ANESTHESIA

Anesthesia can be administered by topical, local, or regional routes. The toes can be anesthetized using standard digital blocks. Epinephrine-containing local anesthetics can be safely used for digital blocks in toes (see Chapter 36, "Local and Regional Anesthesia").

Lacerations to the dorsum of the foot can be sufficiently anesthetized by infiltration of local anesthetic. Topical agents may also be used if there is a concern for tissue disruption with infiltration of anesthetic. The plantar surface of the foot is sensitive to the infiltration of a local anesthetic, so regional nerve blocks may be helpful. The sural nerve block and the posterior tibial nerve block (see Chapter 36) are the two

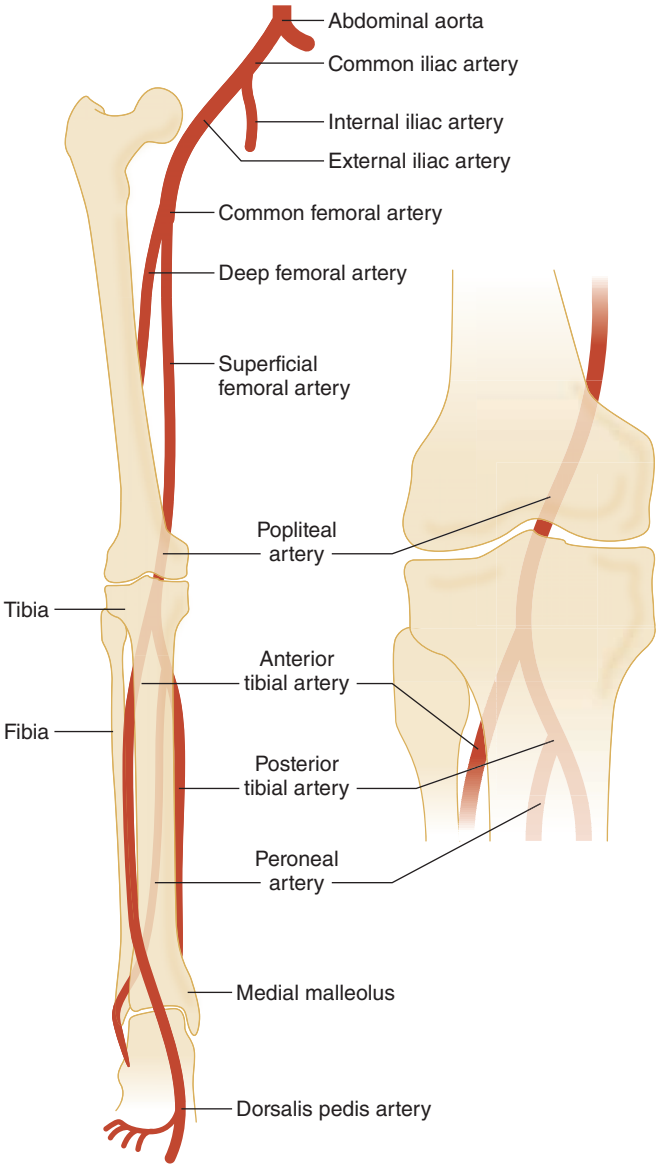

FIGURE 44-4. Major arteries of the lower leg.

most commonly used nerve blocks for the foot. Topical local anesthetic preparations can achieve adequate anesthesia on the dorsum of the thigh, leg, and foot, but may be ineffective on the dense epidermis of the plantar surface of the foot. In children, distraction techniques, use of child-life specialists, anxiolytics, and conscious sedation may help alleviate anxiety and pain response (see Chapter 115, "Pain Management and Procedural Sedation in Infants and Children").

WOUND PREPARATION

Wound irrigation with copious amounts of saline is recommended due to the increased risk of infection with lower extremity lacerations (see Chapter 40, "Wound Preparation"). Debridement to remove devitalized tissue is an important aspect of wound care to reduce the risk of wound complications, but debridement should be limited on the plantar surface of the foot or on the shin as skin in those areas is not pliable enough to be stretched and cover a defect. Any opening resulting from debridement would then require repair under tension across the laceration.

A lower risk of wound infection if the repair is performed within 6 hours after the injury is not substantiated by published evidence (see Chapter 40, "Wound Preparation"). Repair of clean-appearing wounds without visible contamination presenting after 6 hours is acceptable if primary closure is felt beneficial. Otherwise, consider delayed primary closure in cases of delayed presentation or heavy contamination (see Chapter 41, "Wound Closure").[14]

WOUND CLOSURE

Wound location, size, and shape guide the decision to close with adhesive strips, sutures, or staples. Staples are acceptable for linear lacerations through the dermis as long as the wound is sharp with straight and accurately aligned wound edges, minimizing the potential for scar formation. Most leg lacerations do not have these characteristics, so using staples will often result in less aesthetic wound healing. Staples should not be used on the foot because they are uncomfortable when attempting to walk during recovery. Lacerations of the lower extremity can be under increased wound tension compared with other anatomic sites, so these lacerations are frequently repaired using tension-reducing techniques such as multiple-layered closure or horizontal mattress closure.

Repair is guided by the type of tissue injured. Subcutaneous fat is not sutured as even absorbable suture material will tear through fat based on the consistency of the tissue. The large muscle groups of the leg, particularly the quadriceps and the gastrocnemius complex, are somewhat superficial and thus are prone to lacerations. Laceration to the fascia overlying muscle should be repaired using absorbable suture. Small lacerations to underlying muscle do not require repair, but larger lacerations to a muscle belly or the musculotendinous joint typically require operative repair.[15-17]

LEG LACERATIONS

THIGH LACERATIONS

Proximal lower extremity lacerations are usually straightforward, and thickness of the soft tissue layers helps to prevent injury to vital structures. Lacerations to the proximal lower extremity also have less tension on them, allowing for easier exploration, debridement, and repair. Assess lacerations to the proximal femoral area for injuries to the femoral artery, vein, and nerve. Acute traumatic femoral artery injuries are uncommon, but are associated with a high incidence of limb loss and morbidity.[2]

Chainsaws can produce serious injury to the leg.[18] Obtain additional historical information relating to this injury, including the size of the blade, the type of material being cut, and whether the patient fell into other debris once the laceration was sustained. Remove obvious foreign bodies or debris, and use copious irrigation during wound cleansing. Radiographs should be obtained to evaluate bony involvement in the injury as blade speed can lead to significant injury. **Do not remove the blade if the patient arrives with it embedded in the muscle;** removal should be done in the operating room to determine the location of the blade relative to the major arteries.

KNEE LACERATIONS

Close simple lacerations in the knee area with 4-0 nonabsorbable sutures, using interrupted or horizontal mattress sutures because of the marked active skin tension in this area. **As already noted, assess for joint capsule penetration and laceration of the patellar and quadriceps tendons.** The common peroneal nerve is prone to injury as it runs over the head of the fibula laterally, so distal limb motor function should be assessed (foot eversion and dorsiflexion). Deep popliteal wounds can injure the popliteal artery and tibial nerve. Popliteal artery injuries typically require emergent repair because, in most individuals, there is minimal collateral circulation at the level of the knee (Figure 44-4).

The knee should be splinted or placed in a knee immobilizer to decrease active tension and promote better wound healing. Knee area lacerations in children can be closed with tissue adhesives and splints to restrict movement.

PRETIBIAL LACERATIONS

Managing pretibial skin lacerations, especially in the elderly patient with comorbidities, is challenging. These wounds often occur on the distal

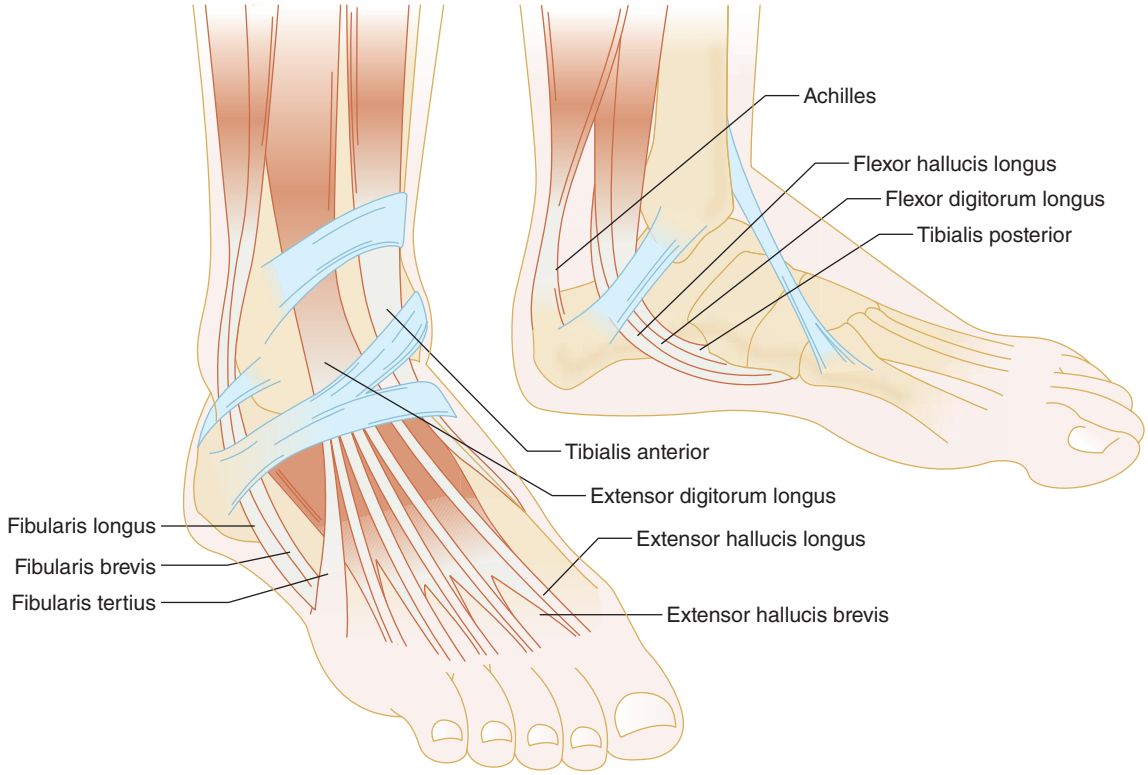

FIGURE 44-5. Tendons of the foot.

third of the pretibial region, which is poorly vascularized and slow to heal.[19,20] Pretibial wounds are approached according to the type and severity (**Table 44-1**).[21,22]

Wounds where the edges can be approximated without tension can be closed with adhesive tapes or simple sutures. Wounds with tension can be closed using horizontal mattress sutures with 4-0 nonabsorbable sutures. Occasionally, the 4-0 suture is too fine and cuts through the skin, so use 3-0 sutures. The natural contraction of the thin skin makes closure more difficult because sutures often cut through the fragile skin when attempting to approximate the wound edges. A technique to overcome this problem is to reinforce the wound edges with adhesive tape applied along the edges before closure with placement of percutaneous sutures penetrating through the adhesive tape.[23-25] Additionally, to minimize tension across the wound, tincture of benzoin can be applied over the sutures, and then broad adhesive tape strips (1/2 in.) can be placed over the sutures to minimize tension across the wound. Alternatively,

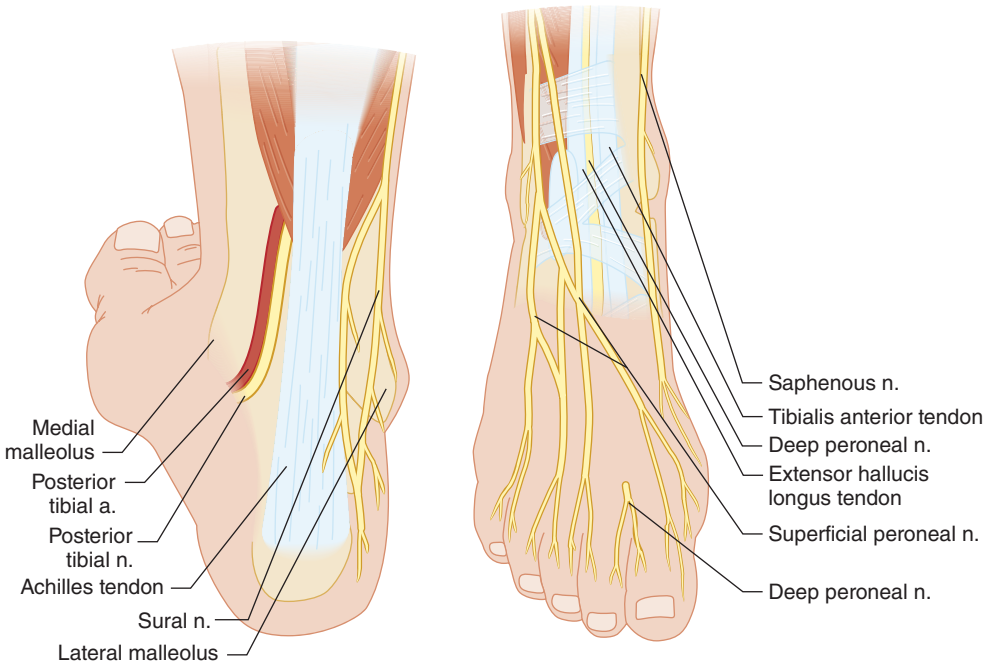

FIGURE 44-6. Nerves of the foot. a. = artery; n. = nerve.

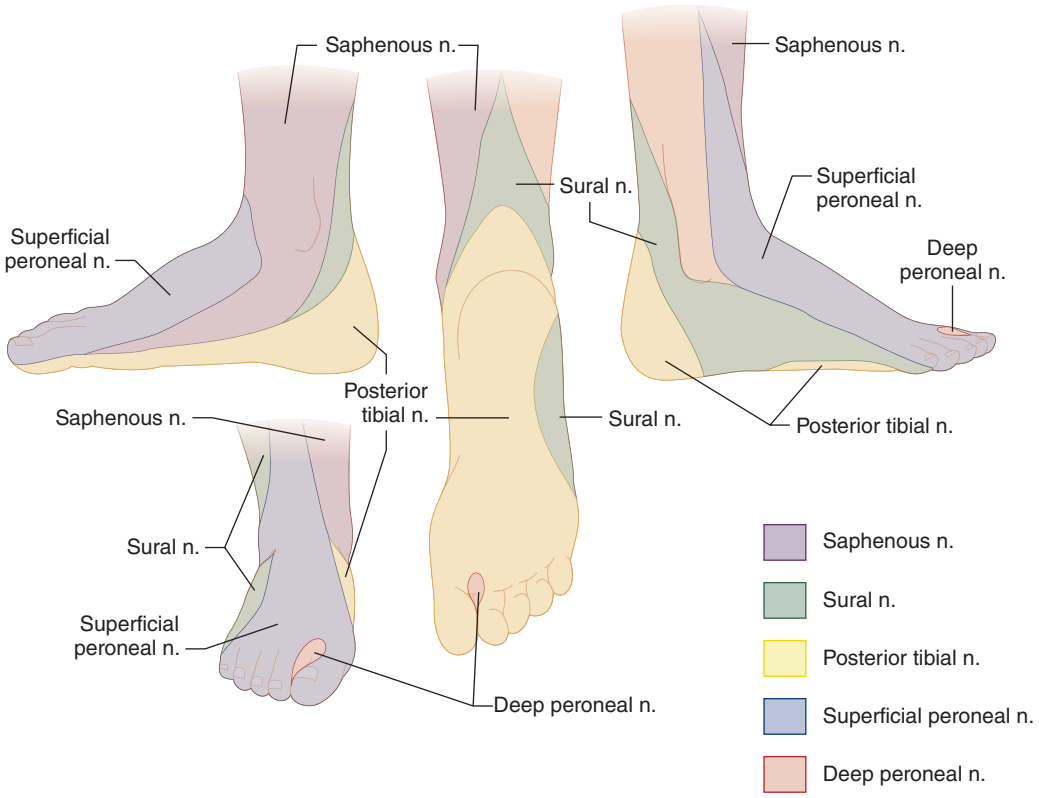

FIGURE 44-7. Sensory innervation of the foot. n. = nerve.

the wound edges can be held in place by adhesive strips perpendicular to the wound, with sutures placed through the strips, thereby removing the shear force of the strip on the skin.

Flap lacerations with significant skin loss are best repaired with primary excision and skin grafting.[19,22,26] Apply a foam adhesive dressing (such as 3M Tegaderm®; 3M, St. Paul, MN) to absorb exudate and reduce healing time. Patients should remain ambulatory during the healing of pretibial injuries, even after skin grafting.[27] Protecting the repair from the tension created by foot plantarflexion is useful; consider using a lightweight plastic ankle-foot orthosis.[28]

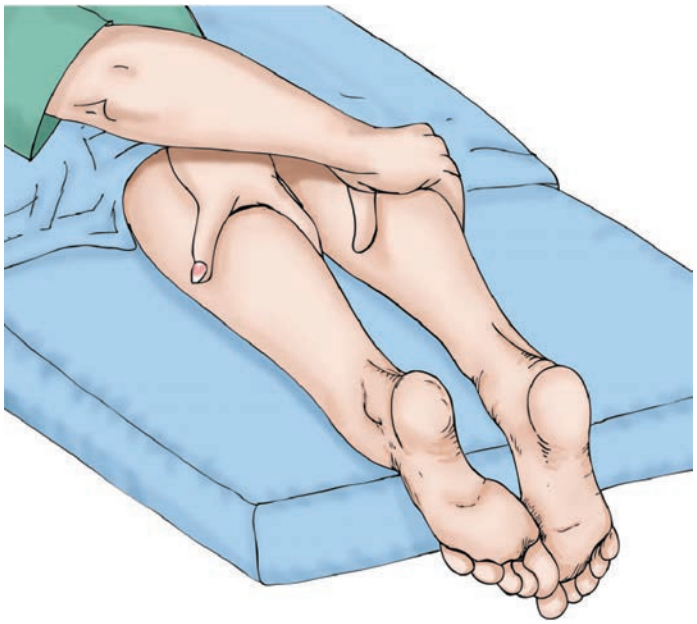

FIGURE 44-8. Thompson test.

FOOT AND ANKLE LACERATIONS

DORSAL FOOT AND ANKLE LACERATIONS

Dorsal surface lacerations are repaired almost exclusively with nonabsorbable, monofilament suture material, most commonly 4-0 or 5-0 for small lacerations. Use careful technique suturing the skin to avoid vessels, nerves, and tendons that lie just under the surface. Deep sutures are not recommended for the same reason. Running sutures are acceptable on the dorsal surface, and smaller lacerations may be closed with adhesive tapes or tissue adhesives. For lacerations under tension, consider applying a splint to restrict movement, allowing for healing during the first 5 to 7 days.

The decision to repair tendon lacerations in the foot depends on the functional impairment caused by the injury compared with the benefits of repair. Many extensor tendon lacerations involving the mid-foot and forefoot can go unrepaired without compromising foot function. The skin is closed and the foot splinted, leaving the injured tendon alone.

TABLE 44-1 Pretibial Lacerations

Classification	Description	Management
Ia	Simple linear laceration not under tension	Primary closure with adhesive strips or sutures
Ib	Simple linear laceration under tension	Primary closure using methods to reduce skin tension
IIa	Flap laceration with no skin loss and/or wound hematoma	Close with adhesive strips
IIb	Flap laceration with some necrosis and/or hematoma	Excise small nonviable areas; close with adhesive strips
III	Flap laceration with significant skin loss or necrosis	Primary excision and skin grafting under local anesthesia
IV	Degloving injury	Plastic surgery consult

Lacerations of the extensor hallucis longus or tibialis anterior require consultation with an orthopedist or podiatrist because dorsiflexion of the great toe and foot is important in walking and running.[29] Flexor tendon lacerations across the toes (excluding the great toe) can usually be left unrepaired without significant functional sequelae, but occasionally a hammer toe or claw toe deformity develops. Lacerations of the flexor hallucis longus are frequently repaired, although long-term benefit is unproven, even in athletes.[29]

PLANTAR FOOT LACERATIONS

Repairing a laceration on the plantar surface is best done with the patient placed in a prone position, with the foot overhanging the cart or elevated by placing a pillow beneath the ankle. A large suture needle with thick thread is required to penetrate the hypertrophied epidermis and dermis of the sole of the foot. If there is tissue loss or the site is under tension, vertical mattress sutures may be required. In the arch area, achieving tissue eversion can be difficult. Do not use adhesive tapes, tissue adhesives, and staples on the plantar surface. Repair small plantar lacerations if the wound gapes open, but small or superficial wounds to the plantar surface where the edges approximate typically heal rapidly without sutures.

DIGITAL LACERATIONS

Digital lacerations may injure the nail bed, often accompanied by digital fractures. Clinical signs such as bleeding from the eponychium and a laceration proximal to the nail bed suggest a possible open fracture.[30] Nail bed lacerations place the underlying bone at risk for bacterial contamination because the skin is directly attached to the periosteum with no intervening layer of subcutaneous tissue. Missed open fractures have resulted in osteomyelitis and growth delay of the digit in children. Consider removal of the nail to evaluate for nail bed laceration if a subungual hematoma occupies a large portion of the nail plate or if there is disruption of the nail or nail folds.[31] Repair the nail bed with either absorbable sutures or tissue adhesives.[32] Conversely, simple nail trephination is adequate for drainage of subungual hematomas without nail or nail fold deformities.

Tendon injuries of the digits may require consultation, especially when the extensor hallucis longus is involved, because injury to this tendon impairs functionality during the swing phase of the gait cycle. Surgery is often recommended for patients with extensor hallucis longus tendon lacerations, and grafting may be needed.

INTERDIGITAL LACERATIONS

Lacerations between the toes are difficult to repair because the confined interdigital space is difficult to access for suturing. An assistant gently separating the toes enhances exploration and repair of interdigital lacerations. Simple interrupted sutures often lead to skin inversion and risk of failure of the initial wound repair with interdigital lacerations. The more effective closure technique, albeit somewhat more difficult to perform, is to place horizontal or vertical mattress sutures. Use 5-0 monofilament nonabsorbable sutures on a small cutting needle. Use monofilament absorbable sutures in young children, thus avoiding suture removal. When a web space laceration involves the neurovascular bundle, the skin is usually closed without attempting to repair the neurovascular injury, followed by subsequent referral to a specialist.

HAIR-THREAD TOURNIQUET SYNDROME

Hair-thread tourniquet syndrome, also referred to as *acquired constriction ring syndrome*, is an unusual type of toe injury usually seen during infancy and rarely seen in older children.[33-35] A long strand of hair or thread becomes wrapped around a toe, often producing strangulation and digital ischemia. This can be an occult source of irritability for infants. Complete removal is required to restore perfusion and allow skin healing. Approaches to salvage the compromised digit are to either unwind the hair or thread, apply a chemical depilatory agent to dissolve the hair, or cut the hair or thread with suture removal scissors.[35,36] If there is soft tissue swelling and the hair or thread is imbedded and not easily accessible, make a midline longitudinal incision along the extensor surface of the toe to cut the hair or thread.[37] To cut the encircling material, it will often be necessary to split the fibers of the extensor ligament, but avoid transecting the fibers. The multiple strands of hair or thread are then removed using fine forceps without teeth.

After removal of the hair or thread, the toe often retains the initial appearance, making the physician uncertain whether all of the strands have been released. Hair-thread tourniquet syndrome can cause deep cutaneous lacerations that result in tendon lacerations requiring operative repair.[38] Hair-thread tourniquet syndrome is not the result of intentional injury and does not warrant reporting as suspected child abuse.[39]

DISPOSITION AND FOLLOW-UP

Most patients with lower extremity lacerations will be able to go home after ED evaluation and treatment. Patients at high risk for compartment syndrome, those with limited mobility and inadequate home assistance, and patients requiring operative repair should be admitted. Patients may require ancillary devices such as crutches, walkers, and wheelchairs. Elevation of the extremity decreases swelling and infection risk. Sutures are typically removed in 10 to 14 days.

Significant tendon lacerations of the lower extremity are usually repaired a few days to weeks after the initial injury. Treatment in the ED consists of skin closure; splinting of the foot, ankle, or leg; initiation of prophylactic antibiotics; instruction for non–weight-bearing crutch use; and arrangement for the patient to follow up with an orthopedist or podiatrist.

SPECIAL CONSIDERATIONS

AGE CONSIDERATIONS

The preverbal child may have particular difficulty limiting movement of the injured extremity and is more likely to contaminate the wound. Generous dressings aid in protecting a lower extremity laceration according to the general rule, **"the smaller the child, the larger the dressing."**

Elderly patients tend to have thin skin and decreased subcutaneous fat, especially over the pretibial surface, making wound edges more difficult to appose and resulting in closure under tension. Additionally, fragile skin in elderly patients predisposes sutures to tear through the skin. Adhesive tapes may be needed to reinforce the closure. Elderly patients are more likely to have medical conditions that can delay wound healing and are less likely to be adequately immunized against tetanus. Assess for fall risk and the ability to perform daily tasks after repair and immobilization of the injured leg.

TOE AMPUTATION

Reimplantation of a severed toe is not typically performed. Reattachment of an amputated great toe, forefoot, or entire foot is occasionally done, although it is extremely complex. Immediate consultation with a reimplantation surgeon is essential in such circumstances. Any severed part should be gently washed (not scrubbed) with sterile saline to remove gross debris, wrapped in saline-soaked gauze, and placed in a plastic bag that is then closed and placed in an ice water bath.

RETAINED FOREIGN BODIES

Retained nonreactive foreign bodies, such as glass, can cause chronic pain, especially during walking, if the material is not removed. In the absence of chronic discomfort, inert foreign bodies can remain in the foot, where they typically become encapsulated without causing injury or infection. Conversely, reactive organic material does not become encapsulated and does promote infection. Therefore, reactive organic material should be aggressively identified and removed. Sonography or fluoroscopy may be useful to guide removal of foreign bodies. Deep foreign bodies in the foot can be extremely difficult to remove in the ED, and such cases are best referred to the surgeon for location and removal in the operating room.

PROPHYLACTIC ANTIBIOTICS

Although infection occurs in 3% to 8% of lower extremity lacerations, there is no evidence to support routine antibiotic prophylaxis in uncomplicated lacerations (see Chapter 47, "Postrepair Wound Care"). However, use prophylactic antibiotics for complicated lacerations in the setting of bites, open fractures, tendon or joint involvement, presence of foreign debris, and obvious infections. Diabetes and other predisposing medical conditions, wound contamination, and laceration length >5 cm are factors that predispose to wound infection.[40]

Most lower extremity wound infections are due to either methicillin-sensitive *Staphylococcus* and/or *Streptococcus* species. Animal bites to the leg and foot require additional coverage for *Pasteurella.* Asplenic or immunocompromised patients who sustain a dog bite should receive coverage against *Capnocytophaga canimorsus.* Amoxicillin-clavulanate will cover all four organisms (see Chapter 46, "Puncture Wounds and Bites").

Staphylococcus and *Streptococcus* are the most common cause of soft tissue infections following plantar puncture wounds. *Pseudomonas aeruginosa* is a frequent cause of osteomyelitis and osteochondritis when the puncture occurs through the sole of a shoe (see Chapter 46).

Open fractures associated with wounds <10 cm in size without extensive soft tissue damage or contamination should receive antibiotic prophylaxis using cefazolin, 2 grams IV (alternatively clindamycin, 900 milligrams IV, if severe beta-lactam allergy), plus vancomycin, 15 milligrams/kg IV if there is known methicillin-resistant *Staphylococcus aureus* colonization.[41] For open fractures with extensive soft tissue damage, antibiotic prophylaxis should use ceftriaxone, 2 grams IV, with metronidazole, 500 milligrams IV, added if soil or fecal contamination is present and vancomycin, 15 milligrams/kg IV, if there is known methicillin-resistant *S. aureus* colonization.[41]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 45

Soft Tissue Foreign Bodies

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Joshua Mastenbrook

INTRODUCTION

Soft tissue foreign bodies may be encountered when managing new wounds or evaluating complications of old wounds. This chapter discusses methods of detecting and removing them.

In the setting of a fresh wound, methodically search fresh wounds for contamination by foreign material. If a foreign body is discovered within a wound cavity or deeply embedded in tissue, decide if removal of the material is urgent, can be delayed, or is even necessary. The decision to remove foreign bodies located below the dermal layer of skin depends on the size, location, composition, accessibility, and anticipated mechanical and inflammatory effects of the object. Many foreign bodies should be removed in the ED; for example, all foreign material within the cavities of fresh lacerations should be irrigated away, debrided, or extracted with instruments. Occasionally, patients with subcutaneous foreign bodies should be referred to appropriate specialists for delayed removal.

Most foreign bodies are detectable during clinical examination.[1,2] Imaging studies are used to evaluate wounds when a concealed object is possibly present.[3]

PATHOPHYSIOLOGY

Transient inflammation is an integral part of normal wound healing. A small amount of foreign debris in a wound provokes an inflammatory response in an effort to eliminate or contain the invader. Large quantities of devitalized tissue, foreign debris, bacteria, or other irritants present within a wound intensify this protective response. Excessive or prolonged inflammation delays wound healing and destroys surrounding soft tissue and bone, producing periosteal reactions, osteolytic lesions, synovitis, and arthritis. If the body fails to dissolve or extrude foreign material, it may become encapsulated within a fibrous capsule. Once a retained foreign body is encapsulated, inflammation subsides.

The type, timing, and intensity of an inflammatory reaction are determined primarily by the chemical composition and physical form of the foreign object. Material that is inert—such as glass, metal, or plastic—may not elicit any abnormal tissue response. Objects with smooth, nonporous surfaces produce less inflammation and fibrosis than those with rough surfaces. Most metals are inert, but those that oxidize will cause mild to moderate inflammation. Earrings with studs dipped in gold paint cause earlobe swelling and inflammation when the paint flakes off. Vegetative foreign bodies, such as wood, thorns, and spines, trigger the most severe inflammatory reactions. Sea urchin spines, other marine foreign bodies, and hair may cause chronic inflammation with granuloma formation.

In some cases, inflammation is caused by a local toxic reaction. For example, blackthorns contain an alkaloid that produces intense inflammation. The oils and resins in redwood and cedar splinters also cause considerable inflammation. Sea urchin spines and catfish spines contain venom that causes severe burning pain at the puncture site and a variety of systemic symptoms (see Chapter 213, "Marine Trauma and Envenomation"). A sudden, local inflammatory reaction from a rose thorn or cactus spine may be an allergic response to fungi on the plant. Some cacti cause a delayed hypersensitivity reaction. Systemic toxic and allergic reactions are unusual but serious complications of foreign bodies. Although toxicity is unlikely, foreign bodies containing lead, such as bullets, have the potential to produce systemic lead poisoning, particularly if they are in contact with pleural, peritoneal, cerebrospinal, or joint fluid.[4-6]

Infections are the most common complication of retained foreign bodies, producing local wound infection, cellulitis, abscess formation, lymphangitis, tenosynovitis, bursitis, septic arthritis, and osteomyelitis.[7,8] Infections associated with retained soft tissue foreign bodies are characteristically resistant to pharmacologic therapy; antibiotics, anti-inflammatory drugs, and steroids may produce a partial regression but seldom eradicate the infection.[9] Some infections will resolve spontaneously once the foreign bodies are removed. Bacteria are infrequently detected after plant thorn injuries, possibly due to the empiric use of antibiotics, but when bacteria are found, gram-negative aerobic bacillus Enterobacteriaceae family member *Pantoea agglomerans* is a commonly reported isolate.[10,11] Vegetative foreign bodies may also cause fungal infections, particularly in immunosuppressed patients.

Foreign objects can also cause mechanical damage by compressing or lacerating anatomic structures or occluding vessels. Repeated movement of tissue containing a foreign object increases the fibrous reaction.

CLINICAL FEATURES

HISTORY

Every wound has the potential for concealing a foreign body, but only a small percentage of lacerations and puncture wounds actually contain them.[1,2,12] Historical factors associated with a higher risk for a retained foreign body include the mechanism of injury, composition and shape of the wounding object, and the shape and location of the resulting wound. Blows to the mouth may fracture teeth, embedding fragments in the lip, tongue, or buccal mucosa of the patient or in the hand of the assailant.[13-15] Objects that shatter, splinter, or break in the process of causing a wound often leave remnants behind. Thorns, spines, and sharp wooden branches are usually brittle and tend to penetrate deeply

into puncture wounds before breaking. Wood splinters are notorious for fragmenting, especially when they are pulled out of a puncture wound.

Patients impaled by long, thin metallic objects, such as hypodermic or sewing needles, may remove them without realizing that a portion of the object broke off beneath the skin surface. Both remnants of a needle and impurities in street drugs can cause persistent pain or abscess formation at the site of IV drug use. Nails that penetrate socks and shoes may drive leather, rubber, or cloth into the plantar surface of a patient's foot. Blunt objects with a diameter >4.5 mm may push a plug of skin deep into a wound, resulting in an epidermal inclusion cyst. If any object pulled from a wound does not appear intact, the wound should be explored for further contaminants.

The patient's description of a foreign body sensation in a fresh wound is a useful sign in adults—the perception of a foreign body more than doubles the likelihood of one being present.[12] However, foreign body sensation is less useful in verbal-age children.[16] If a patient reports a sudden, sharp pain on the bottom of the foot while walking barefoot, consider the possibility of impalement with a needle, toothpick, splinter, or shard of glass.

Patients with retained foreign bodies may present to the ED after a wound heals complaining of sharp pain with movement or with pressure over the site. Failure of a wound to heal also may be evidence of a retained irritant. Chronic, delayed, and recurrent infections are associated with retained foreign bodies (**Figure 45-1**). New puncture wounds that become infected and infections that are resistant to antibiotic therapy suggest a retained foreign body. Arthritis in a joint near an old puncture wound may be plant thorn–induced synovitis.[8,9] Unsuspected foreign bodies may present as soft tissue masses.[17]

PHYSICAL EXAMINATION

Physicians are occasionally surprised by foreign bodies that are embedded in small or seemingly superficial wounds. Physical findings that are associated with the presence of a foreign body include a discoloration or visible mass under the epidermis, palpation of a mass, sharp well-localized pain with palpation over or adjacent to a wound, and limitation of passive range of movement of a joint near a wound.

Old wounds with retained foreign bodies may have a persistent purulent drainage, a chronic draining sinus, or a chronic granulomatous reaction. A sterile abscess that complicates wound healing may be the result of a foreign body.

Some foreign bodies are discovered in wounds unexpectedly, but most are found during a deliberate and careful exploration of wounds considered to be at risk.[1,2,12] Adequate lighting, good hemostasis, appropriate anesthesia, and patient cooperation are essential. Magnifying loupes can enhance visualization of small debris fragments or foreign bodies. Make effort to visually inspect all recesses of a wound. **Wounds deeper than 5 mm and wounds whose depth cannot be visualized have a higher association with foreign bodies.** If punctures and other narrow wounds make direct visualization difficult and there is concern about a foreign body below the surface, the wound margins should be extended with a scalpel (**Figure 45-2**).



A



C



B

FIGURE 45-1. **A.** A diabetic patient presented with redness, swelling, and mild pain of her left foot. Although she admitted to walking barefoot on occasion, she had no recollection of stepping on a sharp object. **B.** A small, healing puncture wound was visible on the plantar surface of her foot. **C.** Lateral radiographic view.



FIGURE 45-2. This patient's leg was punctured by a wooden stake 2 days before presentation. **A.** Surrounding cellulitis and point tenderness lateral to the wound indicated the probability of a retained foreign body. **B.** The entrance to the wound was extended. **C.** A 1.7-cm piece of wood was removed.

Wounds that penetrate deeply into adipose tissue are difficult to explore and easily hide foreign material. Gentle probing with a hemostat is a less effective but sometimes acceptable alternative to wound exploration when the wound is narrow and deep and extending the wound is not desirable. This method is used frequently to evaluate plantar puncture wounds caused by nails and to search for clear glass, which is difficult to see in a wound. A closed hemostat should be introduced into the wound and either used as a probe or spread open and then withdrawn. If an instrument strikes a metallic or glass foreign body, it will produce a grating sensation. The instrument should not be used to grasp blindly in hopes of clamping an unseen object. Blind probing is especially dangerous in hands, feet, or face, where direct visualization is the preferred method of exploration.

DIAGNOSIS

Imaging studies should be ordered in most cases in which a retained foreign body is suspected but not found during wound exploration or when exploration of the entire wound is technically impossible.[3,18] Imaging is also useful after initial removal of multiple foreign bodies to determine if all the pieces were found.

Four imaging modalities are available: plain radiography, US, CT, and MRI.[19] The sensitivity and specificity of each imaging modality depend on the object's size, shape, density, and orientation relative to the imaging beam (**Table 45-1**).[3,19] Materials that are the same density as surrounding soft tissue are difficult to see with any type of radiographic or sonographic technique.

TABLE 45-1 Imaging Modalities for Detection of Soft Tissue Foreign Bodies[20-23]

Material	Plain Radiographs	US	CT	MRI
Wood	Poor	Good	Moderate to good	Moderate
Metal	Excellent	Good	Excellent	Poor
Glass	Excellent	Good	Excellent	Good
Organic (most plant thorns and cactus spines)	Poor	Good	Good	Good
Plastic	Moderate	Moderate to good	Good	Good
Palm thorn	Poor	Moderate	Good	Good

LOCALIZATION METHODS

Accurate localization of a foreign body before removal is important because blind searching is time consuming and can cause further injury. However, it is usually easier to detect the presence of a foreign body than to locate its exact position. If a foreign body is radiopaque, one can estimate its location and depth by taping radiopaque skin markers, such as lead circles, paper clips, or a grid, on the skin at the wound entrance or directly over the object.[24] With multiple projections, the object can be seen in relation to the markers. Hypodermic needles can be used as skin markers. Two or three needles are inserted into the skin near the object at approximately 90 degrees to each other to provide a frame of reference around the object. Plain films taken in multiple projections allow the physician to gauge the distance of the object from the closest needle or its distance between two needles (**Figures 45-3** and **45-4**).

The limitations of this technique are that it does not provide a true three-dimensional view and that images on radiographs are distorted by divergence and parallax. Tendons and other structures may block the most direct path to the foreign body.

IMAGE STUDY SELECTION

Unless a foreign body is embedded at a relatively superficial level or lies within the cavity of a fresh wound, it will not be easily detected or located by physical examination. If a foreign body is suspected based on the mechanism of injury but not found during exploration of a wound, a radiograph should be ordered first, because plain radiography will detect as many as 80% to 90% of all foreign bodies. It is also prudent to order films if a patient believes there is a retained object.[12,16,18] If the wound was caused by metal, glass, or gravel and no foreign body was found on plain films or wound exploration, the physician can end the search. For objects not routinely visible (or not found) on plain radiography, like wood, sonography is the modality of choice, with CT or MRI as alternatives.[19] **In summary, no single imaging modality is ideal for all types of foreign bodies.**

PLAIN RADIOGRAPHY

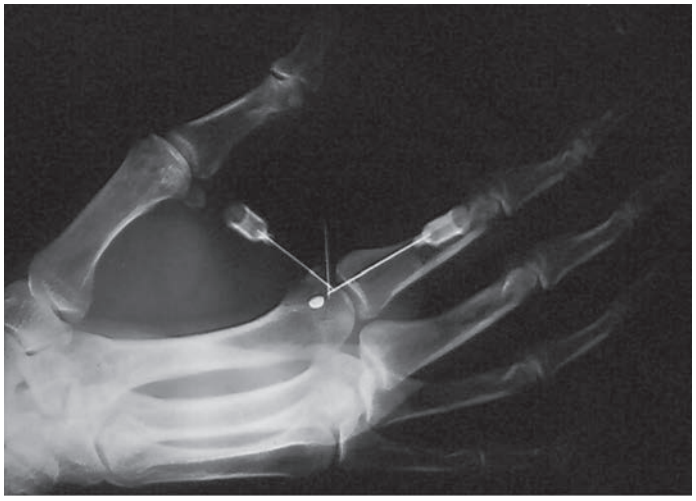
Most foreign bodies that can be missed during the initial clinical evaluation can be seen on plain radiographs, but the images must be inspected



FIGURE 45-3. Hypodermic needles used as skin markers.



A



B

FIGURE 45-4. Needle markers are used to triangulate the location of a radiopaque foreign body. **A.** Plain radiograph, anteroposterior view. **B.** Oblique view.

carefully to detect small and faint objects.[3] **Metal, mammalian bone, some types of fish bones (cod, haddock, grey mullet, red snapper, and sole), teeth, pencil graphite, certain plastics, glass, gravel, sand, and aluminum are visible on plain radiographs.** Almost all glass is visible on radiographs if it is 2 mm or larger, and glass does not have to contain lead to be visible on plain films (**Figure 45-5**).[25] A radiopaque fragment is more easily seen if its long axis is positioned parallel to the central ray of the x-ray beam, increasing its apparent density; thus, a foreign body may be evident on one radiographic view but not another.

Obtain plain film radiographs using an underpenetrated soft tissue technique, producing a lighter image that increases the contrast between the foreign body and surrounding tissue. **If the radiograph is displayed on a digital imaging system, the contrast and brightness of the image can be adjusted to achieve the same effect as an underpenetrated film.** Digital edge enhancement adjustments may make the foreign object stand out from the background. Radiographs should be taken in multiple projections to separate the shadow of the foreign body from underlying bone and to help gauge the depth of the object in the tissue (**Figure 45-6**). Chronic inflammatory changes may create secondary bony changes, such as osteolytic and osteoblastic lesions, pseudotumor formation, and periosteal reaction, revealing the object's location.

Many common or highly reactive materials, such as wood, thorns, cactus spines, some fish bones, other organic matter, and most plastics, are not visible on plain radiographs.[3,19,26] Sometimes, there is indirect evidence of their presence. A radiolucent filling defect may occur when the object is less dense than surrounding tissue. However, even radiopaque foreign bodies may be invisible on plain films if they are obscured by, or impacted in, bone.

COMPUTED TOMOGRAPHY

CT is capable of detecting more types of foreign materials than plain film radiography because it is 100 times more sensitive in differentiating densities (**Figure 45-7**).[19] One study found CT to be superior to plain radiography for detecting glass foreign bodies <3 mm in size.[27] Subtle density differences can be distinguished with a narrow radiographic density window adjustment, particularly if a computer workstation is used to vary the gain and contrast settings. **Thorns, spines, wood splinters and toothpicks, fish bones, and plastic foreign bodies can be identified with CT.**[3] In dry wood, the interstices between the fibers are filled with air, imparting reduced radiodensity and making dry wood less visible on CT.[19] Water-rich wood, either fresh from a tree or as occurs when dry wood has

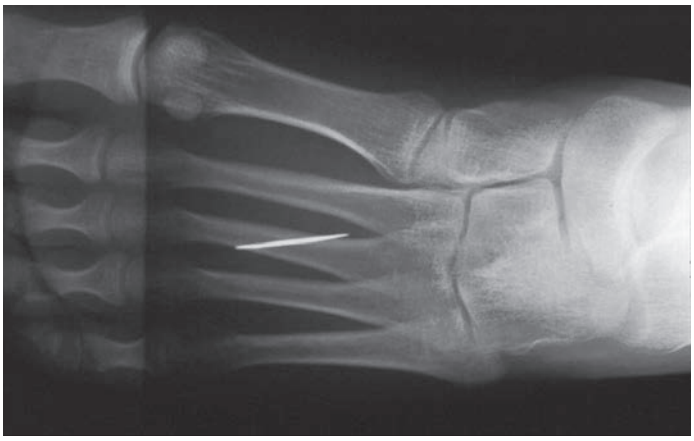


A



B

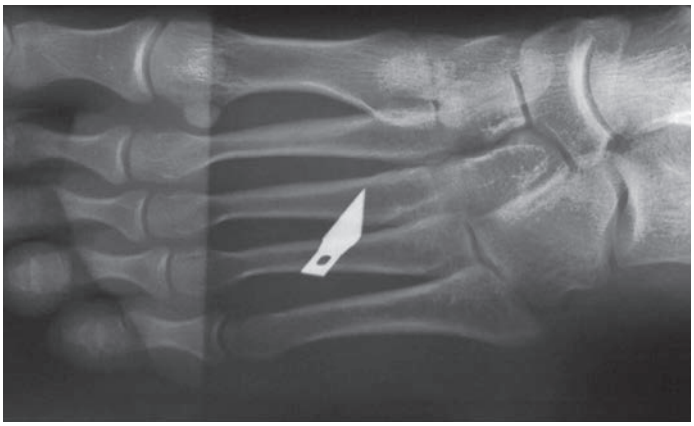
FIGURE 45-5. **A.** The marker points to a glass fragment in the plantar surface of this patient's foot on the lateral view of this radiograph. **B.** Oblique view.



A



B



C

FIGURE 45-6. **A.** The identity of this metallic foreign body is not apparent on the anteroposterior view of this radiograph. **B.** The shape and depth of the blade are best seen on the lateral view. **C.** Oblique view.

been embedded in tissue long enough to absorb serohematic fluid, is more visible as a slightly hyperdense object on CT.[28]

CT will often detect the inflammatory response to an object that has been in place long enough to elicit the reaction. CT may detect objects embedded in bone, and isodense objects may be outlined by surrounding air within the wound. Digital edge enhancement can further improve the visibility of these objects. CT images can be created in multiple planes and can demonstrate the relationship of a foreign object to important anatomic structures. The principal disadvantages of CT are its cost, higher radiation dose, and the fact that wood and other organic material have radiographic density close to water, making them difficult to distinguish from surrounding tissue. **Another pitfall of CT is that wood foreign bodies may initially mimic air bubbles on CT images.[29]**

ULTRASOUND

US is becoming the modality of choice for identifying radiolucent foreign bodies, as well as for directing exploration and foreign body removal.[30-35] **US can identify a wide variety of soft tissue foreign bodies such as wood, fish bones, sea urchin spines, other organic material, fiber, and plastic,** with ≥94% sensitivity for foreign bodies >4 to 5 mm (**Figure 45-8**).[36-41] However, the sensitivity and specificity of this test are highly dependent on the size and sonographic nature of the foreign body,[42,43] as well as the number of foreign bodies, the presence of confounding factors (e.g., bone, blood, purulence, scars, old sutures) associated with the foreign body, and operator skill and experience. Foreign bodies appear as hyperechoic foci, usually with acoustic shadowing extending distally.[44] Metal is brightly echogenic and has an associated reverberation artifact (comet tail), while glass has a more scattered reverberation artifact. Wood, plastic, gravel, and sand are hyperechoic and produce an acoustic shadow.[33] A hyperechoic rim, or **halo sign**, indicates an abscess or granuloma around the object. Sonography can estimate the depth of a foreign body below the skin surface.[39]

With experience, sonography can be applied to body areas previously difficult to image for soft tissue foreign bodies, such as the hands and feet.[45-48] Soft tissue gas may not reduce the ability to detect a foreign body but does decrease the ability to discriminate between metal and wood.[49]

An important technical aspect of US for soft tissue foreign body detection is the transducer frequency.[50] **Higher frequencies have a reduced effective depth of penetration for the US wave. A 3.5-MHz**



FIGURE 45-7. This patient sustained forehead lacerations when he struck his head on a car windshield. Glass foreign bodies were not identified before wound closure and were not visible on plain films, but were evident on CT.

transducer will locate foreign bodies that are as deep as 10 cm, a 5-MHz transducer at depths of approximately 7 cm, a 7.5-MHz transducer at depths of 5 cm, and a 12.5-MHz transducer at depths of 2.0 to 0.2 cm. Conversely, the resolution of the image—ability to distinguish two adjacent objects and detect small objects—is greatest with higher frequencies. Thus, low frequencies can detect larger objects at greater depth but may miss smaller objects and may not be able to discriminate multiple objects. Higher frequencies will detect smaller and multiple objects, but only at shallower depths, and may miss deeper objects. **Use both low and high transducer frequencies for best advantage.**

US has a unique set of limitations. Areas with many echogenic structures, such as calcifications, sesamoid bones, and tendons, may hide foreign bodies within their acoustic shadows, so these areas must be scanned slowly to detect foreign bodies that are small or oriented perpendicular to the skin surface. Some areas of the body that are prone to foreign body penetration, such as the web spaces of the hands or toes, may not accommodate a US probe using standard gel. In this circumstance, a water-bath interface between the probe and body part is useful.[45-47,50,51] False-positive findings result in an unnecessary surgical dissection. False-positive rates for sonography vary from 3% to 46% in clinical case series, depending on the material being studied.[39,41-43,52,53] Accuracy of detection will increase with physician experience. However, a negative bedside US does not exclude the possibility of a retained foreign body when a history and physical exam are concerning for a retained foreign body. In such cases, further radiologic imaging or delayed assessment may be necessary.[33]

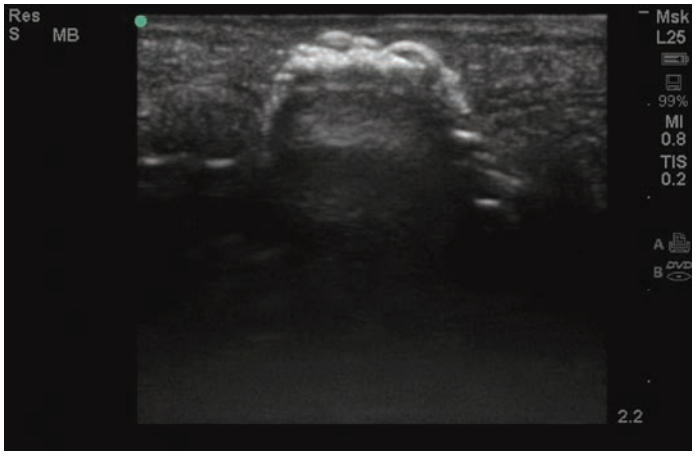
Once a foreign body is confirmed by plain films or CT studies, US can be used in place of fluoroscopy to guide an instrument to the object during retrieval.[30-32,45,46] The scanning beam should be oriented parallel to the long axis of a hemostat, which can be directed toward the long axis of the foreign body. Transverse and longitudinal scans provide views in multiple planes. A 7.5-MHz linear-array transducer can be used to find objects that are small and superficial (up to 5 cm deep), and a 5.0-MHz transducer can be used for larger and deeper objects. The linear scan is preferred for localization, and the sector scan for retrieval.[30] The primary advantage of sonography is the avoidance of radiation exposure. US may also be useful to localize and then confirm successful foreign body removal, for objects that were initially identified using other imaging modalities.

MAGNETIC RESONANCE IMAGING

MRI can detect nonmetallic radiolucent foreign bodies and, in comparison studies, is more accurate (less sensitive than US but fewer false-positive interpretations) than any other modality in identifying wood, plastic, spines, and thorns.[3,19,54] **MRI should not be used with gravel or metal-containing foreign bodies because ferromagnetic streaks obscure visualization.** MRI may provide more information than CT about the position of a foreign body relative to (and its effects on) nearby structures, such as tendons, neurovascular bundles, joints, and muscles.

FLUOROSCOPY

Bedside fluoroscopy accurately detects radiopaque (metal, gravel, glass, and pencil graphite) foreign bodies as small as 3 mm.[55,56] Using fluoroscopy to accurately detect glass foreign bodies can be accomplished in



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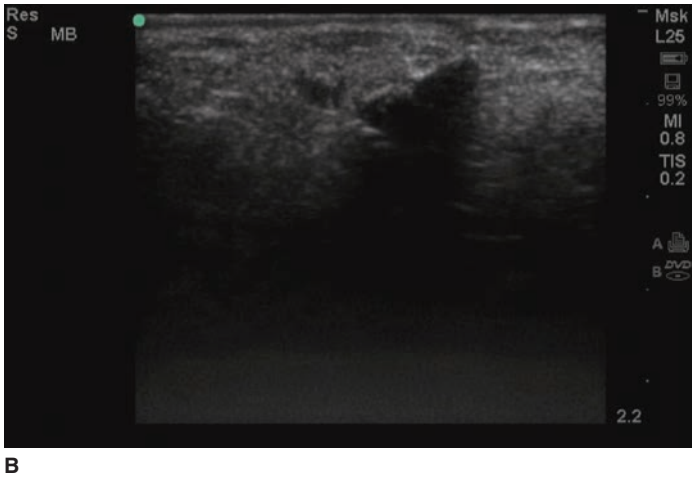
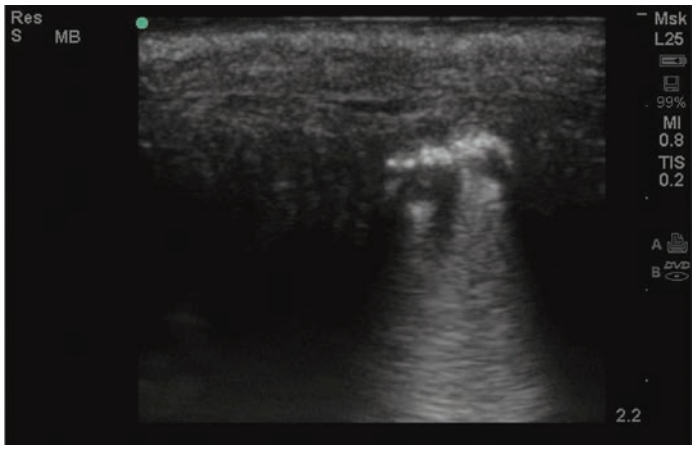


B

FIGURE 45-8. **A.** Tooth fragments can be embedded in facial and hand wounds. Sonographic image of an intact tooth. **B.** Fragments of shoes can be found in plantar puncture wounds. Sonographic image of rubber from sole of a shoe. Object is slightly hyperechoic; note the flat edge and acoustic shadowing. **C.** Fragments of clothing can be carried into gunshot wounds. Sonographic image of cloth (cotton). **D.** Sonographic image of a small fragment of glass; note the acoustic shadow. **E.** Sonographic image (long axis parallel to the scan plane) of a metal sewing needle; note the reverberation artifact typical of metallic objects. **F.** Sonographic image (short axis) of a sewing needle with a comet tail artifact. **G.** Sonographic image (long axis) of a wooden toothpick that was invisible on plain film radiography. **H.** Sonographic image (short axis) of a wooden toothpick surrounded by air that was invisible on plain film radiography. **I.** Sonographic image (long axis) of a cactus spine that was invisible on plain film radiography. **J.** Sonographic image (short axis) of a cactus spine that was invisible on plain film radiography; note the acoustic shadow.



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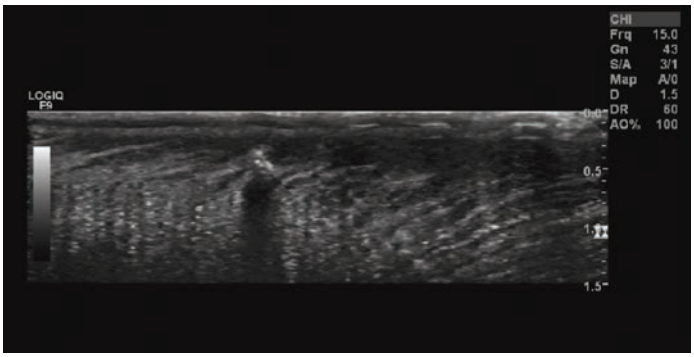

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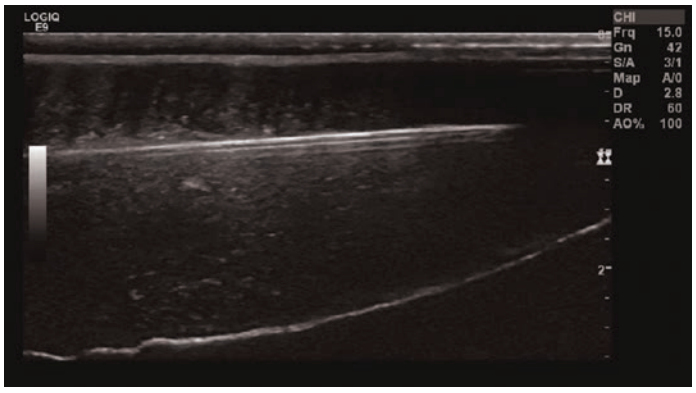

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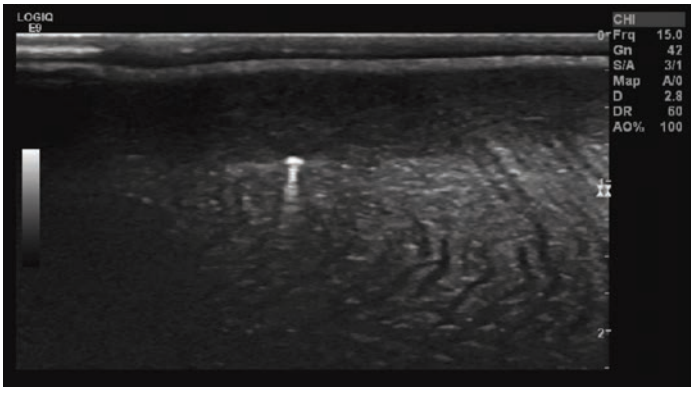

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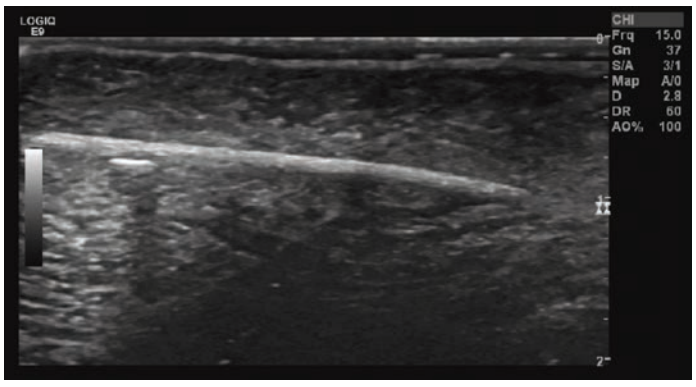

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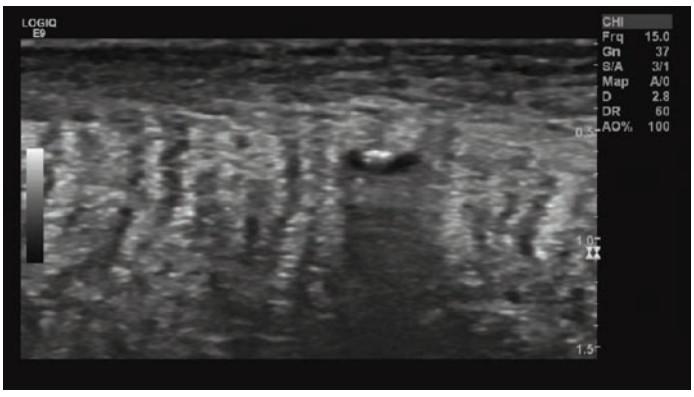

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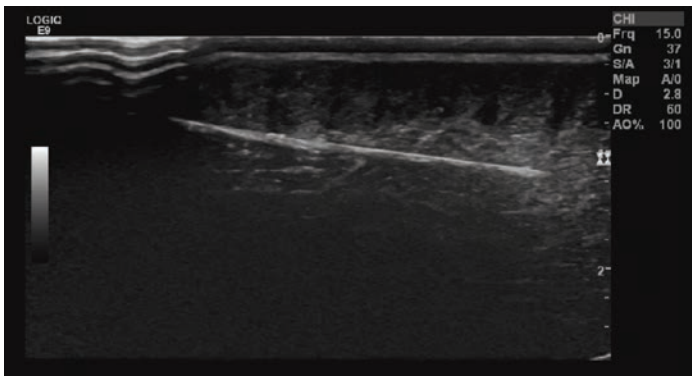

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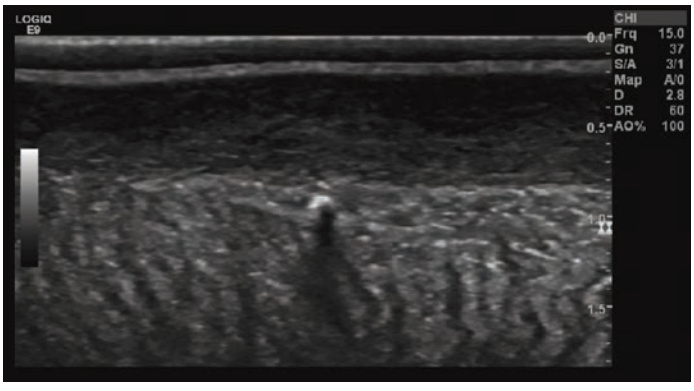

J

FIGURE 45-8. (*Continued*)

a brief training session.[57,58] Advantages are convenience, reduced cost, shortened ED time, and, if done with brief intermittent imaging and appropriate shielding, less radiation exposure than CT. An important limitation is that the body part must be able to fit within the fluoroscopic beam path and be thin enough that a viewable image can be obtained. For most adult patients, this limits fluoroscopy to the limbs. Fluoroscopy can be used to assist foreign body removal by helping guide the instrument, as the body part (usually extremity) can be rotated during fluoroscopic imaging to provide a real-time, three-dimensional view of the object relative to the physician's instruments, skin surface, or skin markers.[55,56] An incision is made between needles or markers, or dissection is carried along the path of the closest needle. Safe and effective metallic foreign body extraction under fluoroscopic guidance and local anesthesia is possible (outside of the ED) even when objects are in close proximity to important vessels.[59]

GENERAL TREATMENT PRINCIPLES

Once a soft tissue foreign body is discovered, weigh the risk of leaving the foreign body in place against the potential harm of attempting to remove it. Not all foreign bodies must be removed, and not all that require removal must be extracted in the ED. General indications for foreign body removal include potential for later infection, toxicity, injury, and functional problems (**Table 45-2**). Usually, objects that are small, inert, deeply embedded, and causing no symptoms can be left in place. Bullets that come to rest deep within a muscle belly are usually not removed because the procedure can cause more damage than leaving the foreign object in place. However, projectiles may drag bits of clothing or skin into the wound, so the entrance wound deserves cleaning and debridement. Bullet migration and embolization are rare but possible complications. Bullets near vessels can enter the systemic circulation. Bullets that cause distal ischemia, thrombus formation, or wall erosion or that lie within the lumen of a blood vessel require immediate removal in the operating room.

Thorns, spines, wood splinters, and other vegetative materials should be promptly removed because they cause intense and excessive inflammation. Foreign objects that are heavily contaminated, such as fractured teeth and soil-covered objects, should be removed as soon as possible. Antibiotic treatment cannot replace foreign body removal. Glass, metal, and plastic are relatively inert, and removal can be postponed, if necessary. Glass foreign bodies in hands or feet can cause persistent pain with gripping or walking, and they can sever nerves or tendons years after the initial injury. Patients with deep, sharp foreign bodies in these locations should be referred to appropriate specialists for eventual removal.

Sometimes, harmless foreign bodies are psychologically distressing to patients, particularly when they are visible under the skin surface or produce a lump. Patient concern may be a justification for elective removal.[60]

In general, recommended techniques for soft tissue foreign body removal are based on clinical experience.[61,62] Successful removal of foreign bodies requires adequate local or regional anesthesia and good lighting. Depending on location and depth, tourniquet control of bleeding and assistance may be needed. Depth and accessibility of the object and physician time are the limiting factors for removal of foreign bodies by the emergency physician. Foreign bodies buried deeply in adipose tissue or muscles are difficult to locate. Although most foreign bodies in hands should be removed because the hand is mobile and sensitive, deep exploration of the hand by the emergency physician is not recommended because knowledge and experience are needed to avoid injury to numerous closely spaced vital structures. The "no man's land" of the hand (see Figure 268-10 in Chapter 268, "Injuries to the Hand and Digits") should not be explored.

In a busy ED, it may only be possible to devote 15 to 30 minutes to a removal procedure, particularly when other patients demand attention. This amount of time is sufficient for locating most foreign bodies. Inform the patient before the procedure that the duration of the exploration will be limited and a best effort will be made to locate and remove the foreign body. If unsuccessful, referral to an appropriate specialist will be made.

TABLE 45-2 Indications for Foreign Body Removal

- Potential for inflammation or infection
- Vegetative or chemically reactive material
- Heavy bacterial contamination (e.g., teeth, soil)
- Proximity to fractured bone
- Established infection
- Allergic reaction
- Potential for toxicity, as with heavy metals
- Spines with venom
- Impingement on nerves, vessels, or tendons
- Intra-articular or intravascular location

POSTREMOVAL TREATMENT

After removal of a foreign body, irrigate the wound thoroughly with standard wound irrigation techniques (see Chapter 40, "Wound Preparation"). A puncture wound is difficult to clean adequately because either the small wound diameter prevents the irrigation fluid from reaching the wounded tissue or the fluid enters the wound but does not completely drain (see Chapter 46, "Puncture Wounds and Bites"). In general, if the puncture site is contaminated, the entrance wound can be enlarged to allow more effective cleaning, and if foreign debris is impregnated in tissue, the contaminated area can be debrided or excised. **If multiple radiopaque or US-visualized objects were removed, or if there are concerns about fragmentation of foreign bodies with remnant material in the wound, consider repeat radiography or US.**

The decision to close lacerations, incisions, and block excisions depends on the potential for infection. **Wounds in which all foreign contaminants can be removed and those in locations with good blood supply can be closed primarily. Otherwise, delayed primary closure is preferred.** Provide necessary tetanus immunization. There is no proven benefit for prophylactic antibiotics for uninfected wounds containing foreign bodies.[63] Antibiotics are justified for infected wounds, particularly when removal must be postponed.

If a foreign body is deliberately left in place, inform the patient of the proposed plan and necessary follow-up. If foreign material was removed, warn the patient that there is always a possibility that not all pieces were found despite careful exploration and imaging studies.

DELAYED REMOVAL

Refer patients to surgeons or interventional radiologists for delayed removal of foreign bodies.[64-66] Inform the patient that the object is present but unlikely to cause harm before it is removed. **If a foreign body is near a joint or highly mobile region, the affected area should be splinted before removal to prevent further injury or migration of the object.**

Patients may also present late (>1 week after injury) to the ED for removal of a soft tissue foreign body. Evidence supports use of US for locating and removing soft tissue foreign bodies <30 mm from the skin surface, even in patients who delay seeking care for a penetrating soft tissue foreign body.[67]

SPECIFIC FOREIGN BODIES AND REMOVAL PROCEDURES

METALLIC NEEDLES

Long, thin foreign bodies, such as sewing and hypodermic needles, may be difficult to locate in soft tissue. There are several techniques available for removing needles that are parallel to the surface of the skin. If the needle is superficial enough to be palpable, make an incision at one end to expose and grasp it with a hemostat. The US probe can be used to locate the long axis of the foreign body; an incision is then made at the end closest to the skin, and the needle is grasped with forceps and removed with traction in the direction of the long axis.[68] If the

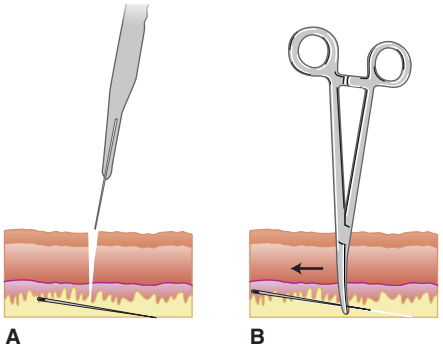

FIGURE 45-9. **A.** An incision is made perpendicular to the needle at its midpoint. **B.** The needle is grasped through the incision with a hemostat and backed out of the puncture wound.

needle is deep, make an incision perpendicular to the needle at its midpoint, where it can be clamped with a hemostat and pushed out of the entrance of the original wound (**Figure 45-9**). Sometimes application of an industrial magnet may attract the foreign body to the magnet for removal. After locating the area of greatest attraction, the overlying skin is prepared and anesthetized, and a small incision is made at the site. The magnet is then placed over the incision to attract the metallic foreign body and remove it from the soft tissue by pulling the magnet away from the incision site. Do not apply magnets in patients with pacemakers or implanted defibrillators.[69]

Long, thin foreign bodies that are oriented perpendicular to the skin surface can be elusive. If a needle or nail can be reached with an alligator forceps or hemostat, it can be pulled straight out. If a needle lies beyond the reach of an instrument, the entrance wound can be enlarged with a skin incision (**Figure 45-10**). However, the incision may easily pass to the side of the object, so undermine the skin edges and apply pressure on the skin edges that will displace the foreign body into the center of the wound, where it can be seen and grasped. Once removed, the needle and the wound should be inspected to ensure that the object was removed in its entirety.

WOOD SPLINTERS AND ORGANIC SPINES

Solid foreign bodies can be pulled out of puncture wounds with forceps, but wood splinters and organic spines (e.g., cactus, sea urchin, and fish) may disintegrate with this technique. Only superficial splinters that are a few millimeters long can be grasped and removed with a fine-point splinter forceps. A splinter parallel to the skin surface should be lifted out of the wound after incising the skin along the long axis of the object. If the splinter is lodged in the subcutaneous tissue, the entrance wound should be enlarged with a skin incision so the foreign body can be grasped under direct visualization. Occasionally, foreign bodies migrate from their initial entrance site. If the original entrance is incised in this situation, additional tissue dissection may be required. Ultrasonography can be used to confirm the current location of the foreign body and to determine its longitudinal axis. An incision can then be made at the end of the object nearest the skin surface.[70]

Wood fragments may be impossible to locate precisely. One solution is to create an elliptical incision around the puncture wound and extract the fragment in a block of tissue (**Figure 45-11**). Avoid incorporating nerves, vessels, or tendons within the excised block. Either technique creates a larger wound, but allows a better inspection and more thorough cleaning after removal.

Subungual splinters should be removed because of the risk of subsequent infection with the possibility for distal phalanx osteomyelitis. If the splinter is underneath the distal end of the nail, it can be grasped by a splinter forceps or hooked by a hypodermic needle bent at its tip. More proximal splinters can be reached by anesthetizing the finger and removing a wedge of the nail overlying part of the foreign body (**Figure 45-12**). If there are multiple splinters, the entire nail can be removed in one piece, the foreign bodies extracted, and the nail placed back under the cuticle and tacked down on to the nail bed (see Chapter 43, "Arm, Forearm, and Hand Lacerations").

Numerous, tiny cactus spines in the dermis can be plucked out individually with forceps or extracted together with depilatory wax, professional-quality facial gel, rubber cement, or household glue. Larger spines and thorns should be removed with incision or excision techniques.

FISHHOOKS

Fishhooks have a variety of sizes and shapes based on a common pattern (**Figure 45-13**). The barb, which is a projection extending backward from the point of the hook, keeps the point embedded in the fish's mouth and makes removal from skin a challenging task. Most fishhook injuries involve the hands, head, or face.

There are several methods for removing fishhooks embedded in skin.[71] The best strategy depends primarily on the depth of the hook. If the hook has multiple barbs, take precautions to avoid impaling the treating physician, bystanders, or the patient (a second time) during removal by taping or cutting off the exposed barbs. With any technique, the skin should be cleaned and anesthetized at the entry site. If the hook is superficial, use the **retrograde technique** by applying gentle downward pressure on the shank while the hook is simply pulled back out along the path of entry (**Figure 45-14**). (See Video: Fishhook and Taser Removal.)

The **needle-cover technique** is commonly described but rarely successful. The technique requires physician dexterity and is useful only if the hook is superficial. Insert an 18-gauge needle into the entrance wound alongside the shank of the hook. Have the needle follow the bend of the hook until the lumen of the needle can be placed over the barb to sheathe it. The hook and needle are then withdrawn from the wound as a unit (**Figure 45-15**).

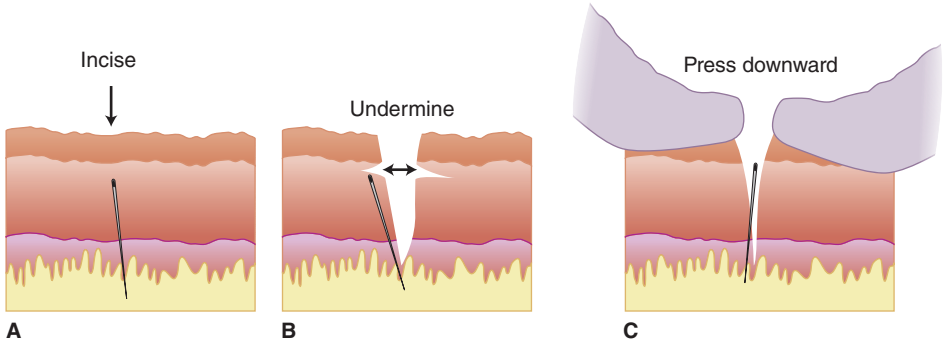

FIGURE 45-10. **A.** The entrance site is enlarged with a skin incision. **B.** If the incision passes to the side of the object, the skin is undermined. **C.** Pressure on the skin edges displaces the foreign body into the center of the wound.

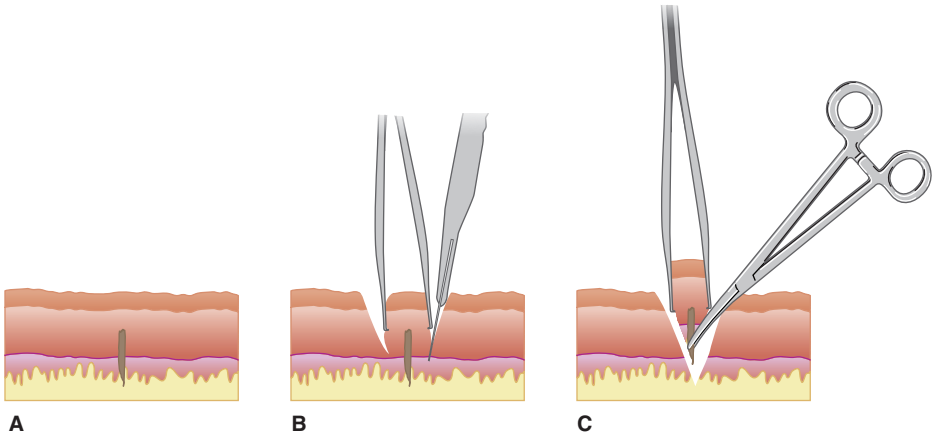

FIGURE 45-11. Block excision is effective for foreign bodies that are friable, difficult to find, buried in fatty tissue, or stain surrounding tissue. **A.** A small, elliptical incision is made around the original wound. **B.** The incision is undercut until contact is made with the foreign body. **C.** The block of tissue is grasped with a forceps, the foreign body is clamped with a hemostat, and both are removed.

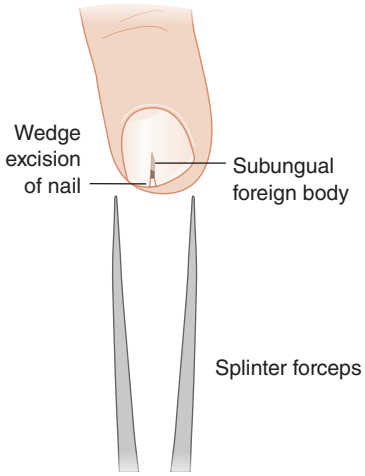

FIGURE 45-12. Subungual foreign bodies that are beyond the reach of a splinter forceps can be exposed by excising a wedge of the overlying nail.

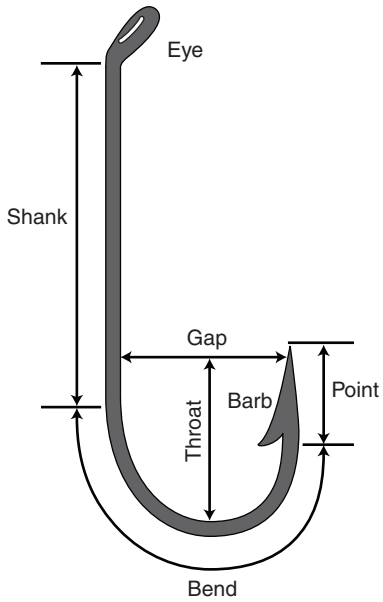

FIGURE 45-13. Anatomy of a fishhook.

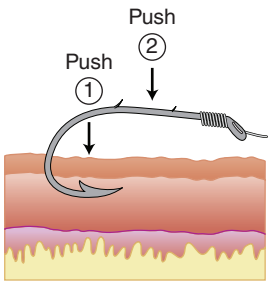

FIGURE 45-14. Simple retrograde technique for fishhook removal. While pressing the skin over the tip of the hook to disengage the barb and applying gentle downward pressure on the shank, back the hook out of the skin. If the barb catches on skin fibers, other techniques must be used.

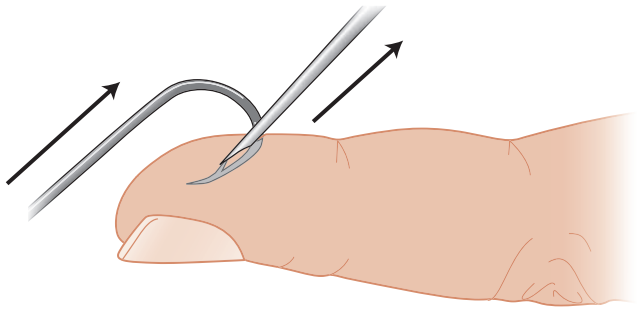

FIGURE 45-15. Needle-cover technique for fishhook removal. The area is anesthetized, and an 18-gauge needle is inserted into the entrance wound along the hook. The lumen of the needle is placed over the barb to cover it, and both the hook and needle are backed out of the wound.

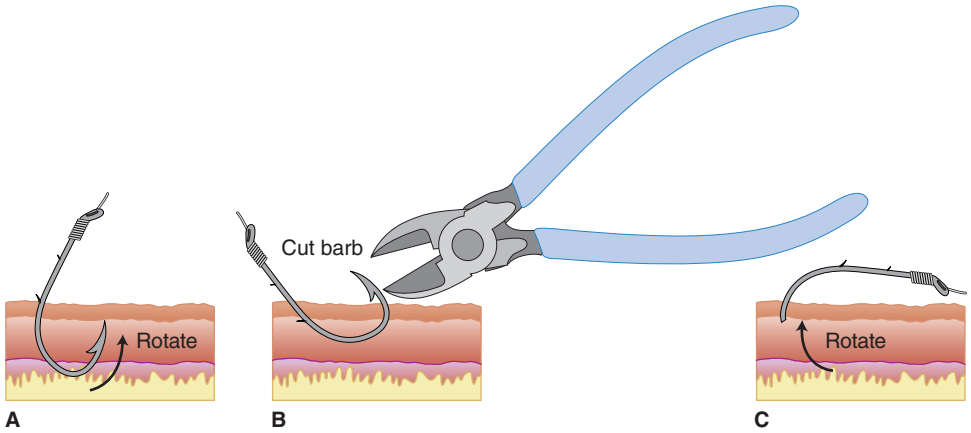

FIGURE 45-16. Advance-and-cut technique for fishhook removal. The area is anesthetized, and the tip of the hook is advanced through the skin surface (**A**), the barb is cut (**B**), and the hook is rotated back out of the original wound (**C**).

The **advance-and-cut technique** is useful for deeply penetrated and larger fishhooks (**Figure 45-16**). Advance the tip of the hook through the skin surface. Once exposed, the point and barb are cut with wire cutters, and the remaining part of the hook is rotated back out of the original wound. If barbs along the shank are embedded beneath the dermis, the shank can be clipped near the hook's eye. The remaining part of the hook is then passed antegrade through the skin. The advance-and-cut method traumatizes and contaminates tissue, but is an effective method in the ED if the barb has nearly or already penetrated the surface of the skin.

The **incision technique** is nearly always successful in removing fishhooks. Enlarge the entrance wound 2 to 3 mm with a #11 scalpel blade. Continue the incision along the bend of the hook to the barb until the barb is disengaged from the soft tissue. The hook can then be withdrawn easily through the larger entrance (**Figure 45-17**). If necessary, the barb can be grasped with a hemostat to prevent it from snagging tissue on the way out. There are two major benefits to enlarging puncture wounds containing foreign bodies. First, the wound is more easily inspected for additional foreign bodies. In the case of fishhook impalement, the wound may be harboring the bait that was on the hook. Second, the wound tract is more easily irrigated through a larger opening. However, the incising scalpel can easily injure tendons, nerves, and vessels.

TRAUMATIC DERMAL TATTOOING

Foreign particulates may be embedded in the epidermal and dermal layers of skin by an abrasion, which permanently stains or "tattoos" the surrounding tissue. If vigorous scrubbing does not remove the particulates, refer the patient to specialists for dermabrasion or block excision.

A slit-lamp microscope can be used to remove multiple, tiny (usually <2 mm), superficial particles embedded in the face or hands. After vigorous scrubbing and flushing with saline, the affected area is positioned and visualized under ×16 magnification. The light beam is narrowed and lumens increased, with the beam directed adjacent to the area in question. A 26-gauge hypodermic needle or #11 scalpel is then used to palpate and extract the superficial particles.[72]

The graphite from pencil lead can produce a pigmentation that may never dissolve; therefore, graphite should be excised in cosmetic areas.

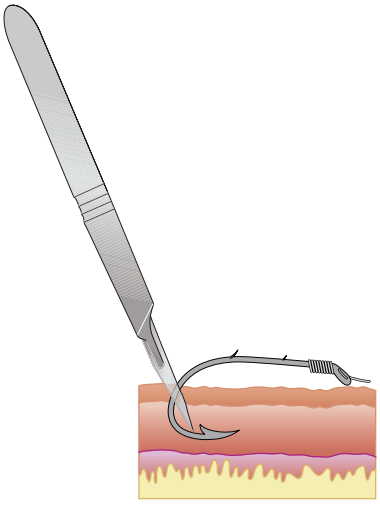

FIGURE 45-17. Incision technique for fishhook removal. The area is anesthetized, and a small incision is made along the shaft of the hook to the barb. The hook is withdrawn through the incision.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 46

Puncture Wounds and Bites

James Quinn

PUNCTURE WOUNDS

A puncture wound is defined as a wound whose depth is greater than its width. Injuries occur when great focal pressure is applied to a sharp object that can then penetrate the skin and deep tissues. Given the force and depth of penetration, puncture wounds are problematic regardless of location and are independently associated with higher incidence of infections and complications compared to other wounds.[1,2] Despite a relatively innocuous appearance, puncture wounds carry a significant risk of infection and injury to underlying structures. Puncture wounds caused by high-pressure injection equipment and animal bites and those involving exposure to body fluids have the potential for unique complications.

PATHOPHYSIOLOGY

With puncture wounds, shear forces between the penetrating object and tissue result in tissue disruption, producing hemorrhage and devitalization of skin and underlying tissues. Inoculation of infectious organisms into the deeper tissues can occur from the penetrating object (with or without leaving behind a foreign body from the object or material that has been pierced)[3] or from the skin surface. When the penetrating object is removed,

TABLE 46-1 Risk Factors for Puncture Wound Complications

Patient characteristics
- Elderly
- Diabetes with or without microvascular complications
- Immunocompromised (acquired immunodeficiency syndrome, steroids, chemotherapy)
- Peripheral vascular disease

Wound characteristics
- Contaminated with soil or debris
- Bite wounds
- Containing foreign body
- Occurring outdoors
- Occurring through a shoe and/or sock
- Deeper penetration (jumping, falling, running)

TABLE 46-2 Indications for Imaging in Puncture Wounds

Plain radiographs
- Suspicion of fracture
- Infected wound
- Wound caused by materials prone to fragment (wood, glass, etc.)
- Foreign body sensation reported by patient

US
- Organic, nonradiopaque material
- Suspected abscess

CT or MRI
- Suspected deep-space infection
- Persistent pain after injury
- Failure to respond to treatment

a small skin wound often closes spontaneously, creating a favorable environment for the development of infection. The reported infection rate from plantar puncture wounds is approximately 6% to 11%.[4,5] Furthermore, exploration of infected plantar puncture wounds results in foreign material being found in about 25% of patients.[6] The rate of infection from puncture wounds associated with dog bites is about 10% to 11%.[7]

Most soft tissue infections from puncture wounds are caused by gram-positive organisms. *Staphylococcus aureus* predominates, followed by other staphylococcal and streptococcal species.[4,8-11] Puncture wounds over joints can penetrate the joint capsule and produce septic arthritis. Those that penetrate cartilage, periosteum, and bone can lead to osteomyelitis. *Pseudomonas aeruginosa* is the most frequent pathogen isolated from plantar puncture wound–related osteomyelitis, particularly when the injury occurs through the rubber sole of an athletic shoe.[6,10-12] The source appears to be *Pseudomonas* that colonizes the foam lining of athletic shoes. Infections from punctures caused by bites have unique pathogens discussed in more detail later in this chapter.

Difficulty in visualizing and cleaning to the full depth of the injury contributes to the higher risk for infection for puncture wounds compared with other traumatic lacerations. Other host and wound factors are associated with delayed healing and/or infection (**Table 46-1**).[13,14]

ASSESSMENT

Ask the patient about the time of injury and circumstances involved.[15] Wounds >6 hours old with increasing pain and redness are likely infected. Falling or jumping onto an object or bites from powerful clenched jaws suggest deeper penetration with potential for greater injury. Footwear (for plantar injuries) or clothing through which the object passed increases the potential for foreign body retention and infection. Ask the patient to estimate the depth of penetration and about a foreign body sensation in the wound. Ask about postinjury care rendered before presentation and about host factors predisposing to infection.

Ask about the penetrating object. Materials such as wood, glass, teeth, or plastic are prone to break or splinter, leaving retained fragments in the wound and increasing the risk for infection. Thin objects, such as teeth, needles, or pins, can break off cleanly beneath the skin surface, leaving a fragment behind.

Examine the puncture wound site and the function of underlying structures. Note the size and location of the wound, condition of surrounding skin, and presence of foreign matter or devitalized tissue. Assess for proximity to underlying structures. Assess distal function of adjacent tendons and nerves and the integrity of distal perfusion. Ask about amount of bleeding or any pulsatile bleeding or numbness, as arteries and nerves tend to travel and get injured together. These symptoms can also give an idea of the depth of a puncture wound. This is especially important with puncture wounds of the hand and wrist.[16]

Because the entire depth of a puncture wound cannot be reliably explored, assessment for a possible foreign body is complicated. Patient perception of a foreign body is modestly useful in predicting the presence of one.[17,18] The practice of probing the wound with a blunt instrument to assess depth and the presence of a foreign body is of unproven utility, but may improve the ability to cleanse wounds.

DIAGNOSIS

Plain film radiographs using soft tissue visualization techniques are indicated in most puncture wounds, especially when the base cannot be visualized and there is any risk of a retained penetrating object. Unless there is concern for fracture, puncture wounds from knives can forgo imaging. Otherwise imaging is necessary in wounds with a concern for fracture, in wounds caused by materials prone to fragment, and whenever the patient reports a foreign body sensation (**Table 46-2**) (see Chapter 45, "Soft Tissue Foreign Bodies").[19] **Plain radiographs will detect >90% of radiopaque foreign bodies >1 mm in diameter** (**Figure 46-1**). Most organic substances, such as wood, thorns, and other plant matter, have radiodensities close to that of soft tissue and cannot reliably be detected in puncture wounds with plain radiographs.

US can identify some soft tissue foreign bodies, but the ability to detect small objects that might have been introduced through a puncture wound is limited.[20-22] US can be helpful with identifying an abscess and facilitating foreign body extraction.

CT can accurately detect most radiolucent foreign bodies and is the imaging modality to use when a retained foreign body is suspected but the plain radiograph does not show one. MRI provides excellent visualization of foreign bodies, but cannot be used to image metallic objects or objects containing certain minerals due to the production of ferromagnetic artifacts. CT or MRI is indicated in patients with deep-space infection, persistent pain after a puncture wound, or when superficial infections fail to respond to therapy (Table 46-2). Rubber from athletic shoes is difficult to visualize with any imaging modality.[3]

TREATMENT

Treatment recommendations for puncture wounds are largely based on anecdotal evidence and reviews of uncontrolled case series.[4,8-13] Traditional wound-cleaning techniques are largely ineffective as a result of the small entrance wound that has often spontaneously sealed by the time of presentation. The occurrence of serious infections after puncture wounds leads some clinicians to recommend more aggressive wound debridement and irrigation, although there is no evidence that this treatment reduces the rate or severity of post–puncture wound infections. In general, the majority of puncture wounds have a benign course, and potentially catastrophic complications are uncommon.[1,4,5] It is thus sensible to limit the most aggressive treatment to those wounds and patients at greatest risk of complications. Remember to update tetanus immunization if needed.

WOUND CLEANSING, IRRIGATION, AND DEBRIDEMENT

Uncomplicated clean punctures presenting <6 hours after injury require superficial wound cleansing and tetanus prophylaxis as indicated.[11] Soaking



A



B

FIGURE 46-1. Puncture wound to heel. **A.** Physician enlarged the wound in an unsuccessful attempt to locate and remove foreign body. **B.** Radiograph showing retained foreign body.

of the wound in an antiseptic solution has no proven benefit other than perhaps keeping a tract open so any retained foreign material can migrate out.[23] Low-pressure (e.g., approximately 0.5 psi) irrigation of wounds will assist in surface cleansing and allow visualization of the entrance site, but will not penetrate the puncture tract. High-pressure (e.g., approximately 7 psi) injection of irrigation fluid into the wound might penetrate the tract but has no proven benefit and theoretically could force foreign matter and bacteria deeper into the surrounding tissue.[24]

Debridement or coring of the wound tract in clean wounds does not reduce infection or facilitate accurate diagnosis of deeper structural injury. Adverse effects from debridement or coring include increased pain and a wound that is larger than the initial injury.

ANTIBIOTICS

The role for prophylactic antibiotics in the management of all wounds is controversial. Most studies lack power to determine significance or are so poorly done that using them in a meta-analysis is problematic. For punctures, the same problem exists. Despite the lack of adequately sized randomized controlled trials on the subject, there is general consensus that prophylactic antibiotics have benefit in some circumstances.[25] Thus, **antibiotic prophylaxis is recommended for use in high-risk patients with puncture wounds or in high-risk punctures such as plantar punctures, punctures due to bites, or punctures with heavy contamination.**[26-29] High-risk patients includes those with diabetes or any immunosuppression.[14]

If prophylactic antibiotics are used, agents typically used for established wound infection are recommended, such as a first-generation oral cephalosporin, amoxicillin–clavulanic acid, or a fluoroquinolone.[26] Although methicillin-resistant *S. aureus* has become a common cause of skin and soft tissue infections, postinjury antibiotic prophylaxis to cover this pathogen is not necessary.[26] **For plantar puncture wounds through athletic shoes, an oral fluoroquinolone with antipseudomonal activity (e.g., ciprofloxacin) is recommended.**[30] Agents such as trimethoprim-sulfamethoxazole and tetracycline can provide antistaphylococcal coverage but lack antipseudomonal activity. If antipseudomonal coverage is desired and oral fluoroquinolones are contraindicated, a combination of oral antistaphylococcal and parenteral antipseudomonal antibiotics (e.g., ticarcillin, ceftazidime, or cefepime) would be an acceptable albeit inconvenient choice.

COMPLICATIONS

Infectious complications of puncture wounds include cellulitis, localized abscess, deep soft tissue infection, and osteomyelitis. The hallmark of all complications is persistent pain. Patients with continued or increasing pain >48 hours after injury should undergo an evaluation for retained foreign body or abscess.

CELLULITIS

Cellulitis usually presents within 4 days after injury. The patient typically notes pain with or without swelling and redness. Physical examination may demonstrate tenderness, erythema at the site of injury, warmth, and swelling. Postinjury cellulitis is an indication for imaging to evaluate for a retained foreign body. Cellulitis is generally caused by streptococcal and staphylococcal skin flora and usually responds to a 7- to 10-day course of a first-generation cephalosporin, antistaphylococcal penicillin, or clindamycin.

ABSCESS

Localized abscess is usually associated with a retained foreign body. Patients may note swelling and possibly drainage. A tender, warm, fluctuant mass can be palpated and further defined with US. Standard incision and drainage is generally curative. Where possible, the incision should be longitudinal or parallel to underlying tendons, vessels, or nerves. A short course of antibiotics is indicated if surrounding cellulitis, high-risk patient factors, or signs of systemic illness are present.

DEEP SOFT TISSUE INFECTION

Deep soft tissue infection is generally more painful than cellulitis or localized abscess. The key physical examination finding is tenderness, redness, or swelling remote from the puncture site. With plantar or palmar injuries, redness on the dorsum of the foot or hand, respectively, suggests a deep-space infection. CT or MRI is indicated. Treatment requires parenteral antibiotics and surgical exploration with drainage, excision of necrotic tissue, and irrigation of infected areas.

OSTEOMYELITIS

Osteomyelitis is the most disastrous consequence of puncture wounds, occurring in 0.1% to 2.0% of all plantar puncture wounds and perhaps with a greater prevalence in forefoot punctures occurring through athletic shoes.[8-12] Patients with osteomyelitis present later than patients with other infections, often >7 days after injury and sometimes after a period of symptomatic improvement.[11] Pain is present in nearly every case, but the examination may be deceptively normal. Radiographs are normal in the early stages of osteomyelitis. Elevated erythrocyte sedimentation

rate or C-reactive protein supports the diagnosis, but a normal value does not exclude osteomyelitis.[11,31,32] The imaging modality most helpful in the diagnosis of osteomyelitis is MRI.[33] Once the diagnosis is made, immediate surgical referral should be made. Antibiotic administration should be withheld pending discussion with the consultant, as pathogen identification is best done from cultures obtained during operative debridement. If antibiotics are necessary before surgery, staphylococcal and pseudomonal coverage is recommended.

DISPOSITION AND FOLLOW-UP

Cellulitis and localized abscesses are almost always treated on an outpatient basis with oral antibiotics or incision and drainage, respectively. Follow-up is recommended in 48 hours to assess response.[11] Inpatient therapy is indicated when the patient has a significant systemic response to this localized infection, the infection is extensive, comorbidities or drug allergies preclude safe oral therapy, patients cannot tolerate oral medications, or patients cannot reliably care for the infection outside of the hospital setting. Deep soft tissue infection and osteomyelitis require admission, surgical intervention, and IV antibiotics.

SPECIAL CONSIDERATIONS

NEEDLESTICK INJURIES

Needlestick injuries are common among healthcare professionals, especially in nurses and physicians who perform invasive procedures.[34-36] Mechanical damage from needlestick injuries is essentially negligible. The major concerns are the risk of infection with hepatitis viruses and human immunodeficiency virus (HIV). **The risk of infection in a nonimmune recipient after an inadvertent needlestick contaminated from an infectious source has been estimated to be negligible for hepatitis A, up to 37% to 62% for hepatitis B if the source was hepatitis B e antigen positive, about 2% for hepatitis C, and 0.3% for HIV.[37]**

Postexposure prophylaxis is available for hepatitis B and HIV, but not for hepatitis C.[37] Recommendations for the assessment and management of occupational exposures to blood and body fluids (such as needlesticks) are complex and change frequently. Hospitals should have predetermined protocols endorsed by local infectious disease specialists that are readily available and periodically reviewed. Consensus recommendations for postexposure prophylaxis of HIV are updated regularly by the Centers for Disease Control and Prevention[37] and are available from the Clinicians Consultation Center, accessible via the Internet at http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/ or by phone at the PEPline at 1-888-448-4911. When available, the use of rapid HIV testing on the source (patient, blood, or fluid) can reduce the need for unnecessary prophylaxis in the exposed individual.

HIGH-PRESSURE INJECTION INJURIES

High-pressure injection injuries are caused by industrial equipment designed to force grease, paint, or other liquids through a small-diameter nozzle at high pressures.[38-43] When the nozzle is applied close to or directly on the skin surface, the high-pressure results in penetration of intact skin, forcing the material deep into the underlying structures and along fascial planes. The nozzle pressures for these devices are typically 5000 to 10,000 psi for grease guns, 2000 to 6000 psi for diesel fuel injectors, and up to 5000 psi for paint and water sprayers. Such extreme pressure can lacerate skin and fracture bones (**Figure 46-2**). The type, amount, and viscosity of material injected will determine the degree of tissue inflammatory response, and in less distensible tissue compartments, sudden pressure elevations can produce vascular injuries, ischemic necrosis, and gangrene.[39,42]

Most high-pressure injection injuries occur in the nondominant hand of an operator using a trigger-activated gun. The initial injury may cause little pain and appear relatively innocuous, leading to delays in presentation and underappreciation of the extent of injury. Within hours, pain typically becomes severe, with evidence of ischemia or spreading inflammation. Delays in initial management increase the risk of amputation or disability.[39-42] Despite an initial appearance that suggests only a minor injury (**Figure 46-3**), the history of high-pressure injection device use alone should prompt immediate consultation with a hand surgeon.[39-42]



A



B

FIGURE 46-2. **A.** Skin and soft tissue injury of left index finger due to high-pressure water device. **B.** Radiograph showing fractures of metacarpal and proximal phalanx as well as subcutaneous air. [Photo contributed by J. S. Stapczynski, MD.]

ED evaluation includes assessment of neurovascular integrity and tendon function, pain management using IV opioids, prophylactic antibiotic coverage against skin flora, and tetanus prophylaxis as indicated. Radiographs will often demonstrate wide dissemination of radiopaque material as well as injected air along fascial planes (Figures 46-2 and 46-3). **Digital nerve blocks should be avoided, as they may further increase pressure in finger compartments. The risk of subsequent amputation is reduced if surgical debridement is performed within 6 hours of the injury, especially in cases of organic solvents.[39,40,42]** For patients with high-pressure injection of water only into the hand, it may be possible to forgo exploration and manage with antibiotics, analgesics, and elevation, but that decision should be made in consultation with a hand specialist.[42,44]

EPINEPHRINE AUTOINJECTOR INJURIES

Epinephrine autoinjector injuries occur most often to the finger.[45] The typical scenario involves a patient who is unfamiliar with the proper use of the autoinjector or who errs as a result of the stress of the situation.[46,47] Patients present with pain due to the needlestick, paresthesias, and



A



B

FIGURE 46-3. **A.** High-pressure injection paint injury to index finger. **B.** Radiograph showing radiopaque material. [Photo contributed by J. S. Stapczynski, MD.]

epinephrine-induced vasospasm to the injected area. In the extreme, the entire digit can be blanched and cold.[48,49] The intensity of digital ischemia and response to treatment can be assessed with digital pulse oximetry of the involved finger. The natural history of this injury is spontaneous resolution over several hours, with a reported range of resolution from 6 to 13 hours.[46-50] The published case reports sometimes express concern that the intense vasospasm can lead to tissue loss or gangrene, although the chance of this occurring appears rare.[51,52] Additionally, patients sustaining accidental injection without acute symptoms or signs of ischemia do well.[50,52] **There is no clear evidence that active treatment is better than observation alone**,[52] although patients and physicians may be uncomfortable with a prolonged ischemic and painful finger.

Attempts to increase blood flow to the ischemic digit with massage, warm water immersion, amyl nitrite inhalations, metacarpal nerve block, or topical nitroglycerin paste application have no proven value.[46,51] Subcutaneous phentolamine injection into the affected area is the one treatment consistently described that rapidly reverses digital ischemia from accidental epinephrine injection but is rarely indicated.[46,48-51] Phentolamine doses described range from 1.5 to 3.0 milligrams, and response is usually seen within minutes. A mixture of 0.5 mL of standard phentolamine solution (5 milligrams/mL concentration) and 0.5 mL of 1% lidocaine solution will produce a 1-mL total volume containing 2.5 milligrams of phentolamine that can be subcutaneously injected directly through the site of autoinjector puncture. Once the ischemia is resolved, the patient can be discharged, as relapse appears very unlikely.

MAMMALIAN BITES

Most patients presenting for ED care of bite injuries have been bitten by domestic dogs or cats. In the United States, an estimated nearly 4 million people are bitten each year, approximately 800,000 seek medical attention, and 10 to 20 will die of their injuries.[53] Children have greater potential for serious injuries.[54-57] Dogs that are specifically bred or trained for guard duty cause a disproportionate number of serious injuries and deaths.[54,56]

GENERAL PRINCIPLES OF BITE WOUND MANAGEMENT

Complications from bite wounds include the mechanical injury inflicted by the bite itself, local bacterial infection, and systemic infection or illness.[58] A large animal or multiple animals attacking a child or small adult can inflict severe injuries, including vascular damage and blunt or penetrating trauma. Standard assessment and resuscitation protocols for trauma victims should be employed if the patient is seriously injured. Take particular care when assessing children with facial and scalp bites from large dogs, as there are numerous case reports of innocuous-looking wounds associated with skull penetration resulting in brain abscess and intracranial injuries.[59,60] In most animal bite wounds, there is an isolated soft tissue injury, and wound management and prevention of infection are the key issues.[58] A recent large observational study reported that the infection rate after a dog bite was about 5%, but if the wound was a puncture wound, it was four times more likely to become infected, and wounds that were sutured were three times more likely to become infected.[7]

Meticulous examination and cleansing measures, including aggressive irrigation and debridement of devitalized tissue, are important.[61] Determine the extent of underlying tissue damage, with special attention to the potential for penetration into joint spaces and tendon sheaths. Management of wounds involving the face, hands, or perineum can be challenging due to the close proximity of delicate structures. If there is suspicion of retained foreign material in the wound, such as animal teeth, imaging is needed.[62]

Some bite lacerations can safely undergo primary repair (**Table 46-3**).[63-65] If desired for cosmetic or functional reasons, a skilled practitioner can primarily close the wound with percutaneous sutures with a risk of postrepair wound infection of 5% to 15%, and we recommend antibiotic prophylaxis with amoxicillin–clavulanic acid if wound closure is desired. Otherwise nonclosure or delayed primary closure is applicable for the management of contaminated bite injuries, especially in areas other than the face (see Chapter 41, "Wound Closure").[7,15]

Case reports have described the occurrence of bacteremia, sepsis, and death after dog bites in immunocompromised individuals, most often due to *Capnocytophaga canimorsus*.[66,67] **Wound closure is associated with a small increased risk of local wound infection, but is unlikely to enhance the risk of serious systemic infection from *Capnocytophaga* (Table 46-4), unless the patient is immunodeficient or the wound is at high risk of infection. The current practice is to avoid primary wound closure in patients with systemic immunodeficiencies and higher-risk wounds (Table 46-5).**[68] High-risk wounds should be cleaned and debrided of devitalized tissue, with closure avoided, and dressed with a nonadherent wound dressing to maintain a moist environment for epithelial regeneration, with reevaluation in 24 to 48 hours. Prophylactic antibiotics are recommended for higher-risk patients and wounds at higher risk of infection (Tables 46-4 and 46-5).[68]

CAT AND DOG BITES

LOCAL INFECTIONS

Mammalian saliva contains large concentrations of microorganisms, and bite wounds should be considered to be contaminated with pathogenic bacteria.[69] The force of a bite, especially a clenching bite, can inoculate bacteria deep into the underlying tissue, leading to cellulitis, tenosynovitis, and septic arthritis. **Most dog bite wounds are relatively**

TABLE 46-3 Indications for Primary Closure of Mammalian Bite Wounds

- Animal: dog
- Location: face or scalp
- Wound characteristics: simple and appropriate for single-layer closure, no devitalized tissue
- Lack of underlying injury: no underlying fracture
- Host: no systemic immunocompromising conditions

TABLE 46-4 Common Bites and First-Line Treatment

Animal	Organism	First-Line Antibiotic
Cat	*Pasteurella multocida*	Amoxicillin-clavulanate
	Bartonella henselae (cat-scratch fever)	Azithromycin
Dog	*Pasteurella*, streptococci, staphylococci, *Capnocytophaga canimorsus*	Amoxicillin-clavulanate
Human	*Eikenella*, staphylococci, streptococci	Amoxicillin-clavulanate, cephalexin
	Herpes simplex (herpetic whitlow)	Acyclovir or valacyclovir
Rats, mice, squirrels, gerbils	*Streptobacillus moniliformis* (North America) or *Spirillum minus/minor* (Asia)	Amoxicillin-clavulanate
Livestock, large game animals	Multiple organisms *Brucella, Leptospira, Francisella tularensis*	Amoxicillin-clavulanate or specific agent for disease
Bats, monkeys, dogs, skunks, raccoons, foxes (all carnivores and omnivores)	Rabies	Rabies immune globulin, rabies vaccine
Monkeys	Herpes B virus (*Cercopithecine herpesvirus*)	Acyclovir or valacyclovir
Freshwater	*Aeromonas* spp., staphylococci, streptococci	Fluoroquinolone or trimethoprim-sulfamethoxazole
Saltwater	*Vibrio*, staphylococci, streptococci	Fluoroquinolone, doxycycline

superficial, and despite the inoculation of bacteria, only approximately 5% of dog bites will become infected.[7]

Cats have narrower, sharper teeth than dogs, giving them the ability to deliver infectious agents deeper into a small-bore puncture wound.[70,71] Thus, **up to 50% of cat bites that present for care will become infected if untreated,** although the true rate of infection is unknown since most patients with cat bites do not present for care unless the bite appears infected (**Figure 46-4**).[69,72] Infection after a cat bite is often due to *Pasteurella multocida* (Table 46-4), particularly if the infection develops within 24 hours.[73-75] Infected dog bites are just as likely to contain *Pasteurella,* as well as anaerobes, streptococcal, and staphylococcal species.[73,75] Postexposure antibiotic prophylaxis of most bite wounds to prevent infection is controversial.[26,76] The only evidence-based benefit for prophylactic antibiotics is with dog or cat bites of the hands, bites that involve punctures, or bite wounds that are closed.[76,77]

A prudent approach is to use prophylactic antibiotics for higher-risk uninfected wounds. These include all cat bites, all bites in immunocompromised hosts, dog bite puncture wounds, hand wounds, and any injury undergoing surgical repair.[26] A 3- to 5-day course of an appropriate antimicrobial (Table 46-4) should be sufficient. Routine follow-up wound check is recommended in all but the most trivial cases. In lower-risk situations, counseling and advice regarding the lack of benefit from prophylactic antibiotics in addition to wound care precautions are warranted.

Amoxicillin-clavulanate is the antibiotic most commonly recommended for prophylaxis of uninfected wounds and for treatment of local infections following dog, cat, or human bites.[26,58,72,76-78] However, penicillin V or ampicillin should be adequate for *P. multocida* infections and represent logical lower-cost alternatives for prophylaxis of cat bites.[77] Penicillin-allergic patients should receive doxycycline or cefuroxime for cat bites and clindamycin plus a fluoroquinolone for dog bites. **Cephalexin, dicloxacillin, erythromycin, or clindamycin should not be used alone for dog or cat bites, as they do not reliably cover *Pasteurella* species.**

TABLE 46-5 Wounds at Higher Risk of Infection

- Cat or human bites
- Livestock bites
- Monkey bites
- Puncture wounds
- Hand or foot wounds
- Bites in immunosuppressed patients
- Wounds sustained in fresh or salt water
- Signs of local infection when first evaluated
- Heavily contaminated wounds that are older with devitalized tissue
- Diabetes mellitus

SYSTEMIC INFECTIONS

Capnocytophaga Serious systemic infection after dog or cat bites is rare, but can develop days after the bite and is not necessarily accompanied by local bite wound infection.[67,79,80] *Capnocytophaga canimorsus* produces a rare but fulminant bacteremic illness after a dog bite, with fatal multiorgan failure, particularly in splenectomized patients and those with alcoholism or other immunosuppressive disorders.[66] Broad-spectrum antibiotics are indicated in concert with aggressive resuscitation.[66] The virulence of this rare infection provides some justification for the prophylactic use of a penicillin-class agent in all immunocompromised patients bitten by dogs.

Cat-Scratch Disease **Cat-scratch disease** is a clinical syndrome of regional lymphadenopathy developing 7 to 12 days after a cat bite or scratch.[81-83] This chronic indolent infection caused by *Bartonella henselae* can result in painful, matted masses of lymph nodes.[82] Mild constitutional symptoms are common, and nonlymphoid organs may be affected in approximately 10% of cases (**Table 46-6**). The causative bacteria cannot be easily cultured from human lymph node tissue, so the diagnosis is usually made using a combination of epidemiologic, clinical, histologic, and/or serologic criteria.[81-83]

Most cases with only lymph node involvement resolve in 2 to 5 months, and therapy consists primarily of pain relief and reassurance. Large,



FIGURE 46-4. Hand infection after a cat bite. Wound fluid culture grew *Pasteurella multocida*. [Photo contributed by J. S. Stapczynski, MD.]

TABLE 46-6 Organ Involvement in Cat Scratch Disease

Constitutional symptoms

- Low-grade fever
- Malaise and fatigue
- Headache
- Nausea and anorexia

Nonlymphoid organ involvement—often with prolonged fever

- CNS: encephalopathy with headache, seizures, confusion, or altered mental status
- Musculoskeletal: synovitis with joint pain and swelling
- Lungs: pneumonitis with dyspnea and cough
- Abdomen: granulomatous hepatitis or splenitis producing abdominal pain
- Eyes: retinitis with vision loss

painful, fluctuant nodes can be aspirated for symptomatic relief. Incision and drainage is to be avoided, as persistent fistula and scarring have been reported. Antibiotics are not indicated in most cases, but in patients with severe painful lymphadenopathy, a 5-day course of azithromycin may speed resolution of adenopathy.[84] Patients with systemic immunodeficiencies are susceptible to severe infection and bacteremia from *B. henselae*, so it is reasonable to treat immunodeficient patients with a 7- to 10-day course of trimethoprim-sulfamethoxazole, ciprofloxacin, or rifampin. Patients with nonlymphoid organ involvement usually require admission for definitive evaluation and parenteral antibiotic treatment. The vast majority of patients, even those with multiorgan involvement, recover without sequelae.

HUMAN BITES

Human bites tend to be more serious than bites from domestic animals.[85-87] The reasons are likely due to the nature of the event, location of the bite, and potential bacteria inoculated into the wound. Treatment recommendations are based on experience. All human bites should be treated as contaminated wounds. Patients with human bites often present for care late after injury.[86] The **closed-fist injury**, incurred when a flexed knuckle strikes a human tooth in the course of an altercation, is a common human bite injury (see Chapter 43, "Arm, Forearm, and Hand Lacerations"). Most human bite wounds should not undergo primary closure, with the possible exception of wounds to the face, where primary closure is associated with a postrepair wound infection rate of approximately 10%.[87,88]

Human bite wound infections are usually polymicrobial, and the most common organisms isolated are staphylococcal and streptococcal species. Other pathogens include the species-specific gram-negative rod *Eikenella corrodens.* Cephalexin is cost effective and adequate as an initial agent; **amoxicillin-clavulanate is an alternative, with prophylaxis recommended after all but the most trivial human bites.**[26,72] For established infections, parenteral agents of choice include ampicillin-sulbactam, cefoxitin, or piperacillin-tazobactam.

Herpes simplex virus can cause local infection, termed **herpetic whitlow**, after a human bite or contact with infected saliva.[89,90] The appearance is usually a painful coalescence of vesicles, typically on the distal phalanx (**Figure 46-5**). Vesicles usually resolve in 3 to 4 weeks. Treatment with oral acyclovir for 7 to 10 days or topical acyclovir ointment for 7 to 14 days may shorten the duration of the symptoms.

RODENTS, LIVESTOCK, AND EXOTIC AND WILD ANIMALS

RODENTS

Patients often seek care or consultation after being bitten by a rodent. The injury is usually trivial, the risk of local wound infection is low, and rodents are not known to carry or transmit rabies, so standard wound care and reassurance should suffice. Of more concern is the potential zoonotic systemic infections carried by mice and rats.[91] **Rat-bite fever** consists of two similar febrile illnesses occurring after a small percentage



FIGURE 46-5. Herpes simplex virus infection: herpetic whitlow. Painful, grouped, confluent vesicles on an erythematous edematous base on the distal finger were the first (and presumed primary) symptomatic infection. [Reproduced with permission from Wolff K, Johnson RA, Saavedra AP, Roh EK (eds): *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 8th ed. New York, NY: McGraw-Hill Education; 2017, Figure 27-35.]

of bites from rats, mice, squirrels, or gerbils due to either *Streptobacillus moniliformis* (more common in North America) or *Spirillum minus/minor* (more common in Asia).[92,93] Infection can also result from exposure to rat feces or urine. The incubation period for the streptobacillary form is typically 3 to 7 days, whereas it is usually longer than 10 days for the spirillary variety. Onset is typically with rigors and fevers and progresses to migratory polyarthralgia and a maculopapular petechial or purpuric rash. Infection can spread to the heart, brain, arteries, liver, kidneys, and lungs. The mortality rate for untreated infection is 10% to 15%. Treatment is with IV penicillin for 5 to 7 days followed by oral penicillin for an additional 7 days. Doxycycline or tetracycline is used for penicillin-allergic patients.

LIVESTOCK AND LARGE GAME ANIMALS

Livestock and large game animals can inflict serious tissue injury with their powerful jaws and grinding teeth.[94] The risk of wound infection is significant, and systemic illnesses, such as brucellosis, leptospirosis, or tularemia, can follow the injury. Aggressive wound care, imaging to detect fractures, and prophylactic broad-spectrum antibiotics are recommended. A febrile illness after such a bite usually requires inpatient antibiotic therapy guided by blood culture results.[67]

FRESHWATER AND SALTWATER WOUNDS

Freshwater fish bite infections can be due to ***Aeromonas*,** streptococci, and staphylococci, and treatment is with a fluoroquinolone or trimethoprim-sulfamethoxazole. Saltwater fish bites or lacerations require coverage for ***Vibrio***, usually with a fluoroquinolone or doxycycline.

SYSTEMIC VIRAL INFECTIONS

Disseminated viral illnesses resulting from mammalian bites include rabies, hepatitis, herpes B virus, and HIV. The risk of infection is variable depending on the number of infectious organisms in the saliva of the biting animal.

Most human rabies cases identified in the United States were acquired from contact with bats while in the United States or from dog bites sustained while traveling abroad (see Chapter 158, "Rabies," for detailed discussion). Local public health agencies and the state veterinarian are good sources of information regarding the rabies risk from contact with specific indigenous animals and recommended postexposure prophylaxis with immunoglobulin and vaccine.

B virus, also called herpes B, is caused by *Macacine herpesvirus 1* and can be transmitted by bites from monkeys and other nonhuman primates, although only monkeys of the macaque family serve as the natural reservoir for B virus infection.[94-97] Human infection with B virus causes myelitis and hemorrhagic encephalitis, with a case fatality rate of 70%. Those at greatest risk for B virus infection are veterinarians, laboratory workers, and others who have close contact with macaques or monkey cell cultures. After a bite or wound from a macaque, immediately and thoroughly wash and gently scrub the area or wound with soap, concentrated solution of detergent, povidone-iodine, or chlorhexidine and water for 15 minutes, and then irrigate the washed area with running water for 15 to 20 minutes to reduce the chance of infection. Consultation with an infectious disease expert is strongly advised before beginning antiviral therapy. The Centers for Disease Control and Prevention maintains a website with current B virus information at (http://www.cdc.gov/herpesbvirus/index.html). Acyclovir or valacyclovir started immediately after injury can prevent or ameliorate this illness.[98]

Viral hepatitis and HIV can both be transmitted by a human bite, although HIV viral concentration in nonbloody saliva is thought to be relatively low. **A protocol similar to that for an occupational needlestick injury should be used when a patient sustains a bite from a high-risk source (see Chapter 155, "Human Immunodeficiency Virus Infections").**

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 47

Postrepair Wound Care

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INTRODUCTION

Postoperative care begins immediately after laceration repair in the ED with gentle cleansing using normal saline or clean (tap) water to remove any residual blood products or contamination. Additional considerations include dressings, topical antibiotics, edema reduction techniques, prophylactic antibiotics, tetanus prophylaxis, and wound drains. Before ED release, give the patient instructions regarding wound care and cleansing, pain control, signs of infection, follow-up dates, and short-term and long-term cosmetic expectations.

WOUND DRESSINGS

Postoperative wound dressing should be tailored to both the type of wound and method of wound closure. Most sutured or stapled lacerations should be covered with a protective, nonadherent dressing for 24 to 48 hours. Maintaining a moist environment increases the rate of re-epithelialization, and occluded wounds heal faster than those exposed to air.[1-3] Conversely, leaving lacerations exposed to air may result in a slightly lower healing rate but does not result in an increased rate of infection.[4]

Useful dressings are semipermeable films manufactured from transparent polyurethane or similar synthetic films coated on one surface with a water-resistant hypoallergenic adhesive. They are highly elastic, conform easily to body parts, and are generally resistant to shear and tear. They are permeable to moisture vapor and oxygen but impermeable to water and bacteria. Common brands of semipermeable wound dressings are OpSite Post-Op® (Smith & Nephew PLC, London, UK), Bioclusive® (Johnson & Johnson, New Brunswick, NJ), and Tegaderm® (3M, St. Paul, MN). The disadvantages of these products are that they cannot absorb large amounts of fluid and exudate and they do not adhere well to very moist wounds.

Topical antibiotic creams and ointments are an alternative to the use of commercial dressings to maintain a moist environment. As an added benefit, topical antibiotics may help reduce infection rates and may also prevent scab formation.[5-7] **However, patients whose lacerations are closed with tissue adhesives should not use topical ointments or creams because they will loosen the adhesive and may result in dehiscence.** Tissue adhesives serve as their own antimicrobial barrier and occlusive dressing; wounds closed with tissue adhesives do not require supplementary dressings.

EDEMA REDUCTION

Instruct patients to elevate the injury site for 24 to 48 hours when soft tissue contusion is present to limit accumulation of fluid in the wound area. Wounds with little edema heal more rapidly than those with marked edema. Pressure dressings can be used to minimize the accumulation of intercellular fluid in the subcutaneous space. Pressure dressings are useful for ear and scalp lacerations (see Chapter 42, "Face and Scalp Lacerations"). For large scalp lacerations that have a tendency to bleed, short-term use of a pressure dressing will limit subcutaneous hematoma formation. Avoid excessive pressure in all pressure dressings, especially in the extremities where they may compromise circulation. Tube gauze dressing applied to fingers or toes should not be twisted at the base of the digit; such twisting may create a tourniquet and lead to distal ischemia.[8,9] Consider a short period of splinting with large lacerations over joints to reduce pain, limit tension on the wound, minimize swelling, and promote healing.

PROPHYLACTIC ANTIBIOTICS

Prophylactic oral antibiotics are not recommended except for select circumstances[10-13] based on guiding principles: the degree of bacterial contamination, the presence of infection-potentiating factors (e.g., soil), the mechanism of injury, and the presence or absence of host predisposition to infection.[14-17] **Compulsive wound cleansing is far more important than antibiotics to reduce postrepair wound infection.[16,17]**

Prophylactic antibiotics are recommended for human bites, cat bites, deep dog bite puncture wounds, bite wounds to the hand, open fractures, and wounds with exposed joints or tendon (see Chapter 46, "Puncture Wounds and Bites," and Chapter 267, "Initial Evaluation and Management of Orthopedic Injuries").[14-16,18-20] Also, consider prophylactic antibiotics after wound closure in a lymphedematous area.[20,22]

The risk of bacteremia during care of grossly contaminated lacerations in the ED is unknown but is likely to be small.[21] However, some patients who have structural heart disease, arteriovenous hemodialysis fistulas, prosthetic joints, cerebrospinal fluid shunts, vascular grafts, or other permanent indwelling "hardware" may trap bacteria from the bloodstream and develop infections in the previously mentioned organs or devices. There is no evidence for preprocedure antibiotic prophylaxis to prevent bacteremic spread of infection from manipulation of a contaminated site. Administer a single dose of an IV antibiotic before the wound is manipulated when antibiotic prophylaxis is desired during the management of a heavily contaminated wound in patients with these conditions or devices.

Antibiotics used for postrepair prophylaxis are similar to those used for treatment of established infections (**Table 47-1**).[10] Oral administration is adequate for the initial dose, and there is no evidence that the parenteral route is better. Antibiotic prophylaxis continues for 3 to 5 days for nonbite injuries and 5 to 7 days for bite wounds.

Although methicillin-resistant *Staphylococcus aureus* has become a common cause of skin and soft tissue infections, postinjury antibiotic prophylaxis to cover this pathogen does not appear necessary.[10] Amoxicillin-clavulanate is the preferred prophylactic treatment for mammalian bite wounds.[14,15] For open fractures or joints, a parenteral first-generation cephalosporin should be used with an aminoglycoside added if extensive soft tissue injury is present.[20]

TABLE 47-1 Postrepair Oral Antibiotic Prophylaxis

Situation	Primary Recommendation	Alternative Recommendation
Uncomplicated patient	First-generation cephalosporin or antistaphylococcal penicillin	Macrolide Clindamycin
Grossly contaminated wounds and/or retained foreign body	Amoxicillin-clavulanate or second-generation cephalosporin	Clindamycin plus a fluoroquinolone
Bite wounds	Amoxicillin-clavulanate	Clindamycin plus either a fluoroquinolone or trimethoprim-sulfamethoxazole
Plantar puncture wounds	Ciprofloxacin	First-generation cephalosporin or antistaphylococcal penicillin
Underlying systemic immunodeficiency (acquired immunodeficiency syndrome, chronic steroid use, poorly controlled diabetes mellitus)	Amoxicillin-clavulanate or second-generation cephalosporin	Clindamycin plus a fluoroquinolone
Impaired local defenses (peripheral arterial disease, lymphedema)	Amoxicillin-clavulanate	Clindamycin or erythromycin

TETANUS PROPHYLAXIS

Tetanus can occur when lacerations, puncture wounds, and crush injuries are contaminated with *Clostridium tetani* spores (see Chapter 157, "Tetanus"). Most cases of tetanus in the United States occur in patients who are inadequately vaccinated.[24] As part of wound care, ask the patient about previous tetanus immunizations. Recommendations for postinjury tetanus prophylaxis are based on the condition of the wound and the patient's immunization history (**Table 47-2**).[25] Because of the emergence of pertussis infections, Tdap (tetanus, diphtheria, and pertussis; containing the acellular pertussis vaccine) should be used in adults who have not previously received a dose of Tdap (either in the primary series, as a booster, or for wound management) or are >65 years old.[25]

The only contraindication to tetanus toxoid is a history of neurologic or severe systemic reaction after a previous dose. Local self-limited reactions, such as erythema, induration, and pain at the injection site, are common after tetanus vaccination. These local side effects do not preclude future tetanus immunization. Exaggerated local reactions occur occasionally after tetanus toxoid and involve extensive pain and swelling of the entire extremity. Exaggerated local reactions occur most often in adults with high serum tetanus antitoxin levels who have received frequent doses of tetanus toxoid. Such patients should not receive tetanus toxoid more frequently than every 10 years. Severe systemic reactions to tetanus immunization include generalized urticaria, anaphylaxis, or neurologic complications, including peripheral neuropathy and Guillain-Barré syndrome. A severe allergic reaction, including acute respiratory distress or cardiovascular collapse after a dose of tetanus toxoid, is a contraindication to further immunization. If the use of a tetanus toxoid is contraindicated, consider passive immunization with tetanus immune globulin in a tetanus-prone wound.

TABLE 47-2 Recommendations for Tetanus Prophylaxis

History of Tetanus Immunization	Clean Minor Wounds		All Other Wounds*	
	Administer Tetanus Toxoid†	Administer TIG‡	Administer Tetanus Toxoid	Administer TIG
<3 or uncertain doses	Yes	No	Yes	Yes
≥3 doses				
Last dose within 5 y	No	No	No	No
Last dose between 5–10 y	No	No	Yes	No
Last dose >10 y	Yes	No	Yes	No

Abbreviation: TIG = tetanus immune globulin.

*Especially if wound care delayed (>6 h), deep (>1 cm), grossly contaminated, exposed to saliva or feces, stellate, ischemic or infected, avulsions, punctures, or crush injuries.

†Tetanus toxoid: Tdap (tetanus, diphtheria, and pertussis) if adult and no prior record of administration or age >65 y; otherwise, tetanus-diphtheria toxoid if >7 y and diphtheria-tetanus toxoid if <7 y, preferably administered into the deltoid.

‡Tetanus immune globulin: adult dose, 250–500 IU administered into deltoid opposite the tetanus-diphtheria toxoid immunization site.

WATER CONTACT AND CLEANING

Sutured or stapled wounds can be gently washed and cleansed with tap water as early as 8 hours after closure without an increase in infection rate.[26-28] Using soap and tap water to cleanse lacerations will not increase the infection rate.[29] Use gentle blotting to dry the area; aggressive wiping could cause wound dehiscence. For routine wounds, tell patients to remove dressings after 24 hours, cleanse the wound, and examine it for signs of infection. When delayed primary closure is anticipated, the dressing should remain undisturbed for 4 to 5 days until the patient is reevaluated by the physician.

Daily cleansing ensures that the patient examines the laceration for early signs of infection. Patients should observe the wound for redness, warmth, swelling, and drainage, and contact a physician if such signs develop. Standardized wound-care instructions improve patient compliance and understanding.[30] Reapplication of topical antibiotics for 3 to 5 days will decrease scab formation, thereby preventing wound edge separation.

Patients with wounds closed with tissue adhesives may occasionally and briefly get the area wet, but should avoid bathing and swimming because prolonged moisture will loosen the adhesive bond and result in earlier sloughing of the adhesive.[31]

PAIN CONTROL

Abrasions and some lacerations can be quite painful. Patients should be educated regarding the expected degree of pain and measures that may help reduce pain. Splints can be used to reduce swelling and pain for extremity lacerations. Appropriate analgesic medications and anti-inflammatory agents will help control pain. The pain from lacerations generally decreases after the initial 48 hours, and opioid analgesics are rarely necessary after that time. Patients with concurrent contusions (such as victims of motor vehicle crashes) will often report worsening pain 24 to 48 hours after the initial injury.

FOLLOW-UP

Tell patients when and with whom to follow up for suture removal or wound examination.[30] Appropriate time to remove nonabsorbable sutures or staples varies by location (**Table 47-3**). Facial sutures are removed in 3 to 5 days to avoid formation of unsightly sinus tracts and hatch marks.[32] Sutures over the joints or on the hands should be left in place for 10 to 14 days, as they may be subject to increased tension during movement.

Debride any scab or crusting engulfing the sutures before suture removal, such as by gently applying gauze soaked with hydrogen peroxide. When removing sutures, grasp the suture at the knot with the forceps for removal (**Figure 47-1**). Avoid applying tension in a direction that would tend to cause dehiscence. Use scissors or a #12 blade to cut the sutures. Skin staples are removed with a device that deforms the center and extracts the legs from the skin (**Figure 47-2**).

Tissue adhesives will slough off, typically within 5 to 10 days of application, and do not usually require removal. Tell the patient to avoid picking at the tissue adhesive, scrubbing the area, or exposing it to water

TABLE 47-3 Suture and Staple Removal Recommendations

Location	Days
Back	10–14
Buttocks	10–14
Chest	7–10
Delayed closure	8–12
Foot	10–14
Face	3–4 (child), 3–5 (adult)
Hand	10–14
Legs	8–10
Neck	2–3 (child), 3–4 (adult)
Overlying joints	10–14
Retention sutures	14–30
Scalp	10–14
Upper extremity	7–10

Source: Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medicine Procedures*, 3rd ed. New York, NY: McGraw-Hill, Inc.; 2019, Table 114-5.

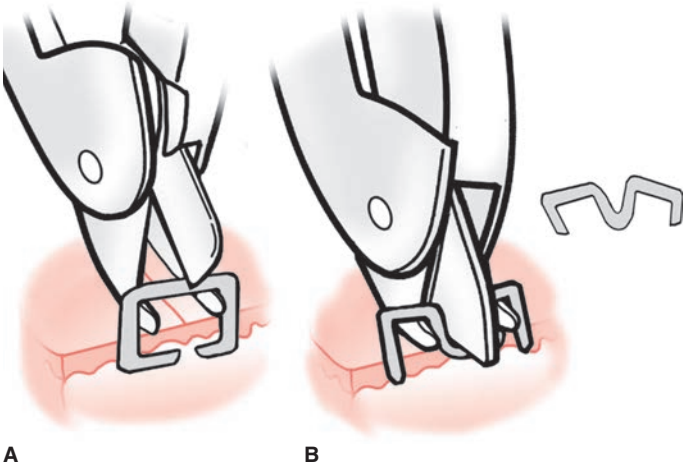

FIGURE 47-2. Skin staple removal. **A.** Place the lower jaw of the staple remover under the horizontal portion of the staple. **B.** The upper jaw deforms the center of the staple and extracts the vertical legs from the skin. [Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medical Procedures*, 3rd ed. New York, NY: McGraw-Hill, Inc.; 2019, Figure 116-28A&B.]

for more than brief periods. If tissue adhesives remain on the skin for prolonged periods, antibiotic ointment, petroleum jelly, or bathing can accelerate removal. When adhesive tapes are used, they can be removed by gentle peeling away from the skin, starting at one end of the laceration and proceeding along and parallel to the wound, avoiding pulling across or perpendicular to the wound.

Scheduled "wound checks" might be useful in high-risk patients, high-risk wounds, or patients unable to identify signs of infection. Because many healing wounds may develop erythema and patients are not able to correctly identify wound infections, do not prescribe antibiotics without a reevaluation.[33] Patients who require further tetanus immunization to complete their primary series should have the second dose 1 to 2 months after the first dose, and the third dose 6 to 12 months after the second dose.

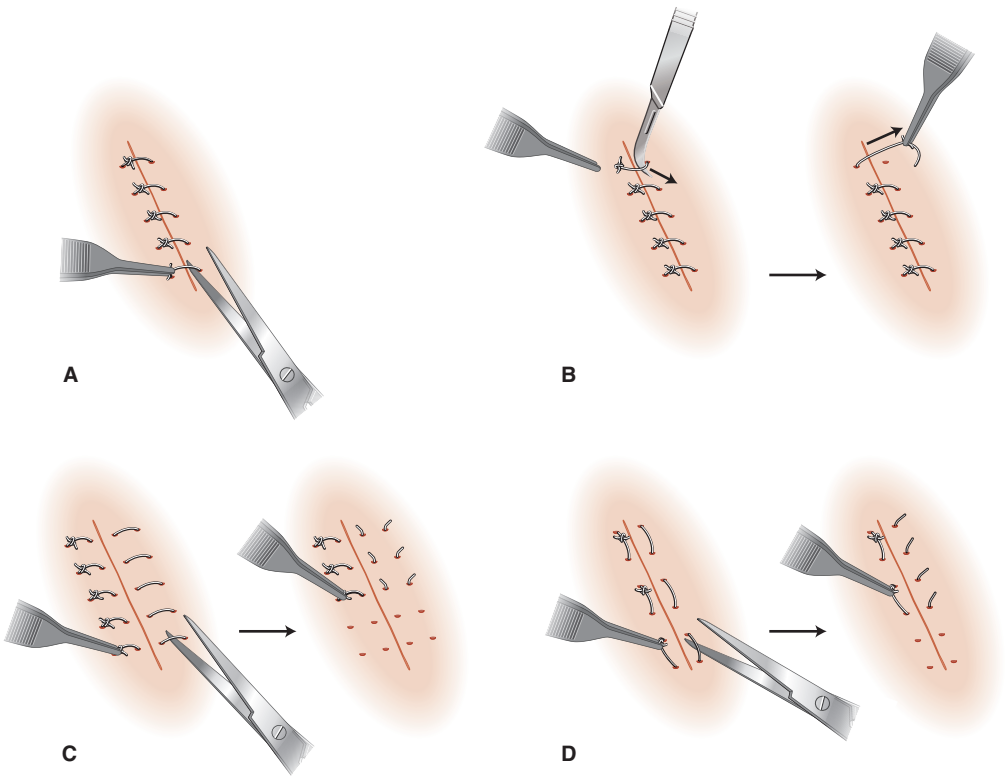

FIGURE 47-1. Suture removal. **A.** For simple interrupted percutaneous sutures, grasp the suture with the forceps at the knot, cut the suture with scissors on the side of the wound opposite the knot, and pull the knot across the wound. **B.** Alternatively, cut the suture with a curved #12 blade on the side of the wound opposite the knot (*left*) and pull the knot across the wound (*right*). **C.** For vertical mattress sutures, cut the suture on the side opposite the knot and pull the knot with forceps. **D.** For horizontal mattress sutures, cut the suture on the side opposite the knot and pull the knot with forceps. [A, C, and D reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medical Procedures,* 3rd ed. New York, NY: McGraw-Hill, Inc.; 2019, Figure 21.]

LONG-TERM COSMETIC OUTCOME

Educate patients about the expected outcome before wound closure. Reinforce the message at the time of suture or staple removal or wound follow-up. Tell patients that all traumatic lacerations result in some scarring and that short-term cosmetic appearance is not highly predictive of the ultimate cosmetic outcome.[34] For patients concerned about scar formation, scar-prevention therapies can be used after the initial phase of wound healing, typically after 2 weeks.[35] Healing lacerations and abrasions should not be exposed to direct sunlight, because sun exposure can result in permanent hyperpigmentation.[36] Protect injured skin with a sun-blocking agent for 6 to 12 months after injury.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 7

Cardiovascular Disease

CHAPTER 48

Chest Pain

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INTRODUCTION AND EPIDEMIOLOGY

About 7 million patients with chest pain present to a U.S. ED each year.[1] Of these, more than 50% are placed into an observation unit or admitted to the hospital, yet only about 10% are eventually diagnosed with an acute coronary syndrome (ACS).[2-6] Still, approximately 2% of patients with acute myocardial infarctions (AMIs) are not diagnosed on initial presentation to the ED.[2] We discuss the features and approach that help differentiate ACS from other causes of chest pain. Chapter 49, "Acute Coronary Syndromes," and Chapter 51, "Low-Probability Acute Coronary Syndromes," discuss management of these specific syndromes.

Acute chest pain is the recent onset of pain, pressure, or tightness in the anterior thorax between the xiphoid, suprasternal notch, and both midaxillary lines. ACS includes AMI and acute ischemia (unstable angina). AMI is defined by myocardial necrosis, evident from elevation of cardiac biomarkers, and is classified by ECG findings into ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI). Unstable angina is a clinical diagnosis defined by chest pain or an equivalent (neck, upper extremity pain) from inadequate myocardial perfusion that is new or occurring with greater frequency, less activity, or at rest. Patients with unstable angina do not have pathologic ST-segment elevation on ECG or cardiac biomarker elevation, but they are at risk of eventual myocardial damage absent recognition and treatment.

PATHOPHYSIOLOGY

The chest wall, from the dermis to the parietal pleura, is innervated by somatic pain fibers. Neurons enter the spinal cord at specific levels corresponding to the skin dermatomes. Visceral pain fibers are found in internal organs, such as the heart, blood vessels, esophagus, and visceral pleura. Visceral pain fibers enter the spinal cord and map to areas on the parietal cortex corresponding to cord levels shared with somatic fibers. Stimulation of visceral or somatic afferent pain fibers results in two distinct pain syndromes. Pain from somatic fibers is usually easily described, precisely located, and often experienced as a sharp sensation. Pain from visceral fibers is generally more difficult to describe and imprecisely localized. Patients with visceral pain are more likely to describe it as *discomfort*, *heaviness*, *pressure*, *tightness*, or *aching*. Visceral pain is often referred to an area of the body corresponding to adjacent somatic nerves, which explains why pain from an ACS may radiate to the neck, jaw, or arms. Factors such as age, sex, comorbid illnesses, medications, drugs, and alcohol may interact with psychological and cultural factors to alter pain perception and communication.

CLINICAL FEATURES

INITIAL ASSESSMENT

Patients with abnormal vital signs, ECG findings of ischemia or injury, a history of prior coronary artery disease, multiple atherosclerotic risk factors, or any abrupt, new, or severe chest pain or dyspnea should be quickly placed into a treatment bed. Initiate cardiac monitoring and IV access, and obtain an ECG, ideally within 10 minutes of arrival. Identify and treat immediate life needs such as supporting the airway, breathing, and circulation. Measure vital signs promptly and at regular intervals. Administer oxygen if ambient saturation is <94%.

Next, focus on history, physical exam, and laboratory findings associated with cardiac (ACS) versus noncardiac chest pain causes. Obtain a directed history of symptoms, abridged past medical history, and review of systems seeking features of life-threatening causes of chest pain, such as ACS, aortic dissection, pulmonary embolism (PE), severe pneumonia, and esophageal rupture. Ask about the onset, timing, severity, radiation, and character of the chest pain; alleviating and exacerbating factors; and presence of associated symptoms, such as diaphoresis, dyspnea, nausea, vomiting, palpitations, and dizziness.

The physical examination seeks findings to aid in detecting life-threatening or common causes of chest pain. Inspect the thorax for prior surgical incisions, chest wall deformities, and symmetric rise and fall with respiration. Palpate the chest wall for tenderness, masses, or crepitus. Auscultate to identify chest consolidation or pneumothorax, murmurs, gallops, or friction rubs, and obtain a chest radiograph to identify immediate life-threatening processes.

HISTORY

Patients with serious and life-threatening intrathoracic disorders, including ACS, may report pain outside the chest, such as in the epigastrium, neck, jaw, shoulders, or arms. Some patients never experience chest pain or have migratory pain that is no longer in the chest at the time of medical evaluation. Patients with AMI who present without chest pain have diagnostic and treatment delays and have an in-hospital mortality rate more than twice that of AMI patients with chest pain.[7]

Classic Chest Pain Terms such as *typical* and *atypical symptoms* are misleading because symptoms among patients with ACS vary and may not include classic findings. **Classic cardiac chest pain** is retrosternal left anterior chest crushing, squeezing, tightness, or pressure. Cardiac chest pain is often brought on by or exacerbated by exertion and relieved by rest. Traditional teaching is that anginal pain lasts 2 to 10 minutes, unstable angina pain lasts 10 to 30 minutes, and pain from AMI often lasts longer than 30 minutes, but great overlap exists. Other classic features of ACS presentations include radiation of the pain to the arms, neck, or jaw; diaphoresis; dyspnea; and nausea or vomiting.[8]

Nonclassic Chest Pain The absence of classic symptoms contributes to delays in seeking care and in evaluation.

Nonclassic presentations are common and include chest pain lasting for seconds, constant pains lasting for 12 to 24 hours or more without waxing and waning intensity, or pain worsened by specific body movements or positions, such as twisting and turning of the thorax. Reports of stabbing, well-localized, positional, or pleuritic chest pain are uncommon with ACS but do not exclude it with certainty. The Multicenter Chest Pain Study reported that 22% of patients with AMI described their chest pain as sharp or stabbing.[9] **Nonclassic presentations of ACS occur more frequently in women, racial minorities, diabetics, the elderly, and patients with psychiatric disease or altered mental status than in other patient groups.**[7,10,11] Multiple prescription medications, drugs, alcohol, patient or provider sex, and cultural differences can impact the pain perception or reporting of symptoms.[12-14] For example, the term *sharp* in some cultures is interpreted to mean *severe*, rather than *knife-like*.[15]

Pre- and early menopausal women with ACS are more likely to present with pain unrelated to exercise, pain not relieved by rest or nitroglycerin, pain relieved by antacids, palpitations without chest pain, or a chief complaint of fatigue.[16] Associated symptoms of nausea, emesis, jaw pain, neck pain, and back pain are more common in women with ACS, whereas diaphoresis is more common among men.[16]

Anginal or Ischemic Symptom Equivalents One large public hospital reported that 47% of 721 consecutive patients with myocardial infarction presented complaining of symptoms other than chest pain.[11] These symptoms include dyspnea at rest or with exertion, nausea, lightheadedness, generalized weakness, acute changes in mental status, diaphoresis, or shoulder, arm, or jaw discomfort. Patients with dyspnea have a fourfold increased risk of sudden death from cardiac causes compared with asymptomatic patients and a twofold increased risk compared with patients with classic angina.[17]

Epigastric or upper abdominal discomfort, even when relieved with antacids, raises suspicion for ACS, especially for patients >50 years old or those with known coronary artery disease. In these two high-risk groups, include an ECG in routine evaluation of abdominal pain. Consider ACS in patients presenting with new palpitations, because myocardial ischemia may increase automaticity and irritability, leading to dysrhythmias. Furthermore, tachycardia can cause an increase in myocardial oxygen demand, triggering myocardial ischemia.

Risk Factors Major risk factors for coronary artery disease include age >40 years old, male or postmenopausal female, hypertension, tobacco use, hypercholesterolemia, diabetes, truncal obesity, family history, and a sedentary lifestyle.[18,19] **Cocaine** use is associated with AMI even in young people with minimal or no coronary artery disease, and chronic cocaine use may accelerate atherosclerosis and severe coronary artery disease.[20] Despite this association, patients with acute chest pain and concomitant cocaine use have low rates of adverse outcomes.[21,22] Human immunodeficiency virus infection and treatment with highly active antiretroviral therapy can accelerate atherosclerosis.[23]

While cardiac risk factors are useful in predicting coronary artery disease risk within a given population, they are less useful for diagnosing the presence or absence of ACS in an individual patient.[8,24,25] Patients with known coronary artery disease and prior ACS are at risk for another ACS event; therefore, identify previous episodes of chest pain; prior echocardiography, stress testing, or coronary angiography; or prior revascularization (stent placement or coronary artery bypass graft surgery).

AMI SIGNS AND SYMPTOMS: LIKELIHOOD RATIOS

There are no historical features with sufficient sensitivity and specificity to either diagnose or exclude ACS. Radiation to the arms and shoulders, particularly to the right arm or both arms, and exertional chest pain are the historical features most strongly associated with ACS.[24,26,27] Dyspnea, diaphoresis, and nausea or vomiting are also associated with ACS but are less predictive.[26,27] Pressure-like chest sensation also has a limited value in the prediction of ACS.[24] Sharp, pleuritic, positional chest pain is associated with a decreased likelihood of ACS, but cannot eliminate the diagnosis.[24] Lack of exertional pain or pain radiation has no diagnostic value for exclusion of ACS.[24,27] Since classic cardiac ischemic pain is not universal, and men and women both present with nonclassic symptoms, the diagnostic utility of specific chest pain descriptions does not differ significantly between men and women.[28] **Tables 48-1** and **48-2** summarize the chest pain characteristics associated with increased or decreased likelihood ratios of ACS.

PHYSICAL EXAMINATION

The examination of patients with ACS is often normal, and there are no exam findings that diagnose or exclude ACS. Use the exam in conjunction with history to search for other causes and guide therapy.

Vital sign abnormalities from ACS may include hyper- or hypotension, tachycardia, or bradycardia. Tachycardia may result from increased sympathetic tone and decreased left ventricular stroke volume. Bradycardia may occur due to ischemia or infarction involving the conduction system or alterations in sympathetic and parasympathetic activation of the sinoatrial or atrioventricular nodes. Patients with acute myocardial ischemia or infarction may have abnormal heart sounds due to changes in ventricular function or compliance, such as an S_3 or S_4 gallop, diminished S_1, or a paradoxically split S_2. New murmurs in patients with chest pain may be associated with AMI with chordae tendineae rupture or aortic root dissection. Ischemia-induced congestive heart failure may produce crackles on auscultation of the lungs.

Physical examination findings most strongly associated with AMI in patients presenting with acute chest pain are hypotension, S_3 gallop, and diaphoresis; however, the frequency, interrater reliability, and added diagnostic value of these are limited.[24] Reproducible chest wall tenderness suggests a musculoskeletal etiology, but is reported in up to 15% of patients with confirmed AMI and cannot exclude the diagnosis of ACS.[29]

TABLE 48-1 Acute Myocardial Infarction–Associated Symptoms

Pain Descriptor	Study	Positive Likelihood Ratio or Odds Ratio (95% CI)
Radiation to right arm or shoulder	Body et al.	2.31 (1.52–3.53)
Radiation to both arms or shoulders	Body et al.	2.58 (1.53–4.34)
Associated with exertion	Hess et al.	2.81 (2.23–3.54)
Radiation to left arm	Body et al.	1.36 (0.89–2.09)
Associated with diaphoresis	Hess et al.	1.50 (1.16–1.94)
Associated with nausea or vomiting	Hess et al.	0.89 (0.68–1.18)
Described as pressure/squeezing	Hess et al.	1.52 (1.21–1.91)
Similar to previous ischemia	Hess et al.	3.35 (2.65–4.24)

Source: Data from Body R, Carley S, Wibberley C, et al: The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. *Resuscitation* 81: 281-6, 2010; and Hess EP, Brison RJ, Perry JJ, et al: Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med* 59: 115-25, 2012.

RESPONSE TO THERAPY

Response to medications poorly discriminates between cardiac and noncardiac chest pain. Although nitroglycerin reduces anginal pain, it may also relieve the pain from noncardiac conditions such as esophageal spasm.[30-32] Similarly, relief from an antacid agent, alone or in combination with other agents, does not eliminate a cardiac cause of pain.[33]

DIAGNOSIS

Life-threatening concerns in acute chest pain are ACS, aortic dissection, PE, pneumonia, tension pneumothorax, and esophageal rupture. Other diagnoses with the potential for morbidity and mortality include simple pneumothorax, myocarditis, pericarditis, aortic stenosis, perforated ulcer, pancreatitis, and cholecystitis. Benign causes of chest pain include anxiety, musculoskeletal pain, esophagitis, and gastritis. Common causes

TABLE 48-2 Symptoms Not Associated With Acute Myocardial Infarction

Pain Descriptor	Study	Odds Ratio (95% CI)
Described as pleuritic	Goodacre et al.	0.5 (0.1–2.1)
Described as worse with movement	Hess et al.	0.69 (0.50–0.95)
Described as sharp	Hess et al.	0.42 (0.30–0.59)
Tender chest wall	Goodacre et al.	0.2 (0.1–1.0)
Radiation to abdomen	Hess et al.	0.34 (0.08–1.42)
Not associated with exertion	Goodacre et al.	0.8 (0.6–0.9)

Source: Data from Goodacre S, Locker T, Morris F, Campbell S: How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med* 9: 203, 2002; and Hess EP, Brison RJ, Perry JJ, et al: Development of a clinical prediction rule for 30-day cardiac events in emergency department patients with chest pain and possible acute coronary syndrome. *Ann Emerg Med* 59: 115-25, 2012.

TABLE 48-3 Common Causes of Acute Chest Pain

Visceral Pain	Pleuritic Pain	Chest Wall Pain
Typical angina	Pulmonary embolism	Costosternal syndrome
Unstable angina	Pneumonia	Costochondritis (Tietze's syndrome)
Acute myocardial infarction	Spontaneous pneumothorax	Precordial catch syndrome
Aortic dissection	Pericarditis	Xiphodynia
Esophageal rupture	Pleurisy	Radicular syndromes
Esophageal reflux or spasm		Intercostal nerve syndromes
Mitral valve prolapse		Fibromyalgia

of chest pain are listed in **Table 48-3**. **Table 48-4** summarizes the classic symptoms of the life-threatening causes of acute chest pain.

PULMONARY EMBOLISM

Symptoms of PE include sharp chest pain (may worsen with inspiration, called "pleuritic"), dyspnea, hypoxemia, syncope, or shock. There may be associated cough or hemoptysis. Patients with PE may be febrile (fever often not very high if present) or have leg swelling or pain, and some patients will report chest wall tenderness. Common physical examination findings include tachypnea, tachycardia, and hypoxemia. PE risk factors include recent surgery, trauma, prolonged immobility, active cancer, estrogens from birth control pills or hormone replacement therapy (particularly when combined with smoking), procoagulant syndromes, or a history of prior PE or deep venous thrombosis.[34]

Clinical decision aids, such as the **Wells and Revised Geneva Scores**, can risk-stratify patients with possible PE.[35] The **Pulmonary Embolism Rule Out Criteria** exclude PE in patients with a low pretest probability without further diagnostic testing.[36] Normal **D-dimer** testing, measured by a sensitive enzyme-linked immunosorbent assay, in a hemodynamically stable, low- to intermediate-risk patient (with a Revised Geneva Criteria Score of 0 to 10) effectively excludes PE; in those with higher risk assessment, a negative D-dimer has limited value.[37,38] In patients with PE, elevated cardiac troponin indicates ventricular dysfunction and identifies patients with an elevated risk of death and complications.[39]

In PE, ECG findings are nonspecific, with the most common finding being sinus tachycardia.

Chest radiographs often have nonspecific changes, but in rare cases, they may show signs of pulmonary infarction. CT pulmonary angiography is the test of choice and is highly sensitive for the detection of large to medium-sized PEs. See more details on PE in Chapter 56, "Venous Thromboembolism Including Pulmonary Embolism."

AORTIC DISSECTION

Pain from aortic dissection is classically described as a ripping or tearing sensation radiating to the interscapular area of the back. The pain is often sudden in onset, maximal at the time of symptom onset, and may migrate or be noted above and below the diaphragm. Lack of sudden-onset pain decreases the probability of aortic dissection but cannot exclude it.[40] Secondary symptoms of aortic dissection result from arterial branch occlusions and include stroke findings (lateralizing weakness or sensory changes), AMI, or limb ischemia. Risk factors include male sex, age over 50 years, poorly controlled hypertension, cocaine or amphetamine use, a bicuspid aortic valve or prior aortic valve replacement, certain connective tissue disorders (Marfan's syndrome and Ehlers-Danlos syndrome), and pregnancy.[41] Physical exam findings for aortic dissection lack sensitivity and specificity. A unilateral pulse deficit of the carotid, radial, or femoral arteries suggests aortic dissection in the setting of acute chest pain (likelihood ratio, 31; 95% confidence interval, 11 to 86).[40] Focal neurologic deficits are rare, occurring in only 16% of patients with aortic dissection, but the combination of chest pain and a focal neurologic deficit increases the likelihood of aortic dissection.[40] Although a completely normal chest radiograph lowers the likelihood, it does not exclude dissection (sensitivity, 52.4%; 95% confidence interval, 44.5 to 60.3). A normal **D-dimer** level also lowers the probability of aortic dissection (detecting the clot/declotting expected), but it also cannot exclude the disease.[42] ECG changes are common among patients with aortic dissection, with up to 40% to 50% presenting with ST-segment or T-wave changes, but there is no diagnostic pattern.[43,44] Elevated troponin among patients with aortic dissection is associated with increased mortality.[45] When aortic dissection is suspected, obtain a CT aortogram or transesophageal echocardiogram. See Chapter 59, "Aortic Dissection and Related Aortic Syndromes."

PNEUMONIA

Pneumonia is potentially life threatening in the elderly, immunocompromised, or patients with multiple comorbid conditions. Chest pain from pneumonia is usually described as sharp or pleuritic and associated with fever, cough, sputum production, and possibly hypoxemia.[46] Auscultation may reveal decreased breath sounds, rales, or bronchial breath sounds over the affected areas of consolidation. A chest radiograph usually confirms the diagnosis. See Chapter 65, "Community-Acquired Pneumonia, Aspiration Pneumonia, and Noninfectious Pulmonary Infiltrates."

ESOPHAGEAL RUPTURE (BOERHAAVE'S SYNDROME)

Patients classically present with a history of sudden-onset sharp substernal chest pain following forceful vomiting. Patients with esophageal rupture are usually ill-appearing and may be tachycardic, febrile, dyspneic, or diaphoretic. Physical examination may reveal crepitus in the neck or chest from subcutaneous emphysema. **Hamman's crunch**, audible crepitus that varies with the heartbeat on auscultation of the precordium, is a rare finding associated with pneumomediastinum. Chest radiography could show a pleural effusion (left more common than right), pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous air, although a normal radiograph cannot exclude esophageal rupture. When suspecting esophageal rupture, obtain a CT with oral water-soluble contrast. See Chapter 77, "Esophageal Emergencies."

TABLE 48-4 Classic Symptoms of Potentially Life-Threatening Causes of Chest Pain*

Disorder	Pain Location	Pain Character	Radiation	Associated Signs and Symptoms
Acute coronary syndrome	Retrosternal, left chest, or epigastric	Crushing, tightness, squeezing, pressure	Right or left shoulder, right or left arm/hand, jaw	Dyspnea, diaphoresis, nausea
Pulmonary embolism	Focal chest	Pleuritic	None	Tachycardia, tachypnea, hypoxia, may have hemoptysis
Aortic dissection	Midline, substernal	Ripping, tearing	Intrascapular area of back	Secondary arterial branch occlusion
Pneumonia	Focal chest	Sharp, pleuritic	None	Fever, hypoxia, may see signs of sepsis
Esophageal rupture	Substernal	Sudden, sharp, after forceful vomiting	Back	Dyspnea, diaphoresis, may see signs of sepsis
Pneumothorax	One side of chest	Sudden, sharp, lancinating, pleuritic	Shoulder, back	Dyspnea
Pericarditis	Substernal	Sharp, constant or pleuritic	Back, neck, shoulder	Fever, pericardial friction rub
Perforated peptic ulcer	Epigastric	Severe, sharp	Back, up into chest	Acute distress, diaphoresis

*Atypical presentations are common.

SPONTANEOUS PNEUMOTHORAX

The symptoms of spontaneous pneumothorax are sudden-onset, sharp, pleuritic chest pain with dyspnea. Classically, spontaneous pneumothorax occurs in tall, slender males. Risk factors for spontaneous pneumothorax include smoking and chronic lung diseases such as asthma and chronic obstructive pulmonary disease. Approximately 1% to 3% of patients with a spontaneous pneumothorax may develop a tension pneumothorax.[47] Auscultation may reveal decreased breath sounds and hyperresonance to percussion on the ipsilateral side. However, the physical exam findings of a simple pneumothorax are inconsistent and cannot be used to exclude presence, with the diagnosis made by chest radiography. See Chapter 68, "Pneumothorax."

ACUTE PERICARDITIS

Pain from acute pericarditis is classically described as a sharp, severe, constant pain with a substernal location. The pain may radiate to the back, neck, or shoulders; is worsened by lying flat and by inspiration; and is relieved by sitting up and leaning forward. A pericardial friction rub is the most specific physical exam finding, but is not always evident. The classic ECG findings are diffuse ST-segment elevation with PR depression.[48] See Chapter 55, "Cardiomyopathies and Pericardial Disease."

MITRAL VALVE PROLAPSE

Symptoms attributed to mitral valve prolapse include sharp chest pain, palpitations, fatigue, anxiety, and dyspnea unrelated to exertion. A midsystolic click may be heard on auscultation. However, most patients are asymptomatic and have no consistent association of chest pain, dyspnea, or anxiety with the disorder.[49,50] See Chapter 54, "Valvular Emergencies."

CHEST WALL PAIN

Musculoskeletal or chest wall pain is characterized by sharp, highly localized, and positional pain. The pain should be completely reproducible by light to moderate palpation or by specific movements and may be increased by inspiration or coughing. However, chest wall tenderness is also reported by some patients with ACS and PE. **Costochondritis (Tietze's syndrome)** is an inflammation of the costal cartilages or their sternal articulations and causes chest pain that is variably sharp, dull, and often increased with respirations. **Xiphodynia** is inflammation of the xiphoid process that causes sharp, pleuritic chest pain reproduced by light palpation. **Texidor twinge** or **precordial catch syndrome** is a short, lancinating chest pain occurring in bunches lasting 1 to 2 minutes near the cardiac apex and is associated with inspiration, poor posture, and inactivity. *Pleurisy* is inflammation of the parietal pleura resulting in sharp pleuritic chest pain.

GI PAIN

GI disorders often cannot be reliably differentiated from ACS by history and physical examination alone.[25] **Gastritis** and **esophageal reflux** typically produce burning or gnawing pain in the lower half of the chest, with a brackish or acidic taste in the back of the mouth. The pain may be lessened with antacids and exacerbated by recumbency. **Peptic ulcer disease** is classically described as a postprandial, dull, boring pain in the epigastric region. Patients often describe being awakened from sleep by discomfort. Duodenal ulcer pain may be relieved after eating food, whereas gastric ulcer pain is often exacerbated by eating. Antacid medications usually provide symptomatic relief. **Acute pancreatitis** and **biliary disease** typically present with right upper quadrant or epigastric pain and tenderness, but can also cause chest pain. Esophageal spasm is often associated with reflux disease and is characterized by a sudden onset of dull or tight substernal chest pain. The pain is frequently precipitated by consumption of hot or cold liquids or a large food bolus and may be relieved by nitroglycerin. See Chapter 77, "Esophageal Emergencies," and Chapter 78, "Peptic Ulcer Disease and Gastritis."

PANIC DISORDER

Panic disorder is characterized by recurrent, unexpected, and discrete periods of intense fear or discomfort (panic attacks) with at least four of the following symptoms: chest pain, dyspnea, palpitations, diaphoresis, nausea, tremor, choking, dizziness, fear of losing control or dying, paresthesias, chills, or hot flashes. In one study, 25% of ED patients with chest pain met diagnostic criteria for panic disorder. Conversely, 9% of the patients identified as having panic disorder were ultimately diagnosed with ACS on hospital discharge.[51] This means panic disorder is best a diagnosis of exclusion or a co-diagnosis with ACS (or another cause). Do not assume panic disorder in a patient with chest pain in the ED until further testing allows better risk stratification. See Chapter 289, "Mood and Anxiety Disorders."

DIAGNOSTIC TESTING

Focus initial diagnostic testing for patients with chest pain on the exclusion or confirmation of serious pathology based on the differential diagnosis drawn from the history and physical examination. When history and exam make ACS a potential cause, testing commonly includes an ECG, chest radiograph, and cardiac biomarkers. Stress testing, advanced cardiac imaging, serial or continuous ECG monitoring, and serial cardiac biomarker measurements are discussed in Chapter 51, "Low-Probability Acute Coronary Syndrome."

IMAGING

Chest radiography is commonly performed in the evaluation of ED patients with chest pain. Most patients with ACS have a normal chest radiograph, but the images are useful to diagnose or exclude other conditions such as pneumonia and pneumothorax.[52] Other imaging modalities such as CT help evaluate conditions such as aortic dissection or PE.

ECG

Guidelines recommend a screening ECG within 10 minutes of ED arrival in patients with chest pain or other symptoms concerning for ACS.[53] Rapid ECG screening limits delays in identifying STEMI, allows more rapid time to reperfusion, and improves patient outcomes.[54-58]

Fewer than 5% of patients presenting to the ED with chest pain have evidence of a STEMI on ECG.[59,60] However, new ST-segment elevation of ≥1 mm in at least two contiguous leads represents an AMI that will benefit from rapid reperfusion interventions.[53] ST-segment elevation also occurs in patients with pericarditis, myocarditis, early repolarization, left ventricular hypertrophy, and ventricular aneurysms. New ST-segment depression and T-wave inversions are also associated with an increase in risk of AMI.[53]

A normal ECG lacks the sensitivity to exclude ACS, notably unstable angina or NSTEMI. In a large, multicenter, observational study of 391,208 patients with an evaluable ECG and diagnosis of AMI, 57% had "diagnostic" ECG changes, 35% had nonspecific changes, and 8% had normal ECGs. Diagnostic changes were defined as ST-segment elevation, ST-segment depression, or left bundle branch block.[61] Other studies document normal or near-normal ECGs in 5% to 10% of patients with AMI.[62-65] A normal ECG is also an independent risk factor for missed AMI and inappropriate ED discharge (odds ratio, 7.7; 95% confidence interval, 2.9 to 20.2).[2] However, among young patients (<40 years old) without known coronary artery disease, a normal ECG is associated with a cardiovascular event rate of <1% at 30 days.[66]

Misinterpretation of ECGs or failure to detect ischemic changes that are present occurs in up to 40% of missed AMI cases.[65] Furthermore, the initial ECG represents only a single time point in a dynamic pathophysiologic process. Thus, if there is a high concern for ACS, the ECG should be repeated at 15- to 30-minute intervals and compared to prior ECGs.[53]

CARDIAC BIOMARKERS

Cardiac Troponins **Cardiac troponins (cTn)** are proteins essential to cardiac muscle contraction that are complexed with actin and myosin

TABLE 48-5 Conditions Associated With Elevated Cardiac Troponin Levels in the Absence of Ischemic Heart Disease

- Cardiac contusion
- Cardiac procedures (surgery, ablation, pacing, stenting)
- Acute or chronic congestive heart failure
- Aortic dissection
- Aortic valve disease
- Hypertrophic cardiomyopathy
- Arrhythmias (tachy- or bradyarrhythmia)
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary hypertension
- Pulmonary embolism
- Acute neurologic disease (e.g., stroke, subarachnoid hemorrhage)
- Myocardial infiltrative diseases (amyloid, sarcoid, hemochromatosis, scleroderma)
- Inflammatory cardiac diseases (myocarditis, endocarditis, pericarditis)
- Drug toxicity
- Respiratory failure
- Sepsis
- Burns
- Extreme exertion (e.g., endurance athletes)

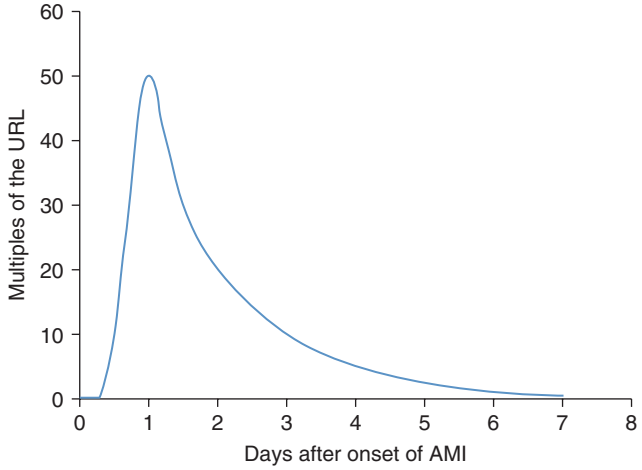

FIGURE 48-1. Typical pattern of cardiac troponin elevation after acute myocardial infarction (AMI). URL = upper reference limit.

filaments within cardiac myofibrils and are present within cardiac myocyte cytoplasm.[67] Myocardial injury resulting in the disruption of myocyte cell membrane integrity or myofibril destruction results in extracellular cTn leak, which can be detected in the patient's peripheral blood and used to identify and quantify myocardial damage.[68] Due to its high sensitivity and nearly complete cardiac specificity, cTn is the biomarker of choice for the detection of myocardial injury.[69]

Although cTn elevation is specific for myocardial injury, elevation does not indicate the mechanism of injury. There are numerous nonischemic causes of cTn elevations, which are summarized in **Table 48-5**. AMI can be differentiated from nonischemic cTn elevations based on the pattern of cTn elevation and the clinical context. The diagnostic criteria for AMI includes a gradual rise and fall of cTn with a maximum value above the 99th percentile of a reference population (the upper reference limit), combined with any of the following: symptoms consistent with ischemia, characteristic acute ECG changes (ST-segment and T-wave changes, new left bundle branch block, or new Q waves), or imaging evidence of a new regional wall motion abnormality or new loss of viable myocardium.[69] cTn testing has made older cardiac biomarkers, such as myoglobin and creatine kinase-MB, obsolete in ACS care.

Immunoassays have been developed for the isoforms of cTnI and cTnT. Isoforms I and T provide nearly identical information except in the setting of renal failure, where elevation in cTnT is more common than cTnI.[70,71] A single manufacturer produces the cTnT assay; however, multiple manufacturers produce cTnI assays, which differ in their upper reference limits (the cTn value above the 99th percentile of a reference population), coefficients of variability, and lower limits of detection.[72-74]

Recently developed fifth-generation assays, commonly referred to as **high-sensitivity troponin assays**, have a 10-fold higher analytical sensitivity compared to previous assays.[75] The first of these assays, which have upper reference limits ranging from 10 to 40 ng/L, were approved by the U.S. Food and Drug Administration in 2017.[76,77] In comparison with preceding assays, high-sensitivity cTn assays are more sensitive for the detection of AMI (94% to 96% vs. 85% to 90%) and increase the early detection of myocardial injury.[78,79] Among patients presenting within 3 hours of chest pain onset, high-sensitivity cTn assays are 92% to 94% sensitive for AMI compared to 76% for the previous assay.[78] However, the increased sensitivity of high-sensitivity cTn assays for AMI also creates the potential of oversensitivity and unneeded care by detecting more patients with non-AMI cTn elevations.[74,77,78]

The prognostic value for populations with elevated cTn levels is clear. A meta-analysis of 18,982 patients with ACS found that an elevated cTn was associated with an increased risk of cardiac death or AMI at 30 days (odds ratio, 3.4; 95% confidence interval, 2.9 to 4.0).[80] Even in the absence of chest pain, elevations in cTn portend a worse prognosis at 30 days and 1 year that is independent of ECG findings.[81] Higher cTn elevations impart a stronger risk for adverse events, and even patients with minimally detectible cTn (below the upper reference limits) are at greater risk for adverse events than those with undetectable cTn.[82]

Patients with **renal disease** often have an elevated cTnT (15% to 50%), whereas cTnI elevations are less common (<10%). After dialysis, serum levels of cTnT generally increase, whereas cTnI levels decrease.[83] Despite these features, cTnT and cTnI assays remain highly sensitive for AMI in patients with renal failure, particularly when new measures can be compared to baseline measures. Furthermore, renal failure patients with elevated cTn levels are at higher risk for death and adverse events than patients with normal cTn levels.[84]

Obtain cardiac cTn levels in all patients with suspected ACS.[53] A single fourth-generation cTn assay will identify most patients (approximately 80%) with AMI within 2 to 3 hours of ED arrival, and the sensitivity of two high-sensitivity cTn samples drawn within 3 hours of presentation approaches 100% for AMI.[78,79,85] Thus, serial measurements of cTn are generally needed to safely exclude AMI in most patients presenting with chest pain.[53] AMI may safely be excluded with a single cTn in select, low-risk patients with constant symptoms for >6 to 12 hours. Rapid diagnostic pathways using short interval testing (1 to 3 hours) or a single high-sensitivity cTn evaluation to exclude AMI are being used in Europe, but U.S. data are limited.[86-89]

B-Type Natriuretic Peptide Natriuretic peptide elevations are not specific to myocardial ischemia or infarction, and rise with any ventricular dysfunction. Patients with ACS and an elevated natriuretic peptide level have higher short-term mortality, although the lab test does not aid in specific patient management actions.

Other Biomarkers Troponin testing has made older cardiac biomarkers, such as myoglobin and creatine kinase-MB, obsolete in ACS care. High-sensitivity C-reactive protein aids in long-term cardiac event prediction, but this test is not recommended for ED care (**Figure 48-1**).[53] A variety of other assays have been studied as cardiac biomarkers, such as ischemia-modified albumin, interleukin-6, vascular cell adhesion molecule, intercellular adhesion molecule, E-selectin, P-selectin, pregnancy-associated plasma protein A, myeloperoxidase, copeptin, and heart-type fatty acid binding protein. Current evidence does not support the use of these novel biomarkers for ED chest pain evaluations.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 49

Acute Coronary Syndromes

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EPIDEMIOLOGY

Ischemic heart disease is the leading cause of death among adults in the United States, with more than 400,000 people dying annually. Atherosclerotic disease of the epicardial coronary arteries—termed *coronary artery disease*—accounts for the vast majority of patients with ischemic heart disease. The predominant symptom of coronary artery disease is chest pain, and patient concern over potential acute heart disease contributes to the >8 million visits each year to U.S. EDs. In a typical adult ED population with acute chest pain, about 15% of patients will have an acute coronary syndrome (ACS). ACS encompasses unstable angina through acute myocardial infarction (AMI). Of patients with an ACS, approximately one third have an AMI, and the remainder have unstable angina.

The three principal presentations of unstable angina are listed in **Table 49-1**.[1] These definitions assume that the anginal chest pain is due to ischemia, and this categorization does not apply to patients presenting to the ED with chest pain from other causes. During the initial ED assessment, it may not be possible to determine whether the patient has or will sustain permanent damage to the myocardium, has reversible ischemia (injury or unstable angina), or has a noncardiac cause of symptoms.

The American College of Cardiology and American Heart Association have a tool for estimating the short-term risk for death or AMI in patients with unstable angina (**Table 49-2**).[1]

TABLE 49-1 Three Principal Presentations of Unstable Angina

Class	Presentation
Rest angina*	Angina occurring at rest and that is prolonged, usually >20 min
New-onset angina	New-onset angina that markedly limits ordinary physical activity, such as walking 1–2 blocks or climbing 1 flight of stairs or performing lighter activity
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, has a longer duration, or is lower in threshold, limiting ability to walk 1–2 blocks or climb 1 flight of stairs or perform lighter activity

*Patients with non–ST-segment elevated myocardial infarction usually present with angina at rest.

ANATOMY

The left coronary artery divides into the left circumflex and the left anterior descending branches (**Figure 49-1**). The left anterior descending branch courses down the anterior aspect of the heart providing the main blood supply to the anterior and septal regions of the heart. The circumflex branch supplies blood to some of the anterior wall and a large portion of the lateral wall of the heart. The right coronary artery supplies the right ventricle and provides some perfusion to the inferior aspect of the left ventricle through its continuation as the right posterior descending artery.

The atrioventricular conduction system receives blood supply from the atrioventricular branch of the right coronary artery and the septal perforating branch of the left anterior descending coronary artery. Similarly, the right bundle branch and the posterior division of the left bundle branch each obtain blood flow from both the left anterior descending and right coronary arteries. The posteromedial papillary muscle receives blood supply from one coronary artery, usually the right coronary artery.

PATHOPHYSIOLOGY

Ischemia occurs when there is an imbalance between oxygen (O_2) demand and O_2 supply. O_2 supply is influenced by the O_2-carrying capacity of the

TABLE 49-2 Short-Term Risk of Death or Nonfatal Myocardial Infarction by Risk Stratification in Patients With Unstable Angina

Feature	High Likelihood (at least 1 of the following features must be present)	Intermediate Likelihood (no high-risk feature, but must have 1 of the following)	Low Likelihood (no high- or intermediate-risk feature, but may have any of the following)
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior myocardial infarction, peripheral or cerebrovascular disease, or coronary artery bypass grafting; prior aspirin use	
Character of the pain	Prolonged, ongoing (>20 min) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (>20 min) or relieved with rest or sublingual nitroglycerin Nocturnal angina New-onset or progressive angina in the past 2 wk without prolonged (>20 min) rest pain but with intermediate or high likelihood of CAD (**Table 49-3**)	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New-onset angina with onset 2 wk to 2 mo before presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening mitral regurgitation murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age >75 y old	Age >70 y old	Chest discomfort reproduced by palpation
ECG	Angina at rest with transient ST-segment changes >0.5 mm Bundle branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes, pathologic Q waves, or resting ST depression <1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG
Cardiac markers	Elevated cardiac troponins above threshold for myocardial infarction	Slightly elevated cardiac troponins	Normal

Abbreviation: CAD = coronary artery disease.

TABLE 49-3 Likelihood That Signs and Symptoms Represent Acute Coronary Syndrome Secondary to Coronary Artery Disease

Feature	High Likelihood (any of the following)	Intermediate Likelihood (absence of high-likelihood features and presence of any of the following)	Low Likelihood (absence of high- or intermediate-likelihood features but may have the following)
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of coronary artery disease, including myocardial infarction	Chest or left arm pain or discomfort as chief symptom Age >70 y old Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate-likelihood characteristics Recent cocaine use
Examination	Transient mitral regurgitation murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (≥1 mm) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5–1.0 mm or T-wave inversion >1 mm	T-wave flattening or inversion <1 mm in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac troponin I, troponin T, or MB fraction of creatine kinase	Normal	Normal

Note: Estimation of the likelihood of significant coronary artery disease is a complex, multivariable problem that cannot be fully specified in a table such as this. Therefore, the table is meant to illustrate major relationships rather than offer rigid algorithms.

blood and the coronary artery blood flow. The O_2-carrying capacity of the blood is determined by the amount of hemoglobin present and O_2 saturation. Coronary artery blood flow is determined by the duration of diastolic relaxation of the heart and peripheral vascular resistance. Humoral, neural, metabolic, and extravascular compressive forces and local autoregulation mechanisms determine the coronary vascular resistance.

Exercise-induced myocardial ischemia and its sequelae usually occur as a result of fixed atherosclerotic lesions. ACS may be caused by secondary reduction in myocardial blood flow due to coronary arterial spasm, microvascular dysfunction, disruption or erosion of atherosclerotic plaques, and platelet aggregation or thrombus formation at the site of an atherosclerotic lesion. Secondary causes of myocardial ischemia are less common and prompted by factors extrinsic to the coronary arteries such as increased myocardial O_2 demand (i.e., fever, tachycardia, thyrotoxicosis), reduced blood flow (i.e., hypotension), or reduced O_2 delivery (i.e., anemia, hypoxemia). In the event of a secondary cause, global ischemia may occur widely or focally.

Atherosclerotic plaque forms through repetitive injury to the vessel wall. Macrophages and smooth muscle cells are the main cellular elements in plaque development, whereas lipids are predominant in the extracellular milieu. Plaque fissuring and rupture are affected by features inherent to the plaque, such as its composition and shape; local factors,

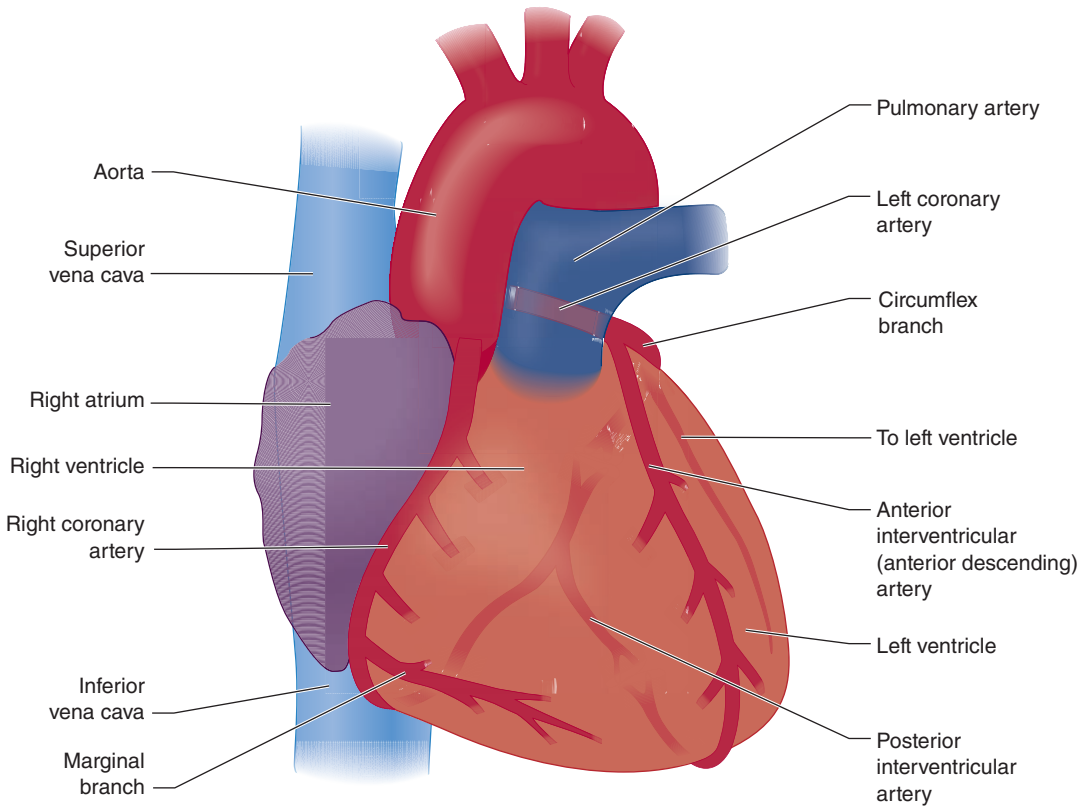


FIGURE 49-1. Schematic diagram of the coronary arteries.

such as shear forces, coronary arterial tone, and coronary arterial perfusion pressure; and movements of the artery in response to myocardial contractions. When plaque rupture occurs, potent thrombogenic substances activate circulating platelets.

The platelet response involves adhesion, activation, and aggregation. Platelet adhesion occurs through the weak platelet interactions with subendothelial adhesion molecules, such as collagen, fibronectin, and laminin, and the binding of the glycoprotein IIb receptor to the subendothelial form of von Willebrand factor. Adherent platelets are strongly thrombogenic. Lipid-laden macrophages in the plaque core and adventitia of the vessel wall release tissue factor, which stimulates the conversion of prothrombin to thrombin. Thrombin and the local shear forces are also potent platelet activators. Platelet secretion of adenosine diphosphate, thromboxane A_2, and serotonin trigger platelet activation. Activated platelet glycoprotein IIb/IIIa receptors become cross-linked by fibrinogen or von Willebrand factor in the final common pathway of platelet aggregation.

The extent of O_2 deprivation and the clinical presentation of any coronary disease depends on the limitation of O_2 delivery imposed by any thrombus and the plaque. In stable angina, ischemia occurs only when activity induces O_2 demands beyond the supply restrictions imposed by a partially occluded coronary vessel. Ischemia occurs at a relatively fixed point and changes slowly over time. In this scenario, the atherosclerotic plaque has not ruptured, and there is little or no superimposed thrombus. In ACS, atherosclerotic plaque rupture and platelet-rich thrombus develop. Coronary blood flow is reduced suddenly, and myocardial ischemia occurs. The degree and duration of the O_2 supply–demand mismatch determine whether the patient develops reversible myocardial ischemia without necrosis (unstable angina) or acute myocardial ischemia with necrosis. More severe and prolonged obstruction increases the likelihood of infarction.

AMI may inhibit myocardial contractility and impair both central and peripheral perfusion. When an area of the myocardium does not receive adequate O_2, the functional deterioration progresses; as the size of the infarcted myocardium increases, left ventricular pump function decreases. This creates increased left ventricular end-diastolic pressure and end-systolic volume. Cardiac output, stroke volume, and blood pressure may decrease. When left atrial and pulmonary capillary pressures increase, heart failure or pulmonary edema may develop. Poor perfusion to the brain and kidneys can result in altered mental status and impaired renal function, respectively.

CLINICAL FEATURES

HISTORY AND ASSOCIATED SYMPTOMS

The main symptom of ischemic heart disease is chest discomfort or pain; the characterization of the severity, location, radiation, duration, and quality might be helpful. In addition, the presence of associated symptoms such as nausea, vomiting, diaphoresis, dyspnea, lightheadedness, syncope, and palpitations may help detect myocardial ischemia (see Tables 48-1 and 48-2 in Chapter 48, "Chest Pain"). Obtain information regarding the onset and duration of symptoms, activities that precipitate symptoms, and prior evaluations for similar symptoms to assess the possibility of acute myocardial ischemia.

Symptoms of acute myocardial ischemia may use descriptions other than pain, such as *discomfort*; look for descriptions of chest pressure, heaviness, tightness, fullness, or squeezing. Less commonly, patients describe their symptoms as knife-like, sharp, or stabbing. The classic pain or discomfort location is substernal or in the left chest, with radiation to the arm (either), neck, or jaw. Reproducible chest wall tenderness occurs in some patients.

Exercise, stress, and a cold environment classically precipitate angina. Angina typically has a duration of symptoms of <10 minutes, occasionally lasting up to 10 to 20 minutes, and usually improves within 2 to 5 minutes after rest or nitroglycerin. In contrast, acute myocardial ischemia is usually accompanied by more prolonged and severe chest discomfort, more prominent associated symptoms (e.g., nausea, diaphoresis, shortness of breath), and little response to initial sublingual nitroglycerin. Easy fatigability may be a prominent symptom of ACS, especially in women.[2]

Ask about the frequency of anginal episodes and any change in frequency of episodes over the past few months. Determine if there is any increase in severity or duration of symptoms, or whether less effort is required to precipitate symptoms.

Advanced age, female gender, and a history of diabetes mellitus are associated with less typical ACS presentations. *Presentations with nonclassic features or silent myocardial ischemia are common*; for example, as many as 37.5% of women and 27.4% of men present without chest pain.[3] Up to 30% of patients with acute myocardial ischemia identified in large longitudinal studies do not seek medical care or recall any symptoms. The prognosis for patients with nonclassic symptoms (e.g., fatigue, weakness, not feeling well, vague discomfort) at the time of infarction is worse than that of patients with more classic symptoms. Women and the elderly are more likely to have presentations that differ from classic ones in the younger, male patients; across all age groups, those with unstable angina have nonclassic features nearly half the time. Even in patients <55 years old, women were more likely than men to present with associated symptoms such as epigastric pain, palpitations, and jaw pain. This is why the term *atypical chest pain* is misleading, because nonclassic presentations are common despite being often called atypical.[4]

Cardiac risk factors are poor predictors of risk for AMI or other ACSs.[5] Traditional cardiac risk factors for coronary artery disease, such as hypertension, diabetes mellitus, tobacco use, family history at an early age, and hypercholesterolemia, are not helpful to predict ACS in ED patients >40 years old.[5] The cardiac risk factors predict risk of coronary artery disease over time, not likelihood of presence at one moment.

PHYSICAL EXAMINATION

Patients with ACS may appear well or may be uncomfortable, pale, cyanotic, or in respiratory distress. The pulse rate may be normal or fast, slow or irregular. Bradycardic rhythms are more common with inferior wall myocardial ischemia; in the setting of an acute anterior wall infarction, bradycardia or new heart block is a poor prognostic sign. Blood pressure can be normal, elevated (due to baseline hypertension, sympathetic stimulation, and anxiety), or decreased (due to pump failure or inadequate preload), although extremes of blood pressure are associated with a worse prognosis.

An S_3 is present in 15% to 20% of patients with AMI; if detected, an S_3 may indicate a failing myocardium. **The presence of a new systolic murmur is an ominous sign because it may signify papillary muscle dysfunction, a flail leaflet of the mitral valve with resultant mitral regurgitation, or a ventricular septal defect**.

The presence of rales, with or without an S_3 gallop, indicates left ventricular dysfunction and left-sided heart failure. Jugular venous distention, hepatojugular reflex, and peripheral edema suggest right-sided heart failure.

DIAGNOSIS

The diagnosis of ST-segment elevation myocardial infarction (**STEMI**) depends on the ECG in the setting of symptoms suggestive of myocardial infarction. The diagnosis of non–ST-segment elevation myocardial infarction (**NSTEMI**) depends on abnormal elevation of cardiac biomarkers but may include ECG changes not meeting criteria for STEMI. The diagnosis of **unstable angina** is based on history (Table 49-1) because the ECG and cardiac injury biomarkers are nondiagnostic. Early risk assessment for the likelihood of myocardial infarction uses all of these data to aid decision making (Table 49-3).

ELECTROCARDIOGRAPHY

The standard 12-lead ECG is the single best test—although it can be fallible—to identify patients with AMI upon ED presentation.[1] **Obtain the initial 12-lead ECG and interpret the tracing quickly, ideally within 10 minutes of presentation in those patients with symptoms suggestive of myocardial ischemia**. Prehospital ECGs reduce the time

TABLE 49-4 ECG ST-Segment–Based Criteria for Acute Myocardial Infarction

Location	ECG Findings
Anteroseptal	ST-segment elevations in V_1, V_2, and possibly V_3
Anterior	ST-segment elevations in V_1, V_2, V_3, and V_4
Anterolateral	ST-segment elevations in V_1–V_6, I, and aVL
Lateral	ST-segment elevations in I and aVL
Inferior	ST-segment elevations in II, III, and aVF
Inferolateral	ST-segment elevations in II, III, aVF, and V_5 and V_6
True posterior*	Initial R waves in V_1 and V_2 >0.04 s and R/S ratio ≥1; right-sided ECG shows 0.5-mm ST elevation in V_7–V_9
Right ventricular (RV)	ST-segment elevations in II, III, and aVF and ST-segment depression in lateral leads; ST-segment elevation in RV leads V_3R–V_6R

*Posterior wall infarction does not produce Q-wave abnormalities in conventional leads and is diagnosed in the presence of tall R waves in V_1 and V_2.

from symptom onset to reperfusion therapy in STEMI patients.[6,7] (See Videos: ECG: Ischemia, ECG: MI Mimics, ECG: Myocardial Ischemia/Infarction, ECG: Old MI; ECG: Posterior MI; ECG: ST Depression; ECG: STEMI; Right Ventricular MI.)

ST-segment–based diagnostic ECG criteria for AMI are shown in **Table 49-4**. STEMI in the listed distributions suggests acute transmural injury. ST-segment depressions in these distributions suggest ischemia. **Inferior wall AMIs should have a right-sided lead V_4 (V_4R) obtained**, because ST-segment elevation in V_4R is highly suggestive of right ventricular infarction. For patients with a nondiagnostic tracing and persistent symptoms who have a high risk of ACS, repeat the ECG to detect developing changes.[1,6,8] Early studies of fibrinolytic therapy identified an increased risk of mortality in patients with new bundle branch block; this led to interpreting a new left bundle branch block as being a "STEMI equivalent." However, <10% of patients with new or possibly new left bundle branch block have AMI.[9]

Reciprocal ST-segment changes—those in leads away from or opposite the elevation area—are from subendocardial ischemia and denote a larger area of injury risk, an increased severity of underlying coronary artery disease, more severe pump failure, a higher likelihood of cardiovascular complications, and increased mortality. In general, **the more elevated the ST segments and the more ST segments that are elevated, the more extensive is the injury**.

The ECG changes correlate often, but not always, with the infarct-related vessel (**Table 49-5**). A right sided ECG (**Figure 49-2A**) and posterior ECG (**Figure 49-2B**) are sometimes needed to determine extent of infarction. Inferior wall AMIs can result from occlusion of the left circumflex artery or the right coronary artery. In the setting of an inferior wall AMI, ST-segment elevation in at least one lateral lead (V_5, V_6, or aV_L) with an isoelectric or elevated ST segment in lead I is strongly suggestive of a left circumflex lesion (**Figure 49-3**). Elevation of avR > V_1 suggests left anterior descending artery occlusion (**Figure 49-4**). The presence of ST-segment elevation in lead III greater than that in lead II predicts a right coronary artery occlusion (**Figure 49-5**). When accompanied by ST-segment elevation in V_1 or a V_4R, it predicts a proximal right coronary artery lesion with accompanying right ventricular infarction (**Figure 49-6**), demonstrated by right-sided ECG leads. RV infarction associated with inferior infarction has higher morbidity than isolated inferior infarction. Reciprocal anterior ST-segment depressions in V_1 through V_4 are equally prevalent in right coronary and left circumflex inferior wall AMIs. **Figure 49-7** shows anterior myocardial infarction from distal left anterior descending artery occlusion, whereas **Figure 49-8** shows anterior myocardial infarction from proximal left anterior descending artery occlusion. Posterior wall MI can be associated with inferior or lateral MI, or can be isolated. As leads V_1-V_3 indirectly reflect the posterior wall, a posterior wall MI can be identified with posterior lead placement (Figures 49-2B and 49-9). **Figure 49-9** shows posterior wall myocardial infarction.

TABLE 49-5 ECG Findings and Culprit Coronary Artery[10-14]

ECG Findings	Culprit Artery	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
ECG findings for inferior ST-segment elevation myocardial infarction					
ST-segment elevation in lead III greater than in lead II plus ST-segment depression of >1 mV in lead I, lead aVL, or both	Right coronary artery	90	71	94	70
In addition to the findings immediately above, ST-segment elevation on V_1, V_4R, or both	Proximal right coronary artery	79	100	100	88
Absence of the above findings plus ST-segment elevation in leads I, aVL, V_5, and V_6 and ST-segment depression in leads V_1, V_2, and V_3	Left circumflex coronary artery	83	96	91	93
ECG findings for anterior ST-segment elevation myocardial infarction					
ST-segment elevation in leads V_1, V_2, and V_3 plus any of the features below:					
ST-segment elevation of >2.5 mm in lead V_1, or right bundle branch block with Q wave, or both	Proximal left anterior descending coronary artery	12	100	100	61
ST-segment depression of >1 mm in leads II, III, and aVF	Proximal left anterior descending coronary artery	34	98	93	68
ST-segment depression of ≤1 mm, or ST-segment elevation in leads II, III, and aVF	Distal left anterior descending coronary artery	66	73	78	62
ECG findings for left coronary artery lesions*					
>0.5-mm elevation in aVR; possibly also ≥1-mm ST elevation in lead V_1	Left coronary artery or severe multivessel disease				
Wellen's sign: deeply inverted or deep biphasic T waves in V_1 and V_2; T-wave findings may persist or be present even when patient is chest pain free	Left anterior descending artery				

Note: 10 mm = 1 mV with standard ECG calibration.

*Nabati M, Emadi M, Mollaalipour M, et al: ST segment elevation in lead aVR in the setting of acute coronary syndrome. *Acta Cardiol* 71: 47, 2016. [PMID: 26853253]

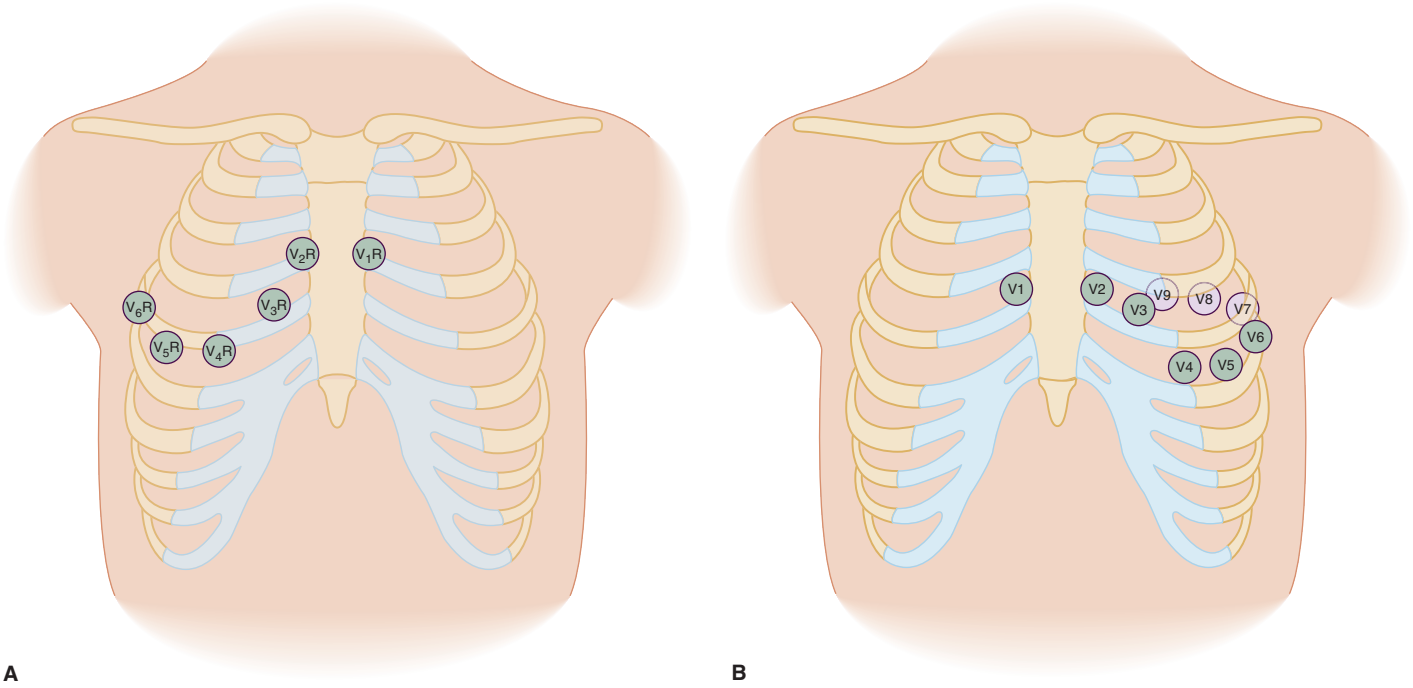


FIGURE 49-2. **A.** Right-sided lead placement. **B.** Posterior lead placement. Leads V_4 to V_6 are removed from the anterior chest wall and replaced as V_7 to V_9 on the back. Lead V9 is placed paraspinal.

ECGs are frequently misinterpreted.[15] False-positive interpretations of the ECG, indicating STEMI when no injury exists, occur between 11% and 14% of the time.[14] Balancing this is the observation that **even patients with normal or nonspecific ECGs have a 1% to 5% incidence of AMI and a 4% to 23% incidence of unstable angina**. Patients with nondiagnostic ECGs or evidence of ischemia that is age indeterminate have a 4% to 7% incidence of AMI and a 21% to 48% incidence of unstable angina. Demonstration of new ischemia in ECG increases the risk of AMI from 25% to 73% and the unstable angina risk from 14% to 43%. Thus, the standard 12-lead ECG is useful for cardiovascular risk stratification of patients with ACS. Guideline-recommended additions to the standard 12-lead ECG are the use of right-sided precordial leads such as V_4R in the setting of acute inferior myocardial infarction to detect right ventricular involvement and V_7 to V_9 in patients with suspected posterior myocardial infarction from a circumflex lesion.[1,6,16]

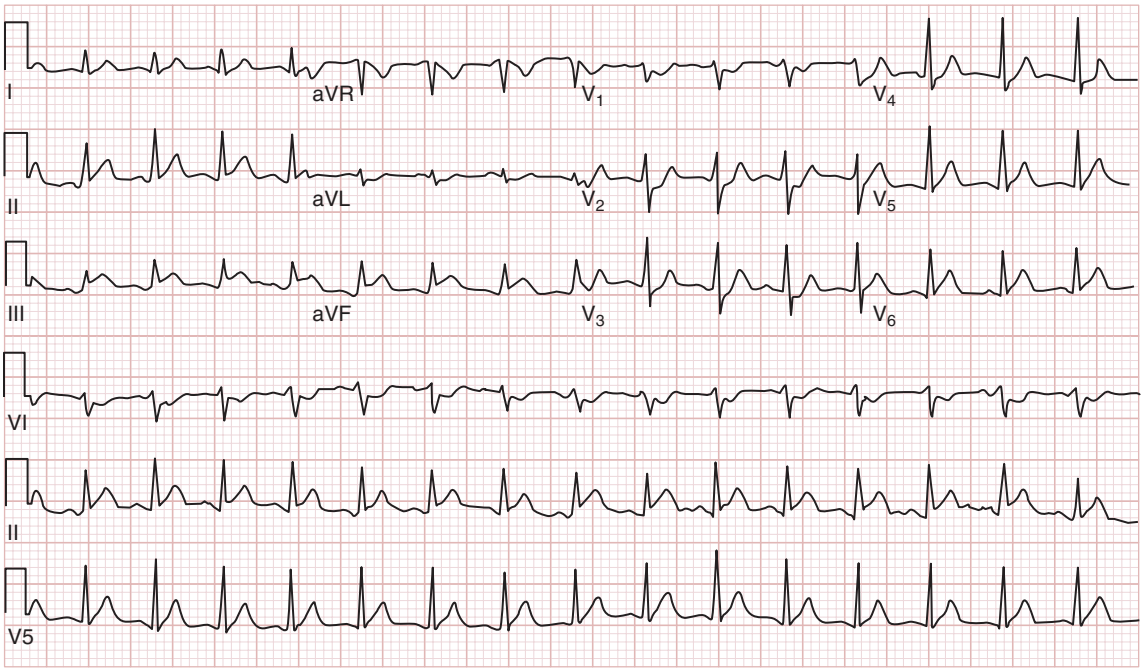


FIGURE 49-3. ECG showing **inferior-lateral myocardial infarction** from left circumflex coronary artery occlusion. ECG from a 42-year-old man presenting with chest pain. ECG shows ST-segment elevation in limb leads II, III (inferior), and aVF, as well as lead V_6 (lateral). ST-segment depression is evident in leads V_1, V_2, and V_3, reflecting reciprocal changes in the anterior leads. The patient was found to have 100% occlusion of the left circumflex coronary artery at cardiac catheterization. [Used with permission of David M. Cline, MD, Wake Forest University.]

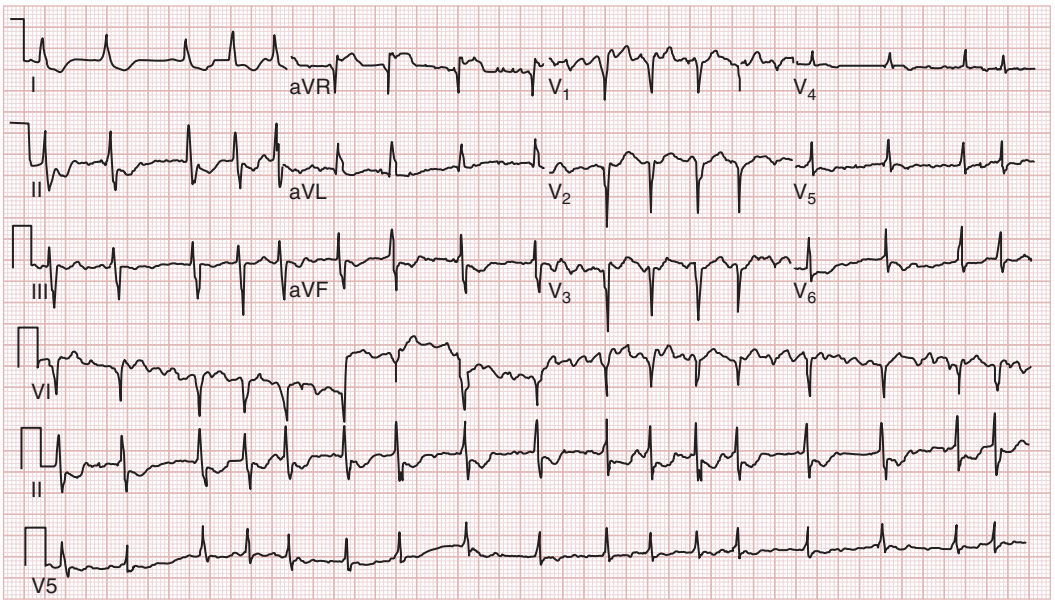


FIGURE 49-4. ST-segment elevation in lead aVR. First ED ECG taken in a patient with acute chest pain. Note elevation in aVR greater than that of V_1, suggesting left anterior descending artery occlusion. Initial troponin was normal; second troponin was abnormal. Emergency cardiac catheterization demonstrated 90% occlusion of left main coronary artery. [ECG used with permission of Department of Emergency Medicine, University of North Carolina Hospitals.]

There are several clinical conditions in which ECG interpretation is difficult (**Table 49-6**). In the setting of paced rhythms or left bundle branch block, acute myocardial ischemia can be identified (**Figure 49-10**) with select findings. **In those with a preexisting left bundle branch block, the following patterns are indicative of AMI:** (1) ST-segment elevation of 1 mm or greater and concordant (in the same direction as the main deflection) with the QRS complex (odds ratio, 25.2; 95% confidence interval [CI], 11.6% to 54.7%) seen in Figure 49-10C; (2) ST-segment depression of 1 mm or more in leads V_1, V_2, or V_3 (odds ratio, 6.0; 95% CI, 1.9% to 19.3%) seen in Figure 49-10D; and (3) ST-segment elevation of 5 mm or greater and discordant (in the opposite direction) with the QRS complex (odds ratio, 4.3; 95% CI, 1.8% to 10.6%) seen in Figure 49-10E.[15]

Right ventricular pacing, the common pacemaker lead location, causes secondary repolarization changes of opposing polarity to that of the predominant QRS complex. Most leads have predominant negative QRS complexes followed by ST-segment elevation and positive T waves. ST-segment elevation of at least 5 mm is most indicative of AMI in leads with predominantly negative QRS complexes.[17] Any ST-segment elevation concordant to the QRS complex in a predominantly positive QRS complex is highly specific for AMI. The QRS complex is predominantly negative in leads V_1 to V_3 with right ventricular pacing. ST-segment depression in these leads has 80% specificity for AMI.[17]

Wellens' sign or syndrome describes a pattern of abnormal T waves in the precordial leads V_2 and V_3 associated with **critical stenosis of**

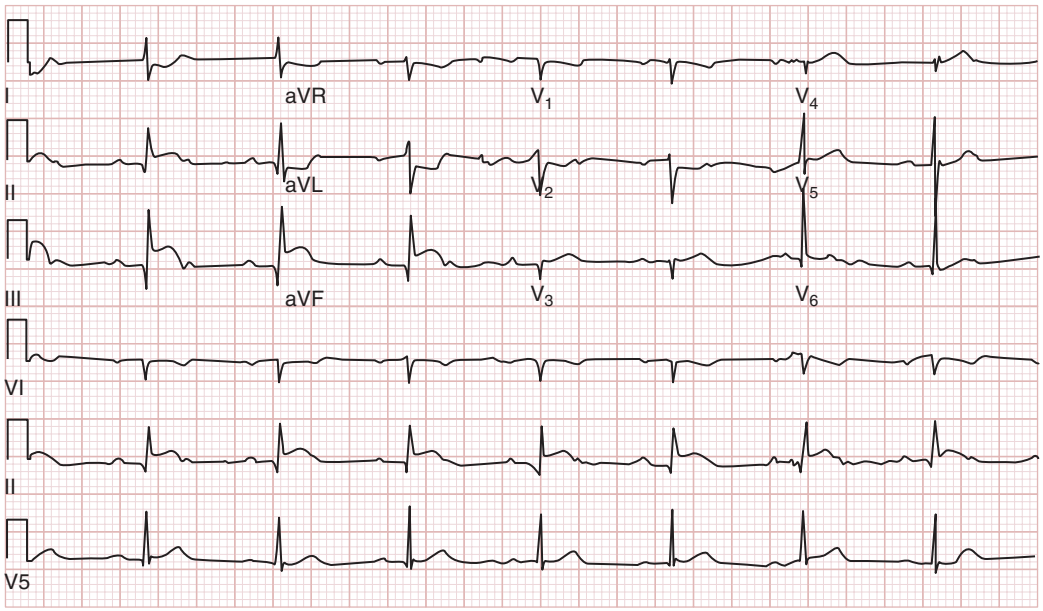
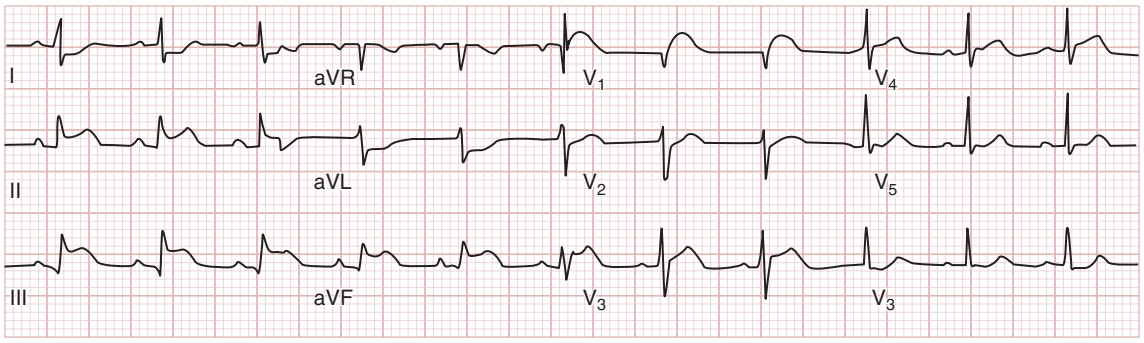
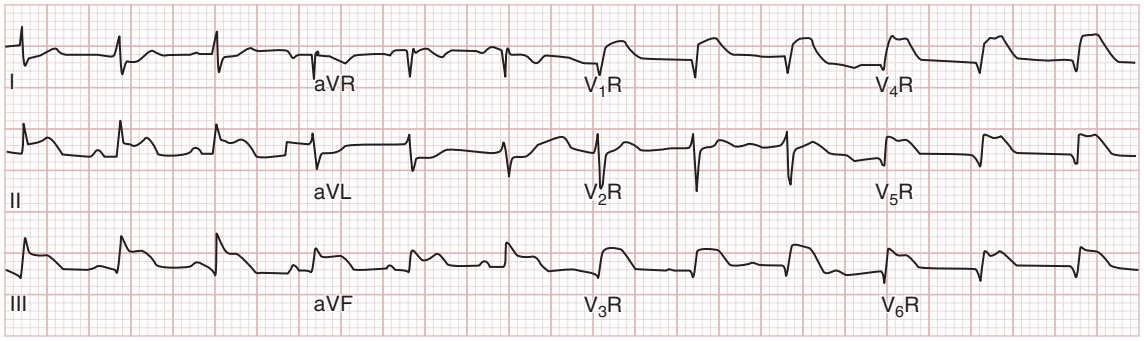


FIGURE 49-5. ECG showing inferior myocardial infarction from **right coronary artery occlusion**. ECG from an 80-year-old man presenting with acute chest pain. The ECG shows ST-segment elevation in lead III greater than in lead II plus ST-segment depression of >1 mm in lead I and lead aVL. The patient was found to have 100% occlusion of the right coronary artery at cardiac catheterization. [Used with permission of David M. Cline, MD, Wake Forest University.]



A



B

FIGURE 49-6. Right ventricular infarction. A. ECG showing inferior ST-segment elevation myocardial infarction and ST-segment elevation in lead V_1 suggestive of **right ventricular infarction**. **B.** Same patient with placement of **right ventricular leads**, see Fig. 49-2A, showing ST-segment elevation in V_3R, V_4R, V_5R, and V_6R compatible with right ventricular infarction. [Used with permission of J. Stephan Stapczynski, Maricopa Medical Center.]

the left anterior descending artery[18] (**Figure 49-11** and **Table 49-7**). Approximately 75% of patients with this finding have deeply inverted T waves, and about a quarter of patients will display a variant pattern of biphasic T waves in the same leads.[19,20] T-wave abnormalities are often also seen in leads V_1 and V_4 or occasionally in leads V_5 and V_6. The abnormal T waves of Wellens' syndrome are usually visible when the patient is pain free and may normalize when pain recurs; repeating the ECG when pain resolves or recurs can aid in detection of these dynamic changes.[20] Up to

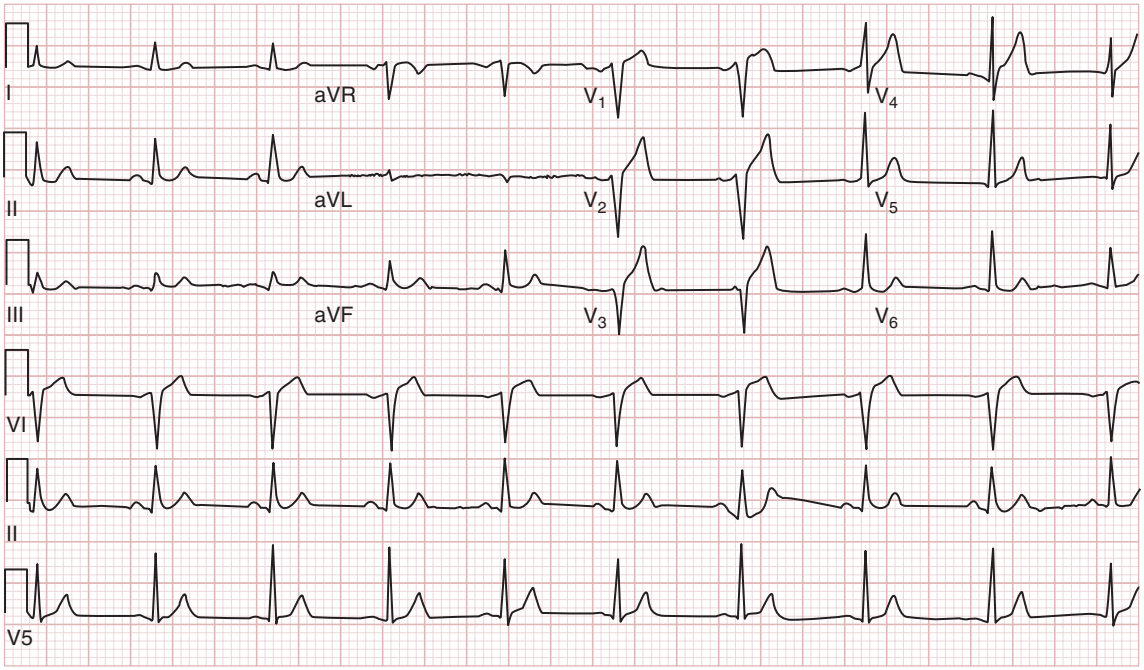


FIGURE 49-7. ECG showing **anterior myocardial infarction** from distal left anterior descending coronary artery occlusion. ECG from a 52-year-old man presenting with chest pain. ECG shows ST-segment elevation in V_1, V_2, and V_3, with the absence of ST-segment depression in leads II, III, and aVF. The patient was found to have 100% occlusion of the distal left anterior descending coronary artery at cardiac catheterization. [Used with permission of David M. Cline, MD, Wake Forest University.]

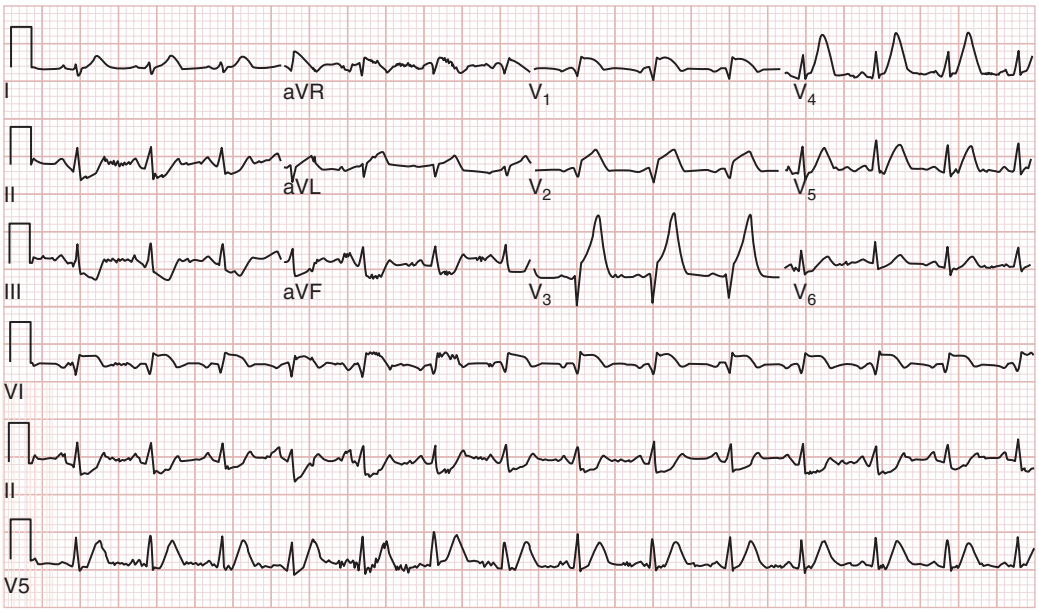
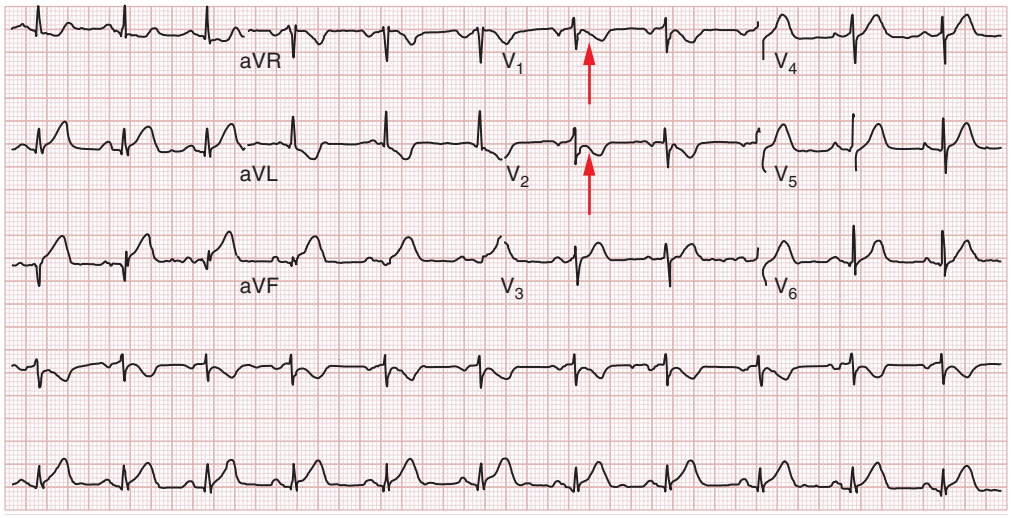


FIGURE 49-8. ECG showing **anterior myocardial infarction** from proximal left anterior descending coronary artery occlusion. ECG from a 65-year-old man presenting with chest pain. ECG shows ST-segment elevation in V_1, V_2, and V_3, and >1 mm of ST-segment depression in leads II, III, and aVF. The patient was found to have 100% occlusion of the proximal left anterior descending coronary artery at cardiac catheterization. [Used with permission of David M. Cline, MD, Wake Forest University.]



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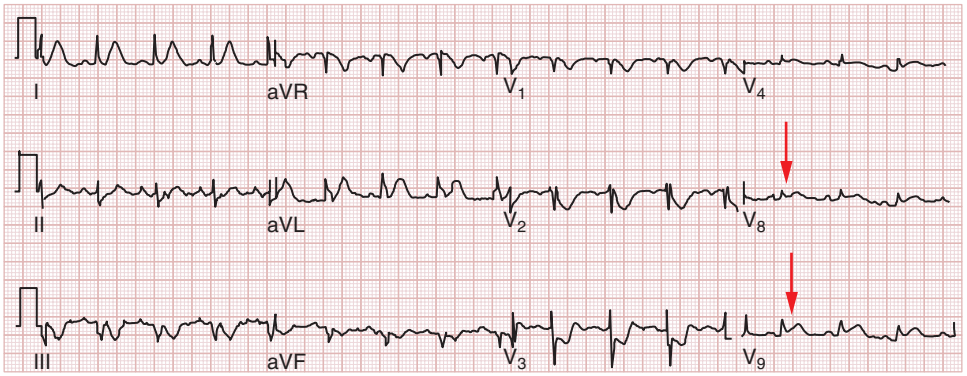

B

FIGURE 49-9. **A.** ECG with acute inferior wall myocardial infarction (MI) but ST-segment depression in V_1 and V_2 suggesting accompanying posterior wall MI. **B.** Posterior lead placement with ST-segment elevation in V_8 and V_9 confirming posterior wall MI.

TABLE 49-6 Conditions in Which ECG Interpretation Can Be Difficult

- May have ST-segment elevation in the absence of acute myocardial infarction
- Early repolarization
- Left ventricular hypertrophy
- Pericarditis
- Myocarditis
- Left ventricular aneurysm
- Hypertrophic cardiomyopathy
- Hypothermia
- Ventricular paced rhythms
- Left bundle branch block
- Takotsubo cardiomyopathy
- May have ST-segment depressions in the absence of ischemia
- Hypokalemia
- Digoxin effect
- Cor pulmonale and right heart strain
- Early repolarization
- May have T-wave inversions in the absence of ischemia
- Persistent juvenile pattern
- Stokes-Adams syncope or seizures
- Posttachycardia T-wave inversion
- Postpacemaker T-wave inversion
- Intracranial pathology (CNS hemorrhage)
- Mitral valve prolapse
- Primary or secondary myocardial diseases
- Pulmonary embolism or cor pulmonale from other causes
- Spontaneous pneumothorax
- Myocardial contusion
- Right bundle branch block

15% of patients presenting with unstable angina will display the Wellens' sign.[18,21] Because of the high incidence of critical coronary stenosis and the potential for acute infarction, patients with Wellens' syndrome should receive early interventional management. Similarly, those with hyperacute

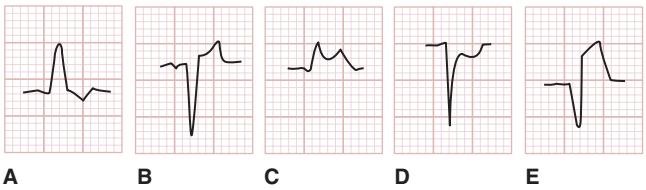

FIGURE 49-10. Discordant and concordant ST elevation and depression in the setting of left bundle branch block. ST-segment abnormalities in left bundle branch block. **A.** Discordant ST-segment depression ("normal"). **B.** Discordant ST-segment elevation ("normal"). **C.** Concordant ST-segment elevation (strongly suggestive of acute myocardial infarction [AMI]). **D.** Concordant ST-segment depression (suggestive of AMI). **E.** Excessive (>5 mm) discordant ST-segment elevation (weakly suggestive of AMI). [Used with permission of William Brady, MD, University of Virginia.]

T waves, de Winter ST-T–wave complex (upsloping of ST segment with overall ST depression), and posterior STEMI patterns should receive early attempts at reperfusion. (See Video: Wellens' Sign.)

SERUM MARKERS OF MYOCARDIAL INJURY

Patients with diagnostic ST-segment elevation on their initial ECG do not require serum marker measurement to make treatment and disposition decisions. Conversely, serum markers are useful in patients with nondiagnostic ECGs for diagnosis of NSTEMI and risk stratification of patients with STEMI, NSTEMI, and unstable angina. Even low-level cardiac marker elevations are independent risk factors for acute (<30 days) cardiac complications and short-term (<1 year) prognosis in unstable angina.[22] Low-level elevations in either troponin correlate with risk for cardiovascular complications in unstable angina, coronary artery disease, and renal failure.[22] Troponin is sensitive and specific for cardiac myocardial necrosis, but there are many causes of myocardial necrosis unrelated to ACS (see Table 48-5).

New high-sensitivity cardiac troponins have improved ability to detect ischemia. The high-sensitivity troponins identify 90% to 100% of patients with AMI at the time of arrival using the lowest cut point, albeit with limited specificity (between 34% and 80% depending on the cutoff used).[23-25] Troponin values above the 99th percentile reflect myocardial injury, but not all myocardial injury is acute. Delta or changing values

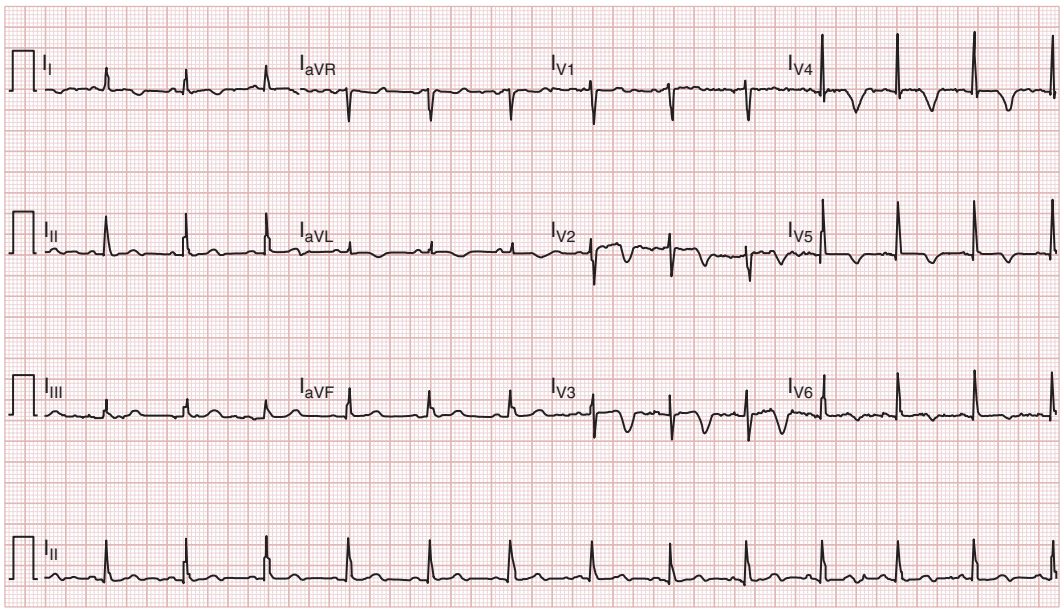

FIGURE 49-11. Wellens' sign with ECG showing deep symmetric T-wave inversions in leads V_2 to V_5. [Reproduced with permission from Lefebvre C, O'Neill J, Cline D (eds): *Atlas of Cardiovascular Emergencies*. New York, NY: McGraw-Hill Education, Inc. © 2015. Fig 2.32.]

TABLE 49-7 General Criteria for Wellens' Syndrome

- History of episodic chest pain consistent with unstable angina
- During pain, the ECG may not display abnormal T waves
- When pain free, abnormal T waves seen, most prominent in leads V_2 and V_3, often in leads V_1 and V_4, and occasionally in leads V_5 and V_6
- Deep symmetric T-wave inversion seen in about 75% of Wellens' syndrome patients
- Biphasic T waves seen in about 25% of Wellens' syndrome patients
- No pathologic Q waves or loss of R waves
- Normal or minimally elevated ST segments
- Normal or minimally elevated cardiac biomarkers

over a 1- to 3-hour period can help distinguish acute from chronic injury, although it is important to realize that not all acute myocardial injury is due to AMI. Authors of large observational studies suggest that a single undetectable high-sensitivity troponin plus no ECG evidence of ischemia identifies patients at a very low risk for ACS.[26]

Despite the new sensitive assays, guidelines[1,6,7] and experts[27] recommend serial troponin testing to identify acute disease. A serial high-sensitivity troponin interval as short as 2 hours coupled with a low Thrombolysis in Myocardial Infarction risk score (<2) virtually excludes AMI.[28] The European Society of Cardiology recommends a 3-hour serial interval when high-sensitivity troponins are used or a 0 hour and 1 hour blood draw when a rapid algorithm exists that incorporates a delta change.[29,30]

Elevated levels of the cardiac troponins in patients with NSTEMI increase the short-term risk of death by 3.1-fold (1.6% vs. 5.2%).[23] Although patients with elevated troponins in the absence of ACS may be "false positive" for AMI, elevated troponin of any amount is associated with a high frequency of worse outcomes. Taken together, the data strongly support the claim that any **measurable elevated troponin is always worse than no elevated troponin and that more troponin elevation is always worse than less troponin elevation with respect to prognosis**.[26,31,32]

B-type natriuretic peptide, an established marker for patients with heart failure, is often elevated in patients with ACS; if elevated, ACS patients are at higher risk for adverse cardiovascular events, heart failure, or death.[6] When used in conjunction with other markers, the addition of B-type natriuretic peptide increases sensitivity at the cost of decreased specificity, with only a slight increase in overall diagnostic accuracy. For this reason, B-type natriuretic peptide is not routinely measured in those with suspected ACS.

GENERAL TREATMENT

The treatment of ACS is based on duration and persistence of symptoms, cardiac history, and findings on physical examination and the initial ECG (**Figure 49-12**). Establish IV access, give aspirin if not already given by EMS, and, as long as there are no contraindications, provide ECG monitoring. Many recommend supplemental O_2[7]; however, there is little evidence for benefit in patients without hypoxemia, and small studies have shown a negative effect with high-flow O_2.[33] The key treatment strategies aim to achieve immediate reperfusion and limit infarct size (**Table 49-8** and **Table 49-9**).

STEMI TREATMENT

Patients with persistent symptoms and STEMI should receive mechanical or pharmacologic reperfusion attempts. **Percutaneous coronary intervention (PCI)** with or without stent placement is the dominant current approach to mechanical reperfusion.[6] Pharmacologic reperfusion is accomplished with fibrinolytic therapy, which is improved with adjuvant antiplatelet and antithrombin therapy.

American Heart Association/American College of Cardiology guidelines target a treatment goal of ≤90 minutes for a patient who arrives at a hospital with PCI capability or of ≤120 minutes for patients arriving at a hospital without PCI capability to account for transfer time.[6,7] Fibrinolysis should be given within 30 minutes of ED arrival if PCI cannot be accomplished within these time frames.[7] The concept of "first medical contact to device/balloon time" replaces the "door to needle" or "door to balloon" time.[7] Each health system and institution treating ACS patients should develop protocols to drive optimal methods of reperfusion, determining which strategy it will use depending on its capabilities.

Most STEMI patients receive antiplatelet agents, antithrombins, and nitrates in the ED. Treat patients with unstable angina or NSTEMI with antiplatelet agents, antithrombins, and nitrates.[1] Those with unstable angina or NSTEMI refractory to these therapies or those scheduled to undergo PCI also may benefit from the use of glycoprotein IIb/IIIa antagonists (Table 49-8 and Table 49-9).[1]

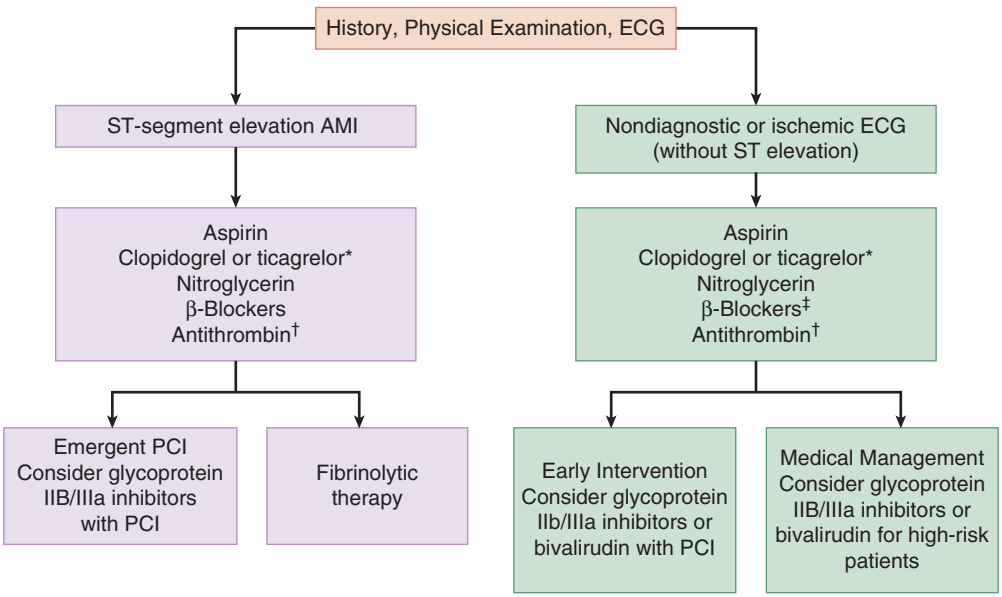

FIGURE 49-12. Treatment considerations for acute coronary syndrome (ACS) patients. *Prasugrel should be considered at the time of PCI in patients who have not yet received either clopidogrel or ticagrelor. †Enoxaparin, unfractionated heparin, or fondaparinux. Note: See text for discussion of individual treatment options, indications, and contraindications. ‡Risk factors for cardiogenic shock/adverse effects: (1) signs of heart failure; (2) evidence of a low cardiac output state; (3) increased risk for cardiogenic shock (cumulatively: age >70 years old, systolic blood pressure <120 mm Hg, sinus tachycardia >110 beats/min or bradycardia <60 beats/min, and longer duration of ST-segment elevation myocardial infarction symptoms before diagnosis and treatment); or (4) standard relative contraindications to β-blockade (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). AMI = acute myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 49-8 Drugs Used in the Emergency Treatment of STEMI

Antiplatelet Agents		
Aspirin	162–325 milligrams	
Clopidogrel	Loading dose of 600 milligrams PO followed by 75 mg PO daily. No loading dose is administered in patients >75 y old receiving fibrinolytics	
Prasugrel	Loading dose of 60 milligrams promptly and no more than 1 h after PCI once coronary anatomy is defined and a decision is made to proceed with PCI	
Ticagrelor	Loading dose is 180 milligrams PO followed by 90 milligrams twice a day	
Antithrombins		
Unfractionated heparin	Bolus of 60 units/kg (maximum, 4000 units) followed by infusion of 12 units/kg/h (maximum, 1000 units/h) titrated to a partial thromboplastin time 1.5–2.5 × control	
Enoxaparin	30 milligrams IV bolus followed by 1 milligram/kg SC every 12 h	
Fondaparinux	2.5 milligrams SC*	
Fibrinolytic Agents		
Streptokinase	1.5 million units over 60 min	
Anistreplase	30 units IV over 2–5 min	
Alteplase	Body weight >67 kg: 15 milligrams initial IV bolus; 50 milligrams infused over next 30 min; 35 milligrams infused over next 60 min Body weight <67 kg: 15 milligrams initial IV bolus; 0.75 milligram/kg infused over next 30 min; 0.5 milligram/kg infused over next 60 min	
Reteplase	10 units IV over 2 min followed by 10 units IV bolus 30 min later	
Tenecteplase	Weight	Dose (total dose not to exceed 50 milligrams)
	<60 kg	30 milligrams
	≥60 but <70 kg	35 milligrams
	≥70 but <80 kg	40 milligrams
	≥80 but <90 kg	45 milligrams
	≥90 kg	50 milligrams
Glycoprotein IIb/IIIa Inhibitors†		
Abciximab	0.25 milligram/kg bolus followed by infusion of 0.125 microgram/kg/min (maximum, 10 micrograms/min) for 12–24 h	
Eptifibatide	180 micrograms/kg bolus followed by infusion of 2.0 micrograms/kg/min for 72–96 h	
Tirofiban	0.4 microgram/kg/min for 30 min followed by infusion of 0.1 microgram/kg/min for 48–96 h	
Other Anti-Ischemic Therapies		
Nitroglycerin	Sublingual: 0.4 milligram every 5 min × 3 PRN pain IV: Start at 10 micrograms/min, titrate to 10% reduction in MAP if normotensive, 30% reduction in MAP if hypertensive	
Morphine	2–5 milligrams IV every 5–15 min PRN pain	
Metoprolol	50 milligrams PO every 12 h on first day, unless significant hypertension, may consider 5 milligrams IV over 2 min every 5 min up to 15 milligrams; withhold β-blockers initially if the patient is at risk for cardiogenic shock/adverse effects‡	
Atenolol	25–50 milligrams PO, unless significant hypertension, may consider 5 milligrams IV over 5 min, repeat once 10 min later; withhold β-blockers initially if the patient is at risk for cardiogenic shock/adverse effects‡	

Abbreviations: MAP = mean arterial pressure; PCI = percutaneous coronary intervention; PRN = as needed; STEMI = ST-segment elevation myocardial infarction.

*Fondaparinux should not be used as monotherapy for PCI; if used, addition of unfractionated heparin or bivalirudin is recommended before PCI.

†American College of Cardiology/American Heart Association 2009 focused update for STEMI patients recommended glycoprotein IIB/IIa inhibitors be given at the time of PCI; benefit prior to arrival in the cardiac catheterization laboratory is uncertain.

‡Risk factors for cardiogenic shock/adverse effects: (1) signs of heart failure; (2) evidence of a low cardiac output state; (3) increased risk for cardiogenic shock (cumulatively: age >70 y old, systolic blood pressure <120 mm Hg, sinus tachycardia >110 beats/min or bradycardia <60 beats/min, and longer duration of STEMI symptoms before diagnosis and treatment); or (4) standard relative contraindications to β-blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease).

NSTEMI TREATMENT

For patients with NSTEMI (which by definition requires the time for biomarkers to become elevated and the clinical laboratory to perform the measurement), an invasive approach within 24 to 48 hours using PCI reduces the composite of death, myocardial infarction, or recurrent ACS by 19% in women and 27% in men.[34] Therefore, the **early** invasive approach deployed in STEMI is recommended in NSTEMI patients only with refractory angina or hemodynamic or electrical instability or in patients at increased risk for clinical events.[1]

Based on the results of trials and a meta-analysis,[35,36] the American Heart Association/American College of Cardiology guidelines for the management of unstable angina/NSTEMI patients recommend early (within 24 hours) invasive therapy in patients with signs and symptoms such as recurrent angina/ischemia with or without symptoms of congestive heart failure, elevated cardiac troponins, new or presumably new ST-segment depression, high-risk findings on noninvasive stress testing, depressed left ventricular function, hemodynamic instability, sustained ventricular tachycardia, PCIs within the previous 6 months, or prior coronary artery bypass grafting.[1] More aggressive and earlier PCI in these patients has not proven beneficial compared to the within 48 hours approach.[37,38] If patients with unstable angina/NSTEMI are hemodynamically unstable, guidelines recommend invasive strategy within 2 hours.

PERCUTANEOUS CORONARY INTERVENTION

The American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend PCI as the preferred method of reperfusion therapy if the first medical contact to first balloon inflation time is <90 to 120 minutes.[6,7,39] In the early presenting cohort (within 3 hours of symptom onset), the decision to use primary PCI rather than fibrinolysis is based on institutional

TABLE 49-9 Drugs Used in the Emergency Treatment of Unstable Angina or NSTEMI

Antiplatelet Agents	
Aspirin	162–325 milligrams
Clopidogrel	Loading dose of 300–600 milligrams PO followed by 75 milligrams/d
Prasugrel	Loading dose of 60 milligrams promptly and no more than 1 h after PCI once coronary anatomy is defined and a decision is made to proceed with PCI
Ticagrelor	Loading dose of 180 milligrams PO followed by 90 milligrams twice a day
Antithrombins	
Heparin	Bolus of 60 units/kg (maximum, 4000 units) followed by infusion of 12 units/kg/h (maximum, 1000 units/h) titrated to a partial thromboplastin time 1.5–2.5 × control
Enoxaparin	1 milligram/kg SC every 12 h
Fondaparinux	2.5 milligrams SC
Direct Thrombin Inhibitor	
Bivalirudin	0.75 milligram/kg IV bolus followed by 1.75 milligrams/kg/h infusion for duration of procedure
Glycoprotein IIb/IIIa Inhibitors	
Eptifibatide	180 micrograms/kg bolus followed by infusion of 2.0 micrograms/kg/min for 72–96 h
Tirofiban	0.4 microgram/kg/min for 30 min followed by infusion of 0.1 microgram/kg/min for 48–96 h
Other Anti-Ischemic Therapies	
Nitroglycerin	Sublingual: 0.4 milligram every 5 min × 3 PRN pain IV: Start at 10 micrograms/min, titrate to 10% reduction in MAP if normotensive, 30% reduction in MAP if hypertensive
Metoprolol	50 milligrams PO every 12 h first day; unless significant hypertension, may consider 5 milligrams IV over 2 min every 5 min up to 15 milligrams; withhold β-blockers initially if the patient is at risk for cardiogenic shock/adverse effects*
Atenolol	25–50 milligrams PO; unless significant hypertension, may consider 5 milligrams IV over 5 min, repeat once 10 min later; withhold β-blockers initially if the patient is at risk for cardiogenic shock/adverse effects*

Abbreviations: MAP = mean arterial pressure; NSTEMI = non–ST-segment elevation myocardial infarction; PRN = as needed.

*Risk factors for cardiogenic shock/adverse effects: (1) signs of heart failure; (2) evidence of a low cardiac output state; (3) increased risk for cardiogenic shock (cumulatively: age >70 y old, systolic blood pressure <120 mm Hg, sinus tachycardia >110 beats/min or bradycardia <60 beats/min, and longer duration of ST-segment elevation myocardial infarction symptoms before diagnosis and treatment); or (4) standard relative contraindications to β-blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease).

expertise, availability of the cardiac catheterization team, and the individual patient's risk of complications from fibrinolysis.

Coronary angioplasty with or without stent placement is the most common PCI; alternatives include atherectomy and laser angioplasty. Balloon angioplasty increases the size of the arterial lumen through endothelial denudation; cracking, splitting, and disruption of atherosclerotic plaque; dehiscence of intima and plaque from underlying media; and stretching or tearing of underlying media and adventitia. With successful dilatation, small amounts of arterial wall dissection and aneurysmal expansion may be seen. The greater the increase in luminal size, the lower is the risk of restenosis. However, more aggressive balloon inflation can augment dissection, platelet deposition, thrombus formation, and plaque hemorrhage.

Alternative PCI procedures attempt to limit complications. Directional and rotational coronary atherectomy extracts atherosclerotic tissue from the coronary artery. Excimer laser atherectomy vaporizes atheromatous tissue. It results in larger luminal diameters but has not reduced rates of restenosis or other complications associated with percutaneous angioplasty procedures.

Coronary stents are fenestrated stainless steel tubes that are expanded by a balloon to provide scaffolding within the coronary arteries. Adding antiplatelet therapy (in particular, thienopyridines and glycoprotein IIb/IIIa inhibitors) results in lower adverse events at 6 months. Drug-eluting stents are associated with **decreased early** (within months) vessel closure but a **higher delayed** closure, particularly once antiplatelet agents (clopidogrel) are stopped.

In centers with expertise in direct angioplasty, primary PCI reduces the cardiovascular complication rate in patients with AMI compared to fibrinolysis.[6,40,41] The longer the duration of symptoms, the greater is the benefit to primary PCI over fibrinolysis. PCI is more effective in establishing flow and reducing reocclusion in the infarct-related artery than fibrinolytic therapy and is associated with a decreased incidence of short- and long-term death, nonfatal reinfarction, and intracranial hemorrhage compared with fibrinolytic therapy.[7]

Registry data show that the targeted reperfusion time goal is met less than half the time.[39] Strategies[42,43] to optimize door to balloon time include EMS direct or emergency physician activation of the catheterization laboratory without cardiologist consultation by a one-call system (similar to trauma activations); having a trained catheterization team ready in 20 minutes; a feedback loop providing the EMS provider and emergency physician with data on the individual case; quality assurance processes in place to measure and report back times; and continually enhancing the team-based approach.

FIBRINOLYTICS

Fibrinolytic agents (tissue plasminogen activator, recombinant tissue plasminogen activator, tenecteplase, streptokinase, and anistreplase) act on the acute thrombosis directly or indirectly as plasminogen activators. Plasminogen, an inactive proteolytic enzyme, binds directly to fibrin during thrombus formation to form a plasminogen–fibrin complex. This plasminogen–fibrin complex incorporated into the clot is more susceptible than circulating plasma plasminogen to activation (thus, the concept that fibrinolytic agents are to a varying degree "clot specific," promoting fibrin proteolysis).

Fibrinolytic therapy improves left ventricular function and short-term and long-term mortality. A meta-analysis found that the net benefit of fibrinolytic treatment in the first 3 hours was >30 lives saved per 1000 patients.[44] The loss of benefit per hour delay in fibrinolytic administration was 1.6 lives per 1000 patients per hour.

Fibrinolytic therapy is indicated for patients with STEMI (as a reperfusion option) if time to treatment is <6 to 12 hours from symptom onset and the ECG has at least 1 mm of ST-segment elevation in two or more contiguous leads.[6,7] Therapy is more beneficial if given early and for larger infarctions and anterior infarctions than for smaller or inferior infarctions. In the elderly, the overall risk of mortality from AMI is high. The proportionate reduction in mortality rate appears to be

less in patients >75 years old, but the absolute number of patients who may be saved is still considerable.

After failed fibrinolytic administration, rescue PCI is recommended for patients in cardiogenic shock who are <75 years old, patients with severe heart failure or pulmonary edema, patients with hemodynamically compromising ventricular arrhythmias, and patients in whom fibrinolytic therapy has failed and a moderate or large area of myocardium is at risk.[6]

Because tissue plasminogen activator, recombinant tissue plasminogen activator, and tenecteplase have similar efficacy and safety profiles, the choice of which to use is usually based on ease of administration, cost, and the local preferences.

Contraindications to fibrinolytic therapy are those that increase the risk of hemorrhage (**Table 49-10**). The most catastrophic complication is intracranial bleeding. Clinical variables that can be assessed in the ED and predict an increased risk of intracranial hemorrhage are age (>65 years old), low body mass (<70 kg), and hypertension on presentation.[6] Intracranial hemorrhage is more common with tissue plasminogen activator than with streptokinase (odds ratio of 1.6). Patients with relative contraindications may still receive fibrinolytic therapy when the benefits of therapy outweigh the risks of the complications.

Patients treated with fibrinolytics benefit from early follow-up invasive intervention, called **pharmacoinvasive therapy**.[45] In the TRANSFER-AMI study, high-risk patients treated with fibrinolytics for STEMI at non–PCI-capable centers were randomized to standard care or immediate transfer for PCI within 6 hours after fibrinolysis.[46] The patients who underwent the pharmacoinvasive strategy had a 6.2% absolute reduction in the composite end point of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days.

Facilitated PCI refers to a planned initial pharmacologic treatment followed by PCI for treatment of STEMI. The ASSENT-4 PCI trial found no benefit and a higher incidence of death, congestive heart failure, or shock at 90 days in the group receiving fibrinolytics compared with the PCI-only group. Current guidelines state that a facilitated approach might be considered in high-risk patients with low bleeding risk with long duration to PCI.[6] However, no clear benefits are apparent for this method.

TABLE 49-10 Contraindications to Fibrinolytic Therapy in ST-Segment Elevation Myocardial Infarction

Absolute contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- Known intracranial neoplasm
- Ischemic stroke within 3 mo
- Active internal bleeding (excluding menses)
- Suspected aortic dissection or pericarditis

Relative contraindications

- Severe uncontrolled blood pressure (>180/100 mm Hg)
- History of chronic, severe, poorly controlled hypertension
- History of prior ischemic stroke >3 mo or known intracranial pathology not covered in contraindications
- Current use of anticoagulants with known INR >2–3; no evidence with direct oral anticoagulants available as of this writing, but safety data can be extracted from stroke studies with recombinant tissue plasminogen activator and direct oral anticoagulants
- Known bleeding diathesis
- Recent trauma (past 2 wk)
- Prolonged CPR (>10 min)
- Major surgery (<3 wk)
- Noncompressible vascular punctures (including subclavian and internal jugular central lines)
- Recent internal bleeding (within 2–4 wk)
- Patients treated previously with streptokinase should not receive streptokinase a second time
- Pregnancy
- Active peptic ulcer disease
- Other medical conditions likely to increase risk of bleeding (e.g., diabetic retinopathy)

Fibrinolytic therapy in STEMI is limited in several ways. First, even the most potent fibrinolytic agents do not achieve early and complete restoration of coronary blood flow in 40% to 50% of patients. Fibrinolytics are plasminogen activators. When fibrin is lysed, thrombin is exposed. The exposed thrombin is a potent biologic platelet activator. As a result, the more fibrin that is lysed, the more thrombin is exposed, and the more prothrombotic substrate is engendered. This may be one reason why optimal antithrombin therapy (enoxaparin rather than unfractionated heparin) and dual antiplatelet therapy (both aspirin and clopidogrel) lead to improved outcomes. The second limitation of fibrinolytic therapy is that approximately 0.5% to 1.0% of patients have intracranial hemorrhage, which usually results in death or disabling stroke.

STEMI patients who received fibrinolytics should get full-dose anticoagulants for a minimum of 48 hours.[6] Recommended therapies include unfractionated heparin, enoxaparin, or fondaparinux.[6,7]

ANTIPLATELET AGENTS

The glycoprotein IIb/IIIa antagonists are stronger antiplatelet agents than aspirin, interrupting platelet activation regardless of the agonist. In contrast, aspirin only inhibits platelet aggregation stimulated through thromboxane A_2 and mediated through the arachidonic acid pathway.

ASPIRIN

Give aspirin, ≥162 milligrams and preferably 325 milligrams if naive of aspirin, as soon as possible to all patients with STEMI, NSTEMI, and unstable angina. Aspirin prevents formation of thromboxane A_2, an agonist of platelet aggregation. This inhibition persists for the 8- to 12-day life of the platelet, because platelets are unable to generate new cyclooxygenase. In patients with STEMI, aspirin alone reduces relative mortality rate by 23%.[6] The estimated number needed to treat to aid is 41 patients, with the number needed to harm (nondangerous bleeding) being 167 patients.[47] Aspirin used in conjunction with fibrinolytic therapy further reduces ischemic events and coronary artery reocclusion. Aspirin doses >162 milligrams cause immediate, near-complete inhibition of thromboxane A_2. Smaller doses may not be effective for acute use. Aspirin reduces vascular events in patients with AMI and patients with unstable angina, especially in those with prior myocardial infarction or stroke (decrease by about 4%).

The side effects of aspirin are mainly GI, accumulative, and dose related. Diluted or buffered aspirin solutions, lowest possible doses, or concurrent antacid or H_2 antagonist administration reduces aspirin harm. Due to the benefits **during ACS, do not withhold early aspirin from patients with minor contraindications** (vague allergy, history of remote peptic ulcer, or GI bleeding).[6] Other antiplatelet agents such as clopidogrel are alternatives if true aspirin allergy or active peptic ulcer disease exists.

ADENOSINE DIPHOSPHATE RECEPTOR ANTAGONISTS

Prasugrel Prasugrel is an irreversible, potent platelet receptor antagonist in this class. In the TRITON-TIMI 38 trial, prasugrel compared favorably with clopidogrel,[48] reducing the primary composite outcome by an absolute 2.2%, although with an increased frequency of bleeding. In post hoc analysis, this increased bleeding risk was greatest in patients with a history of stroke and patients age ≥75 years.[49] The **U.S. Food and Drug Administration issued a warning for prasugrel, indicating use is contraindicated in patients with a prior cerebrovascular accident or transient ischemic attack or with pathologic bleeding. Additional risk factors for bleeding are age ≥75 years, propensity for bleeding, and concomitant use of medications that increase the risk of bleeding**. Prasugrel has only been studied in patients with known coronary anatomy, so it has limited generalizability to ED patients.

Ticagrelor Ticagrelor is a reversible nonthienopyridine P2Y12 receptor antagonist, with the effect gone within 3 days of stopping the agent. The PLATO study compared ticagrelor to clopidogrel[50] in patients with ACS (with or without ST elevation). The composite primary outcome in those treated with ticagrelor was decreased by an absolute frequency of 1.9% without any difference in major bleeding. In patients with STEMI

undergoing PCI, there was an increase in stroke in patients receiving ticagrelor (1.7% vs. 1.0%, $P = 0.02$).

Clopidogrel The addition of clopidogrel to aspirin and antithrombin therapy improves cardiovascular outcomes in patients receiving fibrinolysis for STEMI. The CLARITY-TIMI 28 trial[51] and the COMMIT trial[52] both demonstrated improvements in hospital and 30-day outcomes with the addition of clopidogrel to standard therapy. The American College of Cardiology/American Heart Association STEMI guidelines consider this dual therapy a Class I, level of evidence A recommendation.[6]

Clopidogrel reduces a composite outcome of death, AMI, and stroke in patients with unstable angina/NSTEMI. The CURE trial randomized patients with unstable angina/NSTEMI to clopidogrel (300-milligram loading dose and 75-milligram daily dose) or placebo,[53] with all patients receiving aspirin. The clopidogrel group had a 20% reduction in death, AMI, or stroke between 3 and 12 months. There was an excess of bleeding in the clopidogrel group compared with controls; however, this was reduced in patients who received lower doses of aspirin.

Give clopidogrel to patients with true aspirin allergy. Use this agent early in patients with ACS regardless of whether noninvasive management or PCI is planned.[54] For patients undergoing urgent PCI, 600 milligrams is superior to 300 milligrams in preventing postprocedure myocardial infarction.[55,56] However, the results of the CURRENT-OASIS-7 trial reported that although increasing the clopidogrel dose to 600 milligrams caused a decrease in ischemic events, there was also an increased rate of bleeding.[57] Therefore, the current guidelines still provide a clopidogrel dose range of 300 to 600 milligrams in patients with unstable angina/NSTEMI.[1]

The U.S. Food and Drug Administration issued warnings on the efficacy of clopidogrel in two selected patient groups. First, patients taking omeprazole experience an approximately 50% reduction in the antiplatelet aggregation effects of clopidogrel. Second, patients with the variant *CYP2C19* gene have impaired metabolism of clopidogrel and hence a reduced ability to convert the drug to its active form, leading to an increase in stent thromboses and recurrent ischemic events. Consider alternative antiplatelet agents in this group of patients.

Because of an increased bleeding risk, withhold clopidogrel for 5 days before coronary artery bypass grafting when possible. About 5% to 20% of patients with unstable angina/NSTEMI eventually have near-term coronary artery bypass grafting; do not withhold clopidogrel unless coronary artery bypass grafting is imminent.

Cangrelor Cangrelor is an intravenous adenosine diphosphate receptor inhibitor that has been shown to reduce ischemic events in patients who undergo PCI when compared to clopidogrel. The proportion of STEMI patients in trials evaluating this agent is low; therefore, the level of recommendation for use by the European Society of Cardiology is Class IIb.[58]

GLYCOPROTEIN IIB/IIIA INHIBITORS

Abciximab is a chimeric antibody that binds irreversibly to the glycoprotein IIb/IIIa antagonists. The duration of action is longer than that of the smaller peptide molecules. **Eptifibatide** is a synthetic heptapeptide that binds reversibly to the glycoprotein IIb/IIIa receptor. **Tirofiban** is a synthetic small molecule with reversible binding to the glycoprotein IIb/IIIa receptor. All require an IV infusion to demonstrate sustained benefits. Reversal of platelet inhibition after cessation of infusion is more rapid with the polypeptide or small-molecule agents eptifibatide or tirofiban, an advantage when bleeding complications occur.

Despite potential benefits, routine initiation of a glycoprotein IIb/IIIa inhibitor in the ED is not recommended due to conflicting information about the timing of PCI after administration and potential for bleeding.[59]

The glycoprotein IIb/IIIa inhibitor recommendations include patients with high-risk features, such as positive troponins, or patients treated with an early invasive strategy, but initiation prior to catheterization does not have proven benefit over initiation in the catheterization laboratory. Four large trials evaluated glycoprotein IIb/IIIa antagonists for the medical stabilization of patients with unstable angina/NSTEMI. Tirofiban and eptifibatide reduced the rates of the triple composite end point of death, AMI, and recurrent ischemia. However, abciximab did not benefit patients who did not undergo coronary angiography within 48 hours. Thus, **the American Heart Association/American College of Cardiology guidelines for the management of unstable angina/NSTEMI patients make administration of glycoprotein IIb/IIIa inhibitors in patients treated with an early invasive strategy who are intermediate/high risk a Class IIb recommendation with eptifibatide and tirofiban the preferred agents.**[1]

ANTITHROMBINS

Unfractionated Heparin Unfractionated heparin reduces the risk of AMI and death during the acute phase of unstable angina. The combination therapy of aspirin and heparin reduces the short-term risk of death or AMI by 56% compared with aspirin alone. When unfractionated heparin is used in combination with aspirin, recurrence of ischemia is diminished after cessation of the infusion. **Thus, combination therapy with aspirin and heparin is indicated for patients with ACS.**

Unfractionated heparin has an unpredictable anticoagulant response because the bioavailability of heparin is variable. Even in clinical trials, less than half of patients are appropriately anticoagulated within 24 hours. Unfractionated heparin requires careful laboratory monitoring and dose adjustment. The weight-adjusted regimen is recommended, with an initial bolus of 60 units/kg (maximum of 4000 units per American Heart Association/American College of Cardiology guidelines[1,6]) and an infusion of 12 units/kg/h (maximum, 1000 units/h[1,6]). Unfractionated heparin dosing according to the European Society of Cardiology is 70 to 100 units/kg IV bolus when no glycoprotein IIb/IIIa inhibitor is planned and 50 to 60 units/kg IV bolus when given with glycoprotein IIb/IIIa inhibitors.[7] Optimally, cease unfractionated heparin after 48 hours of therapy to reduce the risk of developing heparin-induced thrombocytopenia.[6] Use other agents if ongoing anticoagulation is needed.

Low-Molecular-Weight Heparins The low-molecular-weight heparins have greater bioavailability, lower protein binding, and a longer half-life, and achieve a more reliable anticoagulant effect. As a result, they are given in a fixed dose subcutaneously once or twice a day and achieve a stable therapeutic response without the need for monitoring anticoagulation.

Large clinical trials show that enoxaparin, rather than unfractionated heparin, improved outcome in STEMI patients treated with aspirin and fibrinolysis.[60] **Enoxaparin is not considered a first-line antithrombin for patients receiving primary PCI for treatment of STEMI**[6]; however, in the event that a patient previously started on enoxaparin goes for PCI, enoxaparin should be continued.

A meta-analysis of six trials comparing enoxaparin with unfractionated heparin demonstrates a 0.9% reduction in death or recurrent AMI in patients receiving enoxaparin rather than unfractionated heparin, in addition to other standard therapies.[61] The benefit of enoxaparin is greater in patients with higher risk, with a significant decrease in the composite end point of death, AMI, and recurrent ischemia requiring PCI at 14 days in patients with a Thrombolysis in Myocardial Infarction risk score of >3. Trials with high rates of PCI have demonstrated the safety and efficacy of low-molecular-weight heparins in patients receiving PCI. The SYNERGY trial demonstrated improved outcomes in patients with consistent therapy (use of a single antithrombin from the ED through the catheterization laboratory) and increased bleeding when the patient was changed from one antithrombin to another. **The best approach is for the emergency physician and cardiologist to work in collaboration** to choose the antithrombin agent used from ED through PCI and aftercare. If coronary artery bypass grafting is planned, hold low-molecular-weight heparin for 12 to 24 hours, bridging with unfractionated heparin.

Fondaparinux Fondaparinux is a synthetic pentasaccharide that binds to antithrombin III to form an antithrombic complex, but unlike heparin, this complex is very specific for factor Xa inhibition. Fondaparinux has been evaluated in two large clinical trials. In STEMI patients, it has similar efficacy to unfractionated heparin in patients receiving fibrinolytics or primary PCI. However, the European Society of Cardiology does not recommend fondaparinux in patients going for PCI.[7] American College of Cardiology/American Heart Association guidelines make the following caution: **fondaparinux is not a monotherapy for PCI; if used, add unfractionated heparin or bivalirudin before PCI.**[6]

In unstable angina/NSTEMI patients, bleeding was lower in fondaparinux-treated versus enoxaparin-treated patients. For NSTEMI patients in whom conservative management is to be used, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommended fondaparinux over enoxaparin,[62] as did the European Society of Cardiology,[29] but it is not yet U.S. Food and Drug Administration approved for this indication.

Direct Thrombin Inhibitor: Bivalirudin Direct thrombin inhibitors bind to the catalytic site of thrombin, bind to thrombin in clot, and are resistant to agents that degrade heparin. Bivalirudin reduces the short-term risk of postischemic complications relative to high-dose unfractionated heparin in patients undergoing PCI for unstable or postinfarction angina. The ACUITY trial demonstrated that bivalirudin is safe and effective for intermediate- to high-risk unstable angina/NSTEMI patients receiving PCI.[62] The HORIZONS-AMI trial showed that, in patients with STEMI who are undergoing PCI, anticoagulation with bivalirudin alone, as compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors, resulted in significantly reduced 30-day rates of major bleeding.[63]

LIMITING INFARCT SIZE

NITRATES

Nitrates relax vascular smooth muscle in arteries, arterioles, and veins through the metabolic conversion of organic nitrates to nitric oxide. The pulmonary capillary wedge pressure, systemic arterial pressure, and left ventricular end-systolic and end-diastolic volumes decrease. Reductions in right and left ventricular filling pressures that result from peripheral dilatation combined with afterload reduction that results from arterial dilatation decrease cardiac work and myocardial O_2 requirements. Nitroglycerin has direct vasodilator effects on the coronary vascular bed and increases global and regional myocardial blood flows. When obstructing atherosclerotic lesions contain intact vascular smooth muscle, nitrates may dilate these vessels, thereby improving blood flow. Platelet aggregation is also inhibited by nitroglycerin.

When nitroglycerin is used in AMI patients not treated with thrombolytics, it reduces infarct size, improves regional function, and decreases the rate of cardiovascular complications. The mortality rate is lowered by 35% with the use of nitrates. It is important to note that in most studies, IV nitroglycerin titration to 10% reduction in mean arterial pressure for normotensive patients and to 30% reduction in mean arterial pressure for hypertensive patients occurred, not for symptom resolution. **In AMI, titrate IV nitroglycerin to blood pressure reduction rather than to symptom (chest pain) resolution.** Data are confounded regarding a benefit of nitroglycerin in those receiving fibrinolytic therapy.

The American College of Cardiology/American Heart Association recommends the use of IV nitroglycerin for the first 24 to 48 hours for patients with STEMI and recurrent ischemia, congestive heart failure, or hypertension.[5] Benefits are likely to be greatest in patients not receiving concurrent fibrinolytic therapy. For unstable angina/NSTEMI, IV nitroglycerin is used in patients who are not responsive to sublingual nitroglycerin tablets.[1]

The most serious side effect of nitroglycerin is hypotension, which may result in reflex tachycardia and worsening ischemia; paradoxical bradycardia can also follow nitrate use. **Use nitroglycerin cautiously in patients with inferior wall ischemia**, because one third of such patients might have right ventricular involvement; nitrates reduce preload and commonly trigger hypotension in this setting, worsening infarct. If nitroglycerin results in hypotension, stop the drug and administer fluid for blood pressure. Avoid nitrates in patients with ACS who recently received a phosphodiesterase inhibitor for erectile dysfunction (within 24 hours of sildenafil use or within 48 hours of tadalafil use).

β-BLOCKERS

β-Adrenergic antagonists have antidysrhythmic, anti-ischemic, and antihypertensive properties. During AMI, they diminish myocardial O_2 demand by decreasing heart rate, systemic arterial pressure, and myocardial contractility. Prolongation of diastole may augment perfusion to ischemic myocardium.

Contemporary trials show no benefit from early β-blocker therapy, and data from one large trial have changed the guideline recommendations for β-antagonists.[64] The COMMIT/CCS-2 trial randomized 45,852 patients within 24 hours of myocardial infarction symptom onset to receive either IV metoprolol followed by PO metoprolol or placebo. **Metoprolol reduced the absolute risks of reinfarction by 5 per 1000 and of ventricular fibrillation by 5 per 1000, but importantly, it increased the risk of cardiogenic shock by 11 per 1000**. Overall, metoprolol did not significantly reduce mortality in the hospital.[64,65] **American College of Cardiology/American Heart Association recommendations are to start PO (not IV) β-antagonists in patients with STEMI or NSTEMI within 24 hours provided the patient has none of the following**: (1) signs of heart failure, (2) evidence of a low cardiac output state, (3) increased risk for cardiogenic shock (cumulatively: age >70 years old, systolic blood pressure <120 mm Hg, sinus tachycardia >110 beats/min or bradycardia <60 beats/min, and longer duration of STEMI symptoms before diagnosis and treatment), or (4) standard relative contraindications to β-blockade (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease).[1,6] IV therapy is reserved for patients with significant hypertension.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors reduce left ventricular dysfunction and left ventricular dilatation and slow the development of congestive heart failure during AMI. Oral angiotensin-converting enzyme therapy lowers mortality after AMI.[66]

The American College of Cardiology/American Heart Association recommend that patients with STEMI or heart failure receive treatment with oral angiotensin-converting enzyme inhibitors within the first 24 hours (**not necessarily in the ED**).[6] For unstable angina/NSTEMI, angiotensin-converting enzyme inhibitors should be administered within the first 24 hours in patients with pulmonary congestion or a left ventricular ejection fraction <40%, in the absence of hypotension or contraindications.[1]

Contraindications to angiotensin-converting enzyme inhibitors include hypotension, bilateral renal artery stenosis, renal failure, or history of cough or angioedema due to prior angiotensin-converting enzyme inhibitor use. The efficacy of angiotensin-converting enzyme inhibitors in unstable angina has not been well evaluated.

MAGNESIUM

Magnesium produces systemic and coronary vasodilatation, possesses antiplatelet activity, suppresses automaticity, and protects myocytes from calcium influx during reperfusion. However, studies are conflicting: some have found that the mortality rate is reduced, whereas others have shown no benefit at all. In light of these conflicting data, correct documented hypomagnesemia during AMI and give magnesium for torsades de pointes–type ventricular tachycardia or with a prolonged QT interval.[6] Magnesium bolus and infusion in high-risk patients, such as the elderly and those in whom reperfusion therapy is not suitable, are considered possibly beneficial.[6]

CALCIUM CHANNEL ANTAGONISTS

Calcium channel blockers have antianginal, vasodilatory, and antihypertensive properties. **Calcium antagonists do *not* reduce mortality rate after AMI, and they may be harmful to some patients with cardiovascular disease.[6]**

Verapamil and diltiazem are potentially beneficial in patients with ongoing ischemia or atrial fibrillation with rapid ventricular response who do not have congestive heart failure, left ventricular dysfunction, or atrioventricular block, and when β-adrenergic antagonists are contraindicated.

COMPLICATIONS OF ACUTE CORONARY SYNDROME

Myocardial perfusion and cardiac function affect blood flow to the entire body. As a result, any end organ can be damaged when cardiac pump function is decreased. In this section, discussion of the

TABLE 49-11 Early Dysrhythmias After Acute Myocardial Infarction

Dysrhythmia	Frequency of Occurrence (%)
Bradydysrhythmias	
Sinus bradycardia	35–40
First-degree AV block	4–15
Second-degree AV block, type I	4–10
Second-degree AV block, type II	0.5–1.0
Third-degree AV block	5–8
Asystole	1–5
Tachydysrhythmias	
Sinus tachycardia	30–35
Atrial premature contractions	50
Supraventricular tachycardia	2–9
Atrial fibrillation	4–10
Atrial flutter	1–2
Ventricular premature beats	99
Accelerated idioventricular rhythm	50–70
Ventricular tachycardia, nonsustained	60–69
Ventricular tachycardia, sustained	2–6
Ventricular fibrillation	4–7

Abbreviation: AV = atrioventricular.

complications of ACS is limited to the direct effects on the heart. The systemic effects of cardiac function are discussed in organ-appropriate chapters of this book.

DYSRHYTHMIAS AND CONDUCTION DISTURBANCES

The genesis, diagnosis, and treatment of dysrhythmias are presented in Chapter 18, "Cardiac Rhythm Disturbances." The effect dysrhythmias have in complicating the course of patients with ACS is the subject of this section.

Dysrhythmias occur in 72% to 100% of AMI patients treated in the coronary care unit. **Table 49-11** shows the approximate frequency of the various dysrhythmias observed in patients with AMI. Many dysrhythmias occur in the prehospital and ED settings. The main consequences of dysrhythmias are impaired hemodynamic performance, compromised myocardial viability due to increased myocardial O_2 requirements, and predisposition to even more serious rhythm disturbances due to diminished ventricular fibrillation threshold. (See Video: Zoll Live Vest.)

Wearable Cardioverter-Defibrillators A wearable cardioverter-defibrillator, of which one is the LifeVest®, is a cardiac monitor and a vest-like garment worn under clothing to monitor cardiac rhythm and automatically deliver cardioversion or defibrillation when a lethal dysrhythmia develops. It is often used as a bridge to automatic implantable cardioverter-defibrillator placement or immediately after STEMI. ED patients wearing a LifeVest® or other such garment should keep the garment on in the ED. It can be removed for procedures or radiographs, as long as the patient is placed on a cardiac monitor and can be observed for the development of a life-threatening dysrhythmia. Do not cut the device off as it is usually a rented device and is returned to the company when no longer needed. As of this writing, whether the device can prevent post–myocardial infarction sudden cardiac death is unclear.

The hemodynamic consequences of dysrhythmias are dependent on ventricular function. Patients with left ventricular dysfunction have a relatively fixed stroke volume. They depend on changes in heart rate to alter cardiac output. The range of heart rate that is optimal becomes narrowed with increasing dysfunction. Slower or faster heart rates may further depress cardiac output.

In addition, maintenance of the atrial filling of the ventricle (or "the atrial kick") is important for patients with AMI. Patients with normal hearts have a loss of 10% to 20% of left ventricular output when the atrial kick is eliminated. Patients with reduced left ventricular compliance, common in AMI, have up to 35% reduction in stroke volume when the atrial systole is eliminated. "Pump" failure with resultant increased sympathetic stimulation can also result in sinus tachycardia, atrial fibrillation or flutter, and supraventricular tachycardias.

Sinus tachycardia is quite prominent in patients with anterior wall AMI. Because of increased myocardial O_2 use, **persistent sinus tachycardia is associated with a poor prognosis in AMI; seek the cause and resolve it**. Causes may include anxiety, pain, left ventricular failure, fever, pericarditis, hypovolemia, atrial infarction, pulmonary emboli, or use of medications that accelerate heart rate. Similarly, paroxysmal supraventricular tachycardia, atrial fibrillation, and atrial flutter are associated with an increased mortality.

Atrial fibrillation associated with AMI most typically occurs in the first 24 hours and is usually transient. It more often occurs in patients with excess catecholamine release, hypokalemia, hypomagnesemia, hypoxia, chronic lung disease, and sinus node or left circumflex ischemia. Patients with supraventricular tachycardia, atrial fibrillation, or atrial flutter who have hemodynamic compromise are best treated with direct current cardioversion (see Chapter 18). Patients who are partially or fully compensated or who do not respond to cardioversion can receive amiodarone or β-adrenergic antagonists to slow the ventricular rate[67] absent any contraindications. Patients with ongoing ischemia but without hemodynamic compromise, clinical left ventricular dysfunction, reactive airway disease, or heart block should have rate control with β-adrenergic antagonists, such as atenolol (2.5 to 5.0 milligrams over 2 minutes to a total of 10 milligrams) or metoprolol (2.5 to 5.0 milligrams every 2 to 5 minutes to a total of 15 milligrams). Patients with contraindications to β-adrenergic antagonists can be treated with digoxin (0.3- to 0.5-milligram initial bolus with a repeat dose in 4 hours) or a calcium channel antagonist.[6] Anticoagulate patients with atrial fibrillation and AMI to limit systemic embolization.

Sinus bradycardia without hypotension does not appear to increase mortality during AMI. Prognosis is related to the site of infarction, the site of the block (intranodal vs. infranodal), the type of escape rhythm, and the hemodynamic response to the rhythm. Atropine is used for sinus bradycardia when it results in hypotension, ischemia, or ventricular escape rhythms and for treatment of symptomatic atrioventricular block occurring at the atrioventricular nodal level (e.g., second-degree type I). Atropine can improve heart rate, systemic vascular resistance, and blood pressure; use it with caution in the setting of AMI since the parasympathetic tone is protective against infarct extension, ventricular fibrillation, and excessive myocardial O_2 demand.

Complete heart block can occur in patients with anterior and inferior AMI because the atrioventricular conduction system receives blood supply from the atrioventricular branch of the right coronary artery and the septal perforating branch of the left anterior descending coronary artery. In the absence of right ventricular involvement, the mortality is approximately 15%. It rises to >30% when right ventricular involvement is present. Complete heart block in the setting of an anterior myocardial infarction portends a grave prognosis. Junctional rhythms are usually transient and occur within 48 hours of infarction.

The increased mortality in patients with heart block during AMI is related to more extensive myocardial damage and not to the heart block itself. As a result, pacing does not reduce mortality in patients with atrioventricular block or intraventricular conduction delay. Nonetheless, pacing is recommended to protect against sudden hypotension, acute ischemia, and precipitation of ventricular dysrhythmias in certain patients.

Use temporary **transcutaneous** pacers in patients at moderate to high risk of progression to atrioventricular block (**Table 49-12**). **Transvenous** pacing follows for patients with a high likelihood (>30%) of requiring permanent pacing (Table 49-12). Patients with right ventricular infarction who are very dependent on atrial systole may require atrioventricular sequential pacing to maintain cardiac output.

Ventricular premature contractions are common in patients with AMI and are benign. **Accelerated idioventricular rhythms** in patients with AMI do not affect prognosis or require treatment. **Ventricular tachycardia** shortly after AMI is often transient and does not confer a poor prognosis. When ventricular tachycardia occurs late in the course of AMI, it is usually associated with transmural infarction and left ventricular dysfunction, induces hemodynamic deterioration, and is associated with a mortality rate approaching 50%. Primary **ventricular fibrillation** occurring shortly after symptom onset does not appear to have a large effect on mortality and prognosis, as long as it is quickly and

TABLE 49-12 Indications for Temporary Pacemaker Placement

Temporary transcutaneous pacemaker indications

- Unresponsive symptomatic bradycardia
- Mobitz II or higher AV blocks
- New LBBB and bifascicular blocks
- RBBB or LBBB with first-degree block
- Some cases with stable bradycardia and new or indeterminate-age RBBB

Temporary transvenous pacemaker indications

- Asystole
- Unresponsive symptomatic bradycardia
- Mobitz II or higher AV blocks
- New or indeterminate-age LBBB
- Alternating bundle branch block
- RBBB or LBBB with first-degree block
- Consider in RBBB with left anterior or posterior hemiblocks
- Overdrive pacing in unresponsive ventricular tachycardia
- Unresponsive recurrent sinus pauses (>3 s)

Abbreviations: AV = atrioventricular; LBBB = left bundle branch block; RBBB = right bundle branch block.

effectively treated. Delayed or secondary ventricular fibrillation during hospitalization is associated with severe ventricular dysfunction and 75% in-hospital mortality.

New right bundle branch block occurs in approximately 2% of AMI patients, most commonly with anteroseptal AMI; it is associated with an increased mortality and complete atrioventricular block. **New left bundle branch block** occurs in <10% of patients with AMI and is also associated with a higher mortality than in patients without left bundle branch block. Recognizing STEMI in the presence of left bundle branch block is difficult,[9] and due to this uncertainty and false catheterization lab activation, new or suspected new left bundle branch block alone has been removed from the most recent recommendations for emergency perfusion.[6] The left posterior fascicle is larger than the left anterior fascicle. Thus, left posterior hemiblock is associated with a higher mortality than is isolated left anterior hemiblock, because it represents a larger area of infarction. Bifascicular block (right bundle branch block and a left hemiblock) has an increased likelihood of progression to complete heart block; it represents a large infarction and has more frequent pump failure and greater mortality.[24] See Chapter 18, "Cardiac Rhythm Disturbances," for more detail.

HEART FAILURE

Approximately 15% to 20% of patients with AMI present with some degree of heart failure. One third of these patients have circulatory shock. In AMI, heart failure occurs from diastolic dysfunction alone or a combination of systolic and diastolic dysfunction. Left ventricular diastolic dysfunction leads to pulmonary congestion. Systolic dysfunction is responsible for decreased forward flow, reduced cardiac output, and reduced ejection fraction. In general, the more severe the degree of left ventricular dysfunction, the higher is the mortality. The degree of left ventricular dysfunction in any single patient depends on the net effect of prior myocardial dysfunction (prior myocardial infarction or cardiomyopathy), baseline myocardial hypertrophy, acute myocardial necrosis, and acute reversible myocardial dysfunction ("stunned myocardium"). For further discussion, see Chapter 50, "Cardiogenic Shock," and Chapter 53, "Acute Heart Failure."

Mortality for patients with AMI increases as cardiac output decreases or pulmonary congestion increases, with mortality rates as follows: no heart failure, 10%; mild heart failure, 15% to 20%; frank pulmonary edema, 40%; and cardiogenic shock, 50% to 80%. Elevated levels of B-type natriuretic peptide or pro-B-type natriuretic peptide early in the hospital course portend a worse 30-day outcome.

The presence of shock in AMI results in a complex spiral relationship. Coronary obstruction leads to myocardial ischemia, which impairs myocardial contractility and ventricular outflow. The resulting reduction in arterial blood pressure leads to further decreases in coronary arterial perfusion, resulting in worsening myocardial ischemia and more severe myocardial necrosis. Interruption of this downward spiral requires careful attention to fluid management and the use of inotropic agents. Resolution of ischemia and preventing or minimizing the area of stunned myocardium that progresses to infarction are imperative; guidelines recommend that patients with STEMI and cardiogenic shock who are <75 years of age should be considered for PCI.[6] For further discussion, see Chapters 50 and 53.

MECHANICAL COMPLICATIONS

Sudden decompensation of previously stable patients should raise concern for the mechanical complications of AMI. These complications usually involve the tearing or rupture of infarcted tissue, not seen in unstable angina. The clinical presentation of these entities depends on the site of rupture (papillary muscles, interventricular septum, or ventricular free wall).

Ventricular free wall rupture occurs in 10% of AMI fatalities, usually 1 to 5 days after infarction. Rupture of the left ventricular free wall usually leads to pericardial tamponade and death (in >90% of cases). Patients may complain of tearing pain or sudden onset of severe pain. They will be hypotensive and tachycardic and may have onset of confusion and agitation. Increased neck veins, decreased heart sounds, and pulsus paradoxus may be present. In the ED, echocardiography is the diagnostic test of choice. Near equalization of right atrial, right ventricular mid-diastolic, and right ventricular systolic pressures on pulmonary artery catheterization is also useful but seldom available in the ED. Treatment is surgical.

Rupture of the interventricular septum is more often detected clinically than rupture of the ventricular free wall. The size of the defect determines the degree of left-to-right shunt and the ultimate prognosis. Clinically, interventricular septal rupture presents with chest pain, dyspnea, and sudden appearance of a new holosystolic murmur. The murmur is usually accompanied by a palpable thrill and is heard best at the lower left sternal border. Doppler echocardiography is the diagnostic procedure of choice. Demonstration of left-to-right shunt by pulmonary catheter blood sampling may be useful. An O_2 step-up of >10% from right atrial to right ventricular samples is diagnostic. Rupture of the interventricular septum is more common in patients with anterior wall myocardial infarction and patients with extensive (three-vessel) coronary artery disease. Treatment is surgical.

Papillary muscle rupture occurs in approximately 1% of patients with AMI, is more common with inferior myocardial infarction, and usually occurs 3 to 5 days after AMI. In contrast to rupture of the interventricular septum, papillary muscle rupture often occurs with a small- to modest-sized AMI. Patients present with acute onset of dyspnea, increasing heart failure and pulmonary edema, and a new holosystolic murmur consistent with mitral regurgitation. The posteromedial papillary muscle is most commonly ruptured, because it receives blood supply from one coronary artery, usually the right coronary artery. Echocardiography often can distinguish rupture of a portion of the papillary muscle from other etiologies of mitral regurgitation. Treatment is surgical.[6,7]

PERICARDITIS

In the current era of early PCI intervention, early post-AMI pericarditis occurs in <5% of patients,[67] a drop from 20% since the 1980s. It is more common in patients with transmural AMI and delayed initial presentations. Pericarditis results from inflammation adjacent on the epicardial surface of a transmural infarction, often 2 to 4 days after AMI. Pericardial friction rubs are detected more often with inferior wall and right ventricular infarction, because the right ventricle lies immediately beneath the chest wall. The pain of pericarditis can be confused with that of infarct extension or post-AMI angina. Classically, the discomfort of pericarditis becomes worse with a deep inspiration and may be relieved by sitting forward.

Echocardiography may demonstrate a pericardial effusion; pericardial effusions are much more common than pericarditis and often are present in the absence of pericarditis. Similarly, pericarditis can be present in the absence of a pericardial effusion. The resorption rate of post-AMI pericardial effusions is slow, often taking several months. Treatment is symptomatic with aspirin, 650 milligrams PO every 4 to 6 hours, or colchicine, 0.6 mg twice daily. Ibuprofen interferes with the antiplatelet

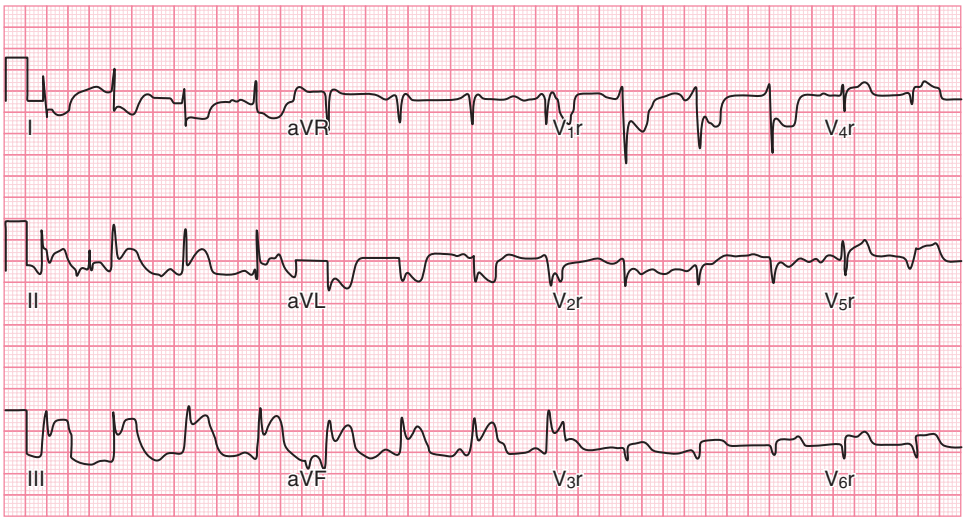

FIGURE 49-13. Right-sided leads demonstrating **right ventricular infarction** associated with inferior wall myocardial infarction. Right-sided leads have replaced the normal left-sided V leads. In this example, the ST-segment elevation is prominent in leads V_3R to V_6R.

effect of aspirin and can cause myocardial scar thinning and infarct expansion. **Dressler's syndrome** (late post-AMI syndrome) occurs 2 to 10 weeks after AMI and presents with chest pain, fever, and pleuropericarditis. Dressler's syndrome is treated with aspirin and colchicine.[68-70]

RIGHT VENTRICULAR INFARCTION

Isolated right ventricular infarction is extremely rare and is usually seen as a complication of an inferior infarction (**Figures 49-6** and **49-13**). The right ventricle most commonly receives its blood supply from the right coronary artery. In patients with left dominant systems, the blood supply may come from the left circumflex. The anterior portion of the right ventricle is supplied by branches of the left anterior diagonal artery. Approximately 30% of inferior wall myocardial infarction involves the right ventricle. The presence of right ventricular infarction is associated with a significant increase in mortality and cardiovascular complications. Right ventricular infarction can be diagnosed by the presence of ST-segment elevation in the precordial V_4R lead in the setting of an inferior wall myocardial infarction (Figure 49-6). The presence of elevated neck veins or hypotension in response to nitroglycerin is also suggestive. Echocardiography or nuclear imaging can be diagnostic, but they are less readily available in the ED.

The most serious complication of right ventricular infarction is shock. The severity of the hemodynamic derangement in the setting of right ventricular infarction is related to the extent of right ventricular dysfunction, the interaction between the ventricles (the right and left ventricles share the interventricular septum), and the interaction between the pericardium and the right ventricle. Right ventricular infarction results in a reduction in right ventricular end-systolic pressure, left ventricular end-diastolic size, cardiac output, and aortic pressure as the right ventricle becomes more of a passive conduit to blood flow. Left ventricular contraction causes bulging of the interventricular septum into the right ventricle, with resultant ejection of blood into the pulmonary circulation. As a result, right ventricular infarction with concurrent left ventricular infarction has a particularly devastating effect on hemodynamic function. Fluid balance and maintenance of adequate preload are critical in the treatment of right ventricular infarction. Factors that reduce preload (volume depletion, diuretics, and nitrates) or decrease right atrial contraction (atrial infarction and loss of atrioventricular synchrony) and factors that increase right ventricular afterload (left ventricular failure) can lead to significant hemodynamic derangements.

Treatment of right ventricular infarction includes maintenance of preload, reduction of right ventricular afterload, and inotropic support of the ischemic right ventricle, in addition to early reperfusion. Patients with right ventricular infarction should not be treated with drugs, such as nitrates, that reduce preload. **In the setting of right ventricular infarction, nitrates often will reduce cardiac output and produce hypotension**. Instead, patients with marginal preload or hypotension should be treated with volume loading (normal saline). The increased preload will improve right ventricular cardiac output. **If cardiac output is not improved after 1 to 2 L of normal saline, begin inotropic support**.

High-degree heart block is very common in patients with right ventricular infarction. The loss of right atrial contraction can greatly compromise right ventricular cardiac output. Restitution of atrioventricular synchrony is important. Patients who do not attain hemodynamic improvement after placement of a ventricular pacer may still improve with atrioventricular sequential pacing.

When right ventricular infarction is accompanied by left ventricular dysfunction, the use of nitroprusside to reduce afterload or intra-aortic balloon counterpulsation may be of benefit. Reduction in left ventricular afterload may help passive movement of blood through the right ventricle.

OTHER COMPLICATIONS

Other complications of AMI that occur but are not usually seen in the ED include left ventricular thrombus formation, arterial embolization, venous thrombosis, pulmonary embolism, postinfarction angina, and infarct extension. With the more rapid discharge of uncomplicated AMI patients, keep these possibilities in mind for patients who return to the ED shortly after hospital discharge.

RECURRENT OR REFRACTORY ISCHEMIA

Patients unresponsive to medical management with continued ischemia require an individualized approach to treatment. Refractory ischemia is investigated with coronary catheterization. Treat patients with ACS after stent placement with antithrombin and antiplatelet therapy, and these patients may require urgent coronary catheterization.

In situations where emergent catheterization is not available or the patient is hemodynamically unstable, an **intra-aortic balloon pump** may be used. Intra-aortic balloon counterpulsation delivers phased pulsations synchronized to the ECG, so that balloon inflation will occur at the time of aortic valve closure and deflation occurs just before onset of systole. The augmented coronary perfusion pressure during diastole enhances coronary blood flow. Balloon deflation during systole allows the left ventricle to eject blood against a lower resistance. The net effect of intra-aortic balloon counterpulsation is an increase in cardiac output, reduction in systolic arterial pressure, increase in diastolic arterial pressure, little change in mean arterial pressure, and reduction in heart rate. The reduction in left ventricular afterload leads to reduced myocardial O_2 consumption, thereby decreasing the amount of myocardial ischemia. Intra-aortic balloon counterpulsation is recommended for patients with ACS who are refractory to aggressive medical management

or are hemodynamically unstable as a means to bridge a patient's stability en route to definitive treatment.

SPECIAL POPULATIONS

POSTPROCEDURE CHEST PAIN

Patients who present with symptoms of an ACS shortly after PCIs, such as angioplasty or stent placement, should be assumed to have had abrupt vessel closure, until proven otherwise. Subacute thrombotic occlusion after stent placement occurs in approximately 4% of patients 2 to 14 days after procedure. **Bare metal stents are more likely to restenose in the short term. Drug-eluting stents are more likely to present with late stent thrombosis after cessation of daily clopidogrel, 9 to 12 months later**. Treat patients aggressively for an ACS, and obtain emergent cardiology consultation. Patients with chest pain syndromes after coronary artery bypass grafting also may have abrupt vessel closure. However, symptoms of recurrent ischemia can be confused with post-AMI pericarditis, as discussed earlier.

COCAINE- AND AMPHETAMINE-INDUCED ACUTE CORONARY SYNDROME

AMI occurs in approximately 6% of patients who present to the ED with chest pain after cocaine use. Cocaine-associated myocardial infarction occurs in younger patients, but over the past two decades, the average age has increased from 38 years[71] to 50 years,[72] highlighting the increased use of cocaine in middle-age patients. The sensitivity, specificity, positive predictive value, and negative predictive value of the ECG to identify cocaine-associated MI are 36%, 89.9%, 17.9%, and 95.8%, respectively.[73] Cardiac troponin is the most sensitive biomarker for cocaine-associated myocardial infarction. Aspirin, nitrates, and benzodiazepines are the mainstays of therapy for initial stabilization; β-blockers are contraindicated in the first 24 hours.[73] Patients with cocaine-associated STEMI are best managed with PCI.[71] Antithrombotic and antiplatelet therapy may be given according to current guidelines for non–cocaine-related ACS.

There are fewer cases of amphetamine-induced myocardial infarction to guide therapy and no care guidelines. The initial ECG may be unreliable in the setting of methamphetamine-related ACS, with false-positive ST-segment elevation prompting unneeded thrombolytic therapy. In one case series of 33 patients admitted for chest pain who were methamphetamine positive, nine (25%) were diagnosed with ACS (positive markers or required revascularization). Three patients (8%; two ACS and one non-ACS) suffered cardiac complications (ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia, respectively). Only one patient had Q-wave myocardial infarction treated with PCI. Medical management was the mainstay of therapy.

ACUTE MEDICAL DISORDERS ASSOCIATED WITH ACUTE CORONARY SYNDROME

Those with GI bleeding,[72] stroke,[73,74] and severe infection have a higher frequency of ACS[75]; even those with disorders considered otherwise benign, such as acute anxiety or emotional upset, have a higher frequency of myocardial infarction.[76] In the case of stroke and GI bleeding, the primary disease process (which came first) is sometimes unclear or underdiagnosed until late in the patient's course. In a group of patients admitted to the intensive care unit for GI bleeding, approximately 13% sustained myocardial infarction; however, this did not affect mortality in this intensive care unit population. A case-control study found increased risk of death in patients with GI bleeding meeting criteria for myocardial infarction when compared with those with negative markers (33% vs. 8%).[72] In general, treatment of the GI bleed takes priority, which precludes the major treatments for AMI. **For patients with acute ischemic stroke, 17% have positive troponin assessment, which is associated with 3.2 relative risk of death compared with patients with normal troponin**. The risk of stroke complicating the course of AMI has been formerly reported as 2.4% to 3.5%,[77] but with improved treatments for AMI, the risk has dropped to 0.6% to 1.8%. Hospital mortality in patients with stroke after AMI is high (17% to 27%). ECG abnormalities are common in patients with subarachnoid hemorrhage, and elevated troponin levels occur in 28%, with over half of these demonstrating transient left ventricular dysfunction. However, simultaneous STEMI is not common with a subarachnoid hemorrhage. Approximately 50% of patients with severe sepsis and septic shock have impairment of left ventricular systolic function, frequently with an elevated troponin level.[76] AMI occurs in 5.3% of patients hospitalized with community-acquired pneumonia, with the risk increasing to 15% in those with severe pneumonia.[78]

For all patients with dual or multiple acute medical issues, individualize management and weigh the risks of AMI guideline therapies. When indicated, use PCI over thrombolysis to identify the lesion and need for additional therapy.

AFTER HOURS AND WEEKEND PRESENTATIONS

The management of patients with ACS is time sensitive and intensive. Patients who present "after hours" and on weekends wait longer for interventions, with an adverse impact on outcome. Patients who present when the ED is busy with other ill patients (e.g., trauma patients), patients who present in settings with increased health system dysfunction and high levels of ED boarding, and patients who are not expeditiously transferred to an inpatient bed have worse outcomes.[79-81] Systems solutions to improve hospital flow for patients with ACS will help optimize the care of patients with ACS.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 50

Cardiogenic Shock

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INTRODUCTION AND EPIDEMIOLOGY

Cardiogenic shock results from decreased cardiac output, leading to inadequate tissue perfusion despite adequate circulating volume, and it carries an in-hospital mortality rate of 27% to 51%.[1,2] The true incidence is unknown because many patients die before hospital arrival. Cardiogenic shock occurs in 4% to 8% of patients with ST-segment elevation myocardial infarction (STEMI) and is the leading cause of in-hospital death in patients with acute myocardial infarction (AMI).[3-6] Cardiogenic shock occurs less frequently (2.5%) in those with non–ST-segment elevation myocardial infarction (NSTEMI).[7,8] Only approximately 10% of AMI patients who will develop cardiogenic shock have it at initial ED presentation, with the median time of onset after arrival being 6 hours.[9] This highlights the therapeutic opportunity possible with rapid treatment of myocardial ischemia. Over the past decade, a strategy of early revascularization by percutaneous coronary intervention or coronary artery bypass surgery has improved the survival of cardiogenic shock patients with acute ischemia compared to medical therapy alone.[3,10-13] As more risk factors for cardiogenic shock exist (**Table 50-1**), a greater amount of vulnerable myocardium and greater likelihood of cardiogenic shock also exist.

PATHOPHYSIOLOGY

The most common cause of cardiogenic shock is extensive myocardial infarction that depresses myocardial contractility. Additional causes are listed in **Table 50-2**. Regardless of the precipitating cause, cardiogenic shock is primarily "pump failure," which results in reduced cardiac output.[14] The systolic blood pressure drops due to poor cardiac output, causing hypoperfusion of vital organs. Without a rise in systemic

TABLE 50-1 Risk Factors for Cardiogenic Shock

Elderly

Female

Acute or prior ischemic event associated with the following

- Impaired ejection fraction
- Extensive infarct (evidence of large myocellular leak)
- Proximal left anterior descending coronary artery occlusion
- Anterior myocardial infarction
- Multivessel coronary artery disease

Prior medical history

- Previous myocardial infarction
- Congestive heart failure
- Diabetes

vascular resistance, the diastolic blood pressure drops, resulting in coronary artery hypoperfusion. This creates a cycle of worsening myocardial ischemia and pump dysfunction and eventual decompensation.

Both increased afterload and systolic/diastolic dysfunction of the heart can lead to increased left ventricular end-diastolic pressures (LVEDP) and pulmonary edema. Pulmonary edema leads to hypoxia and hypoxemia, which worsens ischemia and causes progressive cardiac dysfunction.

Decreased cardiac output due to decreased stroke volume leads to poor peripheral perfusion and vasoconstriction. Augmenting peripheral vasoconstriction may improve coronary artery and peripheral perfusion, but the resultant increased afterload can decrease cardiac output.

In addition, a cardiogenic shock triggers a systemic inflammatory response, with release of nitric oxide and other mediators, that has a negative inotropic effect and creates systemic vasodilation.[15-19] The inflammatory response depresses pump function, dilates the peripheral vasculature, and increases the risk of death.[20,21] Studies looking at directed interventions to blunt the inflammatory response, complement cascade, and vasodilation have to date failed to decrease mortality.[17,22]

The classic and most common picture of acute cardiogenic shock is due to left ventricular (LV) infarction and is characterized by the physiologic triad of low cardiac index, high systemic vascular resistance indices, and increased pulmonary capillary wedge pressure, with peripheral vasoconstriction and pulmonary edema.[23,24] When right ventricular (RV) infarction is the cause of cardiogenic shock, the RV filling pressures increase, and forward flow to the LV is decreased, resulting in lowered cardiac output. Euvolemic cardiogenic shock occurs subacutely in patients with heart failure; normotensive cardiogenic shock is rare.

TABLE 50-2 Causes of Cardiogenic Shock

Mechanical complications

- Acute mitral regurgitation secondary to papillary muscle dysfunction or chordal rupture
- Ventricular septal defect
- Free wall rupture
- Right ventricular infarction
- Acute aortic insufficiency (aortic dissection)

Severe depression of cardiac contractility

- Acute myocardial infarction
- Sepsis
- Myocarditis
- Myocardial contusion
- Cardiomyopathy
- Medication toxicity (e.g., β-blocker overdose, calcium channel–blocker overdose)
- Unstable dysrhythmia

Mechanical obstruction to forward blood flow

- Aortic stenosis
- Hypertrophic cardiomyopathy
- Mitral stenosis
- Left atrial myxoma
- Pericardial tamponade

TABLE 50-3 Shock With Pump Failure: A Limited Differential Diagnosis

Cardiogenic Shock (see Table 50-2)

Acute pulmonary decompensation

- Chronic obstructive pulmonary disease exacerbation
- Cor pulmonale
- Massive pulmonary embolism

Distributive shock

- Sepsis
- Anaphylaxis
- Neurogenic shock (spinal cord injury)

Hypovolemic shock

- Hemorrhage
- Severe dehydration

Dissociative shock

- Toxins/drugs of abuse (cyanide)

CLINICAL FEATURES

HISTORY

Patients commonly have shortness of breath, chest pain, or weakness. Be sure to ask about and consider other causes of shock or pump failure (**Table 50-3**). Ask about a history of preexisting valvular disease, congestive heart failure, reduced ejection fraction (EF), recent illnesses, hypercoagulable states, substance abuse, and other risk factors (Table 50-1).

PHYSICAL EXAMINATION

Cardiogenic shock results in hypoperfusion due to a low cardiac index; this is not always accompanied by hypotension.[9] Systolic blood pressure is usually <90 mm Hg, although it can be higher with preexisting hypertension or peripheral vasoconstriction response. A pulse pressure <20 mm Hg is another finding if systemic resistance has not plummeted, and sinus tachycardia is common unless the patient is on medications that block a tachycardic response. Until respiratory fatigue sets in, tachypnea is common. If there is LV compromise, chest examination demonstrates rales from pulmonary edema. Patients are usually pale or cyanotic and may have cool skin, mottled extremities, and/or other signs of hypoperfusion. Diaphoresis indicates activation of the sympathetic nervous system. Cerebral hypoperfusion may result in altered mental status, and renal hypoperfusion often creates low urine output.

In isolated RV infarction, the lungs are spared and venous congestion occurs, presenting as increased jugular venous pressure, a rise in jugular venous pressure with inspiration (Kussmaul sign) or compression of the liver (hepatojugular reflux), an enlarged liver, peripheral edema, and a third heart sound (S_3) originating from the RV.

About 10% of cardiogenic shock after AMI is caused by mechanical complications.[23] A new murmur may be the only physical exam finding of mechanical catastrophe; carefully seek any loud or new systolic murmurs. **Acute mitral regurgitation,** characterized by a soft holosystolic murmur at the apex radiating to the axilla, can occur from chordae tendineae rupture or papillary muscle dysfunction. An **acute ventral septal defect** is associated with a new loud holosystolic left parasternal murmur, often with a palpable thrill, that decreases in intensity as the intraventricular pressures equalize. Suspect **acute aortic insufficiency** when you find a soft diastolic murmur and a softer S_1 sound.

DIAGNOSIS

Shock exists whenever there is evidence of tissue hypoperfusion (i.e., end-organ dysfunction/damage and a systolic blood pressure usually <90 mm Hg or mean arterial pressure <65 mm Hg). To identify the heart

Evaluation:

1. Physical exam specifically for
   a. Rales
   b. Jugular venous distention/hepatojugular reflex/edema
   c. Murmurs
2. ECG
   a. Rule out STEMI
   b. Look for ischemic changes
3. Echocardiogram
   a. Ejection fraction
   b. Wall motion abnormality
   c. Dilated RV
   d. Pericardial fluid
   e. Valvular dysfunction
   f. Aortic root <3 cm
   g. Volume status of Inferior vena cava
   h. Lungs for B-lines

Treatment (based on cause):

If ECG shows STEMI: Emergent revascularization in cardiac catheterization lab
If valvular failure, ventricular rupture, or aortic dissection: Emergent operative management
If pulmonary embolism: Thrombolytics

Treatment of Hypotension (SBP <90 mm Hg):

1. If no evidence of pulmonary congestion:
   a. Attempt fluid boluses of 250–500 mL and reassess.
2. If pulmonary congestion is present or develops:
   a. If blood pressure is <90 mm Hg, combine dobutamine with dopamine or norepinephrine.
      i. If on β-blockers, administer milrinone as inotrope.
   b. If blood pressure is <70 mm Hg, administer norepinephrine.

FIGURE 50-1. Approach to patient with cardiogenic shock. RV = right ventricle; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

as the cause of the shock state, rapidly assess the heart with clinical exam (discussed earlier), ECG, and echocardiogram (**Figure 50-1**).

LABORATORY TESTING

There are no laboratory markers specific for the diagnosis. Cardiac biomarkers (primarily troponin) may not be elevated upon initial presentation from an acute myocardial ischemic triggering event. A CBC identifies anemia, which can contribute to cardiac ischemia. Hypoperfusion may result in an elevated serum lactate, and serum electrolytes and renal and hepatic studies can identify end-organ dysfunction.

Serum B-type natriuretic peptide is an indicator of LV dysfunction but does not identify the cause. Because of its high negative predictive value, a normal B-type natriuretic peptide level (<100 picograms/mL) eliminates cardiogenic shock as the cause of hypoperfusion unless very early after onset or with isolated right heart failure. Conversely, an elevated B-type natriuretic peptide does not diagnose cardiogenic shock.[21,25]

Blood gas measurements help identify those at risk of acute respiratory failure/carbon dioxide retention, quantify the presence and severity of acidosis, and determine the contribution of metabolic or respiratory components to acidosis.

IMAGING AND ANCILLARY STUDIES

Electrocardiogram The ECG may identify ischemia, STEMI, or rhythm abnormalities and give evidence of cardiac response to identify electrolytic abnormalities (e.g., hypokalemia) or drug toxicity (e.g., digoxin). Obtain right-sided ECGs to identify RV infarction accompanying inferior infarction, looking for ST elevation in lead V_1 and ST-segment elevation in leads V_3R to V_6R; this finding elevates the short-term risk of death[26,27] (**Figure 50-2**).

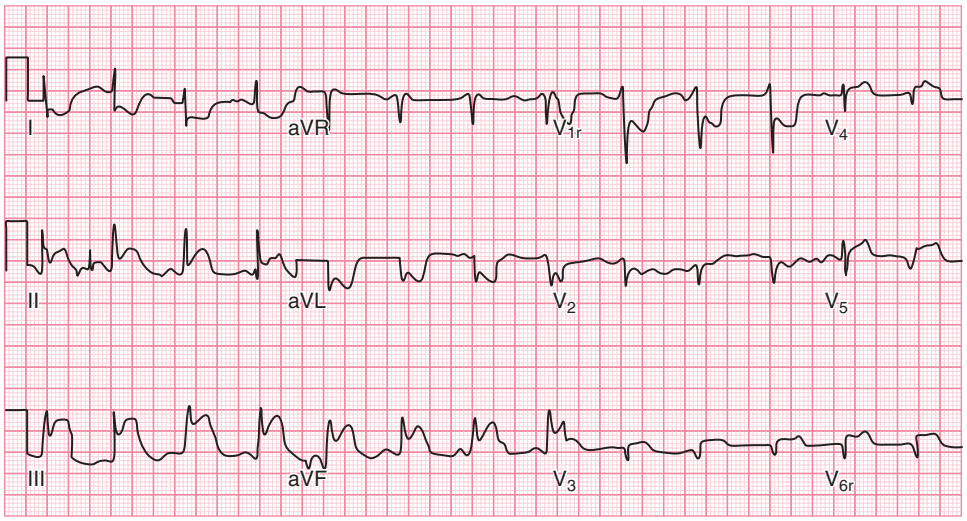

FIGURE 50-2. Right-sided leads demonstrating right ventricular infarction associated with inferior wall myocardial infarction. Right-sided leads have replaced the normal left-sided V leads. In this example, the ST-segment elevation is prominent in leads $VR_{3\text{-}6}$.

Chest Radiography Obtain a portable chest radiograph, seeking pulmonary congestion or edema, alveolar infiltrates, and pleural effusion. Such findings may lag by hours, so their absence does not exclude cardiogenic shock. Preexisting disease can confound the radiographic appearance, with pulmonary edema difficult to detect in patients with severe chronic obstructive lung disease or interstitial lung disease. Cardiomegaly is the result of long-standing myocardial remodeling, and its presence may not explain the acute symptoms. The chest radiograph can suggest alternative or confounding diagnoses, such as pneumonia, pneumothorax, aortic dissection, or progressive pericardial effusion.

Bedside Point of Care Ultrasound POCUS can help exclude alternative etiologies of shock, identify mechanical concerns, and guide therapy. Assessment should include a volume status evaluation of the inferior vena cava and estimation of right atrial pressure. A subcostal four-chamber view visualizes pericardial effusion and cardiac tamponade. When tamponade exists, there is a pericardial effusion, dilation of the inferior vena cava, and diastolic collapse of the RV with systolic collapse of the right atrium. When cardiac rupture occurs, there may be a visible clot in the pericardial space. Subcostal, parasternal, and apical views together can help estimate EF and cardiac contractility. An aortic root >3 cm is concerning for ascending aortic dissection, especially when associated with a pericardial effusion. Assess the valves for appropriate motion and flow characteristics, specifically the mitral valve. Apical four-chamber views are helpful for evaluating chamber size. In cases of acute right heart failure due to ischemia, the RV will be dilated and the LV will appear to be smaller than expected due to low filling pressures. In left heart failure, there will be dilation of the LV secondary to decreased cardiac output and increased filling pressure.[28] On lung assessment, B-lines (three B-lines in two bilateral lung zones) are the US equivalent of the Kerley B-lines found on chest radiograph and are commonly present with interstitial edema.[29] The line will traverse the entire US screen in a vertical manner as well as cross any present A-lines.[29]

Bedside echocardiography is an adjunct, not replacement, for emergent formal transthoracic echocardiography. Formal echocardiography uses color and spectral Doppler to identify mechanical complications and to characterize the nature of cardiac impairment. Echocardiography detects regional wall motion abnormalities and a lack of compensatory hyperkinesis in uninvolved cardiac segments. Loss of RV contractility, RV dilatation, and normal estimated pulmonary pressures occur more commonly with RV infarction.

Color flow Doppler transthoracic echocardiography identifies mechanical causes of cardiogenic shock, such as acute mitral regurgitation or ventricular septal defect. Echocardiography detects other causes of decreased cardiac output, notably pulmonary embolism. Acute RV dilatation, tricuspid insufficiency, paradoxical systolic septal motion, and high estimated pulmonary artery and RV pressures suggest pulmonary hypertension from an acute pulmonary embolus.

Mechanical Catastrophe Diagnosis When suspecting a mechanical catastrophe, consult a cardiothoracic surgeon immediately while obtaining a bedside echocardiogram. In the case of **myocardial free wall rupture**, death is likely unless a pseudoaneurysm forms, which may present as an acute pericardial effusion on echocardiography. An acute **ventricular septal defect** appears on color Doppler echocardiography or right heart catheterization by showing oxygen saturation flow or step-up from the right atrium to the RV.[28] **Acute mitral regurgitation**, from papillary muscle rupture or dysfunction, can complicate AMI.

Hemodynamic Monitoring Patients in cardiogenic shock require continuous monitoring of blood pressure and other hemodynamic measures. Typically, patients with cardiogenic shock have a low cardiac index (<2.2 L/min/m^2) and elevated LVEDP (pulmonary artery occlusion pressure >15 mm Hg).[9,12,14] Cardiac output measurement via pulmonary artery catheterization provides continuous measurements of pulmonary artery occlusion pressure, vascular resistances, ventricular work, and other hemodynamic parameters.[30,31] Although numerous trials have assessed the value of pulmonary artery catherization in intensive care patients, most have demonstrated no harm, but also no benefit.[31] Noninvasive blood pressure measurements may underestimate systolic pressure by >30 mm Hg; however, mean arterial pressure varies by only 1 to 2 mm Hg whether central or peripheral.[32] Arterial blood pressure monitoring allows accurate assessment of cardiovascular instability during resuscitation and is particularly useful when giving vasoactive medications. Central venous pressure, an indirect indicator of central blood volume, can aid assessment of global volume status, but isolated values outside extremes to guide resuscitation in critically ill patients are less helpful (see "Hemodynamic Monitoring").[33]

ED TREATMENT AND STABILIZATION

The most important definitive intervention for acute ischemia-related cardiogenic shock is emergent revascularization.[8,11,14,15,23,34] In anticipation of the need for revascularization, EMS should direct any suspected cardiogenic shock patient to a facility that has 24-hour full-service emergency cardiac revascularization capability (including a cardiac bypass team).[35]

Initial ED management focuses on airway stability and improving myocardial pump function to maintain end-organ perfusion while arranging definitive care.

AIRWAY

Give supplemental oxygen to keep saturations >91%, and monitor closely for impending or acute respiratory failure that will require immediate mechanical ventilation. Noninvasive ventilation using continuous positive airway pressure, bilevel positive airway pressure, or high-flow nasal cannula can provide temporary airway support.

Endotracheal intubation is often necessary to maintain oxygenation and ventilation. However, **the change to positive-pressure ventilation may further decrease preload and cardiac output and worsen hypotension.** Be prepared to administer a fluid bolus in the absence of severe pulmonary congestion and in the presence of RV infarction, while also considering the use of push dose pressors (small discrete doses of vasopressors) to mitigate the potential hypotensive effects of intubation.[36] Keep end-expiratory pressures and tidal volumes as low as possible (see Chapter 29B, "Mechanical Ventilation") to avoid impairing preload. Recognize that patients may need additional vasopressor support after positive-pressure ventilation.

STABILIZATION

Continuous cardiac monitoring and IV access are necessary. Correct any hypoxemia, hypovolemia, rhythm disturbances, electrolyte abnormalities, and acid-base alterations rapidly. Although not needed immediately, many benefit from a urinary drainage catheter to follow renal output.

In AMI, give aspirin early (if not already taking long term) unless there is an absolute contraindication.[37] If blood pressure is >90 mm Hg systolic, you may use IV nitroglycerin. **Do not use α-blockers in patients with myocardial infarction in cardiogenic shock or who are at risk for cardiogenic shock** (Table 50-1).[37] Withhold angiotensin-converting enzyme inhibitors or other vasodilators.

HYPOTENSION

Guide initial therapy by the clinical findings. Give crystalloid fluid boluses (250 to 500 mL, and repeat after assessing benefit or harm) if pulmonary congestion is absent or for an RV infarct with hypotension. If there is no improvement with the fluid bolus or if pulmonary congestion develops, use vasopressors (for hypotension) or inotropes (for congestion without profound hypotension) (**Table 50-4**).

Inotropes do not change outcome alone but can temporize while ED personnel arrange interventions to restore coronary artery perfusion and LV function.[38] In the absence of profound hypotension, **dobutamine** is a mainstay of initial pharmacologic treatment. Dobutamine increases cardiac contractility and is most effective if the systolic blood pressure is ≥90 mm Hg. Avoid the use of dobutamine alone when the systolic

TABLE 50-4 Inotropic Medications Used in Cardiogenic Shock

Drug	Dose	Comments
Dobutamine	2–5 micrograms/kg/min, titrated up to 20 micrograms/kg/min	Inotrope and potential vasodilator; lowers blood pressure; give as individual agent as long as systolic blood pressure (SBP) ≥90 mm Hg. Can use with dopamine or norepinephrine. Avoid if on β-blocker.
Dopamine	3–5 micrograms/kg/min, titrated up to 20–50 micrograms/kg/min as needed	Inotrope and vasoconstrictor; increases left ventricular end-diastolic pressure and causes tachycardia. Can use with dobutamine. Increased risk of dysrhythmia.
Norepinephrine	2 micrograms/min, titrate to response	Vasoconstrictor and inotrope; preferred as a single agent over dopamine if SBP <70 mm Hg. Can use combined with dobutamine.
Epinephrine	0.1–0.5 microgram/kg/min	Inotrope and vasoconstrictor; second-tier choice because it causes acidosis and dysrhythmias.
Milrinone	0.5 microgram/kg/min	Inotrope and vasodilator; lowers blood pressure. Second tier to dobutamine. Use if on β-blocker.

blood pressure is <90 mm Hg because of its vasodilatory potential. Often, a vasoconstrictor added to dobutamine is helpful, but only when the blood pressure allows this dual therapy. **Dopamine** is a vasopressor with some inotropic effect, but it may increase cardiac work by increasing heart rate and may also increase LVEDP by its β-agonist effect. Combination therapy with a vasopressor (dopamine or norepinephrine) and an inotrope (dobutamine) may be more effective than either agent alone. **Norepinephrine,** when combined with dobutamine, has a more profound effect on peripheral vasoconstriction than dopamine alone or when combined with dobutamine. If the systolic blood pressure is <70 mm Hg, most prefer norepinephrine rather than dobutamine.[39] If shock persists despite use of these agents, consider an intra-aortic balloon pump or other assist device.[40]

Epinephrine is associated with more systemic acidosis, tachycardia, and dysrhythmias compared to the combination of norepinephrine and dobutamine.[38,39,41] Patients on β-blocker therapy may have an attenuated response to dobutamine, making milrinone a better choice. **Milrinone** (a selective phosphodiesterase-3 inhibitor) **can be substituted for the catecholamine if dobutamine is ineffective.** Pure vasoconstrictors and α_1-adrenergic receptor agonists, such as phenylephrine (often a push dose drug), are contraindicated because they increase cardiac afterload without augmenting cardiac contractility.

DEFINITIVE MANAGEMENT

EARLY REVASCULARIZATION

In ischemic cardiogenic shock, early revascularization by percutaneous coronary intervention or coronary artery bypass grafting is the treatment of choice.[42,43] The greatest short-term benefit is reported in patients <75 years old, those without previous myocardial infarction, and those treated within 6 hours of symptom onset. Survival is higher in those receiving early revascularization compared with medical stabilization, even in the elderly.[44] Current guidelines do not have an age cutoff for percutaneous coronary intervention.[42,43,45,46]

THROMBOLYTIC THERAPY

Emergency coronary intervention in the catheterization laboratory or operating suite is the preferred definitive treatment for cardiogenic shock.[42-45] Thrombolytic therapy is not as effective in establishing reperfusion in AMI with cardiogenic shock as it is in uncomplicated AMI. Survival from cardiogenic shock is highest with emergency coronary intervention, followed by intra-aortic balloon pump combined with thrombolytic therapy; thrombolytic therapy alone is least effective in reducing mortality.[44,46]

Rescue percutaneous coronary intervention does not convey the same mortality benefit as primary percutaneous coronary intervention for these patients.[47,48] If no other definitive treatment modalities for cardiogenic shock are available, if the hospital does not have a catheterization laboratory, or if there is prolonged transport time for coronary intervention, thrombolytics should be considered, but do not delay access to percutaneous coronary intervention.[14,15,48]

INTRA-AORTIC BALLOON PUMP COUNTERPULSATION

Intra-aortic balloon pump counterpulsation provides hemodynamic support by decreasing afterload (which lowers myocardial oxygen consumption) and increasing diastolic blood pressure (which augments coronary perfusion).[40,49] Intra-aortic balloon pump improves survival after thrombolytic therapy by augmenting diastolic perfusion pressure and unloading the LV.[50,51] Outside of those receiving reperfusion, the long-term benefits of intra-aortic balloon pump use are not clear.[50-53]

In hospitals without direct angioplasty capability, stabilization with intra-aortic balloon pump and thrombolysis followed by transfer to a tertiary care facility may be the best management option in severe cardiogenic shock.[50,53,54]

VENTRICULAR ASSIST DEVICES

When cardiogenic shock is refractory to medical therapy, engage experts to assess for percutaneous mechanical circulatory support (cardiogenic shock) candidacy, which usually consists of a team of intensivists, cardiologists, and cardiothoracic surgeons. Acute cardiogenic shock devices range from intra-aortic balloon pumps to percutaneous ventricular assist devices to extracorporeal membrane oxygenation, and can aid, maintain, or restore adequate tissue perfusion. Current percutaneous ventricular assist devices include nonpulsatile (e.g., Impella®, TandemHeart®) and pulsatile versions (e.g., iVAC®, HeartMate®) designed to provide LV unloading.[55-59] Although the degree of hemodynamic support varies, they can effectively serve as a bridge to long-term devices, such as an LV assist device and/or heart transplantation. (See Video: Left Ventricular Assist Device.)

Current LV assist devices are continuous-flow pumps with noncontact bearings (magnetic levitation) to enhance rotation without friction or wear and decrease pump thrombosis and stroke. Increasingly, case studies and small cohort studies have described successful ventricular assist device support and weaning of patients suffering from cardiogenic shock in the setting of acute infarction.[56-60] However, despite current device improvements, there are no data demonstrating a mortality benefit for LV assist devices compared with intra-aortic balloon pumps in patients with cardiogenic shock refractory to inotropic and vasopressor support; either is a stabilizing bridge to potential transplantation.[58-61] Complications, including pump thrombosis, stroke, bleeding events, and driveline infection, remain a concern with these interventions.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation can provide almost total circulatory support for a failing heart. Extracorporeal membrane oxygenation usually follows emergency situations when maximum medical therapy has failed. The Survival After Veno-arterial Extracorporeal Membrane Oxygenation score can predict survival in patients receiving extracorporeal membrane oxygenation for refractory cardiogenic shock[62] (www.save-score.com). In the best cases, extracorporeal membrane oxygenation provides support until percutaneous coronary intervention or

until the heart begins to recover after intervention. In other cases, it can provide a bridge to decision for transplantation or permanent LV assist device placement.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 51

Low-Probability Acute Coronary Syndrome

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INTRODUCTION AND EPIDEMIOLOGY

Of ED patients with undifferentiated chest pain, 7% will have ECG findings consistent with acute ischemia or infarction, and 6% to 10% of those in whom cardiac markers are ordered will have initially positive results.[1] The remaining patients who do not have diagnostic ECG changes or initially positive cardiac marker results have *low-probability* or *possible acute coronary syndrome* (ACS; either infarction or ischemia including unstable angina pectoris). The evaluation of those with possible ACS costs approximately $10 billion to $12 billion each year in the United States.[2]

Of all patients with *possible ACS*, 5% to 15% ultimately prove to have ACS.[3] The rate of discharge from the ED for patients with ACS remains approximately 4%. Patients with ACS discharged home from the ED have worse outcomes and higher mortality compared with patients who are initially hospitalized. The clinical data readily available to the emergency physician, such as historical features, examination findings, and ECG results, cannot exclude ACS among most patients, because 3% to 6% of patients thought to have noncardiac chest pain or a clear-cut alternative diagnosis will have a short-term adverse cardiac event.[4,5] Therefore, most patients with *possible* ACS are observed or admitted for further testing.

PATHOPHYSIOLOGY

ACS is a constellation of signs and symptoms resulting from an imbalance of myocardial oxygen supply and demand. There are three general ACS classifications: unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. A detailed discussion regarding these diagnoses is provided in Chapter 49, "Acute Coronary Syndromes."

Patients presenting soon after infarction may have normal biomarker results and initially be categorized as having *possible ACS*. However, patients with evolving myocardial infarction generally have other high-risk features of ACS such as ST-segment depression, and they develop positive injury biomarker patterns over time.[6,7]

CLINICAL FEATURES

HISTORY AND COMORBIDITIES

The history is the base tool to assess patients with possible ACS, but it alone cannot exclude the condition. Key data are symptom quality, location, duration, severity, associated symptoms, precipitating and relieving factors, and similarity to prior episodes known to be from ACS. Consider other noncardiac but life-threatening causes of chest pain (see Chapter 48, "Chest Pain").

Among patients with possible ACS, historical data allow patients to be placed into categories of low risk, probable low risk, probable high risk, and high risk. **However, even patients with low-risk features or in a low-risk category have a residual risk of ACS.**[8] Lowest-risk features include pleuritic, positional, reproducible, or sharp/stabbing pain. Another low-risk feature is pain that is not exertional or located in a small inframammary area. Higher-risk features include chest pressure (positive likelihood ratio [LR+] 1.3), pain similar to or worse than prior cardiac pain (LR+ 1.8), and associated nausea/vomiting or diaphoresis (LR+ 1.9 and 2.0, respectively). The highest-risk features include radiation to the right arm or shoulder (LR+ 4.7), left arm (LR+ 2.3), or both arms or shoulders (LR+ 4.1), and exertional chest pain (LR+ 2.4).

Traditional cardiac risk factors, such as hypertension, diabetes mellitus, tobacco use, family history of coronary artery disease (CAD) at an early age, and hypercholesterolemia, are modestly predictive of the presence of CAD in asymptomatic patients; additionally, in decision making during acute episodes, **cardiac risk factors are poor predictors of cardiac risk for myocardial infarction or other ACS.**[9] CAD is rare in patients <30 years old, and when present, it is usually accompanied by other risk factors.

Although a true alternative diagnosis decreases the likelihood of ACS, many patients with ACS are mistakenly diagnosed with gastric reflux or musculoskeletal pain.[5] Clinical response to treatment with antacids (18% to 45% of ACS patients have relief of pain with antacids), viscous lidocaine, or NSAIDs cannot exclude ACS. Lack of pain relief with nitroglycerin is similarly unreliable because 65% of patients with an ACS do not fully respond.

Prior cardiac testing (previous ECG tracings, echocardiograms, cardiac catheterization reports, and stress testing reports) aids the ED evaluation. ECG changes offer strong bedside evidence of new disease. Recent cardiac catheterization reports are especially useful, because a truly negative (defined as no luminal irregularities) result is associated with a very low incidence of subsequent infarction or ACS in the next 2 years. Although a prior positive stress test increases the likelihood of a subsequent acute cardiac ischemic event,[10] a prior negative stress test provides little reassurance that a current chest pain event is from a benign cause. Patients with a recent negative evaluation for ACS that included objective cardiac testing (mostly stress testing) have a 6-month incidence of ACS as high as 14%. Furthermore, patients with a prior negative stress test have a similar incidence of ACS compared with those with no prior stress testing when presenting with chest pain to the ED.[11] Overall, previous stress test results add evidence but cannot confirm disease presence or absence.

PHYSICAL EXAMINATION

Usually, the exam in the low-risk or possible ACS patient seeks to find complications or alternative causes of the symptoms. When an alternate diagnosis is not clear, the physical examination cannot distinguish between those with and without ACS. High-risk ACS features on physical examination are uncommon but include signs of cardiac failure such as hypotension, diaphoresis, pulmonary rales, jugular venous distention, new mitral regurgitation, bradycardia, tachycardia, and an S_3 gallop.[12] Rhythm abnormalities, including either bradycardia (seen with ischemia, especially in the inferior myocardium) or infarction that has led to disturbance of the conduction system, or tachycardia (from pump failure, pain, or stress, or from an alternative diagnosis such as pulmonary embolism), can aid on occasion. Positional changes in the pain severity suggest pericarditis or another pleural-based syndrome as a cause of pain.

DIAGNOSIS

The diagnostic process is conceptually split into a primary and secondary evaluation (**Figure 51-1**).

PRIMARY EVALUATION

The goal during the primary evaluation is to distinguish patients with definite ACS from those with either possible ACS or those with symptoms that are definitely not from ACS. This involves gathering information from the history, physical examination, ECG, chest radiography, and medical record.

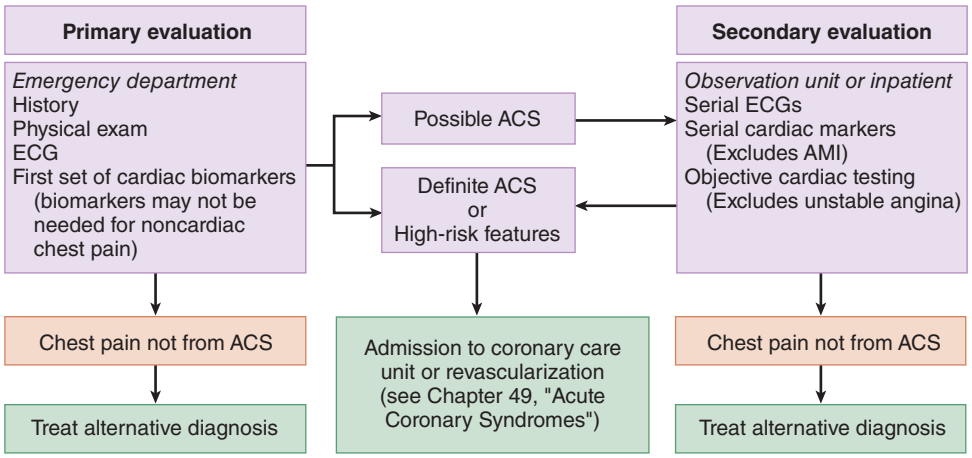

FIGURE 51-1. Evaluation process for patients with possible acute coronary syndrome (ACS). AMI = acute myocardial infarction.

ECG

For adult patients with chest pain in whom cardiac causes are possible, obtain a 12-lead ECG rapidly[12,13] and compare it to any previous tracings. Patients with ST-segment elevation, a new left bundle branch block, or ST-segment depression have an ACS and are treated as outlined in Chapter 49. Between 1% and 6% of ED chest pain patients with a normal ECG have non–ST-segment elevation myocardial infarction, and at least another 4% have unstable angina.[12] Obtaining follow-up ECG(s) in patients with ongoing or worsening symptoms helps detect changes diagnostic of ACS, or it can show reversal of previous ST-segment or T-wave changes thought to be old—both define *dynamic changes* and the high likelihood of ACS. In the setting of dynamic ECG changes, incidence of CAD is 84% with classic anginal symptoms and 8% with nonclassic anginal symptoms as assessed by coronary angiography.[14]

CHEST RADIOGRAPH

Chest radiography provides modest additional cardiovascular information, including cardiac silhouette size, pulmonary edema, and aortic contour. Additional causes of chest pain, such as pneumothorax, bony metastasis, rib fracture, and pneumonia, may be detected on chest radiography. Patients presenting with anterior chest pain have findings on chest radiography that influence management 14% of the time.

CARDIAC MARKERS

Laboratory testing during the primary evaluation focuses on two goals: detecting myocardial necrosis and excluding alternative causes of chest pain. Usual testing includes a CBC, serum electrolytes with renal function, and serum troponin. Other testing is guided by the history and physical examination.

RISK ASSESSMENT

The goal of early decision making is to determine if the patient actually belongs in the *possible ACS* cohort and is at high enough risk to warrant cardiac testing. All available data are used to create a composite picture for decision making. **Some posit that when the pretest probability of ACS is ≤2%, further testing is not indicated[15]; others have suggested a threshold of <1% to stop testing.[16] Detecting patients with a zero chance of any ACS in the presence of ACS-like symptoms is virtually impossible.**

Two clinical decision aids help in identifying a very-low-risk (<1%) cohort that does not require further cardiac testing and that is eligible for discharge: the **HEAR Score** (part of the **HEART Pathway**) and **Emergency Department Assessment of Chest Pain Score** (**Tables 51-1** and **51-2**). Current evidence suggests that patients at low risk by the HEART Pathway or with an Emergency Department Assessment of Chest Pain Score of <16 have a <1% risk for major adverse cardiac events within 30 to 60 days of presentation.[17-19]

The **HEAR Score** is used in conjunction with the **HEART Pathway** to appropriately categorize patients into low or high risk. Before calculating a HEAR Score, obtain an ECG and review the past medical history for known CAD. If there are any ischemic changes or the patient has known CAD, the patient is in a high-risk category and does not need a more formal score (**Figure 51-2**). If the ECG is nonischemic and there is no known CAD, calculate a HEAR Score to risk-stratify the patient. Patients in the low-risk category and no elevation of troponin(s) can be safely discharged home to follow up with their primary care physician within 30 days. Those categorized as high risk are bedded for testing to evaluate for ACS (Figure 51-2).

Both the HEART Pathway and Emergency Department Assessment of Chest Pain Score involve use a score and an initial and a 3-hour repeat troponin to increase the sensitivity for major adverse cardiac

TABLE 51-1 The HEAR Score

	Points
History	
Highly suspicious	2
Moderately suspicious	1
Slightly suspicious	0
ECG	
Significant ST-segment depression	2
Nonspecific repolarization abnormality	1
Normal	0
Age	
≥65	2
45–65	1
≤45	0
Risk factors*	
3 or more risk factors	2
1–2 risk factors	1
No risk factors	0
Total	

Low risk = 0–3, high risk ≥4.

*Risk factors include currently treated diabetes mellitus, current or recent (<90 days) smoker, diagnosed and/or treated hypertension, diagnosed hypercholesterolemia, family history of CAD, obesity (body mass index >30 kg/m^2), or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke, or peripheral arterial disease).

TABLE 51-2 Original Emergency Department Assessment of Chest Pain Score

Factor	Points
Age (years)	
18–45	2
46–50	4
51–55	6
55–60	8
61–65	10
66–70	12
71–75	14
76–80	16
81–85	18
86+	20
Known coronary artery disease (CAD)	4
Male sex	6
Typical symptoms	
Diaphoresis	3
Pain radiating to arm, shoulder, neck, or jaw	5
Atypical symptoms	
Pain with inspiration	Subtract 4 points
Pain reproduced by palpation	Subtract 6 points

Low risk, 0–15 points; non–low risk, ≥16 points. Known CAD includes previous myocardial infarction, coronary bypass surgery, or percutaneous coronary intervention *or* ≥3 cardiac risk factors in patients age ≤50 years. Risk factors include family history of CAD in first-degree relative age <55 years, hyperlipidemia, diabetes, smoking within past 90 days, and hypertension.

events. This raises sensitivity for major cardiac event detection to 100% while allowing for less index visit cardiac testing (CT or stress imaging). Low-risk patients with two negative biomarkers are able to be safely discharged; others get more testing. Newer high-sensitivity troponin assays may make this high-sensitivity approach achievable with one test or within a shorter sequential two-test interval.

DISPOSITION AFTER THE PRIMARY EVALUATION

After the primary evaluation, if the treating physician estimates that the probability of ACS is <1% to 2%, further testing for ACS is not warranted. After exclusion of other life-threatening causes of chest pain, these patients may be discharged home. These patients may benefit from primary care follow-up or care from another specialty physician depending on the suspected cause (e.g., GI, pulmonary).

Be wary of overconfidence in an alternative diagnosis; the rate of ACS is as high as 4% among patients with chest pain and a "clear-cut" noncardiac alternative diagnosis.[5] Reserve determinations of noncardiac chest pain to patients with a very low likelihood of coronary disease (<1%) and clear evidence of an alternative diagnosis or with atypical historical features. The rest of patients with ACS-consistent symptoms should have further testing.

SECONDARY EVALUATION

Base the diagnostic plan for patients with possible ACS after the primary evaluation on the clinical data and the available resources at each facility. This may include inpatient secondary testing, hospital-based observation testing, or ED-based observation testing. Once ACS is determined to be present or likely, admission and care by an internist or cardiologist are started.

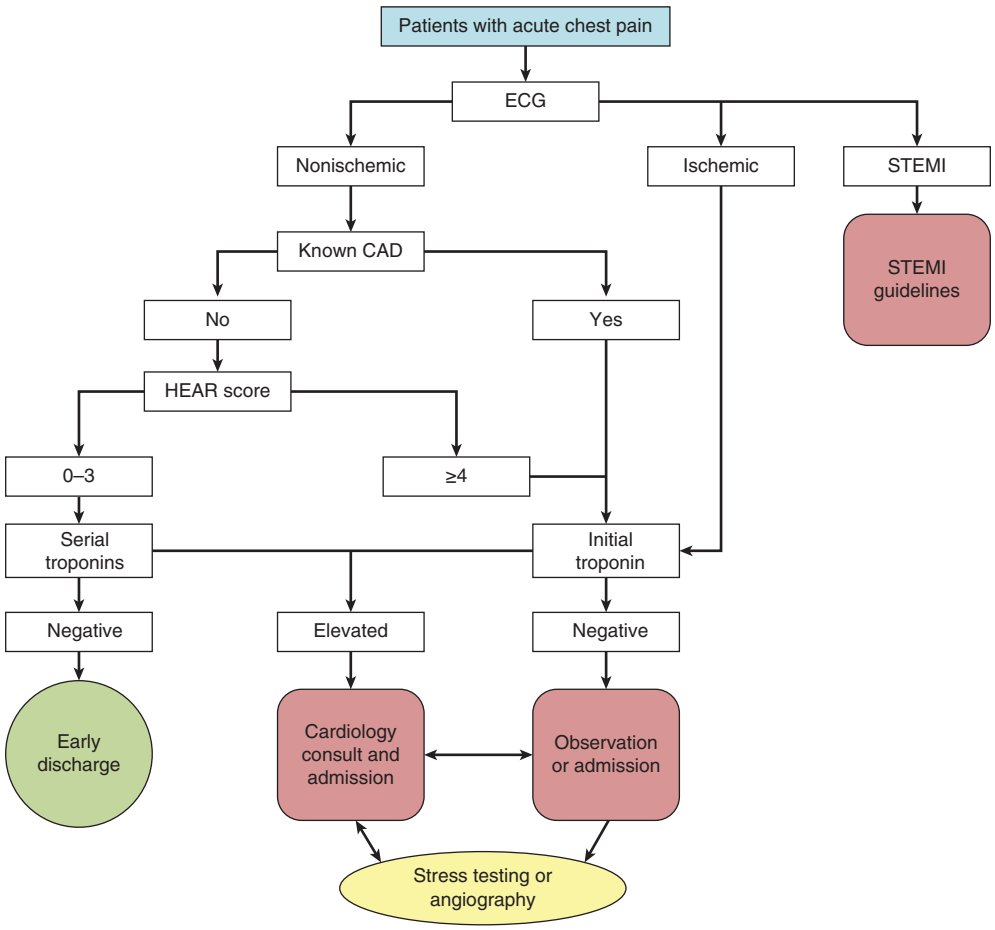

FIGURE 51-2. The HEART Pathway. CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction.

SERIAL MARKER APPROACH

Patients with possible ACS require serial serum markers to detect necrosis. The purpose of serial markers is twofold. First, evidence of myocardial necrosis confirms the diagnosis of ACS and should change treatment. Second, the presence of necrosis places the patient at higher risk for an adverse event during provocative cardiac testing. Many facilities have moved to an accelerated diagnostic protocol for serial marker timing, due to similar efficacy when compared to conventional longer protocols. Traditional testing protocols for patients with possible ACS involve obtaining serial troponins at presentation and after 6 hours of observation, whereas accelerated protocols repeat troponins at 2 or 3 hours. However, given the imperfect sensitivity and inability to exclude unstable angina, accelerated cardiac marker protocols are not the sole determination to exclude ACS but are used in combination with clinical decision aids and/or cardiac imaging. Again, the impact of higher-sensitivity troponin test is evolving and may alter the need for sequential tests to identify injury, even if subtle.

ADVANCED CARDIAC TESTING

Normal serial ECGs and myocardial marker measurements reduce the likelihood of acute myocardial infarction, but do not exclude unstable angina, which still puts the patient at high risk for a subsequent adverse cardiac event. Therefore, patients with possible ACS who are not identified as low risk using a validated decision aid should undergo cardiac testing to evaluate coronary anatomy, cardiac function, or both. Common modalities used include stress electrocardiography, stress echocardiography, resting and/or stress nuclear medicine testing, stress cardiac MRI, and CT coronary angiography (CTCA).

Advanced cardiac testing occurs after normal biomarkers are present and no clear ischemic ECG changes exist; this happens either as an inpatient or during an observation unit stay, with the latter being less expensive. Another option proffered by the American College of Cardiology/American Heart Association guidelines is to do the advanced testing as an outpatient and within 72 hours of ED discharge if patients are at low risk for ACS, are pain free without recurrent symptoms, have no evidence of ischemia on their ECG, and have normal serial cardiac markers over 6 to 8 hours.[12]

Low-risk patients may safely undergo immediate stress testing. One center performed over 3000 immediate exercise stress tests in low-risk patients who had at least one negative serum cardiac marker, noting no adverse events.[20]

ECG-BASED EXERCISE TREADMILL TESTING

The accuracy of ED stress testing is particularly difficult to quantify, because test sensitivity and specificity are influenced by characteristics of the population being tested. As the pretest probability of CAD increases, the likelihood of a false-negative test also increases. Conversely, when a population with a very low pretest probability of disease is tested, the likelihood of a false-positive result increases. **Based on current data, use diagnostic stress testing in patients with a low to moderate pretest probability of CAD; it is unlikely to be helpful in those at very low risk or at high risk (Figure 51-3).[21]**

ECG-based exercise treadmill testing is commonly used for patients without known coronary disease. Subjects exert on a treadmill until a predetermined percentage of predicted maximum heart rate or other end points are reached. A positive exercise test shows ≥1 mm of horizontal or downsloping ST-segment depression or elevation for at least 60 to 80 milliseconds after the end of the QRS complex; ST-segment elevation is not sought because it signals acute injury (not a desired outcome), although it is diagnostic.

Sensitivity of exercise treadmill testing depends on the risk and severity of disease of the patient population to which it is applied. A meta-analysis of 24,000 patient encounters identified the sensitivity and specificity for significant coronary disease as 68% and 77%, respectively.[21] Advantages of exercise treadmill testing are low cost, wide availability, and short test performance time. Exercise stress testing is

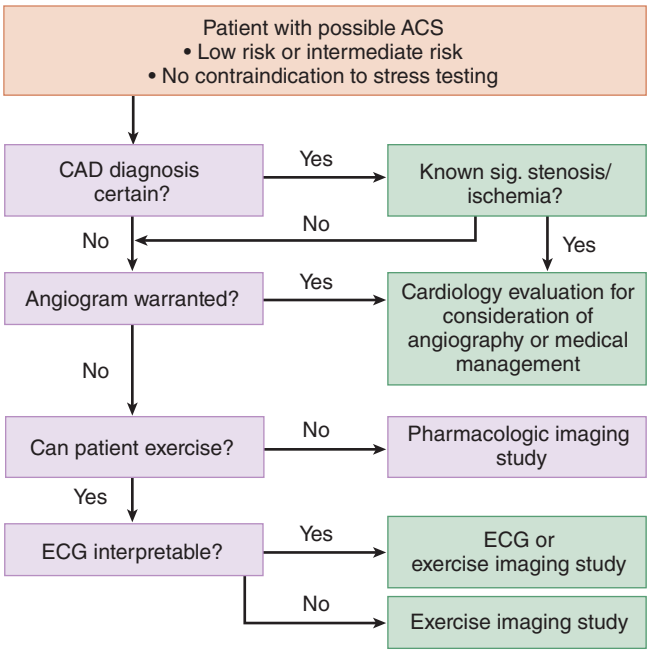

FIGURE 51-3. Stress testing decision making for patients with possible acute coronary syndrome (ACS). CAD = coronary artery disease; sig = significant.

contraindicated for various reasons (**Table 51-3**).[21] Exercise testing may not be safe for patients at high risk for acute ischemia or those with other uncontrolled cardiovascular or pulmonary pathologies. Furthermore, patients with an abnormal baseline ECG, such as those with left ventricular hypertrophy, bundle branch block, or digoxin effect, are less likely to benefit from standard exercise testing due to difficulties in interpretation of exercise-induced ECG changes.

ECHOCARDIOGRAPHY

Echocardiography assesses wall motion at rest and while under stress (either exercise or pharmacologically induced); advantages over exercise treadmill testing are improved accuracy for coronary disease and

TABLE 51-3 Contraindications to Exercise Testing

Absolute
- Acute myocardial infarction (within 2 d)
- High-risk unstable angina
- Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or pulmonary infarction
- Acute myocarditis or pericarditis
- Acute aortic dissection

Relative*
- Left main coronary stenosis
- Moderate stenotic valvular heart disease
- Electrolyte abnormalities
- Severe arterial hypertension (>200 mm Hg systolic, >110 mm Hg diastolic)
- Tachydysrhythmias or bradydysrhythmias
- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
- Mental or physical impairment leading to inability to exercise adequately
- High-degree atrioventricular block

*Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

nondependence on the ECG. Compared with other cardiac imaging techniques, echocardiography is noninvasive, delivers no ionizing radiation, and provides information on myocardial function.

The echocardiogram cannot distinguish between myocardial ischemia and acute infarction, cannot reliably detect subendocardial ischemia, and may be falsely interpreted as positive in the presence of several conditions (notably conduction disturbances, volume overload, heart surgery, or trauma). Timing of the test relative to the onset of symptoms is critical, because transient wall motion abnormalities may resolve within minutes of an ischemic episode. Resting echocardiography within 12 hours of ED arrival does not provide additional predictive value for myocardial infarction over myocardial markers alone. **A normal resting echocardiogram does not exclude ACS, although it lowers the likelihood**.

Stress echocardiography combines a standard ECG stress test with cardiac imaging at rest and after exercise-induced or pharmacologically induced tachycardia. Overall, stress echocardiography is 80% sensitive and 84% specific for significant coronary disease, and superior to ECG-based stress testing. In low-risk ED patients, three studies have reported negative predictive values for subsequent cardiac events to be 97% to 100%, comparable to that of stress testing using nuclear imaging techniques.

NUCLEAR MEDICINE

Nuclear medicine techniques use an IV-injected radioactive tracer. Local myocardial uptake and images depend on regional coronary flow and myocardial cell integrity. Tracer uptake occurs in direct proportion to regional myocardial blood flow.

Thallium-201 has been in use longest and is rapidly redistributed after initial uptake. The image generated after thallium injection represents blood flow at the moment of imaging. Areas of positive uptake reflect adequate coronary flow and viable myocardium, whereas areas without uptake represent infarcted or ischemic myocardium. On repeat imaging several hours later, continued lack of perfusion ("irreversible defect") indicates an area of infarction, and tracer uptake only on delayed images ("reversible defect") represents ischemic but not infarcted myocardium. Combined with conventional ECG-based stress testing, thallium imaging offers improved sensitivity and specificity for detection of significant CAD over ECG-based testing alone, and it is not hampered by baseline ECG abnormalities. Thallium-based imaging must be performed soon after injection, making it impractical for use in patients with ongoing chest pain. In addition, the long half-life requires a lower injected dose to avoid excessive radiation exposure. This may impair imaging and create false-negative and false-positive results, especially in women and obese patients. Due to these limitations and the lack of ED-based outcome studies, thallium-201 imaging alone is not an ideal agent for use in the ED.

Myocardial perfusion imaging using technetium-99m (^{99m}Tc)-labeled agents such as **sestamibi** offers advantages over thallium for ED use. Because the half-life of ^{99m}Tc is much shorter than that of thallium (6 vs. 73 hours), a larger dose is possible without harm to the patient. This produces superior image quality, decreased tissue attenuation–related artifacts, and higher ACS detection specificity for sestamibi imaging. In contrast to thallium, ^{99m}Tc is stable for several hours, allowing accurate imaging up to 3 hours after injection; the image represents the blood flow at the moment of injection. By using gated image acquisition technology, sestamibi scanning also estimates ejection fraction. As with thallium, resting and stress (exercise or pharmacologic) images can be compared to yield additional data.

Perfusion sestamibi imaging of patients *with current or recent* (within 30 minutes of injection) *pain* and no cardiac ischemia on ECG and biomarker analysis is very sensitive in detecting physiologic ischemia; a negative test allows discharge to home. This latter approach requires broader study but is promising in select patients.

Dual-isotope stress testing using thallium and sestamibi is an increasingly common component of ED ACS evaluation protocols. In this technique, a resting thallium scan is first performed. Patients without resting defects can then immediately undergo stress testing with sestamibi imaging, thereby avoiding the delay usually required for isotope "washout" in single-isotope techniques. Dual-isotope stress testing in one trial reliably identified or excluded ACS.

CARDIAC MRI

Cardiac MRI assesses wall motion, perfusion, and coronary anatomy, either at rest or after pharmacologic stress. It is noninvasive and does not expose the patients to radiation. However, cardiac MRI cannot be performed on approximately 11% of ED patients with chest pain due to contraindications such as claustrophobia and implanted metallic objects. Another limit is the longer test performance time, although this is improving with newer scanners and software. Cardiac magnetic resonance stress imaging has excellent test performance but currently is not a common tool for early ACS evaluation.

CT CORONARY ANGIOGRAPHY

CTCA allows gated images of the coronary arteries after rapid, peripheral (not central) IV contrast. Images are improved when the heart rate is <65 beats/min in 16-slice CT scanners, sometimes necessitating β-blocking medications; dual-source scanners (128-slice) can image adequately at higher heart rates but are less available. The advantages of CTCA are ready access to necessary equipment, rapid image acquisition, and the ability to image coronary structure. Notable disadvantages include ionizing radiation exposure, IV contrast exposure (and risk of allergy or kidney injury), need for specially trained technicians, and nondiagnostic scans due to nonvisualization of coronary segments. In addition, CTCA provides a limited assessment of cardiac function. CTCA-detected lesions of >50% stenosis correlate with lesions on standard left-heart angiography; this means the test offers limited information in those with known coronary disease. Patients with positive scans require confirmation either with a cardiac catheterization or a functional advanced cardiac test.

Two recent clinical trials evaluated the usefulness of CTCA in decreasing ED length of stay and assessing for serious cardiac events within 30 days of discharge.[22,23] Both studies included patients with low to intermediate risk for ACS and considered CTCA results of <50% stenosis as negative. These trials found that patients randomized to CTCA versus traditional care had a higher rate of discharge from the ED and a decreased overall length of stay. No significant coronary disease was missed on CTCA evaluation versus traditional stress testing, although one study found that patients with positive CTCA findings had more overall testing and increased radiation exposure. The cost of care was similar for both groups of patients. Overall, these studies provide evidence that CTCA allows for faster and safe discharge of patients from the ED.[22,23] While ED CTCA helps deliver a prompt, safe disposition of patients in the ED, up to 24% of patients will have nondiagnostic CTCA imaging.[2] The ideal approach to these patients is undefined and usually reverts to the previous strategies for evaluating low-risk ACS patients.

DISPOSITION AFTER THE SECONDARY EVALUATION

Use of modern validated risk stratification tools incorporating a second troponin measurement can safely identify patients for discharge without objective testing. Those not classified as low risk should undergo further evaluation to diagnose or exclude ACS. Upon completion of these protocols, those with negative cardiac markers, no dynamic ECG changes, and negative objective cardiac testing can be safely discharged home. Patients with positive cardiac markers, diagnostic ECG changes, or diagnostic testing supporting ACS are admitted to the hospital for cardiac care. Those with nondiagnostic cardiac testing are handled on a case-by-case basis, often in conjunction with a cardiologist.

SUGGESTED FOLLOW-UP INTERVAL

Despite advanced testing, a negative evaluation does not entirely exclude ACS. Patients discharged after exclusion of ACS should be given precautions describing reasons to return to the ED. Ideally, patients should follow up with their primary care physician within the next 2 to 3 days.

DIAGNOSTIC PATHWAYS FOR PATIENTS WITH POSSIBLE ACUTE CORONARY SYNDROME

INPATIENT ADMISSION

If observation beds are unavailable, patients with possible ACS needing additional testing beyond one or two troponin measurements are admitted to an inpatient bed. Specific destinations and care level are driven by stratification; those with a prior history of CAD, evidence of congestive heart failure on physical examination, recurrent chest pain, or new or presumed new ischemic ECG changes are at higher short-term risk and may be more appropriately managed in an intermediate-care (step-down) unit.

ED OBSERVATION AND TESTING

ED observation unit management decreases hospital admissions, length of stay, and hospital cost while providing a high level of care. The traditional observation unit chest pain protocol was refined by Lateef and colleagues,[24] with patients observed for 9 hours with continuous 12-lead ST-segment ECG monitoring and serial creatine kinase-MB testing at 0, 3, 6, and 9 hours after presentation. Those who completed a negative 9-hour evaluation subsequently underwent echocardiography followed by graded exercise stress testing in the ED before discharge. With this approach, 82.1% of patients were released home from the cardiac evaluation unit. The approach of **serial cardiac markers followed by objective cardiac testing remains the foundation of ED and other observation unit protocols**. Although early observation unit protocols focused on low-risk patients, more recent investigations successfully studied patients with intermediate-risk chest pain.

Some observation units adequately manage patients at intermediate risk for ACS, whereas some facilities manage these patients in the hospital. Any protocol that treats all patients with possible ACS equally should incorporate serial cardiac markers and stress testing. In addition, early stress testing after a negative ultra-short cardiac marker testing strategy, or exercise stress testing after one negative cardiac marker in patients with possible ACS, appears safe in low- and intermediate-risk patients. Finally, outpatient stress testing is an option for reliable low-risk patients in whom acute myocardial infarction has been excluded presenting to a facility where a mechanism exists to arrange this testing. Compliance with follow-up testing is better when scheduled before discharge.[25]

TREATMENT

Clinical trials often do not include patients with possible ACS and instead focus on the higher-risk patients with positive cardiac markers or ST-segment changes on their ECG. Therefore, treatment recommendations for patients with possible ACS are derived from reviewing the risk-to-benefit profile suggested from clinical trial results in the higher-risk patient populations. Additional information on the mechanisms of action and data from clinical trials are discussed in Chapter 49, "Acute Coronary Syndromes."

Therapy for patients with possible ACS is linked to the patient's stratification level. In general, patients at low risk of adverse events receive aspirin and anti-ischemic therapy with nitroglycerin while their evaluation is being completed.

SPECIAL POPULATIONS

Age, ethnic, racial, and gender differences are well described in patients presenting with ACSs. Most current knowledge of ACS-related symptoms and risk factors comes from population-based studies. Studies have suggested that women are more likely to present without chest pain and often have a prodrome of fatigue. Similarly, the elderly less often present with a chief complaint of chest pain and, less frequently, have typical chest pain. Other studies have noted delayed presentation for ACS in black women[26] and less frequent chest pain with ACS in those of Asian descent.[27] The Framingham criteria overestimate the risk of coronary disease when applied to Chinese patients,[28] and these patients are less likely to experience classic symptoms of ACS. Be aware of all these confounders as you assess the clinical likelihood of ACS.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 52

Syncope

James Quinn

INTRODUCTION AND EPIDEMIOLOGY

Syncope or fainting is a symptom complex consisting of a brief loss of consciousness associated with an inability to maintain postural tone that spontaneously resolves without medical intervention with the person returning to their baseline neurologic condition. Syncope accounts for approximately 1% to 2% of ED visits each year and 1% to 6% of hospital admissions.[1-4] Over a lifetime, the prevalence of syncope ranges from 10.5% to 19%.[1,5] Syncope in the preceding year is the best predictor of recurrence.[6] It can affect the young and the old, with the elderly having the greatest morbidity.[7] **Near syncope**, a premonition of fainting without loss of consciousness, shares the same basic pathophysiologic process as syncope and carries the same risks.[8-11]

PATHOPHYSIOLOGY

The final common pathway of syncope is the same regardless of the underlying cause: about 10 seconds of complete disruption of blood flow or nutrient delivery to both cerebral cortices or to the brainstem reticular activating system, or reduction of cerebral perfusion by 35% to 50%. Most commonly, an inciting event causes a drop in cardiac output, which decreases oxygen and substrate delivery to the brain. Cerebral perfusion and consciousness are restored by the supine position, the response of autonomic autoregulatory centers, or restoration of a perfusing cardiac rhythm.

The causes of syncope are numerous (**Table 52-1**). The most common causes of syncope identified in the **Framingham Heart Study** were vasovagal (reflex mediated, 21%), cardiac (10%), orthostatic (9%), medication related (7%), neurologic (4%), and unknown (37%).[5] Even with exhaustive patient evaluation, the cause remains unknown in about 18% to 40% of individuals.[12,13] After ED investigation, the unknown proportion may be 50% to 60%. Diagnosis is important, because each diagnostic classification carries with it prognostic risk. Cardiac syncope doubles the risk of death, neurologic syncope increases the risk of death by 50%, and syncope of unknown cause increases the risk of death by 30%.[5] Individuals with neutrally mediated/reflex-mediated or vasovagal syncope have no increased risk of death,[5] but patients with recurrent syncope have an increased risk of injury.[14]

CLINICAL FEATURES

CARDIAC-RELATED SYNCOPE

Patients with documented cardiac syncope have a 6-month mortality rate that exceeds 10%. Thus, a timely and thorough evaluation is warranted.[5,13] The causes of cardiac syncope are divided into two categories: structural disease and dysrhythmias (Table 52-1). In both settings, the heart is unable to provide adequate cardiac output to maintain cerebral perfusion.

TABLE 52-1 Causes of Syncope

Cardiac*	Neural/Reflex Mediated
Structural cardiopulmonary disease	**Vasovagal**
Valvular heart disease	**Situational**
Aortic stenosis	Cough
Tricuspid stenosis	Micturition
Mitral stenosis	Defecation
Cardiomyopathy	Swallow
Pulmonary hypertension	Neuralgia
Congenital heart disease	**Carotid sinus syndrome**
Myxoma	**Other**
Pericardial disease	**Orthostatic hypotension** (see text)
Aortic dissection	**Psychiatric**
Pulmonary embolism	**Neurologic**
Myocardial ischemia	Transient ischemic attacks
Myocardial infarction	Subclavian steal
Dysrhythmias	Migraine
Bradydysrhythmias	**Medications (Table 52-2)**
Short or long QT syndromes	**Breath holding** (children)†
Stokes-Adams attack	
Sinus node disease	
Second- or third-degree heart block	
Pacemaker malfunction	
Tachydysrhythmias	
Ventricular tachycardia	
Torsades de pointes	
Supraventricular tachycardia	
Atrial fibrillation or flutter	

*See Chapter 130, "Syncope, Dysrhythmias, and ECG Interpretation in Children."

†See Chapter 117, "Brief Resolved Unexplained Events."

Syncope can occur if **structural disease** limits the heart's ability to increase cardiac output to meet demand. Examples of structural cardiac disease associated with syncope include aortic stenosis, hypertrophic cardiomyopathy, pulmonary embolism, and myocardial infarction. **Consider aortic stenosis as a structural cardiac cause of syncope in the elderly.** The classic symptom constellation of aortic stenosis is chest pain, dyspnea on exertion, and syncope. **Hypertrophic cardiomyopathy** is characterized by a stiff noncompliant left ventricle, diastolic dysfunction, and outflow tract obstruction. Although it is the most common cause of sudden cardiac death in young adults, it may be first recognized in those >60 years old.[15] Massive acute **pulmonary embolism** may cause syncope due to obstruction of the pulmonary vascular bed and reduction in cardiac output.[16] **Acute myocardial infarction** may cause syncope if myocardial dyskinesia reduces cardiac output. Individual chapters in the "Cardiovascular Disease" section of this text provide more discussion on structural cardiopulmonary disorders that may cause syncope.

TABLE 52-2 Drugs Commonly Implicated in Syncope

- Erectile dysfunction drugs
- Antihypertensives
- β-Blockers
- Cardiac glycosides
- Diuretics
- Antidysrhythmics
- Antipsychotics
- Antiparkinsonism drugs
- Antidepressants
- Phenothiazines
- Nitrates
- Alcohol
- Cocaine

Although both **brady- and tachydysrhythmias** may lead to transient cerebral hypoperfusion (Table 52-1), there is no absolute high or low heart rate that will predictably produce syncope. Symptoms depend on the autonomic nervous system's ability to compensate for a decrease in cardiac output, the heart's structural ability to compensate, and the degree of underlying cerebrovascular disease. Dysrhythmias usually occur in patients with congenital or acquired structural conditions (e.g., myocardial infarction, cardiomyopathy especially resulting in congestive heart failure) in which the conduction system is damaged or compromised. These people are at high risk for arrhythmias and sudden death. Arrythmias may also occur in structurally normal hearts in patients with a primary electrolyte imbalance, as in hypomagnesemia (e.g., torsades de pointes) and in the familial disorders of **Brugada syndrome**, long or short **QT syndromes**, and catecholamine-associated polymorphic ventricular tachycardia. **Syncope from dysrhythmias is typically sudden without prodromal symptoms.**

VASOVAGAL AND NEURALLY OR REFLEX-MEDIATED SYNCOPE

Vasovagal syncope is the result of autonomic dysfunction that is reflex mediated or neurally mediated. It is associated with inappropriate vasodilatation, bradycardia, or both, as a result of inappropriate vagal or sympathetic tone.[17-19] A prodrome of lightheadedness, with or without nausea, pallor, and/or sweating, and an associated feeling of warmth may accompany vasovagal syncope. **A slow, progressive onset with associated prodrome suggests vasovagal syncope.** Vasovagal syncope may occur after exposure to an unexpected or unpleasant sight, sound, or smell; fear; severe pain; emotional distress; or instrumentation. It may also occur in association with prolonged standing or kneeling in a crowded or warm place. **Situational syncope** occurs during or immediately after coughing, micturition, defecation, or swallowing.

Carotid sinus syndrome is a type of reflex-mediated syncope associated with **carotid sinus hypersensitivity**, characterized by bradycardia or hypotension.[20,21] The carotid body, located at the carotid bifurcation, contains pressure-sensitive receptors. The stimulation of an abnormally sensitive carotid body by external pressure may lead to two autonomic responses. Most commonly, there is bradycardia and a pause (asystole) of >3 seconds. Less commonly, there is a vasodepressor response, leading to a decrease in blood pressure of >50 mm Hg without a significant change in heart rate. Carotid sinus hypersensitivity is more common in men, the elderly, and those with ischemic heart disease, hypertension, or head and neck malignancies. Although some patients may demonstrate a hypersensitive carotid sinus response on provocative testing, unless this response culminates in syncope or recurrence of prodromal symptoms and unless it is associated with an inciting event, such as shaving or turning of the head, it cannot be definitely diagnosed as the cause of syncope. About 25% of patients with carotid sinus hypersensitivity have true carotid sinus syndrome with spontaneous symptoms.[22] **Consider carotid sinus hypersensitivity in older patients with recurrent syncope and negative cardiac evaluations.**

ORTHOSTATIC SYNCOPE

Orthostatic syncope is suggested when postural hypotension (drop in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg) is associated with syncope or presyncope.[21,23] When a person assumes an upright posture, gravity shifts blood to the lower part of the body, and cardiac output drops. This change triggers the healthy autonomic nervous system to increase sympathetic output and decrease parasympathetic output, increasing heart rate and peripheral vascular resistance, and thus increasing cardiac output and blood pressure.[24,25] If the autonomic response is insufficient to counter the drop in cardiac output upon standing, decreased cerebral perfusion and syncope may follow. Syncope with postural hypotension to dysfunction of the autonomic nervous system is termed **neurogenic orthostatic hypotension.**[21] Symptom onset is usually within the first 3 minutes after assuming the upright posture, but may be more delayed in some patients.[21] However, positive orthostatic changes have been documented in up to

40% of asymptomatic patients >70 years old and in about a quarter of those <60 years old, so orthostasis does not always result in syncope.[18,26] Causes of orthostatic syncope include intravascular volume loss and poor vascular tone caused by α-receptor disorders or medications. **Many serious causes of syncope may be associated with orthostatic changes, so consider other life-threatening causes before attributing syncope to orthostasis and autonomic dysfunction, especially in the elderly.**

PSYCHIATRIC DISORDERS

Psychiatric disorders are associated with up to 40% of those with vasovagal syncope and 37% to 62% of those with unexplained syncope.[27-29] The most frequent psychiatric diagnoses associated with syncope are generalized anxiety disorder and major depressive disorder.[30,31] A psychiatric cause for syncope should be one of exclusion, assigned only after organic causes have been excluded. **Psychogenic pseudosyncope** is a term reserved for patients with apparent loss of conscious without impaired cerebral perfusion. Eye closure during the event, long periods of apparent transient loss of consciousness, and increased heart rate and blood pressure are commonly seen in psychogenic pseudosyncope.[21,32] Hyperventilation may be associated with panic disorder or generalized anxiety disorders and can lead to hypocarbia, cerebral vasoconstriction, and syncope.[33]

MEDICATION-INDUCED SYNCOPE

Medications may contribute to syncope by a variety of means, and a careful history and consideration are required (Table 52-2). The most common effect is worsening orthostasis.[34]

β-Blockers or calcium channel blockers may lead to a blunted heart rate response after orthostatic stress, and nitrates can cause venous pooling and vascular dilation. Diuretics may produce volume depletion. Some medications have proarrhythmic properties, especially as combination agents, increasing the concern for dysrhythmia as the cause of syncope.

NEUROLOGIC DISORDERS ASSOCIATED WITH LOSS OF CONSCIOUSNESS

Neurologic causes of syncope are rare. To meet the definition of syncope, symptoms must be transient and with no persistent neurologic deficits. **Patients with loss of consciousness with persistent neurologic deficits or altered mental status do not have true syncope;** such patients have alternate medical disorders, many of them life threatening (e.g., stroke, sepsis, overdose). Transient brainstem ischemia, vertebrobasilar atherosclerotic disease, or basilar artery migraine may result in a decrease in blood flow to the reticular activating system, leading to sudden, brief episodes of loss of consciousness. Loss of consciousness due to this mechanism is not only rare but also typically preceded by other signs or symptoms, such as diplopia, vertigo, focal neurologic deficits, or nausea. **Subclavian steal syndrome** is a rare cause of brainstem ischemia. It is characterized by an abnormal narrowing of the subclavian artery proximal to the origin of the vertebral artery, so that with exercise of the ipsilateral arm, blood is shunted, or "stolen," from the vertebrobasilar system to the subclavian artery supplying the arm muscles. Anatomically, narrowing is more common on the left. Physical examination may identify decreased pulse volume and diminished blood pressure in the affected arm.

Spontaneous subarachnoid hemorrhage may present as a cause of syncope, but is usually accompanied by other symptoms such as focal neurologic deficits, headache, or persistent altered mental status, removing it from the true definition of syncope. In this case, the mechanism for syncope is thought to be an increase in intracranial pressure with a decrease in cerebral perfusion pressure. That being said, syncope from any cause can result in head injury with traumatic **subarachnoid hemorrhage**. See Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage," for further discussion.

Seizure may be confused with syncope, because brief tonic-clonic movements are often associated with syncope. Distinguishing features of seizure over syncope include a previous history of seizure, confusion (postictal state) lasting more than several minutes, tongue biting, incontinence, or an epileptic aura.

PRINCIPLES OF EVALUATION

The goal of ED evaluation is to identify those at risk for immediate and future morbidity or sudden death. Patients presenting after near-syncope should be managed the same as patients with syncope.[8-11] For patients with a specific diagnosis, the diagnosis directs the disposition plan. For patients without a specific diagnosis, risk stratification can guide disposition and care. Risk stratification is based on a careful history, thorough physical examination, ECG interpretation, and additional testing as needed.

HISTORY

Obtain clinical history from the patient and any witnesses of the event. Begin with a detailed description of the events preceding the loss of consciousness, including patient position, environmental stimuli, strenuous activity, or arm exercise. One should inquire about premonitory symptoms such as auras, headache, diplopia, vertigo, or focal weakness. Ask about chest pain and palpitations. Clarify the duration of loss of consciousness and symptoms occurring after regaining consciousness. Symptoms associated with syncope that should raise concern of an immediately life-threatening diagnosis include **chest pain** (acute myocardial infarction, aortic dissection, pulmonary embolism, aortic stenosis), **palpitations** (dysrhythmia), shortness of breath (pulmonary embolism, congestive heart failure), **headache** (subarachnoid hemorrhage), and **abdominal or back pain** (leaking abdominal aortic aneurysm, ruptured ectopic pregnancy). A sudden event without warning and events associated with exertion raise suspicion for a cardiac dysrhythmia or structural cardiopulmonary lesion.[35] Ask about antecedent illness and alcohol ingestion or substance abuse. The past medical history should include questions regarding underlying structural heart disease, including congenital heart disease, valvular heart disease, coronary artery disease, congestive heart failure, pulmonary embolism and venous thromboembolism risk, and ventricular dysrhythmias. Document any prior history of syncope because patients with more than five syncopal episodes in 1 year are more likely to have vasovagal syncope (autonomic dysfunction) or a psychiatric diagnosis than dysrhythmia as the cause.[6,29,31] Record all medications, including over-the-counter medications such as laxatives. Patients aggressively dieting to lose weight may have electrolyte disturbances or may be taking amphetamine-like medications. The family history is important in regard to history of prolonged QT syndrome, dysrhythmias, sudden cardiac death, or other cardiac risks.

Pay special attention to patients presenting after falls or single-car motor vehicle crashes without apparent cause (frequently with a history of driving off the road), particularly if the patient is ≥65 years old, has a history of coronary artery disease, or has an abnormal ECG.[36] Clinicians may become preoccupied by the trauma evaluation and miss the possibility of a syncopal event.

Seizure is the most common event mistaken as syncope. Mild, brief, tonic-clonic activity ("convulsive syncope") may accompany syncope of any etiology. The two conditions do not share the same pathophysiologic mechanisms. A previous seizure disorder or premonitory and postevent symptoms may assist in differentiation.[37] A classic aura or postictal confusion and muscle pain indicate seizure, whereas characteristic prodromal symptoms of nausea and diaphoresis suggest reflex-mediated (vasovagal) syncope. Witness information of the event may also be useful. Witnessed head turning or unusual posture during the event is consistent with seizure. A prolonged postictal phase is more common with seizure. Urinary incontinence is not useful in the distinction.

PHYSICAL EXAMINATION

Signs of trauma without defensive injuries to the hands or knees may be due to a sudden event without warning, such as a dysrhythmia. Focus the physical examination on the cardiovascular and neurologic systems. Obtain blood pressure measurements in both arms. Consider

aortic dissection or subclavian steal if blood pressures are unequal. Take orthostatic blood pressures after 5 minutes in the supine position. Repeat measurements after 1 and 3 minutes of standing. A symptomatic decrease of >20 mm Hg in the systolic pressure is considered abnormal, as is a decrease in pressure <90 mm Hg independent of the development of symptoms. Cardiac examination may reveal the murmur of hypertrophic cardiomyopathy or aortic stenosis. The neurologic examination may uncover findings of focal neurologic disease or evidence of autonomic instability such as peripheral neuropathy. Perform rectal examination to check stool guaiac to evaluate for GI bleeding.

DIAGNOSIS

The diagnosis of syncope is clinical, with careful evaluation of the presentation and selected use of diagnostic tests. History is most important, and most diagnostic tests have low diagnostic yield and should be guided by the history and physical examination.[38] The differential diagnosis is presented in Tables 52-1 and 52-2.

ECG AND ED MONITORING

Obtain a 12-lead ECG and place the patient on a cardiac monitor. Even though the ECG leads to a diagnosis in only a few patients, it is a simple, noninvasive test and is important for risk stratification.[21,39,40] Assess the ECG for evidence of prior cardiopulmonary disease, acute ischemia or new ECG changes, dysrhythmia, heart block, and prolonged or short QT_c interval. A prolonged QT_c interval has a variable definition, but the literature suggests it is defined as >470 milliseconds, with >500 milliseconds associated with significant outcomes,[41-43] whereas a short QT_c interval <350 milliseconds is concerning as well.[44] New or old left bundle conduction abnormalities (e.g., left bundle branch block, posterior or anterior fascicular block, QRS widening) are 3.5 times more likely to be associated with morbidity than ECGs lacking these findings. Nonsinus rhythms are 2.5 times more likely to be associated with morbidity than sinus rhythms.[45] Numerous studies have pointed out that the value of ED monitoring is additive to a single ECG done in the ED.[46-48] For further discussion, see below and Chapter 18, "Cardiac Rhythm Disturbances."

LABORATORY TESTING

Laboratory testing is directed by results of the history and physical examination, and no test other than an ECG should be considered "routine." For example, a patient with orthostatic symptoms and a heme-positive stool test warrants at least a CBC. A reproductive-age female should have a urine pregnancy test. A transitory, wide anion gap acidosis follows a generalized seizure but is not present in simple syncope. Serum electrolytes rarely determine the cause of syncope; however, an elevated blood urea nitrogen is a predictor of serious adverse outcome within 30 days after syncope.[49] B-type natriuretic peptide or pro–B-type natriuretic peptide levels appear to be predictive of those at risk for morbidity. One study suggests that a level >300 picograms/mL in the setting of syncope indicates risk,[50] but whether this adds any value over a history of congestive heart failure or structural disease is unclear.[51,52] See Chapter 53, "Acute Heart Failure," for a discussion of the diagnostic use of B-type natriuretic peptide.

ANCILLARY TESTING

Carotid Massage Carotid massage is used to diagnose carotid sinus hypersensitivity in the patient with a history suggestive of carotid sinus syndrome. However, given the small benefit of the maneuver and potential adverse events, most do not routinely perform carotid massage as part of the ED evaluation.

Carotid massage can be done at the bedside with continuous ECG and blood pressure monitoring, after obtaining informed consent. Each carotid body is separately massaged for 5 to 10 seconds. The test is considered positive if symptoms are reproduced in the presence of asystole >3 seconds or a decrease in systolic blood pressure of >50 mm Hg. **Do not perform carotid massage if the patient has known carotid stenosis, if bruits are present, if there is history of recent (<3 months) stroke or myocardial infarction, or if there is a history of ventricular tachycardia or fibrillation.** Neurologic deficits resulting from carotid massage are rare, with deficits lasting more than 24 hours in approximately 0.1% of patients.[53] Only a small number of patients with carotid hypersensitivity will have the true carotid sinus syndrome.

Hyperventilation Maneuver A hyperventilation maneuver (open-mouthed, slow, deep breaths at a rate of 20 to 30 breaths per minute for 2 to 3 minutes) can be very useful in the young patient with undiagnosed syncope and suspected psychiatric illness. A recurrence of prodromal symptoms or syncope significantly correlates with psychiatric (anxiety-provoking) causes of syncope.[30]

Neurologic Testing When the history or physical examination does not reveal head trauma or neurologic findings, the clinical yield of CT scanning,[54] electroencephalogram, or lumbar puncture is very low. Consequently, in asymptomatic patients who have returned to baseline with an isolated syncopal event, CT or MRI is not warranted unless there is concern for a neurologic cause.

Pulmonary Embolism The Pulmonary Embolism in Syncope Italian Trial study reported a 17% prevalence of pulmonary embolism in patients admitted to the hospital as a result of syncope.[55] However, a much larger multicenter study found the pulmonary embolism prevalence to be 0.15% to 2%.[56] For all ED patients presenting with syncope, the prevalence of pulmonary embolism ranges from 0.06% to 1.4%.[56,57] Therefore, pulmonary embolism assessment need not be routine, but should be reserved for those with venous thromboembolism risk factors or history or examination findings suggestive of pulmonary embolism.

DECISION MAKING AND RISK ASSESSMENT

DIAGNOSIS ESTABLISHED

If a cause of syncope can be determined by the initial history, physical examination, and ECG, the disposition is simple. Patients with cardiac or neurologic syncope should have appropriate specialty consultation and be admitted as necessary. Patients with clear vasovagal, orthostatic, and medication-related syncope have no increased risk of cardiovascular morbidity or mortality[7] and do not need admission as long as deficits or medication misadventures are corrected.

UNEXPLAINED SYNCOPE

Despite best efforts, a diagnosis will not be established in about 40% of the patients with syncope. **Table 52-3** summarizes several studies that have assessed risk-stratification variables to identify patients at risk of both short-term and 1-year morbidity and mortality.[2,58-65] Quinn et al[2,59] assessed adverse outcomes at 7 and 30 days in their derivation and validation of the **San Francisco Syncope Rule**. Significant predictors of adverse events (primarily dysrhythmia) included (1) a **history of congestive heart failure**, (2) an **abnormal ECG** (a rhythm other than sinus, including those on rhythm strips or monitoring, conduction delays or new changes as minimal as first-degree atrioventricular block, or any morphologic changes to the QRS complex or ST segment that could not be proven to be old by prior tracings), (3) **a hematocrit of <30%**, (4) a complaint of **shortness of breath**, or (5) **a systolic blood pressure of <90 mm Hg in the ED**. The presence of any one of the five high-risk criteria listed above has an 89% sensitivity and 52% specificity for death at 1 year.[65] There have been inconsistent findings when validating the San Francisco Syncope Rule, which have been primarily related to definitions of syncope and the application of variables.[60] Other studies identified age >65 years,[61,62] syncope without prodrome or lack of vasovagal etiology,[61,63,64] positive troponin,[64] systolic blood pressure >180 mm Hg, and concomitant trauma as high-risk features.[63] Using the risk factors identified in these studies can help clinicians determine patient risk and appropriate disposition. There is a consistent theme that patients with an **abnormal ECG** on presentation and/or **a history of heart disease**, particularly structural heart disease especially characterized by a **history of congestive heart failure**, are clearly at increased risk. Additional risk factors suggested by guidelines[40,66,67] include **syncope while supine, syncope during exercise, syncope without prodromal symptoms, palpations preceding syncope, and the specific age cut points of >60 or >65 years**.

TABLE 52-3 Selected Syncope Scores Identifying Risks for Adverse Outcomes After Syncope

Risk Rule	Martin et al,[58] Pittsburgh	San Francisco Syncope Rule[2,59]	OESIL Score for Syncope[61]	Sarasin et al,[62] Geneva	STePS[63]	Canadian Syncope Risk Score[64]
Publication Year	1997	2004	2003	2003	2008	2016
Adverse outcomes assessed	Arrhythmia or death at 1 y	Adverse events at 7 and 30 d	Death at 1 y	Subsequent arrhythmia	Death or need for major procedure at 10 d and 1 y	Death or serious neurologic or cardiac adverse event at 30 d
Risk factors for adverse outcomes after syncope						
ECG	Abnormal ECG*	Abnormal ECG* or monitoring	Abnormal ECG*	Abnormal ECG*	Abnormal ECG*	Abnormal ECG*
Cardiac disease	History of CHF	History of CHF	History of cardiac disease	History of CHF	History of cardiac disease	History of cardiac disease
Age criteria	Age >45 y	†	Age >65 y	Age >65 y	†	†
Prodrome/vasovagal	†	†	No prodrome	†	No prodrome	Lack of vasovagal etiology
Additional factors	History of arrhythmia	Dyspnea SBP <90 mm Hg Hematocrit <30% (<0.30)	†	†	Concomitant trauma	+ Troponin SBP <90 mm Hg or >180 mm Hg

Abbreviations: CHF = congestive heart failure; OESIL = Osservatorio Epidemiologico sulla Sincope nel Lazio; SBP = systolic blood pressure; STePS = Short-Term Prognosis of Syncope.

*The definition of an abnormal ECG varies between studies, from any ECG findings other than completely normal, to more specific rhythm abnormalities, conduction disorders, ventricular hypertrophy, axis deviation, or ST-segment or T-wave abnormalities/changes.

†Variable not included in risk score.

TREATMENT

Treatment should be guided by the diagnosis. Patients with or at risk for life-threatening dysrhythmias can be treated with pacemakers or automatic implantable defibrillators as indicated. For patients with suspected medication causes, remove the offending agent. Rehydrate those with orthostasis and dehydration. Educate patients with vasovagal syncope; episodes are likely to recur, and patients should lie or sit down when they sense a prodrome. β-Blockers do not decrease episodes of vasovagal syncope.[68]

DISPOSITION AND FOLLOW-UP

Guidelines recommend using known risk factors, such as those outlined in the text and Table 52-3, to separate patients into risk groups for disposition and management.[21,40,69] European Society of Cardiology guidelines identify high- and low-risk patients,[40] and the American Heart Association guidelines also identify intermediate-risk patients.[21,69] There is agreement that low-risk patients (those with clear reflex-mediated syncope, without a history of heart disease, who are currently asymptomatic and with a normal physical exam and ECG) can be discharged with nonurgent primary care follow-up.[21,40] There is less agreement as to which patients are at high or intermediate risk of adverse outcome, reflected by guideline discrepancies and regional variation.[70] However, **patients thought to be high risk by the examining physician and those with active chest pain or dyspnea, exertional syncope, sudden-onset palpitations prior to syncope, ECG evidence of conduction abnormalities or ongoing arrhythmia, history of CHF or structural heart disease, or family history of sudden cardiac death are recommended for admission** to the hospital or to a syncope observation unit (if now asymptomatic).[21,69] Decisions on testing should be determined by the patient's presentation and comorbidities.

INPATIENT EVALUATION

With the exception of patients with acute life-threatening diagnoses (e.g., stroke, aortic dissection), the core of the inpatient evaluation is focused on identification of underlying heart disease and detection of dysrhythmias. The indications and utility of postsyncope testing are listed in **Table 52-4**. Most patients, even those at higher risk, can be

TABLE 52-4 Post-ED Testing for Syncope/Syncope Mimics

Test	Indication	Utility
Cardiac syncope		
ECG monitoring	Admission Outpatient ambulatory monitoring if no significant cardiac disease suspected	Cardiac syncope confirmed if recurrent symptoms occur during monitored dysrhythmia; excluded if recurrent symptoms reported during sinus rhythm
Implantable loop recorder	Recurrent syncope after admission evaluation	Long-term use with diagnostic yield of >50% in patients with recurrent syncope
Echocardiography	History, examination, or ECG suggestive of structural heart disease	Confirms and quantifies suspected structural heart disease
Electrophysiology testing	Documented dysrhythmia, preexcitation, or serious underlying heart disease	Identifies inducible tachydysrhythmias and some bradydysrhythmias
Stress testing	Exercise-related syncope	Identifies exercise-induced dysrhythmias and postexercise syncope
Neurologic syncope		
CT/magnetic resonance angiography/carotid Doppler	Neurologic signs or symptoms	Identifies cerebrovascular abnormality or subclavian stenosis
Electroencephalography	Suspected seizure	Documents underlying seizure disorder
Reflex-mediated syncope		
Tilt-table testing	Recurrent syncope, cardiac etiology excluded	Positive test establishes diagnosis of neurocardiogenic syncope
Psychogenic		
Psychiatric testing	Young patient, no underlying heart disease	Identifies underlying psychiatric disorder predisposing to syncope

monitored for a period of time in the ED or observation area and, if well, discharged with a prolonged monitoring device.[38,71,72] Monitoring is the key investigation of arrhythmia detection, whether inpatient or outpatient. Echocardiogram abnormalities are uncommon in patients with a negative cardiac history, in the setting of a normal cardiac examination and ECG. Electrophysiology testing involves invasive electrical stimulation and cardiac monitoring to uncover possible conduction abnormalities that predispose to tachydysrhythmias (both ventricular and supraventricular) or bradydysrhythmias.

OUTPATIENT EVALUATION

Most low-risk patients need no workup unless symptoms are recurrent. Long-term cardiac monitoring includes many different ambulatory or event monitors, which are useful to identify dysrhythmias, especially in intermediate- to high-risk patients who are discharged after a period of hospital monitoring (Table 52-4). The duration one should wear an ambulatory monitor has not been established with certainty. However, prolonged monitoring for patients with syncope has now become a recommendation in the newest American Heart Association guidelines.[21] Long-term use of implantable loop recorders has a diagnostic yield of >50% in patients with recurrent syncope.[73-75] Tilt-table testing is designed to identify reflex-mediated syncope by rapidly moving the patient from a supine position on the tilt table to an upright position of 60 degrees for 45 minutes. A positive end point is reached if syncope, hypotension, or the patient's typical symptoms are reproduced. Recurrent reflex-mediated syncope resistant to conservative therapies can be treated with a cardiac pacemaker. Psychiatric referral is recommended for young patients without underlying heart disease who have frequent syncopal events. Generalized anxiety and depressive disorders are the most commonly assigned diagnoses. Patients with a prolonged QT segment should be referred for genetic testing for the *LQTS* gene. Those who are gene negative have very little risk for fatal syncope.[76]

SPECIAL POPULATIONS

THE ELDERLY

Because of both normal physiologic changes with aging and age-related disease processes, the elderly are at increased risk for adverse outcomes after syncope or near-syncope.[9,11] Syncope in the elderly is often multifactorial and difficult to establish in the ED. Twelve percent of patients over 60 years of age who sustain cardiac arrhythmia within 30 days after syncope have a completely normal ECG at the index ED visit.[77]

Various specified ages have been studied as risk factors for fatal or serious outcomes after syncope; however, there is a gradual continuum of increasing risk with increasing age. Cardiovascular risk factors appear to be better predictors than age itself. Decreased adrenergic responsiveness contributes to the diminished chronotropic response seen after orthostatic stresses in the elderly. The incidence of vasovagal syncope actually decreases with age, in part as a consequence of the decreased responsiveness of the autonomic nervous systems. The elderly also have a less sensitive thirst mechanism and a decreased endocrine response to volume depletion, exacerbating orthostatic hypotension. Postprandial hypotension is more common in the elderly, especially in nursing home patients, and is thought to be due to a rapid rate of nutrient delivery from the stomach into the small intestine. Aortic stenosis is the most common obstructive cardiac lesion in the elderly, producing a fixed cardiac output. Diabetes may lead to autonomic dysfunction and peripheral neuropathy. Finally, medication usage is much more common in the elderly population, increasing the risk of orthostasis and decreasing autonomic responsiveness to orthostatic stress.[26]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 53

Acute Heart Failure

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INTRODUCTION AND EPIDEMIOLOGY

Acute heart failure covers a wide spectrum of illness severity, ranging from a gradual increase in leg swelling, shortness of breath, or decreased exercise tolerance to the abrupt onset of pulmonary edema. While the alternative terms *decompensated heart failure*, *acute heart failure syndrome*, or *hospitalized with heart failure* are often used in an overlapping manner, we refer to patients with either an acute exacerbation of chronic heart failure or a new-onset heart failure as having *acute heart failure*. The outdated term *congestive heart failure* describes patients with signs and symptoms of fluid accumulation.

Most ED visits for acute heart failure result in hospital admission.[1] ED physicians drive most disposition decisions in this setting.[2,3] With the aging population, increased survival from acute myocardial infarction, and outpatient treatment options, the prevalence of heart failure is expected to increase over the next decade.[4-6] Although long-term heart failure management has improved through the use of β-blockers, angiotensin-converting enzyme inhibitors, spironolactone, and cardiac resynchronization therapy,[4,5] acute heart failure therapy is largely unchanged and includes nitrates, diuretics, and positive-pressure ventilation.[7] Only one new therapy, nesiritide, was recently approved for acute heart failure treatment, but it does not improve outcomes compared to standard treatment.[8]

Heart failure has a poor prognosis, with approximately 50% of patients dying within 5 years of diagnosis.[9] Hospitalization is an inflection point in this disease, with those hospitalized having higher mortality than a matched nonhospitalized cohort.[10]

PATHOPHYSIOLOGY

Heart failure is a complex clinical syndrome manifested by cardinal symptoms (shortness of breath, edema, and fatigue) occurring from functional or structural cardiac damage, impairing the ability of the heart to act as an efficient pump. Symptoms may limit exercise tolerance and lead to fluid retention, driving pulmonary and/or splanchnic congestion and/or peripheral edema.[4] There are numerous responsive adaptations in the kidney, peripheral circulation, skeletal muscle, and other organs to maintain short-term circulatory function. Eventually, these responses may contribute to long-term disease progression and to acute exacerbations.

As cardiac output drops from myocardial injury or stress, a neurohormonally mediated cascade including activation of the renin-angiotensin-aldosterone and sympathetic nervous systems occurs. Responses include release of norepinephrine, vasopressin, endothelin (a potent vasoconstrictor), and tumor necrosis factor-α. Although not measured in routine care, elevated levels of these hormones correlate with higher mortality.

The clinical effects of neurohormonal activation are sodium and water retention coupled with increased systemic vascular resistance. These maintain blood pressure and perfusion, but at the cost of increasing myocardial workload, wall tension, and myocardial oxygen demand. Although some patients are initially asymptomatic, a secondary pathologic process called cardiac remodeling begins to occur, eventually triggering more dysfunction.

Natriuretic peptides are the endogenous counterregulatory response to neurohormonal activation in heart failure. Three types exist: atrial natriuretic peptide, primarily secreted from the atria; B-type natriuretic peptide, secreted mainly from the cardiac ventricle; and C-type natriuretic peptide, localized in the endothelium. Natriuretic peptides produce vasodilation, natriuresis, decreased levels of endothelin, and inhibition of the renin-angiotensin-aldosterone system and the sympathetic nervous systems. B-type natriuretic peptide is synthesized as

N-terminal pre–pro-B-type natriuretic peptide, which is cleaved into two substances, inactive N-terminal pro-B-type natriuretic peptide, with a half-life of approximately 2 hours, and physiologically active B-type natriuretic peptide, with a half-life of about 20 minutes. Assays for both B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide are available for ED use.

Heart failure may also result from pump dysfunction from acute myocardial infarction. Mechanistically, loss of a critical mass of myocardium results in immediate symptoms. If there is symptomatic hypotension with inadequate perfusion, cardiogenic shock is present (see Chapter 50, "Cardiogenic Shock"). Acute pulmonary edema may be precipitous and is the clinical manifestation of a downward spiral of rapidly decreasing cardiac output and rising systemic vascular resistance on top of underlying cardiac dysfunction. Even small elevations of blood pressure can drop cardiac output, which triggers increasing systemic vascular resistance and eventually further decreases cardiac output. Acute pulmonary edema can be abrupt, severely symptomatic, and rapidly fatal.

ACUTE HEART FAILURE CLASSIFICATION

There are six phenotypes to assist with investigating the causes and precipitants for the acute presentation, as well as directing initial therapy (**Table 53-1**).[11] Those with acute heart failure and hypertension often have a precipitous presentation and may have pulmonary edema and hypoxemia. Symptoms may be due to fluid redistribution more than fluid overload, and treatment initially focuses on antihypertensive therapy.[12,13] Patients with pulmonary edema may benefit from noninvasive ventilation to decrease the work of breathing and avoid intubation.[14,15] Acute heart failure accompanied by hypotension or poor perfusion without another cause may be an ischemic or structural heart trigger creating cardiogenic shock. Such patients often benefit from inotropic agents and invasive hemodynamic monitoring to guide other therapies.

Patients with acute decompensation of chronic heart failure tend to present with gradual symptoms (breathing changes or weakness common) and weight gain over days to weeks. High-output heart failure has a relatively normal ejection fraction and is often caused by anemia or thyrotoxicosis. Those with isolated right heart failure have lower extremity edema and jugular venous distension but little or no pulmonary congestion; the cause is usually from pulmonary disease, valvular disease such as tricuspid regurgitation, or obstructive sleep apnea. Treatment approaches center on identifying and treating the underlying cause, often without volume removal because low-output states and volume dependence may coexist.

TABLE 53-1 Classification of Acute Heart Failure

Classification	Characteristics
Hypertensive AHF	Signs and symptoms of AHF with relatively preserved left ventricular function, systolic blood pressure >140 mm Hg, typically with a chest radiograph compatible with pulmonary edema and symptom onset <48 h
Pulmonary edema	Respiratory distress, rales on chest auscultation, reduced oxygen saturation from baseline, verified by chest radiograph findings
Cardiogenic shock (see Chapter 50)	Evidence of tissue hypoperfusion (systolic blood pressure typically <90 mm Hg)
Acute-on-chronic HF	Signs and symptoms of AHF that are mild to moderate and do not meet criteria for hypertensive HF, pulmonary edema, or cardiogenic shock, systolic blood pressure <140 mm Hg and >90 mm Hg, typically associated with increased peripheral edema and symptom onset over several days
High-output failure	High cardiac output, typically with tachycardia, warm extremities, and pulmonary congestion
Right heart failure	Low-output syndrome with jugular venous distention, hepatomegaly, and may have hypotension

Abbreviations: AHF = acute heart failure; HF = heart failure.

SYSTOLIC AND DIASTOLIC HEART FAILURE

Heart failure classifications also identify systolic or diastolic dysfunction based on ejection fraction, which is normally 60%. **Systolic dysfunction**, or heart failure with reduced ejection fraction, has an ejection fraction <50%. Mechanistically, the ventricle has difficulty ejecting blood, leading to increased intracardiac volume and *afterload sensitivity*. With circulatory stress (e.g., walking), failure to improve contractility despite increasing venous return results in increased cardiac pressures, pulmonary congestion, and edema.

Diastolic dysfunction, or heart failure with preserved ejection fraction, has impaired ventricular relaxation, causing an abnormal relation between diastolic pressure and volume. This results in a left ventricle that has difficulty receiving blood. Decreased left ventricular compliance necessitates higher atrial pressures to ensure adequate left ventricular diastolic filling, creating a *preload sensitivity*. The frequency of diastolic dysfunction increases with age and is more common in chronic hypertension, which leads to left ventricular hypertrophy. Coronary artery disease also contributes, as diastolic dysfunction is an early event in the ischemic cascade.

DIAGNOSIS

Most hospitalized patients with heart failure receive initial care in the ED.[6] Commonly, patients present with dyspnea, which has a large differential diagnosis including acute heart failure, chronic obstructive pulmonary disease, asthma, pulmonary embolus, pneumonia, and acute coronary syndrome. Misdiagnosis increases mortality, prolongs hospital stay, and increases treatment costs.[16-20] The approach to those with dyspnea is covered in Chapter 62, "Respiratory Distress." ***There is no single diagnostic test*** for heart failure; it is a clinical diagnosis based on all clinical data, especially the history and physical examination.

HISTORY AND PHYSICAL EXAMINATION

There is ***no singular historical or physical*** examination finding with excellent sensitivity and specificity for the diagnosis of acute heart failure.[19] The initial *global* clinical judgment has a sensitivity of 61% and specificity of 86%. A history of heart failure is the most useful historical parameter, but has a sensitivity of only 56% and specificity of 80% (positive likelihood ratio = 2.7; negative likelihood ratio = 0.58).[19] Risk factors for acute heart failure may be helpful, including hypertension, diabetes, valvular heart disease, old age, male sex, and obesity. The symptom with the highest sensitivity for diagnosis is dyspnea on exertion (84%).[19,20] The most specific symptoms are paroxysmal nocturnal dyspnea, orthopnea, and edema (76% to 84%).[19,20] Evaluation for precipitating factors (**Table 53-2**) may aid diagnosis.

On exam, an S_3 has the highest positive likelihood ratio for acute heart failure (4.0), but its absence is not useful (negative likelihood ratio = 0.91).[19] Further, the interrater reliability of an S_3 is not good,[21-23] and the ambient noise in a busy ED may interfere with detection.

When clinicians are 80% confident of the diagnosis of acute heart failure, the "clinical gestalt" outperforms ED diagnostic tests[19]; however,

TABLE 53-2 Common Precipitants of AHF

- Nonadherence
  - Excess salt or fluid intake
  - Medication nonadherence
- Renal failure (especially missed dialysis)
- Substance abuse—cocaine, methamphetamines, ethanol
- Poorly controlled hypertension
- Iatrogenic
  - Recent addition of negative inotropic drugs (e.g., calcium channel blocker, β-blocker)
  - Initiation of salt-retaining drugs (e.g., NSAID, steroids, thiazolidinediones)
  - Inappropriate therapy reduction
  - New dysrhythmic agents

Abbreviations: AHF = acute heart failure.

clinical gestalt may be only 50% accurate in a primary care setting.[24] Data from the seminal study of B-type natriuretic peptide for the diagnosis of heart failure in the ED found that clinical judgment and a single B-type natriuretic peptide value had a similar accuracy performance.[25]

CHEST RADIOGRAPHY

Although chest radiographs showing pulmonary venous congestion, cardiomegaly, and interstitial edema are most specific for a final diagnosis of acute heart failure,[18,19] the absence of these does not exclude the diagnosis. Up to 20% of patients subsequently diagnosed with acute heart failure have chest radiographs without signs of congestion at the time of prior ED evaluation.[26] In late-stage heart failure, patients may have few radiographic signs, despite symptoms and elevated pulmonary capillary wedge pressure.[18]

ECG AND BIOMARKERS

The ECG is best used to find an underlying cause or precipitant. ECG signs of ischemia, acute myocardial infarction, or dysrhythmias (commonly atrial fibrillation) may point to the trigger.

B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide may add value in the setting of undifferentiated dyspnea in the ED, improving diagnostic discrimination in a variety of settings[25,27] and correlating with cardiac filling pressures and ventricular stretch.[28] As a result, B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide testing is recommended when the cause of dyspnea is unclear after standard evaluation; when the other bedside data make acute heart failure very likely, these assays add little actionable information (**Table 53-3**).

Despite the established value of natriuretic peptide testing, there are many situations where interpretation of results is unclear. Levels can be affected by age, gender, and body mass, and may elevate later in patients who present with flash pulmonary edema.[29] Dyspnea and modest B-type natriuretic peptide elevation are evident in conditions such as pulmonary hypertension, pulmonary embolism, pneumonia, sepsis, and renal failure. As many as 25% of patients will fall into the diagnostic "gray zone" (100 to 500 pg/mL for B-type natriuretic peptide), complicating test interpretation. Heart failure can largely be excluded in patients presenting with acute dyspnea and N-terminal pro-B-type natriuretic peptide <300 pg/mL or B-type natriuretic peptide <100 pg/mL. In addition, N-terminal pro-B-type natriuretic peptide has age-specific cutoffs to further increase accuracy, with cutoff levels of 450, 900, and 1800 pg/mL in patients <50, 50 to 75, and >75 years old, respectively.[30] **B-type natriuretic peptide/N-terminal pro-b-type natriuretic peptide testing is best used when diagnostic uncertainty exists and as an addition to the physician assessment, rather than as a routine measurement.**[27] Similarly, although marked natriuretic peptide elevations are associated with worse short-term outcomes, even low elevations have increased mortality risk, limiting usefulness in bedside prognostication in the ED.[31,32]

TABLE 53-3 Natriuretic Peptide Cut Points for Clinical Decision Making

	Low Cut Point (rule out HF)	High Cut Point (HF likely)		
BNP	100 pg/mL	500 pg/mL		
	Sensitivity 90%	Sensitivity 75%		
	Specificity 73%	Specificity 90%		
N-terminal pro-BNP[30]	300 pg/mL	450 pg/mL if <50 years old	900 pg/mL if 50–75 years old	1800 pg/mL
	Sensitivity 93%	Sensitivity 86%	Sensitivity 79%	Sensitivity 76%
	Specificity 71%	Specificity 94%	Specificity 84%	Specificity 75%

Abbreviations: BNP = B-type natriuretic peptide; HF = heart failure.

POCUS

Point-of-care cardiopulmonary US can help to determine the cause of dyspnea, including cardiac tamponade, and can determine left ventricular function and volume status, but is not a substitute for comprehensive echocardiography.[31,32] Bedside cardiopulmonary US can also address three questions (**Figure 53-1**): (1) Are there signs of pulmonary

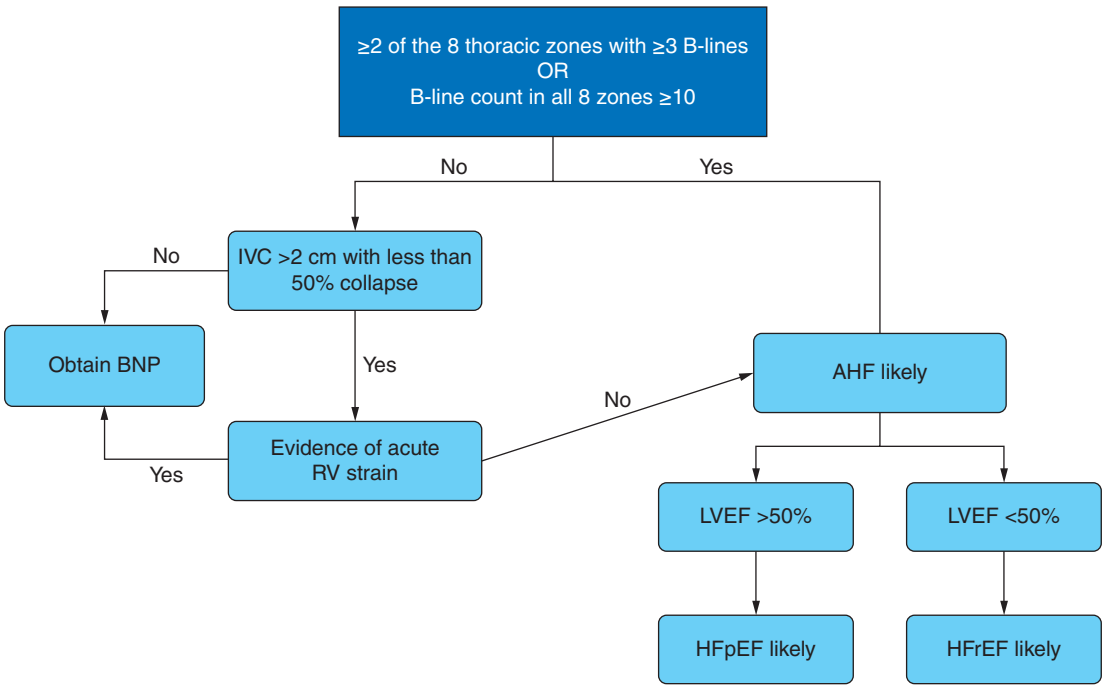

FIGURE 53-1. Bedside US use to identify acute heart failure (AHF) in dyspneic ED patients using a curvilinear transducer or phased array probe to a depth of 15 cm. BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IVC = inferior vena cava; LVEF = left ventricular ejection fraction; RV = right ventricle. [Data adapted from Anderson KL, Jenq KY, Fields MF et al: Diagnosing heart failure among acutely dyspneic patients with cardiac, inferior vena cava, and lung ultrasonography. *Am J Emerg Med* 31: 1208-1214, 2013.]

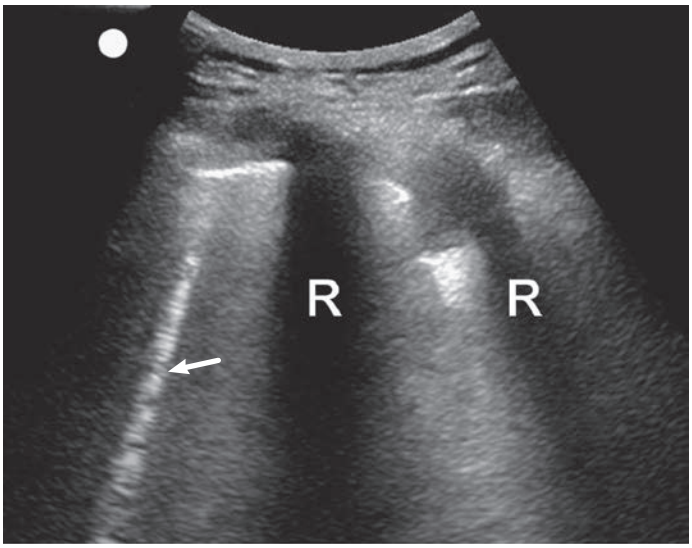

FIGURE 53-2. B-lines representing thickened interalveolar/interlobular septa. R = rib; arrow = B-line. [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA (eds): *Emergency Ultrasound*, 3rd ed. New York, NY: McGraw-Hill, Inc.; 2014. Fig. 7-5, Part C only.]

congestion? (2) Are there signs of volume overload by measuring the size of the inferior vena cava and its collapsibility? (3) Is the left ventricular ejection fraction low or normal?

Pulmonary US is used first to determine if pulmonary congestion is present by looking for B-lines. **Sonographic B-lines** (**Figure 53-2**) are ring-down artifacts that arise from the interface of the visceral and parietal pleura when there is swelling of the lung's interlobular septa due to lymphatic congestion, as is seen in pulmonary edema.[33] They are the sonographic equivalent of Kerley B-lines seen on chest radiography.[34] The presence of more than two B-lines in any one sonographic window along the anterior and anterolateral chest is pathologic and highly specific for alveolar and interstitial edema.[35]

Because bilateral B-lines can be present in other conditions not caused by pulmonary edema (e.g., pulmonary fibrosis, pulmonary contusion, bilateral pneumonia), rapid assessment for elevated central venous pressure follows.[36] An inferior vena cava size >2 cm or collapsibility index of <50% is indicative of elevated central venous pressure. In the absence of significant pulmonary disease, these measures are highly correlated with pulmonary capillary wedge pressure and are specific for acute heart failure. Use US to look for other clinical conditions that cause an elevation in right heart pressure, including pulmonary embolism or tricuspid regurgitation, both of which could cause inferior vena cava changes consistent with heart failure.

Determining the crude left ventricular ejection fraction is the final piece of ED-based bedside US. With focused training, emergency physicians have reasonable agreement with expert cardiology interpretations by classifying a visual US estimation of left ventricular ejection fraction into broad categories of normal, moderately reduced, and severely reduced.[37,38] Other markers, such as E-point septal separation and fractional shortening, are less reliable markers and may be more time consuming in the ED setting.[39]

TREATMENT

The initial approach is driven by the presentation acuity, hemodynamics, and volume status. In critically ill patients, airway management is the first priority to ensure adequate oxygenation and ventilation. In those who are less acutely ill, a focused evaluation ensues next, followed by treatment.

Use pulse oximetry and supplemental oxygen to keep oxygen saturation at or above 95%. Because hypoxemia is a greater risk than hypercarbia, do not withhold oxygen if saturations are depressed or unknown, even when there is concern about carbon dioxide retention. Capnometry and blood gas measurements can later help titrate therapy in the critically ill. In those with extreme findings, use endotracheal intubation.

Noninvasive positive-pressure ventilation often improves the symptoms in patients with heart failure or pulmonary edema.[14,40] Successful noninvasive ventilation requires close monitoring, hemodynamic stability, facial anatomy allowing an adequate facemask seal, and patient cooperation (see Chapter 28, "Noninvasive Airway Management and Supraglottic Airways"). Noninvasive ventilation plus standard medical therapy reduces the need for intubation and improves respiratory distress and metabolic disturbance versus standard therapy alone.[14,15] The effect on hospital mortality remains unclear.[14]

Alternatively, **high-velocity nasal insufflation** of oxygen via nasal cannula (flow rates between 20 and 35 L/min) may be superior to standard oxygen delivered by nasal cannula and noninferior to noninvasive positive-pressure ventilation in treatment of undifferentiated respiratory failure in adult patients presenting to the ED. However, in the only randomized trial of high-velocity/flow oxygen, its benefit relative to noninvasive positive-pressure ventilation was unclear. High-velocity nasal insufflation provides high concentrations of oxygen and a mild distending pressure, and it may improve ventilatory efficiency by way of dead-space washout. High-velocity nasal insufflation is easier to use and better tolerated by many patients compared with noninvasive positive-pressure ventilation.[41]

Acute heart failure with hypotension occurs in approximately 3% of patients, often in conjunction with acute coronary syndrome. Management may require reperfusion therapy or vasomotor support (see Chapter 49, "Acute Coronary Syndromes," and Chapter 50, "Cardiogenic Shock").

Other standard initial care measures include cardiac monitoring, IV access, and frequent vital sign assessments. A urinary drainage catheter may aid in monitoring fluid status in the severely ill or incontinent, but this is best reserved for those with extreme illness or an inability to void (to avoid catheter-related complications later).

HYPERTENSIVE ACUTE HEART FAILURE

The failing heart is sensitive to increases in afterload, with some patients developing pulmonary edema with a systolic blood pressure as low as 150 mm Hg. Prompt recognition and afterload reduction with vasodilators can avoid the need for intubation.[42]

Nitroglycerin A short-acting, rapid-onset, systemic venous and arterial dilator, **nitroglycerin** decreases mean arterial pressure by reducing preload; at high doses initially, it reduces afterload. Nitroglycerin may have coronary vasodilatory effects, decreasing myocardial ischemia and improving cardiac function. Choose the routes—IV, sublingual, or transdermal—based on symptom severity. Sublingual nitroglycerin spray is easily administered, rapidly bioavailable, and titratable to reach a desired clinical end point provided there is adequate blood pressure. An initial approach is sublingual administration of nitroglycerin, 0.4 milligrams (400 micrograms), 1-2 sprays or tablets every 5 minutes until relief or replacement with IV nitroglycerin. **A starting dose of 0.5 to 0.7 microgram/kg/min IV is common and titrated every few minutes up to 200 micrograms/min based on the blood pressure tolerance** and symptoms (**Table 53-4**). High doses aid in the acute setting, and adverse events are uncommon.[43] Apply transdermal nitroglycerin (0.5–2 inches to the chest wall based on blood pressure) **only** after initial therapy has improved conditions or if the symptoms are minor, because transdermal medication has a slow onset of action.

The most important nitroglycerin complication is hypotension, often lasting only transiently and, at times, even seen with overall clinical improvement. Hypotension usually resolves after cessation of nitroglycerin (**Table 53-5**). If persistent, think of concomitant volume depletion or right ventricular infarct, and deliver a normal saline fluid bolus (250 to 1000 mL). Headache is frequent, but acetaminophen usually is adequate therapy. Methemoglobinemia is a theoretic possibility, but not a concern unless high doses are used for extended intervals. Despite

TABLE 53-4 Management of Hypertensive Acute Heart Failure*

Stepwise Approach	Comments
Administer oxygen as needed for saturation ≥95%; give sublingual nitroglycerin.	Sublingual nitroglycerin may be repeated 1-2 sprays or tablets every 5 minutes.
If severe dyspnea, consider NIV or intubation.	
If BP >150/100 mm Hg, add IV nitroglycerin or nitroprusside; if BP falls below 100 mm Hg, stop nitrates, and monitor for persistent hypotension or symptoms (see Chapter 50, "Cardiogenic Shock"). If BP <150/100 mm Hg after sublingual administration and if improved, consider transdermal nitroglycerin.	See Chapter 58, "Pulmonary Hypertension"; see text for discussion of these agents.
Start IV loop diuretic (furosemide or bumetanide) in the setting of volume overload.	Initiate nitrates before diuretics.
Assess for severity of illness/high risk: altered mental status persistent, hypoxia despite NIV, hypotension, troponin elevation, ischemic ECG changes, tachycardia, tachypnea, or inadequate urine output.	See Chapter 49, "Acute Coronary Syndromes," for ECG criteria.
Admit to intensive care unit if high severity of illness or risk of decompensation.	
Choose discharge or ED observation unit admission if good response to therapy, no high-risk features, and good social support. Admit the rest. Admit to intensive care unit if any ongoing cardiorespiratory compromise or acute ischemia.	Scoring systems may not reliably identify all patients at risk.

*Inclusion: SBP >140 mm Hg.

Abbreviations: BP = blood pressure; NIV = noninvasive ventilation; SBP = systolic blood pressure.

broad uptake into regular clinical practice, nitroglycerin use has little supporting prospective data.

Nitroprusside If requiring further afterload reduction (i.e., continued high systemic vascular resistance usually manifested by persistent elevated blood pressure and continued symptoms despite nitroglycerin doses >200 micrograms/min), use IV **nitroprusside**. This is a potent arterial vasodilator; its hemodynamic effects include decreased blood pressure, left ventricular filling pressure reduction, and increased cardiac output. The initial dose of nitroprusside is 0.3 microgram/kg/min, titrated upward every 5 to 10 minutes based on blood pressure and clinical response (maximum 10 micrograms/kg/min). The major complication is hypotension. It is also associated with thiocyanate toxicity, especially with high doses, prolonged (>3 days) use, and hepatic or renal impairment.

The critical end point is rapidly lowering filling pressure to prevent the need for endotracheal intubation. Give or titrate up IV vasodilators as soon as possible when the blood pressure remains elevated.

Loop Diuretics After vasodilator therapy (or with near-normal blood pressure and symptoms; see next section), patients may require diuresis (see Table 53-6 and next section) based on continued symptoms after blood pressure is controlled. Loop diuretics (furosemide is the most commonly used) administered alone without vasodilators for hypertensive heart failure may increase mortality[44] and worsen renal dysfunction. Ultimately, successful management of blood pressure and cardiac filling pressure creates marked improvement in respiratory status long before any diuresis.

TABLE 53-5 Causes of Hypotension After Vasodilator Use

- Excessive vasodilation
- Hypertrophic obstructive cardiomyopathy
- Intravascular volume depletion
- Right ventricular infarction
- Cardiogenic shock/myocardial infarction
- Aortic stenosis
- Anaphylaxis
- Unsuspected sepsis

Contraindications and Alternatives to Vasodilation in Select Settings Because all vasodilators exert hypotensive effects, do not use if there are signs of hypoperfusion or existing hypotension. **Flow-limiting, preload-dependent states such as right ventricular infarction, aortic stenosis, hypertrophic obstructive cardiomyopathy, or volume depletion increase the risk of vasodilator-associated hypotension** (Table 53-5). Combined with acute pulmonary edema, the latter preload-dependent states are very difficult to manage. In these settings, aim therapy at decreasing the outflow gradient by slowing heart rate and cardiac contractility. Although this can be accomplished with IV β-blockers, it is best done with invasive hemodynamic guidance. If there is coexistent shock in the setting of hypertrophic obstructive cardiomyopathy, phenylephrine (40 to 100 micrograms/min IV) is a good choice because it creates peripheral vasoconstriction without increasing cardiac contractility.

NORMOTENSIVE HEART FAILURE

Shortness of breath, orthopnea, jugular venous distention, rales, and an S_3 may exist in the presence of normal vital signs, oxygenation, and ventilation. In this situation, diuresis should occur first, with further treatment based on response to therapy (**Table 53-6**).

Loop diuretics provide rapid symptomatic relief of congestive symptoms and improve the effects of angiotensin-converting enzyme inhibitors by decreasing intravascular volume. Most ED patients with anything but modest symptoms should receive IV dosing because bowel wall edema may prevent proper GI absorption. Choose the dose based on symptoms and prior usage (Table 53-6). In general, dose loop diuretics at the lowest possible dose that relieves congestion. After initial relief, a fixed maintenance dose helps prevent recurrence.

Loop diuretics promote water and sodium excretion; they are effective except in severe renal dysfunction or diuretic resistance (failure to achieve the therapeutically desired reduction in congestion despite a full dose of diuretic). Furosemide is inexpensive and effective. Alternatives are bumetanide (1 milligram equivalent to 40 milligrams of furosemide) or torsemide (20 milligrams equivalent to 40 milligrams of furosemide). All usually trigger rapid diuresis after an IV dose, often within 10 to 15 minutes.

The DOSE trial suggests that a reasonable starting point for IV diuretic dosing is 1 to 2.5 times the patient's previous total daily oral dose, divided in half and administered by IV bolus every 12 hours.[45] For example, if the patient is on furosemide 80 milligrams PO twice a day, then an initial ED dose is 80 to 200 milligrams IV bolus. Higher doses create more rapid symptom improvement but also a slight decrease in renal function. For patients who are loop diuretic naive, a reasonable starting dose is furosemide 40 milligrams IV bolus. Ethacrynic acid (0.5 to 1 milligram/kg; maximum 100 milligrams) is another option. Sulfa allergy is generally not a concern with nonantibiotic drugs such as diuretics that contain a sulfa moiety.

Diuretics may worsen renal function and create hypokalemia. If a prolonging QT interval exists, look for hypocalcemia, hypokalemia, or hypomagnesemia. Ototoxicity is rare but may occur if using diuretics with aminoglycoside antibiotics. Potassium-sparing diuretics, such as spironolactone (25 to 50 milligrams PO), are common in care of those with advanced chronic heart failure; these are used more for their mortality benefit than diuretic effect.

Urinary diuretic response requires monitoring. With greater symptoms or less response to initial IV diuretics, double the dose and repeat in 30 to 60 minutes or as needed based on urine output. Ongoing congestion or dyspnea after a loop diuretic may signal the need for another therapy, such as a vasodilator.

Several studies have evaluated the relationship of timing of diuretic therapy in relationship to patient outcomes in the setting of acute

TABLE 53-6 Medications for Acute Heart Failure

Vasodilators for Acute Heart Failure			
Vasodilator	**Dose**	**Titration End Point**	**Complications**
Sublingual NTG	0.4 milligram every 1–5 min	Blood pressure	Hypotension
IV NTG	0.5–0.7 microgram/kg/min (starting dose if blood pressure okay)	Symptoms	Headache, hypotension
Nitroprusside	0.3 microgram/kg/min (starting dose), 10 micrograms/kg/min (maximum)	Blood pressure Symptoms	Hypotension, cyanide/thiocyanate toxicity, coronary steal
Diuretics for Heart Failure			
Diuretic	**Dose (IV)**	**Effect**	**Complications**
Furosemide	No prior use: 20–40 milligrams IVP If prior use: total daily IV dose 1–2.5 times the patient's previous total daily oral dose, divided in half and given IV bolus every 12 h If no effect by 20–30 min, increase subsequent dose	Diuresis starts within 15–20 min Duration of action is 4–6 h	↓ K^+, ↓ Mg^{2+}, hyperuricemia, hypovolemia Ototoxicity, prerenal azotemia
Bumetanide	1–3 milligrams IV (40:1 furosemide)	Diuresis starts within 10 min Peak action at 60 min	Same as above
Torsemide	10–20 milligrams IV (2:1 furosemide)	Diuresis starts within 10 min Peak action in 1–2 h	Same as above

Abbreviations: IVP = IV push; NTG = nitroglycerin; ↓ = decreased.

heart failure. One trial noted a hospital mortality benefit (2.3% vs. 6%) for patients receiving diuretics within 60 minutes of ED arrival.[46] Conversely, another trial found no significant difference in in-hospital mortality or mortality 1 month after hospital discharge between those who received IV diuretics early compared to those who received them later.[47] Such confounding results may be related to the heterogeneity of presentation of acute heart failure leading to variations in the timing of diagnosis (and thus associated therapy).

Morphine is not a good choice for acute heart failure due to the potential for adverse events, including the need for mechanical ventilation, prolonged hospitalization, intensive care unit admission, and mortality.[48] If desired for its venodilation properties or pain control, use morphine in small, titrated doses (2 to 4 milligrams IV) and with monitoring.

Oral angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are given for hypertension and chronic heart failure, but there are no solid data to recommend use in the ED for acute heart failure.[49] Ongoing oral angiotensin-converting enzyme inhibitors decrease mortality and hospitalizations in patients with reduced ejection fraction.[4] Consider these *after observation care* if no contraindications exist and with coordination together with the follow-up physician. Oral angiotensin receptor blockers are alternatives or can be added to angiotensin-converting enzyme inhibitors in select heart failure patients with reduced ejection fraction.[4] IV enalaprilat appears safe and perhaps efficacious in patients with acute heart failure, but further data are required to define an ED role.

β-Blockers are not usually initiated in the acute setting except to control rate-related heart failure. Norepinephrine levels are elevated in heart failure, contribute to myocardial hypertrophy, increase afterload and coronary vasoconstriction, and are associated with mortality. β-Blockers reduce sympathetic nervous system activity and are used for mortality reduction and symptom relief.

Oral **calcium channel blockers** have myocardial depressant activity and are not routine treatment for acute heart failure; trials demonstrate either no benefit or worse outcomes.

Avoid selective or nonselective **NSAIDs** in patients with acute heart failure. They can cause sodium and water retention and blunt the effects of diuretics[4] and may increase morbidity and mortality.

DISPOSITION DECISIONS

Emergency physicians serve as major decision makers for approximately one half of all inpatient admissions for acute heart failure in the United States. A lack of national guideline disposition recommendations, the absence of robustly validated decision tools, and the high rates of relapse and mortality after an ED discharge lead to ED admission for >80% of patients treated in the ED for acute heart failure.[6,12] Consensus guidelines have addressed acute heart failure risk stratification, but they provide little objective instruction for ED disposition decision making.

Thus, disposition decisions are often based on physician judgment, a physiologic risk evaluation, and an assessment of barriers to successful outpatient care such as caregiver support, medication access, and timely follow-up (**Figure 53-3**).[3] There have been many investigations of high-risk physiologic markers in ED patients with acute heart failure (**Table 53-7**), but most were retrospective, involved hospitalized patients, lacked a measurement of additive value to clinical assessment, and did not use a rigorous acute heart failure diagnostic standard.[12,50] These limitations notwithstanding, renal dysfunction, low blood pressure, low serum sodium, and elevated cardiac biomarkers (troponin or natriuretic peptides) are consistently associated with an increased risk of morbidity and mortality. Unfortunately, high-risk markers are not present in up to 50% of ED patients, limiting the impact in disposition decisions.[12]

Admit patients with high-risk features to the hospital (**Table 53-8**).[51] Those who require invasive monitoring or procedures require intensive care unit admission. Others may be appropriate for non–intensive care unit level care. Observation unit management is an option in those who lack higher-risk features. Many patients do not have high-risk features at initial evaluation and experience improvement in dyspnea during their ED stay after treatment with standard therapy.[52] Many have complete symptom resolution within 12 to 24 hours of initial therapy, a typical time period of observation. The monitoring of blood pressure, heart rate, urine output, and body weight is easily accomplished in the observation unit, and additional diagnostic testing (labs, echocardiography) needed can occur. Finally, an extended observation interval allows patients to receive heart failure education, confirm outpatient medications, assess self-care barriers, and arrange follow-up prior to discharge. If discharged directly or after an observation stay, outpatient follow-up within 5 days can decrease readmissions.[53]

Prior studies suggest 75% of patients will respond to therapy, will have no identifiable high-risk features, and will be discharged home. Their rates of readmission are similar to or better than those who are managed in an inpatient setting.[54,55] Patients with an inadequate response to initial therapy or with high-risk features identified during observation should be admitted to the hospital for further management. An observation unit strategy can help reduce costs while delivering quality care for select lower-risk ED patients with acute heart failure.[54]

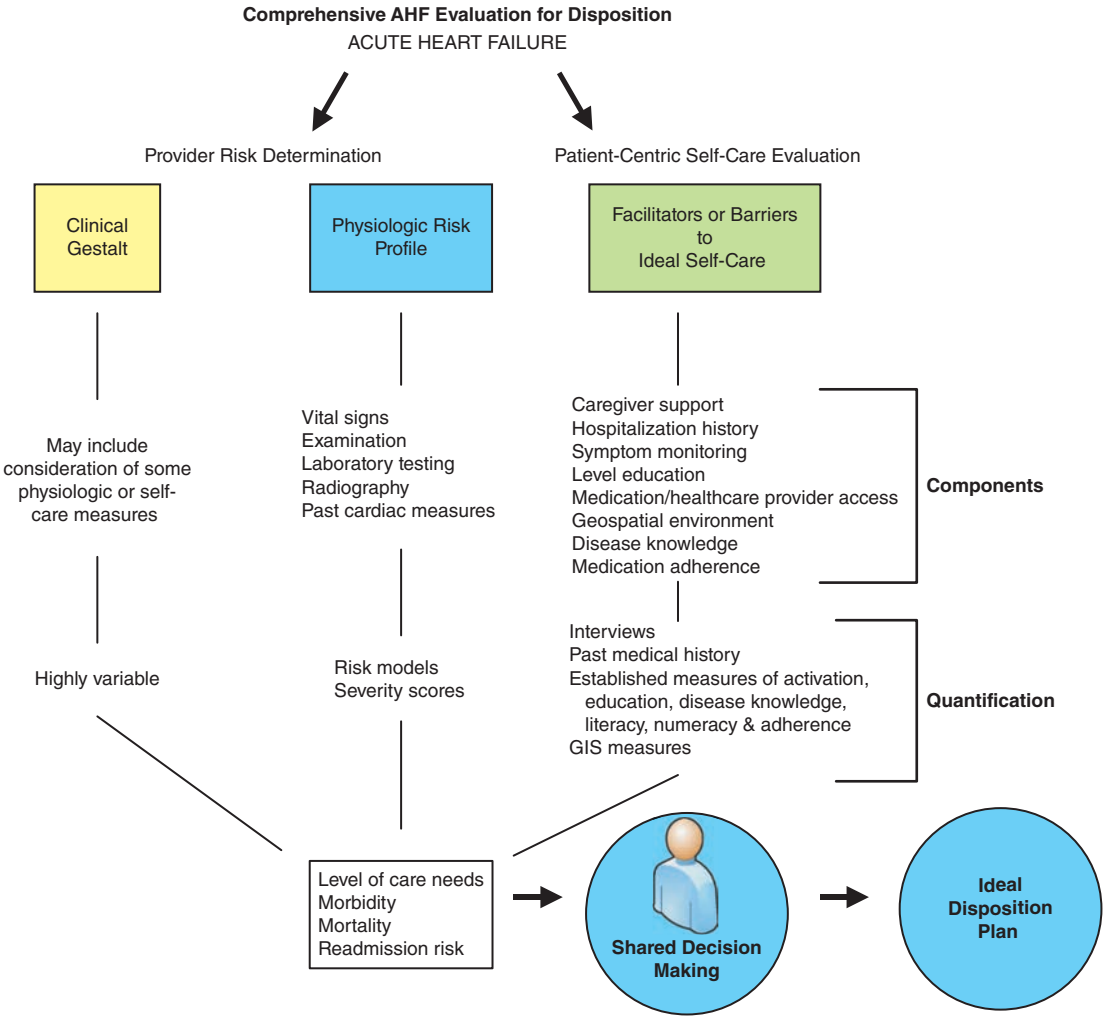

FIGURE 53-3. Factors impacting disposition decisions in ED patients with acute heart failure (AHF). [Reproduced with permission from Collins SP, Storrow AB: Moving toward comprehensive acute heart failure risk assessment in the emergency department: the importance of self-care and shared decision making, *JACC Heart Fail*. 2013 Aug;1(4):273-280.]

TABLE 53-7 Selected ED-Based Risk-Stratification Studies That Examine Events Within 30 Days or Less of Index ED Presentation

Author/Year	No. of Patients	Predicted Outcome	Variables in Final Model	Low-Risk Markers
Miro 2017	4867/3229	30-day mortality	Barthel index of activities of daily living, SBP, age, NT-proBNP, potassium level, Tn, NYHA classification, RR, low-output symptoms, saO_2, ACS, hypertrophy on ECG, creatinine level	No
Collins 2015	1033	ACS, coronary revascularization, emergent dialysis, intubation, mechanical cardiac support, cardiopulmonary resuscitation, death	Age, BMI, BNP, BUN, dialysis, DBP, sodium, supplemental oxygen, outpatient ACEI, QRS duration, RR, O_2 saturation, Tn	No
Lassus 2013	441–4450 (pooled analysis, total number varied by biomarker evaluated)	30-d and 1-y mortality	ST2, MR-proADM, CRP, NT-proBNP, BNP, and MR-proANP in addition to clinical model (age, gender, BP on admission, estimated glomerular filtration rate <60 mL/min/1.73 m^2, sodium and hemoglobin levels, and heart rate)	No
Stiell 2013	559	30-d death and 14-d serious nonfatal events	History of TIA/CVA, vital signs, ECG and lab findings	No
Lee 2012	15,164	7-d mortality	Creatinine, BP, O_2 saturation, Tn, history of cancer, home metolazone, EMS transport	Yes
Hsieh 2008	8384	Inpatient mortality or serious medical complications, 30-d mortality	pH, pulse, renal function, WBC, glucose, sodium	Yes
Lee 2003	2624/1407	30-d mortality	Age, RR, BP, BUN, sodium, cerebrovascular disease, dementia, COPD, cirrhosis, cancer, hemoglobin	Yes
Auble 2005	33,533	Inpatient mortality or serious medical complications, 30-d mortality, and AHF readmission	pH, pulse, renal function, WBC, glucose, sodium	Yes
Fonarow 2005	65,275	In-hospital mortality	BUN, systolic BP, creatinine	No

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ADM = adrenomedullin; AHF = acute heart failure; ANP = atrial natriuretic peptide; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CVA = cerebrovascular accident; DBP = diastolic blood pressure; MR = midregional; NT = N-terminal; NYHA = New York Heart Association; RR = respiratory rate; saO_2 = arterial oxygen saturation; SBP = systolic blood pressure; TIA = transient ischemic attack; Tn = troponin.

TABLE 53-8 Heart Failure Observation Unit/Short Stay Exclusion Criteria

Recommended Exclusions

- Positive troponin
- BUN >40 milligrams/dL
- Creatinine >3.0 milligrams/dL
- Sodium <135 mEq/L
- New ischemic changes on ECG
- New onset of acute heart failure*
- IV vasoactive infusions being actively titrated
- Significant comorbidities requiring acute interventions
- Respiratory rate ≥32 breaths/min and/or requiring noninvasive ventilation at the time of OU consideration
- Signs of poor perfusion at the time of OU consideration

Suggested Exclusions

- Poor social support
- Poor follow-up

*Although part of the published guidelines, many institutions admit patients to OUs with new-onset heart failure.

Abbreviation: OU = observation unit.

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 54

Valvular Emergencies

William D. Alley

INTRODUCTION

Although acute valvular dysfunction may cause dramatic symptoms, most valvular heart disease encountered in the ED is chronic and incidentally noted on exam. Adaptive responses preserve cardiac function and delay the diagnosis of chronic valvular disease but contribute to eventual cardiac dysfunction. Compared with the general population, patients with clinically evident valvular heart disease have a 2.5-fold higher death rate and a 3-fold increased rate of stroke.[1]

THE NEWLY DISCOVERED MURMUR

After discovering a new murmur, the first step in the ED is to determine its clinical significance. Seek a new murmur in patients with acute dyspnea or weakness. Benign or physiologic murmurs are common and do not cause symptoms or findings compatible with cardiovascular disease; they are generally soft systolic ejection murmurs that begin after S_1, end before S_2, and are not associated with other abnormal heart sounds. Systolic murmurs may be associated with anemia, sepsis, volume overload, or other conditions causing an increased cardiac output. Focus the evaluation and treatment on the trigger. Patients without chest pain, dyspnea, fever, or other signs attributable to valvular disease do not need emergent treatment.

Any diastolic murmur or new systolic murmur with symptoms at rest is pathologic and warrants emergent echocardiography (**Figure 54-1**). Think of endocarditis, especially in suspected valvular insufficiency. **Table 54-1** presents a grading system for murmurs.

MITRAL STENOSIS

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Mitral stenosis prevents normal diastolic filling of the left ventricle. Rheumatic heart disease remains the most common cause worldwide. Rheumatic carditis causes fusion of valvular commissures, matting of chordae tendineae, and eventual calcification and limited mobility of the valve. Valvular obstruction is slowly progressive, often with 20 to 40 years before onset of symptoms. Mitral valve obstruction causes left atrial pressure to rise, resulting in left atrial enlargement, pulmonary congestion, pulmonary hypertension, and frequently atrial fibrillation. In severe disease, pulmonary hypertension may lead to pulmonic and tricuspid valve incompetence, pulmonary edema, right-sided heart failure, and bronchial vein rupture.

Mitral annular calcification is a slowly progressive nonrheumatic cause of mitral stenosis. It is more common among women, the elderly, and those with hypertension or with chronic renal failure.[2] Due to its slow progression, mitral annular calcification rarely causes severe symptoms.

CLINICAL FEATURES

Exertional dyspnea is the most frequent presenting complaint, and orthopnea and palpitations/premature atrial contractions are also common. Symptoms associated with left- or right-sided heart failure may occur with more severe obstruction. Systemic emboli are also a risk. Hemoptysis is a rare presenting symptom, although it can be massive.

Signs of mitral stenosis include a mid-diastolic rumbling murmur with crescendo toward S_2. With the onset of atrial fibrillation, the presystolic accentuation of the murmur disappears. Typically, the S_1 is loud and is followed by a loud opening snap that is high pitched and best heard to the right of the apex (**Table 54-2**). The apical impulse is small and tapping due to an underfilled left ventricle. Systemic blood pressure is typically normal or low. If pulmonary hypertension is present, signs may include a thin body habitus, peripheral cyanosis, and cool extremities.

DIAGNOSIS AND TREATMENT

The ECG is not diagnostic but may demonstrate notched or biphasic P waves and right axis deviation in patients with mitral stenosis (**Figure 54-2**). On chest radiograph, straightening of the left heart border, indicating left atrial enlargement, is a typical and early radiographic finding. Eventually, pulmonary congestion occurs.

Echocardiography is the test to diagnose mitral stenosis (**Figure 54-3**). Before any interventions, transesophageal echocardiography offers the best assessment of any mitral regurgitation and the presence of a left atrial thrombus.[3]

Medical management focuses primarily on symptom control and anticoagulation. Patients in atrial fibrillation or with dyspnea on exertion may benefit from heart rate control with a β-blocker or calcium channel blocker. Experts recommend anticoagulation if the left atrial diameter is >55 mm or the patient has atrial fibrillation, a left atrial thrombus, or history of systemic emboli. In patients with hemoptysis from mitral stenosis–induced pulmonary hypertension, bleeding may be severe enough to require blood transfusion, emergent bronchoscopy, and consultation with a thoracic surgeon.

The most important ED action for patients with suspected but asymptomatic mitral stenosis is recognition and referral. The primary treatment for symptomatic disease is percutaneous mitral commissurotomy, optimally performed before onset of severe pulmonary hypertension.

MITRAL REGURGITATION

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Mitral regurgitation occurs when a dysfunctional valve allows retrograde blood flow from the left ventricle into the left atrium during systole. Most patients with mitral regurgitation follow a chronic and slowly progressive course. Fibroelastic deficiency syndrome is the most

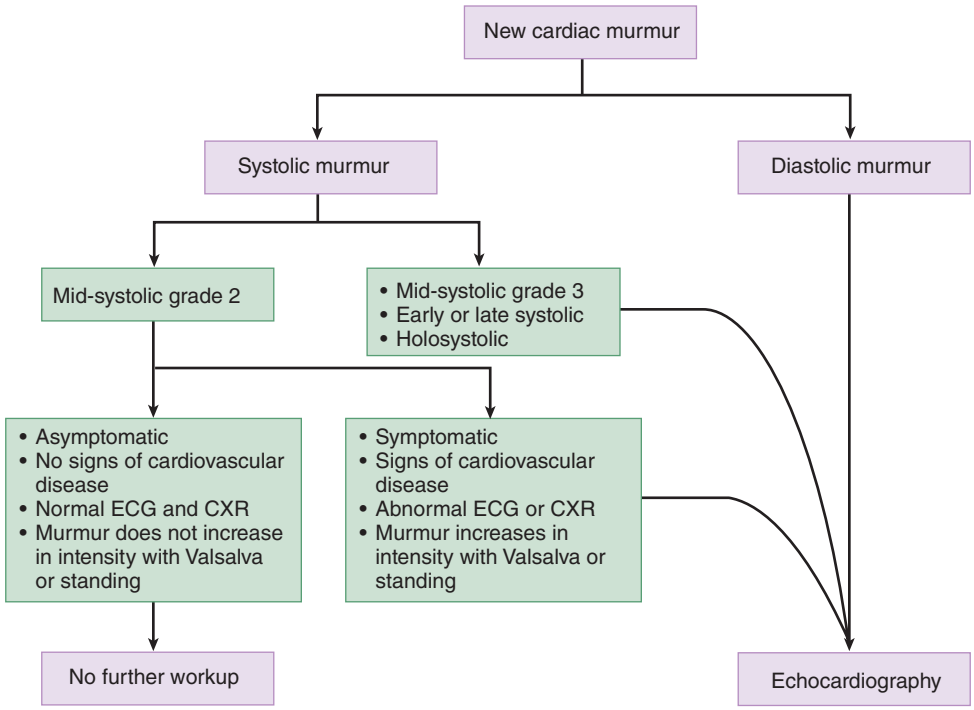

FIGURE 54-1. Algorithm for evaluation of newly discovered systolic murmur. CXR = chest radiograph.

TABLE 54-1 A Grading System for Murmurs

Grade	Description
1	Faint, may not be heard in all positions
2	Quiet, but heard immediately with stethoscope placement onto the chest wall
3	Moderately loud
4	Loud
5	Heard with stethoscope partly off the chest wall
6	Heard when stethoscope is entirely off the chest wall

TABLE 54-2 Comparison of Heart Murmurs, Sounds, and Signs

Valve Disorder	Murmur	Heart Sounds and Signs
Mitral stenosis	Mid-diastolic rumble, crescendos into S_2	Loud snapping S_1, small apical impulse, tapping due to underfilled ventricle
Mitral regurgitation	Acute: harsh apical systolic murmur starts with S_1 and may end before S_2 Chronic: high-pitched apical holosystolic murmur radiating into S_2	S_3 and S_4 may be heard
Mitral valve prolapse	Click may be followed by a late systolic murmur that crescendos into S_2	Mid-systolic click; S_2 may be diminished by the late systolic murmur
Aortic stenosis	Harsh systolic ejection murmur	Paradoxical splitting of S_2, S_3, and S_4 may be present; pulse of small amplitude with a slow rise and sustained peak
Aortic regurgitation	High-pitched blowing diastolic murmur immediately after S_2	S_3 may be present; wide pulse pressure

common cause, seen primarily in the elderly.[4] **Mitral valve prolapse** is another cause and is typically found in younger patients. Secondary mitral regurgitation occurs when a dilated left ventricle causes papillary muscle displacement and valve dysfunction.

In chronic mitral regurgitation, the left atrium dilates to accommodate increasing regurgitant flow to keep left atrial pressure near normal. Stroke volume augments flow, maintaining effective forward flow despite a large regurgitant volume. In contrast, acute mitral regurgitation results in acute left-sided heart failure. Cardiogenic shock may ensue from impaired forward blood flow. **Acute mitral regurgitation** is typically caused by papillary muscle or chordae tendineae rupture from myocardial infarction or valve leaflet perforation from infective endocarditis. Blunt thoracic trauma and spontaneous chordae tendineae rupture are other rare causes.

CLINICAL FEATURES

Symptoms of acute mitral regurgitation are severe dyspnea, tachycardia, and pulmonary edema. Cardiogenic shock or cardiac arrest can develop rapidly. Typical signs include an S_3 gallop and a harsh apical systolic murmur loudest in early or mid-systole, diminishing before S_2 (Table 54-2), although the murmur may not be audible over breath sounds. A hyperactive apical impulse may be apparent. Overwhelming dyspnea may mask chest pain in the setting of ischemia.

Chronic mitral regurgitation can be tolerated for years without symptoms. Eventually exertional dyspnea develops, sometimes associated with palpitations or atrial fibrillation. Signs include a late systolic left parasternal lift and lateral displacement of the apical impulse. A high-pitched holosystolic murmur is best heard in the fifth intercostal space and mid-left thorax and radiates to the axilla. The first heart sound is soft and often obscured by the murmur. An S_3 is usually heard and is followed by a short diastolic rumble, indicating increased flow into the left ventricle.

DIAGNOSIS AND TREATMENT

Think of acute mitral regurgitation in any patient with new-onset and marked pulmonary edema, especially in patients with near-normal heart size on chest radiograph or in those who do not respond to conventional therapy. Obtain an ECG to look for signs of ischemia, frequently

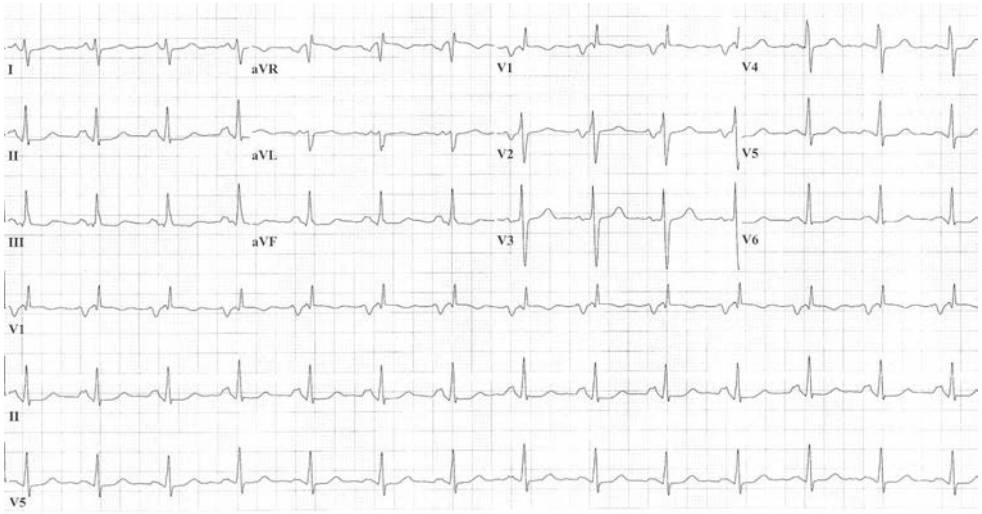

FIGURE 54-2. The ECG in mitral stenosis, demonstrating left atrial enlargement and right axis deviation. Note abnormal P waves in lead V_2.

in the inferior or anterior walls. In chronic mitral regurgitation, the ECG may demonstrate left atrial enlargement and left ventricular hypertrophy, and the chest radiograph shows left atrial and ventricular enlargement that is proportional to the severity of the regurgitant volume. Transthoracic echocardiography (**Figure 54-4**) diagnoses mitral regurgitation but may underestimate the severity of regurgitation. If nondiagnostic, cardiac MRI or transesophageal echocardiography may be undertaken.[3] Exercise stress echocardiography may aid diagnosis.

For acute mitral regurgitation due to papillary muscle rupture, emergency surgery is the treatment of choice. In the ED, start therapy with oxygen and positive-pressure ventilation for respiratory failure (see Chapter 53, "Acute Heart Failure"). Nitrates provide afterload reduction, which results in increased forward flow into the aorta. Inotropic therapy with dobutamine may be necessary. Aortic balloon counterpulsation increases forward flow and mean arterial pressure while diminishing regurgitant volume and left ventricular filling pressure.

Treatment of severe mitral regurgitation from acute myocardial infarction includes emergent revascularization.[5] Endocarditis causing acute mitral valve insufficiency requires additional antibiotic therapy (see Chapter 156, "Endocarditis").

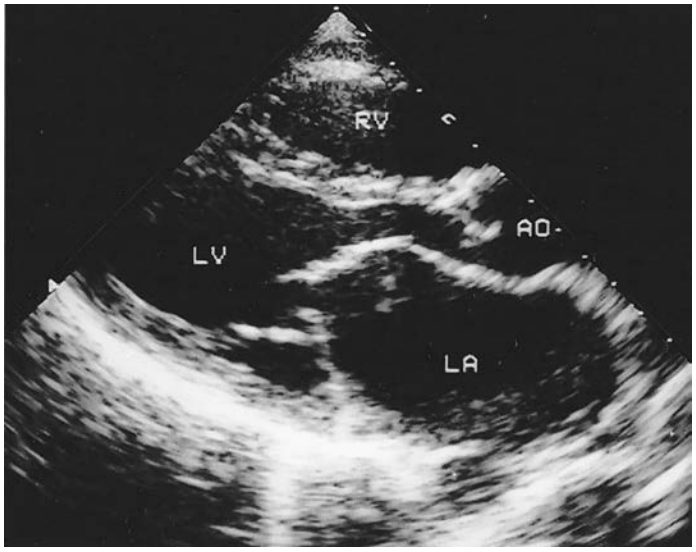

FIGURE 54-3. Parasternal long-axis view of mitral stenosis. The left atrium is enlarged, mitral opening is limited, and doming of the anterior mitral leaflet is present. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle. [Reproduced with permission from Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P (eds): *Hurst's the Heart*, 12th ed. © 2008, McGraw-Hill, New York.]

Medical therapy may improve regurgitant flow and allow a delay to surgery. The key is emergency cardiology and surgical consultation while medically optimizing care.

In patients with chronic mitral regurgitation, emergency treatment is based on acute symptoms. Control atrial fibrillation with rapid ventricular response with β-blockers or calcium channel blockers, and start anticoagulation to avoid embolization. Long-term management is best decided by the primary care provider or a cardiologist.

MITRAL VALVE PROLAPSE

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Mitral valve prolapse is a systolic billowing of one or both leaflets into the left atrium occurring with or without mitral regurgitation. It is characterized by myxomatous degeneration of the valve caused by heritable defects in connective tissue proteins. It is the most common valvular heart disease in industrialized countries, affecting approximately 2.4% of the population.[6] Morbidity and mortality follow the presence of concomitant mitral regurgitation.[7]

CLINICAL FEATURES

Most patients with mitral valve prolapse are asymptomatic, but symptoms may include chest pain, palpitations, fatigue, anxiety, and dyspnea unrelated to exertion. Signs such as scoliosis, pectus excavatum,

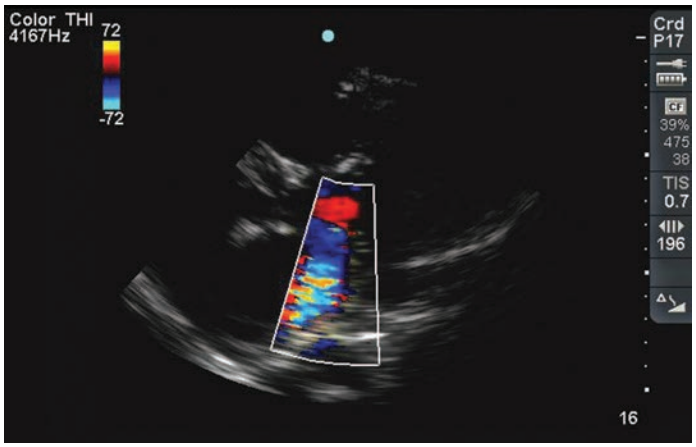

FIGURE 54-4. A transthoracic echocardiogram demonstrating severe mitral regurgitation. Color flow Doppler shows regurgitant flow back into the left atrium.

and low body weight can exist. If exercise induces symptoms, morbidity increases.[8]

The classic auscultatory finding is a mid-systolic click (Table 54-2). Maneuvers that decrease preload, such as Valsalva or standing, will cause the click to occur earlier in diastole. Increasing preload by squatting or afterload by hand grips causes the systolic click to move later in systole. A late systolic murmur that crescendos into S_2 may be present.

DIAGNOSIS AND TREATMENT

The diagnosis is unlikely to be made in the ED. The emergency evaluation focuses on late complications such as atrial fibrillation or heart failure. The ECG is usually normal. If suspecting mitral valve prolapse, refer the patient for outpatient echocardiography to confirm the diagnosis and to identify any complications.[9]

ED treatment is rarely required. Patients with palpitations attributed to mitral valve prolapse may respond to oral β-blockers, but that is typically left to the cardiologist or primary care physician. Antithrombotic therapy is not routinely recommended unless complicated by transient ischemic attacks, stroke, or atrial fibrillation.[10,11] Patients with concomitant mitral regurgitation require endocarditis prophylaxis (see Chapter 156).[9]

AORTIC STENOSIS

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Aortic stenosis prevents left ventricular outflow. In the United States, the most common cause in adults is degenerative calcification (calcific aortic stenosis), associated with increasing age, hypertension, smoking, elevated cholesterol, and diabetes.[12,13] Rheumatic heart disease is a major cause of aortic stenosis worldwide. Bicuspid aortic valves and congenital heart disease are causes as well, especially in younger patients.

The typical course involves a long asymptomatic period, during which the left ventricle hypertrophies to preserve ejection fraction. Ventricular hypertrophy eventually impairs diastolic filling and increases myocardial oxygen demand. Slowly, aortic valve obstruction worsens, cardiac output diminishes, and systemic blood flow and coronary blood flow are impaired.

CLINICAL FEATURES

The classic triad of aortic stenosis is dyspnea, chest pain, and syncope. However, many patients with severe stenosis (aortic valve area <1.0 cm^2) are asymptomatic. Often, a long asymptomatic period is followed by stepwise onset of symptoms starting with dyspnea followed by chest pain, then syncope, and finally signs of heart failure. Once symptoms start, mortality increases.[14] Decreased exercise tolerance and exertional dyspnea or dizziness may be unnoticed or unreported prior to more ominous symptoms.

Classic physical examination findings are a late peaking systolic murmur at the right second intercostal space radiating to the carotids, a single or paradoxically split S_2, an S_4 gallop, and a diminished carotid pulse with a delayed upstroke (*pulsus parvus et tardus*; Table 54-2). Brachioradial delay may also be a useful early finding, as is a narrowed pulse pressure.

Aortic stenosis with atrial fibrillation can have dire consequences given the common diastolic dysfunction and preload dependence to maintain cardiac output. Without effective atrial contraction, cardiac output drops dramatically, especially if the patient is given nitroglycerin to treat chest pain or dyspnea.

DIAGNOSIS AND TREATMENT

ECG and chest radiograph lack sensitivity and specificity. The ECG usually demonstrates left ventricular hypertrophy, and a left or right bundle branch block may be present. The chest radiograph is normal early in the disease, but eventually signs of left ventricular hypertrophy and acute heart failure develop. Echocardiography confirms the diagnosis and determines severity (**Figure 54-5**). Low-dose dobutamine stress echocardiography aids identification prior to the development of classic symptoms.[3]

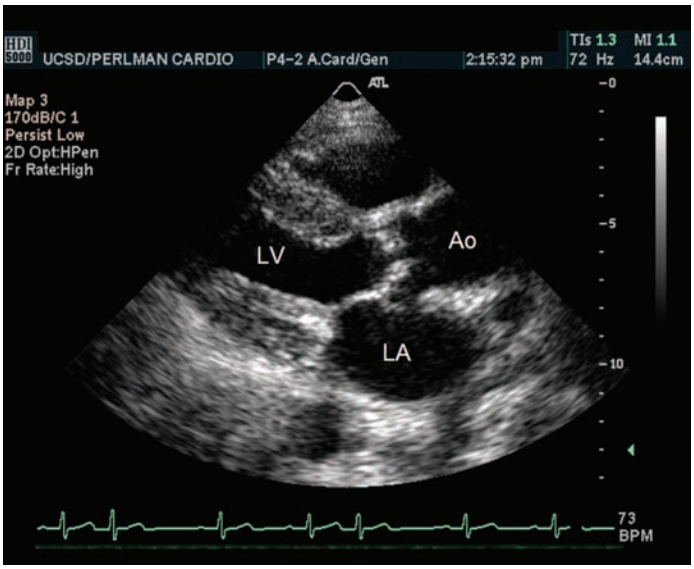

FIGURE 54-5. Parasternal long-axis plane demonstrating a thickened, stenotic aortic valve. Ao = aorta; LA = left atrium; LV = left ventricle. [Reproduced with permission from Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P (eds): *Hurst's the Heart*, 12th ed. © 2008, McGraw-Hill, New York.]

Treat pulmonary edema with oxygen and positive-pressure ventilation as necessary. Negative inotropic drugs, such as β-blockers or calcium channel blockers, are often poorly tolerated. **Use nitrates, vasodilators, and diuretics with close monitoring** because reducing preload may cause significant hypotension. New-onset atrial fibrillation may require cardioversion to maintain cardiac output.

Surgical management, either open or by transcatheter approach, is a mainstay of treatment. Without surgery, 40% to 50% of patients with classic symptoms die within 1 year.[15,16] Patients discharged from the ED should avoid vigorous physical activity and be seen promptly by a cardiologist. Endocarditis in isolated aortic stenosis is uncommon, and antibiotic prophylaxis is not routinely recommended (see Chapter 156).[9]

AORTIC REGURGITATION

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Aortic regurgitation occurs when valve leaflets fail to close fully, causing blood to flow from the aorta into the left ventricle during diastole. Over time, increased left ventricular wall stress leads to hypertrophy. Increased stroke volume followed by a rapid pressure drop during diastole causes wide pulse pressures. Tachycardia shortens diastole, which decreases regurgitant volume and mutes symptoms early in the disease. In contrast, increased afterload during stress or isometric exercise exacerbates regurgitant flow and may precipitate symptoms. Over time, the combination of increasing left ventricular dilatation and hypertrophy compromises systolic function, resulting in heart failure.

Among patients in the Framingham Heart Study receiving echocardiography, aortic insufficiency existed in 13% of men and 8.5% of women, mostly of trace or minor severity.[17] Approximately half of cases are due to valvular leaflet problems from bicuspid aortic valves, infective endocarditis, or rheumatic disease. Nonvalvular causes include aortic dissection, Marfan's syndrome, or aortitis.[18] Aortic regurgitation is also frequently associated with aortic stenosis.

CLINICAL FEATURES

Acute aortic regurgitation generally presents rapidly, with dyspnea and pulmonary edema being the most common presenting symptoms. To maintain cardiac output, tachycardia develops but is often inadequate, resulting in cardiogenic shock or cardiac arrest. Sudden-onset ripping

or tearing interscapular pain suggests **aortic dissection**. Fever or history of IV drug abuse suggests endocarditis.

On physical exam, the classic finding is a high-pitched blowing diastolic murmur heard immediately after S_2, in the second or third intercostal space at the left sternal border (Table 54-2). In acute disease, the murmur may be inaudible due to tachycardia, tachypnea, and rales. A systolic ejection murmur due to increased stroke volume and an S_3 due to ventricular dilatation may exist. In the left lateral decubitus position, listen for a mid-diastolic rumble (Austin Flint murmur) using the bell of the stethoscope at the cardiac apex. A widened pulse pressure is also common. The classic "water hammer pulse" (Corrigan pulse) is a peripheral pulse with a quick rise in upstroke due to increased stroke volume followed by collapse from a rapid fall in diastolic pressure. Other classic findings include accentuated precordial apical thrust, pulsus bisferiens, Duroziez sign (a "to-and-fro" femoral murmur), de Musset sign (pulsatile head bobbing), and Quincke sign (capillary pulsations visible at the proximal nail bed while pressure is applied at the tip).

Patients with chronic aortic regurgitation typically present with exertional dyspnea or fatigue. Chest pain may occur from myocardial ischemia due to low diastolic pressures that decrease coronary blood flow. Symptoms of left ventricular failure may occur late in the disease, but greater than one quarter of patients with chronic aortic regurgitation die or develop left heart dysfunction before symptoms occur.[9]

DIAGNOSIS AND TREATMENT

ECG findings are generally nonspecific. The most common abnormality is left ventricular hypertrophy. Ischemic changes or ST elevation may be seen from aortic dissection involving the coronary arteries. In chronic aortic regurgitation, the chest radiograph reveals cardiomegaly, aortic dilatation, and, possibly evidence of congestive heart failure. Echocardiography confirms the diagnosis and determines the cause and severity of regurgitation.[3] Unstable patients require emergency echocardiography (**Figure 54-6**). Chest radiograph may show acute pulmonary edema without cardiac enlargement. If due to aortic dissection, the chest radiograph may show a widened mediastinum (see Chapter 59, "Aortic Dissection and Related Aortic Syndromes"). If suspecting aortic dissection, perform CT angiogram.

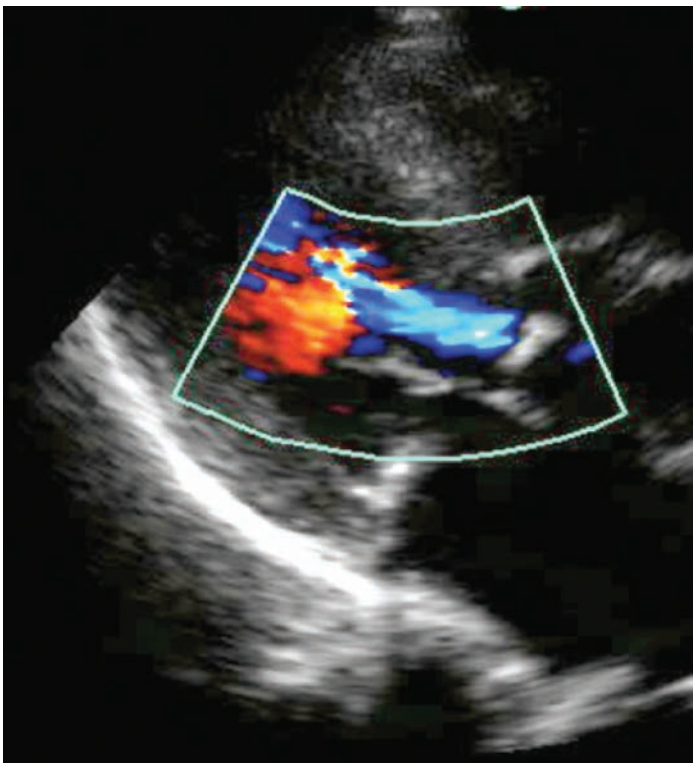

FIGURE 54-6. Parasternal long-axis view with blue regurgitant jet demonstrating severe aortic regurgitant flow back into the left ventricle. [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA (eds): *Ma & Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill Education; 2014, Figure 6-73B.]

Acute aortic regurgitation requires immediate surgical intervention. Treat pulmonary edema with oxygen and intubation for respiratory failure. Vasodilators such as nitroprusside, combined with inotropic agents such as dobutamine or dopamine, may augment forward flow and reduce left ventricular end-diastolic pressure. Diuretics and nitrates are usually ineffective. **Although β-blockers are commonly used in aortic dissection, avoid these in acute aortic regurgitation** because they block the compensatory tachycardia that is critical in maintaining cardiac output. Intra-aortic balloon counterpulsation is also contraindicated because it worsens regurgitant flow. Despite intensive medical management, death from ventricular dysrhythmias, pulmonary edema, or cardiogenic shock is common. In patients with only mild acute aortic regurgitation due to endocarditis, antibiotics may be adequate treatment without acute surgical intervention.

Chronic aortic regurgitation is usually treated with vasodilators such as angiotensin-converting enzyme inhibitors or dihydropyridine calcium channel blockers.[3] If acute symptoms such as pulmonary edema or chest pain occur, admit the patient for stabilization and further management. Patients who become symptomatic, have a low ejection fraction, or have significant left ventricular dilatation are candidates for aortic valve replacement, either open or by transcatheter approach.

RIGHT-SIDED VALVULAR HEART DISEASE

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The incidence of true right-sided valvular heart disease is unknown because normal subjects frequently have a small amount of tricuspid and pulmonary valve regurgitation at baseline. Pathologic **tricuspid regurgitation** is usually due to elevated right heart pressure or volume overload, such as from pulmonary hypertension, chronic lung disease, pulmonary embolism, or atrial septal defects. **Tricuspid stenosis** is rare and is generally accompanied by regurgitation. The **pulmonic valve** is the least likely valve to be affected by acquired disease. Most pulmonic valvular disease is congenital (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease"), although pulmonary hypertension, rheumatic heart disease, and carcinoid syndrome can rarely cause some degree of pulmonic valve disease. Acute onset of symptomatic tricuspid disease is most often due to endocarditis. Tricuspid valve endocarditis typically involves aggressive organisms, such as *Staphylococcus aureus,* which can cause rapid valve destruction.

CLINICAL FEATURES

Clinically significant right-sided valvular disease causes signs and symptoms of right heart failure such as jugular venous distention, peripheral edema, hepatomegaly, splenomegaly, and ascites. Exertional dyspnea is often the first symptom in patients with right-sided valvular disease associated with pulmonary hypertension. Patients with tricuspid valve regurgitation from endocarditis may have signs of sepsis. The murmur of **tricuspid valve regurgitation** is soft, blowing, and holosystolic. It is best heard along the lower left sternal border and increases with inspiration. A systolic waveform in the jugular vein, hepatic pulsations, and systolic eyeball propulsion may be seen in severe tricuspid incompetence. **Tricuspid valve stenosis** is associated with a rumbling crescendo-decrescendo diastolic murmur occurring just before S_1. This murmur is best heard along the lower left sternal border, increases with inspiration, and is often preceded by an opening snap.

Pulmonic stenosis often presents with exertional dyspnea, syncope, chest pain, and signs of right heart failure. There is a harsh systolic murmur, best heard in the left second intercostal space, which increases with inspiration. A loud ejection click may precede the murmur, and an S_4 is often heard. Pulmonic regurgitation is associated with a

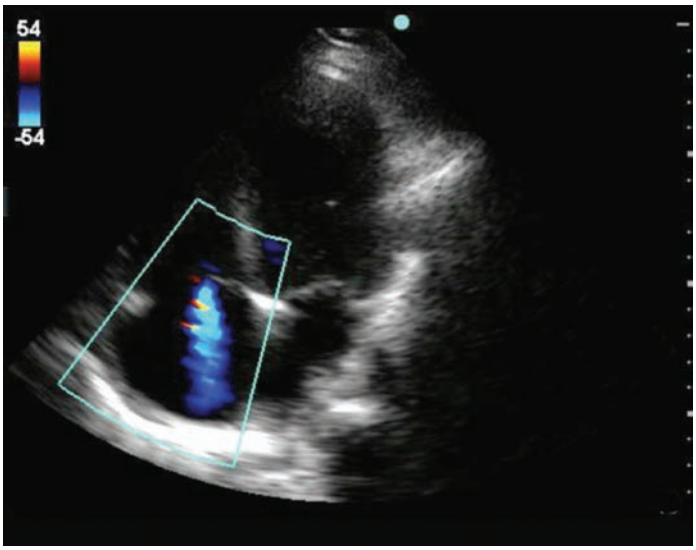

FIGURE 54-7. Apical view color flow Doppler echocardiogram of tricuspid regurgitation. The regurgitant jet is blue in color. [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA (eds): *Ma & Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill Education; 2014, Figure 6-36.]

high-pitched and blowing diastolic murmur (Graham Steell murmur), which increases in intensity during inspiration and is best heard over the left second and third intercostal spaces. An S_3 gallop is often present. Patients with severe right-sided valvular disease typically have a palpable right ventricle thrill or heave.

DIAGNOSIS AND TREATMENT

The diagnosis of right-sided valvular heart disease requires echocardiography (**Figure 54-7**), with transesophageal echocardiography being the most sensitive modality. Chest radiograph and ECG are often nonspecific. Chest radiograph may show signs of right atrial and ventricular enlargement. In pulmonic stenosis, there may be dilatation of the left pulmonary artery. ECG may demonstrate right atrial enlargement and signs of right ventricular hypertrophy.

Treatment of right-sided valvular heart disease is aimed at the underlying cause. Treat endocarditis with antibiotics. For patients with functional tricuspid or pulmonic regurgitation, treat the cause of pulmonary hypertension or right-sided failure. Diuretics treat the effects of elevated venous pressure, such as lower extremity edema, ascites, and hepatic congestion.[19] Patients with symptomatic pulmonic or tricuspid stenosis may be candidates for balloon valvotomy, and those with severe tricuspid regurgitation due to a structural valve abnormality may require valve replacement.

PROSTHETIC VALVE DISEASE

PATHOPHYSIOLOGY

Prosthetic valves are divided into two basic groups: mechanical and bioprosthetic. Mechanical valves are more durable with lower failure rates, but have a higher risk for thromboembolic complications. Lifelong anticoagulation is necessary to reduce the thromboembolic risk.[10] Mechanical mitral valves require an INR of 2.5 to 3.5, whereas bileaflet mechanical valves in the aortic position require an INR of 2.0 to 3.0.[3,10] Without anticoagulation, the risk of valve thrombosis or thromboembolism is about 8%, falling to 1% to 2% per year with anticoagulation.[20,21] Embolic risk is highest during the first 3 postoperative months. Emboli are more common from mitral rather than from aortic valves. Bioprosthetic valves, from porcine, bovine, or human sources, are less thrombogenic but are more likely to fail and require repeat surgery. Antiplatelet therapy is recommended for all patients with prosthetic valves.

Prosthetic valves may malfunction in several ways, including thrombosis, dehiscence of sutures, gradual degeneration, or even sudden fracture. Symptoms are often slowly progressive, but in acute failures, severe symptoms and death may occur rapidly. Prosthetic valve endocarditis occurs in up to 6% of patients within 5 years of surgery and carries high mortality.[6,22]

CLINICAL FEATURES

Symptoms of prosthetic valve dysfunction depend on the type and location of the valve. Patients with prosthetic valves experience some symptoms specific to the presence of the artificial valve. Thromboembolism may cause systemic symptoms such as transient neurologic symptoms, amaurosis fugax, or self-limited ischemic episodes in the extremities or organs. Major embolic events include stroke, mesenteric infarction, or sudden death. Prophylaxis against thrombotic complications of prosthetic valves with systemic anticoagulation causes major bleeding in approximately 1.4% of patients per year,[23] with hemorrhagic stroke being the most common lethal bleeding complication.

Acute onset of respiratory distress, pulmonary edema, and cardiogenic shock may be associated with mechanical valve failure, tearing of a bioprosthesis, or a large clot obstructing the valve or preventing closure. Failures often result in sudden death. A paravalvular leak also presents with congestive heart failure. The severity of symptoms is dependent on leak size and how rapidly the leak develops.

Patients with bioprostheses usually have a normal S_1 and S_2, with no abnormal opening sounds. Mechanical valves normally have a loud, clicking, metallic sound associated with valve closure. Systolic murmurs of prosthetic aortic valves are common, but loud diastolic murmurs should be considered pathologic; a "quiet" mechanical valve is concerning. A loud holosystolic murmur indicates prosthetic mitral valve dysfunction. Aortic bioprostheses usually cause a short mid-systolic murmur, and mitral bioprostheses may cause a short diastolic rumble.

DIAGNOSIS OF PROSTHETIC VALVE DYSFUNCTION OR COMPLICATIONS

Echocardiography is the diagnostic test of choice. Chest radiograph lacks sensitivity and specificity but may show a change in valve position or signs of heart failure. Obtain a head CT in patients with focal neurologic deficits to evaluate for hemorrhage or embolic stroke. Patients on anticoagulation require specific measures of that effect along with a CBC; in addition, obtain blood cultures for suspected endocarditis in these patients.

TREATMENT AND DISPOSITION

Emergency treatment for acute prosthetic valve dysfunction requires cardiology and cardiothoracic surgery consultation. Emergent surgery, thrombolytic therapy, and intensification of anticoagulation are potential therapies for acute valve thrombosis.

REVERSAL OF ANTICOAGULATION WITH PROSTHETIC VALVES

Patients with prosthetic valves seen in the ED are frequently on prophylactic anticoagulation. Emergency physicians must know how to treat supratherapeutic anticoagulation with or without bleeding. An INR >5 confers a high risk of excess bleeding, but rapid changes in anticoagulation pose an equally ominous risk of valve thrombosis and thromboembolism. Factor Xa levels help guide direct oral anticoagulant use, but these agents are not commonly used in valve care. Patients with an INR of 5 to 10 without bleeding have warfarin withheld; another possible

added step is low-dose oral vitamin K reversal, 1.0 to 2.5 milligrams. **Patients with severe bleeding complications are best treated with fresh frozen plasma or prothrombin complex concentrate.**[3] **Avoid parenteral, high-dose vitamin K due to risk of overcorrection.**[9]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 55

Cardiomyopathies and Pericardial Disease

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James T. Niemann

INTRODUCTION

The term *cardiomyopathy* describes a heterogeneous group of diseases that directly alter cardiac structure, impair myocardial function, or alter myocardial electrical properties. Discoveries in molecular genetics and the description of (ion) channelopathies as diseases have prompted periodic revisions of definitions and classifications of cardiomyopathies. The **MOGE(S)** classification is the most recently proposed and describes the morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiology (E; which includes genetic defect or underlying disease), and functional status (S).[1,2] In simple terms, primary cardiomyopathies are diseases that solely or predominantly involve the myocardium and are usually familial in origin; the most common disorders are listed in **Table 55-1**. Secondary cardiomyopathies include heart muscle diseases associated with specific systemic disorders. Secondary cardiomyopathies often present with morphofunctional phenotypes and hemodynamic findings similar to those of the dilated or restrictive forms of cardiomyopathy. The most common causes of secondary cardiomyopathies are listed in **Table 55-2**. As a group, cardiomyopathies are the third most common form of cardiac disease encountered in the United States, following coronary (ischemic) heart disease and hypertensive heart disease. **Hypertrophic cardiomyopathy** is the second most common cause of sudden cardiac death in the adolescent population and the leading cause of sudden death in competitive athletes.[3]

TABLE 55-1 The Primary Cardiomyopathies

Genetic
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy/dysplasia
- Left ventricular noncompaction
- Conduction system disease
  - Long QT syndrome
  - Brugada syndrome
  - Short QT syndrome
  - Idiopathic ventricular fibrillation

Mixed (genetic and nongenetic)
- Dilated cardiomyopathy
- Primary restrictive nonhypertrophied cardiomyopathy

Acquired
- Myocarditis (inflammatory cardiomyopathy)
- Stress (takotsubo) cardiomyopathy
- Peripartum cardiomyopathy

TABLE 55-2 Common Causes of Secondary Cardiomyopathies

Toxins
- Ethanol
- Chemotherapeutic agents (doxorubicin)
- Antiretroviral agents (zidovudine, didanosine)
- Phenothiazines
- Cocaine
- Methamphetamine

Infiltrative diseases
- Amyloidosis

Storage diseases
- Hemochromatosis

Autoimmune disorders
- Scleroderma
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Dermatomyositis

Metabolic
- Nutritional deficiency (thiamine, selenium)
- Endocrine (diabetes mellitus, hypothyroidism, hyperthyroidism)
- Electrolytic disturbance (hypophosphatemia, hypocalcemia)

Neuromuscular disorders
- Muscular dystrophy
- Friedreich's ataxia

An in-depth discussion of each of the primary familial and secondary cardiomyopathies is beyond the scope of this chapter, and emergency providers are unlikely to make a specific diagnosis in the ED. This chapter discusses selected cardiomyopathies (**Table 55-3**). Arrhythmogenic ventricular cardiomyopathy is discussed in Chapter 130, "Syncope, Dysrhythmias, and ECG Interpretation in Children." The cardiomyopathies usually present with signs of systolic and diastolic ventricular dysfunction. The ED evaluation will generally guide the need for urgent treatment, admission, or referral for further diagnostic evaluation.[4]

TABLE 55-3 Features of Selected Cardiomyopathies

Type	Cardiomyopathy Type	Clinical Features	ECG
Systolic and diastolic dysfunction	Dilated cardiomyopathy	Congestive heart failure Chest pain Regurgitant murmurs	LVH Poor R-wave progression
	Myocarditis	Fever Tachycardia Myalgias Chest pain	Nonspecific ST-T–wave changes
Diastolic dysfunction	Hypertrophic cardiomyopathy	Dyspnea on exertion Chest pain Palpitations Syncope Pulsus bisferiens Systolic ejection murmur, increases with Valsalva and decreases with squatting	LVH Large septal Q waves
	Restrictive cardiomyopathies	Presentation as heart failure with preserved EF; may be confused with constrictive pericarditis	In some, low voltage of QRS; conduction disturbances; atrial fibrillation

Abbreviations: EF = ejection fraction; LVH = left ventricular hypertrophy.

CARDIOMYOPATHIES WITH SYSTOLIC AND DIASTOLIC DYSFUNCTION

DILATED CARDIOMYOPATHY

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Dilated cardiomyopathy is not a single disease but should be viewed as a nonspecific phenotype. It may be familial or occur with specific cardiac or systemic disorders (Tables 55-1 and 55-2). **Peripartum cardiomyopathy** most commonly manifests as dilated cardiomyopathy and is discussed in Chapter 99, "Comorbid Disorders in Pregnancy." The dilated cardiomyopathies are a major cause of heart failure and are a major indication for cardiac transplantation in the United States. Most patients with a familial form of dilated cardiomyopathy are diagnosed between the ages of 20 and 50 years, and the majority have advanced symptoms at the time of initial presentation.[5]

Dilated cardiomyopathy is characterized by systolic and diastolic dysfunction and diminished left ventricular (LV) and, often, right ventricular contractile force, resulting in a low cardiac output and increased end-systolic and end-diastolic ventricular volumes. A decrease in ventricular compliance leads to an increase in intracavitary pressures. LV and, often, right ventricular dilatation accompanied by normal LV wall thickness are the hallmarks of dilated cardiomyopathy.

CLINICAL FEATURES

As a result of systolic pump failure, the patient presents with signs and symptoms of heart failure: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, bibasilar rales, and dependent edema. Depressed ventricular contractile function and dilatation may result in the formation of mural thrombi, and the patient may develop signs of peripheral embolization (e.g., an acute neurologic deficit, flank pain, and hematuria or a pulseless, cyanotic extremity). Chest pain, if present, is felt to be due to limited coronary vascular reserve rather than atherosclerotic coronary artery disease, but the cause cannot be distinguished clinically.

Murmurs may be heard during auscultation but do not necessarily indicate primary valvular disease. Annular dilatation and displacement of the papillary muscles of the atrioventricular valves inhibit complete valve closure. Holosystolic mitral or tricuspid regurgitant murmurs are frequently heard at the apex or lower left sternal border. An apical diastolic rumble may be heard and is due either to accentuated, early diastolic atrial-to-ventricular flow (the result of mitral regurgitation and left atrial overload) or to a loud summation gallop. The liver will be enlarged and pulsatile if tricuspid insufficiency is significant.

DIAGNOSIS

The diagnosis may be suspected in patients with typical clinical history, physical exam, and radiographic and ECG findings, but the diagnosis is typically made at follow-up with echocardiography and additional testing as indicated by individual characteristics.[4,5] The chest radiograph invariably shows an enlarged cardiac silhouette and increased cardiothoracic ratio. Biventricular enlargement is common. Evidence of pulmonary venous hypertension ("cephalization" of flow and enlarged hila) is also frequent and may serve to differentiate cardiac enlargement due to myocardial failure from that due to a large pericardial effusion.

The ECG is almost always abnormal. LV hypertrophy and left atrial enlargement are the most common findings. Q or QS waves and poor R-wave progression across the anterior precordium may produce a pseudoinfarction pattern. Atrial fibrillation and ventricular ectopy are common rhythm disturbances.

Echocardiographic studies in a symptomatic patient demonstrate a decreased ejection fraction, increased systolic and diastolic volumes, and ventricular and atrial enlargement. Echocardiography is indicated when the cause of heart failure is uncertain, to exclude known causes of heart failure that may be correctable (e.g., pericardial effusion or valvular disease), to estimate ejection fraction, and to rule out other potential complications (e.g., mural thrombi) that may be amenable to therapy. The acuity of the patient's presentation determines the urgency of echocardiography.

TREATMENT AND DISPOSITION

For the treatment of acute decompensated heart failure, see Chapter 53, "Acute Heart Failure." Chronic therapy may include diuretics and digoxin, but these drugs do not appear to improve survival rates.[6] Guidelines from the American College of Cardiology for the management of heart failure (and other cardiovascular disorders) are available online at https://www.acc.org/guidelines. The use of angiotensin-converting enzyme inhibitors and β-blockers, specifically carvedilol and metoprolol, improves survival in patients with dilated cardiomyopathy and heart failure.[6] Selected patients may benefit from cardiac resynchronization therapy.[5] Patients with complex ventricular ectopy who are found to be at risk for sudden cardiac death may benefit from amiodarone therapy or an implantable cardioverter-defibrillator.[5] Implantable cardioverter-defibrillator placement for primary prevention of sudden cardiac death is not decided solely on ejection fraction, but also by consideration of family history of dilated cardiomyopathy, sudden cardiac death, and cardiac MRI.[5]

Patients with a known dilated cardiomyopathy and chronic heart failure may present to the ED with a mild to moderate worsening of symptoms.[7] If the cause is noncompliance with medical therapy or diet, ED treatment with nitrates, IV diuretics, reinstitution of prescribed medications, patient counseling, and timely referral to the primary care physician are appropriate. However, life-threatening causes of acute exacerbations, such as cardiac ischemia, should be considered before assuming benign causes.[7] Acutely symptomatic patients require hospitalization for definitive diagnosis and management. Important subsets of patients with dilated cardiomyopathy are treated with LV assist devices while awaiting heart transplantation or as destination therapy.[8,9] Principles of patient assessment and management and device complications are described in the **Left Ventricular Assist Devices** box.

MYOCARDITIS (INFLAMMATORY CARDIOMYOPATHY)

PATHOPHYSIOLOGY

Myocarditis is a common cause of dilated cardiomyopathy but is discussed separately to highlight its acute presentation and individual therapy. Myocarditis is inflammation of the heart muscle and is most frequently characterized pathologically by focal infiltration of the myocardium by lymphocytes, plasma cells, and histiocytes. Varying amounts of myocytolysis and destruction of the interstitial reticulin network are also seen.[10] Because many episodes are mild, they do not always come to medical attention. **Table 55-4** lists some common infectious causes of myocarditis. Myocarditis may be accompanied by pericarditis.

TABLE 55-4 Common Infectious Causes of Myocarditis

Viral Agents	Bacteria
Coxsackie B virus	*Corynebacterium diphtheriae*
Echovirus	*Neisseria meningitidis*
Influenza virus	*Mycoplasma pneumoniae*
Parainfluenza virus	β-Hemolytic streptococci (rheumatic fever)
Epstein-Barr virus	Lyme disease
Hepatitis B virus	
Human immunodeficiency virus	

LEFT VENTRICULAR ASSIST DEVICES (See Video: Left Ventricular Assist Device)

Left ventricular assist devices (LVADs) were originally designed as a bridge to transplant in end-stage heart failure patients but offer long-term quality of life improvement for patients who are not candidates for transplant (destination therapy). LVADs augment left ventricular output in patients with severe cardiomyopathy. There are several models of LVADs in current use that share many similar features.

In all LVADs, the implanted **pump** transfers blood from the apex of the left ventricle to the proximal aorta (**Figure 1**). The pump is powered by an external power source (battery or bedside unit), which is connected to a **controller**. Both the **battery** and controller reside outside of the body and can be carried or worn by the patient. The controller drives the pump through a **driveline**, which connects the implanted pump to the external controller through a surgical incision in the abdominal wall.

Most contemporary LVADs use pumps that drive blood through a continuous-flow mechanism (e.g., axial or centrifugal flow), maintaining a normal mean arterial blood pressure in the absence of a palpable pulse. However, many patients may still retain some cardiac contractility; in these individuals, the LVAD serves to assist (and not replace) normal physiologic cardiac output, and a pulse may be present. Because the LVAD can (in some patients) maintain systemic perfusion even with minimal cardiac function, an LVAD patient can sometimes be clinically stable even in the setting of ventricular fibrillation. LVAD patients still rely upon reasonable right ventricular function to pump blood to the lungs.

Patients and families are thoroughly trained on the management of the LVAD and its complications, and they should be involved during patient assessment and management.[8] It is important to call the patient's LVAD coordinator as soon as possible to assist with management decisions; this information should be present in the patient's travel bag, along with a spare controller and batteries.

CLINICAL FEATURES

LVAD patients should have a normal mean arterial pressure of approximately 65 to 90 mm Hg. Blood pressure can be assessed by a mechanical cuff or by Doppler US. If using a Doppler, remember that blood flow has to be continuous and not pulsatile. When auscultating the heart, the continuous whirr of the pump is heard.

The ECG should have discernible QRS complexes (**Figure 2**).

The LVAD is visible on a chest radiograph (**Figure 3**). Bedside US can be used to assess right ventricular function and to evaluate for pericardial effusion/tamponade. Plain imaging and CT scans are safe, but MRIs are contraindicated.

THE HEMODYNAMICALLY UNSTABLE LVAD PATIENT[9]

CAN ONE PERFORM CHEST COMPRESSIONS ON AN LVAD PATIENT? Chest compressions can potentially dislodge the LVAD from the heart and aorta, causing left ventricular rupture and intractable hemorrhage. Evaluate for causes of pump failure or lack of perfusion first. Avoid chest compressions if at all possible unless absolutely necessary; use your clinical judgment.

Immediately auscultate the precordium to hear an audible "whirr," which indicates that the pump is functioning. If nothing is heard, search for a cause of mechanical LVAD failure. With the help of family if needed, check and/or change the batteries and/or controller. **Do not disconnect anything. If unable to restart the LVAD, start CPR with special attention to proper positioning. Avoid excessively deep compressions.**[11]

If the pump is audible and functioning, obtain a blood pressure (by automatic cuff or manual Doppler) and place the patient on a cardiac monitor and continuous pulse oximetry. If the LVAD model does not provide pulsatile flow, it is difficult to obtain a reading by pulse oximetry.

For **hypotension** or low-perfusion states (mental status, skin temperature/color, capillary refill, etc.), give a small bolus of normal saline because LVADs are preload dependent. Assess for bleeding (most common reason for ED visit), especially from GI hemorrhage, due to either an acquired von Willebrand disease, supratherapeutic anticoagulation, or a GI arteriovenous malformation. **If hypotension persists despite adequate fluid resuscitation or in the presence of right ventricular failure or LVAD malfunction, initiate IV inotropes.** Dopamine and dobutamine are reasonable first-line inotropes. **Obtain an ECG** to rule out right ventricular myocardial infarction or strain. Obtain standard laboratory studies as clinically indicated. **Bedside US** can assess for right ventricular dilatation or failure. If there is right ventricular strain, consider pulmonary hypertension or pulmonary embolism. Give heparin if **pulmonary embolism or device thrombosis** is suspected and bleeding has been excluded. Consider tissue plasminogen activator for pump thrombosis, especially if the patient is decompensating and peri-code.

Ventricular fibrillation or ventricular tachycardia in an unstable patient requires defibrillation/cardioversion using standard advanced cardiac life support energy recommendations. **Do not place defibrillator pads over the driveline.** If the patient is clinically stable, give amiodarone according to advanced cardiac life support protocols.

MEDICAL COMPLICATIONS

Medical complications include anemia, bleeding, thromboembolism, or infection. **Anemia** can be caused by hemolysis (erythrocyte destruction from the pump) or bleeding. LVAD patients are typically anticoagulated with warfarin to an INR target of 2 to 3. **Bleeding and coagulopathy** are investigated and treated with standard measures. LVAD patients are also at risk for **thromboembolism**, such as pulmonary embolism, stroke, and mesenteric ischemia, especially in the setting of suboptimal anticoagulation. Heparin is safe and indicated for such events once bleeding has been ruled out. **Infection** is a common complication, especially at the driveline exit site. Treat sepsis with volume resuscitation, blood cultures, and antibiotics.

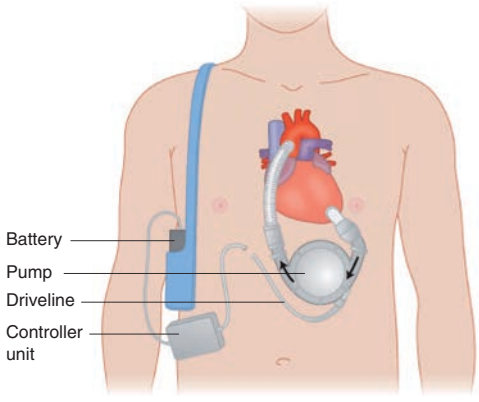


FIGURE 1. A left ventricular assist device carries blood from the left ventricle to the aorta.



FIGURE 3. Posteroanterior chest radiograph of a patient with a left ventricular assist device and an implantable defibrillator. The outflow conduit to the proximal aorta is not radiographically visible. [Image used with permission of Daniel Renner, MD.]

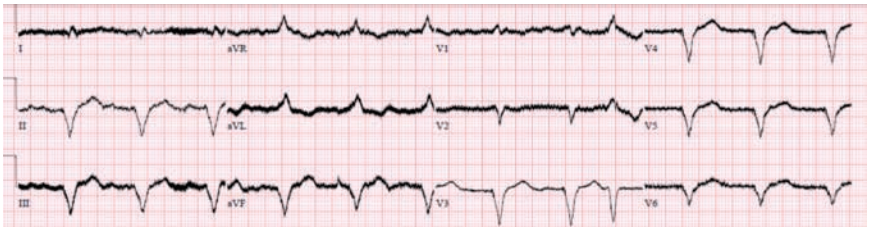


FIGURE 2. ECG of a patient with a left ventricular assist device. QRS is evident, and baseline shows some electrical interference from the pump. [ECG used with permission of Daniel Renner, MD.]

CLINICAL FEATURES

Fever, myalgias, headache, and sinus tachycardia, often out of proportion with fever, are common signs and symptoms. Heart failure develops in severe cases. With less extensive myocardial involvement, the clinical manifestations of systemic illness (fever, myalgias, headache, and rigors) may overshadow clinical signs of myocardial dysfunction, leaving the diagnosis unsuspected. Retrosternal or precordial angina-type chest pain may occur and is usually due to pericardial inflammation **(myopericarditis)**. A pericardial friction rub may be heard.

DIAGNOSIS

The gold standard for diagnosis of myocarditis is endocardial biopsy, but this invasive modality is uncommonly used.[12] The diagnosis is more commonly made clinically based on symptoms with supportive testing. The chest radiograph is usually normal or nondiagnostic. Cardiomegaly and pulmonary venous hypertension or pulmonary edema are present with severe disease. ECG changes include nonspecific ST-T–wave changes, ST-segment elevation or PR depression from associated pericarditis, atrioventricular block, and QRS interval prolongation. Troponin or B-type natriuretic peptide may be elevated.[13] Echocardiographic studies are also nonspecific, with myocardial depression and wall motion abnormalities in severe cases. Newer imaging modalities include nuclear imaging with positron emission tomography and cardiac MRI.[14]

TREATMENT AND DISPOSITION

Admission is usually indicated in all cases to monitor progression of disease. Treatment for idiopathic or viral myocarditis is supportive. Antibiotics are needed for myocarditis complicating rheumatic fever, diphtheria, or meningococcemia. Immunosuppressive therapy (e.g., prednisone, azathioprine, and others) may be of value in selected patients, but large trials have not consistently demonstrated benefit.[15] Immunosuppressive therapy is usually reserved for more severe cases and is rarely begun in the ED. Although most patients have a good long-term prognosis, those with fulminant myocarditis have a worse outcome and worse LV function at follow-up.

CARDIOMYOPATHIES WITH DIASTOLIC DYSFUNCTION

HYPERTROPHIC CARDIOMYOPATHY

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Hypertrophic cardiomyopathy is now generally defined as "a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers is the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient."[16] The echocardiographic hallmark of the disease is LV wall thickening, usually >15 mm. Cardiovascular magnetic resonance is also useful for diagnosis.[17] Additional echocardiographic findings that might be observed include asymmetric septal hypertrophy and systolic anterior motion.

The disorder is usually familial, with autosomal dominant inheritance, or it can occur sporadically. There is no apparent sex or ethnic predilection. Hypertrophic cardiomyopathy is a clinically and genetically heterogeneous disease associated with more than 1500 mutations in more than 11 major genes.[18] Particular genotypes have more rapidly progressive courses. More benign genotypes may be associated with substantial risk of stroke and mortality in the setting of atrial fibrillation. The prevalence in the general population is approximately 1 in 500. The annual mortality rate in the overall hypertrophic cardiomyopathy population is <1% per annum.

Hemodynamically, hypertrophic cardiomyopathy is characterized by abnormal LV diastolic function due to reduced compliance of the hypertrophied left ventricle. Decreased compliance is reflected by an increase in LV filling pressure. Cardiac output, ejection fraction, and end-systolic volumes are usually normal. Most clinical symptoms are the result of impaired diastolic relaxation and restricted LV filling.

CLINICAL FEATURES

Dyspnea on exertion is the most frequent initial complaint and is due to exercise-induced sinus tachycardia, which results in an abrupt elevation of LV diastolic pressure and pulmonary venous hypertension due to decreased LV filling time. Additional symptoms include chest pain, palpitations, and syncope. A family history of death due to cardiac disease is not uncommon.

Chest pain in hypertrophic cardiomyopathy patients is due to an imbalance between the oxygen demand of the hypertrophied left ventricle and the available myocardial blood flow.[16] In older patients, associated atherosclerotic coronary artery disease may further limit myocardial perfusion. Precordial or retrosternal chest discomfort in hypertrophic cardiomyopathy may mimic angina pectoris or may be "atypical." Response to nitroglycerin is poor and highly variable.

The hypertrophic cardiomyopathy patient may be aware of forceful ventricular contraction and complain of an abnormal heartbeat or "palpitations." Atrial fibrillation is poorly tolerated because of the increased importance of the atrial contribution to LV filling.

Jugular venous pressure is usually not elevated. However, a prominent a (atrial) wave may be noted on close inspection of the neck veins. The upstroke of the carotid arterial pulse is rapid and frequently biphasic or bifid (pulsus bisferiens). The apical impulse is sustained and hyperdynamic, and a presystolic lift is common.

The first and second heart sounds are usually normal, with an S_4 heard in most patients. A systolic ejection murmur may occur and is heard best at the lower left sternal border or at the apex, and rarely radiates to the carotid arteries. Easily performed bedside maneuvers can be used to increase the intensity and duration of the murmur (**Table 55-5**). **Interventions that decrease LV filling and the distending pressure in the LV outflow tract or that increase the force of myocardial contraction accentuate the murmur of hypertrophic cardiomyopathy.** Such interventions include standing and the strain phase of the Valsalva maneuver. **Maneuvers that increase LV filling (squatting, passive leg elevation, and hand grip) decrease the murmur.** The murmurs of hypertrophic cardiomyopathy and mitral valve prolapse, when associated with murmur, are similar and are compared in Table 55-5.

DIAGNOSIS

The diagnosis may be suspected in the ED based on symptoms, family history, and physical exam findings and confirmed with cardiac MRI or echocardiography. The chest radiograph is usually normal or nonspecific. The resting ECG is nonspecific in most, often demonstrating LV hypertrophy and left atrial enlargement. Q waves >0.3 mV, termed septal Q waves, may be seen in anterior, lateral, or inferior leads. Q waves may mimic those seen after myocardial infarction (pseudoinfarction pattern). The polarity of the T wave can differentiate between hypertrophic cardiomyopathy septal Q waves and Q waves due to myocardial infarction. Upright T waves in those leads with QS or QR complexes are usually found in hypertrophic cardiomyopathy (**Figure 55-1**), whereas

TABLE 55-5 Effect of Bedside Interventions on the Murmur of Hypertrophic Cardiomyopathy Compared to Mitral Valve Prolapse

Intervention	Hypertrophic Cardiomyopathy	Mitral Valve Prolapse
Valsalva maneuver (strain phase)	Murmur increased	Click closer to S_1, murmur increased
Standing after squatting	Murmur increased	Click closer to S_1, murmur increased
Passive leg elevation in supine patient	Murmur decreased	Click closer to S_2, murmur decreased
Hand grip	Murmur decreased	Click closer to S_1, murmur increased
Squatting	Murmur decreased	Click closer to S_2, murmur decreased

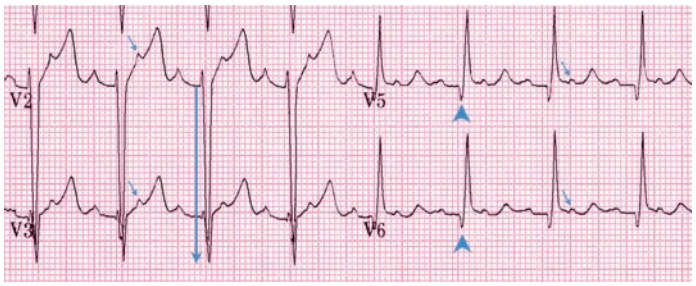


FIGURE 55-1. Hypertrophic cardiomyopathy ECG findings. Deep S-wave voltage (28 mm S in V_2, *large arrow*) signifies left ventricular hypertrophy, and narrow septal Q waves in V_5 and V_6 (*arrowheads*) are noted. T waves are upright in the leads with the septal Q waves, with upright T waves in leads V_5 and V_6, typical of hypertrophic cardiomyopathy. This patient also has atrial flutter with 2:1 block. The additional P waves appear in the ST segments (*small arrows*). [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *The Atlas of Emergency Medicine*, 3rd ed. New York: McGraw-Hill; 2010; Fig 23.40B.]

T-wave inversion in such leads is highly suggestive of ischemic heart disease.

Echocardiography plays a substantial role in the diagnosis of hypertrophic cardiomyopathy, in the correlation of the auscultatory and hemodynamic events with LV anatomic changes, and in defining inheritance patterns. Cardiac MRI is recommended when echocardiography is inconclusive in patients clinically suspected of having the disease and is also helpful in risk stratification.[17]

TREATMENT AND DISPOSITION

The majority of patients with hypertrophic cardiomyopathy who seek medical care typically do so because of declining exercise tolerance, chest pain, or syncope. The patient who presents complaining of exercise intolerance or chest pain in whom the typical murmur of hypertrophic cardiomyopathy is heard should be referred for echocardiographic evaluation after other causes have been considered. Syncope in patients with hypertrophic cardiomyopathy typically occurs during or immediately after exercise. **If hypertrophic cardiomyopathy is suspected in a patient with syncope, hospitalization is indicated.[16,19] Syncope in patients with hypertrophic cardiomyopathy may presage sudden cardiac death.** The diagnostic evaluation is extensive and includes echocardiographic studies as well as extended cardiac monitoring, exercise stress testing to assess blood pressure response, and tilt testing. Beta-blockers are the mainstay of therapy for symptomatic patients.[16,20]

RESTRICTIVE CARDIOMYOPATHY

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Restrictive cardiomyopathy is most commonly idiopathic, but may be of genetic origin with autosomal transmission and due to mutations in cardiac sarcomere protein genes.[21] A restrictive cardiomyopathy may also result from systemic disorders that cause infiltration of the myocardium, resulting in replacement or displacement of normal myocardium. Systemic diseases that may be associated with a restrictive cardiomyopathy include amyloidosis, sarcoidosis, hemochromatosis, progressive systemic sclerosis (scleroderma), carcinoid heart disease, endomyocardial fibrosis, and hypereosinophilic syndrome.[22]

Restrictive cardiomyopathy is characterized by "restricted" ventricular filling, with normal or decreased diastolic volume of one or both ventricles. Systolic function is usually normal, and ventricular wall thickness may be normal or increased, depending on the underlying cause. The restrictive cardiomyopathies may account for up to 15% of cases of heart failure with preserved ejection fraction. The hemodynamic hallmarks include (1) elevated LV and right ventricular end-diastolic pressure, (2) normal LV systolic function (ejection fraction >50%), and (3) a marked decrease followed by a rapid rise and plateau in early diastolic ventricular pressure observed during invasive hemodynamic assessment. The rapid rise and abrupt plateau in the early diastolic ventricular pressure trace produce a characteristic "square root sign" or "dip-and-plateau" filling pattern due to increased myocardial stiffness. This pattern is not diagnostic, however, and may be seen in constrictive pericarditis, with which restrictive cardiomyopathy is commonly confused. Differentiation between the two is critical because constrictive pericarditis can be cured surgically. The diagnosis of restrictive cardiomyopathy should be considered in a patient presenting with congestive heart failure but no evidence of cardiomegaly or systolic dysfunction.[22]

CLINICAL FEATURES AND DIAGNOSIS

Symptoms are typical of heart failure and include dyspnea, orthopnea, and pedal edema. Right-sided heart failure may predominate and results in hepatomegaly, right upper quadrant pain, and ascites. Chest pain is uncommon, except in amyloidosis.

Findings on physical examination depend on the stage or severity of myocardial involvement. An S_3 and an S_4 are often heard. Pulmonary rales, jugular venous distention, Kussmaul sign (jugular venous pulse rises during inspiration rather than falling), hepatomegaly, pedal edema, and ascites are also typical findings. On chest radiograph, there may be signs of heart failure but a normal heart size. Chamber enlargement due to wall thickening, but not dilatation, and nonspecific ST-T–wave changes are usually noted on the ECG. Cardiac conduction disturbances are common in amyloidosis and sarcoidosis. Atrial fibrillation may occur in the setting of atrial enlargement. Low-voltage QRS complexes (QRS amplitude <0.7 mV) are frequently described in patients with restrictive cardiomyopathy secondary to amyloidosis and hemochromatosis. The differential diagnosis includes constrictive pericarditis or diastolic LV dysfunction (most commonly due to ischemic heart disease, hypertension, or age-related changes in ventricular diastolic compliance). Doppler echocardiographic studies, cardiac MRI, and cardiac catheterization with hemodynamic assessment are often required for specific diagnosis.[22]

TREATMENT AND DISPOSITION

CT and MRI of the heart can differentiate constrictive pericarditis from restrictive cardiomyopathy.[22] Correct diagnosis is important because constrictive pericarditis can be surgically corrected, and diastolic LV dysfunction usually responds well to beta-blockers or calcium channel blockers. The medical management of restrictive cardiomyopathy is less effective and symptom directed (diuretics and angiotensin-converting enzyme inhibitors) unless due to sarcoidosis (corticosteroid therapy) or hemochromatosis (chelation therapy). The need for admission is usually determined by the severity of symptoms and the availability of diagnostics. Genetic testing is often recommended.

PERICARDIAL DISEASE

ANATOMY AND PATHOPHYSIOLOGY

The pericardium consists of a serous or loose fibrous membrane (visceral pericardium) overlying the epicardium and a dense collagenous sac (parietal pericardium) surrounding the heart. The space between the visceral and parietal pericardium may normally contain up to 50 mL of fluid.[23] Because its layers are serosal surfaces and because of its proximity and attachments to other structures, the pericardium may be involved in a number of disease processes (**Table 55-6**). In this section, the clinical manifestations and evaluation of acute and constrictive pericarditis and nontraumatic cardiac tamponade are discussed.

ACUTE PERICARDITIS

CLINICAL FEATURES

The most common symptom of acute pericarditis is sharp or stabbing precordial or retrosternal chest pain. Pain may be of sudden or gradual onset; radiate to the back, neck, left shoulder, or arm; and aggravated by inspiration or movement. Referral of pain to the left trapezial ridge

TABLE 55-6 Common Causes of Acute Pericarditis

- Idiopathic
- Infectious
  - Viral (coxsackie virus, echovirus, human immunodeficiency virus)
  - Bacterial (especially *Staphylococcus, Streptococcus pneumoniae*, β-hemolytic streptococci [acute rheumatic fever], *Mycobacterium tuberculosis*)
  - Fungal (especially *Histoplasma capsulatum*)
- Malignancy (leukemia, lymphoma, metastatic breast and lung carcinoma, melanoma)
- Drug induced (procainamide, hydralazine)
- Systemic rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polyarteritis nodosa, dermatomyositis)
- Radiation induced
- Postmyocardial infarction (Dressler's syndrome)
- Uremia
- Myxedema

(due to inflammation of the joining diaphragmatic pleura) is a particular distinguishing feature. Chest pain due to acute pericarditis may be aggravated by inspiration or movement. Typically, chest pain is most severe when the patient is supine and is relieved when the patient sits up and leans forward. Associated symptoms may include fever, dyspnea due to accentuated pain with inspiration, and dysphagia from irritation of the esophagus by the posterior pericardium.[24,25]

A pericardial friction rub is the most common and important physical finding in pericarditis, but may be difficult to appreciate in a noisy ED. It is best heard with the diaphragm of the stethoscope at the lower left sternal border or apex when the patient is sitting and leaning forward. It may be audible only during a certain phase of respiration and characteristically is intermittent. A pericardial friction rub is most often triphasic, with a systolic component due to ventricular contraction, an early diastolic component during the early phase of ventricular filling, and a presystolic component synchronous with atrial systole. It is less commonly biphasic, with a systolic component with either an early diastolic or presystolic component. A monophasic rub is less common but is most often systolic.

DIAGNOSIS

The ECG is the most important tool for initial diagnosis. **Serial ECG changes during acute pericarditis and its convalescence are characterized by four stages** (**Table 55-7** and **Figure 55-2A** and **B**).

If a large pericardial effusion develops during the course of acute pericarditis, low-voltage QRS complexes and electrical alternans may be evident. Pericardial fluid attenuates myocardial electrical signals, and the pendular motion of the heart within the fluid-filled pericardial space results in electrical alternans (see Figure 55-5 in the "Nontraumatic Cardiac Tamponade" section of this chapter).

Although serial ECG tracings are of diagnostic value in acute pericarditis, sequential ECG assessment is not a diagnostic luxury afforded the emergency physician. The classic ECG findings in acute pericarditis include diffuse ST-segment elevation (most pronounced in the lateral precordial leads), PR-segment depression, and ST-segment depression in lead aVR. ST-segment elevation is due to the inflammation of the epimyocardium. Classic ECG changes are not observed in uremic pericarditis because the epicardium is not involved in the inflammatory process. The ST-segment/T-wave amplitude ratio in leads V_6, or I can differentiate pericarditis from early repolarization.[26] Using the end of the PR segment as a baseline, or 0 mV, the amplitude or height of the ST segment at its onset (the J point) is measured in V_6 or lead I and recorded in millivolts. The height of the T wave in the same lead is measured from the baseline to the T-wave peak. If the ratio of ST amplitude (in millivolts) to T-wave amplitude (in millivolts) is >0.25, acute pericarditis is likely (Figure 55-2), and if the ratio is <0.25, acute pericarditis is unlikely. Sensitivity at an ST/T ratio of >0.25 for acute pericarditis is over 85%, and the specificity is over 80% (positive likelihood ratio of about 4 and negative likelihood ratio of about 0.2). Pericarditis alone does not cause significant cardiac rhythm disturbances.

TABLE 55-7 Serial ECG Changes of Acute Pericarditis

Stage	PR Segment	ST Segment	T Wave
1 (acute)	Depression, especially in II, aVF, and V_4–V_6	Elevation, especially in I, V_5, and V_6; ST amplitude: T-wave amplitude >0.25	—
2	Isoelectric or depressed	Returns to isoelectric line	Amplitude decreases, inversion rare
3	Isoelectric or depressed	Isoelectric	T-wave inversion, especially in I, V_5, and V_6
4	Isoelectric	Isoelectric	Normal

Chest radiographs are of limited value. The cardiac silhouette may be of normal size and contour in acute pericarditis and, in some instances, the setting of cardiac tamponade. If previous chest radiographs are available for comparison, a recent increase in the size of the cardiac silhouette or an increase in the cardiothoracic ratio without radiographic evidence of pulmonary venous hypertension can distinguish an expanding pericardial effusion from left heart failure. The "epicardial fat pad sign" is rarely seen on the lateral chest radiograph and has been reported in only 15% of cases of acute pericarditis during fluoroscopy with image intensification. If acute pericarditis is suspected on the basis of history, physical examination, or ECG, a chest radiograph may help establish an underlying cause, such as neoplasm or infection.

Echocardiography is the procedure of choice for the detection and confirmation. Normally, the pericardial sac is only a "potential" space, and the myocardium is echocardiographically in direct contact with surrounding thoracic structures. The anterior right ventricular wall is in contact with the chest wall, and the posterior LV wall is in contact with the posterior pericardium and adjacent pleura. When a pericardial effusion is present, the pericardial space fills with echo-free fluid (**Figure 55-3**). For serial follow-up of patients with acute pericarditis and a pericardial effusion, CT and cardiac MRI may be complementary.[27]

Echocardiographically, a separation is seen between the right ventricle and the chest wall and between the left ventricle and the posterior pericardium. Quantitation of the size of the effusion is arbitrary and is determined by where the hypoechoic space is seen (anterior or posterior) and when in the cardiac cycle it occurs. For example, when a hypoechoic space is seen only posteriorly and only during systole, a small effusion is said to be present. The sensitivity of CT for detecting pericardial effusion is similar to that of echocardiography (**Figure 55-4**).

Suggested laboratory studies are listed in **Table 55-8**. **Serum troponins may be elevated in acute pericarditis due to associated myocarditis.**[13]

TREATMENT AND DISPOSITION

Treatment of pericarditis depends on the cause.[24,25] Most patients with idiopathic or presumed viral pericarditis have a benign course lasting 1 to 2 weeks. Symptoms respond well to NSAIDs administered for 7 days to 3 weeks. However, this class of drugs should be used with caution due to known risks of acute coronary syndromes.[28] Corticosteroid treatment can alternatively be used for patients with poor NSAID tolerance, contraindication, or failure of NSAIDs. Colchicine, 0.5 milligram orally twice a day, may be a beneficial adjuvant and may prevent recurrent episodes and symptoms persistent at 72 hours.[24] Hospitalization is not necessary in most cases. Indicators of a poor prognosis include temperature >38°C (100.4°F), subacute onset over weeks, immunosuppression, history of oral anticoagulant use, associated myocarditis (elevated cardiac biomarkers, symptoms of heart failure), failure to respond to therapy with NSAIDs after 1 week of therapy, a large pericardial effusion (an echo-free space >20 mm), or cardiac tamponade.[25] In general, patients with these risk factors or with an enlarged cardiac silhouette

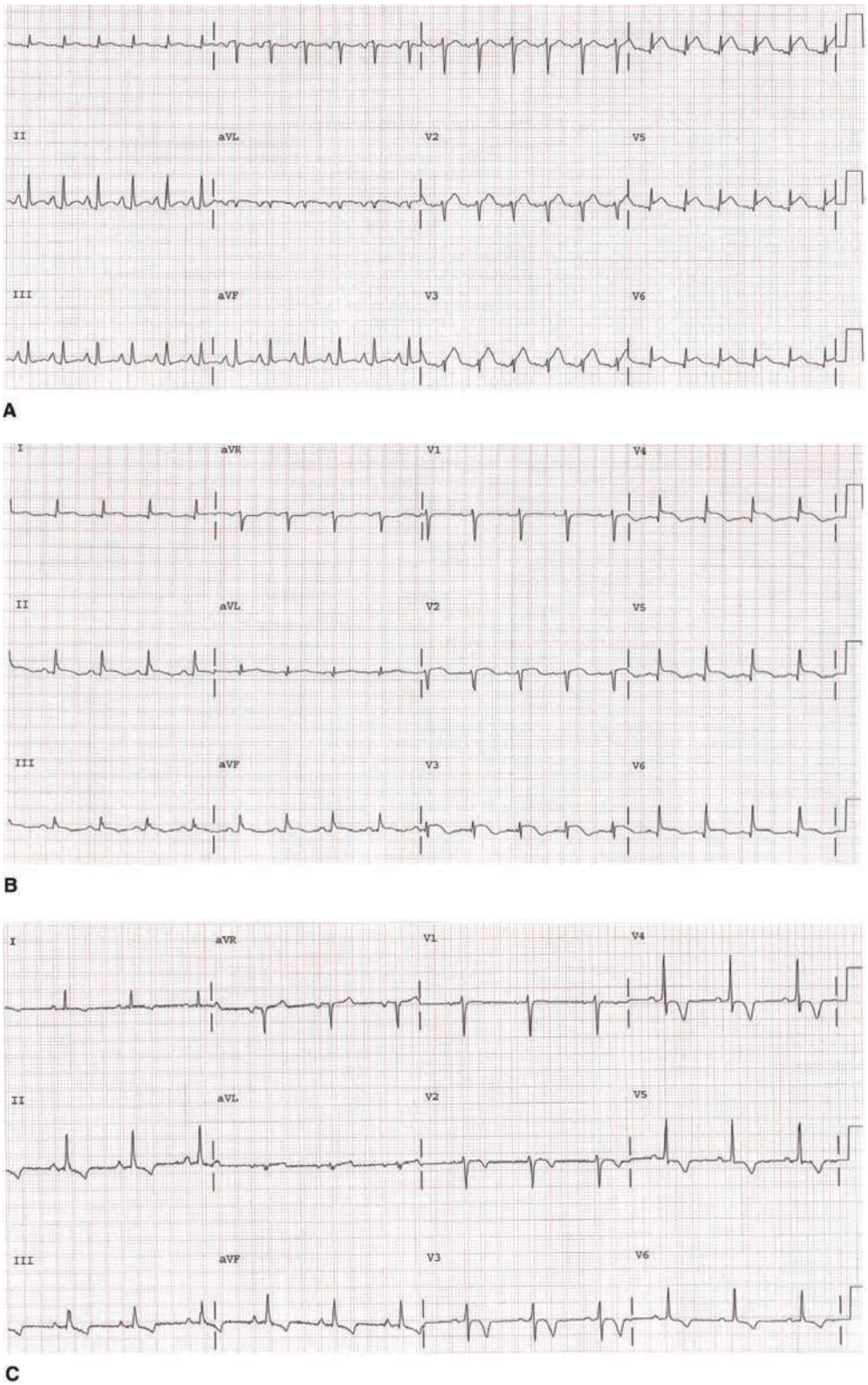


FIGURE 55-2. This series of three ECGs shows the typical progression of changes associated with acute pericarditis. **A.** In stage I pericarditis, the ECG shows diffuse ST-segment elevation and PR depression in leads I, II, III, and aVF. The ST-segment to T-wave amplitude ratio measured in V_6 is 2 mm/4 mm, or 0.50, thus meeting criteria for pericarditis rather than early repolarization (see the text under "Diagnosis"). **B.** In stage II pericarditis, ST segments are returning toward the isoelectric point in most leads in which they had been elevated. **C.** In stage III pericarditis, we see resolution of ST changes and the appearance of diffuse T-wave inversion. These evolutionary changes are typical of and diagnostic for pericarditis and usually occur over several weeks.

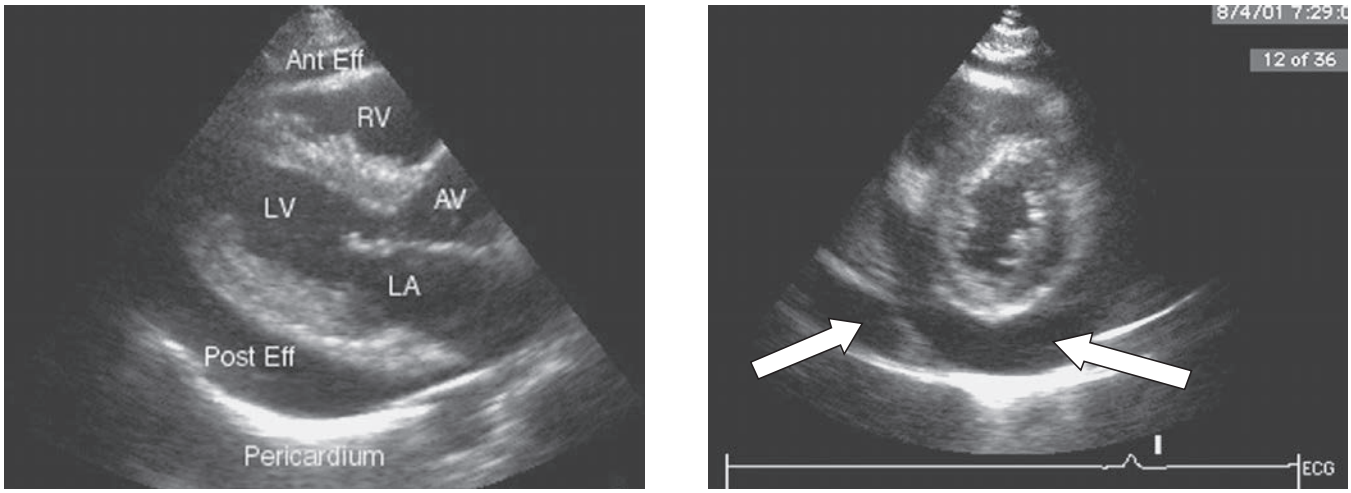


FIGURE 55-3. **A.** Pericardial effusion on parasternal long-axis view. Ant Eff = anterior effusion; AV = aortic valve; LA = left atrium; LV = left ventricle; Post Eff = posterior effusion; RV = right ventricle. **B.** Pericardial effusion (*arrows*) on parasternal short-axis view. [Reprinted with permission from Reardon RF, Joing SA: Cardiac, in Ma OJ, Mateer JR, Blaivas M (eds): *Emergency Ultrasound*, 2nd ed. Copyright © 2008, The McGraw-Hill Companies, Inc., all rights reserved, Figure 6-24.]

on chest radiograph should be admitted for serial echocardiography to assess changes in effusion size, degree of hemodynamic compromise, and cardiac dysfunction.

NONTRAUMATIC CARDIAC TAMPONADE

PATHOPHYSIOLOGY

An increase in the amount of fluid within the pericardial sac results in an increase in intrapericardial pressure. The normal fibrocollagenous parietal pericardium has elastic properties and stretches to accommodate increases in intrapericardial fluid. The initial portion of the pericardial volume-pressure curve is flat: Relatively large increases in volume result in comparatively small changes in intrapericardial pressure. The curve becomes steeper as the parietal pericardium reaches the limits of its distensibility.[29] If fluid continues to accumulate, intrapericardial pressure rises to a level greater than that of the normal filling pressures of the right heart chambers. When this occurs, ventricular filling is restricted and results in cardiac tamponade. The point at which this occurs is determined by the rate of fluid accumulation, pericardial compliance (a thickened parietal pericardium is less distensible), and intravascular volume (hypovolemia lowers ventricular filling pressure). Common causes of cardiac tamponade in nontrauma patients are listed in **Table 55-9**.

CLINICAL FEATURES

Symptoms are nonspecific, and patients most commonly complain of dyspnea at rest and with exertion. Additional symptoms may be due to the underlying disease (e.g., uremia or tuberculous pericarditis).

Physical examination may reveal tachycardia and low systolic arterial blood pressure with a narrow pulse pressure. **Pulsus paradoxus** may also be present.[29] A paradoxical arterial pulse is said to be present when the cardiac rhythm is regular and there are apparent dropped beats in the peripheral pulse during inspiration. There is usually a <10 mm Hg decrease in systolic blood pressure during inspiration in the supine position. A value >10 mm Hg usually separates true tamponade from lesser

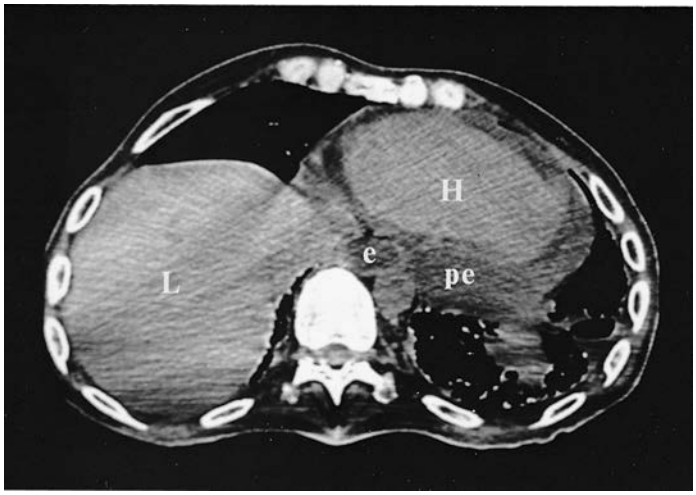


FIGURE 55-4. This CT scan of the chest shows a large pericardial effusion (pe) predominantly posteriorly located in a patient with scleroderma and pericarditis. No pericardial thickening or calcification was detected. Esophageal (e) dilatation is noted. Cardiac function cannot be evaluated. H = heart; L = liver. [Reprinted with permission from Roldan CA: Connective tissue diseases & the heart, in Crawford MH (ed): *Current Diagnosis & Treatment in Cardiology*, 3rd ed. Copyright © 2009, The McGraw-Hill Companies, Inc., all rights reserved, Figure 33-5.]

TABLE 55-8 Ancillary Diagnostic Studies in Acute Pericarditis

Diagnostic Study	Considerations
Cardiac markers	Indicate myocardial involvement (epimyocarditis)
CBC and differential WBC count	May suggest infection or leukemia
BUN/creatinine	May suggest a diagnosis of uremic pericarditis
Chest radiograph	Infiltrate or mass suggests infection or malignancy as etiology
Blood cultures	If bacterial infection suspected
Serologic studies	Antinuclear antibodies, anti-DNA titers, or rheumatoid factor in patients with systemic symptoms
Erythrocyte sedimentation rate, C-reactive protein	Will not determine specific diagnosis, but can confirm clinical suspicion of pericarditis and can be followed serially to assess response to therapy
Acute and convalescent viral antibody titers	May suggest viral origin; titers would not be expected to change the course of treatment
Thyroid function studies	Thyrotoxicosis is a rare cause of pericarditis; hypothyroidism can cause pericardial effusion without the typical ECG changes and symptoms of pericarditis

TABLE 55-9 Common Causes of Cardiac Tamponade in Medical (Nontrauma) Patients

Cause	Approximate Frequency (%)
Metastatic malignancy	40
Acute idiopathic pericarditis	15
Uremia	10
Bacterial or tubercular pericarditis	10
Chronic idiopathic pericarditis	10
Hemorrhage (anticoagulant)	5
Other (systemic lupus erythematosus, postradiation, myxedema, etc.)	10

degrees of restricted cardiac filling. Pulsus paradoxus is not diagnostic of cardiac tamponade and may be noted in other cardiopulmonary processes. In cardiac tamponade, the neck veins may be distended with an absent "y" descent. The apical impulse is indistinct or tapping in quality. Cardiac auscultation may reveal "distant" or soft heart sounds. Pulmonary rales are usually absent, and there may be right upper quadrant tenderness from hepatic venous congestion.

DIAGNOSIS

The chest radiograph may or may not reveal an enlarged cardiac silhouette because this finding depends on the amount of intrapericardial fluid accumulation. The pulmonary vasculature typically appears normal. An epicardial fat pad sign may occasionally be seen within the cardiac silhouette.

The ECG usually shows low-voltage QRS complexes (<0.7 mV) and ST-segment elevation (due to the inflammation of the epicardium) with PR-segment depression, as in pericarditis. Electrical alternans (beat-to-beat variation in the amplitude of the P and R waves unrelated to the respiratory cycles; **Figure 55-5**) is a classic but uncommon finding.

Suspect the diagnosis based on the clinical examination and chest radiographs. Echocardiography is the diagnostic test of choice. In addition to a large pericardial fluid volume, typical echocardiographic findings described in cardiac tamponade are right atrial compression, right ventricular diastolic collapse, abnormal respiratory variation in tricuspid and mitral flow velocities, and dilated inferior vena cava with lack of inspiratory collapse.[30]

TREATMENT AND DISPOSITION

Volume expansion with a bolus of normal saline solution (500 to 1000 mL) will increase intravascular volume, facilitate right heart filling, and increase cardiac output and arterial pressure. However, it is a temporary measure. Pericardiocentesis is necessary for definitive therapy and for specific diagnosis.

If there is hemodynamic instability, emergency pericardiocentesis is indicated in the ED. The technique is described in Section 4, "Resuscitative Procedures," Chapter 34, "Pericardiocentesis." (See Video: Pericardiocentesis.)

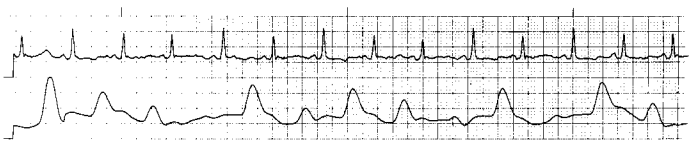


FIGURE 55-5. This rhythm strip (lead II, top tracing) and plethysmograph (bottom tracing) were recorded in a patient who presented with dyspnea, hypotension, and clinical and echocardiographic evidence of cardiac tamponade. A paradoxical pulse was noted on palpation of the radial artery. The amplitude of the R waves varies from beat to beat (electrical alternans).

However, pericardiocentesis is optimally performed in the cardiac catheterization laboratory using echocardiographic guidance to avoid cardiac perforation and coronary artery laceration. In addition, fluid samples for culture, cytology, and so on can be obtained in a more controlled setting, and following needle aspiration, a pigtail catheter can be inserted to allow continuous fluid drainage and prevention of reaccumulation.

CONSTRICTIVE PERICARDITIS

PATHOPHYSIOLOGY

Constrictive pericarditis results from pericardial injury and inflammation, resulting in fibrous thickening of the layers of the pericardium, which prevents passive diastolic filling of the cardiac chambers.[31] Some causes include postcardiac trauma with intrapericardial hemorrhage, after pericardiotomy (open heart surgery, including coronary revascularization), in fungal or tuberculous pericarditis, and in chronic renal failure (uremic pericarditis), but in most cases, a specific cause is not determined.

CLINICAL FEATURES

The symptoms of constrictive pericarditis usually develop gradually and may mimic those of congestive heart failure and restrictive cardiomyopathy.[22] However, clinical signs may occur early if fluid also accumulates within the thickened, noncompliant pericardial sac (effusive constrictive pericarditis).

Common signs and symptoms include exertional dyspnea, pedal edema, hepatomegaly, and ascites. Examination of the neck veins with the patient at a 45-degree angle from horizontal will reveal jugular venous distention and a rapid "y" descent of the cervical venous pulse. Elevated venous pressure is also seen in congestive heart failure, but a rapid "y" descent is infrequently encountered. The Kussmaul sign (inspiratory neck vein distention) is frequent in constrictive pericarditis but rare in congestive heart failure. A paradoxical pulse is uncommon, and its absence does not exclude constrictive pericarditis. On cardiac auscultation, an early diastolic sound, a pericardial "knock," may be heard at the apex 60 to 120 milliseconds after the second heart sound. The pericardial knock sounds like a ventricular gallop, but occurs earlier than the S_3 of congestive heart failure, which it may mimic. The knock is due to accelerated right ventricular inflow in early diastole and early myocardial distention, followed by an abrupt slowing of further ventricular expansion.

DIAGNOSIS AND DISPOSITION

On the ECG, low-voltage QRS complexes and inverted T waves are common, but there are no specific diagnostic ECG signs. Chest radiographs most commonly demonstrate a normal or slightly enlarged cardiac silhouette, clear lung fields, and little or no evidence of pulmonary venous congestion. Pericardial calcification may be seen. Thoracic CT and MRI may also demonstrate a thickened pericardium.

On occasion, two-dimensional echocardiography may demonstrate pericardial thickening and abnormal ventricular septal motion in a patient with suspected constrictive pericarditis. However, its diagnostic utility is much less than that in a patient with acute pericarditis. Doppler echocardiography, cardiac CT, and MRI are preferred.

In many instances cardiac catheterization with measurement of intraventricular pressures will be required to confirm the diagnosis. A characteristic dip and plateau (the "square root sign") of the right ventricular pressure trace is characteristic of the disease.[22]

In cases of significant constriction and impaired ventricular filling, admission for pericardiectomy is the treatment of choice.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 56

Venous Thromboembolism Including Pulmonary Embolism

Jeffrey A. Kline

INTRODUCTION AND EPIDEMIOLOGY

Pulmonary embolism (PE) occurs when clotted blood enters the pulmonary arterial circulation. Most PEs result from deep vein thrombosis (DVT) in the legs, arms, or pelvis and occasionally from the jugular vein or inferior vena cava. The term *venous thromboembolism* (VTE) includes PE and DVT.

In the United States, approximately 200,000 people will have new or recurrent PE diagnosed each year, and twice that many will have DVT without confirmed PE.[1] About 1 in 500 children (age <18 years) are tested for VTE in EDs, with about 10% being diagnosed with VTE; the rate of diagnosis in children is rising, perhaps as a result of longer survival of children with chronic complex comorbidity and increased use of estrogen-containing oral contraceptives.[2-4] VTE incidence varies slightly with geography across the United States but varies widely among hospitals.[5] EDs with older, sicker patients diagnose more VTE cases. The incidence of VTE increases with age, peaking at 1 in 100 per year at age 80. Based on autopsy data, PE is the second leading cause of sudden, unexpected, nontraumatic death in outpatients.[6] The case fatality rate from PE depends on the hemodynamic severity of the PE, age, and comorbid conditions; the case fatality rate is 45% for PE with circulatory shock, but only about 4% to 5% of patients with PE have shock. In patients with hemodynamically stable PE who are less than 50 years old and without other comorbidities, the case fatality rate is 1%.[7]

Morbidity from PE includes the *post-PE syndrome*, which occurs in about 25% of patients after PE and is characterized by chronic fatigue, dyspnea, exercise intolerance, and low perception of health status.[8] An extreme form of post-PE syndrome, occurring in about 3% of PE patients, is chronic thromboembolic pulmonary hypertension, which causes disabling dyspnea.[9] Morbidity from DVT includes PE and the postthrombotic syndrome, with the latter manifested as chronic leg swelling and pain; it occurs in about 20% of all ED patients with proximal DVT.[10] Both PE and DVT have a spectrum of severity, with minor forms of the disease including distal PE (called subsegmental) and distal DVT (usually in the calf or saphenous veins).[11]

PATHOPHYSIOLOGY

Blood clots occur when coagulation exceeds the removal by fibrinolysis. *Thrombophilias* are conditions that tip the balance of coagulation-fibrinolysis toward excessive clotting. Most guidelines categorize VTE as provoked or unprovoked (also called idiopathic).[12] Provoked VTEs are *a consequence* of a triggering risk factor for clots, such as recent surgery, trauma, or any condition associated with limb or body immobility; active cancer can be a persistent provoking factor for VTE. Other provoking factors generally include diseases or conditions that impede venous blood flow, infection, chronic disease, estrogen use, pregnancy or initial postpartum interval, and age >50 years (each year after 50 increases the risk).

Most VTEs diagnosed in the ED are unprovoked.[7,13] Patients with unprovoked VTE have a 15% chance of recurrence in the next year compared with 5% for those with a provoked episode. Those with provoked VTE have a higher 1-year death rate, likely from the comorbid conditions (notably cancer).[14]

Venous thrombi that are large enough to cause clinically important PE can form in the popliteal, common femoral, superficial femoral, pelvic, axillary, jugular, and great veins. At least one third of patients with DVT have concomitant PE, even when the patient lacks symptoms of PE.[15] Although 75% to 80% of hospitalized patients with PE have image-demonstrated DVT, only 40% of ambulatory ED patients with PE have concomitant DVT.[16]

Patients without prior heart or lung disease generally begin to experience symptoms from PE with at least 20% of lung vasculature occluded.[17] With larger clot burden, the pulmonary arterial pressure increases, leading to right ventricular dilation and myocardial damage, causing the release of troponin and B-type natriuretic peptide. Right ventricular dilation or injury, detected by an increased right ventricular to left ventricular ratio on CT scan or echocardiography; right ventricular strain suggested by elevated troponin or B-type natriuretic peptide; or signs of an acute pulmonary hypertension on 12-lead ECG indicate right heart failure and increased risk of circulatory shock and death.[18-20] Patients with PE generally die from one of the following two mechanisms:

1. Abrupt near-total pulmonary artery occlusion that leads to pulseless electrical activity or asystole from ischemic effect on the His-Purkinje conduction system.
2. Progressive right heart failure and circulatory shock, which occurs over hours to days.

Blood clots in the femoral and iliofemoral veins usually form on the valves, leading to scarring and poor function of the venous valves. This causes venous reflux and pooling of venous blood in the legs, leading to varicose veins, pain, swelling, skin hyperpigmentation, and ulcers, known as the postthrombotic syndrome.[4]

Inherited thrombophilias increase risk of first-time VTE, although most of these patients are unaware of this condition until a clot occurs. The risk of recurrent VTE in those with a known thrombophilia is the same as patients with unprovoked VTE and no known thrombophilia.[21]

With limb immobility, VTE risk *increases* depending on joint, as follows: elbow (least), shoulder, ankle, knee, and hip (most). Acute immobilization of the hip and knee in one leg with non–weight bearing causes the greatest risk for VTE, whereas immobilization of the wrist alone probably causes no added risk. In addition to the presence of limb immobility, risk of VTE increases with whole-body immobility or neurologic immobility and with travel >8 hours.[22]

Over half of patients with postoperative PE are diagnosed after hospital discharge, and the average time from surgery to PE diagnosis is >10 days. Risk increases with patient age, longer surgery, open surgery, and surgery absent thromboprophylaxis. The highest-risk surgical procedures include abdominal surgery to remove cancer, joint replacement surgery, and surgery on the brain or spinal cord in the setting of neurologic deficits. The 4-year risk of postsurgical acquired PE recurrence ranges from 5% to 11% per year depending on the procedure.[23]

Thrombogenic potential of cancer varies with host factors, tumor stage, and tumor type. In general, the risk of VTE increases with the more undifferentiated the cell type and the larger the tumor burden (especially distant metastasis). Adenocarcinoma (pancreatic, ovarian, and colon), glioblastoma, metastatic melanoma, lymphoma, and multiple myeloma are particularly thrombogenic.[24] Cancers with lower risk of VTE include localized breast, cervical, prostate, and nonmelanomatous localized skin cancers such as squamous cell carcinoma and basal cell carcinoma not treated with chemotherapy. In general, patients with cancer are at their highest risk of developing VTE during chemotherapy.

A family history of VTE increases longitudinal risk of VTE[25] and may increase risk of VTE diagnosis in symptomatic ED patients.[13,26] Although sex does not significantly modify the risk of first-time VTE, men have more recurrent VTE.[27]

Table 56-1 presents a list of risk factors for VTE relevant to ED practice.

Although smoking causes conditions that increase risk (e.g., cancer) and acts synergistically with obesity and possibly oral contraceptive use, smoking alone does not increase the risk of VTE diagnosis in symptomatic ED patients.[7]

Patients with missed PE who are admitted to the hospital for other reasons tend to have a higher frequency of altered mental status (either new or existing) and preexisting heart and lung disease.[28-31] One study examined patients discharged with PE and found they were more likely to not have dyspnea, but instead to have isolated pleuritic chest pain

TABLE 56-1 Risk Factors for Venous Thromboembolism (VTE) That Are Generally Relevant to Emergency Medicine

Factor	Comment
Age	Risk becomes significant at 50 y and increases with each year of life until age 80 y.
Obesity	In the general population, VTE risk starts at BMI >35 kg/m^2 and increases with increasing BMI.
Pregnancy and postpartum state	PEs can occur in any trimester and postpartum.
Prior VTE	Highest risk of recurrence is for unprovoked VTE in men, particularly if D-dimer remains elevated.
Solid cancers	Risk greatest with adenocarcinomas and metastatic disease. A history of remote, inactive cancer probably does not increase risk.
Hematologic cancers	Acute leukemias and myeloma confer the greatest risk, particularly when treated with L-asparaginase and the thalidomide derivatives.
Thrombophilias	Non-O blood type, lupus anticoagulant, shortened aPTT, factor V Leiden, and familial protein C and S and antithrombin deficiency have the strongest risk.
Recent surgery or major trauma	Risk increased with endotracheal intubation or epidural anesthesia and continues at least 4 weeks after exposure. Risk varies with type of surgery.
Immobility	Acute limb immobility of two contiguous joints confers the highest risk.
Bed rest	Becomes a risk factor at approximately 72 h.
Indwelling catheters	Cause approximately one half of arm deep venous thromboses.
Long-distance travel	Published data are controversial. In general, risk becomes significant after 6 h of continuous travel.
Smoking	A population risk factor, but not a factor that increases probability of VTE in the ED setting. May increase risk of other factors such as obesity.
Congestive heart failure	Related primarily to severity of systolic dysfunction.
Stroke	Risk greatest in first month after deficit.
Estrogen	Highest-risk period is in the first few months. All contraceptives containing estrogen increase risk of VTE including transdermal and transvaginal preparations.
Noninfectious inflammatory conditions	Examples are inflammatory bowel disease, lupus, and nephrotic syndrome. Risk of VTE increases roughly in proportion to severity of underlying disease.

Abbreviations: aPTT = activated partial thromboplastin time; BMI = body mass index; PE = pulmonary embolism.

TABLE 56-2 Factors That Can Affect the Clinical Presentation of Patients With Pulmonary Embolism (PE)

Cofactor	Clinical Impact	Comment
Previously healthy and young age	Less severe signs and symptoms	One half of previously healthy patients with first-time PE have normal vital sign values at diagnosis.
Prior cardiopulmonary disease	Can either amplify or obscure history and findings	Most patients with PE complicating baseline cardiopulmonary disease describe dyspnea with PE as "worse than usual."
Patient cognitive dysfunction	Causes the history to be less reliable	Approximately 20% of patients with PE missed by ED clinicians had baseline dementia.
Clot size and location	Affects severity of dyspnea, pain, and signs	Proximal clots cause ventilation–perfusion mismatch and dyspnea; distal clots cause infarction with pain.
Gradual loading of PE over time	Gradual onset of dyspnea on exertion and fatigue	Has symptom overlap with left ventricular dysfunction. Fewer than one half of patients with PE describe symptom onset as sudden.

and hemoptysis together with a pulmonary infiltrate on imaging and a lower D-dimer concentration with a small distal clot seen on pulmonary vascular imaging.[30]

CLINICAL FEATURES OF PULMONARY EMBOLISM

PE symptoms range from none to sudden death. Patients with similar comorbidities and clot burden may have drastically different clinical presentations. **Table 56-2** lists factors that affect symptoms.

The hallmark of PE is dyspnea unexplained by auscultatory findings, ECG changes, and without a clear alternative diagnosis on chest radiograph. Chest pain with pleuritic features is the second most common symptom of PE, although about one half of all patients diagnosed with PE in the ED have no chest pain.[7] The classic PE pain is in the thorax between the clavicles and the costal margin that increases with cough or breathing; it is not substernal and emanating from the skin or muscle. Pulmonary infarction (lung tissue destruction) can inflict severe focal pain, usually occurring 1 to 3 days after the embolic event.[32] Pulmonary infarction in basilar lung segments can refer pain to either shoulder, or it can mimic biliary or ureteral colic. Proximal PE without infarction can also cause pleuritic chest pain without focal pain.

HISTORY

In addition to the common symptoms of chest pain and dyspnea, approximately 3% to 4% of ED patients with PE have syncope, and another 1% to 2% present with new-onset "seizure" (or convulsion-like activity) or confusion.[3] Because about 20% of people have a patent foramen ovale, PE that increases right-sided pressures can lead to right-to-left transit of thrombotic material in the atria and showers into the brain circulation, producing stroke-like symptoms called the **paradoxical embolism syndrome**. Neurologic symptoms can vary widely, from classic localized findings to staring spells, transient altered mental status, and atypical myelopathy symptoms (e.g., numbness in an extremity or below the waist), all of which can fluctuate.[33] Presence of a patent foramen ovale worsens the prognosis in PE.

PHYSICAL EXAMINATION

On physical examination, abnormal vital signs suggest acute cardiopulmonary stress in a patient with PE; these include tachycardia, tachypnea, a lowered pulse oximetry reading, and sometimes mild fever. Unfortunately, PE does not predictably alter any vital sign; approximately one half of patients with proven PE have a heart rate of <100 beats/min at diagnosis, and approximately one third have abnormal early vital signs that normalize in the ED.[34] The mechanism of altered vital signs results in obstruction to blood flow and clot-derived autacoids, which together stimulate adrenergic efferent fibers to the heart and cause ventilation–perfusion mismatch on the lungs. The amount of clot burden does not predict vital sign changes reliably, with no clear correlation between measured clot and initial heart rate or oximetry. Fever neither increases nor decreases the probability of PE diagnosis in symptomatic ED patients.

The physical examination, aside from vital signs, is most likely to be helpful through two findings:

1. Unilateral limb swelling (with or without an indwelling catheter), which increases probability of PE diagnosis by three-fold
2. Wheezing, which reduces probability of PE by one half

Most patients with PE have clear lungs on auscultation. Wheezes or bilateral rales make an alternative diagnosis of bronchospasm or

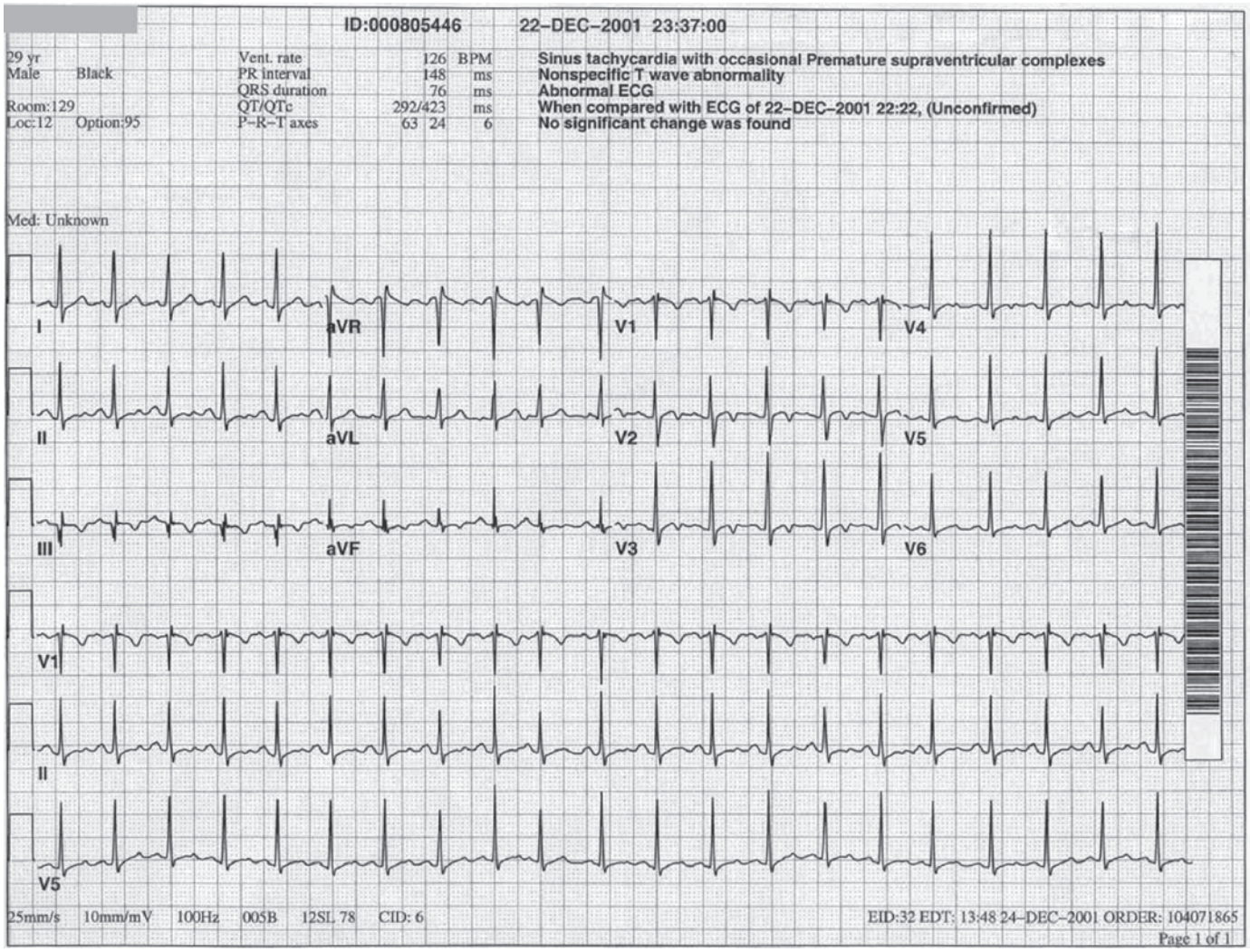


FIGURE 56-1. This 12-lead ECG shows many features of a severe pulmonary embolism: tachycardia, an incomplete right bundle branch block, an S_1-Q_3-T_3 pattern, and T-wave inversion in the anterior leads. [Image contributed by Department of Emergency Medicine, Wake Forest Baptist Hospital.]

pneumonia possible but do not completely exclude PE; pulmonary infarction may produce rales over the affected lung segment. The overall gestalt interpretation of "sick/not sick" appearance of ED patients with possible PE can be deceiving; one study found that patients diagnosed with PE were more likely to smile during their physical examination.[35]

PULSE OXIMETRY, CHEST RADIOGRAPH, AND ECG

Pulse oximetry, chest radiograph, and ECG obtained in the ED generally demonstrate nonspecific findings in patients with PE. The mean pulse oximetry reading is lower in patients with proven PE than in those without PE; while lowered room air oxygen saturation is common, a pulse oximetry reading of 100% does not reliably exclude PE. Spontaneously breathing patients with PE also demonstrate a lower end-tidal carbon dioxide compared with healthy individuals.[36]

Most patients with PE have a chest radiograph with one or more abnormalities, including cardiomegaly, basilar atelectasis, infiltrate, or pleural effusion; all are nonspecific for PE. In <5% of patients, a wedge-shaped area of lung oligemia (called *Westermark's sign*—usually from complete lobar artery obstruction) or peripheral dome-shaped dense opacification (*Hampton's hump*—indicative of pulmonary infarction) exists. **The presence of hypoxemia or dyspnea with clear lungs on physical exam and chest radiography suggests the need to test for PE.**

Findings of acute pulmonary hypertension on ECG increase the probability of PE. These findings are not typically recognized by computer interpretations and include a heart rate >100 beats/min, T-wave inversion in leads V_1 to V_4, incomplete or complete right bundle branch block, and the S_1-Q_3-T_3 pattern (**Figure 56-1**).[37] A clinical ECG score also allows severity assessment in those with diagnosed PE (higher score equates to higher mortality, **Table 56-3;** See Video: ECG: Pulmonary Embolism).[38,39]

CLINICAL FEATURES OF DEEP VEIN THROMBOSIS

Patients with DVT complain of extremity pain, swelling, or cramping. A difference of ≥2 cm between right and left leg diameter at 10 cm below the tibial tubercle doubles the likelihood of DVT. Patients presenting with upper extremity catheter-related DVT often complain of hand swelling or tightness around finger rings. About one quarter of patients with DVT have tenderness and redness in the swollen extremity, findings that are like those of cellulitis. Calf or saphenous vein clots are more likely to cause thrombophlebitis, defined formally as inflammation (pain, tenderness, redness, and swelling) over a vein secondary to the presence of thrombotic material in the vein. Signs and symptoms of thrombophlebitis can persist after the venous recannulation and after the clot has dissolved entirely. Calf vein thrombosis may cause **Homan's sign**, which is calf pain that occurs with passive foot dorsiflexion; this test has such low sensitivity and specificity that it has no predictive value.

Proximal DVT that causes complete venous obstruction can create elevated compartmental pressures, manifested as an extremely painful,

TABLE 56-3 ECG Scoring Method to Assess Severity of Pulmonary Embolism[39]

Characteristics	Score
Tachycardia (>100 beats/min)	2
Incomplete right bundle branch block	2
Complete right bundle branch block	3
T-wave inversion in leads V_1 through V_4	4
T-wave inversion in lead V_1*	
<1 mm	0
1–2 mm	1
>2 mm	2
T-wave inversion in lead V_2*	
<1 mm	1
1–2 mm	2
>2 mm	3
T-wave inversion in lead V_3*	
<1 mm	1
1–2 mm	2
>2 mm	3
S wave in lead 1	0
Q wave in lead 3	1
Inverted T wave in lead 3	1
If all S_1-Q_3-T_3 pattern, add	2
Total score (maximum: 21)	

*If present, check maximum only.

swollen extremity. **Phlegmasia alba dolens** is a swollen, painful, and pale or white limb with a proximal venous thrombosis, whereas a limb with a dusky or blue color is **phlegmasia cerulea dolens**. Either condition poses the threat of limb loss, demanding aggressive treatment that can include clot disruption.

DIAGNOSTIC TESTING FOR VENOUS THROMBOEMBOLISM

DECISION RULES AND CLINICAL ASSESSMENT

Estimating the pretest probability for VTE in a patient is the first step in selecting a diagnostic pathway. Figure 56-2 shows the author's diagnostic algorithm; **no singular diagnostic test or algorithm perfectly excludes or diagnoses VTE**. Aggressive diagnostic searches can cause harm from hemorrhage caused by anticoagulation for a false-positive result or self-limited small clot diagnosis or from toxicity related to testing itself, such as contrast allergies, kidney injury, or cancer risk. One approach is to test further only in those with pretest probabilities of >2.5%[40]; those with a pretest probability of PE of <2.5% are more likely to be harmed—either directly or by responding to a test result with more testing or care—than helped by a diagnostic test, including a simple D-dimer assay.

The PE rule-out criteria (**Table 56-4**) reliably forecast a probability of PE that is below the 2.0% test threshold in patients *with a gestalt low clinical suspicion*.[41-43] The American College of Emergency Physicians, the American College of Physicians, and the American Society of Hematology current guidelines all recommend use of the PE rule-out criteria rule,[44-46] which has been validated in multiple groups.[41,47] The weight of the available information indicates that PE can be reliably excluded by the combination of a low gestalt pretest probability plus a negative PE rule-out criteria rule. However, *not all patients with any positive PE rule-out criteria must undergo an objective test for PE,* since anyone over 50 years old would be tested with any finding even if suspicion was low. **The key is generating a clinical gestalt first**; if low, then use the PE rule-out criteria to guide testing.

Other PE and DVT prediction tools exist. The Wells' original rules separate patients into low-, moderate-, and high-probability groups for PE and DVT, with a stepwise increase in probability of clot presence with higher scores (**Tables 56-5** and **56-6**) . The newer modified Wells' scoring system classifies patients into a low-risk (score ≤4) or a non–low-risk group (score >4)[48] and has become popular.[49]

The Wells' rule has a subjective component—clinical judgment of the likelihood of an alternative diagnosis. Both the Charlotte and the **simplified, revised Geneva score** (**Table 56-7**) exclude subjective assessments.[50]

Unstructured gestalt pretest probability, divided into low (<15%), moderate (15% to 40%), and high (>40%) categories, is an alternative and valid method to estimate pretest probability; ultimately, well-done estimation using any tool or gestalt is better than none.[51]

D-DIMER TESTING

The D-dimer assay is the only useful blood test to exclude VTE, working on the principle that clots contain fibrin that is degraded naturally through the action of plasmin. D-Dimer levels are reported either as fibrinogen equivalent units in nanograms per milliliter or D-dimer units in nanograms per milliliter. In general, 1 D-dimer unit equals 2 fibrinogen equivalent units. Different D-dimer assays have different thresholds for normal, which can generate confusion, but in general, emergency physicians are advised to use the locally recommended threshold. For PE and DVT, the diagnostic sensitivity of automated quantitative D-dimer assays ranges from 94% to 98%, and the specificity ranges from 50% to 60%.[46,52] **The D-dimer has a half-life of approximately 8 hours and can be elevated for at least 3 days after symptomatic VTE.**

The most common causes of a false-negative or false-positive D-dimer result are listed in **Table 56-8**; notably, all risk factors for VTE may elevate the D-dimer level. D-Dimer increases with age; the acceptable normal threshold is adjusted upward for age to increase exclusionary ability in older patients.[53] The most common formula studied is age×10 nanograms/mL (e.g., an 80-year-old patient would have an adjusted threshold for abnormal at 800 nanograms/mL).[49] This assumes the conventional D-dimer cutoff of 500 nanograms/mL; in a large multicenter study, this adjusted approach resulted in a very low false-negative rate (0.3%) when used in conjunction with a Wells' score ≤4 or a simplified revised Geneva score <5.[49] The YEARS study reported that patients with a low pretest probability and a D-dimer concentration that is twice the usual cutoff value (e.g., at 1000 ng/mL instead of 500 ng/mL) have a <1% probability of PE.[54]

IMAGING

CHEST CT ANGIOGRAPHY

Chest CT angiography is the most common imaging modality for PE, identifying a clot as a filling defect in contrast-enhanced pulmonary arteries (**Figure 56-3**). The diagnostic sensitivity and specificity of a technically adequate multidetector CT pulmonary angiography scan are both approximately 90%. The sensitivity of CT is not adequate to exclude PE in patients with a high pretest probability.[55] Most CT pulmonary angiography protocols require the patient to lie supine and hold their breath for a few seconds, and the scan requires injection of approximately 120 mL of contrast by a computer-controlled injection device. The patient must have a peripheral IV catheter (20 gauge or larger) or an approved indwelling line to allow injection of the contrast, and a central catheter cannot be used for injection.

In addition to clot recognition, a CT scan can detect alternative diagnoses, often pneumonia (8% to 22% of cases).[56] Interobserver agreement in identifying segmental or larger filling defects is very good, but interobserver agreement for subsegmental clots is poor. In practice, approximately 10% of CT scans are inadequate from secondary motion artifact or poor pulmonary artery opacification, commonly in obese or very tachypneic patients. About 15% of patients undergoing contrast-enhanced chest CT scan develop mild contrast nephropathy.[57,58] **At present, no clearly helpful prophylactic measure exists to reduce**

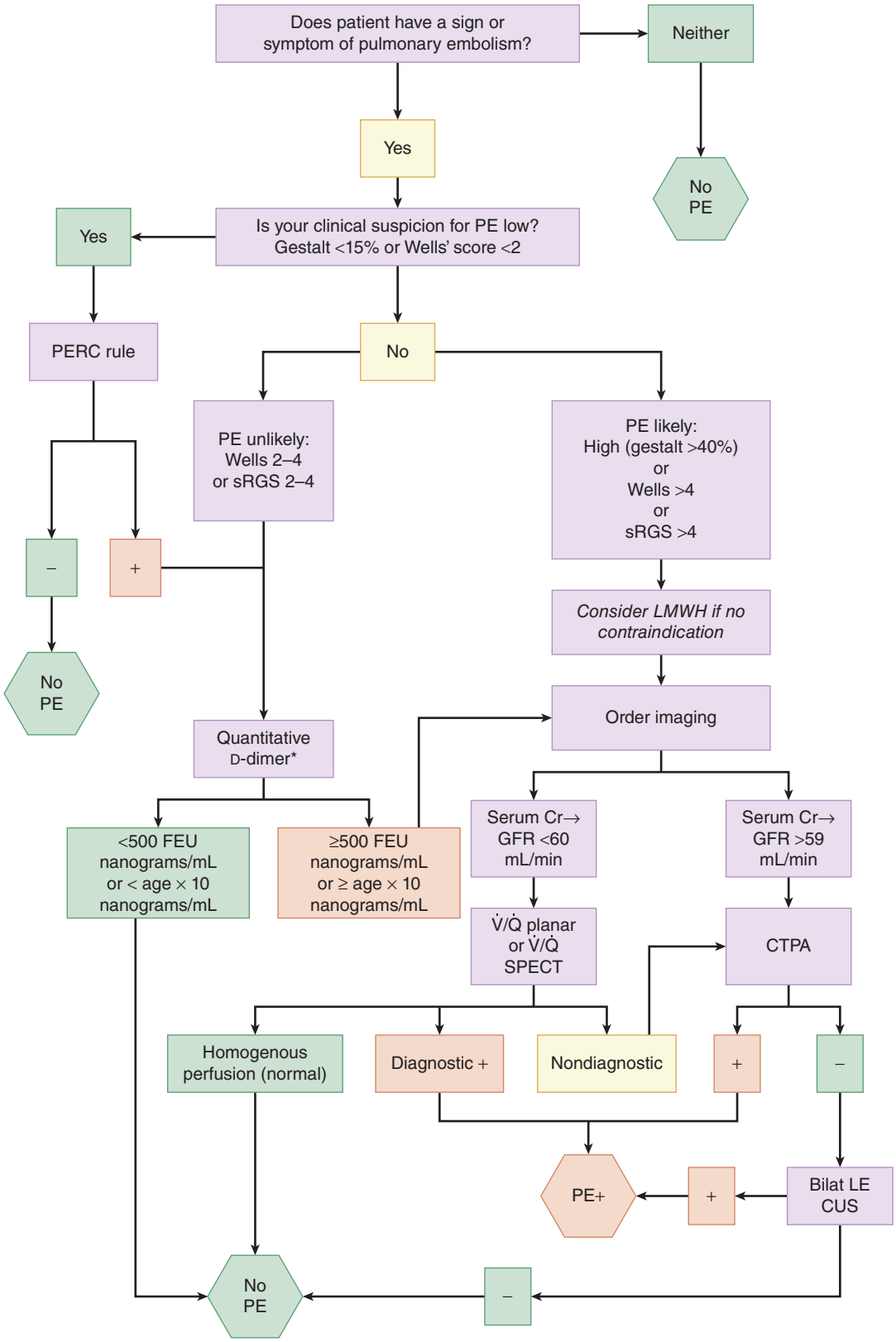


FIGURE 56-2. Proposed algorithm for evaluation of suspected pulmonary embolism. Begin with the pulmonary embolism rule-out criteria (PERC) rule—diagnostic algorithm for pulmonary embolism (PE). *Some physicians prefer to start with a clinical decision rule such as the Wells' score (where <2, 2–6, and >6 are used instead of <15%, 15% to 40%, and >40%, respectively). Note: Determine renal function by clinical picture (healthy, no risk factors for reduced glomerular filtration rate [GFR]) or calculated GFR. Nondiagnostic ventilation–perfusion (V̇/Q̇) scan findings require confirmation from results of another test, such as CT pulmonary angiography (CTPA), if benefits outweigh risks. + = positive for PE; – = negative for PE; Bilat LE CUS = bilateral lower extremity compression US; Cr = creatinine; FEU = fibrinogen equivalent units; High = high-probability scan findings; LMWH = low-molecular-weight heparin; Nondiagnostic = any reading other than normal or high probability; quant = quantitative; SPECT = single-photon emission CT; sRGS = simplified, revised Geneva score; V̇/Q̇ = ventilation/perfusion ratio.

TABLE 56-4 Pulmonary Embolism Rule-Out Criteria Rule (all nine factors must be present to exclude pulmonary embolism)[41]

- Clinical low probability (<15% probability of pulmonary embolism based on gestalt assessment)
- Age <50 years
- Pulse <100 beats/min during entire stay in ED
- Pulse oximetry >94% at near sea level (>92% at altitudes near 5000 feet above sea level)
- No hemoptysis
- No prior venous thromboembolism history
- No surgery or trauma requiring endotracheal or epidural anesthesia within the last 4 wk
- No estrogen use
- No unilateral leg swelling, defined as asymmetrical calves on visual inspection with patient's heels raised off the bed

TABLE 56-5 Original Wells' Score for Pulmonary Embolism

Factor	Points*
Suspected deep venous thrombosis	3
Alternative diagnosis less likely than PE	3
Heart rate >100 beats/min	1.5
Prior venous thromboembolism	1.5
Surgery or immobilization within prior 4 wk	1.5
Active malignancy	1
Hemoptysis	1

*Risk score interpretation (probability of pulmonary embolism): >6 points = high risk (78.4%); 2–6 points = moderate risk (27.8%); and <2 points = low risk (3.4%).

Source: Adapted with permission from Wells PS, Anderson DR, Rodger M, et al: Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the model utility with the SimpliRED D-dimer. *Thromb Haemost* 2000 Mar;83(3):416-420. Figure 3, Pg 418.

TABLE 56-6 Wells' Score for Deep Vein Thrombosis (DVT)

Clinical Feature	Points*
Active cancer (treatment within 6 mo, or palliation)	1
Paralysis, paresis, or immobilization of lower extremity	1
Bedridden for >3 d because of surgery (within 12 wk)	1
Localized tenderness along distribution of deep veins	1
Entire leg swollen	1
Unilateral calf swelling of >3 cm (10 cm below tibial tuberosity)	1
Unilateral pitting edema	1
Collateral superficial veins	1
Alternative diagnosis as likely as or more likely than DVT	–2
Prior history of DVT or pulmonary embolism†	1

*Risk score interpretation (probability of DVT) in original Wells DVT model: ≥3 points = high risk (75%); 1 or 2 points = moderate risk (17%); <1 point = low risk (3%).

†Only awarded in the modified (dichotomized) Wells DVT model: ≤1 point = DVT unlikely; >1 point = DVT likely.

Source: Adapted from Geersing GJ, Zuithoff NP, Kearon C, et al: Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. *BMJ* 348: g1340, 2014.

TABLE 56-7 Revised and Simplified, Revised Geneva Score (RGS) for Pulmonary Embolism[50]

	Points	
Clinical Variable	RGS*	Simplified RGS†
Age >65 y	1	1
Previous venous thromboembolism	3	1
Surgery requiring anesthesia or fracture of lower limb in past month	2	1
Active malignancy	2	1
Unilateral leg pain	3	1
Hemoptysis	2	1
Pain on lower limb deep vein palpation with unilateral leg edema	4	1
Heart rate		
75–94 beats/min	3	1
>95 beats/min	5	1

*Total score of 0–3 indicates low probability, score of 4–10 indicates moderate probability, and score of >10 indicates high probability of pulmonary embolism.

†Score ≤4 indicates that pulmonary embolism is unlikely.

TABLE 56-8 Factors Known to Alter the D-Dimer Level From Expected Values

Potential False-Positive Levels	Potential False-Negative Levels
Age >70 y	Symptoms lasting >5 d
Pregnancy	Presence of small clots
Active malignancy or metastasis	Isolated small pulmonary infarction
Surgical procedure in previous week	Isolated calf vein thrombosis
Liver disease	Lipemia
Rheumatoid arthritis	
Infections	
Trauma	

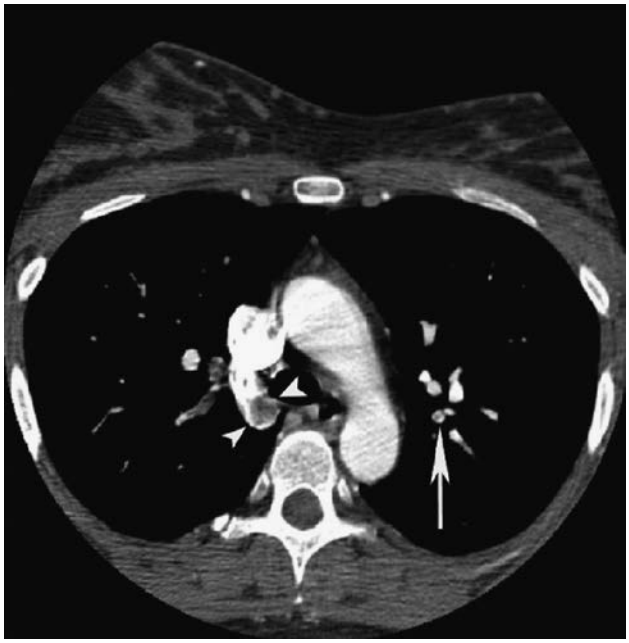


FIGURE 56-3. Axial image from a chest CT angiogram demonstrating a filling defect consistent with acute pulmonary embolism. Two *white arrowheads* outline a circular filling defect in the right middle lobar pulmonary artery. The *long white arrow* projecting in the left lung points to a filling defect in a segmental artery in the posterior medial segmental artery.

contrast nephropathy, including hydration with IV balanced crystalloid solutions.[59-61] Other CT angiogram complications include anaphylactoid reactions (<1:1000), contrast extravasation into a limb that can cause pain or compartment syndrome, and creation of a secondary thrombophlebitis.[62]

PLANAR VENTILATION–PERFUSION LUNG SCANNING

Ventilation–perfusion ($\dot{V}/\dot{Q}$) lung scanning can identify a perfusion defect when ventilation is normal. The perfusion images are usually obtained first and require a peripheral IV catheter for injection; the patient must be able to sit up and then lie down during the procedure. The ventilation component requires the patient to breathe a nebulized aerosol with isotope. A $\dot{V}/\dot{Q}$ scan with homogeneous scintillation throughout the lung in the perfusion portion is nearly 100% sensitive in excluding PE, regardless of the appearance of the ventilation portion. A $\dot{V}/\dot{Q}$ scan with two or more apex central wedge-shaped defects in the perfusion phase (**Figure 56-4A**) with normal ventilation in these regions indicates >80% probability of PE. All other $\dot{V}/\dot{Q}$ scan findings are nondiagnostic; taken alone, these cannot exclude or diagnose PE.

The $\dot{V}/\dot{Q}$ single-photon emission CT technique produces three-dimensional images with better diagnostic accuracy and lower interobserver variability than planar $\dot{V}/\dot{Q}$.[63] The pooled diagnostic accuracy of $\dot{V}/\dot{Q}$ single-photon emission CT is extraordinarily good; a 2015 systematic review and meta-analysis of 3454 patients found a pooled sensitivity of 96% (95% confidence interval [CI], 95% to 97%) and a specificity of 97% (95% CI, 96% to 98%). $\dot{V}/\dot{Q}$ single-photon emission CT detects subsegmental perfusion defects.[63] Single-photon emission CT can also be combined with low radiation dose CT scanning to produce color-mapped images that can be even more revealing (**Figure 56-4B**).

MAGNETIC RESONANCE IMAGING

MRI is a zero-radiation option for imaging the pulmonary vasculature that may have utility in pregnant patients. However, pooled data suggest that the diagnostic accuracy of MRI for all examinations, regardless of technical adequacy of images, is too low (sensitivity of 75% with specificity of 80%) to consider as a first-line modality.[64]

LUNG US

Lung US is an adjunctive modality to help diagnose and exclude PE at the bedside. One study found an improvement in the diagnostic accuracy of the Wells' score when using lung US to determine the presence or absence of an alternative diagnosis.[65] Pooled data suggest that lung US has a sensitivity of 85% (95% CI, 78% to 90%) and specificity of 83% (95% CI, 73% to 90%).[66]

VENOUS US

Venous US is the imaging test of choice in DVT; it can be done quickly, does not use ionizing radiation, and provides direct evidence of intravascular thrombus by observing noncompressibility of the vein (**Figure 56-5**). When performed by experienced ultrasonographers, compression venous US has a diagnostic sensitivity of 96% and a specificity of 96% for DVT; it also has a sensitivity of about 40% as a surrogate method to diagnose PE. The mean sensitivity for DVT of US performed by a trained emergency physician compared with the reference imaging test is 96.1% (95% CI, 90.6% to 98.5%), with a weighted mean specificity of 96.8% (95% CI, 94.6% to 98.1%).[67] However, the details of test performance and training remain important, because two-point compression

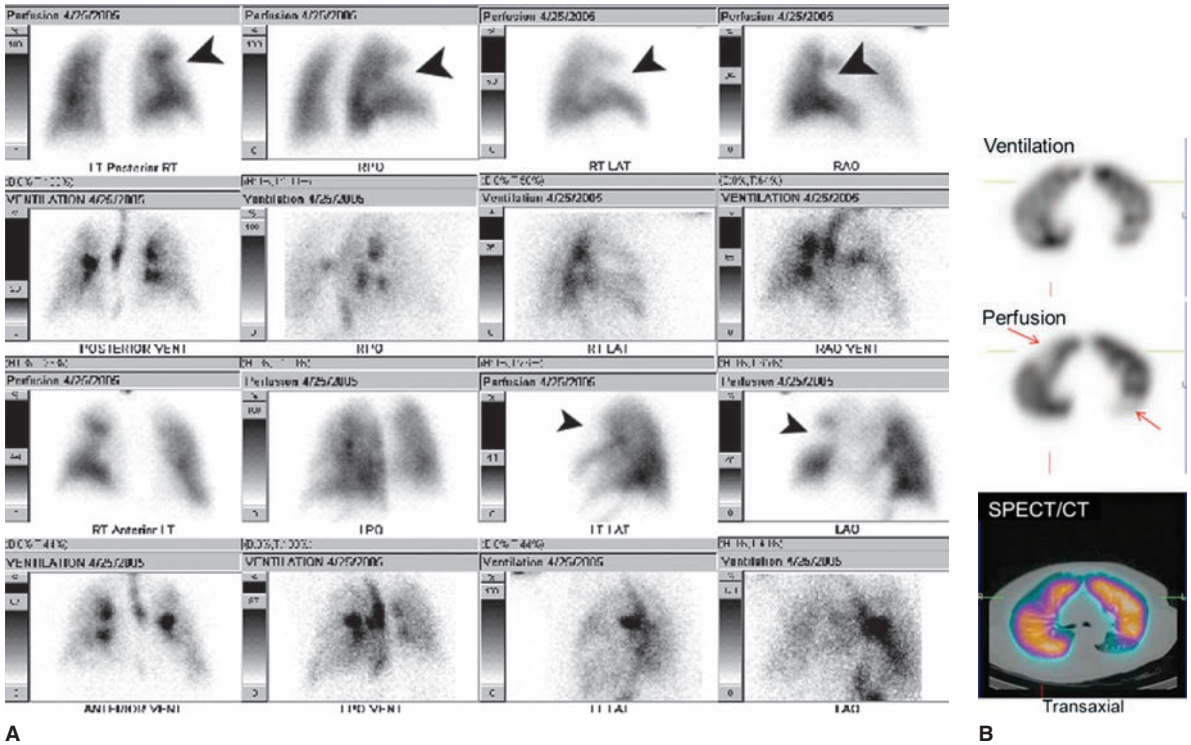
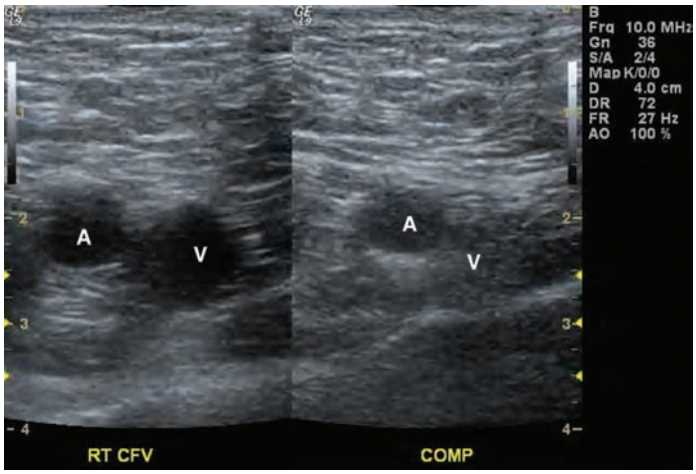


FIGURE 56-4. A. Planar ventilation–perfusion lung scan series consistent with a high probability of acute pulmonary embolism (PE) using standard criteria. The first and third rows project the perfusion phases of the examination, and the second and fourth rows show the ventilation phases. The *black arrowheads* point to wedge-shaped defects in the perfusion images. Comparison with the corresponding ventilation view immediately below shows relatively homogeneous scintillation activity in the anatomic segments that lack perfusion. These defects are consistent with an acute PE. **B.** Ventilation and perfusion single-photon emission CT (SPECT) images from a patient with PE. The *red arrows* point to the perfusion defects indicative of PE. The lower panel shows the color-mapped images produced by SPECT/CT; the segments of lung without blood flow appear black. [Part B: This research was originally published in JNM. Roach PJ, Schembri GP and Bailey DL. $\dot{V}/\dot{Q}$ scanning using SPECT and SPECT/CT. *J Nucl Med*. 2013;54(9):1588-1596. Figure 4. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.]



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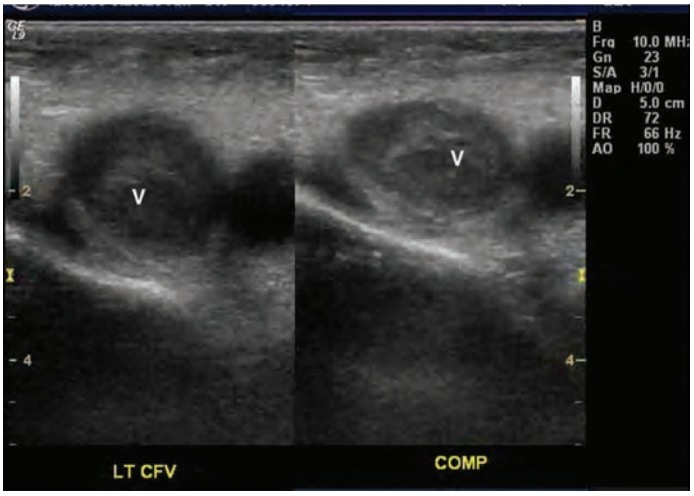


B

FIGURE 56-5. Compression venous US images showing normal findings and findings indicating deep venous thrombosis. **A.** Compression venous US of the common femoral vein and femoral artery. The left view shows a sonographic image of the right femoral artery (A) and common femoral vein (V) obtained immediately inferior to the inguinal ligament. The image on the right shows the same view after manual compression by the operator. The image demonstrates obliteration of the vein while the artery remains open. This is a normal US finding for the vein. **B.** Venous US image showing evidence of common left femoral vein thrombosis after compression (right panel). The common femoral vein (V) does not compress. Echogenic thrombolytic material can be observed within the vein.

US may miss some clots and new users require experience with at least 10 examinations before gaining adequate skill.

Planar pulmonary angiography and venography directly visualize filling defects in the pulmonary arteries or extremity veins, respectively. However, neither test is currently used as a first-line diagnostic modality.

INTEGRATED APPROACH TO DIAGNOSIS AND TREATMENT

STEP ONE

For a patient to enter a PE testing regimen, he or she should have at least one physiologic manifestation of PE. This may be a symptom (e.g., pain in the chest or torso, a breathing problem, or altered mental status) or a finding (e.g., an abnormal vital sign) that could be produced by a clot in the lung. The physiologic manifestation must be placed in the context of the given patient—an untreated asthmatic patient with shortness of breath and wheezing should be treated first for bronchospasm and reevaluated and not immediately tested for PE. A risk factor or even multiple risk factors for VTE in the absence of a known sign or symptom or a positive PE rule-out criteria rule with a <2% gestalt pretest probability of PE ***does not*** mandate testing for PE or DVT.

STEP TWO

After finding a physiologic manifestation of PE, the next step is to ask, "Do I have more than a low initial suspicion for PE?" Low suspicion means that the physician's gestalt interpretation of the overall clinical picture is PE likelihood of <15%. If the answer to this question is yes, then a diagnostic test is needed. If the answer is no, then it remains possible that PE can be excluded using the PE rule-out criteria rule. If all eight criteria of the PE rule-out criteria rule are met in the setting of a gestalt-based low suspicion, then no further testing is necessary. In general, if any one of the eight criteria is not met or if a prominent finding exists, order a diagnostic test for PE.

STEP THREE

If PE cannot be excluded with the PE rule-out criteria rule, choose a diagnostic test result that can produce a posttest probability of <2.0%. An age-adjusted quantitative D-dimer assay is the best diagnostic test in patients for whom clinical suspicion is low or moderate based on either gestalt estimation, a Wells' or simplified revised Geneva score of ≤4, or a "safe" designation according to the PE rule-out criteria rule. Patients with a low pretest probability (e.g., a reasonable alternative diagnosis to PE, no hemoptysis, and no signs of DVT) can have PE excluded with a D-dimer at twice the usual threshold (**Table 56-9**).[46,52]

STEP FOUR

Test further only those with a positive D-dimer result or a high pretest probability; base the choice of the next test on patient and facility factors. *The algorithm presented in* Figure 56-2 *is one path.* In general, the next best step for a patient with suspected PE and a positive D-dimer result is chest CT angiography. V̇/Q̇ scan may be a preferred option in a

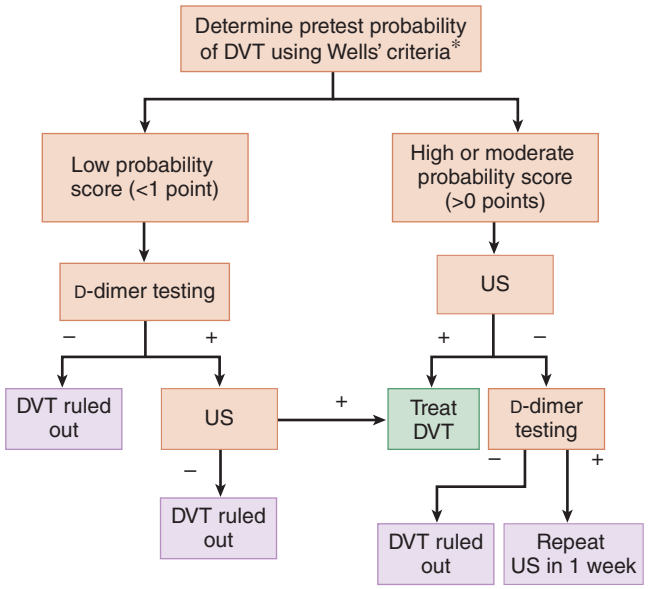
TABLE 56-9 Likelihood Ratios (LRs) of Diagnostic Tests and Pretest Probabilities Required to Diagnose or Exclude Pulmonary Embolism (PE)

Test	LR for PE if Test Result Is Negative	LR for PE if Test Result Is Positive*	Examples of Scores on Published Methods That Would Allow Pretest Probability to Rule Out VTE if Test Result Is Negative
Qualitative D-dimer	0.25	2	Wells' score <2, all pulmonary embolism rule-out criteria negative
Quantitative D-dimer†	0.1	2	Gestalt estimate low, Wells' score ≤4, or Charlotte rule negative ("safe") Age adjustment of the D-dimer cutoff using the formula age × 10 nanograms/mL
CT angiography	0.12	12	Gestalt estimate low, Wells' score ≤4, or Charlotte rule negative ("safe")
V̇/Q̇ scan: normal	0.05	NA	Any
V̇/Q̇ scan: high probability	NA	12	NA

Abbreviations: FEU = fibrinogen equivalent units; NA = not applicable; V̇/Q̇ = ventilation–perfusion; VTE = venous thromboembolism.

*A positive D-dimer result should not be used to rule in VTE.

†Assumes a U.S. Food and Drug Administration–cleared assay with cutoff of 500 FEU nanograms/mL as threshold.



*Wells PS, Anderson DR, Rodger M, et al: Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model utility with the SimpliRED D-dimer. *Thromb Haemost* 83: 416-20, 2000.

FIGURE 56-6. Diagnostic algorithm for deep vein thrombosis (DVT), applied in patients with leg symptoms compatible with DVT. + = positive test result; – = negative test result.[109]

pregnant patient or in a patient with renal insufficiency or prior adverse reaction to contrast material. Performing lower extremity venous US is another option; it lacks ionizing radiation, and its ability to diagnose DVT in a patient with PE symptoms is tantamount to diagnosing PE directly. However, **the diagnostic sensitivity of lower extremity US for PE is <40%,** so all patients suspected of having PE for whom US findings are negative require pulmonary vascular imaging. A good-quality CT scan (adequately opacified vessels to the segmental artery level) or a normal $\dot{V}/\dot{Q}$ scan excludes PE. Anticoagulation should be started for all patients with a segmental or larger filling defect consistent with PE seen on CT scan, a high probability $\dot{V}/\dot{Q}$ scan, or a DVT seen on US.

If the patient has no image-detected DVT or PE and has an elevated D-dimer concentration, then further imaging before anticoagulation is an option, especially if the patient has any increased risk of bleeding complications. Commonly, a repeat venous US within 2 to 7 days is an alternative option to exclude VTE.

Figure 56-6 is one algorithm describing the diagnostic decision making for DVT. Patients with a low pretest probability (score <1) or patients without cancer, with a modified Wells' DVT score ≤1 (Table 56-6), and with a normal D-dimer result are safely considered negative for DVT; any positive result requires US in this group. Patients with moderate to high Wells' scores or DVT likely (modified Wells' DVT score) should undergo US testing, assessing D-dimer as additional confirmation at physician discretion only if the US result is negative. In these patients, assume no clot exists if both US and D-dimer tests are negative; if patients have negative US findings and positive D-dimer results, repeat the US 2 to 7 days later.

VENOUS THROMBOEMBOLISM TREATMENT

TREATMENT OF PULMONARY EMBOLISM AND DEEP AND SUPERFICIAL EXTREMITY THROMBOSES

Treatment of VTE requires systemic anticoagulation to prevent further clot formation and allow endogenous fibrinolysis to proceed. In many cases, the initial treatment for VTE is heparin or a heparin-like drug. Patients with DVT diagnosed in the ED are typically discharged after receiving the first dose of low-molecular-weight heparin, apixaban, or rivaroxaban (**Table 56-10**), with anticoagulation continued as an outpatient. Indications for admission in patients with DVT are primarily dependent upon social determinants, comorbid conditions, and the presence of iliofemoral DVT with signs of phlegmasia.

TABLE 56-10 Antithrombotic Therapy for Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

Therapy	Dosage	Comments
Unfractionated heparin	80 units/kg bolus, then 18 units/kg/h infusion	Recommended if outpatient therapy not appropriate or in cases of severe renal failure
LMWH		Outpatient treatment with LMWH preferred
Dalteparin	100 IU/kg SC every 12 h or 200 IU/kg SC every day	
Enoxaparin	1 milligram/kg SC every 12 h or 1.5 milligrams/kg SC every day	
Tinzaparin	175 IU/kg SC every day	
Factor Xa inhibitors		
Fondaparinux	<50 kg, 5 milligrams SC every day; 50–100 kg, 7.5 milligrams SC every day; >100 kg, 10 milligrams SC every day	Do not use in renal failure
Target-specific anticoagulants		
Rivaroxaban (Xarelto®)	15 milligrams BID for 21 d, then 20 milligrams every day with food	No heparin requirement; good choice for outpatient treatment
Apixaban (Eliquis®)	10 milligrams BID for 7 days, then 5 mg BID	No heparin requirement; good choice for outpatient treatment
Dabigatran (Pradaxa®)	150 milligrams BID	Requires run-in of heparin for 5–10 d; renal excretion
Thrombolytic therapy	Tissue plasminogen activator or alteplase (Activase®), 10-milligram IV bolus followed by 90 milligrams infused over 2 h	For PE with hemodynamic compromise; after infusion, begin unfractionated heparin or LMWH

Abbreviations: BID = twice a day; LMWH = low-molecular-weight heparin.

The two most common options are unfractionated heparin or a low-molecular-weight heparin (Table 56-10).[12] Initial anticoagulation treatment for VTE can also include oral apixaban or rivaroxaban.[12] For detailed discussion of antithrombotic therapy, see Chapter 239, "Thrombotics and Antithrombotics."

Current data favor the use of low-molecular-weight heparins over unfractionated heparin for treatment of both PE and DVT in terms of composite outcomes (bleeding and death) and cost, although the magnitude of benefit is not large.[6] If uncertain about PE presence, the likelihood can guide anticoagulation therapy; the benefit of empiric anticoagulation for 24 hours exceeds the risks (bleeding and heparin-induced thrombocytopenia) for any patient with a pretest probability of PE of >20%.[68] Delay in administration of heparin to patients with PE is associated with increased mortality, but no study has found that heparin, administered early and prior to imaging, improves morbidity or mortality.

In patients with severe renal insufficiency and acute DVT or PE, most experts recommend unfractionated heparin over low-molecular-weight heparin.[12] **Treat upper extremity DVT the same as lower extremity DVT**, and consider removing any indwelling catheters associated with clot. **Do not delay unfractionated heparin for thrombophilia testing.**[69]

Most DVT can be treated with anticoagulation, but iliofemoral DVT that causes **phlegmasia cerulea dolens** requires rapid action to

reduce the venous pressure. In addition to initiating anticoagulation, place the affected limb at a neutral level; remove constrictive clothing, cast, or dressing; and arrange for vascular consultation and consultant-delivered catheter-directed thrombolysis.[70] If no such service is available and emergency transfer cannot be arranged within 6 hours, consider systemic fibrinolytics if there are no absolute contraindications. One regimen for the latter is 50 to 100 milligrams of alteplase infused IV over 4 hours.

TREATMENT FOR SUPERFICIAL THROMBOPHLEBITIS

Treatment for localized superficial thrombophlebitis is an oral NSAID or topical diclofenac gel until symptoms resolve; there is no need for systemic anticoagulation. For extensive superficial vein involvement, full-dose anticoagulation is recommended.[6] Compression stockings may provide some relief in selected individuals.[71]

TREATMENT FOR ISOLATED CALF VEIN THROMBOSIS

There are no universally accepted treatment guidelines for thromboses isolated to the calf veins (soleal or gastrocnemius) or the saphenous vein, although many use 3 months of oral anticoagulation.[72] Alternatives include no acute treatment, with repeat US in 1 week to identify progression of clot, or outpatient treatment with low-molecular-weight heparin (Table 56-10). Patients with a history of VTE or risk factors for VTE (Table 56-1) should receive 3 months of full-dose anticoagulation when calf thrombosis exists unless contraindications are present.[12]

OUTPATIENT TREATMENT OF PULMONARY EMBOLISM

For carefully selected low-risk patients with PE, many centers have begun ED treatment protocols with a first dose of low-molecular-weight heparin, apixaban, or rivaroxaban given in the ED (Table 56-10), followed by a period of ED observation, and then ED discharge with anticoagulation continued as an outpatient, as long as patients are able to obtain the drug and adhere to therapy.

Patients with PE and a low risk of death plus adequate home support can qualify for outpatient anticoagulation.[73,74] The incidence of short-term mortality and the bleeding risk are very low with outpatient treatment, the overall cost of care is less, and the experience is preferred by patients.[75,76] Select low-risk patients using either the modified Hestia criteria or the Simplified PE Severity Index criteria (**Table 56-11**).[18,77,78] If low risk, assess the patient's wishes and ability to comply; if no high-risk features exist (elevated troponin, a B-type natriuretic peptide >100 picograms/mL, pulmonary arterial hypertension on ECG, or bleeding risks[79]), outpatient care after an ED stay (up to 23 hours) is an option; otherwise, short-term hospitalization is a good choice.

FIBRINOLYSIS FOR PULMONARY EMBOLISM

PE is classified into three categories based on severity: massive, submassive, and less severe PE. **Massive PE** patients have a systolic blood pressure of <90 mm Hg for >15 minutes, a systolic blood pressure of <100 mm Hg with a history of hypertension, or a >40% reduction in baseline systolic blood pressure. **Submassive PE** patients have normal or near-normal blood pressure, but with other evidence of cardiopulmonary stress (**Table 56-12**).

All other PE cases are "less severe." Patients with low-risk PE should not receive fibrinolysis; those with massive PE (defined as a systolic blood pressure <90 mm Hg or an observed decrease of 40 mm Hg) benefit from fibrinolysis. Patients with more severe submassive PE (i.e., causing increased right ventricular to left ventricular ratio on CT scan or hypokinesis, elevated troponin or B-type natriuretic peptide, or persistent hypoxemia with distress) may also benefit from fibrinolysis, including higher survival and better quality of life, although at a higher bleeding risk.[80]

TABLE 56-11 Two Prognostic Systems That Can Select Low-Risk Patients for Outpatient Treatment[18,73,74]

Simplified PE Severity Index Score

- 0 = low risk; 1 = high risk
  - Age >80 y
  - History of cancer
  - History of heart failure or chronic lung disease
  - Pulse >110 beats/min
  - SBP <100 mm Hg
  - Oxygen saturation <90%

Modified Hestia Criteria

- Identifies low-risk PE if:
  - SBP >100 mm Hg
  - No thrombolysis needed
  - No active bleeding
  - Oxygen saturation >94% on room air
  - Not already anticoagulated
  - No more than two doses of IV narcotics in ED
  - Absence of other medical or social reasons to admit
  - Creatinine clearance >30 mL/min
  - Not pregnant, no severe liver disease or HIT

Abbreviations: HIT = heparin-induced thrombocytopenia; PE = pulmonary embolism; SBP = systolic blood pressure.

SYSTEMIC FIBRINOLYSIS

The best evidence suggests **considering systemic fibrinolysis in patients with no contraindications to fibrinolysis** *and any of the following:* cardiac arrest; hypotension (any systolic blood pressure >90 mm Hg); respiratory failure, evidenced by severe hypoxemia (pulse oximetry reading <90%) despite oxygen administration, together with evidence of increased work of breathing; or evidence of right-sided heart strain on echocardiography or elevated levels of troponin T or I, or

TABLE 56-12 Modalities to Risk-Stratify Pulmonary Embolism (PE)

Test	Less Severe PE	More Severe PE (massive and some submassive PE)
Hestia criteria	All negative	Any positive
PE Severity Index score	<80	>120
Simplified PE Severity Index criteria	All negative	Any positive
Shock index (heart rate/systolic blood pressure)	<1.0	≥1.0
Pulse oximetry reading	>94%	<95%
Echocardiography	Normal RV systolic function Normal RV size No tricuspid regurgitation	RV hypokinesis RV dilation RVSP >40 mm Hg
Troponin I or T level	Normal	Elevated
B-type natriuretic peptide level	<90 picograms/mL	≥90 picograms/mL
N-terminal pro-B-type natriuretic peptide	<900 picograms/mL	≥900 picograms/mL
D-Dimer level	<4000 nanograms/mL	>8000 nanograms/mL
Serum sodium concentration	<125 mEq/L	≥125 mEq/L

Abbreviations: RV = right ventricular; RVSP = right ventricular systolic pressure.

both (Table 56-12). **Major contraindications to thrombolytic therapy** include intracranial disease, uncontrolled hypertension at presentation, recent major surgery or trauma (past 3 weeks), and metastatic cancer. Any patient with head trauma from syncope should have a CT scan prior to therapy to detect hemorrhage.

Alteplase (tissue plasminogen activator) is the only currently approved agent for PE, dosed at 100 milligrams IV over 2 hours. Either enoxaparin (1 milligram/kg SC) or unfractionated heparin (80 units/kg IV bolus followed by 18 units/kg/h) is the anticoagulant, with the activated partial thromboplastin time kept at <120 seconds for unfractionated heparin. Heparin or low-molecular-weight heparin is typically started after the thrombolytic infusion. Use of 50 mg of alteplase may reduce bleeding risk with similar outcomes as 100 mg of alteplase, although the safety and efficacy of this approach remain controversial.[81,82] For further discussion of fibrinolytic agents, see Chapter 239, "Thrombotics and Antithrombotics."

CATHETER-DIRECTED THROMBOLYSIS

Recent systematic reviews suggest that catheter-directed fibrinolysis for intermediate-risk PE produces good hemodynamic improvements and an intracranial bleeding rate <2%.[83-86] Catheter-directed thrombolysis for PE requires a far lower dose of alteplase (approximately 10 milligrams total), which may confer a lower bleeding risk. Catheter-directed thrombolysis is an option for patients over 65 years old, in whom intracranial bleeding risk is highest.[87] Because of the time delay needed to activate the vascular intervention suite, intrapulmonary fibrinolytic delivery should not be used in most patients with massive PE.[88]

SURGICAL EMBOLECTOMY

If available, surgical embolectomy is an option in young patients with large, proximal PE accompanied by hypotension. Because surgical embolectomy is often delayed, the reported mortality rate is approximately 30%. The amount of clot that can be extracted is often extensive, and removal may help limit later cardiopulmonary complications.

SPECIAL POPULATIONS

PREGNANCY

The clinical assessment of VTE in pregnant women is difficult because many signs and symptoms suggestive of VTE are seen in normal pregnancy.[89-91] Fewer than 2% of pregnant women with Wells' score ≤4 had PE in prior retrospective studies.[92,93] In one prospective study, the revised Geneva score resulted in a stepwise increase in probability of PE (7 of 192 [3.6%] in the low–pretest probability group, 18 of 200 [9.0%] in the intermediate-probability group, and 3 of 3 [100%] in the high-probability group).[94] The PE rule-out criteria rule has not been adequately tested in pregnant patients to recommend its use in isolation to exclude PE.

The D-dimer has low specificity in pregnant patients; by the third trimester, almost all healthy pregnant women have a positive D-dimer.[95,96] Studies that have examined the diagnostic sensitivity of the D-dimer have been hampered by low numbers and problems with D-dimer measurements made after systemic anticoagulation, which degrades test sensitivity.[97] Some have advocated for sequentially increasing the cutoff by approximately 50% for the D-dimer per trimester (first trimester, 750 nanograms/mL; second trimester, 1000 nanograms/mL; third trimester, 1250 nanograms/mL), although this approach has not been tested in a management study.[96,98-100]

The diagnostic accuracy of US for DVT appears to be similar to that of nonpregnant patients.[101,102] The best choice of pulmonary vascular imaging in pregnancy is controversial and uncertain.[103] Both a normal CT pulmonary angiogram and V̇/Q̇ scanning have shown 100% diagnostic sensitivity for technically adequate studies.[91] MRI has not been adequately tested in pregnancy to provide any basis for recommendation, but it had too low of a sensitivity (78%) to rule out PE in nonpregnant patients.[91,104]

Pregnant patients diagnosed with VTE in the ED should be anticoagulated with low-molecular-weight heparin. In the case of massive PE, options include systemic fibrinolysis, catheter-directed fibrinolysis, or the use of cardiopulmonary venoarterial extracorporeal membrane oxygenation. Current literature suggests a >80% probability of survival of both mother and fetus with the use of systemic fibrinolytics in the setting of massive PE.[105] For additional discussion, see Chapter 99, "Comorbid Disorders in Pregnancy."

ISOLATED SUBSEGMENTAL PULMONARY EMBOLISM

Isolated subsegmental PE is a filling defect seen in one small pulmonary artery, usually <3 mm in diameter and in the absence of DVT; radiologists often do not agree when viewing these images separately. The optimal treatment of subsegmental PE remains uncertain. Pooled data suggest that patients without high risk of recurrence (e.g., prior unprovoked VTE, active cancer, or other major active risk factor) may not benefit from anticoagulation.[106] However, no randomized trial has been performed to test this hypothesis. The author's choice is to treat subsegmental PE as an outpatient with apixaban or rivaroxaban and check a D-dimer in 1 month and, if normal, stop anticoagulation. It is best to discuss the risks and benefits of treatment of subsegmental PE with patients and their physicians to help make the best decision about anticoagulation.

CANCER PATIENTS WITH VENOUS THROMBOEMBOLISM

Current data and guidelines recommend treatment of patients with active cancer with low-molecular-weight heparin for at least 6 months.[107] One randomized trial suggested that rivaroxaban can be used in patients with active cancer, with a reduction in VTE recurrence but increased risk of bleeding.[108]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 57

Systemic Hypertension

Brigitte M. Baumann

INTRODUCTION AND EPIDEMIOLOGY

Hypertension affects approximately 40% of the U.S. population, and 1% to 6% of all ED patients present with severe hypertension.[1-5] Of the latter, between one quarter and one half will have end-organ damage.[2-5] Risk factors for the development of acute hypertensive events include obesity, cigarette smoking, older age, lack of access to health care, and noncompliance with antihypertensive medications.[6]

Chronic hypertension is categorized into three classifications: prehypertension, stage 1 hypertension, and stage 2 hypertension (**Table 57-1**).[7]

Hypertensive crisis is an acute elevation of blood pressure, where the systolic blood pressure is >180 mm Hg and/or the diastolic blood pressure is >120 mm Hg. There are two forms of hypertensive crisis.

Hypertensive emergency is a hypertensive crisis (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >120 mm Hg) *with concomitant* end-organ damage; the targeted end organs include the brain, heart, aorta, kidneys, or eyes (**Table 57-2**).[7]

Hypertensive urgency is a controversial term—some believe it does not exist distinctly apart from severe hypertension—denoting a marked and acutely elevated blood pressure *without* acute or worsening target organ dysfunction.[7] Often, an arbitrary blood pressure of >180/120 mm Hg is cited as an indication for rapid pharmacologic intervention (typically parenteral) to reduce blood pressure within hours. There is no clinical

TABLE 57-1 Categories of Blood Pressure in Adults*

BP Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	<120	*and*	<80
Elevated	120–129	*and*	<80
Hypertension			
Stage 1	130–139	*or*	80–89
Stage 2	≥140	*or*	≥90

Abbreviation: BP = blood pressure.

**Data adapted from:* 2017 High Blood Pressure Clinical Practice Guideline: Executive Summary, where BP is based on an average of ≥2 careful readings obtained on ≥2 occasions.[7]

benefit of such treatment (hence the concern about the term *urgency*), and precipitous drops in blood pressure can be harmful.[7-9] Current recommendations for patients with hypertensive urgency are reinstitution or intensification of oral antihypertensive therapy and prompt outpatient follow-up.[7] Gradual blood pressure reduction should occur over days to weeks.

TABLE 57-2 Hypertensive Emergencies

Diagnostic Category	Signs and Symptoms	Evidence of Acute End-Organ Damage
Acute aortic dissection	Chest pain, back pain Unequal blood pressures (>20 mm Hg difference) in upper extremities	Abnormal CT angiogram of chest and abdomen/pelvis or transesophageal echocardiogram of the aorta
Acute pulmonary edema	Shortness of breath	Interstitial edema on chest radiograph
Acute myocardial infarction	Chest pain, nausea, vomiting, diaphoresis	Changes on ECG or elevated levels of cardiac biomarkers
Acute coronary syndrome	Chest pain, nausea, vomiting, diaphoresis	Clinical diagnosis, changes on ECG, or elevated levels of cardiac biomarkers
Acute renal failure	May have systolic or diastolic abdominal bruit	Elevated serum creatinine level, proteinuria
Severe pre-eclampsia, eclampsia	Seizures, shortness of breath, headache, or vision abnormalities (blurred vision, flashing lights, scotomata)	Proteinuria (no longer required for the diagnosis of preeclampsia), low platelet count, renal insufficiency, elevated liver enzyme levels, pulmonary edema
Hypertensive retinopathy	Blurred vision	Retinal hemorrhages and cotton-wool spots (**Figure 57-1**), hard exudates, and sausage-shaped veins
Hypertensive encephalopathy	Altered mental status, nausea, vomiting, headache	May see papilledema or arteriolar hemorrhage or exudates on funduscopic examination, may note cerebral edema with a predilection for the posterior white matter of the brain on MRI
Subarachnoid hemorrhage	Headache, focal neurologic deficits	Abnormal CT of the brain; red blood cells on lumbar puncture
Intracranial hemorrhage	Headache, new neurologic deficits	Abnormal CT of the brain
Acute ischemic stroke	New neurologic deficits	Abnormal MRI or CT of the brain
Acute perioperative hypertension	Bleeding unresponsive to direct pressure	Clinical diagnosis; manifestations of other hypertensive emergencies
Sympathetic crisis*	Anxiety, palpitations, tachycardia, diaphoresis	Clinical diagnosis in the setting of sympathomimetic drug use (i.e., cocaine or amphetamines) or pheochromocytoma (24-h urine assay for catecholamines and metanephrine or plasma fractionated metanephrines)

*In this syndrome, acute end-organ dysfunction may not be measurable, but complications affecting the brain, heart, or kidneys may occur in the absence of acute treatment.

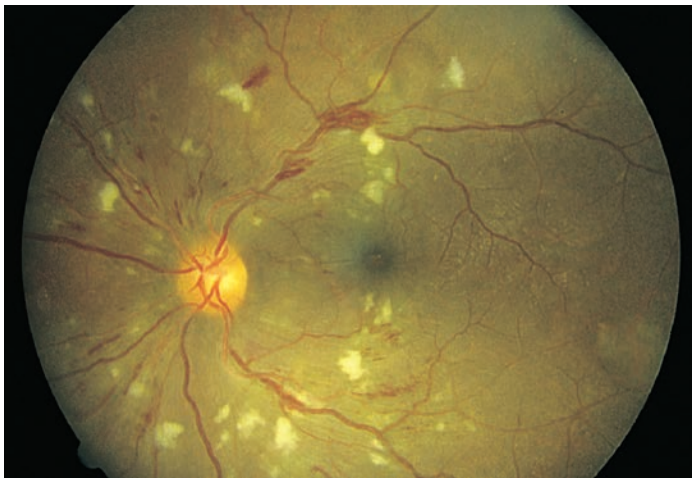


FIGURE 57-1. Hypertensive retinopathy. Scattered flame (splinter) hemorrhages and cotton-wool spots (nerve fiber layer infarcts) in a patient with headache and a blood pressure of 234/120 mm Hg.

PATHOPHYSIOLOGY

At baseline, chronic hypertensive patients have biochemical and structural changes in the arterial walls that shift the vascular autoregulatory curve, requiring higher arterial pressures to maintain end-organ blood flow, notably in the brain.[10-12] Eventually, the ability to adapt is passed. The resultant mechanical wall stress and endothelial injury lead to increased permeability and hyperperfusion of the cerebral, cardiac, and renal vascular beds. This may be followed by activation of the coagulation cascade and platelets, and deposition of fibrin results in fibrinoid necrosis of the arterioles. Clinically, this produces hematuria (involvement of the renal vasculature), arterial hemorrhages, or exudates on funduscopic examination.[12] Further contributing to the damage are prostaglandins, free radicals, cytokines, and mitogenic, chemoattractant, and proliferation factors, causing endothelial damage, smooth muscle proliferation, and thrombosis.[10,12] The renin-angiotensin system may also be activated, which leads to vasoconstriction. Pressure natriuresis occurs, leading to volume depletion, prompting additional release of vasoconstrictors from the kidney. These combined effects produce hypoperfusion, ischemia, and dysfunction of end organs. Endothelial dysfunction from such crises can persist for years after the acute event.[13]

CLINICAL FEATURES

Measure blood pressure in both arms in a narrow time interval while the patient is quietly resting. Check blood pressure several times before starting antihypertensive therapy. Blood pressure differences between extremities can result from aortic dissection, coarctation, peripheral vascular disease, and some unilateral neurologic and musculoskeletal abnormalities. Interarm blood pressure differences exist in some normal individuals, particularly the elderly, due to the loss of vascular elasticity or asymmetrical atheromatous narrowing of subclavian or brachial arteries. Although no guidelines regarding blood pressure disparities exist, an interarm difference >10 to 20 mm Hg is meaningful and increases long-term risks of cardiovascular events and mortality.[14,15] **When an interarm blood pressure difference is detected, treat the higher blood pressure and ensure that subsequent measurements are made on the same arm.**[15] Avoid wrist oscillometric devices as these give lower readings than upper arm measurements.[16]

A modest drop (up to 12 mm Hg) in systolic and diastolic blood pressures can occur absent therapy in patients presenting with elevated blood pressures. Conversely, do not discount a diagnosis of hypertensive

TABLE 57-3 Specific Diseases Associated With Elevated Blood Pressures

Disease	Threshold Value Raising Risk	% of Patients With Elevated Pressures
Subarachnoid hemorrhage[19]	≥140 mm Hg SBP	100%
Ischemic stroke[19,20]	≥140 mm Hg SBP	77%–82%
	≥160 mm Hg SBP	47%–54%
Intracerebral hemorrhage[19]	≥140 mm Hg SBP	75%
	≥160 mm Hg SBP	27%
Type B aortic dissection[21,22]	≥140 mm Hg SBP or ≥90 mm Hg DBP	67%–77%
Type A aortic dissection[23]	>150 mm Hg SBP	36%–74%
Acute heart failure[24,25]	>140 mm Hg SBP	52%–54%
NSTEMI-ACS[24,26]	≥140 mm Hg SBP	57%–59%
	≥160 mm Hg SBP	31%

Abbreviations: DBP = diastolic blood pressure; NSTEMI-ACS = non–ST-segment elevation myocardial infarction acute coronary syndrome; SBP = systolic blood pressure.

emergency in patients with no prior history of elevated blood pressure[17,18] because up to 16% have no history of hypertension.[4]

Table 57-3 lists the proportion of patients who present with elevated blood pressure by stroke subtypes, aortic dissection subtypes, heart failure, and acute coronary syndrome. Although elevations in blood pressure accompany most of these presentations, note that **severe** elevations of blood pressure are *far less common* in presentations typically labeled as hypertensive emergencies.

CHEST PAIN AND SEVERE HYPERTENSION

Rapid identification of acute aortic dissection is critical because delays in management increase mortality. Differentiating aortic dissection from the more common acute coronary syndromes is imperative given that blood pressure control differs in these two disorders and anticoagulation can prove catastrophic in acute aortic dissection.[27]

Acute aortic dissection presents with abrupt, sudden onset of pain, usually in the chest, often described as tearing or ripping, and radiating to the interscapular region[22,23,28-30] (see Chapter 59, "Aortic Dissection and Related Aortic Syndromes," for more discussion).

ACUTE NEUROLOGIC SYMPTOMS AND SEVERE HYPERTENSION

Elevated blood pressure, headache, and focal neurologic deficits are associated with either ischemic or hemorrhagic strokes (see Chapter 167, "Stroke Syndromes") (**Figure 57-2**).

Hypertensive encephalopathy is a clinical diagnosis made after excluding focal ischemia or bleeding. Patients with this condition have altered mental status, headache, vomiting, seizures, or visual disturbances, and most patients will have papilledema. When MRI findings demonstrate reversible edema that is predominantly posterior (occipital), the **posterior reversible encephalopathy syndrome** (**Figure 57-3**) exists, which carries a poor prognosis.

ACUTE RENAL FAILURE, PERIPHERAL EDEMA, AND SEVERE HYPERTENSION

Patients with new-onset renal failure may have peripheral edema, oliguria, loss of appetite, nausea and vomiting, orthostatic changes, or confusion. However, some patients have few or no specific symptoms (see Chapter 88, "Acute Kidney Injury"). Elevated serum creatinine confirms the diagnosis, and urinary sediment is also abnormal.

PREECLAMPSIA AND ECLAMPSIA

Preeclampsia presents with elevated blood pressure (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) on two occasions at least 4 hours apart in pregnant patients beyond the 20th week



FIGURE 57-2. Intracerebral hypertensive hemorrhage. Noncontrast head CT scan with acute intraparenchymal hemorrhage, mass effect, midline shift, and intraventricular extension. [Image used with permission of Todd Siegal, MD.]

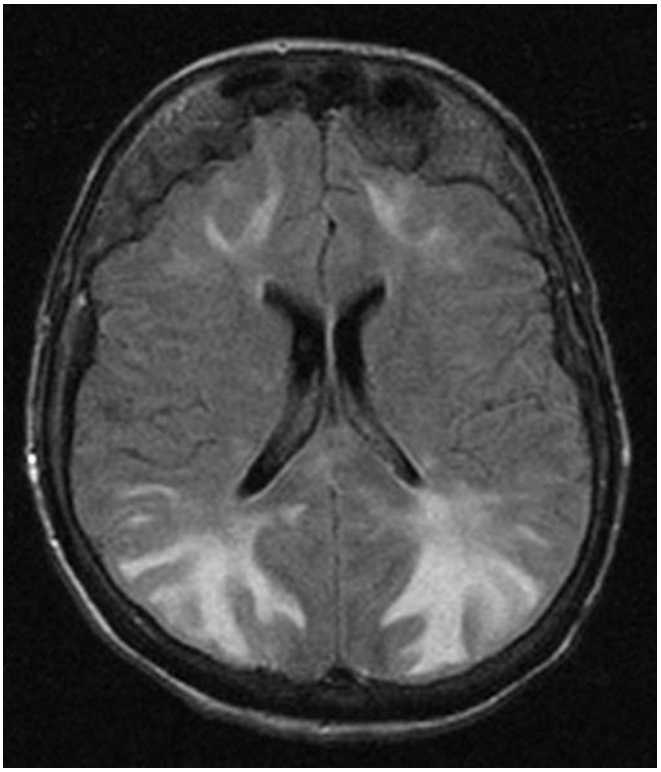


FIGURE 57-3. Axial fluid-attenuated inversion recovery MRI showing white matter hyperintensity in the occipital lobes bilaterally consistent with posterior reversible encephalopathy syndrome. The patient's confusion improved with blood pressure control. Repeat MRI after several days of therapy demonstrated remarkable improvement. [Image used with permission of Michael Farner, MD.]

of gestation. **Eclampsia** is the progression of preeclampsia to new-onset grand mal seizures in the absence of other neurologic conditions that could account for the seizure[31] (see Chapter 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period").

SYMPATHETIC CRISIS AND SEVERE HYPERTENSION

There are four settings in which an excess of catecholamines can result in a hypertensive emergency. An acute catecholaminergic syndrome may occur with abrupt discontinuation of oral or transdermal **clonidine**. This withdrawal syndrome is potentiated by concomitant β-blocker therapy due to unopposed α-mediated vasoconstriction.

Pheochromocytoma is rare, and between 5% and 20% of tumors are malignant. Patients may experience life-threatening hypertension.[32] Signs and symptoms of pheochromocytoma include asymptomatic periods punctuated by episodic headache, elevated blood pressure, tachycardia, and diaphoresis.

Sympathomimetic drugs such as cocaine, amphetamines, phencyclidine hydrochloride, and lysergic acid diethylamide can precipitate a hypertensive emergency, with tachycardia, diaphoresis, chest pain, and mental status changes.[33] Patients receiving **monoamine oxidase inhibitors** who consume tyramine-containing foods may develop a hyperadrenergic state.[34]

Autonomic dysfunction due to spinal cord or severe head injury or abnormalities such as spina bifida may also present as a hypertensive emergency, with the diagnosis made clinically. Often, the associated blood pressure measurements are marginally elevated in this condition; do not let "near normal" values falsely exclude this diagnosis.

ASYMPTOMATIC PATIENTS WITH SEVERE HYPERTENSION

Formal recommendations for the *evaluation* of an ED patient presenting with asymptomatic but severe hypertension do not exist.[9] Commonly ordered tests include basic metabolic panel, ECG, chest radiograph, and urinalysis, but in the asymptomatic population, abnormal results attributable to acute hypertensive target organ injury are found in <6% of patients.[3,35] Until more data are available, base ED evaluation on the patient complaint, history, and review of systems, and perform selected testing.

TREATMENT

Patients presenting with a hypertensive emergency should be admitted to a critical care setting for continuous monitoring of blood pressure and target organ function. Use parenteral antihypertensive agents to reduce systolic blood pressure no more than 25% in the first hour; if stable, then reduce to 160/100 mm Hg over the next 2 to 6 hours and then to normal over the following 24 to 48 hours. Balance the reduction of blood pressure with avoidance of hypoperfusion of cerebral, coronary, and renovascular beds, which can exacerbate end-organ damage. **More aggressive blood pressure control is needed** for acute aortic dissection, pheochromocytoma crisis, severe preeclampsia or eclampsia, and acute intracerebral hemorrhage.[7] **Table 57-4** lists agents used in the management of hypertensive emergencies categorized by diagnosis. In selecting therapy, be familiar with the administration of the selected agent and establish a target range for blood pressure reduction.

AORTIC DISSECTION

The therapeutic goal in acute aortic dissection is a systolic blood pressure between 100 and 120 mm Hg and a heart rate ≤60 beats/min, ideally within the first hour of presentation.[7,22,36] The resultant reduction in tachycardia decreases the shearing forces and aortic wall stress, limiting the progression of the dissection.[36] Pain control with opioids helps decrease sympathetic tone.

ACUTE HYPERTENSIVE PULMONARY EDEMA

Tailor the treatment of hypertensive pulmonary edema to the underlying pathophysiology. Most patients have existing poorly controlled hypertension with cardiac remodeling and left ventricular hypertrophy, stiffness, and diastolic dysfunction. With an acute rise in blood pressure, there is an increase in afterload and a decrease in venous capacitance. This leads to fluid shifts from the splanchnic and peripheral vascular beds into the pulmonary circulation. Interventions that improve forward flow, via afterload reduction, tend to work better than diuresis. Other causes of acute hypertensive pulmonary edema include transient left ventricular systolic or diastolic dysfunction, acute dyssynchrony, or ischemic mitral regurgitation.[39] For these reasons, one must provide individualized management.

The mainstay of therapy is vasodilators, predominantly **nitrates**.[39] IV, sublingual, and topical nitrates reduce blood pressure, decrease myocardial oxygen consumption, and improve coronary blood flow.[39,40] If adding diuretics, be careful using loop diuretics in combination with **nesiritide** because together these might worsen renal function.[40,41,60] In patients with systolic dysfunction, IV **nicardipine** or clevidipine may help by increasing both stroke volume and coronary blood flow.[7,61,62]

ACUTE MYOCARDIAL INFARCTION

Patients presenting with severely elevated blood pressure and ischemic changes on ECG should be treated with sublingual or IV **nitrates**.[7,42,43] Currently, IV β-blockade is only recommended for patients presenting with severe hypertension. Oral β-blockade in patients presenting with ST-segment elevation myocardial infarctions and non–ST-segment elevation myocardial infarctions remains part of early care, but this route may not provide sufficient or rapid enough blood pressure control in a hypertensive emergency.[42,43]

ACUTE SYMPATHETIC CRISIS

Manage patients in acute sympathetic crisis due to either cocaine or amphetamines with an IV **benzodiazepine**, such as lorazepam or diazepam, to decrease adrenergic stimulation.[33,44] Monitor patients for respiratory depression and sedation. If benzodiazepines are not effective, add **nitroglycerin or phentolamine**. A calcium channel blocker can serve as a third-line agent.[42,44] β-blockers can result in unopposed α-blockade, which then can worsen coronary vasoconstriction and increase blood pressure.[44] If a β-blocker is selected, labetalol, due to its α-adrenergic blocking effects, should be used in conjunction with a vasodilator.[42]

IV phentolamine is the first-line agent for patients with pheochromocytoma and a hypertensive emergency. Intramuscular administration is an option if venous access is absent.[32] Second-line agents include clevidipine and nicardipine.[7] Phenoxybenzamine, a long-acting oral adrenergic α-receptor blocker, is used only in the preoperative setting in patients who are hypertensive but not in crisis.

Patients with monoamine oxidase inhibitor toxicity often respond to an IV benzodiazepine; if more therapy is needed, use phentolamine, nitroglycerin, or nitroprusside. Nitroglycerin is the preferred agent for these hypertension events associated with chest pain or cardiac ischemia. Monitor patients closely after reaching a targeted blood pressure because the hypertensive phase is often followed by a hypotensive one.

ACUTE RENAL FAILURE

Fenoldopam, nicardipine, and clevidipine are all suitable for acute hypertension-induced isolated renal failure, because they reduce systemic vascular resistance while preserving renal blood flow.[7] Fenoldopam improves natriuresis and creatinine clearance in patients with elevated blood pressure and impaired renal function.[45]

ECLAMPSIA AND PREECLAMPSIA

Obstetrical hypertensive emergencies can occur well below the blood pressure threshold for other hypertensive emergencies. Hydralazine and labetalol have good safety profiles in pregnancy. Another option is oral nifedipine.[31] (See Chapter 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period," for further details.)

NEUROLOGIC EMERGENCIES

Hypertensive encephalopathy (defined as a change in sensorium or seizure from the blood pressure elevation) warrants rapid and uniform

TABLE 57-4 Treatment of Hypertensive Emergencies by Diagnosis

Diagnosis	Therapy Goals	Agents	Risks	Comments
Aortic dissection	Reduce shear forces by ↓ BP and PR Lower SBP to 100–120 mm Hg ↓ PR ≤60 beats/min[7,36]	**Esmolol*** IV bolus, then continuous infusion[7,36,37] OR **Labetalol*** IV bolus or continuous infusion[7,36,37] **Nicardipine** IV continuous infusion (after β-blocker)[7,38] **Nitroprusside** continuous infusion (after β-blocker)[7]	**β-blockers:** Respiratory distress in asthma, COPD patients; test dose of esmolol recommended, switch to diltiazem if esmolol intolerant	Measure BP in both arms and treat higher BP Always use β-blocker prior to vasodilators; nitroprusside alone increases wall stress from reflex tachycardia; cyanide and thiocyanate toxicity in patients with reduced renal function or therapy >24–48 h
Acute hypertensive pulmonary edema	Reduce BP by 20%–30%; diuresis through vasodilation; symptomatic relief[39]	**Nitroglycerin*** SL, topical, or IV continuous infusion[7,39,40] **Clevidipine** IV continuous infusion[7] **Nitroprusside** IV continuous infusion[7,39,40] **Enalaprilat** IV[40] **Nicardipine** IV continuous infusion[7] **Nesiritide** IV[41]	**ACE inhibitors**, can worsen renal function **ACE inhibitors:** Avoid hypotension and use with caution; some patients experience a negative inotropic effect **Nitroprusside:** Cyanide and thiocyanate toxicity in patients with reduced renal function or therapy >24–48 h	**IV nitrates** dilate capacitance vessels at low doses; higher doses dilate arterioles and lower BP Mixed outcomes (favorable and unfavorable) with **nesiritide**, with most recent ASCEND-HF trial showing no difference in dyspnea and mortality when compared to placebo[4]
Acute myocardial infarction	Reduce ischemia; avoid ≤25% reduction of MAP[7]	**Nitroglycerin*** SL, aerosol, or IV continuous infusion[7,42,43] **Esmolol*** IV continuous infusion[7] **Labetalol or metoprolol** IV bolus[7,42,43]	Do not give **nitrates** in patients who have taken phosphodiesterase inhibitors for erectile dysfunction ≤24 h for sildenafil and 48 h for tadalafil[42] Do not give **β-blockers** in CHF, low-output states, or other contraindications to β-blockers	**β-blockers:** Monitor for hypotension; consider RV infarct and volume depletion if this occurs SBP >180 mm Hg or DBP >110 mm Hg is a relative contraindication for thrombolytics[43]
Acute sympathetic crisis (cocaine, amphetamines, MAOI toxicity)	Reduce excessive sympathetic drive and symptomatic relief Aim for SBP <140 mm Hg in the first hour[7]	**Benzodiazepine*** IV bolus[33,44] **Nitroglycerin** SL, topical, or IV continuous infusion[42,44] **Phentolamine*** IV or IM[32] **Nicardipine or clevidipine** IV continuous infusion[7]	**Benzodiazepines** may induce respiratory depression; monitor patients closely **Labetalol** remains controversial, especially for cocaine-induced hypertension; if given, administer along with a nitrate[44]	**Benzodiazepines** are first-line agents for cocaine-induced hypertension **Phentolamine** is first-line therapy for pheochromocytoma **Calcium channel blockers** in cocaine-induced hypertension are considered third-line agents, after benzodiazepines and nitroglycerin[44]
Acute renal failure	Reduce BP by no more than 20% acutely	**Fenoldopam** IV continuous infusion[7,45] **Nicardipine** IV continuous infusion[7,45] **Clevidipine** IV continuous infusion[7]		Avoid **nitroprusside**, as it results in cyanide and thiocyanate toxicity Avoid **ACE inhibitors** acutely
Eclampsia, preeclampsia	Aim for SBP <140 mm Hg in the first hour[7]	**Hydralazine*** IV bolus[31] **Labetalol*** IV bolus[31] **Nifedipine*** oral[31]	**Hydralazine** can lead to reflex tachycardia and hypotension **Labetalol** may cause fetal bradycardia, and there is risk in patients with asthma, COPD, and heart failure **Nifedipine** may cause maternal tachycardia and overshoot hypotension	**Hydralazine, labetalol,** and **nifedipine** are all considered first-line agents. **Nifedipine** is ideal if IV access cannot be established **Contraindicated:** ACE inhibitors, ARBs, renin inhibitors, and nitroprusside
Hypertensive encephalopathy	Decrease MAP 20%–25% in the first hour of presentation[46]; more aggressive lowering may lead to ischemic infarction	**Labetalol** IV bolus or continuous infusion[7] **Nicardipine** IV continuous infusion[47] **Clevidipine** IV continuous infusion[47]	Avoid **β-blockers** in sympathetic crisis from drugs	Autoregulation of cerebral perfusion may be significantly impaired, so avoid rapid BP lowering to prevent cerebral hypoperfusion Do not give **nitroglycerin**[48] as it may worsen cerebral autoregulation
Subarachnoid hemorrhage	SBP <160 mm Hg to prevent rebleeding BP parameters have not yet been defined[49,50]	**Nicardipine** IV continuous infusion[49,51] **Labetalol** IV bolus, 10–20 milligrams IV, or continuous infusion[49,52] **Esmolol** IV bolus, then continuous infusion **Clevidipine** IV continuous infusion[49]	Avoid hypotension to preserve cerebral perfusion	**Nimodipine** is used to decrease mortality. BP control is not its primary goal, but some decrease in BP may be seen[49] **Clazosentan** is used with success in lieu of nimodipine and has similar hypotensive effects[53]

(*Continued*)

TABLE 57-4 Treatment of Hypertensive Emergencies by Diagnosis (*Continued*)

Diagnosis	Therapy Goals	Agents	Risks	Comments
Intracerebral hemorrhage	If SBP >220 mm Hg, consider aggressive management with IV infusion[54] If SBP 150–220 mm Hg, IV boluses of antihypertensive medications should be used to acutely lower SBP to 140 mm Hg[54]	**Labetalol** IV bolus or continuous infusion[52,55] **Nicardipine** IV continuous infusion[52,55] **Esmolol** IV bolus, then continuous infusion		Drops in SBP <150 mm Hg are not associated with increased morbidity[56] Early hemorrhage growth often occurs in first 6 h. Recent data suggest that at this time, aggressive BP control (SBP 130–139 mm Hg) diminishes hematoma growth, morbidity, and mortality[56-58]
Acute ischemic stroke, rtPA candidate (BP ≤185/110 mm Hg)	If fibrinolytic therapy planned, treat if BP remains >185/110 mm Hg after 3 measurements[59] The following antihypertensive recommendations (agents section) are for immediate BP control prior to reperfusion; BP management during and after reperfusion therapy is outlined in comments section	**Labetalol*** 10–20 milligrams IV over 1–2 min; may repeat once[55] **Nicardipine*** 5 milligrams/h IV infusion, titrate up by 2.5 milligrams/h every 5–15 min until desired BP is reached; maximum 15 milligrams/h[59] **Clevidipine*** 1–2 milligrams/h IV infusion, double the dose every 2–5 min until desired BP is reached; maximum 21 milligrams/h **Nitroprusside** may be used if BP is not controlled with above agents or DBP >140 mm Hg[59]	Excess BP lowering may worsen ischemia	**Management of BP during and after reperfusion therapy** If SBP >180–230 mm Hg or DBP >105–120 mm Hg, then consider: **Labetalol** 10 milligrams IV bolus followed by continuous IV infusion 2–8 milligrams/min **Nicardipine** 5 milligrams/h IV infusion, titrate up by 2.5 milligrams/h every 5–15 min to desired effect; maximum 15 milligrams/h **Clevidipine** 1–2 milligrams/h IV infusion; titrate up by doubling the dose every 2–5 min to desired effect; maximum 21 milligrams/h
Acute ischemic stroke, hypertension excludes reperfusion therapy	Treat if ≥220/120 mm Hg on third of 3 measurements, spaced 15 min apart; BP should be reduced by ~15% in the first 24 h[59] Early treatment of hypertension is indicated if required by other comorbid conditions (i.e., acute coronary syndrome, aortic dissection, preeclampsia/eclampsia). Lowering by 15% acutely is probably safe[59]	Same agents and doses as above acute ischemic stroke rtPA candidate	Be careful with BP control efforts in patients taking oral β-blockers or clonidine; antihypertensive withdrawal syndrome may occur.	Do not lower SBP by >15% in first 24 h[59] BP that is lower during the acute ischemic stroke than the premorbid pressure could be considered hypotension

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; MAP = mean arterial pressure; MAOI = monoamine oxidase inhibitor; PR = pulse rate; rtPA= recombinant tissue-type plasminogen activator; RV = right ventricular; SBP = systolic blood pressure; SL = sublingual.

*Preferred agents.

blood pressure reduction once other neurologic emergencies, notably ischemic or hemorrhagic stroke, are excluded.[46,63]

Management includes cessation of inciting agents, such as chemotherapy and immunosuppressants, and blood pressure control in hypertensive patients with IV nicardipine, clevidipine, labetalol, or fenoldopam.[7,47,64] Avoid nitroglycerin because it dilates cerebral arteries and alters both global and regional blood flow, which may worsen the autoregulation failure.[48]

The ideal targets for blood pressure control in subarachnoid hemorrhage and ischemic stroke are not clear and should be balanced to avoid worsening ischemia or rebleeding. For **subarachnoid hemorrhage**, recommended agents include IV labetalol, nicardipine, nitroprusside, and clevidipine, with no superior agent identified to date.[49] Oral nimodipine is a good choice for those with modest blood pressure elevations because it lowers blood pressure and reduces vasospasm and subsequent cerebral infarction rates, improving neurologic outcomes.[49,50,65] High-dose clazosentan can also decrease the incidence of vasospasm-related delayed ischemic neurologic deficits and has similar blood pressure–lowering effects as nimodipine.[53] If an anticonvulsant that can also reduce blood pressure is used, such as IV phenytoin or a benzodiazepine, be cautious with additional blood pressure reduction attempts.

The treatment of hypertension in patients with **intracerebral hemorrhage** includes labetalol, nicardipine, and esmolol.[52,55,66] Enalaprilat may also be used, but due to concerns of precipitous blood pressure drop, start with a smaller test dose (0.625 mg).[66] Lowering systolic blood pressures from >180 mm Hg to 130 to 160 mm Hg may improve clinical outcomes.[54-58]

In **ischemic stroke**, moderately elevated blood pressure may be beneficial in preserving cerebral perfusion of ischemic areas. Conversely, it may also worsen edema and contribute to hemorrhagic transformation. Ideal blood pressure ranges for ischemic stroke subtypes have not yet been determined. For the treatment of ischemic stroke, labetalol, nicardipine, and clevidipine are the recommended agents; however, the route and degree of blood pressure reduction depend on whether the patient is a candidate for reperfusion therapy (Table 57-4).[59] **Fibrinolytic therapy is contraindicated in patients with ongoing blood pressure >185/110 mm Hg *after* antihypertensive therapy**. In patients who maintain blood pressures ≤185/110 mm Hg (with or without antihypertensive therapy) and undergo fibrinolytic therapy, blood pressure goal is ≤180/105 mm Hg for the first 24 hours. Monitor blood pressure closely from the start of recombinant tissue plasminogen activator therapy for 24 hours.

PHARMACOLOGIC AGENTS

Parenteral agents used for hypertensive emergencies, including dosage, mechanisms, and warnings, are listed in Table 57-4 and **Table 57-5**. See Chapter 19, "Pharmacology of Antiarrhythmics and Antihypertensives," for detailed discussion of individual agents.

TABLE 57-5 IV Agents Used for Hypertensive Emergencies

Drug	Dosage	Mechanism/Comments	Warnings
β-Blockers			
Labetalol	Bolus: 10–20 milligrams (0.25 milligram/kg for an 80-kg patient) IV over 2 min; may administer 40–80 milligrams at 10-min intervals, up to 300 milligrams total dose. Continuous infusion: initially, 2 milligrams/min; titrate to response up to 300 milligrams total dose, if needed.	Combined selective α_1-adrenergic and non-selective β-adrenergic receptor blocker with an α- to β-blocking ratio of 1:7.[67] Effect in 2–5 min, peaking by 15 min, duration 2–4 h. Renal, cerebral, and coronary blood flow maintained; minimal placental transfer. **Safe in pregnancy.**	Avoid use in patients with bradycardia, greater than first-degree heart block, uncompensated cardiac failure, or active bronchospasm, and in patients receiving IV verapamil or diltiazem. Caution in patients with liver impairment (effects may be prolonged); the elderly have a less predictable response and more toxicity.
Esmolol	Loading dose: 250–500 micrograms/kg infused over 1–3 min IV, follow with: Maintenance infusion: 50 micrograms/kg/min IV over 4 min; if adequate effect not observed, repeat loading dose and increase infusion rate using increments of 50 micrograms/kg/min IV (for 4 min). This regimen can be repeated for 4 bolus doses and to an infusion rate of 300 micrograms/kg/min.	Ultra-short-acting, cardioselective, β-adrenergic receptor blocker. Onset within 60 s, duration 10–20 min. Ideal for use in patients at risk for complications from β-blockers, especially patients with mild to moderately severe left ventricular dysfunction or peripheral vascular disease. Duration 10–20 min; easily stopped.	Avoid use in patients with bradycardia, heart block, cardiogenic shock, decompensated cardiac failure, or active bronchospasm, and in patients receiving IV verapamil or diltiazem. Caution in patients with asthma, COPD, uncompensated cardiac failure; extravasation can lead to skin necrosis and sloughing; anemic patients will have a prolonged half-life, because drug is metabolized by red blood cell esterases.
Calcium Channel Blockers			
Nicardipine	Continuous infusion: start at rate of 5 milligrams/h. If target BP not achieved in 5–15 min, increase dose by 2.5 milligrams/h every 5–15 min until target pressure or the maximum dose of 15 milligrams/h is reached.	Second-generation dihydropyridine calcium channel blocker with vascular selectivity for the cerebral and coronary arteries. Onset of action is 5–15 min; duration is 1–4 h.	Avoid in patients with advanced aortic stenosis. Caution in decompensated heart failure. Avoid in patients receiving IV β-blockers. Common side effects are headache, hypotension, vomiting, and tachycardia.
Clevidipine	Continuous infusion: initiate infusion at 1–2 milligrams/h. Dose titration: double dose at short (90-s) intervals initially. As BP approaches goal, increase dose by less than doubling and lengthen time between dose adjustments to every 5–10 min. Maximum dose 32 micrograms/h; maximum duration is 72 h.	Very rapid onset and offset of effect due to its ultra-short half-life, approximately 2–4 min. Clevidipine is rapidly hydrolyzed to its inactive metabolite in blood and extravascular tissues. It exerts a selective vasodilating action on arteriolar resistance vessels but has no effect on venous capacitance vessels. Its metabolism is independent of the kidney or liver.	Cautions: Clevidipine contains approximately 0.2 gram of lipid per mL (2.0 kcal). Lipid restrictions may be necessary for patients with significant disorders of lipid metabolism. Clevidipine may produce hypotension and reflex tachycardia. Contraindicated in patients with severe aortic stenosis and egg or soy hypersensitivity. Use caution and lower doses in elderly.
Vasodilators			
Hydralazine	10 milligrams slow IV infusion (maximum initial dose is 20 milligrams). Repeat every 4–6 h as needed.	Potent direct arteriolar vasodilator with minimal effect on venous circulation. Onset begins at 10–30 min (can be sooner and precipitous); duration is 2–4 h. **Safe in pregnancy.**	Avoid in patients with myocardial ischemia, pulmonary edema, and aortic dissection. Reflex tachycardia increases myocardial demand.
Nitroglycerin	Sublingual: 0.4 milligram. Paste: 1–2 in. Continuous infusion: start 5 micrograms/min, increase by 5 micrograms/min every 3–5 min to 20 micrograms/min; if no response at 20 micrograms/min, increase by 10 micrograms/min every 3–5 min, up to 200 micrograms/min (note: many clinicians initiate with a higher infusion rate).	Potent venodilator and only affects arterial tone at high doses. Onset begins at 2 min; duration is 10–20 min (paste duration 3–4 h, unless removed). Reduces BP by reducing preload and cardiac output. Decreases coronary vasospasm and cardiac workload.	Avoid in cases of compromised cerebral and renal perfusion; avoid concurrent use (within past 24–48 h) with phosphodiesterase-5 inhibitors (sildenafil, tadalafil, or vardenafil). Caution: may cause hypotension with reflex tachycardia, which is exacerbated by volume depletion.
Nitroprusside	Continuous infusion: 0.3–0.5 microgram/kg/min IV initial infusion, increase in increments of 0.5 microgram/kg/min; titrate to desired effect. Rates >2 micrograms/kg/min may lead to cyanide toxicity. Use lowest possible dose. For infusions ≥4–10 micrograms/kg/min, institute a thiosulfate infusion.	Arterial and venous vasodilator due to its interaction with oxyhemoglobin to produce nitric oxide. It decreases preload and afterload. Onset of action is in seconds; duration is 1–2 min. Cerebral blood flow is decreased, whereas ICP is increased.	Avoid in patients with kidney or hepatic failure, arteriovenous shunts, hereditary optic nerve atrophy (increases nerve ischemia), or elevated ICP. Caution: intra-arterial monitoring is recommended; must be protected from light. Nitroprusside is recommended only when other agents fail. Coronary steal syndrome may occur.
Other Agents			
Phentolamine	Bolus load: 1–5 milligrams IV; may repeat every 10 min. Continuous infusion: 0.2–0.5 milligram/min.	α_1- and α_2-adrenergic blocking agent; effective for pheochromocytoma and hypercatecholaminergic-induced hypertension.	Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have occurred after administration.
Fenoldopam	Continuous infusion: start 0.1–0.3 microgram/kg/min, titrate by 0.05–0.1 microgram/kg/min every 15 min to desired BP. Maximum infusion rate: 1.6 microgram/kg/min.	Dopamine 1 receptor agonist. Onset of action in 5 min; peak effect at 15 min; duration 30–60 min. Metabolized by liver, without P450 system. Improves creatinine clearance, urine flow, and sodium excretion.	Caution: causes reflex tachycardia at higher dosages. Concurrent use of acetaminophen may increase fenoldopam levels. May cause flushing, dizziness, vomiting. Caution in patients with increased ocular pressures and ICP; caution in patients who have sulfite sensitivity (it is contained in a solution of sodium metabisulfite).

(*Continued*)

TABLE 57-5 IV Agents Used for Hypertensive Emergencies (*Continued*)

Drug	Dosage	Mechanism/Comments	Warnings
Enalaprilat	Bolus: 1.25 milligrams IV over 5 min every 4–6 h; titrate at increments of 1.25 milligrams every 12–24 h, with a maximum of 5 milligrams every 6 h.	Angiotensin-converting enzyme inhibitor. Test dose of 0.625 milligram recommended when concern for first-dose hypotension exists.[66] **AVOID in pregnancy.**	Avoid in pregnancy and those with myocardial ischemia or bilateral renal artery stenosis. Caution: first-dose hypotension is common, especially in high-renin states; may cause dizziness and headache.

Abbreviations: BP = blood pressure; COPD = chronic obstructive pulmonary disease; ICP = intracranial pressure.

β-BLOCKERS

Labetalol is unique among commonly used β-blockers because it also has modest selective α_1-inhibitory effects, with an α- to β-blocking ratio of 1:7.[67,68] It is recommended for nearly all hypertensive emergencies with the exception of cocaine intoxication and systolic dysfunction in association with decompensated heart failure. In the latter, nicardipine and clevidipine are preferred when nitroglycerin fails. Oral **metoprolol** use is common in patients presenting with acute coronary syndromes. Oral β-blockers improve survival, whereas mortality data are conflicting with IV formulations.[42,43] However, if blood pressure control is needed in a patient with acute coronary syndrome, use the IV formulation first, then change later. Esmolol has a short duration of action and is titratable, an advantage in patients at risk for the adverse effects of β-blockers, such as those with severe asthma and chronic obstructive pulmonary disease.

CALCIUM CHANNEL BLOCKERS

Clevidipine is a third-generation dihydropyridine calcium channel blocker with ultra-short-acting selective arteriolar vasodilator properties.[68-70] Its advantage is its ability to be titrated with a half-life less than a minute. **Nicardipine** has a rapid onset of action and can be titrated at 5- to 15-minute intervals. It is safe and effective in neurologic hypertensive emergencies and has a favorable effect on myocardial oxygen balance, increasing both stroke index and coronary blood flow. Compared to labetalol, nicardipine achieves physician-specified targeted blood pressure goals more often within 30 minutes of therapy.[67] Use **oral nifedipine** (10 milligrams) only in peripartum patients.[31]

VASODILATORS

Hydralazine is a potent vasodilator with a rapid onset of action that can have an unpredictable effect on blood pressure, which may not always be dose dependent. A potentially adverse effect is reflex tachycardia, which can worsen myocardial ischemia. Given the availability of other, more easily titratable agents, it is limited to pregnancy-related care. **Nitroglycerin** is a potent venodilator, showing arterial dilatation only at very high doses. Use may cause hypotension and reflex tachycardia, both worsened by the volume depletion characteristic of hypertensive emergencies. **Nitroglycerin is a first-line agent only in the treatment of heart failure and acute coronary syndromes** due to its favorable effects on coronary blood flow and cardiac workload.[7] Its hypotensive effects are due to its reduction of preload and cardiac output, which makes it a poor choice in other hypertensive emergencies.

Sodium nitroprusside is best used when other agents fail. It requires invasive monitoring to prevent "overshoot" in blood pressure control and has demonstrated higher mortality rates in cardiac surgery patients when compared to clevidipine.[7,71] Concerns about cyanide toxicity, heightened in patients with renal or hepatic insufficiency, and the potential for tachyphylaxis curtail use.[7] Combination therapy is the most common current use, as in aortic dissection patients who also receive esmolol to achieve blood pressure targets at lower doses.

OTHER AGENTS

Fenoldopam is a unique peripheral dopaminergic-1 receptor agonist, and due to its ability to promote diuresis, natriuresis, and creatinine clearance, it is useful in renal hypertensive emergencies.[68] **Phentolamine** is used successfully in cocaine-, amphetamine-, and pheochromocytoma-related hypertensive emergencies and also to counteract soft tissue catecholamine injection extravasation and ischemia (by injecting in the same area).[32,68,72] **Enalaprilat**, the only available IV angiotensin-converting enzyme inhibitor, has special application in patients with heart failure or acute coronary syndrome, but monitor carefully because of first-dose hypotension.[66]

Clonidine, a central α_2-agonist, generally does not have a role in the treatment of patients with hypertensive emergencies except for those who have recently stopped taking the drug. The resultant rebound hypertension may be difficult to control with other agents. When used, 0.2-0.3 mg PO clonidine is a common start, with blood pressure reduction starting within 30 to 60 minutes and peaking at 2 to 4 hours.[68] In patients who are unable to take oral medications, a clonidine patch for dermal delivery is an option, although the onset of action may be delayed by 2 to 3 days and titration is challenging. For maximum absorption, apply the patch to the chest or upper arm.[68,73] Although abrupt cessation of either clonidine or a β-blocker may result in rebound hypertension, clonidine withdrawal tends to be more severe and often will not respond to therapy without reinstitution.

TREATMENT OF ASYMPTOMATIC SEVERE HYPERTENSION

Acute treatment of asymptomatic severe hypertension does *not* prevent or reduce short-term patient morbidity or mortality.[8] However, uncorrected hypertension is associated with an eventual increased risk of cardiovascular events and renal dysfunction.[74] In addition, if severe hypertension is not addressed in the ED setting, patients may not seek further outpatient blood pressure management. These considerations support initiating outpatient blood pressure reduction regimens prior to ED discharge. **Table 57-6** lists oral agents commonly used for hypertension. The drugs listed are chosen for their relatively rapid onset of action and their potential use for ongoing control of chronic hypertension. Choosing an agent that can be used once daily and is inexpensive is often an ideal plan (e.g., generic hydrochlorothiazide, started at 25 milligrams daily). If choosing an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, check the patient's creatinine and potassium first.

DISPOSITION AND FOLLOW-UP OF ASYMPTOMATIC HYPERTENSION

Table 57-7 provides a summary of the 2017 blood pressure management recommendations from the American Heart Association.[7] Although the American Heart Association recommendations are comprehensive, they fall short of providing common ED guidance and management of patients who present with severe hypertension with no prior history of hypertension. In all cases, reinforce the need for outpatient follow-up, with or without ED-initiated oral therapy, even if elevated blood pressure was not part of the chief complaint.[7,75]

Table 57-8 lists indications for recommended oral antihypertensive classes based on trial data and consensus guidelines.[7,75]

Be sure to inform patients about potential adverse effects when prescribing an antihypertensive medication. The most common side effects stratified by drug class are provided in **Table 57-9**. Pediatric regimens are in **Table 57-10**; start these in close consultation with a pediatrician.

TABLE 57-6 Oral Agents for Hypertensive Urgencies

Agent	Mechanism of Action	Dosage	Onset of Action	Duration	Contraindications	Adverse Effects
Carvedilol	α_1-, β-Adrenergic blocker	6.25 milligrams PO	30–60 min	7–10 h	Asthma, chronic obstructive pulmonary disease, bradycardia, heart block, heart failure, hepatic impairment	Hypotension, bradycardia, syncope, dizziness
Labetalol	α_1-, β-Adrenergic blocker	200–400 milligrams PO, repeat every 2–3 h	30–120 min	6–12 h	Asthma, chronic obstructive pulmonary disease, bradycardia, heart block, heart failure	Bronchoconstriction, bradycardia, hyperkalemia
Metoprolol	β-Adrenergic blocker	50 milligrams PO	Oral (IR): ≤1 h	3–4 h	Asthma, chronic obstructive pulmonary disease, bradycardia, heart block, heart failure	Bronchoconstriction, bradycardia, heart block, weight gain, hyperglycemia
Captopril	Angiotensin-converting enzyme inhibitor	12.5–25 milligrams PO	15–30 min	4–6 h	Renal artery stenosis, pregnancy	Acute renal failure, angioedema, side effect of chronic cough
Losartan	Angiotensin II antagonist	50 milligrams PO	60 min	12–24 h	Second and third trimesters of pregnancy	Allergic reaction (rare)
Hydrochlorothiazide **Ideal first choice medication in most patients, but onset of action is delayed**	Thiazide diuretic	25 milligrams PO	2 h; peak effect at 4 h	24 h	Renal insufficiency, pregnancy Caution in diabetics; may raise glucose levels	Hypokalemia, dehydration, increased uric acid levels (may precipitate gout attacks)
Nifedipine (extended release) **Indicated for preeclampsia only**	Calcium channel blocker	10 milligrams PO, may repeat every 30–60 min	5–15 min	3–6 h	Angina, acute hypertension	Myocardial infarction, cerebrovascular accident, syncope, heart block, CHF
Clonidine **Primary indication for rebound hypertension**	Central α_2-agonist	0.1–0.2 milligram PO	30–60 min	6–8 h	CHF, second- or third-degree heart block Would not recommend as a new or singular antihypertensive agent	Drowsiness, sedation, tachycardia, dry mouth

Abbreviation: CHF = congestive heart failure; IR = immediate release.

TABLE 57-7 Recommended Treatment Protocol for ED Patients With Increased Blood Pressure (BP)*

SBP (mm Hg)		DBP (mm Hg)	Follow-Up/Treatment
130–139	*or*	80–89 AND ASCVD† risk <10%	Lifestyle modification and outpatient follow-up
130–139	*or*	80–89 AND ASCVD† risk ≥10%	Lifestyle modification; initiate antihypertensive; follow-up in <1 month
140–179	*or*	>90–109	Lifestyle modification; initiate antihypertensive therapy (ideally 2 agents); follow-up in <1 month
≥180	*or*	≥110	Evaluation for target organ damage; initiate lifestyle modification and antihypertensive therapy (ideally 2 agents); prompt outpatient follow-up (within a week)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

*To assess 10-year risk, please refer to http://tools.acc.org/ASCVD-risk-estimator/.

†Use the lowest values for cholesterol, if unknown, to obtain a conservative risk value.

Data adapted from: Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.[7]

TABLE 57-8 Indications for Specific Antihypertensive Therapy

	Heart Failure	Post–Myocardial Infarction	High Coronary Artery Disease Risk	Recurrent Stroke Prevention	Diabetes	Chronic Kidney Disease
Blood pressure goal	<130/80 mm Hg	<130/80 mm Hg	<130/80 mm Hg	<140/90 mm Hg	<130/80 mm Hg	<130/80 mm Hg
First-line therapy	Diuretic with ACE inhibitor	β-Blocker, ACE inhibitor or ARB	β-Blocker, calcium channel blocker (if angina pectoris)	Thiazide diuretic with ACE inhibitor or ARB	Nonblack: Thiazide diuretic, ACE inhibitor, ARB, or CCB Black: Thiazide diuretic or CCB	ACE inhibitor or ARB
Second-line therapy	β-Blocker	Aldosterone antagonist	ACE inhibitor, calcium channel blocker, or diuretic	—	Above alone or in combination	Above alone or in combination with other drug class

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

Data adapted from: Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.[7]

TABLE 57-9 Common Adverse Effects of Antihypertensive Drugs

Antihypertensive Class	Recommended Ancillary Testing Before Therapy	Most Common Adverse Effects
Diuretic	Chemistry panel: renal function and electrolytes	Hypokalemia, hypomagnesemia, hyperglycemia, hypercalcemia, hyperuremia, hyponatremia
Angiotensin-converting enzyme inhibitor	Chemistry panel: renal function and electrolytes Pregnancy test	Cough, hyperkalemia, acute renal failure, angioedema, myopathy, fetal abnormalities
Angiotensin receptor blocker	Chemistry panel: renal function and electrolytes Pregnancy test	Hyperkalemia, acute renal failure, angioedema, myopathy, fetal abnormalities
β-Blocker	ECG	Bronchospasm, bradycardia, depression, erectile dysfunction
Calcium channel blocker	ECG	Bradycardia, constipation, lower extremity edema
Aldosterone antagonist	Chemistry panel: renal function and electrolytes Pregnancy test	Hyperkalemia, gynecomastia, feminization of male fetuses

TABLE 57-10 Agents for Severely Hypertensive Pediatric Patients With Life-Threatening Symptoms

Agent	Dosage	Indications/Comments/Cautions
Esmolol	100–500 micrograms/kg/min IV infusion	Typically used in perioperative cardiac patients Risk of bradycardia
Hydralazine	0.1–0.2 milligram/kg per dose IV or IM; up to 0.4 milligram/kg per dose	Likely the most commonly used agent; caution with inadvertent overshooting of BP reduction Risk of tachycardia Give every 4 h if given as bolus
Labetalol	IV bolus: 0.2–1.0 milligrams/kg per dose; up to 40 milligrams per dose Infusion: 0.25–3.0 milligrams/kg/h	Rapid onset if given IV (2–5 min) Avoid in asthma and heart failure Risk of hypotension in children <24 months and concomitant ischemic or traumatic brain injury
Nicardipine	IV bolus: 30 micrograms/kg up to 2 milligrams per dose Infusion: 0.5–4 micrograms/kg/min	May need central access to avoid thrombophlebitis Risk of tachycardia; increases cyclosporine and tacrolimus levels
Nitroprusside	Starting: 0–3 micrograms/kg/min Maximum: 10 micrograms/kg per min	Significant experience in pediatric population Risk of cyanide poisoning after >48 h or earlier in renal/liver dysfunction patients
Oral Agents for Severely Hypertensive Pediatric Patients With Less Significant Symptoms and No Target Organ Damage		
Clonidine	2–5 milligrams/kg per dose up to 10 milligrams/kg per dose given every 6–8 h (PO)	Often used in patients with chronic hypertension and those refractory to other agents Risk of dry mouth, drowsiness
Fenoldopam	0.2–0.5 milligram/kg/min up to 0.8 milligram/kg/min IV infusion	Higher doses may lead to tachycardia without much more BP reduction
Hydralazine	0.25 milligram/kg per dose up to 25 milligrams per dose given every 6–8 h (PO)	Half-life varies with genetically determined acetylation rates
Isradipine	0.05–0.1 milligram/kg per dose up to 5 milligrams per dose given every 6–8 h (PO)	Exaggerated BP decrease in patients receiving azole antifungal agents
Minoxidil	0.1–0.2 milligram/kg per dose up to 10 milligrams per dose given every 8–12 h (PO)	Most potent oral vasodilator; long acting

Abbreviation: BP = blood pressure.

Data adapted from: Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.[76-79]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 58

Pulmonary Hypertension

John C. Greenwood
Michael Winters

INTRODUCTION AND EPIDEMIOLOGY

The pulmonary vascular system is normally a high-flow, low-resistance circuit, with a mean pulmonary arterial pressure that constitutes approximately 15% to 20% of the systemic circulation.[1] Normal pulmonary arterial systolic pressures range from 15 to 30 mm Hg, and diastolic pulmonary arterial pressures range from 4 to 12 mm Hg.[1] Pulmonary hypertension exists when a mean pulmonary arterial pressure is >25 mm Hg at rest or >30 mm Hg during exertion.[1,2]

Pulmonary hypertension classification uses measurements of pulmonary arterial pressure, pulmonary vascular resistance, and pulmonary capillary wedge pressure (**Table 58-1**).[1,3] Although echocardiography estimates pulmonary arterial pressure in a patient with suspected pulmonary hypertension, definitive diagnosis requires right heart catheterization.

Patients with group 1 pulmonary arterial hypertension have a mean pulmonary arterial pressure >25 mm Hg, a pulmonary vascular resistance >240 dynes/s/cm^5, and a pulmonary capillary wedge pressure <15 mm Hg.[2] Group 2 disease is caused by left heart disease and is the most common etiology.[2] Group 3 occurs with chronic hypoxemic lung disease. Chronic thromboembolic pulmonary hypertension, group 4, develops in up to 4% of patients with thromboembolic disease.[4-6] Regardless of the cause, pulmonary hypertension is associated with high rates of morbidity and mortality,[4,7] with a 5-year death rate for patients with idiopathic pulmonary arterial hypertension exceeding 30%.[8]

TABLE 58-1 World Health Organization Classification of Pulmonary Hypertension

Group 1: Pulmonary Arterial Hypertension
- Idiopathic
- Genetic/heritable abnormalities
- Drug or toxin induced
- Associated with known risk factors for pulmonary arterial hypertension (human immunodeficiency virus, portal hypertension, pulmonary veno-occlusive disease, collagen vascular disorders)

Group 2: Pulmonary Venous Hypertension (left heart disease)
- Left ventricular systolic or diastolic dysfunction
- Mitral or aortic valve disease

Group 3: Chronic Hypoxemic Lung Disease
- Obstructive lung disorders (chronic obstructive pulmonary disease)
- Interstitial lung disease
  - Idiopathic pulmonary fibrosis
  - Collagen vascular disorders
- Sleep-disordered breathing (obstructive sleep apnea)
- Chronic exposure to high altitude

Group 4: Chronic Thromboembolic Pulmonary Hypertension

Group 5: Miscellaneous
- Lymphatic obstruction
- Hematologic disorders: myeloproliferative disorders
- Systemic disorders: sarcoidosis, neurofibromatosis
- Metabolic disorders: glycogen storage disease, thyroid disorders

PATHOPHYSIOLOGY

Pulmonary *arterial* hypertension consists of vascular remodeling in all layers of small and mid-sized pulmonary arterioles, plus inflammation and in situ thrombosis formation.[9] Additional pathology includes alterations in microvascular permeability, hypoxic vasoconstriction, and plexiform lesion formation in arteriolar walls. The cumulative effect of these changes is sustained elevations of pulmonary vascular resistance and impaired pulmonary blood flow.

With persistent elevations in pulmonary vascular resistance, the right ventricle (RV) dilates. RV dilation leads to increased ventricular wall tension during systole, increased oxygen consumption, and eventually decreased contractility. With progressive RV dilation, the intraventricular septum displaces toward the left ventricle, which inhibits left ventricular filling and ultimately impairs cardiac output and systemic perfusion.

Perfusion of the right coronary artery depends on the coronary perfusion pressure (systemic diastolic pressure – right atrial pressure), which normally occurs during both systole and diastole. In patients with advanced pulmonary hypertension, right coronary artery perfusion occurs almost exclusively during diastole.[10,11] Decreased perfusion results in RV ischemia and further impairment of cardiac output. Eventually, this cycle results in RV failure and cardiovascular collapse.

CLINICAL FEATURES

The most common symptom of pulmonary hypertension is dyspnea, either at rest or with exertion, and is present in over 50% of patients.[1,12] Other symptoms include fatigue, chest pain, syncope, and exertional lightheadedness.[3,12,13] Delays in diagnosis are common, with a mean interval between symptom onset and diagnosis of 2 years.[14] As pulmonary artery pressure increases, patients can develop symptoms of advanced heart failure such as early satiety, anorexia, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema.

The physical examination is often normal in the early stages.[1] As the disorder worsens, findings of RV failure emerge (e.g., a holosystolic tricuspid regurgitation murmur, jugular venous distention, hepatomegaly, ascites, increased intensity of the pulmonary component of the second heart sound [P_2], and lower extremity edema).[1,4]

DIAGNOSTIC TESTING

ECG

The most common ECG abnormality is right axis deviation.[13] Additional findings include signs of RV hypertrophy or RV failure, such as an R/S ratio >1 in lead V_1, an R/S ratio <1 in leads V_5 and V_6, a qR complex in lead V_1, an $S_1Q_3T_3$, right atrial enlargement in the inferior leads, and an incomplete or complete right bundle branch block (**Figure 58-1**).[15] These findings are neither sensitive nor specific for pulmonary hypertension.

The ECG may show signs of RV ischemia or dysrhythmia. The most common dysrhythmias in patients with pulmonary hypertension are atrial fibrillation, atrial flutter, and atrioventricular nodal reentrant tachycardia.[16,17]

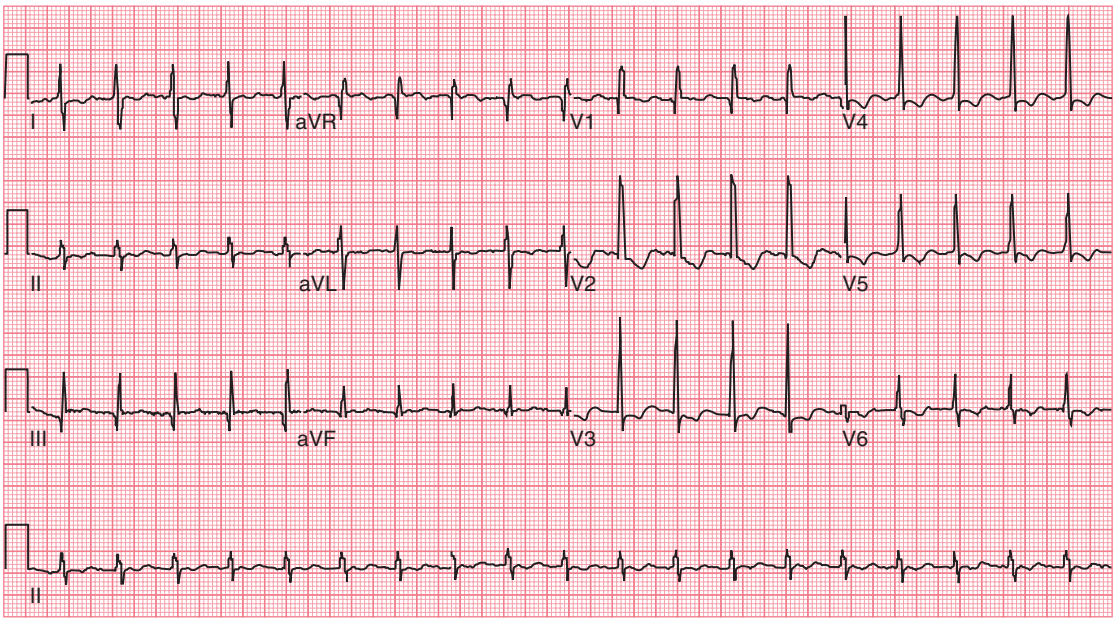


FIGURE 58-1. ECG with atrial fibrillation and findings predictive of pulmonary hypertension: R/S ratio in V_1 >1, right axis deviation, and ST depressions in V_3 to V_5 indicating possible right ventricular strain.

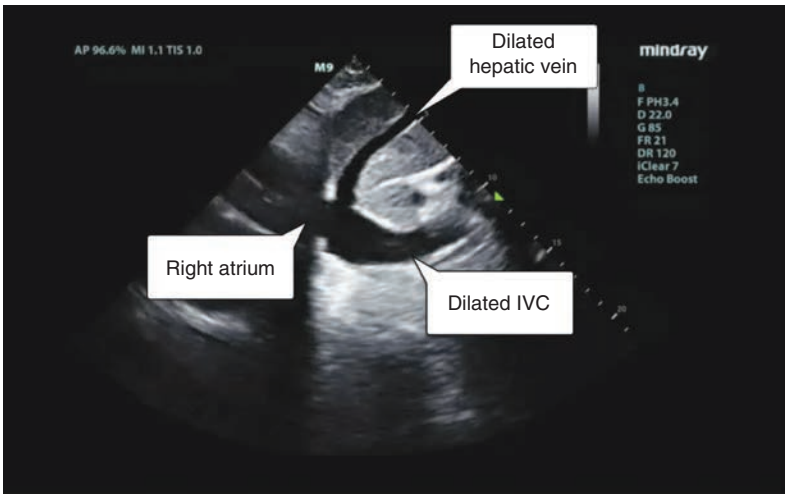


FIGURE 58-2. US of elevated right atrial pressures. Inferior vena cava (IVC) and hepatic vein dilation.

LABORATORY TESTING

Routine laboratory testing (e.g., CBC, comprehensive metabolic panel) is nonspecific. Elevations in troponin from myocardial ischemia or a strain-induced leak of B-type natriuretic peptide are associated with more serious disease.[18-21] Elevated liver function tests, lactate, and coagulation panel can reflect liver congestion and are a poor prognostic finding.[22]

IMAGING

Common chest radiographic abnormalities associated with pulmonary hypertension include enlargement of the right atrium, RV, and hilar pulmonary arteries.[13,23] Depending on the cause, additional radiographic findings might include pulmonary edema, hyperinflation, or interstitial lung disease. In most patients presenting with dyspnea, a chest radiograph may identify other causes of dyspnea, such as pneumonia or pneumothorax.

Transthoracic echocardiography (TTE) is the best initial diagnostic test to assess pulmonary hypertension in the ED. Signs of disease severity include RV hypertrophy, decreased RV function, and tricuspid regurgitation.[1,4] Echocardiography detects precipitating factors for RV failure, including ventricular regional wall motion abnormalities and acute valvular abnormalities.[24] Additional findings in patients with severe disease include leftward deviation of the intraventricular septum and an RV-to-left ventricle end-diastolic diameter >1 in the four-chamber view.[1,25] **Figures 58-2, 58-3, and 58-4** demonstrate typical echocardiographic findings in patients with pulmonary hypertension.

CT pulmonary angiography is the imaging method of choice to evaluate for acute pulmonary embolism (PE). TTE should not be used to exclude acute venous thromboembolism (VTE).[26] Given the high risk for VTE in this patient population, obtain a CT angiogram early if an acute PE is suspected, which also allows RV assessment.[27,28]

TREATMENT

The mainstays of ED therapy are supplemental oxygen, optimizing intravascular volume, augmenting RV function, maintaining coronary artery perfusion, and decreasing RV afterload (**Table 58-2**).[29]

OXYGEN AND MECHANICAL VENTILATION

Consensus opinion is to titrate supplemental oxygen to maintain a level >90% (rather than routinely targeting higher saturations).[29] Although intubation and mechanical ventilation are common ED therapies for the patient with acute respiratory failure, **RV failure is often exacerbated by positive-pressure ventilation**, with rapid cardiovascular collapse due to increased intrathoracic pressure and reduced coronary perfusion.

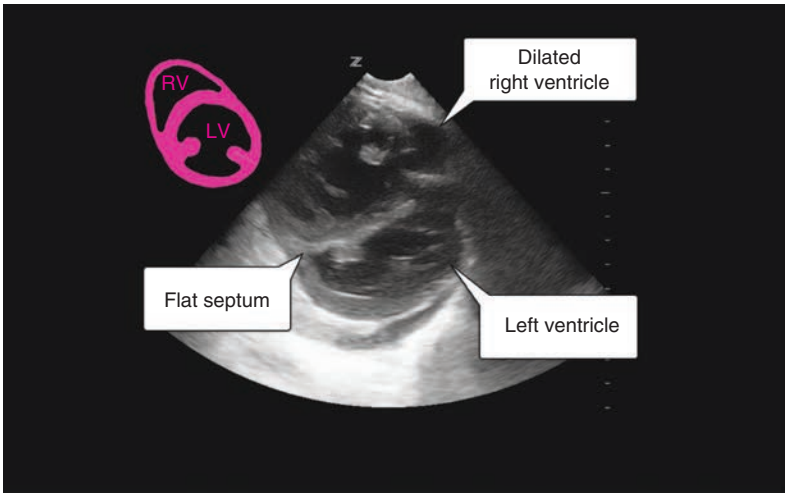


FIGURE 58-3. Cardiac US, parasternal short-axis view (PSS), of right ventricle (RV) and left ventricle (LV). Notice the flattening of the interventricular septum occurring in systole, suggesting elevated right ventricular systolic pressures. This is also known as a D-shaped septum. Illustration of normal PSS view in top left corner.

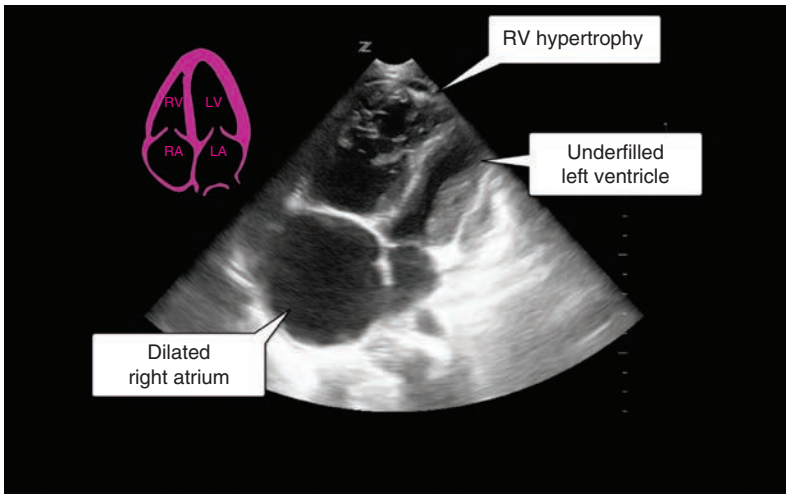


FIGURE 58-4. Apical four-chamber (A4C) view of right ventricle (RV) and left ventricle (LV). The right atrium (RA) and RV are dilated, with RV is dilated with hypertrophy of the RV trabeculae, indicating chronic RV overload. The interventricular septum is shifted toward the LV in systole, suggesting RV pressure overload. Illustration of normal A4C view in top left corner.

If ventilation is needed, set the ventilator to maintain low airway pressure, using lung-protective settings (i.e., a tidal volume of 6 to 8 mL/kg of ideal body weight and the lowest positive end-expiratory pressure to maintain the oxygen saturation >90%),[29] and target a plateau pressure of <30 cm H_2O. Adjust the respiratory rate to avoid hypercapnia, which can increase pulmonary vascular resistance, pulmonary artery pressure, and RV strain.[30]

INTRAVASCULAR VOLUME

Volume overload can cause RV dilation, impaired left ventricular output, and ultimately compromise tissue perfusion.[3] For patients who are hypovolemic, fluid challenges with 100- to 250-mL of isotonic crystalloid is a good first step.[26] Dynamic measures of volume responsiveness may be unreliable due to baseline elevations in right-sided pressures.[31] Eventually, diuresis may be accomplished to remove any excess fluid.

RV FUNCTION

For RV failure without hypotension, inotropic therapy to augment contractility and RV afterload can improve cardiac output. **Dobutamine** (a β_1 agonist) is preferred, starting at 2 micrograms/kg/min and titrated to 10 micrograms/kg/min.[29,32,33] Higher doses of dobutamine can cause tachydysrhythmias and hypotension.[34,35] For patients unable to tolerate dobutamine, **milrinone**, a phosphodiesterase-3 inhibitor, is an option.[29] Initiate milrinone at 0.125 microgram/kg/min and titrate to a maximum of 0.75 microgram/kg/min. Higher doses of milrinone can cause hypotension and require cardiac output monitoring for titration.

TABLE 58-2 Pharmacotherapy for Acute Pulmonary Hypertension

Condition	Drug	Comments
RV failure	Dobutamine 2–10 micrograms/kg/min *or* Milrinone 0.125–0.375 microgram/kg/min	Avoid >10 micrograms/kg/min Higher doses can cause hypotension
RCA perfusion	Norepinephrine 0.05–0.75 microgram/kg/min	Avoid high doses of norepinephrine; avoid dopamine and phenylephrine
RV afterload	Inhaled epoprostenol: 50 nanograms/kg/min Inhaled nitric oxide: 20–80 ppm IV prostanoids	Inhaled therapy limits vasodilatory effect to pulmonary circulation. Rarely initiated in ED; obtain consultation

Abbreviations: RCA = right coronary artery; RV = right ventricle.

RIGHT CORONARY ARTERY PERFUSION

Adequate perfusion of the right coronary artery is necessary to maintain RV function. To maintain right coronary artery blood flow, arterial pressure at the aortic root must be higher than the pulmonary artery pressure. For the hypotensive pulmonary hypertension patient, initiate vasopressor therapy. Although there are limited data regarding a singular superior agent, most experts recommend norepinephrine,[29] aiming to improve cardiac output, initiated at a dose of 0.05 microgram/kg/min. Avoid high doses of norepinephrine, which may increase pulmonary vascular resistance and impair RV output. Avoid dopamine, which can cause tachydysrhythmias, and avoid phenylephrine, which may provide less benefit compared to norephinephrine.[36]

RV AFTERLOAD

Patients with chronic pulmonary hypertension may be prescribed pulmonary vasodilators as outpatients. Such agents are rarely initiated in the ED. The most commonly prescribed outpatient pulmonary vasodilators are prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors (**Table 58-3**).

For the acutely ill patient receiving outpatient IV prostanoid therapy, restart the home infusion quickly. The first step is to confirm patency of the home IV catheter and check for proper infusion pump function. **If occlusion or malfunction is detected, immediately restart the home-administered prostanoid through a peripheral IV.**

If initiating pulmonary vasodilator therapy for acute exacerbations of pulmonary hypertension with RV failure, inhaled therapy with epoprostenol or nitric oxide therapy can be administered by facemask, high-flow nasal cannula, or endotracheal tube to reduce RV afterload and improve patient hemodynamics.[50] Initiation of IV pulmonary vasodilators is not recommended in the acutely ill patient.

DISPOSITION AND FOLLOW-UP

When patients with pulmonary hypertension present to an ED, they are often critically ill and with evidence of acute right heart failure. Nearly all require admission, often to an intensive care or coronary care unit with expertise in pulmonary hypertension. On rare occasions, a mildly symptomatic patient may be discharged home after consultation, care plan development, and close follow-up with the primary provider.

TABLE 58-3 Commonly Prescribed Outpatient Pulmonary Vasodilators

Prostanoids		Potent vasodilators, antiplatelet and antiproliferative properties
	Epoprostenol	2- to 5-min half-life; is provided by continuous IV infusion[29,37,38] Can be administered in aerosolized form for acute pulmonary hypertension with RV failure
	Treprostinil	IV and SC administration; 4- to 5-h half-life; not for acute RV failure
	Iloprost	Aerosol; use if unable to tolerate parenteral prostanoid as outpatient therapy[29] Not for acute RV failure
Endothelin receptor antagonists[1,39-43]		Elevated transaminase levels and decrease in hemoglobin[1]
	Bosentan Ambrisentan	Oral agents; not for acute RV failure[29]
Phosphodiesterase-5 inhibitors[1,44-49]		Headache, flushing, dyspepsia, hypotension when used with nitrates[1]
	Sildenafil Tadalafil	Oral agents; not for acute RV failure

Abbreviation: RV = right ventricle.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 59

Aortic Dissection and Related Aortic Syndromes

Gary A. Johnson
Louise A. Prince

INTRODUCTION AND EPIDEMIOLOGY

Acute aortic syndromes encompass a number of life-threatening aortic emergencies. These include aortic dissection, penetrating atherosclerotic ulcer, intramural hematoma, and aortic aneurysmal leakage and ruptured abdominal aortic aneurysm (see Chapter 60, "Aneurysmal Disease").

Acute aortic syndromes are uncommon but frequently fatal. The incidence ranges from 2.9 to 4.7 cases per 100,000 people per year.[1,2] The 1-, 5-, and 10-year actuarial survival rates are 92%, 77%, and 57%, respectively, for operative patients.[3] Twenty-two percent of cases are undiagnosed prior to death.[3] The most common cardiovascular complication of Marfan's syndrome is aortic root disease and type A dissection (ascending aorta). The identification of gene mutations associated with Marfan's syndrome, such as *TGFBR2* and *FBN1*, combined with regular follow-up can reduce fatal outcomes.[4]

PATHOPHYSIOLOGY

Acute aortic syndromes occur in the setting of chronic hypertension and other factors that lead to degeneration of the media of the aortic wall. Bicuspid aortic valve, Marfan's syndrome, Ehlers-Danlos syndrome, and familial history of aortic dissection all predispose to aortic syndromes. Chronic cocaine or amphetamine use accelerates atherosclerosis and increases the risk for dissection. Prior cardiac surgery is also a risk factor for aortic dissection. All mechanisms involve weakening of the medial layer and increasing intimal wall stress. Response to stress may include aortic dilation, aneurysm formation, development of a penetrating ulcer, intramural hemorrhage, aortic dissection, and aortic rupture.

Aortic dissection occurs after a violation of the intima allows blood to enter the media and dissect between the intimal and adventitial layers. The two most common intimal tear sites are the sinotubular junction at the start of the acending aorta (50% to 65%) and just beyond the left subclavian artery (20% to 30%) at the junction between the acending and descending aorta.[3] The dissecting column of blood forms a false lumen and may extend distally (most common), proximally, or in both directions. Blood may dissect and reenter the intima, reestablishing blood flow, and this may falsely suggest to the clinician a spontaneous resolution of the patient's presenting complaint. Alternatively, the blood may dissect through the adventitia, which nearly always proves rapidly fatal.

Aortic dissection has a bimodal age distribution.[3] The first peak involves younger patients with specific predisposing conditions such as connective tissue disorders. The second peak includes those aged >50 years with chronic hypertension and/or ischemic heart disease.[5] Prior aortic dissection is a risk factor for recurrent dissection.[6]

Aortic dissections are classified using two separate systems, the Stanford and DeBakey systems. The **Stanford classification** considers any involvement of the ascending aorta a type A dissection. Stanford type B dissections are restricted to only the descending aorta. **DeBakey** type 1 dissections simultaneously involve the ascending aorta, the arch, and the descending aorta. DeBakey type 2 dissections involve only the ascending aorta, and type 3 involve only the descending aorta.

An **aortic intramural hematoma** results from infarction of the aortic media, usually from injury to the vasa vasorum. An intramural hematoma may resolve spontaneously or may lead to dissection.[7] **Penetrating atherosclerotic ulcer** can lead to intramural hematoma, aortic dissection, or perforation of the aorta. There appear to be sex-related differences between patients with aortic dissections and intramural hematoma.[8] Intramural hematoma affects female individuals in approximately 62% of cases.[9] Aortic dissections in women appear to have a higher age of onset, frequent inpatient complications, and a higher in-hospital mortality.[8,9]

CLINICAL FEATURES

HISTORY

The site of initial intimal disruption often predicts the initial symptoms.[10] Symptoms may change as the dissection extends along the aorta or involves other arteries or organs. Classically, dissection presents with abrupt[5] and severe pain[5] in the chest that radiates to an area between the scapulae and may be accompanied by a feeling of impending doom. In a case series of 464 dissections,[3] 60% of patients had anterior chest pain (more common in Stanford type A); abdominal pain was more common in Stanford type B. Most patients describe the pain as severe or the worst they have ever experienced.[3] Sixty-four percent describe sharp pain, and 50% describe tearing or ripping pain.[5] A significant number of patients present without chest pain, as much as 40%, as reported in a study from Asia.[11] Syncope occurs almost 10% of the time,[5] which is more common in Stanford type A dissections. Twenty-two percent of dissections occur in patients with prior cardiac surgery.[6]

Dissection in or near a carotid artery may present as a classic **stroke**, and 20% of patients with type A dissection display neurologic findings, which predicts a poorer prognosis.[12,13] Interruption of blood supply to the spinal cord may lead to paraplegia. Further distal dissection may present as back, flank, or abdominal pain. A proximal dissection to the aortic root may lead to **cardiac tamponade** and is generally fatal.

PHYSICAL EXAMINATION

For most patients with aortic dissection, examination findings are relatively normal. An aortic insufficiency murmur may occur (32%),[7] and a

TABLE 59-1 Acute Aortic Dissection: Features From the International Registry of Acute Aortic Dissection

Category 1: Underlying Condition	Category 2: Pain in Chest, Back, or Abdomen	Category 3: Abnormal Examination
Marfan's syndrome	Abrupt onset	Pulse amplitude difference or systolic blood pressure differential in extremities
Family history of aortic disease	Severe in intensity	Focal neurologic deficit and chest, back, or abdominal pain
Aortic valvular disease	Ripping or tearing	New murmur of aortic insufficiency and chest, back, or abdominal pain
Recent aortic manipulation		Shock or hypotension
Thoracic aortic aneurysm		

pulse deficit in radial arteries or femoral arteries may be found (15%).[7,14] A blood pressure difference >20 mm Hg between arms is independently associated with aortic dissection[15]; however, 19% of ED patients without dissection also have this clinical finding.[16] Hypertenstion is common (49%), but hypotension occurs in 18% to 25% of patients,[3] which makes the diagnosis more likely and worsens prognosis.[7,14] Aneurysmal dilation of the aorta may compress regional structures such as the esophagus, the recurrent laryngeal nerve, or the superior cervical sympathetic ganglion, causing dysphagia, hoarseness, or Horner's syndrome.

Using retrospective data from the International Registry of Acute Aortic Dissection, three clinical categories (underlying condition, pain quality and location, and examination findings) were parsed into 12 features[17,18] associated with acute aortic dissection (**Table 59-1**). The clinical features listed in Table 59-1 form the basis of the **Aortic Dissetion Detection Risk Score**; 1 point is given for each category with a feature present by history or physical exam, and scores range from 0 to 3. Two studies published in 2018 support the strong association of the features listed in Table 59-1 with acute aortic dissection in symptomatic patients.[5,14]

DIAGNOSIS

The large differential diagnosis for the complaint of chest pain plus the many end-organ ischemic manifestations associated with aortic dissections make the diagnosis challenging. The most important differential diagnoses are listed in **Table 59-2**.

Ischemic manifestations may change with time (as the dissection progresses), and this may distract the physician from making the correct diagnosis. Rupture of the dissection into the true aortic lumen may cause a cessation of symptoms, and the correct diagnosis may then be inappropriately dismissed. History, physical examination, and chest radiography can suggest the diagnosis, but only if one is alert to aortic dissection as one of the diagnostic possibilities in a patient with acute chest, back, or abdominal pain; syncope; or acute focal neurologic signs. Factors associated with misdiagnosis include walk-in mode of admission, normal mediastinal width/aortic contour on chest radiograph, equal extremity pulse amplitudes, and nonspecific symptoms.[19-21]

ECG

It may be difficult to differentiate aortic dissection from acute coronary syndromes on ECG, because both conditions are associated with ECG changes and dissection may limit or obstruct coronary artery blood flow. Abnormal ECG findings include new Q waves or ST-segment elevation in 3% to 4%, ST-segment depression in 15% to 22%, and nonspecific ST- and T-wave changes in 41% to 62%.[3,7,22] The ECG is normal in only 19% to 31% of patients.[3,22]

TABLE 59-2 Differential Diagnosis of Aortic Dissection

- Myocardial infarction or acute coronary syndromes
- Pericardial disease
- Stroke
- Musculoskeletal disease of the extremity
- Spinal cord injuries and disorders
- Intra-abdominal disorders
- Pulmonary disorders, including pulmonary embolus, pneumonia, pleurisy, pneumothorax

BIOMARKERS

Several potential biomarkers have been investigated for their utility to identify or exclude aortic dissection.[23] **D-Dimer** is the marker most thoroughly investigated. A meta-analysis of five studies involving 473 subjects with acute aortic dissection and 1084 without acute aortic dissection found a sensitivity of 98% (95% confidence interval, 96% to 99%) and negative likelihood ratio of 0.05 (95% confidence interval, 0.03 to 0.09) using a D-dimer cut point of 500 nanograms/mL (1620 nmol/L).[24] The specificity was low at 41% (95% confidence interval, 39% to 44%). Guidelines do not endorse the use of D-dimer as the sole means of excluding aortic dissection,[14] and several authors have cautioned against this practice.[25-27] The false-negative rate using D-dimer is as high as 18%[25] and may be associated with a high platelet count.[26] Despite extensive study, there is no clinical decision rule that can be reliably used to identify very-low-risk patients for whom no further diagnostic workup is needed.[28] The Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes study of 1850 patients clinically suspected of having aortic dissection found that patients with none or only one of the features listed in Table 59-1 and a negative D-dimer (<500 nanograms/mL) had a low rate of aortic dissection (0.3%).[29] The Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes study needs to be externally validated.

IMAGING

A plain chest radiograph may provide important clues for the diagnosis. However, 12% to 37% of patients have no abnormality, and this study should not be used to exclude dissection.[3] The most common radiographic abnormality is a widened mediastinum or abnormal aortic contour. Other possible findings include pleural effusion, displacement of aortic intimal calcification, and deviation of the trachea, mainstream bronchi, or esophagus (**Figure 59-1**).

CT is the imaging modality of choice for diagnosis of dissection.[17,23,30] CT can reliably identify a false lumen (**Figure 59-2**) and can provide additional details such as the anatomy of the dissection, the location of the dissection flap, extension of the flap into great vessels (**Figure 59-3**), signs of aortic rupture, and signs of end-organ damage. CT protocols should be both with and without IV contrast. Individual physicians' practice varies; the utilization of CT imaging of patients for presenting with possible dissection varies between 0.6% and 12% of patients with chest, back, or abdominal pain.[31] Invasive catheter angiography is rarely necessary.

CT may also diagnose intramural hematoma and penetrating atherosclerotic ulcer.[30] Penetrating atherosclerotic ulcer can be difficult to distinguish from large atheromatous plaques (**Figure 59-4**). CT diagnosis of penetrating atherosclerotic ulcer depends on extension of the ulcer past the intima. Ulcers often have overhanging edges and focal outpouchings of the aorta itself. Intramural hematoma is often identified by a high-signal mass in the aorta on CT (**Figure 59-5**). This often appears as a crescent and is best seen on noncontrasted images.

In experienced hands, **transesophageal echocardiography** may be as sensitive and specific as CT. The procedure generally must be performed under moderate sedation or even general anesthesia. Known esophageal disease is a relative contraindication. Sound transmission is disrupted by air in the trachea or left bronchia, which may make evaluation of the ascending aorta difficult. The accuracy and precision of transesophageal echocardiography are highly operator dependent. **MRI** has been used to evaluate stable patients with suspected aortic disease.[30]

Coronary/pulmonary/aortic CT angiography, or the "**triple rule-out**," which is used to differentiate acute coronary artery disease, pulmonary embolism, and acute aortic dissection,[32,33] has not been shown to improve diagnostic yield, reduce clinical events, or diminish

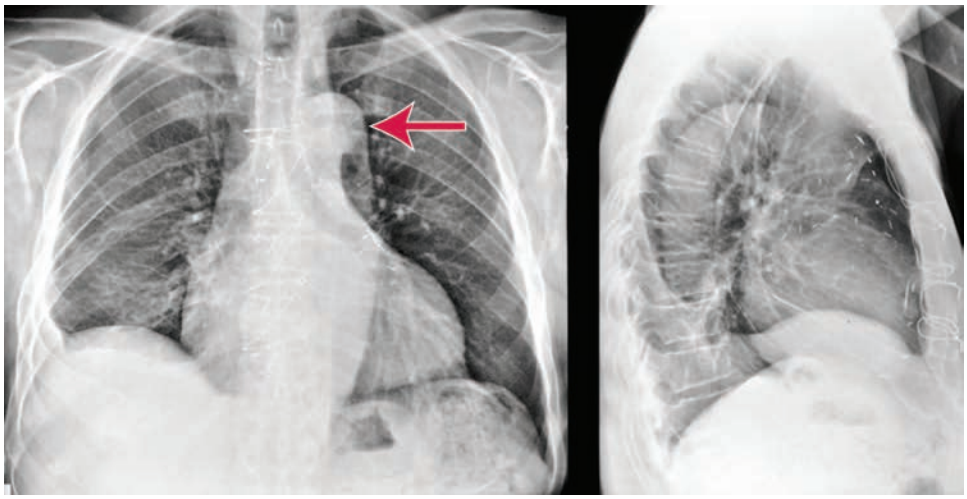


FIGURE 59-1. Abnormal aortic contour on chest radiography. Frontal and lateral radiographs of the chest in a patient with type B aortic dissection reveal an abnormal aortic contour (*arrow*). A right pleural effusion is present, and multiple postoperative clips and wires are also seen.

downstream resource use.[34] Therefore, in its current form, it cannot be recommended.

TREATMENT

ANTIHYPERTENSIVES: NEGATIVE INOTROPIC AGENTS

While aortic dissections may cause hypotension that requires fluid or blood product resuscitation, suspected aortic dissection commonly requires antihypertensive treatment. Initial treatment should be a negative inotropic agent in order to lower blood pressure without increasing the shear force on the intimal flap of the aorta. β-Blockade is ideal, and short-acting β-blockers such as esmolol or labetalol are preferred over long-acting β-blockers. The ideal target blood pressure is undefined by controlled trials and must be tailored to each patient (see Chapter 57, "Systemic Hypertension" and Chapter 58, "Pulmonary Hypertension"). However, **a systolic pressure of 120 to 130 mm Hg is a reasonable starting point; some guidelines suggest a goal of 100 to 120 mm Hg (in the absence of aortic regurgitation)**.[17,35]

Esmolol may be given as an initial bolus of 0.1 to 0.5 milligram/kg IV over 1 minute followed by an infusion of 0.025 to 0.2 milligram/kg/min. **Labetalol** (a β-blocker with limited α-blocking characteristics in a 7:1 ratio) also may be used at an initial dose of 10 to 20 milligrams IV with repeat doses of 20 to 40 milligrams every 10 minutes to desired effect or a maximum dose of 300 milligrams. β-Blocker use has been associated with improved survival in the International Registry of Acute Aortic Dissection database.[36]

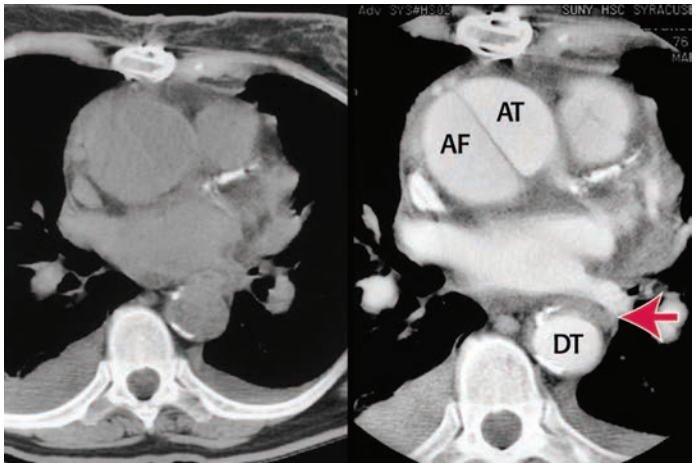


FIGURE 59-2. CT image of a type A aortic dissection. True and false lumens are present in the ascending aorta and descending aorta (descending false lumen at arrow) on noncontrast (*left*) and contrast (*right*) images. AF = ascending false lumen; AT = ascending true lumen; DT = descending true lumen.

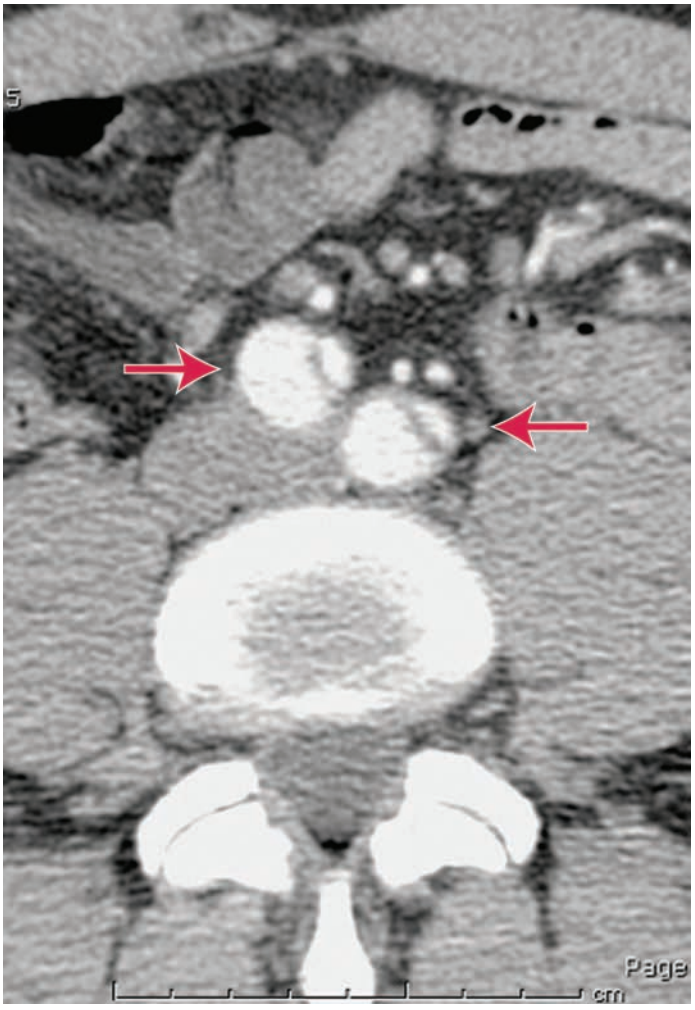


FIGURE 59-3. Type B dissection into the iliac arteries. Contrast CT image of dissection extending into the iliac arteries (anterior to vertebral body). True and false lumens are visible in both arteries (*arrows*).

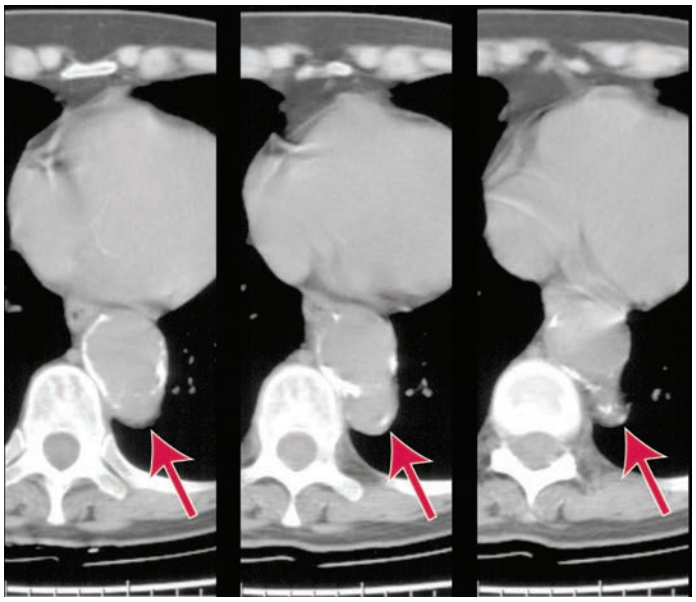


FIGURE 59-4. Noncontrast CT image of a penetrating aortic ulcer in the descending aorta (*arrows*), demonstrating an outpouched, abnormal contour of the aorta in three sections. [Image used with permission of Dr. Ernest Scalzetti, MD.]

VASODILATORS

Vasodilators may be added for further antihypertensive treatment after successful administration of esmolol or labetelol. IV **nicardipine, clevidipine, nitroglycerin, or nitroprusside** (see Chapters 57 and 58) are options.[37]

DISPOSITION AND FOLLOW-UP

Rapid referral to a vascular surgeon is mandatory. Emergency open repair remains the treatment of choice for most patients; however, endovascular repair is being used more frequently.[38-43]

Patients with acute aortic syndromes are likely to require admission to an intensive care unit for hemodynamic therapy and careful monitoring. Acute intermural hematomas and penetrating ulcers have an unclear clinical course and natural history. Therefore, the management of patients with these disorders remains controversial.[44] Clearly, no patient with an acute aortic syndrome should be discharged without speciality consultation.

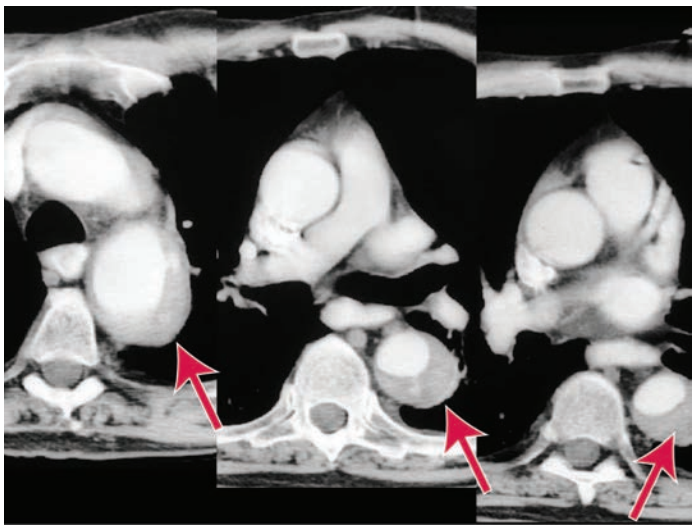


FIGURE 59-5. Contrast CT image of an intramural hematoma (*arrows* point to the crescent-shaped lesion along the posterior lateral aortic wall) in the descending aorta. [Image used with permission of Dr. Ernest Scalzetti, MD.]

SPECIAL CONSIDERATIONS

AORTIC DISSECTION COMPLICATING PREGNANCY

Aortic dissection in pregnancy is rare and usually occurs in the third trimester and postpartum period. Risk factors are bicuspid aortic valve, connective tissue disorders, hypertension, and a family history. Pregnancy increases the risk of dissection in patients with Marfan's syndrome, complicating 4.4% of pregnancies in women with the syndrome.[45] Simultaneous consultation with obstetrics and cardiovascular surgery is needed if the diagnosis is considered. See Chapter 99, "Comorbid Disorders in Pregnancy," for further discussion.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 60

Aneurysmal Disease

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INTRODUCTION

An aneurysm is dilation of the arterial wall to >1.5 times its normal diameter. Aneurysms have been classically distinguished as true aneurysms, pseudoaneurysms, and mycotic aneurysms. The wall of a **true aneurysm** involves of all layers of the vessel. Risk factors for these include smoking, increasing age, white race, hypertension, hyperlipidemia, connective tissue disorders, and familial history of aneurysm.[1]

PATHOPHYSIOLOGY

A progressive decrease in elastin, collagen, and fibrolamellar units results in thinning of the media of the vascular wall and a decrease in its tensile strength. In aortic true aneurysm, the dilatation and increased wall force are intertwined, creating more dilatation (Laplace law: wall tension = pressure × radius). The rate of aneurysmal dilatation is variable, with larger aneurysms expanding more quickly and changing a mean 0.25 to 0.5 cm per year. However, abrupt expansion occurs and is not predictable, and larger aneurysms are more likely to rupture. Rupture is catastrophic, occurring once the stress on the vessel wall exceeds its tensile strength. Patients with low socioeconomic position are at greater risk to present with a ruptured aortic aneurysm (versus intact aneurysm) and are more likely to have poor outcomes after surgical repair.[2]

The wall of a **pseudoaneurysm** consists partly of the vessel wall and partly of fibrous or other surrounding tissue. A pseudoaneurysm can develop at the site of previous vessel catheterization and at anastomoses from prior vascular reconstruction, trauma, or infection.[3] Small pseudoaneurysms may eventually spontaneously thrombose.

Mycotic aneurysms and **infected aneurysms** occur due to an infection in the vessel wall, often in an immunocompromised patient. A mycotic aneurysm occurs secondary to a septic embolization from valvular endocarditis, while an infected aneurysm develops in an existing aneurysm after bacteremia or direct extension from a neighboring infection.[4] IV drug abuse is a significant risk factor for both types of these aneurysms. The clinician should be vigilant for this diagnosis in patients abusing IV drugs because the misdiagnosis of cellulitis or abscess is possible.[4]

Peripheral and visceral aneurysms are less frequent but an important subset of arterial aneurysmal disease. Popliteal artery aneurysms are

the most common peripheral aneurysm; they often coexist with contralateral popliteal aneurysms or abdominal aortic aneurysms.[5] Aneurysms of the femoral artery are uncommon and often accompany aneurysmal disease at other sites. Visceral artery aneurysms may occur anywhere but are most common in the renal, splenic, and hepatic arteries. Most visceral aneurysms remain silent and undetected until a complication such as rupture occurs. All but splenic artery aneurysms are more common in elderly men. Complications of aneurysms include rupture, which has an 80% mortality rate,[6] and thrombosis, creating ischemia in the perfused organ.[7,8]

GENERAL CLINICAL FEATURES OF ANEURYSMS

Clinical signs and symptoms can be nonspecific; often, the symptoms are driven by location, the pressure exerted upon neighboring structures, or the signs of peripheral embolization from an intramural thrombus. Visceral aneurysms are often detected after an abdominal CT scan for abdominal or flank complaints; similarly, lower extremity aneurysms are often detected during an extremity Doppler US examination in a search for deep venous thrombosis. Once rupture occurs in any truncal aneurysm, hemorrhagic shock develops, and mortality is high without prompt surgical intervention.

SYMPTOMATIC ABDOMINAL AORTIC ANEURYSMS

An abdominal aortic aneurysm is defined as an aorta ≥3.0 cm in diameter; repair is considered for an aneurysm ≥5.0 cm in diameter. Patients with an abdominal aortic aneurysm often have a first-degree relative with an aortic aneurysm (18%). Most patients are >60 years old, and males have increased risk. Patients with aneurysms involving other major arteries and those with peripheral arterial disease are also at increased risk for aortic aneurysmal disease. Smoking is the most important environmental risk factor, with the prevalence of abdominal aortic aneurysm being more than four times that in lifelong nonsmokers. In addition, smoking is a major risk factor for accelerated aneurysmal growth and rupture.[1,9]

CLINICAL FEATURES

Back or abdominal pain is the most common presenting symptom with aortic aneurysm or rupture. The pain is classically severe and abrupt in onset, with about half of patients describing a ripping or tearing pain. The classic triad of a ruptured abdominal aortic aneurysm—abdominal pain, pulsatile abdominal mass, and hypotension—occurs in only one third of patients.[10] Syncope occurs in about 10%. Many patients present with nonclassic sites of pain, such as the flank, groin, isolated quadrants of the abdomen, and hip. Other common presenting symptoms include nausea, vomiting, bladder pain, hip pain, or tenesmus. Eleven percent of patients deny existence of pain.[9]

Symptomatic abdominal aortic aneurysms may present with GI bleeding from an aortoenteric fistula, extremity ischemia from embolization of a thrombus in the aneurysm, shock, or sudden death. Sudden death most commonly occurs from intraperitoneal rupture of the aneurysm, which leads to massive, rapid blood loss. Syncope without warning symptoms followed by severe abdominal or back pain suggests rupture of an abdominal aortic or visceral aneurysm with some temporary containment. Syncope is caused by rapid blood loss and a lack of cerebral perfusion. Patients may regain consciousness, but irreversible hemorrhagic shock follows without prompt diagnosis and intervention.

DIAGNOSIS

Diagnosis is suspected clinically and confirmed by imaging if the urgency for intervention allows. Physical examination has only a moderate ability to detect a large abdominal aortic aneurysm. The sensitivity of abdominal palpation increases with aortic aneurysm diameter, ranging from 29% for a diameter of 3.0 to 3.9 cm to 50% for a diameter of 4.0 to 4.9 cm and 76% for a diameter of ≥5.0 cm.[10] Tenderness to palpation of an aneurysm is commonly interpreted as a sign of aneurysmal expansion or rupture. However, a lack of tenderness does not indicate an intact aorta. Examination is difficult in obese patients, and aortic size may be overestimated by palpation in thin patients. Hypotension and tachycardia are found in a minority of cases.[11]

The differential diagnoses include the causes of syncope, abdominal pain, chest pain, back pain, and shock. When seeing a patient with abrupt back pain with syncope or shock, consider aortic aneurysm rupture. However, other cardiac, abdominal, and retroperitoneal diseases may be the cause, including renal disorders, hepatobiliary disorders, and pancreatic disease. If symptoms are insidious, it is possible that some patients may appear well enough and receive benign diagnoses, such as musculoskeletal back pain, and are discharged from the ED. Beware of misdiagnosis as renal colic.

Diagnosis is confounded by coexisting pathology. Coronary artery disease and chronic lung disease are often present, and signs and symptoms of these disorders may distract the physician from the diagnosis of aneurysmal disease. This is especially true in patients without severe pain or with findings that seem congruent with another cause (e.g., ECG changes or dyspnea).

External signs of acute rupture are rare and include periumbilical ecchymosis (**Cullen sign**) or flank ecchymosis (**Grey Turner sign**). Retroperitoneal blood may dissect into the perineum or groin, causing scrotal or vulvar hematomas or inguinal masses. Retroperitoneal blood may irritate the psoas muscle, triggering an "iliopsoas sign" (pain upon extension of the hip, typically with the patient lying on the opposite side). Blood may compress the femoral nerve and present as a neuropathy. The presence or rupture of an abdominal aortic aneurysm typically does not alter femoral arterial pulsations.[12]

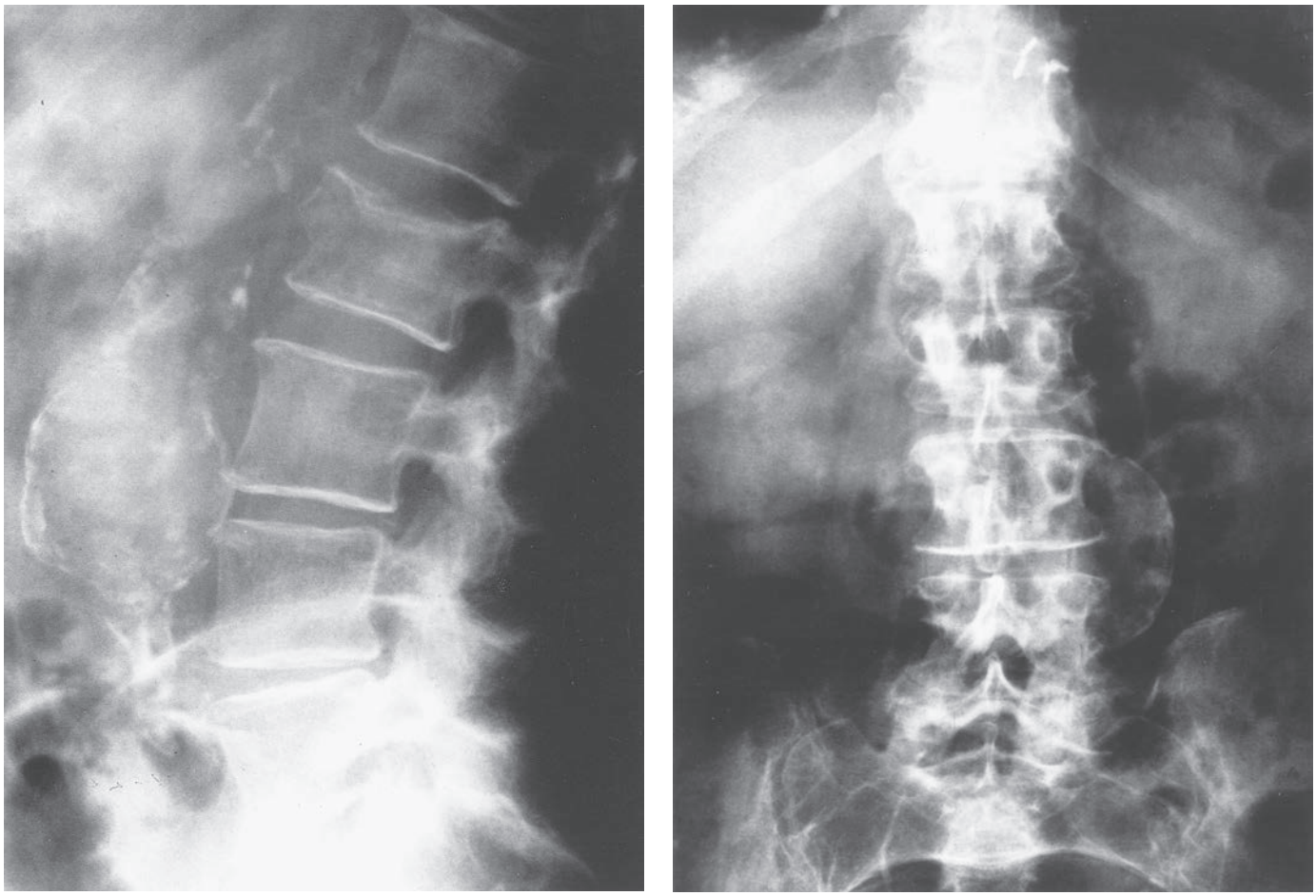
Think of **aortoenteric fistulas** in patients with unexplained or high-volume upper or lower GI bleeding, especially in patients without liver disease. A history of aortic graft placement increases the risk of fistula. Fistulas most frequently involve the duodenum, with hematemesis, melenemesis, melena, or hematochezia. While life-threatening bleeding is common, mild sentinel bleeding may be the first sign. Aortic aneurysms also may erode into the venous vasculature and form **aortovenous fistulas**, which cause high-output cardiac failure, decreased arterial blood flow distal to the fistula, and increased central venous volume.

Contained chronic abdominal aortic aneurysmal ruptures are not common. A retroperitoneal rupture may cause enough fibrosis to limit blood loss, and the patient may look well. The inflammatory response commonly causes pain, with pain continuing for an extended interval, clouding the diagnosis.

Imaging Unstable patients should not be sent out of the ED for imaging. Bedside US is the imaging modality of choice for unstable patients. Occasionally, an aneurysm is picked up on plain abdominal radiography (**Figure 60-1**). For stable patients in whom an aortic aneurysm is suspected, imaging may involve US (**Figure 60-2**), CT scanning (**Figure 60-3**), or uncommonly for ED patients, MRI. Plain abdominal films may show a calcified and bulging aortic contour, implying the presence of an aneurysm (Figure 60-1). Approximately 65% of patients with symptomatic aortic aneurysmal disease have a calcified aorta, which may be more obvious on a lateral view. Plain film radiographs do not exclude the presence of abdominal aortic aneurysm or detect rupture and should be omitted for most patients.

Bedside US (Figure 60-2) is ideal for initial screening.[13] **A technically adequate US study has >90% sensitivity for demonstrating the presence of an aneurysm and measuring its diameter.**[13] Obesity, bowel gas, and abdominal tenderness may make the study difficult to perform. Measure aneurysms from the outside margin of one wall to the outside margin of the opposite wall in both the transverse (**Figure 60-4**) and longitudinal (**Figure 60-5**) planes. Identifying the superior mesenteric artery (**Figure 60-6**) allows distinguishing the aorta from the vena cava. **An aortic diameter <3.0 cm excludes acute aneurysmal disease.**

CT scanning with IV contrast (Figure 60-3) best detects the anatomic details of the aneurysm and associated hemorrhage. Scan all **stable** patients with suspected abdominal aneurysmal disease or rupture. For those who cannot have IV contrast, unenhanced CT can reveal aneurysm size and retroperitoneal hemorrhage.



A B

FIGURE 60-1. Plain radiographic images of an abdominal aortic aneurysm. **A.** Lateral view of a calcified infrarenal aortic aneurysm. **B.** Posteroanterior view of a calcified infrarenal aortic aneurysm.

TREATMENT

ED interventions are listed in **Table 60-1**.

In the ED, aortic aneurysm recognition and facilitating rapid surgical intervention for hemorrhage control are key. Consult a surgeon early while evaluating a patient with the triad of abdominal and/or back pain, a pulsatile abdominal mass, and hypotension. Never delay consultation for imaging if hypotension or acute end-organ perfusion deficit is evident; bedside US can provide a measurement of the aortic diameter and a tentative diagnosis in most cases.[13] Use advanced imaging only in

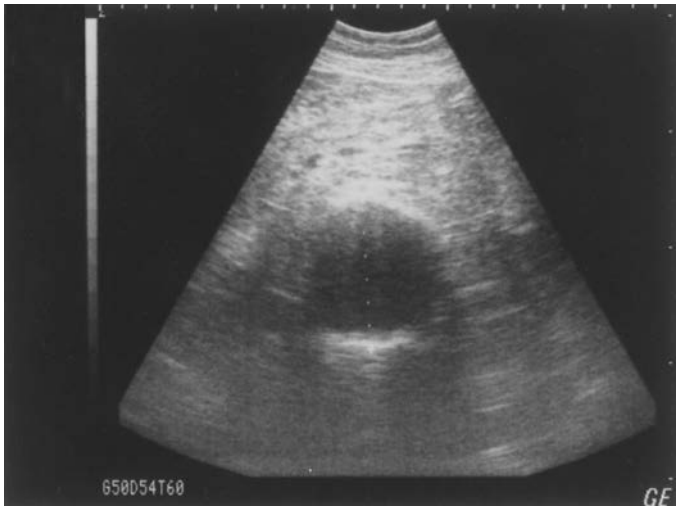


FIGURE 60-2. Bedside US image of an abdominal aortic aneurysm. This aneurysm measures 6.5 cm.

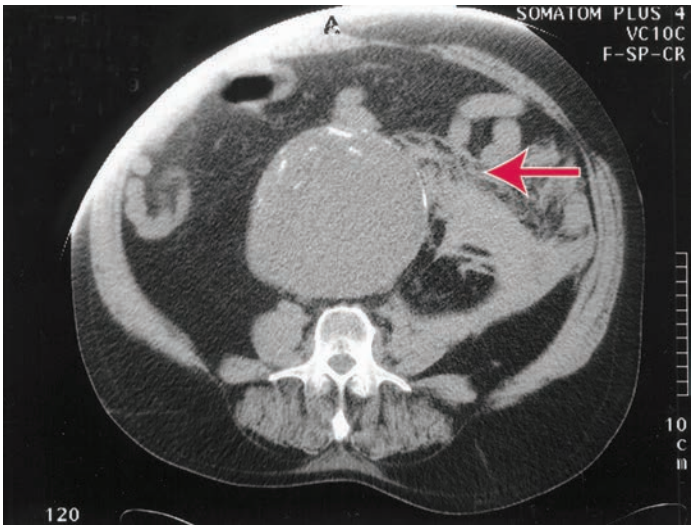


FIGURE 60-3. CT scan of a patient with a 12-cm abdominal aortic aneurysm. Calcification of the aortic wall is seen in the anterior aspect of the aneurysm. Evidence of hemorrhage and surrounding inflammation (*arrow*).

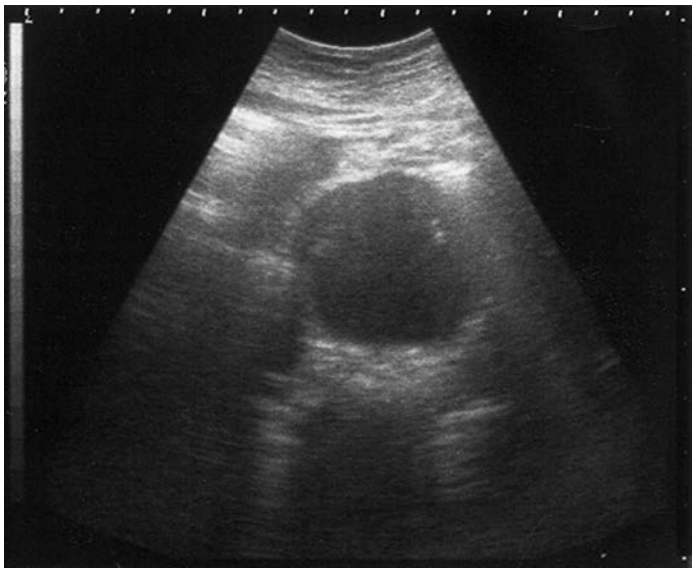


FIGURE 60-4. US image of an abdominal aortic aneurysm in the transverse plane.

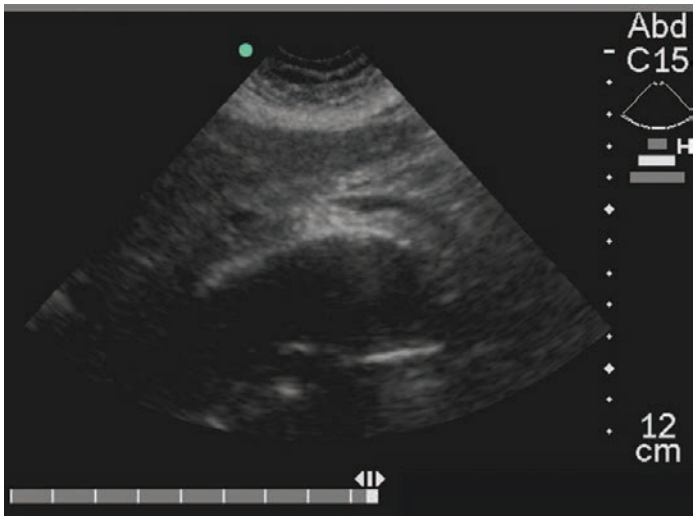


FIGURE 60-5. US image of an abdominal aortic aneurysm in the longitudinal plane.

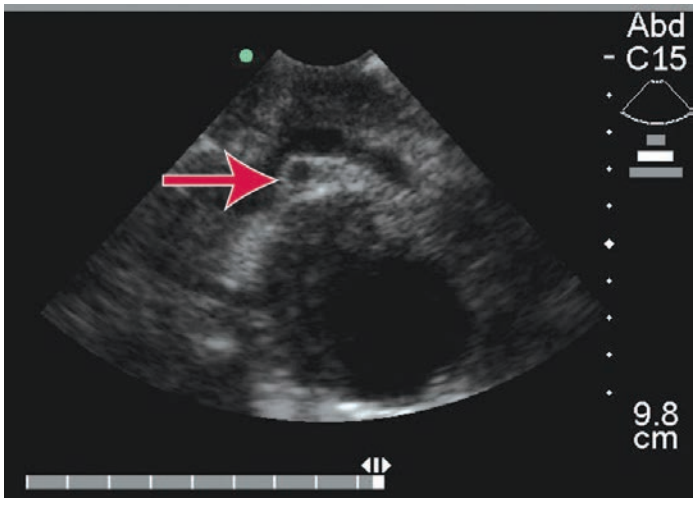


FIGURE 60-6. US image of an abdominal aortic aneurysm in the transverse plane showing the superior mesenteric artery (*arrow*) coursing parallel to the aorta.

TABLE 60-1 ED Interventions for Symptomatic Abdominal Aortic Aneurysms

Intervention	Comments
IV access	Place two large-bore IVs in place for rapid administration of crystalloids, blood, or medication.
Consultation	As soon as the diagnosis is suspected, consult vascular or general surgery or transfer to an institution capable of emergency repair.
Blood and fluids	Targets unclear; restoring normal blood pressure may worsen outcomes; permissive hypotension, a systolic blood pressure of 80–90 mm Hg, is recommended.[14] Level of consciousness (responds appropriately) is another target for volume replacement.[15]
Pain control	Avoid severe hypotension and respiratory depression.

patients **fully** compensated or for patients unlikely to have a ruptured abdominal aortic aneurysm.

Standard resuscitative actions include insertion of two large-bore IV catheters, initiation of cardiac monitoring, and supplemental oxygen. Vigorous fluid resuscitation may be harmful; there are limited data,[15] but guidelines from the Society of Vascular Surgery support limiting resuscitation to a systolic blood pressure target of 80 to 90 mm Hg with intact mentation until surgical control occurs.[14,15] **In the event of suspected expanding aneurysm and severe hypertension, esmolol (half-life, 9 minutes) is recommended** for its ability to be titrated to a target systolic blood pressure of 120 mm Hg. Esmolol can be quickly stopped if the patient's blood pressure drops suddenly.[14,15]

Resuscitative endovascular balloon occlusion of the aorta has been used in the setting of ruptured abdominal aortic aneurysms to occlude the aorta above the aneurysmal rupture (see discussion in Chapter 254, "Trauma in Adults"). Currently, the studies are small and inconclusive as to mortality reduction.[16] Use of resuscitative endovascular balloon occlusion of the aorta requires training as well as a patient management plan after its insertion. Currently, its use is seen primarily in the setting of trauma, and its availability is limited to larger centers with vascular teams available to manage the patient.

Symptomatic aneurysms of any size are considered emergent. If at a site without appropriate surgical capacity, initiate patient resuscitation and arrange for immediate transfer to a medical center capable of emergency repair. Outcomes are better if prompt transfer occurs rather than using local diagnostics (aside from bedside US).[17,18] Immediate transfer with providers able to recognize and treat shock (having fluid, blood, and blood products available) is the best option for unstable patients. In comparison to asymptomatic aneurysmal repair, patients with symptomatic aneurysms have a twofold increased risk of perioperative mortality, and those with rupture have a sevenfold increased risk.[19]

All asymptomatic aortic aneurysms should be referred for follow-up. **Abdominal aortic aneurysms ≥5 cm in diameter are at an increased risk of rupture (size is measured from outer wall to outer wall) and require prompt (days) follow-up.** The patient should be instructed to return immediately for worsening symptoms or syncope. Abdominal aortic aneurysms in women have a greater likelihood of rupture than in men, often at smaller sizes.[9,20] The risk of rupture is elevated in pregnancy and the postpartum period.[21] Aneurysms of 3 to 5 cm are less likely to rupture, and these patients can be followed by their primary care physicians or surgeons. The management of patients with small, asymptomatic aneurysms (including the timing of surgery) varies. The patient should follow up with a vascular surgeon and a primary care provider, the latter for blood pressure control. Repairing abdominal aortic aneurysms smaller than 5.5 cm does not improve survival in men,[22] but may be indicated in women.[20]

Endovascular aortic repair is sometimes favored as a less invasive management technique for the repair of asymptomatic abdominal aortic aneurysms. Emergency providers should be aware of the complications that may present following endovascular aortic repair, which include, but are not limited to, graft leak and occlusion, renal dysfunction, aortoenteric fistulization, and bowel ischemia.[23-25]

TABLE 60-2 Nonaortic Large-Artery Aneurysms

Artery	Risk Factors	Clinical Presentation	Management
Popliteal (>2 cm or >150% of normal caliber)	Advanced age, male gender, trauma, congenital disorders	Most common peripheral aneurysm; discomfort behind knee with swelling with or without deep venous thrombosis	Thrombolysis, ligation, arterial bypass, endovascular repair
Subclavian	Arteriosclerosis, thoracic outlet obstruction	Pulsatile mass above or below clavicle, dysphagia, stridor, chest pain, hoarseness, upper extremity fatigue or numbness and tingling, limb ischemic symptoms	Surgical repair
Femoral	Advanced age, male gender, trauma, congenital disorders	Pulsatile mass with or without pain, limb ischemic symptoms, peripheral embolic symptoms	Thrombolysis, ligation, arterial bypass, endovascular repair
Femoral pseudoaneurysm	Prior femoral artery catheterization, trauma, infection	Pulsatile mass with or without pain	Surgical repair
Iliac	Arteriosclerosis, male gender	Pain in groin, scrotum, or lower abdomen; sciatica; vulvar or groin hematoma with rupture	Surgical repair
Renal	Age 40–60 y, no gender preference, HTN, fibrodysplasia, arteriosclerosis	Flank pain, hematuria, collecting system obstruction, shock if ruptured	Surgical repair, nephrectomy
Splenic	Advanced age, female gender, HTN, congenital, arteriosclerosis, liver disease, multiparous, rupture increased in pregnancy	Rapid symptom onset; epigastric or left upper quadrant pain first, then diffuse abdominal pain with rupture, shock	Surgical repair, splenectomy, embolization if unruptured
Hepatic	Infection, arteriosclerosis, trauma, vasculitis	Obstructive jaundice, hemobilia from rupture into common bile duct, right upper quadrant pain, peritonitis, upper GI bleed	Surgical ligation, embolization
Mycotic or infected aneurysms	Intravenous drug user, patients with known aneurysms	Fever, pain at the site of the infected aneurysm	Intravenous antibiotics, surgical repair

Abbreviation: HTN = hypertension.

THORACIC AORTIC ANEURYSMS

Thoracic aortic aneurysms may compress or erode into adjacent structures. Presenting symptoms include esophageal, tracheal, bronchial, or even neurologic complaints. A thoracic aneurysm that erodes into an adjacent structure is generally immediately fatal unless in the presence of rapid hemodynamic resuscitation. Refer any asymptomatic thoracic aortic aneurysm patient to a surgeon and primary care provider for management, including blood pressure control. Repair may involve open or endovascular methods, with controversy over the best long-term outcomes between approaches.[26]

EXTREMITY AND VISCERAL ANEURYSMS

Aneurysms of arteries other than the aorta cause symptoms by expansion or rupture. **Table 60-2** lists the risk factors, clinical presentation, and management of nonaortic large-artery aneurysms. Aneurysms of peripheral arteries, such as the popliteal, subclavian, or femoral, may present with limb-threatening complications, including rupture, thrombosis, and peripheral embolization. Visceral artery aneurysms typically remain silent until a complication occurs. Complications include renovascular hypertension, renal artery thrombosis, organ infarction from distal embolization, arteriovenous fistula formation, and rupture.[26] Consider visceral artery aneurysms in the differential diagnosis of a patient with sudden acute abdominal pain and evidence for intraperitoneal hemorrhage.[7,8,27,28]

A **popliteal aneurysm** is a localized dilation of the popliteal artery of >2 cm or >150% of the normal arterial caliber. Symptoms include discomfort behind the knee, leg swelling with or without deep venous thrombosis, or claudication. Rupture is rare. Sudden acute limb ischemia caused by thrombosis or embolization from the aneurysm is the most serious common complication.[5] On physical examination, a firm mass or a palpable pulsatile mass is evident in the popliteal fossa. Confirm the diagnosis with arterial US, and assess both extremities since popliteal aneurysms can be bilateral.

Femoral or iliac artery aneurysms present as a pulsatile mass in the groin or upper thigh, scrotal hematoma, or acute limb ischemia. Iliac artery aneurysms are notoriously difficult to suspect clinically because the iliac artery cannot be examined directly, and symptoms suggest urologic, bowel, or groin disorders.

Hepatic artery aneurysms result from atherosclerosis or trauma and present as acute hemorrhagic shock with intraperitoneal or retroperitoneal rupture. **Quincke's triad** (jaundice, biliary colic, and upper GI bleeding) is seen when hemobilia from a leaking hepatic artery aneurysm occurs.

Splenic artery aneurysms present with left upper quadrant pain, undifferentiated shock, or intra-abdominal hemorrhage. A rupture of the splenic artery has a poor prognosis because of its intraperitoneal location and nondescript presentation; be wary of these in the third trimester of pregnancy.[28] Portal hypertension is also a risk factor for splenic artery aneurysms.

Symptomatic **subclavian and innominate artery aneurysms** can lead to limb ischemia. When evaluating a patient with upper extremity pain, weakness, pallor, or nondermatome sensory changes, think of these aneurysms as a possible cause.

Anastomotic aneurysms may occur in the aortic, iliac, or femoral arteries. These aneurysms cause catastrophic bleeding if they rupture; however, they may present with smaller sentinel hemorrhages noted as pain or transient hypotension. Anastomotic aneurysms may erode into the adjacent intestine and form an aortoenteric fistula. Severe lower GI bleeding in a patient with a history of abdominal aortic aneurysm repair is a classic presentation of this event.

Doppler US is the initial noninvasive diagnostic study for peripheral aneurysmal disease of the femoral, popliteal, and subclavian artery. If ischemia and thrombosis exist, emergent CT angiography is usually performed for both diagnosis and potential treatment.

Symptomatic peripheral artery aneurysms require rapid diagnosis and consultation, especially in light of the potential for rupture, thrombosis, and limb ischemia (Table 60-2). For patients with clinical extremity ischemia, consult immediately with a vascular surgeon to expedite repair and limb salvage. Asymptomatic peripheral aneurysms are managed by a vascular consultant as an outpatient.

Mycotic and **infected aneurysms** require appropriate IV antibiotics, often for prolonged periods, and consultation for surgical repair. Emergent consultation should be sought for suspected rupture.[4]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 61

Arterial Occlusion

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Anna K. Nowacki

INTRODUCTION AND EPIDEMIOLOGY

Limb ischemia occurs when blood flow—and by extension, tissue perfusion—is limited enough to create symptoms; acute limb ischemia denotes rapid new event or a progression of a flow deficit, requiring recognition and rapid therapy for limb salvage. **Critical limb ischemia** is one end of the spectrum of peripheral arterial disease, when **pain at rest**, ulceration, or gangrene exists. Smoking and diabetes are the most important risk factors for peripheral arterial disease.[1] Additional risk factors include hyperlipidemia, hypertension, elevated blood homocysteine, and an elevated C-reactive protein level.[2]

The severity of peripheral arterial disease is linked to the risk of myocardial infarction, ischemic stroke, and death from vascular disease.[3] The most frequently diseased arteries leading to limb ischemia are, in order of occurrence, the femoropopliteal, tibial, aortoiliac, and brachiocephalic vessels. Despite improvements in the management of peripheral arterial disease, current 1-year mortality after the onset of critical limb ischemia is 25%, and up to one quarter of survivors require amputation.[4,5]

Over 200 million people are living with peripheral artery disease globally, with 70% of those in low- and middle-income countries. Between 2000 and 2010, the number of individuals with peripheral artery disease increased by nearly 30% in low- and middle-income countries and by 13% in high-income countries.[6] Data from the Global Burden of Disease projects show that on a global scale, there has been a significant increase in both disability and mortality associated with peripheral arterial disease, with a greater increase among women than among men.[7] In the United States, it is estimated that critical limb ischemia has an annual incidence of 0.35% and an average prevalence of 1.33%. This exceeds previous estimates and parallels the incremental increase in cardiovascular risk factors.[8]

PATHOPHYSIOLOGY

Acute limb ischemia results from a sudden decrease in blood supply to a limb, leading to tissue hypoperfusion and threatening limb viability. As time proceeds, cell death or irreversible tissue damage occurs. Without the presence of collateral vessels, peripheral nerves and skeletal muscle may suffer irreversible changes within 4 to 6 hours of vessel occlusion.

Following restoration of blood flow, **reperfusion injury** can occur and may manifest as compartment syndrome, rhabdomyolysis, or metabolic derangements. Often, hyperkalemia, myoglobinemia, metabolic acidosis, and an elevation in creatine kinase level exist. The extent of reperfusion injury depends on the duration and location of the arterial blockage, the amount of collateral flow, and the previous health of the involved limb. Approximately one third of all deaths from occlusive arterial disease are secondary to metabolic complications after revascularization.[9]

Disorders that can lead to arterial occlusion are listed in **Table 61-1**.

THROMBOSIS

Thrombotic occlusion is the most common cause of *acute* limb ischemia and can occur in native vessels and bypass grafts. In the lower limbs, thrombotic occlusion accounts for >80% of cases.[15] In the upper limbs, about half of all cases of acute limb ischemia are due to thrombosis, while about one third are due to embolism.[16] The clinical distinction between thrombosis and embolism in any given patient is not always clear. Thrombosis most often occurs in the presence of atherosclerosis; due to the presence of collateral vasculature, thrombotic ischemia presents more gradually than an acute embolic event. However, it is also possible for plaque to embolize directly or to foster thrombus formation that embolizes and creates an acute high grade.

Other than plaque rupture, progression of ischemic injury can occur by: (1) propagation of clot to occlude collateral vessels, (2) ischemia-related distal edema leading to high compartment pressures (compartment syndrome), (3) fragmentation of clot into the microcirculation, and (4) edema of the microvasculature cells. Large-vessel reperfusion may not resolve obstruction of the microvasculature.

Uncommonly, arterial thrombosis develops in an apparently normal vessel without plaque; these patients should be evaluated for an underlying hypercoagulable condition. Subclinical vessel injury (from injections, catheters, or other mechanical events) or early atherosclerosis may still exist in these patients.

EMBOLISM

Occlusion from embolism is less common than occlusion from thrombosis. The heart is the predominant source of peripheral emboli, with atrial fibrillation being responsible for most cases. Another cardiac source is a **mural thrombus** in the ventricle after recent myocardial infarction. Both atrial fibrillation and acute myocardial infarction predispose to poor cardiac wall motion and stagnant blood flow that promote clot formation. Patients with an acute myocardial infarction may develop a left ventricular thrombus as early as 24 hours and as late as 3 months after the event, with overall rates reported as about 3%, with anterior infarct thrombi rates as high as 9%.[17] Less common causes include emboli from mechanical valves, tumor emboli from atrial myxomas, vegetations from valve leaflets, and parts of prosthetic cardiac devices.

Noncardiac sources of arterial emboli include thrombi from aneurysms and atheromatous plaques. Mural thrombi in aneurysms of aortoiliac, femoral, popliteal, and subclavian arteries are the most notable sources. Atheroemboli consist of cholesterol-laden debris and platelet aggregates and result from plaque fragmentation that causes obstruction of the microcirculation, producing symptoms in the hands, feet (blue toe syndrome), or cerebral circulation (transient ischemic attack). Paradoxical embolization occurs when a venous clot passes from the right to the left side of the heart through an intracardiac shunt, most commonly a patent foramen ovale.

An embolus may fragment and embolize distally, or it may propagate locally and create a larger clot. Emboli tend to lodge in places where vessels taper or branch, with the most common location in the leg being the bifurcation of the common femoral artery, followed by the popliteal artery. In the upper limb, the brachial artery is most commonly affected by an embolism.

OTHER CAUSES

Intentional or accidental **intra-arterial drug injections** can result in local vasospasm, infectious arteritis, thrombosis, pseudoaneurysm, endocarditis, and mycotic aneurysm. Inert particles or drug crystals can embolize to obstruct end arteries, which can lead to gangrene of the digits. The prolonged use of vasopressor medications may result in arterial ischemia; when using these agents, observe closely for adequate extremity perfusion, particularly in patients with known preexisting vascular disease.

An **aortic dissection** can propagate into the subclavian or iliofemoral systems and present with neurologic dysfunction and/or extremity ischemia findings. The false lumen created by the dissection occludes flow in the involved artery.

CLINICAL FEATURES

Patients with acute limb ischemia exhibit one or more of the **"six Ps": pain, pallor, paralysis, pulselessness, paresthesias, and poikilothermia (for cold)**. A lack of one or more of these findings does not exclude ischemia. Pain alone may be the earliest symptom of ischemia, localized in the limb distal to the site of obstruction.

Skin changes include pallor first, followed by blotchy and mottled areas of cyanosis, and then associated petechiae and blisters. Late findings consist of skin and fat necrosis.

TABLE 61-1 Disorders Associated With Acute Arterial Occlusion

Disorder	Cause	Symptoms/Signs	Management
Thrombus	Atherosclerosis or thrombosis of bypass grafts	Intermittent claudication	Medical first, then consider interventional
Embolism	Cardiac source: atrial fibrillation, rheumatic heart disease, mechanical valves, post–myocardial infarction thrombus, atrial myxomas, and leaflet vegetations/endocarditis	Sudden onset of territorial arterial symptoms	Preventive anticoagulation, embolectomy
Catheterization complication (brachial or femoral)	Can occur during standard angioplasty, angiography, or arterial blood gas	Expanding hematoma, pain, temperature and pulse changes	Conservative vs. operative repair
Trash foot or blue toe syndrome	Cholesterol/platelet aggregate emboli	Painful cyanotic discoloration of isolated portion of foot; remainder of the foot is warm	Conservative therapy
Vasculitis: rheumatoid arthritis, lupus, polyarteritis nodosa	Autoimmune inflammation of small arteries	Systemic symptoms and multiorgan ischemia	Steroids, immunosuppressive agents
Raynaud's disease	Vasospasm in small arteries or arterioles provoked by cold or stressors	Local pain, pallor, cyanosis, numbness, paresthesias in hands usually resolving in 30–60 min	Rewarming, medications: calcium channel blockers, α-blockers, vasodilators
Takayasu's arteritis	Autoimmune vasculitis of aortic arch and branches	Young Asian women: peripheral ischemia and necrosis leading to pulseless phase; may have fever, rash, muscle aches, arthritis	Steroids, immunosuppressive agents
Thromboangiitis obliterans (Buerger's disease)	Nonatherosclerotic segmental inflammation of small/medium vessels; typically, seen only in smokers	Painful nodules, ulceration, and gangrenous digits in young adults (age 20–40 y)	Smoking cessation
HIV arteritis[10]	Chronic inflammation of arteries associated with low CD4 counts	Intermittent claudication	Optimization of HIV management, angioplasty, or vein graft
Hypothenar hammer syndrome	Repeated trauma to the hypothenar area with hammering in laborers, as well as those using vibrational tools, causing narrowing of ulnar artery or aneurysmal degeneration	Painful discoloration of one or more ulnar fingers with sparing of thumb	Aspirin, nifedipine, intra-arterial fibrinolysis, interposition vein graft
Popliteal artery entrapment (young males) and popliteal aneurysms (older males)[11]	Anatomic crowding of popliteal fossa with anomalous relationships between popliteal artery and surrounding muscle and fascia or luminal narrowing and thrombosis of aneurysm	Pain in anterior aspect of lower one third of leg with exercise, reproducible with active ankle plantar flexion or passive dorsiflexion	Surgical repair of popliteal fossa or aneurysm and grafting
External iliac artery endofibrosis[12]	External iliac artery fibrosis secondary to prolonged hip flexion	Thigh pain and numbness in cyclists and triathletes: measure pre- and postcycling ankle-brachial indexes	Surgical management or catheter dilatation
Local arterial trauma[13,14]	Penetrating or blunt damage to vessel	Suspect in patients with knee dislocation or penetrating extremity trauma	Surgical repair
Shock-related arterial ischemia	Low cardiac output states: congestive heart failure, sepsis, cardiogenic or hypovolemic shock	Generalized hypoperfusion	Resuscitation with fluids, blood products, vasopressors, inotropes; treat infection
Thoracic aortic dissection	False lumen of dissection occludes arteries	Chest or back pain	Surgical repair

Abbreviation: HIV = human immunodeficiency virus (infection).

With vessel occlusion, severe and steady pain in the involved extremity associated with decreased skin temperature is common. Hypoesthesia or hyperesthesia due to ischemic neuropathy is typically an early finding, as is muscle weakness. Two-point discrimination, vibratory sensation, and proprioception are often diminished prior to the loss of deep sensation. Absence of a palpable distal pulse is not a particularly helpful sign in a patient with long-standing vascular disease unless accompanied by skin changes compatible with acute arterial obstruction. An abrupt loss of a previously strong pulse is suggestive of acute embolization.

Atheroemboli present clinically with several different areas of involvement, with pain and cyanosis in the involved digit, petechiae, and local muscle pain and tenderness at the site of infarction (**blue toe syndrome**). Pulses are generally preserved, assuming they were present prior to the event. Table 61-1 notes symptoms of other related disorders.

As ischemic injury progresses, anesthesia and paralysis become evident and foreshadow impending gangrene and the loss of limb viability. Preservation of light touch on skin testing is a good guide to tissue viability. A patient with an acute ischemic limb with signs of muscle paralysis, sensory loss, and prolonged ischemia has a limb that is likely nonviable. The **Rutherford criteria** (**Table 61-2**) provide a more formal prognostic stratification of the clinical stages of acute limb ischemia.

Limb viability is dependent on the effectiveness of collateral circulation, and no arbitrary time period can exclude treatment options despite the common belief that "treatment must occur in 4 to 6 hours."[2]

ACUTE VERSUS CHRONIC ARTERIAL DISEASE

Acute limb ischemia is defined as symptoms starting within a 2-week period. Pain over the distal forefoot waking the patient at night or

TABLE 61-2 Rutherford Criteria for Acute Limb Ischemia

Category	Description/Prognosis	Findings		Doppler Signals	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Source: Reproduced with permission from Rutherford RB, Baker JD, Ernst C, et al: Recommended standards for reports dealing with lower extremity ischemia: revised edition. *J Vasc Surg* 26: 517, 1997.

requiring the patient to hang his or her feet over the bed is suggestive of severe arterial occlusion and requires prompt consultation and treatment.

In contrast to acute disease, chronic peripheral arterial disease has intermittent claudication, which may progress to intermittent ischemic pain at rest. **Claudication** is a cramp-like pain, ache, or tiredness that is brought on by exercise and relieved by rest, similarly to angina in the heart. It is reproducible, resolves within 2 to 5 minutes of rest, and recurs at consistent walking distances. Unlike claudication, the pain of acute limb ischemia is not relieved by rest or gravity, is not well localized, and can present as marked worsening of chronic pain.

Classical teaching suggests that single-vessel disease in one of the segments noted in **Table 61-3** may result in localized claudication, whereas multivessel disease results in less focal rest pain or tissue loss. Table 61-3 lists symptom sites of commonly compromised arteries.

OTHER DIAGNOSES THAT MIMIC ARTERIAL ISCHEMIA

The pain of intermittent vascular claudication can be confused with other triggers (**Table 61-4**) including spinal stenosis or lumbosacral radiculopathy. Other causes of extremity pains include chronic compartment syndrome, venous claudication, nerve root compression, Baker's cyst, or foot, hip, or ankle arthritis.

It is important to consider the following three steps in the differential diagnosis of acute limb ischemia:

1. Look for conditions mimicking acute limb ischemia.
2. Consider nonatherosclerotic causes of arterial occlusion.
3. If neither of the above exists, determine if the ischemia is caused by an arterial thrombus or embolus.[2]

DIAGNOSIS

Obtain an adequate history, focusing on the timing and acuity of symptom onset, pattern of claudication, any previous revascularization or diagnosis of ischemia, and assessment of risk factors. Patients with known peripheral arterial disease or previous revascularization may have subacute symptoms due to the development of collateral vessels. A history of an abruptly ischemic limb in a patient with atrial fibrillation or recent myocardial infarction strongly suggests an embolus. Acute ischemia in the limb of a patient known to have advanced peripheral arterial disease is more likely due to thrombosis or a low cardiac output state. In patients without antecedent claudication and a *normal* uninvolved limb, embolic occlusion is likely (**Table 61-5**).

TABLE 61-3 Artery-Specific Claudication Sites

Artery Involved	Claudication Site
Iliac artery	Buttocks, thigh, and sometimes calf (if bilateral, may cause impotence in men)
Common femoral artery	Thigh
Superficial femoral artery	Upper two thirds of calf
Popliteal artery	Lower one third of calf
Infrapopliteal (tibial and peroneal) artery	Foot

On physical examination, look at the skin and palpate peripheral pulses of both extremities, comparing the less or unaffected and the affected limbs. Shiny, hyperpigmented skin with hair loss and ulceration, muscle atrophy, and poor pulses are the hallmarks of chronic peripheral arterial disease.

Listen to the heart and abdomen, seeking bruits and murmurs. POCUS helps detect an abdominal aortic aneurysm. Use a hand-held Doppler US device over pulse areas to detect presence or absence of blood flow and the amplitude. Approximately 10% of patients have only one pedal or ankle pulse present secondary to an anatomic variation. If Doppler-detected blood flow is in the affected limb, measure the **ankle-brachial index** to assist in risk-stratifying the patient. The ankle-brachial index is the ratio of the systolic blood pressure with the cuff just above the malleolus (with the Doppler probe over the posterior tibial or dorsalis pedis artery) to the highest brachial pressure in either arm. Patients with chronic peripheral arterial disease have an ankle-brachial index of <0.9, while values of <0.4 suggest severe disease. An ankle-brachial index of >1.3 is likely secondary to a noncompressible vessel. In

TABLE 61-4 Differential Diagnosis of Acute Limb Ischemia

***Conditions mimicking acute limb ischemia**

- Systemic shock (especially if associated with chronic occlusive disease)
- Phlegmasia cerulea dolens
- Acute compressive neuropathy

Differential diagnosis for acute limb ischemia (other than acute peripheral arterial disease)

- Arterial trauma
- Aortic/arterial dissection
- Arteritis with thrombosis (e.g., giant cell arteritis, thromboangiitis obliterans)
- HIV arteriopathy
- Spontaneous thrombosis associated with a hypercoagulable state
- Popliteal adventitial cyst with thrombosis
- Popliteal entrapment with thrombosis
- Vasospasm with thrombosis (e.g., ergotism)
- Compartment syndrome

Acute Peripheral Arterial Disease

- Thrombosis of an atherosclerotic stenosed artery
- Thrombosis of an arterial bypass graft
- Embolism from heart, aneurysm, plaque or critical stenosis upstream (including cholesterol or atherothrombotic emboli secondary to endovascular procedures)
- Thrombosed aneurysm with or without embolization

*Two of the three conditions (deep vein thrombosis, neuropathy) that may mimic arterial occlusion should be expected to have arterial pulses, except if occult chronic peripheral arterial disease existed prior to the acute event.

Low cardiac output makes the chronic arterial ischemia more manifest in terms of symptoms and physical findings.

Source: Reproduced with permission from Norgren L, Hiatt WR, Dormandy JA, et al: Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 45: S5A, 2007.

Abbreviation: HIV = human immunodeficiency virus.

TABLE 61-5 Embolic Versus Thrombotic Occlusion

Factor	Embolism	Thrombosis
History of claudication	No	Yes
Physical examination	Normal contralateral limb	Marked signs of occlusive arterial disease bilaterally
Source identified	Often	None
Timing	Sudden, exact time known	More gradual
Radiologic features	Sudden abrupt cutoff in blood flow with no collateral circulation and minimal diseased vessel	Widespread disease with collaterals present and gradual narrowing of blood flow seen

such cases, do more detailed pressure measurements like a toe-brachial pressure using specialized equipment. (See Video: Ankle Brachial Index)

LABORATORY EVALUATION

Aside from seeking markers of cellular ischemia or injury (e.g., creatine kinase, myoglobin, and serum lactate), assess the metabolic status (electrolytes and glucose), renal function (BUN and creatinine plus urinalysis), potential anemia and infection (CBC), and bleeding tendency (prothrombin and partial thromboplastin times). Levels of cardiac injury markers and ECG may identify triggers including infarction or rhythm change.

IMAGING

Acute critical limb ischemia is a time-sensitive diagnosis; once suspected, consult a surgeon as soon as possible, even while obtaining diagnostic imaging. Duplex US is very accurate for detecting complete or incomplete arterial obstruction. Sensitivity declines for localization of thromboembolic occlusion at or below the calf level. Emergency physician–performed POCUS focusing on the aorta, iliac vessels, and femoral artery bifurcation may localize emboli or thromboses, expediting diagnosis and management.[18] Transthoracic cardiac echocardiography can help detect embolic sources, and transesophageal approaches add the ability to detect aortic root pathology.

Arteriography often occurs in the operating room or intervention lab just prior to direct therapy. CT with contrast is the most readily available study in the ED, and it has a sensitivity similar to that of conventional uniplanar contrast studies in large vessels. MRI has higher sensitivity and specificity than CT angiography but is less readily available. The selection of most timely and appropriate imaging technique is best a joint decision between the ED physician, vascular surgeon, and/or interventional radiologist.

TREATMENT

The objectives of therapy for acute arterial obstruction are restoration of blood flow to preserve limb and life and prevention of recurrent thrombosis or embolism (**Table 61-6**).

In the ED, **IV unfractionated heparin** (weight-based 80 units/kg bolus followed by an infusion of 18 units/kg/h) is the initial therapy of choice. It prevents clot extension, recurrent embolization, venous thrombosis, microthrombi distal to the obstruction, and reocclusion after reperfusion.[19,20] Direct thrombin inhibitors, such as lepirudin or argatroban, are an alternative treatment option when heparin-induced thrombocytopenia with thrombosis is of concern.[19,21] Aspirin (325 milligrams in naive patients) may enhance clot reduction through antiplatelet actions. Pain management and optimization of limb perfusion by treating low-flow states such as heart failure are also important steps in care.

TABLE 61-6 ED Medical Therapy for Acute Limb Ischemia

Intervention	Comments
Unfractionated heparin[19]	80 units/kg IV bolus followed by infusion of 18 units/kg/h
Antiplatelet therapy[19]	Aspirin 325 milligrams PO first dose or clopidogrel 75 milligrams if patient is allergic to aspirin
Pain control	As needed for patient comfort and cooperation
Optimize perfusion	Treat low-flow states and shock Place extremity in dependent position
Environment protection	Protect ischemic limb from temperature extremes

Stratifying patients with acute limb ischemia by Rutherford criteria (Table 61-2) in conjunction with early surgical consultation guides initial care. Patients with stage I and stage IIa limb ischemia may undergo diagnostic imaging workup prior to more definitive treatments. Patients with stage IIb ischemia often require immediate revascularization without additional prior diagnostic imaging. Patients with stage III ischemia have irreversible damage and likely require amputation. The vascular surgeon will determine definitive treatment, which can include catheter-directed thrombolysis, percutaneous mechanical thromboembolectomy, revision of an occluded bypass graft, and revascularization with either percutaneous transluminal angioplasty or standard surgery.[2,18] Catheter-directed intra-arterial thrombolysis is more common now than systemic IV thrombolysis for peripheral artery embolic or thrombotic disease.[19,20] In a subacute thrombotic occlusion with a well-developed collateral blood supply, medical management is common.

The longer-term nonsurgical management of peripheral arterial disease focuses on the combination of smoking cessation, structured exercise, and pharmacotherapy. Antiplatelet therapy with either aspirin (75 to 100 milligrams daily) or clopidogrel (75 milligrams daily) can reduce mortality from cardiovascular causes in patients with peripheral arterial disease. Dual antiplatelet therapy is not initially recommended.[19]

The American College of Cardiology/American Heart Association 2016 guidelines include cilostazol, a phosphodiesterase inhibitor, as a Class I recommendation for the treatment of intermittent claudication. Pentoxifylline is no longer recommended.[19,20]

A multidisciplinary approach including a team of specialists, wound care experts, and nutritionists helps to decrease morbidity and improve long-term outcome.[22]

DISPOSITION AND FOLLOW-UP

Patients with acute or worsening chronic ischemia require observation, hospital admission, or immediate transfer to a center with vascular surgery capability. Patients with chronic peripheral arterial disease without an immediate threat to limb viability absent other acute illness can be discharged home to follow up with a vascular surgeon or primary care physician. Instruct patients to return immediately for worsening of symptoms (especially pain) and to start aspirin (81 milligrams daily after first dose of 325 milligrams if there are no contraindications).

SPECIAL CONSIDERATIONS

UPPER EXTREMITY ISCHEMIA

Acute arterial occlusion in the upper extremities is much less common than in the lower limbs. Due to well-developed collateral circulation around the shoulder and elbow, ischemia here is better tolerated, with ischemic pain at rest and gangrene rare absent distal embolization. Causes of upper limb ischemia include vasospasm, arteritis, trauma, atherosclerotic plaque rupture, embolism, iatrogenic injury (e.g., during brachial artery access for cardiac catheterization), thoracic outlet syndromes, aneurysms, and hypercoagulable states. After clinical examination, investigate with segmental blood pressure measurements above and below the elbow, Doppler evaluation, duplex US, and arteriography. Treatment of acute limb-threatening ischemia of the hand and forearm includes heparin (Table 61-6) and emergent surgical thromboembolectomy.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 8

Pulmonary Disorders

CHAPTER 62

Respiratory Distress

Joseph Stephan Stapczynski

GENERAL APPROACH TO RESPIRATORY DISTRESS

INTRODUCTION AND DEFINITIONS

Dyspnea is a feeling of difficult, labored, or uncomfortable breathing, often described as "shortness of breath," "breathlessness," or "not getting enough air."[1-3] Dyspnea is usually caused by pulmonary or cardiac disease. **Tachypnea** is rapid breathing. **Orthopnea** is dyspnea in the recumbent position; it is most often the result of left ventricular failure but can be seen with diaphragmatic paralysis or chronic obstructive pulmonary disease. **Paroxysmal nocturnal dyspnea** is orthopnea that awakens the patient from sleep, prompting an upright posture in order to resolve breathlessness. **Trepopnea** is dyspnea associated with lying on one side (lateral decubitus position) but not the other side. Trepopnea can occur when one lung is more diseased than the other and the patient lies on the side of the more affected lung where gravity increases blood flow to the worse lung and reduces it to the better lung.[4] **Platypnea** is the opposite of orthopnea: dyspnea in the upright position. Platypnea results from the loss of abdominal wall muscular tone and, in rare cases, from right-to-left intracardiac shunting as occurs from a patent foramen ovale. **Hyperpnea** is essentially hyperventilation and is defined as minute ventilation in excess of metabolic demand. **Respiratory distress** is a term used by the physician, combining the patient's subjective sensation of dyspnea with signs indicating difficulty breathing. **Ventilatory or respiratory failure** occurs when the lungs and ventilatory muscles cannot move enough air in and out of the alveoli to adequately oxygenate arterial blood and eliminate carbon dioxide.

PATHOPHYSIOLOGY

Dyspnea is a complex sensation from multiple pathophysiologic mechanisms.[1] Sensory information about respiratory activity generated by multiple afferent receptors integrates within the CNS at both the subcortical and cortical levels. The sensation of dyspnea occurs when imbalance exists among the inspiratory drive, efferent activity to the respiratory muscles, and feedback from these afferent receptors.

CLINICAL FEATURES

Dyspnea is a feature of several disorders seen in the ED (**Table 62-1**).[5-8] Physical signs associated with dyspnea include tachypnea and tachycardia; use of the accessory respiratory muscles, including the sternocleidomastoid, sternoclavicular, and intercostals; nasal flaring; inability to speak normally as a consequence of breathlessness; agitation or lethargy as a consequence of hypoxemia; depressed consciousness due to hypercapnia; and paradoxical abdominal wall movement when the abdominal wall retracts inward with inspiration, indicating diaphragmatic fatigue.[2,9]

HISTORY AND EXAMINATION

Assess the patient for signs of respiratory failure (altered conscious, inability to speak, diaphoresis, inspiratory retractions, nasal flaring, paradoxical respirations) and hypoxemia (using a pulse oximeter). Administer supplemental oxygen if the patient is hypoxemic. Ask about prior diagnosis and treatment of heart or lung disease. Question patients who require daily medications for symptom control about compliance and possible drug interactions. Ask about recent infectious and environmental exposures that may impair respiratory function.

Dyspnea is a prominent symptom of acute heart failure, and differentiating heart failure from pulmonary causes of dyspnea is occasionally difficult.[10] Treatment differs, and embarking down the wrong pathway of treatment can have adverse consequences.[11] Several findings can assist in this differentiation, although few of them are definitive by themselves (see Chapter 53, "Acute Heart Failure").[12]

An S_3 gallop on physical examination or pulmonary venous congestion/interstitial edema (especially with concomitant cardiomegaly) on chest radiograph strongly suggests heart failure as the cause of the dyspnea. The physician's overall gestalt of the diagnosis, the presence of jugular venous distention on examination, and alveolar edema on chest radiograph together also suggest heart failure, although any one finding is not specific. Wheezing, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and leg edema are not useful in discriminating between cardiac and pulmonary causes. Conversely, the absence of these findings does not exclude heart failure.

LABORATORY TESTING AND IMAGING

The cause of dyspnea in most ED patients can be identified by the history, the physical examination, ECG, point of care US, and chest radiograph.[13]

Pulse oximetry provides a rapid assessment of arterial oxygen saturation, but is an insensitive screening test for disorders of gas exchange. Arterial blood gas analysis is more sensitive for detecting impaired gas exchange but cannot evaluate the work of breathing. Arterial blood gas testing can find the patient with dyspnea or tachypnea who exhibits no evidence of hypoxemia or pulmonary disease, suggesting hyperventilating from metabolic acidosis.

Bedside spirometric analysis (e.g., peak expiratory flow), especially if performed before and after bronchodilator therapy, can diagnose dyspnea resulting from obstructive airway disease. Spirometry requires voluntary effort that might be difficult for dyspneic patients. Negative inspiratory force can assess strength of the diaphragm and inspiratory

TABLE 62-1 Common Causes of Dyspnea in the ED

Most Common Causes	Most Immediately Life-Threatening Causes
Obstructive airway disease: asthma, chronic obstructive pulmonary disease	Upper airway obstruction: foreign body, angioedema, hemorrhage
Decompensated heart failure/ cardiogenic pulmonary edema	Tension pneumothorax
Ischemic heart disease: unstable angina and myocardial infarction	Pulmonary embolism
Pneumonia	Neuromuscular weakness: myasthenia gravis, Guillain-Barré syndrome, botulism
Psychogenic	Fat embolism

muscles, which is useful in patients with neuromuscular disease to assess respiratory muscle weakness.

Bedside lung US can differentiate acute decompensated heart failure from noncardiac causes of acute dyspnea (see Chapter 53, "Acute Heart Failure").[14,15] Bedside US can also identify pleural effusion, pneumothorax, cardiac tamponade, cardiac functional abnormalities, pulmonary consolidation, and intravascular volume status.[16,17]

B-type natriuretic peptide (BNP) and D-dimer testing can be useful in evaluating dyspnea in the ED. BNP or its precursor, N-terminal pro-BNP, is elevated with any cause of ventricular overload, including heart failure and strain (both right or left sided), myocardial ischemia, pulmonary embolism, sepsis, or chronic obstructive pulmonary disease (see Chapter 53, "Acute Heart Failure"). A normal BNP (<100 picograms/mL) or N-terminal pro-BNP (<300 picograms/mL) excludes heart failure in low and moderate pretest probability patients outside of "flash" pulmonary edema settings.[18] Conversely, a high level (BNP >500 picograms/mL or N-terminal pro-BNP >900 picograms/mL) is moderately useful for establishing the diagnosis of heart failure. BNP values between 100 and 500 picograms/mL have no utility in excluding or including heart failure in the dyspneic patient.[19] Overall, BNP measurement usually is not needed for diagnosis and adds little impactful prognostic information, and it is best used when diagnostic uncertainty is present rather than routinely.

A normal D-dimer test can exclude pulmonary embolism in patients with low and moderate pretest probability (see Chapter 56, "Venous Thromboembolism Including Pulmonary Embolism").[20]

TREATMENT

In severe dyspnea, the initial treatment goal is maintenance of the airway and oxygenation, seeking an arterial oxygen partial pressure (Pa_{O_2}) >60 mm Hg (>8 kPa) and/or arterial oxygen saturation (Sa_{O_2}) ≥90%. Next, or in those with lesser dyspnea, treat the underlying disorder. Opioids or benzodiazepines provide comfort for terminal patients with dyspnea.[21]

HYPOXIA AND HYPOXEMIA

INTRODUCTION

Hypoxia is insufficient alveolar oxygen content or insufficient delivery of oxygen to the tissues. The amount of oxygen available to the tissues is a function of the arterial oxygen content (Ca_{O_2}) comprising a small portion dissolved in plasma and a larger portion bound to hemoglobin:

$$Ca_{O_2} = 0.0031 \times Pa_{O_2} + 1.38 \times \text{Hemoglobin} \times Sa_{O_2}$$

Oxygen delivery (D_{O_2}) is a product of arterial oxygen content and cardiac output:

$$D_{O_2} = Ca_{O_2} \times \text{Cardiac output}$$

Tissue hypoxia occurs in states of low cardiac output, low hemoglobin concentration, or low Sa_{O_2}. The level of oxygen saturation in arterial hemoglobin is, in turn, dependent on the Pa_{O_2}, as determined by the oxygen–hemoglobin dissociation curve. **Hypoxemia** is an abnormally low arterial oxygen tension (defined as a Pa_{O_2} <60 mm Hg or <8 kPa). Although alveolar hypoxia is the most common cause of hypoxemia, *hypoxia* and *hypoxemia* are not interchangeable; one can occur without the other. For example, in states of low Pa_{O_2} (hypoxemia) with concomitant polycythemia, the patient may have no tissue hypoxia. Alternatively, severely anemic patients may suffer tissue hypoxia despite a normal Pa_{O_2}.

Relative hypoxemia is the term used when the arterial oxygen tension is lower than expected for a given level of inhaled oxygen. The degree of relative hypoxemia can be assessed by calculating the alveolar–arterial (A-a) oxygen partial pressure gradient, $P_{(A\text{-}a)}O_2$, which measures efficiency of oxygen transfer from the lungs to the circulation. Alveolar oxygen partial pressure calculation uses the inhaled oxygen concentration (21% for room air), atmospheric pressure (760 mm Hg at sea level), and displacement by water vapor (47 mm Hg for full saturation) and carbon dioxide (CO_2). Gas in the alveolus is fully saturated with water vapor, and the amount of alveolar oxygen is further reduced by CO_2 that freely diffuses from the pulmonary capillaries in an amount determined by the ratio between oxygen consumption and CO_2 production, termed the *respiratory quotient*, which is affected by diet. On a typical mixed diet, the respiratory quotient is 0.8. Breathing room air at sea level allows this alveolar formula:

$$P_{A}O_2 = 0.21 \times (760 - 47) - Pa_{CO_2}/0.8$$

The A-a gradient at sea level for room air is:

$$P_{(A\text{-}a)}O_2 = 149 - Pa_{CO_2}/0.8 - Pa_{O_2}$$

A simplified formula often used is:

$$P_{(A\text{-}a)}O_2 = 145 - Pa_{CO_2} - Pa_{O_2}$$

A normal $P_{(A\text{-}a)}O_2$ is <10 mm Hg in young, healthy patients and increases with age, predicted by the formula:

$$\mathbf{P_{(A\text{-}a)}O_2 = 2.5 + 0.21\ (\text{age in years})\ (\pm 11)}$$

This normal A-a gradient is for healthy, asymptomatic individuals measured in an upright or sitting position. The supine position and many chronic cardiac or pulmonary diseases may raise the A-a gradient. The supine position is a common ED patient position, impairing the assessment.

PATHOPHYSIOLOGY

Hypoxemia results from any combination of five mechanisms.

1. *Hypoventilation.* Hypoxemia from hypoventilation alone has an increased Pa_{CO_2} and a normal A-a O_2 gradient. The additional CO_2 displaces inhaled oxygen in the alveolus. However, the remaining alveolar oxygen diffuses and mixes normally into the arterial blood, displaying a normal A-a O_2 gradient as long as there is no alveolar or interstitial disease.
2. *Right-to-left shunt.* Right-to-left shunting occurs when blood enters the systemic circulation without traversing ventilated lung. There is always a small degree of right-to-left shunting because of the direct left atrial return of deoxygenated blood from both the coronary veins and the bronchial arteries. Increased right-to-left shunting occurs in a variety of conditions, including congenital cardiac malformation and acquired pulmonary disorders (pulmonary consolidation, pulmonary atelectasis). Regardless of the specific cause of the right-to-left shunt, it is always associated with an increase in the A-a O_2 gradient. **A hallmark of significant right-to-left shunting is the failure of arterial oxygen levels to increase in response to supplemental oxygen.** Although a small improvement may be observed with supplemental oxygen, hypoxemia is never fully eliminated because of the mixing of deoxygenated blood in the systemic circulation.
3. *Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch.* Ideal pulmonary gas exchange depends on a balance of ventilation and perfusion. Any abnormality resulting in a regional alteration of either ventilation or perfusion can adversely affect pulmonary gas exchange, resulting in hypoxemia. There are many causes of $\dot{V}/\dot{Q}$ mismatch, including pulmonary emboli, pneumonia, asthma, chronic obstructive pulmonary disease, and even extrinsic vascular compression. Regardless of cause, hypoxemia from ventilation-perfusion mismatch is associated with an increased A-a O_2 gradient, and hypoxemia improves with supplemental oxygen.

4. *Diffusion impairment.* Pulmonary gas exchange requires diffusion across the alveolar–blood barrier. Regardless of the specific cause of the diffusion impairment, the A-a O_2 gradient is increased, and hypoxemia improves with supplemental oxygen.
5. *Low inspired oxygen.* Decreased ambient oxygen pressure results in hypoxemia. This is commonly seen at high altitude (including commercial air travel) or in nonobstructive asphyxia. The A-a O_2 gradient is normal, and hypoxemia improves with supplemental oxygen. For example, Denver, at 5400 ft (1646 m) above sea level, has an atmospheric pressure of 620 mm Hg (82.7 kPa) and an inhaled Po_2 of only 0.21 × 620 = 130 mm Hg, as opposed to 160 mm Hg at sea level.

There are acute compensatory mechanisms for hypoxemia. Initially, minute ventilation increases. Next, pulmonary arterial vasoconstriction decreases perfusion to hypoxic alveoli. Although vasoconstriction balances ventilation and perfusion to restore arterial oxygenation, it may also cause acute right heart failure and is ineffective with diffuse lung disease. Finally, sympathetic tone increases and improves oxygen delivery by increasing cardiac output, usually with an increased heart rate. Chronic compensatory mechanisms include an increased red blood cell mass and decreased tissue oxygen demands. These compensatory mechanisms appear to be activated at different levels of hypoxemia among different individuals. However, the acute compensatory mechanisms are always activated when Pao_2 reaches 60 mm Hg (8 kPa), and compensatory mechanisms fail when Pao_2 falls below 20 mm Hg (2.67 kPa).

CLINICAL FEATURES

CNS manifestations of tissue hypoxia include agitation, headache, somnolence, coma, and seizures. Although tachypnea and hyperventilation are often present, by the time Pao_2 is <20 mm Hg (<2.67 kPa), there is a central depression of respiration. **Cyanosis, the blood or tissue discoloration associated with a lowered arterial oxygenation saturation, is not a sensitive or specific indicator of hypoxemia.** Patients with chronic compensatory mechanisms may display polycythemia or alterations in body habitus (e.g., pulmonary cachexia).

DIAGNOSIS AND TREATMENT

Pulse oximetry accurately predicts significant hypoxemia, although clinically acceptable pulse oximetry saturation readings (>90%) may not exclude hypoxemia. If certain hemoglobin abnormalities exist (e.g., methemoglobin or carboxyhemoglobin), pulse oximetry analysis may overestimate oxygen saturation and underestimate the response to supplemental oxygen (see the section "Cyanosis," below). Regardless of the specific cause of hypoxemia, the initial approach remains the same: ensuring a patent airway and providing supplemental oxygenation with a goal of maintaining a Pao_2 >60 mm Hg (>8 kPa). **Except in patients with right-to-left shunts, arterial oxygenation responds to supplemental oxygen.**

HYPERCAPNIA

INTRODUCTION

Hypercapnia is exclusively caused by alveolar hypoventilation and is defined as a $Paco_2$ >45 mm Hg (>6 kPa). Alveolar hypoventilation has many causes, including rapid shallow breathing, small tidal volumes, underventilation of the lung, or reduced respiratory drive. **Hypercapnia never results from increased CO_2 production alone (Table 62-2).**

PATHOPHYSIOLOGY

A portion of each tidal volume remains in the non–gas-exchange portion of the respiratory system—termed the *dead space*—that is determined by the anatomic size of the conducting airways (trachea and bronchi). The portion of the tidal volume that reaches the alveoli is that which remains after the dead space volume is subtracted:

$$Ta \text{ (alveolar volume)} = V_T \text{ (tidal volume)} - Td \text{ (dead space)}$$

Alveolar ventilation (V_A) per minute is the alveolar volume multiplied by the respiratory rate (R):

$$V_A = Ta \times R = (V_T - Td) \times R$$

Alveolar hypoventilation can result from a decrease in respiratory rate, a decrease in tidal volume, or an increase in dead space. Dead space volume can increase above that due to the anatomic size of the conducting airways when ventilated portions of the lung have deficient or absent perfusion; these ventilated portions do not participate fully in gas exchange because of inadequate blood flow.

Medullary chemoreceptors stimulate both respiratory rate and tidal volume in response to increased CO_2, so that alveolar ventilation is finely controlled relative to CO_2 production and $Paco_2$ is maintained within a narrow range. Decreased respiratory drive is associated with CNS lesions and toxic depression (Table 62-2). Thoracic cage and neuromuscular disorders produce hypoventilation by slowing respiratory rate and/or decreasing tidal volume relative to the production of CO_2. Intrinsic lung diseases, such as chronic obstructive pulmonary disease, produce alveolar hypoventilation because of an increase in dead space.

TABLE 62-2 Causes of Hypercapnia

- Depressed central respiratory drive
- Structural CNS disease: brainstem lesions
- Drug depression of respiratory center: opioids, sedatives, anesthetics
- Endogenous toxins: tetanus
- Thoracic cage disorders
- Kyphoscoliosis
- Morbid obesity
- Neuromuscular impairment
- Neuromuscular disease: myasthenia gravis, Guillain-Barré syndrome
- Neuromuscular toxin: organophosphate poisoning, botulism
- Intrinsic lung disease associated with increased dead space
- Chronic obstructive pulmonary disease
- Upper airway obstruction

CLINICAL FEATURES

The signs and symptoms of hypercapnia depend on the absolute value of $Paco_2$ and its rate of change. Acute elevations increase intracranial pressure, and patients may have headache, confusion, or lethargy. Severe hypercapnia can trigger seizures and coma. Extreme hypercapnia can result in cardiovascular collapse, but this is usually seen only with acute elevations of $Paco_2$ >100 mm Hg (>13.3 kPa). As opposed to acute hypercapnia, chronic hypercapnia, even >80 mm Hg (>10.7 kPa), may be well tolerated.

DIAGNOSIS

Diagnosis of hypercapnia requires arterial blood gas analysis or end-tidal CO_2 measurement. With acute hypercapnia, the serum bicarbonate level increases slightly as a result of mass action through the CO_2–bicarbonate equilibrium: bicarbonate increases about 1 mEq/L for each increase of 10 mm Hg (1.3 kPa) in the $Paco_2$. Patients with chronic hypercapnia have an elevated serum bicarbonate concentration and near-normal pH due to the renal retention of bicarbonate in response to increased $Paco_2$: the serum bicarbonate concentration increases about 3.5 mEq/L for each increase of 10 mm Hg (1.3 kPa) in the $Paco_2$.

TREATMENT

Hypercapnia is treated by increasing minute ventilation by increasing either the respiratory rate or the tidal volume, or often both, as needed. This involves ensuring a patent airway and may require noninvasive positive-pressure ventilation, mechanical ventilation, the use of an antidote to reverse drug toxicity, or rarely, the use of a respiratory stimulant such as doxapram.[22-24] **Do not withhold oxygen required to maintain minimum oxygen saturation levels in any chronic lung disease patient in an effort to stimulate ventilation and reduce hypercapnia.**

The disposition of hypercapnic patients depends primarily on the underlying cause and severity. In general, hospitalize patients with hypercapnia with new acidosis or that causes CNS symptoms, along with patients with neuromuscular disease, either congenital or acquired, who present with acute hypercapnia. Some chronic obstructive pulmonary disease patients have chronic hypercapnia and do not require admission provided they are stable clinically and the arterial pH is normal. Conversely, patients with chronic obstructive pulmonary disease who display worsening hypercapnia or added respiratory acidosis (pH lowered from baseline) despite maximal outpatient therapy require hospital admission.

COUGH

INTRODUCTION

Cough is a protective reflex for clearing secretions and foreign debris from the tracheobronchial tree.[25] Coughing starts with stimulation of irritant receptors located largely in the larynx, trachea, and major bronchi. These receptors respond to inhaled irritants (e.g., dust), allergens (e.g., ragweed pollen), toxic substances (e.g., gastric acid), hypo- or hyperosmotic liquids, inflammation (e.g., asthma), cold air, instrumentation, and excess pulmonary secretions. Minor cough receptors located in the upper respiratory tract (sinuses and pharynx) and chest (pleura, pericardium, and diaphragm) may stimulate coughing. Signals from these receptors travel by means of the vagus, phrenic, and other nerves to the cough center in the medulla.

Once stimulated, the cough center initiates the stereotypical cough pattern: a deep inspiration followed by attempted expiration against a closed glottis that suddenly opens, providing for a forceful exhalation of gas, secretions, and foreign debris from the tracheobronchial tree. The coughing sound is generated at the larynx and resonates in the nasal cavity and the lungs.

CLINICAL FEATURES

Acute cough is cough lasting <3 weeks and is usually associated with self-limited upper respiratory or bronchial infections (Table 62-3).[26] Subacute cough lasts 3 to 8 weeks and is most commonly postinfectious, but causes of subacute cough overlap with causes of acute and chronic cough. **Chronic cough is present for >8 weeks.**[27-29]

TABLE 62-3 Differential Diagnosis of Cough

Acute	Chronic	Chronic: Less Common
Upper respiratory infection: rhinitis, sinusitis, pertussis	Smoking and/or chronic bronchitis	Heart failure
Lower respiratory tract infection: bronchitis, pneumonia	Upper airway cough syndrome (postnasal discharge syndrome)	Bronchiectasis
Allergic reaction	Asthma: reactive airways disease	Lung cancer or other intrathoracic mass
Asthma	Gastroesophageal reflux	Emphysema
Environmental irritants	Angiotensin-converting enzyme inhibitor	Occupational and environmental irritants
Transient airway hyperresponsiveness	Angiotensin II receptor blocker	Recurrent aspiration or chronic foreign body
Foreign body	Postinfectious; pertussis	Psychiatric
		Miscellaneous: cystic fibrosis, interstitial lung disease

ACUTE COUGH

Acute cough is most often caused by upper respiratory tract infection, lower respiratory tract infection, and allergic reactions.[26] Common upper respiratory infections are often a combination of rhinorrhea, sinusitis, pharyngitis, and laryngitis, with the cough a result of drainage from the nasopharynx onto cough receptors in the pharynx and larynx. A productive cough is the hallmark of acute bronchitis. Although pneumonia generally produces a cough, pulmonary secretions may be scant and the cough nonproductive. Pertussis in adults has been associated with acute cough lasting 1 to 6 weeks.[30] The observed increased incidence of pertussis in adolescents and young adults is likely due to waning vaccine immunity with increasing age.

SUBACUTE COUGH

Postinfectious cough is the most likely cause of subacute cough. The mechanisms include postviral airway inflammation with bronchial hyperresponsiveness, mucus hypersecretion, upper airway cough syndrome (postnasal discharge), or asthma.

CHRONIC COUGH

The most common causes of chronic cough are (1) smoking, often with chronic bronchitis; (2) upper airway cough syndrome (formerly postnasal discharge); (3) asthma; (4) gastroesophageal reflux; and (5) angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy (Table 62-3).[27-29] Smoking-induced coughing is usually worse in the morning and, with chronic bronchitis, usually productive. Upper airway cough syndrome, formerly called *postnasal discharge syndrome*, is associated with mucus drainage from the nose, a history of "allergies or sinus problems," and frequent clearing of the throat or swallowing of mucus.[27] The postnasal drainage itself may not only directly stimulate a cough, but the conditions producing postnasal drainage (e.g., allergic rhinitis) may also cause irritation or inflammation of upper airway structures that directly stimulates cough receptors independently of the drainage. Chronic cough associated with asthma is usually worse at night, exacerbated by irritants, and associated with episodic wheezing and dyspnea.[31] Asthma can be exacerbated by β-blocker therapy and also presents with nocturnal coughing. Cough associated with gastroesophageal reflux often has a history of heartburn, is worse when lying down, and improves with anti-acid therapy (antacids, H_2 blockers, or proton pump blockers).[32,33]

The incidence of angiotensin-converting enzyme inhibitor–induced cough is approximately 5% to 10% in the Western world, although higher values have been reported in other areas.[34] The observed incidence of angiotensin receptor blocker–induced cough is about 35% to 40% that of angiotensin-converting enzyme inhibitors.[35] Angiotensin-converting enzyme inhibitor–induced cough is thought to result when the blockade of angiotensin-converting enzyme leads to accumulation of bradykinin and substance P, which stimulate the pulmonary cough receptors and enhance the formation of irritating prostaglandin metabolites. Angiotensin-converting enzyme inhibitor–induced cough is highly variable in onset (as early as 1 week to as late as 1 year after starting treatment), severity (only slightly bothersome to debilitating symptoms), and variation during the day. Cough typically resolves in 1 to 4 weeks after angiotensin-converting enzyme or angiotensin receptor blocker therapy is stopped but may linger up to 3 months (see Chapter 14, "Allergy and Anaphylaxis").

DIAGNOSIS AND TREATMENT

Most causes of acute cough do not warrant ancillary tests. A chest radiograph is wise for patients with purulent sputum and/or fever, and spirometry can document the presence of airflow obstruction in patients with asthma; a flow-volume loop can detect vocal cord dysfunction masquerading as recurrent asthma-like wheezing or cough. Pertussis is

TABLE 62-4 Sequential Approach to Chronic Cough

- Obtain chest radiograph, if not already done.
- Reduce exposure to lung irritants (e.g., smoking) and discontinue angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers.
- Treat for postnasal discharge with an oral first-generation antihistamine/decongestant with or without an inhaled nasal steroid. If the cough improves, continue treatment and consider evaluating for sinus disease with imaging studies.
- Evaluate for bronchospasm with spirometry (include flow-volume loop to detect vocal cord dysfunction) with or without methacholine provocation; if positive, treat with inhaled bronchodilators and corticosteroids if lower source identified.
- Treat for gastroesophageal reflux with lifestyle changes, H_2 blockers, or proton pump inhibitors.
- If cough persists, obtain CT scan of the chest, especially if patient is a smoker and cough persists despite smoking cessation.
- If cough persists, consider referral to otolaryngologist for laryngoscopy, gastroenterologist for endoscopy and/or esophageal pH monitoring, or pulmonologist for bronchoscopy.

a clinical diagnosis in patients with subacute cough as the commonly available culture, and polymerase chain reaction tests have decreasing sensitivity after the third week of coughing.[36]

ACUTE COUGH

In addition to disease-specific therapy,[37] patients with acute cough may benefit from antitussives.[38,39] Demulcents, part of most proprietary cough preparations, soothe the pharynx and modestly alter the cough reflex. Of the herbal agents, menthol and the pungent spices (e.g., pepper, mustard, garlic, radish, and onions) have an antitussive effect.[40] Naproxen reduces coughing in patients with acute bronchitis.[41] In both children and adults, acute coughing illnesses can last up to 3 weeks.[42,43] For intractable coughing paroxysms in the ED, some patients respond to 4 mL of 1% or 2% preservative-free lidocaine (40 or 80 milligrams) by nebulization. This will cause transient suppression of the gag reflex due to posterior pharyngeal anesthesia.

SUBACUTE AND CHRONIC COUGH

Determine if the subacute cough is postinfectious—one following a recent respiratory infection. If postinfectious, then assess for transient bronchial hyperresponsiveness, asthma, pertussis, upper airway cough syndrome, pneumonia, or an acute exacerbation of chronic bronchitis. Treatment is then directed at the presumed cause. If subacute cough is not postinfectious, it is evaluated and treated in the same manner as a chronic cough.

Chronic cough is most often the result of a few common disorders, so an algorithmic approach to treatment using sequential steps is recommended (**Table 62-4**).[44,45]

For patients with refractory chronic cough, moderate reduction in cough severity has been observed with opioid antitussives, dextromethorphan, moguisteine, gabapentin, and pregabalin.[46,47]

HICCUPS

INTRODUCTION

Hiccup, or singultus, is an involuntary spastic contraction of the inspiratory muscles. Hiccups have no specific protective purpose.[48] The afferent arm of the hiccup reflex consists of the phrenic and vagus nerves as well as the thoracic sympathetic chain. Normally, glottis closure inhibits inspiration and prevents aspiration during swallowing. Conversely, inspiration normally inhibits glottic closure and maintains an open airway. The hiccup reflex disrupts the connection between these two processes so that 30 to 40 milliseconds after the onset of inspiration, glottic closure is stimulated. In most cases in which a specific cause can be assigned, hiccups appear to result from stimulation, inflammation, or injury to one of the nerves of the reflex arc.

TABLE 62-5 Differential Diagnosis of Consequence: Hiccups

Acute: Benign, Self-Limited	Chronic: Persistent, Intractable
Gastric distention	CNS structural lesions
Alcohol intoxication	Vagal or phrenic nerve irritation
Excessive smoking	Metabolic: uremia, hyperglycemia
Abrupt change in environmental temperature	General anesthesia
Psychogenic	Surgical procedures: thoracic, abdominal, prostate and urinary tract, craniotomy
	Foreign body in ear touching tympanic membrane (especially hair)

CLINICAL FEATURES

Hiccups are classified as benign and self-limited when they last for <48 hours, persistent if present for >48 hours, and intractable if they last longer than a month (**Table 62-5**).[49]

Benign hiccups are generally initiated by gastric distention from food, drinking (especially carbonated beverages), or air. Alcohol ingestion appears to precipitate hiccups by relaxing the relationship between inspiration and glottic closure, making it easier for other stimuli to trigger the reflex.

Persistent hiccups are usually a result of injury or irritation to a branch of the vagus or phrenic nerves. One rare but readily treatable stimulus is a foreign body (often a hair) in the external auditory canal that is pressing against the tympanic membrane and stimulating the auricular branch of the vagus nerve. Several drugs (e.g., dexamethasone and chemotherapeutic agents) are implicated in inducing hiccups.[50]

DIAGNOSIS AND TREATMENT

Determine if a specific triggering event exists (Table 62-5). Ask if the hiccups persist during sleep; resolution during sleep suggests a psychogenic cause, although this distinction is not absolute. Look in the external auditory canal for a foreign body. Obtain a chest radiograph for patients with chronic hiccups. Fluoroscopy can evaluate for unilateral versus bilateral diaphragmatic movement during hiccups but is not part of the ED evaluation. Unilateral movement suggests focal injury to the phrenic nerve on the affected side.

A variety of physical maneuvers and medications have been used to terminate an acute episode of hiccups (**Table 62-6**).[51-53] Many of these physical maneuvers are based on the concept that stimulating the pharynx will block the vagal portion of the reflex arc and abolish the hiccups.[51] No one method appears to be more effective than another. Swallowing a teaspoon of dry granulated sugar is about as effective as others and does not involve the infliction of noxious or painful stimulation.

Drug treatment for persistent hiccups (**Table 62-7**) is believed to work by inhibiting the reflex arc.[52,53] Several agents are described as effective, but only chlorpromazine has U.S. Food and Drug Administration approval for treatment of intractable hiccups. Chlorpromazine and metoclopramide take effect within 30 minutes. Adverse effects include extrapyramidal symptoms with both agents and hypotension with chlorpromazine. Nifedipine, valproic acid, baclofen, and gabapentin are options usually started by the primary care physician if the hiccups do not respond to chlorpromazine or metoclopramide.

TABLE 62-6 Treatment of Hiccups: Physical Maneuvers

- Remove foreign body from ear
- Swallow a teaspoon of sugar
- Sip ice water
- Drink water quickly

TABLE 62-7 Treatment of Hiccups: Drug Treatment

Drug	Initial Dose in ED	Maintenance Dose on Discharge
Chlorpromazine	25–50 milligrams IV; repeat in 2–4 h if needed	25–50 milligrams PO 3–4 times a day
Metoclopramide*	10 milligrams IV or IM	10–20 milligrams PO 3 times a day for 10 d
Haloperidol*	2–5 milligrams IM	2–4 milligrams PO 3 times a day
Nifedipine*	10–20 milligrams PO	10–20 milligrams PO 3–4 to times a day
Valproic acid*	15 milligrams/kg PO	15 milligrams/kg PO 3 times a day
Baclofen*	10 milligrams PO	10 milligrams PO 3 times a day, titrated up to 75 milligrams per day
Gabapentin*	100 milligrams	100 milligrams PO 3 times a day, titrated up to 120 milligrams per day

*Not approved by the U.S. Food and Drug Administration for treatment of hiccups.

CYANOSIS

INTRODUCTION

Cyanosis is a bluish color of the skin and mucous membranes resulting from an increased amount of reduced hemoglobin (deoxyhemoglobin) or hemoglobin derivatives.[54] The detection of cyanosis is subjective and is not a sensitive indicator of the state of arterial oxygenation; cyanosis is determined by the absolute amount of deoxygenated hemoglobin in the blood, not the amount of oxygenated hemoglobin. Cyanosis is divided into central or peripheral categories (**Table 62-8**). **Central cyanosis is cyanosis of the mucous membranes and tongue due to inadequate pulmonary oxygenation or an abnormal hemoglobin. Peripheral cyanosis is cyanosis of the fingers or extremities from vasoconstriction and diminished peripheral blood flow.** All conditions that cause central cyanosis also result in peripheral cyanosis.

CLINICAL FEATURES

Cyanosis is usually visible when deoxygenated hemoglobin exceeds 5 grams/dL (50 grams/L), but individuals with sensitive vision in ideal circumstances may detect central cyanosis with deoxyhemoglobin concentration as low as 1.5 grams/dL (15 grams/L). Various physiologic, anatomic, and physical factors other than the amount of reduced hemoglobin may influence the appearance of cyanosis, making an accurate clinical detection of the degree or even the presence of cyanosis difficult (**Table 62-9**).

The tongue and buccal mucosa are sensitive sites for observing central cyanosis. Peripheral cyanosis is caused by the slowing of blood flow to an area and an abnormally large extraction of oxygen from normally saturated arterial blood. Peripheral vascular disease, shock states, heart failure, and cold exposure all create states of vasoconstriction and decreased peripheral blood flow, with cyanosis of the nail beds. Massage or gentle warming of a cyanotic extremity will increase peripheral blood flow and abolish peripheral, but not central, cyanosis.

TABLE 62-8 Differential Diagnosis of Cyanosis

Central Cyanosis	Peripheral Cyanosis
Hypoxemia	Reduced cardiac output
Decreased fraction of inspired oxygen: high altitude	Cold extremities
Hypoventilation	Maldistribution of blood flow: distributive forms of shock
Ventilation–perfusion mismatch	Arterial or venous obstruction
Right-to-left shunt: congenital heart disease, pulmonary arteriovenous fistulas, multiple intrapulmonary shunts	
Abnormal hemoglobin	
Methemoglobinemia: hereditary, acquired	
Sulfhemoglobinemia: acquired	
Carboxyhemoglobinemia	

TABLE 62-9 Factors Influencing the Physical Appearance of Cyanosis

Physiologic factors
- Oxygen content of blood
- Degree of oxygen extraction
- Oxyhemoglobin dissociation curve

Anatomic factors
- Status of microcirculation
- Skin pigmentation
- Skin thickness

Physical factors
- Quality/intensity of light in examination area
- Skill of examining physician

Pseudocyanosis is a bluish or slate-gray skin discoloration due to drugs (chlorpromazine, minocycline, amiodarone, nicorandil) or heavy metals (gold, silver).[55,56] In pseudocyanosis, the lips and mucous membranes are of normal color, the abnormal skin discoloration does not blanch with pressure, and the discoloration tends to be more intense in sun-exposed areas. Focal areas of pseudocyanosis may be due to local contact with color dyes, gold, or silver.

DIAGNOSIS AND TREATMENT

Pulse oximetry can detect hypoxemia and provide an accurate oxygen saturation measurement. However, with hemoglobinopathies, standard pulse oximetry is often inaccurate. In methemoglobinemia, pulse oximetry will read 80% to 85% regardless of the oxygen level, potentially overestimating the true oxygen saturation (it may be lower, but pulse oximetry will not read lower). **With carboxyhemoglobinemia, the pulse oximetry reads carboxyhemoglobin as oxyhemoglobin**, reporting a higher percentage for oxygen saturation (see Chapter 207, "Dyshemoglobinemias," and Chapter 222, "Carbon Monoxide"). **Arterial blood gas analysis using co-oximetry (a specific multiwavelength measurement of oxygen saturation) accurately detects oxygenation in those with cyanosis.** In central cyanosis, the oxygen saturation measured from the arterial blood gas is lower because of the underlying hypoxemia. In peripheral cyanosis, the oxygen saturation should be normal. With methemoglobinemia or carboxyhemoglobinemia, arterial blood gas co-oximetry will show a normal Pao_2 (reflecting a normal amount of dissolved oxygen in the plasma), a normal calculated oxygen saturation (from the normal Pao_2), and a decreased measured oxygen saturation (because of a decreased number of oxygen-binding sites).

Administer oxygen to all patients with central cyanosis; failure to improve suggests impaired circulation (shock), abnormal hemoglobin, or pseudocyanosis.

PLEURAL EFFUSION

INTRODUCTION

Pleural effusions result from fluid accumulating in the potential space between the visceral and parietal pleurae.[57] Although pleural effusions can result from many causes, in developed countries, the most common causes are heart failure, pneumonia, and cancer, with tuberculosis a common cause in the developing world (**Table 62-10**).[57-60] Multiple causes may be common, as seen in 30% of patients with a unilateral pleural effusion in a single study.[61]

Continuously secreted fluid from the parietal pleura into the pleural space is absorbed by the visceral pleural microcirculation, averaging about 8 L/d in an adult. This fluid reduces friction between the pleural layers and allows for smooth lung expansion and contraction with respiration. Any process that increases fluid production or interferes with fluid absorption will result in accumulation in the pleural space. Pleural effusions are traditionally divided into exudates or transudates.[57,60]

TABLE 62-10 Differential Diagnosis of Pleural Effusion

Common	Less Common
Transudates	
Heart failure	Cirrhosis with ascites
	Peritoneal dialysis
	Nephrotic syndrome
Exudates	
Cancer: primary or metastatic	Viral, fungal, mycobacterial, or parasitic infection
Bacterial pneumonia with parapneumonic effusion	Systemic rheumatologic disorders: systemic lupus erythematosus, rheumatoid arthritis
Pulmonary embolism	Uremia, pancreatitis
	Postcardiac surgery or radiotherapy
	Drug related: amiodarone
Inconclusive; features of both transudate and exudate	
Transudates after diuretic therapy	Pulmonary embolism

Exudative effusions result from pleural disease, usually inflammation or neoplasia that produces active fluid secretion or leakage with high protein content. Transudative effusions result from an imbalance between hydrostatic and oncotic pressures. This imbalance results in the production of an ultrafiltrate with low protein content into the pleural space.

CLINICAL FEATURES

A pleural effusion may be clinically silent or come to detection as a result of symptoms of an underlying disease, an increase in volume of the effusion causing dyspnea, or the development of inflammation and associated pain with respiration. Physical findings of a pleural effusion include percussion dullness and decreased breath sounds. Because pleural fluid typically pools in the dependent portions of the hemithorax, small or moderate-size effusions have percussion dullness and decreased breath sounds at the lung base with relatively normal lung findings above the level of fluid. With large or massive effusions, it may be impossible to distinguish a fluid level on clinical examination.

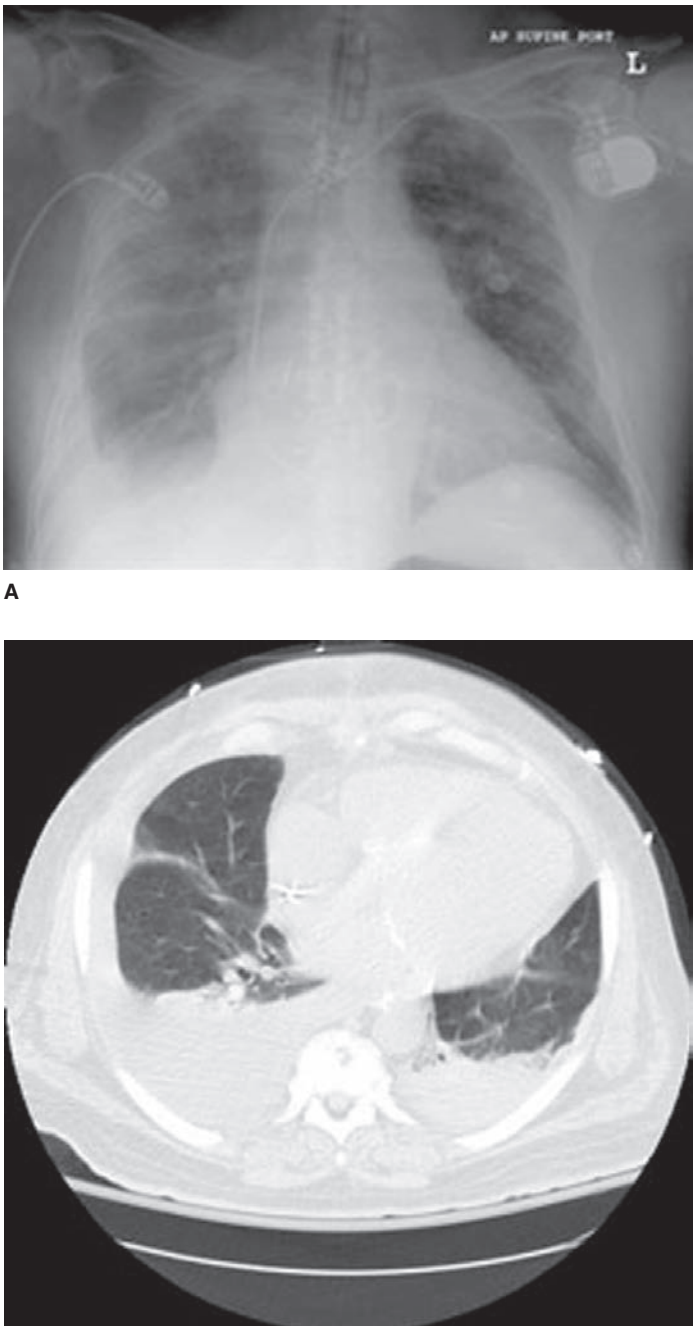
DIAGNOSIS

In an adult, at least 150 to 200 mL of pleural fluid in the hemithorax exists if seen on upright chest radiography. Supine chest radiographs may demonstrate only a hazy appearance of pleural fluid from layering in the posterior pleural space (**Figure 62-1A**). US detects pleural fluid at the bedside. CT scans of the chest may clarify uncertain findings on chest radiograph (**Figure 62-1B**). Small free-flowing pleural effusions are better visualized on decubitus radiographic views (**Figure 62-2**). US can also identify a pleural effusion. **A significant pleural effusion is large enough to produce a pleural fluid strip >10 mm wide on lateral decubitus radiographic views or by US.**

Diagnostic thoracentesis obtains pleural fluid for analysis in cases without a clearly evident cause, to confirm a suspected diagnosis, or to detect pleural space infection. Diagnostic thoracentesis is not initially necessary if the cause is likely heart failure based on a typical clinical appearance; a period of treatment with monitoring for pleural fluid resolution can be initiated with thoracentesis reserved for patients who do not experience resolution in 3 to 4 days.

The Light criteria are widely used to differentiate transudates from exudates using serum and pleural fluid protein and lactate dehydrogenase levels (**Table 62-11**).[62] The overall sensitivity of the Light criteria to identify exudative pleural effusion is 98% to 99%, with specificity from 65% to 86%.[77,60,62] Standard tests for pleural fluid analysis should include protein and lactate dehydrogenase levels (Table 62-11).[60]

The distinction between exudates and transudates may be obscured by the effect of diuretic therapy in patients with transudative pleural effusions. During diuresis, the resorption of water is faster than that of protein, so the protein concentration rises into the range consistent with an exudative etiology. A serum to pleural albumin difference of >1.2 grams/dL (12 grams/L) may help in this scenario, but this approach will reduce the sensitivity of exudative pleural effusion detection by >10%.[62]



A

B

FIGURE 62-1. **A.** Supine radiograph showing a right-sided pleural effusion. The right lung field is hazy compared to the left, and a small layer of fluid is noted inferiorly. **B.** CT scan of the same patient. A moderate pleural effusion is seen in the right lung field, and a small effusion not seen in the left lung field of the plain radiograph is present on the CT scan.

TREATMENT

Therapeutic thoracentesis with drainage of 1.0 to 1.5 L of fluid is indicated if the patient has dyspnea at rest. Acute drainage of larger volumes is associated with reexpansion pulmonary edema, so large-volume drainage is to be avoided. Optimization of medical therapy typically resolves >80% of effusions due to heart failure within 2 weeks.[63,64]

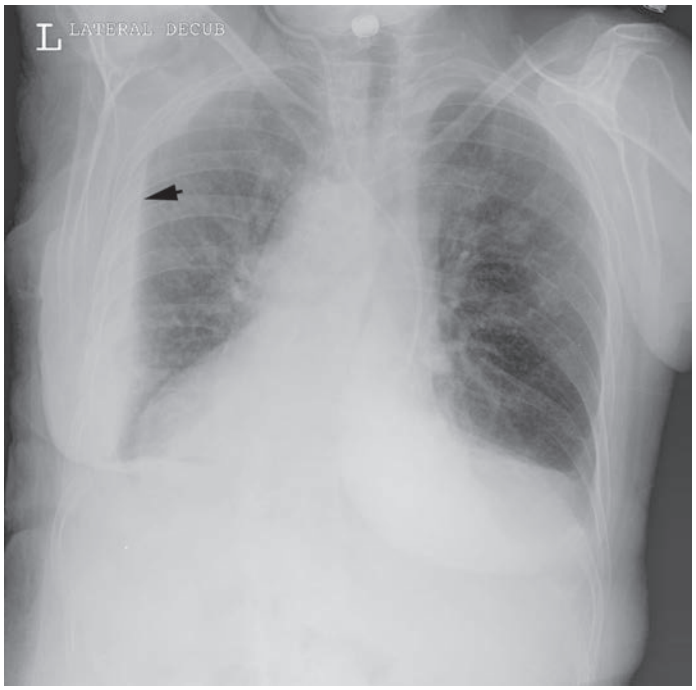


FIGURE 62-2. Left lateral decubitus radiograph showing a layering of a small pleural effusion. *Arrowhead* points to the layer of fluid.

TABLE 62-11 Pleural Fluid Diagnostic Tests

Detection of exudative pleural effusion

- Light criteria for pleural exudate: 1 or more of the following present:
  - Pleural fluid/serum protein ratio >0.5
    or
  - Pleural fluid/serum LDH ratio >0.6
    or
  - Pleural fluid LDH greater than two thirds of the upper limit for serum LDH

Standard tests for evaluation of pleural effusion

- Serum protein and LDH
- Pleural fluid protein and LDH
- Pleural fluid Gram stain and culture to detect bacterial infection
- Pleural fluid cell count
  - Neutrophil predominance: parapneumonic, pulmonary embolism, pancreatitis
  - Lymphocytic predominance: cancer, tuberculosis, postcardiac surgery
- Glucose: low glucose seen in parapneumonic, malignant, tuberculosis, and rheumatoid arthritis causes of pleural effusions

Additional tests according to clinical circumstances

- Cytology for malignancy: highest yield is with adenocarcinoma, much lower with squamous cell carcinoma, lymphoma, or mesothelioma
- Pleural fluid pH: normal pleural fluid pH around 7.64. In parapneumonic effusions, a pleural fluid pH <7.10 predicts development of empyema or persistence and indicates need for thoracostomy tube drainage.
- Pleural fluid amylase: elevated in pleural effusions due to pancreatitis or esophageal rupture
- Mycobacterial and fungal stains and cultures: as suggested clinically
- Tuberculosis pleural fluid markers: polymerase chain reaction for mycobacterial DNA, pleural fluid adenosine deaminase, or pleural fluid interferon-γ

Abbreviation: LDH = lactate dehydrogenase.

Patients with pleural empyema (gross pus or organisms on Gram stain) require drainage with thoracostomy tubes. Parapneumonic effusions are managed according to size and the presence of bacteria on Gram stain or culture (see Chapter 66, "Lung Empyema and Abscess").[65-67]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 63

Hemoptysis

Troy Christian Sims

INTRODUCTION AND EPIDEMIOLOGY

Hemoptysis is the expectoration of blood. Severity ranges from mild to severe, and it can be difficult to stop. The challenge is to stabilize the patient while simultaneously determining the source and providing treatment. Most cases of hemoptysis are minor and resolve spontaneously; predicting which individual will develop massive, large-volume bleeding is difficult. Determining the cause and treatment of hemoptysis requires a multidisciplinary approach.[1]

Assessing the amount of expectorated blood is difficult; patients may either exaggerate or be unable to quantify the amount. The definition of **massive hemoptysis** varies, with reported ranges from 100 mL per 24 hours to >1000 mL per 24 hours,[2,3] and a midpoint value of 600 mL per 24 hours accepted by many.[4] However, because even small volumes of blood can cause asphyxiation, any hemoptysis requires prompt attention.[5] Morbidity and mortality depend on the rate of bleeding, the ability of the patient to clear the blood, and the presence of underlying lung disease, which potentiates the effects of blood in the airways. We define **"minor" hemoptysis** as self-limited, small-volume expectoration of blood in a patient with no comorbid lung disease, normal/stable oxygenation and ventilation, normal vital signs, and no risk factors for continued bleeding.

PATHOPHYSIOLOGY

Hemoptysis results from disruption of blood vessels within the walls of the airways, from trachea to bronchi, bronchioles, and the lung parenchyma (**Table 63-1**). The pulmonary arteries account for 99% of the blood flow to the lungs but are a low-pressure system involved in gas exchange and rarely the source of massive hemoptysis. The bronchial arteries accounts for only 1% of the blood flow to the lungs but 90% of the cases of hemoptysis because it is a high-pressure system.[6] Bronchial arteries typically branch off the thoracic aorta at thoracic vertebrae levels 5 and 6 and are responsible for supplying oxygen and nutrients. Approximately one third of the time, they are ectopic and originate from other parts of the aorta. Extensive anastomoses occur between the bronchial and pulmonary arteries, producing a physiologic right-to-left shunt composing 5% of cardiac output.[7]

In general, hemoptysis develops from either airway, parenchymal, or cardiovascular processes. For example, coughing in the setting of transient airway inflammation (e.g., acute bronchitis) can lead to minor bleeding in otherwise healthy lungs. However, the most common causes of potentially massive hemoptysis are parenchymal in origin, such as tuberculosis, mycetoma, neoplasm, and bronchiectasis.[8]

In chronic inflammatory states (e.g., chronic obstructive pulmonary disease), the bronchial arteries proliferate to enhance the delivery of blood to the alveoli, and this neoangiogenesis creates thin-walled, fragile vessels prone to rupture. In addition, chronic disease states can

TABLE 63-1 Causes of Hemoptysis

Infectious
- Acute bronchitis
- Tuberculosis
- Fungal (aspergilloma)
- Parasitic (paragonimiasis, echinococcus, schistosomiasis)

Structural
- Bronchiectasis (cystic fibrosis, organizing pneumonia, chronic bronchitis)
- Tracheoarterial fistula (tracheostomy)
- Aortobronchial fistula (aortic aneurysm erosion)

Vasculitides
- Goodpasture's syndrome (also known as antiglomerular basement membrane disease)
- Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
- Systemic lupus erythematosus (lupus pneumonitis)
- Behçet's disease (Hughes-Stovin syndrome)
- Osler-Weber-Rendu disease (telangiectasias and arteriovenous malformations)
- Takayasu arteritis

Cardiopulmonary
- Pulmonary embolism
- Pulmonary hypertension
- Mitral stenosis
- Congestive heart failure
- Obstructive sleep apnea
- Congenital heart disease

Neoplastic
- Bronchogenic carcinoma
- Bronchial adenoma

Iatrogenic
- Lung biopsy
- Pulmonary artery catheter injury (Swan-Ganz)
- Bevacizumab treatment

Traumatic
- Ruptured bronchus from deceleration injury
- Lung contusion from blunt injury
- Penetrating trauma

Miscellaneous
- Nitrogen dioxide inhalation (ice arenas)
- Cocaine inhalation
- Catamenial (pulmonary endometriosis)
- Dieulafoy's disease

lead to bronchiectasis (chronic bronchial wall inflammation), resulting in destruction of the cartilaginous support predisposing blood vessels to rupture. In the case of infection (e.g., *Aspergillus* and tuberculosis), there can be necrotic destruction of tissue resulting in cavitary **lesions**. Neoangiogenesis can occur in the cavity walls and bridge them.[5] A **Rasmussen's aneurysm** is a false aneurysm of dilated blood vessels crossing the wall of a tuberculosis cavity. Neoplasms are protean and extensive, affecting airways and lung parenchyma while promoting neoangiogenesis. In particular, squamous cell carcinoma accounts for a large number of cases of massive hemoptysis.[5]

Cardiopulmonary processes (e.g., pulmonary embolism and pulmonary hypertension) compromise the pulmonary artery blood flow, causing compensatory increased bronchial artery blood flow via dilation and hypertrophy at the anastomotic level and resulting in hemoptysis within the alveoli.

Bleeding from small vessels at the anastomotic level can be indolent or massive and may affect foci or be diffuse. Osler-Weber-Rendu disease manifests in friable telangiectasias comprised of pulmonary vessel arteriovenous malformations in the lungs as well as other organs, including the skin and mucous membranes.

Vasculitis and collagen vascular diseases such as Goodpasture's syndrome and granulomatosis with polyangiitis (formerly Wegener's granulomatosis) damage the lung parenchyma, predisposing to alveolar hemorrhage. Anemia can result from chronic alveolar hemorrhage.[9]

Traumatic causes of hemoptysis include deceleration injuries and penetrating trauma leading to disruption of the tracheobronchial tree. Iatrogenic causes include direct arterial injury by pulmonary artery catheterization or biopsy of lung tissue during bronchoscopy. Biopsy of a carcinoid tumor can be associated with impressive hemoptysis.[5]

Hemoptysis secondary to fistulae between the airways and an aortic aneurysm can precipitate catastrophic hemoptysis. Tracheoinnominate fistulae result from erosion of a tracheostomy into the innominate artery that courses posterior to the upper sternum.

Historically, the cause of hemoptysis in roughly 30% of the cases cannot be determined, and these cases are considered cryptogenic.[1] Advances in CT, specifically multidetector CT, have led to a decrease in cryptogenic cases.

CLINICAL FEATURES

First, identify whether the condition is truly hemoptysis and exclude hematemesis and epistaxis. Upper GI bleeding is identified by a history of dark stools, nausea, or abdominal pain and a positive stool guaiac test. Epistaxis can be identified on examination. Expectorated blood is bright red if the source is the upper airway or lungs.

HISTORY

If hemoptysis resolves prior to ED evaluation, history is then paramount.

Patients give an accurate history regarding the source of bleeding about half the time. Ask about risk factors for hemoptysis, such as smoking, thromboembolic disease, connective tissue disease, and vasculitis. Tuberculosis is a leading cause of hemoptysis worldwide, so ask about a history of emigration or travel from a high-prevalence area including Africa, innercity New York, the Middle East, and Southeast Asia. Hematuria or renal insufficiency could suggest Goodpasture's syndrome or granulomatosis with polyangiitis, which is also associated with saddle nose deformity from septal perforation. The lung fluke, *Paragonimus* species, infects humans after ingestion of infected crab and crayfish, leading to hemoptysis in chronic infection. The tapeworm, *Echinococcosis* species, is associated with hydatid cysts within the lungs. Cyclical hemoptysis coordinating with a woman's menstrual cycle could indicate a catamenial source from pulmonary endometriosis.

Cocaine and heroin inhalation and nitrogen dioxide exposure in indoor ice arenas can trigger diffuse alveolar hemorrhage. Finally, ask about use of anticoagulants and recent procedures such as Swan-Ganz catheter insertion and bronchoscopy.

PHYSICAL EXAMINATION

Examine the sputum to see if it is blood-streaked or contains clots of blood. Patients often bring a sample of expectorated sputum to the ED, which helps assessment. Look for signs suggestive of massive hemoptysis or underlying lung disease, such as tachypnea, tachycardia, hypotension, labored respirations, and hypoxemia.

If airway, breathing, and circulation are adequate, focus on the physical exam. Evaluate the nares and posterior pharynx for evidence of epistaxis. Next, assess airway patency and potential difficulty of intubation. Auscultate the lungs for any wheezing suggesting airway inflammation or focally reduced breath sounds indicating a location of bleeding. Occasionally, crackles may be present, suggesting diffuse alveolar hemorrhage or heart failure. On the cardiac exam, auscultate for murmurs of valvular disease. Check for telangiectasia and petechiae on the skin exam.

DIAGNOSIS

Most patients with minor hemoptysis need no specific tests unless on anticoagulation medication. For patients with massive or recurring hemoptysis, obtain a metabolic profile, renal function tests, CBC, coagulation studies, and urinalysis. Baseline hemoglobin concentration may

be falsely normal in acute, rapid bleeding as equilibration may not occur for 6 hours. Thrombocytopenia and coagulopathy increase recurrence risk and morbidity from hemoptysis. Urinalysis and renal function tests help in developing the differential diagnosis and can identify those at risk for contrast nephropathy since multidetector CT is often indicated.

IMAGING

Chest radiography is the initial imaging modality, yielding a diagnosis up to 50% of the time[1]; in massive hemoptysis, the radiograph is rarely normal. Diffuse alveolar hemorrhage manifests as scattered alveolar infiltrates on chest radiograph, whereas focal alveolar hemorrhage, infiltrates, masses, and cavitation are potential sources of hemoptysis.

High-resolution CT delineates abnormal bronchial and nonbronchial arteries using reformatted images and limits scan time and respiratory motion artifact. Multidetector CT can be performed during a single breath hold using a 16-detector row or greater scanner.[7] It can also identify bleeding from a pseudoaneurysm as in Rasmussen's aneurysm or from an anomalous vessel as in Dieulafoy's disease, a tortuous dysplastic artery within the submucosa. Bronchial arteries are the main source of bleeding amenable to treatment and are almost always detected on multidetector CT.[10] Although CT angiography has been preferred for diagnosing pulmonary embolism, multidetector CT is preferred in evaluating massive hemoptysis.

TREATMENT: MILD HEMOPTYSIS

Hemoptysis creates anxiety in the patient and family members, so the goal is to identify the cause, reassure those with minor features and no threat of imminent harm, and provide an appropriate ED disposition. The amount of blood expectorated, respiratory status, and risk factors for continued bleeding dictate the disposition. Assess patients with mild hemoptysis as described in **Figure 63-1**.

DISPOSITION AND FOLLOW-UP

Most cases of hemoptysis are mild and self-limited. For mild hemoptysis, arrange follow-up with a primary care physician, otolaryngologist, or pulmonologist. Choose a pulmonologist if suspecting lung cancer or lung structural disease, and treat acute bronchitis with appropriate antibiotics.

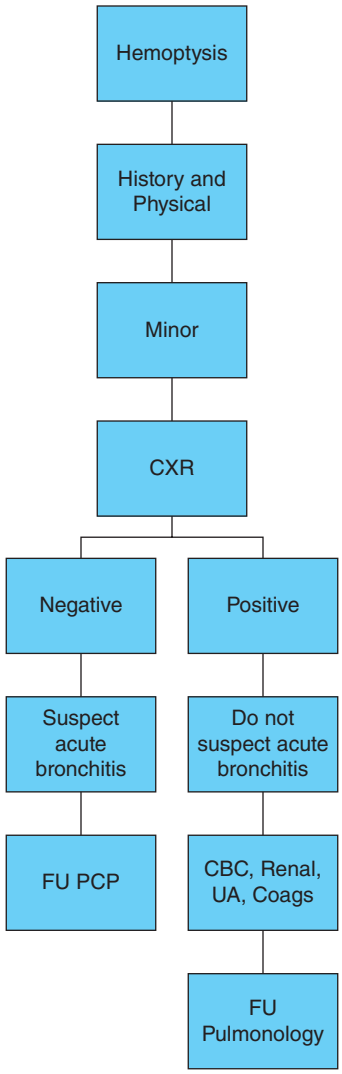


FIGURE 63-1. Diagnosis and management of minor hemoptysis. CXR = chest radiograph; FU = follow-up; PCP = primary care physician; UA = urinalysis.

TREATMENT: SEVERE HEMOPTYSIS

Massive hemoptysis requires airway control, and consultation with interventional radiology (**Figure 63-2**) for consideration of bronchial artery embolization and with cardiothoracic surgery or pulmonology for emergent bronchoscopy. Recent studies suggest that both multidetector CT and bronchoscopy provide the best outcomes in treating massive hemoptysis, with most recommending multidetector CT prior to bronchoscopy.[11,12]

AIRWAY CONTROL

In patients with more severe bleeding, assessing and ensuring the airway patency and ongoing oxygenation are key. If the patient has a tracheostomy, look for a trachea-innominate fistula; control this with direct digital pressure on the anterior portion of the trachea against the posterior aspect of the sternum using the tracheostomy as the point of access. If the patient does not have a tracheostomy and requires airway control, proceed immediately with rapid sequence intubation,[10] using a larger-diameter endotracheal tube to allow for bronchoscopy. Once intubation is successful, place the patient so the affected lung is in a dependent position to prevent spilling of blood into the unaffected side. If bleeding is uncontrollable, you may preferentially intubate the main bronchus of the unaffected lung. Alternatively, to stop bleeding, some use a Fogarty catheter (14F/100 cm) to tamponade the bronchus of the affected lung.[5] The latter can be accomplished by passing the Fogarty catheter adjacent to the endotracheal tube once the patient is intubated (**Figure 63-3**). If attempts at intubation fail, cricothyrotomy is an option.

Once the airway is secured, restore volume with crystalloid and transfusion of blood products to correct for coagulopathy as indicated.

BRONCHOSCOPY

Urgent bronchoscopy can identify the origin of bleeding and provide stabilizing treatment. Bronchoscopy is possible in the ED, usually by a consultant with a tenuous patient. Awake flexible, fiberoptic bronchoscopy provides visualization of the more peripheral and upper lobes but does not provide optimal suctioning and does not allow for local treatment. Rigid bronchoscopy usually requires general anesthesia but is possible with deep sedation; it allows for improved airway control. Rigid bronchoscopy cannot fully view the upper lobes and peripheral lesions, but it offers greater suctioning ability than fiberoptic bronchoscopy and can provide treatment, such as the passage of Fogarty balloon catheters for tamponade of bleeding, epinephrine instillation, and ice water lavage. After rigid bronchoscopy, a flexible bronchoscope through the lumen of a rigid bronchoscope allows for more detailed inspection. However, massive bleeding impairs visualization during bronchoscopy, compromising both diagnostic ability and treatment.

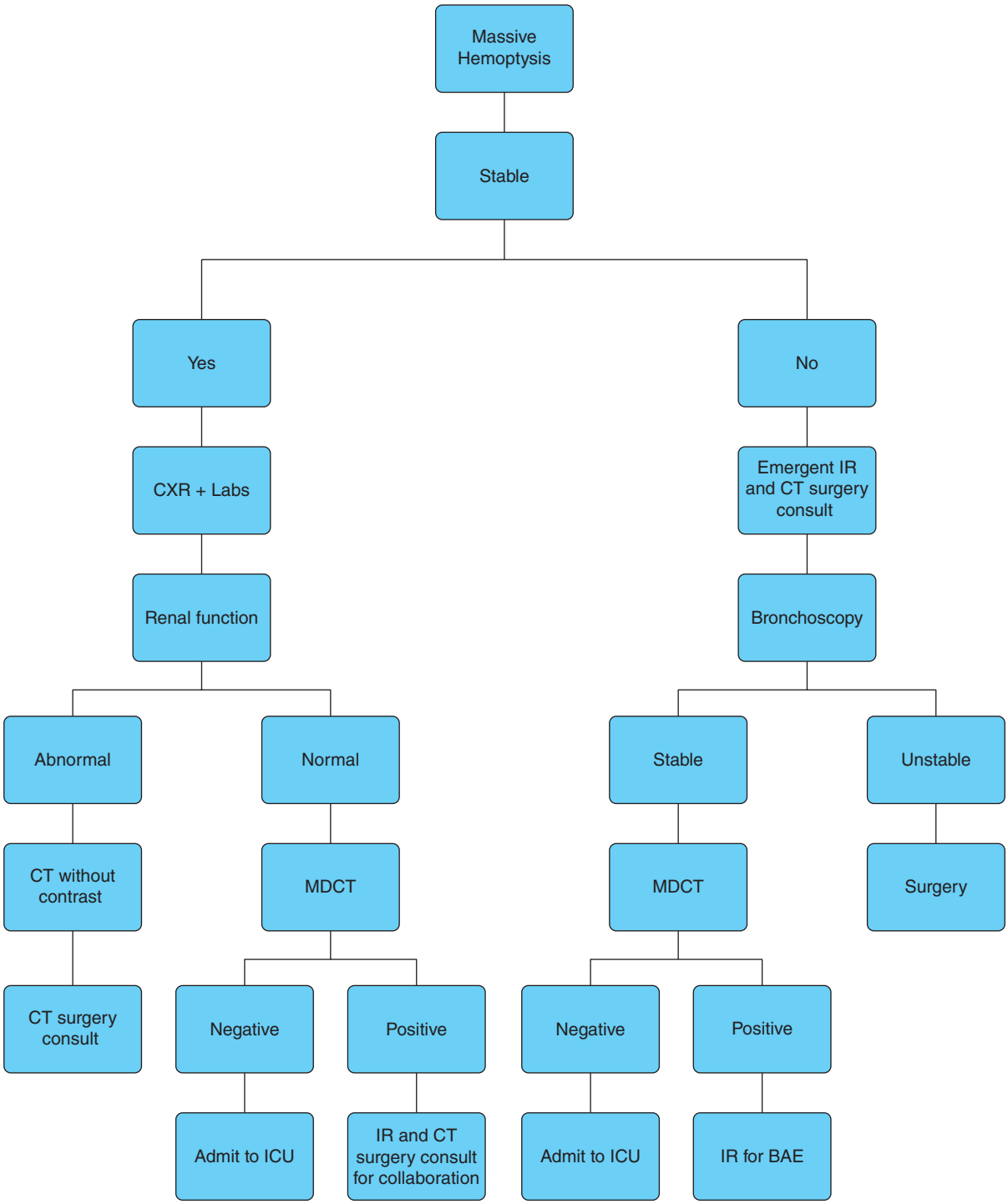


FIGURE 63-2. Algorithm for massive hemoptysis. Determine whether patient is stable based on history provided by patient, rate of ongoing bleeding, ability of patient to clear the blood, and comorbidities. BAE = bronchial artery embolization; CT surgery = cardiothoracic surgery; CXR = chest radiograph; ICU = intensive care unit; IR = interventional radiology; MDCT = multidetector computed tomography.

DEFINITIVE BLEEDING CONTROL

Historically, surgery was the treatment of choice if bronchoscopic interventions failed, but now it is reserved for massive hemoptysis resulting from specific conditions including iatrogenic pulmonary artery injury, thoracic trauma, or bleeding from a tracheoinnominate artery fistula at a tracheostomy site.[9,13-15] Bronchial artery embolization followed by bronchoscopy, if necessary, is considered the initial and most effective treatment of massive and recurrent hemoptysis.[8,16,17] Risks of bronchial artery embolization include transverse myelitis due to spinal cord ischemia and pulmonary artery infarction from spread of embolic material beyond its intended site.[10]

DISPOSITION

Admission to an intensive care setting or transfer to a tertiary care center is necessary for management of severe hemoptysis.

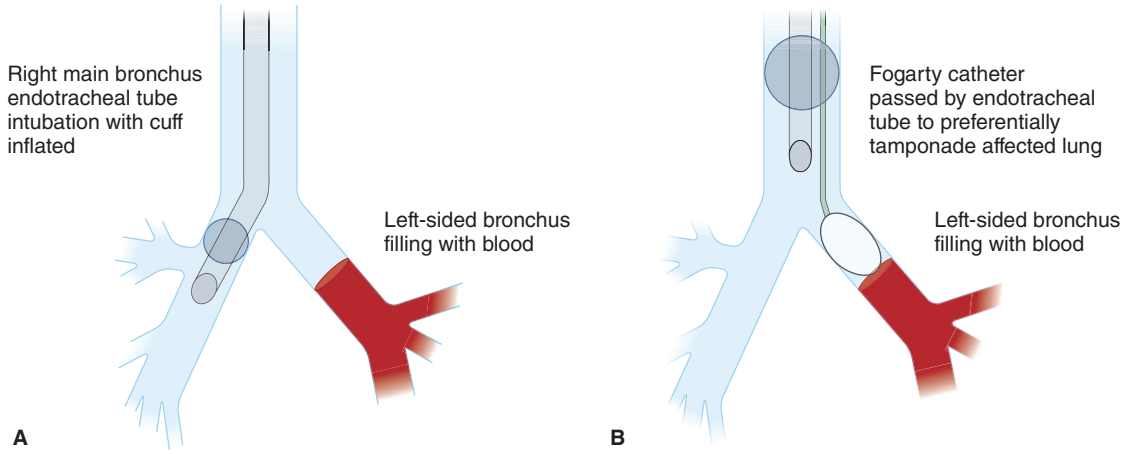


FIGURE 63-3. These are examples of techniques to control bleeding from the left lung. **A.** Selective right main bronchus intubation for left-sided massive hemoptysis. **B.** Using Fogarty catheter to direct control of hemoptysis coming from affected lung. The same techniques are used to control bleeding from the right lung. [Adapted with permission from Lordan JL, Gascoigne A, Corris PA. The pulmonary physician in critical care. Illustrative case 7: Assessment and management of massive haemoptysis. *Thorax* 58: 814, 2003. Copyright BMJ Publishing Group.]

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CHAPTER 64

Acute Bronchitis and Upper Respiratory Tract Infections

Cedric W. Lefebvre

INTRODUCTION

Acute bronchitis is a self-limited respiratory infection causing inflammation of the large airways characterized by cough without evidence of pneumonia. The common cold is a viral infection of the upper respiratory tract, primarily affecting the nasal mucosa causing congestion, rhinorrhea, and sneezing. Influenza, or the flu, is a respiratory illness with fever, myalgias, cough, and fatigue. The clinical syndromes associated with these conditions overlap, and their causative pathogens are often similar. Infections of the upper respiratory tract also cause specific clinical conditions such as otitis media (see Chapter 242, "Ear Disorders"), pharyngitis and epiglottitis (see Chapter 246, "Neck and Upper Airway"), bronchiolitis (see Chapter 116, "Neonatal Emergencies and Common Neonatal Problems"), tracheitis (see Chapter 126, "Stridor and Drooling in Infants and Children"), and sinusitis (see Chapter 244, "Nose and Sinuses").

ACUTE BRONCHITIS

Bronchitis is the ninth most common diagnosis for adult patients presenting to the ED in the United States[1] and ranks as one of the 10 most common outpatient diagnoses worldwide.[2]

PATHOPHYSIOLOGY

Respiratory viruses are the most common documented causative agent in acute bronchitis[2-4]; however, epidemiologic studies are hampered by inadequate specimen sampling.[3] The most common viral isolates are influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, coronavirus, adenovirus, and rhinovirus.[1,3] Bacteria have been detected by polymerase chain reaction in 6% to 15.5% of acute bronchitis cases,[3,4] excluding patients with chronic bronchitis, for whom bacterial detection rates are higher (see Chapter 70, "Chronic Obstructive Pulmonary Disease," for management). *Haemophilus influenzae* and *Streptococcus pneumoniae* were the most common bacterial isolates.[3] Atypical bacterial species such as *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Chlamydia pneumoniae* have also been isolated.[3,4]

Epithelial infection of the bronchi leads to inflammation and thickening of the bronchial and tracheal mucosa. This inflammatory condition results in airflow obstruction and bronchial hyperresponsiveness, which can cause decreased forced expiratory volume in 1 second. These physiologic changes can manifest as cough, wheezing, and dyspnea. Sputum production may or may not be prominent. Expectorated sputum is composed of lower respiratory tract secretions along with nasopharyngeal and oropharyngeal secretions, cellular debris, and microorganisms.[5] Discoloration of sputum from clear or white to a yellow or green color may be due to cellular debris or a combination of microorganisms and cellular debris.[5,6]

CLINICAL FEATURES

The clinical manifestations of acute bronchitis include fever, mild dyspnea, and cough (with or without sputum production) persisting for more than 5 days and lasting up to 3 or 4 weeks.[2] During the first few days of infection, the symptoms of an acute upper respiratory infection and acute bronchitis may be indistinguishable. However, the cough will persist for more than 5 days, and abnormal pulmonary function testing (e.g., reversible decrease in forced expiratory volume in 1 second) consistent with bronchial hyperresponsiveness can be observed in acute bronchitis.[7-9] Cough due to acute bronchitis can persist for 10 to 20 days. History of yellow or green sputum is a poor predictor of bacterial infection and may be present in patients with acute viral bronchitis.[6,8]

DIAGNOSIS

Acute bronchitis is a clinical diagnosis. Acute bronchitis is diagnosed when acute cough (dry or productive) is present for more than 5 days and when evidence of bacterial pneumonia, acute asthma, and exacerbation of chronic bronchitis is absent. Routine sputum cultures are not necessary.[9] Since bronchitis is a self-limited respiratory disorder, other diagnoses should be considered if cough persists for more than 3 weeks.[9,10] Acute bronchitis and bacterial pneumonia can have very similar clinical characteristics. Unlike acute bronchitis, however, pneumonia is not self-limiting and is associated with significant morbidity and mortality if not treated properly. Therefore, it is important to distinguish between the two respiratory infections, especially in the elderly, among whom distinctive signs and symptoms of pneumonia may be lacking.[11]

If there is suspicion for pneumonia, obtain a chest radiograph.[10] The absence of fever, tachycardia, tachypnea, hypoxia, and abnormalities on chest auscultation makes the diagnosis of pneumonia unlikely.[9-11] As a method of differentiating bacterial from viral etiology in lower respiratory tract infections and reducing unnecessary antibiotic prescribing, both calcitonin and rapid point-of-care molecular viral testing have been advocated as a trigger to guide antibiotic treatment decisions.[12,13] However, large, well-conducted, randomized controlled trials failed to show reduction in unnecessary antibiotic prescriptions using calcitonin (ProAct)[14] or rapid point-of-care molecular viral testing (ResPOC)[15] as decision points.

TREATMENT

Antibiotics do not provide significant benefit in patients with acute bronchitis.[15-18] Although patients given antibiotics report shorter mean cough duration and a reduction in days feeling ill, the net benefit is small (approximately ½ day), and adverse effects of antibiotic therapy are significant.[2] Despite the lack of evidence supporting antibiotic use for acute bronchitis in any patient population, the majority of acute bronchitis patients receive antibiotics, especially elderly patients and smokers.[1,10,19-21] Antibiotics should be considered when there is strong suspicion for a specific treatable pathogen (e.g., *B. pertussis;* see "Pertussis" below).[9,10] Additional study is needed to help clinicians determine which patients with acute bronchitis are most likely to benefit from antibiotic treatment.[2]

The routine use of β_2-agonists for acute bronchitis should be avoided.[1,10,19,22] However, among patients with evidence of airflow obstruction (wheezing), β_2-agonist use is associated with lower symptom scores and faster resolution of cough.[22,23] Recent evidence does not support the use of oral corticosteroids in acute bronchitis patients with no history of chronic obstructive pulmonary disease or asthma.[24] Antitussives, expectorants, antihistamines, and mucolytics can be considered for cough relief in acute bronchitis; however, limited quality data exist on the efficacy of these agents.[10,19] Benzonatate and guaifenesin may provide modest cough relief.[25]

COMMON COLD

EPIDEMIOLOGY

The common cold afflicts adults up to two or three times every year, whereas children suffer up to eight colds annually, with peak activity during autumn months.[26,27] Responsible for 26 million missed school days and 23 million lost work days, the common cold generates an enormous economic burden.[28]

PATHOPHYSIOLOGY

Rhinovirus is the most common causal agent for the common cold.[29] Coronavirus and adenovirus infection are also associated with the common cold.[30] After these viruses are spread by contact with or inhaling aerosolized secretions from an infected individual, they invade the upper respiratory tract, triggering symptoms as soon as 10 to 12 hours after inoculation.

CLINICAL FEATURES

A common cold is commonly characterized by sore throat, malaise, rhinitis, rhinorrhea, and cough, which typically persist for up to 7 days. Fever is more common in children than in adults with the common cold.[31,32] Clinical signs of rhinovirus infection include nasal discharge and hoarse voice.

DIAGNOSIS

The diagnosis of the common cold is made on clinical grounds alone, based on the typical symptoms listed earlier. Consider alternative causes of symptoms, such as allergic rhinitis, sinusitis, nonviral pharyngitis, Epstein-Barr virus, influenza, pertussis, and human immunodeficiency virus seroconversion illness.

TREATMENT

The goal of treatment for the common cold is supportive care. Decongestants and antihistamines provide modest symptom improvement in some adults with the common cold.[32-34] Topical nasal decongestants such as oxymetazoline provide moderate benefit in reducing nasal airway resistance.[26,31,35] Cough and cold preparations are associated with harm in young children and should be avoided in children age 6 years or younger.[36]

Natural remedies are widely advertised by manufacturers and used by patients, although strong evidence to support their use is lacking. Vitamin C, zinc, and *Echinacea* are purported to decrease the duration, frequency, and symptoms of the common cold. Studies examining their efficacy have had mixed and inconclusive results.[37,38]

INFLUENZA

EPIDEMIOLOGY

The Centers for Disease Control and Prevention estimates that influenza has afflicted 9 to 60 million people and caused 12,000 to 56,000 deaths annually since 2010.[39] In 2009, a swine-origin H1N1 influenza strain resulted in the century's first global pandemic.[39-41] This event signaled the emergence of a new pandemic threat, underscoring the importance of understanding the epidemiology of influenza and its potential to impact global health. Influenza viruses are unique pathogens because their evolution involves a complex process of antigenic shifts and sporadic cross-species transmissions between humans, swine, and birds. The intensity of seasonal influenza varies from one year to the next, and localized influenza outbreaks can occur during interpandemic years.[42]

PATHOPHYSIOLOGY

The Orthomyxoviridae family includes a diverse array of influenza viruses capable of causing seasonal, endemic, and pandemic infections. Influenza viruses A and B account for most seasonal influenza epidemics.[39,43] Direct contact and droplet transfer are the predominant modes of transmission for influenza into the upper respiratory tract.[44] The incubation period for influenza is 1 to 4 days. Complications of influenza infection include primary influenza viral pneumonia, secondary bacterial pneumonia, and severe hypoxemic respiratory failure.[45] The mortality associated with influenza infection rises in patients with immunosuppression and bacterial coinfection.[46] Children with influenza-associated pneumonia are more likely than children admitted for influenza illness to develop respiratory failure and require intensive care unit admission.[47] Influenza is also a significant cause of morbidity and mortality in pregnant and postpartum women.[48,49]

CLINICAL FEATURES

Influenza infection is characterized by abrupt onset of fever, chills, malaise, headache, dry cough, sore throat, myalgias, rhinitis, and fatigue. Oropharyngeal irritation and mild cervical lymphadenopathy may be present. Fever and intense myalgias are generally more prevalent during influenza infection than other viral upper respiratory infections. Up to one third of patients do not have fever.[50] Healthy individuals with uncomplicated influenza illness generally experience resolution of symptoms in 3 to 7 days, although cough and malaise may persist beyond 2 weeks.

DIAGNOSIS

During seasonal influenza outbreaks, most cases of influenza can be diagnosed on clinical grounds alone. Testing should be performed on patients in whom results will influence management, such as hospitalized patients, pregnant women, and patients at higher risk for complications (**Table 64-1**).

When testing for influenza, specimens should be obtained as close to symptom onset as possible, and nasopharyngeal swabs or aspirates are preferred.[51] Commercially available rapid influenza diagnostic tests are the most practical in ambulatory settings. However, with reported

TABLE 64-1 Persons at Higher Risk for Complications of Influenza Infection

- Children <5 y (especially <2 y)
- Adults ≥65 y
- Persons with chronic illnesses and/or conditions*
- Persons with immunosuppression, including secondary to human immunodeficiency virus infection or medications
- Women who are pregnant or postpartum (within 2 wk of delivery)
- Persons <18 y receiving long-term aspirin therapy
- Residents of nursing homes and other chronic care facilities
- Persons who are morbidly obese (body mass index ≥40 kg/m^2)
- American Indians/Alaska Natives

*Includes persons with chronic pulmonary (including asthma, cystic fibrosis), cardiovascular (except hypertension alone), renal, hematologic (including sickle cell disease), and hepatic diseases; metabolic disorders (including diabetes mellitus); cancers; or neurologic and neurodevelopment conditions including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury.

sensitivities of <80%, rapid antigen detection influenza tests do not completely exclude infection.[52,53] A study of a rapid molecular assay reported sensitivities of over 90% for both influenza A and B; however, specificity was only 54% to 63% (**Table 64-2**).[54-56]

TREATMENT

The antiviral neuraminidase inhibitors available in the United States for treating and preventing influenza A and B infections include oral oseltamivir, inhaled zanamivir, and intravenous peramivir (**Table 64-3**). Antiviral treatment for influenza infection within 48 hours of symptom onset shortens the duration of influenza symptoms (0.5 to 1 day), but increases the risk of nausea and vomiting (4% to 5%) and psychiatric symptoms (hallucinations, abnormal behavior; 1%).[57] Approved in 2018, baloxavir marboxil inhibits an endonuclease involved in viral RNA replication.[58] Single dose treatment with baloxavir reduces symptom duration (see Table 64-3), providing a benefit similar to oseltamivir, but may have 4% fewer side effects.[58] Antiviral treatment may reduce the risk of complications and reduce mortality in hospitalized patients,[59,60] but these benefits have been challenged.[61,62] Antiviral medication should be started as early as possible, preferably within 48 hours of illness onset, in patients with confirmed or suspected influenza infection who are hospitalized, have severe or progressive illness, and are at higher risk for influenza complications (Table 64-2).[63] Antiviral treatment can provide benefit even after 48 hours in pregnant and other high-risk patients.[64,65]

Recommendations for the treatment of influenza are updated frequently based on epidemiologic data and antiviral resistance patterns. Consult the Centers for Disease Control and Prevention for the latest updates on influenza treatment guidelines including pharmacotherapy, patient selection, dosing, and prophylaxis.[66] Annual vaccination is recommended for all persons aged 6 months and older because it is the most effective method of preventing influenza illness and decreasing all-cause mortality in those infected with influenza.[67-70]

TABLE 64-2 Rapid Influenza Testing Modalities

Test	Time to Results	Comments
Rapid influenza test–antigen detection (EIA)	<15 min	Sensitivity <80% in adults; follow-up testing with RT-PCR should be considered to confirm negative result
Rapid molecular assay (influenza viral RNA or nucleic acid detection)	15–30 min	Detects influenza viral RNA or nucleic acids with higher sensitivity than rapid antigen detection tests (range 66%–94%)
RT-PCR	2 h	High sensitivity and specificity; highly recommended test for influenza

Abbreviations: EIA = enzyme immunoassay; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction.

TABLE 64-3 Antiviral Medications for Influenza: Dosing

Medication	Treatment	Chemoprophylaxis
Oseltamivir (Tamiflu®)	75 milligrams orally twice daily × 5 d*	75 milligrams orally once daily × 7 d†
Zanamivir (Relenza®)	10 milligrams (2 inhalations) twice daily × 5 d*	10 milligrams (2 inhalations) once daily × 7 d†
Peramivir (Rapivab®)	600 milligrams IV over 15 to 30 minutes as a single dose	No current recommendation for chemoprophylaxis
Baloxavir Marboxil‡ (Xofluza®)	40 milligrams single dose (two 40-milligram pills if weight over 80 kg)	No current recommendation for chemoprophylaxis

*Longer courses can be considered for patients who remain severely ill after 5 days of treatment.

†For controlling outbreaks in long-term care facilities, the Centers for Disease Control and Prevention recommends a minimum of 2 weeks of chemoprophylaxis and up to 1 week after the last identified case, and 7 days after most recent known exposure in other cases.

‡Initial studies did not establish safety in pregnancy, patients <12 or >65 years of age.

PERTUSSIS

Pertussis, or "whooping cough," is an acute respiratory infection in humans caused by the aerobic gram-negative rod *B. pertussis*. Pertussis toxins cause respiratory epithelial and mucosal injury and interfere with immune cell function. Pertussis pneumonia can occur in children, but in school-age children, adolescents, and adults, upper respiratory infections are the rule.

IMMUNIZATION

Although pertussis is often considered a disease of infants (primarily in those <1 year old who have not completed three doses of vaccination) and a disease in developing countries where immunization is not universal, in North America, the disease is now more common in school-age children and adults. School-age children are the usual sources of infection, and adults may serve as carriers of disease. Cyclical outbreaks occur every 3 to 5 years.[71] However, the incidence and deaths due to pertussis have decreased over the past 20 years.[72]

There are two types of vaccines, whole cell and acellular. Whole-cell pertussis vaccination is effective for about 10 years and is used in developing nations. The acellular diphtheria, tetanus, and pertussis vaccine (DTaP), developed to remove toxins from the cell membrane, does not protect as long as the whole-cell vaccine and is typically used in the developed world.[73] The typical immunization schedule is at 2, 4, 6, and 18 months of age with a booster at age 5. Adolescents should receive a DTaP booster. **Pregnant women** should receive a booster of DTaP to protect neonates and infants and to prevent infection in the mother. For the unimmunized elderly (>65 years old), one dose of DTaP is recommended.[74] Although the vaccine is specifically not registered for the elderly,[75] a study of nearly 120,000 individuals ≥65 years old did not demonstrate any increase in inflammatory or allergic events in those receiving DTaP compared with those receiving only the tetanus and diphtheria vaccine.[76] There is no lifelong immunity after a clinical episode of pertussis.

CLINICAL FEATURES

Clinical features in adults are those of the common cold, but after 1 week, prolonged, paroxysmal, and sleep-disturbing cough develops. Whooping is uncommon in adults. Consider pertussis in situations of chronic cough >2 weeks in duration. Cough may last for several months. Since pertussis is highly communicable, with an attack rate of about 20% even in the immunized, suspect pertussis if there is contact with other individuals with prolonged cough. Except in the elderly, pertussis in adults is not associated with pneumonia. Clinical or radiologic evidence of pneumonia in adults or the elderly suggests secondary bacterial infection.

DIAGNOSIS

Diagnosis is often clinical, especially during epidemics; however, less than 10% of patients with prolonged cough or posttussive emesis will test positive.[77] Definitive diagnosis is usually by polymerase chain reaction of nasopharyngeal secretions or serologic detection of antibodies. Other causes of respiratory illnesses with prolonged cough include *Mycoplasma*, *Chlamydophila*, influenza virus, and other respiratory viruses. In adults, chronic cough can be associated with angiotensin-converting enzyme inhibitors, gastroesophageal reflux, or asthma.

TREATMENT

Treatment of pertussis is azithromycin, 500 milligrams PO on day 1 and 250 milligrams PO on days 2 to 5.[78] Trimethoprim-sulfamethoxazole, 160 milligrams/800 milligrams twice a day for 14 days (check renal dosing), is an alternative to those allergic to, or unable to tolerate, macrolides. Treatment is best if started early, in the first week. After that, antibiotic treatment does not alter the duration of cough. Chemoprophylaxis (same regimen as for treatment) is typically given for household contacts.[78] No antitussive agent has been shown to be clearly effective in reducing the symptoms of the spasmodic (whooping) cough.[79]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 65

Community-Acquired Pneumonia, Aspiration Pneumonia, and Noninfectious Pulmonary Infiltrates

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COMMUNITY-ACQUIRED PNEUMONIA

INTRODUCTION AND EPIDEMIOLOGY

Pneumonia is an infection of the alveolar (gas-exchanging) portion of the lung. Community-acquired pneumonia (CAP) accounts for approximately 3 million cases and 1.6 million hospitalizations per year in the United States.[1,2] One third of pneumonia cases occur in adults over age 65 years, and approximately 4 in 100 children will develop pneumonia each year. According to 2016 data, 544,000 ED visits were due to pneumonia. Pneumonia accounts for 16.1 deaths per 100,000 population, making it the eighth leading cause of death, particularly among older adults, with an age-adjusted death rate of 22%.

Pneumococcal pneumonia produces typical symptoms of fever, cough, and rigors, but atypical infections, infections in compromised hosts, and infections in patients at the extremes of age may produce atypical findings, such as a change in mental status or a decline in function. Patients with **healthcare–associated pneumonia** are at risk for infection with resistant organisms. When predicting the causative organism and selecting treatment choices in pneumonia patients, think of the acquiring environment, especially community versus healthcare settings (**Table 65-1**).[3,4]

TABLE 65-1 Acquisition Environment Classification for Pneumonia

Classification	Criteria
Community-acquired pneumonia	Acute pulmonary infection in a patient who is not hospitalized or residing in a long-term care facility ≥14 d before presentation
Hospital-acquired pneumonia	New infection occurring ≥48 h after hospital admission
Ventilator-acquired pneumonia	New infection occurring ≥48 h after endotracheal intubation
Healthcare–associated pneumonia	Patients hospitalized for ≥2 d within the past 90 d Nursing home/long-term care residents Patients receiving home IV antibiotic therapy Dialysis patients Patients receiving chronic wound care Patients receiving chemotherapy Immunocompromised patients

PATHOPHYSIOLOGY

Pathogenic organisms are inhaled or aspirated directly into the lungs, with aspiration being more common, especially in healthcare settings. Some bacteria, such as *Staphylococcus aureus* or *Pneumococcus*, may produce pneumonia by hematogenous seeding. Patients most at risk for pneumonia are those with a predisposition to aspiration, with impaired mucociliary clearance, or likely to have bacteremia (**Table 65-2**).

Some forms of pneumonia produce an intense inflammatory response within the alveoli that leads to filling of the air space with exudate and WBCs. Organisms can distribute throughout the lung by spreading along the bronchial tree or through pores between adjacent alveoli

TABLE 65-2 Risk Factors for Pneumonia

Aspiration risk
- Swallowing and esophageal motility disorders
- Stroke
- Nasogastric tube
- Intubation
- Seizure and syncope

Bacteremia risk
- Indwelling vascular devices
- Intrathoracic devices (e.g., chest tube)
- Debilitation
- Alcoholism
- Extremes of age
- Neoplasia
- Immunosuppression
- Chronic diseases
- Diabetes
- Renal failure
- Liver failure
- Valvular heart disease
- Congestive heart failure

Pulmonary disorders
- Chronic obstructive pulmonary disease
- Chest wall disorders
- Skeletal muscle disorders
- Bronchial obstruction
- Bronchoscopy
- Viral lung infections

(pores of Kohn). Bacterial pneumonia results in an intense inflammatory response and tends to cause a productive cough. Atypical organisms do not cause an intense inflammatory response and may trigger a mild, nonproductive cough.

In about half of patients with CAP, a specific pathogen is not identified. When identified, *Pneumococcus* is still the most common, followed by viruses and the atypical agents *Mycoplasma, Chlamydia*, and *Legionella*. Two organisms that account for the most severe CAP in otherwise healthy adults are *Streptococcus pneumoniae* and *Legionella*. The treatment of CAP targets covering at least these two organisms.

In up to 5% of cases, multiple agents exist. In special populations, including nursing home residents, chronic alcoholics, and human immunodeficiency virus (HIV)–infected patients, a different spectrum of agents causes pneumonia.

CLINICAL FEATURES

Patients with pneumonia frequently will present with cough (79% to 91%), fatigue (90%), fever (71% to 75%), dyspnea (67% to 75%), sputum production (60% to 65%), and pleuritic chest pain (39% to 49%).[5] However, the individual symptoms and physical findings vary and make clinical diagnosis and differentiation from upper respiratory tract disease difficult.[6,7] The classic presentation of pneumococcal pneumonia is a sudden onset of illness with fever, an episode of severe rigor, dyspnea, bloody sputum production, chest pain, tachycardia, tachypnea, and abnormal findings on lung examination; that pattern is not common. Pneumonia may be preceded by symptoms of a viral upper respiratory infection, such as coryza, low-grade fever, rhinorrhea, or nonproductive cough. Weight loss, malaise, dizziness, and weakness may also be associated with pneumonia. Some of the atypical agents trigger headache or GI illness. Occasionally, pneumonia is associated with extrapulmonary symptoms, including joint pain, hematuria, or skin rashes.

The physical examination may show evidence of alveolar fluid (inspiratory rales), consolidation (bronchial breath sounds), pleural effusion (dullness and decreased breath sounds), or bronchial congestion (rhonchi and wheezing).[6,7]

Radiologic findings in pneumonia are nonspecific and do not provide a specific radiologic diagnosis; typical radiologic features are listed in **Table 65-3**. Immunocompromised hosts, such as those with acquired immunodeficiency syndrome or neutropenia, may not manifest radiographic evidence of pneumonia despite clinical findings suggestive of pneumonia. Clinical and radiographic findings do not necessarily correspond; the patient may be improving clinically despite having a worsening appearance on their chest radiograph.

PNEUMOCOCCAL PNEUMONIA

The elderly, children <2 years old, minorities, children who attend group daycare centers, and persons with underlying medical conditions (including HIV infection and sickle cell disease) are at higher risk for pneumococcal pneumonia. Patients will frequently have lobar pneumonia (**Figure 65-1**), with parapneumonic pleural effusions occurring in about 25% of patients. Patients with functional or anatomic asplenia or those being treated with immunosuppressive drugs, such as transplant patients or inflammatory bowel disease or connective tissue disease patients, may have a very rapid progression of disease, with acute prostration and septic shock progressing to multisystem organ failure. Patients with chronic lung disease, nursing home patients, or otherwise healthy elderly patients tend to have a slower progression of pneumonia, with symptoms of malaise with minimal cough or sputum production.

Laboratory findings in pneumonia include leukocytosis, elevation of the serum bilirubin or hepatic enzymes, or hyponatremia.

Pneumococcal pneumonia responds to a variety of antibiotics, although there is an increased incidence of penicillin-, macrolide-, and fluoroquinolone-resistant pneumococci.[8] Penicillin resistance ranges from 5% to 80%, depending on location, with increasing resistance reported in Spain, Italy, and Eastern Europe. The risk factors for relative penicillin resistance include patients at the extremes of age, day care attendance, immunosuppression from alcoholism or cancer, and recent use of broad-spectrum antibiotics or travel to areas where penicillin resistance is common. Resistance is increasing to tetracycline and trimethoprim-sulfamethoxazole. Patients with intermediate penicillin-resistant pneumococci can receive routine antibiotics so long as an adequate dose is administered.[9] A typical regimen for patients admitted to the hospital with CAP has been the use of a third-generation cephalosporin and a macrolide, and outpatient treatment often starts with macrolide monotherapy. There have recently been reports of increasing macrolide

TABLE 65-3 Clinical Characteristics of Common Bacterial Pneumonias

Organism	Symptoms	Sputum	Chest Radiograph
Streptococcus pneumoniae	Sudden onset, fever, rigors, pleuritic chest pain, productive cough, dyspnea	Rust-colored; gram-positive encapsulated diplococci	Lobar infiltrate, occasionally patchy, occasional pleural effusion
Staphylococcus aureus	Gradual onset of productive cough, fever, dyspnea, especially just after viral illness	Purulent; gram-positive cocci in clusters	Patchy, multilobar infiltrate; empyema, lung abscess
Klebsiella pneumoniae	Sudden onset, rigors, dyspnea, chest pain, bloody sputum; especially in alcoholics or nursing home patients	Brown "currant jelly"; thick, short, plump, gram-negative, encapsulated, paired coccobacilli	Upper lobe infiltrate, bulging fissure sign, abscess formation
Pseudomonas aeruginosa	Recently hospitalized, debilitated, or immunocompromised patient with fever, dyspnea, cough	Gram-negative coccobacilli	Patchy infiltrate with frequent abscess formation
Haemophilus influenzae	Gradual onset, fever, dyspnea, pleuritic chest pain; especially in elderly and COPD	Short, tiny, gram-negative encapsulated coccobacilli	Patchy, frequently basilar infiltrate, occasional pleural effusion
Legionella pneumophila	Fever, chills, headache, malaise, dry cough, dyspnea, anorexia, diarrhea, nausea, vomiting	Few neutrophils and no predominant bacterial species	Multiple patchy nonsegmented infiltrates, progresses to consolidation, occasional cavitation and pleural effusion
Moraxella catarrhalis	Indolent course of cough, fever, sputum, and chest pain; more common in COPD patients	Gram-negative diplococci found in sputum	Diffuse infiltrates
Chlamydophila pneumoniae	Gradual onset, fever, dry cough, wheezing, occasionally sinus symptoms	Few neutrophils, organisms not visible	Patchy subsegmental infiltrates
Mycoplasma pneumoniae	Upper and lower respiratory tract symptoms, nonproductive cough, bullous myringitis, headache, malaise, fever	Few neutrophils, organisms not visible	Interstitial infiltrates (reticulonodular pattern), patchy densities, occasional consolidation
Anaerobic organisms	Gradual onset, putrid sputum, especially in alcoholics	Purulent; multiple neutrophils and mixed organisms	Consolidation of dependent portion of lung; abscess formation

Abbreviation: COPD = chronic obstructive pulmonary disease.



FIGURE 65-1. Lobar pneumonia.

resistance among pneumococcus, with respiratory quinolones becoming the preferred regimen in some regions.

OTHER BACTERIAL PNEUMONIAS

S. aureus is a consideration in patients with chronic lung disease, patients with laryngeal cancer, immunosuppressed patients, nursing home patients, or others at risk for aspiration pneumonia. *S. aureus* pneumonia may occur in otherwise healthy patients after viral illness, such as during an influenza epidemic, although pneumococcal pneumonia is still more common. Patients with staphylococcal pneumonia typically have an insidious onset of disease with low-grade fever, sputum production, and dyspnea. The chest radiograph usually demonstrates extensive disease with empyema, pleural effusions, and multiple areas of infiltrate (**Figure 65-2**). Patients with healthcare-acquired pneumonia are at risk for infection with methicillin-resistant *S. aureus*.[4,10] The rare methicillin-resistant *S. aureus*–associated Panton-Valentine leukocidin mutation infection creates severe, necrotizing infection due to a cytotoxin; unless it is recognized and treated before toxin is entrenched, outcomes are poor.

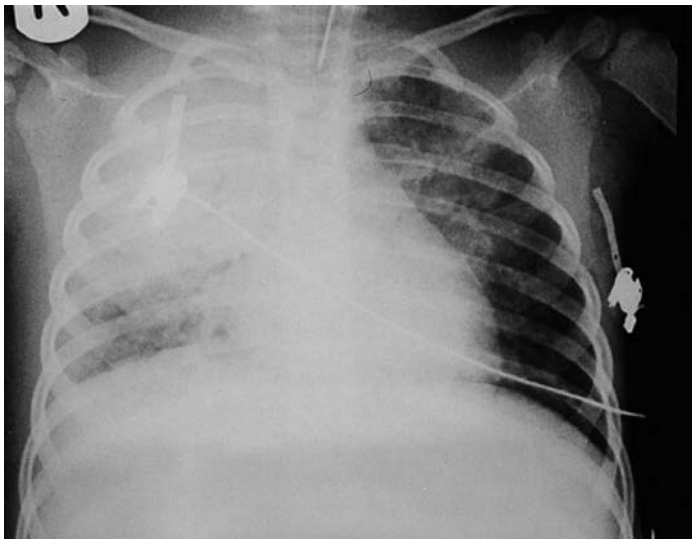

FIGURE 65-2. Staphylococcal pneumonia with extensive infiltration and effusion or empyema.

Klebsiella pneumonia often occurs in compromised patients: patients at risk of aspiration, alcoholics, the elderly, and other patients with chronic lung disease. In contrast to *S. aureus*, patients with *Klebsiella* have acute onset of severe disease with fever, rigors, and chest pain. Herpes labialis is occasionally associated with *Klebsiella* pneumonia. Patients with *Klebsiella* may develop abscesses, although more commonly they have a lobar infiltrate. The classic currant jelly sputum is not common in routine clinical practice.

Pseudomonas causes a severe pneumonia with cyanosis, confusion, and other signs of systemic illness. The chest radiograph may show bilateral lower lobe infiltrates, occasionally associated with empyema. *Pseudomonas* is not a typical cause of CAP, but may develop in patients with a prolonged hospitalization or patients who have received broad-spectrum antibiotics or high-dose steroid therapy, who have structural lung disease, or who are nursing home residents.

Haemophilus influenzae pneumonia occurs in the elderly and should be considered in patients with chronic lung disease, sickle cell disease, or immunocompromised disorders and in alcoholics and diabetics; its frequency in the young (and even adults) is markedly diminished now with vaccination. Patients may either have a gradual progression of disease with low-grade fever and sputum production or occasionally have the sudden onset of chest pain, dyspnea, and sputum production. Bacteremia may be seen in older adults. Pleural effusions and multilobar infiltrates are common findings in *H. influenzae* pneumonia.

Moraxella catarrhalis pneumonia has clinical features similar in spectrum to those of *H. influenzae*. Typically, patients with *M. catarrhalis* have an indolent course of cough and sputum production. Fever and pleuritic chest pain are common clinical symptoms. The chest radiograph usually shows diffuse infiltrates.

PNEUMONIA FROM ATYPICAL AGENTS

Atypical agents are a cause of pneumonia in older children, in young adults, and in the elderly. The atypical agents are *Legionella, Chlamydia, Mycoplasma*, and viruses. Because these agents lack a cell wall, they do not respond to β-lactam antibiotics but are treated with macrolides or a respiratory fluoroquinolone.

Legionella can cause a range of illness from benign self-limited disease to multisystem organ failure with acute respiratory distress syndrome. Patients at higher risk include cigarette smokers, patients with chronic lung disease, transplant patients, and the immunosuppressed. There is no seasonality to *Legionella* pneumonia, making it a more prominent cause of pneumonia in the summer when other pathogens decline in frequency. *Legionella* pneumonia is commonly complicated by GI symptoms, including abdominal pain, vomiting, and diarrhea. In addition, *Legionella* can affect other organ systems, causing sinusitis, pancreatitis, myocarditis, and pyelonephritis. The chest radiograph frequently shows a patchy infiltrate, with the occasional appearance of hilar adenopathy and pleural effusions (**Figure 65-3**). Use of urinary *Legionella* antigen testing in patients with appropriate clinical suspicion can confirm the diagnosis.

***Chlamydia* pneumonia** is a common cause of respiratory infection, with about half of the population demonstrating antibodies by the age of 15 years old. Infection with *Chlamydia* usually causes a mild subacute illness with sore throat, mild fever, and nonproductive cough, although occasionally patients have a more severe course. Patients with chlamydial pneumonia frequently have abnormal physical examination findings with rales or rhonchi. The chest radiograph usually shows a patchy subsegmental infiltrate. Chlamydial infection may be linked to adult-onset asthma.

***Mycoplasma* pneumonia** also occurs year-round, although it tends to cluster in epidemics every 4 to 8 years. Mycoplasma may cause a subacute respiratory illness with cough, sore throat, and headache. Mycoplasma pneumonia is also frequently associated with retrosternal chest pain. Unlike *Legionella*, *Mycoplasma* usually is not associated with GI symptoms. The chest radiograph shows patchy infiltrates, with the common occurrence of hilar adenopathy and pleural effusions. *Mycoplasma* occasionally causes extrapulmonary symptoms, including bullous myringitis, rash, neurologic symptoms, arthritis and arthralgia, hematologic abnormalities, and, rarely, renal failure.



FIGURE 65-3. Pneumonia suggesting *Legionella*.

Q fever is an uncommon cause of pneumonia in the United States, although there have been outbreaks in Southwest Asia. The causative organism is *Coxiella burnetii*, transmitted via infected animals through dried urine that is inhaled or unpasteurized milk. It can cause an acute infection with lobar infiltrates and pleural effusions or a more indolent infection with multisystem involvement including endocarditis and hepatitis. The chronic form of Q fever has a higher mortality than the acute form, with nearly 100% of Q fever patients with endocarditis dying without treatment. Doxycycline or a respiratory quinolone are first-line treatment. Human-to-human Q fever transmission is rare, and isolation of an infected person is unnecessary.

Viruses can cause severe pneumonia. The outbreak of severe acute respiratory syndrome in 2003, associated with group 2 coronavirus, is one example of a virus causing rapid worldwide involvement.[11] The emergence of pandemic influenza is an ongoing pressing public health issue. The 2017 to 2018 influenza season had >30,000 U.S. hospitalizations for influenza, with pneumonia, from either primary viral or secondary bacterial infection, being the most common reason for admission. The most recent pandemic viral infections have been H1N1 and H5N1 influenza over the past years.[12] Pregnant women are particularly susceptible to developing severe influenza-associated pneumonia, and use of antivirals is recommended for pregnant women with an influenza-like illness. Varicella, typically benign in most childhood infections, can likewise lead to a virulent pneumonia in pregnant patients. Antiviral agents are recommended in pregnancy, but are not currently recommended for varicella or influenza pneumonia in children and nonpregnant immunocompetent adults.[13]

DIAGNOSIS

Pneumonia is a clinical diagnosis based on a constellation of symptoms and signs; any individual symptom and clinical finding may lack accuracy for precise diagnosis. Physician judgment for chest radiographs or treating pneumonia (with or without a chest radiograph) is more sensitive than scoring systems to predict the need for chest radiography to diagnose pneumonia.[14] Diagnosis is based on fever, cough, and the presence of rales or rhonchi on lung examination with radiographic infiltrate confirmation.[15] Other findings, such as egophony or pectoriloquy, are specific for pneumonia but infrequently encountered in physical exam.

The Infectious Diseases Society of America revised its CAP guidelines in 2017; it emphasizes clinical judgment by the provider and shared decision making with the patient regarding decisions on admission and testing and treatment options. No single set of recommendations for diagnostic testing can apply to all patients, and additional ancillary studies are used based on clinical judgment. In otherwise healthy, mildly ill, ambulatory patients, no further ancillary testing may be necessary. If a patient requires admission, additional tests may be necessary, including CBC and determination of serum electrolyte, BUN, creatinine, and glucose levels. Evaluation of arterial blood gas aids if patients are markedly desaturated or have severe respiratory distress.

The usefulness of blood or sputum cultures depends on the degree of illness severity and the likelihood of hospital admission. Most patients do not require identification of a specific organism through blood or sputum analysis to direct antibiotic treatment. The incidence of positive blood cultures in nonhospitalized patients with CAP is low, pathogen identification usually does not alter treatment, and the overwhelming majority of patients respond to empiric antibiotic treatment. The value of sputum culture is similar to the value of blood cultures in these circumstances.

In patients with fever, cough, and radiographic abnormalities, or in whom bacteremia is suspected, the etiology of the infection can be confirmed, but >80% of the time, no added information is possible, often because of poor sampling (sputum) or infrequent growth (blood). Detecting atypical agents usually requires titers from acute and convalescent sera or direct fluorescent antibody testing.

In patients with CAP who are hospitalized, the incidence of positive blood cultures increases with increasing disease severity.[16] Blood cultures are recommended for selected patients, including those admitted to the intensive care unit (ICU) and those with leukopenia, cavitary lesions, severe liver disease, alcohol abuse, asplenia, or pleural effusions (moderate level of evidence).[15] Regarding the usefulness of sputum cultures, many patients are unable to produce adequate sputum, the Gram stain is frequently negative, and results rarely change therapy.[17] Send sputum culture and Gram stain only when a good-quality specimen exists. Obtain a *Legionella* urine antigen test in ICU patients, alcoholics, or patients with a recent (within the past 2 weeks) travel history.

The differential diagnosis of patients with cough and radiographic abnormality includes lung cancer, tuberculosis, pulmonary embolism, chemical or hypersensitivity pneumonitis, connective tissue disorders, granulomatous disease, and fungal infections. Because radiographic signs of pneumonia vary, it is difficult to predict the causative microorganism by its radiographic appearance. In general, patients with bacterial pneumonia are more likely to have unilobar or focal infiltrates than patients with viral or atypical pneumonia. Hilar adenopathy is more common in patients with atypical pneumonia. Pleural effusions can accompany bacterial, viral, or atypical pneumonia. Cavitary lesions occur in patients with bacterial pneumonia or tuberculosis. Lung abscesses are rare complications of pneumonia in the antibiotic era, but they sometimes occur due to *S. aureus* or *Klebsiella*. Pneumonia may mimic the appearance of lung masses, particularly when the cause is pneumococcal ("round pneumonia") or staphylococcal. Q fever and tularemia may appear radiographically as discrete masses.

PNEUMONIA IN SPECIAL POPULATIONS

PNEUMONIA IN ALCOHOLICS

Alcoholics have a higher risk than the normal population for many lung diseases, including pneumonia, tuberculosis, pleurisy, bronchitis, empyema, and chronic obstructive pulmonary disease. Alcoholics often are undernourished, aspirate, have poor dentition, are smokers, and have concomitant liver disease. Compared with the nonalcoholic, the alcoholic has greater oropharyngeal colonization with gram-negative bacteria and is more likely to have pulmonary function abnormalities, including reduced long volumes, increased airway resistance, and decreased diffusion capacity. In addition, alcohol depresses granulocyte

and lymphocyte counts and impairs delivery of neutrophils to sites of infection.

S. pneumoniae is still the most common pathogen causing pneumonia in alcoholics, but *Klebsiella* species and *Haemophilus* species are also important agents of infection. In general, rates of pneumonia and death from pneumonia are higher in alcoholics compared with nonalcoholic patients.

PNEUMONIA IN DIABETICS

Diabetes mellitus is an independent risk factor for pneumonia. Diabetic patients between the ages of 25 and 64 years old are four times more likely to have pneumonia and influenza, and diabetics are two to three times more likely than nondiabetics to die with pneumonia and influenza as an underlying cause of death. Pathogens that occur with increased frequency in diabetic patients include *S. aureus*, gram-negative bacteria, mucormycosis, and *Mycobacterium tuberculosis*. Infections due to *S. pneumoniae* and influenza are associated with increased morbidity and mortality in diabetic patients.

PNEUMONIA IN PREGNANT WOMEN

CAP in pregnancy is one of the most serious nonobstetric infections complicating pregnancy. Maternal mortality from antepartum pneumonia is approximately 3%. Pregnancy does not seem to alter the course of bacterial pneumonia, but the prognosis of viral pneumonia during pregnancy is more serious than in the nonpregnant patient.

Pregnant women who develop varicella pneumonia are five times more likely to be smokers and approximately 16 times more likely to have skin lesions suggestive of the disease. Do chest radiography in pregnant patients with symptoms of respiratory tract infection and varicella exposure. Pulse oximetry or arterial blood gas analysis helps identify patients with early respiratory compromise. IV acyclovir is often started in the ED, although there is little evidence that the timing of administration affects outcome.

Influenza, particularly the H1N1 influenza strain, triggers severe viral pneumonia in pregnant women. Death from H1N1-associated pneumonia in pregnant women was higher among women who have underlying medical conditions (asthma, diabetes, hypertension, malignancy, rheumatologic, renal and cardiovascular disease). The death rate did not stratify out by age, trimester, or ethnicity. Of note, the death rate was lower in women treated with a neuraminidase inhibitor and directly correlated to time from onset of symptoms to initiation of treatment with a neuraminidase inhibitor. Therefore, initiate treatment as soon as possible when a pregnant or postpartum patient presents with an influenza-like illness.

Pneumocystis jirovecii pneumonia (still called **PCP for *p*neumo*c*ystis *p*neumonia**) is the most common cause of acquired immunodeficiency syndrome–related death in pregnant women in the United States, with a mortality rate of approximately 50%. Respiratory failure requiring mechanical ventilation occurs in over half of these patients. Combination treatment with pentamidine, steroids, and eflornithine improves survival compared with patients treated with trimethoprim-sulfamethoxazole alone.

PNEUMONIA IN THE ELDERLY

Pneumonia is the most common infection in the elderly and represents the fifth leading cause of death among the elderly.[18] The incidence of lower respiratory tract infection in the elderly ranges from 25 to 44 cases per 1000 in the general population, with a mortality rate approaching 40%. Chronic obstructive pulmonary disease, congestive heart failure, cardiovascular and cerebrovascular disease, lung cancer, dementia, diminished gag reflex, and other disorders that predispose the elderly to aspiration make them more susceptible to infection.

The elderly are three times more likely to have pneumococcal bacteremia than younger patients. The mortality from pneumococcal pneumonia is three to five times greater in the elderly (up to 40%) than in those younger than age 65 years old. Atypical pathogens, such as *Mycoplasma*, are still more common in younger populations, but they do occur in the elderly. Influenza is the most common serious viral infection in the elderly. Postinfluenza bacterial pneumonia is most commonly caused by *S. pneumoniae, S. aureus*, or *H. influenzae*. This usually presents as a worsening of respiratory symptoms after several days of improvement.

Elderly patients with pneumonia may present with falls, weakness, tremulousness, functional decline, GI symptoms, and delirium or confusion. Elderly patients are more likely to be afebrile on presentation, but are more likely than younger adults to have a serious bacterial infection when the temperature is higher than 38.3°C (100.9°F).

Up to one third of elderly patients with CAP will not manifest leukocytosis. Poor prognostic indicators for pneumonia in the elderly include hypothermia or a temperature >38.3°C (100.9°F), leukopenia, immunosuppression, gram-negative or staphylococcal infection, cardiac disease, bilateral infiltrates, and extrapulmonary disease. Elderly patients with pneumonia frequently require hospitalization, and about 10% may require intensive care.

PNEUMONIA IN NURSING HOME PATIENTS

Pneumonia is a major cause of morbidity, mortality, and hospitalization among nursing home residents.[18,19] Nursing home–acquired pneumonia affects the oldest patients and those who have cerebrovascular disease, and is associated with high mortality risk scores at ED presentation.

Nursing home patients are less likely than those living independently to have a productive cough or pleuritic chest pain, but more likely to be confused and have poorer functional status and more severe disease.[19] Eight variables are significant independent predictors of pneumonia in nursing home patients: increased pulse rate, respiratory rate ≥30 breaths/min, temperature ≥38°C (100.4°F), somnolence or decreased alertness, presence of acute confusion, lung crackles on auscultation, the absence of wheezes, and an increased leukocyte count.[20] A patient with one of these variables has a 33% chance of having pneumonia, whereas three or more variables suggest a 50% likelihood of pneumonia.[20] Fewer than 10% of nursing home patients with pneumonia will have no respiratory symptoms. Fever, although nonspecific, is present in approximately 40% of cases of nursing home–acquired pneumonia.

The most frequently reported pathogens among patients with nursing home–acquired pneumonia are *S. pneumoniae*, gram-negative bacilli, and *H. influenzae*. Because nursing home patients live in close proximity to each other, residents are subject to outbreaks of influenza. Unfortunately, vaccination against influenza is only approximately 33% to 55% effective in preventing postinfluenzal pneumonia in nursing home patients. *M. pneumoniae* and *Legionella* are uncommon causes of pneumonia in nursing home patients.

Those with nursing home–acquired pneumonia are often admitted to the hospital for care, although some studies have suggested that patients can be treated in nursing homes with either IM or PO antibiotics.[21] Nursing home patients are at risk for the organisms linked to healthcare–associated pneumonia, and treatment for methicillin-resistant *S. aureus* is recommended.[3]

PNEUMONIA IN HUMAN IMMUNODEFICIENCY VIRUS PATIENTS

Among HIV-seropositive individuals, the incidence of bacterial pneumonia is 5.5 per 100 person-years, an incidence higher than pneumocystis pneumonia in this population.[22] Among hospitalized patients with HIV, the incidence of bacterial pneumonia is as high as 12.5 per 100 person-years. CAP accounts for three fourths of bacterial pneumonia diagnosed in patients hospitalized with HIV infection. Compared with HIV-seropositive patients hospitalized without pneumonia, those admitted with pneumonia generally have a lower CD4+ T-cell count, a higher Acute Physiology and Chronic Health Evaluation II score, a longer length of hospital stay, a greater chance of ICU admission, and a higher case fatality rate.

S. pneumoniae is the most common cause of bacterial pneumonia in patients with HIV, recovered on blood culture in 60% of patients with HIV compared with 15% to 30% of patients without HIV infection who have pneumococcal pneumonia. *Pseudomonas aeruginosa* is a common cause of bacterial pneumonia in HIV-positive patients. HIV-positive patients with *P. aeruginosa* pneumonia are more likely to have a lower leukocyte and CD4+ T-cell count and a longer hospital stay, but similar case fatality rate.

Opportunistic infections are more likely to occur with a lower CD4+ count. Bacterial infections are more likely to cause pneumonia when the CD4+ count is >800 cells/mm^3. Between 250 and 500 cells/mm^3, infection from *M. tuberculosis*, *Cryptococcus neoformans*, or *Histoplasma capsulatum* poses a greater risk. The risk of pneumocystis pneumonia is more likely when the CD4+ count is <200 cells/mm^3.

Bacterial pneumonia produces a pleural effusion in up to about 60% of patients with acquired immunodeficiency syndrome, most commonly due to *S. pneumoniae* and *S. aureus*. Non-Hodgkin's lymphoma, Kaposi's sarcoma, and adenocarcinoma of the lung are the three leading noninfectious causes of pleural effusion in HIV patients. Patients with Kaposi's sarcoma, cytomegalovirus pneumonia, and hydrostatic pulmonary edema may present with alveolar hemorrhage as seen by bloody fluid on bronchoalveolar lavage or frank hemoptysis. Pulmonary nodules in the HIV patient are often caused by opportunistic infection, bacterial pneumonia, and tuberculosis. Fever, cough, and a nodule size of <1 cm are independent predictors of an opportunistic infection. Miliary pneumonia on CT scan or chest radiograph may represent varicella pneumonia.

PNEUMONIA IN TRANSPLANT PATIENTS

Bacterial pneumonia is less common after renal transplantation, but more common in patients receiving liver, heart, or lung transplants during the first 3 months after surgery, compared with other surgical patients. Gram-negative bacilli (especially *P. aeruginosa* associated with mechanical ventilation), *S. aureus*, and *Legionella* predominate in the first 3 months after transplantation. *Klebsiella pneumoniae, Escherichia coli,* and fungi may also cause pneumonia in this time period. These early-onset nosocomial bacterial pneumonias have a high mortality rate, approximately 33%. Cytomegalovirus, *P. jirovecii*, and fungal infections, especially *Aspergillus* species, are opportunistic infections and may be seen in the first 6 months after surgery. After 6 months posttransplant, bacteria more typical of CAP (*S. pneumoniae, H. influenzae*) are the most likely pathogens and portend less mortality (see Chapter 297, "The Transplant Patient").

TREATMENT

Emergency physicians play a prominent role in the initiation of treatment for pneumonia. The timing of antibiotics for CAP has been a source of controversy. The previous 4-hour guideline has been largely discredited, and The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) is no longer assessing this measure. Patients should receive antibiotics promptly after diagnosis, although it is difficult to ascribe a particular time frame within which this should be accomplished.

Many different specialty societies and task forces have developed guidelines for the treatment of adults with CAP, and these guidelines undergo periodic revision. These guidelines are interpreted and implemented based on local practices, hospital formularies, and the particular characteristics of individual patients. The Infectious Diseases Society of America revised its guidelines in 2017, and a joint Infectious Diseases Society of America/American Thoracic Society guideline is due out in 2018. The drugs listed in **Tables 65-4 through 65-9** are representative of recommended treatments[3,15,23] based on site acquisition and/or comorbidities, but are not meant to be a comprehensive list. Treatment should take into account local resistance patterns.[15] **Outpatient treatment** is provided in Tables 65-4 and 65-5. **Inpatient treatment** is provided in Tables 65-6 through 65-9.

TABLE 65-4 Therapy for Outpatient Treatment of Uncomplicated Patients*

Class	Examples	Comments
Macrolide	Clarithromycin XL, 1000 milligrams PO each day for 7 d *or* Azithromycin, 500 milligrams PO on day 1 and 250 milligrams on days 2–5	Respiratory fluoroquinolones could also be used, but the Centers for Disease Control and Prevention recommends reserving these agents for those who cannot tolerate or have failed other therapy. See Table 65-5.
Tetracycline	Doxycycline, 100 milligrams twice a day for 10–14 d	Second-line choice.

*Other drugs may also be effective.

TABLE 65-5 Therapy for Outpatient Management of Patients With Significant Comorbidities* Without Criteria for Healthcare-Associated Pneumonia

Class	Examples	Comments
Fluoroquinolone	Levofloxacin, 750 milligrams daily for 5 d *or* Moxifloxacin, 400 milligrams daily for 7–14 d	Other respiratory fluoroquinolones may also be used.
β-Lactamase inhibitor penicillin derivative	Amoxicillin-clavulanate, 2 grams twice daily	A third-generation cephalosporin may be used instead of the aminopenicillin.
Plus	Plus	
Macrolide	Azithromycin, 500 milligrams PO on day 1 and 250 milligrams on days 2–5	

*Significant comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; and asplenia. See text. Dosing may need adjustment for patients with renal insufficiency. Other therapies may also be effective.

OUTPATIENT TREATMENT

Outpatient treatment is listed in Tables 65-4 and 65-5. Recommended agents include a newer macrolide or a respiratory fluoroquinolone for a varying duration, depending on the agent. Doxycycline may also be used. Erythromycin is a very cost-effective agent for CAP but is associated with GI side effects in about 25% of adult patients and also causes photosensitivity. Clarithromycin has fewer GI side effects, although some patients may complain about a metallic taste. Azithromycin has the advantage of once-a-day dosing or single-dose therapy with the newer formulations. The newer fluoroquinolone agents, including moxifloxacin and levofloxacin, have extended coverage that includes both common bacterial agents and atypical agents, along with the advantage of once-a-day dosing. The Centers for Disease Control and Prevention's Working Group recommends reserving fluoroquinolones for patients who cannot tolerate other agents, with documented pneumococcal resistance, or failing other therapies. **Do not give fluoroquinolones to patients with myasthenia gravis**. Patients with significant comorbidities, including chronic cardiac, pulmonary, renal, or hepatic disease; severe diabetics; chronic alcoholics; patients on immunosuppressive therapy; or patients with asplenia may require additional therapy. Patients who received broad-spectrum antibiotics within the previous 3 months may be at risk for drug-resistant infection; in these patients, consider a respiratory fluoroquinolone or treatment with combination therapy using either an aminopenicillin or a third-generation cephalosporin with either a macrolide or doxycycline.

TABLE 65-6 Inpatient Therapy for Non–Intensive Care Unit Patients* With Community-Acquired Pneumonia

Class	Examples	Comments
Fluoroquinolone	Levofloxacin, 750 milligrams IV *or* Moxifloxacin, 400 milligrams IV	Other respiratory fluoroquinolones may also be used.
Cephalosporin	Ceftriaxone, 1 gram IV	Other third-generation cephalosporins may also be used in combination with other macrolides or doxycycline.
Plus	Plus	
Macrolide	Azithromycin, 500 milligrams IV	

*Other drugs may also be effective; dosing may need adjustment for patients with renal insufficiency. Oral therapy with selected drugs may be acceptable for non–intensive care unit patients.

TABLE 65-7 Empiric Therapy for Patients With Suspected Healthcare-Associated Pneumonia

Three-Drug Regimen Recommended

Class	Examples	Comments
Antipseudomonal cephalosporin	Cefepime, 1–2 grams every 8–12 h *or* Ceftazidime, 2 grams every 8 h	An aminoglycoside may be substituted in place of the fluoroquinolone. Levofloxacin, 750 milligrams every 8 h, may be substituted for ciprofloxacin. Linezolid, 600 milligrams every 12 h, may be substituted for vancomycin.
Plus	Plus	
Fluoroquinolone	Ciprofloxacin, 400 milligrams every 8 h*	
Plus	Plus	
Anti-MRSA drug	Vancomycin, 15 milligrams/kg every 12 h	
Antipseudomonal carbapenem	Imipenem, 500 milligrams every 6 h *or* Meropenem, 1 gram every 8 h	An aminoglycoside may be substituted in place of the fluoroquinolone. Levofloxacin, 750 milligrams every 8 h, may be substituted for ciprofloxacin. Linezolid, 600 milligrams every 12 h, may be substituted for vancomycin.
Plus	Plus	
Fluoroquinolone	Ciprofloxacin, 400 milligrams every 8 h*	
Plus	Plus	
Anti-MRSA drug	Vancomycin, 15 milligrams/kg every 12 h	
β-Lactam/β-lactamase inhibitor	Piperacillin-tazobactam, 4.5 grams every 6 h	An aminoglycoside may be substituted in place of the fluoroquinolone. Levofloxacin, 750 milligrams every 8 h, may be substituted for ciprofloxacin. Linezolid, 600 milligrams every 12 h, may be substituted for vancomycin.
Plus	Plus	
Antipseudomonal fluoroquinolone	Ciprofloxacin, 400 milligrams every 8 h*	
Plus	Plus	
Anti-MRSA drug	Vancomycin, 15 mg/kg every 12 h	

Note: Healthcare-associated pneumonia risks include (1) patients hospitalized for 2 or more days within the past 90 days, (2) nursing home/long-term care residents, (3) patients receiving home IV antibiotic therapy, (4) dialysis patients, (5) patients receiving chronic wound care, (6) patients receiving chemotherapy, and (7) immunocompromised patients.

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*.

*See text. Dosing may need adjustment for patients with renal insufficiency.

INPATIENT TREATMENT

Inpatient treatment is provided in Tables 65-6 through 65-9. Inpatients not admitted to the ICU benefit from coverage for both atypical organisms and cell-walled organisms. If trying monotherapy, use a respiratory fluoroquinolone, although this is discouraged (see above) to avoid resistance and *Clostridium difficile* outbreaks. Do not use monotherapy with macrolides or doxycycline; use aminopenicillins or cephalosporins and a macrolide or doxycycline.

Patients ill enough for ICU care are optimally treated with combination agents, including an aminopenicillin or cephalosporin with either a respiratory fluoroquinolone or a macrolide. Penicillin-allergic patients can receive a respiratory fluoroquinolone with either aztreonam or clindamycin. For patients at risk for *Pseudomonas* infection, including those with chronic structural lung disease, patients on high-dose steroids, and patients recently in an ICU, add coverage with at least two agents active against the organism. This may include an antipseudomonal β-lactam such as piperacillin-tazobactam or cefepime with a respiratory fluoroquinolone. Alternatively, a carbapenem, such as imipenem, along with either a fluoroquinolone or aminoglycoside, may be appropriate. Treat penicillin-allergic patients with a monobactam along

TABLE 65-8 Inpatient Therapy for Intensive Care Unit Patients*

Class	Example	Comments
Cephalosporin	Ceftriaxone, 1 gram IV	Other β-lactams may also be used in place of ceftriaxone. See Table 65-9 for additional recommendations.
Plus	Plus	
Macrolide	Azithromycin, 500 milligrams IV	
Cephalosporin	Ceftriaxone, 1 gram	Other β-lactams may also be used in place of ceftriaxone. See Table 65-9 for additional recommendations.
Plus	Plus	
Fluoroquinolone	Either moxifloxacin, 400 milligrams IV *or* Levofloxacin, 750 milligrams IV	
Fluoroquinolone	Moxifloxacin, 400 milligrams IV	Aztreonam is generally well tolerated in penicillin-allergic patients.
Plus	*or*	
Either a monobactam	Levofloxacin, 750 milligrams IV	
or	Plus	
A lincosamide	Either aztreonam, 1–2 grams IV *or* Clindamycin, 600 milligrams IV	
Anti-MRSA drug (add if HCAP or MRSA risk)	Vancomycin, 10–15 milligrams/kg IV *or* Linezolid, 600 milligrams IV	To be added to one of the above regimens for patients with MRSA or HCAP risk.

Abbreviations: HCAP = healthcare-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*.

*Other combinations may also be used. Dosing may need adjustment for patients with renal insufficiency.

TABLE 65-9 Inpatient Therapy for Patients With Pseudomonas Risk*

Class	Example	Comments
β-Lactam/β-lactamase inhibitor	Piperacillin-tazobactam, 3.375 milligrams IV	Other antipseudomonal cephalosporins or quinolones may be used. Carbapenems are also appropriate. Consider adding an aminoglycoside if substituting a macrolide.
Plus	Plus	
Fluoroquinolone	Ciprofloxacin, 400 milligrams IV	
Monobactam	Aztreonam, 1 gram IV	May be used for patients with penicillin allergy. Carbapenems and aminoglycosides may also be appropriate.
Plus	Plus	
Fluoroquinolone	Either moxifloxacin, 400 milligrams IV *or* Levofloxacin, 750 milligrams IV	
Anti-MRSA drug (add if HCAP or MRSA risk)	Vancomycin, 10–15 milligrams/kg IV *or* Linezolid, 600 milligrams IV	To be added to one of the above regimens for patients with MRSA or HCAP risk.

Abbreviations: HCAP = healthcare-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*.

*Other combinations may also be used. Dosing may need adjustment for patients with renal insufficiency.

with a fluoroquinolone. If the combination does not include two drugs with antipseudomonal activity, then consider adding in an aminoglycoside. Patients admitted to the ICU with healthcare-associated pneumonia require coverage for methicillin-resistant *S. aureus* with drugs such as vancomycin or linezolid.[23,24]

DISPOSITION AND FOLLOW-UP

Most patients with CAP do not require hospitalization.[25] Many factors influence the prognosis and outcome of CAP. There are multiple clinical decision tools available to assist in the disposition process. The **Pneumonia Severity Index** is the best studied and recommended tool; many perceive it to be accurate but hard to use (although online tools exist) (**Table 65-10**). The **CURB-65** rule looks at the presence of confusion, uremia >7 mmol/L, respiratory rate ≥30 breaths/min, diastolic blood pressure ≤60 mm Hg, and age ≥65 years old.[21] The **CRB-65** uses the same variables but eliminates the uremia measurement. Patients with a CURB-65 or CRB-65 score of <2 have a low mortality rate, but neither the CURB-65 nor CRB-65 score is as well studied or validated as the Pneumonia Severity Index.

Scoring systems provide a starting point for evaluation of the patient. Some patients may be eligible for admission based on other social or medical factors not assessed by these scores, but their best utility for scoring systems is as a tool to increase the number of appropriate patients treated on an outpatient basis and to limit unnecessary admissions. Admission decision patterns for CAP patients among emergency physicians are widely variable and often not linked to illness or patient factors.

After admission, the next decision is to determine which patients require admission to the ICU. Admit patients with sepsis or those requiring mechanical ventilation to an ICU setting. Other criteria for ICU admission include a markedly elevated respiratory rate, a Pao_2/Fio_2 ratio ≤250, multilobar infiltrates, confusion, uremia with a BUN >20 milligrams/dL, leukopenia, thrombocytopenia, hypothermia, hyponatremia, lactic acidosis, and asplenia (**Tables** 65-10, **65-11,** and **65-12**). Pneumonia Severity Index class V and CURB-65 patients with a score of ≥3 may need intensive care.[21]

Most patients will achieve some measure of resolution within 3 to 5 days after the initiation of antibiotics. Many hospitalized patients can be switched to oral antibiotics at approximately 3 days and subsequently discharged to complete a course of therapy. However, about half of patients are still symptomatic at 30 days, with a significant minority of patients experiencing chest pain, malaise, or mild dyspnea even 2 to 3 months after treatment. Educate patients about smoking cessation and moderation of alcohol use, and provide information about rest, nutrition, hydration, follow-up, and the importance of pneumococcal and influenza vaccination.

TABLE 65-10 Pneumonia Severity Index

Step 1: Assignment to risk class I

- Age >50 y old
- Comorbid conditions
- Neoplastic disease
- Cerebrovascular disease
- Congestive heart failure
- Renal disease
- Liver disease
- Physical examination abnormalities
- Altered mental status
- Pulse >125 beats/min
- Respiratory rate >30 breaths/min
- Systolic blood pressure <90 mm Hg
- Temperature <35°C (95°F) or >40°C (104°F)

If any criteria positive, go to Step 2 which is collecting more laboratory and other data and assigning points (Table 65-11).

If all negative, then assign to risk class I.

TABLE 65-11 Pneumonia Severity Index Risk Classes II to V

Criteria	Points
Demographics	
Male gender	Age (y)
Female gender	Age (y) – 10
Nursing home resident	10
Coexistent illness	
Neoplastic disease	30
Congestive heart failure	20
Cerebrovascular accident	10
Renal disease	10
Liver disease	10
Physical examination	
Abnormal mental status	20
Pulse ≥125 beats/min	20
Respiratory rate >30 breaths/min	20
Blood pressure (<90 mm Hg)	15
Temperature <35°C (95°F) or >40°C (104°F)	10
Ancillary studies	
Arterial pH <7.35	30
BUN ≥30 milligrams/dL	20
Sodium >130 mEq/L	20
Glucose >250 milligrams/dL	10
Hematocrit <30%	10
Pao_2 <60 mm Hg	10
Pleural effusion	10
Summary points risk assignment	
Sum of points <70 = risk class II	
Sum of points 71–90 = risk class III	
Sum of points 91–130 = risk class IV	
Sum of points >130 = risk class V	

ASPIRATION PNEUMONIA

INTRODUCTION AND EPIDEMIOLOGY

Aspiration is the inhalation of oropharyngeal contents into the respiratory tract.[26-29] Aspiration pneumonia is the inhalation of infectious material from the oropharynx into the lower respiratory tract that causes infection of the lung parenchyma.[29] Aspiration alone does not cause pneumonia.

Approximately half of healthy adults aspirate when sleeping. Aspiration pneumonitis is an irritation and inflammatory response to aspirated material. Pneumonitis can develop when the aspirated material has a low pH (<2.5) or when other components of the aspirate cause an inflammatory response.

TABLE 65-12 Prediction of Mortality From Pneumonia

Class	Points	Mortality (%)	Treatment Recommendation
I	No predictors	0.1	Outpatient
II	<70	0.6	Outpatient
III	71–90	2.8	Individualized
IV	91–130	8.2	Inpatient
V	>130	29.2	Inpatient

PATHOPHYSIOLOGY

Aspiration pneumonia is a result of a complex interplay of the aspirated material, aspirated volume, pH, patient physiology, and pulmonary defense mechanisms. There is a large overlap in the etiology, symptoms, and bacterial flora of aspiration pneumonia and CAP, which often makes clinical differentiation difficult. In addition, over the years, microbiology patterns of aspiration pneumonia have changed.[30]

Risk factors for aspiration pneumonia include prior history of aspiration, altered level of consciousness, anatomic abnormality of the airway, neuromuscular disease, GI disease, retained gastric contents, percutaneous gastric or jejunal tube, nasogastric tube, prolonged supine position, poor oral hygiene, and advanced age[31] (**Table 65-13**).

Oral hygiene risk factors for development of aspiration pneumonia include four or more decayed teeth, gingivitis, periodontitis, periodontal disease–causing organisms in saliva, and dental plaque.[32] Medications that decrease saliva production also predisposed to higher oral bacterial counts. Medications (diuretics, anticholinergics, anxiolytics, antipsychotics, levodopa) can reduce salivary flow and lead to increased oral bacterial counts.[33]

Aspiration in younger patients tends to result from obtundation secondary to intoxication, seizures, or medication overdose. If a large volume of fluid is aspirated, it may lead to asphyxia. Younger patients with aspiration pneumonia may remember the aspiration incident several days earlier or have a history of substance abuse with frequent periods of amnesia or loss of consciousness.

Aspiration in older patients results from preexisting risk factors such as enteral feeding, anatomic abnormalities (head, neck, and esophagus), physiologic abnormalities of the mechanisms of deglutition and decreased immune response (cellular and humeral), decreased mucosal ciliary function, decreased mucus production, and decreased cough reflex. An increased stimulus is needed to provoke a cough reflex in older patients.[32]

Aspiration pneumonia is the second leading cause of infection in nursing homes, behind urinary tract infections.[34] It is the leading cause for transfer from nursing home to the hospital and the leading cause of death in nursing home patients.[34] In nursing home patients, the aspiration incident may not be witnessed, and time of aspiration will be unknown.

CLINICAL FEATURES AND TREATMENT

Symptoms of aspiration pneumonitis tend to develop rapidly, with onset of shortness of breath, bronchospasm, hypoxia, and low-grade fever within a few hours of the aspiration. Symptoms typically resolve within 48 hours.[35]

Recent research by Driver et al[36] demonstrated that 8% of patients developed aspiration pneumonia after **emergency endotracheal intubation**. There were no intubation factors that were different in those patients who developed aspiration pneumonia and those who did not.[36] The National Emergency Airway Registry III investigators demonstrated witnessed aspiration in 5% of emergency endotracheal intubations,[37] and occult aspiration occurs in 22% to 50% of prehospital emergency intubations.[38]

TABLE 65-13 Risk Factors for Aspiration[29,31]

- Advanced age
- Altered level of consciousness
- Anatomic abnormality of upper airway
- Dementia
- Esophageal disorders
- Gastroesophageal reflux
- Neuromuscular/neurologic disease
- Poor oral hygiene
- Prior history of aspiration
- Prolonged supine position
- Retained gastric material
- Tube feedings

TABLE 65-14 Aspiration Syndromes[29,39]

- Acute airway obstruction
- Aspiration pneumonias
- Aspiration pneumonitis
- Chronic interstitial fibrosis
- Diffuse aspiration bronchiolitis
- Exogenous lipoid pneumonia
- *Mycobacterium fortuitum* pneumonia

Aspiration syndromes include aspiration pneumonia, aspiration pneumonitis (Mendelson's syndrome), acute airway obstruction, exogenous lipoid pneumonia, chronic interstitial fibrosis, *Mycobacterium fortuitum* pneumonia, and diffuse aspiration bronchiolitis[39] (**Table 65-14**).

There is a broad spectrum of physical presentations for patients with aspiration pneumonia. The nursing home patient may appear in no distress and present with decreased appetite, weakness, altered sensorium, or fever; vital signs may be normal or show fever, tachycardia, tachypnea, and hypotension. Younger patients with acute aspiration of solid or liquid material may present in a more dramatic fashion with cough, shortness of breath, and possible hypoxia. Rales, rhonchi, and wheezes may exist. Unilateral (total occlusion) or sonorous (partial occlusion) breath sounds may be present in the case of occlusion of a mainstem bronchus. Aspiration of irritative substances such as oils, sterile gastric contents with pH of ≤2.5, activated charcoal, diatrizoic acid, or alendronate sodium all can cause an intense inflammatory reaction. Aspiration of pills such as potassium, iron, or metformin can cause local inflammation and may lead to bronchial stenosis. Sucralfate and pomegranate supplements can expand when in contact with the bronchial mucosa and cause bronchial obstruction.[40]

A few patients may require chest CT to evaluate for lung abscess or foreign body, as aspiration is a risk factor for pulmonary abscess formation.

After obtaining blood (and possibly adequate sputum) cultures, initiate antibiotic treatment, but do not delay antibiotics to obtain cultures. **Clindamycin, a carbapenem, ampicillin-sulbactam, and moxifloxacin** are all reasonable treatments for suspected community-acquired aspiration pneumonia.[30] Bronchodilators aid aspiration-induced bronchospasm.

DISPOSITION

Healthy persons who aspirate small volumes of nontoxic material may be observed for a short time, approximately 1 to 2 hours, and if stable and reliable, discharged to return for worsening symptoms. Antibiotic treatment is not needed for witnessed aspiration of a small amount of nontoxic liquid provided the patient's symptoms (cough, low-grade fever) resolve within 24 to 48 hours.[39]

Most patients with community-acquired aspiration pneumonia require admission. It is difficult to clinically distinguish aspiration pneumonia from non–aspiration-related pneumonia.[30] The history and clinical environment (older patient, nursing home, sedation, dysphagia, poor dentition, substance abusing) will lead to an impression of aspiration pneumonia. The same admission guidelines apply to aspiration pneumonia as for other pneumonias.

NONINFECTIOUS PULMONARY INFILTRATES

INTRODUCTION AND EPIDEMIOLOGY

A noninfectious pulmonary infiltrate is a radiologic abnormality that is not due to an infection. Suspect it when no other infectious findings exist or after antibiotics fail to improve symptoms. Noninfectious infiltrates occur in response to a wide variety of pathophysiologic processes

TABLE 65-15 Noninfectious Causes of Pulmonary Infiltrates

Disease	Pathophysiology	Chest Radiography Findings	Symptoms
Allergic bronchopulmonary Aspergillosis	Hypersensitivity reaction to *Aspergillus fumigatus*. Most common in patients with asthma or cystic fibrosis. Eosinophils fill small airways and alveolar spaces due to inflammation. Bronchiectasis.	Branching tubular opacities may be seen, usually predominantly or exclusively involving upper lobes.	Dyspnea, wheezing, productive cough; may have hemoptysis and occasionally fever.
Acute eosinophilic lung disease	Cause unknown. Association with new or binge smoking. Eosinophils accumulate in distal airways and alveolar and interstitial spaces.	Nonspecific bilateral consolidations and reticular opacities.	Dyspnea, fever, nonproductive cough, and wheezing. In acute forms, hypoxia and potential for rapid progression to respiratory failure. Steroid responsive.
Hypersensitivity pneumonitis (extrinsic allergic alveolitis)	Inflammation of the alveoli secondary to hypersensitivity in response to inhaled organic dust.	Diffuse micronodular interstitial infiltrates. May see ground-glass densities in the lower or mid-lung fields. Bases spared.	Fever, chills, malaise, cough, chest tightness, dyspnea, and headache.
Organizing pneumonia (bronchiolitis obliterans organizing pneumonia [BOOP])	Inflammation of the bronchioles and surrounding tissues, leading to loss of the integrity of the bronchioles and organizing pneumonia without infection. Cryptogenic organizing pneumonia if immunocompromised or connective tissue diseases (e.g., SLE, rheumatoid arthritis, dermatomyositis).	Patchy multifocal alveolar infiltrates without effusion.	Cough, dyspnea, fever.
Antinuclear cytoplasmic antibody (ANCA)–associated vasculitides: granulomatosis with polyangiitis (Wegener's granulomatosis), Churg-Strauss syndrome	Both systemic vasculitides of small and medium-sized vessels of unknown origin. Wegener's characterized by necrotizing granulomatous vasculitis with involvement of upper respiratory tract, lung parenchyma, and kidneys. Churg-Strauss disease is an allergic eosinophilic condition. Most are asthmatic.	Bilateral peripheral, patchy, alveolar infiltrates and nodules.	Cough, dyspnea, allergic rhinitis/sinusitis. May have skin, coronary, or intestinal involvement.
Acute interstitial pneumonia	Idiopathic or secondary (chemical agents). Three stages: interstitial edema spreads to alveoli with hemorrhage and hyaline membrane formation (exudative), organization of fibrinous exudate (proliferative), scarring and cyst formation and honey comb fibrosis (fibrotic).	Normal for first 12–24 h. Bilateral opacities with sparing of costophrenic angles. Minimal or no pleural effusion. "White lung" due to extensive consolidation.	Rapid progression to respiratory failure. Mortality rate higher in those with comorbidities.
Sarcoidosis	Systemic granulomatous disease of unknown etiology. Noncaseating pulmonary granulomas.	4 stages: bilateral hilar adenopathy; bilateral hilar adenopathy with reticulonodular pulmonary opacities; pulmonary opacities only; pulmonary fibrosis.	Dyspnea, cough, weight loss; skin lesions may also be found. May be asymptomatic.
Anti–glomerular basement membrane antibody disease (Goodpasture's syndrome)	Autoimmune disease affecting the lungs and kidney due to autoantibodies to type IV collagen. Causes hemorrhagic interstitial pneumonitis.	Diffuse, bilateral, predominantly alveolar densities with sparing of the apices and costophrenic angles.	Fatigue, dyspnea, cough with hemoptysis; may have simultaneous hematuria.
Drug-induced pneumonitis	Causes include chemotherapeutic, immunosuppressive, antimicrobial, and herbal agents.	Typically, bilateral interstitial infiltrates.	Cough, mild fever, dyspnea. Potentially hypoxia.
Chemical pneumonitis	Inflammatory reaction to the presence of foreign substance, such as barium, petroleum distillates, pesticide, or irritating gases.	Diffuse alveolar and interstitial infiltrates.	History of exposure or aspiration of substance; acute dyspnea, cough, and possibly wheezing.
Radiation pneumonitis	Interstitial pulmonary inflammation seen in 5%–15% of patients with thoracic radiation treatment.	Subtle hazy ground-glass densities to marked patchy infiltrates or homogenous consolidation. Air bronchograms are commonly present.	Symptoms occur 1–6 months after treatment: low-grade fever, cough, fullness in the chest.
Alveolar cell carcinoma, often called bronchiolar or bronchioloalveolar carcinoma	Adenocarcinoma originating in a terminal bronchiole and spreading across the alveolar walls.	Peripheral alveolar infiltrates. May see peripheral nodule or mass.	Often severe coughing dyspnea and copious sputum production. May mimic pneumonia, but no fever, leukocytosis, or response to antibiotics.
Leukemic infiltrates	Most common in myeloid leukemia when peripheral blast cell counts exceed 100,000/mL. Primitive myeloid leukemic cells invade through the endothelium of the lung capillary beds, yielding hemorrhage.	Interstitial or alveolar infiltrates. Diffuse infiltrates associated with hypoxia and need for intubation; focal infiltrates associated with coexistent pneumonia.	Respiratory distress, hypoxemia, and may progress to respiratory failure.
Fat emboli	ED presentations are typically after trauma, associated with long bone fracture.	Interstitial prominence, suggesting interstitial edema. Radiographic findings may be delayed by hours after trauma	Dyspnea, cough, hemoptysis, and pleural pain. May be associated with confusion, stupor, delirium, and a petechial skin rash, most commonly on the chest.
Alveolar hemorrhage	In the setting of chemotherapy induction for leukemia and thrombocytopenia (<20,000/mL), hemorrhage filling alveoli is common from endobronchial and interstitial sources. Also seen with SLE.	Focal or diffuse alveolar infiltrates.	Dyspnea, hemoptysis; symptoms are frequently less severe than radiographic appearance would predict.
Acute respiratory distress syndrome	Reaction of the lung to a number of precipitating causes, including sepsis, trauma, surgeries, transfusions, and therapeutically induced immunosuppression.	Classically, patchy peripheral infiltrates that extend to the lateral lung margins suggest the diagnosis.	Hypoxia, tachypnea, rales.

Abbreviation: SLE = systemic lupus erythematosus.

involving the respiratory, cardiovascular, and immune systems or may be due to the infiltration of malignant cells. Some common noninfectious causes of pulmonary infiltrates are congestive heart failure, aspiration pneumonitis, and pulmonary embolism.

CLINICAL FEATURES

The main symptom of noninfectious pulmonary infiltrates is dyspnea. Some disorders present with hemoptysis, cough, chest pain, or fatigue. Fever can also be a symptom of autoimmune disease exacerbation. It may be impossible to clinically differentiate a noninfectious source from an infectious source of fever in the ED. **Table 65-15** lists the most common causes of acute noninfectious pulmonary infiltrates and their key clinical features, pathophysiology, and chest radiology findings.[41-48] Diffuse alveolar hemorrhage is the most common manifestation of pulmonary vasculitis from asymptomatic chest radiograph abnormalities to severe respiratory failure.[45,48]

TREATMENT

Treatment is guided by the main differential diagnosis. Assess gas exchange with pulse oximetry in all patients, and use selective arterial blood gas analysis in patients who are ill, hypoxemic, or with underlying chronic lung disease; use noninvasive or mechanical ventilation as needed. Definitive treatment for noninfectious pulmonary disease depends on the underlying cause and will occur after ED stabilization. Many of the disorders listed in Table 65-15 are treated acutely with corticosteroids such as methylprednisolone (0.5 to 1 gram IV).[49] Additional immunosuppressive drugs may be initiated by the admitting physician.

DISPOSITION AND FOLLOW-UP

Patients suspected of having a noninfectious cause of pulmonary infiltrates require testing beyond the capabilities of the ED. Hospitalization should be based on the severity of the medical illness, with attention to hypoxemia, hypercapnia, and work of breathing. Stable patients with mild symptoms may be referred to a pulmonologist, rheumatologist, or another specialist for further outpatient evaluation and treatment.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 66

Lung Empyema and Abscess

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EMPYEMA

INTRODUCTION AND EPIDEMIOLOGY

Empyema is pus in the pleural space. A parapneumonic effusion is a pleural effusion associated with a lung infection, usually pneumonia but infrequently a lung abscess. Bacterial pneumonia with a parapneumonic effusion is the most common precursor, seen in about 60% of empyema patients.[1] Other causes of empyema are complications of chest surgery (22%), trauma (4%), esophageal perforation (4%), complications of chest tube/thoracentesis (4%), an extension from a subdiaphragmatic infection (3%), and assorted triggers (7%), including a hemothorax, chylothorax, or hydrothorax that becomes infected due to a systemic infection with hematogenous spread such as septicemia.[1,2]

Of the approximately 1 million pneumonia patients hospitalized each year in the United States, 20% to 40% develop a parapneumonic effusion; 5% to 10% of patients with a parapneumonic effusion develop an empyema.[3,4] Mortality in adults is about 20%.[5] With the advent of antibiotics, the incidence of empyema decreased in the first half of the 20th century, but since the 1990s, the incidence of empyema has increased in the United States and worldwide.[3,6]

Predisposing factors for empyema include aspiration (and the conditions causing this event, notably altered swallowing), respiratory disease impairing ciliary function, immunocompromise, malignancy, IV drug abuse, alcoholism, diabetes, gastroesophageal reflux disease, and poor oral hygiene.[1]

CLINICAL FEATURES

Suspect empyema if symptoms of pneumonia (fever, cough, dyspnea, pleuritic chest pain, and malaise) do not resolve with therapy. The onset of empyema may be insidious, with patients appearing chronically ill with weight loss, anemia, and night sweats.[3]

Physical examination findings include decreased breath sounds, dullness to percussion, decreased tactile fremitus, and occasionally a friction rub.[7] Pain from an underlying effusion or empyema may cause splinting with respiration. If there is an underlying pulmonary infection, rales or rhonchi may exist.

DIAGNOSIS

Diagnostic criteria for empyema are aspiration of grossly purulent material on thoracentesis and at least one of the following: thoracentesis fluid with a positive Gram stain or culture, pleural fluid glucose <40 milligrams/dL, pH <7.2, or lactate dehydrogenase >1000 IU/L. For empyema from tuberculosis, absolute lymphocyte count on pleural fluid is useful, although other markers such as interferon release assays or adenosine deaminase show promise.[4] Pleural biopsy is diagnostic in 55% to 70% of patients, demonstrating a granuloma and/or being culture positive.[4]

A pleural-based opacity on a chest radiograph, including a lateral decubitus film, suggests a pleural effusion or empyema. POCUS accurately identifies pleural effusions and empyemas, differentiates a loculated effusion from a mass, and guides thoracentesis and chest tube placement. A chest CT scan with IV contrast can assess for a loculated effusion or empyema and identify any other abnormalities present.

TREATMENT

The definitive treatment of an empyema is drainage and antibiotics.[3,8] In addition, treat any underlying disease, especially pneumonia. NSAIDs or opioids can decrease pleuritic pain. Thoracentesis and drainage aid in the diagnosis and provide symptomatic relief for dyspnea. The common organisms in empyema stratified by associated pathology are listed in **Table 66-1**.[2,9] In about 40% of cases, cultures are negative,[10] and anaerobic species are particularly difficult to culture. Newer molecular analysis or nucleic acid amplification technology may lead to a higher detection rate for the underlying pathogen(s).

The choice of antibiotics depends on the clinical presentation, local patterns, and results of diagnostic studies including cultures. Most antibiotics have adequate penetration into the pleural space with the exception of the aminoglycosides.[11] The detection of an aerobic organism does not preclude antibiotic coverage for anaerobes because there is a 23% incidence of mixed aerobic and anaerobic infections, according to one study.[12] Thus, empiric antibiotic coverage usually includes anaerobic coverage as well as coverage for other pathogens as indicated by the clinical situation, at least initially until culture results are known.

Choices for empiric therapy for anaerobes include a β-lactam with β-lactamase activity, such as piperacillin-tazobactam or ampicillin-sulbactam, a carbapenem, or clindamycin. Options for gram-negative aerobic pathogens are a second- or third-generation cephalosporin plus metronidazole, a carbapenem, or a β-lactam aminopenicillin with β-lactamase activity (e.g., piperacillin-tazobactam or ampicillin-sulbactam). There are many antibiotic options for gram-positive

TABLE 66-1 Common Organisms in Empyema and Associated Pathology[2,9]

Pathology	Organism
Pneumonia	*Streptococcus pneumoniae* *Staphylococcus aureus*
Pneumonia (unimmunized with *Haemophilus influenzae* type B vaccine)	*H. influenzae*
Lung abscess	Mixed oropharyngeal anaerobes
Aspiration pneumonia	*S. aureus*
Recent thoracotomy	Gram-negative bacilli
Chest trauma	*S. aureus* Gram-negative bacilli
Contiguous abdominal infection	Gram-negative bacilli Anaerobes
Esophageal rupture	Mixed oropharyngeal organisms
Postprocedure	Methicillin-resistant *S. aureus* *Pseudomonas*
Hospital-acquired empyema	Methicillin-resistant *S. aureus* *Pseudomonas*
Pneumonia in the setting of human immunodeficiency virus	Tuberculosis Fungal infections

organisms including a β-lactam, with the exception of coverage for methicillin-resistant *Staphylococcus aureus*, which requires vancomycin or other antibiotics that cover methicillin-resistant *S. aureus*. In patients with postprocedure or hospital-acquired empyema, consider coverage for methicillin-resistant *S. aureus* and *Pseudomonas aeruginosa*. Initial therapy often consists of two antibiotics to cover both *Staphylococcus* and anaerobes; monotherapy with a penicillin derivative or metronidazole is inadequate coverage. After initial drainage of the empyema plus IV antibiotics, switch to oral agents until there is clinical and radiographic improvement. Modify empiric antibiotics once culture results return and the clinical course is apparent.

Fibrinolytics (e.g., urokinase, alteplase, or streptokinase) can improve drainage of loculated parapneumonic effusions and empyemas. The Multicenter Intrapleural Streptokinase Trial (MIST) 1 used intrapleural streptokinase, and MIST 2 used alteplase and DNAase for pleural infection.[13,14] The results are mixed, making fibrinolytics an option that may lessen the frequency of later surgical intervention.[15-17] A blinded randomized trial comparing double placebo, alteplase and DNase, alteplase and placebo, or DNAase and placebo found that DNase alone or alteplase alone was ineffective, but the combination of alteplase and DNase improved fluid drainage, decreased the frequency of surgical referral, and decreased the length of hospital stay.[15]

About one third of patients treated with antibiotics and chest tube drainage need surgical drainage.[15] The MIST 1 found no difference in mortality or need for thoracic surgery between large (15F to 20F), medium (10F to 14F), or small (<10F) tubes, but did report that pain was much decreased with the smaller tube sizes.[14] Video-assisted thoracoscopic surgery allows debriding of empyemas that fail tube thoracostomy drainage and antibiotic therapy. Video-assisted thoracoscopic surgery can be followed by or converted to a thoracotomy if pleural fluid drainage remains insufficient.

LUNG ABSCESS

INTRODUCTION AND PATHOPHYSIOLOGY

Lung abscess is characterized by localized necrosis of the lung parenchyma and is typically caused by suppurative microbial infection. Initial infection is usually caused by aspiration of oral contents. Type 3 *Streptococcus pneumoniae* and *S. aureus* are major causes of lung abscess, with an increasing frequency of *Klebsiella pneumoniae* infection.[17] In a Japanese study, *Streptococcus* spp. (59.8%), anaerobes (26.2%), and *Gemella* spp. (9.8%) all existed in community-acquired lung abscesses.[18] *Mycobacterium tuberculosis* and *Actinomycetes* spp. were more common in lung abscesses that extended to the chest wall.[18]

TABLE 66-2 Cavitary Lung Lesions

Infectious	
Bacterial	Anaerobic abscess
	Aerobic abscess
	Infected bullae
	Tuberculosis
	Actinomycosis
	Pleural empyema
Fungal	Coccidioidomycosis
	Histoplasmosis
	Blastomycosis
	Aspergillosis
	Cryptococcus
Parasitic	Echinococcosis, *Entamoeba histolytica*
	Amebiasis, *Paragonimus westermani*
Neoplastic	Bronchogenic carcinoma (squamous cell or adenocarcinoma)
	Metastatic cancer (colorectal or renal)
	Lymphoma or Hodgkin's disease
Inflammatory	Sarcoidosis
	Wegener's granulomatosis
Other	Foreign body aspiration

Primary lung abscess can occur in individuals in good health or in those prone to aspiration. Approximately 80% of lung abscesses are primary,[19] and the overall reported mortality rate varies between 1% and 38.2%.[18,20,21] Secondary lung abscess is associated with malignancy, immunosuppression, extrapulmonary infection, sepsis, or complications of surgery. The mortality rate in secondary lung abscess is often >50%. Lung abscesses present for <1 month are termed acute, and those present for >1 month are chronic.[19]

Lung abscess may also develop as a result of hematogenous spread of infectious material to the lung parenchyma or complicating lung infarction. Think of hematogenous spread from another infectious focus, such as endocarditis, in those with multiple lung abscesses. Other less common causes of pulmonary abscess include penetrating chest trauma or fungal and parasitic infections. Primary and metastatic neoplasms and inflammatory conditions such as Wegner's granulomatosis and sarcoidosis may also manifest as pulmonary cavitary lesions and become infected (**Table 66-2**).

CLINICAL FEATURES

Lung abscess typically has an indolent course, with patients presenting after 2 to 4 weeks of symptoms. Symptoms include cough, fever, pleuritic chest pain, hemoptysis, weight loss, and night sweats. The development of the infection is slow, so fever, tachycardia, and tachypnea are often absent. The cough may or may not be productive.

DIAGNOSIS

Chest radiograph may show an area of dense consolidation or an air-fluid level inside of a cavitary lesion, indicating that the abscess cavity communicated with a bronchiole. Bronchiole communication occurs in most patients with lung abscess. Chest CT will diagnose cavitary lesions with and without bronchiolar communication. Conditions that may appear cavitary on a chest radiograph include infected bullae, pleural fluid collection with bronchopleural fistula, loop of bowel extending through a diaphragmatic hernia, hiatal hernia, and objects lying on or

TABLE 66-3 Reasons for Medical Treatment Failure in Lung Abscess

- Bronchial obstruction: neoplasm, foreign body
- Nonbacterial cause: neoplasm, fungi, vasculitis, pulmonary sequestration
- Large cavity size: >6 cm diameter
- Empyema
- Mycobacteria

behind the patient at the time of the radiograph. Causes of other cavitary lung lesions are noted in Table 66-2. Laboratory results are nonspecific.

TREATMENT

After stabilization of immediate life-threatening conditions, the next step is usually antibiotic therapy. Empiric therapy targets anaerobes and facultatively anaerobic streptococci.[22] Ampicillin-sulbactam, 3 grams IV every 6 hours, or a carbapenem (imipenem, meropenem) are appropriate choices.[20,22] Clindamycin is another option but is often avoided due to the risk of subsequent infection with *Clostridium difficile*.[22] Clindamycin plus a cephalosporin is another option.[17]

Drainage usually occurs spontaneously from communication of the abscess cavity with the tracheobronchial tree. This is signaled by the development of an air-fluid level on the chest radiograph.

Patients who fail to respond to antibiotics are candidates for percutaneous or transbronchial drainage or open drainage of the abscess cavity. Approximately 11% to 21% of lung abscesses require surgical or percutaneous drainage.[18] The overall success rate of percutaneous drainage of lung abscess is 84%, with a complication rate of 16%.[23] Percutaneous abscess drainage with CT or US guidance is a simple method to drain the abscess cavity and provides more accurate material for culture of causative organism.[24] Transbronchial drainage carries the complication of possible contamination of the unaffected lung. Open surgical techniques can resect the lung abscess.

DISPOSITION

Admit patients with newly diagnosed lung abscesses for antibiotic treatment. Reserve surgical interventions for large or complicated abscesses or for those failing antibiotic treatment (**Table 66-3**).

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 67

Tuberculosis

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INTRODUCTION AND EPIDEMIOLOGY

Tuberculosis is an important worldwide infection, with more than one third of the overall population harboring the bacterium. It is the second leading infectious cause of death, especially among those with human immunodeficiency disease (HIV).[1,2] Despite therapeutic progress over the past 20 years, drug resistance and HIV coinfection continue to challenge global control of tuberculosis.[2]

Tuberculosis infections declined in the United States from 2000 to 2010.[3] This reduction is primarily due to efforts targeting high-risk individuals. Improved infection control policies, increased vigilance among physicians, implementation of directly observed therapy, and standardized drug regimens all contributed to the decline of tuberculosis (**Table 67-1**). Although overall national cases have decreased, the incidence in foreign-born patients remains 12 times that of U.S.-born persons.[3] In those foreign-born patients, clinical tuberculosis is usually from reactivation of latent disease. Overall, reactivation of latent tuberculosis is responsible for 70% of active tuberculosis cases.[4]

TABLE 67-1 Patients With a High Prevalence of Tuberculosis (Highest to Lowest Risk)

- Immigrants from high-prevalence countries
- Patients with the human immunodeficiency virus
- Residents and staff of prisons or shelters for the homeless
- Alcoholics and illicit drug users
- Elderly and nursing home patients

Screening and treatment of latent infection in high-risk individuals are key to reducing tuberculosis in the United States.[4] However, case detection rates are approximately 64%, with close to 3.3 million people with tuberculosis missed in 2013.[5]

PATHOPHYSIOLOGY

Mycobacterium tuberculosis is a slow-growing aerobic rod that settles in areas of high oxygen content and blood flow. Transmission occurs via aerosolization of bacteria and inhalation of droplet nuclei into the lungs. Persons with active tuberculosis who excrete mycobacteria in saliva or sputum are the most infectious.[6] Only 30% of patients become infected after a droplet exposure.[7]

PRIMARY AND LATENT INFECTION

Once the organisms reach the lungs, host defenses activate. Mycobacteria are highly antigenic, resulting in a rapid immune response. Some organisms survive in the regional lymph nodes, where the host cell-mediated immunity contains the infection. Granulomas, known as *tubercles*, form from this process, which involves activated macrophages, T lymphocytes, and active bacteria. Tubercles are a sign of primary infection and may progress to caseation necrosis and calcification. These tubercles create a protective area for bacterial growth. In the lung, the **Ghon complex** (**Figure 67-1**) is a tubercle, appearing as calcified hilar lymph nodes.

If the tubercle fails to contain the infection, the mycobacteria may spread by hematogenous, lymphatic, or direct mechanical routes. The tendency is for survival in areas of high oxygen content or blood flow, such as the apical and posterior segments of the upper lobe and the superior segment of the lower lobe of the lung, the renal cortex, the meninges, the epiphyses of long bones, and the vertebrae. In these

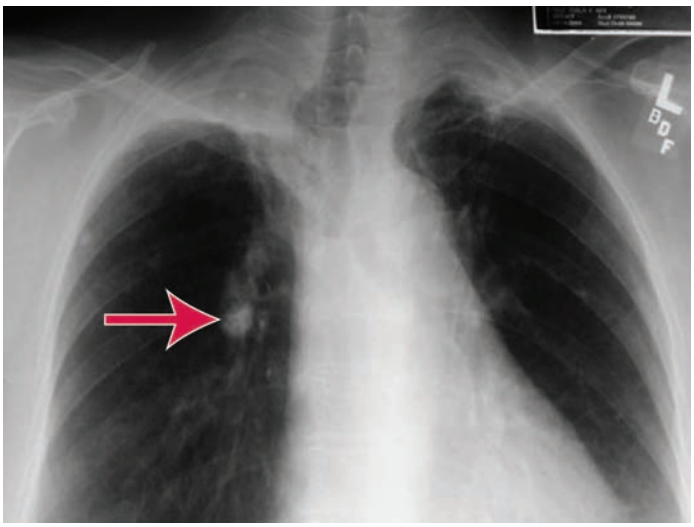

FIGURE 67-1. Primary Ghon complex (*arrow*).

areas, the mycobacteria can remain dormant for years. During dormancy (or latent infection), a positive tuberculin skin test detects the disease. **The skin test becomes positive 1 to 2 months after initial exposure.** Only 1% to 13% of otherwise healthy patients develop active postprimary disease. Children and HIV patients have a higher risk, approaching a 20% frequency of postprimary infection.[6,8] Latent infection is not transmissible.

REACTIVATION TUBERCULOSIS

Whether latent infection progresses to recurrently active (or "reactivation") tuberculosis is dependent on the immune status of the host.[6,7] As the host defense system weakens, it is no longer capable of containing the foci of previous hematogenous spread, and active tuberculosis may develop. The risk for reactivation is higher among HIV-infected persons and those over 50 years old.[7] In 5% of persons, latent infection may progress to active disease within 2 years after initial exposure, with another 5% developing disease later in life.[6,8] In immunocompromised hosts, spread often occurs rapidly, and progression of early active disease is more frequent. HIV-infected patients have higher progression to active disease reported (7% to 10% per year).[6] Other groups at risk for developing tuberculosis activation include those immunocompromised from cancer of solid organs, leukemia, transplantation, or medications such as antagonists of tumor necrosis factor-α (etanercept or infliximab) or corticosteroids (≥15 milligrams/d for ≥4 weeks of prednisone or its equivalent).[9] Those with select chronic diseases such as diabetes, chronic renal failure requiring hemodialysis, psoriasis, and silicosis are also at increased risk for tuberculosis activation.[6,10]

CLINICAL FEATURES

PRIMARY TUBERCULOSIS

The initial infection is usually asymptomatic, often detected only by a positive screening tuberculin skin test or by abnormalities on chest radiograph. When the infection is primary and active, common symptoms include cough, fever, malaise, weight loss, and chest pain.[6] The lungs are the most common site affected, with over 85% of patients presenting with pulmonary symptoms. Infrequently, a pneumonitis similar to a viral or bacterial infection appears. Hilar adenopathy is present but rarely massive. In some cases, especially in immunocompromised patients, the primary infection is rapidly progressive and fatal.

REACTIVATION TUBERCULOSIS

When latent infection progresses to tuberculosis reactivation, symptoms may be systemic or pulmonary. The most common reactivation symptoms are similar to those seen in primary tuberculosis: fever, night sweats, malaise, fatigue, and weight loss. Productive cough, hemoptysis, dyspnea, and pleuritic chest pain develop as the infection spreads within the lungs. Physical examination is unremarkable, although rales may be noted in areas of pulmonary infection.

Although most cases of active tuberculosis involve the lungs, up to 20% of cases will have other manifestations.[6] The most common extrapulmonary site of tuberculosis is the lymphatic system—painless lymphadenopathy (i.e., scrofula, cervical lymphadenitis). Other extrapulmonary manifestations include abdominal pain due to hepatosplenomegaly, peritoneal tubercles, prostatitis, epididymitis, or orchitis; adrenal insufficiency; bone pain with arthritis, osteomyelitis, or Pott's disease (bony destruction, often in the spine); hematuria and sterile puree; and meningitis. Tuberculosis can also cause pericarditis, which can lead to tamponade and constrictive symptoms. *Extrapulmonary tuberculosis can mimic many other common diseases*, especially in the elderly and HIV patients.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In ED patients with undiagnosed tuberculosis, this infection is often not considered[11]; consider tuberculosis in all patients over 50 years old with a pneumonia-like presentation or prominent respiratory complaint, especially if treatment of the condition has failed.[6,7] Similarly, those with HIV or on immunosuppressive medications (notably after transplantation or with a connective tissue disease) are often infected with minimal symptoms. The variable clinical presentation and the time required to culture the organism make diagnosis in the ED challenging. The goal is to consider the infection, test for it, and start respiratory precautions in at-risk patients while awaiting results. Place patients with possible tuberculosis in separate waiting areas, provide them with surgical masks, and instruct them to cover the mouth and nose when coughing. Evaluate and isolate immunocompromised patients with respiratory symptoms promptly and until tuberculosis is excluded based on a chest radiograph.[12] A negative-pressure room is ideal for isolation when available. Clues that suggest tuberculosis include hemoptysis, night sweats, and weight loss. On chest radiograph, look carefully for upper lung field involvement, fibrocalcific changes, pleural capping, or a calcified Ghon complex.[6]

Once tuberculosis is suspected, staff should wear high-efficiency disposable masks when caring for the patient.

MANTOUX OR TUBERCULIN SKIN TEST

The most common method for screening for exposure to *M. tuberculosis* is a skin test. The Mantoux test uses intradermal injection of 0.1 mL of **purified protein derivative** into the forearm. The test relies on a delayed-type hypersensitivity reaction triggered in those with past infection or those with a significant recent exposure to tuberculosis, with sensitivity developing 2 to 10 weeks after infection. The test interpretation is between 48 and 72 hours after administration and assesses the extent of skin induration at the test site; erythema or other skin changes are not useful (**Table 67-2**).[12] Results are less reliable after 72 hours, with repeat testing required. All persons with a new positive skin test or recent conversion require evaluation for current symptoms, physical examination, and chest radiograph. Also, refer newly positive patients for treatment of latent tuberculosis if no evidence of active tuberculosis is present. Finally, test close contacts of known infected patients because 4% will be positive despite having no symptoms, half of whom will have detectable disease less than 1 month after exposure.[13] Sensitivity of the purified protein derivative test depends on the size of induration: 5 mm demonstrates a sensitivity of 98%, whereas 10 and 15 mm possess sensitivities of 90% and 50% to 60%, respectively.[14]

In a few situations, a positive skin test is not diagnostic of tuberculosis. Those who received **bacillus Calmette-Guérin** immunization for tuberculosis prevention will often have a positive skin test response absent infection. Exposure to nontuberculosis mycobacteria also can result in a false-positive test. False-negative skin test results occur with improper administration, with improper test reading, very early in the disease, with recent measles-mumps-rubella vaccination, or with

TABLE 67-2 Interpretation of a Purified Protein Derivative Skin Test*

≥5-mm induration is positive in:

- Patients with the human immunodeficiency virus
- Patients with close contact with a tuberculosis-infected individual
- Patients with abnormal chest radiograph suggestive of healed tuberculosis
- Patients with organ transplants and other immunosuppressed patients receiving the equivalent of prednisone >15 milligrams per day for >1 month

≥10-mm induration is positive in patients not meeting the above criteria but who have other risks:

- Injection drug users
- High-prevalence groups (immigrants, long-term care facility residents, persons in local high-risk areas)
- Patients with conditions that increase the risk of progression to active disease (silicosis; diabetes; carcinoma of the head, neck, or lung)
- Children <4 y of age
- **≥15-mm induration is positive in all others**

Detection of newly infected persons in a screening program:

- ≥10-mm induration increase within any 2-y period is positive if <35 y
- ≥15-mm induration increase within any 2-y period is positive if >35 y
- If the patient is anergic, other epidemiologic factors must be considered

*A positive reaction does not necessarily indicate disease.

profound underlying immunosuppression (notably in HIV).[8,10,15] In immunocompromised patients with a negative test but recent close contact to infectious tuberculosis, retest in 8 weeks and consider treatment. A negative tuberculin skin test does not rule out the disease, because 20% of patients with active tuberculosis have a negative test result.[16-18] Adverse reaction to tuberculin skin testing is rare.[19]

BLOOD TESTS

Interferon-γ release assays (IGRAs) indirectly assess for tuberculosis. The test seeks the response to peptides present in all *M. tuberculosis* proteins, which trigger the release of interferon-γ by the infected host.[15] These proteins are absent in the bacillus Calmette-Guérin vaccine and in most nontuberculous mycobacteria. IGRA has a specificity of >95% and sensitivity approximating 90% for latent tuberculosis.[10,15,20,21] IGRA is used in conjunction with history, chest radiograph, and culture in those with suspected active tuberculosis.[15,22] Currently used IGRA tests give results in 16 to 24 hours, and results are reported as positive, negative, or indeterminant. IGRA tests are especially helpful when follow-up care compliance is a concern, notably in the homeless or drug-abusing patient (it does not require two visits), and can aid detection in patients in whom skin testing is not helpful for the previously mentioned reasons or in patients with known previous exposure (e.g., a healthcare worker).[10,15] IGRA cannot distinguish between latent and active infection, and it may be falsely negative in immunocompromised patients. In the setting of active tuberculosis, IGRA sensitivity and specificity are poor and the test should not be used for diagnosis or exclusion.[18,23,24]

CHEST RADIOGRAPH

The chest radiograph identifies disease in patients with pulmonary symptoms or after a positive skin test. No singular findings are pathognomonic for primary tuberculosis,[25] and the most common finding is a normal chest radiograph, especially in immunocompromised patients.[6] In primary infection, parenchymal infiltrates in any area of the lung may be found (**Figure 67-2**). Isolated ipsilateral hilar or mediastinal adenopathy is sometimes the only finding. Calcified lymph nodes exist in up to 35% of cases. Pleural effusions are usually unilateral and occur alone or in association with parenchymal disease, with 30% to 40% of radiographs having effusion with other findings. During primary infection, younger patients are more likely to have enlarged hilar lymph nodes, whereas adults more frequently have parenchymal abnormalities and effusions. The enlarged lymph nodes encountered in children may cause external compression, leading to bronchial obstruction, atelectasis, and postobstructive hyperinflation. Cavitation exists in 10% to 30% of patients and is uncommon in primary tuberculosis. Comparison with previous films is extremely helpful in determining the significance of an abnormal or unusual chest radiograph finding.[6,25]

In **latent tuberculosis**, nonspecific findings include upper lobe or hilar nodules and fibrotic lesions, sometimes calcified. Other findings are bronchiectasis, volume loss, and pleural scarring. Healed primary areas of infection appear as Ghon foci, areas of scarring, and calcification (Figure 67-1).

Reactivation infections often have the classic findings of tuberculosis: cavitary or noncavitary lesions in the upper lobe or superior segment of the lower lobe of the lungs, either bilateral or unilateral (**Figures 67-3** and **67-4**).

The radiographic appearance of tuberculosis is often dependent on the integrity of the immune system rather than the stage of tuberculous disease, with classic findings seen in the immunocompetent patient.[25,26] The frequency of classic findings on chest radiographs is directly related to the degree of immunosuppression; HIV patients with low CD4 counts have more atypical findings on radiographs. Normal radiographs occur in up to 22% of tuberculosis patients with advanced HIV.[26,27] CT is more sensitive than plain chest radiography for the identification of early or subtle parenchymal or nodal disease, especially in immunocompromised patients, although CT is typically not required for diagnosis.

MICROSCOPY AND CULTURES

Sputum culture detects the presence of *M. tuberculosis*. Obtain samples spontaneously (coughing) or with inducement, seeking at least 5 to 10 mL per sample to improve yield. In the absence of a satisfactory sputum sample, gastric aspirates, pleural and other body fluids (blood and urine samples in HIV patients), or tissue samples are options for culture and other diagnostic tests. Samples are stained using either a Ziehl-Neelsen stain or a fluorochrome procedure followed by exposure to an acidic agent. Mycobacteria will not lose the stain despite being rinsed with an acidic chemical (hence the term ***acid-fast bacilli***) on microscopic smears. Unfortunately, the staining procedure is not sufficiently sensitive or specific to confirm or exclude the diagnosis of tuberculosis, and expertise affects sample interpretation.[2] Negative smears are found in approximately 60% of culture-positive cases of tuberculosis, with higher false-negative smear results in children and HIV patients (approaching 80%).[25,27]

Sputum or other tissue cultures for *M. tuberculosis* are the best method of confirming diagnosis and the most specific test for the disease, detecting as few as 10 bacteria/mL. Culture results confirm infection and drug susceptibility, detecting resistance to treatment regimens. However, culture results are not available for weeks, thus creating the need for newer adjunctive tests to expedite diagnosis and treatment.



A



B

FIGURE 67-2. Reactivation tuberculosis. **A.** This elderly patient was treated with antibiotics for community-acquired pneumonia. **B.** When the patient did not respond, a past history of asymptomatic exposure to tuberculosis was elicited. Infiltrates were noted to be worse on hospital day 5 when tuberculosis skin test turned positive, diagnosing reactivation pulmonary tuberculosis.



FIGURE 67-3. Cavitary tuberculosis of the right upper lobe.

Newer rapid culture techniques use liquid rather than solid media, with growth typically within 1 week, although liquid media are costlier and more prone to contamination compared to solid media.[28] Blood cultures require specialized systems to detect growth.

Probe-based tests, or the **nucleic acid amplification test (NAAT),** can yield results within 1 day and detect as few as 1 to 10 organisms/mL sample.[29-33] The World Health Organization endorses NAAT for diagnosis of pulmonary and extrapulmonary tuberculosis.[34,35] Sensitivity of NAAT is greater than smears, with a detection rate of 50% to 80% in patients who are smear negative.[36] In patients with positive smears, NAAT has a sensitivity of greater than 90% to 95%. Patients with positive smears and positive NAAT should receive treatment pending culture results.[2]

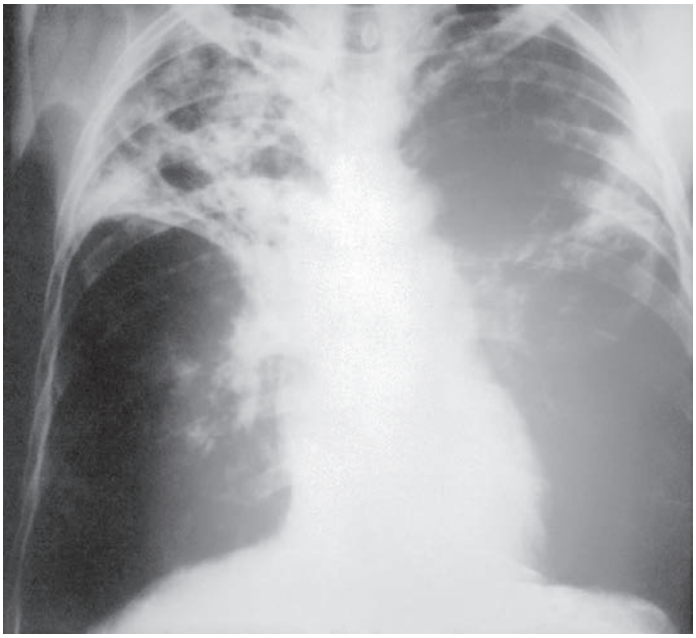

FIGURE 67-4. Advanced pulmonary tuberculosis involving apex and upper lobe.

False-positive NAAT results may occur with prior treated disease, contamination, or laboratory error. NAAT will remain positive in the setting of adequate therapy, as it detects dead and live organisms, making it best used for diagnosis of tuberculosis. A negative NAAT result cannot exclude tuberculosis.[25] Molecular testing detects *M. tuberculosis* DNA associated with drug resistance.[37] Urine-based antigen detection assays also aid detection in patients with concurrent HIV, especially for those with CD4 counts <200 cells/mm^3 and with smear-negative results.[38]

TREATMENT

TREATMENT OF ACTIVE TUBERCULOSIS

Active tuberculosis treatment requires the use of a combination of antituberculous medications to overcome resistance.[22] Treatment consists of two phases: an intensive phase and a continuation phase.[39,40] Initial therapy includes four first-line medications (isoniazid [INH], rifampin [RIF], pyrazinamide, and ethambutol) for 8 weeks, followed by two-drug continuation treatment for 18 to 31 weeks based on culture results. This long duration of therapy is a challenge to compliance, with 7% to 53.6% of patients defaulting on therapy after 4 weeks.[41] Second-line medications, including fluoroquinolones, are options for drug-resistant cases or when side effects from initial therapy are not tolerable.[39,42] In most cases, antituberculous medications will not be started in the ED unless done in consultation and for classic cases. The recommended Centers for Disease Control and Prevention regimens are as follows[22]:

- Daily four-drug (INH, RIF, pyrazinamide, and ethambutol) therapy for 8 weeks, followed by either INH/RIF or INH/rifapentine for 18 weeks *or*
- Daily four-drug therapy for 2 weeks, followed by two times per week for 6 weeks, with subsequent INH/RIF or INH/rifapentine for 18 weeks *or*
- Three times weekly four-drug therapy for 8 weeks, followed by INH/RIF three times weekly for 18 weeks *or*
- Daily three-drug therapy (INH, RIF, and ethambutol) for 8 weeks followed by INH/RIF for 31 weeks

Combination therapy taken daily reduces the risk of relapse and the development of secondary resistance to RIF. Administration of fixed drug combination tablets optimizes effectiveness. Use prolonged therapy in immunocompromised patients, patients with cavitary pulmonary tuberculosis and positive sputum culture after 2 months of therapy, or patients with extrapulmonary disease (disseminated, CNS involvement, skeletal tuberculosis, and drug-resistant tuberculosis).

Once available, modify initial therapy based on drug susceptibilities. Direct observation of therapy is paramount in patients for whom compliance is a concern; the Centers for Disease Control and Prevention recommends that all regimens using twice- or thrice-weekly approaches be given using direct observation.[2,22] Patients usually experience clinical improvement within days to weeks of beginning therapy. A variety of medications under evaluation (e.g., bedaquiline, delamanid, pretomanid, SQ-109) may allow shorter treatment regimens.

Although the standard medications used to treat tuberculosis are generally effective and safe, side effects or drug interactions may occur (**Table 67-3**). Hepatotoxicity is the major adverse effect of INH, with rates ranging from 5% to 33%.[43] An asymptomatic increase in aspartate transaminase levels occurs in many patients, which usually resolves within several weeks. If serum transaminases are greater than five times the upper limit of normal or if serum bilirubin is >3 milligrams/dL, stop antituberculous medications.[39] Patients do not require routine monitoring of liver function unless a higher risk for hepatotoxicity exists, such as preexisting liver disease, use of other liver-affecting medicines, pregnancy, ethanol use, HIV, and hepatitis C infection.[2,22,27,43]

A portion of patients treated for tuberculosis worsen after the initiation of antituberculous medications.[12,27,44] This effect is called a **paradoxical reaction** or **immune reconstitution syndrome** and can be seen in any patient receiving treatment for tuberculosis, although it is more

TABLE 67-3 Treatment of Tuberculosis (Adults)*

Drug	Daily (maximum)	Three Times Weekly DOT (maximum)	Two Times Weekly DOT (maximum)	Potential Side Effects and Comments
Isoniazid	5 milligrams/kg PO* (300 milligrams)	15 milligrams/kg PO (900 milligrams)	15 milligrams/kg PO (900 milligrams)	Hepatitis, peripheral neuropathy, drug interactions.
Rifampin (RIF)	10 milligrams/kg PO* (600 milligrams)	10 milligrams/kg PO (600 milligrams)	10 milligrams/kg PO (600 milligrams)	Hepatitis, thrombocytopenia, GI disturbances, drug interactions.
Rifapentine	Not given daily	Not given 3 times weekly	600 milligrams PO twice weekly in adults; not approved in children <12 y old	Hepatitis, thrombocytopenia, exacerbation of porphyria. Recommended by Centers for Disease Control and Prevention for continuation therapy only for human immunodeficiency virus–negative patients.
Rifabutin	5 milligrams/kg PO (300 milligrams)	5 milligrams/kg PO (300 milligrams)	5 milligrams/kg PO (300 milligrams)	Similar to RIF; used for patients who cannot tolerate RIF.
Ethambutol	15–20 milligrams/kg PO (1.6 grams)	25–30 milligrams/kg PO (2.5 grams)	50 milligrams/kg PO (2.5 grams)	Retrobulbar neuritis, peripheral neuropathy.
Pyrazinamide	15–30 milligrams/kg PO (2 grams)	50 milligrams/kg PO (3 grams)	50 milligrams/kg PO (2 grams)	Hepatitis, arthralgia, hyperuricemia.

Abbreviation: DOT = directly observed therapy.

*See http://www.cdc.gov/tb for more accurate weight-based protocols and dosages for children.

commonly seen in those with HIV infection, specifically with CD4 counts ≤50 cells/mm^3. Findings include fever, worsening respiratory status and pulmonary infiltrates, lymphadenopathy, hepatosplenomegaly, ascites, meningitis, and new or worsening CNS lesions. **Hypercalcemia** is a unique finding in paradoxical reactions. Because treatment of both tuberculosis and HIV improves immune function, the paradoxical reaction emanates from improvement in the ability to mount an inflammatory response as mycobacteria clear. The dilemma is differentiating this from treatment failures, drug resistance, and medication noncompliance. (See the "Special Populations" section.)

TREATMENT OF LATENT TUBERCULOSIS

Treatment of latent infection with INH alone is for those with recent asymptomatic skin test conversion (Table 67-2), any person in close contact with an actively infected patient, and anergic patients with known tuberculosis contact.[15,22] Treatment of latent infection is associated with a marked reduction in risk of conversion, approximating 70%.[45] Unless contraindicated, therapy is given for a minimum of 9 months. For those exposed to INH-resistant strains or those who are intolerant, use RIF and pyrazinamide for 2 months with hepatotoxicity monitoring.[22] Rifapentine with INH for latent tuberculosis is useful in those unlikely to complete 9 months of treatment.[46-48]

DISPOSITION AND FOLLOW-UP

OUTPATIENT CARE

Most patients with tuberculosis start therapy as outpatients. If planning discharge or transfer for other nonmedical care, start or maintain therapy while awaiting smear and culture results on all patients with suspicious findings of active tuberculosis, notably cavitary lesions or known previous infection with new weakness or fevers.

Contact primary care physicians and public health services and arrange for long-term care before patient discharge. In the United States, tuberculosis is a reportable disease in most states, and patients with suspected or confirmed tuberculosis should be reported to a public health authority within 24 hours.[49,50] Discharge instructions include home isolation procedures and follow-up at the appropriate clinic to receive medication and ongoing care. **Antituberculous medications should not be instituted in the ED unless there is joint agreement with the consultant and follow-up providers.**

HOSPITAL ADMISSION

Hospital admission is best for ill-appearing, hypoxemic, or dyspneic patients; if the diagnosis is uncertain; if noncompliance is likely or if the social situation makes it difficult to complete evaluation and start care; or for patients with active drug-resistant tuberculosis. Hospitalized patients with suspected tuberculosis require respiratory isolation in a negative-pressure room (**Table 67-4**). An alternative to admission for therapy compliance alone is a court-ordered drug observation program (if available), where scheduled outpatient contacts to ensure medication use occur for the course of therapy.[2]

SPECIAL POPULATIONS

PATIENTS WITH TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS

HIV infection is the strongest known risk factor for tuberculosis, and the incidence of tuberculosis in HIV-positive patients is much higher than in the general population. Patients with a new diagnosis of tuberculosis are almost 20 times more likely to have HIV, and HIV patients are 20 to 30 times more likely to develop tuberculosis, especially within the first year of HIV infection.[51] Tuberculosis (pulmonary and extrapulmonary) often can be the initial clinical manifestation of immunodeficiency and is a defining event in the acquired immunodeficiency syndrome. In 2013, close to 1.1 million people were coinfected with HIV and tuberculosis, with 80% of these cases in Africa.[52] Once active tuberculosis develops, the risk of rapid progression and drug resistance is higher in the HIV patient. Successful treatment with antiretroviral therapy lowers the rate of tuberculosis and reduces the incidence of extrapulmonary involvement.[53] **For these reasons, physicians considering a diagnosis of tuberculosis should obtain HIV testing to provide early diagnosis and therapy.**

TABLE 67-4 Engineering Controls to Reduce the Transmission of Tuberculosis

- High airflow (at least 6 room air changes per hour) with external exhaust
- High-efficiency particulate filters on ventilation system
- Ultraviolet germicidal irradiation
- Negative-pressure isolation rooms
- Personal respiratory protection: high-efficiency particulate filter masks or respirators

Treatment of tuberculosis in HIV-positive patients is effective and not markedly different from others with the infection. However, due to the number of medications taken by patients with HIV, potential drug interactions are common, and compliance may become an issue. Protease inhibitors and several nonnucleoside reverse transcriptase inhibitors have interactions with RIF, and rifabutin can be used in place of RIF in patients with HIV.

The ideal timing of antiretroviral therapy in those with active tuberculosis is uncertain.[1,54] Beginning antiretroviral therapy early reduces progression to acquired immunodeficiency syndrome in patients with HIV, but in those with higher CD4+ counts, delaying initiation of antiretroviral therapy until the continuation phase may be beneficial.[55] (See Chapter 155, "Human Immunodeficiency Virus Infection.")

MULTIDRUG-RESISTANT TUBERCULOSIS

Multidrug-resistant tuberculosis is tuberculosis with isolates that demonstrate resistance to at least INH and RIF, with approximately 20% of *M. tuberculosis* isolates meeting this definition.[56] These forms are also highly infectious, with conversion rates approaching 50% in those exposed.[57,58] *M. tuberculosis* becomes resistant by spontaneous genetic mutation, often as a result of inadequate drug therapy or noncompliance with initial treatment. While resistance confirmation requires culture and sensitivity data, certain historical and clinical features raise the level of suspicion for multidrug-resistant tuberculosis. These include a history of tuberculosis treatment in the past, residence in or travel to an area with high prevalence of drug-resistant tuberculosis, exposure to multidrug-resistant tuberculosis, known INH resistance in the community above 4%, progressing radiographic findings despite therapy, and persistent symptoms or persistently positive sputum cultures despite 4 months of standard treatment.[59]

Extensive drug-resistant tuberculosis occurs when resistance to INH, RIF, any fluoroquinolone, and at least one injectable second-line medication exists[57]; this is an intense worldwide threat to public health and tuberculosis control, associated with poorer outcomes and higher mortality. Extensive drug-resistant tuberculosis exists in New York, California, Italy, Iran, and India.[60,61]

Treatment of multidrug-resistant tuberculosis is challenging and depends on sensitivity patterns from culture. INH provides the strongest bactericidal action, and RIF has important action against dormant bacilli. Some countries may use standardized regimens based on known local resistance patterns. Usually combination therapy with four to six medications (three to five previously unused medications), including the more toxic and less potent second-line medications, is administered for up to 2 years. A fluoroquinolone is typically a part of a long-term regimen, and rifabutin is often used in place of RIF. Success rates rarely exceed 60%.[57,62] In refractory cases, resectional surgery may be necessary in addition to ongoing medical therapy.[59]

The "Global Plan to Stop Tuberculosis" calls for better compliance and new medications to fight against the problem of multidrug-resistant tuberculosis, especially **delamanid**.[62] Other new options include bedaquiline, approved in 2012.[63-65] Treatment for this difficult pathogen is administered for 18 to 24 months *after* negative sputum culture samples.

CHILDREN

The clinical course and disease manifestations of tuberculosis in children have several unique aspects. Although children are at greater risk for developing rapidly progressive and disseminated disease, their presenting signs and symptoms can be subtle. When a child develops tuberculosis, test for infection of family members. Primary tuberculosis in children is often asymptomatic and identified only through screening programs or contact tracing.[66] Children may be asymptomatic even with abnormal radiographs, but many have fever, cough, wheezing, poor feeding, and fatigue. The classic symptoms of fever, night sweats, and weight loss occur more often in older children; however, in those younger than 5 years, presentation may be that of miliary tuberculosis (see below), meningitis, or a pneumonia that does not respond to therapy. The most common extrapulmonary presentation is **cervical lymphadenitis,** but other regions may be involved including the meninges, pericardium, abdomen, bone, joints, kidneys, skin, and eyes. Bony involvement is more common in pediatric patients compared to adults.

The yield of sputum smears and cultures is lower in children because of difficulty in obtaining adequate samples in addition to the lower incidence of cavitary disease.[67,68] Traditionally, obtaining three early morning consecutive gastric lavage or gastric aspirate samples occurred. However, this is invasive, unpleasant, and often requires an overnight admission and trained staff. Sputum induction using bronchodilators, followed by nebulized saline and expectoration of mucus, can improve sampling.[68]

Tuberculosis confirmation in children using culture happens in only 30% to 40% of cases.[25] IGRA and NAAT are not recommended for children less than 5 years old as the immune response differs in this age group, making the tests less reliable.[15] Often, treatment is initiated based on a skin test or on clinical grounds (symptoms, a history of exposure, or abnormal radiographs), and the diagnosis is presumed.[67] Chest radiographs in children typically only demonstrate hilar lymphadenopathy or patchy infiltrate. Multidrug therapy is used for all children with active disease, whereas monotherapy is used for latent infections.

MILIARY TUBERCULOSIS

Miliary tuberculosis is a historic term noting the gross appearance of the lung during disseminated tuberculosis. In such cases, the lung has many small lesions resembling millet seeds. Classic miliary tuberculosis shows diffuse nodules on radiographs (1 to 3 mm) in a patient with positive laboratory testing or by demonstration of mycobacteria in multiple organs. The classic radiographic findings may not appear on films until the disease has progressed over time. A miliary pattern on radiographs exists in conditions other than tuberculosis including histoplasmosis, malignancy, siderosis, and sarcoidosis.[69]

Today, miliary tuberculosis refers to wide hematogenous spread during primary or reactivation disease, and it is associated with higher mortality. Children, the elderly, and immunocompromised patients are all at increased risk of developing miliary disease.

Miliary disease during primary tuberculosis is generally more rapid and severe, often presenting with multiorgan failure, shock, and acute respiratory distress syndrome. Conversely, miliary reactivation often manifests with a chronic, nonspecific clinical course affecting any number of organ systems. Fever, anorexia, night sweats, cough, weight loss, splenomegaly, lymphadenopathy, and signs of multisystem illness should cause one to suspect miliary disease. Cutaneous involvement, seen more often in HIV patients, manifests as papules or vesiculopapules (*tuberculosis cutis miliaris disseminata* or *tuberculosis cutis acuta generalisata*). Choroidal tubercles found on ocular exam are pathognomonic for miliary tuberculosis.

EXTRAPULMONARY TUBERCULOSIS

Approximately 20% of patients with tuberculosis will have extrapulmonary involvement, and 60% will not have concomitant pulmonary infection. The dermatologic, ophthalmologic, nervous, renal, GI, musculoskeletal, endocrine, and cardiac systems all are targets, with high-oxygen tension areas more commonly infected.

TUBERCULOUS MENINGITIS

Tuberculous meningitis is more common in children, although those with HIV or others who are immunocompromised may also be afflicted. The presentation is subtle and subacute over days to weeks, with gradual fever, headache, and cognition or sensorium changes that often are not accompanied by neck stiffness or irritation; this is in contrast with findings in other forms of bacterial meningitis. Focal neurologic deficits or cranial nerve palsies may occur. Suspecting the infection and requesting tuberculosis cultures and smear are key to making a diagnosis.[70] Cerebrospinal fluid findings typically demonstrate lymphocytic pleocytosis, elevated protein, increased opening pressure, and a cerebrospinal fluid–to–protein ratio of <0.5. CT of the head may be normal in 30% of patients with mild CNS disease. Long-term neurologic dysfunction is common, with ventriculoperitoneal shunting needed in 25% of

patients for hydrocephalus. Tuberculous meningitis often seeds after a miliary infection. Treatment parallels other forms of tuberculosis with prolonged therapy, and adjunctive corticosteroids reduce complications.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 68

Pneumothorax

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INTRODUCTION AND EPIDEMIOLOGY

Pneumothorax arises when free air enters the potential space between the visceral and parietal lung pleura. **Primary pneumothoraces** occur without clinically apparent lung disease, either spontaneously or from penetration of the intrapleural space by trauma. **Secondary pneumothoraces** happen in patients with underlying lung disease.

The incidence of **primary spontaneous pneumothorax** admissions is 14.1 per 100,000 population age 15 years and older with a higher rate for males (20.8) than females (7.6), reflecting an increase over earlier years.[1,2] Associated factors increasing the risk of occurrence include cigarette smoking, male gender, mitral valve prolapse, Marfan's syndrome, and changes in ambient pressure. Familial patterns also suggest an inherited association.[2] Physical activity or exertion can precipitate pneumothorax but is not a common pneumothorax-triggering factor. **Traumatic pneumothoraces** are iatrogenic or noniatrogenic. Noniatrogenic pneumothoraces are discussed in the Chapter 261, "Pulmonary Trauma."

Causes of **secondary spontaneous pneumothorax** are listed in **Table 68-1**. Chronic obstructive pulmonary disease is the most common cause.[2,3] Pneumothorax occurs in 5% of patients with acquired immunodeficiency syndrome, often from subpleural necrosis secondary to *Pneumocystis* infection, and carries a high mortality. Because of a continued air leak due to necrosis of lung tissue, simple aspiration fails as treatment in this group of patients.

Hemopneumothorax occurs in 2% to 7% of patients with secondary pneumothorax; if associated with a large amount of blood in the pleural cavity, this can be life threatening.[4-8] Treating the underlying disease may help decrease the risk of future pneumothorax.

TABLE 68-1 Causes of Secondary Pneumothorax

Airway disease
• Chronic obstructive pulmonary disease
• Asthma
• Cystic fibrosis (8%–20% will develop one in lifetime)
Interstitial lung disease
• Sarcoidosis
• Pulmonary fibrosis
• Tuberous sclerosis
Infection
• Human immunodeficiency virus infection, *Pneumocystis* pneumonia
• Tuberculosis
• Bacterial pneumonia, necrotizing
• Lung abscess
Connective tissue disease
• Marfan's syndrome
• Ehlers-Danlos syndrome
• Scleroderma
• Rheumatoid arthritis
Cancer
• Primary lung or metastatic disease
Catamenial pneumothorax

PATHOPHYSIOLOGY

Under normal conditions, the parietal and visceral pleura are in contact, sliding on each other. The pleural space is under negative and dynamic pressure (–5 mm Hg with fluctuations of 6 to 8 mm Hg between inspiration and expiration). The tendency of the chest wall is to expand and for the lungs to collapse from elastic recoil. With the loss of the normal negative pressure in the pleural space that "adheres" the visceral pleura (lungs) to the parietal pleura (ribs), the affected lung collapses. A primary spontaneous pneumothorax occurs when a subpleural bleb ruptures, disrupting pleural integrity and usually involving the lung apex.[7-9] In secondary spontaneous pneumothoraces, disruption of the visceral pleura occurs secondary to underlying pulmonary disease processes.

Once there is a break in the visceral pleura, air travels down a pressure gradient into the intrapleural space, until pressure equilibrium occurs with partial or total lung collapse. Altered ventilation–perfusion relationships and decreased vital capacity contribute to dyspnea and hypoxemia. If air continues to enter the pleural space, intrapleural pressure becomes positive. **Tension pneumothorax** develops as inhaled air accumulates in the pleural space but cannot exit due to a one-way valve system. As intrathoracic pressure (>15 to 20 mm Hg) increases, venous return and cardiac and lung function are severely restricted, resulting in hypoxemia and shock.[9]

CLINICAL FEATURES

Classic symptoms of primary spontaneous pneumothorax are sudden onset of dyspnea and ipsilateral, pleuritic chest pain. The pleuritic component may resolve within the first 24 hours. Profound dyspnea is rare unless the patient has poor reserve due to underlying parenchymal disease or develops a tension pneumothorax. Sinus tachycardia is the most common physical finding. Other classic (albeit uncommon) findings include ipsilateral decreased breath sounds, hyperresonance to percussion, and decreased or absent tactile fremitus. In *traumatic pneumothorax*, the positive predictive value of decreased breath sounds is 86% to 97% for the diagnosis.[10] Physical exam alone is not sensitive enough to exclude the diagnosis.

The clinical hallmarks of **tension pneumothorax** are tracheal deviation away from the involved side, hyperresonance of the affected side, hypotension, and profound dyspnea.[9]

DIAGNOSIS

Pneumothorax is an important consideration in patients with chest pain or shortness of breath, especially in those with underlying lung disease. Patients with pleurisy, pleural effusions, infiltrates, or shingles can present with symptoms like those with pneumothorax.

IMAGING

Chest Radiograph A standard erect posteroanterior chest radiograph is the usual initial test and demonstrates loss of lung markings in the periphery and a pleural line that runs parallel to the chest wall (**Figure 68-1**). Ensure that the line does not extend outside of the chest cavity, suggesting a confluence of shadows or skin line. A lateral radiograph identifies an existing pneumothorax in an additional 14% of cases.[11] An expiratory radiograph does not identify many additional pneumothoraces. The sensitivity of anteroposterior chest radiography, when compared with CT, was 75.5% (95% confidence interval, 61.7% to 86.2%), with a specificity of 100% (95% confidence interval, 97.1% to 100%).[11-13] In critically ill patients who cannot be moved to an erect



FIGURE 68-1. Spontaneous hemopneumothorax. Upright chest radiograph of a 19-year-old male college student with spontaneous hemopneumothorax. Note the large air-fluid level in the inferior portion of the right hemithorax in addition to the complete collapse of the entire right lung. [Reproduced with permission from Stone CK, Humphries RL (eds): *Current Diagnosis & Treatment: Emergency Medicine*, 8th ed. New York: McGraw-Hill Education, Inc. © 2017. Fig 24-2.]

position, look for the **deep sulcus sign**, a profound lateral costophrenic angle, on the affected side.

Large bullae in patients with chronic obstructive pulmonary disease may look like a pneumothorax, although a pneumothorax pleural line will run parallel with the chest wall, whereas bullae will have a medially concave appearance. Pneumothoraces usually cross more than one lung segment, whereas bullae follow a single lobe. A chest CT scan can differentiate these. Placing a chest tube inserted into a bulla mistaken for a pneumothorax results in a large pneumothorax, associated bronchopulmonary fistula, and other complications.[13] Pleural adhesions can cement the visceral and parietal pleura together, changing the appearance of the pneumothorax.

Pneumothorax size calculations use measurement from the apex of the lung to the cupula of the thoracic cavity on an upright posteroanterior film.[11,14] A measurement of <3 cm in this cephalad area is considered a small pneumothorax. Another method is to measure the interpleural distance at the level of the hilum; in this area, a distance of 2 cm correlates with a pneumothorax of approximately 50% by volume.[11,15] The British Thoracic Society defines a small pneumothorax as one with a <2-cm rim between the lung edge and chest wall; a large pneumothorax is defined as one with a ≥2-cm rim.[11,15]

US US detects traumatic pneumothorax, with a reported sensitivity of 98.1% (95% confidence interval, 89.9% to 99.9%) and specificity of 99.2% (95% confidence interval, 95.6% to 99.9%).[16,17] The movement of the lung (ocean) against the stationary chest wall (shore) is referred to as the "seashore." In a normal lung, there is a sonographic reverberation distal to the pleura that looks like a **comet tail** and a **sliding sign** of the movement of the visceral pleura along the parietal pleura (**Figure 68-2**); these are not seen in pneumothorax. In loculated pneumothoraces (from adhesions), the sliding sign and the comet tail findings are altered and limit the specificity for pneumothorax.[18,19] In addition, a bleb point may lose a sliding sign and inaccurately suggest a pneumothorax.[13]

Chest CT Chest CT detects an additional 25% to 40% of pneumothoraces not seen on plain chest radiographs.[16] CT can detect other pathology such as pulmonary blebs. If a chest radiograph does not demonstrate pneumothorax but there is clinical suspicion for the condition (e.g., in symptomatic high-risk patients, those with underlying lung disease or positive-pressure ventilation, or after lung biopsy), obtain a chest CT (**Figure 68-3**).

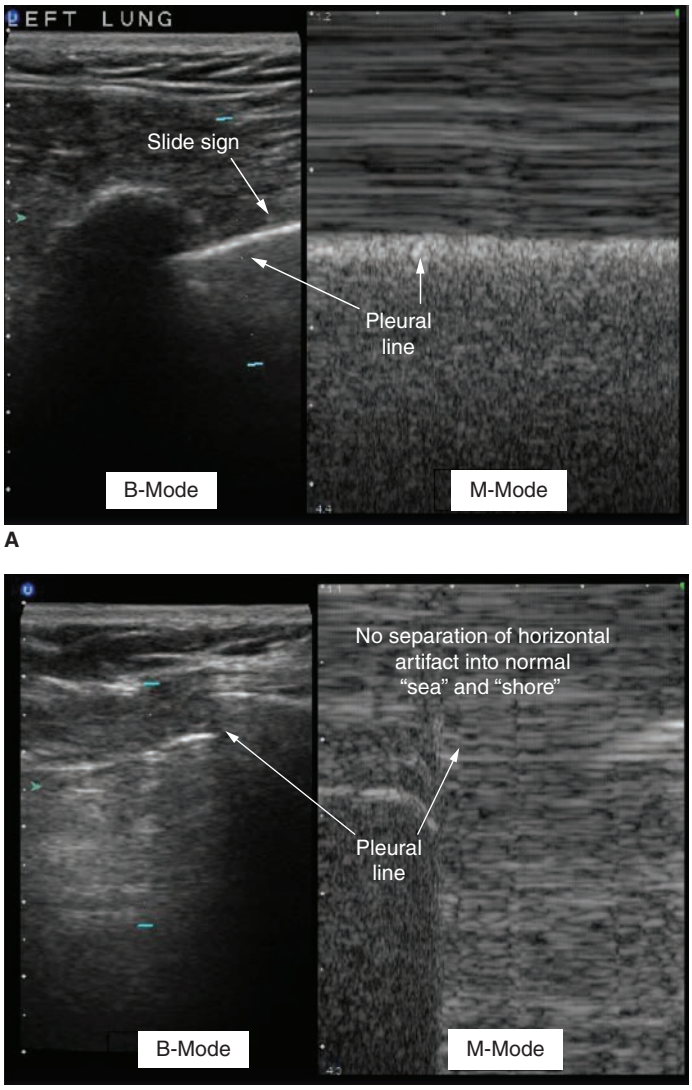

FIGURE 68-2. US with M-mode and B-mode imaging of normal (**A**) and abnormal (**B**) pleura. [Image used with permission of Casey Glass, MD, Wake Forest School of Medicine.]

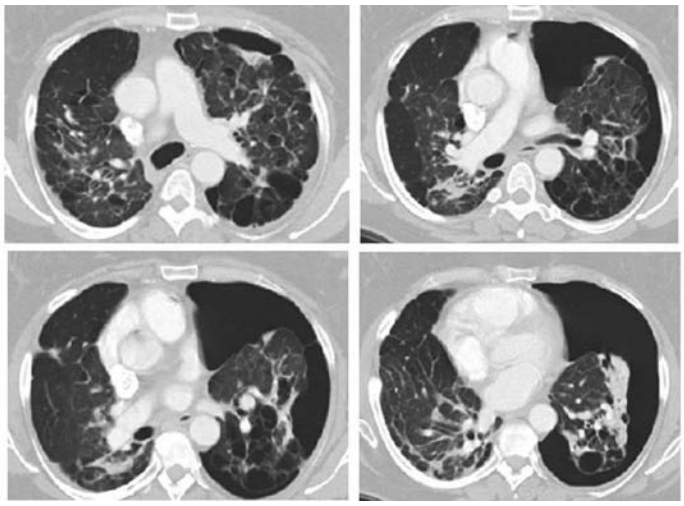

FIGURE 68-3. Secondary spontaneous pneumothorax. CT of a large, left-sided secondary spontaneous pneumothorax. Note diffuse bullous emphysema.

TABLE 68-2 Criteria for Stable Patient With Pneumothorax

- Respiratory rate <24 breaths/min
- No dyspnea at rest, speaks in full sentences
- Pulse >60 and <120 beats/min
- Normal blood pressure for patient
- Room air oxygen saturation >90%
- Absence of hemothorax

TREATMENT

The ED treatment goal is the elimination of intrapleural air. **Tension pneumothorax is a clinical diagnosis—ideally before a radiograph—and is *immediately* treated by needle decompression and/or a tube thoracostomy.**

Treatment options are oxygen, observation, needle or catheter aspiration (either single or sequential aspirations), and tube thoracostomy (either small-size or standard chest tube) (**Tables 68-2** and **68-3**). **Oxygen** administration (>28%) increases pleural air resorption three- to fourfold over the base 1.25% reabsorbed per day by creating a nitrogen gas pressure gradient between the alveolus and trapped air.[20-22] Without supplemental oxygen, a 25% pneumothorax would take approximately 20 days to resolve. Recommended oxygen dosing ranges from 3 L/min by nasal cannula to 10 L/min by mask. Monitor for hypercapnia in patients with chronic obstructive pulmonary disease.

Observation is appropriate for small, stable pneumothoraces. If selecting this option, observe the patient for at least 4 hours on supplemental oxygen, and repeat the chest radiograph. If symptoms and chest radiograph improve, the patient should return in 1 to 2 weeks for repeat examination. First-time spontaneous pneumothorax of <20% lung volume in a stable, healthy adult is a scenario where initial oxygen therapy and observation are possible.[20-25]

Aspiration or tube thoracostomy therapy is based on the likelihood of recurrence and likelihood of spontaneous resolution. Pneumothoraces in patients with underlying pulmonary disease are likely to recur. Large (>2 cm) pneumothoraces and those with an air leak are also unlikely to resolve without drainage. Inability to return for care or to tolerate any pneumothorax increase (i.e., those with poor cardiopulmonary reserve) should prompt drainage.

Many factors guide interventions: The stability of the patient, the degree of symptoms, the size and relative change in size over time, the cause of the pneumothorax, the degree of underlying lung disease, the presence of a hemothorax, the likelihood of recurrence and resolution, and the need for positive-pressure ventilation are factors to consider (**Tables** 68-2, 68-3, and **68-4**).[15-17,20-27]

The selection of catheter or chest tube size is based on the flow rate of air that the device can accommodate. Select large-bore tubes for anticipated bigger air leaks, notably from mechanical ventilation. Tension pneumothorax can develop if a large air leak develops despite small-bore tubes or catheters. Every chest tube has a proximal hole, called the sentinel eye, which is visible radiographically and helps ensure that all drainage holes are inside the pleural cavity.[27-31]

TABLE 68-3 Aspiration and Thoracostomy Devices*

Single aspiration	Insertion of a needle or catheter, aspiration of air using an attached syringe, and immediate removal of the device
Needle aspiration	18-gauge needle (provided in kits as an 8F catheter over an 18-gauge needle)
Small-size catheter	≤14F
Small-size chest tube	10F–14F
Pigtail catheter	14F, placement using Seldinger technique
Moderate-size chest tube	16F–22F
Large-size chest tube	24F–36F

*The term "catheter" is used for a thin flexible tube; the term "chest tube" is used for a more rigid, larger tube. French (F) sizes represent tube or catheter diameter (1 French = $^1/_3$-mm diameter), and the larger the French number, the larger the device.

TABLE 68-4 Treatment of Pneumothorax

Condition	Treatment Options
Small primary pneumothorax (<20% or 3 cm apex-cupula and asymptomatic)	Observation for >3 h on oxygen, repeat chest radiograph, discharge if no symptoms, and return for evaluation if symptoms recur or in 2 wk *or* Small-size catheter aspiration with immediate catheter removal, then observe for >3 h, discharge if no symptoms, and return for evaluation if symptoms recur in 2 wk *or* Small-size catheter aspiration or small-size chest tube insertion, Heimlich valve, or water seal and admission
Small secondary pneumothorax	Small-size catheter or small-size chest tube insertion, Heimlich valve, or water seal and admission
Large pneumothorax, either primary or secondary, or bilateral pneumothoraces	Moderate-size chest tube and admission; large-size chest tube if fluid or hemothorax present; water seal and admission
Tension pneumothorax	Immediate needle decompression followed by moderate or large-size chest tube insertion, water seal drainage, and admission; immediate chest tube placement ideal

NEEDLE DECOMPRESSION

To decompress, use a 14-gauge needle for adults at least 2 inches (5 cm) long to penetrate the pleural cavity. Two locations are optimal: into the **second intercostal space just above the rib** (to avoid the intercostal artery) at the midclavicular line, or in the **fourth intercostal space just above the rib and at the anterior axillary line** (**Figure 68-4**). Recent

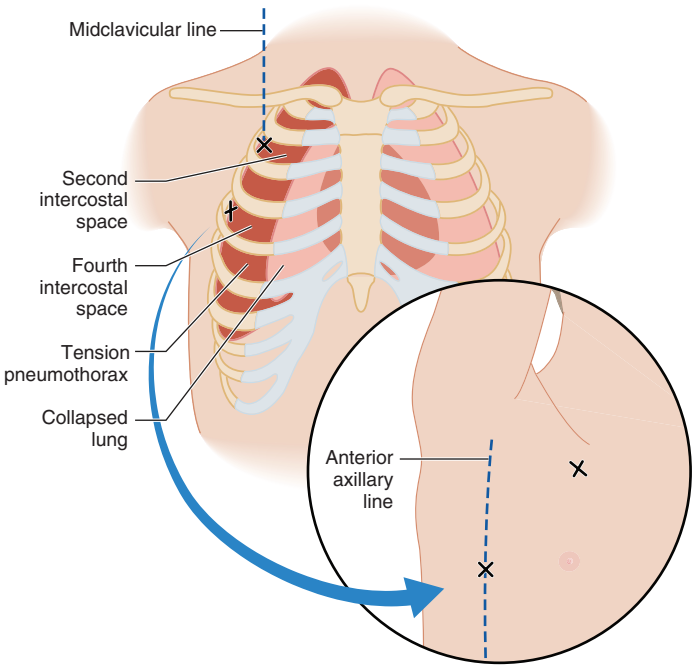

FIGURE 68-4. Needle placement for decompression of a right-sided tension pneumothorax. A site for a needle thoracostomy is the 2nd intercostal space in the midclavicular line, or the 4th intercostal space at the anterior axillary line.

studies suggest a decompression success rate of only 65% using these approaches and a 51-mm needle; a longer needle may be necessary.[31-33] If the needle insertion is medial to the midclavicular line, mediastinal vessels can be injured.

NEEDLE OR CATHETER ASPIRATION

Needle or catheter aspiration is as effective as thoracostomy for treating the first episode of small primary or secondary spontaneous pneumothorax,[26] with success ranging from 37% to 75% and higher in those with primary spontaneous pneumothorax.[27] Techniques include simple one-time aspiration with a large-gauge needle or a small-bore catheter, repeated aspirations through a small-size catheter, or chest tube attached to a one-way valve (including the Heimlich valve) or water seal drainage. The catheter technique has the advantages of both aspiration and chest tube placement.[28]

Small-Size Catheters The catheter technique involves placing a small catheter either into the second anterior intercostal space in the midclavicular line or laterally at the fourth or fifth intercostal space in the anterior axillary line after local anesthesia and sterile preparation. Attach a three-way stopcock and use a 60-mL syringe to aspirate the pleural space until resistance is met, often triggering a cough. Close the stopcock, secure the tube, and obtain a follow-up chest radiograph to ensure lung reexpansion. Aspiration of more than 4 L suggests continued air leak and failure of simple aspiration. Failure of the lung to fully expand warrants formal tube thoracostomy and admission.

Pigtail Catheters Using Seldinger Technique Advantages of this technique are a smaller incision, less tissue dissection, and smaller scar. Insert the needle into the pleural space, making sure placement is in the "triangle of safety" (**Figure 68-5**).[29,30] Aspirate fluid or air to verify location in the pleural space, and advance a guidewire through the needle. Place a dilator over the guidewire until entering the pleural space. Remove the dilator and place the chest tube over the wire into the pleural space. Remove the wire, secure the tube, and attach to suction.

Tube Thoracostomy Chest tube thoracostomy is best for treating a large pneumothorax, recurrent or bilateral pneumothorax, or coexistent hemothorax, or if there are abnormal vital signs or dyspnea. A chest tube aids care for those with small spontaneous secondary pneumothoraces where large air leak is anticipated or noted. Standard chest tube thoracostomy with underwater seal drainage is the most commonly used approach, with a low complication rate and a success rate of 95%.[25,26] Most guidelines suggest a 10F to 14F chest tube for nontraumatic pneumothoraces, reserving larger 14F to 22F chest tubes if a large air leak is probable, such as from mechanical ventilation or with underlying pulmonary disease. Chapter 261, "Pulmonary Trauma," describes the procedure. (See Video: Chest Tube Insertion.)

There is no clear difference between simple aspiration and intercostal tube drainage in overall short- and long-term outcomes,[25] and simple aspiration is safe and effective for a small-volume air leak primary spontaneous pneumothorax.[26] Pleurodesis helps prevent recurrence in those with first spontaneous pneumothorax with a persistent air leak, second spontaneous pneumothorax, bilateral spontaneous pneumothoraces, first episode of a secondary pneumothorax, or recurrent high-risk activities (flying or diving).[4,9]

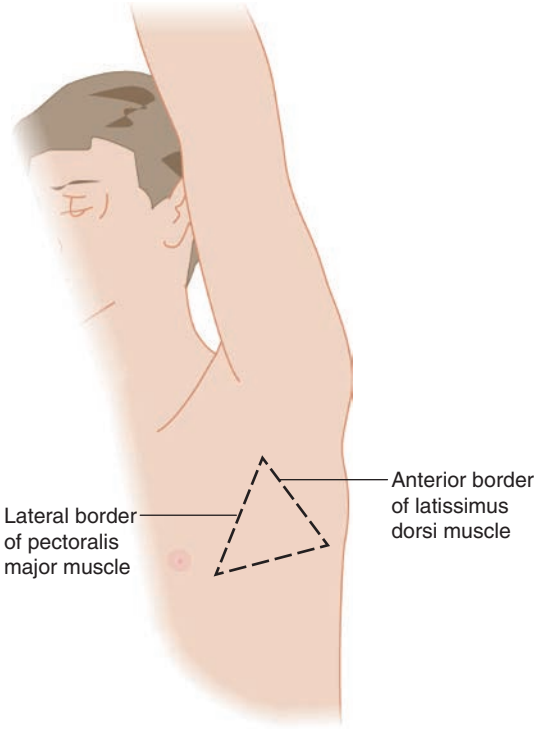

FIGURE 68-5. Safe location of chest tube, within a triangle bordered by the fifth intercostal space, pectoralis major, and latissimus dorsi.

TREATMENT COMPLICATIONS

Complications of a pneumothorax can include those due to hypoxia, hypercapnia, and hypotension. Reexpansion lung injury is uncommon and seen more often when there is collapse of the lung for >72 hours, a large pneumothorax, rapid reexpansion, or negative pleural pressure suction of >20 cm.[4,9] Most patients need no treatment for reexpansion injury aside from observation or oxygen, with few adverse outcomes.[34]

Intervention complications include intercostal vessel hemorrhage, lung parenchymal injury, empyema, and tube malfunction (development of an air leak or tension pneumothorax).

SPECIAL CONSIDERATIONS

IATROGENIC PNEUMOTHORAX

Iatrogenic pneumothorax is a subset of traumatic pneumothorax; it occurs more often than spontaneous pneumothorax and is common, underdetected, and underreported.[26,27,35] Transthoracic needle procedures (needle biopsy and thoracentesis) account for approximately half of iatrogenic pneumothoraces, and subclavian vein catheterization accounts for one fourth. Factors associated with the increasing frequency of iatrogenic pneumothorax include the patient population, underlying disease, body habitus, and experience of the operator. US guidance for central venous catheter insertion for thoracentesis reduces the pneumothorax complication rate.

Although it is routine to obtain a chest radiograph after central line placement or transthoracic needle procedures, this may not identify a pneumothorax if supine or if there is inadequate time for the pneumothorax to develop, with up to one third detected later.[27] Bedside US is an excellent rapid alternative to chest radiograph to detect central venous catheter misplacement and iatrogenic pneumothorax, with a reported specificity of 99% and sensitivity of 68%.[16]

Treatment for iatrogenic pneumothorax is the same as that for spontaneous pneumothorax. Patients with a small pneumothorax after a needle puncture and those not requiring positive-pressure ventilation are often observed or treated with simple catheter aspiration (with or without a Heimlich valve), which is adequate for 60% to 80% of patients.[27] Long-term recurrence is not a concern with iatrogenic pneumothorax.

AIR TRANSPORT WITH PNEUMOTHORAX

Increased elevation causes an increase in gas volume (Boyle's law), increasing the risk for tension pneumothorax in air transport patients with pneumothorax, particularly when transported in fixed-wing vehicles (airplane) given the altitudes reached.[21] Air medical experts recommend no high-altitude flying for at least 7 to 14 days after pneumothorax resolution.

DIVING

Similarly and also due to Boyle's law, development of a pneumothorax at depth may lead to a tension pneumothorax with ascent. Current

guidelines suggest that a history of spontaneous pneumothorax is a contraindication to underwater diving unless treated by surgical pleurectomy and normal lung function exists.[21]

DISPOSITION

Discharge to home patients with a primary spontaneous pneumothorax successfully treated with observation or with catheter aspiration if the pneumothorax does not increase in size over 3 to 6 hours and symptoms resolve or do not worsen. Observe for longer or admit the remaining patients.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

TABLE 69-1 Physiologic Consequences of Airflow Obstruction in Acute Asthma

- Increased airway resistance
- Decreased maximum expiratory flow rates
- Air trapping
- Increased airway pressure
- Barotrauma
- Adverse hemodynamic effects
- Ventilation–perfusion imbalance
- Hypoxemia
- Hypercarbia
- Increased work of breathing
- Pulsus paradoxus
- Respiratory muscle fatigue with ventilatory failure

CHAPTER 69

Acute Asthma and Status Asthmaticus

Tadahiro Goto
Kohei Hasegawa

INTRODUCTION AND EPIDEMIOLOGY

Asthma is a chronic inflammatory disorder characterized by increased responsiveness of the airways to multiple stimuli. In susceptible individuals, the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes—acute asthma—usually have widespread and varying airflow obstruction.

Although most acute asthma episodes improve spontaneously or within minutes to hours with treatment, with symptom-free intervals in between, many patients with asthma develop chronic airflow limitation. This impacts the diagnosis and management of episodes and the attempts to prevent recurrent acute asthma.

Asthma affects approximately 8% of the U.S. population, is the most common chronic disease of childhood (9% prevalence), and has a similar prevalence in developed nations around the world.[1-3] Approximately one half of asthma cases develop before the age of 10 years, and another one third develop by the age of 40 years.

PATHOPHYSIOLOGY

Asthma sufferers have an abnormal accumulation of eosinophils, lymphocytes, mast cells, macrophages, dendritic cells, and myofibroblasts in airways. The pathophysiologic hallmark of asthma is a reduction in airway diameter caused by smooth muscle contraction, vascular congestion, bronchial wall edema, and thick secretions. These changes create pulmonary function changes, increased work of breathing, and abnormal distribution of pulmonary blood flow (**Table 69-1**). Large and small airways contain plugs composed of mucus, serum proteins, inflammatory cells, and cellular debris. Inflammation affects all bronchial pulmonary structures.

Asthma is a continuum from acute bronchospasm through airway inflammation to permanent airway remodeling. Airway remodeling, with sub-basement membrane thickening, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, angiogenesis, and mucous gland hyperplasia and hypersecretion, can become a trigger for nonreversible loss of lung function.[4]

Acute allergic bronchoconstriction results from immunoglobulin E–dependent release of mediators from mast cells. These mediators include histamine, leukotrienes, tryptase, and prostaglandins that directly contract airway smooth muscle.[4] Bronchospasm induced by aspirin and other NSAIDs also involves mediator release from airway cells.[4] Airway inflammation occurs as inhaled antigens activate immunoglobulin E, mast cells, dendritic cells, T helper cells, and epithelial cells in the airway and induce inflammatory mediators and cytokines. In turn, this initiates a cascade of inflammatory response, which is multicellular, redundant, and self-amplifying.

Acute asthma is an exaggerated airway response to a variety of external exposures. Viral acute respiratory infections are the most common acute asthma stimulus,[5] accounting for 40% to 80% of episodes in adults and 80% in children.[6] Exercise is another common precipitant of acute asthma. Environmental conditions, such as atmospheric pollutants and indoor antigens (e.g., mold, house dust mites, cockroaches, and animal dander), trigger acute asthma and may result in severe cases. Occupational exposures, such as metal salt, wood and vegetable dust, pharmaceuticals, industrial chemicals, plastics, biological enzymes, vapors, gases, and aerosols, also may stimulate acute asthma. Agents such as aspirin, β-blockers, and NSAIDs may prompt acute asthma. Exposure to cold air alone can induce acute bronchospasm. Endocrine factors, such as changing levels of estradiol and progesterone during the normal menstrual cycle and pregnancy, contribute to the level of airway reactivity.[7] Emotional stress also can produce acute asthma.

CLINICAL FEATURES

Early recognition of acute asthma and treatment before the exacerbation becomes severe are the essentials of acute asthma management in the ED. Focus the initial assessment on history and physical examination; for most patients, an objective assessment of lung function (e.g., peak expiratory flow rate [PEFR]) aids assessment. The typical symptoms of acute asthma include dyspnea, wheezing, and cough. Many, but not all, patients will relay the history of asthma. Other historical features guide care for acute asthma[8-11] (**Table 69-2**). In addition, because patients who are at the highest risk for fatal asthma require special attention, seek out risk factors for a fatal exacerbation. The severity of acute asthma is categorized based on clinical features[8-11] (**Table 69-3**).

Physical examination includes general appearance (e.g., respiratory distress, level of consciousness), vital signs (e.g., tachycardia, tachypnea), and chest findings (e.g., wheezing). Wheezing can be an unreliable indicator of airflow obstruction in acute asthma. A silent chest without wheezing occurs in extremely severe airflow obstruction.[12] Use of accessory muscles, inability to speak in full sentences or phrases, and presence of pulsus paradoxus help identify severe acute asthma.[8] Look also for concomitant illnesses (e.g., pneumonia, pneumothorax) or mimicking conditions such as upper airway obstruction from foreign bodies and vocal cord dysfunction (**Table 69-4**). The latter is a common reason why patients who fail therapy and have frequent ED return visits get labeled as having "refractory asthma"; such patients simply do not have *lower* airway disease.

TABLE 69-2 Key History Points in Patients With Acute Asthma[8-11]

Symptoms	Pattern	Disease History	Risk Factors for Death From Asthma
Cough	Perennial and/or seasonal	Cigarette smoking	Past history of severe exacerbation
Wheezing	Continual or episodic	Present management and medications	≥2 hospitalizations for asthma in the past year
Shortness of breath	Onset	Medication regimen adherence	>3 ED visits for asthma in the past year
Chest tightness	Duration	History of corticosteroid use (chronic and/or intermittent)	>2 canisters per month of inhaled short-acting β_2-agonist
Sputum production	Frequency	Intensive care admissions	Difficulty perceiving airflow obstruction or its severity
Fever	Aggravating factors	History of intubation	Low socioeconomic status or inner-city resident
	Usual pattern of exacerbation and outcome	Best spirometry measures	Illicit drug use
			Psychiatric disease or medical comorbidities

DIAGNOSIS AND PATIENT MONITORING

Physical examination findings and subjective symptoms do not necessarily correlate well with the severity of airflow obstruction, making objective measures valuable. Forced expiratory volume in 1 second (FEV_1) and PEFR are key objective measures of severity of acute asthma. The FEV_1 advantage is that in contrast to PEFR, it can help distinguish between poor effort, restrictive lung disorders, vocal cord dysfunction, and obstructive disorders (e.g., asthma). PEFR measurements using peak flow meter provide a reasonable estimate of the severity of acute asthma in the ED. In addition, PEFR measurements help monitor the response to the treatment. Repeat either FEV_1 or PEFR because comparing measures at ED presentation and 1 hour after treatment is the best predictor of hospitalization in patients with acute asthma.[13,14] Patient education and cooperation are essential for these measurements to be reliable.[8-11]

Pulse oximetry assesses oxygen saturation during treatment. Arterial blood gas measurement is not needed in patients with mild to moderate asthma exacerbation and should be reserved for suspected hypoventilation with carbon dioxide retention and respiratory acidosis. With acute asthma, ventilation is stimulated, resulting in a decrease in partial pressure of arterial carbon dioxide ($Paco_2$); if a normal or slightly elevated $Paco_2$ (e.g., >42 mm Hg) exists, think of extreme airway obstruction, fatigue, and potential acute ventilatory failure. Patients with impending respiratory failure almost always have clinical evidence of severe acute asthma or spirometry demonstrating a PEFR or FEV_1 of <25% predicted. The use of capnography in acute asthma management is unclear. One small study reported good concordance between expired carbon dioxide levels measured by capnography and arterial carbon dioxide concentration,[15] but another reported differences of up to >10 mm Hg between the two approaches.[16]

Chest radiographs help to detect pneumothorax, pneumomediastinum, pneumonia, or other causes for symptoms (e.g., acute heart failure) or complications of acute asthma. Plain radiographs are not needed for all patients with acute asthma, but are better selectively used when there is suspicion for the previously mentioned conditions. In patients hospitalized for acute asthma, less than one third of patients have an abnormal chest radiograph.[17]

A CBC is not routinely needed and likely will show modest leukocytosis secondary to administration of β-agonist therapy and/or corticosteroids. For patients with severe acute asthma (e.g., those hospitalized for acute asthma), serum total immunoglobulin E level and eosinophil quantification may aid chronic asthma management using biologic agents (e.g., anti–immunoglobulin E monoclonal antibody).[18,19] Routine ECG is also unnecessary and often normal or nondiagnostic, but may reveal right ventricular strain, abnormal P waves, or nonspecific ST- and T-wave abnormalities, which resolve with treatment. Use cardiac monitoring in older patients and those with coexisting heart disease.

TABLE 69-3 Classifying Severity of Acute Asthma in Patients Aged >12 Years Old and Adults*

	Symptoms and Signs	Initial PEF (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity	PEF ≥70% predicted or personal best	Prompt relief with inhaled SABA.
Moderate	Dyspnea interferes with or limits usual activity	PEF 40%–69% predicted or personal best	Relief from frequent inhaled SABA. Symptoms for 1–2 d after oral corticosteroids begun.
Severe	Dyspnea at rest; interferes with conversation	PEF <40% predicted or personal best	Partial relief from frequent inhaled SABA. Symptoms for ≥3 d after oral corticosteroids begun.
Subset: life-threatening	Too dyspneic to speak; perspiring	PEF <25% predicted or personal best	Minimal or no relief from frequent inhaled SABA; IV steroids; adjunctive therapy; needs ED or intensive care unit.

*The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation. Many of these parameters have not been systemically studied, so they serve only as general guides.

Abbreviations: FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow; SABA = short-acting β_2-agonist.

Source: www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf (National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services: NIH Publication Number 08-5846, October 2007, Fig. 20). Accessed June 15, 2018.

ACUTE ASTHMA STANDARD TREATMENT

The goal is a rapid reversal of airflow obstruction by repetitive or continuous administration of inhaled β_2-agonists, adequate oxygenation, and decrease in inflammation.[8-11] **Figure 69-1** shows the National Asthma Education and Prevention Program ED treatment algorithm.[11]

β-ADRENERGIC AGENTS

Rapid-onset β_2-adrenergic agonists are the preferred initial therapy for acute bronchospasm (**Table 69-5**). Stimulation of β_1-receptors increases rate and force of cardiac contraction, whereas β_2-adrenergic stimulation promotes bronchodilation and vasodilation.

TABLE 69-4 Important Asthma Mimickers

- Acute heart failure ("cardiac asthma")
- Upper airway obstruction
- Pulmonary embolism
- Aspiration of foreign body or gastric acid
- Tumors/disorders causing endobronchial obstruction
- Interstitial lung disease
- Vocal cord dysfunction

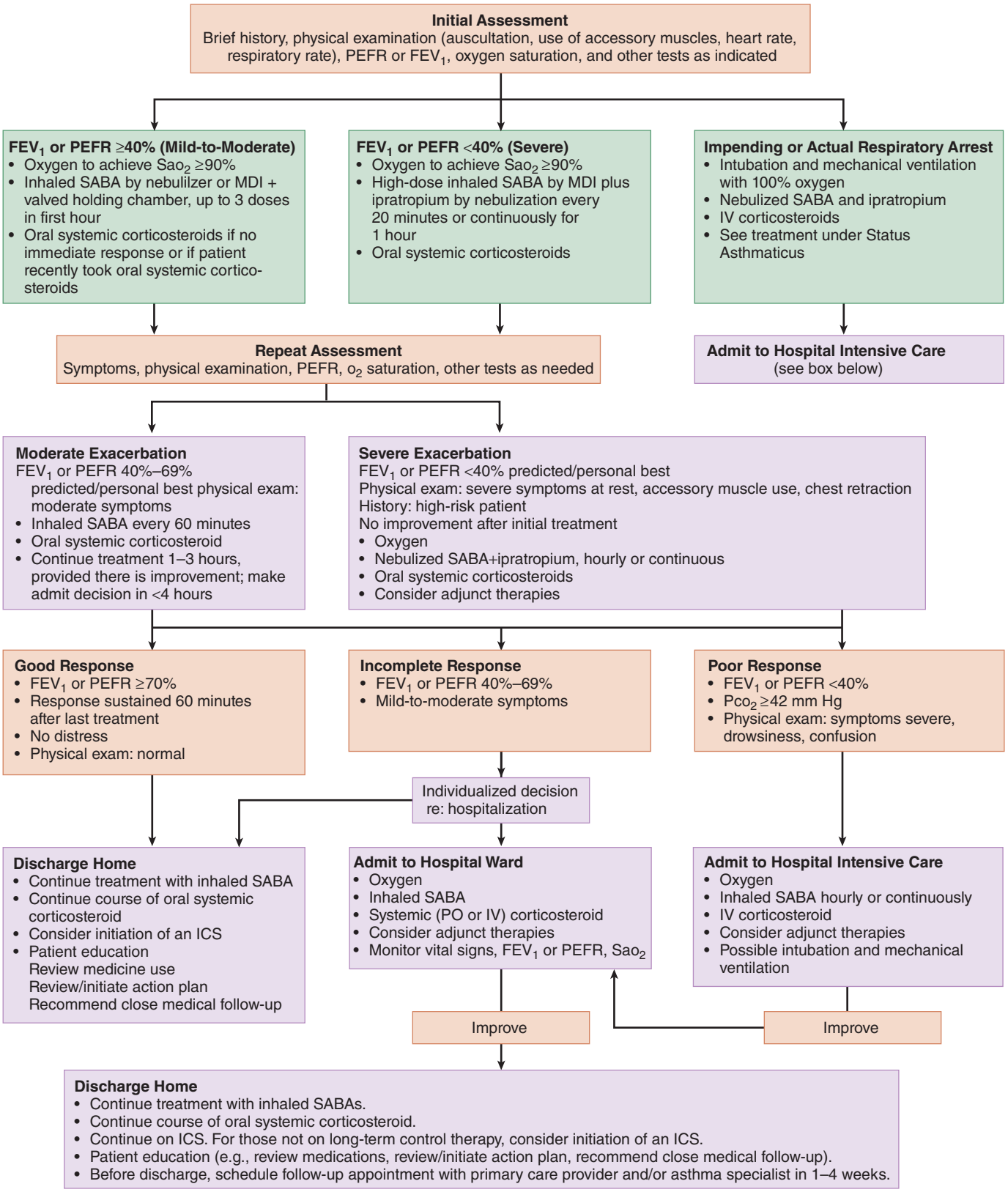

FIGURE 69-1. Management of asthma exacerbations: ED and hospital-based care. FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; MDI = metered-dose inhaler; PEFR = peak expiratory flow rate; SABA = short-acting β_2-agonist; Sa_{O_2} = oxygen saturation by pulse oximetry. [Source: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf (National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services: National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Publication No. 08-4051. Bethesda, MD, National Institutes of Health, 2007). Accessed November 18, 2014.]

TABLE 69-5 β-Adrenergic, Anticholinergic, and Steroid Dosages of Drugs for Asthma

Medication	Dose	Comments
Inhaled β_2-Agonists		
Albuterol		
Nebulizer solution (0.63 milligram/3 mL, 1.25 milligrams/3 mL, 2.5 milligrams/3 mL, 5.0 milligrams/mL)	2.5–5 milligrams every 20 min for 3 doses, then 2.5–10 milligrams every 1–4 h, as needed, or 10–15 milligrams/h as continuous nebulization.	Only selective β_2-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min. Use large-volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution.
MDI (90 micrograms/puff)	4–8 puffs every 20 min up to 4 h, then every 1–4 h as needed.	In mild-to-moderate exacerbations, MDI plus valved holding chamber is as effective as nebulized therapy with appropriate administration technique and coaching by trained personnel.
Levalbuterol (R-albuterol)		
Nebulizer solution (0.63 milligram/3 mL, 1.25 milligrams/3 mL)	1.25–2.5 milligrams every 20 min for 3 doses, then 1.25–5 milligrams every 1–4 h, as needed.	Levalbuterol administered in one half the milligram dose of albuterol provides comparable efficacy and safety. Has not been evaluated for continuous nebulization.
MDI (45 micrograms/puff)	See albuterol MDI dose.	
Systemic (Injected) Agents		
Epinephrine (α- and β-agonist) 1:1000 (1 milligram/mL)	0.3–0.5 milligram every 20 min for 3 doses SC or IM.	No proven advantage of systemic therapy over aerosol.
Terbutaline (β_2-agonist) (1 milligram/mL)	2 micrograms/kg may be given over 5 min, followed by continuous infusion of 5 micrograms/kg/h.	No proven advantage of systemic therapy over aerosol.
Anticholinergics/Combinations		
Ipratropium bromide		
Nebulizer solution (0.25 milligram/mL)	0.5 milligram every 20 min for 3 doses, then as needed.	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to SABA therapy for severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized.
MDI (18 micrograms/puff)	Eight puffs every 20 min, as needed, up to 3 h.	Should use with valved holding chamber and facemask for children <4 y. Studies have examined ipratropium bromide MDI for up to 3 h.
Ipratropium with albuterol		
Nebulizer solution (each 3-mL vial contains 0.5 milligram of ipratropium bromide and 2.5 milligrams of albuterol)	3 mL every 20 min for 3 doses, then as needed.	May be used for up to 3 h in the initial management of severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized.
MDI (each puff contains 18 micrograms of ipratropium bromide and 90 micrograms of albuterol)	Eight puffs every 20 min as needed up to 3 h.	Should use with valved holding chamber and facemask for children <4 y.
Systemic Corticosteroids		Applies to all 3 corticosteroids for oral medications.
Prednisone	For inpatients: oral "burst," use 40–80 milligrams/d in 1 or 2 divided doses until PEFR reaches 70% of predicted or personal best.	For outpatients: oral "burst," use 40–60 milligrams in 1 or 2 divided doses for 5–10 d.
Methylprednisolone	IV: 1 milligram/kg every 4–6 h.	For outpatients: a single IM dose of 150 milligrams depot methylprednisolone may be used.[19]
Prednisolone	1–2 milligrams/kg/d for 5–10 d; may be divided twice daily.	More frequently used over prednisone in children due to increased palatability of available liquid formulations.

Notes: There is no known advantage for higher doses of corticosteroids in severe asthma exacerbations, nor is there any advantage for IV administration over oral therapy provided GI transit time or absorption is not impaired.

The course of systemic corticosteroids for an asthma exacerbation requiring an ED visit or hospitalization may last from 3 to 10 days. For corticosteroid courses of <1 week, there is no need to taper the dose. For slightly longer courses (e.g., up to 10 days), there probably is no need to taper, especially if patients are concurrently taking inhaled corticosteroids. Inhaled corticosteroids can be started at any point in the treatment of an asthma exacerbation.

Abbreviations: MDI = metered-dose inhaler; PEFR = peak expiratory flow rate.

Source: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf (National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services: National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Publication No. 08-4051. Bethesda, MD, National Institutes of Health, 2007). Accessed June 20, 2019.

β-Adrenergic drugs cause bronchodilation by stimulation of the enzyme adenyl cyclase, which converts intracellular adenosine triphosphate into cyclic adenosine monophosphate. β-Adrenergic drugs also inhibit mediator release and promote mucociliary clearance.

The most common side effect of β-adrenergic drugs is skeletal muscle tremor. Patients also may experience nervousness, anxiety, insomnia, headache, hyperglycemia, palpitations, tachycardia, and hypertension. *Clinical toxicity is rare and less common than undertreatment complications*. Provoking dysrhythmias or myocardial ischemia is sporadic, especially in those without a prior history of coronary artery disease. The early-generation bronchodilators, such as epinephrine, are not β_2 specific and have a short duration of action.

Albuterol (racemic mixture) and levalbuterol (isomer form, Xopenex®) are β_2-adrenergic drugs. Both racemic albuterol and levalbuterol can be

given as intermittent or continuous nebulization.[20-22] Levalbuterol costs 5 to 25 times more than albuterol, and it has no clear advantage over albuterol regarding improvement in symptoms, hospitalization, or tachycardia.

Aerosol therapy with β_2-adrenergic drugs produces excellent bronchodilation and is favored over oral or parenteral routes. The aerosol route achieves topical administration of a relatively small dose of drug, thereby producing local effects with minimum systemic absorption and fewer side effects. Aerosol delivery occurs with a metered-dose inhaler coupled to a spacing device or with a compressor-driven nebulizer.[23] A spacing device attached to the inhaler improves drug deposition; when optimally used, ***metered-dose inhaler therapy delivers the most drug to target airways, better than nebulized therapy***. Even with optimum technique, a maximum of 15% of the drug dose is retained in the lungs, regardless of the aerosol method used. Give aerosol treatments every 15 to 20 minutes or on a continuous basis.[24] SC epinephrine and terbutaline are options for patients unable to coordinate aerosolized or metered-dose inhaler treatments, seen often in severe airflow-limited states. IV β-agonist infusions offer no advantage over aerosolized or metered-dose inhaler–delivered agents and carry an increased risk of systemic side effects.[25]

Salmeterol xinafoate and formoterol are long-acting β_2-adrenergic agonists that bind with greater affinity to the β_2-receptor site than albuterol. These are maintenance, not acute, therapy. Bronchodilator effects last at least 12 hours, and tachyphylaxis is undocumented with long-term use. Long-acting β_2-adrenergic agonists are an effective treatment for long-term control of asthma, especially in conjunction with inhaled corticosteroids. Use short-acting β_2-adrenoreceptor agonists (e.g., albuterol) for infrequent or breakthrough symptoms that occur despite the use of long-acting β_2-adrenoreceptor agonists.[8-11,24]

CORTICOSTEROIDS

Corticosteroids produce beneficial effects by restoring β-adrenergic responsiveness and reducing inflammation and are used in all but mild, easily fully reversed episodes of acute asthma. The peak anti-inflammatory effect occurs at least 4 to 8 hours after IV or PO administration. Early use is wise; corticosteroids given within 1 hour of arrival in the ED reduce the need for hospitalization.[26] Although there is disagreement over the optimal dose in acute asthma, an initial dose of **PO prednisone** of 40 to 60 milligrams or **IV methylprednisolone** of 1 milligram/kg is sufficient, and higher-dose corticosteroid therapy has no clear advantage.[26,27] Give patients who are being discharged home after ED treatment a **5- to 10-day nontapering course of prednisone** (40 to 60 milligrams/d in a single daily dose or its equivalent) or a **2-day course of oral dexamethasone** (16 milligrams/d in a single daily dose).[8-11,28-30] A single dose of **depot methylprednisolone**, 150 milligrams IM, is another option if compliance is a concern.[31]

Current recommendations are to use **inhaled corticosteroids** for all patients with mild persistent asthma or more severe chronic asthma.[8-11,32] This means discharging patients with mild persistent or more severe asthma on maintenance inhaled corticosteroids in addition to any systemic bursts.[33-35] Inhaled corticosteroid options are beclomethasone, 80 to 240 micrograms/d; budesonide, 180 to 600 micrograms/d; flunisolide, 500 to 1000 micrograms/d; fluticasone, 88 to 264 micrograms/d; mometasone, 200 micrograms/d; and triamcinolone acetonide, 300 to 750 micrograms/d.

ANTICHOLINERGICS

Anticholinergics are additive therapy to β-adrenergic agents in ED patients with acute asthma. Anticholinergics affect large, central airways, whereas β-adrenergic drugs dilate smaller airways.

The anticholinergic commonly used is inhaled ipratropium bromide, available as a nebulized solution and a metered-dose inhaler or in combination with albuterol[8-11] (Table 69-5). Use an aerosolized ipratropium bromide solution, 0.5 milligram, in ED patients with moderate to severe exacerbation.[8-11] **Adding multiple doses of ipratropium bromide to a short-acting selective β-agonist may improve bronchodilation and decrease the rate of hospitalization among patients with moderate-to-severe acute asthma,[36] although this benefit is not universal.**[37] Potential side effects with anticholinergics include dry mouth, tachycardia, restlessness, irritability, confusion, difficulty in micturition, ileus, blurring of vision, and an increase in intraocular pressure. Long-acting anticholinergic agents have no role in acute asthma care.

FOLLOW-UP OF PATIENTS WITH ACUTE ASTHMA

Disposition decisions should take into account a combination of subjective parameters, such as resolution of wheezing and improvement in air exchange, as assessed by auscultation and patient opinion; objective measures, such as normalization of PEFR; and historical factors, such as compliance, history of ED use, and hospitalization. Some degree of residual airflow obstruction, airway lability, and inflammation persists after treatment and discharge from the ED.

Advise discharged patients to use a short-acting β-agonist on a scheduled basis for several days and to complete any oral corticosteroid regimens. Start inhaled corticosteroids in patients with a history of persistent asthma not already using this regimen.[33-35]

A good response to treatment resolves symptoms and results in PEFR of >70% predicted; these patients can be safely discharged home. **Patients with a poor response to treatment have persistent symptoms and FEV_1 or PEFR of <40% predicted; these patients are usually best observed or hospitalized.** An incomplete response to treatment, the middle ground, commonly has some persistence of symptoms and FEV_1 or PEFR between 40% and 69% predicted. Most patients with asthma treated in the ED fall into this category and may be discharged home safely, although some benefit from prolonged observation or hospitalization[8-11] (Table 69-2). Patients who fail to improve adequately over a period of several hours because they are in the late phase of their exacerbation and those with significant risk factors for death from acute asthma are best placed in an observation unit or hospital bed. Many patients can be successfully treated in an ED observation unit with evidence-based care protocols.[38]

Arrange follow-up care by primary care physician or asthma specialist (within 1 to 4 weeks) to ensure resolution and to review the long-term medication plan for the chronic management of asthma.[8-11] Deliver an appropriate written discharge plan of action that addresses routine care and care of worsening symptoms (**Table 69-6**). Educate patients on asthma triggers (including smoking cessation education if indicated), and review all discharge medications and the correct use of the inhaler and a peak flow meter (for daily tracking).

STATUS ASTHMATICUS (ACUTE SEVERE ASTHMA)

Status asthmaticus is an acute severe asthma that does not improve with usual doses of inhaled bronchodilators and corticosteroids. Findings include hypoxemia, tachypnea, tachycardia, accessory muscle use, and wheezing (although this may be absent when airflow is severely reduced). Rapid and aggressive bronchodilator treatment is the key to preventing cardiopulmonary arrest. In addition to bronchodilators and early corticosteroids, other treatment adjuncts are often necessary.

MAGNESIUM

IV magnesium sulfate can aid the management of acute, very severe asthma (FEV_1 or PEFR of <25% predicted).[39] The magnesium dose is 1 to 2 grams IV over 30 minutes. Nebulized magnesium is effective and may improve pulmonary function in severe acute asthma when it follows aggressive β-agonist and corticosteroid therapy.[39-41] Dosing regimens vary; one regimen is 95 milligrams of nebulized magnesium sulfate in four divided doses 20 minutes apart, and another is 384 milligrams of nebulized magnesium sulfate in sterile water.[42] When using magnesium in any form, monitor blood pressure and deep tendon reflexes during administration[42] because hypotension or neuromuscular blockade may occur, although this is exceptionally rare in the doses recommended.

TABLE 69-6 Checklist for ED Discharge in Patients With Acute Asthma

Intervention	Dose/Timing	Education/Advice	MD/RN Initials
Inhaled medications (e.g., MDI with valved holding chamber; nebulizer)	Select agent, dose, and frequency (e.g., albuterol).	Teach purpose.	
Short-acting β_2-agonist	2–6 puffs every 4 h until symptoms completely resolve.	Teach and check technique.	
Corticosteroids	Low to medium dose for patients with chronic persistent asthma.	For MDIs, emphasize the importance of using a spacing device or holding chamber.	
Oral medications	Select agent, dose, and frequency (e.g., prednisone 40 milligrams once a day for 5 d).	Teach purpose. Teach side effects.	
Peak flow meter	For selected patients: measure a.m. and p.m. peak expiratory flow, and record best of 3 tries each time.	Teach purpose. Teach technique. Distribute peak flow diary.	
Follow-up visit	If possible, make appointment for follow-up care with primary clinician or asthma specialist or advise patient to make appointment in 1–4 wk.	Advise patient (or caregiver) of date, time, and location of appointment, ideally within 7 d of hospital discharge.	
Action plan	Before or at discharge.	Instruct patient (or caregiver) on simple plan for actions to be taken when symptoms, signs, and peak expiratory flow values suggest recurrent airflow obstruction.	

Abbreviations: MD = physician; MDI = metered-dose inhaler; RN = nurse.

Sources: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Noninvasive positive-pressure ventilation (see Chapter 28, "Noninvasive Airway Management and Supraglottic Airways") improves airflow and respirations compared with usual care. Despite little research, it is commonly used in clinical practice for status asthmaticus.[43,44] Noninvasive positive-pressure ventilation may decrease the need for tracheal intubation and result in clinical improvement.[44] Do not institute noninvasive positive-pressure ventilation when altered sensorium or near respiratory collapse exists; those situations require intubation. Exclude pneumothorax before beginning noninvasive positive-pressure ventilation.

KETAMINE

Ketamine inhibits reuptake of noradrenaline and increases circulating catecholamines, aiding some with severe acute asthma. An IV bolus dose of 0.15 milligram/kg followed by an infusion of 0.25 milligram/kg/h is sometimes used.[45] If intubation is needed, ketamine is a premedication and/or sedative agent to aid during the procedure and after mechanical ventilation starts. There are limited controlled trial data on ketamine and outcomes in treating severe acute asthma.

EPINEPHRINE

Although epinephrine is standard treatment for anaphylactic asthma, it is an adjunct to treat status asthmaticus. Give epinephrine SC or IM, 0.5 milligram, in adults (standard adult EpiPen® dose) for refractory situations.[11]

MECHANICAL VENTILATION

If the patient manifests progressive hypercarbia or acidosis or becomes exhausted or confused, intubation and mechanical ventilation (see Chapter 29A and 29B, "Tracheal Intubation and Mechanical Ventilation") are necessary to prevent respiratory arrest. **Mechanical ventilation does not relieve the airflow obstruction—it merely reduces the work of breathing and enables the patient to rest while the airflow obstruction is resolved.**

The potential complications of mechanical ventilation in patients with acute asthma include high peak airway pressures with subsequent barotrauma and hemodynamic impairment (e.g., decreased preload). Mucous plugging is frequent, leading to increased airway resistance, atelectasis, and obstructive pneumonia. Due to the severity of airflow obstruction during the early phases of treatment, the tidal volume may be larger than the returned volume, leading to air trapping and increased residual volume (intrinsic positive end-expiratory pressure). Using rapid inspiratory flow rates at a reduced respiratory frequency (12 to 14 breaths/min) and allowing adequate time for the expiratory phase can mitigate these effects. Also, it is reasonable to target adequate arterial oxygen saturation (≥90%) without concern for "normalizing" the hypercarbic acidosis. This approach is called *controlled mechanical hypoventilation* or *permissive hypoventilation*. Ventilation of patients with acute asthma requires sedation. Neuromuscular blocking agents may be required, but extended use may cause postextubation muscle weakness.[46]

AGENTS OF UNCERTAIN OR NO BENEFIT IN STATUS ASTHMATICUS

Heliox A mixture of 80% helium and 20% oxygen (heliox) can lower airway resistance and aid treatment of severe acute asthma.[47] Although there is no role for this intervention in routine care, it is an option for patients who do not respond to standard therapy.[8,48]

Methylxanthines Aminophylline (5 milligrams/kg IV over 20 minutes) is no longer a first- or second-line treatment for acute asthma.[49] The most common side effects of methylxanthines are tachycardia, nervousness, nausea, vomiting, anorexia, and headache. At plasma levels >30 milligrams/mL, there is a risk of seizures and cardiac dysrhythmias.

Other Agents **Mast cell modifiers**, such as cromolyn and nedocromil, exert their anti-inflammatory action by blockage of chlorine channels, modulating mast cell mediator release and eosinophil recruitment. These agents inhibit early and late responses to allergen challenge and exercise. Neither is indicated for treatment of acute bronchospasm.

Leukotrienes are potent proinflammatory mediators that contract airway smooth muscle, increase microvascular permeability, stimulate mucus secretion, decrease mucociliary clearance, and recruit eosinophils into the airway. Several leukotriene modifiers, such as montelukast, zafirlukast, and zileuton, are available as oral medications for the treatment of asthma. Leukotriene modifiers improve lung function, diminish symptoms, and diminish the need for short-acting β_2-agonists. They may be used as an alternative to low-dose inhaled corticosteroid therapy in mild persistent asthma and as steroid-sparing agents with inhaled corticosteroids in moderate persistent asthma.[7-10] Despite trials with adjuvant IV montelukast for acute asthma,[50,51] there is limited evidence to support a role for PO or IV leukotriene modifiers in acute asthma management.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 70

Chronic Obstructive Pulmonary Disease

Craig G. Bates

INTRODUCTION AND EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1-6] COPD often presents with symptoms of dyspnea, chronic cough or sputum production, and/or a history of exposure to known risk factors for the disease such as cigarette smoke. The World Health Organization Global Initiative for Chronic Obstructive Lung Disease COPD definition encompasses chronic bronchitis, emphysema, bronchiectasis, and asthma, recognizing that most patients have a combination of the different diseases. COPD is the third leading cause of death in the United States, with women now accounting for >50% of COPD-related deaths.

CHRONIC COMPENSATED OBSTRUCTIVE PULMONARY DISEASE

PATHOPHYSIOLOGY

Although tobacco smoke is the major risk factor for developing COPD, only 15% of smokers will develop COPD. Occupational dust, chemical exposure, and air pollution are other risk factors for developing COPD. α_1-Antitrypsin deficiency accounts for <1% of COPD patients.

Irritants, notably tobacco smoke and air pollutants, trigger an increase in inflammatory cells in the airways, lung interstitium, and alveoli. Proteases break down lung parenchyma and stimulate mucus secretion. Mucus-secreting cells replace cells that normally secrete surfactant and protease inhibitors. These changes result in a loss of elastic recoil, narrowing, and collapse of the smaller airways. Mucous stasis and bacterial colonization then develop in the bronchi. The earliest objective changes in the evolution of COPD are often clinically imperceptible; these early changes are small increases in peripheral airway resistance or lung compliance. Because dyspnea and hypersecretion often progress insidiously, it may take decades before COPD becomes clinically evident. The Global Initiative for Chronic Obstructive Lung Disease guidelines are helpful for the early diagnosis and treatment of COPD (**Table 70-1**),[6] although there is only a weak correlation between forced expiratory volume in 1 second (FEV_1), symptoms, and health-related quality of life.[6]

The central element of chronic lower airway obstruction is impedance to expiratory airflow due to increased resistance or decreased caliber of the small bronchi and bronchioles. Airflow obstruction results from a combination of airway secretions, mucosal edema, bronchospasm, and bronchoconstriction. Exaggerated airway resistance reduces total minute ventilation and increases respiratory work.

In emphysema, distortion or destruction of alveolar and capillary surfaces results in alveolar hypoventilation and ventilation–perfusion mismatch, creating arterial hypoxemia and hypercarbia. The right ventricle hypertrophies and dilates, resulting in pulmonary hypertension and right ventricular failure. Right ventricular pressure overload may trigger atrial or ventricular dysrhythmias. (See Chapter 57, "Systemic Hypertension," and Chapter 58, "Pulmonary Hypertension.")

TABLE 70-1 Classification of COPD Severity[2-6]

Stage	In Patients with FEV_1/FVC <0.7:
Mild COPD	FEV_1 ≥80% predicted
Moderate COPD	FEV_1 between 50% and 79% predicted
Severe COPD	FEV_1 between 30% and 49% predicted
Very severe COPD	FEV_1 <30% predicted

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

CLINICAL FEATURES

The hallmark symptoms are chronic and progressive dyspnea, cough, and sputum production; these often vary from day to day.[2-6] Minor hemoptysis is frequent, especially in those with chronic bronchitis and bronchiectasis, although it may herald lung cancer. Physical findings may include tachypnea, accessory respiratory muscle use, or pursed-lip exhalation. Lower airway obstruction causes expiratory wheezing, especially during maximum forced exhalation, and prolongation of the expiratory time. Patients with chronic bronchitis exhibit coarse crackles as uncleared secretions move about the central airways. In patients with emphysematous disease, there is expansion of the thorax, impeded diaphragmatic motion, and global diminution of breath sounds. Poor dietary intake and excessive caloric expenditure for the work of breathing cause weight loss, notably in emphysema. In the early stages, arterial blood gas analysis reveals mild to moderate hypoxemia without hypercapnia.

As COPD advances, especially when the FEV_1 falls below 1 L, hypoxemia becomes more severe and hypercapnia develops. Arterial oxygenation worsens during acute exacerbations, exercise, and sleep. Clinical signs of severe COPD include facial vascular engorgement from secondary polycythemia, and tremor, somnolence, and confusion from hypercarbia. Right heart failure may occur and bring edema or ascites, and the signs are often disguised or underestimated by the seemingly more overwhelming signs of respiratory disease. If concomitant left heart failure exists, the cardiac auscultatory findings are sometimes hard to appreciate given the pulmonary inflation abnormalities of COPD.

DIAGNOSIS

Suspect chronic, compensated COPD based on symptoms and risk exposure profiles, and confirm it by spirometry with a postbronchodilator FEV_1–to–forced vital capacity ratio of <0.7.[6] Once the disease progresses, the percentage of predicted FEV_1 is a better measure of disease severity.[2-6]

Chronic bronchitis is not radiographically apparent unless bronchiectasis is present. In emphysema, radiographs show hyperaeration, seen as increased anteroposterior chest diameter, flattened diaphragms, increased parenchymal lucency, and attenuation of pulmonary arterial vascular shadows (**Figure 70-1**).

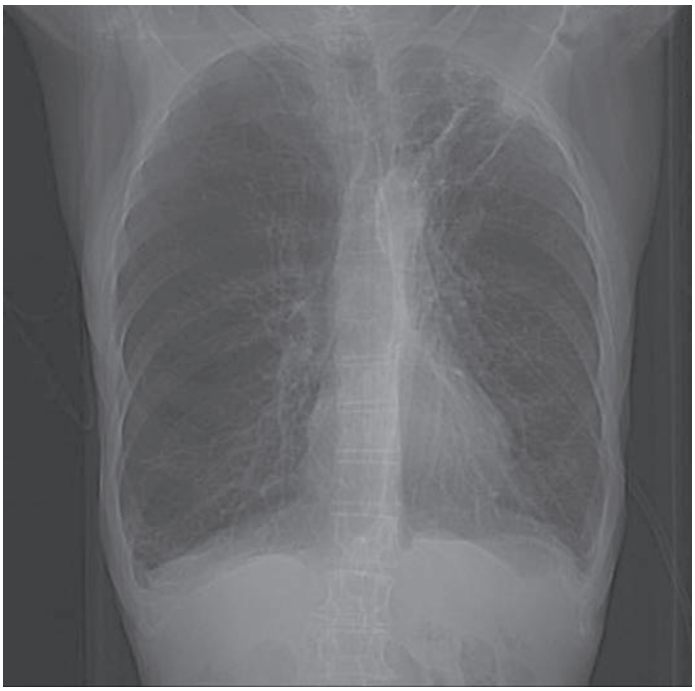

FIGURE 70-1. Posteroanterior chest radiograph in a patient with chronic obstructive pulmonary disease.

It is important to acknowledge that COPD is underdiagnosed due to a variety of factors. **More than 50% of patients with spirometric criteria for COPD did not carry that diagnosis.**[7] Patients attribute declines in respiratory function or a chronic cough as simply due to aging and/or a normal side effect of smoking. ED clinicians will sometimes have to make a clinical assessment and treat undiagnosed COPD. Such a situation is especially true in patients with poor access to care and/or poor utilization of primary care resources.

Distinguishing acute heart failure from COPD can be difficult. A B-type natriuretic peptide level <100 picograms/mL supports a diagnosis of COPD; levels >500 picograms/mL have a sensitivity of 80% and positive predictive value of 47% for acute heart failure (see Chapter 62, "Respiratory Distress").[8] The ECG detects dysrhythmias or ischemia, but does not accurately assess the severity of pulmonary hypertension or right ventricular dysfunction.

TREATMENT

Treatment for chronic compensated COPD includes oxygen, pharmacotherapy, measures to decrease mucus secretion, smoking cessation, and pulmonary rehabilitation.

Oxygen Long-term oxygen therapy reduces COPD mortality. The goal is to increase the baseline partial pressure of arterial oxygen (Pao_2) to ≥60 mm Hg or the arterial oxygen saturation (Sao_2) to ≥90% at rest. Criteria for long-term oxygen therapy are a Pao_2 ≤55 mm Hg, an Sao_2 ≤88%, or a Pao_2 between 56 and 59 mm Hg when pulmonary hypertension, cor pulmonale (sustained right ventricular failure), or polycythemia is present.[6]

Pharmacotherapy Pharmacotherapy does not alter disease progression but provides symptomatic relief, controls exacerbations, improves quality of life, and improves exercise performance.[9] Most prefer inhaled long-acting β_2-agonists for baseline care over short-acting formulations. Long-acting inhaled β_2-agonists, such as salmeterol, formoterol, olodaterol, and indacaterol, are options. Short-acting inhaled β_2-agonists, usually albuterol, are added as needed. Combining bronchodilators with different mechanisms and duration of action may increase bronchodilation without increasing side effects.[10] Combination inhalers of short-acting β_2-agonists with anticholinergic agents include fenoterol/ipratropium and salbutamol/ipratropium. Anticholinergic agents cause bronchodilation by blocking the effect of acetylcholine on muscarinic-3 receptors. Long-acting anticholinergic agents, such as tiotropium, aclidinium, umeclidinium, and glycopyrronium, are preferred over short-acting agents, such as ipratropium bromide or oxitropium bromide.[11,12] Bronchodilators often improve FEV_1 by 10%.

Experts do not recommend long-term systemic corticosteroid therapy for all COPD patients[13] because only about 20% to 30% improve. Short-term steroid use (days) aids in treating exacerbations. Use daily inhaled corticosteroids for patients with a documented spirometric response to inhaled corticosteroids, with an FEV_1 of <50%, or with predicted and recurrent exacerbations requiring antibiotic treatment or systemic corticosteroids.[6] Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is best for patients at high risk of exacerbation. Combination inhalers with long-acting β_2-agonists plus corticosteroids include formoterol/budesonide, formoterol/mometasone, salmeterol/fluticasone, and vilanterol/fluticasone.[6]

Although retrospective studies suggest that statins decrease the rate and severity of exacerbations, rate of hospitalization, and mortality, a large prospective trial failed to demonstrate benefit of daily simvastatin over placebo.[14] Daily azithromycin may decrease acute exacerbations in older patients and those with milder COPD.[15]

Secretion Mobilization Mobilize respiratory secretions with generous oral fluid intake and room humidification. Limit the use of antihistamines, antitussives, mucolytics, and decongestants. Expectorants are not of clear benefit.

Smoking Cessation, Pulmonary Rehabilitation, and Vaccination Smoking cessation is the only intervention that can reduce both the rate of decline in lung function[6] and mortality from respiratory causes.[2-6] The ED is one key site to attempt smoking cessation interventions.[16] A combination of nicotine replacement therapy or medications and behavioral interventions can assist patients with smoking cessation, especially with referral to a program.[17]

Pulmonary rehabilitation can improve exercise capacity and quality of life for patients with moderate to severe COPD. Pneumococcal vaccination and influenza vaccination are key to dampen acute infections.[6]

ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Acute exacerbations of COPD result in worsening of respiratory symptoms beyond normal day-to-day variations[18] and are usually triggered by an infection or respiratory irritant. More than 75% of patients with acute exacerbations have evidence of viral or bacterial infection, with up to half specifically due to bacteria.[19,20] There is also evidence for gastroesophageal reflux disease as an additional risk factor for COPD exacerbations, although there is no evidence that treatment of gastroesophageal reflux disease reduces exacerbations.[21,22] Other important triggers for exacerbations are hypoxia, cold weather,[23] β-blockers, opioids, or sedative-hypnotic agents.

The final common pathway for a COPD exacerbation is the release of inflammatory mediators that result in bronchoconstriction, pulmonary vasoconstriction, and mucus hypersecretion. The work of breathing increases due to higher airway resistance and lung hyperinflation. The oxygen demand of respiratory muscles increases, generating additional carbon dioxide and causing hypercapnia, resulting in further physiologic stress.[23] Acute exacerbations of COPD are primarily due to ventilation–perfusion mismatch rather than the expiratory airflow limitation seen with asthma exacerbations.[24] Supplemental oxygen increases blood oxygen concentrations and can help reverse pulmonary vasoconstriction.

CLINICAL FEATURES

The most life-threatening feature of an acute exacerbation is hypoxemia (arterial saturation <90%). Signs of hypoxemia include tachypnea, tachycardia, systemic hypertension, cyanosis, and a change in mental status. With increased work of breathing, carbon dioxide production increases; alveolar hypoventilation creates arterial carbon dioxide retention and respiratory acidosis.

The patient tries to overcome severe dyspnea and orthopnea by sitting in an up-and-forward position, using pursed-lip exhalation, and engaging accessory muscles to breathe. Pulsus paradoxus (a decrease of >10 mm Hg in systolic blood pressure during respiratory cycles) may be noted during palpation of the pulse or during blood pressure recording. **Complications, such as pneumonia, pneumothorax, pulmonary embolism, or an acute abdomen, may exacerbate COPD. Other acute triggers include asthma, congestive heart failure, pneumonia, pulmonary embolism, tuberculosis, and metabolic disturbances.**

DIAGNOSIS

With the history, seek causes for exacerbation and triggers plus sputum changes; then assess oxygenation and acid-base status, and perform a physical examination.

Pulse oximetry may identify hypoxemia, and capnography may identify hypercarbia. Arterial blood gas analysis is the best tool in acute evaluation for assessing oxygenation, ventilation, and acid-base disturbances. Arterial blood gases clarify the severity of exacerbation and the probable clinical course. Respiratory failure typically shows an arterial Pao_2 of <60 mm Hg or an arterial Sao_2 <90% in room air. Respiratory acidosis is present if the partial pressure of carbon dioxide (Pco_2) is >44 mm Hg. If the pH is <7.35, there is an *acute* and uncompensated component of respiratory or metabolic acidosis present. While arterial blood is best, the pH on a venous blood gas shows good agreement with that on an arterial blood gas, a potentially useful screening tool.[25]

In acute respiratory acidosis, the serum bicarbonate rises by 1 mEq/L for each 10-mm Hg increase in Pco_2, and the pH will change by $0.008 \times (40 - Pco_2)$. In chronic respiratory acidosis, the bicarbonate rises by 3.5 mEq/L for each 10-mm Hg increase in Pco_2, and the pH will

change by 0.03 × (40 – Pco_2). Changes outside of these ranges suggest an accompanying metabolic disorder (see Chapter 15, "Acid-Base Disorders," and Chapter 62, "Respiratory Distress").

Frequently, patients with an acute COPD exacerbation are too dyspneic to perform bedside pulmonary function tests, so measurements are often inaccurate.[2-6] Similarly, physical examination and physician estimates of pulmonary function are inaccurate.[26]

Assessment of sputum includes questions about changes in volume and color, especially an increase in purulence. An increase in sputum volume and change in sputum color suggest a bacterial infection and the need for antibiotic therapy.[24,27] Sputum cultures usually contain mixed flora and do not help guide ED antibiotic selection.[2-6]

Ancillary Studies Radiographic abnormalities are common in COPD exacerbation and may identify the underlying cause of the exacerbation, such as pneumonia, or may identify an alternative diagnosis such as acute heart failure.[28]

The ECG can identify ischemia, acute myocardial infarction, cor pulmonale, and dysrhythmias. Measure levels in patients who take theophylline. Obtain other tests, such as CBC, electrolytes, troponin, B-type natriuretic peptide, D-dimer, and CT of the chest based on clinical findings.

TREATMENT

The goals of treatment are to correct tissue oxygenation, alleviate reversible bronchospasm, and treat the underlying cause (**Table 70-2**). Factors that influence therapy in the ED include any mental status changes; the degree of reversible bronchospasm; recent medication usage and assessment for drug toxicity; prior history of exacerbation courses, hospitalization, and intubation; presence of contraindications to any drug or drug class; and specific causes or complications from the exacerbation. Patients who do not respond as expected to standard therapy need a prompt reevaluation for other potentially life-threatening issues. See **Table 70-3** for an overview of the differential diagnosis of COPD exacerbations.

Oxygen **Administer oxygen to achieve a Pao_2 of 60 to 70 mm Hg or an Sao_2 between 88% and 92%.**[29] There is potential harm in targeting higher oxygen levels. Use any of the following devices: standard dual-prong nasal cannula, simple facemask, or Venturi mask. It may take 20 to 30 minutes from administration of supplemental oxygen for improvement to occur. Be aware that oxygen administration may produce hypercapnia through worsening ventilation–perfusion mismatching; this is one reason non-rebreathing masks are best used cautiously. Assess arterial blood gases and/or continuous end-tidal carbon dioxide and oxygen saturation monitoring with venous blood gases to allow optimal assessment of the Pco_2 and acid-base status. If adequate oxygenation does not exist or respiratory acidosis develops, assisted ventilation is an option.

TABLE 70-2 ED Management of COPD Exacerbations[2-6]

- Assess severity of symptoms
- Administer controlled oxygen (target arterial oxygen saturation of 88%–92%)
- Continuous cardiovascular status monitoring
- Perform arterial blood gas measurement after 20–30 min if arterial oxygen saturation remains <90% or if concerned about symptomatic hypercapnia
- Administer bronchodilators
  - β_2-Agonists and/or anticholinergic agents by nebulization or metered-dose inhaler with spacer
- Add oral or IV corticosteroids
- Consider antibiotics if increased sputum volume, change in sputum color, fever, or suspicion of infectious etiology of exacerbation
- Consider noninvasive mechanical ventilation
- Evaluation may include chest radiograph, CBC with differential, basic metabolic panel, ECG
- Address associated comorbidities

TABLE 70-3 Critical Differential Diagnosis of Chronic Obstructive Pulmonary Disease (COPD) Exacerbations[2-6]

Diagnosis	Clinical Features	Caveats
Asthma	Earlier onset Varying symptoms Family history Reversible airflow	Can coexist with COPD. Many patients diagnosed with asthma actually have COPD or mixed asthma-COPD.
CHF	Presence of orthopnea (LR, 2.0) and dyspnea with exertion (LR, 1.3) slightly favors CHF Jugular venous distention, hepatojugular reflux, bibasilar rales Chest radiograph may show cardiomegaly or interstitial edema BNP <100 picograms/mL not likely to be CHF; BNP >500 picograms/mL more likely to be CHF	Can coexist with COPD. Shares some historical elements also found in COPD. Multiple conditions can falsely elevate or decrease the BNP level.
PE	Risk factors include older age, recent surgery or trauma, prior venous thromboembolic disease, hereditary thrombophilia, malignancy, smoking, and use of medications containing estrogen Patients with intermediate to high pretest probability may require further testing, such as CT angiography; D-dimer may be useful in ruling out PE in low-risk patients	20%–25% of patients with a severe COPD exacerbation with an unclear trigger have a PE. Triad of PE (pleuritic chest pain, dyspnea, tachycardia, and hypoxemia) unusual.
ACS	Obtain ECG or troponin in those with chest pain or dyspnea and risk factors for ACS	Dyspnea may be the primary complaint in patients with ACS.
Pneumothorax	Obtain chest radiograph, US, or CT	COPD is a risk factor for spontaneous pneumothorax.
Pneumonia	Obtain chest radiograph	Frequently coexists with a COPD exacerbation.

Abbreviations: ACS = acute coronary syndrome; BNP = B-type natriuretic peptide; CHF = congestive heart failure; LR, likelihood ratio; PE = pulmonary embolism.

β_2-Adrenergic Agonists Short-acting β_2-agonists are first-line therapies in the management of acute, severe COPD.[2-6] Aerosolized forms, using nebulizer or metered-dose inhalers, deliver drug to the target area optimally and minimize systemic toxicity. β_2-Agonists are best given every 30 to 60 minutes if tolerated.[2-6] Nebulized aerosols every 20 minutes may result in more rapid improvement of FEV_1, but more frequent side effects,[30] including tremor, anxiety, and palpitations. If the patient can cooperate, metered-dose inhalers (multiple puffs given closely together along with coaching on technique, then repeated) with a spacer deliver drug to target receptors most efficiently; reserve nebulizers for when this fails, cannot occur, or in extremes of age. Use air to drive nebulizers, supplementing oxygen as described earlier.[31] Continuous cardiac monitoring is helpful, especially for patients with heart disease.

Anticholinergics These agents are best combined with β_2-agonists. There is moderate evidence showing benefit. Ipratropium bromide given as a single dose by metered-dose inhaler with a spacer or as an inhalant solution by nebulization (0.5 milligram or 2.5 mL of the 0.02% inhalant solution) is the usual agent of choice, although aerosolized glycopyrrolate (2 milligrams in 10 mL of saline) is also effective. Side effects are minimal and limited to dry mouth and an occasional metallic taste.

Evidence regarding the effectiveness of the combination of a β_2-adrenergic agent and an anticholinergic agent compared with a single agent alone is conflicting, although many physicians favor using this combination initially and some favor using it if the response to maximal doses of a single bronchodilator is poor. Do not use long-acting inhaled anticholinergics, such as tiotropium, aclidinium, and glycopyrronium, for the acute management of COPD.[2-6]

Corticosteroids A short course (5 to 7 days) of systemic steroids improves lung function and hypoxemia and shortens recovery time in acute COPD exacerbations.[29] Use of corticosteroids in the ED does not affect the rate of hospitalization but decreases the rate of return visits. There appears to be no benefit from oral prednisone > 40 to 60 mg as a single or divided twice daily total dose.[32] There is also no benefit to IV administration of glucocorticoids except in patients who cannot tolerate oral intake or are in shock and have impaired absorption of medication from the GI tract. Hyperglycemia is the most common adverse effect.

Antibiotics Prescribe antibiotics in moderately or severely ill patients if there is evidence of infection, such as change in volume of sputum and increased purulence of sputum.[6,27] There is little controversy about use of antibiotics in severely ill patients, but varying guidelines exist for guiding these decisions in moderately ill patients. **Choose agents directed at the most common pathogens associated with COPD exacerbation: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.** There is no specific agent shown to be superior.[6,24,27] Initial antibiotics for uncomplicated COPD include macrolides (azithromycin), tetracyclines (doxycycline), or trimethoprim-sulfamethoxazole. Consider providing coverage for *Pseudomonas aeruginosa* in patients with one or more of the following risk factors: admission and/or antibiotic course in past 3 months, prior culture showing *Pseudomonas* infection, or concomitant bronchiectasis.[33] There is little evidence regarding the duration of treatment, which ranges from 3 to 14 days.

Noninvasive and Invasive Mechanical Ventilation Indications and relative contraindications of noninvasive ventilation are in **Table 70-4.** See Chapter 28, "Noninvasive Airway Management and Supraglottic Airways," for more discussion on this option. All patients receiving noninvasive positive-pressure ventilation require continuous cardiorespiratory monitoring and frequent reassessment for setting changes and for tolerance of therapy.[34]

Use assisted mechanical ventilation when there is evidence of respiratory muscle fatigue, worsening respiratory acidosis, deteriorating mental status, or refractory hypoxemia (Table 70-5). The goals of assisted mechanical ventilation are to rest ventilatory muscles and to restore adequate gas exchange. After endotracheal intubation, the methods most commonly used are assist-control ventilation, pressure support ventilation, or pressure support ventilation in combination with intermittent mandatory ventilation. See Chapter 29B, "Mechanical Ventilation," for more detail. Adverse events associated with invasive ventilation include pneumonia, barotrauma, and inability to wean the COPD patient from the ventilator.

Other Therapies While selectively used, current evidence does not support the routine use of magnesium sulfate (2 to 4 grams IV over 10 minutes) or methylxanthines (aminophylline 3 to 5 milligrams/kg IV over 30 minutes) in the treatment of an acute COPD exacerbation. The utility of high-flow nasal cannula, particularly as an alternative to nasal intermittent positive-pressure ventilation, is currently unclear.

TABLE 70-4 Indications and Relative Contraindications for Noninvasive Ventilation[2-6]

Selection criteria	Acidosis (pH <7.36)/hypercapnia ($Paco_2$ >50 mm Hg)/oxygenation deficit (Pao_2 <60 mm Hg or Sao_2 <90%)
	Severe dyspnea with clinical signs such as respiratory muscle fatigue or increased work of breathing
Exclusion criteria (any)	Respiratory arrest
	Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
	Change in mental status; uncooperative patient
	High aspiration risk
	Viscous or copious secretions
	Recent facial or gastroesophageal surgery
	Craniofacial trauma
	Fixed nasopharyngeal abnormalities
	Burns
	Extreme obesity

Abbreviations: $Paco_2$ = partial pressure of arterial carbon dioxide; Pao_2 = partial pressure of arterial oxygen; Sao_2 = arterial oxygen saturation.

TABLE 70-5 Indications for Intubation With Mechanical Ventilation[2-6]

- Unable to tolerate noninvasive ventilation (NIV) or NIV failure
- Respiratory or cardiac arrest
- Respiratory failure
- Decreased consciousness or increased agitation
- Massive aspiration
- Persistent inability to remove respiratory secretions
- Hypotension
- Persistent hypoxemia despite optimal respiratory treatment
- Hemodynamic instability

DISPOSITION AND FOLLOW-UP

Admit patients who fail to improve, those who deteriorate despite medical therapy, those with significant comorbidity, and those without an intact social support system; the destination unit must have adequate nursing and respiratory monitoring ability. The Global Initiative for Chronic Obstructive Lung Disease guidelines help guide the ED disposition decision-making process (**Tables 70-6** and **70-7**). Select patients without respiratory failure may avoid hospitalization with nurse-administered home care ("hospital at home care").[35] After ED discharge, 25% to 43% of patients with COPD exacerbation show ongoing symptoms or relapse of symptoms.[36-38]

The following are associated with a higher risk for relapse within 2 weeks after an ED visit: five or more ED or clinic visits in the past year, the amount of activity limitation (based on a 4-point scale), the initial respiratory rate (for each 5 breaths/min over 16 breaths/min), and use of oral corticosteroids before arrival in the ED.[36-38]

If discharging from the ED or observation unit, arrange the following: (1) a supply of home oxygen, if needed; (2) adequate and appropriate bronchodilator treatment (usually a metered-dose inhaler with a spacer *and* teaching; nebulized therapies are reserved for those who cannot use the metered-dose inhaler); (3) short course of oral corticosteroids[2-6]; and (4) a follow-up appointment with the primary care physician or pulmonologist, preferably within a week. Reassess inhaler technique, reinforce importance of completion of steroid therapy and antibiotics, if prescribed, and review management plan.

TABLE 70-6 Indications for Hospital Admission[6]

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea or inability to walk from room to room
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities
- Newly occurring dysrhythmias, heart failure
- Frequent exacerbations and/or frequent relapse after ED treatment
- Older age
- Insufficient home support

TABLE 70-7 Indications for Intensive Care Admission[6]

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia (Pa_{O_2} <40 mm Hg) and/or severe/worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and NIPPV
- Need for invasive mechanical ventilation
- Hemodynamic instability
- (Local resources and capabilities may dictate different decision making; with NIPPV patients in particular, different systems dictate different dispositions.)

Abbreviations: NIPPV = noninvasive positive-pressure ventilation; Pa_{O_2} = partial pressure of arterial oxygen.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 9

Gastrointestinal Disorders

CHAPTER 71

Acute Abdominal Pain

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INTRODUCTION AND EPIDEMIOLOGY

More adult patients visit the ED for "stomach and abdominal pain, cramps, or spasms" than for any other chief complaint.[1] Demographics (age, gender, ethnicity, family history, sexual orientation, cultural practices, geography) influence both the incidence and the clinical expression of abdominal disease.[1] History, physical examination, and laboratory studies can be helpful, but imaging is often required to make a specific diagnosis. Clinical suspicion for serious disease is especially important for patients in high-risk groups.

PATHOPHYSIOLOGY

Abdominal pain is divided into three neuroanatomic categories: visceral, parietal, and referred.

VISCERAL PAIN

Obstruction, ischemia, or inflammation can cause stretching of unmyelinated fibers that innervate the walls or capsules of organs, resulting in visceral pain. Visceral pain is often described as "crampy, dull, or achy," and it can be either steady or intermittent (colicky). Because the visceral afferent nerves follow a segmental distribution, visceral pain is localized by the sensory cortex to an approximate spinal cord level determined by the embryologic origin of the organ involved (**Table 71-1**).

Because intraperitoneal organs are bilaterally innervated, stimuli are sent to both sides of the spinal cord, causing intraperitoneal visceral pain to be felt in the midline, independent of its right- or left-sided anatomic origin. For example, stimuli from visceral fibers in the wall of the appendix enter the spinal cord at about T10. When obstruction causes appendiceal distention in early appendicitis, pain is initially perceived in the midline periumbilical area, corresponding roughly to the location of the T10 cutaneous dermatome.

PARIETAL PAIN

Parietal (somatic) abdominal pain is caused by irritation of myelinated fibers that innervate the parietal peritoneum, usually the portion covering the anterior abdominal wall. Because parietal afferent signals are sent from a specific area of peritoneum, parietal pain—in contrast to visceral pain—can be localized to the dermatome superficial to the site of the painful stimulus. As the underlying disease process evolves, the symptoms of visceral pain give way to the signs of parietal pain, causing tenderness and guarding. As localized peritonitis develops further, rigidity and rebound appear. Patients with peritonitis generally prefer to remain immobile.

REFERRED PAIN

Referred pain is felt at a location distant from the diseased organ. Referred pain patterns are also based on developmental embryology. For example, the ureter and the testes were once anatomically contiguous and therefore share the same segmental innervations. Thus acute ureteral obstruction is often associated with ipsilateral testicular pain. Referred pain is usually perceived on the same side as the involved organ, because it is not mediated by fibers that provide bilateral innervation to the cord. Referred pain is felt in the midline only if the pathologic process is also located in the midline.

CLINICAL FEATURES

CLINICAL RISK

To determine the urgency and method of the diagnostic approach, we recommend the use of a pragmatic scheme based on patient acuity and the identification of risk factors.

- Patient Acuity: Is this patient critically ill? If so, simultaneously resuscitate and evaluate.
- Risk Factors: Are there special conditions or risk factors that affect clinical risk or mask the disease process?

Patient Acuity: Is This Patient Critically Ill? **Critically ill patients need immediate stabilization.** Markers of high acuity include extremes of age, severe pain of rapid onset, abnormal vital signs, dehydration, and evidence of visceral involvement (e.g., pallor, diaphoresis, vomiting). The intensity of abdominal pain may bear no relationship to the severity of illness. Serious illness may be present even if vital signs are normal, particularly in high-risk groups such as the elderly and the immunocompromised. Shock that develops rapidly after the onset of acute abdominal pain is usually the consequence of intra-abdominal hemorrhage. Systolic pressure does not drop until blood loss reaches 30% to 40% of normal blood volume. Tachycardia is a useful parameter for the assessment of volume depletion, but its absence does not exclude blood/fluid loss. Tachypnea may indicate a cardiopulmonary process, metabolic acidosis, anxiety, or pain. Temperature is neither sensitive nor specific for disease process or patient condition. The presence or absence of fever cannot be used to distinguish surgical from medical disease.

Resuscitation of the critically ill patient with abdominal pain includes a cardiac monitor, oxygen (2 to 4 L/min via nasal cannula or mask), large-bore IV access, and an isotonic fluid bolus adjusted for age, weight, and cardiovascular status. For critically ill patients, blood samples should be drawn at the time of IV insertion, including, at a minimum, electrolytes, BUN and creatinine, CBC with platelets, clotting studies, and a type and antigen screen of blood. Order cross-matched blood if hemorrhage is suspected or if urgent transfusion is anticipated. A bedside US should be performed rapidly in an attempt to expedite identification of emergent causes of abdominal pain in the patient with hemodynamic collapse. The presence of an abdominal aortic aneurysm and intra-abdominal hemorrhage can be quickly discovered.[2] Bedside US can also be used to help assess hemodynamic status by focused evaluation of heart function and inferior vena cava size and respiratory response. This information can help guide resuscitative efforts.

Risk Factors: Are There Special Conditions or Risk Factors That Affect Clinical Risk or Mask the Disease Process? Identify pertinent past medical illness (diabetes, heart disease, hypertension, liver disease, renal disease, human immunodeficiency virus status, sexually transmitted diseases), previous abdominal surgeries, menstrual history and pregnancies (deliveries, abortions, ectopic), medications (steroids, immune suppressants, acetylsalicylic acid/nonsteroidal anti-inflammatory drugs, antibiotics, laxatives, narcotics, fertility agents, intrauterine devices, chemotherapeutic agents), allergies, and any recent trauma.

TABLE 71-1 Visceral Pain Features

Embryologic Origin	Involved Organs	Location of Visceral Pain
Foregut	Stomach, first/second parts of duodenum, liver, gallbladder, pancreas	Epigastric area
Midgut	Third/fourth parts of duodenum, jejunum, ileum, cecum, appendix, ascending colon, first two thirds of transverse colon	Periumbilical area
Hindgut	Last one third of transverse colon, descending colon, sigmoid, rectum, intraperitoneal GU organs	Suprapubic area

Ask about previous episodes of similar abdominal pain, diagnostics, and treatments. Review previous medical records. Obtain a social history that includes habits (tobacco, alcohol, other drug use), occupation, possible toxic exposures, and living circumstances (homeless, dwelling heat source, running water, living alone, other family members ill with similar symptoms).

A number of conditions camouflage critical illness in patients with acute abdominal pain. High-risk groups include patients with cognitive impairment secondary to dementia, intoxication, psychosis, mental retardation, or autism; patients who cannot communicate effectively because of aphasia or language barriers; patients in whom physical or laboratory findings may be minimal (the elderly) or obscured (patients with spinal cord injury); asplenic patients; neutropenic patients; transplant patients; patients whose immune systems are impaired by illness (human immunodeficiency virus; chronic renal disease; diabetes, cirrhosis, hemoglobinopathy; malnutrition, chronic malignancy, autoimmune disease, mycobacterial infection); and patients taking immune-suppressive or immune-modulating medications, such as steroids, calcineurin inhibitors, tumor necrosis factor inhibitors, antimetabolic agents, monoclonal and polyclonal antibodies, and chemotherapeutic agents.

In general, patients with mild to moderate immune dysfunction have delayed or atypical presentations of common diseases. Patients with severe immune dysfunction are more likely to present with opportunistic infections. The CD4 count is the most important measure of immune competency in patients with acquired immunodeficiency syndrome. **Patients with CD4 counts over 200/mm^3 are much less likely to have opportunistic infections.**

HISTORY AND PHYSICAL EXAMINATION

Obtain a clear description of the pain itself (**OP^{2}QRST^2: onset, provocative/palliative factors, quality, radiation, associated symptoms, timing, and what the patient has taken for the pain**).

Before the complete physical examination, take a few moments to gain the patient's trust by explaining what needs to be done, exposing only what needs to be seen, and re-covering exposed parts of the body sequentially. Provide patient privacy. Note the patient's skin (color, temperature, turgor, perfusion status), and perform a targeted heart and lung examination.

Inspection Inspect the abdomen for signs of distention (ascites, ileus, obstruction, volvulus), obvious masses (hernia, tumor, aneurysm, distended bladder), surgical scars (adhesions), ecchymoses (trauma, bleeding diathesis), and stigmata of liver disease (spider angiomata, caput medusa).

Auscultation of Bowel Sounds Bowel sounds are nonspecific diagnostic signs. Decreased bowel sounds suggest ileus, mesenteric infarction, narcotic use, or peritonitis. Hyperactive bowel sounds may be noted in small bowel obstruction.

Percussion Liver size can be estimated by the presence of percussion dullness in the midclavicular line, except in cases of severe bowel distention. A fluid wave may suggest ascites, and tympany may suggest dilated loops of bowel.

Palpation The vast majority of clinical information is acquired through gentle palpation, using the middle three fingers, and saving the painful area for last. Voluntary guarding (contraction of the abdominal musculature in anticipation of or in response to palpation) can be diminished by asking patients to flex the knees. Those who remain guarded after this maneuver will often relax if the clinician's hand is placed over the patient's, and the patient is then asked to use his or her own hand to palpate the abdomen. Distracting the patient with conversation may divert attention from the examination. Optimally, the patient's tenderness will be confined to one of the four traditional abdominal quadrants (right upper, right lower, left upper, left lower), and pain location can be used to generate a differential diagnosis. Often, this is not the case, and one finds more diffuse tenderness involving two or more of the four abdominal quadrants. Peritoneal irritation is suggested by rigidity (involuntary guarding or reflex spasm of abdominal muscles), as is pain referred to the point of maximum tenderness when palpating an adjacent quadrant. Rebound tenderness, often regarded as the *sine qua non* for peritonitis, has several important limitations. In patients with peritonitis, the combination of rigidity, referred tenderness, and pain with coughing usually provides sufficient diagnostic confirmation such that little additional information is gained by eliciting the unnecessary pain of rebound. More than one third of patients with surgically proven appendicitis do not have rebound tenderness.[3] False positives occur without peritonitis, perhaps due to a nonspecific startle response. One might reasonably question whether rebound has sufficient predictive value to justify the discomfort it causes patients.

Evaluate the abdominal aorta, particularly in patients >50 years of age with acute abdominal, flank, or low back pain. Palpation cannot reliably exclude abdominal aortic aneurysm, and the presence or absence of femoral pulses is generally not helpful in the clinical diagnosis of abdominal aortic aneurysm.

It is wise to perform a pelvic examination in the evaluation of lower abdominal pain in women of reproductive age who have not had a total hysterectomy. The presence of peritoneal signs, vaginal discharge, cervical motion tenderness, and unilateral or bilateral abdominal and/or pelvic tenderness suggests pelvic infection, or ectopic gestation in pregnant women. In males, hernia, testicular, and prostate examinations are indicated because disorders of these structures can cause lower abdominal pain.

The rectal examination does not increase diagnostic accuracy beyond what has already been obtained by other components of the physical examination. The main value of the rectal examination is the detection of grossly bloody, maroon, or melanotic stool.

One common approach to the evaluation of acute abdominal pain is to use the location of the pain (diffuse, right upper quadrant, right lower quadrant, left upper quadrant, left lower quadrant) to guide the generation of a differential diagnosis (**Figure 71-1**).[4]

Alternatively, abdominal crises may be grouped according to presenting symptomatology: pain, vomiting, abdominal distention, muscular rigidity, and/or shock (**Table 71-2**).

Although the location of the patient's pain and the grouping of symptoms can both help to differentiate among known diseases, clinical suspicion and an understanding of the individual are paramount, because the causes of acute abdominal pain vary considerably with patient demographics. For example, older adults are more likely than younger adults to have biliary disease, diverticulitis, and bowel obstruction. Appendicitis occurs more commonly in younger adults. In the words of Sir William Osler, it is important to know "what sort of patient has the disease."

SYMPTOM TREATMENT AND FURTHER CLINICAL DIAGNOSIS

At this point, provide symptomatic relief. Do not withhold analgesia from patients with acute undifferentiated abdominal pain. The choice of analgesia agent is dependent upon patient condition, clinical situation, and provider preference. Opioid analgesia relieves pain and will not obscure abdominal findings, delay diagnosis, or lead to increased morbidity/mortality.[5,6] The information on the safety of opioids cannot be extrapolated to NSAIDs such as parenteral ketorolac because NSAIDs are not pure analgesics and can mask early peritoneal inflammation.

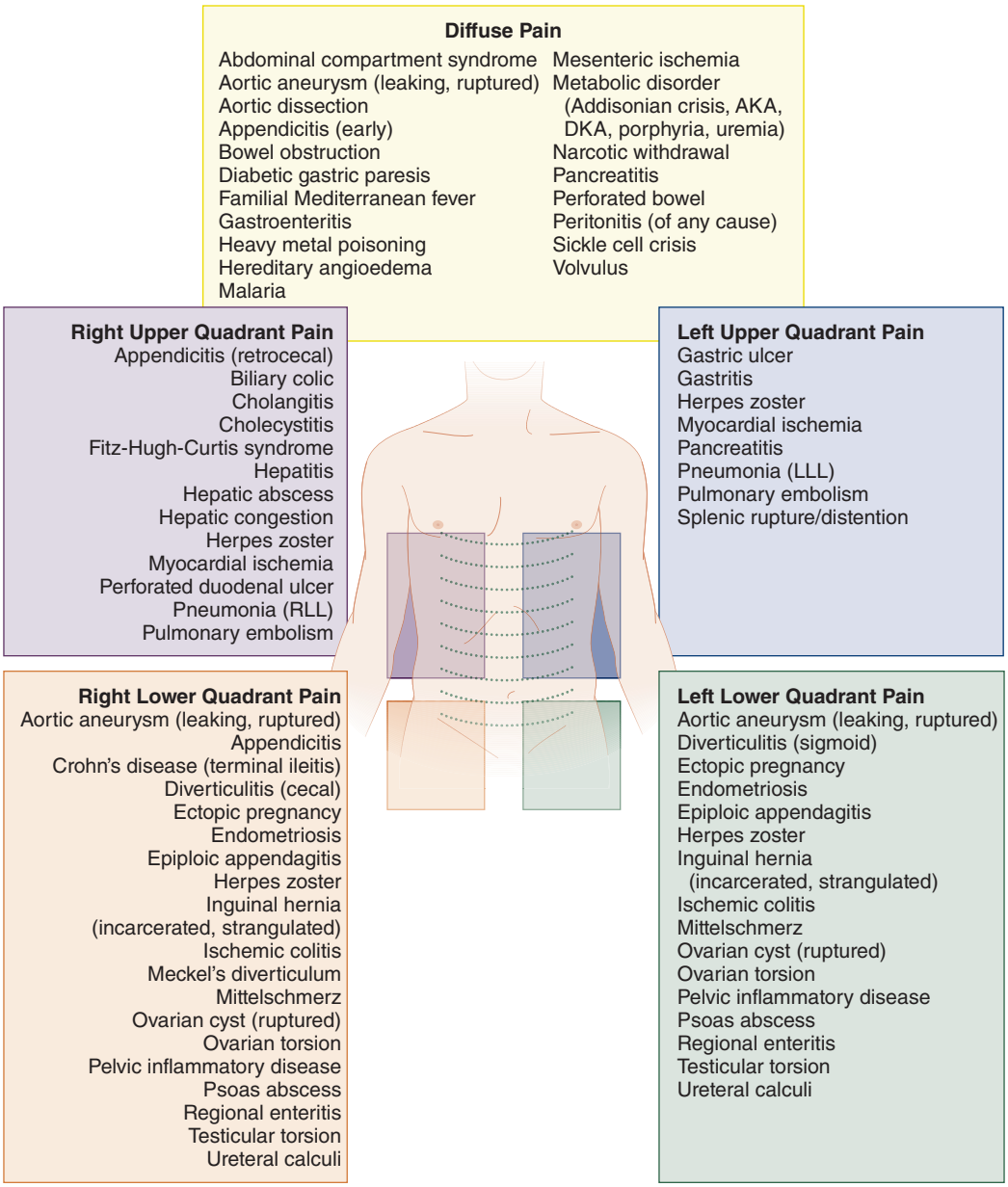

FIGURE 71-1. Differential diagnosis of acute abdominal pain by location. AKA = alcoholic ketoacidosis; DKA = diabetic ketoacidosis; LLL = left lower lobe; RLL = right lower lobe.

Opioid medications are not benign. The practice of high-intensity opioid prescribing by EMS providers can contribute to long-term opiod use in their patients.[7] Opioids have adverse side effects and potential for abuse. A recent trend toward a decrease in EMS provider prescribing of opioids may reflect increased public awareness of the disadvantages of these medications.[1]

Administer antiemetics as needed. A Cochrane review reported that ondansetron and metoclopramide reduced postoperative nausea and vomiting.[8] Both drugs had equivalent effects. The dosage of IV ondansetron is 4 or 8 milligrams (0.45 milligram/kg total daily) to a maximum of 32 milligrams daily. Headache is a reported side effect. The dosage of IV metoclopramide is 10 milligrams, given slowly to minimize extrapyramidal side effects. Sometimes, 25 to 50 milligrams of IV diphenhydramine are administered as prophylaxis against dystonia. Patients with akathisia or dystonic reactions from metoclopramide cannot tolerate any other agents of the same class and should be given ondansetron. Such reactions are extremely rare from ondansetron. (See Chapter 72, "Nausea and Vomiting," for further discussion of antiemetics.)

Consider placement of nasogastric and urinary catheters. Nasogastric aspirate may confirm upper GI bleeding, and nasogastric suction may be used to decompress a bowel obstruction. A urinary catheter will relieve bladder obstruction, and hourly urine output helps to gauge renal perfusion.

LABORATORY TESTING

Laboratory testing does not take the place of a conscientious history and physical examination, and there is no evidence to support the usefulness of "routine abdominal labs." Information obtained by laboratory testing should help refine the differential diagnosis or alter the plan of treatment. **Table 71-3** lists laboratory studies that may be appropriate in the evaluation of acute abdominal pain based on the clinical suspicions. Obtain an ECG for patients with upper abdominal pain, especially in elderly patients.

Be aware of the limitations of laboratory studies. The CBC does not offer sufficiently powerful likelihood ratios to revise disease probability. In a review of adult patients with appendicitis, only 65% had a serum WBC ≥12,000/mm^3.[9] A higher degree of leukocytosis was not associated with perforation. One approach to the use of the WBC is to take note only of high threshold abnormalities (e.g., a very elevated WBC [>20,000/mm^3]) and to resist the temptation to draw any reassurance from a "normal" WBC. **A single WBC cannot exclude serious or**

TABLE 71-2 Groupings of Known Abdominal Diseases by Symptoms

Pain/vomiting (± rigidity)	Pain/vomiting/distention	Pain (± vomiting)
Acute pancreatitis	Bowel obstruction	Acute diverticulitis
Diabetic gastric paresis	Cecal volvulus	Adnexal torsion
Diabetic ketoacidosis		Mesenteric ischemia
Incarcerated hernia		Myocardial ischemia*
		Testicular torsion
Pain/shock	**Pain/shock/rigidity**	**Distention (± pain)**
Abdominal sepsis	Perforated appendix	Elderly with bowel obstruction/volvulus
Aortic dissection	Perforated diverticulum	
Hemorrhagic pancreatitis	Perforated ulcer	
Leaking/ruptured abdominal aortic aneurysm	Ruptured esophagus Splenic rupture	
Mesenteric ischemia (late)		
Myocardial ischemia*		
Ruptured ectopic pregnancy		

Note: These symptoms and etiologic groupings are a guideline and are not intended to be a rule.

*The symptoms of myocardial ischemia are variable.

TABLE 71-3 Suggested Laboratory Studies for Goal-Directed Clinical Testing in Acute Abdominal Pain

Laboratory Test	Clinical Suspicion
Amylase (if lipase not available)	Pancreatitis
Lipase	Pancreatitis
β-Human chorionic gonadotropin Serum or urine Qualitative or quantitative	Pregnancy Ectopic or molar pregnancy
Coagulation studies (prothrombin time/ partial thromboplastin time)	GI bleeding End-stage liver disease Coagulopathy
Electrolytes	Dehydration Endocrine or metabolic disorder
Glucose	Diabetic ketoacidosis Pancreatitis
Gonococcal/chlamydia testing	Cervicitis/urethritis Pelvic inflammatory disease
Hemoglobin	GI bleeding
Lactate	Mesenteric ischemia Sepsis
Liver function tests	Cholecystitis Cholelithiasis Hepatitis
Platelets	GI bleeding
Renal function tests	Dehydration Renal insufficiency Acute renal failure
Urinalysis	Urinary tract infection Pyelonephritis Nephrolithiasis
ECG	Myocardial ischemia or infarction

(Reproduced with permission from Fitch M: Utility and limitations of laboratory studies, in Cline DM, Stead LG (eds): *Abdominal Emergencies*. New York, NY: McGraw-Hill Medical; 2008, p. 19.)

surgical disease. Among patients with acute mesenteric ischemia, up to 25% have a normal serum lactate on initial presentation,[10] and studies on the utility of serum lactate values are limited by (among other things) varying intervals from the onset of symptoms to ED presentation. In a large study of patients with acute pancreatitis, serum lipase was 90% sensitive and 93% specific when drawn at the time of ED presentation.[11] Nineteen patients had pancreatitis with normal initial lipase levels; 14 of these had elevated lipase levels when the test was repeated later on the day of admission.[11]

DIAGNOSTIC IMAGING

Diagnostic imaging does not take the place of a conscientious history and physical examination. Not all patients with abdominal pain require imaging. Moreover, if the clinical impression suggests that the need for surgery is obvious, surgical consultation should be initiated immediately. It is not necessary to wait for diagnostic imaging before surgical consultation.

Plain Radiographs In some institutions, an "abdominal series" includes an upright abdomen; in others, an upright chest; in still others, only a single supine film is obtained. If plain radiographs are obtained, make sure the inguinal region is included to help identify incarcerated hernia. Radiographic evidence of small bowel obstruction may be seen 6 to 12 hours before symptoms develop. However, signs may be absent in up to half of patients with developing small bowel obstruction.[12,13] Although an upright chest film is better to detect free air than an abdominal film, the sensitivity for small amounts of free air is only about 30%.[12,13] The use of plain abdominal radiographs should be limited to screening for obstruction, sigmoid volvulus, perforation, or severe constipation.

Ultrasound In adults, an abdominal US examination can visualize the gallbladder, pancreas, kidneys and ureters, urinary bladder volume, and aortic dimensions. Abdominal US is not useful for diagnosis of small or large bowel disorders. The detection of free air or appendicitis by US is operator dependent and limited by patient obesity and bowel gas.[14]

US is the preferred modality for the evaluation of biliary tract disease. When acute cholecystitis or biliary dyskinesia is strongly suspected but the US is normal, cholescintigraphy is recommended.

POCUS EMS POCUS use continues to rise, and many ED physicians have incorporated this modality into routine practice.[15] Abdominal resuscitative POCUS involves rapid assessment for free intra-abdominal fluid (FAST), abdominal aortic aneurysm, and cardiac/inferior vena cava status. Abdominal diagnostic POCUS studies are focused urinary tract and biliary evaluations.[15]

Abdominal-Pelvic CT Scanning CT scanning is a sensitive and specific diagnostic tool for many causes of abdominal pain. Its clinical usefulness is balanced by delays in surgical management and increase in ED times if oral contrast is used and by radiation dose.[16] The radiation dose of abdominal CT is about 10 mSv, about 10 times that of plain abdominal radiographs.[12]

Options for CT scanning include noncontrast studies, or PO, PR, and/or IV contrast. Protocols vary depending on institutional, surgical, and radiology protocols; the prior probability of specific GI disorders in the patient population served; and individual radiologist preference. There are many contradictory studies on the best approach, especially for undifferentiated abdominal pain, for which the differential diagnosis is broad. Most studies have focused on the CT diagnosis of appendicitis.[17]

Noncontrast abdominopelvic CT has about 97% specificity for the diagnosis of acute appendicitis, with the possible exception of patients with a low body mass index (<25 kg/m^2). Noncontrast CT is the preferred imaging modality for the diagnosis of kidney and ureteral stones.

The use of oral contrast for the ED diagnosis of acute abdominal pain as a general protocol has been called into question.[17,18] Factors that affect the usefulness of oral contrast include patient vomiting, type and volume of oral contrast administered, transit time to the distal colon (variable, may be several hours), gastric emptying time (delayed induction of anesthesia, several hours), inadequate bowel opacification, and prolonged ED throughput time.[17] However, PO contrast CT is the imaging modality of choice in many institutions for suspected GI abscess, perforation, or fistula.

Rectal contrast CT can identify distal large bowel obstruction if that is the focused question.

IV contrast CT provides superior visualization of bowel mucosa, visceral organs, and vascular structures. It can identify small and large bowel obstruction and the transition point. It is the initial test of choice for suspected abdominal aortic aneurysm rupture or mesenteric ischemia. The risks of IV contrast are nephrotoxicity and allergic reactions. The association of IV contrast with acute kidney disease has been questioned.[19] Limitations regarding IV contrast use, renal function cutoff values, and pretreatment guidelines vary depending on institutional, ED, and radiology department practice protocols. A common practice is if the serum creatinine is >1.5 milligrams/dL or the glomerular filtration rate is <60 mL/min/1.733 m^2, then the use of IV contrast is generally not recommended except in life-threatening situations. IV contrast is contraindicated in patients with a history of allergy to IV contrast or to iodine. There is no literature to support an allergy to shellfish as a contraindication to the use of IV contrast.

Common diagnoses for acute abdominal pain are listed in **Table 71-4**.[20-25]

TREATMENT

ANTIBIOTICS

Antibiotics are indicated for suspected abdominal sepsis and peritonitis. Endogenous gut flora cause abdominal infections in the GI or GU tract. In all intra-abdominal nongynecologic infections, coverage should minimally be targeted at anaerobes and facultative aerobic gram-negative bacteria. High-risk community-acquired (septic, elderly, comorbid conditions, immunosuppressed, delayed presentation, known resistant organism) and healthcare-associated intra-abdominal infections require broader-spectrum antibiotic coverarge.[26,27] Antibiotic treatment is summarized in **Table 71-5**.

The treatment of pelvic inflammatory disease (PID) requires different antibiotic combinations than do GI and GU infections. (For a detailed discussion, see Chapter 103, "Pelvic Inflammatory Disease.")

DISPOSITION AND FOLLOW-UP

Surgical consultation is required once a surgical diagnosis is made. Otherwise, consider hospital admission or observation for high-risk patients with acute abdominal pain. Patients who are elderly, immunocompromised, unable to communicate, or cognitively impaired are especially high risk. Patients who appear ill, have intractable pain or vomiting, are unable to comply with discharge or follow-up instructions, or who lack appropriate social support should also be considered for admission. **Patients with an unclear diagnosis at discharge, even if the CT scan is "negative" (or for whom response to treatment is a concern), should be asked to return to the ED or their primary care physician for re-evaluation within 12 hours.** Discharge instructions should address diet (e.g., clear liquids only, push fluids, no fatty foods, no acidic foods) and medications (e.g., antacids, analgesics, avoid narcotics). The patient and the patient's family should understand that the diagnosis is uncertain, and they should know which symptoms warrant a return to the ED (e.g., increased/different pain, fever, vomiting, syncope, bleeding).

SPECIAL POPULATIONS

WOMEN

Gynecologic and nongynecologic disease can cause acute lower abdominal or pelvic pain in women (**Table 71-6**).

Hemorrhage from an ectopic gestation is the leading cause of pregnancy-related maternal death in the first trimester, despite improved diagnostic and treatment modalities. **Obtain a qualitative or quantitative urine or serum pregnancy test in women of childbearing age with acute abdominal pain who have not had a hysterectomy.** If the qualitative human chorionic gonadotropin is positive, transvaginal sonography should be the next diagnostic test to answer the question: Is this pregnancy in the uterus? Either inside or outside the uterus, a gestational sac is typically visible if the patient's serum β-human chorionic gonadotropin is >1500 mIU/mL (the operator-dependent "discriminatory zone"). Detailed discussion of ectopic pregnancy is provided in Chapter 98, "Ectopic Pregnancy and Emergencies in the First 20 Weeks of Pregnancy." **Suspect ectopic pregnancy in a woman of reproductive age with hemodynamic collapse.** The presence of right lower quadrant pain in a woman who has an appendix is a common diagnostic dilemma. In general, the results of pelvic examination, consideration of patient risk factors for gynecologic versus GI disease, and the clinician's best estimate of pretest probability for gynecologic versus GI disease are the best guides for further imaging. If pretest probability favors gynecologic disease, a transvaginal US would be the next step. If pretest probability favors GI disease or appendicitis, abdominopelvic CT scanning would be the next step.

ELDERLY PATIENTS

Symptoms in the elderly may be mild, vague, or underreported, and presentations may be late and atypical. Among those >80 years old, mortality almost doubles if the diagnosis is incorrect at the time of admission.[28] Poor hearing, decreased vision, and impaired cognition may affect the ability to give an adequate history. Surgical complications are more common: perforated viscus, gangrenous gallbladder, necrotizing pancreatitis, strangulated hernia, and infarcted bowel. Fever is not a reliable marker for serious disease, and the elderly may be hypothermic in the presence of serious abdominal infection. Fewer than 20% of elderly patients with perforated appendicitis have a "classic" presentation.[29] A WBC has a low predictive value for surgical disease in the elderly. **Although certain variables have been associated with poor outcome (age >84 years old, bandemia, free air) and others with the need for surgery (hypotension, abnormal bowel sounds, massively dilated loops of bowel, extreme leukocytosis), the absence of these variables does not preclude significant disease.**

Cholecystitis is the most common surgical entity in elderly patients with abdominal pain, followed by small bowel obstruction, perforated viscus, appendicitis, and large bowel obstruction. Viral gastroenteritis is uncommon among the elderly, but diarrhea occurs in 31% to 40% of patients with mesenteric ischemia.[10,30]

Any acute abdominal pain is important in an elderly patient. No single test can distinguish among patients who should be admitted and patients who can be safely discharged. **A liberal imaging/admission/observation policy is strongly advocated when the diagnosis is in doubt or follow-up is uncertain.**

BARIATRIC SURGERY PATIENTS

The purpose of bariatric surgery is to limit the absorption of nutrients from ingested food by reducing the size of the stomach, with or without a degree of associated malabsorption (**Table 71-7**). The refinement of laparoscopic surgical technique has resulted in decreased perioperative morbidity and mortality after gastric bypass surgery.[31] Detailed discussion of bariatric surgery complications is provided in Chapter 298, "The Patient With Morbid Obesity."

Staple breakdown after gastroplasty and band slippage after laparoscopic adjustable gastric banding may present as sudden intolerance to food or gastroesophageal reflux. Obstruction and erosion may also occur at the site of a gastric band. Diarrhea is a frequent complaint with predominantly malabsorptive procedures, and long-term malabsorption may result in protein depletion and vitamin deficiencies (particularly fat-soluble vitamins: A, D, and K).

Several specific problems can occur after successful Roux-en-Y gastric bypass (**Table 71-8**).

The most common early complications are leakages, stenosis, and bleeding.[31] The diagnosis of enteric leak requires a high index of suspicion, because the clinical presentation varies widely.[31,32] With Roux-en-Y gastric bypass, leaks occur most commonly at the gastrojejunostomy anastomosis. Patients with enteric leak typically present with features suggestive of sepsis (tachycardia, fever, abdominal pain, hypotension). CT may show extravasation of oral contrast material, a finding highly suggestive of

TABLE 71-4 Common Diagnoses for Acute Abdominal Pain in Adults

Diagnosis	Epidemiology	Typical Location	Typical Radiation	Typical Quality	Helpful	Cautions	Laboratory	Imaging	Complications
Appendicitis	Peak age: adolescence and young adulthood	Early: periumbilical; late: RLQ. If retrocecal or third trimester pregnancy may be RUQ	—	Initially dull, becomes severe	RLQ pain; pain migrated from periumbilical area; pain before vomiting; rigidity	Anorexia, vomiting, fever, and elevated WBC have poor individual sens	No WBC count or CRP level can exclude or confirm the diagnosis[20]	CT preferred in adults and nonpregnant women	Perforation, abscess
Biliary colic	F >> M before age 60 y old, Hispanic > white > black	RUQ > epigastric	Right subscapular area	Initially colicky, becomes continuous; colic typically resolves <6 h	Bloating and dyspepsia are not related to gallstones	—	Suspect common bile duct stone if elevated bilirubin	US	Cholecystitis
Bladder outlet obstruction	Benign prostatic hypertrophy	Suprapubic	—	—	—	—	—	Bedside US	—
Bowel obstruction	History previous abdominal surgery	Diffuse	—	Colicky	Vomiting, distention	—	—	Plain films: 77% sens; CT: 93% sens[21]	Incarceration, strangulation
Cholecystitis	Most common surgical cause of abdominal pain in elderly	RUQ > epigastric	Right subscapular area	Continuous	(+) Murphy sign increases likelihood of cholecystitis (odds ratio 2.3–2.8); jaundice suggests obstruction	Up to 90% afebrile; elevated WBC only 63% sens and 57% spec. Cholangitis: elevated WBC only 80% sens	No single test can exclude diagnosis; elevated bilirubin/aspartate aminotransferase/alkaline phosphatase each only 70% sens and 42% spec	US: 81% sens; hepatobiliary iminodiacetic acid scan: 96% sens[22]	Common bile duct obstruction; ascending cholangitis; gangrene
Diverticulitis	M > F before age 40 y old; incidence increases with age	Sigmoid (85%): LLQ; cecal/Meckel: RLQ	—	—	50% report previous episode of similar pain	Temperature may be normal; 25% (+) fecal occult blood	WBC may be normal	CT: sens 93%–100%; spec 100%	Perforation; abscess; fistula; obstruction
Epiploic appendagitis	Middle age; M > F	LLQ	—	—	Fever unusual; n/v infrequent; diarrhea 25%	In general, pts are not systemically ill	—	CT	—
Mesenteric arterial occlusion	Atrial fibrillation	Any	—	Severe	Pain out of proportion to physical findings; n/v	Atrial fibrillation	Lactate: 86% sens; not specific[23]; elevated WBC: 90%	Selective CT angiography: 94% sens[23]	Metabolic acidosis
Mesenteric venous thrombosis	Hypercoagulable states, liver disease	Most commonly: generalized or epigastric	—	—	—	—	—	Contrast-enhanced CT	—
Mesenteric ischemia (nonocclusive)	Critically ill pts; vasoactive drugs	—	—	—	—	—	—	Angiography	—
Myocardial ischemia	—	Upper midline	—	Steady, dull	Abnormal ECG	ECG may be normal	Troponin sens and spec vary based on available assay	—	—
Pancreatitis	M > F. Risks: alcohol; biliary disease; drugs; endoscopic retrograde cholangiopancreatography	Epigastric	Back	Severe, constant	Nausea and vomiting common	May have low-grade fever	Lipase: 90% sens first 24 h	Contrasted CT is the gold standard[24]; US may show edema	Hemorrhage; pseudocyst; adult respiratory distress syndrome; sepsis

PID	Sexually transmitted diseases; prior PID; multiple partners	RLQ and/or LLQ	—	—	Vaginal discharge; dyspareunia; cervical motion tenderness	Fever not necessary for diagnosis	Elevated WBC not necessary for diagnosis	—	Tubo-ovarian abscess; perihepatitis; infertility; ectopic pregnancy; chronic pain
Peptic ulcer disease	Peak age: 50s; M > F; chronic aspirin or NSAIDs; smoking; alcohol; *Helicobacter pylori*	Epigastric	—	Severe, persistent	Vomiting, tachycardia	Nonulcer dyspepsia more likely if: age <40 y old, no weight loss, no night pain, no vomiting	—	—	Perforation bleeding
Perforated viscus	—	Any	—	Severe	—	—	—	CT excellent Plain radiography has clinical utility[25]	—
Ovarian torsion	—	RLQ or LLQ	Back, flank, or groin	Sudden onset, severe, sharp; may have nausea/vomiting	Adnexal mass	—	—	Pelvic US with Doppler flow	Ovarian salvage decreases with delay in diagnosis
Renal/ureteral colic	Average age: 30–40 y old; white > black; family history of stones	Right or left flank	Ipsilateral groin/scrotum	Severe; colicky; nausea and vomiting common	85%–90% have hematuria; only 30% have gross hematuria	—	Urinalysis	CT, US	Obstruction Infection
Ruptured ectopic pregnancy	Previous ectopic; PID; infertility treatment; intrauterine device <1 y; tubal surgery	RUQ or LLQ	—	Sudden onset; severe pain	Pelvic mass	Pelvic exam may be normal	Pregnancy test	Transvaginal US	Shock
Ruptured/leaking abdominal aortic aneurysm	Older; male; atherosclerotic cardiovascular disease; smoker; (+) family history	Mid-abdomen or flank	Back, groin, or thigh	Severe; sudden onset; constant	Pulsatile mass detected: 22%–96% sens	Only 50% are hypotensive at presentation. Normal pulses do not exclude diagnosis	—	Bedside US 100% sens	Shock
Tubo-ovarian abscess	PID	Unilateral or bilateral lower abdominal or pelvic pain	—	—	—	Fever may be absent	Leukocytosis may be absent	Transvaginal US	Rupture, peritonitis, shock

Abbreviations: > = more than; >> = much more than; < = less than; + = positive; CRP, C-reactive protein; F = female; LLQ = left lower quadrant; M = male; n/v = nausea and vomiting; PID = pelvic inflammatory disease; pts = patients; RLQ = right lower quadrant; RUQ = right upper quadrant; sens = sensitivity; spec = specificity; US = ultrasound.

TABLE 71-5 Antibiotic Regimens for Intra-abdominal Infections

Antibiotic	Comments
Combination Therapy	
Cephalosporin Cefazolin 1–2 gram IV every 8 h or Ceftriaxone, 1 gram IV once daily or Cefotaxime 1–2 grams IV every 6 h or Cefepime 2 grams IV every 8 h or Ceftazidime 2 grams IV every 8 h plus Metronidazole 500 milligrams IV every 8 h	Cefepime and ceftazidime are indicated for high-risk or healthcare-associated intra-abdominal infections.
Fluoroquinolone Ciprofloxacin 400 milligrams IV every 12 h or Levofloxacin 750 milligrams IV once daily plus Metronidazole 500 milligrams IV every 8 h	
Single-Agent Therapy	
Ertapenem1 gram IV once daily	—
Piperacillin-tazobactam 3.375–4.5 grams IV every 6 h	Higher dose for high-risk or healthcare-associated intra-abdominal infections
Imipenem-cilastatin 500 milligrams IV every 6 h	Indicated for high-risk or healthcare-associated intra-abdominal infections
Meropenem 1 gram IV every 8 h	Indicated for high-risk or healthcare-associated intra-abdominal infections
Additional Agent	
Vancomycin 15 to 20 milligrams/kg every 8–12 h	Add to provide MRSA and increased enterococcal coverage.

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*.

leak in the early postoperative period. Primary repair is the treatment of choice. The mortality for undiagnosed enteric leak is extremely high.

Bowel obstruction may be caused by internal hernia, anastomotic stenosis, or adhesions. Symptoms may be nonspecific (nausea, bloating, abdominal pain). Bowel obstruction in the immediate postoperative period after Roux-en-Y gastric bypass is a surgical emergency, as distention of biliopancreatic limb and distal stomach can result in gastric rupture and peritonitis. Bilious emesis after Roux-en-Y gastric bypass is pathognomonic for common channel obstruction, which requires immediate surgical intervention.[33] Gallstone formation is increased during the period of rapid weight loss after bariatric surgery. "Dumping syndrome" is caused by rapid postprandial gastric emptying, the release of gastric hormones, and splanchnic vasodilation. Patients with early dumping complain of nausea, vomiting, bloating, abdominal cramps, diarrhea, and sweating 30 to 60 minutes after a meal. Late dumping occurs 1 to 3 hours postprandially. It is a hyperinsulinemic and hypoglycemic state. Dietary modification is the initial treatment for dumping syndrome; patients should be advised to avoid highly concentrated foods, to separate eating and drinking, and to avoid rapidly absorbed sugars and lactose.[34] Severe cases of dumping syndrome have been successfully treated with subcutaneous octreotide.[35]

TABLE 71-6 Common Gynecologic Causes of Lower Abdominal/Pelvic Pain

- Adnexal torsion*
- Endometriosis
- Endometritis/salpingitis (pelvic inflammatory disease)*
- Myoma (degenerating)
- Ruptured ectopic pregnancy*
- Ruptured ovarian cyst*
- Tubo-ovarian abscess*
- Adnexal/uterine masses

*Potential threat to life.

TABLE 71-7 Types of Bariatric Surgical Procedures

Restrictive	Primarily Malabsorptive; Mildly Restrictive	Primarily Restrictive; Mildly Malabsorptive
Vertical banded gastroplasty ("stomach stapling")	Biliopancreatic diversion	Roux-en-Y gastric bypass
Laparoscopic adjustable gastric banding	Duodenal switch	

EPIPLOIC APPENDAGITIS

Epiploic (omental) appendages are fatty pedicular structures, typically 3 cm in length, that are found on the serosal surface of the normal colon. Their function is not known. It is estimated that each person has 50 to 100 epiploic appendages, most commonly on the sigmoid colon and cecum.[36] Acute epiploic appendagitis is a self-limited inflammatory condition usually caused by the torsion of an epiploic appendage. The cardinal sign is pain, which can mimic acute diverticulitis or acute appendicitis. In general, patients do not appear systemically ill, and fever is unusual. Nausea and vomiting are infrequent, but diarrhea has been reported in up to 25% of cases.[36] On US, epiploic appendagitis appears as an oval noncompressible hyperechoic mass at the site of maximal abdominal tenderness, with no color Doppler blood flow.[37] Normal epiploic appendages are not visualized on abdominal CT images in the absence of significant intraperitoneal fluid (e.g., hemoperitoneum, ascites).[37] Epiploic appendagitis appears on CT as an oval fatty mass with a slightly hyperdense rim and surrounding mesenteric stranding suggestive of inflammation.[37] The treatment is supportive and nonoperative. Pain control should be provided. Antibiotics are not indicated. Most cases resolve spontaneously within 1 to 2 weeks.

THE POSTOPERATIVE PATIENT WITH ACUTE ABDOMINAL PAIN

ILEUS AND EARLY POSTOPERATIVE BOWEL OBSTRUCTION

Anesthesia and surgical manipulation of the bowel decrease the normal propulsive activity of the gut. In the absence of precipitating factors, no specific treatment is necessary, and normal bowel function returns 2 to 3 days postoperatively. Mild cramps and flatus signal the return of peristalsis. A delay in the return of normal GI function may be caused by electrolyte abnormalities, intra-abdominal inflammation or infection, pancreatitis, or medications (particularly opioids, anticholinergics, phenothiazines, and psychotropics). The clinical findings of adynamic postoperative ileus are nausea, vomiting, abdominal distention, cramps, and obstipation. Plain radiographs of the abdomen demonstrate diffusely dilated loops of bowel, with air present in the distal colon and rectum. Adynamic ileus is treated supportively and by correction of precipitating factors.

TABLE 71-8 Complications After Roux-en-Y Gastric Bypass

- Anastomotic leak
- Bowel obstruction (includes internal hernia and volvulus of Roux limb)
- Cholelithiasis
- Dumping syndrome
- Enteric leak
- Marginal ulcer
- Metabolic complications (vitamin B_{12}, iron, thiamine, vitamin and mineral deficiencies; hyperoxaluria)
- Stenosis of gastrojejunostomy site

The clinical differentiation of adynamic ileus and mechanical small bowel obstruction can be difficult. Patients with obstruction may report a temporary return of GI function postoperatively. The symptoms of obstruction are similar to those of adynamic ileus, but vary depending on the location and extent of the obstruction. Proximal obstruction is usually associated with early emesis and less abdominal distention, distal obstruction with later (sometimes bilious or feculent) emesis, and significant abdominal distention. High-pitched bowel sounds suggest mechanical obstruction. Plain abdominal radiographs show air-fluid levels (which suggest but are not pathognomonic for obstruction), thickened valvulae conniventes proximal to the obstruction, and little air in the bowel distal to the obstruction. The amount of dilated bowel is variable. Abdominal CT can reliably identify the transition point of normal to abnormal bowel, the degree of mechanical obstruction, and the presence of complications (perforation, abscess). In the absence of complications, partial small bowel obstruction is managed with observation. Surgery is generally required for high-grade obstruction or peritonitis. Mechanical small bowel obstruction is most often caused by adhesions.

ACUTE URINARY RETENTION

Acute urinary retention after ambulatory surgery should be an obvious diagnosis based on the patient's report of inability to urinate. Bedside bladder US confirms the diagnosis. Treatment is urinary bladder drainage.

ABDOMINAL COMPARTMENT SYNDROME

Abdominal compartment syndrome is a serious condition seen in critically ill patients. Intra-abdominal hypertension is defined as persistent intra-abdominal pressure above 12 mm Hg. Abdominal compartment syndrome occurs as increased intra-abdominal pressure, often above 20 mm Hg, causes associated organ dysfunction. It is most often seen in critically ill septic, trauma, burn, and postoperative patients who receive aggressive fluid resuscitation. The diagnosis of abdominal compartment syndrome should be considered in the critically ill unstable patient with a tense abdomen, although a tense abdomen is not required to make the diagnosis. Abdominal compartment syndrome is confirmed by assessing intra-abdominal pressure, which is most often measured via urinary bladder pressure monitoring. Medical management involves identification and treatment of the contributing factors of abdominal compartment syndrome, evacuating intraluminal contents, improving abdominal wall compliance, and optimizing fluid administration and perfusion.[38,39] Surgical decompression is required in patients with severe or refractory abdominal compartment syndrome.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 72

Nausea and Vomiting

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INTRODUCTION AND EPIDEMIOLOGY

Nausea and vomiting accompany a variety of illnesses. Symptoms may be due to primary GI disorders such as bowel obstruction or gastroenteritis. However, symptoms may also represent pathology of the CNS (increased intracranial pressure, tumor), psychiatric conditions (bulimia nervosa, anxiety), endocrine or metabolic abnormalities (DKA, hyponatremia), or iatrogenic causes (medications, toxins). Also, nausea and vomiting may be the result of severe pain, myocardial infarction, sepsis, or other systemic illnesses. A comprehensive history and physical examination, as well as the use of various diagnostic modalities, are needed to determine the cause and its complications.

In the United States, the most common cause of acute nausea and vomiting is viral gastroenteritis. Other important considerations are side effects from medication and, in young women, pregnancy.[1]

PATHOPHYSIOLOGY

Multiple neurons in the medulla oblongata are activated in a sequential fashion to induce vomiting. The vomiting center is the chemoreceptor trigger zone, located in the area postrema of the fourth ventricle. Chemoreceptors in this area are outside the blood–brain barrier and are stimulated by circulating medications and toxins, including dopaminergic antagonists (levodopa, bromocriptine), nicotine, digoxin, and opiate analgesics. Another important peripheral pathway for emesis is mediated through vagal afferents. Vagal activation is triggered by direct gastric mucosal irritants (such as NSAIDs) or increased luminal distention (gastric outlet obstruction, gastroparesis). Vagus activation stimulates neurons in the area postrema and nucleus tractus solitarius. These areas are rich in serotonin receptors and are a major site of action of antiemetic drugs, such as granisetron and odansetron.[2] Similar receptors are found throughout the GI tract, as well as the cortex and limbic system, vestibular system, heart, and genitalia.

CLINICAL FEATURES

The differential diagnosis of nausea and vomiting is exhaustive, as pathology of almost every organ system may lead to nausea and vomiting (**Table 72-1**). A thorough history and physical examination will help guide the diagnostic approach to the patient presenting with nausea and vomiting.

HISTORY

Identify the onset and duration of the symptoms. The evaluation of acute conditions differs from a more chronic condition. For chronic conditions, understanding the scope of prior testing and treatment may help narrow the diagnostic possibilities. Chronic symptoms are defined as those symptoms present for >1 month.

Frequency of the episodes and interval between episodes are helpful to gauge the severity of illness. Timing, such as increased number of episodes in the morning, may suggest pregnancy or a CNS cause, whereas postprandial vomiting suggests a GI cause such as gastroparesis or gastric outlet obstruction.

The content of the vomitus may be helpful to determine whether an obstruction is present and its location. Esophageal disorders produce vomitus with undigested food particles. Bile is often associated with a small bowel obstruction, whereas vomitus composed of food particles and devoid of bile often represents a gastric outlet obstruction. Large bowel obstruction often is composed of feculent material and has a foul odor.

Because of the number of organ systems that are the potential cause of pathology, it is important to ask the patient about associated symptoms. The presence or absence of abdominal pain is a focal starting point. If pain is present, elicit its location and quality. Pain preceding the nausea and vomiting is most particularly associated with an obstructive process.[2] Fever or, possibly, diarrhea suggests gastroenteritis. Ask about sick contacts or ingestion of food suspicious for a foodborne illness. A history of recent weight loss is associated with a malignancy or psychiatric component. Any CNS sign, such as headache, visual changes, vertigo, or neurologic deficits, may suggest a central cause for the nausea and vomiting. Obtain a thorough past medical and travel history. Prior abdominal surgery is a major risk factor for bowel obstruction from adhesions. Review the patient's medication list to identify a medication with a common side effect of nausea and vomiting, such as NSAIDs, chemotherapeutic agents, antibiotics, various antihypertensives and antiarrhythmics, and oral contraceptives. Other medications at toxic

TABLE 72-1 Differential Diagnosis of Nausea and Vomiting

GI	Neurologic	Infectious	Drugs/Toxins	Endocrine	Miscellaneous
Functional disorders	Head injury	Bacterial toxins	Digoxin	Pregnancy	Myocardial infarction
Psychogenic	Stroke	Pneumonia	Aspirin	Adrenal insufficiency	Acute glaucoma
Irritable bowel syndrome	Pseudotumor	Spontaneous bacterial peritonitis	NSAIDs	DKA	Nephrolithiasis
Obstruction	Hydrocephalus	Urinary tract infection	Acetaminophen	Parathyroid disorders	Pain
Adhesions	Mass lesion	Viruses	Opiates	Thyroid disorders	Psychiatric disorders
Esophageal disorders	Meningitis	Adenovirus	Alcohol	Uremia	Anorexia nervosa
Achalasia	Migraines	Norwalk virus	Theophylline	Electrolyte disorders, especially hyponatremia	Bulimia
Intussusception	Labyrinthitis	Rotavirus	Chemotherapeutics		Conversion disorder
Tumor	Ménière's disease		Anticonvulsants		Depression
Pyloric stenosis	Motion sickness		Antibiotics		
Strangulated hernia			Antiarrhythmics		
Volvulus			Hormones		
Organic disorders			Illicit drugs		
Appendicitis			Radiation therapy		
Cholecystitis			Toxins		
Cholangitis			Arsenic		
Hepatitis			Organophosphates		
Irritable bowel disease			Carbon monoxide		
Mesenteric ischemia			Ricin		
Pancreatitis					
Peptic ulcer disease					
Peritonitis					

levels are known to cause nausea and vomiting. Examples include acetaminophen, salicylates, and digoxin.

PHYSICAL EXAMINATION

Assess vital signs for hypotension and tachycardia. Observe skin turgor, mucous membrane hydration, and capillary refill to assess for dehydration. In children, the most useful predictors of significant dehydration (>5% loss of body weight) are abnormal capillary refill, abnormal skin turgor, absent tears, and abnormal respiratory pattern.[3] The abdominal examination is particularly important to assess for an emergent problem, as well as to help narrow the differential diagnosis to a possible GI cause.[4] Inspect, auscultate, and palpate the abdomen. (For further discussion of abdominal evaluation, see Chapter 71, "Acute Abdominal Pain.")

Investigate any other important examination findings particular to various organ systems, as findings may provide valuable information regarding the cause of the nausea and vomiting (**Table 72-2**).

IMAGING AND ANCILLARY TESTING

Diagnostic testing in the ED depends on differential diagnosis raised by a detailed history and physical exam. Often, CBC and basic metabolic panel are part of the initial evaluation. However, liver function tests and lipase may be considered if the patient is presenting with signs of biliary obstruction or upper abdominal pain. A pregnancy test should be considered for all woman of childbearing age. Further imaging with abdominal radiographs, CT scan, or US depends on the presentation and concern for acute intra-abdominal pathology. Head CT or brain MRI is ordered to evaluate for an intracranial mass or lesion.

TREATMENT

After initial evaluation of airway, breathing and circulation, focus on providing symptomatic relief (**Table 72-3**). Definitive management will often require disease-specific treatment. First-line supportive treatment should include fluid hydration with normal saline or lactated Ringer's and may be sufficient for most patients. H_1 histaminergic agents such as promethazine or a serotonin receptor antagonist such as ondansetron may also be helpful for initial treatment.[5] However, promethazine is more sedating, with the potential side effect of vascular damage during IV administration. Metoclopramide and prochlorperazine are also commonly used drugs in the ED. Patients given these drugs may develop akathisia up to 48 hours after administration.[6] Studies comparing the efficacy of different drugs for treatment of nausea and vomiting in the ED report no definitive evidence to support the superiority of one drug over another or over placebo.[7,8]

ONDANSETRON

In the ED, serotonin receptor antagonists such as ondansetron have been first-line therapy for undifferentiated nausea and vomiting for all age groups. In 2011, the U.S. Food and Drug Administration issued a safety advisory for ondansetron due to concern for QT prolongation.[9] Despite this warning, the clinical impact of QT prolongation associated with ondansetron use in the ED is unclear.[10] There are a few pediatric case reports of cardiac death possibly associated with ondansetron use.[11] In a recent pediatric study, the risk of ventricular arrhythmia was three in 100,000 patients and increased with underlying cardiac conditions.[12] Thus, patients with congenital long QT syndrome, congestive heart failure, or bradyarrhythmias or taking concomitant medications that prolong QT interval are at risk, and cardiac monitoring should be instituted for this population. In addition, electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia) should be corrected prior to administration of ondansetron. Consider ordering an ECG prior to ondansetron administration for a patient with a history of cardiac disease.

GASTROPARESIS

PATHOPHYSIOLOGY

Gastroparesis is delayed gastric emptying in the absence of an obstructing lesion. This condition, which is typically chronic, is associated with decreased quality of life and increased healthcare utilization, although it is not typically associated with significant mortality.[13-15] The most common cause is idiopathic, but other causes include diabetes, bariatric

TABLE 72-2 Differential Diagnosis Based on Physical Examination Findings

Physical Examination	Abnormal Signs or Symptoms	Some Diagnostic Considerations
General	Toxic appearing	Dehydration
	Generalized weakness	Chronic malnutrition
	Weight loss	Malignancy
Vital signs	Fever	Infection (gastroenteritis, appendicitis, cholecystitis)
	Tachycardia	Bowel perforation secondary to peritonitis
	Hypotension	Severe volume depletion
	Hypertension	Intracranial hemorrhage or stroke
Head, eyes, ears, nose, throat	Nystagmus	Peripheral vs. central causes (benign positional vertigo, cerebellar infarct)
	Exophthalmos	Graves' disease
	Pinpoint pupils	Opiate abuse
	Fixed-dilated pupil, eye pain	Acute glaucoma
	Dry mucous membranes	Dehydration Bulimia
	Poor dental enamel, parotid gland enlargement	Bulimia
Abdomen	Distention, decreased bowel sounds, surgical scars	Small bowel obstruction, gastroparesis, gastric outlet obstruction, ileus
	Hernias or palpable masses	Incarcerated hernia, tumors
	Abdominal rigidity	Peritonitis
Neurologic	Mental status Cranial nerve findings or neurologic deficits Papilledema	Dehydration, intracranial lesion or pathology, brainstem tumor, elevated intracranial pressure
Extremities	Scarring on dorsal surface of the hands	Bulimia
Skin	Jaundice	Hepatobiliary disease (hepatitis, choledocholithiasis)
	Poor skin turgor	Dehydration
	Hyperpigmentation	Addison's disease
	Decreased elasticity	Scleroderma
	Skin track marks	Drug abuse/withdrawal

and gastric surgery, viral illness, gastroesophageal reflux disease, and nonulcer dyspepsia.[13-16] Connective tissue or neurologic disease, and even pregnancy, can also be associated with gastroparesis. The incidence appears to be increasing, especially in diabetics.[16-18]

DIAGNOSIS

Symptoms of gastroparesis typically include early satiety, bloating, postprandial nausea, gastroesophageal reflux, vomiting, and abdominal pain.[13-15] If severe and chronic, patients may develop weight loss, electrolyte abnormalities, and nutritional or vitamin deficiencies. Physical examination may reveal a succussion splash, which indicates excessive gastric fluid from delayed emptying or mechanical outlet obstruction.[13-15,19] Significant abdominal tenderness and peritoneal findings should be absent.[13-15,19]

Initial investigations include serum electrolytes, liver function studies, serum lipase, and pregnancy test. If concern for mechanical obstruction is present, image with abdominal/pelvic CT. US has been used to diagnose gastroparesis and determine effectiveness of treatment.[20] Outpatient diagnostics include endoscopy, scintigraphy, electrogastrography, and assessment with the wireless motility capsule.[13-15]

TREATMENT

Management includes volume resuscitation with electrolyte repletion. Several medications may be used for symptomatic treatment. Prokinetic agents include metoclopramide (dopamine antagonist, 5 to 20 milligrams) and erythromycin (motilin receptor agonist, 40 to 250 milligrams). Both agents may decrease symptoms and increase gastric emptying. Metoclopramide can decrease nausea, provide analgesia, and act as a prokinetic and is a first-line agent. Erythromycin may demonstrate tachyphylaxis and should be a second-line medication. Other medications include domperidone (a peripherally selective dopamine D_2 receptor antagonist that is approved in Canada but, as of January 2018, not in the United States), diphenhydramine, prochlorperazine, and ondansetron. Opioids can treat pain; however, they may result in delayed gastric emptying and are not recommended for first-line therapy.[13-15]

Haloperidol can treat symptoms of nausea, vomiting, and pain. Haloperidol may be administered IV or IM. One study demonstrated a significant decrease in ED and hospital length of stay, hospital admission, and opioid administration, with no adverse events.[21] A randomized controlled trial reported that haloperidol 5 milligrams IV significantly reduces pain and nausea.[22] Patients whose symptoms improve are appropriate for discharge and follow-up with a primary care provider or gastroenterologist for further management.

CYCLIC VOMITING SYNDROME

PATHOPHYSIOLOGY

Cyclic vomiting syndrome usually presents in childhood, with more than half of cases resolving by the teenage years. The condition is rare in adults. Predisposing mitochondrial DNA mutations (15519T and 3010A) have been found in many patients with cyclic vomiting syndrome. It is more common in females than males. In adults, there is a higher incidence of opiate and tobacco use.

The cause is unknown, but it is thought to be related to dysregulation of the neuroendocrine system. Accompanying symptoms of lethargy, anorexia, pallor, abdominal pain, or autonomic symptoms such as sweating and salivation implicate abnormal vagal tone. It has also been suggested that cyclic vomiting syndrome is a functional disorder associated with migraines. Patients commonly have a history of migraines and report a prodrome with nausea and photophobia prior to attacks.[23]

DIAGNOSIS

Cyclic vomiting syndrome is characterized by recurrent nausea and vomiting separated by symptom-free periods. Since there is no specific confirmatory test for cyclic vomiting syndrome, diagnosis is clinical and involves excluding other common causes of symptoms. The diagnosis is often delayed for years after multiple ED visits and hospitalizations. Patients may be given the label of "drug-seeking." Comorbid conditions may include anxiety, depression, and irritable bowel.

Cyclic vomiting syndrome has been well described with four phases: (1) asymptomatic periods of several or many months; (2) prodrome phase lasting minutes to hours, with lethargy, photophobia, anorexia, sweating, or salivation; (3) hyperemesis phase, which usually starts in the morning with severe nausea and vomiting, lasting for days to a week, with the mean duration being 3.4 days; and (4) finally, recovery phase with improvement in symptoms and energy levels.

The Rome III diagnosis criteria include recurrent episodes of intractable vomiting that are self-limiting, last less than 7 days, and do not have an organic cause. Typically, patients have more than two episodes of vomiting in the past year with symptom-free intervals in between.

TREATMENT

Management in the ED is symptomatic, with antiemetics (ondansetron), sedatives (lorazepam), analgesics, and IV fluids. For prophylaxis, patients can try to avoid triggers such as sleep deprivation, diet, and physical or emotional stress. Amitriptyline is the standard for medical prophylaxis and has shown response rates as high as 86%. Other therapies include migraine prophylaxis drugs such as sumatriptan,

TABLE 72-3 Antiemetic Agents for the Treatment of Nausea and Vomiting

Medication Class	Route	Common Side Effects	Comments
Antihistamines		Drowsiness	Also show efficacy in prevention of motion sickness. Useful for migraines and vertigo.
Dimenhydrinate (Dramamine®)	PO		
Diphenhydramine (Benadryl®)*	IV, IM, PO		Used in migraines and vertigo, which are vestibular in origin.
Meclizine (Antivert®)	PO		
Benzodiazepines		Sedation	Adjunct for chemotherapy-induced nausea and vomiting.
Alprazolam (Xanax®)	PO		
Diazepam (Valium®)	PO, IV, PR		
Lorazepam (Ativan®)	PO, IV, IM		
Butyrophenones		Agitation, restlessness, sedation	Treatment of acute chemotherapy-induced symptoms; can prolong QT_c.
Haloperidol (Haldol®)*	PO, IM		
Corticosteroids		Insomnia	Used as an adjunct in severe cases of chemotherapy-induced nausea and vomiting; reduces prostaglandin formation.
Dexamethasone	PO, IV, IM		
Serotonin antagonists		Constipation, dizziness	Well tolerated; all serotonin antagonists can prolong QT_c in electrolyte- or drug-induced or congenital long QT_c syndrome; uncommon side effects include headache; rare case reports of anaphylaxis.
Ondansetron (Zofran®)*	PO, IV, SL		
Granisetron (Kytril®)*	PO, IV		
Dolasetron (Anzemet®)*	PO, IV		
Phenothiazines		Extrapyramidal symptoms,‡ sedation, orthostatic hypotension	Treatment in migraines, vertigo, and motion sickness; rare side effects include neuroleptic malignant syndrome, blood dyscrasias, and cholestatic jaundice.
Prochlorperazine (Compazine®)†	PO, IV, IM, PR		
Promethazine (Phenergan®)†	PO, IV, IM, PR		
Benzamides		Extrapyramidal symptoms,‡ hyperprolactinemia	Used in treatment of gastroparesis and children with reflux.
Metoclopramide (Reglan®)	PO, IV, IM		
Trimethobenzamide (Tigan®)	PO, IM		

*QT interval prolongation reported.

†Nonspecific Q or T distortions reported.

‡Extrapyramidal symptoms: dystonia, tardive dyskinesia, oculogyric crisis, parkinsonism.

propranolol, and topiramate. Mitochondrial-targeted therapies such as L-carnitine, coenzyme Q10, and riboflavin have shown excellent efficacy in combination with amitriptyline and alone.[24]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 73

Disorders Presenting Primarily With Diarrhea

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GENERAL ASSESSMENT OF PATIENTS WITH DIARRHEA

INTRODUCTION AND EPIDEMIOLOGY

This chapter discusses the general assessment of patients with diarrhea and the special considerations of acute infectious and traveler's diarrhea, *Clostridium difficile* diarrhea and colitis, inflammatory bowel disease, ileitis and colitis, and ulcerative colitis.

Acute diarrhea is the sudden onset of an increase in the normal water content of stool. In general, humans lose approximately 10 mL/kg/d of fluids in stool. The increased water content of diarrhea results in an increased frequency of stools from three or more times daily to more than 20 bowel movements in a 24-hour period. Diarrhea is an increased frequency of defecation, usually greater than three bowel movements per day for a daily stool weight exceeding 250 grams.[1] Practically speaking, however, diarrhea is present when the patient is making more stools of lesser consistency more frequently.

PATHOPHYSIOLOGY

There are four basic mechanisms of diarrhea: increased intestinal secretion, decreased intestinal absorption, increased osmotic load, and abnormal intestinal motility. Normally, the jejunum receives between 6 and 8 L per day of fluid in the form of oral intake and gastric, pancreatic, and biliary secretions. Dietary intake actually constitutes a small portion of the jejunal load (1.5 L). A healthy small intestine absorbs nearly 75% of the fluid to which it is exposed. The 2 L of fluid not absorbed by the small intestine then enters the colon, where fluid is absorbed at an even higher rate. The absorptive power of the colon approaches 90% efficiency and far exceeds that of the small intestine. In fact, the colon can make up for a decrease in small intestinal absorption. Under normal conditions, very little fluid (<100 mL) is lost in the stool each day.[2]

In diarrheal states, normal intestinal physiology is disrupted. At a cellular level, intestinal absorption occurs through the villi, and secretion occurs through the crypts. Fluids are absorbed by two mechanisms: passively with the transport of sodium and actively with the absorption of glucose. Selected enterotoxins block the passive sodium resorption and specifically stimulate sodium excretion, resulting in a net loss of fluid. The glucose-dependent mechanism of water absorption, however, is unaffected by these toxins and can be exploited by including glucose in the rehydration treatments. The composition of oral rehydration therapies recommended by the World Health Organization is based largely on this physiology. In addition, diarrheal states, enterotoxins, inflammation, or ischemia disrupt the structure of the intestinal villi preferentially with less involvement in the crypts. As a result, diarrhea occurs because of diminished intestinal villi absorption *and* unopposed crypt secretion (the crypts are more resilient after injury).[3]

Another mechanism by which disease processes cause diarrhea is by the delivery of an osmotic load to the intestine. For example,

administration of a laxative results in the collection of an osmotically active, nondigestible agent within the intestinal lumen. Other substances such as diet products and medications (e.g., colchicine) have similar effects. Osmosis occurs, drawing fluid into the intestinal lumen, and results in diarrhea. Increased intestinal motility also causes diarrhea. This mechanism is responsible for diarrhea in patients with irritable bowel syndrome, neuropathies, or a shortened intestine secondary to surgery.

Diarrheal illness is primarily a viral infection (norovirus) but can also be caused by bacteria and parasites. Antibiotic and nosocomial diarrhea is most often caused by *C. difficile*. Many drugs affect gastrointestinal function. Erythromycin accelerates gastric emptying. Clavulanate stimulates small bowel motility. Other drugs that cause diarrhea are laxatives, sorbitol, lactose, nonsteroidal anti-inflammatory drugs, and cholinergics. Inflammatory bowel disease, ulcerative colitis, and Crohn's disease are characterized by diarrhea. **If patients have fecal evidence of inflammation and *Shigella*, *Salmonella*, *Campylobacter*, *C. difficile*, or *Entamoeba histolytica* have been excluded, suspect inflammatory bowel disease.** Less common causes of severe diarrhea include GI bleeding, thyrotoxicosis, toxin exposure, and mesenteric ischemia, which are addressed elsewhere in the text.

CLINICAL FEATURES

History After confirming a diarrheal illness, focus on identifying the cause. Determine whether the diarrhea is acute (<3 weeks) or chronic (>3 weeks). The acute diarrheas are of greatest concern to the emergency physician as they are more apt to be a manifestation of an immediately life-threatening illness (infection, ischemia, intoxication, or inflammation).[1] In the United States, most infectious diarrheal illnesses are caused by noroviruses or rotaviruses and occur in the winter.[4]

Ask directed questions to characterize the diarrhea: Is the diarrhea bloody or melenic? Is it associated with possible food poisoning or the ingestion of certain foods, such as milk or sorbitol? Does it resolve or persist with fasting? If so, this can indicate an osmotic or secretory diarrhea, respectively. Are the stools of smaller volume, localizing to the large intestine, or of larger volume, indicating small intestine pathology? What symptoms accompany the diarrhea? Is there fever or abdominal pain, which may suggest diverticulitis, infectious gastroenteritis, or inflammatory bowel disease? Seizures accompanying diarrhea often point toward shigellosis but could also indicate theophylline toxicity or hyponatremia. Does the patient have heat intolerance and anxiety, suggesting thyrotoxicosis, or paresthesias and reverse temperature sensation, suggesting ciguatera poisoning?

Next, define the host by obtaining the medical and surgical history. The differential diagnosis for diarrhea is broadened if the patient is immunocompromised. Is the patient taking medication that may cause diarrhea? Has the patient recently traveled outside the United States or to a rural area? Rural hiking places the patient at risk for *Giardia,* particularly if water-purification procedures were not strictly followed, and travel to developing countries increases the chances of parasitic infection and traveler's diarrhea. A patient's occupation may be a clue to a diagnosis of organophosphate poisoning.

Physical Examination Some examination findings helpful for diagnosis include thyroid enlargement, masses, oral ulcers, erythema nodosum, episcleritis, or an anal fissure, which would point toward inflammatory bowel disease. Reiter's syndrome, the triad of arthritis, conjunctivitis, and urethritis or cervicitis, should cause concern for *Salmonella, Shigella, Campylobacter,* or *Yersinia* infection.

Abdominal and rectal examinations are critical. Especially in the elderly, fecal impaction may result in diarrhea as liquid stool passes around the impaction. Pay attention to the presence or absence of surgical scars, tenderness, masses, or peritoneal signs. Check the stool for blood, because bloody diarrhea can be caused by inflammation, infection, or ischemia. An elderly patient with bloody diarrhea and abdominal pain out of proportion to the physical examination may have mesenteric ischemia—a true emergency.

DIAGNOSTIC STOOL EVALUATION

Diagnostic testing is rarely immediately helpful in the ED, but it can be helpful at patient follow-up. Since most diarrheal illnesses are self-limited, viral, or last less than 24 hours, most patients who present within 24 hours of onset need no microbiologic examination. **Patients who have severe abdominal pain, fever, and diarrhea that is voluminous, purulent, or bloody may have acute infectious diarrhea associated with the following pathogens: *Salmonella*, *Campylobacter*, *Shigella*, Shiga toxin–producing *Escherichia coli*, *Yersinia*, *Vibrio*, or *C. difficile*.**[1] Patients fitting this subset will require microbiologic evaluation, as described next. In the past, authors have described Wright's stain for fecal leukocytes and ova and parasite evaluation of the stool. These are not included as they have poor sensitivity and specificity and better tests have emerged.

Bacterial Stool Culture Bacterial stool culture is expensive and labor intensive and plays a minor role in the ED evaluation of diarrhea. The diagnostic yield of stool cultures is probably <5%, unless there is careful patient selection.[1] Obtain stool cultures for bacteria in ill children; toxic, dehydrated, or febrile patients; patients with a diarrheal illness >3 days; patients with blood or pus in the stool; and the immunocompromised. For systemic illness, fever, or bloody stools, test for *Salmonella*, *Shigella*, *Campylobacter*, Shiga toxin–producing *E. coli*, or amoebic infection.[5] Most laboratories are capable of detecting *Shigella, Salmonella, Campylobacter*, Shiga toxin–producing *E. coli* O157:H7 strains, *Giardia, Cryptosporidium, E. histolytica*, and rotavirus. In patients with persistent diarrhea due to a presumed parasitic infection, three separate stool samples should be collected to detect the causative organism.[1]

***Clostridium difficile* Toxin Assay** *C. difficile* infection is the most common cause of antibiotic-associated or nosocomial diarrhea. Diagnosis is by the *C. difficile* toxin assay. Unfortunately, this assay has a 10% false-negative rate, and the current recommendation is to include other testing such as glutamate dehydrogenase detection along with nucleic acid amplification testing to confirm the diagnosis.[5,10]

Other Diagnostic Tests If diarrhea is not infectious in origin, data acquisition should be dictated by the differential diagnosis. Severely dehydrated patients need serum electrolyte and renal function measurements. Serum drug levels can assist the physician in making the diagnosis of theophylline, lithium, or heavy metal intoxication. In patients with a history of abdominal surgery, abdominal films may help rule out partial obstruction as a cause of diarrhea. A chest radiograph may help diagnose *Legionella* pneumonia in a patient with diarrhea and a cough. For patients in whom mesenteric ischemia is suspected, obtain a serum lactate, IV contrast CT scan, or mesenteric angiography.

TREATMENT

Severely dehydrated patients need IV hydration. Oral rehydration with a glucose-based electrolyte solution can be initiated in patients without associated nausea or vomiting and without severe dehydration. Glucose-containing, caffeine-free beverages are the fluids of choice. The glucose transport mechanism is unaffected by enterotoxins, allowing for water absorption in the small intestine. For patients who can afford to buy it, Gatorade® is a good rehydration choice for patients with mild dehydration. The World Health Organization recommends a solution with a higher sodium concentration for more extensive dehydration. Ingestion of 400 to 600 mL/h may be needed to treat dehydration and keep up with stool fluid losses in severe diarrhea. Nausea and vomiting should be treated because they may compromise oral rehydration therapy.[2]

Counsel patients to avoid caffeine, which stimulates gastric motility, and sorbitol-containing chewing gum or raw fruits, which can worsen osmotic diarrhea. Initially, avoid lactose until the colonic villi are able to recover and produce the necessary digestive enzymes. Encourage patients to attempt early solid food intake, but with the previously mentioned restrictions, because eating expedites the recovery from diarrheal illnesses.[6]

ACUTE INFECTIOUS AND TRAVELER'S DIARRHEA

INTRODUCTION AND EPIDEMIOLOGY

Viruses cause the vast majority of infectious diarrheas, followed by bacterial and parasitic organisms. **Norovirus causes 50% to 80% of all** infectious diarrhea in the United States, followed with much less frequency by non–Shiga toxin–producing *E. coli*, *C. difficile*, invasive bacteria, Shiga toxin–producing *E. coli*, and protozoa.[1,4]

The incidence of traveler's diarrhea during a 2-week trip remains 10% to 40%, depending on destination and traveler. Improved hygiene and awareness have reduced the risk of traveler's diarrhea in many destinations.[7] The most important risk factor for traveler's diarrhea is the destination of travel, with the risk increasing with travel to areas of lower socioeconomic status. South Asia and West and Central Africa remain the destinations with the highest risk of traveler's diarrhea. Decreasing rates are being seen in South America and East and Southeast Asia.[7] Other risk factors include the level of food contamination, the season of travel (rainy seasons are associated with a higher risk of traveler's diarrhea), use of a proton pump inhibitor, previous contraction of traveler's diarrhea (suggests genetic susceptibility), and the type of travel (adventure travel, camping, backpacking, and living with native inhabitants are associated with higher risk).[8] The major bacteria responsible are the toxin- and non–toxin-producing strains of *E. coli*. These strains of *E. coli* make up most identifiable cases in Mexico and South America. The invasive bacteria, such as *Campylobacter jejuni*, *Shigella*, and *Salmonella,* are more commonly seen in travelers to southern Asia.[7]

CLINICAL FEATURES

The presence of severe abdominal pain, fever, or bloody stool requires microbiologic studies to rule out bacterial or amoebic infection.[1]

Laboratory Testing Obtain stool culture for *Salmonella*, *Shigella*, *Campylobacter*, and *E. coli* O157:H7; assay for Shiga toxin; and microscopy or antigen assay for *E. histolytica*.[3]

Exposure of a traveler or hiker to untreated water and illness that persists for more than 7 days should prompt evaluations for protozoal pathogens. Test stool for *E. histolytica* antigen, *Giardia intestinalis* antigen, and *Cryptosporidium parvum* antigen by enzyme immunoassay. Rarely, helminthes such as *Ascaris, Enterobius,* and *Strongyloides* have been implicated.

TREATMENT

Treatment of infectious diarrhea includes antibiotics, antimotility agents, restoration of fluid balance, and avoidance of agents that worsen diarrhea (**Table 73-1**). **Loperamide and antibiotics improve outcome.[9]**

Antibiotics shorten the duration of illness by about 24 hours.[1] Even though most cases of infectious diarrhea are self-limited, because of the inconveniencing and debilitating nature of the disease, **we recommend ciprofloxacin treatment for all patients believed to have an infectious diarrhea who do not have a contraindication to the drug** (e.g., children, allergy, pregnancy, or drug interaction). There are reports of growing fluoroquinolone resistance in bacterial pathogens.[7] Concerns remain about the impact of ciprofloxacin on the intestinal flora[9] and its side effect profile, and other non–GI-absorbed agents such as rifaximin are an option.[11] (See **Table 73-2** for specific treatments.)

Loperamide shortens the duration of symptoms when combined with an antibiotic regimen. Loperamide, bismuth subsalicylate, and kaolin are the only agents that are labeled as antidiarrheals. **Do not use antimotility** agents in the subset of patients with bloody diarrhea or suspected inflammatory diarrhea because of the possibility of prolonged fever, toxic megacolon in *C. difficile* patients, and hemolytic uremic syndrome in children infected with Shiga toxin–producing *E. coli*.[6]

Probiotics are safe and beneficial when used alongside rehydration therapy.[12] Proton pump inhibitors are not effective.[9]

DISPOSITION

Admit the toxic patient and any patient who cannot comply with oral rehydration. Be conservative in admitting those at extremes of age. Most patients with diarrhea can be discharged home.

The best way to combat many infectious diarrheas is with prevention. Counsel families about frequent hand washing to minimize spread of disease and about the proper selection and preparation of food and beverages consumed while traveling as a cornerstone of prevention. Encourage the use of boiled, bottled, and carbonated water for drinking, brushing teeth, and preparing food and infant formula. Water can be made safe by boiling, treating it chemically, or filtering.[7] A quick phrase for prevention is, "Peel it, boil it, cook it, or forget it!"

In addition, vaccines against the most common etiologic agent, rotavirus, are now available.[13]

Provide work excuses for patients employed in the food, day-care, and healthcare industries.

CLOSTRIDIUM DIFFICILE–ASSOCIATED DIARRHEA AND COLITIS

INTRODUCTION AND EPIDEMIOLOGY

C. difficile is a spore-forming obligate anaerobic bacillus that causes infection ranging from mild diarrhea to severe pseudomembranous colitis. The frequency of *C. difficile* infection increased from 4.5 cases per 1000 discharges in 2001 to 8.2 in 2010, with a mortality rate of approximately 7%.[14] Although many cases are found among hospitalized adults, up to one third of cases occur in the community. A more virulent

TABLE 73-1 Empiric Treatment of Traveler's Diarrhea in the Adult

	Trade Name	Dosage	Comments
Rehydration			
Fluids: chicken broth with fruit juices, Gatorade®, noncaffeinated sodas, packages of salts and glucose to be reconstituted with boiled or treated water, CeraLyte 90®, Pedialyte®			
Foods: complex carbohydrates (bananas, bread, rice, apple juice, and tortillas), potatoes, crackers, *Lactobacillus*-containing yogurt			
Antimotility Agents			
Bismuth subsalicylate	Pepto-Bismol®	30 mL or 2 tablets every 30 min for 8 doses; repeat on day 2	Salicylate toxicity may occur with excessive dosing; may cause bismuth encephalopathy in HIV-positive patients.
Loperamide	Imodium®	4 milligrams initially, then 2 milligrams after each unformed stool for no more than 2 days; maximum, 16 milligrams per day	Preferred first-line agent for antimotility, with minimal central opiate effects. Can be used with antibiotics.
Diphenoxylate and atropine	Lomotil®	4 milligrams four times a day for 2 days	Second-line agent with more central opiate effects (narcotic related to meperidine); may potentiate the action of barbiturates, tranquilizers, and alcohol.
Antibiotics			
Ciprofloxacin	Cipro®	500 milligrams single dose or 500 milligrams twice a day for 3 days	For moderately severe illness in adults; complete 3-day course if single dose fails; significant drug–drug interactions may occur. Often first choice for use except in South and Southeast Asia.
Azithromycin	Zithromax®	1000 milligrams in a single dose	First choice for use in South and Southeast Asia. Safe for children and pregnant women.
Rifaximin[11]	Xifaxan®, Salix®	200 milligrams PO three times daily for 3 days	For moderately severe illness; do not use for fever or bloody stools; class C in pregnancy.

Abbreviation: HIV = human immunodeficiency virus.

TABLE 73-2 Antimicrobial Recommendations for Infectious Pathogens in Adults

Organism	Primary Treatment	Alternative Treatment
Empiric treatment—but not for bloody diarrhea; not for Shiga toxin *E. coli* 0157:H7	Ciprofloxacin 500 milligrams PO twice a day for 5 days	Trimethoprim-sulfamethoxazole DS, 1 tab PO twice a day for 5 days
C. difficile	Vancomycin 125 milligrams PO 4 times a day for 10 days	Fidaxomicin, 200 milligrams PO two times a day for 10 days
E. coli 0157:H7	No antibiotics	No antibiotics
Listeria monocytogenes	No antibiotics	No antibiotics
Yersinia	No antibiotics; usually self-limited	Ciprofloxacin 500 milligrams PO twice a day for 3 days; or trimethoprim-sulfamethoxazole DS, 1 tab PO twice a day for 3 days
Salmonella non-typhi	Ciprofloxacin 750 milligrams PO twice a day for 5 days	Azithromycin 500 milligrams PO once a day for 7 days
Shigella	Ciprofloxacin 750 milligrams PO twice a day for 3 days	Azithromycin 500 milligrams PO once a day for 3 days
V. cholerae	Doxycycline 500 milligrams PO for one dose *OR* Azithromycin 1 gram PO for one dose	Trimethoprim-sulfamethoxazole DS, 1 tab PO twice a day for 3 days
E. histolytica	Metronidazole 750 milligrams PO three times a day for 10 days *AND* paromomycin 10 milligrams/kg three times a day PO for 7 days	Metronidazole *AND* iodoquinol 650 milligrams PO three times a day for 20 days *OR* Tinidazole 2 grams PO once a day for 3 days *AND* paromomycin or iodoquinol
Cyclospora	Trimethoprim-sulfamethoxazole DS, 1 tab PO twice a day for 10 days	
Giardia	Tinidazole 2 grams PO for one dose	Nitazoxanide 500 milligrams PO twice a day for 3 days *OR* Metronidazole 750 milligrams PO three times a day for 10 days *OR* Paromomycin 10 milligrams/kg/d PO three times a day for 10 days

Note: Length of treatment often varies with different sources.

strain of *C. difficile* called B1/NAP1/027 causes more severe disease that often progresses to toxic megacolon.

The organism secretes two toxins, A and B, that cause a secretory diarrhea. At the most severe end of the spectrum, three different syndromes have been described: neonatal pseudomembranous enterocolitis, postoperative pseudomembranous enterocolitis, and antibiotic-associated pseudomembranous colitis. In pseudomembranous colitis, membrane-like yellowish exudative plaques overlie and replace necrotic intestinal mucosa. A pseudomembrane is present in only 50% of laboratory-confirmed cases of *C. difficile* colitis. Recent antibiotic use, GI surgery or manipulation, severe underlying medical illness, chemotherapy, gastric acid suppression with proton pump inhibitors or H_2 blockers, and advancing age are risk factors for pseudomembranous colitis. Transmission of the organism is by direct human contact as well as contact with inanimate objects (commodes, telephones, rectal thermometers).

PATHOPHYSIOLOGY

Hospitalized patients are colonized with *C. difficile* in 20% to 50% of cases, so the development of diarrhea in recently discharged patients is suggestive of *C. difficile* infection. There is a linear relationship between the length of hospital stay, colonization with *C. difficile,* and the development of *C. difficile* diarrhea. Up to 70% of residents of long-term health facilities are *C. difficile* carriers. Broad-spectrum antibiotics reduce fecal anaerobes, which are needed for carbohydrate metabolism and bile acid breakdown. One study ranked cephalosporins, clindamycin, carbapenems, trimethoprim/sulfonamides, fluoroquinolones, and penicillin combinations as the most frequent offenders.[15] Accumulation of gut carbohydrates can cause osmotic diarrhea, and the accumulation of bile acids, which are colonic secretory agents, also results in diarrhea. Toxin-producing *C. difficile* then flourishes within the colon. Almost any antibiotic (including metronidazole and vancomycin) can lead to pseudomembranous colitis, and chemotherapeutic agents, proton pump inhibitors, and antiviral agents have also been implicated. Bowel ischemia, inflammatory bowel disease, recent bowel surgery, uremia, malnutrition, shock, advanced age, peripartum status, and Hirschsprung's disease also contribute to the development of *C. difficile* infection and pseudomembranous colitis. Probiotics have been implicated in reducing the incidence of *C. difficile* infection if taken concomitantly with antibiotics but have no role in treating active or recurrent disease.

Most disease-producing strains of *C. difficile* produce two toxins—toxin A, an enterotoxin, and toxin B, a cytotoxin—that interact in a complex way to produce pseudomembranous colitis and its associated symptoms. B1/NAP1/027 produces a third (binary) toxin, contributing to its more virulent course.

CLINICAL FEATURES

The disease typically begins 7 to 10 days after the institution of antibiotic therapy, although symptoms may occur up to 60 days after the antibiotic is discontinued. *C. difficile* colitis results in a spectrum of clinical manifestations that vary from frequent, mucoid, watery stools to a toxic picture that includes profuse diarrhea (20 to 30 stools per day), crampy abdominal pain, fever, leukocytosis, and dehydration. Stool examination may demonstrate fecal leukocytes, which are not generally found in more benign forms of antibiotic-induced diarrhea. In 3% of patients, toxic megacolon or colonic perforation may occur in patients with pseudomembranous colitis.

DIAGNOSIS

The diagnosis is suggested by a history of diarrhea that develops during administration of antibiotics or within 2 weeks of their discontinuation. The patient should experience a minimum of three unformed stools in a 24-hour period to be considered as having an active infection.

Stool Assays Cell culture cytotoxicity assays remain the "gold standard" but take up to 48 hours for results. The organism is best identified by stool culture using a selective growth medium. This technique has a sensitivity approaching 100% but lacks specificity because the presence of *C. difficile* does not necessarily implicate it in the cause of the disease.

Instead, *C. difficile* toxins are detected directly using a number of techniques including enzyme-linked immunosorbent assays, latex

agglutination, dot-immunobinding assays, and polymerase chain reaction. Tests vary in their sensitivity, specificity, and time to completion. Many laboratories are using polymerase chain reaction technology, which has excellent sensitivity (71% to 100%) and specificity (73% to 100%)[16] and rapid test turnaround, usually within 1 hour.[17] As noted, confirmatory testing should be included in establishing the diagnosis.[5]

Colonoscopy Colonoscopy reveals characteristic yellowish plaques within the intestinal lumen. Lesions may be seen throughout the entire alimentary tract, although they are typically limited to the right colon. Colonoscopy is not routinely needed to establish a diagnosis and carries the risk of perforation in severe colitis but may be used in patients who require a rapid diagnosis and those who cannot produce a stool specimen due to ileus or in whom the initial assay is negative.

TREATMENT

Mild *C. difficile* infection in an otherwise healthy patient is treated by discontinuing the offending antibiotic. This is effective in only about 20% of cases, however. Severely ill persons must be hospitalized. For specific antibiotic regimens, see **Table 73-3**. Fidaxomicin (macrolide antibiotic) 200 milligrams PO twice a day for 10 days has replaced metronidazole as a primary agent.[5]

Rarely, emergency colectomy may be required for patients with severe *C. difficile* infection. Indications for emergency colectomy based on 30-day mortality include leukocytosis >20,000 mm^3, lactate >5 mmol/L, age >75 years, immunosuppression, shock, toxic megacolon, colonic perforation, rapidly progressive disease, or multiorgan system failure. This procedure carries a high mortality rate. Recently, creation of a loop ileostomy with colonic lavage has been reported to be an effective surgical approach.

Relapses occur in 20% to 30% of patients. Patients with prolonged antibiotic use, prolonged hospitalization, advanced age, diverticulosis, or multiple comorbidities are at increased risk for relapse. The addition of monoclonal antibodies against the toxin to antibiotics reduces infection recurrence.[18] The use of antidiarrheal agents is contraindicated. Steroids are rarely needed. Finally, fecal microbiota transfer has emerged as a therapy for refractory cases of recurrence.[19]

Ensure contact isolation, use of personal protective equipment, and good hand washing with soap and water when caring for patients with suspected *C. difficile*–associated disease. Alcohol-based rubs are not effective in eliminating the spores of *C. difficile*.

TABLE 73-3 Treatment of *Clostridium difficile* Infection Based on Severity of Illness[5]

Disease Severity	Treatment
Asymptomatic carrier	No treatment
Initial episode	Discontinue inciting antibiotics
Mild: WBC <15,000 mm^3	Vancomycin 125 milligrams PO four times a day for 10 days
Moderate: WBC >15,000 mm^3, patient able to tolerate PO	Fidaxomicin 200 milligrams PO twice daily for 10 days
First relapse	Fidaxomicin 200 milligrams twice daily for 10 days if vancomycin was used for the initial episode *OR* tapered and pulsed vancomycin regimen if a standard regimen was used for the initial episode (e.g., 125 milligrams four times per day for 10–14 days, two times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks)
Second relapse	Tapered and pulsed vancomycin regimen of 125 milligrams four times per day for 10–14 days, two times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks *OR* vancomycin 125 milligrams four times per day by mouth for 10 days followed by rifaximin 400 milligrams three times daily for 20 days *OR* fidaxomicin 200 milligrams given twice daily for 10 days
Severe disease or complicated disease	Vancomycin 500 milligrams IV or via nasogastric tube every 6 hours *AND* vancomycin 500 milligrams per rectum every 6 hours; also, metronidazole 500 milligrams IV every 8 hours or fecal microbiota transfer

Note: Assume the offending antibiotic is discontinued.

Source: Data from McDonald LC, Gerding DN, Johnson S, et al: Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), *Clin Infect Dis* 2018 Mar 19;66(7):987-994.

DISPOSITION

Hospitalize patients with severe diarrhea, clinical toxicity, or symptoms that persist despite appropriate outpatient management. Consult the surgeon for acutely ill patients with *C. difficile* infection, especially those with suspected toxic megacolon or intestinal perforation for consideration of colectomy. For patients who are discharged, discontinue antibiotics and encourage good oral hydration. Follow the antibiotic recommendations in Table 73-3.

INFLAMMATORY BOWEL DISEASE/ILEITIS/COLITIS/CROHN'S DISEASE

INTRODUCTION AND EPIDEMIOLOGY

Crohn's disease is a chronic granulomatous inflammatory disease of the GI tract of unknown origin, but genetic and environmental factors have been implicated in causing the disease. **Crohn's disease can involve any part of the GI tract from the mouth to the anus.** The ileum is involved in the majority of cases. In 20%, the disease is confined to the colon, making differentiation from ulcerative colitis difficult. The terms *regional enteritis, terminal ileitis, granulomatous ileocolitis,* and *Crohn's disease* are all used to describe the same disease process.

The peak incidence of Crohn's disease occurs between 15 and 22 years of age, with a secondary peak from 55 to 60 years. The incidence has remained steady in the past several years. The disease is four times more common among Jews than non-Jews and is more common in whites than blacks, Asians, or Native Americans. A family history of inflammatory bowel disease is present in 10% to 15% of patients, particularly with early onset of disease. Ulcerative colitis as well as Crohn's disease may be present in other family members, and siblings of patients with Crohn's disease have a higher incidence of the disease. Smoking, oral contraceptive use, and the use of nonsteroidal anti-inflammatory agents worsen the course of the disease. Smoking is also associated with a twofold increased risk of developing Crohn's disease.

PATHOPHYSIOLOGY

The most important pathologic feature of Crohn's disease is the involvement of all the layers of the bowel and extension into mesenteric lymph nodes. The disease is discontinuous, with normal areas of bowel ("skip areas") located between one or more involved areas. Longitudinal, deep mucosal ulcerations are characteristic. If ulcerations penetrate the bowel wall, fissures, fistulas, and abscesses result. Late in the disease, a cobblestone appearance of the mucosa results from the criss-crossing of ulcers with intervening normal mucosa.

CLINICAL FEATURES

Patients presenting to the ED do so because of chronic symptoms such as abdominal pain and weight loss that remain undiagnosed, acute flares in patients with known disease, and most commonly, complications of Crohn's disease. Occasionally, side effects and complications of therapy bring the patient to the ED.

The clinical course of Crohn's disease varies and in the individual patient is unpredictable. There are three general types of Crohn's presentations: inflammatory, stricturing, and penetrating disease. The disease is classified as mild, moderate, and severe based on the Clinical Disease Activity Index.[20] Abdominal pain, anorexia, diarrhea, and weight loss are present in most cases. Chronic abdominal pain, weight loss, fever, and diarrhea may be present for several years before definitive diagnosis is

established. Perianal fissures or fistulas, hematochezia, abscesses, or rectal prolapse can develop, particularly with colonic involvement. Patients may also present with complications of the disease, such as obstruction with vomiting, crampy abdominal pain, and obstipation, or an intra-abdominal abscess with fever, abdominal pain, and a palpable mass. In children with Crohn's disease and ulcerative colitis, growth retardation and delay in the onset of puberty are prominent.

In 10% to 20% of patients, the extraintestinal manifestations of arthritis, uveitis, or liver disease may be presenting symptoms. Crohn's disease should also be considered in the differential diagnosis of patients with fever of unknown etiology. The incidence of stroke, ischemic heart disease, chronic obstructive pulmonary disease, and thromboembolic disease is increased in patients with inflammatory bowel disease and should be considered when such patients present to the ED.[21]

The clinical course and manifestations of the disease appear to be related to its anatomic distribution: in 30%, the disease involves only the small bowel; in 20%, only the colon is involved; and in 50%, both the small bowel and colon are involved. A small percentage of patients present with disease involving the mouth, esophagus, and stomach. Crohn's disease of the stomach may cause symptoms of dyspepsia.

Extraintestinal manifestations are seen in up to 50% of patients with Crohn's disease (**Table 73-4**), The types of extraintestinal complications are similar in patients with Crohn's disease and ulcerative colitis, although they are most commonly seen in Crohn's disease patients with colonic involvement.

DIAGNOSIS

In most patients, the definitive diagnosis of Crohn's disease is established months or years after symptom onset. A provisional diagnosis of appendicitis or pelvic inflammatory disease may change to Crohn's disease after imaging or at the time of surgery. A detailed history asking about previous bowel symptoms that preceded the onset of acute right lower quadrant pain provides clues to the correct diagnosis.

ED evaluation focuses on determining the severity of the attack; identifying significant complications such as obstruction, intra-abdominal abscess, life-threatening hemorrhage, or toxic megacolon; and eliminating other possible causes of the patient's complaints.

Laboratory Testing Laboratory evaluation should include a CBC, serum electrolytes, BUN, creatinine, and a type and cross-match where appropriate. C-reactive protein levels and erythrocyte sedimentation rate can be obtained to monitor disease activity. Other studies should include electrolytes, calcium, and liver function studies. Fecal markers of inflammation (calprotectin and lactoferrin) are other markers of disease activity.[22] Anemia is common in Crohn's disease and may be caused by iron deficiency, chronic disease, and vitamin B_{12} deficiency. Stool cultures and *C. difficile* toxin can be obtained if diarrhea is a prominent symptom.

Imaging Plain radiographs have essentially been replaced by abdominal and pelvic CT scanning with PO and IV contrast, which can identify bowel wall thickening, segmental narrowing, destruction of the normal mucosal pattern, mesenteric edema, fistulas, and abscesses, suggestive of Crohn's disease. However, be vigilant about the cumulative radiation risk (severe exposure defined as lifetime accumulation of >50 mSv) in patients with inflammatory bowel disease. MRI has similar diagnostic accuracy as CT. MRI is more expensive and has limited availability but involves less radiation exposure and avoids the use of iodinated contrast. Additionally, pelvic MRI is the best modality for imaging perianal fistulae. Ultrasound can be used to identify bowel wall thickening in the small intestine and portions of the large bowel. It is the diagnostic modality of choice for biliary complications. Extraintestinal complications such as gallstones, renal calculi, sacroiliitis, and osteomyelitis can also be seen on CT scan. Diagnosis is confirmed by colonoscopy.

TABLE 73-4 Common Extraintestinal Manifestations of Inflammatory Bowel Disease

Manifestation	Description
Arthritic	
Peripheral arthritis	Migratory monoarticular or polyarticular pain in peripheral joints (hip, knee, ankle, wrist) with effusion
Ankylosing spondylitis	Pain and stiffness of spine, hips, neck, and rib cage with limitation in truncal motion, loss of lumbar lordosis; decreased chest expansion and forward cervical flexion in advanced disease
Sacroiliitis	Low back pain with morning stiffness, relieved by exercise; progressive joint sclerosis
Ocular	
Episcleritis	Eye burning or itching without visual changes or pain; scleral and conjunctival hyperemia
Uveitis	Acute blurring of vision, photophobia and pain; perilimbic scleral injection
Dermatologic	
Erythema nodosum	Painful, red, raised nodules on extensor surfaces of arms or legs
Pyoderma gangrenosum	Ulcerative lesions with a necrotic center and violaceous skin typically found in pretibial region or trunk
Hepatobiliary	
Cholelithiasis	Varies from asymptomatic stones to right upper quadrant pain, fever, vomiting
Fatty liver	Mild right upper quadrant pain; hepatomegaly
Pericholangitis	Mild elevation in serum alkaline phosphatase, asymptomatic
Chronic active hepatitis	Autoimmune elevation of liver aminotransferase enzymes, may progress to cirrhosis
Primary sclerosing cholangitis	Pruritus progressing to jaundice, fatigue, and lethargy; laboratory findings vary from mild elevations of alkaline phosphatase to cirrhosis, portal hypertension, and liver failure; male predominance
Cholangiocarcinoma	Extrahepatic biliary mass, evidence of biliary obstruction, jaundice, right upper quadrant pain, fever, malaise
Pancreatitis	Varies from painless elevation of serum amylase to clinically apparent central abdominal pain radiating to back; may be associated with drugs such as azathioprine, 6-mercaptopurine, sulfasalazine, mesalamine, olsalazine, metronidazole
Vascular	
Thromboembolic disease	Symptoms of deep venous thrombosis and pulmonary emboli; portal vein, mesenteric vein, and hepatic venous thrombosis reported
Other	
Malnutrition	Fatigue, malaise, muscular wasting, cachexia
Chronic anemia	Fatigue, malaise, pallor, dyspnea; may be microcytic (blood loss), macrocytic (B_{12} deficiency), or autoimmune hemolytic
Nephrolithiasis	Flank pain, nausea, vomiting, hematuria; stones result from increased dietary oxalate absorption (calcium oxalate stones) and dehydration (urate stones)

Differential Diagnosis The differential diagnosis of Crohn's disease includes lymphoma, ileocecal amebiasis, sarcoidosis, deep chronic mycotic infections involving the GI tract, GI tuberculosis, Kaposi's sarcoma, *Campylobacter* enteritis, and *Yersinia* ileocolitis. Fortunately, most of these are uncommon conditions and can be differentiated by appropriate laboratory tests and imaging. *Yersinia* ileocolitis and *Campylobacter* enteritis may cause chronic abdominal pain and diarrhea similar to Crohn's disease but can be diagnosed by appropriate stool cultures. It is not uncommon that a bout of acute bacterial diarrhea may uncover a diagnosis of inflammatory bowel disease. **Acute ileitis** should not be confused with Crohn's disease. Young patients with acute ileitis usually recover without sequelae and should not undergo surgery. When Crohn's disease is confined to the colon, ischemic bowel disease (particularly in the elderly) and pseudomembranous colitis as well as ulcerative colitis must be included in the differential diagnosis. Concomitant infection with *C. difficile* colitis is more common in patients with inflammatory bowel disease and is associated with refractory *C. difficile* infection and a greater incidence of surgery and disease flares in these patients. Some clinical guidelines call for *C. difficile* testing in any inflammatory bowel disease patient with a disease flare.[23]

TREATMENT

The aim of therapy for this incurable disease includes relief of symptoms, induction of remission, maintenance of remission, prevention of complications, optimizing timing of surgery, and maintenance of nutrition.

Initial treatment (**Table 73-5**) consists of adequate fluid resuscitation and restoration of electrolyte balance. Place a nasogastric tube for obstruction, peritonitis, or toxic megacolon. Administer broad-spectrum antibiotics for fulminant colitis or peritonitis. Patients with severe disease should receive IV steroids such as hydrocortisone 300 milligrams per day or an equivalent dose of methylprednisolone (48 milligrams per day) or prednisolone (60 milligrams per day).

Salicylates Sulfasalazine 3 to 5 grams per day is for mild to moderate Crohn's disease. Sulfapyridine is a by-product of the colonic breakdown of sulfasalazine. Many of the toxic side effects of sulfasalazine (e.g., vomiting, anorexia, nausea, headache, diarrhea, epigastric distress, pancreatitis) are attributable to sulfapyridine.

The active moiety in sulfasalazine is mesalamine. Many of the newer 5′-acetyl salicylic acid drugs feature a derivative of mesalamine without the sulfapyridine component. Oral mesalamine, rectal mesalamine, olsalazine, and balsalazide are first-line agents in treating Crohn's disease. The mesalamine formulations are most effective in patients with colonic disease and particularly in those with mild disease.

Corticosteroids Oral glucocorticoids such as prednisone (40 to 60 milligrams per day) have traditionally been reserved for more severely affected patients but are now used as induction therapy. An ileal-released form of budesonide (9 milligrams per day) may be beneficial in inducing a remission in patients with ileal and right colon disease. Glucocorticoids are not preferred for maintaining remission because of their complications, but 50% of patients may ultimately be steroid dependent.

Immunosuppressives Immunosuppressive drugs such as 6-mercaptopurine, azathioprine, and thioguanine are useful in maintenance, as steroid-sparing agents, in healing fistulas, and in patients in whom there are serious contraindications to surgery.[24] These agents have been associated with leukopenia, fever, hepatitis, and pancreatitis, necessitating the need for close follow-up, particularly during the initial phase of therapy. Parenteral methotrexate (25 milligrams per week) is considered third line and has been used following steroid and thiopurine metabolite failure.

Antibiotics Antibiotics are first-line agents for perianal disease and help induce remission. Ciprofloxacin (500 to 1000 milligrams per day) induces remission in approximately 55% of cases. Metronidazole (750 to 1500 milligrams per day) is also effective for perianal complications and fistulous disease. Combination therapies with antibiotics and biologic agents (see next section) have produced dramatic improvements in response. Rifaximin is a broad-spectrum antibiotic that is not absorbed from the GI tract. Rifaximin 800 milligrams twice daily for 12 weeks is effective for mild to moderate disease. However, antibiotics raise concerns about precipitating *C. difficile* colitis infection.

Biologics Patients with medically resistant moderate to severe Crohn's disease may benefit from the anti–tumor necrosis factor antibodies infliximab, adalimumab, and certolizumab pegol. These agents have been used to induce remission in patients who fail conventional therapy with steroids or 5-aminosalicylic acid and in patients with exclusively colonic disease. Additionally, biologics are particularly effective in cases of disease relapse and fistulizing disease.[25] Anti-adhesion therapies, natalizumab and vedolizumab, and the anti-interleukin agent ustekinumab have been used when anti–tumor necrosis factor agents fail.[16,26,27] All biologics increase the risk of infections, especially those caused by hepatitis B and tuberculosis. Both immediate and delayed hypersensitivity reactions are possible, especially with infliximab. Concern about the emergence of lymphomas and progressive multifocal leukoencephalopathy, especially with natalizumab, has limited the long-term use of these agents.

Maintenance therapy and the effectiveness of various therapeutic agents in Crohn's disease are variable. A reduced dose of 5-aminosalicyclic acid derivatives is used for the maintenance of remission of colonic disease. The addition of sulfasalazine, azathioprine, and 6-mercaptopurine to prednisone does not improve the response rate and increases side effects. Infliximab or adalimumab and an immunosuppressive (azathioprine, 6-mercaptopurine, or methotrexate) can maintain remission.

Antidiarrheal Agents Diarrhea can be controlled by loperamide (Imodium®) 4 to 16 milligrams per day, diphenoxylate (Lomotil®) 5 to 20 milligrams per day, and in some cases, cholestyramine (Questran®) 4 grams one to six times a day. The mechanism of action of cholestyramine is binding bile acids and eliminating their known cathartic action.

TABLE 73-5 Treatment of Fulminant Colitis

Restore fluid and electrolyte balance

Nothing by mouth

Nasogastric suction for

- Obstruction
- Adynamic ileus
- Suspected toxic megacolon

Parenteral corticosteroids

- Hydrocortisone 300 milligrams per day or methylprednisolone 48 milligrams per day or prednisolone 60 milligrams per day

Broad-spectrum antibiotics

- Piperacillin-tazobactam 4.5 grams IV four times a day *OR*
- Ampicillin 2 grams IV four times a day + metronidazole 500 milligrams IV three times a day + ciprofloxacin (Cipro®) 750 milligrams IV once a day

Observe for complications

- Obstruction
- Perforation
- Toxic megacolon
- Life-threatening hemorrhage
- Intra-abdominal abscess

Outpatient management (nontoxic patients)

- Liquids only for first 48 h

Oral antibiotics

- Ampicillin, trimethoprim-sulfamethoxazole, ciprofloxacin, cephalexin, or rifaximin *AND*
- Metronidazole or clindamycin

DISEASE COMPLICATIONS

More than three out of four patients with Crohn's disease will require surgery within the first 20 years of the onset of initial symptoms. **Abscess and fissure formation** is common. Abscesses can be characterized as intraperitoneal, visceral, retroperitoneal, interloop, or intramesenteric. Signs and symptoms are worsening abdominal pain and tenderness,

fever, and possibly a palpable mass. Retroperitoneal abscesses may cause hip or back pain and difficulty ambulating.

Fistulas are the result of extension of the intestinal fissures seen in Crohn's disease into adjacent structures. The most common sites are between the ileum and the sigmoid colon, the cecum, another ileal segment, urinary bladder, vagina, or the skin. Suspect an internal fistula when there are changes in the patient's symptom complex, such as bowel movement frequency, amount of pain, or weight loss.

Obstruction is the result of both stricture formation due to the inflammatory process and of edema of the bowel wall. It is the most common reason for emergent surgery in Crohn's disease. The distal small bowel is the most common site of obstruction. Symptoms include crampy abdominal pain, distention, nausea, and bloating.

Perianal complications include perianal or ischiorectal abscesses, fissures, fistulas, rectovaginal fistulas, and rectal prolapse. Perianal fistulas occur in 20% to 30% of Crohn's patients. These are more commonly seen in patients with colonic involvement.

Major GI bleeding is rare. Bleeding results from erosion into a vessel in the bowel wall. Toxic megacolon is also uncommon but is associated with massive GI bleeding in over half the cases.

When bowel symptoms are present, malnutrition, malabsorption, hypocalcemia, and vitamin deficiency can be severe. In addition to the complications of the disease are complications associated with the treatment of the disease with mesalamine, steroids, immunosuppressive agents, and antibiotics. These include leukopenia, thrombocytopenia, fever, infection, profuse diarrhea, pancreatitis, renal insufficiency, and liver toxicity.

The incidence of malignant neoplasm of the GI tract is three times higher in patients with Crohn's disease than for the general population, especially in patients with disease involvement of more than one third of their colon.

DISPOSITION

Patients with colitis, peritonitis, or complications such as obstruction, significant GI hemorrhage, severe dehydration, or fluid/electrolyte imbalance should be hospitalized. Hospital admission should be considered in less severe cases that cannot be managed successfully with outpatient management. Surgical intervention is indicated in patients with complications of the disease, including intestinal obstruction or hemorrhage, perforation, abscess or fistula formation, toxic megacolon, and perianal disease.

Before discharging patients with Crohn's disease, discuss alterations in the therapeutic regimen with the gastroenterologist. Ensure close follow-up after discharge.

ULCERATIVE COLITIS

INTRODUCTION AND EPIDEMIOLOGY

Ulcerative colitis is a chronic inflammatory disease of the colon. The inflammation tends to be progressively more severe from the proximal to the distal colon. The rectum is involved nearly 100% of the time. The characteristic symptom is bloody diarrhea. The cause is unknown.

The disease is more prevalent in the United States and northern Europe than in other parts of the world, and peak incidence occurs in the second and third decades of life. It is more common in men. First-degree relatives of patients with ulcerative colitis have a 15-fold risk of developing ulcerative colitis and a 3.5-fold risk of developing Crohn's disease.

PATHOPHYSIOLOGY

Ulcerative colitis involves primarily the mucosa and submucosa. Microscopically, the disease is characterized by mucosal inflammation with the formation of crypt abscesses, epithelial necrosis, and mucosal ulceration. The submucosa, muscular layer, and serosa are usually spared. In the usual case, the disease increases in severity more distally, with the rectosigmoid being involved in the vast majority of cases. In the early stages of the disease, the mucous membranes appear finely granular and friable. In more severe cases, the mucosa appears as a red, spongy surface dotted with small ulcerations oozing blood and purulent exudate. In very advanced disease, one sees large oozing ulcerations and pseudopolyps (areas of hyperplastic overgrowth surrounded by inflamed mucosa).

CLINICAL FEATURES

The clinical features and course of ulcerative colitis vary and depend on the anatomic distribution of the disease in the colon. Crampy abdominal pain, bloody diarrhea, and tenesmus are typical symptoms. The disease is classified as mild, moderate, or severe depending on the clinical manifestations. Of all patients with ulcerative colitis, 60% have mild disease; in 80% of cases, the disease is limited to the rectum. Occasionally, constipation and rectal bleeding are the presenting complaints. Progression to pancolitis occurs in 10% to 15% of patients with mild disease.

Moderate disease is seen in 25% of patients. Patients demonstrate a good response to therapy. These patients usually have colitis extending to the splenic flexure (left-sided colitis) but may develop pancolitis.

Patients with severe disease constitute 15% of those with ulcerative colitis and are most likely to be seen in the ED. Severe disease is associated with greater than six bowel movements per day, tachycardia, fever (>37.8°C), anemia (hemoglobin <10.5 milligrams/dL), an elevated erythrocyte sedimentation rate, low serum albumin, and more frequent extraintestinal manifestations. Patients with severe disease account for 90% of deaths from ulcerative colitis. Virtually all severely affected patients have pancolitis.

Ulcerative colitis is usually characterized by intermittent attacks of acute disease with complete remission between attacks. Sometimes, the first attack is followed by a prolonged period of inactivity, or the disease is chronically active. The factors associated with an unfavorable prognosis and increased mortality include higher severity and extent of disease, a short interval between attacks, systemic symptoms, and onset of the disease after 60 years of age.

Extraintestinal complications are listed in Table 73-4. Peripheral and axial arthritis and skin lesions including erythema nodosum and pyoderma gangrenosum are the most common extraintestinal complications.

DIAGNOSIS

Laboratory findings in patients with ulcerative colitis are nonspecific and may include leukocytosis, anemia, thrombocytosis, decreased serum albumin, and abnormal liver function studies. There are many biomarkers, such as antineutrophil cytoplasmic antibodies, for diagnosis and prognosis, but none are available in the ED. These serologic markers also lack sensitivity. Therefore, the diagnosis of ulcerative colitis rests on the following: a history of abdominal cramps and diarrhea, mucoid stools, stool examination negative for ova and parasites, stool cultures negative for enteric pathogens, and confirmation of diagnosis by colonoscopy.

Differential Diagnosis The major diseases that should be considered in the differential diagnosis of ulcerative colitis include infectious colitis, Crohn's colitis, ischemic colitis, radiation colitis, toxic colitis from antineoplastic agents, and *C. difficile* infection. When the disease is limited to the rectum, consider rectal syphilis, gonococcal proctitis, lymphogranuloma venereum, and inflammations caused by herpes simplex virus, *E. histolytica, Shigella,* and *Campylobacter.*

TREATMENT

Patients with severe ulcerative colitis should be treated with IV steroids, replacement of fluids, correction of electrolyte abnormalities, broad-spectrum antibiotics (ciprofloxacin, metronidazole, and ampicillin), mesalamine, and steroids (Table 73-5). IV cyclosporine (4 milligrams/kg per day) or infliximab (5 to 10 milligrams/kg per dose) can be effective in fulminant colitis nonresponsive to IV corticosteroids. Triple-antibiotic therapy has been used for pediatric patients with severe ulcerative colitis.[28]

When toxic megacolon is suspected, place a nasogastric tube and obtain imaging and surgical consultation.

The majority of those with mild and moderate disease can be treated as outpatients. In the treatment of patients with mild active proctitis, proctosigmoiditis, and left-sided colitis (<60 cm of active disease), topical treatment with mesalamine suppositories or enemas is effective. Topical glucocorticoid enemas or 5-aminosalicylic enemas (Rowasa®, 2 to 4 grams/60 mL per day for 3 weeks) or suppositories (500 milligrams

twice a day) are quite effective in inducing remission in mild to moderate attacks of distal proctosigmoiditis and have lower systemic side effect profiles. If topical therapy is unsuccessful, oral glucocorticoids are effective in inducing a remission in the majority of cases. Daily doses of 40 to 60 milligrams of prednisone are usually sufficient and can be adjusted depending on the severity of the disease.

Infliximab (5 milligrams/kg per dose) is the only biologic indicated for ulcerative colitis. It should be used in patients with mild to moderate disease who are corticosteroid dependent or refractory and in patients who have immunomodulator refractory disease.[29]

Hydrophilic bulk agents such as psyllium (Metamucil®) can be used in some patients to improve stool consistency. Antidiarrheal agents are generally ineffective and may precipitate toxic megacolon.

DISEASE COMPLICATIONS

Blood loss from sustained hemorrhage is the most common complication, but toxic megacolon, which occurs in up to 10% of patients with ulcerative colitis, must not be missed.

Toxic megacolon develops in advanced cases of colitis when the disease process extends through all layers of the colon (**Figure 73-1**). This complication occurs in patients with severe ulcerative colitis. Toxic megacolon results from a loss of muscular tone within the colon, with dilatation and localized peritonitis. If the colon continues to dilate without treatment, signs of toxicity will develop. Plain radiography of the abdomen demonstrates a long, continuous segment of air-filled colon greater than 6 cm in diameter. Loss of colonic haustra and "thumb printing," representing bowel wall edema, may also be seen. The distended portion of the atonic colon can perforate, causing peritonitis and septicemia. Mortality is high.

A patient with toxic megacolon appears severely ill; the abdomen is distended, tender, and tympanic. Severe diarrhea (>10 bowel movements per day) is often seen but may have ceased. Fever, tachycardia, and hypotension are typically part of the clinical picture. Leukocytosis, anemia, electrolyte disturbances, and hypoalbuminemia are the supporting laboratory results.

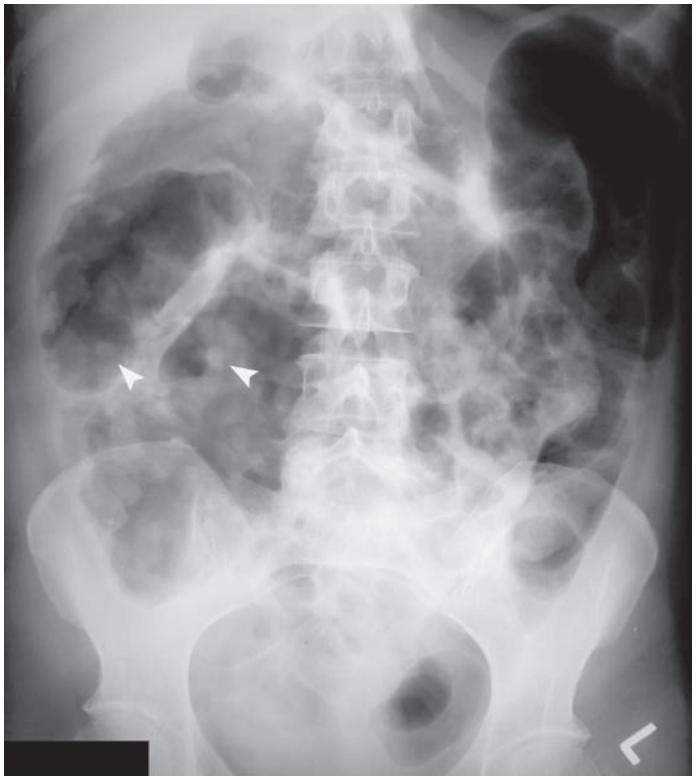

FIGURE 73-1. Abdominal distention due to toxic megacolon. *Arrows* point to mucosal nodules. [Reproduced with permission from Schwartz DT (ed): *Emergency Radiology: Case Studies.* © McGraw-Hill, Inc., 2008. Chapter II-2, Fig. 23.]

Some of the more prominent features of toxic megacolon, such as leukocytosis and peritonitis, can be masked in the patient taking corticosteroids. Antidiarrheal agents, hypokalemia, narcotics, cathartics, pregnancy, enemas, and recent colonoscopy have been implicated as precipitating factors in toxic megacolon. Medical therapy with nasogastric suction, IV prednisolone 60 milligrams per day or hydrocortisone 400 milligrams per day, parenteral broad-spectrum antibiotics active against coliforms and anaerobes, and IV fluids should be attempted as initial therapy, along with early surgical consultation. Cyclosporine A (4 milligrams/kg per day) and infliximab have been used as rescue therapy to prevent colectomy if steroids are not effective.[29] Cyclosporine A should not be given to patients with hypertension, renal impairment, epilepsy, sepsis, and age >80 years.

Perirectal fistulas and abscesses may occur in up to 20% of patients with ulcerative colitis. Massive GI hemorrhage, obstruction secondary to stricture formation, and acute perforation are other complications of the disease.

There is a 10- to 30-fold increase in the development of carcinoma of the colon in patients with ulcerative colitis. The major risk factors for the development of carcinoma of the colon are extensive involvement and prolonged duration of the disease. The cumulative risk of cancer after 20 and 30 years is 5% to 10% and 12% to 20%, respectively. Additional factors that constitute increased risk of cancer in patients with ulcerative colitis include early onset of the disease and a family history of colon cancer.

DISPOSITION

Patients with fulminant attacks of ulcerative colitis need hospitalization for aggressive fluid and electrolyte resuscitation and careful observation for the development of complications. Patients with complications such as GI hemorrhage, toxic megacolon, and bowel perforation must also be admitted with consultation to both a gastroenterologist and a surgeon. In addition to toxic megacolon, the indications for surgery include colonic perforation, massive lower GI bleeding, suspicion of colon cancer, and disease that is refractory to medical therapy (large doses of steroids required to control the disease).

Patients with mild to moderate disease can be discharged from the ED. Close follow-up should be arranged with the patient's physician or gastroenterologist, and any adjustment in medical therapy should be discussed prior to discharge.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 74

Constipation

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INTRODUCTION AND EPIDEMIOLOGY

Constipation is an extraordinarily common cause of patient morbidity.[1-4] The incidence of constipation increases with age, with overall prevalence rates in North America from 12% to 19%.[5] Constipation affects as many as 80% of critically ill patients and is directly associated with patient mortality in this population.[6]

Physicians and patients define constipation differently. Physicians have traditionally defined constipation as fewer than three bowel movements per week. Patients commonly define constipation in terms of symptoms such as abdominal discomfort, bloating, straining during

bowel movements, or the sensation of incomplete evacuation. Constipation should not be defined simply by stool frequency alone, because doing so can lead to underdiagnosis for a significant number of patients who suffer from the condition.[7] The Rome criteria for the definition of constipation consist of two or more of the following signs or symptoms: (1) straining at defecation at least 25% of the time, (2) hard stools at least 25% of the time, (3) incomplete evacuation at least 25% of the time, (4) fewer than three bowel movements per week, and (5) rarely having loose stools without the use of laxatives and having symptoms for at least 3 months in the preceding 6 months for chronic constipation.[8]

PATHOPHYSIOLOGY

Constipation is a complicated condition with multiple, often overlapping causes (**Table 74-1**). Gut motility is affected by diet, activity level, anatomic lesions, neurologic conditions, medications, toxins, hormone levels, rheumatologic conditions, microorganisms, and psychiatric conditions. Constipation is best thought of as either acute or chronic, as doing so helps formulate a differential diagnosis (Table 74-1). Acute constipation should primarily prompt evaluation for intestinal obstruction, and history and physical examination can identify other causes. Chronic constipation can be caused by many of the same conditions that cause acute constipation (Table 74-1).

CLINICAL FEATURES

HISTORY

The differential diagnosis of constipation is broad, so obtain a thorough history. Determine when the symptoms started and if there are any temporally related clues that can help narrow the differential diagnosis. Was a new medication or dietary supplement added at that time? Was there a decrease in fiber or fluid intake? Was there a change in activity level? Past medical and family history can help shed light on the cause of the constipation. Is there a history of hypothyroidism or diabetes? Identify past abdominal surgical procedures. Does the patient have frequent kidney stones, which might point to hyperparathyroidism? Although most patients who present with constipation do not have emergent conditions and may be treated symptomatically as outpatients, there are several historical elements that hint to a more ominous cause of symptoms, such as intestinal obstruction. Worrisome findings, in addition to constipation, include rapid onset, nausea or vomiting, inability to pass flatus, severe abdominal pain and distention, unexplained weight loss, rectal bleeding, unexplained iron deficiency anemia, or a family history of colon cancer.[2] Consider ovarian carcinoma in women with new concerning symptoms of obstruction or bloating. Any of these findings should prompt a more rigorous evaluation. Diarrhea does not rule out constipation/obstruction, as liquid stool can move past an obstructive source.

TABLE 74-1 Differential Diagnosis of Constipation

Acute causes

- GI: bowel obstruction, quickly growing tumors, strictures, hernias, adhesions, inflammatory conditions, and volvulus
- Medicinal: narcotic analgesic, antipsychotic, anticholinergic, antacid, antihistamine
- Exercise and nutrition: decrease in level of exercise, fiber intake, fluid intake
- Painful anal pathology: anal fissure, hemorrhoids, anorectal abscesses, proctitis

Chronic causes

- Gastrointestinal: slowly growing tumor, colonic dysmotility, chronic anal pathology
- Medicinal: chronic laxative abuse, narcotic analgesic, antipsychotic, anticholinergic, antacid, antihistamine
- Neurologic: neuropathies, Parkinson's disease, cerebral palsy, paraplegia
- Endocrine: hypothyroidism, hyperparathyroidism, diabetes
- Electrolyte abnormalities: hypomagnesemia, hypercalcemia, hypokalemia
- Rheumatologic: amyloidosis, scleroderma
- Toxicologic: lead, iron, chronic opioid use

PHYSICAL EXAMINATION

Focused abdominal, pelvic, and rectal examinations are essential. Examine the patient for the presence of hernias and abdominal or pelvic masses. Bowel sounds will be decreased in cases of slow gut transit and increased in cases of obstruction. Ascites in the presence of constipation can be a sign of ovarian or uterine neoplasm in women. External rectal examination may demonstrate anal fissures, hemorrhoids, abscesses, or protruding masses. Digital rectal examination may demonstrate fecal impaction or an obstructing rectal mass. Watery stool making its way around a fecal impaction is common in elderly patients. Normal rectal tone is useful in ruling out neurologic causes of obstruction. Stool retrieved from the rectal vault should be visually inspected and tested for occult blood. The finding of grossly bloody or guaiac-positive stool in the setting of constipation raises concern for cancer, bowel ischemia, stercoral ulcer, or inflammatory bowel disease.

LABORATORY EVALUATION AND IMAGING

The evaluation of a constipated patient depends on the level of concern for organic causes. If the patient is chronically constipated, little is usually gained from any testing if the history and physical examination do not point toward a new organic cause. If the patient has a history concerning for intestinal obstruction (e.g., acute onset of symptoms, vomiting, significant abdominal distention or pain), abdominal flat and erect films (or left lateral decubitus films if the patient cannot stand) are useful. In cases of complete or partial intestinal obstruction, these films may demonstrate air-fluid levels or dilated bowel. If there continues to be high clinical suspicion for intestinal obstruction despite a normal chest and abdominal series of radiographs, then abdominal CT with PO and IV contrast may be necessary to make the diagnosis. In cases of suspected fecal impaction, an abdominal film should be obtained (**Figure 74-1**). In a constipated patient, such a film will

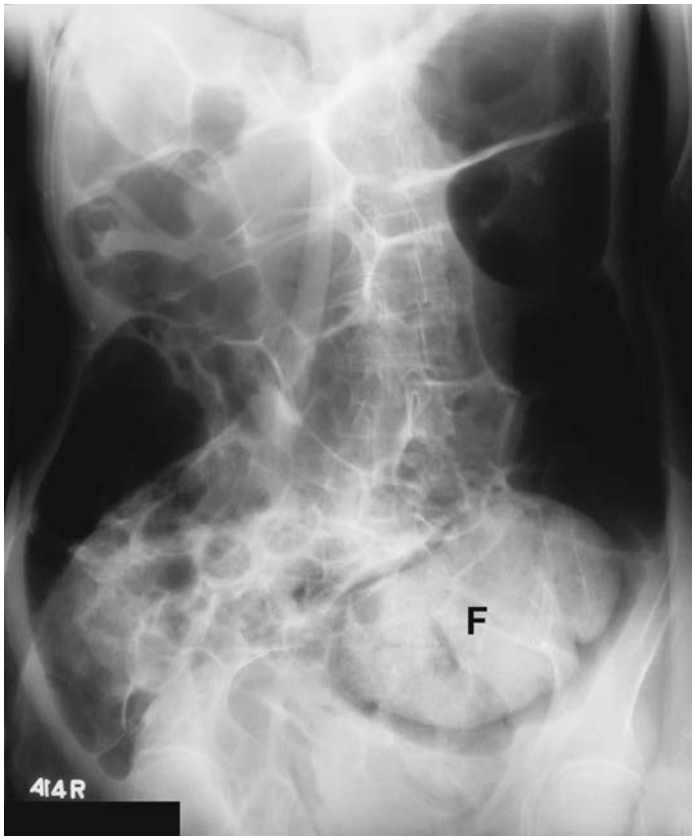

FIGURE 74-1. Large bowel obstruction due to fecal impaction (F). [Reused with permission from Schwartz DT (ed): *Emergency Radiology: Case Studies*. © McGraw-Hill, Inc., 2008. Chapter II-2, Fig. 19.]

demonstrate colonic or rectal dilation with or without air-fluid levels. Normal maximum diameter of the colon is 6 cm, whereas normal maximum diameter of the rectum is 4 cm.[2] In all patients in whom an organic cause of constipation is suspected, laboratory evaluation should include a CBC to screen for anemia, and electrolytes to evaluate for hypomagnesemia, hypercalcemia, and hypokalemia. Obtain thyroid function tests for suspected hypothyroidism. Obtain serum lead and iron levels for suspected heavy metal toxicity.

SPECIAL CONSIDERATIONS

FUNCTIONAL CONSTIPATION

The treatment of chronic (functional) constipation is best managed using a multidisciplinary approach. Unfortunately, there is no simple medication fix for this common problem. Emergency medicine providers are encouraged to stress lifestyle and diet modification. A strict dietary and exercise regimen is important, because without adequate fluid (1.5 L per day), fiber (10 grams per day), and exercise, medicinal treatments usually fail.[4] The bulking agent psyllium can improve bowel movement frequency in adults with chronic constipation. Osmotic laxatives such as polyethylene glycol and lactulose have been shown in randomized controlled trials to be effective at improving stool frequency in patients.[9] Newer prescription drugs that stimulate GO motility via the serotonin 4 receptor (prokinetics), as well as agents that directly stimulate intestinal secretion to increase stool water content (colonic secretagogues), are being marketed.[10]

Medications often employed in the treatment of constipation are listed in **Table 74-2**. Although some evidence supports polyethylene glycol as a first-line agent in children, the literature does not clearly demonstrate the superiority of any one laxative for use in pediatric patients.[11] Also, there is no gold standard management of constipation in palliative care and no evidence to support the use of one laxative, or combinations of laxatives, over another.[12] There has been some promise recently with the use of subcutaneous methylnaltrexone and oral naloxegol in multiple studies of patients with opioid-induced constipation.[13-18] The effectiveness of rectal irrigation for functional bowel disorders has not been clearly demonstrated in prospective trials. Nevertheless, the procedure is felt to be safe and will benefit some patients.[16] In its extreme form, functional constipation can result in a variety of potentially life-threatening complications, especially fecal impaction and intestinal pseudo-obstruction (Ogilvie's syndrome[19,20]).

OPIOID-INDUCED BOWEL DYSFUNCTION

Opioid-induced bowel dysfunction is a common complication of long-term opioid therapy, which affects 40% to 80% of patients.[16,17] Novel treatments for opioid-induced constipation, such as purely peripherally acting mu-opioid receptor antagonists, work to decrease the constipating effects of opioids without reversing their central analgesic effects.[18,21,22] These medications can be useful when conventional laxative treatments are ineffective.

TABLE 74-2 Medical Adjuncts for the Treatment of Constipation

Type	Generic Name	Trade Name	PRN Doses	Side Effects	Mechanism
Fiber	Psyllium	Metamucil®	1 teaspoon three times a day	Bloating, flatulence	Increases stool bulk or transit time
Emollient	Docusate sodium	Colace®	100 milligrams daily/twice a day	Cramping	Facilitates mixture of stool fat and water
Stimulants	Bisacodyl	Dulcolax®	10 milligrams PR three times a day	Incontinence, rectal burning	Stimulates the myenteric plexus, thereby increasing intestinal motility
	Anthraquinones	Peri-Colace®	One to two tablets PO daily/twice a day	Melanosis coli, degeneration of myenteric plexus	
	Senna	Senokot®, Ex-lax®	Two tablets PO daily/twice a day or 15–30 mL daily/twice a day	Laxative abuse, nausea, melanosis coli, cramping	
Saline laxative	Magnesium	Milk of magnesia	15–30 mL daily/twice a day	Magnesium toxicity, especially in renal insufficiency	May decrease colonic transit time; osmotic laxative
		Magnesium citrate	100–240 mL daily/twice a day	Cramping, flatulence, hypermagnesemia	
Suppository	Glycerin suppository	NA	1 PR daily	Rectal irritation	Local rectal stimulation
Hyperosmolar agents	Lactulose	NA	15–30 mL daily/twice a day	Cramps, flatulence, belching, nausea	Osmotically active nonabsorbable sugars pull fluid into the gut
	Sorbitol	NA	15–30 mL daily/twice a day	Cramps, flatulence	
	Polyethylene glycol	GoLYTELY®	1 gallon/4 h	Nausea, cramping, anal irritation	
		MiraLAX®	17 grams daily, onset of effect 1–3 days		
Enemas	Mineral oil	NA	100–250 mL PR	Local trauma	Colonic distention encourages evacuation
	Tap water	NA	500 mL PR	Local trauma	
	Soap suds	NA	1500 mL PR	Local trauma	
	Monophosphate	Fleets®	1 unit PR	Local trauma, hyperphosphatemia (especially in patients with renal failure)	
Serotonergic agents	Prucalopride	Resolor®	2 mg daily	Nausea, diarrhea	Stimulates GI motility
Prosecretory agents	Lubiprostone	Amitiza®	24 micrograms twice a day	Nausea, diarrhea	Stimulates the movement of ions and water into the lumen
Peripherally acting mu-opioid receptor antagonists	Naloxegol	Movantik®	25 milligrams daily	Abdominal pain	Mu-opioid receptor antagonist

Abbreviations: NA = not applicable; PRN = as needed.

TABLE 74-3 Key Aspects to Address Before Discharging a Constipated Patient

- Possible obstructing lesion
- Systemic illness
- Medication interaction/effect
- Electrolyte imbalance
- Potential for intestinal perforation with self-administered enemas

FECAL IMPACTION

Physician resistance to manual disimpaction does the patient a disservice, as enemas provide little or no relief. Diarrhea does not rule out fecal impaction, especially in the elderly or debilitated patient. Failure to perform a rectal examination will result in misdiagnosis. Manual disimpaction is a painful procedure that often requires sedation. A novel instrument invented by an emergency physician termed The Dis-Impactor® is a U.S. Food and Drug Administration–registered disposable medical device that is being retailed that claims that with its use, uncomfortable digital disimpaction can be avoided. After disimpaction, prescribe a regimen of medications and medical adjuncts to properly reestablish fecal flow.

INTESTINAL PSEUDO-OBSTRUCTION (OGILVIE'S SYNDROME)

Ogilvie's syndrome, or acute colonic pseudo-obstruction, is a clinical disorder with the signs, symptoms, and radiographic appearance of an acute large bowel obstruction with no evidence of distal colonic obstruction. The colon may become massively dilated (>10 cm). If the bowel is not decompressed the patient risks perforation, peritonitis, and death.[19,20] The exact mechanism is not known, but is thought to be secondary to a dysregulation of colonic motor activity by the autonomic nervous system. Predisposing factors include recent surgery, underlying neurologic disorders, and critical illness.[23] Treatment is varied and determined with surgical consultation. The symptoms may resolve with conservative management but may require operative or colonoscopic decompression of the dilated intestine.

ORGANIC CONSTIPATION

Symptoms suggestive of organic constipation are acute onset, weight loss, rectal bleeding/melena, nausea/vomiting, fever, rectal pain, and change in stool caliber.[24] Intestinal obstruction or carcinoma is the primary consideration. If fecal impaction is the cause, manual disimpaction is the treatment.

DISPOSITION AND FOLLOW-UP

Many constipated patients can be safely discharged from the ED with the caveat that certain key aspects have been adequately addressed[25] (**Table 74-3**). Fecal impaction requires disimpaction before discharge. Patients with organic constipation of a nonobstructive cause also can be managed safely as outpatients. The primary care provider should be contacted to ensure follow-up and to communicate concern for an organic process.

Referral to a gastroenterologist is warranted for patients with nonorganic constipation of recent onset; chronic constipation associated with weight loss, anemia, or change in stool caliber; refractory constipation; and constipation requiring chronic laxative use.[10,26] Patients with organic constipation of obstructive origin require hospitalization, gastric decompression, and surgical consultation.

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 75

Upper Gastrointestinal Bleeding

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INTRODUCTION AND EPIDEMIOLOGY

Upper GI bleeding is any GI bleeding originating proximal to the ligament of Treitz. The overall annual incidence of upper GI bleeding ranges from 39 to 172 per 100,000 in Western countries.[1-3] Difference in prevalence between countries is attributed to variations in *Helicobacter pylori* rates, socioeconomic conditions, and prescription patterns of ulcer-healing and ulcer-promoting medications.[2] Increasing age, coexistent organ system disease, and recurrent hemorrhage are factors associated with increased morbidity and mortality.[3]

PATHOPHYSIOLOGY

PEPTIC ULCER DISEASE

Despite a downward trend in prevalence over the past 20 years, peptic ulcer disease, which includes gastric, duodenal, esophageal, and stomal ulcers, is still considered the most common cause of upper GI bleeding.[2,4] However, the Analysis of Clinical Outcomes Research Initiative found gastric and duodenal ulcers in only 20.6% of 7822 endoscopies performed for suspected upper GI bleeding.[4] This number is much lower than previous estimates of up to 50%.[5,6] Awareness that aspirin, NSAIDs, and smoking cause bleeding and increased recognition and treatment of *H. pylori* infection may be responsible for decreased incidence.[7-10]

EROSIVE GASTRITIS AND ESOPHAGITIS

Erosive gastritis, esophagitis, and duodenitis are also common causes of GI hemorrhage.[11] Common predisposing factors include alcohol, salicylates, and NSAIDs. Infection, toxic ingestion, radiation, and stress from severe illness may also cause erosive gastritis. Stress-related mucosal disease occurs in patients with overwhelming sepsis, trauma, or respiratory failure requiring mechanical ventilation. *Candida*, herpes simplex virus, cytomegalovirus, and human immunodeficiency virus are potential sources of esophageal bleeding from infection.

ESOPHAGEAL AND GASTRIC VARICES

Esophageal and gastric varices result from portal hypertension and, in the United States, are most often a result of alcoholic liver disease.[12] Although varices account for a small percentage of all cases of upper GI hemorrhage, they can rebleed and carry a high mortality rate. However, many patients with end-stage cirrhosis never develop varices; many patients with documented varices never bleed; and many patients with a documented history of varices presenting with upper GI bleeding will actually bleed from nonvariceal sites. Variceal bleeding is the cause of upper GI bleeding in cirrhotics 59% of the time, followed by peptic ulcer disease in 16% of cases.[13] In-hospital mortality rates for any type of GI bleed in cirrhotics are essentially double those of noncirrhotic patients.[14]

MALLORY-WEISS SYNDROME

Mallory-Weiss syndrome is bleeding secondary to a longitudinal mucosal tear at the gastroesophageal junction. The classic history is repeated vomiting followed by bright red hematemesis. The syndrome can be associated with alcoholic binge drinking, DKA, or chemotherapy administration. The Valsalva maneuver, such as from coughing or seizures, is also a reported cause.

DIEULAFOY LESIONS

Dieulafoy lesions are arteries of the GI tract that protrude through the submucosa. They are most commonly found in the lesser curvature of the stomach but may be found anywhere in the GI tract; 80% to 95% are found within 6 cm of the gastroesophageal junction.[15] These lesions are characterized by intermittent massive GI bleeding, without the standard predisposing factors of liver disease or NSAID use. Dieulafoy lesions are difficult to diagnose endoscopically, and sometimes patients report multiple previous diagnostic maneuvers with negative results.

OTHER CAUSES

Arteriovenous malformation and malignancy are other causes of upper GI hemorrhage. Significant bleeding from ear, nose, and throat sources can also masquerade as GI hemorrhage. An aortoenteric fistula secondary to a preexisting aortic graft is an unusual but important cause of bleeding to keep in mind. Classically, this presents as a self-limited "herald" bleed with hematemesis or hematochezia, which precedes massive hemorrhage and exsanguination.

DIAGNOSIS

HISTORY

Ask about hematemesis, coffee-ground emesis, or melena. Classically, hematemesis and coffee-ground emesis suggest an upper GI source. The presence of melena and age <50 years old more likely indicate an upper GI bleed versus a lower GI bleed, even in patients without hematemesis.[16] Vomiting and retching, followed by hematemesis, suggest a Mallory-Weiss tear. Be sure to ask about prior episodes of GI bleeding and any interventions performed. A history of an aortic graft should suggest bleeding from an aortoenteric fistula. Review the patient's medication list carefully. Salicylates, glucocorticoids, NSAIDs, and anticoagulants all place the patient at high risk for GI bleed. Alcohol abuse is strongly associated with a number of causes of bleeding, including peptic ulcer disease, erosive gastritis, and esophageal varices. Ingestion of iron or bismuth can simulate melena. Liquid medications with red dye, as well as certain foods, such as beets, can simulate hematochezia. In such cases, stool guaiac testing will be negative. Inquire about past history of GI bleeding, even though recurrent bleeding episodes may originate from different sources.

Although the medical history may suggest the source of bleeding, history can also be misleading. For instance, what initially appears to be lower GI bleeding may actually be an upper GI bleed in disguise. **Bright red or maroon rectal bleeding unexpectedly originates from upper GI sources about 14% of the time.**[16] Although patients volunteer complaints of hematemesis or melena, if there is no vomiting or the patient has not noted tarry stools, signs may be subtle. Patients with hypotension, tachycardia, angina, syncope, weakness, confusion, or cardiac arrest may have underlying GI hemorrhage.

PHYSICAL EXAMINATION

Visual inspection of the vomitus for a bloody, maroon, or coffee-ground appearance is the most reliable way to diagnose upper GI bleeding in the ED. Consider keeping a sample of the vomitus or nasogastric aspirate at bedside for the gastroenterologist to view.

Vital signs may reveal obvious hypotension and tachycardia or more subtle findings such as decreased pulse pressure or tachypnea. Younger patients and those without comorbidities can tolerate substantial volume loss with minimal or no changes in vital signs. Paradoxical bradycardia may occur even in the face of profound hypovolemia. Remember that comorbid conditions and medications may mask the body's physiologic response to volume loss. β-Blockers, for example, will prevent tachycardia. Patients with baseline hypertension may have relatively normal blood pressure in the setting of hypovolemia.

Cool, clammy skin is an obvious sign of shock. Spider angiomas, palmar erythema, jaundice, and gynecomastia suggest liver disease. Petechiae and purpura suggest an underlying coagulopathy. Facial lesions, cutaneous macules, or telangiectasias may be suggestive of the Peutz-Jeghers, Rendu-Osler-Weber, or Gardner's syndromes. A careful ear, nose, and throat examination can reveal an occult bleeding source that has resulted in swallowed blood and subsequent coffee-ground emesis. Abdominal examination may disclose tenderness, masses, ascites, or organomegaly.

Perform rectal examination to detect the presence of blood and its appearance, whether bright red, maroon, or melanotic.

LABORATORY TESTING

In patients with significant bleeding, the single most important laboratory test is to obtain blood for type and cross-match in case transfusion is needed. A CBC is also important, although the initial hematocrit level may not reflect the actual amount of acute blood loss. In addition, consider BUN, creatinine, electrolyte, glucose, coagulation, and liver function studies. Upper GI hemorrhage will elevate BUN levels through digestion and absorption of hemoglobin. A BUN:creatinine ratio ≥30 suggests an upper GI source of bleeding.[17] Coagulation studies, including INR, partial thromboplastin time, and platelet count, are useful in patients taking anticoagulants and those with underlying hepatic disease. Obtain an ECG in patients with underlying coronary artery disease. Silent cardiac or mesenteric ischemia can develop if bleeding decreases cardiac or mesenteric perfusion. A single elevated lactate level is a sentinel sign of severe illness. The success or failure of resuscitation efforts can be assessed by following dynamic lactate levels, because a rising lactate level in the hospital setting is a clear predictor of in-hospital mortality.[18]

Routine abdominal and chest radiographs are of limited value and are not needed in the absence of specific clinical indications. Barium contrast studies are contraindicated because barium may hinder subsequent endoscopy or angiography.

In cases where traditional endoscopy is unavailable or endoscopic visualization is unable to find the source, consider tagged red-cell scintigraphy or visceral angiography. Both of these tests will demonstrate the source only in cases of active bleeding. Scintigraphy and angiography help localize the source of bleeding to determine whether medical or surgical management is optimal.

NASOGASTRIC LAVAGE

A negative nasogastric aspirate does not conclusively exclude an upper GI source. Intermittent bleeding, pyloric spasm, or edema preventing reflux of duodenal blood can cause false-negative results. Ultimately, nasogastric aspiration yields a positive result in only 23% of patients without hematemesis who have occult upper GI bleeding.[19]

Nasogastric intubation and aspiration are diagnostically useful.[20] In patients without a history of hematemesis, a positive aspirate provides strong evidence for an upper GI source of bleeding. High-risk lesions are more likely in patients with bloody aspirates. Visual inspection of the aspirate to identify bloody, maroon, or coffee-ground material verifies upper GI bleeding. Early nasogastric lavage is associated with decreased time to endoscopy.[21] Nasogastric tube placement and lavage can confirm the diagnosis of upper GI bleeding and correlate with risk of high-risk lesions on endoscopy.[22]

Guaiac testing of nasogastric aspirate can yield both false-negative and false-positive results. Conventional stool guaiac cards may be falsely negative. However, guaiac cards specifically designed for upper GI sources are available. Conversely, even minimally traumatic nasogastric intubation can result in positive guaiac testing even in the face of a clear aspirate. **Visual inspection of the aspirate for a bloody, maroon, or coffee-ground appearance is the most reliable way to diagnose upper GI bleeding in the ED.**

If bright red blood or clots are found in the nasogastric aspirate, perform gentle gastric lavage. Room temperature water is the preferred irrigant. Maintain the nasogastric tube on mild, intermittent suction. Suction that is too vigorous may produce gastric erosions that can confuse findings on subsequent endoscopy.

As of this writing, there is no evidence to support concerns that nasogastric tube passage may provoke bleeding in patients with varices.[23]

TABLE 75-1 Upper GI Bleeding Risk

Very Low Risk	High Risk
<60 y old	Advanced age
No major comorbidities	Comorbidities and prior endoscopic or transjugular intrahepatic portosystemic shunt procedures
No history of red hematemesis	Red hematemesis
No hematochezia	Hematochezia or melena
Negative nasogastric aspirate	Positive nasogastric aspirate
Hemodynamically stable at ED presentation	Hemodynamically unstable
Normal laboratory studies	Abnormal laboratory studies

RISK STRATIFICATION

Risk stratification depends on clinical judgment. There are no universally accepted pre-endoscopy risk stratification practice guidelines. However, the literature does seem to agree on those individuals that qualify as very low risk (**Table 75-1**). Pre-endoscopic predictors of higher risk include advanced age, comorbidities, red hematemesis, hematochezia, red blood on nasogastric aspirate, hemodynamic instability, and abnormal laboratory studies.[24-28] Other high-risk factors include prior variceal banding, clamping or cauterization of an ulcer bed, or the transjugular intrahepatic portosystemic shunt procedure.

TREATMENT

Initial management is stabilization. Patients in hemorrhagic shock require emergent resuscitation, including two large-bore IVs, typed and cross-matched blood with the consideration of massive transfusion protocols, and in selected cases, early airway management. Intubating a patient with an upper GI bleed who is hemodynamically unstable can be a perilous procedure. Aggressively resuscitate prior to intubation, and consider using smaller doses of the induction agent to minimize peri-intubation hypotension or arrest.[29] ED treatment is summarized in **Table 75-2**.

BLOOD TRANSFUSIONS

When upper GI bleeding is severe, blood transfusions can be lifesaving. If a large amount of blood product is anticipated, use massive transfusion protocols.[30] See Chapter 13, "Approach to Traumatic Shock," for discussion of massive transfusion. In less severe cases, the decision to transfuse can be difficult because hemoglobin concentrations do not fall until after hemodilution has occurred. Individualize thresholds for transfusion based on underlying comorbidities and hemodynamic status.[31] Liberally transfusing all bleeding patients using a high threshold (hemoglobin <9 grams/dL) can cause harm.[5] A restrictive transfusion threshold using hemoglobin concentrations of <7 grams/dL in most patients and <9 grams/dL in older patients with comorbidities who are not tolerating the acute anemia is recommended.[5,31]

TABLE 75-2 Treatment of Upper GI Bleed

Treatment	Dose	Comments
Blood transfusion		Transfuse if ≤7 grams/dL in most; ≤9 grams/dL in older patients or patients with comorbidities
Correct coagulopathy		Correct if INR is elevated or platelets <50,000; or if bleeding severe, correct coagulopathy unless contraindications to correction (e.g., stents, valves)
Omeprazole	80-milligram IV bolus then infusion of 8 milligrams/h	Labeled use for ulcer bleeding
Octreotide	50-microgram bolus then infusion of 25–50 micrograms/h	Unlabeled use for varices; for elderly, begin at lower dose range of 25-microgram bolus and infusion of 25 micrograms/h
Antibiotics	Ciprofloxacin 400 milligrams IV or ceftriaxone 1 gram IV	Antibiotics for cirrhotics with upper GI bleeding

COAGULOPATHY

In patients with life-threatening bleeding receiving anticoagulants, reverse the coagulopathy without concern for the INR unless there are contraindications to reversal, such as cardiac or vascular stents or prosthetic valves. In less severe bleeding, carefully consider the risks of reversal therapy. An INR ≥1.5 is a significant predictor of mortality in patients with an upper GI bleed who are receiving anticoagulants.[32] International consensus guidelines recommend reversal of coagulopathy for upper GI bleed patients who have an elevated INR or platelet counts <50,000/μL.[31,33] Coagulopathies from other causes such as the newer oral antithrombin and Xa inhibitors should be managed according to institutional protocols. See Figure 239-1 and Table 239-4 in Chapter 239, "Thrombotics and Antithrombotics," for recommendations for anticoagulant reversal. Reversal should not delay time to endoscopy. Tranexamic acid, in a small systematic review study, has been shown to reduce the risk of death in patients with upper GI bleeding,[34] but a much larger randomized controlled trial is due to be published soon.

PROTON PUMP INHIBITORS

Consensus guidelines continue to recommend proton pump inhibitors for patients with nonvariceal bleeding from peptic ulcer disease.[35] When proton pump inhibitors are given at high dose, the gastric pH remains neutral. Clot formation from platelet aggregation is dependent on a pH >6.0.[36] Administer a high-dose proton pump inhibitor such as omeprazole 80 milligrams IV bolus followed by infusion of 8 milligrams/h[37] because the cause of bleeding cannot be determined without endoscopy. In patients with peptic ulcer bleeding, proton pump inhibitors reduce the need for surgery, the length of stay in the hospital, and signs of bleeding.[38]

SOMATOSTATIN ANALOGUES/OCTREOTIDE

Octreotide is a long-acting analogue of somatostatin that elicits several actions in patients with upper GI bleeding. It inhibits the secretion of gastric acid, reduces blood flow to the gastroduodenal mucosa, and causes splanchnic vasoconstriction.[39] The dose is a 50-microgram bolus followed by a continuous infusion of 25 to 50 micrograms/h. Octreotide does not appear to provide a clear benefit on mortality,[40] but when combined with early endoscopy, it may reduce bleeding.[41]

ANTIBIOTICS

Patients with cirrhosis have an impaired immune system and have an increased risk of gut bacterial translocation during an acute bleeding episode. Prophylactic antibiotics (e.g., ciprofloxacin 400 milligrams IV or ceftriaxone 1 gram IV) reduce infectious complications, rebleeding, days of hospitalization, mortality from bacterial infections, and all-cause mortality,[42] and should be started as soon as possible.

PROMOTILITY AGENTS

Erythromycin and metoclopramide are examples of promotility agents used to enhance endoscopic visualization.[43] Consider administration if the patient is undergoing endoscopy in the ED and the patient is suspected to have large amounts of blood in the upper GI tract.[31]

ENDOSCOPY

Upper GI endoscopy is the diagnostic study of choice. Endoscopy allows visualization of the source of bleeding (in most cases) and administration of hemostatic therapy.[44] The optimal timing relates to the severity of the bleeding. Early endoscopy (within 6–24 hours of presentation for unstable patients if adequately resuscitated and 12–36 hours for stable patients[45]) is recommended for most patients because it is associated

with decreased in-hospital mortality, a significant cost reduction, and decreased length of stay.[19,20,44-47]

Endoscopic treatment options commonly used for variceal bleeding include variceal ligation and sclerotherapy. Clips, thermocoagulation, and sclerosant injections alone or in combination with epinephrine injections are commonly used in ulcerative lesions.

In some practices, the ED physician is asked to provide sedation for the endoscopist. Pretreat with an antiemetic such as ondansetron. Use short-acting titratable drugs with both analgesic properties (fentanyl) and sedative properties (midazolam or propofol). Ideal agents can be reversed if the patient's condition changes.[48-50] In unstable patients, consider using cardiovascular stable agents such as etomidate or ketamine. While providing sedation, consider that the most noxious part of the procedure is when the scope is passed around the tongue.

BALLOON TAMPONADE

Balloon tamponade is an effective short-term solution for life-threatening variceal bleeding. Today, it is generally reserved for temporary stabilization of patients for transfer to an appropriate institution or until endoscopy can be done. The **Sengstaken-Blakemore tube** (which has a 250-mL gastric balloon, an esophageal balloon, and a single gastric suction port) and the **Minnesota tube** (with an added esophageal suction port above the esophageal balloon) are examples of balloons that have been used. Tube placement is discussed in Chapter 86, "Gastrointestinal Procedures and Devices."

SURGERY

Patients who do not respond to both pharmacologic and endoscopic treatments may require emergent surgery. In patients with variceal bleeding, there are two basic types of operations: shunt operations (transjugular intrahepatic portosystemic shunt procedure) and nonshunt operations (esophageal transection or gastroesophageal junction devascularization). In nonvariceal bleeding, percutaneous embolization or subtotal or total gastrectomy can be performed. Emergent surgical consultation is considered prudent in case of uncontrolled bleeding.

DISPOSITION AND FOLLOW-UP

Patients with significant upper GI bleeding require intensive care unit admission and early endoscopy. Very-low-risk patients (Table 75-1) may be eligible for ED observation or be discharged home with adequate outpatient follow-up.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 76

Lower Gastrointestinal Bleeding

Bruce Lo

INTRODUCTION AND EPIDEMIOLOGY

Historically, lower GI bleeding is the loss of blood from the GI tract distal to the ligament of Treitz. However, management and outcomes differ if the bleeding originates from the small intestine compared with the colon.[1] Nevertheless, lower GI bleeding is a common problem in emergency medicine and should be considered potentially life threatening until proven otherwise.

Lower GI bleeding occurs more often than upper GI bleeding, with an annual incidence of approximately 109 per 100,000 and a mortality of <1%.[2] Because blood must travel through the upper GI tract down to the lower GI system, upper GI bleeds are the most common source for all causes of blood detected in the lower GI system. **Among patients with an established lower GI source of bleeding, the most common cause is diverticular disease, followed by colitis, hemorrhoids, and adenomatous polyps/malignancies.**[3]

About 80% of episodes of lower GI bleeding resolve spontaneously.[4] However, one cannot predict which episodes will spontaneously resolve or which episodes will result in complications. This is partly due to the difficulty in establishing a pathophysiologic diagnosis. In one study, a cause for bleeding was found in <50% of the cases.[5]

PATHOPHYSIOLOGY

Hematochezia is either bright red or maroon-colored rectal bleeding. If hematochezia originates from an upper GI source, it indicates brisk upper GI bleeding, which may be accompanied by hematemesis and hemodynamic instability. Approximately 10% of hematochezia episodes may be associated with upper GI bleeding.[6] **Melena** is dark or black-colored stools and usually represents bleeding from an upper GI source (proximal to the ligament of Treitz) but may also represent slow bleeding from a lower GI source.

DIVERTICULOSIS

Diverticular bleeding is usually painless and results from erosion into the penetrating artery of the diverticulum. Diverticular bleeding may be massive, but up to 90% of episodes will resolve spontaneously. Bleeding can recur in up to half of patients.[7,8] Although most diverticula are located on the left colon, right-sided diverticula are thought to be more likely to bleed.[9] Elderly patients with underlying medical illnesses, those with increased needs for transfusion, and those taking anticoagulants or NSAIDs have increased morbidity and mortality.[7]

VASCULAR ECTASIA

Vascular ectasia, which includes arteriovenous malformations and angiodysplasias of the colon, is a common cause of lower GI bleeding. Vascular ectasia can also be present in the small bowel and is difficult to diagnose. The development of vascular ectasia in the large bowel seems to be due to a chronic process and increases with aging. Inherited conditions can also give rise to arteriovenous malformations. There is also a suggestion that valvular heart disease is a risk factor for developing bleeding vascular ectasias, although this is an area of debate.[4]

ISCHEMIC COLITIS AND MESENTERIC ISCHEMIA

Ischemic colitis is the most common cause of intestinal ischemia and is usually transient. The colon is predisposed to ischemia because of its poor vascular circulation and high bacterial content. Aneurysmal rupture, vasculitis, hypercoagulable states, prolonged strenuous exercise, cardiovascular insult, irritable bowel syndrome, and certain medications that cause vasoconstriction or slow bowel motility are known risk factors. Diagnosis is usually made by endoscopy. Although most cases will resolve on their own, some patients require surgical intervention.[10]

Mesenteric ischemia can lead to bowel necrosis. Causes include thrombosis or embolism of the superior mesenteric artery, mesenteric venous thrombosis, and nonocclusive mesenteric ischemia associated with low arterial flow with vasoconstriction. Diagnosis is difficult, and the presentation can mimic other intra-abdominal pathologies. Diagnosis requires a high index of suspicion, especially in patients >60 years old and in those with atrial fibrillation, congestive heart failure, recent myocardial infarction, postprandial abdominal pain, or unexplained weight loss. CT has a specificity of 92% but a sensitivity of only 64%. Angiography remains the diagnostic study of choice. Despite aggressive treatment, prognosis is poor, with a survival of 50% if diagnosed within 24 hours.[11]

MECKEL'S DIVERTICULUM

Meckel's diverticulum consists of embryonic tissue, most commonly found in the terminal ileum. More than half of lesions contain ectopic

TABLE 76-1 Causes of Lower GI Bleeding

- Upper GI bleed
- Diverticulosis
- GI carcinoma
- Angiodysplasia
- Arteriovenous malformations
- Mesenteric ischemia
- Ischemic colitis
- Meckel's diverticulum
- Hemorrhoids
- Infectious colitis
- Inflammatory bowel disease
- Polyps
- Radiation colitis
- Rectal ulcers
- Trauma
- Foreign bodies
- Carcinoma
- Prostate biopsy sites
- Endometriosis
- Dieulafoy lesions
- Colonic varices
- Portal hypertensive enteropathy

gastric tissue, which can secrete gastric enzymes, eroding the mucosal wall and causing bleeding. It is a rare but important condition, especially in the younger population.

HEMORRHOIDS

Although hemorrhoids are the most common source of anorectal bleeding, massive hemorrhage is unusual.[10] Bleeding is usually associated with bowel movements and is usually painless. Diagnosis can sometimes be made at the bedside as a cause for lower GI bleeding. For further discussion of hemorrhoids, see Chapter 85, "Anorectal Disorders."

OTHER CAUSES OF LOWER GI BLEEDING

Numerous other lesions may result in lower GI hemorrhage (**Table 76-1**), including infectious colitis, radiation colitis, rectal ulcers, trauma, and inflammatory bowel disease. Polyps and carcinomas can cause lower GI bleeding and are usually a source of chronic anemia. Delayed hemorrhage can occur up to 3 weeks after polypectomy. Patients with left ventricular assist devices are prone to GI bleeding especially due to anticoagulation, risk of arteriovenous malformations, and acquired von Willebrand's disease.[12]

DIAGNOSIS

As with any emergency, the medical history, physical examination, and diagnostics often must be accomplished simultaneously with resuscitation and stabilization. **Factors associated with a high morbidity rate are hemodynamic instability, repeated hematochezia, gross blood on initial rectal examination, initial hematocrit <35%, syncope, nontender abdomen (predictive of severe bleeding), history of diverticulosis or angioectasia, elevated creatinine, aspirin or NSAID use (predictive of diverticular hemorrhage), and more than two comorbid conditions.**[1,3,13]

HISTORY

Although most patients will volunteer complaints of hematochezia or melena, signs and symptoms of hypotension, tachycardia, angina, syncope, weakness, or altered mental status can all occur as a result of lower GI bleeding.

Ask about previous GI bleeding as well as a history of pain, trauma, ingestion or insertion of foreign bodies, and recent colonoscopies. Weight loss and changes in bowel habits may suggest malignancy. A history of an aortic graft may suggest the possibility of an aortoenteric fistula. Medications, such as antiplatelets (e.g., salicylates, clopidogrel), NSAIDs, and anticoagulants (e.g., warfarin, rivaroxaban, apixaban), increase the risk of lower GI bleeding.[1,14-16] Ingestion of iron or bismuth can simulate melena, and certain foods, such as beets, can simulate hematochezia. However, stool guaiac testing in those cases will be negative.

PHYSICAL EXAMINATION

Hypotension and tachycardia, or decreased pulse pressure or tachypnea, develop with significant bleeding. However, changes in vital signs may be masked by concurrent medications, such as β-blockers, or medical conditions, such as poorly controlled hypertension. Thus, relative tachycardia and hypotension may represent subtle clues to ongoing bleeding. Some patients can tolerate substantial volume losses with minimal or no changes in vital signs.

Cool, pale skin and an increase in capillary refill can be signs of shock. Physical findings of liver disease, as well as petechiae and purpura, suggest an underlying coagulopathy. The abdominal examination may disclose tenderness, masses, ascites, or organomegaly. In patients with lower GI bleeding, a lack of abdominal tenderness suggests bleeding from disorders involving the vasculature, such as diverticulosis or angiodysplasia. Inflammatory bowel disorders with lower GI bleeding are associated with abdominal tenderness on examination.

Thorough examination of the rectal area may reveal an obvious source of bleeding, such as a laceration, masses, trauma, anal fissures, or external hemorrhoids. A vaginal or urinary source of bleeding mistaken for a GI source will be identified by examination and testing. Perform a digital rectal examination to detect gross blood (either bright red or maroon) and for guaiac testing. Rectal examination can also detect the presence of masses.

Anoscopy can also be performed at the bedside. A source of bleeding such as hemorrhoids can sometimes be elucidated by anoscopy. However, blood originating beyond the level of visualization should raise the suspicion for other causes.[10]

LABORATORY TESTING

The most important laboratory tests are the CBC, coagulation studies, and typed and cross-matched blood. Coagulation studies, including prothrombin time, partial thromboplastin time, and platelet count, are of obvious benefit in patients taking anticoagulants or those with underlying hepatic disease. In addition, obtain BUN, creatinine, and electrolytes. In acute, brisk bleeding, the initial hematocrit level may not reflect the actual amount of blood loss. **Bleeding from a source higher in the GI tract may elevate BUN levels through digestion and absorption of hemoglobin (BUN-to-creatinine ratio of >30:1).**

IMAGING

Routine abdominal radiographs are of limited value without specific indications such as perforation, obstruction, or foreign bodies. Similarly, routine admission chest radiographs for patients with acute GI hemorrhage, even those admitted to the intensive care unit, are of limited utility in the absence of known pulmonary disease or abnormal findings on lung examination.[17] Barium contrast studies are not helpful and can interfere with subsequent emergent endoscopy or angiography.

The initial diagnostic procedure of choice—angiography, scintigraphy, or endoscopy—depends on resource ability and consultant preference.[18-21] Angiography can sometimes detect the site of bleeding and help guide surgical management. Moreover, angiography permits therapeutic options such as transcatheter arterial embolization or the infusion of vasoconstrictive agents. However, **angiographic diagnosis and therapy require a relatively brisk bleeding rate (at least 0.5 mL/min). Serious complications can also occur with angiography in up to 10% of cases.**[10]

Technetium-labeled red cell scans can also localize the site of bleeding in obscure hemorrhage. Such localization can be used to help determine

if angiography or surgery is the optimal approach. **Scintigraphy appears more sensitive than angiography and can localize the site of bleeding at as low a rate as 0.1 mL/min. It also has potential value over angiography if bleeding occurs intermittently but requires a minimum of 3 mL of blood to pool.**[22]

Multidetector CT angiography has a sensitivity and specificity of up to 100% and 99%, respectively, for detecting active or recent GI bleeding and is about 93% accurate in determining the site of bleeding.[23,24] It can be a useful tool, especially in unstable lower GI bleeds, prior to treatment with conventional angiography and can detect bleeding at as low a rate of 0.4 mL/min.

TREATMENT

Resuscitate unstable or actively bleeding patients. Administer oxygen if patient is hypoxic and institute cardiac monitoring. Place two large-bore IV lines and replace volume with crystalloids. Correct coagulopathy including if international normalized ratio is >1.5 or platelets are <50,000/μL. Blood transfusion should be based on the clinical findings of significant blood loss or continued bleeding rather than on initial hematocrit values as it takes several hours for the hematocrit to decrease. **General guidelines for initiation of blood transfusion are continued active bleeding and failure to improve perfusion and vital signs after crystalloid infusion or if hemoglobin falls below 7 g/dL.** The threshold for blood transfusion should be lower in the elderly and those with multiple comorbid conditions.

Consider the placement of a nasogastric tube if lower GI bleeding is significant. **Hematochezia unexpectedly originates from upper GI sources approximately 10% to 14% of the time.**[6,25] Factors that suggest an upper GI source for hematochezia include anemia and previous history of upper GI bleeding.[6] Nasogastric aspiration has low sensitivity and negative predictive value for upper GI bleeding.[26] In one study, 15% of patients with hematochezia had a negative nasogastric aspirate but had an upper GI source of bleeding.[26] A nasogastric tube is likely beneficial only for those with significant ongoing upper GI bleeding in whom immediate intervention will occur.[10,26]

Obtain early consultation for severe lower GI bleeding to expedite the next steps of care. Surgical consultation along with consultation from the gastroenterologist is prudent for uncontrollable bleeding.

ENDOSCOPY AND SURGERY

Flexible sigmoidoscopy can evaluate possible distal colonic and rectal sources of bleeding but cannot identify more proximal sources of bleeding. Colonoscopy can diagnose various sources of lower GI bleeding, such as diverticulosis or angiodysplasia, and may allow ablation of bleeding sites with various endoscopic hemostasis methods (injection sclerotherapy, electrocoagulation, heater probe therapy, banding, and clipping). If colonoscopy fails to determine the source of bleeding, the specialists may consider upper endoscopy to evaluate for an upper GI source of bleeding, although upper endoscopy may be indicated first in certain situations.[27] Timing of endoscopy can vary. Some studies suggest that urgent colonoscopy is both safe and accurate within 12 to 24 hours of admission, but others report that delayed colonoscopy is appropriate in stable patients.[8-10,27]

Patients with continued bleeding and failure of endoscopic hemostasis may need emergency surgery. The reported proportion of patients requiring surgery varies from 5% to 25%.[10,18]

DISPOSITION AND FOLLOW-UP

Patients with lower GI hemorrhage will often require hospital admission and early referral to an endoscopist. Those who are unstable or with active bleeding may require admission to the intensive care unit. Although risk stratification scores have been developed for upper GI bleeding for possible outpatient management, **currently no reliable scoring system exists to risk stratify which patients with lower GI bleeding may be discharged home safely**. However, those with an obvious cause of mild bleeding (such as mild bleeding from hemorrhoids or anal fissures), or who have no bright red blood or maroon or melanotic stool on rectal examination and are hemodynamically stable and without major comorbidities, may be candidates for outpatient treatment.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 77

Esophageal Emergencies

Michael J. Bono

INTRODUCTION

The complaints of dysphagia, odynophagia, and foreign body sensation immediately implicate the esophagus. The esophagus also is often the site of pathology in patients who present with chest pain, upper GI bleeding (see Chapter 75, "Upper Gastrointestinal Bleeding"), malignancy, and mediastinitis. Esophageal foreign body and esophageal perforation demand the attention of the emergency physician, but many diseases of the esophagus can be evaluated over time in an outpatient setting.

ANATOMY AND PATHOPHYSIOLOGY

The esophagus is a muscular tube approximately 20 to 25 cm long, primarily located in the mediastinum, posterior and slightly lateral to the trachea, with smaller cervical and abdominal components, as shown in **Figure 77-1**. There is an outer longitudinal muscle layer and an inner circular muscle layer. The upper third of the esophagus is striated muscle, while the lower two-thirds is all smooth muscle, including the lower esophageal sphincter. The esophagus is lined with stratified squamous epithelial cells that have no secretory function.

Two sphincters regulate the passage of material into and out of the esophagus. The upper esophageal sphincter prevents air from entering the esophagus and food from refluxing into the pharynx. The lower esophageal sphincter regulates the passage of food into the stomach and prevents stomach contents from refluxing into the esophagus. The upper sphincter is composed primarily of the cricopharyngeus muscle, with a resting pressure of around 100 mm Hg. The lower sphincter is not anatomically discrete. The smooth muscle of the lower 1 to 2 cm of the esophagus, in combination with the skeletal muscle of the diaphragmatic hiatus, functions as the sphincter, with a lower resting pressure around 25 mm Hg. An empty esophagus collapses, but three anatomic constrictions affect the adult esophagus:

1. At the cricopharyngeus muscle (C6)
2. At the level of the aortic arch (T4)
3. At the gastroesophageal junction (T10 to T11)

The pediatric esophagus gets two additional areas of constriction:

1. At the thoracic inlet (T1)
2. At the tracheal bifurcation (T6)

The innervation of the esophagus mirrors that of the heart, with visceral and somatic stimuli converging within the sympathetic system. This anatomy makes pain of esophageal and cardiac origin similar. The esophageal venous circulation includes a submucosal plexus of veins that drains into a separate plexus of veins surrounding the esophagus. Blood flows from this outer plexus in part to the gastric venous system, an important link between portal and systemic circulation. Variceal dilatation of the submucosal system can lead to massive upper GI bleeding.

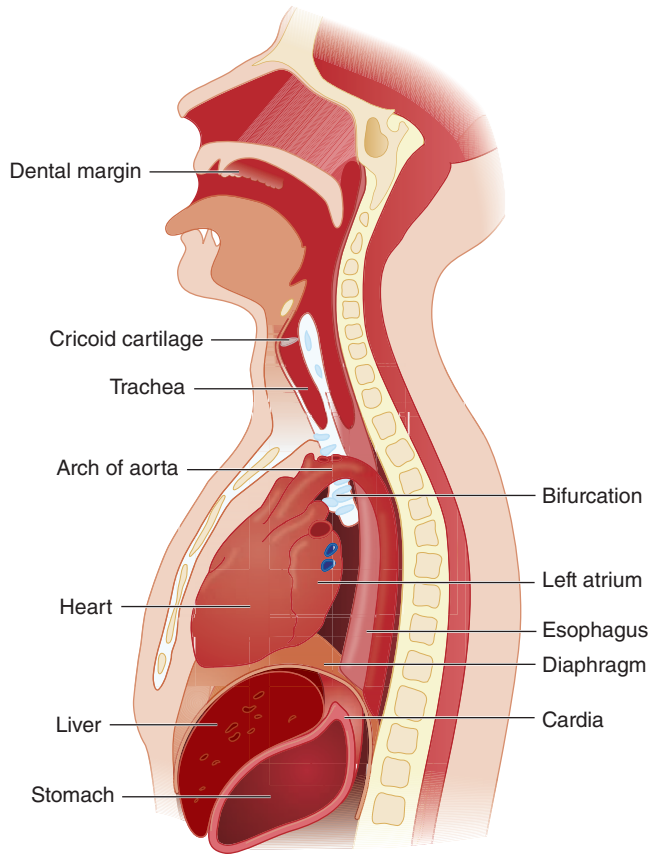

FIGURE 77-1. Anatomic relations of the esophagus (seen from the left side). The distance from the upper incisor teeth to the beginning of the esophagus (cricoid cartilage) is about 15 cm (6 in.); from the upper incisors to the level of the bronchi, 22 to 23 cm (9 in.); and to the cardia, 40 cm (16 in.). Structures contiguous to the esophagus that affect esophageal function are shown.

TABLE 77-1 Causes of Dysphagia

Oropharyngeal Dysphagia	Esophageal Dysphagia
Discoordination in transferring bolus from pharynx to esophagus	Improper transfer of the bolus from the upper esophagus into the stomach: solids worse than liquids = mechanical obstruction; solids and liquids = motility disorder
Swallowing symptoms—gagging, coughing, nasal regurgitation, inability to initiate swallow, need for repeated swallows	Swallowing symptoms—food "sticking," retrosternal fullness with solids (and eventually liquids), possibly odynophagia
Risk of aspiration present	Risk of aspiration present, generally less pronounced than in transfer dysphagia
Long term—weight loss, malnutrition, chronic bronchitis, asthma, multiple episodes of pneumonia	Long term—malnutrition, dehydration, weight loss, systemic effects of cancer
Neuromuscular disease—cerebrovascular accident, cerebral palsy, polymyositis and dermatomyositis, scleroderma, myasthenia gravis, tetanus, Parkinson's disease, botulism, lead poisoning, thyroid disease	Obstructive disease—foreign body, carcinoma, esophageal webs, peptic esophageal strictures, Schatzki ring, thyroid enlargement, esophageal diverticulae, congenital or acquired large-vessel abnormalities
Localized disease—pharyngitis; aphthous ulcers; candidal infection; peritonsillar and retropharyngeal abscesses; carcinoma of tongue, pharynx, or larynx; Zenker's diverticulum; cricopharyngeal bar; cervical osteophytes	Motor disorder—achalasia, peristaltic dysfunction (nutcracker esophagus), diffuse esophageal spasm, scleroderma
Inadequate lubrication—scleroderma	Inflammatory disease

DYSPHAGIA

Dysphagia is difficulty with swallowing. Oropharyngeal **dysphagia** occurs as the food bolus moves from the oropharynx through the upper sphincter. Symptoms include drooling, inability to begin swallowing, or a feeling of food catching in the neck. Common causes are listed in **Table 77-1**. Esophageal **dysphagia** is impaired movement of the bolus down the esophagus and through the lower sphincter. A feeling of "food getting stuck" occurs after swallowing is initiated. Esophageal dysphagia can be caused by mechanical obstruction in the esophagus or motility disorders (Table 77-1). Functional or motility disorders usually cause dysphagia that is intermittent and variable. Mechanical or obstructive disease is usually progressive, first with difficulty swallowing solids, then liquids.[1] Odynophagia is throat and chest pain with swallowing and usually signifies esophageal inflammation, infection, or erosion. Common causes include *Candida*, herpesvirus, or cytomegalovirus.

The diagnosis of the underlying pathology is most often made outside of the ED, with upper endoscopy, videoesophagography, barium swallow, or esophageal manometry.[2-6] If neoplasm is suspected by history and physical examination, CT imaging of neck and chest may be indicated in the ED.

GASTROESOPHAGEAL REFLUX DISEASE

Reflux of gastric contents into the esophagus causes a wide array of symptoms and long-term effects. Classically, a weak lower esophageal sphincter has been the mechanism held responsible for reflux, and this is seen in some patients. However, transient relaxation of the lower esophageal sphincter complex (with normal tone in between periods of relaxation) is the primary mechanism causing reflux. Hiatal hernia, prolonged gastric emptying, agents that decrease lower sphincter pressure, and impaired esophageal motility predispose to reflux.[7] **Table 77-2** lists some common contributors.

Heartburn is the classic symptom of gastroesophageal reflux disease (GERD). The burning nature of the discomfort is probably due to localized lower esophageal mucosal inflammation. Many GERD patients report other associated GI symptoms, such as odynophagia, dysphagia, acid regurgitation, discomfort with meals, and hypersalivation. Reflux symptoms can sometimes be dramatically exacerbated with a head-down position or an increase in intra-abdominal pressure. Symptoms are often relieved by antacids, but pain can return after the transient antacid effect wears off. Some patients with symptoms caused by cardiac ischemic disease also report improvement with antacids. Symptoms of cardiac and GERD pain are very similar. Both may be squeezing and pressure-like, and the history may include pain onset with exertion and offset with rest. Both types of pain may be accompanied by diaphoresis, pallor, and nausea and vomiting. Radiation of esophageal pain can occur

TABLE 77-2 Causes of Gastroesophageal Reflux Disease

Decreased Pressure of Lower Esophageal Sphincter	Decreased Esophageal Motility	Prolonged Gastric Emptying
High-fat food	Achalasia	Medicines (anticholinergics)
Nicotine	Scleroderma	Outlet obstruction
Ethanol	Presbyesophagus	Diabetic gastroparesis
Caffeine	Diabetes mellitus	High-fat food
Medicines (nitrates, calcium channel blockers, anticholinergics, progesterone, estrogen)		
Pregnancy		

to one or both arms, the neck, the shoulders, or the back. Given the serious outcome of unrecognized ischemic disease, distinguishing GERD from cardiac disease is often best accomplished in a protocol-driven observation unit.

Over time, GERD can cause complications including strictures, dysphagia, and inflammatory esophagitis. Barrett's esophagus, a complication of GERD, is the extension of gastric epithelium from the stomach to the distal esophagus, with a risk of dysplasia and metaplasia.[8-10] Less obvious presentations of GERD include asthma exacerbations, sore throat, and other ear, nose, and throat symptoms. GERD has also been implicated in dental erosion, vocal cord ulcers and granulomas, laryngitis with hoarseness, chronic sinusitis, and chronic cough.

Treatment of reflux disease involves decreasing acid production in the stomach, enhancing upper tract motility, and eliminating risk factors. Mild disease is often treated empirically, and the optimal approach to choice of treatment is unclear. A reasonable approach is to start treatment with histamine-2 receptor antagonists, and if there is no improvement in 2 weeks, stop the current treatment and start a proton pump inhibitor. At ED discharge, remind patients to avoid agents that exacerbate GERD (ethanol, caffeine, nicotine, chocolate, fatty foods), sleep with the head of the bed elevated (30 degrees), and avoid eating within 3 hours of going to bed at night. The need for additional testing can be determined at outpatient follow-up care.

ESOPHAGITIS

Esophagitis can cause prolonged periods of chest pain and almost always causes odynophagia as well. Diagnosis of more established esophagitis is by endoscopy. Low-grade disease can be seen by histopathologic examination.

GERD may induce *inflammatory esophagitis* in the lower esophageal mucosa. Over time, ulcerations, scarring, and stricture formation can develop. Treatment is pharmacologic therapy with acid-suppressive medications.[7] Ingested medications can also be a source of inflammatory esophagitis and ulcerations. Common offenders include NSAIDs and other anti-inflammatory drugs, potassium chloride, and some antibiotics (e.g., doxycycline, tetracycline, and clindamycin). Risk factors for pill-induced esophageal injury include swallowing position, fluid intake, capsule size, and patient age. Withdrawal of the offending agent is generally curative. **Eosinophilic esophagitis** is a chronic allergic-inflammatory condition in which eosinophils and other immune system cells infiltrate the esophagus and induce an inflammatory response, in response to foods, allergens, or acid reflux.[10] Diagnosis is by endoscopy. Treatment is avoidance of allergens and oral liquid corticosteroids or inhaled corticosteroids. Dilatation is necessary if strictures form.

Patients with immunosuppression can develop *infectious esophagitis*. The diagnosis of infectious esophagitis in an otherwise seemingly healthy host should prompt an evaluation of immune status. Candidal species are the most common pathogens, often associated with dysphagia as a primary symptom. However, oral candidiasis is not always present. Empiric treatment is often begun with oral fluconazole, 400 milligrams per day for 2 weeks. Herpes simplex or cytomegalovirus infection and aphthous ulceration are also seen and may be more frequently associated with odynophagia. Other causative agents are rare and include fungi, mycobacteria, and other viral pathogens such as varicella-zoster virus and Epstein-Barr virus. Endoscopy with biopsy and specimen culture establishes the specific diagnosis.[11]

ESOPHAGEAL PERFORATION

Iatrogenic perforation is the most frequent cause of esophageal perforation,[12] with a large number of other responsible processes listed in **Table 77-3**.

Boerhaave's syndrome is full-thickness perforation of the esophagus after a sudden rise in intraesophageal pressure. The mechanism is sudden, forceful emesis in most cases; coughing, straining, seizures, and childbirth have been reported as causing perforations as well. The perforation is usually in the distal esophagus on the left side.

TABLE 77-3 Causes of Esophageal Perforation

Cause of Perforation	Description
Iatrogenic	Intraluminal procedures Endoscopy Dilatation Variceal therapy Gastric intubation Intraoperative injury
Boerhaave's syndrome	"Spontaneous," usually associated with transient increase in intraesophageal pressure
Trauma	Penetrating Blunt (rare) Caustic ingestion
Foreign body	Includes pill-related injury
Infection	Rare
Tumor	May be intrinsic or extrinsic cancer
Aortic pathology	Aneurysm Aberrant right subclavian artery
Miscellaneous	Barrett's esophagus Zollinger-Ellison syndrome

PATHOPHYSIOLOGY

Perforation causes a dramatic presentation when esophageal contents leak into the mediastinal, pleural, or peritoneal spaces. Fulminant, necrotizing mediastinitis, pneumonitis, or peritonitis can rapidly lead to shock. If the perforation is small and leakage is contained by contiguous structures, the course may be indolent. Most spontaneous perforations occur through the left posterolateral wall of the distal esophagus.[12] Proximal perforation, seen mostly with instrumentation, tends to be less severe than distal perforation and can form a periesophageal abscess with minimal systemic toxicity.

CLINICAL FEATURES

The pain of rupture is classically described as acute, severe, unrelenting, and diffuse, and is reported in the chest, neck, and abdomen. Pain can radiate to the back and shoulders. Back pain may be a very predominant symptom. The pain is often exacerbated by swallowing. Dysphagia, dyspnea, hematemesis, and cyanosis can be present as well.

Physical examination varies with the severity of the rupture and the elapsed time to presentation. Abdominal rigidity with hypotension and fever often occur early. Tachycardia and tachypnea are common. Cervical subcutaneous emphysema is common in cervical esophageal perforations. Hamman's crunch, caused by air in the mediastinum that is being moved by the beating heart, can sometimes be auscultated. Pleural effusion can result from intrathoracic perforation but is uncommon in cervical perforation. Pleural fluid can be caused by either direct contamination of the pleural space or a sympathetic serous effusion from mediastinitis.

DIAGNOSIS

Obtain surgical consultation as soon as the diagnosis is seriously entertained. Resuscitate the patient from shock, and administer broad-spectrum parenteral antibiotics. Obtain IV contrast CT of the neck or chest. Obvious perforation requires emergency surgery. If CT is negative but clinical suspicion is still high, flexible video esophagoscopy or esophagography, or both, are next steps depending upon resources and local preferences.[12-14] Esophagoscopy is extremely accurate for finding esophageal injuries, with a sensitivity of 95% to 100%, and specificity of 90% to 100% if performed by an experienced endoscopist. If an experienced endoscopist is not available, esophagography should be performed with water-soluble contrast material initially (i.e., Gastrografin).

SWALLOWED FOREIGN BODIES AND FOOD IMPACTION

PATHOPHYSIOLOGY

Children 18 to 48 months of age and those with mental illness account for most cases of ingested foreign bodies. Small objects, such as coins, toys, and crayons, typically lodge in the anatomically narrow proximal esophagus. In adults, dentures are sometimes swallowed, because diminished palatal sensitivity leads to unintentional ingestion. Adult candidates for swallowed foreign bodies are those with esophageal disease, dementia, prisoners, and psychiatric patients. In adults, most impactions are distal. In children and adults, once an object has traversed the pylorus, it usually continues through the GI tract and is passed without issue. If, however, the object has irregular or sharp edges or is particularly wide (>2.5 cm) or long (>6 cm), it may become lodged distal to the pylorus.[15] Esophageal impaction can result in airway obstruction, stricture, or perforation, the latter being the result of direct mechanical erosion (e.g., ingested bones) or chemical corrosion (e.g., ingested button batteries). Esophageal mucosal irritation (often mechanical from a swallowed bone, for example) can be perceived as a foreign body by the patient as well.

CLINICAL FEATURES

Adults with an esophageal foreign body generally provide unequivocal history. Patients often complain of retrosternal pain and may localize the object (often accurately in the upper third of the esophagus). Patients may have dysphagia, vomiting, and choking. If the patient attempts to wash down the object with liquid or if swallowed secretions pool proximal to the obstruction, coughing or aspiration can occur. **In children, the history can be unclear. Signs and symptoms can include refusal or inability to eat, vomiting, gagging and choking, stridor, neck or throat pain, and drooling. A high degree of suspicion is necessary for unwitnessed ingestions in children, especially in those <2 years of age**. Physical examination starts with an assessment of the airway. The nasopharynx, oropharynx, neck, and chest should also be examined but are often unremarkable. Occasionally, a foreign body can be directly visualized in the oropharynx.

TABLE 77-4 Circumstances Warranting Urgent Endoscopy for Esophageal Foreign Bodies

- Ingestion of sharp or elongated objects (including toothpicks, aluminum soda can tabs)
- Ingestion of multiple foreign bodies
- Ingestion of button batteries
- Evidence of perforation
- Coin at the level of the cricopharyngeus muscle in a child
- Airway compromise
- Presence of a foreign body for >24 h

DIAGNOSIS

Plain films are used to screen for radiopaque objects.[16,17] Coins in the esophagus generally present their circular face on anteroposterior films (coronal alignment), as opposed to coins in the trachea, which show that face on lateral films (**Figure 77-2**). Obtaining plain films in patients with food impaction is rarely helpful and can generally be omitted. CT scanning is a very high-yield test for esophageal foreign body and has generally replaced the barium swallow test to evaluate ingestion of nonradiopaque objects. CT also delivers excellent information regarding perforation and subsequent infection.

TREATMENT

Endoscopy Patients in extremis or with pending airway compromise are resuscitated and often require active airway management. Complete obstruction of the esophagus (often distal esophageal food impactions) can lead to proximal pooling of secretions and aspiration. Emergent endoscopy is needed. **Table 77-4** lists other situations that require urgent endoscopy, even if patients are clinically stable. Some of these ingestions are discussed in more detail in the sections "Food Impaction," "Coin Ingestion," "Button Battery Ingestion," "Ingestion of Sharp Objects," and "Narcotics Ingestion" later in the chapter. In general, if endoscopy is clearly indicated, performing advanced imaging studies delays definitive intervention while adding little value to the care of the patient. In the vast majority of cases, the foreign body can be removed relatively easily with endoscopy without complication. Hospital admission is generally not needed.

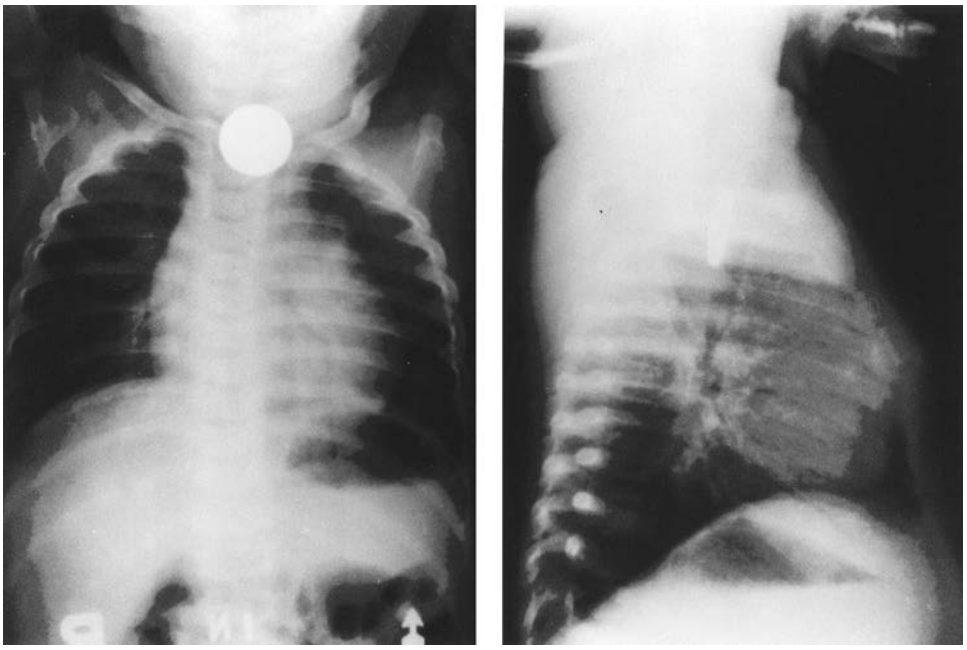

FIGURE 77-2. A coin lodged in a child's esophagus is visible on an anteroposterior radiograph. [Reproduced with permission from Effron D (ed): *Pediatric Photo and X-Ray Stimuli for Emergency Medicine*, vol II. Columbus, OH, Ohio Chapter of the American College of Emergency Physicians, 1997, case 27.]

Laryngoscopy In stable patients, indirect laryngoscopy or visualization of the oropharynx using a fiberoptic scope may allow removal of very proximal objects. For more distal objects, imaging studies are used to define the location and nature of the ingestion. Objects that persist over time or are in the upper half of the esophagus are less likely to pass, and consultation for endoscopy is prudent.

Expectant Treatment If the object is distal to the pylorus, has a benign shape and nature, and the patient is comfortable and tolerating intake by mouth, treatment is expectant. For worrisome foreign bodies that are in the more distal GI tract, surgery consultation may be necessary.

Foley Catheter Removal Alternatives to endoscopy have been advocated by some authors. These include use of a Foley catheter to remove coins (see section "Coin Ingestion" later in the chapter) and bougienage (a procedure involving the use of a bougie) to advance the object from the esophagus into the stomach. Generally, the Foley catheter technique and bougienage should only be attempted in patients with blunt foreign bodies present for <24 hours and in patients without underlying esophageal disease. Provider comfort with the procedure likely influences the generally low complication rates in published series.[18]

Glucagon For distal esophageal objects, glucagon, 1 to 2 milligrams IV in adults, has been reported to relax the lower sphincter and allow passage of the object. **Success rates of glucagon therapy are generally reported as poor, however, and it may be no better than watchful waiting without other intervention.**[19]

FOOD IMPACTION

Meat is the food most commonly identified in food impaction. Food impaction with complete esophageal obstruction or impaction of food containing bony fragments requires emergency endoscopy. Uncomplicated food impaction may be treated expectantly. Time and sedation often allow the bolus to pass into the stomach, but the bolus should not be allowed to remain impacted for >12 to 24 hours. **The use of proteolytic enzymes (e.g., Adolph's Meat Tenderizer®, which contains papain) to dissolve a meat bolus is *contraindicated*, because of the potential for severe mucosal damage and esophageal perforation, and the availability of superior alternatives.** If **glucagon** therapy is attempted, an initial dose of 1 to 2 milligrams IV is given (for adults). If the food bolus is not passed in 20 minutes, an additional dose can be given.[19]

COIN INGESTION

Many centers use endoscopy to remove esophageal coins in children. Removal with a Foley catheter is done under fluoroscopy, and advanced airway management should be immediately available. The patient is placed in the Trendelenburg position to prevent aspiration of the object. The catheter is passed down the esophagus beyond the object, the balloon inflated, and the catheter slowly withdrawn, bringing the object with it. Complications can include airway compromise and mucosal injury, although in experienced hands, the rate of these events is low.[18]

BUTTON BATTERY INGESTION

A button battery lodged in the esophagus is a true emergency requiring prompt removal, because the battery may quickly induce mucosal injury and necrosis. Perforation can occur within 6 hours of ingestion. Morbidity caused by the battery is likely related to the flow of electricity through a locally formed external circuit. Lithium cells are associated disproportionately with adverse outcome, probably due to higher voltage.[18]

Figure 77-3 outlines a management algorithm for button battery ingestion. Button batteries that have passed the esophagus can be managed expectantly, as long as follow-up in 24 hours can be ensured. Repeat films should be obtained at 48 hours to ensure that the cell has passed through the pylorus, which may not occur if the battery is of large diameter and/or the patient is <6 years old. Most batteries pass completely through the body within 48 to 72 hours, although passage can take longer. Any patient with symptoms or signs of GI tract injury requires immediate surgical consultation. The National Button Battery

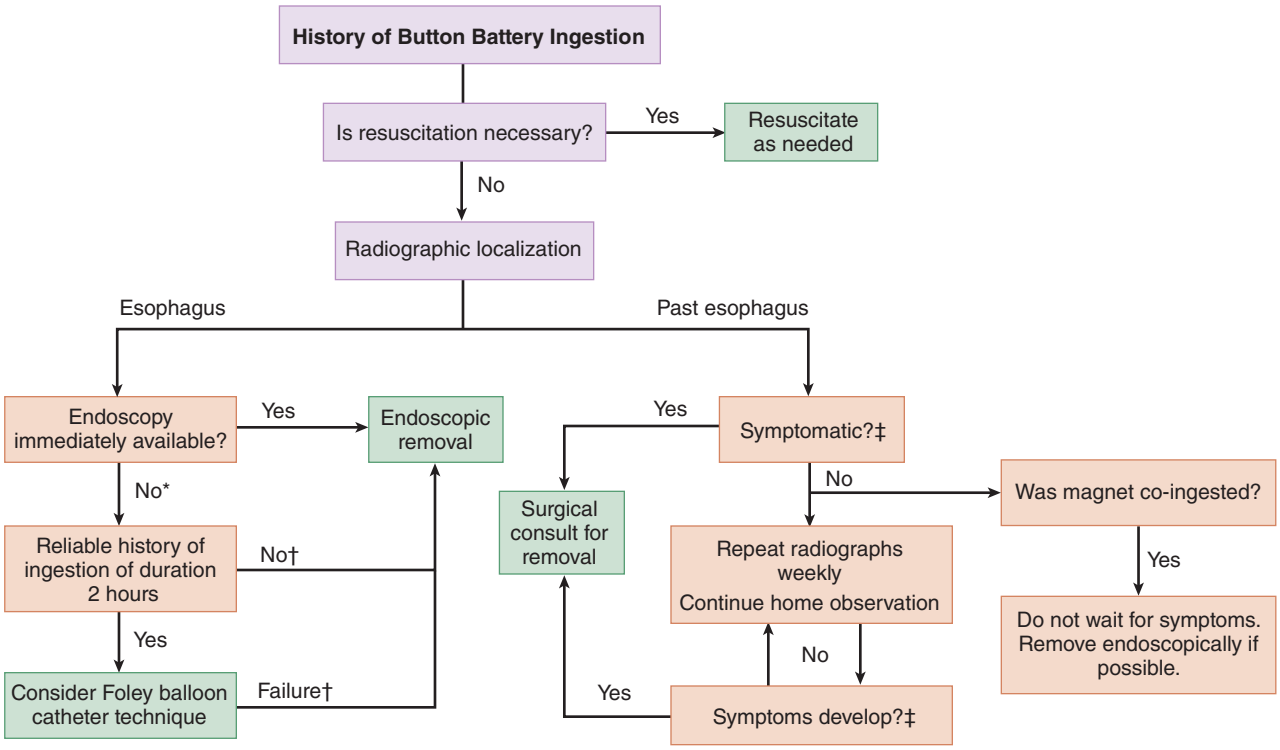

FIGURE 77-3. Algorithm for management of button battery ingestion. *Button batteries in the esophagus must be removed. Endoscopy should be used, if available. The balloon catheter technique can be used if the ingestion occurred ≤2 hours previously, but it should not be used after this period, because it may increase the amount of damage to the weakened esophagus. †When the Foley technique fails or is contraindicated because >2 hours have elapsed, the button battery should be removed endoscopically. This may require transfer of the patient. ‡Acute abdomen, tarry or bloody stools, fever.

Ingestion Hotline (National Capital Poison Center, Washington, DC) at 202-625-3333 is a 24-hour/7-day-a-week resource for help in management decisions.

INGESTION OF SHARP OBJECTS

Sharp objects in the esophagus need immediate removal. Sharp objects may pass into the stomach spontaneously. **Because intestinal perforation from ingested sharp objects that pass distal to the stomach is common, the American Society for Gastrointestinal Endoscopy guidelines recommend removal of sharp objects by endoscopy while they are in the stomach or duodenum.** If intestinal perforation occurs, it is usually at the ileocecal valve.

If the object is distal to the duodenum at presentation and the patient is asymptomatic, the object's passage should be documented with daily plain films. Surgical removal should be considered if 3 days elapse without passage. The development of symptoms or signs of intestinal injury (e.g., pain, emesis, fever, GI bleeding) requires immediate surgical consultation.[15]

NARCOTICS INGESTION

Narcotic couriers (body packers) ingest multiple small packets of a drug in order to conceal transport. A favored packet is the condom, which may hold up to 5 grams of narcotic. These packets are often visible on plain films. Rupture of even one such packet may be fatal, and endoscopy is contraindicated because of the risk of iatrogenic packet rupture. If the packet(s) appears to be passing intact through the intestinal tract, observation until the packet reaches the rectum is the favored treatment. Some authors advocate the use of whole-bowel irrigation to aid the process.

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 78

Peptic Ulcer Disease and Gastritis

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INTRODUCTION AND EPIDEMIOLOGY

Peptic ulcer disease is a chronic illness manifested by recurrent ulcerations in the stomach and proximal duodenum. Acid and pepsin are thought to be crucial to ulcer development, but the great majority of peptic ulcers are directly related to infection with *Helicobacter pylori* or NSAID use.[1,2] **Gastritis** is acute or chronic inflammation of the gastric mucosa and has various etiologies. **Dyspepsia** is continuous or recurrent upper abdominal pain or discomfort and may be caused by a number of diseases or may be functional.[3] Uncomplicated peptic ulcer disease has an estimated incidence of 0.1% to 0.3% per year, and about 5% to 10% of people living in the Western world will experience a peptic ulcer at some point during their lives.[2] *H. pylori* infection, one of the main risk factors for peptic ulcer disease, is one of the most prevalent human infections in the world, affecting at least 50% of the world's population.[4] The age-adjusted prevalence of *H. pylori* infection is decreasing in industrialized countries, likely due to an improved standard of living and to the increased use of proton pump inhibitors and antimicrobial therapy.[2,3] This may explain the decreasing incidence of peptic ulcer disease in the United States, but this may be partially offset by the widespread use of low-dose aspirin and NSAIDs.[2] Currently, at least a fifth of peptic ulcer disease cases have been found to be *H. pylori*–negative, NSAID-negative, and aspirin-negative.[2] Certain medical conditions such as *Helicobacter heilmannii*, cytomegalovirus infections, Behçet's disease, Zollinger-Ellison syndrome, Crohn's disease, and cirrhosis with portal hypertension may contribute to the development of peptic ulcers.[2] Other risk factors include antiplatelet agents, psychological stress, older age, and African-American ethnicity.[2,5]

PATHOPHYSIOLOGY

Hydrochloric acid and pepsin destroy gastric and duodenal mucosa. Mucus and bicarbonate ion secretions protect mucosa. Prostaglandins protect mucosa by enhancing mucus and bicarbonate production and by enhancing mucosal blood flow, thereby supporting metabolism. The balance between these protective and destructive forces determines whether peptic ulcer disease occurs. *H. pylori* bacteria or NSAIDs are thought to be the causal agents of peptic ulcer disease in most cases.[1,2] Although traditional treatment of peptic ulcers by various modalities heals most ulcers, eradication of *H. pylori* has been shown to accelerate healing and decrease both relapse and rebleeding of ulcers that are not associated with the use of NSAIDs.[2,6]

H. pylori is a spiral, gram-negative, urease-producing, flagellated bacterium that is found living between the mucous gel and the mucosa. The bacterium's production of urease, cytotoxins, proteases, and other compounds is thought to disturb the mucous gel and cause tissue injury. In addition, increased gastrin levels and decreased mucus and bicarbonate production are associated with *H. pylori* infection. Chronic active (usually asymptomatic) gastritis is an almost universal finding with *H. pylori* infection, but only some infected people develop peptic ulcer disease.[2] It is unclear why most infected persons do not develop symptomatic peptic ulcer disease, but it most likely reflects an interaction of factors, including characteristics of host and pathogen (different virulence of strains of bacteria). In 2005, Marshal and Warren were awarded the Nobel Prize in Physiology or Medicine for their discovery of *H. pylori* and its role in gastritis and peptic ulcer disease.

H. pylori is a causative agent of mucosa-associated lymphoid tissue lymphoma, and eradication of infection causes a remission in a sizable percentage of patients with low-grade tumors.[3] In addition, *H. pylori* infection is a risk factor for adenocarcinoma of the stomach. However, because the prevalence of gastric cancer in the United States is very low and the *H. pylori* infection rate is high, other factors undoubtedly are involved. There is some evidence that eradication of the infection reduces the risk of gastric cancer.[3,7,8] *H. pylori* infection has been associated with the development of iron deficiency anemia, with possible mechanisms including decreased iron absorption and/or occult blood loss from chronic gastritis. Eradication therapy plus iron improves hemoglobin levels more than iron alone.[3] Improvement in the platelet count in some patients with idiopathic thrombocytopenic purpura has been demonstrated with *H. pylori* eradication, but more work remains to be done in this regard.[3]

NSAIDs inhibit prostaglandin synthesis, thereby decreasing mucus and bicarbonate production and mucosal blood flow, which allows ulcer formation. Gastrin-secreting tumors produce ulceration due to high levels of acid and pepsin production, but acid alone rarely causes ulceration. However, inhibition of acid secretion may allow ulcers to heal and is the basis for traditional ulcer treatments.

Acute gastritis may be related to ischemia from severe illness (e.g., shock, trauma, severe burns, organ failure) or to the direct toxic effects of agents (e.g., NSAIDs, steroids, bile acids). *H. pylori* infection causes acute and chronic gastritis (both usually asymptomatic). Chronic gastritis may also be caused by autoimmune factors that destroy gastric parietal cells; this results in the loss of acid production and the loss of intrinsic factor production, which in turn cause malabsorption of vitamin B_{12} and, hence, pernicious anemia.

Dyspepsia has multiple causes. Endoscopy of patients with dyspepsia demonstrates that less than 10% have peptic ulcer disease and less

than 1% have gastroesophageal cancer. More than 70% have no definite findings on endoscopy and are said to have "functional" dyspepsia.[9] Patients with functional dyspepsia may have evidence of abnormal gastric emptying, abnormal sensitivity to distention, abnormal ability of the stomach to distend with a meal, abnormalities in acid clearance, and abnormal duodenal sensitivity to acid. In addition, there appears to be an as yet poorly characterized interaction between the stomach and intestine and the CNS, which may contribute to symptoms.[9]

CLINICAL FEATURES

Symptoms are nonspecific; however, burning epigastric pain is the most classic symptom of peptic ulcer disease. The pain also may be described as sharp, dull, an ache, or an "empty" or "hungry" feeling. Pain may be relieved by ingestion of milk, food, or antacids, presumably due to buffering and/or dilution of acid. **Pain recurs as the gastric contents empty, and the recurrent pain may classically awaken the patient at night.** Pain tends to occur daily for weeks, resolve, and then recur in weeks to months. Postprandial pain and nausea may be associated with gastric ulcers; however, food intolerance, retrosternal pain, and belching are not related to peptic ulcer disease.[2] Older patients (>65 years old) frequently will have no symptoms or only mild symptoms or may have more atypical symptoms such as nausea, vomiting, anorexia, weight loss, and bleeding.

A change in the character of typical pain may herald a complication. Abrupt onset of severe or generalized pain may indicate perforation with peritoneal spillage of gastric or duodenal contents. Rapid onset of mid-back pain may be due to posterior penetration into the pancreas, resulting in pancreatitis. Nausea and vomiting may indicate gastric outlet obstruction from scarring or edema. Vomiting of bright red blood or coffee-ground emesis or passage of tarry or melanotic stool or hematochezia may indicate ulcer bleeding.

On physical examination, the only positive finding in patients with uncomplicated peptic ulcer disease may be epigastric tenderness. This finding is neither sensitive nor specific for the diagnosis. Other physical findings may be indicative of complications: a rigid abdomen consistent with peritonitis in perforation; abdominal distention or a succussion splash due to obstruction; or occult or gross rectal blood or blood in the nasogastric aspirate signaling ulcer bleeding.

Epigastric pain, nausea, and vomiting may be present with acute gastritis, but the most common presentation of gastritis is GI bleeding, ranging from occult blood loss in the stool to massive upper GI hemorrhage. Physical findings may be normal, may reflect only the GI bleeding, or may reflect a severe underlying associated illness (as listed earlier).

DIAGNOSIS

A definitive diagnosis of peptic ulcer disease cannot be made on clinical grounds alone. Uncomplicated peptic ulcer disease can be strongly suspected in the presence of a "classic" history, including epigastric burning pain; relief of pain with ingestion of milk, food, or antacids; and night pain accompanied by "benign" physical examination findings, including normal vital signs with or without mild epigastric tenderness. The differential diagnosis of epigastric pain is extensive and, in addition to peptic ulcer disease, includes gastritis, gastroesophageal reflux disease, cholelithiasis, pancreatitis, hepatitis, abdominal aortic aneurysm, gastroparesis, and functional dyspepsia. Careful history taking may elicit features that point away from peptic ulcer disease: burning pain radiating into the chest, water brash, and belching may suggest gastroesophageal reflux disease; more severe pain radiating to the right upper quadrant and around the right or left side suggests cholelithiasis; radiation through to the back indicates pancreatitis or abdominal aortic aneurysm; chronic pain, anorexia, or weight loss may indicate gastric cancer. Myocardial ischemic pain may also present as epigastric pain and should be strongly considered in the appropriate clinical setting.

Physical examination findings may suggest other diagnoses: right upper quadrant tenderness points to cholelithiasis or hepatitis, an epigastric mass to pancreatitis (pseudocyst) or pancreatic or gastric neoplasm, a pulsatile mass to abdominal aortic aneurysm, jaundice to hepatitis, and peritoneal findings to an acute abdomen.

TABLE 78-1 "Alarm Features" for Endoscopy

- Age >50 y, with new-onset symptoms
- Unexplained weight loss
- Persistent vomiting
- Dysphagia or odynophagia
- Iron deficiency anemia or GI bleeding
- Abdominal mass or lymphadenopathy
- Family history of upper GI malignancy

ANCILLARY TESTING

Ancillary tests may help exclude peptic ulcer disease complications and narrow the differential diagnosis. Normal results for CBC rule out anemia from chronic GI bleeding due to peptic ulcer disease, gastritis, or cancer (but do not rule out acute blood loss). Elevated liver function test results may indicate hepatitis, and an elevated lipase level may indicate pancreatitis. An acute abdominal series may show free air associated with perforation. A limited ED US examination may show gallstones or an abdominal aortic aneurysm. An ECG and cardiac enzyme determination are indicated if there is a suspicion of myocardial ischemic pain.

The gold standard for diagnosis of peptic ulcer disease is visualization of an ulcer by **upper GI endoscopy.**[2] Although not all patients with undiagnosed dyspepsia require endoscopy, those with "alarm features" do[2,9] (**Table 78-1**). Alarm features raise the index of suspicion for gastric or esophageal cancer, as well as other potentially serious conditions, but the features are not specific.

***H. pylori* Tests** Because many peptic ulcers are caused by *H. pylori* infection and eradication of *H. pylori* dramatically decreases the ulcer recurrence rate, it is important to know how to diagnose infection. *H. pylori* infection can be diagnosed by endoscopic tests, including the rapid urease test, histologic study, and culture, all of which rely on a biopsy of the gastric mucosa.[10] Noninvasive tests include serologic tests, urea breath tests, and stool antigen tests.[10,11]

The **rapid urease test** detects the presence of urease in a biopsy specimen (presumptive evidence of *H. pylori* infection) with >85% to 95% sensitivity and >95% specificity.[10] Histologic studies allow direct assessment of *H. pylori* infection and culture of the organism, but these tests require highly trained technicians in appropriate facilities and are not widely available. The major disadvantage of all the aforementioned tests is the cost in time, dollars, and potential complications of endoscopy.

Serologic studies detect **immunoglobulin G antibodies to *H. pylori*** and are readily available, but the sensitivity and specificity are not very good.[11] Serologic studies are not useful as a test of cure, because antibodies remain for several months to years after eradication of infection.

The **urea breath test** relies on the presence of urease produced by *H. pylori*. Urea labeled with carbon-13 or carbon-14 instead of carbon-12 is ingested and, in the presence of bacterial urease, is broken down into labeled carbon dioxide and ammonia. The labeled carbon dioxide is detected in the breath later. Sensitivity and specificity are >90%.[11,12] The urea breath test can be used to determine the presence of infection after eradication therapy.[10] *H. pylori* antigens can be detected in the stool with about 95% sensitivity and specificity.[11] Testing performed ≥4 weeks after completion of *H. pylori* eradication therapy is useful as a test of cure.[10] The sensitivity of all tests that rely on active infection with *H. pylori* is decreased significantly by recent treatment with proton pump inhibitors, histamine-2 (H_2) antagonists, antibiotics, and bismuth compounds, and most recommend stopping these agents for 2 to 4 weeks before testing.[11]

TREATMENT

Traditional ulcer therapy (proton pump inhibitors, H_2 receptor antagonists, sucralfate, and antacids) heals the ulcer, relieves pain, and prevents complications but does not prevent recurrence. Treatment of *H. pylori* infection dramatically decreases the recurrence rate and accelerates ulcer healing.[2,6] If NSAID-associated ulcers are present, the offending agent should be stopped whenever possible.

Traditional ED treatment would entail initiating a trial of a proton pump inhibitor or an H_2 receptor antagonist, with antacids for breakthrough pain and referral to a primary care provider to direct evaluation and subsequent treatment. Current literature supports using proton pump inhibitors as first-line noneradication therapy for peptic ulcers.[6] This usually remains the best option. Practice guidelines and reviews support treatment of known *H. pylori*–positive dyspeptic patients with antimicrobial and antisecretory therapy followed by endoscopic study only in those with persistent symptoms.[3] It might be reasonable for the ED physician to order a test for *H. pylori*, begin symptomatic therapy after the *H. pylori* test is obtained, and refer the patient for early follow-up with a primary care provider for initiation of antibacterial therapy if the test results are positive. This specific strategy has not been tested. However, there is some evidence that a "test-and-treat" strategy in the ED using the urea breath test to identify patients positive for *H. pylori* may be both beneficial and feasible in an area with a known high prevalence.[12] Immediate referral for definitive diagnosis is mandated if alarm features are present (Table 78-1).

PROTON PUMP INHIBITORS

Proton pump inhibitors (e.g., esomeprazole, lansoprazole, omeprazole, pantoprazole) decrease acid production by irreversibly binding with an H^+K^+ ATPase molecule (proton pump) located on the gastric parietal cell, thus blocking hydrogen ion secretion.[11] Proton pump inhibitors are most effective if taken 30 to 60 minutes prior to a meal. **Proton pump inhibitors generally heal ulcers faster than H_2 receptor antagonists and also have some in vitro inhibitory effect against *H. pylori*.**[11] Proton pump inhibitors are metabolized in the liver by the cytochrome P450 system and therefore may decrease the metabolism of many other drugs. In addition, proton pump inhibitors may inhibit the absorption of drugs that rely on gastric acidity. Proton pump inhibitors are well tolerated by most patients; however, headache and GI upset can occur.[11] Long-term use of proton pump inhibitors may be associated with *Clostridium difficile*–associated diarrhea, fracture and pneumonia risk, chronic kidney disease, and hypomagnesemia.[11] Discontinuing a proton pump inhibitor may result in rebound acid hypersecretion and dyspeptic symptoms.[11] Symptoms can be minimized by gradually discontinuing the proton pump inhibitor over a few weeks, and replacing it with an H_2 receptor antagonist or antacids. All proton pump inhibitors, even those available over the counter, appear to have similar efficacy in treating peptic ulcer disease and are the treatment of choice in a patient who develops an ulcer while taking NSAIDs and must continue NSAID therapy.[6,13]

H_2 RECEPTOR ANTAGONISTS

H_2 receptor antagonists competitively inhibit the actions of histamine on the H_2 receptors of the gastric parietal cells. All four H_2 receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine) heal ulcers approximately equally and are available in over-the-counter preparations.[11] **Because of renal excretion, make dosage adjustments in patients with renal failure**. Long-term use of H_2 receptor antagonists can lead to tolerance, and discontinuation can lead to rebound hypersecretion of acid.[11] Side effects are uncommon but can include headache, confusion, lethargy, depression, and hallucinations.[11] Cimetidine has more significant drug interactions than do the other H_2 receptor antagonists due to inhibition of cytochrome P450 activity.[11]

OTHER AGENTS

Sucralfate, an aluminum hydroxide complex of sucrose, appears to protect the ulcer from acid exposure by forming a sticky gel that adheres to the ulcer crater and allows healing to occur but does not relieve pain as well as proton pump inhibitors and H_2 receptor antagonists.[11] Sucralfate has few side effects but can cause constipation and aluminum toxicity, as well as inhibit absorption of a number of medications.[11] **Antacids** heal ulcers by buffering gastric acid. Magnesium- and aluminum-containing antacids can inhibit absorption of drugs and should be avoided in patients with renal insufficiency or renal failure. In renal failure, aluminum can accumulate and cause osteoporosis and encephalopathy, and hypermagnesemia can also result. Due to the simplicity of proton pump inhibitor and H_2 receptor antagonists dosing requirements, antacids currently are used mainly on an as-needed basis for ulcer pain until healing occurs.

Although NSAIDs should be stopped in patients with peptic ulcer disease whenever possible, **misoprostol** may prevent ulcer formation in those concurrently receiving NSAID therapy but has not been proven to heal ulcers.[11] Misoprostol is a prostaglandin analogue that may act by increasing mucus and bicarbonate production and by increasing mucosal blood flow. Because it is an abortifacient, do not use misoprostol in women who could become pregnant.[11]

H. PYLORI ERADICATION

If *H. pylori* infection is diagnosed in the presence of peptic ulcer disease, eradication is clearly indicated but has become more challenging due to increasing antibiotic resistance.[3,6,8] Multiple regimens have been proposed and studied, and most commonly, "triple therapy" with a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole has been prescribed.[3,6,8,11] Authorities in the United States recommend 10- to 14-day regimens for the best cure rates, and tailoring decisions regarding first-line therapy on local antibiotic resistance.[3,6,8,11,14] In areas where clarithromycin resistance is high, quadruple therapy or sequential therapy may be preferred.[11] If *H. pylori* is not eradicated after treatment with two different regimens, resistance testing should be considered.[11]

Patients generally do not present to the ED with a definitive diagnosis of *H. pylori*–positive peptic ulcer disease but rather with a symptom, such as epigastric pain. If appropriate history, physical examination, and laboratory evaluation result in a physician's impression of "possible peptic ulcer disease" or "dyspepsia," the physician is left with three main options: empiric treatment with conventional antiulcer medication, immediate referral for definite diagnosis (endoscopic study), or noninvasive testing for *H. pylori* followed by antibiotic therapy for patients with positive test results.

COMPLICATIONS

HEMORRHAGE

Upper GI bleeding is the most common cause of GI-related hospital admissions, and of those, peptic ulcer disease is the most common underlying etiology.[1,15,16] Due to advances in endoscopic and medical management of peptic ulcer disease, the overall incidence of upper GI bleeding is decreasing; however, the mortality rate has remained the same at 10% to 14%.[2,15] Bleeding from peptic ulcers is most commonly seen in the elderly.

ED treatment for ulcer bleeding focuses on restoring hemodynamic stability by IV administration of isotonic saline solution and packed red blood cells (see Chapter 75, "Upper Gastrointestinal Bleeding" for details of treatment). Transfusion of red cells is recommended for hemoglobin levels less than 7 grams/dL or in patients who are hypotensive with severe GI bleeding before the hemoglobin level is known or if it falls below that threshold.[1] Early upper endoscopy is recommended in most patients to confirm the diagnosis and target endoscopic treatment.[1,15] Before endoscopy, a bolus dose of a proton pump inhibitor followed by a continuous infusion can be considered, as can use of a prokinetic agent, such as erythromycin, given IV. Neither has been consistently shown to improve clinical outcomes; however, erythromycin administered 30 minutes prior to endoscopy may improve visualization of the gastric mucosa.[1] There is no clinical benefit to either a nasogastric or orogastric tube.[1]

Most patients should undergo upper GI endoscopy within 24 hours for diagnostic, prognostic, and treatment purposes.[1,15,16] Lesions can be described using the Forrest classification to predict risk of rebleeding.[15] Ranging from highest to lowest risk, the classification is as follows: active spurting of blood (Ia); active oozing (Ib); nonbleeding visible vessel (IIa); adherent clot (IIb); flat pigmented spot (IIc); and an ulcer with a clean base (III).[15] Endoscopic management is indicated for those ulcers at high risk for rebleeding. Treatment through endoscopy

includes injection therapy (epinephrine, sclerosing agents), thermal therapy (electrocoagulation, heater probe, argon plasma coagulation), and mechanical clipping and banding.[1,15,16] All of these treatments stop bleeding, prevent recurrences, and decrease transfusion rates and length of hospital stay. The technique chosen depends on the equipment available and the experience of the endoscopist. Recently, topical therapy using a hemostatic spray and endoscopic US-guided angiotherapy has shown promising results, but additional studies are needed to confirm their utility, efficacy, and safety.[15]

Hospitalization in an intensive care setting is indicated for patients with significant upper GI bleeding due to peptic ulcers. If clinical and endoscopic features suggest a low risk of rebleeding, a ward bed may be acceptable.

PERFORATION

Perforation occurs in 2% to 14% of ulcers.[17] Its presentation is heralded by the abrupt onset of severe epigastric pain as gastric or duodenal contents spill into the peritoneal cavity, followed by the development of chemical and then bacterial peritonitis. Mortality can be as high as 10% to 40%, depending on age, comorbidities, and timeliness of diagnosis and management.[2,17] Patients may not have a history of peptic ulcer disease and may in fact have no history of ulcer-like symptoms; thus, a high index of suspicion based on history of present illness and physical exam is necessary. Elderly patients may not have dramatic pain or impressive peritoneal findings.

When the diagnosis is suspected, obtain appropriate laboratory tests, including a CBC, type and cross-match, and a lipase level; place two large-bore IV lines; provide oxygen for hypoxemia, and place a cardiac monitor; insert a nasogastric tube with suction; and obtain an acute abdominal series. Free air seen on radiographs in the setting of peritonitis on exam and appropriate history are enough to justify broad-spectrum antibiotics and prompt surgical consultation.[17] About 60% to 75% of patients with perforated peptic ulcer have free air on an upright chest radiograph.[18,19] If the plain films are ordered and do not demonstrate free air, then an abdominal CT should be ordered because the sensitivity is reported to be 98% and it can also demonstrate other potential pathology.[17-19] In some cases, nonsurgical therapy may be recommended, but operative intervention is the standard in the United States.

OBSTRUCTION

Obstruction occurs because of scarring of the gastric outlet due to chronic peptic ulcer disease, edema due to an active ulcer, or some combination of both. Resulting symptoms include abdominal fullness, nausea, and vomiting, and signs may include abdominal distention and a succussion splash. Dehydration and electrolyte imbalances may occur. Treatment includes rehydration with IV fluids, correction of electrolyte abnormalities, and relief of distention with nasogastric suction. Hospitalization is almost always indicated. The outlet may open as edema subsides, but surgical correction is often necessary.

DISPOSITION AND FOLLOW-UP

Patients with complications always require consultation, and most require admission to an appropriate inpatient unit based on the diagnosis and hemodynamic stability. Most patients with epigastric pain or dyspepsia do not leave the ED with a definitive diagnosis, but, if critical diagnoses (e.g., abdominal aortic aneurysm or myocardial ischemia) are still in the differential, obtain consultation for admission, and further evaluation is indicated. When uncomplicated peptic ulcer disease, gastritis, or dyspepsia is strongly suspected, the great majority of patients can be discharged with acid-suppressive therapy with a proton pump inhibitor or an H_2 receptor antagonist and instructions to follow up with their primary care providers. If alarm features (indicating possible cancer or bleeding) are present, obtain consultation for early endoscopy.

Discharge instructions should include an explanation of the diagnosis and home treatment, specific follow-up instructions, and warning symptoms that should prompt immediate reevaluation. The explanation of the diagnosis should specify that peptic ulcer disease is a presumptive diagnosis and that more definitive diagnostic testing may be necessary. Instructions for home treatment should include a reminder to take medications as directed; a warning against use of alcohol, tobacco products, and aspirin or other NSAIDs; and a recommendation to avoid foods that appear to upset the individual's "stomach." Specific follow-up instructions should include the name and phone number of the appropriate provider whenever possible and a time frame for reevaluation, generally 24 to 48 hours if not improving or 1 to 2 weeks if improving. Warning symptoms that merit immediate reevaluation include those that may be attributed to ulcer complications or confounding illness: worsening pain, increased vomiting, hematemesis or melena, weakness or syncope, fever, chest pain, radiation of pain to the neck or back, and shortness of breath.

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CHAPTER 79

Pancreatitis and Cholecystitis

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Christine R. Stehman

PANCREATITIS

INTRODUCTION/EPIDEMIOLOGY

Pancreatitis is an inflammatory process of the pancreas that may be limited to just the pancreas, may affect surrounding tissues, or may cause remote organ system dysfunction. Most patients will have only one episode of acute pancreatitis, whereas 15% to 30% will have at least one recurrence.[1-3] Between 5% and 25% of patients will ultimately develop chronic pancreatitis.[2,3]

Most cases (~80%) involve only mild inflammation of the pancreas, a disease state with a mortality rate of <1%, which generally resolves with only supportive care.[1,4] A small proportion of patients suffer from more severe disease that may involve pancreatic necrosis, inflammation of surrounding tissues, and organ failure.[5,6]

Factors associated with acute pancreatitis are listed in **Table 79-1**.[7-11] Most cases are related to either gallstones or alcohol consumption. About 5% of all patients who undergo endoscopic retrograde cholangiopancreatography for treatment of gallstones develop pancreatitis within 30 days.[7]

Alcohol use and pancreatitis have a complex relationship, thought to be founded in toxicity and immunologic mechanisms.[12]

MEDICATIONS

Over 500 drugs have been linked to acute pancreatitis, but together, they account for fewer than 2% of cases. **Table 79-2** lists the drugs found to be most well linked to acute pancreatitis based on number of case reports and recurrence after drug reexposure.[13]

Medications associated with acute pancreatitis can be categorized into three groups: antiretrovirals, chemotherapy, and immunosuppressants. Patients taking these medications are at particular risk of severe disease because of the underlying disease combined with the medication side effects. 2′,3′-Dideoxyinosine can cause potentially fatal pancreatitis, whereas patients receiving the antiretrovirals lamivudine and nelfinavir are at lower risk.[13]

Cancer patients undergoing chemotherapy with one or more of seven medications have a risk of pancreatitis complicating the disease course.

TABLE 79-1 Causes of Acute Pancreatitis

Common	Gallstones (35%–75%)[8] Alcohol (25%–35%)[8] Idiopathic (10%–20%); increases with age[9]
Uncommon	Hypertriglyceridemia (fasting triglycerides >1000 milligrams/dL) (1%–4%)[10] Endoscopic retrograde cholangiopancreatography[7] Drugs (1.4%–2%); usually mild disease
More uncommon (total <8% of cases)	Abdominal trauma Postoperative complications, especially post–cardiopulmonary bypass Hyperparathyroidism Infection (bacterial, viral, or parasitic) Autoimmune disease Tumor (pancreatic, ampullary) Hypercalcemia Cystic fibrosis
Rare	Ischemia Posterior penetrating ulcer Toxin exposure
Unknown	Congenital abnormalities[11]

These medications are L-asparaginase, cisplatin, cytarabine, ifosfamide, mercaptopurine, pegaspargase, and tamoxifen.[13] These agents are used to treat leukemias, lymphomas, sarcomas, and breast, cervical, lung, ovarian, and testicular cancers.

Patients receiving azathioprine for posttransplantation immunosuppression or treatment of inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease are also at risk of developing pancreatitis.[13]

PATHOPHYSIOLOGY

The pathophysiology of pancreatitis is not completely understood. Under normal circumstances, trypsinogen is produced in the pancreas and secreted into the duodenum where it is converted into the protease trypsin. In acute pancreatitis, for unclear reasons, although possibly related to transient obstruction of the pancreatic duct, trypsin is activated within the pancreatic acinar cells. Activation continues in an unregulated fashion, and elimination of activated trypsin is inhibited, resulting in high pancreatic levels of activated trypsin. Activated trypsin in turn activates other digestive enzymes, complements, and kinins, leading to pancreatic autodigestion, injury, and inflammation. Pancreatic injury activates local production of inflammatory mediators, which cause further inflammation.[14,15] Fortunately, most cases never progress beyond local inflammation. However, in a minority of cases, termed necrotizing pancreatitis, pancreatic injury progresses to involve surrounding tissue or possibly remote organ systems.[16] The release of inflammatory mediators from the pancreas, in particular from the acinar cells, and extrapancreatic organs such as the liver leads to remote organ injury and failure, the systemic inflammatory response syndrome, multiorgan failure, and even death.[14-16]

TABLE 79-2 Drugs Associated With Acute Pancreatitis[13]

- Acetaminophen
- Amiodarone
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (enalapril and losartan)
- Antibiotics (erythromycin, metronidazole tetracycline, trimethoprim-sulfamethoxazole)
- Antiepileptics (carbamazepine, valproic acid)
- Azathioprine
- Cannabis
- Chemotherapy agents (6-mercaptopurine, cisplatin, L-asparaginase, ifosfamide, tamoxifen, cytarabine, pegaspargase)
- Codeine (and other opiates)
- Dexamethasone (and other steroids)
- Didanosine
- Diuretics (chlorothiazide, hydrochlorothiazide, furosemide)
- Estrogens
- Mesalamine
- Methimazole
- Pravastatin/simvastatin
- Tuberculosis antibiotics (dapsone, isoniazid, rifampin)

CLINICAL FEATURES

HISTORY AND PHYSICAL EXAMINATION

Acute pancreatitis causes acute, severe, and persistent abdominal pain, usually associated with nausea, vomiting, anorexia, and decreased oral intake.[17] The pain is located in the epigastrium or occasionally in one or both upper quadrants. Pain may radiate to the back, chest, or flanks. Pain may worsen with oral intake or lying supine and may improve with sitting up with the knees flexed.[18-20] Other symptoms include abdominal distention, diaphoresis, hematemesis, and shortness of breath. **Pain described as lower abdominal pain or dull or colicky pain is highly unlikely to be pancreatitis**.[19]

Vital signs may be abnormal, with tachycardia, tachypnea, fever, or hypotension. Pain is often associated with guarding and decreased bowel sounds.[17] Occasionally patients will be jaundiced, pale, or diaphoretic.

Rare physical findings associated with late, severe necrotizing pancreatitis include Cullen's sign (bluish discoloration around the umbilicus signifying hemoperitoneum), Grey-Turner sign (reddish-brown discoloration along the flanks signifying retroperitoneal blood or extravasation of pancreatic exudate), and erythematous skin nodules from focal subcutaneous fat necrosis.[20,21]

DIAGNOSIS

Formal diagnosis is based on at least two of three criteria: (1) clinical presentation consistent with acute pancreatitis, (2) a serum lipase or amylase value significantly elevated above the upper limit of normal, or (3) imaging findings characteristic of acute pancreatitis (IV contrast-enhanced CT, MRI, or transabdominal US).[19,22] The differential diagnosis is wide and consists of all causes of upper abdominal pain, as detailed in Chapter 71, "Acute Abdominal Pain."

LABORATORY STUDIES

There is no gold standard laboratory diagnosis for acute pancreatitis. Two current guidelines recommend that the amylase or lipase value be at least three times the upper limit of normal[19,22]; some recommend a lipase of two times normal or an amylase of three times normal in a patient with the appropriate clinical presentation[23]; and some recommend that any elevation above normal is consistent with the diagnosis.[17] Normal levels for amylase and lipase are based on values in young, healthy patients, making it difficult to determine applicable levels for older patients or those with multiple comorbidities.[23] Consequently, the combination of an elevated laboratory value with a clinical presentation consistent with pancreatitis is key for diagnosis.[19]

Amylase is not a good choice for diagnosis.[19] Amylase rises within a few hours after the onset of symptoms, peaks within 48 hours, and normalizes in 3 to 5 days.[23] About 20% of patients with pancreatitis, most of whom have alcohol- and hypertriglyceridemia-related disease, will have a normal amylase.[24] Because of these facts, amylase has a sensitivity of about 70%, with a positive predictive value ranging from 15% to 72%.[17] Amylase can be elevated in multiple non–pancreas-related diseases, such as renal insufficiency, salivary gland diseases, acute appendicitis,

cholecystitis, intestinal obstruction or ischemia, and gynecologic diseases, lowering its specificity for pancreatitis.[17,24]

Lipase is more specific to pancreatic injury and remains elevated for longer after the onset of symptoms than amylase. Although lipase may be elevated in diabetes and some nonpancreatic diseases such as renal disease, appendicitis, and cholecystitis, it is less associated with nonpancreatic diseases than amylase.[19,25] Lipase is more sensitive both in patients with a delayed presentation and in pancreatitis associated with alcohol use and hypertriglyceridemia.[23]

If a combination of elevated lipase and amylase is used to diagnose pancreatitis, the diagnosis is more specific and less sensitive than when using elevation in only one value; however, there is no evidence that adding amylase to a nondiagnostic lipase improves diagnostic accuracy over lipase alone.[23]

The urine trypsinogen-2 dipstick test is a rapid, noninvasive test with high sensitivity (82%) and specificity (94%).[26] However, given its current limited availability, it is not included as part of the diagnostic criteria for pancreatitis.[22]

In addition to serum lipase and amylase, obtain blood studies to evaluate renal and liver function, electrolyte status, glucose level, WBC count, and hemoglobin/hematocrit. These lab results help the clinician predict disease severity and outcome (detailed below), optimize the clinical status of the patient, identify complications that need immediate treatment (cholangitis, organ failure), and assess effectiveness of treatment.

An **alanine aminotransferase** of >150 U/L within the first 48 hours of symptoms predicts gallstone pancreatitis with a greater than 85% positive predictive value.[27]

IMAGING

Imaging can identify the cause of pancreatitis and can identify complications and severity. For patients with acute pancreatitis where gallstones have not been excluded, obtain a transabdominal US in the ED to detect gallstone pancreatitis.[3,22,28] For any patient with respiratory complaints, obtain a chest radiograph to evaluate for pleural effusions and pulmonary infiltrates, both associated with more severe pancreatitis.

In patients who meet the clinical presentation and laboratory criteria, routine early CT, with or without IV or PO contrast, is not recommended for multiple reasons. Most patients have uncomplicated disease and are readily diagnosed by clinical and laboratory criteria. There is no evidence that early CT, with or without contrast, improves clinical outcomes, possibly because CT findings are delayed compared to clinical presentation and may underestimate disease severity.[22,29,30] Peripancreatic fluid collections or pancreatic necrosis detected by CT of any kind within the first few days of symptoms generally require no treatment, and the complete extent of these local complications is usually not appreciated until at least 3 days after onset of symptoms. The magnitude of morphologic change on imaging studies does not necessarily correlate with disease severity.[31] Finally, IV contrast infusion can cause allergic reactions, nephrotoxicity, and worsening of pancreatitis.[32]

If the clinical diagnosis of acute pancreatitis is in doubt, consider further evaluation with IV contrast **abdominal CT**. Characteristic findings include: (1) pancreatic parenchymal inflammation with or without peripancreatic fat inflammation; (2) pancreatic parenchymal necrosis or peripancreatic necrosis; (3) peripancreatic fluid collection; or (4) pancreatic pseudocyst.[19,33] **Figure 79-1A–D** compares CT image of a normal pancreas to images in various complications. Although noncontrast MRI is not readily available to the ED, this imaging modality can identify the complications of pancreatitis and choledocholithiasis. It can be an alternative for patients with renal failure, patients who are allergic to IV contrast, or pregnant patients.[34]

TREATMENT

Treatment is supportive and symptom based (Table 79-3). No specific medication effectively treats acute pancreatitis; however, early aggressive hydration decreases morbidity and mortality.[35-37] The benefit of fluid resuscitation may result from increased micro- and macrocirculatory support of the pancreas, which prevents complications such as pancreatic necrosis.[38]

Provide fluid resuscitation. Fluid loss results from vomiting, third spacing, increased insensible losses, and decreased oral intake. Patients generally need a total of 2.5 to 4 L of fluid over the first 12 to 24 hours.[19,22] The specific rate of fluid delivery depends on the patient's clinical status. In the situation of renal or heart failure, deliver fluid more slowly to prevent complications such as volume overload, pulmonary edema, and abdominal compartment syndrome. Crystalloids are the resuscitation fluids of choice. Normal saline in large volumes may cause a nongap hyperchloremic acidosis and can worsen pancreatitis, possibly by activating trypsinogen and making acinar cells more susceptible to injury.[19,39] A single randomized study showed a decreased incidence of systemic inflammatory response syndrome in patients who received lactated Ringer's instead of 0.9% normal saline.[39] Regardless of which fluid is selected, monitor vital signs and urine output for response to hydration.

Control pain and nausea. Pain control is best achieved with IV opioid analgesics. Initially, place patients on NPO (nothing by mouth) status and administer antiemetics. There is no benefit to nasogastric intubation.

Prolonged bowel and pancreas rest increases gut atrophy and bacterial translocation, leading to infection and increasing morbidity and mortality.[40] In the ED, if nausea and vomiting have resolved and pain has decreased, transition the patient to oral pain medications and small amounts of food.[41] A low-fat solid foods diet provides more calories than a clear liquid diet and is safe.[42]

Acute pancreatitis by itself is not a source of infection, and prophylactic use of antibiotics and antifungals is not recommended.[43] Administer antibiotics if a source of infection is demonstrated, such as cholangitis, urinary tract infection, pneumonia, or infected pancreatic necrosis.[43]

COMPLICATIONS OF ACUTE PANCREATITIS

Although most patients with acute pancreatitis have mild uncomplicated disease, a small percentage of patients have more severe disease. In the ED, it is difficult to distinguish disease severity, because most patients present so early in the disease course that complications that define moderately severe or severe disease are not evident. Moderately severe acute pancreatitis is characterized by transient organ failure (<48 hours), local complications, or systemic complications. Severe disease includes one or more local or systemic complications and persistent organ failure (>48 hours). Critical acute pancreatitis is defined as persistent organ failure and infected pancreatic necrosis.[44]

Local complications, including acute peripancreatic fluid collections, pancreatic pseudocyst, acute pancreatic or peripancreatic necrosis, walled off necrosis, gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic inflammation/necrosis, are not usually well demonstrated on CT scan until at least 72 hours after the onset of symptoms.[16] Suspect local complications in patients who have persistent or recurrent abdominal pain, an increase in pancreatic enzyme levels after an initial decrease, new or worsening organ dysfunction, or sepsis (fever, increased WBC count).

Organ failure can be seen in any system, but three organ systems are particularly susceptible: cardiovascular, respiratory, and renal. Because of the susceptibility of these three organ systems, pay special attention during the patient's initial evaluation.

Other possible complications of acute pancreatitis are listed in **Table 79-4.**

PREDICTION OF DISEASE SEVERITY

Many different scoring systems exist, including the Ranson criteria, Acute Physiology and Chronic Health Examination-II, modified Glasgow score, Bedside Index for Severity in Acute Pancreatitis, and Balthazar CT Severity Index. These scoring systems include many data points, some of which are not collected until at least 48 hours after presentation, limiting their utility in the ED.[45] None of these scoring systems is superior to another, and all have high false-positive rates.[46] **Systemic inflammatory response syndrome at admission and persistent at 48 hours predicts severe acute pancreatitis more simply and as accurately as the various scoring systems.**[6,46,47] **Besides systemic inflammatory response syndrome, a number of other clinical findings at initial assessment are associated**

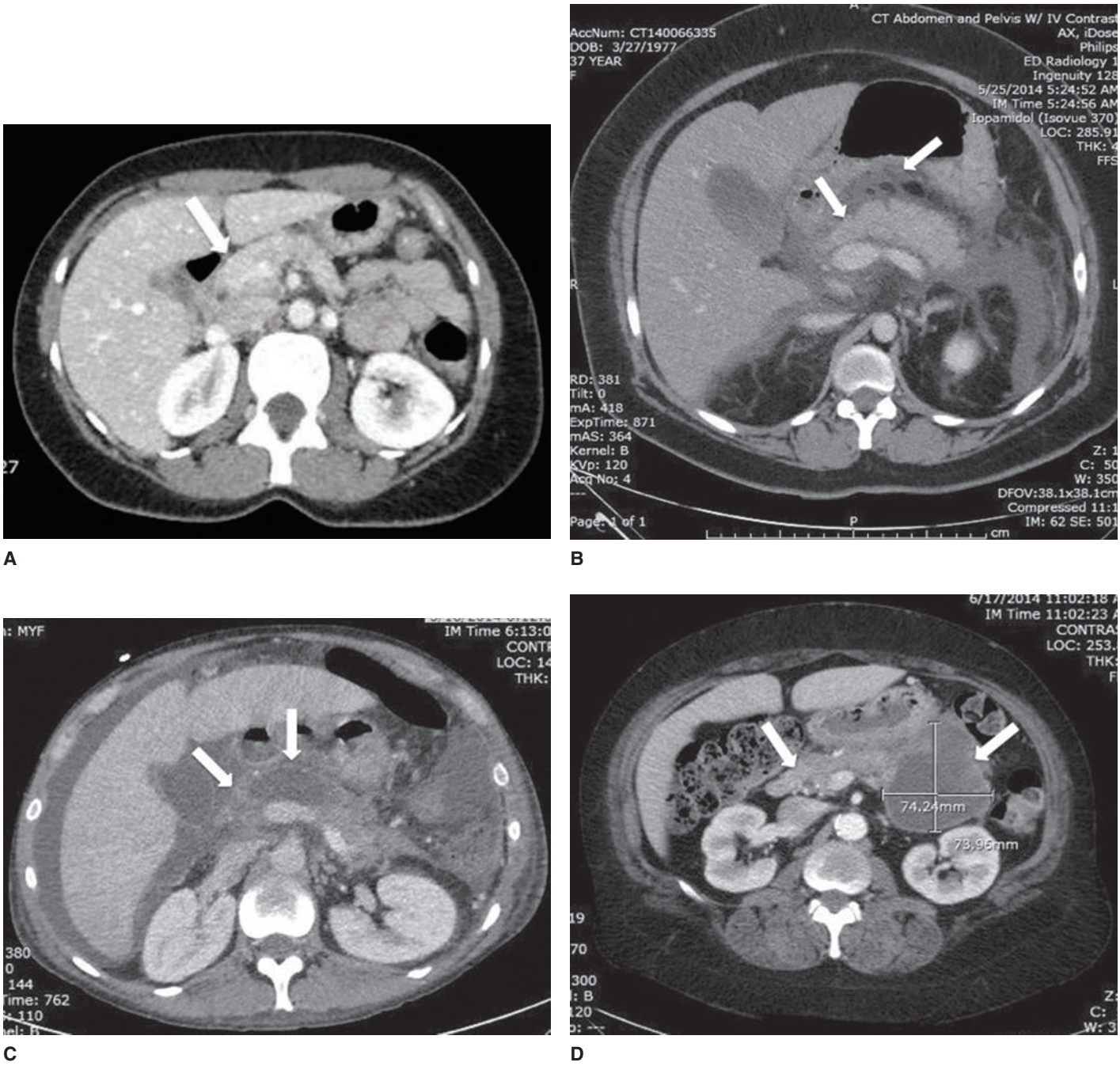

FIGURE 79-1. Abdominal IV contrast-enhanced CT scans showing: **A.** normal pancreas (*arrow*) with smooth outer contours, clear demarcation between pancreas and surrounding tissues, and without peripancreatic fluid; **B.** mild pancreatitis with indistinct pancreatic borders (*left arrow*), pancreatic edema, and peripancreatic fluid (*right arrow*); **C.** edematous pancreas with indistinct borders (*left arrow*) and area of nonenhancing parenchyma pancreatic necrosis with area of acute pancreatic necrosis (low attenuation representing nonenhancing parenchyma; *right arrow*); and **D.** edematous pancreas with indistinct pancreatic borders (*left arrow*) and a pseudocyst in the pancreatic tail (*right arrow*). [Images contributed by Bart Besinger, MD, FAAEM.]

with severe disease. These findings include patient characteristics (age >55 years, obesity, altered mental status, comorbidities), laboratory findings (BUN >20 milligrams/dL or rising; hematocrit >44% or rising; increased creatinine), and radiologic findings (many or large extrapancreatic fluid collections, pleural effusions, pulmonary infiltrates).[16,35,48]

Overall, acute pancreatitis has a mortality rate of approximately 1%.[4] Moderately severe and severe disease mortality rates are 5% and 30%, respectively.[6,49] Most patients who die do so from multiorgan failure. The sensitivity of systemic inflammatory response syndrome on admission for mortality is 100% with a specificity of 31%, whereas the sensitivity and specificity of systemic inflammatory response syndrome at 48 hours (persistent systemic inflammatory response syndrome) are 77% to 89% and 79% to 86%, respectively.[6,47] Systemic inflammatory response syndrome at admission and 48 hours, combined with patient characteristics (age, comorbidities, and obesity) and response to treatment, helps predict outcome.

DISPOSITION AND FOLLOW-UP

Patients with nonbiliary pancreatitis whose pain can be controlled in the ED and who can tolerate oral feeding can be discharged. Patients who are discharged from the ED should be referred for appropriate follow-up to help prevent recurrence.

Consider admission for a first bout of acute pancreatitis, for any case of biliary pancreatitis, and for patients needing frequent IV pain

TABLE 79-3 Treatment of Acute Pancreatitis

Treatment	Comments
Aggressive crystalloid therapy	Lactated Ringer's preferably 2.5–4 L, at least 250–500 mL/h or 5–10 mL/kg/h Use caution in congestive heart failure, renal insufficiency Monitor response: – Hematocrit 35%–44% – Maintain normal creatinine – Heart rate <120 beats/min – Mean arterial pressure 65–85 mm Hg – Urine output 0.5–1 mL/kg/h (if no renal failure)
Vital signs/pulse oximetry	Monitor closely/frequently; initially at least every 2 h, but patients may require more frequent monitoring
Electrolyte repletion	Correct low ionized calcium, hypomagnesemia Control hyperglycemia
Pain control	Parenteral narcotics
Supplemental oxygen	As needed for respiratory insufficiency
Antiemetics	Control nausea/vomiting NPO status with early transition back to oral intake Nasogastric tube/suction typically not indicated
Antibiotics	If known or strongly suspected infection, give appropriate antibiotics based on cause Not indicated prophylactically or for mild pancreatitis
Consultation for endoscopic retrograde cholangiopancreatography	In first 24 h for those with documented biliary obstruction or cholangitis

Abbreviation: NPO = nothing by mouth.

medication, not tolerating oral intake because of vomiting or increasing pain, with persistent abnormal vital signs, or with any signs of organ insufficiency (e.g., increased creatinine).

Admit to the intensive care unit a patient with severe pancreatitis or anyone who meets local criteria for an intensive care or at least an intermediate care unit admission. Biliary pancreatitis requires either admission by surgeon or early surgical consultation for consideration of early cholecystectomy.[50] Cholecystectomies in patients not suffering from documented gallstone pancreatitis are associated with increased recurrence of acute pancreatitis.[51]

Patients with cholangitis or known biliary obstruction on admission may benefit from early endoscopic retrograde cholangiopancreatography.[52] Early routine endoscopic retrograde cholangiopancreatography in patients without one of these two complications does not improve mortality or modify or prevent local complications.[52]

SPECIAL CONSIDERATIONS

CHRONIC PANCREATITIS

Chronic pancreatitis is a continuum of acute pancreatitis. From 5% to 25% of patients can progress to chronic pancreatitis.[2,3] Progression is most common in alcohol-induced disease, but may happen in any situation.[2,3]

Attacks are similar to acute pancreatitis. The goal of treatment is hydration and pain and nausea control. The mortality risk of chronic pancreatitis recurrences is generally lower than that of acute pancreatitis.[2,3]

CHOLECYSTITIS

INTRODUCTION AND EPIDEMIOLOGY

Cholecystitis is inflammation of the gallbladder that is usually caused by an obstructing gallstone.

Gallstones produce disease states, including acute cholecystitis, that vary considerably in their severity, clinical presentation, and management strategies. In the United States, the prevalence of gallstones is 8% among men and 17% among women.[53] Prevalence increases with age and with increasing body mass index. Bariatric surgery is also a risk factor for the development of gallstones.[54] The vast majority of gallstones are asymptomatic. *Asymptomatic gallstones* may be discovered incidentally on diagnostic imaging. The risk of developing symptoms or complications is 1% to 4% per year.[55]

Biliary colic is the most common complication of gallstone disease. Patients experience recurrent attacks of upper abdominal pain that typically last no more than a few hours and resolve spontaneously when the gallstone moves from its obstructing position. If the obstructing stone remains in place, acute cholecystitis may develop over time as the gallbladder becomes distended, inflamed, and in some cases infected. As acute cholecystitis evolves, it may result in necrosis and gangrene of the gallbladder wall (**gangrenous cholecystitis**). **Emphysematous cholecystitis** occurs when the inflamed gallbladder becomes infected with gas-producing organisms. **Gallbladder perforation** is an uncommon but life-threatening complication of cholecystitis. Gangrenous

TABLE 79-4 Complications of Acute Pancreatitis

Pancreatic	Peripancreatic	Extrapancreatic	
Fluid collection	Fluid collection	*Cardiovascular*	*GI*
Necrosis	Necrosis	Hypotension	Peptic ulcer disease/erosive gastritis
Sterile or infected	Intra-abdominal or retroperitoneal hemorrhage	Hypovolemia	GI perforation
Acute or walled off	Pseudoaneurysm (of contiguous visceral arteries, e.g., the splenic)	Myocardial depression	GI bleeding
Abscess	Bowel inflammation, infarction, or necrosis	Myocardial infarction	Duodenal or stomach obstruction
Ascites	Biliary obstruction with jaundice	Pericardial effusion	Splenic infarction
	Splenic or portal vein thrombosis	*Pulmonary*	*Renal*
		Hypoxemia	Oliguria
		Atelectasis	Azotemia
		Pleural effusion (with or without fistula)	Acute renal failure
		Pulmonary infiltrates	Thrombosis of renal artery or vein
		Acute respiratory distress syndrome	*Metabolic*
		Respiratory failure	Hyperglycemia
		Hematologic	Hypocalcemia
		Disseminated intravascular coagulation	Hypertriglyceridemia

cholecystitis, emphysematous cholecystitis, and gallbladder perforation may occur with or without the presence of gallstones.

Choledocholithiasis, gallstones within the common bile duct, may be either primary (arising from within the bile ducts) or, more commonly, secondary (forming in the gallbladder and then migrating to the common bile duct). Choledocholithiasis or other causes of common bile duct obstruction, such as stricture or tumor, may be complicated by *cholangitis*, an infection of the biliary tree. **Chronic cholecystitis** is a state of prolonged gallbladder inflammation typically caused by recurrent episodes of cystic duct obstruction by gallstones. **Biliary sludge** is microlithiasis composed of cholesterol crystals, calcium bilirubinate pigment, and other calcium salts. Biliary sludge may be visualized on CT or US. The clinical course of biliary sludge is variable. It may resolve spontaneously or progress to cause complications including biliary colic, cholecystitis, cholangitis, or pancreatitis. **Acute acalculous cholecystitis** occurs in the absence of gallstones. It occurs much less commonly than calculous cholecystitis but is more likely to result in complications. It tends to occur in the setting of critical illness such as septic shock, burns, and major trauma or surgery. Old age, diabetes, and immunosuppression are also risk factors.

PATHOPHYSIOLOGY

Bile is produced by hepatocytes and transported via the biliary system to the small intestine where bile acids are necessary for the digestion and absorption of lipids. Bile is also the vehicle for eliminating a number of substances from the body including bile pigments (e.g., bilirubin), cholesterol, and some drugs. Bile is stored and concentrated in the gallbladder. When a meal is eaten, the gallbladder is provoked to contract by cholecystokinin and neural stimulation, resulting in the expulsion of bile into the cystic duct and then to the common bile duct, where it reaches the duodenum at the sphincter of Oddi.

Gallstone formation is a multifactorial process that involves supersaturation of bile components, crystal nucleation, and gallbladder dysmotility.[56] Gallstones are classified based on their composition into two categories: pigment stones and cholesterol stones. Pigment stones may be further divided into brown and black stones (**Table 79-5**).

Nonobstructing gallstones typically do not cause symptoms. As gallstones migrate through the biliary tree, they can obstruct the gallbladder neck, cystic duct, or common bile duct. The resultant distention and increased intraluminal pressure cause pain, nausea, and vomiting. Symptoms are relieved if the gallstone returns to a nonobstructing position within the gallbladder lumen or if it passes through the biliary tree into the duodenum. If the obstruction does not resolve, inflammation results from a complex process that involves mechanical distention, ischemia, and inflammatory mediators including prostaglandins. Interestingly, this long-held notion that gallbladder outlet obstruction is the inciting event in acute cholecystitis has been challenged.[57]

Bile cultures are positive in about half of patients with acute cholecystitis.[58-60] Gram-negative organisms predominate (*Escherichia coli*, *Klebsiella*), although gram-positive (*Streptococcus*, *Enterococcus*) and anaerobic (*Clostridia*, *Bacteroides*) infections occur as well.[59] Polymicrobial infections are common.

TABLE 79-5 Gallstone Types

	Cholesterol Stones	Pigment Stones
Composition	Cholesterol monohydrate crystals	Black: Calcium bilirubinate Brown: Mixed composition; usually occur in setting of bacterial or helminthic infection of bile
Relative frequency	80%	20%
Radiographic appearance	Radiolucent	Radiopaque
Typical patients and types of stones	Obese, female, elderly, rapid weight loss	Black stones: Chronic liver disease or hemolysis Brown stones: Bile duct stasis (sclerosing cholangitis, strictures); more common in Asia

CLINICAL FEATURES

HISTORY

Biliary colic presents with pain in the epigastrium or right upper quadrant of the abdomen that occasionally radiates to the back. Despite its name, the pain of biliary colic is more often described as steady than colicky. Pain is often accompanied by nausea and vomiting. Its association with food intake is variable. Fatty food intolerance is not a reliable predictor of gallstone presence.[61,62] Biliary colic demonstrates significant circadian periodicity, with a peak in symptom occurrence around midnight.[63]

Symptoms of biliary colic typically last a few hours or less. If pain persists longer, gallstone complications of greater severity, such as acute cholecystitis or cholangitis, must be considered. In acute cholecystitis, pain becomes more localized to the right upper quadrant and increases in severity as peritoneal irritation occurs.[64]

PHYSICAL EXAMINATION

Patients with biliary colic typically have mild right upper quadrant tenderness without peritoneal signs. In acute cholecystitis, tenderness is more severe and may occasionally be accompanied by rigidity or rebound tenderness. Murphy's sign (the sudden cessation of deep inspiration due to pain when examining fingers reach the inflamed gallbladder upon palpation of the right subcostal region) is 65% sensitive and 87% specific for acute cholecystitis.[65] Patients with biliary colic are afebrile. Fever is classically described in acute cholecystitis but is in fact present in only about one third of cases.[65] Jaundice is rarely seen in acute cholecystitis. Jaundice in the setting of biliary tract stone disease implies an obstruction of the common bile duct from choledocholithiasis or extrinsic compression of the bile duct by an impacted cystic duct or gallbladder stone or adjacent inflammation (Mirizzi's syndrome).

DIAGNOSIS

The diagnosis of gallstones can be readily established with radiographic studies. However, it is important to distinguish the patient with simple biliary colic from the patient with a more serious gallstone complication such as acute cholecystitis, choledocholithiasis, cholangitis, or gallstone pancreatitis.

Establishing the diagnosis of acute cholecystitis requires the integration of data from the history and physical examination with the results of laboratory and radiographic studies. There is no single clinical or laboratory finding that can be relied upon to rule in or rule out the diagnosis.[65] Diagnostic criteria for acute cholecystitis have been proposed (**Table 79-6**).[66]

TABLE 79-6 Diagnostic Criteria for Acute Cholecystitis*

Local signs	Murphy's sign
	Right upper quadrant mass, pain, or tenderness
Systemic signs	Fever
	Elevated C-reactive protein
	Elevated WBC count
Imaging	Imaging findings characteristic of acute cholecystitis (see Table 79-7)
Diagnosis	Suspected: One local sign and one systemic sign Definite: One local sign, one systemic sign, and imaging findings of acute cholecystitis
Accuracy	Sensitivity 91.2%, specificity 96.9% for definite diagnosis criteria compared with surgical pathology gold standard

*Acute hepatitis, chronic cholecystitis, and other acute abdominal disorders should be excluded.

The classic presentation of cholangitis is *Charcot's triad*: fever, right upper quadrant abdominal pain, and jaundice. It is present in less than half of the cases.[67] Most patients will have a fever and right upper quadrant pain; the presence of jaundice is less common, occurring in about two thirds of patients. *Reynolds' pentad* adds altered mental status and shock to Charcot's triad.[68] It is seen in less than 10% of patients with cholangitis.[67]

The differential diagnosis of acute cholecystitis includes other diseases of the biliary tract such as biliary colic, choledocholithiasis, and cholangitis and other conditions of the GI tract such as pancreatitis, hepatitis, peptic ulcer disease, gastritis, and functional dyspepsia. Appendicitis occasionally presents with right upper quadrant pain. Chest disease such as pneumonia, pleurisy, or pulmonary embolism may present with pain of the upper abdomen.

LABORATORY TESTING

Laboratory tests are typically normal in biliary colic. A leukocytosis may be seen in acute cholecystitis, but its absence does not exclude the diagnosis. A leukocyte count of >10,000/mm^3 has a 63% sensitivity, 57% specificity, positive likelihood ratio of 1.5, and negative likelihood ratio of 0.6.[65] The mean leukocyte count in cholecystitis is 12,600/mm^3.[69] Elevation of C-reactive protein is associated with acute cholecystitis but is nonspecific.[70]

Liver function tests, including bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase, are often normal in acute cholecystitis. They are more likely to be elevated in the setting of choledocholithiasis or other cause of bile duct obstruction.[71,72] Abnormal γ-glutamyl transpeptidase is the most sensitive and specific serum marker of choledocholithiasis.[73] Marked elevations (>1000 IU/L) of alanine aminotransferase or aspartate aminotransferase can occur in the setting of choledocholithiasis but are more suggestive of a hepatocellular necrotic process.[74]

IMAGING

Plain radiography of the abdomen is of minimal value in assessing for biliary tract stone disease. Most gallstones do not contain sufficient amounts of calcium to be visible on plain radiographs. Plain radiography may demonstrate biliary tree air reflective of emphysematous cholecystitis or biliary-enteric fistula, but these are more reliably demonstrated with other imaging modalities.

Ultrasound **Abdominal US (Figure 79-2) is the imaging modality of choice for acute cholecystitis**.[75] Its sensitivity and specificity for acute cholecystitis are 81% and 83%, respectively.[76] Advantages of US include its availability, lack of ionizing radiation, short study time, excellent sensitivity for gallstones, and ability to elicit tenderness with placement of the US probe. Sonographic Murphy's sign, maximal tenderness over a sonographically identified gallbladder, is particularly important in the US diagnosis of cholecystitis. The presence of gallstones and a sonographic Murphy's sign has a positive predictive value of 92% for acute cholecystitis. The absence of both gallstones and the sonographic Murphy's sign has a negative predictive value of 95%.[77] Gallbladder wall thickening and pericholecystic fluid are relatively nonspecific for cholecystitis and may result instead from conditions such as ascites, heart failure, liver disease, or pancreatitis.

Point-of-care US (POCUS) of the right upper quadrant performed by emergency physicians is a useful modality for the diagnosis of cholelithiasis.[78] For emergency physicians who are highly trained in its use, POCUS for cholecystitis is comparable to that performed by US technicians and interpreted by radiologists.[79] Additionally, acute cholecystitis is highly unlikely if cholelithiasis is not found on POCUS.[80]

CT, MRI, and Hepatobiliary Iminodiacetic Acid Scanning Acute cholecystitis may be demonstrated on IV contrast-enhanced **abdominal CT** (**Figure 79-3**). The sensitivity and specificity of CT for cholecystitis are ill-defined, although in one retrospective study, the sensitivity of CT for cholecystitis was found to be superior to that of US.[81] IV contrast-enhanced CT may reveal complications of cholecystitis, such as gangrenous cholecystitis, emphysematous cholecystitis, gallstone ileus, and gallbladder perforation, that are not as reliably demonstrated on US.[82] Limitations of CT include its relative insensitivity (~75%) for gallstones and its inability to detect a Murphy's sign.

Technetium-99m hepatobiliary iminodiacetic acid cholescintigraphy is 96% sensitive and 90% specific for acute cholecystitis.[76] An injected radiotracer is excreted by the liver into bile, allowing visualization of the bile ducts and gallbladder. In acute cholecystitis, the obstructed cystic duct results in nonvisualization of the gallbladder. Cholescintigraphy may also reveal delayed gallbladder emptying (*biliary dyskinesia*). Cholescintigraphy requires hours to perform, limiting its use in the ED.

MRI, including magnetic resonance cholangiopancreatography, may be used to evaluate the gallbladder and biliary tree. The sensitivity and specificity of IV gadolinium-enhanced MRI for cholecystitis are similar to those of US.[76] MRI, however, demonstrates more consistent visualization of the biliary tree, has less interpreter variability, and is an alternative for patients who are difficult to examine with US.[75]

Imaging for Choledocholithiasis Choledocholithiasis is difficult to exclude with US or CT. US fails to visualize the entire extrahepatic biliary tree in many patients and has a sensitivity for choledocholithiasis of

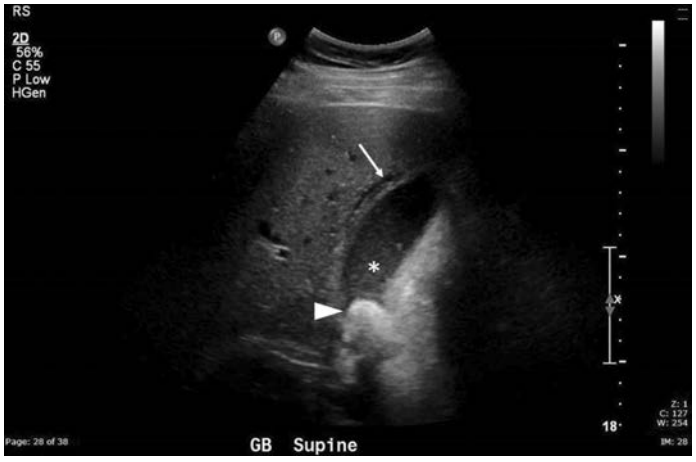

FIGURE 79-2. Abdominal US demonstrating acute cholecystitis with a gallstone (*arrowhead*), gallbladder sludge (*asterisk*), and pericholecystic fluid (*arrow*). [Image contributed by Bart Besinger, MD, FAAEM.]



FIGURE 79-3. Enhanced abdominal CT showing acute cholecystitis with a radiodense gallstone at the gallbladder neck (*arrow*) and a thickened gallbladder wall (*arrowheads*). [Image contributed by Bart Besinger, MD, FAAEM.]

TABLE 79-7 Imaging for Acute Cholecystitis

Modality	Findings	Comment
US	Sonographic Murphy's sign Gallbladder wall thickening >3 mm Pericholecystic fluid Gallbladder distention: short axis >40 mm	Preferred initial imaging test.
CT	Gallbladder wall thickening >3 mm Pericholecystic fluid Pericholecystic fat stranding Hyperdense gallbladder wall Gallbladder distention	Demonstrates complications such as gangrene, gas formation, and perforation. Insensitive for gallstones. Useful in evaluating alternative diagnoses.
HIDA	Nonvisualization of gallbladder	Excellent sensitivity and specificity. Time consuming, limited availability, ionizing radiation.
MRI/MRCP	Gallbladder wall thickening >3 mm Pericholecystic fluid Pericholecystic fat signal changes Gallbladder distention: short axis >40 mm	Specificity and sensitivity similar to US. Excellent visualization of biliary tree. Time consuming, limited availability.

Abbreviations: HIDA = hepatobiliary iminodiacetic acid cholescintigraphy; MRCP = magnetic resonance cholangiopancreatography.

about 60%.[83] CT, although limited by its inability to detect poorly calcified stones, performs somewhat better than US.[84,85] On either US or CT, the combined findings of gallbladder stones and common bile duct dilation provide indirect evidence of choledocholithiasis. Normal common bile duct diameter is <5 mm, although diameter is increased in patients with prior cholecystectomy and in the elderly. More definitive evaluation for choledocholithiasis can be accomplished by magnetic resonance cholangiopancreatography, endoscopic US, or endoscopic retrograde cholangiopancreatography.

Imaging findings in acute cholecystitis are summarized in **Table 79-7**.

TREATMENT

Asymptomatic gallstones generally require no treatment. Elective cholecystectomy is occasionally recommended for those at high risk for gallstone complications such as patients with sickle cell disease, patients with planned organ transplantation, or those belonging to ethnic groups at high risk for gallbladder cancer.

ED management of **biliary colic** includes symptom control and referral to a general surgeon for outpatient laparoscopic cholecystectomy. Symptom management includes antiemetics and analgesics. NSAIDs are first-line therapy. The analgesic efficacy of parenteral NSAIDs is comparable to that of opioids in biliary colic. Additionally, NSAIDs decrease the frequency of short-term gallstone complications such as cholecystitis.[86] Opioid analgesics are often required for pain control. All opioids cause some degree of sphincter of Oddi spasm.[87] The clinical significance of this is unclear, and there is no evidence that any particular opioid drug is superior in treating the pain of biliary colic. Anticholinergic agents such as atropine and glycopyrrolate do not improve biliary colic pain.[88,89]

Acute cholecystitis and its complications are managed in the hospital with surgical consultation. Early laparoscopic cholecystectomy is often the treatment of choice. ED treatment includes the provision of analgesia, administration of antiemetics for nausea and vomiting, cessation of oral intake, volume and electrolyte replacement, and administration of antibiotics. Appropriate antibiotic regimens include second- and third-generation cephalosporins, carbapenems, β-lactam/β-lactamase inhibitor combinations, or the combination of metronidazole and a fluoroquinolone.[90-92] The value of antibiotics in mild acute cholecystitis has been questioned.[93]

Cholangitis can be a life-threatening disease that demands aggressive care including generous fluid resuscitation, the timely administration of antibiotics, and early biliary decompression. Endoscopic retrograde cholangiopancreatography is the decompression procedure of choice in most instances. When cholangitis is suspected, emergency consultation with a GI surgeon or gastroenterologist is needed. Percutaneous or surgical drainage is an alternative when endoscopic retrograde cholangiopancreatography is not feasible or is unsuccessful.

DISPOSITION AND FOLLOW-UP

Once symptoms are adequately controlled, patients with biliary colic are typically discharged from the ED to follow up with a general surgeon. They should be instructed to return to the ED if symptoms of gallstone complications (e.g., prolonged pain, fever, jaundice) arise. Patients who present to the ED with acute cholecystitis or cholangitis require hospital admission. For suspected cholangitis, emergency consultation or transfer to an institution with treatment capabilities for endoscopic retrograde cholangiopancreatography is necessary. Patients with severe illness, including many with cholangitis, should be admitted to a critical care unit.

SPECIAL CONSIDERATIONS

Emphysematous cholecystitis is characterized by gas in the gallbladder wall or lumen resulting from infection with gas-producing organisms such as *Clostridium* species, *E. coli*, and *Klebsiella* species (**Figure 79-4**). It is associated with underlying diabetes and is more common in older patients. Its association with gallstones is variable. Gas occupying the gallbladder may be seen on plain radiographs, US, or, more reliably, IV contrast-enhanced CT. Emphysematous cholecystitis is notable for a mortality rate much higher than that for uncomplicated cholecystitis.[94] In addition to broad-spectrum antibiotics, patients with emphysematous cholecystitis require prompt surgical consultation and consideration for urgent cholecystectomy. Percutaneous cholecystostomy is an alternative therapy for severely ill patients.

Gallstone ileus is a mechanical small bowel obstruction caused by an ectopic gallstone that has reached the intestinal lumen via a biliary-enteric fistula. Such a fistula may occur in the setting of inflammation secondary to cholecystitis. Gallstone ileus may be diagnosed on plain films of the abdomen or, more dependably, with CT. The classic radiographic appearance is Rigler's triad: a small bowel obstruction, pneumobilia, and an ectopic gallstone.[95] Operative therapy is typically indicated.

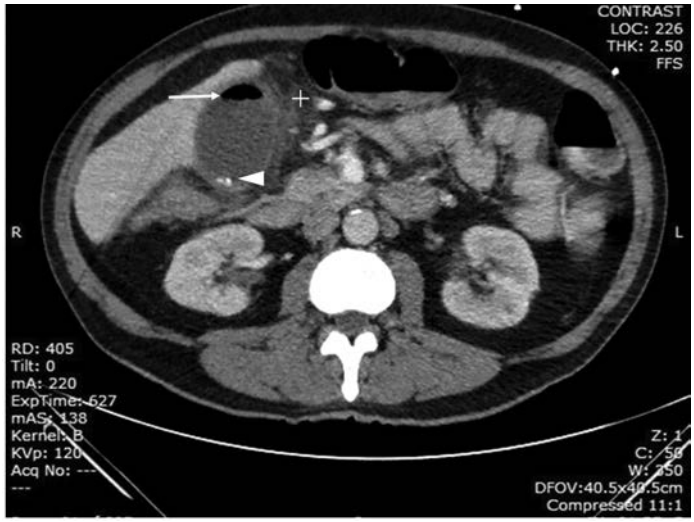

FIGURE 79-4. Contrast-enhanced abdominal CT showing emphysematous cholecystitis with gallstones (*arrowhead*), intraluminal gallbladder gas (*arrow*), and pericholecystic inflammatory changes (*plus sign*). [Image contributed by Bart Besinger, MD, FAAEM.]

Acalculous cholecystitis represents a small minority of cholecystitis cases and most often occurs in the inpatient setting among patients with critical illness. Nevertheless, it may be occasionally encountered in the ED, particularly in immunocompromised patients. Diagnosis is challenging because the clinical presentation is variable and no test result is pathognomonic. US, IV contrast-enhanced CT, and cholescintigraphy are helpful in establishing the diagnosis, but sensitivity and specificity are less than for calculous cholecystitis. Acalculous cholecystitis runs a more fulminant course than cholecystitis associated with gallstones. Complications such as gangrene and perforation are common, and mortality is high.[96]

Chronic cholecystitis is gallbladder inflammation and scarring that occurs over time, usually secondary to intermittent cystic duct obstruction. It presents in a manner similar to biliary colic or acute cholecystitis, although symptoms and examination findings may be more subtle. Patients may report recurrent episodes of pain.

Postcholecystectomy syndrome refers to a heterogeneous group of disorders that present with persistent abdominal symptoms after removal of the gallbladder. In the early postcholecystectomy period, bile leak is the principal concern. Choledocholithiasis is a common cause of postcholecystectomy pain. Symptom-producing common bile duct stones may be "retained" (present at the time of surgery) or may develop postoperatively, formed primarily in the bile ducts often in the setting of bile stasis.[97] Postcholecystectomy syndrome may result from nonbiliary pain that was erroneously attributed to a biliary cause and therefore not remedied by cholecystectomy.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 80

Hepatic Disorders

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INTRODUCTION AND EPIDEMIOLOGY

This chapter discusses the ED presentation, evaluation, and treatment of acute hepatitis, chronic liver disease, and fulminant liver failure. Specific entities addressed in this chapter include viral and toxic hepatitis, nonalcoholic fatty liver disease (NAFLD), and complications of cirrhosis including coagulopathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy. Cholecystitis and biliary colic are addressed in Chapter 79, "Pancreatitis and Cholecystitis." Variceal bleeding is addressed in Chapter 75, "Upper Gastrointestinal Bleeding."

PATHOPHYSIOLOGY

Acute hepatitis is caused by an infectious, toxic, or metabolic injury to hepatocytes. The initial injury leads to inflammation, cellular death, and eventual scarring in the liver. In chronic disease, liver parenchyma is replaced by fibrous tissue, which separates the functioning hepatocytes into isolated nodules. This disruption of the normal tissue structure can become severe and lead to the central characteristics of cirrhosis and liver failure: loss of metabolic and synthetic function at the cellular level, and portal hypertension, ascites formation, and portal-systemic shunting at the gross level.

Hepatic disease impairs the liver's **synthetic functions**, including production of albumin as well as coagulation and anticoagulation factors. The liver is responsible for production of the vitamin K–dependent clotting factors II, VII, IX, and X; proteins C and S; and other elements of the clotting and thrombolytic processes.[1] Inadequate production of these clotting factors makes uncontrolled bleeding one of the life-threatening features of liver disease and a potentially serious complication of hepatic failure.

Portal hypertension is the increased hydrostatic pressure in the portal vein and its feeder vessels caused by resistance to blood flow through the cirrhotic liver. It eventually causes esophageal and gastric varices and portal-systemic shunting. Increased hydrostatic pressure in the intraperitoneal veins, hypoalbuminemia, and poor renal management of sodium and water lead to ascites in the cirrhotic patient. Ascites can cause respiratory compromise when abdominal distention increases intrathoracic pressure. It can also lead to spontaneous bacterial peritonitis (SBP), which occurs when normal flora translocate across an edematous bowel wall into the peritoneal cavity. Bacteremia and infection of preexisting ascitic fluid ensue.[2]

Encephalopathy is a pivotal characteristic of chronic liver disease and is a hallmark of liver failure. Ammonia is often presumed to be the cause of confusion and lethargy in encephalopathic patients but, in fact, the pathophysiology is not completely understood. In cirrhosis, portal hypertension allows ammonia formed by colonic bacteria to enter the general circulation through portal-systemic shunting. Large intestinal protein loads, such as a high-protein meal or GI bleeding, fuel this process. Although levels of ammonia do not reliably correlate with mental status, it is reasonable to think of ammonia as a contributing factor to alterations in mental status. In fulminant liver failure, cerebral edema and resulting increased intracranial pressure can develop. In this end-stage state, loss of autoregulation of cerebral blood flow, ammonia-related edema, and a systemic inflammatory response are all thought to contribute to this deadly complication.[3]

Jaundice can be present in any stage of liver disease. Jaundice is caused by elevated levels of bilirubin in the circulation, leading to bile pigment deposits in the skin, sclerae, and mucous membranes. Hyperbilirubinemia can occur for one of three reasons: overproduction, inadequate cellular processing, or decreased excretion of bilirubin. Another way to think about this is prehepatic, hepatic, and posthepatic jaundice. Prehepatic jaundice is caused by any form of hemolysis, including inborn errors of bilirubin metabolism, which overwhelm the liver's ability to conjugate bilirubin. Viral infection and ingested toxins are typical causes of hepatic jaundice. When hepatocytes necrose, the liver's ability to conjugate bilirubin is impaired, and the level of unconjugated bilirubin rises in the blood. Unlike prehepatic and hepatic jaundice, which present with elevated unconjugated (indirect) bilirubin, posthepatic jaundice produces a rise in conjugated (direct) bilirubin. Typical causes of posthepatic jaundice are a pancreatic tumor or a gallstone in the common bile duct. Parasitic infestation and biliary atresia are rare causes of posthepatic jaundice in the United States but are more common in other parts of the world.

CLINICAL FEATURES

At ED presentation, a **chief complaint** of jaundice, nausea, vomiting, diarrhea, right upper quadrant or epigastric pain, pruritus, inappropriate bruising or bleeding, or altered mental status should raise the question of liver disease. In the **history of present illness**, pay attention to onset of symptoms after eating out or reported ingestion of acetaminophen (in one-time overdose or chronically high doses), mushrooms, or raw oysters. **Past medical history** can reveal risk factors for liver disease, which include chronic hepatitis, transfusion of blood products, positive human immunodeficiency virus status, frequent use of pain medications, and depression. Obesity, type 2 diabetes, and hyperlipidemia are risk factors specific to NAFLD. A **social history** positive for injection drug use, chronic alcohol abuse, sexual promiscuity, or travel to countries with endemic parasitic liver diseases represents increased risk for liver disease.

Several elements of the **review of systems** can suggest liver pathology. Weight loss is common at the end stage of chronic liver disease. Cholestasis causes white (acholic) stools and brown or tea-colored urine. Stools can be black or bloody from variceal or other GI bleeding. Patients may notice yellow skin or sclerae, indicating elevated bilirubin. Ascites can increase abdominal girth or cause shortness of breath, and portal hypertension leads to generalized weakness, encephalopathic

changes in mental status, and lower extremity edema. Lightheadedness or near-syncope can result from intravascular depletion and abnormalities in renal sodium and water excretion.

A number of findings on **physical examination** are hallmarks of liver disease. Liver enlargement and tenderness with or without jaundice are characteristic of acute hepatitis. Chronic liver disease is accompanied by a number of physical findings, including sallow or jaundiced complexion, extremity muscle atrophy, Dupuytren's contracture, palmar erythema, cutaneous spider nevi, distended abdomen with a fluid wave, enlarged veins on the surface of the abdomen (caput medusae), and asterixis. Extraordinary bruising or other signs of bleeding diathesis can be seen in liver failure.

LABORATORY EVALUATION AND IMAGING

Laboratory tests for hepatobiliary disease can be divided into four categories: (1) markers of acute hepatocyte injury or death, (2) measurements of hepatocyte synthetic function, (3) indicators of hepatocyte catabolic activity, and (4) tests to diagnose specific disease entities. Traditional liver function panels include a mix of markers of hepatocyte injury, usually including aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, as well as indicators of hepatocyte catabolic activity (direct and indirect bilirubin). Tests that reflect hepatocyte synthetic function include prothrombin time and albumin. Ammonia reflects catabolic function of the liver. Viral hepatitis serologies are used to differentiate various types of hepatitis; acetaminophen levels can determine whether treatment for poisoning is appropriate; and various tests of ascitic fluid are used to diagnose SBP.

Bilirubin is a metabolite of heme proteins. The total level is usually reported along with the levels of conjugated (direct) and unconjugated (indirect) portions. In a functioning liver, unconjugated bilirubin is taken up by hepatocytes, conjugated, and then secreted into bile. Bilirubin is then excreted in the stool, with a small percentage being recirculated through the liver. An increased total and *indirect* bilirubin signifies either an overwhelming supply of unconjugated bilirubin to the hepatocytes (e.g., hemolytic anemia) or an injury to the hepatocytes themselves that damages their capacity to conjugate a normal supply of bilirubin (e.g., acute or chronic viral hepatitis). Total and *direct* bilirubin is increased when there is some obstruction preventing the secretion of the conjugated bilirubin that is produced by normally functioning hepatocytes (e.g., obstructing gallstone, pancreatic mass, or biliary atresia).

Transaminases (aspartate aminotransferase and alanine aminotransferase) are intracellular enzymes found in hepatocytes and some other cell types. Hepatocyte injury or necrosis releases these enzymes into the circulation. Elevations in the hundreds of units per liter suggest mild injury, or smoldering inflammation. Levels in the thousands suggest extensive acute hepatic necrosis. Less significant elevations, less than five times normal, are typical of alcoholic liver disease and nonalcoholic steatohepatitis. Marked elevations are commonly seen with acute viral hepatitis. These enzyme levels may be near normal in end-stage liver failure, when the hepatocytes are beyond the stage of acute injury. An aspartate aminotransferase–to–alanine aminotransferase ratio of greater than 2 is common in alcoholic hepatitis because alcohol stimulates aspartate aminotransferase production. Incidental findings of transaminase elevations of three to five times normal and alkaline phosphatase of up to twice normal in diabetic or obese patients suggest the presence of nonalcoholic steatohepatitis in diabetic or obese patients.[4] Alanine aminotransferase is a more specific marker of hepatocyte injury than aspartate aminotransferase. Aspartate aminotransferase is found not only in liver but also in heart, smooth muscle, kidney, and brain. Elevated aspartate aminotransferase can be due to medications, including acetaminophen, NSAIDs, angiotensin-converting enzyme inhibitors, nicotinic acid, isoniazid, sulfonamides, erythromycin, griseofulvin, and fluconazole.

γ-Glutamyl transpeptidase production is stimulated by alcohol consumption. It is also elevated by drugs inducing hepatic microsomal enzyme activity, such as phenobarbital and warfarin, and may rise in acute and chronic pancreatitis, acute myocardial infarction, uremia, chronic obstructive pulmonary disease, rheumatoid arthritis, and diabetes mellitus. An elevated γ-glutamyl transpeptidase in the setting of hepatitis suggests an alcoholic cause.

Alkaline phosphatase elevation is associated with biliary obstruction and cholestasis. Mild to moderate elevations accompany virtually all hepatobiliary disease, whereas elevations greater than four times normal strongly suggest cholestasis. Alkaline phosphatase is a nonspecific marker also derived from bone, placenta, intestine, kidneys, and leukocytes. A level of up to double the expected value is normal in pregnancy.

Lactate dehydrogenase is a nonspecific marker. Moderate elevations are seen in all hepatocellular disorders and cirrhosis, whereas purely cholestatic conditions cause minimal elevations. Hemolysis can produce elevation of lactate dehydrogenase and unconjugated bilirubin. The isoenzyme lactate dehydrogenase-5 is specific to the liver. Tests for lactate dehydrogenase-5 are sometimes useful although not widely available.

Ammonia is generated by hepatic metabolism of nitrogen-containing compounds. The hepatic metabolic failure seen in acute and chronic liver disease can, therefore, cause an elevated serum ammonia level. Very high ammonia levels, seen in fulminant liver failure, contribute to overall toxicity and signify poor prognosis.

Prothrombin time prolongation in liver disease reflects the decreased synthesis of the vitamin K–dependent coagulation factors II, VII, IX, and X and, as such, serves as a true measure of liver function. Prolonged prothrombin time is a common complication of advancing cirrhosis, although it also occurs in acute hepatitis and exacerbations of chronic compensated liver disease. When present in acute viral hepatitis, prolonged prothrombin time often indicates severe disease with widespread hepatocellular necrosis. There is some correlation between the extent of prothrombin time prolongation and clinical outcome in fulminant liver disease. Although prothrombin time is useful as a marker of hepatic function, abnormal values may occur in the presence of a normal liver. Vitamin K deficiency from another entity (i.e., malabsorption of fat and, therefore, of fat-soluble vitamins) can be distinguished from liver synthetic dysfunction by administration of parenteral vitamin K (phytonadione, 10 mg IV). A 30% reduction in prothrombin time should occur within 24 hours in vitamin deficiency states.

Albumin also reflects the liver's synthetic function. It may decrease in advancing cirrhosis or severe acute hepatitis and suggests a poor short-term prognosis. Because its half-life is approximately 3 weeks, albumin is less useful than prothrombin time in evaluating fulminant liver disease. Prothrombin time becomes prolonged in a matter of days. Serum albumin levels are also low in malnutrition, so low albumin levels do not necessarily correlate with the degree of hepatic disease in a chronically ill patient.

Viral hepatitis serologies are often grouped into screening panels by hospital laboratories. The diagnosis of specific viral hepatitis entities is complicated by phase of illness, preexisting infections, and likelihood of a given type of infection. The patient who is acutely ill with hepatitis A virus will have positive immunoglobulin M anti–hepatitis A virus antibodies. Acute clinical illness in hepatitis B virus correlates with positive hepatitis B virus surface antigen. Positive immunoglobulin M antibodies correlate to the hepatitis B virus core antigen. Diagnosis of hepatitis C virus is initiated by ordering anti–hepatitis C virus antibodies. This diagnosis is sometimes masked by the 6- to 8-week delay between infection and antibody detection as well as by the acute asymptomatic phase of the hepatitis C virus infection.[5]

Ascitic fluid aspirate is tested for cell count, glucose and protein, Gram stain, and culture to identify bacterial peritonitis. The procedure for obtaining ascitic fluid, paracentesis, is explained in Chapter 86, "Gastrointestinal Procedures and Devices." **A total WBC count >1000/mm^3 or a neutrophil count >250/mm^3 diagnoses SBP.** Low glucose or high protein values suggest infection. Gram stains and culture results can be falsely negative 30% to 40% of the time, so empiric antibiotics should be started in the ED based on clinical suspicion. Culture sensitivity increases by using 10 mL of ascitic fluid per culture bottle and by transferring the fluid to culture bottles at the patient's bedside. Additional studies of ascites that can help with inpatient evaluation are cytology, albumin, lactate dehydrogenase, and tumor markers.

NONHEPATIC CAUSES OF ABNORMAL LIVER TESTS

Multiple nonhepatic causes may lead to abnormal liver function tests. Abnormal liver test results occur in up to one third of those screened, and only 1% of these indicate clinically significant liver disease.

Hypoalbuminemia accompanies protein-wasting enteropathies, malnutrition, and nephrotic syndrome. Alkaline phosphatase elevations occur with a variety of bone diseases, pregnancy, and malignancies. Aspartate aminotransferase elevations accompany acute myocardial infarction and rhabdomyolysis. Bilirubin elevations occur in severe hemolysis, sepsis, and syndromes involving abnormal erythropoiesis. Prothrombin time elevations occur in vitamin K deficiency, chronic antibiotic use, and anticoagulant therapy.[6,7]

Urine bilirubin and urobilinogen are sometimes used as screening tests for liver disease in the ED. The sensitivity of these urine assays is 70% to 74% for identifying elevated serum bilirubin. For correlation with other liver function tests, their sensitivity is in the 43% to 53% range. Specificity for showing either bilirubin or transaminase abnormality is 77% to 87%. Blood-tinged urine will give a false-positive urobilinogen on a urine dipstick test. Taken together, these statistics do not support screening for liver disease with urine dipstick testing.[8]

IMAGING

US and CT scanning are both useful for initial evaluation of liver disease. Bedside US can identify ascites and guide paracentesis, whereas formal US with duplex Doppler is the test of choice for identifying portal vein and hepatic vein thrombosis. Both sonogram and CT scan of the abdomen can be used to identify cancerous, vascular, or infectious lesions of the liver. CT scanning of the brain is used to identify intracranial hemorrhage in patients with liver disease and altered mental status.

ACUTE, CHRONIC, AND FULMINANT HEPATIC DISEASE

Liver disease can be categorized as acute, chronic, or fulminant. **Acute hepatitis** typically presents with nausea, vomiting, and right upper quadrant abdominal pain. Other symptoms include fever, jaundice, bilirubinuria, and an enlarged, tender liver. The most common causes are viral infection and toxic ingestion. Alcohol and acetaminophen are the most common toxic causes.

Patients with **chronic hepatitis** display evidence of long-standing hepatocellular damage and scarring. Cirrhotic patients with portal hypertension complain of abdominal pain and/or ascitic distention and lower body edema. Abnormal bleeding (excessive bruising, bleeding gums, epistaxis, blood in the stool) is a late finding in chronic disease. The chronic liver patient may also exhibit signs of infection, encephalopathy, ascites, and electrolyte derangement. Skin examination can reveal spider nevi, caput medusae, and other manifestations of abnormal shunting of blood to surface vessels.

Liver failure is the potential final common pathway for both acute and chronic liver disease. If there is a delay in seeking medical attention or a rapid acute course, **fulminant liver failure** can be the presenting disorder. For cirrhotic patients, the transition to liver failure is marked by the advent of coagulopathy, encephalopathy, abnormal fluid shifts, and hepatorenal syndrome.

ACUTE HEPATITIS—VIRAL

Hepatitis A virus is transmitted by fecal–oral contamination. Although it is popularly associated with improper food handling or oyster consumption, the most common transmission occurs from asymptomatic children to adults. Implementation of the hepatitis A vaccine in children has dramatically decreased overall rates of infection. Hepatitis A virus infection has an incubation period of 15 to 50 days, followed by a prodrome of nausea, vomiting, and malaise. About a week into the illness, patients may note dark urine (bilirubinuria). A few days later, they develop clay-colored stools and jaundice. Hepatitis A virus does not have a chronic component, and death from hepatic failure is rare.[9]

Hepatitis B virus is transmitted sexually, by blood transfusion, by contaminated needles, and by perinatal transmission. Incubation period is 1 to 3 months, and patients can be infectious for 5 to 15 weeks after onset of symptoms if they clear the infection. Individuals who develop chronic disease will remain infectious indefinitely. Chronic infection occurs in only 6% to 10% of patients who contract hepatitis B virus as adults, whereas 90% of infants and 30% of children under the age of 5 progress to chronic status, which underlines the importance of vaccination of infants and women of childbearing age.[10] In the acute phase of hepatitis B virus, presentation to the ED is similar to that for hepatitis A virus, including complaints of malaise, nausea, vomiting, fever, abdominal pain, and jaundice. Treatment for the acute phase of hepatitis B is supportive. For patients with chronic active hepatitis B, treatment includes antiviral medications and interferon. Side effects of treatment are generally mild (nausea, fatigue, headache), but the interferons can cause neutropenia and thrombocytopenia.

Hepatitis C virus transmission occurs primarily through exposure to contaminated blood or blood products. In contrast to hepatitis A virus and hepatitis B virus, hepatitis C virus is most often asymptomatic in the acute phase of infection, and >75% of patients advance to the chronic stage. The rate of progression to liver failure varies and depends on the natural course of the virus and cofactors such as alcoholism and human immunodeficiency virus. Along with hepatitis B virus, hepatitis C virus is one of the most common causes of hepatocellular carcinoma. Of the patients who develop chronic hepatitis C virus, 1% to 5% will die of either cirrhosis or liver cancer.[11] Effective treatment has been developed for hepatitis C: novel antiviral therapy with direct-acting antivirals is curative in more than 95% of infections. However, access to diagnosis and treatment remains a barrier to reducing morbidity and mortality.[12] The drugs themselves are very well tolerated, with fatigue, headache, and nausea as the most common side effects.[13] The most sinister side effect of treatment with direct-acting antivirals is the reactivation of dormant hepatitis B infection. This is a rare event; only 24 cases were reported to the U.S. Food and Drug Administration between 2013 and 2016, with three of these progressing to fulminant liver failure. The U.S. Food and Drug Administration has issued a "Boxed Warning" regarding the use of direct-acting antivirals in patients who have coinfection with hepatitis B.[14] If a patient should present with acute GI illness during treatment for hepatitis C, the ED workup should include assessment for an acute phase of hepatitis, which could represent emergence of dormant hepatitis B disease.

Hepatitis D virus is uncommon and is typically seen in patients with preexisting chronic hepatitis B virus infection. Hepatitis D superinfection can result in a rapidly progressive or fulminant form of liver disease that carries a high short-term mortality rate. This variety of infection is most commonly associated with injection drug use.[11]

Acute illness with liver function test abnormalities can also be caused by infection with other hepatotropic viruses such as cytomegalovirus, herpes simplex virus, coxsackievirus, and Epstein-Barr virus. These agents are unlikely to cause clinically significant hepatitis in an otherwise healthy host.

Treatment for the acute phase of viral hepatitis is primarily supportive. While treating acute hepatitis, pay attention to any signs of progression to fulminant liver failure signified by worsening signs and symptoms and trending lab abnormalities.

ACUTE HEPATITIS—TOXIC

A toxic insult to the liver can cause acute hepatitis and/or fulminant liver failure. The most common of these is acetaminophen overdose. **Acetaminophen** accounts for >40% of liver failure cases in the United States and one third of deaths secondary to toxic ingestion. Tylenol overdose is reviewed in Chapter 190, "Acetaminophen."

In addition to acetaminophen, there are a variety of **prescription medications** (e.g., phenytoin, valproate, and propylthiouracil), **herbal remedies**, and **dietary supplements** that have been associated with acute hepatitis and liver failure. The list of prescription medications that have been implicated in liver disease is so long that it is prudent to refer to a pharmaceutical database to identify a potential culprit when toxic insult is suspected. While statins are commonly associated with liver toxicity, only 3% of patients taking statins have mild transaminase elevations; clinically significant hepatotoxicity is rare.[15] The most common herbal remedies that have been implicated in hepatic injury are listed in **Table 80-1**. With several multi-ingredient nutritional supplements available to consumers, it is important to review all ingredients for potential hepatotoxic effects.

TABLE 80-1 Common Herbal Remedies Associated With Hepatic Toxicity

Herbal Remedy	Application	Nature of Injury
Black cohosh (*Actea racemosa/Cimiifuga racemosa*)	Menopausal symptoms	Hepatic necrosis and bridging fibrosis
Chaparral (*Larrea ridentate*)	Antioxidant, health tonic	Cholestasis, chronic hepatitis, cholangitis, cirrhosis
Coltsfoot (*Tussilago farfara*)	Cough suppressant, asthma symptoms	Hepatic veno-occlusive disease
Comfrey (*Symphytum*)	Broken bones, wound healing, reduce joint inflammation	Hepatic veno-occlusive disease
Echinacea (*E. angustifolia, E. pallida, E. purpurea*)	Respiratory infections, fever, immune booster	Acute cholestatic autoimmune hepatitis
Germander (*Teucrium chamaedrys*)	Digestive aid	Liver cell necrosis
Kava (*Piper methysticum*)	Anxiolytic, sleeping aid	Acute and chronic hepatitis, cholestasis, fulminant hepatic failure
Kombucha "mushroom" tea (symbiotic colony of bacteria and yeast) and usnic acid	Weight loss, increasing T-cell count, well-being, antiaging	Acute liver failure and hepatitis
Ma huang (*Ephedra sinica*)	Weight loss	Acute hepatitis
Mistletoe (*Viscum album*)	Hypertension, insomnia, epilepsy, asthma, infertility, urinary disorders	Acute hepatitis
Noni juice (*Morinda citrifolia*)	Health tonic	Subacute hepatic failure, acute hepatitis
Saw palmetto (*Serenoa repens*)	Benign prostatic hyperplasia	Cholestatic hepatitis
Senna (*Cassia angustifolia*)	Laxative	Acute hepatitis, acute cholestatic hepatitis, acute liver failure
Skullcap (*Scutellaria baicalensis*)	Sedative, anti-inflammatory	Hepatic veno-occlusive disease, cholestasis, hepatitis
Valerian (*Valeriana officinalis*)	Sedative, anxiolytic	Hepatitis

Source: Adapted with permission from Abdualmjid RJ, Sergi C: Hepatotoxic botanicals: an evidence-based systematic review. *J Pharm Pharm Sci* 16: 376, 2013.

Alcoholic liver disease can range from asymptomatic, reversible fatty liver to acute alcoholic hepatitis, cirrhosis, or a combination of acute and cirrhotic features. Consistent heavy alcohol use of six drinks per day will induce alcohol-related steatosis in 90% of drinkers, and 30% of those with alcoholic fatty liver will progress to cirrhosis. The diagnosis of alcoholic liver disease carries a 35% 5-year survival rate. If a patient has asymptomatic liver disease (i.e., fatty liver seen on imaging), but the patient's drinking continues and acute alcoholic hepatitis develops, the mortality can be much higher.[16] Other nonhepatic features of alcohol abuse, such as malnutrition, stocking-glove neuropathy, and cardiomyopathy, can be clues to alcohol-induced liver disease.

Mushroom poisoning is an uncommon but important cause of acute hepatitis with a high risk of liver failure. *Amanita phalloides* ("death cap") is the most lethal of the more than 50 types of mushrooms that are toxic to humans. For discussion, see Chapter 220, "Mushroom Poisoning."

Treatment of acute hepatitis from toxic causes includes supportive care and attention to associated conditions such as hyponatremia, alcohol or narcotic intoxication or withdrawal, alcoholic ketoacidosis, and hypoglycemia. Treatment with *N*-acetylcysteine should be considered whether the insult is from acetaminophen, nonacetaminophen medication, or mushroom toxicity, according to the American Association for the Study of Liver Diseases guidelines.[17]

CHRONIC HEPATITIS AND CIRRHOSIS

Most patients live for years with hepatitis B virus, hepatitis C virus, NAFLD, or alcoholic hepatitis without symptoms. During the asymptomatic period, normal liver parenchyma is being gradually replaced by scar tissue, and hepatic disease can manifest as mild transaminase elevation or, in cases of NAFLD and alcoholic hepatitis, as an incidental finding of fatty liver on abdominal imaging studies. When a critical amount of liver parenchyma is replaced by fibrotic tissue, symptoms of cirrhosis develop, such as abdominal pain, ascites, SBP, general weakness resulting from electrolyte derangement, or altered mental status due to hepatic encephalopathy. **Treatment** of chronic hepatitis in the ED means taking care of its many sequelae such as ascites, encephalopathy, coagulopathy, and variceal bleeding. Chronic hepatitis infection is typically treated by gastroenterologists in an outpatient setting.

Ascites One of the hallmarks of cirrhosis, ascites causes a protuberant abdomen and a fluid wave on physical exam. Intra-abdominal fluid can displace the diaphragm upward and produce sympathetic pleural effusions with the possibility of respiratory compromise. Smaller amounts of ascites can be difficult to identify on examination; bedside ultrasound can be particularly helpful in patients in whom the presence of ascites is uncertain (**Figure 80-1**).

Mild- to moderate-volume ascites can be managed with a salt-restricted diet and diuretics, both of which create a negative sodium balance and encourage loss of ascitic fluid. Recommended diuretics include spironolactone, 50 to 200 milligrams/d, and amiloride, 5 to 10 milligrams/d. Furosemide can be problematic because it can lead to overdiuresis.[2] To facilitate monitoring for adverse side effects, prescribe diuretics in collaboration with the outpatient physician.

Paracentesis is recommended therapy for large-volume ascites. There are several important considerations when performing paracentesis on a cirrhotic patient. First, the patient's prothrombin time/INR is likely to be elevated. Second, the amount of fluid that can be removed without infusion of albumin to prevent intravascular collapse is controversial. For any tap, guidelines from the American Association for the Study of Liver Diseases state that paracentesis should be considered safe from a

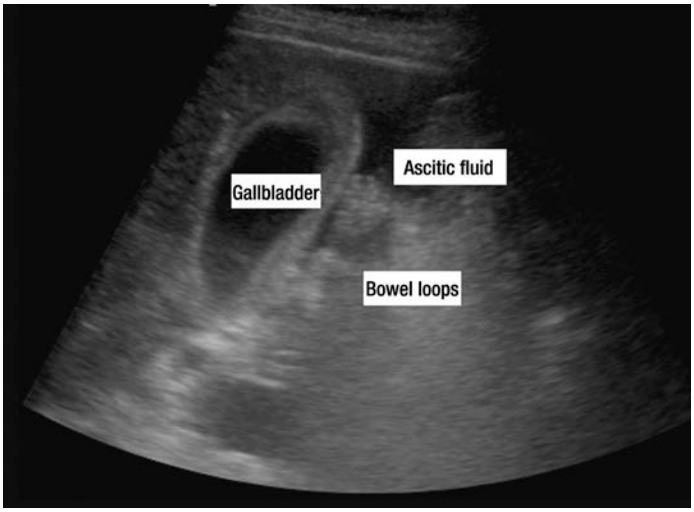

FIGURE 80-1. Sonographic image of ascitic fluid showing bowel loops and an edematous gallbladder wall, a common finding in patients with ascites. [Courtesy of and used with permission of Michael S. Antonis, DO, sonographer.]

bleeding perspective unless there is evidence of fibrinolysis (i.e., three-dimensional bruising, oozing from IV start sites) or overt disseminated intravascular coagulation. For therapeutic paracentesis, American Association for the Study of Liver Diseases guidelines recommend the use of IV albumin, 6 to 8 milligrams/L of fluid removed, for amounts greater than 4 L.[2]

Spontaneous Bacterial Peritonitis SBP is the most common life-threatening complication of ascites. In patients with known ascites, the 1-year incidence of SBP is 30%, and recurrence is as high as 44%. The survival rate for patients with a first episode of SBP is 68.1% at 1 month and 30.8% at 6 months. This is probably a result of acute infection occurring in the fragile setting of advanced liver disease.[18]

The classic presentation of SBP is fever and diffuse abdominal pain and tenderness. However, any or all of these features may be absent. Consequently, patients who are diagnosed with ascites for the first time or who have ascites and develop fever, abdominal pain, GI bleeding, vomiting, or encephalopathy should undergo paracentesis to check for SBP.

Initial treatment is empiric antibiotic therapy to cover typical enteric flora. The most common isolates in SBP are *Escherichia coli, Klebsiella pneumoniae*, and *Streptococcus pneumoniae*. Empiric antibiotic treatment recommendations from the most recent (2012) guideline from the American Association for the Study of Liver Diseases are shown in **Table 80-2**.[2] Cefotaxime is a widely accepted first-line parenteral treatment for SBP. Oral therapy with broad-spectrum quinolones is an option in patients with mild, uncomplicated disease and close follow-up.[19] Patients may have had prior infections with resistant organisms, so review microbiologic sensitivities from prior admissions, if available. The addition of IV albumin (1.5 grams/kg at diagnosis, 1 gram/kg on day 3) to antibiotic therapy may reduce renal failure and hospital mortality in patients with SBP.[19]

Hepatic Encephalopathy Hepatic encephalopathy is a poorly understood phenomenon attributed to the accumulation of nitrogenous waste products normally metabolized by the liver. Hepatic encephalopathy causes a spectrum of illness ranging from chronic fatigue or mild confusion to acute lethargy.

The development of hepatic encephalopathy suggests either that the liver is no longer able to metabolize the usual supply of nitrogenous waste or that the supply of such waste has increased. Sources of increased supply include protein loads from a large meal or from occult GI bleeding. In addition to progressive liver disease, constipation, hypo- or hyperglycemia, alcohol withdrawal, hypoperfusion states such as sepsis, and iatrogenic interventions can also compromise the liver's metabolic capacity. Hepatic encephalopathy is a common complication after transjugular intrahepatic portosystemic shunt, a procedure in which portal blood is shunted to the inferior vena cava, bypassing the liver. Although this procedure may succeed in reducing portal hypertension and variceal bleeding, it also slows metabolism of nitrogenous wastes by reducing hepatic blood flow. Adding or removing antibiotics from a patient's medicine regimen can also precipitate encephalopathy by changing the intestinal flora and altering the gut's ability to metabolize proteins.[21]

TABLE 80-2 Diagnosis and Treatment of Spontaneous Bacterial Peritonitis

Diagnosis	Ascitic fluid, obtain 50 mL for cell count, Gram stain, and culture (transfer fluid to culture bottles at the bedside for best results) WBC count >1000/mm^3 or Polymorphonuclear leukocytes >250/mL or Bacteria on Gram stain
Empiric treatment	Cefotaxime or other third-generation cephalosporin or IV fluoroquinolone (ineffective in patients who have received prophylactic quinolone treatment) or Oral fluoroquinolone in a very mild case with close follow-up

TABLE 80-3 Stages of Clinical Hepatic Encephalopathy

Stage	Features
I	General apathy
II	Lethargy, drowsiness, variable orientation, asterixis
III	Stupor with hyperreflexia, extensor plantar reflexes
IV	Coma

To appreciate the presence or worsening of encephalopathy, determine if there are changes in personality, memory loss, a decreased level of consciousness, or declining neuromuscular function. **Table 80-3** lists clinical stages of encephalopathy. Asterixis, which characterizes stage II, is elicited by having the patient hold the arms straight up and extending the wrists. The hands begin to flap repetitively. Another manifestation of asterixis is back-and-forth tongue movement when the tongue is extended. A patient with known encephalopathy in stage I or II who is otherwise well and has no other acute comorbidities may be managed as an outpatient after consultation with the primary care physician or gastroenterologist.

Hepatic encephalopathy is a diagnosis of exclusion. This holds true even in the presence of an elevated serum ammonia level. Patients with end-stage liver disease are typically coagulopathic and may develop a spontaneous or traumatic intracranial hemorrhage. Decreased hepatic gluconeogenesis and glycogen stores and poor nutritional status increase the risk of hypoglycemia and nutritional encephalopathies such as Wernicke-Korsakoff syndrome. Cirrhotic patients often are treated with diuretics and can develop hyper- or hyponatremia. Altered mental status can result from decreased hepatic clearance of drugs such as benzodiazepines and opiates, prolonging the effect and resulting in accidental overdose. Renal failure, meningitis, and sepsis are other causes of altered mental status in the cirrhotic patient that could mimic hepatic encephalopathy.

Treatment of hepatic encephalopathy is aimed at reducing the production of nitrogenous wastes by reducing protein intake and suppressing the metabolic activity of intestinal bacteria. Lactulose is the current mainstay of therapy for hepatic encephalopathy. Lactulose is a synthetic disaccharide. It is minimally absorbed in the bloodstream. In the colon, it degrades primarily into lactic acid. In the acidified environment, ammonia is trapped and excreted in the stool. Blood ammonia levels can decrease up to 50% using lactulose therapy. Lactulose also inhibits glutamine-dependent ammonia production in the gut wall. Lactulose is given PO or PR. The oral dose is 20 grams diluted in a glass of water, fruit juice, or carbonated drink. For rectal administration, dilute 300 mL of syrup with 700 mL of water or normal saline. The enema should be retained for 30 minutes.

Antibiotics including rifaximin, neomycin, vancomycin, and metronidazole have been suggested as a second-line therapy for hepatic encephalopathy. These agents work by reducing intestinal flora. Of these, rifaximin is best tolerated, but is costly.[22] Although effective, neomycin is limited in use due to its adverse effects of renal toxicity and ototoxicity.[23]

Hepatorenal Syndrome Hepatorenal syndrome is a complication of cirrhosis that often accompanies SBP. It is defined as acute renal failure in a patient with histologically normal kidneys in the presence of preexisting chronic or acute hepatic failure. The cause is not well understood. There are two types of hepatorenal syndrome. Type 1 is more serious and is identified by progressive oliguria and doubling of serum creatinine over a 2-week period. Type 2 is represented by a gradual impairment in renal function that may or may not advance beyond moderate dysfunction. The discovery of abrupt renal failure in a cirrhotic patient that cannot be attributed to any other cause is a marker of extreme morbidity. Median survival for type 1 hepatorenal syndrome without medical treatment is 2 weeks.[24]

Coagulopathy Coagulopathy is one of the more dangerous complications of cirrhosis. It needs to be treated if the patient has uncontrolled

bleeding or is scheduled to undergo a procedure with potential bleeding complications. Vitamin K deficiency can be treated with vitamin K, 10 milligrams IV or PO. Fresh frozen plasma can be given in doses appropriate for the patient's prothrombin level. Finally, decreased or malfunctioning platelets should be replaced with pooled donor platelets. Gastroesophageal varices and hemorrhage are complications of cirrhosis that are covered in Chapter 75, "Upper Gastrointestinal Bleeding."

HEPATIC FAILURE

Liver failure is the final common pathway for several types of liver disease. Progression to liver failure is varied and depends largely on comorbid entities, such as human immunodeficiency virus/acquired immunodeficiency syndrome, diabetes, obesity, continued injection drug use, and alcohol intake. Patients who develop acute liver failure have an extremely poor prognosis, with survival rates of <30%.[25] Among the most common of the entities that present as acute liver failure in the United States are acetaminophen overdose (46%), indeterminate causes (14%), other drugs (11%), hepatitis B virus (7%), and autoimmune hepatitis.[26]

The clinical hallmarks of acute liver failure are hepatic encephalopathy, hepatorenal syndrome, and coagulopathy. The electrolyte imbalances seen in chronic liver disease can become extreme. Cerebral edema and intracranial hypertension are the most ominous complications. The catabolic nature of liver failure leads to negative nitrogen balance and immunodeficiency. Other clinical findings in acute liver failure include hypotension, hypoglycemia, and relative adrenal insufficiency. ED evaluation should include assessment for sepsis. Liver failure requires critical care in the ED and consultation with a liver transplant center. Recognizing fulminant hepatic failure is critical because transfer to a transplant center may be the most appropriate disposition.

Treatment of fulminant liver failure in the ED involves care of the patient's respiratory status, blood pressure, and encephalopathy; correction of electrolyte derangements; identification of cerebral edema or intracranial hemorrhage; attention to active bleeding; and careful disposition, ensuring that the patient will be assessed for liver transplant in a timely fashion.

Patients with respiratory failure due to ascites, effusions, or decreased alertness require intubation. Bilevel positive airway pressure is not typically an option in these cases because patients are too somnolent and at risk for aspiration. Blood pressure at this stage of liver disease is typically low due to malnutrition, bleeding, vomiting, diarrhea, and third spacing of fluid. Treat with a judicious initial fluid challenge; normal saline is the recommended resuscitation fluid. Norepinephrine is the initial vasopressor of choice for volume-refractory hypotension in hepatic failure, with the addition of vasopressin when escalating doses of norepinephrine are required. Take care when using vasopressin in severely encephalopathic patients, due to potential risk of increased cerebral vasodilatation and intracranial hypertension. The American Association for the Study of Liver Diseases also recommends a trial of hydrocortisone in cases of persistent hypotension.[17]

In fulminant liver failure, cerebral edema and intracranial hemorrhage should rise to the top of the differential for altered mental status. Patients with grade III or IV hepatic encephalopathy and concomitant renal failure, critically elevated ammonia levels, or hypotension are at high risk for cerebral edema; in this case, prophylactic hypertonic saline may be considered with a goal sodium level of 145 to 155 mEq/L. For patients with confirmed increased intracranial pressure, mannitol 0.5 to 1 gram/kg is recommended.[3] In the case of intracranial hemorrhage, treat coagulopathy. Consult neurosurgery or refer to a facility with neurosurgical services if the patient could benefit from hematoma evacuation or intracranial pressure monitoring.

NONALCOHOLIC FATTY LIVER DISEASE

NAFLD is a spectrum of disease ranging from steatosis (fatty liver) and steatohepatitis (nonalcoholic steatohepatitis) to cirrhosis and liver failure. It is strongly correlated with obesity and metabolic syndrome. NAFLD cirrhosis is now the second most common diagnosis among patients awaiting liver transplant (hepatitis C is first, and alcoholic liver disease is third).[4] The most common manifestation of NAFLD is hepatic steatosis or simply fatty liver, affecting approximately 30% of the overall U.S. population and up to 90% of obese individuals. The inflammatory subtype of NAFLD, nonalcoholic steatohepatitis, is less common, estimated to have a prevalence in the United States of 3% overall and 33% among obese patients. In the ED, steatosis and nonalcoholic steatohepatitis usually manifest as an incidental finding of fatty liver on abdominal imaging or as a mild rise in aspartate aminotransferase and alanine aminotransferase, although nonalcoholic steatohepatitis can produce mild abdominal pain and nausea. While patients with steatosis have a benign course, a percentage of patients with nonalcoholic steatohepatitis will progress to cirrhosis and liver failure over a number of years. The size of this subset has not been accurately established yet.[27]

There is no **treatment** for NAFLD that has been proven to be particularly effective. The mainstays of treatment are weight loss and exercise, which have been shown to reduce fat deposition and inflammation of the liver parenchyma, but not fibrosis. Various medication classes, such as angiotensin-converting enzyme inhibitors, insulin-sensitizing agents, antioxidants, and statins are used, but none of these is considered standard treatment or has been found to make a dramatic difference in outcome.[27] When NAFLD is found incidentally during ED evaluation, the patient should be advised to abstain from alcohol and to pursue outpatient follow-up for further diagnosis and potential treatment.

GENETIC AND AUTOIMMUNE LIVER DISORDERS

Gilbert's syndrome is a familial liver disorder that produces occasional elevations in liver function tests and bilirubin. This syndrome does not cause cirrhosis or affect the synthetic or metabolic functions of the liver. Wilson's disease, hemochromatosis, and α_1-antitrypsin deficiency are familial disorders that can lead to severe chronic disease and liver failure. Autoimmune hepatitis is a progressive, chronic disease that is presumably triggered by viral hepatitis or by medications. Primary biliary cirrhosis is considered an autoimmune disorder with a chronic or chronic-degenerative course.

PRE- AND POSTHEPATIC VENOUS THROMBOSIS

Vascular diseases of the liver are rare but important, because timely diagnosis and treatment can improve outcome. **Portal vein thrombosis** affects the prehepatic portal venous system and is associated with hypercoagulable states, abdominal trauma, sepsis, pancreatitis, cirrhosis, and hepatocellular carcinoma.

In acute thrombosis, the major symptom is colicky abdominal pain caused by venous congestion in the wall of the small intestine. Chronic portal vein thrombosis is usually painless and found incidentally on imaging studies ordered for other reasons. In long-standing portal vein thrombosis, there is cavernous transformation of the portal vein due to the development of multiple small collateral vessels. In cirrhotic patients, it can be hard to know if portal vein thrombosis is acute or chronic because the findings for chronic portal vein thrombosis are the same as those for long-standing cirrhosis with portal hypertension.[28] **Hepatic vein thrombosis, or Budd-Chiari syndrome**, is the thrombotic obstruction of the posthepatic portal venous system and also has both acute and chronic presentations, progressing from abdominal pain and hepatomegaly through ascites. Rather than being caused by cirrhosis, hepatic vein thrombosis is dangerous because it can cause the rapid development of fibrosis, cirrhosis, and liver failure if untreated. Risk factors for hepatic vein thrombosis include coagulopathies, myeloproliferative disorders such as polycythemia vera, infection, paroxysmal nocturnal hemoglobinuria, and congenital webs of the vena cava.[29]

Treatment of thrombotic liver disease varies with the presence or absence of cirrhosis. In the non–cirrhosis-associated cases, anticoagulation is the first-line treatment and can be started in the ED. Cirrhosis raises the issue of increased risk of bleeding from esophageal or gastric varices; patients with this potential for catastrophic bleeding should *not* be anticoagulated, and the only therapy for consideration is clot removal, transjugular intrahepatic portosystemic shunt procedure, or surgical shunting.[5]

DISPOSITION AND FOLLOW-UP

The disposition of a patient with acute or chronic hepatitis is complex and requires careful planning with the patient and caretakers. Discussion with the primary care physician and gastroenterologist can clarify a vague clinical picture. Patients with acute hepatitis require supportive treatment with pain management, antiemetic medication, and fluid resuscitation. Consider admission for high-risk patients, including the elderly and pregnant women, and patients who do not respond adequately to supportive care. Admit those who have a bilirubin ≥20 mg/dL, prothrombin time 50% above normal, hypoglycemia, or GI bleeding, which requires further evaluation to determine the presence of varices.[30]

In patients with chronic hepatitis, admission may be indicated for patients with ascites if they have significant respiratory compromise or abdominal pain. In addition, admit the patient with fever, acidosis, or leukocytosis and for evaluation and treatment of SBP.[31] New-onset or worsening hepatic encephalopathy, hepatorenal syndrome, and coagulopathy with bleeding are also strong indications for admission.[32] Patients with severe hyponatremia and severe hyper- or hypovolemia should also be managed in the hospital.[33]

Consider patient safety in the disposition of patients with advanced cirrhosis. Weakness, muscle wasting, and mild encephalopathy are serious risks for falls, and coagulopathy is a risk for cerebral bleed. Patients must be stable on their feet or have supervised assistance for discharge to home.

Discharge planning should include follow-up care by a gastroenterologist or transplant specialist. Patients and family members can be referred to Alcoholics Anonymous, Al-Anon, or support groups for transplant or other special needs. Discharge medications may include antibiotics, diuretics, lactulose, antiemetics, and pain medications.

SPECIAL CONSIDERATIONS

PAIN CONTROL IN PATIENTS WITH HEPATIC DISEASE

It can be difficult to decide on appropriate pain medications and sedatives for patients with compromised liver function. Avoid NSAIDs in patients with chronic hepatitis and cirrhosis due to GI toxicity and possible potentiation of renal dysfunction. Acetaminophen has traditionally been avoided in patients with any type of liver disease, but there are several trials indicating it to be safe for short-term use, at a reduced dose of 2 grams total per day. Gabapentin and pregabalin are safe options for neuropathic pain. Avoid opioids whenever possible because opioids are metabolized by the liver and their sedative effects can be unpredictable in patients with compromised liver function. Avoid opioids in patients with a history of encephalopathy or substance use. Only if absolutely necessary, fentanyl and tramadol at reduced doses and increased dosing intervals are possible choices in select patients because they lack the toxic metabolites of traditional opioids.[34] When sedation or pain control is required for the critically ill patient with liver failure, a titratable infusion of a non-benzodiazepine medication with a short half-life and no toxic metabolites is useful. Propofol has been well studied in the setting of endoscopy and is safe at least in the short term for patients with cirrhosis.[35] Fentanyl provides pain relief and some degree of sedation.

MEDICATION DOSE ADJUSTMENT

Patients with liver disease have several factors that contribute to pharmacokinetic variability including portal hypertensive gastropathy, portosystemic shunting, decreased serum protein binding of drugs, high intestinal permeability, impaired gastric motility, impaired hepatic clearance, and impaired enzymatic activity. Be careful with drugs with a narrow therapeutic range and high toxicity. Drugs with high hepatic extraction may have clinically significant increased bioavailability in cirrhotic patients. For drugs with high hepatic extraction, reduce the initial and maintenance doses. For drugs with intermediate hepatic extraction, initially use the low range of the normal dose, and reduce maintenance dosing. For drugs with low hepatic extraction, initial dosing remains unchanged, but reduce the maintenance dose.[36] See **Table 80-4** for a list of medications commonly used in the ED, classified by hepatic extraction.

TABLE 80-4 Hepatic Dose Adjustments for Common ED Medications

Hepatic Extraction Category and Suggested Dose Adaptation	Medication Class	Medications
High: *Reduce initial and maintenance dose*	Analgesics	Morphine
	Antihistamines	Promethazine
	Antimigraine agents	Sumatriptan
	Antipsychotics	Chlorpromazine, quetiapine, perphenazine
	Anxiolytics	Midazolam
	β-Adrenoceptor antagonists	Labetalol, metoprolol, propranolol
	Calcium channel antagonists	Nicardipine, verapamil
	Vasodilators	Nitroglycerin, isosorbide dinitrate
Intermediate: *Low-normal initial dose and reduce maintenance dose*	Analgesics	Codeine
	Antiarrhythmics	Amiodarone, lidocaine
	Antibacterials	Ciprofloxacin, erythromycin
	Antipsychotics	Haloperidol, olanzapine, clozapine
	Antiulcer agents	Omeprazole, ranitidine
	Anxiolytics	Alprazolam, diazepam, lorazepam
	Beta-adrenoceptor antagonists	Carvedilol
	Calcium channel antagonists	Diltiazem, felodipine, nifedipine

Source: Adapted with permission from Delco, F, Tchambaz L, Schlienger R, et al: Dose adjustment in patients with liver disease. *Drug Safety*. 2005; 28(6):529-545. Copyright Springer.

PREGNANCY

Pregnant women can present with various hepatic or cholestatic disorders not specific to pregnancy. HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), however, stands apart as a life-threatening process that must not be missed in the ED. HELLP occurs as part of the pre-eclampsia–eclampsia spectrum in the late third trimester or in the postpartum period. A complete discussion of HELLP is provided in Chapter 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period."

LIVER TRANSPLANT PATIENT

Liver transplant patients can develop a variety of illnesses, most commonly metabolic and infectious in nature. This topic is addressed in Chapter 297, "The Transplant Patient."

TRAVELERS AND GLOBAL CITIZENS

Travelers who have been outside the United States who present with abdominal pain, vomiting, diarrhea, or fever are at risk for having liver disease caused by parasitic infection. For detailed discussion, see Chapter 162, "Global Travelers."

PALLIATIVE CARE

Palliative care benefits patients with end-stage liver disease whether or not they are a candidate for transplant. Goals of care and advance care planning should be discussed early in the initiation of care for patients with end-stage liver disease, particularly because disease progression can be rapid, providing little time for patients to develop the coping skills needed to face the progression of their disease and end-of-life consideration.[37]

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 81

Acute Appendicitis

E. Paul DeKoning

INTRODUCTION AND EPIDEMIOLOGY

Between 250,000 and 300,000 appendectomies for acute appendicitis are performed each year in the United States,[1] with an additional 700,000 patients affected in the European community.[2] The lifetime risk of acute appendicitis in the United States is an estimated 12% for males and 25% for females.[3] Yet, the epidemiology of this common ED diagnosis continues to change. Data suggest a reversal of a previous decline in incidence, with the annual rate increasing from 7.62 to 9.38 per 10,000 between 1993 and 2008,[4] whereas the rate of negative appendectomy has declined.[5] Similarly, between 2001 and 2008, the rate of perforation decreased, but this declining trend has not been consistent.[4,6] Acute appendicitis is most common in patients age 10 to 19 years,[4] remains the most frequent cause of atraumatic abdominal pain in children >1 year old,[7] and is the most common nonobstetric surgical emergency in pregnancy, complicating up to 1 in 1500 pregnancies.[8,9] Despite advances in lab testing and imaging, accurate diagnosis is a challenge. Both "missed appendicitis" and unnecessary surgery for a false diagnosis are not without consequence. **Thus, consider appendicitis in any patient with acute atraumatic abdominal pain without prior appendectomy.**

PATHOPHYSIOLOGY

Luminal obstruction of the vermiform appendix, typically by a fecalith, is considered the traditional cause of appendicitis. Continued secretion from the luminal mucosa results in increased intraluminal pressure and appendiceal vascular insufficiency, leading ultimately to bacterial proliferation and inflammation. Left unchecked, perforation may occur. While certainly the cause in many instances, the traditional pathophysiology of luminal obstruction may be more the exception than the rule; the full range of specific causes remains unknown.[10,11] Other known causes include obstruction by lymphatic tissue, gallstone, tumor, or parasites.

Visceral innervation produces the vague, hard to localize periumbilical or central abdominal discomfort frequently observed early in the clinical course. Progressive inflammation and subsequent irritation of the somatically innervated parietal peritoneum produces the classic migration of pain to the right lower quadrant, to **McBurney's point**, located one third of the distance from the anterior superior iliac spine to the umbilicus. Up to 50% of patients may have an atypical presentation[12] due in part to anatomic variation. For example, a retrocecal appendix produces right flank or pelvic pain, whereas malrotation of the colon results in transposition of the appendix and, subsequently, pain to the left upper quadrant. Abdominal organ displacement from a gravid uterus may lead to right upper quadrant tenderness in pregnancy. Even so, a right lower quadrant location of pain remains the most common location of pain in pregnant women with appendicitis.[9]

CLINICAL FEATURES

The signs and symptoms of acute appendicitis lie along a spectrum that correlates with pathophysiology. Early on, patients classically complain of nonspecific symptoms of general malaise, indigestion, or bowel irregularity. Anorexia is common but not universally present. Alterations in bowel function are highly variable and can include constipation, diarrhea, and even obstruction as a late complication.[13] Periumbilical or central abdominal pain generally develops after nonspecific symptoms. If nausea develops, it typically follows the onset of pain.[14] Vomiting may or may not be present. Subjective or objective fever is frequent.

As the clinical course progresses, discomfort traditionally migrates to the right lower quadrant. Flank pain, dysuria, or hematuria can occur, given the typical proximity of the appendix to the urinary tract.[13]

Aggravating and alleviating features can help establish the diagnosis: worsening pain with deep inspiration may be present if there is peritoneal irritation, and individuals may state that the trip to the hospital was painful, particularly when encountering bumps in the road. Such features suggest a peritoneal process is under way. The release of intraluminal obstruction with perforation often results in sudden alleviation of pain; consider appendiceal perforation if the patient's pain has suddenly improved.[13] Examination findings evolve with the clinical course. Progressive inflammation and peritoneal irritation yield reproducible tenderness to palpation in the right lower quadrant. The exception to right lower quadrant pain is a retrocecal appendix, which does not contact the anterior parietal peritoneum.[15] Rebound tenderness and involuntary guarding suggest peritonitis. Patients may have costovertebral tenderness, and percussion of the right heel or shaking of the hospital stretcher may elicit abdominal pain. There is no evidence that the digital rectal exam aids significantly in the diagnosis of acute appendicitis.[12] **Rovsing's sign** reproduces pain over McBurney's point as the clinician palpates the descending colon in the left lower quadrant. A positive psoas sign or obturator test suggests an inflammatory peritoneal process. The **psoas sign** is elicited if abdominal pain is produced with passive extension of the right leg at the hip while the patient lies on the left side. The **obturator test** elicits pain with passive internal and external rotation of the flexed right thigh at the hip. The presence of abdominal rigidity, a positive psoas sign, fever, or rebound tenderness increases the likelihood of acute appendicitis. Prior episodes of similar pain, the absence of right lower quadrant pain, and the absence of classic pain migration make appendicitis less likely. The presence or absence of any exam finding in isolation is neither sufficiently sensitive nor specific to rule out or rule in the diagnosis.

In a systematic review of 42 studies investigating appendicitis in patients age 18 years or younger, fever was the single most useful sign, with a positive likelihood ratio [LR(+)] of 3.4 (95% confidence interval [CI], 2.4 to 4.8), whereas its absence decreased the likelihood of appendicitis (negative likelihood ratio [LR(–)], 0.32; 95% CI, 0.16 to 0.64). Rebound tenderness and pain migration to the right lower quadrant were also strong predictors.[16] In comparison, a classic study of exam findings in adult patients showed right lower quadrant pain as the single most useful sign (sensitivity, 0.81; specificity, 0.53; LR(+), 7.31 to 8.46; LR(–), 0 to 0.28), followed by rigidity and migration of pain. Fever in adults had an LR(+) of 1.94 (95% CI, 1.63 to 2.32) and a LR(–) of 0.58 (95% CI, 0.51 to 0.67).[17] **In both children and adults, however, no single historical or physical examination finding is sufficient to rule in or rule out appendicitis. Their utility is increased in combination.**[16,17]

DIAGNOSIS

Despite the advent of cross-sectional radiographic imaging and high-definition ultrasonography and a more than doubling of their use in recent years, detection rates for appendicitis have essentially remained the same.[18] There are numerous appendicitis mimics, and the differential diagnosis is broad (**Table 81-1**). Perform a complete physical examination, including a pelvic examination in women of childbearing age. Acute appendicitis is largely a clinical diagnosis, and no one adjunctive test is universally indicated.

Consider appendicitis in any patient with atraumatic right-sided abdominal, periumbilical, or flank pain who has not previously

TABLE 81-1 Differential Diagnosis of Right Lower Quadrant Pain

GI
- Cecal/Meckel's diverticulitis
- Cecal volvulus
- Colitis/terminal ileitis
- Constipation/ileus/bowel obstruction
- Crohn's/ulcerative colitis flair
- Epiploic appendagitis
- Functional abdominal pain
- Incarcerated inguinal hernia
- Intra-abdominal abscess
- Intussusception
- Malrotation
- Mesenteric lymphadenitis

GU
- Ectopic/heterotopic pregnancy
- Ovarian torsion
- Ovarian vein thrombosis
- Pyelonephritis
- Referred testicular pain
- Renal colic
- Tubo-ovarian abscess/salpingitis

Musculoskeletal
- Abdominal wall/rectus sheath hematoma
- Psoas abscess

undergone appendectomy. Available diagnostic adjuncts include peripheral WBC and other acute inflammatory markers (e.g., C-reactive protein or erythrocyte sedimentation rate), urinalysis, and a pregnancy test. Diagnostic imaging should be considered in atypical presentations or if significant diagnostic uncertainty exists after thorough history and examination.

SCORING SYSTEMS

Scoring systems, such as the Alvarado and Samuel scores, have been developed to aid in diagnosis. The modified **Alvarado score** for acute appendicitis ranks symptoms (migration, 1 point; anorexia or urinary acetone, 1 point; nausea or vomiting, 1 point), signs (right lower quadrant tenderness, 2 points; rebound, 1 point; fever, 1 point), and WBC count (>10,000/mm^3, 2 points) into low-risk appendicitis (score, 1 to 4) and possible or probable appendicitis (score, 5 to 9). However, the low-risk score (score, 1 to 4) was demonstrated as only 72% sensitive compared to a sensitivity of 93% for clinical judgment when appendicitis was either the most likely or second most likely diagnosis.[19] Despite continued technologic advances and development of decision rules, different scoring systems often yield conflicting results and should not replace clinical judgment; the clinical impression of the experienced physician has the highest impact on patient outcome.[20-23]

LABORATORY TESTING

An increase in peripheral WBC may be the earliest marker of inflammation.[24] A study of 722 children identified both prospectively and retrospectively found acute appendicitis to be the most common diagnosis in children >4 years old with nontraumatic abdominal pain and leukocytosis.[25] However, a normal WBC is not uncommon, and leukopenic presentations have been documented.[26] **While numerous studies have evaluated the use of the WBC, there is no clear consensus on its utility.**[24,25,27-29] WBC does not distinguish between simple and perforated appendicitis.[27] A C-reactive protein >10 mg/L in children <6 years old may be of value in predicting acute appendicitis[30]; however, C-reactive protein and the erythrocyte sedimentation rate used alone lack the sensitivity and specificity to rule in or rule out the diagnosis. If the only diagnostic consideration is acute appendicitis (yes or no), the greatest utility of laboratory tests may be in combination[31]; an elevated WBC and/or C-reactive protein may have a combined sensitivity as high as 98%. Normal values of both in patients with a low pretest probability of acute appendicitis make pathologically confirmed appendicitis very unlikely.[29,32-35] However, WBC and C-reactive protein levels are elevated in a number of other appendicitis mimics, so these markers are not useful if the differential diagnosis of pain is broad.[36,37] Other novel biomarkers have not yet demonstrated consistent utility in the diagnosis of acute appendicitis to warrant routine use.[10,31]

Obtain a urinalysis because isolated microscopic hematuria may support a diagnosis of renal colic, and pyuria may suggest pyelonephritis. However, hematuria or sterile pyuria can be present in acute appendicitis.[13] Document a negative pregnancy test in females of reproductive age to rule out ectopic or heterotopic pregnancy. Other laboratory tests are not routinely indicated but may be beneficial when considering other diagnoses.

IMAGING

Obtain early surgical consultation before imaging in straightforward cases of suspected appendicitis in adults. Imaging is not universally necessary but may be of benefit in certain populations.[38-40] In children, some centers prefer pediatric surgery consultation prior to imaging with ionizing radiation.

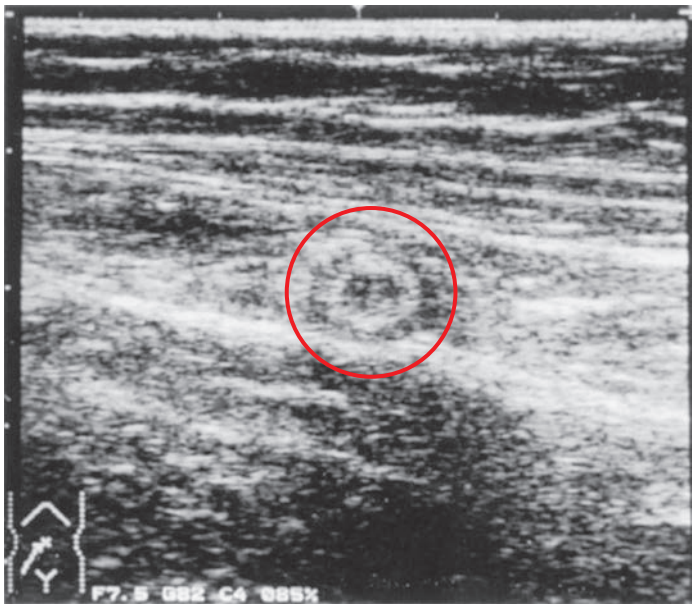
When adjunctive imaging is indicated, early surgical consultation may aid guidance in imaging selection. The goal of imaging is to establish the diagnosis of appendicitis, avoid a negative appendectomy, identify perforation, and exclude other causes of abdominal pain with minimal radiation, cost, and time.

Plain radiography is not helpful. Findings are typically nonspecific but may demonstrate a nonspecific bowel gas pattern or adynamic ileus. An appendicolith may be visualized in up to 50% of children with appendicitis.[39]

US **Graded compression US should be the initial imaging modality of choice in both pregnant females[41] and children.[42,43] It should likewise be considered in young, nonobese adults.[42]** Reports of the effectiveness of US diagnosis of appendicitis in pregnancy are conflicting, with some reporting US as useful[44] and others reporting it as ineffective for diagnosis.[45] POCUS is increasingly present in EDs, and more emergency physicians are experienced in performing and interpreting these studies. POCUS can be of utility in experienced hands in ruling in appendicitis. However, like other testing modalities, it should not be used as a stand-alone test to rule out the diagnosis.[46-48] Regardless, US is safe, fast, well-tolerated, and cost-effective.

The appendix is oval in the axial plane, ends blindly in the longitudinal plane, and should be compressible with a maximal diameter not exceeding 6 mm.[49] The normal appendix is typically differentiated from small bowel on US by the absence of peristalsis and the lack of change in configuration over time; its small size distinguishes it from large bowel. **Typical findings in appendicitis are a thickened, noncompressible appendix > 6 mm in diameter (Figure 81-1).** Doppler US may illustrate hyperemia.[39] It is important to image the entire length of the appendix, because inflammation may be more pronounced at or localized to the distal end.[49] Given the highly operator-dependent nature of US, centers treating larger volumes of children may have greater reproducibility of high-quality studies. The diagnostic accuracy of abdominal US in children is better at ruling in acute appendicitis than excluding it.[50] Besides operator skill, other limitations to accuracy include cases of retrocecal appendicitis or perforation, excessive abdominal guarding or bowel gas, a gravid uterus or obese habitus, a decompressed bladder, and lack of patient cooperation. **Perforation may lead to disappearance of specific imaging hallmarks and difficult visualization of the appendix on US.** Pelvic US may be useful in cases of suspected appendicitis and a nondiagnostic abdominal US or CT,[51] or in the differentiation of appendicitis from pelvic inflammatory disease[52] (see Chapter 97, "Abdominal and Pelvic Pain in the Nonpregnant Female").

Abdominopelvic CT In most adult males and nonpregnant females for whom the diagnosis of appendicitis is not sufficiently clear, consider abdominal CT that includes the abdomen and pelvis. Typical



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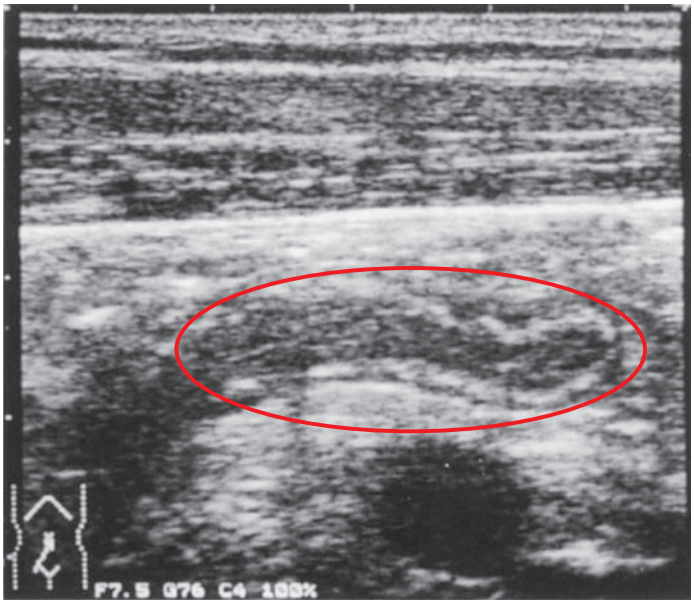

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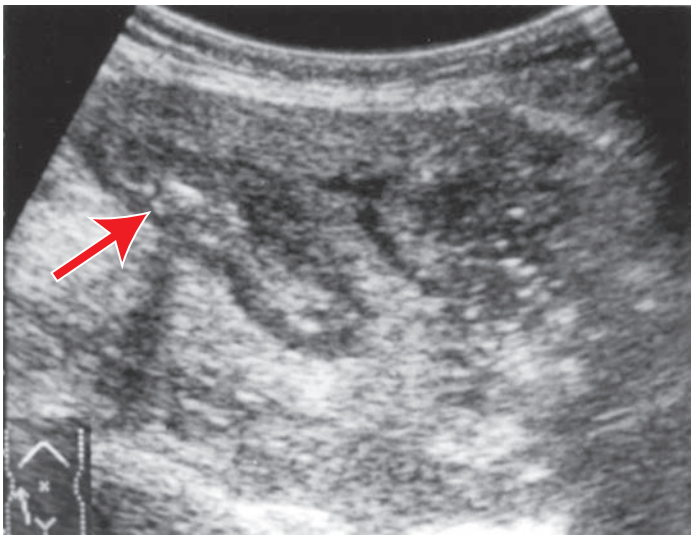

C

FIGURE 81-1. Ultrasonographic demonstration of acute appendicitis. A noncompressible, inflamed appendix (*red circles*) is shown in a cross-sectional view (**A**; 7.5 MHz) and a longitudinal section (**B**; 7.5 MHz). Mural lamination of the swollen appendix is maintained in the early stages of acute appendicitis. **C.** An appendicolith (*arrow*) with acoustic shadowing is demonstrated (5 MHz). [Reprinted with permission from Ma OJ, Mateer JR, Reardon RF, Blaivas M. *Emergency Ultrasound*. 3rd ed. Copyright © The McGraw-Hill Companies, 2014. All rights reserved. Chapter 11, General Surgery Applications, Figures 11-31A&B & 11-33.]

CT findings include a dilated appendix >6 mm with a thickened wall, periappendiceal inflammation, and potential visualization of an appendicolith or abscess.[53] Luminal obstruction and dilation may be relieved in cases of perforation, leading to disappearance of specific imaging hallmarks and difficult visualization of the appendix on CT.[13]

The accepted sensitivity of CT (composite studies using PO or IV contrast or no contrast) for the diagnosis of acute appendicitis is typically >94%, with a positive predictive value >95% (**Figure 81-2**).[38,40] In a comparison of CT versus US, the overall sensitivity of CT in patients >2 years old was 96%, with a 96% positive predictive value; graded compression US had an overall sensitivity of 86%, with a 95% positive predictive value. In this same study, women who had preoperative imaging had a statistically significant lower negative appendectomy rate than women who had no imaging, suggesting that women with suspected acute appendicitis derive the greatest benefit from preoperative imaging.[40] The 2015 American College of Radiology Appropriateness Criteria for right lower quadrant pain state that although US is the preferred initial imaging modality in children, CT is overall the most accurate imaging modality for suspected appendicitis.[54] **Appendiceal CT**, a less frequently used protocol, uses rectally administered contrast only with acquisition of thin cuts through the right iliac fossa. This avoids the difficulties of PO contrast administration in patients with active emesis and prevents potential adverse reactions of IV contrast. Time to acquisition of images is much shorter, typically around 15 minutes after administration of rectal contrast, but may produce significant patient discomfort.[55,56]

PO and IV Contrast Versus Nonenhanced CT PO contrast medium has historically been recommended for CT of the abdomen and pelvis when investigating a broad differential of GI or pelvic diagnoses, and many centers continue to recommend CT imaging with both IV and PO contrast. Yet, the current body of literature does not support this as routine practice, and multiple studies indicate that nonenhanced CT has excellent performance in the diagnosis of acute appendicitis.[57-62] The imaging evaluation of abdominal pain is time intensive and impacts ED overcrowding. Unenhanced studies can significantly decrease the time to

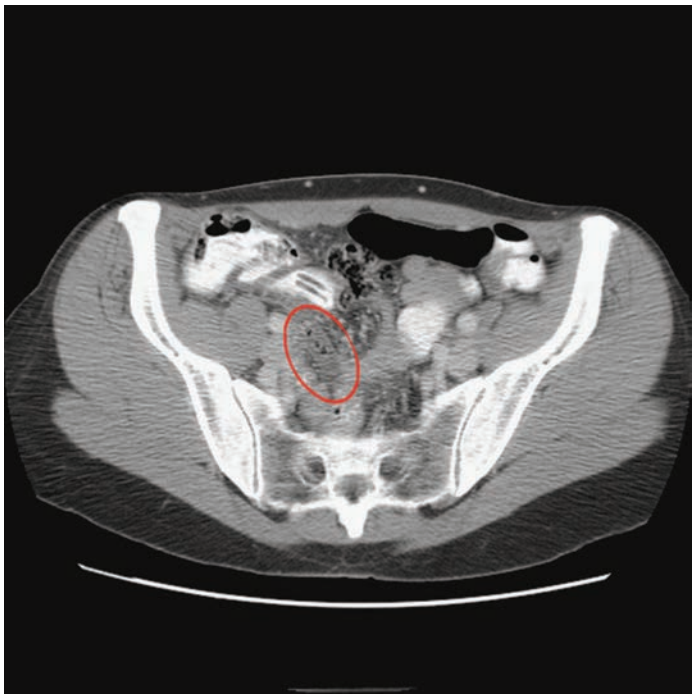

FIGURE 81-2. Acute appendicitis on contrast CT scan as evidenced by dilated and inflamed appendix (*red circle*).

diagnosis and eliminate patient discomfort from PO (especially in vomiting patients) or rectal contrast, and avoids altogether the risk of renal injury from IV contrast. More than 52% of 462 patients who underwent CT imaging in at least one study had no PO, IV, or rectal contrast administered, with a combined sensitivity of 93% and a positive predictive value of greater than 92%, supporting the suitability of nonenhanced CT imaging for making the diagnosis.[40] A comparison of nonenhanced CT with findings on laparoscopy reported 95% sensitivity and 100% specificity of nonenhanced CT in suspected appendicitis,[2] whereas another systematic review reported a pooled sensitivity of 92.7% (95% CI, 89.5% to 95.0%) and specificity of 96.1% (95% CI, 94.2% to 97.5%).[57] Another systematic review of 23 studies showed equivalent or improved diagnostic performance of nonenhanced CT when compared to PO contrast.[40] PO contrast frequently does not reach the terminal ileum at the time of imaging, yet in this group of patients, at least one author has shown no diagnostic compromise in the performance of imaging.[62] Several studies attribute disagreement between nonenhanced CT and contrasted studies more to interobserver variability than contrast medium.[60,63] Furthermore, the 2015 American College of Radiology Appropriateness Criteria favor the use of IV contrast but do not endorse enteric contrast when IV contrast is used.[54] **Noncontrast CT should be considered an acceptable imaging modality in the workup of acute appendicitis.** In patients with renal insufficiency or dye allergy, administration of IV contrast is contraindicated. Body habitus may limit reproduction of noncontrast CT test characteristics; intraperitoneal fat serves as an intrinsic contrast medium in unenhanced CT, and its paucity in very thin patients can affect imaging interpretation.[53,55,64]

MRI Consider MRI as another reliable imaging technology in the evaluation of acute appendicitis, particularly in pregnant women. MRI may be applicable to pediatric patients >5 years of age at tertiary hospitals with MRI capability and is also a reasonable option after equivocal US.[65] MRI avoids ionizing radiation and visualizes the entire abdomen in multiple planes. In a survey of U.S. academic medical centers with radiology residency programs, MRI was preferred over CT (39% vs 32%) for evaluation of appendicitis in the first trimester of pregnancy. This preference reversed in the second and third trimesters.[41] **IV gadolinium crosses the placenta and is not used in pregnancy** given the teratogenic effects seen in animal studies.[66] **Gadolinium is not given to patients with renal insufficiency because it may cause nephrogenic fibrosing dermopathy.** Avoid MRI in the evaluation of the unstable patient given the time necessary for study acquisition. Sedation may be required for small children, rendering it impractical in many pediatric cases. However, the continued advancement of technology and scanning technique has resulted in the ability to perform faster studies without the need for contrast media or sedation and the traditional adverse impact on ED throughput.[65]

TREATMENT

Patients with acute appendicitis typically require appendectomy, so immediate surgical consultation is needed. Patients should be maintained as "nothing by mouth" to avoid operative delay. Provide resuscitation and maintenance IV fluids with appropriate antiemetics and analgesia. Initiate perioperative antibiotics upon diagnosis or if the patient exhibits signs of peritonitis. Appropriate choices should broadly cover aerobic and anaerobic gram-negative organisms. Acceptable regimens include ampicillin/sulbactam 3 grams IV (pediatric dose, 75 milligrams/kg IV); piperacillin/tazobactam 4.5 grams IV (100 milligrams/kg IV); cefoxitin 2 grams IV (40 milligrams/kg); or metronidazole 500 milligrams IV plus ciprofloxacin 400 milligrams IV.[67]

Given the nonoperative management of uncomplicated diverticulitis, salpingitis, and neonatal enterocolitis with antibiotics, some suggest a similar nonoperative approach to uncomplicated acute appendicitis.[1] A nonoperative approach is also occasionally used for older, sicker patients who are considered high-risk surgical candidates. However, recent reports suggest that the features that make these patients "high risk" in the first place may actually make them even higher risk nonoperative patients with worse outcomes.[11,68] **Numerous studies including randomized clinical trials have yet to provide sufficient evidence to support the routine use of nonoperative management. While an antibiotics-only approach may be feasible and safe in select, uncomplicated patients, surgical management remains the accepted standard of care.**[69-74]

DISPOSITION AND FOLLOW-UP

Surgery is the accepted standard of care for acute appendicitis. If the local surgical services are inadequate or unavailable, transfer the patient to an appropriate institution. For the patient in whom the diagnosis remains elusive despite a rigorous diagnostic evaluation, consider extended observation in the ED or hospital with serial examinations, allowing for evolution of the patient's condition. Alternatively, the stable, reliable patient without significant comorbidities may be a candidate for discharge provided they have a scheduled return visit to the ED or their primary physician (typically within 12 hours) for repeat examination. Patients must have adequate pain control and be able to tolerate oral hydration. Provide clear abdominal pain discharge instructions, including a list of concerning signs or symptoms that should prompt earlier return to the ED.

SPECIAL POPULATIONS

Uninsured/underinsured patients, individuals from low-income communities, and some ethnic minorities may be more likely to develop appendiceal perforation, but previously observed trends have been inconsistent in recent years.[6,75] The elderly are likely to have preexisting comorbidities that alter presentation, management, and outcomes. Institutionalized patients, those with communication difficulties, those with poor access to medical care, and the elderly may have more vague complaints, including diffuse pain, fever, or alteration in mental status. Such individuals commonly present later in the course of the disease and are more likely to have worse outcomes.[76] In such patients, an "atypical" presentation should be considered the norm. A low threshold for prolonged observation or admission can avoid unnecessary morbidity and mortality.

Pregnant women warrant special attention. Acute appendicitis is the most common surgical emergency in pregnancy, and delay in diagnosis

is the greatest cause of increased morbidity in the pregnant woman with an acute abdomen.[8,9,77] Ovarian torsion and ectopic or heterotopic pregnancy are additional considerations. If abdominal US is nondiagnostic, consider pelvic US, CT, or MRI. Consult with the radiologist to select the most appropriate imaging study. Many radiologists avoid CT in the first trimester given teratogenic concerns of ionizing radiation.[41] In addition, although iodinated contrast material is safe in pregnancy, avoid IV gadolinium.[66]

Children are a diagnostic challenge, particularly if they cannot adequately verbalize their complaints. In such cases, physical examination, parallel history from the parent or guardian, and a high index of suspicion are the keys to accurate diagnosis. Pediatric imaging should begin with US, but many centers advise early surgical consultation before any ionizing imaging if appendicitis is a consideration.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 82

Diverticulitis

Autumn Graham

INTRODUCTION AND EPIDEMIOLOGY

Diverticular disease is increasingly common in industrialized nations, and the prevalence of diverticulosis increases with age: 5% in patients age <40 years, 30% by age 60, and >70% by age 85.[1] Based on National Emergency Department Sample records from 2006 to 2013, evolving diverticulitis prevalence and management have resulted in a 27% increase in diverticulitis-related ED visits and a 105% increase in aggregated national cost, whereas ED admissions for diverticulitis decreased from 58% to 47% and surgical management decreased by 33%.[2]

The natural history of the disease appears to be more benign than previously believed. Only 15% of patients with diverticulitis develop complicated disease.[3] Recurrence occurs in 20% to 30% of patients with diverticulitis treated conservatively.[3,4] Although surgery played a prominent role in diverticulitis management in the past, most cases of diverticulitis can be managed medically, even with recurrent episodes. In one study following 2366 Kaiser Permanente patients hospitalized with acute diverticulitis and treated nonoperatively, 86% required no further inpatient care for diverticulitis during a 9-year follow-up period. Only 4% had a second recurrence. No patient with a second recurrence required an operation.[5]

PATHOPHYSIOLOGY

Diverticula are small herniations at sites where the vasculature, called *vasa recta*, penetrates the circular muscle layer of the colon. Although *true diverticula* involve all layers of the colon wall, most acquired diverticula are considered *false diverticula*, involving only the mucosal and submucosal layers. Diverticula usually range from 5 to 10 mm, but can extend up to 20 mm in length. Diverticulitis occurs when inflammation develops and, in complicated diverticulitis, leads to translocation of bacteria, microperforation, and abscess or phlegmon formation.[6]

There are similar chemical and histologic changes seen in inflammatory bowel disease and irritable bowel syndrome, but no unifying mechanism has been demonstrated.[6,7] Common bacterial pathogens are anaerobes, including *Bacteroides*, *Clostridium*, and *Peptostreptococcus*, as well as aerobic bacteria such as *Escherichia coli, Enterococcus*, *Pseudomonas aeruginosa*, and *Klebsiella*. While most GI infections are both anaerobic and aerobic, *Bacteroides fragilis* and *E. coli* are the dominant bacteria isolated.[8]

Altered bowel motility leads to high intraluminal colonic pressures and diverticula formation. The role of diet remains unclear. Smoking and obesity increase risk for diverticulitis, and an active lifestyle is said to decrease the risk. NSAIDs, opioids, and steroids increase the risk of perforation.[6]

In the United States, diverticular disease is almost exclusively a left-sided colon disease, specifically the descending and sigmoid colon. Right-sided disease accounts for only 2% to 5% of cases and is found predominantly in Asian populations.[9]

CLINICAL FEATURES

Classically, diverticulitis presents with left lower quadrant abdominal pain, fever, and leukocytosis. Patients with a redundant sigmoid colon, of Asian descent, or with right-sided disease may complain of right lower quadrant or suprapubic pain. The pain may be intermittent or constant and is often associated with a change of bowel habits, either diarrhea or constipation. Other associated symptoms include nausea/vomiting, anorexia, and urinary symptoms. On physical examination, patients may exhibit findings ranging from mild abdominal tenderness to moderate tenderness with a tender palpable mass, to distended abdomen, to peritonitis with rebound and guarding. Urinalysis may demonstrate sterile pyuria due to inflammation of the bladder.

DIAGNOSIS

In stable patients with a history of confirmed diverticulitis and a similar acute presentation, no further diagnostic evaluation is necessary unless the patient fails to improve with conservative medical treatment. If a prior diagnosis has not been confirmed or the current episode differs from the past episode, diagnostic imaging is required to exclude other intra-abdominal pathology and to evaluate for complications. The differential diagnosis of diverticulitis is extensive, including gynecologic emergencies, cancer, and inflammatory or infectious colitis (**Table 82-1**). Laboratory data are rarely diagnostic for diverticulitis, but liver function panels, CBC, renal panel, lipase, C-reactive protein, and urinalysis may aid in the exclusion of other disorders and prediction of diverticulitis severity.

TABLE 82-1 Differential Diagnosis of Diverticulitis

- Acute appendicitis
- Colitis—ischemic or infectious
- Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- Colon cancer
- Irritable bowel syndrome
- Pseudomembranous colitis
- Epiploic appendagitis
- Gallbladder disease
- Incarcerated hernia
- Mesenteric infarction
- Complicated ulcer disease
- Peritonitis
- Obstruction
- Ovarian torsion
- Ectopic pregnancy
- Ovarian cyst or mass
- Pelvic inflammatory disease
- Cystitis
- Kidney stone
- Renal pathology
- Pancreatic disease

IMAGING

CT is the preferred imaging modality because of its ability to evaluate the severity of disease and the presence of complications. The American College of Radiology Appropriateness Criteria recommends CT of abdomen and pelvis with IV contrast and states that "oral and/or colonic contrast may be helpful for bowel luminal visualization" due to its documented sensitivities of 97% and specificities approaching 100%.[10] Multiple retrospective and small prospective studies have shown that variable contrast strategies including no IV or PO contrast and low-dose radiation CTs have been sensitive and specific for diverticulitis.[11-13] For most patients, CT of abdomen and pelvis with IV contrast only for patients with a body mass index >20 kg/m^2 and addition of PO contrast for patients with a body mass index <20 kg/m^2 is appropriate. CT findings include increased soft tissue density within the pericolic fat, indicating inflammation; presence of diverticula; bowel wall thickening >4 mm; soft tissue masses representing phlegmon; or pericolic fluid collections representing abscesses.[14]

Compression US is operator dependent and limited based on the patient's body habitus. Sensitivity and specificity of US for diverticulitis vary but are >80% in experienced hands. CT is preferred to detect complications.[14]

TREATMENT

Treatment varies with disease severity. Uncomplicated diverticulitis is isolated to inflammation of the diverticula with or without phlegmon or small abscess confined to the bowel wall. Complicated diverticulitis includes diverticular inflammation associated with abscess, stricture, obstruction, fistula, or perforation.

Current treatment and disposition recommendations are provided in **Tables 82-2** and **82-3**.

Uncomplicated diverticulitis treatment is rapidly evolving. The cornerstone of treatment has been antibiotics (Table 82-2). With increased understanding of the inflammatory rather than infectious etiology of uncomplicated diverticulitis, recent studies have reported no benefit to routine antibiotic use. The 2015 American Gastroenterology Association recommends "that antibiotics should be used selectively, rather than routinely, in patients with acute uncomplicated diverticulitis" confirmed by CT.[15] These recommendations are similar to those adopted in Denmark,[16] Italy,[17] Germany,[18] and the Netherlands.[19]

In the United States, this guideline recommendation was based in large part on the multicenter, randomized AVOD trial (20) in Sweden and Iceland. Of the 623 admitted patients with CT-verified, acute, left-sided diverticulitis, 309 patients were randomized to IV fluids with no antibiotics and 314 patients to IV antibiotics. Six patients (2%) who did not receive antibiotics and three patients (1%) who received antibiotics developed complications (e.g., abscess or perforation). There were no differences between the antibiotic and no antibiotic groups in symptoms at 30-day follow-up, need for emergency surgery, or median hospital stay.[20]

Other retrospective and prospective studies have reported similar findings.[21,22] Daniels and colleagues[23] published a multicenter, open-label, pragmatic, randomized controlled trial of 528 patients with acute, CT-confirmed diverticulitis enrolled in one of the following strategies: (1) admission with 48 hours of IV antibiotics with conversion to oral antibiotics for the remainder of a 10-day antibiotic treatment course, or (2) an outpatient observation arm for those who met criteria for outpatient treatment. No significant differences were reported between the observational versus antibiotic group in recovery time (14 vs. 12 days), complications (3.8% vs. 2.6%), recurrent disease (3.4% vs. 3.0%), surgery (3.8% vs. 2.3%), readmission (18% vs. 12%), or mortality (1.1% vs. 0.4%).[23]

These studies and expert opinion suggest that observational treatment without antibiotics may be appropriate for CT-confirmed, uncomplicated, acute diverticulitis in immunocompetent patients with mild symptoms and without systemic infectious signs or symptoms or red flags for progression to complicated diverticulitis. Procalcitonin has been suggested as a tool to guide the use of antibiotics in diverticulitis, similar to its role in upper respiratory infection management, but more research is needed before clinical application.[24]

Dietary restriction or modification is commonly recommended, but efficacy is not clear.[6] It is not necessary to limit the patient to a clear diet, but patients can be advised to eat foods as tolerated. During the acute episode, our personal recommendations also include no dairy foods, because ability to process lactate can change, and no red meat, because it is difficult to digest.

TABLE 82-2 Antibiotics for Diverticulitis

Outpatient 4–7 days	First line	Metronidazole 500 milligrams PO QID PLUS Ciprofloxacin 750 milligrams PO BID OR Levofloxacin 750 milligrams PO daily OR Trimethoprim-sulfamethoxazole (160 milligrams/800 milligrams) 1 double-strength tablet PO BID OR Cefuroxime 500 milligrams PO BID
	Alternate	Amoxicillin-clavulanate 875 milligrams 1 tablet PO BID OR Moxifloxacin 400 milligrams PO daily
Inpatient		
Moderate disease	First line	Metronidazole 500 milligrams IV q6h or metronidazole 1 gram IV q12h PLUS Ciprofloxacin 400 milligrams IV q12h OR Levofloxacin 750 milligrams IV q24h OR Aztreonam 2 grams IV TID OR Ceftriaxone 1–2 grams IV q24h OR Cefuroxime 1.5 grams IV q8h
	Alternative	Ertapenem 1 gram IV q24h Piperacillin-tazobactam 3.375 grams IV q6h or 4.5 grams IV q8h Ticarcillin-clavulanate 3.1 grams IV q 6h
Severe, life-threatening	First line	Imipenem/cilastatin 500 milligrams IV q6h OR Meropenem 1 gram IV q8h OR Piperacillin-tazobactam 4.5 milligrams IV q8h OR Ticarcillin-clavulanate 3.1 grams IV q4h
	Alternative	Ampicillin 2 grams IV q6h PLUS Metronidazole 500 milligrams IV q6h PLUS Ciprofloxacin 400 milligrams IV q12h OR Amikacin 15 milligrams/kg/day IV divided q12h
	Penicillin allergy	Aztreonam 2 grams IV q6h PLUS Metronidazole 500 milligrams IV q6h

Note. Adult dosing only. Dose adjustments may be required for renal and/or liver impairment. Antibiotic choice should be guided by local antibiograms and local antibiotic resistance patterns.

TABLE 82-3 Disposition Options for Diverticulitis

Disposition		
Appropriate for Outpatient Management +/- antibiotics		
• Uncomplicated diverticulitis • Normal vital signs • Mild to moderate symptoms with mild tenderness on physical exam • No associated abdominal distention • No vomiting, able to tolerate fluids and take medications • Able to control pain with oral medications • Able to follow up with physician in 2–3 days • Able to care for self at home		
Inpatient Management		
• Complicated diverticulitis (phlegmon, abscess, perforation, fistula, stricture, obstruction) • High-risk patients		
High Risk of Complications and Treatment Failure		
Clinical Risk Factors	**Diagnostic Risk Factors**	**CT Imaging Risk Factors for Progression to Complicated Diverticulitis**
• Age >70 years • Fever • Vomiting/Inability to tolerate PO • Poor follow-up or inability to care for self at home • Multiple comorbid conditions • Immunocompromised • Corticosteroid use • Malnutrition • Active malignancy • Chronic opiate use	• Generalized abdominal pain/tenderness versus localized to left lower quadrant • Leukocytosis – WBC 11×10^9/L (sensitivity 82%, specificity 45%) • CRP >90 mg/L (sensitivity 88%, specificity 75%) • Signs of sepsis	• Fluid collections (frequently anterior to rectum) • Greater length of inflamed colon (85 mm vs. 65 mm) • Inflamed diverticulum greater than 2 cm

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If antibiotics are warranted, a shorter duration of antibiotics (4 to 5 days) compared to the standard antibiotic course (7 to 10 days) may be appropriate. The Infectious Diseases Society of America recommends "antimicrobial therapy for established infections should be continued until resolution of clinical signs of infection occurs, including normalization of temperature and WBC count and return of gastrointestinal function."[25] The natural history of diverticulitis suggests symptom improvement in 2 to 4 days. A study of admitted patients receiving IV ertapenem found that a 4-day course of antibiotics was as effective as a 7-day course.[26] There is no proven advantage of IV antibiotics over PO antibiotics for diverticulitis.[6] Thus, for stable, immunocompetent patients with established follow-up in 2 to 4 days, a short course of antibiotics (4 to 5 days) may be appropriate.

Complicated diverticulitis generally requires admission. In addition to bowel rest and IV antibiotics, treatments directed at specific complications are needed. Complicated diverticulitis is classified by the Hinchey classification scheme[10]: Stage 1 is small, confined pericolic or mesenteric abscesses; stage 2 is larger abscesses, extending to the pelvis; stage 3 is perforated diverticulitis and purulent peritonitis; and stage 4 refers to free perforation with fecal contamination of the peritoneal cavity.

Abscesses and phlegmon are among the most common complications. Phlegmon is inflammation and infection of tissue without abscess. Patients with abscesses that measure <3 cm and phlegmon (Hinchey stage 1) are admitted for IV antibiotics and monitoring for progression. Percutaneous drainage of abscesses >3 cm have allowed many patients to forgo invasive surgical management. Initial nonoperative treatment fails in up to 20% of patients.[27] Perforation has a high mortality rate, and patients need volume resuscitation, IV antibiotics, and emergent exploratory surgery. For Hinchey stage 3, the mortality rate approaches 13% and increases to 43% for Hinchey stage 4.[10,28]

DISPOSITION AND FOLLOW-UP

Table 82-3 provides detailed disposition options. ED discharge is appropriate for uncomplicated diverticulitis with instructions to follow up in 2 to 3 days with a primary care provider or to return to the ED for recurring pain, fever, nausea and vomiting, or abdominal tenderness.

Patients with intractable nausea or vomiting, significant comorbid diseases,[29] poor support at home, high leukocytosis, or high fevers, as well as the elderly, the immunocompromised, and those with persistent pain should be admitted. The immunocompromised and those taking chronic steroids often present atypically and are at risk for complications. Admit patients with complicated diverticulitis or failed outpatient management.

Acknowledgments: Special thanks to Elaine Bromberek, Brandon Ruderman, Sreeja Natesan, Traci Thoureen, and Sara Scott for their assistance with this chapter.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 83

Bowel Obstruction

Timothy G. Price

INTRODUCTION

Intestinal obstruction is the inability of the intestinal tract to allow for regular passage of food and bowel contents secondary to mechanical obstruction or adynamic ileus.

Mechanical obstruction is caused by either intrinsic or extrinsic factors. It requires identification of the cause and definitive intervention in a relatively short period of time to minimize morbidity and mortality (**Tables 83-1** and **83-2**). Adynamic ileus (paralytic ileus) is usually self-limiting and does not require surgical intervention.

Both large and small intestines may be obstructed by various pathologic processes (Table 83-1). Extrinsic, intrinsic, or intraluminal processes precipitate mechanical obstruction. Differentiating small bowel obstruction from large bowel obstruction is important, because the incidence, clinical presentation, evaluation, and treatment vary depending on the anatomic site of obstruction. Intestinal pseudo-obstruction (Ogilvie's syndrome) may mimic bowel obstruction.[1]

PATHOPHYSIOLOGY

Normal bowel contains gas as well as gastric secretions and food. Intraluminal accumulation of gastric, biliary, and pancreatic secretions continues even if there is no oral intake. As obstruction develops, the bowel becomes congested and intestinal contents fail to be absorbed. Vomiting and decreased oral intake follow. The combination of decreased absorption, vomiting, and reduced intake leads to volume depletion with hemoconcentration and electrolyte imbalance and may lead to renal failure or shock.

Bowel distention often accompanies mechanical obstruction. Distention is due to the accumulation of fluids in the bowel lumen, an increase in intraluminal pressure with enhanced peristaltic contractions, and air swallowing. When intraluminal pressure exceeds capillary and venous pressure in the bowel wall, absorption and lymphatic drainage decrease, the bowel becomes ischemic, and septicemia and bowel necrosis can develop. Shock ensues rapidly. Mortality is high if bowel obstruction has progressed to this degree. This sequence of events may occur more rapidly in a closed-loop obstruction with no proximal escape for bowel contents. Examples of closed-loop obstruction include an incarcerated hernia and complete colon obstruction in the presence of a closed ileocecal valve.

SMALL BOWEL OBSTRUCTION

Small bowel obstruction accounts for most bowel obstructions. The most common cause of small bowel obstruction is adhesions after abdominal surgery. Although in most cases, several months to years have passed from the time of the previous surgery, small bowel obstruction may occur within the first few weeks after surgery. The second most common cause of small bowel obstruction is incarceration of a hernia. See Chapter 84, "Hernias," for detailed description of types of hernias. In the elderly, adhesions and hernias are still common causes of small bowel obstruction.

TABLE 83-1 Common Causes of Intestinal Obstruction

Duodenum	Small Bowel	Colon
Stenosis	Adhesions	Carcinoma
Foreign body (bezoars)	Hernia	Fecal impaction
Stricture	Intussusception	Ulcerative colitis
Superior mesenteric artery syndrome	Lymphoma	Volvulus
	Stricture	Diverticulitis (stricture, abscess)
		Intussusception
		Pseudo-obstruction

TABLE 83-2 Key Features of Ileus and Mechanical Bowel Obstruction

	Ileus	Bowel Obstruction
Pain	Mild to moderate	Moderate to severe
Location	Diffuse	May localize
Physical examination	Mild distention, ± tenderness, decreased bowel sounds	Mild distention, tenderness, high-pitched bowel sounds
Laboratory	Possible dehydration	Leukocytosis
Imaging	May be normal	Abnormal
Treatment	Observation, hydration	Nasogastric tube, surgery

Bariatric surgery may be complicated by internal hernias after Roux-en-Y gastric bypass.[2,3] Other causes of small bowel obstruction are much less common and generally are the result of intraluminal or intramural processes. Primary small bowel lesions include polyps, lymphoma, or adenocarcinoma. Hamartomatous polyps are common in Peutz-Jeghers syndrome; polyps occur in patients between the ages of 10 and 30 years and can cause obstruction.[4] An unusual cause of intraluminal obstruction is gallstone ileus, in which a gallstone has eroded from the gallbladder through the bowel wall and causes obstruction at the ileocecal valve. Signs of gallstone ileus include bowel obstruction and pneumobilia. Lymphomas may be the leading point of intussusception and present as small bowel obstruction. Bezoars are most commonly composed of vegetable matter or pulp from persimmons. Patients who have undergone GI pyloroplasty or pyloric resection are most susceptible to intraluminal obstruction by bezoars.

Inflammatory bowel disease or its complications may obstruct the small bowel at various sites. Radiation enteritis is a possible cause of small bowel obstruction in patients who have undergone radiation therapy. Blunt abdominal trauma may cause a duodenal hematoma. This condition is seen in individuals restrained solely by a lap belt or as a result of striking the handlebar of a bicycle and may present as intra-abdominal pain and vomiting similar to other causes of small bowel obstruction.

Capsule endoscopy, used to visualize the entire small bowel, may be complicated by capsule retention, with literature-reported frequencies of 1% to 20%.[5] Capsule retention can lead to obstruction and perforation, so patients with abdominal pain after capsule introduction should be carefully evaluated for these complications.[5]

LARGE BOWEL OBSTRUCTION

Neoplasms are by far the most common cause of large bowel obstruction, especially in the elderly. However, incidence is rising in younger patients, even those <40 years old. Colonic obstruction is almost never caused by hernia or surgical adhesions and should prompt an evaluation for a neoplasm. Diverticulitis may create significant mesenteric edema and secondary obstruction. Stricture formation may occur with chronic inflammation and scarring. Fecal impaction is a common problem in the elderly or debilitated and may present with symptoms of colonic obstruction.

The next most frequent cause of large bowel obstruction after cancer and diverticulitis is sigmoid volvulus. Elderly, bedridden, or psychiatric patients who are taking anticholinergic medication are most at risk for volvulus. Cecal volvulus has been reported in pregnant patients.[6]

CLINICAL FEATURES

HISTORY

The site and nature of the obstruction and the preexisting condition of the patient will determine the clinical presentation. Although some generalizations are possible, there are no components of the history able

to reliably predict small bowel obstruction.[7] Abdominal pain is nearly universal. Pain generally is crampy and intermittent. Pain of mechanical small bowel obstruction is often episodic, lasting for a few minutes at a time, and may be periumbilical or diffuse. Pain tends to be less intense and more constant in adynamic ileus. Proximal obstruction usually causes vomiting. Vomitus is usually bilious in proximal obstruction but is feculent in distal ileal or large bowel obstruction. The pain of large bowel obstruction is usually hypogastric.

Other features that are consistently present with obstruction of small bowel or colon include the inability to have a bowel movement or pass flatus. "Constipation" is a common symptom of bowel obstruction. Partial bowel obstruction, however, is often associated with regular passage of stool and flatus. Additional risk factors are advanced age and anticholinergic or tricyclic antidepressant use, which depress bowel motility.

PHYSICAL EXAMINATION

Physical findings vary depending on the site, duration, and cause of obstruction. In small bowel obstruction, distention is the most reliable sign, and some distention is usually present early in the disease process.[7] Abdominal tenderness may be minimal to severe and localized or diffuse. Peritonitis causes severe pain. The abdomen may be tympanitic to percussion. Mechanical obstruction produces active, high-pitched bowel sounds with occasional "rushes." If obstruction has been present for several hours, peristaltic waves and bowel sounds may be diminished. Localized or rebound tenderness may be a sign of gangrenous or perforated bowel, which requires immediate surgical intervention. Patients with an adynamic ileus may have some abdominal distention associated with diminished or absent bowel sounds.

Careful examination coupled with radiographic investigation will often distinguish bowel obstruction from ileus. Emptiness of the left iliac fossa is a reliable sign of sigmoid volvulus. Organomegaly or masses may suggest a cause of the obstruction. The *absence* of stool or air in the rectal vault supports a diagnosis of obstruction and may aid in the diagnosis of bowel obstruction, but its *presence* does not eliminate a more proximal obstruction. A rectal examination may identify fecal impaction, rectal carcinoma, occult blood, or stricture. Consider a pelvic examination in women to identify gynecologic pathology causing obstruction. A vaginal pessary can cause colonic obstruction due to extrinsic compression of the colon.[8] See Table 83-2 for the key causes of ileus and mechanical bowel obstruction.

DIAGNOSIS

Consider bowel obstruction or ileus in any patient with abdominal pain and distention. Numerous other pathologic processes may also cause these symptoms, but additional evaluation guided by the history and physical examination may be necessary to confirm or rule out obstruction or ileus.

LABORATORY TESTING

Laboratory studies usually include a CBC and electrolyte levels, the results of which may vary widely depending on the duration and site of obstruction and the presence of bowel necrosis. A leukocytosis of >20,000/mm^3 or left shift should make one suspect bowel gangrene, intra-abdominal abscess, or peritonitis. Extreme leukocytosis (>40,000/mm^3) suggests mesenteric vascular occlusion. The serum amylase and lipase levels may be mildly elevated. Increases in hematocrit, BUN, and creatinine are consistent with volume depletion and dehydration. Other indications of the severity of obstruction or secondary complications include increased urine specific gravity, ketonuria, elevated lactate levels, and metabolic acidosis. Small studies suggest that procalcitonin may predict bowel ischemia or failure of conservative management.[9]

IMAGING

In the ED, flat and upright abdominal radiographs with an upright chest radiograph or a lateral decubitus view are of little utility. Plain films may reveal severe constipation, but be cautious of prematurely attributing symptoms to the presence of colonic stool, even large burdens. Perhaps the greatest value of the plain radiograph is in demonstrating free air secondary to rupture and expediting surgical management. CT scan with oral and IV contrast is the imaging method of choice in the ED (**Figures 83-1** and **83-2**). The CT scan provides information not only about the presence of an obstruction but often also its location, severity, and cause.[1] In the presence of renal insufficiency or contrast allergy, oral contrast alone may provide sufficient diagnostic information. US can identify small bowel obstruction,[10-12] but management relies on further imaging with CT.[11]

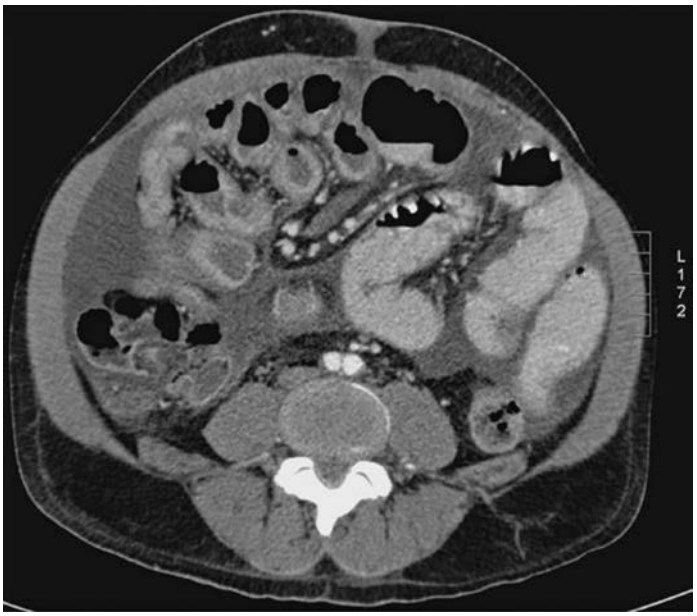

FIGURE 83-1. Distended loops of small bowel are evident, and decompressed loops are visible in the right lower quadrant. Findings suggest the presence of a transition point. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. New York, NY: McGraw-Hill Education, Inc.; 2013. Fig 7.38 Part B.]

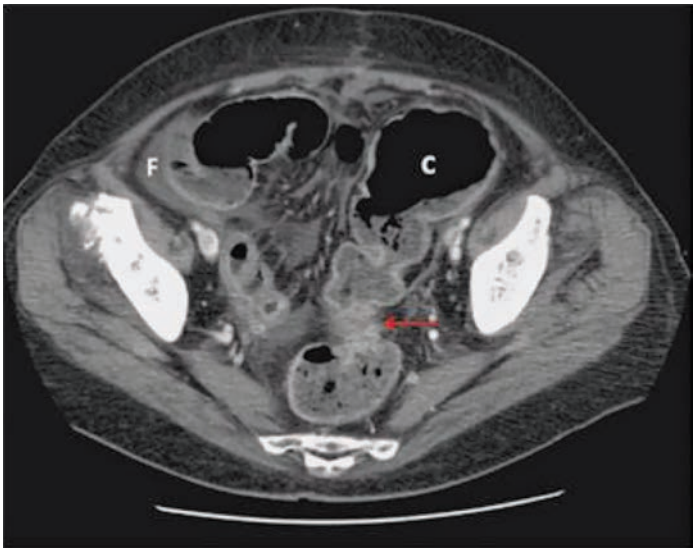

FIGURE 83-2. CT scan of large bowel obstruction. *Arrow* indicates an apple core lesion; *C* shows dilated colon proximal to the stricture; and *F* shows fluid in the right paracolic gutter. [Reproduced from Butler KL, Harisinghani M (eds): *Acute Care Surgery: Imaging Essentials for Rapid Diagnosis*. New York, NY: McGraw-Hill, Inc., 2015. Fig. 10-11.]

TREATMENT AND DISPOSITION

Many patients with small bowel obstruction may be successfully managed nonoperatively, whereas most patients with large bowel obstruction will require surgery.[13] For colonic obstruction due to malignancy, tumor resection is the gold standard treatment. Self-expanding endoluminal stents can be used to relieve the obstruction and avoid emergent surgery.[14] Use of a nasogastric tube is often unnecessary, but should be considered in the presence of severe distention and vomiting. Local surgeon preference continues to dictate local practice with regard to nasogastric tube use. Vigorous IV fluid replacement is needed because of loss of absorptive capacity, decreased oral intake, and vomiting. Monitor adequacy of fluid resuscitation by the response of blood pressure, heart rate, and urine output. **Closed-loop obstruction, bowel necrosis, and cecal volvulus are surgical emergencies.** Administer preoperative broad-spectrum antibiotics in the ED. There are many possible regimens. Monotherapy could be tazobactam-piperacillin, 3.375 grams IV every 6 hours, ticarcillin-clavulanate, 3.1 grams IV every 6 hours, or a carbapenem.

If adynamic ileus is suspected or the diagnosis is uncertain, conservative inpatient management, including IV fluids and observation, generally is effective in allowing the bowel to resume normal activity and function. Discontinue medications that inhibit bowel mobility.

Admit patients with bowel obstruction to the hospital. Surgical consultation should generally be obtained in the ED or at the time of admission. Patients with adynamic ileus should also be admitted for the treatment of the underlying cause and until resolution of the ileus.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 84

Hernias

Don Byars
Turan Kayagil

INTRODUCTION

With nearly 10% of the population developing some sort of hernia during their lifetime, this is among the most common of surgical problems.[1] Hernias are classified by anatomic location, hernia contents, and the status of those contents (e.g., reducible, strangulated, or incarcerated).[2]

A hernia is called **reducible** when the hernia sac itself is soft and easy to replace back through the hernia neck defect. A hernia is **incarcerated** when it is firm, often painful, and nonreducible by direct manual pressure. **Strangulation** develops as a consequence of incarceration and implies impairment of blood flow (arterial, venous, or both). A strangulated hernia presents as severe, exquisite pain at the hernia site, often with signs and symptoms of intestinal obstruction, toxic appearance, and, possibly, skin changes overlying the hernia sac. A strangulated hernia is an acute surgical emergency. This chapter discusses hernias in adults. Hernias in children are discussed in Chapter 133, "Acute Abdominal Pain in Infants and Children."

ANATOMY OF COMMON HERNIAS

INGUINAL HERNIA

Seventy-five percent of all hernias occur in the inguinal region, making it the most common form of hernia, with two thirds of these being of the indirect type (**Figure 84-1**). Although there is a clear male predilection, inguinal hernias are also the most common hernias in women. Inguinal hernias present as a groin mass. Typically the mass has been present for some time, but may have recently become larger or the patient may have begun to develop symptoms of incarceration or strangulation. The differential diagnosis for a groin mass is somewhat broad and includes, in addition to hernia, hidradenitis, other abscess, sebaceous cyst, lymphoma, hydrocele, varicocele, femoral hernia, and femoral aneurysm. Thankfully, the physical examination for most hernias is fairly straightforward. Bedside US can be very helpful in the identification of an inguinal hernia if the diagnosis remains in question (**Figure 84-2**). One study reported 100% sensitivity and 100% specificity of bedside emergency US for the diagnosis of groin hernia.[3]

A **direct inguinal hernia** passes directly through a weakness in the transversalis fascia in the Hesselbach triangle. Hesselbach triangle is constructed with the lateral border of the inferior epigastric arteries, a medial border with the rectus sheath, and an inferior border of the inguinal ligament (**Figure 84-3**).[4]

The hernia sac from an **indirect inguinal hernia** passes from the internal to the external inguinal ring through the patent process vaginalis, and then to the scrotum (**Figure 84-4**).

VENTRAL AND INCISIONAL HERNIAS

Ventral hernias develop as a result of a defect in the anterior abdominal wall and can be either spontaneous or acquired. They are typically characterized by their anatomic location as epigastric, umbilical, incisional, or hypogastric (**Figure 84-5**).[5]

Incisional hernias account for up to 20% of all abdominal wall hernias. They are often the result of excess wall tension or inadequate wound healing. They are also associated with surgical wound infections. Risk factors for the development of incisional hernias include obesity, age, wound infection, and medical conditions (i.e., chronic obstructive pulmonary disease) that increase intra-abdominal pressure.[6] Incisional hernias can become quite large and produce symptoms varying from discomfort to extrusion of abdominal contents to incarceration and strangulation. Despite primary repair, incisional hernias can recur.

UMBILICAL HERNIA

The adult form of umbilical hernia is largely acquired and due to medical conditions that increase intra-abdominal pressure, including ascites, pregnancy, and obesity. Although strangulation is unusual in most patients, those with chronic ascites (i.e., cirrhotics) are at risk for umbilical hernia strangulation, rupture, and death from peritonitis.[7]

ANATOMY OF UNCOMMON HERNIAS

FEMORAL HERNIA

Femoral hernia (Figure 84-1) is so named because the hernia sac protrudes through the femoral canal and produces a mass that is typically below the inguinal ring. Femoral hernias are more common in women, with a 10 to 1 female predilection. The femoral hernia is particularly prone to complications, such as incarceration and strangulation. One study reported a 40% emergency surgery rate due to such complications in patients with a known femoral hernia.[8] All femoral hernias should be urgently referred for elective repair. Delays in femoral hernia repair lead to increasing rates of strangulation, reaching 45% at 21 months.[9] A small study by Malek et al[10] reported worrisome complication rates (31%) and surprising high mortality (13%) from delayed repair of femoral hernias.

SPIGELIAN HERNIA

Spigelian hernia (Figure 84-5), also known as a *lateral ventral hernia*, arises at the lateral edge of the rectus muscle and the arcuate (semilunar) line. Spigelian hernias are nearly always acquired conditions due to comorbidities that increase intra-abdominal pressure. These hernias are very difficult to diagnose, especially given the variability in presentation. The classic presentation is abdominal pain associated with an anterior lateral abdominal wall mass or bulge. Physical examination is unreliable,[11]

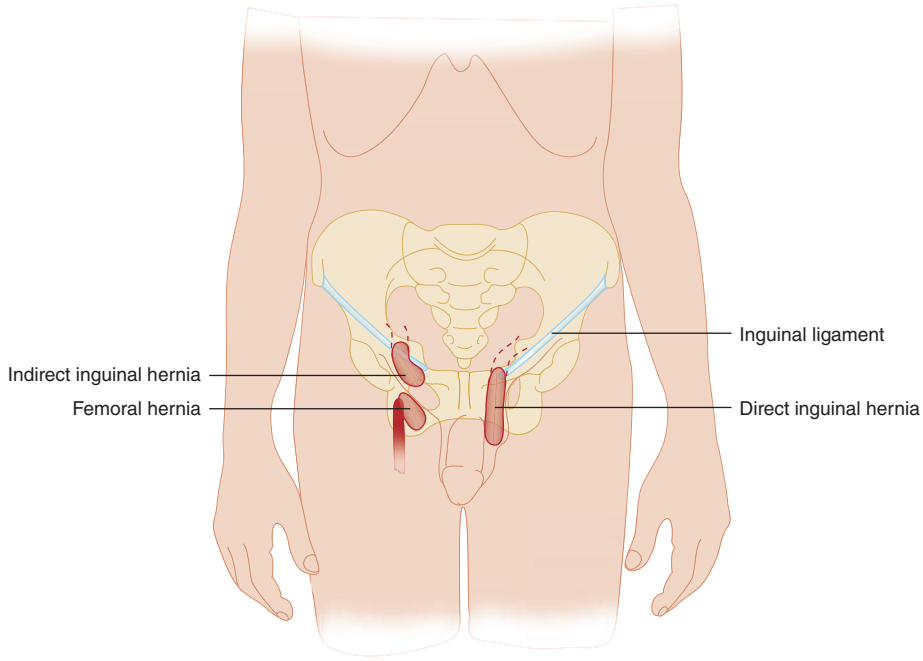

FIGURE 84-1. Groin hernia.

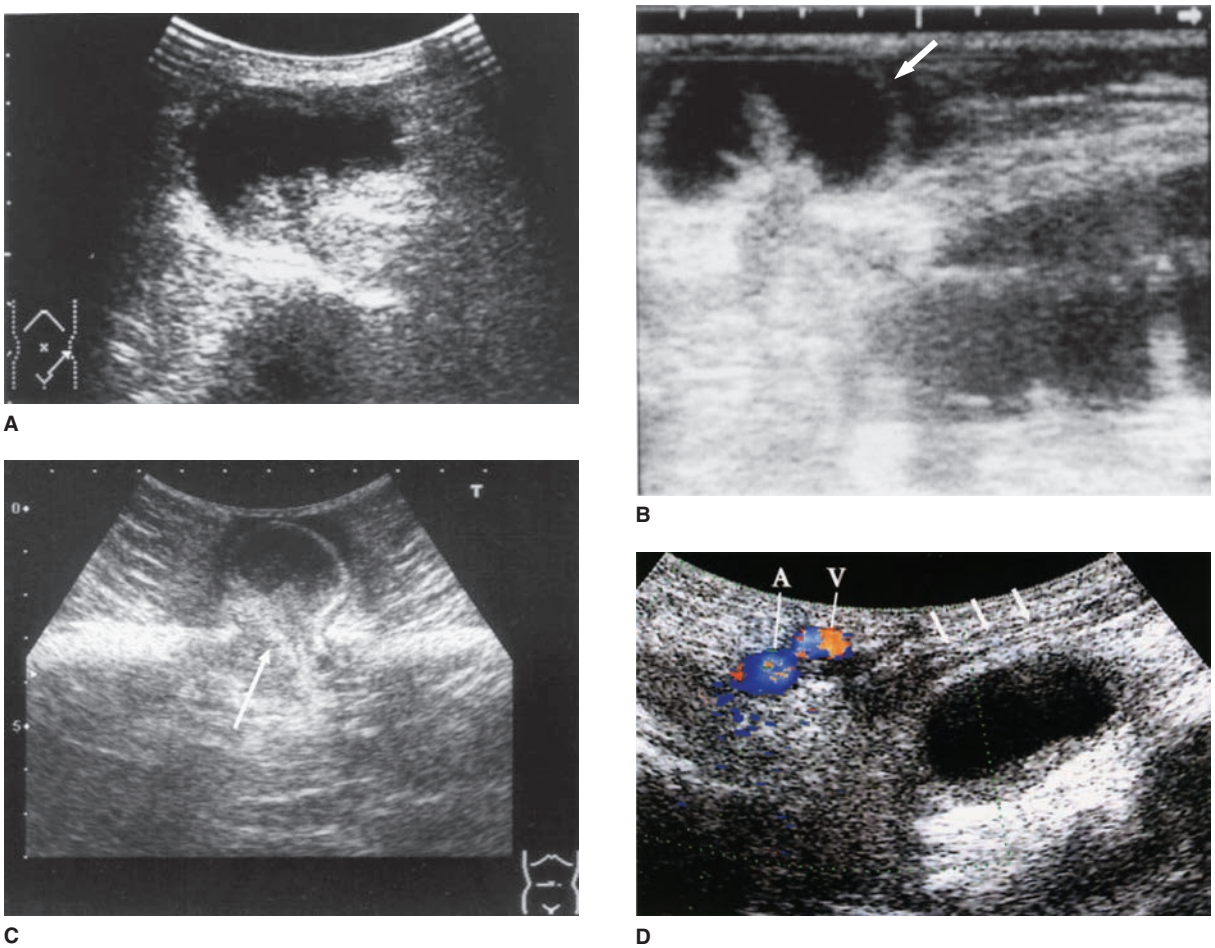

FIGURE 84-2. Incarcerated hernia. **A.** An incarcerated femoral hernia is demonstrated as a small-bowel segment herniated through the femoral canal. **B.** In an incarcerated incisional hernia, a small-bowel segment (*arrow*) is demonstrated as herniated through a small orifice in the abdominal wall. Dilated small-bowel loops are evident proximal to the incarceration. **C.** In an umbilical hernia, a herniated small-bowel segment is demonstrated within the fluid space in the hernia sac. The segment was softly strangulated at the hernia orifice (*arrow*) formed by a defect of the fascia and was easily reduced by manipulation in this case. **D.** An incarcerated obturator hernia is demonstrated deep in the femoral region. It locates posterior to the pectineus muscle (*arrows*) and medial to the femoral artery (A) and vein (V). [Reproduced with permission from Ma OJ, Mateer JR, Blaivas M (eds): *Emergency Ultrasound*, 2nd ed. Copyright © 2008 The McGraw-Hill Companies. All rights reserved. Chapter 9, General Surgery Applications, Common Abnormalities, Incarcerated Hernia. Figure 9-16.]

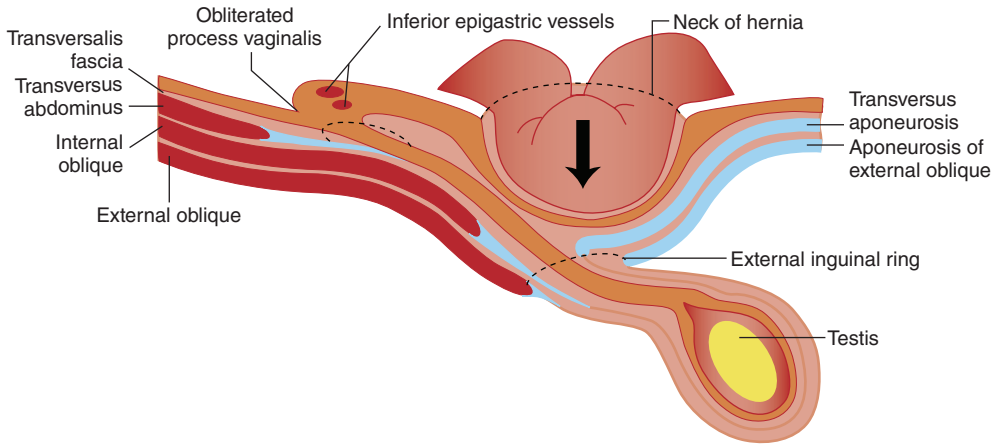

FIGURE 84-3. Direct inguinal hernia.

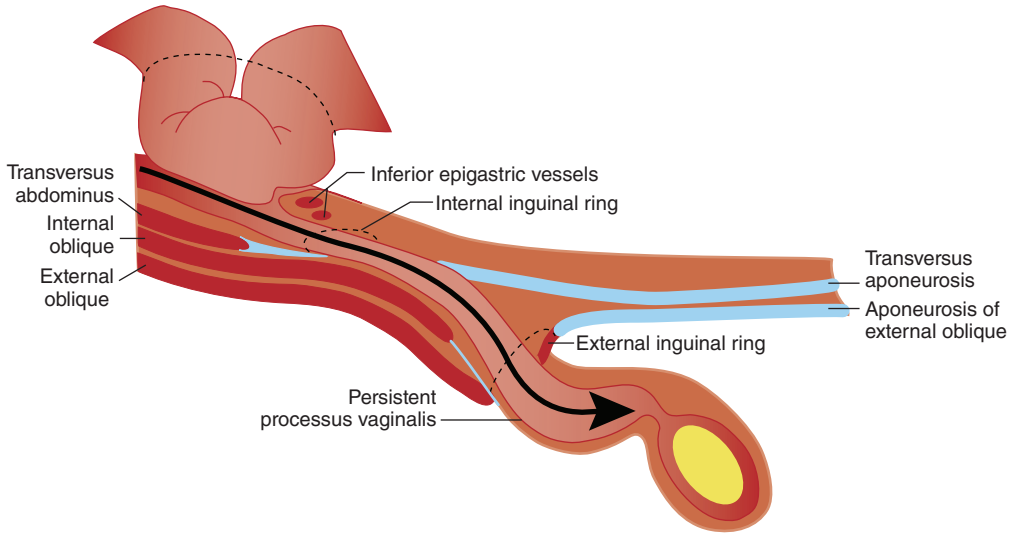

FIGURE 84-4. Indirect inguinal hernia.

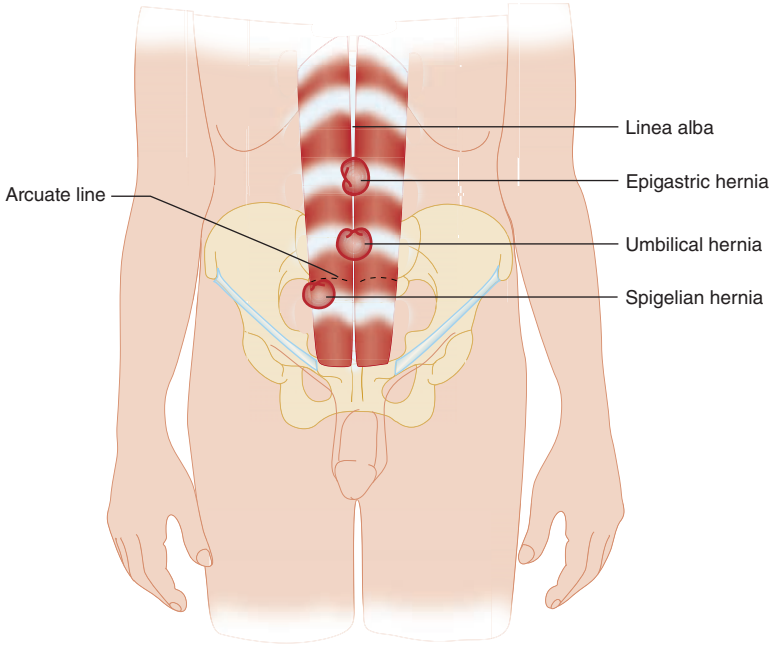

FIGURE 84-5. Anterior abdominal wall hernia.

and accurate diagnosis often requires diagnostic imaging. Bedside emergency US can accurately and quickly make the diagnosis.[12] CT scan remains the best imaging for diagnosis. Spigelian hernias should be surgically corrected given their high rates of incarceration.

OBTURATOR HERNIA

Obturator hernia is bowel herniation through the obturator canal (**Figure 84-6**) and nearly always presents as either a partial or complete bowel obstruction. The typical patient is an elderly frail female with signs and symptoms of intestinal obstruction. Although physical examination findings, such as the Howship-Romberg sign (pain in medial portion of the thigh due to obturator nerve compression), are well documented in the literature, the sign is not as useful in routine practice. Diagnosis is made by CT scanning of the abdomen and pelvis. It is important to properly diagnose this hernia given its high complication rate reported as perforation in >50% of cases and mortality approaching 20%.[13]

RICHTER HERNIA

Richter hernia involves only the antimesenteric border of the intestine and involves only a portion of the wall circumference. The Richter hernia presents differentially from a traditional incarcerated/strangulated hernia, as it often presents without vomiting or intestinal obstruction due to the incomplete involvement of the circumference of the intestine. Thus, the Richter hernia more often leads to strangulation and gangrene than other more standard hernias. Surgical repair is indicated.[14]

DIAGNOSIS

Traditional laboratory studies, such as a CBC, serum chemistries, and urinalysis, are routinely ordered but are of minimal value in the evaluation unless seeking an alternative diagnosis or for preoperative clearance.

IMAGING

Plain films are not required in hernia patients without significant symptoms. The acute abdominal series can reveal the presence of free air and signs of intestinal obstruction, but otherwise, plain films are usually indeterminate or nondiagnostic.

US has many advantages for diagnosis, but US is both operator and body habitus dependent. The primary role of US is the identification of the hernia itself. The **dynamic abdominal sonography for hernia** examination has good results in experienced hands as compared to CT for hernia diagnosis.[15] When a hernia is identified by US, note hernia size, contents, reducibility, location of the facial defect, and tenderness.[16] In addition to determining whether bowel is present in a hernia sac, US can sometimes identify signs of incarceration and strangulation.[16–18] Strangulated bowel, by definition, has vascular compromise. In the natural history of an incarcerated hernia, the thin-walled veins and lymphatics become compressed and compromised before the thick-walled arterial supply. Doppler US can detect the arterial flow to the loop of bowel, but is usually not sensitive enough to detect venous flow and cannot detect lymphatic flow. Thus, Doppler US can be insensitive for strangulation.[16,17,18] However, preservation of arterial inflow with obstruction of venous outflow causes increased intravascular pressure and extravasation of fluid into the extracellular space. This manifests itself as free fluid in the hernia sac on B-mode US, which is a sensitive finding for incarceration and strangulation. The specificity of free fluid in the hernia sac is good per se, but may be confounded by patients with ascites. Other US findings associated with incarceration and strangulation include hyperechoic fat, isoechoic thickening of the hernia sac, thickening of the wall of the herniated bowel, and free fluid within the herniated bowel loop.[16,18] Absence of peristalsis in a herniated bowel loop is suggestive of incarceration, and the presence of peristalsis implies that bowel resection is less likely to be necessary when the patient undergoes operative intervention.[18] US is most useful for diagnosis in children and pregnant women given its lack of ionizing radiation.[12]

It can be clinically difficult to differentiate hernia from hydrocele when assessing a scrotal mass. Obtaining a scrotal US in the standing position, with and without Valsalva maneuver, is a good way to demonstrate hernia.

CT is the best-performing radiographic test for hernia diagnosis and can identify uncommon hernia types (e.g., Spigelian or obturator) as well as demonstrate incarceration and strangulation.[19]

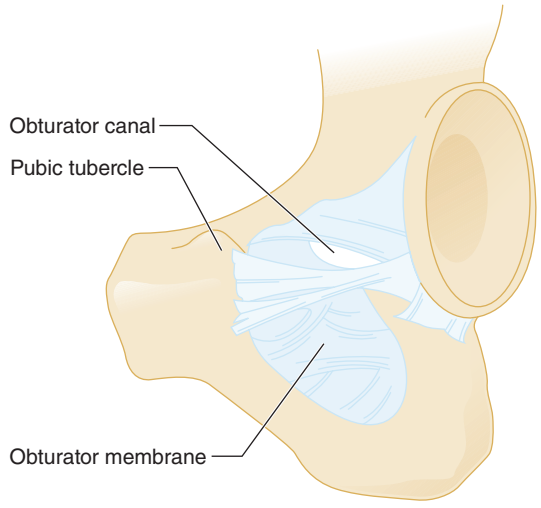

FIGURE 84-6. Obturator foramen. [Reproduced with permission from Pansky B: *Review of Gross Anatomy*, 6th ed, © 1995, The McGraw-Hill Companies, 1995, p. 511.]

TREATMENT

If the hernia is easily reducible on physical examination, then refer the patient for elective outpatient surgical repair.

If the hernia is exquisitely tender and is associated with systemic signs and symptoms, such as intestinal obstruction, toxic appearance, peritonitis, or sepsis, then assume hernia strangulation. Consult general surgery immediately.[20] Administer broad-spectrum IV antibiotics, provide fluid resuscitation and adequate narcotic analgesia, and obtain preoperative laboratory studies.

If the hernia is incarcerated but the patient does not yet show signs of strangulation, then make one or two attempts at reduction in the ED. Steps for hernia reduction[21] are listed in **Table 84-1**.

After ED reduction of an incarcerated hernia, it is reasonable to observe the patient in the ED for a period of time for serial abdominal examinations. Persistent significant abdominal pain must raise clinical concern for "**reduction en mass**."[22] Although a rare complication of reduction attempts, it has been reported in the literature from the early 1900s to the present day.[23,24] A reduction en mass occurs when an incarcerated hernia is reduced back into the peritoneal cavity but a loop

TABLE 84-1 Steps for Hernia Reduction

- NPO status in case reduction attempts are unsuccessful.
- Adequate IV narcotic analgesia.
- Apply cold packs to the hernia site to reduce swelling and make reduction attempts easier.
- Grasp and elongate the hernia neck with one hand, and with the other hand, apply firm, steady pressure to the proximal part of the hernia at the neck at the site of the fascial defect. US can aid in the identification of the fascial defect if it is not clinically obvious. Applying pressure on the most distal part of the hernia can cause bulging (or ballooning) at the hernia neck and prevent reduction.
- Consult surgery if the reduction is unsuccessful after one or two attempts.

of bowel remains inside the hernia sac even after reduction, so that the retained bowel remains incarcerated.[22,24] In cases of reduction en masse, the patient will continue to exhibit signs and symptoms of incarceration despite apparent clinical reduction. Imaging can assist in the detection of this distinctly uncommon but serious diagnosis.

If there is any concern for strangulation, do not attempt hernia reduction. The reintroduction of ischemic, necrotic bowel back into the peritoneal cavity can result in subsequent perforation and sepsis.[25] Bedside US using a linear high-frequency probe with color or power Doppler of the hernia sac can be useful in borderline cases to establish the presence or absence of arterial blood flow.[12]

Acknowledgments: The author gratefully acknowledges the contributions of Frank W. Lavoie and Mary Harkins Becker, the coauthors of the chapter on hernias in adults and children in the previous edition. (Hernia in children is now discussed in Chapter 133.)

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 85

Anorectal Disorders

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Brian E. Burgess

INTRODUCTION

Anorectal disorders range from simple to complex and can manifest signs and symptoms of underlying serious local or systemic disorders that may be life threatening. Precise causes may be difficult to determine; thus, a focused history and careful examination can narrow the differential diagnosis and aid timely and appropriate management.

ANATOMY

The rectum begins at the S3 vertebral body and descends for about 13 to 15 cm becoming the anus, which is comprised of the anal canal, anal verge, and anal margin. The rectum narrows and traverses through the muscular pelvic floor, at the level of the levator ani and coccygeal muscles, and becomes the anal canal, 4 cm in length, surrounded by the anal sphincter muscle.

The dentate line marks the junction of these two structures as the anal canal continues more distally joining the perianal skin at the anal verge (**Figure 85-1**). The anal canal mucosa consists of stratified squamous epithelium and contains no hair follicles or sweat glands. At the anal verge, the anoderm thickens and includes hair follicles and other cutaneous appendages. Proximal to the dentate line, the rectal ampulla narrows to conform to the opening of the anal canal. In doing so, its mucosa takes on a pleated appearance, forming 8 to 14 convoluted longitudinal folds: the columns of Morgagni. Each adjacent column is connected at the dentate line by a flap of mucosa that forms a small anal crypt, normally 1 to 3 mm deep. Anal sepsis, cryptitis, perianal abscesses, and fistulas result from inflammation, obstruction, and infection of the crypts and glands. Just proximal to the dentate line, the mucosa transitions from rectal columnar to cuboidal to squamous epithelium. The submucosa, which normally contains the bulk of the bowel's blood vessels and autonomic nerves, thickens considerably proximal to the dentate line. The superior hemorrhoidal artery, from the internal mesenteric artery, supplies the proximal two thirds of the rectum, whereas the middle hemorrhoidal artery, from the internal iliac artery, supplies the distal one third of the rectum. The inferior hemorrhoidal artery supplies the anus, but also supplies the rectum by a submucosal network. The venous and lymphatic system mirrors the arterial supply. The superior rectal vein drains into the portal system, whereas the middle rectal vein drains into the inferior vena cava. The inner circular muscle layer of the rectum thickens considerably as it terminates distally in the anorectum to form the involuntary internal sphincter muscles. The more attenuated longitudinal muscles of the rectum extend caudally, blending with fibers of voluntary skeletal muscles from the levator ani and external sphincter groups, to form the intersphincteric space (Figure 85-1).

The external sphincters are voluntary skeletal muscles and are actually a caudal extension of the puborectalis muscle, which interacts with the levator ani muscle, forming the pelvic floor. The puborectalis, the proximal external sphincters, and the internal sphincters form the ring of muscles that one palpates when performing a digital examination of the anorectum.

Lateral to the external sphincters is the ischiorectal space, and superior to the levator ani is the supralevator (pelvirectal) space, where deep, life-threatening infections can occur. Inferior mesenteric and para-aortic nodes drain the proximal two thirds of the rectum, whereas the lower one third of the rectum and proximal anal canal are drained by both the inferior mesenteric nodes and the internal iliac nodes. The inguinal nodes usually drain lymphatics distal to the dentate line. Proximal to the dentate line, the anus is supplied by the sympathetic and parasympathetic nerves, yet is devoid of somatic pain fibers, unlike distal to the dentate line, where somatic fibers are present. Parasympathetic nervous stimulation (S2 to S4) contracts the rectal wall and relaxes the internal anal sphincter, whereas sympathetic stimulation (L1 to L3) maintains continence through rectal wall inhibition and contraction of the internal anal sphincter.

PHYSICAL EXAMINATION

A definitive diagnosis cannot be made without a careful examination of the anus and rectum. Patient education before and during the examination will be helpful in obtaining maximal cooperation. The lateral or Sims position is the most common position for routine digital rectal examination and anoscopy. This position is preferred for the elderly or pregnant women. Elevating the upper buttock provides better exposure of the perianal area. In debilitated patients, one may have to perform the examination with the patient in a supine, lithotomy position.

A digital examination of the entire inner wall with a lubricated index finger should always be performed before doing any endoscopic procedure. In men, palpate the prostate to determine its size, texture, and tenderness or if masses are present. In women, palpate the posterior vaginal wall for a mass, rectocele, or rectovaginal fistula. Note anal tone and sensation. After performing a digital rectal examination, one can determine that the patient will tolerate passage of an anoscope. No bowel preparation is required for anoscopy, suction should be available, and cultures can be obtained. Introduce a well-lubricated, lighted anoscope with the obturator in place. Next, remove the obturator, and gently rotate the anoscope as needed to view the anorectum circumferentially while withdrawing the anoscope (**Figure 85-2**). The anal mucosa, fissures, external and internal hemorrhoids, condyloma, dentate line, and distal rectal mucosa can be evaluated with the use of an anoscope. More proximal sources of rectal bleeding may be distinguished utilizing the anoscope. After visual inspection, ask the patient to bear down to detect any rectal mucosal prolapse.

ANAL TAGS

Skin tags are minor projections of skin at the anal verge and are sometimes residuals of prior hemorrhoids (**Figure 85-3**).

CLINICAL FEATURES

Skin tags are usually asymptomatic, but inflammation may cause itching and pain. Skin tags covering anal crypts, fistulas, and fissures are

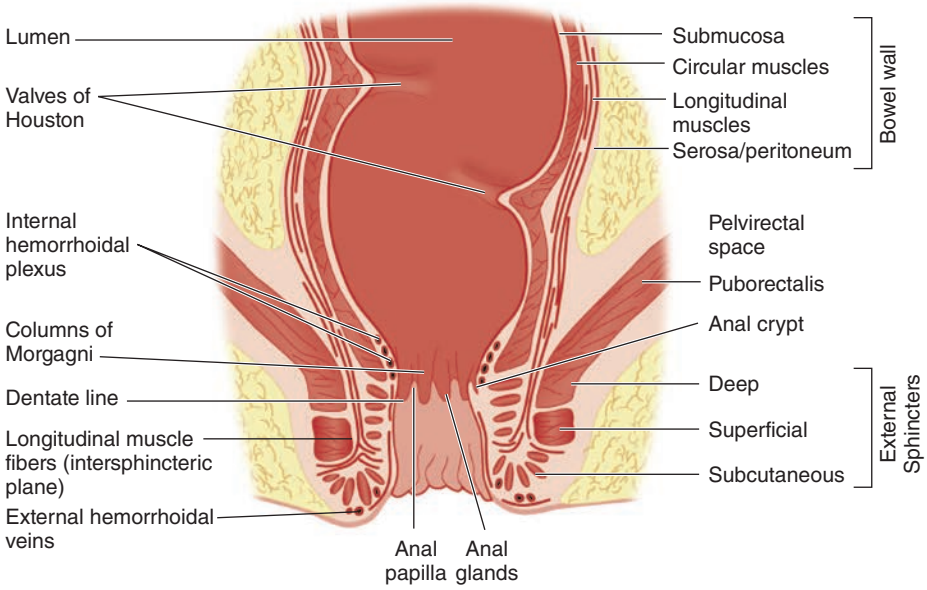


FIGURE 85-1. Coronal section, anorectum.

called "sentinel tags." **Surgical referral for excision and/or biopsy is warranted because inflammatory bowel disease may be associated with sentinel tags.**

HEMORRHOIDS

ANATOMY

Hemorrhoids are vascular cushions that become enlarged and distally displaced within the anal canal. Current theory suggests that there is anal canal sliding and that hemorrhoidal formation occurs when the supporting tissues of these cushions deteriorate.[1] Consequently, the downward displacement of these cushions causes the internal and external hemorrhoidal plexuses to become excessively engorged, referred to as *hemorrhoids*—one of the most common problems afflicting human beings (**Figure 85-4**).

Hemorrhoids may become inflamed, thrombosed, prolapsed, ulcerated, or ischemic. **Internal hemorrhoids originate proximal to the dentate line**, from terminal branches of the superior rectal artery. They are constant in their location, coursing longitudinally at the right posterolateral, right anterolateral, and left lateral positions; **2-, 5-, and 9-o'clock positions**, when the patient is viewed prone (**Figure 85-5A**). Commonly, they are single and are located at the 5-o'clock position. **Internal hemorrhoids are not readily palpable and can best be visualized through an anoscope.** Their appearance is consistent with the columnar epithelial surface of the surrounding anal canal (**Figure 85-5B**). **External hemorrhoids**, **distal to the dentate line**, are located anywhere along the anoderm, form as a result of dilatation of veins at the anal verge, and **can be seen at external inspection**. Their appearance is consistent with the stratified squamous epithelium of the surrounding anoderm, which has exquisite sensory innervation.

CLINICAL FEATURES

Enlarged hemorrhoids are associated with constipation and prolonged straining at stool, frequent diarrhea, and older age. Increased abdominal pressure may cause obstruction of venous return and engorgement of the hemorrhoidal plexus. Consider inflammatory bowel disease in patients with frequent diarrhea and hemorrhoids. Hemorrhoidal veins can have high resting pressures and are devoid of valves, and as patients age, the supportive connective tissue surrounding the vasculature diminishes. Hemorrhoids can develop during pregnancy and may be the result of sustained increased pressure on the venous drainage of the rectum. Increased portal pressure, from chronic liver disease, may produce marked dilatation and varix formation, distinct from true hemorrhoids, resulting in bleeding that can be extremely difficult to control. Tumors of the rectum and sigmoid colon, often associated with constipation, tenesmus, and incomplete evacuation, may cause hemorrhoids. **Although the most common cause of bright red rectal bleeding is hemorrhoids, tumors must be ruled out as a cause of rectal bleeding in patients >40 years of age.** Ascites, ovarian tumors, distended bladders, and excessive fibrosis from radiation therapy may contribute to the formation of external hemorrhoids. **Hemorrhoidal bleeding is usually limited, with the bright red blood on the surface of the stool, on the toilet tissue, or noted at the end of defecation, dripping into the toilet bowl. When patients describe the passage of blood clots, one should suspect colonic lesions. Chronic slow blood loss detected on fecal occult blood testing resulting in anemia requires further investigation. Hemorrhoids themselves generally do not cause pain unless they are thrombosed or are strangulated fourth-degree internal hemorrhoids**. If the patient complains of pain, but on examination the hemorrhoids are not thrombosed, suspect perianal or intersphincteric abscesses or anal fissures. Thrombosed external hemorrhoids are painful and are often described as a burning perianal lump, and they usually exhibit a bluish-purple discoloration (**Figure 85-6**). Hemorrhoids may become more prominent with a Valsalva maneuver. As hemorrhoids increase in size, they may prolapse, requiring periodic reduction by the patient. Pain can be quite severe at the time of defecation and usually subsides with time.

Uncomplicated internal hemorrhoids are painless due to visceral innervation and lack of sensory innervation. Anoscopy reveals bulging, purple-colored veins at the distal rectum or anal canal (**Figure 85-7**). Often a chief complaint is painless, bright red rectal bleeding with defecation. Internal hemorrhoids may be palpable on digital examination when thrombosed or prolapsed.[2] Nonreducible, prolapsed, internal hemorrhoids may become thrombosed and strangulated. They appear dark red, exhibit rectal bleeding, and cause exquisite pain and possibly urine retention. Ulceration, necrosis, gangrene, sepsis, and hepatic abscess formation may ensue. Internal hemorrhoids are classified by the amount of prolapse into the anal canal.

TREATMENT

Conservative therapy with warm baths is often successful for mild to moderate symptomatic grade I (luminal protrusion above dentate line) and II (prolapse with spontaneous reduction) internal hemorrhoids. Manual reduction of grade III (prolapse needing manual reduction) internal hemorrhoids and warm baths (which decrease sphincter pressures) for at least 15 minutes three times a day and after each bowel movement are the most effective ways to relieve symptoms. After the

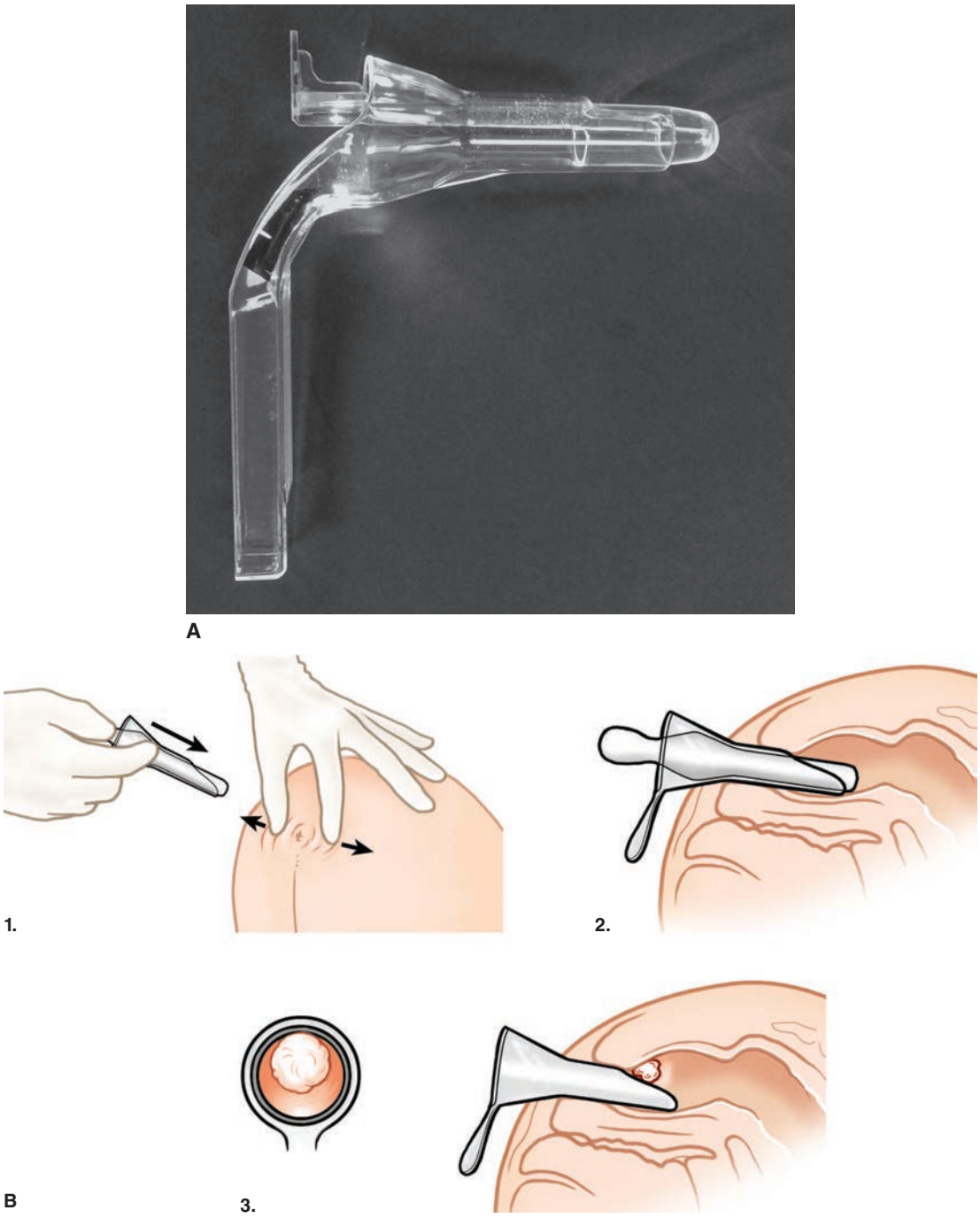


FIGURE 85-2. **A.** Anoscope. **B.** Anoscope insertion technique (1, 2, and 3). [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures,* 2nd ed. McGraw-Hill, Inc., 2013. Figure 70-5A-C.]

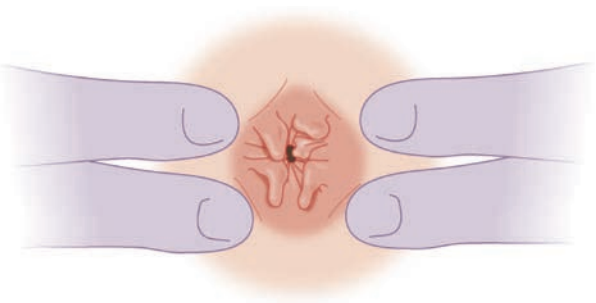


FIGURE 85-3. Anal skin tag.

bath, the anus must be dried gently but thoroughly to avoid maceration of the perianal skin. Topical analgesics and steroid-containing ointments may provide relief. The patient should not sit on the commode for a prolonged period. Bulk laxatives and stool softeners should be used after the acute phase is treated. Avoid the use of laxatives causing liquid stool, because cryptitis and anal sepsis can result. A high-fiber, low-fat diet, with increased water consumption, regular exercise, and avoidance of constipating medications, should help prevent future problems. Recommend surgical referral for symptomatic hemorrhoids, because a variety of procedures (sclerosing injections, rubberband ligation, photocoagulation, cryotherapy, electrocautery, laser treatments, radiofrequency ablation, staple repair, or excision) can provide definitive treatment. A rare complication of hemorrhoidal banding is pelvic sepsis.[2] Obtain

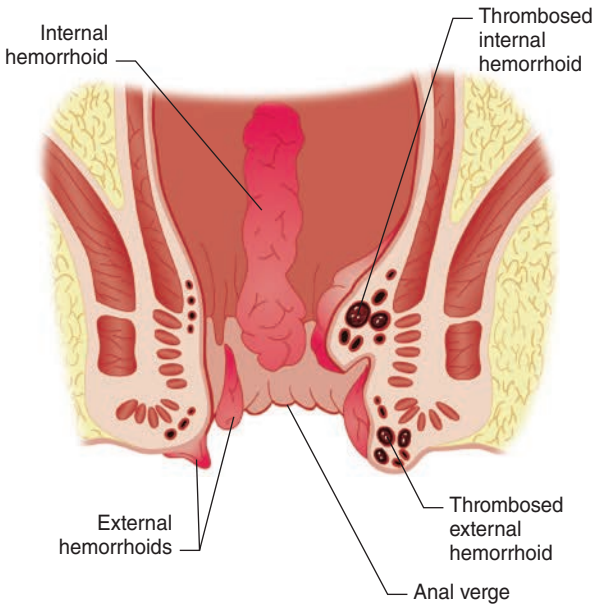


FIGURE 85-4. Coronal section of anorectum.

surgical evaluation in the ED for continued and severe bleeding, pain, incarceration, and/or strangulation (grade IV internal hemorrhoids, nonreducible prolapse). Early external hemorrhoidal thrombosis is usually self-limiting, with resolution in 1 week. Therapy for thrombosed external hemorrhoids depends on the severity of symptoms. If the thrombosis has been present for more than 48 hours, the swelling has started to shrink, the hemorrhoid is not tense, and the pain is tolerable, the patient may be treated with warm baths and bulk laxatives. Suppositories, which are placed proximal to the anorectal ring, are of no help.

If, on the other hand, the thrombosis is acute, has lasted less than 48 hours, and is extremely painful, significant relief can be provided by clot excision. **Excision of thrombosed external hemorrhoids should not be performed in the ED on immunocompromised patients, children, pregnant women, patients with portal hypertension, and those who are anticoagulated or have a coagulopathy.** Obtain optimal exposure by placing the patient in the side-lying or prone position. The area of the overlying skin to be incised is infiltrated using a 30-gauge needle with a local anesthetic such as bupivacaine 0.5%, with epinephrine (1:200,000), and bicarbonate buffering. An elliptical incision distal to



FIGURE 85-6. Nonthrombosed (**A**) and thrombosed (**B**) external hemorrhoids. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, Inc., New York.]

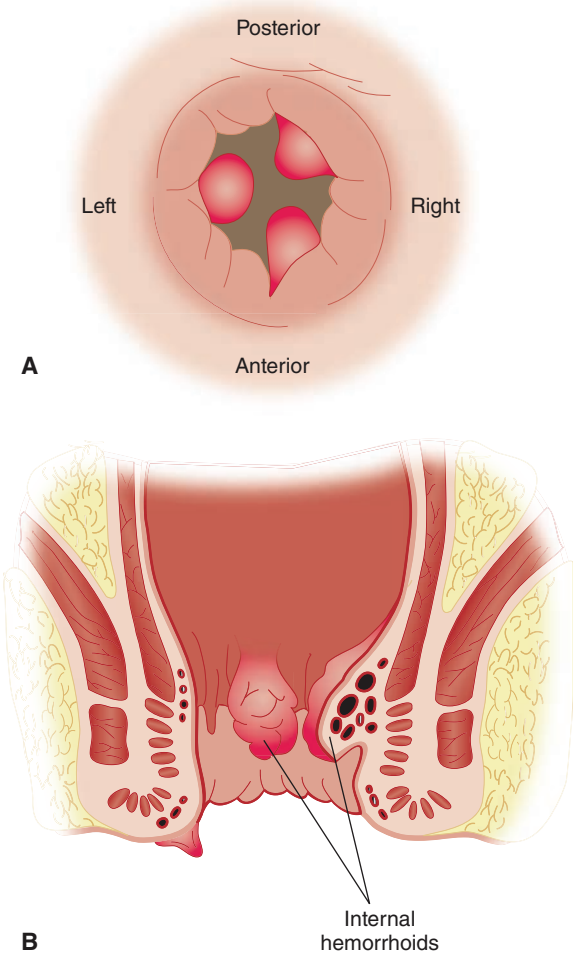


FIGURE 85-5. **A.** Internal hemorrhoids at 2, 5, and 9 o'clock. **B.** Protrusion of internal hemorrhoids.

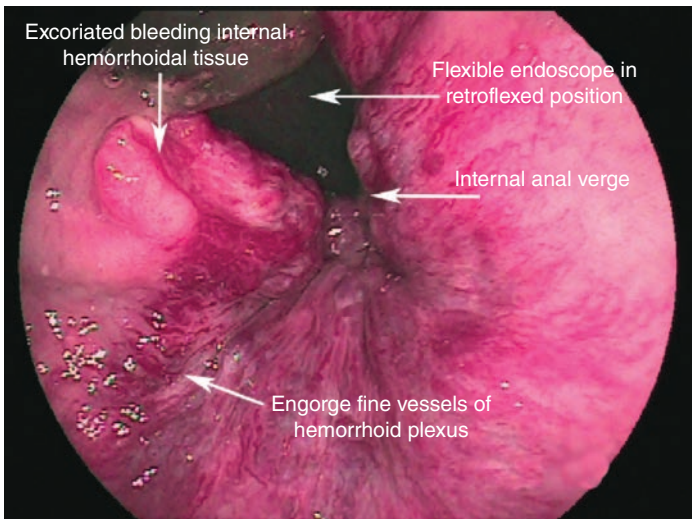


FIGURE 85-7. Grade I internal hemorrhoids. [Photo contributor: Philip E. Stack, MD.]

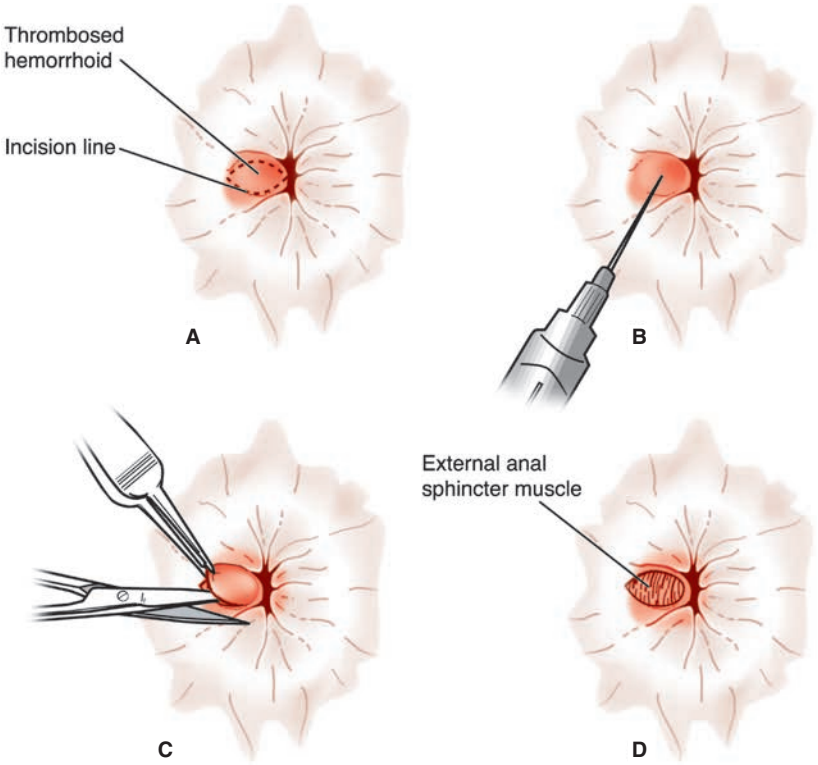


FIGURE 85-8. Excision of the thrombosed external hemorrhoid. **A.** The dotted line represents the incision lines to remove the skin and underlying thrombosis. **B.** Injection of local anesthetic solution. **C.** The skin incision has already been performed. The skin and underlying thrombosis are dissected free with scissors. **D.** The ellipse of skin and the underlying thrombosis have been removed. The fibers of the underlying external anal sphincter muscle are visible. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures,* 2nd ed. McGraw-Hill, Inc., 2013. Figure 68-4 A-D.]

the anal verge in the overlying skin will expose the thrombosis. Remove the clot through the incision site. Because multiloculated clots can be present, the technique of unroofing a thrombosed hemorrhoid with an elliptical incision and removing the overlying skin gives far better results than the simple incision and evacuation of a clot (**Figure 85-8, A–D**).

Control the bleeding by tucking the corner of a small piece of gauze into the wound and leaving it in place for a few hours. A small pressure dressing may be applied external to the gauze and removed when the patient takes the first warm bath in 6 to 12 hours. Opioids should be prescribed only at the lowest dose and shortest time necessary for acute pain control, as opioids cause constipation. Complications, such as continued bleeding, recurrence, infection, fistula, and abscess formation, may occur; thus, follow-up in 24 to 48 hours is recommended. Referral for definitive hemorrhoidectomy is prudent. Recently, small studies suggest that patients with acutely thrombosed internal or external hemorrhoids can be treated with topical nifedipine and 1.5% lidocaine ointment or isosorbide dinitrate ointment with surgical follow-up.[2,3]

ANAL FISSURES

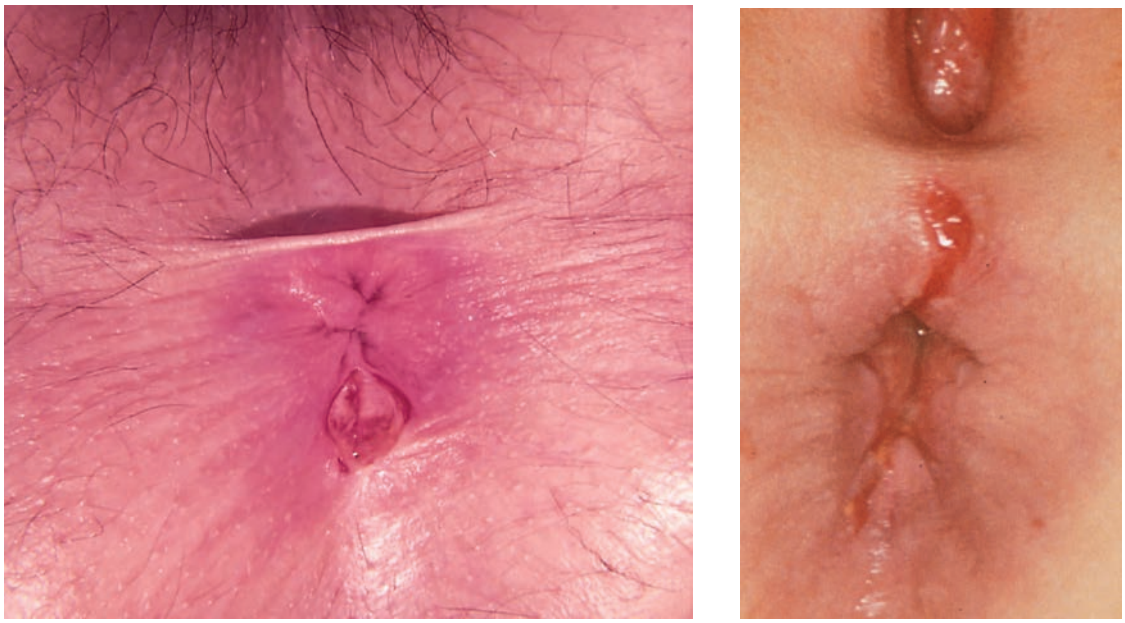
ANATOMY

An anal fissure is the result of a superficial linear tear of the anal canal below the dentate line and extending distally to the anal verge (**Figure 85-9**). Acute fissures are present for less than 6 weeks; fissures are chronic if they persist longer. The mucosa of the anal canal has a rich supply of somatic sensory nerve fibers. Chronic anal fissures are pale in color with edema of the surrounding tissues. Fissures persist because of the severe, chronic, internal sphincter spasm that may occur along with development of a secondary infection at its base. The fissure edges become fibrotic and raised, possibly exposing sphincter fibers, hypertrophic papillae proximally, and the characteristic sentinel tag distally. The latter is frequently misdiagnosed as an external hemorrhoid when, in actuality, it is the result of edema and fibrosis secondary to the ulcerating fissure. The fissure may become inflamed and form a perianal or intersphincteric abscess that may drain into the anal canal or in the posterior midline externally.

CLINICAL FEATURES

Anal fissures are usually single and occur in the midline posteriorly in 80% to 90% of cases.[4] The posterior location of anal fissures may be because of the posterior angulation of the rectum on the anus where the posterior midline of the anorectal canal becomes the "lesser curvature" for the passage of stool. Anterior anal fissures are associated with younger age (33 years vs. 41 years for posterior fissures), female sex, obstetric trauma, and occult external anal sphincter injury.[5] A chronic nonhealing fissure, lasting more than 6 weeks, or one not located in the midline should arouse suspicion that another, potentially serious cause may be involved. Such diagnostic possibilities include Crohn's disease, chronic ulcerative colitis, squamous cell carcinoma of the anus, adenocarcinoma of the rectum invading the anal canal, localized anal cancers such as Bowen's disease and extramammary Paget's disease, leukemia, lymphoma, syphilitic fissures, chlamydia, gonorrhea, human immunodeficiency virus, and a tuberculous ulcer. Consideration of these diagnoses requires referral for diagnostic biopsy of the ulcer edge, culture of the anal canal, and a systemic evaluation. **Fissures due to Crohn's disease are multiple, off midline, and asymptomatic more commonly than in the general population.**[6] Most often, the traditional midline anal fissure is caused by the trauma produced by the passage of a particularly hard and large fecal mass, but it also may be seen after frequent acute episodes of diarrhea. Children with constipation will commonly complain of painful defecation only to find an anal fissure upon closer inspection (**Figure 85-9A**). Child abuse should be considered as a possible cause (**Figure 85-9B**).

Anal fissures are characterized by tearing pain with defecation and rectal bleeding. The pain may persist as a dull ache and burning sensation for a few hours after each bowel movement. Invariably it subsides between movements, which is a feature that distinguishes fissures from other forms of painful anorectal disease. The bleeding



A B

FIGURE 85-9. Anal mucosal fissures. **A.** Constipation. **B.** Sexual assault. [**A:** Photo contributor: Paul J. Kovalcik, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York. Figure 9-32; **B:** Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York.]

is bright red and small in quantity, usually being noticed only on the toilet paper. In infants, the presence of small amounts of bright red blood on the stool or toilet paper is usually the presenting complaint from an anal fissure. Sphincter spasm and pain may be severe enough to make the patient retain stool and avoid defecation. The diagnosis of an anal fissure is usually suggested by the history, but the anal area must be examined in all cases. Fissures may often become more noticeable if the patient bears down as if having a bowel movement. With the patient relaxed, gentle separation of the buttocks will often expose the fissure. The mere retraction of the buttocks and the anal skin may cause considerable spasm and discomfort and may not permit digital examination. Topical 2% lidocaine jelly may provide some relief for examination, but severe pain may require sedation. If the fissure can be visualized, and is present in the posterior midline, rectal examination can be deferred until the patient is having less spasm and pain.

TREATMENT

Healing is by the development of granulation tissue and the reepithelialization of the ulcerated area. Most uncomplicated acute fissures will heal in a few weeks, but relapse can be as high as 50%. If healing does not occur within 6 weeks or relapses are frequent, surgical referral is recommended. Treatment is aimed at providing symptomatic relief, extinguishing the anal sphincter spasm, and preventing stricture formation. Warm baths for at least 15 minutes three to four times a day and after each bowel movement along with stool softeners may suffice. The addition of fiber to the diet will serve to prevent stricture formation by providing a bulky stool. Warm baths and increased fiber will result in healing in about half of all anal fissures.[6] Topical lidocaine ointments and 1% hydrocortisone creams may provide symptomatic relief. Medical therapies for anal fissure are generally no more effective than placebo, and for chronic fissures, all medical therapies are less effective than surgery.[7,8]

ANAL STENOSIS

Anal stenosis occurs when the pliable tissue is replaced by scarred fibrotic tissue. Congenital and primary causes may occur, yet secondary causes are more common. Stenosis most commonly occurs after surgical hemorrhoidectomy.[4] Other causes include radiation, fistulectomy, trauma, inflammatory bowel disease, chronic laxative use, sexually transmitted diseases, and chronic diarrhea.

CLINICAL FEATURES

Typical complaints include constipation, bleeding, pain with stool evacuation, and narrow-caliber stools. As stenosis progresses, performing a digital exam with the little finger is met with severe resistance. Incontinence secondary to overflow constipation may occur. Careful specialist examination, often with sedation, may be necessary.

TREATMENT

Treatment involves stool softeners, fiber supplementation, and daily gradual anal dilatation after initial dilatation in the operating room. Stricturotomy and stricturoplasty are used when conservative management has failed.

CRYPTITIS

Anal crypts are superficial mucosal pockets that lie between the columns of Morgagni. Formed by the puckering action of the sphincter muscles, crypts normally flatten out during the passage of a stool. Sphincter spasm and superficial trauma caused by repeated bouts of diarrhea or chronic constipation may cause breakdown in the mucosal lining of the crypts, leading to cryptitis. Infecting organisms enter crypt pockets, and inflammation extends into the lymphoid tissue of both the crypts and anal glands. Cryptitis could well be the common denominator for the development of fissure-in-ano, fistula-in-ano, and perirectal abscesses (**Figure 85-10, A and B**).

Visualized by anoscopy, the anal papillae appear as slight projections of pink epithelium that produce the serrated appearance of the dentate line. Initially, the locally inflamed crypts are asymptomatic, producing a bead-like spot of pus. Inflammation of the crypts extends to the adjacent papillae. Hypertrophied anal papillae may be palpated as small, hard nodules and are associated with cryptitis.

CLINICAL FEATURES

Anal pain, spasm, and itching with or without bleeding are the cardinal signs and symptoms of cryptitis. Rarely, papillae may hypertrophy and

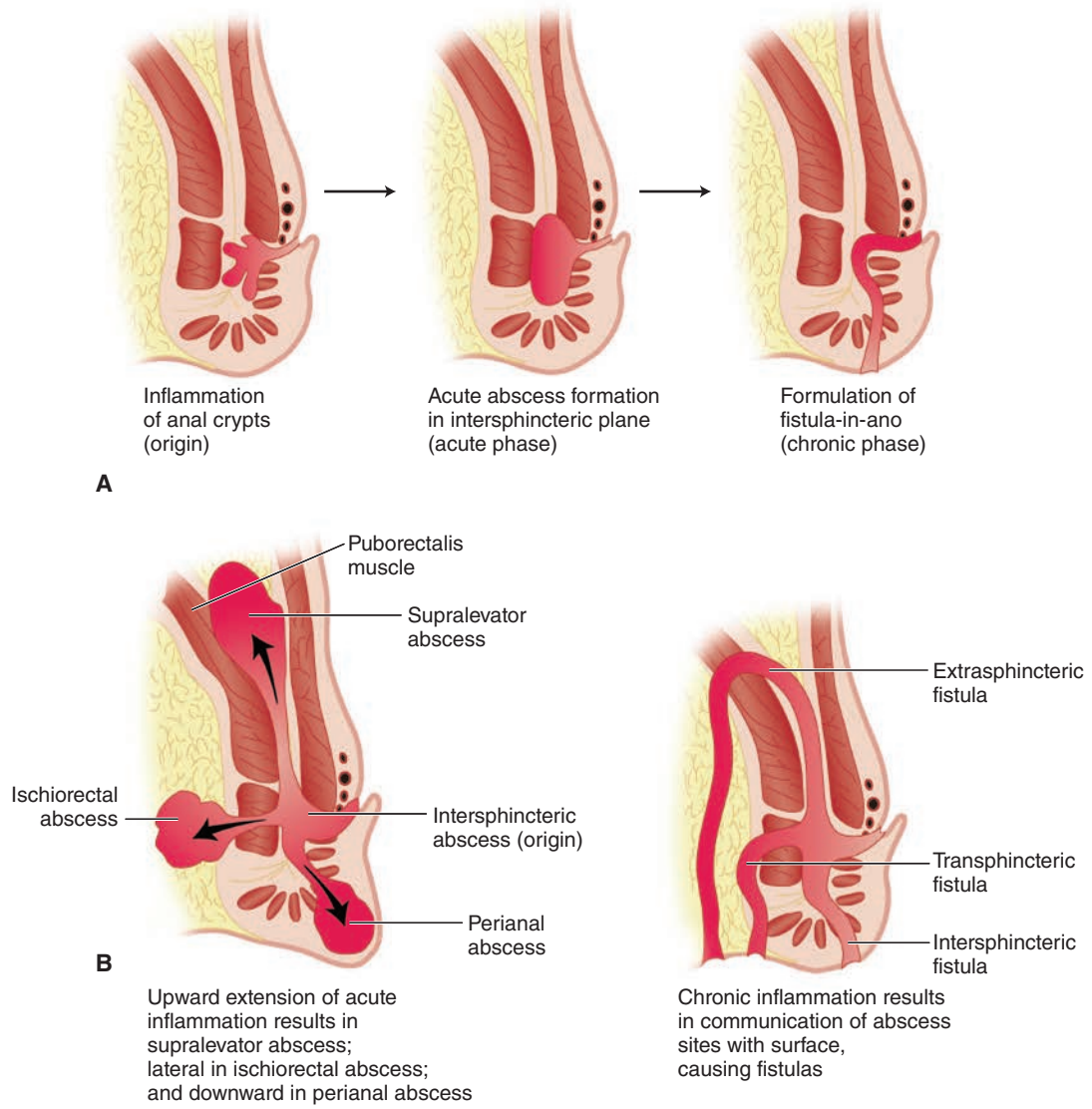


FIGURE 85-10. **A** and **B.** Illustration of the mechanism for anorectal abscess and fistula formation.

present as a prolapsing polypoid tumor. **The crypts most commonly involved are in the posterior half of the anal ring and, in most cases, in the posterior midline, the same location where anal fissures occur.** The definitive diagnosis of cryptitis is made by visualization of the erythema, inflammation, and pus during anoscopic examination.

TREATMENT

Treatment when the patient is symptomatic includes bulk laxatives and additional roughage added to the diet to produce formed, soft stools. Warm baths enhance healing by keeping the anus clean and the crypts empty. Refer to a surgeon for drainage when the infection has progressed and there is a deep, redundant crypt that will not drain adequately on its own. Cryptitis may be associated with underlying infections from parasites, inflammatory disorders, and localized trauma.

FISTULA-IN-ANO

Fistula-in-ano may result after drainage of an anorectal abscess. Fistulas may also be associated with ulcerative colitis, Crohn's disease, colonic malignancies, radiation, leukemia, sexually transmitted disease, actinomycosis, anal fissures, foreign bodies, or tuberculosis. Fistula-in-ano originates from an infected crypt and tracks to the skin. Fistulas are characterized according to the relationship to the anal sphincter: submucosal, intersphincteric, suprasphincteric, transsphincteric, or extrasphincteric (Figure 85-10). Goodsall's rule is used to help determine the location of the internal opening. Although anterior-opening fistulas tend to follow a simple, direct course to the anal canal, posterior-opening fistulas may follow a devious, curving path, including some that are horseshoe-shaped, opening in the posterior midline.

CLINICAL FEATURES

Open fistulous tracts may produce painless, blood-stained mucus, perianal itching, and malodorous discharge. If the tract becomes blocked, inflammation may be followed by spontaneous rupture or abscess formation. Abscess formation is associated with throbbing pain that is constant and worsened by sitting, moving, and defecation. Induration or a fibrous cord (more chronic fistula) may be palpated. A fistulous opening adjacent to the anal margin suggests a more superficial connection from the intersphincteric region. An opening more proximal to the anal margin suggests a deeper, more superior abscess. In one study, endoscopic US was more accurate than CT scan (82% vs. 24%) in the evaluation of perirectal fistulas, although endoscopy was comparable to MRI (91% vs. 87%).[9]

TREATMENT

IV fluids, analgesics, antibiotics (ciprofloxacin and metronidazole), antipyretics, and surgical consultation are appropriate. Definitive treatment

may involve placement of a drain through the fistula, fibrin glue (fibrinogen, thrombin, and calcium), fistulotomy, fistulectomy, or more complex procedures. Improperly excised fistulas may result in permanent fecal incontinence. Monoclonal antibody use may be considered in patients with Crohn's disease.

ANORECTAL ABSCESSES

Anorectal abscesses, more common in middle-aged males, begin with involvement of an anal crypt and its gland. Abscesses are typically polymicrobial with both aerobic and anaerobic bacteria. Infection with *Staphylococcus aureus, Streptococcus* and *Enterococcus* species, *Escherichia coli, Proteus,* and *Bacteroides* can progress to involve any of the potential spaces that are normally filled with fatty areolar tissue with little inherent resistance to the progression of infection. These spaces include the perianal, submucosal, intersphincteric, ischiorectal, postanal (connecting the ischiorectal space on each side posteriorly), and supralevator (pelvirectal) (**Figure 85-11, A–C**).

A variety of diseases and other conditions are less commonly associated with the development of abscesses, including Crohn's disease, carcinoma of the anorectum and adjacent organs, trauma, ulcerative colitis, radiation fibrosis, Hodgkin's disease, tuberculosis, gonococcal proctitis, *Chlamydia*, *Actinomyces*, herpes, lymphogranuloma venereum, and immunocompromised states. **The most common anorectal abscess location is perianal, and the least common is supralevator (pelvirectal)** (**Figure 85-11, C–E**).

CLINICAL FEATURES

Located close to the anal verge, often posterior midline, the perianal abscess is a superficial tender mass that may or may not be fluctuant (Figure 85-11D). Ischiorectal abscesses, which are the second most common, traverse the external anal sphincter; tend to be larger, indurated, and well circumscribed; and are located more laterally on the medial aspect of the buttocks (Figure 85-11C). The patient may exhibit edema, fever, and anorexia. The deeper postanal abscess may not manifest cutaneous signs, but rectal pain and tenderness are invariably present (**Figure 85-12**).

Isolated perianal abscesses are generally the only type of anorectal abscess that can be adequately treated in the ED. Surgical referral after drainage is suggested because fistula formation is not uncommon. Clinical evaluation of a perianal abscess is usually sufficient, but CT or MRI is recommended if pain is out of proportion to physical findings or if the extent of the abscess is uncertain. Ischiorectal abscesses can be problematic and complicated as the ischiorectal fossa forms a large potential space on either side of the rectum, communicating behind it through the deep postanal space. Ischiorectal abscesses may be palpable through the rectal wall or on the overlying skin. Intersphincteric, submucosal, postanal, and supralevator abscesses may not demonstrate edema but are often associated with constitutional symptoms. Infections in this area are insidious and extensive and can spread to an area some distance from the anal verge. If a complicated abscess is suspected, obtain CT or MRI (**Figure 85-13, A–B**).

Perianal abscesses are easily palpable at the anal verge, whereas deeper perirectal abscesses may be palpated through the rectal wall or more lateral to the anal verge, on the buttocks. Initially, the patient notices a dull, aching, throbbing pain that becomes worse immediately before defecation, is lessened after defecation, but persists between bowel movements. Pain is exacerbated by movement and sitting. Perianal abscesses, unlike more complicated perirectal abscesses, are usually not accompanied by fever, leukocytosis, and sepsis in the immunocompetent patient. Pain is aggravated by straining or coughing, particularly when due to intersphincteric abscesses. **Ischiorectal abscesses** are often painful on rectal examination and are lateral to the anal verge. **Intersphincteric abscesses**, painful with defecation, may be associated with rectal discharge and fever, and a tender mass may be palpable on digital examination of the rectal canal, often in the posterior midline. **Supralevator abscesses**, often an extension of an intersphincteric abscess, frequently present with few outward signs. Generalized, nondistinct perirectal pain with fever, malaise, leukocytosis, and urinary retention may occur. Tender inguinal adenopathy is often a clue to these deeper abscesses. Supralevator abscesses may be palpable on vaginal examination.

TREATMENT

All perirectal abscesses (ischiorectal, submucosal, intersphincteric, and supralevator) should be drained in the operating room. Simple, isolated, fluctuant perianal abscesses may be drained in the ED using local anesthetics and, occasionally, procedural sedation. Adequate patient positioning, preparation, and good exposure are necessary. Lidocaine with epinephrine should be administered with a small-gauge needle. Needle aspiration (18-gauge) over the painful region may be done to localize the purulent pocket. US can delineate the size and depth of the abscess. Drainage can be accomplished with a linear or cruciate incision. If using a linear incision, loosely pack the abscess cavity with strips of gauze to prevent premature closure of the skin edges. To ensure adequate drainage, a cruciate incision can be made over the fluctuant part of the abscess. Trimming the flaps is suggested to prevent closure, and packing is not required (**Figure 85-14, A and B**).

Cover the wound with a bulky dressing, and have the patient take frequent warm baths starting the next day. Antibiotics are not necessary after adequate drainage in healthy patients. Twenty-four hour follow-up is recommended. For the elderly or those with fever, leukocytosis, diabetes, valvular heart disease, cellulitis, or immunosuppression, give broad-spectrum antibiotics (e.g., piperacillin-tazobactam, 3.375 grams IV), obtain surgical consultation, provide tetanus prophylaxis as needed, and admit to the hospital.

PROCTITIS

Proctitis is inflammation of the rectal mucosa. Clinical manifestations often include anorectal pain, itching, discharge, ulcers, diarrhea, bleeding, or lower abdominal cramping. Anoscopic examination may reveal mucosal inflammation, erythema, bleeding, ulcerations, and/or discharge. Proctitis may develop from prior radiation treatments, autoimmune disorders, vasculitis, ischemia, and infectious diseases, including enteric pathogens and sexually transmitted infections (**Table 85-1**).

If the patient has an anorectal infection caused by a sexually transmitted organism, screen for other sexually transmitted organisms. Also, obtain appropriate blood tests, specimens from anoscopy for Gram stain and cultures (viral and bacterial), and start empiric therapy. For detailed discussion of sexually transmitted infections, see Chapters 153, "Sexually Transmitted Infections," and 252, "Skin Disorders: Groin and Skinfolds."

ANORECTAL ACQUIRED IMMUNODEFICIENCY SYNDROME–RELATED INFECTIONS

Patients rendered immunodeficient by human immunodeficiency virus are subject to a variety of opportunistic infections that affect the intestinal, anorectal, and other body systems (**Table 85-2**). Severe rectal pain, diarrhea, and hematochezia are common presenting symptoms. Anoscopy confirms anal canal ulcers and acute proctitis. Obtain serology for syphilis, and start antibiotic therapy.

Stool softeners, sitz baths, careful anal hygiene, and pain medications will provide some relief. Enteric pathogens may require antibiotics such as trimethoprim and sulfamethoxazole (*Isospora*), metronidazole (*Entamoeba*, *Giardia*), azithromycin (*Campylobacter*), acyclovir (herpes), or fluoroquinolones (*Salmonella, Shigella*). Provide empiric therapy against gonorrhea, nonlymphogranulomatous chlamydia, and incubating syphilis for human immunodeficiency virus–associated acute proctitis. Refer for appropriate follow-up, further evaluation, and definitive treatment.

RECTAL PROLAPSE

Rectal prolapse is the circumferential protrusion of part or all layers of the rectum through the anal canal. Basically, there are three types of rectal prolapse: (1) prolapse involving the rectal mucosa only, (2) prolapse

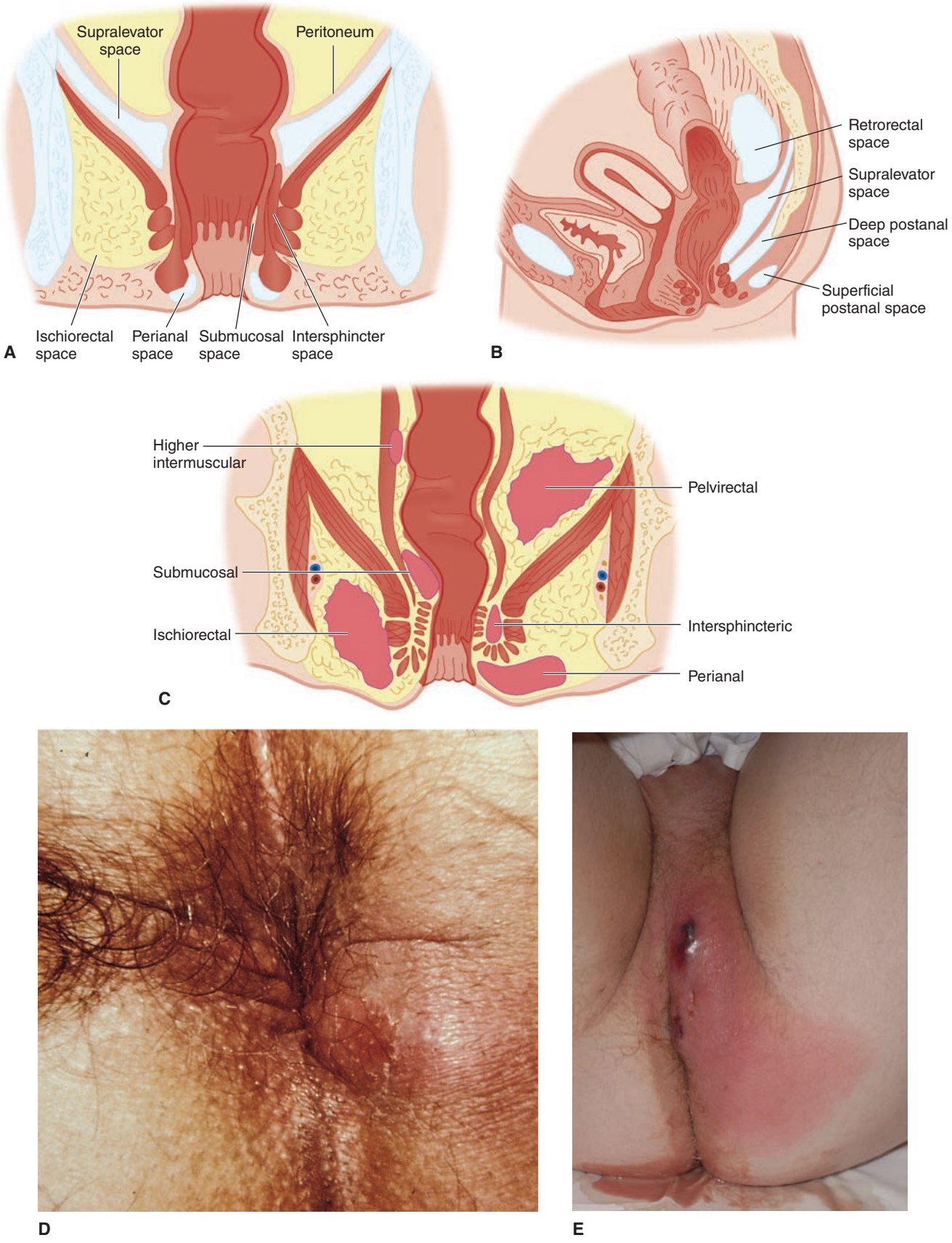


FIGURE 85-11. **A** and **B.** Anatomic classification of anorectal spaces. **C.** Anorectal abscesses. **D.** Perianal abscess. **E.** Complicated perirectal abscess. [**A** and **B:** Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures,* © 2010, McGraw-Hill, Inc., New York. **D:** Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York. **E:** Photo contributor: Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York. Figure 9-35.]



FIGURE 85-12. CT scan, postanal abscess (*arrow*).

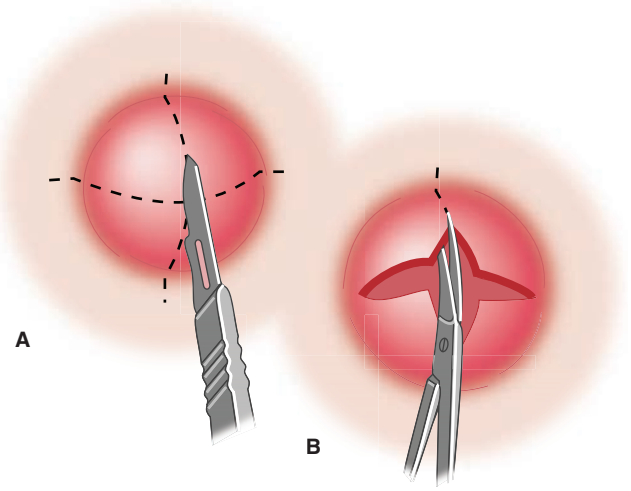
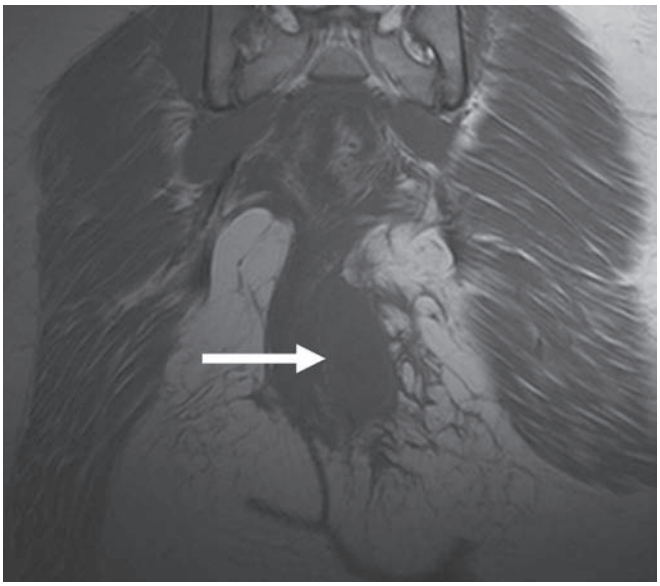


FIGURE 85-14. **A** and **B.** Technique to drain a perianal abscess.



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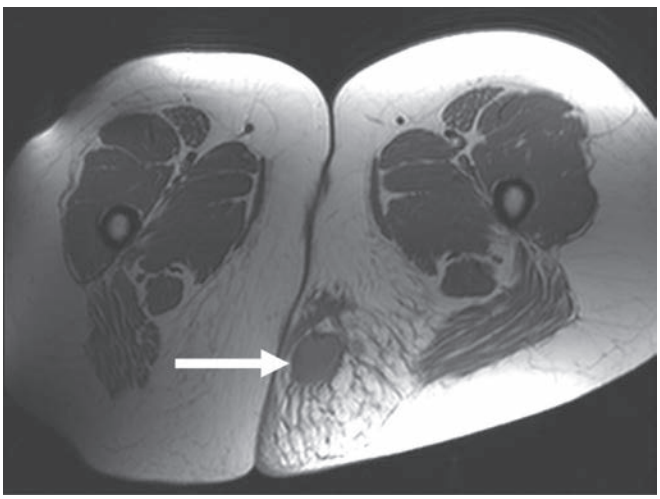

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FIGURE 85-13. MRI of left ischiorectal abscess (*arrows*) in a pregnant woman, early second trimester. **A.** MRI of left ischiorectal abscess, T1 coronal view. **B.** MRI of left ischiorectal abscess, T1 axial view.

involving all layers of the rectum (complete), and (3) intussusception of the upper rectum into and through the lower rectum so that the mucosal apex of the intussusception nearly extends to the anus (incomplete or internal).

Rectal prolapse in children is generally mucosal and occurs more commonly in males less than 3 years old. The prolapse may appear as a painless, maroon-colored, protruding mass with possible mucus and blood. The mucosal prolapse rarely protrudes more than 5 cm beyond the anal verge.[10] With children, parents often mistakenly believe that the prolapsed mucosa is a hemorrhoid. Mucosal prolapse is believed to occur due to a lack of the natural sacral curve reducing the anorectal angulation. With increased intra-abdominal pressure from coughing, diarrhea, vomiting, and straining, mucosal prolapse can develop. Incomplete/internal and full-thickness prolapses occur because of the laxity of the pelvic fascia and muscles, in addition to a generalized weakening of the anal sphincters.

CLINICAL FEATURES

Patients with partial prolapse may experience stool seepage or constipation. With more advanced cases, patients are able to detect the presence of a mass, especially after defecation or strenuous activity, or even with standing or walking. Irritation to the rectal mucosa caused by recurrent prolapse results in a mucous discharge along with bleeding. Associated anal sphincter weakness may result in fecal incontinence. With complete prolapse, the anus appears normal in contrast to a mucosal prolapse in which the anal edges appear everted. **Pain is not a significant feature with complete prolapse, but abdominal or pelvic discomfort may be present.**[10] Digital rectal examination reveals a thick muscular wall with decreased tone, in contrast to a much thinner wall from a mucosal prolapse. Complete prolapse appears as a red, ball-like mass, with concentric folds in the protruding mucosa (**Figure 85-15, B and C**). Prolapsing internal hemorrhoids may be confused with mucosal or rectal prolapse. A distinguishing feature of prolapsed hemorrhoids are the radially directed folds (**Figure 85-15A**). With complete prolapse, a sulcus may be palpated between the extruded bowel and anus, compared to no sulcus with a mucosal prolapse.

TREATMENT

In young children, after appropriate analgesia and sedation, the prolapse can be reduced manually by first gently spreading the buttocks and then replacing the protruding mucosa, proximal to the anorectal ring of sphincter muscles, with a slow, steady pressure applied to the prolapsed segment. Digital rectal examination should then be performed. Every effort should be made to prevent constipation. **Refer the**

TABLE 85-1 Anorectal Sexually Transmitted Infections

Bacteria	Viruses
*Neisseria gonorrhoeae**	Herpes simplex type 2*
*Chlamydia trachomatis**	Human immunodeficiency virus
*Treponema pallidum**	Human papillomavirus

*Most common sexually transmitted pathogens

child for further evaluation due to a possible underlying condition such as cystic fibrosis, polyps, pelvic floor weakness, diarrhea, and malnutrition.

In adults, a complete prolapsed rectum can sometimes be reduced with gentle continuous pressure, which may take several minutes. The buttocks may be taped apart while the prolapsed segment is grasped in such a way that the thumbs are placed over the luminal surfaces medially while the fingers grasp the outer walls laterally. Continuous pressure, starting with the thumbs followed by an internal rolling force of the fingers, will aid in reduction (**Figure 85-16**).

After reduction, perform a digital rectal examination to ensure that reduction is complete and to evaluate for a rectal mass or polyp. Obtain surgical consultation for repair, or refer for colonoscopy and dietary changes depending on the clinical circumstances.

Once the rectal walls become edematous, reduction is difficult. Prolonged prolapse may lead to venous engorgement, thrombosis, superficial ulcerations, rectal incarceration, strangulation, and ischemia. **An effective technique is the early application of generous amounts of granulated sugar over the entire prolapsed segment. Synthetic sweeteners are not effective. After 15 minutes or so of sugar application, the edema reduces, allowing for easier prolapse reduction.**[11] Gauze with lubricant can be placed over the anal verge after reduction and taped in place for a few hours. If the prolapse cannot be reduced, is severe, or recurs after reduction, or if ischemia or gangrene of the prolapsed segment is suspected, emergency surgical consultation and hospitalization are needed for reduction or surgical treatment (rectopexy).

ANORECTAL TUMORS

Carcinoma of the anal area is uncommon. Factors such as smoking, anal intercourse, human immunodeficiency virus, and human papillomavirus, particularly types 16 and 18, resulting in genital warts, have been associated with the development of anorectal cancer (**Figure 85-17**).

At the level of the dentate line and extending approximately 1 cm proximal is a transitional zone of epithelium connecting the squamous cell epithelium of the anoderm with the columnar epithelium of the rectum. This transition zone includes columnar, cuboidal, transitional, and squamous epithelial cells that represent the source for a variety of malignancies that arise in the anal canal. Anorectal malignancies can generally be divided into two regions: (1) malignancies of the portion proximal to the dentate line and including the transitional zone, which are referred to as *anal canal neoplasms*, and (2) tumors arising in the anoderm distal to the dentate line, which are referred to as *anal margin neoplasms* (**Table 85-3**).

Anal margin neoplasms have a low-grade malignant potential and are slow to metastasize, with the exception of melanoma. Anal canal neoplasms are far more virulent, metastasize early, and have a poor prognosis. Squamous cell carcinoma of the anal canal has a much poorer

TABLE 85-2 Anorectal Acquired Immunodeficiency Syndrome–Related Infections

Herpes simplex virus types 1 and 2	*Campylobacter*
Mycobacterium avium-intracellulare	*Entamoeba*
Cytomegalovirus	*Cryptosporidium*
Salmonella enterocolitis	*Isospora*
Shigella	*Giardia*

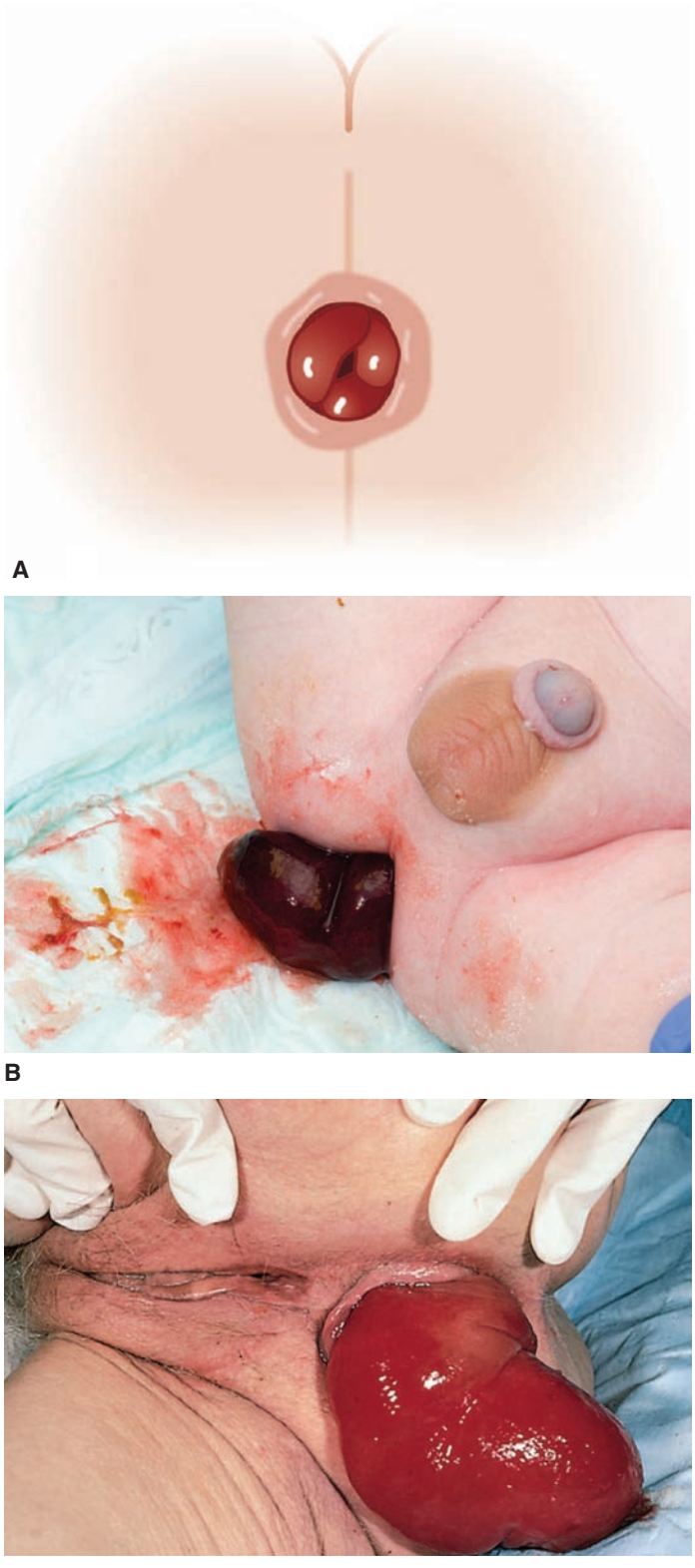


FIGURE 85-15. Differentiation: Prolapsed internal hemorrhoids from rectal prolapse. **A.** Prolapsing internal hemorrhoids with radial folds. **B.** Complete rectal prolapse with concentric folds. **C.** Complete rectal prolapse with a sulcus. [**B:** Photo contributor: Lawrence B. Stack, MD. **C:** Photo contributor Alan B. Storrow, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York.]

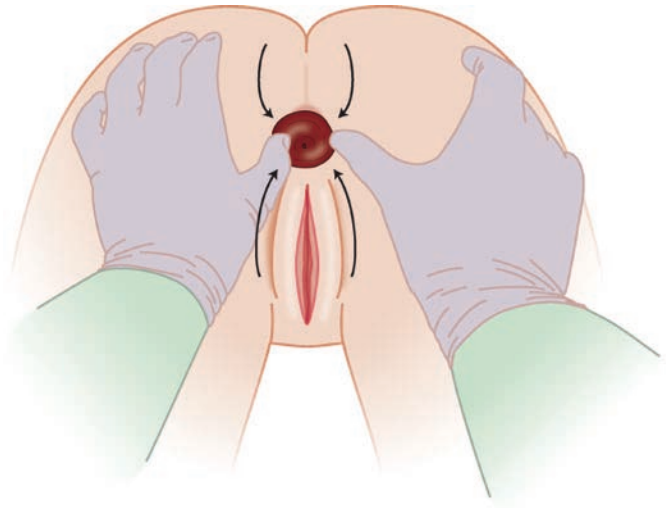


FIGURE 85-16. Reduction of complete rectal prolapse.

prognosis than its anal margin counterpart. Anal margin neoplasms generally metastasize to femoral and inguinal lymph nodes, whereas anal canal malignancies metastasize to the perirectal, mesenteric, and paravertebral lymph nodes via the portal circulation. **The anal canal is the third most common site of malignant melanoma (after the skin and the eye), which, when it occurs there, may not be pigmented and is frequently missed.**

CLINICAL FEATURES

Early anal canal malignancies usually cause nonspecific symptoms, such as pruritus, pain, and bleeding admixed with stool, but may be asymptomatic. Rectal pain may also be referred from retrorectal tumors and pelvic vessel aneurysms. As the tumor progresses, rectal fullness develops. The sensation and presence of a lump in the anal canal may be erroneously diagnosed as a hemorrhoid. As the neoplasm progresses, the patient experiences anorexia, bloating, weight loss, diarrhea, constipation, narrowing of the caliber of the stool, and, eventually, tenesmus with or without a bowel movement. Anal canal tumors may produce partial rectal prolapse and hemorrhoidal dilatation. More advanced malignancies may present as perirectal abscesses, fistulas, and bloody mucous discharge. Villous adenomas, which arise from the rectal columnar epithelium, frequently produce clear, watery diarrhea and a profuse rectal discharge, with secondary excoriation of skin and pruritus. Watery diarrhea may cause hypokalemia or hyponatremia. Anal margin neoplasms tend to be circumferential and may present with bleeding, persistent ulcers, or chronic dermatologic conditions such as eczema or mycotic infections. Any ulcer that fails to heal within 30 days or any discrete skin lesion that fails to improve with appropriate therapy must be biopsied to rule out the presence of malignancy. **Virtually all anorectal tumors can be detected by careful visual examination of the perianal area, digital palpation of the distal rectum and anal canal, and proctoscopic or sigmoidoscopic examination.**

Specific diagnosis and treatment require surgical consultation and referral.

TABLE 85-3 Anorectal Tumors

Anal Canal Neoplasms	Anal Margin Neoplasms
Adenocarcinoma of glands and ducts	Bowen's disease
Transitional cell carcinoma	Squamous cell carcinoma (SCC)
Melanoma, SCC	Basal cell carcinoma
Kaposi's sarcoma	Melanoma
Villous adenoma	Paget's disease

RECTAL FOREIGN BODIES

The medical literature is replete with the variety of foreign bodies that have been reported to have been inserted into the rectum (**Figure 85-18**).

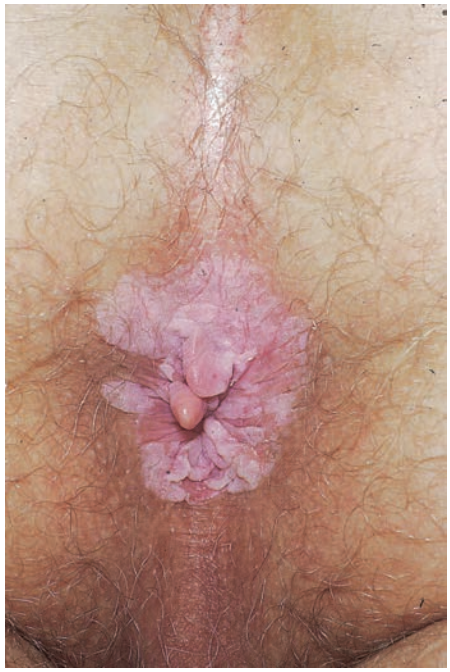


FIGURE 85-17. Perianal human papillomavirus–induced squamous cell carcinoma in situ. [Reproduced with permission from Wolff K, Johnson RA: *Color Atlas and Synopsis of Clinical Dermatology,* © 2009, McGraw-Hill, Inc., New York.]



FIGURE 85-18. Rectal foreign body. [Photo contributor: Kevin J. Knoop, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York.]

CLINICAL FEATURES

Patients may complain of abdominal pain and cramping, anorectal bleeding, discharge, and discomfort and may not initially be forthcoming with an accurate history. Most foreign bodies are in the rectal ampulla and are therefore palpable through careful digital examination. Anoscopy may detect signs of trauma and should replace the digital exam when sharp objects are suspected. Foreign bodies lodged above the rectosigmoid junction are usually not palpable. Injuries may consist of hematoma formation, various lacerations with potential perforation, and ischemic segments (particularly a delayed presentation). Radiographs of the abdomen may demonstrate not only the position, shapes, and number of foreign bodies, but also the possible presence of free air. Perforation of the rectum or colon, although uncommon, is a serious complication. Perforation of the rectum below the peritoneal reflection often causes retroperitoneal injuries, and plain radiographs may demonstrate extraperitoneal air along the psoas muscles. Perforation above the peritoneal reflection usually reveals intraperitoneal free air under the diaphragm noted on an upright chest radiograph. **CT scan is useful when the foreign body is radiolucent and for the detection of free air. Fever, leukocytosis, abdominal pain, rectal bleeding, and peritoneal signs are clinical manifestations suggestive of perforation.** Both can result in life-threatening sepsis, although perforation below the peritoneal reflection may be managed with more conservative therapy.

TREATMENT

Although some distal rectal foreign bodies can be removed by the emergency physician, many objects require surgical intervention, particularly if they are made of glass, have sharp edges, or show signs of perforation.[11] Foreign bodies with greater success of being removed in the ED are those that are located in the mid to lower rectum. When assessing the likelihood of removal in the ED, determine the type of object inserted and likelihood of injury to the GI tract or sphincter from removal. Prior to removal, consider infiltration of local anesthetic circumferentially around the anus. Sims, lithotomy, or knee-chest position with application of suprapubic pressure while the examiner digitally grasps the foreign body may help expulse the foreign body. After anal lubrication and with the aid of obstetric forceps, ask the patient to assist extraction by bearing down (**Figure 85-19A**). If the foreign body is removed in the ED and is of a size or shape that could cause perforation or laceration, proctoscopic examination and radiograph studies must be performed. In questionable cases, observation for at least 12 hours should be done to ensure that perforation has not occurred. Rectal and anal lacerations may be present and require repair. For removal of large foreign bodies, surgical consultation or emergency colonoscopy by a gastroenterologist is usually required. Large bulbar objects create a vacuum-like effect in the rectal ampulla, making it difficult to retrieve the object by simple traction. The vacuum can be overcome by passing a 20- to 26-French, three-way catheter beyond the object and injecting up to 30 mL of air. Inserting Foley catheters around the foreign body may then be used as traction devices to deliver the foreign body or manipulate it into a more accessible position (**Figure 85-19B**). If there is a risk of sphincter injury, ischemia, or perforation, or if excess manipulation will be needed to remove the foreign body (potential for bacteremia), obtain emergent surgical evaluation and appropriate laboratory studies, initiate IV therapy with crystalloid solution, and administer a broad-spectrum antibiotic (e.g., piperacillin-tazobactam, 3.375 grams IV).

PRURITUS ANI

Pruritus ani is a symptom complex that occurs secondary to a variety of anal and systemic problems (**Table 85-4**). Primary or idiopathic disease occurs when no cause is identified. **Pruritus ani is the second most common anorectal condition after hemorrhoids.**[12] It affects 1% to 5% of the population; men are affected four times more often than women; and it most commonly occurs in the fourth to sixth decades of life.[13]

CLINICAL FEATURES

Symptoms are often worse at night. The skin becomes macerated by constant mucous and purulent discharge. Bacterial infections, such as staphylococci and streptococci, in addition to all sexually transmitted organisms, can cause pruritus.

Pinworms (*Enterobius vermicularis*) are a common cause of anal pruritus in children. Institutionalized adults may also develop pinworms.[12] *Candida albicans*, particularly in diabetic patients, is commonly found on the perianal skin, but is not usually associated with pruritus; the *Trichophyton* species, on the other hand, are associated with pruritus. **Fecal contamination resulting from loose bowel movements, diarrhea, and poor anal hygiene is a frequent irritant to the perianal skin.** Excessive anal cleansing and wearing of synthetic, tight-fitting underwear that retains moisture can cause pruritus. Any of the anal margin neoplasms may initially cause pruritus. Systemic conditions, such as diabetes mellitus, psoriasis, pemphigus, leukemia, lymphoma, thyroid disorders, hepatic diseases, renal failure, iron deficiency anemia, and certain vitamin deficiencies (vitamins A and D and niacin), because of their secondary effect on the perianal skin, can cause pruritus. Lumbosacral radiculopathy has been associated with idiopathic pruritus ani.[12] The skin appears normal with early, mild cases. Superficial cracks seen on examination do not extend to the dentate line, as do fissures. With acute, more severe exacerbations, the perianal skin will appear reddened, edematous, excoriated, and moist. In chronic cases, the perianal skin takes on a thickened, almost leathery, depigmented appearance. The normal radiating folds of skin thicken into rugae and may produce factitiously induced superficial fissures.

TREATMENT

Diagnose and treat the underlying cause. Perianal streptococcal dermatitis (**Figure 85-20**) is well known in children, where it can cause systemic infection, but is also recognized and can cause serious infection in adults. Obtain cultures and treat empirically with penicillin or erythromycin.[14] Pinworms can be identified by touching the perianal skin with transparent tape to collect the worm and then viewing under a microscope. Idiopathic causes may be treated by adding fiber to the diet, which can bulk the stools and help prevent persistent soiling and irritation when the patient is plagued by frequent loose stools. To avoid scratching at night, the patient can wear gloves at bedtime. Warm baths are recommended for at least 15 minutes two to three times a day for hygiene, instead of soap, followed by thorough drying. Zinc oxide ointment can provide a protective covering for the perianal skin and may promote healing, while athlete's foot powder may enhance drying. One percent hydrocortisone cream is effective for the allergic component of the inflammation. Fungicidal creams, antibiotics, and antiviral and antiparasitic medications should be prescribed for patients with infectious causes. Hydroxyzine hydrochloride may be used as an effective bedtime sedative. Refer to a proctologist or dermatologist for resistant symptoms.

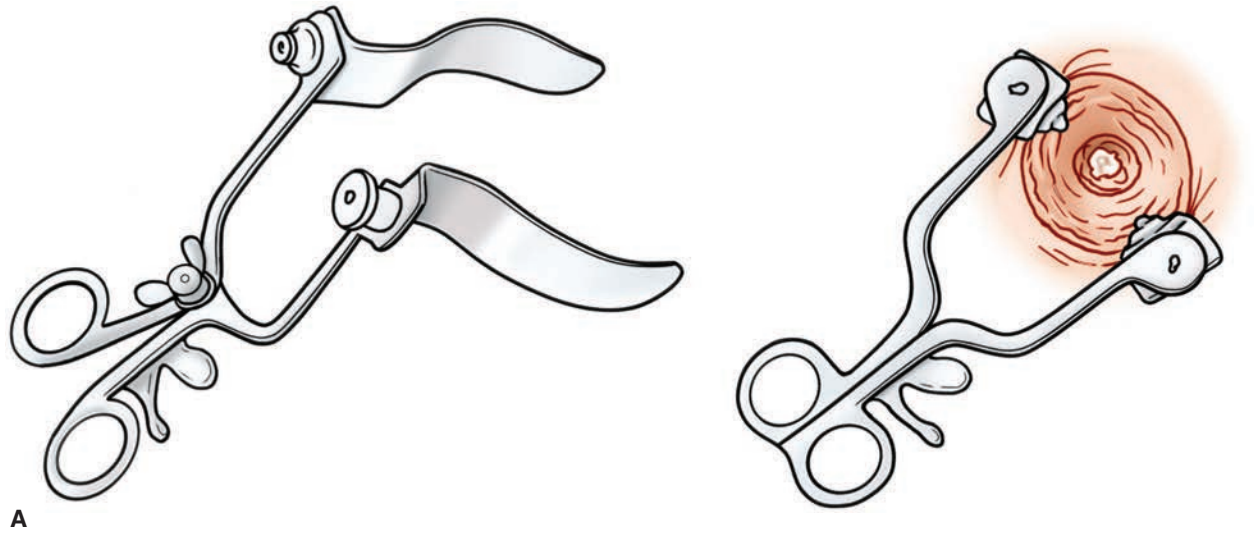
PILONIDAL SINUS

Pilonidal sinus is an acquired problem formed by the penetration of the skin by an ingrown hair, which causes a foreign body granuloma reaction. The sinus is perpetuated by the presence of the hair and repeated bouts of infection.

CLINICAL FEATURES

Pilonidal sinuses or cysts occur in the midline in the upper part of the natal cleft, which overlies the lower sacrum and coccyx. Because of their proximity to the anus, infected pilonidal cysts (abscesses) are sometimes mistakenly diagnosed as perirectal abscesses (**Figure 85-21, A–C**).

Occasionally, an inflamed cyst may refer pain to the coccygeal region. **An abscessed pilonidal sinus is almost always located in the posterior midline over the sacrum and coccyx.** Although there may be secondary fistulous openings on either side of the midline, they



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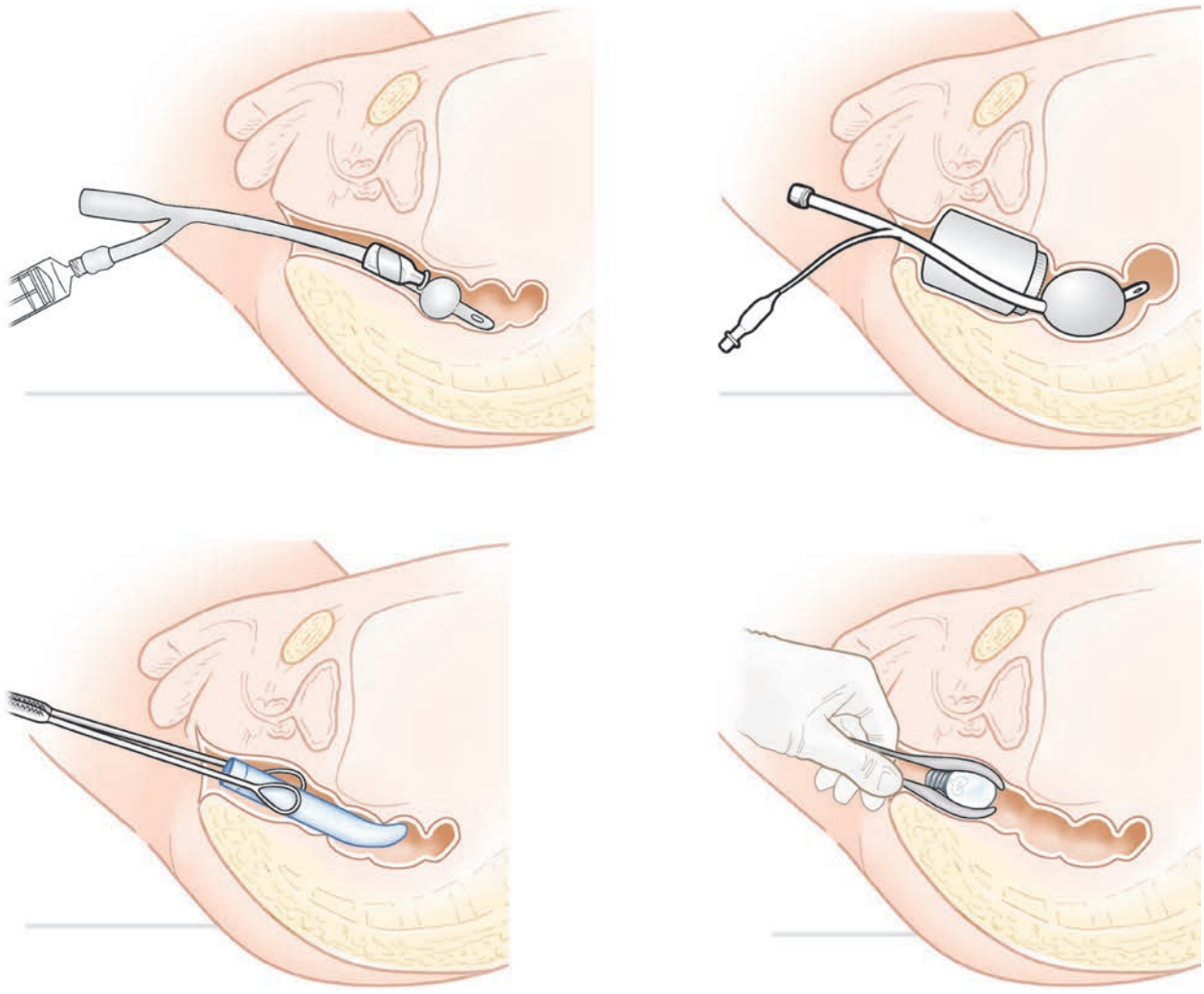


B

FIGURE 85-19. **A.** Foreign body exposure. **B.** Removal techniques. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures,* 2nd ed. McGraw-Hill, Inc., 2013. Figures 72-3, 72-4.]

TABLE 85-4 Some Secondary Causes of Pruritus Ani

- Anorectal disease: Draining perirectal abscess, fissures, hemorrhoids, rectal prolapse, fistulas
- Dietary factors: Caffeine, cola, calcium, chocolate, citrus, alcohol, tomatoes, spices, peanuts
- Local infection: Bacteria, viruses, fungi, worms, lice, scabies, bed bugs, hidradenitis
- Local irritants: Perfumed toilet tissue, soaps, detergents, hygiene sprays
- Dermatologic: Atopic dermatitis, lichen planus, psoriasis, seborrheic dermatitis
- Systemic illness: Diabetes, various malignancies, Crohn's disease, acanthosis
- Psychogenic: Stress, obsessive compulsive disorder

do not communicate with the anorectum. On the other hand, long, horseshoe-type fistulas emanating from a perirectal abscess may drain close to the location of a pilonidal sinus but not in the midline. Fistulous tracts most commonly ascend superiorly. Pilonidal disease may present as a painless cyst, an acute abscess, or chronic recurring cysts with draining sinuses. Alternate causes for draining fistulas should be considered, such as anal fistulas, syphilitic and tuberculous granulomas, simple furuncles, fungal infections, and sacral osteomyelitis. Carcinoma is a rare complication of chronic, recurring pilonidal sinus disease. It is more frequent in men and is usually a well-differentiated, dermal-type squamous cell carcinoma.

TREATMENT

Treatment is incision and drainage, and antibiotics are needed only if cellulitis is present. Ultrasonography can delineate the extent of the abscess. Following incision and drainage in the ED, refer to a surgeon for definitive care.

HIDRADENITIS SUPPURATIVA

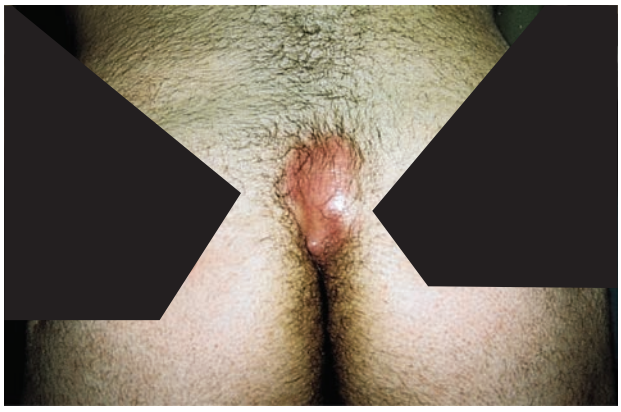
In postpubertal males and females (the second to fourth decades of life), the perianal surface containing hair follicles and apocrine sweat glands may become blocked, which generally occurs in the perineal, groin, axillary, or inframammary regions. Perineal disease is more common in males, whereas axillary disease is more common in females.[15]

CLINICAL FEATURES

Fistulas with a malodorous discharge may develop, but do not extend to the intersphincteric plane, and the abscesses are quite superficial and do not originate at the dentate line. Fistulas that extend above the dentate line may suggest coexisting cryptoglandular or Crohn's disease.[15] Chronic inflammation, edema, tissue induration, fibrosis, and significant pitted scarring may occur (**Figure 85-22**).



FIGURE 85-20. Example of pruritus ani. Pruritus ani from perianal strep infection. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, Inc., New York.]



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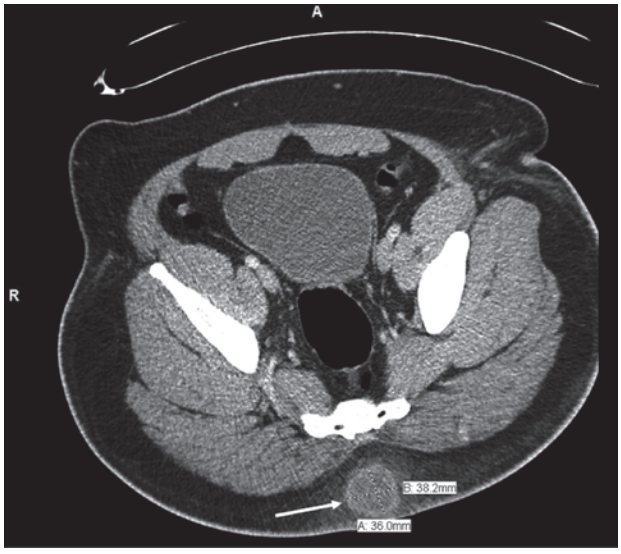


B



C

FIGURE 85-21. **A.** Pilonidal sinus. **B.** CT scan of a pilonidal sinus with abscess (*arrow*). **C.** Pilonidal sinus. [**A:** Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York. **C:** Photo contributor: Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw-Hill, Inc., New York. Figure 9.43.]



FIGURE 85-22. Perianal hidradenitis suppurativa in a 27-year-old man. Abscesses, draining sinuses, and scars are seen in the sacral region. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology,* 6th ed. McGraw-Hill, Inc., New York, 2009.]

TREATMENT

Recurrence is common, particularly in the perineal region, resulting in scarring, edema, painful nodules, induration, and draining sinus tracts, all of which are difficult to treat. Small abscesses can be drained in the ED, but extensive lesions require surgical or dermatologic referral. Topical clindamycin or oral clindamycin with rifampin can be helpful.[15] Other treatments include erythromycin, tetracycline, and doxycycline as well as retinoids, hormones, and immunosuppressive and anti-inflammatory agents. Some success is seen with radiation, cryosurgery, and laser treatments. With advanced disease characterized by recurrent abscesses, multiple interconnecting fistulas, and scarring, resection of the skin and subcutaneous fat down to the fascia yields the lowest recurrence rate.[15]

RECTOVAGINAL FISTULA

The lower rectum and anal canal abut the posterior wall of the vagina, so the fistula may be located anywhere along this region.

CLINICAL FEATURES

The presenting complaint of patients with a rectovaginal fistula is usually flatulence and/or malodorous vaginal discharge or gross stool emanating from the vagina. They may note air or stool in the urine, or rectal urine. **Table 85-5** lists various causes. A rectovaginal fistula can arise from the rectum or small or large bowel. Usually, stool is seen during the pelvic examination. CT scan or MRI confirms the diagnosis. Surgical consultation is required.

TABLE 85-5 Causes of Rectovaginal Fistulas

Gynecologic or surgical trauma or foreign body	Gynecologic malignancies
Pelvic irradiation	Leukemia
Local infection	Inflammatory bowel disease
Congenital	

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 86

Gastrointestinal Procedures and Devices

Michael D. Witting

NASOGASTRIC ASPIRATION

Nasogastric (NG) aspiration is used to remove liquid contents from the stomach and decompress the stomach and small bowel. The need for NG aspiration often varies with the clinical presentation (**Table 86-1**). Gastric decompression is useful in small bowel obstruction, although some studies have shown that medical therapy with octreotide or somatostatin has allowed safe treatment of bowel obstruction associated with malignancy.[1,2] NG aspiration and decompression are no longer considered routine for the treatment of adynamic ileus.[3,4] **Removal of liquid contents is useful in cases of GI bleeding, but most patients with GI bleeding can be managed without NG aspiration.**

In GI bleeding, a common and controversial situation for NG aspiration,[6] aspiration of stomach contents can localize the source of bleeding, indicate the rate of bleeding, and clear the stomach for endoscopy. Patients with hematemesis virtually always have an upper GI source, and NG aspiration is helpful to assess the rate of hemorrhage rather than identify the source. In significant upper GI bleeding, such as suggested by refractory hemodynamic instability or large quantities of bright red bloody emesis, the rate of bleeding can determine the success of medical interventions and the need for emergent endoscopy. When the clinical picture suggests a slower rate of bleeding, such as with coffee-ground emesis or blood-streaked emesis, the need for NG aspiration is less clear because less sensitive methods of assessing the rate of hemorrhage, such as observation of spontaneous bleeding, hemodynamic assessment, and serial hematocrit measurement, are often adequate.

In patients without hematemesis, NG aspiration lacks sensitivity to detect an upper GI source.[7,8] Although it has been reported that 10% of patients with hematochezia have an upper GI source, many of these are from a duodenal source and are beyond the reach of the NG tube.[9] Most patients with melena have an upper GI source and require upper endoscopy regardless of the results of NG aspiration. In severe, ongoing rectal bleeding with hemodynamic instability, NG aspiration is relatively useful because severe upper GI bleeding is generally easier to stop than severe lower GI bleeding.

The literature is riddled with case reports of bizarre mishaps resulting from the use of NG tubes, some of which are listed in **Table 86-2**.

TABLE 86-1 Selection of Patients for Nasogastric Aspiration

Clinical Situation	Best Uses	Consider Withholding
GI bleeding with hematemesis	Rapid bleeding (large hematemesis, refractory hemodynamic instability)	Slow or mild bleeding (coffee grounds, blood-streaked emesis)
GI bleeding without hematemesis	Massive rectal bleeding with hemodynamic instability	Clinical picture suggests lower GI source (bright red blood per rectum, age >50 y, blood urea nitrogen/creatinine <30)[5]
Small bowel dilation	Small bowel obstruction	Ileus

TABLE 86-2 Complications of Placement of Nasogastric and Nasoenteric Tubes

- Epistaxis
- Intracranial placement
- Bronchial placement
- Pharyngeal placement
- Esophageal obstruction or rupture
- Bronchial or alveolar perforation
- Pneumothorax
- Charcoal instillation into the lungs and pleural cavity
- Gastric or duodenal rupture
- Vocal cord paralysis
- Pneumomediastinum
- Laryngeal injuries
- Knotting (preventing removal)

However, the rate of adverse effects has not been systematically addressed. The main morbidity from the procedure is probably related to pain, followed by epistaxis, both of which can be minimized by good technique.

The equipment required for NG tube insertion is listed in **Table 86-3**. The optimal positioning is with the patient seated upright with the neck slightly flexed. Topical application of anesthetic can reduce the pain of the procedure, and a vasoconstrictor can shrink the turbinates, creating a larger nasal opening, but use a vasoconstrictor with caution in hypertensive patients. One option is to mix 4% lidocaine with oxymetazoline and instill this solution using a nasal atomizer.[10] Nebulized lidocaine also provides effective analgesia.[11] Although it is tempting to use viscous lidocaine on the tip of the tube instead of premedication, this maneuver does not allow time for the lidocaine to be effective. A right-handed operator may choose the right side or the side of patient preference. Premedication with IV metoclopramide, in adults, or lingual 24% to 25% sucrose, in infants, may also decrease pain.[12-14] Also, in adults, premedication with a small dose of midazolam (2 milligrams) improves pain relief compared with topical anesthesia alone.[15]

Describing the procedure to the patient in advance and talking to the patient during the procedure will minimize anxiety. Insert the lubricated tube into the selected nostril. Direct the tube posteriorly, not superiorly, and it should naturally bend inferiorly toward the glottis. Resistance is expected at the level of the glottis. At this point, have the patient take a drink of water, and advance the tube at the time of swallowing. This step minimizes the potential for false passage at the level of the glottis. Warming the distal tip of the tube will make it more pliable and may further decrease the pain of the procedure. Once the tube is past the glottis, quickly advance the tube and aspirate stomach contents. If the patient coughs during the procedure, stop and make sure that the patient can speak clearly. Failure to aspirate stomach contents should prompt visualization of the pharynx to ensure the tube is not coiled in the posterior pharynx. If the appearance of the gastric aspirate is inconclusive, its pH can be tested, or air can be insufflated during auscultation over the stomach (**Table 86-4**). A chest radiograph can also be obtained to confirm tube placement. If the NG tube is to remain in place, it can be taped to the patient's nose and connected to low-intermittent suction.

TABLE 86-3 Equipment for Nasogastric Tube Insertion

- Absorbent pad (blue Chux®)
- Kidney basin
- Materials for anesthesia and vasoconstriction
  - Nebulizer or nasal atomizer
  - Local anesthetic (4% lidocaine)
  - Vasoconstrictor (oxymetazoline, phenylephrine)
- Water-soluble lubricant
- Cup of water with straw
- Nasogastric Salem sump tube—16F
- Catheter-tip syringe
- Tubing connected to suction device, such as wall suction

TABLE 86-4 Techniques for Identifying Nasogastric and Nasointestinal Feeding Tube Placement

Indicates gastric placement

- Epigastric auscultation of air insufflated through the tube
- Aspiration of visually recognizable GI secretions
- pH testing of aspirates (pH <6 indicates gastric placement)

Indicates tracheobronchial placement

- Coughing or choking
- Inability to speak
- Air bubbles when proximal end of tube is placed in water

Some situations make NG tube insertion more difficult, such as obstructed nares, lack of patient cooperation, or endotracheal intubation. In patients with obstructed nares, the orogastric route may be used, although this is often less comfortable than the NG route. In obtunded patients with a poor gag reflex, endotracheal intubation may prevent aspiration. In patients with endotracheal intubation, flexing the neck or cooling the tube in ice water to stiffen it may facilitate passage.

ANOSCOPY

Anoscopy can identify an anorectal cause of bleeding in patients with hematochezia. Although an uncomfortable test, it is safe if performed properly. Contraindications include suspected rectal perforation. For detailed description of technique, see Chapter 85 "Anorectal Disorders."

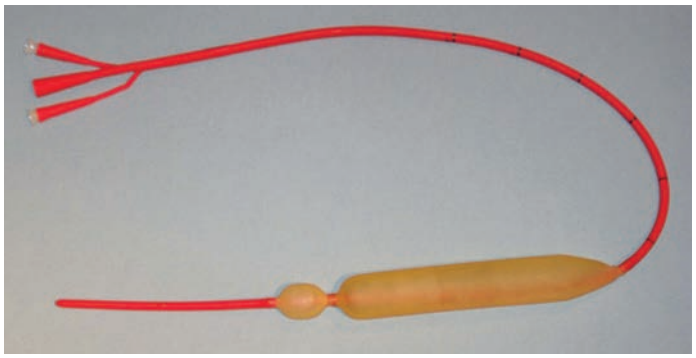
OROGASTRIC LAVAGE

Orogastric lavage is used to remove pills and fragments from the stomach. It is only appropriate for patients presenting well within 1 hour after a potentially lethal ingestion.[16] Because an NG tube is too small to retrieve pill fragments, gastric lavage for solids is done orally with a large-bore tube. Gagging and vomiting during the procedure are common, and aspiration is a significant risk, particularly when airway protection is in doubt. Many other complications are possible, including tube misplacement into the bronchi, pharyngeal injury, and viscus perforation. Endotracheal intubation before this procedure can minimize these risks when a patient is, or may become, obtunded.

Equipment for the procedure includes a large-bore tube, such as the Ewald tube® or the Tum-E-Vac® (Ethox Corp, Buffalo, NY); lubricant; suction; emesis basin; blue absorbent pad; a catheter-tip syringe; irrigation fluid; and a bite block or oral airway to prevent patients from biting down on the tube. Patient positioning, tube advancement, and confirmation of placement are similar to NG tube insertion, but be especially sure to aim the proximal end away from others. After inserting a bite block in uncooperative patients, insert the gastric tube to the level of the glottis, and encourage the patient to swallow. Then pass the tube quickly into the stomach. Coughing or airflow from the tube raises concern for tracheal malpositioning. Have the patient vocalize to exclude tracheal placement. After suction and irrigation of gastric contents, charcoal and sorbitol can be instilled before withdrawal of the tube.

ESOPHAGEAL BALLOON (SENGSTAKEN-BLAKEMORE) TAMPONADE

The Sengstaken-Blakemore tube is designed to tamponade bleeding from esophageal varices (**Figure 86-1**). With the increasing availability of endoscopy and success of medical therapy with octreotide, somatostatin, and vasopressin, its use has declined. Nevertheless, it still has a role in cases in which endoscopy is unavailable or hemorrhage is refractory to endoscopic techniques. In one series, most survivors received a transjugular intrahepatic portosystemic shunt procedure, in addition



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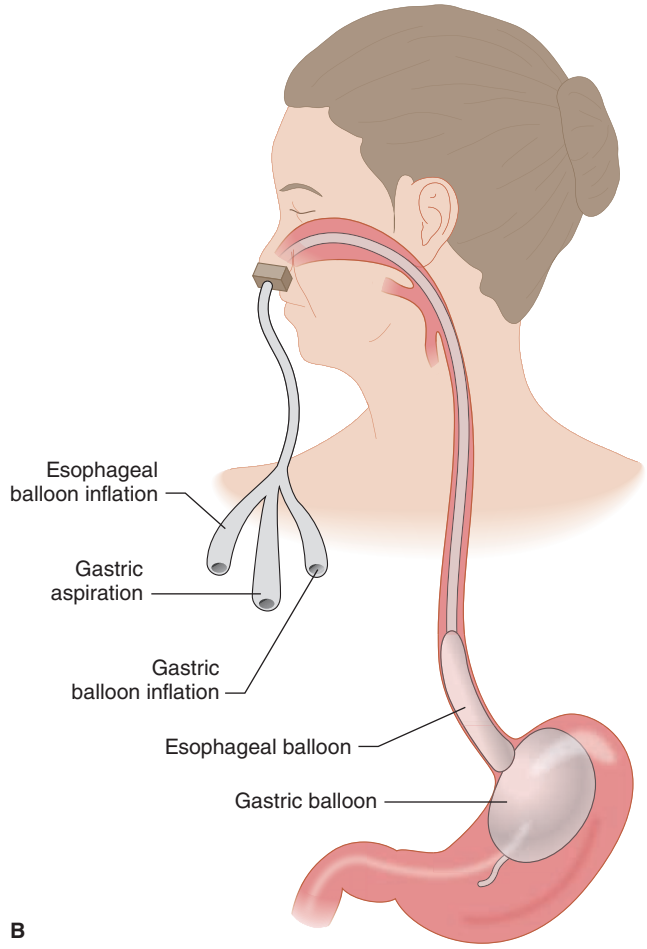

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FIGURE 86-1. **A.** Sengstaken-Blakemore tube. **B.** Insertion of Sengstaken-Blakemore tube.

to balloon tamponade.[17] It is only useful in patients with esophageal varices that are known or suspected from the clinical picture, such as in patients with severe hematemesis and signs of cirrhosis. The procedure frequently provokes emesis, and aspiration can be minimized by endotracheal intubation. Other risks include gastric or esophageal rupture.

Insert the tube orally after the same procedure described in the section "Orogastric Lavage." After confirming tube placement as described earlier, expand the distal balloon with water or normal saline and apply gentle traction to the tube. Because varices are often at the gastroesophageal junction, this often stops the bleeding. If not, expand the proximal balloon. To maintain traction, tape the proximal end of the tube to the face guard of a baseball catcher's mask or lacrosse helmet that has been already placed onto the patient. The patient will not be able to swallow secretions with this in place, so proximal suction, whether from a proximal port in the device or an NG tube inserted proximally, will further minimize the risk of aspiration.

Once the tube is in place, maintain traction to the minimum amount necessary to stop the bleeding to minimize the risk of tissue ischemia. Maintain balloon tamponade until more definitive measures can be taken.

ABDOMINAL PARACENTESIS

In paracentesis, ascitic fluid is removed for diagnostic or therapeutic purposes. Patients with ascites and abdominal pain or other GI symptoms may have peritonitis, requiring diagnostic paracentesis. This may be true even if the abdominal pain is mild and unaccompanied by signs of systemic infection.[18] Patients with respiratory compromise or severe pain due to tense ascites require therapeutic paracentesis, in which a large quantity of fluid, often greater than 5 L, is removed. Large-volume paracentesis, in which greater than 5 L is removed, is time-consuming and associated with complications such as hyponatremia, renal impairment, and encephalopathy. Many of these patients require other treatment, including albumin infusion.[19,20] Therefore, it is generally best reserved for the admitting team or ED observation unit, except in rare cases in which pain or respiratory compromise cannot be controlled in the ED with medications or supplemental oxygen. Other risks of paracentesis in general, whether diagnostic or therapeutic, include bowel perforation, ascitic fluid leak, hemorrhage, and introduction of infection.

Equipment for **diagnostic paracentesis** (See Video: Abdominal Paracentesis) includes sterile drapes (both fenestrated and nonfenestrated), sterilizing solution (povidone-iodine or chlorhexidine), gauze, assorted syringes (3, 10, or 30 mL), a small-bore (27-gauge or smaller) needle, three medium-bore (21-gauge) needles, local anesthetic (lidocaine), and containers for cell count and culture for the laboratory. If paracentesis is also to be therapeutic, a three-way stopcock, sterile tubing, and a source of suction—either vacuum bottles or a setup for wall suction—are necessary, and a large-bore needle or plastic catheter (18- or 16-gauge) will speed the procedure. Ultrasonography can confirm ascites and identify a target fluid collection to minimize the potential for bowel perforation (**Figure 86-2**). US guidance can also assist the operator in avoiding subcutaneous vessels dilated by portal hypertension, and it decreases the risk of bleeding.[21]

If the patient has severe coagulopathy (INR >2.5) or thrombocytopenia (platelets <50,000/μL), consider correcting deficiencies before paracentesis.[22,23] Place the patient in a comfortable supine position, and cleanse and sterilely prepare the site of expected needle insertion. The left lower quadrant is generally a good area because this minimizes the potential for liver injury, but the right lower quadrant may also be used if the left lower quadrant has distorted anatomy, such as with prior scarring or ostomy surgery (**Figure 86-3**). Anesthetize the skin over the target area by raising a wheal, and then switch to a larger-bore needle to infiltrate to the level of the peritoneum. A Z-track technique, in which traction on the skin is used to create a displaced track to the peritoneum,

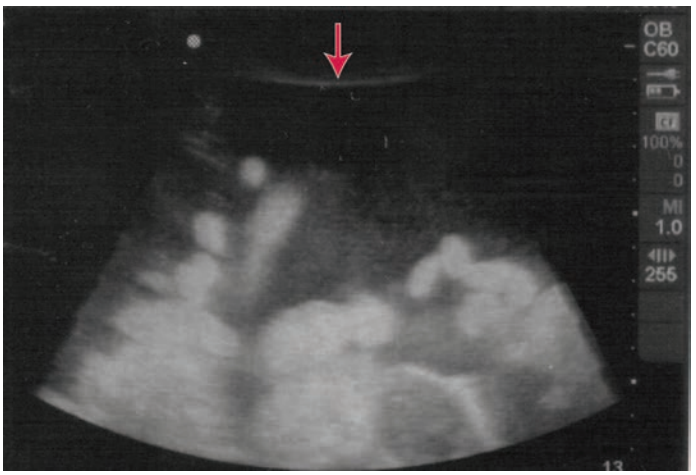

FIGURE 86-2. US view of a desirable puncture site for paracentesis (*arrow*).

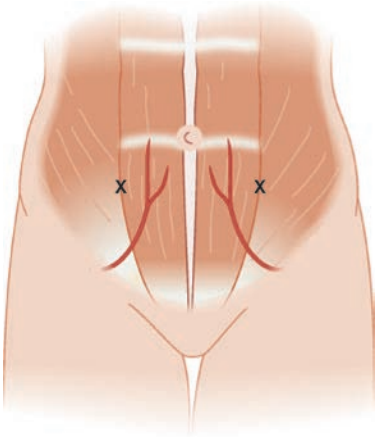

FIGURE 86-3. Sites for needle introduction in the left or right lower quadrant (x) for abdominal paracentesis.

can minimize the potential for infection and persistent leakage.[20] At a depth expected to be near the peritoneum, apply suction to the syringe and infiltrate lidocaine while advancing until peritoneal fluid is aspirated. Once the fluid is aspirated, change the syringe with the needle still in place, and then aspirate at least 50 mL of fluid into the fresh syringe for laboratory analysis. In therapeutic paracentesis, attach tubing to the needle, catheter, or stopcock, and connect to suction. Even if the goal is diagnosis, removal of 1 to 2 L is unlikely to cause complications and may provide significant symptomatic relief. Then withdraw the needle or catheter and cover the insertion site with a dressing. A purse-string suture can be placed to minimize leakage. Recheck the patient in 30 minutes to identify persistent leakage or an increase in symptoms to suggest a complication. Patients with large-volume paracentesis should be monitored for hypotension for several hours after the procedure. Cover the puncture site with a dry dressing for 48 hours.

TRANSABDOMINAL FEEDING TUBES

Although the techniques for the initial placement of transabdominal feeding tubes (gastrostomy [G-tube], jejunostomy [J-tube], and gastrojejunostomy) are beyond the scope of emergency physicians, complications related to these tubes need to be recognized (**Table 86-5**). These tubes can be placed by a surgeon using open technique, by a gastroenterologist using endoscopic technique (percutaneous endoscopic gastrostomy), or by a radiologist with percutaneous techniques. The radiographic technique has been associated with fewer complications than has open or endoscopically assisted placement.[24]

Frequent minor complications are associated with the use of these tubes, including purulent drainage and leakage around the stomal site, clogging, dislodgement, diarrhea, and vomiting.

Drainage from the stomal site is a common finding and represents a foreign-body reaction due to the catheter. As long as there is no evidence of cellulitis or necrotizing fasciitis, local skin care will usually clear up the problem. Local bleeding from granuloma formation may be treated with silver nitrate.

Leakage of gastric contents is a common problem. Gastric contents may leak due to excessive pressure between bolsters, which can limit blood flow (**Figure 86-4**).[25] Leak can also result from excessive tube mobility, either in-and-out (from excessive distance between bolsters) or side-to-side. Tube malposition can also cause leakage. Management strategies include gently withdrawing the tube and adjusting the outer bolster, tube replacement, or removing the tube for 24 to 48 hours to allow healing (if tract is mature).[25] CT or plain radiographs, after injection of gastrografin through the tube, can be used to assess placement of the original or replaced tube. Consider surgical consultation for assistance with bolster adjustment or tube replacement (if tract maturity is uncertain).

TABLE 86-5 Complications Seen With Transabdominal Feeding Tubes

Complication	Initial Considerations
Leakage from stoma	Check outer bolster position, consider tube malposition.
Tube occlusion	Attempt irrigation; most often, just replace.
Dislodged tubes	Gently replace; confirm placement with x-rays.
Pneumothorax	High index of suspicion; consider needle aspiration.
Bacteremia	Consider as potential source in septic patient.
Bleeding from tract	If recently inserted, consider local injection, consult.
Bleeding from granuloma buildup	Local therapy with silver nitrate.
Infection of surrounding skin	Consultation, pull tube, IV antibiotics.
Necrotizing fasciitis	Consider MRI to help confirm; surgical debridement.
Peritonitis	Determine if fistula exists; consultation, IV antibiotics.
Pulmonary aspiration of feedings	Reduce flow rate, half-strength feeds, consider J-tube.
Vomiting or diarrhea	Reduce flow rate, half-strength feeds, stop feeds.
Gastroesophageal reflux	Reduce flow rate, half-strength feeds, consider J-tube.
Intestinal obstruction	Step feedings, NPO, admit, and observe.
Gastric outlet obstruction	Reposition tube.
Gastric volvulus	Surgical consult.
Gastric perforation	Surgical consult.
Esophageal perforation	Surgical consult.
Colonic perforation	Surgical consult.
Colocutaneous fistula	Surgical consult.
Electrolyte abnormalities	Change feedings or increase free water.
GI bleeding	Endoscopy and therapy directed at cause.
Bolster buried in abdominal wall	Surgical consult.

Abbreviations: J-tube = jejunostomy tube; NPO = nothing by mouth.

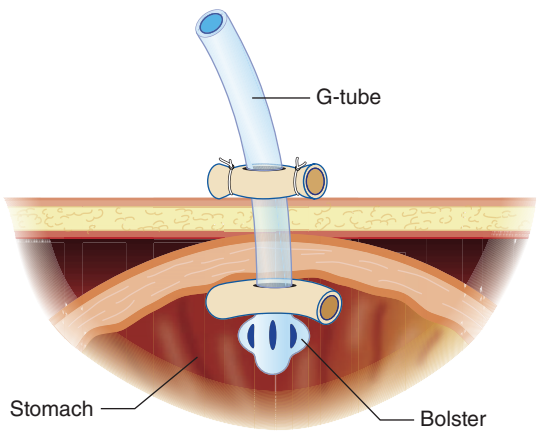

FIGURE 86-4. Percutaneous endoscopic gastrostomy tube (G-tube) with a mushroom bolster in place.

Prevention is the best treatment for clogging of gastrostomy and jejunostomy tubes. Frequent flushing with water and careful crushing of pills usually can prevent this problem. Vomiting and diarrhea can be relieved by decreasing the amount of the feedings and/or diluting the feedings. To unclog the tube, instill warm water or carbonated beverage (cola is most often used) and let it remain for 20 minutes. Then attempt flushing.[26] Alkalinized pancreatic enzymes (12,000 lipase units dissolved in 650 mL bicarbonate) have also proven effective in about 50% of cases.[27]

TUBE REPLACEMENT

If the tube cannot be unclogged or if it has fallen out, replacement will be necessary. If the tube was placed by a surgeon or gastroenterologist and has not been replaced, it probably will have a bolster (also called a *mushroom* or *bumper*) holding the tube in place (Figure 86-4). This will prevent the tube from being removed. The bolster must be removed endoscopically, or the tube may be cut off and the bolster allowed to pass through the GI tract.[28] The latter technique is generally safe in adults, but passage in children has complications,[29] and tube removal should be done by the endoscopist or surgeon. Endoscopic removal in adults is advisable when there is suspected or potential obstructive disease of the GI tract, such as pyloric stenosis, intestinal pseudo-obstruction, and intestinal stricture (e.g., due to radiation, ischemia, or inflammatory bowel disease). If the tube is cut, an abdominal radiograph should be obtained 1 week later to confirm passage of the internal component. Most reported complications from a retained internal bolster have occurred when the bolster did not pass within 1 to 2 weeks.[30] If the bolster or bumper becomes buried in the abdominal wall, consult with the endoscopist or surgeon who placed the device. Do not attempt removal by traction. Some specially designed tubes have internal bumpers that can be removed by external traction, but consultation with the endoscopist or surgeon who placed the device is necessary before any traction is applied to verify the type of tube and the appropriate method of removal[31] (Figure 86-4).

If the tube has become dislodged or has fallen out, **replace it as quickly as possible (within a few hours) to prevent closure of the tract**. **Most tracts mature after 2 to 3 weeks. Do not attempt to replace a tube with an immature tract.**[26] First determine, if possible, which type of tube is being used. If the tube is available, replacement with the same size is usually possible. If the tube is not available, it can be difficult to determine whether the tract is for a jejunostomy or gastrostomy tube. Location site on the abdominal wall is not helpful to differentiate the two. A tract for a gastrostomy tube is usually larger. Old records may be useful and should be obtained, if possible. After determining the type of tract and size of tube used previously, insert the tube using a water-soluble lubricant. If the size of the tube being replaced is not known, it is reasonable to start with a 16- or 18-F replacement gastrostomy tube or Foley catheter. The lubricated tube should pass easily into the stoma without additional equipment. If resistance is met, abandon the attempt. A smaller tube can be tried to keep the tract open. After replacing the tube, instill a 20- to 30-mL bolus of a water-soluble contrast material (e.g., diatrizoate meglumine and diatrizoate sodium solution [Gastrografin]) through the tube, and obtain a supine abdominal radiograph within 1 to 2 minutes. The radiograph should demonstrate rugae of the stomach for a gastrostomy tube and flow into the small bowel for a jejunostomy tube. US can also be used to verify gastric placement. The tip of the tube can be visualized within the stomach, and confirmation of placement can be done by injecting 10 mL of normal saline into the tube and observing the fluid entering the stomach, using real-time US. Another way of determining placement is to withdraw gastric fluid and check pH to make sure it is acidic. If there is any question of improper placement, obtain immediate consultation.

A special caution regarding jejunostomy tubes should be noted. Jejunostomy tracts are smaller, and smaller tubes are used (8- to 14-F). These tubes usually are not sutured in place and frequently become dislodged. They can be replaced with catheters made specifically for jejunostomies or with Foley catheters. **If a Foley catheter is used to replace a lost jejunostomy catheter, the balloon should never be inflated** because it can cause a bowel obstruction or damage the jejunum. The tube is lubricated, inserted into the stoma, and advanced 20 cm. These tubes are easily replaced if the tract is mature; however, if resistance is met, referral to a radiologist for fluoroscopic placement using guidewires is recommended.

OSTOMY COMPLICATIONS

Emergency physicians frequently encounter patients with ostomies and their complications. Common ostomies include colostomies, ileostomies, catheterizable ileal pouches, and ileal conduits. As expected, ostomy surgery can result in the following surgical complications: wound infection, dehiscence, parasomal herniation, bowel obstruction, including from volvulus, and bleeding. These complications generally require surgical consultation. Dermatitis is commonly caused by exposure to urine or feces, abrasion, or allergy to adhesive or ostomy material.[32] Remedies include resizing ostomy contact and changing ostomy material, perhaps guided by referral for patch testing. Ostomy powder is available to help dry skin, and ostomy paste can be used to prevent leakage from poor ostomy contact.

The ileum is commonly used for two types of urinary diversion—ileal conduit and catheterizable ileal pouch. In either case, a part of the ileum is detached from the alimentary canal and reformed into a reservoir; the remaining ileum is reconnected end-to-end. The ileal conduit, which is more common, does not require catheterization, has a small reservoir, and has a relatively continuous ostomy output.[33] In the catherizable ileal pouch, the patient catheterizes a larger reservoir and can maintain continence. Both reservoirs are prone to urinary infection and colonization, and patients with a catheterizable pouch must irrigate periodically to minimize the risk of urinary infection.[34]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 87

Complications of General Surgical Procedures

Edmond A. Hooker

INTRODUCTION

Outpatient surgical procedures are common, and with increasing pressure for cost containment, admitted patients are being discharged earlier in their postoperative course. As a result, more patients are coming to the ED with postoperative fever, respiratory complications, GU complaints, wound infections, vascular problems, and complications of drug therapy (**Table 87-1**). This chapter reviews the complications common to all surgical procedures and those specific to a specific procedure.

The operating surgeon should be called when one of his or her patients appears in the ED with a surgical complication. This is not just a courtesy, but provides continuity of care important for the patient's well-being.

FEVER

Fever is a common presenting complaint (**Table 87-2**). A mnemonic for the common causes of postoperative fever is the "five Ws": *wind* (atelectasis or pneumonia), *water* (urinary tract infection), *wound*, *walking* (deep vein thrombosis), and *wonder drugs* (drug fever or pseudomembranous colitis).[1] Respiratory complications, such as atelectasis,

TABLE 87-1 Complications of General Surgical Procedures

Complication	Important Points
Fever	"Five Ws" (wind, water, wound, walking, wonder drugs) are common causes
Pulmonary complications	
Atelectasis	<24 h, treat with pulmonary toilet, discharge unless ill or hypoxemic
Pneumonia	2–7 d, polymicrobial, most require admission
Pneumothorax	Multiple causes, consider expiratory views, consider needle aspiration
Pulmonary embolism	Dyspnea is main symptom, high index of suspicion
GI complications	
Intestinal obstruction	Obtain radiographs, search for causes
Intra-abdominal abscess	CT diagnosis, early administration of broad-spectrum antibiotics
Pancreatitis	Always consider in postoperative patients with abdominal pain
Cholecystitis	Usually in older patients, can be acalculous
Fistulas	Can be high output, admit if concerns over output
GU complications	
Urinary tract infection	2–5 d, oral antibiotics, most discharged
Urinary retention	Rapid catheter drainage, most discharged
Acute renal failure	Prerenal, renal, and postrenal causes, most admitted
Wound complications	
Hematoma	Caused by poor hemostasis, can drain most, but be careful with neck hematomas and hematomas after vascular surgery
Seroma	Painless swelling, clear fluid, drain and discharge
Infection	Open, drain, and culture specimens; be careful with wounds associated with respiratory tract, GI tract, or GU tract, or secondary to trauma
Necrotizing fasciitis	Pain out of proportion to physical findings
Dehiscence	Be careful with abdominal incisions (potential for evisceration)
Vascular complications	
Superficial thrombophlebitis	Usually aseptic, provide local therapy and discharge
Deep venous thrombosis	Upper and lower extremity, perform Doppler studies
Complications of drug therapy	
Diarrhea	Consider pseudomembranous colitis
Drug fever	Many drugs implicated, requires admission
Tetanus	Can occur after GI surgery
Procedure-specific complications	See text

and IV catheter–related problems, such as thrombophlebitis, are the predominant causes of fever in the first 72 hours. Necrotizing streptococcal and clostridial infections also occur in surgical wounds early in the postoperative course.

Urinary tract infections become evident 1 to 5 days postoperatively. Seven to 10 days postoperatively, clinical manifestations of wound infections develop. Deep venous thrombosis can result in fever any time but usually not until the fifth postoperative day. Antibiotic-induced pseudomembranous colitis occurs up to 6 weeks postoperatively. An approach for evaluating and managing fever in postoperative patients is presented in **Table 87-3**.

RESPIRATORY COMPLICATIONS

ATELECTASIS

Atelectasis, the collapse of pulmonary alveoli, is very common. Contributing factors include inadequate clearance of secretions after general anesthesia, decreased intra-alveolar pressure, and postoperative pain, which results in hypoventilation. Although atelectasis can occur after any procedure, it frequently occurs after upper abdominal and thoracic surgery. The presentation varies from an isolated fever to tachypnea, dyspnea, and tachycardia.

Evaluation includes chest radiography, pulse oximetry, and a CBC. Chest radiographs may show normal findings or exhibit platelike linear densities, triangular densities, or lobar consolidation. CT scan can be done when other diagnoses are a consideration. US may be useful in confirming the diagnosis of atelectasis.[2] Mild hypoxemia from ventilation and perfusion mismatch is common, but hypercarbia is uncommon. Patients with mild atelectasis and no evidence of hypoxemia may be managed as outpatients with pain control and increased deep breathing. Admission is indicated for aggressive pulmonary toilet and supplemental oxygenation in debilitated patients, patients with underlying lung disease, patients with hypoxemia, or those in whom the diagnosis is in question.

PNEUMONIA

Pneumonia usually becomes evident between 24 and 96 hours postoperatively. Predisposing factors include prolonged ventilatory support and atelectasis. Presenting symptoms can include dyspnea, chest pain, productive cough, fever, and tachypnea. Postoperative pneumonia is likely to be polymicrobial. After specimens of sputum and blood are obtained for culture, parenteral antimicrobial therapy is given. There are many options for polymicrobial coverage. Follow local recommendations for hospital-acquired pneumonia.

PNEUMOTHORAX

Pneumothorax can occur as a complication of thoracic wall surgery, breast biopsy, laparoscopic abdominal surgery, abdominal paracentesis, nasogastric and feeding tube insertion, thoracic surgery, central venous catheter insertion, endoscopic procedures, shoulder arthroscopy, and tracheostomy. For further discussion, see Chapter 68, "Pneumothorax."

PULMONARY EMBOLUS

Pulmonary embolism may present any time during the postoperative period. For further discussion of signs, symptoms, and treatment, see Chapter 56, "Venous Thromboembolism Including Pulmonary Embolism."

GU COMPLICATIONS

URINARY TRACT INFECTION

Urinary tract infections can occur after any surgical procedure, but the incidence increases in patients who have undergone instrumentation of the GU tract or bladder catheterization. The cause is direct contamination of the urinary bladder, most commonly with *Escherichia coli*. Other organisms isolated include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella*, *Pseudomonas*, and enterococci. Oral antibiotics (ciprofloxacin, 500 milligrams PO twice daily, or levofloxacin, 750 milligrams PO once daily) are appropriate for most infections, and choice of antibiotic should be based on local susceptibility patterns. Elderly or debilitated patients and those with sepsis require admission for parenteral administration of antibiotics (usually levofloxacin, 750 milligrams IV once daily).

URINARY RETENTION

Postoperative acute urinary retention is a common problem for surgical patients. Urinary retention occurs as the result of catecholamine stimulation of α-adrenergic receptors in the bladder neck and urethral smooth

TABLE 87-2 Common Causes of Postoperative Fevers in General Surgical Patients

Cause of Fever	Presentation	Signs and Symptoms	Diagnostic Test	Treatment
Atelectasis	First 24 h	Isolated fever; may have tachypnea, dyspnea, and/or tachycardia	Chest radiography	Pulmonary toilet; admission if unsure or patient is ill appearing
Pneumonia	3–7 d	Dyspnea, chest pain, productive cough, fever, and/or tachypnea	Chest radiography	Admission and coverage with broad-spectrum antibiotics
Urinary tract infections	2–5 d	Often none; possibly dysuria	Urinalysis	Admission if patient is elderly or toxic
Skin and soft tissue infection	5–10 d	Increasing pain, erythema, swelling, drainage, and tenderness at incision site	Examination, aspiration and/or opening of wound	Drainage, packing, and outpatient antibiotic therapy
Thrombophlebitis (septic and sterile)	<3 d	Warm, tender, and swollen vein	None	If not septic, warm soaks If septic, surgical removal
Deep vein thrombosis	4–6 d	Extremity swelling and pain	US	Admission and anticoagulation
Intra-abdominal abscesses	4–21 d	Fever and elevated WBC count without specific focal abdominal findings	CT	Admission and antibiotic administration
Pseudomembranous colitis	Anytime	Diarrhea	Stool testing using immunoassay	Metronidazole or vancomycin
Peritonitis	4–21 d	Tachycardia and abdominal pain, peritoneal irritation	CT	Admission and antibiotic administration
Pulmonary embolism	Anytime	Shortness of breath, tachypnea, and/or hemodynamic instability	CT or ventilation–perfusion scanning	Admission and anticoagulation
Transfusion reaction	First 24 h	Fever, chills	Transfusion check for incompatibility	Admission depending on condition of patient

muscle. Increased incidence of urinary retention is likely to occur in elderly patients, females, patients receiving excessive fluid administration during surgery, those undergoing anorectal surgery, patients undergoing longer procedures (>2 hours), and those for whom spinal or epidural anesthesia was used.[3,4]

TABLE 87-3 Evaluation and Management of Postoperative Fever

History

- Presenting signs and symptoms
- Onset of symptoms, time since procedure
- Procedures performed and complications
- Medications
- History of blood transfusion

Physical examination

- Particular attention to
  - Operative sites and contiguous areas
  - Sites of catheters and invasive monitors
  - Signs of deep venous thrombosis and pulmonary embolism
  - Decubitus ulcers
  - Lungs

Ancillary studies

- CBC with differential
- Chest radiograph
- Gram stain and culture of wound exudate
- Urinalysis (urine culture if infected)
- Sputum Gram stain and culture
- Blood cultures
- CT to exclude intra-abdominal pathology
- If diarrhea present, consider immunoassay of specimen for *Clostridium difficile* toxin
- Further tests as indicated (e.g., CT, radionuclide studies, venography, arteriography)

Treatment

- If source identified, start antibiotics; admission based on condition of patient
- If no source identified, consider admission, change all catheters and culture catheter specimens, stop all medication that might cause fever

Patients with urinary retention present with lower abdominal discomfort, urinary urgency, and inability to void. The diagnosis is confirmed by US. The bladder can be safely drained quickly with a Foley catheter, and there appears to be no foundation for the fears of hematuria, postobstructive diuresis, and hypotension. For patients with normal renal function and no anatomic obstruction, continued catheter drainage is not necessary. For patients with retention after GU procedures, a urologist should be consulted prior to instrumentation. Antibiotics can be given if the GU tract has been instrumented, if retention is prolonged, or if the patient is at risk for infection (see "Urinary Tract Infection" section above).

ACUTE RENAL FAILURE

Acute renal failure is classified according to the primary cause: prerenal, intrinsic, or postrenal. Volume depletion is the most common prerenal cause. Treatment is a fluid bolus. Intrinsic causes include acute tubular necrosis and drug nephrotoxicity. Obstructive uropathy is a common cause of postrenal failure. In patients with urinary outlet obstruction, placement of a urinary catheter is diagnostic and therapeutic. Renal US is needed to identify hydronephrosis or hydroureter.

WOUND COMPLICATIONS

Inform the operative surgeon about all postoperative wound complications.

HEMATOMAS

Wound hematomas result from unrecognized inadequate hemostasis. Patients have pain, pressure, and swelling within the wound. Patients with wound hematomas may be febrile and have sanguineous or serous wound drainage. Differentiating between hematoma and wound infection can be difficult. A few sutures should be removed to allow the hematoma to drain, and culture of wound specimens should be performed. If there is no evidence of infection and hemostasis can be maintained, the patient can be discharged. In patients who have a hematoma of the neck or who have undergone vascular surgery, extreme caution and consultation are appropriate.

SEROMAS

A seroma, a collection of serous fluid, is usually the result of inadequate control of lymphatics during dissection but can occur under

split-thickness skin grafts and in areas with large dead spaces (e.g., axilla, groin, neck, or pelvis). Patients have painless swelling below the wound or graft, and needle aspiration yields a serous fluid. Aspiration confirms the diagnosis and alleviates the problem, although aspiration may have to be repeated later.

INFECTION

Systemic factors (e.g., extremes of age, poor nutrition, or diabetes) contribute to wound infections. However, local factors (e.g., necrotic tissue, poor perfusion, foreign bodies, and hematomas) are of greatest significance. In nontraumatic, uninfected operative wounds in which the respiratory, alimentary, and GU tracts were not entered, infection rates are low. In such cases, the infecting organism is usually from the skin but can originate from remote infected sources (e.g., urinary tract infection). If there is a remote infected source, the organism is probably the same in both infections. Wounds associated with entering the respiratory, alimentary, or GU tract or wounds secondary to trauma have a higher risk of infection.

Presenting signs and symptoms of wound infections include increasing pain, erythema, swelling, drainage, and tenderness at the incision site. Wounds not involving the perineum and not associated with entry into the GI or biliary tract are most often infected with *S. aureus* or streptococci. Such wounds can be safely managed with drainage, culture of a wound sample, irrigation, loose packing with gauze, and outpatient administration of antibiotics. Wounds involving the perineum or associated with the GI or biliary tract are often infected with multiple organisms, including gram-negative bacteria and anaerobes. Parenteral broad-spectrum antibiotics are administered, and hospital admission is necessary.

NECROTIZING FASCIITIS

Necrotizing fasciitis is a feared complication. The usual cause is direct contamination of the wound with group A streptococci or *S. aureus*. However, mixed aerobic and anaerobic infections have been reported. Risk factors include diabetes mellitus, hypertension, obesity, alcoholism, immunosuppression, and peripheral vascular disease, but necrotizing fasciitis also occurs in young, otherwise healthy individuals.[5] Early clinical differentiation from cellulitis can be difficult. CT may show asymmetric fascial thickening, gas tracking along fascial planes, or focal fluid collections. MRI is sensitive but not totally specific for necrotizing fasciitis and can be a useful adjunct.[6] Hallmarks of fasciitis are the presence of marked systemic toxicity and pain out of proportion to local findings. In more advanced cases, there may be deep pain with patchy areas of surface hypesthesia, crepitation, or bullae. Treatment should include antibiotics and immediate surgical debridement. Antibiotic choice is controversial, but triple antibiotic therapy with penicillin or a cephalosporin, an aminoglycoside, and clindamycin probably should be used.[6] For further discussion, see Chapter 152, "Soft Tissue Infections."

WOUND DEHISCENCE

Wound dehiscence can be superficial or can extend into the deeper fascial planes. Dehiscence is caused by inadequate closure or intrinsic host factors, such as malnutrition, glucocorticoid use, or diabetes. Serosanguineous fluid may leak from the wound. Dehiscence of abdominal incisions has the potential for evisceration. If evisceration is not present, conservative management using abdominal binders is appropriate. However, if there is any uncertainty about the extent of dehiscence, operative exploration is indicated.

VASCULAR COMPLICATIONS

SUPERFICIAL THROMBOPHLEBITIS

Superficial thrombophlebitis of the lower extremities is most frequently secondary to stasis in varicose veins. It is usually aseptic. There is redness and warmth of the affected vein. If there is no evidence of surrounding cellulitis or lymphangitis and no evidence of deep vein involvement on US, treatment is local heat, elevation, and NSAIDs. Suppurative superficial thrombophlebitis is characterized by erythema, palpable tender cord, lymphangitis, and pain. Suppurative thrombophlebitis requires excision of the affected vein.

DEEP VENOUS THROMBOSIS

When lower extremity superficial thrombophlebitis is seen in a postoperative patient, consider the possibility of concurrent deep venous thrombosis. Deep venous thrombosis is typically characterized by leg pain or swelling, or both. For suspected deep venous thrombosis, Doppler US is the preferred diagnostic test. Patients with normal color flow Doppler study results should be treated with elevation and bed rest. Repeat color flow Doppler US studies should be performed in 3 days if symptoms persist, but sooner if symptoms worsen. For further discussion, see Chapter 56, "Venous Thromboembolism Including Pulmonary Embolism."

COMPLICATIONS OF DRUG THERAPY

Complications of drug therapy are numerous, but the most common implicated classes of drugs are anticoagulants, diabetic medications, antibiotics, and opioids.[7] Another common problem is antibiotic-associated diarrhea. Many antibiotics can cause diarrhea, but the greatest concern in postoperative patients is pseudomembranous colitis. Pseudomembranous colitis is due to the toxin produced by the bacterium *Clostridium difficile*. Pseudomembranous colitis is related to antibiotic use, which destroys the normal enteric bacterial flora, allowing an overgrowth of *C. difficile*. Even short courses of antibiotics have been associated with pseudomembranous colitis. Patients have watery and sometimes bloody diarrhea, fever, and crampy abdominal pain. There are three common ways to diagnose *C. difficile*: nucleic acid amplification tests, glutamate dehydrogenase, and enzyme immunoassay. The current recommendation for symptomatic patients is to use a nucleic acid amplification test technology like polymerase chain reaction.[8] For patients with moderate disease, discontinue the offending antibiotic and prescribe metronidazole. For severe disease, discontinue the offending antibiotic and give vancomycin.[8] For further discussion, see Chapters 71, "Acute Abdominal Pain" and 73, "Disorders Presenting Primarily With Diarrhea."

Many medicines can cause drug fever, but antibiotics are the drug class most commonly implicated. The mechanisms proposed are hypersensitivity reactions, pyogenic effect, and disturbed thermoregulation. In patients in whom no source for fever can be found, it is appropriate to consider stopping medications known to cause drug fever. Most often, the patient will require admission to rule out this diagnosis.

COMPLICATIONS OF BREAST SURGERY

Complications of breast surgery are infrequent, but patients can develop minor wound infections and hematomas. Rarely, pneumothorax has been reported. Wound hematomas frequently require operative control for proper evacuation and hemostasis.

Early complications seen with mastectomies include wound infection, necrosis of skin flaps, and the accumulation of seromas. The incidence of postmastectomy lymphedema ranges from a low of 5.5% to a high of 80%, and it is increased with the more extensive the surgery.[9]

COMPLICATIONS OF GI SURGERY

In addition to the complications already reviewed, patients who have undergone any GI surgery may have intestinal obstruction, intra-abdominal abscess, pancreatitis, cholecystitis, fistulas, and tetanus. Certain procedures, such as anastomoses, bariatric surgery, placement of gastrostomy tubes, biliary tract surgery, other laparoscopic surgery, stoma creation, colonoscopy, and rectal surgery, are associated with specific complications.

INTESTINAL OBSTRUCTION

Ileus, a functional obstruction of the bowel, is postulated to be the result of stimulation of the splanchnic nerves, leading to neuronal inhibition of coordinated intrinsic bowel wall motor activity. It is expected after any operation in which the peritoneal cavity is violated. After GI

surgery, small bowel tone usually returns to normal within 24 hours, and colonic function returns within 3 to 5 days. Ileus can also occur after non-GI procedures and is usually secondary to anesthetic agents; function returns to normal after 24 hours. Prolonged ileus can be caused by peritonitis, intra-abdominal abscess, hemoperitoneum, pneumonia, electrolyte imbalance, sepsis, and medications.

Presenting symptoms of ileus include nausea, vomiting, obstipation, constipation, abdominal distention, and abdominal pain. When these symptoms are present in the first few days after surgery, they are most often due to adynamic ileus. The symptoms of adynamic ileus are most often mild and respond to nasogastric suction, bowel rest, and IV hydration. However, in cases of prolonged ileus, look for an underlying cause. Evaluation includes abdominal radiography to identify air-fluid levels, chest radiography, CBC, measurement of electrolyte levels, and urinalysis to search for secondary causes of ileus.

Mechanical ileus of the bowel is most often secondary to adhesions, and is discussed in detail in Chapter 83, "Bowel Obstruction." In the ED, differentiating between functional ileus and mechanical bowel obstruction can be difficult. Abdominal CT scanning is helpful to identify ischemia or obstruction due to bowel strangulation.[10] Although CT is still more definitive, US has a sensitivity of approximately 85% and does not involve exposing the patient to radiation.[11] The results of CT may have an impact on the decision to manage the obstruction expectantly or not. Once the diagnosis of mechanical obstruction is suspected or confirmed, surgical consultation is indicated.

INTRA-ABDOMINAL ABSCESS

Intra-abdominal abscess is caused most frequently by preoperative contamination, spillage of bowel contents during surgery, contamination of a hematoma, or postoperative anastomotic leaks. Patients may have abdominal pain, nausea, vomiting, ileus, abdominal distention, fever, chills, anorexia, and abdominal tenderness. If the diagnosis is suspected, obtain CT or US of the abdomen. The patient should receive broad-spectrum antibiotics (see Chapter 71, "Acute Abdominal Pain"). Treatment is percutaneous drainage or surgical exploration.

PANCREATITIS

Pancreatitis after abdominal surgery is secondary to direct manipulation or retraction of the pancreatic duct. Pancreatitis most commonly occurs after gastric resection, biliary tract surgery, and endoscopic retrograde cholangiopancreatography. Clinical presentation varies from mild nausea, vomiting, and abdominal discomfort to intractable vomiting, leukocytosis, and left-sided pleural effusion. Severe hemorrhage can cause lumbar pain accompanied by blue-gray discoloration of the skin in the flank area (Turner sign) or similar changes around the umbilicus (Cullen sign). Although the serum amylase level rises in acute pancreatitis, it is also elevated in patients with severe cholecystitis, renal insufficiency, intestinal obstruction, perforated ulcer, or ischemic bowel. A serum lipase measurement may help to identify those with true pancreatitis, although it may be elevated in a patient with a perforated viscus and other conditions. Abdominal radiographs may show localized ileus in the region of the pancreas (sentinel loop). US and CT are useful in defining pancreatic fluid collections or abscesses. In general, the treatment of postoperative pancreatitis is similar to the treatment of nonoperative pancreatitis (see Chapter 79, "Pancreatitis and Cholecystitis").

CHOLECYSTITIS

Postoperative complications related to the gallbladder include biliary colic, acute calculous cholecystitis, or acute acalculous cholecystitis. The cause of these disorders in the postoperative period is not clear. US studies of the gallbladder and pancreas should be performed to aid in the diagnosis.

Acalculous cholecystitis is of particular concern in the postoperative period. The disorder seems to be more common in elderly men, but can occur in any sex and age group. There is no single test with adequate diagnostic accuracy to either diagnose or exclude the possibility of acalculous cholecysticis.[12] Clinicians must use a combination of high diagnostic suspicion, a good history and physical, as well as appropriate diagnositic testing. Signs and symptoms are similar to those for calculous cholecystitis. Results of liver function studies and the neutrophil count may be normal. Important findings on US include gallbladder enlargement, wall thickening, and pericholecystic fluid collection, but no gallstones. Hepatobiliary scintigraphy may be helpful. Early diagnosis is critical because early operative intervention can reduce morbidity and mortality.

FISTULAS

Enterocutaneous fistulas can occur almost anywhere in the GI tract and are usually the result of technical complications or direct bowel injury. High-output fistulas can result in electrolyte abnormalities and volume depletion. Fistulas involving the proximal GI tract are frequently high output and are of the greatest concern. Sepsis is the other major complication. Most patients require admission, although many fistulas ultimately close spontaneously.

TETANUS

Although most cases of tetanus in the United States occur after minor trauma, there have been numerous reports of tetanus after general surgical procedures.[13] *Clostridium tetani* is found in the GI tract of 1% of the population. During GI surgery, there is spillage of *C. tetani*. Proliferation of the organism is facilitated by the presence of devitalized tissue, blood clots, and surgical suture. Incubation can take from 0 to 73 days, at which time the toxin leads to clinical tetanus. The classic symptoms of tetanus, trismus, and opisthotonos may not be evident initially. Patients may present with nonspecific symptoms of abdominal discomfort, fever, and abdominal wall rigidity. Diagnosis is based on physical examination and a history of inadequate immunization.

ANASTOMOTIC LEAKS

Anastomotic leaks occur most frequently after esophageal and colonic surgeries and least frequently after gastric and small intestinal anastomoses. The cause of anastomotic leakage is related mainly to surgical technique.

Intrathoracic esophageal anastomotic leaks usually manifest within 10 days of surgery. The presentation is dramatic, with fever, chest pain, tachypnea, tachycardia, and possibly shock. Chest radiograph may reveal a pneumothorax with pleural effusion. Disruption can be confirmed by contrast esophagography using a water-soluble contrast agent. Even with immediate reoperation, morbidity and mortality rates are high.

The signs and symptoms of gastric anastomotic leaks include abdominal pain, fever, leukocytosis, gastric outlet obstruction, hyperamylasemia, hyperbilirubinemia, peritonitis, and shock. Plain radiographs may reveal pneumoperitoneum or air-fluid levels. Provide volume resuscitation, parenteral broad-spectrum antibiotics, and nasogastric tube drainage. Immediate surgery is required.

Small intestinal anastomoses infrequently leak because of the excellent blood supply and rapid healing of the area. However, if a leak occurs, the patient usually presents with local abscess formation or peritonitis. Treatment is immediate reoperation.

Colorectal anastomoses are prone to disruption because of the large number of pathogenic bacteria found, the propensity for colonic distention, and the presence of only a single thin layer of circular muscle to support sutures. Patients usually present 7 to 14 days postoperatively with fever and abdominal pain. CT confirms the diagnosis. Patients should receive broad-spectrum parenteral antibiotics, nasogastric tube drainage, and adequate fluid resuscitation in preparation for surgery.

BARIATRIC SURGERY COMPLICATIONS

Four main bariatric procedures are currently being performed for morbid obesity: laparoscopic adjustable gastric banding using the LAP-BAND® device (Allergan, Inc., Irvine, CA), sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion with duodenal switch. Overall operative mortality is <2%, but postoperative complications are common and are likely related to the technical skill of the surgeon.[14] Common complications are listed in **Table 87-4**.[15,16]

Nausea, vomiting, and abdominal pain are common symptoms in ED patients with a history of bariatric surgery. In the first few postoperative

TABLE 87-4 Complications of Gastric Bypass Procedures

Complication	Presentation	Signs and Symptoms	Diagnostic Test
Anastomotic leak	0–28 d	Tachycardia, fever, abdominal pain, nausea, vomiting, hypotension	Clinical suspicion. CT scan or upper GI study is useful, but may be negative
Intra-abdominal bleeding	0–28 d	Tachycardia, abdominal pain, hypotension	CT scan or upper GI study
Intraluminal GI bleeding	Hours to months	Melena, hematemesis, hypotension, altered mental status	Emergent endoscopy
Ventral hernia	Anytime	Pain at incision site or palpable hernia	Clinical diagnosis
Bowel obstruction	1 wk to 8 mo	Nausea, vomiting, abdominal pain	Plain radiography or CT looking for air-fluid levels
Stomal stenosis	2 mo to 1 y	Postprandial abdominal pain, nausea, vomiting	Endoscopy or upper GI study
Stomal ulcer	Months to years	Abdominal pain, upper GI bleed	Endoscopy
Stomal obstruction	Months to years	Nausea and vomiting with solids and liquids	Endoscopy
Cholelithiasis/cholecystitis	Months to years	Abdominal pain with fatty foods, fever, tachycardia	US
Dumping syndrome	Anytime	Diarrhea, abdominal cramps, nausea, vomiting, tachycardia, palpitations, flushing, dizziness, syncope	Clinical diagnosis or endoscopy
Vitamin deficiencies	Months to years	Weakness, bone loss, anemia, fractures, neuropathy, hypercalcemia	CBC, iron studies, parathyroid hormone studies, vitamin levels
Gastric slippage	Days to years	Abdominal pain, dysphagia, food intolerance, reflux	Upper GI study
Esophageal, gastric pouch dilation	After band adjustment	Epigastric abdominal pain, dysphagia, reflux	Upper GI study
Gastric necrosis	Anytime	Abdominal pain	Upper GI study

weeks, consider life-threatening problems such as anastomotic leak and intra-abdominal bleeding. In patients with abdominal pain, tachycardia, or abdominal tenderness in the early postoperative period, a CT scan is often required to rule out these diagnoses.

A common complication of the Roux-en-Y gastric bypass is dumping syndrome, which can occur either right after the meal (early) or 2 to 4 hours later (late). Dumping symptoms occur when the pylorus is bypassed or removed. The hyperosmolar chyme contents of the stomach are dumped into the jejunum, causing rapid influx of extracellular fluid and an autonomic response. Patients experience nausea, epigastric discomfort, palpitations, colicky abdominal pain, diaphoresis, and, in some cases, dizziness and syncope. Patients with early dumping symptoms experience diarrhea, whereas those with late dumping symptoms, 2 to 4 hours postprandially, usually do not. The late dumping syndrome is believed to be due to a reactive hypoglycemia. The mainstay of treatment is dietary modification; consumption of small, dry meals; and separation of solids from liquids. In refractory cases, pyloroplasty can be tried. Most patients with dumping syndrome do not require hospital admission.

Patients with gastroesophageal reflux disease present with burning epigastric pain that is aggravated by meals and unrelieved by vomiting. The syndrome is caused by reflux of bile into the stomach. Diagnosis is made clinically, but other potential diagnoses are often ruled out with endoscopic examination.

Wernicke's encephalopathy is a rare, but serious, complication that must be considered in a patient with a history of bariatric surgery who presents with any cerebellar signs, ophthalmoplegia, weakness, and/or memory disturbances. Although vitamin deficiencies are common with both Roux-en-Y gastric bypass and biliopancreatic diversion, vitamin B_{12} deficiency is the only one that requires emergent intervention.

NONBARIATRIC GASTRIC SURGERY

Patients who have undergone partial or complete gastrectomy for nonbariatric reasons can present with a few distinct syndromes: dumping syndrome, alkaline reflux gastritis, afferent loop syndrome, and postvagotomy diarrhea. Although these complications are rare, the symptoms can be disabling. Dumping syndrome as a result of nonbariatric gastric surgery is treated in the same way as dumping syndrome after bariatric procedures.

Patients with afferent loop syndrome also develop severe epigastric pain 1 to 2 hours after eating, which is relieved by vomiting. The vomitus is bilious, without food. The syndrome occurs in patients who have undergone gastroenterostomy (Billroth II) reconstruction after partial gastrectomy. Diagnosis is made by contrast radiography or endoscopy. Operative reconstruction is required.

Truncal vagotomy usually results in increased bowel movements, but occasionally results in diarrhea. Diarrhea is variable in occurrence and not associated with food intake. It is often unpredictable and explosive, which can lead to weight loss, malnutrition, and severe social complications. The incidence of the diarrhea decreases with time, and treatment is mostly symptomatic.

LAPAROSCOPIC SURGERY

BILIARY TRACT SURGERY

More than 90% of all cholecystectomies are now performed laparoscopically. Complications can occur after open and laparoscopic cholecystectomies (**Table 87-5**); complications can also be related to the laparoscopic technique (**Table 87-6**).[17]

The evaluation of abdominal pain after cholecystectomy depends on the clinical condition of the patient. If there are signs of peritoneal irritation or fever, an injury to the biliary system is likely. Obtain an abdominal CT in addition to a CBC, electrolyte measurements, liver function tests, and serum lipase level. A collection of bile can be seen on CT, but endoscopic retrograde cholangiopancreatography is required to identify the specific site of the injury. Depending on the endoscopic

TABLE 87-5 Complications of Cholecystectomy

- Bile leak
- Bile duct stricture
- Bleeding
- Bowel injury
- Intra-abdominal abscess
- Acute myocardial infarction
- Pancreatitis
- Peritonitis
- Pulmonary complications
- Retained common duct stones or stones spilled into peritoneum
- Splenic injury
- Umbilical hernia
- Wound infection

TABLE 87-6 Complications of Laparoscopy

Related to pneumoperitoneum
• Cardiac arrhythmias during the procedure
• Subcutaneous emphysema
• Pneumothorax
• Pneumomediastinum
• Carbon dioxide embolization
Related to insertion of needle and trocar
• Bleeding from trocar site
• GI tract injuries
• Laceration
• Intestinal burns
• GU tract injuries
• Major vessel injuries
• Hernia from trocar site
• Wound infection
Miscellaneous
• Retained intra-abdominal gallstones
• Biliary cutaneous fistula
• Chronic pain
• Infertility
• Cholelithiasis
• Metastases to the trocar site

retrograde cholangiopancreatography results, reoperation may be necessary. Small collections of bile may require only observation or percutaneous drainage.

Patients presenting soon after cholecystectomy with pain, pancreatitis, and/or jaundice may have retained common duct stones. If US does not demonstrate a dilated common bile duct or if CT does not reveal an intra-abdominal collection of fluid, an endoscopic retrograde cholangiopancreatography should be performed. Endoscopic sphincterotomy is usually an effective means of dealing with retained stones. Patients presenting late after cholecystectomy with fever, pain, and jaundice may have bile duct stricture. Diagnosis requires endoscopic retrograde cholangiopancreatography. Insertion of stents is usually tried first, but surgical repair may be necessary. A more recent concern has been the spillage of gallstones into the peritoneal cavity at the time of surgery. Initially, such stones were thought to be innocuous. However, they have been linked to abdominal pain, pelvic pain, dysmenorrhea, intra-abdominal abscess, colocutaneous fistula, and implantation into the ovary with subsequent infertility.

OTHER LAPAROSCOPIC SURGERIES

Laparoscopic techniques are used for cholecystectomy, appendectomy, colon resection, antireflux surgery, herniorrhaphy, fundoplication, and most gynecologic and urologic surgical procedures. As with any laparoscopic procedure, there are risks related to the pneumoperitoneum and insertion of the trocar (Table 87-6). In addition to the potential for bowel injury, major vessel injury, and splenic injury, gynecologic and urologic procedures carry a risk of injury to the urinary bladder and ureters.

STOMAS

The two most commonly placed stomas are the ileostomy and the colostomy. Problems with stomas can be quite debilitating. Most acute complications are related to technical errors of stoma placement. Other complications include the development of Crohn's disease or carcinoma at the stomal site, stomal ischemia and necrosis, peristomal skin irritation, peristomal hernia, and stomal prolapse.

Ischemia and stomal necrosis are manifested very early in the postoperative course. The cause is inadequate blood supply to the stoma. Normally, the stoma is pink, without evidence of cyanosis. Any evidence of compromised blood flow requires surgical evaluation.

Peristomal maceration and skin destruction are most likely secondary to a poor seal of the stomal appliance. Consult an enterostomal therapist for a properly fitting appliance.

Stomal prolapse can occur with ileostomies and colostomies. The cause is usually inadequate fixation of the intra-abdominal portion or too large an abdominal wall opening. Patients present with stoma protrusion, with or without pain. Examine the stoma for viability. It should be pink and painless. If the tissue is viable, attempt reduction and follow with surgical consultation. Definitive therapy requires surgical revision.

Parastomal hernias can develop if the abdominal wall opening is too large. Determine if the hernia is incarcerated, attempt reduction, and consult a surgeon. Definitive therapy requires local reconstruction of the orifice.

COLONOSCOPY

Potential complications of colonoscopy include hemorrhage, perforation, retroperitoneal abscess, pneumoscrotum, pneumothorax, volvulus, postcolonoscopy distention, splenic rupture, appendicitis, bacteremia, and infection.[18] Hemorrhage is the most common complication and can be secondary to polypectomy procedures, biopsies, laceration of the mucosa by the instrument, or tearing of the mesentery or spleen. If the bleeding is intraluminal, the patient will develop rectal bleeding. Patients with mesenteric or splenic injury have signs of intra-abdominal bleeding. Treatment of intraluminal bleeding depends on the magnitude of hemorrhage. Intra-abdominal bleeding requires emergency laparotomy. Colon perforation with pneumoperitoneum usually is evident immediately, but can take several hours to manifest.[19] Perforation is usually secondary to intrinsic disease of the colon (e.g., diverticulitis) or to vigorous manipulation during the procedure. Most patients require immediate laparotomy, but in some patients presenting late (1 to 2 days later) without signs of peritonitis, hospital observation may be appropriate.

RECTAL SURGERY

Patients who have undergone hemorrhoidectomy frequently have problems with postoperative urinary retention, the management of which has been discussed previously in the section "Urinary Retention." Three other problems that can occur are constipation, rectal hemorrhage, and rectal prolapse.

The management of constipation in a patient who has undergone rectal surgery is no different from management in any other patient. Perform gentle rectal examination to identify fecal impaction, and if present, remove the impaction. Otherwise, enemas can be used. Posthemorrhoidectomy rectal hemorrhage can occur immediately postoperatively but may be delayed up to weeks after the surgery. Causes of delayed bleeding include sepsis of the pedicle, disruption of a clot, and sloughing of tissue. Bleeding can be scant or massive. Temporary balloon tamponade using a Foley catheter may temporize until surgical ligation of the involved vessel is performed.

Mucosal prolapse occurs when the surgeon has not removed all redundant mucosa during hemorrhoidectomy and is much more common than rectal prolapse. Local treatment by a surgeon is usually corrective. *Rectal prolapse* can occur after any anorectal surgical procedure and likely is related to injury of the puborectalis muscle. The diagnosis is obvious on examination. The treatment is reduction (see Chapter 85, "Anorectal Disorders") and surgical consultation.

Infection after anorectal surgery is surprisingly uncommon. The patient usually complains of increasing pain and fever. Examination of the area is necessary to detect an abscess or cellulitis. Fournier's gangrene may follow anorectal surgery. If this is suspected, give broad-spectrum parenteral antibiotics immediately. The patient must undergo immediate surgical debridement.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 10

Renal and Genitourinary Disorders

CHAPTER 88

Acute Kidney Injury

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INTRODUCTION AND EPIDEMIOLOGY

Acute kidney injury (AKI) is the deterioration of renal function over hours or days, resulting in the accumulation of toxic wastes and the loss of internal homeostasis. Definitions based on renal function are listed in **Table 88-1**[1-4]; AKI is classified using the Risk, Injury, Failure, Loss, and End-Stage Renal Failure (RIFLE),[2] the Acute Kidney Injury Network (AKIN),[3] and the Kidney Disease: Improving Global Outcomes (KDIGO)[4] classifications. These definitions assume that renal function has reached a steady state, which limits their applicability to ED patients with AKI whose renal function may be deteriorating.

Reversible mechanisms, such as volume depletion, medications, infection, or urinary obstruction,[5-9] cause the majority of **community-acquired AKI** cases presenting to the ED (55% to 79%).[5,6,10-12] Despite favorable renal recovery rates, community-acquired AKI is associated with significant hospital mortality, from 7.3% to 19.6%,[13,14] and 3-year mortality is as high as 45% to 66%.[7,14,15] **Hospital-acquired AKI** by definition occurs or worsens in the hospital, where mortality ranges from 27% to 62%.[6,10,12] For both types of AKI, mortality has a graded relationship with advancing age and severity of AKI.[8,16]

PATHOPHYSIOLOGY

The functions of the kidneys are glomerular filtration, tubular reabsorption, and secretion. Normal glomerular filtration rate (GFR) in early adulthood is approximately 120 mL/min/1.73 m^2 and typically decreases by 8 mL/min/1.73 m^2 every decade thereafter. The driving force for glomerular filtration is glomerular capillary pressure, which depends on renal blood flow and autoregulation. For most causes of AKI, global or regional decrease in renal blood flow is the final common pathway. Recovery from AKI first depends on restoration of renal blood flow.

Renal insult is classified as **prerenal** (decreased perfusion of a normal kidney), **intrinsic** (pathologic change within the kidney itself), or **postrenal** (also called postobstructive, due to obstruction of urine outflow).

In **prerenal AKI**, tubular and glomerular functions are initially maintained. Timely restoration of circulating blood volume or discontinuation of an implicated medication restores function in most cases. **Postrenal AKI** causes increased tubular pressure, which decreases the driving force for filtration. This pressure gradient soon equalizes; thereafter, the maintenance of the depressed GFR depends on vasoconstrictors. Rapid relief of urinary obstruction in **postrenal AKI** results in a prompt decrease of vasoconstriction and a return to normal renal function.

Diseases of the glomerulus, small vessels, interstitium, and tubule cause **intrinsic AKI;** all are associated with the release of renal vasoconstrictors. The most common cause of intrinsic AKI is **ischemic injury** or **ischemic tubular necrosis** (also historically called **acute tubular necrosis**), when renal perfusion is decreased so much that the kidney parenchyma is affected.

During the period of depressed renal blood flow, the kidneys are especially vulnerable to further insults. Exposure at this time to known nephrotoxins such as NSAIDs or aminoglycosides can cause iatrogenic AKI. **Figure 88-1** illustrates the cellular and subcellular events leading to ischemic tubular necrosis.

In intrinsic AKI, clearance of tubular toxins and initiation of therapy for glomerular diseases decrease vasoconstriction and help restore renal blood flow. Once the cause of injury is resolved, the remaining functional nephrons increase filtration and eventually hypertrophy. Depending on the size of the remnant nephron pool, GFR will proportionately recover. If the number of remaining nephrons is below some critical number, continued hyperfiltration results in progressive glomerular sclerosis, eventually leading to nephron loss. A vicious cycle of nephron loss then ensues until complete AKI occurs. This sequence explains the commonly observed scenario in which progressive AKI occurs after initial recovery from AKI, contributing to delayed mortality.

CLINICAL FEATURES

HISTORY AND COMORBIDITIES

AKI itself has few symptoms until severe uremia develops. Uremia causes nausea, vomiting, drowsiness, fatigue, confusion, and if untreated, coma. Patients are more likely to present with symptoms related to the underlying cause of AKI, which should prompt assessment of renal function. See **Table 88-2** for risk factors for community-acquired AKI.[6-10,12,16-19]

Patients with **prerenal AKI** from volume depletion commonly develop thirst, orthostatic lightheadedness, and decreased urine output. Excessive vomiting, diarrhea, urination, hemorrhage, fever, or sweating can reduce circulating volume sufficiently to precipitate AKI. Causes of endothelial leak and third spacing, such as sepsis, pancreatitis, burns, and hepatic failure, can also result in prerenal AKI, although these settings may also be associated with renal parenchymal injury. Progression of heart failure from any cause or overdiuresis of the patient with compensated congestive heart failure may cause AKI. Decreased fluid intake from physical or cognitive disability can result in hypovolemia.

Intrinsic renal diseases can often be anticipated because of symptoms of the precipitating cause. Anticipate **ischemic AKI** after cardiac arrest, in severe sepsis, or with other causes of systemic hypotension. AKI from **crystal-induced nephropathy, nephrolithiasis, and papillary necrosis** can present as flank pain and hematuria. Suspect pigment-induced AKI in **rhabdomyolysis**[20] (see Chapter 89, "Rhabdomyolysis") or with hemolysis after recent blood transfusion. Darkening urine and edema, with or without constitutional symptoms such as fever, malaise, and rash, suggest **acute glomerulonephritis**, which may have been preceded by pharyngitis or cutaneous infection. Fever, arthralgia, and rash are common with **acute interstitial nephritis**. **Acute renal arterial occlusion** is usually marked by severe flank pain. Cough, dyspnea, and hemoptysis raise the possibility of **Goodpasture's syndrome** or **Wegener's granulomatosis**.

Suspect postrenal AKI in men with prostatic disease or advanced age and patients with indwelling bladder catheters. Anuria strongly suggests obstruction, although vascular obstruction and fulminant renal disease are also possible. Alternating oliguria and polyuria is virtually pathognomonic of obstruction.

PHYSICAL EXAMINATION

Assess for abnormal volume status. Evaluate mucous membranes, jugular vein distention, lung auscultation, peripheral edema, and tissue turgor to identify dehydration. Carefully assess for rashes, evidence of

TABLE 88-1 AKIN and RIFLE Criteria for Acute Kidney Injury

AKIN Stage	RIFLE Category	Change in Creatinine/GFR Criteria	Urine Output Criteria
Stage 1	Risk	Serum Cr increased 1.5 times* *or* (AKIN only) Cr increase >0.3 milligram/dL (≥26.5 µmol/L) over <48 h* *or* GFR decrease 25%–50%*	0.5 mL/kg/h for 6 h
Stage 2	Injury	Serum Cr increased 2.0–3.0 times* *or* GFR decrease 50%–75%*	0.5 mL/kg/h for 12 h
Stage 3	Failure	Serum Cr increased >3.0 times* *or* Cr >4 milligrams/dL (≥354 µmol/L) and acute increase >0.5 milligram/dL (44 µmol/L)* *or* GFR decrease >75%*	0.3 mL/kg/h for 24 h *or* Anuria for 12 h
N/A	Loss	Complete loss of kidney function for >4 weeks	
	End-stage renal disease	Need for renal replacement therapy for >3 months	

Abbreviations: AKIN = Acute Kidney Injury Network; Cr = creatinine; GFR = glomerular filtration rate; N/A = not applicable; RIFLE = Risk, Injury, Failure, Loss, End Stage.

*All changes are relative to the patient's premorbid baseline.

vasculitis, jaundice, abdominal or pelvic masses, or a distended palpable urinary bladder. On cardiac exam, check for atrial fibrillation, abdominal aortic aneurysm, and signs of heart failure, and assess extremity pulses. Suspect fluid overload in patients with rapid weight gain, peripheral or facial edema, pulmonary rales, or dullness to percussion of the chest wall over the lower portions of the lungs (suggesting plural effusion).

DIAGNOSIS

In the ED, the goals are to identify patients at risk for AKI, correct metabolic effects, decrease ongoing renal injury, and prevent iatrogenic injury. **Determine if kidney injury is prerenal, postrenal, or intrinsic through history, physical, and diagnostic testing.** Obtain CBC, electrolyte levels including magnesium and phosphorus, and hepatic function tests and blood cultures as clinically appropriate. Obtain urinalysis, urine osmolality, urine sodium and urea levels, and urine culture if infection is suspected. Indicators of hypovolemia include base deficit, increased lactate level, decreased central venous pressure, or an US showing collapse of the inferior vena cava (see "Imaging" section). If acute decompensated heart failure is suspected as a contributing factor to worsening renal function (see "Cardiorenal Syndrome" section), obtain a B-type natriuretic peptide level or pro–B-type natriuretic peptide level.

ECG is the fastest screening test for **hyperkalemia**, but sensitivity for a level over 6.5 mmol/L ranges from 14% to 60%.[21] Peaked T waves are only seen in 34% of patients[22] (see Chapter 17, "Fluids and Electrolytes"). Chest radiography helps evaluate for increased volume, effusions, and pneumonia, all of which can result from or precipitate AKI.

Obtain bedside US to assess urinary bladder volume. A large postvoid bladder residual volume (>125 mL) suggests bladder outlet obstruction, for which you would place a urethral catheter. See Chapter 92, "Acute Urinary Retention," for further discussion. Anuria is defined as <100 mL of urine per day and can be present with prerenal, postrenal, or intrinsic AKI.

PRERENAL ACUTE KIDNEY INJURY

The causes of prerenal azotemia can be broken down into volume loss, hypotension, and diseases of the large and small renal arteries (**Table 88-3**). Prerenal AKI is also a common precursor to ischemic and nephrotoxic conditions, leading to intrinsic AKI.

POSTRENAL ACUTE KIDNEY INJURY

In the elderly population, the rate of postrenal AKI is as high as 22%. The most common cause is prostatic hypertrophy. Consider this diagnosis in elderly patients of both sexes; patients with indwelling urinary catheters, GU surgery, known or suspected abdominal malignancy, nephrolithiasis, or retroperitoneal disease; or patients on medications known to affect the urinary sphincter. See Chapter 92, "Acute Urinary Retention," for a detailed list of causes.

INTRINSIC ACUTE KIDNEY INJURY

Intrinsic kidney injury is not common in patients with community-acquired disease, but it is the most common cause in hospitalized patients. Intrinsic AKI can result from injury to the glomerulus, tubule, interstitium, or vasculature. In community-acquired intrinsic AKI, drugs (**Table 88-4**), infection, and vascular events are common precipitants. Hospital AKI is due to toxic and ischemic insults in most cases.[16,17]

Contrast-Induced Nephropathy Contrast-induced nephropathy is defined by a relatively small change in serum creatinine (25% increase from baseline or an absolute increase of 0.5 milligram/dL [44 µmol/L] 48 to 72 hours after infusion). The studies documenting contrast-induced nephropathy incidence, risks, and outcomes suffer biases common to many observational studies: confounding bias and selection bias. Confounding bias occurs when an exposure is inappropriately causally linked to an outcome, when a separate exposure (the confounding variable) other than the one of interest better explains the observed outcome. To account for this potential selection bias, multiple studies have compared the incidence of AKI between contrast-exposed and unexposed patients using propensity scoring matching to balance baseline outcome risks between groups.[23] These studies failed to find a statistically higher incidence of AKI in the contrast-exposed group compared to the unexposed group of hospitalized patients with similar comorbidities.[24-29] These studies also found no differences in mortality, development of chronic kidney disease, or need for dialysis or renal transplantation in the future between contrast-exposed patients and unexposed patients.[24-29] Prevention of worsening renal function due to contrast exposure continues to serve as an indication for hydration prior to contrast-enhanced imaging for patients with preexisting chronic kidney disease[30-32] (see "Preventing Renal Injury" section).

Crystal-Induced Nephropathy Crystal-induced nephropathy is the precipitation of crystals within the renal tubules, resulting in mechanical and inflammatory injuries of the tubular epithelium. Chronic renal insufficiency and hypovolemia predispose patients to this form of renal injury, and urinary pH affects the formation of many of these crystals. Elevated uric acid levels in the setting of **tumor lysis syndrome** and some medications—in particular, acyclovir, sulfonamides, indinavir, and triamterene—are the most common causes of crystal-induced acute kidney injury.

Angiotensin-Converting Enzyme Inhibitors Angiotensin-converting enzyme inhibitors can simultaneously decrease the GFR and increase renal blood flow, resulting in a 10% to 20% increase in serum creatinine. Because they inhibit angiotensin II, they cause a preferential efferent arteriolar vasodilation in the renal glomerulus. These arteriolar changes may precipitate significant AKI in a patient with undiagnosed **bilateral renal artery stenosis**, a condition that typically requires angioplasty and stenting or bypass surgery. Volume depletion and concomitant use of vasoconstricting medications are other common precipitators of angiotensin-converting enzyme inhibitor–induced AKI. Angiotensin receptor blockers have similar effects. Hyperkalemia, which is usually mild, is a relatively common complication of angiotensin-converting enzyme inhibitor administration.

NSAIDs NSAIDs may cause AKI because they decrease both GFR and renal blood flow (prerenal AKI). With chronic use, they may cause interstitial nephritis (intrinsic AKI). Risk factors for adverse reactions to these medications are older age, chronic renal insufficiency, congestive

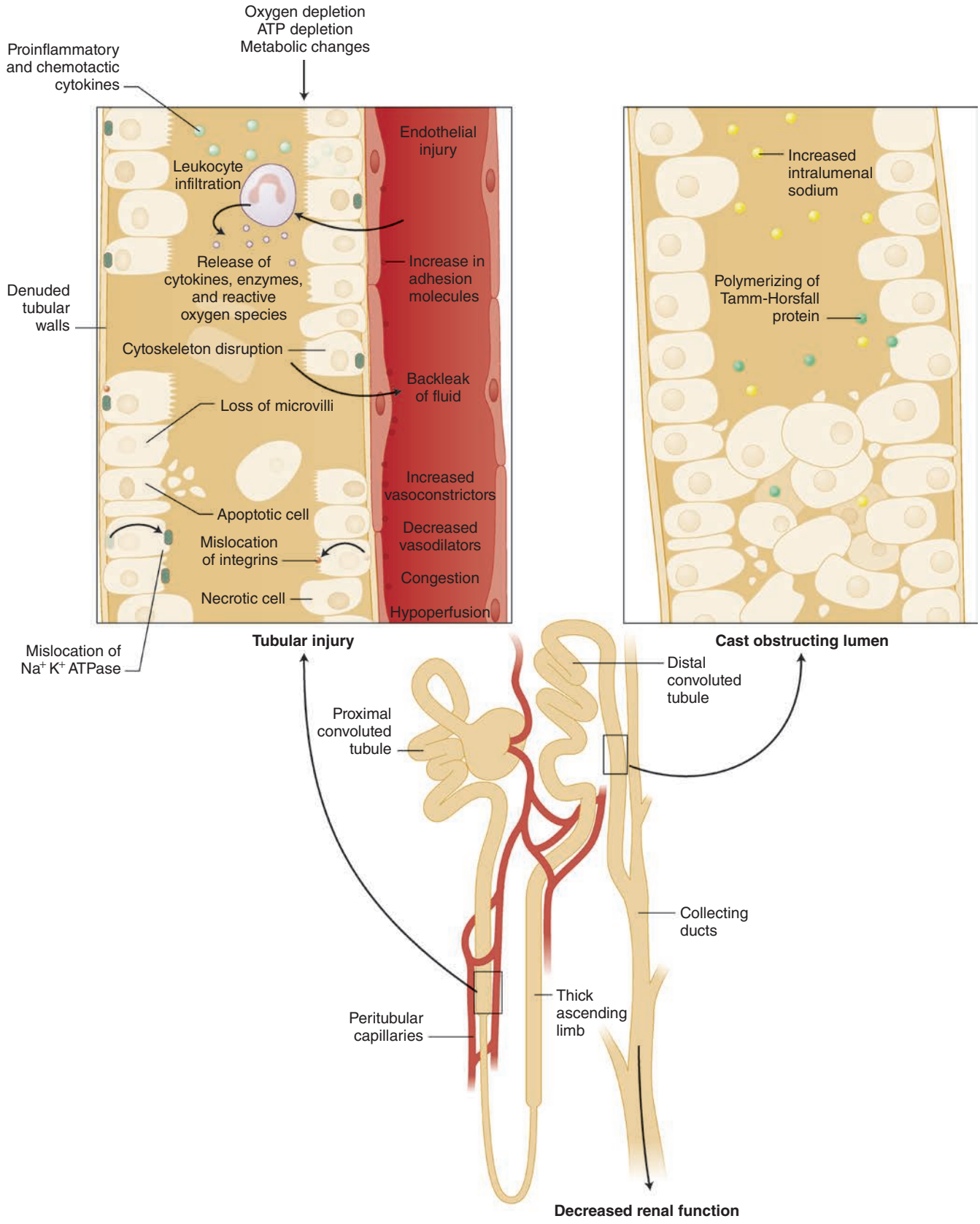


FIGURE 88-1. Ischemic tubular necrosis. Tubular injury is a direct consequence of vasoconstriction, inflammation, endothelial changes, disruption of cell–cell and cell–matrix connections, and apoptotic changes. ATP = adenosine triphosphate.

TABLE 88-2 Risk Factors for Acute Kidney Injury

Dehydration*

Sepsis*

Advanced age*

Medications

- Diuretics*
- NSAIDs*
- ACE inhibitors*
- Angiotensin receptor blockers*
- Antiretroviral therapy
- Acyclovir, valacyclovir
- Statins
  - Rhabdomyolysis
- Trimethoprim/sulfamethoxazole
- Aminoglycosides, vancomycin

Immunosuppressive drugs, kidney transplantation

- Tacrolimus
- Cyclosporine, others

Failure to dose medications for CKD

- Antibiotics, metformin, proton pump inhibitors

Drugs of abuse

- Cocaine, ethanol, ethylene glycol

Systemic disease

- CKD (preexisting)*
- Cardiovascular disease*
  - CAD, heart failure, hypertension, vascular disease
- Diabetes
- Hepatic disease
- Autoimmune/rheumatologic disease
- Gout, elevated uric acid
- Outflow obstruction: prostatic/urethral disease
- Malignancy
  - Renal parenchymal invasion, bladder obstruction
  - Multiple myeloma/hypercalcemia
- Eclampsia and preeclampsia

Contrast agents

- Iodinated contrast media
- Gadolinium
  - Nephrogenic systemic fibrosis

Abbreviations: ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CKD = chronic kidney disease.

*Most common risks for community-acquired disease.

heart failure, diabetes, volume depletion, and concomitant use of diuretics or angiotensin-converting enzyme inhibitors.

Antibiotics Antibiotics, particularly aminoglycosides, are another important cause of iatrogenic renal injury. Other antibiotics frequently implicated are vancomycin, ceftriaxone, sulfamethoxazole/trimethoprim, amoxicillin, cefazolin, and fluoroquinolones.[9,33-35] The most common antiviral medications implicated in AKI are the antiretrovirals, acyclovir, and valacyclovir.

Pigment Nephropathy Hemoglobin and myoglobin from hemolysis or rhabdomyolysis are deposited and concentrated in the renal tubules. Renal injury occurs through tubular obstruction and direct toxicity (pigment nephropathy).

Glomerulonephritis Glomerulonephritis is an uncommon cause of acute kidney injury. Glomerulonephritis may present as a nephrotic syndrome with edema, proteinuria, hypoalbuminemia, and hyperlipidemia, or a nephritis syndrome with hematuria, red blood cell casts, decreased urine output, and hypertension. Glomerulonephritis may be postinfectious, be associated with toxic exposure, or occur in association with an immune disorder, such as systemic lupus erythematosus.

TABLE 88-3 Causes of Prerenal Acute Kidney Injury

Hypovolemia

- GI: decreased intake, vomiting, diarrhea
- Pharmacologic: diuretics
- Third spacing
- Skin losses: fever, burns
- Miscellaneous: hypoaldosteronism, salt-losing nephropathy, postobstructive diuresis

Hypotension (overt and relative)

- Septic vasodilation
- Hemorrhage
- Decreased cardiac output: ischemia/infarction, valvulopathy, cardiomyopathy, tamponade
- Pharmacologic: β-blockers, calcium channel blockers, other antihypertensive medications
- High-output failure: thyrotoxicosis, thiamine deficiency, Paget's disease, arteriovenous fistula

Renal artery and small-vessel effects

- Pharmacologic: NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, cyclosporine, tacrolimus (microvasculature effects that decrease renal blood flow; may lead to intrinsic AKI)
- Hypercalcemia: vasoconstriction, may lead to intrinsic AKI
- Embolism: thrombotic, septic, cholesterol*
- Thrombosis: atherosclerosis, vasculitis, sickle cell disease*
- Dissection*
- Microvascular thrombosis: preeclampsia, hemolytic-uremic syndrome, disseminated intravascular coagulation, vasculitis, sickle cell disease*

Abbreviation: AKI = acute kidney injury.

*These causes include a component of ischemic AKI.

DIAGNOSTIC TESTING

Creatinine and GFR Creatinine is the mainstay for measuring renal function; it is a breakdown product of the skeletal muscle protein creatine, and its level is thus linked to muscle mass. **In patients with no renal function (GFR = 0), serum creatinine level increases 1 to 3 milligrams/dL (88 to 265 µmol) a day.** Lesser increases in creatinine indicate residual renal function, whereas faster increases suggest rhabdomyolysis. Elevation of serum creatinine may take 48 hours after onset of decreased function, and a patient with a very low baseline creatinine

TABLE 88-4 Intrinsic Acute Kidney Injury Due to Drugs

Reduced renal perfusion by altered intrarenal hemodynamics	Amphotericin B, ACE inhibitors, cyclosporine, interleukin-2, NSAIDs, radiocontrast agents, tacrolimus
Direct tubular toxicity	Aminoglycoside antibiotics, amphotericin B, cisplatin, cyclosporine, foscarnet, heavy metals, IV immunoglobulin methotrexate, organic solvents, pentamidine, radiocontrast agents, tacrolimus
Rhabdomyolysis	Cocaine, ethanol, lovastatin
Intratubular obstruction	Acyclovir, chemotherapeutic agents, ethylene glycol, methotrexate, sulfonamides
Interstitial nephritis	Allopurinol, cephalosporins, cimetidine, ciprofloxacin, furosemide, NSAIDs, phenytoin, penicillins, sulfonamides, rifampin, thiazide diuretics
Hemolytic-uremic syndrome	Cocaine, cyclosporine, conjugated estrogens, mitomycin, quinine, tacrolimus

Abbreviation: ACE = angiotensin-converting enzyme.

TABLE 88-5 Stages of Chronic Kidney Disease

Stage	GFR	Comments
Stage 1	GFR ≥90 mL/min/1.73 m^2	Non-GFR evidence of kidney damage present
Stage 2	GFR 60–89 mL/min/1.73 m^2	Mild disease
Stage 3	GFR 30–59 mL/min/1.73 m^2	Mild to moderate disease
Stage 4	GFR 15–29 mL/min/1.73 m^2	Moderate to severe disease
Stage 5	GFR <15 mL/min/1.73 m^2	Dialysis or transplant needed

Abbreviation: GFR = glomerular filtration rate.

level can lose more than half of the functioning nephrons before serum creatinine elevates to an abnormal level.

In the ED, using automated laboratory devices, useful measures of kidney function (creatinine clearance and GFR) are estimated using equations that use information from the electronic medical record, including the measured creatinine level, age, weight, sex, and race. Patients with lower muscle mass (e.g., older patients and women) have lower actual GFRs for any given creatinine level. Acute changes in creatinine levels may be independent of renal function. For example, creatinine rises in rhabdomyolysis and fenofibrate use due to effects on muscle tissue, whereas in sepsis, creatinine production is decreased. These extrarenal changes in creatinine alter the relationship between creatinine and estimates of GFR. Glomerulonephritis increases tubular secretion of creatinine, but trimethoprim, cimetidine, and salicylates decrease tubular secretion of creatinine, thus altering the creatinine level independently of the GFR. **Normal kidney function is a GFR >90 mL/min/1.73 m^2**, where 1.73 m^2 is used as the average body surface area. Stages of kidney disease are characterized in **Table 88-5.**

Unfortunately, all GFR calculations are based on a steady-state creatinine level, severely limiting their applicability in AKI seen in the ED.

Cystatin C A protein produced by all nucleated cells has been proposed as a replacement for creatinine in estimating GFR. Cystatin C is formed at a constant rate unchanged by infections, inflammatory, and neoplastic conditions and, unlike creatinine, is not affected by diet, drugs, or body mass. Estimated GFR can be calculated by the Chronic Kidney Disease Epidemiology cystatin C equation, which corrects for age and sex. As with creatinine, elevations of cystatin C are only detected 24 to 48 hours after AKI has already occurred. Cystatin C may be more accurate in predicting death and progression to chronic kidney disease or need for dialysis.[36] Experts continue to search for a biomarker that could identify AKI early in the course of renal deterioration, but such a marker has yet to be identified.[37]

Urine Output Exact measurements of urine output require a urinary catheter to be in place for greater than 6 hours to meet the criteria of AKI as required from the Risk, Injury, Failure, Loss, and End-Stage Renal Failure (RIFLE) criteria in Table 88-1, limiting the applicability of urine output in an ED setting.

BUN-to-Creatinine Ratio The ratio of BUN to creatinine can suggest hypovolemia because of differences in the way each is handled in the nephron. Both substances are passively filtered at the glomerulus, but where creatinine remains within the tubule, the renal tubule is highly permeable to urea, which is passively reabsorbed with sodium. Therefore, in the setting of avid sodium retention, urea clearance is as low as 30% of GFR, whereas in the setting of adequate volume and sodium, urea clearance can increase to 70% to 100% of GFR. Thus, if the patient has normal concentrating ability, in the setting of prerenal AKI, the serum ratio of BUN to creatinine is typically >10. BUN level is depressed in patients with malnutrition and hepatic synthetic dysfunction and can be increased in the setting of protein loading, GI hemorrhage, or trauma. Despite the use of the BUN-to-creatinine ratio by clinicians to identify prerenal disorders since the 1940s, two recent studies question its accuracy.[38,39] The ratio fails to accurately identify AKI cases that resolve with volume replacement alone.[38,39]

Fractional Excretion of Sodium The fractional excretion of sodium ($Fe_{Na} = U_{Na}/P_{Na} \div U_{Cr}/P_{Cr}$, where Na = sodium, Cr = creatinine, U = urine, and P = plasma) is another indicator that is commonly used to identify hypovolemia, but it has important limitations. For example, in the setting of intrinsic AKI in which tubular concentrating capacity is retained, as in the case of glomerulonephritis, the fractional excretion of sodium may be depressed if there is concomitant volume depletion. With tubular injury such as ischemic acute tubular necrosis, the loss of concentrating ability results in a dilute urine, with a fractional excretion of sodium >1%, even if the patient is volume depleted (**Table 88-6**).

Urinalysis Microscopic examination of urine is useful in establishing the differential diagnosis. In acute glomerulonephritis, red blood cells enter the filtrate at the glomerulus and, on microscopic urinalysis, appear as casts and dysmorphic cells due to the increased tonicity of the renal medulla. In acute tubular necrosis, the tubular epithelium breaks down and allows protein to leak into the filtrate, and tubular epithelial cells may be seen in the sediment.

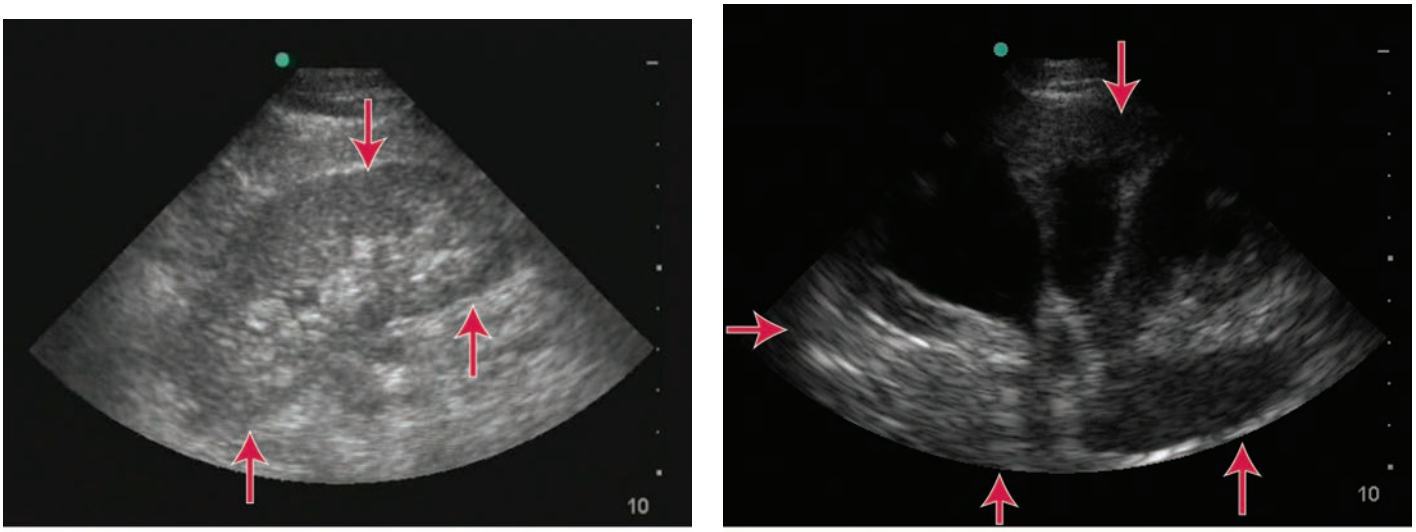
Hyaline casts are common in prerenal AKI and can be a normal finding; pigmented granular casts are common with ischemic or toxic tubular injury. Brown granular casts are common in hemoglobinuria or myoglobinuria. **The finding of hemoglobin on urine dipstick analysis with no red cells on microscopy suggests myoglobinuria.** Some crystals may be present in a normal urinalysis. Crystals are best seen with polarized light microscopy. Red cell casts and proteinuria suggest glomerulonephritis or an underlying autoimmune disease.

Imaging Renal US is the test of choice for urologic imaging in the setting of AKI. It has approximately 90% sensitivity and specificity for detecting hydronephrosis due to mechanical obstruction. **Figure 88-2** contrasts normal kidney US findings with US findings indicating hydronephrosis. If renal US detects hydronephrosis, a secondary imaging study to define the location of obstruction may be required. Bipolar renal length is easy to assess by US, and **kidney dimension of <9 cm suggests chronic kidney disease.** Renal parenchyma should be isoechoic or hypoechoic compared with that of the liver and spleen.

TABLE 88-6 Laboratory Findings in Conditions That Cause Acute Kidney Injury

Category	Dipstick Test	Sediment Analysis	Urine Osmolality (mOsm/kg)	Fractional Excretion of Sodium (%)
Prerenal	Trace to no proteinuria, SG >1.015	A few hyaline casts possible	>500	<1
Renal				
Ischemia	Mild to moderate proteinuria	Pigmented granular casts, renal tubular epithelial cells	<350	>1
Nephrotoxins	Mild to moderate proteinuria	Pigmented granular casts	<350	>1
Acute interstitial nephritis	Mild to moderate proteinuria; hemoglobin, leukocytes	White cells, eosinophils, casts, red cells	<350	>1
Acute glomerulonephritis	Moderate to severe proteinuria; hemoglobin	Red cells and red cell casts; red cells can be dysmorphic	>500	Depends on volume status
Postobstrutcive or postrenal	Trace to no proteinuria; hemoglobin and leukocytes possible	Crystals, red cells, and white cells possible	<350	>1

Abbreviation: SG = specific gravity.



A B

FIGURE 88-2. US of normal kidney and kidney showing hydronephrosis. **A.** Normal kidney; capsule margin at *arrows*. **B.** Hydronephrosis as would be expected in obstructive uropathy; the dilated kidney fills the majority of the screen; capsule at *arrows*. [Image used with permission of Michael B. Stone, MD, RDMS.]

Hyperechogenicity indicates diffuse parenchymal disease. Color flow Doppler US allows assessment of renal perfusion and can allow diagnosis of large-vessel causes of AKI. Resistive index is the ratio of the difference between systolic and diastolic flow to systolic flow [$(V_{max} - V_{min})/V_{max}$] as measured by color flow Doppler. In the vasoconstrictive phase of ischemic AKI, in which there may be no diastolic flow, the ratio may be as high as 1.0. The normal ratio is <0.7.

In *intermittent or partial obstruction*, hydronephrosis may be present, and it may even be absent in *complete obstruction* in the setting of retroperitoneal fibrosis. Furthermore, functional dilatation can occur in the setting of chronic ureteral reflux.

Noncontrast CT has a sensitivity for hydronephrosis that is equivalent to that of US and has the added advantage of demonstrating the site and often the cause of obstruction. If functional obstruction is a consideration in the presence of a dilated GU tract, radionuclide scans and magnetic resonance urographs before and after administration of diuretics can be obtained.

TREATMENT

For the critically ill patient with AKI, resuscitation is the first priority, and multiple diagnostic and therapeutic processes advance simultaneously. Look for and treat hypovolemia, sepsis, myocardial ischemia, respiratory failure, acute decompensated heart failure, electrolyte disturbances, acidosis, volume overload, and urinary obstruction, as clinically indicated.[40-42] The initial priority is treatment of the underlying cause of AKI.[40-42] While determination of the AKI type helps to determine priorities for treatment (i.e., prerenal AKI is most likely to require fluid resuscitation), this treatment section is organized based on the manifestations of AKI most likely to require acute management regardless of AKI type. See also "Cardiorenal Syndrome" under the "Special Populations" section below. Rhabdomyolysis is discussed in Chapter 89.

VOLUME DEPLETION

Correct intravascular volume deficits with crystalloids.[43] Balanced crystalloids, such as lactated Ringers' solution, may offer a small advantage over normal saline solution. In a large randomized trial involving 15,802 critically ill patients, subjects receiving balanced crystalloids had a lower rate of the composite outcome of death from any cause, new renal replacement therapy, or persistent renal dysfunction after discharge (14.3%), compared to patients receiving normal saline (15.4%).[44] A separate randomized trial involving 13,347 non–critically ill patients, did not find a mortality difference; however, patients receiving balanced crystalloids had a lower rate of adverse kidney events (4.7% vs. 5.6%).[45] Accurate determination of volume status is essential to prevent volume overload, which has been shown to worsen AKI and increase mortality.[46] Using bedside US, inspiratory collapsibility of the intrahepatic segment of the inferior vena cava is one noninvasive measure of volume status and expected fluid responsiveness[47,48] (**Figure 88-3**).

PREVENTING RENAL INJURY

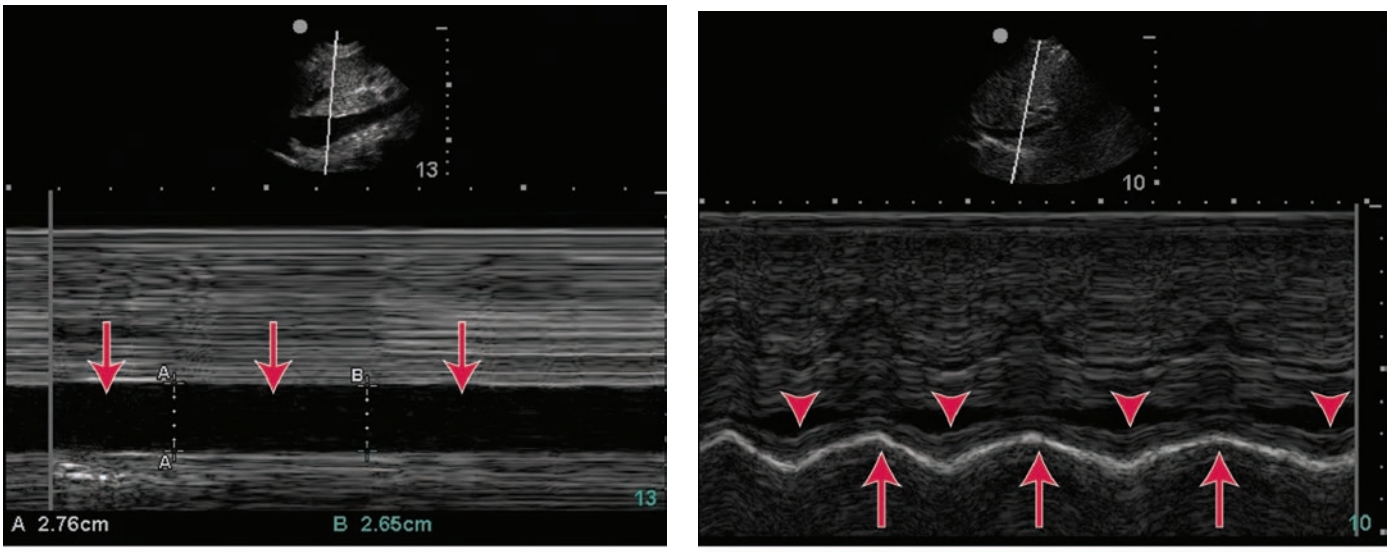
Hold medications that could be causing AKI (Tables 88-3 and 88-4). Make sure that renal dose adjustments are made for medication orders and that renal function is considered before ordering radiographic contrast studies. In general, for IV contrast studies in patients with GFR of 30 to 59 mL/min/1.73 m^2, weigh benefits of the study against the risk of renal function decline. For patients with GFR <30 mL/min/1.73 m^2, avoid IV contrast studies if possible. Emergency contrast studies for major trauma, aortic dissection, or ST-segment elevation myocardial infarction are examples in which benefits typically outweigh risk for most patients. Avoid gadolinium for GFR <30 mL/min/1.73 m^2. For patients with abnormal kidney function, for whom contrast-enhanced imaging is planned, the ideal rate and volume of fluid administration is not defined.[32] Commonly used volumes are 500 to 1000 mL of crystalloid (lactated Ringer's or 0.9% normal saline) prior to the procedure and an equal volume after the procedure; however, significantly dehydrated patients may need additional volume. The administration rate should be determined by the patient's comorbidities, as well as any additional needs for urgent hydration.

RELIEVE URINE OUTFLOW OBSTRUCTION

Timely relief of obstruction is essential for the return of normal renal function. **Permanent loss of renal function develops over the course of 10 to 14 days in the setting of complete obstruction. The risk of chronic kidney disease increases significantly if obstruction is complicated by urinary tract infection.** Consider both urethral and ureteral obstruction or sphincter dysfunction as potential causes. For additional discussion of postrenal AKI management, see Chapter 92, "Acute Urinary Retention."

FLUID OVERLOAD

Diuretics are the mainstay of treatment for fluid overload in patients with normal kidney function. Fluid overload is associated with increased mortality in patients with AKI.[49] In the absence of fluid overload, diuretics are not recommended for patients with AKI,[40-42] nor have they been shown to prevent AKI.[50] However, diuretics are used in the setting of mild to moderate AKI when fluid overload is present.[40-42,51] The alternative to diuretics for the treatment of fluid overload is dialysis, and failure to respond to diuretics is frequently used as an indication for dialysis. A **furosemide stress test** can be used in the setting of mild AKI (AKIN



A **B**

FIGURE 88-3. US of the inferior vena cava. **A.** Dilated inferior vena cava (*arrows*) with little respiratory variation as might be expected in volume overload. **B.** An almost fully collapsed inferior vena cava at inspiration (*arrows*) and expiration (*arrowheads*) as might be expected in prerenal acute kidney injury. [Image used with permission of Michael B. Stone, MD, RDMS.]

stage ≤2) to determine diuretic responsiveness as well as to predict worsening renal function. Administer 1 milligrams/kg of furosemide in naive patients or 1.5 milligrams/kg in those with prior exposure; a urine output of <200 mL over 2 hours has a sensitivity of 87.1% and a specificity of 84.1% to predict progression to AKIN stage 3 AKI[52-55] (Table 88-1). Mannitol has no role in the treatment of AKI.[40] Low ("renal")-dose dopamine does not improve renal recovery or decrease mortality.[40,41]

HYPERTENSION

Fenoldopam and nicardipine are commonly used in this setting; see Chapter 57, "Systemic Hypertension," for a detailed discussion of management.

METABOLIC ACIDOSIS

In cases were the pH is greater than 7.1, treat the underlying cause of the AKI first. If pH is ≤7.1, consider treatment. Dialysis is preferred in the setting of anuria, or fluid overload, because safe effective use of sodium bicarbonate requires urine flow and ability to tolerate a fluid load. See Chapter 15, "Acid-Base Disorders."

ELECTROLYTE DISORDERS

Suspected hyperkalemia should be treated in the setting of prolongation of the PR interval, peaked T waves, or widening of the QRS complex; proven hyperkalemia should be treated. For the diagnosis and management of hyperkalemia and other electrolyte abnormalities, see Chapter 17, "Fluids and Electrolytes."

GLOMERULONEPHRITIS

Management includes consultation with nephrology, plan for renal biopsy, corticosteroids, cyclophosphamide, and consideration for plasmapheresis.[56]

DISPOSITION AND CONSULTATION

Patients with mild prerenal AKI (AKIN stage 1) are eligible for treatment in ED observation protocols anticipating reversibility of renal dysfunction before discharge. Patients who do not improve or patients with more severe AKI require hospital admission for evaluation and treatment. For patients with severe AKI or for patients with uncertain etiology, nephrology should be consulted.

DIALYSIS/RENAL REPLACEMENT THERAPY

Timing of renal replacement therapy is controversial. The Early Versus Late Initiation of Renal-Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) Investigators' study of intensive care unit patients meeting KDIGO stage 2 criteria with either severe sepsis or fluid overload refractory to diuretics found reduced mortality (39.3% vs. 54.7%) and improved renal recovery (53.6% vs. 38.7%) in the group treated with early renal replacement therapy (within 8 hours of KDIGO stage 2 diagnosis) versus the group receiving delayed renal replacement therapy (within 12 hours of KDIGO stage 3 diagnosis).[57] However, two subsequent meta-analyses that included the ELAIN data found no improved mortality overall.[58,59] Indications for emergency dialysis or renal replacement therapy are listed in **Table 88-7**.

SPECIAL POPULATIONS

CARDIORENAL SYNDROME

Cardiorenal syndrome is a complex pathophysiologic disorder of the heart and kidneys where acute or chronic dysfunction of one organ induces acute or chronic dysfunction of the other organ. Cardiorenal syndrome type 1 is characterized by acute deterioration in cardiac function that causes AKI. Cardiorenal syndrome type 3 (also called acute renocardiac syndrome) is characterized by an AKI that causes acute cardiac injury and/or dysfunction, such as cardiac ischemia, congestive heart failure, or arrhythmias. Type 2 and 4 cardiorenal syndromes are chronic; type 5 is secondary to a separate systemic condition such as sepsis. Comparing

TABLE 88-7 Indications for Emergent Dialysis or Renal Replacement Therapy

- Uncontrolled hyperkalemia (potassium >6.5 mmol/L or rising)
- Refractory fluid overload in association with persistent hypoxia or lack of response to conservative measures
- Uremic pericarditis
- Progressive uremic/metabolic encephalopathy; asterixis, seizures
- Serum sodium level <115 or >165 mEq/L (<115 or >165 mmol/L)
- Severe metabolic acidosis with concomitant acute kidney injury; treat underlying source of lactic acidosis and tolerate pH >7.2 in setting of permissive hypercapnia
- Life-threatening poisoning with a dialyzable drug, such as salicylates, lithium, isopropanol, methanol, or ethylene glycol
- Bleeding dyscrasia secondary to uremia
- Excessive BUN and creatinine levels: trigger levels are arbitrary; it is generally advisable to keep BUN level <100 milligrams/dL (<37.7 mmol/L), but each patient should be evaluated individually

prior serum creatinine and serum B-type natriuretic peptide to the current value can help determine if the acute presentation is more likely due to a primary heart disorder where the B-type natriuretic peptide will be elevated from baseline in a higher proportion than creatinine or due to a primary renal disorder where serum creatinine will be elevated from baseline in a higher proportion than B-type natriuretic peptide.

Treatment includes management of acute decompensated heart failure (see Chapter 53, "Acute Heart Failure"), with special consideration for the use of ultrafiltration to manage fluid overload. Ultrafiltration is a form of renal replacement therapy primarily used to remove excess fluid. A meta-analysis and systematic review of randomized trials including 608 patients comparing diuretics with ultrafiltration found similar outcomes between groups assessing mortality and risk for renal deterioration.[60] Most patients in the trials met criteria for AKIN stage ≤2 AKI, with creatinine ranging from 1.4 to 2.2 milligrams/dL. According to the Heart Failure Society of America, the European Society of Cardiology, and the Canadian Cardiovascular Society, ultrafiltration should be reserved for patients refractory to diuretics.[61-63] See "Furosemide Stress Test" above. Immediate ultrafiltration or other renal replacement therapy should be considered for life-threatening hyperkalemia or pulmonary edema unresponsive to less invasive treatment; otherwise, early renal replacement therapy has not been shown to improve survival or renal recovery.[64]

IV CONTRAST IN PATIENTS TAKING METFORMIN

Metformin is one of the most frequently prescribed treatments for patients with type 2 diabetes mellitus. The most significant adverse effect of metformin therapy is a metformin-associated lactic acidosis, which is most likely to occur in patients who have been prescribed metformin despite an existing contraindication to the drug. Taking a more conservative approach, the U.S. Food and Drug Administration states that metformin should be withheld temporarily in patients receiving iodinated contrast media if their GFR is between 30 and 60 mL/min/1.73 m^2 and restarted after creatinine has been checked 48 hours after contrast administration, and patients with lower GFRs should have metformin held and not restarted.[65] In contrast, the American College of Radiology has reviewed the data on metformin-associated acidosis following the administration of contrast media and found the complication to be uncommon in patients with normal or near-normal renal function. The American College of Radiology has made the following recommendations. For patients with estimated GFR ≥30 mL/min/1.73 m^2, there is no need to discontinue metformin prior to the procedure or following the procedure. For patients with eGFR ≤30 mL/min/1.73 m^2, metformin should be withheld at the time of the contrast infusion and for 48 hours after the procedure.[32] The renal function should be reassessed at 48 hours to determine the safe administration of subsequent metformin therapy.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 89

Rhabdomyolysis

Francis L. Counselman

INTRODUCTION AND EPIDEMIOLOGY

Rhabdomyolysis is the destruction of skeletal muscle caused by any mechanism that results in injury to myocytes and their membranes. Acute necrosis of skeletal muscle fibers and the leakage of cellular contents into the circulation result in myoglobinuria.

Table 89-1 lists commonly recognized conditions associated with rhabdomyolysis. **In general, the most common causes of rhabdomyolysis in adults are drugs of abuse and alcohol, followed by medications, muscle diseases, trauma, neuroleptic malignant syndrome, seizures, immobility, infection, strenuous physical activity, and heat-related illness.**[1,2] Multiple causes are present in more than half of patients.[1] In children, rhabdomyolysis is less common and is more benign.[3,4] In a large study of children, the most common causes of nonrecurrent rhabdomyolysis were viral myositis, trauma, and connective tissue disease.[4] For adults and children, inherited metabolic disorders should be suspected with recurrent episodes of rhabdomyolysis, especially if associated with exercise intolerance.

Patients in coma are at risk for rhabdomyolysis from unrelieved pressure on gravity-dependent body parts. Alcohol consumption can result in rhabdomyolysis secondary to coma-induced muscle compression and a direct toxic effect. Drugs of abuse and alcohol should be suspected as a primary or contributing cause of rhabdomyolysis in adults. **Statin-related myopathies** include myalgias with or without elevation of creatine kinase level, muscle weakness, and rhabdomyolysis. Statin-related rhabdomyolysis varies with the particular statin and is dose related. Polypharmacy, including combinations with cyclosporine, macrolide antibiotics, warfarin, digoxin, and dual statin therapy, carries an increased risk for rhabdomyolysis.[3,5]

A number of bacterial and viral infections including human immunodeficiency virus have been associated with rhabdomyolysis.[3,6] Strenuous physical activity, as seen in athletes, marathon runners, military recruits, and outdoor laborers, is a common cause of rhabdomyolysis but is less likely than other etiologies to provoke acute kidney injury.[7] Physical activity that produces high-force eccentric contractions (resistance), such as strength training or heavy lifting, leads to greater breakdown in muscle and higher levels of creatine kinase than concentric contractions, such as endurance-based (aerobic) exercises.[7] Factors that increase the risk in this group of patients include poor physical conditioning, male sex, inadequate fluid intake, wearing of restrictive clothing, high ambient temperatures, and high humidity levels.[7]

PATHOPHYSIOLOGY

Rhabdomyolysis is a syndrome characterized by injury to skeletal muscle with subsequent effects from the release of intracellular contents. These contents include myoglobin, creatine kinase, aspartate aminotransferase, and potassium. Although numerous causes of rhabdomyolysis have been described, the common terminal event appears to involve the disruption of the Na^+K^+ATPase pump and calcium transport, which results in increased intracellular calcium and subsequent muscle cell necrosis. In addition, calcium activates phospholipase A_2 and various vasoactive molecules and proteases and induces the production of free oxygen radicals.[3,8]

CLINICAL FEATURES

The presenting symptoms of rhabdomyolysis are usually acute in onset and include myalgias, weakness, malaise, low-grade fever, and dark (usually brown) urine. Muscle symptoms, however, may be present in only half of cases.[3,4] Nausea, vomiting, abdominal pain, and tachycardia can occur in severe rhabdomyolysis. Mental status changes may develop from urea-induced encephalopathy. Swelling and tenderness of the involved muscle groups and hemorrhagic discoloration of overlying skin may be observed but are not common. Muscle involvement may be localized or diffuse, depending on the cause. Commonly, the postural muscles of the thighs, calves, and lower back are involved. Muscle swelling may not become apparent until after rehydration with IV fluids. Acute rhabdomyolysis may be present without any signs or symptoms, with a normal physical examination.

DIAGNOSIS

An elevated **serum creatine kinase** is the most sensitive and reliable indicator of muscle injury. The degree of elevation correlates with the

TABLE 89-1 Common Conditions Associated With Rhabdomyolysis in Adults

Trauma	**Immunologic diseases involving muscle**	**Medications**
Crush injury	Dermatomyositis	Antipsychotics
Electrical or lightning injury	Polymyositis	Barbiturates
Drugs of abuse	**Bacterial infection**	Benzodiazepines
Amphetamines [including ecstasy (3,4-methylenedioxymethamphetamine)]	*Clostridium*	Chemotherapeutic agents
Caffeine	Group A β-hemolytic streptococci	Clofibrate
Cocaine	*Klebsiella*	Colchicine
Ethanol	*Legionella*	Corticosteroids
Heroin	*Mycoplasma*	Diphenhydramine
Lysergic acid diethylamide	*Salmonella*	Hypnotics and sedatives
Methadone	*Shigella*	Isoniazid
Methamphetamines	*Staphylococcus aureus*	Lithium
Opiates	*Streptococcus pneumoniae*	Monoamine oxidase inhibitors
Phencyclidine	**Viral infection**	Narcotics
Environment and excessive muscular activity	Coxsackievirus	Neuroleptic agents
Contact sports	Cytomegalovirus	Phenothiazines
Delirium tremens	Epstein-Barr virus	Propofol
Dystonia	Enterovirus	Salicylates
Excessive exercise (e.g., CrossFit, spinning)	Hepatitis virus	Selective serotonin reuptake inhibitors
Immobilization	Herpes simplex virus	Statins
Psychosis	Human immunodeficiency virus	Theophylline
Seizures	Influenza virus (A and B)	Tricyclic antidepressants
Marathons, military basic training	Rotavirus	Zidovudine
Heatstroke	**Ischemic injury**	
Genetic disorders	Compartment syndrome	
Glycolysis and glycogenolysis disorders	Compression	
Fatty acid oxidation disorders		
Mitochondrial and respiratory chain metabolism disorders		

amount of muscle injury and the severity of symptoms, but not the development of acute kidney injury or other morbidity. **Most authors consider a fivefold or greater increase above the upper threshold of normal in serum creatine kinase level, in the absence of cardiac or brain injury, as the requirement for the diagnosis of rhabdomyolysis** (approximately 800 to 1000 IU/L).[3] In general, the level begins to rise approximately 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and then declines at the relatively constant rate of 39% of the previous day's value.[1] Ongoing muscle necrosis should be suspected in patients with elevated values that fail to decrease in this manner. The MB fraction of creatine kinase (found primarily in cardiac but also in skeletal muscle) also may be elevated but should not exceed 5% of the total creatine kinase.

Myoglobinuria develops once skeletal muscle injury is >100 grams.[2] Myoglobin elevation occurs before creatine kinase elevation, and then is rapidly cleared from the plasma through renal excretion and metabolism to bilirubin. Myoglobin causes the typical reddish brown discoloration when the urine myoglobin level is >100 milligrams/dL.[3,9] **Because myoglobin contains heme, qualitative tests such as the dipstick test do not differentiate among hemoglobin, myoglobin, and red blood cells.** Therefore, suspect myoglobinuria when the urine dipstick test is positive for blood but zero or rare red blood cells are present on microscopic examination. Because myoglobin levels may return to baseline quickly, the absence of an elevated serum myoglobin level or of myoglobinuria does not exclude the diagnosis. In a study of 475 patients with rhabdomyolysis, only 19% were found to have myoglobinuria.[1]

Urinalysis is essential. Other laboratory studies may be useful to identify the common complications of rhabdomyolysis and the underlying cause. Obtain serum electrolyte, calcium, phosphorus, and uric acid levels to identify hyperkalemia, abnormal calcium and phosphorus levels, and hyperuricemia. Obtain an ECG if hyperkalemia is suspected clinically or confirmed with testing. Serum creatinine and BUN levels are needed to identify acute kidney injury. Because disseminated intravascular coagulation is a potential complication, obtain a baseline CBC and consider a coagulopathic screen (e.g., prothrombin time, partial thromboplastin time, fibrin split products, and fibrinogen level [see Chapter 233, "Acquired Bleeding Disorders"]). Other common laboratory findings in rhabdomyolysis include elevated levels of lactate dehydrogenase, urea, creatine, and aminotransferases. In addition, a falsely elevated cardiac troponin I (TnI) is common, especially in elderly patients.[10] Further laboratory testing to identify the underlying cause(s) of rhabdomyolysis should be based on the medical history and clinical presentation. Imaging plays a secondary role in the diagnosis, after clinical and laboratory studies.[11] US and CT provide only nonspecific findings, unless being used to rule out vascular (or boney) injury that could have provoked rhabdomyolysis. MRI is the imaging modality of choice for evaluating focal muscle damage but is rarely needed for managment.[11] See discussion below and Chapter 278, "Compartment Syndromes," for diagnostic criteria of associated compartment syndrome.

DIFFERENTIAL DIAGNOSIS

Other causes of muscle pain and weakness besides rhabdomyolysis should be considered in the appropriate clinical setting. Such causes include acute myopathies, periodic paralysis, polymyositis or dermatomyositis, or Guillain-Barré syndrome. Rhabdomyolysis associated with strenuous exercise or fasting or repeat episodes of rhabdomyolysis suggest an inherited metabolic myopathy.[3]

TREATMENT

PREHOSPITAL CARE

For victims of **crush injury**, patients strongly suspected of having rhabdomyolysis, or accident victims with prolonged extrication and transport times, early and vigorous IV fluid resuscitation is the most important treatment to prevent acute kidney injury.[12,13] Once a limb is extricated, IV normal saline should be initiated at 1 L/h. After extrication, IV normal saline should be continued at 500 mL, alternating with 5% dextrose in normal saline at 1 L/h. Because rhabdomyolysis may be associated with hyperkalemia and lactic acidosis, **avoid potassium- or lactate-containing solutions until electrolyte and acid-base status is known.**

EMERGENCY DEPARTMENT CARE

Once the patient is in the ED, continue aggressive IV rehydration for the next 24 to 72 hours. One method is rapid correction of the fluid deficit with IV crystalloids followed by infusion of 4 mL/kg/h, with the goal of maintaining a minimum urine output of 3 to 4 mL/kg/h.[3,14] Another method is a goal of 200 to 300 mL of urine output each hour.[15]

No prospective controlled studies have identified ideal fluid choice or demonstrated benefit from alkalinization of the urine with sodium bicarbonate or forced diuresis with mannitol or loop diuretics.[13-17] However, one recent 10-year retrospective study found that the use of mannitol and bicarbonate in patients with a creatine kinase greater than 10,000 IU/L decreased the development of acute renal dysfunction (creatinine >2 milligrams/dL [152.50 µmol/L]).[18] If bicarbonate is given, maintain an isotonic solution and avoid metabolic alkalosis or hypokalemia.[15] Mannitol may be harmful because it may cause osmotic diuresis in hypovolemic patients. In nontraumatic rhabdomyolysis, lactated Ringer's solution was compared to normal saline in a cohort of 28 patients.[19] The rate of reduction of creatine kinase and the prevalence of acute kidney injury was not different between groups; none of the 13 patients receiving lactated Ringer's developed metabolic acidosis (mean serum pH 7.44), whereas many of the patients receiving normal saline developed acidosis (mean serum pH 7.25).[19]

Place a urinary catheter in patients in critical condition and those with acute kidney injury to monitor urine output. Institute cardiac monitoring because electrolyte and metabolic complications can cause dysrhythmias. For patients with heart disease, comorbid conditions, or preexisting renal disease or for elderly patients, hemodynamic monitoring may be necessary to avoid fluid overload.

Hypocalcemia observed early in rhabdomyolysis usually requires no treatment. Calcium should be given only to treat **hyperkalemia-induced cardiotoxicity** or profound signs and symptoms of hypocalcemia.[3] If hypercalcemia is symptomatic, continue saline diuresis. Hyperkalemia, which is usually most severe in the first 12 to 36 hours after muscle injury, can be significant and prolonged. Traditional insulin and glucose therapy, although recommended, may not be as effective in rhabdomyolysis-induced hyperkalemia. The use of ion-exchange resins (e.g., sodium polystyrene sulfonate) may be effective. Treat hyperphosphatemia with oral phosphate binders when serum levels are >7 milligrams/dL (2.25 µmol/L). See Chapter 17, "Fluids and Electrolytes," for further discussion. Ultimately, dialysis may be needed; see Chapter 88, "Acute Kidney Injury," for indications. Avoid prostaglandin inhibitors such as NSAIDs because of their vasoconstrictive effects on the kidney. Finally, treat the underlying cause of the rhabdomyolysis, which may require consultation.

DISEASE COMPLICATIONS

The complications of rhabdomyolysis include acute kidney injury, acid-base derangements (both acidosis and alkalosis) electrolyte disturbances (potassium, calcium, phosphorus), disseminated intravascular coagulation, and mechanical complications (e.g., compartment syndrome or peripheral neuropathy).[20] Factors that contribute to rhabdomyolysis-induced acute kidney injury include hypovolemia, acidosis or aciduria, tubular obstruction, and the nephrotoxic effects of myoglobin.[3,15] Renal tubular obstruction occurs secondary to precipitation of uric acid and myoglobin. Over all, neither the presence of myoglobinuria nor the degree of creatine kinase elevation is predictive of acute kidney injury; however, the correlation of creatine kinase elevation and acute kidney injury is stronger in traumatic rhabdomyolysis.[21] A risk prediction score for mortality or need for dialysis in patients with rhabdomyolysis was initially derived and validated in 2013[22] and was recently externally validated in 2016[23] (**Table 89-2**).

TABLE 89-2 McMahon Score to Predict Death or Dialysis

Laboratory Parameters at Time of Admission	International Units (IU)	Traditional Units	Points
Creatinine	124–194 µmol/L	1.4–2.2 milligrams/dL	1.5
	>194 µmol/L	>2.2 milligrams/dL	2.5
Calcium	<1.875 mmol/L	<7.5 milligrams/dL	2
Creatine kinase	>40,000 IU/L	>40,000 IU/L	2
Phosphate	1.3–1.174 mmol/L	4.0–5.4 milligrams/dL	1.5
	>1.74 mmol/L	>5.4 milligrams/dL	3
Bicarbonate	<19 mmol/L	<19 mEq/L	2
Historical Variables	**Value**		**Points**
Etiology of rhabdomyolysis	NOT seizures, syncope, exercise, statins, or myositis		1
Sex	Female		1
Age	50–70 y		1.5
	71–80 y		2.5
	>80 y		3

Note. A score of 5 or less indicates a 3% risk of either renal replacement therapy or death. A score of at least 10 indicates a 52% risk of renal replacement therapy or death.

The authors suggest that the score can be used to determine the need for aggressive resuscitation when faced with a patient who is at risk for the complications of resuscitation (e.g., a patient with heart failure).

The mechanical complications of rhabdomyolysis consist of compartment syndrome and peripheral nerve injury. The associated muscle swelling may exert pressure on peripheral nerves, resulting in neuronal ischemia and causing paresthesias or paralysis. Nerve injury is often proximal, and multiple nerves may be involved in the same extremity.[18] Compartment syndrome occurs secondary to marked swelling and edema of the involved muscle groups and is discussed in Chapter 278.

DISPOSITION AND FOLLOW-UP

The majority of healthy patients with *exertional rhabdomyolysis* and *without comorbidities* (e.g., heat stress, dehydration, trauma) can usually be treated with PO or IV rehydration, observed in the ED, and then released.[6] Otherwise, patients should be admitted for IV hydration, management of complications of rhabdomyolysis, and treatment of the underlying cause. For at least the initial 24 to 48 hours, admission should be to a monitored bed to identify dysrhythmias as well as worsening renal function. The nephrology service should be consulted to evaluate the need for dialysis for patients with hyperkalemia unresponsive to therapy or for patients with a high McMahon risk score.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 90

End-Stage Renal Disease

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INTRODUCTION AND EPIDEMIOLOGY

End-stage renal disease (ESRD) is the irreversible loss of renal function, resulting in the accumulation of toxins and the loss of internal homeostasis. Uremia, the clinical syndrome resulting from ESRD, is fatal without some form of renal replacement therapy. At present, renal replacement therapy consists of two basic modalities: renal transplant and dialytic therapy, either hemodialysis or peritoneal dialysis (PD).

Hemodialysis is the initial therapy in the vast majority of new cases of adult ESRD, with a few starting PD and an even smaller number receiving predialytic renal transplants. The proportions are reversed in children, with most children receiving transplants. More than 100,000 Americans await a renal transplant, with a median time of 2.6 years on a transplant wait list.[1]

One-year mortality for hemodialysis patients is 20% to 25%, with 5-year survival of 35%. Cardiac causes account for about half of all deaths.[1] Infections trigger death in up to a quarter of patients, with cerebrovascular events and malignancy being other causes.

PATHOPHYSIOLOGY

Renal failure causes complex physiologic abnormalities (**Table 90-1**).

Excretory failure leads to elevated levels of >70 chemicals in uremic plasma, and these toxins, individually or in combination, cause uremic organ dysfunction and produce the symptoms of uremia. Besides urea, other potential uremic toxins include cyanate, guanidine, polyamines, and β_2-microglobulin.[2] If uremia were simply a toxidrome, then dialysis would reverse all its untoward effects; however, it does not, in part because many toxins are highly protein bound and nondialyzable.[3] Because many uremia-related organ dysfunctions persist after dialysis, other processes are clearly important.

Biosynthetic failure refers to the aspects of uremia caused by loss of the renal hormones $1,25(OH)_2$-vitamin D_3 and erythropoietin. The kidneys are primarily responsible for the secretion of erythropoietin and 1α-hydroxylase, which is necessary to produce the active form of vitamin D_3. Because 85% of erythropoietin is produced in the kidneys, ESRD patients have depressed levels of erythropoietin, which contributes to anemia. Vitamin D_3 deficiency results in decreased GI calcium absorption, inducing secondary hyperparathyroidism and leading to renal bone disease.

Regulatory failure results in an oversecretion of hormones, leading to uremia by disruption of normal feedback mechanisms. The uremic state produces excess free oxygen radicals, which react with carbohydrates, lipids, and amino acids to create advanced glycation end products, linked to atherosclerosis and amyloidosis in ESRD patients.[4] This may explain the progressive nature of the atherosclerosis and amyloidosis seen in ESRD patients.[5]

TABLE 90-1 Clinical Features Associated With Uremia and Dialysis

General
- Diffuse muscle cramping, pruritus

Neurologic
- Uremic encephalopathy: cognitive defects, memory loss, decreased attentiveness, slurred speech, reversal of sleep-wake cycle, asterixis, seizure, coma, symptomatic improvement with dialysis
- Dialysis dementia: progressive neurologic decline, failure to improve with dialysis, fatal
- Subdural hematoma: headache, focal neurologic deficits, seizure, coma
- Peripheral neuropathy: singultus (hiccups), restless leg syndrome, sensorimotor neuropathy, autonomic neuropathy

Cardiovascular
- Coronary artery disease
- Hypertension: essential hypertension, glomerulonephritis, renal artery stenosis, fluid overload
- Heart failure: fluid overload, uremic cardiomyopathy, high-output arteriovenous fistula
- Pericarditis: uremic, dialysis related, pericardial tamponade

Hematologic
- Anemia, decreased red blood cell survival, decreased erythropoietin levels
- Bleeding diathesis
- Immunodeficiency (humoral and cellular)

GI
- Anorexia, metallic taste, nausea, vomiting
- GI bleeding
- Diverticulosis, diverticulitis
- Ascites

Renal bone disease
- Metastatic calcification (calciphylaxis)
- Hyperparathyroidism (osteitis fibrosa cystica)
- Vitamin D_3 deficiency and aluminum intoxication (osteomalacia)

CLINICAL FEATURES OF UREMIA

Uremia is a clinical syndrome (Table 90-1), and no single symptom, sign, or laboratory test result reflects all aspects of uremia. Although a correlation exists between the symptoms of uremia and low glomerular filtration rate (GFR) (8 to 10 mL/min/1.73 m^2), BUN and serum creatinine levels are inaccurate markers of the clinical syndrome of uremia. The decision to start long-term dialysis is based on the severity of the patient's symptoms related to uremia. The most common reasons for emergency dialysis are fluid overload (51%), hyperkalemia (18%), and severe acid-base disturbances.[6] Uremia is the most common indication for nonemergent dialysis.[6]

NEUROLOGIC COMPLICATIONS

Stroke occurs in approximately 6% of hemodialysis patients, with about half being hemorrhagic and half ischemic. Subdural hematomas occur 10 times more frequently in dialysis patients than in the general population.[7]

Uremic encephalopathy is a constellation of nonspecific central neurologic symptoms associated with renal failure. Onset may be sudden mimicking ischemic stroke, or the neurologic function may deteriorate gradually over several days.[8] Uremic encephalopathy is best diagnosed after eliminating structural, vascular, infectious, toxic, and metabolic causes of neurologic dysfunction. MRI may show basal ganglia lesions.[8] Neurologic findings of uremic encephalopathy improve with dialysis in 70% of patients.[8]

Dialysis dementia is nonspecific in presentation from other encephalopathies. This manifestation of ESRD and treatment is progressive, with the 2- to 4-year survival for these patients being 24%. This disorder usually becomes evident after at least 2 years of dialysis therapy and fails to respond to increases in dialysis frequency or renal transplantation.

Peripheral neuropathy is one of the most frequent neurologic manifestations of ESRD, with greater lower than upper limb involvement.[7] The most frequent clinical features reflect large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, muscle wasting, and weakness. Autonomic dysfunction results in impotence, postural dizziness, gastric fullness, bowel dysfunction, and reduced sweating. Reduced heart rate variability and baroreceptor control impairment occur.

Conventional hemodialysis does not seem to improve autonomic dysfunction; however, daily short hemodialysis and long nocturnal hemodialysis may reduce the elevated sympathetic activity. Treatment is only marginally effective, including vitamins, amitriptyline, gabapentin, and carbamazepine.[9] Because few treatments are effective and side

effects are common, the patient's nephrologist or a pain specialist should manage medications.

CARDIOVASCULAR COMPLICATIONS

The mortality from cardiovascular disease is 10 to 20 times higher in dialysis patients than in the general population.[10] Coronary artery disease, left ventricular hypertrophy, and congestive heart failure are common. The etiology of cardiovascular disease in ESRD patients is multifactorial, related to preexisting conditions (e.g., hypertension, diabetes), uremia (e.g., uremic toxins, hyperlipidemias, homocysteine level, hyperparathyroidism), and dialysis-related conditions (e.g., hypotension, dialysis membrane reactions, hypoalbuminemia).[11]

CARDIAC MARKERS

The diagnosis of ischemic cardiovascular disease in ESRD patients often has been clouded by the misconception that the traditional serum protein markers of myocardial damage (troponins I and T) are unreliable in dialysis patients. Elevated levels of **troponin I and T** are common even in asymptomatic hemodialysis patients and probably reflect left ventricular hypertrophy and microvascular disease. Asymptomatic elevations of cardiac biomarkers are, however, associated with long-term risks of coronary artery disease.[12] To account for higher baseline levels of troponin T and I, many define myocardial infarction only by a 20% or more dynamic rise and with at least one value above the 99th percentile[13] (see Chapter 48, "Chest Pain").

HYPERTENSION

Hypertension is primarily due to increased total peripheral resistance. Increases in blood volume, decreased vascular compliance, the vasopressor effects of native kidneys, the renin-angiotensin system, and the sympathetic nervous system also play roles in ESRD hypertension.[14]

Management of hypertension in ESRD patients begins with control of blood volume. If that is unsuccessful, most cases can be controlled with adrenergic blocking agents, angiotensin-converting enzyme inhibitors, or vasodilating agents, such as hydralazine or minoxidil. Bilateral nephrectomy is rarely necessary for blood pressure control.

HEART FAILURE

Hypertension is the most common cause of heart failure in ESRD patients, followed by coronary artery disease and valvular defects. Causes unique to ESRD include uremic cardiomyopathy, fluid overload, and arteriovenous fistula–related high-output failure (see section "Complications of Vascular Access" later in the chapter). **Natriuretic peptide levels** are elevated in hemodialysis patients, often from concomitant left ventricular hypertrophy and systolic dysfunction. Elevation of natriuretic peptides in hemodialysis patients correlates with higher short-term mortality rates, but there are no reliable thresholds to identify fluid overload.

UREMIC CARDIOMYOPATHY

Uremic cardiomyopathy is a diagnosis of exclusion when all other causes of congestive heart failure have been excluded. In most uremic patients, left ventricular dysfunction is related to ischemic heart disease, hypertension, and hypoalbuminemia. Dialysis rarely improves left ventricular function in uremic patients with congestive heart failure.

PULMONARY EDEMA

Pulmonary edema is most commonly ascribed to fluid overload, but acute myocardial ischemia can also trigger depressed left ventricular function.[15] Cornerstones of therapy are supplemental oxygen if needed, bilevel positive airway pressure, nitrates, and angiotensin-converting enzyme inhibitors. Loop diuretics, such as furosemide (60 to 100 milligrams IV), may aid even in those with minimal urine output because loop diuretics have short-lived vasodilatory actions. **Hemodialysis is the ultimate treatment for fluid overload** in ESRD patients. Preload reduction by inducing diarrhea with sorbitol or by phlebotomy may help in low-resource situations. Removing as little as 150 mL of blood is safe and effective in some with pulmonary edema. Improved oxygenation produced by phlebotomy offsets the decrease in oxygen-carrying capacity due to the decrease in hemoglobin. Blood withdrawn during phlebotomy should be collected in transfusion bags, so plasma can be extracted by the blood bank and the red blood cells transfused back to the patient later during dialysis. PD does not remove volume fast enough to have a significant impact on pulmonary edema.

CARDIAC TAMPONADE

Cardiac tamponade is a concern in any critically ill ESRD patient, often presenting without classic findings. Instead, signs of cardiac tamponade include changes in mental status, hypotension, or shortness of breath. Increased interdialytic weight gain, increased edema, and intradialytic hypotension are other warning signs suggesting the diagnosis of tamponade. In addition to hypotension, an increased heart size on chest radiograph suggests effusion and potential tamponade. Bedside US is the best method to detect pericardial effusion and tamponade.[16] Hemodynamically significant pericardial effusions require pericardiocentesis under fluoroscopic or US guidance. Bedside pericardiocentesis (see Chapter 34, "Pericardiocentesis") is used only in hemodynamically unstable patients because of its high complication rate.

PERICARDITIS

Pericarditis is usually due to uremia. Uremic pericarditis is linked to fluid overload, abnormal platelet function, and increased fibrinolysis and inflammation. Pericardial contents are sterile unless infected and are abundant with fibrin and inflammatory cells.

Uremic pericarditis causes pericardial friction rubs, which are louder than in most other forms of pericarditis, often palpable, and frequently persist for some time after metabolic abnormalities have been corrected. BUN level is nearly always >60 milligrams/dL. One of the unique features of uninfected uremic pericarditis is that the inflammatory cells do not penetrate into the myocardium, so typical ECG changes of acute pericarditis are absent. Most often, the ECG demonstrates associated abnormalities, such as left ventricular hypertrophy, ischemia, and metabolic abnormalities (e.g., hyperkalemia and hypocalcemia). When the ECG has features typical of acute pericarditis, suspect infection.

Dialysis-related pericarditis is most common during periods of increased catabolism (trauma and sepsis) or inadequate dialysis due to missed sessions or vascular access problems. The pathophysiology of dialysis-related pericarditis is the buildup of middle molecules and hyperparathyroidism. Dialysis-related pericarditis is more common during hemodialysis than during PD, although now somewhat less frequent because of improved dialysis techniques. Fever and malaise are more common and severe than in uremic pericarditis. Pericardial effusion is the most important complication and tends to be recurrent. Due to the recurrent nature of dialysis pericarditis, adhesions and fluid loculations are common, which complicates the interpretation of echocardiographic scans and images obtained using other modalities.

Management of uremic and dialysis-related pericarditis in patients in hemodynamically stable condition is intensive dialysis.[17] Hemodialysis is preferred over PD because of the higher clearance rates of the former, recognizing the risks of tamponade from heparin and rapid fluid shifts. Hemodialysis is effective in the majority of cases of dialysis-related pericarditis, usually after 10 to 14 days. Systemic anticoagulation should be withheld if pericardiocentesis is being considered or effusion is worsening.[17] Indomethacin, colchicine, and steroids are not useful for ESRD pericarditis. If pericardial effusion persists for longer than 10 to 14 days with intensive dialysis, anterior pericardiectomy is often used, with total pericardiectomy reserved for constrictive pericarditis.

HEMATOLOGIC COMPLICATIONS

ANEMIA

Anemia is multifactorial, caused by decreased erythropoietin, blood loss from dialysis, frequent phlebotomy, and decreased red blood cell survival times. In addition, the wide fluctuations in plasma blood volume seen in dialysis patients often cause factitious anemia. Without specific treatment, the hematocrit should stabilize at 15% to 20%, with

normocytic and normochromic red blood cells. Bone marrow shows erythroid hypoplasia, with little effect on leukopoiesis or megakaryocytopoiesis. Anemia is treated with regular infusions of human recombinant erythropoietin. Erythropoietin replacement therapy improves the quality of life for ESRD patients by increasing exercise capacity and tolerance.

COAGULOPATHY

The **bleeding diathesis** of ESRD patients increases the risks of GI tract bleeding, subdural hematomas, subcapsular liver hematomas, and intraocular bleeding. Several mechanisms, including decreased platelet function, abnormal platelet–vessel wall interactions, altered von Willebrand factor, anemia, and abnormal guanidinosuccinic acid–dependent production of nitric oxide, create uremic bleeding. The skin bleeding test is the best predictor of clinically important defects in hemostasis. Patients receiving aspirin or warfarin are at greater risk of major bleeding. Improvement in bleeding times is seen with infusions of **desmopressin,** 0.3 microgram/kg IV/SC (benefit in 1 hour), or **cryoprecipitate,** 10 units given over 30 minutes (benefit in 4 hours). **Conjugated estrogens,** 25 milligrams IV or 6 milligrams/kg/d (benefit in 6 hours), are also described as an option.[19] Tranexamic acid is another option.[19,20]

IMMUNE DISORDERS

Immunologic deficiency in ESRD patients results in high morbidity and mortality from infectious diseases. Depressed leukocyte chemotaxis and phagocytosis from many causes are the key features, along with abnormal T-cell activation. Dialysis does not improve the immune function and may exacerbate immunodeficiency by complement activation after exposure to the hemodialysis filter membrane.

RENAL BONE DISEASE

As the glomerular filtration rate falls, phosphate excretion decreases, which results in increased serum phosphate levels. When the calcium-phosphate product [Ca^{2+} (milligrams/dL) × PO_4 (milligrams/dL)] is higher than 70 to 80, **metastatic calcification** can ensue. Joint pain from **pseudogout** develops from calcification of synovial membrane–lined joints. Metastatic calcification in small vessels results in skin and finger necrosis, and life-threatening calcifications can occur in the cardiac and pulmonary systems. Short-term mortality rate is higher in ESRD patients with a calcium-phosphate product of >72. Treatment consists of the use of low-calcium dialysate and phosphate-binding gels.

β_2-MICROGLOBULIN AMYLOIDOSIS

Dialysis-related amyloidosis (β_2-microglobulin amyloidosis) can occur in dialysis patients >50 years of age and on dialysis for >10 years.[21] Advanced glycation end products appear central to the chronic inflammatory condition, leading to amyloidosis. Amyloid deposits are found in the GI tract, bones, and joints. Complications include GI perforation, bone cysts with pathologic fractures, and arthropathies, including carpal tunnel syndrome and rotator cuff tears. Patients with amyloidosis have higher mortality rates than do those without this disorder.

HEMODIALYSIS

TECHNICAL ASPECTS OF HEMODIALYSIS

Hemodialysis substitutes a filter for the glomerulus to produce an ultrafiltrate of plasma. Small amounts of IV heparin, 1000 to 2000 units, are used to prevent thrombosis at the vascular access site.[22] Hemodialysis sessions typically take 3 to 4 hours. Adjustment of the pressure gradient across the hemodialyzer filter during hemodialysis controls the amount of fluid removal (ultrafiltration). Solute removal (clearance) during hemodialysis depends on the filter pore size, the amount of ultrafiltration (solute drag), and the concentration gradient across the filter (diffusion). During hemodialysis, blood is removed from the vascular access site by large-bore needles (typically 15 gauge), circulated through the dialysis machine at rates of 300 to 500 mL/min, and returned to the patient. The dialysate usually flows at a rate of 500 to 800 mL/min through the dialysis filter in the direction opposite to blood flow.

COMPLICATIONS OF VASCULAR ACCESS

In cases in which a native artery or vein is not suitable for arteriovenous fistula creation, an interposing vascular graft made of an autologous vein, polytetrafluoroethylene, or bovine carotid artery must be used for vascular access. Such grafts generally are associated with a higher complication rate and shorter functional life expectancies than are natural arteriovenous fistulas. The third form of vascular access for hemodialysis is the use of tunneled-cuffed catheters. The most common site for tunneled-cuffed catheter placement is the right internal jugular vein. Because of the cuff, tunneled-cuffed catheters should not be removed by pulling.

Complications of vascular access account for more inpatient hospital days than any other complication of hemodialysis.[23] The most common complications of hemodialysis vascular access are failure to provide adequate flow (300 mL/min) and infection.[23] If referred to the ED for inadequate access flow that impairs dialysis, missing a single session should not result in uremic encephalopathy, allowing emergency dialysis for those with hyperkalemia and fluid overload in the ED (see Chapter 88, "Acute Kidney Injury").

INADEQUATE FLOW

Thrombosis and stenosis of the vascular access are the most common causes of inadequate dialysis flow. Grafts generally have a higher rate of stenosis than do fistulas. Stenosis or thrombosis presents with loss of bruit and thrill over the access. Stenosis and thrombosis can be treated within 24 hours by angiographic clot removal or angioplasty. Thrombosis of vascular access can also be treated with direct injection of alteplase, usually in conjunction with a vascular surgeon.[24]

INFECTIONS

Vascular access infections occur in 2% to 5% of arteriovenous fistulas and approximately 10% of grafts over their functional lifetimes. Infected arteriovenous fistulas are at increased risk of bleeding.[25] Patients with an infected access often present with fever, hypotension, or an elevated WBC count. The classic signs of infection of pain, erythema, swelling, and discharge from an infected vascular access are often missing. Dialysis catheter–related bacteremia is very common and potentially life threatening. After 6 months with a dialysis catheter, approximately half of patients develop bacteremia, with a serious complication (death, endocarditis, osteomyelitis, septic arthritis, epidural abscess) occurring in 5% to 10% of patients with bacteremia. Most authorities prefer a trial of IV antibiotics in an attempt to maintain the dialysis access before removal, the latter often done if there is ongoing fever after 2 to 3 days of antibiotics.[26] To narrow the potential source of bacteremia, peripheral and catheter blood samples for culture are drawn simultaneously. A fourfold higher colony count in the catheter blood culture than in the peripheral blood culture suggests the catheter as the source of bacteremia.

The most common infecting organism is *Staphylococcus aureus*, followed by gram-negative bacteria. Patients with access infections usually require hospital admission, and vancomycin is the drug of choice (15 milligrams/kg or 1 gram IV) because of its effectiveness against methicillin-resistant organisms and long half-life (5 to 7 days) in dialysis patients.[16,27] An aminoglycoside (gentamicin 100 milligrams IV initially and after each dialysis treatment) is added if gram-negative organisms are suspected, but the patient is monitored closely because of toxicity. Alternatives or adjuncts to IV antibiotics include removal and delayed replacement of the catheter, catheter exchange over a guidewire, and the use of antimicrobial/citrate lock solutions, although limited controlled data exist.

BLEEDING

Life-threatening hemorrhage from a vascular access is a rare but serious complication. Hemorrhage can result from aneurysms, anastomosis

TABLE 90-2 Treatment Options for Control of Vascular Access Hemorrhage

Technique	Comments
Direct pressure to hemorrhage site using gloved finger initially	Hold for 5–10 min minimum, longer if needed.
Absorbable gelatin sponges soaked in reconstituted thrombin, or chemical thrombotic [HemCon®]	Apply pressure after application for 10 min minimum.
Protamine given at a dose of 0.01 milligram per unit of heparin dispensed during dialysis	If the dose of heparin is unknown, protamine, 10–20 milligrams, will be sufficient to reverse the typical 1000–2000 units of heparin given at dialysis.
Urgent consultation to vascular surgery	The need to consult vascular surgery depends on the severity and duration of the bleeding and failure of simple methods.
Tourniquet proximal and distal to vascular access	Temporizing measure only, awaiting vascular surgery, or in preparation to place a suture. Examine for ulceration of fistula wall; ulcerated fistula may not hold suture.
Apply figure-of-eight suture	Tourniquets proximal and distal to bleeding will help complete this procedure.
If all other measures fail, consider tranexamic acid 10 milligrams/kg IV	Consult a vascular surgeon prior to administration if you are able to make verbal contact.
Consider implementing massive transfusion protocol if blood loss is severe	Administration of blood may be needed, especially in the case of preexisting anemia.

rupture, and over-anticoagulation. Control bleeding immediately with manual pressure applied to the puncture sites for 5 to 10 minutes, and observe the patient for 1 to 2 hours if ceased. **Table 90-2**[28,29] lists further options for control of hemorrhage. Consult a vascular surgeon when simple methods fail to control hemorrhage or large-volume bleeding occurs.

ULCERATED HEMODIALYSIS FISTULA

An ulceration may develop due to repeated punctures of the fistula wall, yielding significant weakening and a propensity to bleed or rupture. Placing a figure-of-eight suture may rip the vessel wall rather than close the bleeding point.[30] Brisk bleeding from a fistula may obscure an ulceration until bleeding is controlled with proximal and distal tourniquets. Examine the integrity of the vessel prior to placing a figure-of-eight suture.

VASCULAR ACCESS ANEURYSMS

Aneurysms result from repeated punctures; true aneurysms are very rare. Most aneurysms are asymptomatic; however, when hemorrhage occurs, it is frequently life threatening.[31] Control bleeding using a tourniquet (or a blood pressure cuff) proximal and distal to the access site. Call for emergency consultation to vascular surgery.[16]

VASCULAR ACCESS PSEUDOANEURYSMS

Pseudoaneurysms result from subcutaneous extravasation of blood from puncture sites. Signs are bleeding and infection at the access site. Arterial Doppler US studies identify an aneurysm or pseudoaneurysm, and if detected, a vascular surgeon should be consulted.

VASCULAR INSUFFICIENCY

Vascular insufficiency of the extremity distal to the vascular access occurs in approximately 1% of all patients. This "steal syndrome" is the result of preferential shunting of arterial blood to the venous side of the access. Signs and symptoms are exercise pain, nonhealing ulcers, and cool, pulseless digits. Doppler US or angiography is the best diagnostic approach, and treatment is surgical. Consult vascular surgery.[16]

HIGH-OUTPUT HEART FAILURE

High-output failure can occur when >20% of the cardiac output is diverted through the access. The **Branham sign**, a fall in heart rate after temporary access occlusion, is useful for detecting this complication. Doppler US can accurately measure access flow rate and establish the diagnosis. Surgical banding of the access is the treatment of choice to decrease flow and treat heart failure.

COMPLICATIONS DURING HEMODIALYSIS

HYPOTENSION

Low blood pressure is the most frequent complication of hemodialysis, occurring during 50% of treatments (**Table 90-3**). Fluid removal during hemodialysis averages 1 to 3 L over a 4-hour session, but removal of up to 2 L/h is possible. Maintenance of a normal blood pressure during ultrafiltration depends on cardiovascular compensatory mechanisms and refilling of the vascular space by fluid shifts from the interstitial and intracellular compartments. Excessive ultrafiltration due to underestimation of the patient's ideal blood volume (dry weight) is the most common cause of intradialytic hypotension. Optimal dry weight is often clinically defined when hypotension prevents further fluid removal.

Myocardial dysfunction from ischemia, hypoxia, arrhythmias, and early pericardial tamponade are in the differential diagnosis of intradialytic hypotension. Abnormalities of vascular tone from sepsis or antihypertensive medications also contribute to hypotension. Vascular refilling can be enhanced by improving nutrition, performing ultrafiltration before dialysis, and increasing the sodium concentration of the dialysate solution.

The timing of intradialytic hypotension is often helpful in formulating a differential diagnosis. *Hypotension early in the dialysis session* is usually due to preexisting hypovolemia. Predialysis losses should be suspected when the patient starts hemodialysis at a weight below his or her dry weight; consider GI bleeding, sepsis, vomiting, diarrhea, or decreased intake of salt and water. Intradialytic blood loss can occur from blood tubing or hemodialyzer filter leaks. Hypotension near the end of dialysis is usually the result of excessive ultrafiltration, but pericardial or cardiac disease is possible.

Intradialytic hypotension produces nausea, vomiting, and anxiety. Orthostatic hypotension, tachycardia, dizziness, and syncope may occur. Treatment of intradialytic hypotension includes halting hemodialysis and placing the patient in the Trendelenburg position. If hypotension persists, the patient is given salt by mouth (broth) or normal saline, 100 to 500 mL IV. If these conservative measures fail, a more extensive evaluation is the next step.

When the patient is transferred to the ED for further evaluation, assess for adequacy of volume status, impairment of cardiac function, pericardial disease, infection, and GI bleeding. Further volume expansion or the administration of vasopressors to support blood pressure may require invasive hemodynamic monitoring in an intensive care setting.

DIALYSIS DISEQUILIBRIUM

Dialysis disequilibrium is a clinical syndrome occurring at the end of dialysis and is characterized by nausea, vomiting, and hypertension, which can progress to seizure, coma, and death.[28] Dialysis disequilibrium

TABLE 90-3 Differential Diagnosis of Peridialytic Hypotension

- Excessive ultrafiltration
- Predialytic volume loss (GI losses, decreased oral intake)
- Intradialytic volume loss (tube and hemodialyzer blood losses)
- Postdialytic volume loss (vascular access blood loss)
- Medication effects (antihypertensives, opiates)
- Decreased vascular tone (sepsis, food, dialysate temperature >37°C or 98.6°F)
- Cardiac dysfunction (left ventricular hypertrophy, ischemia, hypoxia, arrhythmia, pericardial tamponade)
- Pericardial disease (effusion, tamponade)
- Sepsis

occurs when large solute clearances occur during hemodialysis, as during the patient's first dialysis session or during hypercatabolic states. The cause of dialysis disequilibrium is believed to be cerebral edema from an osmolar imbalance between the brain and the blood. During high solute removal, the blood has a transiently lower osmolality than the brain, which favors water movement into the brain and causes cerebral edema. This condition can be prevented by limiting solute clearance when initiating hemodialysis. Treatment is stopping dialysis and administering 5 mL of 10% to 23% sodium chloride or mannitol 0.25 gram/kg IV to increase serum osmolality.[16]

AIR EMBOLISM

Air embolism is always a risk when blood is pumped through an extracorporeal circuit. The clinical presentation depends on the patient's body position at the time of the incident. If the patient was sitting, air passes retrograde through the internal jugular vein to the cerebral circulation, causing increased intracranial pressure and neurologic symptoms. In a recumbent position, air goes into the right ventricle and pulmonary circulation, causing pulmonary hypertension and systemic hypotension. The passage of air through a right-to-left shunt (e.g., patent foramen ovale) creates an arterial air embolism, which can lodge in the coronary or cerebral circulation, causing myocardial infarction or stroke.

Symptoms of an air embolism are acute dyspnea, chest tightness, and loss of consciousness, and sometimes full cardiac arrest. Signs include cyanosis and a churning sound in the heart from air bubbles in the blood. If air embolism is suspected, **clamp the venous blood line and place the patient supine.** Give 100% oxygen to aid reabsorption of the air.[28] Other therapies for vascular air embolism include percutaneous aspiration of air from the right ventricle, IV administration of steroids, full heparinization, and hyperbaric oxygen treatment.

ELECTROLYTE DISTURBANCES

Electrolyte abnormalities can occur due to errors in mixing the dialysate concentrate with water, which results in rapid osmolar shifts and hemolysis. However, the most common electrolyte disturbance that requires intervention is **hyperkalemia**[6]; see Chapter 17, "Fluids and Electrolytes," for management. **Hypoglycemia** occurs in diabetic and nondiabetic ESRD patients. In addition to drugs, malnutrition and sepsis are important causes of hypoglycemia.

ED EVALUATION OF HEMODIALYSIS PATIENTS

Patients treated with hemodialysis may develop complications related to ESRD or hemodialysis, or these conditions may be incidental to the reason for the ED visit. The medical history is very important, because many of the same diseases that caused ESRD (e.g., hypertension, diabetes) persist after the patient's kidneys have failed. The patient should be asked about the ESRD and hemodialysis (**Table 90-4**). Repeated episodes of intradialytic hypotension may provide important early clues to pericardial tamponade or myocardial ischemia. Repeated access infections may represent a worsening immunologic status.

TABLE 90-4 Key Historical Elements for Hemodialysis Patients

- Cause of end-stage renal disease
- Dialysis schedule: any missed dialysis sessions?
- Still producing urine?
- Recent complications of hemodialysis
- Dry weight, baseline laboratory values, and vital sign values
- Average intradialytic weight gain
- Does patient usually make dry weight by end of hemodialysis?
- Does patient experience intradialysis hypotension? (Timing of hypotension?)
- Which vascular access is currently functioning?
- Symptoms of uremia
- Retention of native kidneys?

TABLE 90-5 Key Elements of Physical Examination of Hemodialysis Patients

- Vital signs: fever, tachycardia, hypotension, hypoxia
- Vascular access: bruit, thrill, erythema, warmth, swelling, tenderness, discharge, bleeding
- Branham sign: bradycardia in response to compression of an arteriovenous fistula
- Cardiac: signs of heart failure, murmurs, muffled (distant) heart sounds
- Neurologic: mental status changes, peripheral neuropathy, asterixis

Identify the hemodialysis schedule; most patients in the United States are on an every-other-day schedule, with each session lasting approximately 4 hours. Certain centers use high-flux hemodialysis machines with higher blood flows, allowing shorter sessions. Note all missed sessions and reasons, allowing identification about medical or social issues that need to be addressed.

Dialysis patients are often knowledgeable about their dry weights and baseline laboratory test results. If not, the center the patient uses should be contacted and asked about the dry weight, average interdialytic weight gains, and any recent complications. Ask about uremic symptoms as markers of inadequate hemodialysis, and ask if the native kidneys are retained since these can be sources of hypertension, infection, and nephrolithiasis.

Examine the access site (**Table 90-5**), looking for the presence of flow by identifying a bruit and thrill. The classic signs of infection—erythema, swelling, tenderness, and purulent discharge—are often limited until the infection is far advanced. Look for congestive heart failure, effusion, or high-output fistula-related heart failure; peripheral edema, hepatojugular reflux, and jugular venous distention can be present in both fluid overload and pericardial tamponade. A loud cardiac murmur may just represent increased flow secondary to anemia or the arteriovenous access. Neurologic dysfunction in hemodialysis patients is generally diffuse and nonfocal. Any focal neurologic findings require neuroimaging. Assess for GI bleeding with rectal examination and occult blood testing and obtain Doppler US examination if any question about vascular insufficiency, aneurysm, or pseudoaneurysm exists.

PERITONEAL DIALYSIS

TECHNICAL ASPECTS OF PERITONEAL DIALYSIS

In PD, the peritoneal membrane is the blood–dialysate interface. The amount of ultrafiltration is determined by osmotic pressure differences between the blood and dialysate, which are manipulated by changing the dialysate glucose concentration. Similar to hemodialysis, PD relies on the separate processes of clearance (solute removal) and ultrafiltration (fluid removal) to replace the functions of the nephron. Most solute removal occurs via diffusion down chemical gradients established by altering dialysate electrolyte concentrations. Dialysate is supplied in 1.5% and 4.25% glucose formulations, which can be alternated to increase or decrease ultrafiltration.

Typical PD regimens use four exchanges daily, with 2 L of dialysate infused and left in place for several hours before draining. During the day, approximately 8 L are infused and about 10 L are drained, for a removal of approximately 2 L/d of fluid. PD can be accomplished in an acute setting, over the long term via exchanges of solution throughout the day (continuous ambulatory PD), or through multiple exchanges at night while the patient sleeps (continuous cyclic PD).

COMPLICATIONS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

PERITONITIS

Peritonitis is the most common complication of PD, with an incidence of about one episode every 15 to 18 patient care-months.[32] Mortality rates from peritonitis range between 2.5% and 12.5%. Symptoms

TABLE 90-6 Key Historical Elements for Peritoneal Dialysis Patients

- Cause of end-stage renal disease
- Type of peritoneal dialysis (continuous ambulatory peritoneal dialysis vs. continuous cyclic peritoneal dialysis)
- Peritoneal dialysis parameters: concentration, number of exchanges per day
- Recent complications of peritoneal dialysis
- Baseline weight, laboratory values, and vital sign values
- Symptoms of uremia
- Retention of native kidneys?
- Still producing urine?

and signs of peritonitis in PD patients are fever, abdominal pain, and rebound tenderness. Cloudy effluent suggests peritonitis, confirmed by Gram stain, cell count, and culture. **The cell count in PD-related peritonitis is usually >100 leukocytes/mm,[3] with >50% neutrophils.** Results of the Gram staining are positive in only 10% to 40% of cases of culture-proven PD-related peritonitis. Organisms isolated in PD-related peritonitis are *Staphylococcus epidermidis* (approximately 40% of cases), *S. aureus* (10%), *Streptococcus* species (15% to 20%), gram-negative bacteria (15% to 20%), anaerobic bacteria (5%), and fungi (5%).[32]

Empiric therapy begins with a few rapid exchanges of fluid lavaged to decrease the number of inflammatory cells in the peritoneum, with added heparin (500 to 1000 units/L dialysate) to decrease fibrin clot formation. A first-generation cephalosporin (e.g., cephalothin) can be mixed with the dialysate, 500 milligrams/L with the first exchange and 200 milligrams/L with subsequent exchanges. In penicillin-allergic patients, use vancomycin 500 milligrams/L and maintenance doses of 50 milligrams/L per exchange. If seeking gram-negative coverage, add gentamicin 100 milligrams/L and maintenance doses of 4 to 8 milligrams/L per exchange. Most recommend treating for 7 days after the first negative culture results, usually resulting in a total of 10 days of therapy. Admission decisions are based on the patient's clinical appearance. Parenteral antibiotics are not used.

ABDOMINAL WALL COMPLICATIONS

PD Access Site Complications Infections around a PD catheter present with pain, erythema, swelling, and discharge around the catheter exit site. The most common causative bacteria are *S. aureus* and *Pseudomonas aeruginosa*. Empiric therapy consists of an oral first-generation cephalosporin or ciprofloxacin for outpatient therapy. Refer patients to their continuous ambulatory PD centers for follow-up the next day. **Abdominal wall hernias** occur in 10% to 15% of PD patients.[33] Immediate surgical repair of pericatheter hernias is common because of the high risk of incarceration.

ED EVALUATION OF PERITONEAL DIALYSIS PATIENTS

Table 90-6 lists important elements of patient history for PD patients. As with hemodialysis patients, the disease that caused the renal failure frequently persists.

The physical examination focuses on the abdomen: signs of infection of the peritoneum, tunnel, and exit site should be identified (**Table 90-7**).

TABLE 90-7 Key Elements of Physical Examination of Peritoneal Dialysis Patients

- Abdominal examination: inspection for hernia, auscultation of bowel sounds, test for rebound tenderness
- Peritoneal catheter: examination of surrounding skin, palpation of tunnel

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 91

Urinary Tract Infections and Hematuria

Kim L. Askew

URINARY TRACT INFECTIONS

In 2015, urinary tract infection (UTI) was the seventh most common diagnosis in women older than 15 years of age presenting to EDs.[1] Between 2006 and 2009, 10.8 million patients were evaluated in EDs due to UTIs, with 1.8 million admissions.[2] Most visits for UTIs occur in younger women, with nearly half of all women experiencing a UTI during their lifetime.[3] Starting at age 50, men experience an increasing frequency of UTIs as they grow older due to prostatic hypertrophy, debilitation, and instrumentation for relief of urinary obstruction.[4] All age groups from neonates to the elderly are affected, with greater risks in special populations (see Chapter 135, "Urinary Tract Infection in Infants and Children," and Chapter 99, "Comorbid Disorders in Pregnancy").

PATHOPHYSIOLOGY AND DEFINITIONS

UTIs can be grouped based on the anatomic site involved as well as patient characteristics. These classifications are important when determining treatment modalities.

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria is defined by several criteria:

1. The presence of >100,000 (>10^5) colony-forming units (CFU)/mL of a single pathogen on two successive clean-catch urine cultures in a woman without symptoms.[5]
2. The presence of >100,000 (>10^5) CFU/mL on one clean-catch urine culture in asymptomatic men.
3. The presence of 100 CFU/mL of a single isolate in a catheterized urine specimen in a patient without symptoms.

Prevalence of asymptomatic bacteriuria is 3.5% in the general population, but can be up to 10% in pregnant woman, 30% in male and 55% in female residents of nursing homes, and up to 100% in patients with indwelling catheters for more than 1 month.[4] Treatment of asymptomatic bacteriuria is recommended only in pregnant women (see Chapter 99, "Comorbid Disorders in Pregnancy") and in patients immediately prior to invasive urinary procedures in which mucosal bleeding may occur.[5]

URETHRITIS AND CYSTITIS

Infections of the lower urinary tract include urethritis and cystitis. *Acute cystitis* is an infection and inflammation isolated to the bladder. Cystitis from an infection typically starts with colonization of the urethra by a pathogen from the GI system, which migrates into the bladder. Cystitis is typically diagnosed clinically by presence of dysuria, urinary frequency, and hematuria. Urine cultures in as many as 30% to 50% of women with cystitis have 100 to 10,000 CFU/mL, which may be reported as negative by some laboratories.[6] *Urethritis*, commonly associated with sexually transmitted diseases, presents with similar symptoms but typically is associated with a discharge, lesions, or irritation. In women who have dysuria and urinary frequency without vaginal discharge or irritation, the probability of cystitis increases to greater than 90%.[7]

PYELONEPHRITIS

Pyelonephritis is an infection of the upper urinary tract. *Acute pyelonephritis* is infection of the renal parenchymal and pelvicalyceal system. Pyelonephritis is differentiated from cystitis primarily by clinical findings: a syndrome of flank pain or costovertebral angle tenderness, with or without fever, in the setting of a positive urine culture of 10^5 CFU/mL, and frequently other systemic symptoms such as nausea or vomiting.[8-11] Infections of the upper urinary tract can progress into three patterns of renal infection not commonly considered part of the UTI spectrum: acute bacterial nephritis, renal abscess, and emphysematous pyelonephritis. These diagnoses are made based on imaging studies performed in patients who have an inadequate or atypical response to treatment for presumed acute pyelonephritis.

UNCOMPLICATED URINARY TRACT INFECTION

***Uncomplicated UTI* is a UTI in a patient without structural or functional abnormalities within the urinary tract or kidney parenchyma, without relevant comorbidities that place the patient at risk for more serious adverse outcome, and not associated with GU tract instrumentation.**[6,8-11] This classification is limited to young, healthy, nonpregnant women with normal anatomic and functioning urinary tracts. Women are more susceptible than men to UTIs due to a shorter urethra for uropathogenic bacteria to ascend. The traditional diagnostic criterion dating from 1960 had been a positive urine culture of 10^5 CFU/mL; however, in symptomatic patients, low-colony-count infections with $\geq 10^2$ to 10^3 CFU/mL are clinically valid.[6,8,10]

COMPLICATED URINARY TRACT INFECTION

***Complicated UTI* is infection involving a functional or anatomically abnormal urinary tract or infection in the presence of comorbidities that place the patient at risk for more serious adverse outcomes.**[9] Risk factors for complicated UTI, including UTI in males, are listed in **Table 91-1**.[9,10] The diagnostic criterion is the isolation of 10^5 CFU/mL of urine culture. Unfortunately, patients with complicated UTIs are a very heterogeneous group, and few clinical trials have been conducted to guide management. In general, patients in this group are more likely to be infected with resistant organisms.[8,11] Although older literature categorized pyelonephritis as a complicated UTI, current guidelines do not.[9,11] *Uncomplicated pyelonephritis* refers to the clinical syndrome of fever and flank pain or tenderness with or without vomiting in a woman with an anatomically normal urinary tract without comorbidities. However, the recommended treatment of women with uncomplicated pyelonephritis is similar to recommendations for patients with complicated UTI (see "Treatment" later in the chapter).

Catheter-associated UTI (CAUTI) refers to a UTI occurring in a person whose urinary tract is currently catheterized, or has been within the previous 48 hours.[10,12] CAUTI is one of the most common healthcare-acquired infections due to common use of urethral catheters in both acute care and long-term healthcare facilities.[13] The best way to prevent infections after catheterization is to perform catheterization only for strict indications. As the duration of catheterization lengthens, the risk of bacteriuria increases. Identification of bacteriuria is complicated by contaminated biofilm along the catheter. Patients with chronic catheters often have repetitive exposures to antibiotics and thus can develop antimicrobial-resistant organisms. Although a patient with a urinary catheter may have bacteriuria present, treatment for CAUTI is not indicated without additional symptoms. CAUTI is diagnosed when a patient has signs or symptoms compatible with a UTI with no other source identified and the presence of $\geq 10^3$ CFU/mL of one or more bacterial species from a catheter urine specimen or midstream voided specimen if the catheter has been removed in the prior 48 hours.[12]

TABLE 91-1 Risk Factors for Complicated Urinary Tract Infection (UTI)

Risk Factor	Comments
Male sex	In young males, dysuria is more commonly secondary to sexually transmitted disease; suspect underlying anatomic abnormality in men with culture-proven UTI.
Anatomic abnormality of the urinary tract or external drainage system	Indwelling urinary catheter, ureteral stent, nephrolithiasis, neurogenic bladder, polycystic renal disease, or recent urinary tract instrumentation.
Recurrent UTI plus additional risk factor(s)	Recurrent UTI is common in patients with anatomic or functional abnormalities of the urinary tract; however, recurrent infection alone is not a criterion for complicated UTI.
Advanced age in men	Presence of prostatic hyperplasia, recent instrumentation, or recent prostatic biopsy.
Nursing home residency	With or without indwelling bladder catheter.
Neonatal state	See Chapter 135, "Urinary Tract Infection in Infants and Children."
Comorbidities	Diabetes mellitus, sickle cell disease, others.
Pregnancy	See Chapter 99, "Comorbid Disorders in Pregnancy."
Immunosuppression	Active chemotherapy, acquired immunodeficiency syndrome, immunosuppressive drugs.
Advanced neurologic disease	Spinal cord injuries, stroke with disability, others.
Known or suspected atypical pathogens	Non–*Escherichia coli* infections.
Known or suspected resistance to typical antimicrobial agents for UTI	Resistance to ciprofloxacin predicts multidrug resistance.

RECURRENT URINARY TRACT INFECTION

Recurrent UTI is defined as two uncomplicated UTIs in 6 months or three or more uncomplicated UTIs in the preceding 12 months.[14,15] Recurrent UTIs can be classified into two different categories that affect treatment decisions: relapse and reinfection. **Relapse of UTI is a recurrence of a UTI within 2 weeks of treatment completion caused by the same organism** from a focus within the urinary system. **Reinfection is a recurrent UTI caused by a different bacterial isolate** or by previously isolated bacteria after a negative intervening culture or a period of >2 weeks between infections.[13] Reinfection is more common than relapse. Genetic, anatomic, and behavioral factors can lead to increased risk for uncomplicated UTIs. The strongest behavioral risk factors for recurrent UTI (in women) are the frequency of sexual intercourse and the use of a diaphragm and spermicide.[15,16]

MICROBIOLOGY

UTIs typically arise from ascending infection from the urethra to the bladder, although hematogenous and lymphatic spread can occur. Uropathogenic organisms often have adhesions, fibrillae, or pili that allow the bacteria to adhere to and invade the uroepithelium.[17,18] *Escherichia coli* remains the most common pathogen by a large margin (**Table 91-2**).[12,18]

First reported in 1983, but with an increase since 2000,[19] community-acquired extended-spectrum β-lactamase–producing *E. coli* has emerged as a small but growing source of antibiotic resistance, affecting approximately 4% to 6% of outpatients with UTI.[19-21] Emergence of this resistant isolate of *E. coli* has important implications for treatment (see "Treatment" later in the chapter)[20] and can increase mortality in those affected.[22]

CLINICAL FEATURES

Clinical features of UTI vary by anatomic site involved and the patient's risks for complicated UTI. Asymptomatic bacteriuria is a laboratory-based diagnosis (see earlier section, "Pathophysiology and Definitions").

URETHRITIS

In males, dysuria with a urethral discharge indicates urethritis (see Chapter 153, "Sexually Transmitted Infections"). UTI is uncommon in healthy young adult males, but if the clinical diagnosis does not suggest

TABLE 91-2 Etiologic Agents in Different Types of Urinary Tract Infection (UTI)

Uncomplicated UTI	*Escherichia coli* (75%) *Staphylococcus saprophyticus* *Klebsiella pneumoniae* *Enterococcus faecalis*
Complicated UTI	*E. coli* *Enterococcus* spp. *K. pneumoniae* *Candida* spp. *Staphylococcus aureus* *Proteus mirabilis* *Pseudomonas aeruginosa*
Catheter-associated UTI*	*E. coli* *Enterococcus* spp. Coagulase-negative *Staphylococcus* *Candida* spp. *P. aeruginosa* *P. mirabilis* *Morganella morganii*
Recurrent UTI	Same as above depending on patient risk factors

*Long-term catheters (>30 days) will typically have polymicrobial etiologies of catheter-associated UTI.

urethritis or prostatitis in a male with dysuria, bacteriuria is likely due to UTI. In women, *Chlamydia* infection should be suspected in the following settings: a new sexual partner, a partner with urethritis, examination findings of cervicitis, or low-grade pyuria with no bacteria seen on urinalysis. Concurrent gonorrhea is common with *Chlamydia* infections.

CYSTITIS

Symptoms and signs of cystitis are frequency, urgency, hesitancy, suprapubic pain, visible (gross) hematuria, and/or suprapubic tenderness. The nature and severity of symptoms are determined by the etiologic organism(s), the portions of the urinary tract involved, and the patient's ability to mount an immune and inflammatory response.[11] **A history of vaginal discharge or irritation is more often associated with vaginitis, cervicitis, or pelvic inflammatory disease than with UTI.** Fever is uncommon with simple cystitis.

PYELONEPHRITIS

Flank pain, costovertebral angle tenderness, or specific renal tenderness to deep palpation may be associated with cystitis because of referred pain. However, when these findings occur, especially in association with fever, chills, nausea, vomiting, or prostration, the clinical diagnosis is *acute pyelonephritis*.[8,11] Patients with pyelonephritis may or may not have coexistent symptoms of cystitis. The presentation of pyelonephritis may be subtle, and it might be difficult to distinguish lower from upper UTI, especially in patients who do not experience pain normally (those with spinal cord injury), immunocompromised patients, and the aged. A missed diagnosis of cystitis is unlikely to lead to patient deterioration[6]; in contrast, missed pyelonephritis could lead to untreated sepsis.

SEPSIS FROM URINARY TRACT INFECTION

Patients with a UTI may develop or present with sepsis. Patients with sepsis may or may not exhibit the symptoms listed earlier for cystitis or pyelonephritis as part of their presentation. Approximately 10% to 19% of patients treated for sepsis have an etiology from the genitourinary system.[23,24] Presentation, evaluation, and management of sepsis can be found in Chapter 151, "Sepsis."

COMPLICATED URINARY TRACT INFECTION

For patients at risk for complicated UTI (Table 91-1), the clinical features and the classic presenting signs and symptoms of UTI may vary widely or be entirely absent. Fever, pain, and an inflammatory response may be absent. Suspect UTI in more complicated cases involving patients with atypical and diverse signs and symptoms, including weakness, malaise, altered mental status, fever, and flank or abdominal pain. Guidelines suggest the following criteria be used to define symptomatic CAUTI: new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; flank pain; costovertebral angle tenderness; acute hematuria; and pelvic discomfort; and in those whose catheters have been removed, dysuria, urgent or frequent urination, or suprapubic pain or tenderness.[12] In patients with spinal cord injury, increased spasticity, autonomic dysreflexia, and sense of unease are also compatible with CAUTI.[12]

DIAGNOSIS

A definitive diagnosis of UTI combines appropriate historical findings with laboratory confirmation.[6,25] However, a clinical diagnosis of UTI is made in the ED based on history, physical exam, and supportive laboratory findings (rather than confirmatory culture) for the overwhelming majority of patients.[4,11] This clinical diagnosis is used to initiate treatment in most patients, many of whom will have cultures pending definitive confirmation. Regarding uncomplicated cystitis, a clinical diagnosis can be made with a moderate probability based on a history of dysuria, frequency, and urgency, in the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated UTIs.[26] However, the false-positive rate for the diagnosis of UTI based on history alone has been reported to be 33%.[25,27] Empiric treatment of uncomplicated cystitis based on history alone in select women continues to be advocated in the emergency medicine, family medicine, and general internal medicine literature,[4,26,28] while other authors advocate laboratory confirmation to reduce the growing problem of antibiotic resistance.[29-33] Delaying treatment while awaiting cultures is not practical in the ED and jeopardizes a large subset of patients who require treatment but may be lost to follow-up.

URINALYSIS

The *clean-catch, midstream voiding specimen* is as accurate as urine obtained by catheterization if the patient follows instructions carefully. If the sample is properly collected, it should contain no or few epithelial cells. **Bacteria in urine double each hour at room temperature, so urine should be refrigerated if not sent directly to the laboratory.** Catheterization is indicated if the patient cannot void spontaneously, is too ill or immobilized, or is extremely obese.

Visual inspection or assessment of the odor of the urine is unreliable in determining infection. **Table 91-3** lists normal reference values for urinalysis. UTI often results in positive dipstick test for protein in the urine, but this finding is not specific enough to be useful in diagnostic decision making to rule in infection.

Values for individual laboratories may differ from the listed norms in Table 91-3. Dipstick testing is performed on a fresh uncentrifuged urine. Urine for microscopic analysis is routinely centrifuged prior to analysis. If examination of uncentrifuged urine is desired, make a specific request to the laboratory to account for different normal values between centrifuged and uncentrifuged specimens.

TABLE 91-3 Normal Urinalysis Results

Value	Normal Range	Specimen Type
RBCs, female	0–5/HPF	Centrifuged specimen
RBCs, male	0–3/HPF	Centrifuged specimen
WBCs	0–4/HPF	Centrifuged specimen
Bacteria	None/HPF	Centrifuged specimen
Leukocyte esterase	None—dipstick test	Fresh urine
Nitrite	None—dipstick test	Fresh urine

Abbreviations: HPF = high-power field; RBCs = red blood cells.

NITRITE REACTION BY DIPSTICK TEST

The urine nitrite reaction has a very high specificity (>90%), and a positive result is very useful in confirming the diagnosis of a UTI caused by bacteria that convert nitrates to nitrite, primarily the coliform bacteria, including *E. coli*.[34] ***Enterococcus*, *Pseudomonas*, and *Acinetobacter* species do not convert nitrates to nitrites in the urine and therefore are not detected by the nitrite test.** Unfortunately, the urine nitrite reaction has a low sensitivity (~50%), so it is not always useful as a screening examination because a negative result does not exclude the diagnosis of UTI.[34]

LEUKOCYTE ESTERASE REACTION BY DIPSTICK TEST

Using positive culture results as the criterion standard, the leukocyte esterase urine dipstick test has an overall sensitivity of 62% to 98% and a specificity of 55% to 96% for identifying infection.[34] Performance varies greatly when different culture criteria for UTI are used. **A positive urinary dipstick nitrite or leukocyte esterase test result supports the diagnosis of UTI, but a negative test result does not exclude it in the correct clinical presentation.**

URINE WBC COUNT OR PYURIA BY MICROSCOPY

The assessment of pyuria using standard centrifuged urine is imperfect due to variable specimen preparation techniques. A WBC count of >5 cells/high-power field (HPF) in a centrifuged specimen from a symptomatic patient is abnormal. Although the combination of pyuria and bacteriuria is likely to be found with typical coliform infection, lower degrees of pyuria with or without bacteriuria may be clinically significant, especially in the presence of UTI symptoms.

In a symptomatic patient who has <5 WBCs/HPF in a centrifuged specimen, other causes of false-negative pyuria should be considered such as dilute precentrifuged urine, systemic leukopenia, or patient self-treatment with leftover antibiotics. Pyuria may be intermittent or absent if the patient has an obstructed and infected kidney. **In men, >1 or 2 WBCs/HPF in a centrifuged specimen can be significant when bacteria are present.** Urethritis and prostatitis are far more likely causes of pyuria in young males who are sexually active and complain of dysuria, regardless of the presence or absence of urethral discharge.

BACTERIURIA BY MICROSCOPY

Bacteriuria is a sensitive tool for detection of UTI in the symptomatic patient. **The presence of any bacteria on a Gram-stained specimen of uncentrifuged urine (>1 bacterium/HPF or 1000×) is significant and highly correlates with culture results of $>10^5$ CFU/mL.** For Gram-stained centrifuged specimens, >1 bacterium/HPF (1000×) is 95% sensitive and >60% specific to predict a culture with 10^4 CFU/mL. Both of these methods of looking for bacteria under the microscope fail to detect low-colony-count UTI or infection caused by *Chlamydia*. False-positive results can occur when vaginal or fecal contamination is present. Female patients with symptoms suggestive of UTI *and* vaginal discharge or dyspareunia should have a pelvic examination to investigate for pelvic inflammatory disease.

COMBINED RESULTS OF DIPSTICK TESTING, URINE CELL COUNTS, AND HISTORICAL INFORMATION

Two meta-analyses found that classic historical findings of cystitis were weak predictors of positive culture or failed to predict cystitis.[30,31] Vaginal discharge weakly decreased the likelihood of cystitis; however, in both studies, diagnostic accuracy was significantly improved using dipstick testing, particularly a positive test for nitrites.[30,31] A 2013 systematic review of four ED-based studies pooled 948 patients using a reference culture threshold of 10^4 to 10^5 CFU/mL and found that no single historical variable of cystitis could rule in or rule out infection, but a dipstick test positive for nitrates, moderate pyuria, and/or bacteriuria were accurate predictors of a UTI,[29] effectively ruling in the diagnosis of UTI. However, **no single test or combination of testing results can effectively rule out UTI in women presenting to the ED with symptoms of cystitis.** Therefore, there will be a subset of women for whom test results are equivocal who should either be treated empirically or receive phone-in treatment based on culture, if follow-up cannot be ensured in 2 to 3 days.

URINE AND BLOOD CULTURE

For the patient with typical symptoms of *cystitis* or an *uncomplicated UTI* and "positive" findings on urinalysis—pyuria on microscopic examination, bacteria in a Gram-stained specimen, positive leukocyte esterase test result, and/or positive urine nitrite test result—urine culture is not required. The vast majority of patients respond to empiric therapy. Urine culture should be performed for the following patients: those with complicated UTI, pyelonephritis, sepsis, and recent antimicrobial therapy. If the patient is symptomatic, a single positive culture result is significant.

Results of blood cultures in patients admitted for clinical pyelonephritis are positive in up to 40% of cases; organisms in blood culture match those in urine culture in 97% of cases, and blood culture results usually do not alter management.[4] The primary indication for blood cultures in patients with suspected UTI is clinical sepsis.

IMAGING

Renal imaging studies in adults are not indicated in otherwise healthy patients with uncomplicated UTIs who can be managed as outpatients. Imaging is typically reserved for the investigation of patients suspected of alternative diagnoses that may explain the symptoms (i.e., nephrolithiasis) or after failure of conventional treatment in patients with severe symptoms suggesting an undiagnosed complication, such as renal abscess.[11] Other patients who should be considered for imaging include male, elderly, diabetic, severely ill patients, and those with acute worsening renal function (glomerular filtration rate <40 mL/min).[11] The kidneys can be imaged with bedside US to evaluate for obstruction and focal parenchymal abnormalities. Plain film radiography and US have poor sensitivity for detection of intrarenal gas formation in emphysematous pyelonephritis. If kidney or ureteral stones or emphysematous pyelonephritis are suspected, CT is the best imaging modality. US assessment of postvoid residual volume can be assessed to determine causes for repeat UTIs or risk for UTI. In men, a residual volume >180 mL predisposes to bacteriuria.[35] Data are not clear for women.

Table 91-4 lists the differential diagnosis for dysuria.

TABLE 91-4 Differential Diagnosis for Dysuria

Disorder	Comments
Urinary tract infection	Cystitis and pyelonephritis
Vaginitis/cervicitis	Infections (STD), atrophy, allergy
Urethritis	Infections (STD), allergy
Trauma	Trauma involving vagina, urethra, or bladder
Allergy	Typically a reaction to a hygienic product or spermicide
Bladder/urethral cancer	May have prior history of unexplained hematuria
Nephrolithiasis	May have prior history of kidney stone
Urethral stricture or obstruction	May have prior history of STDs
Uterine/bladder/vaginal prolapse	May be suggested by history of swelling or physical exam
Fistulas	Ileovesicular, urethral, urethrorectal, bladder
Urethral foreign body	Includes urethral stone disease
Urethral diverticulum	—
Cystocele	—
Chemical irritation	Spermicides, cleansing douches, feminine hygiene products
Behavioral symptom without detectable pathology	Consider previous rape, sexual abuse
Chronic disorders	Chronic cystitis, chronic urethritis

Abbreviation: STD = sexually transmitted disease.

TREATMENT

ACUTE CYSTITIS AND UNCOMPLICATED URINARY TRACT INFECTION

Selection of antibiotics depends on the organism suspected of causing the infection, the patient's ability to adhere to the treatment regimen, local resistance patterns, potential drug toxicity, and cost. The Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease published updated recommendations on antibiotics for uncomplicated UTI in 2010 (**Table 91-5**).[11] Updated European guidelines have been incorporated into recommendations.[10]

Table 91-5 contains treatment recommendations for three separate groups of patients with UTI: (1) uncomplicated lower tract disease, (2) complicated UTI or pyelonephritis, and (3) women with UTI symptoms in whom coexistent urethritis cannot be excluded.[10,12]

Trimethoprim-sulfamethoxazole continues to be recommended due to its limited adverse effects. Rates of resistance to trimethoprim-sulfamethoxazole are reported to be over the 20% threshold for treatment exclusion in the western and southern United States[37]; however, hospital culture data primarily reflect complicated UTI, and trimethoprim-sulfamethoxazole treatment may be successful for uncomplicated UTI.[38] Fosfomycin has less efficacy than short courses of other regimens. Within regions, local resistance patterns vary widely and change rapidly.

A 5-day course of extended-release nitrofurantoin is as effective as 3 days of trimethoprim-sulfamethoxazole therapy.[39] A single 3-gram dose of **fosfomycin** is a first-line choice for uncomplicated UTI[40] because the resistance rate is only 2%.[41] Both nitrofurantoin and fosfomycin are recommended oral agents in the event of extended-spectrum β-lactamase–producing *E. coli* infection, because resistance is reported to be only 6% and 3%, respectively.[41]

Because of bacterial resistance to traditional antibiotics used for UTI, use local sensitivities to guide the substitution of alternative agents such as cephalosporins. Third-generation cephalosporins are highly effective against enterobacteria, whereas first-generation cephalosporins are more effective against staphylococci. Amoxicillin-clavulanate is less effective than fluoroquinolones or oral cephalosporins for UTI due to enterobacteria. It also often leads to selection of *Klebsiella*. Aminopenicillins are therefore not recommended as first-line therapy in uncomplicated UTI.

If the patient has UTI symptoms and there is also suspicion of *Chlamydia* or *Neisseria gonorrhoeae* infection (cervicitis and/or salpingitis), antibiotic treatment is more complex. The patient should be tested and empirically treated for *Chlamydia* and *N. gonorrhoeae* (see Table 91-5; also see Chapter 153, "Sexually Transmitted Infections."[42,43] Fluoroquinolones were formerly recommended in this setting as a treatment for both cystitis and urethritis, but the Centers for Disease Control and Prevention no longer recommends them due to *N. gonorrhoeae* resistance. If coexistent cystitis is suspected in a patient with clinical urethritis, add a recommended treatment for cystitis (Table 91-5) to the treatment for urethritis; alternatively, culture the urine and treat for cystitis pending results.

TABLE 91-5 Guidelines for Outpatient Management of Urinary Tract Infection (UTI) Including Pyelonephritis (see * footnote for pregnancy)

Patient	UTI Type	Antimicrobial Regimens	Culture/Treatment Comments
Adult female	Lower (cystitis), uncomplicated	Nitrofurantoin monohydrate/macrocrystals, 100 milligrams twice a day × 5 d† *or* TMP-SMX DS (160/800 milligrams), 1 tab twice a day × 3 d *or* Fosfomycin, 3 grams in single dose *or* (where available) Pivmecillinam‡, 400 milligrams twice a day × 5 d (lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)	No initial culture is required. Consider community resistance; if >20%, use another agent. Amoxicillin-clavulanate, cefpodoxime-proxetil, cefdinir, and cefaclor in 3- to 7-d regimens are appropriate choices for therapy when other recommended agents cannot be used. The fluoroquinolones should be reserved for important uses other than acute uncomplicated cystitis.
Adult female or male	Lower (cystitis), upper (pyelonephritis), complicated	Ciprofloxacin, 500 milligrams twice a day × 5–7 d§ *or* Levofloxacin, 750 milligrams once a day × 5–7 d§ *or* Only if susceptibilities are known, consider: TMP-SMX DS (160/800 milligrams), 1 tab twice a day, 14 d minimum *or* Amoxicillin-clavulanate, 875/125 milligrams twice a day *or* Cefpodoxime, 400 milligrams twice a day × 7–14 d	Urine culture is advised. Consider community resistance; if >20%, use another agent. Coliforms are common. Treat for at least 7 d (mild symptoms) or 14 d (more severe symptoms, clear pyelonephritis). Admit if patient is significantly ill, unable to retain fluids or medications, or pregnant. Consider IV dose of ceftriaxone if sensitivity uncertain.
Adult female	Lower (urethritis)	Ceftriaxone, 250 milligrams IM *plus* Azithromycin, 1-gram single dose *or* Doxycycline, 100 milligrams twice a day × 7 d	Culture for *Chlamydia* and *Neisseria gonorrhoeae*. Fluoroquinolones no longer recommended for treatment of *N. gonorrhoeae* and *Chlamydia*. Consider adding a regimen listed above for cystitis if coexistent infections are strongly suspected.

Abbreviations: DS = double strength; TMP-SMX = trimethoprim-sulfamethoxazole.

*β-Lactams, vancomycin, nitrofurantoin, metronidazole, clindamycin, and fosfomycin are generally considered safe in pregnancy. Avoid fluoroquinolones and tetracyclines in pregnancy.[36]

†Nitrofurantoin is not effective against *Staphylococcus saprophyticus*.

‡Not currently available in the United States.

§Fluoroquinolones increase risk of rupture or tear of tendons and aortic wall; also increase risk of hypoglycemia and mental health side effects.

TABLE 91-6 Empiric Initial Treatment for Inpatient Management of Pyelonephritis and Complicated Urinary Tract Infection

- Ciprofloxacin, 400 milligrams IV every 12 h
- Ceftriaxone, 1–2 grams IV once daily
- Cefotaxime, 1–2 grams IV every 8 h
- Gentamicin or tobramycin, 3 milligrams/kg/d divided every 8 h, ± ampicillin, 2 grams every 6 h
- Piperacillin-tazobactam, 3.375 grams IV every 6 h
- Cefepime, 1–2 grams IV every 8 h
- Ertapenem, 1 gram IV every day
- Imipenem, 500 milligrams IV every 8 h
- Meropenem, 1 gram IV every 8 h

Note: Alternatives include ceftazidime, 1–2 grams IV every 8–12 h; amikacin, 7.5 milligrams/kg IV loading dose, then 5 milligrams/kg per dose every 8 h; and others based on local resistance and sensitivity patterns.

ACUTE PYELONEPHRITIS AND COMPLICATED URINARY TRACT INFECTION

Recommendations for antibiotic therapy and cultures for patients whose condition is stable enough for outpatient treatment are listed in Table 91-5. Antibiotics for inpatient management are listed in **Table 91-6**.[10,11] For patients with concern for sepsis, see Chapter 151, "Sepsis." After clinical improvement has been achieved with parenteral antibiotics, treatment should be changed to oral agents as listed in Table 91-5 or by culture sensitivities. Patients may require fluid resuscitation with crystalloids to replace fluid losses due to vomiting or sweating. Although treatment courses as short as 5 days have been studied in patients with pyelonephritis and catheter-associated infections,[6] guidelines recommend a total of 7 to 14 days of therapy for the majority, regardless of whether or not parenteral therapy is used.[10] Men with UTI without immunocompromise may have improved outcomes with therapy for 7 days, rather than 14 days.[44,45] For patients with sepsis syndrome, a total of 21 days of treatment may be required to eradicate bacteriuria.[10] In patients with a CAUTI, replacement or removal of the catheter should be performed prior to collection of cultures and initiation of antibiotics.[12]

RECURRENT INFECTION

Women presenting to the ED with an acute UTI and a history of greater than two UTIs in 6 months or greater than three UTIs in 12 months should be cultured, treated empirically, and referred to a primary care physician in 1 to 2 weeks for repeat culture and possible prophylaxis.[46-49] The patient can be treated with recommended treatments for uncomplicated cystitis from Table 91-5 including 3-day regimens,[47] unless the recurrence is a relapse (see earlier section, "Pathophysiology and Definitions"). Treat relapse with an alternative agent, such as one of those recommended for complicated UTI (Table 91-5).[47] Prophylaxis may take the form of continuous, postcoital, or intermittent self-treatment during symptomatic episodes.[46-48] Woman with recurrent UTI using spermicide with contraception should be encouraged to inquire about an alternative method of contraception.[47,48]

DISPOSITION AND FOLLOW-UP

The decision to admit a patient with UTI is based on age, host factors, and response to initial ED interventions. Admit patients who are unable to retain fluids and medication or those with systemic signs of UTI and a stone (see Chapter 94, "Urologic Stone Disease"), and choose antibiotics as listed in Table 91-6. Eighty-four percent of patients are discharged.[49] Healthy females tolerating fluids and medication with uncomplicated pyelonephritis are candidates for outpatient management.[49] Adjunctive therapies at discharge include increased fluids and frequent voiding to diminish tissue contact with bacteria. An oral bladder analgesic, such as phenazopyridine (200 milligrams PO three times daily), reduces dysuria. Cranberry juice appears to be mildly effective in reducing the incidence of recurrent infection.[50] There is no conclusive evidence that postcoital voiding prevents cystitis.[49] Ask patients to return to the ED if they experience increasing pain, fever, or vomiting. Consider systemic analgesics and antiemetics for patients with pyelonephritis.

Complications of acute pyelonephritis include acute papillary necrosis with possible ureter obstruction, septic shock, perinephric abscesses, and emphysematous pyelonephritis. See Chapter 151, "Sepsis," for the care of critically ill patients with UTI.

SPECIAL POPULATIONS

PREGNANCY

First-line treatment for asymptomatic bacteriuria and simple cystitis is either **amoxicillin** 500 milligrams PO two to three times daily for 3 to 7 days or **cephalexin** 500 milligrams two to four times daily for 3 to 7 days.[51] Recent studies have raised concerns about possible nitrofurantoin-linked birth defects. Although it is still a pregnancy class B medication, current American College of Obstetricians and Gynecologists guidelines recommend to avoid use of nitrofurantoin in the first trimester unless there are no other options available.[52] **See Chapter 99, "Comorbid Disorders in Pregnancy," for detailed discussion.**

PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION/ ACQUIRED IMMUNODEFICIENCY SYNDROME

In human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients, resistance to trimethoprim-sulfamethoxazole is increased due largely to its use in *Pneumocystis jiroveci* prophylaxis. Fluoroquinolones should be the initial antibiotic used for UTI in these patients unless urine culture and sensitivity test results are available to guide therapy. Most UTIs in HIV/AIDS patients are caused by typical pathogens or common sexually transmitted disease organisms. *Mycobacterium tuberculosis* is an infrequent cause of UTI in the HIV/AIDS population. Close outpatient follow-up (recheck in 1 week) and possible infectious disease consultation are warranted when treating UTI in this population (see Chapter 155, "Human Immunodeficiency Virus Infection").

HEMATURIA

INTRODUCTION AND EPIDEMIOLOGY

Hematuria is encountered in ambulatory and ED settings, either as a primary complaint of visible blood in the urine or an incidental finding on urinalysis. *Gross hematuria* is visible to the eye, whereas microscopic hematuria is a laboratory diagnosis. Other pigments, particularly myoglobin, may discolor the urine and simulate gross hematuria. UTI is the most common cause of hematuria associated with urgency, dysuria, and nocturia[29,30]; however, these symptoms are also common in the much smaller group of patients who ultimately are diagnosed with cancer of the urinary tract.[53-55] Painless hematuria is more often due to neoplastic, hyperplastic, and vascular causes.

It takes approximately 1 mL of whole blood per liter of urine to result in visible hematuria. Gross hematuria may also result in false proteinuria. The incidence of gross hematuria in the general population and in patients presenting to the ED is unknown. However, gross hematuria is more common in premenopausal women due to UTIs and contamination with menstrual blood.[56] The incidence of bladder cancer associated with gross hematuria rises with increasing age.

The American Urological Association defines *microscopic hematuria* as ≥3 red blood cells (RBCs)/HPF (400×) on a properly collected and centrifuged urinary specimen in the absence of an obvious benign cause.[57] Normal urine contains a small number of RBCs, usually too few to be detected by routine chemical dipstick testing or microscopic

TABLE 91-7 Most Common Causes of Hematuria

Cause	Associated Age
Urinary tract infections	Any age
Nephrolithiasis	Usually >20 years
Neoplasms	Typically >50 years (except Wilms')
Benign prostatic hypertrophy	Males >40 years
Glomerulonephritis*	Mostly young patients and children
Schistosomiasis†	Any—underdeveloped country inhabitant

*See Chapter 137, "Renal Emergencies in Children."

†See Chapter 162, "Global Travelers."

urinalysis. Population-based studies have found at least one episode of transient microscopic hematuria in 4% to 13% of individuals.

PATHOPHYSIOLOGY

Any process that results in infection, inflammation, or injury to the kidneys, ureters, bladder, prostate, male genitalia, or urethra may result in hematuria (**Tables 91-7** and **91-8**).[57]

In men >50 years old, tumors of the prostate or elsewhere in the ejaculatory system and benign prostatic hypertrophy are considerations when hematuria is present. In patients <40 years, common causes are infections and inflammatory conditions, including prostatitis, urethritis, sexually transmitted diseases, epididymo-orchitis, calculi with inflammation, and tuberculosis. Testicular tumors may occur in men younger than 50 years old.

False hematuria occurs when the urine appears bloody but dipstick test results are negative for blood and there are no RBCs on microscopic evaluation, or blood has been added to a previously blood-free specimen by the patient (**Table 91-9**). Free hemoglobin, myoglobin, or porphyrins in the urine result in a positive urine test strip reaction for blood.

CLINICAL FEATURES

A careful history, including information regarding sexual activity, recent urologic procedures, medications used, and HIV and tuberculosis risk factors, should be obtained. The patient's general health and condition, vital signs, abdomen, external genitalia, and prostate in males should be evaluated.

Initial hematuria is the appearance of blood at the beginning of micturition, with subsequent clearing, and suggests urethral disease including cancer. Gross hematuria more often indicates a lower tract cause.[29] In younger patients, microscopic hematuria is most often caused by nephrolithiasis or UTI.[29] In older patients, infections and nephrolithiasis remain common causes of hematuria; however, hematuria in patients >50 years old warrants follow-up because renal, bladder, and prostate cancer increase in frequency and may coexist with UTI or kidney stones.[53,57] Risk factors for uroepithelial cancer are age >50 years, male sex, smoking, family history of bladder cancer, occupational exposures in the chemical, rubber, or leather industries (e.g., exposure to dyes, benzenes, or aromatic amines), and excessive analgesic use.[53] Hematuria in a patient taking oral anticoagulants should not be attributed to the anticoagulant alone, because the incidence of underlying disease is up to 80% in patients referred to urology for evaluation.[53] Expanding abdominal aortic aneurysms may erode into the urogenital tract or cause inflammation or obstruction from direct pressure.

Malignant hypertension, embolic renal infarction, and renal vein thrombosis are other serious diagnoses that can cause hematuria. In pregnancy, hematuria can be associated with UTI, nephrolithiasis, or preeclampsia. Recent instrumentation of the urinary tract may produce hematuria.

The reported incidence of hematuria in HIV-infected patients is 18% to 50%. Causes include UTI, chlamydial and gonococcal urethritis, glomerulonephritis, neurogenic bladder, thrombocytopenia, subclinical uroepithelial Kaposi's sarcoma, and urethral trauma. However, in up to 80% of patients, no specific cause is found.

The physical examination should note the vital signs and the patient's appearance. Hypertension and edema imply nephrotic syndrome.

TABLE 91-8 Differential Diagnosis of Hematuria

Urologic (lower tract)
- **Any location**
  - Iatrogenic/postprocedure
  - Trauma
  - Infection
  - Stones/calculi
  - Erosion or mechanical obstruction by tumor
- **Ureter(s)**
  - Dilatation of stricture
- **Bladder**
  - Transitional cell carcinoma
  - Vascular lesions or malformations
  - Chemical or radiation cystitis
- **Prostate**
  - Benign prostatic hypertrophy
  - Prostatitis
- **Urethra**
  - Stricture
  - Diverticulosis
  - Foreign body
  - Endometriosis (cyclic hematuria with menstrual pain)

Renal (upper tract)
- **Glomerular**
  - Glomerulonephritis
  - Immunoglobulin A nephropathy (Berger's disease)
  - Lupus nephritis
  - Hereditary nephritis (Alport's syndrome)
  - Toxemia of pregnancy
  - Serum sickness
  - Erythema multiforme
- **Nonglomerular**
  - Interstitial nephritis
  - Pyelonephritis
  - Papillary necrosis: sickle cell disease, diabetes, NSAID use
  - Vascular: arteriovenous malformations, emboli, aortocaval fistula
  - Malignancy
  - Polycystic kidney disease
  - Medullary sponge disease
  - Tuberculosis
  - Renal trauma

Hematologic
- Primary coagulopathy (e.g., hemophilia)
- Pharmacologic anticoagulation
- Sickle cell disease

Miscellaneous
- Eroding abdominal aortic aneurysm
- Malignant hypertension
- Loin pain–hematuria syndrome
- Renal vein thrombosis
- Exercise-induced hematuria
- Cantharidin (Spanish fly) poisoning
- Bites or stings by insects and reptiles having venom with anticoagulant properties

TABLE 91-9 Causes of False Hematuria on Visual Inspection

- Munchausen's syndrome, malingering, drug seeking
- Patients may add blood to voided urine for secondary gain
- Medications
- NSAIDs, phenytoin, phenothiazines, quinine, rifampin, sulfasalazine, others
- Foods and dyes
- Beets, berries, rhubarb
- Serratia marcescens infection
- Amorphous urates
- Hemoglobinuria, myoglobinuria, porphyrins

A new heart murmur (endocarditis) or atrial fibrillation increases the likelihood of embolic disease and renal infarction. A full genital-urinary examination is essential for both males and females. Systemic signs need to be correlated to potential diseases that cause hematuria (Table 91-8).

DIAGNOSIS

Potential causes of hematuria are often suggested by considering the patient's age, sex, demographic characteristics, habits, potential risk factors, history of recent GU instrumentation, and comorbidities.[57]

LABORATORY TESTING

A clean-catch midstream urine collection is appropriate for most patients. Catheter-collected specimens are recommended for women with a vaginal discharge or menstrual or vaginal bleeding; however, urethral catheterization induces hematuria in 15% of patients. Brown or smoke-colored urine, along with dysmorphic RBCs, cellular casts, and proteinuria, suggests a glomerular source.[57] Red, clotted blood in the urine indicates a source below the kidneys.

A urine dipstick test for blood can detect as little as 150 micrograms/L of free hemoglobin, corresponding to 5 to 20 intact RBCs/mL on microscopic analysis. False-negative results may be obtained with urine dipstick tests for blood if the urine has a high concentration of ascorbic acid (>5 milligrams/dL) or a high specific gravity. False-positive results occur in the presence of free hemoglobin, myoglobin, or porphyrins.

For patients with a clinical picture that does not provide a clear cause of hematuria on dipstick analysis (or indication for an urgent evaluation), urinalysis with microscopy should be performed to confirm hematuria before further workup.[57] Hemorrhagic cystitis with invasive infection of the bladder wall by bacteria resulting in shedding and bleeding is a common cause of hematuria and resolves with appropriate antibiotic treatment.

For patients taking anticoagulants, obtain appropriate coagulation studies in the ED, with imaging at follow-up for older patients to exclude malignancy.

The finding of normal RBCs on microscopic examination of the urine together with bacteriuria and leukocytes in a young healthy patient supports UTI as the probable cause of hematuria. Additional laboratory studies may be needed depending on the results of the history, physical examination, and presumptive differential diagnosis. The presence of normal RBCs without evidence of infection should prompt further urologic evaluation to determine the site of bleeding; however, in stable patients without an urgent cause suggested by history and physical examination, an outpatient evaluation is appropriate.

IMAGING

Initial upper and lower urinary tract imaging for hematuria is now typically done with noncontrast helical CT or renal US.[57,58] Helical CT clearly delineates most renal tumors, obstructions, or stones and their precise location.[57,58] These tests can often be done by a follow-up physician.

Renal US is useful when screening for obstruction, hydronephrosis, or abdominal aortic aneurysm. It is the study of choice in pregnant patients with suspected nephrolithiasis. However, renal US rarely identifies or locates stones in the ureters that are not large enough to give findings of obstruction. Renal US also does not provide any assessment of renal function—normal enhancement and excretion of contrast by both kidneys. Helical CT with contrast provides this important information.

Gross hematuria in patients with blunt or penetrating trauma to the abdomen, flank, or back warrants an aggressive approach to identify the source of bleeding and to guide management (see Chapter 265, "Genitourinary Trauma").[55]

TABLE 91-10 Risk Factors for Significant Disease in Patients With Microscopic Hematuria

- Age >50 y
- Male sex
- History of gross hematuria
- Smoking history
- Occupational exposure to chemicals or dyes (benzenes or aromatic amines)
- Analgesic abuse
- History of pelvic irradiation
- Cyclophosphamide use
- Pregnancy
- Known malignancy
- Sickle cell disease
- Renal insufficiency

TREATMENT, DISPOSITION, AND FOLLOW-UP

Treatment of hematuria is directed at the cause (Tables 91-7 and 91-8). Outpatient management and referral for follow-up are appropriate for patients in hemodynamically stable condition without an apparent life-threatening cause of the hematuria. The urgency for follow-up depends on the presence of gross hematuria or risk factors for significant disease (**Table 91-10**).[57,59] Patients with gross hematuria or listed significant risk factors should ideally be reevaluated at follow-up within 2 weeks.

The American Urological Association guideline recommends referral to urology to assess for urinary tract malignancy in all patients >35 years of age with microscopic hematuria without an obvious benign cause.[57] Follow-up within 1 month is acceptable for patients with microscopic hematuria without significant risk factors. The American College of Physicians guidelines for hematuria recommend workup for all adults (18 year or older), including repeat assessment of urinalysis and consideration for CT imaging.[59] This workup can be managed by a primary care physician.

Gross hematuria may lead to intravesical clot formation and bladder outlet obstruction. See Chapter 92, "Acute Urinary Retention," for management.

Patients with intractable pain, intolerance of oral fluids and medications, significant comorbid illness, bladder outlet obstruction, evidence of hemodynamic instability, or possible life-threatening causes of hematuria should be admitted, and the appropriate specialist should be consulted.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 92

Acute Urinary Retention

David E. Manthey
David J. Story

INTRODUCTION AND EPIDEMIOLOGY

Acute urinary retention is a common painful urologic emergency characterized by an inability to pass urine, with lower abdominal distention or pain. Most patients with urinary retention are elderly men with benign prostatic hyperplasia.[1,2] The incidence and risk of this etiology increase with age, with 1 in 10 men in their 70s having an episode of acute urinary retention and 1 in 3 men having one in their 80s. There is a 20% recurrence rate within 6 months of an episode of urinary retention due to benign prostatic hyperplasia.[2] Acute urinary retention in women is relatively uncommon, accounting for only 3 out of 100,000 cases of acute urinary retention each year, with the most common causes being bladder masses, gynecologic surgery, and pelvic prolapse.[3]

PATHOPHYSIOLOGY

The voiding process, or micturition, involves the complex integration and coordination of high cortical neurologic (sympathetic, parasympathetic, and somatic) and muscular (detrusor and sphincter smooth muscle) functions. As the bladder fills, sensory input is transmitted to cortical centers in the brain, which responds by coordinating voluntary urination. The contraction of bladder detrusor muscle (by cholinergic muscarinic receptors) and relaxation of both the internal sphincter of the bladder neck and the urethral sphincter (through α-adrenergic inhibition) are both necessary for successful voiding.[4] Continent urine storage in the bladder requires both relaxation of the detrusor muscle (through β-adrenergic stimulation and parasympathetic inhibition) and contraction of the bladder neck and internal sphincter (through α-adrenergic stimulation).

Urinary retention is the inability to void voluntarily despite a distended bladder resulting from dysfunction of the detrusor muscle and/or coordination of the bladder outlet. If extrinsic compression is the cause of the outlet obstruction (e.g., benign prostatic hyperplasia), the patient may report a history of a weakened urine stream despite forceful and prolonged detrusor contraction. In chronic decompensation of urination, diminished detrusor muscle contractility is more pronounced, with a large amount of residual urine volume, compared to acute decompensation. After prolonged complete bladder outlet obstruction, postobstructive acute kidney injury follows.[5] Upon relief of prolonged obstruction, postobstructive diuresis occurs in 0.5% to 50% of acute urinary retention cases, depending on duration and comorbidities.[6] This form of diuresis represents the normal physiologic response to excess volume and solutes accumulated during the period of prolonged obstruction.[5] Absence of diuresis in patients with significant elevation in serum creatinine predicts poor kidney recovery.[7]

CLINICAL FEATURES

The most common presentation is an elderly male with inability to void for several hours and lower abdominal distention or pain, secondary to benign prostatic hyperplasia. Consider urinary retention in patients complaining of lower abdominal pain, even if they do not offer urinary complaints. Also consider urinary retention as an underlying risk factor when finding a urinary tract infection.

The causes of urinary retention (**Tables 92-1** to **92-3**) are categorized into several domains: obstructive, neurogenic, traumatic, infectious, operative, psychogenic, structural anomalies, and pharmacologic.[4,8-10] A detailed history and physical examination, especially the genitourinary and neurologic examination, supported by imaging, reveal the cause in the majority of patients.

Assess for a history of prostatism, prostate or urinary bladder cancer, nephrolithiasis, indwelling urethral catheter or injury to urethra, prostate surgery, bladder prolapse, pelvic radiation therapy, or recent general or spinal anesthesia. Obtain a history regarding urinary urgency, frequency, or hesitancy; decreased force and caliber of stream; terminal dribbling; nocturia; and incontinence (typically due to overflow phenomena). Elicit a detailed neurologic history, looking for a causative lesion from high cortical function down to peripheral nerves that determine end-organ function. Identify possible spinal cord injury by determining recent activities including any remote trauma. Inquire about Foley catheter insertion, cystoscopy, trauma, radiation therapy, or prior infection that may result in urethral stricture.

Review medication list for anticholinergic, sympathomimetic (common cold medications), nonsteroidal, and narcotic medications because these affect urinary flow via different mechanisms (**Table 92-3**).

Fever and hypotension are more suggestive of infection or sepsis than acute urinary retention. Alternatively, hypertension, tachycardia, and tachypnea may be pain related and may resolve after bladder decompression. On abdominal examination, palpitate or percuss from the epigastric area to the lower abdomen to identify a painful mass (distended bladder) in the lean patient. Examine the external genitalia to identify phimosis, paraphimosis, meatal stenosis or stricture, or evidence of urethral or penile trauma.

Perform digital rectal examination (either before or after relief of obstruction, depending on patient comfort) to evaluate the anal-rectal area and prostate, assessing anal tone, perineal sensation, prostate

TABLE 92-1 Gender-Specific Causes of Acute Urinary Obstruction

Men	Women
Obstructive Causes	**Obstructive Causes**
Benign prostatic hypertrophy*	Cystocele
Prostate cancer	Ovarian tumor
Phimosis	Uterine tumor
Paraphimosis	**Operative Causes**
Meatal stenosis	Incontinence surgery
Urethral strangulation	**Infectious Causes**
Infectious Causes	Pelvic inflammatory disease
Prostatitis	

*Most common cause.

TABLE 92-2 Causes of Acute Urinary Retention in Both Sexes

Obstructive Causes	**Extraurinary Causes**
Urethral stricture	Perirectal or pelvic abscesses
Bladder calculi	Rectal or retroperitoneal masses
Bladder neoplasm	Fecal impaction
Foreign body, urethral or bladder	Abdominal aortic aneurysm
Neurogenic Causes	**Psychogenic Causes**
Multiple sclerosis	Psychosexual stress
Parkinson's disease	Acute anxiety
Shy-Drager syndrome	**Infectious Causes**
Brain tumors	Cystitis
Cerebral vascular disease	Herpes simplex (genital)
Cauda equina syndrome	Herpes zoster involving pelvic region
Metastatic spinal cord lesions	Local abscess
Intervertebral disk herniation	**Operative Causes**
Neuropathy (diabetes, other causes)	Postoperative bleeding (clots)
Nerve injury from pelvic surgery	Epidural anesthesia
Postoperative retention	**Childhood Causes**
Traumatic Causes	Posterior urethral valves
Urethral injury	Rhabdomyosarcoma of the bladder
Bladder injury	Urethral atresia
Spinal cord injury	**Pharmacologic Agents (Table 92-3)**

TABLE 92-3 Pharmacologic Agents Associated With Urinary Retention

α-Adrenergic agents	Carbamazepine
Amphetamines	Decongestants
Androgens	Estrogens
Anesthesia agents	Hydralazine
Anticholinergics	Muscle relaxants
Antihistamines	NSAIDs
Antiparkinsonian agents	Opiates
Antipsychotic agents	Progesterone
Antispasmodics	Selective serotonin reuptake inhibitors
Benzodiazepines	Tetracyclic antidepressants
β-Adrenergic agents	Tricyclic antidepressants
Calcium channel blockers	

TABLE 92-4 Steps in Evaluation and Management of Acute Urinary Retention

Recognition	Recognize a patient with possible acute urinary retention.
Initial assessment	Obtain complete history and physical examination to identify underlying diseases and precipitating factors: obstructive, pharmacologic, infectious, neurogenic, traumatic, childhood, or psychogenic causes. Assess bladder volume with bedside US.
Initial stabilization	Place a urethral or suprapubic catheter.
Risk assessment	Assess for risk of recurrence, need for surgical intervention, and morbidity: age, severity of clinical presentation, causes, comorbidity, prostate size, postvoid residual, and maximum urine flow rate.
Need for inpatient care	Admit for treatment of significant underlying medical illness or precipitating factors. Consider malignancy, spinal cord compression or injury, unresolved hematuria, or urinary tract infection with possible sepsis.
Need for urologic consultation	Discuss with urology consultant in the event of urethral stricture, meatal stenosis, urethral injury, suspected prostate cancer, acute febrile prostatitis, or urologic postoperative complications.
Outpatient management	Acute urinary retention without significant comorbidities and without evidence of complications, such as bleeding, infection, or renal function impairment: discharge with Foley catheter, leg bag, and α-adrenergic receptor blocker (i.e., alfuzosin, 10 milligrams daily, or tamsulosin, 0.4 milligram daily), and follow up with urology in 3–7 d.

enlargement, stool impaction, or evidence of malignancy. A nodular or hard prostate may suggest prostate cancer, which need not be confirmed in the ED, but prompt follow-up should be recommended. Women with urinary retention should receive a pelvic examination to detect possible inflammatory lesions or pelvic or adnexal masses. Perform a neurologic examination to assess for a neurogenic cause. After successful drainage of the distended bladder, a repeat physical examination of the lower abdomen is indicated to evaluate for an unresolved extraurinary bladder problem (e.g., appendicitis) needing further management.

DIAGNOSIS

Bedside US can easily identify bladder distention. Measure bladder volume, and assess possible associated hydronephrosis. A urinalysis should be performed to assess for a urinary tract infection, which may be the cause or the result of the retention.

Beyond that, the need for further diagnostic tests will depend on the nature of the clinical presentation, precipitating factors, and the patient's comorbidities. Gross hematuria may indicate infection, bladder calculi, or urinary tract neoplasm. Hematuria secondary to the physical trauma of catheter insertion that clears over time is common (see Chapter 91, "Urinary Tract Infections and Hematuria"). A CBC should be checked for patients with massive hematuria or in those presenting as septic. Prolonged obstruction may result in impaired renal function and electrolyte imbalance, so consider obtaining renal function studies and serum electrolytes in patients with prolonged retention, underlying risk factors for kidney injury (diabetes, hypertension, prior renal insufficiency), or hydronephrosis on US. Formal abdominal CT may be indicated to identify pelvic or abdominal masses or bladder stones but is not routinely needed if symptoms resolve after catheter placement. Spinal imaging is needed if examination reveals concerns for cord compression or cauda equina.

TREATMENT

The goal of ED management is outlined in **Table 92-4**. Bladder decompression is most commonly by urethral or rarely by suprapubic catheterization. Difficulty placing a urethral catheter in males can result from urethral stricture, prostatic enlargement, or postsurgical bladder neck contractures. **If the patient recently underwent urologic surgery (e.g., radical prostatectomy or complex urethral reconstruction), consult the urologist before attempting catheter placement.**

URETHRAL CATHETERIZATION TECHNIQUE

Most catheters are made of latex, but silicone catheters are available for patients with latex allergy. The retrograde injection of 10 to 15 mL of water-soluble anesthetic lubricant (e.g., 2% lidocaine jelly) 5 to 10 minutes before inserting the catheter can alleviate patient discomfort (**Figure 92-1**). Retract the foreskin of an uncircumcised male when inserting the catheter, but remember to reduce the foreskin once the catheter is in place. Do not inflate the retention balloon until urine begins to flow through the catheter into the clear extension tube. **Severe pain with catheter balloon inflation may indicate it was inflated prior to entering the bladder and could cause urethral damage, in addition to not effectively draining the bladder**[11] (**Figure 92-2**). Forceful attempts at catheter removal with the balloon still inflated can cause edema and tears to the urethra, so take care to adequately secure the catheter to the thigh after insertion.

If urethral catheterization using a standard 14F to 18F Foley catheter fails, passing a specialized coudé catheter can be attempted. A coudé catheter is firmer and has an angled tip, which should be pointed anteriorly during insertion, that more naturally follows the anatomy of the urethra as it courses through the prostate.

Unsuccessful passage of a Foley catheter may be the result of stricture, external urethral compression, kinking of the catheter within the urethra, or the creation of a false lumen, where the catheter tunnels through the urethral wall into the surrounding soft tissue. If catheterization produces gross blood and severe discomfort without returning urine, remove the catheter after ensuring the balloon is deflated. Do not attempt reinsertion because a false passage may have been produced. Urology should be immediately consulted to assess for urethral trauma and for assistance performing alternative methods of bladder decompression, such as passage of a urethral guidewire or flexible filiforms or suprapubic catheterization.

SUPRAPUBIC CATHETERIZATION TECHNIQUE

Suprapubic catheterization can be performed in patients after failure of urethral catheterization if there is no obvious pelvic trauma or abnormal anatomy in the lower abdomen. This may be the only option to decompress an extremely painful, distended bladder when urethral catheterization is not possible. US-guided suprapubic catheterization has a low complication rate.[12]

Visualize the distended bladder with US and make sure no loops of bowel are present between the bladder and insertion site (**Figure 92-3**). The insertion site should be 3 to 4 cm superior to the pubic symphysis in the midline. Clean the area surrounding the insertion site with betadine or chlorhexidine and establish a sterile field. The skin and subcutaneous

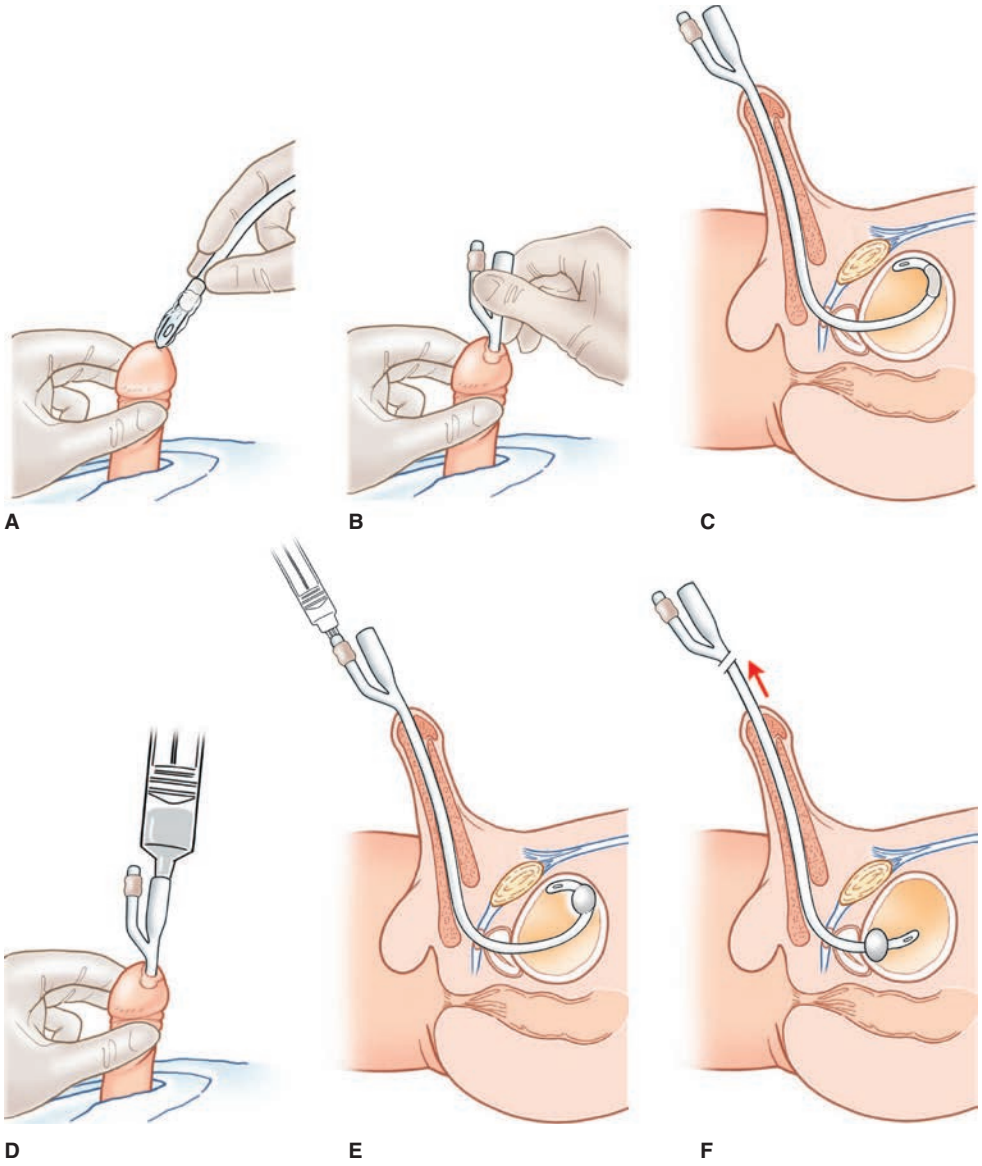

FIGURE 92-1. Urethral catheter insertion. **A.** Insert the lubricated catheter into the urethra. **B.** Advance the catheter until the ports are at the meatus. **C.** Cross-section of the male pelvis showing the distal catheter and cuff positioned within the bladder. **D.** Urine aspiration confirms proper placement of the catheter. **E.** If urine is flowing freely, inflate the balloon at the tip of the catheter. **F.** Gently withdraw the catheter to lodge the cuff against the bladder neck. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures,* 3rd ed. New York, NY: McGraw-Hill Education; 2019.]

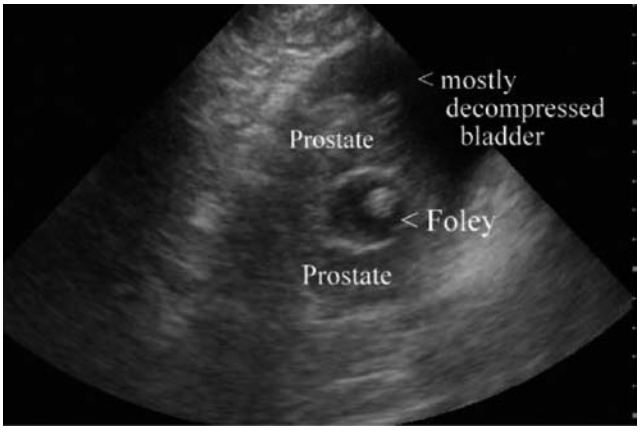

FIGURE 92-2. Foley catheter balloon inflated within the prostatic urethra. [Used with permission of Brady Pregerson, MD, and EMresource.org.]

tract should be anesthetized by local infiltration. The needle should be advanced posteriorly and caudally at a 30-degree angle from true vertical (or 60 degrees from the horizontal plane of the abdomen). Alternatively, aspirate and inject anesthetic until you enter the bladder. Note needle direction and depth to bladder. A small skin incision may be necessary to facilitate passage of the catheter into the bladder. Both techniques described below should be performed with real-time US guidance.

Obturator Technique Insert the needle obturator into the urinary catheter and lock it into the port (**Figure 92-4**). The needle tip will be 2.5 mm beyond the end of the catheter. US visualization of the needle advancement into the bladder and return of urine indicate correct placement. After entering the bladder, advance the obturator/catheter system another 3 cm. Then unlock the obturator and advance the catheter an additional 5 cm before withdrawing the obturator needle, leaving the catheter in the bladder. Inflate the balloon and pull back on the catheter until slight resistance is met as the balloon engages with the anterior bladder wall.

Peel-Away Sheath Technique This technique uses the Seldinger technique for catheter insertion. Once placement of a finder needle in

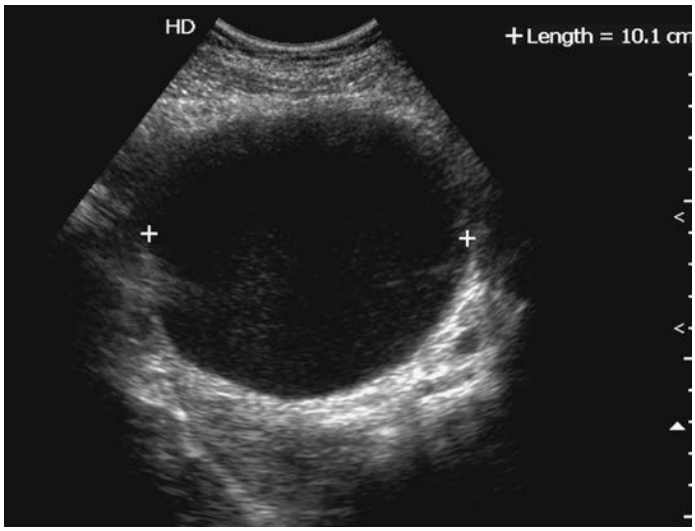

FIGURE 92-3. US visualization of distended bladder. Make sure bladder measurement is at least 2 cm in two planes before attempting suprapubic aspiration. US visualization of the needle advancement into the bladder and return of urine indicate correct placement. [Reproduced with permission from Ma OJ, Mateer JR, Blavais M: *Emergency Ultrasound,* 2nd ed. © 2008, McGraw-Hill, Inc., New York, NY.]

the bladder is confirmed by US and urine return, remove the syringe. Insert guidewire through the needle. Remove the needle, leaving the wire in the bladder. Advance the peel-away sheath over the guidewire into the bladder. Remove guidewire, and then insert the urinary catheter through the peel-away sheath. Inflate the catheter balloon once bladder placement is confirmed by urine return. Remove the peel-away sheath. Retract catheter until slight resistance is met as the balloon engages with the anterior bladder wall.

POSTCATHETERIZATION CARE

Reassess patients after urinary catheter insertion for resolution of symptoms. Patients with long-standing obstruction are at risk for postobstructive diuresis and postobstructive acute kidney injury,[7] which are more common when large urine volumes are drained (800 to 1500 mL).[13] Other risk factors for postobstructive diuresis include prior renal insufficiency, heart failure, altered mental status, and illness severity requiring intensive care unit admission.[6,7] Monitor for 4 hours minimum for significant hourly urinary output (>200 mL/h over intake) after initial return. If this degree of output continues, admit the patient with volume replacement adjusted hourly according to urine output. Patients with significant elevations of BUN or creatinine should also be admitted; see Chapter 88, "Acute Kidney Injury."

Routine use of antibiotics for the prevention of bacteriuria or for the treatment of asymptomatic bacteriuria is not suggested. Antibiotics are reserved for symptomatic urinary tract infection[4]; see Chapter 95, "Complications of Urologic Procedures and Devices."

Pharmacologic therapy with α-adrenergic receptor antagonists, which exert effects on the bladder neck and prostate, may relax bladder smooth muscle, reducing outlet resistance to urinary flow (Table 92-4). Alfuzosin, 10 milligrams daily, and tamsulosin, 0.4 milligram daily, are possible agents to initiate that increase the success of spontaneous voiding after the catheter is removed.[14,15] α-Adrenergic antagonism may also shorten the interval of time before a successful voiding trial and prevent recurrent episodes.[16] Warn patients, especially the elderly, about possible postural hypotension that often accompanies use of these medications.

DISPOSITION AND FOLLOW-UP

Most patients with urinary retention are discharged home with a urinary catheter connected to a leg receptacle. Patients should be educated in Foley catheter care and bag drainage and given a list of concerning symptoms that should prompt a return to the ED. These include fever, persistent vomiting, abdominal pain, decreased urinary output, or penile pain. Penile pain suggests migration of the catheter balloon into the proximal urethra. Feelings of urgency or bladder spasm can be treated with oxybutynin, 2.5 milligrams PO two or three times a day. However, oxybutynin has anticholinergic properties and can cause the same adverse effects as any anticholinergic agent, including urinary retention. There is no satisfactory treatment for urinary leakage around the Foley catheter. Placement of a larger catheter is not typically effective.

Patients presenting with urinary retention attributed to a pharmacologic or a postanesthesia cause may be candidates for a spontaneous voiding trial during the initial ED visit. If they are able to empty their bladder after catheter removal, discontinue the offending medications, if applicable, and discharge without further intervention. Inability to spontaneously void necessitates replacement of the Foley catheter. Urology follow-up is recommended within 3 to 7 days for a repeat voiding trial. A longer period of Foley drainage may be necessary in patients with retention volumes >1.3 L to improve chances of successful voiding.

SPECIAL CONSIDERATIONS

URINE LEAKAGE AROUND A SUPRAPUBIC CATHETER

Leakage of urine around an indwelling suprapubic catheter results in many difficulties for patients and caretakers. Some causes include bladder spasm; constipation, which can aggravate bladder spasms; infection; and urine calculi that cause catheter obstruction. Consult urology concerning choice of medication for spasms or about the use of fenestrated catheters as needed.

FEMALES WITH URINARY RETENTION

Urinary retention in women is uncommon. The obstructive causes of urinary retention in women are usually related to gynecologic problems (Table 92-1), but neurogenic causes can develop in both men and women.[17]

The management of urinary retention in females involves catheterization and attending to any treatable cause. The ideal selection of catheterization method, including in and out catheterization, short-term indwelling urethral catheter followed by a trial of voiding, or clean intermittent self-catheterization, depends on the clinical assessment of precipitating factors and underlying conditions. α-Adrenergic antagonists do not appear to be helpful in women with urinary retention. If there is no apparent cause, refer to a urologist for urodynamic studies.[17]

GROSS HEMATURIA AND CLOT RETENTION

Gross hematuria can lead to clot formation within the bladder and acute urinary retention by obstructing outflow, resulting in pain, hypertension, and tachycardia from acute bladder distention. Management of gross hematuria includes placement of a 20F to 24F triple-lumen catheter (one port for urine drainage, one port for balloon inflation, and one port for bladder irrigation) and irrigation with saline until clear to ensure clot evacuation.[18] Hematuria catheters are also now available to allow for clot passage without obstructing the catheter. Patients with persistent clot burden may require admission, as obstruction may recur and require cystoscopic clot removal. Patients with gross hematuria from coagulopathy (i.e., warfarin) should have clotting parameters corrected as appropriate and be admitted.

POSTOPERATIVE URINARY RETENTION

Treatment is discussed in Chapter 87, "Complications of General Surgical Procedures." For patients with retention after GU or pelvic procedures, consult with the operating surgeon. Otherwise, for patients with normal renal function and no obstruction, bladder catheterization to relieve symptoms and then removal of the catheter and a trial of voiding are usually all that is necessary.

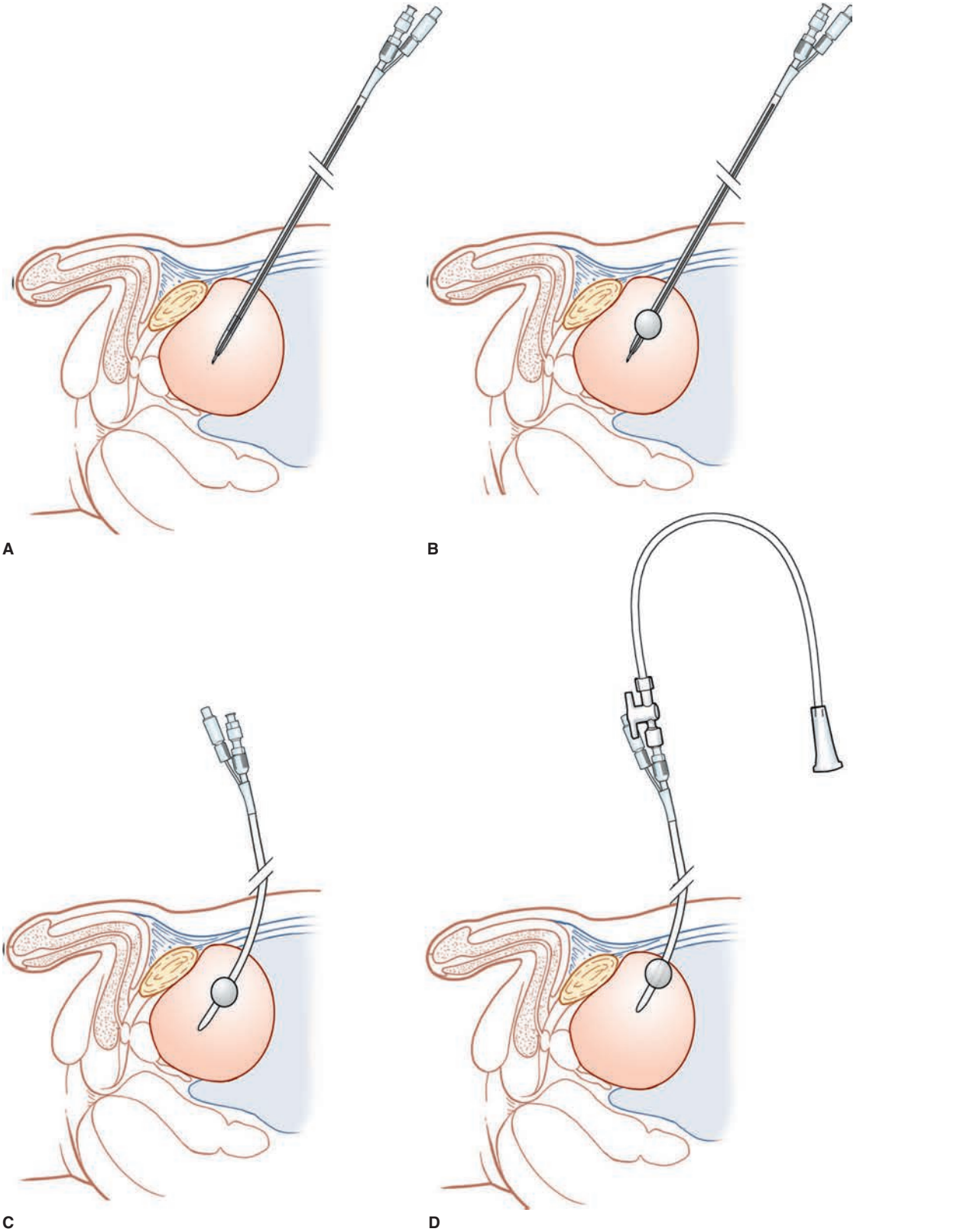

FIGURE 92-4. The obturator technique. **A.** The obturator is within the catheter. The system is inserted 60 degrees to the skin and advanced into the bladder. **B.** The balloon is inflated. **C.** The obturator is removed while the catheter remains within the bladder. **D.** The collecting tube is attached to the catheter. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures*, 3rd ed. New York, NY: McGraw-Hill Education; 2019.]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 93

Male Genital Problems

Jonathan E. Davis

INTRODUCTION

This chapter reviews the common acute infectious and structural or anatomic GU disorders. There are five GU emergencies: testicular torsion, Fournier's gangrene, paraphimosis, priapism, and significant GU trauma (see Chapter 265, "Genitourinary Trauma"). Related emergencies include strangulated inguinal hernia (see Chapter 84, "Hernias") and ruptured abdominal aortic aneurysm (see Chapter 60, "Aneurysmal Disease"), both of which may present with scrotal pain. Chapter 136, "Pediatric Urologic and Gynecologic Disorders," discusses urologic emergencies in children and adolescents.

ANATOMY

PENIS

Three cylindrical bodies—the corpus spongiosum, which surrounds the urethra, and the paired corpora cavernosa—form the shaft of the penis (**Figure 93-1**). The corpora cavernosa are the major erectile bodies, extending distally from the pubic rami and capped by the glans penis. These cylindrical structures are encased in a thick tunic of dense connective tissue, the tunica albuginea. External to the tunica albuginea is Buck's fascia, which fuses with Colles' fascia at the level of the urogenital diaphragm. The internal pudendal artery provides the blood supply, which branches to form the deep and superficial penile arteries. Lymphatics drain from the penis into the deep and superficial inguinal nodes.

SCROTUM

The prepubertal scrotal skin is thin and thickens with subsequent hormonal stimulation during puberty. Immediately beneath the skin are the smooth muscle and elastic tissue layers of Dartos' fascia, similar to the superficial fatty layer (Camper's fascia) of the abdominal wall. The deep membranous layer (Scarpa's fascia) of the abdominal wall extends into the perineum, where it is referred to as *Colles' fascia*, and forms part of the scrotal wall (**Figure 93-2**). The blood supply is derived primarily from branches of the femoral and internal pudendal arteries. Lymphatics from the scrotum drain into the inguinal and femoral nodes.

TESTES

The testes average in size between 4 and 5 cm in length and 3 cm in width and depth and usually lie in an upright position, with the superior portion tipped slightly forward and outward. Each testis is encased in a thick fibrous tunica albuginea except posterolaterally, where it is in tight apposition with the epididymis. The enveloping tunica vaginalis covers the anterior and lateral aspects of the testes and attaches to the posterior scrotal wall. Superiorly, the testes are suspended from the spermatic cord; inferiorly, the testis is anchored to the scrotum by the scrotal ligament (gubernaculum). Maldevelopment with lack of firm posterior fixation of the tunica vaginalis leaves the testes and epididymis at risk for torsion about the spermatic cord. The posterior (visceral) leaf of the tunica vaginalis is adherent with the tunica albuginea of the anterior testicular surface. A potential space exists between this visceral leaf and the anterior (parietal) tunica vaginalis. Any traumatic or inflammatory event can impede the normal parietal tunica vaginalis from absorbing viscerally secreted fluid, resulting in hydrocele formation anterior to the testes (**Figure 93-3**). Hematocele results from accumulation of blood in the potential space.

The internal spermatic and external spermatic arteries provide the blood supply, traveling together in the spermatic cord. Venous return is primarily by the internal spermatic, epigastric, internal circumflex, and scrotal veins. The lymphatics drain toward the external, common iliac, and periaortic nodes.

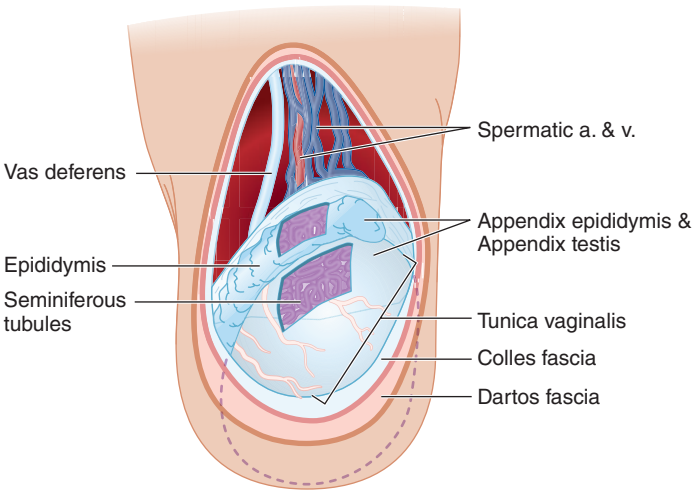

FIGURE 93-2. Anatomy of the scrotum and the testis. a. = artery; v. = vein.

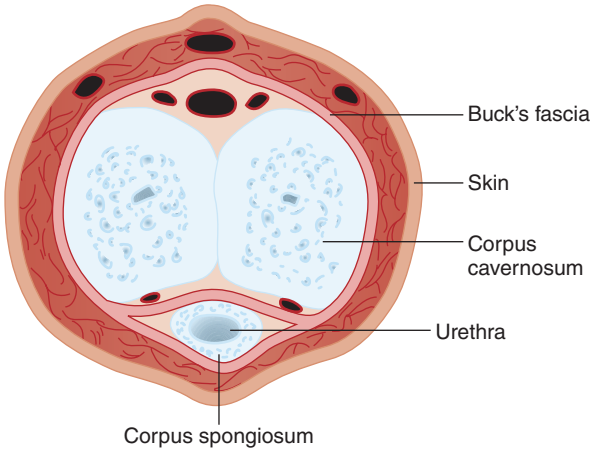

FIGURE 93-1. Cross-section of the penis.

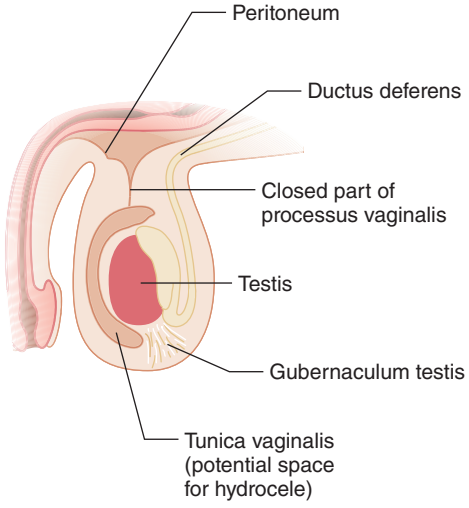

FIGURE 93-3. Embryonic retroperitoneal testis descends into the scrotum and invaginates into the tunica vaginalis, which anchors it to the posterior scrotal wall. Note the potential space in the tunica vaginalis for development of a hydrocele.

EPIDIDYMIS AND VAS DEFERENS

The epididymis is a single, fine, tubular structure approximately 4 to 5 m long compressed into an area of about 5 cm. It serves to promote sperm maturation and motility. Vestigial embryonic structures, the appendix epididymis and the appendix testis, which have no known physiologic function, are often associated with the testes and epididymis. The appendix epididymis is found attached to the head of the epididymis, or globus major. The appendix testis, a pear-shaped structure, is usually situated on the uppermost portion of the testis at the junction of the testis and the globus major of the epididymis, although anatomic variation exists.

The vas deferens is a distinct muscular tube that is easily palpable within the scrotal sac. It extends cephalad in the spermatic cord from the tail of the epididymis (globus minor), traverses the inguinal canal, and crosses medially behind the bladder over the ureters to form the ampullae of the vas, where it joins with the seminal vesicles to form the paired ejaculatory ducts in the prostatic urethra.

PROSTATE

The prostate originates from the urogenital sinus at approximately the third month of embryonic life. It is continually enlarging and, in the young male, is often not definable on rectal examination. As a man matures, the prostate may enlarge dramatically, resulting in significant bladder outlet obstruction. The anterior, median, posterior, and lateral lobes define the divisions of the prostate.

PHYSICAL EXAMINATION

The GU examination should be performed with the male patient in both the supine and upright positions in a well-illuminated, warm room if feasible. In uncircumcised males, fully retract the foreskin to inspect the glans, coronal sulcus, and preputial (foreskin) areas for ulceration or lesions. Note the location of the urethral meatus and presence of discharge. Replace the foreskin to its native position following examination to prevent iatrogenic paraphimosis. Carefully palpate the penile shaft for skin or subcutaneous lesions.

Testicular nodularity or firmness should be considered carcinoma until proven otherwise. The epididymis usually lies on the posterolateral aspect of the testis and has a soft, fleshy feel similar to that of the earlobe. Many males experience pain and tenderness with palpation of a normal globus major (head), body, and globus minor (tail) of the epididymis. Males experience some discomfort during palpation of a normal prostate, and a lateral supine position helps prevent an infrequent vasovagal response. The prostate has a heart-shaped contour, with its apex located more distally, abutting the urogenital diaphragm. The consistency of the normal prostate has the same resiliency as the cartilaginous tip of the nose, whereas suspicious carcinogenic areas feel more like the bony prominence of the chin. The posterior lobe is small and thin, allowing palpation of the median raphe that distinguishes the two lateral lobes. A rectal prostate examination cannot assess the anterior or median lobes. The seminal vesicles, lying just superior to the prostate, cannot normally be distinguished unless there is inflammation, induration, or enlargement.

Examination of the inguinal canals for hernias and the scrotal spermatic cords for varicoceles is best done in the upright position, with the patient straining at the designated time. When the patient is upright, it should be determined whether the testes are aligned along a vertical or horizontal axis. Horizontally aligned testes are at greater risk for torsion. Likewise, an elevated, horizontally aligned testis may be the result of torsion.

DISORDERS OF THE SCROTUM

An acute scrotum is defined as acute pain or painful swelling of the scrotum or its contents, accompanied by local signs or general symptoms. Testicular torsion and Fournier's gangrene are the most time-sensitive diagnoses of the acute scrotum; the first priority in the evaluation of patients with scrotal pain is differentiation of these life- or testicular-threatening disorders from other entities.

SCROTAL EDEMA

Insect bites and contact dermatitis may cause scrotal edema, or it may be idiopathic.[1] In the setting of hypoalbuminemia, or anasarca from any cause, contiguous scrotal and penile edema may occur. Idiopathic scrotal edema presents as unilateral or bilateral mild pain with scrotal, perineal, and inguinal swelling and erythema, most commonly in boys between 5 and 8 years of age.[1] US findings include an easily compressible thickened scrotal wall (mean 11.2 mm), increased peritesticular blood flow, and in some cases, a reactive hydrocele.[2,3] Episodes resolve in 1 to 4 days with scrotal elevation, rest, and NSAIDs, although recurrences occur.[4] Fever, increased warmth, or purulence suggests cellulitis; see Chapter 152, "Soft Tissue Infections."

SCROTAL ABSCESS

Management of a scrotal abscess depends on its depth.[5] In the case of a simple hair follicle abscess, the phlegmon is localized to the scrotal wall. A superficial abscess should be differentiated from a deeper abscess involving or originating from infection in one of the primary intrascrotal organs (i.e., testis, epididymis, or bulbous urethra). This distinction is difficult late in the course of the infection when a general scrotal mass may be the only physical finding. US can determine contiguous involvement of an inflammatory mass in the testis or epididymis with the scrotal skin. A retrograde urethrogram will delineate the integrity of the urethra. Early Fournier's gangrene should also be considered in patients with systemic symptoms or gas in the tissues (see section below).

A simple hair follicle scrotal wall abscess is managed by incision and drainage.[5] If abscess of deeper structures cannot be ruled out clinically or with US, consult urology for definitive management. Antibiotics are rarely needed in an immunocompetent male unless there are signs of cellulitis or systemic involvement.

FOURNIER'S GANGRENE

Fournier's gangrene is a polymicrobial, synergistic, infective necrotizing fasciitis of the perineal, genital, or perianal anatomy. While classically occurring in men 45 and older, women account for 10% to 25% of cases.[6-8] This process typically begins as a benign infection or simple abscess that quickly becomes virulent, especially in an immunocompromised host, and results in microthrombosis of the small subcutaneous vessels, leading to the development of gangrene of the overlying skin (**Figure 93-4**).[9]



FIGURE 93-4. A patient with Fournier's gangrene of the scrotum. Note the sharp demarcation of gangrenous changes (black portion) and the marked edema of the scrotum and the penis.

Patients with diabetes (32% to 66%)[10] and alcohol abuse (25% to 50%)[11] are disproportionately affected with Fournier's gangrene.[12] Mortality rates have historically varied from 3% to 67%,[10,13] but contemporary estimates range from 12% to 30%.[6,7,8,14-16] Age over 60 and complications during treatment are the most important predictors of death.[15,16]

CLINICAL FEATURES AND DIAGNOSIS

Early symptoms include genital or peritoneal pain (65%), often with pruritus and a prodrome of lethargy and fever (but may be afebrile on arrival).[6,10] This is followed by swelling (65%) and erythema (35%).[6,10] As many as 40% of patients will initially have no clear localized symptoms but experience pain.[10] In advanced Fournier's gangrene, the local signs and symptoms are usually dramatic, with crepitus and ecchymosis of the inflamed tissues. Prompt recognition of Fournier's gangrene in its early stages may prevent extensive tissue loss that accompanies delayed diagnosis or treatment. Imaging should not delay urologic consultation or treatment. Bedside US may show scrotal wall thickening, and "dirty shadowing," suggesting air in the tissues.[17,18] CT reveals extent of the disease.[19]

TREATMENT

Treat with aggressive fluid resuscitation and gram-positive, gram-negative, and anaerobic antibiotic coverage (see also Chapter 151, "Sepsis"). Recommended agents include piperacillin-tazobactam, 3.375 to 4.5 grams IV every 6 hours, or imipenem, 1 gram IV every 24 hours, or meropenem, 500 milligrams to 1 gram IV every 8 hours, plus vancomycin.[10,20,21] Urgent urologic consultation is required for wide surgical debridement.[10,13] The addition of clindamycin, 600 to 900 milligrams IV every 8 hours, or metronidazole, 1 gram IV, then 500 milligrams IV every 8 hours, to the antimicrobial regimen may be of benefit.[10,13] Hyperbaric oxygen therapy in the pre- and postoperative setting is a treatment option but does not improve mortality.[22] Admission to the intensive care unit postoperatively is typically required.[10]

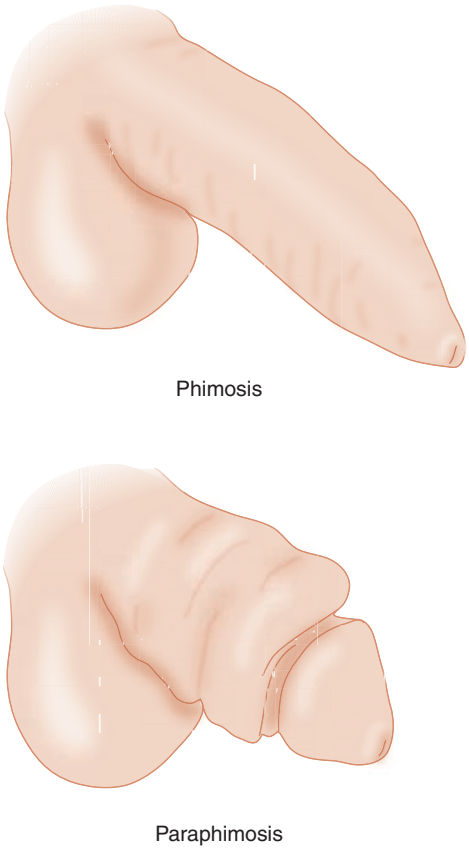

FIGURE 93-5. Phimosis and paraphimosis.

DISORDERS OF THE PENIS

Ischemic priapism, paraphimosis, and entrapment injuries are priority diagnoses that, if left untreated, can result in necrosis of the penis.

BALANOPOSTHITIS

Balanitis (inflammation of the glans penis), posthitis (inflammation of the foreskin), and balanoposthitis (inflammation of the glans and the foreskin) are primarily caused by inadequate hygiene or external irritation with subsequent colonization with *Candida* species, *Staphylococcus* species, *Streptococcus* species,[23] and less commonly, *Mycoplasma genialium*.[24] Infections frequently show mixed flora.[23] On examination, when foreskin retraction is attempted, the glans and apposing prepuce appear purulent, excoriated, malodorous, and tender. **Balanoposthitis can be the sole presenting sign of diabetes.**[25] Consider *Candida*, *Gardnerella*, and anaerobes as potential causes.[23] Treatment consists of cleansing the area with saline, ensuring adequate dryness after cleaning, application of antifungal creams (nystatin or clotrimazole), treatment with an oral azole in severe cases (fluconazole, 150 milligrams orally), and circumcision for recurrent cases.[23] Soap may increase inflammation during the acute phase, but routine hygiene is essential to prevent recurrence. Bacterial infection is suggested by warmth, erythema, and edema of the glans, foreskin, and penile shaft; anaerobic organism is suggested by foul smell.[23] If these signs are present, oral clindamycin, 300 milligrams three times per day for 7 days, or metronidazole, 500 milligrams two times per day for 7 days, is recommended.[23,26] Cases that persist warrant culture for potential infective causes or biopsy and follow-up with urology.

PHIMOSIS

Phimosis is the inability to retract the foreskin proximally and posterior to the glans penis (**Figure 93-5**). Physiologic phimosis occurs naturally in uncircumcised newborns. By 3 years of age, fewer than 10% of foreskins remain nonretractile, with nearly all becoming retractile by late adolescence. Infection, poor hygiene, and previous preputial injuries with scarring are common causes of pathologic phimosis. Scarring at the tip of the foreskin can occlude the preputial meatus, infrequently causing urinary retention. Hemostatic dilation of the preputial ostium will temporarily relieve the urinary retention. Circumcision is curative. Alternatively, topical steroid treatment (such as betamethasone, 0.05% to 0.10% twice daily) applied from the tip of the foreskin to the glandis corona for 1 to 2 months, along with daily manual preputial retraction, has been shown to be an effective nonsurgical management option for phimosis.[27]

PARAPHIMOSIS

Paraphimosis, a true urologic emergency, is the inability to reduce the proximal edematous foreskin distally over the glans penis into its natural position (Figure 93-5). The resulting glans edema and venous engorgement can progress to arterial compromise and gangrene.

Paraphimosis can often be reduced by compression of the glans for several minutes to reduce edema and allow for successful reduction of the now smaller glans through the foreskin. **Tightly wrapping the glans with a 2-inch elastic bandage for 5 minutes will reduce edema.** Topical EMLA® cream (2.5% lidocaine and 2.5% prilocaine) reduces the pain of the wrapping and reduction.[28] The patient may also benefit from an anxiolytic. The thumbs of the operator should be placed on the glans pushing proximally while the fingers distributed circumferentially on the foreskin pull distally over the glans.[29] If these methods are unsuccessful, local infiltration of the constricting band with 1% lidocaine without epinephrine followed by superficial dorsal incision of the band will allow foreskin reduction. US can be used to perform a dorsal penile nerve block.[30] Use of an iris scissor may help prevent damage to underlying tissue. The examining provider should perform this procedure in cases of impaired perfusion to the glans, unless a urologist is immediately available.

ENTRAPMENT INJURIES

Circumferential objects surrounding the penis can occlude the veins and, subsequently, the arterial blood supply. Hair, string, metal rings, and wire have been wrapped around the penis for accidental, experimental, or sexual reasons. Removing the offending object requires care and ingenuity.[31] Removal techniques include compression and cooling the penis, cutting the object, and urologic surgical removal.[31] Lubrication with petroleum jelly may assist. Ice packs can help decrease inflammation and edema, but take care to avoid cooling injury. The compression technique uses the same modified string method recommended for removing finger rings, with the addition of inserting an 18-gauge needle into the end of one of the two corpora cavernosa through the glans to allow edema and blood to be pushed out by the proximal to distal compression of the penis. Start by inserting the short end of the tape under the constriction device to be left proximally, while the long end is used to compress the penis winding in a proximal to distal direction.[31,32] Cutting devices can remove penile rings. Protect underlying skin with a hard object, preferably metal. Also avoid overheating the surrounding tissues. Urologic consultation may be required depending on the entrapment complexity and physiologic concerns.[31]

The **penile hair-tourniquet syndrome** (**Figure 93-6**) seen in young males presents with swelling of the glans. The offending hair may be invisible within the edematous coronal sulcus. Several common techniques for removal consist of unwinding the hair, lancing the hair when easily accessible, or surgical removal when circumferential edema prevents access to the constricting source.[33]

Another common entrapment injury is penile or scrotal entrapment in a zipper. The reported interventions include dismantling the zipper with wire cutters or trauma shears and surgical interventions such as circumcision. First, cleanse the affected area with povidone-iodine and provide local anesthesia with 1% to 2% lidocaine. Next, try coating the zipper and affected area with mineral oil or other nontoxic lubricant. If this does not free the zipper, cut the zipper away from clothing to make the zipper easier to handle. Next, try cutting the sliding bar of the zipper and the zipper teeth.[34] The bottom bar of the zipper apparatus can also be cut and then unzipped from below.



FIGURE 93-6. Hair is entrapped behind the coronal sulcus (*arrow*), constricting and progressively amputating the glans.

FRACTURE OF THE PENIS

A penile fracture occurs when the tunica albuginea of one or both corpus cavernosa ruptures due to direct trauma to the erect penis.[35] It can be associated with partial or complete urethral rupture (9% to 18%) or deep dorsal vein injury.[35,36] The most common cause is sexual intercourse, but other causes include animal bites, stabbing, bullet wounds, and self-mutilation.[35,37] On examination, the penis is acutely swollen but flaccid, discolored, and tender. A retrograde urethrogram may be necessary to ensure urethral integrity, but radiologic evaluation rarely influences surgical managment.[37] If the clinical diagnosis is in doubt, US is recommended to assess for rupture of the tunica albuginea.[38] Surgical treatment consists of hematoma evacuation and suture apposition of the disrupted tunica albuginea. Surgery within 8 hours is recommended to minimize dysfunction.[35,39]

PEYRONIE'S DISEASE

Peyronie's disease is a fibrotic disorder of the tunica albuginea. The fibrosis produces progressive penile curvature and painful erections, yielding erectile dysfunction or unsuccessful vaginal penetration during intercourse.[40] Examination of the penile shaft will disclose a thickened plaque, typically on the dorsum, involving the tunica albuginea of the corpora bodies. Outpatient urologic referral is warranted.[41]

PRIAPISM

Priapism is a urologic emergency that is characterized by persistent, usually painful, pathologic erection in which both corpora cavernosa are engorged with stagnant blood.[42] Even though the glans penis and the corpus spongiosum are characteristically soft and uninvolved, urinary retention may develop. Impotence follows in 35% of cases with sustained erections for prolonged periods, so emergency urologic consultation is needed.

Many cases of priapism in adults are pharmacologically related to intracavernosal injection of vasoactive substances for impotence (papaverine, prostaglandin E_1), use of oral agents for hypertension (hydralazine, prazosin, calcium channel blockers), neuroleptic medications (chlorpromazine, trazodone, thioridazine), or oral agents related to erectile dysfunction.[42] Most cases of priapism in children are due to hematologic disorders, usually sickle cell disease.

Priapism is classified into **ischemic** priapism (veno-occlusive, low-flow) and **nonischemic** priapism (arterial, high-flow). **Stuttering priapism** is a recurrent subset of ischemic priapism. Nonischemic priapism is uncommon, most often painless, and usually results from traumatic fistulae between the cavernosal artery and the corpus cavernosum. Blood gas analysis of the first corporal aspirate is recommended to differentiate nonischemic from ischemic priapism.[42] Nonischemic priapism may be further delineated by color Doppler US (increased flow) and is treated by nonurgent embolization.[43] Ischemic (low-flow) priapism is more common, is usually quite painful, and is characterized by the aspiration of dark acidic intracavernosal blood from the corpus cavernosum. Color Doppler US shows absence of the normal arterial waveform in the corporal arteries, but imaging should not replace blood gas analysis for the diagnosis of ischemic priapism.[42] Provide adequate narcotic analgesia early on in the evaluation process.

ASPIRATION AND IRRIGATION OF CORPORA CAVERNOSA

Corporal aspiration, irrigation, and α-adrenergic agonist (i.e., phenylephrine) injection are the primary treatment methods for persistent priapism. Ketamine, 0.5 milligram/kg per dose for up to four doses, may yield detumescence when narcotic medication fails to resolve priapism and provides procedural sedation for aspiration and irrigation.[44] A ring block, using lidocaine 1% without epinephrine, injected around the base of the penis can be delayed until procedural sedation has been established. Because of the sinusoidal network in the corporal cavernosa, blood can be aspirated and the space irrigated once the needle fully enters the cavernous body. The introduction of vasoactive or other agents into the corpora may precipitate systemic effects, particularly as partial detumescence is achieved.

The urologic consultant usually performs the aspiration, but the examining provider may need to intervene. On each lateral side of the proximal penis, raise a wheal with 1% lidocaine using a 27-gauge needle. After local anesthesia, insert a 19-gauge (or 18-gauge) butterfly needle into the corpora cavernosa on each side, approximately 0.5 cm deep. The needle must penetrate the skin, subcutaneous tissue, and the tunica albuginea in order to enter the corpus cavernosum. The needles can be supported in place by using a combination of small gauze pads on either side of the "butterfly wings" and roller gauze around the penis to secure its position. Blood is typically aspirated from each side.[42] Send first aspiration for blood gas analysis. In 15- to 25-mL aliquots, aspirate until bright red blood returns. Instill up to 25 mL of cold sterile saline into each side, pause 15 to 20 minutes, then aspirate, and repeat. If priapism persists, dilute phenylephrine to 100 micrograms/mL and inject 100 micrograms every 5 minutes as needed, up to a maximum dose of 1 milligram. If this fails to produce detumescence, surgery may be required.[42] If priapism due to sickle cell crisis fails to respond to adequate analgesia and hydration, consult both urology and hematology. Penile aspiration and irrigation, with or without instillation of adrenergic agonists, is recommended for acute ischemic priapism in sickle cell patients.[45]

PENILE CARCINOMA

Carcinoma of the penis is rare, usually appearing in the fifth or sixth decade in an uncircumcised male. Carcinoma may appear as a nontender ulcer or warty growth beneath the foreskin in the area of the coronal sulcus or glans penis and is often hidden by an inflamed phimotic foreskin.

DISORDERS OF THE TESTES AND EPIDIDYMIS

TESTICULAR TORSION

The differential diagnosis of acute scrotal pain includes testicular torsion, torsion of the testicular appendages, epididymitis, incarcerated hernia, and trauma, among others. Frequent causes of acute scrotal pain include testicular torsion or epididymitis in adults, with the added possibility of appendage torsion in children (**Table 93-1**). Because of the potential for infarction and infertility, testicular torsion must be the primary consideration in acute scrotal pain. Testicular torsion presents in a bimodal age distribution, with extravaginal torsion occurring in the perinatal period and intravaginal torsion peaking during puberty.[46,47]

Torsion of the testis or spermatic cord results from abnormal fixation of the testis within the tunica vaginalis. This allows the testis to twist, especially after episodes of minor trauma and during periods of testicular growth such as puberty. Torsion usually occurs in the absence of a preceding event; only a small percentage occurs due to associated trauma. Torsion may occur during sleep, when unilateral cremasteric muscle contraction results in twisting of the testis. Inadequate fixation of the tunica vaginalis to the posterior scrotal wall (bell-clapper deformity) places the testis at risk for torsion. A testis aligned along a horizontal rather than a vertical axis is at particular risk.

CLINICAL FEATURES

Patients usually complain of acute severe pain, usually felt in the lower abdominal quadrant, the inguinal canal, or the testis. Although the pain may be constant or intermittent, it is not positional in nature, because testicular torsion is primarily an ischemic event that becomes inflammatory only after the testis has infarcted. The presence of vomiting makes the diagnosis of testicular torsion more likely.[48]

When examined early, the involved testis is firm, tender, and often higher than the contralateral testis and frequently with a transverse lie.[49] The epididymis may be displaced and not found in its normal posterolateral position. The most sensitive finding in excluding testicular torsion is the unilateral presence of the cremasteric reflex, but the sensitivity ranges from 73% to 96%.[50] The absence of an ipsilateral cremasteric reflex is a nonspecific finding and may be associated with scrotal inflammation from any cause. Relief of pain with elevation of the affected testicle (Prehn's sign–positive for epididymitis) does not reliably distinguish torsion from epididymitis.

DIAGNOSIS

In obvious cases of testicular torsion, the diagnosis is made clinically to facilitate emergent urologic consultation and surgical exploration. Excellent salvage rates are expected with <6 hours of symptoms, but salvage declines rapidly thereafter. There are no readily available clinical or laboratory parameters to judge the degree or duration of testicular ischemia. Therefore, no matter how long the patient has been symptomatic, a rapid evaluation, including emergency scrotal exploration if necessary, should be performed. Doppler US is the diagnostic imaging modality of choice to evaluate patients with equivocal clinical presentations. US is considered "positive" for testicular torsion when ipsilateral intratesticular blood flow is absent or clearly reduced, and "negative" when flow is normal or increased. Older duplex US studies report sensitivities ranging from 69% to 90% and specificities ranging from 98% to 99% for testicular torsion[46]; however, a 2013 prospective study found a sensitivity of only 83%.[51] Importantly, partial torsion may reveal falsely reassuring blood flow in an ischemic testicle. Likewise, normal or increased flow may be seen in a high-risk testicle following spontaneous detorsion.

TABLE 93-1 Differential Diagnosis of Acute Scrotal Pain

	Testicular Torsion	Epididymitis	Appendage Torsion
Historical Features			
Peak incidence	Neonates, adolescents	Adolescents, young adults	Prepubertal
Risk factors	Undescended testicle (neonate), rapid increase in testicular size (adolescent), failure of prior orchiopexy	Sexual activity/promiscuity, GU anomalies, GU instrumentation	Presence of appendages
Pain onset	**Sudden**	Gradual, progressive	Variable
Nausea/vomiting	**More likely**	Less likely	Less likely
Dysuria	Less likely	**More likely**	Less likely
Physical Findings			
Fever	Less likely	**More likely**, particularly in advanced disease (epididymo-orchitis)	Less likely
Location of swelling/tenderness (early)	Testicle, progressing to diffuse hemiscrotal involvement	Epididymis, progressing to diffuse hemiscrotal involvement	Localized to head of affected testicle or epididymis
Cremasteric reflex	Testicular torsion less likely if present	May be present or absent	May be present or absent
Testicle position	High riding, transverse alignment	Normal position, vertical alignment	Normal position, vertical alignment

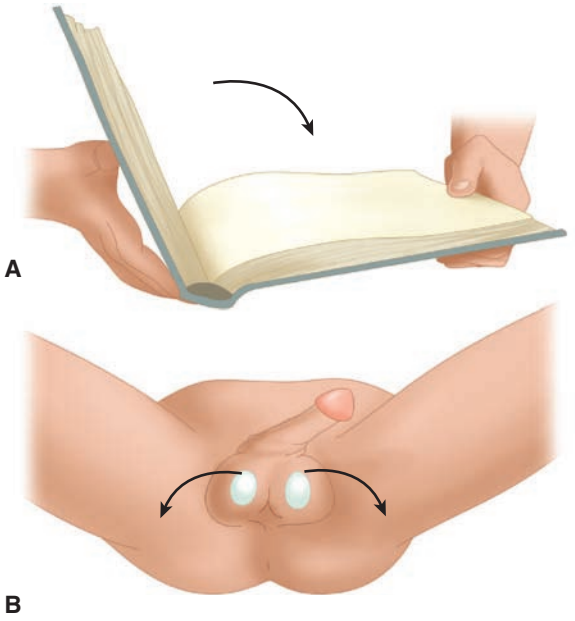

FIGURE 93-7. Testicular detorsion. This procedure is best done standing at the foot of or on the right side of the patient's bed. **A.** The torsed testis is detorsed in a fashion similar to opening a book. **B.** The patient's right testis is rotated counterclockwise, and the left testis is rotated clockwise. [Reproduced with permission from Strange GR, Ahrens WR, Schafermeyer RW, et al: *Pediatric Emergency Medicine*, 3rd ed. © 2009, McGraw-Hill, Inc., New York, NY, p. 679.]

Grayscale US imaging of the spermatic cord itself assessing for coils or kinks may aid in diagnosis. US has the advantage of demonstrating scrotal anatomy, which may indicate an alternative diagnosis.[51] Even after negative imaging, consultation with a urologist should be considered when an alternative diagnosis cannot be found because physical examination and Doppler US are not 100% sensitive or specific.

TREATMENT

For emergency or preoperative treatment, consider manual detorsion of the affected testis, which has been shown to be successful in as many as 76% of cases.[52] Explain to the patient that detorsion is a painful procedure, but that successful detorsion will help to relieve the presenting pain. Most testes twist in a lateral to medial fashion (two thirds of cases); therefore, detorsion initially should be done in a medial to lateral motion.[53] **Detorsion is typically done in a manner similar to opening a book (Figure 93-7A).** If one were to stand at the patient's feet, the patient's right testis would be rotated in a counterclockwise fashion and the patient's left testis in a clockwise fashion (**Figure 93-7B**). The initial attempt should include one and one-half rotations (540 degrees). Any relief of pain is a positive end point, and the success of the maneuver can be assessed with Doppler US, demonstrating restoration of blood flow. An occasional patient will require manipulation beyond the initial one and one-half rotations. A worsening of the patient's pain suggests that detorsion should then be done in the opposite direction (one third of cases). Successful detorsion converts an emergent procedure to an elective one; however, the decision for timing of surgery is the decision of the surgeon. Final management of testicular torsion is surgical fixation by the urologist.

APPENDAGEAL TORSION

The four testicular appendages—appendix testis, appendix epididymis, paradidymis (organ of Giraldes), and vas aberrans—have no known physiologic function. These pedunculated structures are capable of torsion and, in prepubertal boys (median age, 9 to 11 years), probably twist more often than the testes in children.[54] Presenting symptoms, although similar to testicular torsion, classically lack the systemic symptoms of nausea and vomiting.[55] Leukocytosis is usually absent.[55] If the patient is seen early, with the pain localized to the upper pole of the testis or epididymis, a blue spot may be observed through the scrotal skin—the "blue dot sign." This "sign" is considered pathognomonic for torsion of the appendix testis but is infrequently seen. If the diagnosis can be ensured and normal intratesticular blood flow to the involved testis is confirmed by color Doppler US, surgical exploration is not necessary. Torsion of an appendage is usually self-limiting and best managed with analgesics, bed rest, supportive underwear, and reassurance, with the expected symptom resolution within 3 to 5 days. If late in the process and testicular swelling is present, or if the color Doppler US is equivocal, then urologic consultation and surgical exploration are needed to exclude testicular torsion.

EPIDIDYMITIS

The onset of pain in epididymitis or epididymo-orchitis is usually gradual. Bacterial infection is the most common cause. Unless high-risk sexual behavior can be ruled out, sexually active men should be treated with regimens that cover *Gonorrhea* and *Chlamydia*.[34] Consider coliform infection of the lower urinary tract in addition to the more common sexually transmitted infection organisms in the setting of anal insertive intercourse. In older men, epididymitis is commonly caused by urinary pathogens, such as *Escherichia coli* and *Klebsiella*, or sexually transmitted infections depending on risk factors. In elderly men with epididymitis and urinary tract infection, consider associated benign prostatic hypertrophy or urethral stricture. Large residual urine volume (>50 to 100 mL urine) suggests outlet obstruction as the cause of the patient's infection (see Chapter 92, "Acute Urinary Retention").

CLINICAL FEATURES AND DIAGNOSIS

Epididymitis may cause lower abdominal, inguinal canal, scrotal, or testicular pain alone or in combination. The retrograde progression of infection from the prostatic urethra to the epididymis explains the location and progression of pain. Epididymitis represents a more advanced GU tract infection when compared with urethritis. Patients with epididymitis are more prone to lower urinary tract voiding discomfort and may note transient pain relief in the recumbent position with scrotal elevation. Initially, isolated firmness and nodularity of the affected globus minor are noted on examination. As the disease progresses, the sulcus between the epididymis and testis becomes obliterated, and the inflammatory epididymal mass may become contiguous with the testis, producing a large, tender scrotal mass (epididymo-orchitis) that may be difficult to differentiate from testicular torsion or abscess.

Urinalysis may show pyuria in about half of patients. Consider referral for testing for other sexually transmitted infections in the setting of risk features. Obtain urine culture in children and elderly men. Adjunctive diagnostic modalities, such as color flow duplex Doppler sonography or radionuclide scintigraphy, will demonstrate increased or preserved blood flow to the testes. A reactive hydrocele may be seen on US.

TREATMENT

Most cases of epididymitis can be managed with oral antibiotics (**Table 93-2**).[56-59] Although the 2015 Centers for Disease Control and Prevention recommendations direct the coverage of sexually transmitted infections based on an age cut-point of 35 years, recent studies suggest sexually transmitted infections associated with epididymitis occur in all sexually active age groups.[58,59] Therefore, antibiotic treatment should cover sexually transmitted infections unless the care provider can reliably exclude these infections. Admission criteria for epididymitis include fever and clinical toxicity, which can be indicative of epididymal or testicular abscess formation. The ambulatory patient should wear a scrotal supporter, being careful not to lift heavy objects or strain when having a bowel movement, both of which will increase intra-abdominal pressure and exacerbate the inflammatory cycle. The need and urgency for follow-up care depend on illness severity and comorbidities.[56] A patient with severe epididymitis not requiring admission should be seen by a urologist in 3 to 5 days; patients with milder cases can be reevaluated at 5 to 7 days with primary care for clinical improvement and decisions regarding work limitations (i.e., a sedentary worker would be able to return to work sooner than a physical laborer).[56]

TABLE 93-2 Empiric Outpatient Treatment of Epididymitis and Epididymo-Orchitis

- **For acute epididymitis most likely caused by sexually transmitted chlamydia or gonorrhea**
- Ceftriaxone,* 250 milligrams IM single dose, plus doxycycline,* 100 milligrams PO twice a day for 10 d
- **For acute epididymitis most likely caused by sexually transmitted chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex)**
- Ceftriaxone,* 250 milligrams IM single dose, plus doxycycline,* 100 milligrams PO twice a day for 10 d
- Also treat for gram-negative bacilli with:
  - Levofloxacin, 500 milligrams PO every day for 10 d
    or
  - Ofloxacin,† 300 milligrams PO twice a day for 10 d
- **For acute epididymitis most likely caused by enteric organisms**
  - Levofloxacin, 500 milligrams PO every day for 10 d
    or
  - Ofloxacin,† 300 milligrams PO twice a day for 10 d

*European Association of Urology Guidelines recommend 500 milligrams of ceftriaxone IM and 200 milligrams of doxycycline as first dose.

†Ofloxacin is not currently available in the United States or Canada.

ORCHITIS

Isolated orchitis, or inflammation of the testicle, is quite rare and usually occurs in conjunction with other systemic infections, such as mumps or other viral illnesses (coxsackie virus, Epstein-Barr virus, varicella, or echovirus). Mumps orchitis presents with unilateral involvement in 70% of cases, followed by contralateral involvement in 1 to 9 days. Bacterial orchitis is almost always associated with epididymitis. Orchitis in immunocompromised patients can be due to mycobacteriosis, cryptococcosis, toxoplasmosis, or candidiasis. Patients with orchitis usually present with testicular tenderness and swelling of a few days in duration. The diagnosis is primarily clinical using history and physical examination, but US can assist in excluding testicular torsion or abscess. Treatment for acute episodes starts with antibiotic coverage as listed earlier for epididymitis; IV antibiotics should be considered for patients with systemic features.[56,57] Immunocompromised patients or patients with risks for tuberculosis (exposure, uncontrolled human immunodeficiency virus, or diabetes) require further evaluation and, in some cases, admission if they have abnormal vital signs. Some patients can alternatively be referred to urology and/or infectious disease for further management.

TESTICULAR MALIGNANCY

The hallmark of testicular carcinoma is an asymptomatic testicular mass with firmness or induration. Ten percent of tumors will present with pain secondary to acute hemorrhage within the tumor, which may be mistaken for orchitis. Metastatic testicular tumors can be insidious and must be suspected in any male with unexplained supraclavicular lymphadenopathy, abdominal mass, or chronic nonproductive cough from a lung metastasis. Testicular examination may disclose a primary tumor. Any unexplained testicular mass must be approached as a possible tumor with urgent urologic referral.

ACUTE PROSTATITIS

CLINICAL FEATURES AND DIAGNOSIS

Acute prostatitis is bacterial inflammation of the prostate gland. Patient complaints can include irritative or obstructive symptoms such as low back pain; perineal, suprapubic, or genital discomfort; lower urinary tract voiding symptoms; frequency or dysuria; perineal pain with ejaculation; and fever or chills. Risk factors include anatomic or neurophysiologic lower urinary tract obstruction, acute epididymitis or urethritis, anal receptive intercourse, phimosis, intraprostatic ductal reflux, and indwelling urethral catheter or condom drainage. The causative organism is *E. coli* in most cases, with other uropathogens such as *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Serratia, Enterococcus*, or *Proteus* causing the remainder. In contrast to acute prostatitis, chronic bacterial prostatitis is characterized by prolonged or recurrent symptoms and relapsing bacteriuria.

Physical exam findings include perineal tenderness, rectal sphincter spasm, and prostatic tenderness or bogginess. The diagnosis is clinical, because urinalysis and urine culture may both be negative. Prostatic massage is not necessary to make the diagnosis and, in acute prostatitis, may precipitate bacteremia or sepsis.[60-62] Obtain urethral cultures or first-void urine for gonorrhea and chlamydia testing in men younger than 35 years who are sexually active and in men older than 35 years who engage in high-risk sexual behavior. While imaging is not routinely needed, patients with signs of toxicity or those with voiding difficulty and symptom duration longer than 5 days are at greater risk for an associated abscess of the prostate.[63]

TREATMENT

Initial treatment is fluoroquinolone antimicrobial therapy for 2 weeks,[60] such as ciprofloxacin, 500 milligrams orally twice daily for 14 days, with plan for primary care reevaluation at 2 weeks for possible continued therapy as needed. Double-strength trimethoprim-sulfamethoxazole, one tablet PO twice a day, is an alternative, although cure rates may be lower than for the fluoroquinolones. Fosfomycin, 3 grams daily for 7 days followed by 3 grams every 48 hours for 6 weeks, has been successful in treating patients with prostatitis caused by multidrug-resistant *E. coli*.[64] Consider treating for sexually transmitted infection organisms in younger patients or older patients with sexually transmitted infection risk factors; give ceftriaxone, 250 milligrams IM as a single dose, plus doxycycline, 100 milligrams PO twice a day for 10 days. Patients frequently require pain medication.

Most patients can be treated as outpatients. Patients with abnormal vital signs or other systemic symptoms should be admitted and given a broad-spectrum antibiotic such as piperacillin-tazobactam, 3.375 to 4.5 grams IV, combined with an aminoglycoside.[60,61] If associated with urinary retention, urology consultation is needed. Urologic follow-up should be provided for discharged patients to ensure eradication of infection and to provide continuity of care in case of relapse. Chronic prostatitis is managed with urine cultures, long-term antibiotics targeted to culture results, anti-inflammatory medications plus α-blockers for nonbacterial chronic prostatitis, and urology follow-up.

DISORDERS OF THE URETHRA

For discussion of **urethritis**, see Chapter 153, "Sexually Transmitted Infections." For options regarding the management of obstructed urinary flow, possibly caused by **urethral strictures**, see Chapter 92, "Acute Urinary Retention."

URETHRAL FOREIGN BODIES

Patients of all ages, but especially young children, may be victims of innocent urethral exploration or attempts to heighten sexual experiences by using a variety of foreign bodies such as bobby pins; long, thin paintbrushes; or ballpoint pens.[65] Bloody urine combined with infection and slow, painful urination should suggest a possible foreign body in the lower urinary tract. A radiograph of the bladder and urethral areas may disclose the presence of a radiopaque foreign body.

Foreign bodies often require cystoscopic removal or even open cystotomy. Occasionally a gentle milking action of the proximal end of the urethral foreign body by an experienced examiner will allow its retrieval from the distal urethral meatus. Even then, retrograde urethrography or endoscopic confirmation of an intact urethra is indicated.

HEMATOSPERMIA

Hemospermia, or hematospermia, is a disturbing symptom that produces extreme anxiety in sexually active males.[66] The incidence and prevalence of this condition are not known. Most symptomatic men seek medical attention after one or two occurrences. Any process that results in trauma or other injury (e.g., tumor with erosion), inflammation, or infection of the male ejaculatory system may result in bloody semen.[67] It is not uncommon after vigorous sexual activity. Unless the cause can be determined on physical exam, the diagnosis cannot be completed in the ED. Spontaneous resolution occurs in 89% of patients; however, median symptom duration is 6 weeks.[68] Hematospermia should be differentiated from hematuria based on a clean-catch urinalysis (see Chapter 91, "Urinary Tract Infections and Hematuria"). Infection, including sexually transmitted infections, should be considered, and if suspected based on history and physical, the patient should be cultured and treated appropriately. Although all patients with hematospermia should be referred to a urologist, those >40 years old are at higher risk for cancer and should be strongly advised to seek further evaluation by a urologist even when there is spontaneous resolution of hematospermia.[67]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 94

Urologic Stone Disease

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INTRODUCTION AND EPIDEMIOLOGY

Emergency medicine management is directed at relieving pain, assessing kidney function, and determining the likelihood of spontaneous stone passage. This chapter discusses renal and ureteral stones. Bladder stones are discussed in Chapter 92, "Acute Urinary Retention." Renal stones in children are discussed in Chapter 133, "Acute Abdominal Pain in Infants and Children."

The prevalence of kidney stones in the United States has risen from 5.2% in 1994[1] to 8.8% in 2010.[2] The prevalence is 10.6% in men and 7.1% in women.[2] Increasing prevalence is also documented in Europe and Southeast Asia.[3] Obesity and diabetes are strongly associated with kidney stones.[2] For first-time stone formers, recurrence rates at 2, 5, 10, and 15 years are 11%, 20%, 31%, and 39%, respectively.[4]

PATHOPHYSIOLOGY

Stone formation requires supersaturation of dissolved salts in the urine, which condense into a solid phase. Increasing the amount of solvent (urine) and decreasing the amount of solute presented to the kidney (i.e., calcium, oxalate, uric acid) can aid in prevention. Inhibitory substances, such as citrate, and magnesium can prevent crystal precipitation and stone formation.

About 80% of calculi are composed of calcium oxalate, calcium phosphate, or a combination of both. Calcium excretion is elevated in conditions that include hyperparathyroidism, absorptive and renal hypercalciuria, and immobilization syndrome. Complex interactions between the gut, kidney, and bones contribute to calcium oxalate stone formation. A diet restricting calcium paradoxically increases calcium stone formation because there is less calcium to bind oxalate in the intestinal lumen, leading to increased absorption of oxalate from the gut, recruitment of calcium from bones, osteoporosis, and symptomatic stone disease in predisposed patients.

About 10% of stones are struvite (magnesium-ammonium-phosphate), which are found most commonly in women with recurrent urinary tract infections. These stones are associated with infection by urea-splitting bacteria (*Proteus*, *Klebsiella*, *Staphylococcus* species, *Providencia*, and *Corynebacterium*) and are the most common cause of staghorn calculi, which are large stones that form a cast of the renal pelvis. Antibiotic penetration into staghorn calculi is poor, and the potential for urosepsis exists as long as the stones remain.

Uric acid causes about 10% of urolithiasis, occurs more commonly in men, and is associated with gout or chemotherapy. Urate stones are radiolucent, and the urine is typically acidic. Cystine stones account for approximately 1% of all stones and occur in patients with cystinuria, an autosomal recessive genetic disorder affecting amino acid transport (COLA: *c*ysteine, *o*rnithine, *l*ysine, *a*rginine).

Some medications predispose to stone disease. The protease inhibitor indinavir sulfate, used to treat the human immunodeficiency virus, is associated with a 4% to 10% incidence of symptomatic urolithiasis. Pure indinavir stones are radiolucent on plain abdominal radiograph and CT scan. Carbonic anhydrase inhibitors, triamterene, and laxative abuse also increase the prevalence of renal stones.[5] With appropriate evaluation, 90% of patients will have a cause identified, and over 50% of calcium oxalate stone recurrences can be prevented.[6] **Table 94-1** lists risk factors associated with kidney stones.[2,3,7]

Pain associated with kidney stones is due to obstruction of a hollow viscus organ (ureter) and subsequent hydronephrosis creating pressure against Gerota's fascia, causing flank pain. Isolated small renal pelvis stones (not staghorn) do not cause pain unless they cause intermittent obstruction of the entrance to the ureter. A migrating but nonobstructive stone also causes pain. **During acute obstruction, most patients have no rise in serum creatinine because the unobstructed kidney functions at up to 185% of its baseline capacity.** A rise in serum creatinine in acute obstruction suggests a solitary kidney or preexisting renal disease such that the unobstructed kidney is unable to compensate completely. Fortunately, most patients have incomplete ureteral obstruction, and many patients can be safely observed over weeks. Irreversible renal damage from an obstructive kidney stone is rare if obstruction has been present for ≤1 month.[8]

The probability of spontaneous passage of stones is determined by multiple factors, including size, shape, location, and degree of ureteral obstruction. Bizarre or irregularly shaped stones with spicules or sharp edges have a lower spontaneous passage rate. With complete obstruction, there is a lower rate of spontaneous passage than if the blockage is partial. **The most common sites of obstruction include the ureteropelvic junction, where the 1-cm pelvis constricts into the 2- to 3-mm ureter; the pelvic brim, where the ureter courses over both the pelvis and the iliac vessels; and finally, the ureterovesical junction, because**

TABLE 94-1 Kidney Stone Risk Factors

Risk Factor	Mechanisms
Obesity	May promote hypercalciuria
Low urine volume	Allows solute to supersaturate
Excess dietary meat (purine)	Creates acidic urinary milieu; depletes available citrate (inhibitor); promotes hyperuricosuria
Excess dietary sodium	Promotes hypercalciuria
Insulin resistance, metabolic syndrome	Ammonia mishandling; alters pH of urine
Family history	Genetic predisposition
Gout	Promotes hyperuricosuria
Bowel surgery, inflammatory bowel disease	Promotes low urine volume; acidic urine depletes available citrate (inhibitor); hyperoxaluria
Primary hyperparathyroidism	Creates persistent hypercalciuria
Prolonged immobilization	Bone turnover creates hypercalciuria
Medications	Indinavir, ephedrine, loop diuretics, topiramate, acyclovir, triamterene

this is the most constricted site of the ureter due to the muscular coat of the bladder. Based on stone size alone, 98% of stones <5 mm will pass within 4 weeks without intervention. Sixty percent of stones 5 to 7 mm and 39% of stones >7 mm will pass within 4 weeks. **Stone size on plain radiographs is magnified by up to 20%, and a measured stone on CT is 88% of actual stone size.**[9]

CLINICAL FEATURES

The classic symptom complex for nephrolithiasis is the acute onset of a crampy intermittent flank pain that radiates toward the groin. As pain originates from a hollow viscus (ureter), the pain is visceral in nature without associated peritoneal irritation. Patients writhe in pain, unable to find a position of comfort. However, patients with renal colic may demonstrate rebound abdominal tenderness (29%), guarding (61%), and rigidity (8%).[10] Pain is commonly accompanied by nausea and vomiting (50%).[10] The adrenergic response to pain can result in tachycardia, hypertension, and diaphoresis. **Hematuria is present in only 85%** of patients with renal colic, and 30% have gross hematuria.[10]

The location of the pain correlates somewhat with the location of the stone. Stones in the upper ureter refer pain to the flank, whereas those in the mid-ureter radiate to the lower anterior quadrant of the abdomen. A distal ureter stone, which is where 75% of stones are diagnosed, refers pain to the groin. Stones positioned at the ureterovesical junction can mimic a urinary tract infection by causing frequency, urgency, and dysuria in 3% to 24% of patients.[10] Extracorporeal shock wave lithotripsy fractures stones into small particles with the use of focused sound waves. The resulting "sludge" is passed in the urine. When there are large fragments, an acute episode of renal colic occurs.

During the patient interview, elucidate four important items of history: assess risk factors for stone development (Table 94-1), prior stone-related outcome, history of renal disease, and important mimickers. The risk factors for a poor outcome with stones include three categories: renal function at risk, history of difficulty with stones, and infection (**Table 94-2**). Two mimickers that are very important to exclude are abdominal aortic aneurysm and renal artery infarction. **Nephrolithiasis is the most common misdiagnosis given to patients with a rupturing or expanding abdominal aortic aneurysm.** Recall that stones do not usually present in men older than age 60 without a prior history of nephrolithiasis and do not cause hypotension, even transiently. Renal artery thrombosis can mimic stone symptoms due to swelling of the infarcted kidney and can also be associated with hematuria. If the patient is pregnant, consider ectopic pregnancy in the differential diagnosis.

TABLE 94-2 Risk Factors for Poor Outcome With Stones

Renal function at risk
- Diabetes
- Hypertension
- Renal insufficiency
- Single kidney
- Horseshoe kidney
- Transplanted kidney

History of difficulty with stones
- Extractions
- Stents
- Ureterostomy tubes
- Lithotripsy

Symptoms of infection
- Fever
- Hypotension
- Systemic illness
- Urinary tract infection

DIAGNOSIS

The diagnosis of urologic stone disease is clinically suspected and supported by the presence of hematuria; imaging confirms the diagnosis with certainty.

Many diagnoses can be confused with renal colic (**Table 94-3**). History and physical examination can be difficult because the patient's discomfort may interfere with adequate information collection. The most critical diagnoses to consider are aortic dissection and ruptured abdominal aortic aneurysm. Renal colic and abdominal aortic aneurysm may have similar presentations.

LABORATORY EVALUATION

The laboratory evaluation centers on evaluating for infection, kidney dysfunction, and possibility of pregnancy. **Test all females of childbearing potential for pregnancy when considering renal colic, to help direct imaging and to exclude ectopic pregnancy.**

Urinalysis is needed to rule out infection. If infection is found, obtain urine culture and sensitivities to guide antibiotic therapy.[11] A urine culture should be done on all patients with sterile pyuria as renal colic patients with pyuria have 36% positive cultures as compared to those without pyuria (3.3%).[12] In suspected pediatric nephrolithiasis, urine culture is routine (see Chapter 135, "Urinary Tract Infection in Infants and Children").

TABLE 94-3 Differential Diagnoses for Ureterolithiasis

Vascular	Aortic dissection
	Abdominal aortic aneurysm
	Renal artery embolism
	Renal vein thrombosis
	Mesenteric ischemia
Renal	Pyelonephritis
	Papillary necrosis
	Renal cell carcinoma
	Renal infarct
	Renal hemorrhage
Ureter	Blood clot
	Stricture
	Tumor (primary or metastatic)
Bladder	Tumor
	Cystitis
GI	Biliary colic
	Pancreatitis
	Perforated peptic ulcer disease
	Appendicitis
	Inguinal hernia
	Diverticulitis
	Cancer
	Bowel obstruction
Gynecologic	Ectopic pregnancy
	Pelvic inflammatory disease/tubo-ovarian abscess
	Ovarian cyst
	Ovarian torsion
	Endometriosis
GU	Testicular torsion
	Epididymitis
Other	Drug-seeking behavior
	Shingles
	Retroperitoneal hematoma/abscess/tumor

TABLE 94-4 Ancillary Tests in Urologic Stone Disease

Test	Sensitivity (%)	Specificity (%)	LR+	LR–	Comments
Noncontrast CT	94–97	96–99	24–∞	0.02–0.04	Advantages: speed, no RCM, detects other diagnoses Disadvantages: radiation, no evaluation of renal function
US	63–85	79–100	10–∞	0.10–0.34	Advantages: pregnancy, no RCM, no radiation, no known side effects Disadvantages: insensitive in middle third of the ureter, may miss smaller stones (<5 mm)
Plain abdominal radiograph	29–58	69–74	1.9–2.0	0.58–0.64	Advantage: may be used to follow stones Disadvantage: poor sensitivity and specificity

Abbreviations: LR = likelihood ratio; RCM = radiocontrast media.

Hematuria (three or more red blood cells per high-power field), or even its absence, can mislead the physician. Although 10% to 15% of patients with nephrolithiasis will have no hematuria, approximately **24% of patients with flank pain and hematuria have no radiographic evidence of ureterolithiasis**.[13] Therefore, although hematuria may contribute to diagnostic decision making, it should not be used alone to exclude or confirm the diagnosis of ureterolithiasis[13] (see Chapter 91, "Urinary Tract Infections and Hematuria").

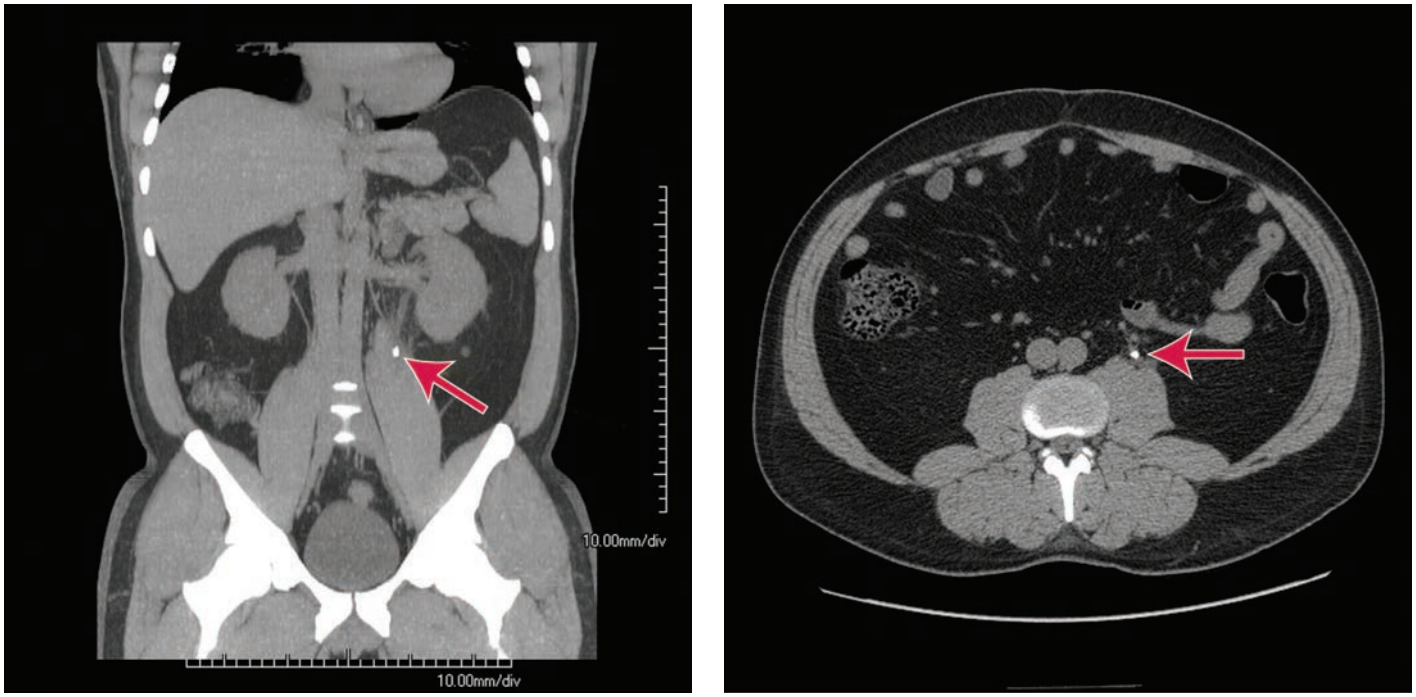
Check renal function because the overwhelming majority of patients who form stones have reduced creatinine clearance.[14] A WBC count does not aid in the evaluation because many patients will have an elevated WBC count due to stress demargination. Other laboratory studies, such as serum calcium or uric acid, are not useful in the initial evaluation or treatment but help determine stone type and long-term therapy.

IMAGING

Imaging confirms the presence of a ureteral stone, rules out other diagnoses, identifies complications, defines stone location, and assists with management if the stone fails to pass spontaneously.[15] Imaging is recommended by the American Urological Association in patients with suspected first-time stones.[16] For young, healthy, stable patients with a history of kidney stones in whom the diagnosis is clinically clear, imaging may be deferred until the follow-up visit, provided that a reliable follow-up mechanism exists.[17] However, clinicians are frequently incorrect in their clinical impression in 20% to 70% of cases.[18] CT scanning reveals an alternative diagnosis in 33% of the patients.[18] Thus, determine the need for confirmation of the diagnosis based on the patient's past medical history, dangers of accumulated radiation exposure, clarity of the clinical diagnosis, and ease of follow-up and ability to return for worsening symptoms.

CT The noncontrast CT scan is sensitive and specific, with "diagnostic" positive and negative likelihood ratios for detection of renal stones (**Table 94-4**).[19] Images are obtained from the top of the kidney to the bladder base. Secondary signs of ureteral obstruction, such as ureteral dilatation, stranding of perinephric fat, dilatation of the collecting system, and renal enlargement, can be helpful in making the diagnosis. In combination, unilateral ureteral dilatation and perinephric stranding have a positive predictive value of 96% for stone disease.[20] If both are absent, the negative predictive value is 93% to 97%[19] (**Figures 94-1** and **94-2**).

Noncontrast CT has advantages over other imaging modalities, including superior speed, the avoidance of radiocontrast media, and greater ability to identify other pathologies. However, because radiocontrast is not used, the specificity and sensitivity for other diagnoses (e.g., abdominal aortic aneurysm, appendicitis, renal infarct, or perinephric abscess) are not as great as with imaging protocols using contrast, and renal function is not assessed.



A B

FIGURE 94-1. **A.** *Arrow* shows 6-mm stone within the proximal third of the left ureter on noncontrast CT reformatted image of upright abdomen. **B.** From same patient as in **A**, note 6-mm stone (*arrow*) within the proximal third of the left ureter on noncontrast CT.

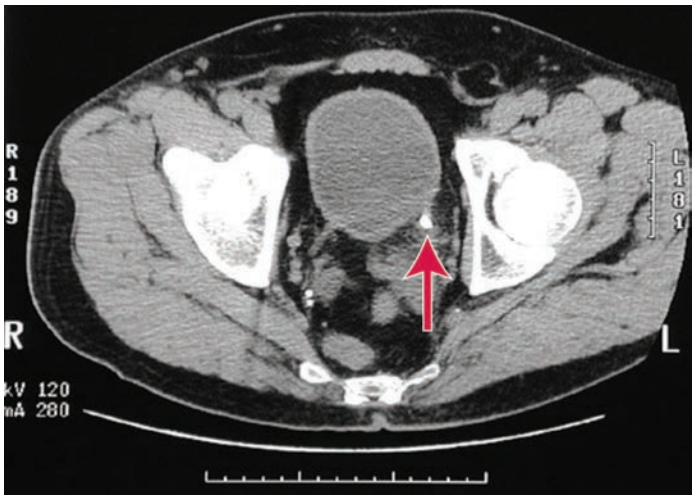


FIGURE 94-2. CT image shows 5-mm stone (*arrow*) at left ureterovesical junction. Other calcifications are seen in the pelvis, unrelated to the urinary outflow system.

Low-dose CT has been studied in small numbers. Low-dose CT is as sensitive as standard CT in detecting stones >3 mm in patients with a body mass index <30 kg/m^2. However, it was not as sensitive for smaller stones or at higher body mass indices.[21]

IV Urography This imaging modality is not a useful imaging modality except in unusual circumstances.[22] Nearly half of patients who received this test to evaluate urologic stones required a second study (usually noncontrast CT) for management.[22]

Plain Abdominal Radiographs Approximately 90% of urinary calculi are radiopaque because calcium phosphate and calcium oxalate stones have a density similar to that of bone. Struvite stones are typically mixed with calcium and thus are radiopaque. A plain kidney-ureter-bladder film is neither sensitive nor specific enough to rule in or rule out a stone. However, once the location of a stone is identified on CT scan, the progression of a radiopaque stone can be followed by a plain abdominal film.

US US should be the first-line imaging modality in pregnant patients. Although useful in the detection of larger stones (**Figure 94-3**), US may miss smaller (<5 mm in diameter) ureteral stones.[23] US is helpful in diagnosing stones in the proximal and distal ureters but is insensitive for mid-ureteral stones. Overall, US has only modest sensitivity and specificity for detecting renal stones (Table 94-4). Reported overall sensitivity of US color Doppler twinkling artifact is about 55%, with a false-positive rate of about 50% compared to CT.[24] It is not unreasonable to consider US as a first-choice modality in a patient with a strong suspicion of stones, but CT should follow US if US is inconclusive.[25] Rapid bolus infusion of crystalloid can result in a false-positive finding of hydroureter.

US provides information on hydronephrosis, renal size, and, with Doppler scanning, renal blood and urine flow. Obesity may interfere with obtaining good-quality scans, and diagnostic accuracy depends on the skill and experience of the operator.

One study assessing diagnostic accuracy of bedside US by ED physicians reported overall sensitivity of visualization of hydronephrosis or stones of 82.4% (95% confidence interval, 75.6% to 85.3%), but with best sensitivity for stones ≥6 mm (sensitivity, 90%; 95% confidence interval, 82% to 98%).[26] A comparison of ED bedside US versus radiology-performed US and CT scan reported similar diagnostic accuracy among the ED and radiology US, but the best diagnostic accuracy was found with CT.[25]

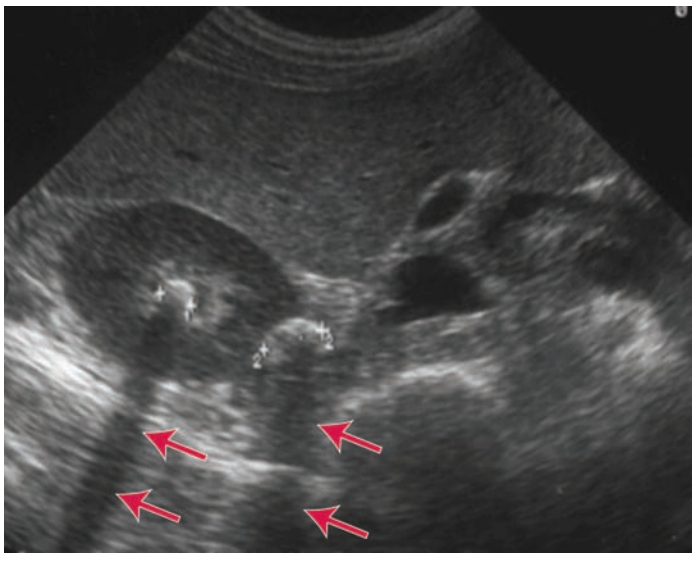


FIGURE 94-3. US of renal pelvis showing stones (marked with 1+ and 2+) with shadowing effects (*arrows*).

TREATMENT

Treatment for symptomatic nephrolithiasis in the ED includes pain and nausea/vomiting control as needed, antibiotics for those with evidence of infection, and in selected cases, medical expulsion therapy.

PAIN AND NAUSEA

Forced IV hydration results in no difference in pain control or stone passage rates when compared to minimal IV hydration.[27] Fluids should be given to correct any fluid deficit due to vomiting or limited oral intake.

NSAIDs have a direct action on the ureter by inhibiting prostaglandin synthesis.[28] IV administration achieves more rapid relief than IM or PO dosing[29] (e.g., ketorolac, 10 to 30 milligrams IV[30]). There are several U.S. Food and Drug Administration boxed warnings regarding NSAID use: Do not give NSAIDS to patients with aspirin or NSAID hypersensitivity; avoid in coagulopathic patients or those at risk for bleeding; and avoid in patients with renal impairment. Inform the urologist if the patient is given antiplatelet drugs (NSAIDS) or if the patient is taking antithrombotics, especially if imminent surgical therapy or lithotripsy is anticipated.[31] **Opioids** (e.g., hydromorphone, 0.5 to 2.0 milligrams IV) are also routinely given for pain control. Because both pain and opioids may cause vomiting, antiemetics are frequently required.

Lidocaine IV can reduce smooth muscle tone and reduce transmission by afferent sensory pathways. The dose is 1.5 mg/kg IV and should be given slowly to avoid numbness or dizziness. IV lidocaine may provide pain relief sooner than IV morphine. It is useful alone or used along with morphine.[32,33]

URINARY TRACT INFECTION

Patients with a ureteral stone and fever, renal insufficiency, and/or systemic signs of infection are treated with IV antibiotics and admitted. Consult urology to determine if surgical options are indicated.[31,34] First-dose antibiotic options include piperacillin-tazobactam, 3.375 grams IV; cefepime, 2 grams IV; ticarcillin-clavulanic acid, 3.1 grams IV; or ciprofloxacin, 400 milligrams IV. For patients without renal compromise, consider gentamicin or tobramycin, 3.0 milligrams/kg/d divided every 8 hours, plus ampicillin, 1 to 2 grams every 4 hours. Local sensitivities should guide antibiotic choice to prevent treatment failure.

Patients who have a ureteral stone with an associated urinary tract infection but no evidence of significant obstruction, fever, or systemic illness can be treated as outpatients, provided follow-up in 48 to 72 hours can be accomplished (see section "Disposition and Follow-Up" later in the chapter). The choice of antibiotic should cover gram-negative rods and be appropriate for antibiotic sensitivity at your institution. Resistance rates of >10% to 20% should preclude use of that antibiotic. Choices include ciprofloxacin, 500 milligrams PO twice a day for 10 to 14 days; levofloxacin, 500 milligrams PO once a day for 10 to 14 days; cefpodoxime, 200 milligrams PO twice a day for 10 to 14 days; or others predicted to be successful based on local sensitivities.

TABLE 94-5 Indications for Admission in Patients With Nephrolithiasis

Absolute Indications for Admission	Relative Indications for Admission
Intractable pain or vomiting	Fever
Urosepsis*	Solitary kidney or transplanted kidney without obstruction
Single or transplanted kidney with obstruction*	Obstructing stone with signs of urinary infection
Acute kidney injury	Urinary extravasation
Hypercalcemic crisis	Significant medical comorbidities
Severe medical comorbidities/advanced age	Stone unlikely to pass—large stone above the pelvic brim

*Indication for urgent decompression.

MEDICAL EXPULSION THERAPY

Studies of medical expulsion therapy have a variety of study designs, and results have sometimes been contradictory.[34-41] Tamsulosin, an α-blocker, is the most commonly used drug for medical expulsion therapy. The most recent guidelines[37,38] indicate that α-blockers may result in shorter stone expulsion times and are more effective for stones >5 mm. Surgical intervention rates appear similar with and without the drug. Inform patients of the drugs' limited benefit and important potential side effects, including orthostatic hypotension, lightheadedness and dizziness, and headache.[37,38] The dose of tamsulosin is 0.4 milligram PO once daily, but terazosin (5 to 10 milligrams once daily) and doxazosin (4 milligrams once daily) are also used.[35,37] Calcium channel blockers are not recommended, as effects appear inferior to α-blockers.[34,38,39] Steroids are not recommended.[34,38]

DISPOSITION AND FOLLOW-UP

Most patients with stones are discharged with urologic or primary care follow-up, at which time preventive therapy may be considered based on stone type.[16] Because of lower rates of spontaneous passage, discuss disposition of patients with large (>5 mm), irregular, or proximal stones (**Table 94-5**) with the urology consultant. Also discuss with the urologist the disposition of patients with renal insufficiency, severe underlying comorbidities, complete obstruction, multiple ED visits associated with the stone, renal transplantation, or associated urinary tract infection without sepsis.

Discharge is appropriate in patients with smaller stones, in the absence of infection, and when pain is controlled by oral analgesics. Give patients a urinary strainer with instructions to save any stones they pass for pathologic evaluation. **Average time for stone passage varies according to size and location but may range up to 7 to 30 days for stones 5 to 6 mm in diameter.** Patients should be counseled to return promptly for fever, vomiting, or uncontrolled pain. A prescription for an oral opiate and NSAIDs should be provided, as well as for medical expulsive therapy if used. Inform the urologist if the patient is using anticoagulant or antiplatelet drugs, especially if imminent surgical therapy or lithotripsy is anticipated.[31] Follow-up with a urologist within 7 days is recommended.

If the stone passes in the ED, no further acute treatment is required. Elective urologic consultation is recommended so that the composition of the stone is evaluated and a prophylactic strategy can be arranged. **Patients with hematuria, negative imaging studies, and no other source require outpatient urologic follow-up to determine the cause of hematuria.**

SPECIAL POPULATIONS/CONSIDERATIONS

PREGNANCY

Stones occur in 1 in 1500 pregnancies, and 80% to 90% present in the second or third trimester. The presentation is the same as in nonpregnant patients with flank pain (89%) and hematuria (95%).[42] The study of choice in pregnancy is US to identify hydronephrosis. However, up to 90% of pregnant patients display physiologic hydronephrosis. US techniques recommended to improve sensitivity and diagnostic accuracy include endovaginal approach and looking for ureteral jets and calculating resistive indices for the kidneys.[43] If US does not provide the information necessary for management, low-dose CT[44,45] or MRI[45] should be considered in consultation with a urologist and obstetrician. **The radiation doses for various imaging modalities for stones are as follows: kidney-ureter-bladder, 0.05 to 0.15 cGy; three-film IV pyelogram, 0.15 to 0.20 cGy; and CT scan, 2.2 to 2.5 cGy.[46]** The American College of Obstetricians and Gynecologists recognizes the need to use CT scan in the evaluation of emergent conditions in pregnancy, including nephrolithiasis; however, the imaging "should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient."[47]

With regard to treatment of pregnant patients, NSAIDS are not recommended, so narcotic pain control is most commonly used.[42] Nifedipine, known to be safe in pregnancy, has been recommended for medical expulsive therapy in pregnant patients,[42] but efficacy in the general population has been questioned.[34] α-Blockers are pregnancy category C drugs; safety is unknown.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 95

Complications of Urologic Procedures and Devices

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COMPLICATIONS OF URINARY CATHETERS

Urinary catheters should be used sparingly. Indwelling urethral catheters are the most common; suprapubic catheters require a surgical procedure but have fewer long-term infectious complications than indwelling urethral catheters after 5 days of use[1,2] (see Chapter 92, "Acute Urinary Retention"). **Table 95-1** lists the complications of urinary catheters.

INFECTION

Catheter-associated urinary tract infection (UTI) is one of the most common causes of nosocomial infections.[3] The risk of bacteriuria is approximately 3% to 8% per day, with the prevalence reaching almost 100% for long-term catheterization (by 30 days).[3] However, bacteriuria does not equate to clinical infection. Infection rates range from 0.5 to 14.8 per 1000 catheter days.[4] Comorbidities that increase the risk of infection include female sex, prostatic hypertrophy, elevated creatinine at time of insertion, diabetes, advanced age, catheter care violations, and debilitation.[3] Associated microbial factors include the source of the organisms, the specific bacteria, the route of invasion, and the duration of catheterization.

Pathophysiology In the noncatheterized urinary tract, bacteria are efficiently eliminated. Most bacterial strains that are introduced into the catheterized urinary tract, in contrast, are able to multiply to high concentrations in 24 hours. Bacteria may be able to gain access to the urinary tract through the catheter lumen (intraluminal) or along the catheter surface (extraluminal). If the drainage tube lumen is colonized, bacteria may ascend the collection bag and catheter and may cause an infection. An infection from the catheter lumen route begins with the formation of a biofilm on the catheter's inner surface. This biofilm extends from the uroepithelium through catheters to the drainage bag and allows adherence of bacteria to a catheter or mucosal surface.

TABLE 95-1 Complications of Urinary Catheters

Indwelling Urethral Catheters	Suprapubic Catheter
Prostatitis	Hematoma formation
Epididymitis	Persistent leakage
Scrotal abscess	Insertion failure/catheter misplacement
Creation of false urethral lumen	Abdominal wall cellulitis/abscess
Urethral disruption	Injury to abdominal organs
Urethral stricture	
Complications Common to Both Indwelling Urethral and Suprapubic Catheters	
Asymptomatic bacteriuria	
Urinary tract infection	
Pyelonephritis	
Intraluminal encrustation	
Mechanical obstruction	
Gross and microscopic hematuria	
Bladder perforation	
Nondeflating catheter balloon	
Allergy to catheter material	

TABLE 95-2 Catheter-Associated Urinary Tract Infection (CAUTI) Symptoms in Different Patient Populations

Symptomatic CAUTI Infection Type/Group	Diagnosis Requires Symptoms or Signs
Cystitis	New onset or worsening of fever, rigors, suprapubic pain or tenderness, altered mental status, malaise, acute hematuria (compare to prior assessment); pelvic discomfort or lethargy with no other identified cause.
Pyelonephritis	Syndrome, including fever, rigors, flank pain, or costovertebral angle tenderness.
Critically ill patient with compromised ability to give a history	Fever, rigors, change in normal appearance, change in normal mental status, subtle signs of either cystitis or pyelonephritis listed above.
Spinal cord injury patient	Fever, rigors, increased spasticity, autonomic dysreflexia, or sense of unease.
Bacteremia	Diagnosis supported by correlation between blood and urine cultures.
Sepsis syndrome	See Chapter 151, "Sepsis."
Suppurative Complications	
Epididymitis	See Chapter 93, "Male Genital Problems."
Prostatitis	See Chapter 93.
Abscess, scrotal, prostate	See Chapter 93.

Organisms become embedded within the biofilm and gain protection from the mechanical flow of urine, host defenses, and antibiotics.[5] The microbiology varies according to the duration of catheter placement. During short-term catheterization, infections are usually due to single organisms, most commonly *Escherichia coli*, followed by *Klebsiella*, *Pseudomonas*, *Enterobacter*, and gram-positive cocci such as staphylococci. With long-term catheterization (≤30 days), catheter-associated UTIs are usually polymicrobial from *E. coli*, *Proteus mirabilis*, *Pseudomonas*, *Morganella morganii*, and *Candida* species.

Clinical Features Signs and symptoms include fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; flank pain; costovertebral angle tenderness; acute hematuria; pelvic discomfort; and in those patients whose catheters have been removed, dysuria, urgent or frequent urination, or suprapubic pain or tenderness. In patients with spinal cord injury, increased spasticity, autonomic dysreflexia, and sense of unease are also compatible with infection.[3]

Diagnosis Specific symptoms of symptomatic infection are listed in **Table 95-2.**[3,6] **Pyuria is universal for patients with long-term (>1 month) indwelling catheters; in the absence of clinical symptoms, pyuria should not be used in the diagnosis of symptomatic infection.**[3-5]

Pyelonephritis (complicated UTI; see Chapter 91, "Urinary Tract Infections and Hematuria") is the most common complication of febrile catheter-associated infections. Other related infections include prostatitis, epididymitis, and scrotal or prostate abscess. Obtain urine cultures prior to empiric antibiotic therapy and obtain blood cultures if the patient is septic or immunocompromised.[5]

Treatment **Remove the catheter if clinically feasible,**[3,5] **or replace the catheter if it has been in place for more than 14 days.**[5] **Antibiotic treatment of asymptomatic bacteriuria in a patient with a short-term indwelling urinary catheter is not recommended, unless the patient is pregnant or a urologic procedure is immediately pending.**[3,5,7] Guidelines and reviews recommend antibiotics for symptomatic catheter-associated infections only. Promptly give empiric antibiotics.[3,5] Assess local resistance patterns before instituting therapy, and tailor therapy once culture results are available. Inpatient treatment for complicated UTI is reviewed in Table 91-6, and outpatient treatment for patients without clinical toxicity is presented in Table 91-5; see Chapter 91, "Urinary Tract Infections and Hematuria." A total of 7 days is the recommended duration of antimicrobial treatment for patients with prompt resolution of symptoms, and a total of 10 to 14 days of treatment is recommended for those with a delayed response.[3] Asymptomatic candiduria does not require treatment, except in high-risk populations, such as immunocompromised or neutropenic patients. If a *Candida* UTI is present, remove or replace the catheter, and treat with antifungal agents for 14 days.[5]

CATHETER OBSTRUCTION AND LEAKAGE

Urethral catheters can become obstructed for many reasons. The most common in the patient without hematuria is the formation of intraluminal encrustations during long-term placement. Concretions are composed of compounds such as ammonium magnesium sulfate (struvite) and calcium phosphate (apatite), often originating from urease-splitting organisms, such as *Protease* and *Morganella*. Such encrustations can increase the risk of formation of infectious bladder stones with continued bladder infection and bladder trauma.[8] A catheter obstruction may lead to urinary leakage around the catheter and acute urinary retention. Replacement of the catheter is the most common management used in the ED. See also Chapter 92, "Acute Urinary Retention." Options to prevent re-obstruction include oral methenamine, catheter management by urology, or management by primary care at follow-up.

NONDEFLATION OF FOLEY RETENTION BALLOON

Nondeflation of the retention balloon on the catheter can be caused by a faulty valve mechanism or crystallization of balloon fluid, yielding entrapment of the Foley catheter.[9] One noninvasive method is introduction of a flexible guidewire into the balloon inflation channel after cutting off the plastic cylindrical valve from the catheter just below its head. The guidewire dilates the channel and may allow the balloon to deflate. If unsuccessful, try step 2; a 22-gauge central venous catheter can be passed over the guidewire. When the catheter tip is in the balloon, the wire can be removed, and the balloon may drain.[9] If step 2 is unsuccessful, instill 10 mL of mineral oil and leave for 15 minutes in an attempt to chemically dissolve the balloon.[9] If simple methods do not work, urologic consultation for intervention and potential cystoscopy or other complex management is recommended.[10] Another alternative is US-guided percutaneous rupture of the balloon using a needle, typically done by interventional radiology with input from urology.

TRAUMATIC COMPLICATIONS

Trauma is another common and sometimes dangerous complication of a urinary catheter. A catheter can cause false passages in the urethra during insertion, hematuria from direct urethral or bladder irritation, pain or erosion at the urethral meatus, and, rarely, bladder perforation.[11] Ureteral intubation has been reported.[12] Bowel perforation has been

reported in the context of bladder perforation, usually from a chronic indwelling catheter.[13] Nontotal deflation of the balloon and ridging (the formation of ridges on the deflated balloon) can cause urethral trauma during catheter removal.[11] Consult urology if injury to the bladder or urethra is suspected.

COMPLICATIONS OF PERCUTANEOUS NEPHROSTOMY AND NEPHROLITHOTOMY

Percutaneous nephrostomy is a urinary drainage procedure used for supravesical or ureteral obstruction secondary to malignancy, pyonephrosis, GU stones, and ureteral strictures. The percutaneous procedure to remove renal calculi is known as *percutaneous nephrolithotomy*. Nephrostomy tubes or stents are commonly left in place during this procedure. In general, the risk of complications is low and includes bleeding, infection, mechanical complications related to the catheter (dislodgement or obstruction), and accidental punctures of adjacent organs.[14-16]

During insertion, injury can occur to the renal collecting system (subintimal dissection), lungs (pneumothorax), liver, spleen, and bowel (perforation).[16,17] Complications usually are clinically apparent during or immediately after the procedure, but recognition may be delayed a few days.

Bleeding Complications Bleeding and hemorrhage can occur, especially if the patient has a coagulopathy. Check hemoglobin, hematocrit, and renal function. Obtain coagulation studies (prothrombin time, PTT, and platelet count) and type and cross-match if bleeding is excessive, if coagulopathy is suspected, or if the patient is unstable. Most bleeding episodes are mild and can be managed with irrigation to clear nephrostomy tube blood clots. Transient hematuria is common and usually resolves spontaneously in 2 to 3 days.[17] More severe bleeding, reported in 0.6% to 1.4% of patients,[16] can be handled by catheter tamponade, a procedure undertaken by the urologist and radiologist. Severe hemorrhage occurs from vascular injury, such as laceration of an artery, formation of an arteriovenous fistula, or bleeding from a pseudoaneurysm, and may occur in the retroperitoneal space or perirenal areas. In such cases, fluid resuscitation and blood transfusion, in addition to more definitive interventions, are required. Angiographic studies with possible embolization may be needed to ascertain the site of bleeding.[15,17]

Infectious Complications Infections from nephrostomy tubes include simple bacteriuria, pyelonephritis, renal abscess, bacteremia, and urosepsis. Septicemia has been reported in 0.8% to 4.7% of cases.[16] Signs and symptoms are fever, chills, rigors, pain, and purulent drainage at the site or from the tube. Obtain urine and wound cultures and give antibiotics.

Mechanical Complications Catheter dislodgement, tube blockage, and residual stone fragments can occur. CT scan may be helpful for specific diagnosis. The risk of catheter dislodgement increases with increasing duration of the nephrostomy and obesity.[18] Dislodgement occurring in the early postoperative period usually requires creation of a new tract at a different site. Dislodgement occurring after some period may be treated by recannulation under fluoroscopic guidance. Tube blockage can occur secondary to encrustations and kinking, which often require urologic intervention.

URINARY DIVERSION AND ORTHOTOPIC BLADDER SUBSTITUTION

The most common method of urinary diversion in the United States is the ileal conduit. With this procedure, a section of small bowel is isolated, and the free ends of the remaining small bowel are reunited, allowing for normal bowel function. The ureters are reimplanted to the isolated section of small bowel, most commonly at the base of the conduit. A stoma is created, typically on the anterior abdominal wall, where a collecting bag is attached. Postoperative complications include bowel obstruction, pyelonephritis, skin breakdown surrounding the stoma, stenosis of the stoma, and inflammatory changes of the upper tract due to reflux of urine back into the ureters. Long-term complications include bowel obstruction or dysfunction (20.3%); deterioration in kidney function (20.2%); symptomatic UTI/pyelonephritis (16.5%); stomal hernia or stenosis (15.4%); urolithiasis (15.3%); metabolic derangements, most often metabolic acidosis (12.8%); and structural conduit dysfunction (11.5%).[19,20]

There are multiple newer methods of creating a neobladder for orthotopic bladder substitution. These methods all have a goal of creating a continent reservoir for urine without reflux of the urine into the reimplanted ureters, which predisposes the patient to pyelonephritis. Options include other means of isolating portions of the small bowel (Kock pouch, T pouch, W-shaped neobladder) or large bowel (ileocecal segment). Evidenced-based evaluations of multiple methods have failed to identify a superior procedure.[21-23] Bacteriuria is very common after the procedure (up to 80%) and mostly involves skin flora, but may occasionally include uropathogenic strains (gram-negative Enterobacteriaceae species such as *E. coli*, *Proteus*, *Pseudomonas*, and *Enterococcus faecalis*).[24,25] Clean intermittent catheterization, frequently required after the procedure, is associated with increased bacteriuria and pyuria. **Diagnosis of infection should be made on evidence of symptomatic infection based on fever, flank pain, a change in chronic symptoms, or culture of pathologic organisms.**[24,25] Consult with urology for optimal management.

LITHOTRIPSY

Extracorporeal shock wave lithotripsy is the application of high-intensity sound waves to fragment GU calculi so they can pass down the ureter. Common complications include colicky pain (15% to 40%), gross hematuria (32%), skin bruising (up to 26%), and steinstrasse ("street of stone," or aggregate of stone fragments lining and/or impacting the ureter; up to 24%).[26,27] In one report of 235 patients, 6% visited the ED after the procedure and 3.4% were admitted.[28] Uncommon complications include spleen rupture, kidney rupture, abdominal or intrahepatic hematoma, pyelonephritis/sepsis, bowel injury, ureteric perforations, psoas abscess, vascular injury, and pancreatitis (a small increase in lipase is common).[26,27,29-31] Postlithotripsy patients may develop abdominal and flank pain, nausea, vomiting (especially 48 hours after procedure), skin ecchymosis, gross hematuria, fever, or sepsis. Hematuria is generally self-limited (<24 hours); however, UTI may coexist. Diagnosis of minor complications usually requires CBC, basic chemistries, urinalysis, and renal US if obstruction is suspected. CT scan or MRI (only if stable) is indicated if serious complications are suspected (consider with flank hematoma, decrease in hematocrit, hypotension, syncope, or significant pain). Acute management may include IV fluid hydration, antiemetics, analgesics, monitoring, fluid resuscitation, blood transfusions, and antibiotics. Consider urology consultation early on, because specific treatments, such as embolization, may be required.[32]

COMPLICATIONS OF URETERAL STENTS

Ureteral stents are used primarily in patients to relieve ureteral obstruction and maintain ureteral lumen patency or as an adjunct to lithotripsy. Obstruction to the ureter may result from causes such as stones, strictures, trauma, malignancies, or retroperitoneal fibrosis. Stents can be placed during ureteroscopy, by the percutaneous nephrostomy route, or during surgery involving the GU tract. **Table 95-3** lists the complications of ureteral stents.

Many factors contribute to stent-related UTIs. Stents induce a foreign body reaction, which increases the risk of infection. Stent encrustation also promotes infection. Pyelonephritis and sepsis can occur but are less common.

Most minor infections can be managed with outpatient antibiotics (see Tables 91-5 and 91-6 in Chapter 91, "Urinary Tract Infections and Hematuria") and do not require stent removal. If pyelonephritis or a systemic infection is suspected, IV antibiotics, radiologic studies to determine the position of the stent, and urologic consultation are required. Stents usually can be visualized by plain abdominal radiographs due to the presence of radiodense marking embedded within the catheters. US imaging can detect hydronephrosis, along with confirmatory CT studies if obstruction or pyelonephritis is present.[33]

TABLE 95-3 Complications of Ureteral Stents

Complication	Management
Fever with pyelonephritis or sepsis	Resuscitate, admit, IV antibiotics, consult urology
Simple urinary tract infection (UTI)	Oral antibiotics
Microscopic hematuria/gross hematuria	Microscopic hematuria is expected; consult urology for gross hematuria
Pyuria	Consider treatment if coexistent bacteriuria
Irritative bladder symptoms: Dysuria/urgency/frequency Flank pain/abdominal pain Pain with voiding Incontinence (urinary)	Analgesics, anticholinergics, rule out UTI
Mechanical/anatomic issues: Obstruction (encrustation, clots, compression) Stent migration/stent fragmentation Erosion of the urinary tract Vascular-ureter fistula Malposition Stent malfunction	Consult urology; resuscitate when needed



FIGURE 95-1. Ureteral stent migration. This abdominal plain film demonstrates stent migration with the distal portion of the stent coiled within the bladder. [Reproduced with permission from Cline D, Stead L: *Abdominal Emergencies*. © 2008, McGraw-Hill, Inc., New York.]

Symptoms and signs suggestive of an irritative bladder, such as dysuria, urgency, frequency, incontinence, and pain during voiding, occur commonly in patients with ureteral stents. Treatment options for these symptoms can include antimuscarinics such as tolterodine, 2 milligrams twice daily, or α-blockers such as tamsulosin, 0.4 milligrams daily; common analgesics have poor efficacy.[34] Obtain urinalysis and culture to exclude UTI. Severe flank pain requires evaluation for stent migration, infection, or obstruction. Asymptomatic microscopic hematuria is usually of no clinical significance, but gross hematuria may indicate stent migration or ureteral erosion. Obtain imaging to identify stent position.[33]

Serious problems, such as stent migration and stent fragmentation—or even rarer, ureteral-arterial fistulization due to stent erosion into a nearby vessel—are usually late complications seen with long-term stent placements. Stent migration can occur upward above the ureteropelvic junction or downward below this junction. See **Figure 95-1** for a radiographic demonstration of ureteral stent migration. Migration can lead to obstruction and infections. Stent migration results in symptoms of new-onset abdominal pain, fever, and irritative bladder symptoms and hematuria.[33] For new anemia without hematuria, obtain a CT without contrast to rule out a stent-caused retroperitoneal hematoma.[35] In the presence of severe gross hematuria and syncope or hypotension, assume that a vascular fistulization from an eroding stent exists until proven otherwise.[35,36] Resuscitate and obtain emergency urologic and surgical consultation.

PROSTATE SURGICAL PROCEDURES

Prostate surgery is performed for symptomatic benign prostatic hyperplasia or prostate cancer. Surgical prostate techniques include needle biopsy, transurethral resection of the prostate (TURP), transurethral electrovaporization, transurethral microwave thermotherapy, transurethral needle ablation, and visually assisted laser prostatectomy.[37,38] For TURP, reported complications include urinary retention (3% to 9%), urethral strictures (2.2% to 9.8% as late complication), clot retention (2% to 13%), UTI (1.7%), and bleeding requiring transfusion (0.4% to 2%).[38,39] Less common complications include urosepsis, myocardial infraction, pulmonary embolism, and cardiac arrhythmia.[37] Bladder rupture following TURP has been reported.[40] Patients may also experience obstructive or irritative voiding symptoms, including incontinence, dysuria, hesitancy, dribbling, urgency, and frequency.

Depending on severity of illness, appropriate laboratory studies may include urinalysis, CBC, blood type and screen, blood chemistries, and renal function. Assess for hemodynamic instability and treat with IV fluids or blood for life-threatening bleeding. Patients with outflow obstruction should be treated with a three-way Foley catheter. Start with manual irrigation to remove clots, and then initiate continuous irrigation with normal saline until clear or slight pink return.[9] If bleeding does not clear, consult urology. **Prolonged irrigation requires monitoring of serum electrolytes to assess for hyponatremia.**[9] If infection is suspected, obtain urine cultures, administer antibiotics, and consult urology.

COMPLICATIONS OF ARTIFICIAL URINARY SPHINCTERS

The artificial urinary sphincter is used for urinary incontinence secondary to sphincter disturbance, postsurgical incontinence, neurogenic bladder with incontinence, trauma to the urethra, and congenital conditions associated with bladder dysfunction, such as exstrophy and epispadias. Sphincters are used predominantly in men, but are also placed in women. Placement of the artificial sphincter increases the resistance around the urethra and provides urinary continence.[41] Mechanical parts of the artificial sphincter include an implanted pump, an inflatable cuff that encircles the urethra, and a pressure-regulating reservoir balloon (**Figure 95-2**). These are connected by a set of two tubes. Continence occurs when fluid is moved from the balloon to the cuff. To allow urination, the cuff is emptied, and fluid moves to the reservoir.

The most common complication after primary implantation is urinary retention, occurring in 31% of patients.[41] **Never introduce a urethral urinary drainage catheter through an artificial urinary sphincter.** Periprosthetic infection can present early or late after surgical implantation (2%).[42] Infections occurring early after implantation are usually due to skin flora. Later infections are usually due to gram-negative organisms of the urinary tract. Symptoms and signs of infection can range from pain, swelling, and induration of the site to localized erythema of the pump or cuff site. More serious infections can present with fever, cellulitis, local abscess formation, drainage from incision sites, and erosion of the pump or the cuff. Infections can cause the cuff to erode to the skin or the urethra.[42] Treat periprosthetic infection with antibiotics and sphincter removal.

Retained air bubbles, tube kinking, fluid leaks, and perforation of the cuff are some of the mechanical complications that can occur leading

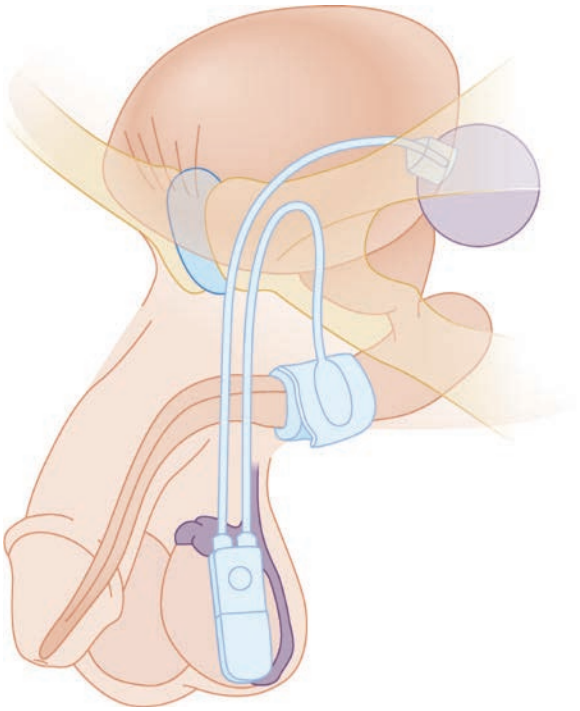

FIGURE 95-2. Diagram of artificial urinary sphincter. [Adapted with permission from James MH, McCammon KA: Artificial urinary sphincter for post-prostatectomy incontinence: a review. *Int J Urol* 21: 536, 2014. Copyright John Wiley & Sons.]

to dysfunction of the artificial sphincter. A careful history may provide clues to malfunction. A pump that is difficult to squeeze implies blockage due to any cause, whereas a pump that remains compressed after squeezing signifies pressure loss or fluid leakage. Urinary catheterization and damage to the device components during other nonurologic surgeries may account for iatrogenic malfunction of the artificial sphincter.[43] Plain radiographs of the pelvis and other imaging studies are used to assess continuity of the mechanical components.

Urethral erosion secondary to infection or excessive cuff pressure around the urethra is another serious complication. Signs and symptoms include pain, swelling along the urethra and in the perineum, difficulty voiding, bloody urethral discharge, and infection.[41-44]

Acute urinary retention in a patient with an artificial sphincter implant may occur as a result of bladder neck contractures, urethral strictures, or cuff erosion. Evaluation usually requires cystourethrography or cystourethral endoscopy.

Diagnosis and Treatment Evaluation in the ED of complications related to the artificial sphincter requires a thorough history noting the model type and make; symptom assessment; a detailed physical examination; urinalysis; appropriate labs, cultures, and imaging studies; and consideration for IV antibiotics as indicated. Consult urology emergently. Do not introduce a urethral urinary drainage catheter through an artificial urinary sphincter.

COMPLICATIONS OF TREATMENTS FOR ERECTILE DYSFUNCTION

The most common causes of erectile dysfunction are diabetes, priapism, vascular disease, Peyronie's disease (deformity especially seen on erection due to nodules/fibrous plaques in penile tissue), pelvic trauma or surgery, spinal cord injury, and psychogenic reasons. Oral phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) are often prescribed for erectile dysfunction. **Nitrates can cause life-threatening hypotension** when taken with phosphodiesterase-5 inhibitors. Sudden hearing loss has also been reported as an adverse effect. Some patients with erectile dysfunction fail oral pharmacologic therapy and are treated with penile injectable medications or nonpharmacologic interventions such as vacuum therapy, external splint devices, and surgically implantable prostheses.[45-47]

Drugs used for **intracavernosal injections** include papaverine, phentolamine, and alprostadil, a prostaglandin E_1 analogue. Side effects include penile pain, prolonged erections (4 to 6 hours), priapism, and localized hematoma. Of these, priapism is the most serious complication (see Chapter 93, "Male Genital Problems").

Intraurethral injection of alprostadil or urethral insertion of a medicated pellet has a similar effect as intracavernosal injections. Intraurethral administration is usually free of any major systemic side effects, but hypotension and syncope secondary to a vasovagal reaction due to the anxiety of the injection and the vasodilatory effects of the drug can occur.[48,49]

Vacuum devices work by use of negative pressure and the use of a constriction ring to cause venous and arterial congestion, thus causing penile engorgement. Serious complications from the use of a vacuum device include penile skin necrosis, urethral bleeding, ischemia, and subcutaneous hemorrhage with ecchymosis. Peyronie's disease and Fournier's gangrene have also been reported.[50,51]

A **penile prosthesis** is reserved for men who fail pharmacologic treatment. Postoperative urinary retention, penoscrotal hematoma formation, and superficial wound infections have been reported. Infection usually occurs soon after the primary surgery for implantation.[45,46] Late infections can occur years after the procedure secondary to bacteremia. Organisms causing penile prosthesis infection are typically *Staphylococcus epidermidis*, *Staphylococcus aureus, E. coli*, and *Candida*. Infections present as pain along the device (e.g., in the scrotum or along the penis), erosion, and purulent urethral discharge. Treatment requires antibiotics and possible removal of the entire device by the urologist.[45,46,52]

Erosion of the prosthesis can occur into penile tissue and often is accompanied by an infection in the same area.[45] Migration of the device may occur proximally or distally, presenting as extrusion through the urethral meatus. Consult urology for erosion problems and device migration.[45,46] Penile ischemia and necrosis are rare but serious complications. Mechanical failures may occur, such as pump autoinflation or fluid leakage from tubing, cylinder, or reservoir. Urologic consultation is necessary to evaluate mechanical problems.

VASECTOMY

With few exceptions, vasectomies are completed in the urologist's office and are a safe procedure, with a complication rate of 1% to 2%.[53] Complications include bleeding and scrotal hematoma (most common), local wound infections (cellulitis, abscess, necrotizing infection), epididymitis, and painful sperm granulomas. Patients may develop persistent testicular pain or congestive epididymitis (pain and testicular tenderness on the affected side) months to years later.[53]

Evaluate for infection, especially if the patient is immunosuppressed, and treat accordingly; consider scrotal US and consult urology for deep abscess (see Chapter 93). When there is no evidence of bleeding or wound infection, treat postvasectomy epididymitis with ice packs, scrotal support, and analgesia with NSAIDs or opiates.

ADULT CIRCUMCISION

Circumcision, or foreskin resection, is usually performed on infant males. However, the procedure is also performed in adolescents and adults.[54] Complications after circumcision include bleeding (most common), infection, pain, edema, and wound dehiscence due to premature erection before completion of healing.[55,56] Treat minor bleeding with direct pressure or a topical thrombostatic agent as needed. Administer oral antibiotics (trimethoprim-sulfamethoxazole or ciprofloxacin) with local wound care for minor infections. Give analgesia as indicated. Consult urology for significant bleeding or infection. Plastic devices used for circumcision may become displaced prior to planned removal date; consult urology for management.[57]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 96

Abnormal Uterine Bleeding

Bophal Sarha Hang

INTRODUCTION

Abnormal uterine bleeding is an overarching term that is defined as bleeding from the uterine corpus that is irregular in volume, frequency, or duration in absence of pregnancy (**Table 96-1**).[1,2] Vaginal bleeding is a common complaint in the ED, and differential diagnoses include pregnancy, structural abnormalities (e.g., polyps, fibroids), endometritis, coagulopathies, trauma, and various other causes. This chapter will focus on the ED evaluation and management of abnormal uterine bleeding.

MENSTRUAL CYCLE

A normal menstrual cycle has an average duration of 4.5 to 8 days and an interval of 24 to 38 days between the onset of menses. The average blood loss is ≤30 mL, and menstrual blood loss >80 mL is considered abnormal. Menstrual cycle variation during early menarche and the perimenopausal period is due to high prevalence of anovulation. **Figure 96-1** depicts hormonal and endometrial changes associated with a normal menstrual cycle.

In response to the rising estrogen levels, the pituitary gland secretes follicle-stimulating hormone and luteinizing hormone, stimulating the release of a mature oocyte. The residual follicular capsule forms the corpus luteum. During the luteal phase, the corpus luteum secretes estrogen and progesterone, which maintains the integrity of the endometrium for implantation. In the absence of human chorionic gonadotropin released by a pregnancy, the corpus luteum involutes, and estrogen and progesterone levels fall. Hormonal withdrawal causes vasoconstriction in the spiral arterioles of the endometrium, resulting in endometrial sloughing and leading to menses.

CLINICAL FEATURES

HISTORY

Obtaining a focused medical history should include bleeding pattern, associated symptoms, and past medical, reproductive, and sexual history (**Table 96-2**). The average tampon or pad absorbs 20 to 30 mL of vaginal effluent. However, judging the amount of blood loss by usage may be unreliable because personal habits vary greatly among women. In women with heavy bleeding, there may be insufficient time for fibrinolysis, so blood clots form.

Determine whether bleeding is acute or chronic. It is also important to elicit whether there is a family history of bleeding disorders or chronic illnesses. **Up to 20% of women with heavy bleeding have an underlying coagulation disorder, with von Willebrand's disease being the most common.** Screening criteria include heavy menstrual bleeding since menarche, postpartum hemorrhage, bleeding related to surgery or dental procedure, and two or more of the following: bruising one to two times a month, epistaxis one to two times a month, frequent gum bleeding, or family history. Medications, such as hormonal contraceptives, anticoagulants, selective serotonin reuptake inhibitors, tamoxifen, and herbal supplements (e.g., ginseng), are also important causes of bleeding.[3]

PHYSICAL EXAMINATION

Evaluate for hemodynamic stability on initial assessment. Significant signs of volume depletion may not be present until bleeding is profuse. A focused physical examination including pelvic is required to exclude life-threatening blood loss and need for emergent surgical intervention. Hirsutism, obesity, and galactorrhea may point toward endocrinologic causes. Petechiae, purpura, and mucosal bleeding require further hematologic investigation.

For pelvic examinations in the ED, both male and female physicians are equally advised to have a chaperone present. Inspect the perineum, vulva, urethra, and perianal region before speculum exam. Evaluate the vaginal canal and cervix for potential causes of bleeding. Bimanual exam of the uterus and adnexal structures should be performed to assess for size, masses, or tenderness.

In elderly patients, immobility and degenerative joint disease may make it difficult to place the patient in the dorsal lithotomy position. Patients may be positioned supine, with the head supported with a pillow and with knees flexed and hips externally rotated (frog-leg position). Consider using a smaller speculum with generous lubrication if there is vaginal atrophy. Abnormalities such as irregular nodules, masses, or thickened rectovaginal septum may suggest malignancy.

CAUSES OF VAGINAL BLEEDING

The causes of abnormal uterine bleeding are classified into structural and nonstructural causes, using the acronym PALM-COEIN: **P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy and hyperplasia, **C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot otherwise classified.[4] Causes of bleeding based on age are shown in **Table 96-3**. The term *abnormal uterine bleeding* encompasses all causes of abnormal bleeding in nonpregnant women, and the most likely causes are largely determined by patient age. Because the first clinical signs of heavy menstrual bleeding (heavy uterine bleeding) are noted after the onset of menses during early adolescence, structural causes are uncommon. Anovulatory and bleeding disorders are most common during this time period (ages 13 to 19). **Pregnancy-related complications become the most common cause of abnormal vaginal bleeding during the reproductive years.** Issues regarding pregnancy are covered in Chapters 98, "Ectopic Pregnancy and Emergencies in the First 20 Weeks of Pregnancy," and 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period."

Abnormal uterine bleeding as a result of local structural pathology such as polyps and fibroids is not typically seen until women reach their mid-30s. Perimenopausal anovulatory bleeding is typically seen in the mid to late 40s. Postmenopausal bleeding is often related to atrophic vaginitis, exogenous hormones, and malignancy.

STRUCTURAL CAUSES OF VAGINAL BLEEDING

POLYPS

Endometrial and endocervical polyps are epithelial proliferations that most often are benign. Although most polyps are asymptomatic, polyps can be a cause of abnormal uterine bleeding in women older than 35 years. A common symptom is intermenstrual bleeding, and diagnosis is made on US or hysteroscopy.

TABLE 96-1 FIGO Terminology for Bleeding[2*]

Type	Definition
Abnormal uterine bleeding	Bleeding that is abnormal in regularity, volume, frequency, or duration. Bleeding may be acute or chronic and is present for at least 6 months.
Heavy menstrual bleeding *(heavy uterine bleeding [HUB] replaces menorrhagia)*	Excessive menstrual bleeding that interferes with a woman's physical, emotional, social, and quality of life. Note that the definition is menstrual bleeding deemed excessive by the patient regardless of duration, frequency, or timing.
Amenorrhea	Bleeding that is absent for >6 months.
Prolonged menstrual bleeding	Menstrual periods that exceed 8 days' duration on a regular basis.
Intermenstrual bleeding *(replaces metrorrhagia)*	Bleeding episodes between normally timed menstrual periods.
Irregular menstrual bleeding	Unpredictable onset of menses, with cycle variations >20 days over a period of 1 year.
Postmenopausal bleeding	Any bleeding that occurs >12 months after cessation of menstruation.

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

Source: https://www.figo.org/news/ground-breaking-figo-classification-published-ijgo-0014139.

*Discarded terms include dysfunctional uterine bleeding, menorrhagia, functional uterine bleeding, hypermenorrhea, hypomenorrhea, menometrorrhagia, metrorrhagia, oligomenorrhea, polymenorrhea, and uterine hemorrhage.[2]

ADENOMYOSIS

Adenomyosis is the presence of endometrial glands and stroma within the myometrium. The histopathology is often diffuse within the uterus, but localized areas of growth are called adenomyomas. Symptoms include painful, heavy periods most commonly seen in the fourth and fifth decade of life. MRI is the imaging modality of choice, but US is a good alternative. Patients with severe bleeding unresponsive to medical management often require surgical management.

LEIOMYOMAS

Uterine fibroids (also called leiomyoma or myoma) are the most common benign tumors of the pelvis in women; an estimated 25% of white women and 50% of black women have fibroids in their reproductive years. The cause is unclear, but fibroids increase with reproductive age and decrease in size during menopause. Thus, growth is thought to be dependent on genetic and hormonal factors. In some cases, fibroids may enlarge early in pregnancy and with oral contraceptive pill use. Most fibroids are asymptomatic, but up to 30% of patients with leiomyomas experience pelvic pain and abnormal bleeding. Acute pain is rare, but severe pain may be experienced with torsion or degeneration. Degeneration results from rapid growth and loss of blood supply, often seen during early pregnancy. A rare case of spontaneous fibroid rupture causing massive intra-abdominal hemorrhage has been reported in the literature.[5]

Signs and symptoms of fibroids vary depending on size and location. Large fibroids may be palpated on abdominal or rectal exam. Symptoms

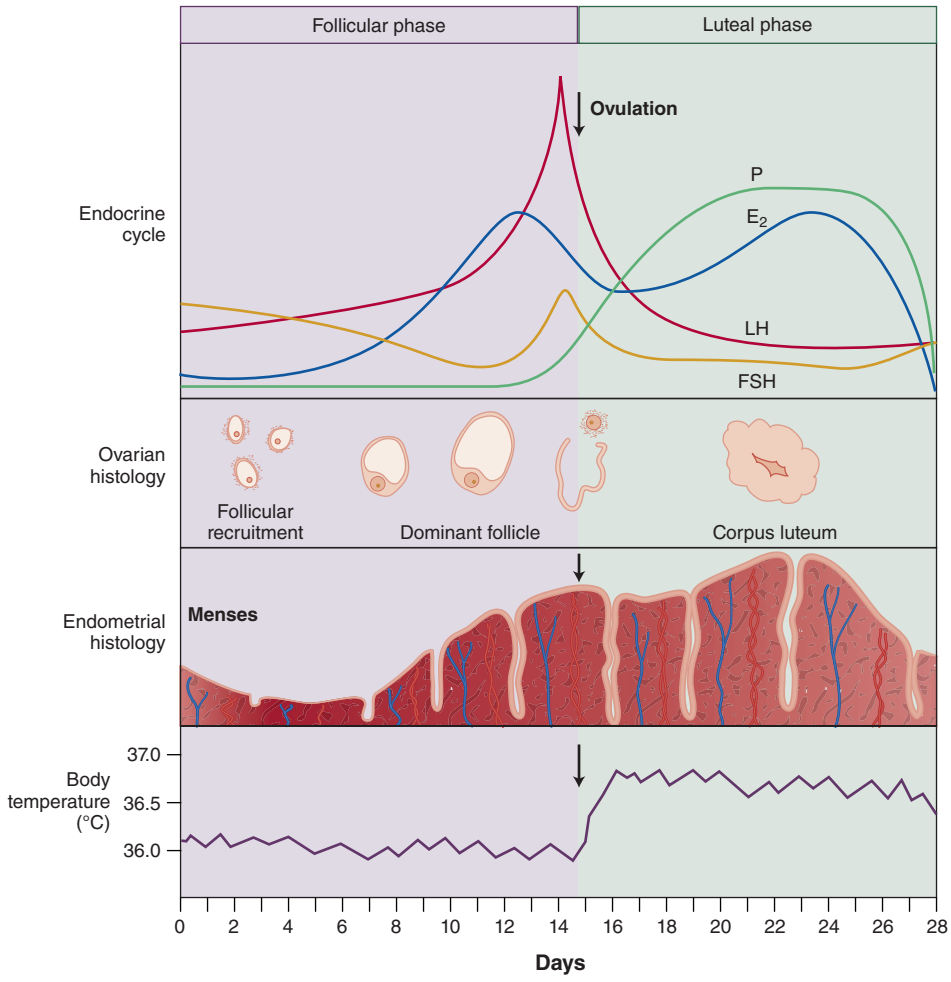

FIGURE 96-1. The hormonal, ovarian, endometrial, and basal body temperature changes and relationships throughout the normal menstrual cycle. E_2 = prostaglandin E_2; FSH = follicle-stimulating hormone; LH = luteinizing hormone; P = progesterone. [Reproduced with permission from Patel DR, Greydanus DE, Baker RJ: *Pediatric Practice Sports Medicine.* © 2009, McGraw-Hill, Inc., New York, NY.]

TABLE 96-2 Important Historical Elements in Uterine Bleeding

Category	Details
Reproductive history	Age of menarche
	Menstrual history
	Date of the last menstrual period
	Pattern of normal and abnormal bleeding or discharge
	Presence of dysmenorrhea
Sexual history	Current sexual activity
	Contraception
	Use of barrier protection
	Pregnant—yes/no?
	Gravida and para
	Previous abortion or recent termination
	History of ectopic pregnancy
	History of pelvic inflammatory disease, sexually transmitted diseases, human immunodeficiency virus, and hepatitis status
History of trauma	Postcoital bleeding
Possibility of retained foreign body	—
Medications, including alternative and complementary medicine	Anticoagulants NSAIDs Ginseng
Past medical history	Signs and symptoms of coagulopathy, including nosebleeds, petechiae, and ecchymoses
	Endocrine disorders, including diabetes, pituitary tumors, polycystic ovary disease, hyperthyroidism, and hypothyroidism
	Liver disease
Associated symptoms	Urinary, GI, musculoskeletal symptoms; fever or syncope

of acute degeneration include tenderness, rebound guarding, fever, and elevated WBC count. Rapid growth at any age or growth after menopause is highly suspicious for malignant transformation. The best diagnostic test is ultrasonography, which is as sensitive as MRI.

In the ED, management is focused on treating complications associated with fibroids. Iron deficiency anemia is often long-standing and may require a blood transfusion. Other complications are rarer, but constipation, urinary retention, vaginal or intraperitoneal hemorrhage, deep vein thrombosis, and mesenteric thrombosis have been reported.[6] NSAIDs are the mainstays for analgesia in the ED. Medical management with hormonal agents may be initiated in the ED with gynecologic consultation. Tranexamic acid can reduce menstrual blood loss from uterine fibroids.[7] See discussion below on tranexamic acid. Surgical removal of fibroids is associated with a 25% to 30% rate of recurrence and significant bleeding complications. Uterine artery embolization is an effective treatment for symptomatic fibroids, resulting in decreased fibroid volume and alleviation of symptoms.[8]

TABLE 96-3 Causes of Bleeding by Age Group*

Adolescent	Reproductive	Perimenopausal	Postmenopausal
Anovulation (hypothalamic-pituitary-ovarian immaturity)	Pregnancy	Anovulation	Atrophic vaginitis (30%)
Pregnancy	Anovulation (PCOS)	Uterine leiomyomas	Exogenous hormone use (30%)
Exogenous hormones or OCP	Exogenous hormone use or OCP	Cervical and endometrial polyps	Endometrial lesions, including cancer (30%)
Coagulopathy	Uterine leiomyomas	Thyroid dysfunction	Other tumor—vulvar, vaginal, cervical (10%)
Pelvic infections	Cervical and endometrial polyps Thyroid dysfunction		

Abbreviations: OCP = oral contraceptive pill; PCOS = polycystic ovary syndrome.

*Prepubertal bleeding is discussed in Chapter 136, "Pediatric Urologic and Gynecologic Disorders."

MALIGNANCY

Any malignancy of the genital tract, in particular endometrial or cervical cancer, may produce bleeding. **Consider endometrial hyperplasia or cancer in women >45 years old or in younger women with other risk factors.**[9] The amount of bleeding does not correlate with the severity of disease. All patients with postmenopausal bleeding warrant prompt outpatient referral for US and endometrial biopsy. Elderly patients may not be able to accurately describe the location of pain or bleeding in the proximity of the bladder, uterus, or rectum. Therefore, make sure to adequately visualize the urethra, vagina, and cervix on pelvic examination.

Vaginal bleeding, especially when seen in conjunction with atrophic vaginitis, may be associated with the use of pessaries and douche solutions, which can irritate the mucosa. Cervical polyps can also cause vaginal bleeding. However, an endometrial biopsy is ultimately required to rule out other serious causes of bleeding.

NONSTRUCTURAL CAUSES OF VAGINAL BLEEDING

COAGULOPATHIES

Primary coagulation disorders account for up to 20% of acute uterine bleeding in adolescents.[10] von Willebrand's disease is the most common cause, but myeloproliferative disorders and immune thrombocytopenia also may be diagnosed. In adults, bleeding may result from anticoagulation agents or acquired bleeding disorders. Cirrhosis may lead to bleeding secondary to reduced capacity of the liver to metabolize estrogens.

OVULATORY DYSFUNCTION

Acute uterine bleeding secondary to anovulation is seen in 10% to 15% of gynecologic patients. Signs include irregular and/or heavy menstruation. Ovulatory dysfunction is common in perimenarchal and perimenopausal women, as well as in patients with endocrine disorders, polycystic ovary syndrome, exogenous hormone use, and liver or renal disease.

Anovulatory uterine bleeding in adolescence is due to the immature hypothalamic-pituitary-ovarian axis. In this situation, the amount of bleeding is usually minimal and painless. Severe anemia from heavy menstrual bleeding in early adolescence should prompt evaluation for bleeding disorders (e.g., von Willebrand's disease, factor VIII deficiency). **Table 96-4** outlines the medical management of acute uterine bleeding from ovulatory dysfunction in the ED.

Anovulatory bleeding in the reproductive-age female may be regular in timing, but more often is irregular because of fluctuating estrogen levels. Characteristically, anovulatory cycles present as prolonged amenorrhea with periodic heavy menstrual bleeding. This pattern of bleeding increases the risk of endometrial hyperplasia and adenocarcinoma.

Hypothyroidism may be associated with heavy uterine bleeding or intermenstrual bleeding from ovulatory dysfunction, with an estimated incidence of 0.3% to 2.5%.[11] Eating disorders, excessive weight loss, stress, and exercise can also cause abnormal uterine bleeding. Consider obtaining thyroid-stimulating hormone levels in women with uterine bleeding of undetermined origin or in those with thyroid nodule or goiter.

ENDOMETRIAL CAUSES

Abnormal uterine bleeding that occurs in the context of normal ovulation and with a structurally normal endometrial cavity is attributed to endometrial causes. Normal ovulation is based on a history of regular menstrual periods. Bleeding may be preceded by breast tenderness, abdominal

TABLE 96-4 Treatment of Massive or Heavy Vaginal Bleeding

Massive or Life-Threatening Bleeding				
General management	Fluid and blood resuscitation	Identify and treat coagulopathies	Exclude pregnancy, foreign body, laceration	
	Initial Dose	**Dose Schedule**	**Comments**	**Contraindications**
Conjugated equine estrogen (Premarin)	25 milligrams IV	Every 4–6 hours until bleeding diminishes/stops	Emergency GYN consultation; provide antiemetics	If VTE, thrombophilia, vascular disease, or malignancy, do not give estrogens and get emergency GYN consultation
Tranexamic acid (FDA approved for menorrhagia)	1.0–1.3 grams IV	Can continue PO 3 times a day; effective in about 3 h	Emergency GYN consultation	If VTE, thrombophilia, vascular disease, or malignancy, do not give tranexamic acid and get emergency GYN consultation
Hemodynamically Stable or Ovulatory Dysfunction				
	Dose	**Dose Schedule**	**Comments**	**Contraindications**
Combined OCP (i.e., Sprintec®): 0.25 milligram norgestimate and 0.035 milligram ethinyl estradiol; Yaz®, Alesse®, Seasonale®, other options with a bit less estrogen)	Monophasic combined OCP that contains ≤35 micrograms of ethinyl estradiol	Three times a day for 7 days *Or* Twice daily for 5 days, then once daily until pack is finished	Provide antiemetics; bleeding diminishes/stops in ~3 days	Smokers >35 years, hypertension, pregnancy, VTE, cerebrovascular accident, breast cancer, liver disease, thromboembolic disorders, diabetes with vascular disease, heart disease, major surgery with immobilization
Medroxyprogesterone acetate	20 milligrams PO	3 times a day for 7 days *Or* Once daily for 10 days	Bleeding diminishes/stops in ~3 days; for patients with contraindications to estrogen; primarily for older or perimenopausal patients	Liver disease; breast, uterine, or ovarian cancer; inconsistent reports of deep venous thrombosis risk
NSAIDs	Naproxen or ibuprofen PO or mefenamic acid	Naproxen 500 milligrams twice a day; ibuprofen 400 milligrams every 6 hours; mefenamic acid, 500 milligrams 3 times daily for 4–5 days or until bleeding stops	Consider for younger patients with relatively stable bleeding and those who cannot receive hormonal therapy	Use NSAIDS with caution in patients with history of GI bleed, bleeding disorders, or renal disease

Abbreviations: FDA = U.S. Food and Drug Administration; GYN = gynecology; OCP = oral contraceptive pill; VTE = venous thromboembolism.

bloating, and pelvic pain. The diagnosis is made when patients have heavy menstrual bleeding with no other identifiable abnormalities.

Ovulatory dysfunction bleeding is generally treated with oral contraceptives, NSAIDs, or progestins (Table 96-4). NSAIDs reduce prostaglandin levels and can reduce menstrual bleeding. Endometrial ablation may be useful for those who do not respond to medical therapy; hysterectomy is reserved for those who fail medical management and have excessive blood loss.

IATROGENIC CAUSES

Oral contraceptive pill use remains the most common cause of intermenstrual bleeding. Additionally, medications (e.g., antiseizure medications) that increase the P450 system of the liver may increase the metabolism of endogenous hormonal glucocorticoids and may cause withdrawal bleeding.

Hormone replacement therapy, which can relieve symptoms associated with menopause, may also be associated with vaginal bleeding. Hormone replacement therapy for symptom control has been called into question, as there is no clear benefit for primary and secondary prevention of cardiovascular disease, and excessive risk of endometrial, breast, and colorectal cancer and thromboembolism has been noted.[12,13]

Forty percent of women receiving continuous oral contraceptive pill therapy will experience abnormal bleeding in the initial 4 to 6 months. Bleeding after 6 months of continuous combined hormone replacement therapy, unexpected bleeding with cyclic hormone replacement therapy, or bleeding that recurs after amenorrhea is established should prompt referral for evaluation. There are no acceptable criteria for "abnormal bleeding" on these therapies. The most common etiologies for bleeding while on hormone replacement therapy are poor compliance, poor GI absorption, drug interactions, failure to synchronize therapy with endogenous ovarian activity, and coagulation disorders.

OTHER CAUSES OF VAGINAL BLEEDING

Pelvic inflammatory disease or infections that cause endometritis can result in abnormal vaginal bleeding. Cervical erosions, polyps, and cervicitis may cause bleeding from the cervix. Vaginal infections, trauma, and foreign bodies may also present with abnormal bleeding. Emergency therapy should be directed at investigating and treating obvious causes of bleeding. For further details, see Chapters 103, "Pelvic Inflammatory Disease," and 102, "Vulvovaginitis."

LABORATORY EVALUATION AND IMAGING

Obtain a pregnancy test in women of childbearing age (except those with hysterectomy) to rule out pregnancy as a cause of bleeding. A CBC identifies anemia. Consider thyroid studies if they have not been recently obtained. Obtain coagulation studies only when indicated by history or physical examination. In individuals with suspected endocrine disorders, determination of prolactin levels may be helpful, but the levels may not be available for ED evaluation.

Ultrasonography is the first-line imaging modality for gynecologic conditions such as vaginal bleeding, adnexal or uterine masses, or pelvic pain. US can determine uterine size and endometrial characteristics and can identify the presence of leiomyoma, ovarian cysts, hydrosalpinx, pelvic adhesions, tubo-ovarian abscesses, endometriosis, and tumors. Transvaginal ultrasonography further delineates ovarian cysts and fluid in the cul-de-sac. Depending on the degree of pain and findings on physical examination, US can be done on an emergency basis or deferred for outpatient evaluation.

CT is used primarily in the ED for the evaluation of acute abdominal or pelvic pain (see Chapter 97, "Abdominal and Pelvic Pain in the Nonpregnant Female"). MRI is used primarily for cancer staging and is rarely indicated during ED evaluation.

TREATMENT

MASSIVE UTERINE BLEEDING

Women who are hemodynamically unstable need immediate resuscitation and emergent gynecologic consultation (Table 96-4). Do not attempt vaginal packing, because it increases the risk of infection and may hide ongoing blood loss. In addition to fluid resuscitation, blood transfusion, and identification and correction of underlying coagulopathies, assess for other potential causes of bleeding including trauma, bleeding dyscrasia, infection, and retained foreign bodies. The options for management of acute hemorrhage include hormonal, surgical, and hemostatic interventions.

Hormonal agents are first-line medical management for massive uterine bleeding in patients without an underlying bleeding disorder.[14] Short-term hormonal treatment allows the endometrium to stabilize and slows acute bleeding. For severe hemorrhage, give conjugated estrogen (Premarin®) at a dose of 25 milligrams IV every 4 to 6 hours until bleeding stops, with further treatment and disposition determined by the gynecologist. In women with a history of blood clot or cardiovascular disease, high-dose estrogen therapy is contraindicated, so obtain emergency gynecologic consultation for other treatment options. Obtain transvaginal US to identify anatomic causes of bleeding.

Tranexamic acid, a lysine derivative that prevents fibrin degradation, has been primarily used for intraoperative gynecologic and obstetric hemorrhage.[15,16] Obtain gynecologic consultation if IV administration is considered, especially to discuss the risks and benefits. Clinical studies on the effectiveness of tranexamic acid have excluded patients with the potential for thrombosis. However, the U.S. Food and Drug Administration has approved **PO** tranexamic acid for treatment of ovulatory abnormal uterine bleeding. A recent review showed no thromboembolic events with the use of PO regimens. The most commonly recommended and studied treatment regimen is PO tranexamic acid 1 to 1.3 grams every 6 to 8 hours for 5 days.[17]

HEAVY OR ANOVULATORY MENSTRUAL BLEEDING

The most common medication treatment options for heavy menstrual bleeding (Table 96-4) include hormonal (i.e., combined contraceptives, progestin-only) and nonhormonal therapies (i.e., NSAIDs). Common side effects include nausea and vomiting. Simplified ED regimens for combined oral contraceptive pills and progestin-only pills are outlined in Table 96-4. The median time to stop bleeding for either regimen (combined oral contraceptive pill or progestin-only regimen) is 3 days. However, multiple different hormonal doses and schedules are also effective. In general, for young healthy women in whom bleeding is often related to anovulation and there is no concern for endometrial pathology, oral contraceptive pills are favored. For older patients or obese/perimenopausal patients in whom there could be concern for endometrial pathology, progestin-only therapy is preferred.

Oral contraceptive pills have long been an excellent choice for adolescents and women requiring contraception. Heavy menstrual bleeding is decreased by 50%, with a similar reduction in the degree of pain associated with bleeding. Alternative therapy at gynecologic follow-up can consist of a levonorgestrel intrauterine device (71% to 95% reduction), which may be superior to combined oral contraceptive pills (35% to 69% reduction) and NSAIDs (10% to 52% reduction).[18]

NSAIDs are effective in reducing pain and blood loss in 20% to 50% of women with abnormal uterine bleeding secondary to ovulatory dysfunction.[19] NSAIDs should be started on the first day of the period and continued until bleeding stops and pain resolves.

All NSAIDs inhibit cyclooxygenase in the arachidonic acid cascade. Prostaglandin inhibitors alter the ratio of prostaglandin $F_2\alpha$, which causes vasoconstriction, to prostaglandin E_2, which causes vasodilation. NSAIDs also increase levels of thromboxane A_2, which causes vasoconstriction and increases platelet aggregation. NSAIDs have a mild side effect profile and are inexpensive. Treatment choices include mefenamic acid, 500 milligrams three times a day PO, naproxen, 500 milligrams twice per day PO, and ibuprofen, 400 milligrams every 6 hours. Any of these may be administered to reduce bleeding and pain associated with use of an intrauterine device.[18] NSAIDs are less useful in patients with uterine leiomyomas.

For women with contraindications to estrogen, progestin-only therapy is an alternative therapy. **Progestin** works by decreasing the number of available estrogen receptors and stabilizing the endometrium. Progestin is used when there is concern for underlying endometrial pathology or hyperplasia. The American College of Obstetricians and Gynecologists recommends medroxyprogesterone acetate, 20 milligrams three times per day for 7 days. Another common regimen is medroxyprogesterone acetate, 10 milligrams daily PO for 10 days.

Gonadotropin-releasing hormone agonists may be used to induce amenorrhea, but women on this therapy become menopausal. Other drawbacks include medication expense and bone loss when used for >6 months. Oral tranexamic acid, a fibrinolytic, reduces vaginal bleeding with minimal side effects. An improved quality of life in patients using tranexamic acid when compared with hormone therapy and NSAIDs has been reported.[20]

Nonmedical invasive management strategies may be required if medical treatment fails. These include hysteroscopy, endometrial ablation, or myomectomy. Hysteroscopy can be used to sample the endometrium and resect polyps and myoma. Endometrial ablation may be performed in patients who do not desire fertility, have no pathologic diagnosis, and for whom medical therapy has failed.[21] Myomectomy may be useful in patients with symptomatic fibroids. Hysterectomy is reserved for selected patient populations. Uterine artery embolization is an effective nonsurgical option for the management of bleeding caused by fibroids.[22]

DISPOSITION AND FOLLOW-UP

Stable patients can be discharged home with arrangements for prompt follow-up.

The need for surgical management is based on clinical stability. If medical management fails or if there is a contraindication (e.g., thromboembolic disease), then surgical management is the next step. Surgical options are directed by suspected etiology and include dilatation and curettage, hysteroscopy, endometrial balloon tamponade, and uterine artery embolization. Hysterectomy is used as a last resort in patients with acute life-threatening bleeding unresponsive to other treatment measures.

Provide referral for endometrial biopsy for patients at risk for endometrial cancer and all women >45 years old. Perimenopausal bleeding is associated with malignancy in 10% of women. Risk factors include obesity, nulliparity, history of anovulation, tamoxifen use, infertility, and a family history of endometrial or colon cancer. Other diagnostic procedures performed at follow-up may include sonohysterography, hysterosalpingography, and hysteroscopy with directed biopsy and dilatation and curettage.[23]

SPECIAL CONSIDERATIONS

ANTICOAGULANTS

Anticoagulation for deep vein thrombosis, pulmonary embolism, artificial heart valves, atrial fibrillation, and other conditions may be a cause of abnormal uterine bleeding. More than 70% of these women report changes in their periods, with more than half reporting heavy menstrual bleeding.[24] The management of women with active or prior thrombotic disease is challenging because first-line treatments such as combined contraceptives and tranexamic acid are contraindicated in this population. Progestin-only may be used with caution and gynecologic consultation due to potential increased risk of thrombosis. Risks and benefits must be evaluated for reversal of anticoagulation.

INHERITED BLEEDING DISORDERS

Abnormal uterine bleeding is the most common symptom of inherited bleeding disorders in women. Of historical interest, the first described case of von Willebrand's disease was in a 13-year-old who died as a result of uncontrollable uterine bleeding.[25] Abnormal uterine bleeding is present in the majority of women with von Willebrand's disease or factor XI deficiency and in carriers of hemophilia.

A multidisciplinary approach is recommended. Initial treatment options are similar to those without bleeding disorder, except the use of NSAIDs is contraindicated. Hormonal agents raise factor VIII and von Willebrand factor levels and are an effective and popular form of therapy. If standard treatment fails, consider **desmopressin acetate** to stimulate endogenous release of factor VIII and von Willebrand factor. Patients must be typed and screened for antibodies before administering desmopressin acetate because it may induce thrombocytopenia in certain subgroups. Antifibrinolytics, such as tranexamic acid and recombinant von Willebrand factor, are other treatment options that have shown reduction in bleeding.[26,27]

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome, one of the most common endocrine disorders, is the association of hyperandrogenism and anovulation without underlying disease of the adrenal or pituitary glands.[28] A triad of obesity, hirsutism, and oligomenorrhea is classically described, although obesity is not universally seen. When menses occurs, it is heavy and prolonged. The syndrome is further characterized by acne, androgen-dependent alopecia, elevated serum concentrations of androgens, hyperinsulinemia, and hypersecretion of luteinizing hormone with a normal or low follicle-stimulating hormone level. Typical ovarian morphology, which may be seen by US, is not necessary for the diagnosis and may, in fact, represent a response of the ovary to chronic anovulation. The differential diagnosis includes hyperprolactinemia, acromegaly, congenital adrenal hyperplasia, and androgen-secreting tumors of the ovary or adrenal gland. Management of menorrhagia in women who do not desire fertility includes low-dose oral contraceptives or cyclic progestin administration.

STRESS, ILLNESS, AND RAPID WEIGHT CHANGE

Periods of physical or psychological stress, illness, malnutrition, rapid weight gain or loss, and intense physical regimens affect the hypothalamus and disrupt the normal pattern of gonadotropin release. This usually causes amenorrhea but may result in irregular, heavy bleeding. In obese women, menorrhagia may be a result of increased circulating levels of estrogen from peripheral conversion of androstenedione to estrone in fatty tissue. Patients with liver and renal disease may also develop irregular bleeding.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 97

Abdominal and Pelvic Pain in the Nonpregnant Female

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INTRODUCTION AND EPIDEMIOLOGY

This chapter reviews diagnosis and treatment of abdominal and pelvic pain in nonpregnant women, with a focus on gynecologic causes of pain. Even after the possibility of pregnancy is eliminated, abdominal pain in women remains a challenging diagnosis because of physical proximity and overlapping spinal segment innervation and similar symptoms of GI, urologic, and gynecologic organ systems. Discussion of the pregnant woman with abdominal/pelvic pain is found in Chapters 71, "Acute Abdominal Pain," 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period," and 103, "Pelvic Inflammatory Disease."

GENERAL APPROACH

HISTORY

Define characteristics of the pain including onset, duration, location, quality, radiation, and exacerbating and alleviating factors. History should include questions about GI symptoms (nausea, vomiting, diarrhea, and constipation), urologic symptoms (dysuria, hematuria, frequency, and urgency), and gynecologic symptoms (vaginal bleeding, discharge, dyspareunia, and menstrual history). **History of sexual activity and menstrual history should never be relied upon to exclude pregnancy.** Obtain past medical, surgical, and family history, as well as details of prior pregnancies and outcomes. Active lactation and medication use, including specific methods of birth control, should be part of the history. Ask about infertility treatments because ovulation-inducing treatments increase risk of ovarian torsion, cysts, and ovarian hyperstimulation syndrome. When obtaining a sexual history and social history, it is wise to interview the patient alone, which may help patients feel more comfortable discussing potentially sensitive or embarrassing topics. Ask about pelvic inflammatory disease risk factors including unprotected intercourse, prior sexually transmitted infections, and multiple sexual partners. While the patient is alone, ask her about safety at home, and assess for any potential abusive situations. Patients with history of physical and sexual abuse may develop a variety of somatic complaints including abdominal and pelvic pain, and this pain is often chronic in nature. Social history should include living situation, occupation, and personal habits (use of tobacco, alcohol, and drugs).

PHYSICAL EXAMINATION

A standard head-to-toe systematic approach beginning with vital signs is essential. The patient should be adequately undressed for a careful examination. In focusing on the examination of the abdomen, it is helpful to determine in what quadrant(s) of the abdomen the pain is located; this may help to narrow the differential diagnosis (see Figure 71-1).

In addition to palpating for tenderness or masses, evaluate for surgical scars, rashes, bruising, or ascites. Peritoneal signs may be less obvious in patients who are elderly, are obese, or have altered neurologic status. A digital rectal exam is helpful, if indicated, to evaluate complaints of rectal pain or bleeding.

A pelvic examination is usually a routine component of the exam of women with lower abdominal pain, but studies report a lack of accuracy and reproducibility of pelvic examination findings.[1,2] Pelvic examination is useful for obtaining lab specimens for sexually transmitted infections, palpation for tenderness or mass, and to check for vaginal bleeding, discharge, or foreign body.

DIAGNOSIS

In a nonpregnant female with abdominal pain, ED testing beyond a thorough history and exam is not always mandatory. For example, in a patient with multiple prior similar presentations and recent normal imaging studies, it is unnecessary, rarely helpful, and potentially harmful to repeat imaging.[3] In cases where further ED testing is determined to be unnecessary, the physician must still pay careful attention to symptom control, careful reassessment, and disposition. At the time of discharge, providers should review with the patient arrangements for close follow-up, often in 12 to 24 hours, as well as indications for return to the ED. **When benign causes are not clear from the initial evaluation and concerns for serious pathology remain, lab and/or imaging tests are necessary.**

LABORATORY EVALUATION

Obtain a pregnancy test in all women of childbearing age who still have a uterus and ovaries. See Chapter 98, "Ectopic Pregnancy and

Emergencies in the First 20 Weeks of Pregnancy," for a detailed discussion of pregnancy testing. A CBC is often obtained, but the WBC count is not reliable to rule in or exclude serious disease.[4] Obtain a urinalysis, and add a urine culture in pediatric patients, pregnant women, and patients at risk for complicated urinary tract infections. See Chapter 91, "Urinary Tract Infections and Hematuria," for detailed discussion of urinalysis. **Be cautious in making a definitive diagnosis of urinary tract infection as the sole cause of a patient's symptoms.**

IMAGING

US is the imaging modality of choice for genital tract pathology (ovarian cyst, ectopic pregnancy, uterine or ovarian mass, or tubo-ovarian abscess). Ready availability, relatively low cost, and lack of ionizing radiation make US a good option for imaging in women of reproductive age. Drawbacks of US include operator dependence and technical limitations including body habitus and bowel gas.[5] **CT is preferred when GI or GU pathology (appendicitis, diverticulitis, bowel obstruction, or renal stones) is highest in the differential diagnosis.**

Bedside US can facilitate rapid diagnosis and treatment. For example, a positive FAST exam could help identify bleeding from a ruptured ectopic pregnancy or significant hemorrhage from an ovarian cyst.[6] ED US can quickly identify a normal intrauterine pregnancy. Pelvic US is the primary imaging modality for evaluation of lower abdominal pain in the female patient in whom a gynecologic diagnosis is considered most likely. US is useful in diagnosis of torsion, pelvic inflammatory disease, tubo-ovarian abscess, leiomyoma, and ovarian cysts. In evaluation of possible ovarian torsion, pelvic US should include Doppler flow. Transabdominal and intravaginal probes are used for imaging of pelvic organs. In transabdominal imaging alone, a full bladder aids visualization of pelvic organs. In transvaginal imaging, an empty bladder aids visualization. US studies should never be delayed waiting for a full bladder, particularly when there is concern for a serious diagnosis such as ovarian torsion. US may be useful to evaluate for appendicitis, but it is less sensitive than CT and is operator dependent.

CT of the abdomen and pelvis is sensitive for evaluation of most abdominal and pelvic conditions. Usually IV contrast alone is sufficiently sensitive for evaluation of possible appendicitis.[7] If there is concern for pelvic abscess, or the patient weighs less than 70 kg, oral contrast may enhance accuracy of evaluation. MRI is accurate in diagnosis of many abdominal and pelvic conditions, but cost and limited availability limit its use in most EDs.

TREATMENT

Specific treatment depends on diagnosis (see below), but because the diagnostic process can be time consuming, control of pain and nausea and fluid resuscitation take priority. There is no evidence that judicious use of opiates obscures abdominal exam findings or negatively impacts outcomes. Opiates can be titrated to control pain, without causing excessive somnolence or respiratory depression. Antiemetics including ondansetron, metoclopramide, promethazine, and prochlorperazine are safe and effective. Antibiotics should be given in the ED for suspected severe intra-abdominal infection or sepsis. Choice of antibiotics depends on severity of infection and factors relevant to patients' individual risk, such as comorbid conditions and possibility of hospital-acquired infections.[8,9] See Chapters 71 and 103 for further discussion of antibiotic selection.

DISPOSITION AND FOLLOW-UP

When a serious or potentially surgical diagnosis is considered likely, early consultation with the appropriate specialist (general surgery, urology, or obstetrics/gynecology) is indicated. If there is persistent concern for serious pathology, admission or observation is appropriate. This applies even if the diagnosis is unclear. Patients with abnormal vitals, poorly controlled pain, and/or vomiting are best served by inpatient treatment. In many cases, diagnosis is clear after a period of observation and serial exams. Many patients seen in the ED have significant symptoms, but a specific condition may not be diagnosable in the relatively brief period of time a patient spends in the ED. Significant comorbid conditions (immunocompromised, unstable medical problems, inability to care for oneself at home) should prompt strong consideration for observation or admission.

In most patients with abdominal/pelvic pain in the ED, hospitalization is not necessary. **It is common and appropriate to discharge patients with a diagnosis of undifferentiated abdominal pain. In patients who are discharged, instructions for follow-up and indications for return to the ED should be very specific. Instructions should specify a time course during which patients should be seen for repeat exam.** Reevaluation in 12 to 24 hours is appropriate for patients with acute abdominal pain and diagnostic uncertainty. In more chronic abdominal/pelvic pain, follow-up with a primary care provider is still important, but timing of follow-up should be specified according to individual patient needs.

OVARIAN CYSTS

Ovarian cysts, when symptomatic, usually present with sudden-onset unilateral pain that is more common on the right than left. Cervical motion tenderness and mild vaginal bleeding are sometimes present. Pain often starts during physical activity such as exercise or sexual intercourse. Functional (benign) cysts are fluid-filled sacs that develop during a normal menstrual cycle. **Follicular cysts** contain a maturing ovum and rupture at ovulation. **Corpus luteum cysts** are present after the ovum is released. If no conception occurs, the corpus luteum involutes. If fertilization takes place, the corpus luteum cyst enlarges and secretes estrogen and progesterone. Both follicular and corpus luteum cysts can cause pelvic pain; this is more likely if there is hemorrhage within the cyst or rupture. Ruptured hemorrhagic cysts can occasionally result in significant hemoperitoneum visible in the upper abdominal quadrants with US.[5] **Hemorrhagic cysts** occur if a blood vessel in the cyst wall ruptures (**Figure 97-1**).

Mittelschmerz (German for middle pain) is midcycle pain at the time of ovulation caused by normal follicular enlargement prior to ovulation or follicular bleeding at ovulation. Pain is usually mild and lasts a few hours up to a few days.

Complicated cyst rupture is characterized by abnormal vital signs and an acute abdomen. Hospitalization or observation is needed for serial examinations and hematocrits. Surgery may be necessary to control hemorrhage.

A **dermoid cyst** is an ovarian germ cell neoplasm that presents as a multicystic mass that contains various types of tissue including fat, skin, hair, and teeth. These cysts usually occur between age 10 and 30 years.



FIGURE 97-1. A 4-cm hemorrhagic ovarian cyst demonstrated by endovaginal US. [Reproduced with permission from Ma OJ, Mateer JR, Blaivas M: *Emergency Ultrasound*, 2nd ed. © 2008, McGraw-Hill, Inc., New York. Fig. 14-10, p. 362.]

Most are benign, but risk factors for malignant teratomas include age over 45, diameter greater than 8 cm, and rapid growth. Most uncomplicated cyst ruptures are from follicular and corpus luteum cysts. Vital signs are stable, and symptoms last only a few days.

Ovarian cysts that are <8 cm, unilocular, and unilateral are generally observed and typically resolve within two menstrual cycles. **Cysts that are large (>8 cm), solid, and multiloculated are worrisome for neoplasm, dermoid cysts, or endometriomas.** Patients with ovarian cysts, regardless of size, and especially if postmenopausal, should be referred to the gynecologist or primary care physician for follow-up.

ENDOMETRIOMAS

Endometriomas are called "chocolate cysts" because they usually contain thick brown fluid. They present as a pelvic mass caused by growth of ectopic endometrial tissue within an ovary. Endometriomas may rupture, and patients can present with peritoneal signs/symptoms. Endometriomas may also present similar to endometriosis (pelvic pain, dysmenorrhea, and dyspareunia).

OVARIAN NEOPLASM

An ovarian mass in a postmenopausal woman is malignant until proven otherwise. The mean age at diagnosis is 50 to 60 years. Patients present with nonspecific and persistent signs/symptoms of undetermined cause, including anorexia, dyspepsia, early satiety, constipation, bloating, abdominal discomfort, and ascites. Nearly half of women are not diagnosed until stage III or IV disease is present. When evaluating nonspecific symptoms, ask about family history of gynecologic cancer. Cancers of the endometrium, breast, and GI tract may metastasize to ovaries and fallopian tubes.

OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome is a complication of ovulation induction treatments, with a clinical spectrum of severity ranging from mild abdominal bloating to critical and potentially fatal conditions. **With incidence and severity of ovarian hyperstimulation syndrome increasing, emergency providers should ask patients of reproductive age about a history of fertility treatments and should be able to recognize the potentially severe complications.**[10] The syndrome can occur early, 5 to 7 days after ovulation, or later, due to rising human chorionic gonadotropin levels. The most common initial symptom is abdominal bloating.

The severe syndrome is characterized by massive transudation of albumin and fluid from the vascular compartment to the peritoneal, pleural, and sometimes, pericardial cavities.[11] Venous and arterial thrombosis are the most dreaded complications. Reports include thrombosis of the jugular, subclavian, retinal, and extremity veins and cerebral venous thrombosis. Stroke, ST-segment elevation myocardial infarction, sepsis, adult respiratory distress syndrome, and pulmonary embolism are also reported.[11]

ENDOMETRIOSIS AND ADENOMYOSIS

Endometriosis occurs when endometrium-like tissue outside the uterus induces a chronic inflammatory reaction. This is a common cause of pelvic pain and infertility. When endometrial tissue is in the uterine wall, it is termed adenomyosis. Both conditions cause chronic, recurrent, and cyclic pain. Dysmenorrhea and dyspareunia are often reported. US may show cystic or solid masses. Laparoscopy is the definitive method of diagnosis. Primary diagnosis is usually not made in the ED. If suspected, pain control and outpatient referral are appropriate.

FOREIGN BODY/TRAUMA

Vaginal foreign bodies (such as a retained tampon) may cause pelvic pain and vaginal discharge or bleeding. Trauma or foreign body should be considered in the differential diagnosis. Patients are not always immediately forthcoming with history due to fear or embarrassment. Complications such as abscess or perforation are rare.

OVARIAN TORSION

Ovarian torsion is a surgical emergency that requires prompt diagnosis to preserve ovarian function. Adnexal torsion is an ischemic condition almost always associated with ovarian enlargement, generally due to ovarian cysts or masses. The enlargement causes the ovary to twist, creating a fulcrum around which the oviduct revolves. Initial blockage of venous return causes congestion, leading to decreased distal arterial blood flow, which produces ischemia and necrosis of the ovary. Although the process may involve the ovary alone, torsion of both the ovary and the oviduct (adnexal torsion) is more common. Nearly 70% of torsions occur on the right side, due to the increased length of the utero-ovarian ligament on the right and the sigmoid on the left, limiting space for movement.[12]

Risk factors for torsion are pregnancy due to enlarged corpus luteum, presence of large ovarian cysts or tumors, polycystic ovaries, chemical induction of ovulation (ovarian hyperstimulation syndrome), and tubal ligation. Torsion can occur in females of all ages including infants, adolescents, and postmenopausal women.[13] Classically, patients present with sudden-onset, severe, unilateral, lower abdominal pain that may develop after episodes of exertion. However, pain may be of gradual onset, mild, or intermittent. Atypical presentations are common, with half of patients reporting gradual onset of pain that is intermittent in nature. Nausea and vomiting are present in 70% of cases.[14]

Clinical findings classically consist of unilateral lower abdominal tenderness with guarding, unilateral adnexal tenderness on bimanual examination, and presence of a latero-uterine mass. Conversely, nearly 30% of patients have bilateral adnexal tenderness on bimanual examination, and a minority of patients may have no tenderness at all. Fifty percent of patients are initially misdiagnosed.[15]

Transvaginal US with Doppler is the primary diagnostic modality for suspected torsion; **however, US with Doppler is not 100% sensitive or specific for diagnosing ovarian torsion.** An ovary >4 cm in size due to cyst, tumor, or edema is the most common ultrasonographic finding associated with torsion.[16] Conversely, given the dynamic nature of the torsion process, up to 26% of US studies reveal normal adnexa. Up to 60% of cases of torsion can be missed on arterial Doppler alone, given that arterial disruption of flow is a late clinical finding.[17] However, a positive Doppler study has a 100% positive predictive value for adnexal torsion. Recent improvements in US technology have led to assessment of venous Doppler flow, which may be the only abnormality identified in early ovarian torsion.[18] A combination of US findings (abnormal blood flow, free fluid, and ovarian enlargement) increases the specificity and positive predictive value of US.[13]

CT is not the imaging modality of choice when torsion is suspected, but it is commonly done in EDs to evaluate women with nonspecific lower abdominal or pelvic pain. The most common CT finding of ovarian torsion is an enlarged ovary (>4.0 cm). Other CT findings of torsion include abnormal ovarian enhancement with contrast, an adnexal mass, thickening of the fallopian tube, displacement of the ovary, and deviation of the uterus to the affected side.[19]

There is no radiologic or clinical finding that conveys with certainty the absence of torsion. Thus, clinical suspicion based on history and physical exam remains important in involving gynecologic consultation if US is negative but clinical concern remains high.[20]

SPECIAL CONSIDERATIONS

OVARIAN TORSION IN ADOLESCENTS AND PREMENARCHAL GIRLS

Ovarian torsion may occur at any age in both pre- and postmenarchal girls but is increased in the first year of life, at menarche, and during pregnancy.[19,21] Pediatric ovarian torsion is rare and difficult to diagnosis, which may result in delayed diagnosis and treatment with resulting ovarian loss. In pediatric and adolescent patients, torsion is more likely to occur in an otherwise normal ovary (without a cyst or mass).[22,23] Presenting symptoms of abdominal pain with nausea and vomiting are

common in all age groups. Premenarchal girls have higher rates of fever, restlessness, and palpable pelvic mass at presentation compared to postmenarchal patients. Ovarian torsion in premenarchal girls is also associated with a longer interval between symptom onset and presentation.[23,24]

Acknowledgment: We wish to gratefully acknowledge the support and assistance of our colleagues in the Department of Emergency Medicine at Indiana University who made this chapter possible.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 98

Ectopic Pregnancy and Emergencies in the First 20 Weeks of Pregnancy

Heather A. Heaton

INTRODUCTION

This chapter discusses common obstetric-related conditions in the first 20 weeks of pregnancy: ectopic pregnancy, spontaneous abortion, septic abortion, gestational trophoblastic disease, and nausea and vomiting of pregnancy. **Ectopic pregnancy is the most important consideration until it can be either confirmed or excluded with conviction.**

GENERAL APPROACH TO WOMEN OF CHILDBEARING AGE

The differential diagnosis for women of childbearing potential who present with abdominal or pelvic symptoms or abnormal vaginal bleeding is broad and provided in **Table 98-1**. Consider ectopic pregnancy in women of childbearing age who report abdominal or pelvic pain or discomfort, vaginal spotting or a cycle of amenorrhea, or unexplained signs or symptoms of hypovolemia.

PREGNANCY TESTING

The diagnosis of pregnancy is central to the diagnosis of ectopic pregnancy. Pregnancy tests currently in use rely on the detection of the β subunit of human chorionic gonadotropin (β-hCG) in the urine or serum. hCG is a hormone produced by the trophoblast. Intact hCG consists of the α and β subunits. Tests based on detection of the intact molecule or the α subunit can cross-react on immunologic assays with hormones found in the nonpregnant individual and are thus less specific than tests for the β-hCG subunit.

hCG preparations are currently standardized in relation to the Third International Reference Preparation. Other standard preparations are not equivalent. A preparation often referred to in earlier literature is the Second International Standard. The Third International Reference Preparation is roughly equal to 1.7 times the Second International Standard. To avoid confusion when interpreting the literature, pay attention to the standard used. In this chapter, hCG and β-hCG concentrations refer to the Third International Reference Preparation unless otherwise noted.

Very early in either an intrauterine pregnancy (IUP) or an ectopic pregnancy, detectable amounts of β-hCG are released into the serum and filtered into the urine. The concentration of β-hCG is fairly closely correlated in the urine and serum, with urinary concentration also depending on urine specific gravity. Qualitative urine and serum tests for pregnancy usually use the enzyme-linked immunosorbent assay methodology. In the laboratory setting, enzyme-linked immunosorbent assay tests can detect β-hCG at concentrations <1 mIU/mL.

Qualitative tests in clinical use are typically reported as "positive" when the β-hCG concentration is ≥20 mIU/mL in urine and ≥10 mIU/mL in serum. A positive qualitative test therefore implies that β-hCG is present in at least this concentration. At this level of detection, the false-negative rate for detection of pregnancy will not be >1% for urine or 0.5% for serum. In clinical use, the performance of urine qualitative testing is 95% to 100% sensitive and specific compared with serum tests.

Dilute urine may cause a false-negative urine pregnancy test, particularly early in pregnancy when β-hCG levels are low (<50 mIU/mL). Additionally, when hCG levels are present in large amounts (generally with concentrations of 1,000,000 mIU/mL), a **"hook effect phenomenon"** can occur, giving false-negative results. This is thought to be related to excess hCG saturating both the fixed, solid-phase antibody and the labeled, soluble antibody of the assay, causing an absence of signal. The resultant false-negative test can be mitigated by diluting the sample.[1] Point-of-care hCG whole-blood testing can reduce the total ED turnaround time compared to urine testing, with 99.6% concordance when compared with standard urine testing.[2]

When a bedside urine test is negative and ectopic pregnancy is still being considered, perform a quantitative serum test. **The sensitivity of quantitative serum testing for the diagnosis of pregnancy is virtually 100% when an assay capable of detecting ≥5 mIU/mL of β-hCG is used.**[3] Estimated β-hCG levels after conception are listed in **Table 98-2**.

TABLE 98-1 Differential Diagnosis of Ectopic Pregnancy

All Patients	Pregnant Patients
Appendicitis	Normal (intrauterine pregnancy)
Inflammatory bowel disease	Threatened abortion
Ovarian pathology	Inevitable abortion
Ovarian cyst	Molar pregnancy
Ovarian torsion	Heterotopic pregnancy*
Pelvic inflammatory disease	Implantation bleeding
Endometriosis	Corpus luteum cyst
Sexual assault/trauma	
Urinary tract infection	
Ureteral colic	

*Heterotopic pregnancy = combined intrauterine pregnancy and ectopic pregnancy.

ECTOPIC PREGNANCY

INTRODUCTION AND EPIDEMIOLOGY

Ectopic pregnancy occurs when a conceptus implants outside of the uterine cavity; ruptured ectopic pregnancies are a leading cause of maternal death in the first trimester of pregnancy.[4]

TABLE 98-2 Estimated β-Human Chorionic Gonadotropin (β-hCG) Levels After Conception[4]

Post Conception Week	β-hCG Levels (mIU/mL)
<1 week	5–50
1–2 weeks	50–500
2–3 weeks	100–5000
3–4 weeks	500–10,000
4–5 weeks	1000–50,000
5–6 weeks	10,000–100,000
6–8 weeks	15,000–200,000
8–12 weeks	10,000–100,000

TABLE 98-3 Major Risk Factors for Ectopic Pregnancy

- Pelvic inflammatory disease, history of sexually transmitted infections
- History of tubal surgery or tubal sterilization
- Conception with intrauterine device in place
- Maternal age 35–44 (age-related change in tubal function)
- Assisted reproduction techniques (cause unknown, as tube is bypassed in implantation)
- Previous ectopic pregnancy
- Cigarette smoking (may alter embryo tubal transport)
- Prior pharmacologically induced abortion

Major risk factors for ectopic pregnancies are listed in **Table 98-3**, but a significant number of ectopic pregnancies occur in women in whom no risk factors are identified.[5,6]

PATHOPHYSIOLOGY

Fertilization of the oocyte usually occurs in the ampullary segment of the fallopian tube. In normal pregnancy, after fertilization, the zygote passes along the fallopian tube and implants into the endometrium of the uterus. An ectopic pregnancy occurs when the zygote implants in any location other than the uterus—the fallopian tube or extratubal sites (the abdominal cavity, cervix, or ovary). Death results from maternal exsanguination after tubal rupture.

The vast majority of ectopic pregnancies implant in the ampullary portion of the **fallopian tube**. The underlying cause is most often damage to the tubal mucosa from previous infection, preventing transport of the ovum to the uterus. Other causes include tubal surgery, defects in the ovum resulting in premature implantation, and elevated estradiol or progesterone levels, which inhibit tubal migration.

Tubal implantation results in the penetration of the ovum into the muscular wall of the tube, and maternal blood seeps into tubal tissue. Intermittent distention of the fallopian tube with blood can occur, with leakage of blood from the fimbriated end of the fallopian tube into the peritoneal cavity. The aborting ectopic pregnancy and associated hematoma can be completely or partially extruded out of the end of the fallopian tube or through a rupture site in the tubal wall.

Abdominal ectopic pregnancies (~1% of ectopic pregnancies) most commonly derive from early rupture or abortion of a tubal pregnancy, with subsequent reimplantation in the peritoneal cavity.

Cervical ectopic pregnancies occur in <1% of ectopic pregnancies, with predisposing factors similar to those associated with ectopic pregnancies (previous dilatation and curettage, previous cesarean delivery, in vitro fertilization, adhesions or fibrosis of the endometrium, prior instrumentation, infertility, previous ectopic pregnancy). Patients develop profuse vaginal bleeding. Bimanual exam reveals a soft, large cervix when compared to the uterus or an hourglass-shaped uterus, and diagnosis is confirmed with US.[7,8]

Cesarean scar pregnancy is rare but can cause massive maternal hemorrhage. Diagnosis is difficult and is based on US demonstrating an empty uterine sac and cervical canal and a gestational sac in the uterine isthmus.

HISTORY

Determine the timing and characteristics of the last few periods. The menstrual history is often, but not always, abnormal. The classic sign of amenorrhea from 4 to 12 weeks after the last normal period is reported in 70% of ectopic pregnancy cases. **No missed menses are reported in 15% of ectopic pregnancy cases.** Although vaginal bleeding is often scant, heavy bleeding does not exclude an ectopic pregnancy.

Ask about previous pregnancies, pregnancy problems, and miscarriages. Typical early pregnancy symptoms may occur and may not differ from symptoms of previous normal IUPs. Discuss previous medical and surgical history, and ask about substance abuse and smoking. Ask about sexual activity and contraception. Identify risk factors for ectopic pregnancy or spontaneous abortion. Determine current medications, including over-the-counter drugs.

Pregnancy in a patient with prior tubal surgery for sterilization is assumed to be an ectopic pregnancy until proven otherwise. Patients are at particularly high risk if they have undergone laparoscopic partial salpingectomy or electrodestruction tubal ligation at a young age (age <28 years), especially 5 to 15 years after the procedure.[9]

In a woman of childbearing age, hysterectomy with oophorectomy excludes ectopic pregnancy. In the situation of hysterectomy without oophorectomy, ectopic pregnancy is exceedingly rare. A literature review identified only 27 such case reports since 1918, after both vaginal and abdominal hysterectomies. The theory is that a fistulous tract after hysterectomy enables embryo implantation in the tube or adnexae.[10]

Abdominal pain or discomfort is the most common symptom of ectopic pregnancy and is reported in 90% of ectopic pregnancies.[11] Pain is due to tubal distention or rupture. The classic pain of rupture is lateralized, sudden, sharp, and severe. Shoulder pain due to diaphragmatic irritation from a ruptured ectopic pregnancy can also occur. Any lateral or bilateral abdominal discomfort or tenderness in a woman of childbearing age requires consideration of ectopic pregnancy. **Lack of pain in a woman with vaginal spotting or bleeding does not exclude ectopic pregnancy.**

PHYSICAL EXAMINATION

Obtain vital signs and focus on the abdominal and pelvic examination. The physical examination in ectopic pregnancy is highly variable, and ectopic pregnancy is difficult to diagnose or exclude based on physical examination. In cases of ruptured ectopic pregnancy, patients may present in shock, with no findings on pelvic examination, or with peritoneal signs and an adnexal mass and tenderness. Cervical motion tenderness can be elicited on pelvic exam in some cases. Relative bradycardia may occur as a consequence of vagal stimulation. Vital signs may be normal due to compensatory mechanisms, despite significant hemoperitoneum.[12] Fever is rare. In the more common situation of an unruptured ectopic pregnancy, the vital signs are likely to be normal.

If an adnexal mass or fullness with tenderness is detected, it may be due to ectopic pregnancy or to a **corpus luteum cyst,** a 3- to 11-cm, thin-walled, unilocular cyst seen after ovulation that can cause pain and tenderness on exam as well as menstrual irregularities, mimicking an ectopic pregnancy. Cervical motion tenderness may be seen, and blood is often present in the vaginal vault; however, the pelvic exam may be completely normal. The cervix may have a blue coloration, as in a normal pregnancy. Uterine size for estimated gestational age is most often normal. Vaginal examinations in stable women presenting with first-trimester bleeding may add little to the clinical diagnosis; some providers are moving away from routine use of vaginal examinations in initial patient assessment as long as a transvaginal US is obtained.[13]

DIAGNOSIS

The definitive diagnosis of ectopic pregnancy is made by US, by direct visualization by laparoscopy, or at surgery. No single or combination of laboratory tests has a sufficient negative or positive predictive value to completely exclude ectopic pregnancy or to definitively establish the diagnosis.

SERUM β-HCG

Differences in the dynamics of β-hCG production in normal and pathologic pregnancy are useful in the diagnosis of ectopic pregnancy. Early in normal pregnancy, β-hCG levels rise rapidly until 9 to 10 weeks of pregnancy and then plateau. Expected postconception ranges of β-hCG are listed in Table 98-2. β-hCG levels decline in nonviable pregnancies and in successfully treated ectopic pregnancy. Absolute levels of β-hCG tend to be lower in pathologic pregnancies than in IUPs, but there is much overlap. Due to the variability in absolute levels and the overlap between normal and pathologic pregnancies, **no single β-hCG level can reliably distinguish between a normal and a pathologic pregnancy**. *Doubling time* refers to the time needed for β-hCG concentration in the serum to double. Absolute levels of β-hCG are lower and doubling times longer in ectopic pregnancy and other abnormal pregnancies. This and many other observations have led to the widely used rule of thumb

stating that the serum concentration of β-hCG approximately doubles every 2 days early in a normal pregnancy and that longer doubling times indicate pathologic pregnancy. Varying degrees of sensitivity (36% to 75%) and specificity (63% to 93%) are obtained using different criteria for evaluating the rate of increase of β-hCG levels for the diagnosis of ectopic pregnancy. The minimum hCG rise in normal pregnancy may be as low as 53% in 48 hours,[14] and the median rise in β-hCG level was 53% in 1 day and 124% in 2 days. Conversely, in spontaneous abortion, hCG is expected to decrease by 21% to 35% in 2 days.[15] Thus, hCG levels that fail to increase by 53% or more in 2 days are suggestive but not diagnostic of ectopic pregnancy or an abnormal IUP. However, **an increase of >53% does not rule out ectopic pregnancy.**

In stable patients, serial measurements of β-hCG are used to either heighten or lower the suspicion for ectopic pregnancy but are not diagnostic. Repeat serum β-hCG measurement made at least 2 days after the initial presentation is useful in characterizing the risk of ectopic pregnancy and the probability of a viable IUP.[16] Although rates of decline vary depending on the initial hCG value, a decrease of less than 21% at 2 days or 60% at 7 days suggests retained trophoblasts or an ectopic pregnancy; additional testing should be performed.[14]

PROGESTERONE

Progesterone is a steroid hormone secreted by the ovaries, adrenal glands, and placenta during pregnancy. During the first 8 to 10 weeks of pregnancy, ovarian production of progesterone predominates, and serum levels remain relatively constant. After the 10th week of pregnancy, placental production increases and serum levels rise. Absolute levels of progesterone are lower in pathologic pregnancies and fall when a pregnancy fails. This observation has led multiple authors to propose various progesterone levels as a diagnostic aid in differentiating an early normal from a pathologic pregnancy. Most pathologic pregnancies have progesterone levels of ≤10 nanograms/mL. With progesterone ≤5 nanograms/mL, nearly 100% of pregnancies will be pathologic; there are no normal pregnancies reported with progesterone ≤2.5 nanograms/mL. Progesterone levels >25 nanograms/mL have 97% sensitivity for viable IUP. An empty uterus or nonspecific fluid collection on US associated with progesterone ≤5.0 nanograms/mL is highly predictive of abnormal IUP or ectopic pregnancy.[17]

There is considerable overlap between progesterone levels in normal and pathologic pregnancy. Thus, very low values for serum progesterone should increase the clinical suspicion for ectopic pregnancy or abnormal IUP, but as with β-hCG levels, no value is diagnostic or can completely exclude or definitively diagnose ectopic pregnancy. Progesterone levels may not be routinely available on an urgent basis, and as noted, many patients have intermediate values, thus limiting the usefulness of the test. Consequently, the role of serum progesterone assays is currently unclear.

Numerous other serum markers for the diagnosis of ectopic pregnancy have been investigated. These include secretory endometrial protein, estradiol, the pregnancy-associated proteins A to D, and others, as well as routine laboratory tests such as amylase, creatine kinase, erythrocyte sedimentation rate, and others. None has been accepted as equal or superior to β-hCG measurements at this time.

US AND ECTOPIC PREGNANCY

The primary goal of US in early pregnancy is determination of a viable IUP and exclusion of ectopic pregnancy (Figure 98-1).

US findings may also be useful in planning therapy when an ectopic pregnancy is discovered. Additionally, US provides information regarding fetal age and viability when an IUP is present.

It has previously been assumed that if an IUP exists, the diagnosis of ectopic pregnancy has been excluded. This assumption is based on the historical incidence of heterotopic pregnancy (combined IUP and ectopic pregnancy), reported to occur in 1 in 30,000 pregnancies. This is no longer a completely safe assumption, with heterotopic pregnancy now occurring in up to 1 in 3000 pregnancies in the general population. **In vitro fertilization and other efforts to enhance fertility with the use of ovulation-inducing drugs have resulted in a higher incidence of heterotopic pregnancy.** A study of 725 in vitro fertilization pregnancies found 4% to be ectopic pregnancies, with 2 of 29 heterotopic

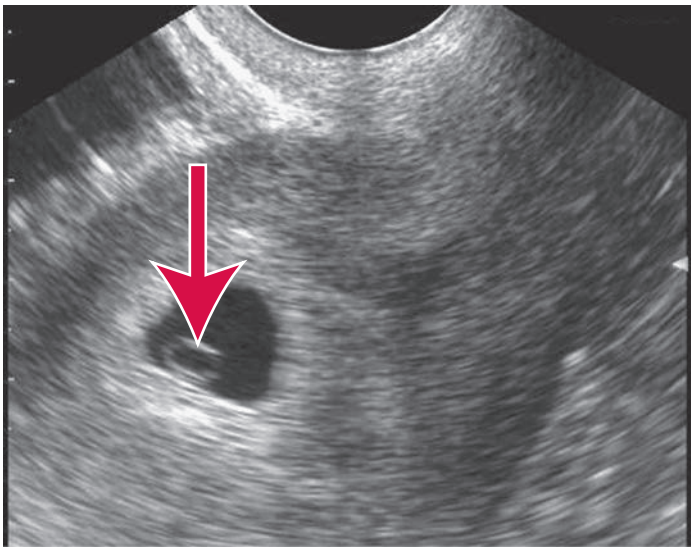

FIGURE 98-1. Yolk sac (*arrow*) within an intrauterine gestational sac. Normal early pregnancy. Transvaginal image. [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA: *Ma & Mateer's Emergency Ultrasound,* 3rd ed. © 2014, McGraw-Hill, Inc., New York.]

gestations.[17] Heterotopic pregnancy should be considered even when US demonstrates an IUP in the assisted reproduction population. For other patients, demonstrating an IUP still provides a high degree of confidence in ruling out ectopic pregnancy. This confidence should be somewhat tempered when a patient has risk factors for ectopic pregnancy.

Advances in sonographic imaging and the use of transvaginal US scanning allow earlier detection of an IUP or an ectopic pregnancy. These advances have contributed to increasing use of real-time, bedside US in the ED performed by emergency physicians. ED US has the further advantage of allowing a potentially unstable patient to remain under continuous observation in the ED. When performed by trained individuals, point-of-care ED US in the first trimester of pregnancy is accurate and can decrease ED length of stay, as long as a conclusive IUP is identified. Inconclusive bedside US requires radiology department–performed US.[18]

The sequencing of transabdominal versus transvaginal US is situation and operator dependent. Usually, transabdominal scanning is performed first. Among other differences, transabdominal scanning is less invasive and offers a wider field of view and easier orientation to the pelvic organs. A full bladder is required for an appropriate acoustic window.

When transabdominal US is not diagnostic, transvaginal scanning should be performed. A full bladder is not required. The shallower depth of field and higher frequencies made possible by the lack of interposed abdominal fat allow better visualization of early pregnancies. There are reports of negative transvaginal but positive transabdominal US in cases of ectopic pregnancy, so both studies should be performed if the study performed first is not diagnostic. However, in one study of >5000 women with early pregnancy, pregnancy location was accurately diagnosed in >90% with a single transvaginal scan.[19]

When US reveals an unequivocal IUP and no other abnormalities, ectopic pregnancy is effectively excluded unless the patient is at high risk for heterotopic pregnancy. An embryo with cardiac activity seen within the uterine cavity is referred to as a *viable IUP*. When an embryo without cardiac activity is visualized within the uterus, the diagnosis of fetal demise can be entertained, provided that the crown–rump length is at least 5 mm. Briefly, transvaginal scanning can usually visualize the early sonographic signs of pregnancy, the gestational sac, yolk sac, and fetal pole, at 4.5, 5.5, and 6.0 weeks, respectively. Visualization by transabdominal scanning can be done approximately 1 week later.

No further diagnostic testing is needed when sonographic findings confirm or are highly suggestive of ectopic pregnancy. An empty uterus with embryonic cardiac activity visualized outside the uterus is diagnostic of ectopic pregnancy. This is seen in <10% of ectopic pregnancies

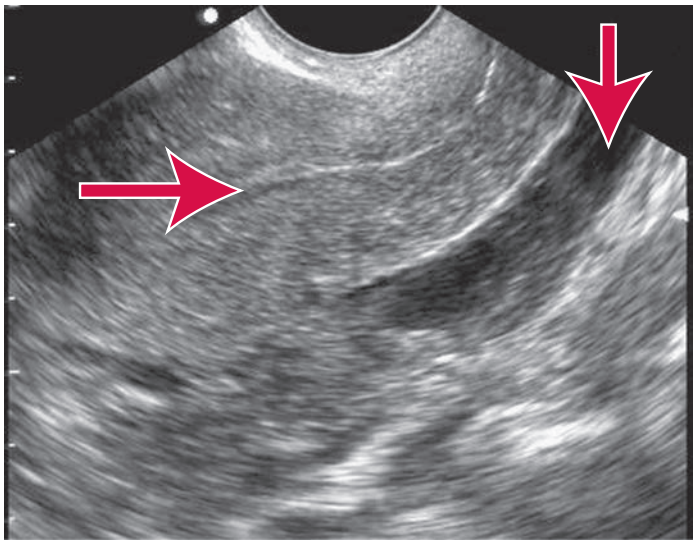

FIGURE 98-2. Ectopic pregnancy: empty uterus and free fluid in the posterior cul-de-sac. Transvaginal sagittal image. *Horizontal arrow* points to empty uterus (uterine stripe), and *vertical arrow* points to fluid in the cul-de-sac. [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA: *Ma & Mateer's Emergency Ultrasound*, 3rd ed. © 2014, McGraw-Hill, Inc., New York.]

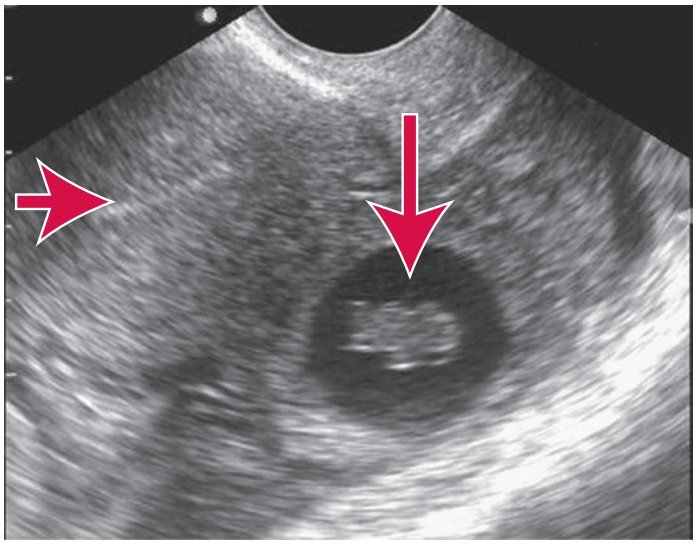

FIGURE 98-3. US of ectopic pregnancy. A living embryo in the adnexa and empty uterus is seen in this ectopic pregnancy (endometrial echo is visible in the left upper portion of the image). Embryonic cardiac activity was present on real-time imaging. Transvaginal image. *Horizontal arrow* points to empty uterus (uterine stripe), and *vertical arrow* points to ectopic pregnancy in the adnexa. [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA: *Ma & Mateer's Emergency Ultrasound*, 3rd ed. © 2014, McGraw-Hill, Inc., New York.]

using transabdominal scanning, but in up to 25% of cases when the transvaginal approach is used. When a pelvic mass or free pelvic fluid is seen in conjunction with an empty uterus, ectopic pregnancy is considered highly likely (**Figure 98-2**). The combination of an echogenic adnexal mass with free fluid in the setting of an empty uterus confers a risk of ectopic pregnancy near 100%, whereas a large amount of free fluid alone has an 86% risk (**Table 98-4**). In addition to a living extrauterine pregnancy, an extrauterine gestational sac is highly predictive of ectopic pregnancy (**Figure 98-3**). Any adnexal mass (other than a simple cyst) seen with US also has high positive predictive value for the diagnosis of ectopic pregnancy.[20,21] It has also been suggested that increased thickness of the endometrial stripe is predictive of ectopic pregnancy when no other diagnostic findings are noted on US. However, the wide overlap between endometrial stripe thickness in normal and ectopic pregnancy limits the usefulness of this observation.[22]

THE DISCRIMINATORY ZONE

If US fails to reveal a definite IUP or fails to show findings strongly suggestive or diagnostic of an ectopic pregnancy, the test should be considered indeterminate and interpreted in light of quantitative serum β-hCG levels (**Figure 98-4**). The concept of the "discriminatory zone" was developed to relate β-hCG levels and US findings in a clinically useful way.[22] The discriminatory zone is the level of β-hCG at which findings of an IUP are expected on US. A β-hCG level higher than the discriminatory zone and an empty uterus on US suggest an ectopic pregnancy. An empty uterus with a β-hCG level below the discriminatory zone is indeterminate, neither confirming nor negating the diagnosis of ectopic pregnancy. The actual level of β-hCG representing the discriminatory zone is operator and technique dependent. With transvaginal scanning, the discriminatory zone is often considered to be 1500 mIU/mL. For transabdominal scanning, an IUP should be detectable when the β-hCG level reaches about 6000 mIU/mL. Clinicians should understand this concept and collaborate closely with imaging specialists in equivocal cases to avoid confusion. **When ectopic pregnancy is suspected, US should be performed even in patients with low β-hCG levels**, because ectopic pregnancy can occur even at very low (<500 mIU/mL) β-hCG levels.[23] Further, decision to intervene on a pregnancy should not be made solely on a single hCG level; if the patient is hemodynamically stable with a β-hCG greater than the discriminatory zone and no visible intrauterine or extrauterine pregnancy, watchful waiting is an appropriate management strategy with close follow-up and strict return precautions.[24]

TABLE 98-4 Ancillary US Findings Suggestive of Ectopic Pregnancy in High-Risk Patients

Ancillary Findings	Risk of Ectopic Pregnancy (%)
Any free pelvic fluid	52
Complex pelvic mass	72
Moderate/large amount of free pelvic fluid	86
Tubal ring	>95
Mass and free fluid	97
Hepatorenal free fluid	~100

Source: Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA: *Ma & Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill, Inc.; 2014; Table 14-2, p. 404.

OTHER DIAGNOSTIC MODALITIES

MRI has high sensitivity and specificity for the diagnosis of ectopic pregnancy, but cost, availability, and the time to perform the study make the use of MRI of only theoretical interest at the present time.

Culdocentesis has been supplanted by tests for β-hCG in combination with US. Sensitivity is poor, and false-positive results occur because of technical errors (entering a vein or other vascular structure with the needle) or from a ruptured corpus luteum cyst.

Laparoscopy may be both diagnostic and therapeutic. Laparoscopy is primarily useful in patients with suspected ectopic pregnancy and a nondiagnostic US. It may provide an earlier diagnosis and a possible route for definitive treatment when compared with serial β-hCG measurements and US.

TREATMENT

The treatment of ectopic pregnancy can be divided into surgical and medical approaches. If laparoscopy is needed for diagnosis, a surgical approach is most appropriate. For unruptured ectopic pregnancy, the most frequently used surgical approach is laparoscopic salpingostomy; the most frequently used medical approach is systemic methotrexate treatment. Medical therapy for ectopic pregnancy has comparable success rates to surgical therapies, while avoiding surgical complications in appropriately selected women with unruptured ectopic pregnancies.[25,26]

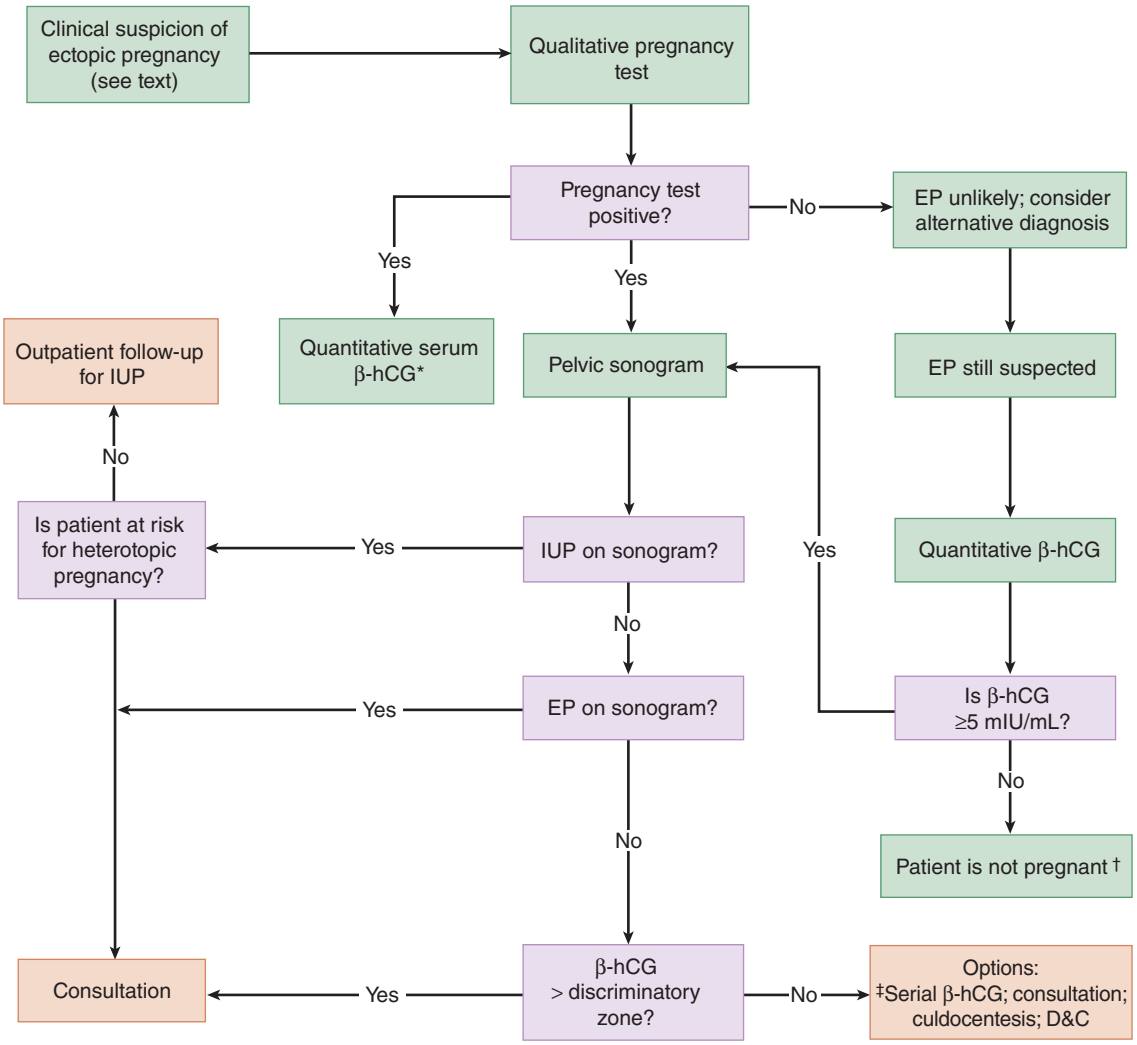

FIGURE 98-4. Diagnostic algorithm for suspected ectopic pregnancy. *Quantitative measurement of β subunit of human chorionic gonadotropin (β-hCG) before US may facilitate rapid patient disposition by saving time. †There have been extremely rare reports of pregnancy with β-hCG <5 mIU/mL. ‡Serial outpatient β-hCG measurements are recommended only for stable patients judged to be at low risk for ruptured ectopic pregnancy. D&C = dilatation and curettage; EP = ectopic pregnancy; IUP = intrauterine pregnancy.

METHOTREXATE

Methotrexate is the only drug currently recommended as a medical alternative to surgical treatment of ectopic pregnancy and is ideally used in patients with hemodynamic stability, minimal abdominal pain, the ability to follow up reliably, and normal baseline liver and renal function tests. Contraindications to methotrexate use are listed in **Table 98-5**.[27] Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase, causing depletion of cofactors needed for DNA and RNA synthesis.

TABLE 98-5 Contraindications to Methotrexate Administration[28]

Absolute Contraindications	Relative Contraindications
Intrauterine pregnancy	Embryonic cardiac activity detected by transvaginal US
Evidence of immunodeficiency	Human chorionic gonadotropin concentrations >5000 mIU/mL
Moderate to severe anemia, leukopenia, or thrombocytopenia	Ectopic pregnancy >4 cm in size as imaged by transvaginal US
Sensitivity to methotrexate	Refusal to accept blood transfusion
Active pulmonary disease	Inability to reliably return for follow-up
Active peptic ulcer disease	
Clinically important hepatic or renal dysfunction	
Breastfeeding	
Hemodynamic instability	

IM methotrexate is the most commonly used approach, 50 milligrams/m^2 as a single IM dose. The failure rate is 14.3% or higher with single-dose methotrexate when pretreatment β-hCG levels are >5000 mIU/mL, compared with 3.7% for levels <5000 mIU/mL.[28] If β-hCG levels are higher than 5000 mIU/mL, multiple doses may be appropriate.[29] The success rate of the multiple-dose regimen is higher than a single dose of methotrexate (92.7% vs. 88.1%).[30]

The most common side effects associated with methotrexate include abdominal pain after treatment (up to 75% of patients) followed by flatulence and then stomatitis. Lower abdominal pain lasting up to 12 hours is common 3 to 7 days after methotrexate treatment and is thought to be secondary to methotrexate-induced tubal abortion or tubal distention due to hematoma formation ("separation pain").[31] The pain is usually self-limited and may respond to NSAIDs.

Abdominal pain after methotrexate treatment represents a clinical dilemma. It is difficult to differentiate expected pain from therapeutic tubal abortion and hematoma formation with fallopian tube distention (separation pain) from pain associated with rupturing persistent ectopic pregnancy.[31] Suggested evaluation of patients presenting with abdominal pain in this time frame after methotrexate administration includes a CBC and abdominopelvic US to rule out tubal rupture and hemoperitoneum and consideration of other causes of abdominal pain.[3] Patients may need admission to the hospital for observation. Hemodynamic instability and/or falling hematocrit require consideration for surgical intervention. Many centers will proceed to surgical intervention in patients with moderate to severe pain, free fluid in the cul-de-sac, or

rebound tenderness, although conservative treatment has proven successful in stable patients after methotrexate therapy.[31] Prognostic factors associated with a higher failure rate for methotrexate treatment include larger tubal diameter, higher initial β-hCG levels, severe abdominal pain, and fetal cardiac activity.[32]

Methotrexate administration in properly selected patients with ectopic pregnancy may be initiated in the ED, clinic, or obstetrician/gynecologist's office. Treatment initiated in the ED should be in close conjunction with an obstetrician/gynecologist or other physician capable of providing follow-up care. Keep pelvic examinations after methotrexate treatment to a minimum to decrease the risk of tubal rupture. Patient instruction on discharge should include the following points[33]:

- Treatment failure occurs in up to 36% of cases.
- Elective or emergency surgical treatment may be necessary if medical therapy fails or tubal rupture occurs (~5% of cases).
- Vaginal bleeding, abdominal pain, weakness, dizziness, or syncope after treatment should be evaluated immediately as possible signs of tubal rupture.[15]
- Patients should refrain from sexual intercourse for 14 to 21 days after treatment (until β-hCG levels are undetectable), because it may increase the risk of tubal rupture.

RH SEROCONVERSION AND INDICATIONS FOR ANTI-D IMMUNOGLOBULIN

Rh_0 (D) antigen can be detected as early as 5.5 weeks and certainly by 6 weeks of gestation. Alloimmunization can occur with as little as 0.1 mL of fetal blood admixing with the mother's. Alloimmunization can occur from ectopic pregnancy. Circulating blood volume of the fetus is <5 mL in the first trimester. **Both the American College of Emergency Physicians and the American College of Obstetricians and Gynecologists recommend treatment with 50 micrograms of RhoGAM® for Rh-negative women with ectopic pregnancy when diagnosed prior to 12 weeks of gestation due to the small volume of red cells in the fetoplacental circulation, although administration of a full dose of 300 micrograms is acceptable as well.**

DISPOSITION AND FOLLOW-UP

Figure 98-4 summarizes the algorithm for management of suspected ectopic pregnancy. Unstable patients with suspected ectopic pregnancy should receive resuscitation, emergency consultation, and operative intervention.

For patients with unruptured ectopic pregnancy, a quantitative β-hCG level facilitates subsequent management. Stable patients with β-hCG levels above the discriminatory zone and an empty uterus on US, with or without other US findings of an ectopic pregnancy, are presumed to have an ectopic pregnancy. These patients should receive gynecologic consultation in the ED.

Management options for stable patients with a β-hCG level below the discriminatory zone and indeterminate US include consultation in the ED or discharge for follow-up in 2 days for reexamination and repeat β-hCG levels.

SPONTANEOUS ABORTION

The World Health Organization defines spontaneous abortion as loss of pregnancy before 20 weeks or loss of a fetus weighing <500 grams. Estimates of pregnancies that abort spontaneously range from 20% to 40%. Approximately 75% of spontaneous abortions occur before 8 weeks of gestation (**Table 98-6**).

The most common cause of fetal loss is chromosomal abnormalities. Other associations include advanced maternal age, prior poor obstetric history, concurrent medical disorders, previous abortion, infection (including syphilis and human immunodeficiency virus), and some anatomic abnormalities of the upper genital tract. Exposure to some agents, such as certain anesthetic agents, certain heavy metals, and tobacco, may also contribute to the incidence of abortion.

TABLE 98-6 Spontaneous Abortion Terminology

Terminology	Definition
Threatened abortion	Pregnancy-related bloody vaginal discharge or frank bleeding during the first half of pregnancy without cervical dilatation
Inevitable abortion	Vaginal bleeding and dilatation of the cervix
Incomplete abortion	Passage of only parts of the products of conception More likely to occur between 6 and 14 weeks of pregnancy
Complete abortion	Passage of all fetal tissue, including trophoblast and all products of conception, before 20 weeks of conception
Missed abortion	Fetal death at <20 weeks without passage of any fetal tissue for 4 weeks after fetal death
Septic abortion	Evidence of infection during any stage of abortion

Bleeding with or without abdominal pain is the most common presenting complaint.

DIAGNOSIS

In addition to the standard medical history, determine the amount of bleeding as pads used per hour to anticipate blood loss, last menstrual period, and past obstetric history. A pelvic examination is needed to define the type of abortion and to determine the amount and site of bleeding, whether the cervix has dilated, and whether any tissue has been passed.

The diagnosis of pregnancy is central to the diagnosis of abortion. Obtain a quantitative serum β-hCG level, CBC to evaluate for blood loss, blood type, Rh factor and antibody screen, and urinalysis (urinary tract infection has been associated with increased fetal wastage). US can help rule out ectopic pregnancy, aid as a prognostic tool for fetal viability, and diagnose retained products of conception. US studies combined with determinations of β-hCG levels can be both diagnostic and prognostic. Although a β-hCG of 1500 mIU/mL is a somewhat arbitrary value when evaluating pregnancy, it is still useful when comparing with US findings. Although institution dependent, an IUP should be visible on transvaginal US at this concentration. **Table 98-7** describes expected US findings at certain gestational ages and β-hCG values.[34]

TREATMENT

Patients with threatened abortion can be discharged safely if follow-up is ensured. Although a low level of activity and even bed rest are sometimes advised, there is no proven effectiveness of this practice.[35] Generally speaking, a miscarriage cannot be avoided. Patients should avoid intercourse and tampons to minimize risk of infection.

Patients with a diagnosis of incomplete abortion should have the uterus evacuated. The decision to proceed with medical treatment, such as PO misoprostol, 600 micrograms, or surgical treatment, such as dilatation and curettage, should be made in consultation with the patient and an obstetrician.[36]

Patients with a complete abortion, as shown by US and complete passage of products of conception, can be discharged safely, with follow-up

TABLE 98-7 Comparison of Gestational Age, β-hCG, and US Findings

Gestational Age	β-hCG (mIU/mL)	Transvaginal US Findings	Transabdominal US Findings
4–5 weeks	<1000	Intradecidual sac	N/A
5 weeks	>2000	Yolk sac (± embryo)	Gestational sac
6 weeks	10,000–20,000	Embryo with cardiac activity	Yolk sac (± embryo)
7 weeks	>20,000	Embryonic torso/head	Embryo with cardiac activity

Source: Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA: *Ma & Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill, Inc.; 2014; Table 14-1, p. 400.

ensured. If there is any doubt, obtain obstetrics consultation for possible dilatation and curettage.

Patients with a nonviable fetus can be either admitted or discharged to be followed up within 1 week, depending on the comfort level of the patient and physician with this decision. Patients should return immediately if there is heavy bleeding (more than one pad per hour for 6 hours), pain, or fever.

Pregnant women with vaginal bleeding who are Rh negative should be treated with Rh_0 (D) immunoglobulin (RhoGAM). RhoGAM should be administered before discharge, if possible, but it also can be administered within 72 hours by the primary care physician or obstetrician when the woman presents several days or weeks after vaginal bleeding has begun.

SEPTIC ABORTION

A septic abortion is a spontaneous or other abortion complicated by a pelvic infection. Presenting complaints include fever, abdominal pain, vaginal discharge, vaginal bleeding, and history of recent pregnancy. The most common causes are retained products of conception due to incomplete spontaneous or therapeutic abortion and introduction of either normal or pathologic vaginal bacteria by instrumentation.

Perform a history and physical examination, including a pelvic examination. Obtain a quantitative serum β-hCG level, CBC to evaluate for anemia due to blood loss, blood type, Rh factor and antibody screen, urinalysis, and blood cultures. A US will help identify retained products of conception in the uterus, adnexal masses, and free fluid in the cul-de-sac. Treatment consists of fluid resuscitation, broad-spectrum IV antibiotics, and early obstetric consultation for evacuation of the uterus. Antibiotics, such as ampicillin/sulbactam, 3 grams IV, or clindamycin, 600 milligrams, plus gentamicin, 1 to 2 milligrams/kg IV, should cover both normal vaginal flora and those causing sexually transmitted disease.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease consists of a broad spectrum of conditions ranging from an uncomplicated partial hydatidiform molar pregnancy to stage IV choriocarcinoma with cerebral metastases.[37] It is a neoplasm that arises in the trophoblastic cells of the placenta. It complicates 1 in 1700 pregnancies in North America and is more common in Asian women. The noninvasive form of the disease is the hydatidiform mole, which is either complete or partial. Complete moles are more common, and in this form, there is no actual fetus, whereas in the partial mole, a deformed, nonviable fetus is present. Both moles and invasive forms are composed of trophoblasts that produce β-hCG. Patients with a history of hydatidiform molar pregnancy are at increased risk of future molar pregnancies, with a risk of 1% in subsequent gestations after one molar pregnancy and a risk as high as 23% after two molar gestations.

Symptoms include vaginal bleeding in the first or second trimester (75% to 95% of cases) and hyperemesis (26%). Gestational trophoblastic disease, or molar pregnancies that persist into the second trimester, are associated with preeclampsia. **When pregnancy-induced hypertension is seen before 24 weeks of gestation, consider the possibility of a molar pregnancy.** The uterus is excessive in size for gestational age and shows a placenta with many lucent areas interspersed with brighter areas on US study. Because not all molar pregnancies are found on US, all tissue extracted from the uterus on suction curettage or during pelvic examination should be sent for histologic examination. If trophoblastic disease is suspected because of abnormally high β-hCG levels, a uterine size either larger or smaller than expected, and US findings suggestive of the diagnosis, obtain obstetric consultation. Treatment is by suction curettage in the hospital setting because of risk of hemorrhage. β-hCG levels that fail to decrease after evaluation are evidence of persistent or invasive disease necessitating chemotherapy. Metastasis to lung, liver, and brain may occur, but the prognosis for most patients is very good. Trophoblastic embolization, although extremely rare, may occur, with resulting rapid onset of respiratory distress resembling amniotic fluid embolus.

NAUSEA AND VOMITING OF PREGNANCY AND HYPEREMESIS GRAVIDARUM

EPIDEMIOLOGY

Nausea and vomiting of pregnancy is quite common, with these symptoms reported in up to 90% of pregnancies.[38] Severe nausea and vomiting of pregnancy is known as hyperemesis gravidarum and is defined as intractable vomiting with weight loss, volume depletion, and laboratory values showing hypokalemia or ketonemia. It occurs in 0.3% to 3% of all pregnancies.[38] Patients with gestational trophoblastic disease also may present with intractable vomiting for unknown reasons.

CLINICAL FEATURES

Findings on physical examination in nausea and vomiting of pregnancy are usually normal except for signs of volume depletion. Laboratory tests to consider include CBC, serum electrolytes, BUN, creatinine, and urinalysis. The finding of ketonuria is important because it is an early sign of starvation. However, there is no evidence that ketosis per se is harmful to the fetus. Serial measurements of urinary ketones can be used to determine success of therapy.

The presence of abdominal pain in nausea and vomiting of pregnancy or hyperemesis gravidarum is highly unusual and should suggest another diagnosis. Ruptured ectopic pregnancies occasionally present with nausea and vomiting, as well as diarrhea and abdominal pain. Gallbladder dilatation and biliary sludge increase in pregnancy, predisposing to stone formation. Cholelithiasis and cholecystitis are more common in pregnant women than in women of comparable age and health status who are not pregnant. Differential diagnosis of vomiting or vomiting with abdominal pain should include cholecystitis, cholelithiasis, gastroenteritis, pancreatitis, appendicitis, hepatitis, peptic ulcer, pyelonephritis, ectopic pregnancy, fatty liver of pregnancy, and the syndrome of *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets (HELLP syndrome).

TREATMENT

Treatment consists of IV fluids containing 5% glucose in either lactated Ringer's solution or normal saline to replete volume and reverse ketonuria. A number of antiemetic drugs can be used (**Table 98-8**) for patients who remain nauseated or continue to vomit. Initially, the patient should be given nothing by mouth. Oral fluids should be started after the nausea and vomiting are controlled but before discharge.

DISPOSITION AND FOLLOW-UP

The patient may be discharged after reversal of ketonuria, correction of electrolyte imbalance, and a successful trial of oral fluids. Discharge with antiemetic medication is usually necessary. There is no clear drug of choice.

Phenothiazines can cause drowsiness or dystonic reactions in some patients. Ondansetron (Zofran®), 8 milligrams IV or 4 milligrams PO three times daily, can cause headache, constipation, diarrhea, or lightheadedness. It does not cause dystonia. Its chief disadvantage is cost. It is apparently no more effective than promethazine.[14] Doxylamine and pyridoxine (Bendectin®), a mainstay of therapy in the past, was discontinued due to fears of teratogenicity, but with new information, it does not represent an increase in fetal risk and has been reintroduced on the North American market as Diclegis®/Diclectin®.[15,39]

Admission guidelines include uncertain diagnosis, intractable vomiting, persistent ketone or electrolyte abnormalities after volume repletion, and weight loss of >10% of prepregnancy weight.

TABLE 98-8 Antiemetics

Antiemetic	Brand Name	U.S. Food and Drug Administration Category	PO	PR	IV
Promethazine	Phenergan®	C	12.5–25 milligrams every 4 h	12.5–25 milligrams every 4 h	IV extravasation causes tissue injury; 12.5–25 milligrams IM or IV every 4 h
Prochlorperazine	Compazine®	—	5–10 milligrams every 3-4 h	25 milligrams every 12 h	10 milligrams over 2 min Maximum of 40 milligrams every 24 h
Chlorpromazine	Thorazine®	C	10–25 milligrams every 4–6 h	100 milligrams every 6–8 h	25 milligrams in 500 mL NS at 250 mL/h
Ondansetron*	Zofran®	B	4–8 milligrams every 8 h	—	8 milligrams IV over 5 min
Metoclopramide	Reglan®	B	10 milligrams orally every 6–8 h	—	10 milligrams over 1–2 min every 6–8 h
Maintenance Therapy for Nausea and Vomiting					
Doxylamine with pyridoxine	Diclegis/Diclectin®	A	2 tablets every evening	—	—
Vitamin B_6	—	—	25 milligrams every 8 h	—	—
Ginger	—	—	500–1000 milligrams daily	—	—
Diphenhydramine	Benadryl®	B	25–50 milligrams every 6 h	—	—

Abbreviation: NS = normal saline.

*Evidence is insufficient to support or refute the teratogenicity of ondansetron. For that reason, many attempt symptom control with other agents first.

Source: Adapted with permission from Pearlman M, Tintinalli JE (eds): *Emergency Care of the Woman*. New York: McGraw-Hill, Inc.; 1998.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 99

Comorbid Disorders in Pregnancy

Lori J. Whelan

INTRODUCTION

This chapter reviews the most common comorbid conditions encountered in pregnant women in the ED environment: diabetes and hypoglycemia; thyroid disorders; cardiac disorders and dysrhythmias; thromboembolism; asthma; urinary tract infections; headache; seizures; substance abuse; and intimate partner violence. Drug risk during pregnancy, lactation, and fetal effects of radiation are summarized based on currently available data. Resuscitation is covered in Chapter 25, "Resuscitation in Pregnancy."

DIABETES IN PREGNANCY

The growing prevalence of gestational diabetes mellitus reflects the increase in obesity, sedentary lifestyles, and type 2 diabetes in the general population. Due to this increased prevalence and proposed new diagnostic criteria, it is estimated that any type of diabetes affects between 8% and 17% of pregnancies,[1] with 86% categorized as gestational diabetes mellitus.[2,3] Because many women do not receive screening for diabetes before pregnancy, it can be challenging to distinguish gestational from preexisting diabetes. Pregnant diabetics are at increased risk for several pregnancy complications, including pregnancy-induced hypertension, preeclampsia, preterm labor, spontaneous abortion, pyelonephritis, and diabetic ketoacidosis (DKA). The goal of treatment during pregnancy is to prevent spontaneous abortions, hyperglycemia-induced congenital abnormalities, and ketoacidosis and hypoglycemia.

The American College of Obstetricians and Gynecologists recommends the following goals for maintaining euglycemia in pregnant diabetic patients: a fasting blood glucose concentration of ≤95 milligrams/dL (5.27 mmol/L) and a 2-hour postprandial glucose concentration ≤120 milligrams/dL (6.66 mmol/L).[3]

A significant portion of gestational diabetics can be managed with diet alone if they can maintain glycemic goals with frequent glucose monitoring. When pharmacologic treatment is indicated, **insulin** is the preferred treatment for diabetes in pregnancy.

Among patients with preexisting type 1 and type 2 diabetes, the need for insulin increases throughout the course of pregnancy. In general, during the first trimester, the initial insulin requirement is 0.7 unit/kg/d. By late pregnancy, patients generally require 1 unit/kg/d.[4]

For basal insulin coverage, intermediate-acting neutral protamine Hagedorn (NPH) insulin has historically been considered first-line therapy and has been widely studied in this patient population. There is also recent literature supporting the use of long-acting insulin analogues, particularly insulin detemir (Levemir®), as an alternative. Insulin detemir is approved by the U.S. Food and Drug Administration for use in pregnancy and is category B. Compared to NPH insulin, it improves fasting plasma glucose and decreases hypoglycemic events. There is a strong evidence base to recommend insulin detemir in pregnancy, but the lack of definitive fetal benefit means that there is no pressing need to switch a woman whose diabetes is well controlled by NPH insulin to insulin detemir.

Insulin glargine (Lantus®) was previously a pregnancy category C medication and was generally not initiated during pregnancy due to concerns of potential mitogenic activity. However, in 2015, the U.S. Food and Drug Administration started phasing out pregnancy class categories, and insulin glargine is now labeled "No human pregnancy data," requiring evaluation and use on an individual basis. Recent studies have shown it to be as safe as insulin detemir, and it seems reasonable to initiate and continue insulin glargine if it is successful in maintaining excellent glycemic control in a woman who is now pregnant.[5-7]

For postprandial glycemic control, rapid-acting insulin analogues, such as insulin lispro and insulin aspart, do not cross the placenta and have been safely used in pregnancy. The American College of Obstetricians and Gynecologists recommends that these be used preferentially over regular insulin because both have a more rapid onset of action, enabling the patient to administer her insulin right at the time of a meal rather than 10 to 15 minutes before an anticipated meal.[3] This should provide less hypoglycemia from timing issues and better glycemic control.

In women who decline insulin therapy, are unable to safely administer insulin, or cannot afford insulin, **metformin** is a reasonable alternative

choice. **Glyburide** treatment is not recommended as a first choice because it does not have equivalent outcomes to insulin.[3]

Recent studies in gestational diabetes have not shown metformin or glyburide to have any harmful fetal effects, but these agents are still not approved by the U.S. Food and Drug Administration for use in gestational diabetes, and long-term safety studies are still needed.

HYPOGLYCEMIA

Women with type 1 diabetes have three to five times more hypoglycemic episodes than the period prior to pregnancy.[8] Risk factors for severe hypoglycemia during pregnancy include a history of severe hypoglycemia in the year preceding pregnancy, impaired hypoglycemia awareness, long duration of diabetes, low hemoglobin A_{1c} in early pregnancy, fluctuating plasma glucose levels, and excessive use of insulin injections between meals.[8] Hypoglycemia generally presents as sweating, tremors, blurred or double vision, weakness, hunger, confusion, paresthesias, anxiety, palpitations, nausea, headache, or stupor. Moderate and infrequent hypoglycemic episodes are generally well tolerated by the fetus.[9] Pregnant diabetic women should be educated about the symptoms and treatment of hypoglycemia. Treat mild hypoglycemia (i.e., a glucose level of <70 milligrams/dL [3.89 mmol/L] in patients who are able to follow commands) by giving juice, glucose, or food by mouth. Provide standard treatment for more severe hypoglycemia, with IV glucose or PO glucose or glucagon 1 to 2 milligrams SC, IM, or IV (see Chapter 223, "Type 1 Diabetes Mellitus," and Chapter 224, "Type 2 Diabetes Mellitus").

DIABETIC KETOACIDOSIS IN PREGNANCY

DKA is a serious medical and obstetrical emergency previously considered typical of type 1 diabetes but now reported also in type 2 and gestational diabetes patients.[10,11]

The incidence of DKA in pregnancy decreases with early diagnosis of insulin-dependent diabetes, improved prenatal counseling, and care with an identifiable primary care provider.[12] DKA still most commonly affects women in the second or third trimester or pregnant women with new-onset type 1 diabetes.[13]

A pregnant diabetic who is ill appearing, has persistent nausea and vomiting, and/or has a blood glucose level ≥180 milligrams/dL [9.99 mmol/L] should be screened for DKA with serum or urine ketones and a serum chemistry panel. Diabetic pregnant women at more than 20 weeks of gestation are more prone to develop more severe and rapidly progressive episodes of DKA (usually over hours) and at lower glycemic levels (<300 mg/dL [<16.65 mmol/L]).[11] Management guidelines for pregnant women with DKA are the same as for nonpregnant patients[11] (see Chapter 225, "Diabetic Ketoacidosis"). In addition to the usual care, obtain fetal heart tones, administer oxygen, and for third-trimester patients, place patient in the left lateral decubitus position to displace the uterus and improve uterine blood flow. Most fetal heart rate abnormalities subside after correction of maternal hypovolemia and acidosis. Consult with the patient's physician, and admit the patient to the hospital.

Women who use continuous SC insulin infusions (the insulin pump) can develop DKA whether they are pregnant or not. DKA can develop very quickly and unexpectedly, especially in patients who have recently started using the pump.[14,15] Use of continuous insulin pumps during pregnancy is equivalent, but not superior, to scheduled injections. Management of DKA in a pregnant woman with an insulin pump is the same as in the nonpregnant patient.

DKA is not an indication for delivery. Although fetal heart rate monitoring in maternal DKA may initially demonstrate a nonreassuring pattern, patterns usually improve as maternal ketoacidosis is corrected, and mother will tolerate delivery or cesarean section better once acidosis resolves.[16]

THYROID DISORDERS

Please refer to Chapter 229, "Hyperthyroidism and Thyroid Storm," for treatment of thyroid storm in pregnancy.

TRANSIENT HYPERTHYROIDISM OF HYPEREMESIS GRAVIDARUM

Women in the first trimester with weight loss, tachycardia, and vomiting consistent with hyperemesis gravidarum may also demonstrate laboratory evidence of hyperthyroidism or biochemical or transient hyperthyroidism. The most likely cause is thyrotropin receptor stimulation from high human chorionic gonadotropin serum concentrations. Women with transient hyperthyroidism have no previous history of thyroid disease, no palpable goiter, and except for tachycardia, no other symptoms or signs of hyperthyroidism. Test results for thyroid antibodies are negative. With transient hyperthyroidism of hyperemesis gravidarum, thyroid-stimulating hormone may be suppressed and free thyroxine elevated, but triiodothyronine is **lower** than in true hyperthyroidism. With true hyperthyroidism, both free thyroxine and triiodothyronine are usually **elevated**, and thyroid antibody tests will usually be positive. Only symptomatic treatment is suggested for transient hyperthyroidism, but hospitalization may be required for management of dehydration. Antithyroid medication is not recommended, although beta-blockers may be considered.[17]

HYPERTHYROIDISM

True hyperthyroidism in pregnancy increases the risk of preeclampsia, low birth weight, maternal congestive heart failure, and possibly congenital malformations. Symptoms of hyperthyroidism can mimic symptoms of normal pregnancy and may consist of nervousness, palpitations, heat intolerance, and inability to gain weight despite a good appetite. Methimazole and propylthiouracil are equally efficacious in the treatment of pregnant women. However, both medications have potential adverse effects. Methimazole is associated with congenital abnormalities during first-trimester organogenesis and has been linked to esophageal and choanal atresia and aplasia cutis. Propylthiouracil can cause hepatotoxicity. Recent studies revealed that children exposed to propylthiouracil *also* developed birth defects.[17] Therefore, current recommendations are to confirm potential pregnancies as soon as possible in patients currently on methimazole and propylthiouracil and evaluate the risk of withholding any antithyroid medication during the first trimester against the risk of thyroid storm. For patients requiring therapy, several expert committees recommend the use of propylthiouracil through 16 weeks of pregnancy,[18] followed by transitioning to methimazole for the second and third trimesters. Agranulocytosis, liver failure, and aplastic anemia are rare but serious complications in patients treated with antithyroid drugs. If such conditions develop, immediately discontinue the medication and obtain obstetrical consultation.

CARDIAC DISORDERS

DYSRHYTHMIAS

Pregnancy can precipitate cardiac arrhythmias not previously present in seemingly well individuals. The risk of arrhythmias rises during labor and delivery. Factors that promote arrhythmias in pregnancy include the direct cardiac electrophysiologic effects of hormones, changes in hemodynamics or autonomic tone, hypokalemia, and underlying heart disease. Reduction of uterine blood flow during prolonged tachyarrhythmic episodes may adversely affect the fetus. The incidence of arrhythmias in pregnancy is rising due to increasing maternal age and pregnancies in women successfully treated for congenital heart disease.[19] **Just as in a nonpregnant patient, treat any hemodynamically unstable arrhythmia in pregnancy with direct-current cardioversion (50 to 200 J).**[20] Treat hemodynamically stable arrhythmias medically. The chronic use of beta-blockers in pregnancy can influence fetal and newborn size, but only atenolol is singled out as being a U.S. Food and Drug Administration class D drug in this regard (some evidence for harm to the fetus). Other beta-blockers are U.S. Food and Drug Administration class B (sotalol) or C. Digoxin, verapamil, diltiazem, and adenosine have their usual efficacy without adverse fetal effects.[19]

CARDIAC DYSRHYTHMIA TREATMENT

Paroxysmal supraventricular tachycardia is the most common nonsinus tachycardia in women of childbearing age. The treatment of supraventricular tachycardia in pregnant women is the same as for nonpregnant women.[19] If vagal maneuvers are ineffective, give adenosine at usual doses. Case reports show both efficacy and a lack of any direct adverse or teratogenic side effects to the fetus.[21] Additionally, acute treatment with beta-blockers, verapamil, and diltiazem is safe in pregnancy when used in standard dosage.

The goal of management of **atrial fibrillation** in pregnancy is rate control or conversion to sinus rhythm. Use diltiazem, beta-blockers, and/or digoxin, all of which are safe in pregnancy and with unchanged dosages.[21] Procainamide has not been associated with teratogenicity. Anticoagulation with unfractionated or low-molecular-weight heparin is safe in pregnancy and should be used if the patient meets criteria for anticoagulation described for nonpregnant patients.

Ventricular arrhythmias may occur during pregnancy, particularly in patients with congenital heart disease, cardiomyopathy, or valvular disease. In hemodynamically stable patients with sustained ventricular tachycardia, both IV procainamide and lidocaine can be used for acute management. Procainamide has the same risks in pregnancy of hypotension and QT prolongation requiring ECG monitoring. Although there are reports that lidocaine may be associated with an increase in myometrial tone, decrease in placental blood flow, and fetal bradycardia, the use of the drug has not been linked to an increased incidence of birth defects.[22] **Amiodarone is categorized as class D** because its main metabolite (desethylamiodarone) and iodine cross the placenta. Chronic fetal exposure to amiodarone and its subsequent iodine overload is associated with neurotoxicity, fetal/neonatal hypothyroidism, and less frequently, goiter. Therefore, the use of amiodarone in pregnancy is limited to maternal/fetal tachyarrhythmias that are resistant to other drugs or are life threatening because short-term use has not been linked to any harmful effects.[21,23]

The presence of an artificial pacemaker or implantable cardiac defibrillator does not affect the course of pregnancy.[24]

CHEST PAIN AND HEART FAILURE

The differential diagnosis of chest pain is similar in pregnant and nonpregnant women. However, **aortic dissection** and **cardiomyopathy** are actually more common in pregnancy. Advancing maternal age has made **acute coronary syndrome** in pregnancy more prevalent. **Acute coronary syndrome is estimated to occur at least three times more often in pregnancy when compared to nonpregnant women of the same age group.**[25] Acute coronary syndrome in pregnancy is especially challenging because it is not only seen in patients over 35 with coronary artery disease risk factors but also presents in younger, healthy women with no risk factors. Acute coronary syndrome in younger pregnant women is more likely caused by **spontaneous coronary artery dissection, coronary vasospasm, or coronary embolus,** which are all extremely rare in the younger, nonpregnant patient.

Spontaneous coronary artery dissection is the most common cause of pregnancy-related acute myocardial infarction, being the documented cause in >40% of cases.[26] The occurrence of spontaneous coronary artery dissection is thought to be due to progesterone and other hormone-related vessel wall changes and shear forces secondary to increased blood volume. It is most frequent in the third trimester or postpartum period. Spontaneous coronary artery dissection is frequently found in multiple vessels and is associated with an increased incidence of cardiogenic shock, life-threatening arrhythmias, and a high maternal and fetal mortality.[27] **Coronary vasospasm** is more prevalent in patients with migraine headaches, suggesting an overall "vasospastic" propensity coupled with an overall increase in reactivity of the vessels in pregnancy. **Coronary emboli** are simply due to the fact that pregnancy itself is a hypercoagulable state, and reports indicate that close to 10% occur in otherwise normal coronary arteries.[25]

Treatment of acute coronary syndrome in pregnancy is complicated given the multiple etiologies discussed earlier. Additionally, many drugs in current acute coronary syndrome guidelines are not recommended in pregnancy (angiotensin inhibitors and statins) or have limited to no human safety data (beta-blockers, nitroglycerin, and novel anticoagulants). Resuscitate and stabilize as you would for any nonpregnant patient and obtain emergent cardiology consultation. Although they may worsen a dissection, **aspirin** and **heparin** are reasonable choices because you will be unaware of a dissection until imaging is obtained. Use of thrombolytics during pregnancy can cause maternal hemorrhage, placental abruption, uterine bleeding, and postpartum hemorrhage. As of this writing, thrombolytic therapy is **not recommended** due to lack of reversibility and the risk of worsening a possible coronary dissection. Thrombolytic therapy could be considered for patients with life-threatening acute coronary syndrome when there is no access to percutaneous coronary intervention.[28] Therefore, immediate transfer to a hospital with catheterization laboratory capabilities is advised.[29] Debate continues regarding whether medical management or stent placement is the best treatment option for spontaneous coronary artery dissection given recent data showing iatrogenic dissections and propagation of dissection during stent placement and successful medical management in stable patients.[27] Overall outcomes are significantly worse for acute coronary syndrome in pregnancy, and many who survive will eventually require emergent coronary artery bypass graft, so prompt and accurate diagnosis and referral are imperative.

Peripartum cardiomyopathy is a dilated cardiomyopathy resulting in left ventricular dysfunction that usually develops in the third trimester or the first few months after delivery. Diagnosis is made when there is no apparent cause or preexisting history of cardiac disease. Risk factors include multiparity, maternal age >40 years old, and gestational hypertension. Peripartum cardiomyopathy needs to be considered in any postpartum patient with dyspnea, especially a younger patient, because is it easily misdiagnosed as an upper respiratory infection or pneumonia. Diagnose and treat congestive heart failure and pulmonary edema with standard modalities[30] (see Chapter 53, "Acute Heart Failure").

Sympathetic crashing acute pulmonary edema is an extreme form of flash pulmonary edema, preceded by long-standing hypertension and ventricular dysfunction, and can accompany preeclampsia or eclampsia. Sympathetic catecholamine release causes worsening of ventricular stiffening, and the physiologic plasma increase associated with pregnancy may make it easier for sympathetic crashing acute pulmonary edema to present in pregnancy even without preceding hypertension. Initial treatment is the same for the nonpregnant patient: high-dose IV nitroglycerin (500 to 1000 micrograms) until stabilization and ventilatory support with bilevel positive airway pressure, high-flow nasal cannula, or intubation, as needed.[31]

VENOUS THROMBOEMBOLISM

Venous thromboembolism includes deep venous thrombosis (DVT) and pulmonary embolism and is the leading cause of maternal morbidity and mortality in industrialized nations as well as developing countries.[32] The risk of venous thromboembolism increases fivefold during pregnancy and is increased by even more in the first 3 months after delivery.[33,34]

Pregnancy-related hypercoagulability, which is necessary to prevent maternal hemorrhage, is due to increased levels of clotting factors, increased platelet and fibrin activation, and decreased fibrinolytic activity. Pregnancy increases venous pooling and uterine compression of the inferior vena cava and iliac veins. Clots develop in the deep venous system of the legs and pelvis. Up to 20% of DVTs may be complicated by pulmonary embolism, so early DVT diagnosis is important.[35]

DEEP VENOUS THROMBOSIS

CLINICAL PRESENTATION

The clinical assessment of DVT is difficult because many of the typical clinical signs and symptoms are seen in normal pregnancy, including leg edema, shortness of breath, and tachycardia. Proximal extension of the DVT into the pelvic veins can result in abdominal or back pain, which is also very common in a normal pregnancy. DVT in pregnant women is more often left-sided (85% vs. 55% nonpregnant) and is more commonly found in proximal iliofemoral veins (72% vs. 9% nonpregnant).[36]

Up to 10% of pregnancy-related DVTs may be found in the pelvic veins, which is uncommon in nonpregnant patients.[37] However, any patient with unilateral calf pain and swelling, swelling of the entire leg, or groin or back pain needs to be evaluated for DVT. Additional risk factors include a previous history or family history of DVT, obesity, maternal age >35 years, smoking, sickle cell disease, diabetes, hypertension, immobility, in vitro fertilization (greater for twins than for single gestation), and preeclampsia.

WELLS' SCORE

The Wells' score for DVT (see Table 56-6), the most validated clinical decision rule in the diagnosis of DVT, has not been validated in pregnant women.[38,39] Chan's LEFt clinical prediction tool is the only pregnancy-specific, validated prediction tool available. Three variables—symptoms in the left leg (L), calf circumference difference >2 cm (edema [E]), and first trimester (Ft) presentation—are predictive of positive imaging for DVT in pregnant women.[40] However, the LEFt rule does not help after the first trimester and has not yet been applied prospectively in clinical trials. Therefore, it should not be used in isolation to rule out DVT.

D-DIMER

D-dimer levels normally increase throughout pregnancy, and there is no agreed-upon cutoff for a venous thromboembolism–associated D-dimer increase in pregnant women. The high negative predictive value of a normal D-dimer in pregnancy has many wanting to forgo imaging; however, thromboembolism has been reported with normal D-dimer levels.[41] As of this writing, the American College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, the Royal College of Obstetricians and Gynaecologists, and the American Thoracic Society/Society of Thoracic Radiology recommend against the use of D-dimer alone to rule out pulmonary embolism in pregnant women.[35]

COMPRESSION DUPLEX ULTRASOUND

Compression duplex US with color flow Doppler is the first-line imaging technique given the safety profile, and sensitivity and specificity for detecting proximal DVT are 96% and 99%, respectively.[35]

Compression US is less sensitive in detecting DVT below the knee just as in nonpregnant patients; therefore, repeat imaging is recommended. There is a large prospective study under way to evaluate the use of whole-leg US to catch distal DVTs, which have a 10% to 20% risk of propagation in the nonpregnant patient.[42,43] There is continued debate on whether to treat distal (below the knee) DVT or to repeat US to rule out progression; however, it is recommended to treat any DVT found in pregnancy.[35] Emergency physicians have become proficient at performing their own DVT US exams at the bedside and have published considerable literature showing the utility of a limited 2-point exam (and D-dimer) to rule out DVT.[44,45] However, there have been no studies of limited US on pregnant patients.

Iliac or pelvic vein thrombosis is more difficult to diagnose if isolated and not associated with clot in the femoral vein. Magnetic resonance venography is an MRI that uses a special technique to specifically look at blood vessels. Magnetic resonance venography has been shown to be sensitive and specific for the detection of pelvic vein thrombosis without the need for gadolinium contrast.[46-48] MRI or magnetic resonance venography **without** contrast should be the preferred method to evaluate pelvic vein thrombosis with the addition of contrast only if absolutely necessary.

PULMONARY EMBOLISM

Pregnant women with symptoms suggestive of pulmonary embolism who are positive for DVT by compression US should receive anticoagulation without waiting for further confirmatory diagnostic studies. In hemodynamically **stable** patients, consider no further imaging to spare the mother and fetus from additional radiation exposure. In **unstable** patients, further imaging may be required to eliminate other causes of hypotension and evaluate the need for aggressive treatment. Bedside or formal echocardiography can detect acute right ventricular dysfunction, which suggests a large clot burden that may benefit from more aggressive therapy than standard anticoagulation alone.[49,50]

Patients with symptoms suggestive of pulmonary embolism with a normal compression US of the extremities require further diagnostic testing. The current acceptable options are CT pulmonary angiography and pulmonary ventilation-perfusion scanning. CT pulmonary angiography has somewhat higher maternal breast radiation, and ventilation-perfusion scans have higher fetal radiation exposure. **However, as of this writing, the fetal and maternal radiation dose with either modality is felt to be within acceptable limits.**[51] Typically, in most institutions, a consensus is obtained between emergency physicians, obstetricians, and radiologists for imaging decisions. **Table 99-1** lists advantages and disadvantages of different imaging modalities.

CT pulmonary angiography is frequently recommended as the first-line diagnostic test of choice.[32,52] However, there are also published algorithms that suggest proceeding to ventilation-perfusion first, if chest radiograph is normal in pregnancy, as there is a lower incidence of artifact or concomitant chronic disease, which typically impedes accuracy in older patients.[35,53] However, if the ventilation-perfusion scan is nondiagnostic, then the patient will need CT pulmonary angiography, and any perceived benefit of less harmful radiation exposure is lost. Time to completion of imaging should also factor in the imaging decisions as there should be as little delay as possible in making the correct diagnosis and initiation of treatment.

TABLE 99-1 Imaging Modalities for Diagnosis of Pulmonary Embolism in Pregnancy

	Radiation	Limitations	Disadvantages	Advantages	Lactation
Chest radiograph	Minimal	Nonspecific and nonsensitive	Results determine next imaging study, requiring more time to diagnosis	May identify another cause of pulmonary symptoms	No change
CTPA	High maternal breast radiation; lower fetal radiation than V̇/Q̇ scan	Contrast allergy and renal insufficiency	Hyperdynamic state in pregnancy can affect interpretation	High sensitivity and specificity; needed if abnormal chest radiograph	No need to discard breast milk
V̇/Q̇ scan	Low breast radiation but higher fetal radiation than CTPA	Not useful if abnormal chest radiograph, asthma, COPD, or underlying pulmonary disease	If negative or inconclusive and suspicion for PE remains, will need a CTPA; limited availability and time for isotope preparation, which delays diagnosis	Negative perfusion study effectively rules out PE	Discard breast milk for 12 h
MRI/MRV	No radiation and no evidence of uncontrasted MRI having adverse fetal effects[14]	Gadolinium during any time of pregnancy associated with an increased risk of negative fetal outcomes[14]	Limited availability	Can detect pelvic and iliac thrombosis	No need to discard breast milk if uncontrasted MRI

Abbreviations: COPD = chronic obstructive pulmonary disease; CTPA = chest CT pulmonary angiography; MRV = magnetic resonance venography; PE = pulmonary embolism; V̇/Q̇ scan = ventilation-perfusion scan.

TREATMENT OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Treatment of venous thromboembolism in pregnancy currently includes unfractionated heparin or low-molecular-weight heparin because neither crosses the placental barrier.[54] Most published guidelines recommend low-molecular-weight heparin as the first-line treatment of pregnant women with acute venous thromboembolism.[35] Low-molecular-weight heparin is highly efficacious, has a low risk of bleeding complications, and has negligible risk of heparin-induced thrombocytopenia, and most patients do not need daily drug activity monitoring.

Unfractionated heparin may be used for patients at extremes of body weight or patients with recurrent venous thromboembolism while on therapeutic anticoagulation, since the activated PTT or anti–factor Xa levels will be monitored and doses can be adjusted to ensure therapeutic effect. Unfractionated heparin can be given IV through a continuous infusion or SC twice-daily injections. Protamine sulfate may be used safely in pregnancy for patients who require rapid reversal of heparin anticoagulation.

Fondaparinux, a synthetic, selective anti–factor Xa inhibitor, is recommended in the United States for the prevention and treatment of venous thromboembolism in heparin-allergic or heparin-intolerant pregnant patients.[55]

Do not use warfarin in pregnancy because it crosses the placenta and is associated with embryopathy in the first trimester; in the second and third trimesters, it may lead to CNS and ophthalmologic abnormalities. Warfarin should only be considered for women with mechanical heart valves who demonstrate a very high risk of venous thromboembolism despite treatment with unfractionated heparin or low-molecular-weight heparin.

An inferior vena cava filter is indicated when anticoagulation is contraindicated, when an acute embolic event occurs despite anticoagulation, or when acute venous thromboembolism occurs with impending delivery of the fetus.

TREATMENT OF LIFE-THREATENING PULMONARY EMBOLISM

Massive or high-risk pulmonary embolism is defined as sustained hypotension (systolic blood pressure of <90 mm Hg for more than 15 minutes) with the patient showing symptoms of shock. Thrombolytic therapy is a key treatment option for patients in extremis from pulmonary embolism, with treatment options ranging from systemic and catheter-guided thrombolysis to surgical or catheter-guided embolectomy. Although data are limited, thrombolytics have been used successfully and data regarding maternal-fetal outcomes are limited to case reports.[56,57] As of this writing, there is no formal consensus on whether systemic versus catheter-guided treatment is preferred. Catheter-guided thrombolysis and embolectomy require precious time for preparation. **Recombinant tissue plasminogen activator** (10-milligram bolus, 90-milligram infusion over 2 hours) does **not** cross the placenta, and reported rates of maternal bleeding complications are between 1% and 6% with no maternal deaths, and rates of fetal loss are between 2% and 5%.[56-59] **Streptokinase** (250,000-unit bolus, 100,000 units/h infusion for 24 hours) is also used, but with higher rates of subchorionic hemorrhage and allergic complications and longer infusion duration than tissue plasminogen activator. Catheter-directed thrombolysis allows for earlier reperfusion and likely improved long-term pulmonary function compared with systemic therapy.

ACUTE ASTHMA

Asthma is the most common medical disease in pregnancy and complicates between 3.7% and 8.4% of all pregnancies.[60,61] The clinical course may improve, remain unchanged, or worsen during pregnancy. Women with asthma have higher odds of preeclampsia, gestational diabetes, placental abruption, placenta previa, preterm delivery, low birth weight, maternal hemorrhage, pulmonary embolism, and intensive care unit admission.[62]

Symptoms of cough, wheezing, and dyspnea are the same as in nonpregnant patients. Initial assessment should include history of asthma exacerbations and intubation, peak expiratory flow rate measurements or forced expiratory volume in 1 second, physical examination, assessment of oxygen saturation, and a fetal assessment (if >20 weeks' gestation). Peak expiratory flow rate is not altered in pregnancy, with normal rates ranging between 380 and 550 L/min. Use peak expiratory flow rate as a guide to therapy. If the pregnancy has reached viability, apply continuous electronic fetal monitoring.

Treat rapidly and aggressively to reduce readmission rates and improve fetal outcomes.[63] **The principles of management are the same as in nonpregnant patients.** Maintain oxygen saturation >95%, administer repetitive or continuous inhaled β_2-agonist (albuterol/salbutamol); give inhaled ipratropium and systemic corticosteroids; give IV magnesium; monitor maternal response to therapy; and monitor the fetus for signs of distress.[64] Terbutaline sulfate, 0.25 milligram every 20 minutes, administered SC, may be used if needed. Avoid epinephrine because concerns exist about epinephrine vasoconstriction of the uteroplacental circulation.

Admission and discharge criteria are the same as in the nonasthmatic patient. For discharged women, prescribe oral prednisone, 40 to 60 milligrams per day (or equivalent), for 5 to 10 days, and a short-acting rescue beta-agonist. Anticipate maternal hyperglycemia when systemic corticosteroids are given. Inhaled corticosteroids reduce recurrence during pregnancy and decrease readmission rates following a hospitalization for asthma. Budesonide has been safely used in pregnancy.[65] Emphasize close follow-up and development of formal asthma treatment plans to minimize exacerbations as the pregnancy progresses.[66]

ASYMPTOMATIC BACTERIURIA, CYSTITIS, AND PYELONEPHRITIS

Hormonal and mechanical changes of pregnancy increase the risk of urinary stasis and subsequent urinary tract infection. After mid-pregnancy, mild right-sided hydronephrosis is found in 75% of women, and mild left-sided hydronephrosis is found in 33%.

Asymptomatic bacteriuria is diagnosed by urine culture, demonstrating the presence of bacteria in the urine in the absence of maternal symptoms of urinary tract infection. Reagent strips have limited sensitivity, and use in screening depends on resources available, but in general, a positive leukocyte esterase or urinary nitrite should be treated and a negative specimen should be cultured.[67,68] Treatment reduces the incidence of pyelonephritis and low birth weight.[69]

Causative organisms of symptomatic cystitis and pyelonephritis are similar to those in the general population and include *Escherichia coli* (75%), *Klebsiella pneumoniae*, *Proteus*, and gram-positive organisms such as group B *Streptococcus*. Obtain a urinalysis and culture with drug sensitivities in pregnant women with urinary tract symptoms and also in those with hyperemesis. Urinary tract infections need prompt treatment because acute pyelonephritis can precipitate preterm labor, bacteremia, or septic shock.

Recurrent infections can occur as a result of bacteriuria, glycosuria, and mechanical compression of the ureter in the third trimester. Reflux nephropathy increases the risk of sudden escalating hypertension and worsening renal function.[70] Urolithiasis is associated with recurrent urinary tract infections.

First-line treatment for asymptomatic bacteriuria and simple cystitis is either **amoxicillin**, 500 milligrams PO two to three times daily for 3 to 7 days, or **cephalexin**, 500 milligrams two to four times daily for 3 to 7 days.[71]

Recent studies have raised concerns about possible nitrofurantoin-linked birth defects, and although it is still pregnancy class B, current American College of Obstetricians and Gynecologists guidelines recommend to avoid nitrofurantoin in the first trimester unless there are no other options available.[72,73]

Trimethoprim-sulfamethoxazole is also **not** a good choice in pregnancy. Trimethoprim, a folate antagonist, can be used **after the first trimester**; sulfonamides can be taken during the first and second trimesters **but not during the third trimester** because sulfonamides can cause kernicterus in the infant. **Do not use fluoroquinolones and tetracyclines** during pregnancy. Fluoroquinolones are avoided because

TABLE 99-2 Causes of Headaches in Pregnancy

Life threatening
- Subarachnoid hemorrhage
- Intraparenchymal hemorrhage
- Central venous thrombosis
- Ischemic stroke
- CNS tumor or infection
- Preeclampsia/eclampsia
- Meningitis

Non–life threatening
- Tension headache
- Migraine
- Sinus headache
- Benign intracranial hypertension (pseudotumor cerebri)

of observed fetal malformations in animal studies. Tetracyclines impair bone and tooth calcification.

Pregnant women with pyelonephritis are generally hospitalized, aggressively hydrated, and treated with parenteral antibiotics. The antibiotic of choice is a second- or third-generation cephalosporin. Continue IV antibiotics until the patient is afebrile for at least 48 hours and costovertebral angle tenderness has resolved. The most common reason for treatment failure is antibiotic resistance. Patients discharged after hospitalization need to complete a 10-day course of therapy. Many providers choose to continue women with an episode of pyelonephritis on antibiotic suppression for the remainder of pregnancy.

HEADACHE AND STROKE SYNDROMES IN PREGNANCY

In pregnant women, headaches can be a symptom of a variety of neurologic or systemic disorders. **Table 99-2** lists the differential diagnosis of headaches in pregnancy (see Chapter 165, "Headache").

Warning symptoms and signs of a potentially life-threatening disease are important to elicit during the initial evaluation and are listed in **Table 99-3**.

Obtain imaging studies if concerning signs or symptoms are encountered. CT scan of the brain can be safely performed with appropriate shielding of the fetus. CT scan is best to evaluate acute intracranial or subarachnoid hemorrhage, whereas MRI is superior for evaluation of cerebral infarct, tumor, infection, or cerebral vein thrombosis.

INTRACEREBRAL HEMORRHAGE

In pregnancy, the incidence of intracerebral hemorrhage ranges from 0.01% to 0.05%, but is the cause for 5% to 12% of all maternal deaths.[74] The risk of cerebral hemorrhage extends from pregnancy through the **6-week postpartum period**.[74] Risk factors include older maternal age, African-American race, and alcohol or cocaine use. The most common cause for spontaneous intracerebral hemorrhage is **hypertension**. If there is no history of hypertension, then consider other causes such as neoplasm, hemorrhagic disorder, and vascular malformation.

Presenting symptoms vary with the location and extent of hemorrhage, so consider cerebral hemorrhage in a woman with an abrupt neurologic change. For diagnosis, obtain CT/MRI and consult the neurosurgeon. Treatment is blood pressure control and correction of coagulopathy.

TABLE 99-3 Warning Symptoms and Signs of Headaches
- New-onset headaches in pregnancy
- Postpartum headaches
- Visual disturbance or visual field defect
- Headaches with different characteristics from previous headaches
- Worst headache of life, reaching maximum intensity in <1 min
- Focal neurologic deficit or seizure
- Meningismus
- Fever
- Altered consciousness or personality changes
- Papilledema or other signs of increased intracranial pressure
- Retinal hemorrhages
- Increased blood pressure (may herald preeclampsia or eclampsia)

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage during pregnancy is the third most common cause of nonobstetric maternal death, and more than half of cases occur **postpartum**.[74] Causes include hypertension,[75] aneurysm, vascular malformation, tumors, and venous thrombosis.

Independent risk factors for subarachnoid hemorrhage from all etiologies include advancing age; African-American race; Hispanic ethnicity; hypertensive disorders; coagulopathy; tobacco, drug, or alcohol abuse; intracranial venous thrombosis; sickle cell disease; and hypercoagulability.

Suspect subarachnoid hemorrhage in a woman with severe headache, nausea, vomiting, decreased level of consciousness, or seizure. Diagnosis is by CT/MRI and/or lumbar puncture. In general, pregnant women should be treated the same as nonpregnant patients with bed rest, analgesia, sedation, neurologic monitoring, and control of blood pressure.[74]

STROKE

Pregnancy is associated with an increased risk of ischemic and hemorrhagic stroke, and stroke contributes to more than 12% of all maternal deaths, with the majority occurring in the **third trimester or puerperium**.[76] Arterial occlusion is the most common cause of pregnancy-related stroke.[76] Risk factors include hypertension, heart disease, smoking, diabetes, lupus, sickle cell disease, African-American heritage, substance abuse, and cesarean delivery. Consider stroke in women with neurologic deterioration or new focal neurologic deficits.

Once hemorrhage and eclampsia are excluded, consider thrombolytic therapy after consultation with neurology and obstetrics. To date, there are no randomized controlled trials of thrombolytics for stroke in pregnancy; however, recombinant tissue plasminogen activator (risk category C) does not cross the placenta, and there is no evidence of teratogenicity in animal studies.[77] There are more than 200 reports in the literature of pregnant women who have received thrombolytic therapy for various indications including myocardial infarction, pulmonary embolism, superior vena cava syndrome, and ischemic stroke.[76] Use of thrombolytics in pregnancy is not without its risks, although the overall maternal mortality and fetal loss are relatively low at 1% and 6%, respectively.[76,78]

CENTRAL VENOUS THROMBOSIS

Central venous thrombosis usually presents in the second and third trimesters and may occur up to 4 weeks postpartum. Symptoms include severe headache, focal neurologic deficit, vomiting, or seizure, depending on which veins are occluded. Venous thrombosis increases venous pressure and cerebral blood volume, elevating dural sinus pressure and leading to rupture of small cortical veins. Treatment is low-molecular-weight heparin, unless there is associated intracranial hemorrhage. Once the patient has been stabilized and hemorrhage from an aneurysm is excluded, the mainstay of treatment for the underlying thrombosis is still anticoagulation for the duration of the pregnancy.[79]

MIGRAINE HEADACHE

Most patients see an improvement in migraine frequency as the pregnancy progresses; therefore, address red flag symptoms and consider other life-threatening causes of severe headache (central venous thrombosis) especially in the second or third trimester before diagnosing

migraine. Although the ergot alkaloids are contraindicated in pregnancy, acute migraine headaches can be successfully treated in pregnancy with the same first-line antiemetics that are used in nonpregnant patients. Metoclopramide (Reglan®) is class B, and prochlorperazine (Compazine®), promethazine (Phenergan®), and droperidol (Inapsine®) are all class C. Avoid NSAIDs. Sumatriptans (class C) do not appear to increase fetal malformations, and if already prescribed by the obstetrician or primary physician during pregnancy, sumatriptans can be continued as an outpatient.[80]

GI DISORDERS IN PREGNANCY

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease is extremely common in pregnancy and is characterized by epigastric pain or burning radiating into the chest and neck, pain with recumbency, and pain exacerbated by acidic foods. Symptoms increase in the second trimester and peak in the third trimester due to loosening of the lower esophageal sphincter and delayed gastric emptying from pregnancy-related hormones. Always reinforce lifestyle modifications such as elevating the head of bed, not eating 3 hours before bed, eating small meals, and eliminating trigger foods. Over-the-counter antacids are safe and effective and should be first-line medical therapy. Treat mild, persisting symptoms with H_2 antagonists such as cimetidine or ranitidine. Moderate to severe symptoms can be treated with sucralfate and proton pump inhibitors. H_2 antagonists, proton pump inhibitors, and metoclopramide have been extensively studied for teratogenic effects, and no significant abnormal findings have been associated with their use in pregnancy.[81]

HEMORRHOIDS

Hemorrhoids are common during pregnancy and are caused by a combination of constipation due to slowed bowel transit from progesterone effects in the last trimester and elevated pressure in the veins below the level of the enlarged uterus. Most symptoms are mild and can be treated with prevention of constipation with increased fluids and high-fiber intake, sitz baths, and topical medications including witch hazel compresses, suppositories, corticosteroids, or topically applied anesthetics.[82] Do not use agents containing epinephrine or phenylephrine. Proctofoam has specifically been studied and is safe.[83] Consider surgical or obstetric referral for prolapsed, bleeding, or incarcerated hemorrhoids or when conservative measures fail. There are no studies of the risks versus benefits of ED excision of a thrombosed clot in pregnancy. Risks include hemorrhage and recurrence.

CHOLECYSTITIS

During pregnancy, approximately 1 in 1000 women will develop cholecystitis. Pregnancy-related hormones affect gallbladder contractility and increase residual gallbladder volume and sludge, which in turn can lead to gallstone formation. Many women ultimately require cholecystectomy during pregnancy for persistent symptoms. It is preferable to wait until the second trimester if the patient's condition allows, as surgery during the first trimester carries a risk of spontaneous miscarriage, and cholecystectomy in the third trimester is technically difficult and can result in preterm labor.[84]

APPENDICITIS

Appendicitis occurs about once in every 500 to 2000 pregnancies and is the most common extrauterine condition requiring abdominal operation in pregnancy. The diagnosis is often missed or delayed because mild abdominal discomfort, nausea, and vomiting occur frequently in normal pregnancies. Additionally, the appendix shifts in location from the right lower quadrant to the right upper quadrant during the second and third trimesters. US has become the first diagnostic test of choice in children and many adults. However, in pregnant patients, adequate visualization of the appendix is difficult, especially later in pregnancy. Recent studies suggest using MRI as the initial imaging modality given the high rate of inconclusive US results.[85-87] **Noncontrast MRI** (without gadolinium) is recommended due to recent concerns of fetal effects from gadolinium exposure. If US or MRI is unavailable, CT should be performed without delay. Focal appendiceal CT may be considered since it provides less radiation to the fetus than full abdominopelvic CT. However, focal abdominal imaging may limit discovery of an alternative diagnosis. An abdomen or pelvis CT confers about 30 mGy of radiation, and 50 mGy of radiation is generally accepted to be safe in pregnancy.[51]

OVARIAN TORSION

Torsion of the ovary is a true gynecologic emergency, and up to one fifth of ovarian torsion occurs during pregnancy. Torsion can occur in any trimester, although it is most common in the first trimester.[88] Infertility treatment is a risk factor. Ovarian torsion can recur in the same pregnancy, in particular in enlarged multicystic ovaries.[89] The corpus luteal cyst and enlarged ovaries stemming from the pregnancy hormones are thought to increase the risk. Tissue necrosis can occur rapidly, so timely diagnosis is essential to preserve ovarian function and the pregnancy. The diagnosis is often missed due to the vague clinical presentation of moderate unilateral lower abdominal pain, which may also be intermittent or constant. US may show an enlarged or edematous ovary with absent or decreased blood flow. **However, the presence of ovarian blood flow does not exclude the diagnosis of torsion if symptoms are suggestive.**[90] Therefore, consult an obstetrician/gynecologist as soon as the diagnosis is clinically suspected.

SEIZURE DISORDERS

Seizure frequency can increase in pregnancy because of the increased volume of distribution and plasma clearance of antiepileptic drugs in pregnancy or because of poor medication compliance.

Most of the antiepileptic drugs can cause a range of birth defects. **Valproic acid, carbamazepine, and phenytoin are still listed under the old U.S. Food and Drug Administration classification as class D.** Yet, discontinuing these drugs can increase morbidity and mortality for both the mother and fetus. Therefore, the risks and benefits of chronic treatment should be discussed and managed by the primary physician. Medication doses may need to be increased in pregnancy. Therapeutic serum target levels remain unchanged. **Monotherapy with levetiracetam or lamotrigine should be used whenever possible.**[91] Acute treatment of seizures in the pregnant woman is similar to that in the nonpregnant patient (see Chapter 171, "Seizures and Status Epilepticus in Adults"). Even though lorazepam and diazepam are class D medications, they are so categorized based on long-term use. **Use of benzodiazepines for an acute seizure outweighs any potential risk to the fetus.**[92,93]

If the seizure if self-limited, administer oxygen and position the patient in the left lateral decubitus position and provide supportive care. Fetal bradycardia lasting for up to 20 minutes may follow a single brief maternal seizure. **Status epilepticus** poses a real threat to both mother and the fetus, with a significant maternal and fetal mortality. Provide aggressive management, including intubation and ventilation, early in the management of pregnant women with status epilepticus (see Chapter 171).

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Pregnancy does not appear to alter the natural course of human immunodeficiency virus (HIV) disease, nor do uninfected babies born to HIV-positive women appear to be at increased risk for neonatal complications when compared with appropriate control patients. With over 1 million women of childbearing age living with HIV in the United States, it is important to initiate antiretroviral therapy as soon as possible not only for the health of the mother but also because appropriate therapy can eliminate mother-to-child transmission.[94]

In general, women who are already on a fully suppressive regimen when they become pregnant should continue their regimens. Key exceptions include medications with high risk for toxicity in pregnancy (didanosine, stavudine, and treatment-dose ritonavir).[95] Another exception would be efavirenz, which is a highly recommended drug as part of a three-drug regimen, but it is not recommended until after the first 8 weeks of pregnancy. However, if an HIV-infected woman who is already taking efavirenz becomes pregnant, the regimen may be continued because changing it risks loss of virologic control.[94] Additionally, some common drug regimens, such as elvitegravir/cobicistat, are not as effective in pregnancy. These drugs should be replaced with antiretrovirals recommended in pregnancy.[95]

Recommended optimal initial regimens for most patients include three different drugs: two nucleoside reverse transcriptase inhibitors plus an integrase strand transfer inhibitor.[94] Other effective regimens include nonnucleoside reverse transcriptase inhibitors or boosted protease inhibitors with two nucleoside reverse transcriptase inhibitors. There are many current drug combinations that can be safely used in pregnancy and that have different side effect profiles, number of pills or doses per day, and price points. The treatment plan should be individualized to optimize compliance and efficacy while minimizing side effects and drug interactions.

Prophylaxis for opportunistic infections is similar to that for nonpregnant patients. Patients with CD4+ T-cell counts of <200/mm^3 should be maintained on prophylaxis for *Pneumocystis jirovecii* pneumonia using trimethoprim-sulfamethoxazole. Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with *P. jirovecii* pneumonia still should be treated with trimethoprim-sulfamethoxazole because of its considerable benefit. Additional folate supplementation (higher than usual doses in pregnancy) may be added, but it is unclear whether the higher doses of folate supplementation lower risk. Alternatively, aerosolized pentamidine may be used in the first trimester, as it is minimally systemically absorbed.[96]

Treatment of overt opportunistic infections in HIV-infected pregnant women is addressed in the same way as in nonpregnant women. Early intubation to reverse hypoxemia may be necessary to improve maternal-fetal outcome in women with respiratory infections.

SUBSTANCE ABUSE DURING PREGNANCY

Substance abuse in pregnancy results in approximately 225,000 infants yearly with prenatal exposure.[97] Refer pregnant women identified in the ED as substance abusers to a high-risk obstetrics clinic and offer them substance abuse counseling.

COCAINE

Cocaine use is associated with placental abruption, fetal death in utero, intrauterine growth restriction, preterm labor, premature rupture of membranes, spontaneous abortion, and cerebral infarcts in the fetus. Maternal complications of cocaine use include myocardial infarction, hypertension (which can result in aortic dissection), pulmonary edema, and cardiac dysrhythmias. Subarachnoid hemorrhage, ruptured aneurysms, and strokes are reported in cocaine users and are most likely related to transient hypertension. Treatment of the pregnant woman with acute cocaine intoxication is handled in the same manner as in the nonpregnant patient (see Chapter 187, "Cocaine and Amphetamines").

OPIOIDS

Although acute opioid withdrawal poses minimal **maternal** risk, there is significant risk to the fetus, including meconium, hypoxia, preterm labor, and fetal demise.[98] Illicit opioid use can cause intermittent fetal withdrawal when there is maternal lack of access to the drug.

Therefore, it is standard to refer opioid-addicted pregnant patients for supervised methadone or buprenorphine therapy for the duration of the pregnancy. Even though methadone/buprenorphine will cause neonatal abstinence syndrome (opioid withdrawal) after birth, this is a treatable condition and carries less harm to the infant than acute opioid withdrawal in utero. Maternal detoxification from opioids should be done in a supervised inpatient setting, and only for select patients, as the relapse rate is very high.[98]

Mild maternal opioid withdrawal can be treated with clonidine, 0.1 to 0.2 milligram every 4 to 6 hours, until the signs of withdrawal resolve. Severe maternal opioid withdrawal may require administration of an opioid agonist and admission for fetal monitoring and induction of methadone therapy.[98,99]

ALCOHOL

Alcohol consumption during pregnancy is a risk factor for fetal alcohol syndrome, birth defects, and low birth weight. Binge drinking is particularly harmful to fetal neurodevelopment.

In the United States, the prevalence of fetal alcohol syndrome has been estimated at 0.5 to 2.0 cases per 1000 births, but even with conservative estimates, the prevalence may be close to 50 cases per 1000 births in certain communities in the United States.[100]

Pregnant women who present in coma due to acute alcohol intoxication or in alcohol withdrawal are managed in the same way as nonpregnant patients. **Disulfiram (Antabuse®) is a potential teratogen. Do not prescribe in pregnancy.**[101] There are no data on disulfiram, acamprosate, or naltrexone in pregnancy, and these agents are not recommended.

INTIMATE PARTNER VIOLENCE

One in four women and one in nine men in the United States have experienced rape, physical violence, or stalking by an intimate partner in their lifetime.[102] Factors associated with intimate partner violence during pregnancy are late entry into prenatal care, unintended pregnancy, drug and alcohol use, depression, and housing problems. Violence increases the risk for preterm labor, placental abruption, fetal fractures, uterine rupture, chorioamnionitis, delivering a low-birth-weight infant, and homicide. The American College of Obstetricians and Gynecologists recommends routine screening for intimate partner violence during pregnancy.[103] See Chapter 294, "Intimate Partner Violence and Abuse," for more discussion.

Pregnant women with injuries should be treated according to usual trauma protocols. Institute fetal monitoring for direct or indirect blunt abdominal trauma and major multiple trauma. Administer Rh immunoglobulin to Rh-negative women with blunt abdominal trauma (see Chapter 25, "Resuscitation in Pregnancy").

MEDICATIONS IN PREGNANCY AND LACTATION

The classic teratogenic period is 2 to 15 weeks of gestation. During this critical time, organs are forming, and teratogens may cause malformation. Administration of drugs early in the period of organogenesis affects the organs developing at that specific time, such as the heart or neural tube. Teratogens given closer to the end of the classic teratogenic period will affect the ear and palate. Before week 2, exposure to a teratogen produces an all-or-none effect (i.e., the conceptus either does not survive or survives without anomalies). If the organism remains viable after exposure before week 2, organ-specific anomalies do not develop because repair or replacement permits normal development. A similar insult at a later stage of development may produce organ-specific defects.

In 1979, the U.S. Food and Drug Administration established five letter risk categories (A, B, C, D, or X) to indicate the potential of a drug to cause birth defects if used in pregnancy (**Table 99-4**). In 2015, the U.S. Food and Drug Administration replaced the former risk letter categories with the **Pregnancy and Lactation Labeling Rule**, which provides more information in a new format to assist providers in assessing benefit versus risk to aid in counseling of pregnant women who need medication

TABLE 99-4 U.S. Food and Drug Administration Pregnancy Drug Categories, 1979

Drug Category	Risk During Pregnancy
A	Controlled studies show no fetal risk in any trimester, and so the possibility of fetal harm is remote.
B	Animal studies show no fetal risk, but there are no controlled human studies. *Or* Animal studies have shown an adverse effect that was not confirmed in controlled human studies in women in the first trimester (and there is no evidence of risk in later trimesters).
C	Animal studies have shown adverse fetal effects (teratogenic or embryocidal), and there are no controlled studies in humans. *Or* No human or animal studies are available. Drugs should be used only if the potential benefit justifies the potential fetal risk.
D	Evidence of human fetal risk exists, but the benefits of use in pregnant women may be acceptable despite the risk.
X	Studies in animals or humans have shown fetal risk, or there is evidence of fetal risk based on human experience. The risk of use in pregnancy clearly outweighs any possible benefit. Drugs are contraindicated for use in women who are or may become pregnant.

(**Table 99-5**). All medications approved after 2015 will be required to use the new format in the package labeling, which gives detailed information about the drug. Medications approved on or after 2001 will be phased in gradually but will eventually be required to provide all the same information. **However, all prescription drugs were required to remove pregnancy letter categories as of June 2018.** The new labeling still does not provide a definitive yes or no answer in most cases, and clinical interpretation will be required on a case-by-case basis.

Some therapeutic agents with adverse effects during pregnancy are listed in **Table 99-6**. The National Library of Medicine provides a detailed reference list in the Developmental and Reproductive Toxicology Database.

TABLE 99-5 2015 U.S. Food and Drug Administration Pregnancy and Lactation Labeling Rule Required Information on Package Insert for Every Medication

In Both Pregnancy and Lactation

- **Risk summary:** What are the known risks in context with background risk?
  - Risk statement based on human data
  - Risk statement based on animal data
  - Risk statement based on pharmacology
  - Background risk information in general population
  - Background risk information in disease population
- **Clinical considerations:** What medical/disease factors should be considered?
  - Disease-associated maternal and/or embryo/fetal risk
  - Dose adjustments during pregnancy and the postpartum period
  - Maternal adverse reactions
  - Fetal/neonatal adverse reactions
  - Labor or delivery
- **Data:** Human and animal data and pregnancy drug registries that support the summary
  - Human data: Description includes study type, number, duration, exposure information, and limitations.
  - Animal data: Description includes study type, species, animal doses and basis for the exposures, duration and timing, findings, presence of maternal toxicity, and limitations.

In Reproductive Potential

- Contraception
- Infertility
- Pregnancy testing

TABLE 99-6 Drugs Used in Emergency Settings With Known Adverse Effects in Human Pregnancy

Drug	Effect
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Renal failure, oligohydramnios
Aminoglycosides	Ototoxicity (gentamicin class D, Black Box Warning)
Androgenic steroids	Masculinize female fetus
Anticonvulsants (carbamazepine, hydantoins, valproate)	Dysmorphic syndrome, anomalies, neural tube defects
Antithyroid agents	Fetal goiter
Aspirin (high doses)	Bleeding, antepartum and postpartum
Cytotoxic agents (e.g., methotrexate)	Multiple anomalies
Erythromycin estolate	Maternal hepatotoxicity
Fluoroquinolones	Fetal cartilage abnormality
Isotretinoin	Hydrocephalus, deafness, anomalies
Lithium	Congenital heart disease (Ebstein's anomaly)
NSAIDs (prolonged use after 32 wk)	Oligohydramnios, constriction of fetal ductus arteriosus
Streptomycin	Fetal cranial nerve VIII damage
Sulfonamides	Fetal hemolysis, neonatal kernicterus (near term)
Tetracyclines	Fetal teeth and bone abnormalities
Trimethoprim, methotrexate	Folate antagonist (first trimester)
Thalidomide	Phocomelia
Warfarin	Embryopathy—nasal hypoplasia, optic atrophy

Table 99-7 lists some general cautions for using drugs during lactation. When prescribing, check each drug individually. Because information can change, we recommend referring to the following sources for information about drug safety in lactation:

- Drugs and Lactation Database (LactMed), U.S. National Library of Medicine—http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT (accessed April 2018)
- World Health Organization, Breastfeeding and Maternal Medication, http://www.who.int/maternal_child_adolescent/documents/55732/en/ (last updated 2003; accessed July 2018)
- Thomas Hale, *Medications and Mothers' Milk*, ISBN-13 (978-0984774630), Hale Publishing, May 2013, 15th ed.

TABLE 99-7 World Health Organization General Cautions for Drugs and Breastfeeding[104]

Guideline	Drugs
Breastfeeding contraindicated	Anticancer drugs, radioactive substances, amphetamines, ergotamines, statins, and nitrofurantoin (for <1 mo old and for those with glucose-6-phosphate dehydrogenase deficiency)
Avoid unless absolutely necessary	Chloramphenicol, tetracyclines, fluoroquinolones
Monitor infant for drowsiness	Selected psychiatric and anticonvulsant agents
Monitor infant for jaundice	Sulfonamides, dapsone, sulfadoxine/pyrimethamine (Fansidar®), mefloquine
May inhibit lactation; use alternative drug	Estrogens, thiazides

TABLE 99-8 Teratogenic Radiation Effects

Gestational Age	Effect of 5–10 rads (50–100 mGy)	Effect of >10 rads (>100 mGy)
0–2 wk	Probably none	Possible spontaneous abortion
3–8 wk	Unknown; probably none detectable	Possible malformations with increasing dose
9–15 wk	Unknown; probably none detectable	Possible mental development defects with increasing dose
≥16 wk	None	None detectable or none

FETAL RADIATION EFFECTS

For radiation imaging during pregnancy, weigh the risks of exposure and subsequent fetal adverse effects against the risk of incorrect maternal diagnosis. The major factor determining the degree of risk to the fetus is the quantity of ionizing radiation exposure during imaging. **Fetal exposure to low-dose radiation, defined as <5 rads (<50 mGy), DOES NOT increase the risk of fetal or infant death, mental defects, or growth retardation**. More than 5 rads (>50 mGy) is considered the threshold for human teratogenesis. By using typical imaging parameters, it is unlikely that a single-phase CT scan would reach this dose level. The fetus is most vulnerable to teratogenicity between 3 and 15 weeks of gestation at doses >10 rads (>100 mGy) (**Table 99-8**).

The estimated radiation doses involved in procedures commonly used for ED diagnosis are listed in **Table 99-9**.[32,105,106]

MRI IN PREGNANCY

The 2013 American College of Radiology guidance document on magnetic resonance safe practices states that MRI can be used in pregnant patients regardless of gestational age when the information gained is likely to alter treatment, when it cannot be obtained through other nonionizing means, and when MRI cannot be delayed until completion of the pregnancy.[32] Noncontrast MRI (abdomen/appendicitis, pelvis/pelvic vein thrombosis) should be used unless contrast is deemed absolutely necessary given the recent concerns with gadolinium exposure to the fetus.[32]

TABLE 99-9 Radiation Exposure to the Uterus/Fetus

Procedure	Dosage in mGy
Threshold for human teratogenesis	100
Accepted as safe in pregnancy	**50**
Abdominal/pelvis CT	25–35
CT, kidney-ureter-bladder protocol (reduced radiation dose)	10
Lumbosacral spine series (three view)	1.6–3.5
Ventilation-perfusion scan (total)	2.1
Abdominal series (two view)	2
Lung perfusion scan with technetium	1.7
Normal background radiation over 9 months	**1**
Head CT	<0.5
Lung ventilation scan with xenon	0.4
Anteroposterior pelvis x-ray	0.4
Chest CT (10-mm slices, 10 slices), for standard or pulmonary embolism protocol	0.2
Cerebral angiography	0.1
Mammography—diagnostic for suspected breast cancers	0.07–0.2
Chest radiography (two view) with shielding of the maternal abdomen	<0.001
Cervical spine (two view)	<0.001

Note: 1 rad = 10 mGy = 10 mSv.

LACTATION AFTER IMAGING

The American College of Radiology and the American College of Obstetricians and Gynecologists advise that patients continue breastfeeding after administration of IV iodinated or gadolinium-based contrast agents. Both have low lipid solubility, and less than 1% of iodinated contrast agents and 0.04% of gadolinium-based contrast agents are excreted into breast milk (Table 99-1).[32]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 100

Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period

Janet S. Young

INTRODUCTION

This chapter examines the diagnosis and treatment of the most important maternal emergencies occurring after 20 weeks of pregnancy and during the postpartum period. The second half of pregnancy is often characterized as ≥20 weeks of gestation for simplicity, but until 24 weeks, the chances of fetal survival are less than 50%. The postpartum period is generally accepted as the 6 weeks after delivery. Vast physiologic shifts in maternal cardiovascular tone occur as pregnancy progresses, highlighting the need for maternal blood pressure recordings and fetal heart tones during any ED visit. Conditions discussed are disorders associated with elevated blood pressure (hypertension, preeclampsia and HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count], and eclampsia); vaginal bleeding in the second half of pregnancy; premature rupture of membranes; peripartum cardiomyopathy; postpartum endometritis; and the emergency transfer of the pregnant patient.

DISORDERS ASSOCIATED WITH ELEVATED BLOOD PRESSURE: HYPERTENSION, PREECLAMPSIA AND HELLP SYNDROME, AND ECLAMPSIA

CHRONIC AND GESTATIONAL HYPERTENSION

The decrease in systemic vascular resistance results in a decrease in maternal blood pressure, and blood pressure reaches its nadir at 16 to 18 weeks of pregnancy. Blood pressure returns to prepregnancy values near the end of the second trimester. Almost 10% of pregnant women have hypertension; hypertension is preexisting in 1%, gestational hypertension without proteinuria develops in 5% to 6%, and preeclampsia develops in 2%.[1]

Chronic hypertension in pregnancy is defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg that existed prior to pregnancy, is diagnosed before the 20th week of gestation, or persists longer than 12 weeks after delivery. Severe chronic hypertension is systolic blood pressure >160 mm Hg or diastolic pressure >110 mm Hg. Women with chronic hypertension are at increased risk for placental abruption, preeclampsia, low birth weight, cesarean delivery, premature birth, and fetal demise.[2,3]

Gestational hypertension is hypertension present only after the 20th week of pregnancy or in the immediate postpartum period but without proteinuria.

Safe treatment options for hypertensive women who are pregnant are labetalol, methyldopa, nifedipine, and hydralazine.[4] **All antihypertensive drugs cross the placenta.** Labetalol is the first-line agent for chronic hypertension in pregnancy.[3,5] The starting dose is 100 milligrams PO twice a day, and the usual maintenance dose is 200 to 400 milligrams PO twice a day. Methyldopa, used safely in pregnancy for decades, is started at 250 milligrams every 6 hours PO and titrated to achieve the desired blood pressure. The usual daily dose is 500 milligrams to 3 grams divided in two to four doses per day, with a maximum of 3 grams per day.[5] The goal is not to normalize blood pressure in the acute setting, but to reach a recommended target blood pressure of 140 to 150/90 to 100 mm Hg.[6]

Long-acting nifedipine may be added if blood pressure is not controlled with methyldopa or labetalol. Nifedipine is started at 30 milligrams PO once daily and can be increased up to 120 milligrams per day slowly if needed. For acute management of **hypertensive emergencies**, hydralazine 5 milligrams IV or IM, labetalol 20 milligrams IV, or nifedipine 10 to 30 milligrams PO (not a U.S. Food and Drug Administration–approved indication) may be used during pregnancy.[3,6-10] **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated because of their teratogenic effects on fetal scalp, lungs, and kidneys.**[3,6,11]

PREECLAMPSIA

Preeclampsia has been redefined as the presence of de novo hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) after 20 weeks of gestation combined with proteinuria *or* other maternal organ dysfunction (renal, liver, neurologic).[12,13] In the absence of proteinuria, thrombocytopenia, liver dysfunction, renal insufficiency, pulmonary edema, and cerebral dysfunction are criteria for preeclampsia. **Table 100-1** summarizes the currently recognized definitions of preeclampsia.

TABLE 100-1 Definitions of Preeclampsia

Hypertension	Proteinuria	Multisystem Involvement
≥140 mm Hg systolic or ≥90 mm Hg diastolic	≥300 mg in 24 h	Thrombocytopenia
Previously normotensive patient >20 wk gestation	Protein/creatinine ratio ≥0.3 mg/dl	Renal insufficiency
BP measured two times at least 4 hours apart[a]	Dipstick ≥1+ (only if other methods not available)	Liver dysfunction Pulmonary edema Cerebral or visual disturbances
Severe features of preeclampsia		
Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg on 2 occasions at least 4 hours apart while the patient is on bed rest		
Thrombocytopenia (<100,000 platelets/mL)		
Impaired liver function (liver enzymes levels increased to twice normal) or persistent right upper quadrant/epigastric pain unresponsive to medication and not accounted for by a different diagnosis)		
Progressive renal insufficiency (serum creatinine >1.1 mg/dL or doubling of creatinine level without other renal disease)		
Pulmonary edema		
Cerebral or visual disturbances		

Abbreviation: BP = blood pressure.

[a]Greater than or equal to 160 mm Hg or greater than or equal to 110 mm Hg diastolic may be confirmed within minutes to facilitate treatment.

Source: Adapted with permission from American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy: Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 122(5): 1122-1131, 2013.

TABLE 100-2 Laboratory Evaluation for Preeclampsia

Test	Comments
CBC with differential	May see hemoconcentration or decreasing hematocrit. Thrombocytopenia suggests severe disease.
Creatinine	Elevation suggests severe disease.
Alanine and aspartate aminotransferase concentrations	Elevation suggests severe disease.
Lactate dehydrogenase level	Elevation suggests microangiopathic hemolysis.
Protein in urine	≥1+ proteinuria; 24-h collection may be done by obstetric service. >5 grams/24 h suggests severe disease.
Protein/creatinine ratio	0.1–0.3 indicates need for 24-h collection.[3]
Uric acid level	Level ≥5.5 milligrams/dL may suggest superimposed preeclampsia on chronic hypertension.[3]

The cause of preeclampsia is unknown. The histologic hallmark lesion of preeclampsia is acute atherosis of decidual arteries. Atherosis and thrombosis are thought to lead to placental ischemia and infarctions. Poor placental perfusion is presumed to lead to the formation of free radicals, to oxidative stress, and to inflammatory responses that may influence the mechanistic development of preeclampsia.[7,14]

Preeclampsia is associated with intrauterine growth retardation, premature labor, low birth weight, abruptio placentae, and future risk of maternal cardiovascular disease.[7,9,12,15,16]

Preeclampsia during an initial pregnancy increases the chances of recurrence in future pregnancies. Other important risk factors for preeclampsia include maternal age >40 years old, hypertension, diabetes, renal disease, collagen vascular disease, and multiple gestation. Low-dose aspirin therapy can prevent preeclampsia and its complications.[10,17,18]

DIAGNOSIS OF PREECLAMPSIA

Diagnostic criteria for preeclampsia and severe eclampsia are listed in Table 100-1, and laboratory evaluation is outlined in **Table 100-2**.[19]

HELLP SYNDROME

The **HELLP syndrome (Table 100-3)** is an important clinical variant of preeclampsia. HELLP is more common in the multigravid patient than in the primigravida. Hypertension may not be present initially or at all. This fact, combined with the usual complaint of epigastric or right upper quadrant pain, makes it easy to misdiagnose HELLP syndrome for other causes of abdominal pain, such as gastroenteritis, cholecystitis, hepatitis, pancreatitis, or pyelonephritis. **A pregnant woman at >20 weeks of**

TABLE 100-3 Laboratory Abnormalities in HELLP Syndrome

Test	Findings
CBC and test of peripheral smear	Schistocytes
Platelet count	<100,000/μL <150,000/μL suspicious for syndrome
Liver function tests (alanine aminotransferase, aspartate aminotransferase levels)	Elevated but below levels usually seen in viral hepatitis (<500 U/L)
Renal function tests	Normal or elevated BUN and creatinine levels
Coagulation profile	Abnormal
Lactate dehydrogenase	>600 U/L suspicious for hemolytic anemia
Total bilirubin	>1.2 milligrams/dL

TABLE 100-4 Antihypertensive Drugs for Treatment of Acute, Severe Hypertension in Preeclampsia and Eclampsia[6,12,13,22,23]

Generic Name	Mechanism of Action	Onset of Action	Dosage	Comment
Labetalol	Selective α and nonselective β antagonist	5 min	20 milligrams IV, then 40–80 milligrams IV every 10 min as needed (maximum, 300 milligrams); IV infusion 1–2 milligrams/min titrated	Less hypotension and reflex tachycardia than hydralazine. Higher doses cause neonatal hypoglycemia. Longer use associated with fetal growth restriction.
Hydralazine	Arterial vasodilator	20 min	5 milligrams IV or 10 milligrams IM, repeat at 20-min intervals; consider other drug if no response at maximum of 20 milligrams IV or 30 milligrams IM	Maternal hypotension, fetal distress; must wait 20 min for response between IV doses.
Nifedipine	Calcium channel antagonist	10–20 min	10 milligrams PO, repeat in 30 min if necessary	Food and Drug Administration does not approve short-acting nifedipine for treatment of hypertension.

gestation or up to 7 days postpartum with abdominal pain should be evaluated for HELLP syndrome.

Complications of severe preeclampsia, HELLP syndrome, and eclampsia include disseminated intravascular coagulopathy, spontaneous hepatic and splenic hemorrhage, end-organ failure, abruptio placentae, intracranial bleeding, maternal death, and fetal death.[12,13,19]

TREATMENT OF PREECLAMPSIA

For **mild eclampsia**, outpatient management is an option after consultation with the obstetrician, as long as arrangements are made for frequent clinical and laboratory evaluation and close fetal surveillance.[5,19] Headache, scintillating scotomata or other visual changes, abdominal pain, vaginal bleeding, and decreased fetal movement require immediate reevaluation. Treat **severe preeclampsia** (blood pressure >160 mm Hg) with antihypertensive agents (**Table 100-4**) and IV magnesium sulfate.[6,12,13,19-23] Consult with the obstetrician for admission or transfer to a center that manages high-risk pregnancy especially in the presence of HELLP syndrome. **The only *definitive* resolution for preeclampsia is delivery.**

The initial management of **HELLP syndrome** is similar to that of **severe preeclampsia** or **eclampsia**: IV magnesium, blood pressure control, and hospital admission for stabilization. Correct coagulopathy if clinically indicated.[24] If HELLP syndrome is suspected and obstetric care is not available locally, stabilize the patient as best as possible and transfer to a tertiary care center with high-risk obstetrics facilities. The definitive treatment is delivery, especially if the patient is ≥34 weeks of gestation. Corticosteroid administration can help delay delivery and improve fetal outcome in pregnancies <34 weeks of gestation.[6]

ECLAMPSIA

Eclampsia is the development of new-onset seizures, superimposed upon preeclampsia, in a woman between 20 weeks of gestation and 4 weeks postpartum.

Eclampsia should be suspected and treated in any pregnant woman who is at >20 weeks of gestation or <4 weeks postpartum who develops seizures, coma, or encephalopathy. **Occasionally, eclampsia can present with seizure in the absence of blood pressure elevation and proteinuria.[7,16] Management of eclampsia includes treatment of seizures, treatment of hypertension, and emergent obstetric consultation to facilitate urgent delivery of the fetus**. Treat seizures with **magnesium sulfate**, 4 to 6 grams IV in 100-mL aliquot given over 20 to 30 minutes followed by an infusion of 2 grams per hour for at least 24 hours.[19-21,25,26] Magnesium is renally excreted, and in women with renal insufficiency, reduce the dose to 2 grams IV bolus and obtain a serum magnesium level before increasing the dose. The main side effects of high levels of magnesium are flushing, diaphoresis, hypothermia, hypotension, flaccid paralysis, and respiratory depression. When levels approach toxicity, patellar reflexes diminish and respiratory rate slows. Administer antihypertensive agents as suggested in Table 100-4. Replace coagulation factors and platelets as indicated, if there is coagulopathy. Obtain emergency obstetric consultation for prompt delivery. If obstetric services are not available, stabilize the patient as best as possible and transfer to a center with facilities for advanced obstetric care.

VAGINAL BLEEDING IN THE SECOND HALF OF PREGNANCY

The causes of serious vaginal bleeding in the second half of pregnancy include abruptio placentae, placenta previa, and vasa previa. All can cause severe hemorrhage. **Do not perform a digital or speculum pelvic examination to assess vaginal bleeding until a transvaginal US is performed to determine the location of the placenta. Mechanical disruption of the placenta by speculum or digital examination may precipitate catastrophic hemorrhage.** When transvaginal US is properly and carefully performed by those experienced in transvaginal US (vaginal probe is angled against the anterior lip of the cervix, probe is not advanced to contact the placenta, probe is not inserted into the cervix), the technique is generally considered safe.[27,28] If there is no evidence of placenta previa or vasa previa, then a sterile speculum examination may be performed to determine if premature rupture of membranes or abruption is present.

ABRUPTIO PLACENTAE

Abruptio placentae is the premature separation of a normally implanted placenta from the uterine lining (**Figure 100-1**). The incidence of spontaneous abruption is highest between 24 and 32 weeks of gestation.[29,30] Abruption can cause uteroplacental insufficiency and fetal distress or demise. Maternal complications include coagulopathy, hemorrhagic shock, uterine rupture,

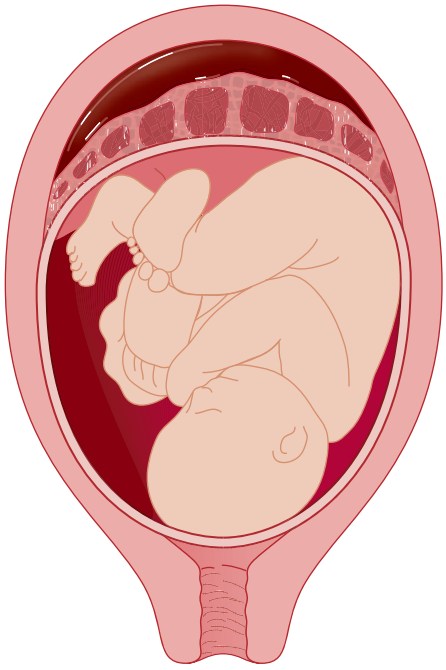

FIGURE 100-1. Abruptio placentae. The placenta has separated from the superior pole of the uterus.

and multiple organ failure.[31] Abruption usually occurs spontaneously, but is also associated with trauma, even minor trauma. See Chapter 256, "Trauma in Pregnancy." Risk factors for abruption include abdominal trauma, cocaine use, oligohydramnios, chorioamnionitis, advanced maternal age or parity, eclampsia, and chronic or acute hypertension.

Clinical features depend on the degree of placental abruption. Mild abruption is characterized by mild uterine tenderness, no or mild vaginal bleeding, normal maternal vital signs, no coagulopathy, and fetal distress. Signs and symptoms of severe abruption are no or heavy vaginal bleeding, fetal distress, coagulopathy, severe uterine pain or tenderness, continuous or repetitive uterine contractions, and maternal hypotension or shock. Nausea, vomiting, and back pain may also be present. **Consider placental abruption in pregnant women with acute, painful vaginal bleeding or with acute abdominal/uterine pain.**

Diagnosis is made by the clinical features. Electronic fetal monitoring (cardiotocodynamometry) is very sensitive for identifying fetal distress as a sign of placental abruption and has a 100% negative predictive value for adverse outcomes when monitoring is reassuring.[32] Transvaginal US is fairly specific for the diagnosis but is not sensitive for the detection of retroplacental clot because the appearance of clotted blood evolves in echotexture over time.[32] MRI is diagnostic but requires the transport of a potentially unstable patient out of the ED or intensive care unit for imaging.[33]

Treatment consists of maternal stabilization, cardiotocographic monitoring to detect fetal distress, and emergency obstetric consultation. Place two large-bore IVs; obtain a CBC, metabolic panel, coagulation panel, fibrin degradation product, and fibrinogen levels; and type and cross-match maternal blood. Administer RhoGAM® if the mother is Rh negative. For disseminated intravascular coagulation, replace coagulation factors. Immediate delivery is indicated for severe abruption.

PLACENTA PREVIA

Placenta previa is a placenta that extends near, partially over, or beyond the internal cervical os. Normal placental implantation is in the corpus or fundal region, whereas in placenta previa, implantation is lower in the uterus. The cause is unknown, although the incidence is increasing due to increasing rates of cesarean delivery, maternal age, and assisted reproductive technology.[34] Although low-lying or partial placenta previa is not uncommon early in pregnancy, the placenta usually migrates to a normal position as the pregnancy nears term.

Risk factors for placenta previa include cesarean delivery, multiple uterine surgeries, advanced maternal age, minority group status, cigarette smoking, and cocaine use. Patients with symptomatic placenta previa present with painless bright-red vaginal bleeding, which should be differentiated from the normal passage of blood-stained mucus that occurs near the onset of labor. There are three subclasses of placenta previa: marginal placenta previa, which reaches the internal os but does not cover it; partial placenta previa, where the placenta partially covers the internal os; and complete placenta previa, which completely covers the internal os (**Figure 100-2**).

While proceeding with further patient assessment, place two large-bore IVs for fluid resuscitation; obtain CBC and coagulation parameters; and type and cross-match blood. **Do not perform a digital or speculum vaginal examination until normal placental position is confirmed by US, as disruption of the cervical–placental junction could precipitate catastrophic hemorrhage**. Carefully perform transvaginal US (see earlier). Once a placenta previa is identified, consult obstetrics for management options. A double setup, in which two teams of staff are available in the operating room during a vaginal examination, may be indicated in cases where the placenta lies within 1 to 2 cm of the cervical os and labor is imminent. Otherwise, women in the second half of pregnancy with placenta previa are usually admitted to the hospital for observation and fetal monitoring.

VASA PREVIA

Vasa previa is a rare cause of late-pregnancy bleeding. In vasa previa, umbilical vessels course in the amniotic membrane at the level of the cervical os, so that when the cervix begins to dilate in labor with membrane rupture, the blood vessels tear. Fetal distress or fetal demise may result from fetal exsanguination or vessel compression. Risk factors associated with vasa previa are placenta previa, in vitro fertilization, velamentous insertion of the umbilical cord, and bilobed placenta. Vasa previa can sometimes be diagnosed by Doppler color US performed early in pregnancy.[35] Otherwise, it is seldom recognized prior to catastrophic vessel disruption during labor. Treatment is rapid operative delivery.

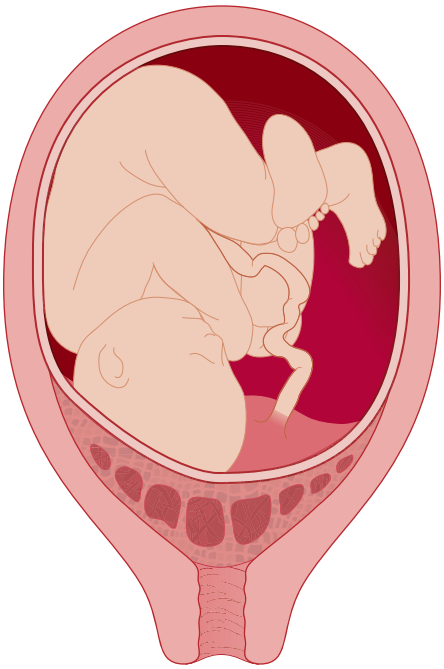

FIGURE 100-2. Complete placenta previa. Placenta overlies the internal os.

PREMATURE RUPTURE OF MEMBRANES, PRETERM LABOR, AND PRETERM BIRTH

Premature rupture of membranes is rupture of membranes prior to onset of contractions. Premature rupture of membranes complicates about 8% of all pregnancies.[36] **Membrane rupture before 37 weeks of gestation is known as preterm premature rupture of membranes**. The time from membrane rupture to fetal delivery, known as the latent period, may allow for pharmacologic intervention to improve fetal lung maturity and increase fetal survival. Worldwide, an estimated 11.1% of all live births in 2010 were born preterm (14.9 million babies born before 37 weeks of gestation).[37] Survival of preterm infants generally increases with increasing gestational age, with a generally expected >50% in-hospital survival when born at 25 weeks of gestation.[38-40]

Preterm (premature) labor is labor prior to 37 weeks of gestation and is often preceded by premature rupture of membranes. Preterm labor is thought to be a syndrome initiated by multiple mechanisms, including infection, inflammation, uteroplacental ischemia or hemorrhage, uterine overdistention secondary to multiple gestation, stress, and other immunologically mediated processes.[41,42] *Chlamydia*, gonorrhea, *Trichomonas vaginalis*, and bacterial vaginosis infections increase the risk of preterm premature rupture of membranes and preterm labor. Several non–genital tract infections, including pyelonephritis, asymptomatic bacteriuria, pneumonia, appendicitis, and periodontal disease, are also implicated in preterm labor. **Preterm birth** is birth before 37 weeks of gestation and may occur spontaneously or as a result of premature rupture of membranes or placental abruption or may be induced for medical reasons. Surviving preterm neonates are at risk for sepsis, neurologic defects, feeding problems, blindness, deafness, and respiratory distress. Infants weighing <1500 grams or born at <32 weeks of gestation

are at greatest risk for these problems, but even infants born at between 34 0/6 and 36 6/7 weeks of gestation (late preterm infants) may require intensive care admission for IV fluids, sepsis, hyperbilirubinemia, and mechanical ventilation.[43]

DIAGNOSIS OF PREMATURE RUPTURE OF MEMBRANES

Details of the history taking and physical examination that aid in the diagnosis of premature rupture of membranes are listed in **Table 100-5**. **Avoid digital cervical examination because it decreases the latent period and may increase the likelihood of infection. Perform speculum examination and visually examine the cervix to identify dilation and test vaginal fluid** (Table 100-5)**.** The combination of history, nitrazine paper, and fern testing (**Figure 100-3**) is reported to diagnose 90% of cases of premature rupture of membranes.[44] US assessment of amniotic fluid volume may give additional information but is not diagnostic of premature rupture.[36] Additionally, a low amniotic fluid volume (<5 cm) may be predictive of impending delivery.[45]

TABLE 100-5 Keys to Diagnosis of Premature Rupture of Membranes

Information Obtained	Comments
History	
Gush of fluid and continued leakage of fluid	Ask patient to perform a Valsalva maneuver while speculum is in place to look for gush of fluid, or apply fundal pressure.
Details of contractions	Determine if active labor is in process.
Date of last menstrual period	Use to calculate estimated date of delivery and gestational age. Gestational age is number of weeks from first day of last menstrual period.
Vaginal bleeding	Raises concern for placenta previa.
Recent intercourse	
Fever	Infection raises fetal and maternal risk.
Physical Examination	
Measurement of fundal height	
Auscultation of fetal heart tones	
Sterile speculum examination	Check for: Cervical dilatation and effacement. Pooling in vagina of fluid leaking from cervix. If no fluid is noted, apply fundal pressure or ask patient to perform a Valsalva maneuver or cough.
Laboratory Evaluation	
Vaginal fluid	Test with nitrazine paper. **Blue color indicates pH >6.5, signaling presence of amniotic fluid.** Note: Blood, semen, bacterial vaginosis, trichomoniasis, soap, and antiseptics may cause false-positive results; false-negative rate, about 7%.[44]
Swab of vaginal walls or posterior fornix; do not swab cervical mucus; cervical mucus produces thick, dark, wide arborization pattern, not delicate fern	Examine glass slide preparation for fern. **Fern indicates presence of amniotic fluid.** Blood may obscure fern. Mucus results in a false-positive fern test finding. Test for *Chlamydia*, *Neisseria gonorrhoeae*, group B streptococci, and bacterial vaginosis.



FIGURE 100-3. Fern of amniotic fluid. [Photo contributed by Robert Buckley, MD.]

Premature labor or premature rupture of membranes requires obstetric consultation. If obstetric services are unavailable, transfer the patient to a center where such services are available. Obstetric treatment includes corticosteroids and antibiotics to treat group B *Streptococcus*.

A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 34 0/7 weeks of gestation.[36] Corticosteroids given at <34 weeks of gestation speed fetal lung maturity, decrease the incidence of intraventricular hemorrhage, reduce the duration of mechanical ventilation, and reduce the incidence of necrotizing enterocolitis without increasing maternal or fetal infection. Betamethasone (12 milligrams IM every 24 hours for 2 days) or dexamethasone (6 milligrams IM every 12 hours for 2 days) can be used for gestations between 24 and 34 weeks, and may be considered for pregnant women as early as 23 0/7 weeks of gestation.[36]

Antibiotics can decrease neonatal infection, prolong latency, and reduce the incidence of postpartum endometritis, chorioamnionitis, neonatal infections, and intraventricular hemorrhage. **Antibiotic administration is recommended to all women less than 34 0/7 weeks of gestation with preterm premature rupture of membranes**. American College of Obstetricians and Gynecologists guidelines recommend ampicillin 2 grams IV every 6 hours and erythromycin 250 milligrams IV every 6 hours for 48 hours followed by oral amoxicillin 250 milligrams every 8 hours and erythromycin base 333 milligrams every 8 hours.[36] Other acceptable antibiotic choices are penicillin G (5 million units IV then 2.5 million to 3 million units every 4 hours until delivery), ampicillin (2 grams IV then 1 gram every 4 hours until delivery), and cefazolin (2 grams IV). Clindamycin and vancomycin are alternatives for those allergic to penicillins. Macrolides are not recommended.[46] Do not give amoxicillin-clavulanate because it is associated with necrotizing enterocolitis. There is no need for prophylactic antibiotics if membranes are intact, unless the patient is a group B streptococci carrier.[36,43]

Tocolytic therapy using magnesium sulfate, β-mimetics, indomethacin, or calcium channel blockers is controversial and is relatively contraindicated in the patient with preterm premature rupture of membranes.[43] Tocolysis may allow time for administration of antenatal corticosteroids and antibiotics and transfer of the patient to an appropriate receiving facility. Magnesium sulfate may provide neonatal neuroprotective effects against cerebral palsy, and indomethacin has been used effectively for short-term tocolysis.[43] Because there are no widely accepted protocols for tocolytic management, consult the obstetrician, who can explain the pharmacologic risks, benefits, and alternatives to the patient.

Management guidelines for expedited delivery in the near-term gestation vary. Expedited delivery was historically recommended in patients with preterm premature rupture of membranes at >34 weeks of gestation to avoid the complications of chorioamnionitis and neonatal sepsis, but recent clinical guidelines suggest that induction of labor does not reduce the risk of neonatal sepsis.[36]

A cervical cerclage is a retention suture placed in a "purse-string" fashion around the cervix in order to support the internal cervical

os and prevent the cervix from dilating prematurely. In patients with premature rupture of membranes or preterm labor, no specific practice guidelines are recommended. Cerclage retention for preterm premature rupture of membranes has been associated with increased neonatal mortality and sepsis. Consult with the receiving obstetrician for case-specific recommendations. Tocolysis may be appropriate. Removal of cerclage sutures with preterm labor is associated with cervical lacerations, but rapidly progressive labor may necessitate emergency removal.[36]

POSTPARTUM ENDOMETRITIS

Most postpartum infections are identified after hospital discharge. **In a postpartum woman with fever, assume pelvic infection until proven otherwise. Also consider respiratory tract infection, pyelonephritis, mastitis, thrombophlebitis, and appendicitis.**[47] Risk factors for postpartum endometritis are listed in **Table 100-6**.

The most common pathogens are gram-positive (streptococci, enterococci) and gram-negative aerobes (*Escherichia coli*), anaerobes (peptostreptococci), *Mycoplasma hominis*, *Chlamydia trachomatis* (>7 days postpartum), and *Neisseria gonorrhoeae*. *Gardnerella vaginalis* is isolated more often in younger women. Many infections are polymicrobial. Group A streptococcal infections are less common, but are increasing causes of postpartum endometritis.[48,49]

Symptoms of postpartum endometritis are fever, foul-smelling lochia, leukocytosis, tachycardia, pelvic pain, and uterine tenderness. Only scant vaginal discharge may be present, especially in patients infected with group B streptococci. In patients who are status post cesarean section, there may be surgical wound tenderness and purulent exudate.

Vaginal samples are of little value because of contamination with local flora. Blood cultures are rarely positive. Culture any purulent material from surgical incisions. Creatine phosphokinase levels may be elevated in group B streptococcal endometritis. Consult the obstetrician for disposition decisions. Admission is needed for patients who appear ill, have had cesarean section, or have underlying comorbidities. Treatment consists of antibiotics (**Table 100-7**), abscess drainage, and debridement of necrotic tissue. Empiric combination of clindamycin (900 milligrams every 8 hours IV or 600 milligrams every 6 hours IV) and an aminoglycoside (most commonly gentamicin 5 milligrams/kg every 24 hours or 1.5 milligrams/kg every 8 hours) remains the most effective regimen to treat postpartum endometritis.[50]

After consultation with and recommendation by the obstetrician, patients with mild illness and those for whom follow-up in 24 hours is ensured can be treated as outpatients with oral antibiotics. Antimicrobial trials of postpartum endometritis treatment and intrauterine microbiology studies suggest five antimicrobial regimens may be effective: oral clindamycin plus intramuscular gentamicin, oral amoxicillin-clavulanate, intramuscular cefotetan, intramuscular meropenem or imipenem-cilastatin, and oral amoxicillin in combination with oral metronidazole.[51] Doxycycline 100 milligrams twice a day plus metronidazole 500 milligrams twice a day; levofloxacin 500 milligrams daily plus metronidazole 500 grams three times a day; and amoxicillin-clavulanate 850 milligrams PO twice a day are all acceptable oral regimen.[51] **Doxycycline is contraindicated in women who are breastfeeding.**

Complications of endometritis include parametrial phlegmons; surgical, incisional, and pelvic abscesses; infected hematomas; septic pelvic thrombophlebitis; necrotizing fasciitis; and peritonitis.

TABLE 100-6 Risk Factors for Postpartum Endometritis

- Cesarean section*
- Multiple gestation
- Younger maternal age
- Long duration of labor and membrane rupture
- Internal fetal monitoring
- Low socioeconomic level
- Digital examination after 37 wk of gestation
- Maternal human immunodeficiency virus infection

*Most significant risk factor.

TABLE 100-7 Inpatient Treatment of Postpartum Endometritis*

- Clindamycin 900 milligrams every 8 h plus gentamicin 5 milligrams/kg every 24 h (and add either ampicillin 2 grams then 1 gram every 8 h *OR* vancomycin 1 gram every 12 h)
- Ampicillin 2 grams then 1 gram every 4 h plus gentamicin 5 milligrams/kg every 24 h plus metronidazole 500 milligrams every 8 h

*Consult the hospital pharmacist to determine if the antibiotic regimen selected is appropriate for breastfeeding.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy is a dilated cardiomyopathy that can occur at any stage of gestation, but is classically defined as occurring in the last month of gestation or within the first 5 months after delivery, without an apparent cause or preexisting history of cardiac disease. The cause is unknown. Risk factors include cardiomyopathy during prior pregnancies, multiparity, maternal age >40 years old, black race, chronic hypertension before pregnancy, gestational hypertension, preeclampsia, and HELLP syndrome. Symptoms and signs of peripartum cardiomyopathy are dyspnea, orthopnea, cough, palpitations, chest pain, edema, rales, and jugular venous distention. Diagnose and treat congestive heart failure and pulmonary edema with standard modalities (see Chapter 53, "Acute Heart Failure") **except that nitroprusside is relatively contraindicated in pregnancy because it can cause thiocyanate and cyanide accumulation in the fetus**. In the postpartum patient, angiotensin-converting enzyme inhibitors may be given, but because there is no information available on breastfeeding, an alternative agent is recommended during lactation. Anticoagulate with heparins because of increased risk of thromboembolism. **Do not use warfarin during pregnancy. Warfarin can be given in the postpartum period and poses little risk to the breastfed infant. Recovery to maximal ejection fraction (>50% left ventricular ejection fraction) usually occurs in the first 6 months postpartum and occurred in a majority of women in one study (>70%).**[52] **Ventricular dysrhythmias are common and may require a permanent implantable cardioverter-defibrillator with persistent dilated cardiomyopathy.**

TRANSFER OF THE PREGNANT PATIENT AND THE EMERGENCY MEDICAL TREATMENT IN ACTIVE LABOR ACT

There are times when a pregnant woman must be transferred to another hospital. Emergency physicians who work in a hospital that does not provide obstetric services should be familiar with the protocols in place for transfer and inpatient care of such patients. The **Emergency Medical Treatment and Active Labor Act** specifically addresses the care of pregnant women before and during transfer (see Chapter 303, "Legal Issues in Emergency Medicine").

A woman having contractions is considered to have an emergency medical condition if there is insufficient time for transfer before delivery or if the transfer may pose a threat to the health or safety of the child. In such a situation, the patient should not be transferred prior to delivery unless the patient requests transfer. If contractions are not present, an emergency medical condition is not automatically present, and the regular rules of providing medical care and determining the need for transfer of patients apply.

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 101

Emergency Delivery

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INTRODUCTION AND EPIDEMIOLOGY

The thought of a woman presenting to the ED in active labor is justifiably a cause for anxiety—the emergency physician must contend not only with the often rusty recollection of the stages of normal delivery but also with the knowledge that there are serious and even fatal complications associated with labor. Maternal and fetal survival may depend on the ability to successfully manage preeclampsia, eclampsia, hemorrhage, shoulder dystocia, malpresentation, cord prolapse, breech delivery, or fetal distress. Every ED should be prepared to take care of a woman in active labor. Tools include a basic delivery kit, an infant warmer or isolate, and medical supplies and equipment for neonatal resuscitation (see Chapter 108, "Resuscitation of Neonates" and **Tables 101-1** and **101-2**).

Out-of-hospital births occurred in 1.36% of births in 2012.[1] Occasionally, planned home deliveries experience medical complications and require rapid transport to the ED to assist with labor and delivery. In a prospective study of home births in the United States and Canada, nearly 12% of 5400 women who had planned a home delivery ultimately required urgent transfer to a hospital during the course of labor.[2] The majority of *intrapartum* transfers were performed for failure to progress, need for pain management, and maternal exhaustion. *Postpartum* transfers encompassed a variety of complications such as maternal hemorrhage, retained placenta, or newborn respiratory distress.

Out-of-hospital deliveries may also occur due to inadequate or nonexistent prenatal care, transportation difficulties, a remote setting, or the onset of premature labor. Occasionally, a woman may attempt to avoid the hospital/physician fees associated with pregnancy until the delivery of her child, presenting to a hospital for the first time when in active labor.

The development of obstetric centers for high-risk pregnancy has led to a significant decline in neonatal mortality in the United States. The most common reasons for transport to such centers include preterm labor (41%), premature rupture of membranes (21%), hypertensive disease (16%), and antepartum hemorrhage (13%).[3] Other indications for transport include eclampsia or preeclampsia, fetal distress, multiple gestation, fetal anomalies, and maternal health problems, including traumatic injuries. EMS units transporting an actively laboring patient should carry sterile delivery packs, relevant medical supplies (Table 101-1), and appropriate medications (Table 101-2). The transport team should be trained to assist in the precipitous delivery of an infant. Prehospital protocols regarding the complications of labor and delivery should be reviewed regularly to ensure that EMS personnel are adequately prepared for both normal delivery and potentially catastrophic pregnancy-related events.

For deliveries in an austere environment or in a disaster zone, the United Nations Population Fund provides a vaginal delivery kit for use during disaster relief, which includes a plastic sheet to lay on the ground, soap for washing hands and the perineum, string and a razor blade to tie and cut the umbilical cord, and a blanket to protect the newborn baby.[4]

TABLE 101-1 Equipment and Supplies for Emergency Delivery

- Sterile gloves
- Sterile towels and drapes
- Povidone-iodine or chlorhexidine to cleanse the perineum neither of these agents require trademark symbol
- Sterile lubricant gel
- Sterile scissors
- Kelly clamps
- Cord clamps
- Rubber suction bulb
- Towel or blanket for the infant
- Gauze sponges (4×4)
- Syringes (10 mL) and needles (22–24 gauge)
- Placenta basin
- Suture (3-0 chromic and 2-0 Vicryl) and needle driver

Note: List excludes standard adult and neonatal resuscitation equipment.

LABOR

PHYSIOLOGY

RUPTURE OF MEMBRANES

Determining rupture of membranes predicts not only the likelihood of imminent labor but also the potential for complications, such as infection or cord prolapse. Spontaneous rupture of membranes occurs during the course of active labor in the majority of patients, although it also happens *prior* to onset of labor in approximately 8% of third-trimester patients.[5] Fifty percent of women who experience premature rupture of membranes deliver within 5 hours, and 95% give birth within 28 hours of this event.[6] The history of spontaneous rupture of membranes typically involves report of a gush of clear or blood-tinged fluid. Occasionally, patients recount continued leaking or dampening of their underwear on standing or with a Valsalva maneuver. Greenish brown fluid suggests the presence of meconium in amniotic fluid.

Rupture of membranes may be confirmed by using nitrazine paper to test residual fluid in the fornix or vaginal vault while performing a sterile speculum examination. **Amniotic fluid has a pH of 7.0 to 7.4 and will turn nitrazine paper a dark blue.** Vaginal fluid, on the other hand, typically has a pH of 4.5 to 5.5; the nitrazine strip, thus, remains yellow. False-positive results may occur, however, in the presence of blood, lubricant, *Trichomonas vaginalis*, semen, or even cervical mucus. **Another test that confirms rupture of membranes is ferning, which is the observation of sodium chloride crystals on a microscope slide as amniotic fluid dries.**

CERVICAL DILATATION

Cervical dilatation describes the diameter of the internal cervical os and indicates the progression of labor. The index and middle fingers of the examining hand are used to estimate the diameter, which is expressed in centimeters (from closed to 10 cm). **Dilatation of 10 cm indicates full dilatation.** As labor progresses, the cervix also undergoes thinning, known as **effacement**, which is described in terms of a percentage of normal cervical length. Unfortunately, this estimate is poorly reproducible among examiners. **Station** indicates the level that the fetus occupies in the pelvis. The maternal ischial spines serve as the reference point and are palpable on either side of the vaginal canal (located at 4 and 8 o'clock). If the presenting fetal part remains above the ischial spines, the station is described as negative. Once the presenting fetal part has reached the level of the ischial spines, the station is 0, with further descent into the pelvis described as +1 or +2. Therefore, a +3 station corresponds to visible scalp at the introitus, indicating a fetal position consistent with impending delivery.

TRUE VERSUS FALSE LABOR

Distinguishing **true from false labor** is an important initial step in the management of the pregnant patient (**Table 101-3**). **False labor** is defined as uterine contractions that do not produce cervical changes and is characterized by irregular, brief contractions that are usually confined to the lower abdomen. Commonly known as **Braxton Hicks contractions**, they are irregular in both intensity and duration. False labor may persist for several days and is commonly treated with hydration and rest.

True labor, on the other hand, is characterized by painful, repetitive uterine contractions that increase steadily in both intensity and duration and result in cervical effacement and dilatation. Specifically, true labor pains typically commence in the fundal region and upper abdomen and radiate into the pelvis and lower back. True labor leads to not only

TABLE 101-2 Medications for Emergency Delivery and Indications for Use

Classification	Medication	Dosage	Indication/Use	Contraindications
Uterotonic	Oxytocin	20 units/1000 mL normal saline or 10 units IM	Stimulation of uterine contraction or as uterotonic for PPH	Hypersensitivity
	Misoprostol	1000 micrograms PR, SL, or PO once	Unlabeled use for PPH	Hypersensitivity
	Methylergonovine	0.2 milligram IM or IV or PO; may repeat at 2- to 4-h intervals	PPH	Hypersensitivity, hypertension, eclampsia, preeclampsia
	Carboprost	250 micrograms IM every 15–90 min (total dose 2 milligrams)	PPH	Asthma
Antihypertensive	Hydralazine	5 milligrams IV, followed by 5- to 10-milligram boluses every 20 min	Preeclampsia/eclampsia, hypertensive emergency	Hypersensitivity
	Labetalol	20 milligrams IV, followed by doubled doses up to 80 milligrams (20–40–80–80) every 10 min; maximum total dose, 220 milligrams	Preeclampsia/eclampsia, hypertensive emergency	Hypersensitivity, sinus bradycardia
Anticonvulsant	Magnesium sulfate	Loading dose of 4–6 grams IV over 15 min, followed by 2 grams/h infusion; can also give 5 grams IM in each buttock; max serum Mg = 8 mg/dL	Seizure prophylaxis in preeclampsia/eclampsia	Myasthenia gravis
Electrolyte supplement toxicity	Calcium gluconate	1 gram IV over 5 min	Magnesium toxicity	Hypersensitivity, cardiac arrhythmia
Analgesic	Lidocaine 1%	1–10 mL injected locally	Local anesthetic	Hypersensitivity
	Fentanyl, 50 micrograms/mL	50 micrograms/mL	Short-acting opiate analgesic	Hypersensitivity
Opiate antagonist	Naloxone	0.4–2.0 milligrams IV every 2–3 min as needed up to 10 milligrams cumulative dose	Narcotic overdose	Hypersensitivity
Antiemetic	Ondansetron	4 milligrams IV	Nausea, vomiting	Hypersensitivity

Abbreviation: PPH = postpartum hemorrhage.

cervical dilatation and effacement but also the progressive descent of the fetus into the pelvis, in preparation for delivery.

STAGES OF LABOR

There are three **stages of labor** (**Table 101-4**). The first stage commences with the onset of regular uterine contractions and ends with full cervical dilatation. The first stage can be subdivided into two phases: latent and active. The latent phase is characterized by moderately uncomfortable uterine contractions that are infrequent and irregular, resulting in gradual cervical changes. In this preparatory phase, the uterus orients to contractions and the cervix undergoes both effacement and softening. The active phase is typically noted to arise once the cervix has dilated to 3 to 4 cm and results in cervical dilatation at an average rate of 1.2 cm/h in nulliparous women and 1.5 cm/h in multiparous women. The second stage of labor commences at full dilatation and ends with the delivery of the infant.[7] The mean length of the second stage of labor is 20 minutes for multiparous women and 54 minutes for nulliparous women.[8] The third stage of labor starts after the delivery of the infant and ends with the delivery of the placenta. The third stage usually lasts less than 10 minutes, and active intervention is usually not required until after 30 minutes, unless hemorrhage occurs.

TABLE 101-3 True Versus False Labor

	True Labor	False Labor
Contractions		
Rhythm	Regular	Irregular
Intervals	Gradually shorten	Unchanged
Intensity	Gradually increases	Unchanged
Discomfort		
Location	Back and abdomen	Lower abdomen
Sedation	No effect	Usually relieved
Cervical dilatation	Yes	No

Source: Reproduced with permission from Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY (eds): *Williams Obstetrics*, 23rd ed. McGraw-Hill, Inc., 2010. Table 17-4 on AccessMedicine.com.

FETAL DISTRESS

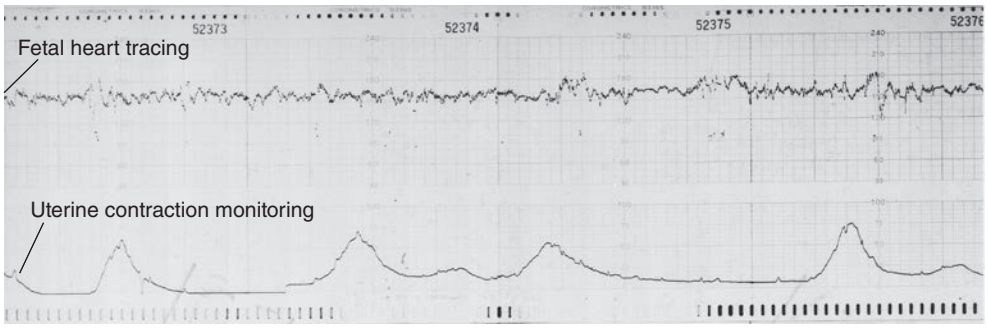
Fetal distress may occur during active labor. Indicators of fetal distress include fetal bradycardia or tachycardia, or late decelerations in fetal heart rate, which are defined as persistent drops in fetal heart rate both during and more than 30 seconds after a contraction. A physician or nurse trained in fetal monitoring can identify fetal distress (**Figure 101-1**). Doppler measurement of fetal heart tones is not reliable to detect decelerations. If decelerations are suspected, obtain emergency obstetrics consultation, and try to increase maternal blood flow by positioning the patient in the left lateral position, provide IV hydration, and administer oxygen. Further information is provided in the Advanced Life Support in Obstetrics course.

CLINICAL EVALUATION

When a patient >20 weeks' gestation presents to the ED with signs of labor, immediately obtain both maternal vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, temperature) and the fetal heart rate. Doppler US can be used to measure fetal heart rate; a **normal fetal heart rate is generally 120 to 160 beats/min, bradycardia is defined as less than 110 beats/min, and tachycardia is greater**

TABLE 101-4 Stages of Labor

Stage	Definition	Comments
First stage	From onset of regular uterine contractions to full cervical dilatation	—
Latent phase	Irregular, infrequent contractions	Preparatory phase, cervix softens and effaces
Active phase	Begins once cervix has dilated to 3–4 cm	Nulliparas: cervix dilates at 1.2 cm/h Multiparas: cervix dilates at 1.5 cm/h
Second stage	From full dilatation to delivery	Nulliparas: mean duration 54 min Multiparas: mean duration 20 min
Third stage	From delivery of infant to delivery of placenta	10 min; intervention not needed until >30 min



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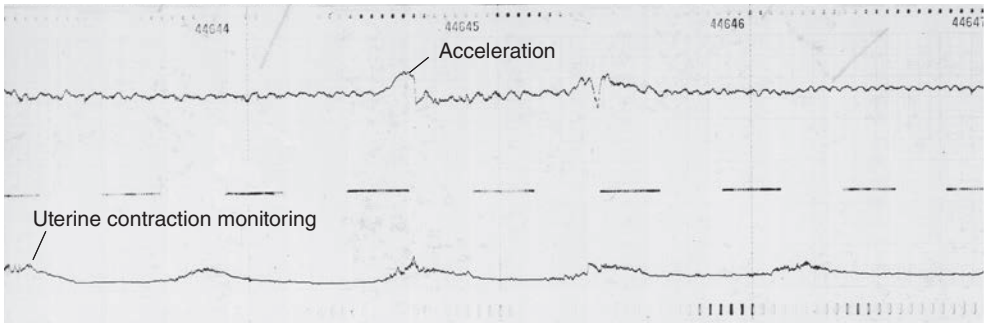

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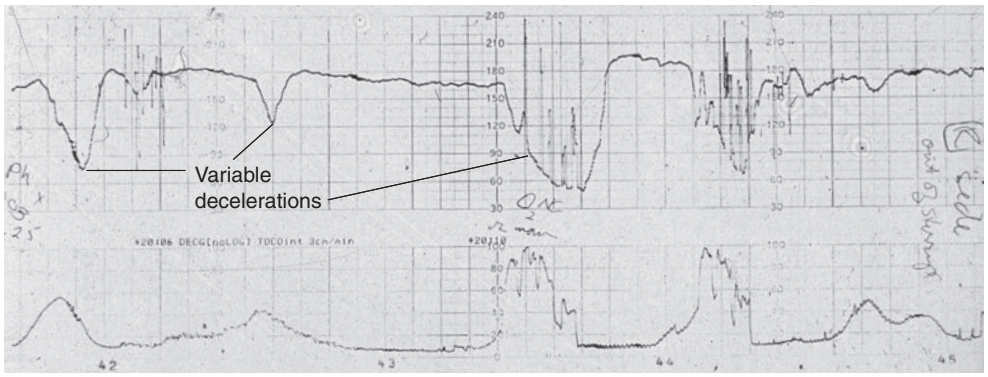

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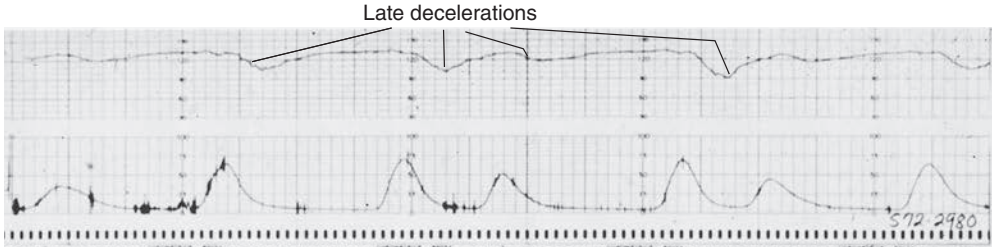

E

FIGURE 101-1. Fetal heart rate variability and uterine contraction patterns. **A.** Good variability. **B.** Good variability with brief accelerations. Fetal heart rises above baseline and quickly returns to normal. A reassuring pattern. **C.** Poor variability. May be due to fetal hypoxia. **D.** Variable decelerations. No relationship to uterine contractions. May represent cord compression. **E.** Late deceleration. Occurs at onset of contraction and slow return to baseline after contraction ends. Signifies uteroplacental insufficiency and fetal hypoxia. [Reproduced with permission from Pearlman MD, Tintinalli JE, Dyne PL (eds): *Obstetric and Gynecologic Emergencies: Diagnosis and Management.* New York: McGraw-Hill, Inc.; 2003. Figs. 10-9 and 10-10, pp. 131 and 132.]

than 160 beats/min.[9] A persistently slow fetal heart rate indicates fetal distress and requires emergency obstetric consultation. As part of the initial evaluation, obtain IV access, procure baseline laboratory studies including blood type, and send a urinalysis.

HISTORY

Ask about the onset and frequency of uterine contractions, fetal membrane status, presence or absence of vaginal bleeding, and presence or absence of fetal movement. The obstetric history should include parity, history of complications with prior deliveries, history of precipitous deliveries, prenatal care during this pregnancy, and estimated date of delivery. Obtain a medical and surgical history and a list of current medications and allergies, and ask the patient about substance abuse. Inquire about symptoms of infection, such as fevers, chills, or foul-smelling vaginal discharge.

Gestational Age If the patient knows the first day of her last menstrual period, the estimated date of delivery can be calculated by adding 9 months and 7 days to that date (**Nägele's rule**). Fundal height also provides a rapid estimate of gestational age once greater than 20 weeks and is measured in centimeters (cm) from the pubic symphysis to the top of the fundus (cm = weeks of gestation ±2 weeks). Fundal height may be falsely overestimated in the obese patient and underestimated in active labor when the fetal head has descended into the pelvis. Bedside US also provides a useful assessment of gestational age in the third trimester, but estimated age can vary by ±3 weeks.

PHYSICAL EXAMINATION

Monitor vital signs for evidence of maternal fever, tachycardia, or elevated blood pressure. Assess fetal heart tones for bradycardia or tachycardia. Do not keep the pregnant woman flat on her back for a prolonged time period. Compression of venous return by the gravid uterus can lead to hypotension in the mother, which in turn results in decreased blood supply to the fetus. Place the **patient in the left lateral position following the physical examination**. On abdominal examination, determine fundal height, abdominal or uterine tenderness to palpation, and presence of uterine contractions. Examine the perineum for perineal lesions, such as those caused by herpes simplex virus, which may be a contraindication for a vaginal delivery.

PELVIC EXAMINATION

Vaginal Bleeding Present **Patients with vaginal bleeding should be evaluated with bedside US prior to speculum or bimanual examination in order to rule out placenta previa.**

No Vaginal Bleeding Patients without vaginal bleeding should be evaluated first with a sterile speculum examination to determine if membranes have been ruptured, to note cervical dilatation, and to determine fetal station and presentation. Bedside US is the simplest method to verify presentation. Vertex presentation and lie can also be confirmed through palpation of the cranial sutures on digital examination. Palpation of small parts, such as feet or hands, often indicates malpresentation and will require urgent obstetrics consultation. If meconium is present on the examining finger, be prepared for neonatal resuscitation (see Chapter 108, "Resuscitation of Neonates").

Rupture of Membranes **If rupture of membranes is suspected**, perform a sterile speculum examination (do not use lubricant because lubricant may produce a false-positive nitrazine test), but **do not perform a digital examination because even one digital examination increases the risk of infection.[10] Also avoid digital examinations in the preterm patient in whom the prolongation of gestation is desired.**

EMERGENCY DELIVERY

If time allows, prepare the perineum by washing it with mild soap and water and swabbing with povidone-iodine. Place drapes over the patient. Medical personnel attending to the patient should don gowns, masks, and gloves.

The first steps in the management of a woman in active labor are to measure vital signs and initiate supportive therapy. Obtain venous access, provide IV hydration, and initiate maternal and fetal monitoring (if available). Delivery is imminent if the pelvic examination reveals complete cervical effacement and the fetus is at the introitus. Labor can progress very rapidly, particularly in multiparous patients. Both the stage of labor and the parity of the patient should be taken into account when considering whether to transport a laboring patient to the labor and delivery suite or to another facility. **If the cervix is fully effaced and dilated or the fetal head is visible during contractions, the obstetrician (if available) should come to the ED rather than risk a precipitous delivery during transport to the delivery suite.**

As the cervix fully dilates, effacement becomes complete, the fetus descends into the pelvis, and the patient will experience the urge to push. The cervix should be fully dilated before the patient begins to push in order to avoid cervical lacerations. If not already done by US, determine fetal presentation by palpating skull sutures and fontanelle or the buttock or extremity.

Six cardinal movements describe the process of fetal descent during labor and delivery: (1) engagement, (2) flexion, (3) descent, (4) internal rotation, (5) extension, and (6) external rotation (**Figure 101-2**). *The following discussion describes delivery in the cephalic, occiput anterior position.* As the fetus descends through the birth canal and reaches the introitus, the perineum bulges in order to accommodate the fetal head. Gentle digital stretching of the inferior portion of the perineum can aid delivery. The perineum undergoes gradual thinning and stretching to enable passage of the newborn. (See Video: Vaginal Delivery With Episiotomy.)

EPISIOTOMY

Routine **episiotomy** for a normal spontaneous vaginal delivery varies with practitioner, institution, and country. Episiotomy may be necessary to expedite a delivery in cases of fetal distress or shoulder dystocia or if forceps or vacuum devices are used (**Figure 101-3**).[11] The episiotomy can be performed in the midline or mediolaterally (45 degrees from the midline). Median episiotomy is easy to perform and has less maternal discomfort during recovery, but mediolateral episiotomy has a lower risk of extension to the anal sphincter (third-degree extension) or to the rectum (fourth-degree extension) than median episiotomy. If an episiotomy is clinically necessary, first inject 5 to 10 mL of 1% lidocaine solution with a small-gauge needle into the posterior fourchette and perineum. While protecting the infant's head, make a 2- to 3-cm incision with scissors in order to extend the vaginal opening, either at the midline or 45 degrees from the midline. A median incision must be supported with manual pressure from below. Take care to prevent extension of the incision into the rectum.

COMPLETION OF DELIVERY

Do not drop the baby. The combination of amniotic fluid, blood, and vernix generates a very slippery infant. Before delivering the rest of the body, place your posterior hand underneath the axilla of the infant. Use the anterior hand to grasp the ankles of the infant with a firm grip. Following delivery, keep the infant warm and provide gentle stimulation. Do not routinely suction the nose and mouth. Suctioning can cause fetal bradycardia and hypoxia. See Chapter 108, "Resuscitation of Neonates," for further discussion of neonatal respiratory distress. If delivery is uncomplicated, and the infant has responded well to initial stimulation with a clear airway and good respiratory effort, the mother may hold the child immediately while the cord is cut.

Apgar scores are calculated at 1 and 5 minutes after delivery. Scoring parameters include general color, tone, heart rate, respiratory effort, and reflexes (**Table 101-5**).

For an APGAR score of <7, refer to Chapter 108, "Resuscitation of Neonates." Provide positive-pressure ventilation for all newborns with a heart rate <100 beats/min or who are gasping or apneic after 30 seconds.

CLAMPING THE UMBILICAL CORD

Do not clamp the umbilical cord of term or preterm infants for at least 1 to 3 minutes after birth. Delayed cord clamping increases neonatal iron stores. **Double-clamp the umbilical cord 3 cm distal to its**

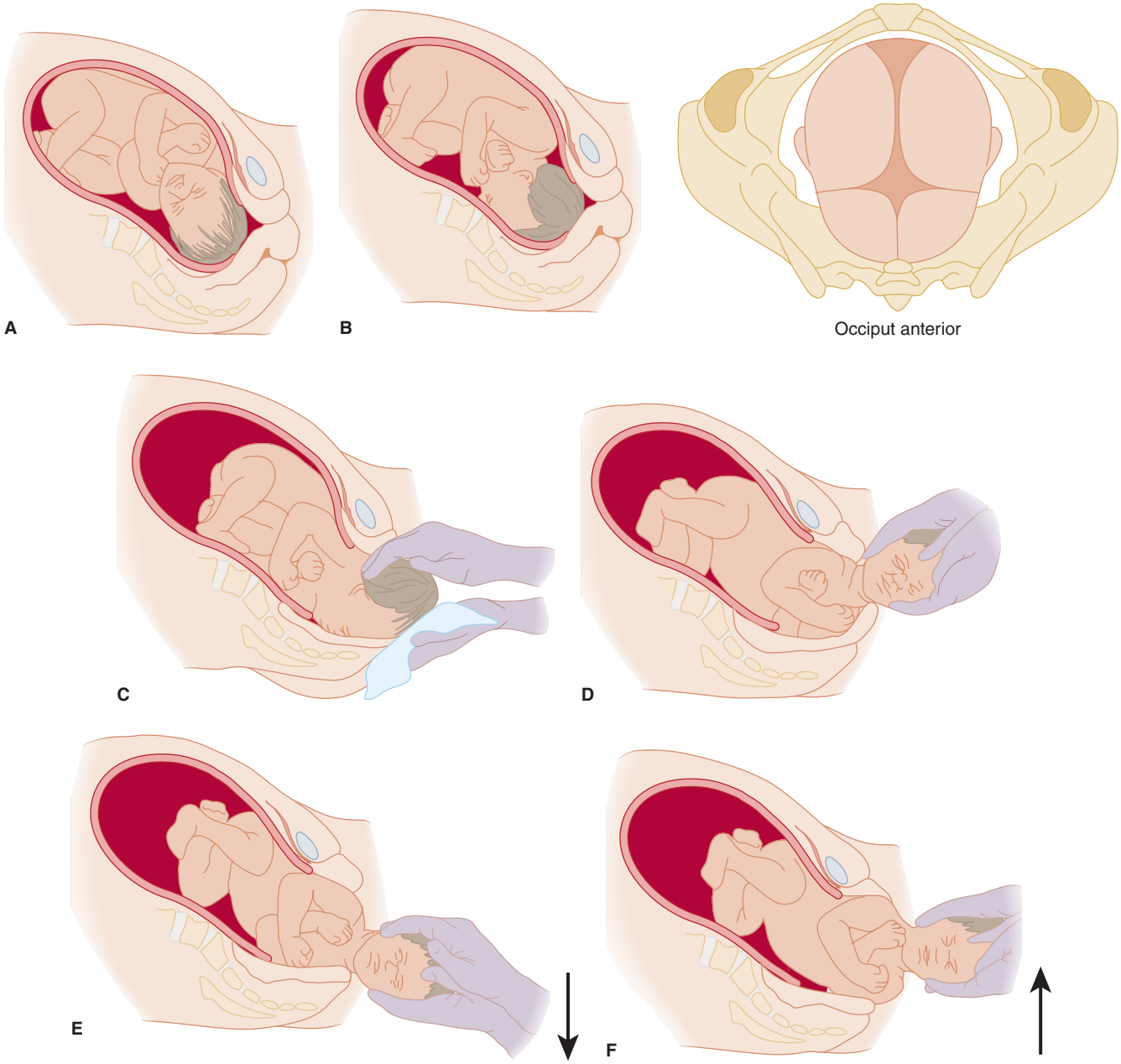

FIGURE 101-2. The movements of normal delivery for a vertex presentation. **A.** Engagement, flexion, and descent with vertex anterior. **B.** Internal rotation with occiput becoming anterior. **C.** Extension and delivery of the head. As the infant's head emerges from the introitus, support the perineum by placing a sterile towel along the inferior part of the perineum with one hand, and support the fetal head with the other hand. Ask the mother to breathe through contractions (rather than bear down) in order to deter rapid expulsion of the baby. Provide mild counterpressure for controlled extension of the fetal head. As the infant's head presents, use the inferior hand to control the fetal chin and keep the superior hand on the crown of the head, supporting the delivery. **D.** External rotation, bringing the thorax into the anteroposterior diameter of the pelvis. As the head delivers, palpate the infant's neck to assess for the presence of a nuchal cord. Nuchal cord is noted in approximately 25% to 35% of all term deliveries.[8] If the cord is loose, move it over the infant's head, and allow delivery to proceed as usual. If the cord is wound tightly around the neck, however, apply two close clamps in the most accessible area, and then cut the cord. **E.** Delivery of the anterior shoulder. Once the head is delivered, it will turn to one side or the other. Grasp the sides of the head with both hands and apply **gentle** downward traction (go with gravity) until the anterior shoulder is delivered. Jerky or aggressive traction may injure the brachial plexus. If you have not checked for a nuchal cord, do so now. As the head rotates, place the hands on either side of the head, providing gentle downward traction. This maneuver allows for the delivery of the anterior shoulder. **F.** Delivery of the posterior shoulder. Use an upward movement to deliver the upward shoulder. Do not apply traction. If meconium is present or the newborn is limp or poorly responsive, stimulate the baby and be prepared to begin the steps of neonatal resuscitation with ventilation and oxygenation (see Chapter 108, "Resuscitation of Neonates").

insertion at the umbilicus and transect with sterile scissors. In delivery settings where aseptic care is routine, there is no clear benefit to any additional topical care of the umbilicus. When aseptic care is *not* available, however, antiseptic topical care of the umbilicus with chlorhexidine reduces the risk of omphalitis and neonatal mortality.[12] Once the umbilical cord is cut, dry the infant and either give the infant to the mother or place it in a warming unit.

DELIVERY OF THE PLACENTA

The placenta usually delivers 10 to 30 minutes after delivery of the infant. Allow the placenta to separate spontaneously and provide only *gentle* traction. Aggressive traction on the cord can lead to uterine inversion, tearing of the cord, or disruption of the placenta, all of which can result in severe vaginal bleeding. After the placenta has been removed,

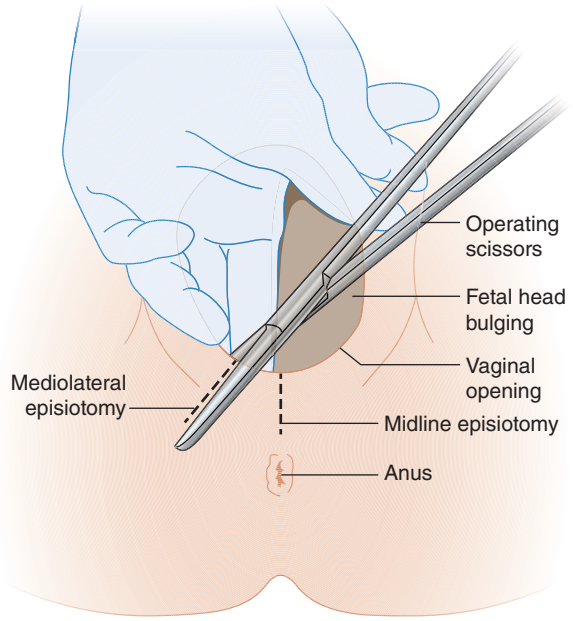

FIGURE 101-3. Methods for episiotomy.

gently massage the abdomen at the level of the fundus to promote contraction. Give oxytocin (10 to 40 units in 1 L normal saline at 250 mL/h or 10 units IM) to sustain uterine contraction.

The estimated blood loss during a vaginal delivery is usually less than 500 mL. Uterine atony, however, which occasionally follows a precipitous delivery, can lead to excessive vaginal bleeding. In that case, give additional oxytocin or another uterotonic of choice (Table 101-2). As contractile agents are administered, provide vigorous bimanual massage.[13] If concerned about an episiotomy complication, delay episiotomy or laceration repair until an experienced obstetrician is available to close the laceration and inspect for fourth-degree perineal lacerations.

COMPLICATIONS OF LABOR AND DELIVERY

UMBILICAL CORD PROLAPSE

Umbilical cord compression is life threatening to the fetus. Obtain immediate obstetric assistance, as emergent cesarean delivery is indicated. **Should the speculum or bimanual examination reveal a palpable, pulsating umbilical cord, elevate the presenting fetal part to reduce compression on the cord. Keep your hand in the vagina while the patient is transported and prepared for surgery to prevent further compression of the cord by the fetal head. Place the mother in the Trendelenburg position. Do not try to reduce the prolapsed cord.**[14]

TABLE 101-5 Apgar Scoring for Newborns

	Sign	0 Points	1 Point	2 Points
A	Activity (muscle tone)	Absent	Arms and legs flexed	Active movement
P	Pulse	Absent	Below 100 beats/min	Above 100 beats/min
G	Grimace (reflex irritability)	No response	Grimace	Sneezing, coughing, pulling away
A	Appearance (skin color)	Blue-gray, pale	Normal, except extremities	Normal over entire body
R	Respiration	Absent	Slow, irregular	Good, crying



FIGURE 101-4. Clinical appearance of shoulder dystocia. The infant's head is impacted against the perineum. [Reprinted with permission from Buckley RG, Knoop KJ: Gynecologic and obstetric conditions, in Knoop KJ, Stack LB, Storrow AB (eds): *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, Inc.; 2002, Figure 10.46.]

SHOULDER DYSTOCIA

Shoulder dystocia is the impaction of fetal shoulders at the pelvic outlet after delivery of the head. Typically, the anterior shoulder is trapped behind the pubic symphysis and prevents delivery of the rest of the infant.[15,16] Complications of shoulder dystocia include fetal brachial plexus injury (due to overaggressive traction), clavicle fracture, fetal hypoxia (due to impaired respirations and/or compression of the umbilical cord), postpartum hemorrhage, and fourth-degree perineal lacerations.

Prior to delivery of the head, the head may retract between contractions. Shoulder dystocia then becomes evident when routine downward traction fails to deliver the anterior shoulder once the head has been delivered. After the infant's head is delivered, the head retracts tightly against the perineum (turtle sign; **Figure 101-4**).[17] Several steps can be used to relieve shoulder dystocia (**Table 101-6**). Immediately place the mother in the extreme lithotomy position, with her legs sharply flexed up to the abdomen and the knees held as widely apart as possible (**McRoberts maneuver**; **Figure 101-5**). Either the mother or an assistant should keep the legs held widely apart. **Simultaneously apply suprapubic pressure. If a second assistant is available, he or she should place their hands in a CPR position and apply downward pressure just above the pubic symphysis for 1 to 2 minutes to disimpact the anterior shoulder. Do not apply pressure to the uterine fundus, as this maneuver can further impact the shoulder.** Suprapubic pressure serves

TABLE 101-6 Steps to Relieve Shoulder Dystocia

Steps	Comments
Flex thighs and keep knees apart as much as possible	McRoberts maneuver
Apply suprapubic pressure	Keep patient in McRoberts position. Place one hand with wrist clenched, immediately above the pubic symphysis, and push the anterior fetal shoulder to dislodge it. If an assistant is available, place two clenched wrists in CPR position just above pubic symphysis, again using pressure to dislodge the anterior shoulder. Compress for 1 min. Do not compress uterine fundus. This worsens impaction.
Deliver posterior arm	Insert hand into posterior vagina, identify arm, and sweep across chest.
Rotational maneuvers	Typically require episiotomy. Attempt to place shoulders in a different diameter. See text.

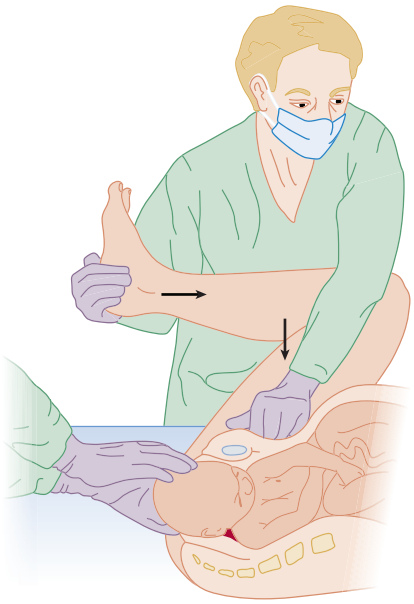

FIGURE 101-5. McRoberts maneuver. Sharply flex the thighs up onto the abdomen, as shown by the *horizontal arrow*, and keep the knees spread widely. Simultaneously provide suprapubic pressure (*vertical arrow*). [Adapted with permission from Cunningham FG, Leveno KL, Bloom SL, et al: *Williams Obstetrics*, 22nd ed. New York: McGraw-Hill, Inc.; 2005, Figure 20-14.]

to rotate the shoulder under the pubic symphysis.[17] The combination of the McRoberts position and suprapubic pressure relieves about 50% of shoulder dystocias.

In the event that the above maneuvers are unsuccessful, the delivery of the posterior arm can be considered as the next maneuver to manage shoulder dystocia.[17] To perform this maneuver, the provider reaches into the vagina and identifies the posterior arm. The elbow is flexed and the arm is swept across the fetal chest. This will usually allow the arm to deliver and the anterior shoulder will be disimpacted, allowing the rest of the fetus to deliver. Should this procedure fail, rotational maneuvers should be attempted. **The Rubin maneuver** is accomplished by placing a hand on the back surface of the posterior shoulder and rotating the fetus toward the fetal face. **The Woods' corkscrew maneuver** (**Figure 101-6**) is accomplished by placing a hand on the anterior surface of the posterior shoulder and rotating toward the fetal back. **Sling procedures** have also been described where a finger or 12F or 14F suction catheter is placed through the axilla of the posterior arm. Moderate traction is applied to deliver the posterior shoulder. Do not rotate the head. All of the above maneuvers require an episiotomy to allow the provider to place a hand in the vagina.[17]

The **Gaskin maneuver** (**Figure 101-7**) can also be employed. It is a simple maneuver, but with IVs and monitors in place or with an exhausted mother, it can be difficult to achieve. Place the patient on all fours. Exert gentle downward traction on the infant's head. To remember the direction of traction, remember to "go with gravity." In 80% of cases, this maneuver allows the posterior shoulder to successfully deliver.[17]

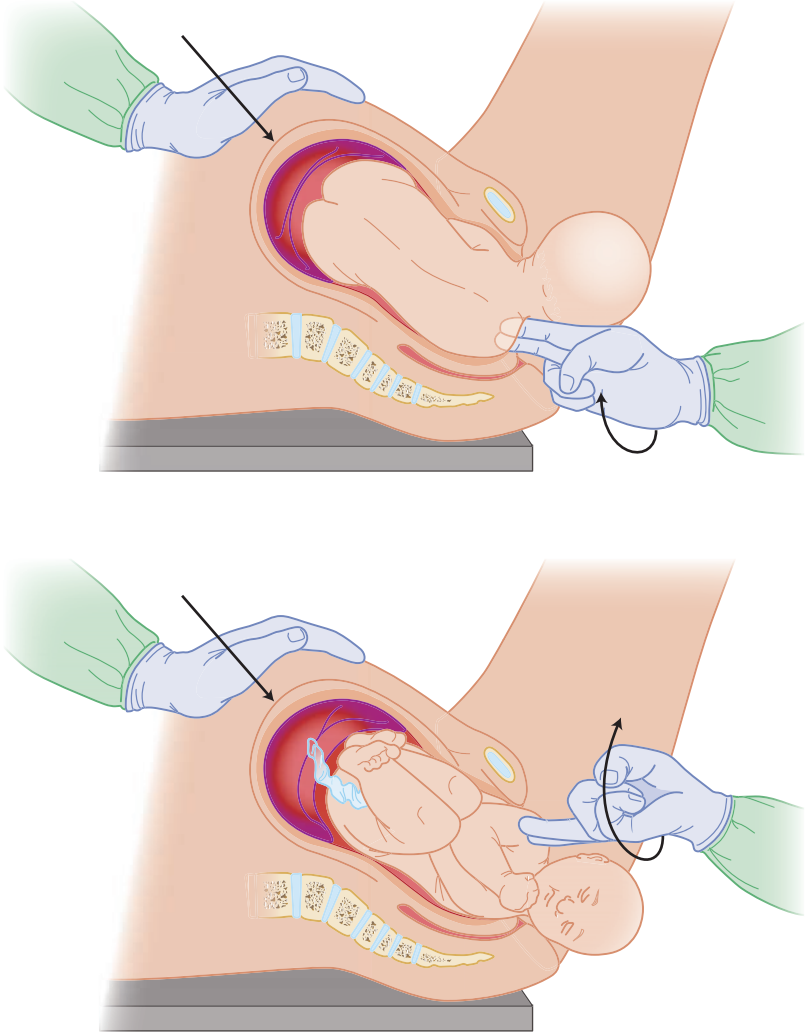

FIGURE 101-6. Woods corkscrew maneuver, rotating the posterior shoulder.



FIGURE 101-7. Gaskin maneuver. Move the mother onto all fours. This maneuver can widen the pelvic outlet.

BREECH PRESENTATION

Breech presentations occur in 3% to 4% of term pregnancies. Risks of breech presentations include umbilical cord prolapse, trauma, hypoxia, and fetal distress. Breech presentations occur most frequently in the delivery of *premature* infants; approximately 25% to 30% of all preterm infants (<28 weeks' gestation) present in breech position.[18] Given the increased perinatal/neonatal morbidity and mortality associated with vaginal breech deliveries, cesarean section is recommended in breech presentations.

Head entrapment is a major concern in a breech delivery. In a normal cephalic delivery, the larger head dilates the cervical canal, which ensures that the rest of the infant's body can follow. In a breech delivery, however, the head emerges last and may become stuck in an incompletely dilated cervix.

In frank and complete breech deliveries, the buttocks dilate the cervix almost as well as the fetal head; therefore, emergency delivery may be able to proceed in an uncomplicated fashion. First, determine breech position and full cervical dilation. Check for prolapsed cord. Footling and incomplete breech positions are not safe for vaginal delivery due to the risk of cord prolapse or incomplete dilatation of the cervix. Immediately obtain emergency obstetric consultation for any breech presentation.

Allow the delivery to proceed spontaneously to the level of the umbilicus and do not apply traction (**Figure 101-8**). The legs will typically deliver spontaneously at this time, or one can insert a finger behind the knee to flex and abduct the baby's thigh to deliver the legs. Once the umbilicus is evident, gently place your thumbs on the sacrum and gently grasp the fetal pelvis with your hands. Keep the trunk at no more than 45 degrees to the horizontal. You may need to kneel on the floor. Maintain or redirect the baby's sacrum anterior. Allow each arm to deliver with slight fetal oblique rotation for each arm, and then maintain sacrum anterior position. You can have an assistant place the baby's torso in a towel fashioned like a sling for better support.

To safely deliver the head, maintain cervical flexion by placing one hand on the fetal occiput and shoulders, and apply flexing pressure on the occiput; and place the fingers of the other hand on the infant's maxillae to aid in cervical flexion. An assistant can apply suprapubic pressure to the mother to maintain cervical flexion. Maintain cervical flexion, and the baby's body will then deliver in a large arc, with the sling providing support.

POSTPARTUM HEMORRHAGE

Postpartum hemorrhage usually occurs within the first 24 hours of delivery and is referred to as **primary postpartum hemorrhage**. The main causes of primary postpartum hemorrhage include **uterine atony**, **retained placental fragments**, **lower genital tract lacerations**, **uterine rupture**, **uterine inversion**, and **hereditary coagulopathy**. **Table 101-7** lists the most common risk factors. **Secondary postpartum hemorrhage** occurs after the first 24 hours and up to 6 weeks postpartum. Common causes of secondary postpartum hemorrhage are failure of the uterine lining to subinvolute at the former placental site, retained placental tissue, genital tract wounds, and uterogenital infection.[19,20]

Excessive blood loss in the postpartum period is defined as a 10% drop in the hematocrit, a need for transfusion of packed red blood cells, or volume loss that generates symptoms of hypovolemia. Normally, plasma volume increases by 40% and red blood cell volume by 25% by the end of the third trimester. The hematologic changes of pregnancy can mask the typical symptoms of hemorrhage; the first sign may be only a mild increase in pulse rate. Up to a 30% loss in total blood volume may occur before the blood pressure drops.

Most cases of postpartum hemorrhage are the results of uterine atony. Another 20% result from cervical, vaginal, or perineal lacerations. Retention of placental tissue may account for 10%, and underlying coagulopathy is an uncommon cause.[20] **The initial resuscitative steps include aggressive fluid and blood resuscitation while identifying and treating the underlying cause (Tables 101-2** and **101-8)**. Nonpneumatic antishock garments can be applied in combination with fluid resuscitation and uterotonics, resulting in reduced blood loss and increased maternal survival in remote settings or with delayed transport.[21]

Uterine atony is the most common cause of postpartum hemorrhage. Risk factors include preeclampsia, protracted use of uterotonics or tocolytics, prolonged labor, multifetal gestation, fetal macrosomia, multiparity, retained placenta, and uterine infection. Initiate bimanual uterine massage; place a fist in the anterior fornix and compress the uterine fundus against the hand in a suprapubic location (**Figure 101-9**).

Retention of placental fragments or **abnormal placental implantation** (placenta accreta) may cause severe hemorrhage and may require emergency pelvic embolectomy, hemostatic brace sutures (B-Lynch sutures), or peripartum hysterectomy.

UTERINE INVERSION AND RUPTURE

Uterine inversion generally results from excessive force or overzealous attempts to remove the placenta in order to manage the third stage of labor.[22] Inversion can also occur in patients with connective tissue disorders and uterine structural anomalies. It can be difficult to detect uterine inversion, particularly if the fundus remains cephalad to the cervix. The diagnosis can be made, however, with transvaginal or transabdominal US. Uterine inversion requires immediate manual replacement of the uterus. A Rüsch balloon catheter can be applied to correct uterine inversion. As with any device, be gentle when inserting anything into an immediate postpartum uterus. The tissue is very soft, and uterine perforation is a very real risk.[22] Of note, the correction of uterine inversion is a very painful and difficult procedure that may require general anesthesia and tocolytic agents.

Though rare, uterine rupture carries a high risk of maternal and fetal mortality. Previous cesarean section is the primary risk factor for uterine rupture, and single-layer surgical closure of the uterus, fetal size >3500 grams, and labor augmentation increase the rate of rupture during a trial of labor. Anatomic abnormalities such as a bicornuate uterus, grand multiparity, history of connective tissue disorders, and abnormal placentation are also associated with rupture. Clinical signs of uterine rupture are persistent abdominal pain, severe vaginal bleeding, loss of fetal station, and palpable uterine defect. Fetal monitors may show fetal

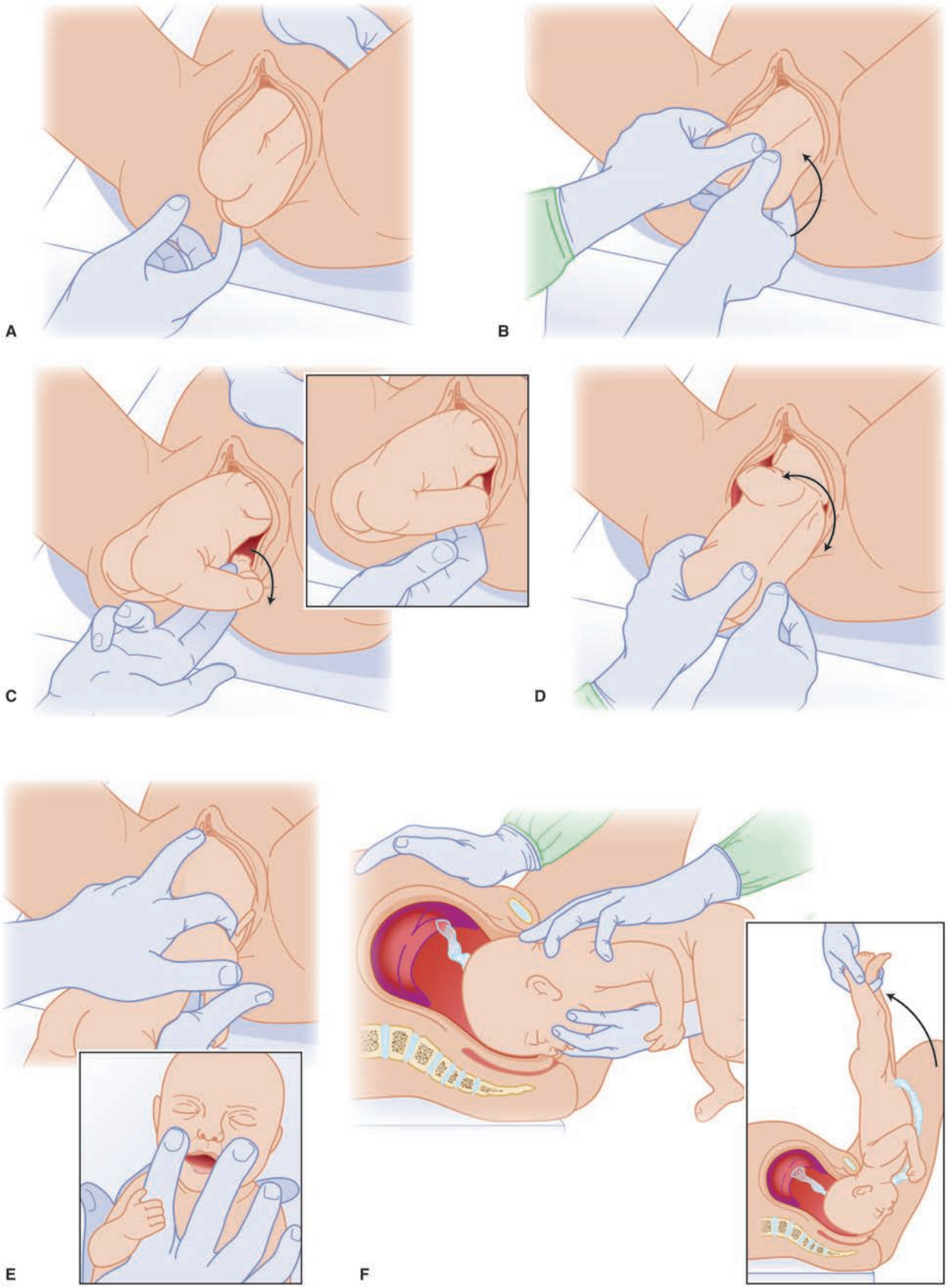

FIGURE 101-8. **A.** Breech usually presents with the sacrum oblique, but most often spontaneously turns to sacrum anterior. **B.** Always allow spontaneous delivery to the umbilicus. If the sacrum has not rotated to the anterior position, put your thumbs on the sacrum and hands underneath on the pelvis (not abdomen) and gently rotate the sacrum anterior. **C.** Freeing the legs. The legs will typically deliver spontaneously. If not, grasp one leg at the popliteal fossa and sweep the leg out. Do the same with the other leg. Inset shows how to sweep the leg out laterally. **D.** Freeing the shoulders. Once the scapulae are evident, to turn the shoulders, grasp the sacrum and pelvis as described in B, and rotate clockwise and counterclockwise to free both shoulders. Then maintain the sacrum in an anterior position. **E.** To safely deliver the head, maintain cervical flexion by placing one hand on the fetal occiput and shoulders, apply flexing pressure on the occiput, and place the fingers of the other hand on the infant's maxillae (inset) to aid in cervical flexion. An assistant can apply suprapubic pressure to the mother to maintain cervical flexion. **F.** The delivery is completed by sweeping the baby through an arc; the infant's body flips over and can be placed in the mother's arms.

TABLE 101-7 Risk Factors for Postpartum Hemorrhage

- Primiparity or grand multiparity
- Previous postpartum hemorrhage
- Preeclampsia
- Prior cesarean section
- Placenta previa or low-lying placenta
- Marginal umbilical cord insertion
- Transverse fetal lie
- Labor induction or augmentation
- Cervical or uterine trauma
- Fetal age <32 weeks of gestation
- Fetal birth weight >4500 grams
- Prolonged third stage of labor

TABLE 101-8 Common Causes and Treatment of Postpartum Hemorrhage

Cause	Treatment
Tone	Perform bimanual uterine massage. Give drugs to improve uterine tone as outlined in Table 101-2.
Trauma	Examine for cervical, vaginal, or perineal lacerations or hematomas. Repair lacerations. Incise, drain, and appropriately ligate bleeding vessels causing a hematoma. Correct uterine inversion with manual replacement. Uterine rupture requires surgery.
Tissue	Inspect the placenta for missing fragments; if a portion is absent, manually evacuate the uterine cavity. Invasive placentation may require hysterectomy. Perform transvaginal or transabdominal US to identify abnormal fluid-filled uterus. Consider a balloon tamponade with either uterine-specific balloon device (Bakri or Rüsch) or an adaptation of a Foley catheter or condom as a temporizing measure.
Thrombin	Consider DIC in the setting of severe preeclampsia, sepsis, placental abruption, shock, or intrauterine fetal demise, although undiagnosed coagulopathies may rarely present in nulliparas. Replace coagulation factors.

Abbreviation: DIC = disseminated intravascular coagulation.

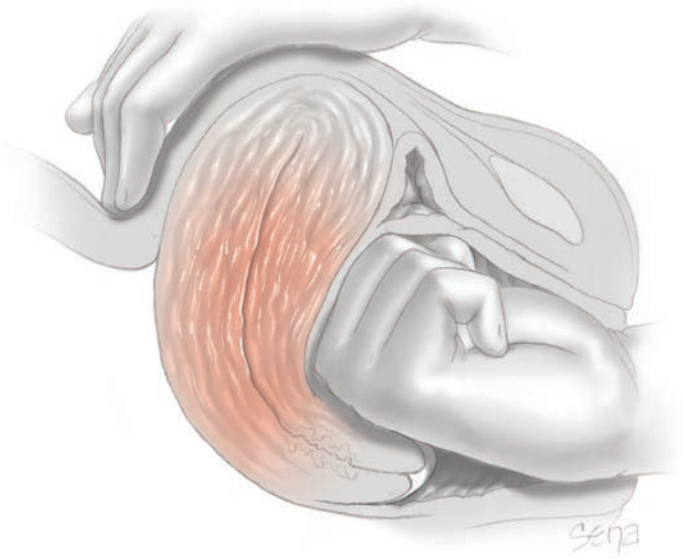

FIGURE 101-9. Treatment of uterine atony. Perform bimanual uterine massage, place a fist in the anterior fornix, and compress the uterine fundus against the hand. [Reproduced with permission from Cunningham G, Leveno KL, Bloom SL, Hauth JC, Rouse DJ, Spong CY (eds): *Williams Obstetrics*, 23rd ed. © 2010. The McGraw-Hill Companies, Inc. New York, Figure 35–17.]

distress and bradycardia. The diagnosis of uterine rupture must be made clinically and rapidly. Treatment is aggressive fluid and blood resuscitation and surgical delivery of the fetus.

AMNIOTIC FLUID EMBOLUS

Amniotic fluid embolus is a rare and often catastrophic complication of pregnancy that occurs when amniotic fluid and cells of fetal origin enter the maternal circulation during labor or delivery. Most cases occur before delivery. Fetal and maternal mortality rates are high. Amniotic fluid embolism is very difficult to diagnose. The onset of symptoms until cardiovascular collapse can range from seconds to >4 hours. Presenting signs include respiratory distress, hypoxia, pulmonary edema, altered mental status, seizures, sudden maternal cardiovascular collapse, disseminated intravascular coagulation, and sudden onset of fetal distress.[23]

Postulated causes are antigenic stimuli or activation of the clotting cascade when amniotic fluid enters the maternal circulation. Physiologically, the hemodynamic changes identified on echocardiogram are the result of acute onset of severe pulmonary hypertension, right ventricular failure with leftward deviation of the septum, and the absence of pulmonary edema. Secondarily, left ventricular filling becomes impaired due to profound right heart failure, eventually resulting in myocardial ischemia.[23]

Death can occur rapidly. Treatment is supportive, and there are no specific interventions currently available. The physician should prevent and/or treat hypoxia, hypotension, and hypoperfusion. Place the woman in the left lateral decubitus position to minimize vena cava compression; give oxygen by nonrebreather mask or endotracheal tube, resuscitate with fluid and blood, and administer pressors to support maternofetal circulation until emergency delivery of the fetus is performed. Obtain emergency obstetric consultation. If the gravid patient cannot be resuscitated, perimortem cesarean delivery within 5 minutes of cardiac arrest increases the chances of neonatal survival.

EMERGENCY CESAREAN SECTION

Perimortem cesarean section or resuscitative hysterotomy is a procedure rarely performed by emergency providers. The decision to deliver a woman while CPR is in progress is daunting. The American Heart Association 2015 guidelines advise that the decision to perform the procedure should be made after 4 minutes of CPR and the delivery should be accomplished by 5 minutes.[24] These guidelines are commonly known as the 4-Minute Rule and the 5-Minute Rule. This is very difficult to accomplish. Even in the scenario of simulation on an obstetric unit with obstetric providers, timing is problematic.[25] Any woman receiving CPR who is ≥20 weeks' pregnant may benefit from delivery, and it is wise to prepare beforehand if possible. To estimate gestational age, keep in mind the uterus will be at the umbilicus at about 20 weeks. Manually displace the uterus to the left to minimize compression of the inferior vena cava.

Ideally there should be an emergency delivery kit in the department. If not, the procedure can be performed with minimal equipment. Required items include skin antiseptic, a scalpel, scissors, suction, Kelly clamps or umbilical cord clamps, and retractors if available. **Time to delivery is critical, so do not move the patient to another location.**[24] Apply the antiseptic solution to the abdomen. Place a drape if available. Make a vertical incision with the scalpel, starting at the xiphoid process and extending to the pubic symphysis. The lengthy incision will allow adequate exposure. The incision should go through the skin, fat, fascia, and peritoneum. Be careful to identify the bladder and retract it.[26] Then carefully incise the uterus with the scalpel, with an incision large enough to accommodate two fingers. In order to protect the fetus from injury, insert two fingers through the initial incision and elevate the uterine wall off the fetus. Use the scissors to divide the uterus between the fingers, and extend the incision in a vertical fashion. Then deliver the fetus (**Figures 101-10** to **101-12**). The mouth and nose should be suctioned if possible. Doubly clamp and cut the cord. If the decision to continue CPR is made, the placenta must be delivered, with gentle traction on the cord. Once the placenta is delivered, the endometrial cavity needs to be swept with a clean, moist

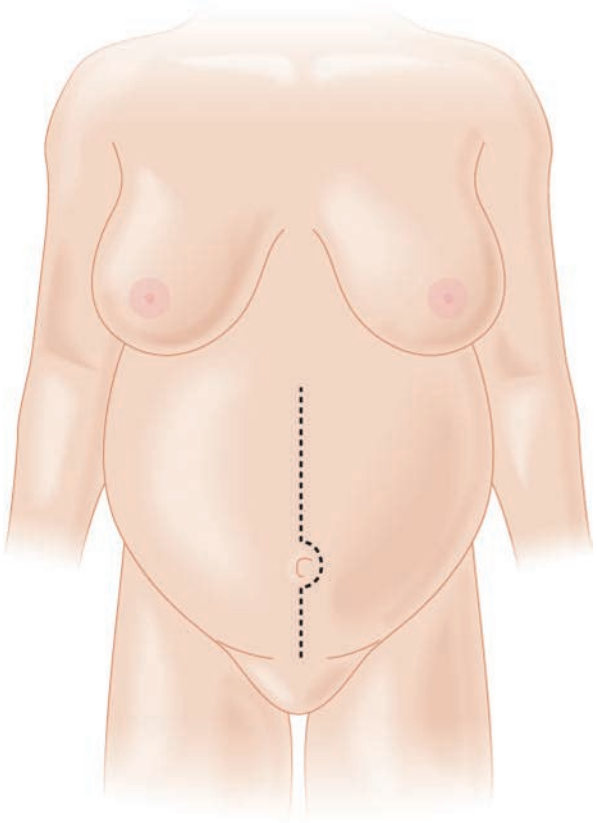

FIGURE 101-10. Midline vertical incision from xiphoid to symphysis pubis. Go through skin, fat, fascia, and peritoneum.

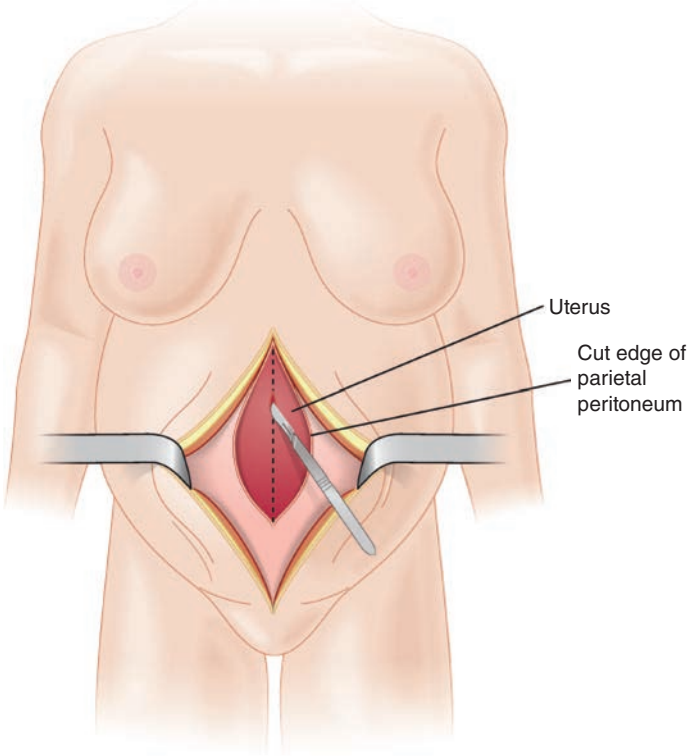

FIGURE 101-11. Uterine midline vertical incision. Make the uterine incision large enough for 2 fingers and elevate the uterine wall off the fetus with your fingers. Then use scissors to divide the uterus between your 2 fingers.

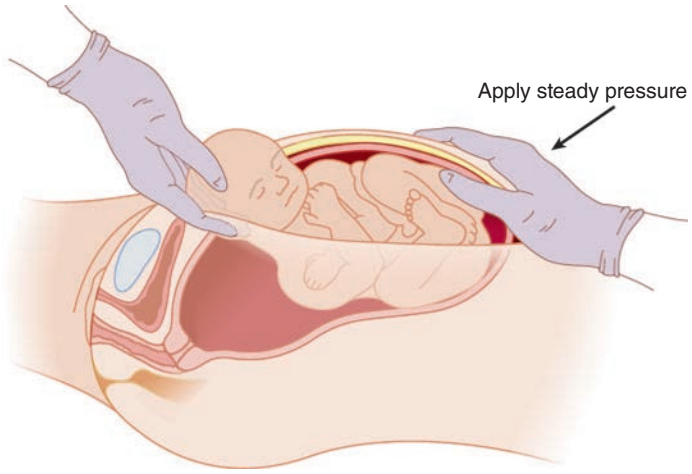

FIGURE 101-12. Delivering the fetus.

lap pad and inspected for any residual membranes. Pitocin should be administered if possible. At this point the provider may decide to pack both the uterus and incision to allow closure by a surgeon in the operating room. However, if there is a need to close the uterus, more equipment is needed. Once the uterine cavity is empty, the uterus can be closed with the 0 or 1–0 delayed absorbable suture in a running fashion. The second layer of the uterine closure is usually closed in a running fashion. In some cases, a third layer may be required. The rest of the incision is closed in mass.[27]

Acknowledgments: The authors gratefully acknowledge the contributions of Michael J. VanRooyen, Jennifer A. Scott, and Kimberly B. Fortner, coauthors of this chapter in the previous editions, and Janet Young for the chapter "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period" in the previous edition.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 102

Vulvovaginitis

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INTRODUCTION

Vulvovaginitis, or vulvovaginal inflammation, results from infectious and noninfectious processes that cause symptoms that include burning, irritation, itching, odor, and abnormal vaginal discharge. The factors associated with acute vaginitis are listed in **Table 102-1**.

The clinical diagnosis may be challenging because more than one disease can be present, signs and symptoms are nonspecific to a single cause, and polymicrobial infection is common. In approximately 30% of women with vaginal complaints, no etiology is determined even after comprehensive testing.[1-3]

Although infectious vaginitis rarely requires hospitalization, it can lead to serious sequelae. Both bacterial vaginosis (BV) and trichomoniasis are associated with premature rupture of membranes, preterm labor, and low infant birth weight.[4,5] *Trichomonas* vaginitis increases the risk of human immunodeficiency virus (HIV) acquisition and transmission

TABLE 102-1 Factors Associated With Acute Vulvovaginitis

- Infections
- Irritant or allergic contact
- Local response to a vaginal foreign body
- Lack of estrogen in perimenopausal and postmenopausal women (atrophic vaginitis)
- Postradiation changes

due to the loss of the protective effect found with normal vaginal lactobacilli and is also associated with pelvic inflammatory disease in patients who are known to be HIV positive.[6,7]

PATHOPHYSIOLOGY

In females of childbearing age, estrogen helps develop a thick vaginal epithelium with a large number of superficial glycogen-containing cells that serves a protective function. Normal flora, such as lactobacilli and acidogenic corynebacteria, use glycogen to form lactic and acetic acids. The resulting acidic environment favors the normal flora, discouraging growth of pathogenic bacteria. Low estrogen levels in postmenopausal women result in atrophy due to loss of the protective glycogen-containing superficial cells and the altered pH environment.

Normal vaginal secretions vary in consistency from thin and watery to thick, white, and opaque. The volume may also vary from a scant to a copious amount. Secretions are odorless and produce no symptoms. Normal vaginal pH varies between 3.8 and 4.5. Alkaline secretions from the cervix before and during menstruation, as well as alkaline semen, reduce acidity and predispose to infection. Before menarche and after menopause, the vaginal pH varies between 6 and 7.

Vulvovaginal inflammation is the most common gynecologic disorder in prepubertal girls and includes both infectious causes (e.g., bacterial, fungal, pinworm) and noninfectious causes (e.g., contact/irritant, lichen sclerosis, foreign body). Factors thought to contribute to vaginitis in prepubertal females include less protective covering of the vestibule by the labia minora, low estrogen concentration resulting in a thinner epithelium, exposure to chemical irritants (e.g., bubble bath), poor hygiene, front-to-back wiping, short distance between the vagina and anus, foreign bodies, chronic medical conditions (e.g., eczema, seborrhea), and sexual abuse. Infectious causes include respiratory and enteric bacterial organisms such as *Haemophilus influenzae*, *Staphylococcus aureus*, group A *Streptococcus*, *S. pneumoniae*, *Escherichia coli*, *Shigella flexneri*, *Neisseria gonorrhoeae*, and *Chlamydia*, as well as *Candida* and pinworms. Infectious causes may be more common in adolescents, especially those who are sexually active.[3]

CLINICAL FEATURES AND DIAGNOSIS

The most common infectious causes of vaginitis in symptomatic premenopausal women are BV, vulvovaginal candidiasis, and *Trichomonas* vaginitis. Candidiasis, contact vaginitis, and atrophic vaginitis may occur in virgins and postmenopausal women.

Obtain a detailed gynecologic history. History should include details of vaginal discharge, odor, irritation, itching, burning, bleeding, dysuria, and dyspareunia. Inquire about associated abdominal pain, new sexual partners, use of barrier protection during intercourse, relationship of symptoms to menses, recent use of antibiotics, hygiene practices, and use of over-the-counter and homeopathic treatments (e.g., douching, boric acid, intravaginal yogurt and probiotics, apple cider vinegar).

Perform a pelvic examination. Note the presence of vulvar edema or erythema, vaginal discharge, cervical inflammation, abdominal tenderness, and cervical motion tenderness. External vulvar inflammation and minimal discharge suggest the possibility of mechanical, chemical, allergic, or other noninfectious causes of vulvovaginitis. During speculum examination, obtain a swab of the discharge. **All sexually active women should be tested for gonorrhea and chlamydial infection.** If a patient refuses pelvic examination or it is not feasible, the patient may submit a self-swab of vaginal secretions and in some cases a urine sample, as self-administered vaginal swabs are accurate screening tests for sexually transmitted infections.[8-11] The Centers for Disease Control and Prevention also recommends HIV and syphilis testing for women engaged in high-risk sexual behavior (i.e., new or multiple sexual partners, unprotected intercourse). Finally, women of childbearing age should have a pregnancy test because pregnancy impacts treatment.

TABLE 102-2 Diagnosis of Vaginitis Based on Vaginal Secretions

Test	Finding	Diagnosis
pH	4.0–4.5	Normal
	4.0–4.5	Candidiasis
	>4.5	Bacterial vaginosis
	>4.5	Trichomoniasis
Microscopy of specimen prepared with normal saline solution	Clue cells	Bacterial vaginosis
	Motile trichomonads	Trichomoniasis
	Pseudohyphae and/or buds	Candidiasis
Whiff test of swab specimen prepared with potassium hydroxide	Fishy odor	Bacterial vaginosis
Microscopy of specimen prepared with potassium hydroxide	Pseudohyphae and/or buds	Candidiasis

Microscopic evaluation of fresh vaginal secretions using both normal saline solution and 10% potassium hydroxide (KOH) slide preparations, the KOH whiff test, and pH testing may help establish a specific diagnosis[12] (**Tables 102–2** and **102–3**).

Microscopic examination is time consuming and tedious. Results depend on operator skill, and although hospitals have laboratories, not all EDs have microscopes and appropriate reagents. Secretions from the mid-sidewall of the vagina are mixed with one to two drops of 0.9% normal saline in a test tube. A slide with a coverslip is prepared for microscopic evaluation. Microscopy should be performed immediately following sample collection as trichomonads lose motility quickly. Additionally, a drop of 10% KOH is added to the test tube and assessed for a fishy (amine) smell. KOH can also aid in the visualization of yeast.

To test the pH, obtain a sample from the mid-portion of the vaginal sidewall to avoid false elevations in pH caused by mucus. **Sampling from the posterior fornix may yield inaccurate results because cervical mucus, blood, semen, douche products, and vaginal medications can elevate the pH.** Apply a small amount of the secretions directly onto pH paper to determine the pH.

BACTERIAL VAGINOSIS

BV is the most common cause of vaginitis in acutely symptomatic women. However, up to 50% of women who meet criteria for this diagnosis are asymptomatic.

BV is usually a polymicrobial infection that occurs when the normal hydrogen peroxide–producing lactobacilli are replaced by other species, including *Gardnerella vaginalis, Ureaplasma, Mycoplasma*, *Mobiluncus*, *Prevotella*, and various other anaerobes. However, research exists suggesting that BV is not a true infection, but rather a bacterial imbalance.[13] Risk factors include multiple sexual partners (female or male), intercourse with an uncircumcised male partner, vaginal intercourse immediately after receptive anal intercourse, lack of condom use, douching, and absence of peroxide-producing

TABLE 102-3 Vaginitis Signs and Symptoms

Causative Organism	Sign or Symptom
Candida	Thick, curdy discharge Itching
Gardnerella or other bacteria	Fishy odor Whitish-gray, thin discharge
Trichomonas	Frothy, odorous discharge Vaginal erythema or edema

lactobacilli in the vaginal flora.[14,15] Women who have never been sexually active are less commonly affected. BV is not caused by the transmission of a single sexually transmitted pathogen; however, it is generally agreed that sexual activity plays a role in transmission and may promote infection.[16]

BV has been associated with several adverse health outcomes, including increased risk of coinfection with sexually transmitted infections such as HIV, herpes simplex virus (HSV) type 2, *Chlamydia trachomatis*, and *N. gonorrhoeae* by decreasing local secretory leukocyte protease inhibitor levels.[17] BV is also linked to complications related to pregnancy and gynecologic surgical procedures, such as spontaneous abortion, premature rupture of membranes, amniotic fluid infection, chorioamnionitis, preterm delivery, postpartum endometritis, pelvic inflammatory disease, postoperative wound infection, and infection after vaginal and abdominal hysterectomy.[18]

DIAGNOSIS

The most common clinical presentation is malodorous, vaginal discharge. Classically, it is described as a thin, whitish-gray discharge associated with increased volume and a fishy smell. The absence of discharge or the presence of only a mild discharge makes the diagnosis less likely. Introital and vaginal irritation are uncommon.

The diagnosis is based on history, pelvic examination, microscopic evaluation of vaginal secretions, and point-of-care testing.

The presence of three of the following four criteria supports the diagnosis and correlates with a positive Gram stain (the gold standard for diagnosing BV)[19]:

1. A thin, homogeneous vaginal discharge
2. More than 20% clue cells on a wet mount (**Figure 102-1**)
3. Positive results on test for amine release or whiff test
4. A vaginal pH level >4.5

The diagnostic criterion with the highest sensitivity is vaginal pH, whereas that with the highest specificity is a positive amine odor. If vaginal pH is >4.5 and there is an amine odor, then the diagnosis of BV can be made with confidence.[20] Commercially available DNA probe–based and vaginal fluid sialidase activity–based tests perform similar to Gram stain.[14] Diagnostic cards that detect an elevated pH and trimethylamine are available, but have a low sensitivity and specificity and thus are not recommended. Cultures are not beneficial because *Gardnerella* is part of the normal vaginal flora.



FIGURE 102-1. Bacterial vaginosis. Saline wet mount with clue cells (*arrow*). [Reproduced with permission from DeCherney AH, Nathan L, Laufer N, Roman AS (eds): *Current Diagnosis & Treatment: Obstetrics & Gynecology,* 11th ed. New York, NY: McGraw-Hill, Inc.; 2013. Fig. 39-9.]

TABLE 102-4 Treatment Regimens for Bacterial Vaginosis

Agent	Dosage
Recommended Regimens	
Metronidazole	500 milligrams PO BID for 7 d
Clindamycin cream 2%	One full applicator intravaginally (5 g) QHS for 7 d
Metronidazole gel 0.75%	One full applicator intravaginally (5 g) QHS for 5 d
Alternative Regimens	
Clindamycin	300 milligrams PO BID for 7 d
Clindamycin ovules	100 milligrams intravaginally QHS for 3 d
Tinidazole	2 grams PO daily for 2 d
Tinidazole	1 gram PO daily for 5 d

Abbreviations: BID = twice a day; QHS = every night at bedtime.

TREATMENT

Treatment is recommended for all symptomatic women and can be considered in asymptomatic women. Beyond symptom control, the benefit of treatment includes reducing the risk of acquiring *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, HIV, and HSV-2.

Recommended treatment regimens are listed in **Table 102-4**. Counsel patients receiving nitroimidazoles against consuming alcoholic beverages during the treatment period and for 24 hours (for metronidazole) and 72 hours (for tinidazole) after the last dose to avoid a disulfiram-like reaction. Advise all patients to refrain from intercourse or to use condoms during treatment. Clindamycin cream and ovules may weaken diaphragms and condoms. Advise patients to use alternative contraceptives or abstain during and for 5 days after treatment.

Symptomatic pregnant women should be treated with the same medications as nonpregnant women (Table 102-4)**.** Asymptomatic low-risk pregnant women should not be screened for BV. Although BV is correlated with poor pregnancy outcomes, studies have not demonstrated that treatment prevents adverse outcomes.[14,21-23]

Overall cure rates 4 weeks after treatment do not differ significantly between a 7-day regimen of oral metronidazole, metronidazole vaginal gel, or clindamycin vaginal cream. Metronidazole vaginal gel has fewer side effects (e.g., GI disturbance and unpleasant taste), but should not be used in women who are allergic to the oral preparation.

Recurrence is common, and some pathogens are developing resistance to standard therapies. Consider suppressive therapy in women with multiple recurrences. The use of *Lactobacillus* intravaginal suppositories and probiotics to restore the normal vaginal flora is an alternative, especially for recurrent BV. Treatment of male sexual partners has not been shown to prevent recurrence.

CANDIDA VAGINITIS

***Candida* species are the second most common cause of infectious vaginitis.**[24] *Candida* is isolated in up to 20% of asymptomatic, healthy women of childbearing age, some of whom are celibate. Incidence decreases after menopause unless using estrogen replacement, which further emphasizes the hormonal dependence of the infection. Women can remain entirely asymptomatic despite being heavily colonized with *Candida* species. *C. albicans* strains account for 85% to 92% of *Candida* organisms isolated from the vagina. *Candida glabrata* and *Candida tropicalis* are the most common non-*albicans* strains and are often more resistant to conventional therapy.

Candidal vaginitis can be classified as an uncomplicated or complicated infection. Uncomplicated infections are sporadic with mild to moderate symptoms, are due to *C. albicans*, and occur in the nonpregnant, immunocompetent host. Complicated infections are recurrent (four or more infections per year), produce severe symptoms or findings, result from suspected or proven non-*albicans Candida* species, or occur in an abnormal host (e.g., women who have uncontrolled diabetes, debilitation, or immunosuppression, or are pregnant).[14,25]

Candidal organisms gain access to the vaginal lumen predominantly from the adjacent perianal area. The growth of *Candida* is limited by

the normal vaginal flora, and symptoms of vaginitis usually occur only when the normal balance is upset. Increased *Candida* colonization resulting in subsequent symptomatic infection may be caused by conditions that (1) inhibit the growth of normal vaginal flora, particularly *Lactobacillus* species (e.g., systemic antibiotics); (2) diminish the glycogen stores in vaginal epithelial cells (e.g., diabetes mellitus, pregnancy, oral contraceptive use, hormonal replacement therapy); or (3) increase the pH of vaginal secretions (e.g., menstrual blood or semen).

Vaginal candidiasis is not considered a sexually transmitted infection, although it may be transmitted by sexual intercourse. The wearing of tight-fitting, synthetic undergarments may also contribute because of increased temperature. Although all of these factors are thought to be associated with symptomatic disease, no causation has been proven.[24]

DIAGNOSIS

Clinical symptoms include discharge, vaginal pruritus, external dysuria, and dyspareunia. **Vaginal pruritus is the most common and specific symptom.** The discharge varies from none to watery to homogeneously thick and "cottage cheese–like."

Symptoms vary in severity. An exacerbation frequently presents in the week prior to menses or following coitus, perhaps because each causes the pH to become more alkaline. Odor is unusual and, if present, favors a diagnosis of BV rather than vulvovaginal candidiasis.

Pelvic examination often reveals vulvar erythema and edema, vaginal erythema, and a whitish discharge that adheres to the vaginal walls.

The diagnosis is confirmed with a normal vaginal pH (4.0 to 4.5) and visualization of budding yeast and pseudohyphae on slide preparation of vaginal secretions (**Figure 102-2**). The sensitivity of microscopic examination using a sample prepared with normal saline is only 40% to 60%. Adding two drops of 10% KOH to the vaginal secretions dissolves the epithelial cells while leaving yeast buds and pseudohyphae intact and increases the sensitivity to 80% and specificity to nearly 100%.

TREATMENT

Recommended treatment regimens are listed in **Table 102-5**. Topically applied azole drugs are more effective than nystatin, with relief of symptoms in 80% to 90% of patients who complete treatment. Consider patient preference because creams, lotions, sprays, vaginal tablets, suppositories, and coated tampons are all equally efficacious.[26]

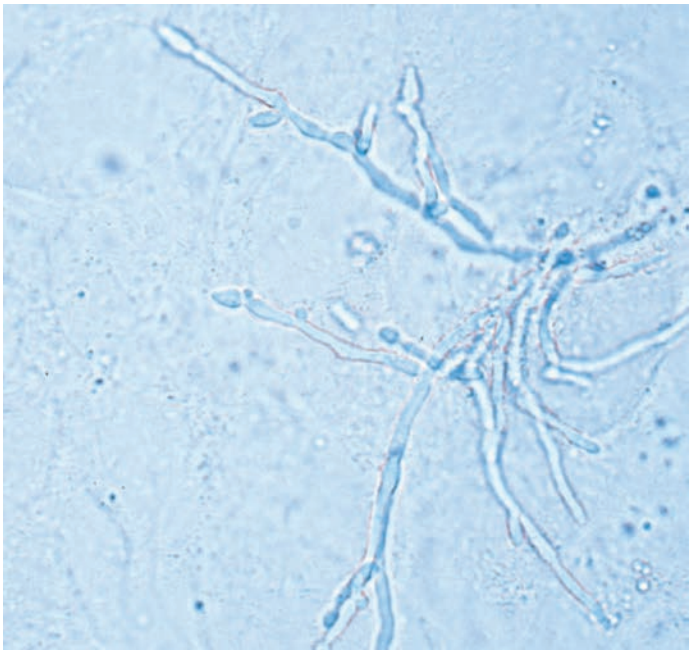

FIGURE 102-2. Hyphae of *Candida albicans,* potassium hydroxide wet mount. [Reproduced with permission from Knoop et al: *The Atlas of Emergency Medicine,* 3rd ed. © 2010 McGraw-Hill, Inc. Fig. 25–16. Photo contributor: H. Hunter Handsfield: *Atlas of Sexually Transmitted Diseases*. New York, NY: McGraw-Hill, Inc., 1992.]

TABLE 102-5 Treatment Regimens for Uncomplicated Vulvovaginal Candidiasis*

Agent	Formulation	Dosage
Butoconazole†	2% cream	1 applicator intravaginally QHS × 3 d
Clotrimazole	1% cream	1 applicator intravaginally QHS × 7 d
	2% cream	1 applicator intravaginally QHS × 3 d
Miconazole	2% cream	1 applicator intravaginally QHS × 7 d
	4% cream	1 applicator intravaginally QHS × 3 d
Nystatin	100,000-unit vaginal tablet	1 vaginal tablet QHS × 14 d
Terconazole	0.4% cream	1 applicator intravaginally QHS × 7 d
	0.8% cream	1 applicator intravaginally QHS × 3 d
	80-milligram suppository	1 suppository intravaginally QHS × 3 d
Tioconazole	6.5% ointment	1 applicator intravaginally QHS × 1 dose
Fluconazole†	150-milligram oral tablet	1 tablet PO × 1 dose

Abbreviation: QHS = every night at bedtime.

*Not all possible regimens listed.

†Not recommended in pregnancy.

Pregnant women should be treated with topical azoles for 7 days. Oral fluconazole is a category C medication and thus should be avoided in pregnancy.

The azole drugs are all available over the counter in treatment regimens of 1, 3, or 7 days. Uncomplicated disease responds to all azoles, including single-dose therapy.[27] Other than initial burning and irritation, side effects of topical agents are unusual. **Single-dose treatment with oral fluconazole is as effective as topical therapy in the treatment of uncomplicated disease**. Patient preference should be considered, because oral therapy is often more convenient. Oral treatment occasionally causes GI symptoms, headache, and rash.[28] Oral azoles interact with a variety of other medications. Sexual partners should not be treated unless they are also symptomatic.

Self-medication is occasionally advised in women with recurrence of previously diagnosed disease, although accuracy of self-diagnosis is poor.[4,29] Women who fail to respond to over-the-counter therapy or have recurrence within 2 months should be evaluated by a physician.

Complicated Vulvovaginal Candidiasis Vaginal and microscopic examinations should be performed if symptoms persist or recur within 2 months, and precipitating factors, such as high blood glucose levels, should be controlled. However, most women with recurrences do not have obvious precipitating causes. Vaginal cultures should be obtained to confirm a clinical diagnosis and identify any unusual species, such as *C. glabrata*, as azoles are ineffective in treating vaginitis caused by *C. glabrata.*

The treatment of **severe or recurrent vulvovaginal candidiasis** requires a longer duration of therapy. Consider treating with a topical azole for 7 to 14 days. More resistant cases may require fluconazole, 150 milligrams orally on days 1, 4, and 7 for a total of three doses.[14,28,29] Very severe cases may require long-term suppression and gynecologic referral.[14]

TRICHOMONAS VAGINITIS

Trichomoniasis, a parasitic infection with the single-celled protozoan *T. vaginalis*, a flagellated organism, **is a sexually transmitted infection.** Both men and women can be infected.

Infection can produce local inflammation when the organism attaches to the vaginal mucosa. Clinically symptomatic women present with vaginal discharge, pruritus, and irritation. Classically, the discharge is frothy, greenish in color, and malodorous. On speculum examination, the cervix may be inflamed and small punctate hemorrhages may be seen ("strawberry cervix"). Symptoms generally develop within 5 to 28 days of exposure; however, untreated infections can last for months to years and produce symptoms at any time.[30] Many infections are asymptomatic.

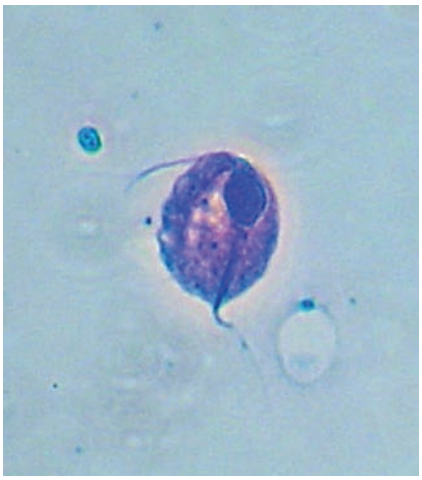

FIGURE 102-3. Trichomonad. [Reprinted with permission of Piotr Rotkiewicz.]

DIAGNOSIS

Clinical diagnosis of *Trichomonas* vaginitis traditionally relies on microscopic examination of the vaginal secretions and visualization of motile trichomonads (**Figure 102-3**). Culture of vaginal secretions is 95% sensitive and has long been considered the gold standard in diagnosis. However, results may not be available for 2 to 5 days. Several newer testing options, such as nucleic acid amplification tests, have been approved by the Food and Drug Administration for the detection of *T. vaginalis* in endocervical, vaginal, and urine specimens. These newer tests provide rapid results and are highly sensitive and specific.[14,31,32]

TREATMENT

Treatment regimens for acute *Trichomonas* vaginitis are listed in **Table 102-6**. The nitroimidazoles, metronidazole, and tinidazole are the only medications effective in treating trichomoniasis. Metronidazole gel is not recommended. Single-dose treatment is preferable because of lower cost, fewer side effects, and greater patient adherence to the regimen. Sexual partners should be treated simultaneously. Counsel patients to abstain from sexual intercourse until (1) therapy has been completed; (2) both the patient and partner(s) have been treated; and (3) all are asymptomatic. Patients receiving nitroimidazoles should be advised to avoid consuming alcoholic beverages during the treatment period and for 24 hours (metronidazole) and 72 hours (tinidazole) after the last dose to avoid a disulfiram-like reaction.

TRICHOMONIASIS COMPLICATIONS

The spread of *T. vaginalis* infection is common because many of those infected are asymptomatic. Reinfection is common and can be difficult to differentiate from treatment failure. If treatment failure is suspected, consider treating those who have failed the single-dose 2-gram metronidazole regimen with a 7-day course because resistance is quantitative, not qualitative. The Centers for Disease Control and Prevention has a hotline to provide assistance for suspected cases of nitroimidazole resistance (telephone 414-718-4141).[14]

T. vaginalis infection is associated with several adverse health outcomes, including preterm birth, delivery of low-birth-weight infants, pelvic inflammatory disease, and increased transmission of several other infections, including HIV, HSV-2, and human papillomavirus infection. Not only does *Trichomonas* infection increase the likelihood of HIV acquisition, but it also promotes transmission and viral shedding.[33,34]

TABLE 102-6 Treatment Regimens for Trichomoniasis

Agent	Dosage
Recommended regimens	
Metronidazole	2 grams PO in a single dose
Tinidazole	2 grams PO in a single dose
Alternative regimen for treatment failures	
Metronidazole	500 milligrams PO twice a day for 7 d

SPECIAL POPULATIONS

HIV-positive individuals are more likely to become infected with *T. vaginalis* and have higher complication rates. HIV-positive patients should be treated with the 7-day metronidazole regimen.[14]

Due to the potential adverse pregnancy outcomes, pregnant women should receive treatment with oral metronidazole. Women can be safely treated with single-dose metronidazole therapy at any stage of pregnancy. Breastfeeding mothers should consider withholding nursing during treatment with metronidazole and for 12 to 24 hours after the last dose. Tinidazole safety in pregnancy is not well studied and should be avoided. If treated with tinidazole, patients should withhold breastfeeding for 3 days after the last dose.

HERPES SIMPLEX VIRUS INFECTION

Genital herpes is a lifelong viral infection caused by HSV-1 or HSV-2. HSV-2 more commonly causes genital lesions and is associated with higher recurrence rates. The majority of infected individuals are asymptomatic and unknowingly expose their sexual partners. Prevalence increases with age, and women are more commonly infected.[35] Genital herpes may present as either a primary or recurrent infection. Classically, the lesions are found on the perineum, labia, urethral meatus, and introitus and are characterized by groups of painful, erythematous vesicles that quickly ulcerate (**Figure 102-4**). Primary infections are more severe and often associated with systemic symptoms (e.g., headache, fever, malaise, reginal lymphadenopathy, myalgias). Dysuria is common, and HSV can mimic symptoms of a urinary tract infection. Recurrent HSV infections result from reactivation of the dormant virus from the dorsal root ganglion following a stressor (e.g., acute illness, immunosuppression, psychological stress). Recurrent infections tend to be less severe but are often preceded by a prodromal period of itching, burning, or tingling before the lesions appear. Over time, recurrences tend to become less frequent.

HSV-2–seropositive individuals are at increased risk of acquiring HIV infection. Extragenital complications include meningoencephalitis, pneumonitis, hepatitis, and disseminated disease. Neonatal HSV infection can result from spread of the infection from an HSV-positive pregnant mother to her child during delivery and is associated with significant morbidity and mortality.

DIAGNOSIS AND TREATMENT

When active lesions are present, polymerase chain reaction swabs are both sensitive and specific; viral culture is less sensitive. Type-specific serologic testing is available as both laboratory and point-of-care tests. A positive HSV-2 test implies an anogenital infection, whereas a positive HSV-1 test is difficult to interpret. Routine screening in the general population is not recommended.

Although oral antiviral therapy does not eradicate the virus, it can help provide symptom relief and shorten the outbreak. Topical antivirals are not effective. Patients should be counseled regarding the possibility of future outbreaks, safe sex practices to reduce the risk of sexual transmission, and consequences of perinatal transmission. Treatment regimens for primary HSV infections, recurrent HSV infections, and daily suppressive therapy are shown in **Table 102-7**. If the patient remains symptomatic after 10 days of therapy, then treatment should be extended. Daily suppressive therapy may reduce viral shedding and decrease, but not eliminate, the likelihood of transmission to sexual partners. Patients with severe disease or complications may require admission and treatment with intravenous acyclovir.

Sexual partners should be advised to seek evaluation, and if asymptomatic, they may benefit from type-specific testing. If a sexual partner's HSV status is unknown or discordant, sexual contact should be avoided during outbreaks with strict condom use between outbreaks.

Immunocompromised patients, such as those with HIV infection, may have more severe symptoms or prolonged outbreaks. Additionally, HSV shedding is increased in HIV-positive patients. Patients with HIV

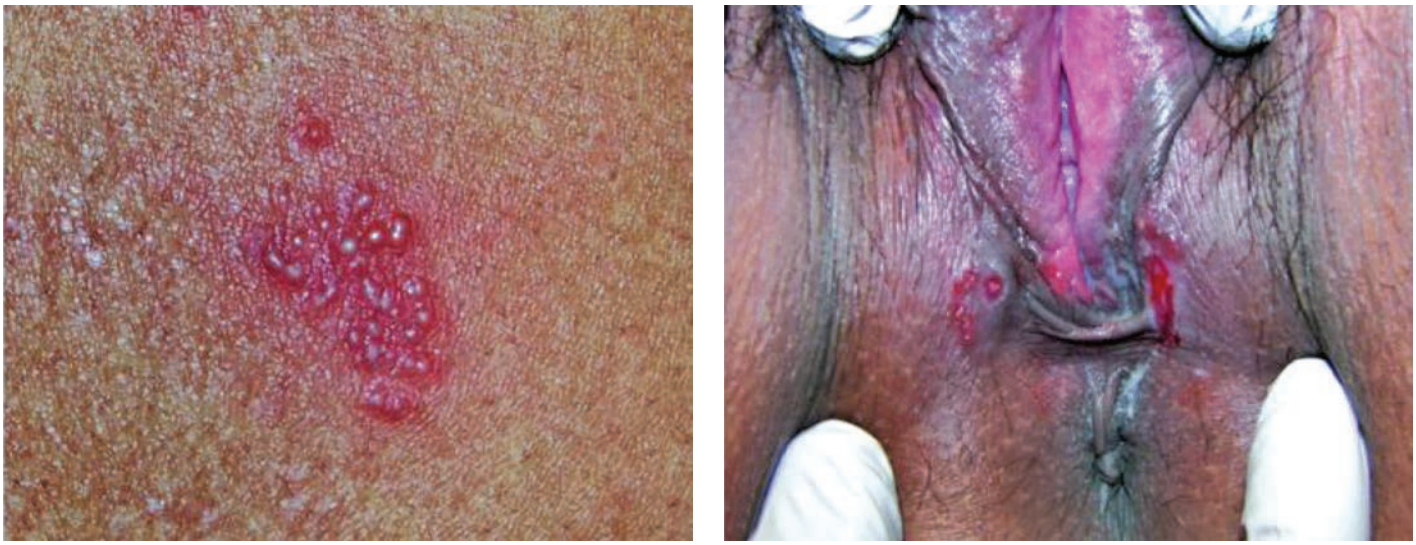

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FIGURE 102-4. Herpes lesions. [Used with permission from Dr. William Griffith.]

often require higher doses and longer durations of therapy in order to achieve symptomatic relief.

CONTACT VULVOVAGINITIS

Contact dermatitis results from the exposure of the vulvar epithelium and vaginal mucosa to a primary chemical irritant or allergen. Irritant dermatitis is more common than allergic dermatitis.[36] Common irritants or allergens include chemically scented douches, soaps, bubble baths, and deodorants; perfumes, dyes, and scents in toilet paper, tampons, pads, and feminine hygiene products; topical vaginal antibiotics; laundry detergents, dryer sheets, and fabric softeners; and tight slacks, pantyhose, and synthetic underwear. Benzocaine, used by women to control vulvar discomfort, can also cause a particularly severe contact dermatitis.

TABLE 102-7 Treatment Regimens for Genital HSV Infections

Antiviral Agent Choices	Dose
Primary Outbreak	
Acyclovir	400 milligrams PO three times a day × 7–10 d *or* 200 milligrams PO five times daily × 7–10 d
Valacyclovir	1 gram PO two times daily × 7–10 d
Famciclovir	250 milligrams PO three times daily × 7–10 d
Episodic Therapy for Recurrent Outbreaks	
Antiviral Agent Choices	**Dose**
Acyclovir	400 milligrams PO three times a day × 5 d *or* 800 milligrams PO three times a day × 2 d
Valacyclovir	500 milligrams PO two times a day × 3 d *or* 1 gram PO once a day for 5 days
Famciclovir	1 gram PO two times a day × 1 d
Suppressive Therapy for Recurrent Outbreaks	
Antiviral Agent Choices	**Dose**
Acyclovir	400 milligrams PO twice a day
Valacyclovir	500 milligrams PO once a day (may be as effective as 1000)
Famciclovir	250 milligrams PO twice a day

Abbreviations: BID = twice a day; QD = once a day; TID = three times a day.

Diagnosis may be difficult due to variation in symptom severity and preexisting conditions. Clinically, patients report localized swelling, itching, or a burning sensation. Physical findings range from local erythema and edema to excoriation, ulceration, and secondary infection. Local vesiculation and ulceration are more common with primary irritants used in strong concentrations, but herpes infection must also be considered. Vaginal pH changes may promote colonization and infection with *C. albicans* that can obscure the primary cause.

Diagnosis of contact vulvovaginitis is made by ruling out an infectious cause and identifying the offending agent. Most cases of mild vulvovaginal contact dermatitis resolve spontaneously when the causative agent is withdrawn. Cool sitz baths and application of wet compresses of dilute boric acid or Burow's solution may afford relief for patients with severe painful reactions. A few days of therapy with topical corticosteroids, such as hydrocortisone acetate (0.5% to 2.5%), fluocinolone acetonide (0.01% to 0.2%), or triamcinolone acetonide (0.025%), applied two or three times daily, provide symptomatic relief and promote healing. If a true allergic reaction is present, then oral antihistamines may be helpful. Superinfection with *C. albicans* should be treated as previously described in the section on *Candida* vaginitis.

ATROPHIC VAGINITIS

Vaginal atrophy, present in 60% of women 4 years after menopause, can result in atrophic vaginitis.[37] Decreased ovarian steroid production in menopausal women leads to profound changes in the vulva, vagina, cervix, urethra, and bladder. The vagina loses its normal rugae with the mucosa becoming attenuated, pale, and almost transparent as a result of decreased vascularity. The cellular glycogen content decreases, resulting in atrophy of the epithelium and loss of elasticity. The vaginal pH ranges from 5.5 to 7.0. The upper one third of the vagina constricts, shortening the length of the vagina. The mucosa is only three or four cells thick and is less resistant to minor trauma and infection. The cervix atrophies and retracts and may become flush with the apex of the vault.

Symptoms include vaginal dryness, soreness, itching, dyspareunia, and occasional spotting or discharge. Discharge is thin, scant, and yellowish or pink. The vaginal epithelium appears thin, inflamed, and even ulcerated.

A clinical vaginal infection with copious purulent discharge may develop due to increased vaginal pH, which permits growth of nonacidophilic coliform organisms and the disappearance of *Lactobacillus* species. *Candida* and *Trichomonas* infections are rare in the postmenopausal woman unless estrogenic replacement therapy is used.

Wet preparations demonstrate erythrocytes, increased polymorphonuclear neutrophils, and small, round epithelial cells, which are

immature squamous cells that have not been exposed to sufficient estrogen.

Treatment of atrophic vaginitis consists primarily of topical vaginal estrogen. Creams, pessaries, tablets, and the estradiol vaginal ring are all effective in treating the symptoms.[37] Side effects of treatment may include uterine bleeding, breast pain, perineal pain, and endometrial hyperstimulation. Estrogen should not be prescribed to patients with a history of cancer of any of the reproductive organs. Atrophic vaginitis is uncommon in patients taking systemic estrogen replacement therapy.

Women should be referred to their primary care provider for treatment and follow-up to monitor therapy, because all formulations of estrogen, even at low dosages, show systemic absorption and have potentially harmful side effects.[38] In addition, any patient with postmenopausal bleeding, either by history or physical examination, should be referred to a gynecologist to rule out carcinoma.

BARTHOLIN GLAND CYST AND ABSCESS

Bartholin glands are located in the labia minora. The ducts of the glands drain into the posterior vestibule at the 4 o'clock and 8 o'clock positions. Normally the glands are pea sized. The glands begin to function at puberty to provide moisture to the vestibule and involute as women age. Obstruction of the duct may result in a cyst or abscess. A cyst does not need to be present before an abscess can develop. Abscesses may become quite large and cause extreme pain. *E. coli* is the most common bacterial isolate, but many abscesses are polymicrobial.[39] Less common organisms include *N. gonorrhoeae* and *C. trachomatis*.

DIAGNOSIS AND TREATMENT

Bartholin gland abscess is characterized as a mass in the posterior introitus near the 4 o'clock or 8 o'clock positions that has developed over several days. If preceded by a cyst, the abscess may develop over a longer period of time. Pain, induration, and fluctuance are usually present. Systemic symptoms (e.g., fever and chills) are rarely present.

Incision and drainage is usually necessary but should not be performed until the abscess is a well-defined, walled-off structure. An ultrasound of the area can confirm the presence of a discrete fluid collection. If the abscess is not clearly defined, prescribe broad-spectrum antibiotics and analgesics and advise warm sitz baths and short-term follow-up. Most patients present with an exquisitely tender, hyperemic, fluctuant mass that needs drainage by the emergency physician. Care should be taken to distinguish a Bartholin's abscess from an abscess of the labia majora, which requires gynecologic consultation.

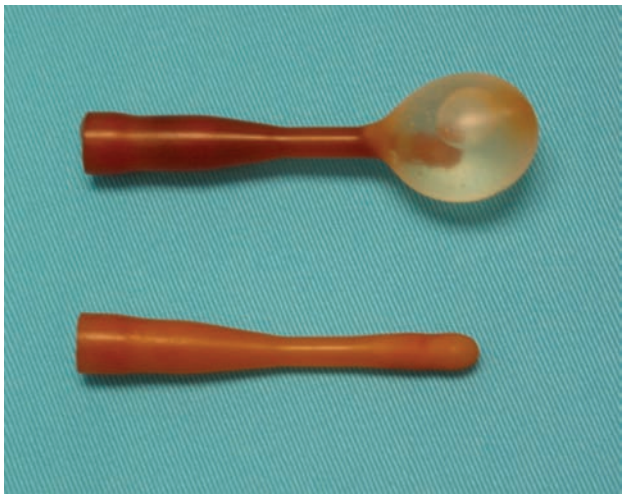

FIGURE 102-5. Word catheter. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures,* 2nd ed. New York, NY: McGraw-Hill, Inc., 2013. Figure 138-2, p. 932.]

Consider providing parenteral analgesia and even conscious sedation or low-dose ketamine in order to facilitate incision and drainage. To drain the abscess, first provide analgesia with a local injection of 2 to 4 mL of 1% lidocaine. Make a stab incision with a #11 scalpel on the mucosal surface of the vestibule, just lateral to the hymenal ring in the region of the Bartholin gland, where the abscess cavity is closest to the mucosal surface and has the greatest fluctuance. Extend the stab incision only for a few millimeters; an incision that is too large will result in displacement of the Word catheter. A Word catheter (**Figure 102-5**) is the size of a #10 Foley catheter with a 1-in. (2.5-cm) stem and an inflatable balloon. Once fully drained, insert a Word catheter into the incision site and inflate the balloon with 2 to 4 mL of water. Tuck the end of the catheter into the vagina. The catheter should remain in place for 4 to 6 weeks to avoid recurrence.[40] Case reports describe using plastic tubing (**Figure 102-6**) when a Word catheter is not available.[41] There are many different treatment techniques, none of which have been found to be superior.[42] Prescribe analgesics and broad-spectrum antibiotics and give instructions for follow-up care. If *N. gonorrhoeae* and *C. trachomatis* infection are possible, direct antibiotic coverage accordingly (Table 102-2). Patients with recurrent abscess may require definitive surgical care and should be provided with specialty referral.

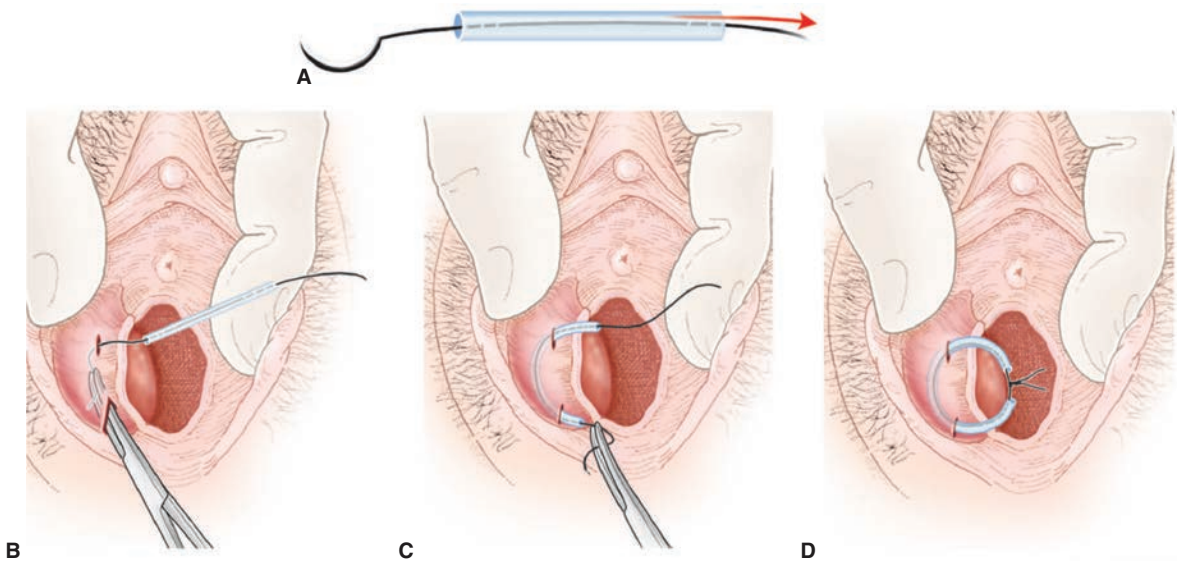

FIGURE 102-6. **A.** Obtain 7 cm of narrow tubing, and insert silk suture through tubing. **B.** After drainage, make a second stab incision into the abscess cavity and insert the threaded tubing. **C.** Use a hemostat to grasp the threaded tubing through both stab sites. **D.** Suture the threads so they are secure. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures,* 2nd ed. New York, NY: McGraw-Hill, Inc., 2013. Figure 138–5, Parts A, E, F, G, p. 934.]

TABLE 102-8 Treatment Regimens for Pinworms

Agent and Dosage	Comments
Mebendazole 100 milligrams PO × 1 Repeated in 2 wk	Teratogenic potential, only if benefits outweigh risk in pregnancy
Albendazole 400 milligrams PO × 1 Repeated in 2 wk	Contraindicated in pregnancy and 1 month prior to conception
Pyrantel pamoate 11 milligrams/kg PO × 1 (maximum single dose = 1 gram) Repeat dose every 2 wk × 2 (total 3 doses)	Available without prescription, no human data on safety

VAGINAL FOREIGN BODIES

Consider a vaginal foreign body in patients with chronic vaginal discharge. Potential objects include tampons and toilet tissue, devices used for sexual stimulation, packets of illegal drugs, and various other objects.

Premenarchal children presenting with vaginal discharge, especially if bloody or brown, should be evaluated for a vaginal foreign body. The discharge associated with a foreign body occurs daily and is often malodorous.[3] Potential foreign bodies include small pieces of toilet paper or cloth and small toys or objects.

Vaginal irrigation with 0.9% normal saline can be attempted to visualize and remove a foreign body in cooperative children >7 years of age. Vaginoscopy under anesthesia in the operating room may be necessary for younger children. The use of imaging modalities is limited by the composition of the foreign body. Radiolucent foreign bodies are not seen on plain radiographs and may not be detected by pelvic ultrasound. MRI may aid in the localization of nonmetallic objects but is not always available and is not necessarily conclusive. Treatment is removal.

PINWORMS

Patients with pinworms (*Enterobius vermicularis*) complain of anal or vaginal pruritus, which is more intense at night (when the gravid female pinworms pass out from the intestinal tract to lay eggs on the perineal skin). The worms may migrate from the anus to the vagina in children.

The diagnosis is made by visualization of 1-cm-long, thin, white worms exiting the anus. Alternately, a sample can be obtained on cellophane tape and used for identification of ova, which are large and double-walled in appearance, on microscopy.

Treat the child and all family members and household contacts with an antiparasitic agent (**Table 102-8**). Treatments are repeated because mature worms are more vulnerable to treatment than young worms.[3]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com

CHAPTER 103

Pelvic Inflammatory Disease

Brian Weiss
Suzanne M. Shepherd

INTRODUCTION AND EPIDEMIOLOGY

The term pelvic inflammatory disease (PID) comprises a spectrum of infections of the female upper reproductive tract. Although accurate estimates of the incidence and prevalence of PID in the United States are lacking due to lack of mandatory reporting and reliance on testing data, it is a common and serious disease initiated by ascending infection from the vagina and cervix. PID includes salpingitis, endometritis, myometritis, parametritis, oophoritis, and tubo-ovarian abscess and may extend to produce peri-appendicitis, pelvic peritonitis, and perihepatitis (Fitz-Hugh–Curtis syndrome). PID is the most common serious infection in sexually active women age 16 to 25 years.[1] In 2001, ambulatory data estimated that more than 750,000 cases of PID occurred in the United States.[2] The percentage of ED visits resulting in a diagnosis of PID decreased during 2006 to 2018 among females age 15 to 44 years (28.1% overall reduction, –4.3% annual change). Patients with less access to health care, including those without insurance or with public health insurance and those with lower median incomes, were the most likely to visit EDs.[3]

Long-term sequelae, including tubal factor infertility, implantation failure after in vitro fertilization, ectopic pregnancy, and chronic pain, may ultimately affect 11% of reproductive-aged women.[4] The most common cause of death is rupture of a tubo-ovarian abscess, with mortality associated with rupture remaining at 5% to 10%, even with current treatment methods.

PATHOPHYSIOLOGY

ORGANISMS ASSOCIATED WITH PID

Neisseria gonorrhoeae and *Chlamydia trachomatis* can be isolated in many cases of PID, and therapy is largely directed against these organisms. *Chlamydia* has developed a number of mechanisms to avoid autophagy and destruction by the host immune system and is able to persist in a nonreplicative form in host epithelial cells.[5-7] Polymicrobial infection, including infection with anaerobic and aerobic vaginal flora, is evident from cultured material from the upper reproductive tract.[8] **Table 103-1** lists common pathogenic organisms associated with acute or subclinical PID. *N. gonorrhoeae*, *C. trachomatis,* and bacterial vaginosis–associated organisms are usually instrumental in initial infection of the upper genital tract. Approximately 15% of cases are due to enteric or respiratory organisms that have colonized the lower genital tract.[2] Anaerobes, facultative anaerobes, and other bacteria are isolated increasingly as inflammation develops and abscesses form.

Bacterial vaginosis is frequently identified in women with PID, and the type of bacterial vaginosis–associated microorganism (*Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum*, pigmented or nonpigmented anaerobic gram-negative rods) may make a difference in the likelihood of developing PID.[5,9,10] Sexually transmitted *Mycoplasma genitalium* has increasingly been implicated as contributory or causative to both cervicitis and ascending disease.[2,11-14]

Infection with ***Trichomonas vaginalis*** is associated with a fourfold increase in the incidence of acute endometritis. Coinfection with **herpes simplex virus type 2** and ***C. trachomatis*, *N. gonorrhoeae*,** or bacteria causing vaginosis is also associated with acute endometritis. Infection with herpes simplex virus type 2 causes fallopian tube inflammation and lower tract ulceration that may disrupt the endocervical canal mucous barrier.[15] **Human immunodeficiency virus 1 (HIV-1)** infection

TABLE 103-1 Organisms Associated With Pelvic Inflammatory Disease

Sexually transmitted organisms
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- Herpes simplex virus (types 1 and 2)
- *Trichomonas vaginalis*

Endogenous genital tract *Mycoplasma*
- *Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum*

Anaerobic bacteria
- *Bacteroides species, Peptostreptococcus, Prevotella bivia, Leptotrichia sanguinegens/amnionii, Atopobium vaginae*

Aerobic bacteria
- *Gardnerella vaginalis, Haemophilus influenzae, Streptococcus agalactiae, Escherichia coli,* and other gram-negative rods, *Actinomyces israelii, Campylobacter fetus*

is associated with an increased incidence of *C. trachomatis* infection, increased incidence of coinfection with *Candida* and human papillomavirus, and increased risk of progression to PID.[16]

Chronic PID may result from ***Mycobacterium tuberculosis*** infection in endemic areas.[17] **Schistosomes** can cause genital infection, including a PID-like tubal infection, infertility, and chronic abortion, and a recent report links schistosomiasis to HIV transmission in Africa. ***Actinomyces*** species have been identified almost exclusively in patients with intrauterine devices (IUDs).[18]

ASCENDING INFECTION

Most cases of PID are presumed to originate with sexually transmitted infections of the lower genital tract, followed by ascending infection of the upper tract. The original sexually transmitted infection may be asymptomatic, as may the ascending infection (subclinical PID).[19] The precise mechanisms by which upper genital tract infection and inflammation are initiated and propagated are not well understood. Although the cervical mucus serves as a functional barrier to ascending infection much of the time, its efficacy may be decreased by a number of factors, including enzymes produced by bacterial vaginosis–associated organisms that degrade cervical mucus and antimicrobial peptides,[20,21] hormonal changes during menstruation and ovulation, and retrograde menstruation. Intercourse may contribute to the ascent of infection due to rhythmic mechanical uterine contractions. Bacteria also may be carried by, or along with, sperm into the uterus and tubes. Uterine infection usually is limited to the endometrium, but can be more invasive in a gravid or postpartum uterus. Tubal infection initially affects only the mucosa, but acute, complement-mediated transmural inflammation may develop rapidly and increase in intensity with repeated infection. Inflammation may extend to uninfected parametrial structures, including the appendix and bowel. Infection may spread by direct extension of purulent material from the fallopian tubes or via lymphatic spread beyond the pelvis to involve the hepatic capsule with acute perihepatitis (Fitz-Hugh–Curtis syndrome) and produce acute peritonitis.

RISK FACTORS FOR PID

Multiple risk factors are associated with development of PID (**Table 103-2**).[9,22-29]

IUD use has been associated with an increased risk for PID. Although the majority of risk occurs within 21 days of insertion, the presence of an IUD is associated with complicated PID irrespective of the duration of use.[18,25-27] The risk of PID in IUD users is more related to the development of sexually transmitted infection than the IUD,[30,31] and sexually transmitted infection screening and treatment at the time of insertion can significantly decrease the likelihood that PID will develop.[32]

Pregnancy decreases the risk of PID because the cervical os is protected by the mucous plug. However, PID can occur during the first trimester and is associated with substantial fetal loss and preterm delivery.

COMPLICATIONS OF PID

PID is associated with a number of serious clinical sequelae. Tuboovarian abscess is reported in up to one third of women hospitalized for PID. Infection and inflammation can lead to loss of ciliated epithelial cells in the fallopian tubes and to scarring and adhesions with obstruction within tubal lumens. **Ectopic pregnancy is more frequent in women who have had PID than in those who have never had an ectopic pregnancy.** Tubal factor infertility is increased by 12% to 50% in women with a past diagnosis of PID, and the incidence increases with the number and severity of past PID episodes.[33] Asymptomatic or silent PID also appears to be associated with tubal factor infertility. Sequelae of PID include recurrence of PID, chronic pelvic pain, menstrual disturbances, and chronic dyspareunia. Recurrence of PID may occur because of inadequately treated infection, nontreatment of partner(s), or reinfection from another sexual contact. In follow-up to the Pelvic Inflammatory Disease Evaluation and Clinical Health trial, those with recurrence of PID were five times more likely to experience chronic pelvic pain.[34] PID may also be associated with an increased risk of borderline ovarian tumors.[35]

TABLE 103-2 Risk Factors Associated With Pelvic Inflammatory Disease[23-29]

- Multiple sexual partners
- History of sexually transmitted infection or pelvic inflammatory disease
- History of sexual abuse
- Frequent vaginal douching
- Intrauterine device insertion within previous month
- Adolescence, younger adulthood
- Lower socioeconomic status
- Post-abortion

CLINICAL FEATURES

The clinical presentation of PID is variable. The most common presenting complaint is lower abdominal pain, most frequently described as bilateral and dull or crampy. Pain may be exacerbated by movement or by sexual activity. Other symptoms include abnormal vaginal discharge (75% of individuals), vaginal bleeding (including increased or prolonged menstrual bleeding) and postcoital bleeding (more than one third of patients), irritative voiding symptoms, and much less commonly systemic signs of fever, malaise, nausea, and vomiting.[36] Symptoms usually occur early in the menstrual cycle or at the end of the menses and are attributed to low progesterone levels and coincident thinning of the cervical mucosal barrier.

The physical examination usually is notable for lower abdominal tenderness, cervical motion tenderness, and uterine or adnexal tenderness. Involuntary guarding and rebound tenderness may be present and may indicate associated peritonitis. The positive predictive value of these findings varies depending on the prevalence of PID in a given clinical population. Adnexal tenderness appears to have a sensitivity of 95%.[37] Mucopurulent cervicitis is common, and its absence should raise consideration of another diagnosis. In women suspected of having PID and for whom there is no likely alternative diagnosis for abdominal pain, the presence of fever, adnexal tenderness, and an elevated erythrocyte sedimentation rate are significant independent predictors of endometritis and correctly classify 65% of patients with laparoscopically proven PID (95% confidence interval, 61% to 99%).[37,38]

Right upper quadrant tenderness, particularly with jaundice, may indicate perihepatic inflammation. **Fitz-Hugh–Curtis syndrome** (perihepatitis) is strongly suggested by right upper quadrant pain, and occasionally slightly elevated transaminases, in a woman with a clinical diagnosis of PID and no other cause for this pain. It is an uncommon complication and responds to standard antibiotic treatment for PID.[39]

The differential diagnosis of PID is broad and includes cervicitis, ectopic pregnancy, endometriosis, ovarian cyst, ovarian torsion, spontaneous abortion, septic abortion, cholecystitis, gastroenteritis, appendicitis, diverticulitis, pyelonephritis, and renal colic. Look for signs of other sexually transmitted infections, such as herpes simplex, syphilis, and human papillomavirus infection.

DIAGNOSIS

The diagnosis is based on history and clinical findings. No single piece of historical, physical, or laboratory information is sensitive and specific for the disease. **Laboratory evaluation of any woman of childbearing age in the ED always should include a pregnancy test.** Consider the possibility of ectopic pregnancy or septic abortion. The most common alternative diagnosis in missed ectopic pregnancy is PID. Concurrent pregnancy also influences patient treatment and disposition.

Current Centers for Disease Control and Prevention guidelines encourage initiation of empiric treatment in women at risk for PID who exhibit lower abdominal pain, adnexal tenderness, and cervical motion tenderness. Guidelines stratify diagnostic criteria into the three groups shown in **Table 103-3**.

TABLE 103-3 Diagnostic Criteria for Pelvic Inflammatory Disease (PID)

Group 1: Minimum criteria. Empiric treatment if no other cause to explain findings.

- Uterine or adnexal tenderness
- Cervical motion tenderness

Group 2: Additional criteria improving diagnostic specificity.

- Oral temperature >101°F (38.3°C)
- Abnormal cervical or vaginal mucopurulent secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein level
- Laboratory evidence of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis* (i.e., culture or DNA probe techniques)

Group 3: Specific criteria for PID based on procedures that may be appropriate for some patients.

- Laparoscopic confirmation
- Transvaginal US (or MRI) showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
- Endometrial biopsy results showing endometritis

Source: Reproduced with permission from Centers for Disease Control and Prevention, Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 59(RR-12): 12, 2010.

LABORATORY TESTING

Obtain saline- and potassium hydroxide–treated wet preparations of vaginal secretions to identify leukorrhea (more than one polymorphonuclear leukocyte per epithelial cell) and trichomonads and to test for bacterial vaginosis (clue cells, pH, and a whiff test). If increased white blood cells are seen with clue cells, this increases the likelihood of accompanying cervicitis or PID, as bacterial vaginosis is not inflammatory. Leukorrhea is sensitive but not specific for upper tract infection,[40] and the absence of leukorrhea is a negative predictor for PID. Although endocervical swab specimens may be sent for culture and can be Gram stained for gonococci, nucleic acid amplification tests and DNA probes for *N. gonorrhoeae* and *Chlamydia* have replaced culture and Gram staining in many settings. If positive, the probability of PID increases significantly. Unfortunately, the latter results are not available to the ED at the time of initial evaluation. Several sensitive and specific diagnostic tests are currently available for *Trichomonas* testing, including a nucleic acid amplification test (Aptima®; GenProbe, San Diego, CA), approved in 2013, that is performed on the same clinical samples as those for *Chlamydia* and gonorrhea testing.[41,42]

If PID is clinically suspected, an elevated WBC count, erythrocyte sedimentation rate, or C-reactive protein level supports the diagnosis.[40] Because a patient may have multiple sexually transmitted infections, also obtain a rapid plasma reagin test for syphilis. Test for HIV and hepatitis. Urinalysis can exclude urinary tract infection, but a positive urinalysis does not exclude PID, because any inflammatory process in the contiguous pelvis can produce WBCs in the urine. Blood cultures do not aid in diagnosis or treatment.

IMAGING AND OTHER DIAGNOSTIC MODALITIES

Transvaginal pelvic US may demonstrate thickened (>5 mm), fluid-filled fallopian tubes or free pelvic fluid in acute severe PID. Pelvic or tubo-ovarian abscesses appear as complex adnexal masses with multiple internal echoes. Pelvic US can demonstrate as many as 70% of adnexal masses missed on physical examination. US also may be helpful in ruling in or out other causes in the differential diagnosis of pelvic pain, including ectopic pregnancy, ovarian torsion, hemorrhagic ovarian cyst, and possibly appendicitis or endometriosis.[43] The addition of power Doppler can identify increased blood flow, which is suggestive of inflammation and infection.[43]

Abdominopelvic CT and MRI may also be used to diagnose PID and tubo-ovarian abscess and to exclude other important causes of pelvic pain. If appendicitis or other surgical or GI diagnoses cannot be excluded, obtain an abdominopelvic CT. For further discussion, see Chapter 97, "Abdominal and Pelvic Pain in the Nonpregnant Female." CT findings in PID include obscuration of the pelvic fascial planes, cervicitis, oophoritis, salpingitis, thickening of the uterosacral ligaments, and the presence of simple or complex pelvic fluid or abscess collections. Both PID and acute appendicitis may produce overlapping radiographic findings, but diagnosis can be improved by accounting for both appendiceal diameter and left tubal thickness.[44] Right tubal thickening does not distinguish the disorders, as inflammation from appendicitis can spread and cause right tubal thickening.[44] An appendiceal diameter cutoff of ≥7 mm in the Hentour cohort was sufficiently sensitive to capture all but one case of acute appendicitis, but left tubal enlargement to ≥10 mm was more suggestive of PID even in patients with dilation of the appendix to ≥7 mm. These measurements together resulted in a diagnostic algorithm with 98% accuracy in distinguishing PID from acute appendicitis.[44] MRI is especially helpful in characterizing complicated soft tissue masses, including dilated fallopian tubes and abscesses. MRI is more specific and accurate than US to assess PID, with a sensitivity of 95% and a specificity of 89%; however, it is often less available acutely in the ED.[45,46]

Laparoscopy has been considered the gold standard for the diagnosis of PID. It is invasive, has a high interobserver variability, may not detect endometritis or early tubal inflammation, and often is not readily available for ED consultation. Transcervical endometrial aspiration and endometrial biopsy, although still invasive, may be more commonly used by consultants when the diagnosis is uncertain and the patient is ill.[2,38,47]

TREATMENT

Treatment is aimed at relieving acute symptoms, eradicating current infection, and minimizing the risk of long-term sequelae. From a public health perspective, another objective of treatment is to reduce the risk of transmission of infection to other new partners and to identify and treat past and current sexual partners to prevent disease spread. Early diagnosis and treatment are critical because duration of symptoms is an independent risk factor for infertility.[48]

Due to the difficulty of diagnosis and the potential for serious sequelae, the Centers for Disease Control and Prevention recommends a low threshold for empiric treatment, with overtreatment preferred to a missed diagnosis with resultant delayed or no treatment.

Provide adequate analgesia, control of emesis and fever, and fluid replacement in those with nausea, vomiting, and dehydration and in those who appear toxic. NSAIDs are very useful for the management of pain of pelvic origin.

ED treatment should include empiric broad-spectrum antibiotic therapy to cover the full range of likely organisms. Screen for bacterial vaginosis and treat when screening is positive. Treatment regimens should follow both national guidelines from the Centers for Disease Control and Prevention and local health department surveillance reports. The Pelvic Inflammatory Disease Evaluation and Clinical Health trial, which included 654 females age 14 to 37 years old, demonstrated no differences between oral and parenteral regimens in women with mild to moderately severe acute PID uncomplicated by pregnancy or the presence of a tubo-ovarian abscess.[49,50]

Currently accepted inpatient and outpatient treatment regimens are summarized in **Tables 103-4** and **103-5**. Changing geographic patterns of drug resistance may alter recommendations. For example, worldwide resistance in gonorrhea has emerged over the past several decades by multiple molecular mechanisms to all the commonly used antibiotics.[51] Patients with PID who require IV antibiotics initially can be switched to oral antibiotics after clinical improvement.

SPECIAL CONSIDERATIONS

TREATMENT WITH IUD IN PLACE

In the past, an IUD was generally removed, based on the belief that because it is a foreign body removal of the IUD would allow treatment to be more effective. There is a low risk of PID from IUD insertion,

TABLE 103-4 Parenteral Treatment Regimens for Pelvic Inflammatory Disease

Cefotetan, 2 grams IV every 12 h, or cefoxitin, 2 grams IV every 6 h
plus
Doxycycline, 100 milligrams PO or IV every 12 h*
or
Clindamycin, 900 milligrams IV every 8 h
plus
Gentamicin, 2 milligrams/kg IV or IM loading dose, followed by gentamicin, 1.5 milligrams/kg every 8 h maintenance dose†
Alternative Parenteral Regimen (limited data on effectiveness)
Ampicillin/sulbactam, 3 grams IV every 6 h
plus
Doxycycline, 100 milligrams PO or IV every 12 h*

*PO doxycycline has the same bioavailability as IV doxycycline and avoids painful infusion.

†Gentamicin dosing may be 3–5 milligrams/kg every 24 h.

Source: Reproduced with permission from Centers for Disease Control and Prevention, Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 64: 1, 2015. CDC.gov.

especially when sexually transmitted infection testing is done concomitantly and immediate treatment is initiated.[32] **Current Centers for Disease Control and Prevention guidelines suggest that there is insufficient evidence to recommend IUD removal before treatment for PID, because the device is usually not the source of infection.** In those with an IUD who develop PID, there are no data to support the use of one treatment regimen over another. Studies were also performed on women with nonhormonal IUDs, with similar results. No data are available regarding treatment outcomes in those with levonorgestrel-releasing IUDs. Close clinical follow-up is prudent. If there is a concern regarding PID in a patient with an IUD newly placed in the past 3 weeks, it is reasonable to consult a gynecologist regarding removal.

TREATMENT IN HIV INFECTION

Microbiologically, HIV-positive women are more likely to have concomitant *Candida*, *M. hominis*, HPV, and streptococcal infection. HIV-positive women with PID may experience more severe symptoms irrespective of CD4 count and are more likely to have sonographically diagnosed tubo-ovarian abscess. However, such patients appear to respond similarly to treatment for uncomplicated PID as do those not infected with HIV.[52-54] HIV-positive status alone is not a criterion for hospitalization.[40,52,55,56]

TABLE 103-5 Oral and Outpatient Treatment Regimens for Pelvic Inflammatory Disease

Ceftriaxone, 250 milligrams IM once, *or* cefoxitin, 2 grams IM once, *and* probenecid, 1 gram PO once administered concurrently
or
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
plus
Doxycycline, 100 milligrams PO twice a day for 14 d
with or without
Metronidazole, 500 milligrams PO twice a day for 14 d
If parenteral cephalosporin therapy is not feasible and community prevalence of fluoroquinolone resistance is low:
Levofloxacin, 500 milligrams PO, *or* ofloxacin, 400 milligrams twice daily every day for 14 d
with or without
Metronidazole, 500 milligrams PO twice a day for 14 d

Note: Other parenteral third-generation cephalosporins can be substituted for ceftriaxone or cefoxitin. Since the Centers for Disease Control and Prevention guidelines were published in 2006, clinically significant resistance to the fluoroquinolones (6.7% of infections in heterosexual men, an 11-fold increase from 0.6% in 2001) has emerged in the United States. Fluoroquinolone antibiotics are no longer recommended to treat gonorrhea in the United States. Fluoroquinolones may be an alternative treatment option for disseminated gonococcal infection if antimicrobial susceptibility can be documented.

Source: Reproduced with permission from Centers for Disease Control and Prevention, Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 64: 1, 2015. CDC.gov.

TREATMENT OF ADOLESCENTS

Early and mid-adolescents were not well represented in the Pelvic Inflammatory Disease Evaluation and Clinical Health study, and of those enrolled, adolescents had increased risk of recurrent PID and a shorter time to pregnancy after an acute episode compared with adult enrollees. However, there is no robust evidence to suggest that adolescent outcomes are improved after hospitalization for PID management. Adolescents hospitalized in pediatric centers often receive services beyond IV antibiotics, including education on risk reduction and pregnancy prevention, emotional support, social work intervention, assistance with communicating the nature of their illness with parents, and assistance to arrange close follow-up.[57,58]

ALTERNATIVE ANTIBIOTICS

For those with severe cephalosporin allergy, **spectinomycin** is recommended in Canada and Europe but is not currently available in the United States. For more information, see the Centers for Disease Control and Prevention Web pages on antibiotic-resistant gonorrhea at http://www.cdc.gov/std/Gonorrhea/arg/default.htm.[40]

Multiple studies have demonstrated poor compliance with doxycycline therapy (25%; 50% with partial compliance), and 20% to 25% of patients never fill their prescriptions.[59-61] Doxycycline also does not cover *Mycoplasma genitalium*. For PID treatment, **azithromycin** is an alternative, with studied dosing of 500 milligrams IV daily for one to two doses, followed by 250 milligrams once daily for 12 to 14 days, or in combination with metronidazole for anaerobic coverage, 250 milligrams PO once a day for 7 days or 1 gram once a week for 2 weeks.[59] The long half-life of azithromycin requires significantly fewer doses, which is thought to improve the likelihood of patient compliance. Azithromycin also provides intrinsic anti-inflammatory effects and may reduce local tissue damage. Weigh these potential benefits against the lack of large-scale or long-term studies comparing the effectiveness of azithromycin to doxycycline in the treatment of PID and the possibility of emerging resistance to azithromycin.[5,59,62-65] A recent meta-analysis of 37 randomized controlled trials, including multiple international trials, found that all Centers for Disease Control and Prevention–recommended regimens studied demonstrated fairly similar treatment efficacy, but that azithromycin might be superior in those with mild to moderate PID. The authors point out the risk of bias in the trials studied and the need for high-quality randomized controlled trials to more robustly address this.

TUBO-OVARIAN ABSCESS

Tubo-ovarian abscesses are most commonly a late complication of PID, and the majority have associated peritonitis. Tubo-ovarian abscess complicates about 2% of PID cases. Due to slower resolution of PID, women coinfected with HIV demonstrate an increased incidence of tubo-ovarian abscess. Disproportionate unilateral adnexal tenderness or adnexal mass or fullness may indicate a tubo-ovarian abscess (**Figure 103-1**). In women with clinical toxicity and asymmetric pelvic findings, obtain a pelvic US. Most tubo-ovarian abscesses (60% to 80%) resolve with antibiotic administration alone.[66-68] In the setting of tubo-ovarian abscess, oral therapy should be continued with clindamycin (450 milligrams PO four times per day) or metronidazole with doxycycline for better anaerobe coverage for 14 days. Patients who do not improve after 72 hours of treatment should be reevaluated for possible CT- or US-guided percutaneous drainage, laparoscopic drainage, posterior colpotomy with drainage, surgical intervention, or reconsideration of other possible diagnoses. Abscesses 9 cm or larger on imaging appear to have a higher likelihood of requiring surgical therapy. An enlarging pelvic mass may indicate bleeding secondary to vessel erosion or a ruptured abscess.

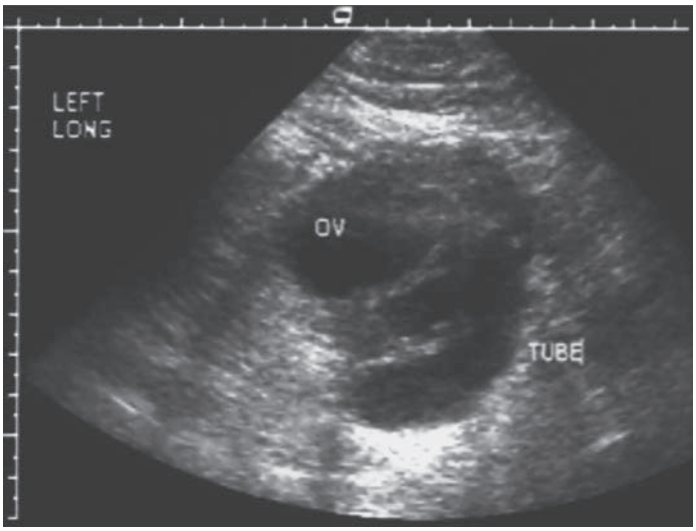

FIGURE 103-1. Tubo-ovarian complex. Endovaginal image of left adnexa shows a distorted ovary (OV) partially encircled by a fluid-filled hydrosalpinx (TUBE). [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA (eds): *Ma & Mateer's Emergency Ultrasound*, 3rd ed. New York, NY: McGraw-Hill Education, Inc.; 2014. Fig. 16-17 Part A, p. 469.]

DISPOSITION AND FOLLOW-UP

Guidelines for admission (**Table 103-6**) and inpatient treatment (Table 103-4) have evolved over the past decade. Among the problems encountered with outpatient care are the provision of adequate guideline-driven treatment, patient adherence to the prescribed therapeutic regimen, difficulty in arranging outpatient administration of parenteral medications, coordination of 72-hour follow-up evaluation, and partner treatment, all of which have been implicated as causes of treatment failure. Consider these and other constraints when determining the patient's ability to follow or tolerate an outpatient regimen.

Institutions should consider adoption of protocolized treatment guidelines to help to ensure fidelity to standards of care. **Admission decisions in the ED are based on severity of illness, likelihood of adherence to outpatient medication regimen, likelihood of major anaerobic infection (IUD, suspected pelvic or tubo-ovarian abscess, or history of recent uterine instrumentation), certainty of diagnosis, coexisting illness and immunosuppression, pregnancy, patient age, and other major fertility issues.**

If the patient is discharged, arrange reevaluation within 72 hours for clinical improvement and adherence to the prescribed regimen. Encourage partner evaluation and treatment. Test and treat for other sexually transmitted infections if not already done. Educate patients about the use of barrier contraceptives and other "safe sex" techniques to lessen the risk of reinfection. Counsel the patient to remain abstinent from sexual activity until 1 week after treatment is finished for both the patient and partner and symptoms have abated.

Partner treatment is crucial to preventing repeated episodes of PID. This can be difficult to ensure. If the current partner has accompanied the patient to the ED, and the patient is willing to tell this partner about her infection, she can be asked to suggest immediate ED evaluation to her partner. If not, the patient should be instructed to notify partners with whom she has had sexual contact in the 60 days preceding the onset of her symptoms to go to the local public health department or sexually transmitted infection clinic for empiric treatment of *N. gonorrhoeae* and *C. trachomatis*. A 6-minute PID outreach video has been developed and was found in one randomized controlled trial to improve partner treatment.[69] Recent European guidelines suggest the use of doxycycline as empirical treatment of partners to reduce exposure to macrolide to avoid increasing resistance in *M. genitalium*.[11]

TABLE 103-6 Admission Considerations

- Inability to exclude surgical emergency from the differential diagnosis
- Pregnancy
- Failure to respond to outpatient treatment
- Inability to tolerate or comply with outpatient treatment
- Severe toxicity, high fever, nausea, vomiting
- Tubo-ovarian abscess

Source: Reproduced with permission from Centers for Disease Control and Prevention, Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 59(RR-12): 12, 2010.

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CHAPTER 104

Breast Disorders

Bophal Sarha Hang

INTRODUCTION

The most common breast complaints in the ED involve breast pain, breast mass, nipple discharge, infection, or postoperative complications. Approximately 30% of women will present to a physician with a chief complaint related to the breasts.[1] Although the problems are rarely emergent except when systemic symptoms such as fever are present, concerns about the potential for breast cancer contribute to patient anxiety.

PATHOPHYSIOLOGY

Adult breast is composed of approximately 20% glandular tissue, and the remaining breast volume consists of fat and connective tissue that give the breast its characteristic texture and shape. Glandular lobules drain into lactiferous ducts, which converge and open at the nipple. The nipple is an important landmark located over the fourth intercostal space.

Normal breast tissue extends from the sternocostal junction medially to the midaxillary line laterally and from the second to the sixth ribs in the midclavicular line. An axillary tail of breast tissue often extends into the axilla. Blood supply arises from the internal mammary, lateral thoracic, thoracodorsal, and subscapular arteries, whereas venous drainage starts in the subareolar plexus and empties into the intercostals, internal mammary, and axillary veins. Lymphatic drainage of the breast is primarily to the axilla, with a small portion going to internal mammary lymph nodes.

Cyclic variances in estrogens, progesterone, follicle-stimulating hormone, and luteinizing hormone signal stromal and glandular changes in breast physiology.

CLINICAL FEATURES

HISTORY

Ask the patient about onset of any mass or pain, location of the affected area, and duration of the symptoms. Complaints that vary with menses suggest a benign cause, whereas cancers are often asymptomatic. Radiation of the pain to any other body site is particularly important when a

malignancy is suspected. The presence of symptoms in the contralateral breast parenchyma is also more reassuring for a benign diagnosis. Assess the color and consistency of any nipple discharge. Changes that the patient notes on breast self-examination may be significant and should be correlated with the menstrual cycle. Ask about family history, specifically about first-degree relatives with breast cancer and other risk factors (delay of childbearing to after age 30 years, biopsy confirmation of atypical hyperplasia, or history of chest irradiation). However, most women who develop breast cancer have no obvious risk factors beyond the two strongest factors, namely, female gender and age. More than 50% of breast cancers are diagnosed in women ≥65 years of age, and women <30 years of age are diagnosed with <1% of all breast cancers.[2]

PHYSICAL EXAMINATION

The breast examination includes both inspection and palpation. Compare the breasts with the patient sitting upright, and note any breast asymmetry or skin dimpling. Also examine the axillae, including the mammary tail and lymph nodes, in the sitting position. Perform the rest of the examination with the patient supine and the ipsilateral hand behind the head. Examine the upper outer quadrant of each breast with extra care, because about half of breast carcinomas originate in that area, with a higher propensity for left-sided involvement.[2,3] Examine the nipple-areola complex with gentle manipulation to detect subareolar masses and latent nipple discharge. Women with breast augmentation may be challenging to examine, but give attention to tissue changes or deviation of the implant.

DISORDERS OF THE LACTATING BREAST

ABNORMAL LACTATION

Any inappropriate secretion of milky discharge from the breast is called *galactorrhea*. Galactorrhea often results from abnormally elevated levels of prolactin, although some women have normal prolactin levels on testing. Hyperprolactinemia may be caused by inadequate inhibition of secretion or increased production of prolactin. Causes of elevated prolactin levels are listed in **Table 104-1**.

Prolactinomas, benign anterior pituitary neoplasms, are distinguished by symptoms of galactorrhea, amenorrhea, hirsutism, facial acne, visual field deficits, and headaches. Chronic renal failure results in a diminished capacity to clear circulating prolactin. Hypothyroidism causes increased levels of thyrotropin-releasing hormone, which results in increased pituitary secretion of prolactin. Hypercortisolism (Cushing's disease) and acromegaly due to elevated growth hormone levels are both associated with galactorrhea.

Evaluation of the patient with galactorrhea focuses on any history of associated menstrual abnormalities and the presence of acne, hirsutism, infertility, or libido changes. Symptoms of increased intracranial pressure and hypothyroidism should be investigated. All medications and dietary supplements should be reviewed.

The physical examination includes evaluations of the visual fields, breasts, skin, and thyroid gland. ED studies include a urine or serum pregnancy test and may include neuroimaging (CT or MRI) and neurosurgical consultation if there is concern for an intracranial mass. Treatment for galactorrhea, other than the discontinuation of a medication suspected to be causative, is deferred to the primary care physician or the follow-up specialist.

TABLE 104-1 Causes of Elevated Prolactin Levels

Physiologic causes	Sleep, stress, exercise, volume depletion, intercourse or orgasm, pregnancy, breast stimulation, seizures
Abnormal stimulation of the chest wall	Surgery, trauma, herpetic infection
Damage to or disruption of the pituitary stalk	—
Endogenous hypothalamic-pituitary signaling	—
Neoplasms	Prolactinomas, renal cell carcinoma, lymphoma, craniopharyngioma, bronchogenic carcinoma, hydatidiform mole
Medications	Antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants), antihypertensives (atenolol, methyldopa, reserpine, verapamil), antipsychotic phenothiazines, antihistamines, herbs and vitamin supplements (anise, fennel, nettle, clover, thistle, fenugreek seed), amphetamines, cocaine, opioids, marijuana
Systemic disease	Chronic renal failure, hypothyroidism, hypercortisolism (Cushing's disease), acromegaly

COMPLICATIONS OF LACTATION

Breast engorgement usually presents on the third to fifth postpartum day, with symptoms of painful, hard, and enlarged breasts. The pain may be accompanied by nausea and low-grade fever. Engorgement results from inadequate removal of milk from the breast. This may be due to infant separation, sore nipples, or improper breastfeeding techniques.[4] Ensuring proper latch-on while breastfeeding or pumping usually alleviates the pain and allows for decompression of the nipple-areola complex. Warm showers or manual massage may also help facilitate milk letdown and relieve pain due to engorgement.

Nipple irritation or soreness is common and usually caused by poor positioning or latch-on techniques. Other causes include trauma, plugged ducts, candidiasis, and inflammatory skin disorders. Purified lanolin cream, analgesics, and breast shields may help facilitate healing. There may be some benefit to applying expressed breast milk to nipples.[4,5] Reynaud's phenomenon can cause nipple pain in some women and may respond to topical nefedipine.[6]

Puerperal mastitis presents with severe pain, tenderness, swelling, and redness. Patients may also develop fever, chills, and myalgias. Mastitis most commonly presents in the second postpartum week due to milk stasis and retrograde infection. Differentials include marked breast engorgement, clogged milk duct, and inflammatory carcinoma, a rare condition.

Mastitis, like other inflammatory processes, has the US appearance of hypoechoic fluid surrounding subcutaneous fat lobules without a discrete fluid collection (**Figure 104-1**), in contrast to abscess (**Figure 104-2**), which presents as a hypoechoic (dark) fluid collection in the tissue with the absence of vascular signals.

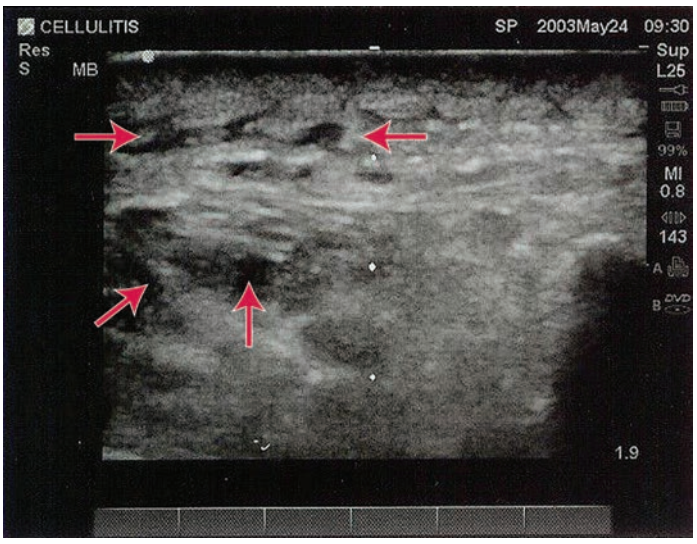

FIGURE 104-1. Mastitis, like other inflammatory processes, has the US appearance of hypoechoic fluid surrounding subcutaneous fat lobules without a discrete fluid collection (*arrows*).

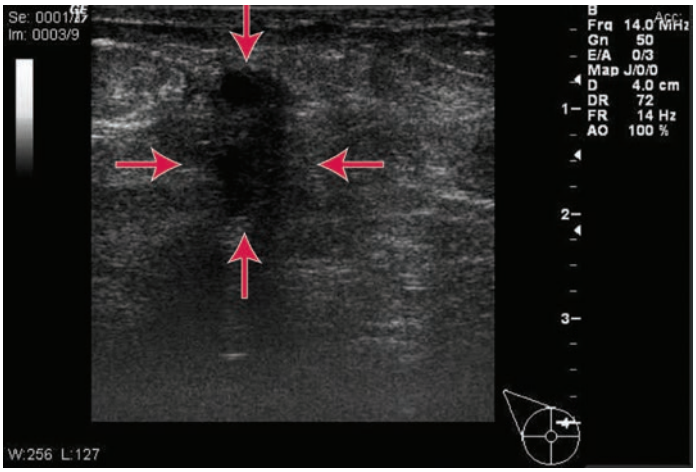

FIGURE 104-2. Breast abscess presents as a hypoechoic (dark) fluid collection in the tissue (*arrows*) with the absence of vascular signals.

Puerperal mastitis is caused by *Staphylococcus aureus* in 40% of cases, although *Escherichia coli* and *Streptococcus* species are also known pathogens. Consider community-acquired methicillin-resistant *S. aureus* infections associated with puerperal mastitis and abscess.[5] **There is no need to interrupt breastfeeding.** Treatment requires frequent analgesia, breast emptying, and antibiotics with antistaphylococcal penicillins or cephalosporins (**Table 104-2**). **Sulfamethoxazole-trimethoprim cannot be given to lactating mothers with infants <2 months old.** If the infection fails to respond rapidly to antibiotics, evaluate for abscess and broaden antibiotic coverage.

Breast abscess is uncommon and complicates mastitis in approximately 3% of cases. If US examination identifies a subcutaneous fluid collection, US-guided drainage is an initial first-line treatment (Figures 104-1 and 104-2). **Breastfeeding should be continued throughout the course of treatment unless the antibiotic regimen is contraindicated with newborns.**[4,7] Surgical drainage is reserved as a last resort in lactating patients to avoid the potential for milk fistulas.[8] Management also includes antibiotic coverage for possible drug-resistant *Staphylococcus* such as oral cephalosporins or clindamycin. Intravenous vancomycin is a good choice for septic patients requiring inpatient hospitalization. In a subset of patients with recurrent infections, the surgeon may need to perform an excisional biopsy of tissue to rule out an associated inflammatory carcinoma.[9]

INFLAMMATORY BREAST CONDITIONS

The differential diagnosis of an inflamed breast includes infectious mastitis, breast abscess, periductal mastitis, ruptured breast cyst, inflammatory neoplasm, metastatic cancer from a primary lesion, tuberculosis, and Paget's disease. Each entity can mimic the other, more benign conditions. **A failure of the condition to improve with antibiotic therapy indicates the need for urgent surgical consultation and possible biopsy to exclude the presence of an inflammatory cancer.**[9]

CELLULITIS, ACUTE MASTITIS, AND BREAST ABSCESS IN NONLACTATING WOMEN

Cellulitis, mastitis, and breast abscesses exist along a continuum, with similar clinical presentation of pain, redness, swelling, fever, and malaise. **Cellulitis** can be identified on US as diffuse thickened and hyperechoic skin and increased echogenicity of subcutaneous tissue. However, breast cellulitis is uncommon and requires referral to a breast surgeon for imaging and possibly biopsies. Initial treatment includes dicloxacillin, amoxicillin–clavulanic acid, or a first-generation cephalosporin. However, the increasing incidence of infection with methicillin-resistant *S. aureus* may necessitate the use of trimethoprim-sulfamethoxazole, clindamycin, or tetracycline depending on the patient's history of infections and the local prevalence of methicillin-resistant *S. aureus*.[10] Cellulitis requires follow-up with a breast surgeon.

Acute mastitis and abscesses in nonlactating women (Figures 104-1 and 104-2) are often seen in women with diabetes, obesity, or a history of smoking. Common organisms are *Staphylococcus* and *Streptococcus*. Follow-up mammography is recommended for patients older than 30 years and should be done after the acute phase has resolved.[11] Initial recommended empiric parenteral antibiotics are third-generation cephalosporins (e.g., ceftazidime), clindamycin, vancomycin, fluoroquinolones, or linezolid with consideration of the addition of metronidazole for deeper abscesses. The prevalence of methicillin-resistant *S. aureus* infections continues to increase and has been reported in up to 20% of cases of breast abscess.[10]

Patients without systemic toxicity can be treated as outpatients. Antibiotics should provide anaerobic coverage. Infections should respond to antibiotics within 48 hours. Refer patients to a breast surgeon for US-guided needle aspiration and therapy.[12-15]

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa frequently presents with recurrent multiple cutaneous abscesses, sinus tracts, and scarring of the breast folds, axillae, and groin and perineum. It is a chronic inflammatory disease involving the obstruction of sweat glands and polymicrobial colonization, usually with *Staphylococcus* and *Streptococcus* species. Frequently, patients present with painful superficial cutaneous abscesses along the inferior, pendulous surface of the breast and require surgical drainage for pain relief. Incision and drainage usually are adequate therapy for a limited area of abscess formation. Antibiotics are rarely used for outpatient management of hidradenitis abscesses in immunocompetent patients, although clindamycin or rifampin may be used by dermatologists or surgeons to decrease the frequency and severity of the disease. There is no cure, and the disease often requires extensive surgical excision of the apocrine tissue.

INFLAMMATORY BREAST CANCER

Of all the potential presentations of a breast malignancy, inflammatory breast cancer is the entity associated with the highest mortality and longest delay from initial presentation to definitive diagnosis. The clinical presentation is characterized by symptoms of mastalgia and breast inflammation due to tumor infiltration of dermal lymphatics and inflammation of the breast stroma. The combination of erythema and edema results in the classic *peau d'orange* appearance of the overlying skin and ultimately nipple retraction as the edema progresses. Initially, the patient presents with a clinical syndrome of breast enlargement, breast warmth, tenderness, edema, erythema, and sometimes discoloration of the overlying skin. The absence of a palpable underlying mass or axillary lymphadenopathy does not rule out the diagnosis. **The signs of inflammatory breast cancer are often indistinguishable clinically from infection.** Prompt mammography and biopsy of the skin and any palpable or radiographic breast lesions will be required by the follow-up physician. **Similarly, the diagnosis of *inflammatory breast cancer* must be considered promptly if there is not an initial good response to antibiotics or if breast cellulitis or abscess fails to completely resolve.**

NONINFLAMMATORY PAINFUL BREAST DISORDERS

MASTODYNIA

Breast pain is also termed *mastodynia* or *mastalgia*. Irritation to the intercostal nerves at T3-T5 can cause pain in the breast or nipple. The pain is bilateral and usually most severe in the upper outer quadrants of the breast. Pain may be referred to the axilla or scapula. Diagnosis relies on findings of the history and physical examination to confirm that the pain actually originates from the breast. Breast pain is an uncommon symptom of breast cancer.[16] Cyclic mastodynia is usually most severe in the immediate premenstrual phase and decreases or resolves completely following menstruation. At times, the examination reveals tender, nodular breasts, which suggests a diagnosis of fibrocystic changes, although breast cancer must remain in the differential diagnosis. For most patients, reassurance and use of a supportive bra provide adequate initial

TABLE 104-2 Mastitis, Abscess, and Hidradenitis

	Signs and Symptoms	Treatment	Comments
Puerperal mastitis	Erythematous area on breast with area of well-localized pain Fever, chills, myalgias, flulike symptoms	Frequent breast emptying Routine hand washing prior to breast manipulation Analgesia Antibiotics: Dicloxacillin, 500 milligrams four times a day for 10–14 d *or* Cephalexin, 500 milligrams four times a day for 10–14 d *or* Clindamycin, 300 milligrams four times a day for 10–14 d	Occurs during first few month or weeks postpartum. Breastfeeding may continue. Early antibiotics and milk drainage are cornerstone of treatment. Must rule out abscess if rapid response to antibiotics does not occur. Cover for MRSA. US to differentiate mastitis from abscess. Follow up with obstetrician.
Nonpuerperal mastitis	Erythematous area on breast with area of well-localized pain Fever, chills, myalgias, flulike symptoms	Analgesia Antibiotics: Dicloxacillin, 500 milligrams four times a day for 10–14 d *or* Cephalexin, 500 milligrams four times a day for 10–14 d *or* Clindamycin, 300 milligrams four times a day for 10–14 d *or* TMP-SMX, 160/800 milligrams twice a day	Must rule out abscess if rapid response to antibiotics does not occur. US helps differentiate between mastitis and abscess. Follow up with surgeon.
Breast abscess	Erythematous area on breast with area of well-localized pain Fever, chills, myalgias, flulike symptoms	US-guided needle aspiration for abscess Analgesia Antibiotics: Dicloxacillin, 500 milligrams four times a day for 10–14 d *or* Cephalexin, 500 milligrams four times a day for 10–14 d *or* Clindamycin, 300 milligrams four times a day for 10–14 d *or* TMP-SMX, 160/800 milligrams twice a day	Needle aspiration is first-line treatment. Obtain surgical consultation for treatment failure and multiloculated abscesses. Immunocompromised patients and those with signs of systemic illness require IV antibiotics, surgical consultation, and admission. Follow up with surgeon.
Periductal mastitis	Varies with age: Younger women—cellulitis or recurrent subareolar abscesses Perimenopausal and postmenopausal women—nipple discharge, nipple retraction, or subareolar mass	Analgesia Antibiotics: Dicloxacillin, 500 milligrams four times a day for 10–14 d *or* Cephalexin, 500 milligrams four times a day for 10–14 d *or* Clindamycin, 300 milligrams four times a day for 10–14 d *or* TMP-SMX, 160/800 milligrams twice a day	Dilated or ectatic ducts with retained secretions. Follow up with surgeon.
Hidradenitis suppurativa	Painful superficial cutaneous abscesses along inferior, pendulous surface of breast	Incision and drainage	Chronic inflammatory disease involving the obstruction of sweat glands. Antibiotics may be indicated in immunocompromised patients.

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.

treatment. Refer to a primary care physician for follow-up treatment and consideration of imaging.[17,18]

SKIN AND NIPPLE ABNORMALITIES

NIPPLE DISCHARGE

Table 104-3 lists some common causes of nipple discharge. In general, nipple discharge that is bilateral, occurs with nipple manipulation, and can be expressed from several ducts is not suggestive of cancer. Nipple discharge that originates in a single breast, emanates from a single duct, and is clear, pink, bloody, or serosanguineous is associated with an increased risk of carcinoma.[19] Follow-up with the patient's primary care physician for mammography and possible fluid analysis of the discharge is always needed.

Intraductal papillomas usually present with a unilateral bloody nipple discharge in women from 20 to 40 years of age. Bleeding is secondary to increased tissue vascularity. A mass may not be palpable on examination. Other causes of bloody nipple discharge include mammary duct ectasia and breast cancer. Ductal ectasia involves the stasis or plugging of lactiferous ducts, which then progresses to an infiltrative inflammatory process. The cause of mammary duct ectasia is unknown.

Bilateral spontaneous milky nipple discharge can indicate an elevated serum prolactin level (see earlier discussion under "Abnormal Lactation"). Any postmenopausal nipple discharges are significant, so refer to a breast specialist.

MONDOR'S DISEASE

Mondor's disease is a benign, self-limited superficial thrombophlebitis, usually seen in young women of childbearing age. Patients present with

TABLE 104-3 Possible Causes of Different Types of Nipple Discharge

Type of Discharge	Cause
Purulent	Infection Periductal mastitis
Milky (galactorrhea)	Pregnancy Prolactinoma Pituitary adenoma or intracranial mass Drugs: hormones, psychotropics (phenothiazines), histamine-2 receptor antagonists, antiemetics (metoclopramide), antihypertensives (methyldopa, verapamil)
Serous or serosanguineous	Intraductal papilloma Ductal ectasia Cancer
Watery	Papilloma Cancer
Green, gray, black, or tan	Duct ectasia or periductal mastitis

painful palpable cord or mass in the superficial tissue of the breast, most commonly in the lower quadrants. Skin discoloration, erythema, and nipple retraction may be present. Although the exact cause is unknown, trauma or a local inflammatory process has been linked to Mondor's disease. US can establish the diagnosis of superficial thrombophlebitis. Treatment is nonsteroidal anti-inflammatory medication. Consider thrombophilic evaluation and treatment with low-molecular-weight heparins after hematology consultation.[20] Refer for appropriate follow-up.

NIPPLE IRRITATION

Nipple irritation may be indicative of atopic dermatitis, erosive adenomatosis, or Paget's disease. Erosive adenomatosis is a benign proliferation of the lactiferous ducts presenting with eczema or an erosion of the nipple. Referral to a breast specialist is needed for the latter condition because the treatment is surgical excision. Paget's disease is often heralded by the appearance of a weeping, eczematoid lesion of the nipple. Paget's disease is almost always associated with an underlying breast carcinoma and usually is diagnosed in postmenopausal women. Paget's disease may present with an associated palpable breast mass, often correlating with the presence of an intraductal carcinoma. Because skin edema and inflammatory changes may respond transiently to incorrectly prescribed topical treatments, there is usually a delay of 6 to 12 months in diagnosis. Provide urgent referral for bilateral mammography and follow up with a breast specialist.

FIBROCYSTIC DISEASE AND THE EVALUATION OF A BREAST MASS

Fibrocystic breast disease is a constellation of symptoms linked by the pathognomonic finding of breast cysts. Breast nodularity and tenderness, which occur as a result of breast tissue responses to hormonal cycling, are referred to as *fibrocystic breast disease* or *fibrocystic changes of the breast*. Fibrocystic changes **do not include** skin thickening, edema, discoloration, nipple retraction, or discharge. If the history and physical examination findings in the ED are normal, then outpatient mammography and follow-up with a specialist should occur, regardless of patient age. Further imaging, including additional mammography and MRI, may also be indicated. Women with recurrent or severe symptoms, skin changes, solid masses, nipple abnormalities, or anxiety about the possibility of cancer should be referred to a breast specialist.

Breast cancer is rare in patients <20 years of age and uncommon in women <30 years of age. Risk factors for young women include inheritance of the *BRCA1* or *BRCA2* gene, a history of childhood malignancy, or a history of chest irradiation. A family history of a first-degree relative with breast cancer, increased exposure to endogenous estrogens (nulliparity or delay of childbearing until after age 30), or biopsy-confirmed atypical breast hyperplasia increases the risk for women ≥30 years old. However, most patients diagnosed with breast cancer have only two risk factors: age >50 years and female gender.[21]

Physical signs that should prompt urgent surgical referral include a palpable mass with or without the following: lymphadenopathy, skin ulceration, mass fixation to the chest wall, fixed axillary nodes, and the presence of ipsilateral arm edema.

Characteristics associated with a delayed diagnosis and poorer survival of breast cancer are black race, lower socioeconomic status, unmarried state, normal or false-negative mammogram results, presentation with nipple lesions or axillary mass, and younger age at time of diagnosis.[22-26]

PERIOPERATIVE AND POSTOPERATIVE COMPLICATIONS

BREAST HEMATOMA

Postoperative hemorrhage or expanding hematoma formation is best evaluated immediately and treated by the operating surgeon. Up to 1.5 L of blood can extravasate into traumatized breast parenchyma. Emergent evaluation requires determination of whether the hematoma is expanding, tensely distended, or stable. Expanding hematomas, especially those occurring within the first few postoperative days, may signify the presence of continued bleeding and usually require surgical evaluation for evacuation of the hematoma or ligation of bleeding vessels. Later presentations of breast hematoma are usually managed conservatively with analgesics, a compressive bra, and the correction of any coagulopathy. Aspiration of the hematoma generally is not effective in the ED. The presence of an infected hematoma requires inpatient management with US-guided percutaneous drainage or open surgical drainage; parenteral antibiotics generally are indicated.

WOUND INFECTION

Postoperative wound infections may be treated with an oral first-generation cephalosporin on an outpatient basis if there is no evidence of abscess, systemic signs of toxicity, or immunocompromise. Worsening signs of cellulitis or systemic response to infection, development of purulent drainage, or failure to improve after 48 hours of treatment requires inpatient management. Infections of postoperative drains generally require drain removal and antibiotic therapy. Any fluid collections that develop subsequently usually require drainage either by repeated aspiration or by incision. The operating surgeon should be consulted regarding any postoperative complications.

BREAST IMPLANTS

Approximately 3.5 million people in the United States have breast implants. Patients may present to the ED with complications such as implant rupture, hematoma, seroma, or infection. The risk of implant rupture increases with age but usually occurs after 20 years. Rupture is most commonly spontaneous, but may also be associated with blunt trauma. For saline implants, rupture is easily detected on physical exam by noting the deflated breast on the affected side. This is typically painless, and outpatient follow-up is appropriate. Silicone implant ruptures are more difficult to diagnose on physical exam. US or MRI imaging confirms the diagnosis. Acutely ruptured silicone implants may present with an inflamed, painful breast mass due to silicone extravasation. Although treatment involves surgical removal, patients should be reassured that there is no danger from silicone leakage.[27,28]

In the early breast implant postoperative period, complications such as seromas and hematomas may occur. Despite best practices, the rate of breast implant infections is about 6%, requiring readmission and additional surgery. Causative organisms are predominantly gram positive, with *S. aureus* being the most common agent. First-line treatment is vancomycin with gentamycin. For outpatient treatment, tetracycline and doxycycline are recommended.[29]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 105

Complications of Gynecologic Procedures

Nikki M. Binz

INTRODUCTION AND EPIDEMIOLOGY

Advancements in minimally invasive gynecologic surgical techniques, such as laparoscopy and hysteroscopy, have allowed more outpatient procedures for patients. Postoperative complications among inpatients are now commonly seen out of the hospital. The prevalence of all postoperative complications after gynecologic procedures is reported to be 9%, whereas 3.7% are considered major complications.[1] Hysterectomy is the most common gynecologic surgical procedure performed in the United States, and although considered a safe operation, it results in complications in one of every two to six patients.[2] The most common reasons for ED visits during the postoperative period after gynecologic procedures are pain, fever, and vaginal bleeding.

CLINICAL FEATURES

HISTORY

Patient risk factors for postoperative complications include age >80 years, medical comorbidities, dependent functional status, and obesity or unintentional weight loss.[1] Key historical questions are listed in **Table 105-1**. The interval between surgery and the onset of symptoms is very important in determining the cause of symptoms. For example, postoperative fever is very common, occurring in about 40% of hysterectomy patients.[2] Most cases of early postoperative fevers (<24 hours) are not infectious but rather result from pulmonary atelectasis, hypersensitivity reactions to antibiotics, pyogenic reactions to tissue trauma, or hematoma formation. Fever occurring on postoperative days 3 to 5 may be due to a urinary tract infection. On postoperative days 4 to 6, consider venous thromboembolism, and ≥7 days after surgery, consider a surgical site infection.[2]

PHYSICAL EXAMINATION

Examine all appropriate body systems. Do not assume that the complaint is gynecologic, and investigate other potential explanations of symptom. Postoperative pain and tenderness can be difficult to assess. After laparoscopy, patients may have shoulder or upper abdominal pain because of carbon dioxide bubbles trapped between the liver and diaphragm after insufflation for the procedure, with 50% to 70% of patients still being affected 48 hours after surgery.[3] Postoperative pain and tenderness are concerning if associated with fever, nausea and vomiting, and a change in bowel sounds.

Examine the surgical wound and perform a pelvic examination, including both a sterile speculum and a bimanual examination. **In patients undergoing fertility treatment, defer the pelvic examination until consulting with the gynecologist, due to the possibility of rupturing enlarged ovarian follicles.** During sterile speculum examination, the cervix or vaginal cuff must be visualized. After vaginal hysterectomy, no special precautions are needed for a speculum examination. Note any evidence of bleeding, discharge, erythema, and cuff or labial cellulitis. After a vaginal or abdominal hysterectomy, record the presence of tenderness, masses, and an intact cuff. After hysteroscopy or dilatation and curettage, evaluate cervical motion, uterine, and adnexal tenderness. Perform a rectal examination to assess for tenderness, masses, or fecal impaction.

TABLE 105-1 Key Historical Questions to Assess Postoperative Complications

- Surgical procedure performed
- Route of procedure
  - Abdominal
  - Vaginal
  - Laparoscopic
- Reason for procedure
- Time of symptom onset
- Proximity of symptom to the surgery
- Complications already experienced
- Other postsurgical history
- Medications prescribed

LABORATORY TESTING

Laboratory studies should be directed toward the patient's complaints. A CBC with a manual differential count is almost always indicated. Obtain a serum β-human chorionic gonadotropin level for all women with childbearing potential. A clean-catch or catheterized urine specimen along with urine, blood, wound, and cervical (if present) cultures should be obtained if the patient is febrile. A complete chemistry panel may be necessary to evaluate hepatic and renal function.

Imaging is often necessary. A chest radiograph can confirm pneumonia or inappropriate air under the diaphragm. **Air or insufflated carbon dioxide should be completely absorbed by the third postoperative day.** Supine and erect abdominal series help confirm bowel obstruction. Although pelvic sonogram is helpful for visualizing the pelvic structures, CT is the gold standard for diagnosing most postoperative abdominal complications, with a sensitivity and specificity of >90%.[4] MRI may be indicated in the evaluation of septic pelvic thrombophlebitis.

COMPLICATIONS OF ENDOSCOPIC PROCEDURES

LAPAROSCOPY

Gynecologic laparoscopy is used for diagnosis and treatment. Indications for laparoscopy are listed in **Table 105-2**. Laparoscopy is almost always an ambulatory surgical procedure and is performed under general anesthesia with endotracheal intubation.

After cesarean section, abortion, cholecystectomy, and coronary angioplasty, surgical tubal sterilization is the next most common operation in the United States, with over 600,000 procedures performed annually.[5] When not performed postpartum with cesarean sections, the procedure is almost always performed laparoscopically.[6] Laparoscopic hysterectomy is another common procedure, usually performed for abnormal uterine bleeding and fibroids.[7]

Reported overall laparoscopic complication rates range from 0.2% to 10.3%.[8] Major laparoscopic procedures are associated with a higher rate of complications compared with minor procedures (0.6% to 18% vs. 0.06% to 7.0%, respectively).[8] Robotic-assisted laparoscopy is becoming more common in gynecologic procedures and may have even lower rates of complications than general laparoscopy (6.3% vs. 16.3%, respectively).[7]

Both diagnostic and therapeutic gynecologic laparoscopy are accomplished by passing a rigid endoscope through a trocar that is inserted bluntly through a small infraumbilical incision into the abdominal cavity after a Veress needle has been used to insufflate the abdomen with carbon dioxide. The pneumoperitoneum must be sufficient to displace the bowel and is maintained throughout the surgery. Additional trocars

TABLE 105-2 Common Indications for Laparoscopy

- Sterilization
- Lysis of adhesions
- Carbon dioxide laser ablation of endometriosis
- Uterine surgery (including myomectomy)
- Tubal surgeries (including salpingectomy)
- Ovarian surgery (including oophorectomy and oophorocystectomy)
- Paraovarian cyst excision
- Hysterectomy

TABLE 105-3 Major Complications Associated With Laparoscopy

- Bowel injury
- Thermal injury
- Vascular injury
- Urinary tract injuries
- Incisional hernia
- Wound dehiscence

TABLE 105-4 Complications Associated With Hysteroscopy

- Fluid overload
- Uterine perforation
- Postoperative bleeding
- Gas embolism
- Infection

may be placed so that other accessories can be used during the surgery. The majority of complications occur during entry of these instruments.

All laparoscopic procedures entail the same potential complications (**Table 105-3**), but more complex surgeries carry considerably more risk.

Bowel injury is uncommon (<1%),[2,9] but may not be noted at the time of surgery. **Patients with greater than expected pain after laparoscopy should be considered to have a bowel injury until proven otherwise.** Signs and symptoms include abdominal pain and distention, fever, nausea, vomiting, and an elevated WBC count. Plain radiographs may show an ileus or free air under the diaphragm. Complications include peritonitis, abscess, enterocutaneous fistula, and septic shock. There are three major types of bowel injury: traumatic, thermal, and vascular.

Although many significant complications of laparoscopy are recognized in the operating room under direct visualization, **thermal injury** can easily be missed. Patients may not develop symptoms for several days or weeks postoperatively.[10-12] Early gynecologic consult is critical if a thermal injury is suspected, because damage is usually more extensive than may be apparent.

Vascular injury is uncommon[10-12] and is usually recognized during the operation. Patients may later present with a postoperative hematoma, which requires wound exploration by the gynecologist.

The rate of **urinary tract injuries** is about 4%.[13] Injuries can occur from mechanical or thermal trauma. Trocar or dissection injuries to the bladder are typically recognized intraoperatively. Thermal injuries, however, may not be initially apparent and may present later as peritonitis or fistula. The diagnosis of a ureteral injury is usually delayed. Thermal injury may present up to 14 days postoperatively with abdominal or flank pain, fever, and peritonitis. An abdominopelvic CT with IV contrast shows extravasation of urine or a urinoma. Mechanical obstruction of the ureter from sutures or staples may be recognized intraoperatively by direct visualization but may also present up to 1 week postoperatively with fever and flank pain. An IV pyelogram or CT helps define the site and degree of obstruction.

Incisional hernias and dehiscence are rare complications after laparoscopy. Incisional hernias are more common when defects >10 mm are made and can develop within the first postoperative week. Patients may be asymptomatic or may note pain, mass, evisceration, or signs and symptoms of a mechanical bowel obstruction. Fever may present if the bowel is incarcerated, and peritonitis may develop after bowel perforation. Dehiscence usually involves protrusion of the omentum and, in rare cases, the small bowel. Immediate incisional repair by a gynecologist is usually sufficient; however, a laparotomy is needed for bowel incarceration or perforation.

Wound infection after laparoscopy is uncommon. Most infections are minor skin infections that can be managed with oral antibiotics and possible drainage. Antibiotics should cover against staphylococci, including methicillin-resistant *Staphylococcus aureus* and streptococci. Excluding minor skin infections, pelvic infection is quite rare and includes pelvic cellulitis, abscess, and necrotizing fasciitis.

HYSTEROSCOPY

Hysteroscopy is the direct visualization of the cervical canal and endometrial cavity using a rigid or flexible fiberoptic instrument. Hysteroscopy can be done as an office procedure under IV sedation or in an operating room. Complications (**Table 105-4**) are uncommon and occur more frequently as a result of operative hysteroscopy than diagnostic hysteroscopy.[14]

The most common indication for hysteroscopy is abnormal vaginal bleeding. Other indications include uterine leiomyomata, intrauterine adhesions, proximal tubal obstruction, removal of intrauterine devices, müllerian anomalies, and infertility evaluation. Therapeutic applications include directed biopsies, removal of small myomata or polyps, and endometrial ablation for menorrhagia. In addition, hysteroscopic sterilization is growing in popularity. The Essure® microinsert system is currently the only method available in the United States. The device is deployed in the fallopian tube and stimulates surrounding tissue growth, resulting in fallopian tube occlusion and permanent sterilization. The failure rate to prevent pregnancy is reported as high as 2.5%.[15] Approximately 4% to 8% of Essure® patients develop new pelvic pain and frequently need subsequent surgery.[15]

With hysteroscopy, uterine perforation is rare and usually noted at surgery. Infection is very rare and most commonly occurs in patients with concurrent genital tract infections. Postoperative bleeding can be uterine or cervical in origin. Cervical lacerations are caused by forceful dilation or tears from the tenaculum. Uterine bleeding can result from resection procedures. Gas embolism is the most feared complication of using carbon dioxide gas as a distention medium for laparoscopy.[16] This complication is likely to occur during or shortly after insufflation.

COMPLICATIONS OF MAJOR GYNECOLOGIC-ABDOMINAL SURGERY

Complications from major abdominal procedures that lead to ED visits usually occur at least 3 days postoperatively (**Table 105-5**).

Hysterectomy remains one of the most common major surgical procedures in the United States, with the abdominal approach composing 60% of cases (14% laparoscopic and 26% vaginal).[2,17] A total hysterectomy is removal of the uterus and part or all of the cervix and is unrelated to removal of the ovaries. A subtotal hysterectomy involves removal of the uterus without removal of the cervix. Patients may be unsure of the type of hysterectomy that was performed.

The risk of postoperative infection after hysterectomy is 3% to 10%, with higher rates in the abdominal versus the vaginal approach.[18] Risk factors for postoperative infections include obesity, diabetes, and long operative time.[18] The overall rate of all complications after hysterectomy is much higher for malignant versus benign indications (19.4% vs. 7.9%, respectively).[19]

WOUND INFECTION

Most wound infections occur within the first 2 postoperative weeks; however, they can present several months after surgery. Symptoms include fever and increased pain at the incision site. Examination reveals

TABLE 105-5 Common Complications Related to Major Gynecologic-Abdominal Surgery

- Wound infection
- Infected vaginal cuff hematoma, cellulites, or abscess
- Ovarian abscess
- Dehiscence and evisceration
- Bleeding
- Phlebitis
- Urinary tract infection/urinary retention
- Bladder and ureteral injury
- Ileus, bowel injury, and bowel obstruction
- Pneumonia and atelectasis

wound tenderness, skin erythema, induration, purulent discharge from the incision, and possible dehiscence.

Empiric antibiotics should provide coverage against staphylococci, including methicillin-resistant *S. aureus*, and streptococci. If an **incisional abscess** is diagnosed, first open and drain the wound. Probe the wound with a sterile cotton swab to confirm an intact fascia. Then, irrigate the wound copiously with normal saline and pack with saline-soaked wet-to-dry dressings. If staples have been placed, they should be removed. Obtain aerobic and anaerobic cultures to tailor antibiotic therapy.

For invasive infections, consult with the operating gynecologist. Give parenteral antibiotics and, usually, admit to the hospital.

WOUND SEROMA AND HEMATOMA

Wound seromas and hematomas are very common. They are characterized by drainage, rather than fever or pain, and can be visualized by bedside US. Small seromas and hematomas can be managed by observation and will usually resolve spontaneously. Large seromas can be aspirated. Infected hematomas typically present 10 to 14 days postoperatively. If there are any signs of infection, the wound should be opened and drained and then packed with wet-to-dry dressings.

VAGINAL CUFF CELLULITIS AND PELVIC ABSCESS

The vaginal cuff formed during hysterectomy is composed of the contiguous retroperitoneal space immediately above the vaginal apex and the surrounding soft tissue. Vaginal cuff cellulitis usually occurs early after surgery. Patients complain of fever; purulent vaginal discharge; and pelvic, back, or abdominal pain. Pelvic examination reveals tenderness and induration of the vaginal cuff and purulent discharge.

Vaginal cuff and pelvic abscesses and infected hematomas are rare and usually present 10 to 14 days postoperatively. Symptoms include fever, chills, tachycardia, pelvic pain, and rectal pressure. Examination findings include lower abdominal and vaginal cuff tenderness, a tender or fluctuant mass near the cuff, and bloody or purulent drainage from the cuff. US or CT can define the size and location of an abscess or hematoma.

Admit patients for parenteral antibiotics and possible drainage by interventional radiology or colpotomy. Give broad-spectrum antibiotics, such as imipenem-cilastatin, gentamicin and clindamycin, or ciprofloxacin and metronidazole, to cover gram-negative and gram-positive bacteria and anaerobic organisms.[20]

DEHISCENCE AND EVISCERATION

Wound dehiscence is the failure of normal healing and the disruption of fascia and peritoneum. Evisceration occurs when omentum or bowel presents through the incision. The classic sign of impending dehiscence is the sudden outpouring of serosanguineous blood from the incision. The patient may describe a "pop" or tearing sensation. Most often, dehiscence occurs between postoperative days 5 and 8 for abdominal surgeries.[21]

Vaginal cuff dehiscence usually occurs 1.5 to 3.5 months after hysterectomy.[22] Patients complain of postcoital bleeding, watery discharge, and pelvic pain. If bowel evisceration has occurred, patients note vaginal and pelvic pressure or a bulge.

When abdominal evisceration has occurred, cover the abdomen with moist sterile towels and support the dressing with tape to prevent further gut extrusion. The patient should be taken directly to the operating room for closure. In cases in which there is a sudden appearance of blood but no bowel, it is best to follow the same procedure because evisceration usually is imminent. Vaginal cuff dehiscence can be managed conservatively if small or partial, whereas large or complete vaginal cuff dehiscence usually requires surgical closure.

GENITOURINARY INJURY

Genitourinary injury occurs more often during the performance of abdominal hysterectomy than during any other pelvic surgery. Most **bladder injuries** are apparent at the time of surgery, but some ureteral injuries go unrecognized. Ureteral injury occurs less frequently than bladder injury but is generally underestimated. Operative injury to the ureter results from one of three types of trauma: crushing, transection, or ligation. Each type of injury can be either partial or complete.

Suspect **ureteral injury** in women who develop flank pain shortly after surgery. Fever, hematuria, and costovertebral angle tenderness may also be present. Obtain a urinalysis and abdominopelvic CT with IV contrast. Admit to the hospital for ureteral catheterization under cystoscopic guidance and possibly exploratory laparotomy. Percutaneous nephrostomy with delayed repair may also be considered. Provide parenteral antibiotics if infection is suspected.

Vesicovaginal fistulas can become evident 10 to 14 days after surgery with a watery vaginal discharge. The diagnosis can be confirmed by inserting a cotton tampon into the vagina and then instilling methylene blue or indigo carmine dye via a transurethral catheter. If the tampon stains blue, a vesicovaginal fistula is present. If no staining occurs, a ureterovaginal fistula must be ruled out by injecting 5 mL of indigo carmine dye IV. If a ureterovaginal fistula is present, the tampon should stain blue within 20 minutes.

Gynecologic consultation is necessary. Patients with a vesicovaginal fistula require prolonged urinary drainage with a Foley catheter. Although some fistulas close spontaneously, most require surgical repair.

OTHER COMPLICATIONS

Urinary tract infection is a common complication.[2] For detailed discussion, see Chapter 91, "Urinary Tract Infections and Hematuria." Urinary retention in a healthy female after gynecologic surgery is uncommon. **Urinary retention** is usually a temporary result of pain or bladder atony resulting from anesthesia. However, many women experience either an inability to void or incomplete emptying of the bladder during the postoperative period, most frequently after radical hysterectomy or surgeries that involve the urethra and bladder neck (i.e., anterior repair or any modification of the retropubic urethropexy). Retention is initially relieved with insertion of a Foley catheter for 12 to 24 hours. Most patients are able to void after this period. For further discussion, see Chapter 92, "Acute Urinary Retention."

Pulmonary emboli account for nearly 40% of all deaths after gynecologic surgery.[2] The prevalence of postoperative deep venous thromboembolism is 11% to 25%.[2] Fifty percent of venous thromboembolic events occur in the first 24 hours after surgery, and 75% occur in the first 3 postoperative days. There is no difference in the incidence of venous thromboembolism between abdominal, vaginal, or laparoscopic hysterectomy, but risk factors include age >60 years, cancer, and other comorbidities.[23] For complete discussion of diagnosis and treatment, see Chapter 56, "Venous Thromboembolism Including Pulmonary Embolism."

Septic pelvic thrombophlebitis complicates 0.1% to 0.5% of gynecologic procedures, more commonly after cesarean delivery than hysterectomy.[24] The two forms of septic pelvic thrombophlebitis, ovarian vein thrombosis and deep septic pelvic thrombophlebitis, often occur together. Signs include abdominal pain and fever. The diagnosis may be aided by CT and MRI, but a negative study does not exclude disease.[24,25] Treatment is anticoagulation and parenteral antibiotics. Long-term anticoagulation is not needed unless septic pulmonary emboli develop.

POSTCONIZATION BLEEDING

High-grade squamous intraepithelial lesions of the cervix are treated by loop electrocautery, laser ablation, or cold-knife conization. The most common complication of conization procedures is bleeding, which can be rapid and severe. Delayed hemorrhage may occur 7 to 14 days postoperatively.

Visualization of the cervix is the key to controlling bleeding. Application of **Monsel solution** (a commercially available ferrous subsulfate solution) is a reasonable first step if it is readily available. Monsel solution should be available from the hospital pharmacy. Direct pressure for 5 minutes with a large cotton-tipped swab may also be effective. Alternatively, cauterization with silver nitrate may be attempted. If these maneuvers are unsuccessful, consult the gynecologist for suturing or cauterization of the bleeding arteriole. The vagina can be packed with

TABLE 105-6 Complications Associated With Induced Abortion

Timing	Complication	Possible Etiologies
Immediate complications: within 24 h after procedure	Bleeding, pain	Uterine perforation, cervical lacerations
Delayed complications: between 24 h and 4 wk after procedure	Bleeding	Retained products of conception, postabortive endometritis
Late complications: >4 wk after procedure	Amenorrhea, psychological problems, Rh isoimmunization	—

gauze if the bleeding is severe while waiting for definitive therapy. Often the patient must be taken to the operating room for repair because adequate visualization is difficult in the ED.

INDUCED ABORTION

There are three major methods for termination of pregnancy: instrumental evacuation by vaginal route, stimulation of uterine contraction, and major surgical procedures. Overall, less than 1% of women have complications.[26] Complications can be categorized by time after procedure: immediate, delayed, or late (**Table 105-6**).

Due to the approval of mifepristone in 2000, medical abortions now account for 36% of abortions at 9 or fewer weeks of gestation.[27] The evidence-based regimen of mifepristone 200 milligrams orally followed by a single dose of buccal misoprostol 800 micrograms 24 to 48 hours later results in a 99.6% efficacy of pregnancy termination.[27] Common side effects include nausea, vomiting, diarrhea, headaches, dizziness, and fatigue. Methotrexate, in combination with misoprostol, is an alternative therapy. A higher frequency of complications occurs in medical induction versus surgical abortion, most notably infection and retained placenta.[28]

Incomplete abortion and **retained products of conception** occur in 0.5% of medical abortions and 0.29% to 1.96% of all abortions.[29] Women present with abdominal pain, bleeding, and possibly fever. On physical examination, the cervical os is usually open, and the uterus is boggy, enlarged, and tender. A pelvic US is the diagnostic test of choice and can identify a thickened endometrium and retained echogenic contents. Treatment consists of dilatation and curettage or medical management with misoprostol. If coexistent endometritis is present, treatment with broad-spectrum antibiotics is required for at least 10 to 14 days.

Postabortal **endometritis** not associated with retained products of conception presents with a closed cervical os and a firm yet tender uterus. Uncomplicated endometritis is treated with antibiotics.

Uterine perforation occurs in approximately 0.1 to 3 per 1000 abortion procedures.[30] Most perforations are noted at the time of surgery; however, small perforations may go unnoticed. Patients can present with pain and/or bleeding and, possibly, signs of shock.

If a **cervical laceration** is noted, treatment includes pressure, followed by application of Monsel solution or use of silver nitrate sticks. Suturing may be necessary if there is no resolution of bleeding.

Women who are Rh negative require Rh0 (D) immunoglobulin, 300 micrograms IM, after spontaneous or induced abortion. If it is not prescribed within 72 hours, the overall risk of sensitization in the second pregnancy is approximately 3%.

Obtain gynecologic consultation for all patients with complications after induced abortion.

INTRAUTERINE DEVICES

Serious complications from intrauterine devices are rare, occurring in less than 1% of patients, and include pelvic inflammatory disease, ectopic pregnancy, and uterine perforation.[31] In the event that an intrauterine device string is not visible on pelvic examination, transvaginal ultrasonography should be performed, as it detects translocation of the intrauterine device in 55% to 85% of patients.[32] If left untreated, translocated intrauterine devices may lead to life-threatening complications such as a pelvic abscess or less commonly bladder or bowel injury; therefore, **all patients with extrauterine or fractured intrauterine devices should have urgent referral to a gynecologist for surgical removal**.[32]

The risk of pelvic inflammatory disease in intrauterine device users is more related to preexisting sexually transmitted infections rather than the intrauterine device itself.[33,34] Patients may present to the ED for intrauterine device removal for other reasons, such as irregular menses or pain; however, patients should be referred to their gynecologist for removal.

If referral is impractical, grasp the string of the intrauterine device with a Kelly clamp or long forceps and pull with steady, gentle force until the intrauterine device emerges from the uterus. Do not jerk the string because it may detach from the intrauterine device, making removal more difficult.

ENDOMETRIAL ABLATION

Endometrial ablation is used to treat abnormal uterine bleeding. Although there are numerous technologies, they share similar postoperative complications, including pregnancy after ablation, pain-related obstructed menses, and infection. Pregnancy incidence after endometrial ablation is 0.7%.[35] There is a much greater risk of complications during these pregnancies, including preterm birth, intrauterine scarring, and postpartum hemorrhage. Also, the ectopic rate is 6.5%, almost three times the baseline risk. Persistent endometrium is common after ablation, as are uterine contracture and scarring. This results in obstructed egress of menses, causing cyclic cramping and pain. The incidence of infectious complications ranges from 1% to 2%, including endometritis, myometritis, pelvic inflammatory disease, and pelvic abscess.[35] Patients present with fever, uterine and/or adnexal tenderness, and vaginal discharge usually within 3 days of surgery.

PELVIC ORGAN PROLAPSE SURGERY AND SYNTHETIC MESH

Surgery using transvaginal mesh can be used to treat pelvic organ prolapse. Associated complications include bladder perforation, mesh erosion and vaginal exposure, chronic pelvic pain, dyspareunia, infection, and fistula formation.[36] This has prompted the U.S. Food and Drug Administration to release several public notifications on the safety and effectiveness of transvaginal mesh for treatment of prolapse; therefore, many surgeons have decreased or eliminated its use.[37]

ASSISTED REPRODUCTIVE TECHNOLOGY

Transvaginal US-guided aspiration of oocytes is used during in vitro fertilization. Complications related to US-guided retrieval and preparation for retrieval of oocytes are rare and include **ovarian hyperstimulation syndrome**, pelvic infection, intraperitoneal bleeding, and adnexal torsion. Occasionally, complications develop hours to weeks after the procedure and require prompt surgical intervention.

Ovarian hyperstimulation syndrome is a clinical diagnosis that commonly occurs in women going through in vitro fertilization. Symptoms may begin as soon as 24 hours after human chorionic gonadotropin administration but become most severe after 7 to 10 days.[38] Mild disease occurs in 20% to 33% of in vitro fertilization cycles, presenting with abdominal distention, ovarian enlargement <8 cm, and weight gain; however, mild ovarian hyperstimulation has little clinical consequence.[38] The moderate-to-severe form is seen in 1% to 6% of patients undergoing assisted reproduction.[38] Symptoms of severe disease include rapid weight gain, ovarian enlargement >12 cm, tense ascites due to third spacing of fluid into the abdominal cavity, pleural effusions, tachypnea, orthostatic hypotension due to hypovolemia, tachycardia, progressive oliguria, and electrolyte abnormalities. Increased coagulability and decreased renal perfusion are also noted. Rarely, it can be a life-threatening complication.

Bimanual pelvic examination is contraindicated due to extremely fragile ovaries that are at high risk of rupture or hemorrhage. Defer examination until after discussion with the gynecologist. Laboratory evaluation includes a CBC, chemistry panel, coagulation studies, and blood for type and cross-match. An ECG to evaluate hyperkalemia should also be obtained.

Treatment in the ED consists of IV volume repletion, respiratory support, pain control, and possibly paracentesis and/or pleuracentesis. Consult the gynecologist for admission. Patients with suspected adnexal torsion should undergo evaluation with Doppler US.

POSTEMBOLIZATION SYNDROME

Uterine artery embolization is a safe, effective approach for treating symptomatic uterine fibroids that may help patients avoid myomectomy and hysterectomy. It is an outpatient procedure performed by interventional radiologists in collaboration with the gynecologist. Compared to hysterectomy, uterine artery embolization is less expensive, results in a move favorable short-term quality of life, and has a significantly lower rate of major complications.[39]

Postembolization syndrome is characterized by abdominal pain, fever, and leukocytosis after embolization and occurs in 2.8% of patients.[39] It is likely caused by an inflammatory response to myometrial and fibroid ischemia and necrotic tissue. Symptoms begin 1 to 2 days after the procedure and can last up to 7 days. In the ED, control pain and consider other possible causes for symptoms, particularly infection such as endometritis. Evaluation may include a CBC and a CT scan. Vaginal discharge and fibroid expulsion may be seen on pelvic exam. Approximately 1% of patients require hysterectomy due to infection. Some patients may require admission for pain control and IV antibiotics.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 12

Pediatrics

CHAPTER 106

Emergency Care of Children

Garth D. Meckler

INTRODUCTION

Children are not just small adults. This standard mantra is heard in EDs around the world. About one third of all ED visits are by children. Anatomic, physiologic, and developmental differences between children and adults give rise to a unique epidemiology, pathophysiology, and differential diagnosis. Key elements of the medical history must often be elicited from caretakers, not from the child, and symptoms are often inferred from observation. It may be difficult to perform a physical examination on a child, and cardinal signs of disease are different in children compared to adults. Diagnostic testing can cause pain or potentially long-term harm. Drugs require weight-based dosing, and equipment selection must be tailored to the child's size. Disposition may require transfer to a specialized children's hospital. Finally, even though the child is the primary patient, management must be family centered and often involves addressing the fears and stresses of family members.

ANATOMY AND PATHOPHYSIOLOGY

Pediatric age groups are divided into *neonates* (birth to 1 month), *infants* (1 month to 1 year), *toddlers* (1 to 3 years), *school-aged children* (3 to 12 years), and *adolescents* (12 to 18 years). Significant developmental and physiologic changes occur across these age groups; **Table 106-1** summarizes the developmental milestones as they relate to the ED evaluation and approach, and **Table 106-2** lists the age-dependent vital signs.

Neonates undergo the most profound changes as they transition from metabolic and respiratory dependence on the placenta to independence as air-breathing beings. The cardiovascular and respiratory systems switch from near complete shunting of blood flow away from the lungs to typical adult circuitry and dependence on the lungs for oxygenation as the ductus arteriosus closes (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease"). Oxygen-avid fetal hemoglobin changes to adult hemoglobin with predictable changes in hemoglobin levels throughout the first years of life. The neonatal and infant immune systems depend on passive maternal humoral protection transferred through the placenta and breast milk until cellular and humoral defenses mature. Immunologic immaturity predisposes to bacterial and viral systemic infections early in life (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children"). The neurologic system is characterized by rapid growth, differentiation, and myelination and changes in the balance of excitatory and inhibitory neurotransmitters, which account for susceptibility to seizures.

Anatomically, growth and development of every organ system characterizes infancy and childhood and affects emergency care across the life span. A relatively large occiput, small jaw, high and anterior larynx, narrow cricoid cartilage, and large tongue require unique considerations in airway management (see Chapter 113, "Intubation and Ventilation in Infants and Children"). A soft, compliant chest wall, obligate nose breathing, and gastric inflation from swallowed air alter the mechanics, symptoms, and signs of respiratory distress in young children. **Neonates, infants, and children increase cardiac output through an increase in heart rate rather than stroke volume.** Tachypnea, an increased rate of breathing, not hyperpnea, an increased depth of respiration, is the primary respiratory compensatory mechanism. The musculoskeletal system of young children differs from that of older children and adults not only in its proportions (e.g., relatively large head), but also because **ligaments are stronger than bones, predisposing to fractures rather than sprains**. Linear growth of long bones occurs from specialized cartilaginous end plates (physes), which results in unique fracture patterns (see Chapter 141, "Pediatric Orthopedic Emergencies").

EPIDEMIOLOGY

In the United States, consider congenital anomalies, inherited disorders (see Chapter 146, "Metabolic Emergencies in Infants and Children"), complications of prematurity and pregnancy, and accidental and nonaccidental trauma in the first year of life. Injuries, malignancy, and congenital heart disease are the predominant causes of death among children after the first year of life, with injury, suicide, and homicide becoming leading killers in adolescents. Worldwide, infectious diseases, including diarrheal illness, respiratory infections, and preventable or treatable conditions such as measles, malaria, and human immunodeficiency virus infection, predominate.

CLINICAL FEATURES

HISTORY

For preverbal children, obtain the medical history from caregivers. The reliability and quality of historical information are variable. Astute caregivers know their children well and often infer symptoms and complaints from subtle changes in behavior that may not be apparent to the ED physician; this is particularly true for children with special healthcare needs whose medical history and technology may be complex (see Chapter 148, "The Child with Special Healthcare Needs"). The expression of some cardinal symptoms of disease varies by age group. For example, vomiting and crying are both common and nonspecific in younger children and may signal serious disease including infection, heart disease, metabolic disease, and surgical abdominal disease.

For neonates and infants, carefully review maternal complications during this and previous pregnancies: a history of spontaneous abortions or maternal liver disease, for example, may indicate inherited metabolic disease, and maternal infections may be congenitally acquired by the neonate. The birth history is important, because gestational age, complications of labor and delivery, and immediate perinatal events alter the differential diagnosis.

Review growth and development and childhood immunizations (**Table 106-3**) to assess overall health. For older children and adolescents, the history should be obtained from both the child and caregiver. Social history becomes important, including questions about risk taking.

PHYSICAL EXAMINATION

The examination is different for children in each developmental stage. Infants are easily separated from parents, whereas children 1 to 3 years of age have stranger anxiety and must be examined in a parent's lap. Crying may make evaluation of the heart, lungs, and abdomen difficult. The sequence of examination should progress from the least to most

TABLE 106-1 Pediatric Developmental Stages and ED Assessment

Stage	Milestone	Strategy
Early infancy (0–6 mo)	Motor: lifts head, reaches	Observation
	Verbal: cooing	Examine in parent's arms
	Social: responsive smile	Direct approach
Late infancy (6–18 mo)	Motor: reaches/obtains, sits, walks	Observation
	Verbal: jargon, few words	Examine in parent's arms
	Social: stranger anxiety/ dependence	Indirect approach
Toddler (18–36 mo)	Motor: walks well, scribbles	Observation
	Verbal: speaks in phrases	Indirect approach
	Social: stranger anxiety/ autonomy	
Preschool (3–5 y)	Motor: runs well, colors	Indirect or direct approach
	Verbal: speaks in sentences	Explain briefly just before procedures
	Social: magical thinking	
School age (5–12 y)	Motor: schoolwork, sports	Direct approach
	Verbal: concrete reasoning	Explain in detail before procedures
	Social: task oriented	
Adolescence (12–17 y)	Motor: adult	Direct approach
	Verbal: abstract reasoning	Confidentiality
	Social: autonomy, rebellion	Treat as adult

invasive aspects. Adolescents require special considerations for privacy and autonomy.

Vital signs are age dependent (see Table 106-2). For best precision, obtain rectal temperature in infants and young children. Measure blood pressure in all four extremities when considering congenital heart disease. Calculate weight and growth percentiles, including head circumference in infants. Observe skin color, capillary refill, and respiratory effort. For infants and children, note the response to stimulation and check motor tone to identify listlessness or lethargy. Meningismus is present in <15% of infants with bacterial meningitis. Focal abdominal tenderness is difficult to appreciate in the younger child, which leads to delay in the diagnosis of conditions like appendicitis. Skin temperature, color, and capillary refill are affected by ambient temperature, fear, and pain. The inability of the infant to take a deep breath on command makes chest auscultation less reliable for the diagnosis of pneumonia in young infants compared with older children (see Chapter 128, "Pneumonia in Infants and Children").

DIAGNOSIS

LABORATORY EVALUATION

The pretest probability of disease varies by the child's age and the potential differential diagnosis. The sensitivity and specificity of many common laboratory tests may be unique for children compared with adults. Urinalysis, for example, may be less sensitive for detecting infection in young infants who do not store urine long enough to allow accumulation of inflammatory or metabolic markers (e.g., leukocyte esterase and nitrites). Conversely, noninvasive collection of urine by perineal bag or "clean catch" in young infants, although sensitive, lacks specificity in infants due to perineal contamination with bacteria. Other common laboratory screening tests, such as the basic metabolic panel and CBC, have little specificity and predictive power for most childhood conditions (see Chapter 131, "Vomiting, Diarrhea, and Dehydration in Infants and Children"; Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children"; and Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children"). Unless specifically directed by the history and examination, screening labs that are commonly used in adults add little value to the routine evaluation of common pediatric emergencies such as dehydration, febrile seizures, and chest pain. Carefully consider the need for blood tests in children, because of the technical difficulties and the anxiety and pain caused by venipuncture.

IMAGING

Weigh the potential risks and benefits of diagnostic imaging in children. The lifetime risk of a fatal malignancy from a single CT scan may be as high as 1 in 2000 in infants and 1 in 5000 for older children.[1] Ionizing radiation from medical imaging increases the risks of both leukemia and brain cancers.[2,3] If infants and young children require sedation for imaging, the risks of sedation are added to the risk of ionizing radiation. Radiographs can be avoided for a number of childhood respiratory conditions (see Chapter 127, "Wheezing in Infants and Children"). Ultrasound is the imaging modality of choice for a number of disease conditions in children, such as pyloric stenosis, appendicitis, and **intussusception**. Bedside ultrasound (e.g., FAST), although standard in adults, is less reliable in children.

TREATMENT

Many treatment parameters are age specific. Resuscitation principles differ for neonates, children, and adults (see Chapter 108, "Resuscitation of Neonates" and Chapter 109, "Resuscitation of Children"). Neonatal resuscitation focuses primarily on respiratory assistance with effective positive-pressure ventilation. **Children maintain normal blood pressure until very late in critical illness**, so compensated shock and respiratory distress require early and aggressive intervention; **cardiac arrest**

TABLE 106-2 Pediatric Vital Signs by Age (Awake and Resting)

Age	Heart Rate, Upper Limit (beats/min)	Respiratory Rate, Upper Limit (breaths/min)	Blood Pressure,* Lower Limit (mm Hg)	Weight,† (kg)
0–1 mo	180	60	60/40	3–4
2–12 mo	160	50	70/45	5–10
12–24 mo	140	40	75/50	10–12
2–6 y	120	30	80/55	13–25
6–12 y	110	20	90/60	25–40
>12 y	100	20	90/60	40–60

*May be estimated by:

Systolic blood pressure (5th percentile) = 70 + [2 × (age in years)]

† May be estimated by:

12 mo: weight (kg) = 4 + (age in months/2)

1–12 y: weight (kg) = 10 + [2 × (age in years)]

TABLE 106-3 Recommended Childhood Immunizations

	Vaccine*												
Age	DTaP (Tdap >6 y)	Hib	Hep B	Polio	Pneumococcal (conjugate)	Rotavirus	HPV	MMR	VZV	Hep A	Meningococcus (conjugate)	Influenza†	BCG
Birth			C, U, W										W
2 mo	C, U, W	C, U, W	C, U, W	C, U, W	C, U, W	C, U, W							
4 mo	C, U, W	C, U, W	C, W	C, U, W	C, U, W	C, U, W							
6 mo	C, U, W	C, U, W	C, U, W	C, U, W	U, W	C, U, W						C, U, W	
12–15 mo		U			C, U			C, U, W	C, U, W	U, W	C, W		
15–23 mo	C, U, W	C		C						U			
2–4 y								C	C		W		
4–6 y	U			C, U				U	U				
10–12 y	U						C, U, W				C, U		
13–15 y	C												
16 y											U		
17–18 y													

Abbreviations: BCG = bacillus Calmette-Guérin; C = Canada (Public Health Agency of Canada); DTaP = diphtheria, tetanus, acellular pertussis; Hep A = hepatitis A; Hep B = hepatitis B; Hib = *Haemophilus influenzae* type b conjugate; HPV = human papilloma virus; MMR = measles, mumps, rubella; U = United States (Centers for Disease Control and Prevention); W = World Health Organization.

*The exact sequence varies according to manufactured brand of vaccine, and many combination vaccines and conjugate vaccines with variable serotypes exist. Schedule is approximate. World Health Organization (W) guidelines recommend additional vaccination of high-risk patients for the following: Japanese encephalitis, yellow fever, tick-borne encephalitis, typhoid, cholera, and rabies. See http://www.who.int/immunization/documents/positionpapers for more information.

†Given annually beginning as early as 6 months of life; requires two-vaccine series for children under 9 years of age; avoid live vaccine in children <2 years of age and those with asthma or who are immunocompromised.

is most commonly secondary to respiratory failure in children, rather than primary as in adults. Try to include parents and caretakers in the room during pediatric resuscitation.

Children require special medication dosage calculations based on weight or body surface area due to age-dependent metabolic pathways and differing body composition, volumes of drug distribution, and organ development. Most prescription medications have not been formally tested in children and do not have specific U.S. Food and Drug Administration approval for use in children due to the ethical and practical difficulties of performing drug trials in children. Common medications can have adverse effects in children, such as dental staining from tetracycline antibiotics and life-threatening complications from antimotility drugs commonly used for adult diarrheal disease.

Children generally do not understand the transient nature of painful procedures or of their relative risks and benefits. Such comprehension allows adults to consent to and cooperate with common emergency procedures. Chapter 115, "Pain Management and Procedural Sedation in Infants and Children," discusses the pharmacologic and nonpharmacologic approach to this important topic.

Caretakers make legal decisions on behalf of their children. Consent for treatment and procedures must be obtained from legal guardians for all minors except in cases of emergency medical necessity. A variable exception is the confidential provision of care to adolescents with regard to their reproductive and mental health.

DISPOSITION AND FOLLOW-UP

Disposition decisions in children require consideration of caretaker abilities and indications for transfer to another institution. Discharge to reliable caretakers is an important part of practice guidelines for many common pediatric conditions, including minor head injury (see Chapter 138, "Seizures in Infants and Children") and fever without source in the infant (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children"). Children requiring hospitalization may require transfer to a tertiary-care pediatric hospital. The emergency physician has responsibility for determining the need, risks, and benefits of transfer, and the mode of transporting children to a higher level of care. Ultimately, the disposition requires close communication with receiving facilities and with the child's family.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 107

Neonatal and Pediatric Transport

Daniel G. Ostermayer

INTRODUCTION

Regionalization, the organization of a coordinated system of care across a geographic area, combines all necessary components of care to optimize patient outcomes. Regionalized intensive care for neonatology and pediatric care[1] focuses expensive, high-technology, labor-intensive therapies to a few regional centers. This model of care originated from trauma center regionalization demonstrating reduction of morbidity and mortality for trauma patients at designated trauma centers.[2,3] Because patients in need of specialized services often present to other hospitals, interfacility transport is an important complement to regionalized intensive care.[4] Specialized pediatric transport services improve safety, decrease unplanned adverse events (especially airway events), and lower mortality.[4-6] This chapter reviews the general and pediatric considerations for the interfacility transport of critically ill neonates and children.

THE TRANSPORT TEAM

The American Academy of Pediatrics has published transport guidelines based on expert consensus.[7] Caring for critically ill children is best accomplished with at least two patient care providers on each team in addition to the driver or pilot. One of the patient care members should be a registered nurse with a minimum of 5 years of experience, typically

at least 3 years of neonatal or pediatric critical care or ED training.[4] Additional member(s) may include a respiratory therapist, physician, or paramedic. The condition of the child and local resources determine the exact composition of the specialized transport team. For helicopter EMS transports, the most common care arrangement involves a paramedic and neonatal or pediatric care nurse in addition to the pilot. Similar arrangements of one paramedic and a critical care nurse or two critical care nurses with neonatal and pediatric expertise are frequently used for ground transports. Accreditation agencies and professional associations will guide local and regional team compositions.

TRANSPORT ENVIRONMENT

Transporting critically ill patients adds to the risks of the illness or injury because of the hazards associated with the transport environment, particularly for neonates and children.[8] The features of transport that distinguish the transport environment from the ED setting and the effects of these features on patients and caretakers are outlined in Chapter 3, "Air Medical Transport." All the risks of transport still apply, with the additional need for awareness of the emotional and mental state of the child. Also, since one parent often accompanies the child, additional weight considerations must be accounted for during aeromedical transport.

PRECAUTIONS

Suggested guidelines to minimize the impact of the limitations inherent in a transport environment are:

1. *Prepare the transport vehicle*. Transport vehicles should be prepared to meet the special needs of children (e.g., accessory lighting, controlled thermal environment) and should be stocked with the necessary equipment. A list of the minimum necessary equipment for ambulances, which can serve as a guide for EMS agencies, has been published by the Emergency Medical Services for Children program.[9] Transport modality–specific risks should also be considered.
2. *Stabilize the patient before transport*. Unless the immediate needs of the patient can only be met in the receiving hospital (e.g., emergent surgery), ample time should be devoted to stabilizing the patient in the referring hospital. Time spent undertaking goal-directed intensive care interventions early in the course of the patient illness at the referring hospital does not worsen patient outcomes.[10]
3. *Monitor as many physiologic parameters as possible electronically*. Because physical examination is difficult during transport and because children often are transported during dynamic changes in their physiologic condition, electronic monitoring is essential. Children are especially **at risk for hypothermia and hypoglycemia**.[11] Important monitoring equipment commonly used during transport includes cardiorespiratory monitor (selected based on its size, weight, battery life, and resistance to motion artifact); continuous pulse oximetry with a plethysmographic waveform to assist in identifying motion artifact; temperature monitor (of infants and incubator air temperature); continuous end-tidal carbon dioxide waveform monitoring, which can aid in early identification of unplanned extubation[12]; and invasive or noninvasive blood pressure monitoring. Lowering endotracheal cuff pressures during aeromedical transport can help reduce excessive tracheal pressure.[13]
4. *Anticipate deterioration*. Preparation of the patient should include not only care for the identified problems but also anticipation of problems that may arise during transport. The application of this principle may lead to performance of procedures or therapies before transport such as gastric decompression, placement of a chest tube for pneumothorax, or transfusion (**Table 107-1**).[14]

SITUATIONS REQUIRING TRANSPORT

There are severe conditions for which interfacility transports are more common, and neonates require more interfacility transports than older children. Although many community hospitals can care for a pregnant mother and child, premature infants require more resources and often need transfer to a neonatal intensive care unit for care. Likewise, pediatric and neonatal patients with sepsis, seizure disorder, shock, or severe neurologic and metabolic conditions can quickly overwhelm the clinical staff at a small hospital. Current expert consensus for transport of sick or injured children recommends physicians understand sending and receiving resources before deciding to transfer (**Table 107-2**).[7]

TABLE 107-1 Pediatric Conditions at Risk for Deterioration During Transport

- Pneumonia
- Recurrent brief resolved unexplained event
- Foreign body aspirations
- Airway obstructions
- Epilepsy
- Poisoning or overdose
- Multisystem or severe intracranial trauma
- Tracheitis
- Severe asthma
- Metabolic derangements
- Severe sepsis

DECISION TO TRANSPORT

Children require transfer to a regional center if the current or anticipated medical care needs of the patient exceed the resources of the local hospital. Arranging transfer to the regional center can occur simultaneously with assessment, resuscitation, and stabilization at the local hospital. Discussion with the receiving hospital and specialists can aid in decisions regarding the mode of transport and composition of the transport team. Preestablished transfer protocols should provide information about each regional center to which a patient might be referred, including (1) special services available; (2) criteria for referral; (3) telephone numbers for consultation, referral, and transport; (4) distance and usual response time; (5) type of transport personnel and their capabilities; (6) type of transport vehicles; and (7) protocols for preparation of patients. Establish formal agreements with regional centers that outline the circumstances under which patients can be transported without prior administrative approval. As with adults, proper assessment of the patient's injury pattern must factor into transport mode. Aeromedical transports have become increasingly more frequent with increased hospital emergency department closure and regionalization of pediatric specialty care facilities, especially for surgical services, trauma, and burns.[15,16]

MODE OF TRANSPORT

In many areas, physicians have a choice between air and ground transportation. This decision should be made collaboratively between the referring and accepting physicians.[17,18] The risks and benefits of air transport are discussed in Chapter 3, "Air Medical Transport." Time, distance, traffic, weather, geographic constraints, and availability all factor into the decision regarding mode of transport. The most important factor determining the type of transport will be team availability and skill level. The most capable care team may not be available for a ground transport, making flight a

TABLE 107-2 Pediatric Conditions Commonly Requiring Interfacility Transports

- Intracranial trauma
- Severe trauma
- Airway (upper or lower) airway disorders
- Sepsis/septic shock
- Seizures
- Developmental or neurologic condition
- Poisoning or overdose
- Intracranial trauma
- Multisystem trauma

safer option. When the transport team arrives, the referring physician and local ED staff should be available to coordinate the transition of care and ensure that any required ongoing therapy can be continued.

PREPARATION FOR TRANSPORT

Nearly all patients should have **intravascular access** during transport. Critically ill children should have at least two lines of vascular access in case one becomes dislodged or several medications need to be administered simultaneously. For newborns, consider using umbilical vessels for vascular access. Intraosseous cannulation is an alternative technique for fluid and drug administration when intravascular lines cannot be placed or the severity of illness demands immediate access (see Chapter 114, "Vascular Access in Infants and Children").

In small children, IV lines should be infused with the use of pumps. Open "drips" should not be used, even with volumetric drip chambers, because of the risk of fluid overload from inadvertent administration of large boluses. The amount of fluid administered before and during transport should be monitored and carefully recorded.

A small subset of children may do better without IV placement, because IV placement can agitate the child and further compromise the airway. This is particularly true for children with a partial airway obstruction from croup, a foreign body, or epiglottitis. The best measure in the situation of partial airway obstruction may be to keep the child as calm as possible, allow the child to sit in the caregiver's lap during transport, and refrain from IV placement.

CONDUCT OF A TRANSPORT

Once the decision has been made to transport a child, the referring hospital has certain legal obligations to the patient in addition to provision of medical care.[19] In the United States, the referring physician is responsible for arranging an appropriate mode of transport to a hospital capable of providing the services needed by the patient and stabilizing the patient as best as possible before transport. The referring physician should inform caregivers of the need for transfer and the risks and benefits, and discuss the transport modality. Written consent for transport should be obtained from a parent or other legal guardian. Important documentation to provide for the receiving facility and care team includes a copy of the current medical record, laboratory data, radiographs, and old medical records, if available.

Clear communication between the referring and receiving physicians is essential. Standardized techniques can help mitigate communication errors, such as the **ISBARQ (introduction, situation, background, assessment, recommendation, questions) model** developed by Children's Hospital of Philadelphia: During the *introduction*, the referring physician and patient are identified; the *situation* is conveyed by the working diagnosis and current medical condition; *background* includes what is known about the patient, such as past medical history and past tests or treatments; *assessment* communicates what is happening at the time of transport (current findings, patient needs, treatments, new test results); *recommendations* are made by receiving physicians regarding further stabilization of the patient, sometimes at the request of the referring doctor (although referring physicians are not obligated to follow these recommendations if they are considered to be medically inappropriate or beyond the capabilities of the referring hospital); and the process concludes with mutual *questions* that allow for further clarification.

For most critically ill children, ideal care is provided when the ED of the referring hospital devotes its energy to providing emergent short-term medical care and the responsibility for transport is left to a regional center. This is particularly true for neonates because of the special equipment and expertise required for transport. When transport services are not provided by the regional center or when time is critical, the only option may be for the referring hospital to provide transport. In these circumstances, it is the responsibility of the referring center to ensure the adequacy of care, as best as possible given available resources and personnel, during transport.

Referring providers should provide the family members with written directions to the receiving institution when they are not able to accompany their child in the transport vehicle. Additional helpful information includes parking information, nearby accommodations, and visiting policies of the receiving institution, if known. Allowing a family member to accompany the child during ground transport is valued by the patient and family and does not interfere with the delivery of care.[20,21] Clear communication with family members about the medical needs of the patient, appropriate parental behavior, and logistics involved may help alleviate disruptions during transport. Ultimately, if it is anticipated that family member involvement will diminish the quality of care, it will be necessary to encourage them to meet their child at the receiving institution.

CONSENT FOR TRANSPORT

In most of the United States, the legal age of majority is 18 years old. However, in most states, mothers <18 years of age have authority to consent for medical therapies for their children unless specifically prohibited by court order. Likewise, in many states, medical care for minors can be given without parental consent when it is emergent or involves reproductive health. Thus, the definition of the age of majority is situational and must be addressed on an individual basis within the confines of both federal and state law. In situations in which transport of a minor patient is advisable and a parent or guardian is not available (often the case with pediatric traumas), the minor patient can be transported under the principle of beneficence. In these cases, legal authorization for interfacility transport requires documentation from the referring physician stating that failure to transport would endanger the patient's well-being.

SHARED DECISION MAKING

Discussing clinical situations will help with solidifying an understanding of balancing potential benefit and risks of harm from transport. Shared decision making allows for both incorporation of patient and family values and preferences. For example, a family may wish to transport a child with an injured extremity to the pediatric hospital by private vehicle. If there is no need for monitoring or risk for decompensation while en route, a private vehicle will offer benefits of lower cost, immediate availability, and familiarity to the child. The disadvantage includes lack of neurovascular or hemodynamic monitoring. On the other extreme, take the example of a rural facility with access to only fixed wing transport that needs to transfer a child with multilobar pneumonia. The process involves waiting on the dispatch, transporting by ground to the runway, awaiting landing, preparation of a plane, and transport. Parents may consent to this delay and cost because the benefits involve the ability to cover a large distance quickly, pressurize the cabin for high-altitude travel, and greater space for safer clinical care. These situations highlight the need for shared family decision making and conversations with transfer centers and transport agencies to individualize pediatric care.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 108

Resuscitation of Neonates

Marc F. Collin

INTRODUCTION AND EPIDEMIOLOGY

Resuscitation of the newborn is required to some extent in nearly 10% of all births. Extensive resuscitation is required in about 1%. Delivery room resuscitation is required for >50% of the high-risk population of very-low-birth-weight (<1500 grams) newborns. Worldwide, nearly 25% of neonatal deaths result from birth asphyxia.[1] With proper antenatal and intrapartum surveillance, the potential need for active

resuscitation at birth can often be identified before birth. Unfortunately, the arrival of a newborn to the ED is never planned. This chapter reviews the principles of emergency resuscitation of neonates.

PATHOPHYSIOLOGY

The transition from intrauterine to extrauterine life is a high-risk time. Even the normal laboring process places significant stress on the placental–fetal unit. Blood flow and, therefore, oxygen delivery are transiently impaired during uterine contractions. Compression of the umbilical cord, when it occurs, further impairs circulatory flow. Although antenatal/intrapartum US imaging and fetal heart tone monitoring have permitted better surveillance of fetal well-being, prediction of fetal status at birth remains inexact. Maternal complications of pregnancy can predispose newborns to complications and include infections, chronic or gestational disease (e.g., diabetes, lupus), and illicit or prescribed medication use. Complications of labor, such as preterm delivery and/or prolonged rupture of membranes, maternal fever, breech or transverse fetal position, placental abruption, and umbilical cord problems such as a nuchal cord (cord wrapped around the neck) or true knots in the cord, can significantly heighten the risk to the fetus.

Once delivery occurs, the newborn still faces a variety of risks as the transition to extrauterine life unfolds. Requirements of this transition include the onset of respiration, absorption of lung fluid, reduction of pulmonary vasculature resistance to allow flow to the pulmonary vascular circuit, and closure of the ductus arteriosus and foramen ovale. Premature infants and infants who are small for gestational age are at risk for additional challenges in transitioning from fetal to infant physiology including insufficient pulmonary surfactant, fragile germinal matrices within the cerebral ventricles, and thin skin that impairs thermoregulation. The transition from the sterile intrauterine environment to the extrauterine world teeming with bacteria places yet another burden on the newborn.

CLINICAL FEATURES

HISTORY

Obtain a brief history from the mother, including the date of last menstrual period/estimation of gestational age, number of fetuses, number of previous pregnancies and living children, history of diabetes, hypertension or pregnancy-related problems, prenatal care (including blood group, infectious serologies, genetic and US screening, and known congenital anomalies), prolonged rupture of membranes, fever, and meconium-stained amniotic fluid.

PHYSICAL EXAMINATION

The need for resuscitation or routine newborn care is determined by the initial physical examination. For the term infant who is crying or breathing and who has good muscle tone at delivery, provide routine newborn care with the infant skin-to-skin on the mother. A slightly more detailed examination using the Apgar scoring system has been used for generations to assist medical personnel in assessing newborns both for the need for resuscitation and the response to resuscitation. Evaluate the newborn at 1 and 5 minutes after delivery for **heart rate** (absent = 0, <100/min = 1, >100/min = 2), **respiratory effort** (absent = 0, weak = 1, crying or normal = 2), **muscle tone** (limp = 0; some flexion = 1; active, fully flexed = 2), **reflex irritability** (no response = 0, grimace = 1, crying or active = 2), and **color** (blue or pale = 0, acrocyanosis = 1, completely pink = 2). If the 5-minute Apgar score is <7, continue Apgar scoring at 5-minute intervals until a score of 7 or more is reached. The expanded Apgar scoring system includes a section to document resuscitative measures.[2] For infants requiring resuscitation, monitor pulse oximetry with the probe placed on the newborn's right hand (preductal) (see discussion of targets for resuscitation below).

LABORATORY EVALUATION

Routine laboratory studies are not required for most term or preterm deliveries. However, obtain point-of-care glucose testing in infants born to diabetic mothers, infants who are small or large for gestational age, or depressed or irritable infants, or if there is poor response to the initial steps of resuscitation. Obtain a CBC and type and screen or cross-match of blood in infants requiring significant resuscitation in the setting of suspected blood loss.

IMAGING

Routine imaging is not required for most deliveries. In rare circumstances, a radiograph of the chest and abdomen may be useful to confirm endotracheal tube placement, suspected pneumothorax, and some congenital defects (e.g., diaphragmatic hernia).

PREPARATION AND EQUIPMENT

EQUIPMENT

Table 108-1 lists equipment that may be needed during neonatal resuscitation. A compressed air source, an oxygen blender with flow meter, pulse oximetry for neonatal use, bag-valve masks, and laryngeal mask airways are standard resuscitation equipment.

UMBILICAL CORD CLAMPING

Do not clamp the umbilical cord of newborns (term or preterm) who do not require positive-pressure ventilation or immediate resuscitation for at least 1 to 3 minutes after birth. Delayed cord clamping reduces the need for blood transfusion, increases neonatal iron stores, and may decrease the risk of requiring treatment for hyperbilirubinemia.[1] For newborns requiring immediate intervention, the cord should be clamped and cut to allow for initiation of therapy.

TABLE 108-1 Neonatal Resuscitation Equipment

- Radiant warmer with servocontrol temperature sensor
- Prewarmed towels/receiving blankets
- Wall suction, suction catheters, bulb syringes
- Heated, humidified oxygen source
- Compressed air source and oxygen blender
- Cardiorespiratory monitor/monitor leads
- Pulse oximeter
- Bag (T-piece, flow-inflating or self-inflating) *with* manometer
- Masks (sizes 1, 2, 3, 4)
- Laryngoscope (0, 1 blade)
- Endotracheal tubes (2.5, 3.0, 3.5, 4.0)
- Meconium aspirator
- CO_2 detector
- Nasogastric tubes (5F, 8F)
- IV infusion equipment
- IV fluids (10% dextrose in water, normal saline)
- Umbilical catheter tray
- Curved hemostat
- Two iris curved forceps, no teeth
- Scalpel handle/blade
- Needle holder
- Scissors
- Syringes
- 2 × 2 gauze sponges
- 3.5F, 5F umbilical catheters
- Three-way stopcock
- Suture material
- Umbilical tape
- Povidone-iodine solution
- Polyethylene bags or plastic wrap

ROUTINE NEWBORN CARE

Provide routine newborn care to term infants who are breathing or crying with good tone. Leave the newborn with the mother, provide warmth (skin-to-skin or blankets), clear the nose and mouth with bulb suction only if signs of obstructed breathing are noted, dry the baby, and provide ongoing assessment of respiratory effort and tone. Even before initiation of the ABCs (airway, breathing, circulation) of resuscitation, provide a neutral thermal environment for the newborn. Although vigorous term infants may be placed skin-to-skin with their mother for warmth, preterm or depressed newborns should be placed under a preheated radiant heat source with care taken not to overheat. Place the infant on his or her back in the warmer. Then, gently dry the newborn with a warm towel while preparing to initiate resuscitation. Very-low-birth-weight newborns and those <29 weeks of estimated gestational age should be placed in polyethylene bags that have been developed for that purpose (plastic food wrap or a food-grade 1-gallon plastic bag may also be used). Avoid hyperthermia, which may precipitate apnea and worsen hypoxic-ischemic injury in depressed infants.

RESUSCITATION

Newborn resuscitation almost exclusively involves care of primary respiratory compromise (**Table 108-2**). Consensus guidelines[3] recommend a timed sequence of steps (30, 60, and >60 seconds). Most important is the rapid establishment of effective ventilation and determining the heart rate before initiating CPR.[4,5]

INITIAL STEPS (FIRST 30 SECONDS)

Within the first 30 seconds of birth, provide warmth, and dry and stimulate the baby. Current guidelines[3] no longer advise the routine suctioning of the newborn nose and mouth. **Infants who are spontaneously breathing, whether delivered through clear or meconium-stained amniotic fluid, do not require tracheal suctioning because tracheal suctioning can cause reflex bradycardia and apnea.** If the infant is not breathing initially, dry and provide stimulation by rubbing the back two to three times; if there is no response, open the airway using jaw thrust and towels beneath the shoulders to provide a sniffing position. If there appears to be obstruction from amniotic fluid, gently suction the nose and throat with a bulb or 8F catheter.

After these initial steps, assess the respiratory effort and heart rate.

ONGOING RESUSCITATION (30 TO 60 SECONDS)

After warming, drying, and stimulating, reassess the respiratory effort and the heart rate. If the infant begins breathing without significant effort and with good color, return to the mother for routine care. If the heart rate is >100 beats/min but there is persistent cyanosis or labored breathing, open the airway and suction the nose and mouth if there is a visible obstruction; attach pulse oximetry to the right hand or wrist (preductal) and apply supplemental oxygen to achieve targeted preductal oxygen saturation goals as per **Table 108-3**.

TABLE 108-3 Targeted Pulse Oxygen Levels During Newborn Resuscitation

Time After Birth	Target Oxygen Saturation (preductal)
1 min	60%–65%
2 min	65%–70%
3 min	70%–75%
4 min	75%–80%
5 min	80%–85%
10 min	85%–90%

Apneic or depressed newborns delivered through meconium are at risk for meconium aspiration syndrome, but current evidence indicates that tracheal suctioning does not reduce morbidity or mortality.[3] Naloxone is not recommended for treatment of neonatal respiratory depression, even after maternal opioid exposure or use, as naloxone may actually precipitate seizure activity in a newborn of an opiate-using mother.[3] Provide usual respiratory support and ventilation.

Initiate positive-pressure ventilation using a bag and mask for infants with a heart rate of <100 beats/min or who are gasping or remain apneic after the initial steps of newborn resuscitation. Begin resuscitation using room air because newborn blood oxygen levels, even in healthy newborns, take time to reach extrauterine values and excessive oxygenation is associated with increased mortality.[6] Table 108-3 provides subsequent oxygen saturation goals throughout neonatal resuscitation.

POSITIVE-PRESSURE VENTILATION

Provide positive-pressure ventilation with a self-inflating or flow-inflating infant bag or a T-piece resuscitator for all newborns with a heart rate <100 beats/min or who are gasping or apneic after 30 seconds. Bradycardia, even extreme, is typically the result of respiratory failure, and chest compressions or medications should not be initiated until effective ventilations have been provided. Administer positive-pressure ventilation if available. Use a manometer to monitor peak inspiratory pressures: a peak inspiratory pressure of 20 cm H_2O is usually sufficient, although initial peak inspiratory pressures as high as 30 cm H_2O may be required. Generally, T-pieces and flow-inflating bags are preferred, because they allow better control of inflation pressures. Self-inflating

TABLE 108-2 Steps in Neonatal Resuscitation

Newborn Appearance	Management	Comments
Infant breathing, crying, good tone	Routine care: warm, dry, delay cord clamping 1–3 min, observe	Vigorous term babies may be warmed skin-to-skin with mother.
Poor tone/respiratory effort *or* respiratory distress	Warm, open airway and clear nose and mouth (only if obstructed), dry, stimulate	Stimulate nonvigorous babies after drying by rubbing back vigorously several times.
Labored breathing or persistent cyanosis with HR >100 beats/min	Clear the nose and mouth, monitor O_2 saturation; provide O_2 only to maintain levels in Table 108-3. Consider CPAP.	Oxygen monitor should be placed on right upper extremity (preductal).
Apnea, gasping, or HR <100 beats/min	PPV Continue PPV for 30 s, taking corrective steps for ventilation if no improvement in HR	Provide PPV with bag-mask ventilation at a rate of 40–60 breaths/min using room air. Provide 30 cm H_2O pressure for term infants and 20–25 cm H_2O pressure for preterm infants.
HR <60 beats/min	Initiate CPR: 3:1 compression-to-ventilation ratio 90:30 compressions and ventilations per minute	Use thumb-encircling technique to provide chest compressions to lower one third of sternum. Consider intubation prior to chest compressions.
HR <60 beats/min after appropriate ventilation and CPR	Administer epinephrine Consider volume expansion if blood loss; treat hypoglycemia	May be given IO, IV, or through a UV or ETT.

Abbreviations: CPAP = continuous positive airway pressure; ETT = endotracheal tube; HR = heart rate; O_2 = oxygen; PPV = positive-pressure ventilation; UV = umbilical vein.

bags are superior if supplemental air or oxygen is unavailable; however, these cannot provide continuous positive airway pressure alone. Be careful when using a self-inflating bag, because pop-off valve pressures, usually set at 30 to 40 cm H_2O, can be exceeded if excessive pressure is applied. T-piece resuscitators have the advantage of delivering a consistent pressure with each artificial breath. **Excessive inflation pressures can cause pneumothorax and compromise resuscitation. Provide 40 to 60 breaths/min**. Good chest rise and an increase in heart rate (usually within 5 to 10 breaths) are the best indicators of effective ventilation.

Most infants will respond to initial positive-pressure ventilation as outlined above. The most likely reason for a poor response to positive-pressure ventilation is inadequate positive-pressure ventilation, and corrective steps should be taken to ensure effective ventilation prior to further resuscitation measures. The American Heart Association recommends use of the mnemonic "MR SOPA," which stands for **M**ask (adjust to improve the seal), **R**eposition the head to open the airway, **S**uction the mouth then nose, **O**pen the mouth with a jaw thrust, and increase the **P**ressure until chest rise is noted (maximum peak inspiratory pressure, 40 cm H_2O), and if none of these is effective, proceed to definitive **A**irway control (endotracheal intubation). Infants with significant labored breathing may benefit from **continuous positive airway pressure ventilation**.

ENDOTRACHEAL INTUBATION

In the absence of improvement with bag-mask ventilation, endotracheal tube insertion and ventilation are indicated. Other potential indications for endotracheal intubation in the newborn include (1) concomitant need for chest compressions, (2) administration of endotracheal medications, and (3) known or suspected congenital diaphragmatic hernia (to avoid inflating stomach/bowel situated in the chest).[7]

The technique and equipment for endotracheal intubation are discussed in detail in Chapter 113, "Intubation and Ventilation in Infants and Children."

ADVANCED RESUSCITATION: CIRCULATION (>60 TO 90 SECONDS)

If, despite adequate assisted ventilation for 30 seconds, the newborn remains severely bradycardic with a heart rate <60 beats/min, start chest compressions. Deliver chest compressions to the lower one third of the sternum to a depth of about one third of the anteroposterior diameter of the chest. The compression phase should be slightly shorter than the relaxation phase to allow for cardiac filling. Avoid simultaneous compressions and ventilation. Deliver chest compressions and ventilations in a ratio of **three chest compressions to one breath for a total of 90 compressions and 30 breaths/min**.

There are two techniques to perform chest compressions.[7] In the "two-thumb" technique, the chest is compressed with both thumbs with the fingers encircling the newborn's back. In the "two-finger" technique, the operator's second and third digits compress the lower one third of the sternum, often with the other hand supporting the newborn's back. The two-thumb technique seems to be superior in generating greater peak systolic pressures. The two-finger technique may be more practical if a colleague is simultaneously attempting umbilical vessel catheterization.

Stop chest compressions when the heart rate exceeds 60 beats/min. Once chest compressions have been discontinued, increase the ventilation rate to 40 to 60 breaths/min, because interference from the chest compressions is no longer an issue. Slowly wean positive-pressure ventilation when the heart rate exceeds 100 beats/min and the newborn has begun to breathe spontaneously.

Medications and Volume Expansion **If bradycardia continues despite bag-mask ventilation followed by endotracheal intubation, adequate ventilation with 100% oxygen, and chest compressions for 45 to 60 seconds, then give epinephrine. Epinephrine is the primary drug used for neonatal resuscitation and should be administered IV or IO, although it can be given** via the intratracheal route **(use larger dose below) if vascular access cannot be obtained (see "Vascular Access" below for umbilical venous catheter placement). The dose of epinephrine is 0.01 to 0.03 milligram/kg IV/IO** (0.1 to 0.3 mL/kg of 1:10,000 solution). Intratracheal dosing is 0.05 to 0.1 milligram/kg or 0.5 to 1 mL/kg of 1:10,000 solution. Naloxone and sodium bicarbonate are no longer recommended for routine use in neonatal resuscitation. **Naloxone is contraindicated in the newborn when maternal narcotic addiction is suspected, because neonatal seizures may result. Sodium bicarbonate may worsen intracellular acidosis.**[8,9]

Consider **volume expansion** when there is known or suspected blood loss (pallor, poor perfusion, or weak pulses). Administer 10 mL/kg of 0.9% saline solution (normal saline) or O-negative blood. Volume should be given slowly (3 to 5 minutes), especially to premature infants who are at risk for intraventricular hemorrhage.

Hypoglycemia in neonates is associated with adverse outcomes following birth asphyxia, whereas hyperglycemia is not. The diagnosis and treatment of hypoglycemia are discussed in detail in Chapter 146, "Metabolic Emergencies in Infants and Children."

Postresuscitation Care Newborns with any degree of asphyxia, even those who respond to resuscitative efforts, require a period of close observation. Transfer or admission to a special care nursery or neonatal intensive care unit will depend on the degree of resuscitation required.

Several large trials have demonstrated significant decrease in mortality and improved 18-month neurologic outcomes among term (≥36 weeks of gestational age) newborns with moderate to severe hypoxic-ischemic encephalopathy treated with hypothermia.[7,10-12] Consider inducing hypothermia at 33.5°C (92.3°F) for term (36 weeks or greater) neonates requiring extensive resuscitative care,[13] and obtain emergency neonatologist consultation whenever possible. If cooling therapy is being considered, turn off the warmer to immediately initiate passive cooling and monitor temperature continuously.

VASCULAR ACCESS

Peripheral venous access is often difficult in the newborn, so IO access is a good alternative. The most readily available site for venous access in the newborn is the umbilical vein. Vascular access techniques, including both IO and umbilical vein cannulation, are discussed in detail in Chapter 114, "Vascular Access in Infants and Children."

WITHHOLDING AND DISCONTINUING NEONATAL RESUSCITATION

The ED is typically the site of precipitous, unplanned deliveries. It is difficult to identify with precision the week of gestation based exclusively on the anatomic features of the fetus. If there is uncertainty about gestational age, infant weight, or viability, it is best to err on the side of resuscitation and call for consultation.

A fetus at <22 weeks of gestation and weighing <400 grams is not viable. At 22 weeks of gestation, survival ranges from about 10% to 50%; at 23 weeks of gestation, survival is about 35% to 60%; and at 24 weeks of gestation, survival is about 60% to 80%.[14,15] Begin resuscitation on newborns ≥22 weeks of gestation.

DISCONTINUING NEONATAL RESUSCITATION

Newborns with no sign of life after 10 minutes of continuous and active resuscitation are virtually certain to suffer severe morbidity and/or mortality if continued resuscitation is successful in restoring vital signs. **Therefore, it is justified to cease resuscitative efforts after 10 minutes and, certainly, after 15 minutes of asystole.**[7]

SPECIAL PROBLEMS IN THE NEWBORN

NEONATAL CYANOSIS

Cyanosis is a common finding in the newborn. The first step is differentiating central cyanosis from peripheral cyanosis.

Peripheral cyanosis, or acrocyanosis, is a normal finding in the first few days of life secondary to vasomotor instability and requires no specific evaluation or intervention. Central cyanosis is cyanosis involving

TABLE 108-4 Causes of Neonatal Central Cyanosis

Airway Obstruction (retractions and/or grunting respirations; stridor)	Cardiac Disorders (tachypnea*, no grunting or retractions)	Pulmonary Disorders (tachypnea* with grunting and/or retractions; rales or rhonchi)	CNS and Metabolic Disorders (slow, shallow respirations without retractions)
Choanal atresia	Transposition of great arteries	Respiratory distress syndrome	Intracranial hemorrhage
Laryngeal web/cyst	Tricuspid atresia	Meconium aspiration syndrome	Brain anomalies (Dandy-Walker malformation, congenital hydrocephalus)
Tracheal stenosis	Truncus arteriosus	Pneumonia	Central hypoventilation syndrome
Pierre Robin sequence	Total anomalous pulmonary venous return	Congenital diaphragmatic hernia	Polycythemia
Cystic hygroma/goiter	Pulmonary atresia	Pulmonary hypoplasia	Hypoglycemia
	Coarctation of aorta Hypoplastic left heart syndrome Primary pulmonary hypertension of the newborn	Congenital lobar emphysema Congenital cystic adenomatoid malformation	Sepsis/shock Methemoglobinemia

*Tachypnea defined as >60 breaths/min.

the mucous membranes/lips, tongue, and skin. It indicates the presence of at least 4 to 5 grams/dL of unsaturated hemoglobin. The very anemic newborn may present as pale but not cyanotic if the level of unsaturated hemoglobin is below the 4 to 5 grams/dL threshold.

The breathing pattern often provides valuable clues to the cause of cyanosis (**Table 108-4**). On auscultation, unilaterally decreased breath sounds with retractions are associated with a pneumothorax or a space-occupying lesion of the chest. Bilaterally decreased breath sounds with retractions may suggest upper airway obstruction. Stridor also suggests an upper airway etiology. Rales and rhonchi may be heard with pneumonia, respiratory distress syndrome, or meconium aspiration syndrome. A thorough knowledge of the differential diagnosis for cyanosis allows for quick, organized assessment, diagnosis, and treatment.

Obtain simultaneous preductal (e.g., right radial) and postductal (e.g., lower extremity) or arterial blood gases to help diagnose persistent pulmonary hypertension of the newborn: the postductal PaO_2 is significantly lower than the preductal PaO_2. Using pre- and postductal pulse oximetry may serve the same purpose.

A discrepancy between upper and lower limb blood pressures or reduced femoral pulses may suggest coarctation of the aorta. Babies with coarctation of the aorta often develop new-onset tachypnea and absent femoral pulses later in the first day of life or into the second day of life. Femoral pulses are palpable at birth but disappear after the ductus arteriosus has closed with coarctation of the aorta.

Patients with hypoplastic left heart syndrome may present with poor pulses in all four limbs, poor perfusion, and tachypnea after the immediate newborn period once the ductus arteriosus has closed (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease").

Stepped evaluation and treatment are described in **Table 108-5**.

Evaluation The **hyperoxia test** is a quick method to help differentiate a cardiac from a noncardiac cause for cyanosis. Place the newborn in a 100% hood for 10 minutes. Cyanotic newborns with a pulmonary disorder can increase their PaO_2 to >100 mm Hg (or oxygen saturation >20% as a proxy). Those with a fixed shunt secondary to congenital cyanotic heart disease or the right-to-left shunting of persistent pulmonary hypertension of the newborn cannot do so.

Obtain a chest radiograph to identify pulmonary disease, abnormalities of pulmonary blood flow, and abnormalities of heart size and shape. If physical examination and chest radiograph have not pointed to a particular diagnosis, an echocardiogram will be needed later on. An echocardiogram is not necessary in the ED during the initial resuscitation.

Treatment **Although oxygen therapy is the mainstay of treatment for cyanosis, treat the underlying cause.** Provide positive-pressure ventilation (continuous positive airway pressure or endotracheal intubation and mechanical ventilation) to the cyanotic newborn with significant respiratory symptoms. Monitor blood gas and pulse oximetry. Establish vascular access and initiate 10% dextrose in water at 3.3 mL/kg/h (80 mL/kg/24 h) if in the first 24 hours of life. Check serum glucose every 30 to 60 minutes until stable. Administer empiric antibiotics for sepsis while obtaining appropriate labs (CBC with differential count and platelets, blood culture, chest radiograph, and, possibly, urine culture and C-reactive protein).

If, after initial examination and testing, cyanotic heart disease cannot be ruled out, begin an infusion of **prostaglandin E_1 starting at 0.05 microgram/kg/min, and titrate to the lowest effective dose** to maintain ductal patency.

PNEUMOTHORAX

Pulmonary air leaks are seen more commonly in newborns with respiratory distress syndrome, meconium aspiration syndrome, pneumonia, pulmonary hypoplasia, and congenital diaphragmatic hernia. Pneumothoraces may occur in the otherwise normal newborn in the first few minutes after birth due to increased intrathoracic pressure created with the onset of respiration in the fluid-filled newborn lungs. Air can also dissect into the pulmonary interstitium, mediastinum, pericardium, peritoneum, and subcutaneous space. Pneumothoraces may also be iatrogenic secondary to overexuberant bagging during resuscitation, especially with already compromised lungs. Unfortunately, the disorders that most commonly lead to pneumothoraces are also associated with respiratory distress and cyanosis, which may delay the suspicion and diagnosis of the pneumothorax.

Clinical Features and Diagnosis Tension pneumothorax requires rapid treatment to avoid severe respiratory compromise, cardiovascular collapse from impaired venous return to the heart, and, possibly, death.

TABLE 108-5 Steps to Evaluate and Treat Neonatal Central Cyanosis

- Identify breathing pattern to characterize infant into airway obstruction, cardiac pulmonary, or CNS/metabolic pattern.
- Obtain peripheral oxygen saturation pre- and postductal, check pulses in all 4 extremities, and obtain ABG.
- Perform hyperoxia test. Deliver 100% oxygen for 5–10 min. Congenital cyanotic heart disease cannot increase oxygen saturation >20% or raise PaO_2 to 100 mm Hg.
- Obtain stat chest radiograph to identify pneumothorax, congenital diaphragmatic hernia, or pulmonary infiltrates, and assess cardiac size and shape and pulmonary vasculature for clues to congenital heart disease.
- Establish vascular access in umbilical or peripheral vein, obtain POC glucose, CBC, and metabolic panel. Treat hypoglycemia (glucose <40 milligrams/dL [2.22 mmol/L]) with 10% dextrose in water, 2 mL/kg IV bolus, or 3.3 mL/kg/h.
- Institute continuous positive airway pressure or intubate and ventilate if oxygen saturation does not improve with standard methods for oxygen delivery.
- If oxygenation still does not improve, treat as presumptive congenital cardiac disease with prostaglandin E_1 starting at 0.05 microgram/kg/min and titrate to the minimum effective dose.

Abbreviations: ABG = arterial blood gas; POC = point of care.

In the preterm newborn, tension pneumothoraces are also highly associated with subsequent intracranial hemorrhage, presumably secondary to venous backup into the cerebral circulation.

Tachycardia, tachypnea, and retractions are noted. On auscultation, breath sounds are decreased on the side of the pneumothorax. If there is a tension pneumothorax, heart sounds and point of maximum impulse may be displaced in the direction away from the pneumothorax. Transillumination of the chest with a bright light is another method to help rapidly establish pneumothorax, by "lighting up" the pleural air. Bedside US can also potentially identify pneumothorax. Chest radiograph will confirm the diagnosis.

Treatment The management of a pneumothorax depends on pneumothorax size and the tension it creates in the pulmonary space. A nontension pneumothorax can be observed without evacuation. In a term or near-term newborn, the nitrogen washout technique, placing the baby in a 100% oxygen hood for 6 to 12 hours, may accelerate clearance of the air leak. This technique is contraindicated in preterm newborns due to concerns of oxygen toxicity to the lungs and retinas.

Emergency evacuation of a tension pneumothorax may be performed with an 18- or 20-gauge 1-inch percutaneous catheter. Instill local anesthetic at the insertion site before the procedure if the patient is not in extremis. After elevating the neonate's affected side with towels under the back, insert the catheter into the fourth intercostal space at the anterior axillary line, which should correlate with the nipple line. Once the pleural space is penetrated, withdraw the needle, and attach the catheter to a three-way stopcock connected to a 10- or 20-mL syringe. Open the stopcock to the syringe, and aspirate the pleural air. More than one syringe of air may be evacuated if a large pneumothorax is present. Clinical improvement should occur after removal of the pleural air. A 10F or 12F chest tube or an 8.5F pigtail catheter can then be placed.

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernias are frequently diagnosed prenatally with US, which expedites proper initial newborn resuscitation.

Anatomically, congenital diaphragmatic hernia is a diaphragmatic defect, either posterolaterally through the foramen of Bochdalek or, less commonly, through the retrosternal foramen of Morgagni. Most are left-sided.[16-19] The diaphragmatic defect allows intra-abdominal contents, including stomach, bowel, and, occasionally, liver, to enter the chest during the second trimester of gestation, leading to pulmonary hypoplasia.

The lung ipsilateral to the diaphragmatic defect is hypoplastic, although the degree of hypoplasia may vary. Ultimate morbidity and mortality are determined both by the extent of hypoplasia of the contralateral lung secondary to compression from the abdominal contents in the thoracic space and whether or not the liver is located in the thorax and associated anomalies.[17] Total lung volumes >45% of normal are predictive of survival.[18] Significant associated malformations, especially cardiac defects, are seen in 25% to 50% of patients with congenital diaphragmatic hernia.

Clinical Features The clinical hallmark is persistent respiratory distress at birth, often with a characteristic "seesaw" side-to-side respiratory pattern due to the severely hypoplastic ipsilateral lung. A halting, gasping type of respiratory pattern along with persistent cyanosis is frequently noted. The abdomen appears scaphoid, because abdominal contents are partially situated in the thoracic space. Auscultation of bowel sounds in the chest strongly suggests the presence of congenital diaphragmatic hernia. Radiographic examination is confirmatory.

Treatment Rapid endotracheal intubation is the treatment of choice for respiratory distress. **Bag-mask ventilation will inflate the GI contents in the chest and will further compromise ventilation.** Endotracheal intubation followed by ventilation with a rate of 40 to 50 breaths/min and lowest peak inspiratory pressures that allow for normal chest rise will help avoid pneumothoraces due to barotrauma to the hypoplastic lungs. Gentle hyperventilation to a P_{CO_2} between 30 and 35 mm Hg may help lower pulmonary vasculature resistance and allow for an easier stabilization phase before surgical correction of the diaphragmatic defect. Place a large-bore (10F) orogastric tube set to low continuous suction to minimize further lung compression from overaerated GI contents.

Obtain chest and abdominal radiographs and blood gas analysis to confirm the initial diagnosis and guide stabilization and management. After initial stabilization, emergent referral to a pediatric specialty center is essential.

GASTROSCHISIS AND OMPHALOCELE

A gastroschisis is a defect located to the right of the umbilicus from which uncovered intestine is extruded. An omphalocele is a large, centrally located defect of the abdominal wall containing stomach, intestine, and, frequently, liver that is covered by the mesentery. The umbilical cord inserts directly into the omphalocele sac. Rarely, an omphalocele may be ruptured either before delivery or during delivery. Associated anomalies are seen in 10% to 21% of patients with gastroschisis and 40% to 75% of patients with omphalocele.[20-22] Associated defects include cardiac defects (such as tetralogy of Fallot), syndromes (Beckwith-Wiedemann), and chromosomal abnormalities (trisomy 13 and trisomy 18), in addition to associated intestinal atresias.

Treatment The initial management of gastroschisis and omphalocele is similar: handle the covered sac and free intestine with care. Place the newborn on a radiant warmer to help prevent hypothermia due to increased heat loss from the exposed abdominal contents. The ABCs of stabilization should be performed as needed.

If an omphalocele is present, note its size and contents. Cover the sac with warmed saline gauze wrapped gently around the baby with Kerlix, and then place an additional cover with plastic wrap to help minimize evaporative losses. Start IV 10% dextrose in water at 1.5 times maintenance (i.e., 5 to 6 mL/kg/h or 120 to 150 mL/kg/24 h) to compensate for the additional insensible water loss. Monitor urine output and electrolytes closely to determine ongoing fluid needs.

If a gastroschisis is present, immediately check for dusky or cyanotic intestine, which indicates reduced flow to the affected bowel due to torsion and vascular occlusion. Gently rotate the bowel to relieve torsion if necessary to prevent bowel infarction. Emergency pediatric surgical consultation is essential. If the intestine appears pink, cover with warmed saline gauze, wrap with Kerlix, and further cover with sterile plastic wrap. **Be careful not to compress the intestine, which could result in obstruction of blood flow to the bowel.** Insensible water loss is much greater in the newborn with gastroschisis due to the open defect with large amounts of extruded bowel. Therefore, IV 10% dextrose in water should be started at 6 to 7 mL/kg/h (150 mL/kg/24 h).

Check glucose periodically. Antibiotics, usually ampicillin, 50 to 100 milligrams/kg IV, and gentamicin, 4 to 5 milligrams/kg IV, should be given.

Immediate consultation with a neonatologist and pediatric surgeon is necessary. The overall outcome for gastroschisis is quite good, with survival exceeding 90%.[23,24] Survival with omphalocele is somewhat less at 73% to 88%, depending largely on the presence of associated anomalies.[23]

TRACHEOESOPHAGEAL FISTULA

Tracheoesophageal fistula develops secondary to a failure of separation of the developing foregut structures, the trachea and esophagus, during the embryologic stage of development. There are five types of tracheoesophageal fistula: (1) esophageal atresia with a distal tracheoesophageal fistula (88% of cases), (2) isolated esophageal atresia without tracheoesophageal fistula (7%), (3) esophageal atresia with proximal tracheoesophageal fistula (1%), (4) esophageal atresia with proximal and distal tracheoesophageal fistulas (1%), and (5) H-type fistula without esophageal atresia (3%). Tracheoesophageal fistula is highly associated with several other malformations, designated as the acronyms VATER or VACTERL association: *v*ertebral anomalies, *a*nal atresia, *c*ardiac anomalies, *t*racheo*e*sophageal fistula, *r*adial anomaly/*r*enal anomalies, and *l*imb anomalies.

Diagnosis The diagnosis of tracheoesophageal fistula can be missed during prenatal US examination. When esophageal atresia is present, polyhydramnios is usually noted before or at delivery. Newborns with tracheoesophageal fistula/esophageal atresia will usually have excessive oral secretions noted shortly after birth. When attempting to pass a nasogastric tube, the tube coils in the esophageal pouch and often comes back

out of the mouth. No air passage will be heard when a 5-mL air bolus is injected into the nasogastric tube. A chest radiograph with a nasogastric tube in place will demonstrate the esophageal pouch. Confirmatory contrast studies are not indicated and may actually be contraindicated because the esophageal contents can be aspirated into the lungs.

Treatment Management of tracheoesophageal fistula includes placing the child in head-up (reverse Trendelenburg) positioning to help prevent passage of gastric contents through the tracheoesophageal fistula into the lungs, placing the nasogastric tube into the esophageal pouch on low intermittent suction to prevent buildup and possible aspiration of oral secretions, and giving the newborn nothing by mouth. Initially, standard 10% dextrose in water IV fluids are best. Immediate referral to a center with neonatologists and pediatric surgeons is essential.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 109

Resuscitation of Children

William E. Hauda, II

INTRODUCTION AND EPIDEMIOLOGY

The resuscitation of children differs from that of adults in a number of important ways. Respiratory failure and shock are more common causes of arrest among children and infants than adults; hypoxemia, hypercapnia, and acidosis subsequently lead to bradycardia, hypotension, and secondary cardiac arrest in children. Overall survival and neurologically favorable survival rates in children are 11.3% and 9.1%, respectively, in the United States.[1] Survival rates to discharge after resuscitation from cardiac arrest are greatest among perinatal children (25%) and adolescents (17.3%).[2] Infancy, unwitnessed arrest, and initial asystolic rhythm are associated with poor survival rates. The best chance for a good outcome is to recognize impending respiratory failure or shock and intervene to prevent the development of cardiopulmonary arrest.

Age-related differences are important considerations when treating children. An appropriate drug dose for a 6-month-old infant may be excessive for a 1-month-old newborn but inadequate for a 5-year-old child. Because other aspects of resuscitation, such as endotracheal tube size, tidal volumes, cardiac compression rates, and respiratory rates, vary with a child's age, equipment selection and medication dosing require specific determination for each child. Valuable time cannot be lost in weight estimation, dosage calculations, and equipment selection. Equipment can be stored on shelves or in drawers labeled by age and weight, or a system of color codes can be used in which color-coded shelves, carts, or equipment organizers correspond to specific length categories, as illustrated in **Figure 109-1**.

BASIC LIFE SUPPORT

The American Heart Association guidelines use the following age group delineations: *newborn*, 1 month or less in age; *infant*, 1 month to 1 year of age; and *child*, 1 year of age to the onset of puberty.[3] As in adults, the priorities of resuscitation are airway, oxygenation, ventilation, and shock management (**Figure 109-2, A** and **B**). Initial basic life support sequence can be initiated with either an airway-breathing-circulation sequence or a circulation-airway-breathing sequence, with circulation-airway-breathing achieving earlier chest compressions but airway-breathing-circulation achieving earlier ventilation.[3,4] To simplify the action sequence, the European Resuscitation Council recommends using the airway-breathing-circulation sequence for basic life support assessment but recommends starting with chest compressions if no pulse is present.[5] The American Heart Association Guideline Update in 2015 recommends "initiating CPR with C-A-B [circulation-airway-breathing] over A-B-C [airway-breathing-circulation] sequence (Class IIb)."[3] Cardiopulmonary arrest should be prevented whenever possible with prompt recognition of and intervention for compromised physiology.[6] International consensus guidelines for basic life support procedures are listed in **Table 109-1**.

CHOKING AND FOREIGN-BODY MANAGEMENT

The back blow and chest thrust are recommended maneuvers to clear an infant's airway. The American Heart Association specifically discourages two common maneuvers used with adult patients: (1) **do not use the "Heimlich maneuver" for patients <1 year old**, because of the potential for injury to abdominal organs; and (2) **do not use blind finger sweeps**, because of the possibility of pushing the foreign body farther into the airway.[6,7]

CONSCIOUS CHILDREN

A child who is choking but can maintain some ventilation or vocalization should be allowed to clear the airway by coughing. Once a child cannot cough, vocalize, or breathe, a sequence of steps must be instituted immediately. ***Choking infants are treated with an alternating sequence of five back blows and five chest thrusts***.[7] With the infant's torso positioned prone and head down along the rescuer's arm, or the older child draped prone and head down across the rescuer's knees, deliver five blows to the interscapular area (**Figure 109-3**). Then reposition the infant supinely along the rescuer's arm, or place the larger infant on the floor, as for external cardiac compression, and deliver five chest thrusts (cardiac compressions; **Figure 109-4**). Continue this sequence until the airway obstruction is relieved or the child becomes unconscious. In children beyond infancy, use the obstructed airway ("Heimlich") maneuver, with the rescuer kneeling or standing behind the child. Place the rescuer's clenched fist at the level of the umbilicus and deliver firm upward thrusts until the obstruction is cleared or the child becomes unconscious.

UNCONSCIOUS CHILDREN

If a child loses consciousness due to a presumed airway obstruction, begin chest compressions immediately.[7] After 30 compressions, open the airway and look for a foreign body in the mouth. Attempt to deliver two rescue breaths. If successful, then check for a pulse. If the obstruction is



FIGURE 109-1. The Broselow® resuscitation tape. [Broselow® tape; Armstrong Medical Industries, Inc., Lincolnshire, IL.]

still present, then continue with alternating cycles of compressions and attempted rescue breaths until the obstruction is relieved. Chest compressions will circulate blood after a loss of perfusion and may relieve the obstruction. After each cycle and before each attempt at ventilation (lone rescuer: 30 to 2; two rescuers: 15 to 2), inspect the airway to see if an object is present and remove visible objects. **Do not perform blind finger sweeps.**

The foregoing recommendations are directed primarily at first responders or healthcare providers who have neither access to nor the skills to use airway management equipment. For unconscious children in EDs, direct laryngoscopy, visualization, and removal of the foreign body with McGill forceps can be attempted. Until this equipment is ready, use basic life support techniques.

AIRWAY

Management of the pediatric airway including anatomic considerations, positioning, and basic and advanced adjuncts is discussed in detail in Chapter 113, "Intubation and Ventilation in Infants and Children."

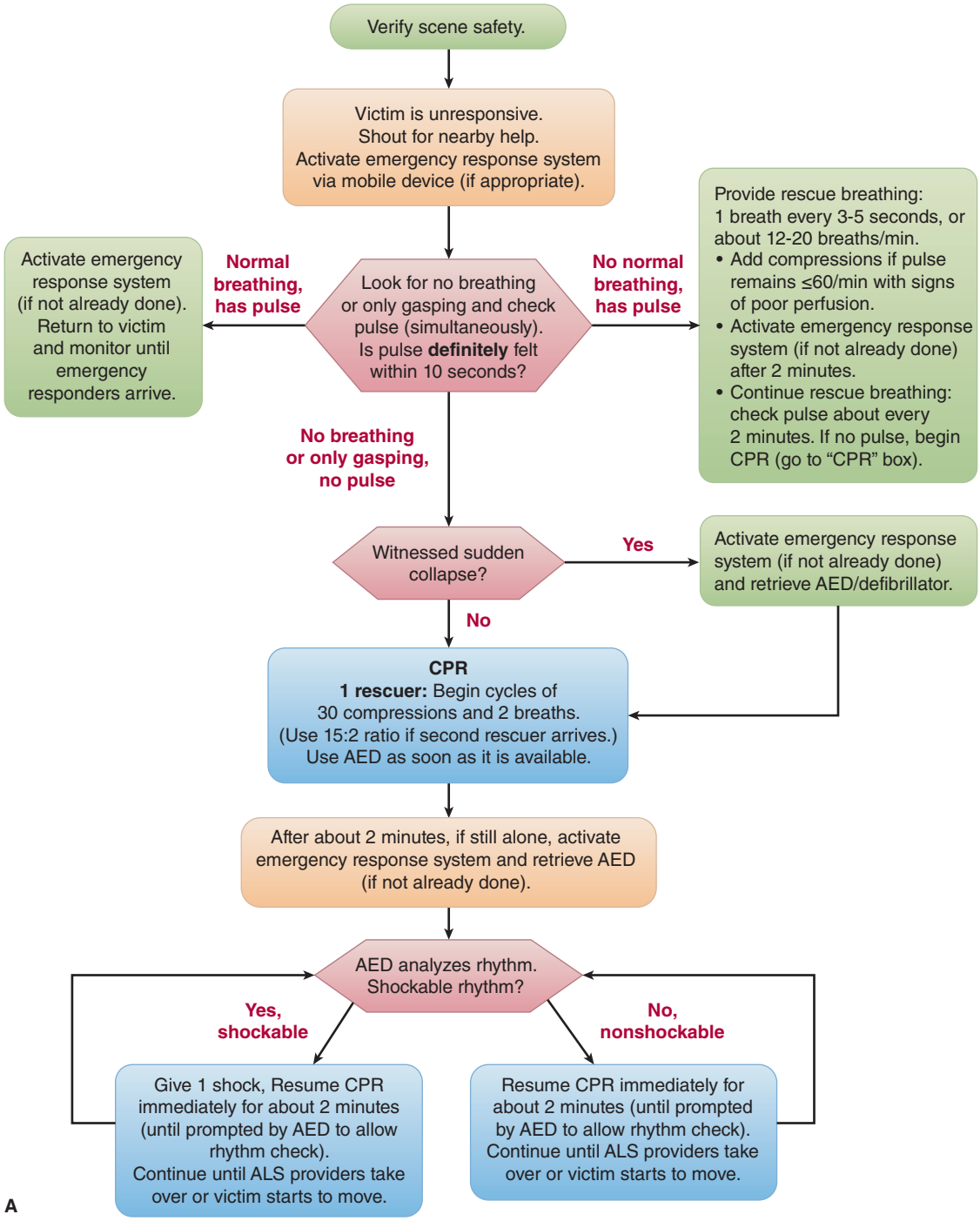
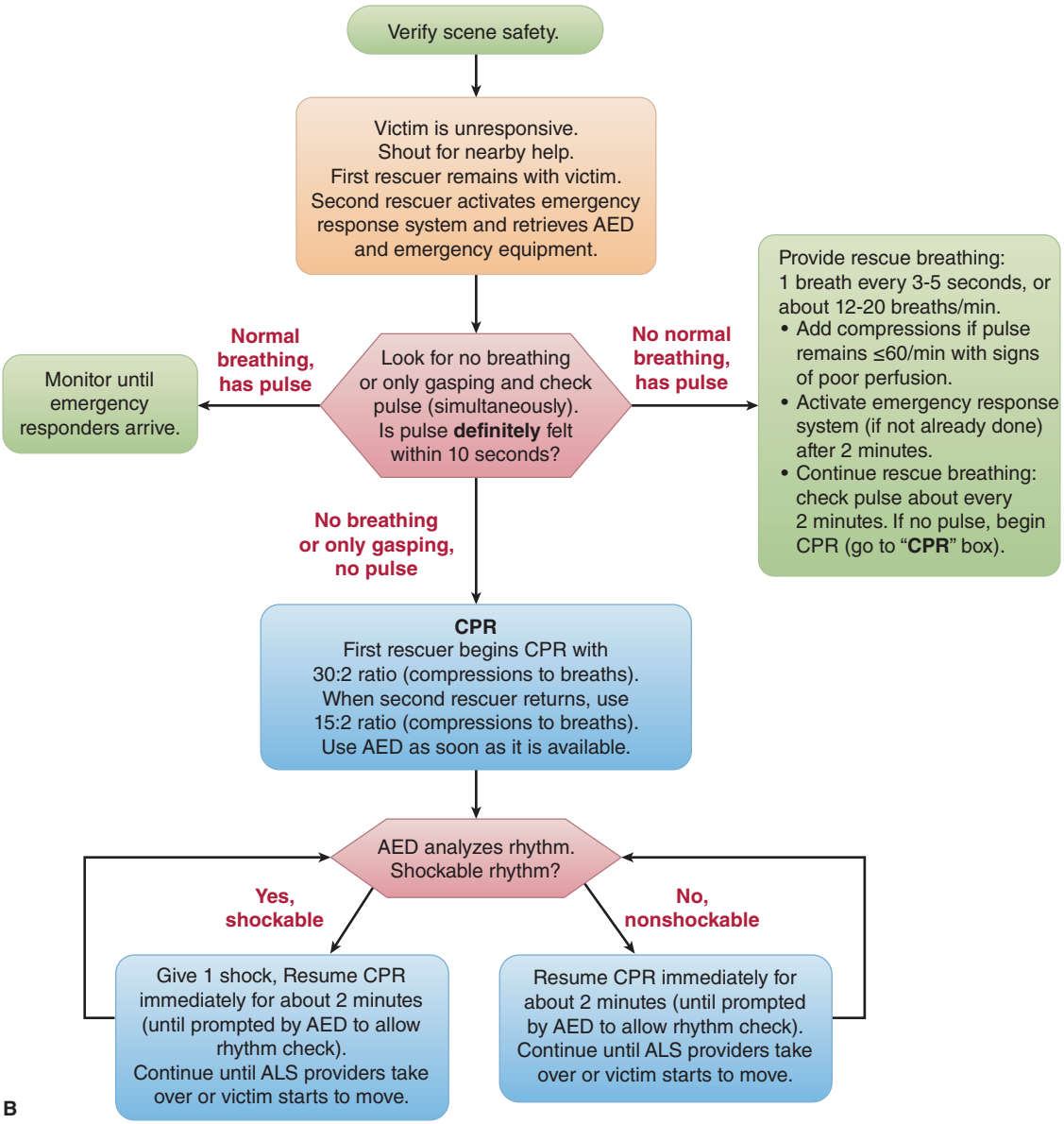


FIGURE 109-2. **A.** Pediatric basic life support (BLS) algorithm for a single rescuer. **B.** Pediatric BLS algorithm for multiple rescuers. AED = automated external defibrillator; ALS = advanced life support. [Reprinted with permission Web-based Integrated 2010 & 2015 American Heart Association Guidelines for CPR & ECC Part 11: Pediatric Basic Life Support & CPR Quality ©2015 American Heart Association, Inc.]



B

FIGURE 109-2. (*Continued*)

TABLE 109-1 Guidelines for Pediatric Basic Life Support[7]

Maneuver	Newborn	Infant <1 Y	Child 1 Y to Puberty	Onset of Puberty to Adult
Airway	Head tilt/chin lift	Head tilt/chin lift	Head tilt/chin lift	Head tilt/chin lift
If trauma	Jaw thrust	Jaw thrust	Jaw thrust	Jaw thrust
If foreign body–conscious	Suction	Back blows and chest thrusts	Abdominal thrusts	Abdominal thrusts
If foreign body–unconscious	Suction	Chest compressions	Abdominal thrusts	Abdominal thrusts
Breathing rate	30–60/min (every 1–2 s)	12–20/min (every 3 s)	12–20/min (every 3 s)	10–12/min (every 5 s)
Circulation				
Pulse check	Umbilical	Brachial	Carotid or femoral	Carotid or femoral
Compression				
Location	One finger below intermammary line	One finger below intermammary line or lower half of sternum	Lower half of sternum	Lower half of sternum
Method	Two fingers or two thumbs	Two fingers or two thumbs	Heel of one hand or two hands	Two hands
Depth	One third of chest	One third to one half of chest	One third to one half of chest	One third of chest
Rate	120/min	100/min	100/min	100/min
Compression-to-ventilation ratio	3:1	15:2 (single rescuer–30:2)	15:2 (single rescuer–30:2)	30:2



FIGURE 109-3. Back blows to clear airway of choking infant. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

BREATHING

MOUTH TO MOUTH

The size of the child dictates whether to use mouth-to-mouth or mouth-to-mouth-and-nose ventilation. The rate of ventilation is shown in Table 109-1. Make sure the breaths are effective by observing chest rise with each breath.

BAG-VALVE MASK

The self-inflating bag-valve mask system is most commonly used for ventilation. **Ventilation bags used for infants and children should have a minimum volume of 450 mL, and those used for older children and adolescents should have a minimum volume of 1000 mL.**[7] Pediatric lung compliance is very good, and children can tolerate relatively high pressures. **Pneumothoraces usually result from the administration of excessive tidal volume rather than from high pressures.** Start ventilation with the smallest volume that causes adequate chest rise, and give each breath slowly, over approximately 1 second. Carefully monitor the rate of ventilation to **avoid excessive hyperventilation**.



FIGURE 109-4. Chest thrusts to clear airway of choking infant. [Image used with permission of Rita K. Cydulka, MD, MS, MetroHealth Medical Center.]

OXYGEN

It is reasonable to provide 100% oxygen during CPR; however, once circulation has been restored, studies suggest improved outcomes when normal arterial oxygen and carbon dioxide levels are maintained. Wean oxygen to maintain saturations of at least 94% and ensure eucapnia.[4,7-10]

END-TIDAL CARBON DIOXIDE

End-tidal capnography has been considered a tool for assessing quality of chest compressions and recognizing excessive ventilation.[8] No studies are available to show an improved outcome in children with targeted end-tidal carbon dioxide monitoring or a specific value for end-tidal carbon dioxide level to target in children.[4]

CIRCULATION

Begin cardiac compression in the absence of pulse or with poor perfusion (heart rate ≤60 beats/min). Place patients on a hard surface to improve the effectiveness of compressions. Perform compressions over the lower sternum ensuring adequate rate and depth (**Table 109-1**). Failure to deliver compressions with sufficient force to depress the chest is common even among healthcare providers.[4] Palpate pulses during compression to assess the adequacy of the compression depth and rate. Pause chest compressions for bag-valve mask ventilation, but only long enough to deliver effective breaths; once an advanced airway is established, deliver chest compressions continuously without pause for ventilations.

INFANTS

Use the two-thumb technique when two healthcare providers are present. Compress at a rate of at least 100 per minute. The compression-to-ventilation ratio is 15:2 for two healthcare providers performing CPR on an infant. If the patient is intubated, then compressions and ventilations may be performed without synchronization, but the rate of compressions should be maintained at 100 per minute. The chest should not be squeezed by the hands, but the sternum should be depressed by the thumbs.[7]

CHILDREN 1 YEAR OLD TO THE ONSET OF PUBERTY

Compress the lower half of the sternum with the heel of one hand. If unable to adequately depress the sternum with one hand, then use the two-hand technique. The rate of compression is at least 100 compressions per minute. If there are two healthcare providers, then perform compressions in a series of 15:2 compressions to ventilations. If there is only one healthcare provider, perform 30 compressions for every 2 ventilations. If the patient is intubated, then compressions and ventilations may be performed without synchronization, but keep the rate of compressions at 100 per minute.

CHILDREN AFTER PUBERTY (ADOLESCENTS)

Children who are of pubertal age or older are treated as adults with respect to basic life support.[7] Use the two-hand technique of chest compressions. The compression-to-ventilation ratio and rate of compressions are the same as with children, 15:2 for two-person CPR and 30:2 for one-person CPR with a rate of 100 compressions per minute.

VASCULAR ACCESS

Difficulty in obtaining rapid IV access is certainly one of the major differences between adult and pediatric resuscitation. Keep several important facts in mind. First, a significant portion of children respond to airway management alone because most cardiac arrests in children are secondary to hypoxia from respiratory arrest. Airway management and ventilation have priority over vascular access; time spent on obtaining vascular access should be limited.[8] Intraosseous infusion and fluid administration are quick, safe routes for resuscitation drugs (see Chapter 114, "Vascular Access in Infants and Children"). If vascular access cannot be obtained but the child is intubated, use the tracheal route to administer drugs, such as *l*idocaine, *e*pinephrine, *a*tropine, and *n*aloxone (mnemonic: LEAN). **Although the ideal endotracheal doses for drugs other than epinephrine have never been studied in children,**

TABLE 109-2 Drugs for Pediatric Resuscitation[8]

Drug	Pediatric Dosage	Remarks
Adenosine	IV/IO: 0.1 milligram/kg, followed by 2–5 mL NS flush Double dose and repeat once, if needed	Maximum single dose: 6 milligrams first dose, 12 milligrams second dose.
Amiodarone	IV/IO: 5 milligrams/kg over 20–60 min; then 5–15 micrograms/kg/min infusion	Maximum bolus repetition to 15 milligrams/kg/d. Use lowest effective dose. Bolus may be given more rapidly in shock states.
Atropine	IV/IO: 0.02 milligram/kg, repeat in 5 min (minimum single dose is 0.1 milligram) Endotracheal: 0.04–0.06 milligram/kg diluted with NS to 3–5 mL	Maximum single dose: 0.5 milligram (child) and 1.0 milligram (adolescent). Maximum cumulative dose: 1.0 milligram (child) and 2.0 milligrams (adolescent). ***Not routinely recommended.*** Use for bradycardia in the setting of suspected increased vagal tone or primary heart block.
Calcium chloride (10%)	IV/IO: 20 milligrams/kg (maximum dose 2 grams)	***Not routinely recommended.*** Use in documented hypocalcemia, calcium channel–blocker overdose, hypermagnesemia, or hyperkalemia. Administer slowly.
Epinephrine	Bradycardia: IV/IO: 0.01 milligram/kg (0.1 mL/kg of 1:10,000) Endotracheal: 0.1 milligram/kg (0.1 mL/kg of 1:1000) Pulseless arrest: IV/IO: 0.01 milligram/kg (0.1 mL/kg of 1:10,000) Endotracheal: 0.1 milligram/kg (0.1 mL/kg of 1:1000)	Maximum dose: 1 milligram IV/IO; 2.5 milligrams ETT. Unlike other agents, epinephrine per endotracheal tube is 10× the IV dose. Follow endotracheal dose with several positive-pressure ventilations. No evidence for high-dose parenteral epinephrine (may worsen outcomes).
Glucose	IV/IO: Newborn: 5 mL/kg $D_{10}W$ Infants and children: 2 mL/kg $D_{25}W$ Adolescents: 1 mL/kg $D_{50}W$	$D_{10}W$ preferred (5 mL/kg) through small guage IV as higher dextrose concentrations may be sclerotic to peripheral IVs. Higher dextrose concentrations may be given through IO if needed.
Lidocaine	IV/IO: 1.0 milligram/kg bolus Endotracheal: double IV dose and dilute with NS to 3–5 mL	
Naloxone	IV/IO: If <5 y or ≤20 kg: 0.1 milligram/kg If >5 y and >20 kg: 2.0 milligrams	Titrate to desired effect.
Sodium bicarbonate	IV/IO: 1 mEq/kg (1 mEq/mL)	***Not routinely recommended.*** Infuse slowly and use only if ventilation is adequate for tricyclic antidepressant overdose and hyperkalemia.

Abbreviations: $D_{10}W$ = 10% dextrose in water; $D_{25}W$ = 25% dextrose in water; $D_{50}W$ = 50% dextrose in water; ETT = endotracheal tube; NS = normal saline.

current recommendations support the use of two to three times the respective IV dose (Table 109-2).

FLUIDS

If hypotension is due to volume depletion, give isotonic fluid boluses of 20 mL/kg as rapidly as possible and repeat as needed.[6] Use a syringe attached to a three-way stopcock and extension tubing to rapidly deliver aliquots of fluid, until the entire bolus is administered. This method is far superior to the use of gravity or pressure bags.

Deliver the bolus in <20 minutes and more rapidly, if possible. **Reassess the child's condition after each bolus.** If blood pressure normalizes, maintain fluid administration at the minimum rate to keep the vein open or at a rate to compensate for ongoing fluid losses. If hypotension persists despite volume repletion, consider a pressor agent.

Always use a pediatric microdrip assembly when resuscitating children to prevent accidental overhydration and for easy monitoring of the total volume given. It is easy to overhydrate infants and children, even when IV lines are set to keep the vein open, if adult equipment is used for children.

WEIGHT ESTIMATION AND MEDICATION CALCULATIONS

Proper dosage of medications in children requires knowledge of the patient's weight, knowledge of the dose (usually given in milligrams per kilogram), and error-free calculation and delivery. Use of charts with precalculated drug doses or electronic calculators can reduce dosage errors (Tables 109-2 and **109-3**).[11]

Other methods to reduce medication errors during resuscitation include reformulating drug preparations so that all children receive 0.1 mL/kg regardless of the medication, limiting the number of concentrations of medication available, and using standardized medication reference tables.[12]

To calculate the proper drug dosage from the table, accurately determine the child's weight. Because it is often not possible to weigh a child during resuscitation, several alternative methods are available for estimating a child's weight, but each of these has inherent challenges and problems (**Tables 109-4** and **109-5**) with errors occurring in all techniques.[13]

LENGTH-BASED ESTIMATION

Systems based on a direct measurement of a patient's length have been developed for estimating weight, determining dosages, and selecting equipment in pediatric emergencies (**Table 109-6**). The use of a length-based system is currently included in the American Heart Association Pediatric Advanced Life Support Course.[6] These systems use a tape measuring device (such as the **Broselow® tape**; Armstrong Medical Industries, Inc., Lincolnshire, IL) to assist in making appropriate selections, with some systems incorporating body habitus to improve accuracy (such as the Paediatric Advanced Weight Prediction in the Emergency Room). Most tapes are two-sided and display emergency resuscitation drug dosage and equipment selection based on length (Figure 109-1).

The length-based systems may not be accurate in all populations of children. The Broselow® tape has been shown to underestimate and overestimate weights and may not be as accurate as newer systems such as the Mercy method and the Paediatric Advanced Weight Prediction in the Emergency Room tape.[14] Although length-based systems for weight estimation have limitations, their use in EDs provides a very rapid tool during a critical resuscitation.

TABLE 109-3 Calculation for Dosage of Medications Delivered by Constant Infusion Using the Rule of 6

Drug	Continuous Infusion Dose	Conversion Factor	Delivery
Epinephrine	0.1–1.0 microgram/kg/min	0.6 milligram × wt (kg)	1 mL/h = 0.1 microgram/kg/min
Dobutamine	2–20 micrograms/kg/min	6 milligrams × wt (kg)	1 mL/h = 1.0 microgram/kg/min
Dopamine	2–20 micrograms/kg/min	6 milligrams × wt (kg)	1 mL/h = 1.0 microgram/kg/min
Norepinephrine	0.1–2.0 micrograms/kg/min	0.6 milligram × wt (kg)	1 mL/h = 0.1 microgram/kg/min
Lidocaine	20–50 micrograms/kg/min	60 milligrams × wt (kg)	1 mL/h = 10 micrograms/kg/min
Nitroprusside	0.5–8 micrograms/kg/min	6 milligrams × wt (kg)	1 mL/h = 1.0 microgram/kg/min
Isoproterenol	0.1–1.0 microgram/kg/min	0.6 milligram × wt (kg)	1 mL/h = 0.1 microgram/kg/min
Dosage of medications delivered by constant infusions is calculated in terms of micrograms per kilogram per minute. Actual calculation can be confusing and a source of lethal decimal errors. The rule of 6 can be used for dopamine and dobutamine to simplify dosage calculation:			
The medication is mixed in an IV set with a measured chamber and a microdrip (1 drop/min = 1 mL/h). Rate of administration is best set by an electric pump.	6 milligrams × wt (kg), fill to 100 mL with D_5W		
Example: For a 10-kg infant requiring dopamine	6 milligrams × 10 = 60 milligrams dopamine		
In a measured chamber, fill to 100 mL with D_5W. Weight is now factored in so that:	1 mL/h = 1 microgram/kg/min 5 mL/h = 5 micrograms/kg/min 10 mL/h = 10 micrograms/kg/min		
For epinephrine and isoproterenol, the rule of 6 is:	0.6 milligram × wt (kg), fill to 100 mL with D_5W 1 mL/h = 0.1 microgram/kg/min 5 mL/h = 0.5 microgram/kg/min		

Abbreviations: D_5W = 5% dextrose in water; wt = weight.

AGE-BASED ESTIMATION

There are several formulas based on a child's age that have been developed to assist in estimating a child's weight (Tables 109-4 and 109-5). Age-based formulas have challenges in application based on requiring calculations and the accuracy of the estimation and whether the estimation is closer to actual body weight or ideal body weight.[15] Although many clinicians still recall and use these formulas, some authors consider these formulas historical curiosities and feel they should no longer be relied upon for estimating a child's weight during a critical resuscitation.[16,17]

TABLE 109-4 Estimating Weight in Infants and Children

Formulas by name	Argall	(Years + 2) × 3
	Luscombe	(Years × 3) + 7
	Advanced Pediatric Life Support	Infants: (age in months × 0.5) + 4 Children 1–5 y: (2 × age in years) + 8 Children 6–12 y: (3 × age in years) + 7
	Nelson	<12 mo: (months + 9)/2 1–6 y: (years × 2) + 8 7–12 y: (years × 7) − 5
	Best Guess	<12 mo: (months + 9)/2 1–4 y: (years + 5) × 2 5–14 y: (years × 4)
Formulas by age	Infants	(Months + 9)/2
	1 to 5 or 6 y	(Years × 2) + (7, 8, or 10) Or (Years × 3) + 7
	6 or 7 to 12 or 14 y	(Years × 2) + 8 Or (Years × 3) + 7 Or Years × 4 Or (Years × 5) − 5

HEALTHCARE PROVIDER ESTIMATION

Estimations by healthcare providers without using a specific tool are quite variable.[18] Healthcare providers should not rely on a visual estimation of the child's weight, but must use some tool in estimating a child's weight for all resuscitation medications.

PARENTAL ESTIMATION

Parental estimations of a child's weight are often as accurate as length-based devices.[17] A recent study, however, suggests that parental estimates of a child's weight may underestimate weight in over 50% of obese children and nearly 15% of normal body habitus children.[19]

PHARMACOLOGIC AGENTS

The pharmacology of resuscitation drugs has been well described in other chapters (see Chapter 19, "Pharmacology of Antiarrhythmics and

TABLE 109-5 Body Weight Estimation by Age

Age	Weight (kg)	Estimation
Term infant	3.5	Birth weight
6 mo	7	2 × birth weight
1 y	10	3 × birth weight
4 y	16	One-fourth adult weight of 70 kg
10 y	35	One-half adult weight

TABLE 109-6 Length-Based Equipment Chart (Length = Centimeters)*

Item	54–70	70–85	85–95	95–107	107–124	124–138	138–155
Endotracheal tube size (mm)	3.5	4.0	4.5	5.0	5.5	6.0	6.5
Lip–tip length (mm)	10.5	12.0	13.5	15.0	16.5	18.0	19.5
Laryngoscope	1 straight	1 straight	2 straight	2 straight or curved	2 straight or curved	2–3 straight or curved	3 straight or curved
Suction catheter	8F	8F–10F	10F	10F	10F	10F	12F
Stylet	6F	6F	6F	6F	14F	14F	14F
Oral airway	Infant/small child	Small child	Child	Child	Child/small adult	Child/adult	Medium adult
Bag-valve mask	Infant	Child	Child	Child	Child	Child/adult	Adult
Oxygen mask	Newborn	Pediatric	Pediatric	Pediatric	Pediatric	Adult	Adult
Vascular access (gauge)							
Catheter	22–24	20–22	18–22	18–22	18–20	18–20	16–20
Butterfly	23–25	23–25	21–23	21–23	21–23	21–22	18–21
Nasogastric tube	5F–8F	8F–10F	10F	10F–12F	12F–14F	14F–18F	18F
Urinary catheter	5F–8F	8F–10F	10F	10F–12F	10F–12F	12F	12F
Chest tube	10F–12F	16F–20F	20F–24F	20F–24F	24F–32F	28F–32F	32F–40F
Blood pressure cuff	Newborn/infant	Infant/child	Child	Child	Child	Child/adult	Adult

*Directions for use: (1) measure patient length with centimeter tape; (2) using measured length in centimeters, access appropriate equipment column.

Source: Reproduced with permission from Luten RC, Wears RL, Broselow J, et al: Length-based endotracheal tube sizing and emergency equipment for pediatric resuscitation. *Ann Emerg Med* 21: 900, 1992, ©1992, Elsevier, Philadelphia, PA. Copyright Elsevier.

Antihypertensives," and Chapter 20, "Pharmacology of Vasopressors and Inotropes"), but a few peculiarities pertain to pediatric resuscitation drug use.

EPINEPHRINE

Epinephrine is the one drug universally used in cardiac arrest; however, its beneficial effect on survival remains questionable.[20-22] It is specifically indicated for hypoxia- or ischemia-induced slow heart rates that fail to respond to adequate oxygenation and ventilation and for pulseless arrest situations (i.e., asystole, pulseless electrical activity, and ventricular fibrillation). If the initial dose of epinephrine is not effective, give subsequent doses at the same dose. High-dose epinephrine (0.1 milligram/kg of the 1:1000 concentration) for resuscitation in infants and children does not increase survival. The American Heart Association currently recommends that subsequent doses of epinephrine be at the standard dose.[8] High-dose epinephrine may be useful in catecholamine-resistant states, such as anaphylaxis, alpha- or beta-blocker overdose, or severe sepsis. Adverse effects associated with the use of high-dose epinephrine include intracranial hypertension, myocardial hemorrhage, myocardial necrosis, and a postresuscitation hyperadrenergic state.[23]

Epinephrine, rather than dopamine, is the vasopressor infusion of choice in children (Table 109-3) because dopamine requires release of endogenous norepinephrine. In children with cardiac arrest, norepinephrine stores may be low. There is no evidence to recommend use of vasopressin over epinephrine in children.

AMIODARONE

Amiodarone can treat atrial and ventricular arrhythmias and is currently included in the algorithm for ventricular fibrillation and pulseless ventricular tachycardia, with **expert consultation strongly recommended prior to administration.**[8] Dosage for pediatric patients is 5 milligrams/kg over 20 to 60 minutes and may be repeated to a maximum of 15 milligrams/kg per day. Administer amiodarone rapidly for ventricular tachycardia or ventricular fibrillation resistant to electrical cardioversion. Lidocaine may be used instead of amiodarone in ventricular fibrillation or pulseless ventricular tachycardia, although neither medication appears to be significantly associated with survival to hospital discharge after cardiac arrest.[24]

Avoid amiodarone if there is the potential for a long QT syndrome either due to a primary cardiac dysrhythmia or medication administration or overdose, because amiodarone prolongs the QT interval and its administration may cause irreversible dysrhythmias in these circumstances.

ATROPINE

Atropine is used for treatment of symptomatic bradycardias associated with increased vagal tone or first-degree heart block **in the absence of reversible causes** (Class IIa). **Epinephrine remains the first-line treatment for symptomatic bradycardia after adequate oxygenation and ventilation**. When used, the recommended dose of atropine is 0.02 milligram/kg IV. Maximum single doses are 0.5 milligram for children and 1.0 milligram for adolescents. A minimum dose of 0.1 milligram of atropine is no longer recommended for premedication for emergency intubation but should still be given when used to treat symptomatic bradycardia.[20] The dose may be repeated once, with maximum total doses of 1.0 milligram for children and 2.0 milligrams for adolescents. Additional doses are unlikely to be beneficial as the maximum recommended dose is considered fully vagolytic. If no response to atropine is seen, then dosing beyond the vagolytic amount is unlikely to be effective. If an effect is seen but not maintained, additional doses can be given. **Large doses of atropine are needed to treat exposure to organophosphates or nerve agents.**

SODIUM BICARBONATE

Bicarbonate therapy has a primary role in treating overdoses of sodium channel–blocking agents, such as procainamide, flecainide, and tricyclic antidepressants (Class IIa). It has an uncertain utility in calcium channel–blocker overdoses (Class Indeterminate). Because other resuscitation drugs are less effective in the face of severe acidosis, sodium bicarbonate may be useful during prolonged resuscitations, although its **routine use in cardiac arrest is not recommended** (Class III). Adverse effects of bicarbonate include reducing systemic vascular resistance (thereby lowering coronary perfusion pressure), inhibiting oxygen release (by shifting the oxyhemoglobin dissociation curve), inducing hypernatremia and hyperosmolality, inactivating simultaneously administered catecholamines, and paradoxical worsening of intracellular acidosis (by the production of carbon dioxide, which diffuses rapidly through cell

walls). **An initial dose of 1 mEq/kg IV is given only after adequate ventilation has been established.** Without adequate ventilation, the child cannot compensate for the release of carbon dioxide by buffering the hydrogen ions, and the adverse effects of bicarbonate therapy surpass any beneficial effects. **In neonates or premature infants, dilute sodium bicarbonate 1:1 with sterile water, not saline, to reduce the hyperosmolarity of the solution.**

CALCIUM

Routine calcium administration is not recommended during resuscitation because of lack of proven efficacy and because of possible harmful effects.[25] Calcium should be used for documented and symptomatic hyperkalemia, hypocalcemia, hypermagnesemia, and calcium channel–blocker overdose.[8] Ionized calcium levels should be used to direct calcium administration, but outcomes of ICU patients do not appear to be affected by ionized calcium level normalization.[26] Calcium may be given as calcium gluconate, 60 to 100 milligrams/kg (0.6 to 1.0 mL/kg of a 10% solution) or calcium chloride, 20 milligrams/kg (0.2 mL/kg of a 10% solution), via the IV or IO route. Calcium gluconate is less tissue toxic than calcium chloride in the case of extravasation.

DYSRHYTHMIAS

Dysrhythmia are discussed in detail in **Chapter 130, "Syncope, Dysrhythmias, and ECG Interpretation in Children."** Ventricular fibrillation is an unusual presenting rhythm in infants and children.[2] Children presenting with an unshockable rhythm rarely develop a subsequent shockable rhythm during the resuscitation.[27] **Because rhythm disturbances are usually secondary to hypoxia and not primary cardiac events, first provide ventilation and oxygenation, and correct hypoxia, acidosis, and fluid balance.** If medications such as epinephrine are administered, they are probably most effective when given 1 to 2 minutes before a defibrillation attempt.

A child with an abnormal cardiac rhythm or rate, coupled with evidence of poor end-organ perfusion (e.g., cyanosis, mottled skin, lethargy) is unstable and requires immediate intervention. **Figures 109-5, 109-6,** and **109-7** summarize the approach to unstable cardiac rhythms in children, and **Table 109-7** lists the weight-based electrical dose when cardioversion or defibrillation is indicated.[8]

The most common rhythms seen in pediatric arrest are the bradycardias, which lead to asystole if untreated. **Again, treatment consists of maximizing oxygenation and ventilation. Begin chest compression in children with a heart rate <60 beats/min and signs of poor perfusion and administer epinephrine (Figure 109-6).**

Differentiating a rapid secondary sinus tachycardia from a rapid primary cardiac tachycardia can be difficult but is critical to patient management. Although heart rates of 150 to 200 beats/min in adults are usually cardiac in origin, small infants and young children not uncommonly have compensatory sinus tachycardias as fast as 200 to 220 beats/min. **A rate of >220 beats/min in an infant or >180 beats/min in a child is likely supraventricular tachycardia.**[8]

CARDIOVERSION, DEFIBRILLATION, AND PACING

Electric conversion is used on an emergency basis to treat ventricular fibrillation (defibrillation) and symptomatic tachydysrhythmia (cardioversion). Energy requirements for defibrillation and cardioversion are listed in Table 109-7. See Chapter 23, "Defibrillation and Electrical Cardioversion," for further discussion.

USING PADDLES

Paddle size is 4.5 cm for infants (who weigh <10 kg) and 8 cm for children. The paddle should be in contact with the chest wall over its entire surface area. The larger, 8-cm paddles can be used for infants in the anteroposterior position. Electrode cream, electrode paste, and saline-soaked gauze pads are acceptable. Alcohol pads should not be used because serious burns may occur. Ensure the interface substance from one paddle does not come in contact with the substance from the other paddle as this contact creates a short circuit and insufficient energy delivery.

USING SELF-ADHESIVE ELECTRODES

Many defibrillation devices use cables with integrated adhesive pads for delivery of energy. Adhesive pads are used with the same general guidelines as metal paddles, including the recommendations on sizing and positioning.

POSITIONING PADDLES OR ELECTRODES

Place one contact to the right of the sternum at the second intercostal space. Place the other contact at the left midclavicular line at the level of the xiphoid. The anteroposterior approach also can be used, although improved success with anteroposterior positioning has not been documented.[8]

DEFIBRILLATION

Defibrillate as quickly as possible for pulseless ventricular tachycardia or ventricular fibrillation, **but do not withhold chest compressions while waiting for the device to charge**. Initially, use 2 J/kg.[20] Immediately after defibrillation provide 2 minutes of high-quality uninterrupted CPR regardless of the subsequent rhythm. Recheck the cardiac rhythm after 2 minutes of CPR. If a shockable rhythm is present, double the defibrillation energy to 4 J/kg, and use this higher energy level for all additional defibrillation attempts; refractory ventricular fibrillation may require higher energy to a maximum of 10 J/kg or the maximum adult dose.[8,20]

CARDIOVERSION

Tachydysrhythmias are generally very sensitive to electric conversion. **The initial dose is 0.5 J/kg, in the synchronized mode** (Table 109-7). Double the energy level if the first attempt is unsuccessful. If the device has only a few energy settings available, choose the one closest to the desired energy setting. If the device does not provide the synchronized mode, then the unsynchronized mode must be used.

TRANSCUTANEOUS PACING

Severe bradycardia due to an intrinsic myocardial block or congenital heart disease may respond to transcutaneous pacing. **Pacing is not indicated if the bradycardia is due to hypoxic myocardial injury, ischemic myocardial injury, or respiratory failure. Oxygenation, chest compressions, and medications should precede attempts at pacing in children with severe symptomatic bradycardia due to heart block or sinus node dysfunction.**

Positioning of the pacing electrodes is the same as for self-adhesive defibrillation electrodes. Ventricular capture is determined by the palpation of a pulse or the appearance of an arterial waveform, if an arterial pressure catheter is present. Maximal energy output should be used until ventricular capture occurs, then the energy setting can be decreased progressively until the lowest setting is found that allows ventricular capture. Set the pacing rate slightly higher than the normal rate for age.

AUTOMATED EXTERNAL DEFIBRILLATORS

Because children ≥8 years old may have life-threatening arrhythmias similar to those in adults and because their body weights approach those of adults, an automated external defibrillator (AED) can be used. A child ≥8 years and weighing >25 kg with sudden collapse should have an AED applied as soon as possible. An AED with a pediatric dose attenuator is ideal for children under 8 years of age because this feature allows the delivery of a lower dose of energy in pediatric patients. More AEDs are available that allow changing the cardioversion energy levels. If an AED with a pediatric dose attenuator is not available, then use a standard AED.

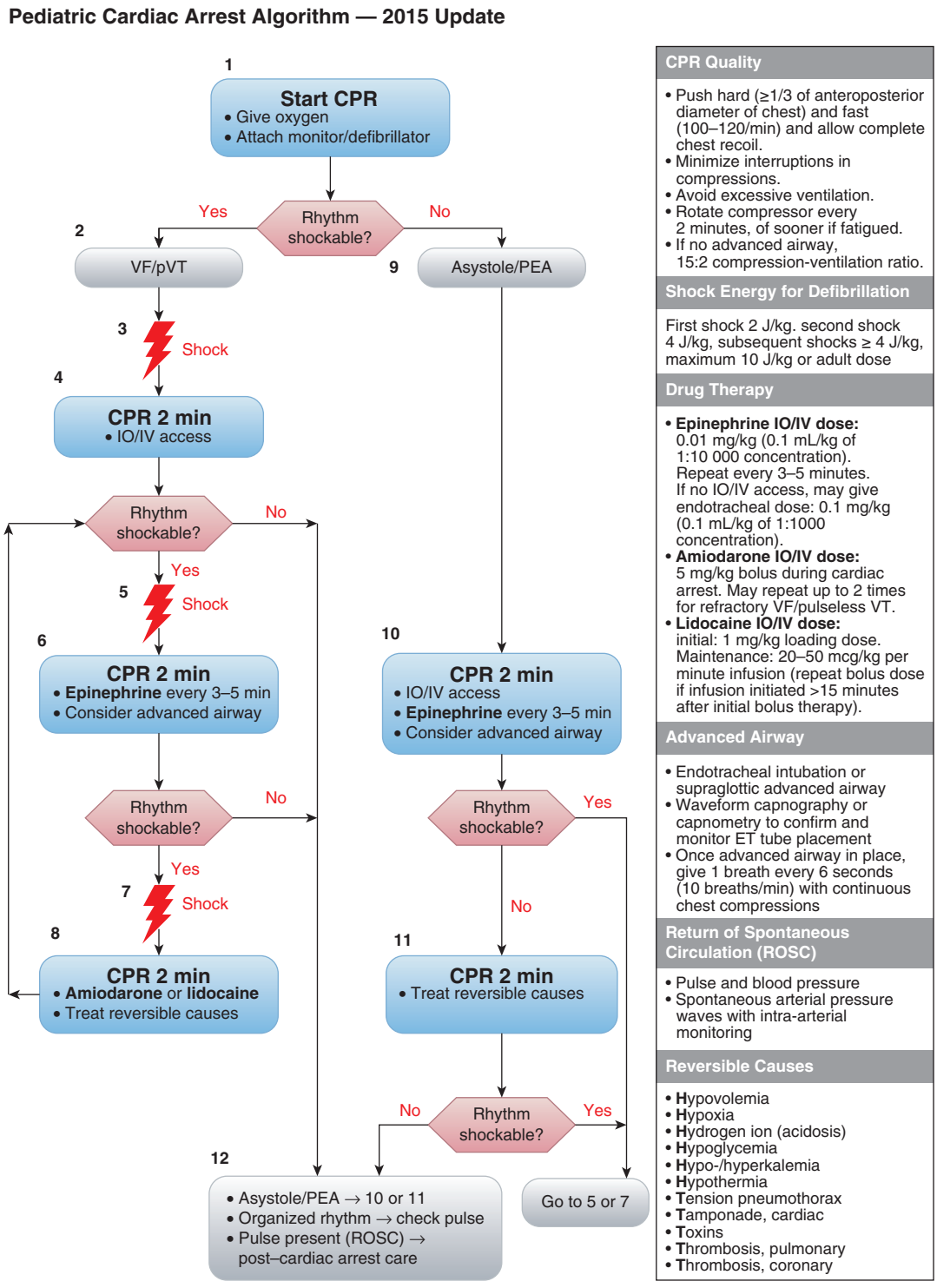


FIGURE 109-5. Pediatric pulseless arrest decision tree. ET = endotracheal; PEA = pulseless electrical activity; pVT = pulseless ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia. [Reprinted with permission Web-based Integrated 2010 & 2015 American Heart Association Guidelines for CPR & ECC Part 12: Pediatric Advanced Life Support ©2015 American Heart Association, Inc.]

For witnessed arrests and arrests in the hospital, the AED should be applied and allowed to analyze as soon as possible. Start chest compressions the instant cardiac arrest is confirmed and continue compressions until the moment the AED is in place and ready to analyze the rhythm. Realistically, with more than one rescuer, a cycle or two of chest compressions can be provided before the AED is able to analyze the rhythm. If the AED does not recommend defibrillation, then continue CPR. Keep the AED applied until other means of cardiac monitoring become available.

SPECIAL SITUATIONS DURING RESUSCITATION

TERMINATION OF EFFORTS

Pediatric cardiopulmonary arrest lasting >20 minutes is associated with a poor outcome.[28] If hypothermia is thought to be responsible for the arrest and cardiac electrical activity is present, resuscitation

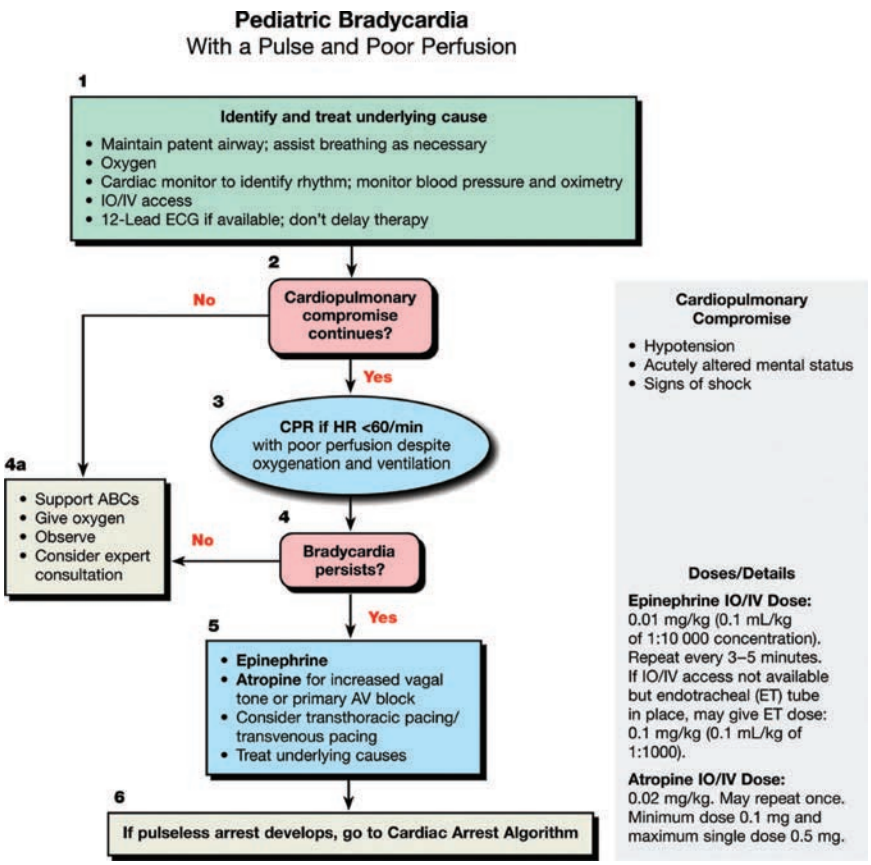


FIGURE 109-6. Pediatric bradycardia decision tree. ABC = airway, breathing, circulation; AV = atrioventricular; HR = heart rate. [Reprinted with permission Web-based Integrated 2010 & 2015 American Heart Association Guidelines for CPR & ECC Part 12: Pediatric Advanced Life Support ©2015 American Heart Association, Inc.]

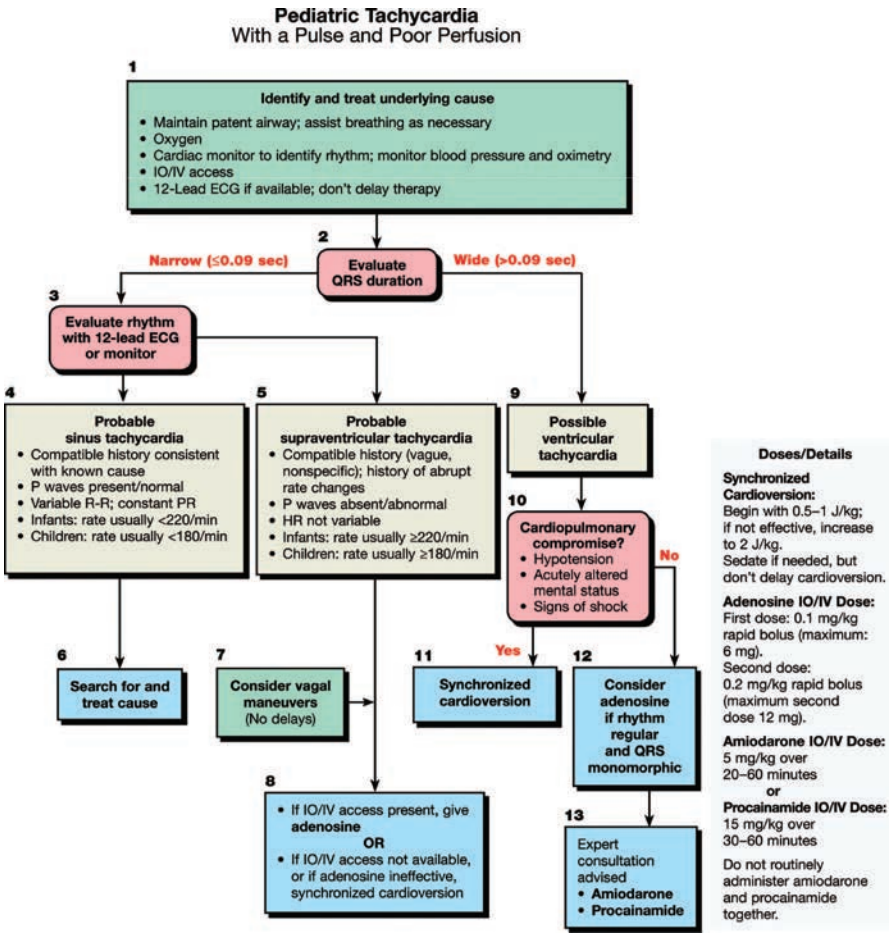


FIGURE 109-7. Pediatric tachycardia decision tree for infants and children with rapid rhythm and poor perfusion. HR = heart rate. [Reprinted with permission Web-based Integrated 2010 & 2015 American Heart Association Guidelines for CPR & ECC Part 12: Pediatric Advanced Life Support ©2015 American Heart Association, Inc.]

TABLE 109-7 Energy Requirements for Defibrillation and Cardioversion

Rhythm	Type of Shock	Initial Dose	Subsequent Doses
Ventricular fibrillation or pulseless ventricular tachycardia	Defibrillation (unsynchronized)	2 J/kg	4 J/kg to maximum of 10 J/kg or adult dose
Unstable supraventricular tachycardia or ventricular tachycardia with pulse but poor perfusion	Synchronized cardioversion	0.5–1 J/kg	2 J/kg

can be continued while attempting to achieve a core temperature of 30°C (86°F). The likelihood of survival and intact neurologic function diminishes as the duration of the resuscitation attempt increases.[28] Unfortunately, no single factor is predictive of outcome, so integrate all the circumstances of the arrest and the patient's premorbid condition before terminating resuscitative efforts. Neurologically intact survival can occur after very prolonged ED resuscitations with high-quality CPR,[8] so developing a strict time for termination of resuscitation efforts is not possible.

FAMILY PRESENCE DURING RESUSCITATION

Family presence during resuscitation efforts should be provided whenever possible. ED staff may worry about the family's critique of the resuscitation or the family's unwillingness to terminate efforts. Some family members may become distressed or exceedingly emotional while care is being given to a loved one. Positive and negative effects from family presence can occur during resuscitation.[29] Most family members wish to be present during resuscitation, and being given the choice to be present contributes to the family's sense of agency.[30] Having family members present during resuscitation is a holistic approach to patient care, with the family's and the patient's needs addressed simultaneously. The current 2015 American Heart Association guidelines consider family presence during the resuscitation to be a Class I recommendation for pediatric patients.[31] A social worker, chaplain, or nurse can assist the family during resuscitative efforts.

COPING WITH THE DEATH OF A CHILD

Both family members and members of the resuscitation team mourn the death of a child. Several *tasks of mourning* have been described that must occur for successful resolution of grieving (**Table 109-8**).[32]

Physicians and other healthcare providers can shape the way families remember the death of a child. Guidelines for communicating with parents are listed in **Table 109-9**.[33] Parents remember how compassionately the bad news is given, but most families still want the "bottom line" when they are first told of their child's death. They are waiting for it. Saying, "I am very sorry, we did everything we could, but Sally died" is compassionate and direct. Most families do not want all the technical details about the resuscitation efforts. After delivering the bad news, have a chaplain or social worker stay with the family to allow the family time to deal initially with the shocking news. The physician should remain quietly in the room or return after a few minutes (or later, if other duties require) to answer questions. This is also the time to ask whether the family would like to see the child and to prepare them for what they will see. Many parents may regret not seeing their child after death.[33]

TABLE 109-8 Tasks of Family Mourning a Lost Child

- Accept the reality of the loss.
- Work through painful grieving.
- Adjust to life without the child.
- Emotional resolution and return to normal activities.

TABLE 109-9 Giving Bad News Effectively

- Use support staff such as chaplains and social workers.
- Early in your delivery of the news, let the family know the child has died.
- Use simple, direct, understandable language.
- Speak with compassion and caring.
- Answer questions from any family members honestly.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 110

Pediatric Trauma

Genevieve Ernst

INTRODUCTION AND EPIDEMIOLOGY

Traumatic injuries are the biggest killer of children in the developed world and can lead to significant disability and healthcare expenditure. On average, one child dies every hour from injuries or violence in the United States.[1] Almost 14,000 children and adolescents died in 2016 in the United States from unintentional or violence-related injury, giving a crude death rate of almost 17 per 100,000; >60% of these deaths were unintentional.[2] Additionally, an average of 22,200 children seek medical attention every day in U.S. EDs for nonfatal injuries.[1] Although often referred to as "accidents," most traumatic injuries in children represent discrete, potentially preventable events.

Pediatric trauma occurs in a bimodal age distribution, with peak incidences in toddlers and adolescents.[1,3] Motor traffic–related injury is the number one cause of death in children >4 years old as well as adolescents. Other leading causes of unintentional injury include pedestrians and cyclists struck by vehicles, falls, and fires.[2] Children are at greater risk of serious injury than adults when operating all-terrain vehicles and snowmobiles.[4] Although blunt force trauma is far more common in children than penetrating injury, firearm-related mortality is one of the top four causes of mortality in American youth.[2] Infants <1 year of age are at greatest risk of death from inflicted injury. Although the rate of pediatric homicides has decreased over the past two decades, death by suicide is on the rise in the adolescent population.[1]

BEHAVIORAL CONSIDERATIONS

The psychological ramifications of traumatic injuries and resuscitation in a busy trauma bay on the seriously injured child should not be underestimated. Behavioral regression is common due to pain, anxiety, and perceived threats in an unfamiliar environment. Making an effort to build a rapport and limit the number of providers in direct contact with the child is essential to gaining the child's trust and cooperation. Understanding normal child development helps identify alterations of the sensorium, which may be the result of traumatic brain injury, hypoperfusion, or hypoxemia.

Family/caregiver presence during resuscitation is an important standard practice in pediatric care. This not only can help comfort the injured child but can also assist in assessing the child's mental status. Studies repeatedly demonstrate that caregiver presence is beneficial for both the patient's and caregiver's psychological well-being, does not interfere with medical efforts, and does not result in increased medicolegal issues.[5] Consider providing a designated support person to help family/caregivers cope.

ED PREPAREDNESS

Prearrival preparedness warrants special consideration when anticipating the arrival of a critically injured child: estimate the child's weight beforehand, precalculate common sedation and intubation medications, and have the appropriate-size equipment readily available. Make sure ED personnel maintain pediatric trauma competency. When anticipating the arrival of a critically injured child, consider drawing up sedation and intubation drugs beforehand using the **"3:2:1 rule": fentanyl 3 micrograms/kg IV, ketamine 2 milligrams/kg IV, and rocuronium 1 milligram/kg.**

PEDIATRIC ANATOMY

Pediatric anatomy and physiology differences compared to adults are outlined in **Table 110-1**. The pediatric head has a larger surface area that is prone to significant bleeding either from open scalp wounds or hematomas, which can cause hypovolemic shock in infants. The cranium is thinner, transmits energy easily, and predisposes to skull fractures. Open sutures in infants can accommodate increases in intracranial pressure and may delay the recognition of serious intracranial injuries. Infants have prominent extra-axial intracranial spaces through which bridging cortical vessels traverse and are prone to sheer and acceleration-deceleration forces such as those sustained in aggressive shaking; this accounts for classic findings such as subdural hemorrhages in inflicted injury victims. Finally, the size of the head in young children is larger compared to the body, which predisposes to closed head injury, giving a higher incidence of concomitant traumatic brain injury in children with polytrauma. A larger head may also lead to airway occlusion when placed supine without back support.

The facets in the pediatric cervical spine are more horizontal than in adults, with less calcified vertebral bodies, increased laxity of spinal ligaments, and weaker supporting musculature, all of which allow translational forces to cause spine injuries without bony abnormalities. Due to the weaker neck musculature and larger cranium, the fulcrum of force is more cephalad, predisposing children to higher cervical spine injuries compared to adults (see Chapter 112, "Cervical Spine Injury in Infants and Children").

Significant anatomic differences between pediatric and adult airways are discussed in Chapter 113, "Intubation and Ventilation in Infants and Children," as they relate to advanced airway management. The pediatric laryngeal cartilages are more pliable and therefore less prone to fracture than the firm ossified adult cartilages. Although the larynx is relatively protected, children have higher risk for airway compromise due to soft tissue swelling or expanding hematoma in relation to the smaller size of the pediatric airway and neck.

The chest wall in children is more compliant, its tracheobronchial structures are more vulnerable, and the heart is more anterior with mobile mediastinal structures, all of which predispose to intrathoracic injury such as pulmonary contusions with minimal thoracic wall injury. Delicate tracheobronchial structures are susceptible to barotrauma especially in situations of excessive volume ventilations during resuscitation generating iatrogenic pneumothorax. The diameter of the respiratory structures is much smaller than in adults, and a change in the inner diameter (from aspirated fluids or secretions) has a four-fold impact on the resistance to air flow as stated by the Hagen-Poiseuille equation, predisposing to airway obstruction.

The child's abdomen is relatively larger in size compared with the rest of the trunk, has underdeveloped musculature, and has relatively larger intra-abdominal organs, which predispose to solid organ injuries in blunt abdominal trauma. Furthermore, a thick capsule limits hemoperitoneum in solid organ injury in children, decreasing the sensitivity of US to detect significant injury. The lower intra-abdominal fat content and elastic ligamentous attachments in children (i.e., perinephric fat, sigmoid and ascending colon peritoneal attachments) contribute to increased vulnerability to injury from acceleration-deceleration or abdominal compression. This can predispose children to hollow viscus injuries from seat belt or handlebar trauma. In infants and younger children, the bladder boundaries extend cephalad to just below the umbilicus, and the bladder is vulnerable to direct blows to the lower abdomen.

The skeleton is incompletely calcified, which renders bones more pliable and leads to bowing and greenstick injuries; multiple active growth centers and weaker epiphysis explain certain fracture types specific to children such as supracondylar fractures of the elbow and epiphyseal

TABLE 110-1 Pediatric Anatomy and Physiology Compared to Adults

Anatomy and Physiology	Differences Compared to Adults	Considerations
Head/brain	Larger surface area	Significant bleeding from lacerations or hematomas
	Thinner cranium	Predisposes to skull fractures
	Open sutures	Accommodate ICP increases; delay recognition of serious intracranial injury
	Larger extra-axial intracranial space	Prone to sheer and acceleration-deceleration forces
	Larger head	Head more likely to be injured in polytrauma
Cervical spine	Facets more horizontal; ligamentous and muscle laxity	Higher level cervical spinal injury and SCIWORA
Airway	Laryngeal cartilages more pliable	Less prone to fracture than adults
	Smaller airway and neck	More risk of soft tissue swelling/bleeding compromising airway
Chest	Compliant chest wall	Minimal wall injury but still serious pulmonary injury
	Heart more anterior and mediastinum mobile	Minimal wall injury but still serious cardiac/mediastinal injury
	Susceptible to barotrauma	Avoid excessive airway pressures during ventilation
	Smaller airways	Small changes in airway diameter by secretions or aspiration cause greater resistance to airflow
Abdomen	Relatively larger sized abdominal organs	Greater risk for blunt abdominal trauma
	Thick visceral capsules	May limit hemoperitoneum and US sensitivity
	Less abdominal fat and elastic ligamentous attachments	More vulnerable to acceleration-deceleration injury and hollow viscus injuries
Skeleton	Incomplete calcification	Bones more pliable; specific fractures unique to children
Body surface area	Higher; thinner skin layers	Greater risk for hypothermia
BP and PR	Vary by age	CO relies on PR rather than stroke volume; BP can remain normal despite loss of 40% of blood volume
Ventilation	Tidal volume fixed; smaller FRC	Minute ventilation maintained by increasing respiratory rate; rapid desaturation during apnea

Abbreviations: BP = blood pressure; CO = cardiac output; FRC = functional reserve capacity; ICP = intracranial pressure; PR = pulse rate; SCIWORA = spinal cord injury without radiographic abnormality.

TABLE 110-2 Normal Pediatric Vital Signs

	Pulse (beats/min)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
Newborn	95–145	60–90	30–45
Infant	125–170	75–100	30–70
Toddler	100–160	80–110	40–90
Preschool	70–110	80–110	45–85
School age	70–110	85–120	45–88
Adolescent	55–100	95–120	60–90

injuries such as the ones described by the Salter-Harris classification (see Chapter 141, "Pediatric Orthopedic Emergencies").

The higher body surface area to overall body mass in children and thin epidermal and dermal layers of the skin along with a paucity of subcutaneous fat and immature thermoregulatory mechanisms lead to increased propensity for hypothermia in cold environments, which must be considered when assessing an exposed child in the trauma bay.

Given their smaller size, multisystem injuries are the rule rather than the exception for children with blunt force trauma. However, increased neuroplasticity in young children and general good health increase their likelihood of a favorable recovery.

PHYSIOLOGY

Table 110-2 shows the expected vital signs according to age. Be alert to abnormalities in heart rate, respiratory rate, and peripheral perfusion that can indicate acute deterioration in the setting of trauma.[6]

Cardiac output is mediated primarily by heart rate in children as opposed to stroke volume in adults. Children with significant blood loss develop tachycardia, which can be sustained for a variable period of time before cardiac output is compromised. In addition, the vasculature is quite sensitive to endogenous catecholamines, allowing children to modify vascular tone in response to hemodynamic changes and regulate perfusion to the core organs. These two parameters, capacity to increase heart rate and modulate peripheral vascular resistance, help children maintain normal blood and perfusion pressures in the face of significant hemorrhage of up to 40% of the total blood volume (80 to 100 mL/kg depending on age), and **hypotension is a very late and ominous sign of cardiovascular compromise in children**.

The mean systolic blood pressure in children 1 to 10 years of age can be estimated using the following formula: 90 + (2 × age) mm Hg; hypotension can be estimated as systolic blood pressure less than 70 + (2 × age) mm Hg.

In children, pulmonary tidal volume is relatively fixed, so minute ventilation is maintained primarily by respiratory rate (tachypnea) rather than depth (hyperpnea). Small residual volumes contribute to atelectasis, and a smaller functional residual capacity contributes to rapid desaturation during apnea.

Finally, the metabolic demands in children are higher than in adults. Children have a higher energy expenditure and caloric requirement at baseline. Although stress-induced **hyperglycemia** is common in the setting of polytrauma, **hypoglycemia** can occur in younger children and should be treated promptly.

THE PRIMARY SURVEY

Despite the many differences between pediatric and adult trauma management, the general approach to assessing the child with multiple trauma is the same: the traditional "(C)ABCDE" (catastrophic bleeding, airway with cervical spine motion restriction, breathing, circulation with hemorrhage control, disability, exposure) approach to the primary survey while addressing life-threatening injuries should be employed in all injured children. (See Chapter 254, "Trauma in Adults," for a summary of primary and secondary survey steps.)

AIRWAY

A significant proportion of traumatic deaths occur from hypoxia, and timely airway management by an experienced provider is of paramount importance. Assess the **patency** of the airway first; note a hoarse or muffled cry or voice, stridor or sonorous respirations, increased work of breathing, or poor chest rise with bag-valve mask ventilation. Evaluate the **maintainability of a protected airway** in the presence of facial or neck trauma or facial burns, or in patients with neurologic compromise that precludes them from having an organized breathing pattern. In a spontaneously breathing child with a partially obstructed airway, use a jaw-thrust maneuver with bimanual in-line spinal motion restriction to open the airway, suction secretions and debris, and apply supplemental oxygen.

A larger occiput in smaller children results in passive extension of the cervical spine and distortion of airway anatomy. The plane of the midface should remain parallel to the spinal board or bed. For infants and toddlers, placement of a 1- to 2.5-in. layer of padding below the entire torso may be required to maintain neutral alignment of the spine. Care should be taken to restrict cervical spine motion in polytrauma patients, especially if obtunded or if a cervical spine injury is suspected (see Chapter 112, "Cervical Spine Injury in Infants and Children").

Endotracheal intubation may be challenging due to distorted anatomy or due to blood, foreign bodies, or teeth occluding the airway. Since in-line stabilization may be required for airway manipulation, airway support in trauma is considered "difficult," with adjuncts such as laryngeal mask airways, bougie, video laryngoscopy, and surgical airways sometimes being required (see Chapter 113, "Intubation and Ventilation in Infants and Children"). Indications for endotracheal intubation in the trauma patient include the following:

1. Glasgow Coma Scale score <8 or lack of airway protective reflexes
2. Respiratory failure due to inadequate oxygenation or ventilation (e.g., pulmonary contusions, large pneumohemothoraces, chest wall or diaphragm injuries)
3. Impending airway comprise (e.g., facial burns, inhalation injury, expanding neck hematoma)
4. Lack of neuromuscular respiratory drive (e.g., cervical spinal cord injuries)
5. Significant hypovolemia with depressed sensorium
6. Unstable patients in need of CT imaging, angioembolization, or operative intervention
7. Transport of critically injured patients to another institution, especially over long distances

Preoxygenate children who require endotracheal intubation for airway control. Having a standardized approach to drug-assisted intubation in pediatric trauma patients can reduce medical errors and improve patient safety.[7,8] The vast majority of pediatric trauma patients can be safely intubated using ketamine followed by a paralytic agent, including those with head or ocular injuries. Ketamine is the induction agent of choice in hypotensive patients and may improve cerebral blood flow in children with raised intracranial pressure.[9,10] Alternatively, etomidate reduces cerebral blood flow, intracranial pressures, and cerebral oxygen consumption, while maintaining arterial blood pressure, and may be considered in children with severe traumatic brain injury. Induction agents with a propensity to cause hypotension, such as propofol, should be avoided in all hemodynamically compromised children, especially those with associated head injuries, because a single hypotensive event can worsen neurologic outcome.[11] Consider premedication with atropine sulfate in infants <1 year of age because they are at risk for bradycardia in response to both laryngeal stimulation and hypoxia.

A needle cricothyroidotomy may be required if orotracheal intubation is not possible due to severe maxillofacial injuries and the patient cannot be adequately ventilated and oxygenated. Laryngeal anatomy is difficult to discern, especially in young children, making needle-jet insufflation via the cricothyroid membrane the preferred temporizing technique for oxygenation. However, lifesaving surgical cricothyrotomy has been successfully performed in older children in whom the cricothyroid membrane is easily palpable (usually by 12 years of age). (See Chapter 113, "Intubation and Ventilation in Infants and Children.")

BREATHING

Once a definitive airway has been established, assess the adequacy of breathing through careful observation of the rate, depth, pattern, and work of breathing, including tracheal position and symmetry of chest wall movements as well as air entry. Note that alterations in the mental status might signify hypoxia (agitation) or hypercarbia (somnolence) from inadequate breathing.

The physiologic consequences of blood or air accumulation in the pleural space are similar in children and adults, and significant hemopneumothoraces are treated with pleural decompression. When there is concern for tension pneumothorax, immediately perform a needle thoracostomy by placing a 16- to 18-gauge IV catheter in the midclavicular line just above the third rib. Be mindful that longer over-the-catheter needles in small children pose a risk of iatrogenic lung injury given their relative size and thinner chest walls.[12] Alternatively, in overweight children or muscular adolescents, consider placing a catheter between the fourth and fifth ribs at the anterior axillary line. Proceeding directly to a decompressive finger thoracostomy should be considered for patients in extremis or in cardiac arrest, as long as this can be performed expediently. A tube thoracostomy (chest tube) should then be inserted to drain air and/or blood from the chest with an appropriate-size tube based on age or weight. Although the open technique with a larger-size chest tube is preferable during a resuscitation, consider inserting a pigtail-type chest tube by Seldinger method in stable children with isolated pneumothoraces.[13]

Of note, infants and toddlers are predominantly diaphragmatic breathers and are highly sensitive to increased intra-abdominal pressure. Early gastric decompression with an orogastric tube can significantly improve their work of breathing.

CIRCULATION

As in adults, catastrophic bleeding should be addressed first in the primary survey. Hemorrhage control with direct pressure, tourniquets, and pelvic binding are essential prehospital interventions that save lives in both children and adults.[12] Infants can lose a substantial amount of blood from their scalps. However, isolated long bone or pelvic fracture are unlikely to be the sole cause of circulatory compromise in the prepubertal child, and other sources of bleeding should be considered, especially intra-abdominal injuries.

Because hypotension is a late and ominous sign of decompensated shock, recognition of early signs of hypovolemia is of paramount importance. Tachycardia and poor skin perfusion are often the only signs of circulatory compromise. Tachycardia may also be caused by pain or fear, which provides an additional challenge when assessing the pediatric patient. Other important signs of blood loss include weakening of peripheral pulses, mottled skin, cool extremities relative to the torso, altered sensorium including dulled response to pain, and narrowing of the pulse pressure to <20 mm Hg.[12]

Vascular access can be challenging in small children, especially in hypovolemic shock, with limited cannulation options. Ideally, place two proximal large-bore IV catheters, but limit attempts in the critically injured child and proceed to intraosseous access if unsuccessful after 90 seconds (see Chapter 114, "Vascular Access in Infants and Children"). Venous cutdowns and central access are rarely used for initial vascular access in children because they can be procedurally difficult and time consuming. Rapid infusion devices can deliver warmed fluids rapidly through a 20-gauge or larger cannula but are not compatible with smaller-gauge catheters. In smaller children, a pressure bag or multiple handheld syringes may be used for rapid fluid resuscitation via the pull–push method. However, neither of these methods accounts for warming the fluids. Instead, consider using prewarmed crystalloids, placing syringes under forced air warmers, or using a Hotline® Fluid Warmer (Smiths Medical, Dublin, OH).[14]

Fluid Management and Hemostatic Resuscitation Ongoing controversy exists with regard to the ideal fluid resuscitation strategy for seriously injured children. Recently, there has been a move away from crystalloid resuscitation in adult hemorrhagic shock in favor of a "damage control resuscitation" approach, with includes early administration of blood products (see Chapter 254, "Trauma in Adults"), the goal of which is to minimize the dilution of clotting factors, tissue edema, and acidosis associated with excessive crystalloids, which are thought to worsen trauma-induced coagulopathy. Many pediatric trauma centers in North America have adopted a crystalloid restrictive balanced fluid resuscitation strategy, although evidence of improved outcomes with this approach is lacking in children. Although the exact threshold for adverse crystalloid effects is not known, excessive crystalloids in pediatric trauma (in excess of 60 mL/kg/d) are associated with increased intensive care and ventilator days.[15,16]

On the other hand, children may be relatively fluid tolerant as compared to adults and usually tolerate initial boluses of 10 to 40 mL/kg.[16,17] For instance, the majority of children with bleeding from an isolated intra-abdominal solid organ injury will respond to a single bolus of normal saline or lactated Ringer's and hence may forgo a blood transfusion.[18]

At this time, judicious use of crystalloids is recommended for injured children with suspected bleeding. Children in compensated hemorrhagic shock should be given an initial bolus of 20 mL/kg (10 to 40 mL/kg) of warmed crystalloids.[12,18] If their condition does not improve, early transition to weight-based blood product resuscitation is advised (10 to 20 mL/kg of packed red blood cells for children <40 kg). On the other hand, children in decompensated shock should receive blood as soon as logistically possible. Keep in mind that aggressive blood component replacement is not a substitute for definitive surgical control of bleeding.[18]

Permissive hypotension, to prevent clot disruption, is not currently recommended in children given that hypotension is a late finding of shock and the high incidence of concomitant traumatic brain injury in polytrauma victims.[18]

Massive transfusion protocols provide balanced ratios of red blood cells, plasma, and platelets with the goal of minimizing the coagulopathy associated with significant hemorrhage. Evidence from combat literature suggests that children requiring >40 mL/kg of blood products in the first 24 hours, or roughly half their blood volume, have an increased risk of both early and late mortality.[19] **Therefore, many centers across the United States have incorporated a definition of >40 mL/kg of anticipated blood product requirements into their massive transfusion guidelines.** Although studies have yet to demonstrate a survival benefit for blood-based massive transfusion protocols in children, they can help organize and expedite blood product delivery, and pediatric trauma centers should advocate for their use.[20] Further research is needed to determine the optimal ratio of packed red blood cells to plasma to platelets in children, and evidence for improved outcomes with any given foundation ratio, including high plasma ratios (1:1:1) as in adults, is lacking.[21]

Most of the evidence supporting use of tranexamic acid in children originates from combat literature,[22] and its use in pediatric polytrauma is not yet standard of care.[23] That said, hemorrhage, as in adults, remains a leading cause of preventable trauma death. Acute traumatic coagulopathy and hyperfibrinolysis exist in severely injured children and can be further exacerbated by traumatic brain injury–associated coagulopathy. Furthermore, tranexamic acid has been shown to be both safe and efficacious when used in high doses in pediatric surgery. Given the minimal risks and plausible benefit, **tranexamic acid should be strongly considered within 3 hours of injury in adolescents as well as children of all ages requiring a blood transfusion.** More research is needed to determine the role of tranexamic acid in isolated solid organ injury.[24]

DISABILITY

Assess mental status by observing the patient's best response to a parent or caregiver. Mental status in preverbal children can be assessed using the **modified pediatric Glasgow Coma Scale (GCS)** (**Table 110-3**). The pediatric Glasgow Coma Scale for infants has a similar accuracy for predicting clinically important traumatic brain injury as the standard Glasgow Coma Scale for older children.[25]

A simpler and validated method to assess mental status in children is by using the AVPU score, which is currently recommended by the pediatric advanced life support guidelines[26] (**Table 110-4**).

Check the pupillary response to light and determine whether the child is moving all four limbs. Pupillary response is predictive of both survival

TABLE 110-3 Modified Pediatric Glasgow Coma Scale

Verbal Response	Eye Opening	Motor Response
Coos or babbles = 5	Spontaneous = 4	Spontaneous = 6
Irritable cry = 4	To voice = 3	Withdraws to touch = 5
Cries to pain = 3	To pain = 2	Withdraws to pain = 4
Moans to pain = 2	None = 1	Abnormal flexion = 3
No response = 1		Abnormal extension =2
		None = 1

and neurologic outcome.[11] Monitor serum glucose because hypoglycemia can lead to an altered mental status as well as worsen neurologic outcome.

Be mindful that pain is often undertreated in children and ensure that appropriate analgesics and sedatives are given. Intranasal medications or inhaled nitrous oxide can be used prior to establishing IV access, and children, as adults, can benefit from regional blocks for musculoskeletal injuries (see Chapter 115 "Pain Management and Procedural Sedation in Infants and Children").

EXPOSURE AND ENVIRONMENTAL CONTROL

Disrobe and expose the child to identify all potential injuries and perform lifesaving procedures; however, children are particularly susceptible to hypothermia when exposed to cold environments or receiving room temperature fluids. Keeping the child warm is imperative as temperature instability can worsen coagulopathy, thereby exacerbating blood loss. To avoid iatrogenic hypothermia, maintain a warm resuscitation environment, remove wet clothing, and cover the child with warm blankets or an external warming device as soon as the assessment is complete. If the child remains hypothermic or ongoing fluid resuscitation is needed, give warmed crystalloids and blood products.

If a log roll is performed to examine the back and spine, make sure to examine the back of the scalp for ongoing bleeding. Note that a digital rectal exam should be performed only in select patients in whom there is concern about serious spinal injury. The digital rectal exam rarely provides additional useful information and may be particularly upsetting for the pediatric patient.[27]

THE SECONDARY SURVEY AND SURVEY ADJUNCTS

After the primary survey is complete and life-threatening injuries have been addressed, perform a secondary survey. This includes an AMPLE history (**a**llergies, any relevant **m**edications, **p**ast medical history, time of **l**ast meal, and **e**vents leading up to the trauma), a "head to toe" examination, and completion of adjunctive laboratory or imaging tests not already performed. See Chapter 254, "Trauma in Adults," for key physical examination findings.

LABORATORY INVESTIGATION

Routine laboratory "trauma panels" are frequently obtained in the evaluation of injured children, but individual laboratory abnormalities, while common, are seldom useful to dictate therapy, and no single laboratory test has acceptable sensitivity or negative predictive value to safely and effectively screen patients when used alone.[26] Even organ-specific chemistries alone predict abdominal injury poorly in children and rarely alter acute management. Although elevated liver function tests, particularly alanine aminotransferase, are suggestive of liver injury, no consensus exists as to the cutoff point for determining risk. An exception to the generally poor utility of liver function tests is in the setting of suspected inflicted injury in infants and young children, for whom liver function tests are recommended as a screening tool to detect occult blunt intra-abdominal injury.[28]

TABLE 110-4 AVPU Score

A = Awake
V = Responds to verbal stimuli
P = Responds to pain
U = Unresponsive

Urinalysis is frequently obtained in trauma patients, but microhematuria alone is poorly predictive of either genitourinary or intra-abdominal injury across a range of cut points for number of red blood cells per high-power field; gross hematuria and mechanism of injury, rather than microhematuria, should guide imaging studies.[28]

Consider obtaining a β-human chorionic gonadotropin in all girls over the age of 8 years. Additionally, obtain toxicology testing in preteens and adolescents, especially if their mental status is altered or if drug or alcohol use is suspected to have contributed to the injury. A visit to the ED for serious injuries may be an opportune time to identify patients who could benefit from a Screening, Brief Intervention, and Referral to Treatment (SBIRT) approach for substance use once the patient is stable.[29,30]

Combining laboratory tests with clinical findings may be useful for prognostication in pediatric blunt trauma. Furthermore, early coagulopathy and acidosis may better predict mortality and ongoing blood product needs than traditional scoring tools such as the Pediatric Trauma Score or Injury Severity Score.[31] A promising score currently being prospectively validated in polytraumatized children is the B.I.G. Score (**b**ase deficit + [2.5 × **I**NR] + [15 – **G**lasgow Coma Scale score]). A score of <16 accurately predicts children with a high probability of survival and allows physicians to rapidly recognize the degree of physiologic derangement. This may prove useful not only in tracking patient outcomes, but also for providing a meaningful way of communicating severity of injury to the referral hospital.[32-34]

IMAGING

Plain Radiography Not all children require a complete "trauma series" in which the cervical spine, chest, and pelvis are imaged. Predictors of intrathoracic injury after blunt trauma in pediatrics include low systolic blood pressure, blood oxygen saturation <95%, abnormal thoracic exam, femur fracture, and altered mental status. However, up to 5% of children with intrathoracic injuries may have no predictors, and therefore, a chest radiograph should be considered in all patients with a concerning mechanism.[35] Complaints of pain or abnormal exam of the pelvis or hip, hematuria, femoral deformity, hemodynamic instability, and Glasgow Coma Scale score of ≤13 are independent risk factors for pelvic fractures. Children with none of these features have <0.5% risk of pelvic injury and may forgo plain films of the pelvis.[36] Furthermore, if an abdominopelvic CT is planned, plain radiographs of the pelvis are not required. Although plain films of critical musculoskeletal injuries, such as long bone fracture, may be needed in the resuscitation bay, radiographs of non–limb-threatening injuries should not delay CT imaging or transfer to definitive care.

US FAST is an appealing test due to its rapid bedside acquisition, relatively low cost, and lack of radiation, but there are a number of limitations in pediatric use. **Due to anatomic and physiologic differences between children and adults, up to 30% of children with solid organ injury have no demonstrable free fluid on FAST, decreasing the sensitivity of this exam for solid organ injuries and limiting its negative predictive value, particularly in hemodynamically normal patients.** FAST can miss intra-abdominal injuries requiring intervention, and CT imaging should be obtained when an injury is suspected on clinical exam regardless of findings on US. Moreover, unlike adults in whom free fluid (hemoperitoneum) usually requires laparotomy, the vast majority of children with hemoperitoneum are successfully managed nonoperatively, so a positive FAST rarely changes management.[37,38] However, in the hemodynamically compromised patient with multiple injuries, FAST may provide valuable information as to the source of bleeding and help to focus resuscitative efforts.[39,40] There is an emerging role for serial FAST in combination with abdominal exam and blood work in patients with suspected blunt abdominal trauma. However, further study is needed to determine how to best incorporate FAST into clinical

practice guidelines for children.[41] In addition, contrast-enhanced US is a novel radiation-free imaging modality that has shown promise for the diagnosis and follow-up of blunt abdominal trauma in children.[42,43]

Currently the greatest advantages of POCUS in pediatric trauma lie in the extension of the traditional FAST to include an assessment of the lungs and heart, especially in penetrating trauma. POCUS is superior to plain films for detecting occult pneumothoraces in the supine patient and is useful for identifying cardiac effusions as well as assessing global cardiac contractility. Other important applications include procedural guidance, such as regional nerve blocks, and airway confirmation for intubated patients.[37,40,44]

CT CT imaging is the gold standard for evaluation of acute intracranial bleeding, pulmonary parenchymal or great vessel injuries, solid organ injuries, and pelvic injuries. However, children are at increased risk of malignancy secondary to ionizing radiation, and judicious use of CT and application of the ALARA (**a**s **l**ow **a**s **r**easonably **a**chievable) principle to limit the dose of radiation received are imperative. A retrospective review of >42,000 pediatric patients with blunt trauma showed no mortality benefit to whole-body CT imaging compared to a selective CT approach. In addition, additional injuries identified on the "pan scan" were not life threatening and did not change management.[45] When possible, CT imaging should be reviewed by a pediatric radiologist with trauma experience, and scans from referring hospitals should be reinterpreted on arrival to a pediatric trauma center.[46] Furthermore, imaging should not delay transfer to a higher level of care.

REFERRAL TO A PEDIATRIC CENTER

Pediatric trauma center designation in the United States is conferred by governmental authority, and requirements vary from state to state. Guidelines have been created by the American College of Surgeons to delineate the capabilities of a designated pediatric trauma center. Necessary resources include 24-hour availability of a pediatric surgeon, pediatric surgical specialists, pediatric anesthesiology, pediatric intensive care, and medical pediatric specialties, and the ability to provide comprehensive care to children of all ages.[47,48]

Use of trauma triage scores can help identify a child with more severe injuries in need of a higher level of care. Two of the most commonly used scores are the Pediatric Trauma Score (**Table 110-5**) and the Revised Trauma Score (**Table 110-6**), which emphasize physiologic variables rather than relying solely on anatomic factors or mechanism of injury. Lower scores are associated with greater need for critical interventions and mortality[49]: **a Revised Trauma Score of <12 or a Pediatric Trauma Score of <8 should prompt transfer to a pediatric trauma center.**[50]

Although mechanism is associated with specific injury patterns, the decision to transfer a patient to a pediatric trauma center should be based primarily on anatomic and physiologic factors as they better predict the need for interventions. Additional indications for transfer to a pediatric trauma center are listed in **Table 110-7**.[51]

Care of seriously injured children at a pediatric trauma center is associated with improved survival.[52,53] If not available, transport to a designated trauma center, adult or pediatric, is still associated with improved outcomes.[54,55] Interfacility transfer of critically injured children is best done by a specialized pediatric transport team or a critical care transport team with pediatric experience when available (see Chapter 107, "Neonatal and Pediatric Transport").

TABLE 110-5 Pediatric Trauma Score*

	−1	+1	+2
Size (kg)	<10	10–20	>20
Airway	Unmaintained	Maintained	Normal
Systolic blood pressure (mm Hg)	<50	50–90	>90
Level of consciousness	Comatose	Altered	Awake
Wounds	Major open	Minor open	None
Skeletal trauma	Open/multiple	Closed	None

*Total score is calculated by adding the score corresponding to the appropriate value from each column.

TABLE 110-6 Revised Trauma Score*

Number	Glasgow Coma Scale Score	Systolic Blood Pressure (mm Hg)	Respiratory Rate (breaths/min)
4	13–15	>89	10–29
3	9–12	76–89	>29
2	6–8	50–75	6–9
1	4–5	1–49	1–5
0	3	0	0

*Total score is calculated by adding the score corresponding to the appropriate value from each column.

HEAD TRAUMA

Minor head injury (Glasgow Coma Scale >13) and concussion, including pathophysiology and clinical decision rules to decide which children require neuroimaging, is discussed in Chapter 111, "Minor Head Injury and Concussion in Children." Inflicted head injuries are discussed in more detail in Chapter 150, "Child Abuse and Neglect." This section focuses on moderate to severe traumatic brain injury.

The first priority for children with severe head injuries is complete and rapid physiologic resuscitation. Cerebral perfusion pressure is dependent on the difference between the mean arterial pressure and intracranial pressure. Keeping this physiologic principle in mind, timely goal-directed therapy is the key to preventing secondary brain insults. Avoid hypoxia as well as hypotension and maintain normothermia, normocapnia, euvolemia, and euglycemia.[56,57] When possible, avoid secondary transfers via hospitals without neurosurgical presence because expedient imaging followed by timely neurosurgical intervention improves survival.[58]

TABLE 110-7 Indications for Transfer to a Pediatric Trauma Center

Physiologic criteria	Depressed or deteriorating neurologic status Respiratory distress or failure Intubated children requiring ventilatory support Shock, compensated or uncompensated Injuries requiring blood transfusion Children requiring pediatric intensive care monitoring Arterial or central venous pressure monitoring Intracranial pressure monitoring Vasoactive medications
Anatomic injury	Multiple severe trauma Two or more major long-bone fractures (i.e., femur, humerus) Fractures of the axial skeleton Spinal cord or column injuries Traumatic amputation of an extremity Moderate to severe head injury Cerebrospinal fluid leaks Open or depressed skull fractures Significant blunt injury to the torso Major pelvic fractures Penetrating head, chest, abdominal, or pelvic trauma Extensive burns or burns with associated trauma

Sources: https://www.doh.wa.gov/portals/1/Documents/Pubs/530092.pdf (Washington State Department of EMS and Trauma Systems: Pediatric Consultation and Transfer Guidelines.); http://www.dshs.state.tx.us/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=8589975024 (The Trauma Center Association of America: Pediatric Trauma Interfacility Transfer Guidelines.); and http://pediatrictraumasociety.org/multimedia/files/Inter-Facility-Tool-Kit.pdf (Pediatric Trauma Society: Interfacility Trauma Toolkit for Pediatric Patients.) Accessed December 12, 2018.

TABLE 110-8 Management of Serious Traumatic Brain Injury in Children

Considerations	Primary Goal	Comments
Cervical spine	Maintain spinal motion restriction	Image the cervical spine in intubated or obtunded patients
Airway	Maintain airway, intubate for Glasgow Coma Scale (GCS) score <8 or as needed for oxygenation and ventilation	Intubation can raise intracranial pressure and should be performed by an experienced provider
Oxygenation and ventilation	Oxygen saturation >90%; P_{CO_2} 35–40 mm Hg	No prophylactic hyperventilation
Blood pressure	Systolic blood pressure >70 + (2 × age)	No permissive hypotension
Cerebral perfusion pressure (CPP)	CPP = 40–50 mm Hg (ref)	Target may vary by age and size of the child
Intracranial pressure (ICP) monitoring	ICP ≤20 mm Hg	Consultation with neurosurgeon
GCS	GCS before paralytics if possible	Serial GCS to document changes
Sedation and pain management	Midazolam, fentanyl, ketamine, etomidate, barbiturates, thiopental (pediatric intensive care unit only)	Consider paralytics once a neurologic examination is completed
Neuroimaging (noncontrast head CT)	Identify intracranial injury and signs of increased intracranial pressure or herniation	Transcranial Doppler may be useful in infants with open fontanelles but requires an experienced pediatric radiologist
Glucose	Treat hypoglycemia and avoid hyperglycemia	Maintain normal blood glucose
Increased ICP/impending herniation	Elevate head of bed 30 degrees	3% normal saline 5 mL/kg bolus over 10 min followed by infusion of 0.1 mL/kg/h to maintain serum sodium within 155–165 mEq/L *or* Mannitol 0.5–1 gram/kg if normotensive (response is not dose dependent) No corticosteroids
Core temperature	Maintain temperature 36°C–38°C	A 24-h course of moderate hypothermia is not indicated
Seizure prophylaxis	Optional: consider for children with witnessed posttraumatic seizures and intracranial blood	Phenytoin 20 milligrams/kg (or fosphenytoin 20 PE/kg) *or* Levetiracetam 20 milligrams/kg (maximum, 500 milligrams/dose)[67] for first week following severe traumatic brain injury
Anemia	Transfuse for hemoglobin <7 grams/dL[68]	
Neurosurgery/transfer	ICP monitoring, evacuation of intracranial hematomas, or cerebrospinal fluid shunt for refractory intracranial hypertension	

Abbreviation: PE = phenytoin equivalent.

There remains substantial practice variation in the management of pediatric traumatic brain injury across the United States as well as a paucity of high-level evidence to support specific therapies.[59] However, adherence to clinical practice guidelines and development of multidisciplinary neurocritical care programs for children have been shown to reduce mortality and improve neurologic outcome.[60-62] Comparative effectiveness studies evaluating different medical therapies on children with severe traumatic brain injury are needed.[59]

TREATMENT

A summary of management recommendations for serious traumatic brain injury is listed in **Table 110-8**.[63-66]

NECK TRAUMA

Penetrating neck trauma is rare in children as compared to adults, comprising only 0.3% of cases reported in the National Trauma Data Bank.[69] Management of penetrating neck trauma in children is similar to adults and includes selective neck exploration based on physical examination and the use of CT angiography in stable patients.[70] Blunt neck injuries are more common than penetrating injuries in children and are a result of falls into stationary objects, direct impact during sports, "clothesline injuries," and intentional hanging injuries. Hanging can result in laryngeal fractures or separation injuries. Blunt cerebral vascular injury in children can be evaluated according to adult guidelines.[71] For a complete discussion of neck injuries, see Chapter 260, "Trauma to the Neck."

An approach to the evaluation of pediatric blunt neck trauma is shown in **Figure 110-1**. Assess children with neck injuries in a position of comfort to avoid airway compromise; avoid forcing a patient into recumbence when the physiology dictates tripoding and neck hyperextension in order to maintain airway patency.

THORACIC TRAUMA

For a general description of thoracic trauma, see Chapter 261, "Pulmonary Trauma," and Chapter 262, "Cardiac Trauma," in the adult section. Thoracic injuries occur infrequently in children, accounting for 5% to 12% of pediatric trauma admissions, but are the second leading cause of death from trauma after closed head injury. More than two thirds of children with chest injuries have other organ system injuries. Isolated chest trauma in children carries 5% mortality rate, but when associated with closed head injuries and abdominal trauma, mortality increases up to 40%.[3,34,72]

Blunt forces account for 90% of pediatric thoracic injuries. Motor vehicle crashes, pedestrian accidents, and inflicted injury are more common in younger children, whereas falls, sports-related injuries, and high-speed crashes are more common in older children and teenagers.[72] Penetrating trauma is rare in children, but is more lethal than blunt trauma. However, firearm injuries continue to have a substantial impact on American youth, and young children are at the greatest risk from accidental access to firearms.[1,73,74]

PULMONARY CONTUSIONS

Pulmonary contusions are the most common injury in blunt chest trauma in children and may present with minimal or no external signs of trauma, as forces are preferentially transmitted to internal organs. Anatomic changes in pulmonary contusion include interstitial edema and alveolar hemorrhage with subsequent consolidation. Areas of ventilation/perfusion mismatch reflect poor lung compliance and are associated with disordered ventilation and oxygenation. Pulmonary contusions evolve over the first 4 to 6 hours after injury, and even for several days, and hence may not be evident on initial chest radiograph. Respiratory deterioration on clinical exam should guide the need for

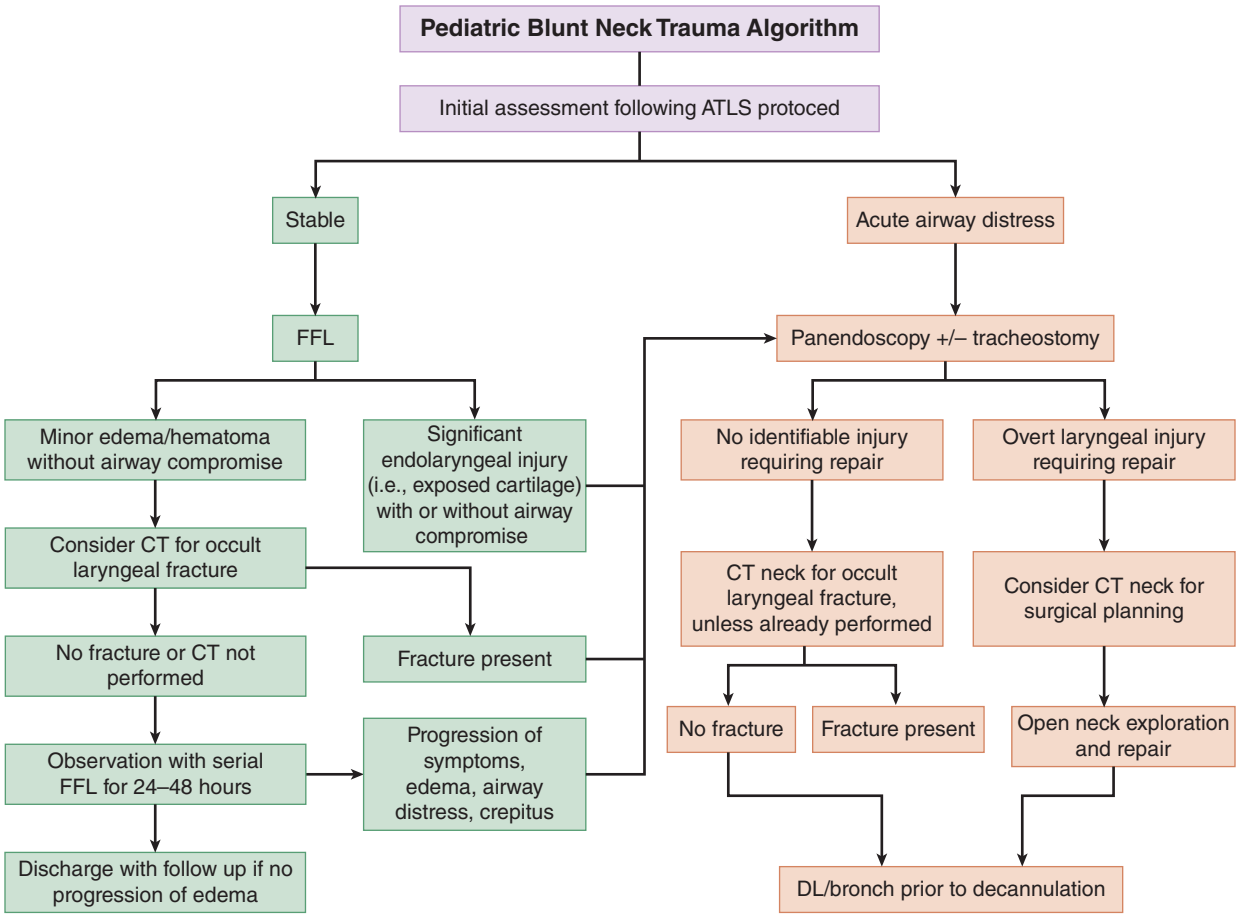


FIGURE 110-1. Algorithm for the evaluation of pediatric blunt neck trauma. ATLS = advanced trauma life support; DL/bronch = direct laryngoscopy/bronchoscopy; FFL = flexible fiber-optic laryngoscopy. [*Source:* Hernandez DJ, Jatana KR, Hoff SR, et al: Emergency airway management for pediatric blunt neck trauma. *Clin Pediatr Emerg Med* 15: 1522, 2014. © 2014 Elsevier Inc. All Rights Reserved.]

repeat imaging. Of note, occult contusions seen only on CT imaging rarely impact management.[75,76] Supportive care, including careful fluid management and lung-injury preventive ventilatory strategies, is the mainstay of management. Consider antibiotic prophylaxis for large contusions given the high rate of associated pneumonia.[77] Interestingly, there have been case reports of refractory traumatic acute respiratory distress syndrome successfully managed with extracorporeal membrane oxygenation.[78,79]

PNEUMOTHORAX

Pneumothoraces are common and present in up to a third of trauma victims; they should alert the clinician to the possibility of associated injuries. Tension pneumothorax is of special concern in younger children due to the relatively easier compromise of cardiopulmonary physiology and detrimental effect on right side heart-filling pressures. Signs such as jugular venous distention are less prominent in children than in adults, and their absence can be falsely reassuring. If a tension pneumothorax is suspected, emergently decompress the chest and place a chest tube without waiting for confirmatory chest radiograph.

HEMOTHORAX

Hemothoraces are relatively less common in children than adults. A child's hemithorax can contain up to 40% of the effective blood volume, and intrathoracic bleeding can lead to hemorrhagic shock. Pediatric recommendations for surgical thoracotomy include chest tube output >20 mL/kg on insertion, drainage exceeding 3 to 4 mL/kg/h, or need for ongoing blood transfusions. Hemothorax is associated with morbidity from infection, lung scarring, and chronic atelectasis.

RIB FRACTURES

Rib fractures are uncommon in children as a result of the elasticity of the rib cage. When present, however, rib fractures are often associated with severe injuries due to the high force required to cause them. In the absence of a witnessed high-energy mechanism, rib fractures, especially posterior, are highly suggestive of inflicted injury in infants. Obtain a chest radiograph to assess for acute or healing rib fractures when abuse is suspected.

Myocardial injury following blunt thoracic trauma in children is extremely rare but potentially lethal. Significant blunt cardiac injury resulting in major vessel disruption or cardiac rupture generally results in immediate death. There should be a high index of suspicion for blunt cardiac injury in children admitted to hospital with evidence of thoracic injury and a high-velocity mechanism. Although no consensus exists in children <14 years of age, most experts agree that a screening ECG and troponin level are reasonable.[80,81] If there are any concerning features on cardiac FAST, ECG, thoracic CT, or elevated troponins, a transthoracic echocardiogram and urgent pediatric cardiology consultation are strongly recommended.

Commotio cordis is a rare condition reported in young athletes; a direct blow to the anterior chest at a critical time in the cardiac cycle results in cardiac dysrhythmia (usually ventricular fibrillation) and cardiac arrest.[82,83]

IMAGING

Thoracic CT with angiography should be used selectively in the pediatric population given the high dose of ionizing radiation to sensitive tissues. Although thoracic CT is more sensitive than chest radiograph for intrathoracic injuries, CT seldom results in significant changes in patient management. Thoracic CT should be reserved for patients with

a high-risk mechanism of injury, such as rapid deceleration injury, *and* an abnormal chest radiograph.[75] Note that tracheobronchial injuries may need to be further evaluated by bronchoscopy.

ABDOMINAL TRAUMA

Abdominal trauma is present in approximately 25% of major trauma patients and is the leading cause of unrecognized fatal injury in children. Ninety percent of abdominal trauma in children is blunt and may result from motor vehicle collisions, pedestrian injuries, falls, direct trauma (e.g., bicycle handlebar), or inflicted injury.[84] Although penetrating trauma is less common in children, a quarter of gunshot wounds involve the abdomen, and >10% of these injuries are fatal.[85] Other causes of penetrating injuries in this age group include impalement, stab wounds, and animal bites.

The spleen is the most commonly injured solid organ, followed by the liver and kidney. Hollow viscus injuries involve the jejunum, duodenum, colon, and stomach (15%) in decreasing order of frequency. Pancreatic injuries are less commonly seen in pediatric abdominal trauma (<5%).[86]

ABDOMINAL IMAGING AND CLINICAL DECISION RULES

Mechanism of injury is much less predictive of clinically important torso injuries than spine or musculoskeletal injuries. Furthermore, the abdominal exam can be misleading; 20% to 30% of children with a normal exam may have significant intra-abdominal injuries on imaging.[84] A number of clinical decision rules have been developed to risk-stratify children with blunt abdominal trauma, and the approach to CT imaging depends on the level of clinical suspicion.

Indications for CT in children at high risk of significant intra-abdominal injuries include[87,88]:

- Polytrauma victims with a history suggestive of severe intra-abdominal injury
- Concerning physical exam findings: abdominal tenderness, peritonitis, a seatbelt sign or other bruising
- Aspartate aminotransferase >200 IU/L or alanine aminotransferase >125 IU/L
- Decreasing hemoglobin or hematocrit
- Gross hematuria

The Pediatric Emergency Care Applied Research Network (PECARN) developed a rule to identify patients at very low risk for intra-abdominal injury requiring intervention (surgery, embolization, transfusion for abdominal bleeding, IV fluid requirement >48 hours). Children are classified as very low risk and may forgo CT imaging if they meet the following criteria[89,90]:

- No evidence of abdominal or thoracic wall trauma
- Glasgow Coma Scale score >13
- No abdominal pain or tenderness
- Normal breath sounds
- No vomiting after injury

Forty-two percent of the study population met these very low-risk criteria, among whom the risk of intra-abdominal injury requiring intervention was 0.1%. The Pediatric Emergency Care Applied Research Network rule has a sensitivity of 97% and negative predictive value of 99.9%.[90]

LIVER AND SPLEEN INJURIES

Nonoperative management is successful in >95% of children with solid organ injuries. Conservative management, with fluid resuscitation and monitoring with serial abdominal exams and laboratory tests (hemoglobin/hematocrit), is the mainstay of treatment.[91] Furthermore, clinical status may better predict the need for admission or intensive care monitoring than grade of injury on CT.[92,93] Blood transfusion, while uncommon, is the most frequent therapeutic intervention; angioembolization and laparotomy are reserved for patients who show evidence of active bleeding after resuscitation.[94] Children who require splenectomy should receive vaccination against encapsulated bacteria (meningococcal and streptococcal pneumonia) as well as antibiotic prophylaxis. Pseudoaneurysm formation is a possible complication of liver and spleen injury, and ongoing monitoring may be required.[95]

RENAL INJURY

Blunt renal injuries in children are seldom isolated, and multiorgan injuries are the rule. The risk of renal injury with blunt trauma is higher in children than adults due to their anatomy. Injury to the kidney is associated with rapid deceleration mechanisms (e.g., motor vehicle and pedestrian collisions, falls from height) or, less commonly, a direct blow to the flank (e.g., sports). Penetrating injury to the flank results in a much higher incidence of renal vascular injury, which is rare in blunt trauma.[96]

Clinical findings include localized flank tenderness, ecchymosis, palpable flank mass, and penetrating wounds in proximity to the kidney. **Microscopic hematuria is common after blunt trauma and does not require further investigation as an isolated finding**. Although gross hematuria indicates potential serious injury, up to 50% of patients with vascular hilar injuries have no hematuria. Furthermore, hematuria >50 red blood cells per high-powered field may also be associated with other solid organ injury, particularly splenic injuries. A four-phase CT with angiography, looking for renal extravasation, should be obtained in patients with history of significant force trauma and gross hematuria. The vast majority of renal injuries, including high-grade injuries, are treated conservatively. Minimally invasive procedures such as angioembolization, stenting, and percutaneous drainage are often used to manage complications.[96,97]

PANCREATIC INJURY

The pancreas is the least commonly injured solid abdominal organ, and injury is usually due to focal upper abdomen trauma, often from bicycle handlebars. Pancreatic injuries are difficult to diagnose due to their nonspecific and indolent clinical presentation. Pancreatic enzymes are neither sensitive nor specific for pancreatic injury in pediatric blunt abdominal trauma: they can be elevated without otherwise demonstrable pancreatic injury and are normal in up to 30% of patients with complete pancreatic transection. Amylase and lipase may be more useful when measured more than 2 hours after injury or serially as pancreatic inflammation tends to increase over time.[98] Ductal injuries can be difficult to identify on CT imaging, and patients with a suspected pancreatic duct injury may require magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography.[99]

Most patients with pancreatic injury can be managed nonoperatively, with close monitoring and nutritional support. Management of major pancreatic injury with ductal transection remains controversial, although higher injury severity is associated with increased need for surgical intervention. Patients with higher injury severity managed nonoperatively are at increased risk of pseudocyst formation, although two thirds of pseudocysts do not require surgery. The role of endoscopy and interventional radiology in these patients is currently being studied.[99,100]

HOLLOW VISCUS INJURY

Intestinal trauma is less common than solid organ injury and is usually associated with motor vehicle versus pedestrian trauma, seatbelt injuries, or inflicted injury. Injury can result from a direct blow producing visceral compression or acceleration-deceleration forces at anatomic points of fixation, resulting in visceral and mesenteric tears. Visceral injuries include bowel perforation, bowel wall hematoma, and mesenteric tears. Acute symptoms are nonspecific and sometimes mild, and a high index of suspicion is required. Moreover, traditional CT imaging can miss important hollow viscus injuries, and oral contrast adds little to the evaluation.[101]

Observation and serial abdominal exams are therefore crucial, regardless of CT findings. Persistent or worsening abdominal pain, vomiting (particularly bilious), or the development of peritonitis or fever should alert the clinician to the possibility of hollow viscus injury. Surgical exploration may be required for definitive diagnosis.

Duodenal injuries are often associated with handlebar injuries and classically present in a delayed manner 48 to 72 hours after the injury,

as expansion of the hematoma causes partial or complete obstruction. Abdominal pain and bilious vomiting are the most common symptoms.[86]

The **seatbelt injury complex** is a pattern of blunt abdominal injury seen in children who are inappropriately restrained with a lap belt positioned over the abdomen instead of the pelvic girdle. Acceleration-deceleration forces crush the bowel between the seatbelt and the spine. Classic findings include a "seatbelt sign" (abdominal wall contusion in the distribution of the lap belt), with small bowel injury and Chance fractures of the lumbar spine. Trauma from the lap belt is also associated with injury to the mesentery, renal vasculature, inferior vena cava, aorta, ureters, and solid organs. A seatbelt sign may be present in >15% of children with blunt torso trauma secondary to motor vehicle collisions and, when present, confers a greater than fivefold increased relative risk of intra-abdominal injury requiring intervention.[102] The presence of a Chance fracture is associated with a 50% incidence of associated intra-abdominal injury.

PEDIATRIC SPINE AND SPINAL CORD INJURY

PEDIATRIC CERVICAL SPINE TRAUMA

Guidelines for immobilization and imaging and information on specific injuries are provided in Chapter 112, "Cervical Spine Injury in Infants and Children."

PEDIATRIC THORACIC AND LUMBAR SPINE TRAUMA

Children account for only 2% to 5% of all spine injuries, and only 5% of pediatric fractures occur in the spine.[103] Up to 60% of pediatric spine injuries involve the thoracic or lumbar spine, with lumbosacral injuries accounting for two thirds of spinal injury hospitalizations.[104] Pediatric spine injury has a bimodal age distribution, with one peak in children <5 years and another in children >10 years of age. Falls and motor traffic–related injury account for the first peak; motor vehicle collisions account for the majority of spine injuries in older children, although sports-related mechanisms are an important cause of thoracolumbar spine injury in adolescents.[105] Penetrating trauma accounts for <5% of pediatric spine injury, occurs primarily in adolescents, and is associated with greater morbidity than blunt trauma.[106]

The pediatric spine differs from that of adults in that children have greater ligamentous elasticity and flexibility, more horizontal facets, wedge-shaped vertebral bodies, and relatively weak musculature, particularly before the age of 8, with a transition toward adult anatomy and physiology after this age. Distraction forces can result in Salter-type fractures of the thoracolumbar spine in children, and anatomic differences make multilevel injuries more common in children aged 9 to 16 years in the setting of compression forces.[103,107]

Evaluate the pediatric spine during the secondary survey with careful palpation of the entire spine and paraspinous region for tenderness, step-offs, crepitus, bruising, or open injuries. Physical examination is 87% sensitive and 75% specific for thoracolumbar injuries.[103]

Obtain anteroposterior and lateral radiographs of the entire spine in all children with symptoms or signs of spinal injury during physical exam, because up to one third of children with spine injury have two or more spinal fractures.[107] CT scan should be limited to those with neurologic deficits, obvious bony injury on plain film, or significant concern for intra-abdominal or intrathoracic injuries requiring cross-sectional imaging for other reasons. Stable children with thoracolumbar spine injury associated with neurologic deficits should be imaged with MRI.

Thoracolumbar injuries can be classified using the Thoracolumbar Injury Classification and Severity Score System, which appears to be valid in children as well as adults and can help guide the need for operative management.[108] Generally speaking, clinically stable pediatric fractures without associated neurologic deficits can be treated nonoperatively. Moderate injuries not necessitating surgical decompression or fixation may be considered for bracing depending on age and the extent of injury (e.g., thoracolumbosacral orthosis). Scoliosis can be a sequel to spinal cord injury, particularly among younger children.[109]

Compression fractures are the most common fracture in the thoracolumbar spine and are usually stable and managed nonoperatively. Fractures of the spinous or transverse processes are often associated with blunt trauma and carry low risk for associated visceral injury; most of these fractures are managed with analgesics and rest, often without immobilization. The flexion-distraction injury known as the Chance fracture deserves special consideration, given the high rate of concomitant intra-abdominal injury.

PEDIATRIC SPINAL CORD INJURY

Pediatric spinal cord injury is uncommon, with an estimated annual incidence of 14 per million population under 18 years.[104] Children under 15 years of age account for only 10% of spinal cord injuries, which are often related to motor vehicle collisions and involve the cervical spine (60% to 80%) far more commonly than the thoracolumbar spine.[68]

Overall, neurologic recovery is better among children than adults with traumatic spinal cord injury, with incomplete injuries associated with better outcomes. **Spinal cord injury without radiographic abnormality**, a unique pediatric entity, is far more common in the thoracic spine than the lumbar spine.[107] Spinal cord injuries are frequently associated with other injuries, with rates ranging from 40% to 60%, and most commonly involve the torso, extremities, and cranium.[107]

The clinical evaluation and presentation of spinal cord injury and syndromes as well as the principles of physical examination and stabilization are similar to those of adults (see Chapter 258, "Spine Trauma"). As with adults, flaccid paralysis with hypotension and relative bradycardia suggests neurogenic shock; early administration of vasopressors is recommended, as aggressive fluid administration can worsen spinal cord edema. **Corticosteroids are not recommended to treat acute spinal cord injury in children. Steroids increase the risk of infection and do not result in significant neurologic improvements in children.**[67]

TRAUMATIC ARREST

Emergency thoracotomy has no role in blunt traumatic arrest in children.[110] As in adults, the resuscitation of children with blunt traumatic arrest should focus on addressing reversible causes, with deemphasis on CPR and vasoactive agents. Key interventions include (1) obtaining a definitive airway, (2) managing major external bleeding, (3) chest decompression and assessment for cardiac tamponade, and (4) administering blood. If there is no return of circulation after these steps, the child is unlikely to survive, and a prolonged resuscitation is futile. ED thoracotomy should be considered for children with penetrating chest injuries who lose vital signs during transport or in the trauma bay, especially if there are signs of life. Keep in mind, emergency thoracotomy poses substantial risk of injury to staff.[110,111]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 111

Minor Head Injury and Concussion in Children

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Franz Babl

INTRODUCTION AND EPIDEMIOLOGY

Head trauma is an important cause of morbidity and mortality in children. Over 750,000 children and adolescents with head injuries present annually to EDs in the United States, double that of a decade ago. The highest incidence is in the 0- to 4-year age group.[1] Annual estimates of pediatric sports-related concussion in the United States range from 1.1 to 1.9 million.[2] Although the majority of concussions are not seen in

healthcare settings, an estimated 378,000 patients were seen as outpatient visits, 150,000 presented to the ED, and 5000 were admitted to hospitals annually in the United States alone.[2]

Concussion, minor head injury, and mild traumatic brain injury historically have had different definitions in medical literature. Typically, minor head injury is defined by Glasgow Coma Scale (GCS) score of 14 or 15 at the time of presentation to the ED. At a major conference of concussion specialists in Berlin in 2016, a consensus definition of concussion was derived: traumatic brain injury induced by biomechanical forces.[3]

Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body, with an impulsive force transmitted to the head. It typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously. However, in some cases, signs and symptoms evolve over a number of minutes to hours.

PATHOPHYSIOLOGY

Concussion may result in neuropathologic changes, but the acute clinical signs and symptoms reflect a functional disturbance rather than gross structural injury, and as such, no abnormality is seen on standard structural neuroimaging studies.

Blunt head trauma in children often causes diffuse rather than focal injuries. A relatively larger calvarium and weaker cervical musculature in children impair protective mechanisms. The brain rotates around its center of gravity, resulting in diffuse axonal injury and possible subdural hemorrhage. Acceleration and deceleration forces initiate a neurochemical cascade that results in neuronal membrane disruption and axonal stretching.[4]

The acute phase of injury is characterized by an increase in cerebral cellular energy demand coupled with insufficient energy substrate delivery resulting in a metabolic crisis. This metabolic mismatch leads to alterations in neuronal depolarization, ion transport, glycolysis, mitochondrial function, and neurotransmitter release. Global and regional cerebral blood flow is reduced. Stretching of axons due to mechanical forces results in indiscriminate release of neurotransmitters and calcium influx and potassium efflux, resulting in widespread depolarization. Cells respond by activating ion pumps in an attempt to restore the normal membrane potential, which accelerates glycolysis and contributes to a state of hypermetabolism. Intracellular magnesium levels appear to diminish and may remain suppressed for several days. Magnesium is essential for generation of adenosine triphosphate, initiation of protein synthesis, and maintenance of cellular membrane potential. High intracellular calcium levels combined with stretch injury can cause destruction of microtubules within axons. The effect of this disruption leads to axonal swelling and detachment. Most cells, however, appear to recover normal cellular function, so the concussed brain undergoes dynamic restoration and brain function returns to the preconcussed state in the majority of children and youth. In some cases, however, brain structure and physiology may undergo reorganization and long-term pathologic changes.[5]

CLINICAL FEATURES

The signs and symptoms of concussion are numerous and highly variable and can develop over seconds to several days following an injury. Children and adolescents may not be fully aware of their symptoms and may not be able to articulate or describe the effects clearly. In infants and very young children, symptoms of neurologic injury may be subtle. Lethargy, irritability, poor muscle tone, breathing abnormalities, and poor feeding should raise concerns of a significant head injury.[4]

The GCS is often used as an initial reliable tool for determining severity of brain injury (**Table 111-1**). Children presenting with a GCS of ≤14 are at increased risk for intracranial injuries.[5]

Red flags for serious injury include neck pain or tenderness, double vision, weakness or tingling in the arms or legs, severe or increasing headache, seizure, loss of consciousness, deteriorating mental status, persistent vomiting, and increasing restlessness. A history of a coagulopathy, previous neurosurgery (e.g., shunt), dangerous mechanism of injury (see Table 111-3), and multiple injuries deserve special consideration.[7]

TABLE 111-1 Modified Glasgow Coma Scale for Infants and Children

Component	Infant	Child/Adult	Score
Eye opening	Spontaneous	Spontaneous	4
	To speech	To speech	3
	To pain only	To pain only	2
	No response	No response	1
Best verbal response	Coos and babbles	Oriented, appropriate	5
	Irritable cries	Confused	4
	Cries to pain	Inappropriate words	3
	Moans to pain	Incomprehensible sounds	2
	No response	No response	1
Best motor response	Moves spontaneously/ purposefully	Obeys commands	6
	Withdraws to touch	Localizes painful stimulus	5
	Withdraws to pain	Withdraws to pain	4
	Abnormal flexion posture to pain	Abnormal flexion posture to pain	3
	Abnormal extension posture to pain	Abnormal extension posture to pain	2
	No response	No response	1

HISTORY

Obtain a comprehensive history including mechanism and severity of injury and eyewitness accounts. Concussions should be considered in the presence of one or more physical, cognitive, emotional, or sleep changes (**Table 111-2**).

Inquire about loss of consciousness, disorientation, confusion, blank stare, poor balance, gait instability, and posttraumatic seizure. Determine if there has been improvement or deterioration since the time of injury, particularly relating to level of consciousness, headache, and vomiting. Gather information relating to previous concussions, preexisting neurologic disorders including migraine, emotional dysregulation, learning difficulties, attention-deficit/hyperactivity disorder, behavioral disorders, and coagulation disorders. Inquire about antegrade and retrograde amnesia, short-term memory loss, and ability to concentrate. If patients present to the ED beyond the acute stage, determine when the injury occurred; if there has been repeat head trauma, change in mood, change in sleep pattern, or symptom triggers; and if school or physical activity has worsened symptoms.

Symptoms of concussion are often nonspecific and may mimic other conditions such as anxiety and depression. Moreover, some individuals may overreport symptoms (reporting resolved symptoms as unresolved, exaggerating the extent and severity of symptoms, fabricating symptoms), whereas others may underreport symptoms. Everyday somatic complaints, such as headache, fatigue, and sleep difficulties, may be misattributed to a head injury.[8]

PHYSICAL EXAMINATION

Obtain vital signs and perform a general examination to determine extent of all injuries. Look for external signs of trauma including facial

TABLE 111-2 Symptoms of Concussion

Domain	Symptoms
Physical	Headache, nausea, vomiting, confusion, dizziness, balance problems, visual changes, fatigue, photophobia, phonophobia
Cognitive	Fogginess of thought, difficulty with concentration, difficulty with memory, forgetfulness, repeating questions, answering questions slowly
Emotional	Irritability, sadness, anxiety, emotional lability
Sleep	Drowsiness, sleeping more than usual, sleeping less than usual, trouble falling asleep, trouble staying asleep

and scalp bruising, boggy scalp hematoma, evidence of an open or depressed skull fracture, hemotympanum, "racoon eyes," "battle sign," otorrhea, and rhinorrhea of cerebrospinal fluid. Scalp hematomas that are large and nonfrontal in location have a higher association with skull fracture in infants <3 months of age, although they are rarely associated with clinically important intracranial injury in otherwise asymptomatic infants and older children.[9,10] Specific bruising and injury patterns in infants and young children raise concern for abusive trauma (see Chapter 150, "Child Abuse and Neglect").[11,12]

Determine the GCS (Table 111-1). Assess orientation and memory for events directly preceding the head injury. Test immediate memory, delayed memory, and concentration. Perform a detailed neck exam, assessing for central spine tenderness, painful or reduced cervical spine range of motion, and focal neurologic deficits. If concerned, the cervical spine should be immobilized until the extent of injury is determined (see Chapter 112, "Cervical Spine Injury in Infants and Children").

Perform a focused neurologic exam including cranial nerve, cerebellar, motor, sensory, balance, and gait assessment. Assess vestibular-ocular reflexes for gaze stabilization, gaze shifting, and vergence. Damage to any of these systems can lead to complex symptoms that exacerbate and complicate recovery, including balance disturbance, eye tracking difficulties, nausea, dizziness, headache, difficulty reading, and difficulty walking. Test visual acuity, extraocular motility, pupillary response to light, and fundoscopy.

IMAGING

After initial assessment and stabilization, the most immediate question in children presenting with head injuries to the ED is whether they require neuroimaging. Currently, there are no recommendations for electroencephalogram, advanced neuroimaging, genetic testing, and serum biomarkers in the ED setting.

Noncontrast head CT identifies and excludes critical intracranial injuries that require immediate or urgent intervention, can be conducted within seconds, and usually does not require sedation.[13,14] Although the need for sedation is increased in agitated or combative children or those <2 years old, the majority can be imaged without sedation by using parental presence. The primary drawback of CT, however, is radiation exposure, which may increase the lifetime risk of brain and other cancers, particularly in young children.[15-17] Although MRI is a radiation-free alternative, it is impractical at this time in the ED due to the time required for imaging.

It is generally agreed that children with GCS score of <13 should undergo neuroimaging based on the increased risk of significant intracranial injury. For milder head injuries (GCS score of 13 to 15), multiple clinical decision rules have been developed to assist clinicians in identifying children at increased risk of intracranial injury, help balance the risk of missing a significant injury, and minimize the risk of radiation-induced cancer. Decision rules for head injuries use elements of injury mechanism, patient history, and physical examination to risk-stratify patients. Although many rules appear superficially similar, they differ in details, inclusion and exclusion criteria (e.g., age limits, injury severity), predictor variables, and the outcomes used (**Table 111-3**). The highest-quality, prospectively derived, and externally validated decision rules[18-21] are (1) the prediction rule for the identification of children at very low risk of clinically important traumatic brain injury developed by the Pediatric Emergency Care Applied Research Network (PECARN, United States),[22] (2) the Canadian Assessment of Tomography for Childhood Head Injury (CATCH, Canada) rule,[23] (3) the Children's Head Injury Algorithm for the Prediction of Important Clinical Events (CHALICE, United Kingdom),[24] and (4) the National Emergency X-Radiography Utilization Study II (NEXUS II, United States).[25,26] These rules were derived based on large numbers of patients in different countries and were based on different baseline imaging rates, ranging from 3% (CHALICE) to 53% (CATCH) for the population under investigation. Whereas PECARN, CATCH, and CHALICE were specifically designed for pediatric head injuries, the premise of NEXUS II was to create a risk decision instrument for head-injured patients of all ages, because the majority of children are seen in mixed EDs that care for both adult and pediatric patients.

The main difference between PECARN and the other three rules is that its goal is to identify patients at very low risk of intracranial injury who *do not need a CT scan* (all predictor variables negative, no CT required), with separate rules for children <2 years and ≥2 years old, **whereas the other rules seek to identify the patients who *do require a CT scan*** (any predictor variables positive, CT required). The rules were also designed for patients of different injury severity, with CHALICE designed for all severities (GCS 3 to 15), PECARN for patients with GCS of 14 and 15, and CATCH for patients with GCS of 13 to 15 and with symptoms of mild head injury (blunt trauma to the head resulting in witnessed loss of consciousness, definite amnesia, witnessed disorientation, persistent vomiting, and persistent irritability in the ED [in children <2 years old]). NEXUS II was designed for patients of all severities who had already been selected for CT scans.[25-27]

Although all four rules had very high sensitivities when using the rule-specific design and outcomes (PECARN <2 years, 98.6%; PECARN ≥2 years, 96.7%; CHALICE, 98.6%; CATCH, 100%; NEXUS II in children <18 years old, 98.6%; with specificities of 53.7%, 58.5%, 86.9%, 70.2%, and 15.1%, respectively), the accuracy of the rules is difficult to compare due to the many differences in their design. Recently a large external cohort of 20,137 head-injured children was used to compare the pediatric-specific rules using a common outcome (clinically important traumatic brain injuries, which are defined as death from traumatic brain injury, neurosurgical intervention for traumatic brain injury, intubation of >24 hours for traumatic brain injury, or hospital admission of ≥2 nights for traumatic brain injury in association with traumatic brain injury on CT) in patients with GCS of 13 to 15.[21] All three pediatric rules had high sensitivities (PECARN, 100% [<2 years] and 99.2% [≥2 years]; CHALICE, 92.5%; CATCH, 91.9%) and overlapping confidence intervals, with PECARN <2 years and ≥2 years missing 0 and 1 injured patient, respectively; CHALICE missing 12 patients; and CATCH missing 13 patients. Sensitivities in detecting traumatic brain injury on CT and identifying patients requiring neurosurgery were similar to the detection of clinically important traumatic brain injuries.

As a widely used and highly accurate decision rule, PECARN is presented in more detail. The PECARN rule provides guidance for children <2 years and ≥2 years of age (**Figure 111-1**).[24] The main difference between older and younger rule is the inclusion of vomiting and severe headache as a predictor variable in children ≥2 years and the inclusion of occipital, parietal, or temporal scalp hematomas or palpable skull fractures and the exclusion of vomiting as predictor variables in children <2 years. If all six predictor variables are negative, the risk of a clinically important traumatic brain injury is so low that a CT scan is not necessary. The PECARN group also provides guidance for patients with one or more positive predictor variables (Figure 111-1). Children with higher risk predictor variables—GCS of 14 or other signs of altered mental status, palpable skull fracture (<2 years), or signs of basilar skull fracture (≥2 years)—are at increased risk of clinically important traumatic brain injury and should undergo a CT scan. Children with any of the other four predictor variables are at intermediate risk of intracranial injury, and other factors should be used, such as multiple findings, worsening symptoms, and clinician and parental preferences.

TREATMENT

The ED management of serious brain injuries is covered in Chapters 110, "Pediatric Trauma" and 250, "Skin Disorders: Face and Scalp", whereas associated cervical spine injury management is discussed in Chapter 112 and abusive head injuries are discussed in Chapter 150. Once these major injuries have been ruled out, the ED management of concussion focuses on relief of acute or persistent symptoms, patient and family education, and appropriate outpatient follow-up. Strategies for the ED management of specific symptoms related to mild traumatic brain injury and education of patients regarding postdischarge care are discussed below.

HEADACHE

Headache is the most common complaint following mild traumatic brain injury, with an onset within 7 days of the initial injury, and can be acute or persistent in nature. Although classified as a secondary

TABLE 111-3 Predictor Variables and Outcome Measures of PECARN, CATCH, CHALICE, and NEXUS II Clinical Decision Rules[22-25]

	PECARN <2 y	PECARN ≥2 y	CATCH	CHALICE	NEXUS II
Primary outcome	Clinically important traumatic brain injury; defined as death from traumatic brain injury, neurosurgical intervention for traumatic brain injury (intracranial pressure monitoring, elevation of depressed skull fracture, ventriculostomy, hematoma evacuation, lobectomy, tissue debridement, dura repair, other), intubation of >24 h for traumatic brain injury or hospital admission of 2 nights or more for traumatic brain injury* in association with traumatic brain injury on CT†		Need for neurologic intervention; defined as either death within 7 d secondary to the head injury or need for any of the following procedures within 7 days: craniotomy, elevation of skull fracture, monitoring of intracranial pressure, insertion of endotracheal tube for the management of head injury	Clinically significant intracranial injury; defined as death as a result of head injury, requirement for neurosurgical intervention, or marked abnormality on CT (defined as any new, acute, traumatic intracranial pathology as reported by consultant radiologist, including intracranial hematomas of any size, cerebral contusion, diffuse cerebral edema, and depressed skull fractures)	Clinically important intracranial injuries; defined as substantial epidural or subdural hematoma (>1.0 cm in width or causing mass effect); substantial cerebral contusion (>1.0 cm in diameter or >1 site); extensive subarachnoid hemorrhage; mass effect or sulcal effacement; signs of herniation; basal cistern compression or midline shift; hemorrhage in the posterior fossa; intraventricular hemorrhage; bilateral hemorrhage of any type; depressed or diastatic skull fracture; pneumocephalus; diffuse cerebral edema; diffuse axonal injury
Predictor variable‡§					
Mechanism	Severe mechanism of injury (MVC with patient ejection, death of another passenger, or rollover; pedestrian/bicyclist without helmet struck by motorized vehicle; falls >0.9 m; head struck by high-impact object)	Severe mechanism of injury (MVC with patient ejection, death of another passenger, or rollover; pedestrian/bicyclist without helmet struck by motorized vehicle; falls >1.5 m; head struck by high-impact object)	Dangerous mechanism of injury (e.g., MVC; fall from elevation ≥3 ft (≥91 cm) or 5 stairs; fall from bicycle with no helmet)	High-speed RTA as pedestrian, cyclist, occupant (defined as accident with speed >40 mph or 64 km/h) Fall >3 m in height High-speed injury from projectile or object	Persistent vomiting Altered level of alertness, abnormal behavior Coagulopathy
History	LOC ≥5 s Not acting normally per parent	Any or suspected LOC History of vomiting Severe headache	History of worsening headache¶	Witnessed LOC >5 min ≥3 vomits after head injury (discrete episodes) Amnesia (antegrade/retrograde >5 min) Suspicion of NAI (NAI defined as any suspicion of NAI by the examining doctor) Seizure in patient with no history of epilepsy	
Examination	GCS <15 Other signs of altered mental status (agitation, somnolence, repetitive questioning, slow response to verbal communication) Palpable or unclear skull fracture Occipital, parietal, or temporal scalp hematoma	GCS <15 Other signs of altered mental status (agitation, somnolence, repetitive questioning, slow response to verbal communication) Clinical signs of basilar skull fracture	GCS <15 at 2 h after injury¶ Irritability on examination¶ Any sign of basal skull fracture (e.g., hemotympanum, "racoon" eyes, otorrhea or rhinorrhea of the cerebrospinal fluid, Battle's sign) Large, boggy scalp hematoma	GCS <14, or <15 if <1 y old Abnormal drowsiness (in excess of that expected by examining doctor) Focal neurologic deficit Signs of basal skull fracture (hemotympanum, racoon eyes, otorrhea or rhinorrhea of cerebrospinal fluid, Battle's sign) Suspicion of penetrating or depressed skull injury, or tense fontanelle	Neurologic deficit Abnormal behavior Evidence of significant skull fracture Presence of scalp hematoma

Note: Although the predictor variables are reproduced verbatim, the order in which the variables from each clinical decision rule are presented has been altered to facilitate comparison.

Abbreviations: CATCH = Canadian Assessment of Tomography for Childhood Head Injury; CHALICE = Children's Head Injury Algorithm for the Prediction of Important Clinical Events; GCS = Glasgow Coma Scale; LOC = loss of consciousness; MVC = motor vehicle crash; NAI = nonaccidental injury; NEXUS II = National Emergency X-Radiography Utilization Study II; PECARN = Pediatric Emergency Care Applied Research Network; RTA = road traffic accident.

*Hospital admission for traumatic brain injury defined by admission for persistent neurologic symptoms or signs such as persistent alteration in mental status, recurrent emesis due to head injury, persistent severe headache, or ongoing seizure management.

†Traumatic brain injury on CT is defined by any of the following descriptions: intracranial hemorrhage or contusion, cerebral edema, traumatic infarction, diffuse axonal injury, shearing injury, sigmoid sinus thrombosis, midline shift of intracranial contents or signs of brain herniation, diastasis of the skull, pneumocephalus, or skull fracture depressed by at least the width of the table of the skull.

‡In each of the four clinical decision rules, the absence of all of the above predictor variables indicates that cranial CT scan is unnecessary.

§NEXUS II predictor variable includes the criterion age >65 years (which is not relevant in pediatric patients).

¶High-risk predictors for CATCH (need for neurologic intervention).

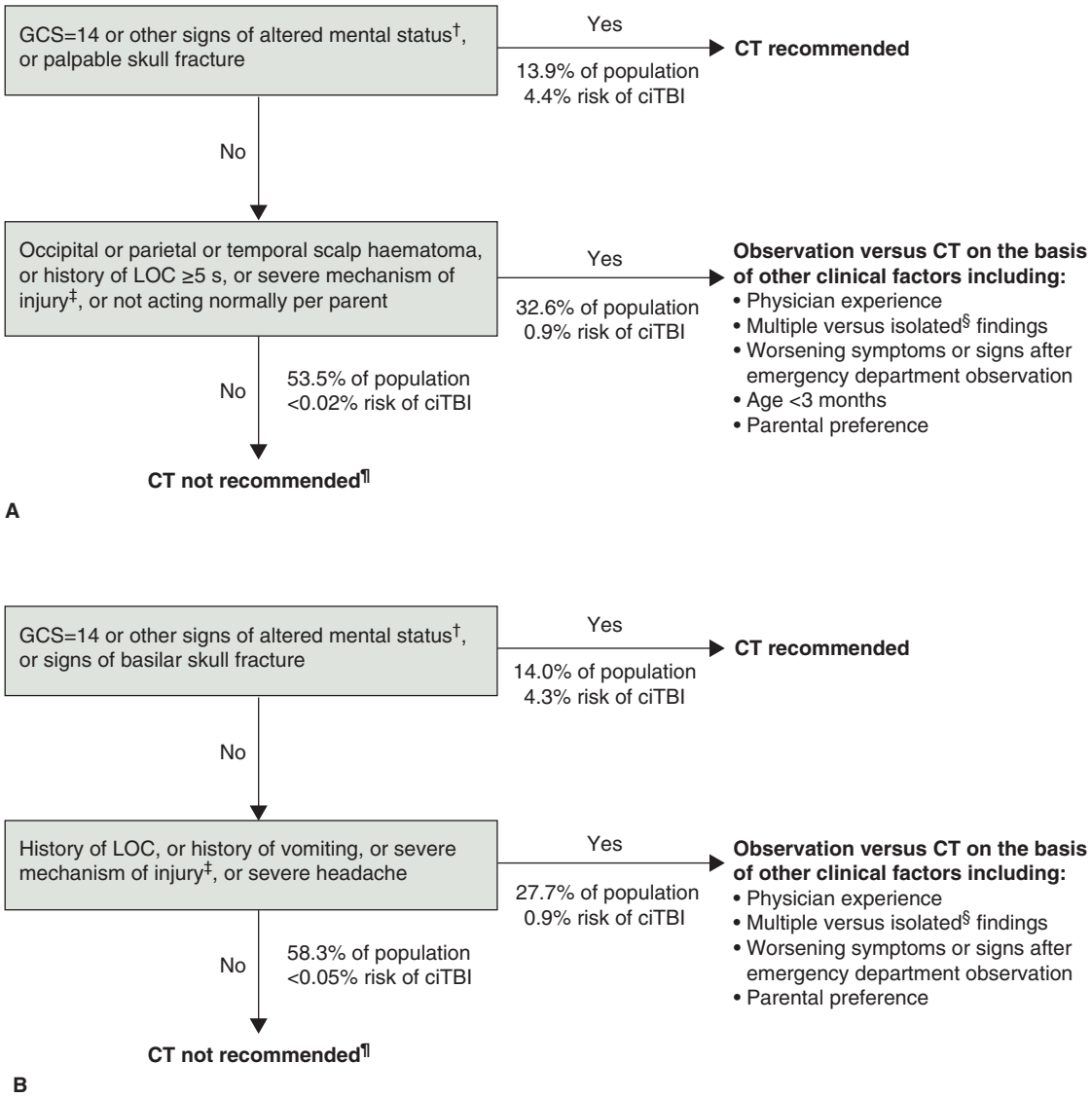

FIGURE 111-1. Suggested CT algorithm for children <2 years old (**A**) and ≥2 years old (**B**) with Glasgow Coma Scale (GCS) scores of 14 and 15 after head trauma. ciTBI = clinically important traumatic brain injury; LOC = loss of consciousness. †Other signs of altered mental status include agitation, somnolence, repetitive questioning, or slow response to verbal communication. ‡Severe mechanism of injury includes motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without a helmet struck by a motorized vehicle; falls of >0.9 m (3 ft) or >1.5 m (5 ft) for panel B; or head struck by a high impact object. §Patient with certain isolated findings (i.e., with no other findings suggestive of traumatic brain injury) such as isolated LOC, isolated headache, isolated vomiting, and certain types of isolated scalp hematoma in infants >3 months old have a risk of ciTBI substantially lower than 1%. ¶Risk of ciTBI exceedingly low, generally lower than risk of CT-induced malignancies. Therefore, CT scans are not indicated for most patients in this group. [Reproduced with permission from Kuppermann N, Holmes JF, Dayan PS, et al: Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet* 2009 Oct 3;374(9696):1160-1170. Copyright Elsevier.]

headache (see Chapter 139, "Headache in Children"), posttraumatic headaches often have characteristics of one of the primary headache disorders (**Table 111-4**), and a history of primary headache disorder may predispose to persistent symptoms after injury. Treat posttraumatic headaches based on the primary headache disorder they most resemble.[28]

Determining appropriate pharmacotherapy in the ED is challenging because there is limited evidence for effective treatment strategies. Acetaminophen and NSAIDs (ibuprofen and naproxen) may provide acute relief. Do not provide NSAIDs until intracranial hemorrhage is excluded. After the first few days, NSAIDS may lose their effectiveness. The frequent and prolonged use of over-the-counter analgesics may result in worsening and rebound headaches.[29]

Although one previous study suggested hypertonic saline for symptomatic treatment of acute concussive symptoms,[30] the 2018 Centers for Disease Control and Prevention guideline on the diagnosis and management of mild traumatic brain injury among children does not recommend hypertonic saline outside of the research setting at this time.[31]

TABLE 111-4 Posttraumatic Headache Symptoms Resembling Primary Headache Disorders

Symptoms	Corresponding Primary Headache Disorder
Bilateral, moderate severity, dull pressure/squeezing sensation. Location is variable. Triggers are stress, reading, sustained poor posture.	Tension type
Unilateral, severe, pulsating, associated nausea, vomiting, photophobia, sensory and visual changes. Location may vary. Triggers can be exercise, lights, and sounds.	Migraine
Unilateral, severe, throbbing, autonomic activation, lacrimation, and rhinorrhea. Pain is often described as retro-orbital or periorbital.	Cluster
Unilateral, mild to severe in quality, often described as aching. Location is focal, involving the neck. Triggers are neck movement. There is often a history of whiplash.	Cervicogenic

For headaches with a migraine component, the use of IV dopamine antagonists (metoclopramide, prochlorperazine, chlorpromazine) and ketorolac may provide temporary relief of symptoms,[32] but does not appear to alter recurrence or persistence.[33] Potential adverse effects of dopamine antagonists include drowsiness, hypotension, and acute dystonic reactions, particularly in adolescents (Chapter 139, "Headache in Children"). The use of migraine-specific abortive triptan medications may be effective, but should be limited to less than 10 times per month. Do not provide opioids for persistent headaches.

Identify headache triggers and relievers if possible. Management strategies should focus on education and expected clinical course. Physical and cognitive overexertion are key factors for worsening headache.

Patients with prolonged and debilitating postconcussive headaches should be referred to a neurologist. Preventive medications including gabapentin, valproic acid, topiramate, amitriptyline, carbamazepine, and cyproheptadine may provide symptomatic relief, but require dosage titration and careful monitoring.

NAUSEA

Consider ondansetron for significant nausea or difficulty tolerating liquids. One study suggested that children treated with ondansetron after head injury had lower rates of ED return visits, and ondansetron did not mask serious underlying conditions in those who did not have imaging.[34] Physical and cognitive rest often results in resolution of nausea. Keep the child well hydrated, as dehydration can worsen nausea.

DIZZINESS

Concussion-associated dizziness tends to resolve quickly with rest. Dizziness may result from an injury to the vestibular system, the effects of visual disturbances (decreased convergence, accommodation, smooth visual pursuits, eye saccades), decreased exercise tolerance, or cervicogenic injury. For prolonged symptoms, refer to a physiotherapist or concussion clinic for targeted exercises including vestibular rehabilitation. A concussion vision specialist may assist in neuro-optometric vision rehabilitation with the goal of improving central-peripheral vision, visual-vestibular and accommodation-vergence integration, pursuit and saccadic eye movement, and convergence ability. Therapy involves strengthening binocularity, reducing visual motion hypersensitivity, and reducing disequilibria.

DISPOSITION AND FOLLOW-UP

ED DISPOSITION

At this time, there is clinical variation and no gold standard regarding the need for, and length of, ED observation. However, we do know the following:

1. Patients who have been imaged and in whom the CT is negative are at extremely low risk for subsequent deterioration from a bleed.
2. Children who meet PECARN low-risk criteria (Table 111-3) are at very low risk for clinically important traumatic brain injury requiring intervention.
3. For children who are symptomatic and not low risk, the PECARN rule recommends observation or CT, but does not specify the duration of observation. This author uses around 4 hours of ED observation, with CT scan if patient is getting worse and discharge if getting better. Provide discharge instructions regarding signs and symptoms for which to seek immediate medical care. This includes lethargy, irritability, focal deficits, seizures, intractable vomiting, slurred speech, paresthesia, and worsening headache.

Caregivers of infants in the first year of life should be warned about the risk of "growing fractures" over the weeks to months following a skull fracture and instructed to see their primary care physician if there is a persistent or worsening palpable defect in the skull >2 weeks after the injury.

Patients with intracranial injury and those thought to be at risk for abusive head trauma should be admitted into hospital with appropriate pediatric subspecialty medical, neurosurgical, and nursing resources.

Children and adolescents with complex, depressed, or basilar skull fractures should be managed in conjunction with neurosurgery and typically require admission. Stable asymptomatic infants and children with linear, nondisplaced skull fractures with no evidence of intracranial injury are safe for discharge with primary care follow-up.

FOLLOW-UP CONSIDERATIONS

The majority of children and adolescents who sustain a concussion will recover within 2 to 4 weeks. The strongest and most consistent predictor of slower recovery is the severity of symptoms during the first few days following injury. A low level of symptoms in the first day following an injury is a favorable prognostic indicator. Approximately one third of concussed children and adolescents, however, will go on to experience ongoing somatic, cognitive, psychological, or behavioral symptoms, commonly referred to as persistent postconcussion symptoms. These symptoms do not reflect a single pathophysiologic entity, but describe a constellation of nonspecific posttraumatic symptoms that may be linked to coexisting or confounding factors (e.g., previous concussions, mental health problems, migraine history, previous neurologic disorders, lack of social supports, female gender, higher level of symptoms, presence of life stressors, substance abuse). They do not necessarily reflect ongoing physiologic injury to the brain. Children and youth who have been diagnosed with attention-deficit/hyperactivity disorder or learning disabilities may require more assistance in returning to school, but are not at increased risk for persistent symptoms.[3,35]

Risk factors for poor prognosis include previous concussion history, persistent posttraumatic headache, depression, anxiety, persisting vestibular-ocular abnormalities, ongoing cognitive difficulties, preinjury sleep disturbances, increased symptoms with return to school and exercise, and return to high-risk contact sports prior to full recovery.[35]

Those who have persistent symptoms should be referred to a concussion specialty clinic. The team should encompass expertise by a pediatrician, sports medicine specialist neurologists, or neurosurgeon, with allied professional specialties including physiotherapy, clinical psychological, neuropsychology, physiatry, kinesiology, and neuro-ophthalmology. Delay in seeking a multimodal assessment and treatment may lead to prolonged functional disabilities.[3]

POSTDISCHARGE COUNSELING

REST AND INITIATING PHYSICAL ACTIVITIES

Following a concussion, there should be a period of physical rest for 24 to 48 hours. Returning to physical activity can be guided by the four P's: **p**rioritize activities, **p**lan in advance, **p**ace appropriately, and **p**osition in a calm environment.[36] Gradually introduce noncontact and low-risk activities. Avoid activities that exacerbate symptoms. Early return to graduated physical activities results in lower rates of prolonged concussion symptoms at 1 month compared to children and adolescents who adhere to strict rest guidelines until symptom free.[37] The proposed mechanism by which exercise may improve recovery is through the promotion of neuroplasticity mechanisms. Controlled aerobic exercise may improve recovery by restoring normal cerebral blood flow regulation.

RETURN TO LEARN

Cognitive rest prevents overtaxing of a functionally injured brain and prevents metabolic overload. The degree and duration of cognitive rest vary from person to person. Mental activity should be resumed gradually, even if the person has not returned to baseline. Activities that worsen symptoms should be avoided. Graded return to learn requires accommodation by schools. Providing teachers with specific symptom-based guidelines for successful reintegration is helpful (**Figure 111-2**). Returning to school, even with restrictions, may have significant psychosocial benefits.

RETURN TO SPORTS

A graduated return to sports protocol should be followed. Children and adolescents must be symptom free, off all medications, have a normal

Return to School

This tool is a guideline for managing a student's return to school following a concussion and does not replace medical advice. Timelines and activities may vary by direction of a health care professional.

AT HOME			AT SCHOOL			
STAGE 1:	**STAGE 2:**		**STAGE 3:**	**STAGE 4:**	**STAGE 5:**	**STAGE 6:**
Physical & cognitive rest • Basic board games, crafts, talk on phone • Activities that do not increase heart rate or break a sweat **Limit/Avoid:** • Computer, TV, texting, video games, reading **No:** • School work • Sports • Work • Driving until cleared by a health care professional	**Start with light cognitive activity:** Gradually increase cognitive activity up to 30 min. Take frequent breaks. **Prior activities plus:** • Reading, TV, drawing • Limited peer contact and social networking Contact school to create *Return to School* plan.	**When light cognitive activity is tolerated:** Introduce school work. **Prior activities plus:** • School work as per *Return to School* plan Communicate with school on student's progression.	**Back to school part-time** Part-time school with maximum accommodations. **Prior activities plus:** • School work at school as per *Return to School* plan **No:** • P.E., physical activity at lunch/recess, homework, testing, sports, assemblies, field trips Communicate with school on student's progression.	**Part-time school** Increase school time with moderate accommodations. **Prior activities plus:** • Increase time at school • Decrease accommodations • Homework – up to 30 min./day • Classroom testing with adaptations **No:** • P.E., physical activity at lunch/recess, sports, standardized testing Communicate with school on student's progression.	**Full-time school** Full days at school, minimal accommodations. **Prior activities plus:** • Start to eliminate accommodations • Increase homework to 60 min./day • Limit routine testing to one test per day with adaptations **No:** • P.E., physical activity at lunch/recess, sports, standardized testing	**Full-time school** Full days at school, no learning accommodations. • Attend all classes • All homework • Full extracurricular involvement • All testing **No:** • Full participation in P.E. or sports until *Return to Sport* protocol completed and written medical clearance provided
	No: • School attendance • Sports • Work					
Rest	**Gradually add cognitive activity including school work at home**		**School work only at school**	**Increase school work, introduce homework, decrease learning accommodations**	**Work up to full days at school, minimal learning accommodations**	**Full academic load**
When symptoms start to improve OR after resting for 2 days max, **BEGIN STAGE 2**	Tolerates 30 min. of cognitive activity, introduce **school work at home**	Tolerates 60 min. of school work in two 30 min. intervals, **BEGIN STAGE 3**	Tolerates 120 min. of cognitive activity in 30-45 min. intervals, **BEGIN STAGE 4**	Tolerates 240 min. of cognitive activity in 45-60 min. intervals, **BEGIN STAGE 5**	Tolerates school full-time with no learning accommodations **BEGIN STAGE 6**	*Return to School* protocol completed; focus on ***RETURN TO SPORT***

Note: A student is tolerating an activity if symptoms are not exacerbated.

Adapted from the Return to Learn protocol by G.F. Strong School Program (Vancouver School Board), Adolescent and Young Adult Program, G.F. Strong Rehabilitation Centre.

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FIGURE 111-2. Return to school staged approach.

neurologic examination, and have successfully returned to learn before returning to competitive sports. The graded return to sport protocol (**Figure 111-3**) advances through the following rehabilitation stages: light aerobic activity, more intensive training, sports-specific exercises, noncontact participation, full practice, and finally game play. The athlete must be symptom free during and after exertion before advancing to the next stage, and there should be at least 24 hours between the stages. If symptoms return at any level, the athlete must rest until the symptoms resolve and then begin the protocol level again, at the previous level of symptom-free exertion. The return to play guideline must be individualized and progressive.

GENERAL LIFESTYLE MEASURES

Encouraging healthy lifestyle choices is an important aspect of initial care. Physical and cognitive rest assists recovery from concussion through conservation of limited adenosine triphosphate supply. Discuss nutrition (three meals, including protein, and two snacks per day), optimal hydration, and the importance of restorative sleep. Limit screen and device time, and gradually resume normal social activities.

Preventing further injury during the time of recovery is essential. Patients should avoid higher-risk recreational activities (cycling, skating, skateboarding) that may result in a second head injury. During recovery, the brain is particularly vulnerable to worsening symptoms, additional concussions, and rarely, second impact syndrome, which results from subsequent low-energy collisions. The injured brain may lose its ability to autoregulate cerebral perfusion, leading to cerebral edema, herniation, and potential death.[38]

SLEEP

Fatigue and sleep disruption are common following head injury. Daytime drowsiness, difficulty falling asleep, and difficulty staying asleep are often experienced. Normalizing sleep patterns hastens recovery.

The American Academy of Sleep Medicine recommends that children 6 to 12 years of age sleep 9 to 12 hours per day and adolescents 13 to 18 years of age sleep 8 to 10 hours per day on a regular basis to promote optimal health.[39] This should be appropriately timed and uninterrupted. Sleeping less is associated with attention, behavior, and learning problems and an increased risk for accidents, injuries, hypertension, obesity, diabetes, and depression. Excessive sleep is linked to obesity and mental health concerns.[40] Sleep difficulties after head injury may be caused by headache, dizziness, and nausea, but are likely to improve when they are effectively controlled.

Provide sleep hygiene strategies. Discuss healthy sleep habits emphasizing the same bedtime and wake time. In the first few hours and days following concussion, daytime naps do not need to be limited. After the initial stages of recovery, lengthy naps should be avoided so as not to interfere with nighttime sleep. If patients have ongoing fatigue, recommend naps <30 minutes long and before 3:00 p.m. Electronic devices should be

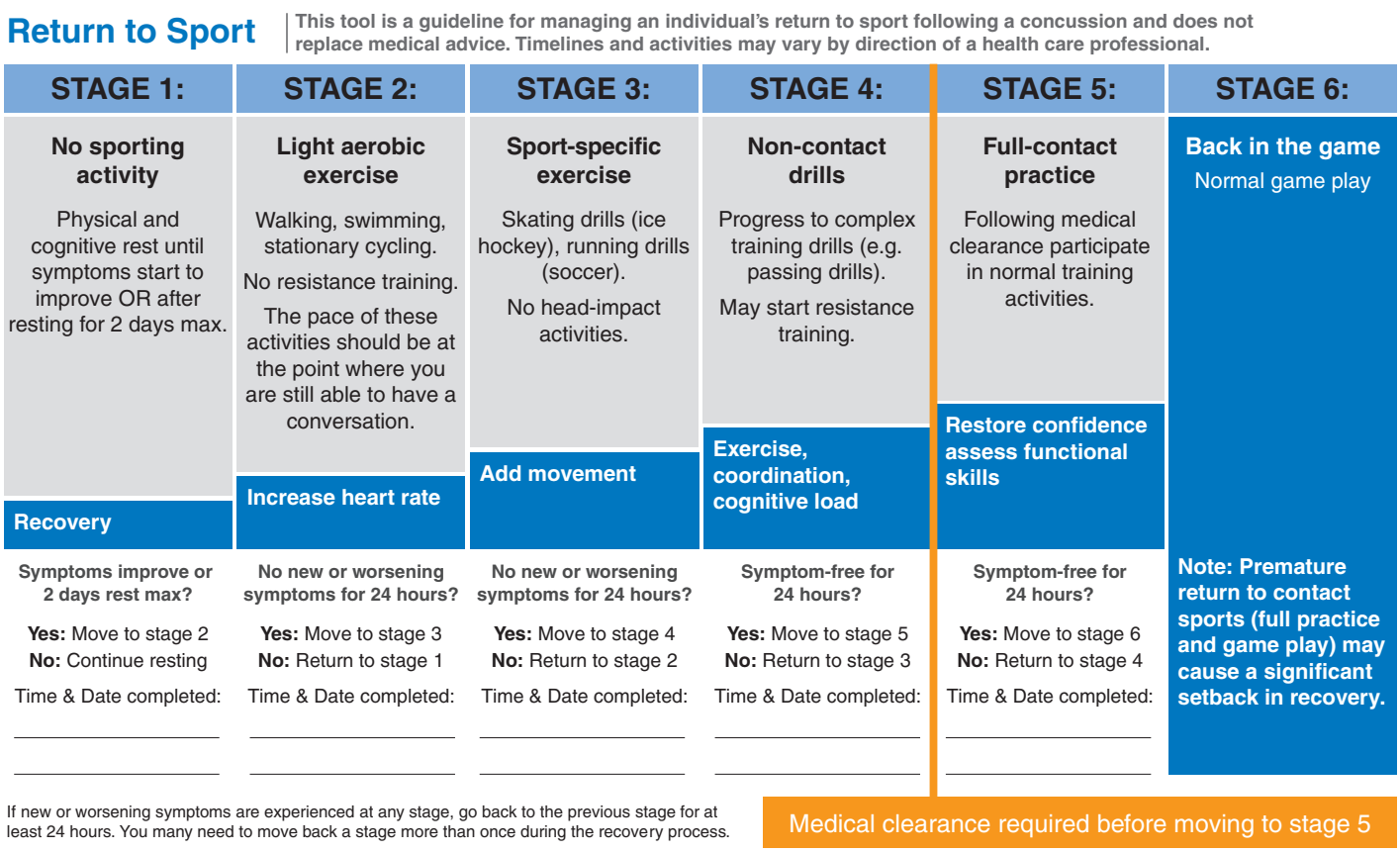


FIGURE 111-3. Return to sport staged approach.

turned off during the evening. The sleeping environment should be dark, cool, tidy, and comfortable. The bedroom should be designated exclusively for sleep and should not have any electronic devices. Heavy meals, caffeinated beverages, and excessive sugar should be avoided. A healthy diet with optimal vitamins, minerals, and iron may facilitate endogenous melatonin production. Regular exercise when tolerated should be encouraged earlier in the day, but should be avoided within 2 hours of bedtime. Patients should be exposed to natural light during the day. If sleep strategies are not effective, a trial of **melatonin** may be indicated; however, its efficacy for concussion has not been studied. As melatonin is not subject to U.S. Food and Drug Administration controls, different preparations may produce variable results. Side effects including daytime drowsiness, headache, dizziness, nausea, depression, and anxiety are uncommon. If melatonin is tried, children should be started at 3 milligrams and adolescents at 5 milligrams approximately 45 minutes before bedtime. Long-acting melatonin should be given if children and adolescents have trouble both falling asleep and staying asleep. Pharmaceuticals including trazadone, mirtazapine, amitriptyline, and quetiapine might be considered but should be prescribed by a concussion specialist, neurologist, or pediatrician. Benzodiazepines should be avoided as they cause daytime drowsiness and may interfere with cognition and memory.

FATIGUE

Fatigue is often disabling and can be managed by optimizing the home and school environment, including ergonomic furnishings and adjusting lighting. Determine optimal hours for learning and physical activities. Schedule regular periods of rest, break down activities into smaller tasks, and set priorities.

MOOD

Mood changes following concussion are often multifactorial and can be transient, persistent, or relapsing. Variables include medical comorbidities, medications, family history of psychiatric disorders, past history of psychiatric disorders, substance abuse, social relationships with family and friends, and cultural factors.

Management is multipronged and a referral to a rehabilitation team including mental health specialists and occupational and physical therapists is advised. Psychotherapy focuses on supportive care (providing hope, minimizing misattributions) and behavioral therapy (daily structure, sleep hygiene, exercise–relaxation balance, impulse control, anger management). Cognitive therapy and mindfulness are important components of care.

There are no U.S. Food and Drug Administration–approved medications for the treatment of neuropsychiatric symptoms associated with concussion, although psychotropic medications have been used "off label" with some success (antidepressants, mood stabilizers, antipsychotics, dopamine agonists, β-blockers).

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 112

Cervical Spine Injury in Infants and Children

Julie C. Leonard

INTRODUCTION AND EPIDEMIOLOGY

Cervical spine injuries occur in approximately 1.8% of pediatric blunt trauma patients.[1,2] Although the incidence of cervical spine injuries in children is lower than adults (2.4%), children have higher rates of mortality (7.4%) compared to adults (1.2%).[3-6] In children <8 years old, nearly three fourths of all spinal injuries occur in the cervical spine,[7] and three fourths of the cervical spine injuries involve the axial cervical spine (occiput through C2).[3] Cervical spine injuries in these younger children are more likely associated with neurologic deficits and head or other major organ injury.[3,8] In addition, **spinal cord injury without radiographic abnormality (SCIWORA)** may occur in children and typically involves the cervical spine. The incidence of SCIWORA among pediatric trauma patients ranges from 0.15% to 0.2%, comprising 4.5% to 35% of pediatric spine injuries.[3,9-11] Motor vehicle crashes are the most common mechanism of cervical spine injuries, followed by falls, and in teenagers, diving and sports injuries.[3] Boys are affected more often than girls. Child abuse can result in cervical spine injuries in younger patients via a shaking mechanism, although this is a rare manifestation of inflicted injury.[12] Note that injuries to the spine and spinal cord outside of the cervical spine are discussed in Chapter 110, "Pediatric Trauma."

PATHOPHYSIOLOGY

A number of anatomic differences between the pediatric and adult cervical spine predispose children to different patterns of injury (**Table 112-1**). In particular, the larger head-to-body ratio in young children creates a fulcrum at C2–C3 (compared to C5–C6 in adults) that accounts for higher rates of cervical spine injury above C3 in children. Weaker muscles and ligaments combined with anterior wedging and shallow facets connecting cervical vertebrae and immature growth centers together allow for easier anterior-posterior slipping of the vertebrae than in adults.

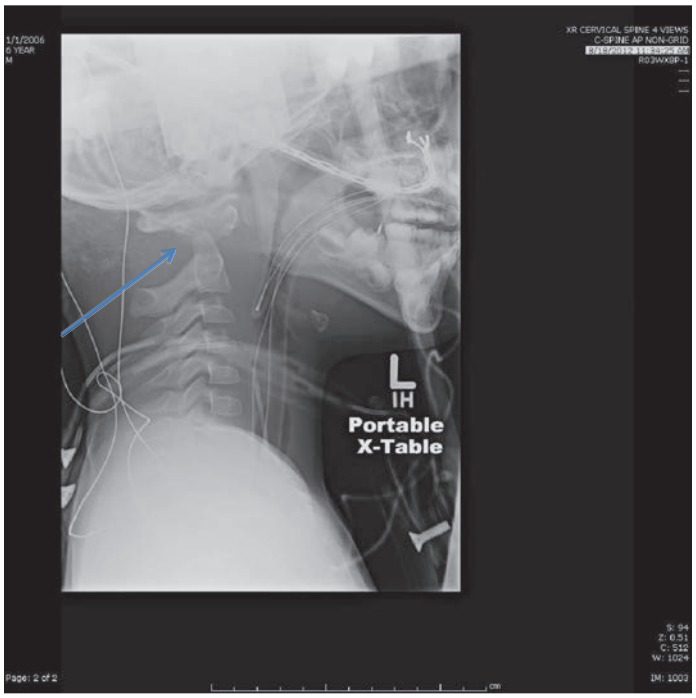
Patients younger than 8 years of age incur high ligamentous injuries more often than older children and adults. Fractures tend to occur at the weak points in the bones—synchondroses and ossification centers. Dens fractures occur most commonly along the synchondrosis, especially in children younger than age 7 years. The mechanism of injury is usually a forward-facing child in a high-speed motor vehicle crash with rapid forward flexion. Atlanto-occipital and atlantoaxial dislocation injuries are devastating vertical distraction injuries that occur in the very young child, most commonly from a motor vehicle crash, and usually result in rapid death (**Figure 112-1**).

SPINAL MOTION RESTRICTION IN INFANTS AND CHILDREN

When cervical spine injury is suspected, measures to restrict the motion of the cervical spine can be challenging. Spinal motion restriction may be difficult in young children who are frightened or agitated, and placement of a cervical collar in young children while on a flat surface (e.g., rigid long board) may cause unwanted flexion of the cervical spine. A number of untoward effects have been associated with the use of a rigid long backboard including development of decubitus ulcers, flexion of the neck, and impedance of chest wall motion causing respiratory compromise, worsening of atlanto-occipital distraction injury, increased intracranial pressure, and musculoskeletal pain that may mimic injury and lead to increased radiologic investigation.[13-25]

TABLE 112-1 Anatomic Considerations in the Pediatric Cervical Spine

- Large head
- Ligamentous laxity
- Absent cervical lordosis
- Weak neck muscles
- Anterior wedging of vertebrae
- Shallow and horizontal vertebral facets
- Ossification centers and synchondroses



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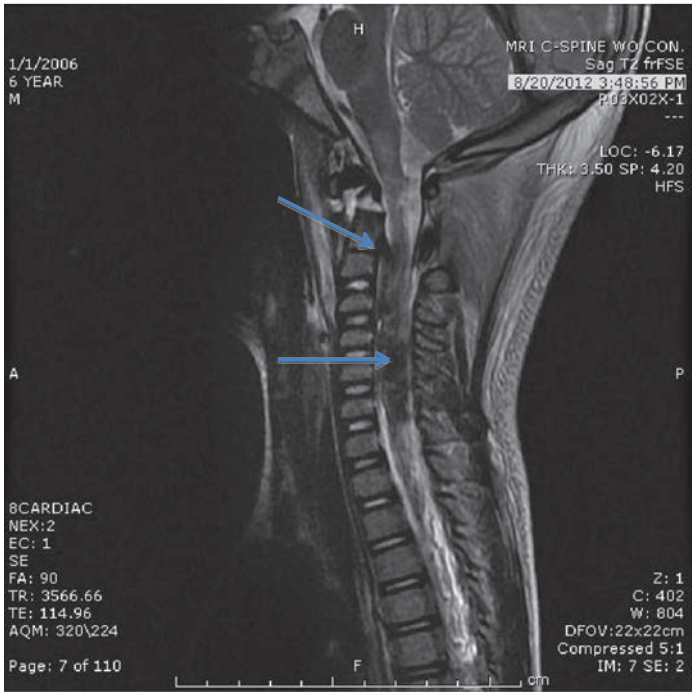


B

FIGURE 112-1. Atlantoaxial dislocation in a 6-year-old boy involved in a motor vehicle crash. **A.** Lateral plain radiograph reveals atlantoaxial dislocation (*blue arrow*). **B.** MRI of the same patient reveals a near-complete transection of the brainstem at the level of the distal medulla, extensive ligamentous injury with resulting atlantoaxial dissociation, extensive intrathecal hematoma and hemorrhage, C1–C2 interspinous ligament tear, and prevertebral soft tissue swelling and edema around the nuchal ligament (*blue arrows*).

For those at significant risk for cervical spine injury, neutral positioning of the neck is important; for those in the supine position, consider elevating the torso 2.5 cm (or more for children <4 years of age) in order to alleviate neck flexion caused by the large occiput. **Neutral position is achieved by aligning the external auditory meatus with the shoulders.** Proper sizing of pediatric cervical collars is equally important and varies depending on the device used. If the proper-size collar is not available or if cervical collar placement initially results in extreme agitation of the child, use padding such as towel rolls or foam blocks placed on both sides of the child's head to help limit motion.

Due to the risks associated with the rigid long board, use should be restricted to children with injuries that limit their ability to self-extricate in the prehospital setting (e.g., obtunded or unable to ambulate).[26,27] If used, upon arrival to the hospital, children should be quickly moved from the rigid long board to a mattress gurney using the log roll maneuver or a slide board.

CLINICAL FEATURES

HISTORY

Ask parents, witnesses, or prehospital personnel about the mechanism of injury: children with cervical spine injury will usually have a history of high-force acceleration/deceleration (as seen in motor vehicle crashes) or axial loading trauma (falls, diving injuries). Trivial mechanisms such as a ground-level fall usually do not lead to serious spine injury unless the patient has a condition associated with cervical spine instability (see "Special Considerations" later in the chapter). In the cooperative, verbal child, ask about symptoms such as neck pain, difficulty moving the neck, sensory deficits, or weakness.

PHYSICAL EXAMINATION

Examine the child with a primary survey of airway, breathing, and circulation, followed by a complete head-to-toe examination to identify major comorbid injuries that increase the risk of cervical spine injury, particularly injuries to the head and thorax.

Pay careful attention to breathing, because damage to C3–C5 can injure the phrenic nerve, impairing innervation to the diaphragm, compromising respiratory mechanics, and leading to apnea. Injury to the high cervical spine can affect hemodynamic stability from spinal shock. Spinal shock is characterized by hypotension in the setting of a normal heart rate. For intubated or obtunded trauma patients, leave a cervical collar in place and obtain imaging.

In children who are cooperative and alert, assess for midline neck tenderness, the presence of torticollis, and neurologic deficits while maintaining inline stabilization of the neck. Sensory symptoms such as numbness or tingling are the most common neurologic deficits among pediatric cervical spine injury patients, and persistent sensory deficits may help localize the level of the injury.

Test for motor function in the cooperative child: shoulder shrug is controlled by C5, elbow flexion and wrist extension by C6, elbow extension and wrist flexion by C7, and finger flexion by C8. Also check deep tendon reflexes; the biceps reflex tests C5, the brachioradialis reflex tests C6, and the triceps reflex tests C7.

DIAGNOSIS

Distinguishing between radiographically apparent cervical spine injury, SCIWORA, and peripheral nerve injury (brachial plexus) can be challenging. Transient burning sensation of the hands and fingers is a concerning complaint described by young athletes with neck injuries, particularly football players. These symptoms can be caused by either neck hyperextension and central cord contusion or stretching or direct blow (supraclavicular fossa) to the brachial plexus. Patients with brachial plexus injuries will not report lower extremity symptoms or posterior midline neck complaints, and compression to the top of the head may reproduce the symptoms (**Spurling test**).

Torticollis and neck pain are presenting findings of cervical spine injury in children. It can be difficult to differentiate decreased movement from direct muscle injury versus muscle spasms due to cervical spine injury. A common cervical spine injury in young children is **atlantoaxial rotatory subluxation**.[28] These injuries can result from very minor traumatic events and present with neck pain and torticollis that is characterized by the head being tilted in one direction and turned in the other (**cock robin deformity**). Atlantoaxial rotatory subluxation can also occur in the setting of positioning for head and neck surgery or spontaneously in the setting of upper respiratory infection (Grisel's syndrome). In most circumstances, atlantoaxial rotatory subluxation is self-limiting with rest and the use of NSAIDs and muscle relaxants.

LABORATORY TESTING

Routine laboratory testing is not helpful in the general evaluation of cervical spine injury in children but may be useful in the context of multisystem trauma.

IMAGING

Imaging should follow the U.S. Nuclear Regulatory Commission guidelines for using the "as low as reasonably achievable" principle. In practice, this means both selecting the right imaging study using clinical criteria and ensuring that imaging protocols are adapted to lower dosing for children. Choice of imaging should be guided by the history and physical examination.

Adult decision rules such as NEXUS (National Emergency X-Radiography Utilization Study) and the Canadian Cervical Spine Rule (see Tables 258-4 and 258-5) for cervical spine clearance may be useful in guiding imaging practice in older children and teens **but have limitations**. **The Canadian rule did not include children in its derivation, and NEXUS did not include children <2 years old and included only four patients <9 years old.**[2,29-33] A prospective study applying NEXUS in children showed that NEXUS did in fact miss two fractures, both in children under 2 years of age, highlighting the difficulty of ruling out cervical spine injury in the very young patient.[34] The Pediatric Emergency Care Applied Research Network conducted a multicenter retrospective case-control study of 540 children with cervical spine injuries matched to noninjured children who underwent cervical spine imaging. This study identified eight factors that were 98% sensitive and 26% specific for cervical spine injury after blunt trauma (**Table 112-2**).[35] If these risk factors had been used to guide clinical decision making, radiographic testing would have been reduced by approximately 25%. The pediatric cervical spine injury risk factors are currently undergoing prospective evaluation for use in a clinical decision tool.

Suggested clinical algorithms have been published by the Trauma Association of Canada's Pediatric Subcommittee[36] and more recently by the Pediatric Orthopedic Society of North America Cervical Spine Clearance Working Group (see Figure 112-4).

Plain Radiographs For patients in whom a cervical spine injury is suspected, plain radiographs should be considered first. The sensitivity of plain radiographs for identifying fractures, dislocations, and subluxations in children varies across the literature, ranging from 74% to 98%, with sensitivity increasing with the number of views taken.[37-44] Combining the cross-table lateral and anterior-posterior views identifies 87% of significant cervical spine injury in children younger than 8 years of age.[44] Consider the addition of an odontoid (open mouth) view in cooperative

TABLE 112-2 Risk Factors for Pediatric Cervical Spine Injury

- Altered mental status
- Focal neurologic examination
- Neck pain
- Torticollis
- High-risk motor vehicle crash
- Substantial torso injury
- Predisposing condition associated with cervical spine injury
- Diving

older children, although the added value in children younger than age 8 years has been questioned.[44]

Interpreting pediatric cervical spine radiographs can be challenging as a result of the anatomic differences across the spectrum of age. The principles of evaluation are similar to adults: assess the anterior and posterior vertebral lines, the spinolaminal line, and the spinous processes for alignment; and carefully examine the soft tissue spaces for swelling that might indicate subtle fracture. Widening of the soft tissue space >7 mm in the retropharyngeal space and >14 mm in the retrotracheal space on lateral radiograph may be an indirect sign of cervical spine injury. In addition, assess the pediatric cervical spine for atlantoaxial instability. Useful measurements include Wackenheim's clivus line (a line along the posterior edge of the clivus should intersect the odontoid) and the rule of thirds (the dens, cord, and empty space should each occupy one third of the spinal space). Craniocervical dislocation is suggested by a C1–C2:C2–C3 ratio >2.5. Important differences between pediatric and adult cervical spine radiographs include:

1. Normal cervical lordosis may be absent in children when imaged in the supine position and/or when a rigid collar is in place.
2. The posterior arch of C1 fuses by age 3 years and the anterior arch by age 10 years.
3. Anterior wedging of the vertebrae caused by secondary growth centers may be mistaken for compression fractures in children under 7 years old.
4. Posterior laminar fusion lines may be mistaken for fractures in children under 7 years old.
5. Children younger than 8 years old may demonstrate pseudosubluxation (up to 46%) on lateral radiograph, usually at the C2–C3 level (**Figure 112-2**).[45]

Swischuk developed a method for distinguishing between true subluxation and pseudosubluxation: draw a line connecting the posterior cortex of the spinous process of C1 to the cortex of the spinous process of C3 (**Figure 112-3**). If this line is >2 mm anterior to the spinous process of C2, suspect cervical pathology, such as a hangman's fracture.



FIGURE 112-2. Pseudosubluxation of C2 on C3. [Reprinted with permission from Yamamoto LG: Cervical spine malalignment—true or pseudosubluxation? In: Yamamoto LG, Inaba AS, DiMauro R (eds): *Radiology Cases in Pediatric Emergency Medicine,* Vol. 1, Case 5. Honolulu, HI: University of Hawaii John A. Burns School of Medicine, Department of Pediatrics, 1994. http://www.hawaii.edu/medicine/pediatrics/pemxray/v1c05.html.]

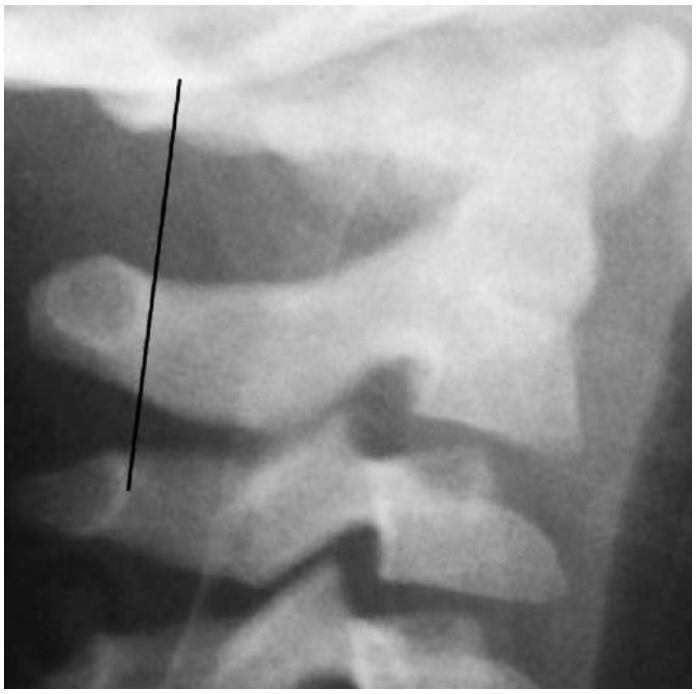


FIGURE 112-3. Posterior cervical line of Swischuk. [Reprinted with permission from Yamamoto L: Cervical spine malalignment—true or pseudosubluxation? In: Yamamoto LG, Inaba AS, DiMauro R (eds): *Radiology Cases in Pediatric Emergency Medicine,* Vol. 1, Case 5. Honolulu, HI: University of Hawaii John A. Burns School of Medicine, Department of Pediatrics, 1994. http://www.hawaii.edu/medicine/pediatrics/pemxray/v1c05.html.]

There is little role for flexion/extension plain radiographs in the ED for children. Obtain an MRI if ligamentous instability is suspected.

Although **CT** is the most cost-effective modality for imaging the cervical spine in adults, it is unclear if this is true for children, in whom radiation exposure is of particular concern. CT scanning exposes a child to 10 to 90 times the radiation of plain films, with an estimated 18-fold increase in thyroid malignancy in a theoretical model if all plain films are replaced by CT scans.[46,47] Given the potential risks and unclear advantages of CT in children, this modality should be reserved for those with abnormal or suspicious plain radiographs and those with significant mechanism of injury who are obtunded or intubated and undergoing CT evaluation for other injuries. **MRI** is the modality of choice for the diagnosis and evaluation of children with focal neurologic deficits on exam or those who report persistent severe cervical spine pain with normal plain radiographs.[9] Patients with normal MRI examinations and SCIWORA have very favorable prognoses; those with minor findings such as cord edema or a minor hemorrhage have good prognoses, whereas those with major hemorrhage or cord transections have poor prognoses for recovery.[48,49] MRI should also be strongly considered as an adjunct test when evaluating for abusive head trauma in infants and young children, as emerging evidence supports a higher rate of cervical spine injury in this subpopulation. The injury patterns in these children are typically multilevel ligamentous injuries and intraspinal hemorrhages.[50-58]

TREATMENT

The ED management of the child with potential cervical spine injury should follow the principles of advanced trauma life support with primary attention to assessment and management of the airway and breathing (especially with a high cervical spine injury, which may compromise respiratory effort) and circulation (particularly in spinal shock). Spinal shock is not responsive to volume expansion and must be treated with vasopressors.

In adult cervical spine injury, steroids are no longer favored (see Chapter 258, "Spine Trauma"), and no large studies have examined the efficacy of steroids in pediatric spine injury, so steroids are not standard of care for children.

Definitive management of cervical spine injury is primarily surgical, through consultation with pediatric neurosurgery or orthopedics.

DISPOSITION AND FOLLOW-UP

Unstable patients and those with radiographic evidence of cervical spine injury require admission, usually to intensive care, and consultation with a spine surgeon. Compared to adults, children's cervical spine injuries infrequently require surgery (15.7%) or traction or halo (16.9%).[3] Due to the age-related variation in cervical spine injury patterns and management, transferring these children to pediatric trauma centers for definitive care is strongly recommended.

Children with persistent neck pain despite normal neurologic exam and normal radiographs and/or CT need further evaluation. If the mechanism of injury is mild, the child may be discharged with an appropriately sized cervical collar and close outpatient medical follow-up. If the mechanism of injury is severe, it is prudent to obtain a spine consultation to determine further evaluation.

Children without neck pain or neurologic symptoms or deficits who have normal radiographs and those who have been cleared clinically should be discharged with instructions to return for symptoms of numbness, tingling, or weakness in the arms, hands, legs, or feet.

SPECIAL CONSIDERATIONS

Certain conditions predispose patients to cervical spine injury as a result of associated abnormalities causing cervical spine instability. These are listed in **Table 112-3**. Children with these conditions should be considered at high risk for cervical spine injury and undergo conservative/extensive evaluation.

TABLE 112-3 Predispositions to Cervical Spine Injury in Children

Genetic syndromes associated with spine malformations; examples:
- Down syndrome: 15% atlantoaxial instability
- Klippel-Feil syndrome: cervical vertebral defects
- Morquio's syndrome (type IV mucopolysaccharidosis): odontoid hypoplasia

Connective tissue disorders associated with ligamentous laxity; examples:
- Marfan's syndrome
- Ehlers-Danlos syndrome

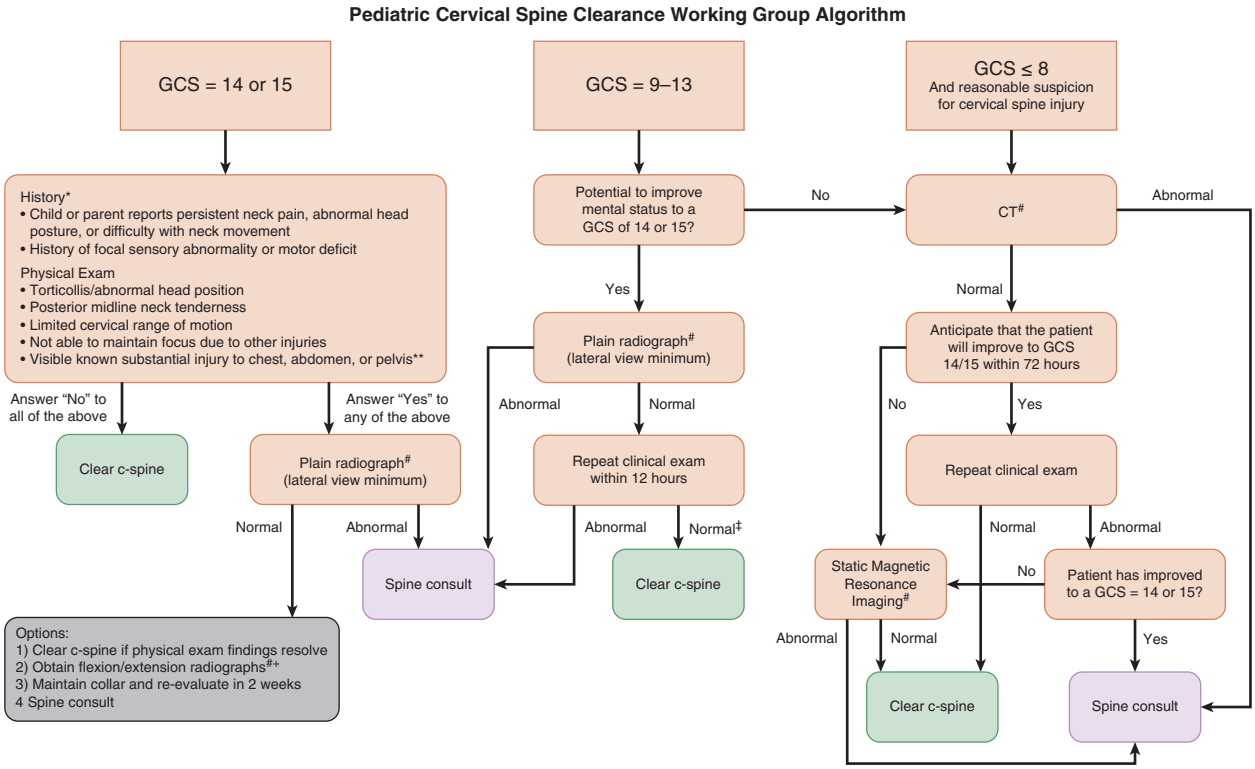
Spondyloarthopathies; examples:
- Ankylosing spondylitis
- Rheumatoid arthritis

Disorders of bone metabolism; examples:
- Osteoporosis
- Rickets

Previous cervical spine surgeries

CLINICAL ALGORITHMS FOR CERVICAL SPINE CLEARANCE

In 2011, the Trauma Association of Canada's Pediatric Subcommittee National Pediatric Cervical Spine Evaluation Pathway released a consensus guideline for evaluation of the pediatric patient and divided its algorithms into two parts: the reliable patient and the unreliable patient.[36] More recently, the Pediatric Orthopedic Society of North America Cervical Spine Clearance Working Group released a consensus algorithm based on Glasgow Coma Scale score rather than age (**Figure 112-4**).



*Stronger consideration for imaging should be given towards patients with the following mechanisms of injury (MOI): diving, axial load, clothes-lining and high-risk MVC (HR-MVC), however the literature findings are controversial. HR-MVC is defined as a head-on collision, rollover, ejected from the vehicle, death in the same crash, or speed > 55mph
**Substantial injury is defined as an observable injury that is life-threatening, warrants surgical intervention, or warrants inpatient observation.
All Imaging should be read by an attending physician
+Adequate flexion/extension is defined as ≥ 30 degrees of flexion and ≥ 30 degrees of extension
‡Patient has achieved GSC 14 – 15 and no longer presents with abnormal head posture, persistent neck pain, or difficulty in neck movement

FIGURE 112-4. Algorithm for evaluation of the pediatric cervical spine (C-spine) in the pediatric patient. GCS = Glasgow Coma Scale. [Reproduced with permission from Herman MJ, Brown KO, Sponseller PD, et al: Pediatric Cervical Spine Clearance: a consensus statement and algorithm from the Pediatric Cervical Spine Clearance Working Group. *J Bone Joint Surg Am* 2018; Jan 2;101(1):e1.

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CHAPTER 113

Intubation and Ventilation of Infants and Children

Matthew L. Hansen
Carl Eriksson

INTRODUCTION

Children have distinct characteristics that result in differences in the approach to supporting oxygenation and ventilation compared to adults. In addition, there are significant physiologic, anatomic, and equipment differences between children and adults that must be considered when managing the pediatric airway. The presentation of a critically ill child requiring significant support of oxygenation or ventilation, potentially leading to endotracheal intubation, is relatively uncommon compared to adults.[1-4] This chapter presents some unique characteristics of pediatric respiratory physiology as well as distinct anatomic characteristics of the pediatric airway. It also discusses strategies for effective airway management, including strategies to select equipment and dose drugs with the goal to minimize errors.[5]

PHYSIOLOGIC CHARACTERISTICS

Due to a higher metabolic rate, oxygen consumption is increased in children, especially in infants. As a result, children are vulnerable to rapid desaturation when oxygenation or ventilation is reduced. Children have relatively small-volume lungs with small functional residual capacities, and tachypnea is the initial response to most insults to oxygenation and ventilation. This also translates into a reduced oxygen reservoir, which decreases the length of safe apnea time after neuromuscular blockade, even when preoxygenation is optimized. Therefore, be prepared to support oxygenation with bag-mask ventilation (BMV) before an intubation attempt, while awaiting the onset of induction and paralysis, and during the apneic period after paralytics have been administered. Below an oxygen saturation of 90%, desaturation is particularly rapid.[6] The vast majority of children are easily bag ventilated when the proper technique is used, even when partial obstruction is present. The key is anticipation and early use of good BMV.

Children can develop gastric distention from swallowing air during distress as well as insufflation during BMV. Gastric distention can further compromise functional residual capacity, tidal volume, and ventilation. Gastric insufflation is generally a more significant problem the younger the age of the child. Proper BMV technique can reduce the risk, and early placement of an orogastric or nasogastric tube may help. Gastric tubes are also recommended to minimize the risk of reflux from an incompetent gastroesophageal junction, but the incidence of aspiration in children appears to be quite low, even in emergent intubation.

Children have a proportionally larger extracellular fluid compartment than adults. This results in a quicker onset and shorter duration of action of drugs and may require higher doses per kilogram for many of the drugs used to facilitate rapid-sequence intubation.

ANATOMIC CHARACTERISTICS

There are a number of anatomic characteristics of children that must be appreciated to optimize the success of airway management including endotracheal intubation (**Table 113-1**). Most of the unique anatomic characteristics are most prominent in infancy. Over the first 8 years of life, there is a transition to a smaller but similarly proportioned anatomy compared to adults. Most children do not have the many acquired anatomic challenges present in older adults, and the differences in children are predictable. With good technique and anticipation of these differences, the majority of pediatric airways are successfully managed.

TABLE 113-1 Anatomic Considerations in the Pediatric Airway

Pediatric Anatomy	Potential Implications	Airway Maneuvers
Large head and occiput	May push head forward, occluding airway	Shoulder roll should be used to align airway axes* in infants
Large tongue	May occlude upper airway in sedated, obtunded, or paralyzed patient	Jaw thrust, chin lift, oral or nasopharyngeal airway
Floppy epiglottis	May obscure laryngeal view	Lifting the epiglottis directly with a straight blade, or potentially a curved blade may be necessary to visualize the glottis
Superior larynx and anterior cords	May make visualization of cords difficult	Shoulder roll may be required to align airway axes*; video laryngoscopy may improve glottic view
Cricoid narrowing	Subglottic space is narrowest portion of the pediatric airway	Monitor cuff insufflation pressures in small children
Large adenoids and tonsils	May cause upper airway obstruction	Oral and nasal airway adjuncts may help; jaw thrust and chin lift are also likely to help
Small cricoid cartilage	Makes open cricothyrotomy technically difficult	Needle cricothyrotomy preferred in young children
Low gastroesophageal sphincter tone, relatively small lungs	Insufflation of stomach with bag-valve-mask ventilation or swallowed air can compromise respiratory status	Use proper bag-valve-mask ventilation technique; consider early placement of orogastric or nasogastric tube to deflate stomach when using positive-pressure ventilation

*Tragus should be aligned with the clavicle. In older children, the roll may need to be placed under the occiput to achieve alignment.

Alignment of the oral, pharyngeal, and tracheal axes, to allow visualization of the glottis, is affected by several features most pronounced in the infant: (1) a relatively large head and occiput, (2) a disproportionately large tongue and small mandible, and (3) a larynx that is more cephalad and thus appears more anterior than in adults. **This acute angle can be overcome by extending the infant's neck (unless cervical injury is suspected) and, in some cases, placing a small roll under the shoulders**.

The infant glottic opening, epiglottis, and aryepiglottic folds are more prominent, soft, and mobile than in an adult or older child. This redundant tissue can obscure the view of the vocal cords. Under tension from a laryngoscope blade, the esophageal inlet can also appear similar to the vocal cords. Many skilled laryngoscopists prefer to use a straight laryngoscope in younger children as it allows the epiglottis to be directly lifted out of view by the laryngoscope.

The narrow trachea, combined with the redundant, mobile periglottic tissues, predisposes the young child to airway obstruction.[7] **The narrowest point of the child's trachea is at the cricoid ring**, which is also the site of mucosal swelling associated with croup. Airway resistance increases disproportionately with any reduction in diameter and dramatically increases when airflow becomes turbulent rather than laminar. A 25% reduction in diameter from swelling (e.g., 4 mm to 3 mm) reduces the cross-sectional area by 50% and increases resistance by 200%. The swollen, mobile tissues create a dynamic obstruction, and, in the agitated, crying, young child with subsequent turbulent airflow, the work of breathing can increase 32-fold.[7] This can lead to complete obstruction and respiratory arrest. **This principle underscores the need to keep children with partial airway obstructions as calm as possible**. Because the obstruction



FIGURE 113-1. Proper facemask size.

often worsens during negative airway pressure associated with inspiration, children with airway edema usually respond well to positive-pressure ventilation including BMV, continuous positive airway pressure, or potentially high-flow nasal cannula at the higher range of flow rates.

Surgical cricothyrotomy is contraindicated in children <10 years old because the cricothyroid membrane is too small. Therefore, in children <10 years of age, needle cricothyrotomy is the subglottic, invasive airway of choice.

BAG-MASK VENTILATION

BMV is a fundamental critical skill for pediatric resuscitation and arguably one of the most important skills to master. BMV alone may be sufficient to support oxygenation in certain clinical scenarios where rapid recovery is expected, such as apnea or hypopnea associated with postictal states or deep sedation. BMV is also commonly required before endotracheal intubation, may be needed during the apneic period following neuromuscular blockade, and is the principal rescue technique in children when intubation attempts fail. Correctly sized bags and masks are essential to good ventilation, regardless of the provider's skill. Proper mask size is illustrated in **Figure 113-1**.

Common errors in pediatric BMV include excessive ventilatory rate, inspiratory pressure, and volume. Many self-inflating "pediatric"-sized bags have a volume of approximately 500 mL. However, a 20-kg child should receive only about 160 mL of air with each breath (8 mL/kg). Thus, providers should generally squeeze the bag only enough to allow for chest rise in order to prevent gastric insufflation and barotrauma. On occasion, the rate or volume will need to be adjusted for the disease state. For example, longer expiratory times are often needed in asthma. **Table 113-2** includes normal initial ventilation parameters.

In infants and younger children, a supine position usually causes flexion of the neck due to the large occiput, and elevation of the shoulders or thorax is helpful to align the airway.

There are two common hand positions to achieve a mask seal. The "E-C" clamp technique is perhaps the most common, with the thumb and index finger positioned on the mask and the remaining fingers pulling the mandible up into the mask, while maintaining extension at the atlanto-occipital junction (**Figure 113-2**). The E-C clamp technique can be used with one or two hands, although the two-handed technique provides a better seal.[8,9] Another technique known as the "V-E" technique, or thenar eminence technique, requires two hands but may allow for a better seal (**Figure 113-3**).[8,10] With either technique, it is critical that the

TABLE 113-2 Initial Ventilation Parameters in Children

Patient weight (kg)	3–9	10–18	19–36
Patient length (cm)	46–75	76–109	110–146
Tidal volume (mL/kg)	6–8	6–8	6–8
Rate (breaths/min)	20–25	15–25	12–20



FIGURE 113-2. Double "E-C" clamp bag-valve-mask technique. Using two hands results in a better mask seal compared to single-hand technique.



FIGURE 113-3. "V-E" bag-valve-mask technique. This technique requires two hands but results in a good seal and potentially less hand fatigue than other methods.

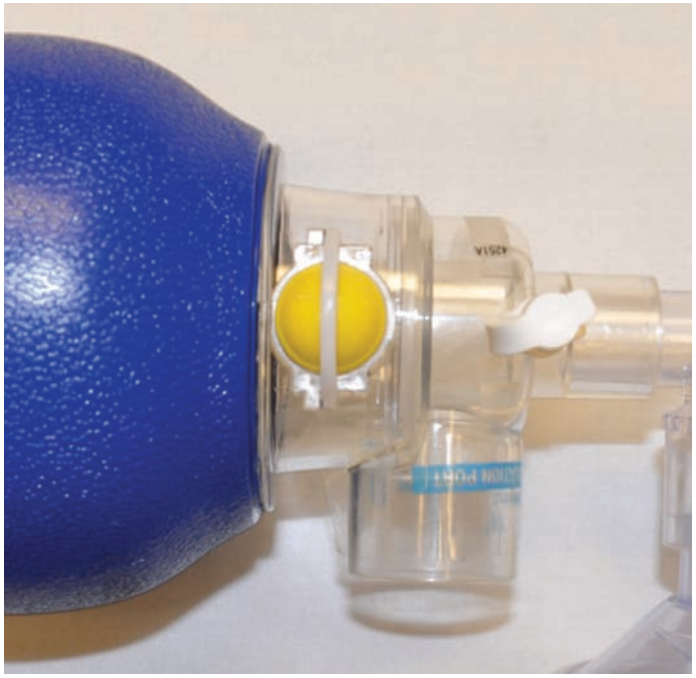


FIGURE 113-4. The pop-off valve on a pediatric bag-valve mask, designed to prevent barotrauma, may need to be occluded when higher pressures are required, such as in patients with asthma.

majority of force be dedicated to pulling the airway up into the mask, rather than pushing the mask down into the face. It is also important to apply pressure to the bony mandible rather than the soft submandibular space, since pressure on the submandibular space can cause the tongue to obstruct the airway. Oral and nasopharyngeal airways can be helpful adjuncts to BMV in children by helping displace the highly mobile tissues of the pediatric airway.

Manometers are available for many BVM systems that allow the user to monitor ventilatory pressures. Keeping inspiratory pressure as low as possible will decrease the likelihood of inflating the stomach. In addition, positive end-expiratory pressure valves can be added to many models that can assist in oxygenating patients with hypoxemia. There are some data to suggest the cricoid pressure may reduce gastric insufflation during bag-valve-mask ventilation, although at higher pressures, especially in smaller children, it can also cause obstruction of the airway.[11,12]

Consider placing appropriately sized oral airways (measured from the mandibular angle to the lip; see Table 113-4) in unconscious children to assist with displacement of the relatively large pediatric tongue.

Finally, most pediatric bags incorporate a pop-off, or pressure-relief, valve (**Figure 113-4**). Designed to avoid barotrauma, the valve will open at a preset peak pressure (usually 35 to 40 cm H_2O of pressure). However, in some diseases associated with high airway pressures, such as asthma or airway obstruction, higher peak pressures may be needed to achieve adequate ventilation. In these circumstances, disable or occlude the pop-off valve manually.

NONINVASIVE VENTILATION

Noninvasive ventilation has been most rigorously studied in adults, and studies in children have focused mostly on respiratory support in bronchiolitis. Nasal continuous positive airway pressure and **high-flow (i.e., 6 L/min) nasal cannula**, where humidified oxygen is delivered via nasal cannula, have been evaluated in the literature as means to support respiratory effort in infants and children with bronchiolitis.[13-17] Use of this technique has been shown to improve ventilation and, in some children, obviate the need for subsequent intubation and should be considered as an adjunct in cases of moderate to severe bronchiolitis. In addition, several retrospective studies have suggested that bilevel positive-pressure ventilation is safe and may be effective for children with status asthmaticus.[18,19] In addition to supporting patients with acute respiratory disorders, noninvasive ventilation may also be useful for chronic conditions; bilevel positive airway pressure may provide ventilatory assistance in neuromuscular disorders, whereas continuous positive airway pressure can improve aeration for patients with syndromes associated with anatomic upper airway obstruction (e.g., craniofacial syndromes, Down syndrome with macroglossia). Noninvasive positive-pressure ventilation is most effective when instituted early on in the disease process and is also more effective for ventilatory failure compared to acute hypoxemic respiratory failure. **Table 113-3** provides an overview of the indications, equipment, settings, advantages, and disadvantages of nasal cannula and noninvasive ventilation strategies in infants and children.

ENDOTRACHEAL INTUBATION EQUIPMENT

The principal challenge with children is selecting the appropriate-size equipment. There are several formulas that can assist in the estimation of equipment sizing. It is ideal for emergency physicians to have basic knowledge of equipment size for endotracheal intubation such as tube sizing, depth of insertion, and blade selection. In addition, all EDs should have an established system to identify the appropriate-size equipment needed for each child. There are many available systems, and

TABLE 113-3 Overview of Pediatric Nasal Cannula and Noninvasive Ventilation Strategies

Method	Equipment	Indications	Common Settings	Comments
Standard NC	Standard cannula	Hypoxemia Apneic oxygenation	0.5–4 L/min	Use higher rates for apneic oxygenation (5 L/min for infants, 10–15 L/min for older children)
High-flow NC	High-flow cannula with heater, humidifier, and flow regulator	Bronchiolitis Status asthmaticus Mildly to moderately increased work of breathing	1–2 L/kg/min	• May also be used with Fio_2 regulator to apply high flow without high Fio_2 • Higher flow rates can create positive airway pressure
CPAP *or* BiPAP	Commercial device (often a ventilator) with circuit and mask or nasal prongs	CPAP • Upper airway obstruction • Status asthmaticus • Moderately to severely increased work of breathing BiPAP • Neuromuscular disease • Respiratory distress not improved with CPAP	CPAP 5–8 cm H_2O BiPAP Inspiratory PAP 8–15 cm H_2O Expiratory PAP 4–8 cm H_2O	• Keep Fio_2 as low as possible to avoid masking hypoventilation • Less helpful in acute hypoxemic respiratory failure • Use caution in patients at high risk for aspiration

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; Fio_2 = fraction of inspired oxygen; NC = nasal cannula; PAP = positive airway pressure.

TABLE 113-4 Age-Based Airway Equipment Size

Age	Internal Diameter (mm)	Blade Size
Premature	3.0 Uncuffed	0 Straight
0–6 mo	3.5 Cuffed	1 Straight
6–12 mo	4.0 Cuffed	1–1.5 Straight
1–2 y	4.5 Cuffed	1.5 Straight
3–4 y	4.5 Cuffed	1.5–2 Straight or curved
5–6 y	5.0 Cuffed	2.0 Curved
7–8 y	5.5 Cuffed	2.0 Curved
9–10 y	6.0 Cuffed	2.0 Curved
≥11 y	6.5 Cuffed	3.0 Curved

each hospital should evaluate the merits of each system and select one that meets their needs. Effective systems can range from relatively high-cost commercial systems to low-cost, internally developed, length-based tables for drug doses and equipment sizes that rely on simple tape measures to determine the length. The Broselow® tape represents a common system that uses length-based estimates of equipment and medications, organized by color.[7] Some EDs organize their airway equipment to align with their chosen system in order to minimize confusion and delay.

ENDOTRACHEAL TUBES

The following formula can reasonably estimate the cuffed endotracheal tube size, as measured by internal diameter, in children >1 year of age: (age/4) + 4.

It is generally recommended that *cuffed* endotracheal tubes be used down to size 3.5, which would typically be the size for a full-term newborn. Previously, it was taught that uncuffed endotracheal tubes were preferred for smaller tube sizes. However, in many cases, uncuffed tubes result in significant air leaks and can require subsequent replacement, which reexposes the patient to the risks of intubation unnecessarily.[20,21] In addition, many children intubated in the ED may require relatively high ventilation pressures to obtain adequate oxygenation or ventilation, which may not be possible with an uncuffed tube. One pediatric endotracheal tube cuff inflation strategy is to inflate the cuff with the minimum amount of air required to prevent a cuff leak. This can be done by having one provider auscultate over the anterior neck while slowly ventilating with a self-inflating bag. Another provider slowly inflates the cuff until air is no longer heard to be leaking around the cuff. It is generally recommended to monitor endotracheal tube cuff pressures to prevent ischemic damage to the trachea. This technology is generally available in pediatric intensive care units but may not be immediately available for many ED providers; thus, it is important to inflate the cuff carefully. **Tables 113-4** and **113-5** display some common equipment sizes by age and length.

LARYNGOSCOPE BLADES

Straight laryngoscope blades (Miller) are preferred to curved blades in young children because the large epiglottis can be lifted directly, and the large tongue is more easily displaced to provide direct visualization.[22] A blade that is too small or short is potentially more difficult to use than one that is too large, because a short blade may not reach the supraglottic area. To determine proper blade length, place the blade handle joint at the child's upper incisors and the tip at the angle of the mandible. The length of the blade from its tip to the handle joint should be within 1 cm proximal or distal of the angle of the mandible.[9,23] The #0 straight (Miller) blade or #1 curved (MacIntosh) blades are used only for the small or premature newborn (**Figure 113-5**).

VIDEO LARYNGOSCOPY

Video laryngoscopy has become quite common in adult airway management in the ED. Video laryngoscopy has also recently become more common in pediatric patients in the ED and the pediatric intensive care unit.[24,25] In general, it appears that for most patients, first-pass success rates are similar in children with direct and video laryngoscopy.[26] However, in children with difficult airways, video laryngoscopy may provide better first-pass success.[27,28] It is reasonable to use video laryngoscopy as first-line technique in children, especially if video laryngoscopy is primarily what a given provider or hospital uses for adults. Standardizing equipment across age groups as much as possible may reduce the likelihood of errors and may reduce stress during uncommonly performed procedures.

AIRWAY ADJUNCTS

The selection of alternative airway techniques or rescue devices for children is limited. However, most children can be bag-mask ventilated should laryngoscopy fail. The typical 15F intubating stylet, or bougie, commonly used for adults will typically only accommodate a 5.5 or larger endotracheal tube. Intubating stylets are available in pediatric sizes small enough to accept a 3.0-mm internal diameter endotracheal tube.

As noted in the earlier section "Anatomic Characteristics," emergency subglottic surgical airways in children <10 years of age are restricted to needle cricothyrotomy. The indications for these alternative airway options are discussed in more detail later in this chapter.

TABLE 113-5 Length-Based Equipment Chart (length in cm)

Item	54–70 cm	70–85 cm	85–95 cm	95–107 cm	107–124 cm	124–138 cm	138–155 cm
Endotracheal tube size (mm)	3.5	4.0	4.5	5.0	5.5	6.0	6.5
Lip–tip length (mm)	10.5	12.0	13.5	15.0	16.5	18.0	19.5
Laryngoscope	1 Straight	1–1.5 Straight	1.5–2 Straight	2 Straight or curved	2 Straight or curved	2–3 Straight or curved	3 Straight or curved
Suction catheter	8F	8F–10F	10F	10F	10F	10F	12F
Stylet	6F	6F	6F	6F	14F	14F	14F
Oral airway	Infant/small child	Small child	Child	Child	Child/small adult	Child/adult	Medium adult
Bag-valve mask	Infant	Child	Child	Child	Child	Child/adult	Adult
Oxygen mask	Newborn	Pediatric	Pediatric	Pediatric	Pediatric	Adult	Adult
Vascular access (gauge)							
Catheter	22–24	20–22	18–22	18–22	18–20	18–20	16–20
Butterfly	23–25	23–25	21–23	21–23	21–23	21–22	18–21
Nasogastric tube	5F–8F	8F–10F	10F	10F–12F	12F–14F	14F–18F	18F
Urinary catheter	5F–8F	8F–10F	10F	10F–12F	10F–12F	12F	12F
Chest tube	10F–12F	16F–20F	20F–24F	20F–24F	24F–32F	28F–32F	32F–40F
Blood pressure cuff	Newborn/infant	Infant/child	Child	Child	Child	Child/adult	Adult

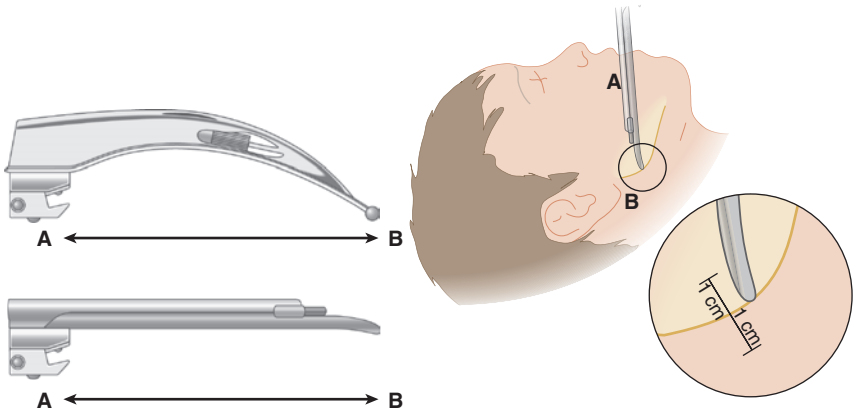


FIGURE 113-5. Measurement of proper laryngoscope length for curved and straight blades. [Instruments on left: Reproduced with permission from Mellick LB, Edholm T, Corbett SW: Pediatric laryngoscope blade size selection using facial landmarks. *Pediatr Emerg Care* Apr;22(4):226-229, 2006. Copyright Wolters Kluwer Health.]

APPROACH TO AIRWAY MANAGEMENT IN NEONATES, INFANTS, AND CHILDREN

PREPARATION FOR INTUBATION

Begin preparation for endotracheal intubation as soon as you anticipate the potential need for invasive airway management. Initiate preoxygenation early, even if oxygen saturation is 100%. Maximize preoxygenation through elevation of the head of the bed when possible. The actual fraction of inspired oxygen of commonly used equipment for pediatric preoxygenation in the ED environment is not well described. However non-rebreather masks at standard flow rates have been shown to achieve a fraction of inspired oxygen that is much lower than the desired 100%.[29] Adult data recommend using either a well-sealed BVM with 15 L/min of oxygen or a non-rebreather mask with oxygen flows at flush rate, which provides better preoxygenation.[30] For children, the addition of a nasal cannula to other preoxygenation techniques may also be beneficial, although the flow needs to be relatively high at 10 to 15 L/min for larger children and 5 L/min for children under 1 year of age.[31,32] This is also a reasonable approach for most children. Applying a nasal cannula during preoxygenation also facilitates apneic oxygenation, which likely reduces the rate of hypoxia during intubation in children.[33-35] Prepare appropriately sized equipment before initiating intubation. Prepare different-sized blades and at least one size smaller endotracheal tube. Make sure that oral and endotracheal suction catheters are functioning and of proper size. Assess airway difficulty (see later section, "The Difficult Pediatric Airway") and have rescue devices at hand. In some situations, such as partial airway obstruction, the best strategy may include anesthesia or otolaryngology consultation and consideration of intubation in the operating room. Even if the plan is to defer final management to another setting or a consultant, have equipment at the bedside in case of clinical deterioration requiring immediate action. Specialty equipment, such as a pediatric Magill forceps for foreign body obstruction, should also be at the bedside. Using an airway checklist throughout airway management is likely to improve preparation and reduce complication rates.[36]

Ensure reliable IV or IO access. Finally, a fluid bolus (20 mL/kg normal saline) is often beneficial before initiation of rapid-sequence intubation. Many children require intubation for respiratory failure, which is often associated with dehydration from reduced oral intake and increased insensible losses. Many medications used during intubation can decrease venous return or ventricular performance. In addition, **positive intrathoracic pressure resulting from ventilation after intubation may further decrease preload, making preintubation fluid resuscitation important**. Push-dose vasopressors are appropriate for children in selected circumstances, such as children who are significantly hypotensive prior to intubation and children with poor cardiac function (likely a result of congenital heart disease) who require intubation. **Push-dose vasopressors** should be prepared and available when intubating the critically ill hypotensive pediatric patient. **Epinephrine is used most commonly in children and is prepared by drawing 1 mL of 1:10,000 epinephrine and adding 9 mL of normal saline to produce a 1:100,000 solution (10 micrograms/mL); administer 0.1 mL/kg (1 microgram/kg) bolus doses as needed to maintain blood pressure > 70 × (2 + age).**

Finally, similar to adults, a subset of pediatric patients may not be suitable for rapid-sequence intubation. Other approaches such as delayed-sequence intubation or techniques that maintain spontaneous breathing may be more appropriate in certain pediatric patients. Specific examples include those with preexisting difficult airways or those unlikely to tolerate apnea due to impaired oxygenation.

LARYNGOSCOPY AND TRACHEAL INTUBATION

The technique for laryngoscopy is similar between children and adults and is described in detail in Chapter 29A, "Tracheal Intubation." Proper positioning is critical, and optimal alignment of the airway axes for laryngoscopy may be different than proper positioning for BMV (**Figure 113-6**). Extension of the neck can help align airway axes to improve glottic view. In infants, elevation of the torso may be necessary to align airway axes and improve laryngeal view. If using a straight blade, the large epiglottis overlies the vocal cords. Pick up the epiglottis with the straight blade to see the cords below. In younger children, there is a tendency to place the blade too deeply, into the esophagus. If identification of structures is impossible, the tip of the blade is usually in the upper esophagus or retroglottic space. Slowly withdraw the blade, and the cords or the epiglottis should come into view.

EXTERNAL LARYNGEAL MANIPULATION

The pediatric airway is relatively cephalad compared to adults. As such, external manipulation of the larynx has the potential to improve the laryngeal view. There is no single technique or movement that has clearly been shown to be superior. Ideally, the laryngoscopist would direct the manipulation of the larynx to optimize the view and have another team member hold it in that position while the tube is delivered. **Cricoid pressure may not be needed, because it has been associated with difficulty with intubation and BMV,[37] and in children, cricoid pressure can occlude the pliable trachea**. If cricoid pressure is applied, release pressure if laryngoscopy and intubation are difficult.

There is a tendency to insert the endotracheal tube too far in the very young child, in whom the distance from laryngeal cords to tracheal carina may just be a few centimeters. Right mainstem intubation is not always appreciated on auscultation, particularly in the infant, because breath sounds may be transmitted throughout the chest. Therefore, predetermine endotracheal tube depth and adhere to that depth during intubation. Depth can be estimated using the formula:

Tube internal diameter × 3 = Tube depth at the lips

For example, a 4.0-mm internal diameter tube should be 12 cm at the lips. Length-based systems can also be used.



A



B

FIGURE 113-6. A. Proper positioning of an infant for intubation. Elevation of the shoulders is often needed to accommodate the prominent occiput and prevent flexion of the neck. **B.** In an older child, elevation of the head with neck extension often results in the best alignment for intubation.

TABLE 113-6 Common Rapid-Sequence Intubation Medications in Children*

Medication	Dose†	Comments
Induction agents		
Etomidate	0.3 milligram/kg	Preserves hemodynamic stability; may suppress adrenal axis even in a single dose; short acting; requires anxiolysis or analgesia after intubation
Ketamine	1–2 milligrams/kg	Bronchodilator; preserves respiratory drive; cardiovascular stimulant; drug of choice for intubation for asthma and early sepsis
Propofol	1–3 milligrams/kg	Rapid push; higher dose in infants; may cause hypotension; short acting; requires ongoing anxiolysis or analgesia after intubation
Paralytics		
Rocuronium	1 milligram/kg	Nondepolarizing agent; longer duration than succinylcholine
Succinylcholine	<10 kg: 1.5–2.0 milligrams/kg >10 kg: 1.0–1.5 milligrams/kg	Shorter duration than rocuronium; may cause bradycardia in children and hyperkalemic cardiac arrest in children with undiagnosed neuromuscular disease
Sedatives		
Midazolam	0.1 milligram/kg	Short-acting sedative
Lorazepam	0.1 milligram/kg	Longer-acting sedative
Analgesics		
Fentanyl	1–2 micrograms/kg	Short-acting analgesic; preserves hemodynamic stability
Morphine	0.1–0.2 milligram/kg	Longer-acting analgesic; may cause histamine release

*Premedication is no longer routinely recommended in children due to a lack of supporting evidence.

†Rapid-sequence intubation medications can be given IO when IV access cannot be obtained. Consider lower doses of induction agents in the critically ill infant or child with hemodynamic instability.

RAPID-SEQUENCE INTUBATION

Rapid-sequence intubation remains the preferred method of intubation in children in the ED and is associated with the highest success and lowest complication rates compared to other methods.[18] Specific induction and paralytic agents for children are presented in **Table 113-6**. The indications and contraindications are the same as for adults.

Succinylcholine and rocuronium are both commonly used neuromuscular blocking agents for paralysis during pediatric rapid-sequence intubation. There are no comparative studies in children demonstrating benefit of one agent over another, although in practice, pediatric emergency medicine and critical care have largely adopted rocuronium as the paralytic of choice. Succinylcholine can cause fatal hyperkalemia in a number of conditions (**Table 113-7**), usually apparent on patient presentation; however, the specific association of hyperkalemia with cardiac arrest in children with undiagnosed neuromuscular disease has caused many pediatric practitioners to prefer the use of rocuronium in children. In children, there is no evidence to support the use of pretreatment agents. Bradycardia in children is typically a sign of hypoxia, which should be corrected. Atropine does not prevent succinylcholine-associated bradycardia and should not be given prophylactically.[38]

POSTINTUBATION AND VENTILATOR MANAGEMENT

Immediately after intubation, confirm endotracheal tube placement using a capnograph or a colorimetric end-tidal carbon dioxide detector.[23] A small-sized colorimetric end-tidal carbon dioxide detector should be used for children weighing <15 kg. For larger children, weighing >15 kg, use the adult-sized carbon dioxide detector, because using the smaller device with larger tidal volumes can increase resistance to flow (**Figure 113-7**). Continuous waveform capnography is optimal for confirmation of endotracheal tube placement, since in some clinical, albeit rare, scenarios the colorimetric detector may give a false-positive reading, such as after carbonated beverages are consumed or the detector becomes contaminated with stomach acid.[39,40] It is also useful in postintubation monitoring.

Visualization of the tube through the cords or fogging of the tube is not adequate confirmation of tube placement in the trachea. Likewise, equal breath sounds do not preclude right mainstem bronchus

TABLE 113-7 Complications and Contraindications of Succinylcholine

- Hyperkalemia
- Burns >5 d old
- Denervation injury >5 d old
- Significant crush injuries >5 d old
- Severe infection >5 d old
- Neuromuscular diseases, myopathies
- Preexisting hyperkalemia
- Masseter spasm
- Increased intragastric, intraocular, and possibly intracranial pressure
- Malignant hyperthermia
- Bradycardia
- Prolonged apnea with pseudocholinesterase deficiency
- Fasciculations

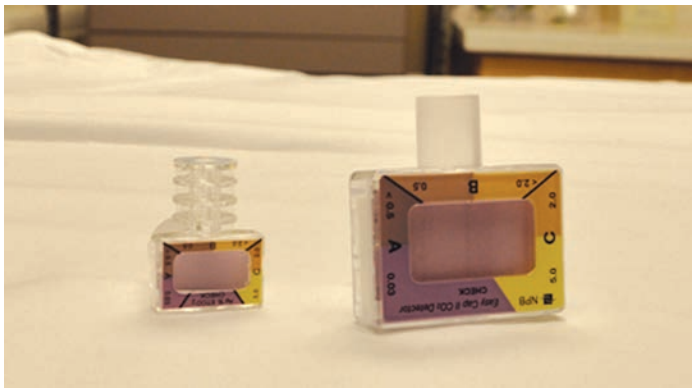


FIGURE 113-7. Examples of a pediatric colorimetric end-tidal carbon dioxide detector for children <15 kg and a standard one for larger children.

intubation, and a chest radiograph should be obtained shortly after intubation to confirm appropriate depth.

Carefully secure the tube at the mouth, using either tape adhered to the maxilla with skin adhesive or available commercial devices.[24] Because of the short distance between the glottic opening and the end of the endotracheal tube, infants are prone to displacement of the tube into the oral pharynx with head extension and into the right mainstem bronchus with head flexion. **Immobilize the head and neck in a neutral position in intubated young children**.

Most pediatric centers preferentially use pressure-limited ventilation, although practitioners must account for their own familiarity with different ventilatory modes when choosing the optimal mode for a particular child. For a child with relatively healthy lungs, a positive end-expiratory pressure of 5 cm H_2O is generally sufficient; children with significant oxygenation defects may require much higher levels of positive end-expiratory pressure. Inspiratory pressure or volume settings are usually titrated to achieve tidal volumes of 6 to 8 mL/kg, with an age-appropriate respiratory rate (often 30 or greater in infants). An initial inspiration-to-expiration ratio of 1:2 is suggested but may need to be adjusted, particularly in the presence of reactive airways, which will require a longer expiratory phase. Regardless of the initial settings, frequent reevaluation and monitoring of vital signs, including end-tidal carbon dioxide and blood gases, should guide ongoing ventilation parameters. Though ventilator management is beyond the scope of this chapter, a guide to initial settings based on physiology is provided in **Table 127-10**.

Provide adequate sedation and analgesia before the effects of induction and paralysis agents wear off. This is particularly important when rocuronium or other longer-acting muscle relaxants are used, because their duration is often much longer than most induction agents used in rapid-sequence intubation.

THE DIFFICULT PEDIATRIC AIRWAY

A difficult airway as defined by the American Society of Anesthesiologists is difficulty with BMV, difficulty with tracheal intubation, or both.[41] Other characteristics of the difficult airway include (1) more than two attempts at intubation with the same laryngoscopic blade, (2) need for a change in blade or use of intubation stylet, and (3) need for an alternative intubation technique or rescue. The incidence of difficult pediatric airways in the emergency setting is not known, although the child who cannot be intubated and cannot be ventilated appears to be less common than the adult.[42] As in adult patients, it is essential to anticipate difficult airway management in children in order to avoid the "can't intubate, can't ventilate" situation. Three questions will help guide management decisions:

1. Will I be able to bag-mask ventilate to maintain oxygenation?
2. Are laryngoscopy and intubation likely to be successful?
3. What rescue device, if needed, is most appropriate for this patient?

CLINICAL FEATURES OF DIFFICULT PEDIATRIC AIRWAYS

Difficult pediatric airways often fall into four categories: acute upper airway infections, such as epiglottitis and retropharyngeal abscesses; acute airway obstructions, such as foreign bodies, trauma, or burns; congenital anatomic airway abnormalities, such as Pierre Robin syndrome; and airways contaminated with significant amounts of body fluids. An approach to each potential difficulty is beyond the scope of this chapter. However, an understanding of the principles of management and the rescue devices available in pediatric airway management will usually lead to an appropriate strategy.

Small changes in airway diameter can significantly increase airway resistance, and when airflow is turbulent, as in a crying, agitated child, the resistance to flow increases exponentially. This is why most significant *partial* pediatric airway obstructions potentially requiring intubation are best managed in the controlled setting of the operating room with assistance from appropriate consultants, such as anesthesiology and otolaryngology. Until that time, maintain the child in a quiet, comforting environment, with minimal stimulation. The emergency physician must remain prepared for potential deterioration.

UPPER AIRWAY INFECTION

See Chapter 126, "Stridor and Drooling in Infants and Children," for a detailed discussion of infectious causes of upper airway obstruction in children. Acute upper airway infections, such as croup, are usually gradual in onset and may respond to medical intervention. Supraglottic infections, such as epiglottitis or pharyngeal abscesses, may make laryngoscopic visualization difficult, and rescue devices (see later section, "Supraglottic Devices"), such as a laryngeal mask airway, should be readily available. If respiratory failure should occur before intubation,

TABLE 113-8 Initial ED Ventilator Settings for Infants and Children

Underlying Pathophysiology	Ventilator Mode	Tidal Volume	Positive End-Expiratory Pressure	Rate	Comments
Normal lungs (e.g., intubation for altered level of consciousness)	Volume control	6–8 cc/kg	5 cm H_2O	Normal for age	In cases of metabolic acidosis, rate may need to be increased to avoid worsening acidosis; target rate to achieve $EtCO_2$ 35–40 mm Hg for intracranial hypertension
Obstructive lung disease (e.g., asthma)	Volume control	6–8 cc/kg	5 cm H_2O	Slow (10–14 or lower may be required)	Slow rate with increased expiratory time required to avoid breath stacking (relative hypercapnia OK); keep plateau pressure to a maximum of 30 cm H_2O to avoid barotrauma
Lung protective strategy (e.g., ARDS)	Volume control	4–6 cc/kg	8–10 cm H_2O	May need to be faster than normal for age due to low tidal volumes	Start at 6 cc/kg tidal volume and 8 cm H_2O and increase PEEP and decrease tidal volume as needed to maintain oxygenation; adjust rate to maintain eucapnea

BMV is usually successful because positive-pressure stents open the mobile soft tissues in extrathoracic airway obstructions.

FOREIGN BODY OBSTRUCTION

Patients with partial obstruction from a foreign body are another category in which expectant management is advised until care is transferred to a consultant skilled in endoscopic removal. Should complete obstruction occur before intervention, perform abdominal thrusts for children >1 year of age (see Chapter 109, "Resuscitation of Children"). For infants, perform five back blows followed by five chest thrusts and repeat these maneuvers and intersperse them with attempts at ventilation if the child remains conscious. If the child becomes unconscious, perform direct laryngoscopy. If the foreign body is supraglottic, it can possibly be removed using Magill forceps during laryngoscopy. If a child loses his or her pulse, then follow the appropriate Pediatric Advanced Life Support algorithm. If the obstruction is subglottic, intubation or BMV may push the foreign body into a mainstem bronchus, allowing temporary ventilation of the other lung until removal with bronchoscopy. Subglottic surgical approaches, such as needle cricothyrotomy and supraglottic rescue devices, are rarely helpful in this setting because the obstruction usually lies within the trachea, below the level of the cricothyroid membrane.

Partial obstruction may progress to complete obstruction with subsequent difficult laryngoscopy and BMV. Early subspecialty consultation may be needed before any transfer out of the emergency setting. Patients with burns, caustic ingestions, expanding hematomas, and anaphylactic reactions not responding to medical therapy fall into this category. Preparation for possible needle cricothyrotomy should be made in these cases.

CONGENITAL AIRWAY ANOMALIES

Children with congenital abnormalities associated with difficult laryngoscopy and BMV, such as Pierre Robin syndrome, are uncommon but challenging. The ideal management is aggressive medical treatment of the underlying disease, in hopes of obviating the need for intubation. Early subspecialty involvement is also needed in most cases. The most common issue is micro- or retrognathia, which decreases the potential space into which the tongue and upper airway structures can be displaced during laryngoscopy and thereby makes direct laryngoscopy very difficult. **Many pediatric patients with micro- or retrognathia respond to noninvasive positive-pressure ventilation, BVM ventilation, or ventilation through a laryngeal mask airway.**[43]

TECHNIQUES FOR MANAGING THE DIFFICULT PEDIATRIC AIRWAY

Consider supraglottic airway devices when ventilation with BMV is inadequate and attempts at endotracheal intubation fail. Supraglottic airway devices generally function by creating a seal superior to the glottic opening. They usually allow for adequate oxygenation and ventilation while potentially providing some protection against aspiration of gastric contents. There are a number of supraglottic devices that are suitable for use in children (**Figure 113-8**).

The laryngeal mask airway has been used for decades to manage pediatric airways and is often included in airway management training courses. The traditional laryngeal mask airway seats over the glottic opening and has an inflatable cuff that helps provide a seal. There are many different brands of traditional laryngeal mask airways in addition to several generations of these devices, some of which include suction ports. Several other supraglottic airway devices are also available in comprehensive pediatric sizing.

The i-gel® (Intersurgical, Workingham, Berkshire, United Kingdom) is one such device that is shaped similarly to a more traditional laryngeal mask but has a soft plastic cuff that is not inflatable as opposed to the inflatable cuff of the more traditional laryngeal mask. It is available with a suction port as well. Several studies have compared the more traditional laryngeal mask airway devices and the i-gel and have generally found them to be comparable.[44-47]



FIGURE 113-8. Supraglottic airways in pediatric sizes. At the top of the figure is an Ambu® AuraGain® laryngeal mask with an inflatable cuff (Ambu, Columbia, MD). Next is an i-gel® laryngeal mask, which does not have an inflatable cuff (Intersurgical, Workingham, Berkshire, United Kingdom), followed by a King® Laryngeal Tube (Ambu).

The King® Laryngeal Tube (Ambu, Columbia, MD) is a supraglottic airway where the tip of the tube is designed to seat in the esophagus, with an air exchange port pointed toward the glottis, while two balloons provide a seal in the esophagus and in the oropharynx. The King LT® is popular in adult out-of-hospital cardiac arrest patients, although it is also available in a comprehensive range of pediatric sizes. However, there are limited clinical data on its use in children. The Combitube device is generally not recommended for pediatric patients.

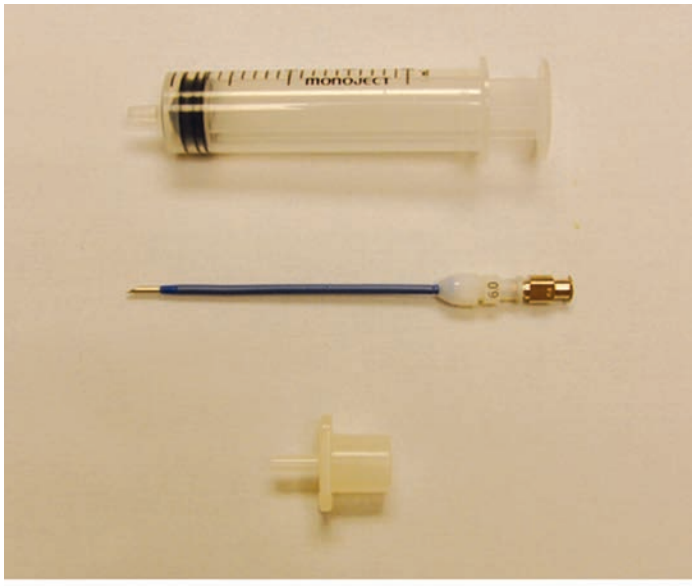
In some cases, the initial attempt to place a supraglottic airway may fail. This is often due to the epiglottis folding over the glottic opening. If this happens, the device will not seal well, and most of the air will leak out through the mouth. To correct this, the device should be removed and replaced with extra attention to patient positioning prior to the next attempt. Providers should use end-tidal carbon dioxide to confirm supraglottic device placement, similar to endotracheal intubation.

INTUBATION THROUGH A SUPRAGLOTTIC AIRWAY

Some supraglottic airways create a conduit that is suitable for the passage of an endotracheal tube or flexible endoscope through their lumen. This allows the provider to attempt to pass an endotracheal tube through a supraglottic airway blindly or with flexible endoscopic guidance with or without the use of an airway exchange catheter. The supraglottic device thus acts as a conduit past the soft tissues to the glottic opening. There are several important limitations of this technique. First, it is a complex multistep process that should be rehearsed prior to implementation in a patient. Next, the internal diameter of the supraglottic airway lumen limits size of the endotracheal tube and endoscope that can be passed. Finally, these procedures potentially expose the patient to longer periods where ventilation is not taking place compared to traditional methods, and thus a patient needs to be able to tolerate periods of apnea or hypopnea.

FLEXIBLE ENDOSCOPIC INTUBATION

Similar to adults, children with difficult airways may be suitable for flexible endoscopic intubation. Experience and practice are needed to



A



B



C

FIGURE 113-9. Technique for needle cricothyrotomy. **A.** Equipment required for a needle cricothyrotomy: a 14-gauge over-the-needle catheter (ideally nonkinking), a 3.0-mm internal diameter endotracheal tube adapter, and a 10-mL syringe. **B.** Placement of catheter into trachea. **C.** Ventilation through the catheter using a 3.0-mm endotracheal tube adapter.

obtain facility with these devices, and the occasion to use them is rare, especially in children, which makes it a challenge to ED application. Furthermore, many instances require an awake, cooperative patient, which is unlikely in the distressed young child, even with good topical anesthesia. Therefore, consultation with experienced subspecialists is often needed. Another aspect of this procedure that is different in children is that the diameter of the endoscope will limit the size of endotracheal tube that is able to be used. Many standard or "adult" size endoscopes will only fit endotracheal tubes that are >5.5 mm in size. Smaller endoscopes are also sold that fit smaller endotracheal tubes, although they may not be available in many EDs. Providers should thoroughly familiarize themselves with the equipment that is available to them prior to clinical use.

SURGICAL AIRWAY

Cricothyrotomy is the final airway solution when traditional laryngoscopy and rescue airways have failed or are impossible and the patient cannot be oxygenated. The most common indication is the "can't intubate, can't ventilate" scenario, which is extremely rare in emergency pediatric airway management. **Open surgical cricothyrotomy is not an option in children <10 years old due to the small cricothyroid membrane. Needle cricothyrotomy is therefore recommended in children <10 years old**. Actual experience in the ED is limited, but success has been described in case reports, animal studies, and the operating room.

The procedure involves placing a large-gauge, over-the-needle catheter through the cricothyroid membrane or upper trachea (**Figure 113-9**). A 14-gauge needle is often described, although in infants and small children, a 16- or 18-gauge needle may be more appropriate. Nonkinking catheters are available for this purpose and are preferred, but a standard over-the-needle catheter scan be used. Jet ventilation, through high-pressure oxygen tubing attached directly to wall-mounted oxygen, is commonly taught and rarely, if ever, performed. Due to its infrequent use, lowering the likelihood of success in a chaotic situation, and the potential for barotrauma, jet ventilation may not be the ideal technique for transtracheal ventilation and should never be used in children <5 years old. Instead, providers can ventilate through the transtracheal catheter with a bag ventilator. Use the adapter from a 3.0-mm internal diameter endotracheal tube to connect a standard catheter to the bag (Figure 113-9C). Alternatively, there are other commercial products suitable for transtracheal ventilation. Transtracheal ventilation is a *temporary* emergency measure to provide oxygenation (albeit with minimal ventilation) until a definitive airway can be achieved. In some scenarios, an emergent tracheostomy may be the only or best airway access. This is typically performed by an otolaryngologist, although in an emergency, it may also be done by others who have been trained in this technique.

NEONATAL AIRWAY CONSIDERATIONS

Conceptually, intubation in neonates is similar to that in infants. The primary difference is that smaller equipment may be needed in premature infants, and the formulas for tube size and depth are different. **Table 113-9** provides recommended equipment sizes for neonatal resuscitation. **If time allows, precut the endotracheal tube proximally at the 13-cm mark at the endotracheal tube adapter site.** This may eliminate the need to do so later, after the newborn has already been intubated. Uncut tubes allow for excessive "dead space" and are also prone to kinking. In contrast to older children, a stylet may not improve success rates of intubation, although existing data come from neonatal

TABLE 113-9 Selection of Intubation Equipment for Neonates

Gestational Age (wk)	Weight (grams)	Tube Size (mm)	Laryngoscope Blade Size	Suction Catheter Size
<28	<1000	2.5	Miller 00–0	5F or 6F
28–34	1000–2000	3.0	Miller 0	6F or 8F
34–38	2000–3000	3.5	Miller 0	8F
>38	>3000	3.5–4.0	Miller 0–1	8F or 10F

intensive care units and may not apply to the ED environment.[48] It is reasonable to use an intubating stylet in order to have consistency in practice across all age groups.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 114

Vascular Access in Infants and Children

Matthew L. Hansen

INTRODUCTION

This chapter presents the indications, advantages, and procedures for vascular access techniques in children: IO, central venous, US-guided peripheral venous, and umbilical venous access in the newborn.

INTRAOSSEOUS (IO) ACCESS

IO access has the advantage of cannulating a noncollapsible structure that connects to the central circulation. IO access is indicated when there is an emergent need for vascular access and other sites are difficult, high risk, or excessively time consuming. Mechanical IO insertion devices have insertion times of only seconds with consistently >90% success rates.[1-8] Insertion devices include simple hand-twist needles, hand-held power drills, and spring-loaded devices.

There are few contraindications to IO placement (**Table 114-1**), and the rate of serious complications from IO insertion is ≤1%. The most common complication is extravasation at the insertion site. By comparison, central venous catheters have complication rates of at least 3.4%.[1,2] Although the indications for IO access are often thought to be limited to unstable patients who need immediate access, IO access is a viable alternative to central venous access in some patients without adequate peripheral access.[9]

MEDICATIONS AND FLUIDS ADMINISTERED BY THE IO ROUTE

Any medication or fluid that can be given through an IV can be administered by the IO route. Paralytics, anticonvulsants, analgesics, benzodiazepines, and vasopressors such as epinephrine have comparable IO and IV infusion rates. Blood and blood products can be given by the IO route.[3] Medications for rapid-sequence intubation can be administered by the IO route, although the time to effect may be delayed.[4] In a study of sheep given IV or IO succinylcholine, the IV route induced respiratory arrest in a mean of 30.8 seconds, whereas the IO route took 57.5 seconds.[5]

The principal limitation of IO access is a relatively low maximum flow rate. Resistance to flow within the bone marrow cavity limits the flow rate of IO needles, and flow rates per kilogram tend to be higher in young patients who have a greater percentage of low-resistance red marrow compared to adults. The speed of administration of IO infusions can be improved with pressure devices.

TABLE 114-1 Contraindications to IO Placement

- Overlying infection
- Exposed bone
- Underlying fracture
- Structural bone disorders (e.g., osteogenesis imperfecta)

TABLE 114-2 IO Laboratory Findings Compared With Phlebotomy

	Equivalent	Use Caution in Interpretation
Hematologic	Hemoglobin	Leukocytes, hematocrit, platelets
Chemistries	Sodium, chloride, glucose, bilirubin, bicarbonate, urea, and creatinine	Potassium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase
Venous gas	pH	Pco_2, Po_2
Transfusion	ABO, Rh typing, and leukocyte activity	—

Abbreviations: Pco_2 = partial pressure of carbon dioxide; Po_2 = partial pressure of oxygen.

LABORATORY TESTING OF BONE MARROW ASPIRATE

The comparison of marrow aspirate with peripheral blood has been explored in small trials of hematology and oncology patients undergoing routine marrow sampling (**Table 114-2**). Two of these human studies have shown a close correlation of marrow aspirate to venous blood in regard to hemoglobin, sodium, chloride, bilirubin, pH, bicarbonate, urea, and creatinine concentrations.[6,7] In another study, bone marrow taken for medical diagnosis correlated with the peripheral blood for ABO, Rh typing, and leukocyte activity.[8] Correlation between bone marrow and peripheral blood is less reliable for leukocytes, platelets, glucose, potassium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, partial pressure of carbon dioxide, and partial pressure of oxygen; however, the degree of discrepancy likely has minimal clinical significance. Aspirates obtained from the marrow after prolonged CPR may be considerably different from serum levels.[9]

IO CANNULATION DEVICES

The two most common manual insertion devices include the Cook® IO needle (Cook Medical, Bloomington, IN) and the Jamshidi® style IO needles. Powered devices are also available for IO needle insertion; two examples are the EZ-IO® (Vidacare Corp., San Antonio, TX) and the Bone Injection Gun (BIG®) (Waismed, Ltd., Hertzliya, Israel). There is one prospective randomized study comparing manual to powered insertion devices in pediatrics in the prehospital setting (22 patients), which compared the Jamshidi needle to the BIG. There were no significant differences in time to insertion, which was less than 1 minute for both devices, or success rate, which was approximately 80% for both devices.[10] In general, powered IO devices in pediatrics are rapid to place with minimal training, modestly faster than manual devices, and felt to be easier to use compared to manual devices. Some of the larger clinical studies have involved the EZ-IO and have demonstrated the efficacy of powered IO access in clinical care.[11,12] Data comparing various powered IO devices have generally come from simulation studies from relatively modest sample sizes, and therefore, it is difficult to draw definitive conclusions about individual products.[4,6,13] Each manufacturer has specific instructions to use each product that should be carefully reviewed and practiced prior to using such a device on a patient.

PLACEMENT AND INSERTION OF IO NEEDLE

Placement Sites (See Videos: Intraosseous Line Placement and Intraosseous Line Placement EZ-IO) The ideal location for IO access is a large bone with easily palpable landmarks, a thin cortex, and limited proximity to vital structures. The proximal or distal tibia, distal femur, and proximal humerus are the sites most commonly described. The flat surface of the anteromedial proximal tibia is easily accessible given the paucity of overlying tissue, making it the most commonly accessed site (**Figure 114-1**). Insert the needle 2 cm inferior (distal) to the tibial tuberosity to avoid the physeal plate in children. When accessing the distal tibia, enter just superior to the medial malleolus, avoiding the saphenous vein (**Figure 114-2**), which is located 2 cm anterior and 2 cm superior to the malleolus. In adults, the distal tibia has thinner cortex than that of the proximal tibia. The anterior distal femur is an alternate site for children when the proximal tibia cannot be used or

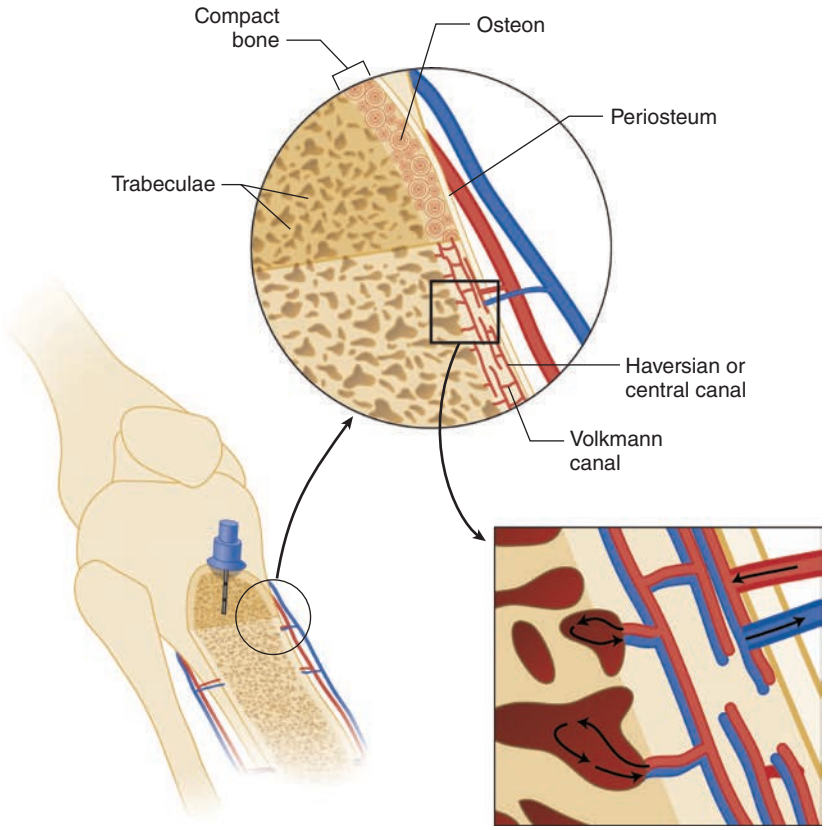


FIGURE 114-1. Anatomy of the proximal tibia for IO placement. [Reproduced with permission from Vidacare Corp., San Antonio, TX. For updates see http://www.vidacare.com/ez-io/index.html.]

has failed (**Figure 114-3**). Insert the needle two fingerbreadths superior (proximal) to the distal end of the femur in the midline.

Steps for Insertion Once the appropriate insertion site has been selected, place the IO needle perpendicular to the bone against the skin. Manual needles are pushed into the bone using steady pressure and slow rotation of the needle back and forth. If using a powered device, follow the specific instructions for that device. Some devices (e.g., EZ-IO) come with multiple needle lengths; in general, the shortest needle is used for young infants, and most children will require an adult size (25 mm). After placing the needle, unscrew the stylet from the needle and attach a 5- or 10-mL Luer-Lok syringe to the IO needle and aspirate. Return of blood or bone marrow confirms placement, but return does not always occur, even when the needle is properly placed. Flush the IO needle with 5 to 10 mL of normal saline, which should flow easily and further confirm placement. If the IO needle has penetrated the posterior cortex or if the tip is not in the medullary cavity for another reason, fluids will extravasate into the soft tissues. This could include spaces posterior to the bone being cannulated, such as the gastrocnemius in a proximal

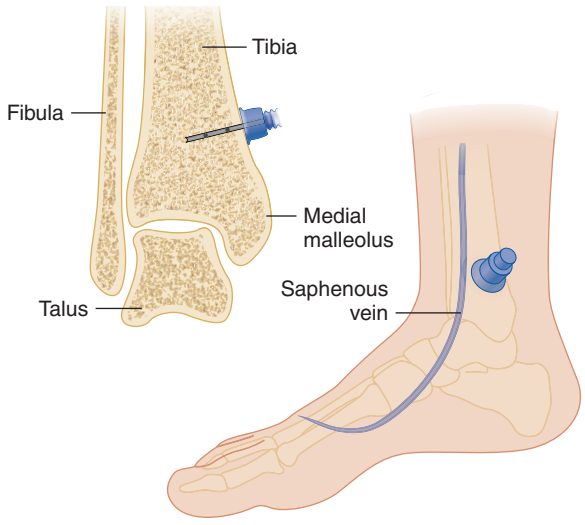


FIGURE 114-2. Anatomy of the distal tibia site for IO placement.

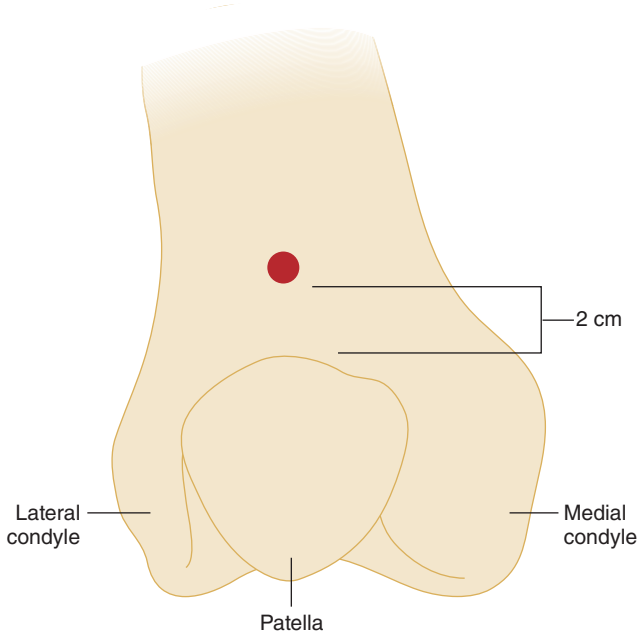


FIGURE 114-3. Distal femur. The distal femur is an alternative site for IO access. The red circle represents the site of insertion of the intraosseous needle. [Reproduced with permission from Hoffman ME, Ma OJ: Intraosseous infusion, in Reichman E, Simon RR (eds): *Emergency Medicine Procedures*. Figure 44-4, http://www.accessemergencymedicine.com/content.aspx?aID=50506.]

tibial attempt. **Palpate the area carefully to ensure that no extravasation is present.** If the needle is misplaced, remove it and select a different bone for subsequent attempts. Frequently, automated gravity-based infusions and even automated pumps may not provide adequate pressure for infusion, and pneumatic pressure bags may be required. Secure the needle with a dressing that stabilizes the needle securely in place to limit the chance of dislodgement, while allowing access to the site to check for extravasation.

COMPLICATIONS OF IO PLACEMENT

The complication rate is low. The most common complication is pain during insertion and infusion. Discomfort during infusion is thought to be due to pressure within the marrow cavity and can be reduced with the administration of lidocaine. The manufacturer of the EZ-IO recommends giving a 0.5 milligram/kg dose of 2% lidocaine without epinephrine (20 to 40 milligrams in adults) followed by a 10-mL normal saline flush after the IO route is established.

In a prospective cohort of 95 patients who had intraosseous IO in the field or in the ED, no complications were noted other than difficulty removing the needle.[11] A retrospective series of 42 patients with IO placement had one serious complication of tibial fracture in a 10-day-old infant.[14] A case series of 58 insertions by a pediatric critical care transport team noted a 12% complication rate, and all complications were minor local tissue edema or infiltration.[15] A population-based study found no serious complications in 281 IO insertions using administrative data.[16] Case reports have described serious complications including compartment syndrome, osteomyelitis, fat embolism, cerebral air embolism, and skin necrosis from extravasation of caustic medications.[16] Soft tissue fluid accumulation may be more likely in the setting of multiple attempts at IO placement in the same bone. As a result, **no more than one attempt per bone is recommended**.[17] Growth plate injuries are possible if not inserted at the proper site.[18] Tibial fracture is a rare complication that is more likely in children with underlying bone disorders. In general, radiographs are not needed after IO removal unless there is suspicion of a complication.

IO REMOVAL

Each device has specific instructions for removal. Generally speaking, a syringe can be attached to the needle to remove it. If the syringe is twisted counterclockwise, it will unscrew from the hub, which can be difficult to grasp. Other needles can be removed with traction and a back-and-forth twisting motion. Remove IO needles as soon as another stable route of vascular access is established.

ULTRASOUND (US)-GUIDED PERIPHERAL VENOUS ACCESS IN INFANTS AND CHILDREN

Peripheral venous access with US guidance is an additional option when blind peripheral attempts fail. Both arm and leg veins can be accessed using either a transverse or longitudinal approach to localize the vein and directly guide cannulation. One randomized trial demonstrated significantly reduced time to peripheral venous access with fewer total attempts when US was used compared to traditional techniques in pediatric patients with difficult IV access.[13] The saphenous vein has also been described as a reliable site for US-guided IV placement. However, a large trial found that neither US guidance nor near-infrared vascular imaging improved first attempt success rate when deployed routinely.[19] Another study showed no improvement in success when using US after one failed IV attempt among practitioners with little experience using US, which suggests that both operator experience and patient characteristics likely play a significant role in success with this technique.[20]

CENTRAL VENOUS ACCESS IN INFANTS AND CHILDREN

Central venous access is safe in all age groups as long as proper techniques are followed. In older children, complications are similar to those encountered in adults. Insertion of central venous catheters >6 French in size in children <1 year old, <10 kg in weight, or <75 cm in height is associated with higher complication rates.[21] Typically, a 5-French catheter is used for term neonates and infants, and a 3-French catheter is used for preterm (<36 weeks) neonates. With the advent of powered osseous access, the importance of central venous access for many pediatric clinical scenarios has decreased. Indications for pediatric central venous access in the ED are listed in **Table 114-3**.

TABLE 114-3 Indications for Pediatric Central Venous Access

- Inability to obtain peripheral access
- Need for invasive hemodynamic monitoring
- Administration of caustic or hypertonic solutions
- Need for long-term vascular access
- Need for transvenous pacemaker placement

Rapid large-volume resuscitation is not always an indication for central access. The rate of flow through a catheter is inversely related to the length of the cannula; thus, central lines have slower flow rates than peripheral catheters of the same diameter. However, large-bore central catheters, which are shorter than common multilumen catheters, allow extremely rapid infusion. The choice of central venous catheter size in children should be predicated on the primary disease and intended use as well as the child's age, weight, and height.

PLACEMENT OF CENTRAL VENOUS CATHETERS

The three most common anatomic locations for obtaining central access in children are the subclavian vein, the internal jugular vein, and the femoral vein (see Chapter 31, "Vascular Access," for descriptions of these procedures). The anatomic landmarks and insertion techniques are the same in adults and children, although key differences are described below. The choice of location depends on patient factors as well as practitioner experience with a particular site. Complications of central venous access are listed in **Table 114-4**. Multiple attempts (more than two) and the subclavian approach are associated with higher complication rates.[17] As in adults, ultrasound guidance improves success and reduces complications in pediatric central line placement and is generally recommended.[19,22,23]

SUBCLAVIAN VEIN

The anatomy of the subclavian vein and technique for line placement are similar in children and adults. The primary disadvantage is a higher rate of mechanical complications of insertion compared to other sites including the relatively high potential for pneumothorax in children given the extension of the lung apices above the clavicles.

Place the child's head in a neutral position, without the use of a shoulder roll, as this maximizes vein diameter.[24] For a detailed explanation of technique, see Chapter 31.

INTERNAL JUGULAR VEIN

The anatomy of the internal jugular vein is similar in adults and children. As in adults, US guidance is recommended in children and likely improves success rates.

TABLE 114-4 Complications of Pediatric Central Venous Access

- Pneumothorax (subclavian and internal jugular vein sites)
- Thoracic duct injury (left-sided internal jugular vein)
- Arterial puncture
- Cardiac tamponade
- Air embolism
- Arrhythmia
- Incorrect position
- Hemothorax (subclavian and internal jugular vein sites)
- Subcutaneous hematoma (subclavian vein cannulation in coagulopathy)
- Neuropathies
- Death
- Infection

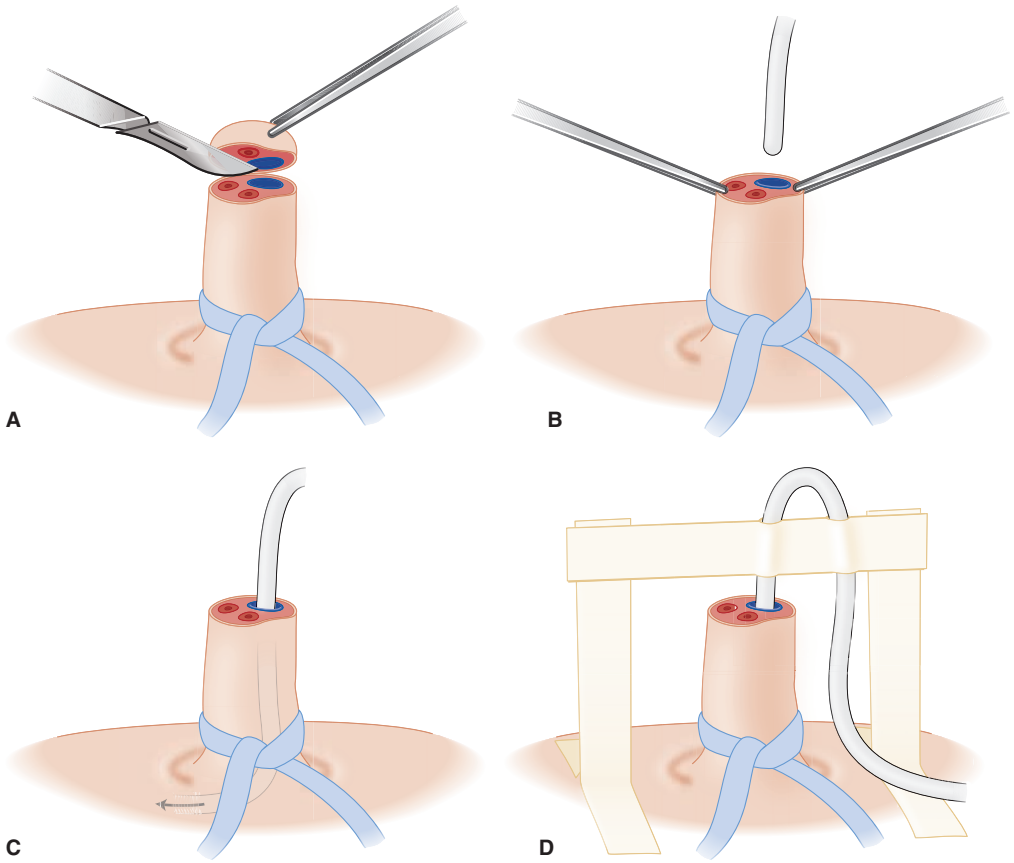


FIGURE 114-4. A through D. Umbilical vein access.

In children, the combination of the Valsalva maneuver, liver compression, and Trendelenburg positioning maximizes the distention of the internal jugular vein. For further discussion, see Chapter 31.

FEMORAL VEIN

The anatomic location of the femoral vein in children is similar to that in adults. In children, as compared to adults, the femoral site may not be associated with higher infection rates and is easier to place in a responsive child, and mechanical complications are less likely to be severe (e.g., pneumothorax and pericardial tamponade).

The femoral artery overlaps the femoral vein at least partially in up to 15% to 20% of children.[25,26] US can be used to optimize the patient's position while improving success rates and reducing complications. For further demonstration of the technique, see Chapter 31.

UMBILICAL VEIN ACCESS

In general, umbilical venous catheterization is limited to the first week of life. The umbilical vein is continuous with the portal vein. An alternative to umbilical access for neonatal resuscitation is IO placement, which may be preferable for those not trained in umbilical access.

UMBILICAL CANNULATION PROCEDURE

Use a 5.0-French catheter for term infants and a 3.5-French catheter for preterm infants. For emergency access, insert the catheter only 4 to 5 cm in depth. Preflush the catheter and attach it to a closed stopcock connected to a syringe. Use standard iodine-based sterile preparation of the umbilicus and sterile drapes. Tie a string loosely around the skin at the base of the umbilicus; this can be tightened in case of bleeding (**Figure 114-4**).

Cut the cord with a scalpel approximately 2 cm from the abdominal wall and identify the vein and two arteries. The vein is larger, thin walled, and usually at the 12 o'clock position. The arteries are smaller with a thicker muscular layer and located roughly at 4 and 8 o'clock. The vein may need to be dilated or thrombus cleared from the lumen with small forceps. Holding the catheter near the tip, insert it into the vein, checking every centimeter for blood return by drawing on the syringe. If resistance is met at the base of the stump, loosen the umbilical tie. In emergency situations, advance the catheter only 1 to 2 cm beyond the point of good blood return; this is typically 4 to 5 cm from the end of the umbilical stump in a term infant. If there is free return of blood, the line can be used. In this technique, the catheter extends only a few centimeters into the abdomen, so radiographic confirmation is not necessary. At that point, tighten the purse string or umbilical tie and tie it off. A suture may be placed through the stump and tied around the catheter, or the catheter can be held in place manually.

COMPLICATIONS OF UMBILICAL VEIN CANNULATION

Umbilical vein cannulation carries serious risks, which are similar to those for standard central venous catheters but also include more serious complications related to deeper insertion than should be performed in emergencies in the ED where the umbilical line is a bridge to other access. Monitor for tachycardia or signs of increasing abdominal distention, which suggests vessel or bowel perforation.[27]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 115

Pain Management and Procedural Sedation for Infants and Children

Samina Ali
Naveen Poonai

INTRODUCTION

Pain is a common reason for an ED visit in children. Even children who do not initially present to the ED in pain often incur pain due to required medical procedures. There is ample evidence that children's pain remains undertreated in the ED.[1-3] Barriers to optimal pain management include failure to use clinical tools for pain assessment,[4] poor documentation of pain,[5,6] inadequate familiarity with pain management options, concerns regarding adverse effects, and perceived time constraints in a busy ED.

Children who receive appropriate pain relief in the ED have significant reductions in distress, improved rapport with the physician, improved intent to comply with discharge instructions,[7] and higher levels of personal and caregiver satisfaction.[8,9] Untreated pain in childhood leads to short- and long-term problems including anxiety, needle phobia,[10] hyperesthesia,[11] and fear of medical care as adults.[12] Effective pain management is a cornerstone of high-quality care, supported by the World Health Organization, the American Academy of Pediatrics, and the Joint Commission on Accreditation of Healthcare Organizations.[13]

The experience of pain and distress in the ED is influenced by the patient (child age, prior experience with health providers, level of distress, developmental level); the illness (presenting complaint, pain severity, required procedures), and provider factors (skill level, ED resources). An appreciation of these elements should be the foundation for planning the approach to pain management. The key tools of analgesia, anxiolysis, and procedural sedation overlap and influence one another. Effective pain management begins at the initial triage assessment and continues with comprehensive discharge instructions (**Figure 115-1**).

This chapter includes best evidence for the assessment of pain in children; physical, psychological, and pharmacologic strategies to manage both pain and distress; and methods for overcoming barriers to providing timely and effective analgesia.

ASSESSMENT OF PAIN AND DISTRESS

The first step in the treatment of pain and distress in children is to quantify the severity of symptoms. The level of pain or distress may be obvious, as with a fracture, or less straightforward, as with abdominal pain or headache. Specific pain scales have been developed for children at different developmental stages and ages (**Table 115-1**). Physiologic parameters, such as heart rate, oxygen saturation, and blood pressure, in

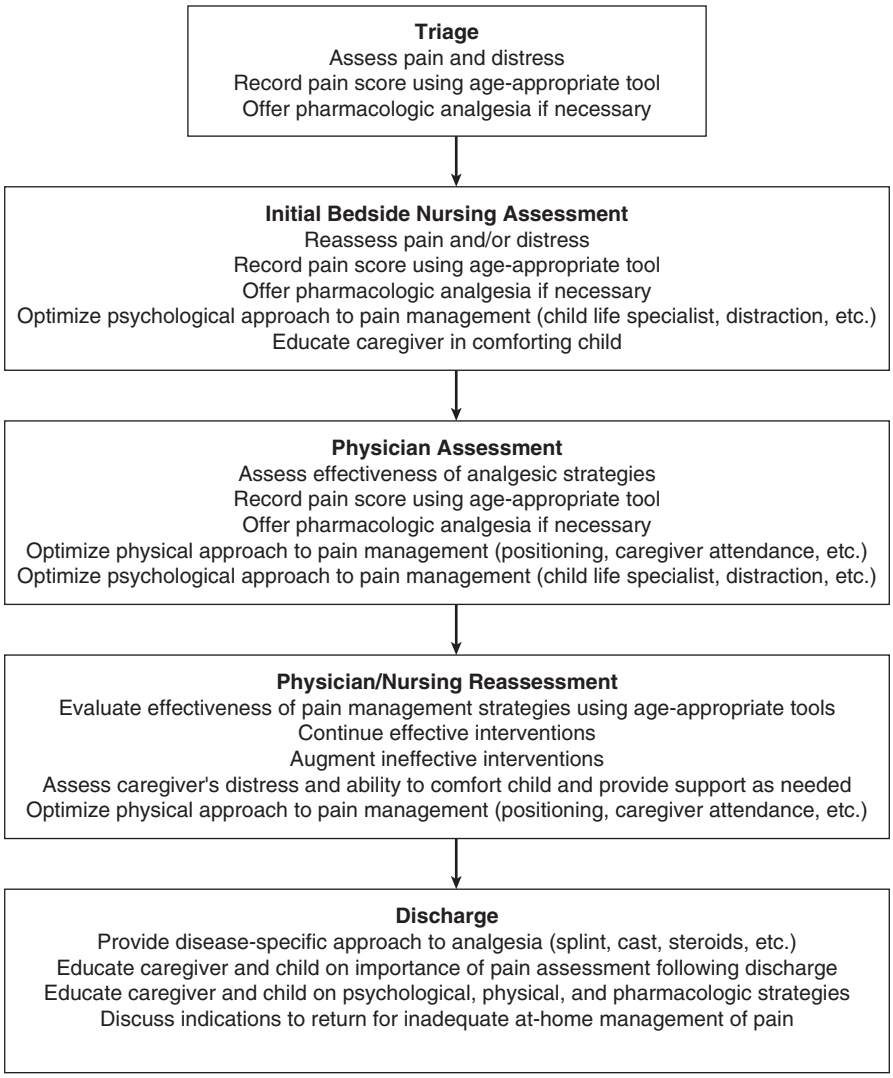


FIGURE 115-1. The continuum of pediatric pain assessment and treatment in the ED.

TABLE 115-1 Assessment of Pain by Age: Currently Recommended Pain Scales

Infants and toddlers (0–3 y)	FLACC© (Face, Legs, Activity, Cry, Consolability) Scale (FLACC) Neonatal Infant Pain Scale (NIPS)
Young children (4–8 y)	Faces Pain Scale–Revised
Older children and youth (6–18 y)	Visual Analog Scale (VAS) Verbal Numeric Scale (VNR)

isolation are inadequate to accurately assessing a child's degree of pain and should not be used as the sole measures of pain intensity.[14]

After initial pain measurement, reassess pain intensity at appropriate intervals. Timing of reassessment is determined by the expected onset and peak of a medication's actions.[15,16] Adopt pharmacologic, physical, and psychological strategies to minimize the impact of procedures and decrease stress.

INFANTS AND TODDLERS <4 YEARS OLD

A variety of observation-based pain scales have been developed for use in infants and young children, as they are unable to self-report and quantify pain. The **FLACC** Scale (Face, Legs, Activity, Cry, Consolability) (**Figure 115-2**) and the Neonatal Infant Pain Scale (**Figure 115-3**) are the currently recommended tools for pain assessment in children <4 years old.[17-19] An individual score of >6 on the FLACC is generally associated with a need for analgesia. For the **Neonatal Infant Pain Scale** (Figure 115-3), scoring is done over a 1-minute interval, and assigned scores can range from 0 (no pain) to 7 (most pain). The Neonatal Infant Pain Scale most accurately detects a change in an individual, but is limited in its ability to consistently describe a child at a single point in time.[20] A Neonatal Infant Pain Scale score >3 is generally associated with a need for analgesia.

SCHOOL-AGED CHILDREN AND YOUTH

Older children are often capable of self-reporting pain, using either a visual or numerical pain scale. Pain scoring varies widely from individual to individual, so trends in pre- and post-treatment pain scores provide the most objective and reliable method for assessing the effectiveness of interventions.

In children 4 to 12 years old, the Faces Pain Scale–Revised (**Figure 115-4**) is the most valid and reliable tool and is recommended especially for children who do not have the ability to serially numerate.[21,22] The Faces Pain Scale–Revised consists of six gender-neutral faces, which are scored from 0 to 10. The scale is easy to explain, quick to use, and requires minimal instruction for the child. It has been translated into >30 different languages and is free to use (https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1519).

For patients 8 to 18 years old, the **Visual Analog Scale** (**Figure 115-5**) can be easily used and requires only a print copy of the tool and a pencil.[23] The Visual Analog Scale consists of a 100-mm line anchored on the left with "no pain" and on the right with "most pain." The child makes a mark on the line to indicate the pain level, and the distance is then measured from the left end point of the scale to the child's mark; this distance, measured in millimeters, represents the child's degree of pain. Minimum score is 0 mm, and maximum score is 100 mm. The Visual Analog Scale is valid and sensitive to changes over time and with analgesic interventions.

The Verbal Numeric Rating Scale can be used in children ages 6 years to adulthood.[24] The Verbal Numeric Rating Scale is a verbally administered scale that rates pain from 0 (no pain) to 10 (worst pain imaginable) and is the most frequently used self-report measure of pain intensity in older children and adults with acute pain.[25,26] Its appeal is due, in part, to the fact that it requires no equipment to administer or score.

SPECIAL NEEDS CHILDREN

Pain assessment and management in children with cognitive impairments pose special challenges. Children with memory, language, or speech deficits or those with an altered level of consciousness may be unable to communicate verbally, which is the main mode by which most pain scales are administered.[27]

One should never assume that children who are differently abled lack the cognitive ability to self-report pain. In cerebral palsy, for example, the extent of physical disability can be incongruent with a child's intellectual capabilities. Whenever possible, use the standard pediatric self-report pain scale that matches the child's developmental age (see previous section). If there are verbal communication difficulties, substitute observation-based assessment.[28,29] Indirect pain measures may introduce bias in the estimation of pain. It is not uncommon for parents of children with mild to moderate cognitive deficits to underestimate their child's pain, whereas the opposite has been reported to occur in those children with severe cognitive deficits.[30]

Face 0 – No particular expression or smile 1 – Occasional grimace or frown, withdrawn, disinterested 2 – Frequent to constant quivering chin, clenched jaw
Legs 0 – Normal position or relaxed 1 – Uneasy, restless, tense 2 – Kicking, or legs drawn up
Activity 0 – Lying quietly, normal position, moves easily 1 – Squirming, shifting back and forth, tense 2 – Arched, rigid, or jerking
Cry 0 – No cry (awake or asleep) 1 – Moans or whimpers; occasional complaint 2 – Crying steadily, screams or sobs, frequent complaints
Consolability 0 – Content, relaxed 1 – Reassured by occasional touching, hugging, or being talked to, distractible 2 – Difficult to console or comfort

FIGURE 115-2. FLACC (Face, Legs, Activity, Cry, Consolability) Scale. [Reproduced with permission from National Institutes of Health (NIH).]

NIPS	0 point	1 point	2 points
Facial expression	Relaxed	Contracted	–
Cry	Absent	Mumbling	Vigorous
Breathing	Relaxed	Different than basal	–
Arms	Relaxed	Flexed/stretched	–
Legs	Relaxed	Flexed/stretched	–
Alertness	Sleeping/calm	Uncomfortable	–

FIGURE 115-3. Neonatal Infant Pain Scale (NIPS).

For children with a cognitive impairment that precludes the ability to self-report pain, there are several tools that have been developed and tested for this specific population, but the revised FLACC (r-FLACC) is the currently recommended tool, and although it is scored in the same manner as the FLACC, it allows comments for individualized child behavior, which can adjust the total score. Caregivers may offer valuable insight or access to unique communication aids (e.g., child-specific sign language or customized tablet software).

ACUTE PAIN TREATMENT

Pain treatment consists of a multimodal approach of physical, psychological, and pharmacologic therapies. Assess initial pain and reassess after interventions. Base initial analgesic medication on pain intensity and escalate as needed. In most instances of mild to moderate pain, use nonopioid medications first, and add opioids as needed (**Table 115-2**). Provision of early analgesia does not affect diagnostic accuracy.

PHYSICAL INTERVENTIONS

Encourage parental presence in almost all circumstances, taking into account family preferences. The parent can provide calm verbal support ("I'm here for you," "I love you"), distraction, companionship, and reassuring touch. If feeding is permitted, breastfeeding can be soothing for younger children; a pacifier can be used if breastfeeding is not possible or allowed due to NPO (nothing by mouth) status. Young infants can be tucked or swaddled with blankets during wait times. For skeletal injuries, use simple techniques such as early immobilization, application of ice or cold packs, and elevation. Cool compresses, dimmed lights, and minimizing noise in the child's room may help with the treatment of headache.

PSYCHOLOGICAL INTERVENTIONS

Acknowledge the child first when entering the patient's room, as this sets the tone and identifies the child as the focus of care. Parents also require some direction as to what to expect, how they can help with positioning and distraction, and how best to support their child. Simple distraction techniques can include bubbles, books, I-spy books/cards, talking with the child, and storytelling. For older children, tablet devices, DVD players, smart phone games, music, videos, and virtual reality are good adjuncts. Many procedures are performed with the child recumbent, so visually engaging artwork on walls or ceilings can provide distraction.

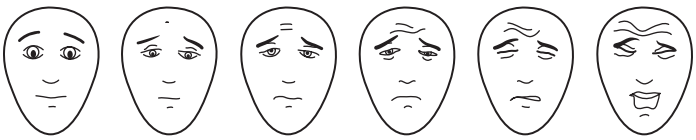


FIGURE 115-4. Faces Pain Scale–Revised (FPS-R). [©2001, International Association for the Study of Pain, www.iasp-pain.org/FPSR.]

PHARMACOLOGIC TREATMENT

Table 115-2 provides oral, intranasal, and parenteral analgesic options and dosing for acute pediatric pain.

ORAL NONOPIOID AGENTS

Oral ibuprofen and acetaminophen are the mainstays of treatment for mild to moderate pain in children. Unless a specific contraindication to one of these exists, they should be used first. **Ibuprofen is especially good for acute musculoskeletal injuries and is more effective than acetaminophen as monotherapy.**[31] Although laboratory studies in tissue culture demonstrate inhibition of osteoblasts by NSAIDs, no human studies have demonstrated clinically significant delay in fracture healing from their use.

When monotherapy with ibuprofen is inadequate or presenting pain is moderate, we suggest combining or alternating therapy with ibuprofen and acetaminophen. Combining ibuprofen with acetaminophen appears to provide similar pain relief to acetaminophen plus opioid and with a significantly better adverse event profile.[32-36]

ORAL OPIOID AGENTS

Oral morphine, oxycodone, and codeine do not appear to confer advantages as monotherapy or in combination with acetaminophen or ibuprofen compared to ibuprofen alone.[31,37-41] **The U.S. Food and Drug Administration and Health Canada advise against the use of codeine in children <12 years old.[42,43] The U.S. Food and Drug Administration has also advised against the use of tramadol in children <12 years old.[44] Health Canada advises against the use of hydrocodone in children <6 years of age.**

INTRANASAL FENTANYL

Intranasal fentanyl is an excellent choice for rapid treatment of moderate to severe pain, especially if IV placement is not otherwise necessary (e.g., clavicular fracture). Intranasal fentanyl provides adequate and rapid analgesia comparable to that of IV morphine.[45,46]

INTRANASAL KETAMINE

Intranasal dosing for subdissociative ketamine is 0.5 to 1 milligram/kg. Similar to intranasal fentanyl, **intranasal ketamine** shares the advantages of early and rapid pain management for children who lack vascular access but is longer lasting (60 minutes for intranasal ketamine vs. 30 minutes for intranasal fentanyl).[47]

FIGURE 115-5. Visual Analog Scale.

TABLE 115-2 Analgesics for Acute ED Pain Management in Children

Route	Class	Agent	Dose	Comments
PO	Nonopioid analgesic	Acetaminophen	15 milligrams/kg	Less effective than ibuprofen; may be combined with ibuprofen
	NSAID	Ibuprofen	10 milligrams/kg	Use singly or in combination with acetaminophen
		Ketorolac	Not applicable	Not approved for children
	Opioid	Morphine	Not recommended	Not better than ibuprofen alone; greater side effects
		Oxycodone		Not better than ibuprofen alone; greater side effects
		Hydrocodone	Not recommended	Contraindicated <6 y old
		Codeine	Not recommended	Contraindicated <12 y old
		Tramadol		Contraindicated <12 y old
Intranasal	Opioid	Fentanyl	1.5–2 micrograms/kg (maximum, 100 milligrams)	Faster and better than IV morphine; duration 30 min
	Other	Ketamine	0.5–1.0 milligram/kg	Analgesic dose (subdissociative); duration 60 min
Parenteral	NSAID	Ketorolac	0.5 milligram/kg (maximum, 30 milligrams)	For use in patients ≥24 mo old
	Opioid	Morphine	0.05–0.1 milligram/kg (maximum, 10 milligrams)	Histamine release/pruritus; seizures in neonates; nausea; hypotension
		Hydromorphone	0.01–0.02 milligram/kg (maximum, 2 milligrams/dose)	Nausea; pruritus
		Fentanyl	1–2 micrograms/kg (maximum, 100 micrograms/dose)	Bradycardia; respiratory depression (outlasts analgesic effect); chest wall rigidity in young infants (increased risk with larger dose, rapid push)
	Other	Ketamine	0.1–0.4 milligram/kg	Analgesic (subdissociative) dose

IV NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

IV ketorolac **is approved by the U.S. Food and Drug Administration for use in children as young as 24 months of age.** Oral ketorolac is *not* more effective than ibuprofen or other NSAIDs, and oral ketorolac is not approved by the U.S. Food and Drug Administration for use in children.

IV SUBDISSOCIATIVE KETAMINE

Ketamine is a noncompetitive *N*-methyl-D-aspartate and glutamate receptor antagonist that provides analgesia by decreasing central sensitization and pain memory.[48] Subdissociative ketamine appears to have the same analgesic efficacy as intranasal fentanyl or IV morphine in early studies for fracture pain in the ED.[47,49,50]

IV OPIOIDS

For children with moderate to severe pain and established vascular access, IV opioids offer a rapid and effective pain management strategy. **Children require more opioids proportionate to their weight than adults**. The specific choice of parenteral opioids is determined by the individual characteristics of the drug, the clinical indication, and the patient's prior experience with opioids.

The initial IV dose of **morphine** is 0.05 to 0.1 milligram/kg (maximum, 10 milligrams per dose) and can be repeated at 10- to 15-minute intervals until adequate analgesia is accomplished. Once an adequate dose is established, it can be redosed every 2 to 4 hours, or more frequently if needed.

Fentanyl is shorter acting, is associated with less histamine release than the nonsynthetic opioids, and has a relatively short duration of action. It can be dosed at 1 to 2 micrograms/kg (maximum, 100 micrograms per dose) for IV use. If fentanyl is given as a rapid IV bolus or in high doses to infants, it can cause "rigid chest phenomenon," which may require emergency reversal with naloxone or neuromuscular blockade. **Hydromorphone** has a much higher potency than morphine and may be useful for ongoing pain in children (e.g., sickle cell pain crisis).

PAIN MANAGEMENT AFTER DISCHARGE

Discharge teaching regarding pain assessment and management at home should be a standard part of emergency care. Without clear guidance, families risk inadequate pain management for the child, slower return to typical activities, and return visits for inadequately treated pain. Ibuprofen is the first-line agent for analgesia at home and can be combined or alternated with acetaminophen. Oral opioids including codeine, morphine, and oxycodone do not appear to offer advantage over ibuprofen alone and are associated with greater risk of side effects.[51,52]

PROCEDURAL PAIN

When painful procedures are unavoidable, use physical, psychological, and pharmacologic interventions to minimize pain. Advise parents to avoid false reassurances, such as "It won't hurt" or "It's over," because one cannot always reliably predict the end of the procedure or the effectiveness of the analgesia that has been provided.

Commonly performed ED procedures, such as IV cannulation, venipuncture, lumbar punctures, and urethral catheterizations, can be associated with significant pain and distress for children.[53,54] Children report needle-related pain as one of the worst things they experience while in hospital.[55] Undertreated pain has short- and long-term negative consequences for children and their families. In addition to causing acute discomfort, inadequate pain management may lead to increased perceived pain during future medical encounters, increased fear of medical procedures, and over- or underuse of future medical care. Thus, addressing the pain and distress associated with common ED procedures for children should be a standard part of practice (**Table 115-3**).

When treating a laceration, when possible, tissue adhesives (e.g., Dermabond®, Glu-Stitch®) are preferred over sutures for all ages, as long as the laceration is not close to the eyes or over an area of tension.[56] If sutures are required, select absorbable sutures for areas of low tension (i.e., not joints) to avoid the retraumatization that some children experience with suture removal.[57]

Children over the developmental age of 4 years generally benefit from simple information regarding what to expect during a medical procedure. They can be told the steps of a procedure, what it might feel like (e.g., cold, wet), and even see what medical supplies will be used. Parents also require preparation regarding what to expect, how they can help with positioning and distraction, and how best to support their child.

TABLE 115-3 Analgesics for Needle-Based Procedures in Children

Route	Agent	Administration/Dose	Comments
PO	Sucrose	2 mL of 24% sucrose PO by syringe	Birth to 12 mo old
Intact skin	4% amethocaine	Cover procedural area and apply occlusive dressing	Onset 30–45 minutes
	4% liposomal lidocaine	Cover procedural area and apply occlusive dressing	Onset 30 minutes
	EMLA® (2.5% prilocaine and 2.5% lidocaine)	Cover procedural area and apply occlusive dressing	Onset 60 min; best relief in 2–3 h
	Needle-free injection (e.g., J-tip®)	Prefilled device	Pressure-driven transdermal lidocaine
Open wounds	LET® (lidocaine 4%, epinephrine 0.1%, tetracaine 0.5%)	0.2 mL/kg Apply half into wound and half around wound edges	Can be applied to end-organ tissues; onset 30–45 min; contraindicated <3 mo of age
Local or regional injection	Lidocaine 1% or 2% with or without epinephrine	Maximum dose, 4 milligrams/kg (without epinephrine)	Warm to room temperature; inject slowly with small-gauge needle; consider buffering with sodium bicarbonate (1:9)
	Bupivacaine 0.25% without epinephrine	Maximum dose, 1.5 milligrams/kg	Slower onset, longer duration than lidocaine; may be mixed with lidocaine for local or regional infiltration

ORAL SUCROSE FOR INFANTS

Oral sucrose is thought to work by activating endogenous opioids through taste receptors.[58] It reduces heart rate and time crying. It works best for infants <1 month of age, including premature babies, and up to 12 months of age. Give orally by a syringe (2 mL of a 24% sucrose solution or dilute dextrose 50% in water with equal parts of sterile water to make dextrose 25% in water) starting 2 minutes prior to the painful procedure. Sucrose solution comes in a variety of commercially available formulations (e.g., Sweet-Ease®, Toot-Sweet®).

TOPICAL ANESTHETICS FOR INTACT SKIN

Two commercially available fast-acting products are **Ametop® (4% amethocaine)** and **LMX® (4% liposomal lidocaine).** Both are fat-soluble creams that anesthetize the skin. Such agents are liposomal encapsulated, which prevents entry into the circulation and acts as epidermal depots for prolonged drug release. The time to maximal effect is 30 minutes, and effect persists for about 30 minutes after cream removal. We recommend fast-acting topical anesthetic creams over EMLA® (eutectic mixture of 2.5% prilocaine and 2.5% lidocaine).[59-61] Nurse-initiated protocols can help avoid any time delays for vascular access.

Another option for topical anesthesia prior to procedures such as venipuncture and lumbar puncture is the use of a **needle-free injection system**. The major advantage is that it is nearly instantaneous.[62-64] Needle-free injection systems deliver lidocaine into the dermis using a self-contained high-pressure delivery system such as a carbon dioxide gas cartridge. The J-tip® (National Medical Products, Irvine, CA) is currently the most widely used needle-free injection system for local anesthesia.[65]

TOPICAL ANESTHETICS FOR OPEN WOUNDS

LET® (lidocaine 4%, epinephrine 0.1%, and tetracaine 0.5%) is a topical anesthetic mixture, often available in gel form, for open wounds and is safe and effective for almost all laceration repairs in children. Consider use before wound cleaning and exam, prior to suturing, and also for tissue adhesive application.[66] It can be applied to fingers, toes, lips, and other end-organ tissues despite the vasoconstrictive effects of the epinephrine.

LET® is most effective for wounds that are not deeper than the subcutaneous tissues. When using LET, apply half into the wound and half on a saturated piece of sterile cotton (rather than gauze) at a maximum dose of 0.2 mL/kg. Then cover with an occlusive dressing (e.g., Tegaderm®). The adequacy of anesthesia from LET is highly dependent on proper application technique. Leave LET in place for at least 30 to 45 minutes for satisfactory wound anesthesia, with longer times (up to 45 minutes or more) generally leading to more complete anesthesia. Blanching of the skin from the vasoconstriction effects of epinephrine is a good sign that topical anesthesia has been achieved. **LET is contraindicated in patients <3 months old and over inner mucosal surfaces.**

LOCAL ANESTHETIC INJECTION

For anesthesia into deeper tissues, inject **lidocaine**. Slow injection with a small-gauge needle (e.g., 27 or 30 gauge) decreases discomfort. The addition of 1 mL of 8.4% sodium bicarbonate to 9 mL of 1% or 2% lidocaine buffers the acidity of the lidocaine and further reduces the pain of injection. Sodium bicarbonate must be added immediately before use or precipitation of the solution may result. Warming the injectable lidocaine to room temperature by rubbing the vial between your hands prior to drawing up the medication can help decrease the sting associated with lidocaine infiltration.

The maximum dose of injected lidocaine without epinephrine is 4 milligrams/kg. When possible, consider regional nerve blocks (see Chapter 36, "Local and Regional Anesthesia"). The onset of action of **bupivacaine** is slightly longer than that of lidocaine, but it provides much longer lasting anesthesia. Combining bupivacaine with lidocaine can provide longer lasting, effective local anesthesia both during a procedure and afterward. **Make sure the doses for injection are carefully calculated.**

ANXIOLYSIS FOR MINOR PROCEDURES

In the ED, midazolam is almost universally preferred over other agents in this class because of its rapid onset and short duration of action. **Benzodiazepines are not analgesic and should be combined with analgesics if a procedure is painful**. Midazolam can cause paradoxical agitation, particularly at lower doses, and can cause respiratory depression and hypotension in high doses, particularly in hypovolemic patients. Fentanyl can also be given by the intranasal route for anxiolysis (**Table 115-4**).

The main advantage of intranasal administration is a more rapid onset of action than the oral route, higher blood levels (by avoiding first-pass effects of the GI system), and no need for IV placement. High-concentration solutions must be used because the maximum volume that can be delivered to each nostril is limited to approximately 0.3 to 0.5 mL at a time. Because the medication particles must be within a specific size range (approximately 10 to 50 microns) to be absorbed by the nasal mucosa, commercially available (and relatively inexpensive) mucosal atomizer devices are recommended for intranasal delivery of these medications.

Nitrous oxide has anxiolytic properties in addition to amnestic and analgesic effects and is an alternative to midazolam for children with needle phobia or procedural anxiety (discussed further below under "Procedural Sedation" and in Table 115-4).

TABLE 115-4 Medications for Pediatric Anxiolysis in the ED

Drug	Concentration	Route	Dose	Onset	Duration	Side Effects/Warnings
Midazolam	5 milligrams/mL	Oral Intranasal IV	0.5 milligram/kg 0.3–0.5 milligram/kg; maximum, 10 milligrams/dose 0.05–0.1 milligram/kg	30 min 5–15 min	0.5–2 h 0.5–2 h	Excitation/paradoxical reaction Somnolence Nasal irritation Bitter taste
Nitrous Oxide	1. 50% N_2O + 50% O_2 fixed mixture (Entonox®) 2. Titratable blend of N_2O and O_2 to a maximum of 70% N_2O	Inhaled (self-administered through mouthpiece or facemask or nasal hood)	Maximum concentration N_2O of 70% (minimum O_2 concentration 30%)	30 seconds (peak effect 3–5 minutes)	Effects decrease 70% within 3 minutes of discontinuation	Nausea Dysphoria Contraindicated with bowel obstruction, pneumothorax, increased intracranial pressure Teratogenic

PROCEDURAL SEDATION

ASSESSING THE PATIENT: THE PRESEDATION CHECKLIST

Once the need to perform procedural sedation has been identified, perform a thorough medical evaluation to mitigate the risk of adverse events during and after sedation. Specific situations that may commonly arise include emergence agitation in children with active psychosis following ketamine sedation; laryngospasm in children with asthma and concomitant upper respiratory tract infection; cervical spine instability in children with trisomy 21; and difficult airway visualization in children with Pierre Robin sequence. The following represents a comprehensive checklist incorporating recommendations from the American College of Emergency Physicians Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department[67] and the American Academy of Pediatrics Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures[68]:

1. Physical status evaluation based on the American Society of Anesthesiologists (ASA) classification system (see Table 37-4, American Society of Anesthesiologists Classification System, in Chapter 37, "Procedural Sedation Analgesia in Adults"). **In general, procedural sedation and analgesia for children in the ED should be limited to American Society of Anesthesiologists class I or II.** For children in American Society of Anesthesiologists class III or IV or with anatomic airway or cervical spine anomalies, consult with the appropriate subspecialist(s) or anesthethiologist.[68]
2. Obtain informed consent according to jurisdiction and institutional requirements.
3. Obtain a comprehensive health evaluation to document baseline status and determine if there are specific health conditions that require additional consultation or considerations in terms of drug selection or dosing. This includes age, sex, weight, allergies, current medications, and relevant personal or family comorbidities (renal, cardiac, or pulmonary conditions; seizures; neuromuscular diseases; congenital anomalies; obstructive sleep apnea; loose teeth; cervical spine anomalies; pregnancy; prematurity; previous sedation or anesthesia with specific inquiries regarding drug hypersensitivity; personal and family history of malignant hyperthermia; pseudocholinesterase deficiency; and complications).
4. Consider NPO status in the context of the urgency of the procedure and other risk factors that may increase the risk for vomiting and aspiration (see later in this chapter).
5. Assess the airway patency using the Mallampati grading scale to predict the technical ease of endotracheal intubation (see Figure 29A-5 in Chapter 29A, "Tracheal Intubation"), and assess tonsillar hypertrophy, mouth opening, lingual anomalies, mandibular anomalies, vital signs (heart rate, blood pressure, temperature, respiratory rate, oxygen saturation), and cervical spine mobility.
6. Ensure equipment is available, functional, and appropriately sized for the child using the acronym **SOAPME: S**uction (appropriate suction catheter and apparatus); **O**xygen (supply is adequate and flowing); **A**irway equipment (bag-valve mask, laryngeal mask airway, oral and nasal airways, laryngoscope handle and blades); **P**harmacologic agents (dissociative, anxiolytic, analgesic, and reversal agents) and **P**ersonnel as required by the institution (respiratory therapist, bedside nurse, etc.); **M**onitors (pulse oximeter, end-tidal carbon dioxide, noninvasive blood pressure, ECG leads); special **E**quipment (medicines or equipment for specific cases).[68]

NPO STATUS

It is now widely held that there exists no correlation between fasting status and the risk of aspiration.[69] The Pediatric Sedation Research Consortium documented only a single aspiration event in 30,037 children who underwent procedural sedation outside the operating room, and the event occurred in a child who fasted for >8 hours.[70] Current recommendations by the American College of Emergency Physicians Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department indicate that procedural sedation should not be delayed based on fasting time (Level B recommendations).[67] Although vomiting or aspiration during procedural sedation performed in the ED is rare,[71] other societal guidelines outside emergency medicine recommend a 2-hour fast for clear liquids, 4 hours for breast milk, and 6 hours for solid food. Nonemergency guidelines are based on data from the anesthesia literature, in which the risk of aspiration is likely increased by endotracheal intubation and extubation, as well as greater depth of sedation.[72]

MONITORING DURING SEDATION

Children should be monitored by qualified personnel for the entire duration of sedation until baseline presedation mental status has been attained. Unlike adults, children are at risk of unintentionally moving from the desired level of sedation to a deeper level of sedation,[73] and personnel with sufficient airway management skills should be in attendance. American Academy of Pediatrics clinical policy states that the individual should be certified in Pediatric Advanced Life Support and be skilled in "the ability to rescue a child with apnea, laryngospasm, and/or airway obstruction including the ability to open the airway, suction secretions, provide CPAP [continuous positive airway pressure], and perform successful bag-valve-mask ventilation."[68] The number and type of personnel mandated to be present during procedural sedation in children are institution specific. Ideally, two healthcare personnel should be present: a physician, respiratory therapist, or their designee performing the sedation, and a physician or their designee performing the procedure. The American College of Emergency Physicians clinical policy states that a nurse or other "qualified individual" should continuously monitor the patient along with the "provider performing the procedure" (Level C recommendation).[67] However, the literature does not provide clear guidance on the number and type of personnel needed in a busy ED with time and staffing constraints and where two simultaneous providers are present

or possible. In fact, several lines of evidence suggest that the frequency of serious complications (apnea, airway obstruction, hypotension, hypoxia) is similar whether one physician performed both the sedation and procedure or the tasks were divided among two physicians.[74,75]

In addition to clinical assessment, monitor vital signs including heart rate, respiratory rate, blood pressure, oxygen saturation using a pulse oximeter, ECG recording, and capnography. The use of prophylactic supplemental oxygen is currently recommended for sedation with propofol and optional for other agents.

POSTSEDATION MONITORING AND RECOVERY

After the procedure, monitor in the ED until recovery is complete and the child has resumed the presedation level of consciousness. Monitoring should include obtaining vital signs at regular intervals (every 5 minutes while sedated and less frequently once awake) and continuous display of heart rate and oxygen saturation if not fully alert.[68] Immediately following the procedure, with the cessation of painful stimuli, the patient may still be under the effect of the dissociative or sedative agent. Consequently, there is an increased risk of respiratory depression during this time. For this reason, patients should be monitored in a recovery area that is equipped with a suction device, the ability to deliver >90% oxygen, positive-pressure ventilation using a bag-valve mask, and rescue equipment for airway and ventilatory support.[68] If sedation was performed using ketamine, even with the preadministration of ondansetron, nausea and vomiting may occur and should be anticipated. Patients should be allowed to recover in a quiet environment with minimal visual and auditory stimuli, and caregivers should be encouraged to be at the bedside. Discharge criteria include the following: vital signs within normal age-related parameters, including blood pressure and pulse oximetry; return to presedation level of consciousness (if sleeping, the patient should be easily arousable); ability to sit unaided (within the context of developmental capabilities); and ability to tolerate oral fluids (protect airway). Parents should also be seated with the child whenever possible in the back seat of a vehicle after discharge.

Parents should review and understand written postsedation discharge instructions, which advise them to closely observe their child for abnormal somnolence and to restrict activities that require coordination until all medication effects have worn off. Parents should also be warned that delayed sequelae of sedation, including vivid dreams, sleep disturbance, and behavioral dysregulation, may occur up to 24 hours after sedation. Advise parents to protect the child from falls due to incoordination for several hours after discharge. Again, whenever possible, for the child who has received sedation, parents should accompany the child in the back seat of the vehicle after discharge.

SELECTING AGENTS FOR SEDATION

Benzodiazepines, ketamine alone, ketamine with propofol, etomidate, propofol, and nitrous oxide are all well-studied agents for procedural sedation and analgesia in children.[71] Dosing regimens for each can be found in **Table 115-5**.

Although several agents can be used to effectively facilitate procedural sedation, the choice of agent(s) and the dose should be determined, at least in part, by the goals of sedation. For nonpainful procedures, the goal is often anxiolysis alone, and benzodiazepines in combination with psychological and physical approaches may be effective in some patients. For minor painful procedures such as laceration repair, the goal is both anxiolysis and moderate analgesia. Intranasal fentanyl or dexmedetomidine, subdissociative dose ketamine, and nitrous oxide are all viable options. For major painful procedures such as orthopedic reduction, the goal is dissociative sedation with amnesia and analgesia. Importantly, procedural sedation may not be necessary in a cooperative patient and a clinician skilled in regional anesthesia.

KETAMINE

Ketamine produces a dissociative sedation characterized by a rapid-onset and potent dissociation, amnesia, and analgesia, while preserving pharyngeal-laryngeal reflexes, respiratory drive, cardiopulmonary stability, and skeletal muscle tone.[71,76] Adequate sedation for a 20- to 30-minute procedure can be achieved with a single IV loading dose, and the drug is safe in children as young as 3 months of age.[77] These properties make it an ideal agent for painful procedures such as fracture reduction and abscess drainage. Preprocedural use of ondansetron can reduce the incidence of vomiting in children,[71,78] but there may be less benefit in children under 5 years of age and adolescents[77] because the baseline risk of vomiting with ketamine is lower in these age groups. Ketamine does exhibit a dose-response relationship with respect to adverse effects. Although higher doses are not associated with an increased risk of serious adverse events or interventions in response to serious adverse events, higher doses are associated with a greater risk of oxygen desaturation and vomiting.[71] Recovery agitation is also common following sedation with ketamine and is not believed to be age related.[77] Unlike in adults,[79,80] pediatric-specific studies have reported that coadministration of midazolam does not reduce the risk of emergence agitation.[77] Benzodiazepines such as midazolam should be reserved for reducing preprocedural anxiety and treatment of emergence agitation.

A subdissociative dose of ketamine (0.3 milligram/kg IV) has analgesic and amnestic effects despite the lack of a dissociative state. Subdissociative doses are not sufficient for more painful procedures such as fracture reduction and have a greater risk of recovery agitation.[77] Ketamine's anesthetic effects manifest at a dosing threshold of approximately 1.0 to 1.5 milligrams/kg IV, and additional doses do not produce enhanced sedation or hemodynamic compromise.[81] The only value of additional ketamine is to prolong the dissociative state for extended procedures.[82] Ketamine may also be administered IM at a dose of 4 to 5 milligrams/kg. However, IM administration is painful, is unpredictable in response, may cause more vomiting, and has a prolonged recovery time compared with the IV route and should therefore be reserved for children in whom IV access is difficult.[76] Opioids are commonly given to children before procedural sedation with ketamine (e.g., prior to imaging), and preprocedural analgesia is important. However, recent evidence demonstrates that preprocedural opioids increase the risk of all adverse events except serious adverse events, regardless of the medication used for sedation.[71]

The combination regimen of ketamine and propofol ("ketofol") has a shorter sedation time (3 minutes)[83] and fewer concomitant analgesic requirements.[84] As a result, this combination has gained popularity over the past decade. However, experts have yet to support the regular use of ketofol because objective benefits have not been demonstrated.[85] In fact, **for procedural sedation in children, there is stronger evidence for the safe administration of ketamine or propofol as sole agents** (Level A recommendation) than for a combination of ketamine and propofol (Level B recommendation).[67] Moreover, a recent multicenter Canadian surveillance study of >6000 children found that the use of ketamine alone was associated with the lowest risk of a serious adverse event or needed intervention. The combinations of ketamine with propofol and ketamine with fentanyl had the highest risks of oxygen desaturation and the need for significant interventions in response to a serious adverse event.[71]

Due to ketamine's tendency to enhance rather than depress airway reflexes, an important consideration surrounding its use in the ED is the risk of **laryngospasm.** In children, the risk of laryngospasm is uncommon (0.3%), and this complication often quickly responds to assisted ventilation and oxygen, without the use of therapeutic agents.[86] Case reports and anecdotal evidence highlight the risk of airway obstruction, laryngospasm, and apnea in infants younger than 3 months, likely due more to age-specific vulnerability of the young infant's airway anatomy and reactivity. **As a result, age <3 months is a notable absolute contraindication to the use of ketamine**.[82] Other groups that may be at increased risk of laryngospasm include children with asthma or concomitant upper respiratory tract infection. However, guidelines do not support withholding ketamine in these situations.[82] Another absolute contraindication is schizophrenia due to a risk of exacerbating psychosis.[82]

MIDAZOLAM

Midazolam is the most commonly used benzodiazepine for procedural sedation or anxiolysis in children.[76] However, there is no high-quality

TABLE 115-5 Medications for Procedural Sedation

Class	Drug	Route	Dose	Onset	Duration	Advantages	Disadvantages	Examples	Comments
Nonpainful Procedures									
Anxiolytic	Midazolam	PO, PR, IV, IM, IN	PO/PR 0.5 milligram/kg IV/IM 0.05–0.1 milligram/kg IN 0.3–0.5 milligram/kg	PO/PR 20–30 min IV 3–5 min IM 10–20 min IN 5–10 min	1–4 h	Flexible route of administration	No analgesia, paradoxical reaction	CT scan; ultrasound; echocardiography	Acidic, nasal administration stings, may cause increased secretions; oral/rectal slow onset, less predictable
Sedative	Pentobarbital	PO	3–5 milligrams/kg	30 min	Variable	Relatively safe in oral doses	No analgesia	CT scan	Variable efficacy; long recovery times
Minor Painful Procedures									
Dissociative	Nitrous oxide	Inhaled	Titrate to effect (30%–70%)	Minutes	Minutes	Self-dosing	Not readily available	Laceration repair; LP; dental procedures	Scavenger system recommended
Analgesic	Fentanyl	IN	1.5 micrograms/kg (maximum, 0.5 mL per nare)	10 min	20 min	Little to no adverse effects	Short lived	Laceration repair; suspected clavicle fracture	Equivalent to IV morphine
Analgesic and mild sedative	Subdissociative dose ketamine	IV/IN	0.3 milligram/kg IV 1 milligram/kg IN	Variable	60 min	Few adverse effects		Laceration repair; abscess drainage	Paucity of pediatric data
Hypnotic/sedative	Dexmedetomidine	IN	0.5–2 micrograms/kg	25 min	85 min	No respiratory/hemodynamic compromise	Long time to onset	Laceration repair; LP; abscess drainage	Paucity of data for ED procedures
Major Painful Procedures									
Hypnotic/sedative	Propofol	IV	1–2 milligrams/kg, followed by 0.5 milligram/kg; repeat doses as needed	Seconds	Minutes	Rapid onset and short duration, motionlessness, muscle relaxant	No analgesia, respiratory and cardiovascular depressant	CT scan, LP with topical analgesic, laceration repair, reduction of dislocation	Nonanalgesic, increased requirement for younger patients, painful injection
	Etomidate	IV	0.2–0.3 milligram/kg	Seconds	Minutes	Rapid onset, short duration	No analgesia, myoclonus, respiratory depressant	CT scan, short procedures requiring motionlessness	Avoid in patients with increased tone (e.g., CP) due to myoclonic jerks, painful injection
Dissociative	Ketamine	IV, IM	IV 1–1.5 milligrams/kg IM 4–5 milligrams/kg	IV 1–2 min IM 3–5 min	IV 15 min IM 30–45 min	Analgesic, anesthetic, motionlessness, respiratory and cardiovascular stimulant, bronchodilator	Increased intraocular pressure, intracranial pressure, salivation; emetogenic; laryngospasm	Painful procedures requiring motionlessness (complex lacerations, fracture reductions, I&D), no reversal agent	Consider pretreatment with ondansetron; atropine and midazolam coadministration unnecessary
	Propofol + ketamine	IV	Propofol 1 milligram/kg, ketamine 0.5 milligram/kg	1 min	Propofol (minutes); ketamine 15–45 min	Decreased dosing for both agents, complementary side effects (lessens respiratory and cardiovascular depression, emesis)	Increased risk of serious adverse events such as oxygen desaturation (compared to ketamine alone)	Fracture reduction, I&D, complex laceration	Recent evidence suggests coadministration is associated with greater risk of adverse events

Abbreviations: CP = cerebral palsy; I&D = incision and drainage; IN = intranasally.

evidence to support the use of midazolam as monotherapy for sedation,[87] and midazolam alone does not provide "reliable sedation for procedures."[76] The combination of midazolam with other agents (fentanyl, nitrous oxide, propofol, and ketamine) has been reported to be associated with apnea, laryngospasm, bradycardia, and hypotension.[88,89] The combination of midazolam and fentanyl was common prior to the routine use of ketamine and propofol. However, midazolam and fentanyl provide less predictable sedation and analgesia and require careful titration (as opposed to ketamine alone).

NITROUS OXIDE

Inhaled nitrous oxide is a mild dissociative anesthetic gas that produces anxiolysis, sedation, and analgesia. It is useful for minor procedures such as IV placement and port-a-cath access. For laceration repair, nitrous oxide can be combined with topical LET® and/or injected local anesthetics. It is commonly administered in a 30% to 50% concentration mixture with oxygen using a flow rate of 5 to 6 L/min.[90] The flow of gas can be initiated with 100% oxygen with nitrous oxide added in 10% increments, titrated to effect.[90] The maximal effect generally occurs within 60 seconds at nitrous oxide concentrations >30%, and the effects dissipate quickly upon discontinuation. Once nitrous oxide flow is terminated, 100% oxygen should be delivered for 3 to 5 minutes to prevent diffusion hypoxemia.[90]

Nitrous oxide does not typically impair hemodynamics, respiratory drive, or protective airway reflexes. Minor adverse effects including nausea, vomiting, dizziness, and voice change have been reported but are uncommon.[76] Hypoxemia is rare, likely because nitrous oxide is administered in combination with oxygen. For minor painful procedures in cooperative children, it has been found to be "both safe and effective" for procedural sedation.[76] However, nitrous oxide does not reliably produce effective sedation for more painful procedures such as fracture reduction, limiting its utility as a single agent in the ED. As a result, it must often be combined with other agents such as opioids for efficacy. The major disadvantage of nitrous oxide is that it requires patient cooperation, limiting its utility children who are not able to reliably follow instructions. In willing patients, it can be administered using a self-administered demand valve, which can theoretically limit the degree of sedation, but in children too young to follow instructions, it must be given by a continuous flow device. In both cases, a gas-scavenging system is recommended to prevent inhalation by healthcare personnel.[90]

PROPOFOL

Propofol is attractive for use in children because of its ultra-short duration of action (shorter than ketamine) and its mildly antiemetic properties. Effective sedation can also be achieved with a single loading dose. **Propofol provides no analgesia when used alone,** so parenteral, local, or regional analgesics/anesthetics must be coadministered with propofol. Propofol may also cause pain at the injection site. Pain may be reduced by delivery through a large vein and immediate preadministration of a small amount of lidocaine at the injection site.[91] Propofol's sedation efficacy following a single IV bolus of 1 to 2 milligrams/kg and short duration of action make it attractive for short, painless procedures such as CT scans. However, it is necessary to directly monitor patients and intervene when necessary, because recent reports have highlighted that although adverse effects are uncommon overall, when compared to ketamine and other sedative agents, propofol alone is associated with the greatest risk of serious adverse events (apnea, hypotension, laryngospasm, bradycardia).[71] Although propofol alone and in combination with fentanyl is associated with an increased risk of serious adverse events, the events were short lived and resolved with minor interventions.[71,92] Propofol-induced hypotension results from a combination of vasodilation and direct cardiac effects and may be exacerbated in hypovolemic patients. **Propofol is contraindicated in children with mitochondrial disorders.**[93]

ETOMIDATE

Etomidate is thought to work at the γ-aminobutyric acid receptor to produce hypnosis without analgesia. Most emergency physicians are familiar with etomidate for its use as a sedative during rapid-sequence intubation. When administered for intubation (0.3 to 0.6 milligram/kg), etomidate provides brief deep sedation with minimal cardiovascular effects, minimal respiratory depression, and maintained or increased cerebral perfusion. Sedative dosing (0.1 to 0.4 milligram/kg) is off-label. Importantly, etomidate is similar to propofol in that the protective airway reflexes may be briefly reduced or lost and the provider must be prepared to manage the airway. As such, other sedative agents such as ketamine may be preferable to etomidate.

BARBITURATES

Barbiturates are useful medications for painless procedures that require a motionless child, such as diagnostic imaging. Although they do not possess analgesic properties, IV pentobarbital and IV methohexital have been used for many years for sedation during radiologic procedures and are particularly useful for imaging in the setting of potential intracranial hypertension.[94,95] The main drawbacks to these agents (hypotension, respiratory depression, and long recovery times) make other sedative agents a safer choice. An advantage of pentobarbital is that it can be administered orally at a dose of 5 milligrams/kg. Oral administration of pentobarbital is theoretically safer than IV administration, but onset of sedation and recovery time can be prolonged with the oral route.

DEXMEDETOMIDINE

Dexmedetomidine is an α_2-agonist that is chemically related to clonidine.[96] It provides both analgesic and sedative effects.[97] Dexmedetomidine can be administered via buccal, IV, intranasal, and PO routes, with the latter having the lowest bioavailability. A number of studies support the use of dexmedetomidine for premedication in children undergoing anesthetic induction, demonstrating superior sedative effects to oral benzodiazepines without respiratory depression or airway compromise.[97] The median time to and duration of sedation following an intranasal dose of 1 microgram/kg is 25 and 85 minutes, respectively,[98] with 2 micrograms/kg producing a shorter onset of sedation.[99] At this time, relatively few studies have been performed involving dexmedetomidine for painful procedures.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 116

Neonatal Emergencies and Common Neonatal Problems

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INTRODUCTION AND EPIDEMIOLOGY

Neonates, defined as infants ≤1 month old, or preterm infants within 30 days of their term due date, often visit EDs with vague and nonspecific symptoms and signs that may not point to a specific diagnosis. For example, respiratory distress can be caused by pulmonary or cardiac disease, generalized sepsis, abdominal pathology, or metabolic disorders. Many visits occur because of caregiver concerns about normal variants of newborn vegetative functions. Such concerns must be distinguished from potentially life-threatening congenital and acquired conditions that can present in the first month of life. This chapter reviews normal neonatal vegetative patterns, life-threatening neonatal emergencies, and common neonatal problems.

NORMAL NEONATAL VEGETATIVE FUNCTIONS

FEEDING PATTERNS

In the first few weeks of life, expect variation in times between feedings, but by the end of the first month, the vast majority of newborns establish a regular feeding schedule. Most healthy, bottle-fed infants eat 2 to 4 ounces (60–120 mL) every 2 to 4 hours, or six to nine feedings in 24 hours by the end of the first week of life; breastfed infants prefer shorter intervals—feeding every 1 to 3 hours. Intake is adequate if the neonate gains weight appropriately and appears content between feedings. Feedings are progressing well if the infant is no longer losing weight by 5 to 7 days of age and is gaining weight by 10 to 14 days of age.

WEIGHT GAIN

Weigh neonates completely undressed. Normal newborns may lose up to 12% of their birth weight during the first 3 to 7 days of life, with earlier and slightly more accentuated weight loss in exclusively breastfed newborns. A weight loss of up to 10% is acceptable if the infant's examination, stooling, and voiding frequency and behavior are normal. On average, infants gain between 20 and 30 grams per day in the first 3 months of life and between 15 and 20 grams per day for the next several months.

STOOL PATTERNS

The number, color, and consistency of bowel movements can vary greatly in the same infant and between infants, regardless of diet or environment. The median daily stools vary between types of nutrition (breast milk, formula, or mixed), ranging from 1 to 4.[1] Stooling once a week or eight times per day may be normal if the clinical history and physical examination are also normal. Increased stools may be a result of excessive intake, concentrated or high sugar formula, maternal use of laxatives, malabsorption/enteropathy, or infection. Infrequent stooling may be normal (especially if breastfed) or may be a sign of constipation. **Failure to pass meconium in the first 48 hours of life may suggest Hirschsprung's disease or cystic fibrosis.** Stool color has no significance unless it is acholic or bloody. The first stool, which consists of meconium, is usually passed within the first 24 hours after birth and is thick, sticky, and black. Transitional stools, which are greenish brown, appear after initiation of milk feeding and are replaced by typical yellow, seedy milk stools 3 to 4 days later.

BREATHING PATTERNS

The normal respiratory rate in neonates is 30 to 60 breaths/min. Newborn breathing is almost entirely diaphragmatic, and the soft front of the thorax is usually drawn inward during inspiration while the abdomen protrudes. Count the respiratory rate for a full minute with the infant resting or preferably asleep. **Neonates increase minute ventilation almost entirely through an increase in respiratory rate rather than inspiratory volume; a neonate with a resting respiratory rate of >60 breaths/min during periods of regular, quiet breathing requires evaluation for the causes of tachypnea.** Indrawing and tachypnea may signify intrathoracic or intra-abdominal pathology. Check the nares and upper airway, as neonates are obligate nose breathers, and nasal congestion, or choanal stenosis or atresia, can cause respiratory distress.

Newborn infants, especially those born prematurely, may exhibit **periodic breathing** that is characterized by alternating periods of a normal or fast rate and periods of a markedly slow rate of respiration, with pauses of 3 to 10 seconds between breaths. Irregular respiratory patterns are seen in many premature babies during sleep, but are less common in term infants. **Periods of apnea >20 seconds or apnea accompanied by bradycardia, cyanosis, or a change in muscle tone is abnormal and requires evaluation** (see Chapter 118, "Sudden Infant Death Syndrome," and Chapter 117, "Brief Resolved Unexplained Events and Apparent Life-Threatening Events").

SLEEPING AND FEEDING PATTERNS

Newborns awaken every 20 minutes to 6 hours, and sleep periods are spread evenly across the day and night. By 3 months of age, most sleep occurs at night, and by 6 months, most infants are sleeping through the night. When the child cries during the night, parents should make sure that there is no physical reason for crying. There are many methods of sleep training, none of which has been documented to be medically superior to others.

CRYING

The symptom complex of crying or irritability is fairly common yet difficult to treat, even in the presence of an identifiable cause. Most neonates exhibit varying degrees and periods of crying during a 24-hour period. Total crying time increases after birth, peaking at 3 to 5 months of age. Infants who present with an episode of acute, **inconsolable crying**, however, require careful evaluation for an underlying cause (**Table 116-1**).

Babies with inconsolable crying are at higher risk of being physically abused or shaken. The Period of Purple Crying is a method for parents to deal with the stress of the crying and prevents babies from being shaken.[2] This program suggests methods to help stop the baby from crying and also reminds parents that it is okay to put the crying baby down in a safe space and to take a few minutes to calm down.

TABLE 116-1 Conditions Associated With Inconsolable Crying, Irritability, and/or Lethargy in Neonates

System	Emergent	Less Serious
CNS	Intracranial hemorrhage (neonatal alloimmune thrombocytopenia, birth trauma, nonaccidental trauma, vitamin K deficiency)	—
	Meningitis	
	Elevated intracranial pressure	
Eye, ear, nose, throat	Nasal obstruction (choanal atresia or stenosis)	Corneal abrasion, ocular foreign body
		Otitis media
		Nasal congestion (upper respiratory infection)
		Oral thrush
		Stomatitis
Pulmonary	Pneumonia	—
Cardiac	Supraventricular tachycardia	—
	Heart failure	
GI	Volvulus	Gastroesophageal reflux disease (reflux)
	Intussusception	
	Incarcerated hernia	Gastroenteritis
		Anal fissure
		Colic
GU	Testicular torsion	Urinary tract infection
	Genital hair tourniquets	Diaper rash
	Paraphimosis	
Musculoskeletal	Hair tourniquet of finger/toe	Injuries (diaper pin, sharp or irritating objects from clothing)
	Nonaccidental trauma	
Infectious	Sepsis	Upper respiratory infection
	Pneumonia	
	Meningitis	
Metabolic	Inborn errors of metabolism	—
	Hypoglycemia	
	Congenital adrenal hyperplasia	

THE CRITICALLY ILL NEONATE

Principles of Basic Life Support, Pediatric Advanced Life Support, and the Neonatal Resuscitation Program are reviewed in Chapter 108, "Resuscitation of Neonates." A brief differential of critical neonatal illness is presented here (**Table 116-2**), with further discussion of specific complaint-based differential diagnosis and management to follow.

For the neonate with respiratory and/or cardiovascular distress, pay primary attention to adequacy of the airway and breathing. There are more stresses and fewer compensatory responses available to the neonate. The neonate has a compliant chest wall and cannot increase inspiratory force; the neonatal airway is small; functional residual capacity in the lungs is small; neonatal metabolism is characterized by high oxygen consumption; and abdominal distention can further impair ventilation. Consider the early use of positive-pressure ventilation or endotracheal intubation for respiratory insufficiency and nasogastric tube placement for gastric distention. **Bradycardia in the neonate is almost always due to respiratory failure and hypoxia and usually corrects with restoration of adequate airway and breathing.**

Tachypnea can be caused by minor problems, such as gaseous abdominal distention, or life-threatening illnesses, such as sepsis. **True tachypnea (respiratory rate >60 breaths/min) or grunting is an emergency**; admit for further investigations, monitoring, and therapy in all but the mildest cases.

Cardiorespiratory symptoms in neonates are nonspecific and may be due to cardiovascular or respiratory failure or to systemic diseases. Search for pathologic conditions in all organ systems. For example, sepsis, meningitis, gastroenteritis, and metabolic acidosis may cause respiratory distress as the predominant symptom. Regardless of the cause, assess and stabilize the cardiac and respiratory systems before, or simultaneously with, further diagnostic evaluation.

When a specific cause cannot be identified, initiate a full sepsis evaluation (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children"), begin broad-spectrum antibiotics, and add IV acyclovir if there are any findings consistent with or suggestive of exposure to herpes simplex virus.

Conditions discussed in the following sections include common and uncommon symptom complexes in the critically ill neonate: neonatal sepsis; congenital heart disease; pneumonia; bronchiolitis; air leak sydromes; anatomic airway lesions; inborn errors of metabolism; congenital adrenal hyperplasia; neuromuscular disorders; intracranial hemorrhage; and abdominal catastrophe.

TABLE 116-2 Causes of Critical Illness in Neonates

- Sepsis (bacteremia, urinary tract infection, meningitis)
- Congenital heart disease (ductal-dependent lesions)
- Pneumonia (bacterial, viral, chlamydia, aspiration)
- Bronchiolitis
- Air leak syndromes (pneumothorax, pneumomediastinum)
- Congenital anatomic airway anomalies (cleft palate, laryngeal or tracheomalacia, laryngotracheal cleft, tracheal webs, tracheoesophageal fistula, tracheal hemangiomas, and vascular rings)
- Neuromuscular disease (infant botulism, muscle weakness)
- Inborn errors of metabolism
- Congenital adrenal hyperplasia
- Intracranial hemorrhage (vitamin K deficiency, nonaccidental trauma)
- Abdominal catastrophe (malrotation, volvulus, necrotizing enterocolitis)

NEONATAL SEPSIS

Neonatal sepsis is the most common cause of neonatal cardiorespiratory distress. **Fever or hypothermia** signals serious infection in the neonate. **Fever in the first month of life is a rectal temperature ≥38°C (100.4°F), and hypothermia is a rectal temperature <36.5°C (97.7°F).** Neonates have about twice the risk of serious bacterial infection as do infants 4 to 8 weeks of age. Neonatal sepsis tends to appear as an "**early-onset**" or a "**late-onset**" syndrome, with some overlap. **Early-onset disease** is seen in the first 7 days of life, tends to be fulminant, and is usually associated with maternal or perinatal risk factors, such as maternal fever, group B *Streptococcus*–positive vaginal swabs, prolonged rupture of membranes, and fetal distress. **Late-onset disease** usually occurs after 1 week of age, tends to develop more gradually, and is less likely to be associated with risk factors. Septic shock and neutropenia are more common with early-onset syndrome, and meningitis is more common in late-onset disease.

TABLE 116-3 Signs of Neonatal Sepsis

- Temperature instability (fever, hypothermia)
- CNS dysfunction (lethargy, irritability, seizures)
- Respiratory distress (apnea, tachypnea, grunting)
- Feeding disturbance (vomiting, poor feeding, gastric distention, diarrhea)
- Jaundice
- Rashes

Clinical signs of early- or late-onset sepsis are not specific. Septic infants may exhibit any of a variety of signs, as described in **Table 116-3**. Tachypnea and respiratory distress may be a sign of sepsis, meningitis, or urinary tract infection. Localizing signs may be absent—for instance, nuchal rigidity and Kernig and Brudzinski signs are present in a small minority of neonates with meningitis.

Bacterial causes of neonatal sepsis reflect organisms that colonize the female genital tract and nasal mucosa of caregivers. In general, the two groups of pathogens most frequently encountered are gram-positive cocci, such as β-hemolytic streptococci, and enteric organisms, such as *Escherichia coli* and *Klebsiella* species, and *Haemophilus influenzae*. *Listeria monocytogenes* also causes sepsis and meningitis in neonates. Viral infections are another cause of fever and are most likely due to enteroviruses (coxsackievirus and echovirus) acquired at the time of delivery or respiratory syncytial virus and influenza A virus acquired postnatally. The height of the temperature does not distinguish a viral versus bacterial cause in neonates.

The clinical investigation for neonatal sepsis is similar to that of an older infant except that the threshold for a full sepsis workup, including cerebrospinal fluid analyses, is lower. Admit all neonates to the hospital, and initiate treatment with empiric IV antibiotics. Initial treatment of a neonate with suspected bacterial septicemia or meningitis usually includes **ampicillin (50 milligrams/kg to cover group B *Streptococcus* and *Listeria*)** and an **aminoglycoside (gentamicin, 2.5 milligrams/kg) to cover *E. coli* and other gram-negative organisms and possible gram-negative meningitis.**[3] **Avoid ceftriaxone in neonates as it can displace bilirubin and cause kernicterus. When gram-negative meningitis is strongly suspected, replace gentamicin with cefotaxime or ceftazidime (50 milligrams/kg)**, which have better CNS penetration. Add **IV acyclovir** for neonates with a maternal history of herpes or suspicious cerebrospinal fluid findings (predominance of lymphocytes and erythrocytes in a nontraumatic lumbar puncture) and all neonates who are ill appearing.[4] For further detailed discussion, see Chapter 119.

CONGENITAL HEART DISEASE

Suspect **congenital heart disease** in a well-developed neonate who presents with unexplained cardiorespiratory collapse, cyanosis, and or tachypnea, especially without chest retractions or use of accessory muscles for breathing (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease"). Undiagnosed **congenital heart disease** may be first identified *after* discharge from the newborn nursery and typically becomes symptomatic at one of two distinct time frames: in the first week of life or after the second week of life (see Chapter 129). In the first week of life, lesions dependent on pulmonary or systemic blood flow through the ductus arteriosus (e.g., hypoplastic left heart syndrome, critical coarctation of the aorta) present with shock and acidosis as the duct begins to close. This can be mistaken for sepsis. Lesions that involve left-to-right shunting of blood (ventricular and atrial septal defects) typically present after the second week of life with congestive heart failure as pulmonary vascular resistance falls, allowing pulmonary overcirculation and the onset of congestive heart failure.

PNEUMONIA

The lungs are the most common site of infection in neonates. Neonatal pneumonia contributes to significant mortality in developing countries, whereas the incidence of neonatal pneumonia in full-term infants in developed countries is lower. **Table 116-4** displays the various causes, the associated clinical picture, and suggested management of neonatal pneumonia.[5] Chapter 128, "Pneumonia in Infants and Children," further addresses pneumonia after the neonatal period.

BRONCHIOLITIS

A detailed discussion of bronchiolitis can be found in Chapter 127, "Wheezing in Infants and Children." Neonates are at particularly high risk for serious complications from bronchiolitis, because of obligate nose breathing and respiratory mechanics. **Factors that predispose to complications of bronchiolitis include prematurity, underlying pulmonary or congenital heart disease, initial oxygen saturation <92%, and bronchiolitis caused by respiratory syncytial virus.**

Acute bronchiolitis is a clinical diagnosis, and neonates present with nasal discharge and sneezing followed by diminished appetite, difficulty with feeds, cough, dyspnea, irritability, and, occasionally, periods of apnea. Respiratory symptoms include hypoxia, wheezing, retractions, and possibly palpable liver and spleen due to pulmonary hyperinflation. **Bronchiolitis caused by any virus can be associated with apnea, especially in neonates and preterm infants who are of corrected age <8 weeks old.**[6] While apnea usually presents within the first 3 days of illness, it may develop even if the neonate displays only minimal respiratory distress, and **there are no reliable predictors for the development of apnea**.

Routine ancillary testing (chest radiograph, blood tests, viral/bacterial cultures) is not recommended and should be used only in the context of clinical suspicion of concomitten severe bacterial infections (Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children"). While bacterial pulmonary infection is not likely in confirmed viral bronchiolitis, **a urinalysis should be obtained in febrile neonates (temperature >38.0°C [100.4°F]), as up to 4% of febrile infants with bronchiolitis have concomitant urinary tract infection.** The risk of bacteremia and meningitis associated with bronchiolitis is quite low, and full sepsis evaluation is not needed unless the neonate appears ill. There is no role for antibiotics, inhaled corticosteroids, or β-adrenergic bronchodilators. The evidence surrounding the use of inhaled epinephrine and hypertonic saline remains equivocal.[7,8]

TABLE 116-4 Neonatal Pneumonia

Etiology	Clinical Presentation	Management Approach
Common bacterial [group B *Streptococcus* (most common), *Escherichia coli*, *Listeria monocytogenes*, *Haemophilus influenzae* B, *Streptococcus pneumoniae*, *Klebsiella* species, *Enterobacter aerogenes*]	Fulminant illness with onset within 48 h of birth, with infection likely acquired in utero from contaminated amniotic fluid environment.	Full evaluation for sepsis (blood and urine cultures, chest radiographs, and CBC). Blood culture results are typically negative. Two culture samples may increase diagnostic yield fourfold.
	Respiratory distress, unstable temperature (high or low), irritability or lethargy, tachycardia, and poor feeding may be present.	A lumbar puncture should be done if there are no contraindications.
		Hospitalization, supportive care (oxygen), and parenteral antibiotics (ampicillin and gentamicin; adjust as per culture and sensitivities when available).
Chlamydia	Develops in 3%–16% of exposed neonates (in colonized mothers).	Sepsis evaluation as indicated.
		CXR may show hyperinflation with interstitial infiltrates.
	Usually occurs after 3 wk of age, accompanied by conjunctivitis in one half of cases. Often afebrile, tachypneic, with prominent "staccato" cough. Wheezing uncommon.	Definitive diagnosis by nasopharyngeal swab for PCR or cultures.
		Eosinophilia may be seen on peripheral blood count.
		Treatment: macrolide (erythromycin, clarithromycin, or azithromycin).
Bordetella pertussis	In addition to pneumonia, may cause paroxysms of cough ± cyanosis and posttussive emesis in otherwise well-looking infant. Characteristic whoop is not present in neonates. Apnea may be the only symptom. Suspect when adult caregiver also has persistent cough.	Sepsis evaluation as indicated.
		Diagnosis via nasopharyngeal swab for PCR and/or culture.
		Lymphocytosis in peripheral blood count is nonspecific but supports the diagnosis.
		Macrolides are effective against *B. pertussis* but are not approved by the U.S. Food and Drug Administration for infants <6 mo.
		No available data on efficacy of azithromycin or clarithromycin in infants <1 mo old, but case series show less adverse effects with azithromycin.
		Neonates should be admitted during treatment and monitored for adverse effects.
Mycobacterium tuberculosis	Half of infants born to actively infected mothers develop TB if not immunized or treated.	Sepsis evaluation as for bacterial pneumonia.
		CXR, culture of urine, gastric and tracheal aspirates.
	May be acquired by transplacental means, aspiration/ingestion of infected amniotic fluid, or postnatal airborne transmission.	Skin testing not sensitive in neonates.
		Routine anti-TB treatment.
	Often presents with nonspecific systemic symptoms with multiorgan involvement (fever, failure to thrive, respiratory distress, organomegaly).	Supportive treatment as needed.
Viral pneumonia/pneumonitis (HSV, respiratory syncytial virus, adenovirus, human metapneumovirus, influenza, parainfluenza)	Initial upper respiratory illness progressing to respiratory distress and feeding difficulty.	Sepsis evaluation as indicated and IV acyclovir if HSV is suspected.
	Hypoxia, apnea, and bradycardia (with HSV) may be present.	Viral testing (direct antigen detection/PCR/cultures) of nasopharyngeal washings (swab).
	Often indistinguishable from bronchiolitis.	Rate of concurrent bacterial infections in confirmed viral infection is low.
		CXR for significant respiratory distress.
		Supportive therapy; monitoring for apnea in young and premature infants.

Abbreviations: CXR = chest roentgenogram; HSV = herpes simplex virus; PCR = polymerase chain reaction; TB = tuberculosis.

AIR LEAK SYNDROMES

Air leak sydromes such as pneumothorax and pneumomediastinum can occur in neonates who have previously had mechanical ventilation, but may also occur spontaneously or after aspiration or be associated with pneumonia or other underlying lung disease (including congenital anatomic lesions). Management is generally conservative, but may require drainage with needle decompression or chest tube (see Chapter 261, "Pulmonary Trauma").

ANATOMIC AIRWAY LESIONS

The anatomically correctable causes of respiratory distress in newborns are less common and include anomalies of the upper respiratory tract (e.g., choanal atresia, laryngomalacia, tracheomalacia, micrognathia, macroglossia, tracheoesophageal fistula, vascular slings) or lower respiratory tract (e.g., congenital lobar emphysema, sequestration, congenital pulmonary airway malformation, congenital diaphragmatic hernia). Most of these anomalies are identified in the newborn nursery, but in the ED, these diagnoses should be considered in any infant with respiratory distress. Admission is needed for diagnosis.

NEUROMUSCULAR DISORDERS

Any form of muscle weakness may be associated with shallow breathing and a compensatory increase in respiratory rate. **Infantile botulism** is one possible acquired cause and is usually preceded by constipation, followed by a weak cry and feeding difficulties. Ocular palsies, apnea, weakness or hypotonia, and lethargy are late symptoms of botulism. Other causes of hypotonia that may cause respiratory symptoms include trisomy 21; hypoxic-ischemic encephalopathy; spinal cord lesions, such as myelomeningocele; spinal muscular atrophy; myasthenia gravis; metabolic disorders; and myotonic dystrophy.

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism may manifest as lethargy or respiratory and/or cardiovascular collapse in the neonate. Although the differential diagnosis of inborn errors of metabolism is extensive, the ED evaluation necessitates only a few tests, including bedside glucose, electrolytes, blood gas analysis, serum ammonia, and urine for ketones. Follow up on newborn screening if available. More specific testing can wait until after resuscitation. Administer dextrose-containing IV fluids for suspected metabolic disease until specialty consultation can be obtained. In cases of neurologic signs and hyperammonemia, consider sodium benzoate and sodium phenylacetate because neurologic outcomes correlate with the duration of hyperammonemia. For further discussion, see Chapter 146, "Metabolic Emergencies in Infants and Children."

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia is one of the few acute life-threatening endocrine emergencies that present in the neonatal period (see Chapter 146, "Metabolic Emergencies in Infants and Children"). Although many newborn screens test for this disorder, infants may present in shock before screening results are known, typically in the first or second week of life. On examination, look for virilization, ambiguous genitalia, and hyperpigmentation. Hyponatremia and hyperkalemia occur in the salt-wasting form of congenital adrenal hyperplasia. Administer hydrocortisone (12.5 to 25.0 milligrams IV/IM/IO) promptly, while undertaking other resuscitative measures. Treat hyperkalemia with standard measurements only if associated with ECG changes.

INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage, either as a result of birth trauma or nonaccidental trauma, is another consideration in the critically ill neonate. Risk factors include home delivery without administration of vitamin K (associated with hemorrhagic disease of the newborn) or traumatic vaginal delivery. Consider head CT after initial resuscitation if a diagnosis is not apparent or intracranial pathology is suspected.

ABDOMINAL CATASTROPHE

Consider **abdominal catastrophe** in the critically ill neonate with abdominal symptoms. Congenital malrotation can lead to midgut volvulus and intestinal infarction, with bilious vomiting, a distended rigid abdomen, sepsis, and circulatory collapse. Necrotizing enterocolitis, while typically a disease of premature infants, can present in the term neonate with poor feeding; abdominal distention, tenderness, and discoloration; lethargy or irritability; vomiting or diarrhea; temperature instability; apnea; and circulatory collapse. These and other abdominal considerations are discussed in Chapter 133, "Acute Abdominal Pain in Infants and Children," and are reviewed briefly later (see "GI Concerns").

SYMPTOM-BASED NEONATAL PROBLEMS

Common symptom-based neonatal problems that may result in ED visits include irritability, colic, upper airway complaints, apnea and periodic breathing, GI symptoms, eye complaints, and abnormal movements.

IRRITABILITY

Normal crying was discussed earlier (see "Normal Neonatal Vegetative Functions"), and Table 116-1 lists the important causes of irritability in the neonate. Obtain a thorough history focusing on symptoms other than crying, such as changes in feeding, temperature instability, and vomiting, and perform a systematic head-to-toe examination. Palpate the fontanelles for signs of dehydration (sunken) or infection or intracranial hemorrhage (bulging). If corneal abrasion is possible, examine the eyes with fluorescein staining. Inspect the mouth for oral thrush and check diaper area and groin for rashes, hair tourniquets (also check fingers and toes), and hernias or testicular torsion. Auscultate the heart to appreciate dysrhythmias or murmurs, and observe respiratory effort that may point to a pulmonary or metabolic cause of irritability. Obtain a bedside glucose in all neonates with altered mental status, vomiting, or a history of poor oral intake. Examine the abdomen for tenderness, distention, or discoloration suggestive of intra-abdominal pathology and the extremities for signs of trauma.

If a careful history and complete physical examination reveal no source for the crying and the infant quiets during the ED visit, further testing is unnecessary and parents can be reassured and advised to follow up with their primary care physician.

INTESTINAL COLIC

Colic is a symptom complex consisting of the sudden onset of paroxysmal crying, a flushed face, circumoral pallor, tense abdomen, drawn up legs, cold feet, and clenched fists. The cause is not known. **Colic is defined as a paroxysm of crying for ≥3 hours per day for ≥3 days per week over a 3-week period.** It may begin as early as the first week of life but seldom lasts beyond 3 to 4 months of age. **Infant colic is a diagnosis of exclusion.** Physical examination is normal, and laboratory tests are not required. However, when the diagnosis is unclear, a careful history, physical examination, and appropriate laboratory investigations are necessary to rule out conditions listed in Table 116-1.

There is no specific treatment for colic. Altering feeding practices (smaller volumes, slower feeds with burping, dairy/soy restriction, alternate hydorlyzed formula) may decrease symptoms. If symptoms do not resolve, **restrictive diets are not recommended**. Administration of drugs or sedatives is contraindicated. Infant colic can create significant caregiver stress and fatigue and is a risk factor for nonaccidental neonatal trauma. Carefully assess the caretaker's mental health and explore strategies to provide respite if needed.

UPPER AIRWAY CONCERNS

Cough and Nasal Congestion Cough associated with sneezing and nasal congestion is usually due to viral upper respiratory infection. Neonates with underlying pulmonary or heart disease such as bronchopulmonary dysplasia or hypoplastic left heart may develop respiratory

failure with even mild upper respiratory infections. Inquire about sick siblings and perinatal infectious risk factors. Pay attention to the relation between respiratory symptoms and feeding that might suggest reflux and aspiration, or even congenital tracheoesophageal fistula, as a cause. Respiratory difficulty when quiet and improvement during crying suggest **choanal atresia**. Treat the underlying condition: cough is the infant's primary protective reflex; do not give cough suppressants to neonates. **Over-the-counter cold medications are not effective, may be dangerous in infants, and are contraindicated for children <6 years old.** Treat nasal congestion with instillation of saline drops and bulb suctioning.

Noisy Breathing and Stridor Noisy breathing is a common presenting complaint in neonates and is usually benign, but consider serious underlying pathology. Distinguish between inspiratory and expiratory sounds through careful listening in order to distinguish stertor, stridor, and wheezing. **Stertor** is an inspiratory sound like snoring or snorting that localizes to the nose or nasopharynx and is usually benign, but can be a symptom of choanal stenosis. Inability to pass a small nasogastric tube through the affected nostril is diagnostic of this condition. **Stridor** is a sign of upper airway obstruction and may be evident on both inspiration and expiration. The most common cause of stridor in neonates is **laryngomalacia**, which is characterized by noisy, crowing, inspiratory sounds, usually present from birth, that usually decrease during the first year of life. These sounds generally resolve when the baby is prone. Nasal pharyngoscopy by an otolaryngologist confirms the diagnosis.

Stridor may also be a symptom of congenital anomalies causing a fixed obstruction anywhere from the nose to the trachea and bronchi, such as webs, cysts, atresia, stenosis, clefts, and hemangiomas. Stridor from fixed lesions is often biphasic, although it may be predominant in either inspiration or expiration. Stridor worsening with cry or increased activity suggests laryngomalacia, tracheomalacia, or subglottic hemangioma (which often become symptomatic after the first few weeks of life). Stridor accompanied by feeding difficulties suggests a vascular ring, laryngeal cleft, or tracheoesophageal fistula. Occasionally an **H-type tracheoesophageal fistula** may present in the first month of life or later with recurrent pneumonia, respiratory distress after feedings, and problems clearing mucus. **Tracheal stenosis** may present initially with noisy breathing or a high-pitched cry and disproportionate respiratory distress with mild upper respiratory infections. Stridor with hoarseness or weak cry suggests **vocal cord paralysis**, which is typically present at birth. Infants who were intubated in the neonatal period may develop **subglottic stenosis** causing stridor. Infection (e.g., croup, epiglottitis, and abscess) as a cause of stridor in neonates is rare and is associated with fever. When the diagnosis is in doubt, admit the neonate for further evaluation, which may include pharyngoscopy, bronchoscopy, radiographs, or even ultrasonography.

APNEA AND PERIODIC BREATHING

Periodic breathing and apnea are defined earlier (in "Breathing Patterns"), and both may occur in the same patient. Apnea signifies critical illness and warrants investigation and admission for monitoring and therapy. Apnea may be precipitated by any of the disease conditions listed in Table 116-3 and usually indicates respiratory muscle fatigue and impending respiratory arrest. Provide airway and ventilatory support, and search for the cause. If no obvious cause is found, presume sepsis, obtain cultures, and initiate broad-spectrum antibiotics and acyclovir if there is concern for herpes simplex virus. Chapter 118, "Sudden Infant Death Syndrome," and Chapter 117, "Brief Resolved Unexplained Events and Apparent Life-Threatening Events" cover conditions associated with apnea in detail.

GI CONCERNS

Emergent surgical causes of vomiting in the neonate include malrotation with volvulus, intussusception, necrotizing enterocolitis, and incarcerated hernia, all of which are discussed in Chapter 133. Common GI symptoms that bring neonates to the ED include feeding difficulties, gastroesophageal reflux, vomiting, blood in the diaper, diarrhea and dehydration, abdominal distention, and constipation. **Table 116-5** reviews common GI disorders with their corresponding frequent presenting concerns.

TABLE 116-5 GI Concerns in Neonates

Diagnosis	Common GI Signs	General Management
Gastroesophageal reflux disease	Regurgitation and GER Feeding difficulties	Supportive
Cow milk protein allergy	Regurgitation and GER Abdominal distention Blood in diaper	Cow milk and soy milk avoidance
Tracheoesophageal fistula	Feeding difficulties Regurgitation and GER Respiratory distress	NPO/IV fluids ENT and bronchoscopy
Pyloric stenosis	Vomiting Dehydration Irritability	US General surgery consult
Bowel obstruction (incarcerated hernia, duodenal/ileal/jejunal atresia)	Vomiting Feeding difficulties Abdominal distention	NPO/IV fluids General surgery consult
Midgut malrotation with volvulus	Vomiting Feeding difficulties Abdominal distention Blood in diaper Irritability	NPO/IV fluids Upper GI General surgery
Necrotizing enterocolitis	Feeding difficulties Vomiting Abdominal distention Blood in diaper	NPO/IV fluids Antibiotics General surgery
Intussusception	Blood in diaper Irritability	US Air enema General surgery
Hirschsprung's	Constipation Abdominal distention	Rectal biopsy General surgery
Gastroenteritis	Diarrhea and dehydration Abdominal distention	Rehydration Uncommonly antibiotics
Sepsis	Feeding difficulties Vomiting Abdominal distention Irritability	IV fluids Antibiotics Acyclovir
Hypothyroidism	Constipation Abdominal distention	Thyroid replacement

Abbreviations: ENT = ears, nose, and throat; GER = gastroesophageal reflux disease; NPO = nothing by mouth.

Feeding Difficulties Most visits for feeding difficulties occur because parents perceive that the infant's food intake is inadequate; normal feeding and benign feeding problems are discussed earlier (see "Normal Neonatal Vegetative Functions"). Rarely, anatomic abnormalities may cause difficulty in feeding and swallowing. A careful history usually pinpoints such difficulties as having started at birth, and these infants appear malnourished and dehydrated. Potential causes include upper GI abnormalities (e.g., stenoses, strictures, laryngeal clefts, or cleft palate) and compression of the esophagus or trachea by a double aortic arch. Infants with a recent decrease in intake usually have acute illness, most often infectious, and should be evaluated urgently.

Regurgitation and Gastroesophageal Reflux Regurgitation of small amounts of milk or formula is common in neonates due to reduced lower esophageal sphincter pressure and relatively increased intragastric pressure. **Regurgitation** is independent of effort or muscular contraction and likely represents the ultimate degree of GI reflux. Parents may confuse regurgitation with vomiting. As long as the neonate is gaining weight, parents can be reassured that regurgitation is of no

clinical significance and will decrease as the infant grows. Strategies to reduce reflux include thickening of feeds and upright feeding positioning. Infants who are not thriving or have respiratory symptoms related to feeding should be investigated for anatomic causes of regurgitation or chronic aspiration.

Regurgitation rarely results from pathologic processes, such as intrinsic compression of the esophagus or, occasionally, compression of the trachea, in which case it is usually accompanied by stridor and cough. Dysphagia, irritability, feeding aversion, anemia, and malnutrition are sequelae of chronic regurgitation with esophagitis, but this condition is rare. Investigations such as pH monitoring, endoscopy, and biopsy confirm the diagnosis of reflux esophagitis. Medications such as H_2 blockers or proton pump inhibitors increase risk of infection in neonates and should be reserved only for infants with failure to thrive or other major symptoms of reflux.

Vomiting **Vomiting** results from forceful contraction of the diaphragm and abdominal muscles. A detailed discussion of vomiting in childhood is provided in Chapter 131, "Vomiting, Diarrhea, and Dehydration in Infants and Children," while surgical conditions that present with vomiting are discussed in Chapter 133, "Acute Abdominal Pain in Infants and Children"; those specific to the neonatal period are briefly discussed here.

Vomiting beginning at birth is most likely due to an anatomic abnormality, such as tracheoesophageal fistula (with esophageal atresia), upper GI obstruction (e.g., duodenal atresia, which has a higher incidence among infants with trisomy 21), or midgut malrotation. Vomiting may be a symptom unrelated to the GI tract, such as increased intracranial pressure, metabolic disorders, or infections (e.g., sepsis, urinary tract infections, and gastroenteritis).

Projectile vomiting is usually seen in infants with pyloric stenosis and may assume its characteristic pattern, projectile vomiting at the end of feeding or shortly thereafter, after the second and third weeks of life. **Pyloric stenosis classically presents between 6 weeks and 6 months of age and is the most common surgically correctible cause of vomiting in newborns.** The vomitus does not contain bile or blood, and typically the infant appears well with an increased appetite. Perform an abdominal examination with the infant relaxed and the stomach empty. Observe for prominent gastric waves progressing from left to right. Palpate for a firm olive-shaped mass under the liver edge. Observe the neonate feeding to confirm projectile vomiting and distinguish this from regurgitation. Definitive diagnosis is most commonly made with ultrasound examination of the pyloric length and diameter.[9]

The well-appearing infant without dehydration, malnutrition, or electrolyte abnormalities can be discharged with a plan for outpatient surgical correction. Admit ill-appearing or dehydrated infants.

Blood in the Diaper Parents may come to the ED complaining of blood in the neonate's diaper. Several important distinctions must be made: first, confirm that the discoloration is blood by testing with a guaiac card if possible; it is not uncommon in the neonatal period to find urinary crystals that may cause an orange or red discoloration in the diaper that can be mistaken for blood. If blood is confirmed, the next important distinction is whether the origin is the GI tract or, in girls, the vagina. Bloody or mucous discharge is common and normal in female neonates due to withdrawal from placental estrogen. Physical examination may reveal a small anal fissure as the source of bleeding. **In the first 2 to 3 days of life, blood in the diaper is most commonly due to maternal blood that is swallowed during delivery.** This possibility may be confirmed by the Kleihauer-Betke or Apt-Downey test, performed on a stool sample or scraped from the diaper if possible, which differentiates fetal from maternal hemoglobin in the stool. **After the first few days of life, most causes of blood in the diaper are idiopathic, but consider coagulopathies, necrotizing enterocolitis, allergic or infectious colitis, and congenital defects.** Cow's milk allergy is an immunoglobulin E–mediated disorder, but most infants have cow's milk protein intolerance rather than true allergy. Both conditions cause changes in the bowel mucosa that result in gassy, bloody, and mucous bowel movements; painful feeds; and worsened reflux. Eosinophils may be present in the stool, and the diagnosis may be confirmed by resolution of the problem after cow's milk is removed from the diet. For unresponsive or severe cases, endoscopy and biopsy may be needed for diagnosis. A newborn with a single event of hematochezia and no concerning findings may be observed as an outpatient. Persistent symptoms or concerning exam findings should be further evaluated, and depending on the infant's condition (hydration status and weight gain), admission with appropriate subspecialty care may be necessary (see Chapter 134, "Gastrointestinal Bleeding in Infants and Children").

Diarrhea and Dehydration Diarrhea and dehydration are discussed in detail in Chapter 131, and fluid and electrolyte therapy in Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children." *Diarrhea* is abnormally frequent and liquid stools. The modifier *abnormal* is critical because stools can normally be frequent and liquid in young children. Consider infection in addition to feeding-related causes, although infectious diarrhea is predominantly seen in older infants in the United States. Neonates are particularly susceptible to dehydration and electrolyte abnormalities associated with severe diarrhea. In an infant, the normal extracellular fluid volume is 25% of body weight; therefore, a loss of 8% of body weight as extracellular fluid results in severe dehydration.

Weigh all neonates with diarrhea unclothed to allow comparison with previous weights and to provide a baseline for monitoring subsequent weights during the course of the disease. Start the physical examination with a general assessment of mental status and hydration (see Table 126-6). Document rectal temperature, pulse, and blood pressure, which provide additional information concerning the degree of illness. Consider rectal examination to look for anal fissures as a potential source of blood, and obtain a stool sample for detection of occult blood, culture, examination for leukocytes, measurement of pH, and detection of reducing substances.

Obtain serum electrolytes, particularly sodium and glucose, in all neonates with diarrhea and dehydration. Markedly elevated serum urea nitrogen with a relatively normal creatinine may indicate recent or rapid dehydration. Serum creatinine values tend to be low in infants and young children, and a creatinine value of 1 milligram/dL may represent a doubling in the normal value. In addition to stool testing as above, obtain a urine sample in the setting of fever to evaluate for urinary tract infection.

Admit most newborns with ongoing GI losses to the hospital for rehydration, since the loss of even seemingly small volumes of stool may cause severe dehydration in the neonate. Diarrhea, particularly when bloody or containing mucus, may be a sign of a more severe surgical abdominal process, such as volvulus, intussusception, or necrotizing enterocolitis, although all three of these conditions typically present with vomiting as well.

Abdominal Distention Abdominal distention may be normal in neonates and is usually due to lax abdominal musculature, relatively large intra-abdominal organs, and distention from swallowed air. If the infant is comfortable and feeding well and the abdomen is soft, there is no need for concern. Abdominal distention may also occur in association with bowel obstruction, constipation, necrotizing enterocolitis, or ileus due to sepsis or gastroenteritis. Congenital organomegaly (e.g., hepatomegaly, splenomegaly, or renal enlargement) undetected in the perinatal period also may cause abdominal distention.

Constipation Infrequent bowel movements in neonates do not necessarily mean that the infant is constipated. Infants occasionally may go without a bowel movement for 5 to 7 days and then pass a normal stool. However, if the neonate has never passed stools, especially if there has not been a stool in the first 48 hours of life, consider intestinal stenosis, Hirschsprung's disease, or meconium ileus associated with cystic fibrosis. Constipation occurring after birth but within the first month of life suggests Hirschsprung's disease, hypothyroidism, anal stenosis, or an anteriorly displaced anus. Correct anatomic positioning of the anus is determined by measuring the distance between the gluteal cleft and the posterior fourchette in girls or the median raphe in boys. The anus should be no more anterior than two thirds of this distance. Neonates with constipation should have a careful evaluation of the lumbosacral spine for evidence of occult dysraphism, which may be associated with neurogenic bowel or bladder. The diagnosis of Hirschsprung's disease is supported by absence of feces on rectal examination, a tonic or tight sphincter tone, and an abrupt change in bowel luminal size on barium enema, and is confirmed by a rectal biopsy demonstrating absence of ganglion cells. Infants with hypothyroidism present with constipation,

feeding problems, a weak or hoarse cry, a large anterior fontanelle, hypothermia, hypotonia, and peripheral edema. Thyroid testing as part of the routine newborn metabolic screen varies from state to state in the United States. **Early treatement of neonatal hypothyroidism is critical to prevent permanent neurodevelopmental delay.**

JAUNDICE (HYPERBILIRUBINEMIA)

Jaundice signifies hyperbilirubinemia and can represent normal newborn physiology or a pathologic process. Bilirubin is a breakdown product of hemoglobin that is conjugated in the liver by glucuronyl transferase before it is excreted with bile into the GI tract. Once bilirubin reaches the intestinal lumen, brush border enzymes deconjugate some of the bilirubin, which is then reabsorbed through enterohepatic circulation. The remainder of the bilirubin is either oxidized by intestinal bacteria to urobilinogen (which is excreted in the urine) or passed in the feces, creating the normal yellow color of neonatal stool. **Physiologic jaundice is characterized by a slow rise in bilirubin (<5 milligrams/dL per 24 hours), with a peak of 5 to 6 milligrams/dL during the second to the fourth days of life and a decrease to <2 milligrams/dL by 5 to 7 days.** Decreased neonatal hepatic glucuronyl transferase activity, a shortened life span of neonatal red blood cells and relative polycythemia, and decreased intestinal bacterial colonization all lead to an increase in enterohepatic circulation that produces the normal rise in bilirubin seen in physiologic jaundice. Other processes, both benign and pathologic, often cause bilirubin levels that are significantly higher than 6 milligrams/dL, and excessive hyperbilirubinemia can lead to permanent brain injury—**kernicterus**. Practice parameters for the evaluation and treatment of neonatal jaundice are summarized in **Table 116-6.**[10]

Distinguishing between physiologic and pathologic neonatal jaundice is important, and the timing of the onset of jaundice in the newborn provides useful clues. **Table 116-7** lists various causes of hyperbilirubinemia in the neonate and their timing.

The evaluation of the jaundiced neonate begins with a thorough history, including maternal infections during pregnancy; maternal blood type and RhoGAM® administration; estimated gestational age (i.e., term or preterm); feeding patterns, including formula or breast milk, frequency, duration, and whether maternal milk supply is adequate and latching successful; stool history, including timing of first stool and transitional stools, color (yellow, acholic), and frequency; regurgitation or vomiting; urine output; and documented fever. A family history of hemolytic anemia or prior neonatal jaundice might indicate an inherited disorder. Review maternal and fetal medications. When possible, obtain results of the infant's blood type and maternal antibody screen.

On physical examination, note the degree of jaundice, which progresses in a cephalocaudal direction, although the level of jaundice does not reproducibly correlate with serum bilirubin levels. Scleral icterus is typically noted with serum bilirubin >5 milligrams/dL. Examine the head for cephalohematoma and assess the fontanelles for signs of dehydration or possible infection. Palpate the abdomen for organomegaly that might signify congenital infection or liver disease.

It is important to distinguish unconjugated hyperbilirubinemia from conjugated hyperbilirubinemia. Unconjugated hyperbilirubinemia is much more common, presents earlier in the neonatal period, and is related to the normal or abnormal breakdown of hemoglobin, although inherited enzyme deficiencies or infection may be pathologic causes. Conjugated hyperbilirubinemia results from the inability to excrete bilirubin into the bile and intestines and is usually the result of primary hepatic or biliary disease such as biliary atresia or hepatitis. Conjugated hyperbilirubinemia is always pathologic and often presents later in the neonatal period with jaundice, acholic stools, and dark urine.

At a minimum, laboratory studies for the jaundiced neonate should include a direct and indirect bilirubin. Transcutaneous bilirubin measurements correlate well with total serum levels but do not distinguish conjugated and unconjugated bilirubin. Transcutaneous measurement is thus limited to very low-risk neonates with a normal physical examination.[11] When other pathologic conditions are suspected, the evaluation should be determined by the differential diagnosis and may include a CBC for anemia and red cell indices, a blood smear for hemolysis, reticulocyte count, liver function tests, and thyroid hormone levels. When infection is a concern, obtain appropriate cultures and Gram stains (urine, cerebrospinal fluid).

Septic infants with hyperbilirubinemia may have an increase in bilirubin by greater than the acceptable 5 milligrams/dL per 24-hour period and have other features of sepsis, such as vomiting, abdominal distention, respiratory distress, and poor feeding. **Breast milk jaundice** is thought to be due to the presence of substances that inhibit glucuronyl transferase in the breast milk; it may start as early as the third to fourth day and reaches a peak of 10 to 27 milligrams/dL by the third week of

TABLE 116-7 Causes of Jaundice in Neonates

<24 h	Hemolysis due to ABO, Rh incompatibility
	Congenital infection (rubella, toxoplasmosis, cytomegalovirus infection)
	Excessive bruising from birth trauma (cephalohematoma or intramuscular hematoma)
	Acquired infection (e.g., sepsis, pneumonia)
2–3 d	Physiologic
3 d–1 wk	Acquired infection (e.g., sepsis, urinary tract infection, pneumonia)
	Congenital decrease in glucuronyl transferase (e.g., Crigler-Najjar syndrome, Gilbert's syndrome)
	Congenital infections (syphilis, toxoplasmosis, cytomegalovirus infection)
>1 wk	Breast milk jaundice
	Acquired infection (e.g., sepsis, urinary tract infection, pneumonia)
	Biliary atresia
	Congenital and acquired hepatitis
	Red cell membrane defects (e.g., sickle cell anemia, spherocytosis, elliptocytosis)
	Red cell enzyme defects (e.g., glucose-6-phosphate dehydrogenase deficiency)
	Hemolysis due to drugs
	Endocrine disorders (hypothyroidism)
	Metabolic disorders (galactosemia, fructosemia)
	Pyloric stenosis

TABLE 116-6 Neonatal Risk and Bilirubin Treatment Threshold for Hyperbilirubinemia

	Age of Neonate						
Bilirubin Treatment Threshold (milligrams/dL)	24 h	48 h	72 h	96 h	5 d	6 d	7 d
Low-risk neonates*	12	16	19	21	22	23	23
Intermediate-risk neonates†	9	13	15	16	17	17	17
High-risk neonates‡	8	11	13	14.5	15	15	15

*Full-term, well-appearing, and no risk factors (isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, hypoalbuminemia [<3.0 grams/dL if measured]).

†Thirty-five to 37 6/7 weeks estimated gestational age without risk factors, or term with risk factors.

‡Thirty-five to 37 6/7 weeks estimated gestational age with risk factors.

life. Although cessation of breastfeeding will result in a rapid decline of bilirubin over 2 to 3 days, it is not routinely recommended. **Breast milk jaundice is unlikely to cause kernicterus and usually can be treated with phototherapy, when necessary.** This should be distinguished from *breastfeeding jaundice*, or *starvation jaundice*, which can occur when a newborn is exclusively breastfed and the mother's milk supply is still inadequate. *Poor oral intake* resulting in reduced bowel movement and bilirubin excretion through the GI tract, coupled with relative dehydration, may accentuate physiologic jaundice. Optimizing the neonate's feeding pattern with controlled supplementation, whether with expressed breast milk, donated breast milk, or formula, usually resolves the problem, but severe hyperbilirubinemia may require treatment.

The treatment of hyperbilirubinemia depends on the cause, but for most cases of unconjugated hyperbilirubinemia, phototherapy is sufficient. **Phototherapy** causes a configurational change in the bilirubin structure that allows it to be excreted in the urine. There is no additional benefit to IV fluids coupled with phototherapy, so enteral feeding should always be encouraged, although the dehydrated infant may require fluid resuscitation. Extreme levels of hyperbilirubinemia are treated emergently with exchange transfusion and require admission to hospital.

Risk factors include hemolysis risks (e.g., isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, ABO incompatibility), sepsis (lethargy, temperature instability, irritability), asphyxia, hypoalbuminemia, and acidosis. In the first 24 hours of life, response to phototherapy is less predictable, and specific exchange transfusion indications are less certain during this period.

EYE COMPLAINTS

Watery Eyes Clear eye discharge, and occasionally crusting over of the eyelashes without associated conjunctival redness or irritation, is commonly seen in neonates and infants and results from narrow or obstructed nasolacrimal ducts. This condition usually resolves spontaneously and requires antibiotics only when complicated by conjunctival erythema and inflammation (conjunctivitis or dacryocystitis). Ophthalmologic consultation for nasolacrimal duct probing is appropriate if this problem persists past 12 months of age or earlier if complicated by recurrent infection.

Red Eye and Irritation Corneal irritation or abrasion can result from an eyelash or scratch from a fingernail. Perform fluorescein staining and evaluate with a Wood's lamp or a hand-held slit lamp to identify **corneal abrasions**. **Acute glaucoma**, although rare, also presents as a red, teary eye. The cornea is cloudy, the anterior chamber is shallow, and the intraocular pressure may be increased. Promptly consult pediatric ophthalmology for all suspected cases of glaucoma.

Red Eye and Discharge Conjunctivitis is described in detail in Chapter 122, "Eye Emergencies in Infants and Children." The most common causes of neonatal conjunctivitis are chemical irritation, bacterial or chlamydial infection, and herpes simplex infection. **Chemical conjunctivitis** due to ocular prophylaxis usually occurs on the first day of life and requires no treatment.

Gonococcal conjunctivitis generally has its peak time of onset between 3 and 5 days after birth. Despite antibiotic prophylaxis at delivery, the failure rate of prophylaxis is about 1%. *Neisseria gonorrhoeae* invades superficial layers of the conjunctiva and, if untreated, causes corneal ulceration and can result in permanent loss of vision. For diagnosis, obtain a Gram stain and culture for *N. gonorrhoeae*. Treat gonococcal conjunctivitis with cefotaxime (50 milligrams/kg IV or IM). **Cefotaxime is recommended for neonates, as ceftriaxone can displace bound bilirubin and precipitate kernicterus.** Perform septic workup including lumbar puncture. Disseminated disease should be suspected until cerebrospinal fluid cultures are negative. Supportive care includes ocular irrigation with normal saline as soon as diagnosis is suspected, with frequent irrigation until the discharge is eliminated. Admit the neonate and obtain ophthalmology consultation. Topical antibiotic treatment alone is inadequate and unnecessary when systemic antibiotic treatment is given.

Chlamydial conjunctivitis becomes evident by the end of the first week throughout the first month after birth. The disorder varies in severity, from mild to severe hyperemia with a thick, profuse mucopurulent discharge and pseudomembrane formation. There often is severe edema of both lids. Because isolation of *Chlamydia trachomatis* requires specialized tissue cultures, ensure proper technique in collecting culture specimens (e.g., Dacron swabs) and specimens for antigen detection.

Treat chlamydial conjunctivitis and pneumonia in neonates with oral erythromycin (50 milligrams/kg PO per day in four divided doses, for 14 days). Oral sulfonamides may be used after the immediate neonatal period for infants who do not tolerate erythromycin. Topical treatment is unnecessary. Because the efficacy of erythromycin therapy is approximately 80%, a second course is sometimes required. A specific diagnosis of *C. trachomatis* infection in an infant should prompt the treatment of the mother and her sexual partners.

The finding of vesicles anywhere on the skin or mucous membranes in association with neonatal conjunctivitis suggests **herpes simplex infection** and warrants a full sepsis evaluation with cerebrospinal fluid evaluation for herpes simplex virus and treatment with acyclovir, 20 milligrams/kg/dose three times a day.

ABNORMAL MOVEMENTS AND SEIZURES

Seizures are covered in detail in Chapter 138, "Seizures in Infants and Children." It is important to distinguish benign sleep myoclonus in infancy and the **normal startle reflex** from actual seizures. **Sleep myoclonus** consists of rhythmic myoclonic jerks observed when the infant is drowsy or in quiet sleep and can be suppressed upon touching and/or waking the infant; the startle reflex is a single myoclonic jerk with extension of the arms and legs triggered by noise or tactile stimulation. Tetany due to **hypocalcemia** is associated with congenital syndromes, such as DiGeorge's syndrome, and must also be distinguished from **seizure** activity.

Recognition of seizures in the newborn period is important, because seizure management and outcome are different than at any other age. Neonatal seizures are likely to present with subtle manifestations, such as eye deviation, tongue thrusting, eyelid fluttering, apnea, pedaling movements, or arching, rather than generalized activity. Neonatal seizures usually indicate a severe underlying structural or metabolic problem and are rarely idiopathic. Common causes include hypoxic ischemic encephalopathy, neonatal stroke, electrolyte disturbances, and underlying metabolic and genetic conditions. Nonaccidental injury must be considered. If seizures occur in the first 6 hours of life, consult neonatology and/or neurology, and consider therapeutic hypothermia to improve neurodevelopmental outcomes in hypoxic ischemic encephalopathy.[12,13]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 117

Brief Resolved Unexplained Events and Apparent Life-Threatening Events

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DEFINITIONS

It is quite common for infants to have events that are brief, self-resolved, and difficult to characterize. Sometimes these events appear respiratory, cardiovascular, or neurologic in origin, and caregivers may seek medical attention for reassurance that the event is not a sign of a serious underlying condition. Through a comprehensive history and physical, clinicians

can explain many of these events as a benign or normal process such as choking or gagging from feeding or gastroesophageal reflux. Sometimes, however, the event remains poorly understood or unexplainable, and this uncertainty poses a diagnostic and management challenge.

APPARENT LIFE-THREATENING EVENT

In 1986, before the risk factors for sudden infant death syndrome were well understood, an expert consensus group from the National Institutes of Health coined the term *apparent life-threatening event* (ALTE). ALTE was defined as an episode that is frightening to a caregiver and involves some combination of apnea, color change (cyanosis, pallor, or plethora), change in muscle tone (limp or stiff), choking, or gagging.[1] Unfortunately, the term ALTE described a constellation of presenting symptoms rather than a diagnosis and relied heavily on the subjective impression of nonmedical caregivers. No differentiation was made between the ~80% of ALTE patients who are well-appearing at the time of presentation[2-5] and patients with ongoing symptoms such as respiratory difficulty or an ill appearance. To address these concerns, in 2016, the American Academy of Pediatrics more precisely defined these events as brief resolved unexplained events (BRUEs).

BRIEF RESOLVED UNEXPLAINED EVENTS

A BRUE specifically includes **infants <1 year of age who have experienced a brief (<1 minute), unexplained event consisting of one or more of the following features: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone (hyper- or hypotonia); and/or altered level of responsiveness. The infant must return to his or her baseline state of health after the brief event and have a reassuring history and physical exam after medical evaluation, including vital signs.**[6] The BRUE guideline provides risk stratification criteria and management recommendations for lower-risk patients (**Figure 117-1**).

BRUE patients considered lower risk for subsequent events or serious underlying diagnosis include those >60 days old, with gestational age ≥32 weeks and postconceptional age ≥45 weeks, only one event (no prior BRUE ever and not occurring in clusters), event duration <1 minute, no CPR required by trained medical provider, no concerning historical features, and no concerning physical examination findings (see "Risk Stratification").

This chapter does not address patients with ongoing symptoms (e.g., fever [Chapter 119], failure to thrive, respiratory distress [Chapters 123 to 125], recurrent seizures [Chapter 138]) because these patients should be evaluated based on their symptoms. Because BRUE is a newer classification that has not yet been specifically studied, most of the studies cited in this chapter were performed using the previous definition of ALTE.

EPIDEMIOLOGY

It can be normal for infants to choke, gag, demonstrate skin discoloration, change tone, or exhibit periodic and irregular breathing. In healthy infants, 43% are reported to have a 20-second respiratory pause and up to 5% of parents recall seeing an apnea event. The incidence of ALTE ranges from 0.05% to 6.0%, depending on the population studied.[7-9] In Europe, 1 out of 250 to 400 children are hospitalized for an ALTE. The peak incidence is between 1 week and 2 months of age, with the majority of ALTEs occurring before 10 weeks of age.[10] The male-to-female ratio is 2:1.[11] Known risk factors for ALTE include respiratory syncytial virus infection, prematurity, recent anesthesia, gastroesophageal reflux, and airway/maxillofacial anomalies. The epidemiology using the more specific term BRUE has not yet been described.

PATHOPHYSIOLOGY AND EVENT CLASSIFICATION

It is important to characterize the event with a comprehensive history, paying particular attention to changes in breathing, skin color, muscle tone, and level of consciousness. To differentiate normal from potentially pathologic events, determine what occurred before, during, and after the event as well as the relationship of the event to feeding, sleeping, and upper and lower respiratory problems.

Many newborns experience physiologic patterns of breathing that can be frightening to a layperson but are normal. Healthy infants often have cyclic periods of rapid breathing interposed with respiratory pauses, termed *periodic breathing*. Periodic breathing is observed in nearly all preterm and most term infants, and lasts until about 2 months of age in term infants. In addition, irregular respirations are the hallmark of active sleep (later referred to as rapid eye movement sleep or dream sleep) at all ages. Irregular breathing during rapid eye movement sleep continues into adulthood and is normal.

Apnea is typically characterized as central, obstructive, or mixed. Apneic pauses of >20 seconds or those associated with changes in color, tone, or heart rate are considered pathologic. Apnea is difficult to characterize subjectively, so the new American Academy of Pediatrics BRUE guideline includes any brief and resolved irregularity in respiration as a component of BRUE, unlike the ALTE definition, which specified apnea. *Central apnea* implies a disruption in the central respiratory centers resulting in a cessation of respiratory effort; there is no attempt to breathe. This can be a manifestation of a number of disorders, including traumatic brain injury and infectious disorders (including both serious bacterial infections and respiratory diseases such as bronchiolitis and pertussis). Infants with *obstructive apnea* appear to be attempting to breathe through an occluded airway, with paradoxical movements of the chest and abdomen.[12] This is commonly described in upper and lower respiratory tract infections. In cases of oral dysphagia or gastroesophageal reflux disease, infants may exhibit obstructive apnea in relationship to feeds. There can be, at least subjectively, components of both central and obstructive apnea, indicating a *mixed picture. Apnea of prematurity* is a disorder in the control of breathing in premature infants, occurring in up to 25% of this group.[13] Its frequency decreases with increasing maturity, and it is usually outgrown by 37 weeks of postconceptual age.

Episodic *changes in infant skin color* are often difficult for observers to characterize, particularly in infants with darker skin tones. The color change may be a manifestation of normal infant physiology (e.g., acrocyanosis) or may indicate more serious problems with perfusion or oxygenation (e.g., central cyanosis). Cyanosis becomes apparent when at least 5 grams/100 mL of blood is deoxygenated. Because young infants are often polycythemic, this threshold is more easily met in this age group, and cyanosis may be observed in normal newborns, typically seen in the dense perioral veins. In the distal extremities, vasomotor instability can cause acrocyanosis without underlying pathology. Both of these entities are benign. Normal infant polycythemia can also lead to a ruddy appearance (plethoric), which, in the crying infant, may be misinterpreted by lay caregivers as cyanosis or "purple" coloring. For this reason, plethora was not included in the definition of BRUE. Pallor is characteristic of the vasovagal response and can be seen in association with gastroesophageal reflux, choking on feeds, or a vagal event.

In neonates, *changes in muscle tone* are difficult to classify because baseline neurologic status varies due to immaturity. Seizures in infants uncommonly present as stereotypical tonic-clonic activity and are more likely to present with altered consciousness or intermittent high and low tone (e.g., infantile spasms). In addition, infants may exhibit changes in tone (either decreased or increased) in the postictal state. Changes in tone may also be secondary to hypoxia resulting from apnea. Stiffening and arching behavior have been well described in infants with gastroesophageal reflux events (Sandifer's syndrome).

An *altered level of responsiveness* is part of the definition of BRUE because it can be an important component of the event associated with a serious underlying disorder. It was not part of the ALTE definition. Infants may lose consciousness or become unresponsive from a seizure, hypoglycemia, or hypoxemia. However, reports of altered consciousness often represent normal physiology or benign events as well. Because of an immature nervous system, infants may normally appear somnolent, appear unresponsive briefly, or lose consciousness after a breath-holding spell.

DIFFERENTIAL DIAGNOSIS

There are many potential causes of a BRUE or ALTE. The vast majority of conditions attributable to events previously referred to as ALTEs are self-limiting and not life threatening. For example, most patients

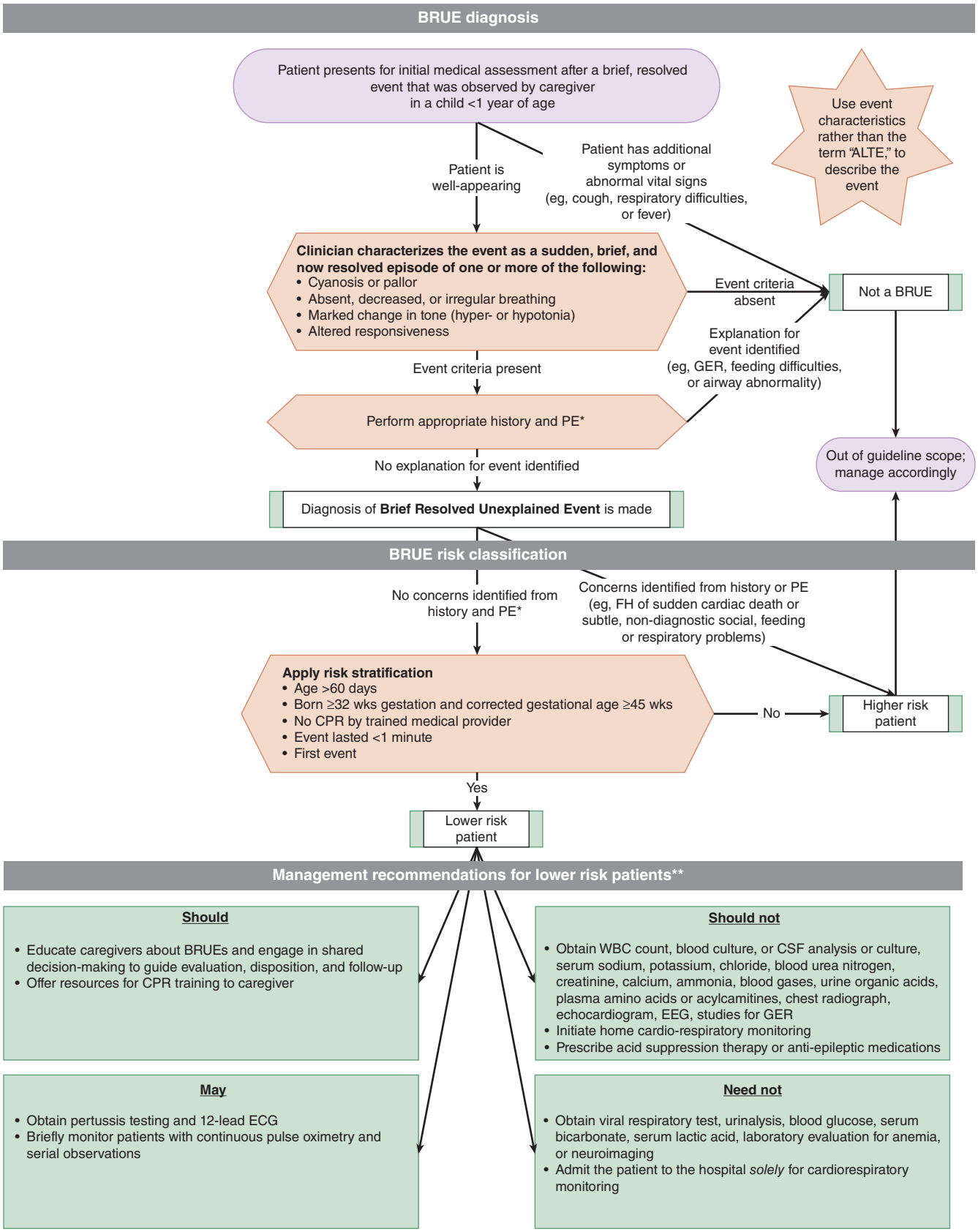

FIGURE 117-1. Diagnosis, risk classification, and recommended management of a brief resolved unexplained event (BRUE). *See Tables 3 and 4 of the original article for the determination of an appropriate and negative family history (FH) and physical examination (PE). **See Figure 2 of the original article for the American Academy of Pediatrics method for rating of evidence and recommendations. ALTE = apparent life-threatening event; CSF = cerebrospinal fluid; EEG = electroencephalogram; GER = gastroesophageal reflux. [Reproduced with permission from Tieder JS, Bonkowsky JL, Etzel RA, et al: Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants, *Pediatrics*. 2016;137(5): pii: e20160590.]

TABLE 117-1 Explanations for Events Previously Referred to as ALTEs

Common, Benign Explanation	Common Serious Pathology	Less Common Serious Pathology
Gastroesophageal reflux/ vomiting episode	Seizure/infantile spasm/ febrile seizure	Maxillofacial obstruction or tracheoesophageal fistula
Upper respiratory tract infection	Lower respiratory infections	Arrhythmia/cardiac
Coughing or choking episode	Laryngotracheomalacia	Pertussis
Periodic breathing	Inflicted injury	Serious bacterial infection
Oral dysphagia		Metabolic disease
Breath-holding spell		Electrolyte/glucose
		Poisoning

presenting with an ALTE are diagnosed as having an idiopathic cause or gastroesophageal reflux.[14,15] However, some patients may have a serious underlying disorder or risk for recurrence. **The risk of a serious underlying disorder or recurrence in BRUE patients is unknown**. **Table 117-1** lists common, uncommon, and rare diagnoses assigned to patients presenting with a concerning event previously termed an ALTE. Select processes are discussed independently below.

GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux is among the most common explanations for these events. Gastroesophageal reflux is the involuntary passage of gastric contents into the esophagus and occurs daily in infants during the first year of life. This form of reflux, or frequent "spitting up," is entirely normal and should be considered physiologic. As a result of the temporal correlation between peak age for these events and that of gastroesophageal reflux and the fact that reflux of gastric contents into the hypopharynx can trigger laryngospasm, a diagnosis of gastroesophageal reflux disease provides an easy explanation for events. Pathologic gastroesophageal reflux disease is defined as regurgitation of gastric contents into the esophagus with accompanying symptoms and complications such as failure to thrive. If events are recurrent and appear to be associated with gastroesophageal reflux events or symptoms, then initiating "reflux precautions" may be helpful, including small frequent feedings, upright positioning after feedings, frequent burping, and avoidance of tobacco smoke. **Routine use of medications to reduce the acidity of the gastric contents (proton pump inhibitors, histamine-2 blockers) is not recommended**.[16] If events persist despite conservative empiric treatment, then further evaluation for GI and other causes (see "Anatomic Causes" below) may be indicated. Unfortunately, testing has limitations, and causation is difficult to prove. Even when invasive testing has linked apnea to gastroesophageal reflux, a difference between acid and nonacid reflux has not been demonstrated.[17,18]

ORAL DYSPHAGIA

Problems with feeding coordination commonly cause these events, particularly in newborn infants. If the events appear to be related primarily to feeding, evaluation by speech or occupational therapy to evaluate and manage feeding and swallowing is recommended.[8,19]

UPPER AND LOWER RESPIRATORY TRACT INFECTIONS AND PERTUSSIS

Respiratory infections such as respiratory syncytial virus and pertussis can cause central, obstructive, or mixed apnea in infants by directly affecting the brain or by causing laryngospasm, coughing, choking, or oral dysphagia. In younger infants, the events can be difficult to characterize particularly because they can precede the typical viral prodrome (Chapter 128, "Pneumonia in Infants and Children"). Obstructive apnea commonly occurs when infants choke on respiratory secretions. Dysregulation of mucosal immune responses and sensorineural stimulation have been postulated as the cause of central apnea.[20-22] Wilwerth and colleagues reported a 2.7% rate of apnea among infants admitted with bronchiolitis, and apnea at presentation is a risk factor for subsequent apneic episodes.[23] Most studies have been performed on clinical or respiratory syncytial virus–proven bronchiolitis, but recently, the same association was found with metapneumovirus-associated bronchiolitis and a spectrum of respiratory pathogens.[24]

Bordetella pertussis, or "whooping cough," causes a respiratory infection that persists despite vaccination due to waning immunity in older individuals, vaccine failures, and vaccine refusal. Infants <6 months old are particularly susceptible because the initial immunization series begins at 2 months of age. Classically, the infection begins with upper respiratory infection symptoms (catarrhal phase) and progresses to paroxysmal coughing (paroxysmal phase) over 3 to 6 weeks. **However, it is important to understand that infants may present with isolated apnea**.[25]

Diagnosis can be difficult because **apnea may be the first presenting symptom of bronchiolitis *or* pertussis in younger infants**. While routine testing of bronchiolitis patients for viral pathogens is not recommended, testing for subclinical viral causes and pertussis in unclear cases presenting with apnea may be beneficial if exposure is of concern and test results are readily available. Infants presenting with apnea associated with proven or probable bronchiolitis or pertussis should be admitted for observation.

SEIZURES

Seizures have been identified in 4% to 7% of infants with ALTEs. Most often, they are the initial presentation of epilepsy in this age group but can rarely be secondary to underlying causes such as congenital brain malformation, metabolic disorders, electrolyte abnormalities, prenatally acquired brain injury, or intracranial bleeding (including abusive head injury). In well-appearing patients, an electroencephalogram seldom leads to a diagnosis of epilepsy and performing it often requires a hospital stay. **The American Academy of Pediatrics BRUE guideline recommends against routine testing for seizures, including electroencephalogram and head imaging for lower-risk patients**. For patients with recurring events and no explanation, particularly those concerning for seizures, neuroimaging and electroencephalogram may be indicated (Chapter 138, "Seizures in Infants and Children").

CHILD ABUSE/POISONING

Child abuse, including suffocation, abusive head injury, and poisoning, are potential serious causes of these events and are reported in 1.4% to 2.5% of all infants presenting with ALTEs (Chapter 150, "Child Abuse and Neglect").[26-28] Clinicians should have a high index of suspicion for these diagnoses since they can be difficult to recognize early on. A careful history and physical examination can determine risk most of the time. Patients meeting the criteria for a lower-risk BRUE and with a negative history and physical exam have an incidence <0.3% of abusive head trauma and likely do not warrant additional investigation for child abuse.[6] However, higher-risk BRUEs and those with social concerns or recurrent unexplained events may warrant additional investigation. Truman and Ayoub[29] reported an increased risk of future death or recurrent ALTEs among ALTE patients presenting with fresh blood from the nose/mouth and higher potential for nonaccidental trauma in infants >6 months of age. Vomiting, irritability, bruising, subconjunctival hemorrhage, rapid head enlargement or head circumference >95% for age, a prior ALTE, a recent emergency services call, and a discrepant history have also been found to be associated with abusive head injury.[30-35] Southall et al[31] performed covert video surveillance in a highly selective population of recurrent ALTE patients considered suspicious for abuse and found an association between intentional suffocation and bleeding from the nose and mouth, marital dissatisfaction and parental personality disorders, and unexplained sibling death. One small study found subsequent abuse-related death to occur in 9% of patients followed for 12 months after an ALTE,[36] and another study

found that 11% of hospitalized ALTE patients became victims of child abuse over a 5-year follow-up period.[37] This would seem to indicate that, while a small percentage of ALTE patients are found to be victims of nonaccidental trauma during their index visit, they are at long-term risk of abuse. It is extremely difficult to discern from the currently available data whether that indicates that the index visit represented subtle abuse or whether presentation with an ALTE may be associated with psychosocial issues that lead later to abuse.

Poisoning as a cause of an ALTE is also a concern and may be intentional or unintentional. Intentional poisonings frequently involve narcotics, benzodiazepines, or phenothiazines in an attempt to quiet or sedate a fussy infant.[38,39] Unintentional poisonings may involve inappropriate dosing of medications or mixing of over-the-counter cough and cold preparations containing ingredients with similar activity. Homeopathic medications, such as colic preparations, have also been associated with ALTEs.[40]

SERIOUS BACTERIAL INFECTIONS

Serious bacterial infections are an extremely rare cause of lower-risk BRUEs, and testing for bacterial infection, including cultures of blood, urine, and cerebrospinal fluid, chest radiographs, and WBC counts, is not recommended. In some situations, higher-risk infants, particularly those under 2 months, may warrant screening tests such as urinalysis. However, infants with fever, hypothermia, localizing symptoms and signs of infection, persistently ill appearance, or concerning comorbidities should receive appropriate testing for serious bacterial infections (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children").

Even for infants below 2 months of age with events previously referred to as ALTE, unless one of the above risk factors is present, a full "rule-out sepsis" will rarely identify an occult infection. A study of 112 infants <60 days old with ALTE who underwent testing for serious bacterial infection identified three cases of bacteremia and one urinary tract infection, as well as one case of pertussis. This constituted 2.7% of the sample, and four of the five affected patients had a history of prematurity.[41]

Chest radiograph is rarely indicated in absence of any respiratory findings. The rare exception to this includes patients under 2 months of age who may present without classic findings for pneumonia.[42,43] Additionally, respiratory symptoms and/or radiograph-proven pneumonia can develop *after* the initial presentation for ALTE,[4] and a paper documenting two deaths after discharge of 176 infants found both to have succumbed to pneumonia.[44] However, neither had a radiograph deemed to be positive in the ED. Careful outpatient follow-up is preferable to identify these patients, not routine radiographs.

BREATH-HOLDING SPELLS

Breath-holding spells occur in 4% to 5% of children <8 years of age and entail a cessation of respiration at the end of expiration, usually in response to pain, anger, or fear. Spells typically last <1 minute and may be accompanied by cyanosis, pallor, syncope, and seizures. Breath-holding spells have not been associated with any underlying medical condition, although there is some literature supporting the finding that pallid spells are associated with pronounced QT dispersion and may have a cardiac etiology. Breath-holding spells are generally easily recognized in older children, but they may be diagnosed in infants as young as 6 months of age: one study found that in 15% of children with breath-holding spells, the age of onset was <6 months.[45]

ANATOMIC CAUSES

Anatomic anomalies of the airway such as laryngomalacia, tracheomalacia, tracheoesophageal fistulas, vascular rings, and clefts may cause obstructive apnea, oral dysphagia, gastroesophageal reflux, sleep-disordered breathing, and obstructive sleep apnea. Subtle dysmorphisms may lead to abnormal breathing and obstruction during sleep, presenting with snoring, apnea, and mouth breathing.[46] An ear, nose, and throat evaluation is indicated for infants experiencing repeat and serious events, particularly those that indicate an unstable airway.

METABOLIC CAUSES

Inborn errors of metabolism rarely present as a BRUE in the face of negative newborn screens and a noncontributory history and physical examination. Therefore, routine testing is not indicated.[42] Inborn errors of metabolism might be suspected in patients who experience an event after their first period of prolonged fasting (e.g., an infant who just began sleeping through the night) or a history of poor feeding and somnolence throughout the neonatal period (see Chapter 146, "Metabolic Emergencies in Infants and Children"). Importantly, these infants are often symptomatic upon presentation and would not qualify as having a BRUE.[47]

CARDIAC CAUSES

Cardiac arrhythmias, channelopathies, Wolfe-Parkinson-White syndrome, cardiomyopathy, and myocarditis can present as a BRUE but are rare causes when there is a noncontributory history and physical examination.[42,48] An ECG, when available, is an accurate and inexpensive test that can be helpful in diagnosing this life-threatening disorder (see Chapter 130, "Syncope, Dysrhythmias, and ECG Interpretation in Children").

ED APPROACH

When a caregiver seeks medical attention for an event, the first step for the provider is to characterize the event as objectively as possible by taking a careful history. Ask targeted questions to understand the event including what happened before, during, and after the event and include any relationship to feeding, color change, central versus obstructive apnea, event duration, loss of consciousness, stereotypical seizure activity, and so on. If patients are currently exhibiting symptoms such as fever or respiratory illness and/or if there is a clear explanation for the event such as gastroesophageal reflux or upper respiratory infection, then manage the patient accordingly. These events should not be called ALTEs or BRUEs. For children with an upper respiratory infection, cough and cold preparations are contraindicated in infancy, even when it appears that an infant has choked on mucus. Infants with a concern for an airway abnormality should be evaluated by an otolaryngologist. Infants presenting with a potential seizure in the first year of life will certainly need neurologic consultation; an immediate electroencephalogram need not be ordered and antiepileptic medications should not be empirically initiated for a lower-risk BRUE patient (see Chapter 138, "Seizures in Infants and Children"). These consultations can be arranged on an urgent, outpatient basis rather than requiring admission for inpatient consultation in a stable infant. Home monitoring is not indicated following discharge.

Infants for whom the diagnosis is not immediately clear but who appear unstable should be resuscitated aggressively, and the aforementioned causes should be considered. The well-appearing infants without an explanation who fall under the guidelines for a BRUE should be risk-stratified and managed in accordance with their risk category.

RISK STRATIFICATION

Once a child has met criteria for a BRUE, implying no current symptoms and no explanation for the event, the next step is to assess the infant for risk of recurrence or a serious underlying disorder in the same manner that a patient with chest pain or young infant with fever might be risk-stratified. Patients who meet all the criteria in **Table 117-2** are presumed to be lower risk.[6] Infants not meeting all of these criteria are considered as having higher-risk BRUE. It is important to recognize that these criteria define a very low-risk group. Infants not meeting lower-risk BRUE criteria are a pleomorphic group to be assessed on an individual basis. Not every infant assigned to this "higher-risk group" is at substantial risk of future events.

DIAGNOSTIC TESTING AND DISPOSITION IN LOWER-RISK BRUE

It has been common to admit infants presenting with ALTE to the hospital for workup and monitoring. However, this is not without cost: the mean adjusted charge for children's hospitals in the United States is

TABLE 117-2 Criteria for Brief Resolved Unexplained Events (BRUE) and Lower-Risk BRUE

Criteria for BRUE	Age <1 y
	Sudden, brief episode
	Patient at baseline state of heath after event
	Event unexplained by history and physical exam
	≥1 of the following • Cyanosis or pallor • Absent, decreased, or irregular breathing • Marked change in tone • Altered level of responsiveness
Criteria for lower-risk BRUE	>60 d old
	Born at a gestational age of ≥32 wk and currently at a postconceptual age ≥45 wk
	First and single event
	Event lasting <1 min
	No CPR required by trained medical provider
	No concerning historical features
	No concerning physical exam features

TABLE 117-3 Recommendations for the Lower-Risk Patient With a Brief Resolved Unexplained Event (BRUE)

Clinician should:	Educate caregivers about BRUE
	Use shared decision making when possible
	Offer CPR resources
Clinician may:	Monitor for 1–4 h with pulse oximetry and serial exams
	Perform pertussis testing
	Perform ECG
Clinician need not:	Admit patient solely for monitoring
	Obtain respiratory viral testing
	Obtain urinalysis
	Obtain blood glucose, bicarbonate, or lactate
	Obtain neuroimaging
	Screen for anemia
Clinician should not:	Obtain WBC
	Obtain blood culture
	Obtain cerebrospinal fluid studies
	Obtain electrolytes
	Obtain metabolic workup
	Obtain chest radiograph
	Obtain echocardiogram
	Obtain electroencephalogram
	Obtain studies for gastroesophageal reflux
	Initiate home monitoring
	Prescribe acid suppression therapy
	Prescribe antiepileptics

$15,567 per admission (average length of stay, 4.4 days).[49] The financial burden is compounded by the frequency of iatrogenic complications, including medical errors and nosocomial infections, and the social implications from unnecessary admission and added anxiety. **The American Academy of Pediatrics BRUE guideline recommends against routine admission of these infants**. This is based on literature indicating which patients are at risk of a serious underlying pathology or recurrent event.[50-53] Instead, a period of observation on pulse oximetry with serial exams lasting 1 to 4 hours can be offered. The duration of this period of observation is a good opportunity for shared decision making with caregivers. A follow-up exam in 24 hours is recommended. Reassurance that **BRUE is not considered a precursor to sudden infant death syndrome** and CPR instruction resources may provide additional reassurance to caregivers. Recommended laboratory and radiographic evaluation of the lower-risk BRUE patient is minimal (**Table 117-3**). In a child without referable symptoms, WBC count, cultures, electrolytes, chest radiograph, echocardiogram, and evaluation for metabolic disease are not indicated. Similarly, viral respiratory testing, blood glucose, bicarbonate, hemoglobin, and neuroimaging are not necessary. Providers are given the option of testing for pertussis and obtaining an ECG in appropriate situations. These recommendations are based on a wealth of literature indicating a negligible yield of routine testing in ALTE patients, particularly those that the new guidelines would place in a lower-risk category.[3,42,54]

DIAGNOSTIC TESTING AND DISPOSITION OF HIGHER-RISK BRUES

Testing and hospitalization are useful in higher-risk BRUE patients, compared to lower-risk infants.[55] The risk of recurrence or an underlying condition is not well understood in this population, and there are no formal guidelines published for the management of the higher-risk BRUE patient. While no evidence exists to support a wide battery of screening labs, testing and observation periods may be warranted for certain populations. In this group, obtain a careful history and physical to uncover potential diagnoses that should be pursued, with emphasis on excluding oral dysphagia, abuse, arrhythmia, and CNS and anatomic problems. Laboratory and radiographic evaluation should be pursued for reasonable differential diagnoses after the history and physical exam. While admission is not mandatory in these patients, have a low threshold for admission and monitoring. For patients experiencing events formerly referred to as ALTE, between 12% and 14% have a subsequent event or are diagnosed with a condition that requires hospitalization. This rate is probably much lower under the BRUE definition. **Premature infants, infants 2 months old, infants with cyanosis, and those with chronic medical conditions seem to be at highest risk of recurrence.**[51,56] If events recur during hospitalization, events can be better explained. For example, oral dysphagia, sleep apnea, breath-holding spells, and seizures may be easily recognized by a medical provider during careful observation, and arrhythmias can be identified by monitoring.

POSTDISCHARGE OUTCOMES

ED physicians and caregivers may worry about subsequent sudden infant death syndrome or occult illness in infants who have experienced BRUE or ALTE. However, such patients are not at increased risk of sudden infant death syndrome.[48,57] That said, an event may be an initial sign of an underlying serious condition, such as nonaccidental trauma, that would place the infant at increased risk of recurrence or death. Overall postdischarge mortality in ALTE studies is 0% to 0.4%.[5,8,37] The likelihood of a subsequent ALTE after discharge ranges from 7.1% to 15.4%.[58] In lower-risk BRUE patients, recurrent events or an underlying disorder are very unlikely. For all BRUE patients, it is important to impart reassurance without offering false guarantees that another event will not occur. Currently, home monitors are not recommended for lower-risk BRUE patients.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 118

Sudden Infant Death Syndrome

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Sudden infant death syndrome (SIDS) is the unexpected death of an infant under 1 year of age for which no pathologic cause can be determined by an examination of the death scene, an autopsy, and a review of the infant's medical history. SIDS is a type of sudden unexpected infant death, a term that encompasses all unexpected infant deaths, both deaths from SIDS and those for which a cause is ultimately determined.[1] Of the 3500 U.S. yearly cases of sudden unexpected infant death, 27% to 43% are due to SIDS.[2,3] A number of other terms are used in pediatrics to refer to sudden and unexpected death. Sudden unexpected death of an infant is interchangeable with sudden unexpected infant death, and sudden death in the young (SDY) refers to such a death in any child ≤19 years old. Sudden unexplained early neonatal death is limited to infants succumbing within the first week of life and is often caused by congenital abnormalities. Sudden intrauterine unexpected death syndrome refers to stillbirths for which a postmortem exam cannot identify a cause, and sudden unexpected death in epilepsy is an unexpected death in an individual with epilepsy (excluding trauma or drowning) in which a postmortem exam does not reveal an anatomic or toxicologic cause.

EPIDEMIOLOGY AND RISK FACTORS

SIDS is the leading cause of death for infants between 1 month and 1 year of age. SIDS rates have declined considerably from 130.3 deaths per 100,000 live births in 1990 to 38.7 deaths per 100,000 live births in 2014.[2] This significant decrease can largely be attributed to the safer sleep practices promoted by the American Academy of Pediatrics' "Back to Sleep" and "Safe to Sleep" campaigns and, to a lesser extent, classifying deaths due to asphyxiation or strangulation in sleep separately from SIDS.[4] The incidence of SIDS peaks between 2 and 4 months of age, and boys account for 60% of SIDS deaths.[5] There are a disproportionate number of SIDS deaths in lower socioeconomic groups, although this is true for deaths in infancy from all causes. Other risk factors include low birth weight and prematurity.[6] There is ethnic variation, with Asian Americans at lower risk and African Americans and Native Americans at higher risk. Mothers of SIDS victims are more commonly <20 years old, overweight, unwed, use drugs, and have made few prenatal and postpartum visits. Prenatal and postnatal maternal smoking increases the incidence of SIDS. SIDS is more likely to occur during the winter months and while the infant is asleep. Thirty percent to 50% of SIDS patients have some acute infection, usually an upper respiratory tract infection, at the time of the event.

Sleep position has received a great deal of attention as a modifiable SIDS risk factor. The prone sleep position is associated with an odds ratio of 4.92 for SIDS. In clinical trials, prone infants were found to rebreathe expired air and experience hypercarbia.[7] In addition, infants normally dissipate heat through their head, and prone sleeping may inhibit heat loss, thereby exacerbating hyperthermia, another noted risk factor for SIDS.[8] A disproportionate number of infants succumb to SIDS while with a babysitter.[9] Many of these infants are found in the prone position. For some infants, this is the first time they have been placed in the prone position, and investigators have proposed that these infants have poor strength and tone in their neck muscles. Side-sleeping is also considered a risk factor for SIDS and discouraged. Because of these observations related to the prone position, the American Academy of Pediatrics has recommended supine sleeping for normal infants since 1992 and issued a statement in 2011 addressing specific issues related to sleep. A supine sleep position does not increase aspiration risk in infants with GI reflux and should apply to premature infants as well, even in neonatal intensive care units, as soon as they are medically stable. Infants should be placed on a firm mattress in a crib, bassinet, or portable crib (rather than adult bed) and protected from overheating. Bed sharing is discouraged, particularly in situations where the infant is less than 3 months of age; if the parent is a smoker, excessively tired, or on sedative substances (particularly alcohol); or on soft surfaces such as couches or beds with soft bedding.[4] Prone sleeping, bed sharing, or sleeping in a location other than a crib or bassinet was associated with 92.2% of SIDS deaths.[10] Sofas are a particularly hazardous sleep environment, accounting for 12.9% of sleep-related infant deaths.[11]

Swaddling, a common practice to minimize crying and colic, has been shown to increase the risk of SIDS, particularly in those who slept prone and those >6 months of age.[12] High ambient temperature might also contribute.[13] Use of a pacifier,[14] breastfeeding,[15] and immunizations[16] are protective against SIDS. Home monitoring has not been shown to prevent SIDS.[17]

Although a recognized case of abuse would not meet the criteria for SIDS, 1% to 5% of cases of sudden unexpected infant death are attributable to infanticide.[18] Familial cases of "SIDS" raise the possibility of abuse. The presence of traumatic head injury, bruises, long-bone fractures, rib fractures, internal hemorrhages, evidence of physical neglect, or blood around the nares suggests abuse.[19] It is so common for a SIDS victim to have a risky sleep position that a SIDS death without that factor might increase suspicion of abuse. Similarly, channelopathies are a common cause of sudden unexpected infant death that need to be excluded before a death is determined to be SIDS.

A registry has recently been developed to capture accurate and comprehensive information on all sudden death in pediatric patients and to further understand the epidemiology and risk factors for both SIDS and sudden unexpected infant death.[20]

PATHOPHYSIOLOGY

The exact cause of SIDS is not known, but it is felt to be multifactorial. Certain autopsy features seem relatively consistent among infants succumbing to SIDS, including intrathoracic petechial hemorrhages, thyromegaly, encephalomegaly, microcardia, unclotted blood in the heart, kidney growth restriction, and an empty bladder and rectum.[6] **The hypothesized mechanism of SIDS includes an interplay between an infant's underlying vulnerability, a critical period of development, and exogenous stressors—the triple-risk theory of SIDS.**[21]

A genetic basis for infant vulnerability has been heavily studied recently. Although no single genetic locus for SIDS has been identified, the 10-fold increased risk among the siblings of SIDS victims suggests a genetic component. Recently, polymorphism in the interleukin-10 gene promoter has been associated with SIDS and sudden unexpected death associated with infection. Brain biomarkers ergothioneine, nicotinic acid, succinic acid, adenosine monophosphate, and azelaic acid have been associated with and may be predictive of SIDS.[22] Recent studies on the brains of infants who have died from SIDS demonstrate the presence of medullary serotonergic (5-hydroxytryptamine) pathology, including abnormal firing, synthesis, release, and clearance,[23,24] and morphologic differences in the brainstem and hippocampus.[25,26] This likely leads to an inadequate response to hypoxemia. Autonomic dysfunction has also been postulated to play a role.[27]

Infancy may represent a critical period for hypoxia, a likely contributor to SIDS. In general, infants are more likely to have apnea, sustained desaturations, and poor ventilatory control. Neonates less than 1 month of age have a better anaerobic capacity for survival and ability to raise their partial pressure of arterial oxygen with a gasp. The fact that SIDS is uncommon in this age group supports a ventilator theory. Studies that look at infants in various altitudes have found an increase in SIDS risk in children who live in higher altitudes, specifically greater than 8000 ft.[28]

An example of environmental stressors can be seen with pre- and perinatal nicotine exposure. It is hypothesized that nicotine blunts ventilation responses to hypercapnia and reduces central respiratory chemoreception by changing the expression of serotonin receptors.[29] The fact that supine sleeping has decreased the incidence of SIDS dramatically also has made investigators look closely at how supine sleep may affect autoregulation of respiratory and cardiac centers. It is possible that supine sleep increases sympathetic tone and decreases rapid eye movement sleep, both of which are thought to decrease the risk of adverse

autonomic events.[30] In rats, a depression of ventilation in response to lipopolysaccharide might explain why infection can serve as an environmental stressor causing apnea during the vulnerable period of infancy.[31]

CLINICAL FEATURES AND MANAGEMENT

Generally, SIDS victims present in one of two ways: not amenable to resuscitation or potentially responsive to resuscitation measures. **Infants with rigor mortis, livedo reticularis, pH <6, and a significantly reduced core temperature in the absence of a history of environmental hypothermia should not be resuscitated.** However, the warm infant with apnea and no pulse may benefit from attempts at resuscitation. Regardless of the presentation of SIDS, obtain a thorough history and perform a complete physical examination. Important questions include complete description of the circumstances, caretakers, recent illness, prenatal and birth history, maternal and family history of miscarriages or other infant deaths, and family history of metabolic disease. For epidemiologic information, documentation of sleep position, sleep location, when and by whom the infant was last seen alive, when and in what position the infant was found, and whether or not bed sharing was involved is helpful to the coroner. Examination of the infant may be unrevealing or may show subtle but relevant signs of trauma, such as facial bruising, petechiae, blood in the nose or the mouth, or a torn frenulum, that raise suspicion of inflicted trauma. Rectal temperature and presence of rigor mortis or lividity will help the coroner in determining an approximate time of death.

The management of a nonresuscitative SIDS infant and interactions with the infant's family is emotionally challenging for many providers. One major responsibility of the physician is to notify, counsel, and educate the family. Frequently, the family wants to spend time with the deceased infant. **In general, the infant's body should not be manipulated or photographed after death has been declared unless permission is granted by the coroner.** If the family wants a hand or footprint, inkless pads must be used, and this must be documented in the medical record. Do not remove any lines or tubes placed during attempted resuscitation. If the presence of tubing is disconcerting to the family, tubes may be cut at the skin to appear less obvious. Unless directed otherwise by the coroner, the family can hold the deceased infant in a private setting but one that allows discreet monitoring of the family.

In most jurisdictions, victims of sudden and unexplained deaths must be reported as soon as possible to the coroner's office. **Treating physicians should complete a form reporting the death, but do not sign the official death certificate, as the cause of death will not be evident until the coroner's investigation is finished.** SIDS is technically a postmortem diagnosis, and *sudden unexpected infant death* is a more appropriate term for an ED record (although not included in the 10th revision of the *International Classification of Diseases*). If blood samples were drawn, put the samples on hold in the laboratory for later access by the coroner. Once death has been pronounced, the physician does not have jurisdiction to perform postmortem sampling or radiography unless directed to do so by the coroner.

Cardiac dysfunction related to prolonged QT interval or Wolff-Parkinson-White syndrome has been reported in sudden unexpected infant death,[32] with an accessory atrioventricular pathway found in 20% of "SIDS" cases on autopsy. Up to 35% have an abnormal result on postmortem cardiac channel testing.[33] If a cardiac anomaly, particularly a channelopathy is found, testing of family members may be lifesaving, and this is one concrete example to offer families to underscore the importance of an autopsy.

A home scene investigation is often conducted. Some jurisdictions have infant death teams that fully evaluate the circumstances surrounding the unexpected death of young infants. If the physician believes the infant is a victim of SIDS, the family should be so advised but told that the final confirmation awaits the autopsy report. Involving the primary care provider, who may follow up on the autopsy and remain in contact with the family, is of paramount importance. The hospital chaplain or social worker may provide additional support, and a chaplain consult may be especially needed in cases in which the laws regarding autopsy before burial are at odds with the family's religious doctrine. For infants requiring a perimortem baptism, this is ideally done by a chaplain but can be performed by a medical provider if no chaplain is available. Some states also require notification of organ procurement agencies.

When interviewed, one of the recurring themes voiced by mothers of SIDS victims is a sense of self-blame.[34] Eliminating interactions that exacerbate this sentiment, while preserving the need for a thorough investigation, is an important tenet in SIDS care. Most communities have organizations for parents of SIDS victims, and information about these organizations can be obtained from First Candle (1-800-221-SIDS, www.firstcandle.org).

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 119

Fever and Serious Bacterial Illness in Infants and Children

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INTRODUCTION AND EPIDEMIOLOGY

Fever is the most common chief complaint of children presenting to the ED, accounting for approximately 30% of pediatric outpatient visits. It is critical to differentiate mildly ill from seriously ill children with fever, especially in the neonate and infant. This challenge is compounded by the nonspecific symptoms and lack of a focus of infection in most children with fever. Many factors influence evaluation and management, including clinical assessment, physical examination findings, patient age, immunization status, and height of the fever.

This chapter focuses on the management of a neonate, infant, or child with acute fever at risk for serious bacterial illness, because morbidity and mortality are high if serious bacterial illness is missed or not properly treated. Neonates, defined as infants <1 month old, are at highest risk. Infants between 1 and 2 months of age are also at risk due to relative immunosuppression. The significance of age groups is discussed in the subsequent sections.

FEVER

Any elevation in temperature above normal is commonly considered a fever. A cutoff temperature formally defining fever is not universally accepted. In infants, the threshold for relative concern has traditionally been 38°C (100.4°F). **In the neonate or infant <2 to 3 months of age, temperature <36°C (96.8°F) is equally concerning.** Historically, occult bacteremia criteria used 39°C (102.2°F) in those 3 to 36 months in age, and a temperature >41°C (105.8°F) was considered to confer increased risk for serious bacterial infection.

In children >36 months old, sources of serious bacterial infection can be reliably ascertained by specific signs or symptoms. In infants and younger children, or children with developmental delay, who have limited ability to demonstrate specific signs and symptoms, the cause of fever may be difficult to determine, and more testing is often necessary.

Axillary temperatures are 0.6°C (1°F) lower than oral temperatures, which are 0.6°C (1°F) lower than rectal temperatures. Temperatures taken with infrared thermometers are of variable reliability and reproducibility.[1,2]

Fever is treated with acetaminophen or ibuprofen. The dosage of acetaminophen is 15 milligrams/kg/dose PO or PR (maximum daily dose, 80 milligrams/kg) every 4 to 6 hours, up to five times per day.

Acetaminophen may also be given IV with dosages, intervals, and maximum daily dose differing by age. The dosage of ibuprofen is 10 milligrams/kg/dose (maximum daily dose, 40 milligrams/kg) every 6 to 8 hours. Ibuprofen can be given to children older than 6 months of age.

SERIOUS BACTERIAL ILLNESS

Infants ≤3 months of age, and especially neonates, are relatively immunodeficient. Neonates and young infants demonstrate decreased opsonin activity, decreased macrophage and neutrophil function, and bone marrow insufficiency.[3] Infants and children demonstrate a poor immunoglobulin G antibody response to encapsulated bacteria until 24 months of age. Immune development is a continuum and improves as the child matures. Therefore, the age of the patient and the virulence of the bacteria are considerations for the evaluation of fever in children and the identification of serious bacterial illness. The most common manifestations of serious bacterial illness in children include urinary tract infection (UTI), bacteremia and sepsis, pneumonia, and meningitis. Of note, the following discussion applies primarily to developed countries.

Urinary Tract Infection Overall, the most common serious bacterial illness is UTI with or without pyelonephritis. The incidence among young children <24 months of age presenting to EDs with fever and no obvious source of infection is between 3% and 8%. In the first 2 months of life, the incidence of UTI is even higher; in a recent study, UTI was found in 11% of infants who presented to the ED with fever and 7.6% among those with a history of parent-reported fever, but no fever on arrival to the ED.[4] **Because UTIs may not produce symptoms other than fever, routinely obtain a urinalysis and culture in the evaluation of the febrile neonate or infant without other source**. Additional details regarding the epidemiology, risk factors, testing, and treatment of UTI can be found in Chapter 135, "Urinary Tract Infection in Infants and Children."

One study reported that 13% of infants (15 of 117 infants) <3 months of age with a febrile UTI admitted to the hospital had a sterile pleocytosis of the cerebrospinal fluid thought to be due to systemic release of inflammatory mediators or low bacterial virulence in the subarachnoid space.[5] A report by the Pediatric Emergency Medicine Research Collaborative Committee in 2011 showed similar findings.[6] However, another study did not replicate these findings.[7] Less than 1% of febrile infants with UTI will have bacterial meningitis, but concomitant infection of the urine and cerebrospinal fluid has been reported.[8]

Bacteremia and Sepsis Most studies of febrile infants ≤3 months old cite a bacteremia/sepsis incidence of 1% to 3%.[4,9] The most common causes of bacteremia in this age group are *Escherichia coli*, group B *Streptococcus*, and *Listeria monocytogenes*. Ill-appearing neonates or those identified as high risk because of laboratory testing have an incidence of serious bacterial illness of 13% to 21%.[10] Overall, however, viral infections are the most frequent cause of fever in infants. Many studies have shown that infants with viral illnesses are less likely to have serious bacterial infections.[10-12]

Most studies of bacteremia/sepsis also cite an incidence of 2% to 3% in febrile infants 3 to 36 months of age. Prior to the widespread use of heptavalent pneumococcal conjugate vaccine in 2000, a temperature of ≥39°C (102.2°F), WBC >15,000/mm^3, and absolute neutrophil count >10,000/mm^3 were independent predictors of occult bacteremia in febrile infants and children between 3 and 36 months old.[13] The presence of any of these factors increased the incidence of bacteremia to 8% to 17%.[13]

Administration of the *Haemophilus influenzae* type b vaccine and the pneumococcal conjugate vaccines (currently in use in the United States is the 13-valent pneumococcal conjugate vaccine) has decreased the occult bacteremia rate of febrile children 3 to 36 months of age to 0.5% to 0.7%.[14-17] The incidence of serious bacterial illness in children 2 to 6 months old who were incompletely or not immunized decreased because the widespread use of the vaccines resulted in herd immunity.[18] In 2009, a decavalent pneumococcal conjugate vaccine was released in Europe, and in 2010, the 13-valent pneumococcal conjugate vaccine was introduced in the United States. Both of these are expected to further decrease the incidence of invasive pneumococcal disease. The Centers for Disease Control and Prevention reports a 90% reduction in invasive infections from *Streptococcus pneumoniae* in children <5 years old when comparing 2016 with 1998 data in the United States.[18] Given these declines and the fact that 80% of pneumococcal bacteremia resolves spontaneously, the traditional standards for routine evaluation of the febrile infant 3 to 36 months old have changed. Guidelines now recommend urine testing only (at the discretion of the treating provider); routine WBC count and chest radiography are not indicated, and the use of routine antibiotics is discouraged.

Pneumonia and Sinusitis Pneumonia and sinusitis are common bacterial infections of childhood, frequently associated with or following upper respiratory tract symptoms (see Chapter 123, "Nose and Sinus Disorders in Infants and Children"; Chapter 124, "Mouth and Throat Disorders in Infants and Children"; and Chapter 128, "Pneumonia in Infants and Children"). Pneumonia occurs in all age groups, with the most common causative agents being the same as those for bacteremia or meningitis in each age group. The incidence of pneumococcal pneumonia in all ages has decreased since the introduction of the pneumococcal conjugate vaccines.[19-21] Sinusitis is uncommon in children <3 years of age because sinus formation is incomplete.

Plain chest radiographs remain the gold standard for diagnosis of pneumonia. In neonates and young infants, routine chest radiographs are not necessary unless the patient has specific physical examination findings suggestive of pneumonia, such as respiratory distress, rales, grunting, significant tachypnea, or hypoxemia.[20,22,23] In older children with chronic medical problems, such as cystic fibrosis, congenital heart disease, chronic lung disease, or malignancy, consider pneumonia in the differential diagnosis of fever and upper respiratory tract symptoms, even if there are no signs of lower tract infection. In one study performed before the widespread use of the pneumococcal conjugate vaccine, a WBC count of 20,000/mm^3 was associated with occult pneumonia in 19% of patients without focal findings.[24] Without predisposing conditions or abnormal test results, the decision to obtain a chest radiograph can otherwise be made clinically. Pneumonia in a febrile but otherwise asymptomatic child is unlikely.

Meningitis In developed countries, most studies of febrile infants <3 months old cite a bacterial meningitis incidence of 1%. The most common organisms are the same as those for bacteremia/sepsis: *E. coli*, group B streptococci, and *L. monocytogenes*. For children >3 months old, the most common organisms are *S. pneumoniae, Neisseria meningitidis*, and *Staphylococcus aureus,* with a lower incidence of *S. pneumoniae* meningitis since routine vaccinations with the conjugate vaccines.

Outside of North America, the epidemiology of meningitis is more complex, depending on the region of the world in which the patient has been living or traveling. *N. meningitidis* and *Mycobacterium tuberculosis* are the more common causes. Although *N. meningitidis* rarely occurs in North America, incidence may be higher elsewhere, especially in the "meningitis belt" of sub-Saharan Africa. **In patients with symptoms of meningitis and recent travel to Africa, meningococcal meningitis should be considered as a diagnosis.** Treatment is similar to other causes of bacterial meningitis. Tuberculosis meningitis is discussed in Chapter 174, "Central Nervous System and Spinal Infections."

The diagnosis of meningitis is made by cerebrospinal fluid analysis (see later section, "Procedures in Children: Lumbar Puncture"). It is often difficult to distinguish between viral and bacterial meningitis because there is a wide overlap in cerebrospinal fluid and peripheral blood findings. Because of the serious morbidity of missed meningitis, administer appropriate antibiotics in the ED and admit any ill-appearing patient or any patient <2 months old with any degree of cerebrospinal fluid pleocytosis.

Infants with aseptic meningitis generally should be hospitalized and ensured adequate long-term follow-up because they are at greater risk for dehydration and subsequent neurologic and learning disabilities. For older children with cerebrospinal fluid pleocytosis and likelihood of viral meningitis, if the child is to be discharged from the ED, it is wise to administer a long-acting parenteral antibiotic (ceftriaxone, 100 milligrams/kg IM or IV) and ensure follow-up in 24 hours.[25] Chapter 120, "Meningitis in Infants and Children," describes the diagnosis and treatment of meningitis in infants and children in more detail.

GENERAL TREATMENT AND DISPOSITION PRINCIPLES FOR FEVER BASED ON AGE

The clinical challenge is to distinguish the cause of fever: a benign viral infection, serious bacterial illness, or a noninfectious illness. Most fevers are due to viral infections, but bacterial infections are not infrequent. The significance of fever depends on multiple factors. If the physical examination identifies the source of infection, evaluation, testing, and treatment are dictated by the presumptive diagnosis. If the physical examination does not identify a source of infection causing fever, decision making is based first on age and then by height of fever. There are no absolute rules in the evaluation and management of fever, but the guidelines in **Table 119-1** are suggested for the management of neonates, infants, and children who are well appearing, have had all relevant immunizations, and have no obvious cause for the fever. Again, this discussion should be applied judiciously to nondeveloped countries or patients recently emigrated from nondeveloped countries, because the epidemiology of fever may be more diverse in international settings and is beyond the scope of this chapter. Detailed discussion of evidence-based information is provided later in the section, "Decision Rules for Assessment of Fever in Neonates and Infants <3 Months Old." Any ill-appearing infant or child should have a complete sepsis evaluation performed and should be admitted for parenteral antibiotic therapy.

FEVER EVALUATION IN NEONATES AND INFANTS ≤3 MONTHS OLD

In infants <3 months of age, review the birth history, including the length of the gestation, the use of peripartum antibiotics in the mother or infant during labor or delivery, and the presence of neonatal complications, such as fever, tachypnea, or jaundice. Signs and symptoms of serious bacterial illness are typically nonspecific in this age group. For example, vomiting and diarrhea accompany many problems, including gastroenteritis, otitis media, UTI, and meningitis. Alternatively, crying may be either a manifestation of serious bacterial illness or a benign condition of infancy (colic or hunger).

TABLE 119-1 Suggested Guidelines for the Evaluation and Management of Neonates, Infants, and Children With Fever Who Are Well Appearing, Have Had All Relevant Immunizations, and Have No Clinical Source for Fever

Age Group	Evaluation	Treatment and Disposition
Neonate, 0–28 d* of age, ≥38°C (100.4°F) SBI incidence of ill appearing: 13%–21%; if not ill appearing: <10%	CBC and blood culture *and* Urinalysis and urine culture *and* CSF cell count, Gram stain, and culture. Chest radiograph is optional, if no respiratory symptoms. Stool culture if diarrhea is present.	*Admit and treat with:* Parenteral antibiotic therapy with ampicillin, 50 milligrams/kg, and either cefotaxime, 50 milligrams/kg, or gentamicin, 2.5 milligrams/kg. **Do not give ceftriaxone to infants <1 month old because it may displace bilirubin and worsen hyperbilirubinemia**.
Infant 29–56 d* of age, ≥38.2°C (100.8°F) (Philadelphia Protocol) SBI incidence of ill appearing: 13%–21%; if not ill appearing: <5%	Same as for neonates.	*Discharge if:* WBC ≤15,000/mm^3 and ≥5000/mm^3 and <20% band forms. Urinalysis negative. CSF WBC <10 cells/mm^3. Negative chest radiograph or fecal leukocytes if applicable. *Admit if:* Any of above criteria is not met, and treat with parenteral ceftriaxone, 50 milligrams/kg with normal CSF, 100 milligrams/kg with signs of meningitis.
Infants 57 d to 6 mo* of age, ≥38°C (100.4°F) Non-UTI SBI incidence is estimated to be negligible. UTI is 3%–8%.	Urinalysis and urine culture alone. *or* For conservative management, treat infants 57–90 d using Philadelphia Protocol above.	*Discharge if negative.* *Treat for UTI* with oral antibiotics as outpatient (see Table 135-6). *Admit and treat* with parenteral ceftriaxone if patient fails conservative criteria for discharge.
Infants 57 d to 6 mo* of age ≥39°C (102.2°F) SBI incidence is estimated as <1%; non-UTI SBI incidence is estimated to be negligible. UTI is 3%–8%.	Urinalysis and urine culture alone. *or* Urinalysis and urine culture in addition to CBC and blood culture.	*Discharge if negative.* *Treat for UTI as above.* If WBC ≥15,000/mm^3, consider treatment with ceftriaxone, 50 milligrams/kg IV/IM, and follow-up in 24 h. If WBC ≥20,000/mm^3, consider chest radiograph and CSF testing.†
Infants/children 6–36 mo of age Non-UTI SBI incidence is <0.4% UTI in girls ≤8% UTI in boys (<12 mo) ≤2% Uncircumcised boys (1–2 y) remains 2%	Urinalysis and urine culture. Girls 6–24 mo Boys 6–12 mo Uncircumcised boys 12–24 mo	*Discharge if negative.* *Treat for UTI* as above as outpatient.
Children >36 mo and older	No workup is routinely necessary.	*Discharge and treat with antipyretics:* acetaminophen, 15 milligrams/kg PO/PR every 4 h, or ibuprofen, 10 milligrams/kg PO every 6 h as needed.

Abbreviations: CSF = cerebrospinal fluid; SBI = serious bacterial illness; UTI = urinary tract infection.

*For preterm infants, count age by estimated postconception date and not by actual delivery date for the first 90 days of life.

†Meningismus is difficult to discern in infants <6 months of age, and especially in infants <2 months of age, and its absence does not exclude meningitis. Because of the declining prevalence of meningitis in the United States as infants age, we recommend routine CSF testing in infants <2 months of age, but selective CSF testing in infants 2 to 6 months of age. Peripheral WBC count (whether elevated or low) does not predict the risk for meningitis, and the decision to perform a lumbar puncture should be made independently of the peripheral WBC count.[26-28]

Reproduced with permission from Tenenbein M, Macias CG, Sharieff GQ, Yamamoto LG, & Schafermeyer RW (Eds). *Strange and Schafermeyer's Pediatric Emergency Medicine*, 5 ed. McGraw-Hill, Inc. © 2019. Table 59-1, Pg 389.

Undress infants completely. Assess age-appropriate normal vital signs. Tachypnea or hypoxemia may be a clue to lower respiratory tract infection. Inconsolable crying or increased irritability when handled is frequently seen in infants with meningitis. Although fullness of the anterior fontanelle may be noted in some infants with meningitis, other signs of meningeal irritation, such as nuchal rigidity, are usually absent. Perform a head-to-toe evaluation to identify a focus of infection, such as an inflamed tympanic membrane or evidence of cellulitis.

Treatment of neonates and infants <3 months old with a focal source for fever is controversial. In a small study of tympanocentesis-confirmed acute otitis media, there were no cases of bacteremia or meningitis, but UTI was found in 9%.[29] The sample size of this study was not adequate to determine that blood testing or lumbar puncture was not necessary. A recent study in Europe[29] that used a step-by-step approach in the evaluation of febrile infants without a source of fever identified a population of infants at low risk for serious bacterial illness that could be managed on an outpatient basis without the use of antibiotics or lumbar puncture. This study used physical appearance (well-appearing or not), age (cutoff of 21 days), urinalysis, and biomarkers in a stepwise fashion to identify these infants. The low-risk group of infants still had a rate of missed serious bacterial illness of 0.7%. Therefore, even with an identified source, laboratory testing, close monitoring, and follow-up, especially in children <3 months old, are recommended to detect occult infection.

DECISION RULES FOR ASSESSMENT OF FEVER IN NEONATES AND INFANTS <3 MONTHS OLD

Clinical assessment of the severity of illness in neonates and young infants is difficult. The three most commonly applied outpatient criteria for the management of fever in well-appearing neonates and young infants are the **Rochester Criteria**, the **Philadelphia Protocol**, and the **Boston Criteria** (**Table 119-2**). All three have limitations for clinical decision making. A comparison of these decision rules is difficult because of differences in inclusion criteria, laboratory testing, and clinical implications for decision making. In addition, the routine administration of antibiotics to pregnant women who test positive for group B *Streptococcus* on vaginal cultures and improved immunization practices have decreased the incidence of serious bacterial illness, making it difficult to extrapolate these three decision rules to current practice.

The **Rochester Criteria** state that in well-appearing neonates and infants ≤60 days old, without prior or peripartum illness and with a normal CBC, a negative urinalysis and negative chest radiograph (if indicated) are sufficient to exclude serious bacterial illness.[30] However, the Rochester Criteria miss 1% of patients with serious bacterial illness and do not include lumbar puncture as one of the diagnostic tests. The Rochester Criteria are the least sensitive of the three guidelines.

In the largest validation study of the Rochester Criteria, the cohort of 1057 patients included 511 who met low-risk criteria (Table 119-2). Five patients, or 1% of patients identified as low risk, had serious bacterial illness that was missed. Lumbar puncture was not included in the rules, so the criteria do not provide the ability to exclude meningitis. Of note, the incidence of meningitis was 0.3% of the entire cohort of 1057 patients, which is lower than the 1% meningitis incidence cited in most other studies. In summary, the Rochester Criteria miss 1% of patients with serious bacterial illness and do not exclude meningitis.

The **Philadelphia Protocol** (Table 119-2) includes the results of lumbar puncture in clinical decision making and includes young infants age 29 to 56 days old.[31] The sensitivity of the low-risk criteria for excluding serious bacterial illness (neonatal bacteremia, UTI, or meningitis) is 98%; specificity is 44%; positive predictive value is 14%; and negative predictive value is 99.7%. The temperature criterion for fever was 38.2°C (100.8°F), not 38°C (100.4°F). The incidence of meningitis in this cohort was 1.2%. Using the Philadelphia Protocol, all patients with meningitis were identified. One of 288 patients, who had otherwise met low-risk criteria, was identified by an elevated cerebrospinal fluid WBC alone. In addition, all cases of bacteremia and UTI were identified by the Philadelphia Protocol.

TABLE 119-2 Comparison of Low-Risk Rochester Criteria, Philadelphia Protocol, and Boston Criteria for Assessment of Fever in Well-Appearing Neonates and Infants*

Low-Risk Criteria for Serious Bacterial Infection*	Rochester Criteria	Philadelphia Protocol	Boston Criteria
Fever	T ≥38°C (100.4°F)	T ≥38.2°C (100.8°F)	T ≥38°C (100.4°F)
Age	≤60 d	29–56 d	28–89 d
Past medical history	Term infant ≥37 wk gestation No perinatal or postnatal antibiotics No treatment for jaundice No chronic illnesses or admissions Not hospitalized longer than mother	No immunodeficiency syndrome	No immunizations within 48 h No recent antibiotics
Physical examination	Well appearing Unremarkable examination	Same	Same
Laboratory values			
Blood count	WBC ≥5000/mm^3, ≤15,000/mm^3 Absolute band count ≤1500/mm^3	WBC ≤15,000/mm^3 Band-to-neutrophil ratio ≤0.2	WBC ≤20,000/mm^3
Urinalysis	WBC ≤10 per high-power field	WBC ≤10 per high-power field	WBC ≤10 per high-power field
Stool	WBC ≤5 per high-power field	—	—
Lumbar puncture and cerebrospinal fluid findings	None	WBC ≤8 per high-power field	WBC ≤10 per high-power field Negative Gram stain
Chest radiograph	None	Negative	Negative if obtained
Comments	Excluded lumbar puncture, so number of missed meningitis cases is unknown. UTIs missed in those with negative urinalysis. The least sensitive of the low-risk criteria.	Sensitivity of low-risk criteria for SBI 98%; specificity 44%; PPV 14%; NPV 99.7%	5% of low-risk neonates and infants had SBI (8 bacteremia, 8 UTI, 10 bacterial gastroenteritis); 96% sensitive to ceftriaxone

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; SBI = serious bacterial illness; T = temperature; UTI = urinary tract infection.

*Any single deviation from the criteria is interpreted as failure of low-risk criteria.

The **Boston Criteria** (Table 119-2) attempted to identify young infants at lower risk of serious bacterial illness and safely treat them as outpatients with empiric ceftriaxone.[32] The Boston Criteria included infants 28 to 89 days of age and accepted a peripheral WBC up to 20,000/mm^3 as normal. Lumbar puncture was performed in all patients, and all patients with meningitis were excluded. In those who met low-risk criteria, <1% of patients had a missed serious bacterial illness, and none had complications after empiric treatment with ceftriaxone. By using the Boston Criteria, a greater number of patients are discharged.

Subsequent studies applying the Rochester, Philadelphia, and Boston decision rules missed serious bacterial illness in neonates 0 to 30 days old.[33,34] The safest course for 0- to 30-day-old infants is sepsis testing, admission, and empiric antibiotic treatment (Table 119-1).

The recognition of occult serious bacterial illness in well-appearing neonates and infants <3 months of age is difficult. No single clinical variable or diagnostic test can correctly or reliably identify it in this age group. In addition, as noted earlier with the Rochester, Philadelphia, and Boston decision rules, these rules differ in their inclusion criteria. Combinations of variables can be helpful. A study from Boston chose statistically significant cutoff points for predictive variables for SBI.[35] In order of greatest statistical significance for prediction were positive urinalysis, WBC >20,000/mm^3, temperature >39.6°C (103.3°F), WBC <4100/mm^3, and age <13 days old. No variable or cutoff point was 100% sensitive or specific, and the number of meningitis cases was too small to lead to the inclusion of results of lumbar puncture in the decision rule. This study challenges the previous study protocols by introducing clinical and diagnostic test variables that were determined to be statistically significant. Although this is not standard of care, this added information may help determine different thresholds for fever evaluation in the neonate or for admission and antibiotic therapy.

TREATMENT, DISPOSITION, AND FOLLOW-UP FOR FEVER IN NEONATES AND INFANTS ≤3 MONTHS OLD

There is no community standard of practice regarding the need for hospitalization of infants 3 months of age and younger. Some physicians hospitalize all febrile infants <3 months old, and others hospitalize selectively. Some have attributed this difference in management to a difference in bias, with physicians in private practice having a bias toward wellness (the infant is basically healthy) and emergency physicians having a bias toward illness (worst-case scenario approach).[36] Because the differentiation between sick and well infants <28 days of age is difficult, with varying reports of missed serious bacterial illness, all febrile infants <28 days of age should have sepsis evaluations, including CBC, blood culture, urinalysis, urine culture, cerebrospinal fluid cell count, Gram stain and culture, and admission for parenteral antibiotics. Infants who are ill appearing or fail to meet the low-risk criteria (Table 119-2) should be admitted and administered parenteral antibiotics. Ampicillin (50 milligrams/kg/dose every 8 hours) and cefotaxime (50 milligrams/kg/dose every 8 hours) is a common antibiotic regimen (or ampicillin and gentamicin, 2.5 milligrams/kg/dose), but choose antibiotics based on regional susceptibility patterns for group B *Streptococcus*, *E. coli*, and *L. monocytogenes*. **Do not give ceftriaxone to infants <1 month old because it may displace bilirubin and worsen hyperbilirubinemia.**

The decision to discharge a febrile infant home must be made after careful clinical and appropriate laboratory assessment and after ensuring the reliability of follow-up. Utilization of the Rochester Criteria, the Philadelphia Protocol, or the Boston Criteria may be considered. No missed cases of meningitis have been described with the Philadelphia Protocol and the Boston Criteria. The Philadelphia Protocol is recommended due to its high sensitivity.

If low-risk criteria are met for the Philadelphia Protocol, the patient may be discharged home without antibiotic administration, with evaluation in 24 hours. Additional factors for outpatient management are a reliable caretaker with a telephone and an infant who can maintain hydration. Any child who is ill appearing should be admitted and given parenteral antibiotics, regardless of the age.

Utilization of the data from viral testing may also influence the decision to discharge to home or admit for observation.

In a large, multicenter, retrospective study, Schnadower et al[37] proposed that febrile infants 29 to 60 days old who demonstrate evidence of UTI, but meet low-risk criteria, may be safely discharged with antibiotic therapy. Significant adverse events, such as meningitis and sepsis, requiring critical care intervention occurred in 2.8% of patients. Bacteremia occurred in 6.5% of patients. Low-risk criteria for both adverse events and bacteremia were lack of ill appearance in the ED and lack of high-risk past medical history. Additional low-risk criteria for bacteremia included peripheral band count of <1250 cells/mm^3 and peripheral neutrophil count of ≥1500 cells/mm^3.[37]

Antibiotics are administered for clinically evident bacterial disease, such as pneumonia, meningitis, otitis media, cellulitis, and septic arthritis. Specific management is outlined in Chapter 121, "Ear and Mastoid Disorders in Infants and Children"; Chapter 128, "Pneumonia in Infants and Children"; and Chapter 142, "Rashes in Infants and Children."

SPECIAL SITUATIONS: NEONATES AND INFANTS <3 MONTHS OLD WITH FEVER AND RECOGNIZABLE VIRAL ILLNESS

Many studies have shown that infants with bronchiolitis may still have a serious bacterial illness, although the risk of serious bacterial illness is significantly lower in febrile infants with bronchiolitis compared to febrile infants without bronchiolitis.[10,11,38-41] ED evaluation should therefore also include a minimum of a urinalysis and urine culture in patients with bronchiolitis. Consider urinalysis, urine culture, CBC, and blood culture in patients with suspected or proven enterovirus or parainfluenza infection.

SERUM BIOMARKERS

Although the serum WBC count, absolute neutrophil count, and band-to-neutrophil ratio remain the standard biomarkers for serious bacterial illness in young infants (see previous section on decision rules), the value of several other potential biomarkers deserves mention. C-reactive protein has been widely studied, but recent studies suggest that procalcitonin may be better. Procalcitonin is emerging as the best biomarker currently available to detect bacterial infections in febrile children, including in infants with fever without a source.[42-46] However, these studies have used varying cutoff levels. In addition, procalcitonin is not widely available, particularly within the United States. An approach combining clinical decision and serum biomarkers, as in the study by Gomez et al,[28] may be the best approach to the evaluation of these infants.

FEVER EVALUATION IN INFANTS 3 TO 36 MONTHS OLD

CLINICAL FEATURES

Clinical assessment is more reliable for older infants and young children than for young infants. Viral illnesses, including respiratory infections and gastroenteritis, account for most febrile illnesses and usually have system-specific symptoms, such as vomiting, diarrhea, rhinorrhea, cough, or rash. Characteristics to note are willingness of patients to make eye contact, playfulness and positive response to interactions, negative response to noxious stimuli, alertness, and ease of consolation. Toxic infants will not respond appropriately.

Otitis media is usually caused by ***S. pneumoniae*** or nontypeable ***H. influenzae***. Although pneumonia is commonly viral, it is difficult to distinguish bacterial from viral causes. In older infants or young children with UTI, fever is usually the only presenting sign, but a history of foul-smelling urine or crying with urination may be noted. Cellulitis is clinically apparent. Abscess may be associated with these patients as well. Bacterial pharyngitis is unlikely under the age of 3 years.

Nuchal rigidity and Kernig or Brudzinski signs may be absent in children with meningitis even up to the age of 2 years old. A bulging fontanelle, vomiting, irritability that increases when the infant is held, inconsolability, or a complex febrile seizure may be the only signs suggestive of meningitis. Infants with aseptic meningitis generally should be hospitalized and provided with long-term follow-up because they are at greater risk for dehydration and subsequent neurologic and learning disabilities.

Petechiae noted on physical examination are concerning for infection by *N. meningitidis*. However, most children with fever and petechiae will have a viral cause, such as adenovirus, whereas **purpura fulminans** (see Chapter 142, "Rashes in Infants and Children"), hypotension, lethargy, and meningismus predict meningococcemia. For the well-appearing child with fever and petechiae, there are no good predictors for serious bacterial illness. Time may be the best diagnostic test, with a brief observation period or admission warranted for cases that are indeterminate.

DIAGNOSIS

The American Academy of Pediatrics practice guidelines that advocate testing for UTI in children 2 months to 2 years of age may be broken down into guidelines for girls and boys.[9] *Ill appearance and history of UTI exclude patients from these guidelines.* For girls, testing should be done if they have two or more of the following risk factors: (1) white race; (2) age <12 months; (3) temperature ≥39°C (102.2°F); (4) fever ≥2 days; and (5) absence of another source of infection. Uncircumcised boys should be tested if no apparent focus of infection is present. Circumcised boys should be tested if two or more of the following risk factors exist: (1) nonblack race; (2) temperature ≥39°C (102.2°F); (3) fever >24 hours; and (4) absence of another source of infection.

Many would advocate that empiric blood testing and treatment for these patients is no longer necessary. Although reports of decreased bacteremia incidence have been published, as of this writing, no studies to determine predictors of bacteremia, outcome of empiric antibiotic use, reduction of complications, or outcome of nontreatment protocols have been published since the introduction of the pneumococcal conjugate vaccines. In addition, no practice parameters have established a current standard of care, and the American Academy of Pediatrics has not renewed its practice guideline since 1993. The physician is therefore left with evidence of decreased incidence of bacteremia, but no studies or practice parameters supporting a selective testing or nontesting protocol.

Given the decrease in invasive pneumococcal disease[14,18,47,48] and the limited predictive value of an elevated WBC for bacteremia,[14,49,50] three options exist. The *first option* is following the previous practice parameters and obtaining a CBC and blood culture on all children between 3 and 36 months old with a fever >39°C (102.2°F), and then treating with ceftriaxone only if the WBC is >15,000/mm^3.[51] Because of the low positive predictive value of an elevated WBC, the *second option* is obtaining a blood culture and waiting for results before beginning empiric treatment. The *third option* is to assume that the incidence of pneumococcal disease has decreased so substantially that laboratory evaluation in a well-appearing child is unnecessary, so discharge with primary care follow-up is reasonable. Variants on the first and second options may be to evaluate children between 2 and 6 months of age because these children have not received the first three vaccine series.

TREATMENT, DISPOSITION, AND FOLLOW-UP IN INFANTS 3 TO 36 MONTHS OLD

Any child who appears ill or toxic, is unable to maintain oral hydration, or has inadequate follow-up after discharge should be admitted for IV hydration and/or parenteral antibiotic therapy. Choices for antibiotics depend on the organism and the regional susceptibilities.

For recognized **bacterial infections**, use appropriate antibiotics based on the type of infection and regional and national standards. Treatment with high-dose amoxicillin (30 milligrams/kg/dose given three times daily, to a maximum adult dose) is recommended for otitis media, pneumonia, and sinusitis. Alternatives include amoxicillin/clavulanic acid, basing the dosing on high-dose amoxicillin, or azithromycin (10 to 12 milligrams/kg on day one (max 500 mg/dose) followed by 5 to 6 milligrams/kg once daily on days 2 to 5) for penicillin-allergic patients.

Patients with **cellulitis** should be treated with appropriate antistreptococcal and antistaphylococcal antibiotic therapy (Chapter 142, "Rashes in Infants and Children"). Cephalexin (20 to 25 milligrams/kg per dose four times a day for 10 days) or amoxicillin/clavulanic acid (22.5 milligrams/kg/d per dose twice daily) are appropriate choices. Given the increase in methicillin-resistant *S. aureus*, consider using an antibiotic regimen effective against this organism: clindamycin (10 milligrams/kg per dose three times a day for 10 days) or a combination of cephalexin and trimethoprim-sulfamethoxazole (trimethoprim, 4 milligrams/kg per dose twice a day for 10 days). The choice of antibiotic therapy for UTIs should be based on regional antibiotic susceptibility testing. Table 135-6 lists common treatment options.

Approximately 80% of patients with *S. pneumoniae* bacteremia will have spontaneous resolution, but in 20% of patients, complications will arise, such as meningitis, pneumonia, or sinusitis. Each of these factors may be considered if occult bacteremia is suspected. If treatment is indicated, obtain a blood culture before administration of ceftriaxone at a single dose of 50 milligrams/kg. Ceftriaxone reduces the risk of complications from bacteremia.[32,52,53] While reducing the incidence of infectious sequelae, the difficulty with empiric antibiotic treatment arises when the blood culture returns as positive but no cerebrospinal fluid studies were sent.

POSITIVE BLOOD CULTURES IN CHILDREN 3 TO 36 MONTHS OLD

Recall all children with positive blood cultures. In the case of positive *S. pneumoniae* cultures, if the child is receiving appropriate antibiotics, is clinically well, and is afebrile, the child should complete the course of therapy. If the child is afebrile and clinically well but not receiving antibiotics, opinions differ regarding the need for additional blood cultures and antibiotic therapy. In general, neither is necessary unless the child has developed a specific focus of infection.

The febrile child with a positive blood culture should receive evaluation (repeat blood culture, CBC, and consider urinalysis and lumbar puncture). For the persistently febrile patient who is well appearing and has a normal evaluation, admission is usual, although empiric treatment with ceftriaxone and follow-up as an outpatient may be considered.

For any patient who is ill appearing, obtain the sepsis evaluation and admit for parenteral antibiotics. Likewise, children who are thought to be at risk for serious bacterial illness and do not have reliable follow-up or the ability to return to the hospital should also be admitted for inpatient management.

Children with cultures positive for *N. meningitidis* or methicillin-resistant *S. aureus* should be admitted for parenteral antibiotic therapy. For organisms other than *S. pneumoniae, N. meningitidis,* or methicillin-resistant *S. aureus*, more conservative management may be warranted.

FEVER IN CHILDREN >36 MONTHS OLD

Children >36 months old are easier to evaluate, and their complaints are usually more specific. Children with infections such as UTI, meningitis, pneumonia, pharyngitis, and otitis media are more likely to complain of symptoms typical for these diagnoses. **Pharyngitis** due to group A *Streptococcus* becomes more common in this age group, especially in the school-aged child (Chapter 124, "Mouth and Throat Disorders in Infants and Children"). However, **infectious mononucleosis** also becomes more prevalent in this age group and may mimic the signs and symptoms of group A streptococcal pharyngitis. Treatment for group A streptococcal infection is amoxicillin (25 milligrams/kg twice daily for 10 days), penicillin G benzathine (50,000 units/kg IM single dose, up to 900,000 units IM for older pediatric patients), or azithromycin (10 to 12 milligrams/kg on day one (max 500 mg/dose) followed by 5 to 6 milligrams/kg once daily on days 2 to 5) for penicillin-allergic patients.

Kawasaki's disease (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease") is the most common cause of acquired cardiac disease in children and typically presents in children <5 years of age. Patients usually have high fevers for 5 days, strawberry-appearing tongue, conjunctivitis and iritis, red mucous membranes in the mouth and dry cracked lips, and swollen lymph nodes. Peeling of the skin in the hands, feet, and genital area may also occur in the later phases. Variants of Kawasaki's disease also occur, with fewer of these classic signs. Untreated patients with Kawasaki's disease may develop life-threatening coronary aneurysms. Treatment for Kawasaki's disease involves aspirin and IV immunoglobulin.

PROCEDURES IN CHILDREN: LUMBAR PUNCTURE

The usual goal of lumbar puncture in children is to obtain cerebrospinal fluid to test for markers of infection. Measuring opening pressure is not necessary, and therefore, the procedure is straightforward.

The condition of children with hypoxemia, respiratory distress, hypotension, and tachycardia may deteriorate when they are positioned for lumbar puncture, so resuscitation and empiric administration of IV antibiotics is needed prior to lumbar puncture. **In children with thrombocytopenia or factor deficiencies, replace platelets or factor before attempting lumbar puncture.**

PATIENT PREPARATION

Anticipate the procedure and its difficulties. Assemble a needle of the correct size, the appropriate specimen containers, and preprinted labels, and ensure a quiet environment without interruptions. Explain the procedure to the caregivers. In some institutions, written informed consent for lumbar puncture is required. Describe the process of procedural sedation if it is needed and obtain consent.

Apply a topical anesthetic cream or spray prior to needle insertion to reduce pain and improve the success rate of the lumbar puncture.[54,55] For infants, sucking on a pacifier dipped in sucrose solution is analgesic and calming and decreases crying. Prepare the skin using sterile technique.

POSITION

Have an experienced healthcare provider, the "holder," restrain the infant or child. Wrapping the child in sheets may help limit leg movement. Flexing the hips is more important than flexing the neck. In addition, flexing the neck may lead to respiratory difficulty. Continuous pulse oximetry may be helpful in monitoring for airway obstruction. Whether to choose the lateral recumbent position or the sitting position depends upon the preference of the physician. In some studies, using US to measure the width between the spinous processes in the sitting position was found to be better than the lateral decubitus position.[56,57] Although the sitting position may improve flexion of the hips, this position may be more difficult for the holder to maintain.

LUMBAR PUNCTURE TECHNIQUE

Most lumbar punctures are performed with a 22-gauge lumbar puncture needle, usually $1^1/_2$ in. in length for infants, $2^1/_2$ in. for children 2 years to 8 years, and $3^1/_2$ in. for older children. In obese patients, choosing a lumbar puncture needle may be more difficult. One study calculated that a lumbar puncture needle length (in centimeters) of 1 + [17 × (weight in kilograms/height in centimeters)] was most accurate.[58] Lumbar puncture depth was measured on abdominal CT scans to derive this formula. Lumbar needles with a clear hub show cerebrospinal fluid flow sooner than those with metal or opaque hubs.

Insert the LP needle between the L4 and L5 spinous processes in the intervertebral space in the midline of the back and direct the needle toward the umbilicus. This interspace is easily located because it lies in line between the iliac crests. Introduce the needle with the bevel of the needle up. Insert the needle until the characteristic "pop" identifies introduction into the subarachnoid space. An alternative method is to remove the stylet from the needle after the needle pierces the skin. Advance the needle, without the stylet, incrementally until cerebrospinal fluid flows. Occasionally rotating the lumbar needle clockwise or counterclockwise up to 360 degrees may help improve flow if the bevel of the needle is sideways. When removing the lumbar needle, replace the stylet.

Bonadio originally reported early stylet removal as the "Cincinnati method" in 1992.[59] Early experience with hollow-bore needles without a stylet associated this technique with the development of epidermoid tumors after the procedure. However, by puncturing the epidermis with the stylet in place and removing the stylet after introduction through the epidermis, this complication should be eliminated. Two separate reports found that the use of this Cincinnati method and the administration of topical anesthetics were associated with improved success rates.[54,55]

After successful entry into the subarachnoid space, collect three tubes of cerebrospinal fluid, each with at least 0.5 mL of fluid. Send the first tube for cell count, which includes WBC and red blood cell counts; send the second tube for protein and glucose measurement; and send the third tube for routine bacterial culture and Gram staining (**Table 119-3**). Additional tubes may be collected for polymerase chain reaction testing for bacteria and viruses as needed (e.g., enterovirus, herpes simplex virus). If the child has been pretreated with antibiotics, latex agglutination testing may be performed for *H. influenzae* type b, *S. pneumoniae*, group B streptococci, *E. coli*, and *N. meningitidis* serogroups A, B, C, Y, and W135. However, latex agglutination testing has poor sensitivity for bacterial infection. Polymerase chain reaction assays for pathogenic organisms, including panels for multiple viral and bacterial pathogens, are also available.

TABLE 119-3 Normal Cerebrospinal Fluid (CSF) Values by Age

CSF Parameter	0–4 wk	4–8 wk	>8 wk
WBCs/mm^3	0–19 cells/mm^3	0–9 cells/mm^3	0–9 cells/mm^3
Glucose (milligrams/dL)	30–60	40–70	50–80
CSF/blood glucose ratio	60%	60%	60%
Protein (milligrams/dL)	60–100	50–80	15–45

Source: Adapted with permission from Tenenbein M, Macias CG, Sharieff GQ, Yamamoto LG, Schafermeyer RW (eds): *Strange and Schafermeyer's Pediatric Emergency Medicine*, 5th ed. New York: McGraw-Hill Education, Inc. © 2019. Table 59-1, p. 389.

After a failed attempt, obtain a new needle and restart the procedure. Insertion into the L3 to L4 intervertebral space or the L5 to S1 intervertebral space may be successful. US- or fluoroscopy-guided lumbar needle insertion may be necessary when all else fails.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 120

Meningitis in Infants and Children

Amy Levine

INTRODUCTION AND EPIDEMIOLOGY

Meningitis is an inflammation of the leptomeninges, tissues that cover the brain and spinal cord. Untreated **bacterial meningitis** has a mortality of nearly 100%, so treat suspected bacterial meningitis promptly. Unfortunately, even with rapid antibiotic treatment, long-term neurologic sequelae occur. **Viral meningitis** has a range of severity: mild cases resolve without sequelae; however, some viruses, such as herpes virus, can cause severe infections. **Meningoencephalitis** is an inflammation of the brain as well as the meninges. It is less common than meningitis but can be devastating.

The most common causes of **bacterial meningitis** vary with the child's age (**Table 120-1**). Vaccination programs have had a huge impact on the epidemiology of bacterial meningitis in developed countries. For instance, *Haemophilus influenzae* vaccine has almost eliminated *H. influenzae* meningitis in countries where the vaccine is utilized and has decreased overall bacterial meningitis rates by 55%.[1] The introduction of the polyvalent vaccinations for *Streptococcus pneumoniae* (PCV7 in 2000 and PCV13 in 2010) has markedly decreased meningitis caused by that organism, although it remains the most frequent cause of pediatric meningitis.[2] *Neisseria meningitidis* remains an important cause of meningitis in children, and vaccines against serotype B have recently been introduced. Other important causes of bacterial meningitis in children include *Mycobacterium tuberculosis* and *Borrelia burgdorferi*, the causative agent of Lyme disease.

N. meningitidis commonly colonizes the upper respiratory tract, but does not commonly cause invasive disease in the Western hemisphere, although worldwide, there are endemic regions, such as the African meningitis belt. In childhood, there are two peaks of infection, one in

TABLE 120-1 Causes and Treatment of Bacterial Meningitis by Age Group

Age Group	Most Common Organisms	Treatment	Comments
Neonates (0–28 d)	Group B *Streptococcus*, *Escherichia coli*	Ampicillin 100 milligrams/kg every 8 h (age <7 d) or 75 milligrams every 6 h (age 7–28 d) AND Gentamicin 4 milligrams/kg every 24 h	Less common organisms: *Streptococcus pneumoniae*, other gram-negative organisms, *Listeria monocytogenes*, *Haemophilus influenzae* type b, *Neisseria meningitidis*
	Herpes simplex virus type 2 in infected mothers	If herpes suspected, add acyclovir 20 milligrams/kg every 8 h	
Young infants (28–90 d)	Group B *Streptococcus*, gram-negative bacilli	Ampicillin 100 milligrams/kg every 6 h AND Gentamicin 2.5 milligrams/kg every 8 h OR Cefotaxime 100 milligrams/kg every 8 h	Less common organisms: *S. pneumoniae*, *N. meningitidis*
	Herpes simplex virus type 2	If herpes suspected, add acyclovir 20 milligrams/kg every 8 h	
Older infants (>3 months) and children	*S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b	Vancomycin 15 milligrams/kg every 6 h AND Ceftriaxone* 50 milligrams/kg every 12 h OR Cefotaxime† 100 milligrams/kg every 8 h	Approximately half of meningitis in the United States is viral Immunization makes infection with *H. influenzae* unlikely in the older infant and child
	Herpes simplex virus type 2	If herpes suspected, add acyclovir 20 milligrams/kg every 8 h	

*For penicillin/β-lactam allergy, substitute chloramphenicol 50 milligrams/kg every 12 hours.[11]

†For penicillin/β-lactam allergy, substitute chloramphenicol 25 milligrams/kg every 6 hours.[11]

children less than 2 years of age and another in adolescents. The disease can be rapidly progressive and fulminant or present with more nonspecific symptoms. For this reason, it is important to maintain a high index of suspicion.[3]

Viral meningitis is much more common than bacterial meningitis. **Enteroviruses** are the leading cause worldwide.[4] Meningoencephalitis can be caused by enteroviruses, arboviruses (including West Nile virus), and herpes viruses. Herpes simplex virus type 1 infection occurs sporadically and causes a severe meningoencephalitis in children and adults. Herpes simplex virus type 2 develops in neonates born to infected mothers. Varicella-zoster virus can cause CNS infections including acute cerebellar ataxia. Many other viruses can cause CNS infections, including cytomegalovirus, Ebstein-Barr virus, mumps virus, adenovirus, influenza virus, parainfluenza virus, rubeola virus, rubella virus, and rabies virus. More recently, chikungunya and Zika viruses have emerged as important pathogens to consider in patients with history of travel in South and Central America, although cases have been diagnosed elsewhere.[5]

Fungal meningitis can occur in both normal and immunocompromised hosts. Important causes include *Cryptococcus neoformans*, *Coccidioides immitis*, and *Candida albicans*. Parasite infections can cause eosinophilic meningitis, defined as meningitis with at least 10 eosinophils/mm^3 of cerebrospinal fluid (CSF). The main causes are *Angiostrongylus cantonensis, Gnathostoma spinigerum*, and *Taenia solium*. These are endemic in the tropics but are spreading due to travel.[6]

PATHOPHYSIOLOGY

Bacterial meningitis in children usually results from bacteremia arising from organisms colonizing the nasopharynx. Less commonly, meningitis is caused by direct spread of bacteria from a contiguous site of infection, such as sinusitis, or from penetration of the CSF space from trauma, dermal sinus tracts, or open neural tube defects. Viral respiratory infections can increase the likelihood of meningitis when the nasopharynx is colonized.

Meningitis starts with breakdown of the blood–brain barrier. Then organisms enter the subarachnoid space. Once there, they can multiply quickly because the CSF has low levels of complement, antibodies, and other host defenses. Bacterial cell wall components and toxins produce an inflammatory response that increases vascular permeability and attracts leukocytes. The inflammatory response is responsible for much of the damage that ensues. Viral pathogens also produce damage by direct tissue destruction as well as inflammation.

CLINICAL FEATURES

HISTORY

Infants ≤30 days old are at risk for meningitis due to an immature immune response. Symptoms in this age group are variable and nonspecific and include both fever and hypothermia. Neonates can present with a history of lethargy, poor feeding, fussiness, bulging fontanelle, vomiting, diarrhea, seizures, grunting, or respiratory distress. Elements in the birth history that increase the likelihood of bacterial meningitis include prematurity, low birth weight, delivery complications, maternal infection, and maternal colonization with group B streptococci or herpes simplex. Some neonates present with few symptoms early in the course of their illness, so maintain a high degree of suspicion for early meningitis when confronted with a potentially sick newborn.

SIGNS AND SYMPTOMS OF BACTERIAL VERSUS VIRAL MENINGITIS

Bacterial Meningitis Certain signs and symptoms are especially helpful for diagnosing bacterial meningitis in infants and children. Caregiver reports of bulging fontanelle (likelihood ratio [LR] 8, 95% confidence interval [CI] 2.4–26), *or* neck stiffness (LR 7.7, 95% CI 3.2–19), *or* seizures (outside of the febrile seizure range of 6 months to 6 years; LR 4.4, 95% CI 3.0–6.4), *or* reduced feeds (LR 2, 95% CI 1.2–3.4) are concerning for meningitis.[7] Children with meningitis can present with the rapid onset of shock and altered mental status or with more gradual symptoms including fever, headaches, photophobia, upper respiratory symptoms, GI symptoms, irritability, and rash.

The World Health Organization's *Pocket Book of Hospital Care for Children* reported the performance of signs and symptoms for bacterial meningitis in infants and children and did not find any single clinical feature distinctive enough to make a "robust diagnosis of bacterial meningitis." However, the combination of fever, seizures, meningeal signs, and altered consciousness was consistently associated with bacterial meningitis.[8]

Viral Meningitis Infants with viral meningitis typically present with irritability and decreased activity. Headache and fever are the usual complaints in children. Other symptoms include photophobia, rashes, nausea, vomiting, and pain in the neck, back, and legs. Most children with West Nile virus will be asymptomatic or have mild illness. Severe neurologic illness from West Nile virus is more common in adults than in children.[9] Arboviruses can cause viral meningitis, encephalitis, or acute flaccid paralysis. A recent outbreak of enterovirus D68 was also associated with acute flaccid paralysis.[10]

Herpes simplex virus can cause devastating infection in neonates. Both type 1 and type 2 herpes simplex virus can cause neonatal disease. Infection can present in three ways: (1) as disseminated disease with involvement of the CNS in 60% to 75% of cases; (2) as primary CNS disease; or (3) as disease localized to the skin, eyes, and/or mouth. About two thirds of infants with disseminated or CNS disease will have skin lesions, but these may not be present at the time of diagnosis.[11]

Herpes infection can be transmitted through an infected maternal genital tract but may also be transmitted from a nongenital infection as well. Herpes simplex encephalitis (herpes simplex virus type 1) beyond the neonatal period presents with fever, altered mental status, seizures, and focal neurologic findings. It occurs sporadically.

PHYSICAL EXAMINATION

Neonates and infants (<90 days old) may have fever, normal temperature, or hypothermia. A normal temperature does exclude meningitis. Toxic appearance, lethargy, mottling, bulging fontanelle, abnormal cry, grunting, respiratory distress, and increased or decreased tone are all supportive of the diagnosis, but these signs can be absent. Jaundice or rash may occasionally be seen. Infants in the first months of life are unlikely to have a stiff neck. **Fever in neonates (rectal temperature of 100.5°F [38.0°C] or higher) should always prompt suspicion for meningitis.** In the absence of fever, a clinician should be concerned about infants who are ill appearing, have the signs or symptoms listed earlier, or are just not "acting right" according to their caregivers.

Older infants (>90 days old) with meningitis may also have fever, hypothermia, toxic appearance, lethargy, mottling, bulging fontanelle, abnormal cry, grunting, and respiratory distress at presentation. Children (>36 months of age) may have fever and nuchal rigidity. The **Kernig sign** (with the patient lying supine and the hip flexed at 90 degrees, the patient cannot extend the knee fully without pain) and **Brudzinski sign** (with the patient lying supine, there is involuntary flexion of the legs with passive neck flexion) may be present. Patients may have altered mental status, shock, focal neurologic signs, or signs of increased intracranial pressure. Rash or another focal sign of infection may be present. Patients may have symptoms of an upper respiratory infection, myalgias, or arthralgias. Look for evidence of methicillin-resistant *Staphylococcus aureus* when examining the skin, although *S. aureus* meningitis is most commonly associated with a history of a neurosurgical procedure.[12] Consider bacterial meningitis in the child with fever and seizures, outside the range of 6 months to 6 years.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

In neonates, the most common causes of meningitis in the United States are group B *Streptococcus* and *Escherichia coli*. Other organisms that cause meningitis include *S. pneumoniae*, *Listeria monocytogenes*, other streptococci, nontypeable *H. influenzae*, *Staphylococcus* species, *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Treponema pallidum*, and *M. tuberculosis*.[13] Neonates can develop meningitis from primary viral infection with herpes simplex virus or enteroviruses. The differential diagnosis of neonatal sepsis and meningitis includes infection from fungi (*Candida*) and protozoa (malaria crosses the placenta, and maternal malaria can infect the neonate). Noninfectious illnesses that can appear similar to sepsis and meningitis include cardiac disease, necrotizing enterocolitis, congenital adrenal hyperplasia, inborn errors of metabolism, and intracranial hemorrhage.

In older infants and children, the usual dilemma is differentiating acute viral and bacterial meningitis. The typical bacterial causes are *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b. Less common organisms include *M. tuberculosis*, *Nocardia* species, *T. pallidum*, and *B. burgdorferi*.[14] Fungal infections and parasitic infections can produce infection of the CNS. Infections around the brain and spinal cord may appear similar to meningitis. Collagen vascular disease, malignancy, and certain drugs and toxins should also be included in the differential diagnosis.

LABORATORY TESTING

Check a bedside glucose in all acutely ill infants and children with altered mental status. All children suspected of having meningitis should undergo a lumbar puncture when they are clinically stable. Although establishing a diagnosis is important, patients who are unstable but suspected of having bacterial meningitis should receive antibiotics as quickly as possible (Table 120-1). Defer lumbar puncture until the child is stabilized and can tolerate the procedure. Positioning an infant or child for lumbar puncture before stabilization can result in hypoxia and hypotension. There are a few contraindications to lumbar puncture in children besides hypoxia and clinical instability. These include focal neurologic findings, thrombocytopenia, local infection at the lumbar site, and vertebral abnormalities. See Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children," for details of pediatric lumbar puncture.

Children with *focal neurologic signs* should receive antibiotics promptly, without waiting for a CT scan or lumbar puncture; the next step is a head CT scan prior to lumbar puncture. CSF abnormalities of meningitis, such as neutrophilic pleocytosis, low glucose, and high protein, will persist for days despite antibiotic treatment. Bacteria are generally not evident on Gram stain after antibiotics have penetrated the CSF (time intervals for clearance of bacteria in the CSF range from 15 minutes to several hours; see later section, "The Child Pretreated with Antibiotics").

Spinal fluid should be sent for cell count, protein, glucose, Gram stain, and culture. In the event of a traumatic tap, send fluid for culture and use clinical judgment in the interpretation of other results. **Decision rules correcting the WBC count based on the number of red cells may not be reliable.**

The CSF of patients with bacterial meningitis tends to have lower glucose, higher protein, higher WBC counts, and a more frequent predominance of neutrophils relative to the CSF of patients with viral meningitis, but there is considerable overlap between the two groups.[15] The **Bacterial Meningitis Score**[14] (**Table 120-2**) identifies any one risk factor associated with bacterial meningitis and has been independently validated in multiple settings.[16-18] A recent meta-analysis showed that procalcitonin had good differentiation between bacterial and viral meningitis. In the same analysis, C-reactive protein did not perform as well.[19] In another systematic review, **procalcitonin** levels of ≥2 ng/mL had a

TABLE 120-2 Pediatric Bacterial Meningitis Score[14]*

Pediatric Bacterial Meningitis Score
• Positive cerebrospinal fluid (CSF) Gram stain (2 points)
• CSF protein >80 mg/dL (1 point)
• Blood absolute neutrophil count ≥10,000 cells/mm^3 (1 point)
• Seizure at or before presentation (1 point)
• CSF neutrophil count ≥1000 cells/mm^3 (1 point)
Interpretation
• 0 points: Aseptic meningitis very likely
• 1 point: Aseptic meningitis less likely
• 2 points: Bacterial meningitis more likely

Source: Adapted with permission from Nigrovic LE, Malley R, Kuppermann N. Cerebrospinal fluid pleocytosis in children in the era of bacterial conjugate vaccines. Distinguishing the child with bacterial and aseptic meningitis. *Pediatr Emerg Care* 25: 112–120, 2009. [PMID: 19225382]. Copyright Lippincott Williams & Wilkins.

sensitivity of 40% to 50% and a specificity of 90% for predicting the presence of a bacterial infection. Using the cutoff of <0.5 ng/mL to predict low risk of bacterial infection had a sensitivity of 80% and a specificity of 70%.[20] Polymerase chain reaction has been used in the past mainly for diagnosing viral meningitis. More recently, multiplex polymerase chain reaction diagnostics capable of detecting all of the major bacterial and viral causes of meningitis have been licensed.[21,22] Line probe assays based on hybridization of multiplex polymerase chain reaction have also been developed.[23] As such diagnostics become more widely available, they can decrease the time to diagnosis and allow for the detection of causative organisms in patients pretreated with antibiotics.

ED TREATMENT

ANTIBIOTICS

Antibiotics may have difficulty penetrating the blood–brain barrier. Therefore, doses used to treat meningitis are frequently higher than the doses used for other pediatric infections (Table 120-1).

For neonates, presumptive therapy for meningitis is generally ampicillin and cefotaxime or gentamicin. For older infants and children, Table 120-1 lists empiric treatment that will cover the three major bacterial causes of meningitis in the United States (*N. meningitidis*, *S. pneumoniae*, and *H. influenzae* type b).[24]

Patients with viral meningitis and meningoencephalitis generally receive supportive treatment, although acyclovir should be used when HSV infection is suspected. Lyme disease, tuberculous meningitis, fungal meningitis, and parasitic infections of the CNS all require specific therapy.

STEROIDS

Much of the damage caused by bacterial meningitis results from the inflammatory response in the CNS. In particular, labyrinthitis can result from bacterial meningitis, producing sensorineural hearing loss. For that reason, **dexamethasone** therapy to reduce CNS inflammation has been proposed as an adjunct to antibiotic therapy. Data supporting the benefits of dexamethasone treatment have been mixed in children. Dexamethasone was shown to reduce the likelihood of hearing loss in children with meningitis due to *H. influenzae* type b in the 1980s, when that was the predominant organism.[25,26] With the emergence of *S. pneumoniae* as the dominant strain, the data are less robust. A recent Cochrane review showed that patients with meningitis due to *S. pneumoniae* who were treated with dexamethasone had a lower death rate, whereas no effect on mortality was seen with meningitis due to *H. influenzae* or *N. meningitidis*. Steroids decreased the rate of hearing loss in patients with meningitis due to *H. influenzae* but not due to other bacteria. In the Cochrane analysis, patients in high-income countries treated with steroids were more likely to have reduced hearing loss or neurologic sequelae than patients in low-income countries.[27] The American Academy of Pediatrics stated in 1990 that dexamethasone may be considered for treatment of infants and children with meningitis due to *H. influenzae* type b, but does not recommend steroid use in other bacterial forms of meningitis.[28] If used for bacterial meningitis, dexamethasone needs to be given before or with the first dose of antibiotics to be most effective. The dose of dexamethasone is 0.15 milligram/kg IV every 6 hours.

DISEASE COMPLICATIONS

Mortality from bacterial meningitis has been reduced to <10% with antibiotics and supportive care.[29] However, survivors can experience sensorineural hearing loss, visual impairment, seizures, hydrocephalus, cognitive impairment, learning disabilities, and emotional problems.[30] Factors predicting hearing loss include *S. pneumoniae* as the etiologic agent and low glucose levels in CSF. Factors predicting mortality include coma, seizures, shock, respiratory distress, neutropenia, and a high protein level in CSF. Factors predicting adverse neurologic consequences in general include coma, seizures, fever for at least 7 days, and a low WBC count in CSF. Additional, although less robust, predictors include symptoms for more than 48 hours, male gender, fever, and absence of petechiae.[31]

In the ED, physicians may see respiratory compromise, shock, seizures, hypoglycemia, and hyponatremia in children with meningitis. Hypoglycemia results from sepsis and physiologic stress and is treated with administration of dextrose. Hyponatremia most commonly results from the syndrome of inappropriate antidiuretic hormone secretion due to brain inflammation. If syndrome of inappropriate antidiuretic hormone secretion is suspected, initiate fluid restriction to 75% of maintenance requirements after treating shock and dehydration. Low sodium can also be due to home oral rehydration with hypotonic liquids. Seizures can be due to brain inflammation, hypoglycemia, or hyponatremia, so **correct glucose and sodium before administering antiepileptic medications.**

Children with meningitis can also develop subdural effusions, empyemas, and strokes during treatment for bacterial meningitis, but these are not usually present at the time of ED presentation.

Viral meningitis and meningoencephalitis can range from mild to fulminant illness leading to death or permanent neurologic disability. Some lasting effects, such as learning disorders, can be subtle. Fungal meningitis can cause death or severe disability, particularly in immunocompromised hosts. Eosinophilic meningitis from helminth infection is generally self-limited and does not require antifungal therapy.

DISPOSITION AND FOLLOW-UP

In almost all circumstances, admit children with suspected bacterial or viral meningitis for definitive diagnosis, treatment, and supportive care. After discharge, children need long-term monitoring for neurodevelopmental problems and hearing loss.

SPECIAL CONSIDERATIONS AND SPECIAL PATIENTS

THE CHILD WITH A VENTRICULOPERITONEAL SHUNT

One of the most common causes of shunt failure in patients with shunted hydrocephalus is shunt infection. Most infections occur soon after shunt placement. The predominant organism is *Staphylococcus epidermidis*, suggesting that the infecting organism is likely introduced at the time of surgery. Other infecting agents include *S. aureus*, gram-negative rods, *Enterococcus faecalis*, and *Propionibacterium* species. Predictors of shunt infection include premature birth, use of a neuroendoscope during shunt placement, and replacement of an infected shunt.[32] Only about 10% of shunt infections occur more than 1 year after shunt surgery. Patients with late infections frequently develop peritonitis, often from appendicitis.[33] Shunt infections can present with symptoms of increased intracranial pressure, fever, redness or swelling along the shunt, or abdominal pain. Treatment should include vancomycin and a third-generation cephalosporin. Add an aminoglycoside if the Gram stain shows gram-negative rods.

Transfer to a tertiary care center for CSF shunt tap is the best option (See Video: VP Shunt Aspiration). Imaging to assess whether the shunt is intact and is functioning should be pursued if there is any question about shunt integrity.

THE UNVACCINATED CHILD

Widespread immunization against *H. influenzae* type b and *S. pneumoniae* has drastically reduced the rate of serious bacterial illness or meningitis from these two organisms. Children who are not immunized benefit from herd immunity. Nevertheless, when unvaccinated neonates or children develop fever, consider meningitis. Prior to the age of 18 months, children are less likely to develop meningismus, and it is difficult to exclude meningitis on clinical grounds alone. The septic-appearing infant or child with no immunizations should be managed conservatively with a lumbar puncture to exclude meningitis.

The real question is what to do with the unimmunized child with a fever who is not toxic appearing and has no obvious source for fever on physical examination. In children who have not been immunized, obtain

a WBC count and blood culture and give ceftriaxone if the WBC count is ≥15,000/mm^3. Arrange 24-hour follow-up either in the ED or with the child's primary provider.

THE CHILD PRETREATED WITH ANTIBIOTICS

Children who have signs or symptoms of meningitis but who have been pretreated with antibiotics present an important challenge. In one study, after receiving ≥50 milligrams/kg of a third-generation cephalosporin, sterilization of the CSF occurred as early as 15 minutes in meningococcal meningitis, about 4 hours in pneumococcal meningitis, and about 8 hours in group B streptococcal meningitis. Blood cultures obtained prior to antibiotic treatment were positive in 74% of cases.[34] Antibiotic pretreatment was examined in another study, which showed that CSF WBC count and absolute neutrophil count were unaffected by antibiotic administration, but patients had higher CSF glucose levels and lower protein levels after about 12 hours of antibiotic administration.[35] In the situation where a child has been pretreated, CSF assays with multiplex polymerase chain reaction may be helpful for the diagnosis of meningitis. As mentioned before, procalcitonin is emerging as a useful test for differentiating bacterial from viral meningitis. WBC count, C-reactive protein, lactate, and erythrocyte sedimentation rate have not performed as well.

THE CHILD WITH CSF LEAK

CSF leaks can occur spontaneously or in association with head trauma or surgical procedures. They can also occur as a complication of hydrocephalus. Children with CSF rhinorrhea or otorrhea are most likely to develop meningitis from *S. pneumoniae*. The signs and symptoms of meningitis tend to be milder in this group than in children with pneumococcal meningitis from bacteremia. Therefore, this is a situation in which meningitis is still a possibility despite a somewhat well-appearing child. Recommended treatment is with a third-generation cephalosporin and vancomycin.[36]

THE CHILD WITH PENETRATING HEAD TRAUMA

Children who have experienced penetrating head trauma can get meningitis from *S. aureus*, coagulase-negative staphylococci such as *S. epidermidis*, and gram-negative rods. Initial therapy should consist of a combination of drugs including vancomycin; cefepime, ceftazidime, or meropenem; plus an aminoglycoside such as gentamicin or amikacin.[37]

THE CHILD WITH A COCHLEAR IMPLANT

A cochlear implant increases the risk of meningitis in children. In most cases, the initial event is an acute episode of otitis media in the side with the implant, followed by the development of meningitis. In the first 2 months after cochlear implant surgery, treat otitis media with parenteral antibiotics. After 2 months, treat nontoxic children with otitis media with oral antibiotics. *S. pneumoniae* is the most common cause of meningitis in children with implants. Obtain cultures of middle ear fluid and CSF in children with suspected meningitis.[38]

Children with meningitis in the first 2 weeks after implantation are at risk of a greater range of pathogens than patients presenting later and should receive broad-spectrum antibiotics, such as meropenem and vancomycin. Children with symptoms of meningitis developing later than 2 weeks after implantation should receive the standard empiric treatment for meningitis. Consult ear, nose, and throat specialists for imaging recommendations and possible surgical management. For further discussion of cochlear implant complications, see Chapter 242, "Ear Disorders."

THE CHILD WITH A FEBRILE SEIZURE

Children with meningitis can present with seizures. However, simple febrile seizures are more common. Simple febrile seizures occur in up to 5% of children between 6 and 60 months of age. About one third of children will experience a recurrence. The American Academy of Pediatrics defines simple febrile seizures as seizures that are generalized, last less than 15 minutes, and do not recur within 24 hours. **Routine lumbar puncture is not indicated for simple febrile seizures, but should be performed if the child has an examination consistent with meningitis.** Children between 6 and 12 months of age should be considered for a lumbar puncture if they are missing immunizations against *H. influenzae* type b or *S. pneumoniae* or if their immunization status is not known. Clinicians should be able to recognize meningitis clinically after 12 months of age. A lumbar puncture should also be considered in children pretreated with antibiotics because antibiotics can mask the development of meningitis. Routine blood work, imaging, and electroencephalogram are not recommended.[39]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 121

Ear and Mastoid Disorders in Infants and Children

Carmen M. Coombs

INTRODUCTION

Ear pain, or otalgia, is one of the most common pediatric outpatient chief complaints. The differential diagnosis is listed in **Table 121-1**. This chapter discusses acute otitis media, otitis media with effusion, otitis externa, acute mastoiditis, and foreign body. The ear is divided into three major parts: (1) the outer ear, which includes the auricle/pinna and the external auditory canal; (2) the middle ear, which is bound by the tympanic membrane laterally, contains the auditory ossicles, and is connected to the nasopharynx via the eustachian tube; and (3) the inner ear, which includes the semicircular canals, the cochlea, and the auditory nerve (**Figure 121-1**).

ACUTE OTITIS MEDIA

EPIDEMIOLOGY

Acute otitis media (AOM) is the acute onset of signs and symptoms of middle ear inflammation. Although the incidence is decreasing in the postpneumococcal vaccine era, otitis media remains the third most

TABLE 121-1 Differential Diagnosis of Acute Ear Pain

Common
- Acute otitis media
- Otitis externa
- Foreign body in the external ear canal
- Impacted cerumen

Less common
- Cholesteatoma
- Referred pain from oral cavity pathology (e.g., dental caries and infections, pharyngitis)
- Cellulitis of the auricle/pinna
- Contact dermatitis (e.g., earrings)
- Trauma to the auricle/pinna (e.g., hematoma with pressure necrosis of cartilage)
- Physical trauma or barotrauma to the tympanic membrane and middle ear

Rare
- Mastoiditis
- Herpes zoster oticus (Ramsay Hunt syndrome)
- Hemotympanum due to basilar skull fracture
- Rhabdomyosarcoma of the ear or temporal bone

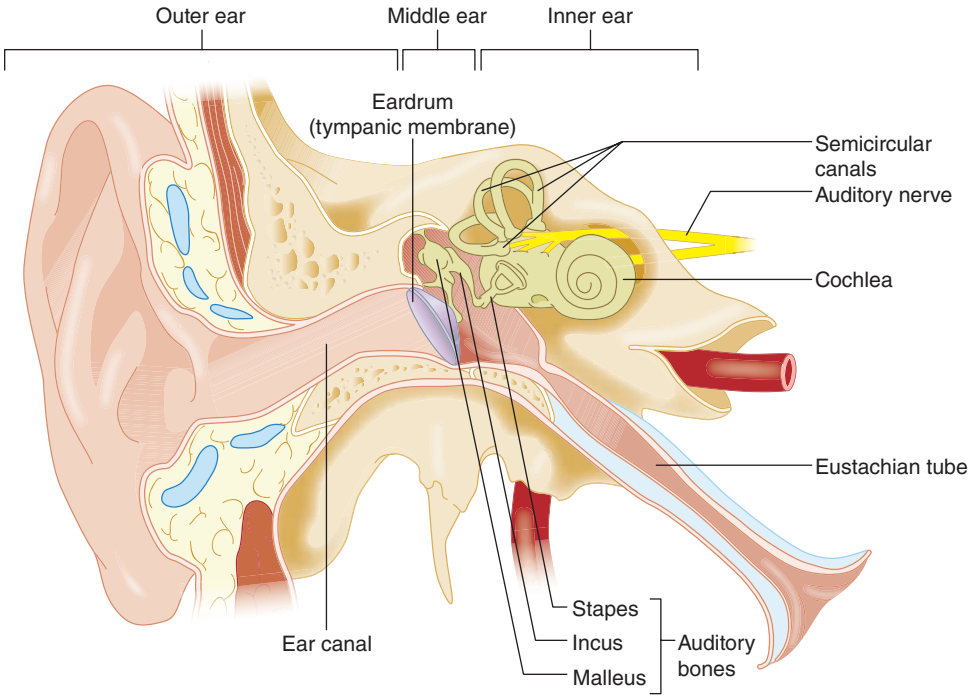


FIGURE 121-1. Anatomy of the outer, middle, and inner ear.

common diagnosis for ED visits in children under 15 years old, accounting for 6.1% of all ED visits.[1]

The peak incidence of AOM is between 6 and 12 months of age.[2] Recent U.S. studies found that 23% to 46% of children had at least one episode of AOM by the age of 1 year,[2,3] and this rate increased to 60% by the age of 3 years.[2] Risk factors include male sex, non-Hispanic white race, family history of recurrent AOM, day care attendance, and early occurrence of the first episode of AOM before 1 year of age.[2] The incidence is also higher in children with atopy,[2] craniofacial anomalies, and immunodeficiency syndromes. Breastfeeding in infancy is protective and decreases the risk of AOM.[2,3]

PATHOPHYSIOLOGY

In the healthy state, the middle ear is aerated via the eustachian tube and its connection to the nasopharynx (Figure 121-1). If the eustachian tube becomes obstructed due to inflammatory edema and/or mucus (often associated with a viral upper respiratory infection), middle ear secretions build up and create conditions favorable to the development of AOM. Compared with adults, the eustachian tube in children is shorter and more horizontally oriented. This orientation is the anatomic rationale for the increased incidence of middle ear disease seen in children.

Microorganisms responsible for AOM originate from the nasopharynx and enter the middle ear space via the eustachian tube. Bacteria can be isolated in 55% of cases of AOM in young children. The most common bacterial pathogens include *Streptococcus pneumoniae* (23.6%), nontypeable *Haemophilus influenzae* (29.1%), *Streptococcus pyogenes* (3.7%), and *Moraxella catarrhalis* (2.8%).[4] Common viruses identified in cases of AOM include picornaviruses (e.g., rhinovirus, enterovirus), respiratory syncytial virus, and parainfluenza virus.[5]

CLINICAL FEATURES

The classic symptom is rapid-onset ear pain. Young or nonverbal children may hold, tug, or rub the ear or be fussy and irritable. Fever is present in many but not all cases. Fever ≥40.5°C (104.9°F) is rare and should prompt consideration of alternative diagnoses.[6] Older children may complain of decreased hearing due to conductive hearing loss from middle ear effusion. An antecedent history of rhinorrhea, congestion, and/or cough is common because an upper respiratory tract infection creates conditions favorable to the development of AOM.

The most common acute complication is tympanic membrane perforation, which typically heals spontaneously after the AOM resolves. More serious acute complications are rare and include mastoiditis, spread to the intracranial cavity (meningitis, encephalitis, abscess, sinus thrombosis, otitis hydrocephalus, or facial or abducens nerve palsy), and involvement of the inner ear (labyrinthitis). Acquired sensorineural hearing loss can result from chronic or recurrent AOM and secondary inflammatory changes in the inner ear.

DIAGNOSIS

The diagnosis is clinical. Tympanocentesis is the gold standard for diagnosis, but is outside the scope of most pediatricians and emergency providers. The three different clinical scenarios that meet the criteria for diagnosis are listed in **Table 121-2**.[7] **Erythema of the tympanic membrane alone is insufficient for the diagnosis of AOM because erythema can be caused by middle ear inflammation, crying, or fever.**

For proper otoscopic examination, use a bright light source, clean otoscope head, and properly fitting speculum. To immobilize the child's head, have the caregiver hold the child's head against the caregiver's shoulder or chest or place the child supine with the examiner controlling the head of the child and the parents holding the child's arms. Remove impacted cerumen with a soft speculum or by gently irrigating the canal with warm water. Both procedures can cause pain and/or traumatic perforation of the tympanic membrane and must be done carefully. Adjunctive use of a topical ceruminolytic agent such as docusate may be helpful in some cases.[8]

Assess for the presence or absence of discharge in the ear canal and the tympanic membrane's position, color, and degree of translucency.

TABLE 121-2 Clinical Criteria for the Diagnosis of Acute Otitis Media (AOM)

Scenario 1	Moderate to severe bulging of the tympanic membrane
Scenario 2	Mild bulging of the tympanic membrane and at least 1 of the following: Acute onset of ear pain (<48 h) Intense erythema of the tympanic membrane
Scenario 3	New onset of otorrhea not due to otitis externa or foreign body (indicating perforation of the tympanic membrane or AOM in a child with tympanostomy tubes)

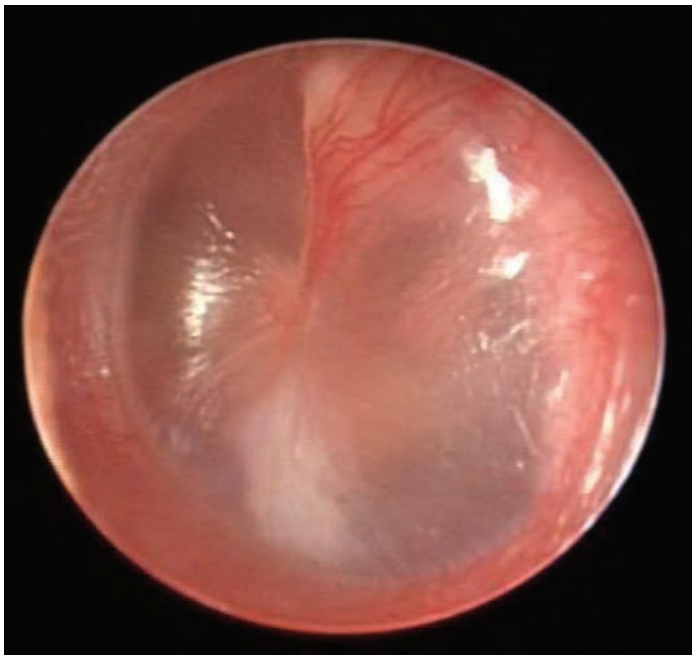


FIGURE 121-2. Normal right tympanic membrane (TM). TM is flat, pearly gray, and translucent. [Image used with permission of Dr. Shelagh Cofer, Department of Otolaryngology, Mayo Clinic.]

A normal tympanic membrane is flat, pearly gray, and translucent (**Figure 121-2**). Erythema and bulging of the tympanic membrane are consistent with AOM (**Figure 121-3**).

TREATMENT

Most cases of AOM resolve spontaneously and without complications. Antibiotics are recommended for some but not all cases of AOM.[7] **Pain control, however, is an essential treatment modality and should be provided whether or not antibiotics are prescribed.**

PAIN CONTROL

The medications most commonly used to treat ear pain are shown in **Table 121-3**. Ibuprofen and acetaminophen are the first-line agents and have the added benefit of also being antipyretics. Opioid medications such as oxycodone and hydrocodone may be considered for severe ear pain, but should be used rarely and reserved as second-line agents. Topical otic analgesic drops may be used in combination with systemic analgesics because they have a rapid onset and may provide temporary relief of ear pain, but they have a short duration of action.[9,10] **Topical analgesics are contraindicated in patients with perforation of the tympanic membrane and those with tympanostomy tubes.**

OBSERVATION OR ANTIBIOTICS

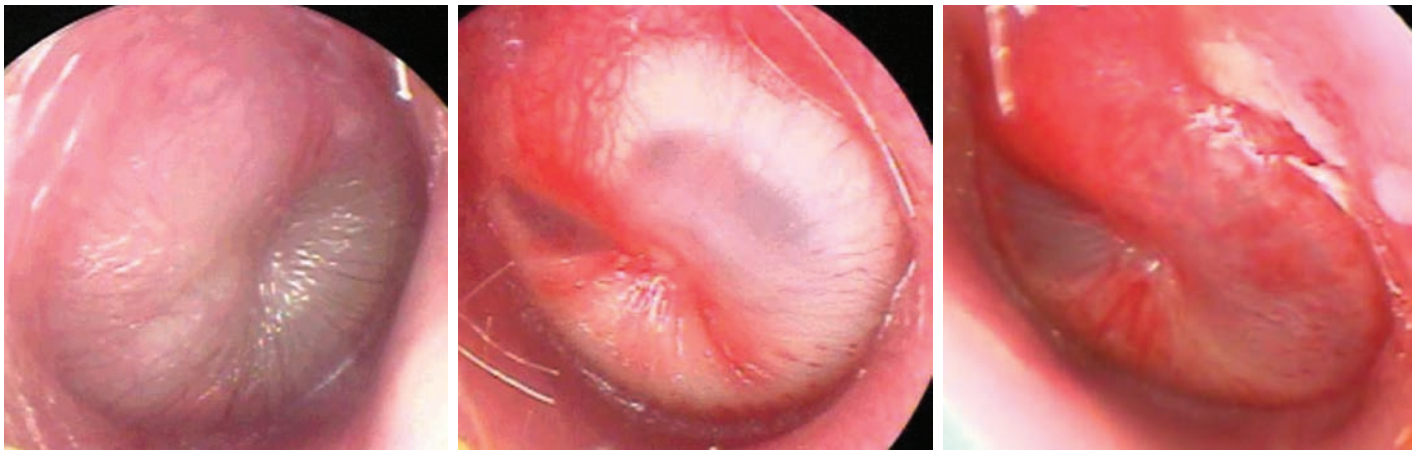
Some but not all cases of AOM require treatment with antibiotics. Consensus guidelines from the American Academy of Pediatrics and American Academy of Family Physicians recommend an initial observation option (defined as withholding immediate antibiotics) for select children with AOM.[7] An observational approach for AOM has been used successfully in areas of Europe with similar rates of mastoiditis (the primary suppurative complication of AOM) compared to the United States,[11] and this approach is now supported by several randomized controlled trials, systemic reviews, and observational studies.[7] **Tables 121-4** and **121-5** describe which children can initially be observed without antibiotics and which children require initial antibiotics.

If acceptable to both the provider and caregivers, initial observation is appropriate for otherwise healthy children with uncomplicated AOM without severe signs or symptoms (mild ear pain for <48 hours and temperature <39°C [102.2°F]) who are 6 to 23 months old with *unilateral* AOM and children ≥24 months old with *unilateral or bilateral* AOM (Table 121-4).[7] Provide follow-up in 48 to 72 hours, and initiate antibiotics only for worsening symptoms or lack of improvement. A wait-and-see antibiotic prescription can be provided at the initial visit with instructions for the caregiver to initiate antibiotics if the child worsens or fails to improve. Patients who do not meet the criteria for an initial period of observation require prompt treatment with antibiotics and include children who are <6 months old, have severe signs or symptoms, are <24 months old with *bilateral* AOM, have recurrent AOM, have AOM with perforation, have myringotomy tubes, and/or have underlying craniofacial abnormalities or immunodeficiencies (Table 121-5).[7]

CHOICE OF INITIAL ANTIBIOTICS

Initial antibiotic treatment for AOM in which antibiotics are prescribed is shown in **Table 121-6**. High-dose amoxicillin (45 milligrams/kg per dose PO twice daily) for 5 to 10 days is the first-line treatment.[7] The higher dose achieves concentrations in the middle ear that exceed the minimum inhibitory concentration for highly resistant forms of *S. pneumoniae*. Alternative regimens are appropriate for children with penicillin allergies, children who have received amoxicillin in the past 30 days, children with concurrent conjunctivitis, children with myringotomy tubes, and those unable to tolerate oral treatment (Table 121-6).[7]

With initiation of appropriate antibiotics, fever and ear pain should be expected to persist for 24 to 48 hours. If symptoms persist



A B C

FIGURE 121-3. Tympanic membrane findings consistent with acute otitis media. **A.** Severe bulging and opaque. **B.** Moderate bulging and opaque with intense erythema. **C.** Mild bulging with intense erythema. [Photos used with permission of Alejandro Hoberman, Department of Pediatrics, Children's Hospital of Pittsburgh.]

TABLE 121-3 Treatment of Ear Pain From Acute Otitis Media

Medication	Comments
Systemic	
Ibuprofen (10 milligrams/kg PO every 6 h PRN)	First-line agents Also work as an antipyretic
Acetaminophen (15 milligrams/kg PO/PR every 4 h PRN)	
Oxycodone (0.1 milligram/kg PO every 4 h PRN)	Second-line agents Consider for severe otalgia
Hydrocodone (0.2 milligram/kg PO every 6 h PRN)	
Topical	
Antipyrine/benzocaine (2–3 drops every 1–2 h PRN)	Apply drops to a small piece of cotton and place in external ear canal Provide rapid but short-term relief Contraindicated with perforation or tympanostomy tubes
Lidocaine (2% aqueous) (2–3 drops every 1–2 h PRN)	

Abbreviation: PRN = as needed.

>48 or 72 hours after antibiotic therapy has been initiated, however, reevaluate and consider adjusting antibiotics. Management of AOM after failure of initial antibiotic is shown in **Table 121-7**. If high-dose amoxicillin fails, change to amoxicillin-clavulanate or ceftriaxone to provide coverage against β-lactamase–producing *M. catarrhalis* and nontypeable *H. influenzae*. If the second antibiotic regimen fails, treat with clindamycin and a third-generation cephalosporin, or consult ear, nose, and throat for tympanocentesis and culture (Table 121-7).

A suggested algorithm for the diagnosis and treatment of AOM is illustrated in **Figure 121-4**.

OTITIS MEDIA WITH EFFUSION

Otitis media with effusion (OME) is fluid in the middle ear space without clinical signs of inflammation or acute symptoms of illness. OME can occur spontaneously as a result of poor eustachian tube function, but more commonly results from an inflammatory response after an episode of AOM. More than 2 million episodes of OME are diagnosed annually in the United States, with an estimated annual cost of $4 billion.[12] The peak incidence is between 6 months and 4 years of age, and 90% of children will be affected at some time before school age.[13]

Many children with OME are asymptomatic. In some children, however, the effusion can cause mild intermittent ear pain, fullness, or a popping sensation. Because the effusion can impair the mobility of the tympanic membrane, mild to moderate conductive hearing loss in the range of 10 to 20 dB can occur and can have adverse effects on speech, language, and learning in the developing child. Children at higher risk of complications of OME include those with permanent hearing loss (independent of OME), speech and language delays, autism or other developmental disorders, Down syndrome, craniofacial abnormalities (e.g., cleft palate), and blindness.[13]

TABLE 121-4 Indications for Consideration of Initial Observation for Acute Otitis Media (AOM)[7]

Children 6–23 mo old with *unilateral* AOM without severe signs or symptoms
- Mild ear pain for <48 h
- Temperature <39°C (102.2°F)

Children ≥24 mo old with *unilateral or bilateral* AOM without severe signs or symptoms
- Mild ear pain for <48 h
- Temperature <39°C (102.2°F)

Note: When observation is used, a mechanism must be in place to ensure follow-up and initiation of antibiotics if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms.

TABLE 121-5 Indications for Initial Antibiotic Use for Acute Otitis Media (AOM): No Observation Period[7]

- All infants <6 mo old
- All children with severe signs or symptoms
  - Moderate or severe ear pain or
  - Ear pain for ≥48 h or
  - Temperature >39°C (102.2°F)
- Children <24 mo old with bilateral AOM
- Recurrent AOM (prior episode of AOM within 2–4 wk)
- AOM with perforation
- Patients with myringotomy (pressure-equalizing) tubes in place
- Patients with craniofacial abnormalities
- Immunocompromised patients
- Any child with AOM if the provider or caregiver is not comfortable with initial observation

TABLE 121-6 Initial Antibiotic Treatment for Uncomplicated Acute Otitis Media (AOM)[7]

	Antibiotic	Dosing
First-line treatment		
AOM (with or without tympanic membrane perforation)	Amoxicillin	40–45 milligrams/kg/dose PO 2 times daily for 5–10 d
Special situations		
Penicillin allergy	Cefdinir	7 milligrams/kg/dose PO 2 times daily for 5–10 d
	Cefuroxime	15 milligrams/kg/dose PO 2 times daily for 5–10 d
	Cefpodoxime	5 milligrams/kg/dose PO 2 times daily for 5–10 d
	Clindamycin	10 milligrams/kg/dose PO 3 times daily for 5–10 d
Amoxicillin received in past 30 d *or* Concurrent purulent conjunctivitis *or* History of recurrent AOM unresponsive to amoxicillin	Amoxicillin-clavulanate	45 milligrams/kg/dose PO of amoxicillin with 3.2 milligrams/kg/dose of clavulanate 2 times daily for 5–10 d
Myringotomy tubes	Ofloxacin otic drops	5 drops in affected ear twice daily for 5–10 d
Unable to tolerate PO antibiotics	Ceftriaxone	50 milligrams/kg/dose IM or IV once daily for 1–3 d

TABLE 121-7 Management of Acute Otitis Media After Failure of Antibiotic Regimen[7]

	Management	Dosing
Failure of initial antibiotic (amoxicillin)		
First-line treatment	Amoxicillin-clavulanate	45 milligrams/kg/dose of amoxicillin with 3.2 mg/kg/d of clavulanate 2 times daily for 10 d
	Ceftriaxone	50 milligrams/kg/dose IM or IV once daily for 3 d
Penicillin allergy	Clindamycin	10–12 milligrams/kg/dose PO 3 times daily for 10 d
Failure of second antibiotic		
Treatment options	Clindamycin + third-generation cephalosporin	10–12 milligrams/kg/dose PO 3 times daily for 10 d
	Consult an otolaryngologist for tympanocentesis and culture	

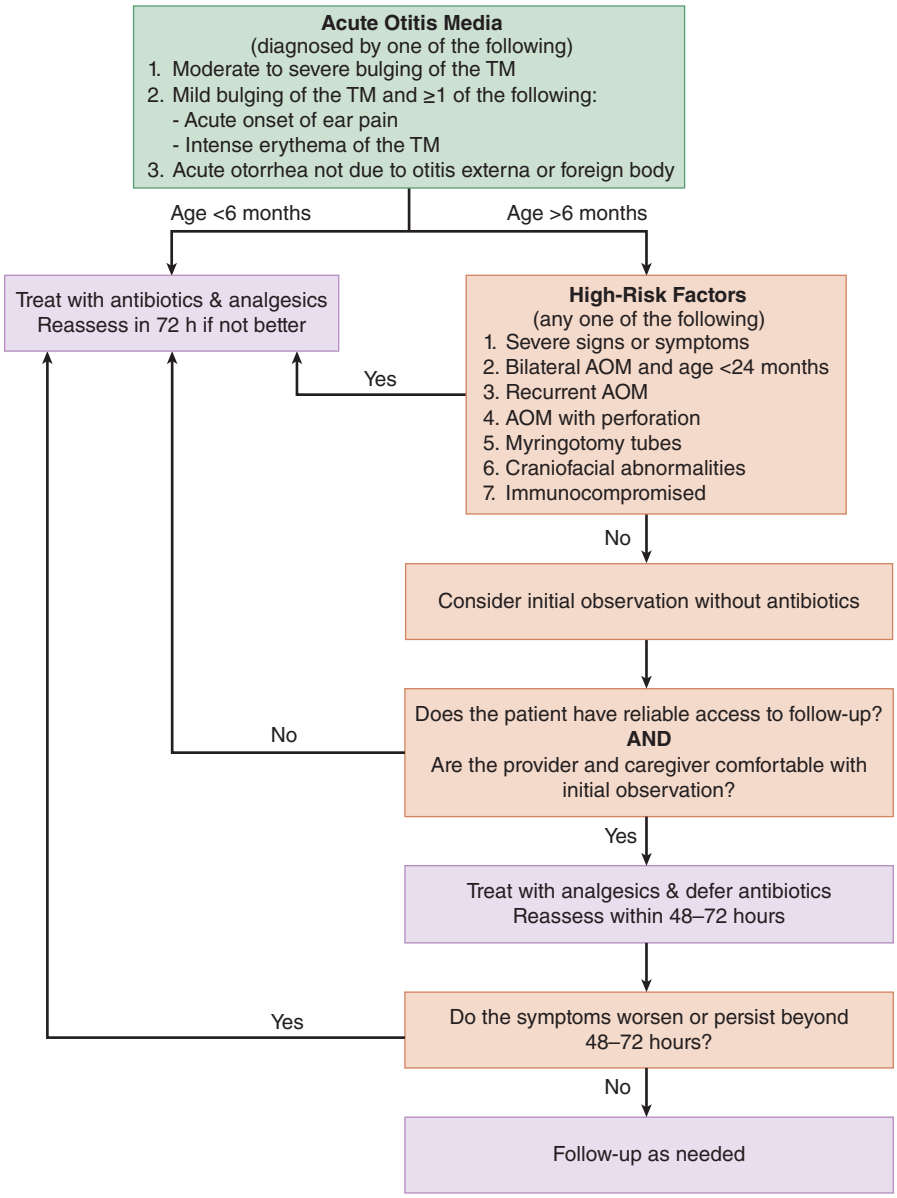


FIGURE 121-4. Algorithm for management of acute otitis media (AOM). TM = tympanic membrane.

DIAGNOSIS

Diagnosis is by pneumatic otoscopy. A cloudy tympanic membrane often with a visible effusion (visualized as either an air-fluid level or bubbles) and with significantly impaired mobility is the classic otoscopic finding of OME (**Figure 121-5**). Although there is overlap of some of the otoscopic findings of OME and AOM, it is important to remember that the disorders are separate entities and distinguishing between the two is essential. The critical distinguishing feature is that AOM has acute signs and symptoms of inflammation and OME does not.

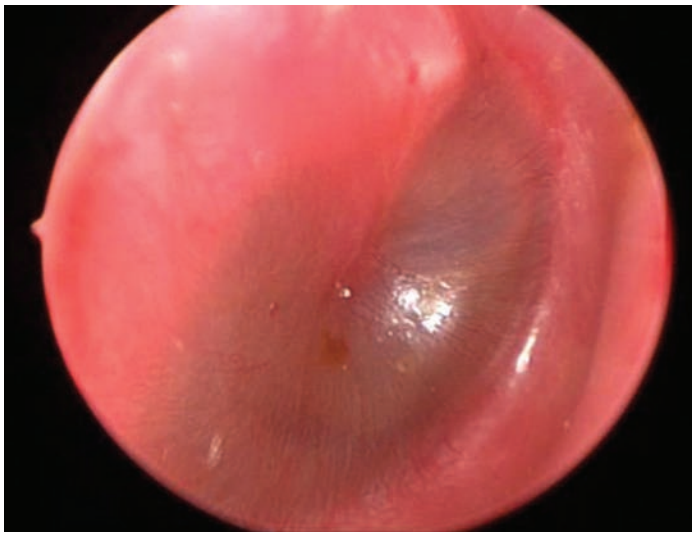


FIGURE 121-5. Well-appearing toddler with middle ear effusion. Note slight bulging of tympanic membrane and visible fluid level. [Image used with permission of Dr. Shelagh Cofer, Department of Otolaryngology, Mayo Clinic.]

TREATMENT

Close to 90% of episodes of OME resolve spontaneously and without complications.[14] Management depends on whether or not children are at risk for complications. Watchful waiting is appropriate for children with OME who are not at risk for complications.[13] Intranasal or systemic steroids, antibiotics, antihistamines, and decongestants can cause more harm than benefit and should not be used.[13] Children should follow up with their pediatrician and be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.[13] Hearing and language testing is recommended if OME lasts >3 months

or at any time that hearing loss or language delay is suspected in a child with OME.[13]

Otolaryngology referral is important for all at-risk children with OME and any child with a complication from OME, recurrent OME, or symptomatic OME lasting >3 months. Tympanostomy tube placement may be indicated.[13,15]

ACUTE OTITIS EXTERNA

Acute otitis externa is an infection of the external ear canal associated with diffuse inflammation and often significant edema. The peak incidence occurs in children between 7 and 12 years of age, and cases are more common in the summer than in the winter.[16] The most common risk factor is hyperhydration and maceration of the epithelial layer lining the canal, often induced when a child is submerged during swimming ("swimmer's ear"). Mechanical debridement of the epithelial layer (e.g., as can occur with a cotton swab inserted in the canal to clean to the ear) is also an important risk factor. Approximately 98% of cases in North America are due to invasive bacteria, the most common of which is *Pseudomonas aeruginosa* followed by *Staphylococcus aureus* and *Staphylococcus epidermidis*.[17-19] Polymicrobial infection is common, and different bacteria often coexist. Fungal infection is rare in primary acute otitis externa and is more commonly associated with chronic otitis externa.

CLINICAL FEATURES

The early stages of otitis externa are characterized by a sense of ear fullness and itching. As the disease progresses, pain becomes prominent and is often severe and exacerbated by manipulation of the auricle as well as by any movement of the jaw. A purulent and sometimes foul-smelling discharge can develop and fill the canal. Because the discharge and canal edema can obstruct sound waves, temporary hearing loss may be present. In the severe form of otitis externa, further anterior spread can cause tenderness and inflammation of the surrounding lymphoid and subcutaneous tissue. Rarely, posterior spread can involve the mastoid or can cause osteomyelitis of the skull. Malignant otitis externa is osteomyelitis of the ear canal and should be suspected with the presence of fever >38.9°C (102°F), severe otalgia, and/or facial paralysis or meningeal signs.

DIAGNOSIS

Diagnosis is clinical. According to the American Academy of Otolaryngology–Head and Neck Surgery Foundation, a diagnosis of otitis externa requires the rapid onset (within 48 hours) in the past 3 weeks of at least one primary symptom (otalgia, itching, or fullness) and one primary sign (tenderness of the tragus/pinna or diffuse ear canal edema/erythema) of ear canal inflammation (**Table 121-8**).[18]

Acute otitis externa must be distinguished from other causes of ear pain, otorrhea, and inflammation such as foreign body and AOM with perforation of the tympanic membrane. Placing the speculum of the otoscope into the external ear canal may induce pain and should be done gently.

TREATMENT

PAIN CONTROL

Analgesic therapy should be based on the severity of the pain. Ibuprofen or acetaminophen is sufficient to reduce pain in most cases.

TABLE 121-8 Diagnostic Criteria for Acute Otitis Externa[18]

Rapid onset (within 48 hours) in the past 3 weeks of
- At least 1 primary symptom of ear canal inflammation AND
- At least 1 primary sign of ear canal inflammation

Primary Symptoms of Otitis Externa	Primary Signs of Otitis Externa
Otalgia (often severe)	Tenderness of the tragus and/or pinna
Itching	Diffuse ear canal edema and/or erythema
Sense of ear fullness	

ANTIBIOTICS AND STEROIDS

Topical fluoroquinolone drops, such as ofloxacin or ciprofloxacin, instilled into the ear canal two to four times daily, are the standard treatment. Ciprofloxacin drops are also available in preparations that include hydrocortisone or dexamethasone, which help relieve itching and pain. Polymyxin B/neomycin/hydrocortisone preparations have also been traditionally recommended as first-line therapy, but they are not as effective as ciprofloxacin/hydrocortisone in eradicating *P. aeruginosa*[19] and neomycin hypersensitivity is common, so fluoroquinolone drops are preferable. Acidifying agents, such as 2% acetic acid drops, are also approved for treatment of otitis externa, but are painful upon application and are contraindicated in the presence of a suspected tympanic membrane perforation or tympanostomy tubes. **Do not give systemic antibiotics for uncomplicated cases of acute otitis externa.** Consider systemic antibiotics only if there is extension of the disease outside of the ear canal and/or there are specific host factors (e.g., immunocompromised) that indicate a need for systemic therapy.[18] Parenteral therapy may be required in severe cases and should involve otolaryngology consultation.

When instilling antibiotic drops, lie the child down with the affected ear upward and have the child remain in this position for 5 minutes after application. Fill the ear with the topical agent and gently move the pinna back and forth to improve delivery throughout the entire external canal. If the external canal is extremely edematous and obstructed, perform aural toilet and/or place an ear wick to improve delivery of the drops (the wick should be removed in 3 days if it has not fallen out on its own as the edema improves).

Reexamine children who fail to improve within 48 to 72 hours of initial therapy and consider other diagnoses.[18] Cultures of the external canal may be useful in such cases.

SUPPORTIVE MEASURES

Avoid swimming until the canal heals. Gentle cleaning and drying of the ear canal may be helpful but should be done cautiously to avoid secondary trauma. With repeated infections in children who swim, use of earplugs while swimming and daily prophylaxis with acidifying and drying drops (e.g., vinegar and isopropyl alcohol as 1:1 solution) during at-risk periods such as swimming season may prevent infection.

ACUTE MASTOIDITIS

Acute mastoiditis is a bacterial infection of the mastoid that almost always develops as a complication of AOM. The initial diagnosis of AOM may occur prior to or at the same time that mastoiditis is diagnosed. At birth, the mastoid consists of a single cell called the *antrum,* but air cells quickly develop during the first few years of life, and most children have well-developed mastoids by 3 years of age. The incidence of mastoiditis is highest in children younger than age 2 years.[20] Risk factors for acute mastoiditis include recurrent AOM, immunocompromise, or the presence of a cholesteatoma. Cholesteatomas are destructive, expanding growths in the middle ear consisting of keratinizing epithelial cells and can be congenital or acquired (**Figure 121-6**).

The relationship between antibiotic usage for AOM and the incidence of mastoiditis is not clear.[21-29]

PATHOPHYSIOLOGY

Acute mastoiditis develops when inflammation and infection in the middle ear spread into the cells of the mastoid through the aditus ad antrum. This process can induce destruction of the mastoid bone and periosteum. The same bacterial organisms most commonly associated with AOM (*S. pneumoniae*, nontypeable *H. influenzae*, and *S. pyogenes*) are common causes of acute mastoiditis, but other important bacteria implicated include *S. aureus* and *P. aeruginosa*.[30,31]

CLINICAL FEATURES

In addition to the signs and symptoms of AOM, patients with mastoiditis have erythema, edema, and/or tenderness of the mastoid area posterior to the auricle. Mastoiditis is rare if the tympanic membrane

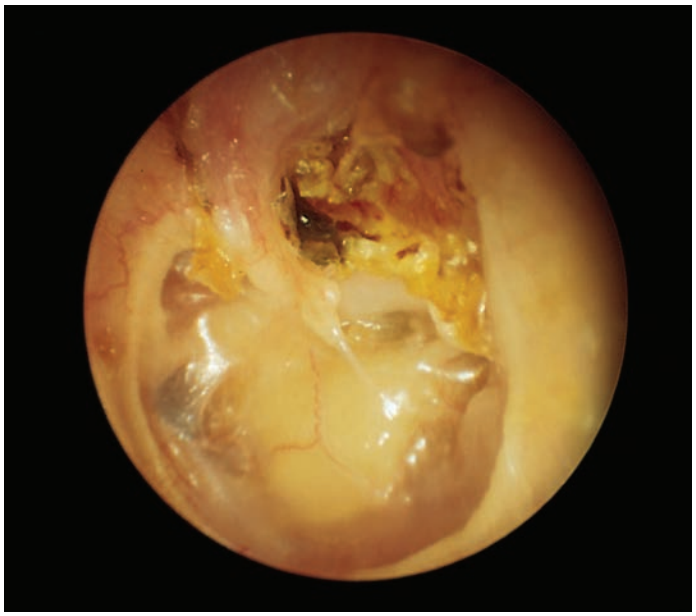


FIGURE 121-6. Cholesteatoma. Cholesteatomas are destructive, expanding growths in the middle ear and/or mastoid that consist of keratinizing squamous epithelial cells. Note the yellow epithelial debris and distortion of anatomy. Cholesteatomas can be congenital or acquired. [Image used with permission of C. Bruce Macdonald, MD; reproduced with permission from Knoop et al: *Atlas of Emergency Medicine*, 2nd ed. Jauch et al: Chapter 5, Ear, Nose, and Throat Conditions, Figure 5-9.]

is normal, but can occur if there is obstruction of the aditus ad antrum and the fluid in the middle ear has drained through the eustachian tube. As the inflammation and infection in the mastoid progress, the auricle becomes visually protruded outward (**Figure 121-7**). Advanced disease may cause palsies of the VI (abducens) or VII (facial) nerves.

Complications include subperiosteal abscess, facial nerve palsy, osteomyelitis of other parts of the skull, direct extension into the intracranial cavity (e.g., intracranial abscess, meningitis), venous sinus thrombosis, hematogenous spread of infection to separate sites, and otitic hydrocephalus. Otitic hydrocephalus is due to thrombosis of the transverse sinus of the dura and should be suspected in children with mastoiditis with signs and symptoms of elevated intracranial pressure.

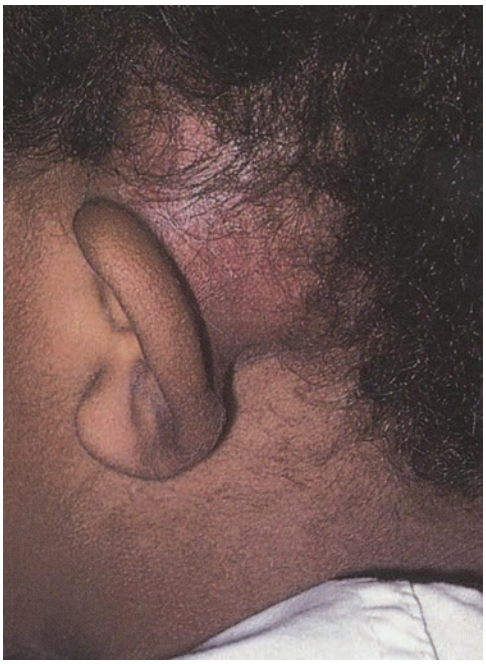


FIGURE 121-7. Acute mastoiditis with postauricular erythema and edema and outward protrusion of the auricle. [Image used with permission of Dr. Shelagh Cofer, Department of Otolaryngology, Mayo Clinic.]

DIAGNOSIS

The diagnosis is clinical. Confirmation is by CT (with IV contrast) of the mastoid but is usually reserved for cases with suspected complications.[32] MRI may be preferred in children with suspected intracranial complications, but is usually only obtained after CT if more information is needed.[32] Laboratory tests rarely change outcome. Consider blood cultures in children with fever. Aspiration and culture of middle ear fluid by tympanocentesis are useful to identify the specific organism.

TREATMENT

Treatment for uncomplicated cases involves broad-spectrum IV antibiotics and drainage of middle ear and mastoid fluid. Direct initial antibiotic therapy toward the most common bacteria (*S. pneumoniae*, nontypeable *H. influenzae*, *S. pyogenes, S. aureus*, and *P. aeruginosa*). Piperacillin-tazobactam plus vancomycin is an example of an appropriate regimen. Antibiotic therapy can be narrowed once a specific organism is identified. Drainage is usually accomplished by myringotomy with or without placement of tympanostomy tubes. Mastoidectomy and more aggressive surgical intervention are typically reserved for cases in which there is no significant clinical improvement within 48 hours and for complications.

FOREIGN BODY IN THE EAR CANAL

Foreign bodies in the ear canal are a relatively common occurrence. The foreign body can be anything from a bead to a small toy to a corn kernel to a piece of paper to a button battery. On occasion, a live insect will crawl into the ear during sleep.

Some children will report putting something in their ear and come to medical attention before symptoms are present. Others will develop ear pain and/or discharge as the ear canal becomes inflamed and may also complain of hearing loss. In the case of an insect, acute onset of extreme pain often with the sensation of something moving in the ear is classic.

Diagnosis is confirmed by direct visualization with otoscopy.

Most foreign bodies can be easily removed at the bedside. An anxiolytic medication such as intranasal midazolam may be helpful in young children. Many foreign bodies can simply be grasped and extracted with alligator forceps. An otoscope with an operational head through which the instrument can be introduced is helpful to allow direct visualization throughout the procedure. Foreign bodies that do not have easily graspable parts but are not deeply embedded can usually be removed with an ear curette, suctioning, or irrigation with warm water.[20] For irrigation, thread a thin catheter attached to a syringe filled with warm water into the ear canal posterior to the foreign body, so that irrigation pushes the foreign body out of the canal. Live insects should be killed by instilling mineral oil into the ear canal prior to removal. Consult otolaryngology if the foreign body is a hazardous material (e.g., button battery); if there is concern for associated injury to the canal, tympanic membrane, and/or middle ear; or if the above techniques are not successful. If inflammation is noted after removal of any foreign body, a short course of topical antibiotic-steroid otic drops (e.g., ciprofloxacin 0.3% and dexamethasone 0.1%) is indicated to prevent otitis externa.

Acknowledgments: We are grateful to Dr. Shelagh Cofer for her otoscopic pictures and photographs of mastoiditis and Dr. Alejandro Hoberman for his otoscopic pictures.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 122

Eye Emergencies in Infants and Children

Janeva Kircher
Andrew Dixon

INTRODUCTION

Pediatric ophthalmologic problems are a common yet challenging issue for all emergency physicians. The history often comes from the parents, particularly in preverbal children, and it may even be difficult for older children to fully articulate their symptoms. The child and the parents need to be calmed and reassured sufficiently to allow for a complete and thorough examination. This chapter includes a review of eye examination techniques and illnesses specific to the care of children. Because the care of pediatric and adult trauma to the eye and its surrounding structures is similar, only those areas of difference are discussed in this chapter. Further discussion of eye emergencies is provided in Chapter 241, "Eye Emergencies." Eye anatomy is presented in **Figures 122-1, 241-2,** and **241-6**.

A visit to the ED is an opportunity to educate the patient and family about prevention of ocular injury and sun exposure. The annual incidence of eye trauma is 8 to 15.2 per 100,000 children, and most events are thought to be preventable.[1] Protective eyewear and adequate supervision during recreational and competitive sports should be available and may prevent injuries.[1]

Discuss the use of sunscreen and sunglasses for children before going outdoors for any sustained period of time. Emphasize the importance of using sunglasses with both ultraviolet A and ultraviolet B protection. Sun exposure is cumulative, and there is some research that it has an effect on development of cataracts and macular degeneration.[2] Ultraviolet B rays may also increase the risk of developing pterygia and pinguecula (yellowish-white vascular conjunctival lesions) later in life.

EYE EXAMINATION IN A CHILD

If a history of chemical exposure is obtained, triage as highest priority, and immediately irrigate the eye with 1 to 2 L of saline.

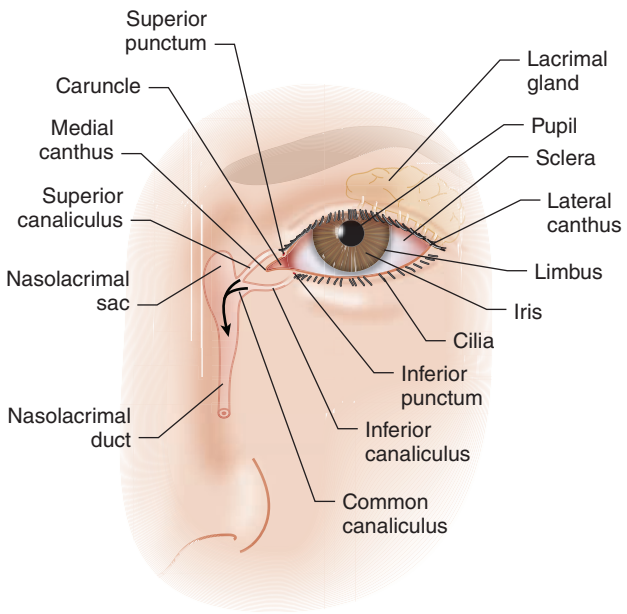


FIGURE 122-1. Anatomic diagram of the eye and the adnexa.

A complete eye exam includes gross examination, assessment of visual acuity, extraocular movements, and ophthalmoscopic exam of the eye. A slit lamp exam of the eye should be performed whenever possible.

Begin by performing a general survey, adopting an outside-in approach, to note any obvious abnormalities such as rash, soft tissue changes, matter on the lashes, ptosis, misalignment of the eyes, injection of the conjunctiva, drainage from the eye, or corneal/lens opacities. Newborns may appear cross-eyed during the first 2 months of life as ocular fixation develops.

VISUAL ACUITY AND EXTRAOCULAR MOVEMENTS

Visual acuity is the vital sign of the eye, and it should be the first objective measurement obtained after the history. Obtaining visual acuity in a child will depend on the child's age and level of development. A child 6 months to 3 years old should be able to fix and follow a face, toy, or light; a child 3 to 5 years old should have a visual acuity of 20/40 or better with one line acuity difference between eyes; and a child >5 years old should have a visual acuity of 20/25 or better with no acuity difference between eyes.[3] Several different eye charts can be used to check distance visual acuity in children, including the Snellen, Allen picture, and tumbling E charts. If the child knows letters of the alphabet (typically 4 to 6 years of age), use the standard Snellen eye chart. Consider using the tumbling E chart if the child is illiterate or has a cognitive disability. To use the Snellen chart, check acuity at a distance of 20 ft. When using the Allen picture or tumbling E chart, assess acuity at a distance of 10 ft.

Check acuity in the nonaffected eye first to establish baseline function. Assess visual acuity with the child's glasses. If not available, then use a commercial pinhole occluder or a card with five to six holes created with an 18-gauge needle. If the child is unable to read the top line of an eye chart, then ask to count fingers and see motion. If the child is unable to see motion, then shine a bright light into the eye and document the presence or absence of light perception.

For visual acuity in children from approximately 3 months to 3 years of age, use a brightly colored object, light source, or moving toy to attract the child's attention. See if the child is able to follow it with both eyes and then with each eye individually with the opposite eye occluded.

Extraocular movements can be assessed after visual acuity. Relieving pain will make your exam much easier, especially in a child unwilling to open his or her eye. With the patient supine, analgesic drops can be applied to the space between the medial canthus and the nose. The drops will flow into the eye when the child eventually opens his or her eye.

EXAMINATION OF PUPILS AND FUNDUS

Older and more cooperative children can be examined sitting independently or on a parent's lap. Infants, toddlers, developmentally delayed children, and uncooperative children may need to be swaddled in a sheet. Some patients require an eyelid retractor to examine the eye.

First, document pupil diameter in ambient light. If the difference between pupils is 0.5 mm or greater, then anisocoria exists. A greater size discrepancy in a dark room when compared with a light room indicates physiologic anisocoria, which is of no clinical significance. It is also important to look for leukocoria (white appearance of pupil), which may be indicative of problems with the cornea, lens, or anterior or posterior chamber. Leukocoria is discussed later in the chapter.

Next, check the direct and consensual light reflexes. Then assess for a relative afferent pupillary defect, a sign of unilateral optic neuropathy. Some children will have a small amount of pupillary movement (dilation and contraction) in the consensual eye when the light is swung from the direct to the consensual eye. This is pupillary escape and can be a normal response.

Continue with examination of the red reflex, which should be performed in children of all ages.[4] In a dimly lit room, look at the pupils through the direct ophthalmoscope or panoptic scope; position yourself at the patient's eye level about 1 to 2 ft. away. Document the presence or absence of the red reflex for each eye (**Figure 122-2**). With older children, perform the same funduscopic examination that you would in an adult.



FIGURE 122-2. Normal red reflexes. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York, Figure 8-18.]

STRABISMUS

Strabismus is ocular misalignment. Knowledge of preexisting strabismus helps differentiate between congenital/childhood strabismus and acquired emergent causes of strabismus. Misalignment can be described as a "tropia," or constant misalignment, or a "phoria," or intermittent misalignment, such as when the patient is tired or fusion is broken. With a "phoria," the eyes will revert to normal (equal) alignment when both eyes are uncovered. Terminology used to describe strabismus is listed in **Table 122-1**. Normal newborns may have transient misalignment that usually improves by 3 to 4 months of age as the strength of extraocular muscles improves.[5] **Amblyopia** is a loss of visual acuity not correctable by glasses in an otherwise healthy eye. Uncorrected strabismus can cause amblyopia. If children have unilateral visual impairment, their brain will "choose" the image presented by the eye with better vision. If amblyopia is not corrected by about age 10 years old, the brain eventually suppresses visual information presented by the impaired eye, leading to permanent vision loss.

TABLE 122-1 Strabismus Terminology

Term	Description
Esotropia	Inward eye deviation
Exotropia	Outward eye deviation
Hypertropia	Upward eye deviation
Hypotropia	Downward eye deviation
Esophoria	Inward eye deviation when the other eye is covered
Exophoria	Outward eye deviation when the other eye is covered



FIGURE 122-3. Pseudostrabismus.

CAUSES OF STRABISMUS

Emergent causes of strabismus include cranial nerve palsy and muscle restriction or entrapment that may be associated with trauma, stroke, tumor, aneurysm, thyroid-associated orbitopathy or other infiltrative process, increased intracranial pressure, or infection. The innervation of the extraocular muscles defines which cranial nerve is involved. Cranial nerve VI innervates the ipsilateral lateral rectus muscle, and palsy will lead to esotropia. Cranial nerve IV innervates the ipsilateral superior oblique muscle, and palsy will cause hypertropia. Cranial nerve III innervates all other extraocular muscles, and palsy will lead to exotropia, hypertropia or hypotropia (depending on which branch is affected), and ptosis.

DIAGNOSIS AND MANAGEMENT

Strabismus is usually suspected after general inspection. Some children have epicanthal folds that lead to pseudostrabismus, or the appearance of ocular misalignment, when the eyes are in fact in proper alignment (**Figure 122-3**). Two simple tests can identify true strabismus.

Begin with the **Hirschberg test** by holding a penlight several feet from the child and observe the reflection of the light on each cornea. In normal ocular alignment (pseudostrabismus), the light reflection will appear on the same position of each eye. In true strabismus, the light reflection will not be on the same position of each eye. Then, perform a **cover test**. Have the child fixate on a distant object and then cover one of the child's eyes. If the uncovered eye then moves, it can be assumed that it was not properly fixated on the object and true strabismus is present. When the eyes are uncovered, they will revert to their original misalignment.

Historical clues to an emergent cause of strabismus include trauma, diplopia, report of abnormal extraocular movements, sunsetting of the eyes (upgaze deficit), nausea, vomiting, and lethargy. If an emergent cause of strabismus is suspected, obtain imaging directed at the suspected condition.

Congenital strabismus caused by extraocular muscle weakness usually self-resolves in infancy. Stable strabismus that persists into childhood should be referred nonemergently to an ophthalmologist. Strabismus caused by amblyopia often resolves with glasses that equalize the vision, although a patch over the "good" eye or surgical correction may be required.

LACRIMAL SYSTEM PROBLEMS

Tears are produced in the lacrimal gland and drain at the medial aspect of the eye through the nasolacrimal duct and lacrimal sac through the canalicular system to the Hasner valve and finally into the nose. Several common problems seen in pediatrics can arise in the gland and canalicular system.

DACRYOSTENOSIS

Dacryostenosis, or nasolacrimal duct obstruction, is a narrowing or obstruction of the nasolacrimal duct. It occurs in 6% of all newborns and usually resolves with conservative management.[6] Dacryostenosis is a common condition presenting to the ED, and infants may present with

epiphora, eyelash matting, and tears that appear thicker and yellowish in color, which may be mistaken by parents as infection. Fluorescein applied to the eye and left for 5 minutes will accumulate, whereas it normally would be cleared by the lacrimal system. An important clinical feature is the lack of accompanying signs or symptoms, such as fever, irritability, or conjunctivitis. If the conjunctiva are not inflamed, the cause is dacryostenosis with evaporation of the aqueous layer of poorly draining tears, which leaves the yellow mucus layer behind and mimics conjunctivitis.

Treatment of dacryostenosis is supportive and does not require antibiotics. Teach parents gentle massage with a downward motion to the nasolacrimal duct three to four times a day. If still present after 12 months of age, ophthalmology referral is indicated for possible dilation of the duct.

DACRYOCYSTITIS

Inflammation and bacterial superinfection of the lacrimal sac will cause dacryocystitis. Common pathogens are *Streptococcus pneumoniae*, staphylococci, and *Haemophilus influenzae*.[6,7] Patients develop a chronic mucopurulent discharge followed by erythema and swelling inframedially to the eye (**Figure 122-4**).

In children of all ages, dacryocystitis is usually a secondary bacterial infection following a viral upper respiratory infection. The diagnosis is made when gentle pressure with a finger or cotton swab applied to the nasolacrimal sac causes a reflux of mucopurulent material. The discharge should be cultured to identify the causative agent.

Improperly treated dacryocystitis may lead to periorbital and orbital cellulitis. Children are often quite ill and require hospital admission with parenteral antibiotics until the infection begins to improve.[8,9] A cephalosporin, such as cefuroxime (50 milligrams/kg IV every 8 hours) or cefazolin (33 milligrams/kg IV every 8 hours), may be used, or clindamycin (10 milligrams/kg IV every 6 hours) may be used for penicillin-allergic patients. If methicillin-resistant *Staphylococcus aureus* is suspected, vancomycin (10 to 13 milligrams/kg IV every 6 to 8 hours) is indicated.[8,10]

DACRYOCELE

A dacryocele is a small, bluish-hued, palpable mass in the location of the nasolacrimal duct (inferior and medial to the eye) without conjunctival erythema, discharge, or other pathologic findings. It is caused by an obstruction at the valve of Hasner and the common canaliculus.[6] Due to possible need for marsupialization, patients should be urgently referred to a pediatric otolaryngologist or ophthalmologist.[5]



FIGURE 122-4. Dacryocystitis. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 2-10.]

DACRYOADENITIS

Dacryoadenitis is inflammation of the lacrimal gland and can be acute or chronic. Chronic dacryoadenitis is caused by noninfectious inflammatory disorders such as Sjögren's syndrome, sarcoidosis, or thyroid disease. Acute dacryoadenitis is usually infectious. In both acute and chronic disease, children will have soft tissue swelling, especially in the region of the lateral upper lid. With infectious causes, systemic symptoms such as malaise and fever may also be present.

Viral dacryoadenitis causes less intense discomfort and erythema than bacterial dacryoadenitis. Causative viral pathogens include Epstein-Barr virus, mumps virus, coxsackievirus, cytomegalovirus, and varicella-zoster virus. Bacterial dacryoadenitis is associated with intense eye discomfort, tenderness, and erythema. The most common causative bacterial pathogen causing dacryoadenitis is *S. aureus*, although streptococci, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Brucella melitensis* have also been implicated.[8]

The first-line treatment of bacterial dacryoadenitis is oral or parenteral antibiotics against *S. aureus*. For mild infections, an oral first-generation cephalosporin, such as cephalexin (25 milligrams/kg PO every 6 hours), until the infection has resolved is appropriate. If methicillin-resistant *S. aureus* is suspected, sulfamethoxazole-trimethoprim (10 mg/killigram PO [or IV] every 12 hours) or linezolid (10 milligrams/kg PO [or IV] every 12 hours) may be used. For more severe infections, parenteral antibiotic therapy is indicated. Nafcillin (37.5 milligrams/kg IV every 6 hours) is appropriate when methicillin-resistant *S. aureus* is not suspected. Vancomycin (10 to 13 milligrams/kg IV every 6 to 8 hours) is indicated for severe dacryoadenitis caused by methicillin-resistant *S. aureus*.[8]

BLEPHARITIS

Blepharitis is inflammation of the eyelid that may present with eye redness, tearing, photophobia, crusting of the lid margin, swelling, or pruritus. Anterior blepharitis is usually infectious in nature (staphylococci) and presents with crusting and debris around the base of the eyelashes and red, irritated skin. Posterior blepharitis affects the conjunctival surface of the eyelid, usually due to meibomian gland dysfunction, and presents with inflammation of the posterior lid margin and eye irritation.[10] Both types of blepharitis are treated with warm compresses and baby shampoo scrubs once to twice daily. Have caregivers apply shampoo to a washcloth and then gently scrub the eyelids. This should be continued until symptoms have resolved completely, which usually requires prolonged treatment. In addition, staphylococcal blepharitis should be treated with erythromycin or bacitracin-polymyxin ointment one to three times a day for 7 days, with the length of treatment depending on severity.[10]

PERIORBITAL AND ORBITAL CELLULITIS

The orbital septum is a connective tissue extension of the orbital periosteum that extends into the upper and lower eyelids and acts as a barrier to the spread of infection. However, infection can be facilitated by the valveless drainage system of the midface region that permits bacteria to travel hematogenously in an anterograde fashion (i.e., away from the heart) despite a retrograde venous system.[5] Periorbital, or preseptal, cellulitis must be distinguished from orbital, or postseptal, cellulitis. The diagnosis may be difficult clinically, and imaging is often required to make the appropriate diagnosis.

PERIORBITAL CELLULITIS

The average age of presentation with periorbital cellulitis is 2 years old. Periorbital cellulitis can be caused by local infection, hematogenous spread, and extension of sinusitis.



FIGURE 122-5. Preseptal cellulitis. Left periorbital cellulitis with edema and erythema of the eyelids in a nontoxic cooperative toddler with a normal ocular exam. (Photo contributor: Kevin J. Knoop, MD, MS. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds). *The Atlas of Emergency Medicine,* 4th ed. © 2016, McGraw Hill Education, Inc., New York, Figure 14.67, Pg 468.)

Local infection, such as conjunctivitis, dacryoadenitis, dacryocystitis, hordeolum, or even a minor traumatic cellulitis after an insect bite or small scratch, can spread to the periorbital area (**Figure 122-5**).

Hematogenous spread of nasopharyngeal pathogens can also lead to periorbital cellulitis. Affected children tend to be younger (often <18 months old) and have a history of a viral upper respiratory infection followed by abrupt onset of fever and eyelid swelling. The most common pathogens are *S. pneumoniae* and *Streptococcus pyogenes*.[8]

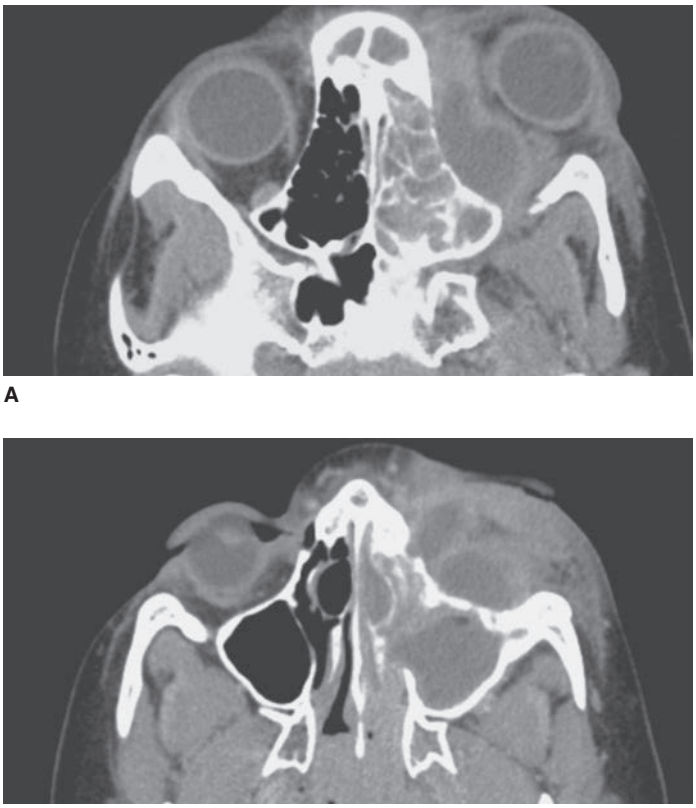
Finally, periorbital cellulitis may be the result of acute sinusitis. Sinusitis can be associated with reactive edema and mild inflammation of the eyelids noted upon awakening that regresses during the day as dependent edema resolves. Unilateral periorbital edema that does not regress may indicate cellulitis. Bacteria that cause sinusitis, such as *S. pneumoniae*, nontypeable *H. influenzae*, and *Moraxella catarrhalis*, are the most common pathogens for this type of periorbital cellulitis.[8]

CLINICAL FEATURES AND DIAGNOSIS

Periorbital (preseptal) cellulitis is characterized by an erythematous, tender, indurated, swollen, and warm eyelid and periorbital area. **There is no associated decrease in visual acuity, conjunctival injection, impairment of extraocular movements, proptosis, pain with eye movement, or other intraorbital pathology.** It may not be possible to always differentiate clinically between an insect bite near the eye, a mild allergic reaction, and early periorbital cellulitis. Children with moderate to severe periorbital cellulitis may have difficulty opening their eyelids for the examiner, so eyelid retractors may be required to fully examine the eye and its movements. A CT scan of the orbits can differentiate between periorbital cellulitis and the often more severe but less common orbital cellulitis.

TREATMENT, DISPOSITION, AND FOLLOW-UP

Children with periorbital cellulitis who are well appearing and are afebrile are candidates for outpatient oral antibiotic therapy. Amoxicillin-clavulanate (20 milligrams/kg PO twice a day) is appropriate oral therapy. Those with more severe periorbital cellulitis or in whom hematogenous spread is suspected require parenteral therapy and hospitalization. Cefuroxime (50 milligrams/kg IV every 8 hours), ceftriaxone (50 milligrams/kg IV every 12 hours), or ampicillin-sulbactam (50 milligrams/kg IV every 6 hours) are appropriate choices. Add vancomycin if methicillin-resistant *S. aureus* is suspected.[5,8]



A

B

FIGURE 122-6. A. Orbital cellulitis. Left orbital cellulitis with subperiosteal abscess and extensive ethmoid and maxillary sinusitis are seen in this postcontrast CT scan. **B.** About 75% to 90% of cases of orbital cellulitis are associated with either preceding or concurrent acute paranasal sinusitis (commonly involved sinuses: ethmoid, maxillary, and frontal). [Reproduced with permission from Shah BR, Lucchesi M, Amodio J (eds): *Atlas of Pediatric Emergency Medicine,* 2nd ed. © 2013, McGraw-Hill Education, New York, Figure 8-3A&B, Pg 311. Photo contributor: John Amodio, MD.]

ORBITAL CELLULITIS

Orbital cellulitis is usually an extension of a sinus infection into the orbit behind the septum but may also be spread hematogenously or from traumatic inoculation (**Figures 122-6** and **122-7**). The average age



FIGURE 122-7. Orbital cellulitis. Severe proptosis, malalignment of globe with restriction of eye movements, swelling of eyelids, and unilateral eye involvement. [Photo contributor: Binita R. Shah, MD.]

of presentation is 12 years old. Complications include subperiosteal abscess, orbital abscess, cavernous sinus thrombosis, panophthalmitis, or endophthalmitis. The most common bacterial pathogens are *S. pneumoniae*, *M. catarrhalis*, *S. aureus*, *S. pyogenes*, and anaerobic upper respiratory flora such as *Bacteroides* and *Fusobacterium* species.[8] Nontypeable *H. influenzae* remains a pathogen in the postvaccine era.[11]

CLINICAL FEATURES AND DIAGNOSIS

Orbital cellulitis is characterized by erythema and swelling around the eye. **Suspect orbital cellulitis if the eyelid or periorbital inflammation is accompanied by any of the following: proptosis, impaired extraocular movements, pain with eye movement, decreased visual acuity, chemosis, or an afferent pupillary defect** (see Figure 241-8). Fever may or may not be present.[12]

Diagnosis of orbital cellulitis is primarily clinical, but an orbital and sinus CT differentiates between periorbital and orbital cellulitis and can identify a concomitant abscess or other pathology. CT findings are also useful to predict the need for surgical intervention.[13] Culture of the blood, nares, and conjunctiva may be obtained to help identify the bacterial source. After neuroimaging, consider lumbar puncture for symptoms such as headache, lethargy, neurologic symptoms, or toxic appearance to exclude associated meningitis.

TREATMENT, DISPOSITION, AND FOLLOW-UP

Orbital cellulitis requires inpatient management. Consult otolaryngology and ophthalmology for evaluation and possible surgical drainage of abscesses. Parenteral therapy is indicated until significant clinical improvement is noted, followed by oral antibiotics to complete a 3-week course. Cefuroxime (50 milligrams/kg IV every 8 hours) and ampicillin-sulbactam (50 milligrams/kg IV every 6 hours) are appropriate first-line antibiotics. If cefuroxime is used or if an anaerobic infection is strongly suspected, add clindamycin (10 milligrams/kg IV every 6 hours) or metronidazole (15 milligrams/kg IV every 12 hours). Also add vancomycin for life-threatening infections or suspected methicillin-resistant *S. aureus*.[5,8]

THE RED EYE

There are many problems that may produce a red eye in a child. In this section, we focus on the most common pediatric complaints, corneal abrasion and conjunctivitis, and then discuss other pertinent pediatric problems, including Kawasaki's disease and pediculosis. Inflammatory conditions including scleritis, episcleritis, uveitis, and iritis are covered in Chapter 241.

CORNEAL ABRASION

CLINICAL FEATURES

Corneal abrasions in older children are characterized by a foreign body sensation, pain, photophobia, injection, and a history of direct trauma, ultraviolet light exposure, or pain from windblown particulate matter in the eye. Smaller children and infants often lack a history of trauma to the eye and may present with a chief complaint of inconsolable crying and an otherwise normal physical examination. If instillation of an anesthetic drop such as tetracaine 0.5% onto the surface of the eye calms the child, it strongly suggests that injury to the surface of the eye may be the source of the child's distress.

DIAGNOSIS AND TREATMENT

A thorough eye examination with instillation of fluorescein confirms the diagnosis of corneal abrasion. An abrasion will fluoresce to a yellow-green color under the cobalt blue filter in the slit lamp or handheld Wood's lamp. The presence of a vertical linear abrasion suggests the presence of a retained foreign body, so make sure to evert the upper eyelid and examine the superior conjunctiva. If details on the iris are not visible due to corneal opacification, this may indicate a corneal ulcer, needing an emergency ophthalmology consult.[14]

Treatment of a corneal abrasion is erythromycin or bacitracin-polymyxin ophthalmic ointment to help avoid superinfection and provide lubrication.[15] See treatment for abrasions in contact lens wearers below. Avoid ointments containing neomycin due to hypersensitivity reactions.[15] Cyclopentolate 0.5% drops may alleviate pain by reducing ciliary spasm. Occasionally nonsteroidal anti-inflammatory drops are also used (such as ketorolac), but the evidence is not robust.[16] Eye patching is not routinely recommended but may be useful for any child who frequently attempts to scratch or rub the injured eye. Instillation of topical anesthetics at home is currently not recommended.[17] Although the need for tetanus prophylaxis of a corneal abrasion is debatable, the ED visit should be used to remind the caregiver to check the child's tetanus status with the primary care provider. In a tetanus-prone injury, using the same criteria as a standard skin abrasion, updating unknown tetanus status is recommended.[18]

For uncomplicated and simple corneal abrasions, recommend follow-up in 48 hours with the pediatrician or other primary care provider. Children with involvement of the visual axis should follow up the next day with ophthalmology. Children or adolescents who use contact lenses, have a history of herpes, or may have a retained foreign body should also be evaluated by an ophthalmologist. **If the child wears contact lenses**, give tobramycin ophthalmic solution to treat *Pseudomonas*. Ciprofloxacin and ofloxacin ophthalmic are acceptable options for children due to limited absorption. Discard that set of contact lenses. Do not resume contact lens use until approved by the ophthalmologist. Corneal abrasions heal quickly, and patients who continue to have foreign body sensation 2 to 3 days after initial presentation require urgent ophthalmologic reevaluation.

OPHTHALMIA NEONATORUM

Ophthalmia neonatorum is conjunctivitis in neonates up to 30 days old. The five primary categories of neonatal conjunctivitis are chemical, gonococcal, chlamydial, other bacterial, and viral (**Table 122-2**). Gonococcal, chlamydial, and viral neonatal conjunctivitis can all lead to severe morbidity. Although specific diagnoses and treatments are discussed in the following sections, in the ED, it may not be possible to determine the specific etiology. A rapid Gram stain of discharge should be obtained in all cases and will aid in management.

CHEMICAL OPHTHALMIA NEONATORUM

Chemical conjunctivitis occurs in the first 24 hours of life following erythromycin ointment prophylaxis.[14] Infants present with bilateral conjunctivitis, inflamed eyelids, and watery discharge. Gram stain of the discharge would reveal the absence of pathologic bacteria and only a few WBCs. Treatment of neonatal chemical conjunctivitis is watchful waiting. Symptoms should resolve within 48 hours. Erythromycin prophylaxis is often used at birth to diminish the risk of conjunctivitis caused by *N. gonorrhoeae*, although this practice has become controversial. The Canadian Paediatric Society advises against routine use, while the American Academy of Pediatrics continues to recommend prophylaxis for all newborns.[19,20]

GONOCOCCAL OPHTHALMIA NEONATORUM

Gonococcal conjunctivitis usually presents at 2 to 7 days of life with intense bilateral bulbar conjunctival erythema, chemosis, and a copious purulent discharge (**Figure 122-8**). The diagnosis is made by Gram stain, revealing gram-negative diplococci, and culture using chocolate agar. **Admit all infants with gonococcal conjunctivitis, obtain ophthalmology consultation, and evaluate for disseminated disease.**[20] Test blood, urine, cerebrospinal fluid, and any other sites with suspected infection. Therapy for isolated conjunctivitis in a neonate without hyperbilirubinemia is a single dose of parenteral ceftriaxone (50 milligrams/kg IV; maximum, 125 milligrams). To avoid exacerbation of hyperbilirubinemia or if disseminated infection is suspected and longer-term antibiotics are required, use cefotaxime (50 milligrams/kg

TABLE 122-2 Ophthalmia Neonatorum

Type	Cause	Age of Presentation	Key Findings	Treatment
Chemical	Erythromycin ointment prophylaxis	24 h	Bilateral, watery discharge, negative Gram stain	Watchful waiting
Gonococcal	*Neisseria gonorrhoeae*	2–7 d	Intense chemosis, copious discharge, gram-negative diplococci on Gram stain	Admission, IV antibiotics
Chlamydial	*Chlamydia trachomatis*	7–14 d	Intense erythema, purulent discharge	Admission, PO and topical antibiotics
Other bacterial	*Staphylococcus aureus,* nontypeable *Haemophilus influenzae, Staphylococcus epidermidis, Escherichia coli, Pseudomonas*	7–14 d	Identify etiology on Gram stain	Topical antibiotics
Viral	HSV-2, less commonly HSV-1	14–28 d	Dendrites on fluorescein exam	Admission, IV and topical antivirals

Abbreviation: HSV = herpes simplex virus.

IV every 8 hours). Irrigate the infant's eyes with normal saline frequently to eliminate the purulent discharge. Gonococcal ophthalmia neonatorum may progress to ulceration and perforation of the cornea if improperly treated.

CHLAMYDIAL OPHTHALMIA NEONATORUM

Symptoms of chlamydial conjunctivitis present slightly later than those caused by gonorrhea, typically around 7 to 14 days of age. Signs are unilateral or bilateral purulent discharge with intense erythema of the palpebral conjunctiva (**Figure 122-9**). Chlamydial ophthalmia may be associated with chlamydial pneumonia. Diagnosis is confirmed with Giemsa stain, culture, or nucleic acid amplification of conjunctival scrapings. Treat chlamydial conjunctivitis with or without associated pneumonia with a 14-day course of oral erythromycin (12.5 milligrams/kg PO every 6 hours) and erythromycin ophthalmic ointment.[14] Ophthalmology consultation is recommended. Patients with isolated chlamydial ophthalmia who do not have respiratory symptoms or evidence of pneumonia may be safely discharged to home with follow-up in 24 hours.

OTHER BACTERIAL OPHTHALMIA NEONATORUM

Bacterial conjunctivitis due to bacteria other than chlamydia and gonorrhea is also less common when erythromycin topical prophylaxis has been given.[20] The most common bacterial pathogens are *S. aureus*, nontypeable *H. influenzae*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Pseudomonas*.[5] Symptoms are variable and usually begin within 2 weeks of birth with hyperemia, purulent discharge, and edema. Gram stain and culture will identify the cause. Parenteral or oral therapy is not necessary in almost all cases, except nontypeable *H. influenzae*, and topical therapy with bacitracin-polymyxin ointment is sufficient.[5] Nontypeable *H. influenzae* requires admission to the hospital, a full septic workup, and parenteral antibiotics.

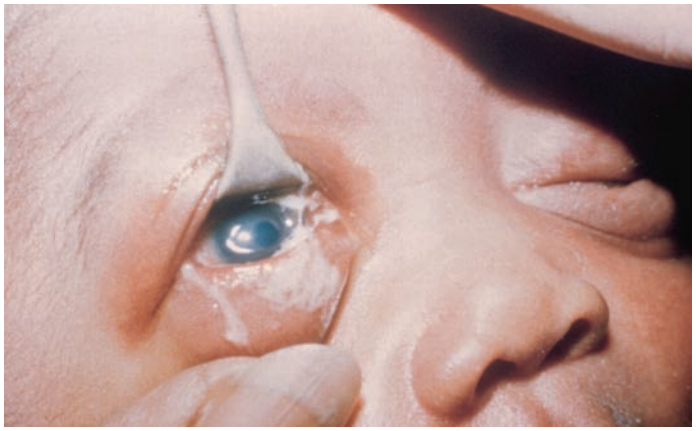


FIGURE 122-8. Gonococcal ophthalmia. Copious purulent drainage in a newborn with neonatal gonococcal conjunctivitis. [Reproduced with permission from *Eye Care Skills: Presentations for Physicians and Other Health Care Professionals, Version 3.0: Eye Trauma and Emergencies.* American Academy of Ophthalmology, Copyright © 2009.]

VIRAL OPHTHALMIA NEONATORUM

Viral neonatal ophthalmia, caused by herpes simplex virus types 1 and 2, is a rare cause of neonatal conjunctivitis. Because there is a significant risk of keratitis and devastating disseminated infection, early identification and treatment are critical. Symptoms develop at 14 to 28 days of life with bilateral lid edema and conjunctival erythema. Suspect herpes infection in a neonate with associated mucocutaneous lesions and a maternal history of herpes; however, a history of maternal infection is not necessary for the diagnosis. Herpes conjunctivitis is confirmed with the presence of keratitis or corneal dendrites on fluorescein examination and viral culture or nucleic amplification tests. Neonates with suspected herpetic ophthalmia require hospital admission, full septic evaluation (including lumbar puncture with herpes polymerase chain reaction testing of cerebrospinal fluid), IV acyclovir (20 milligrams/kg IV every 8 hours for 14 to 21 days), and topical antivirals (1% trifluridine, 0.1% iododeoxyuridine, or 0.15% ganciclovir).[20] **Steroid drops should be strictly avoided in herpes conjunctivitis.**

CHILDHOOD CONJUNCTIVITIS

Conjunctivitis, or inflammation of the conjunctiva, is very common in children and may be caused by viruses, bacteria, or allergy; less commonly, it may be a symptom of a systemic disease. Each type of conjunctivitis is discussed in the following sections.

VIRAL CONJUNCTIVITIS

Viral conjunctivitis in childhood is most frequently caused by adenovirus. Less frequent pathogens are rhinovirus, enteroviruses, influenza, and Epstein-Barr virus.[5] Measles virus can also cause conjunctivitis but is an unlikely diagnosis with proper childhood immunization. Measles outbreaks can occur among unimmunized populations. Conjunctivitis caused by the herpes viruses requires immediate therapy to prevent permanent vision loss and is covered separately below.

Viral conjunctivitis has several distinct presentations. **Pharyngoconjunctival fever** presents with fever, acute onset of conjunctivitis, pharyngitis, and preauricular adenopathy, and may be unilateral or bilateral. **Epidemic keratoconjunctivitis** can present with pain, photophobia, subepithelial defects, and pseudomembranes over the conjunctiva, and is usually bilateral. **Follicular conjunctivitis** often presents with a foreign body sensation and erythema of the conjunctiva. On examination, an aggregation of lymphocytes around networks of blood vessels in the conjunctiva will give the appearance of follicles. Finally, **acute**



A



B

FIGURE 122-9. A and B. Conjunctivitis due to *Chlamydia trachomatis* is the most common infectious cause of ophthalmia neonatorum. This 10-day-old neonate presented with lid swelling with erythema and mild mucopurulent eye discharge. Intense hyperemia of the palpebral conjunctiva is seen (**B**). Direct fluorescent antibody staining for elementary bodies was positive, and both Gram stain and culture were negative for *Neisseria gonorrhoeae*. [Photo contributor: Binita R. Shah, MD.]

hemorrhagic conjunctivitis presents with hyperemic conjunctiva, subconjunctival hemorrhages, chemosis, swelling, photophobia, and pain. **Figure 122-10** shows a child with adenoviral conjunctivitis.

The treatment of these categories of viral conjunctivitis is supportive only. Cool compresses may offer patients symptomatic relief. Artificial tears and topical vasoconstrictors may improve redness and the sensation of dryness. **Topical antibiotics should not be prescribed because there is no evidence of protection against secondary infections and there is suspicion of harm.**[21] Symptoms may last 2 to 3 weeks, and patients should be referred to ophthalmology if conjunctivitis is persistent or worsening. Viral conjunctivitis is very contagious, and families should not share face cloths, towels, or pillows.



FIGURE 122-10. Adenoviral conjunctivitis. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York, Figure 8-3.]

HERPES VIRUS CONJUNCTIVITIS

Conjunctivitis caused by **varicella** most often occurs during primary infections. However, it can also occur with herpes zoster ophthalmicus, which is when the varicella virus lies dormant in the trigeminal nerve and causes recurrent vesicles in the V_1 distribution. **Herpes simplex virus type 1** may also present similarly with unilateral vesicles in the same distribution. A typical dendritic pattern will be seen on the cornea with fluorescein examination.

Treat both primary and secondary varicella conjunctivitis presenting in the first 72 hours of symptoms with oral acyclovir (for age >2 years old: 20 milligrams/kg PO every 6 hours for 5 days; maximum dose, 3200 milligrams/d) and obtain ophthalmology consultation.[22] Similarly, herpes simplex infections of the eye in children also require ophthalmology consultation but may be treated with topical antivirals such as trifluridine, iododeoxyuridine, or ganciclovir.[20] Topical steroids may be prescribed by an ophthalmologist for both varicella and herpes simplex infections of the eye but should not be prescribed by the emergency physician.

CHILDHOOD BACTERIAL CONJUNCTIVITIS

Bacterial conjunctivitis in childhood is most frequently caused by *Haemophilus* species, *S. pneumoniae*, *M. catarrhalis*, and *S. aureus*.[5] Less common pathogens include *Pseudomonas aeruginosa*, group B *Streptococcus*, *E. coli*, *and Neisseria meningitidis*. Oculoglandular syndrome is a rare infection often caused by *Bartonella henselae* (**cat-scratch disease**) or *Francisella tularensis* (**tularemia**), which causes ipsilateral conjunctivitis and lymphadenopathy, often axillary. Physical exam findings include normal vision, mucopurulent matting of the lashes (especially after sleep), and eyelid edema. Photophobia and eye pain are not present, although patients will have some discomfort. Consider **chlamydial and gonococcal conjunctivitis** in the differential diagnosis, especially in sexually active adolescents and neonates.

The diagnosis of bacterial conjunctivitis is primarily clinical. If patients have concomitant otitis media, the diagnosis is most likely conjunctivitis-otitis syndrome caused by nontypeable *H. influenzae*;

prescribe oral antibiotics. Otherwise, treat with a broad-spectrum topical antibiotic such as a fluoroquinolone (ciprofloxacin or ofloxacin ophthalmic, which, due to limited absorption, are acceptable for use in children), bacitracin-polymyxin, or trimethoprim-polymyxin.[5] An ointment is preferable to eyedrops. Although erythromycin ointment is inexpensive, it does not provide adequate coverage for *H. influenzae* or *M. catarrhalis*. Therefore, if erythromycin ointment has been prescribed and the patient is not clinically improving, change the topical antibiotic ointment.

Patients with isolated bacterial conjunctivitis or conjunctivitis-otitis syndrome may be safely discharged to home. Symptoms that do not improve after 7 days of therapy merit ophthalmology referral.

It may be difficult in the ED to differentiate bacterial from viral conjunctivitis. In addition to the earlier noted differences, clues to bacterial etiology include history of discharge causing eyelash matting and mucoid or mucopurulent discharge on exam. Viral conjunctivitis is likely in the presence of preauricular lymphadenopathy, recent respiratory illness, and conjunctivitis that spreads among close contacts.[10] Consider a swab of the conjunctiva for severe or recurrent cases.

ALLERGIC CONJUNCTIVITIS

Children with a history of atopy are most likely to suffer allergic conjunctivitis, but almost any child can be affected. Children with allergic conjunctivitis may have bilateral itchy eyes, tearing, thin mucoid discharge, mild redness, and eyelid edema, as well as chemosis. In severe cases, patients may have mild photophobia. Treat allergic conjunctivitis with allergen avoidance, topical antihistamines, and mast cell stabilizers. Ketotifen (one drop to each eye every 8 to 12 hours) and olopatadine (one to two drops to each eye daily), which are both antihistamines and mast cell stabilizers, are very effective.[23] Topical NSAIDs, vasoconstrictors, and lubricants may provide symptomatic relief. Cool compresses may also be beneficial. Oral antihistamines are discouraged because they can cause eye dryness, exacerbating symptoms.

KAWASAKI'S DISEASE

Kawasaki's disease, a severe medium-sized vessel vasculitis that can cause coronary artery aneurysms, predominantly presents in children 1 to 8 years of age (see Chapter 142, "Rashes in Infants and Children"). Nonpurulent bilateral conjunctivitis is a key diagnostic feature of Kawasaki's disease. In typical cases, patients have a fever (>5 days), dry and erythematous lips and oropharynx, enlarged cervical lymph node (>1.5 cm), nonvesicular rash, edema, or peeling of the hands and feet. A diagnosis of Kawasaki's disease requires inpatient admission, IV γ-globulin, aspirin therapy, cardiology consult, and, in most institutions, either infectious disease or rheumatology consultations.

PEDICULOSIS

Lice can infest the eyelashes of a child of any age, leading to itching and scratching, with a mild conjunctivitis caused by the louse's saliva. Occasionally by scratching, children can cause a secondary bacterial infection or corneal abrasion.

Do not use pediculicide shampoos to treat pediculosis of the eyelashes because the shampoo is toxic to the eyes. Rather, attempt to remove nits (eggs) and then smother the lice with petroleum jelly or other ophthalmic ointment three times a day. Although the head and body louse may frequently involve the eyelashes of children, if *Pthirus pubis* (pubic louse) is identified, consider sexual abuse.

PEDIATRIC GLAUCOMA

Pediatric glaucoma is an important worldwide cause of visual impairment. Primary pediatric glaucoma is the result of dysgenesis of the chamber angle leading to decreased outflow of aqueous humor and increased intraocular pressure. In secondary glaucoma, aqueous outflow is diminished by systemic disease, scarring, trauma, inflammation, or infection. Primary pediatric glaucoma is more common than secondary glaucoma in children and is often familial. Estimates of incidence range from 3.31 to 5.41 per 100,000 births.[24] Approximately 75% of cases are bilateral, and 80% of cases will present before 1 year of age. Pediatric syndromes associated with glaucoma include Sturge-Weber syndrome, Lowe's syndrome, Down syndrome, neurofibromatosis, and maternal rubella syndrome. It is important to be familiar with the presenting signs of pediatric glaucoma so that proper ophthalmologic consultation and referral may be made.



FIGURE 122-11. Infantile glaucoma. An enlarged, hazy cornea resulting from congenital glaucoma. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine.* © 2006, McGraw-Hill, Inc., New York, Figure 8-32.]

Children with pediatric glaucoma will have a number of pathologic ocular signs and symptoms. Intraocular pressure will be elevated (≥20 mm Hg), and the cornea will appear enlarged and often cloudy and edematous (**Figure 122-11**). A full-term newborn cornea is nearly adult sized, with a horizontal diameter range of 9.0 to 10.5 mm versus 10.5 to 13.0 mm in an adult.[5] **Children <1 year of age should not have a corneal diameter >12 mm, and no child should have a corneal diameter >13 mm.**[24] There is associated blepharospasm, conjunctival injection, and myopia. The globe may appear enlarged. If the optic disc can be visualized, abnormal cupping or asymmetry may be found.

Consult ophthalmology, and initiate medical therapy of pediatric glaucoma to temporarily decrease intraocular pressure while awaiting definitive surgical repair. Therapies include oral and topical carbonic anhydrase inhibitors and topical β-blockers.[25] Acetazolamide (3 milligrams/kg PO every 6 hours) can be used for short periods of time, and pediatric doses are prepared by crushing the tablets used for adults. Topical carbonic anhydrase inhibitors such as dorzolamide or brinzolamide may also be used with fewer systemic side effects. Topical β-blockers such as timolol 0.25% are recommended at a starting dose of one drop daily.

LEUKOCORIA

Leukocoria is a white-appearing pupil (**Figure 122-12**). Normally when a bright light is directed at the pupil, a red reflex appears as the light is reflected off the retina. With leukocoria, the red reflection is blocked. Despite routine screening during pediatric well-child examinations, leukocoria is frequently discovered by parents after a photograph with flash photography is noticed to have unequal "red eye."

Leukocoria has many causes, as listed in **Table 122-3**. Of patients age 0 to 10 years old presenting with leukocoria, up to 60% will have



FIGURE 122-12. Cataract. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine.* © 2006, McGraw-Hill, Inc., New York, Figure 8-21.]

congenital cataracts and 18% will have retinoblastoma.[26] Leukocoria requires prompt emergency evaluation by an ophthalmologist to avoid loss of vision or life.

CATARACTS

Cataracts, in addition to retinopathy of prematurity, glaucoma, and abusive head trauma, are one of the most common avoidable causes of childhood visual impairment.[27] Although cataracts are not treated in the ED, it is important for emergency providers to recognize and refer children with cataracts promptly to avoid permanent visual loss.

Pediatric cataracts can be unilateral or bilateral, and can be due to perinatal infection, or can be hereditary, or idiopathic.[27] Hereditary cataracts can be inherited in an autosomal dominant or recessive pattern. Cataracts recognized in the neonatal period are most frequently from the TORCH infections (toxoplasmosis, syphilis, rubella, cytomegalovirus, and herpes simplex). Cataracts may also be associated with a variety of systemic illnesses and syndromes such as Down syndrome, galactosemia, Lowe's syndrome, Alport's syndrome, homocystinuria, Wilson's disease, and many more.

Children with cataracts present with any one of the following: leukocoria (Figure 122-12), strabismus, and/or nystagmus. On direct or slit lamp examination, lens opacities will be seen that can have partial or complete lens involvement, obscuring the retina.

Cataracts require referral to an ophthalmologist. Although there are a wide variety of surgical techniques used, generally central cataracts that are >3 mm warrant surgical removal. Children older than 2 years old may benefit from intraocular lens placement. Patients may also require surgery to repair concomitant strabismus.

TABLE 122-3 Causes of Leukocoria in Children

- Congenital cataracts
- Retinoblastoma
- Retinal detachment
- Retinoschisis
- Retinopathy of prematurity
- Falciform retinal fold
- Persistent hyperplastic primary vitreous
- Coats' disease
- Retinal coloboma
- Endophthalmitis or panophthalmitis
- Posterior uveitis
- Vitreous hemorrhage
- High myopia
- Sarcoma
- Corneal opacity
- Phakomatosis
- Other tumors
- Ocular larva migrans

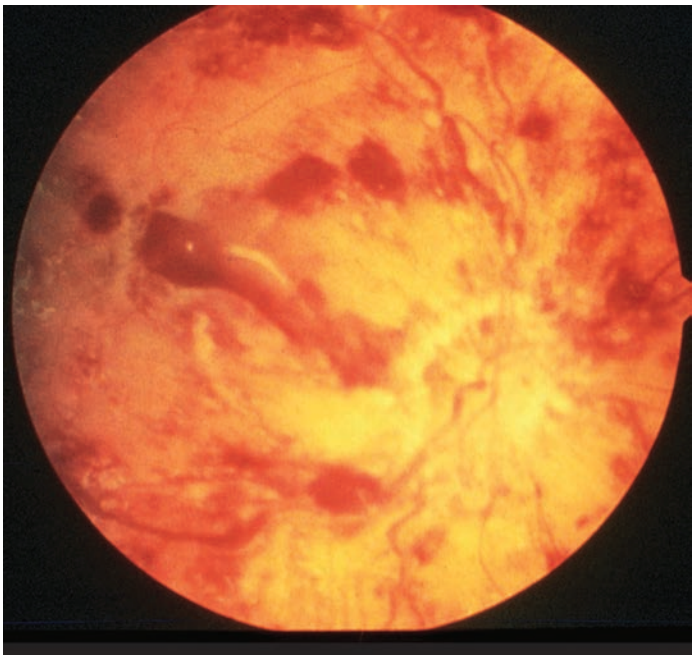


FIGURE 122-13. Retinal hemorrhage. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 15-33.]

RETINOBLASTOMA

The most common presenting signs of retinoblastoma are leukocoria and strabismus, and most children are identified by 3 years of age. Leukocoria in children with retinoblastoma is most often detected by family and friends (80% of cases), and less commonly by ophthalmologists (10%) and pediatricians (8%).[28] Children may also present with proptosis, retinal detachment, glaucoma, hyphema, vitreous hemorrhage, and a red, painful eye due to ocular inflammation that may be confused with orbital cellulitis. Retinoblastoma is further discussed in Chapter 145, "Oncologic Emergencies in Infants and Children."

RETINAL HEMORRHAGES

The incidence of abusive head trauma is approximately 38.8 per 100,000 infants.[29] Retinal hemorrhages are seen in approximately 75% to 80% of cases and are a sensitive finding for this diagnosis (**Figure 122-13**).[30] Retinal hemorrhages appear to be caused by shaking of the infant's head and are not sequelae of intracranial injury.[31] Although retinal hemorrhages are pathognomonic of abusive head trauma in most settings, rarely, victims of a severe head crush injury have similar findings.[30] Although children may suffer vision loss from ocular pathology, the most common cause of blindness in abusive head trauma is cortical blindness, rather than retinal hemorrhage. Obtain ophthalmologic consultation to detect retinal hemorrhage if child abuse is suspected. Child abuse is discussed in detail in Chapter 150, "Child Abuse and Neglect."

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 123

Nose and Sinus Disorders in Infants and Children

Joanna S. Cohen
Dewesh Agrawal

ACUTE BACTERIAL SINUSITIS

Acute bacterial sinusitis is a bacterial infection of one or more of the paranasal sinuses lasting <30 days.[1] The most common predisposing factor is a viral upper respiratory infection (URI). The incidence of viral URIs in children age 6 to 35 months is approximately six episodes per patient-year, with approximately 8% of those becoming complicated by acute bacterial sinusitis. Bacterial sinusitis in children is most common in the 12 to 23 months age group, probably because these children are most likely to be in day care, predisposing them to URIs.[2,3] The cost of acute pediatric bacterial sinusitis in the United States is approximately $20,000 per hospitalized patient, and a large geographic variation in healthcare utilization exists.[4] Total healthcare costs in the United States incurred from treating sinusitis in children <12 years of age had been estimated at close to $2 billion a year.[5]

PATHOPHYSIOLOGY

The sinuses are air cavities lined with ciliated columnar epithelium that helps mucus clearance by pushing mucus and debris out of the sinus ostia into the nasal cavity. Blockage of the ostia by mucus and inflammation predisposes to bacterial sinusitis. The ethmoid and maxillary sinuses are present at birth and are most commonly involved in sinusitis in children. The sphenoid sinuses form at 3 to 5 years of age. The frontal sinuses do not appear until 7 to 8 years of age and remain incompletely pneumatized until late adolescence. The most common predisposing factors for acute bacterial sinusitis are diffuse mucositis secondary to viral rhinosinusitis in about 80% and allergic inflammation in about 20%.[6] Less common predisposing factors include nonallergic rhinitis, cystic fibrosis, dysfunctional or insufficient immunoglobulins, ciliary dyskinesia, and anatomic abnormalities.[7]

The most common pathogen of acute bacterial sinusitis is *Streptococcus pneumoniae*, recovered in 30% of children with acute sinusitis. Nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* are each recovered in 20%.[7,8]

CLINICAL FEATURES

Children with acute bacterial sinusitis typically present with high fever and purulent nasal discharge. Headache, particularly behind the eye, is variable. Complaints of facial pain in children are rare.[2] Parents may report halitosis. The physical examination findings of acute bacterial sinusitis are often similar to those of uncomplicated viral sinusitis, with swollen and erythematous turbinates and mucopurulent discharge. However, reproducible unilateral tenderness to percussion or direct pressure of the frontal or maxillary sinus may indicate acute bacterial infection, and periorbital edema might indicate ethmoid sinusitis.[2] Transillumination of the maxillary sinuses is unreliable in children <10 years of age.[9]

DIAGNOSIS

Although the gold standard for diagnosis of acute bacterial sinusitis is the recovery of $\geq 10^4$ colony-forming units/mL of bacteria from the paranasal sinuses, sinus aspiration is painful and impractical in the ED.[7] Therefore, diagnosis is often based on clinical criteria that help to distinguish acute bacterial sinusitis from an uncomplicated viral URI in an ill-appearing child (**Table 123-1**).[1,10]

Imaging studies should not be obtained to differentiate acute bacterial sinusitis from viral URI because of the high incidence of sinus mucosal abnormalities in patients with simple upper respiratory symptoms or no clinical symptoms at all.[1] In one study, mucosal sinus changes were evident in 97% of infants who had a URI in the 2 weeks preceding a cranial CT done for unrelated reasons.[11] Plain films have limited utility because they require correct positioning that is technically difficult in young children, and there is only a 70% to 75% correlation of culture confirmation with abnormal-appearing sinus radiographs.[12] A paranasal sinus CT with contrast or an MRI with contrast is, however, recommended for suspected orbital or CNS complications of bacterial sinusitis, including preseptal or postseptal cellulitis, subperiosteal abscess, cavernous sinus thrombosis, osteomyelitis of the frontal bone (Pott's puffy tumor), subdural empyema, epidural or brain abscess, and meningitis.[1,12]

TABLE 123-1 Clinical Features of Acute Bacterial Sinusitis[10]

Persistent symptoms lasting >10 d without improvement	Nasal or postnasal discharge and/or Daytime cough
Worsening course	Worse or new onset of nasal discharge, daytime cough, or fever after initial improvement
Severe onset	Fever ≥39°C (102.2°F) Purulent nasal discharge for ≥3 d

TREATMENT

Patients with mild symptoms suggestive of a viral infection can be observed for 7 to 10 days, with no antibiotics prescribed. However, if symptoms persist or are severe (see Table 123-1), suspect acute bacterial sinusitis and prescribe antibiotics to speed recovery, prevent suppurative complications, and minimize asthma exacerbations in susceptible children.[1]

Antibiotic treatment for acute sinusitis is outlined in **Table 123-2** and **Figure 123-1**.

Decongestants, antihistamines, and nasal irrigation are not effective for children with acute bacterial sinusitis.[13] Adjunctive therapy with intranasal steroids (e.g., fluticasone propionate, one to two sprays per nostril daily, or beclomethasone, one to two sprays per nostril twice a day) has modest benefits and may be considered.[1,14,15]

Complications of acute bacterial sinusitis are rare but usually involve the orbit or CNS. If suspected, obtain a contrast-enhanced CT scan or an MRI if possible.[16] Proptosis or impairment of extraocular muscle movement suggests orbital inflammation, usually from extension of an ethmoidal infection (**Figure 123-2**). Frontal and sphenoidal inflammation can lead to intracranial extension, causing frontal lobe and subdural abscesses as well as meningitis and empyema. IV antibiotics are needed, and surgical management may be necessary. Consult an ophthalmologist and/or neurosurgeon promptly for complications.[1] For further discussion of the management of periorbital and orbital sinusitis, see Chapter 122, "Eye Emergencies in Infants and Children."

CHRONIC BACTERIAL SINUSITIS

Chronic rhinosinusitis is an inflammatory process involving the mucosa of the nose and sinuses that lasts >3 months.[17] Factors associated with chronic sinusitis include older age, allergic rhinitis, recurrent viral URIs, immunodeficiency, ciliary dyskinesia, anatomic abnormalities, and fungal colonization of the sinuses.[18] The most common organisms identified are α-hemolytic *Streptococcus, H. influenzae*, and *S. pneumoniae*.[19] Chronic sinusitis has been linked to asthma, and treatment of chronic sinusitis reduces asthma symptoms.[20]

In addition to the more common pathogens seen in acute bacterial sinusitis, chronic sinusitis may also be caused by *Staphylococcus aureus*, anaerobes, and, rarely in children, fungi, including *Aspergillus, Fusarium, Bipolaris, Curvularia lunata*, and *Pseudallescheria boydii*.[20] Antibiotics for chronic sinusitis should cover the usual pathogens of acute sinusitis as well as aerobic and anaerobic β-lactamase–producing bacteria. Commonly used oral antimicrobial agents include amoxicillin-clavulanate (20 to 25 milligrams/kg PO twice daily), clindamycin (8 milligrams/kg PO three times daily), and the quinolones (moxifloxacin, 400 milligrams PO daily) for adolescents.[21] Chronic bacterial sinusitis is treated with prolonged antibiotics, typically for at least 4 weeks.[22]

TABLE 123-2 Antibiotic Treatment for Bacterial Sinusitis

Clinical Scenario	Additional Factors	Treatment	Duration of Treatment
Mild symptoms or age >2 y	Not in day care, no antibiotics in past 4 weeks	Amoxicillin 20–25 milligrams/kg PO twice daily	10–28 d *or* 7 d beyond resolution of symptoms
	>10% resistant *Streptococcus pneumoniae* prevalence	Amoxicillin 45 milligrams/kg PO twice daily	
Moderate-severe symptoms or age <2 years or attending day care or recent amoxicillin administration		Amoxicillin 45 milligrams/kg with clavulanate 3.2 milligrams/kg PO twice daily (use Augmentin® ES formulation with 600 milligrams amoxicillin and 42.9 milligrams clavulanate per 5 mL)	
	Vomiting or unable to tolerate oral antibiotics	Ceftriaxone 50 milligrams/kg IV/IM once a day	Substitute PO agent when tolerable
Penicillin allergic	Only consider cephalosporins with nonsevere or non–type I hypersensitivity penicillin allergy	Cefdinir 7 milligrams/kg PO twice daily *or* Cefuroxime 15 milligrams/kg PO twice daily *or* Cefpodoxime 5 milligrams/kg PO twice daily	10–28 d *or* 7 d beyond resolution of symptoms

For patients with chronic sinusitis who have failed antibiotic trials and nasal saline irrigation, otolaryngology referral is recommended for complete evaluation with nasal endoscopy and consideration of surgical options.[22] Definitive therapies commonly involve adenoidectomy and rarely balloon catheter sinus dilation or endoscopic sinus surgery, in which the ostiomeatal area is opened, antrostomies are created, and ethmoid partitions are removed.[23,24] Endoscopic sinus surgery has an estimated success rate of 83% in a combined pediatric and adult study.[25] In the pediatric population, however, a less invasive approach known as a **functional endoscopic sinus surgery**, which is essentially a drainage procedure, has good efficacy, with 90% of patients showing marked reduction in symptoms.[26]

SPECIAL POPULATIONS

Patients with recurrent acute rhinosinusitis, characterized by multiple episodes of sinusitis between which signs and symptoms resolve completely, may benefit from prolonged antibiotic prophylaxis with azithromycin.[27] Children with recurrent or refractory sinusitis should be evaluated for immune deficiencies with quantitative immunoglobulin levels, immunoglobulin G subclasses, immunoglobulin A, and T- and B-cell counts. The most commonly diagnosed immune deficiencies in patients presenting with recurrent or refractory sinusitis are selective immunoglobulin A deficiency, common variable immunodeficiency, and immunoglobulin G subclass deficiency.[28] Children with **cystic fibrosis** have thick mucus that predisposes them to sinusitis. Cystic fibrosis is primarily diagnosed through sweat chloride testing. Suspect cystic fibrosis in a child who presents with nasal polyps or chronic sinusitis, particularly in conjunction with failure to thrive and chronic cough.[6]

ALLERGIC RHINITIS

Allergic rhinitis is an immunoglobulin E–mediated chronic or recurrent inflammatory response of the nasal mucosa that is induced by an allergen and typically affects children >2 years old. The worldwide prevalence of symptoms of allergic rhinoconjunctivitis is 2.2% to 14.6% in children age 6 to 7 years old and 4.5% to 45.5% in adolescents age 13 to 14 years old.[29] Approximately 80% of children with asthma have allergic rhinitis, and allergic rhinitis makes it more difficult to control asthma, making it an important topic for the emergency medicine physician caring for children.[29]

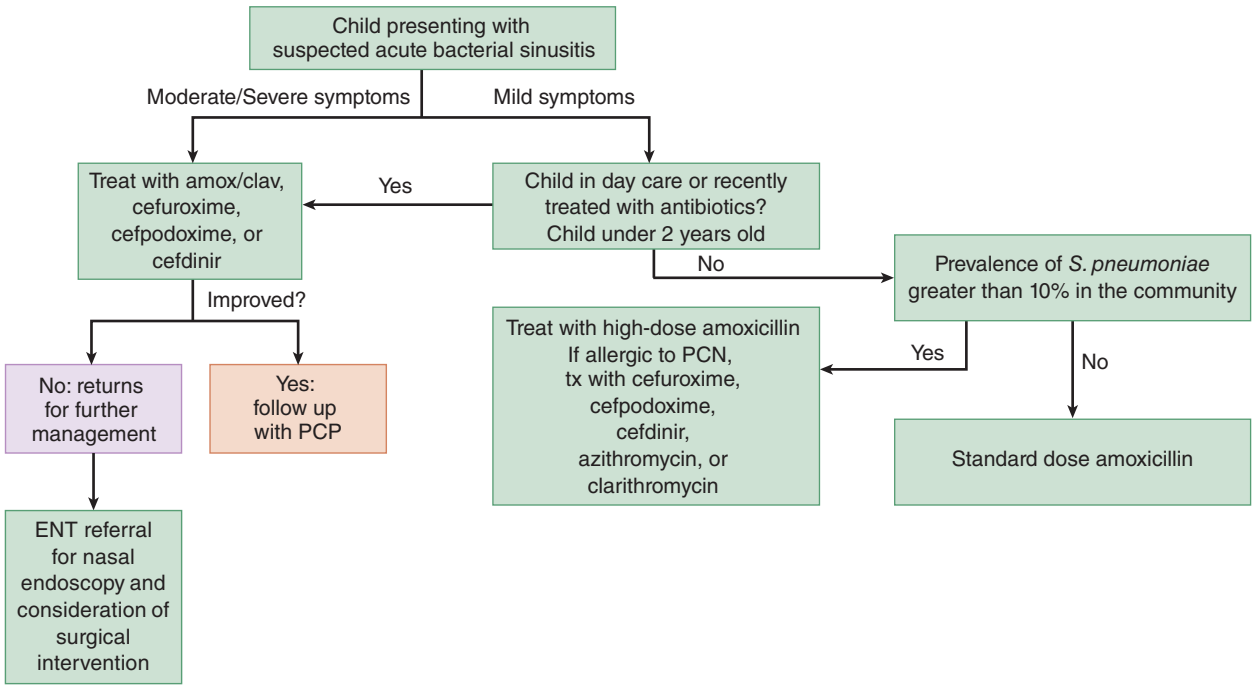


FIGURE 123-1. Management of uncomplicated acute bacterial sinusitis in children. amox = amoxicillin; clav = clavulanate; ENT = ear, nose, and throat; PCN = penicillin; PCP = primary care provider; tx = treat.

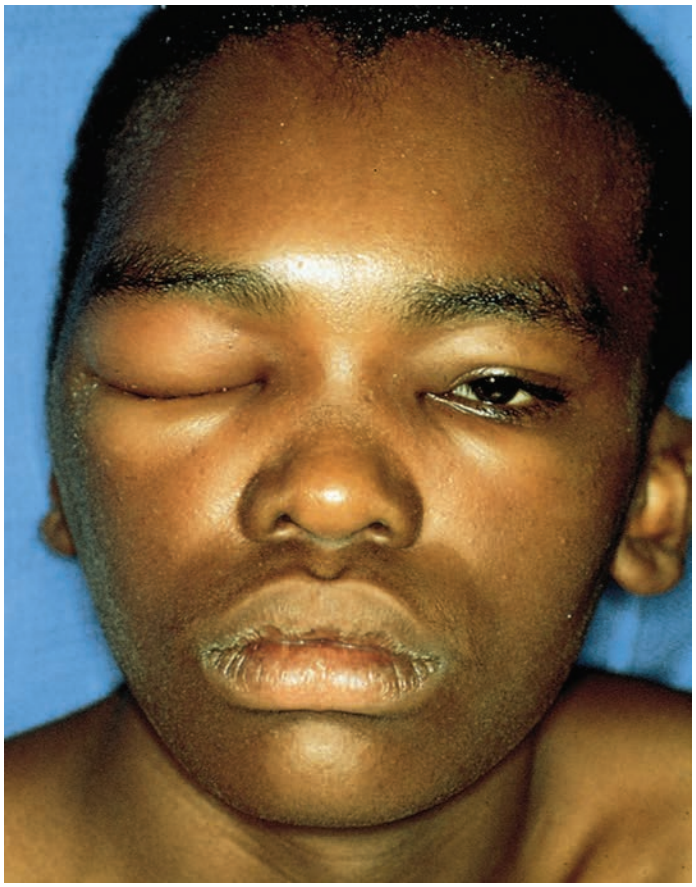


FIGURE 123-2. Sinusitis. Adolescent with pansinusitis complicated by periorbital cellulitis. The patient was also found to have osteomyelitis of the frontal bone (Pott's puffy tumor). [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York.]

PATHOPHYSIOLOGY

Seasonal allergic rhinitis (commonly known as hay fever) is usually caused by airborne allergens such as pollen, whereas perennial allergic rhinitis is usually caused by dust mites, animal dander, and mold. Allergic rhinitis is an immunoglobulin E–mediated inflammatory response in the nasal mucosa that occurs after sensitization with a specific allergen. Immunoglobulin E binding triggers mast cell degranulation and subsequent histamine release. The binding of histamine to the histamine-1 receptor on nasal neurons and nasal vasculature is the ultimate mechanism responsible for the nasal itch, sneeze, rhinorrhea, and nasal obstruction of allergic rhinitis.

CLINICAL FEATURES

Allergic rhinitis presents with clear rhinorrhea, nasal pruritus, and sneezing. Ocular symptoms, such as conjunctival hyperemia and pruritus, may coexist. Symptoms can lead to sleep disturbance, limitations in activity, and poor school performance.[30]

DIAGNOSIS

Patients with allergic rhinitis report symptoms of paroxysmal sneezing, nasal pruritus, rhinorrhea, oropharyngeal pruritus, hyperemia, and ocular pruritus. On physical examination, there may be hypertrophy and edema of the nasal turbinates with associated pale, bluish hue or pallor along with clear secretion from the nares. While it can be difficult to differentiate allergic rhinitis from nonallergic rhinitis, certain physical features may be helpful. For instance, the presence of a horizontal nasal crease ("allergic salute") is more likely to be associated with allergic rhinitis, while Dennie-Morgan folds (a fold or line in the skin below the lower eyelid caused by edema in atopic dermatitis) are more likely to be associated with nonallergic rhinitis.[31] Concomitant wheezing suggests an association with asthma. A patient with severe symptoms who does not respond to treatment may warrant a referral to an allergist for skin testing to detect immediate hypersensitivity reactions to allergens. Total immunoglobulin E levels are neither sensitive nor specific for atopic disease.[32]

TREATMENT

Treatment involves recommending environmental controls such as avoidance of allergens and irritants, including pollutants and cigarette smoke. Nasal saline irrigation with a syringe or spray reduces the use of antibiotics and other medications.[33]

Intranasal steroids, such as fluticasone furoate nasal spray, are effective for treatment of allergic rhinitis.[34] Intranasal corticosteroids reduce inflammation of the nasal mucosa. Daily morning dosing minimizes the impact on the hypothalamic-pituitary-adrenal axis. Oral antihistamines are also commonly used to treat allergic rhinitis, but there is a lack of evidence for the benefit of oral antihistamine therapy in addition to topical nasal steroids for children with allergic rhinitis.[35] Second-generation antihistamines, such as loratadine (5 milligrams daily for age 2 to 6 years; 10 milligrams daily for >6 years of age) and cetirizine (2.5 to 5.0 milligrams daily for age 2 to 6 years; 5 to 10 milligrams daily for >6 years of age), are preferable because they are less likely to cross the blood–brain barrier and therefore cause less sedation than first-generation antihistamines such as diphenhydramine and hydroxyzine. Other therapies target the immune system directly. Montelukast, a leukotriene receptor antagonist, and disodium cromoglycate, a mast cell stabilizer, have been used with success for symptom reduction.[36,37] Sublingual and subcutaneous immunotherapy has also been shown to be effective in improving symptoms of allergic rhinitis in children.[38-40]

NASAL FOREIGN BODIES

Foreign body insertion is a common pediatric complaint in the ED. Foreign bodies in the external ear canal predominate, followed by nasal foreign bodies. Children who insert objects into their nose are, in general, younger than patients with auditory foreign body insertion.[37] Although pharyngeal foreign bodies can present in adults, nasal foreign bodies are almost exclusively a pediatric problem. Common objects include beads, paper, rocks, toy parts, and organic material such as peas, corn, seeds, nuts, and legumes.

CLINICAL FEATURES

The child with a nasal foreign body may present with local pain (23% to 55%), nasal discharge (7% to 36%), epistaxis, or admission by the child. Alternatively, the parent may witness the child placing something in the nose, or the object may be found during routine child care. Most children with nasal foreign bodies are asymptomatic.[41]

DIAGNOSIS

Most nasal foreign bodies can be directly visualized. Have a high index of suspicion for a nasal foreign body in an appropriately aged child who presents with persistent, unilateral, purulent, foul-smelling nasal discharge (**Figure 123-3**).

TREATMENT

Before attempting instrumentation, try less invasive removal using positive-pressure techniques. These include nose blowing in older children while occluding the opposite nostril or applying oral positive pressure by having the parent occlude the unaffected nostril, cover the child's mouth with their own, and blowing ("parent kiss"); finally, a bag-valve mask can be used in a manner similar to the parent kiss. These techniques are successful in more than one half of cases.[42] For more invasive methods, the key to successful removal is immobilization. Approximately 20% of patients undergoing nasal foreign body removal in the ED are given procedural sedation, most commonly with ketamine.[43] Place the child in a supine position, and pretreat the nasal mucosa with topical 1% lidocaine



FIGURE 123-3. A 6-year-old child was brought to the ED with a complaint of a foul-smelling serosanguineous discharge from the right nostril. He confessed to putting a button in his nostril about 1 week before this visit. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York, Figure 9-9.]

and 0.5% phenylephrine.[41] Phenylephrine shrinks inflamed nasal mucosa, allowing for easier removal of entrapped foreign bodies, and also reduces the likelihood of procedural epistaxis. The most common methods for removal include forceps, the Foley catheter technique (advance a lubricated 5- or 6-French Foley balloon catheter past the object, inflating the balloon with air and withdrawing the catheter to gently remove the foreign body), and the use of a suction catheter. All have varying degrees of success and failure. Alligator forceps work best if the object is close to the anterior nares and can be easily grasped. If the object is friable, there is a risk of pulling it apart and leaving pieces in the nose. A particularly deep nasal foreign body may need to be removed by an otolaryngologist. Although it is possible to aspirate a nasal foreign body, this is rare, and most complications of nasal foreign bodies occur during attempted removal.[41] Complications of nasal foreign body removal include failure to remove the object, epistaxis, laceration, and, rarely, septal perforation. If irrigation is attempted and the object is expandable, such as rice, vegetable matter, or sponge, the foreign body can swell, impeding its extraction.

SPECIAL CONSIDERATIONS

Button batteries pose an important risk to children, particularly those less than 5 years old.[44] A button battery in the nasal cavity can cause liquefactive necrosis and septal perforation in as little as 7 hours.[45] For this reason, remove button batteries as quickly as possible. Do not instill any type of nasal drops before removal because the electrical charge of the battery will produce electrolysis with any electrolyte-rich fluid. This results in a severe alkaline burn. Button batteries are often not directly visualized in the ED because of extensive mucopurulent discharge and mucosal edema. For this reason, consider a plain radiograph to characterize a nonvisible foreign body or unilateral foul-smelling nasal discharge.[46]

Although more common in the external ear, live foreign bodies in the nose also require special mention. Cockroaches, mosquitoes, and beetles are all uncommon foreign bodies. They are often related to sleeping on the floor or poor hygiene. The recommended approach is to first kill the insect with 2% lidocaine or mineral oil and then attempt removal.

EPISTAXIS

Epistaxis usually occurs in children age 2 to 10 years old. It is rare in infants and older children.[47] Nosebleeds in children are most often secondary to digital trauma (nose picking) or rhinitis sicca. Rhinitis sicca is more common in northern latitudes during the winter when the humidity is low and dry air heating systems can cause nasal mucosa desiccation and frequent bleeding.

Other causes of epistaxis include facial trauma, foreign bodies, sinusitis, or increased vascular pressure secondary to excessive coughing. Less commonly, epistaxis can be the presenting complaint of a coagulopathy, leukemia, or nasal tumor. Rarely, epistaxis may be the presenting sign of a juvenile nasopharyngeal angiofibroma, a tumor seen exclusively in adolescent males. Most pediatric epistaxis originates from Kiesselbach plexus, a venous vascular plexus on the anterior nasal septum. Although anterior bleeds usually ooze, posterior bleeds tend to be more profuse because they originate from the sphenopalatine artery. This type of bleeding, while rare, carries a higher risk of airway compromise, aspiration of blood, and life-threatening hemorrhage.

TREATMENT

Most epistaxis can be controlled with conservative methods, such as pinching the nostrils together for 5 to 10 minutes with the patient slightly bent forward at the waist so as to avoid aspirating or swallowing blood. Ice or topical vasoconstrictors such as oxymetazoline hydrochloride or phenylephrine can also be applied to the nose to promote vasoconstriction. Cautery with silver nitrate can be used if the bleeding site can be identified. If all else fails, the nares can be packed with absorbable gelatin foam, oxidized cellulose, or preformed devices (Rhino Rocket Child®, Shippert Medical Technologies Corporation, Centennial, CO). See Chapter 244, "Nose and Sinuses," for the procedure and related information.

DISPOSITION AND FOLLOW-UP

Most children with simple epistaxis can be sent home with instructions to avoid digital trauma and apply topical antibiotic ointment to the nares at night to help lubricate the mucosa. Children with recurrent or severe epistaxis and a family history of a bleeding disorder or abnormal screening prothrombin time or activated partial thromboplastin time should be referred to a hematologist for a complete coagulopathy evaluation. Approximately one third will have a diagnosable coagulopathy, most often von Willebrand's disease type 1 (see Chapter 144, "Hematologic Emergencies in Infants and Children").[47] If bleeding is recurrent, unilateral, and associated with nasal obstruction, a neoplasm may be suspected, and an otolaryngology consult is warranted. **In an adolescent male with profuse unilateral epistaxis requiring packing, juvenile nasal angiofibroma should be suspected, and the patient should be evaluated with a CT scan.**

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 124

Mouth and Throat Disorders in Infants and Children

Derya Caglar
Richard Kwun

INTRODUCTION

Lesions of the mouth and throat are common in children and can range from benign conditions that require no intervention to significant systemic illness requiring extensive treatment and support (**Table 124-1**). Making the distinction between these conditions can be difficult. Mouth pain secondary to viral infections of the oropharynx is one of the most common presenting complaints of pediatric patients; however, most

TABLE 124-1 Common Causes of Oral Lesions in Children

Anterior	Posterior	Diffuse
Aphthous ulcers	Adenovirus pharyngitis	Autoimmune disease
Contact stomatitis	Coxsackievirus	Candidiasis (thrush)
Herpes simplex gingivostomatitis	Cytomegalovirus Epstein-Barr virus	Chemotherapy-related mucositis
Trauma	Streptococcal pharyngitis	Medication-related (phenytoin [Dilantin®])
Vincent's angina		
		Stevens-Johnson syndrome Varicella-zoster

patients require no treatment beyond supportive care and pain control. Bacterial infections of the mouth and throat, such as pharyngitis and uvulitis, cause local and systemic illness and rarely can lead to life-threatening complications. The management of dental injuries, whether from neglect or trauma, differs for primary and permanent teeth.

NORMAL VARIANTS

Epstein pearls are remnants of embryonic development that present as white, slightly raised nodules seen most commonly midline at the junction of the soft and hard palates of neonates. They are often seen incidentally during feeding and do not cause the child any pain or discomfort. Most resolve spontaneously.

Geographic tongue or migratory glossitis (**Figure 124-1**) can be a source of great parental concern. It is a benign, asymptomatic condition and is often incidentally noticed by parents during another illness. Findings include an area of erythema and atrophy of the papillae of the tongue surrounded by a serpiginous, elevated white or yellow border usually located in the anterior two thirds. The lesions will improve and disappear gradually over time but tend to recur in other areas of the tongue. There is no known cause, although it has been associated with childhood allergies and atopy. No treatment other than reassurance is necessary.



FIGURE 124-1. Geographic tongue. [Reproduced with permission from Wolff K, Johnson RA, Saavedra AO: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 7th ed. © 2013 by McGraw-Hill, Inc., New York, Figure 33-4.]



FIGURE 124-2. Mucocele. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. © 2009, McGraw-Hill, Inc., New York, Figure 34-14.]

Mucoceles (**Figure 124-2**) and **ranulas** are lesions of the oral mucosa that present as small, bluish, discrete, mucosal swellings on the lower lip or sublingual areas. These are most often caused by minor trauma such as biting the lip. Referral to otolaryngology for intervention is needed only with disruption of feeding or development of speech. Adjacent salivary glands are usually removed in addition to the lesion to prevent recurrence.

Eruption cysts are smooth, painless bluish-black areas of swelling found over an emerging tooth that usually resolve with the eruption of the underlying tooth. Although these findings are frightening to the parent, they are benign in nature, often asymptomatic, and require no intervention.

APHTHOUS ULCERS

Aphthous ulcers, also known as *canker sores*, are the most common form of recurrent oral ulcers, occurring in 5% to 25% of the general population.[1] They present in children and adolescents as painful, shallow ulcers on the oral mucosa (**Figures 124-3**). The etiology of canker sores is unknown, but genetic factors, food allergies, local trauma, endocrine changes, stress, and anxiety are all thought to contribute to recurrence.[1] They are found most frequently on the buccal and lingual mucosa. Spontaneous resolution after 7 to 10 days is the norm. Topical



FIGURE 124-3. Aphthous ulcers: Note the multiple ulcers of various sizes located on the lip and gingival mucosa. These lesions rarely occur on the immobile oral mucosa of the gingiva or hard palate. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 6-33.]

medications, such as antimicrobial mouthwashes and topical analgesics, can achieve the primary goal of reducing pain but do not hasten healing or improve recurrence or remission rates.[2] Some adult trials suggest that oral vitamin B_{12} may reduce recurrence rates for those with frequent outbreaks regardless of initial serum B_{12} levels.

Less commonly, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome (**PFAPA**) can cause aphthous ulcers in children 2 to 6 years of age. Patients present with fever, malaise, exudative pharyngitis, cervical lymphadenopathy, and multiple oral ulcers lasting 4 to 6 days, often recurring multiple times a year. **Recurrence is the key to diagnosis,** as this constellation of symptoms is difficult to distinguish from viral infection, particularly in the ED where patient care is cross-sectional rather than longitudinal. The cause of PFAPA remains unknown, but most patients respond well to oral steroids, with resolution of symptoms within 24 hours and typically remission after 3 to 5 years.[3] Some studies have also shown that tonsillectomy leads to complete resolution of symptoms and that vitamin D supplementation reduces number and duration of PFAPA episodes; colchicine may also be effective for some patients in limiting recurrences.[4-6]

STOMATITIS

The majority of infectious mouth and throat lesions are viral. Enteroviral infections commonly cause oral lesions with or without other physical findings such as fever, rash, abdominal pain, or diarrhea. Herpes viruses can cause oropharyngeal lesions that are extremely painful, may be recurrent, and are usually associated with high fever during primary infection. Adenovirus can cause acute pharyngitis in association with fever and tonsillar erythema. Exudative pharyngitis in association with fevers, fatigue, and malaise is frequent in infections with Epstein-Barr virus and cytomegalovirus.

HERPANGINA

Herpangina is an enteroviral infection that causes a vesicular enanthem (**Figure 124-4**) of the tonsils and soft palate, affecting children 6 months to 10 years of age during late summer and early fall. It is primarily caused by coxsackievirus A16 and human enterovirus 71, although other coxsackie A and B genotypes are also common etiologic agents. These vesicles are often very painful and are accompanied by fever, difficulty swallowing, and dysphagia. Patients may complain of headache, vomiting, and abdominal pain. Diagnosis is primarily clinical. Viral culture is the gold standard for confirmation of infection; however, enteroviral polymerase chain reaction can detect enteroviral RNA from nasopharyngeal secretions, blood, urine, or feces much sooner and with higher sensitivity (87% to 100%; 95% from throat culture).[7]

Treatment is palliative because the symptoms are usually mild and lesions heal spontaneously after 3 to 5 days. Antipyretics and systemic analgesics aid with supportive care. **Viscous lidocaine is generally not recommended for pain relief** because it has no benefit over placebo in improving oral intake in affected children and also carries a risk of toxicity from lidocaine ingestion, with associated seizures.[8,9] A mixture of **diphenhydramine and Maalox** applied orally in a swish-and-swallow fashion can provide local pain relief. When topical treatment does not suffice, systemic analgesics, including narcotics, may be necessary. Pay close attention to hydration status because children can quickly become dehydrated, requiring admission for IV fluid replacement.

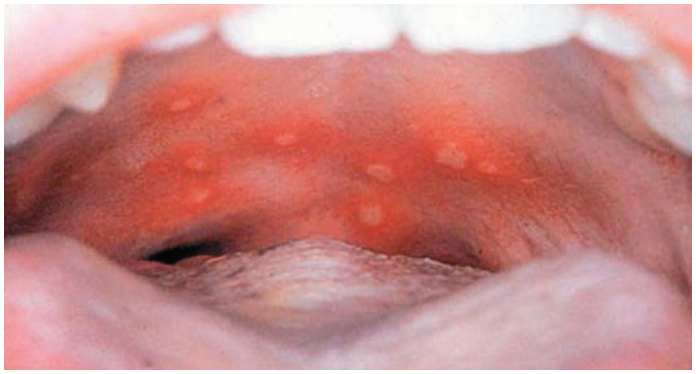

FIGURE 124-4. Herpangina: Typical elliptical or oval-shaped papulovesicular lesions with erythematous rims are seen on the posterior soft palate. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York, Figure 3-67.]

HAND-FOOT-AND-MOUTH DISEASE

Hand-foot-and-mouth disease is also seen with enteroviral infections. Coxsackievirus A16 is the most common cause, but A5, A6, A9, A10, B2, B5, and enterovirus 71 subtypes have also been implicated.[10,11] The disease is typically seen in children <5 years old and is most common in infants and toddlers. The infection has a seasonal distribution and primarily occurs in the spring and summer months.

The illness generally follows a mild course, starting with a low-grade temperature lasting 2 to 3 days, and is associated with decreased appetite, malaise, vague abdominal pain, and mild upper respiratory symptoms. Children will then develop an enanthem of vesicles, followed by the exanthema, although both can occur simultaneously.

Oral lesions usually begin as erythematous macules and evolve into vesicles and ulcers over the course of 1 to 3 days, with new lesions appearing throughout the duration of illness. Lesions typically involve the palate, buccal mucosa, gingiva, and tongue. Pain from these ulcerations often leads to decreased oral intake and mild dehydration.

The associated rash appears on the palms of the hands, soles of the feet, and buttocks (**Figure 124-5**). Lesions begin as erythematous macules that later may develop into small nontender vesicles. The oral and skin lesions tend to resolve over 4 to 7 days.

Diagnosis is primarily clinical, although the virus can be isolated by viral culture or polymerase chain reaction from swabs of the vesicles and from stool specimens. Treatment involves supportive and symptomatic care with antipyretics, topical and oral analgesics, and oral rehydration. In rare cases, pain may lead to inadequate oral intake. Analgesics and IV fluids may be needed to treat dehydration. Rare complications of these infections include viral meningitis, meningoencephalitis, myocarditis, and sepsis.[12,13] Diligent hand washing among children and caregivers is key to preventing spread.[14]

HERPES SIMPLEX GINGIVOSTOMATITIS

Herpes simplex virus can cause a variety of symptoms in the pediatric population. Infants and toddlers will often present with high fever, pharyngitis, and gingivostomatitis during their primary infection. Initial infection is often very difficult to distinguish from other viral etiologies. Most children go undiagnosed with herpes simplex virus until they later present with a more classic painful labial reactivation lesion.

Acute herpetic gingivostomatitis is the most common presentation of primary herpes infection in children (**Figure 124-6**). It usually presents at 6 months to 5 years of age, although primary herpes simplex virus infection may occur in older children and adults. Ninety percent of cases are due to herpes simplex virus type 1; however, herpes simplex virus type 2 has also been found to cause disease.[15,16] Herpes transmission occurs via contact with infectious saliva, typically from caregivers who may be unaware of their infectious risk. The incubation period is 2 to 12 days, with a mean of 4 days.

Clinically, the disease presents with abrupt onset of high fever, irritability, decreased oral intake and drooling, and swollen, erythematous, friable gingiva. Physical findings include vesicular lesions in the oral cavity, ulcerations, and tender cervical lymphadenopathy. Symptoms may persist for up to 3 weeks, but more commonly last <1 week.

Diagnosis is primarily clinical. Viral culture has been the gold standard of laboratory testing for years. However, the recovery of virus from lesions is low (7% to 25%). Herpes simplex virus polymerase chain reaction is a newer, more accurate assay with improved sensitivity in detecting infection from any lesions that are present. Tzanck smear of fluid from unroofed lesions 24 to 48 hours old showing multinucleated



A



B



C

FIGURE 124-5. Hand, foot, and mouth disease: Typical erythematous macules on the palms **(A)** and soles **(B)** and oral lesions **(C)**. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York, Figure 3-65.]

cells can also confirm the diagnosis but cannot differentiate infection between viruses within the herpesvirus family.

Treatment consists of supportive care with oral analgesics/antipyretics, topical analgesics, and systemic antiviral therapy for substantial pain, dehydration, or severe disease (acyclovir, 15 milligrams/kg PO divided five times a day for 7 days).[17,18] Antiviral treatment is most effective within 72 hours of symptom onset. Immunocompromised patients are at significantly higher risk for systemic dissemination, and hospitalization and treatment with IV acyclovir are recommended.[19,20]



FIGURE 124-6. Herpes simplex virus: Primary herpes gingivostomatitis in a 6-year-old girl. Note multiple erosions on gingiva and labial mucosa. [Reproduced with permission from K Wolff, RA Johnson, AP Saavedra, EK Roh: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 8th ed. www.accessmedicine.com. © 2017, McGraw-Hill Education, New York, Figure 27-34.]

Prognosis of a primary herpes simplex virus infection beyond the fetal/neonatal period is very good. As the primary infection resolves, a lifelong latent residency of the virus within the trigeminal ganglion occurs, which may lead to less severe recurrences at the same site in the future.

PHARYNGITIS

It is important to distinguish between superficial and deep space infections of the mouth and throat. Deep space infections are discussed in Chapter 126, "Stridor and Drooling in Infants and Children," and are typically associated with toxic appearance, high fever, drooling, stridor, or changes in phonation, trismus, or torticollis. Sore throat is responsible for 6% of pediatric office visits, resulting in more than 7 million primary care visits annually in the United States.[21,22] In children with acute pharyngitis, 50% to 80% of cases are viral in etiology (**Table 124-2**).

Symptoms associated with acute pharyngitis include sore throat, odynophagia, fever, headache, abdominal pain, nausea and vomiting, cough, hoarseness, coryza, diarrhea, arthralgias, myalgias, and lethargy. Physical examination may reveal tonsillopharyngeal erythema and/or exudates, soft palate petechiae, uvulitis, anterior cervical lymphadenitis, rash, conjunctivitis, anterior stomatitis, and discrete ulcerative lesions. It is often difficult to distinguish between viral and bacterial causes of pharyngitis based on physical examination alone,[23] and *tonsillar exudate does not imply bacterial etiology*. Most viral infections are self-limited and require only symptomatic treatment; 85% of patients experience spontaneous resolution within 1 week. Interestingly, patient satisfaction appears to be greatest when a physician shows concern and provides reassurance and is not related to whether or not antibiotics are prescribed.[24]

TABLE 124-2 Causes of Viral Pharyngitis in Children

- Adenovirus
- Coronavirus
- Enterovirus (coxsackievirus)
- Respiratory syncytial virus
- Rhinovirus
- Measles
- Herpes simplex virus types 1 and 2
- Parainfluenza virus
- Epstein-Barr virus
- Cytomegalovirus virus
- Human immunodeficiency virus
- Influenza virus A and B

VIRAL PHARYNGITIS

Pharyngitis is the best known acute clinical manifestation of **Epstein-Barr virus** infection (**Figure 124-7**). It often begins with malaise, headache, and fevers before development of the more specific signs of exudative pharyngitis and posterior cervical lymph node enlargement. Splenomegaly and hepatomegaly can also occur. Patients mistakenly treated for a bacterial pharyngitis with amoxicillin or ampicillin often develop a characteristic pruritic maculopapular rash that aids in diagnosis.

Diagnosis is often clinical, although a heterophile test (monospot) can aid in diagnosis. It is important to remember that this test relies on cross-reactivity of patient antibodies and is relatively insensitive in pediatric patients (25% positive in 10 to 24 months vs. 75% in 24 to 28 months). Furthermore, the monospot test typically does not turn positive in cases of Epstein-Barr virus until symptoms have been present for 1 week or more. A negative test, therefore, does not exclude the diagnosis of Epstein-Barr virus; when necessary, testing for Epstein-Barr virus immunoglobulin M and immunoglobulin G is both sensitive and specific, although results are not immediately available. Atypical lymphocytes may be present on the CBC, if obtained. Epstein-Barr virus infection may be associated with other organ involvement, including hepatitis. Patients with right upper quadrant tenderness should have liver enzymes evaluated.

Treatment is largely supportive; however, some patients may require IV fluids and pain medication. Although there is no evidence of efficacy,[25] a dose of oral or parenteral steroid can be considered to reduce tonsillar enlargement when swallowing or respiratory symptoms are attributed to enlarged tonsils. When splenomegaly is noted, proper counseling regarding risk factors and symptoms of splenic rupture should be given (avoid contact sports until splenomegaly has resolved as determined by the primary care physician).

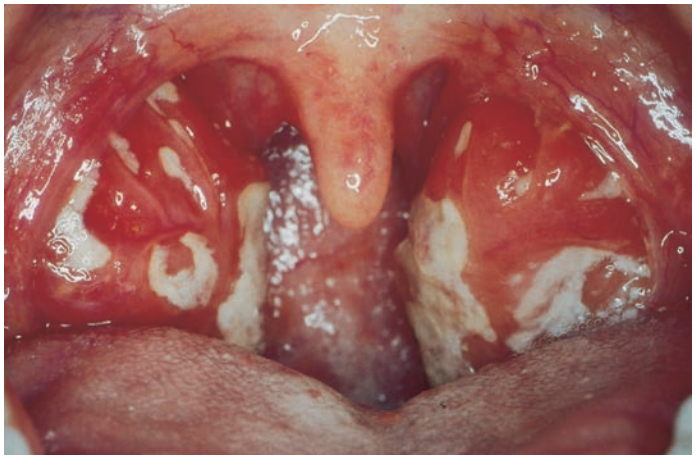

FIGURE 124-7. Marked white exudates on the tonsils of a child with Epstein-Barr virus infection. [Reproduced with permission from Kane KSM, Lio P, Stratigos A, Johnson R: *Color Atlas & Synopsis of Pediatric Dermatology*, 2nd ed. New York, McGraw-Hill, Inc., 2010.]

Cytomegalovirus infection can very closely mimic Epstein-Barr virus mononucleosis. Patients presenting with classic infectious mononucleosis who are heterophile negative are often infected with cytomegalovirus. Fever, malaise, and systemic complaints predominate in the clinical picture of cytomegalovirus, with less prominent cervical lymphadenopathy or splenic enlargement than Epstein-Barr virus. Distinguishing between the two etiologies is difficult, and often, the diagnosis is confirmed with laboratory testing for cytomegalovirus immunoglobulins M and G. Treatment is again supportive.

Acute retroviral syndrome or acute infection with **human immunodeficiency virus** (HIV) may present similarly to Epstein-Barr virus pharyngitis in 50% to 70% of patients. Differences implicating human immunodeficiency virus from other viral illnesses may include presence of high-risk behaviors in the social history, the acuity of onset, the absence of exudate and prominent tonsillar hypertrophy, presence of a rash, and mucocutaneous ulceration.

Acute human immunodeficiency virus is uncommon in the pediatric patient, although it must be considered in adolescents in whom high-risk behaviors are identified. In addition to the usual causes of pharyngitis, opportunistic infections, such as *Candida albicans* and *Mycobacterium avium*, should be considered in the immunocompromised patient.[26]

BACTERIAL INFECTIONS

Group A β-hemolytic *Streptococcus* (GABHS) Pharyngitis GABHS pharyngitis is the most commonly occurring form of acute bacterial pharyngitis for which antibiotic therapy is indicated. It typically occurs in the winter and early spring and primarily affects children age 5 to 15 years old. Although GABHS accounts for up to 37% of pharyngitis in children, 56.2% of children with pharyngitis receive antibiotics.[27-29] In addition, a substantial proportion of patients treated for GABHS pharyngitis receive an inappropriate antibiotic.

Several clinical prediction rules have been created to identify cases of GABHS pharyngitis, and most are modifications of the original Centor criteria (**Table 124-3**). Generally, with zero or one criterion, GABHS is unlikely, and testing and treatment for GABHS are not indicated. With two or more criteria, testing should be performed using a rapid antigen detection test and/or culture.[30] To date, no clinical prediction rule for selective testing has demonstrated sufficient diagnostic accuracy for GABHS pharyngitis. It is also recommended to forgo laboratory testing in patients with overt viral features (e.g., cough, rhinorrhea, oral ulcers/vesicles, and/or conjunctival injection) because a positive test suggests GABHS carriage rather than acute infection.[31]

Although bacterial culture remains the gold standard, with a sensitivity of 90% to 95%, the 18- to 48-hour wait time for definitive diagnosis is often impractical, and the use of a rapid antigen detection test has become popular. The sensitivity of rapid antigen detection tests varies from 80% to 90%. Current guidelines recommend confirmatory throat culture for all patients with a negative antigen test,[27] although backup cultures may not be required in areas with a low incidence of rheumatic fever when antibiotic treatment is not generally recommended.[32] Backup cultures are not necessary for patients with a positive rapid antigen detection test because the test is highly specific.

The antibiotic treatment of GABHS pharyngitis is effective to (1) shorten the duration of illness, (2) prevent transmission, (3) prevent suppurative complications (acute otitis media, acute sinusitis, and peritonsillar abscess), and (4) prevent systemic illness such as rheumatic fever, rheumatic heart disease, and poststreptococcal glomerulonephritis. Antibiotics for the treatment of GABHS pharyngitis should be

TABLE 124-3 Centor Criteria for Likelihood of Group A β-Hemolytic *Streptococcus* Pharyngitis

- Tonsillar exudates
- Tender anterior cervical lymphadenopathy
- Absence of cough
- History of fever

reserved, however, for patients with a positive antigen test or culture or those meeting clinical criteria for diagnosis. GABHS pharyngitis is typically a self-limited disease, with fever and constitutional symptoms diminishing markedly at days 3 and 4 after symptom onset, and antibiotics only decrease the duration of symptoms by approximately 16 hours.[33]

Treatment Treatment can be delayed safely for up to 9 days after symptom onset and still prevent major nonsuppurative sequelae; thus, waiting for confirmatory cultures and providing a wait-and-see prescription for antibiotics are safe. There is no definitive evidence that antibiotic use can prevent acute glomerulonephritis.

No clinical isolate of GABHS has been documented to be penicillin resistant; thus, it remains the treatment of choice based on its efficacy, safety, narrow spectrum, ease of dosing (twice-daily dosing), compliance, and cost (**Table 124-4**).[27] Treatment failures may be attributable to viral pharyngitis with GABHS carriage, medication noncompliance, or reinfection of patients successfully treated for GABHS. A course of 10 days of oral therapy with twice-a-day dosing is recommended for complete pharyngeal eradication; similar efficacy is achieved with once-daily dosing of amoxicillin for 10 days or with a single IM dose of benzathine penicillin.

Several alternative therapy options exist for those unable to take penicillin. The efficacy of amoxicillin appears to be comparable to that of penicillin and is acceptable in children who more easily tolerate the taste of the suspension. Clarithromycin and first-generation cephalosporins are suitable alternatives in penicillin-allergic patients. Clindamycin may be required for macrolide-resistant GABHS in the penicillin-allergic patient. Macrolide resistance is increasing worldwide. Currently, 6% to 7% of GABHS isolates in the United States appear to be macrolide resistant, but this is expected to increase given higher resistance patterns in other parts of the world and the widespread use of macrolides for the treatment of upper and lower respiratory tract infections.[34]

Routine antibiotic prophylaxis is not recommended for household members exposed to GABHS, because the risk of developing subsequent pharyngitis is approximately 10%.[35] Although tonsillectomy is clearly indicated for recurrent tonsillitis in children, there is only modest evidence to support tonsillectomy for recurrent pharyngitis. Patients undergoing tonsillectomy have been shown to have a modest reduction in frequency of GABHS infections for up to 2 years after surgery.[36]

Benefits of antibiotic treatment for other bacterial pharyngitides are unclear at this time. There have been no cases of acute rheumatic fever due to non-GABHS, such as groups C and G *Streptococcus*. If treated, antibiotics used in the treatment of GABHS are appropriate for pharyngitis due to groups C and G *Streptococcus*.

Several other bacterial etiologies must be considered in patients with pharyngitis. These include *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Arcanobacterium haemolyticum*, *Yersinia enterocolitica*, *Yersinia pestis*, *Francisella tularensis*, *Mycoplasma pneumoniae*, *Chlamydia* species, and *Fusobacterium necrophorum*.

Neisseria gonorrhoeae Gonococcal pharyngitis is difficult to distinguish from other bacterial causes of pharyngitis. A careful sexual history, including exposure to partners with known sexually transmitted diseases and oral sex practices, should be elicited in all adolescent patients presenting with pharyngitis. Gonococcal infection of the throat may be associated with infection elsewhere, including proctitis, vaginitis, and/or urethritis. The diagnosis requires special culture on Thayer-Martin medium, although nucleic acid amplification testing is also available. A positive culture in a prepubertal child is highly suspicious for sexual abuse, and further investigation is warranted with involvement of the appropriate child protection agencies. IM ceftriaxone (250 milligrams) is the only therapy recommended by the Centers for Disease Control and Prevention for the treatment of uncomplicated pharyngeal gonorrhea. Empiric treatment for concomitant chlamydia with the addition of 1 gram of azithromycin should be given unless it has specifically been ruled out.

Corynebacterium diphtheriae Although occurrence is rare in developed countries due to vaccination, *C. diphtheriae* should be considered in patients who are under- or unimmunized. Toxigenic strains of this bacterium produce an exotoxin that causes localized necrosis of the respiratory mucosa and can lead to both cardiac and neurologic complications. Pseudomembrane formation in the respiratory tract can result in airway obstruction. Identification of the causative organism is made using Loeffler or tellurite selective medium. Treatment of pharyngeal diphtheria is aimed at bacterial eradication and exotoxin neutralization. Penicillin and erythromycin are the antibiotics of choice, along with equine diphtheria antitoxin. Serious sequelae can be prevented with prompt antibiotic administration, and treatment should be started when diphtheria is clinically suspected.

Arcanobacterium haemolyticum *A. haemolyticum* closely mimics GABHS pharyngitis and may also produce a scarlatiniform rash in teenagers; rarely, it produces a membranous pharyngitis similar to that of diphtheria. It may be missed on routine cultures and may be more readily detected on human-blood agar plates. Both macrolide and β-lactam antimicrobial agents are effective treatments.

Fusobacterium necrophorum In patients of age 15 to 30 years with an acute sore throat, *F. necrophorum* may be causative in 10% to 20.5% of cases. However, carriage rates of 9.4% have been reported.[37] It is associated with retropharyngeal abscesses and Lemierre syndrome. *F. necrophorum* is usually susceptible to penicillin and first-generation cephalosporins.

UVULITIS

Isolated inflammation of the uvula is unusual and has infectious and noninfectious causes. When associated with pharyngitis, the most common bacterial etiology is GABHS. In the unimmunized patient, *Haemophilus influenzae* type b is the next most common cause and may occur with epiglottitis. Other bacterial causes are *Fusobacterium nucleatum*, *Prevotella intermedia*, *Streptococcus pneumoniae*, and *C. albicans*. Noninfectious causes include trauma from instrumentation, irritant inhalation, vasculitis, allergic reaction, and angioedema.[38]

TABLE 124-4 Antibiotics for the Treatment of Streptococcal Pharyngitis

Medication	Dosage	Route	Duration
Penicillin V (first line)	Child: 250 milligrams two times daily Adolescent/adult: 500 milligrams twice a day	PO	10 d
Amoxicillin (first line)	50 milligrams/kg once daily; maximum dose, 1000 milligrams or 25 milligrams/kg/dose twice daily; maximum dose, 500 milligrams	PO	10 d
Benzathine penicillin G	<27 kg: 600,000 units ≥27 kg: 1,200,000 units	IM	One dose
Cephalexin (alternative for penicillin-allergic patients without anaphylaxis)	20 milligrams/kg/dose twice daily; maximum dose, 500 milligrams	PO	10 d
Clindamycin (alternative for penicillin-allergic patients)	7 milligrams/kg three times daily; maximum dose, 300 milligrams	PO	10 d
Azithromycin (alternative for penicillin-allergic patients)	Child: 12 milligrams/kg once daily Adolescent/adult: 500 milligrams on day 1, then 250 milligrams on days 2–5	PO	5 d
Clarithromycin (alternative for penicillin-allergic patients)	7.5 milligrams/kg/dose twice daily; maximum dose, 250 milligrams	PO	10 d

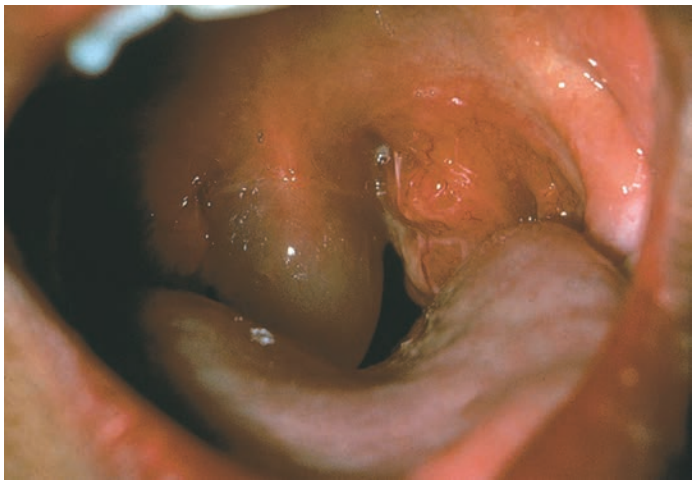

FIGURE 124-8. Uvulitis: Edematous, erythematous uvula. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 5-28.]



FIGURE 124-9. Ellis type 1 fracture: Note the fracture of the left upper central incisor. The sole involvement of the enamel is consistent with an Ellis type 1 injury. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 6-5.]

The inflamed uvula appears erythematous, enlarged, and edematous (**Figure 124-8**). Patients may present with fever, sore throat, difficulty swallowing, odynophagia, drooling, and/or respiratory distress.

Uvulitis is a clinical diagnosis. When there is associated pharyngitis, test for GABHS. *H. influenzae* diagnosis requires culture on Loeffler or tellurite selective medium.

Antibiotics to cover GABHS should be based on antigen testing or throat culture results. Acute airway obstruction is unusual with isolated uvulitis; however, when epiglottitis is also present, intubation may be required. When allergic reaction or angioedema is suspected, treatment may include epinephrine, antihistamines, and steroids. Precipitants, such as inhaled irritants and allergens, and responsible medications, such as an angiotensin-converting enzyme inhibitor, should be discontinued.

ORAL PROBLEMS

DENTAL TRAUMA

The evaluation and management of pediatric dental trauma, including subluxation, luxation, intrusion, extrusion, avulsion, and fracture, differ between primary and secondary (permanent) teeth (see Chapter 245, "Oral and Dental Emergencies," Figure 245-2).

Most traumatic dental injuries occur in the toddler years, when children are learning to walk. Nonaccidental trauma (e.g., physical abuse, sexual abuse, bullying, and injuries from human trafficking) must also be considered.[39,40] More than half of child abuse cases involve craniofacial, head, face, and neck injuries, and a high index of suspicion must be maintained. Two other significant periods of trauma include school-aged children, from play injuries, and adolescents, mainly due to sports. Traumatic dental injury prevalence varies between 6% and 58%.[41] The most commonly injured teeth are the maxillary central incisors.

Primary tooth eruption begins at approximately 6 months of age and is usually complete by 3 years of age. Secondary teeth may begin to erupt at 6 years of age and can continue past adolescence if the wisdom teeth are not extracted.

Subluxation refers to loosening of the tooth without displacement and is due to periodontal ligament damage (see Chapter 245, "Oral and Dental Emergencies," Figure 245-3). On examination, the tooth is mobile, and sulcal bleeding may be present. When subluxation is noted in a primary tooth, no intervention is required; however, permanent teeth may require splinting. Dental follow-up is recommended in either case, as pulpal necrosis may occur.[42]

Luxation is a loosening and displacement of a tooth from its normal anatomic position and occurs when the periodontal ligament is torn. The tooth is often nontender and immobile and may be fixed in its new position. Primary teeth may be allowed to passively reposition, although dental consultation is recommended. Permanent teeth require active repositioning and splinting as soon as possible.

Intrusion occurs when a tooth is driven apically into the socket, displacing into the alveolar bone. The tooth appears shortened, or even absent, and, when visible, is not mobile or tender. Ninety percent of intruded teeth will reerupt spontaneously in 2 to 6 months. Extraction of primary teeth is indicated when the apex is displaced toward the permanent tooth germ, as determined by radiography. Permanent teeth with immature root formation may be allowed to reerupt; mature teeth require orthodontic or surgical extrusion.

Extrusion occurs when a tooth is displaced from its socket. The tooth appears elongated and is mobile, due to tearing of the periodontal ligament. Both primary and permanent teeth should be repositioned and splinted as soon as possible. If the injury is severe enough, primary teeth may require extraction in the ED.

Avulsed primary teeth should not be replanted, because this may damage the permanent tooth germ. Permanent teeth, by contrast, require urgent reimplantation, because success is time dependent. There is 85% to 97% survival of permanent teeth when replaced within 5 minutes, and near-zero survival at 1 hour. Avulsed teeth should be handled by the crown to avoid damaging the periodontal ligament. Debris should be removed with gentle rinsing in saline or water; scrubbing should be avoided because it may cause further damage. If the tooth cannot be replanted within 5 minutes, it should be stored, in order of preference, in ViaSpan, Hanks' Balanced Salt Solution, cold milk, saliva, physiologic saline, or water. Of media available at the scene of an accident, regular pasteurized whole milk is the most recommended storage solution.[43]

Fracture of the tooth enamel alone (a type 1 fracture using the Ellis classification system) or of the enamel and dentin (Ellis type 2 fracture) may be managed conservatively (**Figures 124-9** and **124-10**). Treatment of an Ellis type 3 fracture, involving the pulp (**Figure 124-11**), includes pulp capping and partial and complete pulpectomy. A root fracture, or Ellis type 4 fracture, involves the dentin, pulp, and cementum. In both primary and permanent teeth, the coronal fragment should be repositioned and stabilized in its anatomically correct position. In primary teeth, alternatively, the coronal fragment may be extracted, allowing the periodontal ligament and neurovascular supply to heal.

Radiographs may be obtained to confirm any of the diagnoses above or to confirm a tooth avulsion when there is question of an intrusion into the alveolar bone.

SOFT TISSUE INJURIES OF THE MOUTH

Repair large lacerations of the gingiva with absorbable sutures. Wounds can allow entry of foreign bodies, such as food particles, dental fillings, and tooth fragments, leading to infection. Frenulum lacerations of the



FIGURE 124-10. Ellis type 2 fracture: Bilateral maxillary central incisor injuries with exposed enamel and dentin consistent with an Ellis class 2 fracture. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 6-6.]

maxilla usually heal well without intervention. By contrast, the vascularity around the mandibular frenulum often requires primary closure. Tongue lacerations can usually be treated conservatively, especially if the wound is <1 cm in length, is in the central portion of the tongue, and does not gape, and bleeding is controlled. Tongue lacerations greater than one third of the total diameter and those at the tip causing forking that may affect speech require suturing.

In general, lacerations limited to the inner mucosal surface heal well on their own and do not require primary repair. By contrast, full-thickness lacerations and those that disrupt the vermillion border require suturing.

CARIES

Children are particularly susceptible to developing caries soon after the initial eruption of teeth if care is not taken to properly examine and clean the new teeth. "Baby bottle" caries occur in 24% to 28% of all children age 2 to 5 years old.[44] Risk factors include prolonged breast or bottle feeding (beyond 12 months), prolonged pacifier use, frequent consumption of beverages high in sugar, and use of a bottle at bedtime.

Encourage parents to minimize beverage choices high in sugar content. Teeth should be cleaned daily from time of eruption to 24 months of age with a soft toothbrush and increased to twice a day thereafter. Transition to a training cup by 1 year of age and removal of the bottle can also significantly reduce the occurrence of caries. In addition, an initial screening dental examination between 12 and 18 months of age is recommended to look for signs of decay or a need for fluoride supplementation. In communities without fluoridated water, supplemental fluoride should be prescribed by the primary care provider.

Dental neglect is a form of child abuse probably underreported or unrecognized by medical providers. It is defined as the "willful failure of parent or guardian to seek and follow through with treatment necessary to ensure a level of oral health essential for adequate function and freedom from pain and infection." Poor oral hygiene may be secondary to family isolation, lack of finances, parental ignorance, unfluoridated water, bottle-propping, or lack of perceived value of oral health, and clinicians should determine whether one or more of these situations are contributing factors.[45]

GINGIVITIS

Gingivitis is inflammation of the gums that presents as tender, erythematous, often ulcerated or vesiculated areas of tissue. It is seen mainly in the setting of poor dental hygiene but can occur with viral and bacterial infections, certain medications (e.g., phenytoin [Dilantin®]), or even as a presentation of leukemia. Although there are many causes of gingivostomatitis, viral infections are particularly common in children.

Acute necrotizing ulcerative gingivitis is a progressive infection of the gingiva, leading to pain, significant edema, and ulceration. The incidence typically peaks in the teens to early 20s, but may be seen in younger children in developing countries due to poor access to adequate dental care or malnutrition. Other factors that may predispose patients to acute necrotizing ulcerative gingivitis include smoking, immunosuppression, viral infections, stress, and sleep deprivation. Patients present with fever, halitosis, decreased appetite, and generalized malaise. Acute necrotizing ulcerative gingivitis is a mixed infection that includes spirochetes, specifically, *Prevotella intermedia*. Untreated, acute necrotizing ulcerative gingivitis can spread beyond the gingiva to involve deeper tissues or the tissues of the mouth floor (Ludwig's angina) or face. Treatment consists of analgesia to facilitate better oral hygiene and antimicrobial oral rinses. Patients with more extensive disease or systemic symptoms may require admission for local debridement and parenteral antibiotic therapy with penicillin or metronidazole. The patient should be referred to a dentist for close follow-up care.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.



FIGURE 124-11. Ellis type 3 fracture: A fracture demonstrating blood at the exposed dental pulp. This sign is pathognomonic for an Ellis class 3 fracture. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 6-7.]

CHAPTER 125

Neck Masses in Infants and Children

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Vikram Sabhaney

INTRODUCTION AND EPIDEMIOLOGY

Neck masses are common in childhood, and although most are benign, malignancy must remain a primary consideration. Among patients referred to tertiary centers for surgical excision of a cervical lesion, 90% to 96% of lesions are benign and are predominantly congenital.[1,2] While diagnosis is challenging, differentiating neck masses into inflammatory, congenital, or a neoplastic category is the first step toward diagnosis.

GENERAL APPROACH

CLINICAL FEATURES

A thorough history and physical examination help narrow the broad differential for cervical lymphadenopathy. Both acuity and laterality of node swelling are helpful for diagnosis. Acute bilateral lymph nodes are typically due to a viral infection, acute unilateral nodes are due to a bacterial cause, and subacute/chronic nodes (>4 to 6 weeks) are due to granulomatous bacteria or noninfectious causes. This framework is most effective for diagnosis when combined with the general and specific features of different etiologies (**Tables 125-1** and **125-2**). Carefully document the features (size, location) of all head and neck masses for future comparison. Lymph node location and characteristics give clues based on lymphatic drainage patterns. Look for systemic disease by assessing for generalized lymphadenopathy, hepatosplenomegaly, testicular masses and/or enlargement in males, and the child's overall condition.

GENERAL MANAGEMENT

Ideally, the treatment of a childhood neck mass is directed at the specific cause; however, due to the many etiologies, this is not always possible at first presentation. The majority of presentations are benign; however, the priority of childhood neck masses is to correctly identify those that are neoplastic. **Figure 125-1** provides an approach to management based on suspected etiology and should be adapted to the individual patient. Follow-up of patients who are treated with antibiotics is necessary at 48 to 72 hours: if improvement of symptoms is not seen, then expand antibiotic coverage to include periodontal flora or methicillin-resistant *Staphylococcus aureus* and consider aspiration of fluctuant nodes for culture. Most lymphadenopathy will improve after 2 weeks of observation or antibiotics; however, all cases require 6-week follow-up to ensure resolution.

TABLE 125-1 Key Features From History

Historical Feature	Associated Etiology
Duration >4–6 weeks	Granulomatous lymphadenitis, congenital lesions, malignancies
Rate of growth	Fluctuating → inflammatory Progressive → malignancy
Pain	Infectious, or infected congenital lesion
Recent illness	Viral URTI → Reactive lymphadenopathy Pharyngitis → EBV, GAS
Neonatal period	Group B *Streptococcus*
Pain with meals	Sialoadenitis
Tuberculosis exposure (travel or sick contacts)	Tuberculosis mycobacteria
Undercooked meat or unpasteurized milk exposure	Toxoplasmosis
Cat exposure	Cat-scratch disease or toxoplasmosis
Animal exposure (including rabbits)	Tularemia, cat-scratch disease, toxoplasmosis
Mass since birth	Congenital
Birth trauma, forceps delivery	Fibromatosis colli
Constitutional symptoms (fever, weight loss, night sweats)	Tuberculosis mycobacteria, malignancy
Recent blood transfusions	EBV, CMV, HIV
Recent immunizations (DPT, polio, typhoid)	Reactive lymphadenopathy
Medications	Phenytoin, carbamazepine, isoniazid, hydralazine, and others

Abbreviations: CMV = cytomegalovirus; DPT = diphtheria, pertussis, and tetanus; EBV = Epstein-Barr virus; GAS = group A *Streptococcus*; HIV = human immunodeficiency virus; URTI = upper respiratory tract infection.

TABLE 125-2 Key Features on Examination

Physical Examination Finding	Associated Etiology
Laterality	Bilateral → viral Unilateral → bacterial
Size	>3 cm more likely congenital or malignant; fluctuations in size more likely infectious
Location	Depends on lymph drainage pattern (see Figure 125-2)
Hard, rubbery, fixed, matted nodes	Possibly malignant
Signs of inflammation (tenderness, erythema, warmth)	Bacterial lymphadenitis or infected congenital lesion
Fluctuance	Abscess, often due to *Staphylococcus aureus*, or GAS
Difficulty swallowing or drooling	Deep space infection—retropharyngeal abscess
Viral URTI (cough, rhinorrhea, conjunctivitis)	Reactive lymphadenopathy
Pharyngitis	EBV mononucleosis, GAS
Periodontal disease	Anaerobic bacteria
Purulent salivary duct drainage	Sialoadenitis
Crossing jaw—suggests parotid involvement	Sialoadenitis, mumps, salivary gland malignancy
Violaceous skin change	Granulomatous lymphadenitis (TbM, NTM, CSD, tularemia)
Cold node	Granulomatous lymphadenitis or malignancy
Midline, moves with swallowing or tongue protrusion	Thyroglossal duct cyst
Transillumination	Lymphangioma (cystic hygroma)
Torticollis, laterally mobile, vertically immobile	Fibromatosis colli
Supraclavicular mass	Lymphoma, or less likely metastatic node
Midline mass	Thyroid cancer, thyroglossal duct cyst, dermoid cyst
Posterior mass	Rubella, toxoplasmosis, nasopharyngeal cancer
Hepatosplenomegaly	Malignancy, mononucleosis, systemic disease
Wasting or cachexia	Malignancy

Abbreviations: CSD = cat-scratch disease; EBV = Epstein-Barr virus; GAS = group A *Streptococcus*; NTM = nontuberculous mycobacteria; TbM = tuberculous mycobacteria; URTI = upper respiratory tract infection.

INFLAMMATORY NECK MASSES

The most common pediatric neck mass is an enlarged lymph node caused by infection. Be careful to consider masquerading lesions such as salivary gland infections, acutely infected congenital lesions, and malignancies.

Cervical lymph nodes drain the skin of the head and neck as well as the entire nasal, oral, and pharyngeal mucosa (**Figure 125-2**). Enlarged submandibular and cervical nodes are most common because they drain much of the oropharynx, including the adenoids and tonsils.[3,4] **Supraclavicular lymphadenopathy is suspicious for metastasis as these nodes drain the abdomen and thorax.**[4]

Palpable cervical lymph nodes are found in about 28% to 44% of healthy infants and children, with the incidence peaking in early childhood.[3,5,6] Lymph nodes ≤1 cm in children <12 years old are considered normal.[7,8] Most lymphadenopathy represents nonspecific reactive hyperplasia, often due to a viral upper respiratory tract infection.[9] Lymphadenitis is lymph node inflammation (swelling, tenderness, warmth, erythema) and is most commonly due to viral or bacterial causes. Infection with a

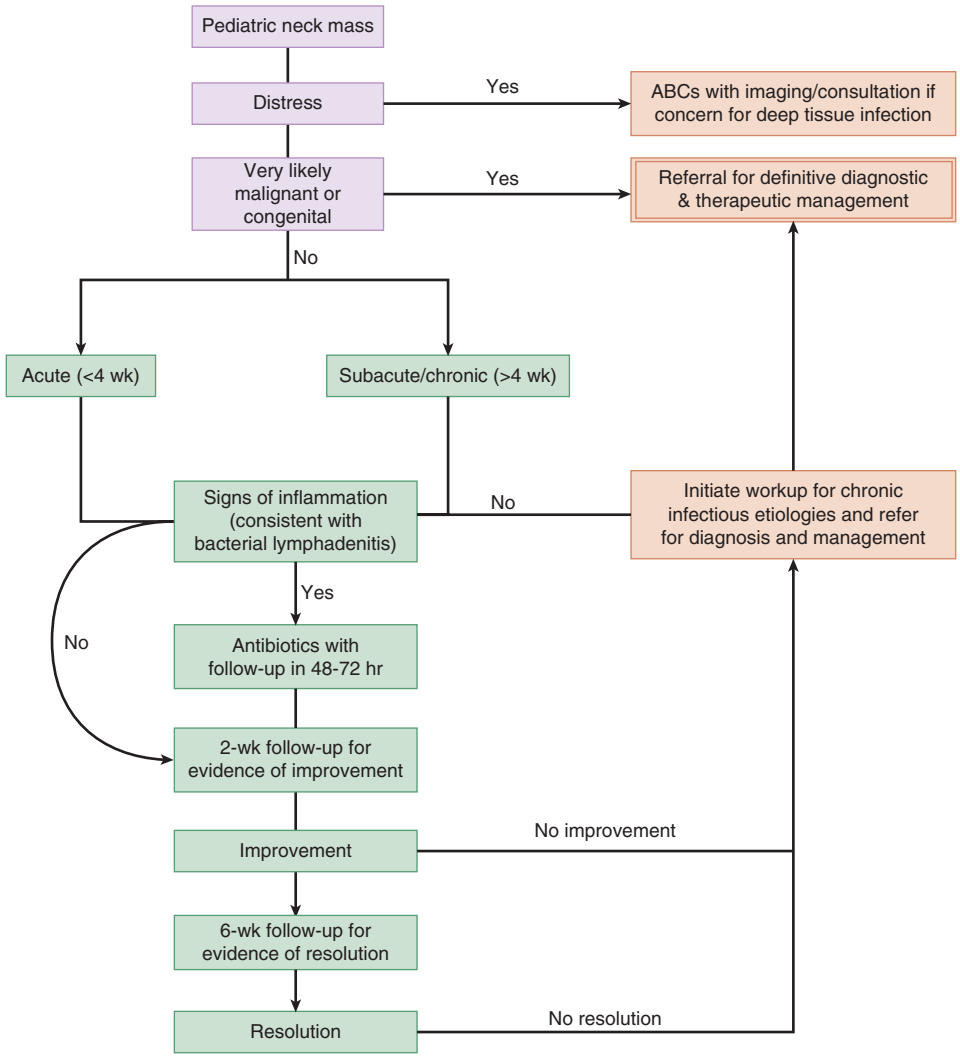


FIGURE 125-1. Approach to the pediatric neck mass in the ED. ABC = airway, breathing, circulation.

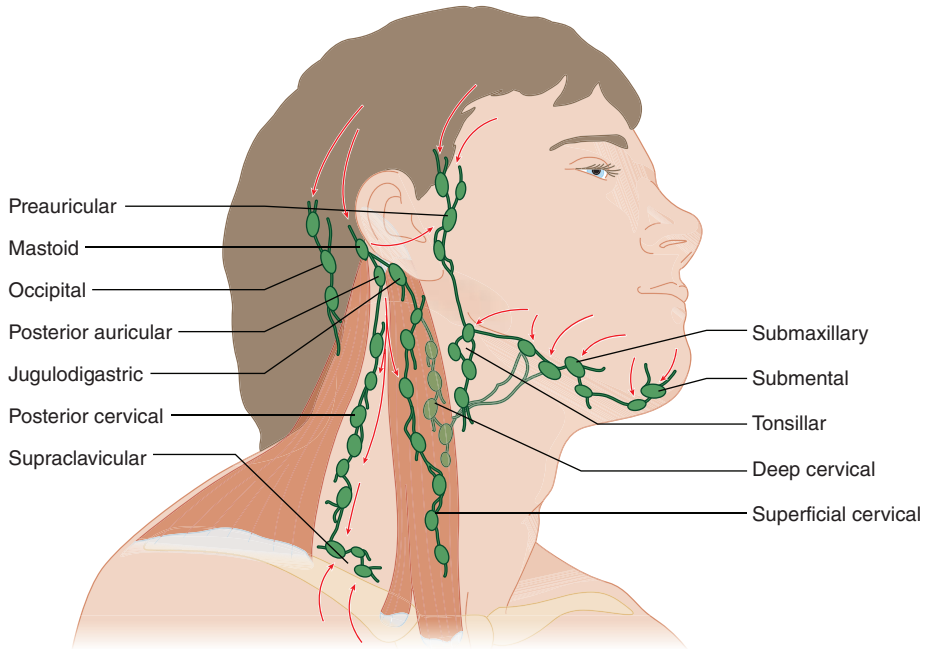


FIGURE 125-2. Cervical lymph node drainage.



FIGURE 125-3. Suppurative lymphadenitis. [Reproduced with permission from Shah BR, Lucchesi M, Amodio J (eds): *Atlas of Pediatric Emergency Medicine*, 2nd ed. © 2013, McGraw-Hill Education, New York, NY, Figure 3-2.]

pyogenic organism may lead to liquefactive necrosis (suppuration) and abscess formation (**Figure 125-3**). If the immune system is unable to eradicate a particular organism, macrophages will attempt to contain it, forming a chronic granulomatous lymphadenitis.

ACUTE BILATERAL LYMPHADENOPATHY

Acute bilateral lymphadenopathy is usually due to viral infection and is self-limited. Common viruses include rhinovirus, parainfluenza, influenza, respiratory syncytial virus, coronavirus, reovirus, and adenovirus.[10] Treatment is symptomatic and expectant.

Alternative viral causes include **infectious mononucleosis**, characterized by fever, exudative pharyngitis, and significant lymphadenopathy (**Figure 125-4**). Heterophile antibodies or Epstein-Barr virus–specific immunoglobulin M confirms the diagnosis, and in immunocompetent patients, treatment is symptomatic. Some viral causes of lymphadenopathy are associated with classic exanthems such as **measles** (Koplik spots, conjunctivitis, and a descending rash) and **rubella** (Forchheimer spots, rash, and polyarthritis). Acute bilateral lymphadenopathy and oral lesions may also be due to **herpes simplex virus** (gingivostomatitis) or **coxsackie virus** (herpangina). Pharyngitis caused by group A *Streptococcus* is accompanied by cervical lymphadenopathy.[11] Bilateral swelling that extends over the jaw suggests **parotid gland** involvement due to mumps and may be associated with orchitis and a rash.

ACUTE UNILATERAL LYMPHADENOPATHY

Acute unilateral lymphadenopathy is most often due to bacterial lymphadenitis (**Figure 125-5**) caused by *S. aureus* and group A *Streptococcus*.[12] Lymph nodes typically have signs of inflammation (erythema, warmth, tenderness), and if an abscess has developed, fluctuance may be appreciated. Often the source of group A *Streptococcus* is the pharynx, whereas *S. aureus* originates from a break in the skin. Careful examination of the head, neck, throat, skin, and ears may identify a source that can be cultured.

Generally, lymph nodes <1 cm do not need treatment. If lymphadenitis measures between 1 and 3 cm, initiate antibiotics to treat group A *Streptococcus* and *Staphylococcus* for up to 10 to 14 days.[13] Nodes >3 cm raise suspicion for malignancy, but if the nodes are acute and inflammatory, a course of antibiotics and observation are reasonable.

Due to increasing β-lactamase–resistant *Staphylococcus*, first-generation cephalosporins or amoxicillin-clavulanic acid are first-line choices,[12,14,15] although clindamycin as a first-line agent is reasonable if local methicillin-resistant *S. aureus* prevalence is high.[16] If the child is unwell or immunocompromised, use IV cefazolin, nafcillin, or clindamycin. All patients require reassessment in 48 hours, and if no improvement is appreciated, expand antibiotic coverage to treat methicillin-resistant *S. aureus.* Clindamycin and trimethoprim-sulfamethoxazole are both effective choices if local resistance



FIGURE 125-4. Infectious mononucleosis typically presents with bilateral lymphadenopathy. A 6-year-old girl demonstrating bilateral lymphadenopathy. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill Education, New York, NY, Figure 11-14.]

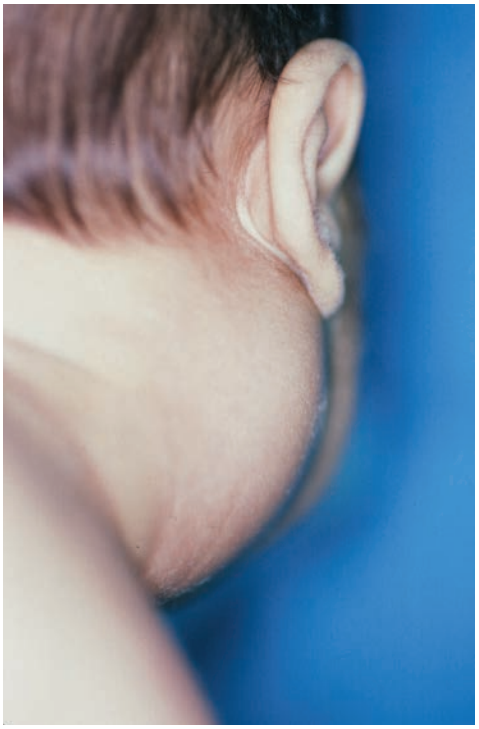
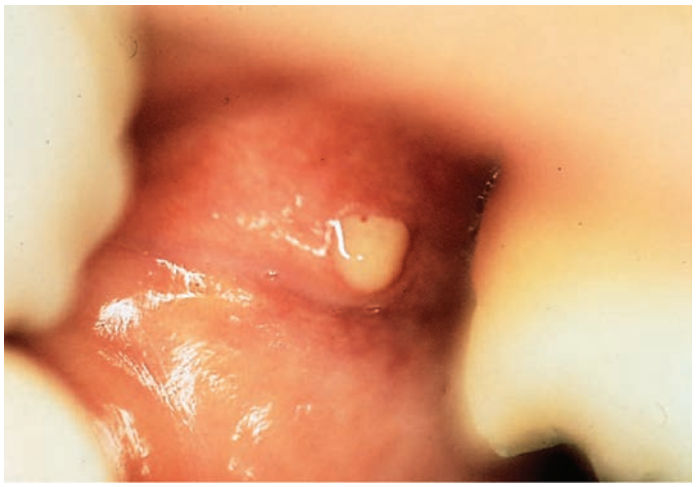


FIGURE 125-5. An infant with unilateral lymphadenitis due to *Staphylococcus aureus* infection. [Photo contributed by Dr. J. P. Ludemann, BC Children's Hospital, Vancouver, British Columbia, Canada.]



A



B



C

FIGURE 125-6. Sialadenitis. **A.** Unilateral swelling crossing the angle of the mandible. **B** and **C.** Purulent drainage from Stensen's and Wharton's salivary ducts, respectively. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figures 5-32 and 5-33.]

is low.[16-18] Failure to improve at 48 hours is not an indication for surgical drainage as outcomes after switching to second-line antibiotics without surgery are similar.[19]

Fluctuance of the node suggests abscess formation due to pyogenic bacteria, typically from a tonsillar source.[15] While fluctuance is associated with a higher rate of surgical drainage,[20] neck abscesses often respond to antibiotics alone.[15,21] Needle aspiration may be helpful to avoid incision in cosmetically important areas.[15] If a superficial abscess is pointing or not resolving within 2 weeks of antibiotics, then evaluation by US and incision and drainage may be necessary.[22] Early US for inflammatory neck masses results in unnecessary cost and drainage, particularly in patients with less than 3 days of symptoms and who are older than 1 year of age.[23] When associated with torticollis or trismus, consider a deep space infection and obtain imaging and/or surgical consultation (see Chapter 126, "Stridor and Drooling in Infants and Children").

Infants have a higher incidence of infection with group B *Streptococcus* than *S. aureus* or group A *Streptococcus*. Group B streptococcal infection can be associated with bacteremia, pneumonia, and meningitis.[24,25] Infections originating from the oral mucosa, seen most commonly in children age 5 to 15 years with periodontal disease, are more likely to contain anaerobic bacteria requiring coverage with penicillin V, amoxicillin-clavulanic acid, or clindamycin.[14] **Sialadenitis** is characterized by unilateral swelling crossing the jaw and tenderness after meals and can be associated with purulent discharge from Wharton's and Stensen's ducts (**Figure 125-6**). Sialolithiasis can cause recurrent infections due to outflow obstruction of the gland.

SUBACUTE/CHRONIC LYMPHADENOPATHY

Chronic lymphadenopathy is defined as persistence for 6 weeks without resolution. Persistent lymphadenopathy, generalized lymphadenopathy, or failure to respond to 2 to 4 weeks of antibiotics requires evaluation for uncommon infectious, congenital, and neoplastic causes. Persistent infectious agents evade eradication by granuloma formation. Generally, the course of evolution is slower than with typical inflammatory lymphadenitis and may be characterized by a violaceous color of the overlying skin. Refer to otolaryngology for definitive diagnosis and management.[26-28] Refer immunocompromised patients to an infectious disease specialist. Some of the more common causes of granulomatous lymphadenitis are covered below.

MYCOBACTERIAL LYMPHADENITIS

Chronic cervical lymphadenitis may be due to tuberculous (*Mycobacterium tuberculosis*) or nontuberculous mycobacterial strains. Clinically, both varieties of lymphadenitis are characterized by a chronic, minimally

tender, "cold abscess," with overlying violaceous skin. Spontaneous drainage can transform into a chronic draining sinus.[27] It is important to differentiate between tuberculous and nontuberculous strains because treatment is different. Differential Mantoux testing with a combination of antigens can identify strains in about 93% of patients.[29] Consider *M. tuberculosis* lymphadenitis in children with tuberculosis exposure,[30] in those exhibiting constitutional signs, and in those with an abnormal chest radiograph and with a strongly reactive purified protein derivative skin test,[31] and treat for 8 to 12 months. Treatment for nontuberculous lymphadenitis is surgical excision.[32]

CAT-SCRATCH DISEASE

Cat-scratch disease is caused by *Bartonella henselae*, with inoculation by a scratch or a bite from a kitten. The inoculation site develops into a painless, erythematous vesicle or pustule after 3 to 10 days, which may disappear before other symptoms develop. After 1 to 3 weeks, regional lymphadenopathy typically develops; suppuration is uncommon. Diagnosis involves serologic testing, but because antibody development may be delayed and the primary lesion may have resolved, rely on a strong history of cat exposure and an inoculating lesion. No treatment is needed due to high rates of spontaneous resolution, although azithromycin may hasten resolution.[33] Serious complications (encephalitis) can develop in immunodeficient patients, with treatment options based primarily on case reports.

TOXOPLASMOSIS

Toxoplasma gondii is a protozoan parasite with a complex life cycle that can infect humans through ingestion of undercooked meat, exposure to oocysts in cat feces, or through maternal-fetal transmission (congenital toxoplasmosis). Infection is widespread: an estimated 22.5% of children in the United States are infected by the age of 12 years old, and in some countries, up to 95% of the population has been infected. The lymphatic system is the most common organ system involved. Diagnosis is usually made serologically with antibody titers. Treatment is not typically needed in healthy children.

TULAREMIA

Tularemia is caused by the bacteria *Francisella tularensis*, which is transmitted by arthropod bites, handling infected animals (classically rabbits), and contaminated food and water. The most common forms are ulceroglandular and glandular tularemia. In the ulceroglandular form, the inoculation site develops from an erythematous tender papule into an exudative ulcer within days. Regionally draining lymphadenopathy subsequently develops that may spontaneously suppurate and drain if not treated. Tularemia is diagnosed serologically with microagglutination testing. Gentamicin is the treatment of choice.

OTHER CAUSES

Other causes of cervical lymphadenopathy include recent immunizations (diphtheria, pertussis, and tetanus; polio; typhoid), blood transfusions (through Epstein-Barr virus, cytomegalovirus, or human immunodeficiency virus exposure), medications (including phenytoin, carbamazepine, isoniazid, and hydralazine), and systemic disease (Kawasaki's disease; sarcoid; periodic fever, aphthous stomatitis, pharyngitis, and adenitis; and autoimmune) (Tables 125-1 and 125-2).

CONGENITAL NECK MASSES

Congenital lesions are the most common cause of noninflammatory pediatric neck masses,[1] but may not be recognized until infection develops. The sternocleidomastoid muscle divides the neck into anterior and posterior triangles, and congenital neck masses can be organized into midline, anterior, and posterior groups (**Table 125-3**). The most common congenital neck masses and their characteristic features are discussed below.

TABLE 125-3 Common Congenital Neck Cysts by Location, Signs, and Typical Age of Onset

Type	Location	Signs	Age
Thyroglossal duct	Midline (infrahyoid mostly)	Cyst moves with swallowing or tongue protrusion.	Birth–elderly
Dermoid/ epidermoid	Midline (suprahyoid)	Cyst may move with swallowing.	Birth–adult
Branchial	Anterior triangle anterior to sternocleidomastoid muscle near angle of the mandible	May be associated with draining sinus.	Childhood–adult
Lymphangioma (cystic hygroma)	Posterior triangle	Soft; enlarges in first few weeks of life. Transilluminates.	Birth–infancy

THYROGLOSSAL DUCT CYSTS

Thyroglossal duct cysts (**Figure 125-7**) account for approximately 70% of congenital neck masses and are the second most common benign neck mass after lymphadenopathy.[34] Thyroglossal duct cysts result from the persistence of any segment of the thyroglossal duct along its course from the foramen cecum of the tongue to the pyramidal lobe of the thyroid and are located in the midline of the neck within the anterior triangle.[35] Most of the lesions are infrahyoid (65%), whereas suprahyoid cysts account for 20%, and another 15% of lesions are at the level of



FIGURE 125-7. Large thyroglossal duct cyst.



FIGURE 125-8. Second arch branchial cleft cyst. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 4th ed. © 2016. McGraw-Hill, Inc., New York, Figure 14-69, p. 469. (Photo contributor: Scott Manning, MD.)]

the hyoid bone.[36,37] The pathognomonic feature is a painless fluctuant mass that moves with swallowing or protrusion of the tongue. Acutely infected cysts require antibiotics. Further investigations and surgical excision are undertaken after infection subsides because they carry a very small risk of malignant transformation.[38]

DERMOID CYSTS

Dermoid cysts are developmental anomalies involving pluripotent embryonal stem cells and occur most often in children <3 years old. Dermoid cysts are usually suprahyoid[39] and midline and are often misdiagnosed as thyroglossal duct cysts.[40,41] Dermoid cysts are mobile, but they do not move with tongue protrusion. Management is surgical excision.

BRANCHIAL CLEFT CYSTS

Incomplete obliteration of the branchial apparatus, predominantly the cleft, leads to branchial cleft anomalies: cysts, sinuses, or fistulae.[35] Up to 95% of branchial cleft cysts arise from remnants of the second branchial cleft,[42] which are most often anterior to the sternocleidomastoid muscle near the angle of the mandible (**Figure 125-8**). The cysts are round, smooth, and mobile, but are not tender unless they become infected. There may be a history of recurrent swelling or infection in the same area. Cysts may spontaneously rupture, forming an external sinus or fistula. Oral antibiotics are indicated for infected cysts prior to definitive surgery.

LYMPHANGIOMAS

Lymphangiomas (also known as cystic hygromas) result from sequestration of lymphatic channels that fail to communicate with the internal jugular vein leading to a blockage of the lymphatic system.[43] They can occur anywhere in the body, but nearly 75% arise within the neck, most commonly along the jugular chain of lymphatics. Cervical lymphangiomas are soft, painless, and compressible, and can be very large (**Figure 125-9**). Morbidity is usually secondary to compression of surrounding structures, and large neck lesions may cause serious airway and feeding problems. Sixty-five percent present at birth, and 90% are clinically detected by the end of the second year.[36,43] Sudden enlargement can occur from infection or hemorrhage into the lesion. Careful inspection of the oral cavity and palpation of the trachea for deviation are important in assessing the airway of patients with large cystic hygromas. Injection of sclerosing agents can be used in some lesions, although surgical excision is the definitive treatment.[43]



FIGURE 125-9. Lymphangioma. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York, Figure 14-35.]

NEOPLASTIC NECK MASSES

Malignancy must always be considered as a potential etiology in the evaluation of a child with a neck mass (see Chapter 145, "Oncologic Emergencies in Infants and Children"). Of childhood malignancies, 5% to 12% present as a head or neck mass, of which 99% are primary tumors.[1,44-47] Diagnosing malignancies is made challenging by their rarity; only 1% of pediatric superficial lumps are malignant.[48] Accordingly, a high index of suspicion and attention to worrisome features from history and physical examination are required (**Table 125-4**).[12,31,46-50] One review demonstrated that in 80% of superficial masses, malignancy can be ruled out with 99.7% accuracy based on the absence of five clinical features (Table 125-4).[48] The presence of any worrying features should prompt urgent referral for further diagnostic workup that may include fine-needle aspiration cytology, imaging, or excisional biopsy.

BENIGN NEOPLASMS

Benign noninflammatory pediatric neck masses compose 5% of presentations.[51] An exhaustive review is not included in this chapter; instead, benign masses with specific identifying features are highlighted.

HEMANGIOMAS

Hemangiomas are congenital vascular tumors that present at 2 to 4 weeks, usually grow rapidly until 9 to 10 months of age, and typically regress thereafter. When palpable, they are soft, mobile, and frequently have a bluish hue.[52] Almost 90% of hemangiomas resolve spontaneously without the need for therapy. Lesions showing unusually rapid growth, hemorrhage, recurrent infection, or compression of adjacent structures may require treatment by a specialist, including beta-blockers, steroids, and

TABLE 125-4 Worrisome Features of Head and Neck Masses

- Constitutional symptoms (fever, weight loss, night sweats, fatigue)
- History of malignancy
- Mass features (onset in the neonatal period*; size >3 cm; duration >4–6 wk; supraclavicular, posterior, or midline location; rapid and progressive enlargement*; hard or rubbery consistency; fixation to skin or deep fascia*; associated skin ulceration*)
- Generalized lymphadenopathy
- Inflammatory mass >3 cm persistent for >6 wk, despite treatment
- Mass >3 cm with firm or hard consistency*

*If these five features are absent, then there is 99.7% accuracy that a superficial lump is not malignant in 80% of cases.[41]

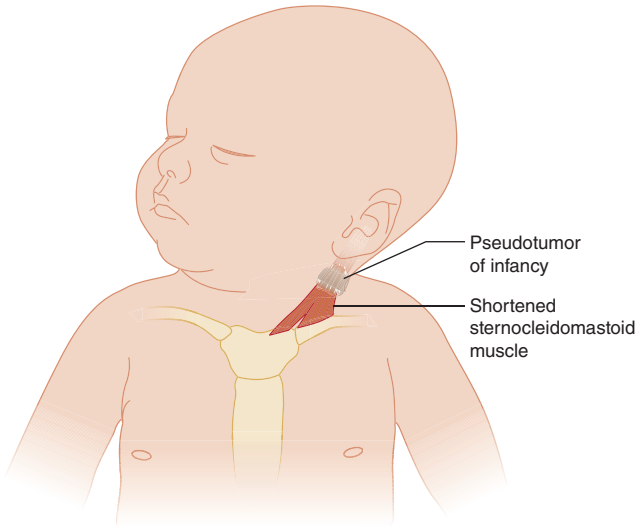


FIGURE 125-10. Schematic of fibromatosis colli or pseudotumor of infancy.

laser or surgical excision. Hemangiomas compromising the airway result in biphasic stridor not responsive to nebulized epinephrine and may be associated with cutaneous lesions in a beard distribution.

NEUROFIBROMAS AND SCHWANNOMAS

Neurofibromas and schwannomas are rare usually large tumors often involving the orbits, the skull base, or the parotid region, and are frequently associated with neurofibromatosis type I, which may present with café-au-lait spots and other classic features.[51]

FIBROMATOSIS COLLI

Fibromatosis colli (also known as pseudotumor of infancy) presents in the neonatal period as a mass in the sternocleidomastoid muscle (**Figure 125-10**). Often due to birth trauma with forceps delivery, part of the involved muscle is replaced by dense fibrous tissue.[51,53] Parents will often notice a mass or limited range of motion of the neonate's neck in the first weeks of life. Physical examination reveals a firm, solid, immobile mass located within the sternocleidomastoid muscle that is horizontally mobile, vertically fixed, and moves with the muscle when the head is turned. It is often associated with some degree of sternocleidomastoid contracture (torticollis). The diagnosis can often be made clinically, and imaging is not necessary. Treatment involves stretching and physical therapy, resulting in spontaneous resolution over a period of 4 to 8 months.[37,51,53]

MALIGNANT NEOPLASMS

Malignant head and neck masses are rare, accounting for approximately 1% of all etiologies. However, assessment for worrying features is important in the ED (Table 125-4); management of a suspected malignant lesion should include urgent referral for definitive treatment. The more common childhood malignancies presenting as a neck mass are highlighted briefly (see also Chapter 145).

LYMPHOMA

Lymphoma is the most common childhood malignancy of the head and neck.[35,46,51] Most lymphomas present as a large, firm mass that is often mobile, but can be fixed and is commonly located in the anterior triangle or the supraclavicular area.[1,44,46,54,55] One study found that 35% of childhood head and neck lymphomas presented as a supraclavicular mass.[1] Hodgkin's lymphoma is more likely nodal, is more often found in the supraclavicular area, and is seen more often in teenagers, whereas non-Hodgkin's lymphoma is primarily extranodal and has increasing incidence with age. Diagnosis requires excisional biopsy. Do not give steroids before biopsy because steroids interfere with staging.

RHABDOMYOSARCOMA

Rhabdomyosarcoma is a frequent malignancy of the head and neck in children. This tumor presents in the neck in 40% of cases, often as a large painless mass, rarely causing compression or infiltration of adjacent structures, most notably the airway.[44,45,56] Peak incidence is at 2 to 5 years old and again at 15 to 19 years old. Neck tumors may present with brachial plexus palsy.

NEUROBLASTOMA

Neuroblastoma in the neck is a malignancy of the sympathetic chain, although the adrenal glands are the most common primary site.[37,57] Most present before the age of 5 years, and those arising in the neck (5%) have a better prognosis than tumors of adrenal origin.[35,58] Neuroblastoma may present with local compressive signs such as hoarseness, dysphagia, airway obstruction, Horner's syndrome, or cranial nerve palsies.

THYROID CANCER

Thyroid cancer accounts for 21% of pediatric head and neck cancers; however, its incidence is decreasing due to declining radiation exposure.[47] Childhood thyroid cancer is usually papillary, presenting at a more advanced stage, with node, muscle, and metastatic involvement in 90% of cases; despite its advanced presentation, the prognosis is better than adult thyroid cancer.[59] Benign causes of diffuse thyroid enlargement include symptomatic thyrotoxicosis or Hashimoto's thyroiditis,[60] although goiter is seen in some parts of the world.

METASTATIC DISEASE

Metastatic disease may also present as cervical lymphadenopathy, accounting for 1% of childhood head and neck cancers. Tumors that metastasize to the neck include nasopharyngeal carcinoma and some thoracic/GI tumors. The location of the metastasis may give a hint to the origin of the primary tumor: posterior triangle nodes are often seen in nasopharyngeal carcinoma, whereas isolated supraclavicular nodes suggest a mediastinal or abdominal mass.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 126

Stridor and Drooling in Infants and Children

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Craig J. Huang

INTRODUCTION

Stridor is characterized as a high-pitched, harsh, monophonic sound produced by turbulent airflow through a partially obstructed airway.[1] Both inspiratory and expiratory stridor are associated with airway obstruction. As air is forced through a narrow tube, it undergoes an increase in speed and a decrease in pressure (Bernoulli's principle). The decrease in lateral pressure causes the walls of the airway to temporarily collapse and vibrate, generating this stridulous sound. Hagen-Poiseuille's law shows that resistance to laminar airflow increases markedly with small decreases in the airway's radius.[2] A small amount of inflammation can result in significant airway obstruction in children.

$$R \text{ (resistance)} = 8 \bullet \eta \text{ (viscosity)} \bullet l \text{ (length)}/\pi \bullet r^4 \text{ (radius)}$$

Immediately assess a child with stridor, as stridor indicates a difficult airway, and advanced airway management may be necessary

TABLE 126-1 Causes of Stridor

Children <6 mo of age	Children >6 mo of age
Laryngotracheomalacia	Croup
Vocal cord paralysis	Epiglottitis
Subglottic stenosis	Bacterial tracheitis
Airway hemangioma	Foreign body aspiration
Vascular ring/sling	Retropharyngeal abscess

(see Chapter 113, "Intubation and Ventilation in Infants and Children"). A thorough history and examination will often lead to a "working diagnosis." Inquire about the time and events surrounding the onset of stridor, the presence of fever, known congenital anomalies, cardiac abnormalities, perinatal complications, prematurity, neonatal intensive care unit interventions, and previous endotracheal intubation or instrumentation.[3]

The level of obstruction can often be identified on examination. Partial obstruction of the upper airway at the nasopharynx and/or oropharyngeal level produces sonorous sounds, called *stertor*. Obstruction above the true vocal cords is generally indicative of inspiratory stridor, whereas expiratory stridor is characterized by obstruction below the true vocal cords. Biphasic stridor suggests obstruction at the level of the true vocal cords.[4]

Consider airway foreign body until proven otherwise if there is marked variation in the pattern of stridor. The noise made by a child with stridor is often interpreted as wheezing by parents unfamiliar with stridor. Clarify what the parent means when the word "wheezing" is used—whether the sound occurs when the child breathes in or breathes out. The differential diagnosis of stridor depends on the child's age (**Table 126-1**).

STRIDOR IN INFANTS <6 MONTHS OLD

An infant <6 months old with a long duration of symptoms often has a congenital cause of stridor. The major causes are laryngomalacia, tracheomalacia, vocal cord paralysis, and subglottic stenosis. Less common but important considerations include airway hemangiomas, vascular rings, and slings. Stridor presenting in the first 6 months of life will often require direct airway visualization through endoscopy or advanced imaging. The timing of this evaluation (emergent or outpatient) is dictated by the severity of symptoms and clinical suspicion.

Laryngomalacia accounts for 60% of all neonatal laryngeal problems and results from a developmentally weak larynx. Collapse occurs with each inspiration at the epiglottis, aryepiglottic folds, and arytenoids. Generally, stridor worsens with crying and agitation but often improves with neck extension and when the child is prone. **Laryngomalacia usually manifests shortly after birth**, which is a key diagnostic feature, and generally resolves by 18 months of age. In many cases, the tracheal support structures are similarly affected, resulting in laryngotracheomalacia. Symptom exacerbations may occur with upper respiratory infections or increased work of breathing from any cause. Definitive diagnosis can often be made with flexible fiberoptic laryngoscopy. Surgery may be required if a child suffers from failure to thrive, apnea, or pulmonary hypertension.

Vocal cord paralysis can be congenital or acquired. Unilateral vocal cord paralysis is more common than bilateral and can present with feeding problems, stridor, hoarse voice, and changes to a child's cry. Children with bilateral cord paralysis often have a normal voice associated with stridor and dyspnea, and symptoms can include cyanosis and apneic episodes.[5] Diagnosis is by flexible nasolaryngoscopy. Endotracheal intubation can be difficult with bilateral cord paralysis, and a surgical airway may be required to secure the airway.

Subglottic stenosis may be congenital or acquired and is diagnosed when there is a narrowing of the laryngeal lumen. Congenital stenosis is usually diagnosed in the first few months of life when the child is noted to have *persistent inspiratory stridor*. Mild cases may present later in childhood as recurrent or persistent croup. Prolonged endotracheal intubation in premature babies is the most common cause of acquired subglottic stenosis.[5] Treatment is based on the severity of the stenosis.

Hemangiomas are benign congenital tumors of endothelial cells or vascular malformations that can occur anywhere on the body (80% are located above the clavicles), including the airway, where they can cause obstruction and stridor. Hemangiomas typically enlarge throughout the first year of life, may not be noticed at birth, and tend to spontaneously regress by age 5 years old. For infants <6 months old, thoroughly examine the skin, because cutaneous hemangiomas, especially in a beard distribution, may be a clue to the presence of an airway hemangioma. **Consider airway hemangioma in new-onset stridor beginning after the first month of life without another explanation; definitive diagnosis requires airway visualization through endoscopy**. Although most hemangiomas spontaneously regress, large malformations and those causing significant respiratory symptoms may require treatment with β-blockers, steroids, laser, or surgery.[6-9]

Vascular rings and slings are rare congenital anomalies of the aortic arch and pulmonary artery in which anomalous vessels can compress the trachea or esophagus. Examples include a double- or right-sided aortic arch. Symptoms are often present from birth or early in the first month of life and may be progressive and exaggerated during intercurrent upper respiratory infections; difficulty with feeding may also occur if the esophagus is compressed. Chest radiograph may reveal subtle narrowing or anterior compression of the trachea on the lateral view or an abnormal (e.g., right-sided) aortic arch. Further evaluation includes bronchoscopy, CT angiography, and echocardiography to evaluate for associated congenital heart anomalies. Definitive treatment is surgical.

STRIDOR IN CHILDREN >6 MONTHS OLD

The child >6 months old with a relatively short duration of symptoms (hours to days) characteristically has an acquired cause of stridor. Causes are either inflammatory/infectious, such as croup or epiglottitis, or noninflammatory, such as a foreign body aspiration (**Table 126-2**).

CROUP

Croup (viral laryngotracheobronchitis) is the most common cause of stridor outside the neonatal period, commonly affecting children 6 months to 3 years old. The incidence is highest in the fall and the early winter months, but sporadic cases can be seen year-round. The most common viruses are parainfluenza virus and rhinovirus, followed by various other respiratory viral pathogens including influenza, respiratory syncytial virus, metapneumovirus, enterovirus, and coronavirus. In areas where measles remains prevalent, this is an important cause of croup. Coinfection by more than one virus is not uncommon, and bacterial superinfection, although rare, is also possible.[10,11]

CLINICAL FEATURES

The clinical course of croup varies, but symptoms typically begin after 1 to 3 days of nasal congestion, rhinorrhea, cough, and low-grade fever. Classic symptoms are a harsh barking cough, hoarse voice, and stridor. Symptoms are often worse at night. The severity of symptoms is related to the amount of edema and inflammation of the airway. Assess for tachypnea, stridor at rest, nasal flaring, retractions, lethargy or agitation, and oxygen desaturation. Most croup is self-limited and short in duration, resolving spontaneously within 3 days, although depending on the etiology, it may last longer.[12]

DIAGNOSIS

Diagnosis is clinical. Laboratory studies, viral tests, or radiographs are needed only in children who fail to respond to conventional therapy or if considering another diagnosis such as epiglottitis, retropharyngeal

TABLE 126-2 Common Acquired Causes of Stridor

	Viral Croup	Epiglottitis	Bacterial Tracheitis	Foreign Body Aspiration	Retropharyngeal Abscess	Peritonsillar Abscess
Etiology	Parainfluenza viruses (occasionally influenza respiratory syncytial virus, rhinovirus, metapneumovirus, enterovirus, and coronavirus)	*Streptococcus pneumoniae*	*Staphylococcus aureus* (most)	Variable	Polymicrobial	Polymicrobial
				Foods	*Streptococcus pyogenes*	*S. pyogenes*
		S. aureus	*S. pneumoniae*	Peanuts	*S. aureus*	*S. aureus*
			S. pyogenes			
		Haemophilus influenzae	*H. influenzae*	Seeds	Gram-negative rods	Oral anaerobes
			Moraxella catarrhalis	Balloons/other toys	Oral anaerobes	
Age	6 mo–3 y old	All ages	3 mo–13 y old	Any	6 mo–4 y old	10–18 y old (most)
	Peak 1–2 y old	Mean, 6–12 y old	Mean, 1–6 y old	6 mo–5 y old most common	Rare >4 y old	6 mo–5 y old (rare)
				80% <3 y old		
Onset	1–3 d	Rapid, hours	2–7 d viral upper respiratory infection (especially influenza)	Immediate or delayed possible	Insidious over 2–3 d after an upper respiratory infection or local trauma	Antecedent pharyngitis
			Suddenly worse over 8–12 h			
Effect of positioning on symptoms	None	Worse supine	None	Usually none	Neck stiffness and hyperextension	Worse supine
		Prefer erect, chin forward		Location dependent		Trismus common
Stridor	Inspiratory and expiratory	Inspiratory	Inspiratory and expiratory	Location dependent	Inspiratory when severe	Uncommon
Cough	Seal-like bark	No	Usually present	Often transient or positional	No	No
			Possible thick sputum			
Voice	Hoarse	Muffled	Usually normal	Location dependent	Often muffled	Muffled
	Not muffled	"Hot potato"	Possibly raspy	Primarily if at or above glottis	"Hot potato"	"Hot potato"
Drooling	No	Yes	Rare	Rare—often if esophageal	Yes	Often
Dysphagia	Occasional	Yes	No	Rare—typically if esophageal	Yes	Yes
Radiologic appearance	Subglottic narrowing "steeple sign" (no diagnostic value)	Enlarged epiglottis; "thumbprint sign"	Subglottic narrowing	Often normal	Thickened bulging retropharyngeal soft tissue	May see enlarged tonsillar soft tissue
		Thickened aryepiglottic folds	Irregular tracheal margins	Possible radiopaque density		
			Stranding across trachea	Ball-valve effect		
				Segmented atelectasis		

abscess, or aspirated foreign body.[10] If radiographs are ordered, provide close monitoring during the procedure, as agitation may worsen existing airway obstruction.[11] Radiographs may demonstrate subglottic narrowing ("**steeple sign**") (**Figure 126-1**); however, the steeple sign may be present in normal children and can be absent in up to 50% of those with croup.

Croup is often classified as mild, moderate, or severe, and treatment is directed primarily at decreasing airway obstruction. Croup scoring systems are more useful as research tools than in clinical practice. The score, if calculated, should be used as only one piece of data in the decision-making process. One of the commonly used scoring guidelines is the modified Westley Croup Score (**Table 126-3**).[13]

Place children in a position of comfort, often in the lap of the caretaker, and assess respiratory distress through observation, without disturbing the child. Agitation and crying increase oxygen demand, creating turbulent airflow and resulting in greater airway resistance. Humidified air or cool mist does not appear to improve clinical symptoms.[14] However, anecdotally, exposing children with croup to cold air at home reduces the intensity of symptoms.[11]

The primary treatments for croup include nebulized epinephrine and corticosteroids (**Table 126-4**). **Give nebulized epinephrine for moderate to severe croup, primarily those with stridor at rest; mild croup generally does not require epinephrine.** Epinephrine decreases airway edema through its vasoconstrictive α-receptor effects. Clinical effects of epinephrine are seen in as few as 10 minutes. Use of epinephrine decreases the number of children with croup requiring hospitalization, intensive care unit stay, or intubation. Studies comparing L-epinephrine with racemic epinephrine show no significant difference in response initially; however, at 2 hours after administration, patients receiving L-epinephrine displayed lower croup scores.[15,16] Administration of nebulized intermittent positive-pressure breathing has no benefit over simple nebulization.[16] ED observation for at least 3 hours is recommended when epinephrine is required because an increase in croup scores can occur between the second and third hours after epinephrine in patients ultimately requiring admission.[17]

All patients with croup, whether mild, moderate, or severe, benefit from the administration of oral steroids as a one-time dose. Steroid administration reduces the severity and duration of symptoms

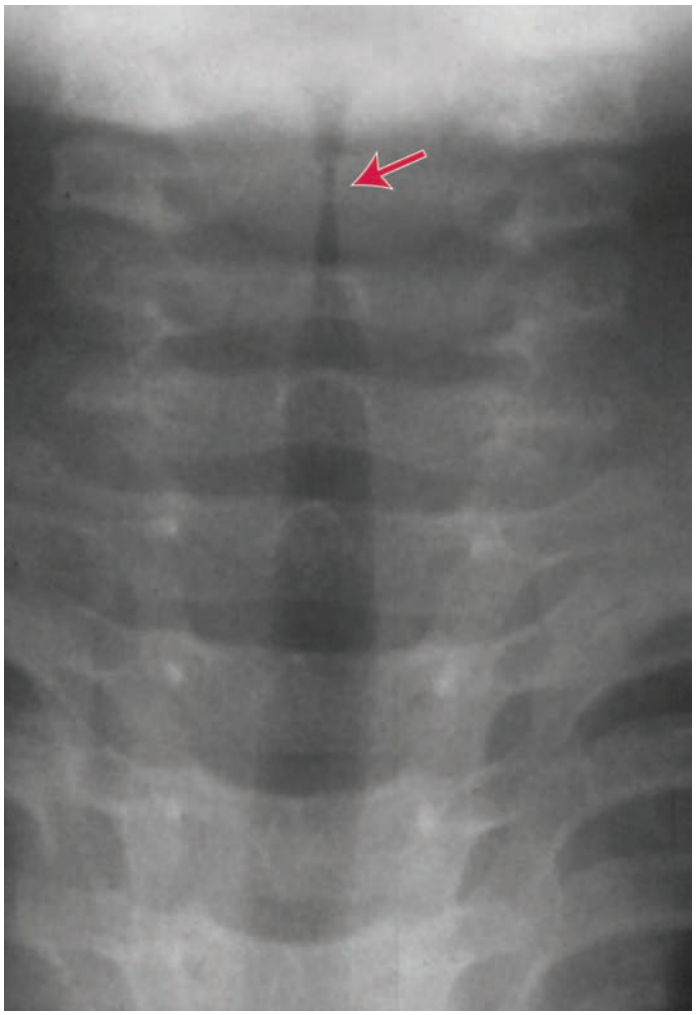


FIGURE 126-1. Anteroposterior neck radiograph in a patient with croup; note presence of "steeple sign" (*arrow*). [Photo used with permission of W. McAlister, MD, Washington University School of Medicine, St. Louis, MO.]

and results in a decrease in return visits to the ED or hospital length of stay.[10,18] A one-time dose of dexamethasone has become the steroid of choice given ease of administration, cost, and medication half-life. **Dexamethasone is equally effective given parenterally or orally.** Currently, a single dose of 0.6 milligram/kg PO of the oral dexamethasone preparation is recommended.[14] The onset of action for oral dexamethasone is generally 4 to 6 hours after oral administration, but effects can be seen within 1 hour.[10] Most clinicians initially prescribe oral corticosteroids because of ease of administration. Using injectable dexamethasone formulation (4 milligrams/mL) for oral administration provides less volume than commercially available oral products (0.1 milligram/mL or 1 milligram/mL) and can improve tolerability and minimize risk of emesis.[19] Nebulized budesonide and IM dexamethasone are alternatives to oral dexamethasone in children who are vomiting.

For severe croup with respiratory failure despite medical therapy, endotracheal intubation may be necessary. When possible, intubation should be performed in a controlled setting such as the operative room or intensive care unit by the most experienced person available. Intubation should be performed using an endotracheal tube 0.5 to 1 mm smaller than normally used for the patient's size given the upper airway edema.

Heliox, in a 70% helium/30% oxygen ratio, has theoretical treatment benefits for severe, refractory croup. Replacing nitrogen with the less dense helium decreases airway resistance and may improve gas flow through a compromised airway. An important limitation is the low fractional concentration of inspired oxygen in the gas mixture. Despite its theoretical benefits, studies show no definitive advantage of heliox over conventional treatment. In certain clinical scenarios, it may still hold some short-term clinical benefit.[20,21] Although historically used in children with mild to moderate croup, the use of humidified air is also likely ineffective.[14]

There are insufficient data to determine whether nebulized β-agonists are beneficial in children with croup.[10,22] In addition, there is theoretical risk of worsening upper airway obstruction with β-agonist use in croup, as β-receptors in the vasculature cause vasodilation (as compared to the vasoconstrictive α effects of epinephrine), which may worsen upper airway edema in croup. **Therefore, β-agonists are not recommended for treatment of croup.**

DISPOSITION AND FOLLOW-UP

Most children with croup can be safely discharged to home (**Table 126-5**). Children who have received nebulized epinephrine should be observed in the ED for 3 to 4 hours after administration. **Children with persistent stridor at rest, tachypnea, retractions, and hypoxia or those who require more than two treatments of epinephrine should be admitted to the hospital.**[10,11,22] Admit children with respiratory failure and those requiring intubation to intensive care.

EPIGLOTTITIS

Epiglottitis, or supraglottitis, is an acute inflammatory condition of the epiglottis that may progress rapidly to life-threatening airway obstruction. Widespread administration of *Haemophilus influenzae* type B vaccine has significantly reduced the number of cases of childhood epiglottitis and shifted the epidemiology toward older children (mean age 6 to 12 years). In the postvaccine era, most cases of infectious epiglottitis are caused by streptococcal and staphylococcal species, whereas *Candida* species can cause epiglottitis in the immunocompromised patient. Noninfectious causes, such as thermal injury, caustic burns, and direct trauma, can cause swelling and inflammation of the epiglottis with a similar clinical picture.[23]

CLINICAL FEATURES

Infection typically presents with the abrupt onset of fever, stridor, drooling, and sore throat. Symptoms may progress rapidly, with inability to handle oral secretions followed by stridor and respiratory distress. Cough is often absent, and the voice may be muffled. Most children appear toxic and anxious and may assume a tripod or sniffing position with the neck hyperextended and the chin forward to maintain the airway.[23]

TABLE 126-3 The modified Westley Croup Score

Inspiratory stridor	None = 0 points	With agitation only = 1 point	At rest = 2 points
Intercostal retractions	Mild = 1 point	Moderate = 2 points	Severe = 3 points
Air entry	Normal = 0 points	Slightly decreased = 1 point	Severely decreased = 2 points
Cyanosis	None = 0 points	With agitation only = 4 points	At rest = 5 points
Level of consciousness	Normal = 0 points		Altered = 5 points
0–17 points total	**<4 points = mild croup**	**4–6 points = moderate croup**	**>6 points = severe croup**

TABLE 126-4 Croup Treatment

Medication	Dose	Notes
Dexamethasone	0.15–0.6 milligram/kg PO/IM (10 milligrams maximum)	Give for mild, moderate, or severe croup. May crush pills and mix in juice or applesauce or administer the IV formulation orally.
Budesonide	2 milligrams nebulized	Consider if PO steroids vomited.
L-Epinephrine (1:1000)	0.5 mL/kg nebulized (5 mL maximum)	Use for moderate or severe croup; may need repeat dose if severe.

DIAGNOSIS

The ideal approach to the diagnosis of epiglottitis varies depending on the practice and the environment. Each institution should have a written protocol for suspected epiglottitis management. Important components of all protocols are listed in **Table 126-6**.

In older children and those with mild respiratory distress, gentle direct visualization of the epiglottis may be attempted. Despite concerns that such maneuvers could trigger worsening distress, no documented reports show this to be unsafe.

Lateral neck radiographs are usually unnecessary in patients with the classic presentation of epiglottitis. When the diagnosis is uncertain, obtain soft tissue neck radiographs with the neck extended during inspiration. Affected children typically hold their heads in a sniffing position and have prolonged inspiration already, making it quite simple to obtain radiographs. Lateral neck radiographs may show an enlarged epiglottis protruding from the anterior wall of the hypopharynx (often called the "**thumb sign**") and thickened aryepiglottic folds[23,24] (**Figure 126-2**). If suspicion for the diagnosis still exists despite normal-appearing radiographs, direct visualization of the epiglottis is necessary to exclude the diagnosis (**Figure 126-3**).

TREATMENT

Keep the child seated and upright in a position of comfort. Provide oxygen only if this does not further agitate the child. Administer nebulized L-epinephrine to decrease airway edema. Alert the referral center or pediatric otolaryngologist as soon as possible so decisions concerning intubation or tracheotomy can be made in concert with consultants and support personnel can be mobilized. The most skilled individual available should perform intubation as soon as the diagnosis is made. Awake, fiberoptic nasotracheal intubation under conscious sedation should be considered in the spontaneously breathing patient. Use paralytics and vagolytics as needed. For a child who is able to maintain an airway, the decision to administer paralytics must be accompanied by absolute certainty that intubation will be successful. Have multiple endotracheal tube sizes immediately available. **Supraglottic devices are not effective in children with upper airway obstruction; if endotracheal intubation is unsuccessful, an emergent surgical airway is required.** Antibiotic coverage should target *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *H. influenzae,* with consideration for methicillin-resistant *S. aureus* (e.g., ceftriaxone and vancomycin). Antibiotics are typically continued for 7 to 10 days. Steroids are often used to decrease mucosal edema of the epiglottis. Admit all children with suspected or confirmed epiglottitis to an intensive care unit setting.

TABLE 126-5 Criteria for Discharge From ED in Patients With Croup

- No stridor at rest and 3 h since last epinephrine (if given)
- Normal color, pulse oximetry, and mental status
- Able to tolerate oral fluids
- Caretaker can recognize worsening symptoms and return to ED if necessary

TABLE 126-6 Suspected Epiglottitis Management Protocol

- Immediate recognition and triage to a resuscitation area
- Continuous monitoring by someone trained in the management of a difficult airway
- Rapid consultation with appropriate colleagues from otolaryngology and anesthesiology
- Consideration and risk-benefit analysis of patient transfer with appropriate personnel present during the transfer
- Bedside radiology without disturbing the patient or, if moved to the x-ray suite, constant monitoring by a physician with appropriate airway equipment and skills

BACTERIAL TRACHEITIS

Bacterial tracheitis, also known as *membranous laryngotracheobronchitis* or *bacterial croup*, is an uncommon infection that can cause life-threatening upper airway obstruction. It can be a primary or secondary infection. The mean age of presentation is now 5 to 8 years of age compared with the 4 years of age that has been classically described.[25,26] The most commonly isolated pathogen obtained from culture at bronchoscopy is *S. aureus*. Other organisms implicated in bacterial tracheitis include *S. pneumoniae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *H. influenzae*, and oral anaerobes.[25-29]

CLINICAL FEATURES

Bacterial tracheitis often develops secondarily after a viral upper respiratory tract infection, particularly influenza A. A history of upper respiratory infection symptoms followed by sudden worsening with high fever, stridor (often biphasic), and cough (which may be productive with thick sputum) and a toxic appearance suggest the diagnosis. Thick mucopurulent secretions of the trachea can result in upper airway obstruction. Children with tracheitis often complain of sore throat and will point to



FIGURE 126-2. Lateral neck view of a child with epiglottitis. Note the swollen epiglottis (*arrow*) resembling a "thumb."

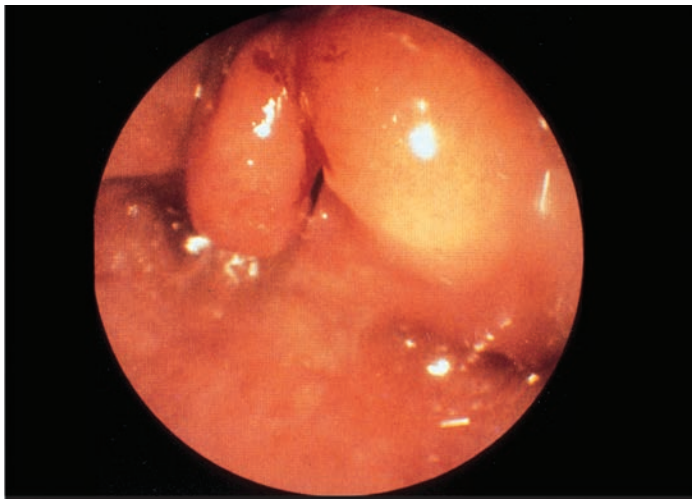


FIGURE 126-3. Epiglottitis at laryngoscopy. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 3rd ed. McGraw-Hill, Inc., New York. Part 2 Specialty Areas, Chapter 14, Pediatric Conditions, Figure 14-38.]

their trachea when asked where it hurts. There is often tenderness with palpation of the trachea.

DIAGNOSIS

Laboratory studies other than tracheal cultures (typically obtained during bronchoscopy) are of limited use in the diagnosis. Neck radiographs are not needed to make the diagnosis. When obtained to evaluate for other potential diagnostic entities, neck films may show subglottic narrowing of the trachea and irregular tracheal margins in patients with tracheitis (**Figure 126-4**). Because no single clinical or radiographic feature can definitively make a diagnosis, bronchoscopy is the diagnostic method of choice in bacterial tracheitis.

TREATMENT

The management of tracheitis is similar to that of epiglottitis, with patients ideally going to the operating room for sedation, intubation, and bronchoscopy. There is no clear benefit from β-agonists or glucocorticoids in bacterial tracheitis. Administer empiric antibiotics in the ED to cover likely pathogens. In children with tracheostomies, prior lower respiratory cultures may also guide initial antibiotic choices. Appropriate choices include vancomycin or clindamycin plus a third-generation cephalosporin. Definitive antibiotic choices depend on cultures and Gram stain of the mucopurulent secretions obtained at the time of bronchoscopy. Bronchoscopy may be therapeutic because the removal of purulent pseudomembranes improves tracheal toilet and may lessen upper airway obstruction. For continued management, most patients with bacterial tracheitis require a definitive airway and ventilatory support.

AIRWAY FOREIGN BODY

Airway foreign body aspiration occurs most commonly in children between 1 and 3 years old as a result of increasing mobility and oral exploration. Foreign body aspiration in children <6 months old often involves a well-meaning sibling who places an object in the infant's mouth. The most common objects aspirated fall into two groups: food and toys. Commonly aspirated foods include peanuts, sunflower seeds, carrots, raisins, grapes, and hot dogs.

Suspect foreign body aspiration with a history of sudden coughing and choking in the child; this is the most predictive of all signs and symptoms in foreign body aspiration.[30-32] In many cases, the choking episode is not witnessed by a caregiver. Consider foreign body aspiration in a young child with respiratory symptoms, regardless of the duration of symptoms, because many children may present >24 hours after foreign body aspiration. If the clinical scenario clearly indicates the presence of a foreign body or airway obstruction, immediately implement a protocol for obstructed airway management (see Chapter 109, "Resuscitation of Children").



FIGURE 126-4. Membranous tracheitis. Lateral soft tissue radiograph of the neck in a 13-year-old girl with the acute onset of stridor after 3 days of sore throat. Membranes (*arrows*) are visible in the subglottic region. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *The Atlas of Emergency Medicine*, 4th ed. McGraw-Hill Education, Inc. © 2016. Fig 14.87, page 478. Photo contributor: Matthew R. Mittiga, MD.]

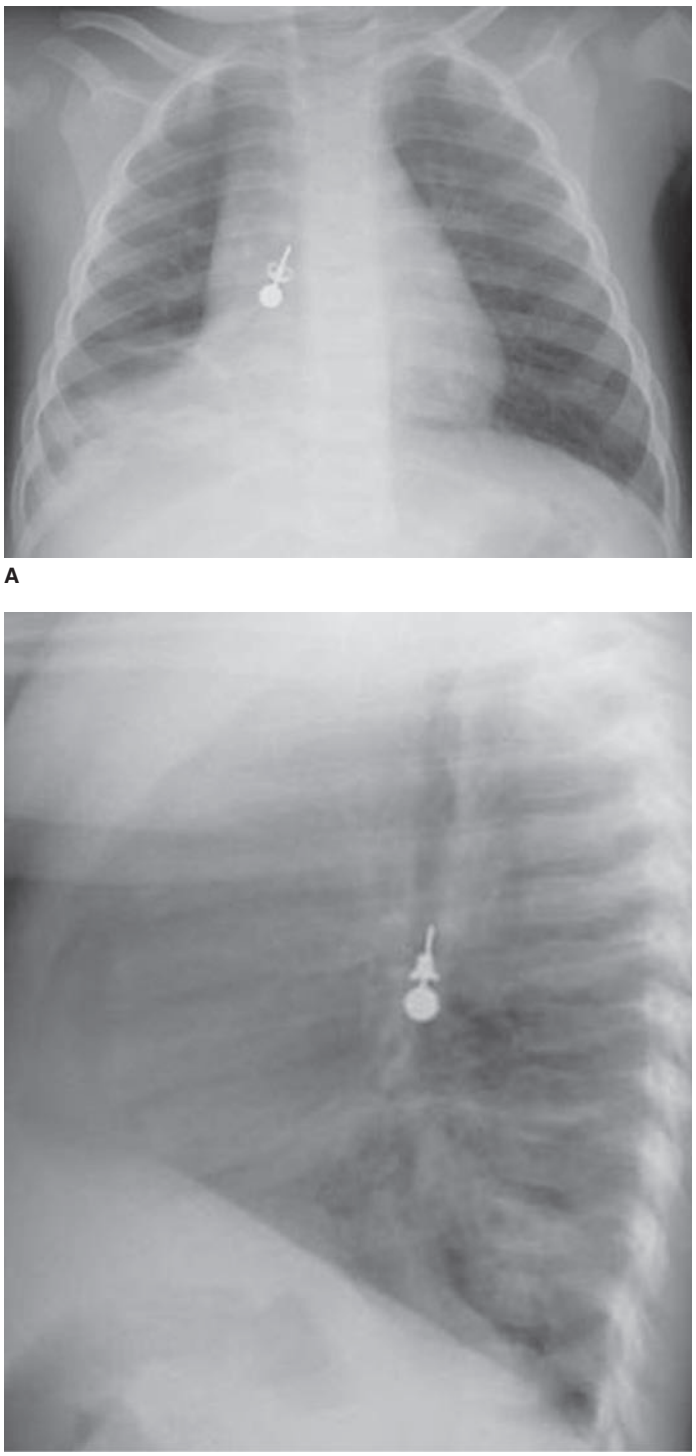
CLINICAL FEATURES

A history of witnessed choking (sudden onset of cough, shortness of breath) is highly suggestive of airway foreign body, although not always observed.[33] Although the location of the aspirated foreign body plays a role in determining the symptoms and signs on presentation, there is great overlap between groups, and some children may be asymptomatic on presentation. "Classic dogma" is that laryngotracheal foreign bodies cause stridor and hoarseness, whereas bronchial foreign bodies cause unilateral wheezing and decreased breath sounds. A large majority of airway foreign bodies are found in the bronchi. Children can develop severe immediate-onset stridor or even cardiopulmonary arrest, but there are a proportion of patients who will remain minimally symptomatic. The most important factor in reducing mortality from an airway foreign body is recognition of the child in acute airway distress.

DIAGNOSIS

Radiographs are helpful to *confirm* the diagnosis of airway foreign body but should not be used to *exclude* the diagnosis. Plain chest radiographs are normal in >50% of tracheal foreign bodies and 25% of bronchial foreign bodies.[34] More than 75% of airway foreign bodies in children <3 years of age are radiolucent.[34,35] Laryngeal and tracheal foreign bodies often constitute an acute emergency, and radiography is omitted. If performed, posteroanterior and lateral neck radiographs are the radiographic examinations of choice. Foreign bodies lodged in the proximal esophagus may also present with airway compression. Tracheal

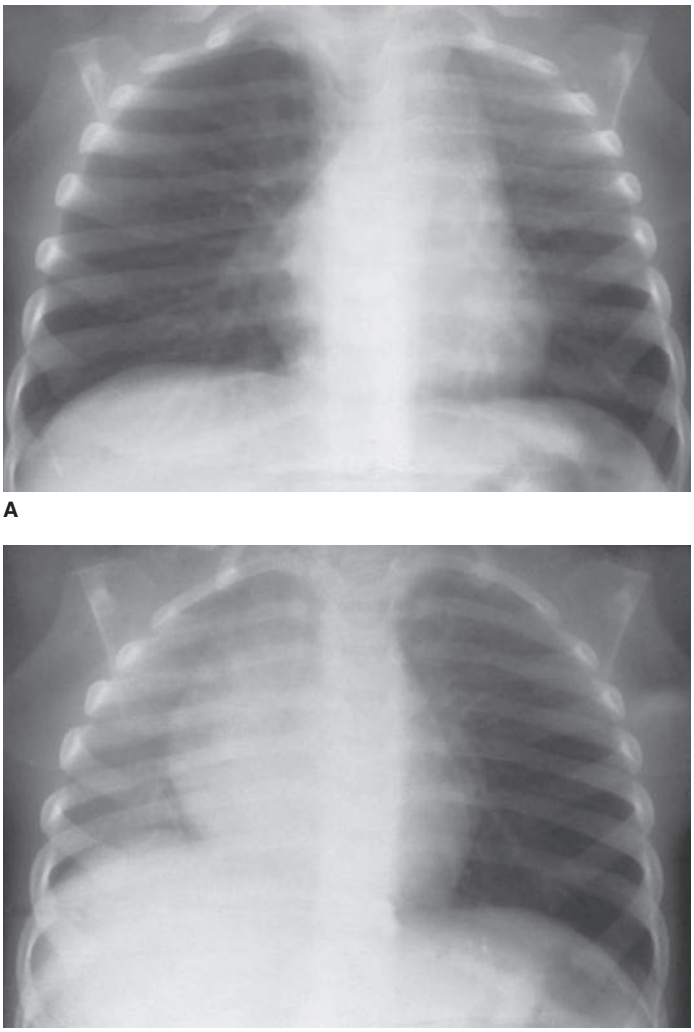
and esophageal foreign bodies can be differentiated on neck radiographs: foreign bodies typically lodge in the trachea in profile and in the esophagus en face. Suspected bronchial foreign bodies can be evaluated with the use of posteroanterior and lateral chest films (**Figure 126-5, A and B**). Indirect radiologic signs of a radiolucent airway foreign body include unilateral obstructive emphysema, atelectasis, and consolidation. Unilateral obstructive emphysema is seen when a foreign body obstructs airflow, mainly on expiration. This generates a check-valve obstruction that results in hyperinflation of the affected side and potential mediastinal shift to the opposite side. A foreign body that obstructs a bronchus may produce focal atelectasis and consolidation visible on chest films. Inspiratory and expiratory chest radiographs can aid in the diagnosis by showing hyperinflation (air trapping) on expiratory films in cooperative patients (**Figure 126-6, A and B**). Bilateral decubitus chest films have been used to demonstrate air trapping; however, they increase false positives without increasing true positives, suggesting a lack of clinical benefit.[34,36-38] A clinically suspected foreign body aspiration should ultimately be ruled out by bronchoscopy, regardless of the chest radiograph findings.[34,36,37]



A

B

FIGURE 126-5. (**A**) Posteroanterior and (**B**) lateral chest radiographs showing radiopaque bronchial foreign body. [Photos used with permission of W. McAlister, MD, Washington University School of Medicine, St. Louis, MO.]



A

B

FIGURE 126-6. (**A**) Inspiratory and (**B**) expiratory chest radiographs showing air trapping on the left with shift of the mediastinum to the right caused by a peanut in the left mainstem bronchus. [Photos used with permission of W. McAlister, MD, Washington University School of Medicine, St. Louis, MO.]

TREATMENT

Children with complete airway obstruction are typically unable to breathe or speak and require emergency basic life support measures to relieve airway obstruction. For detailed discussion, see Chapter 108, "Resuscitation of Neonates," and Chapter 109, "Resuscitation of Children." If basic life support maneuvers fail, perform direct laryngoscopy and foreign body extraction with Magill forceps. When the foreign body is not visible or able to be removed, orotracheal intubation with dislodgment of the foreign body more distally (often into the right mainstem bronchus) may relieve complete obstruction and be lifesaving. If the foreign body cannot be removed and ventilation cannot be provided through an endotracheal tube, attempt a surgical airway (needle cricothyroidotomy

or emergency tracheostomy). For children with partial airway obstruction, monitor respiratory status closely and arrange for bronchoscopic removal under general anesthesia.

RETROPHARYNGEAL ABSCESS

The retropharyngeal space occupies the space between the posterior pharyngeal wall and the prevertebral fascia and extends from the base of the skull to approximately the level of the second thoracic vertebrae. This space is fused down the midline and contains two chains of lymph nodes extending down each side. An important potential complication is caudal spread into this potential space leading to mediastinitis. These lymph nodes tend to regress by age 4 years old, obliterating this potential space, which explains the decreasing frequency of retropharyngeal abscess in older children. The formation of a retropharyngeal abscess is believed to be secondary to suppuration of these lymph nodes that have been seeded from a distant infection. Localized penetrating trauma with subsequent invasion of this space by bacteria is another cause of retropharyngeal infection. This most commonly occurs in children who fall with a stick or other similar object in their mouth. Infection can also occur from traumatic esophageal instrumentation or ventral extension of vertebral osteomyelitis. Retropharyngeal infection typically progresses from an organized phlegmon to a mature abscess.

CLINICAL FEATURES

Most cases of retropharyngeal abscess evolve insidiously over a few days after a relatively minor upper respiratory infection or pharyngitis. Fever is typically present but may be absent in >10% of patients.[39-41] Additional signs and symptoms include neck pain, odynophagia, dysphagia, trismus, excessive drooling, and neck swelling. The child may maintain the neck in an unusual position, with stiffness, torticollis, and hyperextension. The voice may be muffled, and anterior cervical lymphadenopathy is common. A unique finding is bulging of the posterior oropharynx. The diagnosis should be considered in any child who will not fully extend his or her neck to look up (Bolte's sign).[41] Abscess progression can lead to stridor and respiratory distress. Pleuritic chest pain is an ominous sign, indicating extension of the infection into the mediastinum.

DIAGNOSIS

Initial imaging includes a soft tissue lateral neck radiograph. The radiograph should be taken during inspiration with the neck extended to limit false-positive results. **The diagnosis of retropharyngeal abscess/cellulitis is suggested when the retropharyngeal space at C2 is twice the diameter of the vertebral body or greater than one half the width of the C4 vertebral body (Figure 126-7).** Rarely, gas may be seen within the collection. Contrast-enhanced CT scan may demonstrate necrotic nodes, inflammatory phlegmon, or fluid collection within a ring-enhancing abscess (**Figure 126-8**). CT is helpful for diagnosing and defining the extent of the infection and surgical planning. However, CT scans are limited in their ability to differentiate between abscess and cellulitis/phlegmon. Therefore, imaging results should be correlated to clinical findings when guiding the decision of conservative versus surgical treatment.[39-47] Unstable patients should be intubated before going to the radiology suite for CT scan. Patients requiring sedation to obtain a scan may require presedation intubation if airway obstruction is present. A provider accustomed to managing the difficult pediatric airway should escort patients without airway compromise to radiology, and appropriate equipment should accompany the patient.

TREATMENT

Carefully monitor and stabilize the airway. Obtain IV or IO access to administer fluids, antibiotics, and CT contrast. Most retropharyngeal abscesses are found to contain mixed flora when cultured.[39,40] Common organisms include *S. aureus*, *S. pyogenes*, *Streptococcus viridans*, and β-lactamase–producing gram-negative rods. Oral anaerobes are also

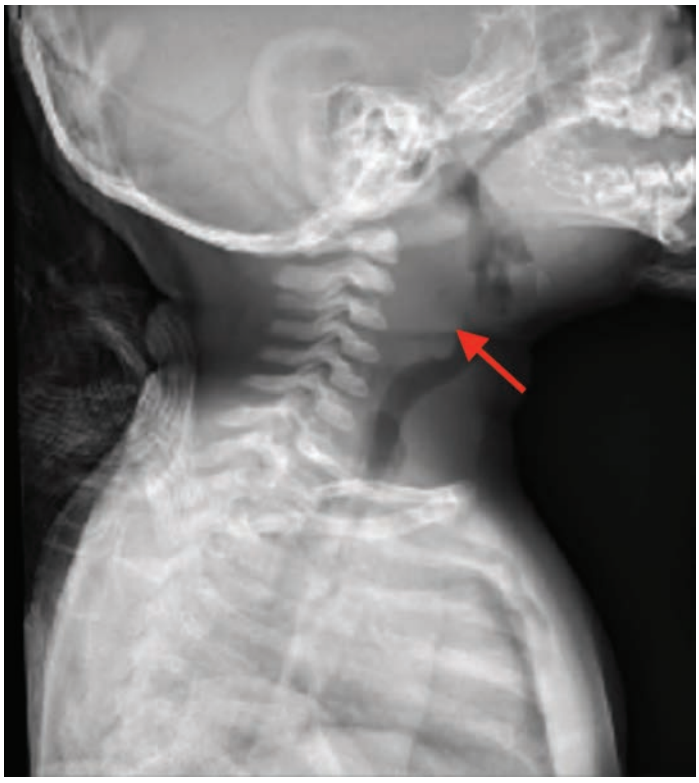


FIGURE 126-7. Lateral soft tissue neck radiograph demonstrating retropharyngeal swelling (*arrow*).

frequently seen. Retropharyngeal cellulitis and small, localized abscesses may be treated successfully with antibiotic therapy alone. All other cases should undergo operative incision and drainage, usually by an otolaryngologist. Initiate empiric antibiotic therapy in the ED with clindamycin (15 milligrams/kg per dose every 8 hours IV) or ampicillin-sulbactam (50 milligrams/kg per dose every 6 hours IV). Unusual complications

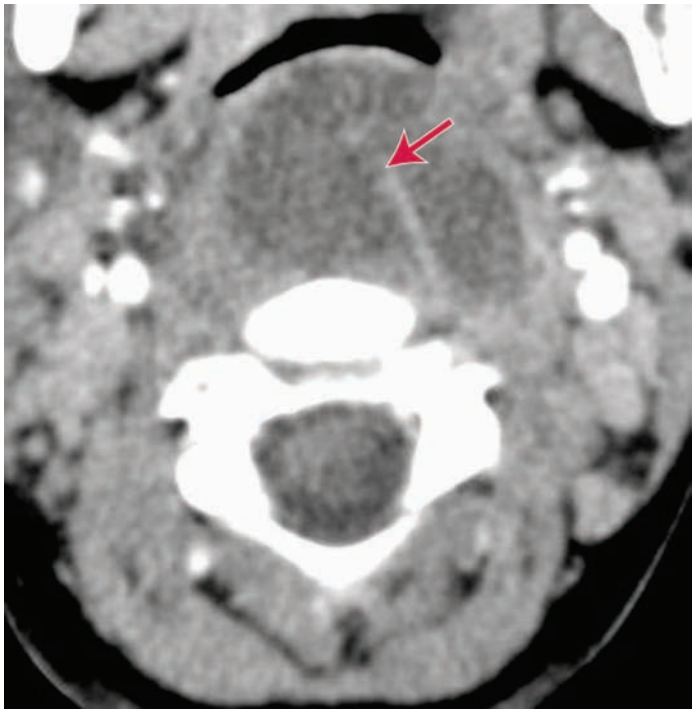


FIGURE 126-8. Contrast-enhanced neck CT showing a retropharyngeal fluid collection (*arrow*).

of retropharyngeal abscess include airway obstruction, spontaneous abscess perforation, mediastinitis, sepsis, aspiration, and jugular venous thrombophlebitis/thrombosis, also known as Lemierre's syndrome.

PERITONSILLAR ABSCESS

Peritonsillar abscess, also known as a quinsy, is a posterior oropharyngeal infection. It can occur in patients of any age, but most commonly occurs in adolescents and young adults. The disease typically begins as a superficial infection that progresses to an accumulation of pus in a space between the tonsillar capsule and the superior constrictor muscle. Most are unilateral, whereas <10% are bilateral at the time of diagnosis. Most peritonsillar abscesses are polymicrobial infections. Predominant organisms include anaerobes, group A β-hemolytic streptococci, *S. aureus*, and *H. influenzae*.[48]

CLINICAL FEATURES

Patients with peritonsillar abscess typically present with sore throat (often unilateral), fever, chills, trismus, and voice change ("hot potato voice"). Patients will often complain of "the worst sore throat" of their life and may drool due to difficulty swallowing their saliva. Ipsilateral ear pain and torticollis may be present. On examination, bulging of the affected tonsil and deviation of the uvula away from the involved tonsil are evident (**Figure 126-9**). Differentiating peritonsillar cellulitis from peritonsillar abscess can be difficult. If the child is toxic, consider a peritonsillar abscess until proven otherwise.

DIAGNOSIS

Peritonsillar abscess is typically a clinical diagnosis, and routine laboratory or imaging studies are not needed. If drainage is performed in the ED, send purulent material for Gram stain and culture. Cases without typical exam findings may require imaging to distinguish cellulitis from abscess. US (intraoral or submandibular) may be helpful in cooperative children. For cases in which deep space neck infection is a consideration, imaging with CT using IV contrast is often helpful. As mentioned earlier, lateral radiographs of the neck may identify retropharyngeal abscess.

TREATMENT

Most cases of peritonsillar abscess are managed as outpatients with prompt aspiration or incision and drainage using local anesthetics in the ED. Young and uncooperative children may require procedural sedation to facilitate adequate evaluation and drainage. Complications of needle aspiration and incision and drainage include hemorrhage, puncture of the carotid artery, and airway aspiration of purulent material. Younger children with few prior episodes of tonsillitis and small abscesses may respond to oral antibiotics without the need for drainage.[49] In non–toxic-appearing adolescents with good follow-up and findings most consistent with peritonsillar cellulitis, a trial of oral antibiotics is also reasonable. Empiric coverage includes amoxicillin-clavulanate (45 milligrams/kg per dose every 12 hours to a maximum of 875 milligrams per dose) or clindamycin (10 milligrams/kg per dose every 8 hours). Adjunct therapy with single high-dose steroid administration seems to improve symptoms in patients with peritonsillar abscess after drainage.[50]



FIGURE 126-9. Examination of the oropharynx illustrating unilateral bulging palate and erythema of the left peritonsillar fossa with the uvula mildly deviated to the contralateral side. [Reproduced with permission from Goldman L, Ausiello D: *Cecil Medicine*, 23rd ed. Philadelphia, PA: Saunders Elsevier; 2008.]

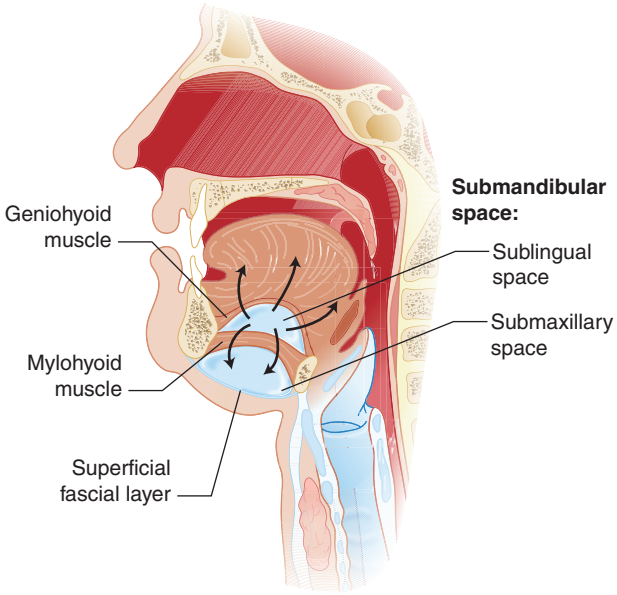


FIGURE 126-10. Spread of infection within the submandibular space of the neck.

LUDWIG'S ANGINA

Ludwig's angina is a potentially life-threatening, rapidly expanding infection of the submandibular space. The submandibular space is composed of two spaces subdivided by the mylohyoid muscle into the sublingual and submylohyoid space (submaxillary space) and extends from the floor of the mouth to muscular attachments at the hyoid bone. Infectious expansion into this space spreads superiorly and posteriorly and often involves the entire submandibular space (**Figures 126-10** and **126-11**). **Most cases arise from an odontogenic source, often from the spread of periapical abscesses of mandibular molars.** Infection is typically polymicrobial involving oral flora.

Ludwig's angina usually begins with a mild infection that progresses rapidly to include fever, chills, severe mouth pain, drooling, trismus, tongue protrusion, and brawny neck swelling. The child may maximize airway diameter by assuming a "sniffing position." Stridor may develop with subsequent progressive airway obstruction. Control the airway early, because intubation can be extremely difficult late in the clinical course of the disease.[51] Treatment includes empiric antibiotics and oral surgery to remove the dental abscess that is the source of the infection. IV antibiotics should cover β-lactamase–producing aerobic or anaerobic gram-positive cocci and gram-negative bacilli (e.g., ampicillin-sulbactam or clindamycin or penicillin G). Consider additional coverage for community-acquired methicillin-resistant *S. aureus* in those at risk for colonization.[51,52]

DIPHTHERIA

Diphtheria is an acute toxin-mediated disease caused by *Corynebacterium diphtheria*, a gram-positive non–spore-forming bacillus, and has largely been eradicated in developed nations through widespread vaccination. It is transmitted from person to person through respiratory



FIGURE 126-11. CT showing soft tissue stranding and inflammation representing infection in the submandibular space (*arrow*) in a patient with Ludwig's angina.

secretions or skin lesions. In cases of pharyngeal diphtheria, symptoms include sore throat, malaise, dysphagia, and low-grade fever. Characteristic thick gray membranes (pseudomembranes) can develop over the tonsils and soft palate and potentially cause respiratory obstruction and death. Laryngeal diphtheria is characterized by a classic "barking" cough, stridor, hoarseness, and difficulty breathing, accompanied by marked edema of the neck referred to as "bull neck."

Complications include myocarditis and neuritis potentially leading to diaphragmatic paralysis and death from respiratory failure. Diagnosis is confirmed by isolation of bacteria by culture of a nasopharyngeal swab. Treatment includes antitoxin, antibiotics, and respiratory support as needed.

OROPHARYNGEAL TRAUMA

Traumatic oropharyngeal injuries in children typically occur during a fall with an object within the mouth. Such injuries are often referred to as "pencil injuries" and most commonly occur in patients between 2 and 4 years of age. When evaluating these injuries, ask if the entire foreign body was removed intact or if part of the object may have broken off into the soft tissue. Pencils, straws, toothbrushes, and toothpicks are the most common culprits.[53-55]

There are rare, but well-known complications of penetrating pharyngeal injury. Entrance of free air into the neck or chest can result in stridor and acute airway obstruction. Subsequent retropharyngeal infection from introduction of oral flora/bacteria into the penetrating wound can occur. A more severe complication of oropharyngeal trauma is **carotid artery injury**, as the carotid artery courses along the lateral aspect of the oropharynx and is therefore at risk of injury from both blunt and penetrating impact forces. Penetrating injury can result in anything from hematoma formation to massive hemorrhage. Blunt injuries can cause compression of the carotid artery between the object and upper cervical vertebrae. The resultant shearing effect can cause an intimal tear in the vessel with subsequent thrombosis formation. Problems such as neck/mediastinal emphysema, retained foreign bodies, abscess formation, thrombosis, and arterial dissection should be considered, as these findings may be delayed after time of presentation. Symptoms may evolve over hours to days and can result in significant neurologic sequelae (stroke in the distribution of the common carotid territory).

CLINICAL FEATURES

Children with acute oropharyngeal trauma may present with bleeding, drooling, or dysphagia. Children may also present in a delayed fashion with complications of oropharyngeal trauma such as retropharyngeal abscess (discussed separately earlier), or even neurologic symptoms of stroke in cases of carotid artery injury or thrombosis from prior trauma.

DIAGNOSIS

Neither mechanism nor degree of injury is helpful in determining the possibility of neurovascular compromise. Soft tissue lateral neck films can assist in the evaluation of air in soft tissues, radiopaque foreign bodies, and evaluating for abscess. CT is superior to plain radiographs for the detection of free air, inflammation, or abscess. No consensus or specific clinical criteria exist with regard to advanced imaging for vascular injury. CT angiography is necessary if carotid injury is suspected and should be considered for patients who are unstable or have neurologic sequelae, who cannot be adequately assessed, and for whom lateral pharyngeal trauma raises concern for vascular injury.[55,56] The risks of radiation from CT may outweigh the potential benefits in well-appearing children, however.[57]

TREATMENT

Most wounds do not require surgical intervention and closure, but large gaping wounds and those with persistent bleeding may require closure under sedation or anesthesia. Lateral wounds adjacent to the path of the carotid artery have a greater risk of arterial injury than more midline injuries, and those involving the soft palate have higher infectious complication rates than those limited to the hard palate. Oral wounds are tetanus prone, and prophylaxis should be given to unimmunized children. The incidence of infectious complications following penetrating palate trauma is approximately 1%, and thus the role of prophylactic antibiotics is unclear.[58]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 127

Wheezing in Infants and Children

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INTRODUCTION

Wheezing is a high-pitched sound that occurs when there is an elevation of airway resistance due to an obstructive process. The clinician must differentiate between stridor and wheeze because this determines location of the airway obstruction. Stridor is a sign of upper airway obstruction (above the thoracic inlet) that is more marked during

inspiration, whereas wheeze signifies lower airway obstruction distal to the thoracic inlet that is more marked during expiration (see Chapter 126, "Stridor and Drooling in Infants and Children").[1-4] Wheezing implies a generalized obstructive airway disease when diffuse and focal obstruction when localized. However, severe flow limitation may exist without wheezing, for example, the silent chest in a severe asthma exacerbation. Bronchiolitis is the most frequent cause of wheezing in infants, and asthma is the most frequent cause in children and adolescents.

RESPIRATORY PHYSIOLOGY

The conducting airways extend from the trachea to the terminal bronchioles and do not participate in gas exchange. The distal transitional and respiratory zones are the gas-exchanging units. Lung tissue has elastic properties; functional residual capacity is the resting balance of stretch and recoil forces. Normally, at functional residual capacity, the tissue is relaxed at end expiration, and inspiration begins with minimal effort at the onset of inspiratory muscle contraction. Inspiration is an active process generated by the diaphragm and external intercostal muscles. During exertion, inspiration is aided by the use of accessory muscles including scalene and sternocleidomastoid muscles.[5] Expiration is normally a passive process, facilitated by elastic recoil of the stretched lung.

In the presence of diffuse (e.g., asthma, bronchiolitis) or focal (e.g., foreign body) intrathoracic airway obstruction, the normally passive process of expiration becomes active in an attempt to overcome airway resistance. Abdominal and internal intercostal muscles are recruited. Positive intrapleural pressure is generated, and increasing external pressure is applied to the airways. This leads to progressively increasing airway obstruction as expiration proceeds, a phenomenon referred to as *dynamic airway compression* (**Figure 127-1**).[6]

Dynamic airway compression results in prolonged expiratory time. The net result is failure of alveoli and distal airways to fully empty at end expiration, resulting in air trapping and increased functional residual capacity. Before subsequent inspiratory flow can begin, inspiratory muscles must overcome this increased elastic recoil, which substantially increases the work of breathing, a phenomenon referred to as **auto–positive end-expiratory pressure**. Finally, air trapping and subsequent atelectasis result in areas with ventilation–perfusion mismatch and hypoxemia.

Infants have smaller airways, highly compliant bronchial and bronchiolar cartilage, and more peripheral airway smooth muscle than older children and adults. These factors result in an even greater tendency toward airway collapse during expiration, air trapping, and auto–positive end-expiratory pressure. Thus, infants not only are more likely to experience wheezing illnesses but are also more likely to suffer the physiologic consequences of airway obstruction.

TABLE 127-1 Important Historical Features and Their Significance in Infants and Children With Wheezing

Feature	Significance
Age	<1 y: bronchiolitis more common 1–2 y: mixed >2 y: asthma more common
Family history	Positive family history of wheeze suggests atopy, making asthma more likely
Pattern	Single episode: any etiology possible Recurrent: asthma Chronic illness: asthma, cystic fibrosis, congestive heart failure, anatomic abnormality
Onset	Sudden onset: foreign body aspiration, allergic reaction, asthma
Identifiable trigger	Concurrent viral illness: bronchiolitis, asthma Pollens, pets, dust, smoke and other irritants: asthma Choking episode: foreign body aspiration
Response to bronchodilators	Improvement with β_2-agonist treatment is diagnostic for asthma Bronchiolitis may improve with inhaled epinephrine
Previous hospitalization	More severe disease, inability to care for child at home
Previous critical care unit admission ± intubation	More severe or life-threatening disease

WHEEZING

Approximately 25% to 30% of infants will have one episode of wheezing, and nearly 50% of children will have a history of wheezing by 6 years of age.[2,7,8] Obtain a thorough history for any child with wheezing (**Table 127-1**), and consider age, family history, onset, pattern, seasonality, positional changes, and associated symptoms.[2] A recurrent and episodic pattern, history of cough, association with identifiable triggers, and documented response to bronchodilators are highly suggestive of asthma in a child >2 years old.[9-11] A prior history of hospitalization, particularly to a critical care unit, and prior endotracheal intubation are important risk factors for severe disease. An exposure to sick contacts during a viral season, nasal congestion, poor feeding, and age <1 year

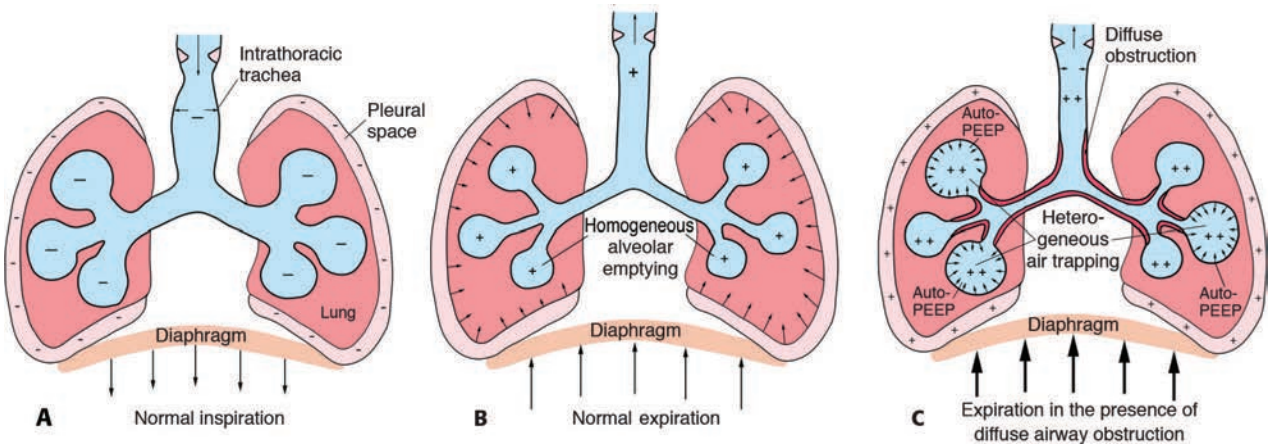

FIGURE 127-1. Normal inspiration and expiration **(A, B)** and dynamic airway compression **(C)** with development of auto–positive end-expiratory pressure (Auto-PEEP).

TABLE 127-2 Age-Specific Respiratory Rate Ranges

Age	Respiratory Rate (breaths/min)
<1 y	30–60
1–2 y	24–40
2–5 y	22–34
6–12 y	18–30
>12 y	12–16

suggest bronchiolitis.[2] Choking or gagging indicates possible foreign body aspiration.

CLINICAL FEATURES

On physical examination, use the pediatric assessment triangle to assess **appearance, work of breathing, and circulation**.[12] Assess the general appearance of the child using the **TICLS** mnemonic (**tone, interactivity, consolability, look, and speech**). Assess work of breathing by observing the child's position (e.g., sniffing, tripod), accessory muscle use (nasal flaring, tracheal tug, scalene retraction, intercostal muscle use, abdominal breathing), and presence of stridor or wheeze. Assess circulation rapidly by observing the patient's color, especially noting cyanosis. Determine respiratory rate (**Table 127-2** shows age-related ranges).

Monitor oxygen saturation by either intermittent or continuous pulse oximetry. It is common for some infants and children with asthma or bronchiolitis to develop ventilation–perfusion mismatch, which may result in mild hypoxemia (92% to 94%) that is correctable with minimum supplemental oxygen (1 to 2 L/min). **More severe hypoxemia (≤92%) suggests moderate to severe disease.** Hypoxemia refractory to bronchodilators and supplemental oxygen may suggest alternative diagnoses such as pneumonia, pneumothorax, pulmonary shunt, or congenital cardiac lesion (especially in the hypoxemic neonate). **Diaphoresis, confusion, and drowsiness are ominous signs indicating imminent respiratory failure**. Check for audibility and symmetry of breath sounds to assess adequacy of ventilation. Inspiratory-to-expiratory ratios of less than the normal 2:1 (e.g., 1:2 or 1:3) reflect the prolonged expiratory times seen with obstructive airway disease. **Perhaps more important than the initial physical examination findings are the changes in these findings in response to bronchodilators and other treatments**.

DIAGNOSIS

Table 127-3 lists the differential diagnosis of wheezing.

Asthma and bronchiolitis account for the majority of wheezing episodes in children, although a broader differential diagnosis must always be considered and ruled out on history, on physical exam, or with ancillary investigations. This is particularly important when the patient's history or physical findings are not consistent with a diagnosis of asthma or bronchiolitis or when the illness does not respond to interventions appropriate to these disease processes. Table 127-3 outlines the signs, symptoms, context, and ancillary testing for the different causes of wheezing.

The association of wheezing with feedings suggests gastroesophageal reflux or tracheoesophageal fistula with aspiration. **Grunting**, a physiologic response to generate positive end-expiratory pressure in an attempt to maintain alveolar inflation, suggests alveolar disease, although it may also result from severe abdominal distention. Inspiratory crackles or rales may be present in bronchiolitis as a result of atelectasis, although pneumonia is also a consideration. **Consider the possibility of foreign body aspiration and congestive heart failure because these disorders may also cause wheezing**.

TABLE 127-3 Differential Diagnosis for Wheezing in Infants and Children

Potential Diagnosis	Typical Age of Onset	Cardinal Symptoms and Signs	Confirmatory Tests
Asthma	>1–2 y	Recurrent episodes of wheeze and/or nighttime cough, identifiable triggers such as seasonality, allergens, exercise Responsive to bronchodilators	Trial of β-agonist Pulmonary function tests Allergy testing
Bronchiolitis	<1–2 y	URI symptoms, seasonal (winter months), nasal flaring and congestion, wheezes, rales, rhonchi	Consider viral antigen testing
Gastroesophageal reflux Tracheoesophageal fistula	Present from birth	Cough, gagging, emesis related to feeding	Esophageal pH probe Barium swallow
Vascular ring, sling, malformation, or airway hemangioma or polyp	Early infancy	Stridor that changes with position of the neck, exacerbations with URI	CXR, CT angiography, bronchoscopy, barium swallow
Laryngomalacia Tracheomalacia	Present from birth, improves during first year of life		Laryngoscopy
Congenital heart disease with left-to-right shunting and congestive failure	2–6 mo	Diffuse or basilar rales, tachycardia, hepatomegaly, cardiac murmur/gallop	CXR, ECG, echocardiography
Myocarditis	Any age		ECG, CXR, troponin, echocardiography
Foreign body aspiration	Usually >6 mo	History of choking episode with subsequent acute onset of stridor and/or wheezing	Inspiratory and expiratory CXRs*
Vocal cord dysfunction (paradoxical vocal cord motion)	From birth (paralysis) Late school age/adolescents	Stridor and/or wheezing, poor response to β-agonists	Flexible fiberoptic laryngoscopy
Epiglottitis	School age or adolescent	Stridor and high fever, toxic appearance, drooling and tripod positioning	Soft tissue radiographs of the neck*
Pneumonia	Any age	Fever, cough, tachypnea, rales, grunting	CXR
Cystic fibrosis Ciliary dyskinesia Immunodeficiency	Present from birth	Recurrent lower respiratory tract infections, failure to thrive	Sweat chloride concentration Ciliary biopsy Immunoglobulin assays

*Consider portable radiographs because patients with possible foreign body aspiration or epiglottitis outside of the ED may experience sudden and complete airway obstruction.

Abbreviations: CXR = chest x-ray; URI = upper respiratory infection.

BRONCHIOLITIS

Bronchiolitis is the most common lower respiratory tract infection in infants and children ≤2 years of age and is the leading cause for hospitalization in children <1 year of age.[13] The most common cause is **respiratory syncytial virus**, although bronchiolitis may be caused by other viruses including, but not limited to, human metapneumovirus, adenovirus, influenza, rhinovirus, and parainfluenza viruses.[14]

PATHOPHYSIOLOGY

The viral infection in bronchiolitis causes inflammation of the lower respiratory tract, with resultant edema, epithelial cell necrosis, bronchospasm, and increased mucus production within the bronchioles.[15] This results in variable degrees of air trapping, atelectasis, and hyperinflation of the lower airways. The increase in airway resistance and development of lower airway obstruction result in increased work of breathing. Because the nasal passages account for 50% of total airway resistance, increased nasal mucus production may cause upper airway obstruction due to the small nasal passages of infants. This in itself can cause modest respiratory distress, particularly in young infants, who are obligate nasal breathers.

Respiratory syncytial virus is transmitted by direct contact with contaminated secretions. Because respiratory syncytial virus is highly infectious, self-contamination and nosocomial spread are common. Hand washing and contact precautions are important to limit the spread of disease.

CLINICAL FEATURES

Although bronchiolitis can be seen throughout the year, its peak occurrence in North America is from November to March. Typical symptoms are rhinorrhea, tachypnea, wheezing, and coughing. Use of accessory muscles, nasal flaring, and fever may also occur. **These symptoms last on average 7 to 21 days and are often the worst in the first week of the illness.**[16] The peak of symptoms is often between the third and fifth day after onset. Associated symptoms include irritability, cyanosis, and poor feeding.

A subset of infants with bronchiolitis will develop severe disease and apnea. **Apneic episodes** may be brief and self-limited or progress to more frequent and prolonged episodes that lead to hypoxia and the need for endotracheal intubation. Some infants presenting with apnea have minimal other symptoms. Several factors associated with a greater risk of severe disease and apnea are listed in **Table 127-4**.[15,17] Infants with bronchiolitis and these risk factors may have prolonged hospital stays, greater need for mechanical ventilation, and higher mortality rates. Consider bronchiolitis in infants with apparent life-threatening events and monitor such infants closely (see Chapters 117 and 118, "Brief Resolved Unexplained Events and Apparent Life-Threatening Events" and "Sudden Infant Death Syndrome").

On chest examination, wheezing and crackles are heard diffusely throughout both lung fields. Respiratory rates should be measured for 1 full minute and may vary from normal to profound tachypnea (Table 127-1). Accessory muscle use and intercostal or subcostal retractions develop as respiratory distress worsens. Patients with bronchiolitis are at risk for dehydration as blocked nasal passages inhibit feeding while increased work of breathing and a higher metabolic rate contribute to increased insensible losses. Assess for signs of dehydration including dry mucous membranes, tachycardia, lethargy, delayed capillary refill, inadequate urine output, and a sunken fontanelle.

TABLE 127-4 Risk Factors for Severe Disease in Infants With Bronchiolitis

Preexisting risk factors

- Prematurity (<37 wk gestational age, especially if <32 wk gestational age)
- Age <2 mo
- Underlying cardiac or pulmonary disease
- Immunodeficiency

Acute risk factors

- Oxygen saturation ≤91% on room air at triage
- Increased work of breathing (retractions, nasal flaring, grunting)
- Dehydration (observed or reported poor feeding)
- Apnea

DIAGNOSIS

Bronchiolitis is a clinical diagnosis based on the findings of the history and physical examination, which include typical symptoms of rhinorrhea, tachypnea, crackles, and/or wheezing in a child <2 years of age. There are several published scoring systems for assessing the severity of illness and change over time used for research purposes, although none has been validated or gained wide acceptance in clinical application. Obtain pulse oximetry readings at presentation to detect hypoxemia that may not be readily suspected on physical examination and repeat readings during the course of the ED visit. Obtain intermittent oxygen saturation monitoring for children with mild disease and continuous monitoring for those with moderate or severe disease.

Rapid viral antigen detection tests are not helpful in the diagnosis of bronchiolitis but should be considered in certain clinical situations. Viral testing should be performed for patients on respiratory syncytial virus prophylaxis presenting with bronchiolitis. In this situation, the presence of respiratory syncytial virus infection may warrant discontinuation of the prophylaxis for the rest of that bronchiolitis season. Viral testing should also be considered in the context of planned admission for the purpose of patient cohorting and infection control.[15]

Ancillary tests, such as blood work and radiographs, are not routinely needed unless other diagnoses need to be excluded.[15] The incidence of serious bacterial infections in infants <28 days of age with bronchiolitis and fever is 3% to 10%, similar to that in other neonates with fever, so the standard testing of blood, urine, and cerebrospinal fluid is indicated. In infants >30 days of age, the incidence of serious bacterial infection in association with bronchiolitis remains 3% to 5%, with the most common infection being a urinary tract infection.[18] **Chest radiographs are not routinely indicated but may be considered when the illness is severe or associated with hypoxia or when pneumothorax is suspected**.[19] Although the chest radiograph in bronchiolitis may demonstrate atelectasis, bacterial pneumonia is unusual. Point-of-care US can be a useful adjunct for the assessment in patients with bronchiolitis. Point-of-care US can be used by the clinician to identify diagnoses such as pneumonia, asthma, and pneumothorax and may also be helpful in identifying patients with more severe bronchiolitis.[20-22]

TREATMENT

Figure 127-2 outlines an ED algorithm for bronchiolitis treatment based on severity of illness. **In 2014, the American Academy of Pediatrics published an updated clinical practice guideline for the treatment of bronchiolitis in children age 1 to 23 months that highlights some of the challenges clinicians encounter in the inpatient and ED settings**.[15]

The main interventions recommended for treatment of children with bronchiolitis are symptomatic supportive measures. As upper airway obstruction is often the main issue for children with bronchiolitis, **the most important treatment is frequent instillation of saline into the nares followed by suctioning**.

Mild dehydration should be managed with more frequent and smaller feeds and the use of prefeed suctioning. If there is concern for more significant dehydration, options include temporary support with nasogastric feeds or IV hydration. In children with respiratory distress requiring respiratory support, the IV route is favored to reduce the risk of aspiration.

The evidence behind the most common interventions to reduce respiratory distress is summarized below.

OXYGEN

The American Academy of Pediatrics recommends maintaining an oxygen saturation of >90%.[15]

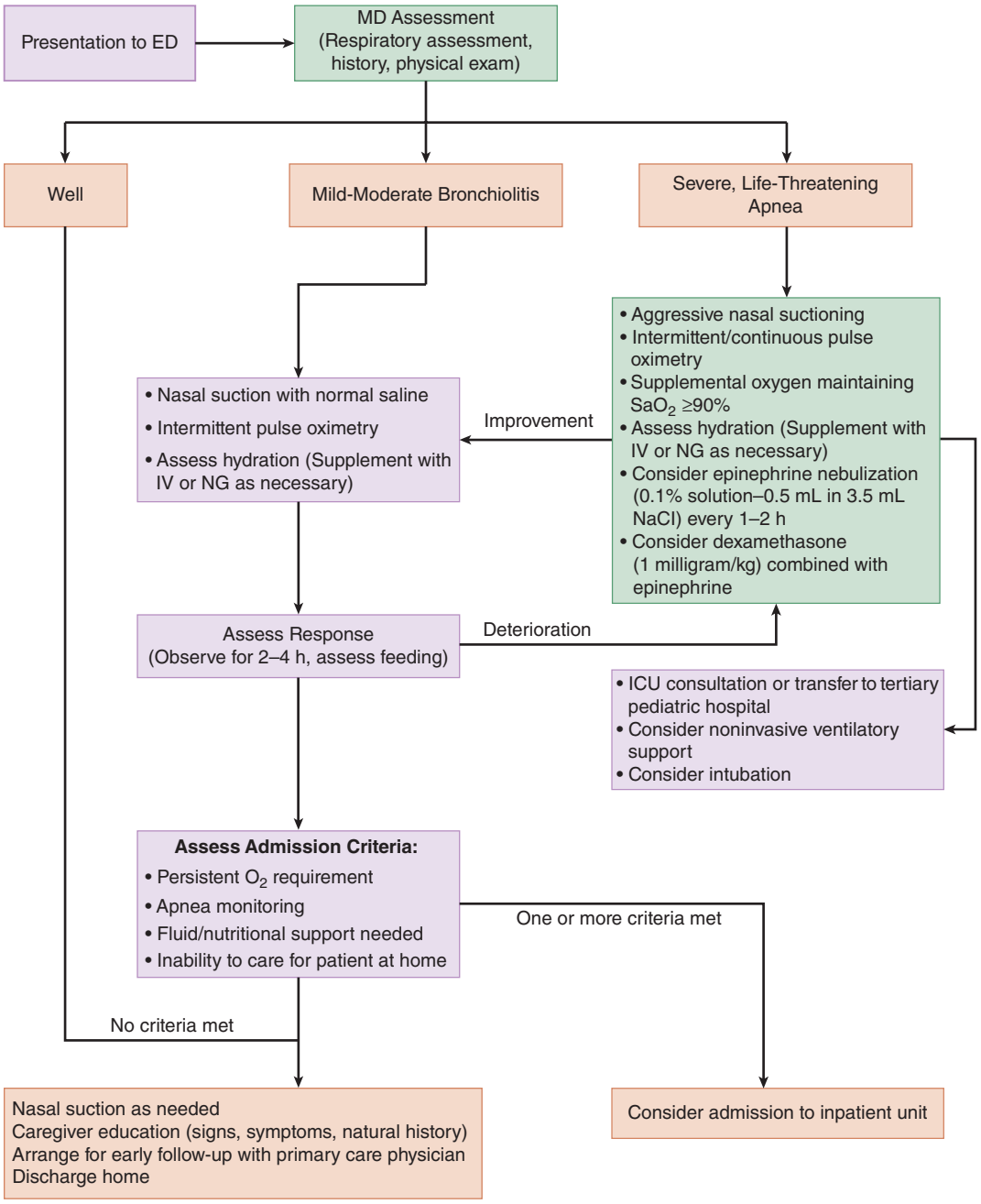

FIGURE 127-2. ED algorithm for the treatment and disposition of a patient with bronchiolitis. ICU = intensive care unit; MD = physician; NG = nasogastric.

BRONCHODILATORS

No benefits have been shown on oxygen saturation, hospitalization rates, or duration of hospitalization by using β_2-agonists (including salbutamol/albuterol, ipratropium bromide, and terbutaline),[23,24] and they should not be given routinely.

Inhaled epinephrine does not reduce rates of admission, although some studies suggest that it may provide temporary clinical improvement when used in the ED. This therapy should not be used routinely but may have a role to play in the management of children with severe or acutely deteriorating bronchiolitis.[15,24,25]

CORTICOSTEROIDS

The combined use of dexamethasone and epinephrine decreased admission rates in a large, multicenter, Canadian study. However, a recent meta-analysis incorporating these data with other studies on the topic did not confirm this association. Therefore, combination therapy should not be used routinely for the treatment of children with bronchiolitis.[24,26,27]

There is no literature to support the use of systemic or inhaled corticosteroids alone in the treatment of bronchiolitis, and most guidelines advise against it.[28]

NEBULIZED HYPERTONIC SALINE

The data on the effect of hypertonic saline in bronchiolitis are mixed. Hypertonic saline may improve mucociliary clearance by loosening mucus plugs through osmotic draw of fluid from submucosal and adventitial spaces. The preponderance of evidence suggests no meaningful clinical benefit from nebulized hypertonic saline (3% or 7%) in the ED, and the 2014 American Academy of Pediatrics clinical practice guidelines recommend against its routine use.

VENTILATORY SUPPORT

Noninvasive ventilation measures, such as high-flow nasal cannula oxygenation, nasal continuous positive airway pressure, and bilevel positive airway pressure, may help avoid or delay the need for endotracheal intubation and mechanical ventilation.[29-31] While continuous positive airway pressure is a more effective respiratory support tool, high-flow nasal cannula is better tolerated by children and may be sufficient for patients who require support but do not have evidence of impending respiratory failure. When other measures do not work, endotracheal intubation with mechanical ventilation may be necessary.

DISPOSITION AND FOLLOW-UP

The majority of children with bronchiolitis can be discharged from the ED. Educate caregivers regarding the signs and symptoms of increasing respiratory distress and dehydration and tell them to bring the child for immediate reevaluation if they develop respiratory distress or dehydration. Demonstrate proper nasal suctioning techniques to caregivers. Counsel parents that symptoms may persist for up to 3 weeks to help avoid unnecessary ED returns for persistent mild symptoms.[16]

Factors that should prompt consideration for admission are listed in Table 127-4. Infants with 1 or more of these risk factors are at risk of requiring more significant interventions and should at least be observed for a period of time in the ED. Alternatively, infants without any risk factors can be safely discharged home, assuming that there are no social concerns and that adequate follow-up can be arranged. Factors such as sex, race, duration of symptoms, parental history of asthma, and prior ED visits are not related to safety for discharge.[32]

ASTHMA

Asthma is a chronic disease characterized by episodic and reversible airflow obstruction due to bronchial smooth muscle hyperreactivity and inflammation that is responsive to bronchodilator and corticosteroid treatments.[9,10,33]

More than 95% of children age 2 to 18 years presenting to the ED with asthma exacerbations exhibit wheezing, shortness of breath, cough, and/or dyspnea secondary to decreased expiratory airflow.[34] Milder cases of acute asthma exacerbations may present with only wheezing or mild dyspnea, whereas severe exacerbations present with dyspnea at rest, inability to speak, and marked increased work of breathing.[10] Severe exacerbations may progress to status asthmaticus and respiratory failure, which may be lifethreatening.[35,36]

PATHOPHYSIOLOGY

The three pathophysiologic processes of asthma are inflammation, bronchospasm, and airway obstruction. The inflammatory cascade either directly leads to or contributes to the severity of bronchospasm and airway obstruction. Multiple inflammatory pathways are activated in asthma and involve a complex interplay of cytokines, chemokines, immunoglobulin E, lymphocytes, mast cells, and eosinophils.

Bronchospasm results in decreased airflow during exacerbations and may be precipitated by triggers such as infection, irritants, or allergens. Irritant-induced bronchospasm may involve non–immunoglobulin E–dependent pathways (e.g., aspirin, NSAIDs), and may also involve as yet undefined mechanisms (e.g., exercise, emotional stress). Allergens precipitate bronchospasm as a result of immunoglobulin E–dependent release of histamine, leukotrienes, and other mediators from mast cells.

The third primary pathophysiologic process in acute asthma is airway obstruction. Inflammation causes airway mucosal edema and contributes to airway obstruction indirectly as a result of mucus hypersecretion, formation of mucus plugs, and structural airway changes. These changes, in a process termed *airway remodeling,* include hyperplasia and hypertrophy of airway smooth muscle, subepithelial fibrosis, and thickening of the sub-basement membrane. As a result of airway remodeling, some asthmatic patients may experience progressive loss of lung function that may not be reversible.[10]

CLINICAL FEATURES AND INITIAL ASSESSMENT

Obtain a thorough, detailed history to determine the progression of illness and ability for ongoing care at home and for disposition planning. Identify possible triggers, such as viral illnesses, pneumonia, or allergens[37]; progression of symptoms at home; and home treatments. Ask about past ED visits, hospitalizations, prior intensive care admission, and any invasive and noninvasive airway support. Obtain any family history of asthma or eczema.

Assess airway and breathing immediately; the degree of respiratory distress and impaired ventilation dictate the tempo of the evaluation and intensity of interventions. Serial assessments are key to ED management because changes in clinical status and response to treatment are usually more relevant to outcome and need for admission than the level of severity at presentation.

Physical signs are useful in determining the severity of airway obstruction. Mental status changes such as agitation may indicate hypoxemia, whereas somnolence may indicate hypercarbia. Respiratory rate (Table 127-2) and air entry indicate the adequacy of gas exchange and ventilation.

Determine oxygen saturation at presentation. Perform continuous pulse oximetry for patients who are hypoxemic or severely ill. Intermittent oximetry should be done in mild to moderate exacerbations or once the patient has improved and does not require bronchodilators more frequently than hourly. Provide supplemental oxygen for oxygen saturation <92%, and maintain at 93% to 98%, because very high saturations of oxygen may decrease minute ventilation and result in elevations of pulmonary end tidal carbon dioxide ($ETCO_2$).[38,39]

Oxygen and β_2-agonists are pulmonary vasodilators and may contribute to ventilation–perfusion mismatch by augmenting perfusion of underventilated lung units. This phenomenon may worsen hypoxemia, but generally resolves by 1 to 2 hours as pulmonary autoregulation corrects mismatch. If oxygen saturation remains <92% after initial treatment, consider worsening asthma, pneumothorax, or pneumonia.[40-42]

Consider $ETCO_2$ monitoring in all children with severe or lifethreatening asthma exacerbations, because a rising $ETCO_2$ is a marker of fatigue or worsening of the disease.[43,44] $PaCO_2$ should be lower than normal in children with asthma exacerbations due to increased minute ventilation (normal range, 35 to 40 mm Hg).[45,46]

Accessory muscle use reflects the work of breathing necessary to overcome auto–positive end-expiratory pressure and airway resistance.[47,48] Subcostal and intercostal muscle use occurs with mild to moderate obstruction, whereas neck muscle use suggests severe obstruction. Wheezing is pathognomonic for airway obstruction and typically occurs more during expiration than during inspiration; **however, the quiet chest is an ominous sign of severely compromised ventilation and indicates insufficient airflow to generate wheezing**.

The severity of an acute asthma exacerbation may be assessed based on signs and symptoms, and classified as **mild, moderate, severe, or imminent respiratory failure**. Asthma scoring systems are a means to assess severity and response to treatment and to communicate among providers. The Pediatric Respiratory Assessment Measure (**Figure 127-3**) has been validated in patients 2 to 17 years old with asthma and is responsive to changes in a patient's respiratory status.[49-51]

DIAGNOSIS

There are three essential diagnostic questions for the child with signs and symptoms suggestive of an acute asthma exacerbation: (1) Does this patient have asthma? (2) What is the severity of airway exacerbation? (3) Is there a treatable trigger for this exacerbation?

For children >2 years old who do not have a history of health professional–diagnosed asthma, a provisional diagnosis of asthma is made when there are signs and symptoms of wheezing, shortness of breath,

Pediatric Respiratory Assessment Measure (PRAM)

SIGNS/SCORING	0	1	2	3	PATIENT'S SCORE
Suprasternal retractions	Absent		Present		(max 2)
Scalene muscle contraction	Absent		Present		(max 2)
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal	(max 3)
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry	(max 3)
O_2 saturation in room air	≥95%	92%–94%	<92%		(max 2)
*If asymmetric findings between the right and left lungs, the most severe is rated. **PRAM SCORE TOTAL**					**(MAX 12)**

PRAM Score 0–3 **MILD** Asthma
PRAM Score 4–7 **MODERATE** Asthma
PRAM Score 8–12 **SEVERE** Asthma

IMPENDING RESPIRATORY FAILURE is based on clinical presentation

[1]Chalut DS, Ducharme FM, Davis GM: The Preschool Respiratory Assessment Measure (PRAM): A responsive index of acute asthma severity. J Pediatr 137: 762, 2000.

[2]Ducharme F, Chalut D, Plotnick L, et al: The Pediatric Respiratory Assessment Measure: A valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr 152: 467, 2008.

FIGURE 127-3. The Pediatric Respiratory Assessment Measure (PRAM).

cough, dyspnea, diminished air entry, or retractions **and** demonstration of reversibility with β_2-agonist bronchodilators (e.g., salbutamol/albuterol).[33] Children 1 to 2 years old with viral-induced wheeze may be treated as having either asthma or bronchiolitis.[51] Children <1 year old with first episode of wheeze should be treated as having bronchiolitis.

Although spirometry may be a useful adjunct to clinical assessment, spirometry cannot be performed in children <6 years old and is challenging to perform in severe respiratory distress.

Atelectasis is common in children with acute asthma exacerbations, whereas bacterial pneumonia is much less common. A chest radiograph for a child with acute asthma and fever is likely to demonstrate atelectasis and is therefore not recommended unless additional features are present, as presented in **Table 127-5**.[52,53] Point-of-care US is an alternative to chest radiographs in the management of children with respiratory illnesses. Point-of-care US is more sensitive than chest radiographs in distinguishing a viral illness from bacterial pneumonia and for detecting pneumothorax, with the added benefits of bedside availability and easy repeatability without any radiation exposure.[54-57] As in bronchiolitis, point-of-care US findings in children with asthma may indicate more serious disease.[58]

TREATMENT

Acute asthma exacerbations often require multiple medications (**Table 127-6**), review of current medication use, and an individualized discharge plan. The Pediatric Respiratory Assessment Measure helps identify the severity of exacerbations and may be incorporated into treatment algorithms such as the Ontario Lung Association Pediatric Asthma Care Pathway (**Figure 127-4**). Dosages of drugs for acute exacerbations are listed in **Table 127-7**, and treatment recommendations for acute exacerbations by severity are provided in **Table 127-8**.

TABLE 127-5 Indications for Imaging in Acute Asthma

- Fever not explained by apparent viral illness (rule out pneumonia)
- Chest pain, cardiovascular instability, or absent breath sounds (rule out pneumothorax)
- Poor response to treatment (consider congestive heart failure or foreign body aspiration)
- Life-threatening exacerbation (consider alternate diagnoses, comorbidities)

SHORT-ACTING β_2-RECEPTOR AGONISTS

β_2-Agonists are the mainstay of acute asthma therapy. They act specifically on β_2-receptors to relax bronchial wall smooth muscles and are the most effective agents for relieving acute bronchospasm. **Salbutamol/albuterol** is the most widely available and used β_2-agonist. After inhalation, the onset of action is within 3 to 5 minutes, the peak effect is seen within 30 to 120 minutes, and the duration of action is 2 to 5 hours.[59]

Levosalbutamol (levalbuterol), the R-enantiomer of salbutamol, is not any more effective or safer than salbutamol and is much more expensive.[60]

β_2-Agonists are frequently delivered by metered-dose inhalers **with an age-appropriate valved holding chamber or via wet nebulization**.

TABLE 127-6 Treatment for Acute Asthma Exacerbations

Treatment	Comments
Short-acting β_2-agonist bronchodilators	For all patients with acute asthma exacerbations in the ED. **Add ipratropium bromide for severe or life-threatening exacerbations.**
Systemic steroids	For all patients with moderate or worse exacerbations as early as possible in course. May be given orally or parenterally.
Oxygen	In patients with arterial oxygen saturation ≤92%.
Magnesium sulfate	IV or nebulized smooth muscle–relaxing bronchodilator for severe exacerbations not responding to initial therapy.
Inhaled corticosteroids	No role in acute ED management, but prescribe inhaled corticosteroids for home use.

Indications to start Paediatric Asthma Clinical Pathway
• Age 1-17 years with wheeze and/or cough
AND
• asthma diagnosis and/or past history of wheeze

Physician assessment required prior to starting on clinical pathway if:
• any active chronic condition other than asthma OR
• prior serious adverse reaction to albuterol/salbutamol, ipratropium bromide, or oral corticosteriods OR
• active chickenpox or suspected incubation of chickenpox OR
• heart rate greater than or equal to 200 beats/min

****PRAM 0 - 3 (Mild)**
***FEV_1 greater than 70% of predicted or personal best, if known

- **MD** to assess within 60 min
- Albuterol/salbutamol now and q 60 min prn (via MDI† + spacer)
- Vital Signs + PRAM q 60 min

****PRAM 4 - 7 (Moderate)**
***FEV_1 50 -70% of predicted or personal best, if known

- **MD** to assess within 30 min
- Administer oxygen to keep $Sp0_2$ greater than or equal to 92%
- Albuterol/salbutamol now and q 30 - 60 min prn (via MDI† and spacer)
- **Give oral corticosteroid AS SOON AS POSSIBLE** after 1st albuterol/salbutamol dose (within 60 min of triage)
- Vital Signs + PRAM q 30 - 60 min if not improving (PRAM unchanged or less than 3 point improvement), consider: ipratropium bromide

****PRAM 8 - 12 (Severe)**
***FEV_1 less than 50% of predicted or personal best, if known

- **MD** to assess within 15 min
- Administer oxygen to keep $Sp0_2$ greater than or equal to 92%
- Albuterol/salbutamol + ipratropium NOW, + q 20 min x 3 doses (via MDI† + spacer or nebulizer), then q 20-60 min prn
- **Give systemic corticosteroid AS SOON AS POSSIBLE** after 1st albuterol/salbutamol/ipratropium dose (within 20 min of triage)
- Vital Signs + PRAM q 20 - 60 min
- Consider IV access and blood gases

Impending Respiratory Failure
lethargy, cyanosis, decreasing respiratory effort, and/or rising pCO_2

- **MD** to assess STAT and remain in attendance until patient stabilized
- Administer 100% oxygen
- Support ventilation if required (bag & mask); do not over-ventilate as this will increase air trapping
- Continuous cardiopulmonary monitoring
- Continuous nebulized albuterol/salbutamoll with ipratropium
- **Systemic corticosteroid AS SOON AS POSSIBLE** after 1st albuterol/salbutamol/ipratropium dose:
- Obtain IV access

MD to consider:
- IV magnesium sulfate (caution: can cause low BP)
- IV fluids
- CXR + blood gas measurement
- Contact ICU or Regional Tertiary Centre regarding management & transport

CritiCall Ontario
1-800-668-HELP (4357)

Complete all of above within 60 min of triage.

Reassess Vital Signs + PRAM q 60 min

If PRAM greater than or equal to 4 or ***FEV_1 less than 70% of predicted:
- MD to reassess and move to top of '**Moderate**' pathway

If PRAM remains less than or equal to 3 or ***FEV_1 greater than or equal to 70% of predicted:
- MD to consider discharge
- Provide asthma teaching
- Provide discharge instructions

Reassess Vital Signs + PRAM q 30-60 min

If at any time PRAM is greater than or equal to 8 or ***FEV_1 is less than 50% of predicted, or if PRAM is unchanged or has improved less than 3 points:
- MD to reassess and move to top of '**Severe**' pathway

If 6-8 hrs post corticosteroid, PRAM is greater than or equal to 4 or ***FEV_1 is less than 70% of predicted:
- MD to reassess and consider admission

If PRAM less than or equal to 3 or ***FEV_1 greater than or equal to 70% of predicted:
- MD to consider discharge; provide asthma teaching and discharge instructions

Reassess Vital Signs + PRAM q 20-60 min

If poor response (PRAM unchanged or less than 3 point improvement) or signs of impending respiratory failure at any time:
- MD to reassess STAT and move to top of '**Impending Respiratory Failure**' pathway

If 4 hrs post corticosteroid, PRAM is greater than or equal to 4 or ***FEV_1 is less than 70% of predicted:
- MD to reassess and consider admission

If PRAM improving, move to 'Moderate' pathway

†Inhaled medication delivery by metered dose inhaler (MDI) and age appropriate valved spacer is preferred unless continuous oxygen is required. Small volume nebulizer is an acceptable alternate.
**See below for PRAM scoring.
***FEV_1 (or as second choice, PEF) should only be used in children aged 6 years and older with demonstrated reproducibility within 10% and when performed by health care personnel trained in spirometry.
NOTE: † FEV_1 results may be discordant with the severity level indicated by the PRAM (as clinical signs and lung function are different parameters); in case of discordance, the physician is invited to use his/her best judgment to decide which parameter to use to manage the child. **Do not delay treatment to obtain FEV_1 and/or peak flow.**

Medication Guidelines

BRONCHODILATORS

Metered Dose Inhaler (MDI)† via age appropriate spacer, allow 30 sec between puffs

albuterol/salbutamol salbutamol (100 mcg/puff)
1 - 3 yrs: 4 puffs/dose 4 - 6 yrs: 6 puffs/dose
7 years and older: 8 puffs/dose

ipratropium bromide (20 mcg/puff)
3 puffs/dose, alternate each puff with albuterol/salbutamol

Wet Nebulization† driven by oxygen flow of 6-8 L/min via well-fitting mask

albuterol/salbutamol (5mg/mL solution or unit dose nebule)
less than 10 kg: dose = 1.25 mg; use 1.25 mg nebule OR 0.25 mL of 5 mg/mL sol'n in 3 mL NaCl
10 to 20 kg: dose = 2.5 mg; use 2.5 mg nebule OR 0.5 mL of 5mg/mL sol'n in 3 mL NaCl
greater than 20 kg: dose = 5 mg; use 2 x 2.5 mg nebule OR 5 mg nebule OR 1 mL of 5 mg/mL sol'n in 3 mL NaCl

ipratropium bromide
all patients: 250 mcg, mixed with albuterol/salbutamol

CORTICOSTEROIDS

Oral route
prednisone/prednisolone 2 mg/kg x 1 (max 50 mg/dose)

Parenteral route
methylprednisolone 1 mg/kg/dose IV or IM (max 125 mg/dose) x 1; could be repeated q 6h

MAGNESIUM SULFATE

magnesium sulfate (requires cardiorespiratory monitoring and frequent BP checks)
50 mg/kg/dose IV x 1 (max 2 g/dose), give over 20-30 min

†Inhaled medication delivery by MDI and age-appropriate valved spacer is preferred unless continuous oxygen is required. Small volume nebulizer is an acceptable alternate.

Disclaimer:
This Clinical Pathway is not intended to set the standard of care applicable in any particular clinical situation. It is merely prepared as a guide to assist physicians, nurses, respiratory therapists and other healthcare providers, in deciding on the appropriate care required for a particular patient. At all times, physicians, nurses, respiratory therapists and other healthcare providers must exercise their independent clinical judgment, based on their knowledge, training and experience, taking into account the specific facts and circumstances of each patient, when deciding on the appropriate course of investigation and/or treatment to recommend in a particular clinical situation. Any reference throughout the document to specific pharmaceutical products as examples does not imply endorsement of any of these products.

The views expressed are the views of the authors and do not necessarily reflect those of the Government of Ontario.

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This clinical pathway was developed with input from and endorsed by:

PRAM scoring table

O_2 Saturation	≥ 95%	0
	92-94%	1
	< 92%	2
Suprasternal retraction	Absent	0
	Present	2
Scalene muscle contraction	Absent	0
	Present	2
Air entry*	Normal	0
	↓ at the base	1
	↓ at the apex and the base	2
	Minimal or absent	3
Wheezing§	Absent	0
	Expiratory only	1
	Inspiratory (± expiratory)	2
	Audible without stethoscope or silent chest (minimal or no air entry)	3
	PRAM score : (max. 12)	

Score	0-3	4-7	8-12
Severity	Mild	Moderate	Severe

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* In case of asymmetry, the most severely affected (apex-base) lung field (right or left, anterior or posterior) will determine the rating of the criterion.
§ In case of asymmetry, the two most severely affected auscultation zones, irrespective of their location (RUL, RML, RLL, LUL, LLL), will determine the rating of the criterion.

FIGURE 127-4. The Ontario Lung Association Pediatric Asthma Care Pathway. CXR = chest x-ray; FEV_1 = forced expiratory volume in 1 second; ICU = intensive care unit; MD = physician; MDI = metered-dose inhaler; PEF = peak expiratory flow; PRAM = Pediatric Respiratory Assessment Measure; q = every. [Reproduced with permission from The Ontario Lung Association. In: *Paediatric Emergency Department Asthma Care Pathway: Information Package March 2014*. The Lung Association Ontario; 2014:4. Available at: http://machealth.ca/programs/paediatric-emergency-department-asthma-care-pathway/m/mediagallery/1921/download.aspx.]

TABLE 127-7 Dosages of Medications for Asthma Exacerbations

Medication	American Pediatric Dosages[59]	Alternative Pediatric Dosages
Bronchodilators		
Salbutamol/albuterol (aerosol or nebulized)	MDI (90 micrograms/puff); *delivered via valved holding chamber*: ≤1 y: 2 puffs/dose 1–3 y: 4 puffs/dose ≥4 y: 8 puffs/dose Nebulization (unit dose nebule or 5 milligrams/mL solution): 0.15–0.3 milligram/kg/dose (minimum 2.5 milligrams) IV: *Not available* PO: *Not recommended*	MDI (100 micrograms/puff); *delivered via valved holding chamber*: ≤1 y: 2 puffs/dose 1–3 y: 4 puffs/dose 4–6 y: 6 puffs/dose ≥7 y: 8 puffs/dose Nebulization (unit dose nebule or 5 milligrams/mL solution): <10 kg: 1.25-milligram nebule or 0.25 mL of 5-milligram/mL solution* 10–20 kg: 2.5-milligram nebule or 0.5 mL of 5-milligram/mL solution* >20 kg: 5-milligram nebule or 1 mL of 5-milligram/mL solution* IV: 0.5–3 milligrams/kg/h continuous infusion (maximum 15 milligrams/h) PO: *Not recommended*
Ipratropium bromide (aerosol or nebulized)	MDI (20 micrograms/puff); *delivered via valved holding chamber:* 4–8 puffs/dose PRN, alternated with salbutamol Nebulization: 250–500 micrograms for all patients, mixed with salbutamol	MDI (20 micrograms/puff); *delivered via valved holding chamber:* 3 puffs/dose for all patients, alternated with salbutamol Nebulization: 250 micrograms for all patients, mixed with salbutamol
Systemic corticosteroids		
Prednisone (PO)	1–2 milligrams/kg/dose (maximum 60 milligrams) for 3–10 d	2 milligrams/kg (maximum 50 milligrams) in ED, then 1 milligram/kg/d for 4 d
Methylprednisolone (IV, IM)	2 milligrams/kg/dose load, then 0.5–1 milligram/kg/dose every 6 h	1 milligram/kg/dose (maximum 125 milligrams/dose), repeated every 6 h or change to oral regimen
Dexamethasone (PO, IV, IM)	0.6 milligram/kg/dose (maximum 16 milligrams) for 1–2 d	Multiple dosing regimens: 0.6 milligram/kg/d for 1–2 d 0.3 milligram/kg/d for 3–5 d
Other medications		
Magnesium sulfate (IV)	25–75 milligrams/kg/dose (maximum 2 grams) × 1	50 milligrams/kg/dose × 1 (*monitor blood pressure*)
Ketamine (IV)†	1–2 milligrams/kg/dose × 1	2 milligrams/kg/dose × 1 (*may alleviate need for intubation, given as induction agent for intubation*)

*Mixed in 3 mL of normal saline solution.

†Consider only if standard therapies have failed in order to prevent intubation.

Abbreviations: MDI = metered-dose inhaler; PRN = as needed.

Metered-dose inhalers are as effective as nebulizers for mild to moderate exacerbations and decrease length of ED stay while causing fewer side effects such as nausea, tachycardia, and tremor.[61] A primarily metered-dose inhaler–based algorithm may also confer benefits for infection control and may be more cost effective than a nebulizer-based algorithm.[62]

There is no therapeutic advantage of β_2-agonist administration by the IV route versus the inhaled route in the child who is ventilating reasonably well. However, for the patient with significantly diminished air entry, the IV route may allow for critical initial bronchodilation that permits subsequent inhaled medications to reach distal airways.[63,64]

TABLE 127-8 Summary of Treatment Recommendations by Severity for Acute Asthma Exacerbations

	β_2-Agonist	Systemic Corticosteroid	Anticholinergic
Mild	+	–	–
Moderate	++	+	–
Severe*	+++	+	+

*Severe patients not responding to full therapy should be considered for IV magnesium and/or other adjuvant therapies.

Oral albuterol is not recommended due to the delayed onset and prominent tachycardia, tremulousness, and behavioral changes accompanying this form.

Epinephrine has α- and β-agonist properties that facilitate vasoconstriction and rapid resolution of mucosal edema and can be an effective emergency treatment for asthma. An Epi-Pen may be used if more readily available than β-selective medication. However, because it is not as selective for lower airways as β_2-agonists, epinephrine causes more short-term side effects.

CORTICOSTEROIDS

Systemic corticosteroids inhibit the inflammatory cascade and enhance β-receptor expression, sensitivity, and function. They provide rapid beneficial physiologic effects, usually within 4 hours, which reduces both the need for hospitalization and the likelihood of relapse. **All patients presenting with a moderate or severe exacerbation should be treated immediately with systemic corticosteroids.** Early administration of corticosteroids by a triage nurse can decrease ED length of stay and admission rates.[65-67]

Oral corticosteroids should be given within the first hour of ED presentation and are usually followed by a short regimen upon discharge. Different regimens have been described in the literature and seem to be equivalent in efficacy and rates of adverse events (Table 127-7).[68,69]

Historically, prednisone was the popular agent, with a total treatment course of 5 days. However, prednisolone suspension is more palatable and therefore has better compliance.[70] Dexamethasone is a less expensive oral corticosteroid that has gained popularity following a series of clinical trials showing that a single dose or a 2-day course is therapeutically equivalent to a 5-day course of prednisolone.[71-73]

When the patient is severely ill or not responding to therapy, IV methylprednisolone may be given every 6 hours.

Inhaled corticosteroids have no role in the acute ED management, but are an essential part of maintenance therapy and should be prescribed to all patients with persistent asthma at discharge (see "Disposition and Follow-Up" section for further discussion).[74]

ANTICHOLINERGIC AGENTS

Anticholinergic agents such as ipratropium bromide relieve bronchiole obstruction by blocking muscarinic receptors in the bronchiole wall, leading to bronchodilation and decreased mucus secretion. However, they are not as potent or rapid as β_2-agonists. When used in combination with short-acting β_2-agonists, anticholinergics decrease hospitalization rates versus using short-acting β_2-agonists alone.[75,76] Addition of multiple high doses of ipratropium (0.5 milligram) to nebulized albuterol treatments has additive benefit and results in reduced hospitalization in children with severe exacerbations.[67]

MAGNESIUM

IV magnesium sulfate acts as a bronchodilator by inhibiting smooth muscle contraction[77,78] and may reduce the need for hospitalization or intensive care admission.[78-80] Nebulized magnesium is not effective.[81-86]

KETAMINE

Ketamine is a dissociative sedative agent that is commonly used for both procedural sedation and as an induction agent for endotracheal intubation. The sympathomimetic properties of ketamine and its bronchodilation effect make it the **ideal induction agent** for the patient with respiratory failure due to asthma. While case reports describe that ketamine alleviated the need to intubate when given as part of induction in children,[87] several randomized controlled trials demonstrated a lack of benefit.[88-91]

HELIOX

Heliox, a mixture of helium and oxygen, is less dense than air, leading to laminar instead of turbulent airflow in obstructed airways.[92,93] It may be a better vehicle for medication delivery and improves gas exchange. It has no direct pharmacologic or biologic effect and has an extremely low risk profile. The evidence for routine heliox use is conflicted, and the equipment required to use it makes this treatment difficult in the ED setting.

METHYLXANTHINES

Methylxanthines (theophylline and aminophylline) have been replaced by safer and more effective short-acting β_2-agonists. Adverse effects include tachycardia, vomiting, and CNS excitation, including seizures.[94,95] Current treatment guidelines recommend against its use primarily due to its side effect profile and narrow therapeutic window.[96,97]

TREATMENT OF NEAR-FATAL ASTHMA

Patients with acute severe asthma who do not respond adequately to maximal medical therapy and who continue to manifest severe airway obstruction and hyperinflation are at risk for fatal asthma. One third of pediatric deaths from asthma are in children who previously had only mild asthma. Clinical signs of this progression include worsening hypoxemia, increasing respiratory rate, diaphoresis, inability to speak, somnolence, and fatigue. The decision to undertake advanced airway management for near-fatal asthma is based on clinical judgment.

One must weigh the need for intubation against the potential adverse outcomes, including worsening bronchospasm, laryngospasm, pneumothorax, ventilator-associated pneumonia, and hemodynamic instability.[98,99]

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Bilevel positive airway pressure is the preferred noninvasive modality in the care of the patient with severe, nonresponsive asthma. It delivers different pressures during inspiration and expiration to decrease the work of breathing, stent the airways open, and improve gas exchange. It also appears to have a bronchodilator effect.[100] The largest study of bilevel positive airway pressure use in children found that 88% tolerated the intervention and demonstrated clinically significant improvements in respiratory rate and oxygenation without adverse effects.[101] Bilevel positive airway pressure may be effective in preventing the need for endotracheal intubation even if applied for only several hours.

Use of a well-fitting facemask and close attention to patient comfort are essential. Most patients tolerate bilevel positive airway pressure well, but sedation is frequently required with low doses of benzodiazepines (0.05 to 0.1 milligram/kg of midazolam or lorazepam) or ketamine (0.5 to 1 milligram/kg followed by 0.25 milligram/kg/h). Reasonable initial applied bilevel positive airway pressures for severe asthma are an inspiratory positive airway pressure of 12 cm H_2O and expiratory positive airway pressure of 6 cm H_2O, with ranges of 12 to 18 cm H_2O and 6 to 12 cm H_2O, respectively.[100-102] Aerosolized medications can be administered through the bilevel positive airway pressure airway circuit.

ENDOTRACHEAL INTUBATION AND ASSISTED VENTILATION

An extremely small number of children will require intubation despite aggressive management. It is best to try to avoid the need to intubate due to challenges in ventilatory management and potential for adverse effects due to air trapping, and noninvasive ventilation strategies such as bilevel positive airway pressure may prevent the need for intubation. **Select the largest appropriate cuffed endotracheal tube**. Preoxygenate with 100% oxygen. If reasonable, give a normal saline fluid bolus (20 mL/kg) prior to intubation to minimize hypotension.

Drugs for rapid-sequence intubation in severe asthma are listed in **Table 127-9** and should be administered with the patient sitting up or

TABLE 127-9 Drugs for Rapid-Sequence Intubation of a Child With Near-Fatal Asthma

Drug	Dose
Intubation Induction	
Ketamine*	2 milligrams/kg
Short-term paralysis during intubation (*Use caution with paralysis*)	
Succinylcholine	<10 kg: 2 milligrams/kg; >10 kg: 1 milligram/kg
or	
Rocuronium	1 milligram/kg
Postintubation paralysis†	
Vecuronium	0.1 milligram/kg/h
Postintubation sedation	
Ketamine†	2–3 milligrams/kg/h
or	
Fentanyl	1–2 micrograms/kg bolus then 1 microgram/kg/h
and	
Midazolam	0.1 milligram/kg/h

*The use of ketamine for sedation may also obviate the need for paralysis.

†Patient–ventilator dyssynchrony may necessitate postintubation paralysis.

TABLE 127-10 Initial Ventilator Settings for the Intubated Pediatric Patient With Asthma

Ventilator Parameter	Setting
Mode	Synchronized intermittent mandatory ventilation/ pressure-regulated volume control
Tidal volume	6–10 mL/kg
Peak pressure	45 cm H_2O
Respiratory rate	8–15/min
Inspiratory time	0.5–1.0 s
Expiratory time	4–8 s

in another comfortable position to maximize preoxygenation. **Ketamine is the preferred induction agent because it provides bronchodilation and does not directly cause hypotension**. Give it immediately before the paralytic agent. Atropine is only indicated to treat symptomatic bradycardia. For full discussion of pediatric intubation, refer to Chapter 113, "Intubation and Ventilation in Infants and Children." Once the endotracheal tube is in place, an appropriate tidal volume and a sufficiently low respiratory rate to allow for expiratory emptying and avoid hyperinflation should be provided manually.

Management of ventilation must consider key pulmonary mechanics of the disease process including hyperinflation, auto–positive end-expiratory pressure, and markedly prolonged expiratory time constants that result in failure of the airways to empty. Therefore, use low respiratory rates and tidal volumes, long expiratory times, and high flow rates (**Table 127-10**).[103,104]

The practice of controlled hypercapnic hypoventilation is a recommended ventilator strategy.[10] The aim is to minimize hyperinflation and airway pressures while providing adequate oxygenation.[105] This mode of ventilation may be key to allowing for the prolonged expiratory times necessary to minimize auto–positive end-expiratory pressure and hyperinflation. Provide adequate sedation to avoid ventilator dyssynchrony, tachypnea, and breath stacking. Ketamine, benzodiazepines, and opiates, or a combination of these, are appropriate, and paralysis is usually necessary.

DISPOSITION AND FOLLOW-UP

The decision regarding hospital admission or discharge of the child with asthma must consider both the adequacy of response to treatment and the ability of the patient and caretaker to provide necessary ongoing care. **The ED relapse rate of 7% to 15% reflects the potential uncertainty of disposition decisions**.[40,106,107] Clinical improvement so that only minimal symptoms remain is a useful guide for discharge. Most patients should be observed for at least 60 minutes after the most recent bronchodilator dose. A PRAM score of 8 or higher at 3 hours after ED presentation strongly predicts the need for admission.[108] If more aggressive therapies have failed, consider early admission.

Dischargeable patients should be prescribed an inhaled short-acting β_2-agonist on discharge from the ED. An age-appropriate valved holding chamber (e.g., AeroChamber®) must be prescribed with the metered-dose inhaler and proper instructions for inhaler technique reviewed. Patients treated with systemic corticosteroids should be prescribed an oral corticosteroid course upon discharge, unless a single-dose dexamethasone regimen (0.6 milligram/kg) was used in the ED. Inhaled corticosteroids should be prescribed at discharge for all classes of asthma severity except mild intermittent asthma.[109] (See **Table 127-11** for dosing guidelines.) In 2015, the Canadian Thoracic Society and Canadian Pediatric Society published a **joint position statement recommending the use of inhaled corticosteroids for all preschool children 1 to 5 years of age with asthma who require systemic steroids in the ED for a moderate or severe asthma exacerbation or who have persistent symptoms**. The statement recommends a 3-month trial of daily inhaled corticosteroids. The guidelines from the United Kingdom and United States also recommend consideration for initiation of inhaled corticosteroids when good reversibility is demonstrated after β_2-agonist treatment in children <5 years old with wheezing.[9,33,110,111]

Partner with the primary care physician to ensure appropriate follow-up, symptom and trigger management, monitoring of anti-inflammatory therapy, and implementation of other elements of the National Asthma Education and Prevention Program guidelines.[112]

National and international guidelines recommend treatment with long-term controller medications in all children with persistent asthma.[10] However, primary care physician adherence to these guidelines has been suboptimal. Despite published guidelines stating that inhaled steroids should be prescribed at discharge, fewer than 50% of children with persistent asthma treated by pediatric emergency physicians receive them.[109]

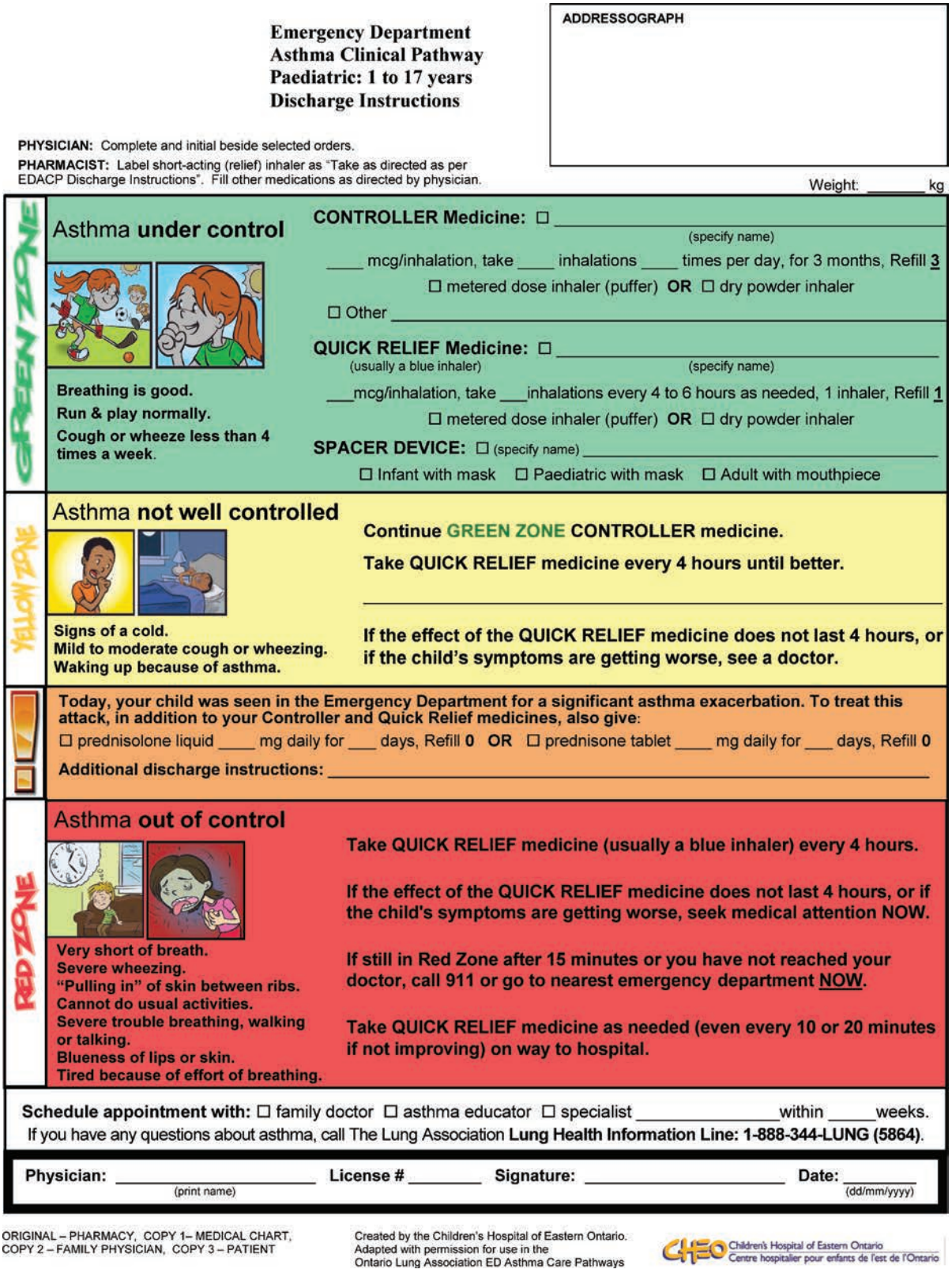
A visit to the ED is an indication of inadequate long-term asthma management and insufficient understanding of how to manage an exacerbation. The goal upon discharge should be to prevent future exacerbations requiring ED visits. A written asthma action plan focused on patient symptoms is superior to action plans based on peak flows.[113,114] The provision of a combined asthma action plan plus prescription increases patient adherence to medications and improves asthma control.[115] One of the proposed benefits of a combined plan with prescription may be the reinforcement of the medical recommendations by the family physician as well as by the pharmacists filling the prescription.[115] At the time of discharge, the physician, nurse, and/or respiratory therapist should review the appropriate use, technique, and timing of all prescribed medications and review early symptom identification and management. Provide clear plans for follow-up appointments and instructions for managing relapse or future exacerbations (**Figure 127-5**).

TABLE 127-11 Recommended Dose Ranges for Inhaled Corticosteroids*

Drug	Dosage	Alternate Formulations
Budesonide (Pulmicort®) dry powder inhaler (90 or 180 micrograms/spray)	180–360 micrograms twice daily	
Budesonide nebulizer suspension (Pulmicort Respules®) (0.25, 0.5, 1 milligram/2 mL units)	0.5–1 milligram divided once or twice daily	
Fluticasone MDI (Flovent®) (44, 120, or 220 micrograms/spray)	88–440 micrograms twice daily For children <5 y: 1 puff of 120 micrograms twice daily	50, 125, or 250 micrograms/spray MDI: 50–250 micrograms twice daily
Beclomethasone (QVAR®) MDI (40, 80 micrograms/spray)	40–80 micrograms twice daily	50, 100 micrograms/spray MDI: 50–100 micrograms twice daily
Ciclesonide MDI (Alvesco®) (80, 160 micrograms/spray)	80–320 micrograms twice daily	100, 200 micrograms/spray MDI: 100 micrograms once daily to 200 micrograms twice daily

*Prescribers should use the lowest effective doses to prevent side effects including adrenal suppression.

Abbreviation: MDI = metered-dose inhaler.



Emergency Department
Asthma Clinical Pathway
Paediatric: 1 to 17 years
Discharge Instructions

ADDRESSOGRAPH

PHYSICIAN: Complete and initial beside selected orders.
PHARMACIST: Label short-acting (relief) inhaler as "Take as directed as per EDACP Discharge Instructions". Fill other medications as directed by physician.

Weight: _____ kg

GREEN ZONE

Asthma **under control**

Breathing is good.
Run & play normally.
Cough or wheeze less than 4 times a week.

CONTROLLER Medicine: ☐ _____
(specify name)
____ mcg/inhalation, take ____ inhalations ____ times per day, for 3 months, Refill 3
☐ metered dose inhaler (puffer) **OR** ☐ dry powder inhaler
☐ Other _____

QUICK RELIEF Medicine: ☐ _____
(usually a blue inhaler) (specify name)
___mcg/inhalation, take ___inhalations every 4 to 6 hours as needed, 1 inhaler, Refill 1
☐ metered dose inhaler (puffer) **OR** ☐ dry powder inhaler

SPACER DEVICE: ☐ (specify name) _____
☐ Infant with mask ☐ Paediatric with mask ☐ Adult with mouthpiece

YELLOW ZONE

Asthma **not well controlled**

Signs of a cold.
Mild to moderate cough or wheezing.
Waking up because of asthma.

Continue GREEN ZONE CONTROLLER medicine.
Take QUICK RELIEF medicine every 4 hours until better.

If the effect of the QUICK RELIEF medicine does not last 4 hours, or if the child's symptoms are getting worse, see a doctor.

Today, your child was seen in the Emergency Department for a significant asthma exacerbation. To treat this attack, in addition to your Controller and Quick Relief medicines, also give:
☐ prednisolone liquid ____ mg daily for ___ days, Refill **0** **OR** ☐ prednisone tablet ____ mg daily for ___ days, Refill **0**
Additional discharge instructions: _____

RED ZONE

Asthma **out of control**

Very short of breath.
Severe wheezing.
"Pulling in" of skin between ribs.
Cannot do usual activities.
Severe trouble breathing, walking or talking.
Blueness of lips or skin.
Tired because of effort of breathing.

Take QUICK RELIEF medicine (usually a blue inhaler) every 4 hours.

If the effect of the QUICK RELIEF medicine does not last 4 hours, or if the child's symptoms are getting worse, seek medical attention NOW.

If still in Red Zone after 15 minutes or you have not reached your doctor, call 911 or go to nearest emergency department NOW.

Take QUICK RELIEF medicine as needed (even every 10 or 20 minutes if not improving) on way to hospital.

Schedule appointment with: ☐ family doctor ☐ asthma educator ☐ specialist _____ within _____ weeks.
If you have any questions about asthma, call The Lung Association **Lung Health Information Line: 1-888-344-LUNG (5864).**

Physician: _____ **License #** _____ **Signature:** _____ **Date:** _____
(print name) (dd/mm/yyyy)

ORIGINAL – PHARMACY, COPY 1– MEDICAL CHART,
COPY 2 – FAMILY PHYSICIAN, COPY 3 – PATIENT

Created by the Children's Hospital of Eastern Ontario.
Adapted with permission for use in the
Ontario Lung Association ED Asthma Care Pathways

CHEO Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

FIGURE 127-5. The Ontario Lung Association Pediatric Asthma Action Plan Pathway. [Reproduced with permission from The Ontario Lung Association. In: *Paediatric Emergency Department Asthma Care Pathway: Information Package March 2014.* The Lung Association Ontario; 2014:4. Available at: http://machealth.ca/programs/paediatric-emergency-department-asthma-care-pathway/m/mediagallery/1921/download.aspx.]

ASTHMA QUIZ FOR KIDZ*

* Adapted from Canadian Respiratory Journal 2004; 11(8):541-6.

	YES	NO
1. Did you **cough, wheeze**, or **have a hard time breathing** **4 or more days** out of the **last 7 days**?	☐	☐
2. Did you wake up at night because you were coughing, or wheezing, or having a hard time breathing **1 or more times** in the **last 7 days**?	☐	☐
3. Did you use your **blue puffer** **4 or more times** in the **last 7 days**?	☐	☐
4. In the **last 7 days**, did you do less exercise or sports because it was making you cough, wheeze, or you were having a hard time breathing?	☐	☐
5. In the **last 30 days**, did you miss school or regular activities because you were coughing, wheezing, or having a hard time breathing?	☐	☐
6. In the **last 30 days**, did you go to a clinic or a hospital without an appointment because you were coughing, wheezing, or having a hard time breathing?	☐	☐

- How many times did you answer YES? _____
- If you said YES 2 or more times, your asthma is not well controlled. Talk to your mom and dad about seeing a doctor. Let your doctor be your asthma coach!

TRIGGERS

Follow these steps to avoid these common triggers:



COLDS: Most common trigger. Wash hands before touching your mouth or nose to prevent colds. Follow Yellow Zone at first sign of a cold.



SMOKE: Don't smoke! Do not allow others to smoke in your home or car. Encourage your parents to STOP smoking. Even if they smoke outside, the smoke in their clothes and hair can trigger your asthma.



AIR POLLUTION: Avoid fumes and chemicals.

Follow these steps if you have any of the following allergies:



PETS: Avoid pets with fur or feathers. If you have pets, wash them often.



DUST MITES: Wash bed sheets in hot water. Vacuum and dust often. Cover pillows and mattresses with dust mite-resistant covers.



POLLEN: Close windows during pollen season (Spring and Fall). Air conditioning helps. Avoid freshly cut grass.



MOLD: Keep bathroom and basement dry. Keep away from decomposing leaves and garden waste.

Controlling your asthma

1. **Avoid your triggers.**
2. **Know your medication and how and when to take it. Take controller medications regularly.**
3. **Follow your action plan.**
4. **After any emergency room visit, you must schedule a follow-up appointment with a doctor in the next 2 weeks.**
5. **Always have spare quick relief medication (blue inhaler) available.**

FIGURE 127-5. (*Continued*)

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 128

Pneumonia in Infants and Children

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INTRODUCTION AND EPIDEMIOLOGY

Pneumonia is an infection of the lung and lower respiratory tract. Globally, pneumonia is the leading cause of death in children less than 5 years of age, with an estimated 120 million cases annually resulting in nearly 1.3 million deaths.[1] The greatest burden of disease and mortality occurs in the developing world, and young children under the age of 2 account for 81% of pediatric deaths from pneumonia. The burden of disease in the developed world remains high, with an estimated 2 to 2.6 million cases annually, resulting in nearly a million hospitalizations and significant economic impact.[2,3] In the United States, it is the second costliest and fifth most common reason for hospitalization in children.[4] This chapter addresses the clinical and radiographic diagnosis of pneumonia, common viral and bacterial causes, evidence-based treatments, and appropriate disposition and follow-up for children seen in the ED. Special mention of unusual microbes, changing patterns of immunization and resistance, and special considerations for children with underlying medical conditions will be highlighted. Clinicians with limited pediatric experience may find the section on the use and interpretation of chest radiographs in children helpful.

PATHOPHYSIOLOGY

Pneumonia results from the invasion and overgrowth of pathogens in the lower respiratory tract.[5] Anatomic and mechanical barriers to infection include the nasal hairs and turbinates, cilia, epiglottis, and cough reflex. Humoral immunity is largely mediated by secretory immunoglobulin A. Cellular immunity and phagocytic cells (e.g., alveolar macrophages) further protect against infection. Infectious agents may be inhaled or aspirated directly into the lungs, invade respiratory epithelium and spread contiguously, or, less commonly, reach the lungs hematogenously. Viral inoculation is typically by droplet or fomite (e.g., influenza, respiratory syncytial virus), whereas bacterial pneumonia often follows colonization of the nasopharynx. Infection can result in injury or death of the respiratory epithelium, interstitial inflammation, or alveolar injury. The air space fills with exudative debris, causing atelectasis, impaired oxygenation, and ventilation-perfusion mismatch.

In most cases, the causative agent is never identified. Rapid viral detection via nasopharyngeal or oropharyngeal sampling may identify pathogens, but identification of true bacterial superinfection remains difficult.[6] Definitive microbiologic diagnosis requires invasive procedures such as bronchoalveolar lavage, lung puncture, or sampling of pleural effusion for culture or polymerase chain reaction, which are typically unavailable or impractical in the ED.

Viruses are the most commonly detected cause of pneumonia in children, accounting for over 70% of hospitalized cases in the United States.[7] Bacterial, atypical, fungal, parasitic, and opportunistic organisms can also cause disease. Infection with *Mycobacterium tuberculosis* can occur in areas where it is endemic and among children with immunodeficiency. Local and regional epidemiology, individual immunization status, and underlying health problems may influence which pathogens cause pneumonia. Causes of pneumonia vary with age. Patterns of disease can also help guide clinical decisions, as described below.[8,9]

CLINICAL FEATURES AND ETIOLOGY

The cardinal symptoms of lower respiratory tract infection include cough, fever, tachypnea, and respiratory distress. However, signs and symptoms vary by age and specific causative agents.

AGE-SPECIFIC CAUSES OF PNEUMONIA

Neonates 0 to 30 Days of Age Neonates require special consideration because they are at risk for acquired perinatal bacterial pathogens. Specific organisms include group B streptococci, gram-negative enteric bacteria such as *Klebsiella* and *Escherichia coli*, and *Listeria monocytogenes*. Late-onset neonatal pneumonia may be caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes*. Pneumonia due to maternal genital *Chlamydia trachomatis* has been largely eliminated in developed countries through the systematic screening and treatment of pregnant women but is still a consideration if the mother has had little or no prenatal care.[10] Any neonate with pneumonia is also at risk of sepsis, and between birth and 3 months, infants with pneumonia should be evaluated for sepsis.

Infants and Children Between 30 Days and 2 Years of Age Pneumonia in older infants and toddlers is usually viral rather than bacterial.[11] Common viruses include respiratory syncytial virus, human rhinovirus, influenza, parainfluenza, human metapneumovirus, and adenovirus.[7] In this age group, the most common **bacterial** cause of community-acquired pneumonia remains *S. pneumoniae*. Other agents include *Haemophilus influenzae* type b in nonimmunized children and nontypeable *H. influenzae* in all children. Less common but important pathogens include *S. aureus*, group A *Streptococcus*, and *Bordetella pertussis*.

Children 2 to 5 Years of Age As children get older and attend day care or school, they come into contact with many pathogens, particularly respiratory viruses. In children between 2 and 5 years of age, most community-acquired pneumonia is caused by respiratory viruses, notably respiratory syncytial virus, human rhinovirus, and human metapneumovirus. Other notable pathogens in this age group include *S. pneumoniae*, *H. influenzae* type b, and nontypeable *H. influenzae*. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are thought to be less common in children <5 years old.[9,12] Pneumonias due to varicella-zoster virus, measles, *H. influenzae* type b, *B. pertussis*, and some strains of *pneumococcus* are increasingly rare in areas of widespread vaccination and herd immunity.

Children 5 to 13 Years of Age While viruses continue to predominate in children older than 5, *M. pneumoniae* is a more commonly detected cause of community-acquired pneumonia, accounting for 17% of cases.[13] *C. pneumoniae* and *S. pneumoniae* remain important considerations.[12,14] Less common bacterial causes include *S. aureus*, *Streptococcus* species (including group A *Streptococcus*), nontypeable *H. influenzae,* and *Legionella*.[11] *M. tuberculosis* is a rare but important agent to consider. Pertussis immunity from the acellular vaccine wanes over time, so consider *Bordetella* even in the immunized child if clinical symptoms are **strongly** suggestive.[15] The proportion of pneumonia cases with any detected pathogen increases with age, from less than 10% in young children to about 35% in adolescents.[7] Advancements in pathogen detection methods may refine our understanding of patterns of infections across age groups.

Adolescents By adolescence, most patients are assumed to have the same infectious risks as healthy adults. The prevalence of specific pathogens may vary according to region, season, and cyclical epidemics in the population. In North America, the role of atypical agents, especially *M. pneumoniae* and *C. pneumoniae*, is estimated to be significant, but data and guidelines from other parts of the industrialized world (e.g., Europe) suggest regional differences.[16]

UNIQUE AND HIGH-RISK GROUPS

Tuberculosis remains a consideration for children with known exposures and those from endemic areas such as Native reserves, Alaska, northern Canada, and some inner-city settings. Consider tuberculosis in immigrants from high-prevalence areas of the world, including Africa, Asia, Venezuela, and parts of Eastern Europe.

Children with underlying chronic disease are at risk for specific infections. For example, younger children with cystic fibrosis are often infected with *S. aureus* in the first years of life, and later with

Pseudomonas. Children with sickle cell disease are particularly susceptible to infection with encapsulated bacteria (e.g., pneumococcus, *Salmonella*, *Klebsiella*), which can cause acute chest syndrome and sepsis. Children with congenital or acquired immune deficiencies such as human immunodeficiency virus infection, malignancy, and congenital immunodeficiencies are at risk for opportunistic infections with agents such as *Pneumocystis jirovecii*, cytomegalovirus, and fungi.[1]

Unvaccinated children and those with incomplete immunization are at risk of serious morbidity and mortality from a variety of vaccine-preventable pathogens.

PATHOGEN-SPECIFIC PATTERNS OF DISEASE

In general, it is not possible to pinpoint specific causative organisms by clinical findings alone. "**Typical pneumonias**" classically present with high fever, chills, pleuritic chest pain, and productive cough. "**Atypical pneumonias**" are characterized by gradual onset over days to weeks, low-grade fever, nonproductive cough, and malaise, and suggest infection with mycoplasma or *C. pneumoniae*. Viral pneumonias may present with similar symptoms.[9,14] Wheezing in children with an acute respiratory infection may suggest bronchiolitis, viral pneumonia, or *Mycoplasma* pneumonia.[10]

Despite these limitations, some patterns of disease do suggest certain etiologies (**Table 128-1**). **Staphylococcal pneumonia,** which may follow influenza, is notorious for rapidly progressing symptoms, high fever, toxicity, and presence of pulmonary abscesses. ***C. trachomatis*** infection in infants (which is rare where there is prenatal screening and treatment) often presents with a staccato cough, diffuse rales, and lack of fever, so-called *afebrile pneumonitis*. Scattered rales, rare wheezes, and bilateral interstitial infiltrates are all possible findings. Older children may complain of sore throat and dysphagia. *B. pertussis* and respiratory viruses are also implicated as possible causes.[17] ***Mycoplasma*** infection typically produces a hacking, dry cough and may be associated with extrapulmonary manifestations including arthralgias, rash, and even CNS symptoms.[18] An upper respiratory tract prodrome followed by paroxysmal cough, gasping respirations, and color change is characteristic of ***B. pertussis*** infection (whooping cough); the postinfection cough may persist for months.

Consider **tuberculosis** with prolonged cough in the setting of identified risk factors and characteristic radiographic findings. Note that classic signs of tuberculosis may be absent in children, especially those with immune deficiencies. Tuberculosis in infants and young children tends to progress more rapidly from infection to clinical disease.[19-21]

TABLE 128-1 Patterns of Disease by Specific Pathogen

Infective Agent	Disease Characteristics	Comments
Staphylococcus aureus	Rapid onset, high fever, toxicity, pulmonary abscesses	Infection with influenza may predispose to secondary *Staphylococcus* pneumonia
Chlamydia trachomatis	Staccato cough, diffuse rales, "afebrile pneumonitis," possible wheeze; bilateral infiltrates	Primarily seen in neonates and young infants but rare with prenatal maternal screening and treatment
Mycoplasma pneumoniae	Hacking dry cough, headache, sore throat; may cause wheezing in school-age children	Extrapulmonary symptoms: arthralgias, rash, CNS involvement
Bordetella pertussis	Upper respiratory prodrome followed by paroxysmal cough, gasping, stridor, color change	Cough may persist for months
Mycobacterium tuberculosis	Prolonged cough and/or fever, extrapulmonary spread	Consider in children from endemic areas and those with known exposure; classic symptoms seen in adults (e.g., hemoptysis) may be absent in children
Respiratory syncytial virus	Upper respiratory symptoms, cough, wheezing, rales, rhonchi	Clinical diagnosis of classic symptoms in child <2 years old; seasonal epidemics

TABLE 128-2 Differential Diagnosis of Pneumonia

Infectious Causes	Noninfectious Causes	Extrapulmonary Causes
Upper respiratory tract infection ("cold"), otitis media	Foreign body aspiration	Sepsis
Bronchiolitis	Inhalation pneumonitis (e.g., hydrocarbon inhalation, chronic gastroesophageal reflux disease)	Cardiac anomalies (cyanotic heart disease, congestive heart failure, myocarditis)
Croup	Intoxication (e.g., salicylate poisoning, carbon monoxide exposure)	Endocrinopathies (e.g., diabetic ketoacidosis)
	Congenital disorders (e.g., cystic fibrosis, sickle cell disease with chest crisis)	Neuromuscular disorders
	Anatomic abnormalities (e.g., congenital lobar emphysema, pulmonary sequestration, tracheoesophageal fistula, congenital cystic adenomatous malformation)	Inborn errors of metabolism
	Neoplasm, metastasis	GI emergencies (e.g., appendicitis with grunting)
	Pulmonary embolism	

SEVERE DISEASE

Criteria for severity of illness in pneumonia are not well defined and severity scoring systems have not been validated in children.[22] Guidelines include high fever, hypoxemia, and signs of respiratory distress as potential markers of severity. Young age, vital sign abnormalities, chest retractions, and multilobar radiographic infiltrates have been associated with more severe disease in hospitalized children with pneumonia.[23] Clinicians should determine severity in the context of physical exam findings and laboratory and imaging studies.[8,24]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pneumonia includes both infectious and noninfectious conditions, as well as extrapulmonary disorders that may mimic or complicate lower respiratory tract infection (**Table 128-2**). Formulating a differential diagnosis is especially important for infants and very young children, who may have undiagnosed congenital anomalies.

Congenital heart disease may present with cyanosis, quiet tachypnea, or respiratory distress related to congestive heart failure (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease"). Kussmaul breathing suggests diabetic ketoacidosis or other metabolic disease. Toddlers are particularly at risk for foreign body aspiration and ingestion of toxins. Adolescents may intentionally or unintentionally take drug overdoses that speed or slow breathing.

DIAGNOSIS

HISTORY

Relevant history depends on the age and underlying health of the child. Many complaints are nonspecific (e.g., cough and fever) and are common to both upper and lower respiratory tract disease. The predictive value of specific signs and symptoms is discussed below (see "Physical Examination" section).

The presence, timing, and duration of cough, fever, rapid breathing, and difficult breathing may provide diagnostic information. Specific

toxic exposures, sick contacts, travel, and pets may be relevant to the diagnosis.

Persistent or recurrent lower respiratory tract symptoms or history of choking suggest foreign body aspiration. Recurrent pneumonias may signify underlying disease such as cystic fibrosis, immune disorders, or anatomic abnormalities.

In young children, lower lobe pneumonia or effusion can cause abdominal pain and may mimic appendicitis.

Fever is a common but nonspecific sign of both upper and lower respiratory tract infections.

Birth History The mother's perinatal health is of particular importance, as neonates are at risk for perinatally acquired infections. Obtain relevant information on maternal infections (e.g., chlamydia, gonorrhea, group B streptococci, genital herpes, and human immunodeficiency virus status), intrapartum or postpartum fever, and any specific antibiotic or antiviral therapy received during labor and delivery. Other perinatal risk factors include prolonged rupture of membranes, prematurity, and immediate peripartum complications. Meconium aspiration may cause chemical or bacterial pneumonia in the first 24 to 72 hours of life. Neonatal stays in hospital suggest an underlying health problem and also increase the risk of nosocomial infection.

Medical History Chronic respiratory illnesses (e.g., asthma), recurrent pneumonia, prior complicated pneumonia, or a complex medical history (e.g., cerebral palsy, developmental delay) may place the child at risk for severe disease or treatment failure. Children with congenital respiratory problems (e.g., cystic fibrosis, neuromuscular disorders, immune compromise, recurrent aspiration) are at increased risk of infection with common and rare agents, respiratory failure, and treatment failure.

Social History A brief, focused social history may influence diagnosis, treatment, and disposition. Exposure to tuberculosis, human immunodeficiency virus–related opportunistic infections, and pathogens during travel may alter the likely etiology of disease. Adequate outpatient management of pneumonia requires that caregivers understand instructions, can afford medication, and have access to required follow-up care (see "Disposition and Follow-Up" section below).

Immunization History Childhood immunizations can provide protection from common pathogens implicated in pneumonia (e.g., *S. pneumoniae, B. pertussis, N. meningitidis, H. influenzae* type b, and measles). Table 106-3 ("Emergency Care of Children") provides a typical childhood immunization schedule. An *unvaccinated* child is at risk of serious morbidity, and even death, from vaccine-preventable illness.

Annual immunization against influenza is recommended for children ≥6 months of age and for those at high risk due to underlying health conditions. Influenza vaccine must be given annually to account for seasonal antigenic changes (see "Special Considerations" section below). Priority is given to children with asthma, cystic fibrosis, and other pulmonary diseases; those with significant cardiac, renal, and immune disorders; and those with diabetes. Caregivers and healthcare providers should also be immunized to avoid transmission to these at-risk children.[25]

Immunization against varicella (chickenpox) should protect against the secondary pneumonias associated with this virus, although use of the vaccine is not yet universal. Similarly, the administration of the bacillus Calmette-Guérin vaccine to provide partial protection against certain forms of tuberculosis varies by state, province, and country.

The introduction of a seven-strain pneumococcal polysaccharide-protein conjugate vaccine (PCV7) in 2000 to 2001 led to dramatic decreases in invasive disease, but an increase in the severity of pneumococcal pneumonia attributed to nonincluded serotypes. The inclusion of additional serotypes in subsequent vaccines (PCV10 and PCV13) in 2010 to 2011 led to a decline in the incidence and severity of pneumococcal pneumonia worldwide.[26,27] Continued surveillance may detect further emerging serotypes beyond those included in PCV13. Children with human immunodeficiency virus infection have shown a robust serologic response to most pneumococcal subtypes included in PCV13.[28,29] The Centers for Disease Control and Prevention recommends PCV13 administration to all children under 4 years of age and to older children with high-risk conditions.[30]

The older 23-valent polysaccharide vaccine (Pneumovax®) is effective in children ≥2 years of age, and it should be confirmed that the vaccine has been given to children with sickle cell disease, those who have undergone splenectomy, and others at high risk for pneumococcal disease. A booster may be required.

TABLE 128-3 Tachypnea as an Indicator for Pneumonia*

Age	Tachypnea	Comments
<60 d old	>60 breaths/min	>70 breaths/min indicates severe disease
2–12 mo old	>50 breaths/min	
>1–5 y old	>40 breaths/min	>50 breaths/min indicates severe disease
>5 y old	>20 breaths/min[22]	>50 breaths/min indicates severe disease

*Determine rate before examination and when child is calm or sleeping; count respiratory rate for a full minute; fever may increase the rate by up to 10 breaths/min for every 1°C (1.8°F) rise in patient temperature.

PHYSICAL EXAMINATION

In the developing world where imaging equipment and laboratory tests are limited, the World Health Organization's classification scheme identifies children with cough and difficult breathing but no other signs as having an upper respiratory infection. Children with associated tachypnea or chest indrawing are considered to have pneumonia to be treated at home with oral antibiotics. Children who also display general danger signs such as dehydration or lethargy are classified as severe pneumonia and treated with parenteral antibiotics.[31] Although physicians in industrialized nations have many tools at their disposal, the diagnosis of pneumonia can still be made clinically.

Rapid respiratory rate is a simple screening tool for pneumonia and may be considered in conjunction with the clinical context (**Table 128-3**).[9] However, pneumonia has been identified in almost 7% of children without tachypnea or auscultatory exam findings.[32]

Children at very high altitudes may have a resting respiratory rate higher than children at sea level do, so oxygen saturation may be a more useful measure. Severely malnourished or dehydrated children, or those with impending respiratory failure, may not be capable of generating rapid respiratory rates.

Markers of respiratory distress include nasal flaring, tracheal tugging, and intercostal indrawing. Lower chest or "abdominal" indrawing or retractions and grunting may suggest more severe pneumonia.[31] **In infants, intermittent apnea, grunting, and an inability to feed are surrogate markers of dyspnea.** Cough is less common in neonates or very young children, and productive cough is rarely seen before late childhood.

Hypoxia in pneumonia typically is defined as oxygen saturation less than 90% to 92% on room air. In developing countries, hypoxia is associated with risk of oral amoxicillin treatment failure in severe pneumonia and is a strong independent predictor of radiographic pneumonia.[32,33]

The chest should be auscultated while fully exposed, assessing all lung zones. Localized fine crackles (rales), coarse breath sounds (rhonchi), or diminished breath sounds suggest pneumonia, but sound recognition may not be consistent across observers.[34] Among clinical exam findings relating to pneumonia, acceptable interrater reliability has been shown only in wheezing, respiratory rate, and retractions.[35] A toxic appearance and overall impression of illness as judged by the clinician show better diagnostic sensitivity than focal auscultatory findings.[9]

CLINICAL DIAGNOSIS

No single physical finding in isolation is diagnostic of pneumonia, and constellations of signs are more useful. For example, the combination of fever plus either tachypnea, decreased breath sounds, or fine crackles predicts radiographic pneumonia with a sensitivity of 93% to 96%. Some studies have shown that the presence of fever plus *all three* of the other variables raises sensitivity to 98%, while others have shown that hypoxia and increased work of breathing have been shown to be more important for diagnosis than tachypnea or auscultatory findings.[36]

Presumptive diagnosis of the causative organism and empiric treatment are made by considering historical and social factors

TABLE 128-4 Bacterial Organisms and Empiric Treatment for Pneumonia in Otherwise Healthy Children

Age Group	Bacterial Pathogens	Outpatient Treatment	Inpatient Treatment
Neonates	Group B *Streptococcus* Gram-negative bacilli *Listeria monocytogenes*	Initial outpatient management not recommended	Ampicillin + Gentamicin or cefotaxime
1–3 mo	*Streptococcus pneumoniae* *Chlamydia trachomatis* *Haemophilus influenzae* *Bordetella pertussis* *Staphylococcus aureus*	Strongly consider inpatient management	*First-line therapy:* Ampicillin or penicillin G[f] *If not fully immunized or if significant local pneumococcal penicillin resistance:* Ceftriaxone Alternative: cefotaxime, levofloxacin *If suspected methicillin-resistant S. aureus* ***ADD:*** vancomycin or clindamycin[*] *If presumed atypical* ***ADD:*** Azithromycin[†]
3 mo–5 y[‡]	*S. pneumoniae* *H. influenzae* type b[#] Nontypeable *H. influenzae* *S. aureus*	*First-line therapy:* Amoxicillin (90 milligrams/kg/d divided in 2 doses) ± clavulanate[f] *If presumed atypical:* Azithromycin (10 milligrams/kg on day 1, then 5 milligrams/kg/d) Alternative: clarithromycin, erythromycin, or doxycycline (if patient >7 y)	
5–18 y	*Mycoplasma pneumoniae* *S. pneumoniae* *Chlamydophila pneumoniae* *H. influenzae* type b[#] *S. aureus*		

[*]For suspected *S. aureus:* cefazolin if methicillin sensitive; vancomycin or clindamycin when methicillin-resistant *S. aureus* is suspected.

[†]Macrolide should be used for suspected atypical infections (e.g., *M. pneumoniae, C. trachomatis, C. pneumoniae, B. pertussis*), and options include clarithromycin, erythromycin, or azithromycin. *Levofloxacin if children have reached growth maturity.*

[‡]The majority of pneumonias in preschool-age children are viral, not bacterial, and do not require antibiotics in children well enough to be cared for in the outpatient setting.

[#]Consider if not fully vaccinated.

[f]For penicillin allergy, consider individualized treatment: trial of amoxicillin under supervision, trial oral cephalosporin with activity against *S. pneumoniae* (cefpodoxime, cefprozil, cefuroxime) under supervision, or treatment with linezolid, clindamycin, or macrolide (if susceptible).

(see above), immunization status (see above), and age of the child. See **Table 128-4** for the most common causes of pneumonia by age as well as their treatment. Use care when assessing children with incomplete or no immunizations. Such children may be partially or fully susceptible to pneumonia associated with *B. pertussis*, *H. influenzae* type b, and all strains of pneumococcus, as well as measles, influenza, and varicella-zoster viruses.

LABORATORY EVALUATION

Because the results of most laboratory investigations are not known in the ED, tests are usually initiated to guide *future* treatment, except for rapid bedside tests for specific respiratory viruses. Nasopharyngeal assays for respiratory syncytial virus, influenza, and human metapneumovirus may be valuable, because they are quick and specific, and results may negate the need for imaging, invasive testing, and antibiotic therapy. Clinicians must remain vigilant and consider this testing within context, as a significant proportion of children with pneumonia demonstrate bacterial coinfection with positive viral swabs.[37] Imaging and antibiotic treatment for nontoxic children with clinical bronchiolitis or influenza may be deferred, especially those with a positive nasopharyngeal swab finding.[8,24]

Bacterial cultures of nasopharyngeal samples are generally *not* helpful, because results are delayed, and oral and nasal flora correspond poorly with the organisms causing disease in the lung. Up to 20% of asymptomatic children under 5 years of age are colonized with *S. pneumoniae*, which makes differentiating infection from colonization with a positive culture challenging.[38] The majority of newer serologic and polymerase chain reaction techniques to detect organisms such as *M. pneumoniae, H. influenzae*, or *C. pneumoniae* have not been validated in children and have produced variable results.[8,10,24]

The routine collection of blood cultures *is not* recommended in healthy children with mild community-acquired pneumonia because rates of bacteremia are low.[24] For toxic-appearing children, those with severe disease requiring hospitalization, and those with complicated pneumonia, a blood culture is recommended, preferably before antibiotic administration. Blood cultures generally offer low yield, thus obtaining them only in targeted patients is cost-effective.[39,40] A CBC may be useful for severe disease to evaluate for complications of pneumonia (e.g., pneumococcal hemolytic-uremic syndrome) but is not useful for differentiating bacterial or viral etiology. Currently, the literature does not support the routine use of inflammatory markers (C-reactive protein or erythrocyte sedimentation rate), acute-phase reactants, or procalcitonin to distinguish bacterial from viral pneumonia in children.[24] However, these markers may be useful to trend disease resolution and inform the need for continued antibiotics in severe pneumonia.[41] Drainage and culture of parapneumonic effusions is indicated for large effusions or patients with severe respiratory compromise. Novel biomarkers and systems biology tools under investigation (e.g., RNA signatures, -omics) show promise for discriminating pathogens and guiding management.[42,43]

When tuberculosis is suspected, induced sputum samples from older children or gastric aspirates from infants for microscopy and confirmatory culture are necessary.[44] These tests require equipment and expertise beyond the scope of the ED.

IMAGING

Guidelines on the use of routine chest radiography are inconsistent.[8,24,45] Consider chest radiographs only when the results are likely to alter diagnosis, treatment, or outcome.

Benefits of radiography include diagnosis or confirmation of pneumonia and occasionally the discovery of a significant congenital abnormality. Risks and disadvantages include cost, delay, repeated exposure to ionizing radiation, and overdiagnosis/misdiagnosis of bacterial pneumonia.[46] Several studies and major guidelines state that imaging should *not* be performed routinely in children with mild, uncomplicated acute lower respiratory tract infections.[8,24,47,48] Most of these studies and guidelines reference outpatient settings, in which children with prolonged cough, severe symptoms, and other "red flag"

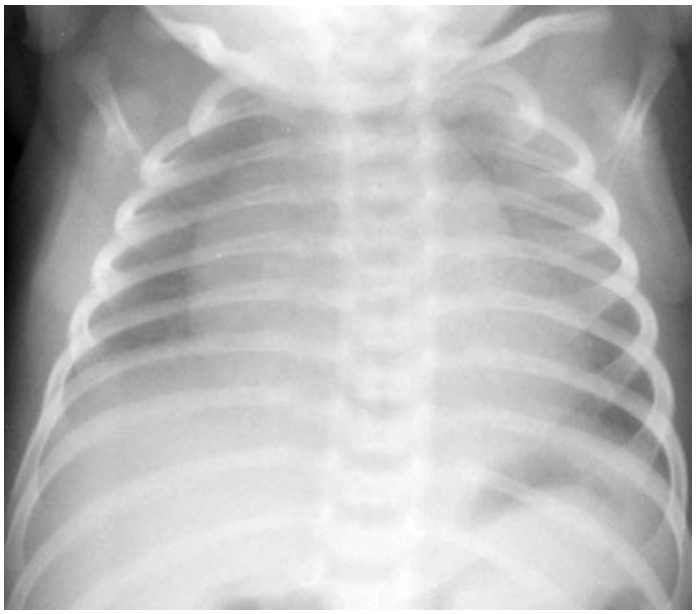


FIGURE 128-1. Poor inspiration results in the appearance of pulmonary infiltrates and cardiomegaly in this normal 4-month-old infant. [Photo contributed by BC Children's Hospital, Vancouver, British Columbia, Canada.]

features were excluded, so these recommendations may not apply to the ED setting.

The chest radiograph is *not* the gold standard of diagnosis, because it is neither 100% sensitive nor 100% specific[49] and may be falsely negative (e.g., when clinical disease precedes radiographic changes) or falsely positive (e.g., poor inspiration or rotation; **Figures 128-1** and **128-2**). While the presence of alveolar infiltrates has shown good interrater reliability among radiologists, other findings such as interstitial infiltrates and pleural effusions are less reliable.[50] Chest radiographs do not reliably distinguish between bacterial and viral causes.[49,51] Young children with straightforward viral bronchiolitis may show radiographic areas of atelectasis or patchy collapse, resulting in initiation of unnecessary antibiotic therapy for viral disease.[52]

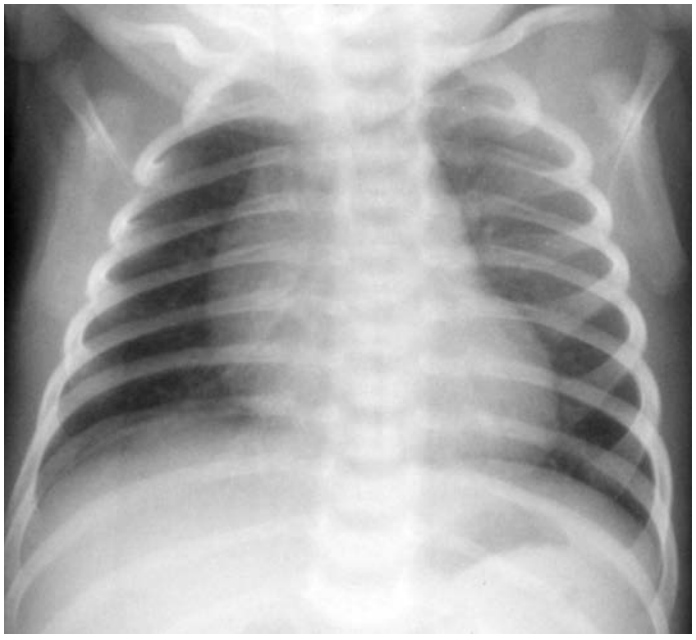


FIGURE 128-2. The same child as in Figure 128-1, with adequate inspiration. Note that persistent rotation (see clavicles) causes a false difference in left and right lung density. [Photo contributed by BC Children's Hospital, Vancouver, British Columbia, Canada.]

The use of ultrasound in the diagnosis of pneumonia is promising. Early studies have shown high interobserver agreement and an acceptable sensitivity and specificity when performed by an experienced sonographer, but it is unclear at this time if ultrasonographic findings correlate with etiology or clinical outcomes.[53-55]

Although routine radiographs are not usually necessary, potential indications for chest radiography include the following[36,56,57]:

1. Infants and children with a toxic appearance and respiratory findings
2. Age of 0 to 3 months with fever and respiratory symptoms, as part of a full sepsis evaluation
3. Child <5 years old, with a temperature of >39°C (102.2°F) lasting 5 days or more, WBC of ≥20,000/mm, and no clear source of infection[8]
4. Suspicion of a complication, such as pleural effusion or pneumothorax
5. Pneumonia that is prolonged or unresponsive to treatment
6. Children with biphasic illness (typical symptoms of upper respiratory tract infection followed by acute worsening of [respiratory] symptoms and high fever)
7. Suspected foreign body aspiration
8. Suspected congenital lung malformation (e.g., sequestration or congenital cystic adenomatous malformation) or chest mass
9. Follow-up of recurrent pneumonia involving the same lobe or with lobar collapse at presentation

For a brief overview of important normal and abnormal radiographic findings unique to children, see the "The Pediatric Chest Radiograph" section at the end of this chapter.

TREATMENT

Treatment is based on the presumptive pathogen using information from history, immunizations, and age group (Table 128-4).

SUPPORTIVE AND SYMPTOMATIC TREATMENT

General supportive measures include supplemental oxygen to maintain oxygen saturation above 90% to 92%; antipyretics; oral, nasogastric, or IV fluids to offset respiratory losses; and bronchodilators for wheezing in the setting of asthma. Do not routinely offer bronchodilators for infants less than 24 months of age if bronchiolitis is suspected. Because children depend on cough to clear mucus, cough suppressants are not generally indicated. **Over-the-counter cough suppressants are not effective and have been withdrawn from the market in several countries for children <5 years of age.** Narcotic-based cough suppressants are occasionally prescribed in older children, but data on their effectiveness and proper dosage are lacking. Codeine in particular is discouraged due to the risk of respiratory suppression in some children.[58] Honey has been shown to be an effective and safe treatment for cough in young children with upper respiratory tract infections.[59]

Treat noninfectious pneumonitis (e.g., chemical inhalation, aspiration) and likely viral pneumonia (e.g., age 3 months to 5 years, audible wheezing, positive bedside test for respiratory syncytial virus, or influenza) with supportive measures as outlined above. **Antibiotics are not indicated for viral pneumonia.** Well-appearing, previously healthy febrile infants 28 to 90 days old with bronchiolitis (clinical and respiratory syncytial virus–positive) are at low risk for concurrent bacterial pneumonia, bacteremia, and meningitis and do not require radiographs, blood or cerebrospinal fluid testing, or empiric antibiotic therapy for their respiratory infection. These young febrile infants have a small increased risk for concurrent urinary tract infections, and urine testing should be considered.[60] Febrile infants younger than 28 days old generally require a full sepsis workup, including blood, urine and cerebrospinal fluid cultures, and empiric antibiotics.

EMPIRIC ANTIBIOTIC TREATMENT

Treat all children with suspected *bacterial* pneumonia with prompt administration of empiric antibiotics.[9,11,24]

Neonates In neonates younger than 1 month of age who are at risk of sepsis, administer ampicillin to cover *Listeria* and group B *Streptococcus* in conjunction with an aminoglycoside (e.g., gentamicin) or a third-generation cephalosporin (e.g., cefotaxime) for expanded coverage of gram-negative organisms, such as *E. coli*. **Ceftriaxone is contraindicated in neonates because it can displace bound bilirubin.**

Young Infants 1 to 3 Months Old The syndrome of **afebrile** pneumonitis described in infants 1 to 3 months old (staccato cough, tachypnea, with or without progressive respiratory distress and diffuse pulmonary infiltrates) may be viral in origin but has also been associated with atypical bacteria, so authors have suggested empiric treatment with erythromycin or clarithromycin in this group.[9] **Azithromycin is not included in the treatment of patients this young, due to an increased reported risk of pyloric stenosis.**

Infants and Children 3 Months to 5 Years Old For these children, treatment choice remains largely empiric. There are notable differences between some North American and European recommendations, but all presume the most frequent cause of bacterial pneumonia to be *S. pneumoniae*.[8,16] **For this reason, high-dose oral amoxicillin (80 to 100 milligrams/kg/d) or another β-lactam antibiotic remains the initial drug of choice in suspected bacterial pneumonia. A third-generation cephalosporin (e.g., ceftriaxone or cefotaxime) should be used as initial therapy if penicillin resistance is high in the community, in incompletely immunized children, or in cases of life-threatening infections, including empyema.[24]**

Children 5 Years to 18 Years Old For children 5 years to 18 years old, some North American guidelines list macrolide antibiotics as initial empirical therapy, given the increased role of atypical agents, such as *M. pneumoniae* and *C. pneumoniae*, in school-age and adolescent children. This recommendation presumes that macrolides will treat both atypical pathogens and pneumococci. In outpatients in whom atypical pneumonia is a strong suspicion, macrolide monotherapy is a reasonable initial choice. However, high rates of pneumococcal resistance to macrolides in vitro are a growing concern, and several major guidelines now recommend amoxicillin with or without clavulanate as initial therapy for *all* children ≥3 months of age with simple community-acquired pneumonia.[8,24] **In hospitalized children in whom the etiology of pneumonia is unclear, β-lactams *plus* macrolides should be used as first-line therapy for children 5 years and older. In cases where resistant pathogens or multiple pathogens are suspected, all guidelines make provisions for coverage with third-generation cephalosporins *plus* macrolides in this age group.** With these considerations in mind, typical choices for primary or secondary bacterial pneumonia are listed in Table 128-4.

For a child with significant underlying illness or fulminant viral pneumonia, special agents and antimicrobials may be indicated, and consultation is strongly advised. These guidelines may need to be adapted according to formulary, familiarity, and local patterns of antibiotic resistance. Antibiotic choices for children with allergies, unusual exposures, or specific risk factors should be tailored in consultation with a specialist.

The choice of oral versus parenteral antibiotics depends on the patient, severity of disease, and predicted response to therapy. Oral antibiotics provide adequate coverage for most mild-to-moderate cases of bacterial pneumonia. Parenteral therapy is usually limited to neonates and those with severe pneumonia requiring hospitalization.[9] Even for children who are admitted, oral treatment may be sufficient within the monitored setting of the hospital.[61]

The recommended duration of outpatient treatment is typically 7 to 10 days (5 days in cases in which azithromycin is used). This is based on historical precedent, although some literature suggests equivalent outcomes in mild pneumonia with as few as 3 to 5 days of outpatient treatment.[62-64] There are theoretical concerns, however, that shorter courses of treatment and poor adherence may drive bacterial resistance. In children, antibiotic choice may also be influenced by important nonmicrobial factors, such as taste, cost, frequency of administration, availability of a liquid formulation, and the child's ability to swallow.

CONTROVERSIES OF TREATMENT

The use of macrolides (erythromycin, clarithromycin, azithromycin) as first-line agents in young children is an area of controversy.[10,65] Macrolides are generally effective against atypical and intracellular agents, which are more common in children after the age of 5 years, but they may be ineffective against *S. pneumoniae*. Pneumococcal resistance to macrolides in Europe and North America ranges from 7.5% to >50.0%.[16] The indiscriminate use of azithromycin in treating upper respiratory tract infections appears to be driving streptococcal resistance in some populations.[66] The liquid suspension of azithromycin is not approved for children <6 months of age due to the risk of pyloric stenosis. Some suggest that children who have fever of <2 days in duration and who are <3 years of age are at very low risk of community-acquired *Mycoplasma* infection; macrolides can thus be safely avoided as first-line antibiotics.[67] If a child fails to improve when taking amoxicillin or an equivalent β-lactam after at least 48 to 72 hours of treatment, consider adding a macrolide.

Pneumococcal resistance to penicillin and other β-lactams is another area of concern around the globe. To date, most antibiotic resistance in community-acquired streptococci has been documented in vitro, rather than in vivo, and clinical response is still satisfactory when clinicians use an increased dosage.[68] The safety and efficacy of fluoroquinolones for respiratory infections in children are not established, and their use is generally restricted due to theoretical risks of arthropathy. Doxycycline, a much older and less expensive agent, has activity against atypical pathogens as well as streptococci, but is restricted to use in adolescents and adults, because use in young children it may cause permanent staining of the adult teeth. As resistance to amoxicillin, macrolides, and other antibiotics grows, the importance of *prevention* using pneumococcal conjugate vaccines is critical.

DISEASE COMPLICATIONS

Most viral pneumonias resolve spontaneously without specific therapy. Complications are similar to those for bronchiolitis and include dehydration, bronchiolitis obliterans (rarely), and apnea. **Apnea is a potential complication of infection with respiratory syncytial virus, *Chlamydia*, or *B. pertussis* infection in very young infants.** Pleural effusions can occur with viral pneumonias but are not common.

Uncomplicated bacterial pneumonia usually responds within 72 hours to antibiotic therapy. Failure to respond or worsening of disease suggests a viral etiology, a resistant organism, or development of a pneumonia-associated complication. Complications include pleural effusion, empyema, pneumothorax, or pneumatocele. Effusions can occur in pneumococcal and *Mycoplasma* pneumonias; they are also associated with *H. influenzae* type b infections. *S. aureus* is associated with empyema, abscess, and pneumatoceles. *Mycoplasma* pneumonia may cause extrapulmonary complications such as arthritis and meningitis. Local and hematogenous spread of tuberculosis can result in myriad manifestations inside and outside the lung. Systemic complications of pneumonia include dehydration, sepsis, and hemolytic-uremic syndrome.

The child with pneumonia who returns to the ED with worsening clinical symptoms should prompt heightened suspicion for severe or complicated disease. If the initial treatment was supportive care for a presumed viral pneumonia, consider secondary bacterial pneumonia or an alternative diagnosis (e.g., cardiac disease, congenital anomaly, foreign body).[69] Similarly, a child receiving antibiotics who returns with diminished breath sounds, dullness to percussion, or worsening respiratory distress should prompt evaluation for complications, such as empyema, effusion, or pneumothorax. If antibiotic-resistant pneumonia is suspected, further investigation with blood or pleural fluid cultures may be warranted.[70,71]

DISPOSITION AND FOLLOW-UP

Recommendations for outpatient, inpatient, and intensive care treatment of pneumonia are presented in **Table 128-5**.[8] In addition to these clinically-based criteria, neonates and infants up to 90 days old often require hospital admission, as do infants and children with significant

TABLE 128-5 Disposition of Infants and Children With Pneumonia

Age	Outpatient Management	Inpatient Management	Intensive Care Management
Infants	Mild-to-moderate symptoms (no cyanosis, grunting, significant retractions), oxygen saturation >90–92%, respiratory rate (RR) <70 breaths/min, feeding well and well hydrated, reliable caretakers and outpatient follow-up	Oxygen saturation <90–92%, RR >70 breaths/min, respiratory distress (retractions, grunting, apnea), poor feeding, dehydration, family unable to provide appropriate home observation or ensure follow-up	Inability to maintain oxygen saturation >90–92% with fraction of inspired oxygen >0.6, severe respiratory distress or recurrent apnea, respiratory fatigue or respiratory failure, need for positive-pressure ventilation (continuous positive airway pressure, bilevel positive airway pressure, intubation with mechanical ventilation), altered mental status, signs of shock or severe sepsis
Children	Mild-to-moderate symptoms (no cyanosis, grunting, significant retractions), oxygen saturation >90–92%, no tachypnea, feeding well and well hydrated, reliable caretakers and outpatient follow-up	Oxygen saturation <90–92%, tachypnea (see Table 128-3), respiratory distress (retractions, grunting, apnea), poor feeding, dehydration, family unable to provide appropriate home observation or ensure follow-up	

comorbid disease (e.g., cystic fibrosis, sickle cell disease, underlying immunodeficiency or malignancy). Social indications for admission include the inability of caregivers to have access to, afford, understand, or ensure outpatient treatment and follow-up.[8]

Infants with suspected *B. pertussis* infection (whooping cough) are at risk for apnea and should be admitted under respiratory isolation. Indications for hospitalizing patients with respiratory syncytial virus pneumonia are the same as those for patients with respiratory syncytial virus bronchiolitis (see Chapter 127, "Wheezing in Infants and Children"). Patients with suspected active pulmonary tuberculosis should be admitted under respiratory isolation. Patients who fail a trial of oral antibiotics and those with complications of pneumonia require admission for further diagnosis and therapy. Moderate to large pleural effusions, pneumatoceles, or findings suggestive of a serious bacterial infection in a child <1 year of age may suggest a pathogen other than *S. pneumoniae* (in particular *H. influenzae* type b or *S. aureus*) and require close monitoring.

DISCHARGE INSTRUCTIONS

All families should be provided with specific instructions on the dosage and scheduling of medications and the signs of worsening respiratory distress, including tachypnea and retractions. Encourage return to medical care for children who cannot take prescribed antibiotics or adequate amounts of fluid. Ensure that all children discharged with the diagnosis of pneumonia have follow-up within a day or two with a primary care provider. Younger children require closer follow-up. Modifiable factors should be reviewed with caregivers:

1. Hand washing and general hygiene to prevent transmission
2. Breastfeeding of infants, which is known to be protective
3. Avoidance of smoking and secondhand smoke
4. Vaccination, including pneumococcal conjugate vaccine as well as polysaccharide vaccine for at-risk children older than 2 years

SPECIAL CONSIDERATIONS

For a child with significant underlying illness or fulminant viral pneumonia, special agents and antimicrobials may be indicated, and consultation is strongly advised.

INFLUENZA

Influenza is a common cause of respiratory infections worldwide. Classic symptoms include fever, cough, runny nose, headache, and myalgias, lasting up to 7 days.

Complications of influenza include secondary bacterial pneumonia and occasionally a pneumonia from the virus itself.[72] Apnea is a rare but serious complication in young infants.

Point-of-care and other rapid testing may be helpful in pinpointing influenza as the source of fever in children and avoiding a search for additional causes. Sensitivities are moderate (40% to 70%), but specificities are high (85% to 100%) if performed within the first 4 days of symptoms.[73] If a false-negative result is suspected, confirmatory polymerase chain reaction can be obtained if confirmation of result is necessary. **Treatment, if indicated, should not be delayed while waiting for test results.**

Treatment of influenza is largely supportive, with fluids, rest, and fever control. **Note that acetylsalicylic acid should not be used for fever control, due to the risk of Reye's syndrome.**

The role for antivirals is unclear. A 2012 Cochrane meta-analysis of the older medications amantadine and rimantadine showed a limited role in prevention and amelioration of influenza A in children. The number needed to treat was high and the quality of evidence was low.[74]

Neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®) may help shorten the duration and severity of symptoms and reduce the risk of complications, especially in hospitalized or high-risk patients. The clinical benefit of these medications is greatest when started early in the disease. The overall utility of these medications remains unclear.[75] Seasonal recommendations from the Centers for Disease Control and Prevention may help guide the clinician in the appropriate use of antiviral medications.

With few treatments available, the best defense against influenza and its associated pneumonias remains annual vaccination, frequent hand washing, and droplet precautions.

The U.S. Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend routine annual influenza vaccination for children 6 months and older. Special emphasis is placed on children 4 years and under, because they are most at risk for complications and most likely to transmit disease in the community.

Children generally require a single dose of the vaccine annually, to account for antigenic changes in the virus from year to year. Those being vaccinated for the first time typically require a second dose at least 28 days later.

A nasal form of the vaccine containing live, attenuated virus is approved for children 2 years of age and older. However, the intranasal vaccines have been shown to be ineffective during multiple recent influenza seasons and have not been recommended. Annual recommendations from the Centers for Disease Control and Prevention should be consulted with regard to administration of the nasal live virus vaccine, as these change from year to year. There is an increased risk of wheezing when used in children with a prior history of wheeze. Those with asthma or immune suppression should use the standard, injectable vaccine, which contains no live virus.

TUBERCULOSIS

Children of all ages are susceptible to tuberculosis, and most have *primary* disease, rather than secondary reactivation. Both upper lobe infiltrates and hilar lymphadenopathy on chest radiograph suggest the diagnosis, but classic findings can be absent in children, especially those with immune deficiencies.[19] Infants and young children tend to progress rapidly from infection to clinical disease, and hematogenous spread can

lead to the radiographic "snowstorm" appearance of miliary tuberculosis.[20] Secondary tuberculosis has a predilection for the upper segments of the lung, as in adults, and may yield a cavitary lesion in some cases. *Mycobacterium avium* lesions may be indistinguishable from those of secondary tuberculosis.

OPPORTUNISTIC INFECTIONS

Nodular findings in the lungs may alert the astute clinician to the presence of other, rare infectious agents, such as *Histoplasma*, *Aspergillus*, and *Pneumocystis*. Pediatric patients with human immunodeficiency virus/acquired immunodeficiency syndrome may be susceptible to all of these, as well as cytomegalovirus, lymphomas, and lymphocytic interstitial pneumonia.

CYSTIC FIBROSIS

Children with cystic fibrosis have decreased mucus clearance, which leads to airway obstruction. More advanced disease results in chest radiograph findings such as peribronchial thickening and mucous plugging, with subsequent cystic or bullous lung lesions, segmental atelectasis, hilar adenopathy, and bronchiectasis. Air trapping may be seen on expiratory views. Patients with cystic fibrosis are also at risk for pneumothorax.

ASPIRATION PNEUMONIA

Patchy atelectasis and air space consolidation in the dependent zones of the lung should raise suspicion of aspiration pneumonia or pneumonitis. Recurrent aspiration pneumonias may occur in children with chronic gastroesophageal reflux disease, tracheoesophageal fistula, developmental delay, immobility, or neuromuscular disorders.

THE PEDIATRIC CHEST RADIOGRAPH

NORMAL NEONATAL ANATOMY

The chest of a neonate (<1 month of age) has a more pyramidal or trapezoidal shape than the long, rectangular form of the adult. The cardiac silhouette may occupy up to 60% or 65% of the chest width on the frontal view and still be considered normal. In infants, bronchial branching may be visible beyond the level of the carina, giving the false impression of pathologic air bronchograms. The thymus appears as a large, dense, anterior mediastinal "sail," until involution occurs around age 6. A normal thymus can often be recognized by the sharp inferior edge of its silhouette and occasionally by a "wave" or "sail" sign at the lateral edge, where the adjacent ribs indent this soft, solid organ. Occasionally the thymus may be confused with a lobar pneumonia, mediastinal mass, or hilar lymphadenopathy (**Figure 128-3**). A lateral view can help to confirm the **anterior** location of the thymus (**Figure 128-4**). A silhouette that extends behind the heart shadow or posterior to the vertical lucency of the trachea should be investigated.

TRANSIENT TACHYPNEA OF THE NEWBORN AND MECONIUM PNEUMONITIS

Occasionally parents may bring a very young newborn to the ED because of real or perceived breathing difficulties. Noninfectious causes of tachypnea and respiratory distress in the first few days of life include transient tachypnea of the newborn, or "wet lung," and chemical pneumonitis from meconium aspiration. The former may cause increased vascular markings, linear interstitial opacities, and even pleural effusions on radiographs due to interstitial edema. Meconium aspiration can block small airways, leading to hyperinflation and bilateral air space opacities on plain radiographs. Signs of interstitial opacities or edema should prompt observation and/or consultation with a specialist.

FOREIGN BODY OR HYDROCARBON ASPIRATION

In addition to pneumonias from the infectious causes, toddlers are susceptible to choking and foreign body aspiration from objects they can reach. These may include organic materials (e.g., food) or inorganic objects (coins, buttons, batteries), as well as volatile toxins such as cleaning products, gasoline, or other hydrocarbons. Retained foreign bodies can lead to respiratory distress and febrile aspiration pneumonia. Radiopaque foreign bodies will appear on the chest radiograph; signs of *radiolucent* foreign bodies include asymmetric air trapping or segmental collapse past an obstructed bronchus. By contrast, inhaled hydrocarbons and irritants may yield a pneumonitis with patchy lower air space opacities and even pneumatoceles if the presentation is delayed.

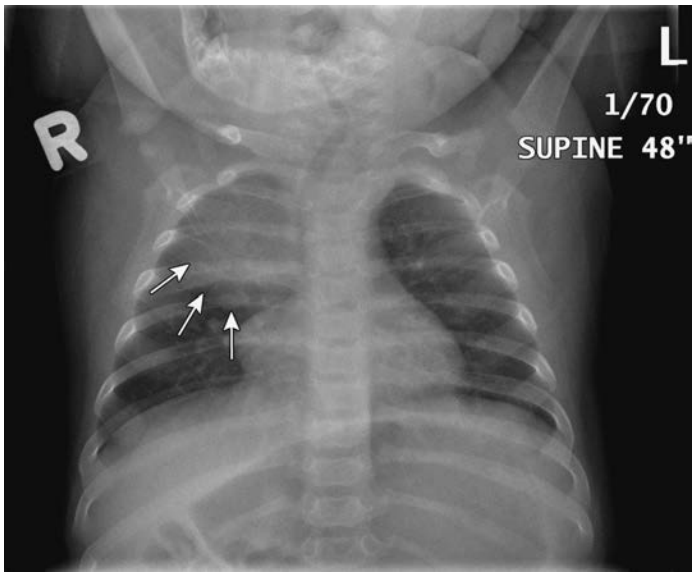


FIGURE 128-3. *Arrows* indicate a normal thymus. Rotation, apparent from the location of the heart, trachea, and clavicles, makes this thymus appear to be far right of midline. [Photo contributed by BC Children's Hospital, Vancouver, British Columbia, Canada.]

PNEUMONIA IN THE OLDER CHILD

By school age, the radiographic signs of chest infection in children appear similar to typical findings in adults. There may be obvious lobar

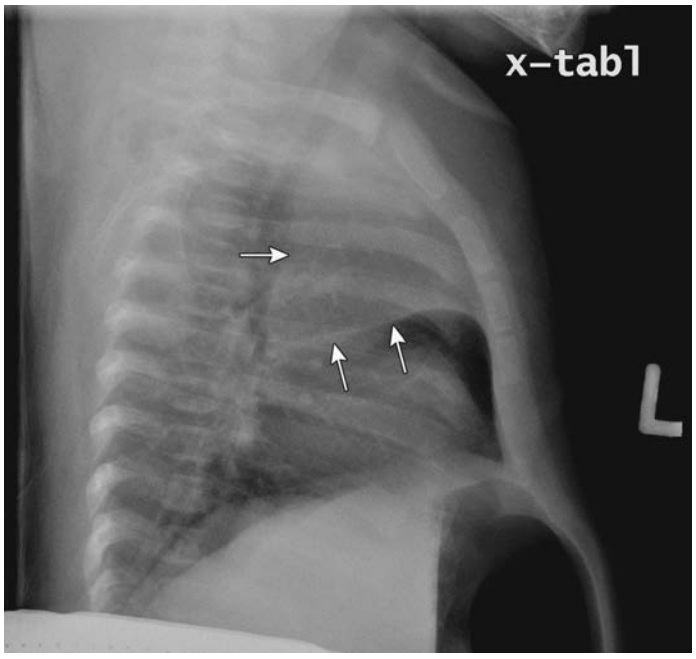
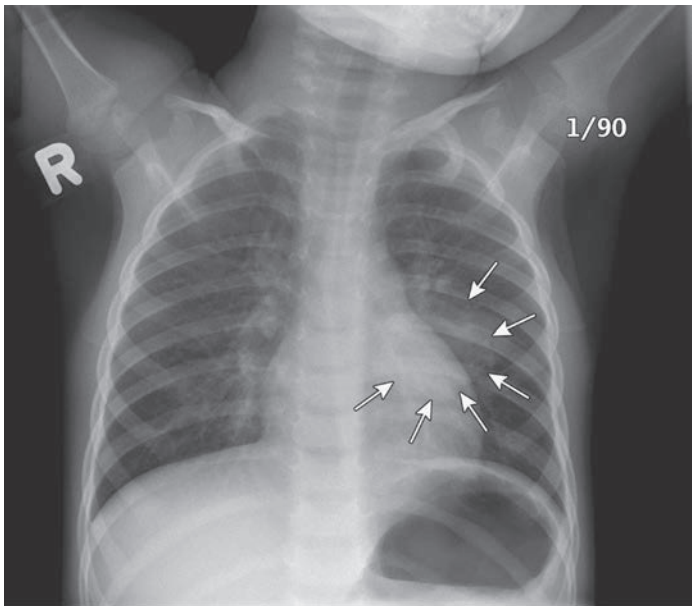


FIGURE 128-4. Lateral view confirms thymic density fully confined to the anterior mediastinum (*arrows*). [Photo contributed by BC Children's Hospital, Vancouver, British Columbia, Canada.]



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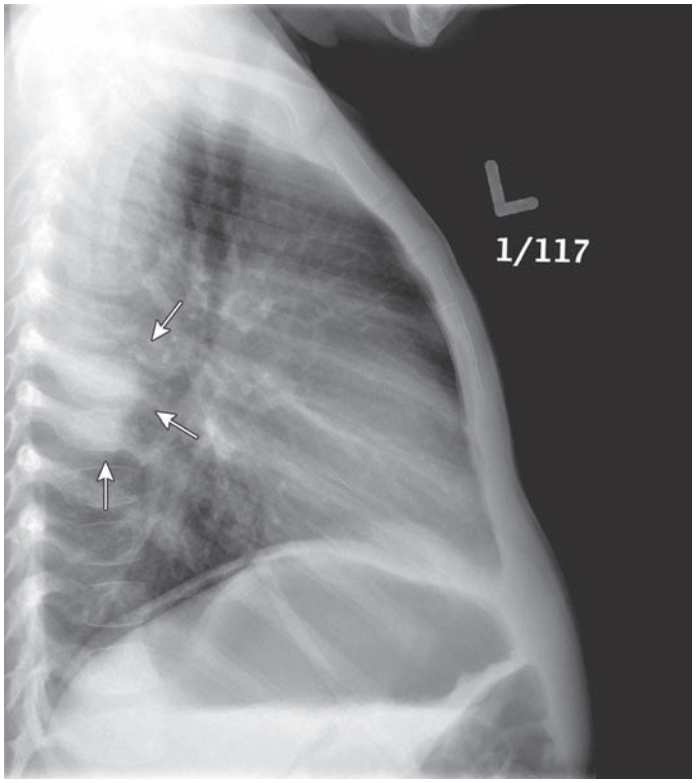

B

FIGURE 128-5. Anterior-posterior (**A**) and lateral views (**B**) show lower lobe consolidation (*arrows*). [Photos contributed by BC Children's Hospital, Vancouver, British Columbia, Canada.]

consolidation or patchy, multifocal findings. Younger children can also present with "round pneumonia" (**Figure 128-5**), a sharply defined consolidation often found in the posterior lower lobe, classically from pneumococcal infection. Cavitation and pleural effusions should arouse suspicion of infection with *S. aureus* or *S. pneumoniae*, particularly penicillin-resistant pneumococcus (**Figure 128-6**).

Acknowledgment: The author would like to thank Joseph E. Copeland for his prior work on this chapter.

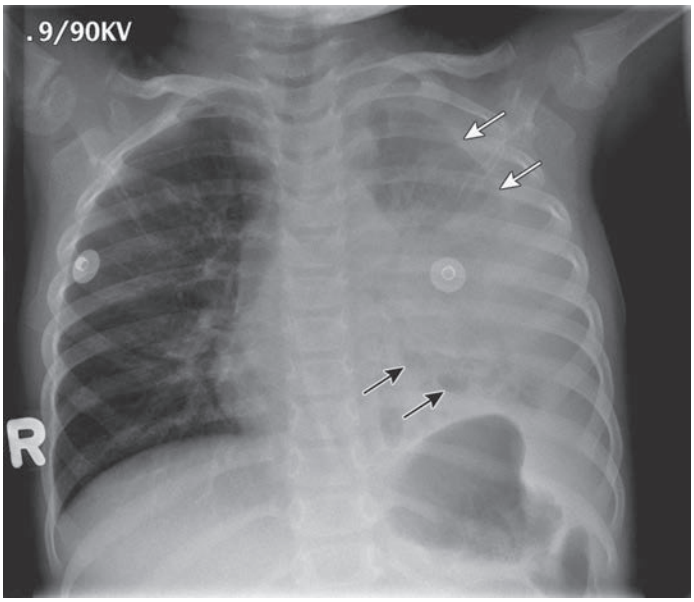

FIGURE 128-6. Complicated left-sided pneumonia. Note the pleural effusion (*white arrows*) and cavitation (*black arrows*). [Photo contributed by BC Children's Hospital, Vancouver, British Columbia, Canada.]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 129

Congenital and Acquired Pediatric Heart Disease

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INTRODUCTION

This chapter reviews congenital and acquired heart disease in children. The section on congenital heart defects begins with a review of fetal and neonatal cardiac physiology, followed by a discussion of specific lesions and their diagnosis and management organized by clinical presentation. A brief discussion of pediatric murmurs follows, and the section concludes with a discussion of common surgical procedures for repairing congenital heart defects and associated complications.

The section on acquired heart disease in children reviews inflammatory and infectious disorders and cardiomyopathies, of which the most important is hypertrophic cardiomyopathy.

PEDIATRIC CARDIAC PHYSIOLOGY

FETAL CIRCULATION

Fetal circulation involves a number of shunts to bypass the liquid-filled lungs, which are incapable of providing oxygen to circulating blood. Blood oxygenated by the maternal lungs passes through the placenta via the umbilical vein to the fetus. Roughly half of the blood flow passes through the liver and half through the ductus venosus to the inferior vena cava, where it mixes with deoxygenated fetal blood returning from the

lower body. The inferior vena cava enters the right atrium, where deoxygenated blood returning from the upper body and head via the superior vena cava mixes with that from the inferior vena cava. Blood from the right atrium travels in one of three routes: a portion passes through the foramen ovale into the left atrium, where it subsequently travels to the left ventricle, through the aorta, and into the vessels supplying the fetal head and upper extremities; most of the remainder enters the right ventricle and passes into the pulmonary artery, where the majority is shunted away from the lungs through the ductus arteriosus connecting the pulmonary artery with the aorta; and a small amount of blood travels to the lungs to provide oxygen and nutrients to support fetal lung growth.[1]

TRANSITIONAL CIRCULATION

The newborn's lungs expand and become air filled with gradual reabsorption of fetal lung fluid. This increases the partial pressure of arterial oxygen (Pao_2) of blood flowing through the newborn lung, which in turn mediates a cascade of events that completes the transition to adult circulatory patterns. Flow through the umbilical arteries ceases, and the venous flow through the cord slows and then stops. Pulmonary vascular resistance falls, and pulmonary blood flow increases (pulmonary vascular resistance continues to fall with increases in blood flow over the first 30 to 45 days of extrauterine life). The ductus venosus and ductus arteriosus close, and decreased pulmonary arterial resistance coupled with increased systemic resistance creates increased blood flow through the atria. Left atrial pressure exceeds right atrial pressure, which leads to closure of the foramen ovale.[2]

NEONATAL CARDIAC PHYSIOLOGY

Because neonates and small children have relatively noncompliant ventricular walls, they cannot increase stroke volume but rely on changes in heart rate to adjust cardiac output. Thus, sinus tachycardia is usually the first response to stress in infants and young children. The neonatal myocardium requires more oxygen than the infant's or child's heart and has a lower systolic reserve, which predisposes to congestive heart failure. Although the ductus arteriosus and foramen ovale are usually functionally closed by 15 hours of life and 3 months of age, respectively, shunting may still occur through these pathways during times of stress. Finally, the neonatal right ventricle is still predominant, whereas the left ventricle is predominant in older infants and children, and pulmonary vascular resistance is relatively high and oxygen responsive.

Preload is the amount of blood that the heart receives to distribute to the body. Decreasing the amount of blood flowing into the heart lowers cardiac output. Similarly, increasing the amount of blood into the heart increases cardiac output in accordance with Starling forces, to the point of maximum compliance of the ventricular wall. When the ventricular wall compliance is exceeded, cardiac output decreases dramatically, and congestive heart failure occurs.

Afterload is the resistance to blood flow out of the heart and is determined in neonates by the size and compliance of the ventricles, peripheral vascular resistance (which is largely mediated by catecholamines), and, when present, anatomic obstructions such as aortic stenosis or critical coarctation of the aorta.

Contractility or *inotropy*, which is the ability of the cardiac muscle to pump blood out of the heart, refers to the force or power of cardiac contraction and determines the amount of work that the heart can perform. Increasing the cardiac contractility increases the stroke volume and hence the cardiac output. Cardiac contractility is normally regulated by neural or humoral mechanisms. The ability of the neonatal heart to increase contractility is limited, as previously mentioned, and stroke volume is primarily increased through increases in rate.

Cardiac rate or *chronotropy* is the ability of the heart muscle to pump blood out of the heart per fixed unit of contraction. In the typical circumstance, chronotropy and inotropy cannot be differentiated with regard to therapeutic maneuvers. Typically, both the cardiac rate and the relatively fixed contractility of the neonatal heart contribute to the overall cardiac output, with the former contributing more of the output. In the hearts of children older than 4 or 5 years, there is a more balanced contribution to cardiac output, with the contractility playing a much more prominent role.

PEDIATRIC HEART MURMURS

Common benign pediatric murmurs need to be distinguished from murmurs that represent congenital heart defects. The characteristic murmurs of specific cyanotic and acyanotic congenital heart defects are described in the subsequent brief overviews of each lesion in this chapter. **Usually, innocent flow murmurs are of low intensity and do not radiate, are brief murmurs, and are most often systolic.**[3,4] **Table 129-1** lists the most common benign pediatric murmurs and their characteristics.

CONGENITAL HEART DISEASE

INTRODUCTION AND EPIDEMIOLOGY

Congenital heart defects can present at different ages with clinical signs and symptoms ranging from cyanosis to cardiovascular collapse or congestive heart failure depending on the anatomy and physiology of the lesion. Long-term survivors are at risk for a number of postoperative complications.

Congenital heart defects occur in approximately 8 in 1000 births and range from benign to life threatening. About 10% of congenital heart defects are associated with genetic syndromes such as trisomy 21, Turner's syndrome, and Noonan's syndrome, and heart defects may accompany other organ malformations in conditions such as **VACTERL** association (*v*ertebral anomalies, *a*nal atresia, *c*ardiac anomalies, *t*racheoesophageal fistulas, *e*sophageal atresia, *r*enal and *l*imb anomalies, and single umbilical artery). The remaining 90% of congenital heart defects result from isolated embryologic malformation or as yet undefined genetic lesions.

Congenital heart disease is usually classified based on physiology (presence or absence of cyanosis, with or without persistent fetal circulation) or on the nature of the anatomic defect (shunt, obstruction, transposition, or complex defect). Most textbooks separate cyanotic from acyanotic lesions.

Cyanotic lesions result in mixing of deoxygenated and oxygenated blood or right-to-left shunting; cyanotic lesions include the "**five Ts**": **tetralogy of Fallot**, tricuspid anomalies including **tricuspid atresia** and **Ebstein's anomaly**, **truncus arteriosus**, **total anomalous pulmonary venous return**, and **transposition of the great arteries**. **Acyanotic lesions** include those that result in pulmonary overcirculation such as **ventricular septal defect**, **atrial septal defect**, **patent ductus arteriosus**, and **atrioventricular canal** as well as those with restricted pulmonary or systemic blood flow such as **pulmonary stenosis**, **aortic stenosis**, and **aortic coarctation**.

It is often more useful to organize congenital heart disease by clinical presentation (**Table 129-2**). Distinct clinical presentations are discussed further in later sections, including the pathophysiology, clinical features and treatment, and individual defects within each group. Discussion of murmurs and arrhythmias included in this chapter is limited to those related to congenital heart disease. Rhythm disturbances are discussed in greater detail in the later section, "Acquired Heart Disease," and syncope and sudden death are discussed in Chapter 130, "Syncope, Dysrhythmias, and ECG Interpretation in Children."

CYANOSIS IN CONGENITAL HEART DISEASE

Cyanosis is the bluish discoloration of the skin that occurs from the presence of deoxygenated hemoglobin (which is blue) in capillary beds. For cyanosis to be clinically apparent, 3 to 5 milligrams/dL of deoxyhemoglobin must be present, corresponding to an oxygen saturation of 70% to 80% on room air. Compression of the placenta during birth typically leads to polycythemia in term newborns, and as a result, clinical cyanosis develops more readily in newborns because a smaller percentage of circulating hemoglobin must be desaturated to manifest this sign. Pulse oximetry is helpful in evaluation of cyanosis; however, its limitations should be recognized. Readings may become inaccurate when

TABLE 129-1 Benign Cardiac Murmurs

Murmur	Age	Character	Positioning	Cause	Differential Diagnosis
Still's vibratory murmur	Most common benign murmur in children 2–6 y; can occur in infancy to adolescence	Grade 1/6–3/6 early systolic ejection murmur, left lower sternal border to apex, vibratory musical quality	Louder when patient is supine	Postulated to be from flow across valvular cordi	Ventricular septal defect murmur is harsher.
Pulmonary flow murmur	Childhood to young adulthood	Grade 2/6–3/6 crescendo-decrescendo, early to midsystolic, left upper sternal border, second intercostal space	Louder when patient is supine, increased on full expiration	Turbulent flow in the pulmonary outflow tract	Atrial septal defect has fixed split S_2; pulmonic stenosis has higher pitched, longer murmur, ejection click.
Peripheral pulmonic stenosis murmur	Birth to 1 y	Grade 1/6–2/6, low-pitched, early to midsystolic ejection murmur in pulmonic area and radiating to axillae and back	Increased with viral respiratory infections, lower heart rate; decreased with tachycardia	Turbulence at peripheral pulmonary artery branches due to acute angles in infants	Significant branch pulmonary artery stenosis in Williams' syndrome; congenital rubella has higher-pitched murmur, extends beyond S_2, older child.
Supraclavicular or brachiocephalic murmur	Childhood to young adulthood	Crescendo-decrescendo, systolic, low pitched, above the clavicles, radiating to neck, abrupt onset and brief	Decreases with hyperextension of shoulders and reclining position	Turbulent flow through major brachiocephalic vessels arising from aorta	Idiopathic hypertrophic subaortic stenosis: louder with Valsalva maneuver and softer with rapid squatting. Aortic stenosis: higher pitched, ejection click.
Venous hum	Childhood	Faint to grade 6, continuous, humming, low anterior neck to lateral sternocleidomastoid muscle to anterior chest below clavicle	Louder when sitting, looking away from murmur; softer when lying, with compressed jugular vein or head turned toward murmur	Turbulence from internal jugular and subclavian veins entering superior vena cava	Patent ductus arteriosus has machinery murmur, not compressible, bounding pulses.
Mammary soufflé	Pregnancy or lactation, rarely adolescence	High pitched, systole into diastole, anterior chest over breast, varies day to day	—	Plethora of vessels over chest wall	Patent ductus arteriosus has machinery murmur, does not vary day to day.

Reproduced with permission from Strange GR, Ahrens WF, Schafermeyer RW, et al (eds): *Pediatric Emergency Medicine*, 3rd ed. New York: McGraw-Hill Professional; 2009, Table 47-2.

oxygen is <80% saturation. Additional factors such as cool extremities, poor peripheral perfusion, skin pigmentation, and probe position may reduce the precision of pulse oximeter readings.[5-7]

Congenital heart defects that present with cyanosis include transposition of the great arteries, tetralogy of Fallot, tricuspid atresia, truncus arteriosus, and total anomalous pulmonary venous return. These lesions have in common the mixing of oxygenated and deoxygenated blood, circulation of desaturated hemoglobin, and a cardinal manifestation as cyanotic heart disease. Another condition resulting in cyanosis is **persistent fetal circulation**, which can be caused by structural heart disease or noncardiac disease, including meconium aspiration, pneumonia, sepsis, and pulmonary hypertension. Lesions that restrict pulmonary blood flow, such as critical pulmonary stenosis, do not typically cause cyanosis without the presence of associated defects (atrial septal defect, ventricular septal defect) that allow for right-to-left shunting.

Congenital heart defects can lead to cyanosis in the first weeks of life or, for some lesions, episodically throughout childhood if uncorrected. Lesions such as transposition of the great arteries are associated with mixing of oxygenated and deoxygenated blood, usually through an associated ventricular septal defect or atrial septal defect and produce cyanosis in the period immediately after birth. Conditions associated with persistent pulmonary hypertension allow blood to shunt right to left through a patent foramen ovale or through a septal defect. Tetralogy of Fallot (see the next section, "Tetralogy of Fallot") can produce cyanosis at birth through mixing, but is also associated with episodic cyanosis ("**tet spells**"; see the later section, "Treatment of Tet Spells") throughout infancy and childhood if uncorrected. Large uncorrected septal defects (e.g., ventricular septal defect) can cause cyanosis in adolescents and young adults in a condition termed Eisenmenger's complex. Chronic left-to-right shunting across a nonrestrictive defect leads to hypertrophy of pulmonary arteriolar musculature that causes a gradual and irreversible rise in pulmonary vascular resistance and right-sided heart pressures until supersystemic pressures develop and shunting switches to right to left, which produces cyanosis.

Noncardiac causes of cyanosis range from benign peripheral vasoconstriction in response to cold or crying, causing peripheral cyanosis, to sepsis with poor perfusion or even effects of toxins such as methemoglobin.[8] The most common congenital heart defects that must be considered in the cyanotic neonate are briefly reviewed in the sections below before returning to a general approach to the evaluation and management of cyanotic congenital heart disease.

TETRALOGY OF FALLOT

Tetralogy of Fallot is the most common cyanotic congenital heart disease manifesting in the postinfancy period and composes as much as 10% of all congenital heart disease.[9,10] There are four primary components of tetralogy of Fallot: a large ventricular septal defect, right ventricular outflow obstruction (created by valvular or supravalvular pulmonic stenosis), an overriding aorta, and right ventricular hypertrophy.

The intensity of cyanosis depends on the amount of obstruction of the right ventricular outflow tract. A nonrestrictive ventricular septal defect balances the systolic pressures in the right and left ventricles. The amount of right ventricular outflow obstruction determines whether shunting is left to right, bidirectional, or right to left. Severe pulmonic stenosis creates a right-to-left shunt, resulting in cyanosis and decreased pulmonary blood flow. The acyanotic form of tetralogy of Fallot is characterized by mild pulmonic stenosis with a left-to-right shunt. In addition to cyanosis, examination findings can include a systolic thrill at the lower and middle left sternal border. A loud single S_2, an aortic ejection click, a loud systolic ejection murmur (heard best at the middle to lower left sternal border), and a continuous patent ductus arteriosus murmur may also be apparent on examination.

TRANSPOSITION OF THE GREAT ARTERIES

Composing about 5% to 8% of all congenital heart disease, transposition of the great arteries is the most common cyanotic heart lesion manifesting

TABLE 129-2 Clinical Presentations of Congenital Heart Disease

Clinical Presentation	Symptoms	Signs	Potential Congenital Cardiac Lesion	Initial ED Management
Shock	• Poor feeding • Fussiness • Progression to lethargy	• Extreme tachycardia • Pallor (often "ashen gray") or acral cyanosis • Weak peripheral pulses • Delayed capillary refill • Mottled skin • Altered mental status • Hypotension with decreased blood pressure in lower extremities versus right arm (in some lesions)	• Critical aortic stenosis • Coarctation of the aorta • HLHS • ALCAPA with myocardial infarction	• Apply monitors • Apply oxygen if hypoxic • Obtain IV or IO • Blood work (glucose, CBC, blood gas, lactate, BUN, creatinine, and blood culture) • Obtain chest radiograph • Consider broad-spectrum antibiotics If abnormal cardiac exam (murmur, gallop, hepatomegaly, no palpable femoral pulses, discrepant limb blood pressures): • If patient <1 mo old, start prostaglandin E_1 infusion 0.05–0.1 microgram/kg/min (**CAUTION:** Contraindicated in TAPVR with obstruction and PPHN) • If patient >1 mo old, administer IV fluid bolus of 10 mL/kg normal saline • Obtain ECG • Consult cardiology for echocardiogram

Cyanosis	• Fussiness	• Central cyanosis (mucous membranes and trunk)
		• Hypoxia not improved with oxygen administration (oxygen saturation typically <80%–85%)
			• Truncus arteriosus
			• Transposition of the great arteries
			• Tricuspid atresia
			• Tetralogy of Fallot
			• TAPVR with obstructed veins
				• Calm the patient
				• Apply monitors
				• Apply oxygen
				• Establish IV or IO
				If known or suspected tetralogy of Fallot:
				• Place patient in knee-to-chest position
				• Administer opioid: morphine 0.1 milligram/kg SC/IM/IV
				or
				fentanyl 2 micrograms/kg intranasal
				• Consult cardiology and intensive care unit
				• Administer IV fluid bolus of 5–10 mL/kg normal saline
				• Consider the following:
				  • Ketamine 0.5–3 milligrams/kg IV/IO/IM
				  • Propranolol 0.2 milligram/kg IV over 3–5 min or esmolol 500 micrograms/kg followed by infusion
				  • Phenylephrine 10 micrograms/kg IV followed by infusion of 2–3 micrograms/kg/min
				  • Sodium bicarbonate 1 mEq/kg IV
				• Transfer to cardiology or intensive care unit

Congestive heart failure	• Feeding difficulty • Sweating with feeds • Fussiness • Failure to thrive • Difficulty breathing	• Tachypnea with labored breathing • Rales • Gallop • Hepatomegaly • Jugular venous distention (difficult to see in infants) • Cyanosis if severe	• Ventricular septal defect • Patent ductus arteriosus • Atrioventricular canal • PAPVR • ALCAPA with recurrent ischemia and cardiac failure	• Apply monitors • Apply oxygen with caution • Establish IV or IO • Blood work (glucose, CBC, blood gas, lactate, B-type natriuretic peptide, BUN, and creatinine) • If patient not protecting airway, intubate and notify intensive care unit and cardiology for extracorporeal life support backup • If patient has stable airway, obtain chest radiograph • If patient has cardiomegaly/pulmonary edema, consider IV furosemide 1 milligram/kg • Consult cardiology for echocardiogram and consider additional medications such as digoxin, β-blockers, or inotropes based on patient need

Abbreviations: ALCAPA = anomalous left coronary artery from the pulmonary artery; HLHS = hypoplastic left heart syndrome; PAPVR = partial anomalous pulmonary venous return; PPHN = persistent pulmonary hypertension of the newborn; TAPVR = total anomalous pulmonary venous return.

in the newborn period. Compared to other congenital heart defects, extracardiac anomalies occur less often in babies with transposition of the great arteries (<10%).[11,12] There are many variations in transposition of the great arteries, but the underlying elements are that the aorta arises from the right ventricle and the main pulmonary artery originates from the left ventricle. This arrangement gives rise to two distinct circulatory systems. Because the main pulmonary artery has higher oxygen saturation than the aorta, hyperoxic blood goes through the pulmonary system and hypoxic blood flows through the systemic system. Mixing of the two circulatory systems is the only manner in which oxygenated blood enters the systemic blood flow. A ventricular septal defect, atrial septal defect, or patent ductus arteriosus must exist in order for the infant to survive. In 20% to 40% of patients, a ventricular septal defect is present. The physical examination is notable for a loud and single S_2, and if a ventricular septal defect exists, a systolic murmur may be heard.

TOTAL ANOMALOUS PULMONARY VENOUS RETURN

Total anomalous pulmonary venous return represents 1% of congenital heart disease.[13,14] The pulmonary veins empty into the right atrium instead of returning blood from the lungs into the left atrium. Total anomalous pulmonary venous return is usually separated into four groups depending on where the pulmonary veins empty. In the supracardiac type (50% of all total anomalous pulmonary venous return cases), the common pulmonary vein is attached to the superior vena cava. In the cardiac type (20%), the common pulmonary vein drains into the coronary sinus. In the infracardiac/subdiaphragmatic type (20%), the common pulmonary vein empties into the portal vein, ductus venosus, hepatic vein, or inferior vena cava. Mixed lesions compose the remaining 10%. Survival depends on the mixing of blood, so an atrial septal defect or a patent foramen ovale must be present.

When pulmonary venous return arrives in the right atrium, there is mixing of the pulmonary and systemic circulations. In the right atrium, blood crosses the atrial septal defect to the left atrium or crosses the tricuspid valve to the right ventricle. Systemic arterial blood becomes desaturated because of the mixing of pulmonary and systemic arterial flow. Pulmonary blood flow determines the degree of desaturation of systemic arterial blood. If there is no obstruction to pulmonary venous return, systemic blood is minimally desaturated. Obstruction to pulmonary venous return results in severe cyanosis. Because of the extra volume returning to the right side of the heart, right ventricular and atrial enlargement can develop.

Although total anomalous pulmonary venous return more commonly presents with signs and symptoms of congestive heart failure (see later section, "Congestive Heart Failure in Congenital Heart Disease"), tachypnea, tachycardia, hepatomegaly, and cyanosis are commonly seen. Children with pulmonary venous obstruction often have a history of frequent pneumonias and growth retardation. The physical examination reveals a right ventricular heave and fixed split S_2. A grade 2/6 to 3/6 systolic ejection murmur heard at the left upper sternal border and a mid-diastolic rumble at the left lower sternal border are also heard. Total anomalous pulmonary venous return with pulmonary venous obstruction leads to respiratory distress and cyanosis with a loud and single S_2 and a gallop but, on most occasions, no murmur.

TRICUSPID ATRESIA

Tricuspid atresia represents 1% to 2% of congenital heart disease.[15,16] There is no tricuspid valve, and the development of the right ventricle and pulmonary artery is interrupted. Pulmonary blood flow is decreased. With no flow existing between the right atrium and right ventricle, an atrial septal defect, ventricular septal defect, or patent ductus arteriosus is necessary for survival because the right atrium requires a right-to-left shunt in order to empty. The great arteries are transposed, with a ventricular septal defect and pulmonic stenosis in 30% of cases. Artery anatomy is normal, with a small ventricular septal defect and pulmonic stenosis in half of cases.

With all of the systemic venous return shunted from the right atrium to the left atrium, right atrial dilatation and hypertrophy occur. Increased volume from the systemic and pulmonary circulations causes enlargement of the left atrium and left ventricle. The extent of cyanosis and the amount of pulmonary blood flow are inversely related.

Usually patients have marked cyanosis, tachypnea, and poor feeding. A single S_2 is evident, as well as a grade 2/6 or 3/6 regurgitant systolic murmur heard best at the left lower sternal border. The continuous murmur of a patent ductus arteriosus may also exist. Hepatomegaly is present if there is congestive heart failure.

TRUNCUS ARTERIOSUS (COMMON ARTERIAL TRUNK)

In truncus arteriosus, all of the pulmonary, systemic, and coronary circulations originate from a single arterial trunk. The defect comprises <1% of all congenital heart disease.[17,18] Associated with truncus arteriosus are a large ventricular septal defect, coronary artery irregularities, and DiGeorge's syndrome (hypocalcemia, hypoparathyroidism, absent or hypoplastic thymus, and chromosomal abnormalities). Pulmonary blood flow is determined by the type of truncus, and flow can be normal, increased, or decreased. There is a direct relationship between the amount of pulmonary blood flow and systemic arterial oxygen saturation. Decreased pulmonary blood flow creates marked cyanosis, whereas increased pulmonary blood flow produces minimal cyanosis but is associated with congestive heart failure from left ventricular volume overload.

Congestive heart failure and cyanosis typically develop within the first few weeks of life. A loud regurgitant 2/6 to 4/6 systolic murmur at the left sternal border may be accompanied by a high-pitched diastolic decrescendo murmur or diastolic rumble. A single S_2 is prominent.

CLINICAL FEATURES OF CYANOTIC CONGENITAL HEART DISEASE

HISTORY

The cardinal clinical presentation of cyanotic congenital heart defects is cyanosis. The history taking should elicit details of the pregnancy, gestational age, fetal US results if applicable, and complications of labor and delivery, including cyanosis in the period immediately after birth. For older infants and children with known congenital heart defects, details of the anatomy and surgical procedures and current medications should be obtained. Baseline oxygen saturations may be known by caretakers and are helpful when intercurrent illness leads to an ED visit. Take a careful feeding history, focusing on changes in oral intake, slow or difficult feeding, sweating with feeds, and growth, and a complete review of systems should be performed.

PHYSICAL EXAMINATION

Measure all vital signs, including blood pressure in the upper and lower extremities. A difference in upper and lower extremity blood pressures may signal an obstructive lesion such as coarctation of the aorta (see later section, "Coarctation of the Aorta"). Document weight and growth parameters. Note if cyanosis is **central** (mucosal) or **peripheral** (acral, involving digits). Listen for cardiac murmurs, noting location, timing, and loudness (see later section, "Pediatric Heart Murmurs"), and a gallop or fixed splitting of S_2 (characteristic of atrial septal defect). Palpate the chest for heaves, lifts, and thrills, and note surgical scars. Observations of the strength, quality, and symmetry of pulses help in the assessment of cardiac output. Hepatomegaly and splenomegaly suggest right-sided heart failure. Observe for signs of increased work of breathing, and auscultate for rales, which suggest congestive heart failure. **Neonates with cyanosis secondary to congenital heart disease rarely have respiratory symptoms other than tachypnea.** Neonates with lung disease producing cyanosis show respiratory distress, grunting, tachypnea, and retractions. Cyanotic infants with CNS disturbances or sepsis have apnea, bradycardia, lethargy, and seizures. Neonates with **methemoglobinemia** show minimal distress despite their cyanotic appearance. Perform a complete head-to-toe examination in the cyanotic patient without a known history of congenital heart defects to exclude noncardiac causes.

DIAGNOSIS IN CYANOTIC HEART DISEASE

Laboratory tests are not typically helpful in the evaluation of cyanotic congenital heart defects, although they help exclude other causes of cyanosis. Results of the **"hyperoxia test" (Pao_2 in response to breathing 100% oxygen)** may help distinguish heart disease from other causes of cyanosis. **Neonates with cyanotic heart disease do not demonstrate an increase in Pao_2 >20 mm Hg, because of the right-to-left shunting of the circulation.** Most neonates with lung disease or sepsis, however, demonstrate an increase in Pao_2 after breathing 100% oxygen for 20 minutes. Infants with persistent pulmonary hypertension may or may not demonstrate a significant rise in Pao_2. There is no response to oxygen in the neonate with methemoglobinemia. **When a blood specimen is exposed to air, it turns pink in all the conditions described earlier except in methemoglobinemia, in which the blood remains chocolate colored.** In an infant without known congenital heart defects, results of arterial blood gas analysis with the infant breathing room air and 100% oxygen can be compared: failure of the Pao_2 to rise significantly with 100% oxygen suggests cardiac mixing or right-to-left shunting, whereas improvement in the Pao_2 in response to oxygen suggests a pulmonary cause.

The primary diagnostic tests for the patient with suspected cyanotic congenital heart defects are chest radiography and ECG (**Table 129-3**). Chest radiographic studies are essential in assessing the size and shape of the heart and in evaluating pulmonary blood flow. The chest radiograph also provides some information about the position of the aortic arch, which should be normally left sided. In the normal left-sided aortic arch, there is rightward displacement of the esophagus and trachea. **An abnormal position of the aortic arch may be a clue to the diagnosis of the congenital cardiac lesion**. Right-sided aortic arches are seen in truncus arteriosus, transposition of the great arteries, tetralogy of Fallot, tricuspid atresia, and total anomalous pulmonary venous return. The chest radiograph is critical to the assessment of pulmonary vascularity. With small left-to-right shunts, the pulmonary vascularity is normal. Pulmonary vascularity can also be normal in conditions that cause pulmonary stenosis, such as valvular pulmonic stenosis or functional pulmonic stenosis associated with tetralogy of Fallot. Increased pulmonary vascularity may be seen with any cause of left-to-right shunting or in any cause of left-sided failure, such as outflow obstruction.

The ECG is useful to evaluate chamber size, electrical axis, and cardiac conduction. Age-related normal values should be used as a reference to determine axis deviation, atrial enlargement, or ventricular hypertrophy.[19] The electrical axis most often defines abnormal chamber diameters and usually does not suggest cardiac ischemia as in the adult population. Table 129-3 lists characteristic chest radiograph and ECG findings of cyanotic congenital heart defects. **Figure 129-1** depicts the typical "boot-shaped heart" of tetralogy of Fallot.

TABLE 129-3 Cyanotic Congenital Cardiac Lesions: Typical Chest Radiograph and ECG Findings

Cardiac Lesion	Chest Radiograph	ECG
Tetralogy of Fallot	Boot-shaped heart, normal-sized heart, decreased pulmonary vascular markings	Right axis deviation, right ventricular hypertrophy
Transposition of the great arteries	Egg-shaped heart, narrow mediastinum, increased pulmonary vascular marking	Right axis deviation, right ventricular hypertrophy
Total anomalous pulmonary venous return	Snowman sign, significant cardiomegaly, increased pulmonary vascular markings	Right axis deviation, right ventricular hypertrophy, right atrial enlargement
Tricuspid atresia	Heart of normal to slightly increased size, decreased pulmonary vascular markings	Superior QRS axis with right atrial hypertrophy, left atrial hypertrophy, left ventricular hypertrophy
Truncus arteriosus	Cardiomegaly, increased pulmonary vascular markings	Biventricular hypertrophy



FIGURE 129-1. Chest radiograph revealing the classic "boot-shaped heart" of tetralogy of Fallot. [Reproduced with permission from Shah BR, Lucchesi M (eds): *Atlas of Pediatric Emergency Medicine*. New York, NY: McGraw-Hill, Inc.; 2006.]

When available, bedside echocardiography may delineate structural heart disease, although adequate imaging depends on the availability of an ultrasonographer with pediatric cardiac experience.

TREATMENT IN CYANOTIC HEART DISEASE

The management of cyanotic congenital heart defects depends on the age of the patient, hemodynamic stability, and prior diagnosis and medical management (Table 129-3). Most cyanotic congenital heart defects are hemodynamically stable. With obstructive lesions, in contrast, adequate circulation often depends on systemic or pulmonary blood flow through a patent ductus arteriosus, and such lesions can be fatal if patency is not maintained with prostaglandins (see later section, "Shock in Congenital Heart Disease"). Although central cyanosis and low oxygen saturation are alarming and may tempt one to administer oxygen immediately, **neonates have significant amounts of oxygen-avid fetal hemoglobin and tolerate oxygen saturation percentages in the 70s (characteristically seen in most mixing lesions) without tissue or brain hypoxemia**. Moreover, oxygen is a potent pulmonary vasodilator. **Oxygen administration and pulmonary vasodilation are helpful in treating cyanotic congenital heart defects associated with pulmonary hypertension or vasoconstriction, but may actually lead to pulmonary vascular overcirculation or even "steal" of systemic blood flow in patients with a patent ductus arteriosus and ductal-dependent systemic blood flow. Oxygen administration should be reserved for patients with signs and symptoms of inadequate tissue perfusion, those without known heart disease in whom it may be diagnostic as well as therapeutic, and patients with known congenital heart defects with oxygen saturation significantly below known baseline values.**

The primary management objective in the cyanotic neonate or infant is the treatment of intercurrent illness, exclusion of noncardiac causes of cyanosis, and diagnosis of cyanotic congenital heart defects in those who do not have a previous diagnosis. Treatment thereafter involves consultation with a pediatric cardiologist and transfer to a tertiary pediatric hospital or clinic.

TREATMENT OF TET SPELLS

A tet spell is caused by right-sided outflow tract obstruction leading to right-to-left shunting through a ventricular septal defect. Hypoxia and acidosis cause pulmonary arterial vasoconstriction, thus increasing pulmonary resistance and exacerbating shunting. The management goals for tet spells are to increase pulmonary blood flow by increasing preload, provide pulmonary vasodilation, and increase afterload in order to reverse right-to-left shunting and promote pulmonary blood flow. **This is often achieved through simple maneuvers such as administering 100% oxygen via a non-rebreathing facemask, calming the child by minimizing stimulation and placing the child**

in a parent's arms, and flexing the child's knees to the chest in order to increase venous return to the heart and increase systemic vascular resistance to mitigate right-to-left shunting. Second-line intervention includes administration of morphine, 0.1 to 0.2 milligram/kg IM, SC, or IV, and isotonic fluid (normal saline 5 to 10 mL/kg bolus) to increase preload. Case reports have demonstrated efficacy of intranasal fentanyl or intranasal midazolam as alternatives to morphine.[20,21] If these measures are unsuccessful, next options include administration of sodium bicarbonate 2 mEq/kg as an IV bolus to treat acidosis and promote pulmonary vasodilation; propranolol 0.2 milligram/kg IV to relieve infundibular spasm; or phenylephrine 2 to 10 micrograms/kg/min to increase systemic vascular resistance. Ketamine may be helpful with its sedative effects and its increase in systemic vascular resistance.[22] Refractory spells may require neuromuscular blockade and rapid-sequence intubation.

SHOCK IN CONGENITAL HEART DISEASE

The presentation of congenital heart defects as shock or cardiovascular collapse is dramatic. Cardiogenic shock can be the final common pathway for a wide variety of disease processes, both noncardiac and cardiac. Sepsis, hypovolemic shock, metabolic disease, adrenal insufficiency, respiratory failure, trauma, and poisonings can all lead to cardiogenic shock and are discussed in other chapters. Consider noncardiac causes of shock and low cardiac output states and treat the patient accordingly while contemplating the possibility of congenital heart disease.

Congenital heart defects that present as shock or cardiovascular collapse include lesions that depend on flow through the ductus arteriosus to provide systemic or pulmonary perfusion (Table 129-4). The classic examples are severe coarctation of the aorta and hypoplastic left heart syndrome. In both of these conditions, systemic blood flow is restricted by the underlying defect but maintained by flow through a patent ductus arteriosus that bypasses the coarctation in the former and allows blood pumped by the functional right ventricle to perfuse the aorta in the latter. The ductus typically closes and becomes the ligamentum arteriosum by the second or third week of life, and as it constricts, patients with duct-dependent flow manifest poor peripheral perfusion with increasing acidosis and eventual cardiovascular collapse.

Once the ductus arteriosus begins to close, some cardiac lesions become incompatible with life, because blood can no longer reach the lungs or systemic circulation. Both cyanotic and acyanotic lesions may present in this fashion.

Acyanotic lesions include severe coarctation of the aorta, critical aortic stenosis, and a hypoplastic left ventricle. Transposition of the great arteries, pulmonary atresia, and hypoplastic right heart syndrome are examples of the cyanotic lesions that may present with shock.

Nonstructural cardiac causes of shock include dysfunctional myocardium, which may mimic the signs and symptoms seen with shunt-dependent anatomic lesions. Such cardiomyopathies are uncommon in pediatric patients but can easily be confused with anatomic lesions. Cardiomyopathies in children are discussed later in "Acquired Heart Disease."

Duct-dependent acyanotic congenital lesions are briefly reviewed in the following sections.

COARCTATION OF THE AORTA

Coarctation of the aorta represents 8% to 10% of congenital heart disease and has a 2:1 male predominance. Congenital narrowing of the aorta takes place around the ductus arteriosus in the upper thoracic aorta. Factors determining the severity and clinical manifestations of disease include the degree of narrowing, the length of narrowing, and the presence of associated defects. Infants who present early have a right ventricle that supplies the descending aorta through a patent ductus arteriosus in fetal life. A ventricular septal defect, patent ductus arteriosus, aortic hypoplasia, and underdeveloped collateral circulation can also be seen.

PATENT DUCTUS ARTERIOSUS

A patent ductus arteriosus delays the obstructive effects of coarctation by allowing blood to flow distal to the obstruction. With closure of the patent ductus arteriosus, pulmonary hypertension occurs, leading to pulmonary venous congestion and congestive heart failure. Blood flow distal to the aortic obstruction is compromised. Shock, metabolic acidosis, tachypnea, and feeding difficulty are common; when congestive heart failure occurs, a loud gallop and weak pulses with or without a murmur can usually be appreciated.[23]

Finding decreased pulses in the lower extremities is essential to diagnosing a coarctation. Comparing right upper extremity blood pressures and pulse oximeter readings with those of the lower extremities aids in diagnosis unless the patient is in shock, in which case pulses may be decreased all over.

HYPOPLASTIC LEFT HEART SYNDROME

Hypoplastic left heart syndrome consists of hypoplasia of the left ventricle and ascending aorta and aortic arch. Atresia or marked stenosis of the mitral and aortic valves and regressed development of the left atrium are also common. These combined lesions lead to minimal left ventricular outflow. In utero pulmonary vascular resistance remains higher than systemic vascular resistance. The right ventricle is able to maintain normal perfusion of the body through right-to-left shunting through the patent ductus arteriosus as a result of elevated pulmonary resistance. Systemic blood flow is based entirely on the ductus arteriosus. After birth, major problems occur as reversal of the fetal pulmonary-systemic pressure gradient takes place and the ductus arteriosus closes. Cardiac output collapses and aortic pressure falls, which results in circulatory shock and metabolic acidosis. Pulmonary edema also develops because of increased pulmonary blood flow and increased left atrial pressure. Signs at presentation include an ashen gray color, tachypnea, and listlessness, and a single heart sound, systolic ejection murmur, and decreased pulses are noted.[23,24]

AORTIC STENOSIS

Aortic stenosis composes 6% of congenital heart disease and has a 4:1 male predominance. Stenosis can occur at the valvular, supravalvular, or subvalvular levels. Infants with severe obstruction (10% to 15%) present with congestive heart failure and poor distal perfusion or shock. Left ventricular hypertrophy typically develops in severe stenosis. Patients with aortic stenosis who are asymptomatic in infancy can present in childhood with syncope and hypertension.

A bicuspid aortic valve is the most common form of aortic stenosis. Supravalvular aortic stenosis, elfin facies, mental retardation, and pulmonary artery stenosis compose Williams' syndrome. A systolic thrill may be noticed at the right upper sternal border, suprasternal notch, or carotid arteries along with an ejection click. There can also be a rough or harsh grade 2/6 to 4/6 systolic murmur at the right or left sternal border with transmission to the neck.

CLINICAL FEATURES OF SHOCK IN CONGENITAL HEART DISEASE

HISTORY

The typical history of the neonate with duct-dependent congenital heart defects is one of a day or two of poor feeding, irritability, or lethargy followed by decreasing responsiveness, often in the second or third week of life. By the time the neonate arrives in the ED, he or she is often in severe shock. Obtain a complete history of the pregnancy, labor and delivery, and immediate perinatal period and carefully review symptoms (e.g., vomiting, diarrhea, fever, respiratory distress) to rule out noncardiac causes of shock such as dehydration or infection.

PHYSICAL EXAMINATION

Measure four-extremity blood pressure to identify a gradient between upper and lower extremities characteristic of coarctation of the aorta. **Pulse oximetry measurements in the right (preductal) and left (postductal) upper extremities may also reveal a difference, suggesting**

duct-dependent flow. Tachycardia is usually severe, and tachypnea may reflect profound metabolic acidosis or may be a manifestation of heart failure. Hypoxemia and cyanosis may accompany cyanotic lesions with duct-dependent flow. An ashen or gray color is characteristic of the infant with left-sided outflow obstruction in systemic shock, and extremities may be cold and mottled with severely delayed capillary refill. A single heart sound is characteristic of hypoplastic left heart syndrome, and a harsh systolic murmur transmitted to the neck may be heard in patients with aortic stenosis. A gallop rhythm may be appreciated when congestive heart failure accompanies shock. Pulses are typically thready and may be absent in the lower extremities with significant delay between right brachial and femoral pulses. The lung examination may reveal rales, tachypnea, and retractions or grunting in neonates with both shock and congestive heart failure. The infant may be limp and lethargic.

DIAGNOSIS IN CONGENITAL HEART DISEASE WITH SHOCK

Laboratory studies that may aid in the diagnosis and management of duct-dependent congenital heart defects include arterial blood gas analysis, which often demonstrates profound metabolic acidosis. Other electrolyte abnormalities are rare, although renal insufficiency from hypoperfusion may accompany severe shock. A CBC is not routinely helpful but may be obtained to rule out noncardiac causes of shock, such as sepsis.

ECG and chest radiography are typically performed and may be useful in narrowing the differential diagnosis of suspected congenital heart defects. **Table 129-4** lists the characteristic findings in duct-dependent acyanotic lesions.

Radiographs are less helpful in duct-dependent acyanotic congenital heart defects than in cyanotic heart disease, but may be useful when clinical symptoms and signs of congestive heart failure exist. Signs of aortic stenosis outside of infancy are cardiomegaly and posterior rib notching of the third to eighth ribs from collateral vessels. Bedside echocardiography requires an ultrasonographer experienced in examining for pediatric heart disease.

TREATMENT OF SHOCK IN CONGENITAL HEART DISEASE

Although oxygen is typically administered to patients in shock in order to increase the dissolved oxygen content of blood and enhance tissue oxygenation, **oxygen is a potent pulmonary vasodilator and decreases right-to-left flow through the ductus arteriosus, potentially worsening systemic perfusion. Oxygen is also a vasoconstrictor of the ductus arteriosus, which further worsens perfusion** (Table 129-2). Infants requiring rapid-sequence intubation are at high risk for complications, and pretreatment with atropine is recommended (0.02 milligram/kg IV 2 minutes prior to sedation and paralysis).[25]

The single most important therapeutic intervention for duct-dependent lesions is the infusion of **IV prostaglandin E_1** to restore ductal patency and improve left-to-right shunting and systemic blood flow. **The initial dose of prostaglandin E_1 is 0.1 microgram/kg/min, and improvement in peripheral perfusion typically occurs in minutes.** Subsequent titration to the lowest effective dosage is recommended, typically 0.05 microgram/kg/min. **Prostaglandin E_1 can be administered through an umbilical venous catheter, central line, IO line, or peripheral IV line with equal efficacy. Side effects include vasodilation and flushing, hyperthermia, hypotension (although blood pressure typically improves), and apnea.** Continuous monitoring of infants receiving prostaglandin E_1 is therefore advised. In certain obstructive variants of total anomalous pulmonary venous return, administration of prostaglandin E_1 can exacerbate the patient's condition because it increases pulmonary flow and decreases pulmonary resistance, thereby increasing pulmonary venous congestion.

Give a bolus of 10 mL/kg of normal saline with careful reassessment after each bolus to increase preload and improve cardiac output. Infants with severe congestive heart failure may not tolerate much volume. Sodium bicarbonate, 1 to 2 mEq/kg, can be considered for severe metabolic acidosis (pH <7.0), but may cause paradoxical intracellular worsening of acidosis and myocardial dysfunction, and adequate ventilation must be ensured. Occasionally, pressors such as dopamine or dobutamine may be helpful after prostaglandin E_1 infusion has been initiated.

Sepsis cannot be excluded on clinical grounds, so also give ampicillin, 100 milligrams/kg, and gentamicin, 4 milligrams/kg; or cefotaxime, 50 to 100 milligrams/kg.

Consultation with a pediatric cardiologist and pediatric critical care specialist is of great importance. Although many practitioners routinely intubate infants receiving prostaglandin E_1 prior to transport to tertiary hospitals, infants in stable condition may safely be transported unintubated.[26]

TABLE 129-4 Duct-Dependent Acyanotic Congenital Cardiac Lesions: Typical Chest Radiograph and ECG Findings

Cardiac Lesion	Chest Radiograph	ECG
Coarctation of the aorta	Cardiomegaly with pulmonary edema (neonate) Rib notching and collateral vascularity (child)	RVH, right bundle branch block (neonate) LVH (child)
Hypoplastic left heart syndrome	Cardiomegaly	Right atrial enlargement, RVH, peaked P waves
Aortic stenosis	Cardiomegaly	LVH in severe cases

Abbreviations: LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy.

CONGESTIVE HEART FAILURE IN CONGENITAL HEART DISEASE

Congenital heart defects can lead to congestive heart failure because of left-sided outflow obstruction resulting in elevated left atrial pressure (e.g., aortic stenosis) or pulmonary overcirculation through a patent ductus arteriosus or septal defect (Table 129-2). Such lesions typically present later in infancy, often in the second through fourth months of life, with failure to thrive, feeding difficulties, sweating with feeds, and gradually increasing respiratory distress that may worsen with respiratory infection. A number of acquired heart conditions, including myocarditis, cardiomyopathy, and arrhythmias, as well as noncardiac conditions, such as sepsis, metabolic disease, or severe anemia, can also cause congestive heart failure in infants and children (see later section, "Acquired Heart Disease").

Important factors in the development of congestive heart failure include increased afterload from left-sided obstructive lesions (e.g., coarctation or stenosis of the aorta), increased preload or pulmonary circulation from left-to-right shunts (e.g., large ventricular septal defect, atrial septal defect, patent ductus arteriosus), decreased inotropic function (e.g., cardiomyopathy), and rhythm abnormalities (e.g., sustained tachyarrhythmias).

In addition to congenital structural heart disease, noncardiac disorders and acquired heart disease should be considered as causes of congestive heart failure. Congenital structural causes of congestive heart failure not already discussed are described further in the following sections.

ATRIAL SEPTAL DEFECTS

Atrial septal defects compose 10% of congenital heart disease.[27,28] Only 10% of infants with an atrial septal defect develop clinical symptoms. Large or multiple defects can cause significant left-to-right shunting with overloading of the pulmonary circulation. Surgical intervention is needed for larger atrial septal defects, whereas smaller ones may close spontaneously. Difficulty feeding and trouble gaining weight are common with larger lesions.

Ostium secundum defects represent the majority of atrial septal defects and result from the incomplete adhesion of the foramen ovale and septum secundum. Ostium primum atrial septal defects result from the insufficient merging of the septum primum and endocardial cushion with associated abnormalities of the mitral and tricuspid valves. Sinus venosus atrial septal defects occur when the atrium does not merge with the sinus venosus. In these lesions, a widely and fixed split S_2 with

a grade 2/6 to 3/6 systolic ejection murmur at the left sternal border can often be appreciated, along with a mid-diastolic rumble.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects are the most common congenital heart defect, composing >30% of all such defects.[27,29] Ventricular septal defects allow blood to mix in the ventricles. The size of the ventricular septal defect determines the clinical extent of disease, with small defects having little or no effect and large defects contributing to pulmonary hypertension and congestive heart failure. Large ventricular septal defects create volume and pressure overload in the right ventricle and volume overload in the left atrium and left ventricle. This results in congestive heart failure and poor weight gain and may lead to developmental delay. A grade 2/6 to 5/6 holosystolic, harsh murmur can often best be heard at the left lower sternal border and may have an associated systolic thrill or diastolic rumble with a narrowly split S_2.

PATENT DUCTUS ARTERIOSUS

A patent ductus arteriosus is present in 10% of cases of congenital heart disease and occurs when the ductus arteriosus fails to close spontaneously.[27] The degree of shunting through the ductus arteriosus depends on the length and diameter of the lesion and the pulmonary vascular resistance. Symptomatic patients have large left-to-right shunts. Normally, the ductus arteriosus closes within 15 hours of birth and seals completely at 3 weeks of age, becoming the ligamentum arteriosum. Prematurity and hypoxia can delay closure of the ductus arteriosus. As with all left-to-right shunts, a large patent ductus arteriosus presents as congestive heart failure. A grade 1/6 to 4/6 continuous "machinery" or "to-and-fro" murmur may be appreciated and is loudest at the left upper sternal border. A diastolic rumble and bounding pulses can also be present.

ENDOCARDIAL CUSHION DEFECT (COMMON ATRIOVENTRICULAR CANAL)

Abnormal development of the endocardial cushion causes defects in the atrial septum, ventricular septum, and atrioventricular valves. Complete defects involve the entire endocardial cushion and involve the atrial and ventricular septum as well as the common atrioventricular valve. Incomplete or partial defects have atrial involvement with an intact ventricular septum. Endocardial cushion defects represent 3% of congenital heart disease cases, with two thirds manifesting as complete defects.[30,31] **Down syndrome and endocardial cushion defects are strongly associated.**

Typical presentations include failure to thrive and frequent respiratory infections. There is a direct relationship between left-to-right shunting and the magnitude of the defects, and complete lesions often lead to congestive heart failure from volume overload of both ventricles early in life.

Usually there is a hyperactive precordium, a systolic thrill, a loud holosystolic regurgitant murmur, and a loud and widely split S_2. The ECG is important and demonstrates a pathognomonic superior QRS axis with right ventricular hypertrophy, right bundle branch block, left ventricular hypertrophy, and a prolonged PR interval.

ANOMALOUS LEFT CORONARY ARTERY ARISING FROM PULMONARY ARTERY

Anomalous left coronary artery arising from pulmonary artery is very rare and occurs when the left coronary artery branches from the pulmonary artery instead of the aorta. The decreased pressure in the pulmonary artery causes significantly lower flow in the anomalous left coronary artery and actually reverses blood flow ("coronary steal"), resulting in left ventricular insufficiency. This is one of the most common causes of myocardial ischemia and infarction in infants, mostly anterolateral infarct; unfortunately, 90% of untreated children die within 1 year of life.[23]

Presenting symptoms in infancy include irritability (angina) and diaphoresis with feeds. There may be a murmur present consistent with mitral regurgitation. Mitral regurgitation results from infarction of the papillary muscle or from annular dilation.

CLINICAL FEATURES OF HEART FAILURE IN CONGENITAL HEART DISEASE

HISTORY

The typical history of congenital heart defects presenting with congestive heart failure depends on the pathophysiology of the underlying lesion. **Cyanotic lesions often present early in the neonatal period, whereas obstructive duct-dependent lesions typically present in the second week of life with feeding difficulties and shock, as previously discussed.** Patients with pulmonary overcirculation from truncus arteriosus, patent ductus arteriosus, and large ventricular septal defect or atrial septal defect lesions usually present after the neonatal period with poor or prolonged feeding, diaphoresis, and respiratory distress associated with feeds, and poor weight gain, sometimes associated with developmental delay. Parents may notice increased work of breathing, cyanosis, or frequent respiratory infections or wheezing. Tachyarrhythmias and anemia can also lead to congestive heart failure.

PHYSICAL EXAMINATION

Assessment of vital signs may reveal tachycardia and tachypnea with or without associated hypoxemia, depending on the underlying defect. Upper and lower extremity blood pressure differences may signal left outflow tract obstruction. Wide pulse pressure suggests a shunting lesion such as patent ductus arteriosus, whereas a narrow pulse pressure may indicate cardiomyopathy or myocarditis. Record weight and compare with birth and previous weights as an indicator of overall growth. Careful palpation of the chest wall may reveal a hyperdynamic precordium or thrill; palpation of the pulses may uncover a delay between upper and lower extremities or weak distal pulses or may reveal bounding pulses characteristic of patent ductus arteriosus. Murmurs may be noted with nearly all congenital heart defects resulting in congestive heart failure and may be characteristic (e.g., continuous murmur of patent ductus arteriosus); the presence of a diastolic rumble suggests significant pulmonary overcirculation, as seen with a large unrestrictive ventricular septal defect. A fixed split S_2 is suggestive of an atrial septal defect. Gallops may be present, especially with cardiomyopathy, and occasionally a friction rub can be appreciated in pericarditis.

The hallmarks of congestive heart failure with elevated left-sided pressure are pulmonary rales and increased work of breathing, although rales are less often detected in infants and young children as compared to older children. Hepatomegaly, with or without splenomegaly, and peripheral or generalized edema suggest right-sided heart failure. Jugular venous distention is often difficult to appreciate in neonates and infants and may be absent.

DIAGNOSIS OF HEART FAILURE IN CONGENITAL HEART DISEASE

The laboratory evaluation of congestive heart failure includes measurement of electrolytes and renal function tests, which may be helpful in determining volume status. A CBC may reveal anemia, and determination of red cell indices may point to a cause.

Chest radiograph may reveal a cardiac silhouette suggestive of a particular congenital defect, cardiomegaly, and pulmonary edema or pleural effusion. **Table 129-5** outlines characteristic chest radiograph and ECG findings in congenital heart defects presenting as congestive heart failure. Echocardiography provides a definitive diagnosis.

TREATMENT OF CONGESTIVE HEART FAILURE IN CONGENITAL HEART DISEASE

Administer oxygen cautiously (Table 129-2). Oxygen saturation of >95% may cause pulmonary vasodilation and worsen congestive heart failure in overcirculating lesions such as ventricular septal defect and patent ductus arteriosus. Elevate the head of the infant's bed. Provide volume expansion cautiously if at all. **A bolus of 5 to 10 mL/kg of normal saline may improve cardiac output in some circumstances but may worsen failure in others.**

The mainstays of congestive heart failure treatment are furosemide (1 to 2 milligrams/kg IV) for diuresis and inotropic support. Adjustments

TABLE 129-5 Acyanotic Congenital Cardiac Lesions Resulting in Congestive Heart Failure: Typical Chest Radiograph and ECG Findings

Cardiac Lesion	Chest Radiograph	ECG
Atrial septal defect	Cardiomegaly with increased vascular markings	Right axis deviation, RVH, RBBB
VSD	Cardiomegaly with increased vascular markings	LAH, LVH (RVH with larger VSDs)
PDA	Cardiomegaly with increased vascular markings	LVH, RVH with larger PDAs
Endocardial cushion defect	Cardiomegaly with increased vascular markings	Superior QRS axis with RVH, RBBB, LVH, prolonged PR interval
Anomalous origin of the left coronary artery	Cardiomegaly	Abnormally deep and wide Q waves with precordial ST-segment changes

Abbreviations: LAH = left atrial hypertrophy; LVH = left ventricular hypertrophy; PDA = patent ductus arteriosus; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; VSD = ventricular septal defect.

to preload (end-diastolic volume is roughly equivalent to intravascular volume), afterload, contractility, and heart rate can be attempted.

Dopamine and/or dobutamine should be considered in the acutely ill patient with congestive heart failure. Dopamine increases heart rate, blood pressure, and urine output. Give dopamine as a continuous infusion at 5 to 15 micrograms/kg/min. Dobutamine reduces afterload through peripheral vasodilation and improves cardiac output without increasing blood pressure. Give dobutamine as a continuous infusion at 2.5 to 15 micrograms/kg/min, but in infants <1 year of age, tachycardia can result, and the dose may need to be lowered. Congestive heart failure associated with hypotension may require treatment with dopamine and dobutamine.[22]

Milrinone has inotropic effects, improves diastolic relaxation, and causes vasodilation, but does not augment heart rate and does not increase myocardial oxygen demand. Milrinone is given as a loading dose of 50 micrograms/kg IV administered over 10 to 60 minutes followed by a continuous infusion of 0.25 to 0.75 microgram/kg/min. While the adjuvant agent synthetic brain natriuretic peptide has been investigated for its vasodilatory and natriuretic effects, there is little evidence to support its use in the pediatric population.[32]

Afterload reduction may be useful for conditions unresponsive to standard measures and in consultation with a cardiologist. Nitroprusside is a mixed vasodilator and can be administered as an infusion of 1 to 10 micrograms/kg/min. Calcium channel blockers may be more effective in cases of diastolic dysfunction and include diltiazem (0.2 to 0.5 milligram/kg/dose PO or sublingual) and nifedipine (0.25 to 1.0 milligram/kg PO) but are contraindicated in infants <1 year of age. Consult a pediatric cardiologist to help guide diagnosis and management and potential transfer to a tertiary care pediatric facility.

For patients in stable condition, digoxin is the inotrope of choice and improves cardiac contractility and output. The *total digitalizing dose* is 20 to 30 micrograms/kg for term neonates weighing >2 kg and 30 to 50 micrograms/kg for infants and children between 1 month and 2 years of age. **The total digitalizing dose is administered over 16 to 24 hours as follows: half the total dose is given as an initial IV bolus; one fourth of the total dose is given 6 to 12 hours after the initial dose; and the remaining one fourth is given 6 to 12 hours later.** Digoxin is less helpful in the acute setting as it takes time to reach therapeutic levels. If digoxin is given, check and recheck doses before administration to avoid dosing errors.

INTERVENTIONAL AND SURGICAL REPAIR OF CONGENITAL HEART DEFECTS

In many infants, heart defects can be definitively corrected through surgical repair or the use of devices delivered through catheterization. This section provides a brief review of commonly used techniques for the correction of congenital heart defects. **Table 129-6** lists some of the congenital heart defects, their respective surgical procedures used in treatment or palliation, as well as potential postsurgical complications.[33]

COMPLICATIONS OF CONGENITAL HEART DEFECTS

This section discusses complications of medical management, common complications related to surgery for repair of congenital heart defects, and infectious complications in children with congenital heart defects. Diagnosis and management typically require pediatric cardiology consultation and transfer to a tertiary care center.

DYSRHYTHMIAS

Dysrhythmias may be caused by the underlying lesion, the surgical repair, or digitalis toxicity. Supraventricular tachycardia is common with procedures that employ atriotomy (Senning operation, Mustard operation, Fontan procedure, atrial septal defect repair, total anomalous pulmonary venous return repair). In a stable patient without evidence of end-organ dysfunction, manage supraventricular tachycardia initially with vagal maneuvers or with a rapid push of IV adenosine (0.1 milligram/kg/dose, maximum 12 milligrams). If the patient is unstable and is showing signs of end-organ dysfunction (altered mental status, hypoxia, poor perfusion, or respiratory distress), treat promptly with synchronized cardioversion (0.5 to 1 J/kg; can increase to 2 J/kg). Bradycardia may occur in patients who have undergone the Fontan procedure, and atrioventricular block is not uncommon after atrioventricular canal repair.

Some lesions recur after surgery. This is most commonly seen with coarctation of the aorta, which recurs in 10% of cases. Pulmonary stenosis and aortic stenosis balloon dilation may also be complicated by restenosis or valvular incompetence.

SURGICAL SHUNT DYSFUNCTION

When palliative shunt procedures are performed in the neonatal period prior to definitive operative repair of complex congenital heart disease, shunts can malfunction. Typically, infants with surgical shunt failure develop acute distress with increasing cyanosis when the shunt flow narrows to <50% of usual. Ordinarily, a continuous murmur should be heard over the shunt. Diminution or disappearance of the murmur suggests occlusion of the shunt. Typically, emergency physicians can do nothing for these infants. Palliative therapy with 100% oxygen is used, and transfer to a tertiary center is expedited. The use of thrombolytic therapy has been attempted, but thrombolytic agents should be administered by a pediatric cardiologist either directly into the shunt or systemically. In all cases, definitive treatment consists of surgical repair.

PULMONARY HYPERTENSIVE CRISIS

Many children with congenital heart disease have increased pulmonary artery pressure, particularly those with large ventricular septal defects. Pulmonary vasospasm can develop in response to painful procedures. In such conditions, cyanosis and lethargy can develop and can mimic the hypercyanotic episodes of tetralogy of Fallot. The goal is to reduce right ventricular afterload by providing adequate ventilation, administering supplemental oxygen to facilitate pulmonary vasodilation, correcting acidosis with IV sodium bicarbonate, 1 mEq/kg, and keeping patients calm with anxiolytics and analgesics. Temporizing measures such as nitrous oxide, calcium channel blockers, prostacyclin infusions, and oral pulmonary vasodilators such as bosentan and sildenafil may also be considered in consultation with a pediatric cardiologist.

DIURETIC COMPLICATIONS

Because dosing of diuretic medications is weight based, normal infant growth may lead to inadequate diuretic therapy that presents as congestive heart failure. Conversely, during times of excess fluid losses, such as from diarrhea or vomiting, dehydration can occur with hemoconcentration that can compromise cardiac function or shunt integrity. Electrolyte imbalances

TABLE 129-6 Common Surgical Procedures and Their Complications in Complex Congenital Heart Disease

Type of CHD	Surgical Procedure (Timing)	Repair	Postsurgical Complications	Comments
TGA	Arterial switch (at birth)	Switch of the aortic and pulmonary trunks, leaving original valve; coronary arteries reimplanted	Myocardial ischemia	N/A
	Rastelli (at birth)	RV to PA conduit and VSD closed with slight LV protrusion into RV	Supravalvular stenosis, atrial dysrhythmias	Typically performed in patients with LVOT obstruction
	Mustard/Senning (at birth)	Atrial switch with prosthetic (Mustard) or native (Senning) intra-atrial baffle	Atrial dysrhythmias, ventricular failure	Rarely used; RV becomes systemic ventricle, LV becomes pulmonary ventricle
HLHS or tricuspid atresia	Staged repair: 1. Norwood (HLHS only) + BTS Or Sano modification (at birth)	Norwood: Neo-aorta created from aorta and part of PA with ligation of main PA BTS: right subclavian artery to right PA conduit Sano: RV to PA conduit	Atrial arrhythmias, sudden death, thromboembolism (pulmonary > arterial), thrombosis of shunt, elevated CVP (SVC syndrome, ascites, hepatomegaly), pericardial or pleural effusion, protein-losing enteropathy	Single-ventricle physiology with mixing of blood through ASD and POX 75%–85% expected
	2. Glenn (age 6 mo)	BTS or Sano taken down, SVC anastomosed to right PA or main PA (bidirectional Glenn)		POX 75%–85% expected
	3. Fontan (age 1.5 y)	IVC connected to PA		At this stage, passive blood flow to lungs, single ventricle pumps to body, mixing no longer, POX normal
CoA, AS	Balloon dilation or surgical repair (timing variable)	Can include end-to-end anastomosis, patch repair, balloon dilation, or aortoplasty	Restenosis at original site or surgical anastomosis	N/A
Truncus arteriosus	Primary repair (around age 2 wk)	Pulmonary arteries removed from common trunk and attached via conduit to RV and closure of VSD	Valvular insufficiency, dysrhythmias (RBBB and heart block), outgrown conduit	Pulmonary edema and hypertension from valvular insufficiency, hypoxia if conduit is outgrown due to decreased pulmonary blood flow
TOF	Complete repair +/– BTS (around age 6 mo)	Augmentation of PA and valve, closure of VSD +/– Right subclavian to right PA conduit (BTS)	Residual VSD, RV failure, conduction defects, valvular insufficiency	N/A

Abbreviations: AS = aortic stenosis; ASD = atrial septal defect; BTS = Blalock-Taussig shunt; CHD = congenital heart disease; CoA = coarctation of the aorta; CVP = central venous pressure; HLHS = hypoplastic left heart syndrome; IVC = inferior vena cava; LV = left ventricle; LVOT = left ventricular outflow tract; N/A = not applicable; PA = pulmonary artery; POX = pulse oximetry; RBBB = right bundle branch block; RV = right ventricle; SVC = superior vena cava; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

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are a common side effect of many diuretics and can be exacerbated during intercurrent illness, so potassium levels should always be checked.

DIGOXIN TOXICITY

Because of digoxin's narrow therapeutic window, digoxin toxicity can easily develop. In infants, toxicity often presents with bradycardia or other dysrhythmias. The usual adult patterns of atrial and ventricular tachycardia are not seen in younger children, although they may occur in adolescents. It is always good practice to monitor digoxin concentrations expectantly during any visit at which blood is drawn. Usually, increased serum concentrations can be managed by withholding dosages of digoxin. Rarely, pharmacologic intervention is required for bradycardia. Ventricular dysrhythmias are managed medically with lidocaine or phenytoin. For severely intoxicated children, the use of digoxin immune globulin (Digibind®) is indicated and reverses toxicity rapidly. Usually, the dosage can be calculated readily based on the amount of digoxin elevation in nanograms above the normal level (see Chapter 193, "Digitalis Glycosides").

ANTICOAGULATION PROBLEMS

Some children with congenital heart disease require lifelong anticoagulant therapy to prevent shunt occlusion or thrombosis of surgically implanted valves or grafts. The risk of serious bleeding is small but must be considered in any elective repair of fractures or lacerations. Prothrombin time and the INR should be monitored. **Reversal of anticoagulation with vitamin K or fresh frozen plasma should be undertaken only after consultation with a pediatric cardiologist.**

ANEMIA AND POLYCYTHEMIA

Children with cyanotic congenital heart defects develop an increase in hemoglobin concentration to compensate for hypoxemia. When hemoglobin concentrations fall to normal, these infants can become symptomatic, with tachycardia, feeding difficulty, or congestive heart failure. Conversely, polycythemia causes increased blood viscosity and the potential for stroke. Iron supplementation is important to prevent anemia. When polycythemia occurs, therapeutic phlebotomy may be warranted.

VIRAL INFECTIONS IN CONGENITAL HEART DISEASE

Children with congenital heart disease are at high risk for serious complications from infection with viruses such as influenza virus, parainfluenza virus, or respiratory syncytial virus, and mortality and morbidity are dramatically higher than in normal infants. Children with lesions that increase pulmonary blood flow are at greater risk because

of pooling of alveolar secretions. Pooled secretions allow for stasis and secondary bacterial overgrowth. Treat acute influenza according to standard current guidelines. Prophylactic treatment after exposure to influenza virus is recommended only if the patient is not vaccinated against the influenza virus strains circulating at the time of exposure. Annual influenza immunization is recommended for all infants with congenital heart defects. Antiviral therapy for respiratory syncytial virus infection is controversial, but prevention with virus-specific immune globulin is recommended for most infants with congenital heart defects. No effective therapy is available for parainfluenza virus infection.

SERIOUS BACTERIAL ILLNESS AND SUBACUTE BACTERIAL ENDOCARDITIS

Although occult bacteremia has the same probability of occurrence in a child with congenital heart disease as in a child without congenital heart defects (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children"), bacterial endocarditis is always a concern in a child with congenital heart defects and fever. Uncorrected congenital heart defects carry a 0.1% to 0.2% annual risk of endocarditis, which falls to 0.02% after correction of most lesions. The highest risk is seen for uncorrected complex lesions and may be as high as 1.5% per year in these cases, whereas atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation, and pulmonary stenosis carry low risk. Transient iatrogenic bacteremia produced by procedures such as dental work or respiratory manipulation can lead to localized colonization and infection. Although the focus of most primary care providers is toward prevention of this disease, cases still occur. The usual presentation is unexplained fever in children with known congenital heart disease. Appropriate evaluation includes multiple blood cultures, urine culture and analysis, and CBC. Parenteral or oral antibiotics should be administered in consultation with a pediatric cardiologist familiar with the child's history. Prophylactic antibiotics prior to invasive procedures or dental work and the management of bacterial endocarditis are further discussed in the later section, "Endocarditis," under "Acquired Heart Disease."

ACQUIRED HEART DISEASE

MYOCARDITIS

Myocarditis is an inflammatory disorder of the myocardium, affecting children of all ages, and is the leading cause of dilated cardiomyopathy requiring transplantation. This inflammatory disease of the heart frequently results from common viral infections as well as postviral immune-mediated responses. Viral causes include parvovirus B19, human herpesvirus 6, and adenovirus and enteroviruses (e.g., coxsackie viruses). Additional causes are influenza (subtypes A and H1N1), human immunodeficiency virus–associated myocarditis, and chronic Epstein-Barr myocarditis.[34] Many bacterial species have been associated with myopericarditis but rarely myocarditis alone. In some regions of the world rickettsial (e.g., typhus), mycotic (e.g., histoplasmosis), protozoal (e.g., amebiasis, trypanosomiasis), and helminthic (e.g., schistosomiasis) infections have been associated with myocarditis. Noninfectious causes include conditions such as **Kawasaki's disease** (see later section, "Kawasaki's Disease"), juvenile idiopathic arthritis, and lupus erythematosus.

CLINICAL FEATURES

Myocarditis is often preceded by a viral respiratory illness. Presenting signs and symptoms include tachypnea, respiratory distress, fever, tachycardia, generalized malaise, and myalgias. Isolated or concurrent GI symptoms such as vomiting, anorexia, and abdominal pain may be present. Arrhythmias may complicate myocarditis and give rise to symptoms of palpitation or syncope in older children. Chest pain may be a symptom of concurrent pericarditis.[34]

The physical examination reveals signs of decreased cardiac output and compensatory response: tachycardia, weak pulses, cool extremities with delayed capillary refill, skin mottling, or cyanotic skin. Auscultation of the heart may reveal distant heart sounds, an S_3 or S_4 gallop, and a regurgitant murmur. There may be signs of congestive heart failure or fulminant shock.

DIAGNOSIS

No single diagnostic test is sensitive or specific for myocarditis. Diagnostic evaluation may include CBC, serum chemistries, liver function tests, and blood cultures to identify bacterial infection. Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, are nonspecific but may be elevated. Respiratory viral cultures or viral titers may help to identify a specific infectious cause. Natriuretic peptide elevation may help distinguish respiratory symptoms caused by heart failure rather than pulmonary etiologies, and elevated levels may be associated with more fulminant cases.[35,36] Troponin T or I may be elevated.

ECG changes are nonspecific, with sinus tachycardia, low QRS voltages (<5 mm in limb leads), flattened or inverted T waves with ST- and T-wave changes, and prolongation of the QT interval. A prolonged QRS duration of >120 milliseconds is associated with poor clinical outcome. Left ventricular hypertrophy or strain can be seen. Arrhythmias include premature ventricular contractions, atrial tachycardias, junctional tachycardia, or, occasionally, heart block or ventricular tachycardia.

Chest radiograph may reveal cardiomegaly and pulmonary edema. Echocardiography is useful to define cardiac function as well as to rule out other causes of heart failure such as valvular disease, hypertrophic cardiomyopathy, or restrictive cardiomyopathy. Emerging modalities such as cardiovascular magnetic resonance are being studied.[35] Endomyocardial biopsy is the diagnostic gold standard.

TREATMENT

The treatment of myocarditis depends on the cause, with the initial goal of managing heart failure and arrhythmias. Therapeutic agents consist of afterload reduction, preload reduction in the case of true volume overload, or inotropic support. Diuretics will worsen the condition if cardiac output is dependent on preload. Children with heart failure should be admitted to a pediatric tertiary care facility where care can be guided by a pediatric cardiologist. Since much of the myocyte damage in myocarditis is caused by the host's immune response, treatments targeting the host's immune system have been studied, namely IV immunoglobulin. However, a systematic review of pediatric and adult literature determined that there is insufficient evidence to support the use of IV immunoglobulin in the treatment of acute myocarditis except in children with concurrent viral encephalitis.[37] Fulminant myocarditis may require extracorporeal life support.

PERICARDITIS

Pericarditis is inflammation of the pericardium and has many causes. Infectious causes are common and can be bacterial, viral, fungal, parasitic, or tubercular. Viral etiologies predominate in the infant. Pericarditis is often associated with myocarditis, with myocarditis being the predominant entity. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and streptococci species are causes of bacterial pericarditis. Noninfectious inflammatory causes include rheumatologic disease, metabolic or endocrine disease (e.g., uremia, thyroid disorders), and Kawasaki's disease.[38] Rarely, pericarditis may be caused by malignant disease, including leukemia, lymphoma, and cardiac rhabdosarcoma.

CLINICAL FEATURES

Pericarditis often follows or accompanies upper respiratory infection. Chest pain may be a symptom of pericardial inflammation and is classically positional, with worsening in the supine position and improvement leaning forward. Pain can worsen with respirations and may be referred to the upper abdomen.

Vital signs may reflect tachycardia, tachypnea, and hypotension with a narrow pulse pressure. Pulsus paradoxus is the sine qua non of

pericardial effusion with cardiac tamponade and is defined by a 20-mm Hg fall in systolic blood pressure with inspiration. Auscultation of the heart may reveal a friction rub (best heard at the left lower sternal border with the patient sitting forward) and muffled or distant heart sounds (when associated with a large effusion). Peripheral pulses may be decreased, with cool extremities, mottled skin, and sluggish capillary refill.

DIAGNOSIS

Routine blood tests are not typically helpful for diagnosis, but specific testing may identify the cause: a positive purified protein derivative or Mantoux screening test suggests tuberculosis, circulating blasts indicate hematologic malignancy, and positive blood cultures may occasionally be seen in bacterial pericarditis. Troponin elevations may be seen in both pericarditis and myocarditis.[38]

ECG abnormalities are almost universal and have been described as progressing through stages (although multiple stages may be present simultaneously): concave ST-segment elevation in leads I, II, III, aVL, aVF, and V_2 to V_6 with ST depression in aVR; ST-segment normalization with T-wave flattening; diffuse T-wave inversion; and normalization. Other ECG findings in pericarditis include PR depression, decreased precordial voltage, and electrical alternans.[38]

The chest radiograph may demonstrate cardiomegaly with a water bottle–shaped heart or a pleural effusion. Echocardiography is best to detect pericardial effusion or tamponade associated with pericarditis but may be normal if there is minimal fluid accumulation or the fluid is loculated. If a tamponade is present, there will be collapse of the right atrial wall or right ventricular wall during diastole.

TREATMENT

Treatment depends on the underlying cause. Tamponade requires emergency pericardiocentesis (see Chapter 55, "Cardiomyopathies and Pericardial Disease," and Chapter 34, "Pericardiocentesis"). Empiric antibiotic therapy for bacterial pericarditis includes oxacillin, 50 milligrams/kg, or vancomycin, 10 milligrams/kg, for methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus*, with the addition of gentamicin in immunocompromised patients. The treatment of pericarditis without effusion or tamponade includes outpatient treatment with NSAIDs such as naproxen, 5 to 10 milligrams/kg/dose every 12 hours, or ibuprofen, 10 milligrams/kg/dose every 6 hours. The addition of colchicine to prevent recurrent disease is recommended for adults, but evidence in children is limited. Patients should be followed for complications such as myocarditis, pericardial effusion, or cardiac tamponade.

KAWASAKI'S DISEASE

Kawasaki's disease (mucocutaneous lymph node syndrome) is a generalized systemic vasculitis of unknown cause. Along with Henoch-Schönlein purpura (see also Chapters 133, "Acute Abdominal Pain in Infants and Children"; Chapter 137, "Renal Emergencies in Children"; and Chapter 142, "Rashes in Infants and Children"), **Kawasaki's disease is one of the principal pediatric systemic vascular diseases and is the leading cause of acquired heart disease in North American and Japanese children**. It affects infants and children <5 years old most commonly and can occur in endemic and community-wide epidemic forms. There is seasonal variation, with more cases in the late fall through early spring, both in North America and in northeast Asia. Male-to-female ratio is about 1.5:1. There is a risk of recurrence (about 3%) and a 10-fold increased risk in siblings of those with Kawasaki's disease in Japan.[39]

CLINICAL FEATURES

The diagnosis is clinical. Criteria for the diagnosis are outlined in **Table 129-7**, and these criteria can be applied after excluding diseases of similar findings such as viral illnesses (measles, adenovirus, enterovirus), bacterial illnesses (cervical adenitis, scarlet fever, staphylococcal scalded skin syndrome), or immune-mediated syndromes (serum sickness, Stevens-Johnson syndrome, toxic shock syndrome).

Cardiac complications are the most severe manifestations of Kawasaki's disease and include coronary artery aneurysms, myocarditis, pericarditis, pericardial effusion, valvular dysfunction, left ventricular dysfunction, and arrhythmias. Coronary artery aneurysms or ectasia occurs in 15% to 25% of untreated children and can lead to myocardial infarction, sudden death, or ischemic heart disease.[39] Left ventricular dysfunction is seen in almost half of patients.

Noncardiac findings of Kawasaki's disease include arthritis or arthralgia, vomiting and abdominal pain, hydrops of gallbladder, extreme irritability due to systemic inflammation, aseptic meningitis, urethritis, and desquamating rash in the groin (as compared to desquamation of fingers and toes in weeks 2 and 3 of illness).

TABLE 129-7 Diagnostic Criteria for Kawasaki's Disease

Classic or Complete Kawasaki's Disease	Incomplete Kawasaki's Disease	Atypical Kawasaki's Disease
Fever for ≥5 d and 4 of the following clinical criteria:	Fever for 5 d and 2–3 clinical criteria of classic Kawasaki's disease	Meets all clinical criteria for complete Kawasaki's disease
• Bilateral bulbar conjunctival injection without exudate • Erythema and cracking of lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa • Rash: maculopapular, diffuse erythroderma, or erythema multiforme–like • Erythema and edema of the hands and feet (acute phase) or periungual desquamation (subacute phase) • Cervical lymphadenopathy (>1.5 cm in size, usually unilateral, anterior cervical, nonfluctuant)	*PLUS* CRP ≥3.0 milligrams/L, and/or ESR ≥40 mm/h	*PLUS* Additional clinical features not typical of Kawasaki's disease (e.g., child with Kawasaki's disease and nephrotic syndrome)
	PLUS A positive echocardiogram, or ≥3 supplemental labs: • Albumin ≤3 grams/dL • Anemia for age • Elevated alanine aminotransferase • Platelet count ≥450,000/mm^3 after 7 d of fever onset • WBC count ≥15,000/mm^3 • Presence of pyuria (>10 WBC cells per high-power field)	

Note: Infants <6 months of age with 7 days of fever without source, even if no clinical criteria met, should undergo laboratory testing and, if indicated, echocardiogram.

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

TABLE 129-8 Cardiac Complications of Kawasaki's Disease

Phase of Illness	Cardiac Complications
Acute (0–2 wk)	Myocarditis, pericarditis, coronary arteritis, arrhythmias
Subacute (2–4 wk)	Coronary artery abnormalities
Convalescent (4–6 wk)	Coronary artery abnormalities

Kawasaki's disease is divided into three phases: the acute febrile phase typically lasts for the first 2 weeks of illness; the subacute phase lasts from 2 to 4 weeks; and the convalescent phase lasts from 4 to 6 weeks. Laboratory results are nonspecific in the acute phase, but for those children who do not fulfill diagnostic clinical criteria, the supplemental lab abnormalities (Table 129-7) lend support to the diagnosis. Additionally, there may be elevated plasma lipid and elevated serum γ-glutamyl transpeptidase. Thrombocytosis is not usually noted until the second week of illness.

Cardiac complications vary depending on the stage of disease and are presented in **Table 129-8**. Patients <1 year old and those >9 years old tend to present with incomplete Kawasaki's disease, leading to delayed diagnosis and higher risk of coronary artery abnormalities.[39,40] Other risk factors for cardiac complication include higher platelet count, higher C-reactive protein, and lower albumen.[41] Due to the importance of identifying patients at risk of developing coronary artery abnormalities, cardiovascular biomarkers will become important for diagnosis in the future. One biomarker, N-terminal pro-B-type natriuretic peptide, is increased in patients with Kawasaki's disease and incomplete Kawasaki's disease compared with febrile controls.[42,43]

The acute phase of disease results in myocarditis and pericarditis, which typically resolve without treatment. The most common cardiac findings include tachycardia out of proportion to fever and a gallop rhythm. Inflammation of aortic and mitral valves can lead to murmurs of valvular incompetence, usually during the acute phase of disease. Pericardial effusions are rarely large or life threatening. Reduced left ventricular function and arrhythmias are more common in the acute phase of illness than in later phases.

Although coronary arteritis begins during the acute phase and aneurysms can be seen as early as 6 days after the fever starts, **most coronary artery aneurysms develop during the third and fourth weeks of illness**. Aneurysms of arteries other than the coronaries (subclavian, brachial, iliac, femoral) can also develop but are rare. Myocardial infarction is a complication of coronary artery aneurysm and is the leading cause of death in Kawasaki's disease. The majority of infarcts occurs in the first 6 months of the disease but may present later.

Echocardiography should be performed during the acute stage of disease and repeated in the subacute and convalescent stages and beyond. Findings include pericardial effusion, poor left ventricular function, aortic or mitral valve regurgitation, perivascular brightness of the coronary arteries (acute phase), and coronary artery aneurysms.

TREATMENT

Treatment is directed at reducing inflammation and preventing cardiac complications. **Administration of IV immunoglobulin (2 grams/kg over 12 hours) results in rapid and dramatic symptomatic improvement in 90% of patients and prevents aneurysm formation in 95%.** In addition to IV immunoglobulin, treat with aspirin (30 to 50 milligrams/kg/d). Although previous guidelines suggested high-dose aspirin therapy during the acute phase, meta-analyses suggest high-dose therapy (80 to 120 milligrams/kg/d) confers no additional benefit over anti-inflammatory doses.[39] Following the acute phase, the aspirin dose is reduced to 3 to 5 milligrams/kg once daily for 6 to 8 weeks. A second dose of IV immunoglobulin may be given (same dosage) if the patient remains febrile 48 hours after the initial dose, because refractory fever may be a risk factor for coronary artery abnormalities. As many as 12% to 38% of patients require a second dose of IV immunoglobulin, and despite retreatment with IV immunoglobulin, 3% to 4% of patients may still not respond. A single dose of corticosteroids administered before IV immunoglobulin does *not* improve coronary outcome. However, for patients with persistent treatment resistance, rescue dosing of corticosteroids is being studied. The use of infliximab, cyclosporine A, methotrexate, and cyclophosphamide remains to be elucidated in future prospective trials.

ENDOCARDITIS

Historically, infective endocarditis was most commonly seen in children affected with rheumatic heart disease; however, more recently, it has been more closely associated with congenital heart disease, both corrected and unrepaired: only 10% of pediatric patients with endocarditis have normal cardiac anatomy.[44] **Table 129-9** lists risk factors for pediatric endocarditis. The annual incidence of infective endocarditis is low, ranging from 0.05 to 0.12 cases per 1000 pediatric admissions.[44] Although mortality has declined, it remains high at 10% to 15%. Significant complications, such as septic emboli, valvular dysfunction, and congestive heart failure, can occur.

Infectious endocarditis occurs when damaged endocardium is exposed to circulating bacteria, and both conditions are necessary for vegetations to develop. Congenital heart defects predispose to infection through turbulent blood flow that creates endothelial damage and promotes thrombus formation. The risk for endocarditis is enhanced by the presence of prosthetic heart valves or graft material within the repaired or palliated heart.

Although a number of bacteria can cause endocarditis, staphylococcal, streptococcal, and enterococcal species predominate. *S. aureus* is seen more commonly in children without heart disease and viridans streptococci are more common in those with underlying heart disease. Gram-negative organisms (e.g., *Klebsiella pneumoniae* and *Enterobacter* species), although rare, can cause endocarditis in neonates. **HACEK organisms** are slow-growing gram-negative bacteria that are part of normal human flora. **The term *HACEK* is derived from the first letter of the bacteria in the group (H*aemophilus*, A*ctinobacillus*, C*ardiobacterium*, E*ikenella*, and K*ingella*).** Fungal infections, particularly *Candida* species, are rare causes of endocarditis more often seen in neonates and children with indwelling catheters.

CLINICAL FEATURES

Infective endocarditis can present as an acute or subacute process. Acute endocarditis can be a fulminant disease with high spiking fevers, clinical sepsis, and rapid hemodynamic deterioration. The symptoms of subacute endocarditis are often vague and difficult to distinguish from common childhood illness. Unexplained or persistent fever is the most common complaint; other symptoms include fatigue, weakness, arthralgias, myalgias, weight loss, rigors, and diaphoresis in older children, and symptoms may be subtler in infants. In the patient with cyanotic heart disease, pneumonia, new neurologic deficits, hematuria, or skin rashes prompt consideration of infective endocarditis.

TABLE 129-9 Risk Factors for Infective Endocarditis

Clinical Conditions	Comments
Congenital heart disease	Unrepaired cyanotic congenital heart disease (including palliative shunts and conduits) Completely repaired defects with prosthetic material or devices within 6 months of procedure* Repaired with residual defects at the site or adjacent to a prosthetic patch or device
Prosthetic cardiac valve or material used for valve repair	
Cardiac transplantation	Especially with subsequent valvulopathy
Previous infective endocarditis	
Central venous catheters	Higher risk for *Staphylococcus aureus*
Rheumatic heart disease	Uncommon in developed countries

*Applies to devices placed surgically or by catheter intervention.

Fever, tachycardia, and a new murmur may be noted on clinical exam. CNS embolization can cause focal neurologic deficits. Rales or decreased breath sounds accompany septic pulmonary emboli. Examine the skin for evidence of cutaneous emboli that appear as splinter hemorrhages of the nail beds, painless erythematous macules on the palms or soles (**Janeway lesions**), and tender subcutaneous nodules on the fingers (**Osler nodes**). Although these skin findings are typical for infectious endocarditis, they can be seen in other conditions such as lupus or typhoid fever. Retinal emboli are difficult to visualize in young children. Splenomegaly may be appreciated.

DIAGNOSIS

The diagnosis is made through a combination of clinical features, laboratory investigations, and echocardiography. Obtain multiple (three separate samples in the first 24 hours, repeated 48 hours later if initial cultures are negative), large-volume (1 to 3 mL in infants, 3 to 5 mL for toddlers and preschool-aged children, and 10 mL for school-aged children and adolescents) blood cultures if endocarditis is suspected.[44] The CBC may reveal anemia of chronic disease, but leukocytosis may be absent. Nonspecific inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, are usually elevated. The mean erythrocyte sedimentation rate in endocarditis is 55 mm/h. Subacute or chronic endocarditis may produce a positive rheumatoid factor. Urinalysis demonstrates proteinuria and microscopic hematuria in roughly half of patients.

An echocardiogram is not 100% sensitive or specific, and a negative echocardiogram does not rule out endocarditis. Transthoracic echocardiography is more sensitive in infants and children than adults and may reveal vegetations, abscess, or valvular regurgitation. Transesophageal echocardiography is recommended for infants and children with previous chest wall surgery or trauma, those with congenital anomalies of the thoracic cage, and those at high risk for aortic root abscess.[44] Histologic confirmation of disease from a vegetation or abscess is sometimes required for definitive diagnosis.

The modified Duke criteria for endocarditis use a combination of diagnostic and echocardiographic findings (**Table 129-10**). Definite endocarditis is diagnosed by pathologic criteria (microorganisms on culture or histologic examination of a vegetation or cardiac abscess or histologic exam showing active endocarditis) or clinical criteria, which require two major criteria, *or* one major and three minor criteria, *or* five minor criteria. The diagnosis of possible endocarditis is made by the presence of one major and one minor criterion *or* three minor criteria.[44]

TREATMENT

The ultimate goal of treatment is complete eradication of the infecting organisms, which often requires a prolonged course of parenteral antibiotics. The clinical condition at the time of presentation determines the initial ED management. After proper blood and urine cultures are obtained, if the child is septic or toxic, administer vancomycin (15 milligrams/kg IV every 6 hours up to 2 grams) *plus* gentamicin (5 to 7.5 milligrams/kg IV every 24 hours) for synergistic bactericidal effect; add rifampin (10 milligrams/kg IV every 12 hours to a maximum of 600 milligrams) for children with prosthetic valves. Penicillin G (50,000 to 100,000 units/kg IV every 6 hours) or ceftriaxone (100 milligrams/kg IV daily) can be used for susceptible streptococcal infections.[44]

Hospitalization and consultation with a pediatric cardiologist are indicated. Patients with hemodynamic instability may require assessment by a pediatric cardiac surgeon for emergent intervention.

TABLE 129-10 Modified Duke Criteria for Infective Endocarditis

Major Criteria	Minor Criteria
1. Positive blood cultures: 2 positive blood cultures for a typical microorganism for endocarditis *or* Persistently positive blood culture—2 or more positive blood cultures for the same organism over 12 h or 3 or more positive blood cultures for the same organism with 1 h between first and last culture *or* Single culture for *Coxiella burnetii* 2. Endocardial involvement demonstrated by echocardiography	1. Fever ≥38°C (100.4°F) 2. Predisposing heart condition or injection drug use 3. Vascular emboli 4. Immunologic phenomena such as elevated rheumatoid factor, immune complex glomerulonephritis, Osler nodes 5. Positive blood culture but not meeting major criterion or serologic evidence of endocarditis

ENDOCARDITIS PROPHYLAXIS

The 2015 American Heart Association guidelines,[44] as well as those from the American Academy of Pediatrics[45] and the Canadian Pediatric Society,[46] recognize that bacteremia from daily activities is a much more common event than bacteremia from specific medical procedures and that only a small number of cases of bacterial endocarditis can be prevented with antibiotic prophylaxis. Indications and recommended antibiotics for prophylaxis are listed in **Table 129-11**; **administer prophylactic antibiotics 30 to 60 minutes before the procedure:**

- Oral: amoxicillin (50 milligrams/kg)
- Parenteral: ampicillin (50 milligrams/kg IM or IV)
- Penicillin allergic: cephalexin (50 milligrams/kg PO) *or* clindamycin (20 milligrams/kg PO/IV) *or* azithromycin (15 milligrams/kg PO) *or* cefazolin (50 milligrams/kg IM/IV) *or* ceftriaxone (50 milligrams/kg IM/IV)

CARDIOMYOPATHIES

Cardiomyopathies are uncommon but significant because of the high mortality and severe disability that they produce. They are the most common cause of heart transplantation in children older than 1 year of age. *Cardiomyopathy* refers to a heterogeneous group of disorders involving abnormalities of the myocardial muscle fibers. They may be inherited or acquired and are usually classified into distinct groups: dilated, hypertrophic, restrictive, and noncompaction. Clinical and therapeutic features differ according to subtypes, the two most common of which are discussed below. The overall annual incidence of pediatric cardiomyopathy in the United States is 1.1 to 1.5 per 100,000.[47] The incidence is highest among infants in the first year of life,[48] with a second peak in children 12 to 18 years of age, and is higher among boys than girls. Ethnic and regional variation also exists. Dilated cardiomyopathies comprise 51% of cases, followed by hypertrophic (42%) and restrictive (3%).[48]

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is characterized by dilation of all four cardiac chambers and may be accompanied by some degree of hypertrophy. Typically, the left side is more involved than the right, and systolic dysfunction predominates. The cause is unknown in most cases, and thus the term *idiopathic dilated cardiomyopathy* is applied. Known causes include myocarditis from infections (coxsackieviruses, echovirus, Epstein-Barr virus, cytomegalovirus, rickettsia, parasites, and fungus), neuromuscular disease (muscular dystrophies, Friedreich's ataxia), collagen vascular disease, anemias, nutritional deficiencies, medications (anthracyclines, cyclophosphamide), metabolic disorders (mitochondrial disorders, glycogen storage disease, fatty acid oxidation defects, mucopolysaccharidoses), and genetic abnormalities (35% to 50%).[47]

Dilated cardiomyopathy is the most common form of cardiomyopathy in children, with an annual incidence of 0.57 per 100,000 in children in the United States, and the average age at diagnosis is 18 months old.[47] Boys are more often affected than girls. There is a genetic component in roughly 20% to 30% of patients who have affected relatives. Patterns of inheritance are varied, with autosomal dominant being the most common.

The majority of children with dilated cardiomyopathy present with signs and symptoms of congestive heart failure, although some may be asymptomatic or present with insidious and vague complaints. Poor

TABLE 129-11 Antibiotic Prophylaxis for Endocarditis[44-46]

Risk Group	Patient Factors	Procedures
High risk: prophylaxis indicated	Prosthetic cardiac valves Previous endocarditis Unrepaired cyanotic CHD including shunts/conduits Repaired CHD with prosthetic material or device within 6 months of repair Cardiac transplant with valvulopathy Rheumatic heart disease with prosthetic valve or material	Dental: manipulation of gingival tissue, periapical teeth, or perforation of oral mucosa Respiratory tract: invasive procedures involving incision or biopsy including tonsillectomy/adenoidectomy GI/GU: cystoscopy or surgical manipulation *plus* established infection or colonization with enterococcus Skin/musculoskeletal: procedures through infected skin
Low risk: prophylaxis not indicated	Atrial septal defects Ventricular septal defects Patent ductus arteriosus Mitral valve prolapse Previous Kawasaki's disease Hypertrophic cardiomyopathy Pacemakers/defibrillators Bicuspid aortic valves Coarctation of the aorta Calcified aortic stenosis Pulmonary stenosis	Dental: routine anesthetic injections; radiographs; placement or manipulation of removable prosthodontic or orthodontic appliances; bleeding from trauma to lips or oral mucosa; loss of deciduous teeth Respiratory tract: bronchoscopy without incision GI/GU: procedures in the absence of infection or colonization Skin/musculoskeletal: procedures through normal skin

Abbreviations: CHD = congenital heart disease.

feeding, irritability, sweating, failure to thrive, and malaise are typical nonspecific symptoms, particularly in infants. Cough, wheezing, and orthopnea are easily confused with upper respiratory infection or reactive airway disease. Older children may complain of chest pain, palpitations, decreased exercise tolerance, or syncope. For asymptomatic children, cardiomegaly or ECG changes may be incidental findings. A careful family history should be obtained given the frequency of inherited disease.

The physical examination may reveal signs of congestive heart failure: tachycardia, tachypnea, rales, or decreased breath sounds. Peripheral pulses may be weak and the skin pale, cool, or mottled with poor capillary refill. Dependent edema and hepatomegaly may be present. The heart examination may reveal a gallop rhythm (S_3/S_4), regurgitant murmurs, and an accentuated P_2.

The diagnosis is often suggested by cardiomegaly noted on chest radiograph, which may also demonstrate a prominent left ventricular apex and elevation of the left mainstem bronchus by left atrial enlargement. Pulmonary congestion or effusions may be present. Echocardiography is the diagnostic study of choice and can evaluate the degree of chamber dilation and cardiac dysfunction. ECG changes are typically nonspecific. The diagnosis is further refined by cardiac MRI, catheterization, angiography, and biopsy.

The treatment in the ED is supportive. Administer oxygen and generally avoid IV fluids; diuretics, inotropes, and mechanical ventilation may be necessary in advanced cases of congestive heart failure (see discussion of congestive heart failure in earlier section, "Congenital Heart Disease"). Admission and pediatric cardiology consultation are required.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a term used for a diverse group of myocardial disorders characterized by intrinsic hypertrophy of one or more of the cardiac chambers. The incidence is 0.47 cases per 100,000 children, and it represents just over 40% of pediatric cardiomyopathy.[47] Males are more commonly affected than females, and the median age of diagnosis is 7 years of age, with peaks in both infancy and adolescence. Hypertrophic cardiomyopathy is more common in adults, and children under the age of 12 years old account for <10% of cases. First-degree relatives of affected children can be shown to have echocardiographic evidence of disease in 25% of cases.

The left ventricle is most commonly involved, although all chambers can be affected. Systolic function is often preserved, and diastolic dysfunction predominates. Hypertrophic cardiomyopathy is usually genetic in origin, specifically in sarcomere and other cardiac genetic abnormalities, and is inherited as an autosomal dominant trait in many cases. The disorder may also result from inborn errors of metabolism, neuromuscular disorders, malformation syndromes (e.g., Noonan's syndrome), and glycogen storage disease.

The pathophysiology depends on the underlying genetic defect. Most familial cases result from defects in genes encoding myosin and actin, which result in disorganized myofibrils, fibrosis, and, ultimately, hypertrophy. Coronary artery abnormalities may be associated with thickened intima predisposing to ischemia. Contractile function of the ventricles is normal, but relaxation (diastolic function) is impaired, leading to increased end-diastolic pressures. Some forms involve asymmetric hypertrophy of the ventricular septum, which may lead to left ventricular outflow tract obstruction. Typically, this obstruction is dynamic and worsened by increased left-sided volume.

The symptoms are variable. Infants typically present with vague symptoms associated with heart failure: poor feeding, irritability or lethargy, sweating with feeds, and increased work of breathing. Older children may complain of chest pain, exercise intolerance, dizziness, syncope or near-syncope (particularly with exercise), or palpitations. **Sudden cardiac death** may be the first indication of disease, is most common in adolescents, and is often associated with exercise.

The physical examination can be normal or with signs of heart failure. The precordial impulse may be laterally displaced and forceful, and the second heart sound may be paradoxically split. Left ventricular outflow obstruction results in a systolic ejection murmur, which is loudest between the apex and left sternal border and radiates to the suprasternal notch. **Maneuvers that increase preload (e.g., Valsalva, squatting) or increase afterload (e.g., hand grip) will *decrease* the murmur, whereas standing (which decreases preload) will *increase* the murmur.** In advanced disease associated with mitral regurgitation, a holosystolic murmur is heard radiating to the axilla.

Chest radiograph is nonspecific but may demonstrate cardiac hypertrophy with left atrial enlargement. Echocardiography is the study of choice and will reveal a thickened septal wall and ventricular hypertrophy. Systolic anterior motion of the mitral valve is commonly seen with obstructive disease. Systolic function is typically normal. ECG findings are nonspecific but may include left ventricular hypertrophy, ST-T wave abnormalities, axis deviation, conduction abnormalities, and atrial arrhythmias. Cardiac catheterization and myocardial biopsy are needed for definitive diagnosis.

Treatment is typically directed by a pediatric cardiologist. The primary role of the emergency physician is to make the diagnosis, exclude

secondary causes (e.g., metabolic disease), and reduce the risk of sudden cardiac death, which includes exclusion of vigorous exercise until cleared by a cardiologist. Hospitalization is recommended for patients with heart failure, arrhythmias, syncope or near-syncope, or other significant symptoms. Outpatient management with exercise restriction may be appropriate for asymptomatic patients.

Pharmacologic therapy includes β-blockers and calcium channel blockers, which may decrease outflow obstruction and improve diastolic relaxation. Propranolol can be initiated at 0.01 to 0.1 milligram/kg IV over 10 minutes or prescribed at 0.5 milligram/kg PO every 6 to 8 hours. Verapamil should be used in children >1 year of age (increased mortality in infants) and can be administered at 0.1 milligram/kg IV over 2 minutes and repeated every 10 to 30 minutes as needed. Maintenance dosing is 1 to 2 milligrams/kg four times a day.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 130

Syncope, Dysrhythmias, and ECG Interpretation in Children

Andrew Dixon

SYNCOPE

INTRODUCTION

Syncope, or fainting, is the abrupt loss of consciousness and postural tone resulting from transient global cerebral hypoperfusion, followed by complete spontaneous recovery.[1] In children, this process is usually benign, but it can be a symptom of serious cardiac, neurologic, or metabolic pathology. Assessing syncope in children is complicated by the variability of symptoms and lack of a gold standard for diagnosis. The primary goal of the emergency physician is to differentiate children with benign syncope from those with serious disease. Noncardiovascular causes of syncope are listed in **Table 130-1**. Although pacemaker use is not common in childhood, any child with a pacemaker who develops syncope or presyncope should be presumed to have a pacemaker malfunction.

EPIDEMIOLOGY

Syncope is a presenting symptom in 1% to 3% of pediatric emergency visits,[2,3] with 2% of patients admitted to hospital,[4] and is more common in adolescents than in younger children. Between 15% and 25% of adolescents experience at least one episode of syncope.[5] Only 10% to 15% of patients evaluated in the pediatric ED for syncope are ultimately diagnosed with a serious illness.[6] Approximately 80% of pediatric fainting is neurocardiogenic (also known as vasovagal) syncope. Neurologic disorders, mostly seizures, account for about 10% of episodes, and 2% to 3% are due to cardiac pathology.[6,7]

TABLE 130-1 Events Easily Mistaken for Cardiovascular Syncope

Condition	Distinguishing Characteristics
Basilar migraine	Headache, rarely loss of consciousness, other neurologic symptoms
Seizure	Loss of consciousness simultaneous with motor event, prolonged postictal phase
Vertigo	Rotation or spinning sensation, no loss of consciousness
Hyperventilation	Inciting event, paresthesias or carpopedal spasm, tachypnea
Hysteria	No loss of consciousness, indifference to event
Hypoglycemia	Confusion progressing to loss of consciousness, requires glucose administration to terminate

PATHOPHYSIOLOGY

Neurocardiogenic syncope, otherwise known as neurally mediated or vasovagal syncope, is a mix of vasodepressor syncope due to vasodilation and cardioinhibitory syncope due to vagal stimulation. Neurocardiogenic syncope can be triggered by a variety of conditions in which a reduction in venous return enhances vagal tone causing hypotension, bradycardia, and reduced cerebral perfusion. Recovery of consciousness occurs over 1 to 5 minutes, but symptoms of nausea and fatigue can last for several hours.

Cardiac syncope occurs when there is an interruption of cardiac output due to an intrinsic cardiac abnormality. These causes are divided into tachydysrhythmia, bradydysrhythmia, outflow obstruction, and myocardial dysfunction.

Any event that causes sufficient cerebral hypoperfusion can lead to sudden death. The most common causes are seizures, cardiac diseases, and metabolic diseases. Little is known about the most common dysrhythmias that cause sudden death in children, because such cardiopulmonary arrests are unwitnessed. In children, bradycardic or asystolic arrests are thought to be most common, especially in infants <1 year old, but ventricular fibrillation is also seen in older children, although at much lower rates than in adults.[8]

CLINICAL FEATURES

Syncope is characterized by the sudden onset of falling with a brief episode of loss of consciousness. Other associated symptoms or signs are usually related to the cause for the syncopal event. Two thirds of children experience a prodrome of lightheadedness or dizziness before the event,[5] and vertigo is uncommon. Involuntary motor movements related to cerebral hypoxia occur with all types of syncopal events, but are more common with seizures. A careful history can usually differentiate tonic-clonic movements associated with seizures from the myoclonus of cerebral hypoxia, due to their onset after loss of consciousness, less rhythmic nature, and shorter duration.

RISK FACTORS FOR A SERIOUS CAUSE OF SYNCOPE

Risk factors for syncope are outlined in **Table 130-2**. Events that may mimic syncope in children are listed in Table 130-1.

A syncopal event during physical exertion increases the suspicion of structural heart disease, specifically cardiac outflow obstruction. Conditions such as aortic stenosis, hypertrophic obstructive cardiomyopathy,

TABLE 130-2 Risk Factors for a Serious Cause of Syncope*

Mid-exertional event

Absence of premonitory symptoms or physical precipitating factors

Syncope triggered by loud noise or when swimming (may be due to long QT)

- Age <6 y

History of cardiac disease

- Family history of sudden death under age 50 y, long QT syndrome, or sensorineural hearing loss
- Recurrent episodes
- Recumbent episode (consider seizure)
- Prolonged loss of consciousness (if >5 min, consider seizure or somatization)
- Associated chest pain or palpitations
- Use of medications that can alter cardiac conduction including QT prolongation

*Bolded risk factors represent those factors at highest risk for a cardiac cause.

and other vascular or valvular anomalies may cause cardiac outflow obstruction.

Prior to age 6 years, syncope is much more likely to be associated with seizures, breath-holding spells, and cardiac arrhythmia. Preexisting cardiac disease heightens suspicion of ventricular dysrhythmias as a cause of syncope. Bradyarrhythmias secondary to ischemia, overmedication, or pacemaker malfunction also cause syncope. A history of heart murmur, or discovery of one on exam, may indicate undiagnosed congenital heart disease.

Several familial inherited syndromes are associated with syncope and sudden death. Romano-Ward syndrome is an autosomal dominant syndrome associated with prolonged QT interval and ventricular dysrhythmias; Jervell and Lange-Nielsen syndrome is an autosomal recessive syndrome associated with prolonged QT interval, deafness, and ventricular dysrhythmias. The presence of a family history of dysrhythmias should prompt a more thorough investigation.

When more than one episode of syncope has occurred, consider the presence of ongoing cardiac disease producing a low-flow state, although neurocardiogenic syncope is also often recurrent. Consider illnesses associated with valvular insufficiency, congestive heart failure and diastolic dysfunction, or recurrent supraventricular tachycardia or atrial fibrillation causing rate-dependent hypoperfusion, even in children. Recurrence also raises the probability of a neurologic cause (i.e., seizures).

Episodes that occur when the patient is supine can suggest ventricular dysrhythmias or seizures, which are unrelated to activity.

An extended period of loss of consciousness is worrisome and can be a sign of hypotension resulting from cardiac disease that causes prolonged cerebral hypoperfusion. Alternatively, prolonged loss of consciousness, lasting up to hours, is often seen with pseudosyncope or pseudoseizures in adolescent females.[9] Syncope in association with chest pain may result from acute myocardial infarction or aortic dissection, whereas preceding palpitations may raise suspicion for possible dysrhythmia, although in adults, palpitations are a common symptom in vasovagal syncope.[10]

Antidysrhythmic medications, blood pressure agents, tricyclic antidepressants, amphetamines, and cocaine are all agents that can precipitate electrical conduction disturbances. Many common medications can prolong QT interval and predispose to syncope (see Table 130-5 in "Long QT Syndrome" section).

No clinical or historical features can reliably exclude all serious causes of syncope.[7] Certain elements in the history increase the likelihood of a potentially serious cause (Table 130-2), and a careful history and physical examination are necessary. Many of the diseases that cause syncope also cause sudden death in children. A syncopal event can be the presenting symptom of these more serious illnesses. Up to 25% of children who die suddenly have a history of at least one prior syncopal event.[11] Syncope is a very common event, however, and a syncopal event by itself is not associated with an increased risk of sudden death unless certain features are present (Table 130-2).[5]

HISTORY

Obtain a history focused on hydration status, last meal, environmental conditions, activity preceding the syncopal event, and the use of drugs and medications. Note the position the child was in when syncope occurred, because recumbent positioning is less consistent with neurocardiogenic syncope. Syncope associated with change of position, warm environment, or prolonged standing is very likely to be neurocardiogenic. Be sure to include interviews with any family members, friends, or witnesses who were with the child just before the event. **A history of syncope during exertion or exercise increases the likelihood of a serious cause**. A prodrome of warmth, nausea, lightheadedness, and a visual gray-out or tunneling of vision is indicative of benign neurocardiogenic syncope. The sequence and timing of motor movements and postural positioning help to differentiate primary seizures from syncope. **Loss of consciousness occurs *with* the onset of movements in seizures, but loss of consciousness *precedes* movements in most cases of true syncope**. Inquire about past history such as previous syncopal events, cardiac disease, diabetes, seizures, medication or drug use, and psychiatric or psychological problems. Ask about a family history of structural cardiac disease, dysrhythmias, sudden death, migraines, or seizures. Take statements by the witnesses that the patient appeared dead and required CPR seriously and characterize the duration of pulselessness and the degree of intervention required. Whenever CPR has been performed, even if by an inexperienced layperson, consider the event resuscitation from sudden death and evaluate comprehensively, although the ultimate diagnosis may be benign.

PHYSICAL EXAMINATION

Complete cardiovascular, neurologic, and pulmonary examinations are crucial, but the findings are normal in the vast majority of children with syncope, regardless of the seriousness of the cause. Perform a neurologic examination including deep tendon reflex, gait, and coordination testing. Examine the cardiovascular system including blood pressure, resting heart rate, oxygen saturation, and respiratory rate. Assess pulse quality in all extremities. Measure blood pressure and heart rate with positional changes (orthostatic vital signs), especially if syncope occurred during positional change. This may indicate an element of dehydration, although there is some evidence that a significant percentage of normal adolescents have abnormal postural vital signs.[12] Auscultate the heart to identify any murmurs, abnormalities in rhythm, and variations or abnormalities in heart sounds. Any abnormal findings in the cardiovascular assessment require an in-depth cardiac evaluation.

LABORATORY EVALUATION

Obtain an ECG in all children with syncope.[13] However, abnormalities on the ECG may not correlate with the syncopal event, and some patients with a dysrhythmic cause of syncope have normal ECGs.[3] The overall yield of ECG is <1%, and ECG overreading often leads to further unnecessary investigations.[14] Therefore, abnormal ECG results should be interpreted with caution and most often with the assistance of a pediatric cardiologist. See the section "ECG Interpretation in Infants and Children" at the end of the chapter for detailed discussion.

A detailed history, physical exam, and ECG have a 96% sensitivity for detecting cardiac syncope.[13] Selection of other laboratory tests should be guided by clinical suspicion (e.g., a hemoglobin measurement for a patient with possible anemia or a glucose measurement for a patient with diabetes). **Routine laboratory studies are not needed in a child with a clear episode of vasovagal syncope.** For patients with an atypical presentation or worrisome associated symptoms, a serum chemistry panel, hematocrit, thyroid function tests, and chest radiograph may be performed in the ED if indicated by history. For example, hyperthyroidism predisposes children to supraventricular tachycardia, so thyroid function tests are appropriate when supraventricular tachycardia is considered. In adolescents, consider serum alcohol level and a urine drug screen to rule out illicit drug use (most commonly cocaine and amphetamines).

Obtain an echocardiogram for those with known cardiac disease, abnormal heart sounds, abnormal cardiac murmurs, evidence of cardiac chamber enlargement, or repolarization abnormalities on ECG, or other features that suggest myocardial dysfunction. If an echocardiogram cannot be obtained in the ED, then consider admission for inpatient evaluation. Echocardiography has very limited utility in patients without known heart disease and no high-risk historical factors.

Electroencephalogram has very low diagnostic yield in syncope and is not needed routinely.[15] The clinical utility of other tests, such as stress tests, tilt-table tests, electrophysiologic studies, and cardiac catheterization, usually is determined by the pediatric cardiologist and is beyond the scope of this chapter.

Children resuscitated from sudden death must undergo a complete evaluation unless a clear cause for the arrest is apparent. The diagnostic possibilities are extensive, so laboratory and radiographic studies should be directed by clinical and historical information. For all such patients, obtain a serum chemistry panel, cardiac enzymes, a CBC, serum alcohol level, urine drug screen, thyroid function tests, chest radiograph, and ECG. Look for complications resulting from the arrest, such as hypothermia, acidosis, rhabdomyolysis, and cerebral edema or

hypoxia. Inpatient evaluation can include an echocardiogram, cardiac catheterization, stress test, and electrophysiologic testing as directed by the pediatric cardiologist.

TREATMENT

Most children experiencing syncope have recovered fully by the time they arrive at the ED.[5,6] Continued altered level of consciousness should prompt an evaluation for continued neurologic, cardiovascular, or psychological derangements. Treatment should be tailored to current symptoms. Correct compromised oxygenation, ventilation, or circulation. Apply a cardiac monitor to document any transient dysrhythmias while gathering the history and physical findings. Manage ongoing cardiac dysrhythmias or seizures as appropriate (see Chapter 109, "Resuscitation of Children," and Chapter 138, "Seizures in Infants and Children"). Most patients, however, have no treatable dysrhythmias in the ED.

Treatment is targeted to specific identified causes of the syncopal event; 80% of the time, this will be neurocardiogenic syncope, and treatment for these patients includes reassurance, increasing water (1.5 to 2.5 L/d or until urine consistently clear) and salt intake (2 to 5 g/d), and isometric counterpressure maneuvers. There is little evidence to support the use of compression devices.

If diet and lifestyle modifications are not sufficient, a trial of midodrine is reasonable in patients with persistent and bothersome vasovagal syncope.[16,17]

DISPOSITION AND FOLLOW-UP

A child who had a syncopal event can present a challenging disposition decision, although in the majority of patients, the condition is benign.

Admit any child with a dysrhythmia documented by prehospital providers or on the ECG in the ED. Ensure that children who have any of the risk factors listed in Table 130-2 are seen by a pediatric cardiologist, either in the ED or in follow-up. Patients with a normal ECG but a history suspicious for dysrhythmia are candidates for outpatient ambulatory cardiac monitoring. Identified causes of syncope should be treated as appropriate in the ED, and admission to the hospital is directed by the need for further evaluation or therapy. Place all children admitted for an evaluation of syncope on a cardiorespiratory monitor.

If, after appropriately thorough history taking, physical examination, and ECG, no concerning features are elicited, the child may be discharged to home with follow-up by the child's primary physician. Because neurally mediated syncope accounts for up to 80% of the cases of syncope in children, most children without cardiac risk factors or exercise-induced symptoms do not require any further cardiac investigations.[18]

SPECIFIC CONDITIONS

SUDDEN DEATH

Sudden unexpected death can be due to many causes, such as a seizure, asthma, or toxic ingestion, whereas sudden cardiac death includes just those events that directly relate to cardiovascular dysfunction. Sudden unexpected death in children occurs in 7.5 cases per 100,000 children overall, with a much higher rate of 96 per 100,000 in children <1 year old.[19] Sudden cardiac death rates range from 0.7 to 6.4 per 100,000,[20,21] and sudden cardiac death accounts for about 2000 deaths per year in those younger than age 25.[22] These numbers are approximate because there is no centralized registry of these cases. Excluding trauma, sudden cardiac death is the most common cause of sports-related death in young athletes, accounting for about 100 deaths per year in the United States.[23] The greatest risk for sudden cardiac death is in patients with congenital or acquired structural cardiac disease, including those with congenital heart disease who have undergone corrective surgery. The most frequent causes of sudden cardiac death in children are listed in **Table 130-3**.[23] Hypertrophic cardiomyopathy and congenital artery anomalies are the most common causes of sudden cardiac death in adolescents without known cardiac disease.[24]

TABLE 130-3 Predisposing Factors for Sudden Cardiac Death in Children

Structural/functional cardiac disease	Hypertrophic cardiomyopathy
	Coronary artery anomalies
	Dilated or restrictive cardiomyopathy
	Acute myocarditis
	Congenital heart disease
	Arrhythmogenic ventricular cardiomyopathy
Rhythm disturbances	Long QT syndrome
	Wolff-Parkinson-White syndrome (WPW)
	Brugada syndrome
	Complete heart block
Systemic disease	Marfan's syndrome (aortic rupture)

Sudden cardiac death is usually an unexpected, unwitnessed, terminal event.

Survival from an out-of-hospital cardiac arrest is very unlikely, with reported rates from 2.5% to 5%.[25,26] Any surviving patients must undergo rapid stabilization, and any identified conditions must be quickly treated. In general, the principles of pediatric advanced life support are followed (see Chapter 109). Wide QRS complex tachydysrhythmias should not be treated with class Ia agents such as procainamide and quinidine or class III agents such as sotalol or amiodarone if long QT syndrome is suspected, as these medications act by prolonging the QT interval. Class Ib drugs, such as phenytoin, should be used instead; torsades de pointes should be treated with magnesium, 25 to 50 milligrams/kg (maximum dose, 2 grams; see Chapter 109).

After stabilization, children who have experienced a sudden cardiac arrest should be transferred to a pediatric intensive care unit that is capable of managing cardiac disorders. A crew capable of treating cardiac arrest from any dysrhythmia must perform any transfers. In general, this should be done by a dedicated pediatric critical care transport team and in consultation with the receiving pediatric intensivist.

NEUROCARDIOGENIC SYNCOPE

The majority of neurally mediated syncope is a mixed pattern of vasodepressor syncope (due to vasodilation) and cardioinhibitory syncope (due to vagal stimulation). **Neurocardiogenic syncope is the most common type of syncope in children[1] and usually is preceded by a sensation of warmth, nausea, lightheadedness, and a visual gray-out or tunneling of vision.**[5] This type of syncope frequently lasts <1 minute. Common precipitating factors include prolonged recumbence just before standing or prolonged standing, sight of blood or disfiguring injury (e.g., fractures or soft tissue injuries), emotional upset, mild physical trauma or pain, physical exertion, and hot or crowded conditions. Other contributing factors that are less common include hypovolemia, anemia, dehydration, and pregnancy. **Breath-holding spells are a variant of this form of syncope.** Medications that alter vascular tone or heart rate may contribute to the development of syncope, including β-blockers, calcium channel blockers, and diuretics. Hypovolemia can result from diuretic use in young athletes, such as wrestlers, who must comply with weight restrictions.

Diagnosing neurocardiogenic syncope in the ED can be challenging, because there is no specific diagnostic test. A history of position change, prodromal symptoms, an absence of previously noted red flags, a normal physical exam, and normal ECG fairly reliably confirm that the syncopal event is benign in nature.

BREATH-HOLDING SPELLS

Breath-holding spells are a form of neurally mediated syncope. Typical occurrence is in a 6- to 18-month-old child, and an intense emotional trigger that causes crying precipitates the spell and then breath-holding during expiration.[27] The child may become cyanotic or pale and lose consciousness from progressive cerebral hypoperfusion. Myoclonic activity or seizure activity may occur. The episode is usually short, requires no specific intervention, and rapidly resolves with gasping

respirations and progressive loss of cyanosis or pallor. Up to 20% of children who have breath-holding spells develop neurocardiogenic syncope in later life.[27]

ORTHOSTATIC SYNCOPE AND POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

Factors that predispose children to orthostatic syncope include anemia, dehydration, and use of certain medications, especially calcium channel blockers and angiotensin-converting enzyme inhibitors.[5] A drop of >20 mm Hg in blood pressure with an increase in heart rate of >20 beats/min when the child changes from a supine position to a standing position is often considered diagnostic of orthostatic hypotension. Postural orthostatic tachycardia syndrome is a form of chronic orthostatic intolerance, defined by elevation in heart rate of >35 to 40 beats/min, with stable or increased blood pressure on tilt-table testing combined with symptoms of orthostatic intolerance and sympathetic overactivation.[28]

SITUATIONAL SYNCOPE

Urination, defecation, coughing, and swallowing have been described as causing syncope. The pathophysiology is thought to be related to an exaggerated Valsalva response causing cardioinhibitory syncope. Stretching, neck extension, external neck pressure, and hair grooming also have been described as causing syncope, presumably due to carotid sinus hypersensitivity or abnormal Valsalva responses.

PEDIATRIC AUTONOMIC DISORDERS

Abnormalities in heart rate and blood pressure control can be inherited as a primary disorder. These disorders are associated with general autonomic dysfunction and present with many more symptoms than syncope. The most common is familial dysautonomia (Riley-Day syndrome). This disorder results from abnormal development of the sensory and autonomic ganglia, due to a genetic defect that inhibits neurotransmitter production. Manifestations include failure to thrive, developmental delay, temperature instability, abnormal sweating, absent lacrimation, breath-holding spells, and seizures.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy, also known as *idiopathic hypertrophic subaortic stenosis*, results in a dynamic and a fixed subvalvular obstruction (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease"). Exertional syncope is a common presentation, but infants may present with congestive heart failure and cyanosis. This diagnosis must be considered in any child with exertion-related syncope. A typical loud crescendo-decrescendo murmur may be heard at the left sternal border, which is accentuated by standing or Valsalva (decreased left ventricular preload). The ECG is abnormal in >75% of patients, usually with findings of left ventricular hypertrophy.[23] Onset of symptoms in early childhood is associated with a greater risk of mortality—the 10-year mortality rate is 50% for children diagnosed before 14 years of age.[29] Syncopal events appear to be related to myocardial ischemia and/or ventricular tachycardia, secondary to the long QT syndrome. Echocardiography is necessary to exclude or confirm this diagnosis and should be performed in the ED or on the inpatient ward. Patients with hypertrophic cardiomyopathy should be advised against playing competitive sports to reduce risk of sudden death. β-Blockers and septal reduction surgery are the mainstays of treatment. The benefit of implanted cardiac defibrillators is controversial in pediatric hypertrophic cardiomyopathy.[30] All patients with this condition should be managed in consultation with a pediatric cardiologist.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is unusual in children but can occur by three general mechanisms: idiopathic, with congenital heart disease, or after myocarditis (see Chapter 129). Syncope and death are thought to be caused by ventricular dysrhythmias or severe myocardial dysfunction.

ARRHYTHMOGENIC VENTRICULAR CARDIOMYOPATHY (FORMERLY ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA)

Arrhythmogenic ventricular cardiomyopathy has a general prevalence of 1 in 2000 population; however, it is a common cause of adolescent death in certain countries such as Italy and parts of Greece.[31] The disorder is more common in older adolescents and adults. Once thought to affect only the right ventricle, this has been shown to be a biventricular disease with a right-sided predominance. Patients usually present with congestive heart failure, cardiomegaly, and syncope or sudden death from a dysrhythmia. ECG abnormalities include left bundle branch block and T-wave inversion, but some patients may have normal ECG findings. Even the echocardiogram, cardiac catheterization, and myocardial biopsy results can be nondiagnostic, which makes exclusion of this disorder by the ED physician problematic.

CONGENITAL CYANOTIC AND NONCYANOTIC HEART DISEASE

Hypercyanotic spells may progress to syncope in tetralogy of Fallot, tricuspid atresia, transposition of the great arteries, and Eisenmenger's syndrome. Children with structural heart disease are also prone to ventricular dysrhythmias and atrioventricular block (see Chapter 129).

VALVULAR DISEASES

Several valvular lesions are associated with syncope and sudden death. In general, the degree of valve dysfunction correlates with the risk of sudden death. *Aortic stenosis* is usually due to a congenital defect and is often associated with a bicuspid valve. Other associated cardiac anomalies, in particular coarctation of the aorta, also may present as syncope. Most patients with valvular disease are identified by the presence of a murmur. Exertional syncope, from valvular disease, is caused by reduced cerebral blood flow and is associated with chest pain, dyspnea on exertion, and poor exercise tolerance. *Mitral valve prolapse* itself is not associated with an increased risk of sudden death, but children with the disorder do appear to have a higher frequency of syncope and dyshythmias.[32] A child with mitral valve prolapse and syncope requires a more intensive diagnostic workup. *Ebstein's malformation of the tricuspid valve* is an uncommon disorder (see Chapter 129). Sudden death in patients with this anomaly is thought to be due to the development of supraventricular or ventricular dysrhythmias.

PULMONARY HYPERTENSION

Primary pulmonary hypertension (without structural heart disease) is uncommon but can present in adolescence. It is often associated with dyspnea on exertion, shortness of breath, exercise intolerance, and syncope. Eisenmenger's syndrome is acquired pulmonary hypertension due to a cardiac shunt. High blood flow to the pulmonary circulation from a left-to-right shunt leads to a reactive increase in pulmonary resistance. After months to years, the development of pulmonary hypertension causes the shunt to reverse to a right-to-left shunt, and cyanosis becomes apparent. One half of patients with pulmonary hypertension develop syncope. Physical findings include an increased ventricular impulse, a loud second heart sound, and cyanosis, which is particularly prominent in patients with Eisenmenger's syndrome. Syncope and sudden death usually are related to a dysrhythmia.

CORONARY ARTERY ABNORMALITIES

Coronary artery abnormalities can cause sudden death during exercise or exercise-induced syncope. Abnormalities of coronary artery origin include the origination of the left main artery from the right sinus of Valsalva and, less frequently, the origination of the right artery from the left sinus. In both cases, the aberrant artery often passes between the aorta and the pulmonary artery, which thus places it at risk for extrinsic compression, especially during physical exertion. The ECG in abnormal left coronary arteries shows evidence of anterolateral myocardial infarction and abnormal R-wave progression. Other coronary abnormalities include myocardial overbridging, coronary artery fistulas, coronary

artery spasm, coronary ostial stenosis, coronary artery aneurysms, and stenosis from Kawasaki's disease.

DYSRHYTHMIAS IN CHILDREN

Outpatient continuous portable ECG monitoring identifies the cause of syncope in <1% of cases.[7,13] Case series indicate value in implantable loop recorders in cases of recurrent syncope with a history concerning for cardiac dysrhythmia. A cardiac dysrhythmia should be suspected if syncope is associated with an intense sympathetic stimulus, such as fright, anger, surprise, or physical exertion. The event usually starts and ends abruptly and may be associated with palpitations, irregularities of heartbeat, or chest pain.

A number of variations in rhythm can occur in normal children that are not considered pathologic. Significant P-P interval variation is common in children and represents an exaggerated respiratory reflex (slowing during expiration) leading to this benign sinus dysrhythmia. Infants in particular may demonstrate sudden prolongation of the P-P interval (up to 1.9 seconds), which is normal. Other common and benign variations include isolated ventricular premature beats (up to 40% of adolescents), which are typically of uniform morphology. Isolated supraventricular premature beats are also common in children of all ages. First-degree atrioventricular block, Mobitz type 1 second-degree atrioventricular block, and junctional rhythms can also be seen in normal children.[33]

Dysrhythmias occur as a result of altered cardiac impulse formation, conduction, or both, and may be related to congenital structural disease (e.g., Ebstein's anomaly, mitral valve prolapse, mitral stenosis), operative repair of congenital heart defect (e.g., corrected transposition of the great arteries, tetralogy of Fallot, atrial septal defect, or Fontan procedure), systemic disease (e.g., electrolyte abnormalities, neuromuscular disorders, metabolic or endocrine disease), acquired heart disease (e.g., myocarditis, endocarditis, Kawasaki's disease), or isolated electrical abnormalities.[34,35]

In general, children are able to tolerate higher rates without the ischemic phenomenon often present in adults. Dysrhythmias can occur in the absence of underlying structural heart disease or metabolic condition. Many conditions that occur in the adult population—such as hypoxia, electrolyte imbalance, collagen vascular diseases, and overzealous use of sympathomimetic agents—rarely occur in children. Because much of the prognosis with regard to the recurrence of a dysrhythmia depends on the nature of underlying structural cardiac defects, cardiologic evaluation is needed for all first-time occurrences of dysrhythmias.

The symptoms of true dysrhythmias can be subtle and nonspecific, particularly in neonates and infants, in whom poor feeding and irritability may be the only signs of early tachyarrhythmia. Sustained tachyarrhythmia may progress to signs of poor cardiac output and the development of congestive heart failure, edema, and poor capillary refill. Older children, on the other hand, may verbalize more classic adult symptoms of palpitations or tachycardia. Symptoms related to decreased cerebral blood flow that may suggest dysrhythmia include syncope or dizziness, whereas those related to decreased coronary blood flow include chest pain. Some dysrhythmias with features or treatments unique to children are discussed below.

ATRIOVENTRICULAR BLOCK

Atrioventricular block is most common in children with congenital heart disease after heart surgery but also occurs as a rare congenital disorder. Congenital atrioventricular block is associated with death in infancy, but children may be asymptomatic into adolescence.[36] Congenital atrioventricular block is more prevalent with connective tissue disease in the mother. Atrioventricular block also occurs with acquired heart diseases, such as hypertrophic cardiomyopathy, myocarditis, and muscular dystrophy, and in 87% of children with carditis associated with Lyme disease.[37] **Syncope from a high-degree atrioventricular block warrants urgent referral to cardiology.**

The treatment of sinus bradycardia in symptomatic patients begins with epinephrine (0.01 milligram/kg every 3 to 5 minutes; maximum dose, 1 milligram). If the bradycardia is due to atrioventricular block or increased vagal tone, then atropine (0.02 milligram/kg IV) as a temporizing measure is the best first-line treatment. The minimum dose is 0.1 milligram, with maximum single doses of 0.5 milligram for children and 1.0 milligram for adolescents. The maximum total dose (which is fully vagolytic) is 1.0 milligram for children and 2.0 milligrams for adolescents. Isoproterenol infusion (0.1 to 2 micrograms/kg/min) or epinephrine infusion (0.1 to 2 micrograms/kg/min of 1:10,000 dilution) can also be used, although definitive treatment usually requires pacing. Transthoracic pacing in children is discussed in Chapter 109, "Resuscitation of Children."

Prophylactic pacemaker insertion is routinely performed in children with acquired or congenital atrioventricular block.

SUPRAVENTRICULAR TACHYCARDIA

Supraventricular tachycardia can lead to syncope while the patient is recumbent if the heart rate is high enough to inhibit cardiac filling or if coincident vasomotor abnormalities occur.[38] Wolff-Parkinson-White syndrome (see next section) and atrial fibrillation are the most common causes, but primary supraventricular tachycardia can also occur. Episodes of supraventricular tachycardia are associated with congenital heart disease, including Ebstein's anomaly and corrected transposition of the great arteries.

The differentiation of sinus tachycardia from supraventricular tachycardia can be difficult in young children. **A rate of >220 beats/min in an infant or >180 beats/min in a child, with a rate out of proportion to clinical status, is likely supraventricular tachycardia**. Causes of sustained high-rate sinus tachycardia important to exclude are severe dehydration, fever, pain, hemorrhage, hyperthyroidism, sepsis, and drug toxicity from ingestion or iatrogenic medication administration. If vagal maneuvers can slow the heart rate and P waves become visible, the diagnosis is sinus tachycardia. Treatment of supraventricular tachycardia is described in Chapter 109.

WOLFF-PARKINSON-WHITE SYNDROME

Accessory pathways are common in infants and children with supraventricular tachydysrhythmias. They consist of thin strands of subendocardial tissue with conductive properties that create a "bypass" tract around the atrioventricular node, allowing direct conduction of atrial impulses to the ventricular myocardium. Accessory pathways often carry impulses faster than the normal atrioventricular conduction system and are not subject to the normal conduction delay of the atrioventricular node. Some accessory pathways carry impulses bidirectionally, whereas others may conduct in only one direction. Those that conduct in a retrograde-only direction are known as "concealed" because they are not visible on ECG during sinus rhythm but can lead to atrial preexcitation and fibrillation. Those that conduct in an antegrade-only fashion can cause atrioventricular reentrant tachycardia that is conducted in the retrograde direction through the atrioventricular node, resulting in wide complex tachycardia.

Wolff-Parkinson-White syndrome is the most common form of ventricular preexcitation in children and was first described in 1930. It has a prevalence of 0.1 to 3.1 per 1000 and is more common in boys than girls. Although most cases of Wolff-Parkinson-White syndrome are sporadic, familial autosomal dominant inheritance has been described. Approximately 1 in 10 patients with Wolff-Parkinson-White syndrome have associated cardiac anomalies including Ebstein's anomaly, hypertrophic obstructive cardiomyopathy, atrial septal defect, ventricular septal defect, transposition of the great arteries, and coarctation. Wolff-Parkinson-White syndrome is characterized by an accessory pathway that may be asymptomatic or can lead to recurrent episodes of tachydysrhythmia through ventricular preexcitation.[39]

The diagnosis of Wolff-Parkinson-White syndrome is typically made electrocardiographically through signs of preexcitation: a short PR interval (<0.12 seconds), a prolonged QRS complex (>0.12 seconds),

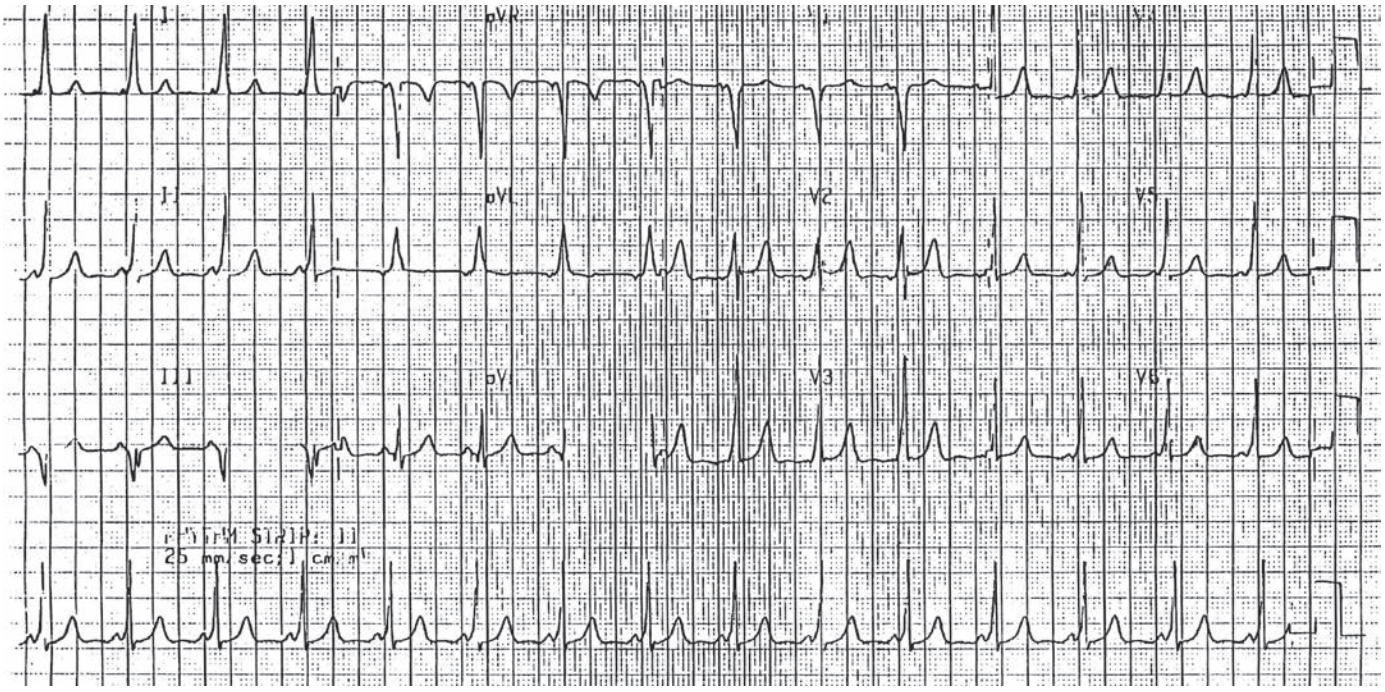

FIGURE 130-1. Wolff-Parkinson-White syndrome. Note the short PR interval and widened QRS with delta waves.

and the delta wave, which represents a slurred upstroke of the QRS complex (**Figure 130-1**). These findings may be subtle during normal sinus rhythm or absent during paroxysmal supraventricular tachycardia, but may be enhanced with vagal maneuvers or immediately after conversion of a tachydysrhythmia. Therefore, it is important to run a rhythm strip during the conversion of all patients with supraventricular tachycardia so any abnormal ECG findings in the immediate postconversion rhythm are observed.

The clinical presentation of Wolff-Parkinson-White syndrome ranges from asymptomatic discovery on ECG to symptoms of dysrhythmia including palpitations, dizziness, shortness of breath, chest pain, or syncope. Dysrhythmias occur in approximately 50% of patients with Wolff-Parkinson-White syndrome and are usually characterized by narrow complex tachycardia through atrioventricular reentrance (antegrade conduction through the atrioventricular node with retrograde conduction through the accessory pathway—"orthodromic"); atrial fibrillation is common in patients with orthodromic accessory pathways with Wolff-Parkinson-White syndrome. Occasionally, antidromic tachycardia (antegrade conduction through the accessory pathway with retrograde conduction through the atrioventricular node) can lead to ventricular fibrillation and death.

The acute management of supraventricular tachycardia in patients with Wolff-Parkinson-White syndrome is similar to that of supraventricular tachycardia from other causes: in stable patients, vagal maneuvers or adenosine may be useful; unstable patients are treated with immediate synchronized cardioversion. Two important caveats, however, should be noted in the pharmacologic management of supraventricular tachycardia with accessory pathways: **verapamil and digoxin should not be used in this setting because they may precipitate lethal dysrhythmias; similarly, flecainide should be avoided in patients with Wolff-Parkinson-White syndrome**. Because of the risk of recurrence of dysrhythmias in Wolff-Parkinson-White syndrome, definitive treatment usually consists of radiofrequency catheter ablation. Pharmacologic options for the treatment of atrial fibrillation associated with Wolff-Parkinson-White syndrome and the prevention of recurrent dysrhythmias are listed in **Table 130-4**.

LONG QT SYNDROME

Long QT syndrome is an inherited or acquired channelopathy and is characterized by a prolonged QT interval on the ECG. Inherited long QT syndrome is relatively rare, occurring at a rate of 1 in 2000 to 5000 births. It is associated with an increased risk of polymorphic ventricular tachyarrhythmias and sudden cardiac death in young individuals with normal cardiac morphology.[40] Classically, a patient with long QT syndrome should have a corrected QT interval that is >0.44 seconds on the ECG; however, registry evidence indicates that the risk of cardiac events

TABLE 130-4 Management of Patients With Accessory Pathways (Wolff-Parkinson-White Syndrome)

Clinical Situation	Treatment	Comments
Supraventricular tachycardia	Pharmacologic: Treat as per Chapter 109 Definitive treatment: radiofrequency catheter ablation	Adenosine may induce atrial fibrillation/flutter with rapid ventricular response; avoid digoxin and flecainide, which can lead to lethal dysrhythmias.
Atrial fibrillation Stable Unstable	Amiodarone 5 milligrams/kg (300 milligrams max) over 20–60 min Synchronized cardioversion 0.5–2 J/kg	Avoid nodal blocking agents such as verapamil, diltiazem, adenosine, β-blockers, and digoxin because these may precipitate ventricular fibrillation.
Prevention of recurrence	Pharmacologic: propranolol 1 milligram/kg/dose 2–3 times a day *or* sotalol 0.5–2 milligrams/kg/dose 2 times a day Definitive treatment: radiofrequency catheter ablation	

TABLE 130-5 Some Common Medications That Prolong QT_c

Drug Class	Examples
Antiarrhythmics	Class Ia and Ic (quinidine, flecainide; procainamide) Class III (sotalol > amiodarone)
Antihistamines	Diphenhydramine, hydroxyzine, terfenadine, astemizole
Antimicrobials	Macrolides (azithromycin, erythromycin, clarithromycin) Fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin) Antifungals (cotrimoxazole, fluconazole, ketoconazole, voriconazole) Other (antimalarials, trimethoprim sulfa, pentamidine)
Psychiatric drugs	Tricyclics Phenothiazines Others (citalopram, clozapine, fluoxetine, haloperidol, lithium, methadone, risperidone, quetiapine, sertraline, trazodone, venlafaxine, ziprasidone)
GI agents	Cisapride, ondansetron
Anticonvulsants	Fosphenytoin, felbamate
Immunosuppressives	Tacrolimus
Migraine medications	Sumatriptan, zolmitriptan
Stimulants	Albuterol, epinephrine, dopamine, dobutamine, isoproterenol, methylphenidate, phenylephrine, terbutaline
Other	Chloral hydrate, octreotide, vasopressin
Over-the-counter/ illicit drugs	Phenylephrine, pseudoephedrine, cocaine, amphetamine

increases only with corrected QT of >0.50 seconds in children and >0.53 seconds in adolescents.[41] Therefore, patients with corrected QT <0.5 seconds and no history of syncope are considered at low risk of cardiac events. Other abnormalities on the ECG associated with long QT syndrome include torsade de pointes, T-wave alternans, notched T waves in three leads, and prominent U waves. Children with long QT syndrome may have a normal ECG in the ED. The disorder may then be diagnosed by discovery of a history of long QT syndrome in a family member (familial), stress testing (exertional), or Holter monitoring (intermittent). On history, review any recent use of medications that can prolong the QT interval. (**Table 130–5** indicates some common medications, but there are many other medications that can cause QT prolongation.) Appropriate treatment can reduce the risk of aborted cardiac arrest and sudden cardiac death by approximately 50%. β-Blockers are the mainstay of treatment, but they are ineffective for some long QT variants. Therapy should be started in consultation with a cardiologist. Genetic studies to date have identified 13 genetic loci associated with long QT syndrome, all of which encode proteins involved in sodium, calcium, and potassium transport.[41]

SICK SINUS SYNDROME

Sick sinus syndrome is also known as *tachycardia-bradycardia syndrome*. Isolated sinus node dysfunction rarely causes syncope, and syncope associated with sick sinus syndrome is more likely to be due to a reentrant atrial tachycardia. Most commonly, these dysrhythmias are associated with prior heart surgery, especially the Mustard or Senning operation for transposition of the great vessels and the Fontan procedure. **Syncope and sudden death can occur after pacemaker placement, because the pacemaker prevents bradycardia but not tachycardia**.

ECG INTERPRETATION IN INFANTS AND CHILDREN

The pediatric ECG is characterized by age-related variations and, as a result, can be very difficult to interpret. The age-related variations reflect the maturation of the pediatric myocardium and vascular system from the neonate to adult. Developmental changes in the pediatric ECG from birth to adolescence include a gradual shift from right to left ventricular dominance, decrease in the resting heart rate, a lengthening of the PR and QRS intervals, and a change from inverted to upright T waves in the precordial leads.[33,42,43] Use a systematic approach to ECG interpretation, checking rate, rhythm, axis, hypertrophy of the atria and ventricles, and repolarization changes. Reference tables with age-specific values are necessary to deal with the progressive changes in heart rate, axis, interval duration, and morphology. The most important changes are described below.

TABLE 130-6 Normal Pediatric Heart Rates[44]

Age	Heart Rate (beats/min)
Birth–4 wk	130–190
1–3 mo	125–185
3–6 mo	110–165
6–12 mo	105–195
1–3 y	100–155
3–5 y	70–120
5–8 y	60–110
8–12 y	55–100
12–16 y	50–100

NORMAL ECG INTERVALS

HEART RATE

The normal heart rate is age dependent (**Table 130-6**). The neonatal and infant heart has a limited capacity to increase stroke volume, and therefore, cardiac output is largely dependent on rate, which is relatively high in the young infant to meet increased metabolic demands. Significant state-dependent and beat-to-beat variability in resting heart rate is characteristic of the normal neonatal and infant heart. Sinus tachycardia in the neonate can often reach 200 to 220 beats/min and is common in the setting of fever or pain. In general, bradycardia with normal perfusion and without evidence of heart block (discussed below) rarely requires treatment or investigation.

P AND QRS AXES

Because blood is shunted away from fetal lungs and the right ventricle provides the majority of systemic blood flow in utero, the right ventricle predominates in the neonate. In the first few months of life, this is characterized by right ventricular dominance and right axis deviation. P waves should be upright in leads I and aVF with the P axis between 0 and +90 degrees. The precordial leads have increased R-wave amplitude in V_1 and V_2 and decreased amplitude in V_5 and V_6. With a subsequent increase in left ventricular size during infancy and early childhood, the QRS axis shifts leftward, so that R-wave amplitude decreases in V_1 and V_2 and increases in V_5 and V_6 (**Table 130-7**).

TABLE 130-7 Age-Specific QRS Axis[44]

Age	Mean Axis in Degrees	Range in Degrees
Birth–4 wk	105	60–160
1–3 mo	85	40–140
3–6 mo	68	0–110
6–12 mo	68	0–120
1–3 y	66	0–120
3–5 y	70	0–115
5–8 y	72	−10 to 120
8–12 y	68	−20 to 120
12–16 y	65	−10 to 110

TABLE 130-8 Age-Specific ECG Intervals[44]

Age	PR (seconds)	QRS (seconds)	QT_c (seconds)
Birth–4 wk	0.08–0.12	0.05–0.09	0.38–0.46
1–3 mo	0.08–0.13	0.05–0.08	0.38–0.46
3–6 mo	0.08–0.14	0.05–0.09	0.39–0.45
6–12 mo	0.08–0.14	0.05–0.09	0.38–0.45
1–3 y	0.08–0.15	0.05–0.09	0.38–0.45
3–5 y	0.1–0.15	0.06–0.09	0.38–0.45
5–8 y	0.09–0.16	0.06–0.1	0.37–0.45
8–12 y	0.1–0.17	0.07–0.1	0.37–0.45
12–16 y	0.1–0.18	0.7–0.11	0.36–0.46

PR, QRS, AND QT INTERVALS

The PR interval varies with age, gradually lengthening from 0.08 to 0.12 seconds in neonates to 0.11 to 0.18 seconds in adolescents.[36] The QRS interval also lengthens over time from 0.05 to 0.09 seconds in the neonate to 0.07 to 0.11 seconds in the adolescent.[44] The QT interval (measured from the onset of the QRS complex to the end of the T wave) is subject to variations in heart rate, and a correction for heart rate is calculated using Bazett's formula: QT_c = QT/the square root of the RR interval. The QT_c should be <0.49 seconds in the first 6 months of life and <0.44 seconds thereafter, although different definitions for prolonged QT_c have been suggested.[42] Age-specific normal intervals are listed in **Table 130-8**.

T WAVES

Pediatric T-wave changes are typically nonspecific. Flat or inverted T waves are usually normal in the newborn. T-wave inversion in the right precordial leads is common in the first years of life and may persist into adolescence or revert in early childhood to the typical upright pattern seen in adults.[42] T-wave changes are common in infants and children and rarely reflect ischemia.

CHAMBER SIZE

Evaluating the ECG for signs of chamber size is important when considering congenital or acquired heart disease in the pediatric patient. P-wave amplitude is relatively age independent and best measured in lead II. P waves >0.25 mV should be considered abnormal and may indicate right atrial enlargement.[44] Left atrial enlargement is suggested by prolonged P-wave duration, which should not be >0.08 seconds in infants or >0.12 seconds in adolescents.[42] Voltage criteria for left ventricular hypertrophy and right ventricular hypertrophy depend on age and are listed in **Table 130-9**.[42,45] Left ventricular hypertrophy is also suggested by a q-wave amplitude >4 mm in V_5 or V_6 or inverted T wave in V_6, whereas right ventricular hypertrophy is suggested by an RSR′ pattern in V_1 with an R′ >15 mm in infants or >10 mm in children after the first year of life, or with a q wave in lead V_1.[33,42,43]

TABLE 130-9 Voltage Criteria for Left Ventricular Hypertrophy (LVH) and Right Ventricular Hypertrophy (RVH) by Age[42,45]

	Age				
	0–7 d	7 d–1 y	1–3 y	3–5 y	>5 y
LVH					
RV_6	>12 mm	>23 mm	>21–23 mm	>24–25 mm	>25–27 mm
SV_1	>23 mm	>15–18 mm	>21 mm	>22 mm	>26 mm
$SV_1 + RV_6$	>28 mm	>35 mm	>38 mm	>42 mm	>47 mm
RVH					
RV_1	>26 mm	>20–22 mm	>18 mm	>14–18 mm	>13 mm
SV_6	>10 mm	>7–10 mm	>7 mm	>6 mm	>4 mm
$RV_1 + SV_6$	>37 mm	>43 mm	>30 mm	>24 mm	>17 mm

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 131

Vomiting, Diarrhea, and Dehydration in Infants and Children

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INTRODUCTION

Acute viral gastroenteritis is the most common cause of vomiting and diarrhea in children and continues to account for over 500,000 deaths globally each year in children <5 years old.[1] Transmission of GI infections can be reduced by attention to good hand washing, which can reduce the incidence of diarrheal disease by approximately 30% in both high- and low-income countries.[2] The provision of alcohol-based hand sanitizer and educational materials can reduce GI illnesses in child care centers,[3] and a multifactorial intervention including hand sanitizer and surface disinfection similarly reduces illness due to enteric pathogens in elementary school students.[4]

Rotavirus previously accounted for the majority of severe cases and contributed significantly to hospitalizations in developed countries. However, the introduction of two live oral rotavirus vaccines, marketed as RotaTeq® and Rotarix®, for use in the United States and numerous other countries has resulted in an approximately 80% reduction in rotavirus-related hospitalizations and ED visits for rotavirus among immunized children.[5,6] Although a prospective postlicensure study of more than 200,000 doses identified an increase in the rate of intussusception after vaccination (attributable risk ~5.3 per 100,000 infants vaccinated), the increased risk must be weighed against the benefits of preventing rotavirus-associated illness.[7] The reduction in rotavirus's burden of disease along with the improved ability to identify norovirus has led to a realization that norovirus is now the pathogen responsible for the greatest burden of medically attended cases of gastroenteritis.[8]

Although the clinical diagnosis of gastroenteritis requires the presence of diarrhea, many infants present with isolated vomiting. This chapter focuses on one of the most frequent and important causes of vomiting and diarrhea in children, gastroenteritis, and will also review other important causes of these symptoms.

VOMITING

Vomiting is the forceful act of expelling gastric contents through the mouth. It is controlled by the vomiting center in the reticular formation of the medulla and the chemoreceptor trigger zone underlying the floor of the fourth ventricle. Trigger areas that excite the CNS vomiting centers are found in the pharynx, cardiac vessels, peritoneum, bile ducts, and stomach. Vomiting results when the stomach relaxes, the gastric pylorus constricts, and the contractions of surrounding muscles cause expulsion of the gastric contents. Acute vomiting is usually caused by a self-limited viral illness. Nonetheless, serious diagnoses that need to be considered include infections, metabolic abnormalities, neurologic processes, acute surgical/GI diseases, or other major organ system dysfunction. The differential diagnosis of vomiting is age specific (**Table 131-1**). **Bilious or bloody vomitus, hematochezia, or significant abdominal pain should trigger concerns of a disease process other than simple viral gastroenteritis or a potential complication of viral gastroenteritis (Tables 131-2 and 131-3).**

TABLE 131-1 Causes of Vomiting, by Age

Newborn	
Obstructive intestinal anomalies	Esophageal stenosis/atresia, pyloric stenosis, intestinal stenosis/atresia, malrotation ± volvulus, incarcerated hernia, meconium ileus/plug, Hirschsprung's disease, imperforate anus, enteric duplications
Neurologic	Intracranial bleed/mass, hydrocephalus, cerebral edema, kernicterus
Renal	Urinary tract infection, obstructive uropathy, renal insufficiency
Infectious	Viral illness, gastroenteritis, meningitis, sepsis
Metabolic/endocrine	Inborn errors of metabolism (urea cycle, amino/organic acid, carbohydrate), congenital adrenal hyperplasia
Miscellaneous	Ileus, gastroesophageal reflux, necrotizing enterocolitis, GI perforation
Infant (<12 mo)	
Obstructive intestinal anomalies	Pyloric stenosis, malrotation ± volvulus, incarcerated hernia, Hirschsprung's disease, enteric duplications, intussusception, foreign body, bezoars, Meckel's diverticulum
Neurologic	Intracranial bleed/mass, hydrocephalus, cerebral edema
Renal	Urinary tract infection, obstructive uropathy, renal insufficiency
Infectious	Viral illness, gastroenteritis, meningitis, sepsis, otitis media, pneumonia, pertussis, hepatitis
Metabolic/endocrine	Inborn errors of metabolism, adrenal insufficiency, renal tubular acidosis
Miscellaneous	Ileus, gastroesophageal reflux, posttussive, peritonitis, drug overdose, food allergy
Child (>12 mo)	
Obstructive intestinal anomalies	Malrotation ± volvulus, incarcerated hernia, Hirschsprung's disease, intussusception, foreign body, bezoars, Meckel's diverticulum, acquired esophageal stricture, peptic ulcer disease, adhesions, superior mesenteric artery syndrome
Neurologic	Intracranial bleed/mass, cerebral edema, postconcussive, migraine
Renal	Urinary tract infection, obstructive uropathy, renal insufficiency
Infectious	Viral illness, gastroenteritis, meningitis, sepsis, otitis media, pneumonia, hepatitis, streptococcal pharyngitis
Metabolic/endocrine	Inborn errors of metabolism, adrenal insufficiency, renal tubular acidosis, diabetes mellitus, Reye's syndrome, porphyria
Miscellaneous	Ileus, gastroesophageal reflux, posttussive, peritonitis, drug overdose, food allergy, appendicitis, pancreatitis, gastritis, Crohn's disease, pregnancy, psychogenic, cyclic vomiting syndrome

TABLE 131-2 Causes of Vomiting With Significant Morbidity, by Age

Newborn Period (birth–2 wk)	
Obstructive intestinal anomaly	Esophageal or intestinal stenosis/atresia, bowel malrotation ± midgut volvulus, meconium ileus/plug, Hirschsprung's disease, imperforate anus, enteric duplications
Other GI disease processes	Necrotizing enterocolitis, perforation with secondary peritonitis
Neurologic	Mass lesion, hydrocephalus, cerebral edema, kernicterus
Renal	Obstructive anomaly, uremia
Infectious	Sepsis, meningitis
Metabolic	Inborn errors of metabolism, congenital adrenal hyperplasia
Infant (2 wk–12 mo)	
Acquired esophageal disorders	Foreign body, retropharyngeal abscess
GI obstruction	Bezoar, foreign body, pyloric stenosis, malrotation ± volvulus, enteric duplications, complications of Meckel's diverticulum, intussusception, incarcerated hernia, Hirschsprung's disease
Other GI disease processes	Gastroenteritis with dehydration, peritonitis
Neurologic	Mass lesion, hydrocephalus
Renal	Obstruction, uremia
Infectious	Sepsis, meningitis, pertussis
Metabolic	Inborn errors of metabolism
Toxic ingestions	—
Child (>12 mo)	
GI obstruction	Bezoar, foreign body, posttraumatic intramural hematoma, malrotation ± volvulus, complications of Meckel's diverticulum, intussusception, incarcerated hernia, Hirschsprung's disease
Other GI disease processes	Appendicitis, peptic ulcer disease, pancreatitis, peritonitis
Neurologic	Mass lesions
Renal	Uremia
Infectious	Sepsis, meningitis
Metabolic	Diabetic ketoacidosis, adrenal insufficiency, inborn errors of metabolism
Toxic ingestion	—

Bilious vomiting suggests an obstructive lesion distal to the ampulla of Vater and portends a surgical emergency. From one third to half of newborns with bilious vomiting have a surgical lesion, often malrotation with volvulus or Hirschsprung's disease.[9,10] For further discussion, see Chapter 133, "Acute Abdominal Pain in Infants and Children." For discussion of hematemesis, see Chapter 134, "Gastrointestinal Bleeding in Infants and Children."

Diagnostically, it is important to consider children with **isolated vomiting** separately from those who present with *vomiting and diarrhea*. The differential diagnosis of vomiting is vast and age specific (Table 131-1). Gastroesophageal reflux, intussusception, pyloric stenosis, and malrotation are discussed briefly below and more fully in Chapter 133, "Acute Abdominal Pain in Infants and Children."

GASTROESOPHAGEAL REFLUX (GERD)

Gastroesophageal reflux is the spontaneous regurgitation of gastric contents into the esophagus. Reflux is physiologic in young infants and usually resolves by the end of the first year of life. It is considered pathologic only in the small subset that experiences complications. The typical infant with uncomplicated gastroesophageal reflux effortlessly brings up small amounts of milk after feeding but continues to grow well. Symptoms may begin as early as the first week of life and often resolve around the time of solid food introduction and the assumption of the sitting position. In infants with significant vomiting, pathologic conditions should be considered. Complications that can occur include esophagitis, **failure to thrive/weight loss**, respiratory disease, refractory asthma, recurrent pneumonia, apnea, and acute life-threatening

TABLE 131-3 Causes of Diarrhea With Significant Morbidity

- Infection: *Salmonella* gastroenteritis with bacteremia, *Shigella*, *Clostridium difficile* (pseudomembranous colitis)
- Anatomic abnormalities
- Intussusception
- Hirschsprung's disease with toxic megacolon
- Partial obstruction
- Appendicitis
- Inflammatory bowel disease with toxic megacolon
- Verotoxigenic *Escherichia coli* infection with the secondary development of hemolytic-uremic syndrome

events. In most infants, the diagnosis can be made based on clinical findings. The gold standard diagnostic test is continuous esophageal pH monitoring to detect the presence of gastric acid in the distal esophagus. Semi-supine positioning (e.g., infant carrier or car seat) may exacerbate gastroesophageal reflux and should be avoided, especially after feeding.[10] Although severe cases may require a histamine-2 receptor antagonist or a proton pump inhibitor, the overuse of medications in the "happy spitter" should be avoided.[11]

INTUSSUSCEPTION

Intussusception occurs when one segment of bowel invaginates into a more distal segment. It is the leading cause of acute intestinal obstruction in infants and occurs most commonly between 3 and 12 months of age. The most common location is ileocolic, and the lead point usually is a hypertrophied Peyer patch. However, in children >2 years of age, a specific pathologic lead point should be considered. The primary manifestation is colicky abdominal pain followed by the onset of vomiting. The "classic" triad of colicky abdominal pain, vomiting, and bloody stools is present in only 20% of cases. For further discussion of intussusception, see Chapter 133, "Acute Abdomnal Pain in Infants and Children."

PYLORIC STENOSIS

Pyloric stenosis results from pyloric muscle hypertrophy that obstructs gastric outflow. The incidence is 1 in 250 live births, and >80% of cases occur in males[12]; other risk factors include white race, first born birth order, and a positive family history. Over 90% of cases are diagnosed by 10 weeks of life, with a sharp increase in the incidence after the second week of life, peaking at the fifth week and then steadily declining until the 10th week.[12] Children typically present with nonbilious projectile vomiting associated with weight loss and dehydration. Initially, the vomiting is mild and often mistaken for regurgitation. However, vomiting progresses and becomes more severe over several days. ED treatment includes the correction of fluid and electrolyte abnormalities. The pathognomonic electrolyte abnormalities are a hyponatremic, hypokalemic, and hypochloremic metabolic alkalosis. At present, the diagnosis is usually confirmed by US.

MALROTATION

Malrotation occurs when incomplete rotation of the gut in utero places the cecum in the right upper quadrant and fixes the dorsal mesentery on a narrow base instead of the broad fixation that usually extends from the ligament of Treitz to the ileocecal junction. These anomalies place the small bowel at risk for twisting on the narrow pedicle of mesentery, resulting in a volvulus that subsequently impairs blood flow to the bowel. Although malrotation can present at any age, roughly one third of patients present in the first month of life.[12] Symptoms may include bilious vomiting, pain, abdominal distention, and, ultimately, shock due to intestinal ischemia. Bilious emesis, particularly in a young infant, should immediately raise a concern for possible malrotation and volvulus. In some children, the volvulus can be intermittent, resulting in episodic vomiting and pain. Prompt diagnosis and surgical repair are needed to minimize the risk of bowel necrosis and death.

DIARRHEA

Diarrhea is loose or liquid stools and/or an increase in the frequency of evacuations with at least three stools in 24 hours. The child's age and diet affect stool consistency and frequency. For example, in the first month of life, a change in stool consistency is more specific for diarrhea than absolute stool number. Breastfed infants typically have several poorly formed, yellow-green stools per day. Recognition of diarrhea in infants is important, because given their small size, they have limited fluid reserves and are at high risk for developing dehydration.

Most children with diarrhea have an acute viral infection, but diarrhea may be a presenting symptom of many conditions (**Tables 131-4** and **131-5**). Preexisting conditions may contribute to the clinical presentation or predispose the patient to an unusual cause of diarrhea, so it is important to inquire about previous GI surgery or chronic illnesses such as inflammatory bowel disease and immunodeficiency states. Bacterial and parasitic infections are more likely in institutionalized children and those returning from travel in low- and middle-income countries. Other causes of diarrhea include food allergies, antibiotic-associated diarrhea, and secondary lactase deficiency.

TABLE 131-4 Causes of Diarrhea

Infection
- Viral: rotavirus, norovirus, enteric adenoviruses, sapoviruses, astroviruses
- Bacterial: *Salmonella, Shigella, Yersinia, Campylobacter, Escherichia coli, Aeromonas hydrophila, Vibrio* species, *Clostridium difficile*
- Parasitic: *Giardia lamblia, Entamoeba histolytica, Cryptosporidium*

Dietary disturbances
- Overfeeding, food allergy, starvation stools

Anatomic abnormalities
- Intussusception, Hirschsprung's disease, partial obstruction, appendicitis, blind loop syndrome, intestinal lymphangiectasia, short bowel syndrome

Inflammatory bowel disease

Malabsorption or secretory diseases
- Cystic fibrosis, celiac disease, disaccharidase deficiency, acrodermatitis enteropathica, secretory neoplasms

Systemic diseases
- Immunodeficiency, endocrinopathy (hyperthyroidism, hypoparathyroidism, congenital adrenal hyperplasia)

Miscellaneous
- Antibiotic-associated diarrhea, secondary lactase deficiency, irritable colon syndrome, neonatal drug withdrawal, toxins, hemolytic-uremic syndrome

Acute onset of **bloody diarrhea** suggests a bacterial cause and a need to perform stool cultures. **If there is a known outbreak of *Escherichia coli* O157:H7 (STEC, or Shiga toxin-producing E. coli), or clinical features of hemolytic-uremic syndrome (HUS), obtain further testing to exclude renal failure, thrombocytopenia, and hemolytic anemia** and provide early volume expansion.[13] An infant with intermittent, crampy abdominal pain, vomiting, and bloody stools raises concern for intussusception, pseudomembranous colitis, parasitic infection, or inflammatory bowel disease.

DEHYDRATION

Regardless of the cause of vomiting and diarrhea, the end result is fluid loss. Parental reports of dehydration, although highly sensitive, have a high false-positive rate. However, a history of *normal fluid intake* and *normal urine output* drastically reduces the likelihood of significant dehydration.[14] Thus, for the majority of children, the physical examination remains crucial and should begin by assessing the child's overall appearance, level of activity, responsiveness, respiratory pattern, and vital signs. Although the American Academy of Pediatrics, Centers for Disease Control and Prevention, World Health Organization, and European Society for Paediatric Gastroenterology, Hepatology, and Nutrition have developed treatment guidelines based on the degree of dehydration, no single variable in isolation is sufficiently accurate to determine the severity of dehydration.[15] The percentage of body weight lost remains the gold standard measurement of dehydration, but it is infrequently available in the ED. Thus, while we recommend that physicians continue to rely on the presence of a combination of clinical findings as well as historical features to determine the degree of dehydration (see Table 132-2), their ability to identify children both with and without dehydration is suboptimal.[16] Moreover, current evidence does not support the routine use of US or urinalysis to determine dehydration severity. A validated dehydration score derived from several clinical studies,[17-19] which correlates with length of stay and need for IV rehydration, is described in **Table 131-6**.[18]

TABLE 131-5 Mechanisms of Infectious Diarrheal Disease

Pathogen Type	Characteristic Examples	Mechanism	Pathologic Impact	Clinical Impact
Viral enteropathogens	Rotaviruses Adenoviruses	Invade small intestinal mucosa villous epithelium	Loss of mature absorptive cells, producing a proliferative response, resulting in repopulation of intestinal epithelial lining with poorly differentiated cells.	Salt and water absorption is decreased Carbohydrate malabsorption and osmotic diarrhea
Bacterial enteropathogens	**Invasive** *Shigella* *Salmonella* *Yersinia enterocolitica* *Campylobacter jejuni* *Vibrio parahaemolyticus*	Adhere to mucosal cells followed by invasion and multiplication, primarily in large intestine	Intramucosal multiplication elicits an acute mucosal inflammatory reaction, resulting in ulceration and synthesis of a variety of secretagogues.	Salt and water absorption is decreased (secretory diarrhea)
	Cytotoxic *Shigella* Enteropathogenic *Escherichia coli* Enterohemorrhagic *E. coli* *Clostridium difficile*	Elaboration of cytotoxins	Cause cell damage and death by inhibiting protein synthesis or by inducing the secretion of one or more inflammatory mediator substances.	Decreased intestinal absorptive surface
	Toxigenic *Shigella* Enterotoxigenic *E. coli* *Y. enterocolitica* *Aeromonas* *Vibrio cholerae*	Colonize small intestine and secrete enterotoxins	Enterotoxin binds to specific mucosal receptors, increasing the concentration of an intracellular mediator (adenosine 3′:5′-cyclic phosphate or cyclic guanosine monophosphate).	Alter intestinal salt and water transport without affecting mucosal morphology
	Adherent Enteropathogenic *E. coli* Enterohemorrhagic *E. coli*	Colonization and adherence to intestinal surface of small and large intestine	Binding to epithelial cells indents the surface and causes glycocalyx dissolution and microvilli flattening.	Decreased intestinal absorptive surface

GASTROENTERITIS

EPIDEMIOLOGY

Diarrheal diseases are the second leading cause of death worldwide in children outside of the neonatal period. Rotavirus is the most common pathogen in areas without a vaccination program, and in areas with widespread rotavirus vaccination, norovirus is the most common pathogen.

PATHOPHYSIOLOGY

To cause diarrhea, an infectious agent must overcome numerous host defense factors, including gastric acidity, intestinal immunity, motility, mucus, and the resident microflora. The interaction between these factors and the infecting agent's virulence mechanisms determines the subsequent clinical course (Table 131-5). No matter what the mechanism is, acute gastroenteritis is associated with fluid shifts and has the potential to cause dehydration, shock, and even death. The common final pathway results in fluid output exceeding the absorptive capacity of the GI tract. Fasting, which sometimes occurs with gastroenteritis, actually worsens the capacity of the bowel to absorb fluids. Continued feeding not only slows the progression of dehydration by increasing the volume of fluid available to the intravascular space, but the presence of nutrients in the bowel lumen also promotes mucosal recovery and improves fluid absorption.[20]

TABLE 131-6 Clinical Dehydration Score

Score	General Appearance	Eyes	Oral Mucosa (Tongue)	Tears
0	Normal	Normal	Moist	Normal
1	Thirsty, restless, lethargic but irritable	Mildly sunken	Sticky	Decreased
2	Drowsy/nonresponsive, limp, cold, diaphoretic	Very sunken	Dry	None

Score >0 = some dehydration; score >5 = moderate-severe dehydration.

CLINICAL FEATURES

Diarrhea associated with acute **viral gastroenteritis** typically lasts <7 days and not longer than 14 days, and it may be accompanied by vomiting or fever. Clinical features associated with the most important causes of **bacterial gastroenteritis** are listed in **Table 131-7**. **Isolated vomiting should not be diagnosed as acute gastroenteritis.** The differential diagnosis for isolated vomiting in the absence of diarrhea is broad.

Abdominal pain is often associated with gastroenteritis, but pain is typically poorly localized and crampy with no peritoneal signs on examination. If peritoneal signs are present, consider an alternative diagnosis, such as acute appendicitis. **Although appendicitis typically manifests with abdominal pain followed by vomiting associated with constipation, it may also cause diarrhea, particularly once the appendix has perforated. This is presumed to occur because the inflammation irritates the colon, resulting in diarrhea.** Stools tend to be frequent, mucus-containing, and small in volume. For further discussion, see Chapter 133, "Acute Abdominal Pain in Infants and Children."

LABORATORY TESTING

Obtain a CBC only if the child is ill appearing or has bloody diarrhea (mainly to identify bacterial enterocolitis or hemolytic-uremic syndrome). The WBC count and C-reactive protein are not reliable for distinguishing viral from bacterial gastroenteritis.[21-23] The C-reactive protein is only helpful for following activity of inflammatory bowel disease. **Given that the reported prevalence of hypoglycemia may be as high as 9% in pediatric gastroenteritis,[24] measuring serum glucose in infants and young children is essential.**

Obtain serum electrolytes only in specific circumstances.[25,26] **Table 131-8** lists the European Society for Paediatric Gastroenterology,

TABLE 131-7 Clinical Features and Treatment of Bacterial Gastroenteritis[24]

Organism	Typical Clinical Features	Risk Factors	Complications	Antimicrobial Therapy*
Shigella	Ranges from watery stools without constitutional symptoms to fever, abdominal pain, tenesmus, mucoid stools, hematochezia; *Shigella dysenteriae* serotype 1 causes more severe symptoms	Contact with infected host or fomite, poor sanitation, crowded living conditions, day care	Pseudomembranous colitis, toxic megacolon, intestinal perforation, bacteremia, Reiter's syndrome, hemolytic-uremic syndrome, encephalopathy, seizures, hemolysis	Typically self-limited Treat if: immunocompromised, severe disease, dysentery or systemic symptoms If susceptibility unknown: azithromycin, ceftriaxone, ciprofloxacin; if susceptible, ampicillin or trimethoprim-sulfamethoxazole
Salmonella	Nontyphoidal: may be asymptomatic or cause watery diarrhea, mild fever, abdominal cramps Enterica serotypes: "enteric fever" may include high fever, constitutional symptoms, headache, abdominal pain, dactylitis, hepatosplenomegaly, rose spots, altered mental status	Direct contact with animals: poultry, livestock, reptiles, pets; consuming food contaminated by human carrier: beef, poultry, eggs, dairy, water	Meningitis, brain abscess, osteomyelitis, bacteremia, dehydration, endocarditis, enteric (typhoid or paratyphoid) fever	Typically self-limited Treat if: <3 mo of age, hemoglobinopathy, immunodeficiency, chronic GI tract disease, malignancy, severe colitis, bacteremia, sepsis Options: ampicillin, amoxicillin, trimethoprim-sulfamethoxazole; if resistant, azithromycin, fluoroquinolone Invasive disease: cefotaxime, ceftriaxone
Campylobacter	Diarrhea, hematochezia, abdominal pain, fever, malaise	Contamination from poultry feces or undercooked poultry, untreated water, unpasteurized milk, pets (dogs, cats, hamsters, birds); person-to-person transmission possible	Acute: dehydration, bacteremia, focal infections, febrile seizures Convalescence: reactive arthritis, Reiter's syndrome, erythema nodosum, acute idiopathic polyneuritis, Miller Fisher syndrome, myocarditis, pericarditis	Often self-limited; 20% have relapse or prolonged symptoms Treat if: moderate-severe symptoms, relapse, immunocompromised, day care and institutions Options: erythromycin, azithromycin, ciprofloxacin
Escherichia coli–Shiga toxin producing	Initially nonbloody diarrhea, often becoming bloody; severe abdominal pain	Food or water contaminated with human or cattle feces, undercooked beef, unpasteurized milk	Hemorrhagic colitis, hemolytic-uremic syndrome	None indicated; increased incidence of hemolytic-uremic syndrome with treatment
E. coli–enteropathogenic	Severe watery diarrhea, usually children <2 years in resource-limited countries	Food or water contaminated with feces	Dehydration	Treat if severe Options: trimethoprim-sulfamethoxazole, azithromycin, ciprofloxacin
E. coli–enterotoxigenic	Moderate watery diarrhea, abdominal cramps; traveler's diarrhea	Food or water contaminated with feces	Dehydration	Treat if severe Options: trimethoprim-sulfamethoxazole, azithromycin, ciprofloxacin
E. coli–enteroinvasive	Fever, bloody or nonbloody diarrhea, dysentery	Food or water contaminated with feces	Dehydration	Treat if severe Options: trimethoprim-sulfamethoxazole, azithromycin, ciprofloxacin
E. coli–enteroaggregative	Watery diarrhea, may be prolonged	Food or water contaminated with feces	Dehydration	Treat if severe Options: trimethoprim-sulfamethoxazole, azithromycin, ciprofloxacin
Yersinia	Bloody diarrhea with mucus, fever, abdominal pain; pseudoappendicitis syndrome: fever, right lower quadrant pain, leukocytosis; *Yersinia* pseudotuberculosis causes fever, scarlatiniform rash, abdominal pain	Contaminated food: improperly cooked pork, unpasteurized milk, untreated water; contact with animals (ungulates, rodents, rabbits, birds)	Acute: bacteremia, pharyngitis, meningitis, osteomyelitis, pyomyositis, conjunctivitis, pneumonia, empyema, endocarditis, acute peritonitis, liver/spleen abscess; convalescence: erythema nodosum, glomerulonephritis, reactive arthritis	Typically self-limited; if severe, treat with trimethoprim-sulfamethoxazole, aminoglycosides, cefotaxime, fluoroquinolones, tetracycline, doxycycline, chloramphenicol
Vibrio cholerae	Voluminous watery diarrhea, usually without cramps or fever, classically described as "rice water" stools	Travel to affected areas, consumption of contaminated water or food (particularly undercooked seafood)	May rapidly lead to hypovolemic shock, hypoglycemia, hypokalemia, metabolic acidosis, seizures	Treat if moderate or severe: azithromycin, doxycycline; ciprofloxacin or trimethoprim-sulfamethoxazole if resistant

*Most experts continue to limit fluoroquinolone use in children to those selected clinical situations where the benefits clearly outweigh the risks of therapy and there are few other antibiotic choices.

TABLE 131-8 Recommendations for Measuring Glucose and Serum Electrolytes

- Moderately dehydrated children whose history and physical examination findings are inconsistent with acute gastroenteritis
- All severely dehydrated children
- All children requiring IV rehydration[31]

Source: Reproduced with permission from Guarino A, Albano F, Ashkenazi S, et al: European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence based guidelines for the management of acute gastroenteritis in children in Europe. *J Paediatr Gastroenterol Nutr* 46: S81, 2008. Copyright Lippincott Williams & Wilkins.

Hepatology, and Nutrition recommendations for measuring electrolytes in children with gastroenteritis.

In a study assessing the utility of routinely obtaining electrolytes in 182 children receiving IV rehydration,[27] an electrolyte abnormality was present in nearly half, and management changed in 10% of children**. All interventions were related to the administration of fluids and glucose or potassium.**

Although BUN is elevated in severe dehydration, it does not identify lesser degrees of dehydration very well. Serum bicarbonate>15 mEq/L makes dehydration unlikely.[28] Last, urinary indices have been demonstrated to correlate poorly with severity of dehydration.[29]

RAPID STOOL TESTS

Classic gastroenteritis of bacterial origin arises in the distal small bowel or colon to cause dysentery, with fecal blood, pus, and mucus. Most viral, parasitic, and toxin-mediated etiologies do not cause significant inflammation. Thus, tests for inflammatory markers might help differentiate between viral and bacterial gastroenteritis. Identifying **fecal leukocytes** has technical limitations, including the need for an experienced technician and a fresh stool sample to provide an accurate identification. More than five WBCs per high-power field has a sensitivity of 73% (95% confidence interval, 0.33% to 0.94%) and specificity of 84% (95% confidence interval, 0.50% to 0.96%) and is moderately useful for identifying bacterial gastroenteritis.[30] A marker for fecal leukocytes, **fecal lactoferrin**, is increased during bacterial infection and in children with clinically more severe disease, and thus it may be a good marker for predicting and monitoring intestinal inflammation in children with infectious diarrhea.[31]

STOOL CULTURES

With a diagnostic yield as low as 2% and a high cost per positive result, **routine stool cultures are not necessary in acute gastroenteritis.** In select instances, however, stool culture is warranted. Several high-risk factors have been identified: >10 stools in the previous 24 hours,[32,33] travel to high-risk country,[32] fever,[32] older age child,[32] blood or mucus in stool,[33,34] and abdominal pain/tenderness.[33] Obtain stool cultures in cases of persistent diarrhea, when a specific antimicrobial treatment is being considered, or when infection must be excluded to support another diagnosis, such as inflammatory bowel disease. **Rectal swabs are an excellent alternative to stool when enteropathogen identification and rapid detection are needed, appropriate molecular diagnostic technology is available, and a stool specimen is not immediately available.[35]**

Five bacterial pathogens commonly produce gastroenteritis in North America (Table 131-7): *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and pathogenic *E. coli*. All but *E. coli* do not normally inhabit the alimentary tract, so their identification in stool specimens diagnoses bacterial gastroenteritis. *E. coli*, however, is part of the usual gut flora and is rarely pathogenic; therefore, serotyping is useful for detecting *E. coli* O157, which causes hemolytic-uremic syndrome. In some parts of the world, *Vibrio cholerae* is a common bacterial cause of gastroenteritis.

IMAGING

In general, radiologic investigations play a very limited role in assessment of pediatric acute gastroenteritis. Imaging is valuable when the diagnosis is uncertain, such as may occur in children with isolated vomiting. Although plain films of the abdomen are usually nonspecific and have low sensitivity, they may be a useful starting point when looking for bowel obstructions, foreign bodies, and bowel perforation. On the other hand, in a group of neonates with bilious vomiting in the first 72 hours of life, 56% of lesions requiring surgical repair were not detected with the use of plain abdominal radiographs, reinforcing the need for further imaging when clinically indicated.[36] A history of abdominal surgery or foreign body ingestion, or evidence on exam of abnormal bowel sounds, abdominal distention, or peritonitis has 93% sensitivity and 40% specificity in detecting diagnostic or suggestive radiographs in patients with major diseases potentially requiring procedural intervention.[37] Abdominal ultrasonography has an important diagnostic role in pediatric centers, but usefulness depends upon technical expertise.

TREATMENT

Oral Rehydration Therapy Treatment is directed at (1) preventing or treating dehydration, (2) replacing ongoing fluid losses, and (3) meeting nutritional needs. The worldwide adoption of oral rehydration therapy has revolutionized the treatment of dehydration. Oral rehydration therapy has reduced mortality in developing nations and is a safe and effective treatment for dehydrated children in developed nations.

The physiologic effectiveness of oral rehydration therapy is based on the coupled transport of sodium and glucose molecules at the brush border of intestinal epithelial cells, which provides a gradient for the passive absorption of water. This mechanism remains relatively intact, even in severe diarrheal disease, and functions optimally when the sodium-to-glucose ratio is 1:1.[26] The World Health Organization recommends an oral rehydration solution with a sodium concentration of 75 mmol/L, and it is effective for children with noncholera diarrhea as measured by reduced stool output, reduced vomiting, and a reduced need for supplemental IV therapy.[25] Most commercially available oral rehydration solution formulations in North America and Europe contain 45 to 60 mmol/L of sodium (**Table 131-9**). **Many other beverages traditionally suggested for children with vomiting and diarrhea, such as tea, juice, or sports drinks, are deficient in sodium and may provide excessive sugar, amplifying fluid losses.** These beverages are not suitable for use as rehydration solutions but, in children with mild gastroenteritis and minimal dehydration, initiating oral hydration with dilute apple juice followed by a child's preferred fluids, results in fewer treatment failures as compared with the use of electrolyte maintenance solutions.[38] Thus, in high-income countries, the use of dilute apple juice and preferred fluids may be an appropriate alternative to electrolyte maintenance fluids in children with mild gastroenteritis and minimal dehydration.

Although oral rehydration therapy should be the first-line treatment for most children with acute gastroenteritis, it is often underused by healthcare providers in industrialized countries, who too often elect to administer IV rehydration. This may be due to misperceptions about the effectiveness of IV rehydration or unfamiliarity with published guidelines.[25,26] **IV rehydration is appropriate and necessary in children with severe dehydration, hemodynamic compromise, or when altered mental status precludes safe oral administration of fluid.[26] Children with mild to moderate dehydration are candidates for oral rehydration therapy and do not need IV rehydration as first-line therapy.** When comparing oral rehydration therapy with IV therapy, a Cochrane review concluded that there is no difference in failure to rehydrate, weight gain, or total fluid intake; oral rehydration therapy is associated with a shorter hospital stay. For every 25 children treated with oral rehydration therapy, one child would fail and require IV rehydration.[39] A sample ED algorithm incorporating oral rehydration therapy is provided in **Figure 131-1**.

TABLE 131-9 Composition of Standard ORS, Reduced-Osmolarity WHO ORS, and Other Commonly Consumed Beverages

	Carbohydrate (mmol/L)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Base (mmol/L)	Osmolarity (mOsm/L)
WHO reduced osmolarity (2002)	75	75	20	65	10	245
Pedialyte®	139	45	20	35	20	250
Enfalyte® (formerly Ricelyte)	167	50	25	45	34	200
Apple juice	666	0.4	44	45	N/A	730
Coca-Cola Classic®	622	1.6	N/A	N/A	13.4	650
Ginger ale	500	3.5	0.1	N/A	3.6	565
Gatorade®	322	20	3	N/A	3	350
Chicken broth	44	260	0.5	260	N/A	450

Abbreviations: N/A = not available; ORS = oral rehydration solution; WHO = World Health Organization.

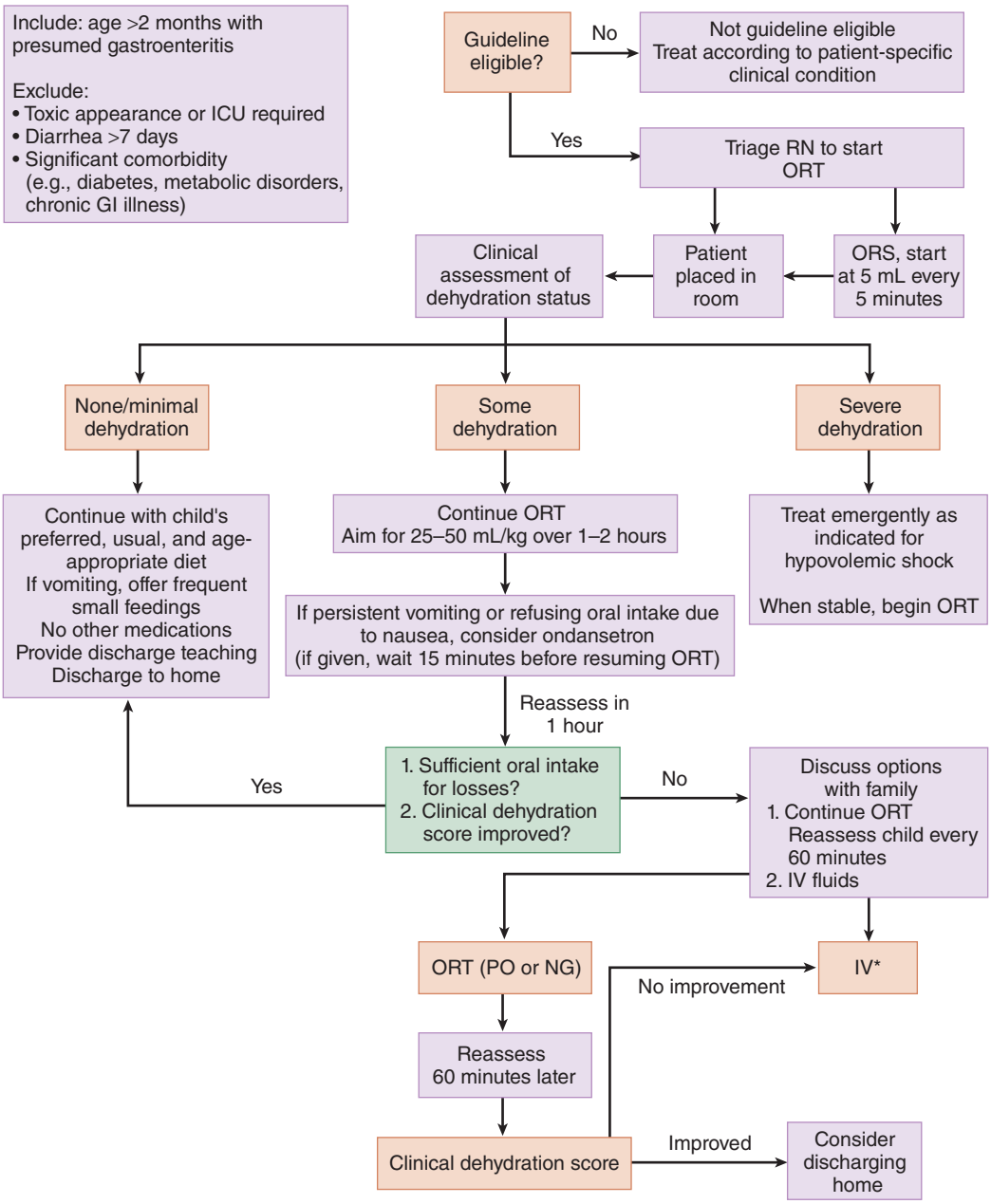


FIGURE 131-1. Algorithm for evaluation and management of acute gastroenteritis in children >2 months of age based on clinical assessment of dehydration status. ORT = Oral rehydration therapy. *If IV access is difficult, consider nasogastric (NG) oral rehydration solution (50 mL/kg) over 3 hours instead. Continue oral rehydration therapy (ORT) during IV therapy. ICU = intensive care unit; ORS = oral rehydration solution; RN = registered nurse.

In children with moderate dehydration undergoing oral rehydration therapy, the fluid deficit should be corrected rapidly (over 4 hours). **Give 50 to 100 mL of oral rehydration solution per kilogram of body weight, plus additional oral rehydration solution to compensate for ongoing losses (approximately 10 mL/kg per stool and 2 mL/kg per emesis).** Offer small volumes initially, such as 5 mL every 2 to 5 minutes, and increase as tolerated. **A general rule is to aim for about 1 ounce (30 mL) of oral rehydration solution per kilogram of body weight per hour.** Do not limit breastfeeding during any phase of oral rehydration therapy, both for the nutritional support of the infant and to avoid a decrease in the mother's milk supply. If necessary, oral rehydration solution may be provided as a supplement. **When oral rehydration is not feasible, enteral rehydration by the nasogastric route provides an effective alternative to IV rehydration.** This method allows for rehydration at a steady rate and is as successful as, and more cost effective than, IV rehydration.[40] Children with severe dehydration requiring IV rehydration can begin oral rehydration therapy when perfusion and mental status return to normal. Caregivers should understand the technique and rationale of oral rehydration therapy and should be provided with helpful equipment such as a clock and a syringe or dropper. Recognizing caregiver expectations and addressing potential obstacles, such as misconceptions about oral rehydration therapy or exhaustion, may also contribute to a successful outcome.

IV Hydration Parenteral therapy is discussed in Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children."

Antiemetics Although vomiting is not a contraindication to oral rehydration therapy and does not usually preclude successful oral rehydration, the presence of ongoing vomiting may be an obstacle to initiating or continuing oral rehydration therapy. **Ondansetron, a 5-hydroxytryptamine (serotonin) receptor antagonist, may be used as an adjunct to oral rehydration therapy in children with persistent vomiting at a dose of 0.15 milligram/kg/dose PO. The use of intravenous ondansetron and multiple dose therapy is not supported by the evidence,**

which associates both such approaches with increased side effects[41] and no additional benefit beyond a single oral dose.[42]

Do not use dopamine receptor agonists (such as promethazine, prochlorperazine, metoclopramide, and droperidol) to treat vomiting in children because of the potential for respiratory depression and extrapyramidal reactions.[43] In addition, they lack evidence of efficacy. The U.S. Food and Drug Administration issued an alert in 2006 indicating that promethazine (marketed as Phenergan®) should not be used in children <2 years of age because of the potential for fatal respiratory depression.

Maintenance Phase and Diet For children with minimal or no dehydration and those who have been successfully rehydrated, the priority is to prevent dehydration by providing maintenance fluid needs and replacing losses. Fluid needs may be met with oral rehydration solution or regular diet. Children undergoing oral rehydration therapy should resume feedings with an age-appropriate, palatable, and nutritionally complete diet as soon as the initial fluid deficit has been replaced. **Do not withhold feedings for >4 hours in a dehydrated child or for any length of time in a child who is not dehydrated.** Early refeeding during oral rehydration therapy has clinical and nutritional benefits and is supported in major guidelines.[25,26] The introduction of full-strength formula or regular diet immediately after rehydration is associated with increased weight gain and does not limit the success of oral rehydration therapy. **Most young children can continue to receive lactose-containing milk or formula.** However, there does appear to be a slight reduction in the duration of diarrhea and the treatment failure rate among inpatients administered lactose-free products, and this approach may be considered in this patient population.[44]

The banana, rice, applesauce, and toast diet is unnecessarily restrictive and may not provide enough nutrition, so it is no longer recommended.[26] Because fats are an important source of calories, low-fat diets are discouraged.

Antidiarrheal Medications **Antidiarrheal medications are not recommended either due to safety concerns or a lack of data to support effectiveness. Potential risks outweigh benefits. Loperamide, a peripheral opiate receptor agonist that can reduce diarrhea, is absolutely contraindicated in children <2 years old and for those with bloody stools or suspected bacterial gastroenteritis from *Salmonella*, *Shigella*, or *Campylobacter*. The drug can cause lethargy and paralytic ileus. Additionally, loperamide may be associated with a possible increased risk of hemolytic-uremic syndrome when used in the setting of enterohemorrhagic *E. coli* infection.** Although older children with viral gastroenteritis who take an age-appropriate dose are unlikely to experience serious events, potential risks likely outweigh benefits in most children.

Adsorbents and Antisecretory Agents Smectite is an aluminomagnesium silicate that binds some toxins, bacteria, and viruses and is used in several European countries as an antidiarrheal agent. Although some trials and a recent meta-analysis have reported effectiveness in reducing diarrhea, the limitations of the studies prevent any firm conclusions from being drawn. Bismuth subsalicylate is an antisecretory agent that is commonly found in over-the-counter diarrhea medications. **Although bismuth has a modest effect on reducing severity of diarrhea, it can cause elevated salicylate levels in children.[45] Consequently, products containing bismuth subsalicylate (e.g., Pepto-bismol®, Kaopectate®) should not exceed dosing recommendations in children less than 12 years of age.** Racecadotril is a prodrug that must be hydrolyzed to its active metabolite (thiorphan), which then acts as an enkephalinase inhibitor that decreases intestinal secretion by preventing the breakdown of endogenous GI opioids. It is available in Europe and Southeast Asia, but not in the United States. In a systematic review including nine trials and 1384 children, twice as many patients had diarrhea resolution at any time point when administered racecadotril relative to placebo.[46] Although racecadotril reduces stool frequency (stool ratio of racecadotril to placebo = 0.63), it does not decrease major clinical outcomes such as hospitalization.[47]

Probiotics Probiotics are living organisms that, when ingested, can modulate mucosal and systemic immunity by altering microbial balance in the intestinal tract. Yogurt is a dietary source of probiotics, though the quantity of bacteria in yogurt is variable. Data from several meta-analyses show a moderate clinical benefit of certain probiotic strains in reducing the duration and/or volume of diarrhea in hospitalized children. While a sizable and growing number of patients are prescribed probiotics to treat intestinal infections,[48,49] only five of 12 AGE management guidelines summarized in a recent review[50] endorse probiotic use. Most published studies suffer from methodologic limitations, including small sample sizes, use of restricted populations, limited knowledge of causative pathogens, and an absence of adverse event reporting.[51] The first pediatric ED study to date that evaluated *Lactobacillus rhamnosus* GG reported no reduction in the time to normal stool or the number of diarrheal stools.[52] Two recently completed multicenter prospective randomized trials of probiotics for acute pediatric gastroenteritis presenting to the emergency department both failed to demonstrate any benefit among more than 1500 combined study participants, suggesting no role for probiotics in this population.[53,54] Lastly, there is some evidence that many probiotic product labels do not adequately identify or quantify microbes and that when tested some products do not match their labeled microbiologic specification.[55]

Prebiotics, which are nondigestible food components believed to improve microbial balance in the intestinal tract, have not been extensively studied and are not recommended. There is no high-quality published evidence regarding the use of homeopathic or herbal medications for the management of gastroenteritis.

Zinc Zinc is necessary for intestinal mucosal healing, and its deficiency has been associated with increased diarrhea severity. Malnourished children >6 months old benefit the most from zinc therapy (27-hour reduction in diarrhea duration), and its use should likely be limited to such groups of children.[56] Because zinc is an effective therapy for diarrhea and reduces morbidity and mortality in the setting of low-income countries,[57] the United Nations Children's Fund and the World Health Organization recommend zinc supplementation as a universal treatment for children with diarrhea in low-income countries at a dose of 20 milligrams/d of any zinc salt orally for 10 to 14 days (10 milligrams/d for infants <6 months old).

Antibiotics for Acute Gastroenteritis Because the cause of gastroenteritis is rarely known upon presentation, treatment decisions must be made before the identification of a pathogen is possible. Because the vast majority of episodes of pediatric gastroenteritis are of viral origin, **do not routinely give antibiotics. In select clinical circumstances, antibiotics may be indicated;** see recommendations for specific pathogens and clinical settings in Table 131-7. In most instances, however, antibiotics should only be provided to extremely unwell (e.g., septic or bacteremic), extremely young, or immunocompromised children. When required, the choice of antimicrobial agent depends on local prevalence and resistance patterns. Parenteral rather than oral antibiotic therapy is appropriate for patients unable to take oral medications, patients with toxic appearance or underlying immunodeficiency, and febrile infants <3 months of age. **Children with watery diarrhea generally should not receive empiric antibiotics unless they have been exposed to cholera.**

Antibiotics are effective in reducing the symptoms and infectivity of *Shigella* gastroenteritis. Because of increasing resistance, use ampicillin or trimethoprim-sulfamethoxazole only if the strain is susceptible. Otherwise, azithromycin is an appropriate first-line agent. Ceftriaxone is the treatment of choice for parenteral therapy.

Do not use antibiotics to treat *Salmonella* gastroenteritis unless specific risk factors are present. A Cochrane review (12 trials, 767 patients) demonstrated no evidence of benefit from antibiotic therapy in otherwise healthy individuals with nontyphoidal *Salmonella* gastroenteritis.[58] Although the number of young children studied was small, adverse events were more common in participants who received antibiotic treatment. Thus, antibiotics should only be administered to high-risk children to reduce the risk of *Salmonella* bacteremia and extraintestinal infections. High-risk children include those with underlying immune deficiencies, sickle cell disease, immunosuppressive therapy, or inflammatory bowel disease and infants <3 months old.

Antibiotic therapy for *Campylobacter* gastroenteritis has a modest effect on symptoms and is most effective if treatment is started within 3 days of disease onset.[59] Antibiotics reduce the duration of fecal excretion of organisms and are recommended to reduce transmission in day care centers and institutions.

Antibiotics for Shiga toxin–producing *E. coli* do not significantly affect the clinical course. Importantly, in children with Shiga toxin–producing *E. coli* infection, there is a significant association between antibiotic use and the risk of developing the hemolytic-uremic syndrome.[60] **Therefore, children with *E. coli* O157:H7 should not receive antibiotics.** Intravenous volume expansion is an underused intervention that may decrease the frequency of oligoanuric renal failure in children with diarrhea-associated hemolytic-uremic syndrome (hematocrit <30% with evidence of intravascular erythrocyte destruction), thrombocytopenia (platelet count $<150 \times 10^3/mm^3$), and impaired renal function.[13] **Antibiotics may be useful for severe forms of enteroinvasive, enteropathogenic, or enterotoxigenic *E. coli* infection.** Azithromycin and trimethoprim-sulfamethoxazole are treatment options.

Antibiotics reduce the severity of *V. cholerae* diarrhea. Treatment options include doxycycline, azithromycin, or trimethoprim-sulfamethoxazole.

Antimicrobial treatment of *Yersinia* species is appropriate if severe disease, bacteremia, or extraintestinal infection is suspected. Options include trimethoprim-sulfamethoxazole, aminoglycosides, cefotaxime, fluoroquinolones, tetracycline, doxycycline, and chloramphenicol.

DISPOSITION AND FOLLOW-UP

There are no established evidence-based criteria for admission of patients with gastroenteritis. In general, well-appearing children with minimal or no dehydration who are able to receive oral rehydration therapy at home should be discharged, and caregivers should be taught how to administer oral rehydration therapy and recognize signs of dehydration. Discharge instructions should be verbal and written. Sample discharge instructions are presented in **Table 131-10**. Ideally, caregivers will have had the opportunity to practice oral rehydration therapy and ask questions while in the ED. Children with moderate or severe dehydration, intractable or bilious vomiting, a suspected surgical condition, or significant laboratory or neurologic abnormalities, including lethargy or seizures, require further testing and should be observed in the ED or admitted. Patients not likely to succeed with home oral rehydration therapy, such as those with large ongoing losses or inadequate support, should also be observed or admitted. Many patients with dehydration who require ongoing treatment can be successfully managed in an observation unit.[56] Young infants are at risk for more rapid and severe dehydration, so the threshold for admission should be low, and follow-up in 24 hours should be ensured if discharge is considered. Families who are discharged should be instructed to return to seek further care if their child becomes unable to receive oral rehydration therapy, has persistent or bilious emesis, or shows increasing evidence of dehydration, or if symptoms are worsening.

SPECIAL SITUATIONS

DIARRHEA WITH OR WITHOUT VOMITING

Adverse Food Reactions Adverse food reactions can be due to either an adverse immunologic response, otherwise known as an allergy, or an adverse physiologic response, often referred to as food intolerance.[61] The National Institute of Allergy and Infectious Diseases recognizes four categories of immune-mediated adverse food reactions: immunoglobin E (IgE)-mediated, non–IgE-mediated, mixed, and cell-mediated.[62] IgE-mediated GI allergic symptoms may consist of nausea, abdominal pain, cramping, vomiting, or diarrhea developing within minutes to 2 hours of the ingestion of a food allergen. GI symptoms are often accompanied by symptoms involving the mouth or skin and may also include respiratory and systemic manifestations. Eosinophilic esophagitis and gastroenteritis are examples of a mixed IgE and non-IgE food allergy, with T-cell–mediated responses playing a significant role in pathogenesis.[63] Patients may present at any age, and many will have other allergic or atopic conditions. The portion of the GI tract involved determines symptoms. Because symptoms tend to be delayed, identifying the offending food(s) may be challenging. Infants often present with feeding difficulties, gastroesophageal reflux, vomiting, and failure to thrive. Older children may present with vomiting, abdominal pain, or symptoms similar to irritable bowel syndrome. A history of dysphagia or food impactions suggests eosinophilic esophagitis.

TABLE 131-10 Sample Gastroenteritis Discharge Instructions

Your child has been diagnosed with gastroenteritis. Gastroenteritis is an illness that consists of vomiting and diarrhea. It is often caused by viruses and usually can be treated without medications. Preventing dehydration is the most important goal in caring for children with gastroenteritis.

How will I know if my child is becoming dehydrated?

- Dry lips and mouth.
- Decreased activity level.
- Sunken eyes.
- Sunken fontanelle (soft spot) in babies <1 y.
- Not urinating as often as usual or dark urine.
- Reduced tears when crying.

What should I give my child to eat and drink?

- Children who do not have signs of dehydration can drink what is usual for them. You do not need to stop giving milk. Drinks with a lot of sugar, such as fruit juices, can make diarrhea worse.
- Your child should return to his or her normal diet as soon as possible. A special diet is not necessary. Good nutrition is important, even if there is still vomiting or diarrhea.
- If you are breastfeeding, continue breastfeeding. Babies taking formula can continue to receive their usual formula.
- Children who are showing some signs of dehydration should receive oral rehydration solutions (see below).

What types of fluids are acceptable for oral rehydration?

- Over-the-counter rehydration solutions are ideal for rehydration. Some brands include Pedialyte and Enfalyte. Generic solutions are also available. Flavored solutions are usually preferred by children.
- Sports drinks are not the same as oral rehydration solutions and should not be used in infants or children who are dehydrated. They may be acceptable in older children with minimal dehydration.
- Plain water and tea do not have sugar or salt and can cause electrolyte changes, especially if given to small babies.
- Soda/pop and juices have too much sugar and not enough salt to be used for oral rehydration.
- Children who are not dehydrated do not need a special oral rehydration solution.

How do I give oral rehydration?

- If your child is vomiting, start with small amounts of oral rehydration fluid, such as one teaspoon (5 mL) every 5 min. Increase the amount gradually, as tolerated.
- If your child is breastfed, continue breastfeeding. Oral rehydration solutions can supplement breast milk after or between breast feedings, but should never take the place of breast milk.

When should I call my child's doctor or seek help?

- Call your doctor immediately or go to the nearest emergency department if:
  - Your child seems dehydrated and is not able to drink.
  - Your child's vomit is green or bloody.
  - Your child has severe abdominal pain.
  - Your child appears to be very sick.
  - Your child has blood in the diarrhea.
  - Your child has a fever and is <3 mo of age.

When should I follow up with my child's doctor?

- If your child is <6 mo of age, follow up within 24–48 h.
- If your child is >6 mo of age, call your doctor's office and schedule a follow-up if symptoms continue.

Non–IgE-mediated food allergies are primarily T-cell–mediated and tend to result in delayed symptoms. Examples include food protein–induced enterocolitis syndrome, food protein–induced allergic proctocolitis, and celiac disease.[63] Food protein–induced enterocolitis syndrome is a potentially severe condition with a peak incidence in infants between 0 and 9 months old. Proteins in cow's milk or soy formulas are the most common triggers in infants, and symptoms consist of profuse vomiting and diarrhea for several hours after exposure, at times resulting in shock. Many other foods have been implicated in food

protein–induced enterocolitis syndrome, and children regularly exposed to the allergenic food may develop chronic vomiting, diarrhea, anemia, or failure to thrive. Food protein–induced allergic proctocolitis most often presents in breastfed infants in the first 2 months of life. Infants generally appear healthy but have stools characterized by the presence of blood and mucus. Cow's milk in the maternal diet is the most common trigger, and symptoms begin to improve within a few days of dietary modification. The condition generally resolves between the ages of 6 months and 2 years. Diagnostic tests used for IgE allergies such as skin prick testing are not useful in identifying the offending agents in non–IgE-mediated food allergies; therefore, the diagnosis is based on clinical suspicion. Dietary avoidance is the mainstay of management.

Celiac disease is a T-cell–mediated inflammatory response triggered by the ingestion of gluten in genetically predisposed individuals. GI presentations are common in children and include chronic or intermittent diarrhea, abdominal pain, abdominal distention, and failure to thrive. Whereas young children most often have a "typical" presentation, extraintestinal symptoms such as fatigue, osteopenia, iron deficiency anemia, and short stature become more common as age increases. Treatment consists of lifelong adherence to a gluten-free diet.[64]

Antibiotic-Associated Diarrhea Antibiotic-associated diarrhea is otherwise unexplained diarrhea that occurs in association with the administration of antibiotics. The frequency of this complication varies, with diarrhea occurring in 5% to 10% of children treated with ampicillin, 10% to 25% treated with amoxicillin-clavulanate, and 15% to 20% treated with cefixime. The spectrum of findings in antibiotic-associated diarrhea ranges from mild diarrhea to severe colitis that may include abdominal cramping, fever, leukocytosis, fecal leukocytes, hypoalbuminemia, and colonic thickening with characteristic changes visible on endoscopy and biopsy. Although infection with *Clostridium difficile* accounts for only 10% to 20% of the cases of antibiotic-associated diarrhea, it accounts for most cases of colitis associated with antibiotic therapy. Nonclostridial antibiotic-associated diarrhea may be caused by other enteric pathogens, by the direct effects of antimicrobial agents on the intestinal mucosa, or by the metabolic consequences of reduced concentrations of fecal flora. **Clindamycin, cephalosporins, and penicillins are the antibiotics most frequently implicated in *C. difficile* diarrhea.**

C. difficile disease can only be firmly diagnosed once its toxin is identified. However, because children can be asymptomatic hosts of toxin-producing strains, testing for *C. difficile* should only be performed when there is ample clinical suspicion and/or risk factors identified. When identified in the stool of children <2 years of age (even if diarrheal), it most commonly is not the cause of diarrhea and usually does not require treatment. The following two-step testing strategy has been proposed: screening should be performed through the conduct of an enzyme immunoassay for glutamate dehydrogenase, which is present in almost all strains of *C. difficile*, including those that do not produce toxin.[65,66] If positive, this should be followed by a confirmatory enzyme immunoassay test for toxins A and B or, preferably, by a cell cytotoxin assay that demonstrates cytotoxicity of stool for human fibroblast cells. Polymerase chain reaction testing is a rapid, sensitive, and specific test that appears promising. However, significant variations exist in testing methodologies and kits, and thus further evaluation of its utility is warranted before widespread adoption.[67,68] Indications for treatment include positive assays for *C. difficile* toxin, plus one of the following: evidence of colitis, moderate to severe diarrhea, persistent diarrhea despite the discontinuation of the implicated agent, or the need to continue treating the original infection. Oral metronidazole is the treatment of choice in most cases of pediatric *C. difficile* colitis. In the most severe cases, vancomycin (oral or rectal) may be used in conjunction with IV metronidazole. The anticipated response to treatment is resolution of fever within 1 day and resolution of diarrhea in 4 to 5 days. Treatment does not eradicate *C. difficile*, and asymptomatic patients should not be retested or treated based on a positive stool test. **Metronidazole is preferred because it is less expensive than vancomycin and avoids the potential risk of promoting vancomycin-resistant enterococci.**

Secondary Lactase Deficiency Secondary lactase deficiency implies that a pathophysiologic condition has resulted in an acquired lactase deficiency and lactose malabsorption. The most common etiology is acute GI infection resulting in small intestinal injury with loss of lactase-containing epithelial cells at the tips of the villi. The immature epithelial cells that replace these are often lactase deficient, leading to secondary lactase deficiency and lactose malabsorption. Despite this, children with infectious diarrheal illnesses who have no or only mild dehydration can continue consuming human milk or standard formula without a significant effect on clinical course. Secondary lactase deficiency with clinical signs of lactose intolerance can be seen in celiac disease, Crohn's disease, and immune-related and other enteropathies, and should be considered as a possible etiology for diarrhea in children with these conditions. Diagnostic evaluation should be performed when secondary lactase deficiency is suspected and infection is not the cause.

Parasitic Infection Parasites are uncommon causes of diarrhea but may be the source of waterborne outbreaks and are more severe in immunocompromised children. *Cryptosporidium* and *Giardia* are the parasites most likely to cause diarrhea. Nitazoxanide is the drug of choice for *Cryptosporidium* infections, and either metronidazole, tinidazole, or nitazoxanide may be used in the treatment of *Giardia* infections. For further discussion of parasitic diseases, see Chapter 160, "Food and Waterborne Illnesses," and Chapter 162, "Global Travelers."

TRAVELER'S DIARRHEA

Limited data suggest that diarrhea is common in children traveling to high-risk regions. Although many cases of traveler's diarrhea are self-limited, antibiotic therapy is appropriate for children with a history of travel to a high-risk region who have severe or prolonged symptoms (>5 days). Macrolides such as azithromycin are the first-line antibiotic therapy, and trimethoprim-sulfamethoxazole may also be considered.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 132

Fluid and Electrolyte Therapy in Infants and Children

Melissa Chan
Paul Enarson

INTRODUCTION

This chapter provides a basic guide to parenteral rehydration, maintenance fluids, and management of common electrolyte abnormalities in children.

The most common cause of fluid and electrolyte abnormalities in children is dehydration. Dehydration results from a negative fluid balance due to decreased intake, increased output (renal, GI, or insensible losses from the skin or respiratory tract), or disease states such as burns, sepsis, or diabetes. Negative fluid balance can occur in the intracellular fluid or extracellular fluid compartments and may be accompanied by derangements in electrolytes. **Table 132-1** lists some of the common causes of dehydration. Common signs of dehydration are listed in **Table 132-2**, and a validated clinical scoring system predicting the need for parenteral rehydration is provided in Table 131-6.

PATHOPHYSIOLOGY

Infants and children are particularly susceptible to dehydration for a number of developmental and physiologic reasons. They are dependent on caretakers to provide oral fluids and therefore cannot regulate

TABLE 132-1 Causes of Dehydration in Children

Decreased Intake:

- Voluntary or involuntary
  - Anatomic or pathologic diseases (pharyngitis, stomatitis, cleft lip/palate, facial dysmorphism, airway obstruction)
  - Neurologic diseases (meningitis, encephalitis, brain tumor, seizures)
  - Febrile illnesses

Increased Output:

- Insensible losses (fever, heat, respiratory diseases, diaphoresis, thyroid disease, cystic fibrosis)
- GI losses (vomiting, diarrhea)
- Renal losses: Osmotic (DKA, acute tubular necrosis)
  Nonosmotic (renal diseases, electrolyte disturbance, diabetes insipidus)
- Sodium losing (adrenal disease, diuretics, kidney disease, pseudohypoaldosteronism)

Systemic Diseases:

- Moderate to severe burns
- Ascites
- Respiratory disease
- Peritonitis: medical or surgical with third spacing
- Anaphylaxis

Abbreviation: DKA = diabetic ketoacidosis.

their intake. In addition, young children and infants have increased fluid requirements and are at risk of increased fluid losses compared to adults and older children. Basal metabolic rates are highest in young children, peaking at 12 months of age and gradually decreasing starting at 3 years of age. Infants also have a higher turnover rate for water. Total body water as a percentage of body weight decreases from 70% in a term infant (75% to 80% in premature infants) to 60% at 1 year of age, remaining at this percentage until puberty.[1] The high percentage of total body water, coupled with a decreased ability to control water loss (e.g., insensible losses from larger surface area–to–body ratio and faster respiratory rate) and a decreased ability to concentrate the urine, predispose infants to dehydration. Furthermore, young children are more prone to hypermetabolic states, such as high fever, which also increases the need for free water. Fever increases the basal metabolic rate by 13% for each degree above 37.8°C.[2]

Because sodium and water are tightly regulated together, dehydration is often described in relation to serum sodium concentrations. Children can develop isonatremic (isotonic) dehydration (sodium level of 135 to 145 mEq/L), hyponatremic (hypotonic) dehydration (sodium level of <135 mEq/L), or hypernatremic (hypertonic) dehydration (sodium level of >145 mEq/L). Isonatremic dehydration is the most common form of dehydration. Isonatremic (isotonic) dehydration occurs when the fluid sodium losses are proportionate in the intracellular fluid and extracellular fluid compartments. Hyponatremic (hypotonic) dehydration occurs when fluid that is lost contains proportionately more sodium than blood, which leads to osmotic shifts of free water from the intracellular fluid to the extracellular fluid compartments. Hypernatremic (hypertonic) dehydration occurs when the fluid lost contains less sodium than the blood, which causes extracellular free water to move into the intracellular fluid space.

TABLE 132-2 Clinical Guidelines for Assessing Dehydration in Children

	None to Minimal Dehydration (<3% loss of body weight)	Some (mild to moderate) Dehydration (3% to 9% loss of body weight)	Severe Dehydration (>9% loss of body weight)
Mental status	Well, alert	Fatigued, restless, irritable	Apathetic, lethargic, unconscious
Thirst	Normal, slight increase, or refusing fluids	Increased, eager to drink	Very thirsty or too lethargic to indicate
Heart rate	Normal	Normal to increased	Tachycardic with bradycardia in severe cases
Blood pressure	Normal	Normal	Normal to reduced
Pulse quality	Normal	Normal to reduced	Weak, thready
Breathing	Normal	Normal to tachypneic	Deep
Eyes	Normal	Slightly sunken orbits	Deeply sunken orbits
Tears	Present	Decreased	Absent
Mucous membranes	Moist	Dry	Parched
Anterior fontanelle	Normal	Sunken	Sunken
Skin turgor	Instant recoil	Recoil in <2 s	Recoil in >2 s
Capillary refill	Normal	Prolonged 1–2 s	Prolonged >2 s
Extremities	Warm	Cool	Cold, mottled, cyanotic
Urine output	Normal to decreased	Decreased (<1 mL/kg/h)	Minimal (<0.5 mL/kg/h)

Courtesy of Stephen Freedman, MD, and Jennifer Thull-Freedman, MD.

CLINICAL FEATURES

HISTORY

Suspicion of fluid or electrolyte disorders can often be raised through a properly taken history. Ask about symptoms (what they are, when they started, where they started; e.g., was the child in a hot environment), whether fever is present, whether the child is tachypneic, and prior treatment. For breastfeeding infants, inquire about frequency of feeds, whether the mother feels she has good milk production, and whether the infant is feeding or engaged in nonnutrient sucking for comfort. If not breastfeeding, ask what type of fluid has been given, because hypotonic fluids (e.g., water) are often used during illnesses and increase the risk of hyponatremia. If the infant is bottle-fed, ask whether the formula is premixed or made from powder; hypernatremia or hyponatremia can result from inappropriately prepared formula. Questions surrounding output aid in assessing whether replacement of losses has been adequate; excess output results from vomiting or diarrhea (quantify the frequency and volume if possible). Assess urine output by asking how often the child is urinating or the number of wet diapers if the child is not yet toilet trained. Inquire about volume status by asking about tear production, the presence or absence of sweat, and the child's general appearance and mental status: is the child increasingly irritable or lethargic? Has the parent noticed a change in the skin (cyanotic, pale, mottled)? **Most important, if known, is a change in weight, because weight loss is the gold standard for assessment of volume status.**[3] In addition to the specific questions, ask about signs or symptoms of infection, recent travel, sick contacts, and underlying chronic disease, which may point to a specific cause of dehydration. Children are at risk for accidental ingestion of toxins or plants, many of which can cause vomiting and lead to electrolyte disturbances.

PHYSICAL EXAMINATION

Physical findings related to individual electrolyte disorders are discussed in relation to specific electrolyte disorders below. In general, children with dehydration demonstrate a spectrum of physical findings ranging from a normal exam if dehydration is mild, to hypovolemic shock if dehydration is severe. Table 131-6 presents a simplified and validated clinical scoring system for dehydration. Tachycardia is an early sign of dehydration as the body compensates for a decreased circulatory volume. Tachycardia can present with normal blood pressure with or without signs of shock (compensated shock) but may be accompanied by hypotension (uncompensated shock) in severe dehydration. Tachypnea

may also be noted as metabolic acidosis develops in moderate to severe dehydration. **Note the mental status and the presence of lethargy or hypotonia, because these suggest severe dehydration or electrolyte abnormalities.** In infants, the quality of the fontanelle (flat or sunken) may aid in assessment of hydration status, along with the presence or absence of tears when crying; assess the mucous membranes for cracked, dry lips or decreased saliva in mouth, and the temperature, color, and turgor of the skin (cool, mottled, cyanotic, decreased elasticity), as well as capillary refill time, which should be less then 2 seconds when normal. Finally, note the character of the pulses because diminished pulses may also reflect significant dehydration.

LABORATORY EVALUATION

Laboratory testing for individual electrolyte disorders is discussed individually below. **Routine laboratory testing for assessing dehydration alone is generally not required**, and several studies have found a lack of correlation between laboratory values and degree of dehydration based on percent weight lost. Measure serum electrolytes if IV insertion is required for rehydration and signs of electrolyte disturbance are present,[4,5] or if electrolyte abnormalities are expected due to certain underlying medical conditions (e.g., diabetic ketoacidosis or congenital adrenal hyperplasia). **Perform a bedside glucose test in any child presenting with altered level of consciousness, and rapidly correct hypoglycemia** (see Chapter 146, "Metabolic Emergencies in Infants and Children").

INITIAL TREATMENT OF DEHYDRATION

Three main modalities exist for rehydration in children: oral, nasogastric, and parenteral. Treatment at each level of dehydration is discussed below and summarized in **Table 132-3**, and a detailed discussion of the treatment of mild to moderate dehydration is presented in Chapter 131, "Vomiting, Diarrhea, and Dehydration in Infants and Children."

TABLE 132-3 Treatment for Mild, Moderate, and Severe Dehydration

	Mild	Moderate	Severe
Primary phase Secondary phase (if primary phase fails)	PO* NG/IV	PO* NG/IV‡	IV†, IO, NG IO Central line
Tertiary phase (after rehydration to ensure ability to maintain oral intake—optional)	PO*	PO*	± PO* after initial IV/IO rehydration
Laboratory studies	None	Optional#	Electrolytes, BUN, creatinine, calcium, glucose levels; urinalysis
Discharge criteria	Appears clinically well, alert, and orientated Vital signs within normal limits for age Urine output during hydrating period Intake is equal or greater to ongoing losses		
Treatment failure	Admit or place in observation unit		

*PO: Use dilute apple juice or patient-preferred fluid or a commercial rehydration solution such as Pedialyte® or Enfalyte® or WHO reduced-osmolality ORS. Rehydrate with 5 mL (1 tsp) every 2–3 min. Increase based on patient tolerance; aim for 50–100 mL/kg replacement plus 10 mL/kg per stool and 2 mL/kg per emesis episode.

†IV (severe dehydration): 20 mL/kg over 5–30 min (NS or lactated Ringer's solution). Aim for 60–100 mL/kg in the first hour. Contraindications include some forms of cardiac disease (e.g., cardiomyopathy).

‡IV NS 20 mL/kg over 20–30 min, repeat as needed; NG oral rehydration solution at a rate of 10–20 mL/kg/h.

#Perform laboratory testing based on dietary history or disease state.

Abbreviations: NG = nasogastric; NS = normal saline; ORS = oral rehydration salts; WHO = World Health Organization.

TABLE 132-4 IV Rehydration for Moderate to Severe Dehydration

Degree of Dehydration	IV Rehydration	Replacement of Ongoing Losses After Initial Rehydration
Severe with uncompensated shock	20 mL/kg 0.9% saline bolus over 5 min, repeated until hemodynamically stable	5–10 mL/kg 0.9% saline or 5% dextrose in 0.9% saline for each watery diarrheal stool *and* 2 mL/kg 0.9% saline or 5% dextrose in 0.9% saline for each emesis
Moderate to severe without signs of shock	20 mL/kg 0.9% saline bolus over 1 h followed by 5% dextrose in 0.9% saline at 1–2× maintenance rate for 1 h	

For children unable to tolerate oral rehydration, nasogastric hydration is effective, even in vomiting patients.[3,6] In a large study comparing nasogastric hydration versus IV hydration over 3 hours, subjects in the nasogastric-treated group had fewer complications, achieved resolution of ketonuria more often, and had greater reduction in specific gravity than IV-treated subjects. Nasogastric treatment is more cost effective than IV treatment.[6]

MODERATE AND SEVERE DEHYDRATION

The child unable to tolerate oral/nasogastric rehydration therapy or with severe dehydration requires prompt fluid resuscitation with large volumes of fluid over a short period of time[7] (**Table 132-4**). Give 20 mL/kg boluses over 5 to 10 minutes repetitively until hemodynamics stabilize. Up to 60 mL/kg or more may be required in the first hour, unless contraindicated based on underlying disease.[8] Use an isotonic solution such as 0.9% saline or a lactated Ringer's solution during this resuscitation phase.[9]

For patients with moderate dehydration requiring parenteral fluids, there is no advantage of rapid or ultrarapid (50 to 60 mL/kg in 1 hour) hydration over standard hydration with 20 mL/kg over 1 hour, and a blinded randomized trial found increased hospitalization rates among those receiving ultrarapid hydration.[10] Furthermore, a study of fluid resuscitation among dehydrated children in Africa found that aggressive bolus fluid resuscitation was associated with increased mortality.[11]

After initial volume expansion, continue replacement with either normal saline or 5% dextrose in 0.9% normal saline. Use clinical judgment, because there is no strong evidence to recommend one fluid over the other, although dextrose-containing fluids help clear ketones in the patient who has not been eating or drinking.[12,13]

MAINTENANCE TREATMENT

Caloric expenditure and therefore fluid requirements can be estimated from body surface area, which is relatively large in infants in comparison with older children and adults. However, in the ED, weight is a sufficiently accurate value for calculating fluid requirements. The primary formula for daily fluid requirements is calculated as follows:

For the first 10 kg: 100 mL/kg/d (4 mL/kg/h)

For the second 10 kg: 50 mL/kg/d (2 mL/kg/h)

For each kg >20 kg: 20 mL/kg/d (1 mL/kg/h)

For example:

A 10-kg baby requires: 100 mL × 10 kg, or a total of 1000 mL/d.

A 20-kg child requires: (100 mL × 10 kg) + (50 mL × 10 kg) = 1500 mL/d.

A 40-kg child requires: (100 mL × 10 kg) + (50 mL × 10 kg) + (20 mL × 20 kg) = 1900 mL/d.

Electrolyte requirements remain constant throughout childhood and can be estimated by body weight. All infant formulas contain sufficient electrolytes to satisfy these requirements, as do the commercially available oral rehydration solutions such as Pedialyte® (see Table 131-9). The requirement is 2 to 3 mEq/kg/d for sodium and 2 mEq/kg/d for potassium.

Because hyponatremia is the most common intragenic complication of IV fluid therapy, it is important that isotonic solutions

be used as maintenance fluid, such as normal saline with 5% dextrose.[14,15] An exception is during the neonatal period. Although there is little evidence as to which maintenance fluids should be used early in life, neonates have immature kidneys and higher glucose requirements compared to older infants and children. Controversy exists on the best maintenance fluids in the first few days of life. The National Institute for Health and Care Excellence guidelines recommend using 5% or 10% dextrose in normal saline for all neonates from birth onward unless respiratory distress syndrome, meconium aspiration, or hypoxic ischemic encephalopathy is present. If any of these are present, give no sodium (e.g., 10% dextrose in water), until the postnatal diuresis with weight loss occurs, typically before day 5 of life.[16] Others recommend using salt-free fluids in all neonates until after the postnatal diuresis occurs.[17]

DISORDERS OF SODIUM

Table 132-5 outlines disease states associated with disruption in serum sodium levels and total body water (volume).

HYPONATREMIA

Hyponatremia is a serum sodium level <135 mEq/L. First determine if a low sodium value is a true value by relating the sodium value to the osmolarity. If hyponatremia occurs in a hyperosmolar state (i.e., >290 mOsm/kg), this suggests an osmotically active solute in the plasma such as excess glucose or alcohol. If hyponatremia occurs in the presence of normal osmolarity (275 to 290 mOsm/kg), this is likely due to hyperlipidemia or hyperproteinemia.[18] In such cases, correct the underlying disorder rather than the serum sodium level. When hyponatremia occurs in a hypo-osmolar state (<275 mOsm/kg), this is likely due to an excess of free water or loss of sodium. The most common causes of hyponatremia seen in the ED are GI losses and water intoxication caused by ingestion of hypotonic replacement fluids, especially during infancy.

Signs and symptoms of hyponatremia depend on the serum sodium level and the speed at which the sodium level falls. Symptoms primarily involve the CNS, as free water moves from the extracellular to intracellular space, and the musculoskeletal system. Neurologic symptoms include nausea, vomiting, headache, mental status changes, altered consciousness, diminished reflexes, hypothermia, pseudobulbar palsy, and seizures. Musculoskeletal symptoms include weakness, muscle cramps, and lethargy.

Although patients may be only mildly symptomatic with sodium levels as low as 120 mEq/L if the low level is chronic (>48 hours), symptoms usually occur with an acute drop in serum sodium level below 120 mEq/L. Without appropriate treatment, complications include respiratory failure, seizures, and death.

Treatment depends on the stability of the patient and associated symptoms. General guidelines are presented in **Table 132-6. Take special care to avoid rapid shifts in sodium levels.** Although hyponatremia itself can have dire consequences, rapid correction can cause severe demyelination of brainstem neurons.[19] Therefore, correct hyponatremia slowly and in a controlled manner (Table 132-6). The exception to this is in the setting of severe neurologic symptoms, such as confusion, altered level of consciousness, or seizures, typically with sodium level <120 mmol/L. When this occurs, a rapid, controlled increase in sodium level is required until neurologic symptoms resolve or a sodium level of 120 mmol/L is achieved.[20]

For euvolemic hyponatremia, after correction of serum sodium level, begin water restriction and treat the underlying disorder. For hypervolemic hyponatremia (edema), start sodium and water restriction and administer diuretics if needed to treat the clinical condition (e.g., congestive heart failure).

TABLE 132-5 Conditions Altering Serum Sodium and Total Body Water Balance

Total Body Water (volume)	Hypernatremia	Hyponatremia
Increased	Excessive saline infusion	Congestive heart failure Cirrhosis Nephrotic syndrome Advanced renal failure
Normal	Hypertonic saline infusion Bicarbonate intoxication Salt poisoning Hyperaldosteronism	SIADH Primary polydipsia Exercise-induced Low solute intake Renal osmostat Hypothyroidism Glucocorticoid deficiency Nephrogenic SIADH
Decreased	Cutaneous losses Sweating Radiant warmers Phototherapy Burns Inadequate intake Improperly prepared formula GI losses Vomiting Nasogastric suctioning Diarrhea Osmotic stool softeners	Diuretics Renal losses Interstitial nephritis Mineralocorticoid deficiency Burns, heat illnesses (exhaustion/stroke) Ascites Cystic fibrosis
	Renal free water losses Diabetes insipidus Increased osmoles (diabetes mellitus, mannitol) Chronic kidney disease ATN (if polyuric) Postobstructive diuresis	

Abbreviations: ATN = acute tubular necrosis; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

TABLE 132-6 Treatment of Hyponatremia

Symptoms	Treatment*
If hypovolemic and hemodynamically unstable	Correct instability with NS boluses (20 mL/kg over 5 min followed by reassessment after each bolus)
Asymptomatic	Correct deficit to normal over 48 h mEq Na required = [(Na^+ desired) – (measured Na^+)] × (0.6 × weight in kg)
Neurologic symptoms (altered mental status, seizures)	1–2 mL/kg/h of 3% sodium chloride until asymptomatic or Na level >120 mEq/mL, then increase Na level 0.5 mEq/mL/h (not to exceed increase of 12 mEq/mL in first 24 h or 18 mEq/mL in first 48 h)

*Does not include maintenance requirements and ongoing losses.

0.9% NS = 0.15 mEq Na/L; 3% saline = 0.5 mEq Na/L

Abbreviation: NS = normal saline.

HYPERNATREMIA

Hypernatremia is a serum sodium level >145 mEq/L. Hypernatremia generally indicates a lack of total body water in relation to total body solute and often occurs as a result of dehydration (loss of water through the GI tract, kidney, or insensible losses), but may also occur secondary to excessive sodium intake (e.g., inadequate water intake or hypertonic solution intake) (**Table 132-7**). Diarrhea is the most common cause in children. Other diseases to consider include renal disease and diabetes insipidus. Children are at risk for hypernatremia if free water is limited or if formula is mixed improperly. Mild hypernatremia is commonly found in ill children, particularly infants with gastroenteritis. If mild, it is usually asymptomatic and corrects with treatment of the underlying

TABLE 132-7 Treatment of Hypovolemic or Euvolemic Hypernatremia

Condition	Treatment*
If hypovolemic and hemodynamically unstable	Correct instability with NS boluses (20 mL/kg boluses followed by reassessment after each bolus)
Once hemodynamically stable and hypovolemic or euvolemic hypernatremia	Correct deficit to normal over 24 h Free water deficit (mL) = 4 mL × body weight (kg) × [desired change in serum sodium mEq/L (mmol/L)] Subtract bolus fluids given from deficit; correct remaining deficit giving half of deficit over first 8 h and remainder over the next 16 h (see text for monitoring criteria)†

*Does not include maintenance requirements and ongoing losses.

†Tonicity of fluid used for correction will depend on initial severity of hypernatremia.

Abbreviation: NS = normal saline.

cause. Serum sodium levels of >160 mEq/L require immediate attention due to the potential for serious complications and permanent neurologic sequelae, including intellectual deficits, seizure disorder, or other neurologic impairments. Conversely, patients who have a sodium level of <160 mEq/L and receive treatment typically have symptoms that are relatively mild and self-limited.

Signs and symptoms of hypernatremia result from cellular dehydration as free water moves from the intracellular to extracellular space and include mental status changes, muscular weakness, ataxia, tremors, hyperreflexia, seizures, unresponsiveness, intracerebral hemorrhage, permanent neurologic dysfunction, and death. In addition, when extracellular fluid hypertonicity develops, brain intracellular osmolar contents increase to prevent or minimize cell shrinkage. In severe hypernatremic dehydration, neurologic findings may include any of the following: increased peripheral tone with brisk reflexes, muscle weakness, high-pitched cry, nuchal rigidity, myoclonus, asterixis, chorea, altered level of consciousness, or seizures.[3,21]

Treatment consists of restoration of intravascular volume while decreasing the serum sodium level. **Correct serum sodium gradually to avoid cerebral edema and associated central pontine myelinolysis** (Table 132-7). **Closely monitor serum sodium levels every hour initially to ensure that the level is reduced no faster than 1 mEq/L/h and no more than 15 mEq/L in the first 24 hours.** This may require more than 48 hours for complete correction. Monitor urine output given the risk of acute tubular necrosis.[21] Correct underlying causes. Hypervolemic hypernatremia may require dialysis if sodium levels cannot be decreased without volume overload. Dialysis may also be required for hypernatremia of any type if the initial serum sodium is >180 mmol/L.

DISORDERS OF POTASSIUM

HYPOKALEMIA

Hypokalemia occurs when the serum potassium level falls to <3.4 mEq/L and most commonly occurs secondary to profuse vomiting and/or diarrhea. Other common causes include therapy with loop or thiazide diuretics, mineralocorticoids, or laxatives and diabetic ketoacidosis. In diabetic ketoacidosis, profound hypokalemia can result from osmotic diuresis, although in the face of the hydrogen–potassium shift that accompanies acidemia, serum levels may be normal or falsely elevated. Uncommon causes of hypokalemia include renal tubular acidosis, Bartter's or Gitelman's syndrome, Cushing's syndrome, and familial hypokalemia-induced paralysis.

In most cases, hypokalemia occurs slowly, and thus patients are asymptomatic. Clinical signs tend to reflect the rate of fall of serum potassium rather than the absolute level. However, severe potassium depletion can result in skeletal muscle weakness, ileus, and cardiac conduction disturbances. A prominent ECG manifestation is the U wave.

Treatment is generally with oral replacement with potassium, 2 to 5 mEq/kg/d in two or three divided doses (maximum 40 mEq/dose). However, dehydration and magnesium abnormalities must also be corrected to maintain normal potassium levels. If IV therapy is necessary, potassium 0.2 to 0.3 mEq/kg/h is generally adequate. In extremely urgent situations, such as hypokalemia-induced respiratory insufficiency or cardiac manifestations, potassium 0.5 mEq/kg/h can be administered (maximum 20 mEq/dose), with continuous ECG monitoring.[22] If potassium chloride infusion concentration exceeds 60 mEq/L, the infusion will need to run through a central line, because potassium is a vein irritant. In diabetic ketoacidosis, potassium repletion should begin early in the course of therapy, because diuresis-induced depletion can result in profound hypokalemia as acidosis is corrected and serum potassium shifts into cells (see Chapter 147, "Diabetes in Children").

HYPERKALEMIA

Hyperkalemia is a serum potassium level of >5.5 mEq/L. In infants and children, a laboratory finding of hyperkalemia is most commonly due to hemolysis from phlebotomy and does not reflect serum levels. However, do not assume hyperkalemia is false; repeat the potassium level, reexamine the patient, obtain an ECG, and place the child on a cardiac monitor. Some common causes of true hyperkalemia include renal failure, rhabdomyolysis, burns, heatstroke, trauma, tumor lysis syndrome, hemolytic anemia, use of potassium-sparing diuretics, and adrenal corticoid insufficiency (e.g., Addison's disease, salt-wasting congenital adrenal hyperplasia). Metabolic acidosis can result in hyperkalemia due to hydrogen–potassium shifts.

Cardiac conduction delay is the most common manifestation of hyperkalemia and is potentially life threatening. Peaked T waves are the first manifestation, followed by prolonged PR interval and then widening of the QRS complex, an ominous finding that can precede the characteristic "sine wave" pattern, leading to ventricular dysrhythmias and asystole. Any patient with ECG changes requires emergent therapy to reverse cardiac conduction toxicity.

Treatment is detailed in **Table 132-8**. Asymptomatic patients with normal ECG findings usually do well with therapy to enhance potassium

TABLE 132-8 Treatment of Hyperkalemia

Purpose	Agent	Dose
Increase cardiac stability	Calcium gluconate 10% (10% calcium gluconate contains 100 milligrams/mL)	100 milligrams/kg (1 mL/kg/dose) IV at rate not to exceed 100 milligrams/min; maximum 3 grams/dose. Can be administered peripherally or centrally. May be repeated in 5 min if necessary.
	Calcium chloride 10% (10% calcium chloride contains 100 milligrams/mL)	20 milligrams/kg (0.2 mL/kg/dose) IV at rate not to exceed 100 milligrams/min; maximum 1 gram/dose. Calcium chloride must be given via central line or IO due to vein sclerosis. May be repeated in 5 min if necessary.
Decrease potassium	Albuterol (Ventolin) 0.5% solution	2.5–5 milligrams via nebulization; every 20 min as needed.
	Sodium bicarbonate	If acidotic (pH <7.3), 1–2 mEq/kg IV/IO; typical adult dose 50–100 mEq. Onset of action is in minutes. May be repeated every 5–10 min as needed.
	Regular insulin	0.1 unit/kg IV in 5 mL/kg 10% dextrose in water, 0.5 gram/kg IV over 30 min; check glucose level every 30 min; onset of action, 30 min. May be repeated every 30–60 min.
	Furosemide	If renal function normal and patient is not hypovolemic, 0.5–1 milligram/kg/dose IV to a maximum of 40 milligrams/dose. Peak effect seen at 30 min.
	Sodium polystyrene sulfonate	1 gram/kg to a maximum of 60 grams orally, via nasogastric tube, or rectally. Onset of action, 1–2 h orally, <30 min rectally.

excretion. In patients with renal failure with a gradual rise in serum potassium levels, sodium polystyrene sulfonate can be given. It is a resin that exchanges sodium for potassium at a 1:1 ratio and therefore enhances potassium excretion and can be administered orally or by enema. A dose of 1 gram/kg lowers the serum potassium level by up to 1.2 mEq/L. When administered orally, it is usually given with a cathartic to speed transit time through the GI tract. Hypernatremia and volume overload are potential complications. In patients with severe hyperkalemia from renal failure, dialysis is usually necessary, but emergency correction of potassium must be done first (Table 132-8). In patients with hyperkalemia secondary to metabolic acidosis, normalization of serum pH usually restores serum potassium to normal levels.[22]

DISORDERS OF CALCIUM

HYPOCALCEMIA

Hypocalcemia is a serum calcium level <8 milligrams/dL (2 mmol/L) or ionized calcium level <4.4 milligrams/dL (1.1 mmol/L); however, levels must be adjusted for albumin levels and pH of the blood. Low calcium levels tend to result from hypoparathyroidism or end-organ resistance to parathyroid hormone. True hypoparathyroidism can be idiopathic, be associated with DiGeorge's syndrome, occur after thyroid surgery, and/or be associated with magnesium deficiency. End-organ resistance to parathyroid hormone is most commonly associated with vitamin D deficiency. The most common causes are dietary deficiency and chronic renal failure. Young infants fed cow's milk, which is high in phosphate, can develop severe hypocalcemia. Another common cause of hypocalcemia is hyperventilation: the decreased partial pressure of carbon dioxide results in an acute respiratory alkalosis that rapidly decreases levels of ionized calcium.

Clinical manifestations of hypocalcemia include muscle weakness, vomiting, and irritability. Infants may simply appear "jittery." In severe cases, tetany, laryngospasm, carpopedal spasm, and seizures can occur. Carpopedal spasm is especially common in children with hyperventilation syndrome. The most characteristic ECG abnormality is a prolonged QT interval. Investigation of hypocalcemia includes laboratory measurement of total serum and ionized calcium, phosphate, total protein and albumin, parathyroid hormone, BUN, and creatinine levels. Urine calcium level should also be collected. If a neonate is seen with hypocalcemia, a chest radiograph should be done to look for a thymic shadow in infants and young children. If the thymus is not present, consider DiGeorge's syndrome.

Treatment is the administration of IV calcium (**Table 132-9**). Give calcium gluconate 10% in a dose of 100 milligrams/kg at a rate not to exceed 100 milligrams/min, with continuous ECG monitoring. Following initial correction, a calcium infusion may be required to maintain calcium levels. Further management depends on the cause.[23]

TABLE 132-9 Treatment of Disorders of Calcium and Magnesium

	Treatment	Comments
Calcium		
Hypocalcemia	10% calcium gluconate IV, 100 milligrams/kg, at a rate <100 milligrams/min	Continuous ECG monitoring
Hypercalcemia	Hydrate with twice maintenance fluids, furosemide 1–2 milligrams/kg IV to a maximum of 40 milligrams	Treat underlying cause
Magnesium		
Hypomagnesemia	10% magnesium sulfate, 25–50 milligrams/kg over 30 min	
Hypermagnesemia	Hydration, diuresis 1–2 milligrams/kg IV furosemide to a maximum of 40 milligrams; or 10% calcium gluconate IV, 0.5 mL/kg	

HYPERCALCEMIA

Hypercalcemia is a serum calcium level of >11 milligrams/dL and most often results from increased bone resorption. Probably the most common cause in children is malignancy involving the lymphoreticular system. Less common causes include vitamin A or D intoxication, hyperparathyroid syndromes, hyperthyroidism, adrenal insufficiency, and pheochromocytoma.

Clinical manifestations include hypotonia, fatigue, irritability, anorexia, vomiting, and constipation. Affected children may be clinically dehydrated and complain of polyuria and/or polydipsia. An ECG may reveal bradycardia and a shortened QT interval.

The laboratory evaluation of hypercalcemia includes measurement of total serum and ionized calcium levels, a CBC, and evaluation of total protein and albumin and alkaline phosphatase levels. An evaluation of the vitamin D level may also be indicated, depending on the patient's medical history.

Treatment (Table 132-9) depends on the cause. Acutely, patients with functioning kidneys can be treated with aggressive IV hydration (e.g., twice maintenance),[24] with or without furosemide, 1 to 2 milligrams/kg IV, to a maximum of 40 milligrams. Then, treat the underlying cause.

DISORDERS OF MAGNESIUM

HYPOMAGNESEMIA

Serum magnesium levels are age independent and range from 1.5 to 2.2 mEq/L. Dietary magnesium is absorbed in the intestine and reabsorbed in the urine, particularly in states of decreased intake. Serum levels of <1.5 mEq/L are considered low and usually result from GI or renal losses as well as some endocrine disturbances. Diarrhea, malabsorption, short gut, and fistulas are potential mechanisms of GI magnesium loss, but iatrogenic causes of renal loss (osmotic diuretics, parenteral fluids, antibiotics, and chemotherapeutics) predominate. Hypercalcemia may cause magnesium loss as well as hypophosphatemia. Hypomagnesemia may also occur in diabetes, disorders of the parathyroid glands, and primary hyperaldosteronism.

Clinical manifestations are similar to those seen with hypocalcemia: muscle spasms, weakness, or even atrophy may occur; CNS symptoms include ataxia, abnormal movements, nystagmus, and seizures and occur with very low magnesium levels. Cardiac changes include prolonged PR and QT intervals and may predispose to arrhythmias such as torsades de pointes.

Treatment (Table 132-9) depends on the underlying cause. Include magnesium in parenteral or enteral nutritional liquids in chronically ill children. In symptomatic patients (e.g., those with seizures, arrhythmias), give IV magnesium sulfate, 25 to 50 milligrams/kg administered as a 10% solution over 30 minutes, and repeat every 4 to 6 hours as needed.

HYPERMAGNESEMIA

Hypermagnesemia is rare. Serum levels of >2.2 mEq/L are considered elevated. The most common cause is ingestion of exogenous magnesium, typically found in antacids and laxatives. Patients with renal dysfunction are at increased risk. Clinical manifestations include hypotension, loss of deep tendon reflexes, and respiratory failure. Cardiac manifestations include widening of the QRS, PR, and QT intervals.

Treatment (Table 132-9) is removal of exogenous sources and hydration accompanied by diuresis. Severe symptoms may be mitigated with IV calcium, 0.5 mL/kg delivered as calcium gluconate. Dialysis is effective in patients with renal failure.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 133

Acute Abdominal Pain in Infants and Children

Ross J. Fleischman

INTRODUCTION

The diagnoses in this chapter are challenging, as emergent surgical conditions in children may present with symptoms other than pain, including vomiting, fever, irritability, or lethargy. **Table 133-1** classifies conditions by age, although many conditions cross categories.

The pathophysiology of abdominal pain is discussed in Chapter 71, "Acute Abdominal Pain." Gynecologic causes are discussed in Chapter 97, "Abdominal and Pelvic Pain in the Nonpregnant Female." Gastroenteritis is the most common cause of abdominal pain in children of all ages (see Chapter 131, "Vomiting, Diarrhea, and Dehydration in Infants and Children").

The largest single group of children will have no definite diagnosis and will receive the *diagnosis of exclusion* of nonspecific abdominal pain. **Patients should not be given unsubstantiated diagnoses such as gastroenteritis, gastritis, or constipation without strong support for these diagnoses.** Patients discharged without a clear diagnosis should have a planned reexamination.

PHYSICAL EXAMINATION

The assessment of young children depends on observation for subtle clues. Stillness suggests conditions that irritate the peritoneum, such as appendicitis. Writhing for a position of comfort suggests obstruction, such as intussusception or renal colic.

Inspect, auscultate, and then palpate the abdomen, starting away from the expected area of maximal tenderness. Bringing the knees up relaxes the abdominal muscles. Move the hips to test for hip pathology or irritation caused by appendicitis or a psoas abscess. **Thoroughly examine the diaper area to identify testicular torsion, paraphimosis, hair tourniquet, hernia, and imperforate hymen, as the young child may be unable to articulate problems in that area and the older child may be embarrassed to do so.** Rectal exam may identify gross or occult blood, constipation, abnormalities of anogenital anatomy, and inflammatory processes. Evaluate for extra-abdominal causes of abdominal pain such as pharyngitis or pneumonia.

TABLE 133-1 Causes of Abdominal Pain by Age Group

Age	Emergent	Nonemergent
0–3 months old	Necrotizing enterocolitis Volvulus Incarcerated hernia Testicular torsion Nonaccidental trauma Hirschsprung's enterocolitis	Constipation Acute gastroenteritis Colic
3 months–3 years old	Intussusception Volvulus Testicular torsion Appendicitis Vaso-occlusive crisis	Urinary tract infections Constipation Henoch-Schönlein purpura Acute gastroenteritis
3 years old–adolescence	Appendicitis Diabetic ketoacidosis Vaso-occlusive crisis Ectopic pregnancy Ovarian torsion Testicular torsion Cholecystitis Pancreatitis Urinary tract infections Tumor Pneumonia	*Streptococcus* pharyngitis Inflammatory bowel disease Pregnancy Renal stones Peptic ulcer disease/gastritis Ovarian cysts Henoch-Schönlein purpura Constipation Acute gastroenteritis Nonspecific viral syndromes

LABORATORY STUDIES

Bedside glucose measurement is a first step in the evaluation of any ill-appearing child or in cases of persistent vomiting or poor oral intake. Obtain a chemistry panel if there is suspicion for electrolyte or renal abnormalities in ill-appearing children and in the first 6 months of life, when sodium or metabolic abnormalities are more common. Urinalysis and urine human chorionic gonadotropin identify urinary tract infection, microscopic hematuria, and pregnancy. **The WBC count and C-reactive protein are poor screening tests for undifferentiated abdominal pain.**

DIAGNOSTIC IMAGING

US is the first-line test for appendicitis, pyloric stenosis, intussusception, testicular torsion, urolithiasis, and biliary and gynecologic pathology. CT scan is the most sensitive study for appendicitis and intra-abdominal abscesses and may uncover a wide variety of pathology. Abdominal CT exposes children to a significant radiation dose to which young children are more sensitive than adults[1] and IV contrast carries a risk of serious allergic reactions and can cause nephropathy; therefore, reducing unnecessary CT use should be a goal of emergency physicians.

Plain radiographs give a much lower radiation dose than CT (1/600th the dose for a chest radiograph compared with an abdominal CT) but are often nonspecific.[2] Use radiography selectively to exclude or support specific diagnoses (e.g., obstruction), rather than undirected screening. Free air from a perforation can be seen on upright or left lateral decubitus views, although these are insensitive tests. Avoid barium oral or rectal contrast if perforation is suspected and use water-soluble contrast instead.

PAIN MANAGEMENT

Contrary to fears that analgesics may mask surgical conditions, analgesia improves the physician's ability to assess pain and does not worsen outcomes. See Chapter 115, "Pain Management and Procedural Sedation in Infants and Children."

SPECIAL CONSIDERATIONS BY AGE GROUP

NEONATES AND YOUNG INFANTS (0 TO 3 MONTHS)

The major life-threatening diagnoses in young infants are necrotizing enterocolitis, malrotation with midgut volvulus, incarcerated hernias, and nonaccidental trauma. Young infants typically eat every 2 hours, so inconsolability and lethargy with poor feeding are signs of serious disease. **The maxim that bilious vomiting portends a surgical emergency is well supported, as between 27% and 51% of children with bilious vomiting require surgery.**[3]

Intermittent, paroxysmal pain is often associated with intussusception (rare in this age group), colic, and gastroenteritis. Necrotizing enterocolitis and volvulus are more typically associated with constant pain. Pain after feeding may be caused by gastroesophageal reflux. **Pyloric stenosis causes progressive painless projectile vomiting followed by renewed interest in feeding.**

Past medical history includes the complications of pregnancy and delivery. Constipation with a history of not passing meconium within the first 24 to 48 hours of life suggests Hirschsprung's disease. Hirschsprung's enterocolitis is a serious complication that presents with

explosive diarrhea, fever, vomiting, abdominal pain, and distention. It is common in the first 2 years after resection of the aganglionic segment but also occurs in patients with undiagnosed disease.

OLDER INFANTS AND TODDLERS (3 MONTHS TO 3 YEARS OLD)

Intussusception, urinary tract infections, testicular torsion, and accidental and inflicted injury are serious causes of abdominal pain in older infants and toddlers. Malrotation with midgut volvulus and appendicitis are less common but remain considerations. Constipation is a common cause of abdominal pain that can be severe and often begins around the time of toilet training. Parents may not offer a stooling history unless asked.

Stranger anxiety is prevalent at this age. Take a few moments to gain the confidence of the child before any examination or procedures. It may be helpful to ask a parent to palpate the child's abdomen while you observe, before palpating yourself or with the toddler's assistance. **Observe the child while coughing, walking, or jumping as a test for peritoneal irritation.** Toddlers may not be able to differentiate pain from nausea.

CHILDREN (3 TO 15 YEARS OF AGE)

Diagnoses in this age group include problems that are common in adults. **Appendicitis is the most common surgical emergency.**

Other important etiologies are diabetic ketoacidosis (Chapter 147, "Diabetes in Children"), urinary tract infection (Chapter 135, "Urinary Tract Infection in Infants and Children"), testicular torsion, ectopic pregnancy, pelvic inflammatory disease (Chapter 136, "Pediatric Urologic and Gynecologic Disorders"), pancreatitis, inflammatory bowel disease, cholelithiasis, sickle cell anemia (Chapter 143, "Sickle Cell Disease in Children"), Henoch-Schönlein purpura, and renal colic (Chapter 137, "Renal Emergencies in Children"). Upper respiratory symptoms may be associated with mesenteric adenitis, which may mimic appendicitis.

An examination of the testicles is required. If two testicles cannot be identified, consider torsion of an undescended testis. Perform a pelvic examination in sexually active girls. Adolescents may offer additional history with parents out of the room.

SPECIFIC CONDITIONS

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis is a neonatal disease thought to be caused by an immune overreaction to an insult to the intestine followed by inflammation, bacterial translocation, and coagulation necrosis of the intestine. Overall mortality is 15% to 30%, with many survivors left with short bowel syndrome and growth retardation.[4] While necrotizing enterocolitis is largely a disease of prematurity, 10% of cases occur in term infants.[5] Predisposing conditions include congenital heart disease, sepsis, neonatal asphyxia, polycythemia, and hypotension.[6] The mean age at onset is between 2 and 9 days. **Therefore, although the disease rarely presents outside of the neonatal intensive care unit, its severity makes it an important consideration in near-term infants or those with comorbidities in the first 3 weeks of life.**

CLINICAL FEATURES AND IMAGING

Presenting signs and symptoms include poor feeding, lethargy, abdominal distention, bilious vomiting, temperature instability, apnea, and abdominal tenderness. Gross or occult blood in the stool increases the likelihood of necrotizing enterocolitis, but is neither sensitive nor specific.[7]

Obtain anteroposterior and left lateral decubitus abdominal radiographs. Including the chest will screen for cardiopulmonary abnormalities. Early in the disease, abdominal radiographs may show signs of ileus or obstruction. **Pneumatosis intestinalis (air in the bowel wall) and portal venous gas are both pathognomonic (Figure 133-1),**[8] but normal abdominal radiographs do not exclude the disorder.



FIGURE 133-1. Plain abdominal film demonstrating air in the intestinal wall (*arrows*), which is pathognomonic of necrotizing enterocolitis. [Reproduced with permission from Strange GR, Ahrens WR, Schafermeyer RW, Wiebe RA: *Pediatric Emergency Medicine*, 3rd ed. © 2009, The McGraw-Hill Companies, Inc. New York, Figure 9-12.]

TREATMENT

Evaluation must include a search for underlying causes, especially sepsis. Management includes nothing by mouth status, gastric tube decompression, aggressive IV hydration, broad-spectrum antibiotics, and surgical consultation. Consider ampicillin to cover gram-positive organisms, gentamicin or cefotaxime for gram-negative organisms, and metronidazole or clindamycin for anaerobes.[9] Although necrotizing enterocolitis is first managed medically, many cases require resection of necrotic bowel. Admit to intensive care.

MALROTATION AND VOLVULUS

Volvulus is a life-threatening complication of malrotation. **Eighty percent of patients with malrotation present within the first month of life and 90% within the first year, but it can present at any age.**[10] At approximately 10 weeks of gestation, the growing intestines return to the abdomen from the yolk sac, and the midgut undergoes a 270-degree counterclockwise turn around the superior mesenteric artery. Abnormal rotation can leave the cecum high in the abdomen, with its peritoneal attachments (Ladd's bands) crossing the duodenum. Down syndrome, heterotaxy, and duodenal atresia are associated with malrotation.

CLINICAL FEATURES

The child may be well until the malrotated gut twists (volvulus) or becomes obstructed by Ladd's bands, causing obstruction and ischemia.

Volvulus is a surgical emergency as it can result in gangrene of the entire midgut within hours. The infant with volvulus often has no significant past medical history and presents with the abrupt onset of constant abdominal pain, bilious vomiting, abdominal distention, and irritability. Patients with volvulus are typically ill appearing and may have signs of shock. The abdomen is diffusely tender and distended and may be rigid. Intermittent volvulus may present with stable vital signs and focal tenderness on abdominal examination. The absence of fever can help distinguish volvulus from sepsis.

IMAGING AND TREATMENT

Imaging studies should not delay surgical consultation, as rapid detorsion of the volvulized bowel is necessary to prevent loss of the entire small intestine. Upper GI series with contrast remains the test of choice for diagnosing malrotation with sensitivities of 93% to 100% for malrotation and 54% to 79% for volvulus.[11] The normal location of the duodenojejunal junction is at the level of the duodenal bulb and to the left of the spine. In malrotation, the junction is commonly located low and to the right of the spine. If midgut volvulus is present at the time of the study, there may be an abruptly tapered cutoff of contrast in the duodenum (bird's beak) or a corkscrew appearance of the bowel. If concern persists after a negative study and surgical consultation, options for additional evaluation include repeat upper GI series to exclude intermittent volvulus, abdominal CT, US, and contrast enema.

Plain abdominal radiographs are neither sensitive nor specific for malrotation. The most common findings on plain abdominal radiographs are an air-filled stomach with little distal gas, which may show a distal obstruction, nonspecific, or even normal gas pattern.[12]

Treatment consists of medical resuscitation and immediate surgical consultation. Obtain electrolytes, CBC, coagulation studies, and a type and cross-match for packed red blood cells.

INTUSSUSCEPTION

Intussusception is the most common cause of intestinal obstruction in children under 2 years of age. It is rare before 2 months. The male-to-female ratio is 2:1.[13,14]

Intussusception occurs when one segment of the intestine telescopes into another, usually the ileum into the colon. Constriction of the mesentery results in engorgement of the intussusceptum and bowel ischemia. In infants, lymphoid hyperplasia from viral illness may cause a "lead point," which drags one portion of bowel into another. In older children, causes of intussusception include Meckel's diverticulum, intestinal polyps, congenital duplications, lymphoma, and Henoch-Schönlein purpura.

CLINICAL FEATURES

Intussusception is notoriously difficult to diagnose because of its two disparate presentations: intermittent pain and lethargy. The classic presentation of ideopathic intussusception is an infant aged 5 to 12 months who suddenly develops a few minutes of severe abdominal pain with the legs drawn to the chest and who then appears well until the next episode of pain. An alternative presentation is an infant with unexplained lethargy, which may divert the provider to an evaluation for altered mental status. Vomiting is not usually present at first but develops over 6 to 12 hours and may be bilious.

The physical examination between attacks may be normal, although a sausage-shaped mass may be palpated in the right upper quadrant. **Occult blood is found in 70% of stools and gross blood in about 50%, although it rarely resembles the classic "currant jelly."**[15]

DIAGNOSIS AND TREATMENT

A history consistent with the intermittent symptoms of intussusception should prompt further evaluation or observation even if the patient is asymptomatic at the time. US should be the first study when the diagnosis is ambiguous. In research settings, the accuracy of US for intussusception is nearly 100% (**Figure 133-2**).[16]

Children with a high suspicion of intussusception should undergo immediate air-contrast enema, which is both diagnostic and therapeutic. Prepare the child for reduction with boluses of normal saline if dehydrated, since volume loss due to intestinal edema, decreased intake, and vomiting is common. Notify a surgeon prior to air-contrast enema in case the reduction is unsuccessful or perforation occurs. **Children with peritonitis, with free air on plain radiographs, or in shock should not undergo air-contrast enema and require emergent surgical reduction.**

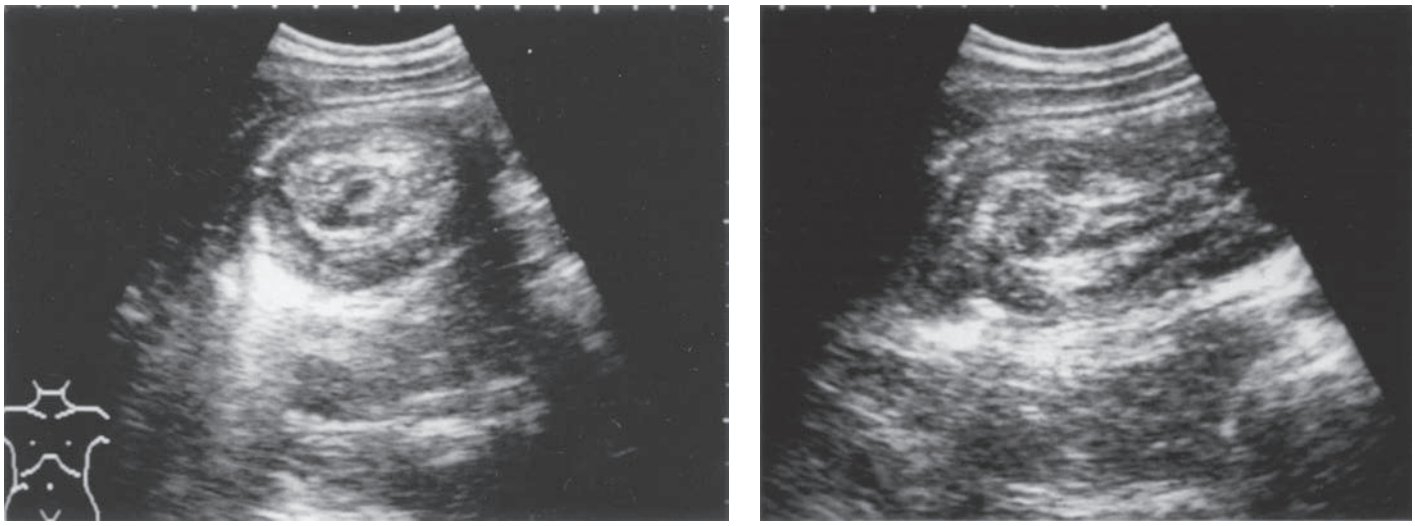
Plain abdominal radiographs are not highly useful unless needed to rule out perforation, but they may show a mass or paucity of bowel gas in the right abdomen, a "crescent sign" where the curved edge of one segment of bowel intrudes into another, or an obstructive pattern (**Figure 133-3**).[15]

Approximately 10% of infants or children will have a recurrence after a successful reduction, usually within the first 24 to 48 hours.[17] However, after a few hours of ED observation, discharge of patients who remain asymptomatic, are able to tolerate oral intake, and can easily return to the ED has been shown to be safe.[18,19] Recurrence should prompt a second enema reduction. Further recurrences may require surgery.

APPENDICITIS

Appendicitis is the most common surgical emergency in children. The peak ages for appendicitis are between 9 and 12 years, with a male predominance.[20]

The appendix is a diverticulum that arises from the cecum. Appendicitis usually begins with obstruction of the appendiceal lumen by fecaliths, lymphoid hyperplasia, or less commonly parasites, tumors, or foreign bodies. Multiplying bacteria and mucus secretion increase pressure on the wall, leading to dilation, ischemia, and perforation.



A B

FIGURE 133-2. A and **B.** US image of intussusception showing the classic target appearance of bowel-within-bowel. [Reproduced with permission from Ma OJ, Mateer JR, Blaivas M: *Emergency Ultrasound,* 2nd ed. © 2008, McGraw-Hill, Inc., New York, Figure 9-15.]



FIGURE 133-3. The crescent-shaped head of the intussusceptum is seen as an intraluminal mass in the gas-filled transverse colon (*asterisk*). [Reproduced with permission from Schwartz: *Emergency Radiology Cases Studies* © 2008, The McGraw-Hill Companies, Inc. New York. Figure II-4-6 Part A.]

CLINICAL FEATURES

The classic progression of periumbilical pain that migrates to the right lower quadrant followed by vomiting and fever is seen in less than 50% of children with appendicitis.[21] Many of the classic symptoms are seen with only moderate frequency: pain of <48 hours in duration (82%), nausea or emesis (71%), anorexia (60%), and migration of pain to the right lower quadrant (50%). Constipation is seen in 9% to 33% of cases and diarrhea in 10% to 33%.[22] **Perforation rates approach 90% in children <4 years old, so younger children are more likely to present with vomiting, fever, peritonitis, or sepsis.**[23]

Children with appendicitis may perforate early in the course of the disease. One study of children aged 3 to 18 found no perforation before 12 hours, but a 10% perforation rate at 18 hours and 44% by 36 hours.[24] Perforation may cause a brief relief of pain prior to the development of peritonitis and worsening symptoms.

Tenderness may be localized to the right lower quadrant (68% of cases) or McBurney's point (two thirds of the way from the umbilicus to the anterior-superior iliac spine) or may involve the entire abdomen. Assessing pain when the child coughs, walks, and jumps is useful for detecting peritoneal inflammation. Rebound tenderness and guarding are more common with perforation and may be absent in early appendicitis. Assess for hernias and perform a testicular examination in boys. A pelvic examination may be needed in adolescent females to compare the tenderness of McBurney's point to the adnexa. Rectal tenderness had a positive likelihood ratio of 2.3 and negative ratio of 0.7 in a summary of three studies.[23]

DIAGNOSIS

There is a high potential for missing the diagnosis of appendicitis in children. The Alvarado and Samuel scores have been widely cited, but have insufficient positive predictive values to safely identify the need for surgery for appendicitis in children, and other decision rules may or may not be generalizable (**Table 133-2**). Problems with interrater reliability make it difficult to apply decision rules in the clinical prediction of appendicitis (**Table 133-3**).[25]

WBC count has insufficient sensitivity or specificity to confirm the diagnosis of appendicitis; however, a normal WBC is strongly correlated with a decreased likelihood of appendicitis.[26] A WBC <10,000/mm^3 is a strong negative predictor for appendicitis (negative likelihood ratio = 0.26). C-reactive protein is a nonspecific later marker of inflammation and correlates with severity of appendicitis and may be helpful for distinguishing ruptured or gangrenous appendicitis from early disease. No single cut point for C-reactive protein has been established as a sensitive or specific marker of appendicitis; some studies suggest that C-reactive protein in conjunction with WBC and clinical signs and symptoms may add to the diagnostic evaluation of children with abdominal pain.[27-32] Sterile pyuria can be seen with acute appendicitis as the inflamed appendix irritates the nearby ureters.

TABLE 133-2 A Clinical Decision Rule to Identify Children at Low Risk of Appendicitis* (rule has poor positive predictive value)

Criterion	Points
Absolute neutrophil count >6.75 × 10^3/μL	6
Rebound pain or pain with percussion	2
Unable to walk or walks with limp	1
Nausea	2
History of migration of pain to right lower quadrant	1
History of focal right lower quadrant pain	2

Note: A score of ≤5 indicates low risk for appendicitis (sensitivity, 96.3%; 99% confidence interval, 87.5%–99.0%). If appendicitis is still suspected, repeat examination during ED observation, repeat examination within 12 hours, or US examination should be considered.

**Caution:* Interrater reliability is only fair to moderate for some of these variables.

IMAGING

Patients with a history and examination compelling for appendicitis should have surgical consultation without imaging. **When the diagnosis is uncertain, US is the preferred initial imaging exam.** Appendiceal findings include a maximal diameter >6 mm, wall thickness ≥3 mm, lack of compressibility, hyperemia on color Doppler US, surrounding edema or fat stranding, and an appendicolith (**Figure 133-4**).[33] US is useful to exclude gynecologic processes such as ovarian torsion and ruptured cysts. If done by experienced technicians and the appendix is visualized, US is highly sensitive and specific (88% and 94%).[34] An US with findings of appendicitis in a patient with a consistent clinical picture is sufficiently specific to warrant surgery. When the appendix is visualized and normal, US is sufficiently sensitive to exclude appendicitis in many cases. If clinical suspicion for appendicitis is very high, visualization of a normal appendix should not exclude the diagnosis, and additional evaluation should be undertaken. This may include surgical consultation, CT scan, admission for observation, or repeat US.

TABLE 133-3 Interrater Reliability of Selected Historical and Clinical Variables Used in the Clinical Assessment of Appendicitis

Sign or Symptom	Agreement, %	Kappa (95% CI)
Focal RLQ pain	84.9	0.48 (0.39–0.58)
Migration of pain to RLQ	68.4	0.37 (0.29–0.45)
Nausea	72	0.44 (0.37–0.52)
Rebound	68.4	0.32 (0.24–0.40)
Abdominal pain with walking, jumping, or coughing	83.6	0.54 (0.45–0.63)

Abbreviations: CI = confidence interval; RLQ = right lower quadrant.

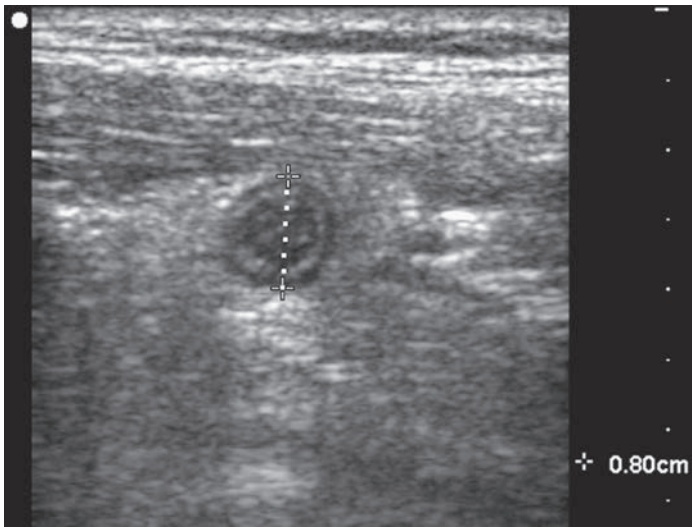


FIGURE 133-4. US of acute appendicitis with a diameter of 8 mm in short-axis view. [Reproduced with permission from Ma OJ, Mateer JR, Blaivas M: *Emergency Ultrasound*, 2nd ed. © 2008, McGraw-Hill, Inc., New York, Figure 18-23.]

The challenge is that many US exams will not visualize the appendix, in which case the presence or absence of secondary signs, including free fluid or abnormal echogenicity of fat in the right lower quadrant, is important. One study demonstrated a high negative predictive value when US did not visualize the appendix but showed no secondary signs of appendicitis, and another did so among patients with a WBC <7500/mm^3.[35,36] Therefore, in settings with skilled pediatric sonographers, nonvisualization of the appendix may be able to exclude appendicitis in lower-risk patients.

Abdominal CT scanning has superior test characteristics compared with US, with a sensitivity and specificity of 94% and 95%, respectively (**Figure 133-5**). Abdominal CT is useful for identifying perforation and abscess formation, which may require percutaneous drainage and antibiotics rather than immediate appendectomy, and therefore, CT may be the preferred imaging modality in children with prolonged pain or diffuse peritoneal signs suggestive of rupture. CT may also identify alternative diagnoses such as mesenteric adenitis, epiploic appendagitis, inflammatory bowel disease, renal stones, and tumors. Disadvantages of CT include radiation exposure, the time required for oral and/or rectal contrast when requested, and the possibility of allergic reactions. Institutional protocols often determine whether oral contrast is preferred in addition to IV contrast.

TREATMENT

Once the diagnosis of appendicitis is highly suspected or confirmed, obtain surgical consultation and administer antibiotics.[37] Antibiotics for nonperforated appendicitis include cefoxitin, ampicillin-sulbactam, and ceftriaxone plus metronidazole; for perforated appendicitis, monotherapy with piperacillin-tazobactam is as effective as multidrug therapy.[38] Percutaneous drainage may be considered for abscess, followed by delayed appendectomy to prevent recurrence. In ambiguous cases, admission for serial abdominal examination by a surgeon is reasonable. While the quality of current evidence is insufficient to recommend nonoperative management of uncomplicated appendicitis with antibiotics alone, future studies may prove it to be a safe alternative to surgery with a significant rate of recurrent appendicitis.[39]

HENOCH-SCHÖNLEIN PURPURA

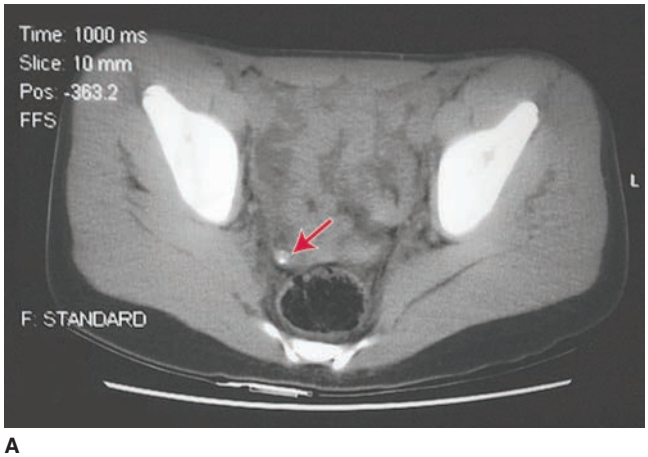
Henoch-Schönlein purpura is a vasculitis of children between 2 and 11 years of age with slight peaks in the fall and winter months. The cause is unknown, although a viral pathogen or group A *Streptococcus* may trigger the condition. Immunoglobulin A deposits are seen in the glomeruli and vessel walls.

CLINICAL FEATURES

The typical clinical presentation of Henoch-Schönlein purpura is **a triad of palpable purpuric rash, acute abdominal pain, and arthritis**. The rash occurs in all cases and is the presenting sign in 50% of cases (see Chapter 142, "Rashes in Infants and Children"). The rash may initially be urticarial or macular-papular. The lesions typically appear first on the extensor surfaces of the lower extremities and buttocks; they may involve the arms and ears. The face, palms, and soles are usually spared.

GI symptoms including abdominal pain and GI bleeding occur in 50% to 75% of cases.[40] The pain is usually diffuse and colicky in nature and may be associated with vomiting. Abdominal pain usually presents after the rash, but can precede the rash in 30% to 43% of patients. **Intussusception occurs in 3.5%.**[41] Arthralgia or arthritis occurs in 80% of cases and is the presenting sign in 25%. Joint symptoms are migratory and usually involve the knees and ankles with periarticular swelling and tenderness.

Renal involvement including hematuria, edema, and proteinuria is the most significant long-term consequence (see Chapter 137, "Renal Emergencies in Children"). Obtain a urinalysis on all patients to detect hematuria. When hematuria is present, obtain renal function tests. Although microscopic hematuria is relatively common in patients with Henoch-Schönlein purpura, proteinuria and gross hematuria represent more extensive renal involvement. Stool guaiac may be positive in nearly



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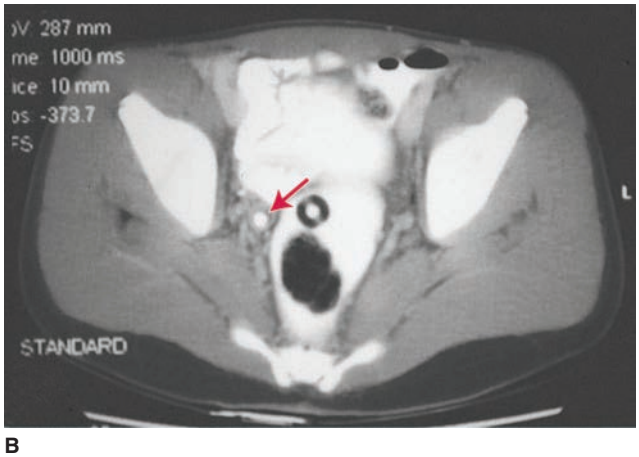

B

FIGURE 133-5. Acute appendicitis. **A.** A non–contrast-enhanced axial CT scan through the pelvis reveals a calcific appendicolith (*arrow*) in a pelvic appendix. Inspissated, sometimes calcified fecal material leads to obstruction followed by secondary bacterial invasion. Radiographic evidence of a fecalith is seen in 20% of cases. The presence of an appendicolith along with inflammation is indicative either of acute appendicitis or of impending appendicitis. **B.** Contrast-enhanced CT scan of the pelvis reveals the previously described appendicolith (*arrow*) in a dilated fluid-filled and thick-walled appendix. Enhancement of the appendiceal wall is also noted. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York, Figure 10-8.]

half of cases and, in the absence of intussusception symptoms, does not require further evaluation. Additional laboratory studies, including CBC and coagulation studies, are not routinely indicated in the patient with a characteristic presentation of Henoch-Schönlein purpura, as these studies are normal in this condition. **If the patient has a history consistent with accompanying intussusception, obtain an abdominal US or air-contrast enema to assess for this.**

TREATMENT

Treatment is mainly supportive. If the child is ill appearing, unable to tolerate oral fluids, or dehydrated, begin IV fluid hydration and arrange for admission. NSAIDs, such as ibuprofen and ketorolac, are used for management of arthritis, painful edema, and abdominal pain if renal function is normal based on urinalysis. Oral corticosteroids reduce symptoms of severe abdominal and joint pain. Care of patients with gross hematuria, more than small proteinuria, abnormal renal function, hypertension, or nephritic syndrome should be discussed with a pediatric nephrologist. Patients without these findings do not need steroids for prophylaxis of renal disease.[42] Arrange for repeat urinalysis and blood pressure measurements within 7 days, continuing for 6 months.[43]

INGUINAL HERNIA

Inguinal hernias occur in up to 45% of children and are more common in those born prematurely.[44] Incarceration refers to a hernia that cannot easily be reduced and is the presenting sign of the hernia in up to 65% of cases.[45] **Incarceration is most common in the first year of life.**

CLINICAL FEATURES

A simple inguinal hernia is often asymptomatic and is noted as a scrotal or inguinal mass. Symptoms of incarcerated hernia may include irritability, poor feeding, and vomiting. **The differential diagnosis includes torsion of the testicle** or testicular appendage, hydrocele of the cord or the scrotum, undescended testicle, inguinal lymphadenopathy, inguinal node abscess, orchitis, and trauma. The incarcerated sac may contain omentum, bowel, or ovary. Because it can be difficult to differentiate an incarcerated hernia from testicular torsion, it may be necessary to proceed with consultation and evaluation for both of these time-dependent emergencies simultaneously.

TREATMENT

An incarcerated hernia may progress to strangulation and is therefore a surgical emergency. Attempt reduction as soon as possible. Place the patient in the Trendelenburg position. Apply pressure to the hernia sac with one hand while the other guides the contents through the inguinal ring. Reduction may take minutes of steady pressure. Sedation and analgesia can be quite helpful. **One third of children redevelop incarceration, so either patients should be admitted for repair or expedited outpatient care should be arranged within 24 hours.** If manual reduction is unsuccessful, request immediate surgical consultation. **Unlike adults, children require referral for early repair even of hernias that have not become incarcerated because of the high risk of subsequent incarceration.**

INFLAMMATORY BOWEL DISEASE

Children account for 20% to 25% of new diagnoses of inflammatory bowel disease.[46] In one series, **95% of those <10 years old with Crohn's disease initially presented with abdominal pain, 77% with diarrhea, and 60% with bloody stools.**[47] The pain in Crohn's disease is often colicky and either diffuse or in the right lower quadrant, mimicking appendicitis. Weight loss is seen in 80% of patients with Crohn's disease. Growth failure may be the only symptom in 5%. Up to 25% of children with inflammatory bowel disease have a positive family history.

Tachycardia and hypotension may be present secondary to dehydration or anemia from chronic blood loss. Inspect the anal area for fistulas, fissures, and skin tags suggestive of Crohn's disease. Extraintestinal signs, including arthritis, ankylosing spondylitis, and erythema nodosum, occur in 20%.

Most children with moderate to severe disease will have anemia and an elevated erythrocyte sedimentation rate. Measure electrolytes in cases of severe diarrhea. If a new diagnosis is being considered, obtain stool culture, ova and parasite examination, and *Clostridium difficile* toxin to assess for infectious causes. An abdominal CT can be useful to evaluate for thickening of the terminal ileum and complications of Crohn's disease such as intra-abdominal abscesses and fistula. Definitive diagnosis requires endoscopy and biopsy. A pediatric GI specialist should be consulted for further management, which may include oral or IV corticosteroids. Toxic megacolon is a complication of severe ulcerative colitis in which large bowel dilation is present on abdominal radiograph or CT in the setting of fever, abdominal pain, and laboratory markers of systemic inflammation.[48] Treatment requires hospital admission for steroids.[49]

RENAL STONES

Calcium-containing renal stones are the most common type in children. Predisposing factors include immobilization, hyperparathyroidism, corticosteroids, diuretics, and neoplasms. Both ketogenic diets and antiepileptic drugs can predispose to stone formation.

CLINICAL FEATURES AND DIAGNOSIS

Children with renal stones present with abdominal pain only 50% of the time. Microscopic or gross hematuria is present in 85% of children with urolithiasis.[50,51] The ED workup should include imaging to exclude severe obstruction (US or CT) and urinalysis to exclude infection, as both of these potentially require immediate intervention. If the patient has never had imaging to confirm the presence of two normal kidneys and labs to confirm baseline normal renal function, these should be obtained. If these studies are abnormal, contact a pediatric nephrologist or urologist.

Because of the risk associated with radiation from CT, US is recommended by the American Urological Association as the first imaging test for urolithiasis in children.[52] US is highly specific for stones but has limited sensitivity (76% in one study compared to CT).[53] If the US is nondiagnostic and the clinician feels the need to confirm the diagnosis, noncontrast CT should be the next test. A negative US alone is sufficient if the goal of testing is not to confirm urolithiasis but to rule out obstruction. Plain radiographs have poor sensitivity for stones.

Because of the high rate of underlying metabolic abnormalities in children with urolithiasis (38% to 90%), all children with a new diagnosis require a metabolic evaluation, although this need not be done in the ED.[54] Workup may include a basic metabolic panel, serum calcium, phosphorus, parathyroid hormone, and 24-hour urine collection.[55] Anatomic abnormalities including vesicoureteral reflux, ureteropelvic and ureterovesicular junction obstruction, and neurogenic bladder are found in 11% of children with urolithiasis, so plans should be made for subsequent imaging.[56] **Parents should be instructed to strain the urine so the stone can be analyzed.**

TREATMENT

ED management is centered on pain and nausea control. If IV placement is indicated for dehydration, pain control, or blood draws, provide aggressive rehydration. Indications for admission include urinary tract infection with obstruction, abnormal renal anatomy or function, uncontrolled pain or nausea, and dehydration. **Most stones in the distal ureters smaller than 3 mm will pass spontaneously, while those larger than 4 mm will likely require intervention.**[57] Discuss patients with larger stones or mild to moderate obstruction with a urologist to plan follow-up. One meta-analysis showed a benefit to tamsulosin or doxazosin for distal ureteral stones in children, but the quality of evidence is not sufficient to conclusively recommend for or against this.[58] Interventional therapy includes extracorporeal shock wave lithotripsy and urethral or transcutaneous endoscopy to extract the stone.

Dehydration contributes to stone formation, so encourage oral fluids for all children discharged. Those with known metabolic causes for their stones may benefit from dietary modification, diuretics, or other medications specific to their condition.

TABLE 133-4 Causes of Acute Pancreatitis in Children

Biliary: gallstones and sludge, pancreas divisum	10%–30%
Medications: valproic acid, L-asparaginase, 6-mercaptopurine	<25%
Idiopathic	13%–34%
Multisystem disease: sepsis, shock, systemic lupus erythematosus	33%
Trauma	10%–40%
Infectious: mumps, hepatitis, other viral infection, *Mycoplasma*	<10%
Metabolic: diabetic ketoacidosis, hypertriglyceridemia, hypercalcemia	2%–7%
Hereditary: cystic fibrosis	5%–8%

PANCREATITIS

Pancreatitis is extremely rare in infants and is most commonly a secondary process in children and adolescents. See Chapter 79, "Pancreatitis and Cholecystitis," for a discussion of its pathophysiology. **Table 133-4** lists causes of acute pancreatitis in children.[59]

CLINICAL FEATURES

The typical history is an acute onset of epigastric or periumbilical abdominal pain associated with anorexia, nausea, and vomiting. Although 62% to 89% of children with pancreatitis complain of epigastric pain, <10% describe back pain or radiation of the pain to the back; nausea and vomiting are present in 40% to 80% of older children, but only 28% of children <2 years of age.[60] Older children may be able to describe dull, constant epigastric pain that is made worse by eating or lying supine. Physical examination reveals guarding or distention in fewer than half of children with pancreatitis, and Grey Turner sign is present in 2%.[61] The child may be lying quietly on his or her side with knees flexed.

DIAGNOSIS AND TREATMENT

Acute pancreatitis is defined by an elevation of either lipase or amylase of three times the upper limit of normal, or imaging consistent with pancreatitis. Lipase is between 82% and 100% sensitive in children.[60,62] Lipase rises within hours and remains elevated for up to 14 days. Also testing for amylase will identify some cases of pancreatitis with normal lipase values.[60] The level of enzyme elevation does not correlate with the severity of the disease. Obtain electrolytes, including calcium, and liver enzymes, which may suggest hepatic disease or biliary obstruction.

Obtain an US or CT scan to assess for biliary causes (gallstones or sludge) or anatomic abnormalities of the pancreas. US has greater sensitivity for gallstones and gives no ionizing radiation. CT is better at identifying complications of severe pancreatitis including necrosis, fluid collections, and hemorrhage, although these complications are more likely to present a few days into the disease. CT should be ordered if trauma is suspected.

Because intra-abdominal third spacing, shock, and multiorgan system failure are potential complications of acute pancreatitis, aggressively administer normal saline or lactated Ringer's solution. Treat pain and admit the patient to the hospital.

CHOLECYSTITIS

Cholecystitis is rare in children compared to adults but rising significantly coincident with the increase in childhood obesity. Whereas gallstones related to **hemolytic disease, such as sickle cell disease, and total parenteral nutrition have historically been the most common causes, biliary disease in children without these risk factors has risen and is now just as common a cause.**[63] Acute or chronic illness with dehydration, fasting, or mechanical ventilation can cause gallbladder sludge and obstruction in the absence of stones (acalculous cholecystitis). When complicated by bacterial infection of the common bile duct, cholangitis results and is associated with a high risk of sepsis and shock. Children who have undergone surgical Roux-en-Y procedures (e.g., Kasai procedure for biliary atresia) are at risk for ascending cholangitis.

CLINICAL FEATURES AND DIAGNOSIS

Children with biliary pain are typically restless and unable to lie still. **Jaundice is more common in children than adults and may occur in the absence of common bile duct obstruction.** Right upper quadrant tenderness and a positive Murphy sign may be elicited in older children and adolescents.

Obtain liver function tests and lipase, which may be normal even in cases of acute cholecystitis. US is the first-line test for evaluation of biliary disease. CT scan may demonstrate acute cholecystitis but misses 20% of gallstones.

TREATMENT

A child with biliary colic (cholelithiasis without acute cholecystitis, whose pain has resolved) may be discharged with outpatient follow-up. Children with cholecystitis or cholangitis should be admitted. Administer antibiotics for findings of gallbladder infection including fever and elevated WBC count: one common regimen is ampicillin, gentamicin, and clindamycin.[64] Cholangitis, with Charcot's triad of right upper quadrant pain, fever, and jaundice, is a medical emergency and requires immediate intervention.

PNEUMONIA

Although a child with pneumonia will often present with respiratory signs and symptoms and fever, the predominant complaint may be abdominal pain. The diagnosis and management of pneumonia in children are discussed in Chapter 128, "Pneumonia in Infants and Children."

STREPTOCOCCUS PHARYNGITIS

***Streptococcus* pharyngitis can cause abdominal pain with or without vomiting and without sore throat.** Examine the oropharynx of any child ≥3 years of age with abdominal pain. If signs of pharyngitis are present, test for group A *Streptococcus*. If the rapid strep test is negative, send a throat culture because of the rapid antigen test's good specificity but poor sensitivity.[65] See Chapter 124, "Mouth and Throat Disorders in Infants and Children."

COLIC

Colic is excessive, unexplained paroxysms of crying in a healthy infant from 2 weeks to 4 months of age, peaking at 6 weeks. Wessel's "rule of threes" is a mnemonic for colic: **crying >3 hours per day for >3 days per week for >3 weeks**. Sufferers will flex their legs, turn red, and pass large amounts of gas. Colic is a diagnosis of exclusion made by the chronicity of episodes and exclusion of dangerous alternative diagnoses. See Chapter 116, "Neonatal Emergencies and Common Neonatal Problems."

CONSTIPATION

Constipation is defined as stools that are hard, infrequent, or painful to pass. **Constipation may cause significant abdominal pain, prompting extensive evaluation.** Normal infants may occasionally go up to 7 days without a bowel movement. As long as the child is not symptomatic and the stool is not hard, no evaluation is necessary.

Hirschsprung's disease is a pathologic cause of constipation in infants. Hirschsprung's disease is caused by a failure of colonic ganglion cells to migrate during gestation and is more common in trisomy 21. A history of failing to pass meconium in the first 24 to 48 hours of life suggests Hirschsprung's disease or cystic fibrosis. Symptoms include infrequent, explosive bowel movements, poor growth and feeding, and progressive abdominal distention.

Constipation may be seen in older children with chronic medical conditions such as anorexia nervosa, cerebral palsy, neuromuscular disease, depression, or hypothyroidism and is common in children with autism.

TABLE 133-5 Treatment of Constipation in Children

- Dietary management: Fruits, vegetables, avoidance of processed foods, water or non-sugar fluids to avoid dehydration.
- Glycerin suppositories: ED treatment of constipation in infants <2 years; 1 suppository × 2.
- Normal saline enemas: ED treatment of acute constipation; 0–6 months, 120–150 mL; 6–18 months, 150–250 mL; 18 months–5 years, 300 mL. Enemas are most effective when held as long as possible.
- Sodium phosphate enemas: ED treatment of acute constipation in children 2–11 years, 2.25-oz pediatric enema. Children >11 years, 4.5-oz adult enema. May repeat.
- Polyethylene glycol (PEG): Initial treatment 1–1.5 grams/kg/d divided to two to four times per day for 3 days. Then decrease to 0.78 gram/kg/d divided daily or twice daily for maintenance therapy. Inpatient treatment for cleanout by nasogastric tube with PEG plus electrolyte solution is 14–40 mL/h.

Acute causes include dehydration, electrolyte abnormalities (hypercalcemia or hypokalemia), or drug ingestions.

Constipation may still be present with a recent, watery bowel movement if the child is passing soft stool around a mass of hard stool. Pencil-like stools suggest a stricture. Spasticity or delayed motor milestones may be signs of occult spinal dysraphism. Toilet training is a common inciting event for functional constipation.

While constipation may be very painful, it should not cause an ill or toxic appearance. The abdomen may be distended, and firm columns of stool may be felt in the descending and ascending colons. A rectal exam with an empty vault and increased sphincter tone that emits a burst of gas on insertion of a finger suggests Hirschsprung's disease. Examine the anal and sacral area for tufts of hair, dimples, and lipomas, which may suggest neurologic malformations including spina bifida and tethered cord.[66] An anteriorly displaced anus (more than two thirds the distance from the coccyx to the scrotal-perineal junction in males and the posterior fourchette in females) should prompt outpatient surgical referral. Check lower extremity tone, reflexes, and gait for signs of spasticity. Botulism may present as a hypotonic child with constipation. Fissures may cause painful defecation, leading to a cycle of retention and functional constipation.

TREATMENT

If the constipation is presumed to be causing acute pain, the physician may wish to treat in the ED with response guiding further evaluation (**Table 133-5**).[67,68] Oral polyethylene glycol is as effective as enemas for outpatient treatment. Children with constipation refractory to ED management may require hospitalization for polyethylene glycol by nasogastric tube.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 134

Gastrointestinal Bleeding in Infants and Children

Sarah M. Reid

INTRODUCTION AND EPIDEMIOLOGY

GI bleeding varies in its epidemiology and presentation depending on whether it originates from the upper or lower GI tract. Upper GI (UGI) bleeding is bleeding proximal to the ligament of Treitz, whereas lower GI (LGI) bleeding originates distal to this ligament. A recent study demonstrated a 14% increase in pediatric GI bleeding associated ED visits between 2006 (82/100,000 children) and 2011 (94/100,000 children).[1] In this sample, 20% of visits were for UGI bleeding, 30% were for LGI bleeding, and the remainder were unspecified. More than three-quarters (81%) of the patients were discharged home from the ED.

The signs and symptoms of GI bleeding in children vary and include the following: bright red blood in small strands or clots in emesis or bowel movements, vomiting of gross blood (hematemesis), black tarry stools (melena), or the passage of bright red or maroon-colored blood from the rectum (hematochezia). Occult bleeding may result in unexplained pallor, fatigue, and anemia. Severity is assessed by vital signs, physical appearance, and the hemodynamic status of the patient, all of which lead to an estimation of the volume of blood loss. Worrisome symptoms and signs include pallor, diaphoresis, lethargy, abdominal pain, tachycardia, hypotension, and altered mental status. GI bleeding can be life threatening. Advances in endoscopy and radiology and newer therapeutic modalities have helped identify the causes of bleeding more accurately and have provided more treatment options.

CLINICAL APPROACH

Assess bleeding and institute resuscitation if the child has signs of hemorrhagic shock. Next, obtain a history and perform a physical examination, and try to establish the level of bleeding as UGI or LGI, because the subsequent diagnostic and treatment steps differ. Then, narrow the differential diagnosis based on history, physical examination, laboratory studies, and the categorization of age-related causes of UGI and LGI bleeding. The presence of any one of melena, hematochezia, unwell appearance, or moderate to large volume of fresh blood in the vomitus was associated with a clinically significant UGI bleed (defined as a hemoglobin drop of >20 g/L, need for blood transfusion, need for emergent endoscopy, or need for surgical procedure).[2]

ASSESS BLEEDING AND BEGIN RESUSCITATION

There are several important questions to consider. Is the patient stable or unstable? Is this really blood, and is it coming from the GI tract? Is it a small amount of blood or a large volume? Has the child had prior episodes of bleeding, and if so, do the parents know the cause and prior treatment?[3]

IS THE PATIENT STABLE OR UNSTABLE?

The presence of tachycardia, pallor, tachypnea, prolonged capillary refill time, altered mental status, metabolic acidosis, and/or hypotension indicates significant GI bleeding. Tachycardia and tachypnea are the first clinical signs, followed by delayed capillary refill, decreased urine output, altered mental status, metabolic acidosis, and pallor. Orthostatic changes in heart rate and blood pressure indicate that significant bleeding has occurred. Hypotension is a late sign and indicates uncompensated hemorrhagic shock. Any signs of hemorrhagic shock require simultaneous resuscitation, diagnosis, and treatment. Maintain the airway, monitor oxygen saturation and provide oxygen, place two large-bore IVs (20 gauge or larger), and administer boluses of crystalloid and, if necessary, blood products.

IS THIS REALLY BLOOD?

Determine whether or not the vomit or stool really contains blood. Beets, food coloring, and fruit juices can look like blood. Black and tarry stools can result from vitamins with iron, bismuth (Pepto-Bismol®), spinach, cranberries, blueberries, or licorice. Urinary (urate) crystals in the neonatal diaper are often orange in color and may be interpreted by a caregiver as blood. The Gastroccult® and Hemoccult® tests (Beckman Coulter, Brea, CA) can be used to document the presence of blood in gastric contents or stool, respectively. These guaiac-based tests rely on the peroxidase activity of the heme portion of hemoglobin. False-positive results are associated with foods that have peroxidase activity such as red meat, melons, grapes, radishes, turnips, cauliflower, and broccoli. False-negative results can result from the ingestion of vitamin C due to its antioxidant properties. Newer guaiac kits have improved specificity.[3]

IS BLOOD COMING FROM THE GI TRACT?

Evaluate the child for epistaxis, recent dental work, or gingival bleeding, because swallowed blood may lead to hematemesis. The neonate can swallow maternal blood during delivery or from breastfeeding if the mother has fissures on her nipples. In the toddler, blood could come from an injury to the oropharynx or nose. Make sure that blood does not originate from the throat or lungs. Distinguish whether the blood in the diaper is from a GU or GI source. Examine the perineum and urethra. Neonatal girls may develop some vaginal bleeding from maternal hormone withdrawal.

IS IT A SMALL OR LARGE AMOUNT OF BLOOD?

It is difficult to gauge the amount of bleeding from caretaker descriptions, because even small amounts of blood can appear alarmingly large. Assess the clinical status of the patient, vital signs, results of laboratory studies, and results of serial clinical examinations to determine the amount of bleeding. The hemoglobin and hematocrit are unreliable indicators of blood loss in the early stages.

See **Tables 134-1**, **134-2**, and **134-3** for potential recurrent causes of GI bleeding organized by age and symptoms.[4,5]

HISTORY

Ask whether the child had prior episodes of bleeding. If so, ask whether the caregivers know the cause and prior treatments. There are many causes of UGI and LGI bleeding in children, and the causes vary significantly by age (Tables 134-1 and 134-2). In addition to the age-based approach to the differential diagnosis of GI bleeding, the clinical presentation and constellation of associated symptoms are often useful in narrowing the differential diagnosis for a particular child. Table 134-3 describes symptom complexes along with the differential diagnosis of GI bleeding.

The type and implications of questioning differ depending on the age of the child (Tables 134-1 and 134-2). If the child is verbal, obtain the history from both the child and the parent or caregiver. Elicit an accurate chronology of events, and ask questions to help frame the differential diagnosis (**Table 134-4**). Vomiting of bright red blood or coffee-ground emesis is the classic presentation of UGI bleeding. Bloody diarrhea and bright red blood mixed with or coating normal stool are the classic presentations of LGI bleeding. Hematochezia, melena, or occult GI blood loss could represent UGI or LGI bleeding.[6]

PHYSICAL EXAMINATION

Obtain vital signs and pulse oximetry. Assess the airway, breathing, and circulation of the patient. Perform a complete physical examination. Gain the confidence of the child before any painful examination or procedures are performed. Examine the nose for any signs of epistaxis and the oral pharynx for any signs of injury, infection, bleeding, or ulcers. Examine the skin for bruises or petechiae (a sign of coagulopathy), jaundice and abnormal venous pattern on the abdomen that would point toward liver disease, cutaneous vascular malformations that may signal lesions of the GI tract, or the palpable purpura associated with Henoch-Schönlein purpura. Allow the young child to rest on the caregiver's lap while examining the abdomen. Start with visual inspection, then auscultate for bowel sounds, and finally, palpate the abdomen for tenderness, guarding, rebound, rigidity, organomegaly, ascites, or masses. External examination of the anus and digital rectal examination are necessary to identify fissures, skin tags, fistulae, hemorrhoids, polyps, and impacted stool and to test for fecal blood.

DIAGNOSIS

Try to determine if the source of bleeding is UGI or LGI. In cases where it is unclear if UGI bleeding is occurring, consider nasogastric lavage. Nasogastric lavage is performed with **a 12-French nasogastric tube in small children and a 14- to 16-French tube in older children.** Instill 50 mL of warmed saline for infants and 100 to 200 mL for older children while keeping the child's head elevated to 30 degrees to reduce the risk of aspiration. After 2 to 3 minutes, gently aspirate gastric contents. Blood-flecked or coffee-ground aspirate suggests a slow rate of UGI bleeding, whereas bright red blood suggests serious hemorrhage. The usefulness of nasogastric lavage is limited, because clear aspirate does not exclude major bleeding from the UGI tract. For example, a duodenal ulcer distal to the pylorus may not reflux blood into the stomach and could yield a negative gastric aspirate.

TABLE 134-1 Age-Based Causes of Upper and Lower GI Bleeding

Upper GI Bleeding		
Neonate	**Infant/Toddler**	**Child/Adolescent**
Common	*Common*	*Common*
Swallowed maternal blood	Non-GI source (e.g., epistaxis)	Mallory-Weiss tear
Milk/soy protein allergy	Mallory-Weiss tear	Gastritis (especially *Helicobacter pylori* gastritis)
Trauma (nasogastric tube in NICU)	Esophagitis	Esophagitis
Uncommon	Gastritis	Peptic ulcer disease
Stress ulcer/gastritis	*Uncommon*	*Uncommon*
Esophagitis	Stress gastritis or ulcer	Esophageal varices
Vascular malformation	Peptic ulcer disease	Toxic/caustic ingestion
Hemorrhagic disease of newborn (vitamin K deficiency)	Vascular malformation	Foreign body
Coagulopathy/bleeding diathesis	GI duplication	Vasculitis
Coagulopathy associated with infection	Gastric/esophageal varices Bowel obstruction Toxic/caustic ingestion Coagulopathy/bleeding diathesis Foreign body	Vascular malformation Bowel obstruction Crohn's disease Coagulopathy/bleeding diathesis GI stromal tumors Dieulafoy's lesion
Lower GI Bleeding		
Neonate	**Infant/Toddler**	**Child/Adolescent**
Common	*Common*	*Common*
Swallowed maternal blood	Anal fissure	Anal fissure
Anal fissure	Milk/soy protein allergy	Infectious gastroenteritis
Milk/soy protein allergy	Infectious gastroenteritis	Polyps; benign, familial
Infectious gastroenteritis	*Uncommon*	*Uncommon*
Uncommon	Intussusception	Henoch-Schönlein purpura
Meckel's diverticulum*	Meckel's diverticulum*	Hemorrhoids
Necrotizing enterocolitis	GI duplication	Inflammatory bowel disease
Vascular malformation	Hemolytic-uremic syndrome	Meckel's diverticulum*
Hemorrhagic disease of newborn (vitamin K deficiency)	Henoch-Schönlein purpura	Hemolytic-uremic syndrome
Intussusception	Malrotation with volvulus	Vascular malformation
Malrotation with volvulus	Polyps; benign, familial	Celiac disease
Hirschsprung's-associated enterocolitis (toxic megacolon)	Coagulopathy/bleeding diathesis	
GI duplication	Vascular malformation	

Abbreviation: NICU = neonatal intensive care unit.

*Most common cause of severe LGI bleeding in all ages.

TABLE 134-2 Causes of GI Bleeding by Type

Hematemesis	
Infant	Swallowed maternal blood Vitamin K deficiency Vascular malformation
Child/adolescent	Swallowed blood from epistaxis, dental work, oral trauma Mallory-Weiss tear Esophagitis/gastritis Peptic ulcer disease Esophageal varices Vascular malformation Toxic ingestion Foreign body Coagulopathy/bleeding diathesis
Hematochezia and melena	
Infant	Upper GI sources Anal fissure Milk/soy protein allergy Infectious gastroenteritis Meckel's diverticulum Intussusception Malrotation with volvulus Ischemic bowel
Child/adolescent	Upper GI sources Anal fissure Infectious gastroenteritis Polyps Henoch-Schönlein purpura Hemorrhoids Inflammatory bowel disease Intussusception Meckel's diverticulum Malrotation with volvulus Ischemic bowel Hemolytic-uremic syndrome Celiac disease Vascular malformation

Laboratory studies are guided by the results obtained from the history and physical examination, the child's appearance (ill or not), and the differential diagnosis (see Chapter 133, "Acute Abdominal Pain in Infants and Children," and Chapter 131, "Vomiting, Diarrhea, and Dehydration in Infants and Children").

The stable child with minimal or self-limited bleeding may require no further diagnostic evaluation. A CBC, type and screen or cross-match of blood, serum electrolytes, renal function tests, liver function tests, coagulation panel, urinalysis, and stool testing for enteric pathogens or *Clostridium difficile* toxin should be obtained, as needed.

For minimal or moderate GI bleeding, it may be difficult to determine the exact cause in the ED. Diagnosis may require ultrasonography, radiographic imaging, endoscopic evaluation, or a technetium-99m (Meckel) scan.[4]

DIFFERENTIAL DIAGNOSIS FOR UPPER GI BLEEDING BY AGE GROUP

Although the differential diagnosis is guided by the results of history and physical examination and age-related causes, there is considerable overlap among age groups (Table 134-1). Mucosal lesions such as gastritis, esophagitis, ulcer disease, and Mallory-Weiss tears can be seen in children of any age. Massive bleeding can occur from esophageal varices, ulcer disease, vascular malformations, Meckel's diverticulum, and GI duplication.

TABLE 134-3 Symptom Complexes and Differential Diagnosis for GI Bleeding

Symptom Complex	Differential Diagnosis
Painless hematemesis	Swallowed blood (non-GI source) Coagulopathy/bleeding diathesis
Hematemesis and abdominal, epigastric, or chest pain	Peptic ulcer disease *Helicobacter pylori*–associated gastritis Esophagitis/gastritis
Hematemesis, hematochezia, or melena with underlying systemic disease	Esophageal varices Inflammatory bowel disease
Vomiting, hematochezia, or melena with abdominal pain	Intussusception Malrotation with volvulus Ischemic bowel Henoch-Schönlein purpura Necrotizing enterocolitis
Vomiting, hematochezia, or melena with fever	Infectious gastroenteritis Inflammatory bowel disease
Painless rectal bleeding	Polyp Meckel's diverticulum GI duplication Vascular malformation

Neonates **Hematemesis in the newborn** is most likely the result of swallowed maternal blood at delivery or during breastfeeding from cracked nipples. The **Apt test** is a qualitative test that distinguishes fetal from maternal hemoglobin. The blood in question is mixed with alkali to detect conversion of oxyhemoglobin to hematin. Fetal hemoglobin is more resistant to denaturation than adult hemoglobin. If the supernatant stays pink after the addition of alkali, the blood is fetal in

TABLE 134-4 Focused Historical Questions

Chief complaint	Frequency and volume of vomiting Blood-streaked, coffee-ground, or bloody vomitus Frequency and volume of diarrhea Bloody diarrhea Constipation with blood-streaked stool Blood on toilet paper or blood in toilet bowl Abdominal pain along with bloody vomitus or stool Dyspepsia; heartburn; dysphagia Fever
Review of systems	Rashes; joint pain; oral ulcers; perianal lesions; ocular symptoms; weight loss; fatigue; delayed puberty; failure to thrive; abnormal bleeding; dehydration
Medications	Iron; aspirin; NSAIDs; steroids; alcohol; recent antibiotics
Environment	Foreign body ingestion; foreign travel; sick contacts; raw meat/poultry; unpasteurized milk/cheese; animal contacts; water source
Trauma	Injury to abdomen (especially epigastrium or right upper quadrant) or significant body surface area burns
Past medical history	Term or premature; umbilical artery catheter; postpartum care; abdominal surgery; sepsis; liver disease; GI disease (enterocolitis, intussusception, congenital anomalies); coagulopathy/bleeding diathesis
Family history	GI bleeding; polyps; vascular anomalies; coagulopathy/bleeding diathesis; inflammatory bowel disease

origin (reported as a positive test). If it turns brown, it is maternal blood. Hemorrhagic disease of the newborn is rare, but if there was failure to administer vitamin K in the immediate postpartum period (e.g., home birth), a prolonged prothrombin time can result in neonatal bleeding.

Infants and Children Infants and children with severe **gastroesophageal reflux** may develop esophagitis and hematemesis. Mallory-Weiss tears after acute forceful vomiting or retching can also cause hematemesis. Any child with significant illness or injury (shock, polytrauma, respiratory failure, burns, head injury, renal failure, or vasculitis) can develop stress-related peptic ulcer disease.

Ingestion of a sharp foreign body or **button battery** can occasionally cause GI bleeding. Removal by endoscopy is indicated. See Chapter 77, "Esophageal Emergencies," for further discussion of button battery ingestions.

Preschool and older children can develop idiopathic ulcer disease. **Peptic ulcer disease** in the child is similar to that in adults, and there may be a positive family history. Young children may have poorly localized abdominal pain, bleeding, or even signs of obstruction or perforation. The adolescent will describe epigastric burning pain in a pattern more typical of the adult. If the bleeding is low grade, chronic symptoms of weakness and fatigue may develop. *Helicobacter pylori* is a leading cause of secondary gastritis and peptic ulcer disease in older children. Diagnosis should be made using endoscopy and is based on either positive culture or *H. pylori* gastritis on histopathology with at least one other positive biopsy-based test.[7] *H. pylori* eradication is confirmed using either the two-step monoclonal stool *H. pylori* antigen test or the ^{13}C-Urea Breath Test (Kimberly-Clark Corp., Roswell, GA).[7]

Variceal bleeding is the most common cause of severe UGI bleeding in children.[5] Consider esophageal variceal bleeding in older children and those with underlying chronic hepatic or vascular disease resulting in portal hypertension. Primary diseases of the liver that may lead to portal hypertension include biliary atresia, cystic fibrosis, hepatitis, α_1-antitrypsin deficiency, or congenital hepatic fibrosis. Portal hypertension may occur following liver transplant or operative repair of liver diseases such as biliary atresia. Other predisposing factors to portal hypertension include neonatal omphalitis, umbilical venous cannulation, abdominal sepsis, and abdominal/surgical trauma, although many cases remain idiopathic.[8]

Reactive gastritis can occur due to anti-inflammatory drugs, alcohol, cocaine ingestion, iron ingestion, *H. pylori*, Crohn's disease, Henoch-Schönlein purpura, or foreign bodies. Rarely, GI stromal tumors can arise from the wall of the GI tract mesentery or omentum. Most of these are found in the stomach and are associated with genetic disorders such as neurofibromatosis.

An unusual cause of UGI bleeding in children is **Dieulafoy's lesion**. Symptomatic lesions result when an abnormal submucosal artery erodes through a tiny mucosal defect, typically in the fundus of the stomach, causing massive bleeding. The characteristic history is recurrent massive hematemesis without any prodromal symptoms. Definitive diagnosis is usually made during endoscopy.[9]

DIFFERENTIAL DIAGNOSIS FOR LOWER GI BLEEDING BY AGE GROUP

The presence of melena, hematochezia, or bright red blood per rectum can help to differentiate causes of LGI in children (**Figure 134-1**). The differential diagnosis for LGI bleeding is also age dependent (Table 134-1). The approach to LGI bleeding in the neonate can be organized based on whether the baby appears well or unwell (**Figure 134-2**).

Neonates and Infants The neonate with dark, tarry stools likely has swallowed maternal blood from delivery or breastfeeding. Birth history is important because failure to replace vitamin K can lead to coagulopathy and massive bleeding.

As the infant ages, other disorders become important. **Anal fissures** are a common cause of bright red rectal blood on the surface of well-formed stools or toilet paper in children of all ages and highlight the importance of a careful rectal examination and spreading of anal skin folds. **Milk protein allergy** has a prevalence of 2% to 3% in infants, and cross-reactivity with soy protein exists in at least 10% of cases.[10] Protein-induced allergic enterocolitis, proctitis, or proctocolitis may lead to blood-streaked, mucousy, loose stools. Food protein–induced enterocolitis is a rare, delayed non–immunoglobulin E–mediated reaction typically presenting with profuse vomiting and diarrhea 1 to 4 hours after ingestion of the offending allergen, most commonly cow's milk, soy, rice, or oats.[11] The diarrhea may be frankly bloody, and in 15% of reactions, the infant may develop profound dehydration and lethargy. The basis of therapy in milk or soy protein allergy is removal of the offending protein using hydrolyzed or elemental formula. Breastfed infants whose mothers ingest dairy or soy may also suffer from this condition, and the offending protein must be eliminated from the maternal diet.[10,11]

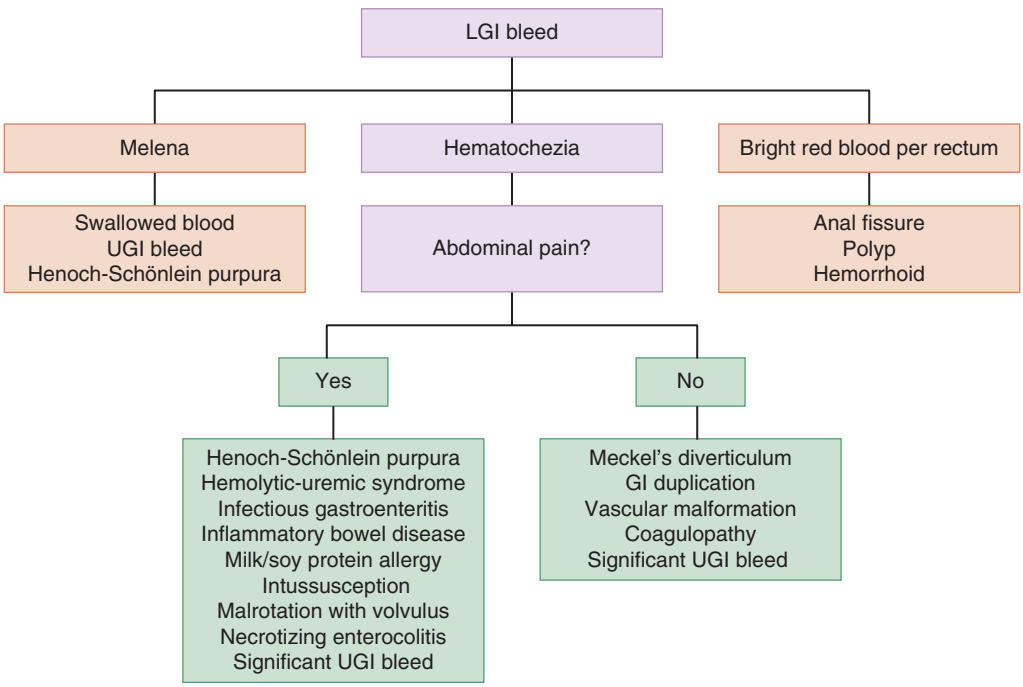

FIGURE 134-1. Diagnostic algorithm for lower GI (LGI) bleeding in children. UGI = upper GI.

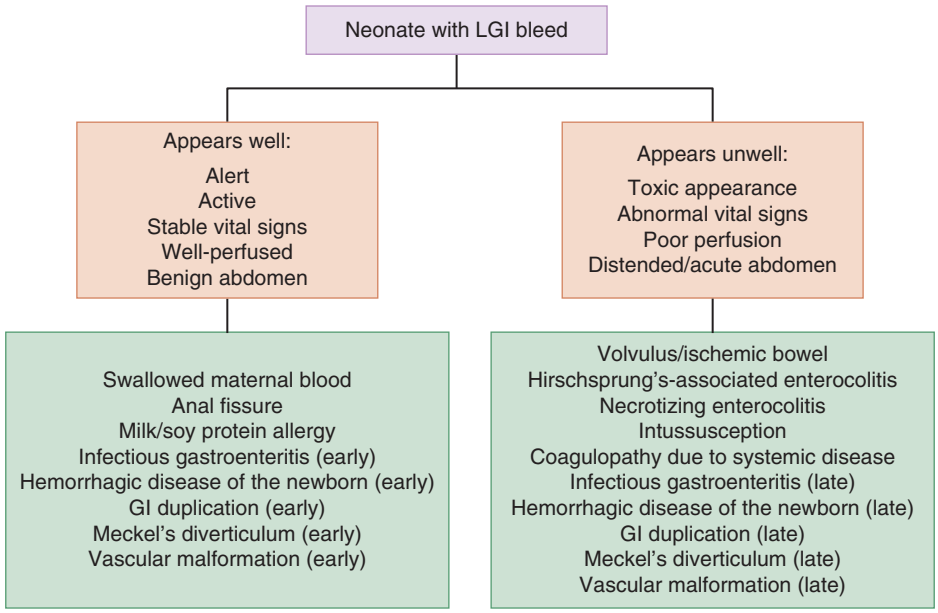

FIGURE 134-2. Approach to lower GI (LGI) bleeding in a neonate.

Necrotizing enterocolitis is most commonly seen in preterm infants in the neonatal intensive care unit, but may rarely be seen in term infants. Infants will be systemically unwell and present with abdominal distention and hematochezia. Plain radiographs reveal ileus and the pathognomonic *pneumatosis intestinalis* diagnostic of this condition. Infants with **Hirschsprung's disease** (congenital aganglionic megacolon) may develop Hirschsprung's-associated enterocolitis, also characterized by abdominal distention and hematochezia. Hirschsprung's-associated enterocolitis should be considered in any infant who appears toxic and has bloody diarrhea.[12]

In older infants who develop sudden painless hematochezia, congenital malformations such as **Meckel's diverticulum** and **GI duplication** must be considered. Meckel's diverticula are remnants of the omphalomesenteric duct in the distal ileum and are present in approximately 2% of the population. They may be lined with ectopic gastric mucosa and typically present with painless rectal bleeding in the 2-month to 2-year-old age group.[13] Diagnosis is made using a Meckel scan. **Intussusception** is another important consideration in infants and young children with a peak incidence between 5 and 10 months of age.[14] Intussusception is associated with episodes of colicky abdominal pain and vomiting. As the intussusception progresses, painful episodes may alternate with periods of lethargy, and gross blood ("currant jelly") may be noted in the stool. Diagnosis is made using US or contrast/air enema. Painful LGI bleeding in the infant can also be a symptom of **malrotation with volvulus**. Volvulus most commonly presents with abdominal pain, distention, and bilious vomiting, but may lead to bowel ischemia and subsequent LGI bleeding as the condition progresses. Both intussusception and volvulus represent true surgical emergencies and are further discussed in Chapters 131 and 133.

Children Age 2 to 5 Years Old Children in the 2- to 5-year-old age range have a different spectrum of disorders causing LGI bleeding: juvenile polyps, infectious gastroenteritis, hemolytic-uremic syndrome, and Henoch-Schönlein purpura. A review of recent literature suggests an estimated detected prevalence of colorectal polyps in 12% of all children with LGI bleeding undergoing colonoscopy.[15] Manifestations of **polyps** range from chronic heme-positive stools to acute hematochezia from autoamputation of the polyp at its stalk. Juvenile polyps are usually benign hamartomas, and most have no malignant potential. Multiple adenomatous polyps should suggest diagnoses such as familial adenomatous polyposis.

Infectious gastroenteritis should be evident by history and physical examination (**Table 134-5**).[16] Also see Chapter 131. When bloody diarrhea is present, stool cultures should be obtained.[12] Patients with typical diarrhea-associated hemolytic-uremic syndrome caused by Shiga toxin–producing strains of *Escherichia coli* have an antecedent episode of hemorrhagic enterocolitis within 2 to 12 days before the onset of thrombotic microangiopathy.[17] Children who have recently been exposed to antibiotics may develop bloody diarrhea from pseudomembranous colitis associated with ***C. difficile* infection**. In **Henoch-Schönlein purpura**, 50% to 75% of patients have episodic abdominal pain and/or blood in their stool from intestinal vasculitis. One-third of Henoch-Schönlein purpura patients develop acute intestinal bleeding manifested as gross or occult blood per rectum.[18] Intussusception develops in 1% to 5% of children with Henoch-Schönlein purpura.[18] Henoch-Schönlein purpura is further discussed in Chapter 133.

Children >5 Years Old In children >5 years of age, juvenile polyps and infectious gastroenteritis remain common causes of LGI bleeding. Both **Crohn's disease** and **ulcerative colitis** also become evident in this age group, and the incidence of these diseases is increasing.[19] Symptoms are varied and involve multiple systems: skin lesions such as erythema nodosum and pyoderma gangrenosum; extraintestinal GI problems such as nonspecific hepatitis, cholelithiasis, sclerosing cholangitis, and pancreatitis; skeletal involvement including aseptic necrosis of bone, arthralgias, and arthritis; ocular problems with uveitis and scleritis; renal disorders such as stones and nephritis; hematologic abnormalities such as anemia, thrombocytopenia, and hypercoagulability; and general failure to thrive. Crohn's disease is twice as common as ulcerative colitis and is characterized by abdominal pain, weight loss, growth failure, and anemia.[19] Ulcerative colitis often presents with rectal bleeding, bloody diarrhea, urgency/tenesmus, and abdominal pain.[19] In the acutely ill patient, diagnosis can be made with a combination of laboratory studies (blood count, erythrocyte sedimentation rate, C-reactive protein, albumin, liver function tests) and CT or MRI enterography.[19] Imaging can show areas of inflammation and can identify complications such as abscess or perforation.[20] Definitive diagnosis requires upper endoscopy, colonoscopy, and biopsy.

TREATMENT

Severe bleeding requires acute resuscitation and teamwork with the pediatric surgeon and/or gastroenterologist, depending on the suspected cause of bleeding. Treatment goals for UGI and LGI bleeding are: (1) resuscitation from hemorrhagic shock and restoring the intravascular volume; (2) restoring normal oxygen-carrying capacity by transfusion with packed red blood cells; (3) identifying the source of bleeding; and (4) stopping ongoing blood loss.

TABLE 134-5 Infectious Causes of Bloody Diarrhea in Children

Infectious Agent	Historical Facts	Symptoms	Diagnosis	Treatment
Salmonella	<4 y Foodborne Reptiles/Amphibians	Fever Abdominal pain	Stool culture	Supportive; antibiotics if enteric fever, sepsis, <3 months old, or immunosuppressed
Shigella	<5 y Child care center Travelers	Fever Abdominal pain	Stool WBC count (nonspecific) Shiga toxin Stool culture	Supportive; antibiotics unless very mild disease
Yersinia	Uncommon Livestock transmission Foodborne Contaminated water	Abdominal pain (pseudoappendicitis) Fever Scarlatiniform rash	Stool culture	Supportive; antibiotics for neonates, immunosuppressed, sepsis, or extraintestinal manifestations; otherwise, clinical benefit not established
Campylobacter jejuni	Unpasteurized milk, improperly cooked poultry Contaminated water	Often self-limited +/– Fever Abdominal pain 10%–20% have severe, prolonged, or relapsing illness	Stool culture	Supportive; antibiotics
Escherichia coli (Shiga toxin)	Ground beef Petting zoos Contaminated raw fruits	Abdominal pain Fever Hemolytic-uremic syndrome	Stool culture for O157:H7 Shiga toxin	Supportive; antibiotics not proven beneficial and may increase risk of hemolytic-uremic syndrome
E. coli (enteroinvasive)	Foodborne Contaminated water Travelers	Fever Vomiting	Stool cultures not helpful (normal flora)	Supportive; antibiotics
Entamoeba histolytica	Resource limited countries Low socioeconomic status Travelers from endemic areas	Increasing severity of diarrhea Lower abdominal pain Tenesmus	Stool for ova and parasites may be negative (serial testing may be necessary) Stool antigen test kits Serology with enzyme immunoassay kit	Supportive; antibiotics followed by luminal amebicide
Aeromonas hydrophila	Warm weather Waterborne	Chronic diarrhea	Stool culture (requires special media)	Antibiotics only in special populations
Clostridium difficile	Recent antibiotic usage or hospitalization	Pseudomembranous colitis Toxic megacolon (rare)	Stool culture not helpful *C. difficile* toxin studies on diarrheal stool	Antibiotics if symptomatic Note: *C. difficile* can be normal flora in infants.

Management begins with an assessment of the airway, breathing, and circulation, followed by the rapid administration of serial 20 mL/kg crystalloid fluid boluses. If three boluses of crystalloid do not restore volume, administer 10 mL/kg of packed red blood cells.

Avoid overexpansion of intravascular volume, particularly if the bleeding is from varices. Correct for shock and restore urine flow, but then titrate additional fluid volume or blood administration based on estimated blood loss and response of the vital signs (**Figure 134-3**).

UPPER GI BLEEDING

Emergency endoscopy is needed for children with moderate to severe, persistent or recurrent bleeding, and may be both diagnostic and therapeutic (e.g., coagulation, sclerotherapy, banding).

Variceal Bleeding For unstable patients in whom endoscopy cannot be performed, **octreotide** is the drug of choice for esophageal variceal bleeding. Octreotide is administered as a bolus followed by a continuous infusion (1 to 2 micrograms/kg bolus up to 50 micrograms, followed with a continuous infusion of 1 to 2 micrograms/kg/h, which may be increased hourly by 1 microgram/kg up to 4 micrograms/kg/h).[6,20] The major adverse effect of octreotide is hyperglycemia, which requires monitoring of serum glucose. If octreotide is unavailable, consult with a pediatric gastroenterologist regarding the use of a **vasopressin** infusion (0.002 to 0.005 unit/kg/min titrated as needed, maximum 0.01 unit/kg/min). If bleeding stops for 12 hours, then vasopressin is tapered off over 24 to 48 hours.[21] Intensive care unit admission is needed. Vasopressin use is limited by the side effects of peripheral and central vasoconstriction. There are limited pediatric data on the use of both octreotide and vasopressin.[3]

Nonvariceal Bleeding Medical treatment of bleeding from mucosal lesions, such as peptic ulcers, can include proton pump inhibitors, histamine-2 receptor antagonists, antacids, and sucralfate. **Proton pump inhibitors** are more efficacious than histamine-2 receptor antagonists.[6] Intravenous pantoprazole, given as a bolus dose followed by an infusion, is used for control of active bleeding (**Table 134-6**).[21]

If bleeding is persistent and endoscopy fails to identify a bleeding site, angiography may be indicated, although it is technically difficult in young children and a minimum rate of bleeding of 1 to 2 mL/min is required for diagnosis using this modality.[3]

LOWER GI BLEEDING

Hemorrhagic shock is not common as a result of LGI bleeding. There are some important exceptions, however. Meckel's diverticulum may result in significant blood loss in children of any age and requires surgical excision. Painless hematochezia should point to this diagnosis, and a Meckel scan is diagnostic. Definitive treatment is surgical resection. Bleeding associated with Henoch-Schönlein purpura can be severe, but resuscitation and stabilization are the mainstays of treatment. GI duplications and vascular malformations may also cause significant bleeding.

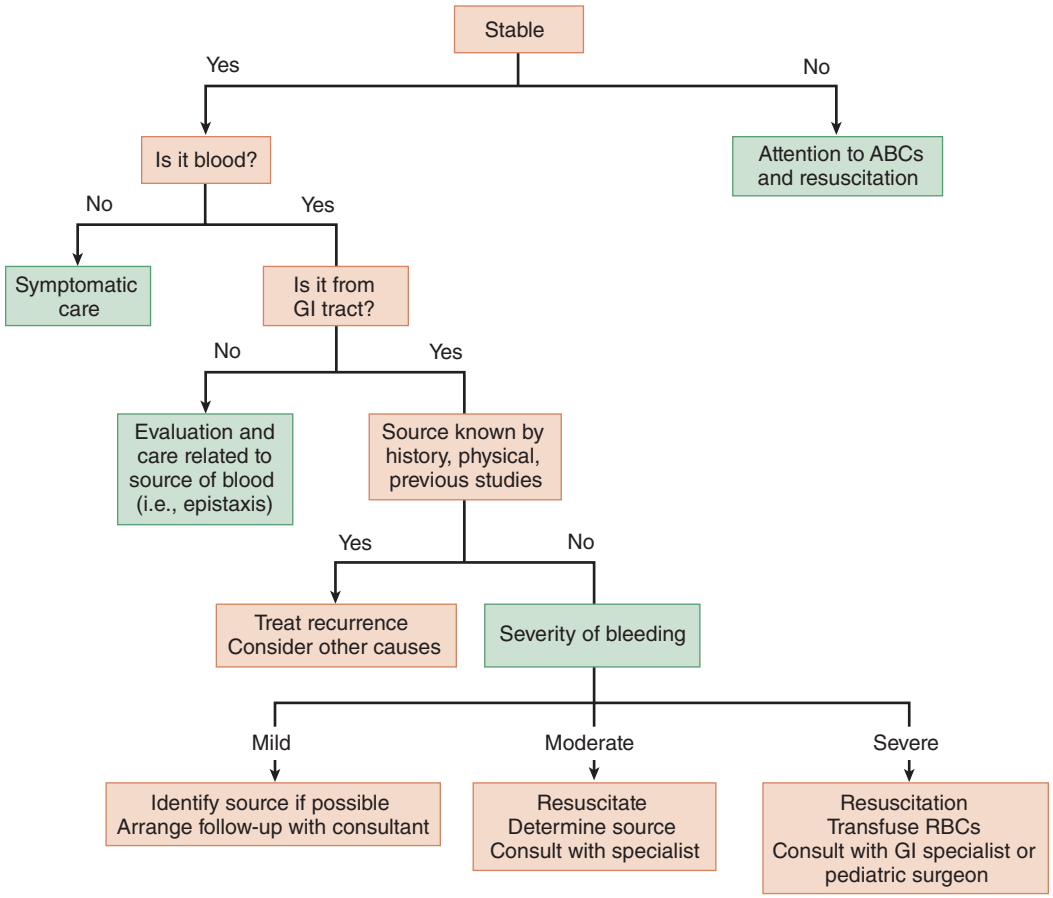

FIGURE 134-3. Initial management of GI bleeding. ABCs = airway, breathing, and circulation; RBCs = red blood cells.

DISPOSITION AND FOLLOW-UP

The management of potential surgical abdominal emergencies such as intussusception and volvulus are discussed in Chapter 133. Children with LGI bleeding associated with abdominal pain should not be discharged from the ED until symptoms have resolved or definitive diagnosis has been made. Small amounts of bright red blood per rectum in an otherwise healthy child or signs of chronic blood loss in well-compensated patients can be referred to a gastroenterologist for outpatient colonoscopy. Infants with suspected milk or soy protein allergy who appear well and in whom close follow-up can be arranged do not require specific therapy in the ED; dietary changes are best left to the primary care physician who will follow these patients longitudinally.

When follow-up in 24 to 72 hours can be ensured, the majority of children with mild GI bleeding can be discharged from the ED without a definitive diagnosis. Hemodynamically stable children without systemic symptoms or significant abdominal pain do not require inpatient treatment or evaluation. Conditions that can generally be diagnosed simply or presumptively in the ED and managed safely in the outpatient setting include swallowed maternal blood in the infant, Mallory-Weiss tears, gastritis, peptic ulcer disease, anal fissures, juvenile polyps, milk or soy protein allergy, and infectious gastroenteritis effectively treated with oral rehydration therapy. Stable patients with suspected inflammatory bowel disease can often have definitive diagnosis made in the outpatient setting as well.

TABLE 134-6 Pantoprazole Dosing

Patient Weight	Bolus	Infusion
5–15 kg	2 milligrams/kg/dose IV	0.2 milligram/kg/h IV
>15–40 kg	1.8 milligrams/kg/dose IV	0.18 milligram/kg/h IV
>40 kg	80 milligrams/dose IV	8 milligrams/h IV

Patients with large-volume blood loss, even with a normal hematocrit on initial evaluation, and those with associated abdominal pain in whom surgical or serious causes cannot be excluded require admission to the hospital for continued evaluation and treatment.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 135

Urinary Tract Infection in Infants and Children

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INTRODUCTION AND EPIDEMIOLOGY

Pediatric urinary tract infections (UTIs) are now the most common serious bacterial infections in young children since the introduction of successful immunizations and the resultant decrease in pediatric sepsis, meningitis, and occult bacteremia. UTI should be considered as a possible diagnosis in all febrile infants and young children presenting to EDs and in all older children with abdominal or urinary symptoms whether or not there is fever.

TABLE 135-1 Risk Factors for Pediatric Urinary Tract Infection (UTI)

Factor	Risk
Gender	3 times higher risk in females
Age	Variably increased risk in infants and younger children
Circumcision status	4–20 times higher risk in uncircumcised males
Race/ethnicity	Half the risk in African American children compared with nonblack children
Fever	Increased risk with fever >39°C (102.2°F) for both boys and girls, and with fever duration >24 h in boys or >48 h in girls
History of UTI	2-fold increased risk
Genital sexual activity	Increased risk
Previous urinary tract infection	Increased risk

Estimates of UTI prevalence are highly variable depending on the population. Pediatric UTI occurs in up to 8% of febrile children presenting to the ED with no obvious source of infection.[1-3] Approximately 1% of boys and 3% of girls are diagnosed with a UTI before puberty.[4] The highest incidence occurs during the first year of life for both genders.[3] Some of the baseline characteristics that increase the risk of UTI are listed in **Table 135-1**.[1,2,5-11] It is unclear why African American children have a lower risk of UTI, but this difference is consistently noted.[11]

PATHOPHYSIOLOGY

Bacteria most commonly cause UTIs, although viruses and other infectious agents can also be urinary pathogens. The vast majority of UTIs in all age groups typically occur from retrograde contamination of the lower urinary tract with organisms from the perineum and periurethral area. In neonates, however, UTIs typically develop after seeding of the renal parenchyma from hematogenous spread.

Escherichia coli is the most common cause of UTI in children, and this is likely because of its ubiquitous presence in stool combined with bacterial virulence factors that improve adhesion to and ascent of the urethra.[4] Additional pathogens include *Klebsiella*, *Proteus*, and *Enterobacter* species. *Enterococcus* species, *Staphylococcus aureus*, and group B streptococci are the most common gram-positive organisms and are more common in neonates. *Staphylococcus saprophyticus* can cause UTI in adolescents, and *Chlamydia trachomatis* may be present in adolescents with urinary tract symptoms and microhematuria. Adenovirus may cause culture-negative acute cystitis in young boys.

Mechanical defenses in humans, such as normal urinary outflow, clear most bacteria that are introduced into the bladder. Anatomic abnormalities can make bacterial proliferation or persistence in the bladder more likely. Additional factors influencing the development of UTI include virulence of the pathogen, vesicoureteral reflux, urolithiasis, poor hygiene, voluntary urinary retention, and abnormal bladder function due to constipation. There are occasionally patients, usually preschool- or school-aged females, who have recurrent UTI without a clear anatomic abnormality or identifiable risk factors. Genetic investigation may allow identification of these at-risk individuals.[12] Rare causes of UTI in children include indwelling urinary catheters or UTI from embolism or secondary to infection of other body areas.

CLINICAL FEATURES

HISTORY AND COMORBIDITIES

Clinical features vary markedly by age. Focus the initial history on the acute illness, including the presence of fever, vomiting, or abdominal or back pain, and identify symptoms that may suggest another source of fever such as rhinorrhea, cough, or diarrhea. Neonates with UTIs may appear septic, with fever, jaundice, poor feeding, irritability, and lethargy.[13] In young infants, fever may be the only sign of UTI, while older infants and young children typically develop GI complaints, with fever, abdominal pain, vomiting, and a change in appetite. GU symptoms in a verbal child should always trigger consideration of a UTI. In school-aged children and adolescents, cystitis and urethritis (lower tract disease) typically present with urinary frequency, urgency, hesitancy, and dysuria, although abdominal pain, back pain, and new-onset urinary incontinence are also associated with UTI in this age group. Pyelonephritis (upper tract disease) typically presents with fever, chills, back pain, vomiting, and dehydration. A parental report of "smelly" urine does not appear to be helpful.[14] **In nonverbal children, a history of high (>39°C [102.2°F]) or prolonged fever appears to be one of the most predictive symptoms of UTI.**[11] Recently, a risk calculator, *UTICalc* (https://uticalc.pitt.edu/),[15] was developed and validated to estimate the pretest probability of a UTI based on variables in the clinical history of a child suspected to have a UTI. These variables include the age, sex, and race of the patient; the height of the temperature; and whether another source for the fever exists. The tool then incorporates the results of urine testing and provides guidance to treatment by giving a posttest probability of a UTI.

Ask about past medical history including whether a late-term prenatal US was obtained because a normal late-term US decreases the likelihood of some GU abnormalities that increase the risk of UTI. Identify additional predisposing factors including chronic constipation, dysfunctional voiding, known vesicoureteral reflux, previous UTIs, and sexual activity in adolescents.

PHYSICAL EXAMINATION

Assess the child's health and degree of acute illness. If the child is lethargic, dehydrated, or in respiratory distress, then institute appropriate therapy. Examine the genitalia for anatomic abnormalities (e.g., labial adhesions, phimosis) or other causes of GU symptoms. Note circumcision status in male infants. Perform a careful abdominal and groin examination to evaluate for suprapubic tenderness,[11] costovertebral angle tenderness, hernias, and any abnormal masses. A complete physical examination helps to exclude other causes of illness. **Although the presence of another source of fever lowers the risk of UTI, it does not eliminate it, and UTI can coexist with common viral syndromes such as respiratory syncytial virus bronchiolitis.**[11,16,17]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In infants and young children, the only cardinal feature of UTI is a febrile illness without another definitive source. UTI is a possible diagnosis in all infants with fever. In children with dysuria but no fever, the most common concerns are listed in **Table 135-2**.

TABLE 135-2 Causes of Culture-Negative Dysuria and Pyuria in Children

Culture-Negative Dysuria

- Viral urethritis/cystitis
  - May be hemorrhagic in some viral infections such as adenovirus
- Meatitis/urethritis
  - Often in young boys due to irritation from clothes or self-stimulation
  - Can be from vaginitis in the vaginal vault in girls. The common causes of vaginitis in young girls include irritant vaginitis from poor hygiene and residual urine that is persistently not cleaned after voiding or irritant vaginitis from soaps or other chemicals. Occasionally, premenarchal girls have bacterial vaginitis. Candidal vaginitis generally does not occur in prepubertal girls.
- Balanitis

Culture-Negative Pyuria

- Kawasaki's disease (from urethritis)
- Pelvic abscess or infection
  - Appendicitis, pelvic inflammatory disease, colitis, etc.
- Sexually transmitted infections (e.g., *Chlamydia*, gonorrhea*)
  - In sexually active adolescents, strongly consider these if there is pyuria with a negative culture.
- Intrinsic renal disease (e.g., glomerulonephritis)
- Allergic bladder or renal disease (e.g., interstitial nephritis)

*Sexually transmitted infection can cause both dysuria and pyuria.

The approach to neonates and infants <3 months of age with fever and no identifiable source is discussed in detail in Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children." Urine testing (including microscopy and culture) is an important part of a more comprehensive evaluation in this age group. As mentioned earlier, UTI should be considered in infants with bronchiolitis, particularly in the presence of high fever (temperature of 39°C [102.2°F]).[17,18] In verbal children, dysuria combined with suprapubic tenderness on examination is the classic constellation of symptoms and signs suggestive of cystitis.

There are no clinical criteria that confirm the diagnosis of UTI in children without urinary testing and culture.[19] Evidence-based clinical practice guidelines for the evaluation and treatment of pediatric UTI from the American Academy of Pediatrics are limited to infants and young children 2 to 24 months of age and require *both* pyuria and bacteriuria with ≥50,000 colonies/mL of a single uropathogenic organism for definitive diagnosis of a UTI.[20] Positive urine cultures in the absence of pyuria/bacteriuria may represent asymptomatic bacteriuria. For infants <2 months old, a positive urine culture is the gold standard for diagnosis.

In adolescents, symptoms of dysuria without vaginal or urethral discharge, or an examination consistent with UTI or pyelonephritis, such as suprapubic or costovertebral angle tenderness, in the presence of a positive urine chemical strip for pyuria and/or nitrites, allow a *presumptive* diagnosis of UTI. A careful sexual history is important in this age group, because urethral symptoms (such as dysuria) may predominate in both UTI and sexually transmitted infections. Urine culture remains important for definitive diagnosis, and pyuria without uropathogenic culture growth may suggest sexually transmitted infection. Consider pelvic examination for sexually active girls and appropriate testing in both boys and girls with dysuria who are sexually active (see Chapter 153, "Sexually Transmitted Diseases").

LABORATORY EVALUATION

Urine Sample Collection If children can *void on command*, then collection of clean catch urine is appropriate. Perineal cleaning before voiding and midstream collection reduce the rate of false-positive urinary dipstick tests and the rate of contaminated culture results.[21]

In infants and children who are not able to void on command, bladder catheterization is the preferred method for urine collection. Suprapubic aspiration, although invasive, is also acceptable. The value of perineal bag specimens is limited by the high false-positive results with a high likelihood of significant contamination with perineal bacterial flora. In infants, clean catch urine collection can be time consuming and unsuccessful. Methods such as the **Quick-Wee method**, using gentle suprapubic cutaneous stimulation with gauze soaked in cold fluid, have been shown to increase the speed and success of obtaining a clean catch urine.[22] In infants, particularly if less than 90 days old, using a stimulation technique involving gentle tapping over the suprapubic area and lumbar paravertebral massage has also been shown to be effective.[23] The only (rare) circumstance where a perineal bag specimen may be used is to **exclude disease** when the pretest probability of UTI is very low, in which case a negative test rules out disease; if the results are positive, confirmation **before giving antibiotics** requires culture of a specimen collected in a sterile manner. Due to this diagnostic delay, many clinicians prefer obtaining a definitive specimen initially.

Urine Culture **The definitive test for UTI is a urine culture,** and colony counts indicating infection are based on the type of sample collection (**Table 135-3**). **Do not give antibiotics until a urine culture is obtained using a sterile method.** Based on the clinical scenario, length of illness, and urinalysis results, lower colony counts or mixed-growth cultures cannot necessarily be dismissed.

Rapid Urine Tests (Dipsticks or Urinalysis) Urine culture results are not available at the first ED visit, so chemical test strips that can detect leukocyte esterase and urinary nitrites, in conjunction with microscopic urinalysis, help predict the results of the urine culture. Leukocyte esterase is an indirect measure of pyuria and can be negative if leukocytes are present in low concentration. Nitrite in the urine depends on coagulase-splitting bacteria that can reduce urinary nitrate to nitrite. A positive nitrite test makes UTI very likely (specificity 98%; range, 90% to 100%).[20] Enterobacteria generally reduce nitrate to nitrite only if the urine has been in the bladder long enough (about 4 hours), but most gram-positive bacteria do not reduce nitrate to nitrite, so nitrite testing has insufficient sensitivity for detection of UTI (53%; range, 15% to 82%).[20] Urinary nitrites and leukocyte esterase alone are not sensitive markers for children who empty their bladders frequently. Urine microscopy for leukocytes and bacteria, and/or Gram stain of unspun urine are also helpful for immediate diagnosis. **Table 135-4** summarizes the test characteristics of the urinalysis.

Table 135-3 Urine Culture Results Indicating Urinary Tract Infection[20]

Sample Collection	Positive Culture*
Clean catch	≥50,000 cfu/mL
Catheterization	≥50,000 cfu/mL
Suprapubic catheterization	Any single species bacterial growth if combined with acute symptoms or signs of urinary tract infection

Abbreviation: cfu = colony-forming unit.

*Urine culture results listed here should be considered indicative of urinary tract infection only in the setting of pyuria.

Regardless of the results from the rapid urine tests, send the sample for a urine culture. There are two situations where one might not send urine for culture: (1) in low-risk patients with a completely normal urinalysis and another explanation for the symptoms; and (2) in older adolescent females with a very high posttest probability of UTI, without severe illness or complicating medical problems, and in an area with a predictable antibiotic resistance pattern. Because pyuria alone does not confirm a UTI, refer to Table 135-2 for some causes of culture-negative pyuria.

Imaging Acute imaging of the urinary tract is rarely necessary in UTI assessment or treatment. If children have persistent fever or are worsening despite appropriate therapy or symptoms are unusually severe, then renal US is indicated to rule out abscess, stone, or obstruction. Recommendations for renal and bladder US vary. The American Academy of Pediatrics recommends follow-up US for all children 2 to 24 months old after the first UTI, whereas the National Institute for Health and Care Excellence in the United Kingdom suggests US for those <6 months of age and those with recurrent or atypical UTI.[24] Routine urethrocystography after first UTI is not recommended.[20,25] Voiding cystourethrography is useful to identify and classify vesicoureteral reflux and is indicated if renal-bladder US reveals hydronephrosis, scarring, or other findings that would suggest either high-grade vesicourethral reflux or obstructive

Table 135-4 Characteristics of Urinary Diagnostic Tests, Alone and in Combination[20]

	Test Characteristic Ranges			
	Sensitivity (%)	Specificity (%)	Test Result	Likelihood Ratio*
Individual Tests[19]				
Leukocyte esterase	67–94 (83)	64–92 (78)	+	3.8
			–	0.2
Nitrite†	15–82 (53)	90–100 (98)	+	26.5
			–	0.5
Leukocytes on microscopy	32–100 (73)	45–98 (81)	+	3.8
			–	0.3
Bacteria on microscopy	16–99 (81)	11–100 (83)	+	4.8
			–	0.2
Combined[19]				
Leukocyte esterase, nitrite or microscopy positive	99–100 (99.8)	60–92 (70)	+	3.3

*Positive and negative likelihood ratio calculated from mean sensitivity and specificity.

†Test characteristics are for all subjects. However, test likely has no use if urine infection is due to gram-positive organism or if urine has not stayed in the bladder.

uropathy. This testing can be arranged on an outpatient basis or is performed during hospitalization.

Other Suggested Testing Testing beyond urinalysis and culture is not necessary for afebrile children with isolated UTI before initiating treatment. Children with atypical presentations or significant comorbidities may require further investigation as directed by the clinical picture. Febrile neonates and young infants (<2 months of age) require further evaluation prior to initiating antibiotics. Approximately 10% of young infants with febrile UTI admitted to the hospital demonstrate a sterile cerebrospinal fluid pleocytosis thought to be due to systemic release of inflammatory mediators.[26,27] Less than 1% of febrile infants with UTI will also have bacterial meningitis. **Perform lumbar puncture and obtain blood cultures in febrile neonates with UTI before starting empiric antibiotics (see Chapter 119).** Lumbar puncture is not needed in febrile older infants and children with UTI unless there are signs or symptoms suggestive of meningitis or if the child is clinically ill or the illness does not respond to treatment.[28]

Most febrile infants with UTI have upper tract involvement, and laboratory tests are unlikely to differentiate those with bacteremia from those without bacteremia.[29] About 5% to 10% of febrile infants with UTI have bacteremia.[26] There is low risk of bacteremia and adverse events in well-appearing infants and children with febrile UTI, and blood cultures are not necessary in these children who are candidates for oral outpatient therapy.[28,30,31]

TREATMENT

Obtain a urine culture before giving antibiotics in stable infants and children as typical choices for antibiotics quickly sterilize the urinary tract and make specific bacteriologic diagnosis difficult.[20] Treatment and disposition depend on the age of the patient and severity of the illness. Most children can be treated orally.[32,33] Goals of therapy are to reduce symptoms, eliminate the acute infection, prevent complications and septicemia, and decrease the risk of renal scarring. The odds of new renal scarring increase significantly if treatment is delayed 48 hours or more. Renal scarring may be associated with adverse long-term outcomes such as hypertension, proteinuria, risk of preeclampsia in pregnant women, and renal insufficiency. Pyelonephritis can be demonstrated by renal scan in up to 61% of children <2 years old with febrile UTI, so children <2 years old with febrile UTI have presumptive pyelonephritis.[29] Treatment guidelines for first UTIs are listed in **Table 135-5. Table 135-6** lists suggested parenteral and oral antibiotics. For children with relapsing or recurrent UTI or with underlying GU anatomic abnormalities, treat according to culture and sensitivity reports.

E. coli is the most common etiologic agent causing UTI, so antibiotics should be directed toward its eradication. Medications listed in Table 135-6 are generally acceptable, but emerging resistance is a continuing problem, and local sensitivities should guide antibiotic selection. Typical effective first-line agents to treat *E. coli* include cephalosporins, aminoglycosides, and extended-spectrum penicillins. Many strains of *E. coli* are now resistant to amoxicillin and trimethoprim-sulfamethoxazole, limiting the use of these two agents for empiric UTI treatment. A fluoroquinolone should be used in children *only* if sensitivities indicate that this is the sole effective agent. Agents that do not achieve therapeutic concentrations in the bloodstream, such as nalidixic acid or nitrofurantoin, should not be used for UTI in febrile children. Once culture results with sensitivities for the infection are known, antimicrobial therapy should be tailored and simplified, based on the actual bacteria isolated. **Children with anatomic urinary tract abnormalities need individualized treatment.**

***Enterococcus faecalis* is a gram-positive organism that can cause UTI in children approximately 5% of the time,[36] and *S. saprophyticus* can cause UTI in adolescents.** When *Enterococcus* is suspected because of prior infections with that organism or gram-positive bacteria are identified on urine Gram stain, add ampicillin-amoxicillin or vancomycin to other therapy. The presence of *Enterococcus* increases the likelihood of an underlying urinary tract abnormality in a patient.[36] *S. saprophyticus* is typically sensitive to standard treatments.

TABLE 135-5 Treatment of First Urinary Tract Infection in Children With Normal GU Anatomy

Age	Comment
<2 mo	Hospital admission and IV antibiotics for 3–5 d followed by variable course of oral antibiotics for 14 d.
2–24 mo	If toxic, admit to hospital and treat with IV antibiotics. If nontoxic, not vomiting, and well hydrated, treat with oral antibiotics (Table 135-6). An initial dose of ceftriaxone, 75 milligrams/kg in ED, can be considered. Ensure follow-up in 24–48 h.
>2 y old	Select an oral antibiotic from Table 135-6 based on local resistance patterns. Children >2 y old to age 13 y, treat for 7 d. Follow up in 2–3 d. Adolescent girls (≥13 y old), option to treat for 3 d.

TABLE 135-6 Antibiotic Treatment of Pediatric UTI[33,35]

Parenteral Antibiotics		
Antimicrobial	**Dosage in Normal Renal Function**	**Neonatal Considerations**
Ampicillin*	25–50 milligrams/kg per dose IV every 6 h (every 8 hours for neonates <7 d old)	50 milligrams/kg per dose IV every 8 hours for neonates up to 7 days of age
Gentamicin	2.5 milligrams/kg per dose IV given every 8h or 7.5 milligrams/kg per dose IV every 24 hours	4 milligrams/kg per dose every 24 hours for neonates <7 days of age 5 milligrams/kg per dose every 24 hours for neonates 7-28 days old
Ceftriaxone	50-75 milligrams/kg per dose IV every 24 h	Contraindicated
Cefotaxime	50 milligrams/kg per dose IV every 8 h	Ampicillin + Gentamicin preferred
Ceftazidime	50-75 milligrams/kg per dose IV every 8 h	Ampicillin + Gentamicin preferred
Cefepime	50 milligrams/kg per dose IV every 12 h to a maximum of 1g per dose	Ampicillin + Gentamicin preferred
Oral Antibiotics		
Antimicrobial	**Dosage in Normal Renal Function**	**Oral antibiotics not recommended for neonates and infants <2 months of age**
Cephalexin	25 milligrams/kg per dose PO every 8 h, max 500 milligrams/dose	
Cefdinir	14 milligrams/kg per dose PO every 24 h	
Cefixime	16 milligrams/kg per dose PO on day one followed by 8 milligrams/kg every 24 h	
Cefpodoxime	5 milligrams/kg per dose PO every 12 h	
Cefibuten	9 milligrams/kg per dose PO every 24 h	
Amoxicillin-clavulanate	25 milligrams/kg per dose PO every 8 h	
Trimethoprim/ Sulfamethoxazole	6 milligrams/kg PO every 12 hrs	

*Ampicillin should be added to empiric treatment with another parenteral agent when enterococcal infection is suspected.

DISPOSITION AND FOLLOW-UP

Admit all neonates and infants <2 months of age as well as those who appear septic or have known immunodeficiency to the hospital for parenteral antibiotics. Infants and children over 2 months of age with

uncomplicated UTI may be appropriate for outpatient care with oral antibiotics if they appear well, can tolerate oral medication, are not dehydrated, and are not immunocompromised. Outpatient IM or IV ceftriaxone (75 milligrams/kg) or gentamycin can be used as an alternative to hospitalization for patients who are unable to tolerate oral therapy but are otherwise nontoxic and well hydrated. Length of antimicrobial therapy should be 7 to 14 days with close pediatric follow-up to ensure appropriate antibiotic use and to consider the need for imaging. Adolescent girls (>13 years old) with UTI may be treated like adults with the option for a 3-day oral antibiotic regimen. Outpatient repeat urine testing as proof of cure is not routinely necessary or recommended.

Of note, after confirmation of a febrile UTI in infants, parents or guardians should be counseled to bring back their child (ideally within 48 hours) for future febrile illnesses to ensure prompt medical evaluation and treatment of possible recurrent UTI.

SPECIAL SITUATIONS

PEDIATRIC UTI WITH UROLITHIASIS

Although uncommon, urolithiasis occurs in children, and the incidence is increasing and may be associated with the increasing prevalence of childhood obesity.[37-39] Children with symptoms suggestive of urolithiasis (colicky abdominal or flank pain, often radiating to the groin, and gross or microscopic hematuria) require imaging to evaluate for the possibility of stones (see Chapter 133, "Acute Abdominal Pain in Infants and Children," and Chapter 137, "Renal Emergencies in Children"). While non–contrast-enhanced CT is the imaging modality of choice in adults, consideration of the potential long-term effects of radiation exposure must be weighed carefully, and renal US or MRI should be considered as alternatives.[40] In the setting of fever, pyuria, and an obstructing stone, initial treatment should be parenteral with inpatient management and consultation with pediatric urology. Additional urine studies may be obtained to identify predisposing factors and chemical composition of stones, which may guide future management.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 136

Pediatric Urologic and Gynecologic Disorders

Deborah R. Liu

SCROTUM

Scrotal pain is one of the most common urologic emergencies seen in boys. Although many causes of scrotal pain may not require an immediate organ-preserving procedure, some causes can lead to rapid and permanent loss of testicular function without timely intervention. Thus, the clinician must identify patients who need emergent diagnostic and/or therapeutic procedures and those who need observation and reassurance.

TESTICULAR TORSION

Consider testicular torsion in males with acute scrotal pain, because torsion is a urologic emergency. The estimated incidence of torsion in U.S. males younger than 18 years is 3.8 per 100,000 children.[1] Testicular torsion has a bimodal age presentation, with one peak in the immediate neonatal period and another peak during early puberty. Because the testicle of neonates with true prenatal torsion is not salvageable, many urologists agree that neonates can be taken to the operating room on a semi-elective basis when the infant is a few months of age to decrease the anesthesia risk. However, in neonates who experience postnatal torsion, the salvage rate is likely similar to adolescent testicular torsion, making early surgical detorsion a priority. The clinical distinction between prenatal and postnatal torsion, however, is sometimes difficult to elucidate.[2]

Most boys with testicular torsion present between 12 and 18 years of age. Classically, the pain is abrupt in onset and severe and is usually associated with nausea or vomiting. The testicle is extremely painful, and often the patient will walk with a wide-based gait to minimize the contact of the scrotum to the thigh. There may be a preceding history of a sports activity or even minor trauma to the area, which may lead the clinician to a misdiagnosis of traumatic injury. In some cases, the patient may recall episodes of previous scrotal pain that rapidly resolved without intervention, which may represent intermittent torsion with spontaneous detorsion. Patients with intermittent testicular pain should be referred for elective orchiopexy, as such patients with intermittent torsion are at risk for acute complete testicular torsion.[3]

Classic physical examination findings of acute testicular torsion include a swollen, tender, high-riding testis, with an abnormal transverse lie. There are often scrotal skin changes. Ipsilateral loss of the cremasteric reflex is often noted, but the presence of a normal cremasteric reflex does not rule out torsion.[4]

Doppler US is the diagnostic imaging study of choice,[5] with radionuclide imaging a distant second. If the time to obtain diagnostic imaging may lead to delay of surgical intervention, advocate for emergent surgical exploration for highly suspected cases of torsion, rather than waiting for an imaging study to be completed. Time is especially critical if the duration of symptoms is <6 hours, as the salvage rate is excellent in such cases. Beyond 6 hours, the salvage rate becomes progressively worse, and after 48 hours of symptoms, the salvage rate is near zero. Patients presenting with equivocal signs of torsion may benefit from a Doppler US, which can visualize blood flow to the testis. In acute torsion, Doppler demonstrates an enlarged testis with decreased or absent flow compared with the unaffected side. In patients with suspected intermittent torsion who have a normal Doppler US and resolution of pain, counsel the patient and family to seek medical attention immediately should the pain recur, and recommend urologic follow-up as an outpatient.

Several recent studies have attempted to develop clinical predictors for acute torsion, with the hopes of decreasing time to surgical intervention for true cases of torsion, reducing the rate of negative explorations, and decreasing the number of unnecessary imaging studies.[4,6-9] The TWIST (Testicular Workup for Ischemia and Suspected Torsion) scoring system was developed in 2013 to predict testicular torsion based on the following findings: testicular swelling (2 points), hard testicle (2 points), absent cremasteric reflex (1 point), nausea/vomiting (1 point), and high-riding testis (1 point).[8] This scoring system was retrospectively validated when used by urologists, and it was suggested that high-risk patients (score of ≥5) should have immediate surgical exploration, intermediate-risk patients (score of 3 or 4) should undergo Doppler US, and low-risk patients (score ≤2) do not require any testing.[8] In 2016, the TWIST score was validated using non-urologists, but it was noted that the trained emergency medical technicians had different cutoffs for high risk (score of ≥6), intermediate risk (score of 1 to 5), and low risk (score of 0).[9] These studies have provided a more objective framework in the management of suspected torsion. To optimize timeliness and minimize unnecessary testing, advocate for immediate surgery in patients with highly suspected torsion, obtain emergent Doppler US for patients with equivocal signs of torsion, and consider no testing for patients with very low suspicion for torsion.

Manual detorsion may be indicated for patients with torsion when there is no surgeon immediately available and when the duration of symptoms is too long for surgical salvage. Administer parenteral opioid analgesia, local anesthesia (infiltrating the spermatic cord near the external ring with lidocaine), or procedural sedation. Because the testis tends to torse in the medial direction, manual detorsion is accomplished by holding the testis between the thumb and index finger and rotating the testis in an outward direction toward the thigh (as if opening a book). However, the spermatic cord may be twisted >180 degrees, making it difficult to recognize how many times the testis should be outwardly rotated. Also, a very swollen hemiscrotum may make isolating the testis between two fingers challenging. The unsedated, older, verbal patient

may be able to describe relatively immediate relief upon successful detorsion. Bedside or formal Doppler US may be useful in determining improvement of flow. The success rate of manual detorsion is quite variable and is not definitive therapy. Even after manual detorsion, patients need emergent surgical exploration to confirm complete detorsion and to perform bilateral orchidopexy.

TORSION OF TESTICULAR APPENDAGE

The appendix testis and appendix epididymis are testicular embryologic remnants that can twist, resulting in venous congestion and subsequent infarction of the appendage. Torsion of a testicular appendage is most common in males between 7 and 12 years of age, although it can occur at any age. Typically, the patient's symptoms are more insidious than true testicular torsion, with less severe pain and lack of systemic symptoms. Early in the course before scrotal edema and erythema develop, it may be possible to localize the point of tenderness to the upper pole of the testis or epididymis. In addition, one may observe the infarcted appendage through the scrotal skin ("**blue dot sign**"). If Doppler US is obtained, there should be normal testicular flow with a small hyperechoic region adjacent to the testis. Management consists of scrotal support, limitation of activity, and oral analgesics (e.g., nonsteroidal anti-inflammatory drugs). If torsion of the testicular appendage is diagnosed early in its course, the pain may worsen before ultimate improvement due to ongoing inflammation, and this is an important point of counseling to prevent return to the ED.

EPIDIDYMITIS

Epididymitis, or inflammation of the epididymis, is a common cause of scrotal pain in pre- and postpubertal boys that does not require surgical intervention. In a 2014 study of 252 patients with epididymitis presenting to an outpatient pediatric urology referral practice, the mean age at first presentation was 10.92 years, with the majority of cases occurring between 10 and 14 years.[10] In sexually active males, acute epididymitis may result from ascending urethral infection due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. Epididymitis may also result from enterovirus or adenovirus infection.[11] Symptoms are insidious in onset, with dysuria, frequency, or fever. Prehn's sign (relief of pain by elevating the scrotum) is not consistently reproducible in boys. Typically, the affected testis is mildly enlarged and tender with hemiscrotal erythema and swelling (**Figure 136-1**). Urinalysis may demonstrate pyuria and bacteriuria. Obtain urine culture and sensitivity, and in suspected sexual transmission, obtain specific testing for *C. trachomatis* and *N. gonorrhoeae*.

Doppler US, if the diagnosis is in doubt, shows an enlarged epididymis with increased blood flow, and normal blood flow to the testis. It is often difficult to differentiate torsion of a testicular appendage from epididymitis by US, but neither disorder requires surgical intervention. Treatment of epididymitis is somewhat controversial, with some advocating analgesics and limited activity only and others supporting treatment with antibiotics. In this era of antibiotic stewardship, consider selectively treating certain cases of epididymitis with empiric antibiotics. In a 2011, retrospective, single-center, pediatric ED study of 140 patients, the incidence of positive urine culture in acute epididymitis was only 4.1%. The authors suggest empiric antibiotics for all young infants regardless of urinalysis results, as well as for all non–sexually active males with a positive urinalysis.[12] Sexually active males should be treated presumptively for *C. trachomatis* and *N. gonorrhoeae*.

HYDROCELE

Hydrocele (**Figure 136-2**), the accumulation of fluid around the testis, is the most common cause of painless scrotal swelling in children. Parents often note intermittent swelling of one or both sides of the scrotum. This painless swelling may resolve when supine or sleeping and become more prominent when awake or crying. Hydrocele is termed *noncommunicating*, if there is residual but static swelling after the processus vaginalis has closed, or *communicating*, if swelling increases and decreases through a patent processus vaginalis. The diagnosis is confirmed by transillumination, whereby an otoscope or other light source is placed on the affected hemiscrotum and the hydrocele fluid is illuminated like a lantern; by contrast, a thickened scrotal wall or pure testicular enlargement will not transilluminate.

Most simple hydroceles resorb by 18 to 24 months of age. A communicating hydrocele is often associated with inguinal hernia, and as long as the hernia is reducible, it does not require emergent surgical repair. Management of most hydroceles includes outpatient scrotal US with referral to urology.

VARICOCELE

Varicocele is another cause of painless scrotal swelling and typically presents at the onset of puberty. It is due to abnormal dilation of spermatic cord veins, also known as the *pampiniform plexus*, due to faulty



FIGURE 136-1. Epididymo-orchitis. A 5-year-old boy with 1 day of left testicular pain and swelling, consistent with epididymo-orchitis.



FIGURE 136-2. Hydrocele. A 3-month-old boy with bilateral hydroceles (left greater than right).

valvular venous return. Most varicoceles occur on the left, possibly due in part to the acute angle of confluence with the left renal vein and resulting higher venous pressure. Classically the mass of enlarged veins can be palpated superior and posterior to the testis ("bag of worms") and is more prominent when standing or with the Valsalva maneuver; even large varicoceles may be missed in the supine position. Varicoceles are managed on an outpatient basis by urology. The implications of possible subfertility should be discussed in the urologist's office.

INTRASCROTAL TUMORS

Intrascrotal tumors are uncommon in young children; however, testicular tumors are the most common solid tumor among adolescent males.[13] The testicular or paratesticular tumor usually presents as a painless, firm, unilateral scrotal mass. Evaluation includes serum α-fetoprotein and tumor β-human chorionic gonadotropin levels, scrotal US, and urgent urologic consultation.

DISORDERS OF THE PENIS

A swollen, red, or painful penis can usually be categorized as a disorder of the foreskin or of the shaft of the penis. The most common abnormalities of the foreskin are phimosis, paraphimosis, and balanoposthitis. Penile shaft disorders occur less commonly and include priapism, tourniquet syndrome, and zipper injury.

PHIMOSIS

Phimosis is caused by stenosis of the distal aspect of the foreskin, preventing retraction of the foreskin over the glans. There may be a history of ballooning of the foreskin during urination, with dribbling of entrapped urine after voiding is complete (**Figure 136-3**). Most uncircumcised infants have normal, physiologic phimosis. Nearly all cases of physiologic phimosis spontaneously resolve by 5 years of age and rarely require treatment other than daily cleaning while bathing. If a patient has persistent phimosis beyond school age and the parent desires treatment, topical steroid cream can be effective. Several studies have shown that application of a medium-potency topical steroid twice daily for 4 to 8 weeks can be a safe and effective treatment for phimosis.[14-16] Acquired cases of phimosis may be secondary to recurrent balanoposthitis, poor hygiene, or forcible retraction of the foreskin. Acquired cases are often refractory to medical management and may ultimately require circumcision. One of the few true emergencies related to phimosis occurs when the foreskin is nearly completely sealed off, causing acute urinary retention. Such cases may require dilation of the foreskin under procedural sedation or dorsal penile block to place a Foley catheter.



FIGURE 136-3. Phimosis in a toddler leading to ballooning of foreskin caused by entrapped urine.



FIGURE 136-4. A 12-year-old boy with paraphimosis for more than 24 hours.

PARAPHIMOSIS

Paraphimosis is a true urologic emergency. This occurs when a tight ring of phimotic foreskin is retracted proximal to the glans and becomes trapped in that position. Subsequent impairment of venous and lymphatic drainage causes progressive swelling of the glans and foreskin. If the paraphimosis is not promptly reduced, arterial blood supply becomes compromised, and the glans may necrose.

Symptoms of paraphimosis are pain, erythema, and swelling of the shaft and glans, distal to the constricting ring of foreskin (**Figure 136-4**). The area of the shaft proximal to the constriction appears normal. Because delay in reduction will lead to worsening edema resulting in a more difficult manual reduction, paraphimosis should be reduced as soon as possible. Mild paraphimosis may be manually reduced without the need for sedation or analgesia. More difficult cases will require either a dorsal penile nerve block or procedural sedation, depending on the age and degree of cooperativeness of the patient.

The dorsal penile nerve provides most of the somatosensory innervation to the shaft and glans penis. The dorsal penile block (**Figure 136-5**) is useful for minor painful procedures of the penis, such as paraphimosis reduction, dorsal slit procedure, or zipper entrapment release. Using a 25- or 27-gauge needle, inject lidocaine hydrochloride *without* epinephrine into the base of penis, at the junction between the penis and the suprapubic skin, off the midline to avoid the superficial dorsal vein. Inject the lidocaine just deep to the Buck fascia, which is located 3 to 5 mm beneath the skin.

A slight "pop" is usually felt as the needle passes through the fascial layer. Aspirate before injecting the lidocaine, because the dorsal arteries and veins are within close proximity to the nerve. Depending on the size of the child, between 1 and 5 mL of lidocaine should be used. Half of the volume is injected at the 10 o' clock position, with the other half injected at the 2 o' clock position. Another technique involves injecting only once at the midline through the Buck fascia, with injection of the full volume directed toward each direction after negative aspiration of blood. Like most nerve blocks, optimal analgesia is achieved after 5 minutes.

Once analgesia is achieved either by dorsal nerve block or procedural sedation, manual reduction of the paraphimosis may be attempted. To decrease penile edema, it is often helpful to use a bag of ice (for 3-minute increments to avoid cold injury) or manual compression before

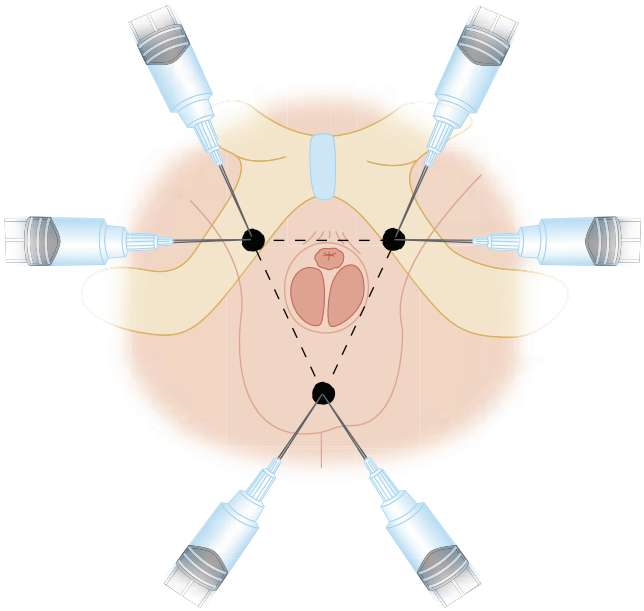

FIGURE 136-5. Dorsal penile block. Local anesthesia infiltration around the base of the penis. *Black dots* represent the locations of the skin wheals. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*, Copyright © 2004, The McGraw-Hill Companies, Inc. All rights reserved. Section 10. Genitourinary Procedures, Chapter 125, Anesthesia of the Penis, Testicle, and Epididymis, Figure 125-3.]

attempting reduction. Squeezing the glans and swollen foreskin using one's palm or a compression dressing for 5 minutes usually decreases the edema to allow successful manual reduction. The most common technique for manual reduction involves placing both thumbs over the glans, with both index fingers and long fingers surrounding the trapped foreskin. One pushes the glans back into the foreskin while pulling the foreskin back into normal position. This may require a few minutes of constant pressure before the glans slips through the paraphimotic ring (**Figure 136-6**).

Manual reduction may fail if there is extreme swelling of the foreskin and glans from prolonged paraphimosis. Emergent urologic consultation is necessary for such cases. Although more invasive procedures are ideally done by a surgeon, the emergency physician may need to perform such procedures if necrosis is imminent. One commonly used technique involves using a 21-gauge needle to make multiple punctures in the foreskin followed by gentle compression, thus draining some of the edema. Manual reduction can then be attempted again. A dorsal slit procedure may be necessary if other attempts at reduction fail. This involves making a vertical incision over the constricting ring to release the paraphimosis. All cases of paraphimosis, whether simple or complicated, require follow-up with a urologist to assess healing and the need for circumcision.

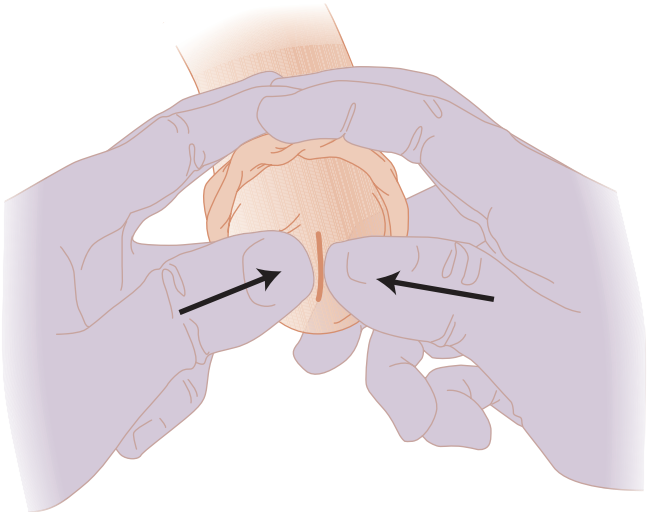

FIGURE 136-6. Manual reduction of paraphimosis. After appropriate analgesia is administered, place both thumbs over the glans, with both index and long fingers surrounding the trapped foreskin. The foreskin can then be reduced by placing pressure on the glans. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*, Copyright © 2004, The McGraw-Hill Companies, Inc., Figure 129-4.]

BALANOPOSTHITIS

Balanitis (cellulitis of the glans), posthitis (cellulitis of the foreskin), and balanoposthitis (cellulitis of the glans and foreskin) are common diagnoses in young males. Poor hygiene and phimosis predispose children to such infections (**Figure 136-7**). On examination, the glans, the foreskin, or both the glans and foreskin are swollen, tender, and edematous. In most cases, empiric treatment with oral antibiotics with a first-generation cephalosporin and warm soaks are sufficient. In cases in which there is an associated erythematous papular rash with satellite lesions, antifungal cream may also be indicated.

PRIAPISM

Priapism is a prolonged, unwanted erection not associated with sexual stimulation. Low-flow (venous) and high-flow (arterial) priapism are managed differently.

High-flow (nonischemic) priapism is generally due to an arteriovenous fistula from trauma (i.e., lacerated cavernous artery shunting blood into the cavernous bodies). This can lead to a persistent partial or full erection for days to weeks but is generally not painful. Because of the continuous inflow of arterial blood, ischemia or impotence does not occur. Therefore, high-flow priapism is not a true urologic emergency. Most cases are treated conservatively, and only a few cases require angioembolization of the lacerated artery.



FIGURE 136-7. A 4-year-old boy with posthitis and phimosis.

Low-flow (ischemic) priapism is caused by sludging of red blood cells, leading to impaired venous drainage, venous congestion, and ischemia. In children, the most common cause of priapism is sickle cell disease.[17] Other less common causes in children include illicit drugs (cocaine and cannabis), antidepressants, antipsychotics, and leukemia (presenting with extreme hyperleukocytosis).[17] Low-flow priapism causes a very rigid and extremely painful erection.

The type of priapism can usually be identified by history and physical examination. Doppler US can distinguish the type of priapism, with low-flow priapism showing decreased or no blood flow in the cavernosal arteries. The most reliable method, however, involves testing aspirated blood from the corpus cavernosum for blood gas analysis. Aspiration of the corpus cavernosum should be done only by an experienced urologist. Blood from low-flow priapism will be dark in color, with a partial pressure of oxygen (Po_2) <30 mm Hg, a partial pressure of carbon dioxide (Pco_2) >60 mm Hg, and a pH <7.25. Cavernous blood gas from high-flow priapism is bright red in color with numeric values similar to normal arterial blood.

Without a history of pelvic, genital, or perineal trauma, nearly all priapism is low flow and usually secondary to sickle cell crisis. Priapism can occur in all forms of sickle cell disease, including sickle hemoglobin C and the sickle thalassemias. Priapism affects 30% of all males with sickle cell disease,[18] with most reporting repetitive painful episodes of prolonged erections.[19] Such recurrent episodes are termed *"stuttering" priapism* and are unpredictable and of variable duration.

Obtain a history including the duration of symptoms and any precipitating events (i.e., medications or illicit drugs). When low-flow priapism lasts for >4 hours, the risk for permanent damage leading to impotence is significant and requires emergency urology consultation. While waiting for the urologist, administer IV fluids, opioid analgesics, and supplemental oxygen, and maintain the patient as NPO (nothing by mouth) for possible procedural sedation or operative management. If sickle cell disease is the underlying cause, treat with IV venous hydration at 1.5 times maintenance rates and consider red blood cell exchange transfusion (see Chapter 143, "Sickle Cell Disease in Children"). Prolonged priapism requires concurrent aggressive urologic management with corporeal aspiration and irrigation, intracavernous injection of a sympathomimetic drug (such as phenylephrine or epinephrine), or, potentially, surgical shunting as a last resort. **Ketamine is an established detumescent**[17] and should be preferentially considered for patients requiring procedural sedation prior to corporeal aspiration or irrigation.

TOURNIQUET SYNDROME OF THE PENIS

First reported in the literature in 1832, Reinisch and colleagues coined the term *hair-thread tourniquet syndrome* in 1988, when they described six cases of young infants with digit strangulation.[20] In a 2004 review, among the 90 cases of tourniquet syndrome found in the literature, toes were affected in 47%, penis in 25%, fingers in 20%, clitoris in 6%, and labia in 2%.[21]

Tourniquet syndrome of the penis presents with penile redness, swelling, and pain. Occasionally, the presenting sign is irritability of unknown cause, so a thorough history and physical are crucial to identify a tourniquet syndrome. On physical examination, the area of the penis distal to the strangulation is erythematous, edematous, and tender. Edema often obscures the hair or thread itself. Treatment includes cutting the hair or thread if visualized, or using a depilatory agent, such as Nair®. **Depilatory creams will not work on synthetic fibers**, however, and if unable to remove the constriction, urologic consultation is necessary. Damage from the tourniquet can range from mild penile edema, to glandular disfigurement, urethral transaction, and even penile amputation.[22] Although most cases are unintentional, they can also result from abuse.

ZIPPER INJURY

Penile zipper entrapment is most often seen in school-age boys, most commonly when not wearing underpants. The patient's shaft, foreskin, or glans becomes entrapped between the locked teeth of the zipper or within the fastener itself (**Figure 136-8**). If the skin is trapped between the teeth of the zipper, cut the cloth between the locked teeth, and separate the teeth of the zipper. However, if the skin is caught within the fastener of the zipper, releasing the skin is more difficult.

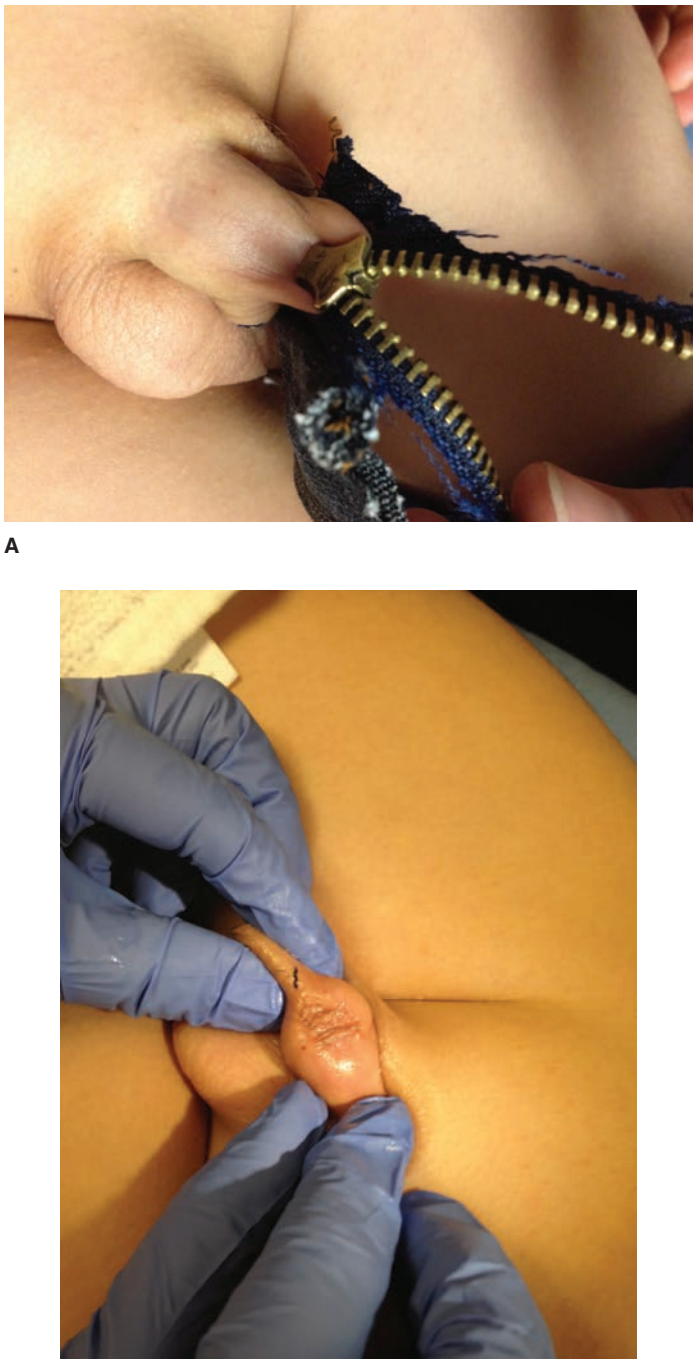

FIGURE 136-8. A 4-year-old boy with (**A**) penile zipper entrapment and (**B**) post-zipper removal after cutting the median bar.

There are several methods described in the literature for zipper release. The most commonly used method is to use sturdy wire cutters or bone cutters to cut the median bar of the zipper (**Figure 136-9**). This requires a special tool, which may not be available, and in some cases, the angle of the zipper and type of zipper preclude easy access to the median bar. Other methods include using a mini hacksaw to cut the median bar,[23] dousing the area with liberal amounts of mineral oil and

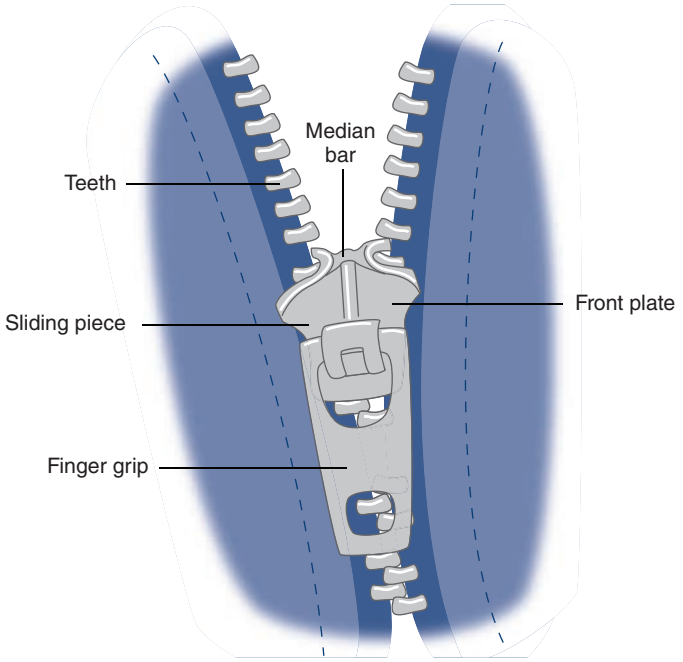

FIGURE 136-9. Parts of zipper are identified for penile zipper release. The most common method is to cut the median bar, thus releasing the entrapped skin. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*, Copyright © 2004, McGraw-Hill, Inc., New York, Figure 131-1.]

then freeing the entrapped skin with gentle traction,[24] or twisting a small flat-head screwdriver between the two faceplates of the zipper to widen the gap and allow release of the tissue.[25]

The age and degree of cooperativeness of the patient will determine type of analgesia and/or sedation needed. The patient may need oral analgesics, IV analgesics, or a dorsal penile block with or without procedural sedation. If all attempts fail at bedside zipper release, consult the urologist for removal under general anesthesia in the operating room.

FEMALE GYNECOLOGIC PROBLEMS

Postmenarchal and sexually active adolescent gynecologic problems are covered in Section 11, "Obstetrics and Gynecology." One of the most challenging physical examinations to perform is the gynecologic examination of the young female. Provide extra care and attention to create a nonthreatening environment to obtain a thorough, less anxiety-provoking examination. Tell the child that the parent approves the examination and that he or she will remain in the room. Tell the child why the examination is necessary and that everything will be explained to her beforehand. It is helpful to have the parent stand near the head of the bed while holding the child's hand. Never forcibly restrain a child for a gynecologic examination. If the examination is difficult, procedural sedation or an examination under general anesthesia is an alternative approach. Regardless of practitioner gender, obtain third-party assistance (such as a nurse or social worker).

The first position in which to examine the young female external genitalia is the frog-legged position (**Figure 136-10**), with the child lying supine (or near-supine on a parent's lap). Spread the child's knees apart. Sometimes, this position can be aided with the soles of the feet brought together. The vestibule and hymen can be seen by gently pressing the labia majora laterally and posteriorly. Examine the child in the knee-chest position (**Figure 136-11**) for visualization of the perianal area and the outer vaginal vault. Ask the child to position herself on the examination table on her hands and knees, like a baby crawling. With her parent standing at the head of the bed, ask the child to put her head down onto her hands, with her elbows resting on the examination table. Apply gentle lateral and upward traction over the buttocks and labia majora to inspect the vaginal vault.

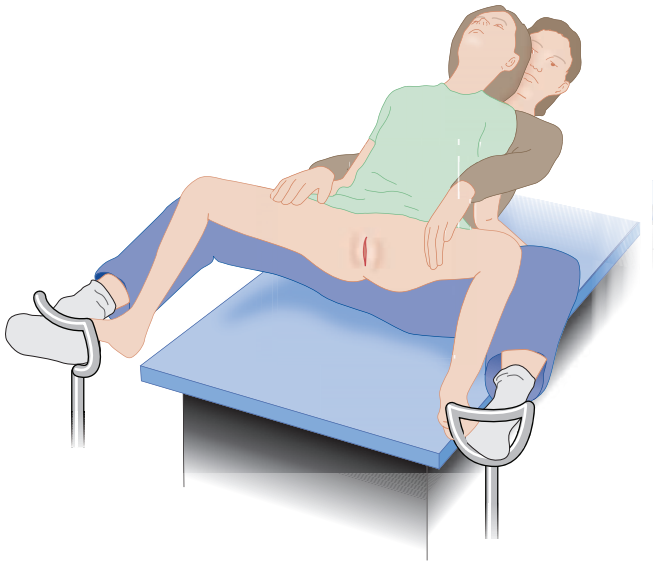

FIGURE 136-10. Girl lying in frog-legged position with knees spread apart and feet together. This position is best for examining the vestibule and hymen.

LABIAL ADHESIONS

Labial adhesions (**Figure 136-12**) are fusions of the labia minora, most commonly seen in infant and preschool-aged girls. The exact cause is unknown, although they are thought to be related to a girl's low level of estrogen, which predisposes the epithelium to irritation. Irritation may be due to poor hygiene, harsh soaps, bubble baths, or minor trauma. Re-epithelialization occurs as a response to irritation, forming the labial adhesions.

The adhesions appear as a flat, connected surface, inferior to the clitoris, with a thin, vertical raphe. Adhesions may extend from the clitoris over the entire introitus, or they can be partial with some perforations.

Labial adhesions are often asymptomatic and may be discovered on routine examination or when obtaining a catheterized urine specimen, although occasionally the child may complain of dysuria. Most labial adhesions resolve spontaneously during puberty, or topical estrogen cream can be applied over the area twice a day for 2 to 4 weeks. Topical estrogen may cause transient hyperpigmentation of the area, and prolonged use may induce reversible secondary sexual characteristics. Once

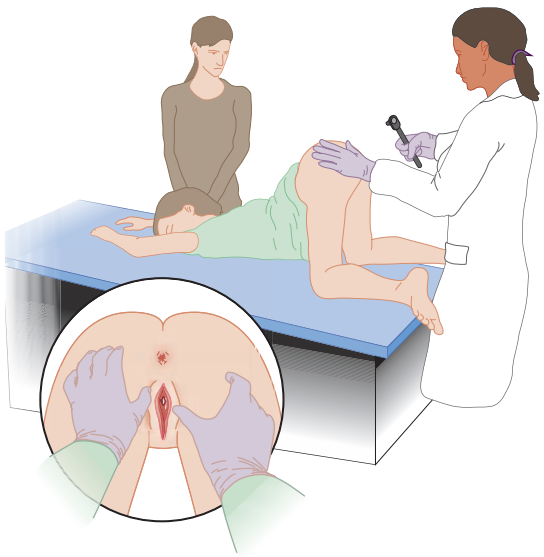

FIGURE 136-11. Girl in knee-chest position with elbows resting on examination table. This position is best for examining the perianal area and the vaginal vault.



FIGURE 136-12. Eight-month-old girl who was noted to have labial adhesions when a catheterized urine specimen was ordered in the ED for a fever workup.



FIGURE 136-13. Teenage female with imperforate hymen (with Foley catheter in place).

lysis of the adhesions occurs, the parent should apply petroleum jelly to the area for another 2 to 3 weeks to maintain labial separation. Do not manually separate adhesions, as they will likely recur.

VAGINAL DISCHARGE

During the first 2 to 3 weeks of life, many infant girls have normal physiologic vaginal discharge. The leukorrhea is thin, slippery, and clear or white in color. Among older infants and young girls, there are two common causes of vaginal discharge: vaginal foreign body and vulvovaginitis. Also, consider sexual abuse with infection from *N. gonorrhoeae*, *C. trachomatis*, or *Trichomonas* as a possibility.

Vaginal foreign bodies present with foul-smelling vaginal discharge, which can be slightly bloody. The patient may complain of voiding symptoms secondary to local irritation. Symptoms are often present for a long period of time before presentation to a physician. The most common vaginal foreign body in prepubertal females is toilet paper. Examination of the patient in knee-chest position (see Figure 136-11) is the best method to visualize the vaginal vault and possible foreign body. If the foreign body is readily seen, it can be removed using forceps or warm water vaginal lavage. If bedside removal is not possible, the patient may require examination and removal under procedural sedation or general anesthesia.

Vulvovaginitis is a very common cause of vaginal discharge, pain, and pruritus. Most cases are not associated with any specific organism, but irritation is secondary to poor hygiene, wiping back to front after urination or defecation, bubble baths, tight clothing or underwear, or perfumed bathing products. Treatment for such cases includes proper hygiene habits and eliminating offending agents. Among bacterial causes of vaginitis in the prepubertal female, the most common are group A β-hemolytic *Streptococcus*, *Staphylococcus aureus*, *Escherichia coli*, and *Shigella*. *Candida* vaginitis is not common among prepubertal females because of the alkaline pH of the vagina.

Vaginal bleeding is another common complaint in the pediatric ED. In the first 2 to 3 weeks of life, as maternal hormonal levels wane, the newborn female may experience sloughing of her endometrium with subsequent vaginal bleeding. This form of nonpathologic bleeding is always self-limited and requires no treatment other than reassurance to the parents.

In children, **urethral prolapse** occurs more commonly in prepubertal black females between the ages of 2 and 10 years old. The complaint is usually painless blood spotting on the underwear, although some patients may also experience mild irritation with voiding. The mucosa of the distal urethra prolapses outward beyond the meatus, causing venous congestion of the prolapsed tissue. Prolapse appears as a red-purple, doughnut-shaped mass with a central dimple. If the diagnosis is in doubt, pass a urinary catheter through the central opening for confirmation. The treatment of choice is sitz baths and topical estrogen cream for 2 weeks. Constipation may exacerbate the prolapse if the child strains with defecation, so providing a stool softener is often helpful. If conservative medical management fails, or if the prolapsed tissue becomes necrotic, the tissue may have to be surgically reduced and/or removed.

Fortunately, most **straddle injuries** cause only minor superficial abrasions, lacerations, or hematomas of the perineum. Such cases can be treated with supportive care and sitz baths. Pain with voiding can be relieved by allowing the child to urinate in a bathtub of warm water. More significant injuries, such as an expanding hematoma, a laceration beyond the superficial layers, a wound that continues to actively bleed, any rectal bleeding, or inability to urinate, require immediate gynecologic evaluation. In addition, sexual abuse or assault should always be considered as a possible cause of genital injury and should be reported to the appropriate state agency as mandated by law.

The vast majority of vaginal bleeding in adolescents is caused by **dysfunctional uterine bleeding**. Irregular menses with or without prolonged bleeding is especially common in females during the first year after menarche, due to the high number of anovulatory cycles. Dysfunctional uterine bleeding is best managed initially with a trial of a combined estrogen-progestin pill. The estrogen stops the bleeding, and the progestin stabilizes the endometrium. There are multiple forms of oral contraceptive pills that would be appropriate as first-line therapy. For further discussion, see Chapter 96, "Abnormal Uterine Bleeding."

IMPERFORATE HYMEN

Cases of imperforate hymen (**Figure 136-13**) typically present to the ED as a teenage female with chronic, vague abdominal pain, who has secondary sexual characteristics, yet is still "premenarchal." Physical examination reveals a bluish bulging membrane covering the introitus, representing accumulated menstrual blood and hematocolpos. If the hematocolpos is large, the patient may have symptoms of urinary urgency, frequency, or dysuria. Treatment in adolescents is urgent surgical repair, but in asymptomatic infants and young girls, surgery is performed on an elective basis.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 137

Renal Emergencies in Children

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ACUTE KIDNEY INJURY

Acute kidney injury (AKI; previously called *acute renal failure*) is the sudden loss of renal function necessary to maintain normal fluid and electrolyte balance and clear metabolic waste.[1,2] AKI is typically manifested by an increase in serum creatinine, although the increase will not necessarily cause the creatinine to be outside the normal range. Use of serum creatinine alone to define AKI, however, is problematic because creatinine is an inaccurate estimate of glomerular filtration rate, it can be removed by dialysis, and variable cutoff values for creatinine have been used in AKI.[3] Therefore, the international classification system, Kidney Disease: Improving Global Outcomes (**Table 137-1**), is preferred.[4,5] The system uses creatinine and urine output criteria and can be applied to both children and adults, minimizing practice variation.[2-4]

In neonates, baseline creatinine is influenced by maternal creatinine and clearance is decreased in premature kidneys. Suggested modifications to the Kidney Disease: Improving Global Outcomes Classification for neonates are listed in Table 137-1.

AKI is common in critically ill children, with an incidence of 27% overall among children hospitalized for intensive care; 12% have severe AKI, and 1.5% require renal replacement therapy.[6,7] Among children admitted to non–intensive care settings, the incidence is approximately 5%.[8] While the incidence is highest among adolescents, it is also common in neonates, and more common in boys than girls.[9] The most common causes of AKI in developed countries include cardiac and oncologic disease and their complications as well as nephrotoxin exposure, whereas sepsis, hypovolemia, and glomerulonephritis are common in the developing world.[3,10-12] Regardless of etiology, AKI is consistently associated with morbidity and mortality among survivors, as well as long-term loss of renal function.[3,12,13]

PATHOPHYSIOLOGY

AKI is the result of nephrotoxic and/or hypoxic injury to the glomeruli and renal tubules. Reduced blood flow causes hypoxic injury and damages the proximal tubular cells. Common nephrotoxins include aminoglycosides, contrast agents, calcineurin inhibitors, amphotericin B, NSAIDs, and cancer chemotherapeutics.[14,15] Inflammatory mediators intensify renal tubular damage.

AKI is frequently classified based on three major anatomic locations of injury: prerenal, renal, and postrenal disease. Prerenal disease is typically caused by inadequate renal perfusion and is the most common class of AKI. Prerenal AKI is typically due to hypovolemia (e.g., bleeding or GI losses such as vomiting and diarrhea), decreased renal artery blood flow, or reduction in effective circulation (e.g., heart failure, cardiogenic shock, third spacing in septic shock). Renal disease or intrinsic renal disease occurs when there is structural damage to the renal parenchyma. Common causes of renal disease include glomerular diseases (e.g., pyelonephritis, nephrotic syndrome, glomerulonephritis, Henoch-Schönlein purpura), vascular diseases (e.g., hemolytic-uremic syndrome, thrombosis, vasculitides), interstitial diseases (e.g., interstitial nephritis, infections), and tubular injuries (e.g., ischemia, nephrotoxins, hypotension). Lastly, postrenal disease is typically due to an obstruction caused by congenital or acquired anomalies to the lower urinary tract. Examples include nephrolithiasis, renal vein thrombosis, pelvic masses (e.g., lymphoma, rhabdomyosarcoma), and urethral obstruction (posterior ureteral valves).

CLINICAL FEATURES

History Direct the initial history to determine risk factors or causes for AKI. Inquire about urine output, hematuria, and edema, which are the most common symptoms noted in AKI from intrinsic renal disease. Other symptoms and signs relate to the underlying disorder, although patients can also be asymptomatic. Vomiting and diarrhea may suggest intravascular depletion and a prerenal cause of AKI. Other important historical features include history of streptococcal infection (suggests poststreptococcal glomerulonephritis), bloody diarrhea (hemolytic-uremic syndrome), and joint symptoms, rash, or purpura (Henoch-Schönlein purpura). Signs of obstruction include complete anuria or poor urinary stream. Symptoms of renal failure itself include nausea, anorexia (secondary to uremia), changes in urine output or color, edema (may be dependent, periorbital, scrotal/labial, or generalized), and headache from hypertension. Perform a full review of systems and obtain the medical history and pertinent family history. Identify all medications used, including prescription and nonprescription drugs, herbals, and sport supplements.

Physical Examination The physical examination should be thorough, with special emphasis on vital signs (especially blood pressure), weight, hydration status, and joint and skin findings. Note the presence or absence of edema. Auscultate the lungs for rales, which suggest fluid overload, and the heart for uremic rubs. Palpate the abdomen for masses (e.g., palpable bladder suggestive of obstruction) and organomegaly, which may indicate fluid overload in young children. Examine the skin for rashes (e.g., palpable purpura of Henoch-Schönlein purpura).

DIAGNOSIS

Laboratory Evaluation AKI laboratory findings include alterations of renal function, such as elevated creatinine and BUN or an abnormal urinalysis. Analysis of the urine can distinguish between prerenal, renal, and postrenal causes of AKI. In children who are not toilet trained, it may be necessary to obtain a urine specimen by catheterization. In prerenal AKI, urinalysis may be normal. Hematuria, presence of casts, and proteinuria characterize the "active sediment" of glomerulonephritis. Proteinuria alone suggests nephrotic syndrome. WBCs and bacteria suggest infection. A urine dipstick test positive for blood in the absence of observed red blood cells (RBCs) suggests myoglobinuria or hemoglobinuria. Hyaline casts may be seen in acute tubular necrosis. Urine specific gravity is often high (>1.025) in prerenal AKI and may be normal to low in acute tubular necrosis.

TABLE 137-1 KDIGO Classification of Renal Injury

Stage*	Lab Criteria	Urine Output Criteria	Other Criteria	Neonatal Criteria
I	Serum creatinine 1.5–1.9 times baseline *or* increase of ≥0.3 milligram/dL	Urine output <0.5 mL/kg/h for 6 h		Creatinine as per children. Urine output <0.5 mL/kg/h for 6–12 h
II	Serum creatinine 2–2.9 times baseline	Urine output <0.5 mL/kg/h for 12 h		Creatinine as per children. Urine output <0.5 mL/kg/h for ≥12 h
III	Serum creatinine 3 times baseline *or* increase in serum creatinine to ≥4 milligrams/dL	Urine output <0.3 mL/kg/h for 24 h *or* anuria for ≥12 h	Initiation or renal replacement therapy	Serum creatinine >3 times baseline or ≥2.5 milligrams/dL. Urine output as for children

Abbreviation: KDIGO = Kidney Disease: Improving Global Outcomes.

*Stage is determined by meeting any criterion (lab or urine output or other) in that row.

Obtain serum electrolyte levels, including calcium, magnesium, and phosphate, when AKI is suspected because hyperkalemia and other electrolyte abnormalities may require emergent treatment. Hyperkalemia may result from a combination of factors including reduced glomerular filtration rate, decreased tubular secretion of potassium, tissue breakdown with release of intracellular potassium, and metabolic acidosis resulting in transcellular movement of potassium. Other electrolyte abnormalities may include hyponatremia secondary to fluid retention or hypernatremia from dehydration in prerenal failure. Hyperphosphatemia from impaired renal excretion may lead to secondary hypocalcemia. A blood gas may show an anion gap metabolic acidosis secondary to impaired renal excretion of acid and reabsorption and regeneration of bicarbonate. A CBC is useful to identify anemia, hemolysis, and thrombocytopenia (characteristic of hemolytic-uremic syndrome), signs of systemic infection, or eosinophilia (interstitial nephritis). Serum compliments (C3, C4, CH50) and serologic testing for streptococcal infections may be useful for immune-mediated AKI. Additional studies are dictated by the clinical picture.

An ECG will identify cardiac arrhythmias and hyperkalemia. Renal biopsy is the definitive study for most cases of intrinsic renal disease and may be done on an outpatient or inpatient basis.

Imaging A chest radiograph can identify an increase in heart size or pulmonary edema. Renal US identifies anatomic abnormalities, hydronephrosis, and/or hydroureter. Voiding cystourethrogram is obtained in boys with suspected posterior urethral valves. Additional imaging depends on the differential diagnosis.

TREATMENT

Treatment of AKI is different for prerenal, renal, and postrenal failure. In all cases, careful monitoring of vital signs, including baseline weight and urine output, is necessary. In prerenal failure, treat dehydration and hypovolemia with a 10- to 20-mL/kg crystalloid bolus of normal saline; if hemorrhagic shock is the cause for hypovolemia, initiate a crystalloid bolus until blood products are available.[16] Packed RBCs are transfused at a volume of 10 mL/kg. Fresh frozen plasma and platelets may be necessary in massive hemorrhage (see Chapter 144, "Hematologic Emergencies in Infants and Children").

In renal failure from intrinsic renal disease, the specific cause must be identified and treated. Depending on the clinical state, manage oliguria and fluid overload with fluid restriction, limiting replacements to insensible losses only. Diuretics may be helpful to reduce fluid overload but are less effective in children with AKI and may require higher than usual doses.[3,16] Discontinue all nephrotoxic medications or adjust dose for glomerular filtration rate. Treat hypertension with antihypertensive agents or diuretics (see later section "Hypertension").

Manage oliguria of postrenal failure with fluid restriction and treatment of hypertension. A Foley catheter may be necessary to relieve the obstruction. In all types of AKI, electrolyte management is important. **Do not administer potassium or phosphorus to children with oliguric AKI unless symptomatic from hypokalemia or hypophosphatemia**. The management of life-threatening hyperkalemia and hyponatremia is discussed in Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children."

When conservative management fails, consider acute renal replacement therapy (dialysis). Indications for acute renal replacement therapy are severe electrolyte abnormalities, fluid overload not relieved by administration of loop diuretics, and intractable metabolic acidosis not responding to bicarbonate therapy. Peritoneal dialysis is the preferred method of acute dialysis for children because it is inexpensive and requires less expertise to perform than hemodialysis.[3]

DISPOSITION AND FOLLOW-UP

Although the primary care physician can manage mild renal insufficiency caused by dehydration, pyelonephritis, postinfectious glomerulonephritis, or Henoch-Schönlein purpura on an outpatient basis, consult a pediatric nephrologist for the management of more significant renal insufficiency, which often requires inpatient therapy. Pediatric urology consultation is needed for postrenal failure.[16] Admit children with severe electrolyte abnormalities and fluid overload to a pediatric intensive care unit.

NEPHROTIC SYNDROME

Nephrotic syndrome is a chronic disease in children that alters permeability at the glomerular capillary wall, which causes a urinary loss of protein. The disease is classically characterized by proteinuria (>40 milligrams/m^2 in 24 hours), hypoalbuminemia (serum albumin <25 grams/L), hyperlipidemia, and edema.[17,18] However, hyperlipidemia and edema are not consistently present. Nephrotic syndrome can be primary (involving only the kidney) or secondary (multisystem). Primary nephrotic syndrome accounts for 95% of pediatric nephrotic syndrome and is idiopathic in 80% to 90% of children age 2 to 8 years old, but is genetic in the vast majority of neonates and young infants.[17,19]

The classification of primary nephrotic syndromes includes minimal change disease, focal segmental sclerosis, membranous nephropathy, membranoproliferative nephritis, and proliferative nephritis (diffuse, focal, or mesangial). Secondary nephrotic syndrome is rare in children, but can be caused by autoimmune disease (Henoch-Schönlein purpura, lupus, diabetes), infections (hepatitis, human immunodeficiency virus, malaria, parasites), drugs, diabetes, or malignancy.[17,18]

PATHOPHYSIOLOGY

When podocytes within the glomerular membrane are damaged by immune dysregulation or systemic circulating factors, the permeability of the glomerulus to proteins normally not able to pass through the glomerular capillary wall is increased.[18] Increased permeability results in the two diagnostic hallmarks of nephrotic syndrome: proteinuria and hypoproteinemia. Nephrotic syndrome also leads to salt and water retention. The combination of low intravascular oncotic pressure from the loss of proteins, coupled with the retention of salt and water, gives rise to the clinical feature of edema. As fluids shift to the extracellular space, the kidney is stimulated through the renin-angiotensin-aldosterone system to increase distal sodium reabsorption, which exacerbates the cycle.

CLINICAL FEATURES

History and Complications Edema is the most common complaint. Anasarca consists of marked peripheral edema, ascites, scrotal or vulvar edema, and severe periorbital edema. Shortness of breath, cough, and orthopnea suggest a pleural effusion. Ask about urine output, because oliguria is often associated with more severe edema. Nausea, vomiting, and anorexia suggest ascites or edema of the bowel wall, and when accompanied by fever, raise concern for spontaneous bacterial peritonitis. Review of systems should note fever, fatigue, arthralgias or arthritis, rash, and the volume and character of the urine (foamy, bloody, or tea colored). The presence of hematuria, hypertension, or reduced renal function, age at onset, medical and family history of disease, and biopsy findings are all important predictors of disease outcome.

The main life-threatening complications of nephrotic syndrome are severe infection and thromboembolic events (venous and arterial).[17,20] Serum complements, antibodies, and coagulation factors are lost as protein in the urine, leading to relative immunocompromise. Steroid therapy for nephrotic syndrome increases the risk of infection. Hyperlipidemia may lead to hyperviscosity, and increased levels of fibrinolytic inhibitors increase thrombotic risks.

Physical Examination Edema is the most common physical exam finding in nephrotic syndrome and is typically more prominent in the morning and in dependent areas. Rebound abdominal tenderness and ascites are other potential findings.[5] Auscultate for findings of pleural effusion and pulmonary edema. Examine the abdomen for signs of peritoneal fluid, and note tenderness or guarding, which may be signs of peritonitis. **Be careful not to confuse facial swelling due to nephrotic syndrome with swelling secondary to allergic reaction.**

DIAGNOSIS

The diagnostic criteria of nephrotic syndrome are as follows[21]:

1. Edema
2. Proteinuria: Urine protein (milligrams/deciliter) to urine creatinine (milligrams/deciliter) ratio >2 in a first morning void or a 24-hour urine protein loss that exceeds 50 milligrams/kg or 40 milligrams/m^2
3. Hypoalbuminemia: Serum albumin <25 grams/L

Renal biopsy is not indicated during the initial episode of acute nephrotic syndrome. Early renal biopsy should be considered for infants with nephrotic syndrome; those with persistent elevation in serum creatinine, hypocomplementemia, or gross hematuria; and those who are treatment resistant.[18,22]

Laboratory Evaluation In general, blood and urine samples are sent for study to confirm the diagnosis of nephrotic syndrome (tests for proteinuria, hypoproteinemia, and hyperlipidemia), distinguish primary from secondary causes (tests for hematuria, serum immunoglobulin and complement levels, and antinuclear antibody level; hepatitis serologic testing), and aid in management (CBC, serum electrolyte levels, renal function tests, coagulation studies).[17] Serum creatinine may be normal for age and height. Total serum calcium is often low, although ionized calcium is usually normal. Serum sodium level is low secondary to increased triglycerides. Imaging studies are rarely indicated unless there is clinical concern for pulmonary edema or effusions. Symptoms or signs suggestive of potential thrombotic complications of nephrotic syndrome should prompt the appropriate evaluation (e.g., duplex US of renal vessels, CT angiography).

TREATMENT

ED Management The goal is to treat acute symptoms, make the diagnosis of nephrotic syndrome, and arrange for appropriate follow-up. Treat hypovolemic shock with isotonic fluid, even if edema is severe. For the mildly to moderately dehydrated patient, provide oral rehydration with small, frequent aliquots of sodium-deficient solutions. Treat volume overload with sodium and fluid restriction and diuretics (furosemide, 1 to 2 milligrams/kg). Diuretics may not be effective when there is profound hypoalbuminemia, and in that situation, infusion of albumin (0.5 to 1.0 gram/kg) followed by furosemide may be effective, but intensive care monitoring is required. Treat infection or thrombotic complications as clinically indicated.

Specific Treatment of Nephrotic Syndrome The mainstay of the treatment of nephrotic syndrome is oral corticosteroids, but the response to steroids varies with the cause. Minimal change disease and mesangial proliferative nephritis are often steroid responsive; membranous nephropathy may respond to steroids; focal segmental sclerosis is typically steroid resistant.[23] When indicated, prednisone is often started at 2 milligrams/kg/d in two or three divided doses, or 60 milligrams/m^2 (maximum 60 milligrams/d). The duration of initial therapy and subsequent tapering vary across national guidelines, but often continue for weeks to months.[17,24-26] In patients with known steroid-responsive disease who experience relapse, the ED physician may restart steroids as above in consultation with a pediatric nephrologist. In steroid-dependent or steroid-resistant nephrotic syndrome, the nephrologist must be consulted for initiation of medications. Common second-line medications for refractory nephrotic syndrome include cyclosporine, cyclophosphamide, mycophenolate, tacrolimus, and rituximab.[17,18,22,26]

DISPOSITION AND FOLLOW-UP

Admit patients with severe edema, pulmonary effusions or respiratory symptoms, or signs and symptoms suggestive of systemic infection or thrombotic complications to the hospital. Children with mild or moderate edema can often be treated as outpatients with a low-salt (<2 grams/d) diet and close follow-up with their primary care physician or pediatric nephrologist.

Children with nephrotic syndrome are at high risk for bacterial peritonitis from *Streptococcus pneumoniae* and should receive the pneumococcal (23-valent) vaccine to avoid peritonitis. The varicella vaccine should also be administered to children with nephrotic syndrome once they are in remission and no longer receiving steroid therapy.

GLOMERULONEPHRITIS

Glomerulonephritis is a spectrum of inflammatory disorders characterized by hematuria and proteinuria. Signs of glomerulonephritis vary from asymptomatic proteinuria and microscopic hematuria to gross hematuria, nephrotic syndrome, hypertension, and impaired renal functioning requiring renal replacement therapy. Glomerulonephritis is caused by several disorders, all of which cause inflammation leading to glomerular injury. It can be caused by immune-mediated disorders, inherited disorders, or postinfectious sequelae. Examples of hereditary glomerular diseases include systemic lupus erythematosus nephritis, thin glomerular basement membrane disease, and Alport's syndrome. Poststreptococcal glomerulonephritis, immunoglobulin A (IgA) nephropathy, and Henoch-Schönlein purpura will be discussed in this section.

PATHOPHYSIOLOGY

Glomerulonephritis is an inflammatory process affecting the glomerulus. Glomerulonephritis usually results from deposition of immune complexes within the glomeruli. These immune complexes activate a number of processes including complement activation, leukocyte recruitment, and release of growth factors and cytokines. This leads to inflammation and injury. Sclerosis occurs within the glomeruli, and fibrosis occurs in the tubulointerstitial cells.[27]

Glomerulonephritis may be classified as primary (isolated to the kidney) or secondary (a result of a systemic disorder). There are four main presentations: acute glomerulonephritis, rapidly progressive glomerulonephritis, recurrent macroscopic hematuria, and chronic glomerulonephritis. Although glomerulonephritis caused by streptococcal disease or Henoch-Schönlein purpura usually resolves completely and without sequelae, glomerulonephritis from other causes can progress to renal damage and ultimately end-stage renal failure.[28]

CLINICAL FEATURES

Hematuria is the most common symptom of glomerulonephritis but may be subclinical (microscopic). "Synpharyngitic" macroscopic hematuria refers to gross hematuria with concomitant pharyngitis and can be seen in IgA nephropathy.[27] Glomerulonephritis is often associated with hypertension, which may cause headaches when severe. Symptoms related to hypertension may be the chief complaint of a child with undiagnosed glomerulonephritis. Patients may complain of bloody or foamy urine (a result of proteinuria), oliguria, nausea, fatigue, or lethargy.[28] The physical examination is often normal.

LABORATORY EVALUATION

In glomerulonephritis, the urinalysis demonstrates macroscopic or microscopic hematuria, RBC casts, and proteinuria. Microscopic examination of urinary sediment shows dysmorphic RBCs and RBC casts. Send urine for culture, because proteinuria and hematuria may represent urinary tract infection, although RBC casts are not typical of infection. Other useful studies include a CBC, creatinine level, and electrolytes. Serum albumin level is often reduced. Send serum complement levels (C3 and C4), because complement proteins (C3) are decreased in >90% of patients with poststreptococcal glomerulonephritis, whereas levels are usually normal in patients with IgA nephropathy.[27,29,30] Consider streptococcal serologic tests (antistreptolysin-I and streptozyme). More specific tests may be needed to make a clear diagnosis in illnesses with systemic manifestations such as systemic lupus erythematosus. A renal biopsy is often required for definitive diagnosis in glomerulonephritic disorders.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Poststreptococcal glomerulonephritis is caused by prior infection with group A β-hemolytic streptococci. Only certain strains of this group

are "nephritogenic," and the pharynx and skin are the most common sites of infection leading to acute glomerulonephritis, occurring 7 to 15 days after pharyngitis and 3 to 5 weeks after skin infection.[31] Group A β-hemolytic streptococci stimulate immune complex formation secondary to deposition of streptococcal nephritogenic antigens within the glomerulus. Other infections such as *Staphylococcus aureus* and *Staphylococcus epidermidis* may also lead to renal disease, usually with a longer latency period.

Clinically, poststreptococcal glomerulonephritis consists of microscopic or gross hematuria, proteinuria, hypertension, and edema. Children may give a history of a recent upper respiratory tract or skin infection or have tea-colored urine. The most common serologic markers include anti–streptolysin O or anti–DNAse B titers (or the combined streptozyme test), which are typically elevated, and a serum C3 level, which is typically decreased.

Treatment is largely supportive. Symptoms of poststreptococcal glomerulonephritis usually resolve in a few weeks. Hypertension rarely requires long-term treatment and tends to resolve within 1 to 2 weeks. Renal biopsy is not indicated for diagnosis, unless atypical clinical features are present. Asymptomatic patients with probable poststreptococcal disease and normal vital signs are eligible for discharge after consultation, and arrangement for follow-up, with a nephrologist.

IGA NEPHROPATHY

IgA nephropathy, also known as Berger's disease, is an autoimmune disease that is responsible for up to 10% of acute glomerulonephritis in the United States and is the most common single cause of glomerulonephritis worldwide.[27] Initially, IgA is deposited on the mesangial cells of the kidney. This alone is not enough to cause IgA nephropathy. In addition, there needs to be reduced IgA clearance, development of glomerular injury, and complement activation, all resulting from dysregulation of mucosal-type IgA immune responses. The cause is unknown.

Clinically, IgA nephropathy may present one of three ways: macroscopic hematuria, microscopic hematuria with mild proteinuria, or acute rapidly progressive glomerulonephritis with edema, hypertension, and renal insufficiency. Macroscopic hematuria is often concurrent with an upper respiratory tract infection (synpharyngitic hematuria). The diagnosis is typically based on the clinical history and laboratory data (including urinalysis). Renal biopsy is confirmatory.

Treatment is symptomatic. Immunosuppressant therapy (e.g., corticosteroids) may be initiated to treat underlying inflammation, depending on disease severity. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may be used to control blood pressure, particularly in patients with proteinuria. IgA nephropathy can either completely resolve or progress to end-stage renal disease.[27] Concern for IgA nephropathy in the ED warrants an outpatient referral to nephrology. Rapidly progressive glomerulonephritis requires admission.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura, also known as IgA vasculitis, is a form of systemic vasculitis associated with IgA deposition in the small vessels of the body. Palpable purpura, arthritis/arthralgias, abdominal pain, and renal disease make up the classic presentation tetrad. Henoch-Schönlein purpura nephritis is often asymptomatic, and it is extremely important to follow up to detect persistent renal inflammation. Renal complications occur in 20% to 54% of patients with Henoch-Schönlein purpura and include gross or microscopic hematuria, proteinuria, or nephritic syndrome.[32,33] Of the children diagnosed with Henoch-Schönlein purpura, 40% have mild nephritis, manifested only by microscopic hematuria or low-grade proteinuria. Risk factors for the development of renal complications include male gender, age >10 years, abdominal pain, GI bleeding, persistent purpura, elevated anti–streptolysin O, WBC >15,000/mm^3, and platelets >500 × 10^9/L.[34] Renal complications may develop any time over a period of 28 days, and 2% of children may develop long-term renal impairment.[35] Obtain a urinalysis to identify RBCs, casts, and protein. Treatment focuses on hydration, rest, and analgesics. **Although corticosteroids may provide symptomatic relief for severe abdominal pain, they do not prevent renal involvement or long-term renal damage and are not recommended.**[36,37] Further discussion of Henoch-Schönlein purpura can be found in Chapter 133, "Acute Abdominal Pain in Infants and Children," and Chapter 142, "Rashes in Infants and Children."

HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome is a multisystem disorder resulting in AKI, thrombocytopenia, and microangiopathic hemolytic anemia. Hemolytic-uremic syndrome is one of the most common causes of AKI in children and typically occurs in those <10 years old. It is classified as typical (diarrhea associated) or atypical. In children, Shiga toxin–producing *Escherichia coli* causes 90% of hemolytic-uremic syndrome cases, presenting with a prodrome of bloody diarrhea; 10% to 15% of children with Shiga toxin–producing *E. coli* develop hemolytic-uremic syndrome (see Chapter 131, "Vomiting, Diarrhea, and Dehydration in Infants and Children").[38,39] Other causes of hemolytic-uremic syndrome are *S. pneumoniae* infection, genetic disorders, oral contraceptive use, pregnancy, and malignancy. Despite widespread immunization for *S. pneumoniae*, the incidence of hemolytic-uremic syndrome associated with invasive disease has not decreased, and nonvaccine strains have replaced vaccine strains in these cases.[40] Mortality and severe renal involvement are higher in *S. pneumoniae*–associated hemolytic-uremic syndrome than typical Shiga toxin–producing *E. coli* associated disease.[39]

Pathophysiology Epidemic hemolytic-uremic syndrome is usually caused by infection with *E. coli* O157:H7, an organism associated with ingestion of undercooked meat, unpasteurized milk, and contaminated fruits and vegetables. *E. coli* O157:H7 produces a Shiga toxin, which is absorbed from the intestines into the circulation, causing endothelial damage and leading to microangiopathic intravascular thrombosis, RBC hemolysis, thrombocytopenia (due to platelet consumption), and decreased glomerular perfusion.[41] Microthrombi are deposited in kidney parenchyma, causing hypertension, oliguria, and anuria. Renal involvement ranges from mild renal insufficiency to AKI requiring dialysis.

In atypical hemolytic-uremic syndrome associated with *S. pneumoniae* (5% of cases), pathogenesis is initiated by the pneumococcal enzyme neuraminidase. This enzyme cleaves *N*-acetylneuraminic acid from the surface of RBCs and endothelial cells, uncovering the T antigen on the surface of endothelial cells. This in turn leads to an immune response, initiating the cascade leading to hemolytic-uremic syndrome.[39]

Clinical Features The majority of hemolytic-uremic syndrome is associated with *E. coli* enteritis, and the disease starts with nausea, vomiting, and bloody diarrhea with or without fever. Within a week of the resolution of the GI symptoms, pallor, edema, oliguria, shortness of breath, and seizures or encephalopathy develop. *S. pneumoniae*–associated hemolytic-uremic syndrome can accompany severe invasive disease, typically in the setting of pneumonia, sepsis, or meningitis. Other complications include hypertension, heart failure, intussusception, diabetes mellitus, acidosis, and colitis.[39] A careful dietary and travel history may identify a potential source of infection to aid public health officials assess epidemic outbreaks.

Laboratory Evaluation Obtain a CBC and peripheral smear; microangiopathic hemolytic anemia, one of the cardinal features of hemolytic-uremic syndrome, may be profound with a hemoglobin level between 5 and 9 grams/dL; the smear demonstrates schistocytes, helmet cells, and burr cells. The platelet count is <150,000/mm^3. The WBC count may be elevated (poor prognosis). If obtained, the Coombs test is negative. Check electrolytes and renal and hepatic function; hyponatremia and hyperkalemia develop as a result of metabolic acidosis from renal failure, and hyperbilirubinemia results from acute hemolysis.

Send a stool specimen for culture and to test for Shiga toxin. Urinalysis demonstrates gross or microscopic hematuria with granular and hyaline casts and variable proteinuria and leukocyturia.

Treatment ED management is supportive, although some studies suggest that **early aggressive volume expansion (in the absence of signs of fluid overload), may improve outcomes in typical hemolytic-uremic syndrome.**[42,43] Correct life-threatening electrolyte disturbances and

treat hypovolemia with IV fluid boluses (10 to 20 mL/kg normal saline). **Antibiotics are contraindicated in pediatric diarrheal illness and may increase the risk hemolytic-uremic syndrome.[44] Antiperistaltic agents increase the risk for systemic complications associated with *E. coli* infection and are also contraindicated.** Blood transfusions may be needed for severe anemia. Platelet transfusion is not recommended because it could worsen the thrombotic process. Treatment with eculizumab or plasma exchange may be helpful.

All patients with hemolytic-uremic syndrome require hospitalization. Patients with neurologic symptoms and oliguric renal failure should be admitted to the intensive care unit.[15] Renal replacement therapy is required in approximately half of cases of acute hemolytic-uremic syndrome.[39] Most children (95%) survive the acute phase of the illness, and most regain normal renal function.

RENAL TUBULAR ACIDOSIS

Renal tubular acidosis is rare. In the absence of diarrhea, it is defined as hyperchloremic metabolic acidosis with a normal anion gap and a normal to near-normal glomerular filtration rate.[45]

In children, renal tubular acidosis is typically secondary to an inherited or acquired defect that affects the kidney's ability to manage bicarbonate, acid, and ammonia. Renal tubular acidosis develops because of impaired distal acidification (type I), reduced proximal bicarbonate reabsorption (type II), or reduced production of ammonium from aldosterone deficiency or resistance (type IV). For example, Fanconi's syndrome causes a type II renal tubular acidosis and may be associated with hypophosphatemia and rickets. Types I and II renal tubular acidosis result in hyperchloremic metabolic acidosis with hypokalemia, whereas type IV renal tubular acidosis results in hyperkalemia, acidemia, and a low urinary pH; the metabolic acidosis has a normal anion gap in all types.[45,46]

There is no single symptom complex that brings children with renal tubular acidosis to medical attention. Chronic acidosis is associated with failure to thrive, and this may result in an ED visit. Depending on the type of renal tubular acidosis, symptomatic hypokalemia or hyperkalemia (weakness, nausea, constipation), rickets, or nephrolithiasis may prompt an ED visit. Often the diagnosis of renal tubular acidosis is suggested by abnormal results on serum chemistry and urine studies that are incidentally discovered in the process of evaluation for unrelated complaints. **Table 137-2** describes the typical laboratory findings in each type of renal tubular acidosis.[45,46]

Acute treatment consists of correcting the underlying electrolyte and acid-base abnormalities. Maintenance treatment includes oral bicarbonate therapy and monitoring of serum potassium for all types of renal tubular acidosis, vitamin D and sodium phosphate for type II renal tubular acidosis, and loop diuretics and fludrocortisone for mineralocorticoid deficiency in type IV renal tubular acidosis.[47]

HYPERTENSION

Pediatric hypertension is increasing in incidence, with prevalence estimates ranging from 0.3% to 4.5% in children.[48,49] This increase is related to higher rates of childhood obesity, greater salt intake, hyperlipidemia, and decreased physical activity.[48] Boys, adolescents, and Hispanic and African American race are associated with higher rates of hypertension in the United States.[49] The definition of hypertension in children has undergone several revisions, and the latest guidelines from the American Academy of Pediatrics (2017) are summarized **in Table 137-3**.

TABLE 137-3 Definition of Elevated Blood Pressure and Hypertension in Children

	Age 1 to <13 y*	Age ≥13 y
Elevated blood pressure	≥90th to <95th percentile or 120/80 mm Hg to <95th percentile	120/<80 to 129/<80 mm Hg
Stage I hypertension	≥95th to <95th percentile + 12 mm Hg or 130/80 to 139/89 mm Hg	130/80 to 139/89 mm Hg
Stage II hypertension	≥95th percentile + 12 mm Hg or ≥140/90 mm Hg	≥140/90 mm Hg

*Use lower value.

Traditionally, hypertensive urgency was a severely elevated blood pressure without evidence of target organ damage that, left untreated, may cause end-organ damage, whereas **hypertensive emergency** was defined as blood pressures exceeding the 99th percentile for age and sex with acute end-organ damage that requires immediate treatment.[50] With the updated American Academy of Pediatrics practice guidelines mentioned earlier, the term *acute severe hypertension* was suggested to describe any acute symptomatic presentation of hypertension.[49] Generally, the CNS, kidneys, and cardiovascular system are the organs most likely to be damaged secondary to hypertension. Hypertensive crises in younger children are usually secondary to an underlying disease.

Essential hypertension is uncommon in younger children and is more prevalent in adolescents. Renal disease (glomerulonephritis, hemolytic-uremic syndrome, chronic infections, obstructive lesions, and renal vascular disease) is the most common cause of secondary hypertension in children. Endocrine causes of hypertension include tumors that secrete vasoactive peptides (pheochromocytoma), abnormal levels of endogenous steroid hormones (Cushing's syndrome), adrenocortical steroid therapy, and hyperthyroidism. Hypertension may also result from congenital heart disease such as coarctation of the aorta. Elevated intracranial pressure may also lead to hypertension in an attempt by the body to maintain cerebral perfusion pressure and can be caused by space-occupying lesions, acute hemorrhage, infection, or obstruction to cerebrospinal fluid flow. Exogenous medications or toxins may also cause hypertension. **Table 137-4** outlines the common causes of hypertension by age group.

CLINICAL FEATURES

Children with hypertensive crisis range from having mild symptoms such as headache, nausea, vomiting, visual changes, and anxiety to life-threatening encephalopathy or focal neurologic deficits, chest pain and shortness of breath from acute heart failure and pulmonary edema, and anuria from AKI. In neonates and young infants, feeding problems,

TABLE 137-2 Laboratory Findings in Renal Tubular Acidosis (RTA)

Type of RTA	Plasma Anion Gap	Urinary Anion Gap	Serum Potassium	Minimal Urine pH (in the presence of acidosis)	Additional Laboratory Tests
Distal or type I RTA	Normal	Elevated	Normal or low	>5.5	Arterial blood gas concentrations, urine pH (>5.3), urine calcium/creatinine ratio elevated
Proximal or type II RTA	Normal	Normal	Normal or low	<5.5	Arterial blood gas concentrations, urine pH (>5.5, except in severe metabolic acidosis), serum K level, fractional excretion of HCO
Type IV RTA	Normal	Elevated	High	<5.5	Arterial blood gas concentrations, urine pH (<5.5 with severe metabolic acidosis), urine to blood Co_2, creatinine clearance

TABLE 137-4 Common Causes of Hypertension in Children

Age Group	Cause
Newborn	Renal: thrombosis, stenosis, polycystic kidney disease Heart: coarctation of the aorta Endocrine: pheochromocytoma, Cushing's disease
Preschool/kindergarten (<6 y)	Renal: parenchymal disease, vascular disease Heart: coarctation of the aorta Endocrine: pheochromocytoma, Cushing's disease
School age (6–10 y)	Endocrine: pheochromocytoma, Cushing's disease, thyrotoxicosis
Adolescence	Essential hypertension (especially in obese adolescents) Renal: parenchymal, vascular Endocrine: pheochromocytoma, Cushing's disease, thyrotoxicosis Drugs of abuse (e.g., cocaine, amphetamines), NSAIDs, monoamine oxidase inhibitors, steroids, calcineurin inhibitors (cyclosporin/tacrolimus)

irritability or lethargy, respiratory distress, or seizures may be manifestations of a hypertensive crisis.[50]

History and Comorbidities Obtain a detailed history of symptoms that suggest end-organ damage including neurologic symptoms, chest pain, shortness of breath, decreased urine output, or hematuria, as described earlier. Other symptoms may help to identify an underlying cause such as palpitations, weight loss, flushing, and diarrhea, which point to an endocrine disorder. Identify any medications or substances associated with blood pressure elevation, such as oral contraceptives, steroids, immunosuppressants, and illicit drugs (e.g., cocaine, amphetamines). Ask about a family history of essential hypertension, diabetes, obesity, renal disease, hyperlipidemia, stroke, or endocrinopathy. For those with an established diagnosis of hypertension, ask about medication adherence or abrupt withdrawal.

Physical Examination Obtain an accurate height and weight and determine percentiles for age. Obtain four-limb blood pressures in infants (a lower blood pressure in the lower extremities compared to the upper extremities or left versus right arms may indicate aortic coarctation). Perform a comprehensive physical examination, including a funduscopic examination (for retinal hemorrhages, papilledema, infarcts) and a neurologic examination. Assess the heart and lungs for signs of congestive heart failure or structural disease (gallops, murmurs, rales). Palpate the abdomen to exclude masses or pregnancy. Auscultation of an abdominal bruit may suggest renovascular disease.

Laboratory Evaluation Assess renal function with a serum BUN, creatinine, electrolytes, glucose, plasma rennin activity, aldosterone levels, and microscopic urinalysis. Obtain a CBC and reticulocyte count to look for rheumatic disorders, appropriate marrow response, and signs of anemia. Perform a pregnancy test in pubertal girls. Ordering of more esoteric tests for endocrine abnormalities should be left to subspecialists.

Imaging Obtain a chest radiograph and ECG. Obtain an echocardiogram to look for left ventricular hypertrophy and to rule out cardiac causes of hypertension. Obtain a head CT if neurologic findings are present. Renal US is indicated to rule out structural kidney abnormalities. If suspicion for renovascular disease is high, then obtain a CT angiography or magnetic resonance angiography.

TREATMENT

Most patients with mild to moderate elevation of blood pressure in the ED are discharged with instructions for follow-up for outpatient evaluation and treatment. **Hypertensive urgency** may be treated with oral antihypertensives (**Table 137-5**).[50]

Treatment of **hypertensive emergency** begins with evaluation and stabilization of the airway, breathing, and circulation. Obtain IV or IO access and start cardiac monitoring; consider placement of a Foley catheter and arterial line. The goal is to reduce the mean arterial pressure by ≤25% over the first 6 to 8 hours, followed by a gradual reduction to normal values over the next 26 to 48 hours toward the 95th percentile for age.[50] Reducing the blood pressure too aggressively can lead to ischemic complications such as acute neurologic issues, blindness, and renal failure. Recommendations regarding the most useful drugs for treating severe hypertensive emergency in children are listed in **Table 137-6**.[50] Medications should be chosen according to their side effect profile, availability, and physician familiarity, as there are limited clinical data in children and infants.

DISPOSITION AND FOLLOW-UP

Mild hypertension should be managed on an outpatient basis by the primary care provider or subspecialist. Hypertensive urgencies and emergencies require ED stabilization and initial pharmacologic treatment in the ED with subsequent admission to the intensive care unit or medical ward depending on the degree of end-organ damage and the response to initial interventions.

TABLE 137-5 Oral Antihypertensives for Hypertensive Urgency in Infants and Children

Drug	Class	Dosage	Route	Onset of Action	Comments
Isradipine	Calcium channel blocker	0.05–0.1 milligram/kg/dose up to 5 milligrams/dose	PO	2–3 h	Tachycardia, headache Caution in those taking azole antifungals (hypotension)
Nifedipine	Calcium channel blocker	0.1–0.25 milligram/kg/dose	PO, sublingual	Immediate release, 20–30 min Extended release, 2.5–5 h	Precipitous drop in blood pressure, tachycardia, headache
Minoxidil	Vasodilator	0.1–0.2 milligram/kg/dose	PO	Within 30 min	Fluid retention
Doxazosin	α-Blocker	1–2 milligrams/kg per dose	PO	2–6 h	Dizziness, orthostatic hypotension Useful in hyperadrenergic states (e.g., pheochromocytoma)
Prazosin	α-Blocker	0.02–0.04 milligram/kg/dose	PO	30–90 min	Dizziness, headache Useful in hyperadrenergic states (e.g., pheochromocytoma)
Clonidine	Central α-agonist	2–10 micrograms/kg/dose every 6–8 h	PO	30–60 min	Rebound hypertension, sedation, dry mouth
Captopril	Angiotensin-converting enzyme inhibitor	0.1–0.2 milligram/kg/dose 0.01–0.1 milligram/kg/dose in neonates	PO	10–20 min	Contraindicated in bilateral renal artery stenosis; not recommended in acute or chronic renal failure

TABLE 137-6 Parenteral Antihypertensives for Hypertensive Crisis in Infants and Children

Drug	Class	Dosage	Route	Onset	Comments
Nitroprusside	Vasodilator	0.5–8.0 micrograms/kg/min IV infusion	IV infusion	Seconds	May increase intracranial pressure. Monitor cyanide and thiocyanate levels for patients with renal and liver disease when administering for >24–48 h.
Hydralazine	Vasodilator	0.1–0.5 milligram/kg/dose; maximum, 20 milligrams/dose	IV, IM	5–30 min	Administer every 4 h when given as IV bolus. Not as strong as other agents. Recommended dose is less than U.S. Food and Drug Administration–approved label. Reflex tachycardia
Diazoxide	Vasodilator	1–3 milligrams/kg every 5–15 min	IV bolus	Within minutes	Risk of hypotension
Nicardipine	Calcium channel blocker	1.0–3.0 micrograms/kg/min IV infusion	IV infusion	Within minutes	May cause increased intracranial pressure, headache, nausea, and hypotension
Labetalol	α- and β-blocker	Bolus: 0.2–1.0 milligram/kg/dose to a maximum of 40 milligrams/dose, then infusion: 0.25–3.0 milligrams/kg/h	IV bolus or infusion	2–5 min	Contraindications include asthma, chronic lung disease, and evident heart failure; may mask hypoglycemic symptoms
Urapidil	α_1-Blocker and central 5-HT_{1A} agonist	Initial dose 0.5–4.0 milligrams/kg/h Maintenance dose 0.2–2.0 milligrams/kg/h	IV infusion	1–5 min	Contraindicated in aortic stenosis; palpitations, nausea, sedation
Esmolol	β-Blocker	100–500 micrograms/kg/min (initial dose), then 50–300 micrograms/kg/min	IV infusion	Immediate	May cause bronchospasm, congestive heart failure, and profound bradycardia
Fenoldopam	Dopamine receptor agonist	0.2–0.8 microgram/kg/min	IV infusion	Within minutes	Tachycardia, flushing, headache
Furosemide	Loop diuretic	0.5–5 milligrams/kg/dose	IV bolus	Within minutes	Useful for volume overload hypertension; may cause hypokalemia
Diazoxide	Vasodilator	1–3 milligrams/kg every 5–15 min	IV bolus	Within minutes	Risk of hypotension

HEMATURIA

Hematuria is the presence of an increased number of RBCs (≥5 RBCs/μL of urine). Hematuria may be macroscopic (apparent to the naked eye) or microscopic (apparent only on urinalysis). It is frequently asymptomatic.

Hematuria can be divided into three types: macrohematuria, transient hematuria, and persistent microhematuria. Macroscopic hematuria is most frequently caused by urinary tract infections or blunt abdominal trauma. Other causes include nephrolithiasis, poststreptococcal glomerulonephritis, IgA nephropathy, and malignancy. Transient hematuria may be caused by strenuous exercise, trauma, menstruation, bladder catheterization, and fever. Persistent microhematuria can be seen in benign familial hematuria,[51] idiopathic hypercalciuria, IgA nephropathy, Alport's syndrome, and sickle cell trait or anemia or with drugs or toxins.[52]

CLINICAL FEATURES

History and Comorbidities Obtain a complete history, because the differential diagnosis is broad. Distinguish between transient, persistent, and recurrent hematuria.[53] Associated dysuria, urinary frequency and urgency, fever, and abdominal or flank pain suggest infection or urolithiasis (see Chapter 94, "Urologic Stone Disease"). A history of an upper respiratory tract infection, sore throat, or skin infection may suggest postinfectious glomerulonephritis. A current infectious process is suspicious for IgA nephropathy. For transient hematuria, ask about blunt abdominal trauma, recent catheterization, or menstruation. The color of the urine (pink, red, or tea colored) and the timing during micturition—at the beginning (associated with pathology of the urethra), throughout micturition (associated with bleeding above the bladder neck), or at the end of micturition (associated with pathology of the bladder neck, posterior urethra, or prostate)—provide useful diagnostic information. Ask about joint pain and rash (Henoch-Schönlein purpura or lupus). Some drugs associated with hematuria are NSAIDs, anticonvulsants, warfarin, diuretics, penicillin, and chlorpromazine. Recent vigorous exercise can cause hematuria, which resolves after a period of rest. Obtain a family history carefully, because many causes of hematuria in children are inherited. Questions about family history should be directed to information regarding deafness, hematuria, hypertension, coagulopathy, hemoglobinopathy, calculi, renal failure, dialysis, and transplant.[53] Staining reported as "blood on the diaper" of an infant without other symptoms may represent benign urinary crystals, extra–urinary tract blood (e.g., vaginal bleeding in female neonates), or blood from the GI tract. The presence of amorphous crystals in the urine is a common and benign finding in neonates, and because these crystals are often pink or orange, they may be interpreted as blood by parents. Dipstick testing is negative for blood in this situation.

Physical Examination The physical examination findings vary depending on the cause of hematuria suggested by historical information. Obtain vital signs to identify hypertension or a fever. Assess for signs of respiratory infection, joint swelling, and skin rashes. Perform a careful GU examination to identify a source of external bleeding such as a periurethral tear.

DIAGNOSIS

Laboratory Evaluation The laboratory evaluation begins with confirmation of hematuria. Medications such as chloroquine, rifampin, isoniazid, malin, and nitrofurantoin may cause a red-brown discoloration of the urine.[53] Similarly, foods such as beets, rhubarb, or blackberries may also cause discoloration. Because such urinary discoloration may be misinterpreted by parents as blood, screen with a urine dipstick test, which can exclude hematuria. A positive dipstick test result, however, must be followed by microscopic evaluation. Microscopic examination of the urine helps narrow the differential diagnosis: dysmorphic RBCs and casts suggest glomerulonephritis; WBCs and bacteria suggest infection; eosinophils may be seen in interstitial nephritis; and intact RBCs suggest lower tract causes of hematuria. Urinary crystals or stones may be seen in urolithiasis. A dipstick test result positive for blood without evidence of RBCs on microscopy suggests hemoglobinuria or myoglobinuria. Further evaluation of the urine includes rapid or quantitative evaluation for proteinuria, which can be seen in nephritis, nephrotic syndrome, and orthostatic proteinuria. Obtain other laboratory studies to identify serious causes of hematuria, such as hemolytic-uremic syndrome, acute poststreptococcal glomerulonephritis, or renal insufficiency.

Imaging US is the imaging method of choice for macroscopic hematuria without proteinuria or RBC casts in the urine and is done to rule out malignancy or structural defects. For patients with trauma or

macroscopic hematuria, a more complete anatomic evaluation is needed, including CT, angiography, or retrograde urethrography depending on the history and clinical suspicion.

TREATMENT

The treatment of hematuria, like its evaluation, depends on the suspected cause. Most children without signs of major or life-threatening etiologies can be managed as outpatients. Children with isolated microscopic hematuria do not require an extensive evaluation if the blood pressure and urine output are normal. Hematuria requires a more rigorous evaluation when the blood pressure is elevated or there is significant proteinuria, so consult with a nephrologist. Refer to a urologist if there is suspicion of a urogenital tract anatomic abnormality, obstructing calculi, tumor, or recurrent nonglomerular macroscopic hematuria.

CHRONIC KIDNEY DISEASE

Chronic kidney disease is defined as a glomerular filtration rate <60 mL/min/1.73 m^2 for more than 3 months regardless of other markers of chronic kidney disease or >60 mL/min/1.73 m^2 with evidence of structural damage, functional abnormalities, or pathologic abnormalities.[54] End-stage renal disease occurs when the glomerular filtration rate is <10% of normal for age. Mortality in end-stage renal disease usually results from cardiovascular causes (40% to 50%) and infection (20%).[55] The only definitive treatment for end-stage renal disease is transplantation; however, the morbidity and mortality associated with chronic renal replacement therapy have decreased.

Chronic kidney disease is classified into five separate stages based on glomerular filtration rate with the addition of categories of albuminuria and proteinuria (**Table 137-7**).[54] The recommended method for determination of glomerular filtration rate is with spot urine and serum creatinine using either the Schwartz or Counahan calculation. Twenty-four–hour urine collections for creatinine are no longer recommended.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Congenital renal disease is the most common cause of chronic renal failure in young children, whereas glomerulonephritis and reflux nephropathy predominate in older children. Congenital structural lesions include dysplasias and cystic malformations (e.g., polycystic kidney disease). Obstructive uropathy leading to end-stage renal disease may be caused by posterior urethral valves in boys, severe vesicoureteral reflux with recurrent infection, and ureteropelvic junction obstruction. End-stage renal disease in children can be caused by hereditary nephritis or acquired nephropathies such as hemolytic-uremic syndrome, glomerulonephritis, and cortical necrosis (more common in children with sickle cell disease).

CLINICAL FEATURES

Take a complete history to obtain information about changes in urination, fatigue, swelling, anorexia, emesis, bone pain, muscle cramps, headache, and change in mental status. Ask about signs and symptoms related to potential complications from chronic kidney disease.

TABLE 137-7 Staging of Pediatric Chronic Kidney Disease

Glomerular Filtration Stage	Albuminuria and Proteinuria Stage
G1: Normal GFR (≥90 mL/min/1.73 m^2)	A1: Normal to mildly increased (<30 milligrams albumin/gram creatinine)
G2: GFR between 60 and 89 mL/min/1.73 m^2	A2: Moderately increased (30 to 300 milligrams albumin/gram creatinine)
G3a: GFR between 45 and 59 mL/min/1.73 m^2	A3: Severely increased (>300 milligrams albumin/gram creatinine)
G3b: GFR between 30 and 44 mL/min/1.73m^2	
G4: GFR between 15 and 29 mL/min/1.73 m^2	
G5: GFR of <15 mL/min/1.73 m^2 (kidney failure)	

Abbreviation: GFR = glomerular filtration rate.

Complications associated with chronic kidney disease include disorders of fluids, electrolytes, and mineral metabolism. Anemia, hypertension, dyslipidemia, and endocrine abnormalities, including growth impairment, are present. End-stage renal disease is associated with cardiovascular problems and cerebrovascular events from malignant hypertension. Skeletal, hematologic, and intestinal abnormalities accompany renal failure. Renal failure predisposes to non-Hodgkin's lymphoma and skin cancer.

Pertinent physical findings in patients with end-stage renal disease include short stature, CNS problems, peripheral neuropathies, and rickets. Fever should prompt an aggressive search for a source. Fluid overload is suggested by peripheral edema and pulmonary congestion. Pericarditis is less common in children with end-stage renal disease than in adults. Abdominal pain and tenderness in children receiving peritoneal dialysis suggests peritonitis.

TREATMENT

The standard of treatment for most patients with end-stage renal disease is hemodialysis. Children <2 years of age are often treated with peritoneal dialysis because it is associated with fewer complications than hemodialysis in young children. Renal transplantation is the ultimate goal.

In dialysis patients presenting to the ED with fever, an aggressive search for infection must ensue. Use of empiric antibiotics is directed by the source of the infection (e.g., *S. aureus, S. epidermidis*), after cultures are drawn. If a patient on peritoneal dialysis presents with abdominal pain, suspect bacterial peritonitis. In patients presenting with severe electrolyte abnormalities, fluid overload, severe hypertension, or uremic pericarditis, urgent dialysis is indicated. Dialysis patients presenting with syncope should be evaluated for electrolyte abnormalities, hypovolemia, and cardiac dysrhythmias. See Chapter 90, "End-Stage Renal Disease," in the adult section for detailed discussion.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 138

Seizures in Infants and Children

Maija Holsti

INTRODUCTION AND EPIDEMIOLOGY

Unusual movements and changes in behavior in children often lead to an ED visit. Most seizure activity stops before the child is seen in an ED; therefore, history is key to the correct diagnosis. Although seizures account for many of these events, as many as 30% or more of paroxysmal events may be misdiagnosed as seizures.[1,2]

There are many different causes of pediatric seizures. The goal is to identify and treat the underlying cause. Some seizures require emergency management and extensive evaluation (e.g., status epilepticus, neonatal seizures), whereas others are common, benign, and need little or no ED evaluation (e.g., febrile seizures, first-time seizure in an otherwise well child). This chapter focuses on the diagnosis and management of ongoing seizures first and then discusses the approach to febrile seizures, neonatal seizures, and seizures in special populations (e.g., children with epilepsy, neurologic shunts, and trauma) under "Special Considerations/Populations."

The prevalence of pediatric seizures in the United States is approximately 1% of all children up to the age of 14 years and is highest in

children <1 year old (120 cases per 100,000) and in certain high-risk groups.[2-4] **Febrile seizures, the most common type of pediatric seizure, affect 3% to 4% of all children between 6 months and 5 years of age.**[5] Epilepsy is defined as recurrent unprovoked seizures.[4,5] Roughly 326,000 American children <15 years old have epilepsy, and the lifetime prevalence of epilepsy is roughly 1%.[3] The incidence of status epilepticus in developed countries is between 18 and 23 cases per 100,000 and is higher for younger children.[6]

PATHOPHYSIOLOGY

Seizures represent abnormal, excessive, paroxysmal neuronal activity in the brain, primarily the cortex. Glutamate released from firing neurons activates *N*-methyl-D-aspartic acid receptors that subsequently initiate and propagate seizure activity.[7] Seizures are inhibited by γ-aminobutyric acid, and failure of this inhibition facilitates seizure spread.[8] Incomplete myelination of the brain may limit secondary generalization of seizure activity in young infants, and a relative imbalance between glutamate and γ-aminobutyric acid with paradoxical excitation from γ-aminobutyric acid makes younger children more susceptible to seizures.[2,7]

Seizures can be primary (unprovoked) or secondary (provoked).[9,10] Primary seizures are often idiopathic or may be caused by congenital developmental abnormalities, in utero CNS insult (e.g., infection, infarct), or genetic factors. Secondary seizures may result from trauma or injury, infection, metabolic abnormalities (e.g., hypoglycemia, electrolyte abnormalities, inborn errors of metabolism), toxins, or systemic illness.[10]

CLINICAL FEATURES

TYPES OF SEIZURE

The clinical manifestation of seizures depends on the area(s) of the brain that are affected and whether the seizure activity is localized (focal) or widespread (generalized). Generalized seizures involve both hemispheres of the brain and lead to loss of consciousness, usually followed by a period of postictal drowsiness. In **convulsive generalized seizures or grand mal seizures,** rhythmic motor activity affects both sides of the body.[7] **Nonconvulsive generalized seizures produce loss of consciousness without motor activity and can only be recognized on electroencephalogram.**[7,11] In one study, nonconvulsive status epilepticus appeared in 51 of 117 critically ill patients, with 75% of these patients showing no clinical evidence of seizure activity.[12] Other examples of generalized seizures in children include **absence seizures** (brief episode of staring without a postictal state), **atonic seizures** (sudden loss of muscle tone with a sudden "drop" to the floor), and **myoclonic seizures.**[2,7]

Partial seizures represent focal neuronal activity, and clinical features correlate with the affected area. In simple partial seizures, the patient remains awake, whereas complex partial seizures are focal but produce alterations of consciousness.[2] Partial seizures may secondarily spread and become generalized. Young children with new-onset focal seizures are at increased risk for structural anatomic abnormalities, and neuroimaging is more likely to be abnormal in these children.[13]

Although status epilepticus was originally defined as a seizure lasting longer than 30 minutes, today **any "prolonged" seizure or recurrent seizures lasting >5 minutes without return to full consciousness are considered status epilepticus.**[6,14] Status epilepticus is a medical emergency, and rapid termination is important to prevent irreversible neuronal damage.[6] Refractory status epilepticus is a prolonged seizure that cannot be controlled with two or more doses of standard treatment.[6] **Nonconvulsive status epilepticus may present as a prolonged postictal state**[12] **and must be considered in any patient with altered mental status**; morbidity and mortality increase when nonconvulsive status epilepticus is untreated, although less so than with untreated convulsive status epilepticus.[7,11]

HISTORY

Obtain a detailed history of the event from a reliable observer. **Table 138-1** lists historical clues that may help identify the etiology of a seizure.[15] Patient age alone is an important consideration in the potential cause of seizures (**Figure 138-1**). Other important details include the events surrounding the seizure (e.g., emotional upset and crying that may indicate breath holding in a toddler), the nature of the seizure activity (e.g., tonic stiffening, clonic jerks, generalized or focal characteristics), the duration of the event (often difficult for frightened parents to accurately report), and postictal observations and duration. Seizure-provoking events can include recent illness, possible trauma, ingestions, and medications (both over-the-counter and prescribed). In addition to the past medical history (especially epilepsy), recent changes or missed doses of medication can also provoke seizure activity. A developmental history is important, as children with underlying developmental delay are at increased risk for epilepsy. A family history of febrile seizures, epilepsy, or neurologic disease is also important for prognosis.

TABLE 138-1 History Relevant to the Child Presenting With Seizure

- Age of child
- Seizure duration and description of seizure activity prior to arrival
- History of trauma
- History of possible ingestion
- History of fever
- History of associated illness (vomiting or diarrhea)
- Feeding problems (especially in an infant)
- Changes in behavior
- History of seizures and type of seizures
- History of developmental delay
- Other medical history
- Medications
  - Anticonvulsants with milligrams per kilogram dose and recent changes or missed doses
  - Recent new medications (may alter metabolism of antiepileptic drugs)
  - Allergies
- Developmental history
- Family history of seizures

PHYSICAL EXAMINATION

Perform a complete head-to-toe examination with the patient undressed. The physical examination should be focused on whether the patient is actively seizing and identify potential causative factors (e.g., head trauma, rash indicative of infection, neurocutaneous lesions). **Table 138-2** outlines a number of clinical signs and symptoms of seizures. Rhythmic repetitive movement, incontinence of bowel or bladder, postictal state after a seizure, and tongue biting are strong clues to a seizure. Lateral tongue biting was found to have a specificity of 100% and a sensitivity of 24% for the occurrence of a seizure.[2,16]

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS AND CONDITIONS MASQUERADING AS SEIZURES

A number of benign conditions may masquerade as seizures, leading to an ED visit; up to 30% of new-onset paroxysmal events may be misdiagnosed as epileptic.[1,2] **Syncope is the most common condition that may be mistaken for seizures**; however, there are many differentiating features.[1,2] Syncope is commonly preceded by dizziness, weakness, tunnel vision, pallor, and diaphoresis (presyncopal aura). It is also associated with a brief loss of consciousness and a quick recovery with no postictal state (see Chapter 130, "Syncope, Dysrhythmias, and ECG Interpretation in Children"). Seizures, on the other hand, may be preceded by an aura but usually do not have a provoking factor noted before the event. Seizures are associated with tongue biting, rhythmic motor activity, incontinence, and a slow recovery and postictal state. **Table 138-3** lists nonepileptic causes of syncope and abnormal movements that can

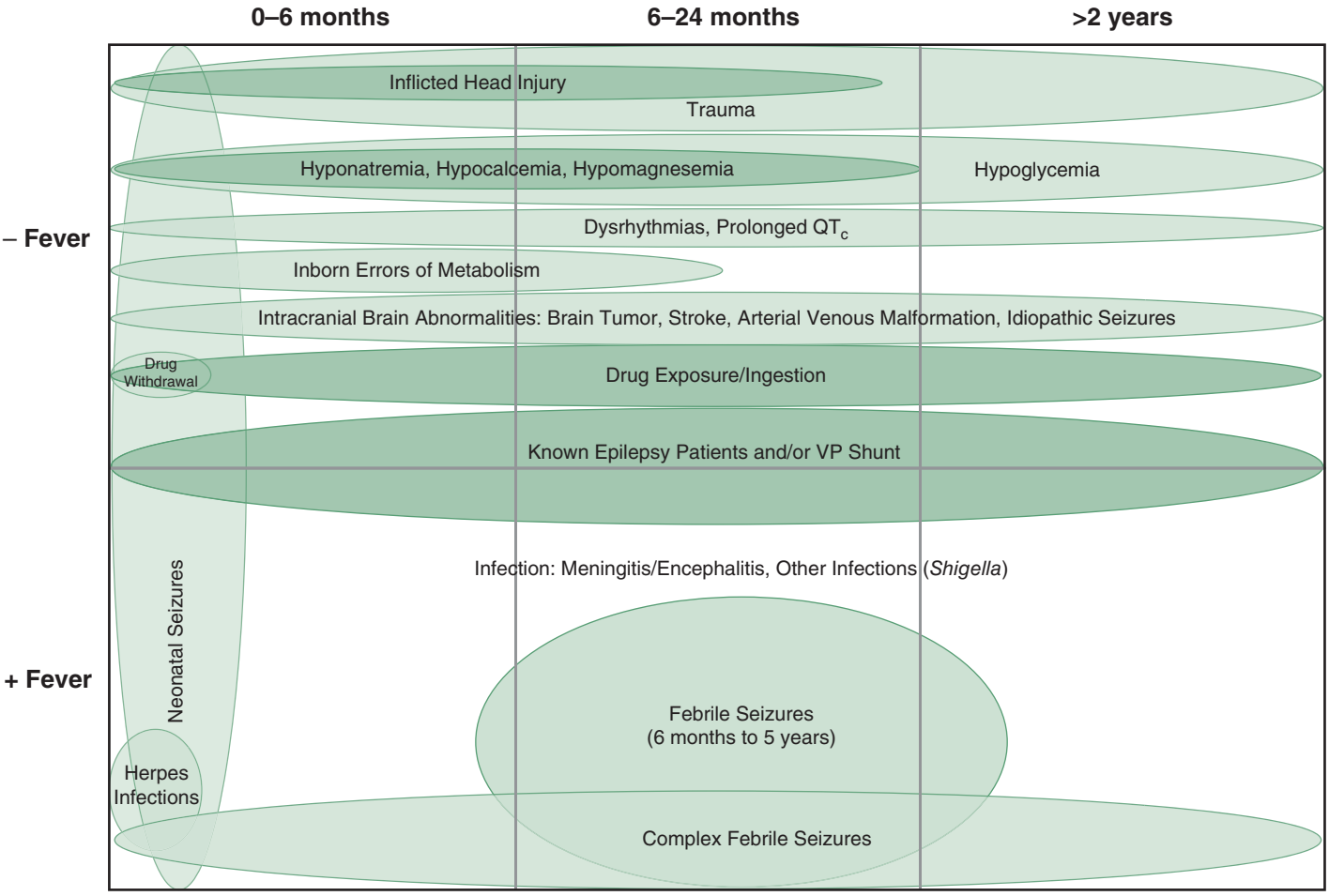

FIGURE 138-1. Age-based approach to the evaluation of pediatric seizures. VP = ventriculoperitoneal.

mimic seizures. In infants, myoclonic jerks, sleep myoclonus, shudder attacks, and Sandifer's syndrome (gastroesophageal reflux) are common.[2] In toddlers, breath-holding spells become more prevalent.[2] Self-stimulation and night terrors should be considered in preschool and young school-age children, whereas tic disorders typically begin in older children.[2] Psychogenic nonepileptic seizures may present in adolescents with and without epilepsy.[2]

TABLE 138-2 Signs and Symptoms Associated With Seizures

- Head deviation
- Eye deviation
- Rhythmic or repetitive arm or leg movement
  - Posturing
  - Stiffening
  - Jerking
- Change in breathing pattern
- Increase in heart rate
- Increase in blood pressure
- Cyanosis or apnea
- Eye dilatation
- Vomiting
- Lip smacking
- Tongue biting
- Incontinence of bowel or bladder
- Postictal or sleepy period after a seizure
- Mood or behavior changes before a seizure
- Subjective aura before seizure (noted in older patients)

LABORATORY TESTING

Check bedside glucose on all seizing or postictal patients. Additional laboratory evaluation is directed by the history and is not routinely indicated for febrile seizures or first-time afebrile seizures that are nonfocal in a child with a normal examination (see "Special Considerations/Populations" below).[15,17] If indicated by the history and examination, labs that may be helpful include electrolytes (including calcium), serum antiepileptic medication levels, toxicologic testing, and spinal fluid for evaluation of possible CNS infection in the appropriate setting.[15] Urine culture and analysis may be indicated in the evaluation of febrile seizures in the child with fever and no identifiable source.

IMAGING

Similar to laboratory testing, imaging should be directed by the history and examination. Routine neuroimaging is rarely indicated or helpful. When trauma is suspected, in infants less than a year old (inflicted injury), or in the setting of focal deficits, obtain a head CT.[13] Todd's paralysis is a temporary condition characterized by a focal deficit of unknown etiology that can last up to 36 hours after a seizure. The paralysis is usually unilateral and lasts on average 15 hours; however, it can be bilateral and involve a patient's speech or vision. It may be impossible to distinguish Todd's paralysis from stroke or hemorrhage, and emergent imaging should be considered. Most first-time seizures in the well-appearing child with a normal examination can follow up with neurology to determine if further imaging is necessary.[13,18] If necessary, outpatient MRI avoids ionizing radiation and provides better anatomic detail.[13,18]

TABLE 138-3 Events Masquerading as Seizures

Syncope

Breath-holding spells

- Cataplexy
- Narcolepsy
- Vasovagal event
- Standing for long periods of time
- Standing quickly from lying or sitting
- Hair-grooming syncope
- Earring-changing syncope
- Micturition syncope
- Emotional distress or pain
- Hypoglycemia
- Hypovolemia

Sandifer's syndrome (gastroesophageal reflux)

- Acute life-threatening event
- Acute dystonic reactions/drug reactions (i.e., promethazine [Phenergan®])
- Movement disorders

Tics

Myoclonic jerks

Chills or rigors

- Shudder attacks
- Mannerisms
- Self-stimulation
- Choreoathetosis

Night terrors, sleep walking

- Migraine variants
- Benign paroxysmal vertigo

Nonepileptic paroxysmal event (pseudoseizures)

Note. Events in bold are more common.

ANCILLARY TESTS

Consider obtaining an ECG for evaluation of syncope with seizure activity to rule out arrhythmia.[15] Emergent electroencephalogram monitoring may be required for patients with refractory status epilepticus (especially those requiring rapid-sequence intubation with a paralytic) or concern for nonconvulsive status epilepticus[19-21]; otherwise, outpatient electroencephalogram may help identify specific epilepsy syndromes and guide future treatment.

SUMMARY OF APPROACH TO EVALUATION

Figure 138-2 summarizes the approach to the evaluation of pediatric seizures.

TREATMENT

PREHOSPITAL

Children may have been treated at home or by EMS personnel. Take this into consideration when treating refractory status epilepticus.[6,22]

Benzodiazepines (**Table 138-4**) are the first-line treatment for prolonged seizures because of their rapid onset and effectiveness[23]; however, their effectiveness is inversely related to the duration of the seizure, and treatment should not be delayed.[6,10,15] Not all benzodiazepines or routes are available in the prehospital setting, and establishing IV access can be difficult in a child who is having a seizure. Benzodiazepines may be given by the intranasal, buccal, rectal, or intraosseous route when an IV is difficult to place. Although not significantly different in efficacy, lorazepam is recommended if an IV has been placed; midazolam is recommended if intramuscular, intranasal, or buccal administration is performed; and diazepam is recommended if given rectally.[2,6,7,10,15,23-28]

Rectal diazepam is one "rescue" medication commonly used at home and by EMS personnel. The advantage is that no refrigeration or IV line is needed. The disadvantage is the need for rectal administration. Midazolam, also an effective rescue medication, can be given via the intranasal route using a mucosal atomization device.[24,25] Midazolam can also be given buccally.[6,10,15,27] Lorazepam is not generally used in the prehospital setting because of its need for refrigeration. Although IV lorazepam is generally preferred, there is evidence that intranasal lorazepam using a mucosal atomization device may be as effective as IV lorazepam in the treatment of status epilepticus.[28]

ED TREATMENT

Most seizures stop within 5 minutes and do not require medical treatment. **Status epilepticus is a medical emergency, however, and is more responsive to medications when treated early, and treatment becomes less effective with time.**[6,10,15] To expedite therapeutic decisions and avoid treatment delays, status epilepticus management guidelines are recommended; an overview of one treatment algorithm for status epilepticus is depicted in **Figure 138-3**.[6,29-31]

Administer oxygen by facemask and institute continuous pulse oximetry and cardiac monitoring. Establish IV or IO access, but administer medication early via alternative routes (intranasal, IM, PR, buccal) if there is delay.[2,6,10,15,32] Providers should obtain bedside glucose testing for afebrile seizures because hypoglycemia represents an easily correctable cause of seizures.[2,6] Additional laboratory studies and imaging should be directed by the history and examination as the yield for routine testing is abysmally low.[2,6,7] Subtherapeutic antiepileptic drug levels are found in almost one third of children with epilepsy presenting in status epilepticus.[32] Meningitis and encephalitis should be considered in all children who present with fever and status epilepticus or multiple seizures; however, research supports using clinical judgment when deciding to do a lumbar puncture because the rate of bacterial meningitis is low (0.5% to 2.4%) in a fully immunized patient.[8,33]

The decision to intubate is clinical. Intubate for apnea and persistent hypoxia. Blood gas concentrations are not needed to guide the decision to intubate because the seizure itself causes a metabolic and respiratory acidosis.[2,6,10] **The use of a paralytic with intubation obscures the ability to assess ongoing seizure activity, so arrange continuous electroencephalogram monitoring for intubated patients with status epilepticus.**[6,21]

Administer a **benzodiazepine** (Table 138-4) as the initial treatment for status epilepticus.[2,6,7,10,22] Benzodiazepines are effective in terminating seizure activity and act by binding to γ-aminobutyric acid receptors[7]; they are preferred over other medications because of their rapid onset of action.[6,7,10,15,22,23] The decision of which benzodiazepine to give should be dictated by the route readily accessible. A particular benzodiazepine has not proven to be more or less effective in the cessation of seizure activity; however, delays in treatment make seizures increasingly harder to stop.[2,6,7,10,15,22,23]

Generally, if two doses of benzodiazepines are administered without effect, additional doses are unlikely to be successful and increase the risk for respiratory depression.[2,6,7,10,15,22,23,31] Because there is no standard treatment for refractory status epilepticus, approaches to treatment and order of medication administration may vary.[2,6,10,17,31,32,34-36] Figure 138-3 represents one approach to refractory status epilepticus.

If a seizure persists after two doses of a benzodiazepine have been given, fosphenytoin, levetiracetam, or valproic acid are preferred second-line treatment choices.[2,6,10,17,31,34-36] The National Institutes of Health–funded Established Status Epilepticus Treatment Trial will compare these three treatment choices for convulsive status epilepticus. A provider should generally choose two of the four medications for refractory status epilepticus and then move on to a fourth-line treatment option if a seizure persists. **Table 138-5** summarizes the medications used for refractory status epilepticus.

Second- And Third-Line Treatments Phenytoin and valproic acid, metabolized hepatically, and levetiracetam, metabolized renally, may affect second- and third-line choices in patients with hepatic and renal dysfunction.[6,7,10,15] **Phenytoin** and its prodrug, **fosphenytoin**, inhibit neuronal firing by stabilizing sodium channels and reducing neuronal

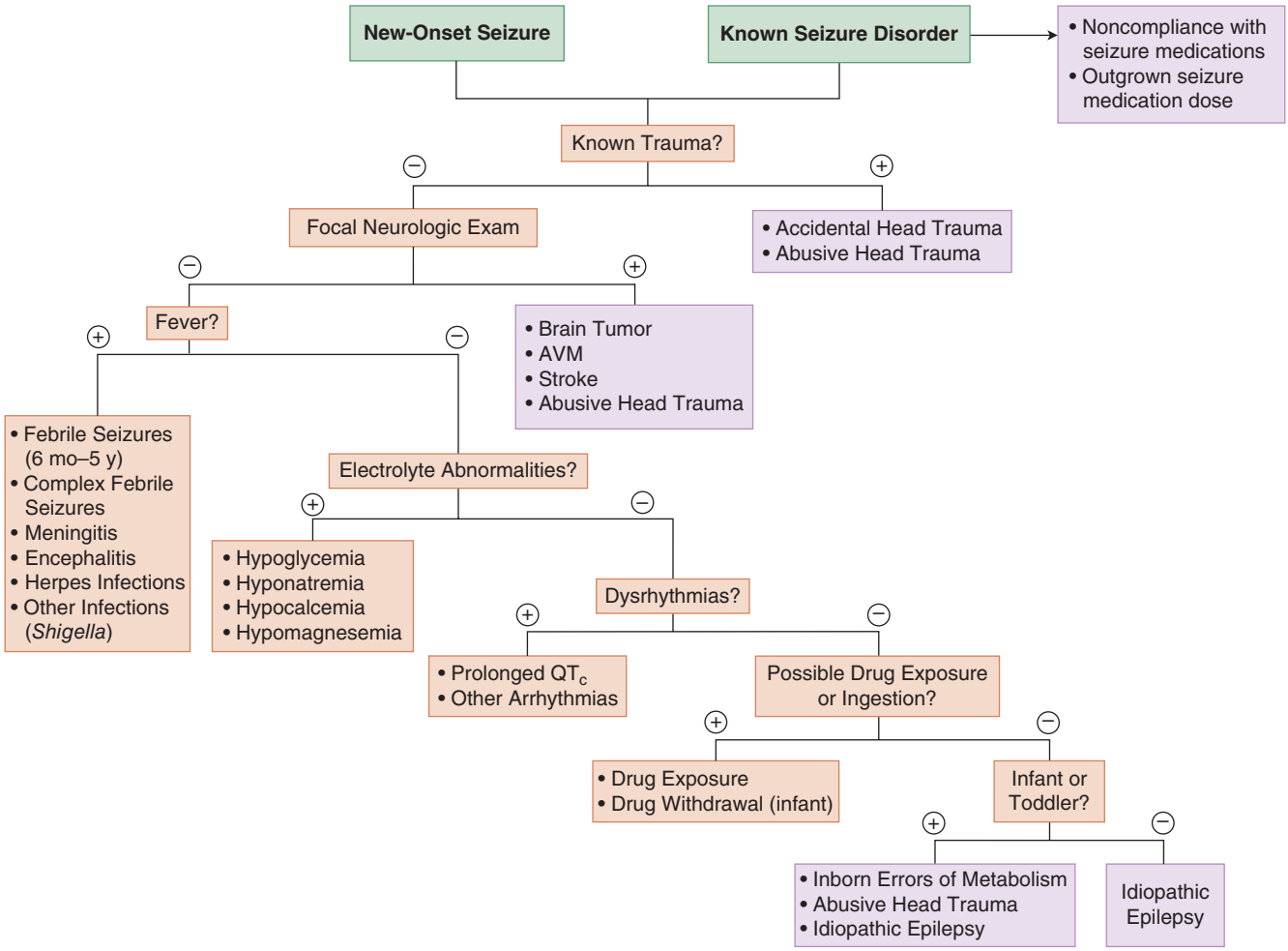

FIGURE 138-2. General approach to the evaluation of pediatric seizures. AVM = arteriovenous malformation.

calcium uptake.[6,7,10,15,34-36] **Fosphenytoin** is safe and effective; it can be administered more rapidly with fewer cardiac effects than phenytoin, which can precipitate in an IV line and cause significant tissue injury with extravasation.[6,7,10,15] Phenobarbital is *not* preferred as a second-line treatment, except in neonates, because both phenobarbital and benzodiazepines have the same mechanism of action and bind γ-aminobutyric acid receptors and can cause significant risk for respiratory failure.[6,7,10,15]

Levetiracetam is also safe and effective for treatment of status epilepticus, although it has not been prospectively compared with other anticonvulsants.[6,10,15,34,37-44] Levetiracetam is eliminated solely via renal excretion and has no hepatic metabolism, and it has few adverse effects and essentially no drug and food interactions.[34,37-44] Another advantage of levetiracetam over fosphenytoin (phenytoin) and phenobarbital is that it is commonly used for maintenance therapy for multiple seizure types.[34,37-44]

Phenobarbital is most commonly used in neonates who are often maintained on daily phenobarbital for subsequent seizure control.[45] Side effects include sedation and cardiorespiratory depression, which may be amplified by benzodiazepines.[6,10,15]

Valproic acid is approved by the U.S. Food and Drug Administration for treatment of status epilepticus and is also effective for partial and generalized seizures.[46] Consider valproic acid for treatment of children already taking this medication who are suspected of having subtherapeutic levels. A dose of 20 to 40 milligrams/kg of IV valproic

TABLE 138-4 Benzodiazepines for Initial Treatment of Prolonged Seizures

Drug	Route	Dose*	Maximum	Onset of Action	Duration of Action
Lorazepam	IV, IO, IN	0.1 milligram/kg	4 milligrams	1–5 min	12–24 h
	IM	0.1 milligram/kg	4 milligrams	15–30 min	12–24 h
Diazepam	IV, IO	0.1–0.3 milligram/kg	10 milligrams	1–5 min	15–60 min
	PR	0.5 milligram/kg	20 milligrams	3–5 min	15–60 min
Midazolam	IV, IO	0.1–0.2 milligram/kg	4 milligrams	1–5 min	1–6 h
	IM	0.2 milligram/kg	10 milligrams	5–15 min	1–6 h
	IN	0.2 milligram/kg	10 milligrams	1–5 min	1–6 h
	Buccal	0.5 milligram/kg	10 milligrams	3–5 min	1–6 h

Abbreviation: IN = intranasal.

*Initial and repeat doses are the same.

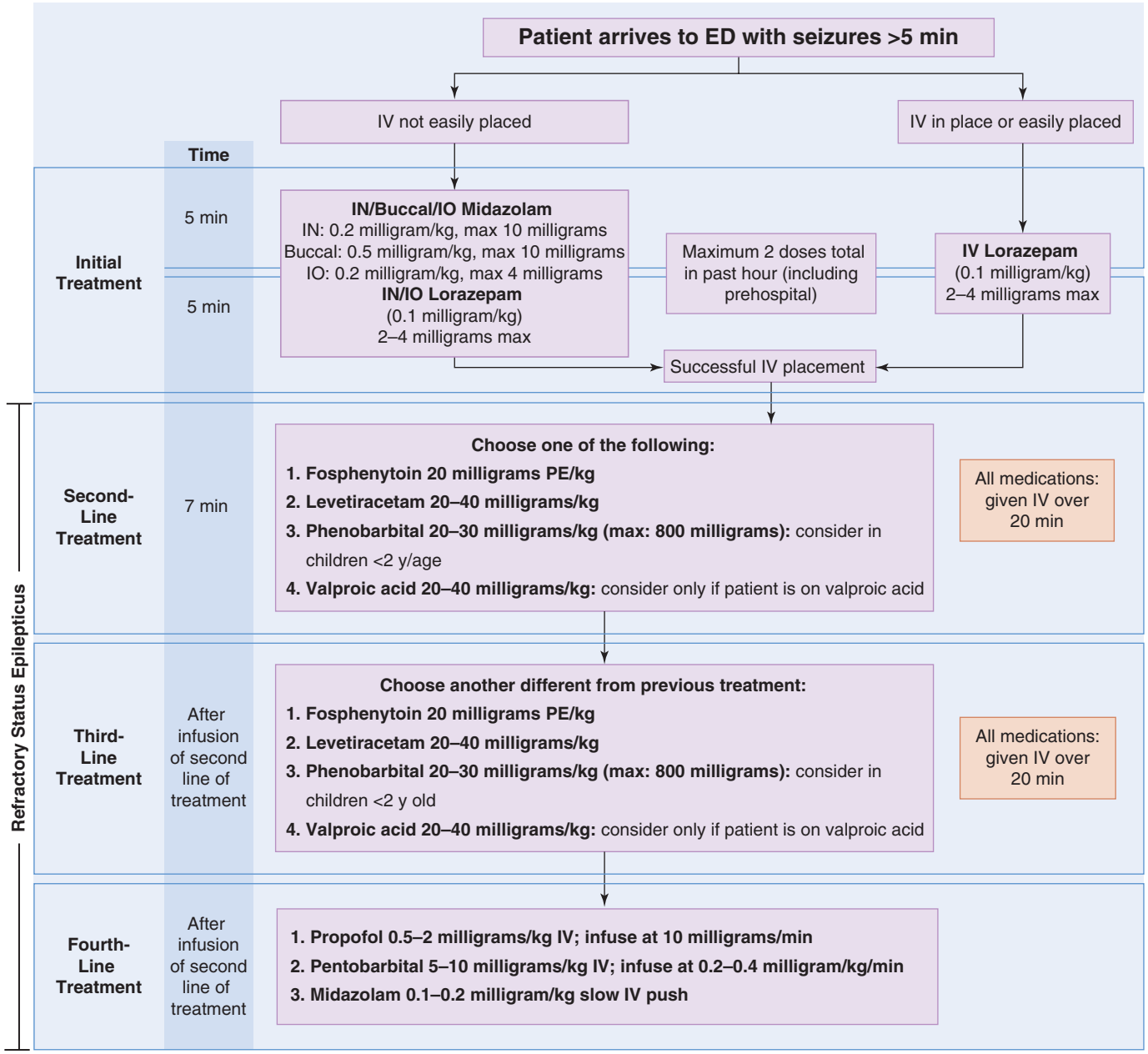

FIGURE 138-3. Initial treatment of status epilepticus: an example of one approach. IN = intranasal; PE = phenytoin sodium equivalents.

acid effectively terminates seizure activity with few side effects or less sedation.[2,6,7,10,15,46,47] Use with caution in children at risk for metabolic disease, because in rare cases it may cause hepatic failure and has rarely been associated with thrombocytopenia.[2,6,7,10,15,46,47]

Fourth-Line Treatment **Propofol** is an IV anesthetic agent that acts on γ-aminobutyric acid receptors differently from benzodiazepines or barbiturates and has been shown to effectively treat refractory status epilepticus better than pentobarbital.[10,15,35,48] Propofol has a rapid onset

TABLE 138-5 Medications for Refractory Status Epilepticus

Drug	Route	Loading Dose	Repeat Dose	Maximum	IV Infusion
Fosphenytoin	IV, IM	20 milligrams/kg PE	5–10 milligrams/kg PE	30 milligrams/kg PE	3 milligrams/kg/min PE
Phenobarbital	IV	20–30 milligrams/kg	5–10 milligrams/kg	40 milligrams/kg	1–30 milligrams/min
Valproic acid	IV	20–40 milligrams/kg	15–20 milligrams/kg	40 milligrams/kg	5 milligrams/kg/h
Levetiracetam	IV	20–40 milligrams/kg	—	3 grams	—
Pentobarbital	IV	5–10 milligrams/kg	1–2 milligrams/kg	15 milligrams/kg	0.5–5.0 milligrams/kg/h
Propofol	IV	0.5–2.0 milligrams/kg	0.5–1.0 milligram/kg	5 milligrams/kg	1.5–4.0 milligrams/kg/h
Midazolam	IV	0.1–0.3 milligram/kg	0.1–0.2 milligram/kg	10 milligrams	0.05–0.4 milligram/kg/h
Ketamine	IV	0.5–2 milligrams/kg	May repeat loading dose	—	5–20 micrograms/kg/min

Abbreviation: PE = phenytoin sodium equivalents.

of action, but it is quickly metabolized and should be followed by continuous infusion if seizure activity persists and must be infused slowly because of the potential for serious side effects, including bradycardia, apnea, and hypotension.[10,15,35,48] Prepare for intubation and provide continuous cardiopulmonary monitoring when administering propofol for seizures.[10,15,35,48] Patients receiving sustained propofol administration (>24 hours) should be monitored for development of "**propofol infusion syndrome**" (metabolic acidosis, rhabdomyolysis, renal failure, and cardiac failure).[49]

Ketamine, a noncompetitive *N*-methyl-D-aspartate–type glutamate receptor antagonist, may be effective in later stages of refractory status epilepticus.[10] It is also commonly used for intubation.[15] Recently, literature does not support concerns that ketamine causes increased intracranial pressure.[10,15,50]

A "**pentobarbital coma**," or continuous infusion, has been used for refractory status epilepticus not responsive to multiple anticonvulsant treatments with reported efficacy between 74% and 100%.[34] Side effects include respiratory depression, hypotension, and decreased cardiac contractility, and most patients require intubation and inotropic support.[6,10,15,35,36]

Midazolam infusion has a low rate of adverse effects; however, compared with propofol and pentobarbital, midazolam has a higher rate of seizure recurrence.[6,7,10,15,35]

Treatment of Glucose and Electrolyte Abnormalities Most laboratory results are not immediately available when treating status epilepticus; however, a glucose should be checked at a minimum (see Chapter 146, "Metabolic Emergencies in Infants and Children").[15] Abnormal glucose, sodium, calcium, and magnesium, especially low levels, can cause seizures, particularly in infants.[2] Seizures caused by abnormal electrolytes respond poorly to conventional medication but do respond to replacement electrolyte therapy (see Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children").[2,6,10,15]

Hypoglycemia can be the cause or an effect of prolonged seizures, and bedside testing is essential in seizing patients. Treat hypoglycemia with a rapid infusion of 2 mL/kg of 25% dextrose in water or 4 to 5 mL/kg of 10% dextrose in water.

Hyponatremia (serum sodium <135 mEq/L) is most commonly seen in infants <6 months of age and sometimes in athletes and can cause seizures, especially if the serum sodium is <120 mEq/L.[9] The goal of therapy is to correct the level to >120 mEq/L quickly and then correct to normal levels over the next 24 hours (see Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children"). Treat the seizing patient with hyponatremia with 3% NaCl 1 to 2 mL/kg over 20 minutes or begin an infusion of 20 mL/kg of 0.9% NaCl if 3% NaCl is not immediately available. The sodium level should be rechecked after the bolus to determine whether a second bolus is necessary.

Hypocalcemia is more common in neonates and young infants and may be associated with congenital anomalies such as DiGeorge's syndrome. Calcium gluconate, 100 milligrams/kg (rate <100 milligrams/min), is preferred over calcium chloride when infusing through a small peripheral IV because calcium chloride can cause local irritation.[9]

Hypomagnesemia (serum magnesium <1.5 mEq/L) is treated with magnesium sulfate, 50 milligrams/kg IV infused over 30 minutes.

DISPOSITION AND FOLLOW-UP

Infants >6 months of age with febrile seizures (see later) and children with single seizures lasting <15 minutes who return to baseline mental status and have no focal neurologic deficits or secondary cause of seizure requiring ongoing treatment are candidates for discharge and outpatient follow-up with their primary care provider or a pediatric neurologist (in the case of new-onset seizures or breakthrough seizures in children with epilepsy).

Parents of discharged children should be given guidance to prevent injury in association with subsequent seizures: children should not be in a position where they could drown, fall, or injure someone else during a seizure. Caregivers should never allow their children to bathe or swim alone. If they are old enough to take a shower, children should not lock the bathroom door. Those old enough to drive should not be allowed to do so until cleared by a neurologist.

Information about recurrence risk should also be provided in the ED. Although the recurrence risk for a particular child cannot be predicted, population statistics pertaining to febrile seizures and first-time seizure recurrence can be shared with parents (see the following section "Special Considerations/Populations").

In many cases, children treated for seizures who return to their baseline may go home with close follow-up. Some children may need to be monitored in the hospital for recurrence or side effects from medication, especially if they have not returned to baseline. Children with refractory status epilepticus usually require intensive care for continuous infusion of antiseizure treatment or induction of a "pentobarbital coma."

SPECIAL CONSIDERATIONS/POPULATIONS

FEBRILE SEIZURES

Febrile seizures are common in the general pediatric population, with an incidence of 2% to 5%.[51]

Simple Febrile Seizures The definition of a simple febrile seizure is a generalized tonic-clonic seizure lasting <15 minutes with a fever 38°C (100.4°F) in a child 6 months to 6 years of age that occurs only once in a 24-hour period.[51] The American Academy of Pediatrics holds that **no blood studies, neuroimaging, or electroencephalogram is necessary for simple febrile seizures** and the evaluation should focus on identifying the source of fever (e.g., urinalysis and culture).[5,17,33,51-54] The American Academy of Pediatrics does recommend that a lumbar puncture be strongly considered in these children when there are **clinical signs or symptoms** that suggest meningitis or intracranial infection (see Chapter 120, "Meningitis in Infants and Children").[17,33,51-53] **Although bacterial meningitis is rare even in children with fever and seizures, the American Academy of Pediatrics recommends consideration of lumbar puncture for infants 6 to 12 months of age who are unimmunized for *Haemophilus influenzae* type B or *Streptococcus pneumoniae* and those taking antibiotics, which can mask the signs and symptoms of meningitis.**[17,33,51-55]

Parents of children experiencing a simple febrile seizure need education regarding the natural history of febrile seizures. Only 50% of children <12 months old and 30% of children >12 months old will have another simple febrile seizure.[17,52,55] Having a febrile seizure does not mean that a child will develop epilepsy. Children who experience a simple febrile seizure have roughly the same 1% risk as the general population of developing epilepsy by the age of 7 years.[17,52,55] Factors that increase that risk up to 7% include a family history of seizures, complex or multiple febrile seizures, and first febrile seizure before 12 months of age.[5,17,51,53,54] Other factors that increase the risk of recurrence include developmental delay, focal seizures, Todd's paralysis, focal neurologic findings on examination, and abnormal findings on electroencephalogram, CT, or MRI.[5,17,51,53,54]

Complex Febrile Seizures Complex febrile seizures are defined as seizures with fever that last >15 minutes, recur within a 24-hour period, are focal, or occur in children <6 months or >6 years of age without any signs of serious infection.[5,17,51-55] **Routine blood tests, lumbar puncture, and imaging are not indicated, even in the setting of complex febrile seizure, in the absence of other signs or symptoms.**[17,33,52,54,55] One study noted that children with fever and seizures lasting >30 minutes had a significantly higher incidence of bacterial meningitis (15% to 18%) than children with simple febrile seizures (0.4% to 1.2%).[56] Other studies, however, found meningitis to be rare without clinical signs and symptoms of meningitis[8,33]; one study found only two patients with meningitis among 526 patients with complex febrile seizures, and both patients had clinical signs and symptoms of meningitis.[55]

Children with a prolonged seizure associated with a fever who appear ill should undergo evaluation to rule out serious bacterial infection in the blood and cerebrospinal fluid,[17] although parenteral antibiotics should not be delayed while sick children are being evaluated (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children" and Chapter 120, "Meningitis in Infants and Children").[17,52,55]

Treatment of Febrile Seizure Anticonvulsant therapy is not recommended for simple febrile seizures because side effects outweigh the

minor risks of seizure recurrence.[51,53] Although antipyretics are indicated in children with fever, there is no evidence that antipyretics can prevent subsequent febrile seizures.[17,51,53,57]

FIRST AFEBRILE SEIZURE

Practice guidelines for the evaluation of a first unprovoked seizure in a child who returns to baseline following the seizure suggest that **routine laboratory evaluations and emergent neuroimaging are not necessary**.[2,18,58] If there is evidence that the child had vomiting or diarrhea, is dehydrated, or has failed to return to baseline, laboratory tests are recommended. A toxicology screen should also be included if there is concern for drug exposure or substance abuse or the cause of the seizure cannot be determined. Lumbar puncture is unnecessary unless there is a clinical concern for meningitis or encephalitis.[2] An electroencephalogram should be performed, although availability may be limited and the timing is unclear in a child who has returned to baseline and it is rarely indicated in the ED.[2,15] An electroencephalogram within 24 hours of the seizure is most likely to show abnormalities and can help identify patients suspected of being in continuous convulsive and nonconvulsive status epilepticus.[2,6,47,59]

Indications for emergent head CT include children with a condition predisposing them to intracranial abnormalities, trauma, and children with focal seizures who are younger than 33 months of age.[2] Patients who do not meet the criteria for high risk and are well appearing may be discharged with outpatient follow-up. Outpatient MRI should be considered in any child with any of the following: significant cognitive or motor impairment, abnormal findings on neurologic examination, abnormal electroencephalogram findings, partial seizure, or infants <1 year of age.[2,58]

The overall risk of recurrence after a single afebrile seizure is approximately 54%.[2] Factors that increase this risk are a family history of seizures, previous febrile seizures, developmental delay, abnormal CT or MRI findings, presence of focal deficits on neurologic examination, Todd's paralysis, abnormal electroencephalogram findings, and seizure occurring during sleep.[2,58] Most neurologists do not recommend initiating daily anticonvulsant medications after a first seizure.[2,58] Noninitiation of treatment does not increase the risk of epilepsy, affect prognosis, or increase the risk of intractable epilepsy or death, but does allow the physician to better clarify the type and frequency of seizures and also avoids the side effects of unnecessary daily anticonvulsant medications in those not destined to experience recurrence.[2,58]

NEONATAL SEIZURES

Neonates do not have a fully developed neurologic system, and seizures in this age group (<1 month) can be subtle, are more likely to be focal, and often carry a poor prognosis.[2,45,60]

Identifying seizure activity in the neonate and distinguishing it from normal newborn myoclonus and jitters can be challenging. Subtle focal movements or stereotyped activities (e.g., lip smacking, eye deviation, or bicycling) may represent 50% of seizure activity; neonates less often have generalized tonic-clonic seizures.[2,45,60] Apparent life-threatening events with pallor or cyanosis and a change in muscle tone may be a manifestation of seizure activity.[11,19,49,61]

A birth and maternal history may identify risks for congenital or neonatal infection (e.g., herpes simplex virus, cytomegalovirus, or group B streptococci) or potential withdrawal from maternal narcotics.[45] Complications with labor and delivery may suggest birth asphyxia with subsequent seizures. Regardless of the history or presence of fever, neonates with witnessed seizures require extensive evaluation. Obtain cultures of blood, urine, and cerebrospinal fluid; test for herpes simplex virus; and begin empiric parenteral antibiotics and acyclovir.[2,45] Toxicologic evaluation may provide the physician with evidence of withdrawal or overdose of abused substances. Neonates with seizures are more likely to have electrolyte abnormalities than older children, and electrolytes including calcium and glucose should be measured.[2,45] Consider head CT for concerns of nonaccidental trauma, intracranial hemorrhage, infarction, or mass (even without external signs of injury).[2,45] Finally, if inborn errors of metabolism are suspected, obtain serum levels of lactate and ammonia, as well as serum amino acids and urine organic acids (see Chapter 146, "Metabolic Emergencies in Infants and Children").[2,45] Neonates with witnessed seizure require admission to the hospital.

Treat the actively seizing neonate with benzodiazepines as with older children; consider phenobarbital for second-line therapy because many will be sent home on phenobarbital. Identify and treat hypoglycemia and electrolyte abnormalities.

TABLE 138-6 List of Anticonvulsants Commonly Used in Children

Before 1993	1993–2005	2009–2011
Carbamazepine	Felbamate	Vigabatrin
Clonazepam	Gabapentin	Rufinamide
Diazepam	Lamotrigine	Lacosamide
Ethosuccimide	Levetiracetam	Clobazam
Lorazepam	Oxcarbazepine	Ezogabine
Phenobarbital	Pregabalin	
Phenytoin	Tiagabine	
Primidone	Topiramate	
Valproic acid	Vagus nerve stimulation	

SEIZURES IN CHILDREN WITH EPILEPSY

Parents, old records, and pediatric neurologists can be very helpful in identifying past causes of seizures, successful (and unsuccessful) treatments, and other issues that can help direct the care of patients with epilepsy presenting to the ED with seizure. **Table 138-6**[62] lists common anticonvulsants prescribed for children with epilepsy. Subtherapeutic drug levels may result when a child outgrows a previously prescribed dose, vomits medications due to an intercurrent illness, starts a new medication (due to changes in drug pharmacokinetics from drug interactions), or does not adhere to the original drug regimen. Subtherapeutic drug levels are a common cause of breakthrough seizures, and serum levels of home antiepileptic medications should be checked as part of the routine ED evaluation of these patients, although results may not be readily available for some newer agents. When low levels are identified, the cause should be determined so that proper adjustments in daily anticonvulsant dosing can be made with advice from the patient's neurologist.

Children with epilepsy may have a lower seizure threshold with febrile illness, even with therapeutic anticonvulsant levels, and the ED evaluation in these situations may be limited to determining the source of fever. Lumbar puncture is unnecessary unless there are clinical signs or symptoms of meningitis.[2,8,33]

SEIZURES IN CHILDREN WITH VENTRICULOPERITONEAL SHUNTS

Many children with ventriculoperitoneal shunts also have a medical history of seizures. Considerations include underlying epilepsy, shunt malfunction, and CNS infection. The standard approach to the evaluation for a shunt malfunction consists of a radiographic ventriculoperitoneal shunt series and a head CT or "quick brain MRI" to evaluate for increased ventricular size. If CNS infection is a concern, a pediatric neurosurgeon should be consulted and the shunt tapped for cerebrospinal fluid analysis and culture. Seizures in children with ventriculoperitoneal shunts are more likely to be related to shunt infection than to mechanical shunt malfunction, especially if associated with fever,[63,64] and the risk of infection increases in children with a history of a prior shunt infections.[63,64] In most cases, consulting past medical records, parents, and the neurosurgeon who placed the shunt is needed for prudent decision making (see Chapter 148, "The Child with Special Healthcare Needs").

SEIZURES IN TRAUMA

"Impact seizures" (seizures that occur within minutes of head trauma) do not, by themselves, increase the risk of having an intracranial injury; seizures that occur in a more delayed fashion, however, are more indicative of severe injuries.[65] Guidelines for the

ED evaluation and management of head injury increasingly focus on strategies for risk stratification in order to avoid the potential long-term effects of ionizing radiation and are discussed in detail in Chapter 111, "Minor Head Injury and Concussion in Children." Children with identified intracranial injury and a witnessed seizure should be treated with a loading dose of antiepileptic medication, typically fosphenytoin or levetiracetam, to prevent short-term recurrence that can worsen traumatic brain injury and increase intracranial pressure[66]; benzodiazepines remain first-line treatment for active seizures in the setting of trauma.

Abusive Head Trauma Infants and toddlers presenting with vague complaints and seizures may be the victims of abusive head trauma (see Chapter 150, "Child Abuse and Neglect"), which can present without external signs of injury. Most children with abusive head trauma are <2 years of age, and the majority of cases occur in the first year of life (shaken baby syndrome).[67-69] Subdural hematoma is the most often identified inflicted intracranial injury in these infants.[67,69] **Maintain a high index of suspicion for trauma in the setting of afebrile seizures in infants.** If intracranial injury is identified, a more complete evaluation for other abusive injuries is necessary, including skeletal survey, retinal examination by an ophthalmologist, screening for blunt abdominal trauma (liver and pancreatic enzymes), and bleeding studies.[70]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 139

Headache in Children

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INTRODUCTION AND EPIDEMIOLOGY

Headache is pain in the scalp and cranium. Headaches in children can be mild, refractory, or life threatening, and can represent an acute, subacute, or chronic process. Headaches are broadly classified as primary headache disorders, which are intrinsic to the nervous system, and secondary headaches, which are caused by another condition such as trauma, infection, or intracranial or systemic disease (see later section, "Headache Classification").

Headaches are common in children, with an increasing prevalence through childhood and a peak in adolescence. The mean prevalence of headache in childhood is 58.4%, with a range of 24% to 90%, and 17% of children in the United States reported frequent or severe headaches in the past year.[1-3] Headache prevalence is similar in girls and boys prior to adolescence, but after puberty, they are more prevalent in girls. Overall, primary headache disorders are more common than secondary headaches, and migraine and tension-type headaches are most common.[4,5] The peak incidence of migraine is earlier for boys (10 to 11 years) than girls (12 to 14 years), and migraine with aura starts 3 to 5 years earlier than migraine without aura in both sexes.[6] Tension-type headache has a mean age of onset of 7 years and is more common in girls.[7] The estimated overall prevalence of migraine in childhood is 3.76% to 18%, and the overall prevalence of tension-type headache is 10% to 25%.[7-10]

Frequent or sustained headaches have a significant impact on children and their families, contributing to school absenteeism and missed parental work, and may even induce behavioral disturbances.[11-13] Migraine headaches are among the top five causes of years lost to disability according to the World Health Organization,[14] and children with migraines experience similar impact on quality of life as those with cancer or juvenile arthritis.[12,15] There is an association between chronic headache and psychiatric comorbidity among children.[16-18]

Headaches compose about 1% to 2% of all ED visits among children, and in the ED setting, secondary headaches are more commonly diagnosed than primary headaches.[2,19-22] Infectious etiologies such as upper respiratory tract infection are the most common cause of secondary pediatric headache in the ED, whereas migraine is the most common primary headache disorder diagnosed in this setting.[2,19-21,23-25] There appears to be some seasonal variation in ED visits for headache, with peaks in September and January and lower visit rates in the spring and summer months.[26-28]

PATHOPHYSIOLOGY

The pathophysiology of headaches is complex and varies according to cause. The cranium, most of the overlying meninges, brain, ependymal lining, and choroid plexus do not possess pain receptors. Extracranial pain may arise from cervical nerve roots, cranial nerves, or extracranial arteries, and intracranial pain may arise from intracranial venous, arterial, or dural structures. Cranial nerve or root pain can radiate to the occiput, ear, retroauricular areas, or throat.

HEADACHE CLASSIFICATION

Headaches are classified as primary or secondary based on the underlying cause. Primary headaches are physiologic or functional and are typically self-limited, although they may become persistent (e.g., status migrainosus) or chronic. Primary headache disorders include migraine, tension-type headache, chronic daily headache, and cluster headache; cluster headaches are more commonly seen in the adult than pediatric population. The gold standard diagnostic criteria are the International Criteria for Headache Disorders 3rd ed, beta version (**Table 139-1**).[29] **Although these diagnostic criteria rely on recurrent attacks, in an ED, a child may present with a first migraine headache due to intractable pain.** One study investigated the utility of applying the International Headache Society criteria in the ED without the "recurrent" requirement ("Irma Criteria") and found the criteria to be quite sensitive in diagnosing first-time migraines when followed long term using the original International Headache Society criteria as the gold standard.[30]

Secondary headaches are a symptom of another underlying disorder and include a wide range of etiologies. **Table 139-2** lists common and life-threatening causes of secondary headaches.[31-33] Although primary headaches can be disabling, secondary headaches result in morbidity and mortality if not treated.

CLINICAL FEATURES

Clinical characteristics of pediatric headache vary greatly by classification and etiology; however, the details of the headache including onset, pattern, location, quality, and associated symptoms are helpful in determining the cause and directing further investigation and treatment. Red flag clinical features associated with life-threatening secondary headaches are listed in **Table 139-3**.[33-37]

TEMPORAL ASPECTS OF HEADACHE

Age of Onset As mentioned earlier, headaches increase in incidence and prevalence throughout childhood, and initial onset varies by etiology. Although overall rare in children <5 years of age, primary headaches can and do occur in this age group; migraine with aura, for example, can begin as early as age 5 to 7 years for boys, and 37% to 50% of 7-year-old children report experiencing headache.[2,6,38,39] Complex migraines (hemiplegic, confusional, or basilar type) may have their onset at a young age as well; however, *incapacitating headache* in a young child, especially when associated with vomiting or gait changes, suggests an intracranial mass with an infratentorial location being the most common location.[40] Among a cohort of children age 2 to 5 years presenting to the ED with headache, the vast majority of headaches were associated with benign viral infections, and only 1 of 364 patients in the cohort was diagnosed with a tumor (this patient had an abnormal neurologic exam).[2]

TABLE 139-1 International Headache Society Diagnostic Criteria for Common Primary Headache Disorders (3rd ed, Beta Version)[29]

Primary Headache Disorder	Diagnostic Criteria	Comments
Migraine without aura	1. At least 5 attacks with features 2–3 below 2. Headache duration 2–72 hours 3. At least 2 of the following: a. unilateral b. pulsating c. moderate or severe intensity d. made worse with activity	In children, pain is more often bilateral and less often pulsating. Usually frontotemporal in location. Photophonophobia may be inferred from behavior in young children. Symptoms persisting >72 h are termed *status migrainosus*.
Migraine with aura	1. At least 2 attacks with features below 2. One or more reversible auras: a. visual b. sensory c. speech/language d. motor e. brainstem f. retinal 3. At least 3 of the following: a. gradual spread of aura (>5 min) b. 2 or more symptoms may occur in succession c. individual symptoms last 5–60 min d. at least 1 symptom is unilateral e. at least 1 symptom is positive f. accompanied or followed by headache within 60 min	Visual and sensory symptoms are common in children, as are autonomic symptoms. Systemic prodromal symptoms (e.g., fatigue, elated or depressed mood) may precede aura by 24–48 h.
Probable migraine	1. Attacks fulfilling all but 1 of the criteria for migraine without aura 2. Attacks fulfilling all but 1 criterion for migraine with aura	Includes those not meeting required number of prior attacks for migraine with or without aura.
Tension-type headache	1. At least 10 episodes of headache occurring on <1 d per month (infrequent episodic) or 1–14 d per month for at least 3 mo (frequent episodic) 2. Headache lasting 30 min to 7 d 3. At least 1 of the following: a. bilateral b. pressing or tightening quality (nonpulsating) c. mild or moderate intensity d. not worsened by routine activity 4. Both of the following: a. no nausea or vomiting b. no more than 1 of photophobia or phonophobia	Probable tension-type headache is missing 1 of the required features for formal diagnosis. Chronic tension-type headache is defined as occurring ≥15 d per month for >3 mo.
Cluster headache	1. At least 5 attacks with features below 2. Severe or very severe unilateral, orbital/supraorbital, and/or temporal pain lasting 15–180 min (untreated) 3. Either or both of the following: a. at least 1 ipsilateral symptom or sign: i. conjunctival injection and/or lacrimation ii. nasal congestion and/or rhinorrhea iii. eyelid edema iv. forehead and facial sweating v. miosis and/or ptosis b. sense of restlessness 4. Occurs with a frequency from 1 every other day to 8 per day	Attacks can occur in series and last weeks to months with symptom-free intervals. Usual age of onset is 20 y, but occasionally seen in children.

Temporal Pattern **Table 139-4** summarizes the association between overall temporal patterns of headaches and potential etiologies. In general, a pattern of acute recurrent or chronic nonprogressive headaches suggests a primary headache disorder.

Headache coinciding with the onset of fever suggests inflammation of some sort, typically infectious (e.g., sinusitis, pharyngitis, otitis, or meningitis), or may be associated with a more general viral syndrome. **Abrupt occurrence of severe headache due to a serious underlying condition, such as a brain tumor or intracranial hemorrhage, is typically associated with one or more objective findings on neurologic examination (e.g., altered mental status, ataxia, nuchal rigidity, papilledema, or hemiparesis).**[3,20,33,36] Cluster headaches also tend to

TABLE 139-2 Common and Life-Threatening Causes of Secondary Headache[31-33]

Etiology	Serious or Life-Threatening Causes	Common Causes
Infection	Meningitis Encephalitis Orbital or intracranial abscess	Viral upper respiratory tract infection Sinusitis Pharyngitis Odontogenic infection
Trauma	Traumatic intracranial hemorrhage	Mild traumatic brain injury (concussion)
Vascular	Intracranial hemorrhage Stroke Hypertension	
Neoplastic	Primary or metastatic intracranial tumor	
Toxic	Carbon monoxide Heavy metals Cocaine	Caffeine
Systemic disease	Diabetic ketoacidosis (cerebral edema) Systemic lupus erythematosus Vasculitis Sickle cell disease	
Other	Idiopathic intracranial hypertension	Temporomandibular joint dysfunction Postictal headache Fasting Sleep apnea

develop acutely, whereas tension headaches have a more subacute onset. Hormonal cycles can trigger migraine headaches in adolescent females. **Migraine headaches in children typically start relatively abruptly, intensify over several minutes, and then reach full intensity in about an hour.**[19] Young children often have headaches that begin in the late afternoon.

HEADACHE PRECIPITANTS

Viral illnesses and fever are among the most common causes of headache in children, and the associated headaches are most frequently frontal or temporal.[21,23-25,41] A history of trauma may suggest posttraumatic headache or traumatic brain injury. Posttraumatic headaches may be chronic as well.[42-45] Migraines, more common and better studied in adults and adolescents, may be accompanied by premonitory symptoms (prodromes such as fatigue, mood changes, or GI symptoms) and have identifiable triggers.[46] Children with prodromes tend to have more characteristic triggers as a whole, which may include specific foods (e.g., chocolate or monosodium glutamate), stress, light, specific odors, and weather changes. Headaches are among the most commonly reported symptoms in toxic exposures such as carbon monoxide poisoning.[47] Additional precipitants include medications (e.g., methylphenidate, steroids, oral contraceptives, or anticonvulsants), infection (e.g., sinusitis, pharyngitis, or meningitis), hypertension, anemia, and substance abuse (e.g., cocaine).[31-33]

LOCATION OF HEADACHE

In a cohort of children with headaches presenting to a pediatric ED, only 27.5% of patients could identify a precise location of the pain. Among children with intracranial diseases, most either were unable to indicate the location of the pain or had an occipital headache.[20] More recently, studies of occipital headache in children have not shown an increased association with serious secondary causes of headache.[48,49] Medications, hypertension, and basilar-type migraines can also cause headaches in the occipital region. Pain at the vertex can be seen with sphenoid sinusitis. Ethmoid, maxillary, and frontal sinus infections tend to cause retro-orbital pain, as does meningitis (along with fever and neck stiffness) and dural sinus thrombosis. Pain seemingly in, around, or in front of the ear (or entire temporal region) is often seen with temporomandibular joint (TMJ) dysfunction and can be reproducible on exam. **Migraine headaches are usually unilateral and involve the frontal or temporal region in adolescents. However, in younger children, they are usually bifrontal or generalized.[29] Only about a third of children have unilateral migraines.** Tension headaches tend to have the greatest variability in location. They may be generalized, frontal, or even occipital/posterior cervical.

QUALITY OF HEADACHE

Younger children and many developmentally normal, otherwise healthy children may have a difficult time describing the quality of their headaches. An ability to describe pain quality or a description of the headache as having a pulsating quality is more frequently associated with benign headaches. An inability to describe the pain or a description of the headache as constrictive indicates a greater likelihood of a more serious cause.[20,32,36,50] Many different qualities of pain can be identified: stabbing or hyperesthetic pain has been associated with herpes zoster; aching pain with tension headaches, meningitis, or encephalitis; and constant pain with sinusitis in all locations. A pulsating quality is one of the diagnostic criteria for migraine headache set forth by the International Headache Society, but can also be seen with headaches caused by hypertension or intracerebral hemorrhage.

SEVERITY OF HEADACHE

The severity of a headache is neither a sensitive nor a specific characteristic in determining cause. Patients with tension headaches can complain of terrible pain, whereas a child with a brain tumor may complain of mild to moderate pain. Nonetheless, complaints of very intense pain should be taken seriously and assessed in context with other historical elements. Ask about and document presenting pain assessments in children with primary headache disorders because treatment end points will be dictated by improved pain scores in the ED.

DURATION OF HEADACHE

Although the duration of a headache is not particularly useful in assessing the majority of headaches, the International Headache Society definition of migraines requires a duration of symptoms of 4 to 72 hours in adults, but the duration may be less (1 to 48 hours) in children. A migraine that lasts >72 hours is known as *status migrainosus*. Children often present to the ED with this condition and should be treated appropriately (see later section, "Treatment").

ALLEVIATING AND EXACERBATING FACTORS

Patients with a sense of restlessness or agitation are more likely to have cluster headaches (rarer in children).[29] They may pace about the room or rock back and forth in a chair. In contrast, patients with migraines typically prefer silence and darkness because the lack of stimulation provides some relief, and photophobia/phonophobia are part of the diagnostic criteria for migraine headache (Table 139-1).[29] Tension headaches can be frequent and frustrating but tend *not* to be aggravated by routine physical activity.[29] Positional preferences (such as a head tilt) may be noted in children with space-occupying lesions in order to avoid positions that increase intracranial pressure or exacerbate diplopia caused by cranial nerve dysfunction. In addition, children with increased intracranial pressure may be unable to look up or may avoid the Valsalva maneuver (e.g., defecation or coughing). Analgesic rebound headaches worsen when the patient goes a certain period of time without taking long-term pain medication or overuses analgesics.

ASSOCIATED SYMPTOMS

Eliciting associated symptoms can help narrow the differential diagnosis. Migraine headache with aura, by definition, is associated with visual, sensory, or speech disturbances (all fully reversible; Table 139-1). Specific

TABLE 139-3 Red Flag Clinical Features of Serious Secondary Headaches

Clinical Features	Red Flags	Potential Causes	Comments
Chronology	Sudden onset New-onset persistent pain (>2 wk)	Vascular etiology Intracranial pathology	SAH
Pattern	Wakens from sleep Early morning headache Progressive frequency/severity	Elevated ICP	Medication overuse can exacerbate the pattern of primary headache disorders, leading to progressive frequency/severity
Location/quality	Inability to describe pain	Secondary headache	Previously occipital location thought to be associated with secondary headaches, but no longer supported by recent evidence
Exacerbating factors	Recumbency Valsalva	Elevated ICP	Idiopathic intracranial hypertension is a less serious cause
Associated symptoms	Fever Morning vomiting Behavior/cognitive change Seizures Motor/gait dysfunction Visual symptoms Systemic symptoms	Serious infection Intracranial pathology Diabetic ketoacidosis	Neurologic symptoms concerning for intracranial pathology
Demographics	Age <4 y	CNS tumor	Primary headaches possible but less common; CNS tumors common in this age group
Medical history	Sickle cell disease Bleeding disorders Rheumatologic disease Malignancy Cranial shunt Phakomatoses	Stroke Vasculitis Elevated ICP/bleed into tumor Intracranial mass lesion	
Family history	No primary headache history Family history of SAH Inherited genetic disorders	Secondary headache	Migraines have a strong genetic component and frequent family history of headaches
Other	Medications Environmental/toxins	Pseudotumor Analgesic overuse Carbon monoxide poisoning Heavy metal poisoning	

Abbreviations: ICP = intracranial pressure; SAH = subarachnoid hemorrhage.

symptomatology may distinguish between types of migraines such as confusional (e.g., distortions of visual size, space, or time) and hemiplegic (e.g., transient hemiparesis or aphasia). Hemiplegic migraines are uncommon, so think carefully about other causes of neurologic deficits when contemplating the differential diagnosis. Abdominal pain, nausea, or vomiting may occur along with migraine headache. Cluster headaches can be associated with multiple ipsilateral symptoms (Table 139-1).[29] Headache with effortless vomiting but no GI complaints is characteristic of elevated intracranial pressure. Irreversible and progressive defects in visual acuity and diplopia are more suggestive of pseudotumor cerebri. Seizures and headache may indicate traumatic brain injury, concussion, arteriovenous malformation, subarachnoid hemorrhage, or tumor. A headache with fever and focal neurologic signs (with or without seizure) may suggest an intracranial abscess, encephalitis, or meningitis (especially with neck stiffness). Children who present with headache, altered mental status, and seizures must be evaluated for meningoencephalitis from herpes simplex virus.[51]

TABLE 139-4 Temporal Patterns of Headache in Children

Type	Temporal Pattern	Causes
Acute headache	Single episode of head pain without history of previous events	Upper respiratory tract infection, sinusitis, first migraine, medication use, trauma
Acute recurrent headache	Pattern of head pain separated by symptom-free intervals	Migraine
Chronic progressive headache	Gradual increase in frequency and severity; may be worse in the morning or awaken at night	Space-occupying lesion, hematoma, pseudotumor cerebri
Chronic nonprogressive headache (chronic daily)	Frequent or constant headache	Tension headache, cluster headache
Mixed headache	Acute recurrent headache superimposed on chronic daily background pattern; variant of chronic daily headache	Typically migraine (acute recurrent headache) superimposed on chronic daily headache

DIAGNOSIS

The diagnosis of pediatric headache is primarily clinical and largely derived from a thorough history and physical examination.

HISTORY

Obtain a thorough history to elicit clinical features related to the presenting headache and past headaches as described earlier. Include a past medical history because acute headaches must be considered both independently and within the context of the child's medical history: secondary headaches can occur even when there is a history of primary headaches; and although it is helpful if a child has a history of similar past headaches, a first-time headache does not preclude a primary headache disorder, as described previously. Concurrent chronic illness may

predispose the patient to unique headaches (e.g., those associated with ventriculoperitoneal shunt malfunction or infection), headaches from infection (e.g., related to anatomic defects or immunosuppression predisposing to meningitis; or acute illness with sinusitis leading to brain abscess), or headaches caused by intracranial hemorrhage (e.g., due to hemophilia or anatomic arteriovenous anomalies).

Ask about family history as well. Headaches occur more often in children who have a family history of headaches in either first- or second-degree relatives.[3,32] This association is particularly true for children with migraines (family history of migraines in up to 90% of cases). Children with cluster headaches rarely have a family history of similar headaches (about 7%). Children with a parent who experienced a subarachnoid hemorrhage are at a four times greater risk of this type of intracranial bleed than the general population. Predisposing genetic disorders may provide some clue to a familial link in headaches (e.g., bleeding diathesis, familial dyslipidemias, or atherosclerotic events).

PHYSICAL EXAMINATION

The physical examination is the most important tool to distinguish benign from life-threatening headaches. **Table 139-5** lists physical exam features and their relation to important secondary headache etiologies. While a careful neurologic examination with attention to cranial nerves (including vision), gait, strength, and mental status is essential to exclude intracranial causes of secondary headache, additional clues to serious secondary headaches include vital signs, growth parameters, and a thorough head-to-toe exam.

LABORATORY TESTING

No laboratory testing is needed for primary headaches, which are a clinical diagnosis. If secondary headache is a consideration, obtain laboratory evaluation directed by the history and physical examination. Blood tests that may be useful in specific clinical situations include CBC, serum glucose level, electrolyte levels, renal function tests, liver function tests, blood culture, and drug screen. Perform a lumbar puncture if meningitis or encephalitis is suspected, and send cerebrospinal fluid for Gram stain, culture, appropriate viral studies, glucose, protein, and cell count (see Chapter 120, "Meningitis in Infants and Children"). If pseudotumor cerebri is suspected, perform a lumbar puncture with the patient in the lateral decubitus position and measure the opening pressure. A lumbar puncture may also be needed to rule out a subarachnoid hemorrhage if there is a high level of suspicion but the findings of a CT scan of the brain are normal.[52,53] Focal neurologic deficits or signs of increased intracranial pressure warrant a CT scan prior to lumbar puncture; however, clinical signs of probable impending herniation are the best indicators of when to delay a lumbar puncture, even in the setting of normal CT scan results.[54]

TABLE 139-5 Physical Examination Findings Associated With Potential Secondary Causes of Headache

Examination Component	Finding	Potential Causes
Growth parameters	Abnormal height, weight, head circumference for age	Failure to thrive indicative of systemic disease; enlarged head circumference suggestive of increased intracranial pressure
Vital signs	Abnormal heart rate, blood pressure, respiratory rate, temperature	Bradycardia, hypertension, and irregular respirations (Cushing's triad) indicative of intracranial hypertension and impending herniation; severe hypertension associated with headache in hypertensive crisis; tachypnea possibly indicative of metabolic acidosis (e.g., diabetic ketoacidosis); fever possibly indicative of CNS or systemic infection (meningitis, encephalitis, viral syndrome)
Head and neck	Cranial or carotid bruits	Arteriovenous malformation
	Bulging fontanelle Splayed sutures Macrocephaly	Hydrocephalus
	Signs of trauma	Accidental or inflicted trauma
	Head tilt	Ocular nerve palsies from CNS tumor
Eyes	Papilledema	Increased intracranial pressure (pseudotumor, tumor, shunt failure, intracranial bleeding, hydrocephalus)
	Inability to look up: "sunset eyes"	Hydrocephalus
	Unilateral conjunctival injection, tearing, eyelid edema without tenderness	Cluster headache
	Retinal hemorrhage	Nonaccidental trauma
	Bilateral periorbital edema, facial tenderness, nasal discharge	Sinusitis
	Proptosis	Orbital cellulitis or tumor
Ear, nose, throat	Signs of infection	Otitis media, mastoiditis, sinusitis, pharyngitis (including streptococcal pharyngitis), dental abscess or caries
	Malocclusion, TMJ tenderness	TMJ dysfunction
Heart	Murmurs	Potential shunting lesion with risk of embolic event or cerebral abscess
Skin	Café-au-lait spots, ash-leaf spots, vascular malformations	Neurofibromatosis, tuberous sclerosis, congenital vascular malformations (risk for CNS hemorrhage)
Neurologic	Cranial nerve deficits Motor weakness Abnormal tone or reflexes Abnormal gait Ataxia Altered level of consciousness	Any focal neurologic deficit may be associated with intracranial pathology or metabolic derangement (e.g., hyper-/hypoglycemia)

Abbreviation: TMJ = temporomandibular joint.

IMAGING

Imaging studies are not needed for primary headache disorders or recurrent headaches when the findings of the neurologic examination are normal. Despite the importance of history and examination, one study reported that almost 40% of all children with headache who were evaluated in the ED underwent head imaging with radiation.[55] There is a very low incidence of positive findings on neuroimaging studies in children with headache who have normal findings on physical examination.[2,34-37,56,57] Consider imaging in children with abnormal findings on neurologic examination, altered mental status, or concurrent seizures, or if medical history indicates the recent onset of severe (worst) headache, a change in the type of headache, or associated features that suggest neurologic dysfunction.[3,32,34-37,58]

Reserve CT scans for instances in which there is a highly suspicious history, neurologic findings on examination are abnormal, or an intracranial hemorrhage or a space-occupying lesion is suspected. Noncontrast head CT is sensitive for detecting skull fracture and brain injury from trauma and may identify supratentorial tumors and stroke; give IV contrast if considering intracranial abscess.

A normal head CT does not exclude an intracranial mass because the posterior fossa is not well visualized. The posterior fossa is the most common location of brain tumors in children, and MRI of the brain provides better visualization of the posterior fossa. Magnetic resonance angiography and venography are useful when vascular malformations or dural sinus thrombosis is suspected. MRI may require sedation based on the patient's age. The decision to admit a child for MRI or to obtain outpatient imaging depends on the practice location and deserves a discussion with an inpatient team as well as a primary care provider.

TREATMENT

Treatment of headache in the ED depends on etiology. Treat the underlying cause of secondary headache and provide analgesia for pain. For secondary headaches, simple analgesics such as NSAIDs and acetaminophen are usually sufficient, although opioid analgesics may be needed for some severe secondary headaches (see Chapter 115, "Pain Management and Procedural Sedation in Infants and Children").

Abortive therapy for primary headaches also varies by type. Few prospective randomized trials for migraine therapy have been conducted on children, and even fewer in the ED setting, so most recommendations are extrapolated from adult trials, and significant practice variation has been observed.[55,59-63] **Table 139-6** lists various pharmacologic options for migraine and cluster headache along with recommended dosing. Overall, abortive therapy in the ED is highly successful, with >85% of children successfully discharged and only a 5.5% ED return visit rate.[64]

FIRST-LINE THERAPY

First-line therapy for all types of primary headaches includes oral NSAIDs and/or analgesics. Both ibuprofen and acetaminophen are effective first-line therapy, although ibuprofen is more effective when given as monotherapy.[65] Ketorolac is an effective parenteral NSAID, although it should not be used if the patient has taken an oral NSAID within 6 hours. Although superior to placebo, ketorolac appears to be less effective than prochlorperazine (see below).[66] **Do not use narcotics for primary headaches.** Long-term use of narcotics can change the pain-modulatory system in the brainstem and can lead to more intense pain.[67,68]

The most widely studied migraine-specific abortive medications are the triptans and the dopamine antagonists. Triptans have demonstrated some efficacy in the outpatient and home setting and are considered first-line therapy in that setting; however, they are more effective when taken early in the course of headache and therefore of less utility in the ED setting.[69,70] If used, intranasal and subcutaneous routes are more effective than oral administration.[63,65,69]

SECOND-LINE THERAPY

Many children with primary headaches presenting to the ED have already tried and failed first-line therapy, and a significant proportion of those with migraine present with status migrainosus.

TABLE 139-6 Pharmacologic Abortive Therapy for Primary Headaches

Class	Medication	Dose
NSAIDs	Ibuprofen	10 milligrams/kg: PO (max: 800 milligrams/dose or 2400 milligrams/d)
	Ketorolac	0.5 milligram/kg: IV (max: 30 milligrams/dose)
Analgesics	Acetaminophen	15 milligrams/kg: PO/PR (max: 1 gram/dose or 4 grams/d)
Dopamine antagonist	Prochlorperazine	0.15 milligram/kg: IV (max: 10 milligrams/dose)
	Metoclopramide	0.1 milligram/kg: IV (max: 10 milligrams/dose)
Other antiemetic	Diphenhydramine	1 milligram/kg: IV (max: 50 milligrams/dose)
	Promethazine	0.25–1 milligram/kg: IV (max: 25 milligrams/dose)
Triptans (more available than listed here)	Sumatriptan	Multiple routes: 5–20 milligrams: intranasal 3–6 milligrams: SC 50–100 milligrams: PO
	Rizatriptan	5–10 milligrams: PO
	Sumatriptan/naproxen combination	Multiple combinations 85 milligrams/500 milligrams: PO (sumatriptan/naproxen) 30 milligrams/180 milligrams: PO 10 milligrams/60 milligrams: PO

Dopamine antagonists are the most studied parenteral abortive medications for migraine in the ED and include prochlorperazine, metoclopramide, promethazine, and chlorpromazine. Small studies suggest differential effectiveness among this class, with highest treatment success for prochlorperazine, followed by metoclopramide; promethazine and chlorpromazine appear to be less effective.[63,64,71,72] One large study using administrative data suggested higher rates of ED return visits among children treated with metoclopramide compared to prochlorperazine.[64] These drugs can cause dystonic or extrapyramidal reactions, which are relieved or prevented by diphenhydramine.[73,74]

Many emergency medicine providers use a "cocktail" of medications for migraine treatment that includes ketorolac, prochlorperazine or metoclopramide, and diphenhydramine. This combination is effective and safe.[48] The authors recommend this approach for patients who have failed first-line therapy, and **Table 139-7** summarizes combination

TABLE 139-7 Suggested ED Treatment Algorithm for Primary Headaches*

Migraine and Cluster Headache	Tension Headache
Normal saline bolus (20 mL/kg IV; max of 1 L) + Ketorolac (0.5 milligram/kg IV; max 30 milligrams)† + Prochlorperazine (0.15 milligram/kg IV; max 10 milligrams) *or* Metoclopramide (0.1 milligram/kg IV; max 10 milligrams) + Diphenhydramine (1 milligram/kg IV; max 50 milligrams)‡ ↓ If no significant relief, consider neurology consultation prior to other therapies such as dexamethasone	Ketorolac (0.5 milligram/kg IV; max 30 milligrams)† + Acetaminophen PO (15 milligrams/kg; max 1000 milligrams)

*For patients who have failed first-line therapy with oral ibuprofen or acetaminophen.

†Do not give ketorolac if ibuprofen taken within 6 h.

‡Diphenhydramine may be given prophylactically as part of a "cocktail" or used only to treat extrapyramidal side effects of dopamine antagonists.

therapy for migraine (cluster headache may be treated the same way) and tension-type headache.

THIRD-LINE THERAPY

Subanesthetic dose propofol has been evaluated in the ED in a randomized controlled trial in children with encouraging results.[75] This study found that propofol, given as a 0.25 milligram/kg IV push every 5 minutes to a maximum of five doses, achieved similar pain reduction as standard therapy with dopamine antagonists and NSAIDs, with significantly fewer 24-hour rebound headaches and a nonsignificant shorter median length of stay. However, depending on institutional policies for propofol administration, monitoring or personnel requirements may make its use provider intensive in some settings, limiting its practicality.

Dihydroergotamine is effective in the inpatient setting, but no studies exist on ED treatment.[76] Although effective in adults, data are lacking with regard to the utility of dexamethasone for prevention of headache recurrence following abortive therapy.[77-80] Antipsychotics such as droperidol and haloperidol are not recommended for children due to high rates of side effects.[63]

Additional therapies specific to cluster headache include 100% oxygen via non-rebreather mask for 20 minutes at onset of headache; lidocaine 20 milligrams intranasal to the ipsilateral nostril, and prednisone 1 to 2 milligrams/kg for 10 days with a subsequent 7-day taper to terminate prolonged clustering of headaches.

PROPHYLACTIC TREATMENT

Children with chronic headaches that disrupt activities of daily living or school performance may benefit from prophylactic treatment. While initiation of daily prophylaxis is typically beyond the scope of ED management, **Table 139-8** lists medications used for the prevention of migraines. Few of these medications are supported by quality evidence, and a recent multicenter randomized, double-blind, placebo-controlled trial comparing topiramate, amitriptyline, and placebo found no difference in headache frequency and higher rates of side effects in the medication arms.[81] The decision to start prophylaxis should be made by the primary care physician or pediatric neurologist, in consultation with the child and the family, and should include a careful weighing of the risks and benefits of daily medication.

TABLE 139-8 Commonly Used Medications for Migraine Prophylaxis in Children

Class	Medication	Dosage
Calcium channel blocker	Flunarizine	10 milligrams/d
	Nimodipine	10 milligrams/d (<40 kg), 16 milligrams/d (40–50 kg), 20 milligrams/d (>50 kg)
β-Blocker	Propranolol	10 milligrams PO twice a day up to 20 milligrams 3 times a day as tolerated for age <14 y; 20 milligrams twice a day to 120 milligrams twice a day as tolerated for age >14 y
Nitrogen alkaloid	Papaverine	5 milligrams/kg/d in divided doses twice a day
Tricyclic antidepressant	Amitriptyline	10 milligrams PO at bedtime to maximum of 50 milligrams PO at bedtime for age <12 y and 100 milligrams PO at bedtime for age >12 y
Antiepileptic	Topiramate	50 milligrams/d titrated to 200 milligrams/d in divided doses 3 times a day
	Divalproex sodium	125–250 milligrams PO at bedtime to twice a day for age >10 y
Nutraceuticals	Riboflavin (B_2)	400 milligrams/d
	Coenzyme Q10	100–150 milligrams/d
	Melatonin	6–12 milligrams before bed
Antihistamine	Cyproheptadine	4 milligrams PO at bedtime to maximum of 12 milligrams at bedtime for age >6 y

NONPHARMACOLOGIC TREATMENT

For tension-type headaches and migraines, a range of nonpharmacologic therapy including biofeedback, relaxation techniques, and cognitive behavioral therapy can be effective.[82,83] In general, 8 to 10 sessions are necessary to teach these techniques in the outpatient setting. Although acupuncture has been used to treat chronic migraine headaches in both children and adults, several randomized controlled studies failed to show benefit over placebo.

DISPOSITION AND FOLLOW-UP

Admit children with emergent, life-threatening causes of headache to the hospital for definitive treatment and pain control. Consider admission for children with primary headaches with intractable pain despite first- and second-line treatment.

Patients with recurrent headaches who are successfully treated and discharged from the ED should be encouraged to keep a daily headache diary to document the frequency of headaches, impact on daily activities, and potential triggers. Healthy lifestyle changes may help reduce headache frequency and can be recalled using the SMART acronym: adequate **s**leep, regular **m**eals and **a**ctivity, **r**elaxation techniques, and **t**rigger avoidance.[3] Remind them that first-line treatments are most effective when taken *early* in the course of headache. For those with frequent headaches, a trial of daily nutraceuticals (Table 139-8) may be reasonable and safe. Ensure follow-up with a primary care provider or headache specialist.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 140

Altered Mental Status in Children

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INTRODUCTION

Altered mental status in children is characterized by the failure to respond to verbal or physical stimulation in a manner appropriate to the child's developmental level. The ED incidence of altered mental status in children varies widely depending on the type of institution reporting, the patient population served, and the specific definition of altered mental status used.[1,2] Children with altered mental status require simultaneous stabilization, diagnosis, and treatment. The objectives of treatment are to sustain life and prevent irreversible CNS damage. Once the patient is resuscitated, the goal is to determine the cause and stop disease progression.

PATHOPHYSIOLOGY

Arousal is mediated by the neural pathways of the ascending reticular activating system that project from the brainstem to the hypothalamus, thalamus, and cerebral cortices. The ascending reticular activating system regulates wakefulness in response to the environment, as well as homeostasis, cardiovascular, and respiratory functions. Altered mental status occurs through dysfunction of the ascending reticular activating system, an insult to bilateral cerebral cortices, or global depression of the central nervous system.[3,4] There are many factors that can cause dysfunction in the ascending reticular activating system and cerebral hemispheres, including inadequate substrate for metabolic demand, insufficient blood

flow, presence of toxins or metabolic waste products, or alterations of body temperature.[4] Typical causes of bilateral cortical impairment are toxic and metabolic states that deprive the brain of normal substrates.

There are multiple pathologic conditions that affect awareness and arousal; etiologies can initially be described as traumatic or nontraumatic. Nontraumatic causes can be further divided into structural and functional lesions. Structural lesions can be categorized as supratentorial or subtentorial. Signs and symptoms of supratentorial lesions include focal motor abnormalities, which are often present from the onset of the altered level of consciousness. Subtentorial lesions lead to reticular activating system dysfunction, in which prompt loss of consciousness is common. Cranial nerve abnormalities are frequent, and abnormal respiratory patterns are seen. Functional etiologies include infectious/inflammatory, metabolic/nutritional/toxic, and neurologic/psychiatric disorders. Depressed consciousness is typically seen before motor signs become depressed, and when present, motor deficits are typically symmetric.[5]

CLINICAL FEATURES AND APPROACH

The spectrum of alteration of mental status ranges from confusion or delirium (disorders in perception) to lethargy, stupor, and coma (states of decreased awareness). A lethargic child has decreased awareness of self and the environment. Patients may be aroused from an apparent deep sleep, but they immediately relapse into a state of minimal responsiveness. A stuporous child has decreased eye contact, decreased motor activity, and unintelligible vocalization. Stuporous patients can be aroused with vigorous noxious stimulation. Comatose patients are unresponsive and cannot be aroused by verbal or physical stimulation, such as phlebotomy, arterial catheterization, or lumbar puncture.[6]

Rapidly assess and support the airway, ventilation, and circulation. When the patient is stabilized, take a methodical and comprehensive history (**Table 140-1**). Ask about the prodromal events before the change in consciousness as well as recent illnesses or infectious exposures, and determine the likelihood of trauma, abuse, or ingestion. Inquire about antecedent fever, headache, head tilt, abdominal pain, vomiting, diarrhea, gait disturbance, seizures, drug ingestion, palpitations, weakness, hematuria, weight loss, and rash. For infants and young children, review developmental milestones. The medical, immunization, and family histories are important in children of all ages. Be alert for any inappropriate responses, inconsistencies, or delays in seeking care that may arouse suspicion for child abuse (see Chapter 150, "Child Abuse and Neglect").[6,7]

Proceed with a general examination only after respiratory, cardiac, and cerebral stabilization. The objectives of the examination are to identify occult infection, trauma, toxicity, or metabolic disease. The neurologic examination should document the child's response to sensory input, motor activity, pupillary reactivity, oculovestibular reflexes, and respiratory pattern. Although several coma scales have been published, such as the Modified Pediatric Glasgow Coma Scale (see Chapter 110, "Pediatric Trauma," and Chapter 111, "Minor Head Injury and Concussion in Children"), the most simplified and functional scale in an emergency setting is the AVPU scale (**Table 140-2**). The Glasgow Coma Scale lacks good interobserver reliability and reproducibility and does not accurately predict outcomes in individual patients.[8] The AVPU score has been validated and is currently recommended by the Pediatric Advanced Life Support guidelines.[9] The A, V, P, and U values correspond to Glasgow Coma Scale scores of 15, 13, 8, and 3, respectively.[10]

After obtaining a comprehensive history and performing a complete physical examination, including thorough neurologic examination, anticipate and carefully observe for improvement or deterioration.[11]

TABLE 140-1 Important Historical Elements for Evaluating Altered Mental Status in Children

Prodromal events	Recent illnesses or infectious exposures
	History of recent trauma
Risk factors	Medications in the home
	Social environment
	Vaccinations
	Family history
	Developmental milestones
Associated symptoms	
Constitutional	Fever, weight loss
GI	Vomiting, diarrhea, abdominal pain
Neurologic	Headache, gait changes, seizure activity, weakness
Cardiac	Palpitations
Musculoskeletal	Head tilt
Dermatologic	Rash

TABLE 140-2 AVPU Score

A = Awake
V = Responds to verbal stimuli
P = Responds to pain
U = Unresponsive

DIAGNOSIS

Once the child is stabilized, the history and physical should suggest either a medical disorder or structural lesion. The mnemonic **AEIOU TIPS (*a*lcohol, *e*ncephalopathy, *i*nsulin, *o*piates, *u*remia, *t*rauma, *i*nfection, *p*oisoning, and *s*eizure)** is a useful tool for organizing the diagnostic possibilities of altered mental status in children (**Table 140-3**). If a metabolic cause is suspected, obtain serum electrolyte levels, renal and hepatic function studies, serum ammonia, CBC, and coagulation studies (see Chapter 146, "Metabolic Emergencies in Infants and Children"). If the history or examination suggests a toxic ingestion, obtain serum levels of suspected agents and a urine toxicology screen. Consider trial of an antidote, if available. Obtain arterial blood gas analysis, CBC, and pulse oximetry in cases of trauma, respiratory distress, or suspected acid-base imbalance. Obtain a 12-lead ECG and provide continuous cardiac monitoring if there are pathologic auscultatory findings, rhythm disturbance, or suspected toxin exposure. For serious bacterial infection, obtain blood and urine cultures. Correct shock, hypotension, and hypoxia before attempting lumbar puncture (see Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children").

The clinical scenario directs imaging. Immobilize the cervical spine and radiograph the cervical spine if spine injury is suspected or in the case of multiple system trauma. If an intracranial lesion is suspected or if there are focal neurologic signs, obtain a noncontrast CT scan of the head. If vascular injury is a possibility, consider CT angiography of the head and/or neck. A chest radiograph confirms or clarifies examination findings and documents endotracheal tube placement. Abdominal radiographs are indicated to assess for acute ingestion of radiopaque material. Abdominal US may be useful to screen for cases of intussusception (see Chapter 133, "Acute Abdominal Pain in Infants and Children").

Other studies that may be useful in specific cases are serum osmolality, blood alcohol level, thyroid function tests, blood lead level, and skeletal survey for suspected abuse. Electroencephalogram will evaluate for nonconvulsive status epilepticus.

TREATMENT

Treatment principles are outlined in **Table 140-4**. Begin with airway, breathing, and circulation, and administer 100% oxygen until adequate oxygenation is confirmed. For suspected increased intracranial pressure, elevate the head of the bed to 30 degrees. Establish an IV and give normal saline to restore and/or maintain perfusion. **Obtain a stat point-of-care glucose and treat hypoglycemia.** If the history or the exam suggests opiate toxicity, give naloxone.[6] For suspected meningitis, give antibiotics and/or acyclovir.

DISPOSITION AND FOLLOW-UP

Once the patient is stabilized, the child should be observed until his or her mental status improves. The patient's clinical condition and specific disorder dictate whether further management can occur on the inpatient

TABLE 140-3 AEIOU TIPS: A Mnemonic for Pediatric Altered Mental Status

A	**Alcohol.** Ethanol. Isopropyl alcohol. Methanol. Concurrent hypoglycemia is common. **Acid-base and metabolic.** Hypotonic and hypertonic dehydration. Hepatic dysfunction, inborn errors of metabolism. **Arrhythmia/cardiogenic.** Stokes-Adams, supraventricular tachycardia, aortic stenosis, heart block, pericardial tamponade.
E	**Encephalopathy.** Reye's syndrome. Parainfectious encephalomyelitis. Autoimmune encephalitis, such as Anti-*N*-methyl-D-aspartate (Anti-NMDA) receptor encephalitis.[12] Posterior reversible encephalopathy syndrome (PRES) may be associated with hypertension, autoimmune disease, and Henoch-Schönlein purpura (HSP).[13] **Endocrinopathy.** Addison's disease can present with AMS or psychosis. Thyrotoxicosis can present with ventricular dysrhythmias. Pheochromocytoma can present with hypertensive encephalopathy. **Electrolytes.** Hypo-/hypernatremia and disorders of calcium, magnesium, and phosphorus can produce AMS.
I	**Insulin.** AMS from hyperglycemia is seen in severe diabetic ketoacidosis, as well as hyperglycemic hyperosmolar syndrome. Hypoglycemia can be the result of many disorders. Irritability, confusion, seizures, and coma can occur with blood glucose levels <40 milligrams/dL (2.22 mmol/L). **Intussusception.** AMS may be the initial presenting symptom.
O	**Opiates.** Common household exposures are to Lomotil® (diphenoxylate hydrochloride and atropine sulfate), Imodium® (loperamide), diphenoxylate, and dextromethorphan. Clonidine, an α-agonist, can also produce similar symptoms. **Oxygen.** Disorders of airway, breathing, or circulation may adversely affect oxygen delivery to the brain; hypercapnia from primary lung disease or neurologic dysfunction also may result in AMS.
U	**Uremia.** Hemolytic-uremic syndrome can produce AMS in addition to abdominal pain. Thrombocytopenic purpura and hemolytic anemia also can cause AMS. In children with chronic renal failure, neurologic dysfunction may develop secondary to stroke, hypertension, or metabolic derangements.
T	**Trauma.** Hypovolemia or hemorrhage from multisystem trauma may lead to insufficient cerebral perfusion and result in AMS. Consider concussion, hemorrhage, contusion, epidural or subdural hematoma. Consider nonaccidental trauma. **Tumor.** Primary, metastatic, or meningeal leukemic infiltration. Intracerebral tumors commonly produce focal neurologic signs, and posterior fossa tumors typically block the ventricular system and create signs and symptoms of hydrocephalus. Shunt malfunction should be considered among patients with a ventriculoperitoneal shunt for hydrocephalus. **Thermal.** Hypo- or hyperthermia. Progressive hypothermia leads to insidious AMS.
I	**Infection.** Bacterial meningitis, encephalitis, and brain abscess usually present with fevers. Brain abscess is characterized by fever and headache before AMS changes. Presenting symptoms also include generalized or focal seizures. Any systemic infection associated with vasculitis or shock may lead to AMS secondary to cerebral hypoperfusion. **Intracerebral vascular disorders.** Subarachnoid, intracerebral, or intraventricular hemorrhages can be seen with trauma, ruptured aneurysm, or arteriovenous malformations. Venous thrombosis can follow severe dehydration or pyogenic infection of the mastoid, orbit, middle ear, or sinuses. Arterial thrombosis is uncommon in children, except in those with homocystinuria. Intracerebral and intraventricular hemorrhages may follow birth asphyxia or trauma in neonates, but in older children, they may signify a congenital or acquired coagulopathy. Cerebral emboli from bacterial endocarditis may cause AMS. Acute confusional migraine may be associated with profound alterations in consciousness. Children with sickle cell anemia can develop cerebral thrombosis, status epilepticus, and coma.
P	**Psychogenic.** Characterized by decreased responsiveness with normal neurologic examination including oculovestibular reflexes. Psychogenic unresponsiveness may be a conversion reaction, an adjustment reaction, a panic state, or malingering. **Poisoning/ingestion.** Drugs, toxins, or illicit substances can be ingested by accident, through neglect or abuse, or in a suicidal gesture. Intentional ingestion of recreational drugs, including synthetic cannabinoids, may be considered.[14]
S	**Seizure.** Generalized motor seizures and absence status epilepticus are often associated with prolonged unresponsiveness in children.[15] In a child with a history of seizures who presents with AMS, consider nonconvulsive status epilepticus. Febrile seizures are seen in children aged 6 months to 6 years.

Abbreviation: AMS = altered mental status.

unit or in an intensive care unit.[6] Only patients with transient, reversible causes may be treated, monitored in the ED, and discharged after observation and a return to their baseline mental status. Patients who are discharged (e.g., those with a closed head injury or simple febrile seizure) should receive disease-specific discharge instructions. Children who are evaluated for altered mental status and discharged home should have a repeat evaluation within 24 hours of discharge.

TABLE 140-4 General Treatment of Altered Mental Status

- Assess airway, breathing, and circulation.
- Immobilize cervical spine for suspected trauma.
- Initiate continuous pulse oximetry; consider capnometry; administer oxygen.
- Give dextrose for hypoglycemia; for children, give 25% dextrose in water 2 mL/kg IV; for newborns, give 5 mL/kg of 10% dextrose in water.
- Provide fluid resuscitation, 20 mL/kg of isotonic crystalloid, and repeat to total of 60 mL/kg as needed.
- Administer broad-spectrum antibiotics for suspected sepsis or meningitis.
- Give naloxone for suspected opiate or clonidine overdose, 0.01 to 0.1 milligram/kg IV every 2 min.
- Administer flumazenil for suspected pure benzodiazepine overdose, 0.01 milligram/kg IV.
- Control seizures with benzodiazepines (lorazepam, 0.1 milligram/kg IV; diazepam, 0.1 milligram/kg IV; or midazolam, 0.1 milligram/kg IV).
- Prevent/treat hypothermia with heat lamps during resuscitation; treat hyperthermia.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 141

Pediatric Orthopedic Emergencies

Kathy Boutis

GENERAL PRINCIPLES

The anatomy of the pediatric musculoskeletal system is unique and reflects the active growth and development that occurs during childhood. Fracture classification, treatment approach, and types of complications are directly related to this unique anatomy. In general, both injury patterns and treatment approaches in children in whom closure

of the physes (growth plates) has already occurred are similar to those of the adult. Therefore, the major focus of this chapter is directed at injuries occurring in the prepubescent child with open physes. In addition, some diseases specific to children that cause nontraumatic musculoskeletal complaints are covered.

The long bones of children consist of discrete anatomic areas. The physis is an area of growth cartilage and may occur at one (e.g., the phalanges) or both (e.g., the tibia and the femur) ends of a long bone. The area of bone between a physis and the adjacent joint is termed the *epiphysis*. An *apophysis* is an outgrowth of bone, usually with its own ossification center in childhood that often serves as a point for muscle or ligament attachment. The midshaft of a long bone is referred to as the *diaphysis*. The *metaphysis* of a long bone represents the area between the diaphysis and the physis (**Figure 141-1**; see Chapter 267, "Initial Evaluation and Management of Orthopedic Injuries").

The long bones of children are less dense and more porous than the long bones of adults. Pediatric long bones respond to mechanical stress by bowing and buckling rather than fracturing through and through like fractures in adult bones. The periosteum of the diaphysis and the metaphysis is thick in children and is continuous from the metaphysis to the epiphysis, surrounding and protecting the mechanically weaker physis. The weakness of the physis is in part related to the reduced oxygen tension found in the hypertrophic zone of the physis. This hypertrophic zone is the location of frequent fractures within the physis. The physis is also sensitive to alterations in the blood supply, and physeal injuries can result in growth disturbance. Compression forces alone may also affect bone growth. This is particularly true when compression forces are applied to the epiphyseal side of the physis. The injury to bone growth caused by compression results from interruption of the epiphyseal circulation to the reproductive cells of the physis.

The growth of the musculoskeletal system and its response to injury are influenced by the growth of muscle and connective tissue. The ligaments of children are stronger and more compliant than in adults, and ligaments tolerate mechanical forces better than the weaker physes. Therefore, apophyseal detachments or epiphyseal fractures are much more common than ligamentous injuries during childhood.

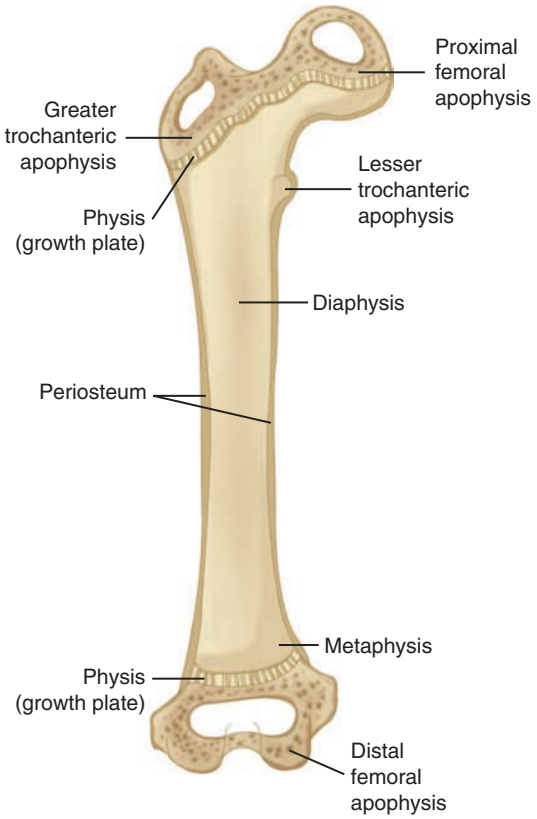


FIGURE 141-1. The anatomy of the pediatric long bone as demonstrated by the femur. Longitudinal growth occurs at the physes (growth plates) located at either end. Bony prominences that serve as sites of muscular or ligamentous attachment are known as apophyses (e.g., greater trochanteric apophysis).



FIGURE 141-2. Salter-Harris type I fracture of distal tibia. Anteroposterior radiograph showing widened physeal line of distal tibia with malalignment of epiphysis with metaphysis (*arrow*). [Photo used with permission of Karen Black, BC Children's Hospital, Vancouver.]

FRACTURE PATTERNS

FRACTURES INVOLVING THE PHYSIS

The Salter and Harris classification system (see Figure 267-7) is based on the relationship of the fracture line to the physis and the prognosis for growth disturbance.

Salter-Harris Type I Fractures Type I physeal injuries occur when the epiphysis separates from the metaphysis. The cleavage is through the hypertrophic cell zone of the physis, with the reproductive cells of the physis remaining with the epiphysis. There are no associated fragments of bone, as the thick periosteal attachments surrounding the physis remain intact. The epiphysis may, however, displace from the metaphysis. **Type I injuries have a very low incidence of growth disturbances.**

Suspect a Salter-Harris type I injury when there is point tenderness over a physis. Radiographic findings are typically subtle or absent, and soft tissue swelling or a joint effusion may be the only abnormality. Epiphyseal displacement can usually be appreciated on radiographs in one or more views (**Figure 141-2**); however, in the absence of epiphyseal displacement, the diagnosis is a clinical one.

Salter-Harris Type II Fractures In a type II injury, the fracture line extends a variable distance along the hypertrophic cell zone of the physis and then out through a piece of metaphyseal bone. The periosteum overlying the metaphyseal fragment remains intact, whereas the periosteum on the opposite side of the fracture is torn away from the diaphysis while remaining adherent to the epiphysis. Growth is preserved because the reproductive layers of the physis maintain their position with the epiphysis and the epiphyseal circulation. Diagnosis is made radiographically by noting a triangular-shaped fragment of metaphysis that is not associated with discernible injury to the epiphysis (**Figures 141-3** and **141-4**).

Salter-Harris Type III Fractures Type III physeal injuries are intra-articular. The fracture line extends intra-articularly from the epiphysis, through the hypertrophic zone of the physis, with the cleavage plane continuing along the physis to the periphery. The prognosis for subsequent bone growth relates to the preservation of circulation to the epiphyseal bone fragment; however, the prognosis is usually quite favorable.

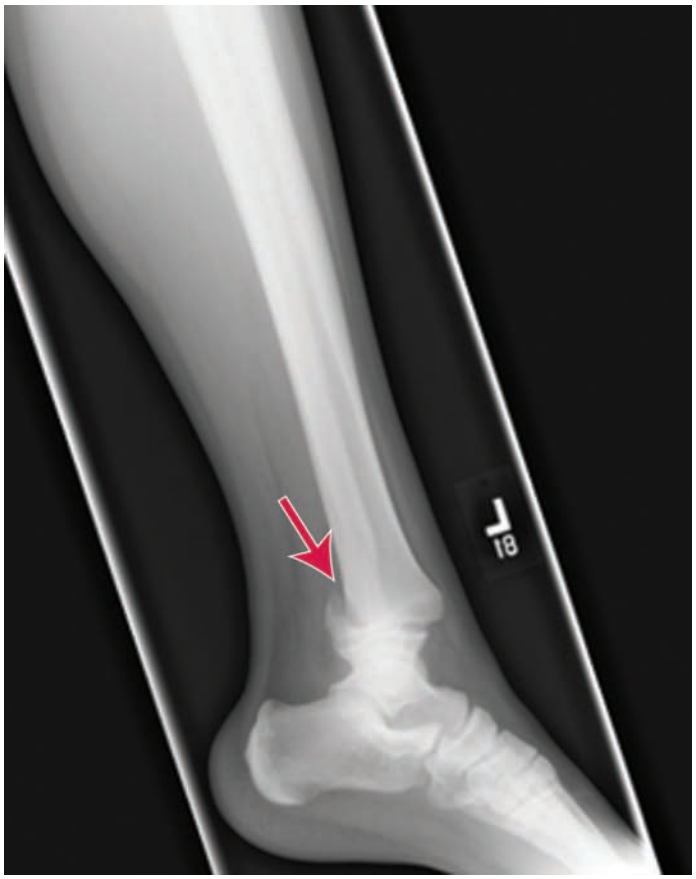


FIGURE 141-3. Salter-Harris type II fracture of distal tibia. Lateral radiograph illustrating fracture extending through physeal growth plate and metaphysis with dorsal displacement of epiphysis requiring reduction. [Photo used with permission of Wake Medical Center, Raleigh, NC.]

The diagnosis of a type III injury is made radiographically and is based on the appearance of an epiphyseal fragment not associated with an apparent metaphyseal fracture. There may or may not be an associated periosteal injury (**Figure 141-5**). Occasionally, additional imaging with CT or MRI is used to better evaluate the extent of fracture and articular surface involvement.



FIGURE 141-4. Salter-Harris type II fracture of distal tibia. CT image illustrating fracture extending through physeal growth plate and metaphysis (*arrow*). [Image used with permission of Wake Medical Center, Raleigh, NC.]



FIGURE 141-5. A radiograph of a Salter-Harris type III fracture of the distal tibia, also known as a Tillaux fracture. Note the intra-articular component extending through the growth plate and the medial epiphysis of the tibia. [Reproduced with permission from Strange GR, Ahrens WR, Schafermeyer RW, Wiebe RA: *Pediatric Emergency Medicine,* 3rd ed. McGraw-Hill, Inc., 2009. Fig 38-8.]

Salter-Harris Type IV Fractures In type IV injuries, the fracture line originates at the articular surface, extends through the epiphysis and the entire thickness of the physis, and continues through the metaphysis (**Figure 141-6**). The risk of growth disturbance with this type of fracture is significant, and reduction must be precise.

The diagnosis of a type IV injury is made radiographically upon identification of epiphyseal and metaphyseal fragments.

Salter-Harris Type V Fractures Type V injuries typically involve the knee or ankle and are the result of a profound compressive force transmitted to the physis, resulting in crushing of the chondrocytes in both the reserve and proliferative zones. Displacement of the epiphysis is usually only minimal despite the significant damage to the physis.

The diagnosis of a type V injury may be difficult initially, leading to a lack of appreciation of the severity of the injury. An initial diagnosis of a sprain or a type I physeal fracture may prove incorrect in view of subsequent development of premature growth arrest during follow-up. Radiographs may appear normal or may demonstrate focal narrowing of the physeal plate. There is also typically a joint effusion. The history, however, should point to a type V injury, as these injuries are typically associated with a significant mechanism.

TORUS FRACTURES

Compressive forces often result in a bulging or buckling of the periosteum rather than a more complete fracture line. Cortical, or *torus,* fractures are so named to describe prominence or bulging of the bony cortex, usually involving the metaphysis. These are also called *buckle fractures*.

A simple torus fracture will not produce a visible deformity to the shape of the extremity; however, there is typically soft tissue swelling and point tenderness over the bony injury.



FIGURE 141-6. Radiograph of a Salter-Harris type IV fracture of distal tibia with a Salter I fracture of the fibula. [Photo used with permission of Karen Black, BC Children's Hospital, Vancouver.]

Radiographically, the torus fracture may be subtle. Carefully inspect the contour of the metaphyseal flare. Any asymmetry, bulging, or deviation of the cortical margin indicates a torus fracture. Soft tissue swelling is also usually evident (**Figure 141-7**). Torus fractures are not associated with angulation, displacement, or rotational abnormalities, so reduction is not necessary.

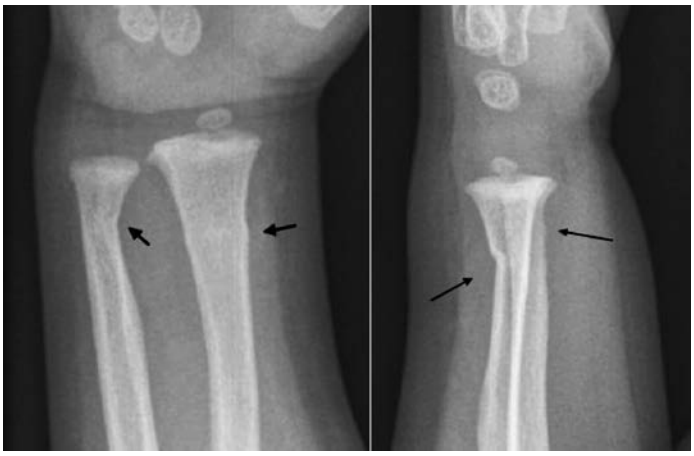


FIGURE 141-7. Torus fractures of the distal radius and ulna. [Figures used with permission of Karen Black, BC Children's Hospital, Vancouver.]

GREENSTICK FRACTURES

A *greenstick* fracture is characterized by cortical disruption and periosteal tearing on the convex side of the bone, with an intact periosteum and on the concave side of the fracture. Greenstick fractures are more stable and somewhat less painful than complete fractures because the area of intact periosteum limits bony displacement (**Figure 141-8**).

PLASTIC DEFORMITIES (BOWING OR BENDING FRACTURES)

Plastic deformities, also referred to as *bowing* or *bending fractures*, are almost exclusively limited to the forearm and lower leg long bones. The classic clinical hallmark is pain out of proportion to physical examination findings, and in the forearm, pain is maximal on pronation/

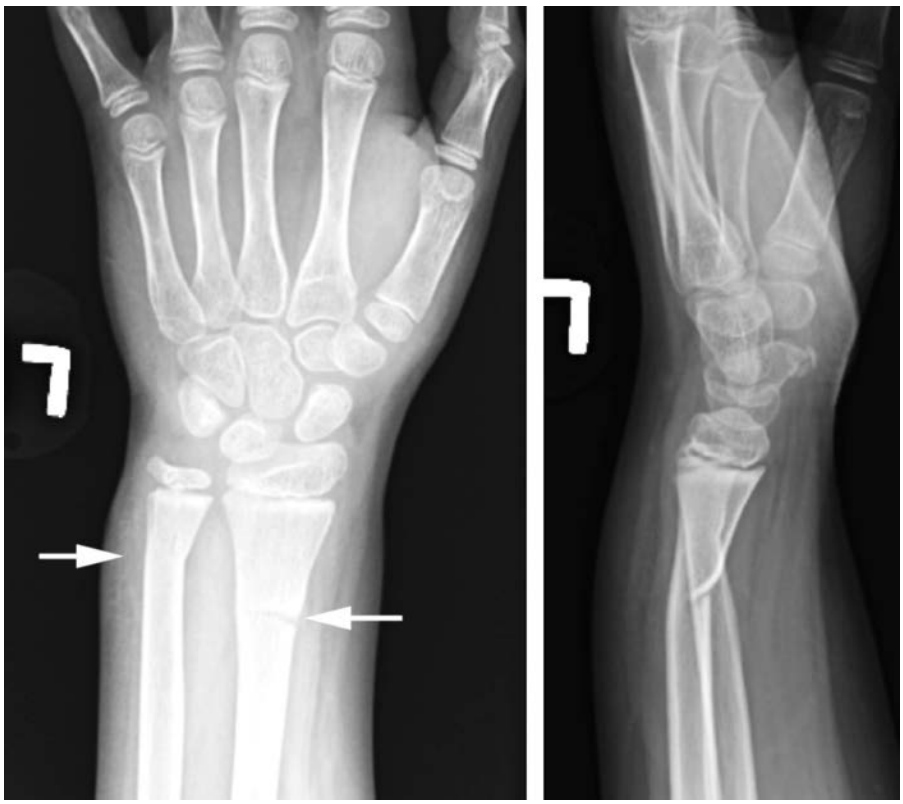


FIGURE 141-8. Anteroposterior and lateral radiographs demonstrating greenstick fractures of the distal radius and ulna in a child. [Reproduced with permission from Sherman SC: *Simon's Emergency Orthopedics,* 7th ed. © 2015, McGraw-Hill, Inc., New York. Fig 13-15.]

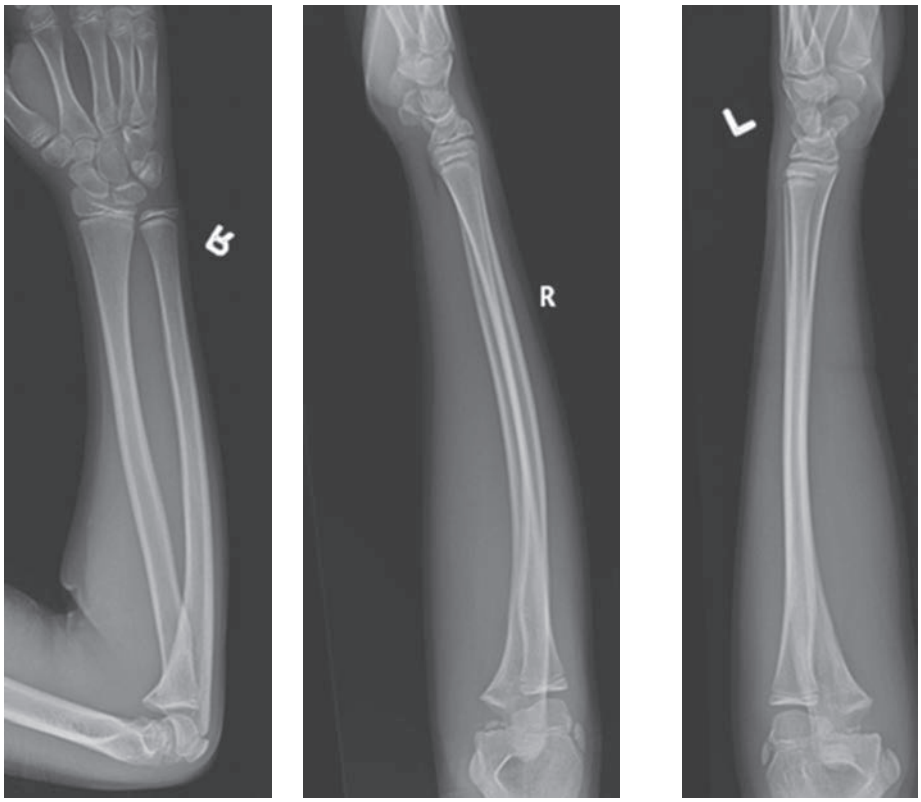


FIGURE 141-9. **A.** Injured right forearm demonstrating mild plastic deformation of the forearm. **B.** Lateral view of uninjured left forearm. [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

supination. The cortex of the diaphysis of the long bone is deformed, but the periosteum along the entire diaphysis is preserved. Moderate-severe plastic deformity is usually obvious clinically, which should guide the inexperienced clinician who may think that in the absence of an obvious fracture the radiograph appearances are normal.

Proper interpretation of the radiographs requires an awareness of the normal shape of the long bones involved because fracture lines and disruptions in the periosteum are absent (**Figure 141-9**). Comparison films of the uninvolved extremity are helpful for mild cases of a bowing injury but typically not necessary for moderate or severe cases of plastic deformation. These fractures can occur in isolation of other fractures but can also be noted in combination with a dislocation or complete fracture of the other bone of the forearm or lower leg.

FRACTURES FROM CHILD ABUSE

In general, any fracture in a nonmobile child should be considered suspicious for abuse. See Chapter 150, "Child Abuse and Neglect," for a complete discussion of child abuse.

UPPER EXTREMITY INJURIES

CLAVICLE FRACTURES

Clavicle fractures occur during two distinct time frames: the newborn period and childhood. Fractures of the clavicle in the newborn usually result from birth injury (**Figure 141-10**). Risk factors include high birth weight and shoulder dystocia. The infant may demonstrate upper extremity palsy secondary to a brachial plexus injury or may have "pseudoparalysis" of the extremity secondary to pain. Although many clavicle fractures are detected at birth, the diagnosis may be delayed, especially if the fracture is nondisplaced. An ED visit may be made when the newborn is not moving one arm during the first week of life, or when a parent notices a small "lump" or callus at the clavicle during the first 2 to 3 weeks of life. Clavicle fractures in the newborn do not need specific treatment. Pain control and careful handling of the baby are usually all that are required.

Clavicle fractures outside of the newborn period usually result from accidental injury in a mobile child. The most common mechanism of injury is either a fall onto an outstretched hand or onto the lateral side of the shoulder. The clavicle may fracture in three general sites: the diaphysis, medial end, or lateral end.

FRACTURES OF THE MIDDLE THIRD OF THE CLAVICLE

Fractures of the diaphysis usually occur in the middle third of the clavicle and are the most common of all clavicle fractures. Most of these injuries can be treated with analgesics, support of the injury with a

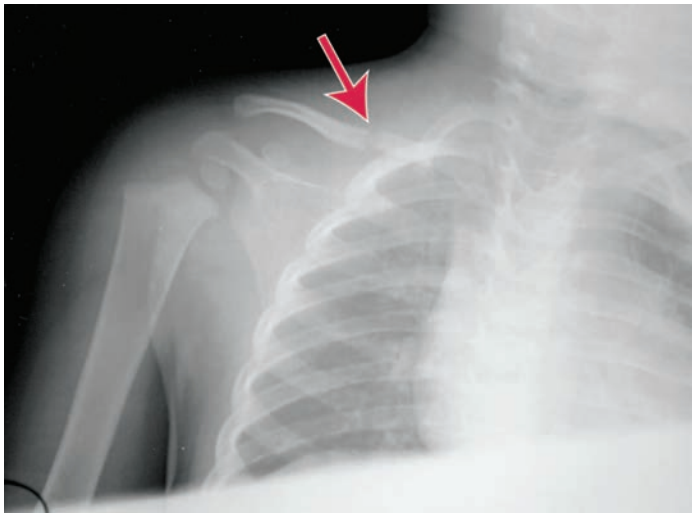


FIGURE 141-10. Nondisplaced clavicle fracture in an infant (*arrow*).

broad arm sling for 3 to 4 weeks, and follow-up with the primary care physician.[1] Urgent orthopedic consultation is indicated when a child is >12 years of age, the fracture is ≥100% displaced and/or shortened ≥2 cm, or there is skin tenting, neurovascular compromise, and/or fracture through a pathologic lesion. Complete healing and remodeling can take more than 1 year, and a small callus will become palpable in most cases if the fracture was displaced.

FRACTURES OF THE MEDIAL CLAVICLE

Fractures at the medial end of the clavicle are uncommon. Given the strong ligamentous attachment of the clavicle to the sternum, injuries to this area are usually epiphyseal disruptions. Orthopedic consultation is recommended for these injuries.

FRACTURES OF THE DISTAL CLAVICLE

Fractures of the distal end of the clavicle are also uncommon in children and again more likely to be epiphyseal disruptions. Minimally displaced distal clavicle fractures only need immobilization with a sling or equivalent. Surgical reduction may be needed for more displaced fractures.

FRACTURES OF THE HUMERUS

Fractures of the humerus are divided into three groups: fractures of the proximal humerus, fractures of the humeral diaphysis, and fractures of the condyles and supracondylar area. Supracondylar and condylar fractures are discussed as part of "The Pediatric Elbow" section below.

FRACTURES OF THE PROXIMAL HUMERUS

Fractures of the proximal humerus may occur at the physis or the proximal humeral metaphysis, and they have an extraordinary ability to repair themselves. Proximal humeral physeal fractures occur more commonly in adolescence because this area becomes relatively weak during this time due to rapid growth. Fractures of the proximal humeral metaphysis are more common in preadolescents. Treatment depends on the age of the child and degree of displacement and/or angulation. In general, children ≤10 to 12 years of age with a proximal humeral fracture that is displaced ≤50% and <60 degrees angulated can be treated in a broad arm sling for 4 weeks and can be followed as an outpatient in an orthopedics clinic within a week. If the child is >10 to 12 years old with >50% displacement or >30 degrees of angulation, if there is a pathologic fracture, or if there is neurovascular compromise, then urgent referral to an orthopedic surgeon is indicated.

FRACTURES OF THE HUMERAL DIAPHYSIS

Fractures of the humeral diaphysis are uncommon in children. Direct trauma can cause a transverse fracture, and violent rotation can cause a spiral fracture. **Spiral/oblique fractures of the humeral diaphysis in infants and toddlers have been strongly linked to child abuse**.[2] Rarely, the fracture fragment may injure the radial nerve as it runs in the radial groove. Thus, **assess radial nerve function on initial examination and following any splinting** (wrist extensors and supinators, sensation of dorsoradial hand, thumb, and second digits). Potential for healing is good, and treatment is usually immobilization in a long arm plaster splint and orthopedic follow-up. Closed reduction (or even open reduction and internal fixation) by orthopedics may be required for displaced fractures in the teenager.

THE PEDIATRIC ELBOW

Compared with other fractures, elbow fractures in children are commonly missed in the ED.[3] The radiologic diagnosis of elbow fractures is challenging because of the large cartilaginous component of the elbow.

ELBOW RADIOGRAPHS

True lateral and anteroposterior radiographs of the elbow are essential to diagnose fractures. There are two lines that should be routinely drawn during the interpretation of pediatric elbow radiographs. Assuming a proper lateral view of the elbow, the first line is the anterior humeral line. A line is drawn from the anterior humerus to the area distal to the capitellum. This line must bisect the middle third of the capitellum. If it is does not, consider an extension-type displaced supracondylar fracture, displaced lateral condyle fractures or, rarely, a transphyseal fracture (**Figure 141-11**). The other line is drawn on the lateral view and is the radiocapitellar line, which runs through the middle-third of the radius and bisects the middle of the capitellum (Figure 141-11). If not, consider lateral condyle fracture, radial neck fracture, Monteggia fracture, or elbow dislocation.[4,5]



FIGURE 141-11. Anterior humeral and radiocapitellar lines. Anterior humeral line is drawn along the anterior cortex of the humeral shaft normally intersects the middle third of the capitellum. The radiocapitellar line is drawn along the long axis of the radial shaft should intersect the middle of the capitellum on each view. [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

Lateral radiographs are also used to evaluate for subtle effusions when an occult fracture is suspected. An anterior fat pad may be normal and appears as a small drop of oil hugging the distal anterior humerus. An anterior fat pad that seems to protrude like a sail from the distal humerus may be pathologic ("sail sign"), but when significant for an associated fracture, this finding typically occurs in association with a visible bony fracture or posterior fat pad (**Figure 141-12**). This is unlike the posterior fat pad that is evidence of a hemarthorsis from an intra-articular injury and is always considered pathologic even in the absence of a visible bony fracture (Figure 141-12).

ELBOW OSSIFICATION CENTERS

It is important to identify the ossification centers around the elbow to avoid confusion with fracture. There are six ossification centers appearing at varying ages in the pediatric elbow. The mnemonic used over the years is **CRITOE** (*c*apitellum, *r*adial head, *i*nternal [medial] epicondyle, *t*rochlea, *o*lecranon, external [lateral] *e*picondyle). All of the ossification centers may be seen on the anteroposterior view of the elbow in the appropriately aged child, although the olecranon may be difficult to identify. On the lateral view, all are seen but the trochlea and external (lateral) epicondyle (**CRIO**).

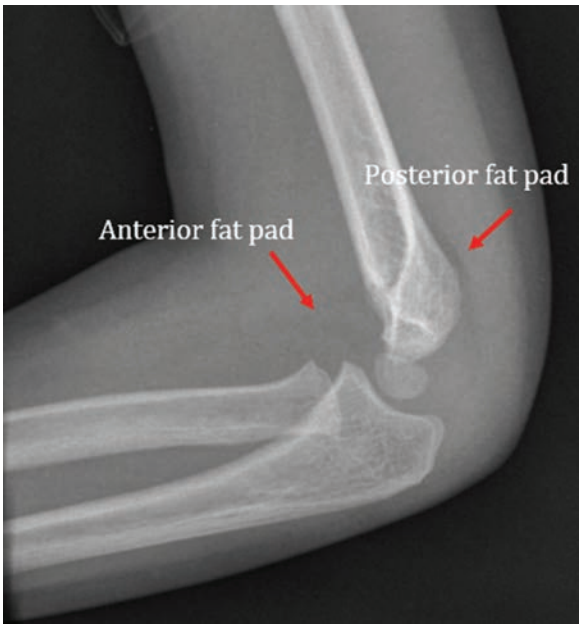


FIGURE 141-12. Lateral elbow radiograph demonstrating anterior (*arrow*) and posterior (*arrow*) fat pad sign. [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

SUPRACONDYLAR FRACTURES

Supracondylar fractures are the most common elbow fractures in children. The majority of supracondylar fractures occur in children from 3 to 10 years of age, with the peak incidence occurring between ages 5 and 7 years old. The extension type is by far the most common, accounting for 90% to 98% of cases (Figure 141-11). An extension-type supracondylar fracture is caused by a fall on an outstretched hand with the elbow hyperextended. A flexion-type fracture results from falling on a flexed elbow and is rare. The complications of a supracondylar fracture, although uncommon, range from transient neurapraxia to Volkmann's ischemic contracture, with the most common being injury to the anterior interosseous nerve resulting in the "pointing finger sign."

Classification of Supracondylar Fractures Classification of supracondylar fractures is based on the extent of fracture fragment displacement. Type I fractures are displaced ≤2 mm and may have a posterior fat pad sign as the only radiographic finding (Figure 141-12). Radiologically occult fractures can often be confirmed on radiographs performed 2 to 4 weeks after the injury with the presence of a periosteal reaction of the humerus. Type II fractures are angulated to varying degrees, but the posterior cortex of the humerus is intact (**Figure 141-13**). Type III fractures are completely displaced with no cortical contact (**Figure 141-14**). The distal fragment may be posteromedially (type IIIa) rotated and, as such, can impinge against the radial nerve or be posterolaterally (type IIIb) rotated. **In posterolaterally displaced fractures, the brachial artery and median nerve are at risk for injury, and compartment syndrome can develop.**[6,7] If compartment syndrome is suspected (see Chapter 278, "Compartment Syndromes"), emergency orthopedic consultation is needed. Traction and reduction are indicated if the hand is cool, pale, and pulseless. The simple absence of a pulse in an otherwise viable hand is a contraindication to manipulation in the ED.

Treatment The level of displacement and the prereduction physical examination dictate treatment of pediatric supracondylar fractures. Type I supracondylar fractures are inherently stable. The goal of therapy is pain control and immobilization with a long-arm posterior splint with the elbow at 90 degrees and the forearm in pronation or neutral rotation for 3 weeks. Arrange orthopedic follow-up within 2 to 7 days. While collar and cuff immobilization is used in some centers, it does not offer as good pain management as splinting.[8,9] Type II and III fractures need urgent orthopedic consultation in the ED for definitive management that typically includes operative pinning.[10] Keep these patients fasting in anticipation of surgical intervention.

LATERAL CONDYLE FRACTURES

Lateral condyle fractures occur when there is varus stress on an extended elbow with the forearm in supination. Swelling and tenderness are usually limited to the lateral elbow, and neurovascular injury is uncommon. Diagnosis can be made with standard anteroposterior and lateral views, but obtain an oblique view if clinical suspicion is high. Fractures can be Salter-Harris type II (most common) or IV. Treatment is based on amount of displacement and articular congruence, and if this fracture is suspected, oblique views are recommended to determine maximal displacement. Type I lateral condylar fractures are defined by ≤2 mm displacement, and the child's elbow injury can be treated in a long-arm backslab with the elbow flexed at 90 degrees and a broad arm sling (**Figure 141-15**). Type II lateral condylar fractures occur when there is >2 mm displacement with congruity of the articular surface, while type III fractures occur with >2 mm displacement and without congruity of the articular surface. Type II and III lateral condylar fractures require urgent orthopedic consultation since these fractures often require open reduction and internal fixation. Nonunion, malunion, osteonecrosis, cubitus valgus, and tardy ulnar nerve palsy are well-described complications. Displacement can occur even within a cast or splint due to the pull of the forearm extensor tendons.

MEDIAL EPICONDYLE FRACTURES

Fractures of the medial epicondyle tend to occur in older children, between the ages of 10 and 14 years old. They are not true Salter-Harris injuries because the apophysis rather than the physis is involved. Simple fractures of the medial epicondyle are extra-articular injuries with limited soft tissue involvement, but nearly half of injuries are associated with elbow dislocation; in such injuries, the epicondyle can become entrapped in the joint.[11,12] Fractures are classified by the amount of displacement and associated extremity injuries (**Figure 141-16**). Typically, if there is <5 mm of displacement, these fractures can be managed in a long-arm backslab at 90 degrees of elbow flexion for 3 weeks and follow-up in orthopedics. The presence of >5 mm of displacement is an indication for urgent orthopedic consultation. It is important to distinguish a medial epicondyle fracture from a medial condyle fracture. Medial condyle fractures are intra-articular and require urgent review by an orthopedic surgeon.

MONTEGGIA FRACTURE DISLOCATION

A Monteggia fracture-dislocation refers to the dislocation of the radial head (proximal radioulnar joint) with fracture of the ulna. This type of injury is the most commonly missed serious fracture of the elbow, and delayed or missed diagnosis is not infrequent. A good general rule is that if there an ulnar fracture, always look for an associated radius injury. Reduction is always required for these injuries. The Bado classification system identifies four types of Monteggia fractures.

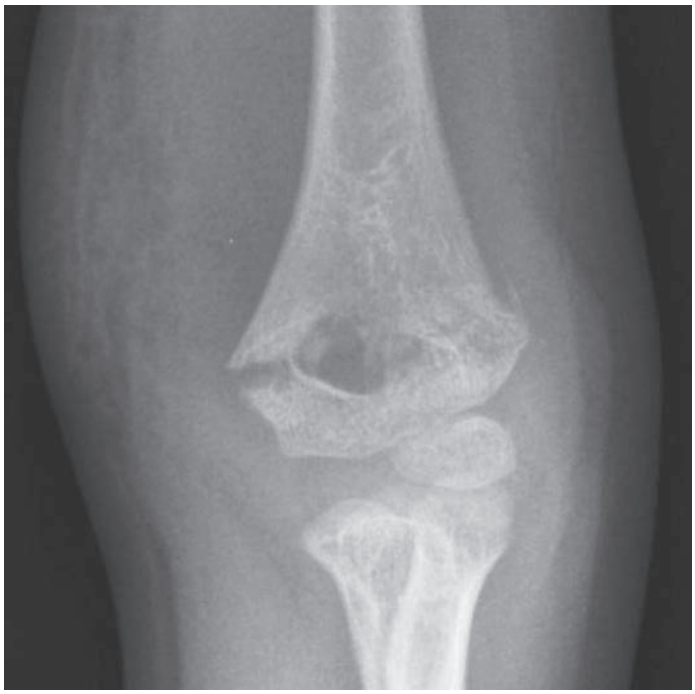
About 70% are type I, which occur when there is anterior dislocation of the radial head with fracture of the ulna shaft (**Figure 141-17**). Type II fractures represent about 5% and occur when there is posterior dislocation of the radial head and an ulnar fracture. About 25% are type III, whereby there is lateral dislocation of the radial head and an ulnar fracture. Finally, type IV, which is very rare, demonstrates anterior dislocation of the radial head and diaphyseal fractures of both the radius and ulna.

OLECRANON FRACTURES

Olecranon fractures generally result from a fall on the elbow and are best seen on the lateral view (**Figure 141-18**). Orthopedic consultation is best to guide treatment. If the fracture is displaced ≤5 mm, it should be immobilized in the most stable position, usually 90 degrees of elbow flexion, for 3 to 6 weeks. Open reduction and internal fixation are indicated for unstable fractures. Olecranon fractures occur in association with fractures of the radial head and neck. A "simple" olecranon fracture may be part of a Monteggia lesion, so radial head position should be evaluated carefully.



A



B



C

FIGURE 141-13. **A.** Clinical picture of a type II supracondylar fracture with marked soft tissue swelling in a child with a history of falling on an outstretched arm. **B** and **C.** Anteroposterior (AP) and lateral views of the elbow, demonstrating a supracondylar fracture with medial opening seen on the AP view and posterior displacement of the distal fragment identified on the lateral view. [**A:** Reproduced with permission from Shah BR, Lucchesi M, Amodio J, Silverberg M: *Atlas of Pediatric Emergency Medicine,* 2nd ed. © 2013, McGraw-Hill, Inc., New York. Fig. 19-33A. **B** and **C:** Image used with permission of Karen Black, BC Children's Hospital, Vancouver.]

RADIAL HEAD AND NECK FRACTURES

Fractures of the radial head and neck are uncommon in children (**Figures 141-19** and **141-20**). The radial neck is fractured more frequently than the radial head, and most radial neck fractures occur through the metaphysis. The most common mechanism is a fall. Obtain orthopedic consultation to guide treatment. Reduction is often necessary when angulation is >35 degrees or displacement is >60%.[13]

ELBOW DISLOCATION

Elbow dislocations occur most frequently in males (70%), usually from a fall on the outstretched hand. The most common type of dislocation is posterior, usually accompanied by some lateral displacement (**Figure 141-21**). Carefully examine the radiographs for associated fractures, particularly of the medial and lateral epicondyle and radial neck. Neurologic injury is associated with approximately 10% of elbow dislocations. Ulnar neuropathy is the most common and is usually associated with medial epicondyle entrapment. Median nerve injury may be caused by entrapment of the nerve inside the joint, behind the medial epicondyle, or in an epicondyle fracture. Radial nerve and arterial injury are both rare. Consult orthopedics emergently if neurovascular injury is suspected (see Chapter 270, "Elbow and Forearm Injuries"). After reduction and review of postreduction radiographs, immobilize the reduced elbow in a posterior mold and refer for orthopedic follow-up within 1 week. The major long-term complication is elbow stiffness.

SUBLUXATION OF RADIAL HEAD (NURSEMAID'S ELBOW)

Subluxation of the radial head, otherwise known as a "pulled elbow" or "nursemaid's elbow" is a common injury in young children. It can occur any time from birth to 6 years of age but commonly occurs from

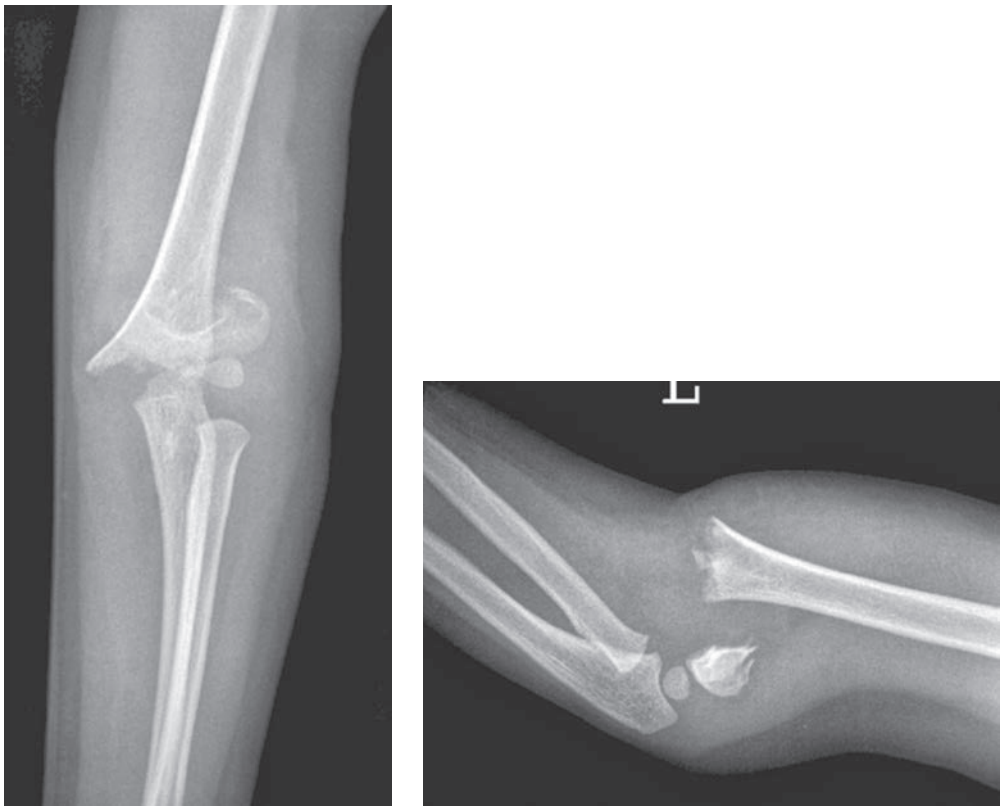


FIGURE 141-14. Type III displaced supracondylar fracture. The distal fragment is displaced posteriorly, proximally, and medially. [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

1 to 4 years of age.[14] It often results from a sudden pull on the arm, usually by an adult or taller person, but can also result from a fall or twist. The force pulls the radius through the annular ligament, resulting in subluxation (partial dislocation) of the radial head. Specifically, the annular ligament slips forward with traction and becomes entrapped between the radial head and the capitellum of the humerus. The child experiences sudden acute pain and loss of function of the affected arm. On examination, the child holds the involved arm in slight flexion and

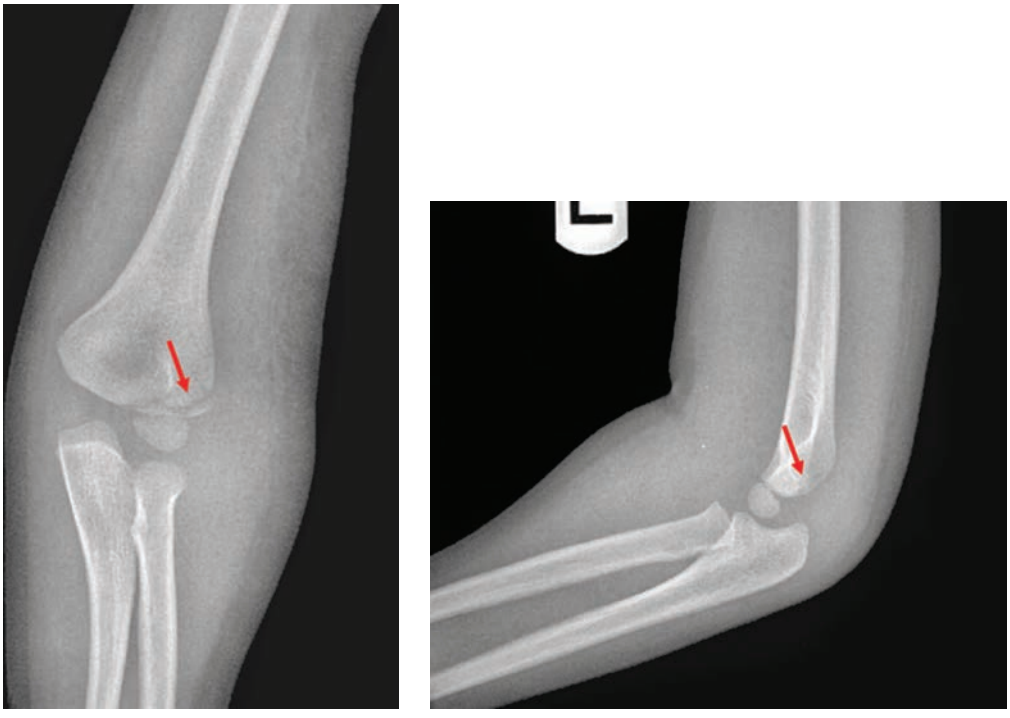


FIGURE 141-15. Lateral condyle fracture (*arrow*) can be subtle in some views but displaces easily in the first week if not fixed operatively. [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]



FIGURE 141-16. Medial epicondyle avulsion. Note a flake of the medial condyle has fractured off as well. [Photo used with permission of Karen Black, BC Children's Hospital, Vancouver.]

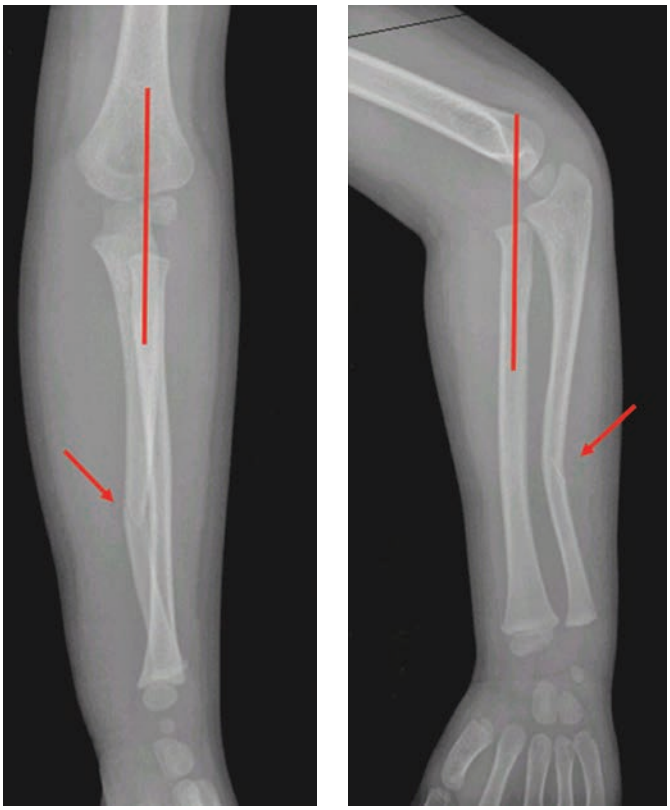


FIGURE 141-17. Anteroposterior and lateral radiographs demonstrating a Monteggia fracture–ulnar fracture (*arrow*) associated with radial head dislocation (*arrow*). [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

pronation, and there is no focal swelling or tenderness. However, there is significant tenderness elicited with pronation/supination of the forearm. This is a clinical diagnosis and should not be confused with other radial head pathology (radial head/neck fractures) or bowing fractures that can also illicit tenderness with pronation/supination. Distinguishing features between these entities in favor of a pulled elbow include lack of focal symptoms/signs, younger age, and relatively benign mechanisms. US may help exclude other injuries such as supracondylar fracture but can miss radial head fracture (See Video: Pediatric Elbow: Ultrasound Evaluation). There are two favored techniques to reduce a pulled elbow. The first is called the supination-flexion method. In this technique, grasp the humeral epicondyles with your thumb over the radial head, and with the other hand, quickly provide supination of the forearm and flex the elbow. An alternative method is called hyperpronation. Hold the child's hand as if you are shaking hands, hold the

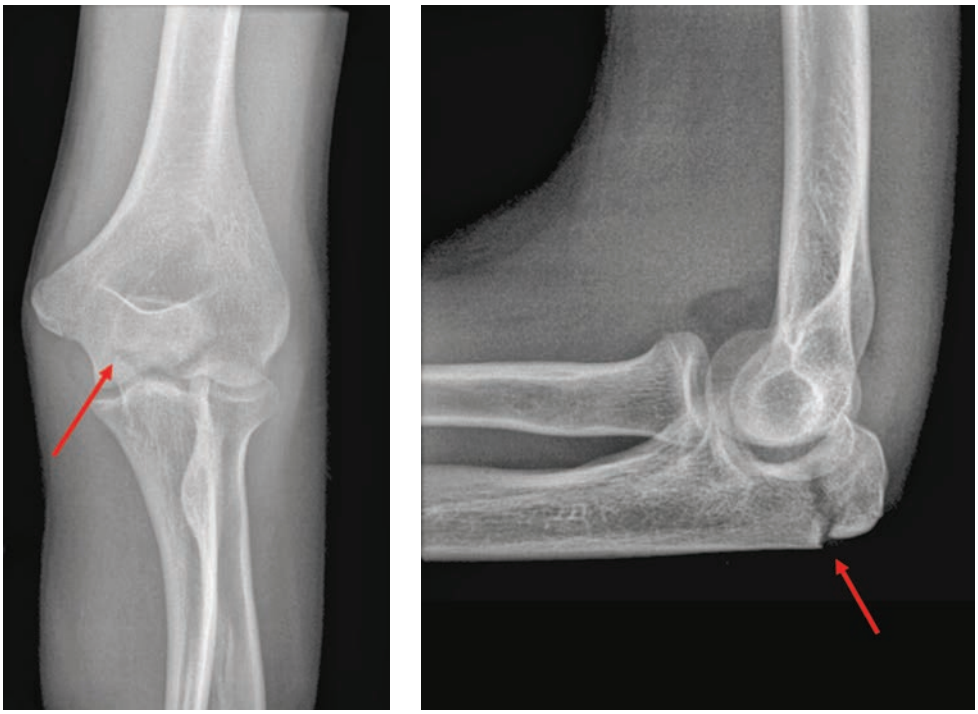


FIGURE 141-18. Anteroposterior and lateral radiographs demonstrating an olecranon fracture (*arrow*). [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]



FIGURE 141-19. Lateral radiograph illustrating radial head fracture (*arrow*). [Photo used with permission of Wake Medical Center, Raleigh, NC.]

epicondyles with your other hand, extend the forearm, and pronate quickly. If one method is not successful, you can try the alternative method. A meta-analysis published in 2017 concluded that hyperpronation was more effective in terms of success rate and seems less painful compared with the supination-flexion maneuver.[15] If successful, pain resolves after reduction and normal arm movement is quickly regained (See Video: Nursemaid Elbow).



FIGURE 141-20. Anteroposterior radiograph illustrating radial neck fracture (*arrow*). [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

FOREARM INJURIES

The vast majority of shaft fractures involve the distal third of the forearm in the metaphyseal area of the bone. Clinically, there is typically point tenderness and swelling, and occasionally, there is deformity. Clinical assessment should include the forearm and the joints above and below the primary injury to assess for the presence of associated fractures or dislocations at those joints. Radiograph assessment above and below the forearm is also indicated if the clinical examination of these areas is limited.



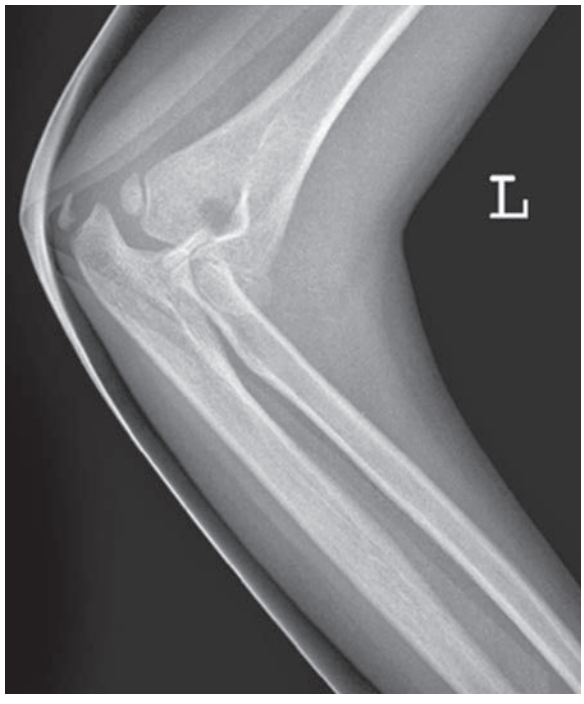


FIGURE 141-21. Radiograph demonstrating elbow dislocation with displacement of both radius and ulna. [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

RADIUS AND ULNA DIAPHYSEAL FRACTURES

Injuries of the shaft can remain unstable despite attempts at closed reduction and occasionally require open fixation. **Proximal third shaft fractures** are relatively uncommon. In skeletally immature children less than 10 years of age, angulation <10 degrees often does not require anatomic reduction.

Bowing deformities can be difficult to diagnose and are often missed, and radiologic comparison with the uninjured side may be necessary in mild cases (Figure 141-9). Failure to correct bowing (which tends to be along the whole bone) may lead to permanent deformity and disability. While minimally angulated bowing fractures can be managed in a splint or cast and follow-up with an orthopedic surgeon, more advanced bowing fractures may require completion of the break to establish proper realignment. Prompt orthopedic consultation is required for any plastic deformities. In general, proper reduction and realignment are recommended for any angulation ≥20 degrees in children less than 10 years of age or ≥15 degrees in children greater than 10 years of age. Consultation with orthopedics in the ED is advised to guide management for when a bowing injury is suspected.

Isolated ulnar fractures are rare and are caused by a direct blow. If caused by an indirect force, typically, there is an associated fracture or dislocation of the radius. **As per above, the combination of an ulnar fracture with a dislocation of the radial head is called *Monteggia fracture* (Figure 141-17). *Galeazzi fracture* is a radial shaft fracture with an associated dislocation of the distal radioulnar joint (Figure 141-22).** Although this injury is uncommon, immediate orthopedic consultation is warranted.

RADIUS AND ULNA METAPHYSEAL GREENSTICK OR COMPLETE FRACTURES

Younger children and more distal injuries have a greater capacity for remodeling. In general, in girls age <10 years and boys age <12 years with fractures that are ≤15 degrees angulated in the sagittal and ≤5 mm displaced in the frontal plane do not need reduction and can be managed in a short-arm circumferential cast or splint for 4 to 6 weeks.[16] Follow-up with an orthopedic surgeon is still recommended since these fractures can be unstable and can displace further in follow-up regardless of whether they are managed in a cast or a splint.[17] For greater degrees of angulation, consult orthopedic surgery to determine the need for urgent reduction.

RADIUS AND ULNA METAPHYSEAL TORUS FRACTURES

Torus or buckle-type fractures (Figure 141-7) of the distal forearm are the most common pediatric fracture. There is point tenderness over the distal radius and/or ulna, occasionally with associated localized swelling. These fractures are best treated by splinting in a position of function with follow-up with the primary care physician within 1 to 3 weeks.[18,19] Orthopedic surgery referral should be reserved for cases that are not healing as expected. Implementing this pathway is completely dependent on the emergency physician getting the correct radiologic diagnosis. Distal radius buckle fractures can be radiologically subtle and therefore can be missed without careful review of both the anteroposterior and lateral radiograph views. In contrast, about 10% of cases thought to have a distal radius fracture actually have more advanced fractures such as distal radius greenstick or distal radius Salter-Harris type II fractures.[20] Although the latter fractures are also likely to heal well in a splint, they are less stable and typically require follow-up with an orthopedic surgeon.

DISTAL RADIUS PHYSEAL FRACTURES

Salter-Harris fractures of the distal radial physis are assumed if there is point tenderness or swelling over the distal radius physis and there is no radiographic evidence of a visible bony fracture. These injuries are rarely associated with growth disturbances. Undisplaced or minimally displaced Salter-Harris I fractures should be immobilized with a below-elbow splint and followed in an orthopedic clinic within 1 week. Significantly displaced



A



B

FIGURE 141-22. Galeazzi fracture. Note the widening of the distal radial ulnar joint space on the anteroposterior view (**A**) and dislocation of the distal radius relative to the ulna on the lateral projection (**B**) (*arrows*). [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed, © 2007, McGraw-Hill, Inc., New York.]

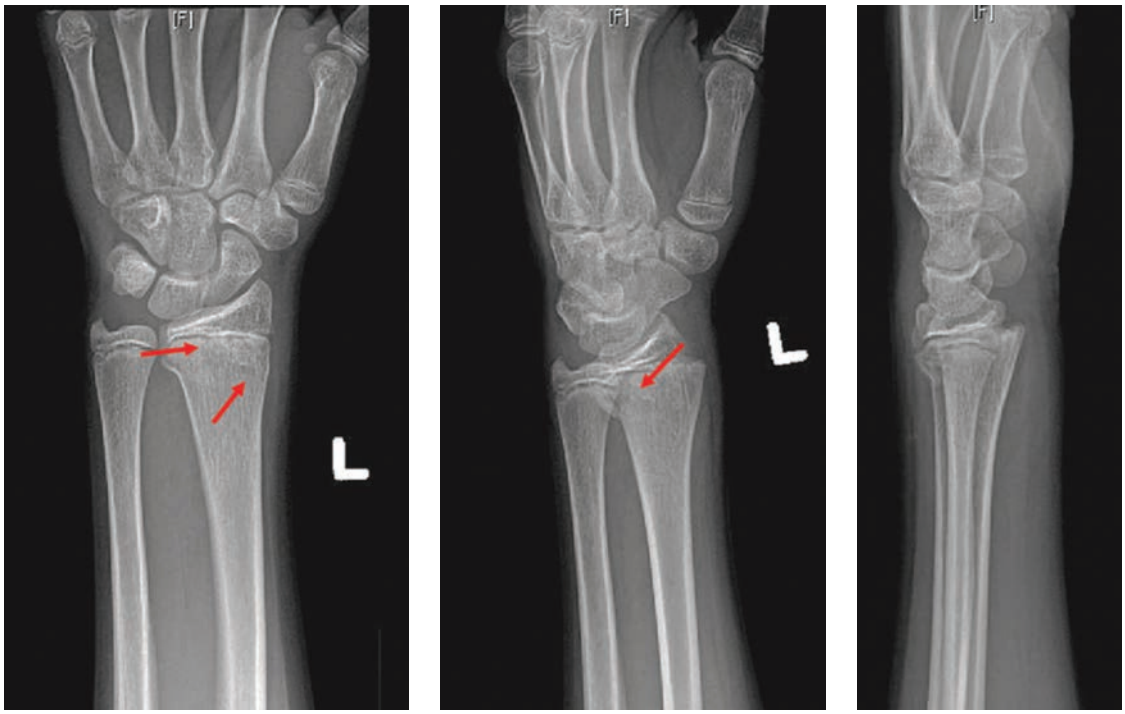


FIGURE 141-23. Anteroposterior, lateral, and oblique radiographs illustrating a minimally displaced Salter-Harris type II fracture (*arrows*). [Reproduced with permission from Hospital for Sick Children 2018, Toronto, Canada.]

Salter-Harris I fractures often require urgent closed reduction in the ED. Consult orthopedic surgery for guidance on when reduction is recommended. Salter-Harris type II injuries (**Figure 141-23**) can be managed as per Salter-Harris I fractures of the distal radius. For Salter-Harris types III, IV, and V injuries, urgent orthopedic consultation is necessary.

CARPAL BONE INJURIES

Fractures of the carpal bones are quite rare in the skeletally immature child. However, these injuries increase in frequency in the skeletally mature adolescent population. Most are sports-related injuries. Fracture patterns and presentation are similar to the adult, and scaphoid fractures are the most common type (**Figure 141-24**), although rare in and of themselves.[21] For example, the scaphoid may be fractured in older adolescents with the typical mechanism being that of a fall on an outstretched hand. There is typically the classically expected snuffbox tenderness and pain with longitudinal compression of the thumb. However, unlike adults, nonunion is less common in children.[22] A high index of suspicion for this type of injury is required. Immobilize any suspected fracture of carpal bone in a thumb spica splint and arrange early orthopedic follow-up, even in the absence of radiographic findings. Repeat plain radiographs, CT, or MRI may be used at follow-up for further assessment of the injury.

PHALANGEAL FRACTURES

The most common injury is that to the distal phalanx resulting from a crush injury, typically seen when the child catches his or her hand in a door. Immobilize a distal phalanx "tuft" fracture with a finger splint. If there is associated nail bed injury, the fracture is considered "open," and orthopedic or plastic surgery follow-up in 1 week or less must be arranged. The role of prophylactic antibiotics in open fractures of the distal tuft remains controversial, with no clear evidence of benefit.[23]

Fractures of the phalangeal shaft should be examined for displacement, rotational deformity, and tendon disruption. Significantly displaced or rotated fractures or those with tendon disruption need orthopedic/plastic surgery consultation for reduction and repair.



FIGURE 141-24. Radiograph demonstrates a mildly displaced fracture of the distal aspect of the scaphoid bone involving the tubercle (*arrow*). This is also minimally displaced with a tiny avulsion fragment. [Reproduced with permission from the Hospital for Sick Children, Toronto, Canada.]



FIGURE 141-25. Avulsion fracture of the anterior superior iliac spine of the pelvis. [Reproduced with permission from the Hospital for Sick Children, Toronto, Canada.]

LOWER EXTREMITY INJURIES

PELVIC FRACTURES

The immature, relatively cartilaginous pediatric pelvis is somewhat pliable. There are two broad categories of pelvic fractures: nonavulsive and avulsive. Nonavulsive pediatric pelvic fractures usually result from a tremendous force, and the most common mechanism for pelvic fractures is pedestrian versus motor vehicle collisions.[24] Assume multisystem injury in a child with a pelvic fracture, and transfer to a facility equipped to manage pediatric multiple trauma. In children, life-threatening hemorrhage usually results from injury to other body areas rather than from injury to the pelvic vessels. Avulsion-type injuries of the pelvis (**Figure 141-25**) result from sudden contraction of musculature attached to the pelvis and typically occur during athletic activities. These injuries are usually seen in the adolescent after secondary ossification centers develop and are unusual before 8 years of age. Clinically the child will complain of sudden pain and have point tenderness and possibly swelling over the fracture site (usually the anterior-superior iliac spine, but can occur at anterior-inferior iliac spine also). MRI or CT may be needed to confirm the diagnosis, but nearly all avulsion fractures can be managed conservatively with rest, limitation of activity until symptoms resolve, and orthopedic follow-up.

HIP FRACTURES AND DISLOCATIONS

Trauma can result in an epiphyseal disruption or a fracture of the head, neck, trochanteric, or subtrochanteric region of the femur. Proximal fractures involving the femoral head or neck have a high risk of complications such as avascular necrosis and growth arrest. Treatment is almost always urgent operative repair.

Traumatic dislocations of the hip are also rare in the pediatric population and are best divided into those occurring in the older adolescent and those occurring in the skeletally immature child. Most hip dislocations in adolescents are posterior and result from significant trauma. Dislocations in children <10 years old can occur with low-energy trauma. Treatment for pediatric hip dislocations is urgent closed reduction. Immediate orthopedic consultation is indicated, as any significant delay in reduction is associated with a higher incidence of complications including sciatic nerve injury. Pathologic fractures are possible through bone cysts or lesions.

FRACTURES OF THE FEMORAL SHAFT

The femur is the second bone to ossify in the fetus and the largest of the long bones in the body. The strength of the femur continues to increase in later childhood, and therefore, significant force is usually required to fracture the femoral shaft. The exception is in young healthy ambulatory children from 1 to 4 years of age, when femur fractures can occur with low-velocity injury such as a short fall or twisting or stumbling injury.[25] **Nevertheless, it is important to consider child abuse in a child with a femur fracture who is not yet walking.**[26]

Pediatric femur fractures occur more commonly in boys and seem to follow a bimodal distribution with peaks during late toddler age and mid-teenage years. The most common mechanisms of injury are falls, pedestrian versus automobile incidents, motor vehicle collisions, and sports-related injuries.

The clinical findings of a femur fracture are usually obvious. There is typically tenderness and swelling over the fracture site. The child may hold the leg externally rotated and will likely refuse to bear weight. The leg may be shortened. Given the high degree of force needed to fracture the femur, perform a thorough evaluation for multisystem trauma. **Hypotension is usually not related to an isolated femur fracture in a young child and should prompt a search for other injuries.**[27] All femoral shaft fractures require immediate orthopedic consultation. Treatment depends on the child's age, size, degree of malalignment, and reliability of follow-up.[28]

SLIPPED CAPITAL FEMORAL EPIPHYSIS

Slipped capital femoral epiphysis (also known as slipped upper femoral epiphysis) is a disorder of childhood characterized by slipping of the femoral epiphysis of the hip. Complications include avascular necrosis of the hip and premature closure of the physis. Slipped capital femoral epiphysis is the most common cause of hip disability in adolescents. Etiology is multifactorial, and any child may develop slipped capital femoral epiphysis during a growth spurt; however, many affected children are obese adolescents whose hips are exposed to repetitive minimal trauma, but some are tall, athletic children. Boys with slipped capital femoral epiphysis present at an average age of 14 to 16 years old. Girls typically present earlier, at approximately 11 to 13 years of age, with occurrence after menarche being rare. Hormonal and genetic factors also appear to play a role in the development of slipped capital femoral epiphysis. Atypical slipped capital femoral epiphysis occurs in children in whom obesity is not a risk factor and can be seen in children with juvenile chronic arthritis, certain human leukocyte antigen types, endocrinopathies, renal failure, and previous radiation or chemotherapy.

The slippage may be chronic, acute, or acute-on-chronic. Acute slipped upper femoral epiphyses are rare but quite dramatic. The child cannot bear weight, and surgery for reduction and fixation is done on an urgent basis. Acute worsening of mild chronic displacement may occur after minimal or no trauma. In cases of chronic slip, clinically, the child may develop hip (groin) pain, or pain is referred to the thigh or, much more commonly, the knee. The pain may be vague and chronic in nature. If you watch the child walk, you will observe that the foot on the affected side has a much more external progression angle, and when you examine the hip, you will note that the hip flexes into obligate external rotation. **Obtain bilateral hip radiographs in any adolescent with chronic pain in the groin, hip, thigh, or knee to evaluate for slipped capital femoral epiphysis because delay in diagnosis can lead to significant disability.** Adequate radiographs include both anteroposterior and lateral hip radiographs (Lowenstein view). Both hips should be imaged given the high incidence of bilateral disease. The use of frog leg views is controversial given the potential for further epiphyseal displacement in this position. Radiographically, epiphyseal slippage may be detected by examining the anatomic relationship of the femoral neck to the femoral head (**Figure 141-26** and **Figure 141-27**).

Several techniques of measuring the presence or degree of slip have been suggested, but subtle cases can be challenging to find on radiographs. Therefore, obtain orthopedic consultation for any child with pain suspicious for slipped capital femoral epiphysis in the ED. Additional imaging with MRI to detect early slips may be recommended. Once the diagnosis is made, the goal of treatment is to prevent further slippage; management includes strict non–weight bearing and

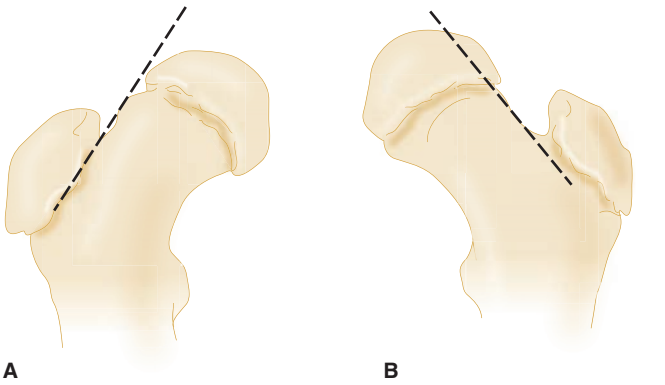


FIGURE 141-26. **A.** A line (Klein's line) drawn along the lateral (superior) aspect of the femoral neck fails to transect the lateral quarter of the femoral head in slipped capital femoral epiphysis (Trethowan's sign). **B.** The normal anatomic relationship is illustrated.

definitive operative management. Prophylactic pinning of the contralateral hip, even if apparently unaffected, is also recommended by some authors.[29]

Prognosis depends on the degree of displacement; however, even in the best of cases, many patients are left with residual limited range of motion and an increased risk for the development of osteoarthritis.

KNEE INJURIES

Compared with the adult, ligamentous injuries to the pediatric knee are much less common than are fractures. Evaluation typically includes two radiograph views (anteroposterior and lateral) of the knee. **The Ottawa Knee Rules (see Chapter 274, "Knee Injuries") have been validated for children greater than 5 years of age** and can help determine the need for radiographs.[30]

FRACTURES OF THE DISTAL FEMORAL PHYSIS

Fractures through the distal femoral physis are uncommon yet carry a significant complication rate. **The popliteal artery lies close to the distal femoral metaphysis and may be injured along with the peroneal nerve.** Growth arrest may also occur secondary to permanent physeal damage. Although Salter-Harris type I injuries may not be appreciated on radiographs, any child suspected of having a significant injury should receive orthopedic follow-up. Any displaced distal femoral physeal disruption needs immediate orthopedic evaluation for reduction (**Figure 141-28**).



FIGURE 141-27. Anteroposterior radiograph illustrating an early slipped capital femoral epiphysis requiring surgical management in right hip (*arrow*). *Dotted line* represents the Klein's line on the unaffected side. Note that the epiphysis on the affected side would not be intersected by a similar line. [Photo used with permission of Karen Black, BC Children's Hospital, Vancouver.]



FIGURE 141-28. Distal femur Salter-Harris type II fracture. [Photo used with permission of Wake Medical Center, Raleigh, NC.]

PATELLAR DISLOCATIONS

Patellar injuries in children are usually dislocations. In fact, patellar dislocation is one of the most common causes of a traumatic hemarthrosis in children. The typical mechanism is one of pivoting the knee on a fixed lower leg. Often reduction has already occurred at the scene, although a history of the "knee popped out of place" can usually be obtained. If the patient remains dislocated at the emergency visit, the displaced patella usually sits laterally and the knee is held in flexion. Reduction need not be delayed for radiographs and is easily accomplished by gently extending the knee while another provider helps "lift" the patella into place. Although the patella does not actually need to be moved into place, the second provider can help prevent a traumatic reduction, resulting in additional fractures. Obtain radiographs after the reduction to assess for fractures, which are most typically seen at either the lateral femoral condyle or the medial margin of the patella. Provide a knee immobilizer and orthopedic follow-up within 1 to 2 weeks. Most patients improve with conservative management and rehabilitation; however, some children are predisposed to chronic dislocations and may eventually need realignment of their extensor mechanism.

PATELLAR FRACTURE

Fractures of the patella are uncommon in children and usually occur from direct blunt force. The "sleeve" fracture of the patella, in which the distal patellar "sleeve" is avulsed from the body of the patella, is a patellar fracture unique to children. The typical mechanism of an avulsion "sleeve" fracture is forceful contraction of the quadriceps against a fixed

lower leg. Consultation with an orthopedist is advised to determine the appropriate treatment.

PROXIMAL TIBIA FRACTURES

FRACTURES OF THE TIBIAL SPINE

Mechanically speaking, an avulsion fracture of the tibial spine is the equivalent of an anterior cruciate ligament rupture in an adult. The anterior cruciate ligament inserts on the tibial eminence, also known as the anterior tibial spine, and this ligament and its insertion are much stronger than the epiphyseal bone in children. Nondisplaced fractures may be managed conservatively with immobilization in extension and orthopedic follow-up. However, any displaced fractures need reduction and immediate orthopedic consultation.

TIBIAL TUBEROSITY FRACTURES

Tibial tuberosity fractures are typically avulsion type and occur most commonly from strong contraction of the quadriceps against a fixed leg. Such injuries are usually sports related. Tibial tuberosity fractures are classified as type I, II, or III, depending on the location of the fracture line. Type I injuries are characterized by a fracture through the small distal portion of the tibial tuberosity. Type II fractures occur after the coalescence of the secondary ossification centers of the tuberosity to the metaphysis. The fracture splits the epiphysis of the tuberosity from the epiphysis of the proximal tibia. **Type III injuries involve a fracture into the joint and are at risk for compartment syndrome.** Types I and II fractures are usually treated with immobilization. Displaced type II and type III injuries need reduction and fixation and require immediate orthopedic consultation.

PROXIMAL TIBIAL PHYSIS FRACTURES

Fractures of the proximal tibial physis are relatively uncommon, and most are Salter-Harris type I. Vascular injury to the popliteal artery is a concern, and documentation of intact pulses is important.

PROXIMAL TIBIAL METAPHYSIS FRACTURES

There is a high risk of drift through healing and growth into a valgus deformity of the knee (Cozen's phenomenon) with proximal tibial metaphyseal fractures, even with proper alignment and immobilization. Arrange orthopedic follow-up for these fractures.

FRACTURES OF THE TIBIA AND FIBULA DIAPHYSES

Fractures of the tibia and fibula at the shaft are common. If the fracture is minimally displaced and there is no evidence of compartment syndrome, immobilize in a long leg posterior splint and arrange orthopedic follow-up. However, if there is >10 degrees of angulation in any plane, orthopedic consultation and reduction are indicated. These are very painful injuries and may require admission for pain relief. The mechanism of injury and the nature of the injury need to be considered when assessing the risk of compartment syndrome. Where there is high-energy injury, if the limb was in highly metabolic state at the time of injury (e.g., taking part in sports), or if there is any element of crush, then there is a risk of compartment syndrome, and the patient should be admitted for observation.

TODDLER'S FRACTURE

The *toddler's fracture* is an isolated spiral fracture of the distal tibia in a toddler (i.e., once learning to walk). The typical mechanism is external rotation of the foot with the knee flexed. Parents report that the child is limping or refusing to bear weight for no evident reason or after seemingly insignificant trauma. Clinically, there is usually pain with palpation and rotation of the distal tibia, although swelling may be minimal or absent, and occasionally there is no tenderness. Obtain radiographs of the leg in the limping toddler, even in the absence of physical examination finding. Radiographically, a fracture line may be noticed at the distal third of the tibial shaft (**Figure 141-29**). At times, initial standard radiographs may be normal. Oblique views may show a fracture line when standard views are negative. If a toddler's fracture is clinically suspected and initial radiographs are negative, splint immobilization and no immobilization are both management options with follow-up in 1 week for repeat radiographs.[31,32] If radiographs are negative and there is also the absence of a traumatic history, clinicians are encouraged to rule out other possible diagnoses that could lead to difficulty weight bearing in a young child. For radiologically evident fractures, there is currently a wide practice variation. Options include immobilization of the injured leg in a long leg splint, removable prefabricated device, or above-knee cast with adequate fixation.[33-35] The most commonly applied standard is a long-leg splint in the ED followed by an above- or below-knee cast with adequate fixation placed in an orthopedics clinic.[35]



FIGURE 141-29. Anteroposterior radiograph illustrating toddler's fracture of tibial shaft (*arrow*). [Photo used with permission of Wake Medical Center, Raleigh, NC.]

ANKLE INJURIES

Ankle injuries in children include both ligamentous disruptions as well as fractures. With the exception of the distal fibula,[36] ligamentous injuries are uncommon before physeal closure because of the generally stronger nature of ligaments when compared with open physes. Ankle sprains in older children with closed physes are graded and treated as they are in adults.

Fractures of the pediatric ankle may involve the distal tibia, the fibula, or both. A thorough evaluation and appropriate treatment are extremely important because any articular surface disruption in this joint can result in long-term complications despite a seemingly benign initial presentation.

The Low-Risk Ankle Rule has been validated exclusively in children >3 years of age and aims to reduce unnecessary radiography in children with ankle injuries (**Figure 141-30**).[37] In a multicenter impact analysis, implementation of this ankle rule reduced radiographs by 22% and demonstrated significant healthcare cost savings.[38,39] Once radiographs are considered necessary, standard views include anteroposterior, lateral, and oblique views. Distal tibia fractures may be at higher risk of

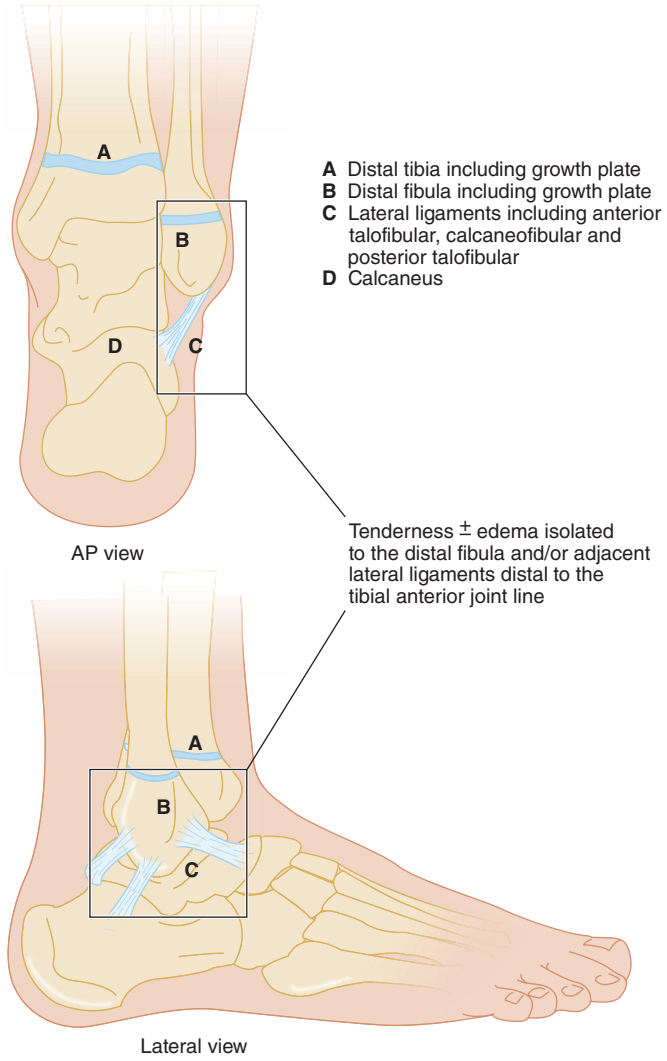


FIGURE 141-30. If a child has tenderness and swelling isolated to the distal fibula or adjacent lateral ligaments distal to the anterior joint line, then radiography may not be necessary to exclude a clinically important ankle injury. AP = anteroposterior. [Reproduced with permission from Boutis K, Komar L, Jaramillo D, et al: Sensitivity of a clinical examination to predict need for radiography in children with ankle injuries: a prospective study. *Lancet* 358 (9299): 2118-2121, 2001.]

complications; thus, additional imaging techniques such as CT and MRI can be used to help define the extent of fracture involvement.

DISTAL FIBULA ANKLE FRACTURES

Distal fibula ankle fractures are the most common lower extremity injury in children over 5 years of age. The key fractures to consider in this location are Salter-Harris I and II and fibular avulsion fractures. Children who present with lateral ankle injuries and no radiographic evidence of a fracture are commonly diagnosed with a distal fibular Salter-Harris I physeal fracture. However, in a recent study that included 135 skeletally immature children with this clinical scenario, MRI demonstrated that, in fact, only four (3%) of these children had Salter-Harris I fractures of the distal fibula, two of which were partial injuries, and all children had ligamentous injuries and/or bony contusions.[36] Thus, radiograph-negative lateral ankle injuries in children are more appropriately diagnosed with ligamentous injuries and managed with a removable ankle brace and self-regulated return to activities.[40] Thus, routine orthopedic follow-up is not necessary for these cases and can be reserved for cases not recovering as expected.

Salter-Harris type II and distal fibular avulsion fractures occur with an inversion injury. In general, when there is no significant displacement, these fractures may be managed by immobilization in a weight-bearing cast or commercial immobilizer, and orthopedic follow-up is usually not necessary.[40-42] In isolation, distal fibular Salter-Harris type III to V fractures are very rare. If suspected, consult with orthopedics for management.

DISTAL TIBIA ANKLE FRACTURES

Salter-Harris I and II fractures of the distal tibia are the most common fractures of the distal tibia. They can be managed with immobilization and follow-up in an orthopedic clinic but may also require closed reduction in the ED if any displacement is present. Salter-Harris III fractures account for approximately 25% of distal tibia fractures and typically require open reduction of any displacement. Tillaux fracture is a Salter-Harris type III fracture of the anterolateral portion of the distal tibia (Figure 141-5). The location of Tillaux fracture is a result of the order in which the distal tibial physis closes. Physeal closure occurs centrally, then medially, and finally, laterally, making the anterolateral portion most vulnerable. Therefore, this type of fracture is typically seen in a child who is nearing skeletal maturity. Treatment is surgical reduction in most cases that demonstrate displacement, and thus, urgent orthopedic consultation is indicated. Salter-Harris IV fractures include the triplane fracture, which involves fractures in the sagittal, coronal, and transverse planes, resulting in multiple fracture fragments. CT scan is helpful in delineating the extent of the joint surface injury in both Salter-Harris type III and IV ankle fractures (**Figure 141-31**). The management is

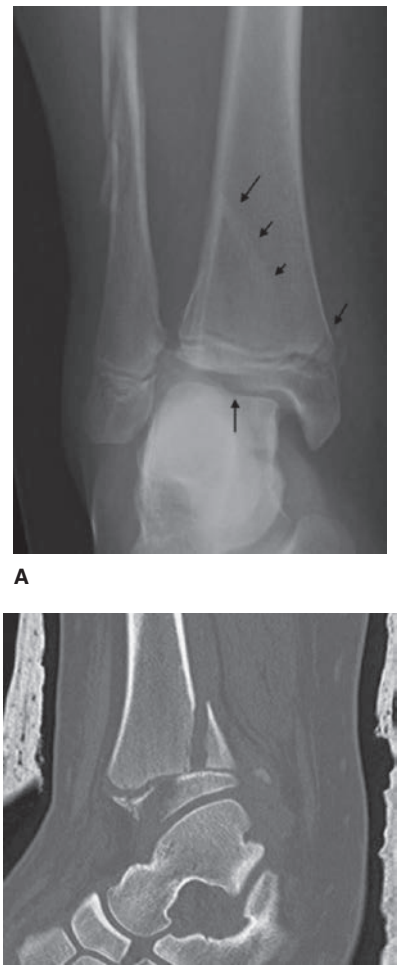


FIGURE 141-31. **A.** Mortise view of the ankle demonstrating a Salter-Harris type IV fracture of the tibia known as the triplane fracture with an associated fibular shaft fracture. **B.** CT lateral projection showing the fracture lines through the metaphysis (coronal plane), physis (transverse plane), and epiphysis (sagittal plane). [Photos used with permission of Karen Black, BC Children's Hospital, Vancouver.]



FIGURE 141-32. Fracture of the base of the fifth metatarsal. **A.** Jones fracture (*arrow*). **B.** Avulsion fracture of the tuberosity. [Reproduced with permission from Sherman SC: *Simon's Emergency Orthopedics,* 7th ed. © 2015, McGraw-Hill, Inc., New York. Fig 23-33A&B.]

often urgent surgical reduction. Premature closure of growth plates is more common in Salter-Harris II to IV fractures, whereas it is relatively infrequent in Salter-Harris I and Tillaux fractures.[43]

FOOT AND TOE INJURIES

In early childhood, the pliability and lack of ossification of the foot make fractures in this area rare. As ossification increases with age, fractures become more common, but significant injuries are still unusual. The foot is divided into the hindfoot (calcaneus and talus), the midfoot (navicular, cuboid, second and third cuneiforms), and the metatarsals and phalanges. Fractures of the mid- and hindfoot are rare; however, when they occur, they usually result from a fall. Recognition of fractures in these areas may be difficult, and CT or MRI may be necessary to identify and define these fractures. Fractures of the metatarsals and phalanges are relatively common in children and typically result from a direct blow from a falling object. They typically heal without sequelae. Crush injury to the foot may cause vascular compromise and compartment syndrome; these patients should be admitted for foot elevation and observation even if no fracture is detected.

Most nondisplaced fractures of the metatarsals and phalanges can be managed by immobilization in a posterior short-leg splint and follow-up with an orthopedist. Significantly displaced fractures of the metatarsals and phalanges as well as those of the great toe that have intra-articular involvement may require fixation, although this can typically be done on an outpatient basis.

Fractures of the base of the fifth metatarsal are common with inversion injuries of the ankle as in adults. The evaluation of ankle injuries should therefore include radiographs of the foot when there is tenderness over the fifth metatarsal. The immature skeleton includes an ossification center lateral to the base of the fifth metatarsal to which the peroneus brevis tendon attaches. This ossification center may be confused with a fracture, although an avulsion fracture at this site can also occur and presents with point tenderness and displacement of the ossification center (**Figure 141-32**). Immobilization and orthopedic follow-up are recommended.

SELECTED NONTRAUMATIC MUSCULOSKELETAL DISORDERS OF CHILDHOOD

ACUTE SEPTIC ARTHRITIS

Septic arthritis occurs in all age groups, but especially in children <3 years of age. The reported incidence of septic arthritis varies from 2 to 5 per 100,000 per year in the general population to 28 to 38 per 100,000 per year in patients with rheumatoid arthritis. Although any joint can be infected and multiple joints can be involved, the hip and the knee account for nearly 80% of cases.

Bacteria are the usual pathogens in acute skeletal and joint infections. Bacteria may access the joint hematogenously, by direct extension from adjacent osteomyelitis, or from inoculation, as in arthrocentesis or femoral venipuncture. Hematogenous spread is the most common. Although *Staphylococcus aureus* is still the most common pathogen in osteoarticular infections, infection with community-acquired methicillin-resistant *S. aureus* and other multidrug-resistant organisms is increasing. In Europe, *Kingella kingae* (gram-negative coccobacilli) is reported to cause bone and joint infections, with only sporadic case reports of outbreaks in the United States.[44] Widespread vaccination has decreased the prevalence of *Haemophilus influenzae* type B, reducing

TABLE 141-1 Causes of Suppurative Arthritis in Children in Order of Decreasing Incidence

Newborn (0–2 mo)	Infant (2–36 mo)	Child (>36 mo)
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	MSSA	MSSA
Methicillin-resistant *S. aureus* (MRSA)	MRSA	MRSA
Group B *Streptococcus*	*Streptococcus* species	*Streptococcus* species
Gram-negative bacilli	Gram-negative bacilli	Gram-negative bacilli
Neisseria gonorrhoeae	*Haemophilus influenzae*	*N. gonorrhoeae*
H. influenzae	Unknown or unidentified	
Candida albicans		

TABLE 141-2 Differential Considerations for the Acutely Inflamed Pediatric Joint

- Reactive or toxic synovitis
- Trauma
- Septic arthritis
- Acute rheumatic fever
- Poststreptococcal reactive arthritis
- Gonococcal arthritis
- Lyme disease
- Sickle cell crisis
- Henoch-Schönlein purpura
- Legg-Calvé-Perthes disease
- Slipped capital femoral epiphysis
- Osteomyelitis
- Juvenile rheumatic arthritis
- Transient synovitis
- Hemophilia
- Osgood-Schlatter disease

invasive disease. Common etiologic organisms also vary with the age of the child (**Table 141-1**).

Even though septic infections of joints in children are uncommon, they are important because of their potential to cause permanent disability.

CLINICAL FEATURES AND DIAGNOSTIC IMAGING

The earliest signs and symptoms of septic arthritis are subtle. Neonates do not characteristically appear ill and, in half of cases, do not have fever. Older infants, toddlers, and children usually have fever and localizing signs. Infants may have only pseudoparalysis (absence of spontaneous movement) of an extremity or apparent pain on movement of the affected extremity. The child with hip or knee septic arthritis will limp or not walk at all. The child maintains the infected hip in flexion, abduction, or internal rotation. On physical examination of the septic knee, the manifestations are those of any localized infection (i.e., erythema, swelling, tenderness, and pain); these signs are not easily detected in the hip. Older children will appear ill, often with high fever (40.0 to 40.5°C [104 to 105°F]), with apprehension and irritability.

Children at special risk for septic infections of the bone and joint include those with underlying immune deficiency or systemic disease, including recent chickenpox, sickle cell anemia, rheumatoid arthritis, and inflammatory bowel disease. Maintain a high index of suspicion for septic arthritis in such children.

Plain film radiographs are nondiagnostic early in the course of infection but should be obtained to help identify osteomyelitis, fracture, or another process in the differential diagnosis.

Widening of the joint space with joint effusion and distention are late findings. Fat lines are displaced early in septic arthritis because of capsular distention. Views of the contralateral side may be useful for comparison. Ultrasonography is useful to document the presence of a joint effusion and aids in needle aspiration. CT and MRI provide improved soft tissue resolution and can aid in the diagnosis. The differential diagnosis is listed in **Table 141-2**.

DIAGNOSIS

If septic arthritis is suspected, obtain a CBC, blood cultures, erythrocyte sedimentation rate, C-reactive protein, and throat cultures; call orthopedics; and keep the child fasted/nothing by mouth. Arthrocentesis provides definitive diagnosis and should not be delayed while awaiting laboratory studies (see Chapter 284, "Joints and Bursae"). Administer empiric antibiotics immediately if septic arthritis is suspected and orthopedic care is not available within 24 hours. **Patients at risk for septic arthritis usually have temperature >38.5°C (101.3°F), a C-reactive protein >20 milligrams/L (usually high), leukocytosis (>12,000 cells/mm^3), severe pain, tenderness on palpation, spasm, and refusal to walk.**

Obtain joint fluid and send fluid for cell count, Gram stain, glucose, and culture and polymerase chain reaction testing.[45] Isolation of an organism from the joint fluid does not occur in approximately one third of cases, but purulent fluid confirms the diagnosis when the clinical exam is suggestive. Fastidious or slow-growing organisms may not grow in culture. Likewise, the bacteriostatic effect of synovial fluid or prior empiric antibiotic therapy may decrease the sensitivity of joint aspirate cultures. When blood cultures are obtained, they are positive in less than half of cases, but they are the only source from which the causative agent is isolated in about 10%. Polymerase chain reaction studies of joint fluid improve organism detection.[45,46]

Concurrent infections at other sites may be associated with septic arthritis, and culture of those sites may help define the pathogen (e.g., urine gram-negative bacilli; skin/wound *S. aureus*; urethra, cervix, rectum, and pharynx *Neisseria gonorrhoeae*).

TREATMENT

Treatment is prompt joint drainage and wash-out (open, in the operating room) followed immediately by IV antibiotic administration. If orthopedic care will be delayed, then IV antibiotics should be started. **Table 141-3** lists possible choices for initial antibiotic therapy, including empiric treatment. The prognosis depends on the length of time between symptom onset and treatment. A treatment delay of more than 4 days increases the likelihood of orthopedic complications, and infants have less favorable outcomes.

TRANSIENT SYNOVITIS OF THE HIP

Toxic or transient synovitis is a benign, self-limiting inflammatory process of the hip. It afflicts males more than females and is the most common cause of acute hip pain in children <10 years of age. The peak incidence is between ages 3 and 6 years old, but it is reported from 9 months of age to adolescence. It is eight times more frequent than septic arthritis of any joint. The cause is unknown, but it is most often believed to be a postviral illness sequela, but trauma, bacterial infection, and postvaccine or drug-mediated reactions have also been cited as possible causes. Arthralgia and arthritis are secondary to a transient inflammation and hypertrophy of the synovial membrane.

CLINICAL FEATURES

Symptoms are characterized by an abrupt onset of unilateral hip pain, limp, and restricted hip motion (preferentially held in abduction and external rotation). The child may complain of pain in the anteromedial or anterolateral thigh and knee. Although children complain of discomfort with movement of the limb, it generally remains possible to put the hip through a full range of motion. This is in contrast to the septic hip in which pain and spasms are more severe and range of motion is decreased. The child is nontoxic appearing, and other signs of systemic illness are absent. There can be either no fever or a low-grade

TABLE 141-3 Initial Antibiotic Therapy of Acute Suppurative Arthritis in Children

Age	Suspected Organism	Antibiotics
Newborn (0–2 mo)	*Staphylococcus aureus*	Vancomycin, 10 milligrams/kg every 6–8 h
		or
		Clindamycin, 10 milligrams/kg every 6–8 h
	Group B *Streptococcus*	Ampicillin, 50–100 milligrams/kg every 6 h
		and
		Cefotaxime, 50 milligrams/kg every 6–8 h
		or
		Ceftriaxone, 50 milligrams/kg every 12 h
	Gram-negative bacilli	Cefotaxime, 50 milligrams/kg every 8 h
	Neisseria gonorrhoeae	Cefotaxime, 50 milligrams/kg every 8 h
	Unknown	Vancomycin or clindamycin and cefotaxime or ceftriaxone (dosing as above)
Infant (2–36 mo)	*S. aureus*	Vancomycin or clindamycin (dosing as above)
	Streptococcus species	Clindamycin/cefotaxime/ceftriaxone (dosing as above)
	Gram-negative bacilli	Cefotaxime or ceftriaxone (dosing as above)
	Haemophilus influenzae	Cefotaxime or ceftriaxone (dosing as above)
	Unknown	Vancomycin or clindamycin and cefotaxime or ceftriaxone
Child (>36 mo)	*S. aureus*	Vancomycin or clindamycin
	Streptococcus species	Clindamycin/cefotaxime/ceftriaxone
	Gram-negative bacilli	Cefotaxime or ceftriaxone
	N. gonorrhoeae	Cefotaxime or ceftriaxone
	Unknown	Vancomycin or clindamycin and cefotaxime or ceftriaxone

Ceftriaxone should not be used in neonates <1 month of age.

temperature elevation. **The mean WBC count and erythrocyte sedimentation rate are significantly lower than in septic arthritis, but they cannot be used to distinguish between transient synovitis and septic arthritis in individual patients** (see discussion of acute septic arthritis above).

Radiographs of the hip may be normal or may demonstrate an effusion. There are no bone changes associated with transient synovitis. US is more sensitive than plain films at detecting joint effusions, although accuracy is decreased in patients <1 year of age. Reports of an effusion of the hip by US in toxic synovitis vary from 50% to 95%.

DIAGNOSIS

This is primarily a clinical diagnosis that is supported by WBC, C-reactive protein, and erythrocyte sedimentation rate levels that are not significantly elevated. Further, hip radiographs are normal. US may demonstrate a small hip effusion. If the peripheral WBC count and erythrocyte sedimentation rate are substantially elevated and a hip effusion is noted on radiograph or US, perform a diagnostic arthrocentesis and obtain orthopedic consultation to exclude a septic joint. Send synovial fluid for Gram stain, aerobic and anaerobic cultures, and acid-fast bacilli with culture. Synovial fluid is sterile and clearly transudative with no organisms on Gram stain.

TREATMENT

Treatment is with rest until the pain resolves, usually 3 to 7 days, followed by limited activity for 1 to 2 weeks. NSAIDs are the first-line therapy for pain. There are no sequelae from transient synovitis. As long as the diagnosis is certain, reevaluation by the primary care physician can be arranged within 2 weeks.

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis is an umbrella term that has replaced the term *juvenile rheumatoid arthritis*. Juvenile idiopathic arthritis includes a heterogeneous group of arthritides of unknown cause that develop in children <16 years old. A detailed presentation of each type of arthritis is beyond the scope of this chapter. Systemic juvenile idiopathic arthritis is discussed in the following paragraphs.

Systemic juvenile idiopathic arthritis is associated with high fevers and chills, characteristically with spikes to at least 39°C (102.2°F) for a minimum of 2 weeks. There is also an accompanying characteristic faint erythematous macular coalescing rash that can involve the trunk, palms, and soles. The arthritis is usually polyarticular. Associated findings are hepatosplenomegaly, lymphadenopathy, and pleuritis or pericardial effusion. Laboratory evaluation is not highly specific but can be significant for anemia, leukocytosis, thrombocytosis, elevated acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), and elevated serum immunoglobulins. Arthrocentesis may be necessary to exclude acute septic arthritis, especially in oligoarticular disease. Early in the course, radiographs demonstrate only soft tissue swelling and, possibly, synovial effusions. Bone and cartilage destruction occurs later.

One of the most life-threatening complications is an entity called *macrophage activating syndrome* caused by macrophage and T-lymphocyte proliferation and is characterized by multiorgan system failure. Clinical findings can include high fever, purpura, spontaneous mucosal bleeding, altered mental status, and hepatosplenomegaly. Laboratory evaluation can reveal pancytopenia, liver dysfunction, disseminated intravascular coagulopathy, hyperferritinemia, hypertriglyceridemia, and low fibrinogen. Treatment may include symptomatic care in addition to pulse corticosteroids and cyclosporine A or a biologic.[47]

Hospital admission is needed to establish the diagnosis and to treat suspected acute suppurative arthritis while synovial fluid cultures are pending. A pediatric rheumatologist should direct management strategies, including intra-articular glucocorticoid injections and use of methotrexate (current first-line agent) and other biologic or nonbiologic disease-modifying antirheumatic drugs.[48]

AVASCULAR NECROSIS AND APOPHYSITIS

Legg-Calvé-Perthes disease is the most common example of avascular necrosis or osteochondrosis. Nevertheless, any primary or secondary ossification center can undergo changes consistent with necrosis and alteration of bone growth, with more common sites being the navicular (Koehler's disease), second metatarsal (Freiberg's disease), capitellum (Panner's disease), and lunate (Kienbock's disease), as well as the apophyses of the patella (Sinding-Larsen-Johanssen disease), tibia (Osgood-Schlatter disease), and calcaneus (Sever's disease).[49]

LEGG-CALVÉ-PERTHES DISEASE

Legg-Calvé-Perthes disease is a hip disorder that occurs in the femoral head that generally has an onset between the ages of 4 and 9 years old in 80% of patients, with a range of occurrence from 2 to 13 years and should be considered in the limping child in this age range. Males outnumber females by a ratio of 4:1, and it is bilateral in 10% of cases. Most children with the disorder are small for their age, with delayed skeletal maturation.

CLINICAL FEATURES

The onset of disease is usually insidious. Mild hip pain and limp have been present for weeks to months before making the diagnosis. Initially, pain is mild to none and is often referred to the anteromedial thigh or



FIGURE 141-33. Legg-Calvé-Perthes disease: note the flattened and radiopaque left femoral epiphysis.

knee. Physical findings include decreased hip abduction and internal rotation. Proximal thigh atrophy and, in advanced cases, limb shortening may also be noted. Radiographically, in the initial stage of the disease (1 to 3 months), the capital femoral epiphysis fails to grow because of the lack of blood supply. The hip radiograph demonstrates widening of the cartilage space of the affected hip and a small-size ossific nucleus of the femoral head (**Figure 141-33**). Next, a subchondral stress fracture line in the femoral head is evident (Caffey's sign). As the disease progresses, new bone is deposited on avascular trabeculae. Subsequently, calcification of the more radiopaque necrotic marrow occurs, with resultant crushing of the avascular trabeculae in the dome of the epiphysis. Further distortion of the femoral head progresses (although this is not inevitable), along with subluxation and extrusion of the femoral head from the acetabulum. The diagnosis of Legg-Calvé-Perthes disease demands a high index of suspicion, because initial radiographs sometimes are normal. Bone scan and MRI can detect disease before plain film abnormalities are evident.

TREATMENT

Once this condition is suspected, urgent orthopedic referral is recommended.

OSGOOD-SCHLATTER DISEASE

Osgood-Schlatter disease is an apophysitis of the tibial tubercle resulting from repeated normal stresses or overuse. These repetitive stresses imposed by the patellar tendon on its site of insertion result in a series of microavulsions of the ossification center and the underlying cartilage. Inflammation causes patellar tendonitis and the development of a remarkable prominence, induration, and tenderness of the tibial tuberosity. There is no avascular necrosis of the tibial tubercle. Children are usually between 10 and 15 years of age at time of onset; it more commonly occurs in running or jumping athletes. Boys are affected more often than girls, and most cases are bilateral, although symptoms are commonly asymmetric.

CLINICAL FEATURES

Signs and symptoms of Osgood-Schlatter disease are chronic, intermittent pain and tenderness over the anterior aspect of the knee and the tibial tuberosity. Pain is aggravated by activities such as running, kneeling, squatting, and climbing stairs; pain improves with rest. On examination, there is a prominence and soft tissue swelling over the tibial tubercle. The patellar tendon is tender and thick. The remainder of the knee examination usually is normal, and there is no knee effusion.

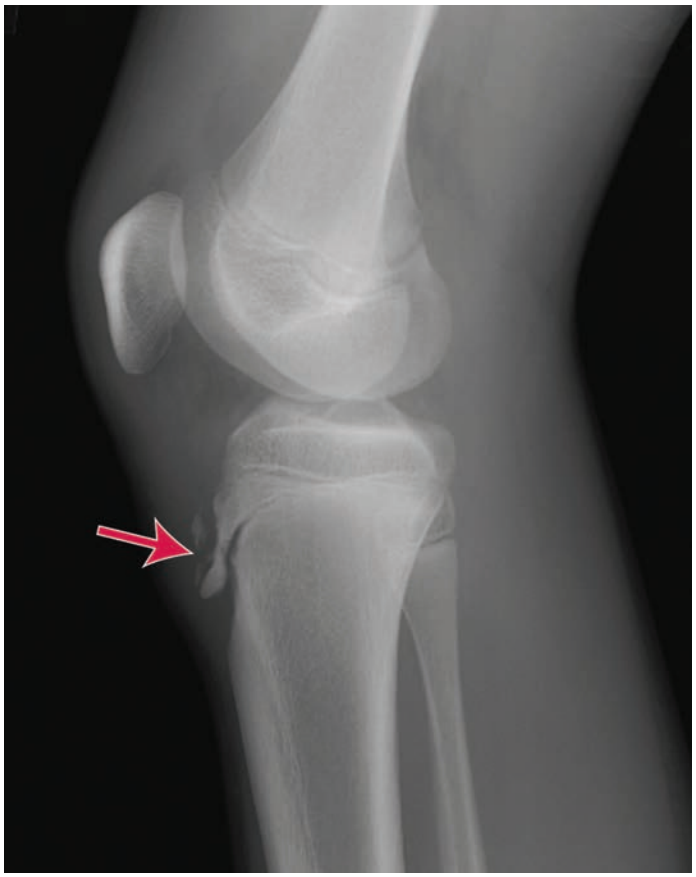


FIGURE 141-34. Lateral radiograph illustrating Osgood-Schlatter disease with prominence of the tibial tuberosity in addition to ossicles separate from the anterior border of the tubercle (*arrow*). [Photo used with permission of Wake Medical Center, Raleigh, NC.]

Radiographs are not essential but are usually obtained. Radiographic findings of soft tissue swelling and irregularities of the tibial tubercle are nonspecific (**Figure 141-34**). The irregularity of the ossification of the tibial tubercle is normal in this age group. A lateral knee radiograph may show prominence of the tibial tuberosity, calcification in the tibial tubercle region, or separate ossicles from the anterior border of the tubercle.

TREATMENT

The disease is self-limited, and most patients' symptoms respond to rest and temporary avoidance of the offending activity. However, complete avoidance of activity or sports is not essential. Immobilization is actually contraindicated and can lead to rapid atrophy of the quadriceps muscle. Physical therapy and flexibility exercises to stretch and strengthen the quadriceps and hamstring muscles may help to alleviate stress on the tubercle and avoid recurrences. Applying ice after activity may decrease swelling, and pain can be controlled with NSAIDs. Corticosteroids should not be injected into the patellar tendon or para-apophyseal soft tissues. Parents should be provided reassurance that the condition is benign and self-limited and will resolve after closure of the proximal tibial growth plate. Rarely, an ossicle may persist after skeletal maturity that causes pain and may require excision.

ACUTE RHEUMATIC FEVER

Acute rheumatic fever primarily affects children of school age. The incidence of acute rheumatic fever has steadily fallen in developed countries over the past 50 years. However, sporadic cases of invasive group A β-hemolytic streptococcal infections with presumably more virulent strains mean that outbreaks of acute rheumatic fever continue to be regularly reported in North America. It is preceded by infection with

TABLE 141-4 Revised Jones Criteria for the Diagnosis of Acute Rheumatic Fever

Major Criteria	Minor Criteria
Carditis	Fever
New or changing murmurs	Arthralgia
Cardiomegaly, congestive heart failure	History of previous attack of acute rheumatic fever
Pericarditis	Elevated erythrocyte sedimentation rate, C-reactive protein
Migratory polyarthritis	Prolonged PR interval on ECG
Chorea	Rising titer of antistreptococcal antibodies
Erythema marginatum	
Subcutaneous nodules	

Note: Diagnosis is likely when two major criteria or one major and two minor criteria are met. Group A *Streptococcus* may be documented by a history of scarlet fever, isolation of group A *Streptococcus* from throat culture, or rising titers of antistreptococcal antibodies.

certain strains of group A β-hemolytic *Streptococcus* (mucoid types 3, 5, and 18). The connective tissue of the heart, joints, CNS, and subcutaneous tissues and skin are targeted by host antibodies that develop secondary to streptococcal infection. The arthritis is characterized by synovial edema and periarticular swelling with joint effusions.

CLINICAL FEATURES

The child develops the disorder 2 to 6 weeks following streptococcal pharyngitis. Although nonspecific symptoms of systemic illness predominate early on, physical examination eventually reveals evidence of arthritis, carditis, choreiform movements, erythema marginatum, or subcutaneous nodules, individually or in combination. **Table 141-4** lists the Jones criteria for establishing a diagnosis of acute rheumatic fever. Either two major criteria or one major and two minor criteria plus evidence of an antecedent streptococcal infection are necessary to establish the diagnosis.

Of specific relevance to the musculoskeletal system, arthritis occurs in 60% to 75% of initial attacks and is characterized as a migratory, fleeting polyarticular arthritis primarily affecting the large joints.

DIAGNOSIS

Diagnostic studies are used to clarify the associated antecedent infection by group A *Streptococcus* (a pharyngeal swab for culture, antistreptolysin titers, or streptozyme titers) or are used to identify and assess the presence and extent of carditis.

TREATMENT

ED treatment is directed primarily toward the diagnosis of this condition. **Admission to the hospital is generally advised in the early stages until the diagnosis is confirmed**. All children with acute rheumatic fever are treated with penicillin, even if the cultures for group A *Streptococcus* are negative. The dose of benzathine penicillin is 600,000 units IM if <27 kg and 1.2 million units IM if >27 kg. Benzathine penicillin G can be administered in a single dose of 1.2 million units. Penicillin V administered PO is also effective. Erythromycin is substituted for the penicillin-allergic patient. Therapy is administered for 10 days.

POSTSTREPTOCOCCAL REACTIVE ARTHRITIS

Poststreptococcal reactive arthritis is a poorly understood clinical syndrome in which arthritis of one or more joints occurs after group A streptococcal infection of the pharynx. It is not certain whether poststreptococcal reactive arthritis represents a mild or early form of acute rheumatic fever or whether it is an entirely separate entity. It falls into a group of postinfectious reactive arthritides with multiple etiologies.[50]

Poststreptococcal reactive arthritis is not associated with carditis or other major Jones criteria and is a milder illness. Poststreptococcal reactive arthritis also begins sooner (approximately 10 days) after streptococcal infection than does acute rheumatic fever (approximately 21 days). The arthritis in poststreptococcal reactive arthritis is generally more severe and prolonged and unusually resistant to treatment with salicylates, in contrast to the migratory salicylate-sensitive arthritis generally associated with acute rheumatic fever.

The differentiation between acute rheumatic fever and poststreptococcal reactive arthritis is clinical. The arthritis of acute rheumatic fever is classically a migratory polyarthritis, whereas the arthritis of poststreptococcal reactive arthritis is a nonmigratory mono- or oligoarthritis. Acute rheumatic fever poststreptococcal nonsuppurative sequelae are more commonly observed in younger patients (mean age, 12 ± 4 years). The typical patient with reactive arthritis is older, but it may occur in children as young as 4 years of age. Erythema nodosum and erythema multiforme are frequently associated with poststreptococcal reactive arthritis, whereas they are encountered only infrequently in cases of acute rheumatic fever.

To establish the diagnosis of poststreptococcal reactive arthritis, establish antecedent infection with group A *Streptococcus*. If group A *Streptococcus* is recovered from the throat, treat with antibiotics. The diagnosis of poststreptococcal reactive arthritis should be made only after careful historical and clinical evaluation for nonsuppurative complications or other causes of polyarthritis. Antibiotic prophylaxis may be considered on a short-term basis. If, after further evaluation, there is no evidence of carditis or chorea, prophylaxis may be discontinued. Treatment of poststreptococcal reactive arthritis is NSAID analgesia.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 142

Rashes in Infants and Children

Michael Nguyen
Amy L. Dunn

INTRODUCTION

This chapter describes disease processes in children for which dermatologic symptoms are diagnostic and serves as a reference for the presenting complaint of "rash" in children and young adults. Additional detailed descriptions of important skin diseases are provided in chapters in Section 20, "Dermatology," with Chapter 248, "Initial Evaluation and Management of Skin Disorders," specifically outlining principles of evaluation of rashes in both children and adults. Several important disease entities presenting with rashes are covered extensively elsewhere within this text (e.g., Lyme disease, Rocky Mountain spotted fever). In addition to the discussion below, Chapters in Section 20, "Dermatology," discuss diagnosis based on anatomic location of the rash.

GENERAL APPROACH

Most exanthems present as an isolated episode in a single child, but outbreaks can also develop in groups of children. When evaluating only a single child with a rash, the diagnosis can usually be made by routine history and physical examination. When several children develop similar-appearing skin lesions, obtain detailed contact and exposure history, and consider the need to involve specialty services or notify local public health authorities.

Ask about the initial location of rash, the pattern and time frame of rash development, initial morphology, and whether any topical or systemic medications have been applied. Also inquire about fever and systemic symptoms, prior immunizations, potential human or animal contacts,

recent bites or stings, travel, recent prescription or over-the-counter drug administration, and recent food and environmental exposure.

Perform a complete physical exam and obtain a full set of vital signs. Completely disrobe all patients and place in a gown; examine patients in a room with good lighting to avoid missing important findings. Most rashes are self-limited and benign in children, but some rashes may be the harbinger of serious illness. An ill-appearing child or a child with a nonblanching rash raises suspicion for a serious condition. Check the scalp, ears, neck, mucous membranes, all skinfolds, digits and web interspaces, palms, and soles. Look for ticks that may be adherent in hair-bearing areas or skinfolds. Identify the morphology and determine the location and distribution of the rash.

VIRUSES

ENTEROVIRUSES

Enteroviruses are a very common cause of illness and rash in young children. Enteroviruses are small, single-stranded RNA viruses belonging to the picornavirus group and include polioviruses, coxsackievirus, and echovirus.[1] The enterovirus family has been associated with a wide variety of illnesses, including polio. Enterovirus infections usually occur in epidemics, with a peak prevalence in the summer and early fall. Transmission usually occurs by the fecal–oral route and sometimes by respiratory or oral–oral transmission.[2]

The clinical signs and symptoms of infection with coxsackieviruses and echoviruses vary and can include nonspecific febrile illnesses, upper and lower respiratory infections, GI infections, aseptic meningitis, or myocarditis. Similarly, the associated skin manifestations include an array of exanthems. Diffuse macular eruptions, morbilliform erythema, vesicular lesions, petechial and purpuric eruptions, rubelliform rash, roseola-like rash, and scarlatiniform eruptions have all been reported.[2] Strict clinical–virologic associations are difficult to demonstrate, unlikely to be practical in the ED, and equally unlikely to change the course of management.

Infection due to **echovirus 9** or **coxsackievirus A9** is common and produces typical examples of exanthems secondary to enteroviral illness. Both viruses may produce a maculopapular rash beginning on the face and neck and then extending to the trunk and feet. The palms and soles are also sometimes affected. Clinical manifestations include fever that may be accompanied by headache, GI complaints, and upper respiratory symptoms. With echovirus 9, occasionally, there are lesions on the buccal mucosa and soft palate that resemble Koplik spots. Petechiae may develop, raising concern for meningococcemia, although the petechiae due to enterovirus do not typically coalesce or progress to purpura. The exanthem persists for approximately 5 days. The exanthem of coxsackievirus A9, by contrast, may be vesicular or urticarial. Aseptic meningitis may be present.

Another common rash caused by an enterovirus is **hand-foot-and-mouth disease**. Initial signs and symptoms include fever, anorexia, malaise, and sore mouth. Oral lesions appear 1 to 2 days later, and cutaneous lesions appear shortly thereafter. The oral lesions begin as vesicles on an erythematous base, which subsequently ulcerate. The vesicles are usually 4 to 8 mm in size and are very painful. They are located on the buccal mucosa, tongue, soft palate, and gingiva (**Figure 142-1**). The exanthem starts as red papules that change to gray vesicles approximately 3 to 7 mm in size. They are found on the palms and soles, but may occur on the dorsum of the feet and hands and on the buttocks as well (**Figure 142-2**). They may be oval, linear, or crescentic and may run parallel to skin lines. They heal in 7 to 10 days. Recent cases have been reported of pediatric patients presenting with onychomadesis (proximal shedding of nails due to nail matrix arrest) several weeks (average 6 weeks) after an illness consistent with hand-foot-and-mouth disease. It is helpful to be aware of this increasingly common complication in order to reassure parents of the benign nature of the condition.[3]

A particularly severe form of hand-foot-and-mouth disease, attributed to enterovirus 71, has been identified in Southeast Asia and has been associated with serious illness including encephalitis and death.



FIGURE 142-1. Oral lesions of hand-foot-and-mouth disease. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 4th ed. McGraw-Hill, Inc., New York. © 2016. Fig. 14-34. Photo contributed by Larry B. Mellick, MD.]

Clinicians caring for patients from this region or those having traveled to that area should be mindful of potential deterioration of these patients. Another recent strain that has circulated in many countries including the United States is enterovirus D68. This strain has been associated with more severe disease including severe respiratory complications and acute flaccid myelitis presenting as paralysis in pediatric patients. These newer more virulent strains have prompted further research into a possible vaccine for enterovirus.[4]

A similar syndrome of fever, mouth pain, and oral ulcers is caused by other subtypes of the coxsackievirus group A and is known as **herpangina**. Like hand-foot-and-mouth disease, the diagnostic finding is small whitish ulcers, typically located on the soft palate and posterior pharynx, without accompanying skin lesions (**Figure 142-3**).

The clinical differentiation of enteroviral disease is difficult, but because there is no specific therapy for enteroviral infection, it is more important to consider bacterial diseases in the differential diagnosis to exclude treatable causes of sepsis, meningitis, myocarditis, and pneumonia. Enteroviral polymerase chain reaction testing is commonly available and may be useful in cases of meningitis in which viral testing may decrease length of hospital stay and use of antibiotics. Symptomatic therapy for enteroviral infections includes hydration, antipyretics, and topical oral pain relief preparations. Combinations of Maalox® (or similar) and diphenhydramine liquids applied with a cotton swab to the painful oral lesions may be useful. This combination may be used orally as well, being mindful of weight-based dosing for both medications. Oral therapy with acetaminophen and ibuprofen has also proved helpful for pain control. **Viscous lidocaine should not be used.** A recent U.S. Food and Drug Administration drug safety communication advises that viscous lidocaine 2% solution should not be used in infants and children.[5] In 2014, 22 serious adverse events, including deaths, in children age 5 months to 3.5 years were attributed to the use of oral topical viscous lidocaine. Rarely, analgesia with oral narcotics is needed to prevent dehydration. Hospitalization in patients requiring this level of pain relief may be considered.

MEASLES

The number of measles cases in the United States in 2013 to 2014 was the highest since 2000. Recent outbreaks among adults and children in many states have been attributed to international travel and unvaccinated populations here in the United States. Thimerosal was taken out of childhood vaccines in 2001, and multiple, large, well-designed epidemiologic studies and systematic reviews have found no evidence of an association between thimerosal and autism or other developmental disorders. In fact, autism rates have continued to rise, which is the opposite of what would be expected if thimerosal caused autism.[6]

Serious complications of measles have been reported including encephalitis, bacterial infections such as pneumonia, and death. These



A



B



C

FIGURE 142-2. Hand-foot-and-mouth disease. Typical lesions on the palms **(A)**, soles **(B)**, and buttocks **(C)**. [Reproduced with permission from Shah BR, Lucchesi M, Amodio J, Silverberg M: *Atlas of Pediatric Emergency Medicine*, 2nd ed. McGraw-Hill, Inc., New York. © 2013. Part A: Fig. 3.66 A, B & D. Photo contributed by Binita R. Shah, MD.]

complications are more common in children under the age of 5 years than school-age and adolescent patients. All medical care providers must be able to identify the exanthem and enanthem typical of measles in any patient presenting with the undifferentiated rash.

Measles virus (rubeola) is a member of the family Paramyxoviridae, genus *Morbillivirus*. After exposure, the incubation period for measles



FIGURE 142-3. Herpangina. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. © 2009, McGraw-Hill, Inc., New York.]

is approximately 10 days (range, 7 to 21 days). The prodromal period lasts approximately 3 days and is characterized by fever, malaise, and anorexia, followed by conjunctivitis, coryza, and cough. The severity of conjunctivitis is variable and may also be accompanied by lacrimation or photophobia, but is typically not exudative. The exanthem develops approximately 14 days following exposure. The rash first appears behind the ears and at the hairline of the forehead and then spreads cephalocaudally and centrifugally to involve the neck, upper trunk, lower trunk, and extremities sparing the palms and soles. It initially consists of erythematous blanching maculopapular lesions but rapidly coalesces, especially where the first lesions appeared on the face (**Figure 142-4**). In general, the extent and degree of confluence of the rash correlate with the severity of the illness in children. Other rash-causing diseases often confused with measles include roseola (roseola infantum) (see Figure 142-12) and rubella (German measles) (see Figure 142-6).

Search carefully for Koplik spots (**Figure 142-5**) in patients with suspected measles, because they are pathognomonic for measles infection and occur about 48 hours before the characteristic exanthem. However, they do not appear in all patients.

Treatment is supportive. Recognition is of the utmost importance in preventing the spread of the disease and associated morbidity and mortality. Immunization remains the most important preventive measure. About 1 in 20 children who receive the measles, mumps, rubella, and varicella vaccine will develop a rash following vaccination, which may prompt a trip to the ED. The rash usually involves the trunk and face, is macular and blanching, does not involve systemic symptoms, and is self-resolving. The only treatment is reassurance.[6]

RUBELLA

Rubella, **German measles**, or **third disease** was once a common childhood disease that had its highest incidence during the spring. The incubation period is 12 to 25 days following exposure, with a 1- to 5-day prodrome of fever, malaise, headache, and sore throat.

The exanthem varies and is sometimes difficult to identify. It may be a short-lived blush, or it may have a more typical and protracted 2- to 3-day course. The exanthem begins as irregular pink macules and papules on the face, spreading to the neck, trunk, and arms in a centrifugal distribution (**Figure 142-6**). The rash coalesces on the face as the eruption reaches the lower extremities and then clears in the same fashion. Forchheimer spots are pinpoint petechiae involving the soft palate that coalesce and may accompany the rash but are nonspecific.

Lymphadenopathy is a clinical manifestation of rubella, with characteristic enlargement of suboccipital and posterior auricular nodes. The clinical diagnosis in an individual case is often difficult, but the epidemic nature of the illness, along with the seasonal variation and high expression rate of



A



B



C

FIGURE 142-4. **A–C.** Measles. An 8-month-old child presented with fever, coryza, and marked conjunctivitis associated with intense photophobia. Confluent, erythematous, and maculopapular rash on the face developed on the fourth day of fever. He developed measles during the measles outbreak seen in New York City in 1993. [For **A** and **B**: Used with permission of Binita R. Shah, MD. Reproduced with permission from Shah BR, Lucchesi M, Amodio J (eds): *Atlas of Pediatric Emergency Medicine*, 2d ed. McGraw-Hill, Inc., 2013. Fig. 3.54 A&B, Pg 100. For **C**: Reproduced with permission from Shah BR, Laude TL: *Atlas of Pediatric Clinical Diagnosis*. Philadelphia, PA: WB Saunders; 2000, Pg 61.]

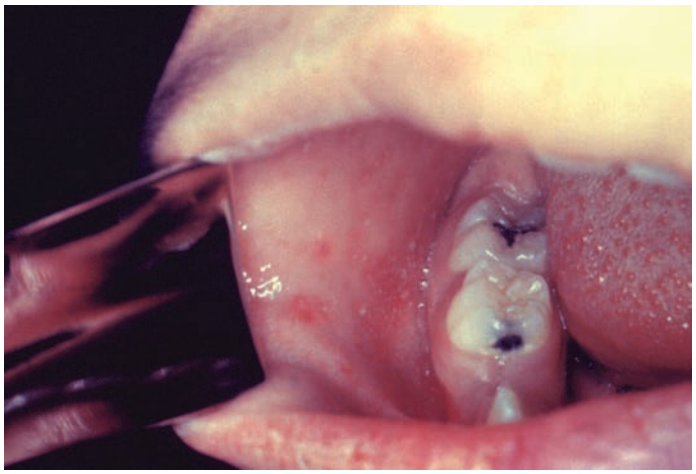


FIGURE 142-5. Koplik spots. [Image used with permission of the Centers for Disease Control and Prevention.]

the exanthem, help in establishing the diagnosis. A history of inadequate immunizations may assist in the diagnosis. There is no specific therapy.

ERYTHEMA INFECTIOSUM

Fifth disease, or erythema infectiosum, is an acute, febrile illness with a unique exanthem. Outbreaks of erythema infectiosum occur primarily in the spring. During epidemics, the attack rate is highest in children 5 to 15 years of age, but all age groups can be affected. The illness is caused by infection with human parvovirus B19, a single-stranded DNA virus.

The abrupt appearance of the rash is frequently the first manifestation of erythema infectiosum. It begins with a characteristic fiery red rash on the cheeks (**Figure 142-7**). The rash is a diffuse erythema of closely grouped tiny papules on an erythematous base. The edges are slightly raised. The erythema is most intense below the eyes and extends over the cheeks in a pattern reminiscent of butterfly wings; it is sometimes referred to as a slapped-cheek appearance. There is circumoral pallor as well as sparing of the eyelids and chin. The facial rash fades after 4 to 5 days.

Approximately 1 to 2 days after the appearance of the facial rash, a nonpruritic macular erythema or erythematous maculopapular rash occurs on the trunk and limbs. It is at first localized to the deltoid areas, trunk, and forearms, but usually extends to involve a large area. This stage of the exanthem may last 1 week. A distinctive aspect of the rash is that it fades with central clearing, giving a reticulated or lacy appearance (**Figure 142-8**). The palms and soles are rarely affected.

The exanthem may recur in the ensuing 3 weeks, sometimes briefly. The intensity of the recurrent exanthem varies and may be related to exposure to environmental factors such as sunlight, hot baths, and, perhaps, physical exertion or emotional upset. Associated symptoms frequently occur and may include fever, malaise, headache, sore throat, cough, coryza, nausea, vomiting, diarrhea, and myalgia. Arthralgia and



FIGURE 142-7. Erythema infectiosum (fifth disease). [Photo contributed by Anne W. Lucky, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]



FIGURE 142-6. Rubella. [Image used with permission of the Centers for Disease Control and Prevention.]

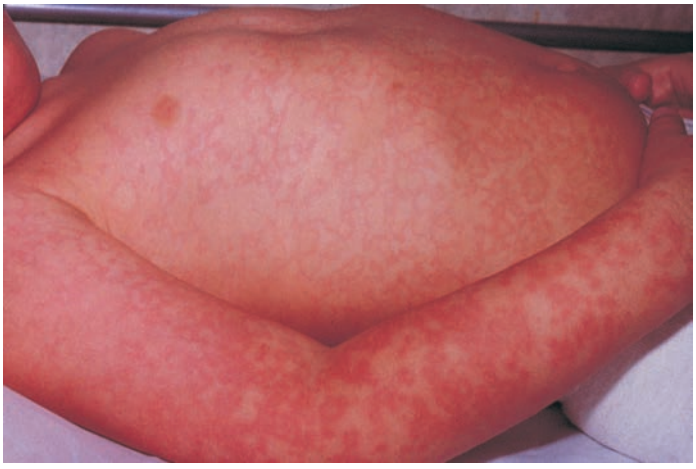


FIGURE 142-8. Erythema infectiosum. Lacy, reticulated rash on the body of a child with erythema infectiosum. [Reproduced with permission from Shah BR, Laude TL: Erythema infectiosum, in: *Atlas of Pediatric Clinical Diagnosis*. Philadelphia, PA: WB Saunders; 2000.]

arthritis can occur, but are more common in adolescents and adults in whom symptoms can be severe. **Parvovirus infection may also be severe in patients with sickle cell disease, in whom it may precipitate aplastic crisis.** Fetal anemia and hydrops may also occur with acute infection in pregnant women in the first half of pregnancy, and those who have been exposed should be counseled appropriately. In general, parvovirus infection requires only symptomatic therapy, and recovery is usually complete.

HERPES VIRUS

The two serotypes of herpes simplex virus (HSV) are HSV-1 and HSV-2, which are double-stranded DNA viruses that can present variably based on the organ systems involved and the competency of the host's immune system. Infections may be disseminated, localized to the CNS, or mucocutaneous. In the infant, HSV-2 is usually contracted during childbirth through vaginal secretions. HSV-1 is typically spread through oral secretions. The incubation period for herpes is from 2 to 14 days. With both serotypes, viral shedding may occur from an asymptomatic source. HSV-1 is the most common type identified in lesions of the skin and oral mucosa, but HSV-2 has also been identified. Autoinoculation may also occur. The clinical appearance of both serotypes is indistinguishable, and this point is important when there is concern for sexual abuse. HSV persists for life in a latent form, with the possibility of both symptomatic and asymptomatic reactivation. Visually identifiable lesions presenting to the ED may include oral lesions, skin lesions primarily of the hand or genitalia, or ocular lesions.

Herpes labialis ("cold sores") and gingivostomatitis are two common mucocutaneous presentations of herpes in children and young adults (**Figure 142-9**). A lesion may be single, or lesions may be clustered or, in the case of gingivostomatitis, may be evident diffusely throughout the oral cavity. The clinical appearance of most herpetic infections is of umbilicated vesicles that are extremely painful. They eventually unroof and crust over. Labialis is typically localized to the vermillion border. Gingivostomatitis causes erythematous edematous bleeding gums that may make eating and drinking painful. As stated earlier, viscous lidocaine preparations should not be used.

Eczema herpeticum (**Figure 142-10**) is the development of vesicular eruptions in the areas of the epidermis previously affected by eczema



FIGURE 142-10. Eczema herpeticum in areas of atopic dermatitis. [Photo contributed by University of North Carolina Department of Dermatology.]

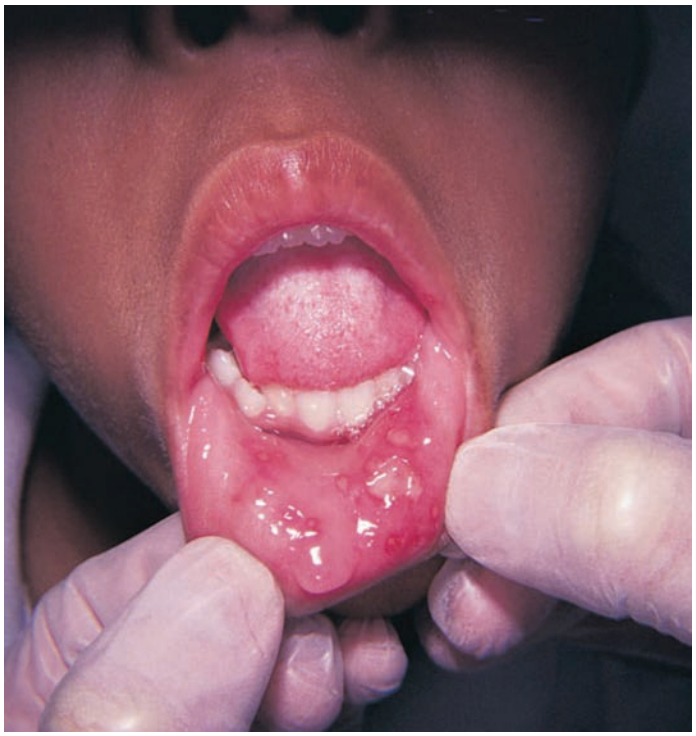


FIGURE 142-9. Primary herpetic gingivostomatitis. Typical lesions of herpes gingivostomatitis on the buccal mucosa. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006 by McGraw-Hill, Inc., New York.]

and may be life threatening. Although fever may present with other forms of HSV infections of children, fever is described more frequently with eczema herpeticum. Examination reveals skin with punched-out erosions, hemorrhagic crusts, or vesicles. Treatment includes oral antibiotics to treat *Staphylococcus* and *Streptococcus* (see Table 142-2 regarding antibiotics for cellulitis), as well as antiviral therapy with acyclovir, 80 milligrams/kg/d every 6 hours for 10 days.[7]

Another herpetic skin manifestation is **herpetic whitlow**. This infection of the distal fingers is usually the result of inoculation from an oral infection. Carefully examine the child's eyes to ensure that no herpetic lesions are present on the cornea secondary to direct contact.

Herpetic infections of the ears, thorax, and extremities have also been reported as a result of close contact sports (wrestling). Genital infections are most commonly the result of sexual transmission (consensual or abuse). Diagnosis is usually based on the clinical appearance, but viral cultures should be obtained for confirmation, particularly when sexual abuse is a consideration; obtain cultures from the fluid of an unroofed vesicle. Culture, enzyme-linked immunosorbent assay, direct fluorescent antibody testing, and polymerase chain reaction are acceptable forms of testing. Providers should confirm with their laboratories the preferred method of sampling at their institution.[7]

Treatment in the case of oral lesions is symptomatic. Oral antivirals may shorten the course of an acute outbreak and viral shedding when provided early in the disease (first 48 hours). Topical acyclovir is ineffective. Limited data suggest that children with herpetic gingivostomatitis presenting early in the course (72 to 96 hours of disease onset) who are unable to drink or have significant pain may benefit from oral acyclovir. The dosing of oral acyclovir is variable based on age, immune status, and location of lesions. A typical dosing regimen suggested by the American Academy of Pediatrics for children and adolescents is as follows: PO 80 milligrams/kg/d in four divided doses for 5 to 7 days;

usual maximum dose, 3200 milligrams/d. This regimen has been shown to be helpful in shortening the duration of symptoms.[7,8] When initiating antiviral medication in children <2 years old or in immunocompromised children, dosing is more variable, and consultation with a pediatric or infectious disease specialist is appropriate. Ophthalmology should be consulted when herpetic lesions are suspected of having invaded the cornea. This may be evidenced by dendritic-appearing lesions with fluorescein staining.

VARICELLA

Varicella, or chickenpox, is a result of infection with varicella-zoster virus, a herpes virus. In normal children, it is characterized by a pruritic generalized vesicular exanthem with mild systemic manifestations. Cases generally occur in late winter and early spring. It is highly contagious in the prodromal and vesicular stage. Varicella most frequently occurs in children <10 years old but may occur at any age. The rates of varicella and associated hospital admissions and deaths have declined dramatically in surveillance areas with significant vaccine coverage, but cases do occur in vaccinated children, although they are typically mild and more limited than in unvaccinated children. Severe side effects from the vaccine are rare.[9,10]

Varicella starts on the trunk, and most lesions are clustered in this body region. Lesions are of different stages presenting simultaneously. Within 24 hours, the rash acquires the typical vesicular appearance of varicella. The rash consists of teardrop vesicles on an erythematous base, which then dry and crust over. Successive fresh crops may appear for a few days. The extent of the rash may be minimal, but usually it will spread centrifugally and become widespread (**Figure 142-11**). Palms and soles are spared. Vesicles may occur on mucous membranes and go on to rupture and form shallow ulcers. Atypical and limited cutaneous involvement may occur among immunized children infected with varicella virus. Low-grade fever, malaise, and headache are frequently present but are usually mild. The diagnosis of varicella is usually made clinically based on its distinctive rash. A Tzanck smear of the vesicle contents may demonstrate varicella giant cells with inclusion bodies; polymerase chain reaction may also be performed on skin scrapings. Fluorescent antibody to membrane antigen testing is regarded as the gold standard for identification of varicella-zoster virus antibodies, but is not readily available.[10]



FIGURE 142-11. Varicella. [Photo contributed by University of North Carolina Department of Dermatology.]

Complications of varicella include encephalitis, pneumonia, hepatitis, and bacterial superinfection of the ruptured vesicles with staphylococci or streptococci. Neonates born to mothers with perinatal varicella infection may develop serious illness.

Uncomplicated varicella requires no specific therapy. Acetaminophen may be used as needed. **Do not give aspirin because it may predispose to the development of Reye's syndrome**. Oral antihistamines may be useful to reduce itching. Over-the-counter oatmeal-based baths may provide temporary symptomatic relief. Clean lesions regularly to prevent secondary infection. In the absence of CNS complications, the prognosis is excellent. **Routine use of antiviral therapy for uncomplicated varicella infections in immunocompetent children is not commonly recommended.** Oral acyclovir (80 milligrams/kg/d divided every 6 hours for 5 days; maximum dose, 3200 milligrams) may be considered if started within 24 hours of onset for children over the age of 2 years who are at increased risk of moderate to severe complications. This includes unvaccinated children over the age of 12 years, children on long-term salicylate therapy, and children on short-term steroid courses. [11]

Infants and immunocompromised children with varicella require aggressive treatment with acyclovir. Those less than 1 year of age are treated with 10 milligrams/kg every 8 hours, whereas children older than 1 year receive 500 milligrams/m^2 every 8 hours. Administration of varicella-zoster prophylaxis should be considered for patients exposed to individuals with varicella if provided within 3 days of exposure.[12]

ROSEOLA INFANTUM

Roseola infantum, or **exanthem subitum**, was previously called **sixth disease**. There is no seasonal association. The most likely cause is the human herpesvirus 6, although other viruses have been associated with a roseola-like illness.

Roseola is characterized by a febrile period of 3 to 5 days, defervescence, and the appearance of a rash for 1 or 2 days (**Figure 142-12**). The appearance of the rash immediately following a nonspecific febrile illness is characteristic and aids in the diagnosis. Primarily, young children are affected, with most patients being between 6 months and 3 years of age. The illness begins abruptly with high fever, sometimes as high as 40.6°C (105°F). The child is usually alert and active but may be irritable, especially with very high fever. Associated symptoms are usually mild and may include cough, coryza, anorexia, and abdominal discomfort. Lymphadenopathy may be present. The fever persists for 3 to 5 days, and the child rapidly becomes well.

Although the exanthem in roseola usually coincides with defervescence, the rash may follow a short afebrile interlude. The rash is an erythematous macular or maculopapular eruption that consists of discrete, rose or pale-pink lesions 2 to 5 mm in size. It is most prominent on the neck, trunk, and buttocks, but the face and proximal extremities may also be involved. The lesions blanch with pressure. There is no mucous membrane involvement. The rash lasts 1 to 2 days but may fade rapidly, usually without desquamation.

There is no specific treatment for roseola. Acetaminophen is useful for fever control. Because of the abrupt nature of the fever, febrile seizures may occur and are treated as any febrile seizure.

FUNGAL INFECTIONS

Tinea refers to a broad spectrum of skin infections caused by dermatophytes. These spore-forming organisms invade the stratum corneum and proliferate by feeding on keratin. These superficial infections can affect the nails, skin, scalp, and hair and are named for the area of the body infected. Tinea capitis (scalp) and corporis (skin) are the two most common infections in younger children. Capitis is most common in children <10 years of age with a peak of 3 to 7 years old. Corporis is also



FIGURE 142-12. Roseola infantum. [Photo contributed by Raymond C. Baker, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]



FIGURE 142-14. Tinea capitis with kerion. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 4th ed. McGraw-Hill, Inc., New York. © 2016. Fig 13.94, Pg 415. Photo contributed by Anne W. Lucky, MD.]

common and may be seen in adolescents participating in contact sports. Tinea pedis (foot) and tinea cruris (groin) also occur in children.

The affected areas are typically scaly and vary with a degree of pruritus from intense (as with cruris) to barely present (corporis). Tinea corporis commonly has a ring appearance with central clearing. Tinea capitis causes patchy alopecia as the hair follicles are invaded and lose their structure, causing them to break at the base (**Figure 142-13**). A more severe form of capitis, known as kerion, may occur when there is an exaggerated inflammatory response producing a painful, boggy mass (**Figure 142-14**). Occipital and posterior auricular lymphadenopathy are common physical findings with a high positive predictive value for tinea capitis.[13] The differential diagnosis of a tinea infection includes pityriasis rosea, lichen planus, psoriasis, eczema, and contact dermatitis. Diagnosis can be aided by direct microscopic observation for hyphae. Wood lamp evaluation is not very useful, because many dermatophytes do not fluoresce.[13]



FIGURE 142-13. Tinea capitis. [Photo contributed by University of North Carolina Department of Dermatology.]

Treatment is typically topical, with the exception of tinea capitis. Some forms of tinea that do not respond to topical treatment may also require oral therapy. For topical treatment, therapy is usually continued for 7 to 10 days beyond resolution of the lesions, which may take 2 to 3 weeks to fade. Multiple topical therapies are available by prescription or over the counter (**Table 142-1**). The treatment of choice for tinea capitis is **griseofulvin** (age >2 years old; microsize 20 to 25 milligrams/kg/d divided every 12 hours or ultramicrosize 10 to 15 milligrams/kg/d also divided every 12 hours). Baseline lab testing is not necessary

TABLE 142-1 Topical Antifungal Treatment for Tinea Corporis, Pedis, and Cruris*

Medication	Dosing	Comments
Clotrimazole 1% cream†	Twice per day × 2–3 wk	None
Miconazole†	Twice per day × 2–4 wk	Not recommended <2 y old
Tolnaftate†	Twice per day × 2–3 wk	Longer treatments in hyperkeratotic patients usually needed
Ketoconazole	Once or twice per day × 2–3 wk	Pedis treated for 4–6 wk; safety in children not established
Oxiconazole 1% cream	Once or twice per day × 2–3 wk	Pedis treated for 4 wk

*Tinea capitis should not be treated topically.

†Available over the counter without prescription in the United States.

with griseofulvin. If treatment is to extend beyond 8 weeks, then check complete blood count and liver and renal function tests. Children with a painful kerion may be treated with prednisone 1 to 2 milligrams/kg/d for 1 week in addition to systemic antifungal therapy.[14,15] Terbinafine (less effective than griseofulvin for *Microsporum* species), itraconazole, and fluconazole are also effective, with shorter courses of treatment, but are expensive.[16] Selenium sulfide 2.5% and ketoconazole shampoos are excellent adjunct therapy. Both should be left on the scalp for approximately 5 minutes to improve effectiveness. There is no recommendation for exclusion from school, because there is a high incidence of asymptomatic carriers and spores may be spread for months.

Tinea capitis and, rarely, tinea corporis may be associated with a papular hypersensitivity dermatitis (dermatophytid reaction, or "id" reaction). These papules or vesicles, having varying degrees of inflammation, may be pruritic. The lesions are seen on the face, trunk, and extremities of children with tinea capitis at the time of the diagnosis or, more commonly, after initiation of systemic therapy. This rash is a manifestation of an immune response and is not a drug reaction. Oral antifungal treatment should be continued, and topical corticosteroids or systemic antihistamines are used as needed.[13]

BACTERIAL INFECTIONS

IMPETIGO

Impetigo is a superficial infection caused by either *Staphylococcus aureus* or β-hemolytic streptococci (**Figure 142-15**). Impetigo can arise at the site of insect bites or superficial cutaneous trauma; sometimes, there is no apparent predisposing skin lesion. Lesions occur most frequently on the face, neck, and extremities. Fever and systemic signs are uncommon. Diagnosis is made on clinical appearance that takes two forms. In nonbullous impetigo (more common), skin lesions start as small erythematous macules and papules that develop into discrete, thin-walled vesicles, which become pustular and quickly rupture. As the vesicles rupture, a yellow fluid forms an exudate, which dries to form a stratified golden yellow crust that can spread the infection to other parts of the body. The crusts can be readily removed, leaving a smooth, red surface. Initially the lesions are discrete, but they may enlarge and become confluent. Local adenopathy may be present. Cultures are only necessary in patients who fail to respond to standard therapy. Ecthyma is a deeper infection than impetigo, and *S. aureus* and less commonly streptococci may be the cause. Lesions begin as vesicles that rupture, resulting in circular, erythematous, "punched out" ulcers with adherent crusts that can resemble a cigarette burn, often with surrounding erythematous edema.[17]

Treatment is aimed at preventing spread and eradicating the offending agent. Appropriate cleansing and general hygiene are mandatory. Mupirocin ointment (2% applied three times a day for 7 to 14 days) is the topical antibiotic of choice for localized areas of infection.



FIGURE 142-15. Impetigo. [Photo contributed by Michael J. Nowicki, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

TABLE 142-2 Antibiotics for the Treatment of Staphylococcal, Streptococcal, and Soft Tissue Infections*

Medication	Dosing	Comments
Mupirocin ointment (topical)	Apply to lesions BID	For patients with localized impetigo
Cephalexin (PO)	25 milligrams/kg PO every 12 hrs	Use for suspected strep or methicillin-sensitive *Staphylococcus aureus* (diffuse impetigo)
Clindamycin (PO/IV)	7 milligrams/kg IV every 8 hours; max daily dose 1800 mg/day; 4 milligrams/kg PO every 8 hrs, max 1800 mg/day	Good strep and *Staphylococcus* coverage in MSSA (MRSA variable-inducible resistance); poor taste and insurance coverage for liquid form; well absorbed orally
TMP-SMX (PO)	For > 2 months old, 6 milligrams/kg TMP PO every 12 hrs; max single dose 160 mg TMP	Poor strep coverage; some resistance in MRSA
Doxycycline (PO/IV)	1 milligram/kg PO or IV every 12 hrs	For >8 y of age; poor strep coverage; limited recent clinical experience
Azithromycin (IV/PO)	10 milligrams/kg on day 1 and then 5 milligrams/kg every day for 4 d PO; max dose for entire course 10 milligrams/kg once daily IV for 5–7 d; max dose 500 mg/dose	PCN-allergic patients; emerging macrolide resistance
Erythromycin (ethylsuccinate or stearate (PO))	10–20 milligrams/kg PO every 8 hrs; max dose 4000 milligrams/day	PCN-allergic patients; emerging macrolide resistance
Linezolid (IV/PO)	10 milligrams/kg every 12 h IV or PO for children <12 y (max, 600 milligrams BID PO/IV); > 12 y 600 milligrams every 12 hrs	MRSA resistant to clindamycin and TMP-SMX; >2 weeks therapy risk of hematologic and neurologic toxicity
Cefazolin (IV)	30 milligrams/kg IV every 8 hrs; max daily dose 6 grams/day	PCN allergic; good strep and MSSA coverage; poor MRSA coverage
Nafcillin/ oxacillin (IV)	5 milligrams/kg IV every 6 hrs; max daily dose 4000 milligrams/day	Good strep coverage; parenteral drug of choice for MSSA; inactive against MRSA
Vancomycin (IV)	20 milligrams/kg IV every 8 hrs	MRSA coverage; initial dosing, monitor serum concentrations for subsequent doses

Abbreviations: BID = twice a day; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus;* PCN = penicillin; strep = *Streptococcus*; TMP/SMX = trimethoprim-sulfamethoxazole.

*Doses are not appropriate for neonates. Refer to NeoFax©2018.

Cephalexin or clindamycin is given when large areas are affected or topical coverage is impractical (**Table 142-2**).

BULLOUS IMPETIGO AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Toxin-mediated erythrodermas, including bullous impetigo and staphylococcal scalded skin syndrome, are part of the spectrum of the same disease. Although the lesions of bullous impetigo are local at the site of infection, those of staphylococcal scalded skin syndrome are distant and widespread. Toxin serotypes A and B produced by *Staphylococcus* are the causative agents for the exfoliative presentation.[18] In bullous impetigo, the epidermolytic toxin acts locally to cause separation of the skin at the granular layer, giving rise to bullae. The infection occurs primarily in newborn infants and young children. The characteristic skin lesions of bullous impetigo are superficial, flaccid, thin-walled bullae that occur



FIGURE 142-16. Bullous impetigo. [Image used with permission of the Centers for Disease Control and Prevention.]



FIGURE 142-17. Staphylococcal scalded skin syndrome. [Photo contributed by Judith C. Bausher, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

most often on the extremities but can occur anywhere. Bullae range in size from 0.5 to 3.0 cm. They can arise from normal skin or may have a thin, red halo. The bullae are filled with a clear, pale-to-yellow fluid and rupture easily, leaving a moist, denuded base that dries rapidly with a shiny coating (**Figure 142-16**). Extensive areas of skin may be involved if left untreated. The clinical appearance of the lesions usually makes diagnosis less complicated. The rash is localized to one area of the body and these children are not typically systemically ill. In most cases, bullous impetigo may be treated locally and as an outpatient. Topical or oral agents directed at both methicillin-sensitive *S. aureus* and *Streptococcus* are recommended. Treatment consists of oral dicloxacillin, a cephalosporin, or clindamycin if methicillin-resistant *S. aureus* (MRSA) is suspected (Table 142-2). Staphylococci cultured from the fluid of aspirated bullae will establish the diagnosis.[19]

Staphylococcal scalded skin syndrome occurs primarily in children under the age of 5 years, and outbreaks in nurseries have been reported. Children are irritable and febrile, as compared to bullous impetigo where systemic symptoms are lacking. The rash appears as generalized, tender, macular erythema that is most prominent on the skin around the mouth and nose and in intertriginous areas. Within 1 or 2 days, the rash begins to peel. The large superficial flaccid bullae are then unroofed, revealing areas of erythematous and shiny skin, which then crust and heal (**Figure 142-17**). Nikolsky sign (separation of the epidermis when pressure is applied) is present with staphylococcal scalded skin syndrome.[17,18]

Obtain cultures of blood, urine, nasopharynx, and cutaneous lesions; treatment often requires inpatient therapy, fluid resuscitation, and parenteral antibiotics. Patients with diffuse disease should be admitted to a burn unit for further care. Patients with localized infection may be discharged to home with appropriate follow-up. Parental nafcillin, oral dicloxacillin, penicillin G procaine, amoxicillin-clavulanate, cefazolin, and cephalexin are all acceptable therapies. For methicillin-resistant *S. aureus*, options include clindamycin, trimethoprim-sulfamethoxazole, or vancomycin. Coverage is often provided for both methicillin-sensitive and methicillin-resistant *S. aureus* (Table 142-2).[18,19]

SCARLET FEVER

Second disease, or scarlet fever, is an acute febrile illness, primarily affecting young children, caused by group A β-hemolytic streptococci. Group C *Streptococcus* has been implicated as well. Clinical manifestations include acute onset with fever, sore throat, headache, vomiting, and abdominal pain followed by a distinctive exanthem in 1 to 2 days.

There is both an enanthem and an exanthem associated with scarlet fever, caused by an erythrogenic toxin elaborated by the streptococcal organism. The tonsils and pharynx are red and covered with exudate, although, occasionally, pharyngeal findings are minimal. The tongue may develop a white coating through which red and hypertrophied papillae project, creating the appearance of a "white strawberry tongue." The white coating disappears by day 4 or 5, and the tongue acquires a bright-red appearance, the "red strawberry tongue" (**Figure 142-18**). Bright-red or hemorrhagic spots may be seen on the soft palate or anterior pillars of the tonsillar fossa.

The exanthem of scarlet fever begins 1 or 2 days after the onset of the illness. It starts on the neck, axillae, and groin and spreads to the trunk and extremities (**Figure 142-19**). The rash is red and finely punctate, consisting of 1- to 2-mm papules that blanch and have a characteristic rough, sandpaper feel. It is sometimes easier to identify the rash by palpation. Linear petechial eruptions, Pastia lines, are often present in the antecubital and axillary folds. There is facial flushing with circumoral pallor. A brawny desquamation occurs at 2 weeks, yielding fine flakes of dry skin.

The diagnosis of scarlet fever is readily made on clinical grounds. Throat swabs usually culture group A β-hemolytic streptococci, although



FIGURE 142-18. Scarlet fever: white and red strawberry tongue. [Reproduced with permission from Wolff K, Johnson RA, Saavedra AP (eds): *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 7th ed. McGraw-Hill, Inc., 2013, Fig. 25-42.]



FIGURE 142-19. Sandpaper-like rash of scarlet fever. [Photo contributed by Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

group C may be cultured as well. Treatment with antibiotics is necessary to reduce the incidence of rheumatic fever and may ameliorate the clinical course of the disease, although the effect on other complications such as nephritis remains unclear. Penicillin and amoxicillin are antibiotics of choice. For penicillin-allergic patients, alternatives include cephalexin and clindamycin; macrolide antibiotics remain an option, although resistance of group A streptococci to macrolides is increasing.[19,20]

ERYSIPELAS AND CELLULITIS

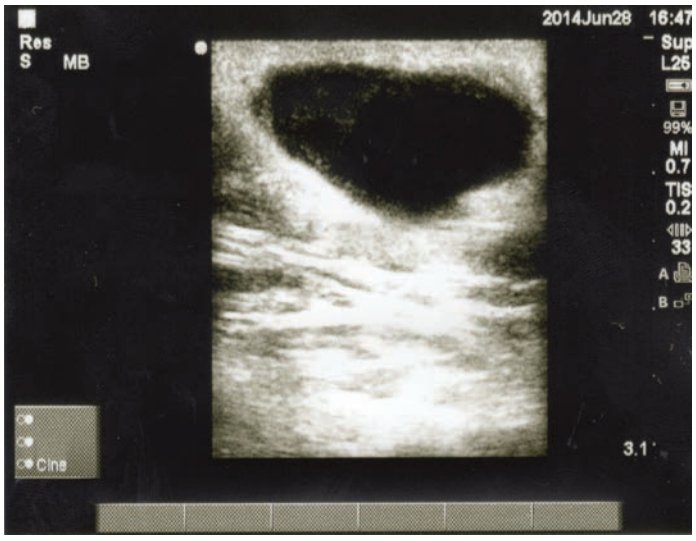
Erysipelas, or St. Anthony's fire, is cellulitis and lymphangitis of the skin caused by group A β-hemolytic streptococci. Infection is frequently accompanied by fever, chills, malaise, headache, and vomiting.

The rash is characterized by local redness, heat, swelling, and a raised, indurated border. There is marked involvement of the superficial dermal lymphatics. The rash starts as an erythematous plaque that rapidly enlarges by peripheral extension. At first, it is scarlet, hot, brawny, swollen, and tender. The edge is raised and sharply demarcated. The rash can vary in appearance from a transient hyperemia to intense inflammation, vesiculation, and bulla formation. The rash may have the appearance of an orange peel. The face was commonly the most frequent site (**Figure 142-20**) of infection, but more recently, infections in children have been more common on the extremities.[19] A skin wound, fissure, or ulcer may act as a portal of entry.

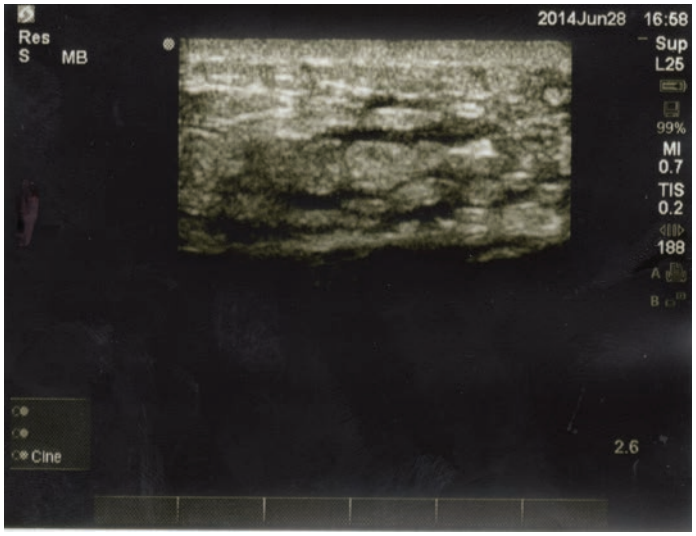
The diagnosis is clinical, and cultures of the blood or from aspiration of the leading edge of the lesion are rarely helpful.[21] A brief course of parenteral penicillin G procaine is usually warranted because of the rapid advancement of the infection, the acutely toxic state of the patient, and the possibility of suppurative complications. Rapid clinical response is usually obtained. Cephalosporins, clindamycin, or



FIGURE 142-20. Erysipelas. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]



A



B

FIGURE 142-21. **A.** Abscess as visualized on US. Essentially anechoic area within the surrounding soft tissue. **B.** Cellulitis. Relatively hypoechoic fluid between hyperechoic soft tissue structures. This classic appearance is referred to as "cobblestones." In some cases, the abscess contents may appear hyperechoic and mimic cellulitis. [Photos contributed by Gary Bonfante, DO, FACOEP, FACEP.]

trimethoprim-sulfamethoxazole may be used in patients unable to take penicillin; macrolides may be considered but are limited by increasing resistance. Other forms of cellulitis are treated in a similar fashion with parenteral or oral antibiotics as listed in Table 142-2.

Cellulitis is most commonly caused by *S. aureus*.[22] The affected area is usually erythematous, warm to palpation, and tender. Lymphangitis or regional lymphadenopathy may be seen. Once a mostly institutional issue, methicillin-resistant *S. aureus* has become increasingly prevalent as a community-acquired skin infection. Maintain a high suspicion for community-acquired methicillin-resistant *S. aureus* and be aware of local antibiotic sensitivities. If abscesses are present, they should be drained and cultures obtained. Small (<5 cm) pus collections can typically be treated with incision and drainage alone.[22,23] Bedside US can localize the abscess and differentiate cellulitis from abscess when the clinical presentation is less clear (**Figure 142-21**).

MENINGOCOCCEMIA

A petechial rash may be the presenting symptom of many viral infections or bleeding disorders or an indication of a very serious life-threatening disease



FIGURE 142-22. Petechial rash seen in meningococcemia. [Reproduced with permission from McKean S, Ross JJ, Dressler DD, Brotman DJ, Ginsber JS (eds): *Principles and Practice of Hospital Medicine*. The McGraw-Hill Companies, Inc., 2012, Fig. 147-22.]

due to bacterial infections such as *Neisseria meningitidis* (**Figure 142-22**). *N. meningitidis* is a gram-negative diplococcus and the causative agent of invasive meningococcal disease. Since the introduction in the United States of *Haemophilus influenzae* type b and pneumococcal polysaccharide-protein conjugate vaccines for infants, *N. meningitidis* has become the leading cause of bacterial meningitis in children and remains an important cause of septicemia. Disease most often occurs in children 2 years of age or younger; the peak incidence occurs in children younger than 1 year of age. Another peak occurs in adolescents and young adults age 16 to 21 years. Outbreaks continue to occur in communities and institutions, including child care centers, schools, colleges, and military recruit camps. However, most cases of meningococcal disease are endemic, with fewer than 5% associated with outbreaks.[24]

The incubation period is 1 to 10 days but usually less than 4 days. Because of the rapid progression from initial symptoms to death, it is important to recognize the first specific clinical symptoms, which can be early indicators of sepsis such as leg pain, cold hands and feet, and abnormal skin color (pallor, mottling). In approximately half of children, the first classic symptom of meningococcal disease is rash, which sometimes evolves from nonspecific to petechial to hemorrhagic over several hours. The petechial rash appears as discrete lesions 1 to 2 mm in diameter, most frequently on the trunk and lower portions of the body. The mucous membranes of the soft palate, ocular, and palpebral conjunctiva should also be examined for signs of hemorrhage. Petechiae may coalesce into larger purpuric and ecchymotic lesions (**Figure 142-23**). The petechiae correlate with the degree of thrombocytopenia and clinically are important as an indicator of the potential for bleeding complications secondary to disseminated intravascular coagulopathy.

Early identification of a petechial rash is essential to allow for rapid intervention to prevent further progression to fulminant disseminated intravascular coagulopathy, meningitis, and sepsis. It is very important to perform a thorough physical exam as well as a close review of a full set of vital signs to look for early indicators of sepsis such as tachycardia or hypotension. The overall case fatality rate for meningococcal disease is 10% and is higher in adolescents.

Children with a transient petechial rash who are well appearing do not need extensive testing. But the presence of petechiae in a febrile and ill-appearing child requires testing, especially a CBC to detect thrombocytopenia and leukocytosis. Cultures of blood and cerebrospinal fluid are indicated for patients with suspected invasive meningococcal disease. Cultures of a petechial or purpuric lesion scraping, synovial fluid, and other usually sterile body fluid specimens yield the organism in some patients.[25]

Treatment The priority in management of meningococcal disease is treatment of shock in meningococcemia and of raised intracranial pressure in severe cases of meningitis. Empiric therapy for suspected



FIGURE 142-23. A–C. Petechial rash can progress to purpuric lesions. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K (eds): *Fitzpatrick's Dermatology in General Medicine*, 8th ed. McGraw-Hill, Inc., 2012, Fig. 180-1 A-C, p. 2180.]

meningococcal disease is an extended-spectrum cephalosporin, such as cefotaxime or ceftriaxone. Once the microbiologic diagnosis is established, definitive treatment with penicillin G (300,000 units/kg/d; maximum, 12 million units/d, divided every 4 to 6 hours), ampicillin, or an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended.[25]

Chemoprophylaxis is warranted for people who have been exposed directly to a patient's oral secretions through close social contact, such as kissing or sharing of toothbrushes or eating utensils, as well as for child care and preschool contacts during the 7 days before onset of disease in the index case. Rifampin and ceftriaxone are the drugs of choice in children, and ciprofloxacin can be used for adult contacts.[24]

INFESTATIONS

Infestations with mites are common in children and readily spread through families, day care, and school settings where close contact with index cases can occur. Both scabies and lice are common causes of pruritic skin rash that can affect children, and scabies, in particular, may present atypically in young infants.

SCABIES

Scabies is caused by infestation with the *Sarcoptes scabiei* mite. The female burrows into the skin, where eggs are deposited and larvae hatch, resulting in the severe pruritus that characterizes the disease. There is typically a 4- to 6-week incubation period after exposure, which may occur at day care, school, or within the home, and infestation occurs across all socioeconomic levels and is not a reflection of poor hygiene. The classic skin findings in older children and adults include a generalized eruption with linear burrows, papules, pustules, and even vesicles. Lesions show a proclivity for the hands, feet, and groin (**Figure 142-24**). In infants, lesions may be widespread, with involvement of the palms and soles, and hyperpigmented nodules may be noted in the axilla and diaper areas (**Figure 142-25**). Excoriations are common from scratching. The differential diagnosis includes impetigo, atopic dermatitis, insect bites, and drug reactions. A careful history evaluating for other family members or close contacts with similar symptoms should be sought and may provide a clue to the diagnosis, although, occasionally, even co-sleeping parents will deny symptoms. Testing is usually not necessary, because the diagnosis is made on history and physical alone, although scrapings of pustules may reveal mites on microscopy. Treatment consists of topical **permethrin cream** applied from the neck down (infants may require application to the scalp and face, avoiding the mucous membranes) and left on for 8 to 12 hours before washing off. **Lindane is contraindicated in young children due to neurotoxicity.** For severe infestations, oral treatment with a single dose of **ivermectin**, 200 micrograms/kg, may be necessary. All linens and clothes should be washed in hot water. Treatment should include all family members to prevent recurrence of infestation. Antipruritics such as diphenhydramine may be useful. Families should be counseled that pruritus may continue for weeks despite successful elimination of infestation.

LICE

As with scabies, infestations with the common head louse, *Pediculus humanus capitis*, are common among children in school and day care. Parents may bring children to the ED because of a diagnosis made at school or reports of an outbreak at day care. Spread is by close contact, and hats and combs may act as fomites for transmission. The mites are more commonly found in long, straight hair and, therefore, are more common among girls than boys and less common among children with dark skin tones. Infestations may be asymptomatic and noticed by a caretaker or may present with scratching from pruritus. The diagnosis is confirmed by direct observation of live mites, although the presence of nits (egg sacks) may be considered a presumptive diagnosis. Nits are



A



B

FIGURE 142-24. **A** and **B.** Scabies on the foot and hand of an infant. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]

small (0.3 to 0.8 mm), oval, white or yellow sacks that are found on hair shafts close to the scalp and often concentrated around the ears or nape of the neck (**Figure 142-26**).

Treatment involves the use of pediculicides, careful grooming, hot water washing of linens and clothing, and co-treatment of close contacts. Several over-the-counter and prescription pediculicides are available. Permethrin, 1% lotion, is the most commonly used (Nix®, available without a prescription), although pyrethrins are also available over the counter (e.g., Rid®). Topical benzyl alcohol (5% lotion) is also effective and safe for children as young as 6 months of age.[26]



FIGURE 142-25. Infantile scabies. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]

The organophosphate malathion is available by prescription as a 0.5% lotion. Malathion is approved for children >6 years of age and is applied to the hair and scalp (dry hair), left on for 8 to 12 hours, and washed out. Re-treat in 7 to 9 days. **Lindane shampoo is contraindicated in young children and pregnant women due to neurotoxicity.** Re-treatment after 7 to 10 days may be necessary with all of these agents, because none is completely effective. Careful removal of the nits with a fine comb (often supplied in over-the-counter products) is an important aspect of successful treatment. Shaving of the head is not necessary.

COMMON NEONATAL RASHES

A number of common rashes affecting neonates and infants are worth noting due to their commonality or unique presentation in this age group and because they are of frequent concern to parents, who often



FIGURE 142-26. Head lice.



FIGURE 142-27. Erythema toxicum neonatorum. [Photo contributed by Kevin J. Knoop, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

present with their child to the ED for evaluation. These include erythema toxicum neonatorum, neonatal acne, seborrheic dermatitis, atopic dermatitis, and diaper rash.

ERYTHEMA TOXICUM

Despite the name, erythema toxicum is a benign, self-limited rash that occurs in up to 50% of all newborns, typically in the first week of life. The etiology is unknown, and the rash spontaneously resolves over approximately 1 week, although new lesions may develop in the second week of life as well. Characteristic erythematous macules, 2 to 3 cm, develop on the face, trunk, and extremities, and may have central 1- to 3-mm pustules (**Figure 142-27**). The diagnosis is clinical, although Wright-stained scrapings of the pustules will reveal eosinophils if performed to differentiate erythema toxicum from impetigo or HSV. No treatment other than reassurance is necessary.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

Transient neonatal pustular melanosis is less common than erythema toxicum. It is most common in black infants. Transient neonatal pustular melanosis consists of three types of lesions: small pustules on a nonerythematous base that may be present at birth, erythematous macules with a surrounding scale that develop as the pustules rupture and may persist for weeks to months, and hyperpigmented brown macules that gradually fade over several weeks to months (**Figure 142-28**).

The diagnosis of transient neonatal pustular melanosis is usually based on the clinical appearance. Microscopic examination of a Wright-stained smear of the contents of a pustule may demonstrate numerous neutrophils and rare eosinophils. This can help differentiate it from the lesions of erythema toxicum, which contain mostly eosinophils. However, this is usually not necessary. Treatment is supportive, and full resolution is expected.

NEONATAL ACNE

Neonatal or baby acne affects up to 20% of infants and typically appears around the third week of life. It results from stimulation of sebaceous glands by maternal hormones, and males are more commonly affected than females. Erythematous papules and pustules are commonly found on the face, although they may also occur on the trunk (**Figure 142-29**). The diagnosis is clinical, and no testing is necessary. Lesions spontaneously resolve, usually by the third month of life, and reassurance is all that is needed.



A



B

FIGURE 142-28. **A** and **B.** Transient neonatal pustular melanosis. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. McGraw-Hill, Inc., 2012, Fig. 107-4A&B, p. 1189.]

SEBORRHEIC DERMATITIS

Seborrheic dermatitis affects neonates and infants as well as adolescents and is an inflammatory condition of unknown etiology, although genetic and environmental factors are thought to play a role. In newborns, the rash typically starts between 2 and 6 weeks of life and improves by 6 months of life. Lesions are greasy yellow or red scales and have a proclivity for the scalp (cradle cap; **Figure 142-30**), but may appear around the eyebrows, ears, cheeks, or neck and intertriginous areas of the body and diaper area. Rarely seborrheic dermatitis can have more widespread plaques on the trunk and extremities and can be easily confused for atopic dermatitis. Unlike atopic dermatitis (see "Atopic Dermatitis"), seborrhea is not usually pruritic and does not involve the extensor surfaces. The differential diagnosis includes atopic dermatitis (which should be considered when the onset occurs in the second or third month of life, when lesions are found to be weeping and pruritic, or with a strong family history of atopy), tinea capitis, and psoriasis. The diagnosis is clinical, and testing is usually not necessary. It is important to emphasize to parents that seborrheic dermatitis is typically self-limited. Treatment for cradle cap includes selenium sulfide–containing



FIGURE 142-29. Neonatal acne. [Reproduced with permission from Wolff K, Goldsmith LA, Katz SI, et al: *Fitzpatrick's Dermatology in General Medicine*, 7th ed. © 2008, McGraw-Hill, Inc., New York.]

shampoos or the application of mineral oil followed by washing and removal of scales with a fine-tooth comb.[27]

ATOPIC DERMATITIS

Infantile atopic dermatitis or infantile eczema is a chronic, recurrent inflammatory disorder of the dermis and epidermis of unclear etiology but with a strong genetic component. A complete discussion of the disorder is beyond the scope of this chapter, but atopic dermatitis is common throughout childhood and often presents in the first months of life. Triggers include excessive bathing or desiccation, heat, contact irritants, and allergens (foods and environmental). The disorder is associated with food allergies, asthma, and allergic rhinitis later in life. The infantile form typically manifests between 2 and 6 months of life, somewhat later than seborrheic dermatitis, from which it must be distinguished. Characteristic findings include xerosis (dry skin) and erythematous papular or papulovesicular lesions and plaques that may become excoriated or weep. The classic flexural distribution seen in older children (**Figure 142-31**) is less common in infants in whom the face is most commonly involved, although diffuse involvement is possible (**Figure 142-32**). The nose and diaper areas are typically spared. Lesions are usually pruritic, which, in infants, may manifest as fussiness. **The differential diagnosis includes scabies and seborrheic dermatitis.** A careful history, including affected caretakers and a family history of atopy, and the clinical appearance are usually all that are needed to make the diagnosis.



FIGURE 142-31. Atopic dermatitis. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]



FIGURE 142-30. Cradle cap or infantile seborrheic dermatitis. [Photo contributed by University of North Carolina Department of Dermatology.]

Treatment involves counseling of parents to establish realistic expectations of probable recurrences. Therapy is aimed at identifying and eliminating triggers, reducing drying of skin (including limiting exposure to water with brief and infrequent bathing and minimal use of drying soaps), liberal application of emollients (e.g., Vaseline®), symptomatic treatment of pruritus (e.g., diphenhydramine), and topical steroids for active inflammation. In general, ointments are more effective than creams, and low-potency steroids (see Chapter 248, "Initial Evaluation and Management of Skin Disorders") should be used on the face and urogenital area, with medium-potency agents reserved for the trunk and extremities. Immunomodulators, such as tacrolimus ointment, are approved for children >2 years of age, but should not be used in infants unless prescribed by a dermatologist. Occasionally, oral antibiotics or antivirals may be indicated for superinfected areas (e.g., impetigo, eczema, herpeticum).

DIAPER DERMATITIS

Diaper rash is a common ED complaint that is specific to neonates and infants. Although rare disorders such as psoriasis, immunodeficiencies, and dietary insufficiencies (e.g., zinc, biotin) may present with diaper



FIGURE 142-32. Infantile atopic dermatitis. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

rash, for all practical purposes, two forms of diaper rash compose the vast majority: contact (irritant) dermatitis and candidal dermatitis. Reducing substances in stool and irritants in the urine can cause a contact dermatitis when left in contact with the skin for prolonged periods of time or during diarrheal illness. The characteristic rash is erythematous, macular, or papular and has well-demarcated borders. The differential diagnosis includes perianal streptococcal infection, which is usually warm and macular and may be associated with desquamation. Treatment of contact diaper dermatitis includes good hygiene, air drying, and the use of barrier creams or ointments such as zinc oxide. Candidal diaper dermatitis results from superficial infection with *Candida* species that are ubiquitous in the infant GI tract. Typical lesions are erythematous with papular and pustular lesions and scaling around margins (**Figure 142-33**).

The classic finding is "satellite lesions," which are small pustules beyond the margins of the main rash. The differential diagnosis includes atopic dermatitis, psoriasis, and contact dermatitis, although the diagnosis is usually made by clinical examination alone based on the characteristic scale and satellite lesions. Treatment is with topical application of antifungal agents, most commonly nystatin cream (100,000 units/gram as a cream, powder, or ointment applied three times a day for 10 to 14 days), which may be applied in combination with barrier ointments (zinc oxide applied after nystatin) and topical steroids (1% to 2% hydrocortisone cream or ointment applied after nystatin, but before zinc oxide if used) for severely inflamed lesions. Infants with candidal diaper dermatitis should be carefully examined for concomitant oral thrush. If oral disease is present, it should be treated with oral nystatin in mixtures of 100,000 units/mL. Use 2 mL four times a day in infants and 4 to 6 mL four times a day in children. Administer for up to 48 hours after resolution of oral lesions.

CUTANEOUS DRUG REACTIONS

Many medications commonly used by children can cause a significant exanthem for which parents will seek medical care. Often, the parents suspect an allergic reaction to the medication. There are a number of medications that are known to cause rash including antibiotics and



FIGURE 142-33. Diaper rash (*Candida*). [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. © 2009, McGraw-Hill, Inc., New York.]

anti-inflammatory and antiepileptic medications. One study found that 45% of drug reactions were manifested in the skin.[23] Most commonly, the rash appears as red macules with papules and can occur any time after drug therapy is initiated (often 7 to 10 days). The rash can take longer to appear, especially with antiepileptic medications, and last 1 to 2 weeks. The reaction usually starts on the upper trunk or head and neck and then spreads symmetrically downward to the limbs (**Figure 142-34**). The eruptions may become confluent in a symmetric, generalized distribution that spares the face. Mild desquamation is normal as the rash resolves. These rashes can sometimes be more morbilliform or even appear as the targetoid lesions of erythema multiforme. Occasionally these rashes can progress to Stevens-Johnson syndrome, toxic epidermal necrolysis (**Table 142-3**), serum sickness, or drug-induced hypersensitivity syndrome. Drug-induced hypersensitivity syndrome involves a distinct triad of fever, rash, and systemic involvement of any internal organ. This should always be discussed with caregivers of children being discharged to home with a diagnosis of cutaneous drug rash as warning signs of worsening illness. Often management just includes discontinuation of the offending drug. Children with more severe skin



FIGURE 142-34. Coalescing papular lesions of a drug eruption. [Reproduced with permission from Strange GR, Ahrens WR, Schafermeyer RW, Wiebe RA: *Pediatric Emergency Medicine*, 3rd ed. © 2009. The McGraw-Hill Companies, Inc., New York, Fig. 16-1.]

TABLE 142-3 Clinical Distinctions Among Common and Serious Skin Infections

Disease	Image Reference	Age	Skin Findings	Mucosal Involvement	Nikolsky Sign	Mortality (normal immune)	Prognosis
Bullous impetigo	Figure 142-16	Newborn and young	Localized bullae. Easily ruptured.	None	Present	None	Excellent.
Staphylococcal scalded skin syndrome	Figure 142-17	<6 y of age	Bullae, easily ruptured. More extensive involvement.	None	Present	Rare	Good.
Erythema multiforme	Figure 142-35	>3 y of age	Target lesions, atypical raised lesions. Blisters less common.	Usually limited to oral mucosa when involved	Usually absent	Possible	Good. May have recurrence.
SJS	Variant of TEN	Usually beyond childhood	Widespread blisters, purple macules. Usually <10% TBSA.	Extensive and may involve more than one mucosal surface	Present	5%–10%	Usually good.
Toxic epidermal necrolysis	Figure 249-4	Usually beyond childhood	Same as SJS. >30% TBSA. May involve nails.	Extensive and may involve more than one mucosal surface	Present	30%	Variable.
Cutaneous drug rashes	Figure 142-34	Child through adult	Diffuse maculopapular; become confluent.	Minimal to no mucosal involvement	Absent	Rare	Excellent.

Abbreviations: SJS = Stevens-Johnson syndrome; TBSA = total body surface area; TEN= Toxic epidermal necrolysis.

findings or evidence of systemic involvement may require hospital admission. Treatment is mostly supportive with topical skin care, hydration, topical steroids if necessary, and oral antihistamines as needed.[28]

ERYTHEMA MULTIFORME

Until the early 1990s, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis were classified as a continuum of a spectrum of disease; it is now appreciated that erythema multiforme is distinct from the more serious or even life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis (see Chapter 249, "Generalized Skin Disorders").[29] Although all may be induced by the use of medications, such as barbiturates, penicillins, sulfonamides, NSAIDs, and phenothiazines, **erythema multiforme in children is most commonly caused by infection, particularly herpes viruses and *Mycoplasma pneumoniae*.**[30] HSV-1 and HSV-2 account for 70% to 90% of all erythema multiforme cases. Erythema multiforme is rare under the age of 3 years old, affects boys more than girls, and does not favor a particular race or ethnicity.

Erythema multiforme typically presents with an abrupt onset of rash, sometimes preceded by a burning sensation. Pruritus is usually absent. The characteristic lesions are described as "target" with two to three zones consisting of a dark, ruddy-appearing center and a lighter colored area surrounding the center (**Figure 142-35**). A red-appearing outer ring is sometimes present. Lesions typically present as plaques and coalesce and frequently involve the palms and soles. When limited in distribution, the term erythema multiforme minor is often applied; rarely there is involvement of the oral mucosa, in which case it is termed erythema multiforme major. Lesions last 1 to 3 weeks and may recur.

Differential diagnosis includes urticaria, viral exanthem, hypersensitivity reaction, cutaneous drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis. Treatment for erythema multiforme is supportive and includes reassurance, although recurrent disease associated with herpes virus has been treated with oral antivirals.[31]

KAWASAKI'S DISEASE

Kawasaki's disease, or mucocutaneous lymph node syndrome, remains a vasculitis of unknown etiology. Infectious processes, toxin-mediated processes, and processes triggering a common inflammatory pathway are all postulated theories of the disease. The most devastating complication is sudden cardiac death in a child as a result of coronary artery aneurysms. However, mortality is less than 0.5% and is most common in the first year following the illness in patients with large aneurysms.[32] Kawasaki's disease peaks at age 18 to 24 months, with most cases occurring by age 10 years and the majority of patients being seen by age 5 years.[32,33] Children younger than 6 months or older than 9 years tend to have poorer outcomes.[34] Because of the potentially devastating sequelae and the potential for incomplete or atypical presentation of the disease, maintain a high index of suspicion for the diagnosis. Younger infants have increased risk for long-term sequelae and sudden death and are more likely to present with incomplete clinical manifestations. Kawasaki's disease is the leading cause of acquired heart disease in children (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease").

Kawasaki's disease is recognized as either complete (classic) disease or incomplete (atypical) disease. The criteria for classic and atypical disease are listed in **Table 142-4**. **Criteria for classic disease are fever of at least 5 days in duration and the presence of four other findings, which may include bilateral nonexudative conjunctivitis, cervical lymphadenopathy, erythema of the lips and oral mucosa, various skin changes of the extremities, and rash.** The fever is usually high and abrupt. The course of illness spans from acute to subacute to convalescent and occurs over several weeks. Infants and children are typically very irritable. Cervical lymphadenopathy is the least common finding of the case definition. The type of rash is variable, although vesicles have not been described. Its appearance usually accompanies the onset of fever and has a predilection for the perineum. Desquamation in this area as well as the fingers and toes may be seen at various times during the disease, but desquamation in the extremities is more common later in the disease course. Erythema and associated edema in the extremities may cause arthralgia and fussiness. The child may refuse to bear weight. In



FIGURE 142-35. Symmetric distribution seen with erythema multiforme. [Reproduced with permission from Strange GR, Ahrens WR, Schafermeyer RW, Wiebe RA: *Pediatric Emergency Medicine*, 3rd ed. © 2009. The McGraw-Hill Companies, Inc., New York, Fig. 16-3.]

TABLE 142-4 Diagnostic Criteria for Kawasaki's Disease[29]

Classic (Complete) Kawasaki's Disease	Atypical (Incomplete) Kawasaki's Disease
Fever for 5 days or more plus four of the following symptoms:	Fever for 5 days and two to three clinical criteria of classic Kawasaki's disease
1. Bilateral nonexudative conjunctivitis	*Plus*
2. Mucous membrane changes (erythema, peeling, cracking of lips, "strawberry tongue," or diffuse oropharyngeal mucosae)	C-reactive protein ≥3.0 milligrams/L and/or erythrocyte sedimentation rate ≥40 mm/h plus three or more of the following supplemental labs or positive echo:
3. Changes of the extremities (erythema or swelling of hands/feet, peeling of finger tips/toes in the convalescent stage)	1. Albumin <3 grams/dL 2. Anemia for age 3. Elevated alanine aminotransferase
4. Rash	4. Platelets >450,000/mm^3 after 7 d of fever onset
5. Cervical adenopathy (more than one node >1.5 cm unusually unilateral anterior cervical)	5. WBC count >12,000/mm^3 6. Presence of pyuria

most cases, all external clinical manifestations have resolved by 6 weeks. Cardiac complications develop early in the illness, but coronary artery aneurysm development is most prevalent as the fever begins to lessen (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease").

Incomplete Kawasaki's disease is suggested by fever for at least 5 days and two of the clinical symptoms of classic disease but with supportive laboratory findings detailed in Table 142-4. Recognition and close follow-up are required in cases of incomplete Kawasaki's disease because the risk for the development of coronary artery aneurysms is greater in incomplete disease than in classic disease. There are no evidenced-based studies upon which to develop strict criteria for incomplete disease.[35] In the presence of fever for 5 days and at least two clinical criteria consistent with the disease, the patient should undergo laboratory evaluation, including C-reactive protein and erythrocyte sedimentation rate. If C-reactive protein is <3.0 milligrams/dL and the erythrocyte sedimentation rate is <40 mm/h, the child is followed daily until resolution or typical peeling occurs. With desquamation, an echocardiogram should be performed. If either C-reactive protein or erythrocyte sedimentation rate is elevated, perform additional laboratory testing. Obtain the specimen tubes for these tests at the time of initial evaluation to avoid additional venipuncture. If less than three criteria are present, the patient should undergo an echocardiogram, and if positive, treatment should be started. If the fever persists after a negative echocardiogram, a repeat study is suggested. If three or more criteria are present, obtain an echocardiogram and begin treatment for the disease.

Once the presence of incomplete Kawasaki's disease is suspected or the disease is thought to be classic, admission and specialty referral are indicated. High-dose aspirin (80 to 100 milligrams/kg/d in four doses for 14 days, then 3 to 5 milligrams/kg/d for 6 to 8 weeks in the absence of coronary aneurysms, and indefinitely in those with aneurysms) with concomitant IV immunoglobulin infusion (2 grams/kg in a single infusion over 8 to 12 hours) is recommended. Aspirin alone does not appear to lessen the appearance of coronary artery aneurysms. IV immunoglobulin should be administered within the first 7 to 10 days of illness. Steroids are not routinely indicated but may be useful in those who do not improve with IV immunoglobulin. There is practice variability with both the duration of aspirin and the use of steroids. Infliximab, cyclosporine, other monoclonal antibodies, and plasma exchange have been studied as possible therapies.[35] Patients who develop aneurysms or coronary sequelae are referred to a pediatric cardiologist and/or cardiothoracic surgeon.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura is the most common vasculitis in childhood and presents with the tetrad of a palpable purpura, renal disease, abdominal pain, and polyarthralgias. A majority of cases are preceded by upper respiratory tract infection. Case reports have described an association with virtually all respiratory pathogens, with *Streptococcus*, *Staphylococcus*, and parainfluenza being the most commonly implicated. Medications and vaccinations have also been associated with episodes of Henoch-Schönlein purpura.[36] Henoch-Schönlein purpura is characterized by deposition of immunoglobulin A, immunoglobulin C3, and other immune complexes in the walls of the smaller vascular supply to multiple organs throughout the body. The kidneys and the GI tract are the two most commonly affected organ systems. Renal involvement occurs in approximately half the cases. Children typically present between the age of 3 and 15 years, with a peak incidence between 5 and 7 years.[31] Males and females are affected equally.[36,37] Adult cases have been reported.[38]

The rash occurs in nearly all patients. It is predominantly seen on the buttocks, legs, and arms. Failure to fully undress the child for examination would lead the clinician to miss the diagnosis. The rash is a nonblanching palpable purpura (**Figure 142-36**). It is not pruritic. Lesions



A



B

FIGURE 142-36. **A.** Henoch-Schönlein purpura on lower extremities. **B.** Henoch-Schönlein purpura on buttocks. [Reproduced with permission from Strange GR, Ahrens WR, Schafermeyer RW, Wiebe RA: *Pediatric Emergency Medicine*, 3rd ed. © 2009. The McGraw-Hill Companies, Inc., New York, Fig. 85-3 A&B.]

range from 2 to 10 mm in size. Colicky abdominal pain is present in about half of patients, and GI bleeding may occur. Nausea, vomiting, and diarrhea may be present and may be the only presenting chief complaint. Arthralgias and painful subcutaneous edema are also typically present, are usually localized to the lower extremities, and occur in 70% to 85% of patients. The patient may refuse to bear weight. The diagnosis may be distinguished from septic arthritis, because Henoch-Schönlein purpura typically presents with bilateral joint pain and fever is usually absent. Bloody stools have also been reported.

The diagnosis is usually readily made by bedside evaluation, and laboratory testing is unnecessary other than evaluation of urine for hematuria and proteinuria, which suggests renal disease. Blood tests may reveal abnormal renal function and mild leukocytosis with elevated eosinophils. Laboratory tests do not alter the course of treatment. *Streptococcus* testing and antistreptolysin O titers have been reported as elevated in approximately 50% of patients. Additional laboratory studies and imaging are only useful to help eliminate other disease processes such as pancreatitis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, and intussusception.

Henoch-Schönlein purpura is typically self-limited and resolves over the course of 3 to 4 weeks. Recurrent disease occurs in approximately one third of patients. Although some patients may have urinary abnormalities for years, only a very small percentage will progress to end-stage renal disease (see Chapter 137, "Renal Emergencies in Children"), and most patients can be discharged to home from the ED with follow-up within 1 week for repeat urinalysis. Although there is no demonstrated impact on preventing the development of nephritis, the use of prednisone, 1.0 milligram/kg/d for 2 weeks followed by a 2-week taper, can attenuate joint and GI symptoms. NSAIDs are effective treatment for pain associated with arthralgias and edema. The treatment of severe nephritis is more controversial, and high-dose steroids, cyclophosphamide, azathioprine, and cyclosporine have all been advocated (see also Chapter 137).

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 143

Sickle Cell Disease in Children

John P. Marshall

INTRODUCTION AND PATHOPHYSIOLOGY

Sickle cell disease is a spectrum of blood disorders of which sickle cell anemia (SCA) is the most serious. SCA is found primarily in children of African, Arab, or Mediterranean descent. It is caused by a single amino acid substitution in the sixth position of the β-globulin chain of normal adult hemoglobin (HbA), which creates the abnormal sickle hemoglobin (HbS). The HbS chain found in patients with SCA creates a hydrophobic region of the hemoglobin tetramer when it is deoxygenated.[1] In this state, noncovalent polymerization of the hemoglobin molecules creates chains that distort the shape of the membrane, causing the characteristic sickle appearance. The altered red blood cell shape and its associated rigidity and decreased deformability cause sickle cells to impede blood flow. This process is primarily responsible for the clinical manifestations of SCA through two mechanisms: hemolytic anemia and vaso-occlusion with subsequent ischemia-reperfusion injury. Interruption of blood flow created by the abnormal cells leads to poor tissue perfusion, acidosis, and hypoxia, which cause further sickling. The need to reverse these conditions is central to the management of SCA-related complications.

Children homozygous for this genetic abnormality have two genetic copies of the HbS mutation and are described as having classic hemoglobin SS (HbSS) disease, whereas heterozygotes for HbS with a second β-globulin chain that is normal (HbA) are considered to have sickle cell trait. These patients have enough HbA to prevent polymerization of the hemoglobin chains and subsequently avoid the more severe complications of the disease. Other patients may be heterozygous for HbS coupled with a second hemoglobin abnormality such as HbC, HbO, or β-thalassemia. Although some of these combinations can cause the severe pathology of SCA, patients with HbSC and the 90% of HbS/β-thalassemia patients with some normal β chains have fewer ischemic and infectious complications than patients with HbSS.

Because fetal hemoglobin (HbF) is unaffected by these genetic mutations, symptoms of SCA do not appear until HbF is replaced by the abnormal HbA. HbF predominates until 4 months of age, after which it rapidly declines, reaching baseline low levels just before 1 year of age. One of the first organs affected by the emerging sickle cells is the spleen. Recurrent splenic infarcts lead to a gradual decline in splenic function between 4 and 12 months of age, resulting in susceptibility to serious infections with encapsulated bacteria.

In the United States, all neonates are screened for SCA using highly sensitive and specific tests, so the diagnosis is rarely made in the ED. The clinical manifestations and potential complications of SCA, however, include symptoms that overlap considerably with diseases not related to SCA. Therefore, the diagnostic portion of this chapter is organized in a symptom-based fashion, and the treatment portion is grouped by disease physiology.

SICKLE CELL ANEMIA SYMPTOMS

EXTREMITY PAIN

Vaso-occlusive crises causing severe extremity pain are the most common manifestation of SCA, accounting for 79% to 91% of ED visits.[2] Common triggers include stress, cold, dehydration, altitude, hypoxia, or illness. Pain preferentially affects the long bones and lower back. Individual patients tend to manifest their pain crises in characteristic locations, but the frequency of vaso-occlusive pain crisis is variable, even among SS homozygotes. Five percent of children with SCA account for 33% of total episodes, averaging between 3 and 10 pain crises per year.[3] Children display variable degrees of tenderness over affected sites and may have slight temperature elevations without true fever. Because anemia can precipitate a crisis, assess patients for an acute drop in hemoglobin; experienced families may know the patient's baseline values.

Severe vaso-occlusive crises can lead to **bony infarction**. Pain episodes caused by bony infarcts typically cause more debilitating and refractory pain than past episodes, and there is often significant localized bone tenderness and an elevated peripheral WBC count. Fat embolism can be a complication. Signs and symptoms of **fat embolism** include acute respiratory distress, hypoxia, and systemic symptoms of petechiae, altered mental status, liver damage, and renal failure. Fat embolism can occur without acute extremity pain, and the aforementioned symptoms should prompt consideration of fat embolization.

When vaso-occlusive crises affect the nutrient arteries of the metacarpals and/or metatarsals, dactylitis results, and children develop tender, painful, swollen hands and feet, which may be accompanied by a low-grade fever (**Figure 143-1**). **Dactylitis** occurs in children <2 years old and may be the initial clinical presentation of SCA, but dactylitis is extremely rare beyond 5 years of age. Any number of extremities can be affected, and symptoms can last from days to 2 weeks. Recurrences are common.

Avascular necrosis of the femoral head occurs in 30% of patients by age 30 years old. Children present with afebrile inguinal pain with weight bearing. Radiographs may demonstrate flattening and collapse of the femoral head (**Figure 143-2**). Less commonly, ischemia can cause similar pain in the humeral head.

Bone and joint infections affect patients with SCA at higher rates than the general population. Infections are often difficult to distinguish from bony infarcts. Symptoms of tenderness, warmth, and swelling may be



FIGURE 143-1. Acute sickle dactylitis. Bilateral cylindrical swelling of soft tissue of the fingers in sickle cell anemia consistent with vaso-occlusive crisis of the hands. [Photo contributed by Donald L. Rucknagel, MD, PhD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2009, McGraw-Hill, Inc., New York.]

indistinguishable from those of a vaso-occlusive crisis, although a high fever is more typical of infection. **Limited range of motion of a joint is unusual in vaso-occlusive crisis and should prompt evaluation for a septic joint.** Although leukocytosis occurs with vaso-occlusive crisis, a left shift is unique to infection. **Erythrocyte sedimentation rates are unreliable in patients with SCA.** Radionuclide imaging or MRI may distinguish infection from infarct.

ABDOMINAL PAIN

Abdominal pain is a difficult symptom to assess in any child and is complicated by the potential abdominal manifestations of SCA. Any acute abdominal condition, such as appendicitis, pancreatitis, and hepatitis, must be considered. However, **the abdomen is the next most common site of pain from a vaso-occlusive crisis after the extremities and back**. Abdominal vaso-occlusive crises are due to mesenteric, splenic, and hepatic ischemia and present as sudden onset of poorly localized abdominal pain. Physical examination may reveal tenderness and guarding, but typically should not demonstrate rebound or rigidity.

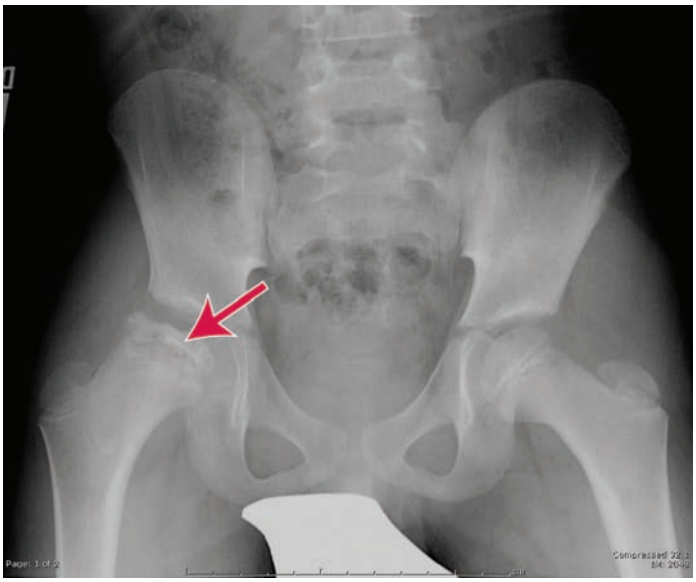


FIGURE 143-2. Avascular necrosis. Note the flattening of the femoral head (*arrow*). [Image used with permission of Dr. Hollie Jackson, MD.]

Gallstones are common due to the elevated bilirubin levels from hemolysis in SCA and can occur as early as 2 to 4 years of age. Diagnosis is by US. Although symptoms in children may resolve with time, occasionally, cholecystitis can be severe, and infection can progress rapidly (see Chapters 79, "Pancreatitis and Cholecystitis," and 133, "Acute Abdominal Pain in Infants and Children"). Right upper quadrant syndrome due to intrahepatic cholestasis is not common. Signs and symptoms include sudden right upper quadrant pain, jaundice, anorexia, tender hepatomegaly, and, often, fever. Bilirubin levels can be as high as 50 milligrams/dL. Although patients with SCA often have bilirubin levels above baseline, bilirubin levels rarely exceed 4 milligrams/dL and are predominantly unconjugated bilirubin. Confirm the diagnosis by US. **Acute hepatic sequestration** is another cause of abdominal pain, and the liver enlarges rapidly. Laboratories are variable, except for low hemoglobin. US or CT scan shows diffuse hepatomegaly in hepatic sequestration.

RESPIRATORY DISTRESS AND CHEST PAIN

Acute chest crisis, due to pulmonary ischemia and infarction, is frequently a complication of pneumonia. The incidence of acute chest crisis in children is higher than in adults (21 per 100 person-years in patients with HbSS), but is associated with better outcomes. Children develop any combination of pleuritic chest pain, cough, fever, and dyspnea. Examination findings include retractions, hypoxia, tachypnea, rhonchi, and rales, although dehydration can minimize the presence of rales on examination. An elevated WBC count is often present in both infarct and pneumonia, and thrombocytopenia may accompany severe crises. **Chest radiograph is indicated in any patient with chest symptoms or hypoxia, although findings may be minimal early on and should not dissuade treatment of a patient with potential chest crisis on clinical grounds only.** Radiography demonstrates a new alveolar pulmonary infiltrate, which is typically located in the upper or middle lobe in children, although adults often have multilobar disease. The cause of pneumonia is typically *Chlamydia*, *Mycoplasma*, viral, *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Haemophilus influenzae*.[4,5] Sputum or blood cultures are rarely positive and not generally recommended, except in patients ill enough to require mechanical ventilation. Multilobe involvement, history of cardiac disease, and low platelets predict poor outcomes.[5] Chest crisis can result in decreased lung function,[6] poor integrity of the pulmonary vessels, and a propensity to pulmonary edema. Asthma is common in patients with SCA, occurring in 17% to 53%. **Asthma not only complicates the diagnosis of acute chest crisis but also increases the likelihood of chest crisis by four- to sixfold.**[6]

Pulmonary hypertension develops in 16% to 35% of children with SCA. By adulthood, about one third have pulmonary hypertension, a condition that is associated with diastolic dysfunction and increased mortality. Increased intensity of the second heart sound, evidence of right ventricular enlargement, or unexplained desaturation should suggest pulmonary hypertension (see Chapters 57 and 58, "Systemic Hypertension" and "Pulmonary Hypertension," respectively). Diagnosis is made by echocardiogram and right heart cardiac catheterization demonstrating a pulmonary artery pressure >25 mm Hg. Progressive disease can cause chest pain, dyspnea on exertion, resting hypoxia, right-sided heart failure, syncope, and pulmonary thromboembolism.

Cardiomegaly and heart murmurs are common in children with SCA. However, overt heart failure is uncommon in children, except in cases of iatrogenic volume overload associated with transfusion. Heart failure is managed by the usual methods and by correcting anemia.

FEVER

Across all ages, infection is the leading cause of death in patients with SCA.[7] Splenic dysfunction and inability to form immunoglobulin G antibodies to polysaccharide antigens increase susceptibility to

TABLE 143-1 Risk Factors for Bacteremia in Children With Sickle Cell Anemia

- Temperature >40°C (104°F)
- WBC count >30,000 or <5000 cells/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin <5 grams/dL
- Ill appearance, poor perfusion, hypotension
- Infiltrate on chest radiograph
- History of pneumococcal sepsis

infection, particularly with encapsulated organisms. **Children age 6 months to 3 years old are at the greatest risk for sepsis, with *H. influenzae* and *S. pneumoniae* more common in the very young, and *Escherichia coli* and *Salmonella* more frequent in older children.** The rate of bacteremia in children ≤3 years old has been about 8 per 100 patient-years. In children who receive pneumococcal 7-valent conjugate vaccine, invasive pneumococcal disease has decreased by as much as 93.4%.[8] **Table 143-1** reviews risk factors for bacteremia. Workup of potential infection in SCA patients should include a CBC, urinalysis, chest radiograph, oxygen saturation measurement, and cultures of the blood, throat, urine, or other potential source of infection.

Children with SCA also have an increased prevalence of meningitis, pneumonia, arthritis, and osteomyelitis compared to the general population, and have poorer outcomes for these diseases. Similarly, viral infections, including influenza, result in greater morbidity, and **yearly vaccination for influenza is recommended**.

PARVOVIRUS INFECTION

Parvovirus B19 infection is of particular concern. The initial infection is usually asymptomatic or associated with nonspecific upper respiratory symptoms. However, parvovirus can cause several different clinical syndromes. Erythema infectiosum is characterized by fever, headache, nausea, coryza, and slapped cheek appearance with circumoral pallor followed by diffuse maculopapular rash (see Chapter 142, "Rashes in Infants and Children," Figures 142-7 and 142-8). Gloves and socks syndrome describes well-demarcated painful erythema and edema of the hands and feet that evolves into petechiae, purpura, vesicles, and skin sloughing. Finally, parvovirus can cause symmetric or asymmetric arthropathy of knees and ankles. **Regardless of the clinical presentation, parvovirus can cause a transient aplastic crisis, with the reticulocyte count dropping 5 days after exposure, followed by a decline in hemoglobin (see Chapter 144, "Hematologic Emergencies in Infants and Children").** Because of the shortened life span of the red cells in SCA, parvovirus can cause serious anemia, which lasts for 2 weeks. Upon recovery, there is an outpouring of nucleated red blood cells from the marrow, and patients late in the illness may have a high reticulocyte count.[9] Infection usually imparts subsequent lifelong immunity to parvovirus.

ANEMIA

Splenic sequestration, or intrasplenic trapping of red cells, is a major cause of mortality in children <5 years old. Two types exist, **major** and **minor**. **Major splenic sequestration** causes a rapid drop of more than three points in the hemoglobin, with the development of pallor, left upper quadrant abdominal pain, and splenomegaly. This can progress within hours to altered mental status, hypotension, and cardiovascular collapse. **Minor splenic sequestration** tends to be more insidious, with a smaller change in hemoglobin levels. Often, attacks occur along with bacterial or viral infections. Laboratory studies in either syndrome demonstrate a decline from baseline hemoglobin level, a normal to increased reticulocyte count, and no change in bilirubin, because there is no hemolytic component to this complication. Mild neutropenia or thrombocytopenia may be noted. Patients with HbSS rarely experience this complication beyond 5 years of age (peak, 3 months to 5 years old) due to infarction and scarring of the spleen, but most patients with HbSC and homozygous S/β-thalassemia have a spleen that persists into adulthood, and thus have a risk of splenic sequestration.

As noted earlier, aplastic crisis is an important cause of anemia in SCA patients and can be induced by parvovirus infection or medications. Signs are the gradual onset of pallor without pain or jaundice. Laboratories demonstrate a decline in hemoglobin and a low reticulocyte count. Full recovery is expected within weeks.

NEUROLOGIC COMPLAINTS

Stroke is 250 times more common in children with SCA than in the baseline population[10]: 11% of children with SCA suffer a clinically overt stroke, and another 20% are found to have silent strokes on imaging. The risk of recurrence, untreated, after one stroke is 49% to 90%, and children with HbSS are at four times greater risk than those with HbSC. SCA patients typically have cerebral vasculopathy involving the intima and media of large arteries, usually the middle cerebral artery. Screening transcranial Doppler studies can identify abnormal flow patterns associated with this vasculopathy, which, if present and untreated, are associated with a 10% risk of stroke within 2 to 3 years of diagnosis.[3,11] Additionally, some children will develop a moyamoya-like syndrome in which clotted vessels induce the development of diffuse small collateral vessels. These weak vessels are prone to aneurysm formation and spontaneous hemorrhage and demonstrate a characteristic "puff of smoke" appearance on cerebral angiography.

Cerebral ischemia can present with fleeting symptoms of transient ischemic attacks, or with hemiparesis, seizure, altered mental status, or coma. Common vascular territories involved include the internal carotid or middle cerebral arteries, but venous sinus thrombosis may cause parieto-occipital or thalamic involvement (**Figure 143-3**).[10] As in adult stroke, the CT scan is less reliable to detect ischemic infarct in the first 36 hours, although CT scan does rule out hemorrhage.

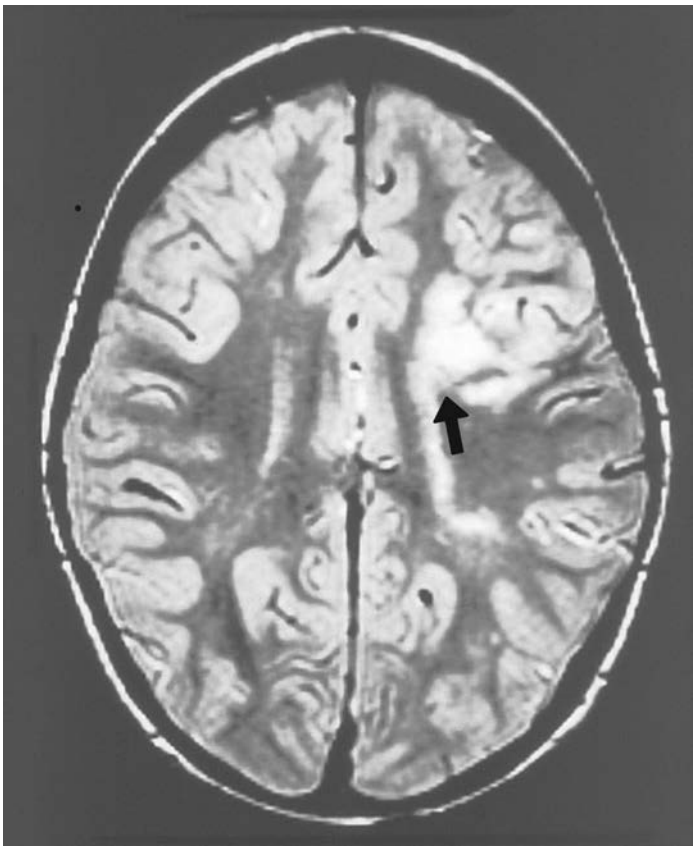


FIGURE 143-3. Acute stroke. T2-weighted MRI scan of the brain shows areas of increased signal intensity (*arrow*) involving the gray and white matter of the left parietal lobe, consistent with an acute infarct. [Reproduced with permission from Shah BR, Laude TL: *Atlas of Pediatric Clinical Diagnosis*, © 2000 WB Saunders, Philadelphia.]



FIGURE 143-4. Priapism in an adolescent male with sickle cell anemia. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*. © 2006, McGraw-Hill, Inc., New York.]

Diffusion-weighted MRI demonstrates changes within minutes and T2-weighted MRI within hours of ischemia.

Patients with SCA also have a higher rate of cerebral aneurysms and intra-cranial hemorrhage than the general population, although hemorrhagic stroke accounts for only 10% of strokes in SCA patients. This complication is rarely seen in children but becomes a concern during late adolescence. Hemorrhagic strokes typically present with headache, vomiting, and alterations in level of consciousness but may present with hemiparesis similar to an ischemic stroke if bleeding is intraparenchymal. There are three potential sites of hemorrhage: subarachnoid from an aneurysm, intraparenchymal from large-vessel vasculopathy or moyamoya, and intraventricular from moyamoya.

Neurologic symptoms are not uncommon in patients with acute chest crisis as well and have been noted in 7% to 10% of cases.[10] Other considerations in the patient with altered mental status and SCA previously mentioned include severe anemia from splenic sequestration and meningitis.

GU COMPLAINTS

Priapism (see Chapter 136, "Pediatric Urologic and Gynecologic Disorders") is common in males, with 27% having at least one episode by age 20 years old.[12] There is a bimodal age peak—5 to 13 years old and 21 to 29 years old. Patients present with a painful, swollen, edematous, tender penis, often with difficulty urinating (**Figure 143-4**). The glans itself remains soft. Sickling of the red cells in the sinusoids of the corpus cavernosum causes decreased venous outflow from the penis.[12]

The most common renal abnormality is hyposthenuria, the inability to maximally concentrate urine. This may cause enuresis, nocturia, and a propensity for dehydration and hyperkalemia. Renal vaso-occlusive crises are also common and can be asymptomatic or accompanied by colicky intermittent flank pain, costovertebral angle tenderness, gross or microscopic hematuria, and passage of renal tissue. Repetitive acute kidney injury can lead to chronic kidney disease and to renal insufficiency at an early age.[13]

Hematuria can also occur with papillary necrosis, a complication seen in both homozygous and sickle trait patients. Urinalysis demonstrates red blood cells without casts or associated pyuria or significant proteinuria.

TREATMENT OF SICKLE CELL ANEMIA SYMPTOMS

ANEMIA

Severe and symptomatic anemia, as well as many of the other complications of SCA, may require transfusion. The general principles of transfusion discussed here are applicable to each of the crises described earlier. **A typical pediatric transfusion of packed red blood cells is 10 mL/kg over a 2-hour period.** In the case of severe anemia, smaller volume transfusions, typically 5 mL/kg, are given more slowly because of the risk of pulmonary edema associated with large fluid shifts. In this case, multiple lower-volume transfusions are indicated with reassessment between each infusion. **In general, transfusions are indicated in the case of symptomatic anemia with a hemoglobin <6 grams/dL and an inappropriately low reticulocyte count, or an acute vaso-occlusive crisis with a hemoglobin below 10 grams/dL**. In these cases, a simple transfusion, rather than an exchange transfusion, is the indicated treatment with the goal of treatment being a hemoglobin >10 grams/dL.

Patients requiring transfusion for a specific crisis in which the hemoglobin is >10 grams/dL require an exchange transfusion, with the goal of reducing the proportion of HbS to <30%. Generally, this requires infusion of normal saline followed by removal of 50 to 60 mL/kg of blood prior to the transfusion. This process reduces vaso-occlusion by essentially replacing the patient's diseased erythrocytes with normal red blood cells. Many centers have an automated exchange transfusion machine, but in the event of an extreme emergency, this procedure can be performed manually at the bedside. **All transfusions should be leukoreduced; washed cells are used in patients with a history of allergic reactions; irradiated cells (from an unrelated donor) are indicated for patients who may be candidates for a bone marrow transplantation**; and extended phenotypic red blood cell matching should be performed whenever possible to minimize the incidence of alloimmunization discussed below.[14]

Anemia secondary to an aplastic crisis is often treated with simple transfusion and close follow-up. Acute splenic or hepatic sequestration with associated anemia is managed with good hydration, analgesia, simple transfusion, and exchange transfusion in refractory cases. Because the recurrence rate for splenic sequestration is 50%, chronic transfusion therapy and/or splenectomy are often considered.

VASO-OCCLUSIVE CRISES

Vaso-occlusive pain crises, regardless of location, are treated with pain control and *gentle* hydration and, in some cases, oxygen. Provide liberal analgesia with frequent reassessment of pain 15 to 30 minutes after medication and repeat dosing until the patient is comfortable. Although standard drug dosing is presented here, patients with pain crises who require narcotics frequently may have tolerance to these drugs and may require much larger doses to achieve adequate analgesia (see Chapter 115, "Pain Management and Procedural Sedation in Infants and Children"). Commonly used analgesics are listed in **Table 143-2**.

TABLE 143-2 Medications for Vaso-Occlusive Crisis in Children

Medication	Route	Dose	Onset	Duration	Common Side Effects
Morphine sulfate	IV	0.1 milligram/kg	10–15 min	1–2 h	Pruritus, nausea, respiratory depression, sedation
	IM	0.1 milligram/kg	15–30 min	3–4 h	
Hydromorphone (Dilaudid®)	IV	0.015 milligram/kg	10–15 min	1–2 h	Nausea, respiratory depression, sedation
	IM	0.015 milligram/kg	15–30 min	3–4 h	
Ketorolac (Toradol®)	IV loading	0.5 milligram/kg	10–30 min	4–6 h	Gastritis, bleeding, allergy
Hydrocodone (Lortab®, Vicodin®)	PO	0.15–0.2 milligram/kg every 3–4 h	10–20 min	3–6 h	Sedation
Ibuprofen (Motrin®, Advil®)	PO	10 milligrams/kg every 6–8 h	Within 60 min	6–8 h	Gastritis, bleeding, allergy

Ketorolac (Toradol®) can be combined with narcotics. IV is the preferred route of administration of morphine, but IM injection can be a temporizing measure. Due to the histamine release from morphine, a frequent side effect is pruritus, which may require treatment with diphenhydramine (Benadryl®) or use of alternative agents. Hydromorphone (Dilaudid®) is a reasonable alternative to morphine and has a similar pharmacokinetic profile. Subsequent narcotic doses may be reduced to half the initial dose, depending on the response and side effects to the initial dose. **Meperidine and fentanyl are not ideal opioid choices due to the side effect profile in the case of meperidine and the short duration of action of fentanyl.** Ketamine is a possible alternative to narcotics, and its use as an adjunctive treatment is becoming more widespread.[15,16] Patient-controlled analgesia has been demonstrated to be useful in vaso-occlusive crisis in adults and may be considered in teenagers.[17] Early initiation of oral opioids in the ED, in conjunction with IV medications, has been demonstrated to shorten hospital length of stay and result in a larger improvement in quality of life.[18]

Provide IV hydration at a rate of 1.5 times maintenance with 5% dextrose in half-normal saline. **Because of the risk of increased permeability of pulmonary vasculature and cardiomyopathy, normal saline boluses are not routinely used except to treat acute dehydration or hypovolemic shock.** Consider transfusion for pain crises accompanied by a significant drop in hemoglobin or a total hemoglobin <5 grams/dL. Oxygen is not useful in the nonhypoxic patient.[19] The decision to admit or discharge is often difficult and is usually made with input from the patient, family, and hematologist. Children requiring two or more doses of narcotic medications in the ED are likely to require admission. Patients discharged home should be instructed to take nonsteroidal anti-inflammatory drugs if no contraindications exist and may require an oral narcotic as well. Hydrocodone (Lortab®, Vicodin®) at a dose of 0.15 to 0.2 milligram/kg given every 3 to 4 hours is generally an effective choice and comes in a solution (Lortab®) for younger children.

For acute chest crisis, treat pain and provide IV hydration and oxygen. Several papers have noted a possible association between morphine sulfate use and the development of acute chest syndrome,[20] but morphine is still commonly and widely used in the treatment of pain associated with SCA. Because pneumonia is frequently a precipitant or complicating factor, give empiric antibiotic treatment with a third-generation cephalosporin and macrolide (see Chapter 128, "Pneumonia in Infants and Children"). For patients whose clinical status deteriorates despite all of these measures, transfusion (simple for hemoglobin <10 grams/dL, or exchange for hemoglobin >10 grams/dL) is indicated. **Generally, a partial pressure of arterial oxygen below 70 mm Hg or an oxygen saturation that has fallen >10% from baseline in a chronically hypoxic patient should be a trigger for transfusion.** Steroids are not beneficial. Respiratory distress associated with fat emboli may respond to prompt transfusion and/or exchange transfusion.

Other crises, such as renal infarct and right upper quadrant syndrome and papillary necrosis, are usually treated with hydration, analgesia, and other supportive measures.

PRIAPISM

Treat priapism with the use of hydration, analgesia, and transfusion and/or exchange transfusion depending on the current hemoglobin. Additionally, urologic consultation and aspiration of the corpora with a 23-gauge needle may be necessary, followed by irrigation and administration of a 1:10,000 epinephrine solution if the priapism continues for more than 4 to 6 hours (see Chapter 136, "Pediatric Urologic and Gynecologic Disorders"). Procedural sedation may be required for children needing corporal aspiration (see Chapter 115, "Pain Management and Procedural Sedation in Infants and Children"). Patients with repeated episodes of priapism may be candidates for prophylaxis with pseudoephedrine, gonadotropin-releasing hormone analogues, diethylstilbestrol, or hydroxyurea.[12]

STROKE

Alteplase (t-PA®) is not recommended for children and has no role in the management of stroke related to SCA. Interventions are aimed at limiting secondary brain injury through aggressive control of hyperpyrexia; correction of hypoglycemia, hypoxia, and hypovolemia; and **urgent exchange transfusion** to decrease the percentage of HbS below 30%. There is currently no consensus opinion on the management of blood pressure.[21] Children with a history of clinical stroke or transient ischemic attack or with abnormal cerebral blood flow on cranial Doppler are often managed long term with a chronic transfusion protocol or hydroxyurea to decrease the risk of subsequent strokes. Neurosurgical consultation is required for management of hemorrhagic stroke.

FEVER

Well-appearing children >1 year old with isolated fever and no signs of sepsis may be candidates for discharge if they are stable for a 4-hour period of observation, have good follow-up, and do not meet the high-risk criteria detailed in the earlier "Fever" section.[22] **Give a dose of ceftriaxone before discharge pending culture results.** Stable children with an identified source for fever (e.g., strep throat, otitis media) can be discharged with disease-specific treatment. Patients <1 year old or those meeting high-risk criteria or demonstrating signs of sepsis require admission. A third-generation cephalosporin (ceftriaxone, 100 milligrams/kg/d, one dose, not to exceed 4 grams/d) is frequently adequate empiric treatment against encapsulated bacteria pending culture results, but areas with high rates of resistant *S. pneumoniae* may consider the addition of vancomycin (10 milligrams/kg IV every 6 hours) as well. Pulmonary infections require the addition of a macrolide. Antibiotics should be started within 60 minutes for these high-risk patients.[23] For specific infections, such as bone and joint infections, treatment should be determined based on available culture results and consultation with appropriate subspecialty services. In the case of meningitis, patients are at increased risk of stroke, and the decision to administer a prophylactic exchange transfusion should be made in conjunction with the hematologist.

OTHER PROCEDURES

SCA patients may be admitted for surgery for reasons related or unrelated to the underlying disease. Before surgery, exchange transfusion can be given to decrease HbS to <30%. This should be considered in consultation with the hematologist for all but the most emergent conditions requiring major surgery.[4] Minor procedures may not require transfusion. Transfusion is not indicated before the administration of nonionic contrast materials.

COMMON OUTPATIENT MEDICATIONS AND TREATMENTS

Due to the risk of bacteremia, children are maintained on **oral penicillin** through age 5 years old. Beyond 5 years of age, there does not seem to be any additional benefit from penicillin.[24] **Folate** supplementation is standard due to the increased turnover of red blood cells.

Hydroxyurea is the only disease-modifying drug available for sickle cell disease and is used in SCA patients to decrease the frequency and severity of complications and to reduce mortality. Hydroxyurea induces the production of HbF in addition to other benefits such as decreasing the number of leukocytes and providing some vasodilation. The additional HbF lowers the percentage of HbS, which decreases hemoglobin polymerization, increases erythrocyte size, and improves cellular deformability, thus decreasing the amount of sickling and consequently reducing vaso-occlusion.[4,25] There is strong evidence that hydroxyurea should be started in all children over 9 months of age regardless of severity of the disease to reduce the risk of complications. Although this medication should be started by a primary care physician or sickle cell disease specialist, emergency physicians caring for SCA patients should counsel patients on the availability of this treatment and refer them appropriately. Side effects can include GI discomfort, modest neutropenia, hyperpigmentation, and renal toxicity.

Hypertransfusion or **chronic transfusion therapy** is an option in patients with severe or frequent crises, with the principle that the transfused red cells will decrease anemia and minimize the patient's own production of abnormal red cells. If the percentage of HbS is kept below

30%, the possibility of a sickle crisis is minimized. Clearly, the known risks of infection and transfusion reaction that pertain to any transfusion apply. Transfusion for sickle cell disease patients more frequently results in alloimmunization (5% to 36% of patients) compared to the general population. Alloimmunization is defined as immunization of the patient by donor red blood cell antigens. The risk can be minimized by using blood matched for minor red blood cell antigens such as C, E, and Kell. In these cases, patients experience a drop in hemoglobin to below pretransfusion levels, despite a negative direct antibody test, due to hemolytic anemia that can be life threatening. This phenomenon also increases the risk for future transfusion reactions in SCA patients.[4,14]

Finally, chronic **iron overload** is another complication of frequent transfusions and may contribute to cardiomyopathy. Iron overload is treated with deferoxamine chelation therapy, a treatment that is also associated with risk: deferoxamine may increase the susceptibility for fungal infections (and other infections such as *Yersinia*) and lead to growth failure, allergic reactions, ophthalmic toxicity, or ototoxicity.[4]

Bone marrow or stem cell transplantation has been successfully used to cure SCA. However, due to the risks associated with transplantation, this is generally only considered in patients who have a human leukocyte antigen–matched sibling.[4]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 144

Hematologic Emergencies in Infants and Children

Jessica A. Bailey
Megan Mickley

INTRODUCTION

Bleeding in a child can be a diagnostic dilemma, because the causes range from benign to serious. Children with mild bleeding disorders may not experience an episode of bleeding until faced with a hemostatic challenge, such as an interventional procedure or trauma. On the other hand, children without an underlying bleeding disorder commonly present with complaints of bruising and bleeding such as epistaxis or menorrhagia. **Red flags for a potential bleeding disorder include bleeding or bruising out of proportion to the injury, prolonged and/or recurrent bleeding (particularly with unknown cause or after a small injury or procedure), spontaneous bruising or bleeding, uncommon sites of bleeding (joints, GI) or bruising (proximal extremities, trunk), and a family history of a bleeding disorder.** Consider nonaccidental trauma in the child with unusual bruising patterns (see Chapter 150, "Child Abuse and Neglect"). **Figure 144-1** provides a basic approach for the initial ED assessment of a child with bleeding. The most common bleeding disorders presenting in childhood are discussed below.

HEMOPHILIA

A detailed discussion of hemophilia is provided in Chapter 235, "Hemophilias and von Willebrand's Disease." **Table 144-1** provides a summary of those bleeding disorders, which are also reviewed below.

EPIDEMIOLOGY

Factor VIII (hemophilia A) and factor IX (hemophilia B) deficiencies are X-linked recessive hematologic disorders and predominantly affect males. One third of cases arise from spontaneous mutations; thus, patients may have a negative family history of bleeding disorders.[1] These disorders are clinically indistinguishable but differ in their treatment.

CLINICAL FEATURES

The severity of disease, and thus risk of bleeding, is defined by the factor activity as a percentage of normal (which is defined as 50% to 100%). Patients with mild disease may never spontaneously bleed but have increased bleeding with trauma (**Figure 144-2**), whereas individuals with severe disease have spontaneous bleeding into the joints (hemarthroses; **Figure 144-3**) and soft tissue (hematomas) and may develop life-threatening hemorrhage.

DIAGNOSIS

Most children with hemophilia have already been identified before an ED visit because of a positive family history of bleeding disorder (prenatal testing is possible through chorionic villus sampling or amniocentesis), intracranial hemorrhage, significant hematoma after birth trauma, or prolonged and excessive bleeding after circumcision. However, some cases, especially mild hemophilia, may escape detection until the child is several years old, when symptoms are provoked by an injury or a small interventional procedure. The event precipitating initial presentation could be as minor as a trip and fall in a newly ambulatory toddler, a common age of diagnosis due to the increased activity level. **Suspect hemophilia in a child who presents with spontaneous bleeding, particularly in unusual locations (e.g., joints, areas not usually injured like the proximal extremities) or with bleeding that is out of proportion to the injury.** Specific bleeding manifestations are listed in Tables 144-1 and 235-2. Hemarthroses are the hallmark of hemophilia, accounting for 80% of bleeding episodes in severe hemophiliacs.[2] Older children and adolescents describe a burning or tingling sensation preceding signs of hemarthrosis development.[2]

Differential diagnosis includes the spectrum of bleeding disorders. The screening test for hemophilia is an **activated PTT, which will be prolonged** in most patients. Platelet count, bleeding time, and prothrombin time will be normal. Quantitative factor levels confirm a diagnosis of hemophilia. Mixing studies identify whether factor inhibitors are present.

TREATMENT

The overall treatment goal is to increase levels of the deficient factor. Treatment of hemophilia depends on the specific factor deficiency, the baseline severity of the disease, and the nature and extent of the injury. In severe hemophiliacs, regular scheduled prophylactic administration of clotting factor concentrate is a well-established practice and significantly reduces the incidence of bleeding.[2]

Even in the absence of physical findings, promptly order and initiate factor replacement for children with a presenting ED history that raises concern about high-risk sites for bleeding. A reliable adage in hemophilia is **"When in doubt, treat,"** preferably within 2 hours.[3] In patients with known hemophilia, coagulation studies are not necessary upon presentation for a new bleeding episode. However, a level of factor VIII or IX or the presence of a factor inhibitor may be requested by the hematologist to assist in the patient's evaluation and treatment.

The dose of factor replacement and goal level of factor percentage are based on the clinical scenario. **A good rule of thumb is to aim for a desired factor level of approximately 40% to 50% following replacement. For high-risk and/or life-threatening bleeds (CNS, retropharyngeal, ophthalmic, iliopsoas/retroperitoneal, intra-abdominal, intrathoracic, and GI), that goal doubles to 80% to 100%.** Specific factor replacement products are listed in Table 235-3, and factor replacement guidelines are listed in Table 235-4. Recombinant and human plasma-derived factors are available, and efforts should be made to use the patient's home product. Treatment regimens will differ for factor VIII and factor IX products because they have different dosing requirements and different half-lives. In most patients, 1 unit/kg of factor VIII will increase the clotting activity of treated plasma by 2%; 1 unit/kg of

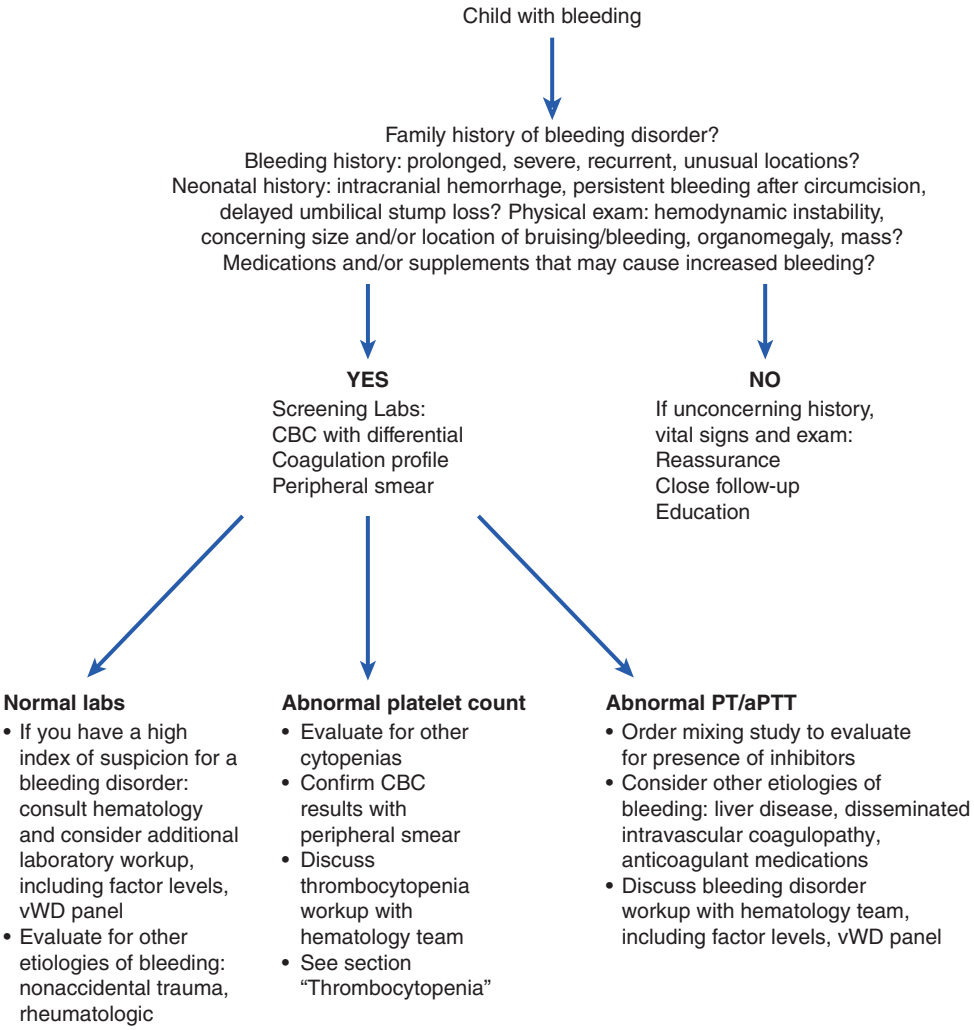


FIGURE 144-1. Algorithm for the approach to a child with undiagnosed bleeding. aPTT = activated partial thromboplastin time; PT = prothrombin time; vWD = von Willebrand's disease.

factor IX will raise factor activity level by only 1%.[3] Given the cost of these products, an effort should be made to use the whole unit dose. In the rare case in which factor replacement products are not immediately available, administer cryoprecipitate for factor VIII deficiency or fresh frozen plasma for factor IX deficiency.

Patients with mild hemophilia A who have been pretested to document a response may be treated with **desmopressin** instead of factor replacement. Desmopressin releases stored factor VIII from the subendothelial compartment. The use of desmopressin is particularly advantageous for pediatric patients, due to its lower cost, availability in intranasal form, and the elimination of viral transmission risk as compared to frequent factor replacement.[3] See Table 235-5 for desmopressin dosing. Of note, desmopressin is an antidiuretic; patients must be monitored for water retention and hyponatremia.

For hemophilia patients requiring surgery and scheduled to go to the operating room from the ED, factor replacement must be given beforehand to optimize factor levels. Adjunctive management for bleeding in joints and muscles should also include rest, ice, compression, elevation, and splinting. Minimal oral bleeding (e.g., after dental procedures) may be treated with topical thrombin or antifibrinolytic drugs such as tranexamic acid or aminocaproic acid.[3] Minimal anterior epistaxis may respond to conservative therapies, such as direct pressure and phenylephrine, without factor replacement. Patients, usually with severe hemophilia A, who have factor inhibitors (antibodies) may require very high doses of standard factor products to overwhelm the inhibitors present. However, some patients will need to be treated with products that bypass factor VIII and factor IX in the clotting cascade (see Table 235-6). These include activated prothrombin complex concentrates (FEIBA®) and recombinant activated factor VIIa (NovoSeven®).

COMPLICATIONS

Hemarthrosis is the most common hemorrhagic complication of hemophilia and most commonly affects the knee, ankle, elbow, and shoulder. Minor, often unrecognized, trauma may precipitate spontaneous intraarticular hemorrhage with pain, swelling, and decreased range of motion. Unfortunately, the presence of blood in the joint precipitates a cascade of inflammation and synovial neovascularization. This increases vulnerability to bleeding and leads to synovium fibrosis, irreversible cartilage destruction, and hemophilic arthropathy (**Figure 144-4**).[2] Aggressive measures must be taken to limit the number and extent of these events.

Spontaneous muscle hematomas account for 10% to 25% of hemophilia bleeds and can also present with severe pain and limited range of motion.[4] **Complications from ongoing bleeding include compartment syndrome and nerve compression.** Particularly concerning are iliopsoas bleeds, which may mimic acute appendicitis or hip pathology, with radiation of pain to the back, groin, and hip. The hip is often held in flexion. Such bleeds can be particularly uncomfortable if there is compression of the femoral nerve or sacral plexus. They require aggressive factor replacement, given the potential for blood accumulation in the retroperitoneal space.

The leading cause of death in children with hemophilia is intracranial hemorrhage, which can be spontaneous or occur after even mild head trauma.[4] Because bleeding can progress slowly, patients may not yet have clinical manifestations of hemorrhage upon presentation. Maintain a

TABLE 144-1 Coagulation Disorders

Disease	Inheritance	Defect	Incidence	Distribution	Subtypes	Inhibitors	Diagnostics	Symptoms	Treatment
Hemophilia A									
Factor VIII deficiency	X-linked recessive	Defect in factor VIII procoagulant activity Quantitative and qualitative	1:5000 live male births	Males	Severe: <1% factor VIII activity Frequency: 50%–70% Bleeding spontaneously into joints or soft tissue Moderate: 1%–5% factor VIII activity Frequency: 10% Bleeding with minor trauma or surgery Mild: >5% factor VIII activity Frequency: 30%–40% Bleeding with major trauma or surgery	30% of those with severe subtype have inhibitors	Platelet count, PT, bleeding time—WNL PTT—prolonged Factor VIII assay—low or absent amount	Intracranial hemorrhage Hemarthroses (large joints) Bleeding after neonatal circumcision Muscle and soft tissue hematomas Retroperitoneal bleeds Epistaxis and mucosal bleeding from oral trauma Pharyngeal bleeding (posttussive and after emesis) Hematochezia and melena from GI bleeding Hematuria Menorrhagia	Factor VIII replacement Desmopressin (in pretested mild hemophiliacs) Activated prothrombin complex concentrates (FEIBA®) Recombinant activated factor VIIa (NovoSeven®) Cryoprecipitate*
Hemophilia B (Christmas disease)									
Factor IX deficiency	X-linked recessive	Defect in factor IX procoagulant activity Quantitative and qualitative	1:30,000 live male births	Males	Severe: <1% factor IX activity Bleeding spontaneously into joints or soft tissue Moderate: <1% factor IX activity Bleeding with minor trauma or surgery Mild: >5% factor IX activity Bleeding with major trauma or surgery	1%–3% with inhibitors	Platelet count, PT, bleeding time—WNL PTT—prolonged Factor IX assay—low or absent amount	Symptoms same as for factor VIII deficiency	Factor IX replacement Activated prothrombin complex concentrates (FEIBA®) Recombinant activated factor VIIa (NovoSeven®) Fresh frozen plasma*
von Willebrand's disease									
vWF deficiency	Autosomal dominant (type 1 and subtypes of 2); autosomal recessive (subtypes of 2 and type 3)	Defect in vWF Quantitative and qualitative Variable factor VIII activity	1%–2% of general population	Males = females	*Type 1 von Willebrand's (classic) disease:* Mild quantitative deficiency of vWF Most common form (80%) *Type 2 von Willebrand's disease:* Variable qualitative abnormalities of vWF *Type 3 von Willebrand's disease:* Severe quantitative deficiency of vWF Rare (1–3 per million)	Inhibitors rare	PT—WNL PTT—prolonged or WNL Factor VIII—borderline or decreased vWF activity, antigen and multimer evaluation	*Types 1 and 2 (mild):* Mucocutaneous bleeding Recurrent or prolonged epistaxis Bleeding after surgery or trauma, e.g., dental procedures GI bleeding Menorrhagia *Type 3:* Spontaneous hemarthroses Muscle hematomas Severe bleeding	vWF replacement Desmopressin for type 1 and some type 2 Antifibrinolytic agents (ε-aminocaproic acid)

Abbreviations: PT = prothrombin time; PTT = partial thromboplastin time; vWF = von Willebrand factor; WNL = within normal limits.

*If concentrated factor products unavailable.



FIGURE 144-2. Hemophilia A. Extensive bruising in a child with factor VIII deficiency. [Photo contributed by Ralph A. Gruppo, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

high index of suspicion. **Unless directed otherwise by the hematology consultant, treat all reports of head injuries, neurologic symptoms, or visible head trauma presumptively with 100% factor correction.**[5] Obtain immediate head CT imaging to identify intracranial hemorrhage.

Bleeding from the GI tract is rarely severe unless a specific anatomic lesion is present. Gross hematuria may require factor replacement. Obtain urinalysis to rule out infection and renal ultrasonography to identify a serious anatomic lesion. Other uncommon but critical lesions that require aggressive factor replacement (100%) and specialist intervention to avoid massive hemorrhage or permanent injury include tonsillar bleeding, solid organ bleeding from blunt abdominal or thoracic trauma, spinal hematoma, and intraocular hemorrhage.

DISPOSITION

Consult a hematologist for all children with hemophilia and active bleeding prior to disposition. Pediatric hemophilia patients and their families are often comfortable participating in that decision, because they may receive some treatments at home. Children with mild bleeding episodes may be discharged home with careful instructions and a concrete hematology follow-up appointment. Patients with moderate or severe bleeding and those with high-risk bleeds require hospital admission, because close monitoring and documentation of adequate response to factor replacement are necessary and repeat doses are frequently required.



FIGURE 144-3. Hemarthrosis. A child with hemophilia A who presented with bilateral knee hemarthroses. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]

VON WILLEBRAND'S DISEASE

A detailed discussion of von Willebrand's disease (vWD) is provided in Chapter 235; vWD classification and basic treatment are outlined in Table 235-7.

CLINICAL FEATURES

vWD type 1 is usually associated with mild mucocutaneous bleeding, including easy bruising, recurrent or prolonged epistaxis, and prolonged postprocedural bleeding (e.g., gingival bleeding after dental work). Menorrhagia may be the sole presenting complaint in young women. In type 3 vWD, clinical features can closely resemble those of hemophilia, because significantly reduced amounts of von Willebrand factor (vWF) allow increased clearance of factor VIII. In general, the severity of bleeding correlates with the degree of reduction of factor VIII.

DIAGNOSIS

A high index of suspicion is necessary for the diagnosis of vWD because clinical features are mild in most patients, and mucocutaneous bleeding (e.g., bruising, epistaxis) is common in childhood. History should include frequency, duration, severity, and location of bleeding, as well as concurrent medications. Note any family history of "easy" bleeding. ED screening labs for vWD usually reveal a normal CBC and prothrombin time, a normal or prolonged activated PTT (if factor VIII is sufficiently reduced), and low vWF levels. More specific testing includes vWF antigen, vWF ristocetin cofactor activity, vWF multimers, and factor VIII level.[6,7] Bleeding time, once the gold standard for vWD diagnosis, has difficulties with reproducibility and poor sensitivity and specificity.[7,8] Levels of vWF can be affected by a variety of normal (e.g., stress) and medical (e.g., active bleeding) conditions.[8] Repeat testing should be done if clinical suspicion is high.

TREATMENT

Treatment of active bleeding in a known vWD patient consists initially of localized measures to achieve hemostasis, including direct pressure on bleeding sites, packing dental extraction sites and nasal passages, and the application of topical hemostatic agents. Antifibrinolytic agents can be used to treat oral trauma. Oral contraceptive pills or an intrauterine device helps to control menorrhagia. Desmopressin (see earlier section on hemophilia treatment), which releases stored vWF from the endothelium, is the preferred initial treatment of bleeding in patients with type 1 vWD. It has no effect in those with type 3 vWD and variable effect in those with type 2.[5] **Pay attention to the fluid status of patients receiving desmopressin, because dilutional hyponatremia is a rare side effect due to its antidiuretic properties.** Children with type 2 or 3 vWD or type 1 with inadequate response to desmopressin usually require treatment with purified plasma-derived vWF replacement. Other emerging therapies, such as recombinant vWF concentrate, have been approved for adults but are not yet routinely used in children.[9] In emergencies only, administer cryoprecipitate if no vWF:factor VIII replacement is available. Cryoprecipitate is not recommended as standard therapy because it has a low concentration of vWF and carries infectious risks because it does not undergo viral inactivation.[5] Advise all patients with vWD to avoid medications with known antiplatelet effects (e.g., aspirin, NSAIDs).

VITAMIN K DEFICIENCY BLEEDING

Vitamin K deficiency bleeding, formerly known as *hemorrhagic disease of the newborn*, is a neonatal bleeding coagulopathy resulting from vitamin K deficiency. Although the American Academy of Pediatrics

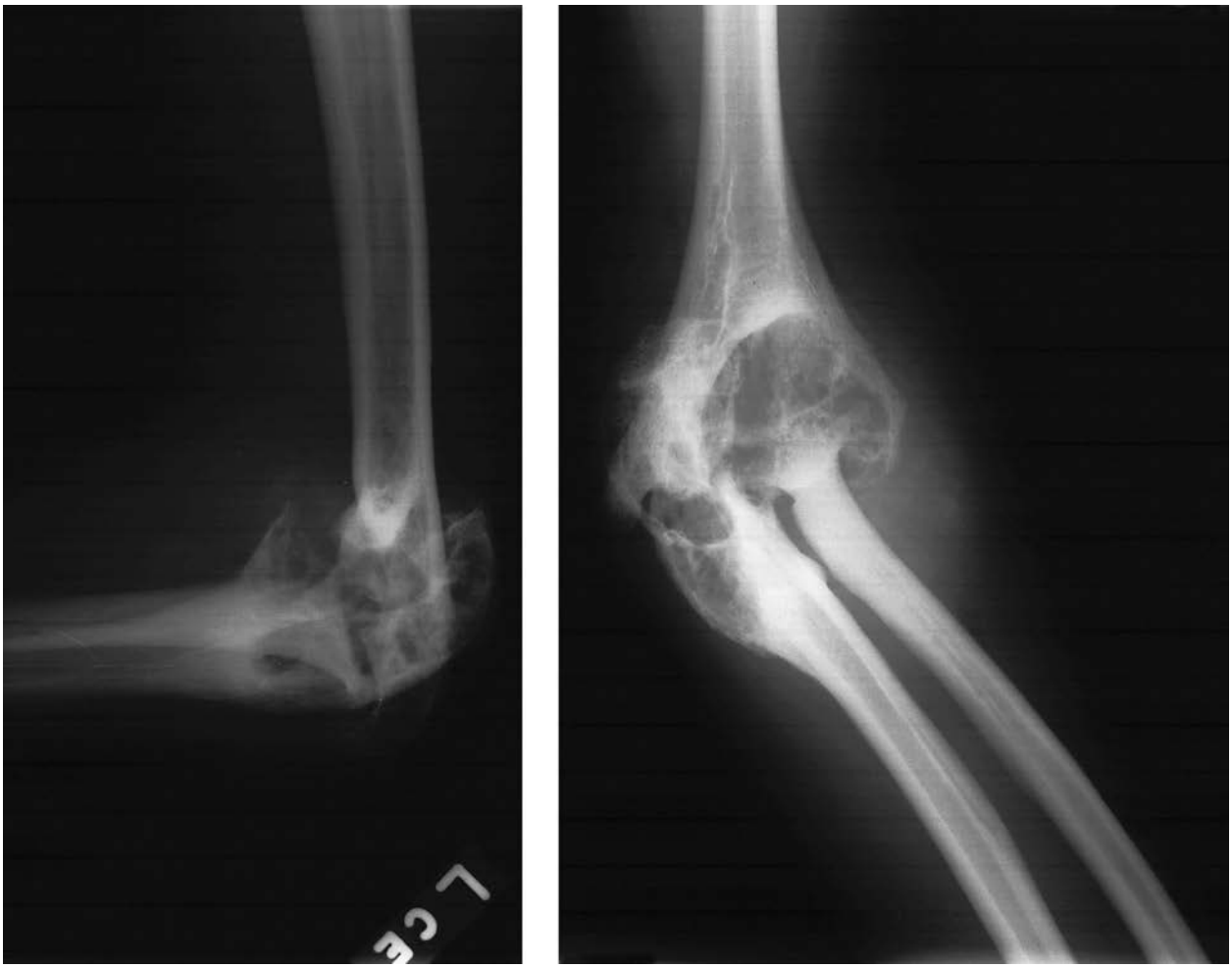


FIGURE 144-4. Hemophilic arthropathy. Note the extensive degenerative changes. [Image used with permission of J. Fitzpatrick, MD, Cook County Hospital. Reproduced with permission from Simon RR, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities*, 5th ed. Copyright © 2007 by The McGraw-Hill Companies, Inc. All rights reserved.]

has recommended intramuscular vitamin K prophylaxis as standard of care in newborns since 1961, there has been an increasing rate of parental refusal in the past decade.[10] Risk factors include breastfed infants (because breast milk contains less vitamin K content than cow's milk formulas), infants with malabsorption or hepatobiliary disorders, and maternal medications (e.g., phenytoin, isoniazid).

In classic cases, bleeding occurs 2 to 14 days after birth; however, there are reports of cases <24 hours after birth and up to 12 weeks after birth.[11] Bleeding can present as mild oozing from the umbilicus or circumcision site or as life-threatening pulmonary and intracranial hemorrhage. Although vitamin K deficiency bleeding is rare in developed countries, 30% to 60% of reported cases are associated with intracranial hemorrhage.[10] Labs reveal a decreased hematocrit, depending upon the severity and duration of the bleed, and prolonged prothrombin time and activated PTT. **Treatment is the immediate administration of 1 milligram of SC, IM, or IV vitamin K (phytonadione). The IM route places the patient at risk for a significant hematoma, whereas the IV route carries a greater risk of an anaphylactoid reaction. Given the risk of intracranial bleeding, do not wait for laboratory results if your clinical suspicion is high.** Life-threatening hemorrhage may require a transfusion of 10 to 20 mL/kg of fresh frozen plasma to increase serum procoagulant levels.

ANEMIA

Children may develop profoundly low hemoglobin levels (e.g., 3 to 4 grams/dL) before coming to medical attention. Patients may be asymptomatic or present with symptoms ranging from pallor and decreased activity to congestive heart failure in an infant. This section reviews the ED diagnosis and management of some important types of anemia in children. The management of anemia due to hemorrhage is discussed in Chapters 13, "Approach to Traumatic Shock" and 110, "Pediatric Trauma." Hemoglobin levels vary with a child's age, peaking at approximately 14 to 15 grams/dL in the full-term newborn period and at approximately 13 grams/dL (females) and approximately 15 grams/dL (males) in the teenage years. The dramatic increase in oxygen availability after birth briefly shuts down erythropoietin production, resulting in a physiologic nadir, or "physiologic anemia," of about 9 to 11 grams/dL at approximately 2 months of age. Hemoglobin levels then rise steadily throughout childhood. After the first year of life, the normal reticulocyte count is 1% to 2% of circulating red blood cells, assuming normal red blood cell physiology.[8] Refer to normal hemoglobin and red blood cell values when evaluating pediatric anemia.

ED TREATMENT OF SEVERE ANEMIA

Children with anemia unrelated to acute blood loss rarely require blood transfusion in the ED. Some children with very low hemoglobin levels and a presentation highly consistent with iron deficiency anemia, for example, may be managed as outpatients if close follow-up is ensured. Exceptions include hemolytic anemias, bone marrow failure, hemodynamic instability, congestive heart failure, or other symptoms due to severe anemia. Obtain a hematology consultation to assist with transfusion management.

The decision to transfuse must take into account whether the child has a chronic or acute anemia; those with chronic anemias are at risk for volume overload. For children with hemoglobin ≤8 grams/dL and

signs of hemodynamic compromise, active bleeding, or consumptive coagulopathy, consider an initial transfusion of packed red blood cells in 10 to 15 mL/kg aliquots. **With extremely low hemoglobin levels (<5 grams/dL) due to chronic anemia, the transfusion should be small (2 to 3 mL/kg packed red blood cells) and slow (1 mL/kg/h), with continuous monitoring and frequent reassessment.** In cases of volume overload, diuretics can be considered, or an exchange transfusion can be performed in severe cases.

CLASSIFICATION OF ANEMIA

As with adults, a differential diagnosis for anemia in childhood can be broken down into microcytic, normocytic, and macrocytic categories (see Figures 231-2, 231-3, and 231-4). The pathologic causes can be classified as those that decrease red blood cell production and those that increase red blood cell destruction, in addition to blood loss and iatrogenic dilutional anemia from fluid administration. To help with those differentiations, a peripheral smear and reticulocyte count should always be sent with the CBC. A more detailed differential diagnosis of anemia is provided in **Table 144-2**. Selected common pediatric anemias are discussed below. For a more thorough discussion of specific etiologies, see Chapters 231, "Anemia and Polycythemia"; 233, "Acquired Bleeding Disorders"; 236, "Sickle Cell Disease and Hereditary Hemolytic Anemias"; and 237, "Acquired Hemolytic Anemia." Hemolytic-uremic syndrome is discussed in detail in Chapter 137, "Renal Emergencies in Children."

IRON DEFICIENCY ANEMIA

Iron deficiency anemia is the leading cause of anemia in childhood and can be profound. Healthy term infants have adequate iron storage for the first 4 to 6 months of life. After this, iron stores are depleted. Decreasing prevalence of iron deficiency anemia may be attributable, in part, to the American Academy of Pediatrics recommendations regarding iron supplementation in breastfed infants, iron-fortified formulas and infant foods, delayed use of cow's milk until after 1 year of age, and universal hemoglobin screening at 1 year of age.[12] However, excessive whole-milk feeding and poor dietary intake of iron make iron deficiency anemia a diagnosis common in the toddler years. Milk proteins may also cause a low-grade colitis with occult GI bleeding. **Nutritional iron deficiency anemia is uncommon in children >3 to 4 years of age and is suspicious for occult bleeding.**[8] Iron deficiency anemia is diagnosed based on clinical suspicion, with labs demonstrating a hypochromic microcytic anemia and low reticulocyte count. Iron studies help to confirm the diagnosis. For hemodynamically stable children, treatment is outpatient oral ferrous sulfate supplementation and primary care follow-up. For children with severe anemia and/or evidence of hemodynamic compromise, inpatient care may be necessary, and hematology should be consulted regarding transfusion guidelines.

TABLE 144-2 Classification of Anemia

Decreased red blood cell (RBC) production

Impaired RBC proliferation

- Parvovirus B19 infection
- Aplastic anemia (congenital or acquired)
- Isolated pure red cell aplasia (Diamond-Blackfan syndrome)
- Transient erythroblastopenia of childhood (TEC)
- Bone marrow infiltration (e.g., leukemia)

Impaired erythropoietin production

- Anemia of chronic disease
- Chronic renal disease
- Malnutrition

Abnormal hemoglobin synthesis

- Lead poisoning
- Iron deficiency
- Thalassemia
- Vitamin B_{12} or folate deficiency
- Sideroblastic anemia

Increased RBC destruction

Hemoglobinopathy

- Thalassemia
- Sickle cell disease
- Membrane defect (e.g., hereditary spherocytosis)

Extrinsic disease

- Autoimmune hemolytic anemia
- Glucose-6-dehydrogenase deficiency
- Disseminated intravascular coagulopathy
- Microangiopathic process (e.g., hemolytic-uremic syndrome)
- Paroxysmal nocturnal hemoglobinuria

PARVOVIRUS B19 INFECTION

Parvovirus, a common virus in childhood, replicates in erythroid progenitor cells and can cause transient red cell aplasia. In the normal host, parvovirus infection may go unrecognized or be identified by its characteristic reticular rash and slapped cheek appearance (erythema infectiosum, or fifth disease); see "Erythema Infectiosum" in Chapter 142, "Rashes in Infants and Children." The red cell aplasia is so short lived that concomitant anemia is usually not discovered. However, in patients with hemoglobinopathy or hemolytic anemias such as sickle cell disease, in whom the life span of a red cell is decreased, even brief periods of red cell aplasia may result in severe anemia and aplastic crisis, often requiring transfusion.

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD

Transient erythroblastopenia of childhood is a gradually developing, self-resolving normocytic anemia caused by a temporary decrease in red blood cell precursors. The cause is unknown. It is most common in the toddlers and preschool age groups, but can be diagnosed in children 6 months to 10 years of age.[13] Other cell lines should not be affected, and iron studies are normal. Bone marrow recovery usually occurs in 1 to 2 months, and transfusions are rarely needed.

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune hemolytic anemia is caused by the production of autoantibodies to red blood cells. In primary autoimmune hemolytic anemia (most common in infants and young children), there is no evidence of an underlying disorder; the disease may manifest after a simple viral illness. Older children are more likely to experience autoimmune hemolytic anemia secondary to an underlying systemic illness, such as malignancy, human immunodeficiency virus, or an autoimmune disorder. The clinical presentation may be abrupt and the anemia severe. White cells and platelets are unaffected, and reticulocytes are increased unless the hemolysis is sudden and recent. Labs reveal spherocytes and schistocytes on peripheral blood smear, an indirect hyperbilirubinemia, elevated lactate dehydrogenase, and urine bilirubin metabolites (hemoglobinuria in the absence of red blood cells on urine microscopy). Definitive diagnosis is made by a direct Coombs test. These patients should be hospitalized, and treatment usually begins with corticosteroids. If transfusion is required, the most compatible packed red blood cells are used.

THROMBOCYTOPENIA

A platelet count <150,000/mm^3 should be considered abnormal, and patients with a count <20,000/mm^3 are at high risk for spontaneous bleeding. Consider thrombocytopenia in patients with petechiae (see Figure 233-1A), easy bruising, epistaxis, gingival bleeding, menorrhagia, hematuria, and GI bleeding. Perform a thorough physical exam to assess for signs of systemic disease. Refer to Figure 144-1 for the general

approach. Common medications associated with thrombocytopenia are listed in Table 233-2.

IMMUNE THROMBOCYTOPENIA

Immune thrombocytopenia, previously called *idiopathic thrombocytopenic purpura*, is an autoimmune disorder of antiplatelet antibodies leading to platelet destruction and, in some cases, decreased megakaryocyte platelet production. In the childhood form, over 80% of cases are self-limited and resolve within 6 months, and the incidence of life-threatening bleeds is <0.5%.[14] Immune thrombocytopenia lasting >3 months after diagnosis is termed *persistent*, and the term *chronic* is now used for children with thrombocytopenia >12 months from the time of diagnosis.[14]

The typical presentation is a preschool- or school-age, previously healthy child with acute onset of petechiae and bruising, often following a viral illness. However, 25% of children present with a more insidious course.[14] Additional symptoms and signs are typically absent and, if found, should raise your concern for different diagnoses including hematologic, rheumatologic, oncologic, and infectious diseases. Laboratory studies typically demonstrate isolated thrombocytopenia.

Pharmacologic treatment is controversial and may include corticosteroids, IV immunoglobulin, or anti-Rh(D) immunoglobulin (WinRho®). There are limited data regarding the use of thrombopoietic agents in children. These treatment options are discussed in further detail in Chapter 233. Consult hematology prior to management, activity restrict patients, and avoid all medications with antiplatelet activity. Admission is necessary for any child with a platelet count <20,000/mm^3, with an IV medication regimen, or with spontaneous bleeding, regardless of platelet count.

If steroids are given, there are a variety of dosing regimens, ranging from 2 milligrams/kg/d of prednisone for 21 days, to 30 milligrams/kg of methylprednisolone daily for 4 days, to 20 milligrams/m^2/d of dexamethasone for 4 days. **Steroids should be started only if the possibility of leukemia or aplastic anemia can be completely excluded on clinical grounds; otherwise, a bone marrow aspirate is necessary to secure the diagnosis before initiating steroid therapy.** IV immunoglobulin is superior to steroids in improving platelet numbers for immune thrombocytopenia patients.[16] The typical IV immunoglobulin dose is 1 gram/kg/d. Anti-Rh(D) immunoglobulin is only effective in Rh-positive patients, and patients require admission due to the risk of severe intravascular hemolysis following infusion. The anti-Rh(D) dose is 50 to 75 micrograms/kg and can lead to a 1 to 2 gram/dL decrease in the hemoglobin concentration. Pretreatment with acetaminophen and diphenhydramine is recommended for both IV immunoglobulin treatments.

On the rare occasion that a child with immune thrombocytopenia develops life-threatening hemorrhage, administer an immediate single-donor platelet transfusion (two to three times normal dose), along with IV methylprednisolone and IV immunoglobulin or anti-Rh(D). The obvious disadvantage of platelet transfusion in immune thrombocytopenia is that platelets will be rapidly consumed by circulating antiplatelet antibodies and repeat transfusions may be necessary.

NEUTROPENIA

Isolated neutropenia in childhood is caused by a heterogeneous group of disorders, ranging from transient and benign to chronic and profound immunodeficiency. Neutropenia in the oncology patient is discussed in Chapter 145, "Oncologic Emergencies in Infants and Children."

Neutropenia is an absolute neutrophil count <1500/mm^3. Lower counts can be noted in infants during the first year of life and in individuals of African and Middle Eastern descent, but counts should not decrease to <1000/mm^3.[17,18] Neutropenia can be stratified into categories that are associated with increasing risk of pyogenic infection: mild neutropenia with absolute neutrophil count of 1000 to 1500/mm^3, moderate neutropenia with absolute neutrophil count of 500 to 1000/mm^3, and severe neutropenia with absolute neutrophil count of <500/mm^3. **Severe neutropenia places the patient at risk for life-threatening infections.** Perform a through history and physical examination to identify a nidus of infection. Physical exam should include the oral mucosa, skin, ears, lungs, abdomen, and perineal region. Avoid digital rectal examinations and rectal temperatures, as well as catheter urine sampling, because these maneuvers can result in a portal of infection. Obtain a family history to evaluate for inheritable conditions.

The underlying cause of isolated neutropenia is critical in defining infectious risk. A benign, transient neutropenia is quite common in healthy children and usually arises in the context of a viral infection, resolving within weeks to months. A number of medications, including antiepileptic drugs, antibiotics, antipsychotics, and antithyroid drugs, can cause severe neutropenia and comorbidities, and reports of drug-induced neutropenia quote a 2.5% to 10% mortality rate.[18] Neutropenia due to bone marrow depletion is a known entity in the septic child; therefore, **suspect serious bacterial infection in a critically ill child with neutropenia**. **Typical symptoms and signs of infection (e.g., purulence) may be absent in a neutropenic patient due to reduced inflammatory response.**

Chronic (>3 months) neutropenia can be idiopathic, autoimmune, nutritional, or associated with congenital or acquired bone marrow failure. Neonates may develop a self-resolving but significant isoimmune neutropenia from maternal/fetal antigen incompatibility or have placental transfer of antibodies from a mother with autoimmune neutropenia.[17] A benign autoimmune neutropenia can also be noted during infancy or early childhood, when repeat CBCs reveal persistent neutropenia. Children with autoimmune neutropenia tend to have more frequent (rather than more severe) infections, and the neutropenia resolves spontaneously within a few years. Lack of resolution should prompt further evaluation. If severe chronic neutropenia is noted in infancy, severe congenital neutropenia and other inherited marrow failure disorders must be excluded. Distinguishing benign neutropenia from worrisome neutropenia often requires a bone marrow examination to distinguish normal versus abnormal myelopoiesis.

Cyclic neutropenia, inherited as an autosomal dominant disorder, is characterized by episodic severe neutropenia on an approximately 21-day cycle. Episodes typically last 4 to 6 days.[18] Affected children are more likely to experience fevers and non–life-threatening infections such as stomatitis, pharyngitis, cellulitis, otitis media, and lymphadenitis. They are also at high risk for more profound infections.

For the otherwise healthy child with acute, asymptomatic neutropenia identified on routine CBC, close outpatient observation and serial blood counts are usually performed. Consult hematology for children with persistent neutropenia, concern for a heritable cause of neutropenia, neutropenia associated with syndromic features on clinical exam, or serious pyogenic infections associated with neutropenia.

Fever in children with neutropenia, regardless of etiology, must be treated as a medical emergency with broad-spectrum antibiotics.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 145

Oncologic Emergencies in Infants and Children

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Megan Mickley

Children and adolescents develop different types of cancers than adults. The 5-year survival rate for all childhood (0 to 19 years of age) cancers in the United States has been steadily increasing and is currently 83% to 84%[1]; however, malignant neoplasms remain the second leading cause of death for U.S. children age 5 to 14 years.[2] The most common childhood malignancies are discussed below.

LEUKEMIA

EPIDEMIOLOGY

Acute leukemias, including acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML), are the most common cancers in children, accounting for over a quarter of all malignancies.[3-6] Chronic leukemias are rare in children and adolescents. ALL accounts for approximately 75% to 80% of pediatric leukemias and, if diagnosed early, carries a 5-year survival rate of 85% to 90% in developed countries.[4-7] The peak incidence of ALL is 3 to 5 years of age, with younger children having the best outcomes.[8] In the United States, ALL is more common in boys and more common in white and Hispanic children than in African American children.[2-5] A number of inherited risk factors, including trisomy 21, are well documented.

AML accounts for approximately 15% to 20% of childhood and adolescent leukemias in the United States.[4,6,9] Cure rates have improved to 57% to 70% but remain lower than those for ALL. Relapsed AML accounts for greater than half of all childhood leukemia-related deaths.[4,9] Incidence of AML peaks in the first 2 years of life.[4,6] Environmental exposures, including chemotherapy agents and radiation received during treatment of other childhood cancers, are known causes of secondary AML. Patients being treated for AML have a higher incidence of complications than those with ALL, especially infections. This is primarily due to the greater intensity of chemotherapeutic regimens necessary to achieve remission.

CLINICAL FEATURES

Most signs and symptoms of acute leukemia are due to bone marrow infiltration by blasts, as well as infiltration of extramedullary sites. A detailed history may reveal nonspecific constitutional symptoms: fever, fatigue, anorexia, and weight loss. **Cytopenias from marrow infiltration can present as pallor, easy bleeding/bruising with petechiae and ecchymoses, infections, or bone pain. The reticuloendothelial system is the most common site of extramedullary infiltration, manifesting as hepatomegaly, splenomegaly, and/or lymphadenopathy**. Other sites include the CNS and testes.

Consider leukemia in cases of recurrent or severe unexplained epistaxis or other mucosal bleeding or in children with unusually extensive or abnormally located bruising. Concerning symptoms include abnormal blood counts, a history of nighttime pain, and recurrent or persistent bony complaints.[10] Bone and joint pain may present as limping or refusal to walk. In rare cases of AML, solid nodules of leukemic blasts (chloromas) may be noted, most commonly in the skin (leukemia cutis) or gingiva. For a subset of patients, diagnosis is made incidentally during an evaluation for infection, lymphadenopathy, priapism, or other presentations.

DIAGNOSIS

Evaluate suspected leukemia with a CBC with differential count, a peripheral smear, a coagulation profile, a type and screen, and serum chemistries including calcium, phosphate, magnesium, uric acid, liver function studies, and lactate dehydrogenase. Obtain a chest radiograph, because some children with T-cell ALL can have an anterior mediastinal mass of leukemic cells. If fever or clinical suspicion of infection is present, obtain a blood and urine culture. **Although almost all children with leukemia have some form of hematologic abnormality including anemia, thrombocytopenia, leukocytosis, or neutropenia, very few have an extremely elevated WBC.** Total WBC counts are often normal or only moderately elevated. Hyperleukocytosis is more likely in patients with AML and in infants with either ALL or AML.[11] Definitive diagnosis requires a bone marrow aspirate.

The differential diagnosis of children with marrow suppression includes aplastic anemia, profound iron deficiency anemia (commonly noted in toddlers with excessive milk intake), viral infections (e.g., Epstein-Barr virus, cytomegalovirus, parvovirus B19), primary immune thrombocytopenia, and rheumatologic diseases. A good rule of thumb is that leukemias commonly involve abnormalities in more than one cell line, whereas other conditions are often restricted to a single cell line.

TREATMENT

The goal is to induce remission while minimizing treatment toxicity. Taking into consideration age and leukocyte count at the time of diagnosis, as well as other risk factors (e.g., genetic abnormalities of leukemic cells with important prognostic significance), children with ALL are usually stratified into different treatment groups.[12] Children with AML receive intensive multiagent chemotherapy. Some receive hematopoietic stem cell transplantation. Molecularly targeted therapeutic approaches are in development.[13,14]

DISEASE COMPLICATIONS

Most children suspected of having leukemia are stable and receive an initial diagnostic workup (see "Diagnosis" section) but no acute treatment. Occasionally, acute treatment is needed for cytopenias, hyperleukocytosis, coagulopathy, electrolyte abnormalities, and infection. Initiate treatment after consultation with a pediatric oncologist.

Anemia Anemia is extremely common and multifactorial, including impaired hematopoiesis due to leukemic marrow infiltration, decreased erythropoietin levels, iron deficiency, hemolysis, occult blood loss, and chronic inflammation. There is no universally recommended threshold for transfusion, and in the ED, the decision to transfuse should depend more on the appearance and clinical condition of the child than on any particular laboratory value.[15] Life-threatening hemorrhage, symptomatic anemia, or rapidly consumptive coagulopathy requires transfusion, with the addition of factor replacement as needed. The general goals of transfusion therapy are to raise the hemoglobin level to >8 to 10 grams/dL, depending on the child's condition.[8] However, in the setting of profound anemia and hyperleukocytosis, transfuse to a much lower level to minimize the effect on blood viscosity. The exact numbers will often depend on institutional protocols (see discussion on transfusion under "Blood Products").

Thrombocytopenia Mild to moderate bruising, petechiae, and/or mucosal bleeding may occur with platelet counts <20,000/mm^3, but the risk of spontaneous intracranial hemorrhage is extremely low until the platelet count dips to <5000/mm^3. **Most protocols reserve prophylactic platelet transfusions in asymptomatic patients to platelet counts <10,000/mm^3 in the absence of other bleeding risk factors. Invasive procedures require a platelet count >40,000 to 50,000/mm^3.**[16]

Blood Products A unit of packed red blood cells has a volume of about 250 mL and a hematocrit of 70% to 80%. The typical volume of packed red blood cells given to a child is 10 to 15 mL/kg. Generally, 10 mL/kg of packed red blood cells are expected to raise the hemoglobin level 3 grams/dL in a patient without active hemorrhage.

A dose of platelets is 0.1 unit/kg random donor equivalent units and is expected to raise the platelet count by 30,000 to 50,000/mm^3.[8,17] Some institutions release platelets as single apheresis units versus random donor units. Platelets express ABO antigens, and even though platelets do not express Rh antigens, Rh-negative donors are used for Rh-negative patients because red blood cell contamination may result in Rh alloimmunization. Rh immunoglobulin can be given if Rh-negative platelets are unavailable. Institutions vary on the use of type-specific platelets and the need for Rh immunoglobulin (**Table 145-1**).

There are several product choices for packed red blood cells and platelets: irradiated, leukocyte reduced, and cytomegalovirus seronegative (**Table 145-2**). Irradiation of blood products is recommended for profoundly immunosuppressed individuals (e.g., severe immunodeficiency, high-dose chemotherapy, post–bone marrow transplant). Many pediatric cancer centers will transfuse only irradiated blood to *all* oncology patients. Consult with the pediatric oncologist for specific directions before administering blood products.

Hyperleukocytosis is a WBC >100,000/mm^3. Leukocytosis can cause leukostasis, tumor lysis syndrome, and disseminated intravascular coagulation.[18] **Leukostasis is a clinical diagnosis.** Intravascular aggregations of leukocytes lead to injury of many organs, most commonly the

TABLE 145-1 Transfusion of Blood Products in Children

Blood Product Component	Volume	Dose	Typical Transfusion Goals*
Packed red blood cells	Citrate phosphate dextrose adenine, 1 unit = 250 mL†	10 mL/kg increases Hb by 3 grams/dL	Hb, 8–10 grams/dL
	Adsol, 1 unit = 350 mL†	12.5–15.0 mL/kg increases Hb by 3 grams/dL	
Platelets	One apheresis unit = 200–400 mL‡	0.1 unit/kg increases platelets by 30,000–50,000/mm^3	50,000–100,000/mm^3
Fresh frozen plasma	1 unit = 200–250 mL (centrifuged)	20 mL/kg will replace ~50% of most coagulation factors	
	1 unit = 500 mL (apheresis)		
Cryoprecipitate	1 unit = 15 mL	0.1 unit/kg increases fibrinogen by ~50 milligrams/dL#	Fibrinogen, 100 milligrams/dL
	1 unit = 80–100 units factor VIII		
	1 unit = 150–200 milligrams fibrinogen		

Abbreviation: Hb = hemoglobin.

*Varies by clinical circumstance.

†The volume in a single unit of packed red blood cells depends on the additive/preservative used.

‡The random donor platelet unit is used when there is a shortage of apheresis units. A single random donor unit contains a volume of 50 to 70 mL. One apheresis unit = 6–8 random donor units.

#In the absence of ongoing bleeding.

lungs and CNS. In the cerebral circulation, symptoms and signs include headache, mental status changes, visual changes, seizures, and stroke (ischemic and hemorrhagic), whereas in the pulmonary circulation, leukostasis can cause dyspnea, hypoxemia, and respiratory failure. Chest radiographs may be normal or may show a diffuse, nonspecific interstitial infiltrate. AML patients are especially at risk because their leukemic blasts are larger, "stickier," and more rigid.

ED treatment consists of aggressive IV hydration and treatment of tumor lysis syndrome (see discussion in "Tumor Lysis Syndrome" section and Table 145-4). **Avoid treatments that increase blood viscosity such as diuretics and packed red blood cell transfusions.** Platelets do not increase blood viscosity and should be administered for levels <20,000/mm^3 to decrease the risk of cerebral hemorrhage. Leukapheresis is a temporizing measure until definitive antileukemic therapy can be given.

Disseminated Intravascular Coagulation Disseminated intravascular coagulation is commonly associated with AML. Some subtypes release a procoagulant tissue factor that can lead to a life-threatening consumptive coagulopathy. ED treatment includes replacement of platelets, depleted coagulation factors, fibrinogen with fresh frozen plasma, and cryoprecipitate.

HODGKIN'S LYMPHOMA

EPIDEMIOLOGY

Hodgkin's lymphoma is a lymphoid neoplasm characterized by progressive enlargement of lymph nodes. Age distribution is bimodal, with peaks in young adulthood and older-aged adults. It is the most common malignancy in adolescents age 15 to 19 years.[4] Risk factors include Epstein-Barr virus (particularly in developing countries) and human immunodeficiency virus.

CLINICAL FEATURES AND DIAGNOSIS

Hodgkin's lymphoma typically presents with painless, firm, "rubbery" lymph nodes, usually cervical or supraclavicular (**Figure 145-1**). If empiric antibiotics are prescribed for presumptive cervical adenitis, the mass continues to increase in size. The lack of overlying erythema and the absence of pain suggest lymphoma. **Systemic "B" symptoms (fever >38°C [100.4°F], night sweats, and weight loss ≥10% over 6 months) are present in 39% to 50% of children and adolescents.**[19,20] Two thirds of pediatric patients will present with mediastinal involvement, which may manifest as cough, stridor, dysphagia, or dyspnea.[21] Hepatomegaly or splenomegaly can be found due to hematogenous spread. Initial ED diagnostic studies should include lab evaluation similar to that of ALL, with the addition of a chest radiograph. Diagnosis is confirmed by lymph node biopsy. A CT of the soft tissues of the neck, chest, abdomen, and pelvis will help delineate the extent of disease. Subdiaphragmatic primary disease is uncommon; more than 97% of Hodgkin's lymphoma patients present with a lesion above the diaphragm.[20]

The differential diagnosis of cervical lymphadenopathy is extensive. See Chapter 125, "Neck Masses in Infants and Children."

TREATMENT

ED treatment before confirmatory diagnosis is usually directed at acute complications such as superior vena cava syndrome or upper airway compression (see "Complications of Pediatric Cancer and Oncologic Emergencies" section). **Use caution with sedation, given the risk of airway compromise with mediastinal involvement. Do not give steroids to patients with significant lymphadenopathy if lymphoma is in the differential diagnosis.** Following risk categorization, therapeutic management of Hodgkin's lymphoma incorporates chemotherapy and radiotherapy.

TABLE 145-2 Blood Component Therapy

Treatment	Description	Goal	Target Recipient
Leukodepleted blood	99.9% reduction in donor WBCs	Reduces incidence of febrile nonhemolytic transfusion reactions Decreases sensitization to HLA-1 antigens Significantly reduces transmission of CMV*	Patients likely to receive multiple platelet or packed red blood cell transfusions in future
CMV-seronegative blood	Gold standard for CMV-negative blood	Eliminates transmission of CMV*	Patients at high risk for CMV-related complications now or in the future
Irradiated blood	Destroys donor lymphocytes' ability to multiply	Prevent transfusion-associated graft-versus-host disease from donor WBCs (does not prevent CMV transmission)	Profoundly immunocompromised patients Stem cell transplant patients

Abbreviations: CMV = cytomegalovirus; HLA-1 = human leukocyte antigen 1.

*Patients at high risk for CMV-related complications include patients receiving stem cell or solid organ transplants and the severely immunocompromised.



FIGURE 145-1. Hodgkin's lymphoma. A 13-year-old adolescent male presented with a painless, rubbery, firm cervical lymphadenopathy of 4 months' duration. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]

NON-HODGKIN'S LYMPHOMA

EPIDEMIOLOGY

Non-Hodgkin's lymphoma accounts for 7% of cancer in children and adolescents in the United States, with a male predominance but little variation by age.[1] Non-Hodgkin's lymphoma includes a heterogeneous group of malignant neoplasms that can originate not only in the lymphatic system but also in almost any organ in the body, including the skin, cortical bone, GI tract, and CNS. The majority of cases have no known cause, although immunodeficiencies and previous exposure to immunosuppressive agents are known risk factors. In equatorial Africa, non-Hodgkin's lymphoma accounts for almost 50% of childhood cancers and is almost universally associated with Epstein-Barr virus.[22]

CLINICAL FEATURES AND DIAGNOSIS

The clinical presentation depends on the site and extent of disease. Constitutional symptoms are not common. Lymphadenopathy, a mass in virtually any location, hepatosplenomegaly, and cytopenias can all be seen. GI manifestations occur with abdominal tumors (usually Burkitt's lymphoma). Mediastinal involvement may lead to pleural or pericardial effusions, upper airway obstruction from mass effect, respiratory symptoms, or superior vena cava syndrome. Testicular, skin, and CNS or spinal manifestations are seen, but less commonly. The differential diagnosis is broad and includes infectious (tuberculosis, toxoplasmosis, Epstein-Barr virus, *Bartonella henselae*, human immunodeficiency virus) and oncologic (Hodgkin's lymphoma, leukemia, rhabdomyosarcoma) processes. Diagnosis is by lymph node biopsy.

TREATMENT

Initial workup should include basic laboratory studies and a chest radiograph to evaluate for mediastinal disease. If there is concern for intra-abdominal obstruction (bowel or ureteral), US or abdominal/pelvic CT may be indicated. A chest CT can further evaluate for chest mass or superior vena cava syndrome. The mainstay of treatment is multiagent chemotherapy.

CENTRAL NERVOUS SYSTEM TUMORS

EPIDEMIOLOGY

CNS tumors are the second most common pediatric cancer, accounting for approximately 21% of all childhood cancer diagnoses.[4] **They are also the leading cause of cancer-related death in children,** with survival rates lowest for young children.[23,24] For the emergency physician, the specifics of the tumor type are less important than tumor location and clinical effects.

The three most common categories of pediatric CNS tumors are astrocytomas, medulloblastomas, and ependymomas. Specific genetic syndromes, including neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome, are predisposing factors. CNS tumors can also be secondary to high-dose cranial radiation for a previously treated childhood cancer.

CLINICAL FEATURES AND DIAGNOSIS

There is heterogeneity in the presentation of CNS neoplasms depending on the extent of the tumor, its location, and the age of the child. In children, tumors are more often infratentorial than supratentorial. Symptoms are often nonspecific (headache, irritability, emesis, behavioral changes), which can delay diagnosis.

The classic presentation of a posterior fossa tumor or other tumors causing obstructive hydrocephalus is **early morning headache and subsequent vomiting.** These symptoms are believed to be due to a rise in intracranial pressure during sleep caused by increased cerebral blood volume in the recumbent position as well as hypoventilation with resultant hypercarbia and increased cerebral blood flow. Additional clinical signs such as a bulging fontanelle, rapidly increasing head circumference in an infant, sunsetting (preferential downward gaze due to obstructive dilatation of the third ventricle with resultant tectal pressure and paresis of upward gaze), cranial nerve palsies (usually sixth nerve), papilledema, or somnolence also suggest increased intracranial pressure.[25] Infiltration of the brainstem can produce cranial nerve deficits, long tract corticospinal motor weakness, and cerebellar ataxia.

Symptoms of supratentorial neoplasms are dictated by location and may include headache, declines in school performance, personality changes, motor weakness, and seizures. Craniopharyngiomas arise in the sellar region and produce visual changes due to their proximity to the optic chiasm, as well as significant endocrinologic abnormalities from hypothalamic dysfunction (including diabetes insipidus, stunted growth and sexual development, and hypothyroidism).

Most CNS malignancies are identifiable on CT, but MRI provides superior visualization of tumors, particularly in the posterior fossa.

TREATMENT

Treatment of the most serious and life-threatening brain tumor threat—increased intracranial pressure leading to herniation—is addressed in the section "Complications of Pediatric Cancer and Oncologic Emergencies." In the ED setting, manage acute seizures and consider giving IV dexamethasone to treat vasogenic edema surrounding the tumor. Consult with neurosurgery and pediatric oncology to arrange definitive treatment.

NEUROBLASTOMA

EPIDEMIOLOGY

Neuroblastoma is a malignant tumor that arises from primitive ganglion cells of the sympathetic nervous system. It accounts for 7% of all childhood cancers and is the most common neoplasm in the first year of life.[4]

CLINICAL FEATURES

The clinical features are highly variable and depend on tumor size and location. Neuroblastoma may arise anywhere along the sympathetic nervous system. The adrenal gland is the most common primary site, but it may also arise from other intra-abdominal sites, the chest, or the neck. Metastasis is quite common to adjacent lymph nodes, liver, skin, bone, and bone marrow.[26]

The variability in tumor location and extent explains the array of signs and symptoms that may lead to the diagnosis of neuroblastoma.

Painless abdominal masses can lead to compression of the bowel, bladder, venous, or lymphatic structures. Compression from thoracic masses can cause respiratory distress or superior vena cava syndrome, while paravertebral tumors can invade the spinal canal, causing spinal cord compression. Horner's syndrome (ptosis, miosis, and anhidrosis) may result from disease involving the superior cervical ganglion.

Unique presentations of neuroblastoma that require a high index of suspicion include proptosis and periorbital ecchymoses ("raccoon eyes") or swelling, characteristic of orbital metastases. Opsoclonus-myoclonus is a paraneoplastic syndrome also highly associated with occult neuroblastoma.

DIAGNOSIS AND TREATMENT

Obtain basic laboratory studies. Cytopenias suggest bone marrow involvement. Radiographs, US, or CT may detect an intra-abdominal or thoracic mass. Because neuroblastomas often lead to increased levels of catecholamines, the metabolites of which are detectable in the urine, urine homovanillic acid and vanillylmandelic acid can aid in diagnosis. Bone marrow and tumor biopsies confirm the diagnosis.

Treatment includes surgical resection and/or radiation therapy and chemotherapy. Select patients undergo stem cell transplant.

WILMS' TUMOR (NEPHROBLASTOMA)

EPIDEMIOLOGY

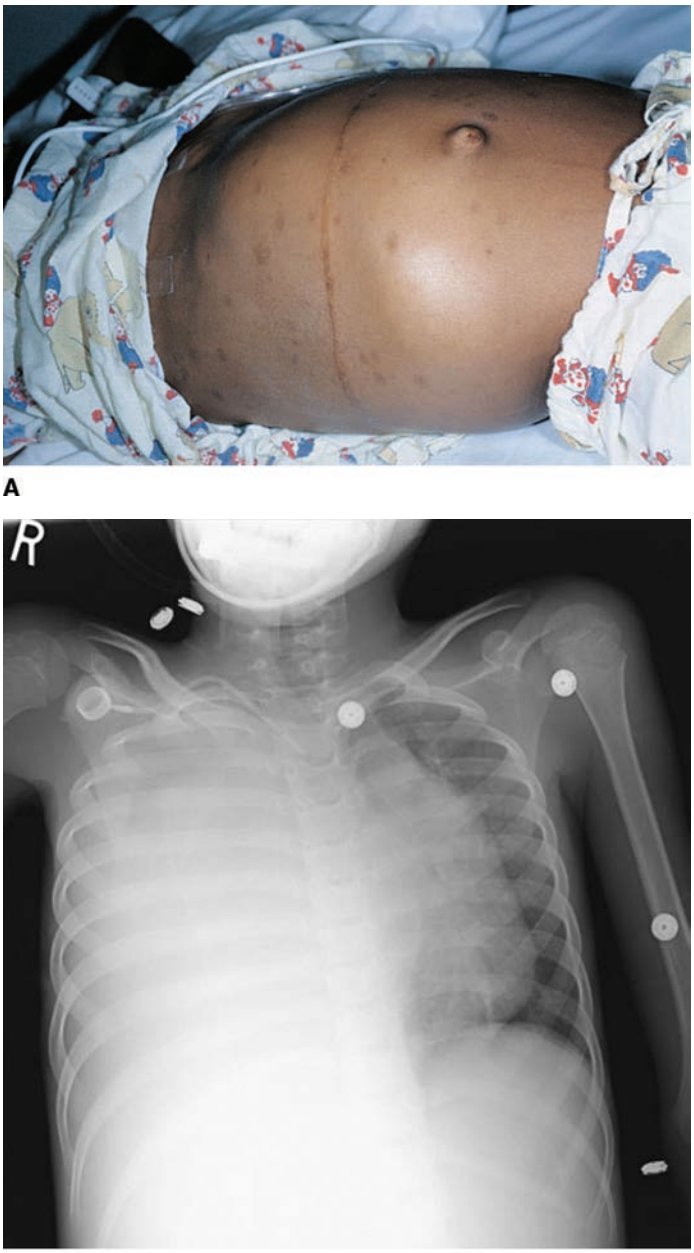
Wilms' tumor, or nephroblastoma, is a malignant embryonal renal tumor that affects children predominantly under the age of 5 years.[4] Overall survival rates are excellent, at approximately 90%.[27]

CLINICAL FEATURES

The classic presentation of Wilms' tumor is an asymptomatic abdominal mass, sometimes noted while dressing or bathing the child. As opposed to neuroblastoma (given that the age group and abdominal mass at the time of presentation can be similar), children often appear remarkably well with no systemic symptoms. Hypertension due to increased renin production is present in 25% of cases.[28] There can be mass effect from the tumor, leading to respiratory distress or intra-abdominal obstruction. Less common symptoms include anorexia, weight loss, emesis, or hematuria. Metastases at the time of diagnosis are uncommon but can occur to the lungs, liver, or lymph nodes.

DIAGNOSIS AND TREATMENT

Obtain basic laboratory studies, urine catecholamines to rule out neuroblastoma, and urinalysis. Obtain a chest radiograph to identify pulmonary metastases (**Figure 145-2**). Ultrasonography is appropriate for initial abdominal imaging in the ED, although **vigorous or excessive palpation of the mass can cause tumor rupture**. CT or MRI identifies the extent of the disease. Definitive treatment is surgical resection and chemotherapy, with or without radiation therapy.



A

B

FIGURE 145-2. Wilms' tumor. **A.** A 7-year-old child presented with a huge abdominal mass and respiratory distress. Pelvic CT scan followed by laparotomy confirmed the mass as Wilms' tumor. Because of the retroperitoneal location of the kidney, these tumors can be quite large at diagnosis without significant impingement of other vital structures. **B.** Right-sided pleural effusion due to metastatic disease. Almost complete opacification of the right hemithorax with mediastinal shift to the left. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]

RETINOBLASTOMA

EPIDEMIOLOGY

Retinoblastoma is the most common pediatric intraocular malignancy, with 90% of cases diagnosed in children <3 years old.[29] There are both heritable and nonheritable forms. The retinoblastoma (*RB*) gene was the first tumor suppressor gene discovered in the human genome.[30] Heritable forms are usually due to a germline mutation in the *RB1* gene and present within the first year of life with bilateral disease. The majority of cases of nonheritable disease are unilateral.

CLINICAL FEATURES

Leukocoria ("white pupil"), in which the white light reflects off of the tumor instead of red light reflecting off of the retina, is the most common presenting sign (see Figure 122-12). This may be noted by a primary physician or occasionally by family members when they note the leukocoria in photographs. Other signs may include strabismus, decreased visual acuity, redness, pain, glaucoma, and proptosis (late stage). Young children do not often report visual complaints. The retinoblastoma can spread into the surrounding orbit, as well as metastasize into the CNS and viscera.[31]

DIAGNOSIS AND TREATMENT

If leukocoria or other signs suggestive of an intraocular tumor are noted, consult ophthalmology in the ED. Definitive diagnosis is usually

obtained by exam and imaging under anesthesia. Obtain a CT or MRI if there is evidence of orbital inflammation. Treatment options depend on the extent of the disease and include enucleation, chemotherapy, cryotherapy, brachytherapy, thermotherapy, radiotherapy, and laser photocoagulation.[32]

GERM CELL TUMORS

EPIDEMIOLOGY

Germ cell tumors are a heterogenous group of neoplasms that can develop at any age, although they are more common in adolescents and young adults.[4] Extragonadal tumor locations, including sacrococcygeal, mediastinal, and intracranial, are more common in young children, whereas during and after puberty, the primary location is the gonads.[33]

Testicular germ cell tumors are the most common solid tumor in young adult men (**Figure 145-3**).[34] **An undescended testicle increases the risk for testicular cancer 10- to 50-fold.**[35] Prognosis for these tumors is extremely good, even if metastases are present, with an overall cure rate of 85% to 90%.[34] Despite that fact, they remain a significant cause of death in young males. This highlights the importance of encouraging young male patients to perform testicular self-examinations.

The median age of diagnosis for ovarian germ cell tumors is 16 to 20 years.[36] Due to the intra-abdominal location, ovarian tumors may go undetected for a longer amount of time than testicular tumors; this increases the potential for rupture.[37]

CLINICAL FEATURES

Testicular tumors typically present with an asymptomatic, nontender testicular mass. Ovarian tumors are most likely to present with abdominal pain (85%).[36] Other ovarian symptoms include abdominal distention, vaginal bleeding, and weight gain. Ten percent of patients with ovarian tumors presenting with abdominal pain from tumor rupture, hemorrhage, or torsion are misdiagnosed.[36] Tumors can metastasize, most commonly to the lymph nodes, liver, lungs, and CNS. Thus, it is important to complete a genitourinary exam on any patient presenting with lymphadenopathy or chronic pulmonary symptoms.

DIAGNOSIS AND TREATMENT

A testicular mass or abdominal mass may be palpated upon exam. Ultrasonography often identifies an ovarian or scrotal mass, whereas CT delineates the extent of disease. Serum tumor markers can be added to the basic laboratory tests. Treatment includes resection, chemotherapy, and/or radiotherapy. Given that many patients are of reproductive age, treatment attempts to preserve fertility if possible.

BONE AND SOFT TISSUE SARCOMAS

The term *sarcoma* refers to a diverse group of malignant neoplasms derived from mesenchymal cell origin that can arise from virtually any location at any age. Sarcomas are divided into two main types: soft tissue sarcomas and bone sarcomas. There are over 70 recognized subtypes. The most common subtypes diagnosed in pediatrics are rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma.

RHABDOMYOSARCOMA

Rhabdomyosarcoma accounts for 3% of childhood cancers and 2% of adolescent cancers.[4] Risk factors include a number of inherited cancer predisposition syndromes (e.g., Li-Fraumeni, neurofibromatosis type 1). The embryonal subtype (>75% of cases) is most common in children <5 years old, tends to occur in the head and neck, and has a better prognosis. The alveolar subtype can occur at any age, is more aggressive, and is commonly found in the trunk or extremities. Orbital rhabdomyosarcoma accounts for 10% of all rhabdomyosarcoma cases.[30]

Signs and symptoms depend on location, but a painless mass is characteristic. Evaluation in the ED may begin with ultrasonography. More extensive evaluation steps are determined by the oncologist. Treatment includes a combination of surgical excision, chemotherapy, and radiotherapy.

OSTEOSARCOMA

Osteosarcoma, also called *osteogenic sarcoma*, is the most common primary pediatric bone tumor and is among the most frequent causes of cancer-related death.[38] Incidence peaks in adolescence, particularly during a growth spurt. It can occur in any bone, but the majority of cases arise from the metaphyses of long bones. Over half of cases originate near the knee joint, either at the distal femur or at the proximal tibia.[39] Twenty percent of patients have metastases at the time of diagnosis, most commonly in the lungs, followed by bone.[4] Previous radiation during treatment for a different pediatric neoplasm increases the risk of osteosarcoma.

Nonspecific symptoms can lead to a delay in diagnosis. The most common presentation is an adolescent with **persistent bone pain that worsens at night or with activity**. Soft tissue swelling may be noted on exam.

Diagnosis is suggested by plain radiography, demonstrating a lytic lesion with cortical destruction near the metaphysis (**Figure 145-4**). The classic radiographic finding is the "sunburst" appearance of periosteal reaction. Pathologic fracture is an uncommon presentation.[40] The differential diagnosis of radiographically similar lesions includes Ewing's sarcoma as well as more benign lesions. Diagnosis is by biopsy, and

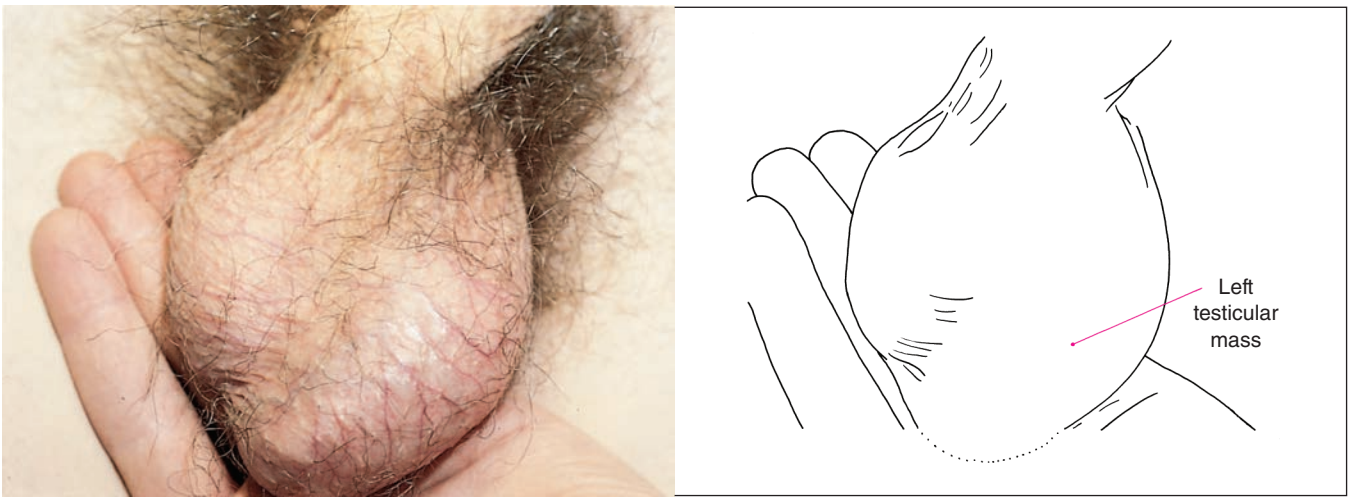


FIGURE 145-3. Testicular tumor. This patient presented with a painless left testicular mass highly suspicious for cancer. [Photo contributed by Patrick McKenna, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]



FIGURE 145-4. Osteosarcoma. Note the lytic femoral lesion with cortical destruction.



FIGURE 145-5. Ewing's sarcoma. Note the destruction of the proximal fibula.

treatment includes chemotherapy and limb-sparing surgery. Osteosarcoma is radiation resistant.

EWING'S SARCOMA

Ewing's sarcoma is an aggressive tumor of uncertain origin that can occur in the bone or soft tissues. It is more common in older children and adolescents, but the incidence is half that of osteogenic sarcoma.[41] Hematogenously spread metastases are present in approximately 25% of patients at the time of diagnosis and are most commonly located in the lungs, bone, and bone marrow.[4] Metastatic disease is the most significant prognostic factor.[42]

Ewing's sarcoma typically presents with persistent pain at the tumor site. Tenderness or swelling may be noted on physical exam. The long bones (femur, tibia, humerus) and the axial skeleton (pelvis, ribs, spine) are the most common sites of disease.

Plain radiographs of the primary tumor site may reveal the characteristic "moth-eaten appearance" of the destructive lesion or the "onion peel" appearance of the periosteal reaction (**Figure 145-5**). Diagnosis is by biopsy, and treatment is multidisciplinary, including chemotherapy and radiotherapy or surgery.

COMPLICATIONS OF PEDIATRIC CANCER AND ONCOLOGIC EMERGENCIES

For the child with cancer, the road to recovery is inevitably interrupted by complications. These complications can be generally classified as **infectious** (e.g., fever and neutropenia), **metabolic** (including tumor lysis syndrome, hypercalcemia, and the syndrome of inappropriate antidiuretic hormone secretion), and **structural** (superior vena cava syndrome, spinal cord compression, and increased intracranial pressure).

INFECTION

Most pediatric cancer patients experience an infectious complication over the course of the illness. Neutropenia is usually seen as an effect of cytotoxic therapy,[43] and many treatment protocols produce profound myelosuppression.

In the context of a febrile cancer patient, "neutropenia" is defined as an absolute neutrophil count <500/mm^3 or an absolute neutrophil count <1000/mm^3 with a predicted decline. Relative risk of infection is highest at this time. **The absolute neutrophil count nadir typically occurs 5 to 10 days after chemotherapy.**

Fever will occur in up to one third of neutropenic episodes, with a rate of documented infection between 10% and 40%. **Fever in this setting is conservatively defined as a single oral temperature >38.3°C (101°F) or multiple temperatures ≥38.0°C (100.4°F) separated by more than 1 hour.[43] Avoid rectal temperatures due to the risk of bacteremia induced by rectal trauma.**

Many patients will not demonstrate a source of fever. Neutropenia, or a decrease in the ability to mount an inflammatory response, limits the development of infectious signs such as abscess, pulmonary infiltrates, or severe abdominal pain. Therefore, perform a meticulous physical examination with close attention to areas of pain, mucosal barriers, and the central line site. Chemotherapeutic regimens that produce profound neutropenia can cause severe mucositis with oral and/or perianal mucosal breakdown.

Typhlitis, or neutropenic enterocolitis, warrants particular attention (**Figure 145-6**). Inflammation usually involves the ileocecal region. The presentation can be as subtle as mild abdominal pain, and **the physical exam may be relatively unrevealing; however, maintain a high index of suspicion for infection**. Other signs and symptoms include fever, nausea, emesis, right lower quadrant pain, abdominal distention, and watery or bloody diarrhea. Due to bowel wall necrosis, bowel perforation with resulting pneumatosis intestinalis is possible. Bacteremia is common and is often polymicrobial.[44]

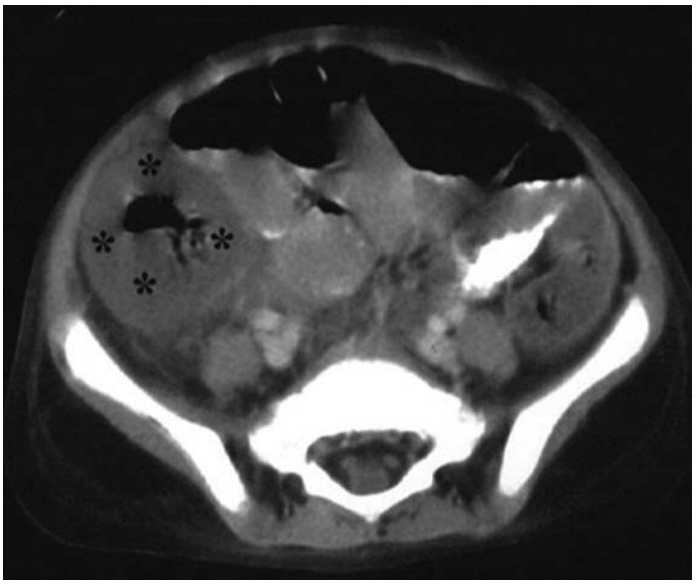


FIGURE 145-6. Neutropenic enterocolitis. *Asterisks* indicate inflamed and thickened bowel wall.

ED TREATMENT

Children with fever history (even if afebrile upon presentation) and potential for neutropenia require **immediate clinical evaluation**, acquisition of appropriate laboratory studies and cultures, and prompt administration of broad-spectrum antibiotics. **Table 145-3** summarizes management of neutropenic fever, including the 2017 updated recommendations from the International Pediatric Fever and Neutropenia Guideline Panel.[45] Individual recommendations may differ across institutions. **Administration of antibiotics in patients at high risk of neutropenia should not wait for laboratory confirmation of neutropenia.**

Obtain blood cultures, if at all possible, before administering empiric antibiotics. Anaerobic cultures are very low yield, and many institutions do not require them unless there are specific concerns for an anaerobic infection. If a clean-catch, midstream urine specimen is available, obtain urinalysis and urine culture because febrile neutropenic patients with urinary tract infection are often otherwise asymptomatic.[46] Other diagnostic studies are patient specific (e.g., chest radiograph, stool cultures, abdominal imaging, lumbar puncture).

As shown in Table 145-3, empiric therapy for febrile neutropenia begins with broad-spectrum antibiotics directed at the most common pathogens. Antibiotic coverage can be tailored to the specific clinical situation and institutional resistance patterns and then be narrowed as more data become available. Given the high prevalence of central venous lines in this population, greater than 50% of bacteremias in neutropenic patients are caused by gram-positive bacteria.[18] The most common gram-positive organisms are coagulase-negative staphylococci, *Streptococcus viridans*, *Staphylococcus aureus*, and enterococci. Gram-negative organisms, however, are known to be particularly virulent and have an association with sepsis. Intestinal flora provide the source of gram-negative organisms, including *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, and *Enterobacter* species.[47] Special infectious considerations include treatment for possible *Pneumocystis carinii* in the immunocompromised patient with respiratory symptoms and broader anaerobic coverage for those suspected of having typhlitis or mucositis. Although some cancer patients (particularly those with AML, with relapsed leukemia, or undergoing stem cell transplant) are at high risk for fungal infections, there is little indication for beginning antifungal agents in the ED.[45] Septic patients require immediate, broad-spectrum antipseudomonal antibiotic therapy in addition to vancomycin for coverage of gram-positive organisms. Consider adding a second agent with activity against gram-negative organisms (e.g., gentamicin) in critically ill patients.

Careful monitoring and reevaluation are essential once treatment has begun. There is recent literature regarding risk stratification of pediatric patients to determine who can safely be treated as an outpatient. The majority of patients with fever and true neutropenia, however, are admitted to the hospital. The decision to discharge should only be made in consultation with the oncologist.

TABLE 145-3 Management of Neutropenic Fever

Definition of neutropenia
- Absolute neutrophil count (segs + bands) <500/mm^3
- Absolute neutrophil count <1000/mm^3 and expected to decrease*

Definition of fever†
- Oral temperature ≥38.3°C (100.9°F) once

  Or
- Oral temperature ≥38°C (100.4°F) >2 times, measured 1 h apart

Caveats
- Some add 0.5°C (1.0°F) to axillary temperatures for oral equivalent
- Confirm with oral temperature when possible
- Avoid rectal temperatures
- Parental history of objective fever is sufficient

Cultures‡
- One culture from each central line lumen (label appropriately)
- Peripheral culture in absence of central line or if recommended by oncologist
- Consider urine culture and urinalysis (clean catch or bagged)

Antibiotics#

Well-appearing[f]
- Broad-spectrum antipseudomonal monotherapy with β-lactam or carbapenem
- Cefepime, 50 milligrams/kg (maximum dose, 2 grams), or ceftazidime, 50 milligrams/kg (maximum dose, 2 grams), or piperacillin-tazobactam, 80 milligrams/kg (maximum dose, 3.375 grams)[§]

Clinically unstable, suspected resistant infection, or center with high rate of resistant pathogens
- Addition of second gram-negative agent and/or glycopeptide:
- As above + gentamicin, 2.5 milligrams/kg, and/or vancomycin, 15 milligrams/kg (maximum, 1 gram)

Abdominal/perirectal pain
- As above + metronidazole, 7.5 milligrams/kg (maximum, 1 gram)

*Based on serial measurements or history of chemotherapy in the previous 5–10 days.

†Definitions will vary by institution.

‡Most patients will require only aerobic cultures. Consider anaerobic cultures if significant GI symptoms or visible mucositis.

#Do not wait for absolute neutrophil count results if patient is *expected* to be neutropenic.

[f]Indications for the addition of vancomycin include relapsed acute lymphoblastic leukemia or acute myelogenous leukemia patients, significant mucositis, evidence of skin or soft tissue or line infections, and presence of orthopedic appliances.

[§]Ceftazidime monotherapy should not be used if there are concerns for gram-positive or resistant gram-negative infections. Use vancomycin + aztreonam for cephalosporin-allergic patients.

METABOLIC COMPLICATIONS

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is a constellation of metabolic derangements resulting from the rapid turnover of tumor cells with cell lysis and subsequent release of intracellular potassium, phosphate, and uric acid. Tumor lysis syndrome is associated with rapidly proliferating malignancies, cancers with a high tumor burden, and cancers that are highly sensitive to chemotherapy such as ALL (with hyperleukocytosis), Burkitt's lymphoma, and non-Hodgkin's lymphoma. It is most commonly precipitated by the induction of chemotherapy, but it can also be present at the time of diagnosis. Symptoms are variable but can be lifethreatening, including cardiac dysrhythmias, seizures, and acute renal failure.[43]

The large quantity of intracellular contents released into the circulation can easily overwhelm the excretory capacity of the kidneys. The metabolic derangements, including hyperkalemia, hyperuricemia,

TABLE 145-4 Initial Management of Tumor Lysis Syndrome

Labs (repeat every 4–8 h)

- CBC
- Electrolytes
- Renal function studies
- Calcium, phosphate, magnesium
- Uric acid, lactate dehydrogenase
- Urinalysis
- ECG
- IV fluids, often at >2× maintenance

Specific therapies, if indicated

- Hyperuricemia: allopurinol, 100 milligrams/m^2, or rasburicase,* 0.2 milligram/kg
- Symptomatic hypocalcemia: calcium gluconate
- Hyperkalemia: calcium/dextrose/insulin/bicarbonate
- Poor urine output: loop diuretic†

*Contraindicated in glucose-6-phosphate dehydrogenase deficiency.

†Patient must be volume replete.

hyperphosphatemia, and hypocalcemia, are exacerbated by developing renal failure. **Uric acid** is insoluble at the low pH commonly found in the renal collecting duct, and crystals may precipitate in the collecting tubules, leading to acute kidney injury.[48] **Hyperkalemia** is the most immediate threat to life and should be treated aggressively, even in the absence of overt ECG changes. Lymphoblasts contain four times more phosphate than normal lymphocytes,[49] and the resulting excess phosphate from cell lysis can bind ionized calcium, leading to hypocalcemia. In addition, calcium phosphate crystalluria and obstructive uropathy can worsen acute kidney injury. The signs, symptoms, and treatment of these electrolyte disorders are discussed in Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children."

Laboratory studies include CBC, renal function studies, electrolytes, calcium, phosphate, uric acid, lactate dehydrogenase, and urinalysis (**Table 145-4**). Send laboratory studies every 4 hours in high-risk patients who remain in the ED for a prolonged period of time. ED treatment is directed at the prevention of renal failure, correction of electrolyte derangements, and reduction of uric acid levels. Coordinate management with an oncologist and include aggressive IV hydration, administration of allopurinol or recombinant urate oxidase (rasburicase) for hyperuricemia, and treatment of hyperkalemia and symptomatic hypocalcemia. Rasburicase is contraindicated in glucose-6-phosphate dehydrogenase deficiency due to its potential to precipitate hemolytic anemia or methemoglobinemia.[18,48] Urinary alkalinization is no longer recommended.[22,48] **Avoid rectal Kayexalate®**, because rectal medication administration increases the risk of bacteremia in neutropenic patients. Refractory electrolyte abnormalities or significant acute kidney injury requires dialysis.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE AND HYPONATREMIA

Causes of hyponatremia in oncology patients include chemotherapeutic agents, adjunct treatments (e.g., diuretics), clinical conditions (e.g., GI losses), and syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH is the leading cause of hyponatremia in children undergoing chemotherapy or stem cell transplant.[50] SIADH can result from CNS disease, infection, drug toxicity, surgical intervention for CNS tumors, and the primary malignancy. Cerebral salt wasting is also a possible cause of hyponatremia with CNS disease or following intracranial surgery.[51] **Whereas syndrome of inappropriate antidiuretic hormone secretion is characterized by euvolemia, cerebral salt wasting is characterized by volume depletion; this distinction is critical in the ED setting, where excessive fluid administration could be catastrophic.**

The presentation of hyponatremia depends on the rate and severity of the decline in sodium level. Patients may be asymptomatic, with low sodium levels incidentally noted on routine laboratory studies. Signs and symptoms of profound hyponatremia include fatigue, lethargy, confusion, coma, and seizures. **Treatment must be tailored to the patient's underlying cause of hyponatremia.** Guidelines for ED management of hyponatremia are outlined in Chapter 132. For SIADH, treatment consists of fluid restriction and slow sodium correction to avoid inducing central pontine myelinolysis. For hypovolemic hyponatremic patients, isotonic fluids are administered. **Treat acutely symptomatic patients with 3% normal saline.**

SUPERIOR VENA CAVA AND SUPERIOR MEDIASTINAL SYNDROMES

Superior vena cava syndrome is the result of compression or obstruction of the superior vena cava causing impaired venous return (**Figure 145-7**). Over 90% of cases are attributable directly to malignancy,[48] but infection and thrombus are additional causes. Superior mediastinal syndrome is superior vena cava syndrome with associated tracheal compression. These two terms are used interchangeably in children because mediastinal pathology often leads to both.[52] Although these entities are rare, the most common pediatric malignancies presenting with superior mediastinal syndrome are non-Hodgkin's lymphoma, ALL, neuroblastoma, and germ cell tumors.[53]

The signs and symptoms of superior mediastinal syndrome are dictated by the acuity and extent of the underlying process. Some patients are asymptomatic, but young children are at particular risk due to the small size and compliance of the airway.[54] Signs and symptoms include dyspnea, cough, stridor, wheezing, chest discomfort, facial and upper body edema and/or plethora, neck/chest vein dilatation, presence of



FIGURE 145-7. Superior vena cava syndrome. Note the prominent collateral veins of the chest and neck. [Photo contributed by William K. Mallon, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

collateral veins, and syncope (from decreased cardiac output). **The threat of acute cardiorespiratory failure makes this a true medical emergency.** Equally concerning are neurologic symptoms suggestive of cerebral ischemia: headache, confusion, and altered mental status.[55]

ED treatment depends on the clinical acuity. Confirm the diagnosis by chest radiograph or CT scan. Supine positioning for imaging may critically compromise the airway, so a prone position is a preferred alternative for older, cooperative children. **Avoid any intervention, such as sedation, that could potentially compromise the airway**. **Superior mediastinal syndrome is one of the few conditions in which rapid-sequence induction and intubation for respiratory distress may be lethal if the endotracheal tube cannot bypass the site of compression.** Temporizing measures include elevating the head of the bed to maintain an upright posture, high-flow oxygen, bilevel positive airway pressure, and possible consideration of heliox where available. Definitive management is treatment of the underlying malignancy to reduce the amount of compression. In cases where the syndrome is due to thrombotic occlusion, fibrinolytic therapy can be considered. Emergency stents have been placed at centers with appropriate expertise.[55]

NEUROLOGIC EMERGENCIES

SPINAL CORD COMPRESSION

Tumors involving the spine or spinal cord account for only 2% of childhood malignancies, but due to delays in diagnosis and deficits that are not always reversible, they are associated with a disproportionate degree of morbidity.[56] The most common neoplasms involving the spinal cord are CNS tumors, neuroblastoma, sarcomas, lymphoma, and germ cell tumors. Spinal cord compression can present in a child with known malignancy or as an initial presentation of disease. Most commonly, spinal cord compression arises from a hematogenously spread metastasis to vertebral bodies, with subsequent expansion and erosion of the lesion into the epidural space (**Figure 145-8**).[55] However, it can also result from direct extension of a paravertebral tumor through an intervertebral foramen into the spinal canal.

Back pain is the most common presenting symptom of spinal cord compression in children and often precedes other symptoms, providing an opportunity for early detection and intervention.[48,55,56] **Consider spinal involvement in any child with a history of cancer presenting with back pain.** If the diagnosis is delayed, progressive symptoms include motor weakness, worsening scoliosis, and gait disturbance. Sensory impairments and sphincter dysfunction are extremely rare in young children. Physical exam findings depend on the location of the lesion(s), the degree of spinal cord impingement, and the rate at which compression takes place.



FIGURE 145-8. Spinal cord compression. MRI demonstrating spinal cord compression at T9 due to epidural extension of tumor. T10 vertebral body also has metastasis (decreased signal intensity). [Reproduced with permission from Schwartz D (ed). *Emergency Radiology: Case Studies*. Copyright © 2008 by The McGraw-Hill Companies, Inc., New York.]

In patients in whom spinal compression is suspected, MRI is the gold standard imaging and should be obtained emergently. Plain films are ineffective for diagnosis. Given that a significant number of patients present with multiple spinal lesions, image the entire spinal cord.[48,55] Obtain brain imaging if a spinal neoplasm is identified. Obtain oncology, neurosurgery, and radiotherapy consultation. ED treatment is IV dexamethasone (0.1 milligram/kg to a maximum of 10 milligrams) to decrease vasogenic edema caused by obstruction of the epidural venous plexus and to improve symptoms. **However, if leukemia or lymphoma is in the differential diagnosis for an initial presentation of a spinal tumor, do not administer steroids without consulting an oncologist; steroid administration can mask the tumor and prevent diagnosis and appropriate treatment.** Neurologic damage is often irreversible once ischemia develops and the spinal cord infarcts. Even with aggressive interventions, studies report that 40% to 70% of children have residual impairment.[57]

INCREASED INTRACRANIAL PRESSURE

Increased intracranial pressure in children with cancer is usually due to primary CNS tumors. Childhood CNS tumors are often infratentorial, a location where there is potential for cerebrospinal fluid flow obstruction.[58] Clinical presentation and risk of herniation depend on the location and growth rate of the tumor, as well as the age of the child. Signs and symptoms are often nonspecific. Cushing's triad is rare but requires emergent intervention.

Brain imaging with MRI or CT can identify a neoplasm, associated vasogenic edema and/or hydrocephalus, and alternative diagnoses; however, CT remains the test of choice in the emergency setting. Management is guided by the severity of the presentation. Initial focus in the ED should be a primary survey; in particular, ensure airway protection in a patient with high intracranial pressure and altered mental status. Use of hyperventilation is now debated, because hypercarbia causes cerebral dilation but hypocarbia is an independent predictor of mortality. Mild hyperventilation (pulmonary end tidal carbon dioxide, 30 to 34 mm Hg) is considered appropriate in cases of herniation. Elevate the head of the bed to 30 degrees to improve venous drainage and consult neurosurgery. Administer IV dexamethasone (0.1 milligram/kg to a maximum of 10 milligrams) to reduce tumor-associated vasogenic edema. There are no pediatric data clearly supporting antiepileptic administration for seizure prophylaxis,[59,60] but fosphenytoin or another longer acting antiepileptic can be considered if the patient requires transport. Maintain appropriate electrolyte levels and correct thrombocytopenia or coagulopathy.

STROKE

Stroke, occurring within the first few years of a childhood cancer diagnosis, is rare.[61] Overall prevalence is estimated at 1%.[62] Hemorrhagic strokes and ischemic strokes occur with equal frequency.[61] Risk factors include coagulopathy, thrombocytopenia, hyperleukocytosis, radiation, medications, and primary or metastatic CNS tumors. Stroke can be the sole clinical manifestation from hemorrhage into a previously occult CNS neoplasm.

Treatment depends on the underlying cause. Standard stroke management applies, including brain imaging. Modifiable risk factors should be addressed, including correction of thrombocytopenia to keep platelet levels >100,000/mm^3. Discuss anticoagulant therapy in consultation with neurology and oncology.

SEIZURES

Seizures are common in pediatric oncology patients and may have a number of causes: primary or metastatic CNS lesion, stroke, metabolic derangement (i.e., hyponatremia), infection (e.g., abscess, meningitis), chemotherapeutic agents, and radiation therapy. Fifteen percent of pediatric brain tumor patients experience seizures, and 12% of pediatric brain tumor patients present with seizures.[60]

Initial evaluation of a seizure in a child with cancer should include brain imaging with CT or MRI to identify the cause. If there are no contraindications, perform lumbar puncture to exclude infection. See Chapter 138, "Seizures in Infants and Children," for further discussion.

CATHETER-RELATED COMPLICATIONS

The vast majority of pediatric cancer patients undergo central venous line placement for their treatment. These devices include external catheters (e.g., Broviac®), totally implantable catheters (e.g., Port®), and peripherally inserted central catheters. Rates of catheter-related complications are 40% to 50%,[63,64] and the complications fall primarily into three categories: infectious, mechanical, and thrombotic.

Infection of the central line occurs from contamination of the hub and luminal migration of pathogens within the catheter, from hematogenous seeding of the intravascular portion of the catheter, or from fractures within the catheter itself. The morbidity and mortality attributable to central line–associated bloodstream infections is significant. The incidence of central line infections is three times greater in ambulatory pediatric oncology patients compared to inpatients.[65] Risk factors include frequent access, poor hygiene and sterility, previous infection, and <1-month duration from line insertion. Tunnel infections of the soft tissue surrounding the catheter may also occur shortly after placement, with typical signs of infection. Totally implantable catheters are associated with the least catheter-associated infectious morbidity.[66,67] Treatment requires IV antibiotics and possible device removal. For further discussion, see "Infection" section.

A central venous line is the single most important risk factor for developing thromboembolism in any child,[64] and 50% of children with cancer are reported to have central line–associated thrombosis.[63] Common morbidities from thrombosis include infection, embolism to other vessels (including pulmonary embolism), catheter malfunction, loss of venous access, and delay of treatment. Venous Doppler ultrasonography can identify upper extremity or jugular vein thrombosis, but ultrasonography is limited in its inability to visualize more proximal (i.e., central) thrombosis. CT or magnetic resonance venogram may also be used for diagnosis. Treatment of central line–associated thromboembolism may require tissue plasminogen activator (a small alteplase infusion administered to the catheter site if there are concerns for an intraluminal partial occlusion of the catheter), removal of the catheter, and/or anticoagulation for more significant thromboembolisms. ED staff should not infuse tissue plasminogen activator into a central line without consulting oncology and/or surgery. When anticoagulant therapy is indicated, low-molecular-weight heparin, using pediatric-specific dosing protocols, is usually the preferred choice in children.[68]

Mechanical complications are also quite common in pediatric oncology patients, with a prevalence of 20% to 39%, and are an independent risk factor for poor outcomes.[63] External catheters have increased rates of mechanical complications and failure.[67] Potential nonthrombotic occlusions include intraluminal precipitation of calcium, bicarbonate, or drugs (e.g., phenytoin).

OTHER COMPLICATIONS OF MALIGNANCY

CARDIOPULMONARY COMPLICATIONS

There are a variety of cardiac and pulmonary oncologic complications that are not unique to pediatrics. These include malignant pericardial effusion through direct or metastatic involvement of the pericardium, treatment-induced transudative pericardial effusion, cardiac tamponade, and pleural effusions. These complications and their management are addressed in the adult chapters of this textbook. Chemotherapeutic agents and adjunct therapies can also be associated with cardiomyopathy, hypertension, arrhythmias, and pulmonary fibrosis.

GASTROINTESTINAL COMPLICATIONS

Mechanical bowel obstruction due to mass effect may occur with any intra-abdominal tumor, most commonly lymphoma. Malignancy should be on the differential for a child presenting with intussusception, because masses can act as lead points for telescoping of the bowel. Postoperatively, patients with oncologic abdominal surgery are at increased risk for developing a bowel obstruction due to adhesions. Patients are also at risk for constipation and ileus due to narcotic administration.

Any component of the GI tract, from mouth to anus, can be affected by mucositis induced by chemotherapeutic agents. Mucosal breakdown can lead to pain, infection, dehydration due to poor oral intake, and bleeding at any location. Herpetic or fungal esophagitis can develop. Typhlitis, or neutropenic enterocolitis, was previously discussed in this chapter (see "Infection" section and Figure 145-6). **Appendicitis must remain a consideration in the oncology patient with right lower quadrant abdominal pain.** Of note, the typical appendicitis presentation may be blunted in children with neutropenia and/or on corticosteroids.[69] Imaging with CT or US can help to differentiate between appendicitis, typhlitis, and other intra-abdominal processes.

GI bleeding can result from mucositis, high-dose steroids or radiation in the treatment regimen, primary tumor or metastatic invasion, or tumor- or treatment-related cytopenias or coagulopathies. Mallory-Weiss tears can develop from severe chemotherapy-related emesis. Primary colorectal cancers are extremely rare in children, but those numbers increase when including secondary GI malignancies following a previously treated pediatric cancer.

GENITOURINARY COMPLICATIONS

Mass effect from abdominal or pelvic tumors can lead to ureteral obstruction and hydronephrosis, necessitating urgent stent placement. Other causes of acute urinary retention include drugs (e.g., narcotics, anticholinergics) or spinal cord compression. Viruses, radiotherapy, and chemotherapeutic agents can all induce hemorrhagic cystitis. Hemorrhagic cystitis treatment requires IV hydration, correction of underlying cytopenias and coagulopathy, and antiviral medications if appropriate. Severe cases warrant urologic consultation for placement of a double-lumen Foley catheter for continuous bladder irrigation or for cystoscopy.[70]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 146

Metabolic Emergencies in Infants and Children

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INTRODUCTION

Metabolic emergencies are challenging childhood disorders, often presenting with nonspecific signs and symptoms that may mimic more common conditions such as sepsis. Delay in accurate diagnosis can lead to significant morbidity and mortality, whereas early aggressive management can be lifesaving and reduce long-term neurologic sequelae. Individually, these disorders are uncommon, but taken together as an entity, they are likely to be encountered by most emergency providers, who must be familiar with the general steps to facilitate expedited emergency management.

In any healthy neonate, sudden acute deterioration should prompt consideration of metabolic disease. **Vomiting, altered mental status, and poor feeding are the most common clinical features of metabolic emergencies**. Appropriate management can be started in the ED without a definitive diagnosis. This chapter reviews the most common metabolic disorders presenting as acute decompensation in the young

infant and their emergency management. Hypoglycemia is discussed separately. Congenital adrenal insufficiency is included here because of the overlap in presentation with other inherited metabolic disorders and the importance of prompt recognition and treatment in the critically ill neonate. Inherited metabolic disorders that present in later childhood, such as lysosomal storage diseases, are often diagnosed and managed outside of the ED and so are not included here.

HYPOGLYCEMIA

Hypoglycemia is defined as at least one blood glucose concentration <47 milligrams/dL (2.65 mmol/L); it is considered severe if the glucose concentration is <36 milligrams/dL (2 mmol/L) and recurrent if three or more episodes have occurred.[1] Hypoglycemia also includes any glucose concentration low enough to cause symptoms or signs of impaired brain function.[2] Transient neonatal hypoglycemia (within 48 hours of birth) has been linked with a decreased proficiency on literary and mathematics fourth-grade achievement tests, as well as low executive and visual motor function.[1,3] This makes detection and treatment of neonatal hypoglycemia especially important to avoid long-term negative neurodevelopmental outcomes.

PATHOPHYSIOLOGY

Neonates are born with 60% to 80% of maternal glucose levels. Within 2 to 4 hours, neonates begin to regulate their own serum glucose levels, and the majority of transient hypoglycemic episodes resolve within 48 hours of birth. Any hypoglycemic episode after 48 hours of birth requires a detailed evaluation to identify the cause. Maintenance of serum glucose depends on intake and endogenous gluconeogenesis and glycogenolysis mediated by various hormones. Serum glucose level is affected when there is an imbalance between insulin (a hypoglycemic hormone) and its counterregulatory hormones cortisol, growth hormone, glucagon, and epinephrine (hyperglycemic hormones). Insulin stimulates cellular glucose uptake and suppresses lipolysis, whereas hyperglycemic hormones stimulate lipolysis and glycogenolysis. Excess insulin (hyperinsulinemia) results in hypoglycemia with the absence of urinary ketones. Hypoglycemia in the neonate or infant may result from inadequate oral intake, excess insulin, deficient hyperglycemic hormones (e.g., growth hormone or adrenal hormone deficiency), disorders of fatty acid oxidation or carbohydrate metabolism, aminoacidopathies and organic acidurias (due to inhibition of gluconeogenesis), or severe systemic illness (e.g., sepsis). Infants of diabetic mothers, postterm infants, and large for gestational age infants are at risk for hypoglycemia due to excess fetal insulin levels in response to elevated maternal serum glucose levels, whereas premature infants or those small for gestational age are at risk due to inadequate glycogen stores.[4-6]

CLINICAL FEATURES

HISTORY

Neonates and infants with hypoglycemia typically present with alterations in mental status. Nonspecific symptoms include poor feeding, an abnormal or high-pitched cry, cyanosis, hypothermia, and varying degrees of irritability and jitteriness or lethargy.[7] Severe hypoglycemia may result in coma or seizures.

Inquire about maternal complications during pregnancy (including gestational diabetes, growth retardation, and infections) as well as any history of prior spontaneous abortions or early infant deaths, which may signal inherited metabolic disease. Obtain a detailed feeding history, and document duration and progression of symptoms as well as the presence of associated signs and symptoms of vomiting, diarrhea, abnormal urine output, jaundice, and temperature instability.

PHYSICAL EXAMINATION

The classic signs of hypoglycemia seen in older children and adults are a result of the hyperglycemic hormones and include signs of adrenergic stimulation such as tachycardia, diaphoresis, tremor, anxiety, and tachypnea. **Neonates and infants may not manifest adrenergic signs, and lethargy, apnea, or seizures may be the prominent finding**. A careful neurologic examination should focus on mental status, tone, and reflexes and may reveal focal neurologic deficits similar to Todd's paralysis in cases of prolonged, severe hypoglycemia. Seizures may be noted.

A complete physical examination is important to search for primary and secondary causes of hypoglycemia. Document the weight and compare with birth weight (if known) in the neonate. Macrosomia, growth retardation, or dysmorphic features may provide a quick clue to a potential cause. Fever or hypothermia suggests infection. The cardiac examination may suggest congenital heart disease (e.g., critical coarctation of the aorta), and the pulmonary examination may reveal tachypnea, apnea, or respiratory distress suggestive of pneumonia or sepsis. The abdominal examination is important in an infant with a history of vomiting to exclude abdominal catastrophe or obstruction (e.g., atresia, volvulus, intussusception, or pyloric stenosis). The GU examination may reveal ambiguous genitalia suggestive of congenital adrenal hyperplasia (discussed later in the "Congenital Adrenal Hyperplasia [Adrenal Insufficiency]" section).

DIAGNOSIS

The most important diagnostic test in the ED for the neonate, infant, or child who is critically ill or shows altered mental status is a **rapid bedside screen for the serum glucose level**. Confirm abnormal results with a venous sample sent to the laboratory. Although the treatment of hypoglycemia must be prompt and should not be delayed, the first blood sample taken from the hypoglycemic neonate or infant is critical for making a definitive diagnosis, and when possible, a gray-topped sample tube should be filled and placed on ice for additional studies, which may include serum insulin, C-peptide, growth hormone, cortisol, and glucagon levels.[2]

Evaluation of serum for beta-hydroxybutyrate (or urine ketones) is the second important step. Ketonemia or ketonuria is characteristic of ketotic hypoglycemia, adrenal or growth hormone deficiency, and other inborn errors of metabolism. A lack of serum or urine ketone elevation suggests hyperinsulinemia or fatty acid oxidation defects.[8-11] Serum insulin, C-peptide, and hormone analysis, as described earlier, can help differentiate among these diagnostic possibilities.

The administration of **glucagon** (0.03 milligram/kg IM or IV) in hypoglycemic states can be diagnostic and therapeutic. If glucagon is effective in normalizing serum glucose level, then the presence of hepatic stores is confirmed and the hypoglycemia is likely due to hormonal deficiency (panhypopituitarism or adrenal insufficiency) (**Figure 146-1**). Lack of response to glucagon suggests poor glycogen stores. Among nonresponders to glucagon, fasting is the most common cause, followed by galactosemia and hereditary fructose intolerance, although children with ketotic hypoglycemia often fail to respond to glucagon as well.

Additional laboratory evaluation is directed by the clinical picture and differential diagnosis and may include cultures of the blood, urine, and cerebrospinal fluid when sepsis is suspected. Definitive diagnosis of specific inborn errors of metabolism may require evaluation of levels of urine organic acids and serum amino acids and serum lactate (discussed later in "Inborn Errors of Metabolism"), as well as serum ammonia and lactate.

Routine imaging studies are not required for most cases of hypoglycemia but may be useful if there are underlying organ anomalies.

TREATMENT

It is important to treat hypoglycemia promptly while awaiting further diagnostic results. Dextrose is the primary treatment and may be given enterally (PO, nasogastric tube) or parenterally (IV or IO). **The dose of dextrose is 0.5 to 1.0 gram/kg regardless of the route of administration. Newborns should receive 5 mL/kg of 10% dextrose, whereas infants and children can receive 1 to 2 mL/kg of 25% dextrose**. With adequate vascular access, 1 mL/kg of 50% dextrose may be administered to older children as to adults. Some recommend a 0.2 gram/kg dextrose bolus to minimize hyperglycemia and resultant insulin secretion, which prolongs hypoglycemia. Use of dilute solutions in younger patients is suggested to minimize vascular injury associated with more concentrated fluids given through small-gauge IVs.

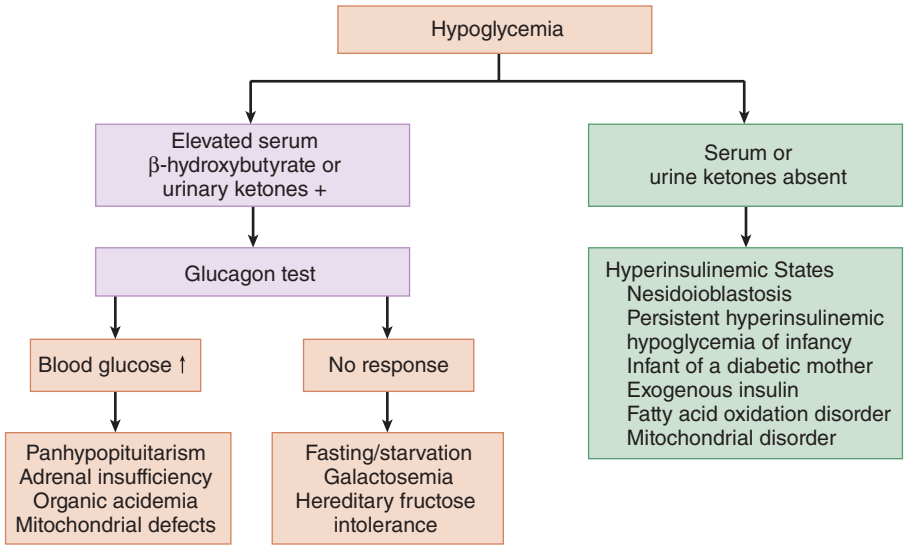

FIGURE 146-1. Evaluation of hypoglycemia in the emergency department.

Provide maintenance dextrose at a rate of 6 to 8 milligrams/kg/min with 10% dextrose, which is 1.5 times the normal maintenance rate for infants and children (see Table 146-1 and Chapter 132, "Fluid and Electrolyte Therapy in Infants and Children"). If IV or IO access or nasogastric tube placement cannot readily be initiated, glucagon, 0.03 milligram/kg IM, may be given. Refractory hypoglycemia may be seen in hyperinsulinemic states such as insulin-secreting tumors and is suggested by hypoglycemia requiring administration of more than 6 to 8 milligrams/kg/min. Frequent reevaluation and titration of infused dextrose are necessary in this situation. **If adrenal insufficiency is suspected, give hydrocortisone, 25 grams IV or IM for neonates and infants, 50 grams for toddlers and school-age children, and 100 grams for adolescents**. The management of hypoglycemia is summarized in **Table 146-1**.

Because sepsis is always in the differential diagnosis of the critically ill neonate, infant, or child with altered mental status, provide prompt broad-spectrum antibiotics as indicated by the clinical picture. This includes ampicillin and gentamycin for neonates, cefotaxime for infants age 28 to 90 days of life, and ceftriaxone for older infants and children (see Table 120-1 in Chapter 120, "Meningitis in Infants and Children" and Chapter 119, "Fever and Serious Bacterial Illness in Infants and Children").

DISPOSITION AND FOLLOW-UP

All neonates and infants with symptomatic hypoglycemia requiring ED resuscitation should be admitted to the hospital for further evaluation and treatment. Patients for whom sepsis is a concern and those requiring dextrose beyond the expected 6 to 8 milligrams/kg/h may require admission to the intensive care unit.

INBORN ERRORS OF METABOLISM

Although the diversity and complexity of inborn errors of metabolism in infants and children may seem overwhelming, it should be noted that making a definitive diagnosis is not as important as maintaining a high index of suspicion and that acute stabilization and management are relatively simple. As a group, these disorders generally involve enzyme deficiencies that lead to errors of metabolism resulting in the accumulation of toxic metabolic products or deficiencies of downstream products, which can cause dysfunction of multiple organ systems, especially the CNS. Although each **individual** type of inborn error of metabolism is extremely rare, as a group, they are relatively common, with an incidence ranging from 1 in 800 to 1 in 2500 live births.[9,10]

Clinical manifestations of inborn errors of metabolism are usually the result of accumulation of toxic metabolites and their effects on end organs. Common symptoms and signs of inherited metabolic disorders include acute encephalopathy, with or without metabolic acidosis, and hypoglycemia. **Because most metabolic toxins cross the placenta and are cleared by maternal enzymes, most newborns are asymptomatic and present after varying delays once enteral feeding begins.** Hypoglycemia may be the primary presentation of some inherited disorders of metabolism and has been discussed earlier (see "Hypoglycemia"). Jaundice and hepatic dysfunction can be seen in a number of inherited disorders such as galactosemia or tyrosinemia.[11] Shock and cardiovascular collapse can occur with congenital adrenal insufficiency, but nonmetabolic

TABLE 146-1 Management of Hypoglycemia in the ED

Patient Age	Dextrose Bolus Dose	Dextrose Maintenance Dosage	Other Treatments to Consider
Neonate	D10 5 mL/kg PO/NG/IV/IO	6 mL/kg/h D10	Glucagon, 0.03 milligram/kg IM Hydrocortisone, 25 grams PO/IM/IV/IO
Infant	D10 5 mL/kg PO/NG/IV/IO *or* D25 2 mL/kg	6 mL/kg/h D10	Glucagon, 0.03 milligram/kg IM Hydrocortisone, 25 grams PO/IM/IV/IO
Child	D25 2 mL/kg PO/NG/IV/IO	6 mL/kg/h D10 for the first 10 kg + 3 mL/kg/h for 11–20 kg + 1.5 mL/kg/h for each additional kg >20 kg	Glucagon, 0.03 milligram/kg/IM Hydrocortisone, 50 grams PO/IM/IV/IO
Adolescent	D25 2 mL/kg PO/NG/IV/IO *or* D50 1 mL/kg PO/NG/IV/IO	6 mL/kg/h D10 for the first 10 kg + 3 mL/kg/h for 11–20 kg + 1.5 mL/kg/h for each additional kg >20 kg	Glucagon, 0.03 milligram/kg IM Hydrocortisone, 100 grams PO/IM/IV/IO

Abbreviations: D10 = 10% dextrose; D25 = 25% dextrose; D50 = 50% dextrose; NG = (via) nasogastric tube.

conditions such as congenital heart disease and sepsis must be considered in the differential diagnosis of infants presenting in extremis (see Chapter 116, "Neonatal Emergencies and Common Neonatal Problems"). The discussion here is limited to conditions that typically present in early infancy with the potential for life-threatening consequences.

PATHOPHYSIOLOGY

Most inborn errors of metabolism result from single-gene defects with a variety of inheritance patterns, most commonly autosomal recessive. The defects result in abnormal metabolism of protein, fat, carbohydrates, or other complex molecules. Affected proteins include enzymes, enzyme cofactors, and transport proteins. The result of these varied deficiencies is the accumulation of toxic substrates upstream of the impaired protein or of intermediates derived from alternate metabolic processes downstream. On the basis of metabolic and clinical manifestations, these disorders can often be grouped into those defects resulting in neurologic abnormalities (secondary to metabolic acidosis as in glycogen storage disease type I or fatty acid oxidation defects), hypoglycemia (as in organic acidemias and glycogen storage disease type I), hyperammonemia (as in urea cycle disorders and organic acidemias), seizures or apnea (as in mitochondrial respiratory chain defects and Zellweger's syndrome), liver dysfunction (galactosemia, tyrosinemia), and cardiac abnormalities (fatty acid oxidation disorders, glycogen storage disease type II).[11]

Examples of organic acidemias that present in the first 24 hours of life are glutaric acidemia and pyruvate carboxylase deficiency (which causes lactic acidemia). Urea cycle defects typically present after the first 24 hours of life and often lack associated metabolic acidosis. Examples are ornithine transcarbamylase deficiency, carbamyl phosphate synthetase deficiency, and citrullinemia. Ornithine transcarbamylase deficiency is X-linked in its inheritance and therefore affects only male infants.

Although organic acidemias can also lead to hyperammonemia, they are typically accompanied by metabolic acidosis. Examples are methylmalonic acidemia, propionic acidemia, and isovaleric acidemia. Defects in pyruvate metabolism, defects in enzymes of the respiratory chain, and mitochondrial disorders also result in metabolic acidosis, which is often independent of protein intake. These disorders result in lactic acidosis with normal urine organic acid levels and include pyruvate dehydrogenase deficiency.

Disorders of carbohydrate, lipid, or fatty acid metabolism include glycogen storage diseases and medium-chain acyl-coenzyme A dehydrogenase deficiency. These disorders impair the ability to use or produce glucose, which leads to hypoglycemia, often in the setting of fasting or poor oral intake. Glycogen and lipid storage diseases usually present later in infancy or childhood with developmental delay, dysmorphic or progressively coarse features, and hepatomegaly. Fatty acid metabolism defects result in nonketotic hypoglycemia (see "Hypoglycemia," earlier), which is a distinguishing characteristic. Secondary carnitine deficiency is often seen in medium-chain acyl-coenzyme A dehydrogenase deficiency.

Hyperbilirubinemia and liver dysfunction may be the presenting feature of inborn errors of metabolism such as galactosemia, tyrosinemia, or α_1-antitrypsin deficiency. Galactosemia results from the deficiency of galactose-1-phosphate uridylyltransferase, which leads to an accumulation of galactose-1-phosphate and other metabolites that are toxic to the liver. In addition to hepatic dysfunction, these infants may develop hypoglycemia, hyperbilirubinemia, hemolysis, or overwhelming infection.

CLINICAL FEATURES

HISTORY

Many inborn errors of metabolism present with nonspecific symptoms, including irritability, lethargy, vomiting, and poor feeding; severe hypoglycemia or metabolic encephalopathy may present with seizures. A careful characterization of these symptoms, however, may point toward a metabolic disorder; poor feeding and lethargy may be more notable in the morning prior to the first feeding as a result of a relative period of fasting. Parents may note aversion to protein or carbohydrates. Diarrhea may accompany carbohydrate metabolism disorders or mitochondrial disease. Parents may report an abnormal body or urinary odor, although this is more commonly noted by clinicians. Abnormal odor is typical of isovaleric academia and glutaric academia (sweaty feet) and maple syrup urine disease, which, as the name indicates, is accompanied by a characteristic sweet smell of the urine.

Obtain a dietary and developmental history. Frequent changes in formula due to vomiting or failure to thrive may indicate an undiagnosed metabolic disease. Unexplained developmental delay may also be a clue to diagnosis. Take a thorough medical history. A history of recurrent hospitalizations with a response to IV fluids and glucose may suggest an underlying metabolic disorder. The maternal history taking should include questions about previous spontaneous abortions or miscarriages and the death of previous infants early in life. Maternal complications during pregnancy, such as acute fatty liver or HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets), may be related to heterozygosity for fatty acid oxidation defects. The family history should include information about relatives with early cardiac disease, sudden infant death syndrome, neurologic disease, and liver disease with onset in childhood, all of which may possibly signal the presence of an inherited disorder of metabolism.

PHYSICAL EXAMINATION

The physical examination begins with attention to the vital signs. Tachycardia is often present during an acute metabolic crisis; congenital adrenal hyperplasia may cause hypotension. Hypothermia may accompany many metabolic diseases, particularly urea cycle defects and organic acidemias. Tachypnea without increased work of breathing may be noted in patients with metabolic acidosis and may result in a respiratory alkalosis. Although the majority of inborn errors of metabolism that present in early infancy are not associated with other specific findings on physical examination, those that present later in childhood, such as glycogen storage diseases, liposomal storage diseases, and mucopolysaccharidoses, may manifest with specific phenotypical features that suggest the diagnosis. Some metabolic disorders have ocular findings, including cataracts (e.g., galactosemia) or dislocated lenses (e.g., homocystinuria). The GU examination is important when adrenal insufficiency is a consideration because females with one specific defect may show signs of virilization (see later section, "Congenital Adrenal Hyperplasia [Adrenal Insufficiency]"). A complete head-to-toe physical examination should be performed, of course, despite the lack of characteristic findings in most inborn errors of metabolism presenting during infancy, in order to exclude alternative diagnoses, including sepsis and congenital heart disease.

DIAGNOSIS

Due to the rarity and diversity of these disorders, the aspects of their acute clinical presentations and ED management have yet to be well defined. A simplified, although not exhaustive, generalized approach to inborn errors of metabolism is presented in the following sections and in **Figure 146-2**. The key laboratory studies that are most useful to the emergency physician in directing immediate management and suggesting potential diagnoses include bedside glucose level, urine ketone level, plasma ammonia concentration, basic metabolic screen, blood gas analysis, and plasma lactate level. These are discussed in more detail in the following sections. Additional clues may be provided by a CBC, liver function tests, and muscle function tests (lactate dehydrogenase, creatine kinase, and myoglobin levels) (**Table 146-2**). Definitive diagnosis often depends on plasma or serum levels of amino acids, acylcarnitine profile, and lactate and pyruvate levels, as well as urine test results for organic acids, acylglycines, and orotic acid, and potentially on results of cerebrospinal fluid studies, including tests for lactate, pyruvate, and organic and amino acids.[10,11] A summary of laboratory evaluations for suspected metabolic disease and their utility and significance is provided in Table 146-2.

Bedside Glucose and Serum or Urine Ketone Levels Hypoglycemia may be a feature of several inborn errors of metabolism, including

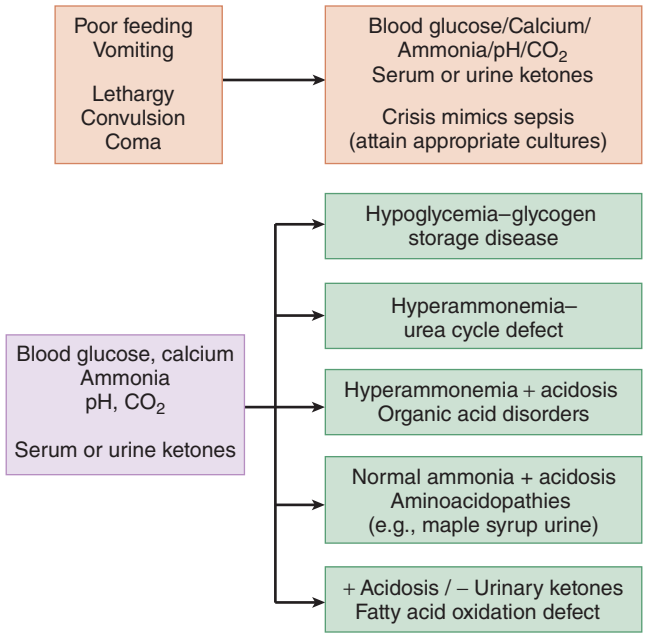

FIGURE 146-2. Approach to suspected metabolic disorders. CO_2 = carbon dioxide.

glycogen storage diseases, fatty acid oxidation disorders, and disorders of gluconeogenesis. Some organic acidemias may also be associated with hypoglycemia. **Hypoglycemia in the absence of serum or urine ketones suggests a fatty acid oxidation defect, and hypoglycemia with serum or urine ketone elevation suggests organic acidemias.**

Plasma Ammonia Concentration Ammonia is formed during the deamination of amino acids and excreted as urea in the urine. Urea is produced in the hepatocyte mitochondria and cytosol through the metabolic process known as the *urea cycle*. Normal neonatal ammonia concentrations are <65 micromoles/L, but may be two to three times this in stressed or nonfasting newborns and infants. Levels >200 micromoles/L suggest metabolic disease and are the hallmark of urea cycle disorders. Hyperammonemia detected in the first 24 hours of life may be seen with pyruvate carboxylase deficiency, whereas hyperammonemia associated with urea cycle defects usually presents after protein feeding has begun and may reach ammonia concentrations well above 400 micromoles/L. The severe hyperammonemia of urea cycle disorders may stimulate central hyperventilation, resulting in respiratory alkalosis. Secondary causes of more modest hyperammonemia include mitochondrial, respiratory chain, or fatty acid oxidation defects, which are often associated with metabolic and/or lactic acidosis.

Blood Gas Analysis, Basic Metabolic Panel, and Plasma Lactate Level Evaluation of the acid-base status is best achieved through analysis of blood gas samples and serum electrolyte levels. Serum lactate levels (discussed later in "Plasma Lactate Level") provide additional information. The anion gap (sodium – [chloride + bicarbonate]) is usually <15 mEq/L but increases with excess acid production. **Organic acidemias are associated with significant anion gap acidosis, often higher than 30 to 50 mEq/L (also associated with ketosis).** Other inborn errors of metabolism associated with metabolic acidosis include respiratory chain disorders, disorders of pyruvate metabolism, and some glycogen storage diseases. In comparison with organic acidemias, these conditions typically include significant lactic acidosis, which helps distinguish them from organic acidemia.[11]

TREATMENT

Despite the diverse etiology and complexity of inborn errors of metabolism, ED resuscitation and stabilization are relatively simple. **Neonates, infants, and children presenting in metabolic crisis, regardless of cause, show some combination of dehydration, metabolic acidosis, and encephalopathy, which must be immediately addressed.** Therefore, the goals of treatment are to remove the inciting metabolic substrate (formula or breast milk), provide energy substrate to halt catabolism and toxin production and help eliminate toxic metabolites, and improve circulatory status by restoring circulatory volume as well as electrolyte balance.[9,11]

FLUID RESUSCITATION

As with any critically ill patient, attending to the ABCDs (*a*irway, *b*reathing, *c*irculation, *d*isability [neurologic status]) is the first step. Apnea, hypoventilation, and hypoxia are treated with positive-pressure ventilation or endotracheal intubation and administration of supplemental oxygen. **Metabolic acidosis can be worsened by respiratory acidosis if sufficient ventilation is not provided.** Restore circulation with crystalloid boluses, typically 10 to 20 mL/kg in the neonate and 20 mL/kg in the infant, with frequent reassessment and further fluid administration as clinically indicated (because congenital heart disease can present similarly to metabolic crisis, careful reevaluation after each fluid bolus is essential). Even a patient who is not in shock may benefit from a bolus of normal saline followed by double the usual level of maintenance fluids with dextrose, because aggressive hydration promotes urine output with increased clearing of toxic metabolites (e.g., organic acids, ammonia) and dextrose provides a substrate for metabolism. **Avoid hypotonic fluids because they may increase the risk of cerebral edema, particularly in hyperammonemic states.** Assess neurologic status before definitive airway management. The cause of altered mental status (hypoglycemia or hyperammonemia) must be

TABLE 146-2 Additional Laboratory Tests in the Diagnosis of Metabolic Disease

Test	Result	Diagnostic Implications
Liver function tests	Unconjugated hyperbilirubinemia	Galactosemia
	Hepatic failure	Fatty acid oxidation disorders, mitochondrial disorders, urea cycle disorders
CBC	Pancytopenia	Aminoacidopathies (propionic acidemia, isovaleric acidemia, methylmalonic acidemia)
Creatine kinase	Elevated	Mitochondrial disorders
Aldolase	Elevated	Fatty acid oxidation defects
Serum amino acids	Abnormal quantitative results	Aminoacidopathies, organic aciduria, urea cycle defect, mitochondrial disorder
Serum acylcarnitine levels	Abnormal profile	Organic acidurias, fatty acid oxidation defects, mitochondrial disorders, carnitine deficiency
Urine-reducing substances	A positive test result is always abnormal	Aminoacidopathies (tyrosinemia), carbohydrate intolerance disorders (galactosemia)
Urine organic acids	Abnormal profile	Aminoacidopathies, organic aciduria, fatty acid oxidation defects, mitochondrial disorders, peroxisomal disorders
Urine orotic acid	Elevated	Urea cycle defects (ornithine transcarbamylase deficiency)
Urine acylglycines	Abnormal	Aminoacidopathies, organic acidurias

determined and may be reversible but is difficult to assess in the paralyzed or sedated patient (see below).

Metabolic acidosis during metabolic crisis can arise from dehydration, which may respond to fluid administration, or from the underlying metabolic defect. The ongoing production of acidic metabolites may necessitate the administration of sodium bicarbonate; however, treatment may be associated with side effects, including sodium overload, cerebral edema, and cardiac dysfunction.

All patients in metabolic crisis should be kept nothing by mouth to remove potential inciting metabolic substrates (protein, carbohydrates, fats), and adequate dextrose should be provided for anabolic substrate. Dextrose 10% is usually preferred and should be administered at one and a half to twice the usual maintenance rates.[12,13]

ELIMINATE TOXIC METABOLITES

Elimination of toxic metabolites is the next step. Hyperammonemia, as seen in urea cycle defects and some organic acidemias, is the most common cause of metabolic encephalopathy in infants. Ammonia levels of <500 micromoles/L should be treated with a combination of sodium phenylacetate and sodium benzoate (Ammonul®); a dose of 250 milligrams/kg (≤20 kg) or 5.5 grams/m^2 (>20 kg) in 25 mL/kg 10% dextrose is administered through a central venous or intraosseous line over 1.5 to 2 hours followed by a repeat of the same dose over 24 hours as a continuous infusion.[12]

Arginine can also be provided, the dosing of which depends on the specific disorder.[12] Empiric therapy with arginine with or without sodium benzoate can reduce ammonia levels drastically. Early aggressive treatment may eliminate the need for hemodialysis for excessive ammonia removal. Additional therapy may include empiric carnitine, 400 milligrams IV/IO, which combines with organic acids to form acylcarnitines that are readily excreted from urine, although no prospective trials have been performed.[14]

ADDITIONAL THERAPIES

For ammonia levels >500 micromoles/L, hemodialysis is indicated.[11] For infants with seizures, empiric administration of pyridoxine, 100 milligrams IV/IO, for pyridoxine-dependent metabolic disease can be tried. If this is ineffective, folinic acid, 2.5 milligrams IV/IO (goal: 3 to 5 milligrams/kg/d), or biotin, 10 milligrams by nasogastric tube (5 to 20 mg/d), can be considered.[15,16] A summary of second-tier therapies for specific suspected inborn errors of metabolism is provided in **Table 146-3**.

COMPLICATIONS

During metabolic crisis, the accumulation of various organic acids can suppress granulopoietic stem cells and thereby cause bone marrow suppression of all cell lines. This leads to an immunocompromised state with an increased incidence of **sepsis** due to unusual organisms, with an **incidence of 15% to 30% per 100 episodes**. Therefore, it is essential to rule out sepsis in all patients with metabolic crisis. Chronic anemia and thrombocytopenia may accompany a number of inborn errors of metabolism and may be exaggerated during metabolic crisis. Give empiric broad-spectrum antibiotics such as ceftazidime.

Hyperammonemia is a specific risk factor for **cerebral edema**, especially when hypotonic solutions are administered during therapy. Cerebral edema is a clinical diagnosis and should be suspected when laboratory parameters improve but altered mental status continues. Treatment for cerebral edema is mannitol (0.5 gram/kg IV/IO) and avoidance of hypo- and hyperventilation. **Do not give steroids because steroids exacerbate hyperammonemia**.

TABLE 146-3 Specific Therapies for Inborn Errors of Metabolism

Inborn Error of Metabolism	Drug	Dosage
Urea cycle defects	Arginine HCl 10% Sodium benzoate and/or phenylacetate	210 milligrams/kg IV/IO over 90 min 250 milligrams/kg IV/IO continuous infusion over 24 h
Organic acidemias	Carnitine	400 milligrams IV/IO or PO
Fatty acid oxidation defects	Biotin	10 milligrams IV/IO or PO
Pyridoxine-dependent seizures	Pyridoxine	100 milligrams IV/IO
Maple syrup urine disease, primary lactic acidosis	Thiamine	25–100 milligrams IV/IO

DISPOSITION AND FOLLOW-UP

All patients in metabolic crisis should be admitted to the hospital or transferred to a tertiary care children's hospital where metabolic specialists are available to help with definitive diagnosis and dietary management. Patients with severe metabolic abnormalities requiring hemodialysis require intensive care.

CONGENITAL ADRENAL HYPERPLASIA (ADRENAL INSUFFICIENCY)

Congenital adrenal hyperplasia results from an autosomal recessive deficiency in one of the five enzymes involved in the production of cortisol. Absence of these enzymes leads to decreased conversion of 17-hydroxyprogesterone to 11-desoxycortisol with resultant cortisol deficiency. Most of the enzyme deficiencies also impair conversion to progesterone and 11-desoxycorticosterone in the mineralocorticoid pathway, which leads to decreased aldosterone production. Deficiency of 21-hydroxylase accounts for most cases.[17] Seventy-five percent of affected newborns manifest the classic salt-losing, virulizing variant in which urinary salt wasting with hyperkalemia and hyponatremia dominates the clinical picture. Twenty-five percent of cases are the non–salt-losing simple virulizing type. Infants with salt-losing forms of congenital adrenal hyperplasia typically present during the second to fifth weeks of life in crisis, sometimes before the results of newborn screening tests for the disease are available.

PATHOPHYSIOLOGY

Congenital adrenal hyperplasia is a group of disorders of adrenal steroid biosynthesis that result from a defect in one of five enzymes (**Figure 146-3**). Depending on the specific enzyme deficiency, cortisol deficiency may be accompanied by mineralocorticoid deficiency, leading to hypoaldosteronism with resultant salt wasting. Because the hypothalamic-pituitary axis is suppressed by cortisol, the deficiency results in increased secretion of adrenocorticotropic hormone without feedback suppression. Uninhibited excess adrenocorticotropic hormone stimulates the adrenal gland, which leads to hypertrophy. Elevated adrenocorticotropic hormone levels can also cause hyperpigmentation of the skin, which is best observed on the labial or scrotal folds and the nipples. Steroid hormone precursors upstream of the enzyme defect build up and are shunted into alternate pathways. Deficiencies in 21-hydroxylase lead to the accumulation of precursors that are metabolized to androgens. This, in turn, causes virilization of affected females, which manifests as clitoromegaly. Affected males may go undetected at birth because their genitalia appear normal.

CLINICAL FEATURES

HISTORY

Salt-wasting variants of congenital adrenal hyperplasia typically manifest as acute crisis in the second week of life. Symptoms are vague and include lethargy, irritability, poor feeding, vomiting, and poor weight gain. Depending on the duration and severity of symptoms, infants may present with significant dehydration or even shock. Obtain a complete

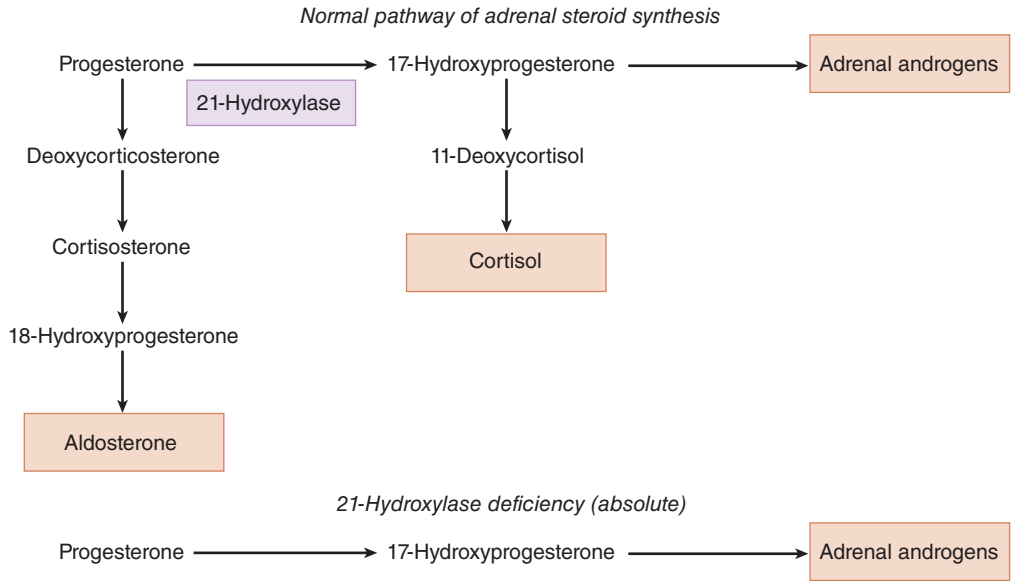

FIGURE 146-3. Normal pathway of adrenal steroid synthesis.

history of the presenting symptoms, because the differential diagnosis of adrenal salt-wasting crisis includes sepsis, congenital heart disease, and other inborn errors of metabolism. Review gestational age and birth weight as well as maternal history regarding complications of pregnancy, prior pregnancies, miscarriages, spontaneous abortions, and previous infant deaths. Try to obtain results of the newborn screening.

PHYSICAL EXAMINATION

Record vital signs and weight and assess hydration and mental status. In addition to performing a complete head-to-toe examination, carefully examine the genitalia. Females may have fusion of the labia and an enlarged clitoris. Males may have normal genitalia or a small phallus or hypospadias. Note any hyperpigmentation, especially in the scrotal or labial folds and around the nipples.

DIAGNOSIS

The most important laboratory studies are a bedside glucose level and serum electrolyte levels. Although hypoglycemia is rare, poor feeding and vomiting may cause secondary hypoglycemia requiring urgent treatment. **The classic electrolyte abnormalities in salt-wasting congenital adrenal hyperplasia are hyponatremia and hyperkalemia.** Serum potassium level may be elevated to between 6 and 12 mEq/L, although changes in cardiac function and ECG are unusual. Metabolic acidosis typically accompanies the classic electrolyte abnormalities as a result of aldosterone deficiency and dehydration.

Definitive diagnosis depends on analysis of blood hormone levels. If possible, obtain results of a steroid profile prior to treatment, but do not delay treatment in the critically ill neonate. Because the presentation of adrenal salt-wasting crisis is nonspecific, consider alternative diagnoses such as sepsis.

Although infants generally tolerate hyperkalemia well, obtain a 12-lead ECG, because hyperkalemic changes may alter emergent therapy and disposition. Imaging studies are not routinely indicated or helpful.

TREATMENT

Circulatory collapse from cortisol deficiency and dehydration is common, so establish IV or IO access rapidly. Administer IV fluids in the form of 10 to 20 mL/kg of normal saline. Fluid loss in congenital adrenal hyperplasia is isotonic, and fluid replacement should be with normal saline. Treat hypoglycemia with 5 mL/kg of 10% dextrose as discussed earlier in "Hypoglycemia."

Initiate steroid hormone replacement urgently: give hydrocortisone, 25 milligrams IV/IO to neonates, 50 milligrams to toddlers and school-age children, and 100 milligrams to adolescents. Although mineralocorticoid deficiency in congenital adrenal hyperplasia is primarily treated by sodium repletion with normal saline, there is some mineralocorticoid effect at these high doses of hydrocortisone.

If hyperkalemia results in ECG changes or arrhythmia, treat with IV calcium gluconate (10%), 100 milligrams/kg (1 mL/kg), and sodium bicarbonate, 1 mEq/kg. **Do not give insulin and glucose for hyperkalemia in infants because this may result in profound hypoglycemia**. The administration of normal saline and hydrocortisone is usually sufficient to lower serum potassium levels in the absence of cardiac manifestations.

DISPOSITION AND FOLLOW-UP

All infants with salt-wasting crisis require admission to the hospital. Infants with signs of shock or severe hyperkalemia with ECG changes should be admitted to the intensive care unit, with endocrinology consultation.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 147

Diabetes in Children

Adam E. Vella

INTRODUCTION AND EPIDEMIOLOGY

Diabetes is subclassified into type 1 and type 2. Type 1 diabetes, previously referred to as *insulin-dependent diabetes mellitus* or *juvenile-onset diabetes* because of its earlier onset, is characterized by an abrupt and frequently complete decline in insulin production. Type 2 diabetes, formerly referred to as *non–insulin-dependent diabetes mellitus* or *adult-onset diabetes*, is marked by increasing insulin resistance and most commonly occurs in the overweight adult or adolescent; there is a strong

genetic tendency toward the disease. Gestational diabetes can affect pregnant teens as well as the infants of diabetic mothers. There has been an increase in the prevalence of type 1 diabetes of 21% between 2001 and 2009 and an increase of 31% in type 2 diabetes in the same time period.[1] While the cause of the increase in type 1 diabetes is unknown, some experts suggest that the increasing prevalence of type 2 diabetes may be a result of minority population growth, obesity, exposure to diabetes in utero, and perhaps endocrine-disrupting chemicals.[1] Diabetes is the most common pediatric endocrine disorder, with an estimated prevalence of 1 in 400. As many as 34% of children with new-onset type 1 diabetes present in diabetic ketoacidosis (DKA).[2] In children with known diabetes, DKA is much less common and tends to be clustered in a small subset of patients, with 5% of children with diabetes accounting for nearly 60% of DKA episodes.[3] DKA is the leading cause of mortality in patients with diabetes <24 years of age, and cerebral edema is the leading cause of mortality in DKA.[4]

PATHOPHYSIOLOGY AND CLINICAL FEATURES

The fundamental cause of DKA is an absolute or relative insulin deficiency that results in the inability of cells to take up and use glucose. Levels of counterregulatory hormones (catecholamines, cortisol, growth hormone, and glucagon) are elevated, which drives many of the physiologic disturbances observed in DKA. These hormones increase glucose production by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis, and further decrease glucose utilization by antagonizing insulin.

As the serum glucose level exceeds the renal absorption threshold, an obligatory osmotic diuresis ensues, which results in the classic symptoms of polyuria and polydipsia. If not recognized early, this can lead to profound dehydration and electrolyte disturbances. Acidosis stems from the complex metabolic derangements induced by insulin deficiency and unopposed glucagon. The cellular milieu of the body is essentially in a state of functional starvation, unable to use the excess serum glucose. Decreased lipid uptake by adipose tissue and increased lipolysis result in an overabundance of circulating free fatty acids, which are converted by the liver into the ketoacids acetoacetate and β-hydroxybutyrate.

Despite this profound shift in substrate production, ketoacid utilization and renal elimination are both impaired, which results in a wide anion gap metabolic acidosis. In certain patients, the acid-base status may be more complex. Persistent vomiting and severe volume depletion may result in a superimposed metabolic alkalosis that may mask the severity of the acidosis by producing a relatively normal pH. Severe dehydration and poor perfusion further lead to lactic acidosis, which results in a superimposed anion gap acidosis. Alternatively, a patient who remains relatively well hydrated will lose sodium with keto anions in the urine while retaining chloride and demonstrate a significant non–anion gap acidosis.

See Chapters 223 and 224, "Type 1 Diabetes Mellitus" and "Type 2 Diabetes Mellitus," respectively, for more discussion of the pathophysiology of diabetes; and Chapter 226, "Ketoacidotic Syndromes."

Polyuria, polydipsia, and polyphagia are the classic symptom triad of type 1 diabetes. Other common symptoms include weight loss, secondary enuresis, anorexia, vague abdominal discomfort, visual changes, and genital candidiasis in a toilet-trained child. The diagnosis is established by demonstrating hyperglycemia, ketonemia, and glucosuria in the absence of other causes such as steroid therapy, Cushing's syndrome, pheochromocytoma, hyperthyroidism, or other rare disorders. Signs of uncontrolled diabetes span the entire spectrum from simple hyperglycemia without ketonuria to diabetic ketosis (hyperglycemia with ketonuria) to full-blown DKA.

DIABETIC KETOACIDOSIS

DKA is a metabolic acidosis (pH <7.30 or serum bicarbonate level of <15 mEq/L) with hyperglycemia (serum glucose level of >200 milligrams/dL [>11 mmol/L]) and ketonemia.[5,6] DKA is much more common in patients with type 1 diabetes than in those with type 2, but it is not uncommon for patients with type 2 diabetes to develop a hyperglycemic hyperosmolar state, which can result in severe total body water, potassium, and phosphorus deficits. Hyperglycemic hyperosmolar state, which is estimated to account for 1% of all diabetic admissions, has a case fatality rate of 5% to 20%.[5,7]

In the patient with known diabetes, the diagnosis of DKA is relatively straightforward. The most common cause of DKA in children and adolescents with known diabetes is poor adherence to the prescribed insulin regimen. Other precipitants include intercurrent viral illness and focal infections such as urinary tract infection or gastroenteritis. Patients complain of polydipsia and polyuria (if not dehydrated), diffuse nonfocal abdominal pain often associated with vomiting, difficulty breathing, and generalized malaise, in addition to any localizing complaints related to a precipitating trigger. Kussmaul breathing may be mistaken for pulmonary pathology or even anxiety with hyperventilation.

CLINICAL FEATURES

Physical findings in DKA are due to dehydration and metabolic acidosis. Children appear dehydrated, are tachycardic, and may be hypotensive. Respiratory compensation for acidosis is noted in the deep Kussmaul respirations, which may be accompanied by paresthesias. Acetoacetate is converted to acetone and is responsible for the classic breath odor of nail polish. The level of consciousness may range from alert to somnolent to comatose. **In a child with DKA and a depressed level of consciousness, consider the development of cerebral edema**. See later discussion under "Cerebral Edema."

Abdominal pain and vomiting often accompany DKA. Distinguish nonspecific abdominal pain or gastroenteritis from more serious intra-abdominal disorders such as acute appendicitis. Focal abdominal tenderness, failure of pain to resolve with fluid therapy, and associated fever suggest an underlying intra-abdominal process.

An elevated glucose level in the presence of ketonemia/ketonuria and acidosis almost always indicates DKA. However, other rare conditions possess similar clinical characteristics. Any condition resulting in prolonged vomiting or excessive fasting can result in ketoacidosis, but the glucose level is not elevated. **In adolescent patients without known diabetes, consider toxic ingestions of ethylene glycol, isopropyl alcohol, or salicylates**.

LABORATORY EVALUATION

Initial blood studies should include CBC; serum glucose level; serum electrolytes including calcium, magnesium, and phosphate; serum beta-hydroxybutyrate[8]; venous blood gas analysis; serum lactate; and urinalysis. Hyperglycemia, metabolic acidosis, and elevated serum beta-hydroxybutyrate confirm the diagnosis of DKA. **The pH determined by venous blood gas analysis is only 0.03 less than that measured by arterial blood gas analysis and is an accurate reflection of the acid-base status.**[9] Obtain other laboratory studies as clinically indicated.

Several factitious laboratory abnormalities may be seen in DKA. An increased WBC count is common in DKA and should be interpreted in the context of physical findings and results of diagnostic studies for infection. **Depending on the type of laboratory analysis used to measure creatinine, serum acetoacetate may result in a factitious elevation in the serum creatinine level, but β-hydroxybutyrate does not.**[10]

The serum glucose level is usually >350 milligrams/dL (19.4 mmol/L), but a glucose level of <300 milligrams/dL (16.6 mmol/L) can be consistent with DKA. Euglycemic DKA may occur in a young, well-hydrated diabetic who is adherent to the insulin regimen but has relative insulin deficiency caused by an intercurrent illness. **Even in the absence of hyperglycemia, insulin is needed when acidosis and ketonemia are present.**

Change in the **serum potassium** level is the most critical electrolyte disturbance in DKA. Hypokalemia can be both profound and present despite relatively normal initial laboratory values due to ion shifts in response to acidosis. The average potassium deficit is 3 to 5 mEq/kg (150- to 250-mEq potassium deficit in a 50-kg adolescent), and the initial serum level is often normal or high. Potassium depletion is a result of insulin deficiency (which normally drives potassium into cells), acidemia (which causes the redistribution of potassium out of the cells in exchange for hydrogen), volume contraction, and tissue catabolism.

These processes all provide increased potassium available for urinary excretion. Within this context, initial hypokalemia signifies a severe deficit and a potentially dangerous situation that requires potassium supplementation once urine output is established.

Serum bicarbonate is invariably low, and a wide anion gap acidosis from the ketonemia is usually noted. In simple DKA, the bicarbonate level should fall to the extent that the anion gap increases. A decrease in the bicarbonate level *less* than expected for a given increase in the anion gap in the vomiting patient indicates the presence of an accompanying metabolic alkalosis. Conversely, a decrease in the bicarbonate level *greater* than expected for the increase in the anion gap indicates a concomitant non–anion gap acidosis. This is frequently seen in well-hydrated patients who are still able to excrete the keto anions while retaining chloride or in severely dehydrated patients with accompanying lactic acidosis.

The **serum osmolality** is increased in DKA, and its increase correlates with the decrease in the level of consciousness at presentation. Osmolarity of >340 mOsm/L often results in a stuporous or comatose state, whereas a serum osmolarity of <300 mOsm/L should prompt reconsideration of the cause of a decreased level of consciousness. The development of cerebral edema may be correlated with the rate of decline in the serum osmolarity; thus, it is critical that fluid deficits be corrected less rapidly in patients with high serum osmolarity. See later discussion under "Cerebral Edema."

Sodium deficits average 5 to 10 mEq/kg, but the serum sodium level may be normal because of excessive free water loss. More typically, the serum sodium level is factitiously low because of hyperglycemia, and a corrected value may be arrived at by using the following formula: corrected sodium level = {1.6 × [(serum glucose level – 100)/100]} + measured serum sodium level.

The major **ketoacid** produced is beta-hydroxybutyrate. Unlike acetoacetate, however, it does not react with the nitroprusside used in urine and serum ketone assays, so measured ketone levels may appear low for the degree of acidosis and do not reflect the true extent of ketonemia. This fact also explains the paradoxical rise in measured ketone levels with therapy; beta-hydroxybutyrate is converted to acetoacetate, which reacts more strongly with the assay. Using bedside ketone testing to monitor recovery is further complicated by the persistence of urine ketones after clearance of serum ketones.[11]

TREATMENT OF PEDIATRIC DIABETIC KETOACIDOSIS

Intensive monitoring and meticulous care of the patient with DKA improve outcome. During treatment, monitor bedside glucose every hour, and check electrolytes and venous blood gases every 2 hours. **Provide continuous cardiac monitoring of all children with DKA,[4] as a prolonged QT_c interval occurs frequently during DKA and is correlated with ketosis.[12]** QT_c prolongation can lead to life-threatening arrhythmias such as torsades de pointes. Avoid medications that may further prolong the QT interval such as ondansetron.

Direct attention to perfusion, electrolyte disturbances, mental status, hyperglycemia, and ketonemia (Table 147-1). Concurrently identify and treat associated infections.

FLUID RESUSCITATION

The average fluid deficit is 5% to 10% of body weight but may be greater. Give an initial 20 mL/kg bolus of normal saline if the child is in shock and repeat if needed. **Once vital signs have stabilized, resist the desire to correct the fluid deficit too rapidly, especially if there is a high calculated osmolarity (i.e., >340 mOsm/L)**. Many institutions replace the deficit evenly over 24 to 48 hours; this moderated approach helps to avoid overhydration, pulmonary complications, and possibly cerebral edema. The traditional approach is 50% deficit replacement in the first 8 hours with the rest replaced over the next 16 to 24 hours.

ELECTROLYTE REPLACEMENT

Sodium depletion from vomiting and urinary losses rarely causes a problem by itself and is most often related to the extent of dehydration.

TABLE 147-1 Management of DKA in Children

- 20 mL/kg NS bolus over 1 h; repeat if hypotensive.*
- After initial bolus and achievement of normotension, begin NS at 1.5 times maintenance level in the ED.†
- If [K^+] is 3.5–5.5 mEq/L and patient is urinating, add 30 mEq potassium per liter (half as potassium chloride and half as potassium phosphate). If initial [K^+] is 2.5–3.5 mEq/L, add 40 mEq [K^+] per liter; consider adding more if the [K^+] is <2.5 mEq/L.
- Begin regular insulin at 0.1 unit/kg/h after IV fluid bolus (if given) is complete. Adjust dose to maintain glucose decline at 50–100 milligrams/dL/h. **Do not decrease insulin infusion to <0.05 unit/kg/h because insulin is required to clear ketosis even when glucose has normalized.**
- Add dextrose to IV fluids when blood glucose level is <200–250 milligrams/dL (11–14 mmol/L).
- Measure serum electrolyte levels every 2 h; measure serum glucose level every hour.

Abbreviations: K = potassium; NS = normal saline (0.9% sodium chloride).

*In the setting of hypotension, bolus patient with 20 mL/kg NS repeatedly until normotensive.

†Alternatively, calculate fluid deficit and correct 50% over the first 12–16 h. Some authorities recommend a higher calculated sodium concentration of between 0.45% and 0.9% sodium chloride.

The main concern with sodium level lies in its correction: **failure of serum sodium level to rise in the treatment of DKA is associated with the development of cerebral edema.[13]** Typical protocols historically recommended 0.9% sodium chloride correction at 1.5 times the maintenance level for empiric replacement therapy. However, in an attempt to decrease the risk of cerebral edema, some newer protocols advocate sodium concentrations of 0.66% (typically mixed by the pharmacist) to 0.9% sodium chloride and calculate fluid replacements to tighten control over biochemical parameters.[4] This approach is effective in ensuring a steady rise in the sodium concentration.

Withhold **potassium** until hyperkalemia (i.e., potassium level of >6.0 mEq/L) is excluded and the child is urinating. ECG findings may be normal in the face of hyperkalemia, so monitor the serum potassium level. Total-body potassium deficits are often large, and both initial rehydration and insulin therapy can cause a precipitous decline in potassium levels due to redistribution.

Initial hypokalemia (i.e., <3.0 mEq/L) indicates a profound deficit, and therapy should be aggressive; insulin will further lower serum potassium, so close monitoring and replacement are essential. **The recommended rates of potassium replacement vary widely, but in general, maintenance fluids should contain between 30 and 40 mEq [K^+] per liter**. Consider higher doses for children with demonstrated hypokalemia, although a central line is needed and intensive care unit monitoring is required at most institutions. Monitor serum potassium at least every 2 hours.

Phosphate depletion in DKA is well described, but the value of IV replacement has never been proven. In the absence of replacement, one should monitor for symptomatic hypophosphatemia (serum phosphate level of <1 mmol/L, muscular weakness, rhabdomyolysis, respiratory depression). The same rule applies to **magnesium** replacement. **Hypocalcemia**, when present, is likely secondary to overaggressive phosphate replacement. For symptomatic hypophosphatemia, phosphate can be added to IV fluids in the form of potassium phosphate, providing half of the calculated potassium needs with potassium phosphate and half with potassium chloride.

INSULIN

Fluid resuscitation will reduce serum glucose levels somewhat but does not correct ketonemia or acidosis. After the patient is hemodynamically stable, begin a low-dose insulin infusion. High-dose insulin therapy does not improve the rate of recovery and places the patient at greater risk of hypoglycemia and hypokalemia. **A loading *bolus* of 0.1 unit/kg is no longer considered beneficial and is considered potentially harmful because it has been associated with an increased risk for cerebral edema.[14]**

The insulin infusion dosage is 0.1 unit of regular insulin per kilogram per hour. As a rule of thumb, decrease serum glucose by

50 to 100 milligrams/dL/h (2.8 to 5.6 mmol/L) in a slow, controlled fashion to prevent intracerebral osmolar shifts. If improvement of the pH is too slow (<0.03 pH units per hour), the insulin infusion rate can be doubled. **Generally, glucose level corrects faster than the ketoacidosis, so add dextrose to the IV fluids when the blood glucose level drops to <250 milligrams/dL (14 mmol/L) without stopping the insulin infusion, with the goal of maintaining a serum glucose level of 150 to 300 milligrams/dL (8.3 to 16.6 mmol/L) until resolution of the ketoacidosis**.

Initiate glucose along with insulin for the patient with **euglycemic DKA**. If the blood glucose level continues to decline, provide additional glucose before considering adjustment of the insulin drip. If the child is receiving the maximum glucose concentration available (or maximum tolerable concentration if through a peripheral line), then the administration of insulin can be temporarily held for 10 to 15 minutes before restarting the insulin drip at a lower rate. **In general, this rate should not be <0.05 units/kg/h**. The short half-life of IV insulin (5 to 10 minutes), along with the continued administration of glucose, will correct transient hypoglycemia. Continued insulin administration is the mainstay of therapy and should be maintained until reversal of ketoacidosis.

Do not transition the insulin infusion to SC administration until the pH is >7.30, bicarbonate level is >15 mEq/L, and serum ketones have disappeared. At that point, taper the IV insulin to 0.02 to 0.05 unit/kg/h and initiate multidose SC insulin using a regular insulin (short acting) at a dose of 0.1 unit/kg every 2 hours to maintain serum glucose between 150 and 200 milligrams/dL (8.3 to 13.8 mmol/L); **do not stop the IV insulin infusion until 1 to 2 hours after initiating SC therapy.** Do not simply discontinue insulin therapy altogether when DKA resolves, because DKA will recur without adequate continued serum insulin. There is institutional variation regarding the preferred SC insulin regimen, so consult with a pediatric endocrinologist about preferred local practices.

BICARBONATE THERAPY FOR ACIDOSIS

The routine use of bicarbonate in the treatment of DKA is not recommended because it does not improve outcome and has been associated with a fourfold increase in the development of cerebral edema.[5] In addition, bicarbonate therapy can lead to volume overload, accelerated hypokalemia, hypernatremia, and paradoxical CNS acidosis.[15] **Bicarbonate administration should be limited to critically ill patients with a pH of <7.0 and hemodynamic compromise (unresponsive to fluid resuscitation) from depressed cardiac contractility and poor perfusion**. If necessary, depending on the pH and the patient's clinical condition, bicarbonate may be administered slowly at 0.5 to 2.0 mEq/kg over 1 to 2 hours. **Correction should never exceed a pH of 7.1 or a serum bicarbonate level of 10 mEq/L.**

DISPOSITION AND FOLLOW-UP

Most patients with DKA require admission to the intensive care unit, even once stabilized, because of intensive monitoring needs. Furthermore, many hospitals restrict the use of insulin infusions to intensive care settings. Patients with known diabetes who have a pH of >7.35 and a bicarbonate level of >20 mEq/L, have a known and resolving precipitant for DKA and a good clinical appearance, and have a solid social situation and will follow up closely with their primary physicians may be discharged home. In as many as 69% of patients with a starting pH of >7.20 or a serum bicarbonate level of >10 mEq/L, acidosis is corrected within 6 hours.[6]

CEREBRAL EDEMA

PATHOPHYSIOLOGY

Cerebral edema, which occurs in approximately 0.5% to 1% of all children presenting with DKA, is the most dreaded complication, accounting for 60% to 90% of all pediatric DKA-associated deaths.[4] Mortality rates range from 21% to 24%, and only 14% to 57% of children who develop the disorder recover neurologically normal.[13] Cerebral edema more commonly develops in children <5 years old and is rare in persons >20 years old (**Table 147-2**).[13] It is likely that all patients with severe DKA have some degree of subclinical cerebral edema,[16] but the **specific risk factors associated with overt, life-threatening cerebral edema are young age, severe hyperosmolality, persistent hyponatremia, and severe acidosis.**[5,13] Failure of serum sodium level to rise commensurately with the fall in glucose level during therapy may be an important predictor.[13] **Newer studies refute the belief that overaggressive fluid resuscitation per se is a significant risk factor.**[2,17] The incidence of cerebral edema has not changed over the past 15 to 20 years, despite the introduction of gradual rehydration protocols over the same interval.[17] Furthermore, a randomized study of two rehydration protocols in DKA was assessed for the risk of associated MRI-documented subclinical cerebral edema and showed no difference in the rate of cerebral edema between an aggressive and a more judicious rehydration protocol.[18] The most recent study, which is likely the largest study to date on the topic, was a multicenter, randomized controlled trial that evaluated the fluid type and administration rate in a two-by-two factorial design in children with DKA.[19] The study demonstrated no difference in neurologic outcomes in children based on either fluid type or the rate of administration and suggests that more rapid administration of fluid is likely safe and does not lead to an increased risk of cerebral edema. A vasogenic process has been postulated as the predominant mechanism of cerebral edema formation in DKA rather than osmotic cellular swelling.[16,20] A study using perfusion MRI during DKA treatment in children demonstrated increased cerebral blood flow, suggesting a difference in the hemodynamic states of dehydrated and resuscitated children with DKA. The authors further noted that the patients with greater dehydration and more profound hypocapnia had an increased risk of cerebral edema, possibly as a result of cerebral hypoperfusion and ischemia prior to treatment.[20] Regardless of the exact mechanism, caution in fluid administration is prudent, particularly in the extremely hyperosmolar child (i.e., osmolarity of >340 mOsm/L).

TABLE 147-2 Risk Factors, Prevention, and Treatment of Cerebral Edema

Factors indicating high risk
• Age <5 y
• Severe acidosis
• Severe hyperosmolality
• Failure of serum sodium level to rise with therapy
Prevention
• Avoid high-dose insulin therapy
• Early clinical recognition
• Avoid administration of sodium bicarbonate
Treatment
• 5–10 mL/kg of 3% saline over 30 min or mannitol, 0.5–1 gram/kg IV bolus
• Fluid restriction
• Appropriate airway management and ventilation

CLINICAL FEATURES

Cerebral edema typically manifests itself 6 to 12 hours after the onset of therapy (**Figure 147-1**).[5] Many children appear to be improving clinically and biochemically prior to deterioration from cerebral edema. **Premonitory symptoms occur in as few as 50% of patients and include severe headache, declining mental status, seizures, and papilledema**. Unfortunately, respiratory arrest may be the first sign of cerebral edema. Early aggressive intervention based on the clinical evaluation, *often before confirmatory CT findings*, is vital to prevent respiratory arrest, herniation, and death.[13,21] Once respiratory arrest has occurred, meaningful recovery is unlikely.[13]

TREATMENT

Standard treatment for cerebral edema is mannitol (0.25 to 1 gram/kg IV bolus) and endotracheal intubation if necessary. A recent case series reported improvement after infusion of hypertonic saline. Four children given **10 mL/kg of 3% hypertonic saline** infused over

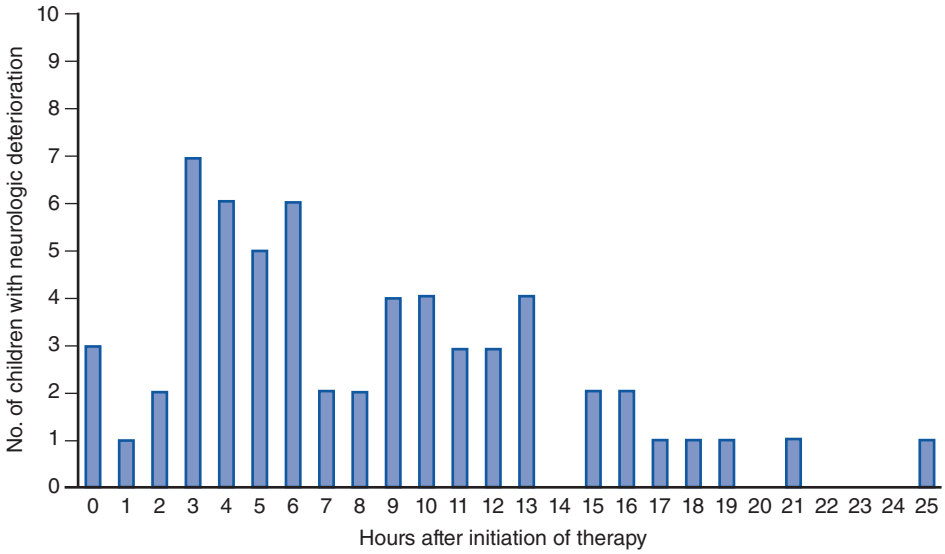

FIGURE 147-1. Diabetic ketoacidosis (DKA) and cerebral edema: time between the initiation of therapy and neurologic deterioration in children.

30 minutes had improved findings on neurologic examination with no apparent complications.[22] Limit additional fluid administration to the minimum possible to retain a functioning IV catheter or use a heparin lock to allow immediate IV access as necessary. If the child appears more clinically stable and is still in the ED, give **half** of normal maintenance fluids until the child reaches the pediatric intensive care unit.

Historically the teaching has been that hyperventilation reduces cerebral blood flow and may worsen cerebral ischemia; however, failure to compensate for the metabolic acidosis through adaptive hyperventilation may lead to hyperemia and worsening of cerebral edema.[23] **Avoidance of a normocapnic state in patients with a severe metabolic imbalance certainly seems prudent**. Consider cerebral venous sinus thrombosis in the child with clinical symptoms of cerebral edema without obvious findings on CT, as this diagnosis may be missed without contrast administration and is better demonstrated on MRI.

SPECIAL CONSIDERATIONS

INSULIN PUMP AND DIABETIC KETOACIDOSIS

Because most episodes of DKA are related to inadequate insulin delivery, this implies malfunctioning of the insulin pump. Alternatively, the pump may be functioning correctly, but the child may have an intercurrent illness with increased and unmet insulin needs. **Either way, shut off the pump and treat the child like any other insulin-dependent diabetic patient with DKA**.

NEW-ONSET HYPERGLYCEMIA

Many children with new-onset diabetes present with classic symptoms of diabetes such as polydipsia, polyuria, and malaise and are identified before significant ketoacidosis develops. They are frequently sent from the outpatient physician's office to the ED for management and admission. ED management for these children is less intensive and should be done in coordination with an endocrinologist. In general, children with hyperglycemia but no DKA are only mildly dehydrated, serum ketones are not elevated, urinary ketones may or may not be present, and the serum pH is >7.3. The speed at which such children descend toward actual DKA is largely a function of hydration status and age. Infants and very young children progress more rapidly because of their inability to access fluids independently and their increased metabolic rate. With appropriate hydration and timely insulin administration, DKA is very unlikely to develop in the hospital in the absence of serious underlying illness.

ED management should be restricted to drawing samples for baseline laboratory studies; providing fluids PO or IV, depending on the need; and possibly administering the first dose of insulin. **An acceptable initial dose is 0.1 unit/kg SC of regular insulin**. Whether or not children with new-onset diabetes are particularly sensitive to insulin is a matter of debate. Still, monitor serum glucose levels closely—every hour after insulin is administered. Consider admission for education and to establish daily insulin requirements. **Daily insulin requirements are generally in the range of 0.5 to 1.0 unit/kg/d in divided doses, two thirds in the morning and one third in the evening.**

HYPERGLYCEMIA IN PATIENTS WITH PREDIAGNOSED DIABETES

For a diabetic child with hyperglycemia with or without an intercurrent illness or injury, management should focus on the primary reason for the ED visit. **An additional dose of 10% of the child's normal daily insulin dose can be administered as regular insulin SC for simple hyperglycemia**.

For children with an intercurrent illness, more specific management guidelines may vary among endocrinologists and also may depend on whether or not urinary ketones are present. **An acceptable approach if the child has an intercurrent illness and no urinary ketones is to administer an additional 5% of the daily insulin dose every 4 to 6 hours until the condition resolves. If the child has urinary ketones, administer 10% of the daily dose every 4 to 6 hours until the ketonuria resolves, and then decrease to 5%, as noted earlier.**

HYPERGLYCEMIA IN PATIENTS TAKING INSULIN GLARGINE

Occasionally, a child will present with hyperglycemia without DKA after missing one or more doses of **insulin glargine (Lantus®)**. Glargine is a long-lasting once-daily insulin preparation that has no peak effect. Generally, glargine is given at approximately 50% of the daily insulin requirement, with the rest given as a short-acting preparation, so that missing a single dose of glargine is not equivalent to missing all insulin doses for the day.

If the child is off schedule for insulin glargine and does not have DKA, a single injection of neutral protamine Hagedorn insulin can be given, followed by resumption of the regular dosing schedule.

If the child is off schedule for insulin glargine and has DKA, treatment is no different from management of other cases of DKA.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 148

The Child With Special Healthcare Needs

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INTRODUCTION AND EPIDEMIOLOGY

Children with special healthcare needs (CSHCN) have or are at increased risk for chronic physical, developmental, behavioral, or emotional conditions and require health and related services of a type or amount beyond those required by children generally.[1,2] This group of children encompasses a wide spectrum of medical complexity, functional limitations, and resource utilization.[3,4] A subset of the CSHCN population, children with medical complexity have substantial healthcare service and resource needs for their chronic conditions.[4,5] Their response to illness and trauma may be unpredictable compared with the normal pediatric patient, sometimes leading to a rapid and unexpected deterioration. This requires a personalized approach that addresses their special needs and chronic medical problems in addition to the emergency medical condition at hand. This unique response to illness and injury accounts for the majority of pediatric hospital days and deaths in this group.[4,6] CSHCN is a growing population, accounting for 15% to 18% (11.2 million) of children in the United States[7,8] and for 40% to 80% of all pediatric healthcare utilization and costs.[7,9,10,11] These trends are largely due to increased survival of premature infants and improved medical or surgical treatment of conditions that were once terminal.[5,6] Compared to typical children, children with chronic conditions tend to be older, male, and from white racial or ethnic groups.[8,10-13] The clinical spectrum of CSHCN conditions is diverse, and complex medical devices are often required for care (**Tables 148-1** and **148-2**).[10-12,14-17] Because of the increasing prevalence of this patient population and their high rate of healthcare utilization, emergency medical practices must adapt to meet the needs of this complex group.[18]

EMERGENCY INFORMATION FORM

An emergency information form provides information and instructions to optimize emergency care for complex medical conditions.[16,22] Components of a comprehensive medical plan include information about the patient's chronic conditions, special instructions for devices or in case of emergencies, and supplies that might be required for routine or emergency medical care.

The individualized information form can be provided at the ED visit by the patient's caregiver. Informational elements of the form include demographic and emergency contact information; names and contact information for the primary and specialty care physicians; diagnoses, past procedures, and baseline examination findings; vitals; allergies; immunizations; procedures to avoid; common acute problems and suggested management; and comments on other specific medical issues or special instructions for device malfunction. Information should be regularly updated. Copies and access to the form should be available at the home, physician's office, and care facilities.

The care plan should include special instructions for EMS personnel, first responders, or family members who may need to provide emergency care for the child.[15,16] A "go-bag" or kit with specialized equipment should accompany the child. These kits can contain needed supplies such as extra tracheostomy tubes and equipment for replacement, appropriate size suction catheters, syringes and adapters to decompress feeding tubes, a bag-valve mask resuscitator, and needles to access central lines.[23] It is important for medical providers to ask for this special equipment in emergency situations.

GENERAL CLINICAL APPROACH

As in typical pediatric emergencies, a standardized approach is needed. Attention to airway, breathing, and circulation is paramount to caring for any child; however, special consideration for known chronic conditions will drive the practitioner's workup and resuscitation. For example, a child with history of comorbidities and resulting temperature instability may present to the ED with hypothermia (<36.5°C) in the setting of infection.[20] Active rewarming and consideration of sepsis even in absence of more classical indicators such as fever and tachycardia are important for approaching the child's treatment. Ancillary clinical data such as cardiac monitoring, pulse oximetry, capnography, continuous temperature monitoring, and near-infrared spectrometry may provide important information to the practitioner. Access to multiple informational resources including family, primary care physicians, specialists, and home health nurses is helpful in tailoring the approach to the individual child (**Table 148-3**).[15,16,23] Long-term caregivers often know the child's baseline status and are familiar with medications and supportive equipment.

HISTORY AND PHYSICAL EXAMINATION

The child may not be able to communicate directly. Elicit essential elements of the history and subtle symptoms of illness from family or care providers; occasionally, a call to a chronic care facility or review of past medical records is necessary to obtain important details. **Inquire about advance directives, limitations of care, and family goals** as well as treatments prior to ED arrival. Carefully review medications including recent changes or missed doses, allergies (e.g., latex), and comorbidities. The physical examination often relies on accompanying family or care providers, particularly with regard to mental status, assessment of pain, and changes from baseline. Obtain vital signs. Baseline vital signs for children with medical complexity may be out of the range of normal. Core temperature may be low at baseline, and a "normal" temperature may represent fever; baseline values for heart rate, respiratory rate, and oxygen saturation may be abnormal; vital signs may be controlled by a pacemaker or ventilator. Baseline pulse oximetry may be lower in children with congenital heart disease. Obtain an accurate weight to calculate weight-based medication dosing. To obtain a current weight, if a conventional floor scale is not appropriate, ask caregivers for the most recent weight, use a bed scale, or consider a length-based tape to estimate weight. When performing a head-to-toe evaluation, pay special attention to medical devices and equipment: palpate the scalp for ventricular shunts for swelling or tenderness; check patency of tracheostomy tubes; assess central or peripherally inserted vascular catheters for patency and signs of infection; and examine gastrostomy sites and feeding tubes. The physical exam should include evaluating the back of nonmobile patients for signs of infection or breakdown.

LABORATORY TESTING AND IMAGING

The specific evaluation depends on the presenting problem and underlying special healthcare needs. Perform bedside glucose testing in all complex patients with altered mental status. Check serum drug levels (e.g., anticonvulsants) as appropriate. Children with complex needs are more likely to have electrolyte disturbances than typical children. Compare plain radiographs and CT scans with prior imaging results to distinguish acute from chronic changes.

TREATMENT

Although treatment is tailored to the presenting condition, the universal approach of prioritizing airway, breathing, circulation, and disability remains the same. A general overview of common respiratory, metabolic, neurologic, GI, and musculoskeletal problems and suspected abuse follows. A review of the complications common to children dependent on medical technology is discussed separately later, under "Technology-Dependent Children."

CONGENITAL HEART DISEASE

Many children presenting to the ED will have one of a broad range of congenital heart diseases. The practitioner may notice cyanosis, fingernail clubbing, or a loud murmur on physical exam. It is important to understand each patient's special cardiac needs. They may have been completely surgically repaired with no residual functional limitations due to their heart condition. Alternatively, they may be awaiting

TABLE 148-1 Congenital or Developmental Disorders and Associated Medical Conditions[19,20]

Chromosomal disorders[10,21]

- Down syndrome (trisomy 21 syndrome)
  - Seizure disorder (12%–15%); atlantoaxial instability (14%–22%); cataracts (15%); serous otitis media (50%–70%); deafness (75%); congenital heart disease (50%): ASD, VSD, AV canal, PDA, tetralogy of Fallot, pulmonary hypertension; GI atresias (12%); Hirschsprung's disease (1%); constipation, fecal impaction from medications or hypothyroidism; thyroid disease (15%); diabetes mellitus; leukemia (1%); acquired hip dislocation (6%); and psychiatric disorders (22%)
- Fragile X syndrome
  - Recurrent serous otitis media (60% in males), strabismus (30%–56% in males), seizures (14%–50% in males), autism (16% in males), self-abusive, and mitral valve prolapse (22%–77% in males)
- Trisomy 18
  - Congenital heart disease (99%): VSD, ASD, and PDA
- Turner's syndrome (XO syndrome)
  - Short stature in females, horseshoe kidney, heart disease (bicuspid aortic valve in 30%, coarctation of the aorta in 10%, valvular aortic stenosis, mitral valve prolapse, aortic dissection later in life, and hypertension)
- Noonan's syndrome
  - Webbing of the neck, pectus excavatum, cryptorchidism, and pulmonic stenosis

Disorders with facial defects as major feature

- Pierre Robin syndrome
  - Micrognathia, glossoptosis, and cleft soft palate; primary defect: early mandibular hypoplasia
- Waardenburg's syndrome
  - Lateral displacement of medial canthi, partial albinism, and deafness
  - Occasional associations: VSD, Hirschsprung's disease, esophageal atresia, and anal atresia
- Treacher Collins syndrome
  - Malar hypoplasia with downward-slanting palpebral fissures, defect of lower lid, and malformation of the external ear

Disorders with limb defects as major feature

- Holt-Oram syndrome
  - Upper limb defect, cardiac anomaly (ASD, VSD, arrhythmia), and narrow shoulders
- Fanconi's pancytopenia syndrome
  - Radial hypoplasia, hyperpigmentation, pancytopenia, and renal anomaly
- Radial aplasia thrombocytopenia (TAR syndrome)

Inherited metabolic disorders

- Phenylketonuria (autosomal recessive)
  - Light pigmentation, eczema (33%), poor coordination, seizures (25%), and autistic behavior
- Hunter's syndrome (X-linked recessive)
  - Developmental lag after age 6–12 mo, coarse facies, growth deficiency, stiff joints by age 2–4 y, clear corneas, and hepatosplenomegaly
- Hurler's syndrome (autosomal recessive)
  - Developmental lag after age 6–10 mo, coarse facies, stiff joints, mental deficiency, cloudy corneas by age 1–2 y, hepatosplenomegaly, and rhinitis

Connective tissue disorders

- Marfan's syndrome
  - Arachnodactyly with hyperextensibility, lens subluxation, and aortic dilatation
- Ehlers-Danlos syndrome
  - Hyperextensibility of joints, hyperextensibility of skin, and poor wound healing with thin scar
- Osteogenesis imperfecta congenital
  - Short, broad, long bones; multiple fractures; and blue sclera

Hamartoses

- Sturge-Weber sequence
  - Flat facial hemangiomata and meningeal hemangiomata with seizures
- Tuberous sclerosis syndrome
  - Hamartomatous skin nodules (thumb print macules), seizures, angiomyolipomata (45%–81%), phakomata, and bone lesions
- Neurofibromatosis syndrome
  - Multiple neurofibromata, café-au-lait spots, presence or absence of bone lesions, seizures and/or EEG changes in 20%, cerebrovascular compromise, and headaches

Environmental agents (toxins)

- Fetal alcohol syndrome
  - Vision problems (94%), recurrent serous otitis (93%), hearing loss (66%), heart defects (29%–41%), renal hypoplasia, duplication of the kidney and collecting system, and bladder diverticula (10%)
  - Other environmental exposures include fetal hydantoin syndrome, fetal trimethadione syndrome, fetal valproate syndrome, fetal warfarin syndrome, and retinoic acid embryopathy

Trauma

- Traumatic brain injury
  - Visual and hearing disturbances; cranial nerve damage; spasticity, incoordination, ataxia, and feeding disorders; GERD; neuropsychiatric disturbances
- Cerebral palsy
  - Seizures (33%), strabismus (50%), hearing loss (10%), hip dislocation, scoliosis, contractures, gait disorder, GERD (8%–10%), chronic aspiration and recurrent RAD, pulmonary fibrosis, and bronchiectasis

Miscellaneous

- Angelman's syndrome (happy puppet syndrome)
  - Puppet-like gait, paroxysms of laughter, and characteristic features; seizures vary from major motor to akinetic, beginning usually at age 18–24 mo
- Beckwith-Wiedemann syndrome
  - Macroglossia, omphalocele, macrosomia, and ear creases; neonatal polycythemia and hypoglycemia in early infancy; associated with Wilms' tumor
- CHARGE syndrome
  - Coloboma, heart disease (tetralogy of Fallot, PDA, double-outlet right ventricle with an atrioventricular canal, VSD, ASD, and right-sided aortic arch), atresia choanae, retarded growth and development and/or CNS anomalies, genital anomalies and/or hypogonadism, and ear anomalies and/or deafness
- Prader-Willi syndrome
  - Mental retardation, hypotonia, hypogonadism, obesity, hyperphagia, gastric perforation, hypoventilation, obstructive sleep apnea, cor pulmonale, NIDDM, scoliosis, strabismus, inability to vomit, decreased sensitivity to pain, seizure disorder, hypoxia, right-sided heart failure, and pulmonary hypertension
- Rett's syndrome
  - Hyperventilation, breath holding, air swallowing, bruxism, ataxia, muscle wasting, poor circulation, scoliosis, seizures, and intermittent flushing
- VATER syndrome
  - Vertebral defects and VSD, imperforate anus, tracheoesophageal fistula, renal anomalies, and single umbilical artery
- Williams' syndrome
  - Elfin-like syndrome, cardiovascular disease, supravalvular aortic stenosis, pulmonic stenosis, coarctation of the aorta, strabismus, joint contractures, hypertension, urethral stenosis, vesicoureteral reflux, constipation, ulcers, and hypercalcemia

Abbreviations: ASD = atrial septal defect; AV = atrioventricular; EEG = electroencephalogram; GERD = gastroesophageal reflux disease; NIDDM = non–insulin-dependent diabetes mellitus; PDA = patent ductus arteriosus; RAD = reactive airway disease; TAR = thrombocytopenia-absent radius; VSD = ventricular septal defect.

TABLE 148-2 Common Home Medical Devices and Equipment

- Apnea monitors
- Central venous lines or percutaneous IV catheters and pumps
- Colostomies
- Feeding tubes and pumps
- Internal pacemakers or defibrillators
- Nebulizers
- Oxygen/suction
- Tracheostomies
- Vagus nerve stimulators
- Ventilators
- Ventricular peritoneal shunts

surgical correction or be somewhere in a series of staged surgical corrections.

Depending on the patient's current cardiac physiology, the patient with cyanotic congenital heart disease may have some degree of venous mixing or shunting causing relatively low oxygen saturations. In some cases, a pulse oximetry reading of 70% may be normal, such as in a child with partially repaired hypoplastic left heart syndrome. The same child will have saturations above 90% after completion of their Fontan surgical correction at 3 years of age. At the other end of the spectrum, the child with pulmonary hypertension depends on a normal oxygen saturation (97% to 100%) to ensure adequate pulmonary blood flow. These children will often be on supplemental oxygen at baseline, and it is essential to correct hypoxemia immediately. Ask the patient's caregiver or consult with a cardiologist to determine an acceptable oxygen saturation for each patient and the patient's specific heart defect.

A thorough evaluation of a patient with congenital heart disease may include careful physical examination, vital signs, pulse oximetry, chest radiography, electrocardiography, and consultation with the patient's cardiologist (see Chapter 129, "Congenital and Acquired Pediatric Heart Disease"). Admission to the hospital or transfer to a pediatric center may be warranted for conditions that might otherwise be treated on an outpatient basis in typical children.

RESPIRATORY DISORDERS

Children with complex medical histories frequently present with respiratory problems. Chronic lung disease due to prematurity, reactive airway disease, restrictive lung disease due to scoliosis, dysphagia, and tracheostomies are common in this population. It is important to ask about special respiratory needs, such as bronchodilator use, home oxygen supplementation, thickened diets, airway clearance, and infection history.

To evaluate acute respiratory complaints, obtain a thorough history of past respiratory function, especially in patients with a history of prematurity: escalating home therapy including supplemental oxygen use; increased, colored, or thickened secretions from a tracheostomy tube; bronchodilator and inhaled steroid use in reactive airway disease; or baseline stridor in patients with tracheomalacia. Compare the radiology and laboratory results obtained to previous studies. Capillary blood gases may be an important indicator of current and chronic respiratory status. Airway instability can develop in the child with poor head control, and simple head repositioning or jaw thrust may improve airway mechanics and decrease pooling of saliva in the oropharynx. A nasal trumpet or cervical collar may help maintain airway position, alleviating obstruction. Suction and change tracheostomies as needed. Consider foreign body aspiration in appropriate clinical circumstances. Treatment of respiratory distress in this population may include deep suctioning, replacement of malfunctioning equipment (tracheostomy tubes, ventilators), β-agonists for bronchospasm, antibiotics for pneumonia, and subspecialty consultation for airway foreign bodies. Admission is generally warranted for worsening respiratory status, pneumonia, increased home oxygen requirement, persistent respiratory distress, or removal of a foreign body.

TABLE 148-3 Checklist for Emergency Care of Children With Special Healthcare Needs

- Fully involve the family and caregivers and use the care plan.
- Inquire about advance directives and family goals of emergency care.
- Use family information when assessing child's pain, mental status, and symptoms.
- Anticipate latex allergy.
- Identify proper equipment sizes (e.g., tracheostomies, gastrostomy tubes, colostomies).
- Anticipate difficult intubation in the child with craniofacial or cervical vertebrae anomalies or contractures.
- Recognize and treat comorbid states.
- Consider physical or sexual abuse in the child with special needs.

METABOLIC DISORDERS

This diverse category of disorders is due to genetic defects that lead to abnormalities in the metabolic pathways of proteins, carbohydrates, and lipids (see Chapter 146, "Metabolic Emergencies in Infants and Children"). Although a detailed understanding of individual biochemical pathways is not necessary for emergency management and evaluation, general familiarity with presenting signs and symptoms is necessary, because recognition in the ED could be lifesaving. **A bedside glucose at presentation is essential because many of these disorders lead to hypoglycemia.** Initial laboratory studies should include a CBC, serum glucose, electrolytes with anion gap, blood gas, ammonia, liver function tests, urine ketones, and lactate dehydrogenase, aldolase, and creatine kinase if there are muscular symptoms. After verifying adequate airway, breathing, and circulation, direct care to correct acute metabolic abnormalities such as hypoglycemia (see Chapter 146, "Metabolic Emergencies in Infants and Children).[24] Consult a biochemical geneticist for further diagnostic evaluation and management guidance.

SEIZURES

The prevalence of epilepsy is estimated at 6.3 cases per 1000 children and seizures are a frequent cause for admission.[4,25-29] In general, the nature and complexity of the seizure syndromes differ considerably between patients, but seizure syndromes are often consistent in the individual. The initial evaluation and management follow the standard approach to seizures (see Chapter 138, "Seizures in Infants and Children"), with a few caveats in children with medical complexity. Note anomalies or comorbid conditions that might lead to airway or respiratory compromise with the use of respiratory depressant anticonvulsants. Obtain a careful history including the baseline frequency and type of seizures and efficacy of past medications (ask about medication or dose changes and what has and has not worked previously). Confirm allergies and potential drug interactions and consult with the primary neurologist if multiple medications are needed for seizure control and to determine if therapeutic adjustments are required. Keep in mind a broad differential including shunt malfunction, infection, electrolyte abnormality, and subtherapeutic medication doses.[4] Obtain serum anticonvulsant medication levels as indicated.

Adequate seizure control may require multiple medications. Intractable seizures, those that do not respond to at least two anticonvulsants, may be associated with underlying disorders or syndromes. Patients with refractory seizures, including those with epileptic encephalopathies (e.g., Lennox-Gastaut or Dravet's syndrome), may be placed on a ketogenic diet or have an implanted vagus nerve stimulator. **For children on a ketogenic diet, it is critical to avoid sugars to maintain ketosis.** Therefore, ask caregivers about baseline serum glucose levels before administering dextrose because dextrose may increase seizures previously controlled by therapeutic ketosis. In addition, consider working with a pharmacist to ensure that the vehicle in which a medication is provided is not contraindicated for a ketogenic diet. For example, most chewable and suspension medications and common medications such as acetaminophen and ibuprofen contain sugar.

GI DISORDERS

GI complaints may include dehydration, feeding tube complications, and constipation. Dehydration may result from poor oral intake, oral

motor dysfunction, or increased fluid losses from infection or gastric tube output. Children with growth retardation (in particular below the fifth percentile) or marginal reserves may dehydrate even from minimal vomiting and diarrhea. In addition to the clinical signs of dry mucous membranes, tachycardia, and oliguria, ask the family about weight loss, changes in baseline function, and ability to orally or enterally hydrate. IV access may be difficult, and the child may require central or intraosseous access (see Chapter 114, "Vascular Access in Infants and Children").

Constipation may be associated with nonspecific symptoms such as abdominal pain, change in bowel habits, anorexia, or overflow diarrhea. Treat acute constipation with enemas, suppositories, polyethylene glycol, and dietary adjustments. Avoid mineral oil in children with aspiration potential to avoid pulmonary complications and impaired fat-soluble vitamin absorption. Do not recommend chronic use of Fleet® enemas because electrolyte abnormalities may result.

MUSCULOSKELETAL/DERMATOLOGIC DISORDERS

Children with disorders that require orthopedic braces, have prolonged periods of immobility, or result in wheelchair dependence may develop painful skeletal or cutaneous complications. The risk of pathologic fractures increases from disuse and nutritionally induced osteopenia. Although fractures may occur from normal handling, therapy, falls, or accidents, practitioners must also **consider abuse**.[30] Assess for orthopedic injuries in the irritable, severely impaired, or nonverbal child by palpating all extremities and checking range of motion. Inspect the skin, especially in dependent areas, for pressure ulcers or skin breakdown. Evaluate wheelchair-dependent children on stretchers and out of their chairs to check the entire body.

NEGLECT AND ABUSE

Children with disabilities are greater than three times more likely to be abused (sexually, physically, and/or via neglect) and endure multiple abuse events when compared with children without disabilities (Sullivan 2000).[31,32] They often place higher emotional, physical, economic, and social demands on their families.[33,35] The added attention required, coupled with limited caregiver resources, can result in failure of the child to receive needed medications, medical care, and appropriate educational placement (see Chapter 150, "Child Abuse and Neglect").

TECHNOLOGY-DEPENDENT CHILDREN

A technology-dependent child is one who needs a medical device to compensate for the loss of a vital body function and substantial nursing care to avert death or further disability.[36] Such patients account for 70% to 90% of technology use, and malfunction accounts for nearly 10% of this population's admissions.[4] Devices include ventilators, pacemakers, tracheostomies, gastrostomy tubes, central venous catheters, ventriculoperitoneal shunts, and vagus nerve stimulators.[36,37] Contact the child's primary physician and home health nurse early in the evaluation process to avoid unnecessary tests, to determine need for inpatient admission, and to simplify care.

TRACHEOSTOMY CARE

There are many types and sizes of tracheostomy tubes, so clarify the exact tube type, size, and most recent change. Common complications related to tracheostomy tubes include decannulation, bleeding at the cannulation site, obstruction, and tube reinsertion into a false passage resulting in subcutaneous emphysema, pneumomediastinum, or pneumothorax. Granuloma or stricture formation at the stoma or tracheal wall can cause bleeding with cannula manipulation or suctioning. Erosion into the innominate artery is rare and is usually related to an inferiorly placed tracheostomy stoma. Consider otolaryngology consultation and urgent bronchoscopy for bleeding.

Infections associated with tracheostomies include tracheitis, bronchitis, and pneumonia. Normal secretions are generally clear to white and thin in consistency. Abnormal secretions are thick and yellow to green in color. Obtain a tracheal aspirate and culture in children with fever, respiratory distress, a new or increasing oxygen requirement, or a change in secretions.

TABLE 148-4 Ventilator Troubleshooting

Alarm	Possible Causes	Interventions
High pressure	Plugged or obstructed airway Coughing/bronchospasm	Clear obstruction Suction tracheostomy Administer bronchodilator
Low pressure/apnea	Loose or disconnected circuit Leak in circuit Leak around tracheostomy site	Ensure all circuits are connected Check tracheostomy balloon Ensure tracheostomy is well seated
Low power	Internal battery depleted	Plug the ventilator into a power outlet
Setting error	Settings incorrectly adjusted	Manually ventilate patient Transport ventilator and patient
Power switchover	Unit switched from AC to internal battery	Press "alarm silent" button after ensuring battery is powering ventilator

MECHANICAL VENTILATION

Chronic respiratory support is necessary for a variety of conditions: neurologic and neuromuscular disease accounts for about half, and chronic lung disease accounts for only 7%.[38] Ventilator-related complications, such as pneumothorax or machine failure, are managed according to standard principles. Provide bag ventilation for total ventilator failure. **Table 148-4** provides a checklist for ventilator troubleshooting.

FEEDING TUBES

Feeding tubes are commonly present.[4] Complications of a nasogastric tube include sinusitis, nasal and esophageal irritation, tube dislodgement or clogging, and pulmonary aspiration. Gastrostomy tubes can be associated with gastroesophageal reflux, tube dislodgement or clogging, peristomal wound infection, abdominal wall abscess, peritonitis, gastric perforation or hemorrhage, gastrocolic fistula, gastric ulceration, and gastric outlet obstruction.

Feeding tubes may become dislodged, break, or otherwise malfunction. It is important to know what size and type of tube to replace. Also knowing the position of feeding tube present (gastric tube, gastrojejunal tube) will help to ensure proper placement. Gastrojejunal tubes will often require a consult to interventional radiology for replacement. Gastrostomy tubes that become displaced require prompt replacement, because a stoma without a tube will close in a matter of hours. A Foley catheter can be placed in a stoma while awaiting appropriate gastrostomy tube replacement. Narrowed stomas may require dilation in order to pass a tube. Confirm proper placement with aspiration of gastric contents. For difficult replacements, stomas that have been present for less than 12 weeks, or uncertainty about position, it is best to confirm placement with a radiographic dye study (see Chapter 86, "Gastrointestinal Procedures and Devices"). Additional complications of gastrojejunostomy tubes include diarrhea, tube migration, small bowel perforation, and intussusception (see Chapter 87, "Complications of General Surgical Procedures").

Stomal complications include dermatitis, allergic hypersensitivity, granulation, cellulitis, and fungal infections. Superficial bleeding due to granulation tissue can be cauterized using silver nitrate sticks.

INDWELLING VENOUS CATHETERS[39]

Indwelling catheters, often tunneled central venous catheters, can be of multiple types but will be accessible through either externalized catheter tubing, such as a Hickman® device, or a subcutaneous reservoir, such as a Port-a-Cath® device. Complications include occlusion, breakage,

dislodgement, air embolism, phlebitis, and infection. Parenteral feeding complications include cholestasis that may lead to irreversible liver disease or metabolic bone disease. Various agents can be used to relieve catheter obstruction in the ED, such as tissue plasminogen activator in the instance of intraluminal coagulated blood, but protocols are typically institution dependent. Surgical or interventional radiology consultation may be necessary if initial attempts at removing the obstruction are unsuccessful. For breakage or dislodgement, clamp externalized catheters proximal to the affected segment and repair with a special kit if available. For nonexternalized catheters, especially when there is concern for dislodgment, seek surgical consultation promptly. Air embolism may be associated with symptoms of respiratory distress and hemodynamic instability. If air embolism is suspected, clamp the catheter and place the child in left-sided Trendelenburg position with supplemental oxygen.[39] For suspected infection, obtain blood cultures and administer antibiotics to cover gram-positive and gram-negative organisms (Gominet 2017).[40]

Fever in patients with externalized catheters represents a medical emergency due to risk for line infection. These patients should have central and peripheral blood cultures and be started on broad-spectrum IV antibiotics to cover both gram-positive and gram-negative organisms. Admission to the hospital is warranted in even well-appearing patients with central line and fever.

CEREBROSPINAL FLUID SHUNTS

Cerebrospinal shunt placement is the most common neurosurgical procedure performed in children.[39] Most commonly, cerebrospinal fluid is diverted from the ventricles to the peritoneal cavity, but occasionally the atria and pleural spaces may be used.[4] Complications include separation or disruption of the tubing or device, infection, and overdrainage[41,42] (**Table 148-5**). Shunt malfunction occurs most often in the year following placement,[43] with approximately 40% of standard shunts malfunctioning during this time.[44] After the first year, the annual rate of shunt malfunction is about 5%.[45]

Seizures are generally accompanied by other signs and symptoms and are seldom, if ever, the only sign of shunt malfunction. Patients with impending herniation may develop **Cushing's triad**: hypertension, bradycardia, and irregular respirations. This is a late sign of impending herniation and a true neurosurgical emergency. When neurosurgical consultation is not immediately available and the patient is experiencing symptoms of herniation, removing cerebrospinal fluid by tapping the shunt reservoir may be lifesaving.

Shunt infections occur most commonly within a few months of shunt placement, many within the first few weeks, and they generally decrease in frequency with time. After 3 months of shunt placement, infection rates fall to a very low occurrence. Infection rates vary from 1% to 40%, with most in the range of 5% to 15%.[46] Signs and symptoms of shunt infection may be nonspecific, such as fever, behavior change (irritability or lethargy), vomiting, and/or abdominal pain. Infected shunts may be accompanied by mechanical shunt failure. Antibiotics should be selected to treat gram-positive (most commonly, coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and *Streptococcus*) and gram-negative (*Escherichia coli*, *Enterococcus* species, and *Haemophilus influenzae*) species. Intra-abdominal cerebrospinal fluid loculations or peritoneal pseudocysts can occur at the distal tip of the catheter with or without peritonitis. Less common intra-abdominal complications are bowel obstruction due to adhesions, subphrenic abscess, and cerebrospinal-enteric fistula.[47]

The evaluation for mechanical shunt malfunction includes plain radiographs of the skull, neck, chest, and abdomen to evaluate continuity of shunt hardware and head CT or MRI to assess ventricular size and shunt positioning. Increased cerebral ventricle size, particularly when compared with previous studies, indicates shunt malfunction. However, malfunction may be present with unchanged ventricular size due to a loss of surrounding tissue compliance. A "negative" neuroimaging study does not rule out shunt malfunction or obstruction. Approximately 11% of shunt failures present with small ventricles, and neuroimaging should not be used as the sole or definitive diagnostic modality when evaluating shunt function. If shunt malfunction or infection is suspected, consult neurosurgery for further evaluation, including shunt aspiration, nuclear medicine flow studies, admission, and monitoring. Programmable shunts will need to be reprogrammed after MRI because the magnet alters the set pressure level. Programming requires an on-site, trained provider.

TABLE 148-5 Symptoms and Signs of Ventriculoperitoneal Shunt Obstruction or Malfunction

Symptom	Signs
Headache	Shunt site swelling or normal exam
Visual disturbances	Papilledema
Nausea or vomiting	Bulging fontanelle, enlarged head, or normal exam
Lethargy and/or irritability	Engorged head veins
Lack of developmental progress and/or poor school performance	McEwen sign (cracked-pot sound during skull percussion)

Note: Neurologic findings include increased deep tendon reflexes or lower extremity tone, positive Babinski sign, lateral (sixth) or upward (fourth) gaze palsy (sun-setting), and respiratory compromise.

URINARY DIVERSIONS

Urinary diversions include vesicostomies, ureterostomies, ileal loop conduits, and bladder augmentations. Complications include prolapse and stomal stenosis in vesicostomies, stenosis of ureterostomies, pyelonephritis, stricture of the ureteroileal anastomosis, peristomal hernia, or stenosis in ileal loop conduits. Small bowel obstruction can be a complication of constriction of the ileal conduit. Most complications are managed in consultation with the child's urologist.

SPECIAL POPULATIONS

DEVELOPMENTAL DISABILITY/DELAY

Developmental disability is a broad term encompassing conditions such as attention-deficit/hyperactivity disorder, cerebral palsy, seizures, stammering, and other developmental delays in children. Developmental disability is occurring with increased frequency and affects approximately one in six children.[48] Children with intellectual disability can be difficult to approach, may have impaired social and communication skills, and may become aggressive or combative when confronted by new or painful stimuli. The parent or primary caregiver is the best source of information for effective interaction strategies. The various medical problems found in these patients can be specific to the underlying syndrome, but treatment is generally the same as with developmentally normal children. Review medication profiles to prevent drug interactions and to identify potential drug side effects.[20]

AUTISM SPECTRUM DISORDER

Autism spectrum disorder is a category of disorders characterized by restrictive, repetitive, and stereotyped patterns of behaviors with impaired social interaction and communication.[49] The disorder has a wide range of clinical expressions, severity, and levels of function. The increase in prevalence over the past few decades may be due to improved and earlier detection.[50] The current prevalence is approximately 1 in 68 children.[51,52] The cause is unknown, but there is no relationship with childhood immunizations. In general, most children with autism spectrum disorder do not have associated medical disorders and have medical needs similar to those of age-matched, normally developing children. Sensory defensiveness, unusual social behaviors, and aggressive self-protective responses to medical procedures and examinations can complicate medical interactions. Always ask the parents or primary caregivers about the most effective means of communication for each child, as well as specific "do's and don'ts." Consider reducing auditory, visual, and tactile stimulation, and allow a period of adjustment to the ED environment. If possible, limit the number of medical providers who

are unfamiliar to the child. Sedation may be needed for examination and procedures.

DOWN SYNDROME

Down syndrome is a relatively common genetic disorder, most often resulting from a trisomy of chromosome 21, that occurs in just over 1 in 1000 live births. The syndrome (Table 148-1) is characterized by developmental delay, intellectual disability, congenital heart defects, GI abnormalities, thyroid dysfunction, insulin-dependent diabetes mellitus, increased risk of upper respiratory and ear infections, atlantoaxial instability, and leukemia. Congenital heart defects affect approximately half of children and include atrioventricular canal defects, ventricular and atrial septal defects, tetralogy of Fallot, and patent ductus arteriosus. These defects generally are detected in early infancy, but pulmonary hypertension and congestive heart failure can develop over time if treatment is not successful. GI abnormalities occur in approximately 5% of cases[53] and include esophageal atresia, tracheoesophageal fistula, pyloric stenosis, duodenal atresia, Meckel's diverticulum, Hirschsprung's disease, and imperforate anus. Therefore, feeding difficulties or vomiting in the infant with Down syndrome requires thorough investigation. Gastroesophageal reflux responds to standard therapy. Midface malformations affect the normal functioning of eustachian tubes, leading to recurrent and chronic infections of the ear, sinuses, and upper respiratory tract. **Asymptomatic atlantoaxial instability is present in approximately 13% of children with Down syndrome. Consider cervical spine injury after trauma, specifically with deceleration injuries, which can cause atlantoaxial subluxation or dislocation.** Children with Down syndrome, compared to those without, have a 10- to 20-fold increased risk of developing leukemia,[54] most commonly acute lymphoblastic leukemia.

CEREBRAL PALSY

The term *cerebral palsy* describes a collection of nonprogressive disorders of movement and posture originating from injury sustained by the developing brain within the first 3 to 5 years of life. The prevalence is 3 to 4 cases per 1000 individuals.[48] Although motor deficits are the primary feature, cerebral palsy can also be associated with seizures, cognitive impairments, and sensory, communication, and behavioral abnormalities. There is a wide spectrum of intellectual and physical function, ranging from normal intelligence and mild motor deficits to severe disability. Cerebral palsy is often classified by the type of motor abnormality, its distribution, and the degree of involvement (**Table 148-6**).

Prenatal injury may occur from teratogen exposure, genetic syndromes, intrauterine infections, brain malformations, intrauterine cerebrovascular accidents, or fetal-placental malfunctions. The perinatal period may be affected by preeclampsia, complications of labor and delivery, sepsis or CNS infection, asphyxia, or prematurity. Older infants and children can develop cerebral palsy as a result of meningitis, traumatic brain injury, or toxic exposures. Approximately 25% of cases have no obvious cause.[55,57] Children with severe spasticity may have an intrathecal baclofen pump. Baclofen pump complications include malfunction, dislodgement, infection, or acute medication withdrawal. **Life-threatening baclofen withdrawal can occur and may present with malignant hyperthermia, hypotension, myoclonus, seizures, rhabdomyolysis, disseminated intravascular coagulation, multisystem organ failure, cardiac arrest, coma, and death.** In addition to lifesaving supportive measures, oral baclofen and benzodiazepines are used to treat symptoms.

TABLE 148-6 Cerebral Palsy

Motor abnormality	Spastic	Increased tone; muscle stiffness
	Dyskinetic	Involuntary, nonpurposeful, uncoordinated movements
	Ataxic	Wide-spaced, unsteady gait; movement uncoordinated and clumsy
	Hypotonic	Floppy; generalized muscle weakness and flaccidity
Distribution	Diplegia	Paralysis affecting symmetrical parts of the body
	Paraplegia	Paralysis of both legs
	Hemiplegia	Involvement of one half of the body
	Quadriplegia	Four-limb paralysis

NEURAL TUBE DEFECTS AND SPINAL CORD INJURY

Neural tube defects result from the failure of the neural tube to close during the early embryonic stage of development and account for most congenital abnormalities of the CNS. The cause is multifactorial, but folic acid deficiency is associated with an increased risk, and maternal supplementation is currently recommended as early as possible in pregnancy.[58] The most common and most severe form of neural tube defect is meningomyelocele, which involves the spinal cord, meninges, and vertebral column. Spina bifida and spina bifida occulta are other examples of neural tube defects. **Patients with neural tube defects are often allergic to latex**. Complex medical problems result from the impairment of sensory and motor control of voluntary and autonomic activities at or below the site of the lesion (**Table 148-7**). Spinal cord injury results in a similar loss of motor and sensory control below the level of the lesion. In these patients, significant osteopenia in their nonfunctioning limbs can lead to underlying fractures presenting as extremity swelling. This can occur with their routine physical therapy and care.

Autonomic dysreflexia is a serious, potentially life-threatening complication of neural tube defects and spinal cord injuries. Autonomic dysreflexia consists of paroxysmal sympathetic and parasympathetic hyperactivity initiated by stimuli below the level of the lesion, such as bladder overdistention, fecal impaction, or fracture. The symptoms of autonomic dysreflexia are sweating, flushing, pounding headache, hypertension, bradycardia, and piloerection. The primary intervention is to determine and eliminate the offending stimulus through bladder emptying, disimpaction, discontinuation of painful procedures, or repositioning. If elevated blood pressure does not respond to repositioning or stimulus reduction, institute standard treatment for hypertensive emergencies.

Chiari Malformation Chiari malformation consists of a downward displacement of the cerebellar tonsils through the foramen magnum, frequently causing obstructive hydrocephalus. Although mild tonsillar herniation seen in type I Chiari malformation can be asymptomatic, the more severe Chiari II is common in children with meningomyelocele and consists of malformation of the cerebellum, hindbrain, and brainstem

TABLE 148-7 Complications of Neural Tube Defects

- Autonomic dysreflexia
- Chiari II malformation
- Cognitive impairment
- Constipation
- Contractures
- Gastroesophageal reflux
- Growth failure
- Hydrocephalus
- Latex allergy
- Neurogenic bowel and bladder dysfunction
- Osteoporosis
- Recurrent urinary tract infections
- Respiratory compromise
- Scoliosis
- Seizures
- Spinal cord syrinx
- Tethering of the spinal cord
- Vesicoureteral reflux
- Vision impairment

TABLE 148-8 Symptoms of Chiari II Malformation

Infant	Older Child
Apnea	Vision dysfunction
Vocal cord paralysis	Motor incoordination
Stridor	Headache
Oral motor dysfunction	Hand weakness
Vision disturbances	
Upper extremity weakness	
Incoordination	

(**Table 148-8**), requiring early ventricular shunt placement. Even minor cervical hyperflexion and extension injuries can cause symptoms in children with Chiari malformation; **any deceleration injury, even mild, requires cervical spine stabilization and assessment for spinal cord injury due to instability of the craniocervical junction.** Consider Chiari II malformation as a possible cause of new-onset stridor in the child with meningomyelocele. Monitor closely for progression to complete airway obstruction. Diagnosis requires emergent MRI of the craniocervical junction. If respiratory function is not severely compromised and the airway remains stable, outpatient disposition may be considered in consultation with subspecialists caring for the child.

URINARY TRACT

Complications of a neurogenic bladder include recurrent urinary tract infection, urinary retention or incontinence, and complications of self-catheterization. Medications or prophylactic antibiotics may be prescribed to enhance continence and minimize damage to the upper urinary tract. Because bacterial colonization of the urine is common, only treat symptomatic infection with antibiotics. Suspect formation of a false passage during self-catheterization with difficult catheter passage, pain, or urethral bleeding. Do not attempt recatheterization in the ED for these symptoms, for fear of compounding the underlying injury, but obtain urologic consultation. Long-term indwelling catheterization predisposes the patient to the development of **latex allergy**.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 149

Behavioral Disorders in Children

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INTRODUCTION

Pediatric mental health emergencies encompass a range of conditions, including psychiatric conditions such as mood and anxiety disorders (depression, bipolar disorder, suicidal ideation, obsessive compulsive disorders, posttraumatic stress syndrome), exacerbations of behavioral disorders (attention-deficit/hyperactivity disorder, aggressive outbursts, conduct disorders), deteriorating neurodevelopmental disorders (autistic spectrum disorders, tic disorders, intellectual disabilities), addictive disorders, and eating disorders. The psychological and sometimes physical aftermath of child maltreatment, mass casualty incidents and disasters, and exposure to violence and unexpected deaths are also likely causes of mental health emergencies.[1-4]

Traditionally, the role of the emergency provider includes medically stabilizing children presenting with a mental health complaint, differentiating physical from mental health causes of symptoms, performing a psychosocial assessment, and directing patients and families toward appropriate resources for acute and long-term needs. Initial management may include pharmacologic therapy, physical restraint, and referral for inpatient admission.[2,5] More recently, increased recognition of the burden of unidentified mental health concerns among vulnerable youth has led to calls for universal screening of psychosocial status for youth seeking medical care in the ED. Barriers to universal screening for mental health conditions in the ED include time restrictions, lack of familiarity with screening instruments, often fragmented or limited local community resources, and reluctance to broach the subject of mental health on the part of families seeking urgent medical care.[6]

Despite these barriers, a number of brief screening tools targeting specific conditions such as suicidal risk (Ask Suicide-Screening Questions and Risk of Suicide Questionnaire; see later section, "Suicidal Ideation and Attempts"), depression (Beck Depression Inventory-II), anxiety (revised parental and child versions of the Screen for Child Anxiety-Related Disorders), and alcohol use disorder (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, 2-Item Scale), have been validated in the ED population to identify youth requiring further assessment.[7] Although concerns about privacy and confidentiality are sometimes raised by families, a study of mental health screening in the ED suggests that most parents and youth find the process acceptable, and clinicians report that screening does not interfere with medical care.[8]

EPIDEMIOLOGY

The mental health crisis involves all socioeconomic and ethnic groups and is not unique to any one geographic area, state, or region. A meta-analysis of worldwide prevalence of mental health disorders suggests that North America has the highest prevalence of mental health disorders in children and adolescents (19.9%) with lower rates in Europe (12%) and Africa (8.3%); there is a peak prevalence among youth age 12 to 18 years.[9] National surveillance data from the United States and Canada report a prevalence of pediatric mental health disorders of 10% to 20% and suicide as the second most common cause of mortality among youth.[10,11]

Although the prevalence of youth mental health disorders remains stable, acute care visits for mental health–related issues are on the rise. In the United States, both the absolute number (from 565,000 to 823,000) and proportion of all ED visits (from 2.0% to 2.8%) by children and youth for a mental health problem are on the rise.[12] The Pediatric Emergency Care Applied Research Network reported that 3.3% of all participating pediatric ED visits were made for psychiatric-related visits. These visits are more frequently arriving by ambulance, are associated with longer length of stay, and result in admission to the hospital more commonly than other causes for ED visits.[13] Between 2006 and 2011, ED visits for a mental health–related concern increased in the United States by 21%, and hospitalizations for a mental health condition increased by 50%.[14] In Canada, ED visits and hospitalizations for mental health conditions increased by 66% and 55%, respectively, from 2007 to 2017. Pediatric psychiatric emergencies show seasonal variation and are more common during the school year, peaking in May and November, while reaching a nadir in July and August. While the visit distribution over days of the week appears to be even, visits occur more frequently in the evening, coinciding with a time period when most outpatient community mental health resources are not easily reachable.[15]

The cause of the dramatic rise in pediatric mental health emergencies is multifactorial and complex. Factors contributing to the high prevalence of mental illnesses among youth include family instability or dysfunction, economic crisis or financial hardship, inadequate numbers of mental health professionals (especially those with pediatric expertise), lack of access to care, shortage of funding for mental health services, and failure to seek care due to cultural stigma.[1] In addition, social networking exposes youths to cyberbullying, online harassment, social isolation, and "Facebook depression," adding further risks for developing mental health illnesses.[16] Multiple economic forces negatively impact

the availability and delivery of mental health services[1,4,5,17,18] and have transformed EDs into the safety net for a fragmented mental health infrastructure.[5] A lack of mental health follow-up or aftercare further contributes to the problem: of patients discharged from psychiatric emergency facilities, 40% to 60% do not receive aftercare, increasing the risk of repeat ED visits.[17]

CLINICAL ASSESSMENT

GENERAL GOALS

First, identify and treat acute life-threatening medical emergencies. Next, determine if the child poses an imminent threat to his or her own life or the life of others, as this determines the need for hospitalization. Finally, exclude organic causes for psychiatric presentations. **Table 149-1** lists medical and psychiatric conditions that may present with agitation, psychosis, or obtundation. **Table 149-2** enumerates some general characteristics that may distinguish organic from psychiatric causes of psychosis.

HISTORY

Focus the history on the chief complaint and details of the presenting symptoms, circumstances, and precipitating events (e.g., social stressors). The timing and sequence of events, associated symptoms, and review of systems may help to distinguish organic from psychiatric conditions. Auditory hallucinations are associated with psychosis, but visual hallucinations may indicate intoxication or organic causes. A history of head injury, chronic or progressive headaches, visual changes, vomiting (especially morning vomiting), and deterioration of motor skills or gait suggests an intracranial process such as a brain tumor or subdural hematoma. Constitutional symptoms that may provide clues to an organic etiology include temperature instability, palpitations, and changes in appetite, stool patterns, hair, or skin.

The past medical history and family history will help identify the pattern and chronicity of the presenting symptoms. Similarly, a review of medications, including adherence to prescribed medication regimens, and their efficacy will guide the treatment plan and disposition. A family history of psychiatric or organic disease may indicate a potential genetic predisposition.

In addition to noting these standard components of history, conduct a focused psychosocial assessment. Children and adolescents presenting to the ED with behavioral or psychiatric emergencies should be asked about exposure to violence at home or school. See also Chapter 150, "Child Abuse and Neglect." Two assessment tools have been designed for this use in the ED: HEADS-ED and HEARTSMAP. HEADS-ED recommends a psychiatric assessment by a mental health clinician for a cumulative score of ≥7 and if the suicide risk score is ≥2.[19] HEARTSMAP provides specific recommendations for the type (social, youth health, psychiatric, and protective) and urgency (in ED consultation vs. community-based resources) of mental health service needs (**Table 149-3**).[20,21]

TABLE 149-1 Medical and Psychiatric Causes of Altered Mental Status in Children

Medical Conditions	Psychiatric Conditions
CNS disorders	Acute mania
Brain tumor	Bipolar disorder
Temporal lobe epilepsy	Depression
Trauma	Acute psychosis (e.g., schizophrenia)
Infection (abscess, encephalitis, meningitis)	Personality disorder
Metabolic/endocrine disorders	Conduct disorder
Hyperglycemia, hypoglycemia	
Thyroid disease	
Uremia	
Hepatic failure	
Porphyria	
Collagen vascular diseases	
Lupus erythematosus	
Vasculitis	
Hyperpyrexia	
Intoxication or withdrawal	
Drugs of abuse (alcohol, stimulants, depressants, hallucinogens)	
Medications (antipsychotics, corticosteroids)	
Environmental substances (anticholinergics, heavy metals)	

TABLE 149-2 Differentiation of Organic and Psychiatric Psychosis

Characteristic	Organic Cause	Psychiatric Cause
History: onset and progression	Acute	Gradual/progressive
Vital signs	Often disturbed	Usually normal
Physical examination		
Focal neurologic symptoms	May be present	Usually absent
Mental status	Delirium, visual hallucinations, agitation	Anger, sadness, auditory hallucinations, agitation
Laboratory findings	May be altered	Usually normal

PHYSICAL EXAMINATION

Assess vital signs, airway, breathing, and circulation, and then perform a detailed neurologic examination. Alterations in vital signs may provide clues to potential intoxication, ingestions, or organic pathology (endocrinologic and metabolic). Tachycardia, hypertension, pyrexia, and tachypnea may suggest intoxication with stimulants such as amphetamines, cocaine, and "ecstasy" (3,4-methylenedioxymethamphetamine). Assess for other toxidromes including anticholinergic symptoms or signs of salicylate toxicity. Pupillary responses, the presence or absence of nystagmus, skin temperature and moisture, and the condition of the mucous membranes are all helpful in identifying toxidromes (see Chapter 176, "General Management of Poisoned Patients").

Focus the neurologic examination on level of consciousness, gait and coordination, and reflexes, and administer the Mini-Mental Status Examination as appropriate for age (Table 288-2). Note the child's affect and general appearance, content and organization of thought, and articulation and expression of speech. Pressured speech with flight of ideas may signal acute mania, whereas echolalia, "word salad," and other disordered thought may indicate acute psychosis.

LABORATORY TESTING AND IMAGING

Laboratory tests and imaging are dictated by the history and physical examination. Pubertal girls should have a urine pregnancy test. Urine drug screening can be helpful when intoxication from drugs of abuse is suspected. Obtain serum acetaminophen (Tylenol®) and salicylate (aspirin) levels in children who have ingested drugs or attempted suicide, as self-report of quantity and type of drug used is not always reliable. Hyperglycemia, hypoglycemia, and hyperammonemia can cause alterations in mental status, so check serum glucose and consider ammonia in obtunded patients. Obtain a 12-lead ECG in cases of potential ingestion or intoxication to identify interval prolongation or conduction abnormalities. Document normal sinus rhythm at baseline before initiating psychotropic medications that may accentuate long QT disorders. Screening laboratory tests performed in psychiatric emergencies vary by institution, and many inpatient psychiatric facilities require basic chemistry panels and screening for thyroid disorders. See Chapter 140, "Altered Mental Status in Children," for further discussion of the approach to altered mental status.

Imaging studies are rarely indicated or helpful except as directed by the history and physical examination. Chest radiographs may identify

TABLE 149-3 HEARTSMAP Structured Mental Health Screening Tool

Psychosocial Sections	Probing Questions	Scoring (With Descriptors) 0	1	2	3	Current Resources
Home	Is there difficulty or fighting at home between family members? How do you get along with [guardian/parents/family]? How do you feel about your home environment?	No concerns	Supportive of youth's difficulties but some conflicts	Unsupportive (parents at risk for burnout) Frequent conflicts	Dysfunctional (parental burnout) Homelessness Major conflicts	Social supports neither requested nor initiated Social supports involved (resource requested and services initiated)
Education and activities	How is school going for you? Are there any difficulties going to school or staying in class? What do you do for fun? Has that changed recently?	No concerns	Struggle to maintain Difficulty attending Attends more than misses	Performance decline Missing classes/activities Misses more than attends	Failing/major issues Not attending Completely truant (excluding holidays)	Educational/activity issues not yet addressed Functional plan in place (counselor involved)
Alcohol and Drugs	How much is alcohol use a part of your life? Do you use any substances like marijuana? How about any others? Do you ever use drugs or alcohol to feel better or to make a problem go away?	No concerns	Infrequent Mild recreational use	Regular recreational use Mild substance misuse	Bingeing recreational use Substance abuse	No detox or rehabilitation services suggested yet Substance use services in place (referred and offered)
Relationships and bullying	How are things going for you with friends and relationships? Do you have a close person/group of people that you can rely on? Do you feel teased, bullied, or excluded by others? Do you have any struggles with your sexual identity or sexual preference?	No concerns	Minor conflicts/bullying Struggle to maintain	Conflicts/bullying Negative changes	Conflicts/bullying Negative changes	No support or resources initiated Educational or social plan in place (school authority or social worker aware and addressing)
Thoughts and anxiety	Do you consider yourself a worrier or think a lot about the past or future? Do you ever experience panic/extreme fear that comes out of the blue? Do you ever have times where you feel your brain is playing tricks on you?	No concerns	Anxiety/odd thoughts (minimal impact)	Anxiety/odd thoughts (minimal impact)	Anxiety/odd thoughts (minimal impact)	No psychiatric assessment or services initiated yet (no appointment in sight) A mental health clinician such as psychiatrist, counselor, or psychologist is involved or will be involved shortly and is available in the long term
Safety	Do you sometimes feel hopeless or that life is not worth living, or have you ever felt that you or your family would be better off if you were dead? In the past few weeks, have you seriously considered ending your life, or have you ever tried to end your life? In the past few weeks, have you thought of harming yourself?	No concerns	Fleeting or improving thoughts Nonsuicidal self-injury	Fleeting or improving thoughts Nonsuicidal self-injury	Fleeting or improving thoughts Nonsuicidal self-injury	No plan for current safety concern Safety planning in place and consistent with current suicidality/homicidality
Sexual health	Are you involved in any sexual activities, not limited to penetration? Do you use any mode of contraception? What of form of protection against sexually transmitted disease do you use, if any? Do you get any counseling about sexual health from a doctor or nurse?	No concerns	Sexually active and safe practice (contraception and sexually transmitted disease protection)	Stable partner but inconsistent use of protection and contraception	Multiple partners or no use of protection or contraception Involved in sex trade	Sexual health issues not yet approached with healthcare professional Has a primary care provider and issues of sexual health/family planning addressed
Mood and behavior	How would you rate your mood, with 0 being as low as possible and 10 being perfectly happy? Do you feel down or depressed recently? Do you feel really happy or energetic lately?	No concerns	Mood instability (minor)	Mood instability (minor)	Mood instability (minor)	No psychiatric assessment or services initiated yet (no appointment in sight) A mental health clinician such as psychiatrist, counselor, or psychologist is involved or will be involved shortly and is available in the long term
Abuse	To child: Has anyone ever hurt you by touching you in a way you didn't like? To adolescent: Have you ever experienced abuse, either physical, emotional, or sexual? To caregiver: Do you have any concerns of abuse or mistreatment?	No concerns	Concern has been raised and reported to the ministry Historical concerns		Current concern of abuse or neglect/not reported	Notification has occurred Notification has not yet occurred
Professionals and resources	Do you feel that there are people or places you can go to for help? Who is working with you on these issues? Does the current plan to help make sense to you?	Service plan in place or available	Referred for service but access delayed (wait-listed)		Longitudinal services unavailable, but necessary Not yet referred or refusing services/treatment	

Note: For full functionality with scoring algorithm–triggered management recommendations, use the online version at www.openheartsmap.ca.

aspiration in the obtunded vomiting patient. Abdominal radiographs may identify radiopaque foreign objects or ingestions. Neuroimaging can exclude intracranial mass lesions in those with suggestive clinical signs and symptoms.

MANAGEMENT OF PSYCHIATRIC PRESENTATIONS

A detailed summary of child and youth mental health issues is beyond the scope of this book. Formal diagnoses of mental health conditions usually occur after the ED presentation. Therefore, this section will focus on the approach to, and treatment of, **psychiatric presentations**. Many care environments use social workers, youth care workers, nurses, and other clinicians to conduct significant portions of the mental health assessment in the ED.

SUICIDAL IDEATION AND ATTEMPTS

Suicide is complex. Contrary to belief, adolescents are not at higher risk for suicide than adults, and the risk for suicide completion starts at age 10 and increases throughout the teen years (**Figure 149-1**).[22] Although it is one of the most common causes of death in youth (4.7 per 100,000 per year between the ages of 10 and 19, more than neoplasm, respiratory, and cardiovascular deaths combined),[22] the vast majority of youth who have suicidal thinking or behaviors do not go on to complete suicide (**Table 149-4**).[23-25] Risk prediction is currently not possible.[26] Therefore, focus on **identifying risk/protective factors and acuity, collateral history, clinical synthesis, and safety management.**

A number of **risk factors** are associated with increased suicide risk, and suicide risk is fluid and can change rapidly. Identification of risk factors should be carried out with the goal of separating **chronic** (long-standing and unlikely to change) from **acute** (recent and possible to change) risk factors. Chronic risk factors convey ongoing risk and are important for informing systemic rather than individual approaches. Acute risk factors allow for individual approaches for suicide safety planning. Protective factors reduce risk overall and should be considered in risk factor identification. A representative, noncomprehensive list of risk and protective factors is presented in **Table 149-5**.[22-26]

TABLE 149-4 Frequencies of Suicide Items in Youth 12 to 17 Years of Age, in the United States

	1-Year Prevalence	Frequency
Feeling sad or hopeless for 2 weeks*	31.5%	1:3.2
Nonsuicidal self-injury	18.0%	1:5.6
Suicidal ideation*	17.2%	1:5.8
Suicide planning*	13.6%	1:7.4
Suicide attempt (any)*	7.4%	1:13.5
Suicide attempt (potentially lethal)*	2.7%	1:41.6
Death by suicide†	0.0059%	1:16,899

Note: Data is from 2017, except nonsuicidal self-injury (meta-analysis 2014) and death by suicide (2016).

*Females generally twice as likely.

†Males generally four times as likely.

Assessment scales and tools for assessment should be used to gather information to contribute to the assessment process rather than rigid structures to guide decision making. In the ED, brief screening questionnaires such as the Ask Suicide-Screening Questions (**Table 149-6**) can help identify patients with suicidal thinking.[27] The Ask Suicide-Screening Questions assess four areas: (1) current thoughts of being better off dead; (2) current wish to die; (3) current suicidal ideation; and (4) past suicide attempt. A positive response to any one question identified 97% of those at risk for suicide (sensitivity 96.7%, specificity 87.6%).[27] The Columbia–Suicide Severity Rating Scale (available for download at http://www.cssrs.columbia.edu/scales_practice_cssrs.html) can help guide assessment of suicidal thinking and behaviors and has been validated for use in multiple settings, including the ED, for both adolescents and adults.[28,29] The internal validity and usability rates are high for such scales. Some more commonly used scales, such as the SADPERSONS, have little evidentiary support, contain many inaccurate assumptions about suicide risk, and do not accurately predict suicide.[30-34]

Clinical interview, impression, and analysis are crucial aspects of suicide risk assessment. Collateral history for the youth (e.g., parents, caregivers, clinicians, teachers) adds to the confidence of the assessment

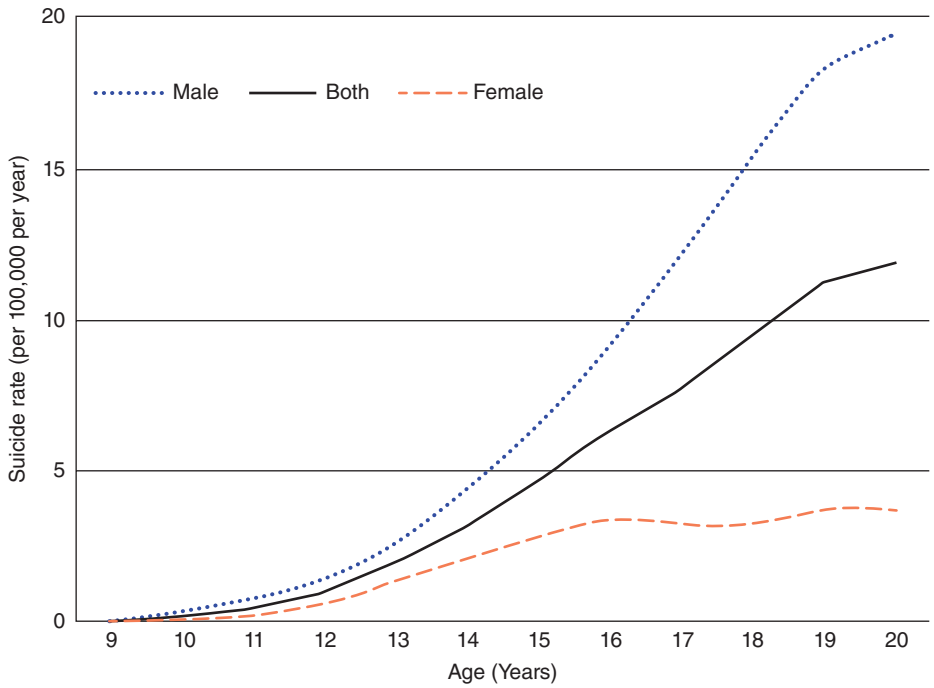

FIGURE 149-1. Suicide rates by sex, United States, 1999 to 2016. [From Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2016 on CDC WONDER Online Database, released December 2017. Data are from the Multiple Cause of Death Files, 1999-2016, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.]

TABLE 149-5 Selection of Common Chronic and Acute Risk Factors and Protective Factors for Suicide

Chronic Risk Factors		
History of suicidal thinking or behavior	Any suicidal factor by history is one of the only consistent predictive measures for suicide risk.	
History of mental health disorder	Lifetime risk of suicide is increased in almost all mental health disorders.	
Age	Exceedingly rare <10 y of age. Risk starts at approximately age 10 and increases consistently until the age of 24. **Adolescents are less at risk for suicide than adults.**	
Sex	Males 4–5 times more likely by adolescence.	
Ethnic or cultural risk group	Aboriginal youth, homeless youth, LGBTQ (lesbian, gay, bisexual, transgender, or queer) youth.	
Chronic illness	Any chronic illness causing pain, disability, or fatigue.	
Family history of suicide	Closer-degree relatives infer a greater risk.	
History of trauma, abuse, neglect, loss	Duration, frequency, and severity of trauma is additive.	
Acute Risk Factors		
Recent suicidal thoughts or behaviors	Ideation < planning < nonlethal attempt < lethal attempt. **New/changing suicidality** should prompt full assessment.	
Suicide planning	Passive (nonspecific wish to die) confers less risk than active (specific, formed plan).	
Accessibility to lethal means	Unsecured substances, medications, firearms. Feasibility of plan.	
High agitation/anxiety presentation	Strong (yet poorly specific) prediction of acute suicide risk.	
Current mental health/substance use disorder	Those with lack of treatment response, noncompliance to treatment, or worsening or rapidly changing disorders should be targets of suicide risk reduction.	
Family dysfunction/caregiver unavailable	Chaotic, dysfunctional homes confer suicide risk. A responsible caregiver must be in place to institute safety management measures.	
Lack of professional supports	Can include supports that are not effective.	
Recent crisis/major life change	Conflicts, relationships, school, failures, losses, etc. **Directly addressing these crises reduces risk.**	
Protective Factors		
Parent connectedness	Sport/activity participation	Positive social supports
Safety of environment	Strong professional supports	Future orientation
Good therapeutic connection	Strong cultural identity	Responding to treatment

TABLE 149-6 Ask Suicide-Screening Questions Tool for Suicidality

Question (Yes/No)	Interpretation
1. In the past few weeks, have you wished you were dead?	"No" to all 4 questions is a negative screen. "Yes" to any question is a positive screen; proceed to question 5 below.
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?	
3. In the past week, have you been having thoughts about killing yourself?	
4. Have you ever tried to kill yourself? (If yes, how? When?)	
5. Are you having thoughts of killing yourself right now? (If yes, describe.)	"Yes" is an acute positive screen and requires emergent mental health evaluation and safety plan. "No" is a nonacute positive screen and requires further safety assessment.

Note: Ask Suicide-Screening Questions tool can be found at https://www.nimh.nih.gov/labs-at-nimh/asq-toolkit-materials/asq-tool/asq-screening-tool.shtml.

and can significantly affect the quality of the risk assessment. If an interview has poor reliability or rapport, the "collected data" may be inaccurate. The tone of the patients themselves, their family, and the support network around them can alter the impression of hope or despair. The importance of clinical and interpersonal factors cannot be understated and is why a reliance on rigid data, forms, or quantities is perilous.[35]

Safety management, following an adequate risk assessment, flows naturally from identified risk and protective factors. By dividing risk factors into acute and chronic categories, targeted interventions for **any acute risk factors** can be made. Creating safety plans for families and youth to use when suicidal ideation occurs can increase compliance with follow-up programming,[36] encourages appropriate re-presentation to the ED, and provides a sense of structure and support to families struggling with suicide concerns. **Figure 149-2** provides an emergency approach to suicidal presentations, and the approach can be done in a multidisciplinary way—a physician is not required for any one step.

Determination of the risk factors will influence the services consulted; social issues require social support services, whereas psychiatric issues require mental health supports. Rigid consultation of all suicidal patients to psychiatric care is neither necessary nor effective; inpatient and involuntary approaches to patients are beneficial when the risk profile is simply too high to manage in the outpatient environment and inpatient services are required to reduce the identified risk factors. Examples of nonpsychiatric risk reduction maneuvers include removing lethal means, securing firearms, creating safety plans, referring to social support services,

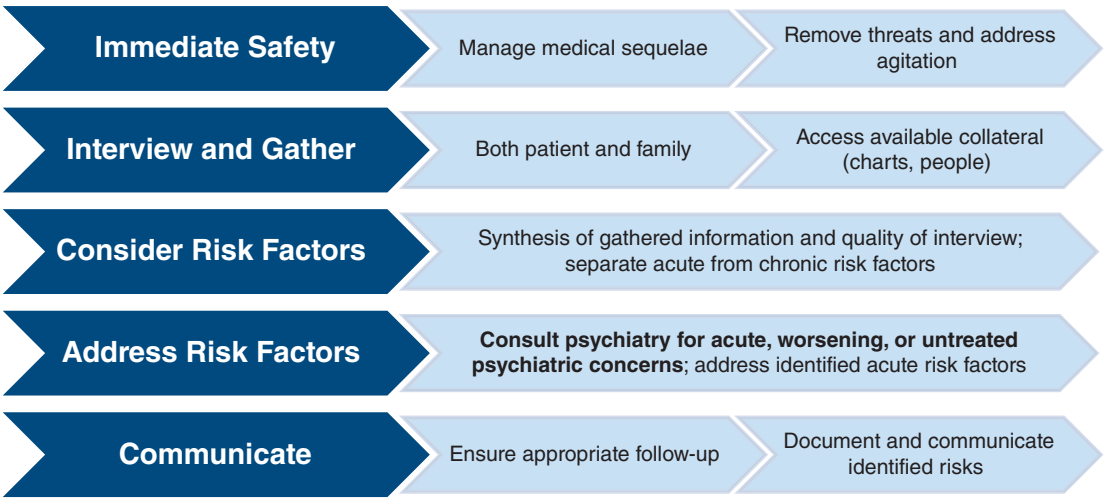

FIGURE 149-2. Approach to suicidality in the ED.

providing family supports, and addressing social and school concerns. Resolution of any triggering crisis severely reduces severity risk.

NONSUICIDAL SELF-INJURY

Nonsuicidal self-injury is "the deliberate, self-inflicted destruction of body tissue without suicidal intent and for purposes not socially sanctioned,"[37] and refers to a wide variety of behaviors including cutting, burning, carving, punching, and picking. Approximately 18% of adolescents have engaged in nonsuicidal self-injury in the past year, and recent studies report that as many as 47% of females have tried it, even briefly. Nonsuicidal self-injury begins in puberty and is twice as common in females, peaking in middle adolescence and declining thereafter. Although it increases suicide risk, over 90% of youth presenting to crisis services with nonsuicidal self-injury have no intent of suicide.[38] Biologic predispositions to self-injury include an absent stress cortisol response, sensitivity of opioid receptors, and genetics.

First, address the sequelae of the injury, and focus on the **distress** and **events** that led to self-injury. Avoid overreaction to superficial injuries; comments such as "You could have killed yourself" or "These injuries look awful" may harm the patient and even increase subsequent behavior. Such comments can confuse the message that self-injury is different from suicide. Second, conduct suicide risk assessment, especially for new or changing self-injury or in the presence of other developing mental health issues. Explain the difference between nonsuicidal self-injury and suicidal behaviors to caregivers. Finally, provide social and mental health support resources to improve **distress tolerance**, **stress management,** and **family supports**.

AGGRESSION

Aggression can occur prior to ED presentation, before or during assessment, and in subsequent care. Consider patient and environmental safety, potential trauma to the child or family, engagement and de-escalation whenever possible, and safe medication and restraint policies.[39]

Pharmacologic interventions require consideration of the *intention* of the intervention. If the underlying issue is psychosis or mania, potent antipsychotic medications are warranted. However, if agitation is behavioral, reactionary, or anxiety driven in nature, and the goal of intervention is sedation, many less potent and potentially less dangerous approaches can be taken. An approach to aggression in the ED is outlined in **Table 149-7**, with pharmacologic options in **Table 149-8**.[40,41]

TABLE 149-7 Approach to the Pediatric Aggressive Patient

Safety	Secure patient and staff safety. Recognize the compromise between security and safety: higher-security measures (e.g., pharmacologic or physical restraint) may also confer greater risk for patient harm. Use these measures when appropriate.
Engagement	Youth often use aggression as their last resort to express or achieve something: expressing anger, being left alone, interfering in treatment, or receiving something desired. Engaging the youth whenever possible to help achieve these goals can reduce the need for further measures. **ALWAYS allow the situation to "step down"** (i.e., reoffer oral medications before injection).
Interventions, in the order they should be attempted when possible:	
1. Environment and engagement	Secure the environment for patient safety and to encourage engagement. Environments with safe furniture and objects, full observation abilities, and adequate staffing are required.
2. Pharmacology (voluntary)	See Table 149-8. Consider low doses and reengage as necessary.
3. Pharmacology (involuntary)	See Table 149-8. Minimize the need for reinjection of medications by choosing dosing appropriately. Physical restraint is often necessary. Offer oral medications immediately before intramuscular medications.
4. Seclusion and restraint	Ensure the facility has appropriate seclusion and restraint policies. All seclusion and restraint policies require 1:1 observation. Remove restraints as soon as possible. Consider the possibility of rhabdomyolysis with physical restraints and asphyxia with person-to-person holds.

TABLE 149-8 Pharmacologic Management of the Agitated Child

Drug	Child Dosing	Adolescent Dosing	Notes
Appropriate for Sedation in Children			
Diphenhydramine 1 milligram/kg May repeat q30min	25–50 milligrams PO/IM Maximum: 200 milligrams/24 h	50–100 milligrams PO/IM Maximum: 300 milligrams/24 h	Anticholinergic. Directly treats dystonia from antipsychotic treatment. Caution in suspected delirium as antihistamines are notoriously responsible for worsening and causing delirium. Liquid form available.
Lorazepam 0.05 milligram/kg May repeat q30min	0.5–2 milligrams PO/IM **Maximum: Until sedated or ataxic**	1–2 milligrams PO/IM **Maximum: Until sedated or ataxic**	Paradoxical reaction can occur (but unlikely, and though vigilance is necessary, do not withhold benzodiazepines to avoid this unless documented reaction). Respiratory depression. Sublingual tablet available.
Appropriate for Sedation and/or Psychosis in Children			
Olanzapine 0.1 milligram/kg May repeat q30min	2.5 milligrams PO/IM Maximum: 5 milligrams/24 h	5–10 milligrams PO/IM Maximum: 20 milligrams/24 h	QT_c sparing. Dystonic reaction can occur but unlikely. Warning: IM preparation coadministered with benzodiazepine IM is not recommended because it can cause bradycardia and hypotension. Dissolvable tablet available. Anticholinergic.
Risperidone 0.05 milligram/kg May repeat q60min	0.25–0.5 milligram PO Maximum: 2 milligrams/24 h	0.5–1 milligram PO Maximum: 4 milligrams/24 h	QT_c sparing. Dystonic reaction can occur. Dissolvable tablet and liquid form available.
Methotrimeprazine 1 milligram/kg PO 0.5 milligram/kg IM May repeat q30min	12.5-25 milligrams PO 12.5-25 milligrams IM Maximum: 100 milligrams/24 h PO 50 milligrams/24 h IM	12.5–50 milligrams PO 12.5–50 milligrams IM Maximum: 200 milligrams/24 h PO 100 milligrams/24 h IM	Hypotension, QT_c prolonging, lowers seizure threshold. Anticholinergic.
Appropriate for Psychosis in Children (when other treatments unavailable or failed)			
Haloperidol 0.05 milligram/kg May repeat q60min	0.5–2 milligrams PO/IM Maximum: 5 milligrams/24 h	2–5 milligrams PO/IM Maximum: 10 milligrams/24 h	QT_c prolonging. **Extrapyramidal symptoms very likely in youth,**[42-46] especially dystonia. Consider coadministration of prophylactic anticholinergic (e.g., diphenhydramine as above or benztropine 1–2 milligrams PO/IM).

ANXIETY AND DEPRESSION

ED presentations for anxiety and depression are common. For anxiety, this is often in the form of panic, dysregulation, or regressive behavior. In depression, common presentations include irritability, hopelessness, or sadness. Signs and symptoms of anxiety and depression vary with age; younger children exhibit more regressive, agitated, or withdrawn behaviors, whereas adolescents tend to be able to express their emotional state through direct conversation. Both anxiety and depression in youth can also present with impaired concentration, fatigue, and insomnia. Perform suicide risk screening and assessments as appropriate.

Anxiety or irritability can be relieved in the ED through the use of sublingual lorazepam. Most often, treatments of anxiety and depressive disorders are combination approaches[47]; proper treatment includes the use of therapeutic approaches (cognitive behavioral therapy, interpersonal therapy) and medications (selective serotonin reuptake inhibitors) that usually exceed the scope of an ED. Severe, disabling, or suicide-related anxiety or depression concerns should warrant a consultation to psychiatric service; for milder issues, referral to appropriate mental health supports can be made.

PSYCHOSIS

Psychosis is a generic term that describes a process in which someone's thought or sensory process no longer conforms to reality. Often it is confused as a diagnosis (e.g., schizophrenia), when in fact, the presentation of psychosis can be brought about by a variety of conditions,[48] including benign (hypnagogic hallucinations that occur in sleep-wake transition, normal bereavement), medical (CNS tumors, delirium), psychiatric (schizophrenia, bipolar mania), and substance induced (steroids, drugs of abuse). Psychosis is a syndrome of exclusion; potentially dangerous medical diagnoses must be considered and ruled out prior to psychiatric treatment (Tables 149-1 and 149-2).

Psychiatric causes of psychosis are rare in prepubertal children; in fact, these disorders usually manifest at around 20 years of age. However, many adolescents can have prodromal presentations, and early-onset bipolar disorder, schizophrenia, and other psychiatric causes of psychosis are possible. Predictors of psychosis include a family history (especially first-degree relatives), progressive decline (rather than abrupt), and a history of subclinical psychotic symptoms.[49]

The approach to psychosis varies depending on the cause (**Table 149-9**). In the ED, the antipsychotic medications listed in Table 149-8 can be tried for agitation or urgent symptom concerns; however, caution must be used, because delirium or substance intoxication as a root cause of the psychosis could be worsened by the addition of psychotropic medications.

TABLE 149-9 Approach to Psychosis in the ED by Suspected Cause

Unknown	Rule out medical causes after thorough history and physical examination. Treat agitated patients or patients with distressing symptoms with antipsychotics as per Table 149-8. Consult psychiatry when medically appropriate.
Substances	Use antidote/countering medication if available or necessary. Use environmental controls to reduce stimulation. May need to use medications as per Table 149-8, but cautiously due to interaction with intoxicant. Mental state often clears as substance is metabolized.
Medical	Treat the underlying medical cause. Caution in using medications in Table 149-8 that have anticholinergic properties. Consult psychiatry to manage psychiatric comorbidities.
Psychiatric	Primary psychosis (e.g., schizophrenia): use medications as per Table 149-8. Mania/psychotic depression: use antipsychotics as per Table 149-8 with combination of sedative medications as necessary. The goal in mania is to "settle the brain down" first; in psychotic depression, urgent psychiatric treatment is required. When psychiatric causes are suspected, consult psychiatry.

BEHAVIORAL DISORDERS

Behavioral disorders is a broad term, generally focused on maladaptive behaviors that have progressed to a point of severe dysfunction, risk, or negative outcome. They are seen as a pathologic extension of normal behavioral issues. **Oppositional defiant disorder** is a persistent pattern of provocative, hostile, and noncompliant behavior characterized by low temper threshold.[50] **Conduct disorder** is a more severe, antisocial pattern of rule-breaking behavior that includes aggression to people and animals, deceitfulness and theft, serious rule-breaking, and destruction of property.[51] Treatment is largely environmental and familial, and pharmacologic interventions are of mixed benefit. Behavioral disorders have extremely high psychiatric comorbidity, particularly with attention-deficit/hyperactivity disorder, and treatment of comorbid conditions is necessary. Stimulants, nonstimulant attention-deficit/hyperactivity disorder medications, clonidine, guanfacine, antiepileptic medications, and antipsychotic medications have mixed evidence, but trials are often necessary to reduce impulsivity and sometimes induce sedation, and many of these medications are used off-label.[52]

SUBSTANCE MISUSE AND WITHDRAWAL

Alcohol use and misuse have decreased over the past 20 years in youth, with record-low numbers being seen in recent surveys, both in extreme (<13 years) underage drinking and overall alcohol use.[23] However, the 1-year prevalence of being drunk at least once is 20% in adolescence, and 6% of adolescents will drink more than 10 drinks in a row, making acute intoxication a common adolescent event. Marijuana use has remained stable, with 40% of adolescents reporting ever using marijuana. However, cocaine, hallucinogen, inhalant, ecstasy, and methamphetamine use has halved in the past 15 years.

The management of individual toxidromes is described in Section 15 ("Toxicology") of this book. A very small percentage of adolescents with alcohol misuse experience any withdrawal symptoms, and an even smaller percentage require pharmacologic treatment. Paced alcohol discontinuation is a successful approach to managing alcohol withdrawal in teens, and treatment of severe symptoms can be carried out as in adults, using benzodiazepines such as diazepam and chlordiazepoxide.[53] Refer any youth with a substance use problem to available substance misuse services; the remission rates are low, but a nonjudgmental, continuous, motivational approach reduces rates of misuse.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 150

Child Abuse and Neglect

Margaret Colbourne
Michelle Clarke

INTRODUCTION AND EPIDEMIOLOGY

Child maltreatment is, unfortunately, a common global problem. In the United States, over 675,000 children suffer some form of child abuse or neglect each year, and approximately 12% of these children will present to a hospital with injuries.[1] It is estimated that between 2% and 10% of children visiting the ED are victims of child abuse or neglect.[2] According to the World Health Organization, 36.3% of children experience emotional abuse, 16.3% experience physical neglect, and 22.6% of adults report suffering physical abuse as a child.[3] The lifetime prevalence of childhood sexual abuse ranges from 8% to 31% for girls and 3% to 17% for boys.[4] Therefore, emergency providers are in a unique position to

TABLE 150-1 Types of Neglect

Types of Neglect	Description
Physical	Failure to provide the basic physical necessities of food, shelter, and adequate clothing.
Emotional	Failure to provide necessary nurturing, affection, and stimulation.
Educational	Failure to provide an educational program; this may include chronic truancy.
Medical/dental	Failure to provide basic medical and dental care, which results, or has the potential to result, in harm; this may include noncompliance with healthcare recommendations.
Supervisory	Failure to adequately supervise and ensure safety of a child, given the child's developmental needs.

identify nonaccidental injuries and potentially prevent further abuse. Child maltreatment takes many forms, including neglect, physical abuse, sexual abuse, emotional abuse, and caregiver-fabricated illness (previously called Munchausen syndrome by proxy).

NEGLECT

Child neglect is the most common form of child maltreatment and the most difficult to evaluate and manage; it contributes to as many as 50% of fatalities from child maltreatment.[5] Neglect occurs when a caregiver fails to meet a child's basic needs in provision of food, shelter, clothing, health care, education, supervision, and nurturance.[5-7] Further, this failure either results or is very likely to result in serious impairment of a child's health or development. While many types of neglect may occur, seldom does any one form exist on its own. Carefully consider each neglect risk factor individually, identifying whether there is overt historical or physical evidence of each subtype of neglect (**Table 150-1**).

Given that neglect is rarely a single act, but is rather an accumulation of harm over time, the often brief, single encounter of an ED assessment cannot provide the comprehensive assessment required. The goals of the ED encounter are to recognize when child neglect may be at issue, to clearly document the presenting concerns, and to trigger the appropriate multidisciplinary team approach for the investigation and management of these complex cases. The recognition of child neglect in the ED requires knowledge of the multiple risk factors associated with neglect (**Table 150-2**).[6-9] Poverty, parental substance abuse, and mental health issues are three of the most common risk factors for child maltreatment and neglect.[6,8] Although not all poor families are neglectful, poverty has an overwhelming effect on the parents' ability to provide basic care for their children and may contribute to social isolation and a lack of supports.[9] Substance abuse may result in a parent who is both physically and emotionally unavailable to the child, and substance abuse may divert funds for basic necessities.

TABLE 150-2 Risk Factors for Child Maltreatment

Child risk factors	Premature birth Young age Multiple gestation (twin/triplet) births Chronic disability Adolescents with emotional/behavioral problems
Parent risk factors	Substance abuse Cognitive impairment Adolescent parents Domestic violence Mental health issues Lack of education/unrealistic expectations
Family/social risk factors	Isolation Single-parent families Unemployment Family illness History of involvement with child welfare services

CLINICAL FEATURES

Children and adolescents may be brought to the ED for a variety of reasons when neglect is the underlying problem. Presenting symptoms may include failure to thrive, malnutrition, chronic respiratory or skin infections, repeated injuries, poisonings, behavioral problems, or mental health concerns. Children with chronic disabilities or chronic medical conditions may present repeatedly with clinical deterioration if a parent is noncompliant with healthcare recommendations.

History Review the hospital record prior to obtaining the medical history from the parent. Be alert to chronic health problems, repeated accidents or injuries, and missed medical appointments. The medical history must address both the presenting complaint as well as any past illnesses or injuries. Note whether the parents are able to provide a clear history and are knowledgeable about their child's health and developmental milestones. Document the child's immunization status and any past or current medications. The young infant or child who presents with feeding problems or failure to thrive requires a thorough perinatal history as well as a detailed dietary record. In the case of maternal depression, the history provided by the mother may be vague and difficult to obtain. Inquiries into the family history should specifically address known risk factors for child neglect including parental mental health issues and substance abuse.

Physical Examination The physical examination begins during the process of gathering the history, with observations of the interaction between the parents and child and notes on the child's clothing and hygiene. Observe for unusual demeanor or extreme behaviors such as flat affect, listlessness, overt fear, or out-of-control behavior. Document objective growth parameters including weight, height, and head circumference, and compare with previously reported measures when possible. In general, weight is the first growth parameter to be adversely affected by inadequate nutrition.

The physical examination is typically focused on the system of chief complaint; however, concern for neglect should prompt special attention to the skin (bruises, scars, infection, diaper rash), hair (alopecia, lice infestation), and teeth (dental caries). Determine if muscular tone is decreased or increased. Ear, nose, throat, and respiratory examinations may reveal evidence of chronic, untreated infection. Abdominal exam should note any distention, organomegaly, or unusual masses. Look for evidence of peripheral edema. Note the presence of adequate subcutaneous fat as well as muscular development, particularly over the suprascapular and buttock regions.

Laboratory Testing and Imaging Investigations vary depending on the severity of illness or injury. For failure to thrive, a comprehensive nutritional and metabolic profile is generally indicated. A complete skeletal survey should be considered in any situation of serious neglect to identify physical abuse and to assess skeletal abnormalities from nutritional deficiency or undiagnosed metabolic disease.

TREATMENT AND DISPOSITION

Focus on initial stabilization of acute medical illness and injury. For severe malnourishment with fluid and electrolyte imbalance, initial management may require intensive care support to manage metabolic complications such as "refeeding syndrome." Most infants with failure to thrive due to environmental neglect will respond rapidly to appropriate feeding.

Educate the parents in a thoughtful, respectful, and culturally sensitive manner on the most urgent problems and need for further investigation and treatment. Early consultation with pediatric specialists or child abuse pediatricians is warranted for all concerns of child neglect, even if hospitalization is not indicated. Comprehensive management of child neglect requires frequent ongoing reevaluation, which goes beyond the routine duties of the emergency physician.

PHYSICAL ABUSE

CLINICAL FEATURES

Physical abuse accounts for approximately 18% of all cases of child abuse and is the most easily identified type of maltreatment.[1] Child physical abuse is defined as injury inflicted on a child by a caregiver. Injuries can occur to all parts of the body, but the more commonly injured areas are the skin (bruising, burns), skeleton (fractures), head, and abdomen. Evaluate the child medically and treat injuries. Medical evaluation and treatment of the child always take precedence over the legal investigation. Although the forensic or legal evaluation is best performed by trained investigators or child abuse specialists, data gathered in the ED often guide and inform further investigation.

History Obtain a detailed history from all involved including the child, parents, caregivers, and any witnesses. Document details of the onset and progression of symptoms leading to the ED visit. Especially in young infants, pinpoint the last time the child was completely well. In a critically ill child, provide immediate resuscitation. In most cases of accidental injury, there is a clear and consistent history of an accident with the child presenting for care soon afterward. **Historical features concerning for abuse include no history of trauma, changing important details of the history, explanations inconsistent with the injury or with the developmental stage of the child, discrepancies in the history provided by different caregivers, or a significant delay in seeking care.**[10-12]

Obtain past medical history including the birth history, chronic or congenital conditions, previous injuries, and previous hospitalizations and surgeries. Document any family history of bleeding or bone disorders and any relevant metabolic or genetic conditions. Review the diet and medication history including vitamin K at birth and any subsequent vitamin or nutritional supplementation. Note current developmental status and progress. The social history should identify the primary caregiver and other caregivers, household composition, any history of past abuse to the child or siblings, and previous child protective services involvement.

Physical Examination Begin with a general assessment of the child's alertness and demeanor. A brief evaluation of the work of breathing, cardiovascular perfusion, and level of consciousness will identify a critically ill child in need of resuscitation. Note whether there is spontaneous and symmetric movement of the extremities. Lack of use of an extremity or pain with examination or movement may indicate a fracture. Document head circumference and examine the scalp, noting any hematomas or step-offs, which may indicate a skull fracture. Funduscopic exam may reveal retinal hemorrhages, although it is often difficult to perform an undilated exam in a child. Injuries to the mouth, such as a torn frenulum, may be indicative of forced feeding. Fully expose the skin and document the precise location, size, and shape of any bruises, burns, bite marks, or scars. Palpate the chest, abdomen, spine, and extremities for any tenderness. Perform and document a neurologic examination if there is concern for head trauma.

DIAGNOSIS

Bruises Bruising is the most common manifestation of physical abuse[8] and is often overlooked. Up to a third of children with fatal or near-fatal abusive injuries have previous medical assessments in which bruising was noted.[13,14] Because bruising is also very common in nonabused children, distinguishing between nonaccidental and accidental bruising requires careful consideration of the child's age and developmental level, the history, and any other associated injuries. **Accidental bruises occur on the front of the body, over bony prominences, on the extremities, and on the forehead.[15] Nonaccidental bruises, on the other hand, are more commonly found on the torso, neck, and ears (Figure 150-1) and the soft parts of the body such as the cheeks and the buttocks**. Nonaccidental bruises are also more likely than accidental bruises to be found in clusters, to be on the back of the body, and to be symmetrical.[15] In addition, nonaccidental bruises tend to be larger and more numerous than accidental bruises.[15] Patterned bruises may be evident if a child has been struck with a hand or an implement (**Figure 150-2**). Although the presence of bruises of different colors was previously thought to indicate bruises of different ages, the dating of bruises is highly inaccurate. The examiner should document the location, color, size, and shape of bruises but should not comment on the timing of the injury.[16]



FIGURE 150-1. Bruising and petechiae on the ear from physical abuse.

Bruises in young infants deserve special consideration because infants very rarely sustain accidental bruises. The adage *those who don't cruise rarely bruise* is supported by the observation of bruising in only 0.6% of infants less than 6 months of age and in only 2.2% of infants not yet able to walk, while bruising is present in over half of toddlers.[17] Bruising in infants is associated with more serious abusive injuries. Additional injuries are diagnosed in up to one half of infants with isolated bruising.[18] The **TEN-4** bruising clinical decision rule identifies bruises to the thorax, ears, and neck, as well as any bruising in infants less than 4 months, as particularly concerning for abuse (**Figure 150-3**).[19]

The **differential diagnosis of bruises** includes skin conditions such as congenital dermal melanocytosis (Mongolian spots) and cultural practices such as cupping and coining. Both acquired and inherited bleeding disorders, such as idiopathic thrombocytopenic purpura and hemophilia, predispose children to bruising from inconsequential trauma. These conditions are readily diagnosed through the history, family history, and basic screening blood work including a CBC and coagulation profile. Other medical conditions causing bruising include infections (e.g., meningococcemia), leukemia, nutritional deficiencies, and Henoch-Schönlein purpura.



FIGURE 150-2. Multiple bruises to the back and buttock from physical abuse. Note the patterned loop bruising from impact with a cord.

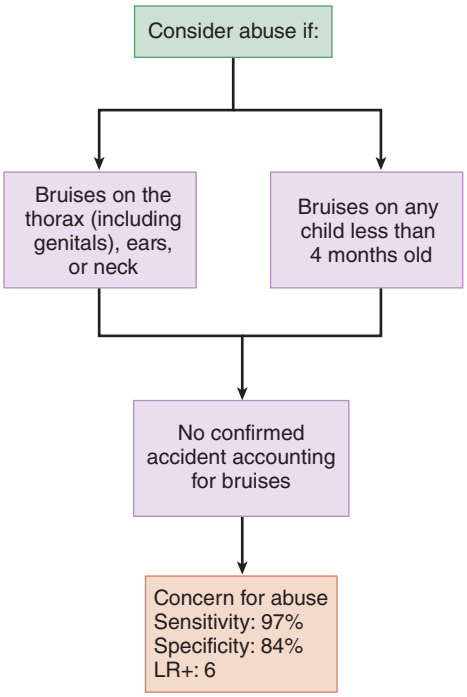

FIGURE 150-3. TEN-4 bruising clinical decision rule for bruises concerning for abuse.[19] LR+ = positive likelihood ratio.

Burns Burns account for 6% to 20% of maltreatment-related fatalities in children. Most burns, both accidental and abusive, are scalds and affect children age 1 to 4 years old.[20] Accidental scalds typically occur when young children pull hot beverages off tables or stovetops, spilling the hot liquid onto themselves. The resulting burns are generally asymmetric, have irregular borders, are of varying depth, and are distributed over the face, neck, and upper torso.[20] In contrast, most inflicted burns are caused by immersion in hot tap water.[20] Abusive burns are often in a glove and stocking distribution with a sharp line of demarcation between the burned and uninjured skin. The child may have been held seated in a tub of hot water, resulting in burns to the perineum and feet with ring-shaped sparing of the buttocks where the skin was in contact with the cooler surface of the tub.

When assessing nonscald burns, consider the distribution and extent of the burn. Children usually burn themselves when they reach out and touch a hot object. Most accidental burns, therefore, occur on the palms and the fingers and have an indistinct contour. In contrast, inflicted burns tend to be on the dorsal surface of the hands and on the back of the body. The margins of inflicted burns are often more distinct and may take the shape of the heated object used to inflict the burn.[20]

Burns due to neglect are nine times more common than inflicted burns.[21] Even when a burn itself does not appear inflicted, it is important to consider whether lack of adult supervision or exposure to an unsafe environment or substances played a role in the injury.

The **differential diagnosis of burns** includes bullous impetigo, Stevens-Johnson syndrome, and severe diaper dermatitis.

Fractures Fractures are the second most common manifestation of physical abuse. Over 80% of abusive fractures occur in children less than 18 months of age, and 12% to 20% of fractures in infants and toddlers are caused by physical abuse.[22,23] Because fractures are also very common accidental injuries, accounting for between 8% and 12% of all pediatric injuries, distinguishing between accidental and abusive fractures can be challenging, particularly when the caregiver may not provide an accurate history.[10,24] In children <3 years old, up to 20% of abusive fractures were initially attributed to accidents or other causes.[25] Children with abusive fractures may present with nonspecific complaints such as irritability, swelling, not using a limb, or refusal to weight bear. Fractures may also be discovered incidentally during evaluation for other conditions or injuries.

TABLE 150-3 Risk Factors for Physical Abuse in a Young Child With Fracture

- Age <1 year old with fracture
- No history/inconsistent history of trauma
- High-risk fractures:
  - Rib fractures
  - Metaphyseal fractures
  - Humerus fracture in child <15 months old
  - Femur fracture in nonambulatory child
- Multiple fractures or fractures of different ages
- Presence of other injuries

There are a number of historical and clinical factors associated with an increased likelihood of physical abuse; however, **the single most important risk factor for abusive fractures is young age** (**Table 150-3**).[24] It is very unusual for nonmobile infants to sustain fractures.[23,24] Abuse accounts for one in two femur fractures in children less than 1 year of age, whereas the likelihood of abuse as a cause of femur fractures in 2- to 3-year-olds drops to less than one in five.[25-28]

Any fracture can be caused by either accidental or nonaccidental means; however, certain fracture types are more specific for abuse and should prompt further investigation. **Rib fractures** are rare in infants and young children and are generally seen only in cases of severe trauma such as motor vehicle collisions (**Figure 150-4**). In the absence of severe trauma, a child with rib fractures has a 7 in 10 chance of having been abused.[24] Posterior rib fractures are most highly correlated with physical abuse.[29]

Classic **metaphyseal fractures** are shear injuries to the immature ends of growing bones in infants caused by the rapid acceleration and deceleration associated with yanking or shaking (**Figure 150-5**). They are highly specific for child abuse.[30]

Additional injuries, such as linear skull fractures and long bone fractures, are common in both accidental and nonaccidental injuries. Knowledge of possible injury mechanisms resulting in each fracture type guides the clinician in assessing whether the reported history accounts for the injury.

Consider the **differential diagnosis of fractures**. Although the lack of any reported history of trauma should raise concern about abusive injuries,

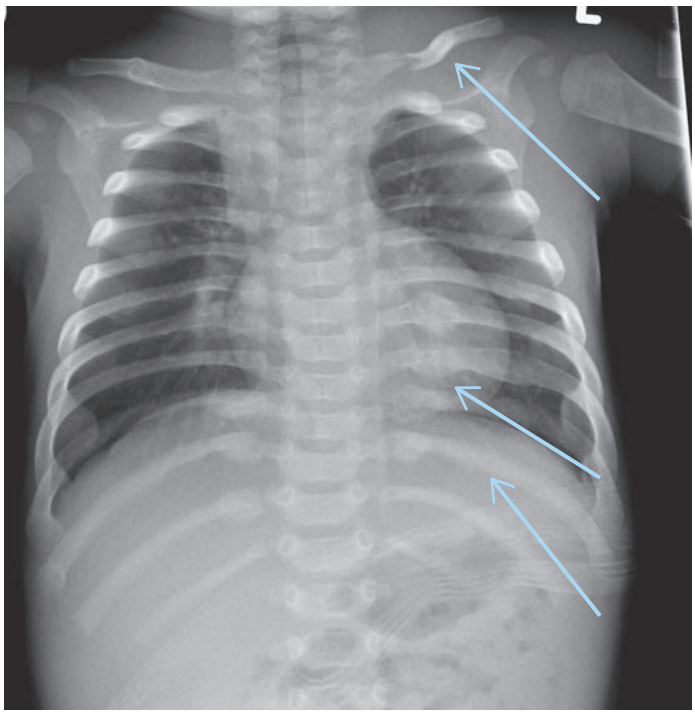

FIGURE 150-4. Acute left clavicle and healing rib fractures in an infant.



FIGURE 150-5. Classic metaphyseal fracture of the humerus with bucket handle appearance.

toddler's fractures are an exception to this rule. **Toddler's fractures** are nondisplaced spiral fractures occurring in the distal third of the tibia in ambulatory children between 9 months and 4 years of age (see Chapter 141, "Pediatric Orthopedic Emergencies"). These are accidental fractures that occur when the child twists and falls on a planted foot. Certain medical conditions such as inherited bone diseases (osteogenesis imperfecta), chronic medical conditions (renal osteodystrophy), or nutritional deficiencies result in weaker bones that may fracture with relatively minor trauma. These conditions are far less common than child abuse and are often easily identified by the medical history, the physical exam, and the radiographic appearance of the bones.

Abusive Head Trauma Abusive head trauma is the most common cause of traumatic death and disability in infancy and early childhood.[31-33] Although a number of terms have appeared in the medical literature over the years to describe the spectrum of cranial and ocular injuries that occur due to inflicted head injury in children, the American Academy of Pediatrics currently recommends the term *abusive head trauma* as the appropriate medical diagnostic terminology.[34]

Abusive head trauma demonstrates a distinct pattern of injuries characterized by intracranial injury (hemorrhage, edema, or infarction) and ocular injury (retinal hemorrhage or retinoschisis).[34-38] Skull, rib, or long bone fractures may be present; however, remarkably, there may also be no external evidence of trauma at all. Retinal hemorrhages occur in up to 80% of patients with abusive head trauma and typically are extensive, occurring in multiple layers of the retina and extending out to the ora serrata.[37,38]

Infants and children with abusive head trauma are brought to the ED with a broad spectrum of clinical concerns and findings. Children may present in extremis, with obvious signs of physical trauma. Alternately, they may present with only very subtle suggestions of irritability or feeding problems and no history of trauma at all. Apnea and seizures both have a significantly higher association with abusive head trauma than with accidental trauma.[39] Unfortunately, a substantial number of cases of abusive head trauma go unrecognized due to the mild, nonspecific nature of the presenting symptoms and signs.[13] The clinician must be careful not to overlook signs such as bruising, large head circumference (>85th percentile), or unexplained mild anemia in infants presenting with nonspecific complaints as these features may identify children who would benefit from neuroimaging.[40]

The **differential diagnosis of abusive head trauma** includes a number of conditions, but perhaps the two most common are birth-related and accidental trauma. Subdural and retinal hemorrhages secondary to birth are typically asymptomatic, resolving well within the first month of life.[38,41] Accidental falls may cause head injury and, very rarely, sparse retinal hemorrhage usually isolated to the posterior pole. Accidental falls are extremely unlikely to result in severe intracranial injury and typically result in focal damage with clear evidence of blunt impact to the head. Other underlying medical conditions such as coagulopathies and metabolic or congenital abnormalities will very rarely present with features similar to abusive head trauma.

Abdominal Trauma Although abdominal injuries due to child abuse are less common than other types of abusive injuries, abdominal trauma is the second leading cause of death in abused children, after abusive head injury.[11] Injuries to virtually every organ have been reported; however, liver and small bowel injuries are the most commonly seen. While no single feature allows identification of children with intra-abdominal trauma, features associated with a higher likelihood of abusive trauma than of accidental abdominal injuries include young age and small bowel injury.[11] Abdominal injuries due to abuse are much more common in toddlers (median age, 2.6 years), whereas accidental injuries are more common in older children (median age, 7.8 years). Accidental injury to the small intestine is exceedingly rare in children less than 5 years of age. In older children, accidental small bowel injuries most commonly are the result of motor vehicle collisions or handlebar injuries. Duodenal injuries in particular are very concerning for abuse in young children.[11] The mechanism of injury is typically a direct blow to the abdomen compressing the fixed duodenum against the spine.

Because many cases of abdominal trauma are asymptomatic or have other confounding injuries and there is often no history of trauma provided, be alert for any potential sign of injury and have a low threshold for investigation. Although bruising to the abdomen is a clear sign to consider intra-abdominal injury, it is present in only 20% of cases.[42] Signs and symptoms of intra-abdominal injury range from nonspecific irritability, lethargy, vomiting, poor feeding, and abdominal discomfort or distention to shock with frank peritonitis.

The gold standard for diagnosis of intra-abdominal trauma is a CT scan of the abdomen; however, given the difficulty in identifying abdominal injuries due to abuse, some advocate screening for intra-abdominal injuries using **hepatic transaminases** in all young children where there are concerns about physical abuse.[12,42,43] Because hepatic transaminases may not be elevated in cases of small bowel injury, obtain abdominal CT scan if clinical suspicion warrants.

LABORATORY TESTING AND IMAGING FOR SUSPECTED ABUSE AND NEGLECT

Investigations for any form of injury are guided by the nature and severity of the injury, the age of the child, and the physical examination findings. In general, the more severe the injury and the younger the child, the more extensive the investigations required and the more likely they are to reveal additional injuries. Consultation with a pediatrician or child abuse specialist is recommended.

Laboratory Testing Laboratory investigations include a CBC with differential and coagulation studies, including a platelet count, a prothrombin time, and a partial thromboplastin time. Results may reveal anemia secondary to an intracranial or intra-abdominal hemorrhage or an abnormal coagulation profile due to the brain injury itself. Further coagulation studies may be indicated in cases of extensive bruising or intracranial hemorrhage. In the child with unexplained fractures, obtain a serum calcium, phosphate, and alkaline phosphatase. Children with severe injuries, including those suspected of abusive head trauma or occult abdominal trauma, should undergo a complete trauma panel including hepatic transaminases.

Imaging **A skeletal survey is a specific series of radiographs of all the long bones, chest, spine, hands, feet, pelvis, and skull that is indicated in all infants and young children when there is a concern for inflicted trauma.**[10,12,18] A properly performed skeletal survey frequently reveals previously unsuspected injuries including multiple fractures or fractures at various stages of healing.

Noncontrast head CT is indicated for any child suspected of sustaining acute intracranial trauma. Radiologic features with significant association for abusive head trauma include subdural hemorrhage, particularly if diffuse, interhemispheric, or infratentorial; hypoxic ischemic injury; and cerebral edema.[44] MRI may further delineate the extent of brain injury and may offer some guidance for the timing of injuries. Inclusion of the neck and spine in MRI studies may identify ligament injury or spinal hemorrhage.[45]

Abdominal CT should be included when there is concern for intra-abdominal injury.[12] Although it may be tempting to screen for intra-abdominal injury by US, US is not sensitive enough to identify all clinically significant intra-abdominal injuries in both abusive and accidental injuries.[43,46]

TREATMENT AND DISPOSITION

Rapidly identify and resuscitate life-threatening injuries. Once the child has been stabilized, attention shifts to further medical and legal evaluation. Because the comprehensive investigation of child abuse requires a multidisciplinary approach, most potential victims of serious physical abuse should be admitted to the hospital while the appropriate medical, surgical, and child protection teams complete their respective investigations. Children with head and abdominal injuries due to abuse have both longer hospitalizations and higher mortality compared with children with accidental injury.[33,47]

Older children with minor or superficial injuries may be discharged provided they have been assessed by child protective services and a safe environment can be ensured.

CHILD SEXUAL ABUSE

Reports suggest that 26% of girls and 5% of boys have experienced some form of sexual abuse by the age of 17 years.[48] When there is concern for possible sexual abuse, the role of the ED provider is to identify children requiring urgent medical and forensic evaluation, to decide when to refer to other professionals and child protection authorities, and to counsel the parents or caregivers. The child's ED visit may be triggered by a broad spectrum of issues including anogenital bleeding, vaginal/urethral discharge, dysuria, urinary tract infection, sexualized behaviors, suicidality, or as commonly happens, a recent disclosure of sexual abuse without any specific physical symptoms. The sexual abuse may be either recent or remote relative to the time of presentation and may have involved numerous contacts over a period of time. The offender is typically well known to the child and, indeed, is often a parent or family member.[48-50] As a result, the child's caregivers typically present in emotional crisis, even though the child may not be suffering any physical trauma. The family requires a patient, supportive individual to listen to their concerns and provide appropriate guidance and reassurance.

First begin by assessing the urgency of the situation and determining when and where the full assessment should most appropriately be performed. In some jurisdictions, **sexual assault nurse examiners** or child abuse pediatricians are available. Emergency evaluation with collection of forensic evidence is indicated if the abuse has been recent, the child has genital bleeding or concerns of acute trauma, or there are other concerns for occult trauma. As yet, there is no consensus on the outside limit for the timing of forensic evidence collection in the pediatric patient. Research suggests that physical examination should be performed as soon as possible after an assault, yet evidence collection is unlikely to produce positive results in child victims outside the first 24-hour period.[50,51] Whether or not forensic evidence is collected, an immediate physical examination is recommended for all children disclosing sexual abuse within 72 hours of the last event.[52,53] Physicians should be aware of the policies for the timing of forensic evidence collection within their own jurisdiction.

CLINICAL FEATURES

There are numerous factors that make conclusive evaluation of alleged child sexual assault challenging:

- **The medical diagnosis of sexual abuse is heavily reliant on the history provided by the child.**[50,52,54] A proper forensic interview should be conducted by trained child protection investigators.
- **The absence of physical findings does not exclude abuse.**[50,54-57] Many sexually abusive activities leave no physical marks on the child, and in the rare instances where traumatic injuries do occur, they often heal well, with no obvious evidence of prior injury.
- **Forensic specimens are typically not positive in child sexual abuse but should be collected when possible.**[50-52,58] Forensic evidence may include blood, seminal fluid, sperm, saliva, or other foreign debris. The majority of evidence will be found on linens or clothing.[50,51,58]

History Obtain the initial historical details from ancillary personnel (parents, guardians, police, or social workers) without the child present. Often the most compelling evidence for criminal prosecution is the detailed, forensic interview of the child performed by child protection investigators. Thus, direct questioning of the child should be limited to a medical history that addresses acute physical symptoms or concerns only. Record verbatim any spontaneous disclosures or statements of significance that the child makes during the course of the history or physical examination.

Document past medical history including any previous genitourinary trauma, urinary tract or anogenital infections, discharge, or toileting concerns. Note immunization status and any recent medications.

Physical Examination Much emphasis is placed on the importance of the physical examination, even though most pediatric victims of sexual abuse have a normal examination. If the child's disclosure suggests the abuse was remote to the time of presentation, then a straightforward physical examination to ensure that the child is currently physically well may be all that is required in the ED. All children should have a parent or supportive adult who is known to them present during the examination. Explain the procedure for the assessment prior to beginning the examination, addressing any parental concerns in advance. For the child, a simple age-appropriate review of systems generally guides them through the various body parts being evaluated. Do not force the examination. Subtle distraction techniques and frequent gentle reassurance are helpful. If the child remains uncooperative, decide whether the examination should continue under procedural sedation or general anesthesia or whether the assessment can be rebooked for a future time.

A complete examination begins with a comment on the child's overall appearance including emotional state and demeanor. Prior to palpation, ask the child about any painful areas. Thoroughly inspect all parts of the skin and hair and document bruises, petechiae, abrasions, areas of swelling, or bite marks. Carefully examine the oropharynx for signs of trauma.

Anogenital Examination Examination of the anogenital area can generally be accomplished with inspection only. The supine, frog-leg position optimizes visualization of the genital structures. Speculum examinations are not required in the prepubescent child. If the hymenal margin is not well visualized while supine or if abnormalities are suspected, then examine the child in the prone knee-chest position. This position allows gravity to pull the margins of the hymen down into clearer view. Toddler-age children who are reluctant to undergo genital examination may be examined while lying supine in the parent's lap.

A systematic approach to anogenital examination is helpful to ensure complete documentation. Initial inspection details the appearance of the labia majora, labia minora, and the posterior fourchette. With gentle separation and traction of the labia, the clitoris, urethra, hymen, vaginal vault, and fossa navicularis come into view (**Figure 150-6**). Describe relevant findings using a "clock face" orientation, with 12 o'clock being anterior/superior and 6 o'clock being inferior/posterior. Document any evidence of trauma including bruising, bleeding, edema, lacerations, or abrasions. Accidental genital trauma typically results in bruises or abrasions to the labia or posterior fourchette. The hymen is rarely injured with accidental trauma given its more protected, recessed position. Note all nonspecific findings of erythema, ulceration, hypopigmentation, or discharge. Describe the hymen by noting both the shape and the integrity of the hymen margin (**Figure 150-7**). Typically, the hymen is thickened and redundant at both infancy and puberty, due to maternal hormonal effect at birth and endogenous hormonal effect later. Small mounds (bumps),

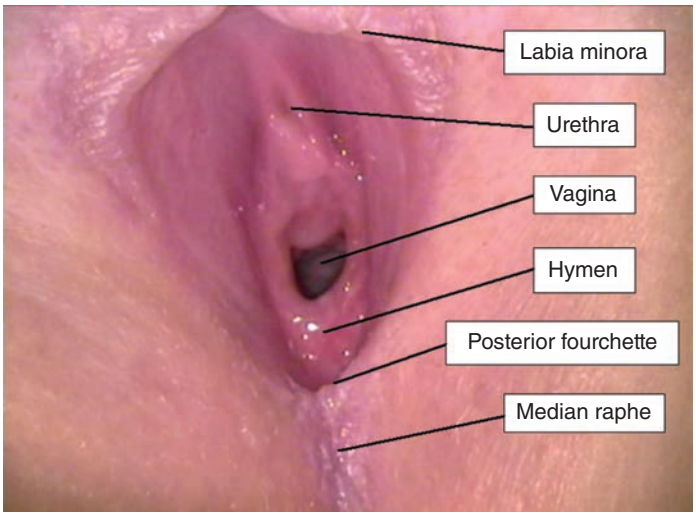

FIGURE 150-6. Normal prepubertal genital anatomy.

tags, or rolled edges are common nonspecific findings contributing to a wide degree of variation in normal genital morphology.[54] Note any deep notches or clefts to the rim of the hymen as well as any transections, either acute or healed, that extend to the base of the hymen. Acute superficial lacerations generally heal well with no intervention; however, deeper lacerations with extension into the vagina are less common and should be assessed by a gynecologist and may require exam under anesthesia.

Genital examination of young boys is generally more straightforward. Note the presence of past circumcision and document any evidence of acute trauma including bruises, bite marks, or petechiae.

Anal examination of both boys and girls is most often normal or nonspecific; however, make note of any acute physical findings including bruising, abrasions, fissures, or edema. Recent anal trauma may result in either spasm of the anal sphincter or anal dilatation. Minor anal dilatation is a normal finding, particularly if there is stool present in the rectal vault.[54]

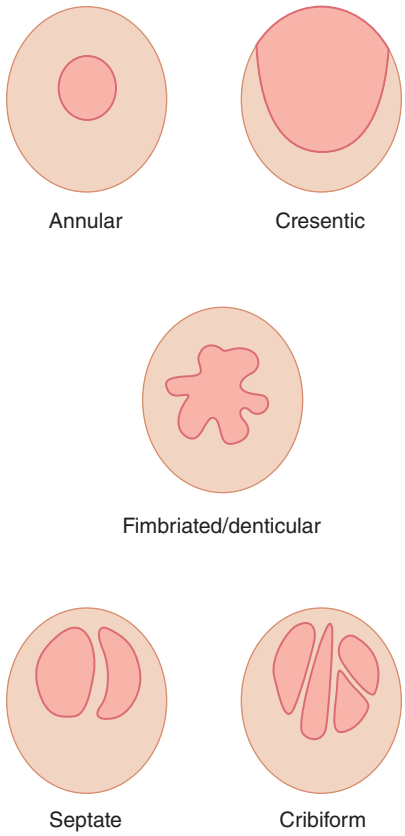

FIGURE 150-7. Normal hymen morphology.

Laboratory and Forensic Investigation Initial investigation is dictated by history and clinical findings. If the child appears stable, laboratory investigations may be limited to assessment for sexually transmitted infections and/or forensic evidence collection.

Sexually Transmitted Infections The prevalence of sexually transmitted infections in the pediatric abuse population is exceedingly low, often less than 1% to 4%.[59,60] Current recommendations suggest testing for the presence of sexually transmitted infections in high-risk situations only.[52] High-risk situations include the following: presence of genitourinary symptoms or injury; assailant has or is at high risk for sexually transmitted infection; a sibling has a sexually transmitted infection; or parents and/or patient request testing. A non–clean catch urine should be sent for nucleic acid amplification technique testing for gonorrhea and *Chlamydia*. Although urine nucleic acid amplification technique testing is an acceptable standard for vaginal infections, it is not yet approved for rectal or oral swabs. For forensic purposes, positive tests should be confirmed with culture or with a second nucleic acid amplification technique probe. Vesicles or ulcerations are not common in the pediatric patient and, if present, should be swabbed for viral studies. Serologic studies for syphilis and the human immunodeficiency virus are not routinely indicated but may be considered if clinical suspicion warrants or if requested by the patient or parent.

Forensic Specimens Be familiar with the forensic evidence collection kits provided by the criminal investigation units in your area. All forensic specimens must be properly labeled and packaged, with appropriate chain-of-evidence documentation. Place the child's underwear and clothing (if worn at the time of the assault) in a paper bag and then seal the bag. Obtain forensic swabs from any areas suspicious for oral, genital, or ejaculatory fluid contact. Examination with an ultraviolet light source may help guide collection of specimens.

TREATMENT AND DISPOSITION

Treatment begins at initial contact with the family. A timely assessment performed by a reassuring health professional is often the first step toward a positive therapeutic outcome for both the patient and family. If the history involves significant behavioral or emotional concerns, a referral to mental health professionals may be indicated on either an urgent or elective basis depending on the child's current state.

Pharmacologic treatment should be dictated by the individual's history and physical examination findings. Pregnancy and sexually transmitted infection prophylaxis are not routinely recommended in the young pediatric patient following a disclosure of sexual abuse; however, prophylaxis should be considered for older girls and adolescents.[52,61] Arrange counseling and follow-up in an outpatient setting to ensure appropriate repeat assessment. It is important to ensure resolution of any physical injuries, to assess for any new symptoms, and to inquire as to any emotional or behavioral sequelae.

CAREGIVER-FABRICATED ILLNESS

Caregiver-fabricated illness, which has been known in the past as **Munchausen syndrome by proxy** or **pediatric condition falsification**, has also been termed **medical child abuse**.[62] This condition is an uncommon form of child abuse in which a parent or caregiver induces and/or fabricates illness or injury in a child. Cases are generally highly complex, often necessitating detailed, comprehensive assessments by multiple subspecialty pediatric teams. Although the role of the emergency physician may seem minor, it is often the detailed emergency documentation of numerous clinical presentations and responses to investigation and intervention that provides objective information needed for eventual diagnosis.

Be alert to the possibility of this condition when presented with a pediatric case that involves persistent or recurrent illness that is not adequately explained and yet results in multiple medical or surgical

procedures. Often the medical diagnoses that the caregiver describes do not match the objective findings, and the child tends not to respond to the usual therapies. Hospitalization is often required to coordinate a multidisciplinary evaluation.

REPORTING

Although laws governing the reporting of suspected child maltreatment vary around the world, in all states and provinces in the United States and Canada, **any physician who has reason to believe that a child is at risk of abuse or neglect has a legal obligation to report to local child welfare authorities**. The legal duty to report overrides any duty of patient confidentiality. It is not necessary to be certain of the diagnosis of abuse, but one should have *reasonable suspicion* that abuse or neglect may have occurred. Healthcare providers reporting concerns of suspected maltreatment are protected from civil litigation. Reports must be made in a timely manner due to the risk of future maltreatment to other children in the home.

Informing parents of your obligation to report to child protection services should be respectful and nonaccusatory. Communication should focus on accurately identifying the underlying medical problem, managing the child's injuries, and providing honest, straightforward medical information.

In some cases, particularly when parents are engaged in legal custody disagreements, the history may be quite vague and the physical examination may be entirely normal. If the only concern for abuse or neglect is with the parent or guardian and there is no disclosure from the child and no witnessed abuse or concerning physical findings, then the emergency physician may provide the parent with the appropriate information to make a report on their own. Be familiar with local laws and the methods for reporting. If uncertainty exists about the need to report, consult with a child abuse pediatric specialist.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 13

Infectious Diseases

CHAPTER 151

Sepsis

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INTRODUCTION AND EPIDEMIOLOGY

Sepsis is a heterogeneous syndrome characterized by widespread inflammation and organ distress initiated by any type of microorganism. Invasion of the blood is not necessary to develop or identify sepsis, which is determined by the host response. As sepsis severity increases, a multifactorial series of events leads to impairments in perfusion, oxygen delivery, and direct cellular damage secondary to inflammation. Eventually, multisystem organ failure occurs, and mortality is high.

The varying clinical presentation leads to a wide range of estimates of the annual incidence of severe sepsis, ranging from 300 to 1000 cases per 100,000 persons per year,[1] and most patients have initial hospital care in the ED. The sepsis incidence is increasing for multiple reasons, including an aging patient population.[2]

Most patients with sepsis spend several hours in the ED, and once admitted, more than half will require care in an intermediate or intensive care unit.[2] Sepsis is the leading cause of hospital death, with mortality rates improved from a decade ago but still high, approximately 15% to 20%[3] in optimal clinical trial scenarios.[4,5] This hospital mortality rate approaches 50% in the sicker subset of those with septic shock.[6] Sepsis hospital mortality exceeds that of many other high-visibility acute care conditions.[7-9] Morbidity is common, even after surviving a year, with a long-term deficit in cognition and functioning prevalent.[10] Estimates from 10 years ago suggest annual national costs reaching $16.7 billion,[2] which has certainly increased in the past decade. Sepsis is the single most expensive inpatient condition.

Gram-positive bacteria are the predominant pathogens of sepsis.[11] Methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and other multidrug-resistant organisms are common organisms.[12] Fungal sources are more common now, particularly in immunosuppressed patients. The most likely causative microorganism varies based on the likelihood of exposure to drug-resistant microorganisms (due to recent healthcare exposures) and the anatomic site of infection.

DEFINITIONS

Sepsis syndromes exist on a continuum and are defined based on the presence of a systemic, dysfunctional host response that leads to organ failure.[13,14] Historic and more recent definitions are often not sensitive or specific. Previously, **sepsis** was a suspected or confirmed infection with evidence of systemic inflammation (demonstrated either through evidence of the systemic immune response syndrome or laboratory abnormalities). ***Severe sepsis*** was sepsis plus evidence of new organ dysfunction thought to be secondary to tissue hypoperfusion. **Septic shock** exists when cardiovascular failure occurs and carries the worst prognosis.

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock removed severe sepsis as a term and narrowed the definition of septic shock (Table 151-1).[15] In Third International Consensus Definitions for Sepsis and Septic Shock, patients with suspected or proven infection, signs of systemic inflammation (without strict definitions), and organ failure (defined as a Sequential Organ Failure Assessment score of at least 2) have sepsis. Septic shock is defined as those with sepsis requiring vasopressors after adequate resuscitation *and* with an elevated lactate. These new definitions are simpler and better identify the highest-risk group. However, the new definitions diminish the sensitivity of detecting those in the middle ground (previously called severe sepsis), in whom death and morbidity rates are elevated compared to those simply infected, and for whom simple detection and care can alter illness trajectories and outcomes.[16]

An overlapping and potentially confusing recent mandate is the **Centers for Medicare and Medicaid Services quality measure called SEP-1**.[17] Enacted prior to the Third International Conference definitions, it mandates specific actions to meet Centers for Medicare and Medicaid Services requirements, but it used the older definitions of severe sepsis and septic shock. **Patients with severe sepsis and septic shock require the following clinical actions between initial recognition and 3 hours:**

1. Lactate measurement
2. Blood and other cultures prior to antibiotic administration
3. Antibiotic therapy directed at specific source or broadly
4. Initial fluid therapy with 30 mL/kg of crystalloid
5. If the initial lactate is elevated (>2 mmol/L), repeat lactate required prior to 6 hours

Patients with septic shock require the following additional actions:

1. A repeat 20 mL/kg fluid bolus for persistent hypotension
2. Initiation of vasopressor for persistent hypotension
3. Reassessment and documentation using clinical or hemodynamic/oxygenation measurements to judge adequacy of volume status and tissue perfusion interventions

Recently, the Surviving Sepsis Campaign changed its recommendations to include measuring a lactate, obtaining blood cultures, starting antibiotics, beginning 30 mL/kg crystalloid for hypotension or a lactate >4 mmol/L, and initiating vasopressors during or after fluid resuscitation to maintain a mean arterial pressure >65 mm Hg, all within 1 hour of ED triage.[18] However, there is no clear evidence yet to support this narrower time window for metric completion, and that aggressive measure is not yet widely adopted.

QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (qSOFA)

The Quick Sequential Organ Failure Assessment (qSOFA) tool is a simple screening tool derived to identify patients at higher risk of death. **Criteria include altered mental status, respiratory rate ≥22 breaths/min, and systolic blood pressure ≤100 mm Hg, with a score ≥2 indicating a high risk for poor outcome**. This tool also aids in the rapid identification of high-risk patients immediately upon presentation whose care might benefit from being expedited.

Like the new definitions, the Quick Sequential Organ Failure Assessment enhances specificity for short-term mortality assessment at the expense of lower sensitivity; it may not identify those at risk for later disease progression. Many sepsis patients who might benefit from early aggressive treatment are negative according to the Quick Sequential Organ Failure Assessment, so it is currently recommended that a full Sequential Organ Failure Assessment score be calculated on patients with infection requiring hospital admission. Unfortunately,

TABLE 151-1 The Third International Consensus Definitions for Sepsis and Septic Shock Definitions of Sepsis and Septic Shock

Condition	Definition	Criteria
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection	Suspected or proven infection *and* Increase in Sequential Organ Failure Assessment (SOFA) score of 2 or more from baseline*
Septic shock	A subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality	Sepsis *and* Vasopressor therapy required to maintain a mean arterial pressure ≥65 mm Hg *and* Lactate >2 mmol/L despite adequate fluid therapy

*Can be assumed to be 0 in patients without known prior organ dysfunction.

this approach is hampered by the need for fairly complex calculations and laboratory testing that may delay identification; therefore, neither the Quick Sequential Organ Failure Assessment nor the full Sequential Organ Failure Assessment should completely replace clinical judgment about presence of sepsis or its perceived severity.[15,19,20]

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS) PROGNOSIS

Having systemic inflammatory response syndrome criteria does not confirm the presence of infection or sepsis because these features are shared by many other noninfectious conditions such as trauma, pancreatitis, and burns (**Figure 151-1**). **The systemic inflammatory response syndrome response is not a diagnosis or a good indicator of outcome; it is a crude means of stratification of patients with systemic inflammation**.

Complementary risk stratification and adjustment can be pursued using various tools, including the Acute Physiology and Chronic Health Evaluation acuity system,[21] the Sequential Organ Failure Assessment score, and the Mortality in Emergency Department Score.[22] With the exception of the Sequential Organ Failure Assessment score, now part of the definition of sepsis, these scoring systems are typically limited to research and are yet to be established as beneficial in the guidance or provision of clinical care.

Serum lactate across a wide spectrum[23] provides prognostic data in those with sepsis, but it is not a singular test to diagnose or exclude sepsis. Lactate arises from anaerobic metabolism, heightened with tissue hypoperfusion; it also accumulates from changes in *aerobic* metabolism that occur in response to widespread inflammation.[24] As lactate increases, the risk of mortality rises, with the degree of lactate elevation

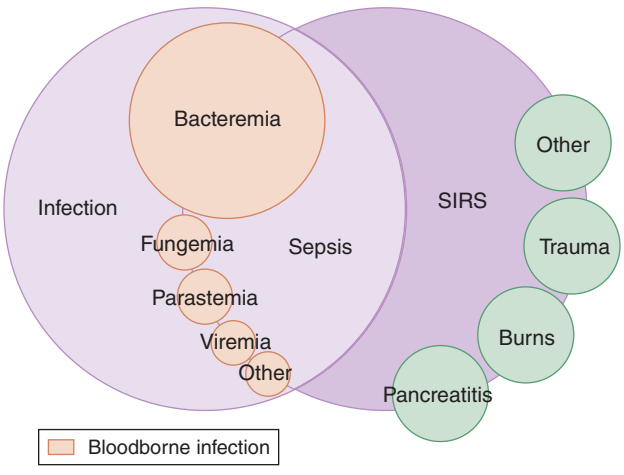


FIGURE 151-1. Interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection.

and hypotension being independent predictors of mortality.[25,26] Specifically, 28-day mortality rate associated with modest elevation of serum lactate to 2 to 4 mmol/L approaches 15% even in those patients without hypotension,[27] and the rate continues to rise with increasing lactate levels. In general, venous or arterial lactate levels on either point-of-care bedside devices or measured in a central laboratory are useful[28]; even better are serial levels using the same method of sampling (arterial or venous) to identify improvement that mirrors clinical responses.[26] This is called **lactate clearance,** defined as a drop over time; lactate clearance provides an independent prognostic value in addition to vital signs and other measurements. Patients with sepsis who do not clear lactate have a higher mortality rate than patients who do.[29,30] The major limitation is that **lactate is nonspecific and can be elevated in a number of conditions, and it must be used together with clinical judgment**.

PATHOPHYSIOLOGY

In sepsis, the host immune response fails to control or overreacts to invasive pathogens, leading to two critical events.[31,32] First, the host first develops a hyperinflammatory response in the early stages of sepsis that evolves into a blunted response. This blunted response leads to an increased risk of secondary hospital-acquired infections and results in programmed death of key immune, epithelial, and endothelial cells, leading to tissue injury and multiorgan dysfunction.

The second event is an imbalance in procoagulant and anticoagulant functioning; in the most extreme of situations, this results in the clinical syndrome of disseminated intravascular coagulation. Disseminated intravascular coagulation causes micro- and macrovascular clot formation and impaired microvascular tissue perfusion. Subclinical disseminated intravascular coagulation can lurk despite relatively normal basic laboratory findings and is associated with a worse prognosis.[33] Microvascular ischemia adds to organ failure and the release of proinflammatory intracellular contents, which further stimulates the innate immune response and perpetuates the underlying pathology.[34] As these events progress, the inflammatory response intensifies and a destructive cycle ensues (**Figure 151-2**). There are no current specific therapies to remedy microvascular dysfunction.

CLINICAL FEATURES

While some presentations are immediately clinically apparent, sepsis can present in a subtle or occult manner, particularly early in the course. Vital sign abnormalities—notably fever, hypotension, and/or tachycardia—are a hint to sepsis, recognizing that many patients with these findings may have another cause. In ED patients with undifferentiated hypotension, 40% will ultimately have an infectious cause of symptoms.[35]

Although traditionally categorized as an example of distributive shock (peripheral vasodilation evidenced by warm extremities with a compensatory increased cardiac output), this presentation does not describe all patients with sepsis. ED patients with sepsis are often volume depleted from decreased intake and increased fluid losses (from emesis, diarrhea, or insensible losses). Intravascular volume depletion affects preload, cardiac output, and ultimately, peripheral perfusion. Further complicating matters is **septic cardiomyopathy**, a reversible process with impaired systolic function and diastolic relaxation.[36] The combination of intravascular volume depletion and septic cardiomyopathy may manifest as "cold shock," impaired peripheral perfusion and cool extremities.

PULMONARY INJURY

Widespread inflammation secondary to sepsis can affect pulmonary function even in the absence of pneumonia. Acute lung injury is common and may result in the acute respiratory distress syndrome, characterized by new lung edema from increased alveolar and capillary permeability. Acute respiratory distress syndrome classification uses the degree of hypoxemia and radiographic findings.[37] The three mutually exclusive categories are mild (partial pressure of arterial oxygen [Pao_2] divided by fraction of inspired oxygen [FIO_2] of 200 to 300), moderate (Pao_2/FIO_2 of 100 to 200), and severe (Pao_2/FIO_2 <100), coupled with

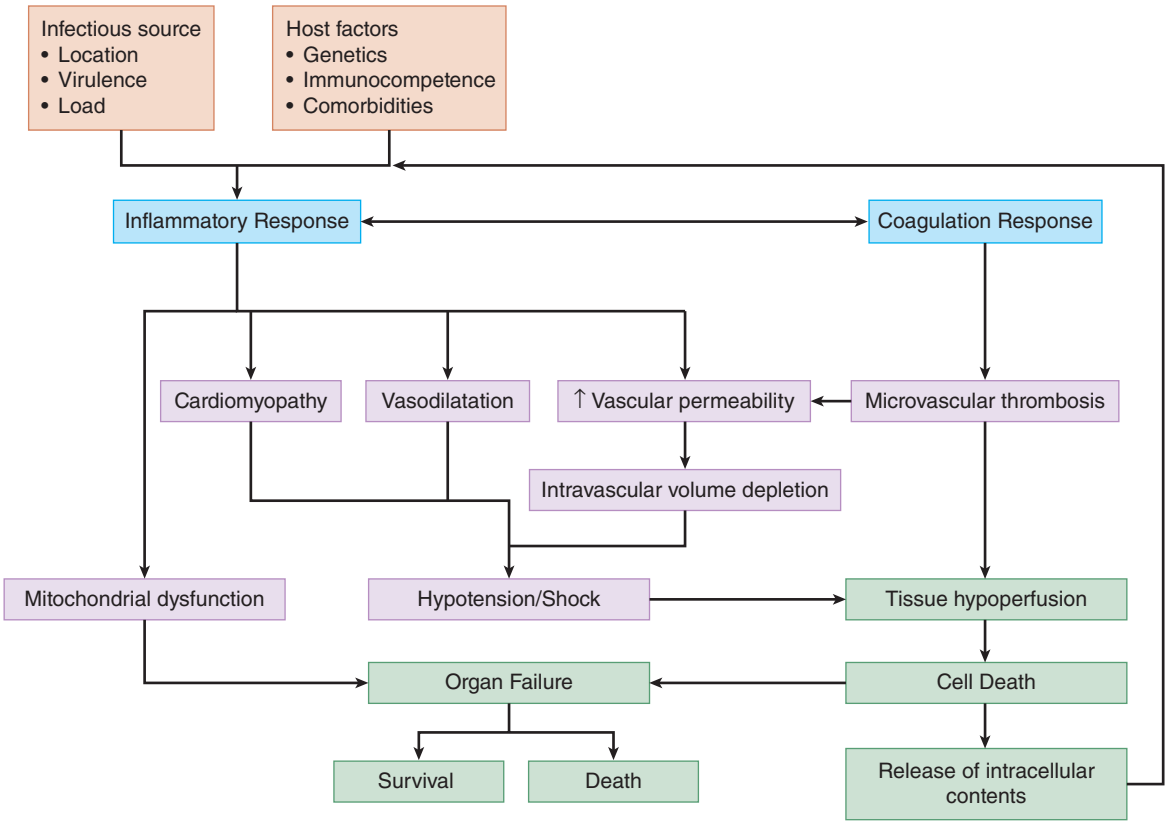


FIGURE 151-2. Pathogenic sequence of events in septic shock.

new bilateral pulmonary infiltrates on chest radiographs not explained by effusions, lung collapse, or nodules and not fully explained by heart failure or volume overload. Clinically, severe refractory hypoxemia, noncompliant lungs noted on mechanical ventilation, and a chest radiograph showing bilateral pulmonary alveolar infiltrates suggest the diagnosis. Mortality increases from 27% to 45% with increasing severity of acute respiratory distress syndrome.

RENAL INJURY

Acute kidney injury can present with azotemia, oliguria, or anuria. Factors increasing acute kidney injury risk include preexisting kidney dysfunction, depth and duration of hypotension, dehydration, and use of nephrotoxic substances (e.g., aminoglycoside antibiotics, nonionic IV contrast). Renal ischemic injury from hypoperfusion is a major factor in the pathogenesis of acute kidney injury in sepsis, although toxic products resulting from neutrophil–endothelial interactions, endothelial damage by various mediators, reperfusion injury, and microvascular thrombosis also contribute.

HEPATIC INJURY

Increased concentrations of transaminase, alkaline phosphatase (one to three times the normal level), and bilirubin (usually not >10 milligrams/dL) are evidence of this injury. Marked elevations of transaminases or bilirubin are less common unless shock is present; if seen, consider a biliary source of infection. Lessor elevations in liver function tests can result from intermittent or prolonged macro- or microvascular hypoperfusion and ischemia or be secondary to direct endotoxin, cytokines, or immune complex damage. Red blood cell hemolysis from microvascular coagulation can cause jaundice.

GI CHANGES

The most common GI manifestation of sepsis is ileus, which may persist for days after shock resolves. Major blood loss secondary to upper GI bleeding is rare in septic patients. Minor GI blood loss within 24 hours of developing severe sepsis can result from painless erosions in the mucosal layer of the stomach or duodenum.

HEMATOLOGIC CHANGES

Multiple abnormalities are possible in the hematologic system in the setting of sepsis, including neutropenia or neutrophilia, thrombocytopenia, or disseminated intravascular coagulation. Neutrophilic leukocytosis with a left shift results from demargination and release of newer granulocytes from the marrow storage pools. However, the presence of excessive bands (the immature neutrophil) is neither sensitive nor specific. **Neutropenia** occurs rarely and is associated with increased mortality. Functional neutropenia creates a relative immunosuppression, particularly later in patients' course. Both red cell production and survival decrease, but anemia is usually preexisting or occurs if the patient has bleeding or experiences a prolonged course.

Thrombocytopenia may arise from disseminated intravascular coagulation but is present in >30% of cases of sepsis even in the absence of disseminated intravascular coagulation. Lower platelet levels are associated with worse outcomes.[38,39] Mechanisms of thrombocytopenia include inhibition of thrombopoiesis, increased platelet turnover (due to a consumptive coagulopathy), increased endothelial adherence, and increased destruction secondary to immunologic mechanisms.

Finally, fulminant **disseminated intravascular coagulation**, where clinical clotting and bleeding coexist, is rare but associated with a very poor prognosis.[32] Occult disseminated intravascular coagulation has microvascular flow abnormalities, subclinical increased activation of the coagulation system, and evidence of increased fibrinogen split products in the absence of overt bleeding and clotting, and is much more common than overt forms. The activation of the hemostatic (clotting) system is due primarily to the activation of the extrinsic pathway of clotting. The fibrinolytic system is also activated and plays an important role in limiting fibrin deposition in the microcirculation. The release of tissue plasminogen activator activates the fibrinolytic system, at least initially. As sepsis progresses, there is an increased release of plasminogen activator inhibitor 1, which blocks plasmin generation and thus contributes to fibrin deposition in the microcirculation. Laboratory studies suggesting

the presence of disseminated intravascular coagulation include thrombocytopenia, prolonged prothrombin and activated partial thromboplastin values, decreased fibrinogen and antithrombin III levels, and increased fibrin monomer, fibrin split products, and D-dimer levels.

METABOLIC CHANGES

Sepsis induces multiple metabolic changes. Abnormalities in lactate metabolism come from tissue hypoperfusion with resultant anaerobic metabolism as well as increased aerobic production of lactate. Hyperglycemia is found in many, including patients without a history of diabetes; in this latter group, it is associated with a worse prognosis, in contrast to less impact of glucose elevations in those with known diabetes.[40] Hypoglycemia, with glucose levels as low as 10 to 20 milligrams/dL, occurs but is uncommon, and it may result due to depletion of hepatic glycogen and inhibition of gluconeogenesis and/or adrenal insufficiency. Adrenal insufficiency[41] exists in many patients and is caused by hypoperfusion of the adrenal glands, adrenal or pituitary hemorrhage, cytokine dysfunction of the adrenals, drug-induced hypermetabolism, inhibition of steroidogenesis by chemotherapeutics (e.g., ketoconazole), and desensitization of glucocorticoid responsiveness at the cellular level.

SKIN

Cutaneous manifestations of sepsis can include direct bacterial involvement of the skin and underlying soft tissues (cellulitis, erysipelas, and fasciitis); lesions from hematogenous seeding of the skin or the underlying tissue (petechiae, pustules, cellulitis, ecthyma gangrenosum); lesions from hypotension and/or disseminated intravascular coagulation (acrocyanosis and necrosis of peripheral tissues); lesions from intravascular infections (microemboli and/or immune complex vasculitis); and lesions caused by toxins (toxic shock syndrome). Look for any necrotizing or surgical source of sepsis, and recall that the toxic shock syndromes present in an overlapping fashion.

DIAGNOSIS

In the ED, **sepsis is a clinical diagnosis** predicated on suspicion or confirmation of infection, systemic inflammation, and evidence of new organ dysfunction and/or tissue hypoperfusion.[42] Septic shock now is a term used for those with sepsis receiving vasopressors after adequate resuscitation *and* with an elevated lactate.

The differential diagnosis of sepsis and septic shock includes other causes of shock. This includes cardiogenic, hypovolemic, anaphylactic, neurogenic, or obstructive shock (pulmonary embolism, cardiac tamponade) or endocrine disorders (adrenal insufficiency, thyroid storm) that mimic sepsis. **Given the high frequency of sepsis in ED patients with undifferentiated shock (40%), think of this cause when uncertain**. Children may not have hypotension until very late during the disease process due to an ability to upregulate their heart rate as a compensatory response to tissue hypoperfusion. This means considering compensated shock and occult sepsis in infected children who do not appear well but with normal blood pressure.

Once sepsis is diagnosed, seek the source, but **do not withhold** interventions such as resuscitative measures and antimicrobials. Often the source is clear, with signs and symptoms attributable to a pulmonary, genitourinary, skin and soft tissue, or intra-abdominal source. However, a source of infection is often not readily apparent.

The most common sepsis trigger is **acute bacterial pneumonia**, although viral and bacterial etiologies are difficult to initially differentiate. The most frequent causative organisms are *Streptococcus pneumoniae*, *S. aureus*, gram-negative bacilli, and *Legionella pneumophila*. A chest radiograph may identify air space changes and pneumonia, although radiograph findings can lag behind the clinical presentation (see also Chapter 65, "Community-Acquired Pneumonia, Aspiration Pneumonia, and Noninfectious Pulmonary Infiltrates").

Acute pyelonephritis, typically due to gram-negative enteric bacteria or enterococci, is another frequent cause of severe sepsis. Other abdominal triggers include **cholecystitis** and **cholangitis**, each rare but devastating sources of septic shock, and both require immediate surgical assessment. If there is abdominal tenderness or peritonitis, the possibilities include perforated viscous, appendicitis, diffuse colitis, or intra-abdominal abscesses. Acute pancreatitis can result in a presentation identical to that of septic shock due to widespread inflammation.[43] If peritonitis or organ ischemia/necrosis exists, early surgical consultation is needed. In women of childbearing age, septic abortion and postpartum endometritis or myometritis are unusual etiologies of septic shock.

The most common skin and soft tissue infection triggering a sepsis syndrome is cellulitis due to *S. aureus* or *Streptococcus pyogenes*. Soft tissue infections caused by gram-negative organisms are indistinguishable from those caused by staphylococci or streptococci.

Necrotizing soft tissue infections often happen in immunocompromised patients, diabetic patients, or patients with a history of poor vascular circulation (see Chapter 152, "Soft Tissue Infections"). Pay close attention to skin and soft tissue infections, particularly in elderly or obtunded patients. Include an assessment for decubitus ulcers and a genitourinary assessment to look for a necrotizing infection such as Fournier's gangrene. In female patients, particularly those with a rash, a pelvic exam including an assessment for a retained foreign body or tampon responsible for toxic shock syndrome is important.

Those without an obvious source of septic shock may have primary bacteremia or endocarditis. The most prevalent causes of primary bacteremia in outpatients are *S. aureus*, *S. pneumoniae*, and *Neisseria meningitidis*. *Pseudomonas aeruginosa* and other gram-negative bacteria are occasional causes of bacteremia and endocarditis in injection drug users. Secondary bacteremia from indwelling medical devices, including intraperitoneal or intravascular dialysis catheters, chemotherapy ports, peripherally inserted central catheters, ventriculoperitoneal shunts, and pacemaker/defibrillators, is possible. Although bacteremia can be suspected, it takes time for a blood culture to be fully assessed, making ED diagnosis difficult.

Acute bacterial meningitis is a devastating but rare cause of septic shock. Community-acquired meningitis with shock is usually caused by *S. pneumoniae* or *N. meningitidis* (see Chapter 174, "Central Nervous System and Spinal Infections"). Brain and spinal abscesses, subdural or epidural empyemas, and viral CNS infections are seldom associated with shock on the initial presentation. Shock is also unusual in neurosurgical patients with *S. aureus* or enteric gram-negative meningitis secondary to neurosurgical procedure or skull fracture.

LABORATORY TESTING AND IMAGING

Tests are useful to assess the general hematologic and metabolic state of the patient and aid in detecting occult bacterial infection, uncovering a specific microbial cause of infection, and identifying occult severe sepsis. Common tests include a CBC with platelet count; serum electrolytes (including calcium and glucose); renal function panel (BUN and creatinine levels); lactic acid level; liver function panel (bilirubin, alkaline phosphate, and aspartate and alanine aminotransferase levels); and urinalysis. An arterial blood gas aids the metabolic, ventilatory, and oxygenation assessment in select patients. In the setting of active bleeding or suspected disseminated intravascular coagulation, obtain prothrombin time, activated PTT, fibrinogen, and D-dimer.

Given the frequency of pneumonia or concomitant acute respiratory distress syndrome, obtain a chest radiograph. Obtain abdominal plain radiographs or CT scan in patients if perforation or diffuse inflammation suspicions exist, and US can identify a biliary source. Soft tissue CT scans to assess for the presence of free air in the tissue or deep space abscesses may assist in making the diagnosis of necrotizing skin and soft tissue infections. Perform head CT and lumbar puncture in any patient with potential meningitis, but do not delay antibiotics pending these tests. Order MRI if possible spinal epidural abscess is present.

In adults with sepsis, obtain at least two separate sets of blood cultures from different venipuncture sites when possible. Order Gram staining and culture of secretions from any potential site of infection when possible.

Other tests of interest in the assessment of sepsis include C-reactive protein and procalcitonin, both of which reflect systemic inflammation; neither of these tests excludes sepsis, and they are not routinely needed

in the ED.[43,44] Both of these tests may be better suited to guide the necessity of initiating or continuing antimicrobial therapy outside of sepsis or after a treatment course.[45]

TREATMENT

The cornerstones of the initial treatment and stabilization of severe sepsis are **early recognition, early reversal (or prevention) of hemodynamic compromise, and early infection control**.[42] Base the resuscitation on administering fluids, frequently assessing response, and adding adjunct therapies including vasopressors based on the conditions. The specific method of titrating resuscitation is less important than treating early and aggressively.

The goals of resuscitation are to improve preload, tissue perfusion, and oxygen delivery. There is no set amount of fluid, although most patients will require a total (bolus plus infusion) of 2 to 5 L of crystalloid in the first 6 hours to achieve optimal outcomes. Similarly, **do not delay vasopressors when blood pressure does not respond to volume or if volume overload seems likely.** Administer appropriate antibiotics and remove any nidus of infection. Each of these interventions will be discussed in detail below. Once the patient is stabilized, other interventions such as appropriate management of oxygenation and ventilation, fever control to reduce metabolic demand, and control of hyperglycemia may be needed to improve patient outcomes.

The following is a sepsis checklist:

- In those with signs or symptoms of infection, look for occult shock: check vital signs and consider lactate early and repeat if in doubt.
- Give appropriate antimicrobials to patients with suspected sepsis as soon as possible.
- Look hard for the infection source, including getting blood cultures and seeking a surgical, gynecologic, or indwelling medical device infection.
- Give at least 1 to 2 L bolus of IV crystalloid (lactated Ringer's) to hypotensive patients or patients with elevated lactate and monitor the response.
- Recheck resuscitation responses using more than one measure—better vital signs/shock index, improved clinical appearance, improved mentation and urine output, decreasing lactate, and/or improved central venous pressure or oxygen saturation.
- A central venous catheter is not mandatory to resuscitate most patients, and central venous pressure trends are more important than absolute values.
- Give more fluids if not clinically better and there is no evidence of volume overload. Often, 3 to 5 L are needed in the first 6 hours. Use balanced fluids after 2 to 3 L when possible.
- Administer norepinephrine as the first-line vasopressor to patients with refractory hypotension despite adequate fluid resuscitation.
- Although not mandatory for all, consider central venous pressure and central venous oxygen monitoring to titrate dobutamine and packed red blood cells, and consider corticosteroids in those with refractory shock.

EARLY QUANTITATIVE RESUSCITATION

The primary deficit leading to poor outcomes in shock states (typically studied in hemorrhagic shock) is a mismatch between oxygen supply and demand,[46] and after a certain time point, processes initiated by this mismatch are irreversible. In 2001, Rivers et al[47] described the use of an early, structured hemodynamic resuscitation protocol driven by a central venous catheter with continuous oximetric capability to titrate fluids to central venous pressure, vasopressors to mean arterial pressure, and transfusion of blood or inotropes to central venous oxygen saturation (S_{CVO2}). This protocol, termed *early goal-directed therapy*, decreased mortality when compared with standard care, although all patients had central venous catheters placed early. Follow-up uncontrolled observational studies confirmed that even partial use of this approach lowered mortality in settings compared with previous time periods prior to education and interventions to increase aggressive early sepsis detection or care.[48-52]

In a second large trial, Jones et al[4] randomized patients to this protocol or a protocol that measured lactate clearance of ≥10% rather than S_{CVO2}. The lactate clearance protocol was noninferior to continuous S_{CVO2} monitoring in the setting of ED-based resuscitation of septic shock. Lactate clearance–guided therapy (titrating fluids and vasopressors) became an alternative to invasive S_{CVO2} monitoring and early goal-directed therapy. Although the ideal lactate clearance target remains unclear, a minimum of 10% relative lactate clearance[29,30] and normalization of lactate to <2 mmol/L emerged as goals.[42,53] Still, about one third of patients with severe sepsis have a normal lactate,[53] and up to one half or more have a normal S_{CVO2},[54] limiting either tool in guiding therapy.

Most recently, the ProCESS,[55] ARISE,[56] and ProMISE trials[57] compared structured, quantitative resuscitation (the Rivers early goal-directed therapy protocol) to usual care chosen by the bedside clinician in ED treatment groups after early identification and antibiotics. These resuscitative approaches all delivered different care, but all groups received aggressive fluids and vasopressors in addition to early recognition and antibiotic use; however, **no one approach was superior** in terms of morbidity or mortality. Furthermore, pooled subgroup analyses failed to demonstrate benefit in any subgroup of patients.[58] These trials emphasize that the **early recognition of sepsis, administration of antimicrobials, adequate volume resuscitation, and assessment of the adequacy of circulation are the important elements that improve outcomes, not any specific path of resuscitation**. These observations allow providers or sites the flexibility of crafting the best approach to care but show that mandatory central venous catheterization and monitoring of central venous pressure or S_{CVO2} are not necessary for all patients with sepsis.

VOLUME RESUSCITATION

When resuscitating an ED patient with sepsis, first assess and replenish circulating volume, typically with an initial 20 to 30 milligrams/kg crystalloid bolus, preferably through large-bore IVs. This amounts to an approximate 1- to 2-L bolus of lactated Ringer's or normal saline solution in a 70-kg adult, although some patients require more or less. Saline can produce a hyperchloremic metabolic acidosis if used in large-volume resuscitation. A large cluster randomized trial that studied the effect of saline versus balanced fluids across an entire hospital (including both EDs and intensive care units) demonstrated that the use of balanced fluids (such as lactated Ringer's) induced less acute kidney injury in sepsis with a modest effect on mortality.[59,60] These effects appear most notable in more critically ill patients receiving large volume. Balanced fluids appear to be preferable, particularly among more critically ill patients or those receiving large volumes of fluids. Colloids are not needed in early sepsis care, and hydroxyethyl starch can worsen acute kidney injury.

The most important variable process in volume replacement is determining whether a patient is volume responsive. There are several more sophisticated measurements that can be used to make this determination such as cardiac output and stroke volume variation. The latter entails lifting the legs of a supine patient for 60 seconds; improved blood pressure or less variation in the peak blood pressure wave (if an arterial line is present) identifies a volume-responsive patient who will likely benefit from more fluid. If these tools are unavailable, assess the need for further volume expansion with empiric crystalloid boluses until the patient fails to demonstrate a physiologic or hemodynamic response.

VASOPRESSORS

Once the patient fails to respond to further IV volume expansion, aid perfusion with vasoactive agents. In general, target a mean arterial pressure goal of 65 mm Hg; routine targeting of a higher mean arterial pressure does not aid outcomes.[61] A mean arterial pressure is preferable to a specific systolic blood pressure goal; however, systolic pressure is commonly used in practice, seeking a goal of 90 mm Hg or higher.

Peripheral vasopressor use to start care is safe; high-dose and prolonged infusions are better deployed using a central venous line to limit

extravasation and resultant tissue necrosis. When using peripheral catheters, make sure they are large, secured, and not distal.

In septic shock, **norepinephrine**, 0.5 to 30 micrograms/min, is the best first choice since the dual α- and β-adrenergic effects result in peripheral vasoconstriction and cardiac inotropy. Dopamine has a higher rate of complications, most notably dysrhythmias and failure, compared with norepinephrine and is no longer routinely recommended.[62] **Vasopressin** is a second-line agent and may allow for the downtitration of the norepinephrine dose.[63] Give vasopressin as a constant infusion at a rate of 0.03 or 0.04 U/min. Do not titrate the dose, because higher rates are associated with vasospasm and high morbidity. **Epinephrine** at a dose of 1 to 20 micrograms/min is an option instead of norepinephrine when dosed appropriately,[64] although the risk of medication dosing errors related to epinephrine concentration may make norepinephrine a superior choice. If tachydysrhythmias are a problem, phenylephrine is an option as a pure α-adrenergic agonist.

CENTRAL VENOUS OXYGENATION

After volume repletion and perfusion pressure optimization, if tissue perfusion is compromised (cool extremities, poor pulses, worsening organ function), assess oxygen balance. Although not needed routinely, measuring continuous S_{CVO2} with a catheter can aid additional therapy as outlined in the early goal-directed therapy approach.[45] An S_{CVO2} <70% implies a relative oxygen supply and demand mismatch.

LACTATE CLEARANCE

A decrease in lactate over time suggests a restoration of adequate tissue perfusion. Measure lactate using the same method 1 to 2 hours apart; improvement of 10% or more is associated with improved clinical outcomes. Larger reductions in lactate are associated with even better outcomes,[53] although whether targeting higher amounts of lactate clearance leads to improved outcomes remains unclear and is not recommended.

TREAT INFECTION

Give broad-spectrum antibiotics as early as possible for severe sepsis.[42] Combination antibiotic therapy as opposed to monotherapy leads to improved outcomes, potentially due to higher rates of bactericidal activity.[65] Recommendations for antibiotic regimens are provided in **Table 151-2**. Therapy can later be tailored based on clinical response and microbiologic data. Given the high rates of community-acquired methicillin-resistant *S. aureus*, ensure this is covered along with gram-negative pathogens and anaerobic organisms. Vancomycin is often underdosed in clinical practice,[65] and guidelines suggest an initial dose of 25 to 30 milligrams/kg in critically ill patients.[66] In immunosuppressed patients, consider antifungal or antiviral agents.

The Surviving Sepsis Campaign recommends giving antibiotics as soon as feasible, ideally within 1 hour of the recognition of severe sepsis and/or within 3 hours of triage. However, a meta-analysis failed to demonstrate that patients receiving antibiotics before versus after 3 hours from triage had improved outcomes. Ultimately, these suggestions are not commonly used or adopted by other organizations for many reasons, including ability to achieve an overall effect.[67]

Whether antimicrobials are best given initially or after hemodynamic stabilization of the patient remains unclear. A randomized controlled trial of prehospital ceftriaxone demonstrated a reduction in time to antibiotics but no effect on mortality, giving further support to the notion of administration as soon as feasible but without an absolute time target.[68] Given the poor prognosis associated with delays in either resuscitation or infection therapies, we recommend delivering both together. Ideally, sample any organ infectious source and obtain blood cultures *prior* to the initiation of antibiotics, *but do not delay* the initiation of antibiotics to obtain cultures.[42]

Infection control is not confined to antimicrobial administration; it also includes addressing potential surgical sources of infection. Drain any source and remove indwelling vascular lines and other medical devices suspected as infected once the patient is stabilized.

OTHER THERAPIES: VENTILATION, GLYCEMIC CONTROL, ACTIVATED PROTEIN C, STEROIDS, AND OTHER ADJUNCTIVE TREATMENTS

Sepsis is the leading cause of acute respiratory distress syndrome; mechanical ventilation is discussed in Chapter 29. In those with acute respiratory distress syndrome findings, low tidal volume ventilation (6 mL/kg ideal body weight) limits barotrauma and improves outcomes.[69] It is unclear whether a fixed tidal volume of 6 mL/kg is best for all; some titration is permissible. Positive end-expiratory pressure adequate to prevent alveolar collapse is recommended. Patients may be allowed some hypercapnia if the accompanying acidosis does not threaten hemodynamic deterioration.

Hyperglycemia is associated with worsened outcomes in the setting of sepsis. Due to the high rate of hypoglycemia, tight (<110 milligrams/dL) glucose control is no longer recommended; modest goals of <180 milligrams/dL allow for similar outcomes.[70] Glucose control is most important after initial care and is best if protocolized, especially for patients receiving extended sepsis care in the ED.

Therapies to manipulate the coagulation cascade are unproven; the most promising candidate to date, activated protein C, failed to improve outcomes and is not used.[71] Systemic corticosteroids are the only anti-inflammatory agent in use in clinical practice but remain controversial.[72-74] Hydrocortisone shortens the time to shock reversal in *refractory* hemodynamic shock (i.e., requiring more than one vasopressor after adequate volume restoration) as well as those receiving mechanical ventilation, although trials have not demonstrated a consistent mortality benefit. Patients with refractory septic shock for at least 6 hours may have a mortality benefit from the combination of hydrocortisone and fludrocortisone.[75] Stimulation testing using adrenocorticotropic hormone is not clinically helpful. Although even a single dose of etomidate may alter adrenal activity as measured by laboratory tests,[76] there is no clear evidence that the use of etomidate to facilitate endotracheal intubation alters any clinically important outcome. A single-center before-and-after study of a cocktail of corticosteroids combined with vitamin C and thiamine demonstrated a dramatic mortality benefit and received significant media attention, although it was limited by the study design and methodology,[77] and it remains unproven at this time. Given that these trials predominantly demonstrate benefit in refractory septic shock that may not be established until intensive care unit admission, deferral to the intensive care unit regarding these therapies is a reasonable approach, although they could be considered in appropriately selected ED patients with a prolonged time to admission.

SPECIAL POPULATIONS

ASYMPTOMATIC PATIENTS WITH POSITIVE BLOOD CULTURES

There is no consensus for interpretation or management of positive ED blood cultures in asymptomatic patients. *Corynebacterium* species, *Bacillus* species, and *Propionibacterium acnes* rarely represent true bacteremia or require action. Other organisms such as viridans group streptococci, enterococci, and coagulase-negative *Staphylococcus* (the most common organism reported on blood culture notifications) may represent a pathogen or require new care in a given patient. In both ambulatory and ED patients, blood cultures are positive in <10% of cases, with only one third to two thirds of those cultures representing true bacteremia.[78]

An important predictor of true-positive first blood culture is persistence of the organism on subsequent culture *if* the latter was done separately (time and location). In a discharged patient, this requires reevaluation, either in the ED or by another provider. Decisions regarding antibiotics or admission are guided by the pathogen and clinical grounds: All highly lethal pathogens should receive therapy and admission, whereas some pathogens in blood culture may clear with or without therapy.

POSTSPLENECTOMY PATIENTS

Patients without a spleen are at increased risk for infection with encapsulated species such as *Salmonella* or *Haemophilus influenzae*. Table 151-2 details treatment recommendations of these patients. Given the frequent

TABLE 151-2 Empiric Antibiotic Selection in Severe Sepsis and Septic Shock

Host	Likely Pathogens	Initial Antibiotic Selection
Adults (nonneutropenic) without an obvious source of infection	*Staphylococcus aureus,* streptococci, gram-negative bacilli, others	Imipenem, 500 milligrams every 6 h to 1 gram IV every 8 h *or* Meropenem, 1 gram IV every 8 h *or* Doripenem, 500 milligrams IV every 8 h *or* Ertapenem*, 1 gram IV every 24 h *plus* Vancomycin†, 15 milligrams/kg loading dose
Adults (nonneutropenic), suspected biliary source	Aerobic gram-negative bacilli, enterococci	Ampicillin/sulbactam, 3 grams IV every 6 h *or* Piperacillin/tazobactam, 4.5 grams IV every 6 h *or* Ticarcillin/clavulanate, 3.1 grams IV every 4 h *plus* Metronidazole, 15 milligrams/kg IV load then 7.5 milligrams/kg every 8 h
Adults (nonneutropenic), suspected pneumonia	*Streptococcus pneumoniae*, methicillin-resistant *S. aureus*, gram-negative bacilli, *Legionella*	Ceftriaxone, 1–2 grams IV every 12 h *plus* Azithromycin, 500 milligrams IV, then 250 milligrams IV every 24 h *plus* Levofloxacin, 750 milligrams IV every 24 h *or* moxifloxacin, 400 milligrams IV every 24 h *plus* Vancomycin†, 15 milligrams/kg loading dose
Adults (nonneutropenic), suspected illicit use of IV drugs	*S. aureus*	Vancomycin†, 15 milligrams/kg loading dose
Adults with petechial rash	*Neisseria meningitidis,* RMSF	Ceftriaxone, 2 grams IV every 12 h *or* Cefotaxime, 2 grams IV every 4–6 h *Consider* Addition of doxycycline 100 milligrams IV every 12 h for possible RMSF
Adults (nonneutropenic), suspected intra-abdominal source	Mixture of aerobic and anaerobic gram-negative bacilli	Imipenem, 500 milligrams IV every 6 h to 1 gram IV every 8 h *or* Meropenem, 1 gram IV every 8 h *or* Doripenem, 500 milligrams IV every 8 h *or* Ertapenem, 1 gram IV every 24 h *or* Ampicillin/sulbactam, 3 grams IV every 6 h *or* Piperacillin/tazobactam, 4.5 grams IV every 6 h *plus* Metronidazole, 15 milligrams/kg IV load then 7.5 milligrams/kg every 8 h#
Adults (nonneutropenic), suspected urinary source (hospitalized with pyelonephritis)	Aerobic gram-negative bacilli, enterococci	Levofloxacin, 750 milligrams IV every 24 h *or* Moxifloxacin, 400 milligrams IV every 24 h *or* Piperacillin/tazobactam, 4.5 grams IV every 6 h *or* Ceftriaxone, 1–2 grams IV every 12–24 h *or* Ampicillin, 1–2 grams IV every 4–6 h *plus* Gentamicin, 1.0–1.5 milligrams/kg every 8 h‡

(*Continued*)

TABLE 151-2 Empiric Antibiotic Selection in Severe Sepsis and Septic Shock (*Continued*)

Host	Likely Pathogens	Initial Antibiotic Selection
Adults (nonneutropenic), suspected urinary source (complicated urinary tract infection/urinary catheter)	Enterobacteriaceae, *Pseudomonas aeruginosa*, enterococci, rarely *S. aureus*	Piperacillin/tazobactam, 4.5 grams IV every 6 h *or* Imipenem, 500 milligrams every 6 h to 1 gram IV every 8 h *or* Meropenem, 1 gram IV every 8 h *or* Doripenem, 500 milligrams IV every 8 h *or* Ampicillin, 1–2 grams IV every 4–6 h *plus* Gentamicin, 1.0–1.5 milligrams/kg every 8 h‡
Neutropenic adults	Aerobic gram-negative bacilli, especially *P. aeruginosa, S. aureus*	Ceftazidime, 2 grams IV every 8 h *or* Cefepime, 2 grams IV every 8 h *or* Imipenem, 500 milligrams IV every 6 h to 1 gram IV every 8 h *or* Meropenem, 1 gram IV every 8 h *or* Piperacillin/tazobactam, 4.5 grams IV every 6 h *plus* Levofloxacin, 750 milligrams IV every 24 h *or* moxifloxacin, 400 milligrams IV every 24 h *plus* Vancomycin†, 15 milligrams/kg loading dose *and consider* Fluconazole, 400 milligrams IV every 24 h *or* micafungin, 100 milligrams every 24 h
Patients with suspected anaerobic source: intra-abdominal, biliary, female genital tract infection; necrotizing cellulitis; odontogenic infection; or anaerobic soft tissue infection	Anaerobic bacteria plus gram-negative bacilli (also see suspected biliary or intra-abdominal source, above)	Metronidazole, 15 milligrams/kg IV load, then 7.5 milligrams/kg every 8 h# *or* Clindamycin, 600–900 milligrams IV every 8 h
Patients with indwelling vascular devices	Coagulase-negative *Staphylococcus*, methicillin-resistant *S. aureus*	Vancomycin†, 15 milligrams/kg loading dose
Patients with potential for *Legionella* species infection		Azithromycin, 500 milligrams IV, then 250 milligrams IV every 24 h *or* Erythromycin, 800 milligrams IV every 6 h *should be added to the regimen*
Asplenic patients	*S. pneumoniae, N. meningitidis, Haemophilus influenzae, Capnocytophaga*	Ceftriaxone, 1 gram IV every 24 h up to 2 grams IV every 12 h if meningitis

Abbreviation: RMSF = Rocky Mountain spotted fever.

*Ertapenem has no antipseudomonal coverage and is not recommended in many intensive care units due to concerns of potentiating pseudomonal antimicrobial resistance.

†Methicillin-resistant *S. aureus* colonization is extremely high, and consideration should be given to including vancomycin in addition to the antibiotic recommendations. Vancomycin dosage is typically suggested at 15 milligrams/kg but can delay effective antimicrobial activity; initial dosages of 25 to 30 milligrams/kg have been recommended by some authorities. If the patient has an allergy to vancomycin, linezolid 600 milligrams IV can be substituted.

‡Multiple daily dosing: 2 milligrams/kg load then 1.7 milligrams/kg every 8 h.

#Metronidazole is often prepackaged as 500-milligram bags. Dosing at 500 milligrams IV every 6 or 8 h to approximate the milligram per kilogram dosing may speed time to antibiotic administration.

rapid and dramatic progression of their disease process, manage asplenic patients quickly. Although not relevant at the time of initial sepsis care, these patients should have appropriate bacterial immunization following a splenectomy.

NEUTROPENIC FEVER

Due to an impaired immune system, neutropenic patients are at increased risk for developing sepsis and worse outcomes. Any fever in a neutropenic patient is suspicious for infection, and all patients should have source organ and blood cultures drawn followed by empiric antibiotics. After conferring with an oncologist, some patients may be treated at home with oral broad-spectrum agents (often including a quinolone) *if* they look well and are closely followed; the rest are admitted.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 152

Soft Tissue Infections

Elizabeth W. Kelly

INTRODUCTION

More than 4 in 100 people seek treatment for skin and soft tissue infections each year in the United States, and these infections are about 20 times more likely to be ambulatory treated than inpatient treated.[1] Abscess or cellulitis are the most common of these infections, with the majority of patients treated in the outpatient setting.[1] This chapter discusses skin and soft tissue infections in adults; impetigo and other soft tissue infections in children are discussed in Chapter 142, "Rashes in Infants and Children." Perirectal abscess and pilonidal abscess are discussed in Chapter 85, "Anorectal Disorders." Bartholin gland abscess is discussed in Chapter 102, "Vulvovaginitis." Hidradenitis suppurativa is discussed in Chapter 252, "Skin Disorders: Groin and Skinfolds." Paronychia and felons are discussed in Chapter 283, "Nontraumatic Disorders of the Hand."

ANATOMY AND DEFINITIONS

The skin consists of the superficial epidermis, dermis, and deeper subcutaneous tissues including fat (**Figure 152-1**). The lymphatics run parallel with the blood vessels. *Cellulitis* is an infection of the dermis and subcutaneous tissue and is divided clinically as *purulent* or *nonpurulent.* Management of the two types is different.[2,3] Purulent cellulitis is a skin or soft tissue infection with purulent drainage or an underlying abscess. Nonpurulent cellulitis has no purulent drainage or exudate and no associated abscess.[2,3] *Erysipelas* traditionally has been defined as a more superficial skin infection involving the upper dermis with clear demarcation between involved and uninvolved skin with prominent lymphatic involvement. *Folliculitis* is an infection of the hair follicle, often purulent, but is superficial without involvement of the deeper tissues. *Skin abscesses* are collections of pus within the dermis and deeper skin tissues, potentially involving the subcutaneous tissues. *Furuncles* (or boils) are single, deep nodules involving the hair follicle that are often suppurative.[3] *Carbuncles* are formed by multiple interconnecting furuncles that drain through several openings in the skin.[3] *Necrotizing soft tissue infections* are characterized by microbial triggered necrosis involving any of the soft tissue layers including the dermis, subcutaneous tissues, fascia, and muscle.[4]

CELLULITIS AND ERYSIPELAS

EPIDEMIOLOGY

Cellulitis accounts for approximately 1.3% of all ED visits. General risk factors for cellulitis are listed in **Table 152-1**.[5,6] Risk factors for specific organisms causing cellulitis are listed in **Table 152-2**.[2,5,7-12] Cellulitis is observed more frequently among middle-aged and elderly patients, whereas erysipelas is more common among children and elderly patients.[13] Patient characteristics demonstrate a male predominance (61%) and a mean age of 46 years, and the vast majority of infections involve either the lower or upper extremities (48% and 41%, respectively). Approximately 10% of patients diagnosed with cellulitis are hospitalized, and the majority of these patients are over age 64 years.

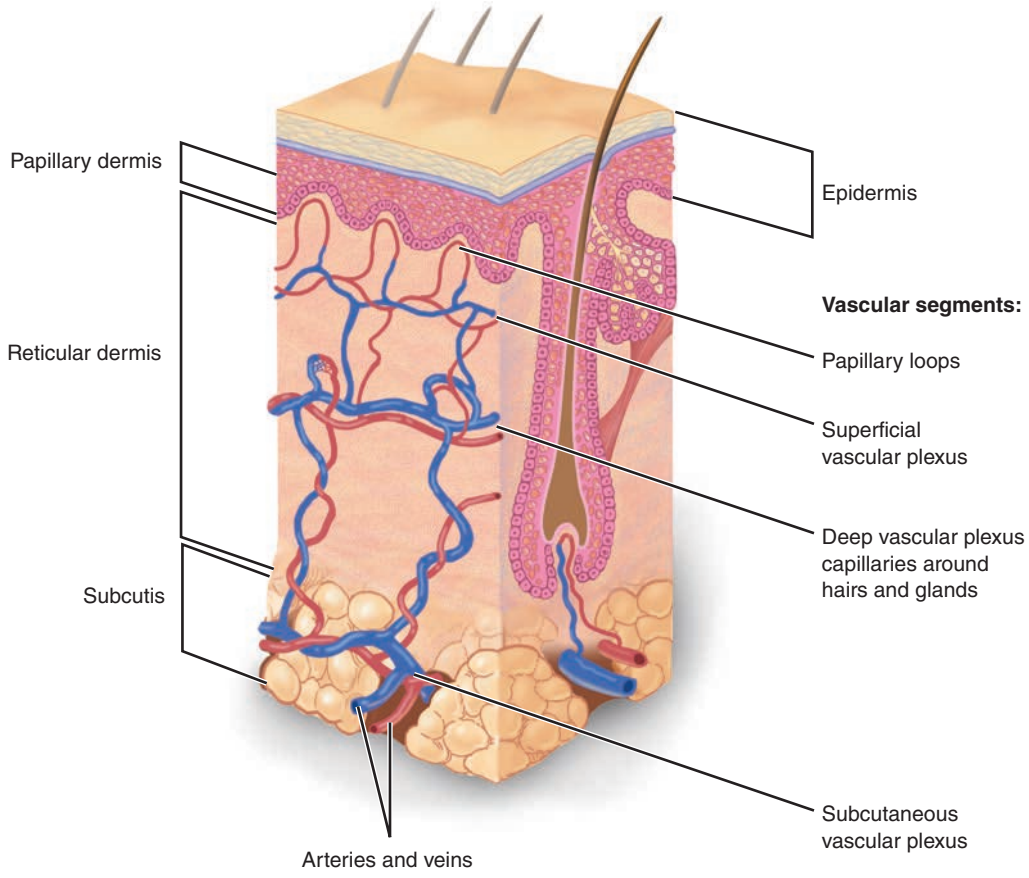


FIGURE 152-1. Schematic diagram of the architecture of the skin. This diagram shows the anatomy of the skin, including the epidermis, dermis, and deeper subcutaneous tissues. Also shown are the blood vessels and a hair follicle. [Reproduced with permission from Wolff K, et al: *Fitzpatrick's Dermatology in General Medicine*, 7th ed. © 2008, McGraw-Hill, Inc., New York.]

TABLE 152-1 General Risk Factors for Cellulitis and Erysipelas

Risk Factors
• Lymphedema
• Skin breakdown/site of entry
• Venous insufficiency
• Leg edema
• Obesity
• Neutropenia
• Immunocompromise
• Hypogammaglobulinemia
• Chronic renal disease
• Cirrhosis

MICROBIOLOGY

Approximately 80% of cellulitis cases are caused by gram-positive bacteria. Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is now the most common cause of skin and soft tissue infections presenting to the ED,[7,14] regardless of patient risk factors. The Infectious Diseases Society of America recommends differentiation of purulent from nonpurulent cellulitis (see detailed definitions earlier) for treatment decisions.[2] MRSA is likely to be the causative agent in purulent cellulitis. For nonpurulent cellulitis, the role of MRSA is unknown, and empirical therapy for β-hemolytic streptococcal infection with β-lactams is recommended.[2,15-18] Gram-negative aerobic bacilli are the third most common etiology. Other less common pathogens causing cellulitis are listed in Table 152-2 with associated risk factors.

Erysipelas is usually caused by β-hemolytic streptococci.[13] Bullous erysipelas is a more severe form and can represent synergy with β-hemolytic streptococci and MRSA.[19]

TABLE 152-2 Risk Factors for Specific Organisms Causing Cellulitis

Organism(s)	Risk Factors
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Purulent soft tissue infections Antibiotic use in past month Previous MRSA infection or colonization Patient report of suspected spider bite Previous hospitalization or surgery within the past year Residence in a long-term care facility within the past year Hemodialysis Crowded living environments including day care or homeless shelters, soldiers, prisons Contact sports Injection drug users Men who have sex with men Household contacts with MRSA infection Children
β-Hemolytic streptococci	Nonpurulent cellulitis that is culture negative by needle aspiration
Gram-negative bacteria	Elderly patients, cirrhosis, diabetic foot infections, fish bone injury
Aeromonas hydrophila	Fresh water lacerations, contact with wet soil
Vibrio vulnificus, Vibrio parahaemolyticus	Salt water lacerations, fish fin or bone injuries, cirrhosis
Pseudomonas aeruginosa	Neutropenia, injection drug use, hot tub exposure
Anaerobic bacteria including clostridia	Bite wounds,* diabetes mellitus, necrotizing infections, gas in tissues
Polymicrobial	Diabetic foot injections, bite wounds*
Pasteurella species	Dog and cat bites*
Capnocytophaga canimorsus	Dog and cat bites*
Mycobacterium marinum	Fish tank exposure
Streptococcus pneumoniae and *Haemophilus influenzae*	Nonimmunized children and adults

*See Chapters 46 and 211 to 213, "Puncture Wounds and Bites," "Bites and Stings," "Snake Bites," and "Marine Trauma and Envenomation," respectively.

PATHOPHYSIOLOGY

Most symptoms of cellulitis are secondary to a complex set of immune and inflammatory reactions triggered by cells within the skin itself. Although bacterial invasion is what triggers the inflammation, the organisms are largely cleared from the site within the first 12 hours. The subsequent inflammatory response is caused by the infiltration of cells, such as Langerhans cells and keratinocytes, which release the cytokines interleukin-1 and tumor necrosis factor that enhance skin infiltration by lymphocytes and macrophages.

CLINICAL FEATURES

Cellulitis In cellulitis, the affected skin is tender, warm, erythematous, and swollen, and typically does not exhibit a sharp demarcation from uninvolved skin. Edema can occur around hair follicles that leads to dimpling of the skin, creating an orange peel appearance referred to as "peau d'orange" (**Figure 152-2**). Symptoms develop gradually over a few days. Lymphangitis and lymphadenopathy are seen occasionally in previously healthy patients, but purely local inflammation is much more common. In cases of purulent cellulitis, exudate drains from the wound[2]; an abscess may or may not subsequently form. Systemic signs of fever, leukocytosis, and bacteremia are more typical in the immunosuppressed. Recurrent episodes of cellulitis can lead to impairment of lymphatic drainage, permanent swelling, dermal fibrosis, and epidermal thickening. These chronic changes are known as elephantiasis nostra and predispose patients to further attacks of cellulitis.

Erysipelas In erysipelas, the onset of symptoms is usually abrupt, with fever, chills, malaise, and nausea representing the prodromal phase. Over the next 1 to 2 days, a small area of erythema with a burning sensation develops. As infection progresses, the affected skin becomes indurated with a raised border that is distinctly demarcated from the surrounding normal skin. The "peau d'orange" appearance is also common in erysipelas. A classic description is a "butterfly" pattern over the face (**Figure 152-3**). Complete involvement of the ear is the "Milian ear sign" and is a distinguishing feature of erysipelas because the ear does not contain deeper dermis tissue typically involved in cellulitis. Lymphatic inflammatory changes, known as toxic striations, and local lymphadenopathy are common. Purpura, bullae, and small areas of necrosis warrant a search for possible



FIGURE 152-2. Cellulitis of the right leg characterized by erythema and mild swelling. [Photo contributed by Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]



FIGURE 152-3. Butterfly rash of erysipelas. The sharp demarcation between the salmon-red erythema and the normal surrounding skin is evident. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006, McGraw-Hill, Inc., New York.]

TABLE 152-3 Differential Diagnosis of Cellulitis and Erysipelas

Diagnosis	Distinguishing Clinical Characteristics
Bursitis	Characteristic locations such as suprapatellar or olecranon, may have palpable fluid collection
Contact dermatitis	Pruritus instead of pain, absence of fever, may have bulla, but patient is nontoxic in appearance
Stasis dermatitis	Bilateral, long-standing, pitting edema, mild tenderness only
Cutaneous abscess	Abscess may appear similar to cellulitis initially; eventual fluctuance and purulent drainage
Deep vein thrombosis	Typically, not associated with skin redness or fever
Drug reactions	Temporal relation to new drug exposure, pruritus instead of pain, absence of fever
Gouty arthritis	Pronounced pain with involved joint movement
Herpes zoster	Characteristic vesicles, dermatomal pattern
Insect stings	Pronounced pain most at onset
Necrotizing soft tissue infection	Rapid progression; triad of severe pain, swelling, and fever; pain out of proportion to exam; severe toxicity; hemorrhagic or bluish bullae; gas or crepitus; skin necrosis or extensive ecchymosis
Osteomyelitis	Deeper involvement, prolonged course, comorbidities
Superficial thrombophlebitis	Typically, not associated with fever, limited to venous path
Toxic shock syndrome	Hypotension, multiorgan involvement, severe toxicity

necrotizing soft tissue infection. On resolution of the infection, desquamation of the site often occurs.

DIAGNOSIS

The diagnosis of cellulitis and erysipelas is clinical. Management should be guided by the clinical differentiation between purulent and nonpurulent soft tissue infections.[2,3] Presence of an abscess or purulent drainage from the area of cellulitis defines the soft tissue infection as purulent.

Mild disease, for both purulent and nonpurulent forms of cellulitis, is distinguished by the absence of systemic symptoms. In cases of mild infection, blood cultures, needle aspiration, punch biopsy, leukocyte count, or other lab data are of little benefit and are not recommended.[3] Needle aspiration of the leading edge of an area of cellulitis produces organisms in 15.7% of cultures (range, 0% to 40%), and punch biopsy reveals an organism only 18% to 26% of the time.[15] Areas with abscess formation have significantly higher yields; **wound culture** is recommend when the decision has been made to place the patient on antibiotics for purulent cellulitis.[3] Blood cultures are positive in only 5% of cases. For both purulent and nonpurulent cellulitis, in patients with systemic toxicity, extensive skin involvement, underlying comorbidities, immunodeficiency, immersion injuries, failed initial therapy, or recurrent episodes, or in circumstances such as animal bites, cultures of pus, bullae, or blood are recommended.[3,20,21] Routine radiographic evaluation is unnecessary, but should be considered if osteomyelitis (see Chapter 281, "Hip and Knee Pain") or necrotizing soft tissue infections are suspected (see later section). **Table 152-3** lists differential diagnoses and characteristics that help distinguish cellulitis from the listed disorder.

POCUS is useful to exclude occult abscess.[22] Doppler studies may be indicated to distinguish lower extremity deep venous thrombosis from cellulitis. The most important diagnosis to exclude is necrotizing soft tissue infection (see later section).

TREATMENT

General Treatment Treatment is elevation of the affected area, incision and drainage of any abscess found (see later section), antibiotics for cellulitis, and treatment of underlying conditions. Elevation helps drainage of edema. Treat skin dryness with topical agents because skin dryness and cracking further exacerbate symptoms. Treat predisposing conditions such as tinea pedis (see Chapter 253, "Skin Disorders: Extremities") and refer to primary care for treatment of lymphedema and chronic venous insufficiency.

Treatment for Purulent Cellulitis or Suspected MRSA Etiology See **Table 152-4** for empiric antibiotic recommendations for purulent cellulitis or when MRSA is suspected.[3,23] Identify and thoroughly drain an abscess. POCUS will aid this procedure. Provide empiric therapy for MRSA for patients who have failed initial non-MRSA therapy, those with a previous history of or risks for MRSA, or those who live in an area with a high prevalence of community-associated MRSA infections.[24] For patients with severe infection or systemic toxicity, consider necrotizing fasciitis (see later section on necrotizing fasciitis). It may be difficult to clinically distinguish MRSA cellulitis from methicillin-susceptible *S. aureus* cellulitis. Treatment failure rates are similar for both β-lactam antibiotics and MRSA-specific antibiotics such as trimethoprim-sulfamethoxazole.[25,26]

Treatment of Nonpurulent Cellulitis/Erysipelas Guidelines no longer differentiate the treatment of nonpurulent cellulitis from erysipelas.[3,23] Oral antibiotics are sufficient for simple cellulitis or erysipelas in otherwise healthy adult patients. In cases where there is no evidence of drainage or identifiable abscess, empiric MRSA coverage is not necessary.[17,18,27] POCUS to confirm lack of an abscess is highly recommended. MRSA coverage should be considered in patients who are diabetic, immunosuppressed, have peripheral vascular disease, have a history of IV drug abuse, or require hospitalization.[17,18] See **Table 152-5** for guideline-recommended antibiotic options.[3,23] Consider surgical consultation in patients with bullae, crepitus, pain out of proportion to examination, or rapidly progressive erythema with signs of systemic toxicity, because these signs and symptoms suggest necrotizing infection (see later section on necrotizing fasciitis).

DISPOSITION AND FOLLOW-UP

Admit patients with cellulitis or erysipelas and evidence of systemic toxicity and those with underlying comorbidities such as diabetes mellitus, alcoholism, or immunosuppression (see later section on necrotizing fasciitis). Healthy patients without systemic toxicity can be discharged to home with close follow-up in 2 to 3 days. Mark the patient's skin with an indelible marker along the perimeter of infection so healing can be determined at follow-up; marks also aid the patient

TABLE 152-4 Empiric Antibiotic Treatment of Purulent Cellulitis* and/or Soft Tissue Abscess

Guide by Severity of Illness	Antibiotics	Comments
No antibiotics for mild disease: Drainable abscess found with no signs of systemic infection	None required for healthy immunocompetent patients where abscess drainage is complete after procedure	1. Presence of an abscess should be carefully investigated clinically and drained; consider use of US.
Oral antibiotics for moderate disease: Purulent cellulitis* without signs of systemic infection **Or** drainable abscess in the presence of mild to moderate signs of systemic infection ***If*** immunocompromised, see below.	Trimethoprim-sulfamethoxazole double-strength 1–2 tablets twice per day PO for 7–10 d† **Or** doxycycline 100 milligrams PO twice per day for 7–10 d† **Or** clindamycin, 300–450 milligrams PO four times daily for 7–10 d†‡	1. Wound culture is recommended in cases where antibiotics are given. 2. Patients who have failed to improve on outpatient antibiotics or are unable to tolerate oral antibiotics should be admitted to the hospital and receive IV antibiotics; see below.
IV antibiotics for severe disease: Purulent cellulitis* with signs of systemic infection **Or** drainable abscess in the presence of moderate to severe signs of systemic infection# or sepsis[f] **Or** an immunocompromised patient	**For MRSA coverage:** Vancomycin 15 milligrams/kg IV every 12 h **Or** linezolid 600 milligrams IV every 12 h† **Or** daptomycin 4 milligrams/kg IV every 24 h† **Or** telavancin 10 milligrams/kg IV every 24 h† **Or** clindamycin 600 milligrams IV every 8 h†	1. Admit to the hospital. 2. Additional antibiotic coverage is listed below. 3. Consider admission to intensive care unit for patients who meet criteria for sepsis (see also Chapter 151, "Sepsis"). 4. For all patients with severe disease, see later section on necrotizing fasciitis.
Additional coverage for patients with sepsis or for patients with selected indications (see last column to the right)	**For patients with sepsis, or for unclear etiology, add:** Piperacillin-tazobactam 4.5 grams IV every 6 h† **Or** meropenem 500–1000 milligrams IV every 8 h† **Or** imipenem-cilastatin 500 milligrams IV every 6 h†	For **fresh water** exposure (*Aeromonas* species) or for **salt water** exposure (*Vibrio* species) consider adding doxycycline 100 milligrams IV every 12 hours,† plus ceftriaxone 1 gram IV every 24 hours.†

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*.

*Purulent cellulitis is defined as cellulitis with drainage or exudate in the absence of a drainable abscess. In all cases of purulent cellulitis, the presence of an abscess should be carefully investigated clinically and drained. Bedside US can help diagnose occult abscess formation and verify complete drainage after procedure.

†Optimal treatment duration has not been established. For mild to moderate disease, 5-day oral treatment regimens have been successful but are recommended only in settings where follow-up at 5 days is feasible.

‡Not recommended if local resistance is >10%.

#Physicians should use their clinical judgment; there are no validated criteria to differentiate moderate from severe signs for systemic infection.

[f]Criteria for sepsis in the presence of an infection are two or more of the following: temperature >38°C, tachycardia (>90 beats/min), tachypnea (respiratory rate >24 breaths/min), WBC count <400 cells/mm^3 or >12,000 cells/mm^3, or immunocompromised patients (see Chapter 151, "Sepsis"). Hypotensive patients should be admitted to the intensive care unit.

in evaluating worsening infection. Reported risk factors for failure of empiric antibiotic therapy include fever, lymphedema or chronic edema, chronic leg ulcers, prior cellulitis in the same area, and cellulitis at a wound site.[28]

CUTANEOUS ABSCESSES, FURUNCLES, AND CARBUNCLES

Furuncles and carbuncles involve the epidermis, and abscesses involve the deeper soft tissue.[3] Skin abscesses, furuncles, and carbuncles can develop in otherwise healthy patients with no risk factors other than skin or nasal carriage of *S. aureus*. Persons in close contact with those who have an active infection with a skin abscess are at increased risk.

PATHOPHYSIOLOGY

Skin abscesses typically begin as a local superficial cellulitis. Many organisms that colonize normal skin can cause necrosis and liquefaction with subsequent accumulation of leukocytes and cellular debris; however, MRSA causes the majority of skin abscesses presenting to the ED in the United States.[7,14] Loculation and subsequent walling off of these products of infection lead to abscess formation. As the infection progresses and the area of liquefaction increases, the abscess wall thins and ruptures spontaneously, draining either cutaneously or into an adjoining tissue compartment.

Infection can be caused by one or multiple pathogens that typically include skin flora or organisms from adjacent mucous membranes. Pathogens implicated in folliculitis are those that can cause furuncles and carbuncles, namely *Pseudomonas*, *Candida*, and others.

Any process causing a breach in the skin barrier heightens the risk for a skin abscess. Examples include trauma, such as abrasions or shaving; skin foreign bodies; insect bites; and IV drug abuse. Other risk factors include diabetes mellitus and immunologic abnormalities. Patients with oral, rectal, or vulvovaginal abscesses are more likely to be infected with multiple organisms, including gram-negative and anaerobic organisms.

CLINICAL FEATURES

Skin abscesses are fluctuant, tender, erythematous nodules, often with surrounding erythema (**Figure 152-4**). Spontaneous drainage of purulent material may occur, and local lymphadenopathy may be present. Signs of systemic toxicity, fever, or chills are rare in the case of simple abscesses. In uncommon cases, skin abscesses may be the result or cause of bacteremia.

Furuncles are clinically very similar to abscesses, and systemic toxicity is rare. Carbuncles are larger infections commonly associated with fever and malaise. Carbuncles are most common on the upper back, chest, buttocks, hips, and axilla but can occur in any hair-bearing region of the body.

DIAGNOSIS

The diagnosis of skin abscesses, furuncles, and carbuncles is clinical; however, physical exam is unreliable for nonsuperficial abscesses.[29] POCUS is an invaluable tool for distinguishing deep abscess from cellulitis, identifying a foreign body within an abscess, and determining the adequacy of drainage[22,30,31] (**Figure 152-5**).

Radiography is not needed routinely, unless a radiopaque foreign body or underlying osteomyelitis is suspected. Disorders that can mimic abscesses include folliculitis, hidradenitis suppurativa, sporotrichosis, leishmaniasis, tularemia, and blastomycosis, as well as conditions in immunocompromised persons such as *Nocardia* and *Cryptococcus*. Wound cultures are not recommended for simple abscess drainage; however, guidelines recommend cultures when antibiotics are given.[3]

TABLE 152-5 Empiric Treatment of Nonpurulent Cellulitis*/Erysipelas

Guide by Severity of Illness	Antibiotics	Comments
Oral antibiotics for mild disease: Typical cellulitis/erysipelas with no focus of purulence and no signs of systemic infection	Cephalexin 500 milligrams PO every 6 h† **Or** dicloxacillin 500 milligrams PO every 6 h† **Or** clindamycin 150–450 milligrams PO every 6 h†	Cultures are not recommended because of poor yields. Consider MRSA coverage in patients who are diabetic or immunosuppressed, have peripheral vascular disease or history of IV drug abuse, or require hospitalization.
Monotherapy IV antibiotics for moderate disease: Typical cellulitis/erysipelas with mild to moderate systemic signs of infection‡ ***If*** immunocompromised, see below.	Ceftriaxone 1 gram IV every 24 h† **Or** cefazolin 1 gram every 8 h† **Or** clindamycin 600 milligrams IV every 8 h†	Patients who have failed to improve on outpatient antibiotics or are unable to tolerate oral antibiotics should be admitted to the hospital and receive IV antibiotics, with coverage dependent on severity of illness.
Broad-spectrum antibiotics for severe disease (including necrotizing fasciitis): Those with sepsis# or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or evidence of organ dysfunction **Or** an immunocompromised patient	Vancomycin 15 milligrams/kg IV every 12 h† **Plus** piperacillin-tazobactam, 4.5 grams IV every 6 h† **Or** meropenem, 500–1000 milligrams IV every 8 h† **Or** imipenem-cilastatin, 500 milligrams IV every 6 h†	1. Consider immediate consultation with surgery for possible debridement (see later section on necrotizing fasciitis for further recommendations). 2. Blood cultures recommended in this treatment group.
Different/additional coverage for patients with selected indications	**Fresh water** exposure (suspected *Aeromonas* species): Doxycycline 100 milligrams IV every 12 h† **Plus** ciprofloxacin 500 milligrams IV every 12 h† **Salt water** exposure (suspected *Vibrio* species): Doxycycline 100 milligrams IV every 12 h† **Plus** ceftriaxone 1 gram every 24 h† **Suspected *Clostridium*** species: Clindamycin 600–900 milligrams IV every 8 h† **Plus** penicillin 2–4 million units IV every 4 h†	1. Consider immediate consultation with surgery for possible debridement (see later section on necrotizing fasciitis for further recommendations). 2. Blood cultures recommended in this treatment group.

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*.

*If exudate or abscess is found on exam, the patient should be treated for purulent cellulitis; see Table 152-4 for treatment recommendations

†Optimal treatment duration has not been established. For mild to moderate disease, 5-day treatment regimens have been successful but are recommended only in settings where follow-up at 5 days is feasible.

‡Physicians should use their clinical judgment; there are no validated criteria to differentiate moderate from severe signs of systemic infection.

#Criteria for sepsis in the presence of an infection are two or more of the following: temperature >38°C, tachycardia (>90 beats/min), tachypnea (respiratory rate >24 breaths/min), WBC count <400 or >12,000 cells/mm^3, or immunocompromised state (see Chapter 151, "Sepsis"). Hypotensive patients should be admitted to the intensive care unit.

TREATMENT

It is best to drain extremely large abscesses or those in deep areas in the operating room. Abscesses of the palms, soles, or nasolabial folds can be associated with complications and usually require a specialist.[32] Input from an appropriate specialist is also recommended in areas of the body with cosmetic concerns.[32]



FIGURE 152-4. Subcutaneous abscess is noted in the axilla. [Reproduced with permission from Slaven EM, Stone SC, Lopez FA: *Infectious Diseases: Emergency Department Diagnosis & Management*, © 2006, McGraw-Hill, Inc., New York.]

In the case of small furuncles (boils), warm compresses can be used to promote drainage, and no other treatment is needed. Sitz baths are helpful for furuncles in the buttock or perineal regions. Repeat evaluation in 2 to 3 days is best to determine whether suppuration has occurred and surgical drainage is required.

Large furuncles, carbuncles, and skin abscesses require incision and drainage.[33] Simple needle aspiration of abscesses is inadequate to treat abscesses caused by MRSA.[34] Prior recommendations for endocarditis prophylaxis in patients undergoing incision and drainage have changed (see Chapter 156, "Endocarditis"). If indicated by the severity of valvular heart disease, the most common regimen is either clindamycin 600 milligrams IV or vancomycin 1 gram IV, 30 to 60 minutes before the procedure.

Incision and Drainage Procedure Before the incision and drainage procedure, obtain consent and explain complications. Use universal precautions, including a face shield with eye protection, because many abscesses are under pressure. There are few complications with superficial abscesses, but these include residual local numbness, the risk of injury to deeper nerves and blood vessels, and poor or delayed wound healing, especially in those with diabetes or peripheral vascular disease. Plan the incision along tension lines to minimize scarring if possible, especially in areas of cosmetic significance.

Position the patient for good access, prepare the area with povidone-iodine solution, and drape in a sterile fashion. To provide local anesthesia, approach the abscess from the side and slowly infiltrate the skin over the abscess. Then infiltrate deeper until resistance of the wall of the abscess cavity is overcome. Distend the abscess with several milliliters of lidocaine, taking care to shield the patient and operator from any material forced from the wound due to pressure. The inflamed abscess wall absorbs the lidocaine and lessens pain associated with the procedure.

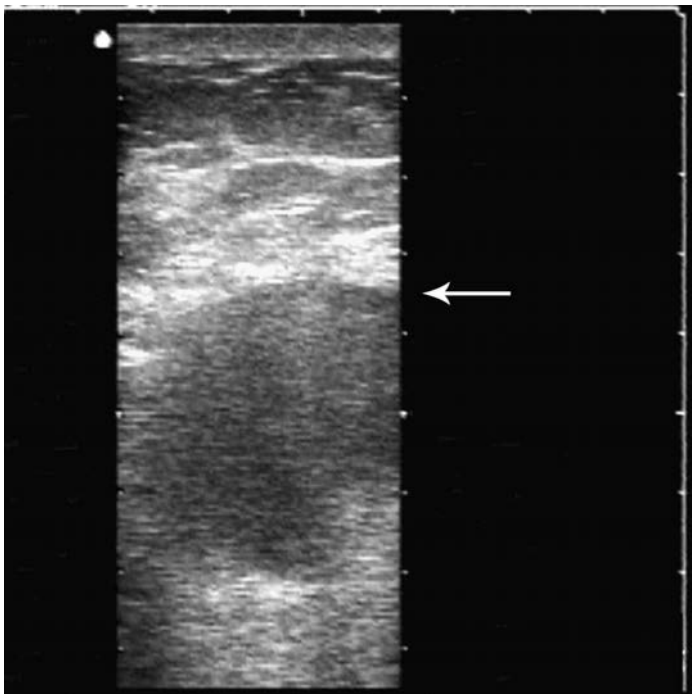


FIGURE 152-5. Long-axis sonogram of a deep midline buttock abscess in the region of the gluteal fold. The skin and immediate subcutaneous tissue exhibit relatively normal echogenicity. The deeper tissues surrounding the rounded abscess cavity appear more hyperechoic and edematous. Note that the superior edge of this large abscess cavity is 3.5 cm from the skin surface (*arrow*). [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing SA: *Ma & Mateer's Emergency Ultrasound*, 3rd ed. New York, NY: McGraw-Hill, Inc.; 2014. From Chapter 18: Musculoskeletal, Soft Tissue, and Miscellaneous Applications, Figure 18-105, p. 561.]

After appropriate anesthesia, using a No. 11 or 15 scalpel blade, incise the abscess over the area of greatest fluctuance, using the results of preparatory US evaluation to guide the length of the incision. Incisions that are too small or superficial are not likely to provide effective drainage. Express as much pus as possible by gentle compression. Insert a hemostat into the abscess cavity, opening and closing the jaws to break up loculations.

Irrigation of the cavity with saline followed by packing with gauze ribbon to promote drainage is commonly done, but the benefit is uncertain.[35,36] Less painful alternatives to packing include placing a catheter,[37] or tying in a rubber drain after placing two small stab incisions, using a small forceps to reach into one incision, coming out the other, and pulling the drain back through the track before making a knot.[38] Primary closure after abscess drainage shortens healing time for patients treated in the operating room[39] and has been studied in a small randomized controlled trial in the ED[40]; however, recommendations for its use await larger trials.

If placed, maintain packing, catheter, or drain long enough for the cavity to heal from the inside out and to prevent re-collection of pus. Patients should apply warm compresses or soaks three times a day. Schedule a follow-up visit in 2 to 3 days for recheck. Maintain catheter or replace packing if the cavity is still draining at the follow-up visit.

Adjuvant Antibiotics Recent studies suggest that in patients with a simple abscess, MRSA antibiotic coverage in conjunction with incision and drainage improves short-term outcome.[41-43] However, the benefit of antibiotics as an adjunct to sufficient abscess drainage must be weighed against the known side effect profile, especially in healthy patients without significant surrounding cellulitis.[44,45] Guidelines recommend antibiotics for patients with multiple lesions, extensive surrounding cellulitis, immunosuppression, or signs of systemic infection; see Table 152-4 for indications and specific antibiotics recommended.[3]

DISPOSITION AND FOLLOW-UP

Most patients with skin abscess, furuncles, and carbuncles are treated as outpatients. Those with systemic toxicity or severe infection typically require parenteral treatment and hospital admission. Age, failed oral antibiotics, and injection drug use impact admission decisions.[46] For those discharged to home, remind patients to keep the wound covered and practice frequent hand washing to prevent spread of the infection.[33] Patients with open wounds should not participate in activities involving skin-to-skin contacts, such as wrestling or football, until wounds are fully healed. Individuals should not share items such as towels, clothing, soap, razors, or other items that come in contact with a contaminated wound.

NECROTIZING SOFT TISSUE INFECTIONS

Necrotizing soft tissue infections are a spectrum of illnesses characterized by fulminant, extensive soft tissue necrosis, systemic toxicity, and high mortality. Early in their course, these infections can appear deceptively benign.[4,47] Terms used to describe necrotizing soft tissue infections are Fournier's gangrene (see Chapter 93, "Male Genital Problems"), necrotizing fasciitis, necrotizing soft tissue infection, or gas gangrene. Risk factors for necrotizing soft tissue infections are advanced age, diabetes mellitus, alcoholism, peripheral vascular disease, heart disease, renal failure, human immunodeficiency virus, cancer, NSAID use, decubitus ulcers, chronic skin infections, IV drug abuse, and immune system impairment.[48,49] However, infections also occur in young and healthy individuals. The incidence is increasing, but mortality has decreased in the United States from 25% to 10% over the past 20 years.[50] Bacteremia is reported in 25% to 30% of cases and is a strong predictor of mortality. Other patient factors that increase mortality are age <1 year old or >60 years old; IV drug use; comorbid conditions, especially cancer, chronic renal disease, and congestive heart failure; and certain characteristics of the clinical course such as positive blood cultures, trunk or perineal involvement, infection related to peripheral vascular disease, and delayed time to diagnosis or treatment.

MICROBIOLOGY

Type I (polymicrobial) infections include 55% to 75% of all necrotizing soft tissue infections, and the causative microbes are a combination of gram-positive cocci, gram-negative rods, and anaerobes. Clostridial infections are now uncommon causes due to improvements in hygiene and sanitation.[47] Type II (monomicrobial) infections are most commonly caused by group A *Streptococcus*. Type II infection is less common (20% to 30%) than type I infection and tends to occur on an extremity in an otherwise healthy host who often has a history of trauma or has had a recent operative procedure at the site of the infection. Community-acquired MRSA is a cause of type II (monomicrobial) infection, particularly in IV drug abusers, athletes, and institutionalized patients.[51,52] Necrotizing infection caused by *Vibrio vulnificus* is classified as a type III infection. This infection is more common in Asia and may occur in patients who have an apparently insignificant break in their skin in a seawater environment. Type IV is associated with fungal infections, primarily in immunocompromised patients.[53]

PATHOPHYSIOLOGY

The rapid necrotizing process typically begins with direct invasion of subcutaneous tissue from external trauma (IV injection, surgical incision, abscess, insect bite, or ulcer) or direct spread from a perforated viscus (usually colon, rectum, or anus). Although spontaneous development is rare, it does occur, and risk factors include diabetes and underlying malignancy. Bacteria proliferate, invade subcutaneous tissue and deep fascia, and release exotoxins that lead to tissue ischemia, liquefaction necrosis, and systemic toxicity.[48]

Skin involvement is secondary to vasculitis and thrombosis of perforating blood vessels. The ischemic tissue environment promotes bacterial growth, propagating the process and resulting in rapid spread of the

infection, which **can spread as fast as 1 inch/h**. Because thrombosis of large numbers of capillary beds must occur before skin findings develop, early infection has little overlying skin change to indicate the extent of infection.[47] As the disease progresses, widespread gangrene of the skin, subcutaneous fat, fascia, and even skeletal muscle occurs.[48]

In polymicrobial infections, a symbiotic relationship between the different kinds of bacteria seems to promote the necrotizing soft tissue infection. Facultative gram-negative organisms lower the oxygen reduction potential of the tissue and facilitate anaerobic organism growth. Anaerobic organisms impede phagocyte function, favoring aerobic bacterial growth. The alpha-toxin produced by the *Clostridium* species causes tissue necrosis and cardiovascular collapse. *S. aureus* and streptococci produce exotoxins and cause the release of tumor necrosis factor and cytokines that can produce the systemic inflammatory response syndrome and lead to septic shock, organ failure, and death.

CLINICAL FEATURES

Classic symptoms of necrotizing soft tissue infections are severe pain, anxiety, and diaphoresis.[47,48] Pain is often out of proportion to physical examination findings with tenderness beyond the area of erythema and thus is perhaps the single most important feature to make the diagnosis early. However, some patients may have little pain, and as the condition progresses, the affected areas may become insensate. About 10% to 40% of the time, patients report trauma or a break in the skin roughly 48 hours before onset of symptoms.

On examination, the painful area may demonstrate a brawny edema, and crepitus caused by bacterial gas production may be present.[48] The lack of crepitus does not rule out the diagnosis. Two different studies reported that the only signs present in >50% of patients were erythema, tenderness, or marked edema beyond the area of redness; crepitus was present in only 13% to 31% of patients. Late in the course of the infection, the skin can develop a bronze or brownish discoloration with a malodorous serosanguineous discharge, and bullae may be present (**Figure 152-6**).

Systemic manifestations include a low-grade fever with tachycardia out of proportion to the fever. In fulminant necrotizing infections, particularly from *V. vulnificus*, patients may have cardiovascular collapse due to release of bacterial toxins and release of cytokines, and they may be confused, irritable, or have a rapid deterioration of mental status.



FIGURE 152-6. Necrotizing soft tissue infection. Large cutaneous bullae are seen on the leg of this patient with necrotizing fasciitis. Note the dark purple fluid in the bullae. [Photo contributed by Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

DIAGNOSIS

The diagnosis is based on clinical assessment in combination with laboratory tests and imaging when the clinical picture is unclear. One or more "hard" signs of necrotizing fasciitis—crepitus, skin necrosis, bullae, hypotension, or gas on radiograph—are present in less than half of patients.[54] Many laboratory abnormalities have been investigated to aid in the diagnosis,[55-61] including the laboratory risk indicator for necrotizing fasciitis (LRINEC score).[55,56] Since its derivation, the LRINEC score ≥ 6 has been proven to miss many cases of necrotizing fasciitis,[60] especially those caused by *Vibrio* species,[57] and neck infections.[61] **Table 152-6** lists laboratory factors and imaging findings associated with necrotizing

TABLE 152-6 Laboratory and Imaging Results Associated With Necrotizing Fasciitis

Laboratory Factors Associated With Necrotizing Fasciitis

Laboratory Test	Threshold	Comments
C-reactive protein	>150 milligrams/L	Positive result adds 4 in LRINEC score
WBC count	>15,000 cells/mm^3	Positive result adds 1 in LRINEC score, level >25,000 cells/mm^3 adds 2
Hemoglobin	<13.5 grams/dL	Positive result adds 1 in LRINEC score,* level <11 grams/dL adds 2 in LRINEC score*
Sodium	<135 mmol/L	Positive result adds 2 in LRINEC score*
Creatinine	>1.6 milligrams/dL	Positive result adds 2 in LRINEC score*
Glucose	>180 milligrams/dL	Positive result adds 1 in LRINEC score*
Potassium	>5.0 mEq/L	Associated with extremity infections
Band count	>7%	Associated with *Vibrio* species
Serum albumin	≤2.0 grams/dL	Associated with *Vibrio* species
Platelets	≤80,000	Associated with *Vibrio* species

Imaging Findings Associated With Necrotizing Fasciitis

Imaging Test	Finding	Comments
MRI with contrast	Extensive thickening of the intermuscular fasciae with an appearance suggesting incomplete vascularization	1. Presence of gas is highly specific for necrotizing infection (but not common). 2. Absence of MRI abnormalities of the intermuscular fasciae virtually rules out necrotizing fasciitis.
CT with contrast	1. Fascial thickening of deep facial planes 2. Nonenhancing deep fascia on contrast imaging suggesting necrosis	1. Presence of gas is highly specific, but found in one third of cases or less. 2. Accurate diagnosis requires contrast; acute kidney injury is common in patients with necrotizing fasciitis and may contraindicate IV contrast.
Ultrasonography	1. Fluid collections along the fascial plane 2. Fascia irregularity 3. Subcutaneous air	Radiologists warn that abnormal superficial hyperechogenicity absorbs US and may block diagnostic deeper findings and give false reassurance.
Plain radiographs	Gas in soft tissues	Poor sensitivity

Abbreviation: LRINEC = laboratory risk indicator of necrotizing fasciitis.

*LRINEC score of ≥6 is associated with increased risk of necrotizing fasciitis but misses many cases and therefore should not be used in isolation for the diagnosis and management.

fasciitis to help clinicians with medical decision making.[55-64] Clinicians are encouraged to consult surgery for possible debridement early when the diagnosis of necrotizing fasciitis is being considered rather than waiting for confirmatory studies that may yield equivocal results. There is no single test or sign that can reliably confirm the early diagnosis of necrotizing fasciitis.[48,49] The finger test has been advocated, which involves making a 2-cm incision over involved tissue down to the fascia after local anesthesia, observing for normal blood flow, and inserting a gloved finger to test for normal tissue firmness.[55] A positive test is lack of normal bleeding, or friable tissue to minimal finger pressure. However, its use has never been studied formally.

Plain radiographs may reveal subcutaneous gas in a minority of patients, but may miss deep fascial gas and are therefore a poor screening tool. CT with contrast is more sensitive (80% to 97%) but has a false-positive rate of 19%. The most reliable sign of necrosis on CT is nonenhancing deep tissues, which requires contrast, or gas, seen in ≤36% of patients.[63] IV contrast is a significant risk in this group of patients who frequently sustain acute renal failure due to sepsis. MRI has better sensitivity (90% to 100%), but false-positive rates are as high as 39%.[64] Finally, MRI imposes significant delays to treatment. Bedside US has been advocated,[62] but radiologists caution against excluding necrotizing fasciitis based on its findings.

TREATMENT

The tissue ischemia produced in necrotizing skin infections impedes immune system destruction of bacteria and prevents adequate delivery of antibiotics.[48] **Thus, antibiotics alone are rarely effective, and immediate surgical consultation and intervention remain the cornerstone of successful management**.[49] Begin aggressive fluid resuscitation immediately as well as transfusion of packed red blood cells as needed. Avoid vasoconstrictors, if at all possible, because vasoconstrictors will decrease perfusion to already ischemic tissue.

Surgery is the gold standard for diagnosis and treatment; however, treatment standards are primarily expert consensus based, rather than evidenced based.[49] Surgical intervention may include fasciotomy, debridement, and/or amputation. Mortality skyrockets if debridement is delayed >24 hours.[48] See Table 152-5, "Empiric Treatment of Nonpurulent Cellulitis/Erysipelas," the row titled "Broad-spectrum antibiotics for severe disease," for patients with selected indications. Provide tetanus prophylaxis as indicated. Controversial therapies that are typically the decision of the surgical consultant include IV immunoglobulin therapy and hyperbaric oxygen therapy.

OTHER SOFT TISSUE INFECTIONS

FOLLICULITIS

Folliculitis is an inflammation of hair follicles related to infection, chemical irritation, or injury. It typically involves a superficial bacterial infection of the hair follicles with purulent material in the epidermis.

Epidemiology/Microbiology Folliculitis is usually caused by *S. aureus*, and nasal carriage of this organism is a risk factor for folliculitis. "Hot tub folliculitis" or "whirlpool-associated folliculitis" is often attributed to *Pseudomonas* species and occurs in inadequately chlorinated hot tubs, whirlpools, and swimming pools. Symptoms of uncomplicated folliculitis and whirlpool-associated *Pseudomonas* folliculitis are often mild and self-limited, and patients do not seek medical attention.

Individuals exposed to whirlpool footbaths at nail salons are at risk for mycobacterial furunculosis. *Candida* species are implicated in patients receiving broad-spectrum antibiotics or glucocorticoids or who are otherwise immunocompromised.[3]

Clinical Features The most common sites of involvement for folliculitis are the apocrine areas of the upper back, chest, buttocks, hips, and axilla, but folliculitis can develop in any hair-bearing region of the body, especially in areas of repeated shaving. Folliculitis presents with clusters of pruritic, erythematous lesions that are usually <5 mm in diameter, with pustules sometimes present at the centers.[3] *Pseudomonas* folliculitis can develop over areas exposed to contaminated water, and lesions are often larger (up to 3 cm in diameter).

Pseudofolliculitis is a related noninfectious condition more commonly seen in persons of African descent secondary to shaving. It occurs when the hair follicle becomes trapped and, instead of exiting the follicle, curls and grows into the follicular wall. Such findings in the beard region are called "sycosis barbae" or "folliculitis barbae" and can progress to deep infections that can cause facial scarring (see Chapter 250, "Skin Disorders: Face and Scalp").

Diagnosis Folliculitis is diagnosed clinically. It should be differentiated from other disorders, such as acne vulgaris, impetigo, fungal infections, contact dermatitis, scabies, insect bites, and viral disorders such as herpes.

Treatment/Disposition and Follow-Up For simple cases of uncomplicated folliculitis or hot-tub folliculitis, stopping exposure or removing the offending agent and twice-daily cleansing with mild hand soap often suffice. Lesions usually resolve spontaneously, but if desired, warm compresses may be applied several times daily, and a topical antibiotic such as bacitracin or polymyxin B can also be used. Shaving should be avoided in the involved areas. Pseudofolliculitis is managed by allowing the hairs to grow 2 to 3 mm above the surface and afterward using commercially available razors designed for this condition. For painful or more extensive cases, oral antibiotics with activity against *Streptococcus* and *Staphylococcus*, such as cephalexin, dicloxacillin, or azithromycin, are recommended.

INFECTED EPIDERMOID AND PILAR CYSTS

Epidermoid cysts originate from the epidermis, and pilar cysts originate from hair follicles; both contain a thick, cheesy collection of keratin, not sebum. True sebaceous cysts, as these cysts have erroneously been called in the past, are rare. Sebaceous glands occur diffusely throughout the body. Blockage of the duct of a sebaceous gland may lead to development of a glandular cyst that can exist for a long period without becoming infected. Once bacterial invasion occurs, abscess formation is common. An infected epidermoid or pilar cyst is an erythematous, tender, fluctuant cutaneous nodule. Simple incision and drainage procedure is the appropriate ED treatment. The cyst always contains a capsule that must be removed to prevent further infection. Capsule excision is typically done at follow-up when the initial inflammation has improved or resolved. Occasionally, the wall of the sac can be grasped with forceps and removed at the time of drainage.

SPOROTRICHOSIS

Sporotrichosis is a mycotic infection caused by the fungus *Sporothrix schenckii*.

Epidemiology Sporotrichosis occurs worldwide but is most common in tropical and subtropical zones.[65] It is endemic in Central and South America and in Africa. The organism is found most commonly in soil, sphagnum moss, and decaying vegetable matter. It is a common disease among florists, gardeners, and agricultural workers. Inoculation into the host most often occurs when a spine or barb on a plant punctures the skin during handling. Approximately 10% to 62% of patients relate infection to penetrating trauma from plant thorns, wood splinters, or contaminated organic material.

Transmission from infected animals, especially cats, has been documented. Veterinary workers, animal handlers, and cat owners are therefore at increased risk. The typical patient is a healthy young adult, but the infection can also occur in immunocompromised individuals such as those with alcoholism, diabetes mellitus, hematologic malignancy, organ transplantation, or human immunodeficiency virus infection.

Pathophysiology *S. schenckii* is a thermally dimorphic fungus that changes from its mycelial form to its yeast form on entering a body-temperature environment. Disease is usually limited to local cutaneous or lymphocutaneous areas. Osteoarticular involvement, including osteomyelitis, septic arthritis, bursitis, and tenosynovitis, occurs and may extend from a local cutaneous infection or may be secondary to hematogenous spread. Although less common, transmission may occur through inhalation of the fungus through the upper respiratory tract, and subsequent hematogenic dissemination can occur. When inhaled, granulomatous pneumonitis with cavitation may arise.



FIGURE 152-7. Fixed sporotrichosis. The ulcer and surrounding erythema of fixed cutaneous sporotrichosis could be confused with a brown recluse spider bite. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, Inc., New York.]

Clinical Features The incubation period averages 3 weeks following initial inoculation, but varies from a few days to several weeks. After the fungus enters the body through a break in the skin, three types of localized infections may occur. The fixed cutaneous type is characterized by lesions restricted to the site of inoculation and may appear as a crusted ulcer or verrucous plaque (**Figure 152-7**). Local cutaneous-type infections also remain local but present as a subcutaneous nodule or pustule. The surrounding skin becomes erythematous and may ulcerate, resulting in a chancre. Local lymphadenitis is common. The lymphocutaneous type is the third and most common type. It is characterized by an initial painless nodule or papule at the site of inoculation that later develops subcutaneous nodules with clear skip areas along local lymphatic channels (**Figure 152-8**). The local reactions in all three types of infections tend to be relatively painless, but show no signs of improvement without treatment.



FIGURE 152-8. Sporotrichosis. Chronic lymphocutaneous type—an erythematous papule at the site of inoculation on the index finger with a linear arrangement of erythematous dermal and subcutaneous nodules extending proximally in lymphatic vessels of the dorsum of the hand and arm. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th ed. © 2009, McGraw-Hill, Inc., New York.]

Patients occasionally develop extracutaneous illness from what is most probably hematogenous spread. Most cases of extracutaneous sporotrichosis involve the skeletal system. An indolent form of monoarticular arthritis is the most common symptom. Osteomyelitis, tenosynovitis, and carpal tunnel syndrome are occasionally seen as well. Multiarticular arthritis is usually only seen in patients with immunocompromise. Pulmonary involvement is rare, typically occurring in elderly alcoholic males and clinically resembling tuberculosis. Chronic lymphocytic meningitis can be a delayed complication of sporotrichosis infection and should be considered in patients with chronic meningeal symptoms.

Diagnosis History and physical findings are the keys to diagnosis.[65] Fungal cultures are the best way to isolate the fungus, and tissue biopsy cultures often are diagnostic. Pus, synovial fluid, sputum, blood, or tissue fragment is suitable for culture.

Routine laboratory tests are nonspecific, but an increased WBC count, eosinophil count, and erythrocyte sedimentation rate may occur. The differential diagnosis includes tuberculosis, subcutaneous abscesses of tularemia, cat-scratch disease, leishmaniasis, staphylococcal lymphangitis, paracoccidioidomycosis, chromoblastomycosis, blastomycosis, bacterial pyoderma, primary syphilis, and infections caused by atypical mycobacteria such as *Mycobacterium marinum*.

Treatment Itraconazole (100 to 200 milligrams daily for 2 to 4 weeks after all lesions have resolved) is the treatment of choice for localized and systemic infections.[66] Fluconazole is less effective than itraconazole and should be reserved for those few patients not tolerating itraconazole. Ketoconazole has shown even poorer results than fluconazole. IV amphotericin B is effective, but adverse reactions limit its use to disseminated forms of the disease. In endemic regions or in epidemic outbreaks, a saturated solution of potassium iodide is an effective low-cost alternative.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 153

Sexually Transmitted Infections

Karen D. Serrano

INTRODUCTION

Sexually transmitted infections (STIs) are a major public health problem. In 2016, there were 1.59 million cases of chlamydia infection, 468,514 cases of gonorrhea, and 27,814 cases of syphilis reported in the United States.[1] The World Health Organization estimates that 357 million people are infected each year by a curable STI.[2]

The primary medical goals are identifying and treating STIs, but important secondary goals include preserving future health (including fertility), protection of any sexual contacts, preventive education, and provision of instructions for future screening. Lack of treatment can contribute to infertility, cancer, and urogenital complications, as well as pregnancy complications and potential harm to a fetus in pregnant women with STIs. Failure of patients to follow up and adhere to a prescribed medical regimen complicates individual care and public health reduction efforts.

Multiple STIs frequently occur together. Once an STI is diagnosed, further testing for human immunodeficiency virus (HIV) infection and hepatitis B is warranted.[3]

Because of frequent changes in treatment guidelines and resistance patterns, we recommend that the reader access the Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report* (http://www.cdc.gov/mmwr) to check any modifications for treatment and also to obtain patient information in several languages.

GENERAL PRINCIPLES FOR DIAGNOSIS AND SCREENING

The signs and symptoms of an STI may be obvious, such as a genital lesion or vaginal discharge, or less specific, such as dysuria, lower abdominal pain, painful intercourse, or spotting between periods. Less specific signs lead to frequent STI underrecognition. Obtain a thorough sexual history in an objective, nonjudgmental manner to determine the risk of STI, HIV infection, or hepatitis. The young (13 to 24 years old), pregnant women, and homosexual men are all at higher risk of STI and subsequent morbidity. The Centers for Disease Control and Prevention has questions that providers can use when obtaining a sexual history and determining a patient's risk for an STI (**Table 153-1**).

Perform a pregnancy test in all females of childbearing potential, because pregnancy may affect treatment options. As appropriate, have chaperones present whenever breast, genital, or rectal examinations are performed. In women, perform a vaginal speculum examination, bimanual examination, and rectal examination. In males, retract the foreskin in uncircumcised patients to fully examine the area. Examine the areas between skinfolds, particularly in obese patients. Obtain directed site test specimens, which may include urine, vaginal, rectal, and urethral samples.

GENERAL RECOMMENDATIONS FOR TREATMENT AND FOLLOW-UP

Based on advice from the Centers for Disease Control and Prevention, we recommend the following[3-5] (**Table 153-2**):

TABLE 153-1 Centers for Disease Control and Prevention Recommended Questions for the Five Ps of Sexually Transmitted Infection (STI) Prevention[4]

1. **Partners**
   - "Are you currently sexually active?" "If no, have you ever been sexually active?"
   - "In recent months, how many sex partners have you had?"
   - "Are your sex partners men, women, or both?"
2. **Prevention of pregnancy**
   - "Are you currently trying to conceive or father a child?"
   - "Are you concerned about getting pregnant or getting your partner pregnant?"
   - "Are you using contraception or practicing any form of birth control?"
   - "Do you need any information on birth control?"
3. **Protection from STI**
   - "Do you and your partner(s) use any protection against STI?" "If not, could you tell me the reason?"
   - "If so, what kind of protection do you use?"
   - "How often do you use this protection?" "If 'sometimes,' in what situations or with whom do you use protection?"
   - "Do you have any other questions, or are there other forms of protection from STI that you would like to discuss today?"
4. **Practices**
   - "What kind of sexual contact do you have or have you had? Genital (penis in the vagina)? Anal (penis in the anus)? Oral (mouth on penis, vagina, or anus)?"
5. **Past history of STI**
   - "Have you ever been diagnosed with an STI?" "When?" "How were you treated?"
   - "Have you had any recurring symptoms or diagnoses?"
   - "Have you ever been tested for HIV or other STI?" "Would you like to be tested?"
   - "Has your current partner or any former partners ever been diagnosed or treated for an STI?"
   - "Were you tested for the same STI(s)?" "If yes, when were you tested?" "What was the diagnosis?" "How was it treated?"

Abbreviation: HIV = human immunodeficiency virus.

1. Patients with symptoms suggestive of cervicitis or urethritis who are high risk for STIs should be treated presumptively for gonorrhea and chlamydia in the ED. Treat the patient in the ED with single-dose antibiotic regimens to maximize compliance.[3]
2. Obtain a pregnancy test and consult or refer promptly if the patient is pregnant.
3. If one STI is suspected or diagnosed, screen for other STIs (HIV infection, syphilis, and hepatitis) in the ED or through follow-up.
4. Report any notifiable infections such as *Chlamydia trachomatis*, gonorrhea, HIV infection, and syphilis. This is often based on final laboratory testing and can be automated.
5. Counsel all patients with suspected STIs about prevention and coinfection risks (notably HIV and hepatitis) in the ED and ensure follow-up options. Although no method aside from abstinence is 100% effective for STI prevention, male latex condoms and female condoms are useful in preventing STIs.
6. Advise that the partner(s) must seek treatment before any reengagement in sex.
7. Arrange follow-up to ensure relief of symptoms, compliance, and STI cure.

Although the Centers for Disease Control and Prevention recommends that healthcare providers in all settings routinely screen for HIV infection in all patients aged 13 to 64 years, the ED remains an underused venue for HIV screening.[6] Rapid HIV testing in the ED is not routine but is becoming more prevalent.[7]

SEXUALLY TRANSMITTED INFECTIONS PRESENTING WITH URETHRITIS, CERVICITIS, AND/OR DISCHARGE

CHLAMYDIAL INFECTIONS

Clinical Features In the United States and the United Kingdom, *C. trachomatis* infection is the most frequently reported STI. It is one of the causes of nongonococcal urethritis and commonly coexists with gonorrhea infections. It is most prevalent in people <25 years of age and is often asymptomatic, especially in women, but also in men.[7]

Chlamydial infections in men can cause urethritis, epididymitis, proctitis, or Reiter's syndrome (urethritis, conjunctivitis, and rash). Women generally have asymptomatic cervicitis when infected with *Chlamydia*, although if present, symptoms include vaginal discharge, bleeding between menses, and dysuria. The discharge may be mucopurulent (**Figure 153-1**) when *Neisseria gonorrhoeae* coinfection is present. **Consider urethral chlamydial infection in the differential diagnosis of sterile pyuria.** Complications of chlamydia in women include pelvic inflammatory disease, ectopic pregnancy, and infertility.

Diagnosis **Chlamydia can be diagnosed in testing first-catch urine in both men and women or by collecting swab specimens from the endocervix or vagina in women and urethral swabs in men.** Nucleic acid amplification testing is the preferred test for diagnosis, with a high sensitivity (90%) and specificity (99%) for *Chlamydia*. Nucleic acid amplification tests that are U.S. Food and Drug Administration cleared for use with vaginal swab specimens can be self-collected by the patient, with equal sensitivity and specificity to provider-collected swabs, a screening strategy that patients may find more tolerable.[8,9]

Treatment The Centers for Disease Control and Prevention recommends single-dose azithromycin or twice-a-day doxycycline for 7 days.[10] Table 153-2 lists dosages and alternative treatment options.[3,11] Azithromycin is safe for pregnant women, and pregnant women should undergo a test of cure 3 to 4 weeks after treatment. Amoxicillin is a safe alternative in pregnancy if azithromycin cannot be given.

Refer partners for testing and treatment if there was sexual contact in the last 60 days. Providers may elect to give the patient medication or a prescription to deliver to their partners. Known as expedited partner therapy, this approach is endorsed by the Centers for Disease Control and Prevention as a way of preventing the spread of this STI.

TABLE 153-2 Treatment of Sexually Transmitted Infections

Sexually Transmitted Infection	First-Line Treatment	Alternative(s)	Pregnancy/Lactation
Bacterial vaginosis	Metronidazole, 500 milligrams PO two times daily × 7 d *or* Metronidazole vaginal gel 0.75%, 5 grams intravaginally daily × 5 d *or* Clindamycin vaginal cream 2%, 5 grams intravaginally at bedtime × 7 d	Tinidazole, 2 grams PO daily × 2 d *or* Tinidazole, 1 gram PO daily × 5 d *or* Clindamycin, 300 milligrams PO twice daily × 7 d *or* Clindamycin ovules, 100 milligrams intravaginally at bedtime × 3 d	Metronidazole, 500 milligrams PO two times daily × 7 d *or* Metronidazole vaginal gel 0.75%, 5 grams intravaginally daily × 5 d
Chancroid	Azithromycin, 1 gram PO single dose *or* Ceftriaxone, 250 milligrams IM single dose* *or* Ciprofloxacin, 500 milligrams PO, two times daily × 3 d *or* Erythromycin base, 500 milligrams PO three times daily × 7 d		Azithromycin, 1 gram PO single dose *or* Ceftriaxone, 250 milligrams IM single dose*
Chlamydia (treat for *Neisseria gonorrhoeae* concurrently)	Azithromycin, 1 gram PO single dose *or* Doxycycline, 100 milligrams PO two times daily × 7 d	Erythromycin base, 500 milligrams PO four times daily × 7 d *or* Erythromycin ethylsuccinate, 800 milligrams PO four times daily × 7 d *or* Levofloxacin, 500 milligrams PO once daily × 7 d *or* Ofloxacin, 300 milligrams PO twice daily × 7 d	Azithromycin, 1 gram PO single dose PLUS test of cure in 3–4 wk *or* Amoxicillin, 500 milligrams PO three times daily × 7 d PLUS test of cure in 3–4 wk *or* Erythromycin base, 500 milligrams PO four times a day for 7 d PLUS test of cure in 3–4 wk *or* Erythromycin base, 250 milligrams PO four times a day for 14 d PLUS test of cure in 3–4 wk *or* Erythromycin ethylsuccinate, 800 mg orally four times a day for 7 d PLUS test of cure in 3–4 wk *or* Erythromycin ethylsuccinate, 400 mg orally four times a day for 14 d PLUS test of cure in 3–4 wk
Gonorrhea (treat for *Chlamydia trachomatis* concurrently)	Ceftriaxone*, 250 milligrams IM single dose, AND azithromycin, 1 gram PO single dose *or* Ceftriaxone*, 250 milligrams IM single dose, AND doxycycline, 100 milligrams PO twice a day for 7 d	Cefixime, 400 milligrams PO single dose, AND azithromycin, 1 gram PO single dose *or* Cefixime, 400 milligrams PO single dose, AND doxycycline, 100 milligrams PO twice a day for 7 d *or* Azithromycin, 2 grams PO single dose, PLUS gemifloxacin, 320 milligrams PO single dose	Ceftriaxone*, 250 milligrams IM single dose, AND azithromycin, 1 gram PO single dose *or* Spectinomycin 2 grams IM single dose
Granuloma inguinale (donovanosis)	Azithromycin, 1 gram PO *weekly* for at least 3 wk and until lesions completely healed *or* Azithromycin, 500 mg PO *daily* for at least 3 wk and until lesions completely healed	Doxycycline, 100 milligrams PO two times daily for at least 3 wk and until lesions completely healed *or*	Erythromycin base, 500 milligrams PO four times daily for at least 3 wk and until lesions completely healed *or*

(*Continued*)

TABLE 153-2 Treatment of Sexually Transmitted Infections (*Continued*)

Sexually Transmitted Infection	First-Line Treatment	Alternative(s)	Pregnancy/Lactation
		Ciprofloxacin, 750 milligrams PO two times daily for at least 3 wk and until lesions completely healed *or* Erythromycin base, 500 milligrams PO four times daily for at least 3 wk until lesions completely healed *or* Trimethoprim-sulfamethoxazole, 1 double-strength (160/800 milligrams) tablet PO two times daily for at least 3 wk and until lesions completely healed	Azithromycin, 1 gram PO weekly for at least 3 wk and until lesions completely healed *or* Gentamicin 1 milligram/kg IV every 8 h (if the above therapy is ineffective)
Herpes simplex *First episode*	Acyclovir, 400 milligrams PO three times daily × 7–10 d *or* Acyclovir, 200 milligrams PO five times daily × 7–10 d *or* Valacyclovir, 1 gram PO two times daily × 7–10 d *or* Famciclovir, 250 milligrams PO three times daily × 7–10 d		Acyclovir, 400 milligrams PO three times daily × 7–10 d *or* Acyclovir, 200 milligrams PO five times daily × 7–10 d *or* Valacyclovir, 1 gram PO two times daily × 7–10 d
Suppressive therapy for recurrent genital herpes in patients without human immunodeficiency virus	Acyclovir, 400 milligrams orally twice a day *or* Valacyclovir 500-1000 milligrams orally once a day (500 milligrams may not be as effective as 1000) *or* Famciclovir 250 milligrams orally twice a day		Acyclovir, 400 milligrams PO three times daily *or* Valacyclovir, 500 milligrams PO daily
Severe	Acyclovir, 5–10 milligrams/kg IV every 8 h × 2–7 d then oral medications for total treatment time of 10 d		Acyclovir, 5–10 milligrams/kg IV every 8 h × 2–7 d then oral medications for total treatment time of 10 d
Lymphogranuloma venereum	Doxycycline, 100 milligrams PO two times daily × 21 d	Erythromycin base, 500 milligrams PO four times daily × 21 d	Erythromycin base, 500 milligrams PO four times daily × 21 d
Syphilis *Primary, secondary, and early latent*	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 milligrams PO two times daily × 14 d *or* Tetracycline, 500 milligrams PO four times daily × 14 d *or* Ceftriaxone, 1–2 grams IM or IV daily × 10–14 d *or* Azithromycin, 1 gram PO single dose. Use only if treatment with penicillin or doxycycline is not feasible.	Benzathine penicillin G, 2.4 million units IM single dose
Latent	Benzathine penicillin G, 2.4 million units IM one time a week × 3 wk	Doxycycline, 100 milligrams PO two times daily × 28 d *or* Tetracycline, 500 milligrams PO four times daily × 28 d	Benzathine penicillin G, 2.4 million units IM one time a week × 3 wk
Trichomoniasis	Metronidazole, 2 grams PO single dose *or* Tinidazole, 2 grams PO single dose	Metronidazole, 500 milligrams PO two times daily × 7 d	Metronidazole, 2 grams PO single dose (weigh risks and benefits of treatment)

*Ceftriaxone is painful IM and may be mixed with lidocaine 1% to decrease patient discomfort with administration.

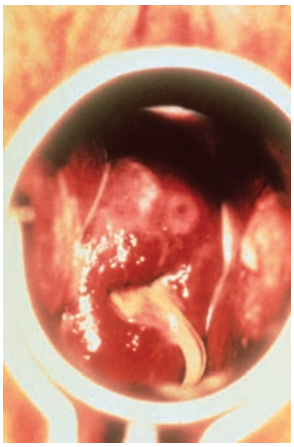


FIGURE 153-1. Viscous, opaque discharge emanating from the cervical os, consistent with mucopurulent cervicitis. The string from an intrauterine device is seen descending through the os in this patient. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine*, 3rd ed. © 2009 by McGraw-Hill, Inc., New York.]

Universal adoption of this method at this time is incomplete because of ethical issues and medicolegal consequences including some state prohibitions.[12] Providers should visit www.cdc.gov/std/ept to obtain updated information for their state.

Counsel patients to avoid sexual contact until 7 days have elapsed after completion of antibiotic treatment and their symptoms have resolved. Encourage women to be retested approximately 3 months after treatment because of the high incidence of recurrence.[3]

GONOCOCCAL INFECTIONS

Gonorrhea is the second most commonly reported STI, caused by *N. gonorrhoeae*, a gram-negative diplococcus.

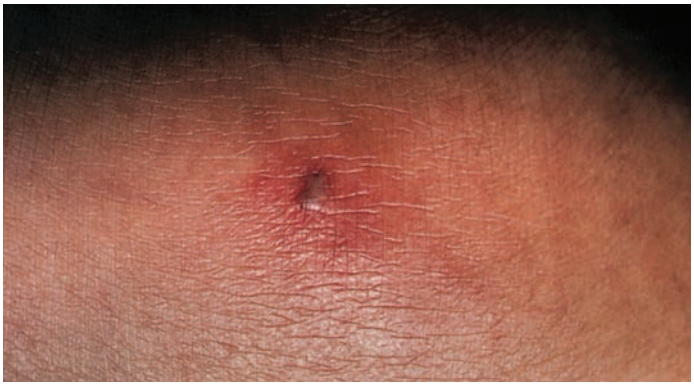
Clinical Features Most gonococcal infections in women are asymptomatic and often coexist with chlamydial infection. Gonorrheal infections result in complications ranging from ectopic pregnancy to chronic pelvic pain to pelvic inflammatory disease. Symptoms, if present, may include nonspecific lower abdominal discomfort and mucopurulent cervicitis after a 7- to 14-day incubation period. In contrast to women, gonorrheal infection is usually symptomatic in men, and 80% to 90% of men develop symptoms within 2 weeks of exposure. Dysuria and profuse, purulent penile discharge (**Figure 153-2**) are the most common presenting symptoms, but symptoms of acute epididymitis and prostatitis may also result. Rectal infection with mucopurulent anal discharge and pain occurs in 30% to 50% of women with gonococcal cervicitis, and the rectum can be the only site of infection in homosexual men. *N. gonorrhoeae* also can be isolated from the pharynx but rarely causes pharyngitis.



FIGURE 153-2. Gonococcal urethritis in a male. Mucopurulent ureteral discharge is caused by infection with *Neisseria gonorrhoeae*. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]



A



B

FIGURE 153-3. Disseminated gonococcal infection. **A.** Maculopapules on the hands. **B.** Lesion on the extensor surface of the wrist in a sexually active adult female. The macropapule has a petechial component and an erythematous periphery.

Signs and symptoms of **disseminated gonococcal infection** include petechial or pustular acral skin lesions on an erythematous base (**Figure 153-3**), asymmetric arthralgias, tenosynovitis or septic arthritis, and fever or general malaise. Infection with *N. gonorrhoeae* and other STIs is associated with increased HIV shedding.[13]

Diagnosis The Centers for Disease Control and Prevention recommends that nucleic acid amplification testing be performed on cervical, vaginal, urethral, or urine specimens. Specimens can be self-collected by the patient. Not all nucleic acid amplification testing is the same; some tests can be used only on certain specimen types, so know what is available at your institution. Culture and nucleic acid hybridization tests require endocervical or urethral swab specimens.

In men, a Gram stain of urethral secretions that demonstrates polymorphonuclear leukocytes with the classic intracellular diplococci confirms the diagnosis. However, absence of this finding is not sufficient to rule out the gonococcal infection, and it is therefore not recommended as a screening tool. Additionally, this diagnostic method is not sufficient for endocervical, pharyngeal, or rectal specimens. Diagnosis of disseminated gonococcal infection is difficult, with only 20% to 50% of cultures of blood, lesion, and joint specimens yielding positive results. Culture of cervical, rectal, and pharyngeal specimens may improve the chance of diagnosis.

Treatment Given emerging resistance patterns, the Centers for Disease Control and Prevention recommends dual therapy with ceftriaxone 250 milligrams IM plus single-dose azithromycin 1 gram PO for the treatment of gonorrhea (Table 153-2).[3,5] Fluoroquinolones are no longer recommended for first-line treatment of gonorrhea because of antibiotic resistance. Pregnant women should be treated with a cephalosporin plus azithromycin or, if allergic to cephalosporins, with 2 grams of either azithromycin PO or 2 grams of spectinomycin IM (not available in the United States) in a single dose. Instructions to sexual contacts are the same as with chlamydial infections. Treat disseminated disease

with higher doses of ceftriaxone (1 gram IM or IV every 24 hours for 1 to 2 days) followed by cefixime 400 milligrams PO twice a day for a minimum of 1 week. Gonococcemia requires hospitalization for IV administration of antibiotics and evaluation for possible endocarditis and meningitis. Patients with gonococcal arthritis rarely require surgical drainage and irrigation of affected joints.

NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis is diagnosed when *N. gonorrhoeae* is absent in someone with clinical symptoms. Although nongonococcal urethritis is usually caused by *C. trachomatis*, other causes of nongonococcal urethritis include *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, herpes simplex virus, and adenovirus. Alternative pathogens are seen more often in older men, and often no singular pathogen is identified. Specific tests for *U. urealyticum* and *M. genitalium* are not indicated.

If a patient's urethral specimen has five or more WBCs per oil immersion field or the first-void urine specimen suggests infection, treat empirically as chlamydial urethritis. If the symptoms persist, the patient was noncompliant with their prior treatment regimen, the patient was exposed to a new sexual partner, or the previous partner was not treated, repeat treatment for chlamydial urethritis. Otherwise, obtain a specimen for culture for *T. vaginalis* and treat with metronidazole, 2 grams as a single oral dose, or with a combination of tinidazole, 2 grams PO, plus azithromycin, 1 gram PO as a single dose.

TRICHOMONAL INFECTIONS

T. vaginalis is a flagellated protozoan that causes urogenital infections mostly in women, with a prevalence of approximately 3%. *T. vaginalis* infection is associated with a high prevalence of coinfection with other STIs, notably HIV, and trichomonas has been identified as a cofactor in HIV transmission.[14,15] Trichomonas is also covered in Chapter 102 "Vulvovaginitis."

Clinical Features Trichomoniasis can range from asymptomatic carrier states to severe, inflammatory disease. Symptoms include a malodorous, thin watery discharge, vulvar irritation, pruritus, dysuria, urinary frequency, dyspareunia, and occasionally low abdominal pain. The classic yellow-green, frothy discharge is infrequently found, and many women have minimal symptoms.[3] Physical examination may demonstrate vulvar irritation, inflamed vaginal mucosa, and punctate cervical hemorrhages. In men, the disease is often asymptomatic, but may present as urethritis.

Diagnosis Nucleic acid amplification tests and other highly sensitive tests are recommended for diagnosis of trichomoniasis, preferred over wet-mount microscopy, a method with poor sensitivity. Culture is the most sensitive and specific test available, although it may take up to 7 days to obtain results. Because of this delay to diagnosis, commercially available tests using DNA probes and monoclonal antibodies are used in some institutions.

Treatment All patients with *Trichomonas* infection should be treated irrespective of symptoms, and sexual partners should be treated to prevent reinfection. Metronidazole, 2 grams PO in a single dose or 500 milligrams PO twice daily for 7 days, cures 90% to 95% of patients.[15] Single-dose regimens are generally preferred due to better adherence, decreased cost, and less vaginal candidiasis, whereas the lower dose, prolonged course has fewer systemic side effects.[3] Patients must avoid alcohol when taking metronidazole given the disulfiram-like reaction. Metronidazole gel is less effective than oral treatment.[15]

Trichomonas infections are linked to an increase in pregnancy-related complications. Because **metronidazole is a pregnancy category B drug**, it is the drug of choice for treating symptomatic pregnant patients, with no high-quality evidence linking metronidazole exposure with teratogenic effects.[16] Despite the Centers for Disease Control and Prevention recommendations of a 2-gram singular dose coupled with evidence supporting the safety of metronidazole treatment in symptomatic pregnant women, some clinicians avoid oral treatment in the first trimester. Treatment of partners includes administration of the same medications as for the patient plus an STI clinic referral given the high rate of cotransmission of other STIs.

SEXUALLY TRANSMITTED INFECTIONS PRESENTING WITH GENITAL ULCERS

Genital ulcers are caused by syphilis, herpes virus infection, chancroid, lymphogranuloma venereum, and granuloma inguinale (donovanosis). These infections have high rates of coinfection with HIV. Not all infections associated with genital ulcers are sexually transmitted. Characteristics of the lesions and their accompanying signs and symptoms are provided in **Table 153-3**.

SYPHILIS

Syphilis is a systemic disease caused by the spirochete *Treponema pallidum*. The organism enters the body through mucous membranes or nonintact skin. *T. pallidum* remains very sensitive to penicillin. The incidence of syphilis in the United States has been on the rise from 2000 to 2016. This was initially attributed to increased cases of male-to-male transmission; however, between 2013 and 2016, there was a significant increase in cases among women. The spike in cases in women is of particular concern because rising syphilis rates in women correlate with a rise in congenital syphilis.[1]

Clinical Features Syphilis is divided into three stages of infection—primary, secondary, and tertiary—and the disease may be diagnosed in any of these stages. Latent syphilis is characterized by absence of clinical manifestations but positive serologic testing.

TABLE 153-3 Clinical Features of Genital Ulcerative Infections

Disease	Clinical Diagnosis	Presence of Pain	Inguinal Adenopathy	Comment
Syphilis	Indurated, relatively clean base; heals spontaneously	No	Firm, rubbery, discrete nodes; not tender	Primary: chancre Secondary: rash, mucocutaneous lesions, lymphadenopathy Tertiary: cardiac, ophthalmic, auditory, CNS lesions
Herpes simplex virus infection	Multiple small, grouped vesicles coalescing and forming shallow ulcers; vulvovaginitis	Yes	Tender bilateral adenopathy	Cytologic detection insensitive; false-negative culture results common; type-specific serologic test
Chancroid (*Haemophilus ducreyi*)	Multiple painful, irregular, purulent ulcers with potential exudative base	Yes	50% painful, suppurative, inguinal lymph nodes potentially requiring drainage	Cofactor for human immunodeficiency virus transmission; 10% have coinfections with herpes simplex virus infection or syphilis
Lymphogranuloma venereum	Small and shallow ulcer, associated proctocolitis with fistulas and strictures	No	Tender lymph nodes	Caused by *Chlamydia trachomatis* L1, L2, L3
Granuloma inguinale (donovanosis)	Painless, beefy red, bleeding ulcers	No	No	Endemic in Africa, Australia, India, New Guinea; rare in United States



FIGURE 153-4. Painless chancre. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. © 2005, McGraw-Hill, Inc., New York.]

Primary syphilis, or the initial stage of infection, is characterized by a painless chancre with indurated borders on the penis (**Figure 153-4**), vulva (**Figure 153-5**), or other areas of sexual contact.

The incubation period is approximately 21 days, with lesions disappearing after 3 to 6 weeks. There are no constitutional symptoms, and a lesion may even be absent with primary disease. The lesion resolves spontaneously.

Secondary syphilis develops 3 to 6 weeks after the end of the primary stage and is characterized by rash and lymphadenopathy. Nonspecific symptoms of sore throat, malaise, fever, and headaches are common. The rash often starts on the trunk (**Figure 153-6**) and flexor surfaces of the extremities, spreading to the palms (**Figure 153-7**) and soles. The rash takes on many forms but is often dull red-pink and papular. Secondary syphilis resolves spontaneously.

Tertiary or latent syphilis develops in about one third of patients after secondary syphilis, occurring 3 to 20 years after the initial infection. Involvement of the nervous and cardiovascular systems is characteristic, with widespread granulomatous lesions (gummata). Specific manifestations include meningitis, dementia, neuropathy (tabes dorsalis), and thoracic aneurysm.

Diagnosis *T. pallidum* cannot be cultured in the laboratory, and there is no single optimal test. The sensitivity and specificity of tests for syphilis depend on the stage of the disease and the type of test. Direct visualization of the organism using darkfield microscopy is diagnostic



FIGURE 153-5. Syphilis chancre in a female. A painless ulcer is seen on the vulva. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]



FIGURE 153-6. Disseminated papulosquamous eruption on the right chest wall characteristic for secondary syphilis. [Reproduced with permission from Wolff K, Johnson RA, Saavedra AO: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 7th ed. © 2013 by McGraw-Hill, Inc., New York.]

of primary, secondary, or early congenital syphilis, no matter what the results on serology. However, failure to visualize the organism does not exclude syphilis. Nontreponemal tests (Venereal Disease Research Laboratory test, rapid plasma reagin test) detect nonspecific antibodies to cardiolipins, which are released as a result of infection. The Venereal Disease Research Laboratory and rapid plasma reagin tests are used as screening tests and also, once diagnosis is made, to assess disease activity and response to treatment. If used for screening, the Venereal Disease Research Laboratory and rapid plasma reagin tests are associated with both false-negative and false-positive results. Tests do not become positive until about 1 to 4 weeks after a chancre appears. Positive results must be confirmed with an immunoassay specific for *T. pallidum* antibodies. Some laboratories now begin the testing sequence with sensitive and specific *Treponema*-specific assays (reverse screening) and follow response to treatment with nontreponemal tests.[17]

For **secondary syphilis**, nontreponemal antibody tests are nearly 100% sensitive with high specificity.[18] The blood of treated patients usually becomes nonreactive on nontreponemal antibody tests. **Patients who develop disease and have a reactive result on a specific treponemal antibody test will have a reactive test result for life regardless of disease activity or treatment.**

A presumptive diagnosis of syphilis is made if a positive result on a nontreponemal antibody test (i.e., rapid plasma reagin or Venereal Disease Research Laboratory test) is supported by a positive confirmatory result on a treponemal antibody test (i.e., fluorescent treponemal antibody absorption test).[18,19] Treat based on strong clinical grounds while results of confirmatory tests are pending, if follow-up is uncertain. When uncertain about testing interpretation, review the Centers for Disease Control and Prevention website (http://www.cdc.gov/STD/syphilis/default.htm) for detailed clarification of laboratory diagnosis or contact the local health department.

Treatment **For primary and secondary syphilis**, treat with penicillin G benzathine, 2.4 million units IM in a single dose. Doxycycline twice daily for 2 weeks may be used in penicillin-allergic patients (Table 153-2). Pregnant women should be treated with parenteral penicillin G; if allergic, they should be desensitized and then given this medication. The **Jarisch-Herxheimer reaction** occurs most frequently in treatment of early syphilis and is characterized by an acute febrile reaction associated with headache and myalgias within the first 24 hours after treatment. Inform patients about this possible reaction. Recommend treatment of sexual partner(s) exposed in the previous 90 days. For a more detailed explanation of partner treatment, please refer to the Centers for Disease Control and Prevention website (http://www.cdc.gov/std/ept/default.htm).

Treat **tertiary syphilis** with 2.4 million units of penicillin G benzathine IM weekly for 3 weeks. Either a primary care physician or the department of public health should closely follow all patients for repeat serologic testing at 6 and 12 months.



FIGURE 153-7. Papulosquamous eruption on the right palm characteristic for secondary syphilis. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]

HERPES SIMPLEX INFECTIONS

Herpes simplex virus (HSV) type 1 or type 2 infections are lifelong. Genital herpes results from exposure of mucosal surfaces or nonintact skin to the HSV virus. While most genital infections are caused by the HSV-2 virus, the incidence of anogenital infections caused by HSV-1 virus is on the rise, especially among young women and men who have sex with men.[20] Only 10% to 25% of individuals who are HSV-2 seropositive report a history of genital herpes, which suggests that most infected people have unrecognized or asymptomatic infections. Viral shedding in persons who are unaware that they are infected is likely responsible for the majority of HSV transmission.[3] HSV is also covered in Chapter 102.

Clinical Features "Classic" outbreaks of primary genital HSV infection begin with a prodrome lasting 2 to 24 hours that is characterized by localized or regional pain, tingling, and burning. Next, constitutional symptoms of headache, fever, painful inguinal lymphadenopathy, anorexia, and malaise develop. As the disease progresses, papules and vesicles on an erythematous base become evident, which eventually ulcerate. Patterns of HSV-1 and HSV-2 infection appear identical: vesicles usually are uniform in size, and the tense center umbilicates to form a depressed center. Lesions usually crust and then reepithelialize and heal without scarring.

In men, HSV ulcers often appear on the shaft or glans of the penis (**Figure 153-8**). In women, ulcers can occur on the introitus (**Figure 153-9**), urethral meatus, labia, and perineum. Lesions are exquisitely painful and may be associated with serous discharge. In both sexes, lesions may be found on the perianal area, thighs, or buttocks. Dysuria is common in women, and urinary retention may develop secondary to severe pain.

Complete healing usually occurs within 3 weeks, and viral shedding persists for 10 to 12 days after the onset of the rash. Recurrent outbreaks are typically milder than the initial episode. There are typically fewer lesions, and viral shedding occurs at a lower concentration and for a shorter duration (i.e., about 3 days).[21]

Diagnosis Diagnosis is usually made based on clinical features. Laboratory diagnosis is either by cell culture or polymerase chain reaction. When obtaining a specimen for analysis, puncture the vesicle and swab the fluid. Swab the base of the lesion vigorously, because the virus is cell associated.[3] Importantly, lack of HSV detection does not confirm absence of HSV infection because viral shedding is intermittent.

Treatment Treatment shortens the duration of outbreaks but is not curative. Antiviral medications decrease the time until all lesions are crusted and healed, decrease pain and constitutional symptoms, and decrease the period of viral shedding by several days.[3]

Treat the first clinical episode of genital herpes with acyclovir, famciclovir, or valacyclovir (Table 153-2). To treat proctitis or oral infections, use higher dosages (acyclovir, 400 milligrams five times a day for 7 to 10 days). For hospitalized patients with severe disease, administer acyclovir, 5 to 10 milligrams/kg IV every 8 hours, for at least 2 days before transitioning to oral therapy.

Treat episodic recurrent infection for 5 days with acyclovir, famciclovir, or valacyclovir at dosages reduced from primary therapy (Table 153-2). For individuals with frequent recurrences, suppressive therapy is a good option and reduces the frequency of recurrences by



FIGURE 153-8. Genital herpes in a male. These formerly vesicular lesions have crusted over. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]



FIGURE 153-9. Genital herpes in a female. These formerly vesicular lesions have crusted over. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]

70% to 80% (according to the Centers for Disease Control and Prevention). **Treat severe recurrent infections** (seen primarily in immunocompromised patients) with acyclovir, 5 to 10 milligrams/kg every 8 hours IV, for at least 2 days before switching to oral therapy. A primary diagnosis of HSV should prompt the search for other STIs including HIV.

CHANCROID

Chancroid is a disease characterized by painful genital ulcers and lymphadenitis that is caused by the pleomorphic gram-negative bacillus *Haemophilus ducreyi*. The disease is on the decline in the United States, and infections are usually seen in association with sporadic outbreaks.[22] Chancroid increases HIV transmission and often is accompanied by other infections. When chancroid is present, 10% of infected patients in the United States also have HSV or *T. pallidum*.[22]

Clinical Features A painful erythematous papule appears at the site of infection (usually confined to the genital region) after an incubation period of 4 to 10 days. One to 2 days later, the lesion becomes eroded, ulcerated, and often pustular. The ulcers are usually 1 to 2 cm in diameter with sharp, undermined margins and are very painful (**Figure 153-10**). The friable base of the ulcer is covered with yellow-gray necrotic exudates. Multiple lesions are present in up to 50% of patients, especially in women, and "kissing lesions" (infection of adjacent skin areas due to autoinoculation) are frequent. Painful inguinal lymphadenopathy develops 1 to 2 weeks after primary infection, and lymph nodes may become necrotic or pus-filled, known as buboes. (**Figure 153-11**). Constitutional symptoms are rare, and ulcerations are rarely recurrent.

Diagnosis Diagnosis can generally be made on clinical grounds with a painful ulcer and regional lymphadenopathy, but other infections (such as HSV infection and syphilis) are possible. A swab of a lesion or pus from a suppurative lymph node can be cultured, but a special medium is required that is not widely available, and culturing has a sensitivity of <80%. There is no current U.S. Food and Drug Administration–approved polymerase chain reaction test, but some clinical laboratories have developed their own polymerase chain reaction tests.

Treatment Azithromycin PO in a single dose, ceftriaxone IM in a single dose, ciprofloxacin for 3 days, or erythromycin base for 7 days are all effective in the treatment of *H. ducreyi* infection (Table 153-2). Treatment choice should be based on local antibiotic resistance patterns and patient factors. Generally, azithromycin and ceftriaxone are used in patients without HIV infection, with ciprofloxacin as an alternative. Erythromycin is inexpensive, but the need for multiple doses and GI toxicity make it less desirable. Incision and drainage or aspiration of buboes can be considered for symptomatic relief, prevention of fistulas, and secondary ulcers.



FIGURE 153-11. Chancroid with characteristic penile ulcers and associated left inguinal adenitis. [Photo contributor: H. Hunter Handsfield. *Atlas of Sexually Transmitted Diseases*. New York: McGraw-Hill, Inc.; 1992. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York. Fig 9-22.]

Symptoms improve in about 3 days, and lesions are visibly improved within a week. Larger ulcers may require 2 to 3 weeks to heal. Partners should be treated if they have had sexual contact in the past 10 days, regardless of symptoms.[3] Pregnant women should be treated with azithromycin or ceftriaxone. All patients should be tested for HSV, syphilis, and HIV at the time of diagnosis of chancroid and again 3 months later if tests are initially negative.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum is a sexually transmitted infection caused by three specific serotypes of *C. trachomatis* (L1, L2, and L3). It is also known as struma, tropical bubo, or Durand-Nicolas-Favre disease. Lymphogranuloma venereum is endemic worldwide, but is seen only sporadically in the United States. The Netherlands has seen an increased incidence of this STI in men who have sex with men.[23] The primary lesion can take many forms and be confused with the lesions of other STIs (Table 153-3).

Clinical Features The painless primary chancre usually goes unnoticed and lasts only 2 to 3 days (**Figure 153-12**). Generally, 1 to 3 weeks after the appearance of the initial lesion, unilateral inguinal lymphadenopathy is noted (60% of cases) (**Figure 153-13**). Often the overlying skin has a purplish hue. The initial lesion progresses to suppurative



FIGURE 153-10. Painful, punched-out ulcer of chancroid. [Reproduced with permission from Fleischer AB Jr, Feldman SR, McConnell CF, et al: *Emergency Dermatology: A Rapid Treatment Guide*. © 2002, McGraw-Hill, Inc., New York.]



FIGURE 153-12. Lymphogranuloma venereum chancre. This ulceration was painless to the patient. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]



FIGURE 153-13. Lymphogranuloma venereum. Marked lymphadenopathy with small central eschar/ulcer. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

lymphadenopathy, resulting in either spontaneous abscess rupture or firm inguinal masses. Lymphogranuloma venereum proctitis (rectal ulcers, bleeding, and discharge) is also seen, primarily in homosexual men, and can be mistaken for inflammatory bowel disease. Scarring of these masses may cause linear depressions parallel to the inguinal ligament, forming the so-called *groove sign* (**Figure 153-14**). Lymphogranuloma venereum infections can cause fever, chills, arthralgias, erythema nodosum, or rarely meningoencephalitis. Lymphogranuloma venereum is easily confused with syphilis, chancroid, and HSV, and it also facilitates the transmission and acquisition of HIV.

Diagnosis **Diagnosis is based on clinical suspicion, epidemiologic data, and exclusion of other causes.** Chlamydia serologic testing for lymphogranuloma venereum is not standardized and not helpful except to support the diagnosis in the appropriate setting. Culture, direct immunofluorescence testing, and nucleic acid detection of a lesion swab or bubo aspirate are not widely available, nor is genotyping. Given these diagnostic constraints, patients with a clinical picture suggestive of lymphogranuloma venereum and epidemiologic information should simply be treated. The Centers for Disease Control and Prevention may be able to assist with testing.

Treatment Doxycycline for 21 days is the preferred regimen, with erythromycin base as an alternative (Table 153-2). Mild untreated cases resolve spontaneously in 8 to 12 weeks. Treat pregnant or lactating women with erythromycin or azithromycin. Refer partners with whom the individual has had sexual contact within the past 60 days for treatment. Sexual activity should be avoided until the full course of antibiotic treatment is completed and lymphadenopathy has resolved.[3]

GRANULOMA INGUINALE (DONOVANOSIS)

Granuloma inguinale, also called donovanosis, is caused by *Klebsiella granulomatis*, a gram-negative intracellular bacterium. The disease is rare in the United States but is endemic in India, the Caribbean, southern Africa, and central Australia.

Clinical Features After a variable incubation period of 2 weeks to 6 months, granuloma inguinale begins as subcutaneous nodules on the penis or vulva. The nodules then progress to the more classic painless, ulcerative lesions (**Figure 153-15**). These lesions are highly vascular, which explains both their beefy red appearance and their tendency to bleed easily on contact. Lymphadenopathy is not usually present, but subcutaneous granulomas may occur and mimic lymphadenopathy. Superinfection may complicate these open, bleeding lesions and obscure the diagnosis. Granuloma inguinale is not highly contagious, and multiple exposures are required to contract the disease. Autoinoculation can occur, leading to oral and GI tract involvement.

Diagnosis *K. granulomatis* is difficult to culture, and diagnosis often requires visualization of characteristic Donovan bodies on tissue biopsy.

Treatment Treatment of choice is azithromycin 1 gram PO weekly or 500 mg PO daily for at least 3 weeks and until all lesions have healed (Table 153-2). Doxycycline, ciprofloxacin, erythromycin base, and trimethoprim-sulfamethoxazole are alternatives for at least 3 weeks and until the lesions heal. Doxycycline, ciprofloxacin, and sulfonamides are contraindicated in pregnancy. Erythromycin base is the recommended treatment for pregnant or lactating women with the potential addition of a parenteral aminoglycoside. Individuals with whom the patient had sexual contact within 60 days of the appearance of the lesions should also be treated if symptomatic.[24]

HUMAN PAPILLOMAVIRUS INFECTION

Over 40 different genotypes of human papillomavirus (HPV) can infect the human genital tract. It is estimated that just under 25% of the U.S. population is currently infected with genital HPV.[25] As many as half of these infections are in adolescents and young adults, age 15 to 24 years.[25]



FIGURE 153-14. An example of the linear depression parallel to the inguinal ligament in lymphogranuloma venereum, the groove sign. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]

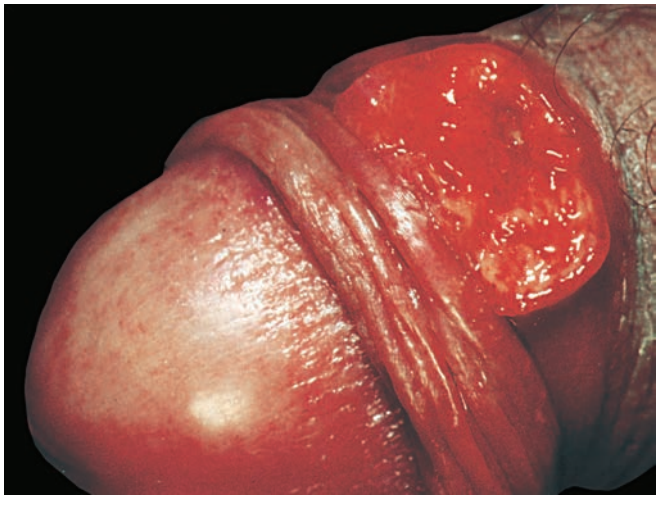


FIGURE 153-15. Granuloma inguinale in a male. The painless, ulcerative lesion is classically beefy red and bleeds easily. [Reproduced with permission from Goldsmith LA, Katz SI, Gilchrest BA, et al: *Fitzpatrick's Dermatology in General Medicine*, 8th ed. © 2012 by McGraw-Hill, Inc., New York.]



FIGURE 153-16. Condylomata acuminata in a 25-year-old male with a 3-month history of penile lesions. Multiple cauliflower floret–like papules are seen on the penile shaft and foreskin. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th ed. © 2009 by McGraw-Hill, Inc., New York.]

HPV infection is so common that most sexually active adults become infected at some point in their lives, and the majority of infections are asymptomatic. HPV infection is clinically important because oncogenic, high-risk subtypes of HPV (e.g., HPV types 16 and 18) cause most cases of cervical, vulvar, penile, anal, and oropharyngeal cancers.[26] Nononcogenic subtypes, such as HPV types 6 and 11, cause genital warts.

Several vaccines with activity against HPV have been developed, with a primary goal of preventing cancer. The bivalent vaccine (Cervarix®) works against oncogenic genotypes 16 and 18 only. The quadrivalent vaccine (Gardasil®) works against genotypes 16 and 18 as well as genotypes 6 and 11 associated with genital warts. A 9-valent vaccine (Gardasil-9®) protects against infection with genotypes 16, 18, 6, and 11, as well as five additional types associated with cervical cancer.[3] A two-dose vaccine series is recommended for girls and boys who initiate the vaccination series between ages 9 and 14. Three vaccine doses are recommended for those who began the series between ages 15 and 26 and immunocompromised individuals.[27]

Clinical Features The majority of cases of HPV infection are asymptomatic, and most people clear serologic evidence of HPV spontaneously. Infection with subtypes leading to genital warts may prompt patients to seek care. Genital warts are flesh-colored papules or cauliflower-like projections that usually appear after an incubation period of 1 to 8 months and may coalesce to form condylomata acuminata (**Figure 153-16**). In women, they are seen on the external genitalia (**Figure 153-17**) and in the perianal region. Genital warts are usually painless, but depending on their anatomic location, they can be friable, painful, or pruritic and often enlarge during pregnancy. Infected males often complain of nonhealing penile lesions, occasionally with pruritus and urethral discharge. Perianal condylomata have been seen in up to 80% of women with vulvar condylomata and are seen frequently in homosexual males.

Diagnosis Diagnosis is clinical.

Treatment Many topical treatments for genital warts exist that can be used for days to weeks, but these are not usually initiated in the ED. Treatment decisions are based on the size and number of lesions, the amount of discomfort they are causing, and patient preferences. The treatment of external genital warts may help reduce viral load but is not a cure. All treatment options are considered equally effective and chosen based on the discretion of the patient and provider.

Patients with HPV infections rarely require emergent management. However, counseling in the ED regarding this distressing condition is relatively common. It is important to emphasize that it is common for sexually active people to have HPV at some point in their lives, and most people clear the infection spontaneously. Condoms are protective with HPV, but they are not preventive, and the only way to decrease exposure is to limit the number of sexual partners. It is an incorrect assumption that having HPV indicates an oncogenic certainty or a change in fertility.

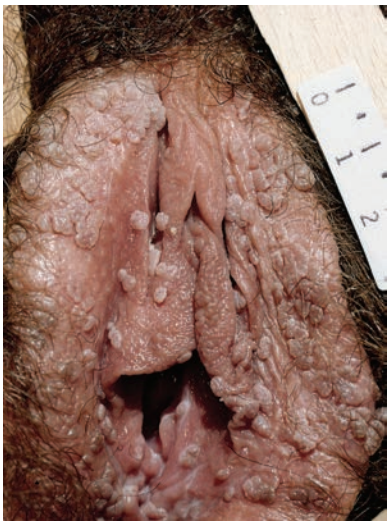


FIGURE 13-17. Condylomata acuminata of the vulva. Multiple pink-brown, soft papules are seen on the labia. [Reproduced with permission from Wolff K, Johnson RA, Saavedra AO: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 7th ed. © 2013 by McGraw-Hill, Inc., New York.]

VIRAL SEXUALLY TRANSMITTED INFECTION TRANSMISSION

Numerous viral infections may be transmitted sexually, including HIV, hepatitis B, herpes simplex virus and HPV (discussed earlier), molluscum contagiosum, and Zika virus.

HUMAN IMMUNODEFICIENCY VIRUS

HIV is an RNA retrovirus in the Retroviridae family. HIV infection involves a spectrum of illness, from asymptomatic individuals to those with profound immunosuppression resulting in a wide array of opportunistic infections and clinical development of AIDS. The World Health Organization estimates that as of 2016, 36 million people are infected with HIV.[28] Sex with an infected partner is the most common method of transmission of HIV worldwide, but the virus may also be spread parenterally and vertically from mother to child during birth or breastfeeding. In the United States, male-to-male sexual contact is the most common method of transmission, accounting for 78% of new infections, although the incidence of infection in women is rising.[29] In sub-Saharan Africa, where the burden of HIV infection is highest worldwide, heterosexual transmission accounts for most new cases, and mother-to-child transmission remains a significant problem.[30]

Acute HIV infection, also called acute retroviral syndrome, causes a mononucleosis-like illness with fever, malaise, headache, sore throat, and sometimes rash and lymphadenopathy. Due to the nonspecific symptoms that resemble many other viral infections, HIV is not usually diagnosed in the acute phase of infection, and affected individuals are unaware of their HIV status. This has important public health implications, because the acute infection is when viral shedding and transmissibility is highest. Epidemiologic studies suggest that up to half of all cases of HIV were contracted from persons with acute HIV infection who likely did not know they carried the virus.[31] The clinical manifestations, diagnosis, and treatment of HIV are discussed in detail in Chapter 155, "Human Immunodeficiency Virus Infections."

HEPATITIS B

The hepatitis B virus may be transmitted sexually, parenterally by blood transfusion or contaminated needles, or vertically from mother to child. Acute hepatitis B may produce acute symptoms, causing a hepatitis-like picture with malaise, nausea, vomiting, fever, abdominal pain, and jaundice. Chronic infection develops in 6% to 10% of patients who contract hepatitis B as adults, but a much higher percentage of patients who become infected as children go on to develop chronic hepatitis,

underscoring the importance of vaccination of infants and women of childbearing age.[32] Hepatitis is discussed in detail in Chapter 80, "Hepatic Disorders."

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a viral skin infection that is common in healthy children and may also be seen in immunosuppressed individuals, especially those with HIV. Molluscum is caused by poxvirus variants molluscum contagiosum virus 1 to 4. It is spread by direct skin-to-skin contact or by contact with an object, such as a towel, which has virus on it. When molluscum is seen in teenagers and adults, it is often due to sexual contact with exposure to lesions in the genital area.[33] Molluscum lesions in the genital area in children may be due to sexual abuse but may also be from autoinoculation.[34]

Molluscum appears as skin-colored, pearly, umbilicated papules, which may be scattered or in clusters (Figure 251-24). Immunosuppressed individuals may have extensive involvement. Molluscum contagiosum is discussed in detail in Chapter 251, "Skin Disorders: Trunk."

ZIKA VIRUS

The Zika virus garnered international attention in 2015 due to outbreaks in South and Central America, the Caribbean, Mexico, and the United States that were associated with severe birth defects. Zika is contracted through the bite of the *Aedes aegypti* mosquito but has subsequently been demonstrated to be transmitted sexually and parenterally.[35]

After an incubation period of 2 to 14 days, symptoms may include headache, fever, malaise, maculopapular rash, and conjunctivitis. While infection tends to be mild and self-limited, a major concern surrounding Zika is potential for teratogenicity when pregnant women acquire the virus. Zika infection in pregnancy is associated with CNS abnormalities such as microcephaly, seizures, clubfoot, and arthrogryposis. Prevention efforts focus on avoiding mosquito bites with use of mosquito repellent and mosquito netting, avoiding travel to Zika-infested areas when pregnant, and avoiding unprotected sexual intercourse with individuals who have traveled to Zika-infested areas. Zika is discussed in Chapter 151, "Sepsis."

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 154

Serious Viral Infections

Sukhjit S. Takhar
Greg Moran

INTRODUCTION

Viral infections are among the most common illnesses encountered in the ED. Although many are self-limited, some are life-threatening, have specific treatments, or have public health implications. We review serious viral infections that cause disseminated illness, viruses with a predilection for the neurologic system, and new viral threats.

INFLUENZA

Human influenza infection comes from a large, single-stranded RNA virus in the orthomyxovirus family. Influenza A and influenza B cause most human infections, with influenza A typically being more serious.

EPIDEMIOLOGY

Influenza is highly infectious and transmitted via aerosolized respiratory secretions, large droplets, or fomites. Seasonal influenza has varying severity, typically peaking in the winter months of temperate climates. Seasonal disease causes 250,000 to 500,000 annual deaths worldwide and between 5000 and 50,000 deaths in the United States. Outbreaks spread quickly throughout a community, largely among school-age children. Mortality occurs mostly among the elderly and young infants.

Influenza viruses undergo minor variations (antigenic drift) in their surface antigens that allow the virus to reinfect individuals and reemerge each winter. Occasionally, there are major antigenic changes that increase population susceptibility and lead to a pandemic. The 1918 influenza pandemic killed between 50 million and 100 million people worldwide; the potential for a recurrence with devastation from a novel influenza virus understandably drives anxiety among clinicians and public health personnel. Mortality during pandemics occurs more frequently among healthy adults compared to seasonal influenza, when the infirm and those at the extremes of age are more likely to die. In 2009, a pandemic H1N1 strain emerged in Mexico and followed this pandemic pattern. Highly pathogenic avian strains of influenza emerged from China, including the H5N1 strain in 1997 and, more recently, the H7N9 strain in 2013.

PATHOPHYSIOLOGY

Influenza is transmitted usually by sneezing or coughing and via touching hands. The incubation period is typically 1 to 4 days. Viral replication in upper and lower respiratory tract epithelium leads to cell damage and respiratory symptoms. Most infections resolve within about a week, but viral pneumonia is one of the more common complications that can result in alveolar damage and hypoxemia.

CLINICAL FEATURES

Patients with influenza typically present with an abrupt onset of fever and respiratory symptoms. Most cases are self-limited; however, some patients, particularly the elderly, the very young, and those with comorbid conditions, require hospitalization or die from complications of influenza. Additionally, influenza can lead to exacerbations of chronic medical conditions, such as congestive heart failure or chronic obstructive lung disease. Delirium is common in the elderly.

Pneumonia complicates some influenza infections. Primary influenza pneumonia develops quickly and can progress to acute respiratory distress syndrome, often within 24 hours. Bacterial superinfections also occur. Classically, secondary *Staphylococcus aureus* pneumonia, including community-acquired methicillin-resistant *S. aureus,* can follow influenza infection.

DIAGNOSIS

Most cases of influenza are diagnosed clinically when a patient presents with fever, aches, and cough with influenza virus circulating in the community. However, clinical features of influenza overlap with other respiratory infections; laboratory confirmation can occasionally be helpful with patient care and infection control, especially before influenza emergence is clear.

Rapid antigen assays identify the surface proteins in influenza A and B. These tests are simple to perform and give results within 15 minutes. However, they often have low sensitivity, with ranges between 10% and 80% reported in clinical use. Specificity of these tests is between 90% and 95%, so a positive test indicates high likelihood of influenza during an outbreak.

Molecular diagnostic tests, such as polymerase chain reaction for nucleic acids, are more sensitive and specific than antigen tests. These tests are best used in patients hospitalized with suspected influenza.[1] Several nucleic acid–based tests can return results within the time frame of an ED visit, although they are more costly than rapid antigen tests.

TREATMENT

The majority of patients will have a self-limited, uncomplicated illness requiring only symptomatic care. Patients with more severe influenza may benefit from IV fluids, respiratory support, and occasionally

TABLE 154-1 Risk Factors for Severe Influenza[4]

- Children younger than age 2 y
- Adults age 65 y and older
- Comorbid conditions
- Immunosuppression
- Pregnancy
- Patients younger than 19 y receiving long-term aspirin
- American Indians/Alaskan natives
- Morbid obesity
- Residents of nursing homes and long-term care facilities

vasopressors (if signs of shock exist). Treat patients with pneumonia with antibiotics, targeting methicillin-resistant *S. aureus* if severe pneumonia exists. Extracorporeal membrane oxygenation aids those with severe cardiorespiratory dysfunction, especially in pandemic settings when younger patients are afflicted.

Neuraminidase inhibitors have limited roles in otherwise healthy adults and children[2]; the Centers for Disease Control and Prevention recommends treating higher-risk populations. In the non–higher-risk population (i.e., relatively healthy patients outside extremes of age), a modest symptoms benefit exists if the patient starts therapy within 48 hours of symptom onset. Antiviral treatment may benefit patients hospitalized with influenza or bacterial complications of influenza even if started after 48 hours of illness. Consider empiric antiviral treatment for patients with severe or progressive illness and those with higher risk of complications (**Table 154-1**).

The Centers for Disease Control and Prevention posts updates regarding influenza treatment, which can be helpful for clinicians (http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

Oseltamivir is the most widely used neuraminidase inhibitor (75 milligrams twice daily for 5 days), with longer treatment for critically ill patients. For chemoprophylaxis, the dose is 75 mg once a day for 1-2 weeks. Peramivir is an IV neuraminidase inhibitor for those unable to tolerate oral oseltamivir. Baloxavir is an endonuclease inhibitor approved for those 12 years and older. It is given as a single PO dose, 40 milligrams for those 40-80 kg, and 80 milligrams for those > 80 kg. It is not approved for chemoprophylaxis.[3]

HERPES SIMPLEX VIRUS INFECTIONS

Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are related double-stranded DNA viruses that cause oral and genital infections; rarely, these result in devastating CNS disease. **Herpes simplex infections are treatable with antiviral drugs, making early recognition of serious infection important**.

EPIDEMIOLOGY

HSV is common throughout the world. HSV-1 is usually acquired during childhood through nonsexual contact; HSV-2 is almost always sexually transmitted (see Chapter 153, "Sexually Transmitted Diseases"). HSV-1 seroprevalence varies by socioeconomic status, age, and geographic location. More than 50% of the U.S. population is seropositive for HSV-1, and 15.7% is seropositive for HSV-2.[5] HSV-1 is one of the most common viral causes of encephalitis in the United States. It occurs most commonly in patients <20 and >50 years of age.[6] The mortality rate for untreated disease is >70%.

Neonates with HSV infection have a high frequency of both visceral involvement and CNS disease. Encephalitis in neonates is acquired from the maternal genital tract at the time of delivery. The risk is highest when the mother acquires the infection in the third trimester.

PATHOPHYSIOLOGY

HSV infections are transmitted through contact with persons with ulcerative lesions or by those who are shedding the virus by the exchange of saliva, vesicle fluid, semen, and cervical fluid. The virus must come in contact with a mucosal surface or abraded skin, where it replicates and causes localized symptoms before becoming latent in the sensory ganglia. HSV-1 typically resides in the trigeminal ganglia, and HSV-2 is found in the sacral ganglia. Reactivated virus travels to the cutaneous surface and results in localized vesicular eruptions (**Figure 154-1**).

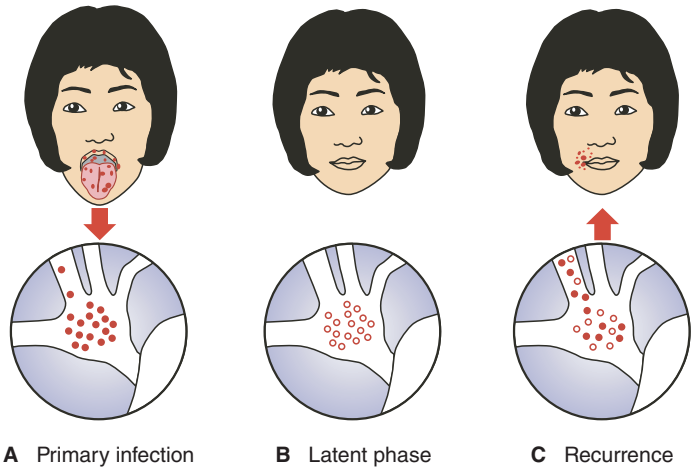


FIGURE 154-1. Herpes simplex virus infection, latency, and recurrence. **A.** Primary infection. **B.** Latent phase. **C.** Recurrence. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th ed., © 2009 by McGraw-Hill, Inc., New York.]

In herpes simplex encephalitis, experts postulate the virus gains access to the brain by the olfactory or the trigeminal nerve, with a predilection for the medial and inferior temporal lobes of the brain.

Most healthy hosts are able to control the virus and limit its replication to mucosal surfaces. Rarely during primary infection, the virus can spread beyond the local dorsal root ganglia and cause more widespread involvement. Multiorgan disease is much more common in the immunosuppressed and in neonates.

CLINICAL FEATURES

HSV infections occur year-round. Symptoms of HSV depend on multiple factors, including the anatomic site involved, the immune status of the host, virus type, and whether the infection is primary or recurrent. Most HSV infections are subclinical. Symptomatic HSV-1 infection most commonly results in recurrent orolabial lesions, whereas HSV-2 is most often implicated in genital herpes. Primary infections typically produce more extensive lesions involving mucosal and extramucosal sites, often accompanied by systemic signs and symptoms. Gingivostomatitis and pharyngitis are typical manifestations of primary HSV-1 infection (**Figure 154-2**), and recurrence presents as herpes labialis (**Figure 154-3**). Less common skin manifestations include herpetic whitlow and herpes gladiatorum (skin). For additional discussion, see Chapter 250, "Skin Disorders: Face and Scalp," and Chapter 253, "Skin Disorders: Extremities."

Eczema herpeticum (see Figure 251-14) can occur in patients with atopic dermatitis. **Bell's palsy** may result from latent HSV-1 in the geniculate ganglia (see Chapter 172, "Acute Peripheral Neurologic Disorders"). Herpetic keratitis presents as a painful, red eye and can be identified by characteristic dendritic lesions on fluorescein slit lamp exam. See Chapter 241, "Eye Emergencies," for further discussion. HSV-1 and HSV-2 can cause identical genital lesions. Genital HSV-2 is more common and has a higher relapse rate, but the proportion of genital disease caused by HSV-1 is increasing.[5] Primary genital infections can present with aseptic meningitis, which is a complication more common in women.

The hallmark of HSV encephalitis is acute onset of fever and neurologic symptoms. Patients can present with hemiparesis, cranial nerve abnormalities, ataxia, focal seizures, and altered mental status or behavioral abnormalities. It can be difficult to distinguish HSV encephalitis from other types of meningoencephalitis. Meningitis occurs in up to 25% of females with primary HSV-2 infections. HSV-2 meningitis, unlike encephalitis, has a benign course, and patients recover uneventfully, although many patients have recurrent episodes.

HSV infections in immunocompromised hosts can lead to widespread dissemination with multiorgan involvement (**Figure 154-4**).

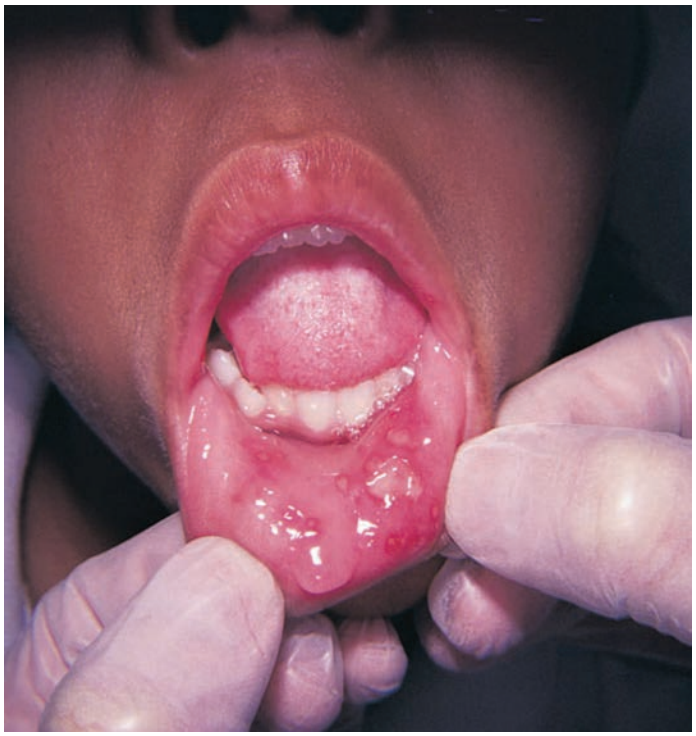


FIGURE 154-2. Primary herpetic gingivostomatitis. Typical lesions of herpes gingivostomatitis on the buccal mucosa. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine*, © 2006 by McGraw-Hill, Inc., New York.]



FIGURE 154-4. Disseminated herpes simplex in an immunocompromised host. The rash of disseminated herpes simplex begins as vesicular lesions on an erythematous base, which may umbilicate and may blister and crust over as seen here. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed., © 2005 by McGraw-Hill, Inc., New York.]

Organ transplant patients may develop esophagitis, hepatitis, colitis, and pneumonia (see Chapter 297, "The Transplant Patient"). Severely burned patients are also prone to potentially fatal disease. HSV infections can also cause immune-mediated manifestations such as erythema multiforme, hemolytic anemia, and thrombocytopenia.

DIAGNOSIS

The preferred diagnostic test for confirmation of suspected HSV infection depends on the presentation. Because mucocutaneous infection

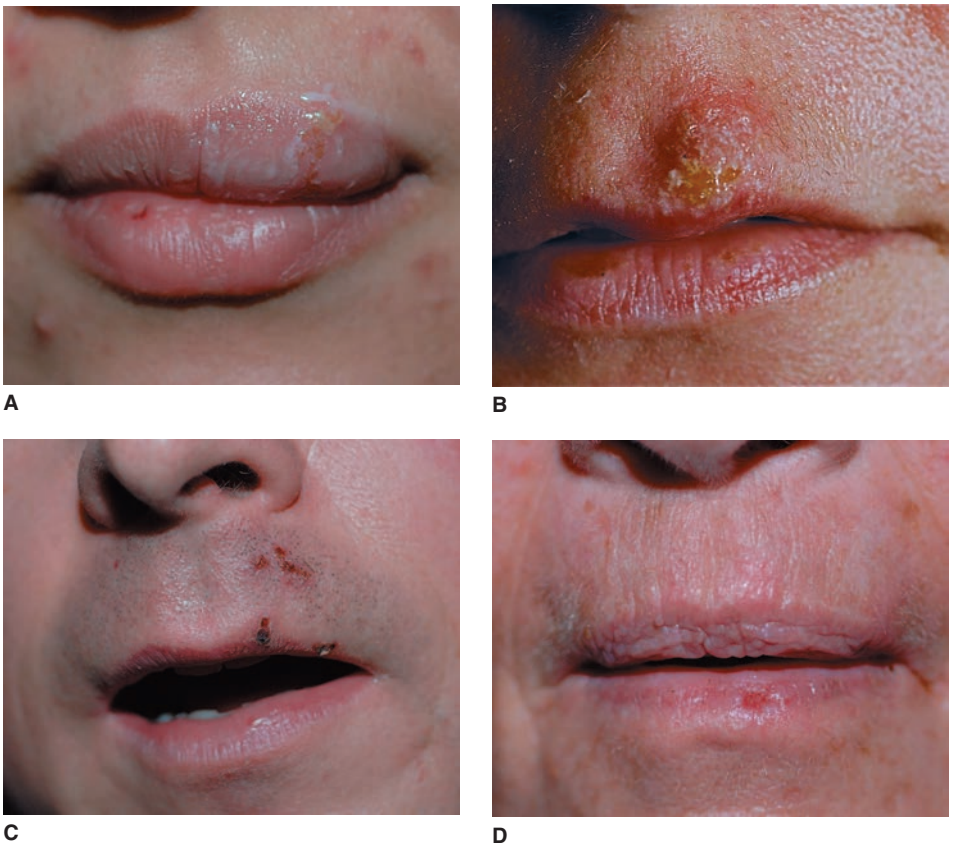
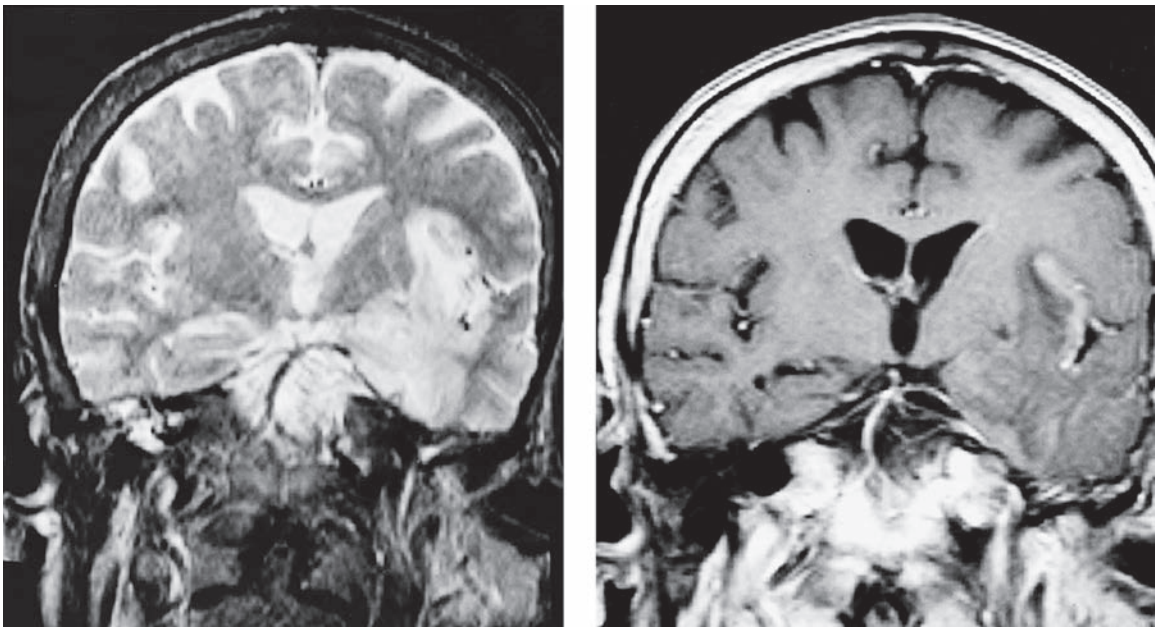


FIGURE 154-3. A through D. Herpes labialis. Typical vesicular lesions of the upper and lower lip. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th ed., © 2009 by McGraw-Hill, Inc., New York.]



A B

FIGURE 154-5. MRI scans showing hyperintensity involving the left temporal lobe and insular cortex in herpes simplex encephalitis. **A.** T2-weighted coronal MRI scan in the axial plane, taken during the acute stage of the illness. There is increased signal from practically all of the inferior and deep temporal lobe and the insular cortex. **B.** T1-weighted image after gadolinium infusion showing enhancement of the left insular and temporal cortices and early involvement of the right temporal lobe. [Reproduced with permission from Ropper AH, Samuels MA: *Adams and Victor's Principles of Neurology*, 9th ed., © 2009 by McGraw-Hill Inc., New York.]

is lifelong, most recommend laboratory confirmation of the clinical diagnosis of primary HSV infection. Viral culture from the fluid of an unroofed vesicle is traditionally the reference criterion for diagnosis. However, polymerase chain reaction testing or a direct fluorescent antibody test have higher sensitivity. A Tzanck smear is not useful.

Identification of temporal lobe lesions on CT scan or MRI is strongly suggestive of HSV encephalitis (**Figure 154-5**). An electroencephalogram shows typical intermittent, high-amplitude slow waves localized to the temporal lobes.

Cerebrospinal fluid analysis typically shows a lymphocytic pleocytosis with the presence of red blood cells. However, some patients have normal cerebrospinal fluid parameters. Polymerase chain reaction testing of the cerebrospinal fluid is the testing modality of choice for HSV meningoencephalitis, with high sensitivity and specificity.[6] Detectable viral DNA in the cerebrospinal fluid occurs within the first 24 hours, and results remain positive for a week or longer. Multiplex polymerase chain reaction panels are available to test cerebrospinal fluid for HSV and other viral, bacterial, and fungal pathogens.

TREATMENT

Treatment depends on the severity of the disease and the immune status of the patient (see Chapter 153, "Sexually Transmitted Diseases"). IV acyclovir is the drug of choice in patients with HSV encephalitis or disseminated disease and in immunocompromised patients with severe mucocutaneous disease (**Table 154-2**). Valacyclovir is a prodrug of acyclovir with less frequent dosing.

Even with early treatment, patients with HSV encephalitis have a high mortality. Without treatment, mortality is >70%. Survivors are often left with long-term neurologic sequelae. Independent predictors of a poor outcome for patients with HSV encephalitis include a Glasgow Coma Scale score of ≤6, focal CNS lesions on CT scan, increased patient age, and start of antiviral therapy >4 days after onset of symptoms.[6] **Because altered mental status and focal neurologic abnormalities are key features of encephalitis and because it can be clinically difficult to distinguish meningitis from encephalitis, consider adding acyclovir to empiric antibiotic therapy in patients with these neurologic findings when the diagnosis of acute bacterial meningitis is also being considered.**[7]

Healthy patients with primary HSV-1 or HSV-2 infections can be treated with oral acyclovir, valacyclovir, or famciclovir for 7 to 10 days. Recurrent herpes labialis usually does not require treatment. Those with severe or frequent recurrences may benefit from daily suppressive therapy.

VARICELLA AND HERPES ZOSTER

Varicella-zoster virus is the causative organism of both varicella (chickenpox) and herpes zoster (shingles). It is extremely contagious; prior to routine vaccination, it was usually acquired in childhood.

Varicella occurs year-round, but there is a higher incidence during winter and spring months. The infection rate ranges from 60% to 100% in exposed individuals. The introduction of the varicella vaccine to routine childhood immunizations in 1995 has dramatically reduced the clinical burden of the virus.[8]

Herpes zoster can occur once immune response against the virus wanes, usually with advancing age. Over 90% of adults have serologic evidence of varicella-zoster virus infection, and unvaccinated persons

TABLE 154-2 Antiviral Treatment of Severe Herpes Simplex Virus (HSV) Infection

Infection	Drug	Dosage	Duration
Mucocutaneous HSV infections in immunocompromised patients	Acyclovir	5 milligrams/kg IV every 8 h	7–14 d
	Valacyclovir	500 milligrams–1 gram PO twice per day	
	Famciclovir	500 milligrams PO twice per day	
Herpes simplex encephalitis	Acyclovir	10–15 milligrams/kg IV every 8 h	14–21 d
Neonatal herpes simplex	Acyclovir	10–20 milligrams/kg IV every 8 h	14–21 d
Visceral herpes simplex disease	Acyclovir	10–15 milligrams/kg IV every 8 h	14–21 d

who live to 85 years of age have a 50% risk of herpes zoster.[9] Iatrogenic immune suppression, certain diseases such as lymphoproliferative disorders, human immunodeficiency virus infection, and organ transplantation increase the risk of herpes zoster.

Vaccines are available to prevent both chickenpox and herpes zoster, although neither is 100% effective. Encourage parents to vaccinate their children, and remind those age 50 years or older about the availability of a vaccine to prevent herpes zoster. Varicella-zoster immune globulin is available, but its use is generally limited to postexposure prophylaxis for nonimmune pregnant women and the severely immunosuppressed. Healthy individuals who are not immune can be vaccinated after exposure. Watch varicella-zoster virus–exposed individuals and give antivirals to high-risk patients if they develop symptoms.[10]

PATHOPHYSIOLOGY

Varicella-zoster virus spreads to the respiratory mucosa of a susceptible host via aerosolized droplets of respiratory secretions of patients with chickenpox. It can also spread from direct contact with vesicle fluid in herpes zoster but is not as highly contagious in this situation. The virus multiplies in regional lymph nodes and then disseminates to the nasopharyngeal surfaces and the skin, causing the characteristic rash. It is contagious until all the lesions have crusted over. VZV remains latent in the dorsal root ganglion and can later reactivate along dermatomes, resulting in shingles (**Figure 154-6**).

VARICELLA CLINICAL FEATURES

Varicella (chickenpox) is a febrile illness with a vesicular rash. Often it is associated with nonspecific symptoms of headache, malaise, and loss of appetite. The rash is superficial and appears in crops, so patients typically have lesions at varying stages, including papules, vesicles, and crusted lesions (**Figure 154-7**). Lesions are concentrated more on the torso and face and typically crust and slough off after 1 to 2 weeks. Most infections are minor and self-limited. Immunized patients can occasionally develop mild chickenpox.

A range of complications can occur, more often in those at extremes of age or the immunocompromised. Bacterial superinfections of skin lesions, most often with group A streptococci, can cause serious illness including necrotizing fasciitis. Children with lymphoma and leukemia may develop progressive varicella in which vesicles continue to erupt into the second week of illness, sometimes with visceral involvement of the lung, liver, and brain. CNS complications such as cerebellar ataxia, meningitis, meningoencephalitis, and vasculopathy are well described. **Pneumonitis can be severe and is more common in pregnant women.**[8]

HERPES ZOSTER CLINICAL FEATURES

Herpes zoster (shingles) often begins with a prodrome of malaise, headache, and photophobia. The patient notes pain, itching, and paresthesias in one or more dermatomes. These symptoms are followed by the development of a maculopapular rash that becomes vesicular. The



FIGURE 154-7. Rash of primary varicella (chickenpox), demonstrating lesions of multiple stages, including papules, vesicles, and crusted lesions. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology,* 6th ed., © 2009 by McGraw-Hill, Inc., New York.]

eruption does not cross the midline (**Figure 154-8**). Most commonly, herpes zoster affects the chest or face, but it can affect any dermatomal level. Herpes zoster ophthalmicus can cause corneal damage and is the result of reactivation along the ophthalmic distribution of the trigeminal nerve (see Chapter 241, "Eye Emergencies"). The seventh cranial nerve involvement can trigger facial nerve paralysis and lesions along the auditory canal (herpes zoster oticus). Postherpetic neuralgia, pain that persists for >30 days, is a feared complication. The incidence increases with advancing age, and pain may last months or years.

Dissemination of varicella-zoster virus can occur in immunocompromised patients. **Herpes zoster involving more than three dermatomes is often a clue to an immunodeficient condition. The presence of herpes zoster in a young, healthy person may be a sign of human immunodeficiency virus infection**. In many cases of disseminated disease, the skin is the only involved structure. However, the virus may spread to the visceral organs and cause pneumonitis, hepatitis, and encephalitis.

DIAGNOSIS

Varicella-zoster virus infections have a characteristic appearance, so a clinical diagnosis is sufficient in most cases. Look for the characteristic rash of chickenpox, which involves vesicles in crops at different stages of development. Herpes zoster diagnosis is clear when clusters of vesicles and papules appear in a dermatomal pattern.

Laboratory diagnosis aids in patients with atypical illness or severe disease. This is accomplished through viral culture, antigen testing, or polymerase chain reaction testing of vesicle fluid. Although smallpox has been eradicated, it remains a potential threat as a biologic weapon,

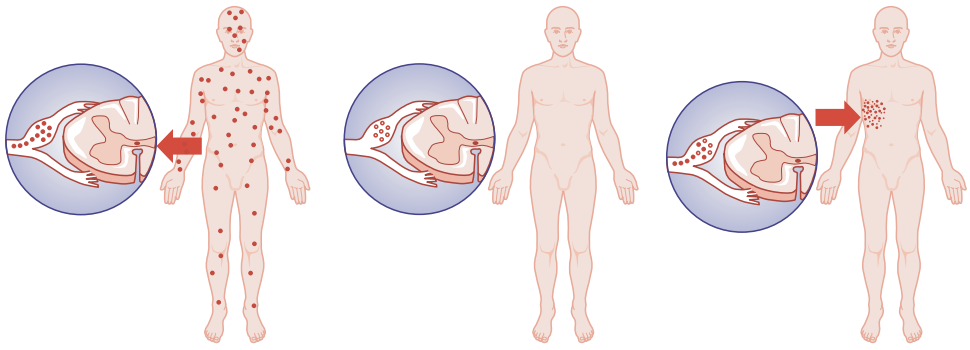


FIGURE 154-6. Primary infection, latency, and reactivation of varicella-zoster virus. **A.** Generalized distribution of primary varicella with infection of sensory ganglia. **B.** Latent phase with persistence in ganglia. **C.** Reactivation phase with descent to sensory nerves and skin involvement. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology,* 6th ed., © 2009 by McGraw-Hill, Inc., New York.]



FIGURE 154-8. Dermatome distribution of the classic rash of herpes zoster (shingles).

and the lesions could be confused with those of varicella. The lesions of smallpox are larger and distributed more on the extremities, and all lesions are at the same stage of development.

Obtain a chest radiograph if there are any breathing symptoms to assess for pneumonitis. An MRI of the brain, lumbar puncture, and polymerase chain reaction cerebrospinal fluid testing for varicella-zoster virus are appropriate for suspected neurologic involvement.

VARICELLA TREATMENT

Most healthy patients need only supportive care for chickenpox. Acyclovir and similar antiviral agents decrease the number of lesions and shorten the course of therapy if started within 24 hours of rash onset. However, the impact of treatment is modest, so it is not routinely recommended for those who are otherwise healthy. Secondary skin infections are typically caused by group A streptococci and can be treated with a first-generation cephalosporin.

Consider acyclovir for those at higher risk for complications, including adults and children >12 years of age, patients with chronic skin or pulmonary disorders, those receiving long-term salicylate therapy, and immunocompromised patients. Varicella-zoster virus is less sensitive to antiviral medications than herpesvirus and requires higher and more frequent dosing.

HERPES ZOSTER TREATMENT

Antiviral agents hasten lesion resolution, reduce new lesions, reduce viral shedding, and decrease acute pain, but **do not reduce the severity of postherpetic neuralgia.**[9] Using antiviral therapy in immunocompromised patients may reduce the risk of severe disseminated disease. **Start antiviral medication within 72 hours of the onset of rash, and consider treatment at >72 hours if new vesicles are still present or developing. Treat immunocompromised patients regardless of the time since rash onset.** Benefits are more pronounced in patients >50 years of age. Therapy is well tolerated, and adverse events are infrequent.

Treat those with disseminated herpes zoster, those with CNS involvement, and severely immunosuppressed patients with herpes zoster with IV acyclovir. Use valacyclovir in those with herpes zoster ophthalmicus, along with ophthalmologist consultation (see Chapter 241, "Eye Emergencies").

Herpes zoster can be extremely painful and require opioid analgesia. Corticosteroids in combination with antivirals may provide a modest decrease in acute pain, but do not decrease the development of postherpetic neuralgia.[9] **Adjunctive corticosteroids can be considered in older individuals with severe pain who do not have contraindications to their use.**

EPSTEIN-BARR VIRUS INFECTION

Epstein-Barr virus is implicated in a variety of human illnesses. It is the causative agent of heterophile-positive infectious mononucleosis. Epstein-Barr virus infection is also associated with cancers such as B-cell lymphoma, Hodgkin's disease, Burkitt's lymphoma, and nasopharyngeal carcinoma.

There are two age-related peaks of infection: early childhood and young adulthood. In developing countries, Epstein-Barr virus infection is widespread in early childhood and is often asymptomatic. College students and military recruits experience the highest morbidity. Epstein-Barr virus requires close contact for transmission. The infection is usually contracted from an asymptomatic individual who sheds the virus.

PATHOPHYSIOLOGY

Epstein-Barr virus is transmitted via salivary secretions. After infecting the oropharyngeal epithelium, it disseminates through the bloodstream. The virus infects B lymphocytes and causes an increase in T lymphocytes, which results in enlargement of lymphoid tissue. In immunocompromised patients with decreased T-cell function, the B cells continue to proliferate, and proliferation may lead to neoplastic transformation.

CLINICAL FEATURES

The manifestations of Epstein-Barr virus infection depend on age and immune status. Infections in infants and young children are often asymptomatic or have mild pharyngitis. Teenagers and young adults can develop infectious mononucleosis, which presents as fever, lymphadenopathy, and pharyngitis. Tonsillar exudates are frequent and often extensive and may be necrotic appearing (**Figure 154-9**). Splenomegaly occurs in more than half of patients. Symptoms generally resolve over 2 to 3 weeks, and most patients recover uneventfully. Severe fatigue is a prominent feature and can persist for months. **Patients treated with ampicillin or amoxicillin for suspected streptococcal pharyngitis often develop a nonallergic morbilliform rash if they have infection with Epstein-Barr virus.**

Epstein-Barr virus can affect nearly all organ systems. Neurologic complications such as encephalitis, meningitis, and Guillain-Barré syndrome have been described. Hepatitis, myocarditis, and hematologic disorders are also known complications. Rarely, death results from splenic rupture, CNS complications, and airway obstruction.

DIAGNOSIS

If suspecting infectious mononucleosis based on the history and physical examination, a CBC and a monospot test aid in diagnosis. Typically, there is lymphocytosis with >50% lymphocytes, and atypical lymphocytes are found on examination of the smear. These are reactive cytotoxic T cells that can also be found in other illnesses, including cytomegalovirus infection, human immunodeficiency virus infection, and viral hepatitis. The monospot test identifies heterophile antibodies that agglutinate animal erythrocytes, and a positive result is considered

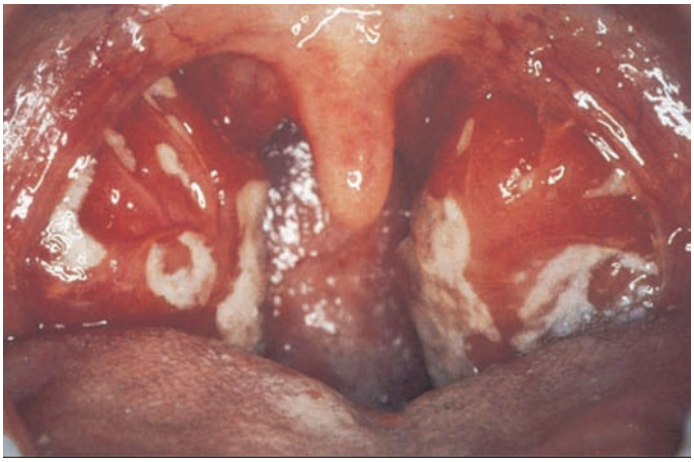


FIGURE 154-9. Classic findings of tonsillopharyngitis associated with infectious mononucleosis caused by Epstein-Barr virus. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine,* © 2006 by McGraw-Hill, Inc., New York.]

diagnostic of Epstein-Barr virus infection in the right clinical setting. The monospot test result may be negative early in the course of disease (first days), requiring a second test later if unclear. The sensitivity of the test is also decreased in infants and the elderly. Testing is particularly important in pregnant patients, because some other causes of heterophile-negative mononucleosis, such as toxoplasmosis and cytomegalovirus, can be teratogenic.

TREATMENT

Rest and analgesia are the mainstays of therapy, with most cases being self-limited and not requiring specific therapy. **Corticosteroid use may increase complications and is recommended only for patients with severe disease, such as upper airway obstruction, neurologic disease, or hemolytic anemia**. Acyclovir is active against Epstein-Barr virus, but is thought to be effective only for oral hairy leukoplakia associated with human immunodeficiency virus infection. **Advise patients to avoid all contact sports for a minimum of 3 weeks after illness onset to avoid splenic injury.**[11]

CYTOMEGALOVIRUS INFECTION

Cytomegalovirus causes a wide variety of diseases, ranging from asymptomatic infections in most to life-threatening pneumonia in transplant patients. Like other herpesviruses, it causes a primary infection and then recedes into lifelong latency.

Cytomegalovirus is not highly contagious, and transmission requires repeated or prolonged exposure. The virus is spread by sexual contact, saliva, breastfeeding, and transplantation, as well as transplacentally and through blood transfusion. Seroprevalence rates approach 100% in Africa and in some Asian countries. In the developed world, it is not unusual for older individuals to acquire a primary infection. This is of particular concern in women of childbearing age because of teratogenic effects. The risk of fetal cytomegalovirus infection is highest in the first trimester of pregnancy in a previously seronegative mother who acquires a primary infection.

Organ transplant patients can acquire infection, most often between 1 and 4 months after transplant. The risk is highest when a seronegative patient receives a cytomegalovirus-positive organ.

PATHOPHYSIOLOGY

Cytomegalovirus is usually inoculated on the mucosal surface of the upper respiratory or genital tract, where the virus multiplies and then disseminates. Most infections are only mildly symptomatic. Primary disease in late adolescence and adulthood results in an infectious mononucleosis syndrome. The virus remains latent in most individuals unless immunity is suppressed.

CLINICAL FEATURES

Primary infection in healthy individuals is usually asymptomatic. Cytomegalovirus can cause a heterophile-negative infectious mononucleosis syndrome, characterized by prolonged fever, myalgias, and atypical lymphocytosis, but no exudative pharyngitis, and mild lymphadenopathy. Severe disease in the otherwise healthy host includes hepatitis, colitis, Guillain-Barré syndrome, encephalitis, and hemolytic anemia.[12]

Congenital and neonatal infections have some of the most important complications of primary cytomegalovirus infection. Symptoms in infants can be devastating and include hepatosplenomegaly, jaundice, microcephaly, petechiae, and growth retardation. Severe infections carry a high mortality, and those who survive often have neurologic sequelae.

Infections in immunocompromised patients can be severe and involve any organ. Infection can be primary or the result of reactivation of latent virus. Severe disease can develop in previously healthy cytomegalovirus-seropositive individuals with an abnormal T-cell response during critical illness. Infections after solid-organ and hematopoietic stem cell transplantation are a leading cause of morbidity (see Chapter 297, "The Transplant Patient").[13] In human immunodeficiency virus–infected patients with CD4 counts of <50 cells/mm^3, retinitis is the most common manifestation of infection, causing painless loss of vision. Other manifestations associated with human immunodeficiency virus infection include encephalopathy, colitis, and peripheral polyradiculopathy.

DIAGNOSIS

A specific diagnosis is usually not made in the ED. Body fluids such as urine, saliva, blood, tears, semen, and vaginal fluid are antigen, polymerase chain reaction, and antibody tested, and tissue is examined or cultured for diagnosis. The hallmark of cytomegalovirus infection on histologic examination is a large cell containing a large basophilic intranuclear "owl's eye" and intracytoplasmic inclusion bodies.

TREATMENT

Several systemic antiviral agents are active against cytomegalovirus infection, including ganciclovir, valganciclovir, foscarnet, and cidofovir. These medications are not started absent consultation with an infectious disease or a transplant specialist. Illness in the otherwise healthy host is usually self-limited and does not require antiviral therapy. Cytomegalovirus-induced infectious mononucleosis is treated symptomatically.

MEASLES

Measles is used to describe rubeola (Morbillivirus) and rubella (Rubivirus), both of which are covered in the MMR (Measles, Mumps, Rubella) vaccine. Rubella infection is typically mild, but when contracted during pregnancy is teratogenic. The current global measles epidemic is due to Rubeola. Rubeola is the most infectious virus known to humans and is communicable before symptoms begin. Most measles deaths occur among children in developing countries, but developed countries are now seeing outbreaks related to parents choosing not to vaccinate their children, largely due to unfounded fears about vaccine safety. After an incubation period of 10 to 14 days, illness starts with fever, malaise, cough, and runny nose, often with conjunctivitis. Small, white Koplik's spots (**Figure 154-10**) appear on the buccal mucosa early in the illness, followed by a red maculopapular rash that typically starts on the head and spreads throughout the body. **Diagnosis is usually clinical, with pathognomonic Koplik's spots and the characteristic rash.** Measles confirmation is by detecting immunoglobulin M antibodies, which are present at rash onset. Polymerase chain reaction testing of urine and throat specimens also is a reference criterion for diagnosis, and can distinguish true measles from IgM elevation with recent vaccination. Results typically take several days. Treatment is supportive, with particular attention to ensuring adequate nutrition, especially vitamin A. Mortality in developed countries is <1 per 1000, but can be up to 20% to 30% among infants in developing countries, often from pneumonia. Most measles suspects can be discharged home with instructions to watch for symptoms of complications such as pneumonia or encephalitis. Suspects should be reported immediately to local public health authorities prior to discharge; they can provide guidance on testing, quarantine, and postexposure management

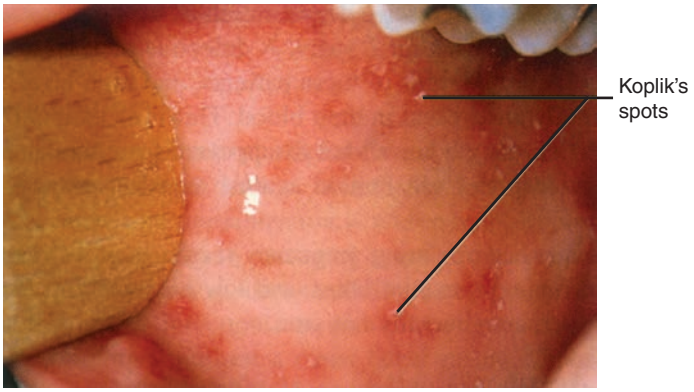


FIGURE 154-10. Oral Koplik's spots on day 3 of measles. [Reproduced with permission from Nester EW, Anderson DG, Roberts CE Jr, Nester MT: *Microbiology: A Human Perspective,* 6th ed. New York: McGraw-Hill, Inc., 2008.]

of contacts. See Chapter 142, "Rashes in Infants and Children," for further discussion of Measles (rubeola) and rubella.

Because measles is so highly infectious, EDs should have protocols for identification of measles suspects at initial point of contact based on characteristic symptoms in the setting of local outbreak or recent travel to an outbreak area. Measles suspects should be immediately placed in airborne isolation. It is helpful to public health to identify family contacts of high-risk suspects in the ED and offer vaccination. It can also be helpful to save a log of potential exposures of both ED staff and other patients at the time of the visit, in case it is later confirmed as measles. See the following for current CDC information: https://www.cdc.gov/measls/hcp/index.html.

ARBOVIRAL INFECTIONS

Arboviral infections are spread by biting mosquitoes, ticks, and flies. Japanese encephalitis is one of the most common and important causes of encephalitis in the world. The emergence of West Nile virus infection renewed interest in North America about epidemic viral encephalitis. This section reviews some of the more important and severe arboviral infections, concentrating on those that occur in North America[14,15] (**Table 154-3**). Other significant arboviral diseases are discussed in Chapter 162, "Global Travelers."

EPIDEMIOLOGY

Arboviral infections tend to be seasonal, with increased incidence in warmer months due to the breeding patterns of the arthropod vectors. The major hosts are mammals and birds. When migratory birds are involved, the virus can spread quickly over large distances. Humans are usually an incidental host and acquire the diseases when they venture into areas occupied by the reservoir host.

The age group affected often depends on local prevalence. Japanese encephalitis, which is highly endemic in certain parts of Asia, usually affects children. Most adults have been exposed and are immune. Elderly adults are at risk for St. Louis encephalitis.

Dengue, yellow fever, Rift Valley fever, and chikungunya viruses are among the viruses causing hemorrhagic fever syndromes (see Chapter 162, "Global Travelers"). Dengue virus is a common cause of fever and rash (**Figure 154-11**) in tropical areas with large mosquito populations, and transmission has been found in the southern United States. Severe dengue hemorrhagic fever can develop in locals who are exposed to a second infection with a different serotype. A novel vaccine to all four serotypes is available in many developing countries. Chikungunya fever causes rash, myalgias, arthralgias, and fever. Although fatalities are rare, arthralgias can be debilitating and last for months. The disease is reported in Asia, Africa, and more recently in the Caribbean and southeastern United States. Yellow fever is found in the tropics of Africa and South America. The *Aedes aegypti* mosquito vector for the yellow fever virus was once eradicated in the United States, but it is now starting to reappear. This mosquito can also spread dengue and chikungunya viruses.

TABLE 154-3 Arboviral Infections in North America

Virus	Geographic Distribution	Groups at Highest Risk
West Nile virus	United States, Canada, Mexico	Elderly adults
St. Louis encephalitis virus	United States, Canada, Mexico	Elderly adults
La Crosse virus	Central, northeastern United States	Children
Eastern equine encephalitis virus	Eastern and Gulf Coast states, eastern Canada	All ages
Western equine encephalitis virus	Western and midwestern United States and western Canada	Infants and elderly adults
Venezuelan equine encephalitis virus	Florida, Texas, Mexico	All ages
Dengue virus	Mexico, Caribbean	All ages
Zika virus	Mexico, Caribbean	Women of childbearing age



FIGURE 154-11. Maculopapular rash of dengue hemorrhagic fever with areas of dermal hemorrhage, petechiae, and edema. [Reproduced with permission from Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology,* 6th ed., © 2009 by McGraw-Hill, Inc., New York.]

Japanese encephalitis virus causes >15,000 deaths yearly, primarily in Asia, and is now spreading to Australia. West Nile virus and the viruses causing La Crosse encephalitis, St. Louis encephalitis, eastern equine encephalitis, and western equine encephalitis are found in North America.[14,15]

Zika virus disease is a mosquito born illness, typically either asymptomatic or causing a few days of mild fever, rash, conjunctivitis, and myalgias. Rare sequelae include Guillain-Barre syndrome, neuropathy, or myelitis. There is no treatment. Zika virus can be transmitted to the fetus during pregnancy, resulting in serious congenital malformations (congenital Zika syndrome). See Chapter 162, "Global Travelers", for further discussion.

PATHOPHYSIOLOGY

A mosquito or other appropriate vector becomes infected after it feeds on the blood of a viremic host. Humans are infected when the arthropod takes a blood meal. The virus replicates near the site of inoculation before it enters the reticuloendothelial system and then disseminates to various target organs.[14,15] There is often a low-grade viremia until the host can produce immunoglobulin M neutralizing antibodies. If the immune system is unable to clear the virus, then the more serious manifestations of disease may become evident.

CLINICAL FEATURES

Most arbovirus infections are either asymptomatic or cause a nonspecific mild illness. Only a few individuals develop hemorrhagic fever or encephalitis. **Severe human arboviral diseases most commonly manifest as four syndromes: fever and myalgia, arthritis and rash, encephalitis, and hemorrhagic fever**. These syndromes can overlap; viruses that cause encephalitis and hemorrhagic fever may also cause fever and myalgia. Headache is a common symptom of most arboviral infections and may be quite severe. Hemorrhagic fever presents with bleeding from the gums, petechiae, and GI tract. The classic presentation of viral encephalitis is fever, headache, and altered level of consciousness. Patients can be lethargic and confused and occasionally present with seizures.[14-16] In general, those at extremes of age are more likely to have

severe manifestations with these infections. The major concern with Zika virus infection is its potential for teratogenicity.

DIAGNOSIS

Obtaining a detailed travel and exposure history and knowing local epidemiologic patterns help in diagnosing arboviral infections. Patients with encephalitis should undergo CT or MRI of the brain. MRI is more sensitive and may show foci of increased signal intensity in the parenchyma.

Cerebrospinal fluid typically shows a lymphocytic pleocytosis and a slightly elevated protein level, although these findings are nonspecific. When encephalitis is in the differential diagnosis, save an extra vial of cerebrospinal fluid for further testing, because less common infections are often diagnosed only with stepwise testing after more common causes have been ruled out.

Serologic testing is the main method for diagnosis of arboviral infections. Viral cultures are labor intensive and technically demanding. Furthermore, patients are viremic for only a few days after the onset of illness. Generally, immunoglobulin M appears within a few days. Patients who are tested very early in the course of illness may have a false-negative result. A presumptive diagnosis of the suspected arboviral infection can be made based on an elevated immunoglobulin M level, and this can be confirmed with an increase in antibody titers between acute and convalescent samples. Many arboviruses are antigenically similar and cross-react on testing. Arboviral infections are reportable to public health authorities in many areas.

TREATMENT

Symptomatic management is the mainstay of treatment after excluding other serious, treatable causes of meningitis and encephalitis. Antiviral drugs, interferon, and steroids are not useful. Empiric treatment with acyclovir and antibiotics is appropriate until excluding HSV encephalitis and bacterial meningitis. Anticonvulsant therapy may aid if seizures occur.

Hemorrhagic fever is treated with supportive care, with careful fluid management to avoid overload.[14,15]

COLORADO TICK FEVER, HEARTLAND VIRUS, AND OTHERS

Many rare and novel viruses are either zoonotic or vector borne. Colorado tick fever is an RNA virus transmitted by a tick bite, usually at altitude. The virus then infects erythrocyte precursor cells, and transmission by blood transfusions has been reported. Symptoms are nonspecific, such as fevers, chills, headaches, and myalgias. Rare fatalities have been reported.

In 2009 a febrile disease was described in two Missouri farmers and later identified as Heartland virus.[17] It has been reported in the midwestern and southern United States and is thought to be spread by infected ticks, with symptoms similar to bacterial tick-borne diseases such as anaplasmosis or ehrlichiosis. These symptoms include headache, fevers, nausea, and occasionally confusion. A virus with similar geographic distribution, Bourbon virus disease, was described in 2014, when a southern farmer died of complications of a previously unknown viral infection.

There is no routine testing available for these viruses, and suspected cases are best referred to local health authorities. The treatment remains supportive, although many also treat for Rocky Mountain spotted fever or other tick-borne bacterial infections when these viruses are suspected. This is because these viral infections have symptoms similar to the tick-borne infections. When symptoms are nonspecific, it is important to obtain a history on exposures and have an understanding of geographic risks. See Chapter 161, "Zoonotic Infections," for more discussion.

EBOLA VIRUS DISEASE AND OTHER HEMORRHAGIC FEVERS

Viral hemorrhagic fevers are caused by several groups of RNA viruses with varying geographic distributions. These rare diseases elicit fear among the public and healthcare providers because of the lethality and transmission patterns, heightened by outbreaks in Western Africa. Examples include hantavirus pulmonary syndromes, Lassa fever, and perhaps the most notorious, Ebola virus disease. Geographic exposure and contact with an infected traveler are the most important clues to suspecting viral hemorrhagic fevers in an individual patient. Clinical presentation varies between viruses, with some causing relatively minor illness and some with high mortality. Symptoms typically begin with fever, myalgia, and malaise, which then progress to GI and other system involvement. Increased vascular permeability results in hypotension, pulmonary edema, and renal failure. Coagulation defects lead to diffuse hemorrhage, which can be worse in patients with thrombocytopenia or platelet dysfunction, sometimes with extensive bleeding, organ damage, and shock. Ebola and most other viral hemorrhagic fevers can be confirmed with acute serology to identify antibodies or, more commonly, reverse transcriptase polymerase chain reaction identification of the virus that is performed at specialized labs such as the Centers for Disease Control and Prevention.

Periodic Ebola virus outbreaks in western Africa have high mortality. The virus is spread through contact with infected body fluids such as bloody vomit and diarrhea, and the lack of personal protective equipment in developing countries contributes to spread within healthcare facilities.[18] Important aspects of preparing for Ebola and other severe viral hemorrhagic fevers in EDs include screening at triage for illness in travelers returning from areas of current outbreak and rapid initiation of appropriate isolation. **Ebola and many other viral hemorrhagic fevers require contact and droplet precautions including full gown, gloves, and facemask with eye protection**. Train staff on proper donning and removal of protective equipment to avoid contamination with body fluids. **It is important to notify the hospital laboratory to take precautions and to plan for sending specimens to specialized labs**. Treatment of Ebola and most other viral hemorrhagic fevers is supportive, with fluids, renal replacement, and respiratory support. Experimental serologic treatments and vaccines are in development.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 155

Human Immunodeficiency Virus Infection

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EPIDEMIOLOGY

The human immunodeficiency virus (HIV) is the leading cause of infectious disease deaths worldwide. As of 2016, an estimated 36.7 million people worldwide and 1.2 million people in the United States[1] have HIV infection or acquired immunodeficiency syndrome (AIDS). Although HIV exists everywhere across the globe, the vast majority of new infections (95%) occur in those living in low- and middle-income countries. In sub-Saharan Africa, the world's most affected region, nearly 1 in every 20 adults is living with HIV.[1]

Despite the global burden, the number of new HIV infections and deaths is falling each year.[2] Since the peak of the epidemic in 1996, new HIV infections dropped by nearly 50%; similar worldwide rates of AIDS-related deaths declined by more than 50% since the peak in 2004.[3]

Risks associated with acquiring HIV infection include homosexuality or bisexuality, injection drug use, heterosexual exposure, receipt of a blood transfusion prior to 1985, and maternal HIV infection (risk for vertical and horizontal maternal–neonatal transmission). Currently, the majority of HIV cases in the United States (67%) have occurred through men who have sex with men. Heterosexual contact accounts for approximately 24% of transmissions (with recent declines in that group), followed by about 6% associated with injection drug use and 3%

with male-to-male sexual contact *and* IV drug use.[4] New HIV infection rates continue to rise among young disadvantaged minority populations (many of whom use the ED for both primary and emergency care).

African Americans represent 12% of the total U.S. population but almost half (43%) of those with new HIV infections, the highest of any group by race and sex, notably in men having sex with men. Hispanics also have a higher proportion of new infections (26%) than accounted for by their relative size in the population (18%).[5] ED visits by HIV-infected individuals occur at rates higher than the general population due to the characteristics of the populations who use the ED, which are the same groups disproportionately affected by HIV/AIDS.[6]

PATHOPHYSIOLOGY

HIV is a cytopathic retrovirus that kills infected cells. The virus is labile and neutralized easily by heat and common disinfecting agents such as 50% ethanol, 35% isopropyl alcohol, 0.3% hydrogen peroxide, or a 1:10 solution of household bleach. There are two major subtypes of HIV; HIV-1 is the predominant subtype worldwide and is the cause of AIDS. HIV-2 causes a similar immune syndrome, but exists primarily in western Africa and is infrequent in the United States, but its incidence is growing.

The HIV virion is a central RNA molecule and a reverse transcriptase protein surrounded by a core protein encased by a lipid bilayer envelope. After infection, HIV selectively attacks host cells involved in immune function, primarily CD4+ T cells. Within the host cell, HIV-encoded RNA uses reverse transcription to enter into DNA, aided by the enzyme reverse transcriptase. The viral genome integrates into the host genome, where it may lie dormant or be transcribed and translated to produce virally encoded proteins and new HIV virions. As a result of infection, immunologic abnormalities eventually occur, including lymphopenia, qualitative CD4+ T-cell function defects, and autoimmune phenomena. Defects in cellular immunity ultimately result in a variety of opportunistic infections and neoplasms.

HIV exists in saliva, urine, cerebrospinal fluid (CSF), pus, brain, tears, alveolar fluid, synovial fluid, and amniotic fluid. Transmission of HIV occurs through semen, vaginal secretions, blood or blood products, and breast milk, and in utero by transplacental transmission. Transmission of HIV infection does not occur with casual contact. There is only one documented confirmed case of transmission from healthcare worker to patient in the United States, which involved an infected dentist in Florida who transmitted the virus to six patients; as of 2018, there were 58 cases of confirmed patient–to–healthcare worker transmissions, with the vast majority occurring before 1991 (see later discussion regarding occupational exposure).

TABLE 155-1 Stage 3 AIDS-Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive†
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV
- Herpes simplex: chronic ulcers (>1 month in duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month in duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary,† disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) pneumonia
- Pneumonia, recurrent†
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

Abbreviations: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency syndrome.

*Only among children aged <13 years. (Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *Morbid Mortal Wkly Rep* 1994;43[No. RR-12].)

†Only among adults and adolescents aged >13 years. (Centers for Disease Control and Prevention: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbid Mortal Wkly Rep* 1992;41[No. RR-17].)

NATURAL HISTORY AND CLINICAL STAGES OF HIV INFECTION

Stage 1 or acute HIV infection occurs 2 to 4 weeks after infection with HIV. Also called *acute retroviral syndrome,* this is the initial response to infection, causing symptoms in the majority of those infected. The clinical presentation is nonspecific, resembling a flulike or mononucleosis-like syndrome; the diagnosis is missed in about 75% of cases. Symptoms of acute HIV infection typically occur within 1 month of becoming infected, may last for 2 to 10 weeks, and include fever (>90%), fatigue (70% to 90%), pharyngitis (>70%), rash (40% to 80%), headache (30% to 70%), and lymphadenopathy (40% to 70%); other reported symptoms are weight loss, headache, and diarrhea.[7] **Seroconversion and detectable antibody response to HIV usually occur 3 to 8 weeks after infection,** although delays can be up to 11 months.

Stage 2 of HIV infection is the period of clinical latency or HIV inactivity during which time patients generally have no complaints or findings on physical examination except for possible persistent generalized lymphadenopathy (enlarged lymph nodes in at least two noncontiguous sites other than inguinal nodes). For patients not taking any medication, the median incubation time from exposure to the development of AIDS is estimated at 10 years for adults; shorter incubation periods occur in untreated infants and older adults. Virologic studies of patients during this period suggest that a steady state of HIV replication and CD4+ T-cell death and replacement exists until increased levels of HIV replication occur. Variables most predictive of disease stage are viral load and CD4+ T-cell counts, with a steeper decline in CD4+ T-cell count and a higher viral burden associated with more rapid progression and more adverse outcomes. Other non–HIV-related factors, such as age and malignancy, also impact disease progression. Toward the end of the clinical latency period, as the CD4 count begins to drop and viral load starts to rise, patients begin to develop symptomatic infection characterized by conditions that are more common and more severe in the presence of HIV infection, but are not AIDS-indicator conditions. These include thrush, persistent vulvovaginal candidiasis, peripheral neuropathy, cervical dysplasia, recurrent herpes zoster, and idiopathic thrombocytopenic purpura.

Stage 3 of HIV infection has either laboratory markers of severe immunosuppression (CD cell counts <200 cells/mm^3) or occurrence of one of any opportunistic infections or AIDS-defining illnesses (**Table 155-1**).

DIAGNOSIS

Early diagnosis of acute HIV infection allows the benefit of limiting risk of unrecognized HIV and also initiation of antiretroviral therapy (ART), which reduces symptoms and slows disease progression.

Acute HIV is the time from HIV transmission to seroconversion. Diagnosis of acute HIV infection can now be made with newer

fourth-generation HIV tests (see later discussion). Other methods for earlier detection of HIV-1 include techniques to detect DNA, RNA, or HIV antigens, although these tests are not always available in the ED. Mean times from transmission to detection are shortest for viral load (17 days), followed by p24 antigen (22 days), enzyme-linked immunosorbent assay positivity (25 days), and Western blot positivity (31 days).[8]

For patients with suspected acute HIV that has not been confirmed (i.e., those with a high-risk profile presenting with fever of unknown origin and/or a syndrome suspicious for acute seroconversion), counseling and urgent referral to outpatient follow-up are best.

HIV TESTING METHODS

HIV infection diagnosis uses identification of HIV nucleic acid, detection of viral-specific antigen, detection of antibodies to HIV, and isolation of the virus by culture (now rarely used in practice). The most commonly used testing method for HIV is detection of antibodies to the virus. These newer testing methods revolutionized the ability of ED providers to diagnose patients with HIV. Previously, HIV testing involved sequential use of an enzyme-linked immunosorbent assay, followed by a Western blot assay. Enzyme-linked immunosorbent assay is approximately 99% specific and 98.5% sensitive; Western blot testing is nearly 100% sensitive and specific if performed under ideal laboratory conditions. Enzyme-linked immunosorbent assay detects specific serum antibodies to HIV antigens. Western blot assay detects HIV antibodies to viral antigens. Reasons for indeterminate test results include early seroconversion, cross-reacting antibodies, pregnancy, presence of an autoimmune disease, or technical errors.

RAPID HIV TESTS

There are numerous rapid HIV tests approved for use by the U.S. Food and Drug Administration, usable as single-use disposable tests of blood, serum, plasma, or oral fluid.[9] Sensitivity and specificity are comparable with those of standard serologic testing, and minimal training is required for administration. Relay any point-of-care results to the patient as *preliminary positive* if reactive, and confirm the results with Western blot testing. Negative test results may miss patients in the window period before seroconversion; this requires a repeat test at 3 months.

THE HIV TESTING ALGORITHM

The Centers for Disease Control and Prevention recommends laboratory testing approaches for HIV.[10] The algorithm calls for automated testing for antibody to HIV-1 and HIV-2 simultaneously with detection of HIV-1 p24 antigen, permitting detection of acute infections. In instances where this set of tests is negative, no further testing occurs, and the patient is counseled that he or she tested negative. For those with positive results, follow-up testing differentiates HIV-1 and HIV-2. In cases where the differentiation test is negative, a nucleic acid amplification test confirms acute seroconversion. Turnaround time for the combined assay and HIV-1/2 differentiation assay is about 60 minutes. Turnaround time for confirmatory testing with nucleic acid amplification can take up to a few days. This new algorithm allows better early detection; ED-based studies show this is feasible and will detect new, acutely infected patients.[11-13]

CD4+ T-CELL COUNTS

CD4+ T-cell counts of <200 cells/mm^3 and a viral load of >50,000 copies/mm^3 are associated with increased risk of AIDS-defining illnesses. When this information is unavailable or the stage of disease is unknown, use the total lymphocyte count to approximate the CD4+ T-cell count. In a recent ED study, **a total lymphocyte count <1700 cells/mm^3 had a sensitivity of 95% for a CD4 count of <200 cells/mm^3.**[13]

HIV TESTING PRACTICES IN THE ED

Historically, HIV testing challenges in the ED were time limitations, difficulty with follow-up, confidentiality requirements, costs, and questions regarding reimbursement. Advances in testing technologies coupled with new policy guidelines address these barriers. In 2006, the Centers for Disease Control and Prevention recommended testing guidelines that included an opt-out approach to consent, meaning that HIV testing can be performed after notifying the patient that testing will be done (without separate written consent) unless they explicitly decline.[14] Further, the U.S. Preventive Services Task Force gave a "Grade A" recommendation for routine HIV screening for all people age 15 to 65 years, as well as younger adolescents and older adults who are at an increased risk for HIV infection and all pregnant women, including those in labor whose HIV status is unknown. The Patient Protection and Affordable Care Act requires new insurance policies to pay for preventive services with "Grade A" recommendation. The American College of Emergency Physicians supports ED HIV testing based on clinical need and supports screening with caveats. While overall rates of HIV testing in EDs in the United States in the early part of the century were low (approximately 0.2% of all ED visits), programs are increasing, particularly in urban and/or academic centers; in some areas, increases in testing paralleled declines in undiagnosed HIV and control of the epidemic.[15] Ongoing research targets best ED testing approaches (e.g., nontargeted universal vs. targeted), with local prevalence playing a key role in the screening plan chosen.

CLINICAL FEATURES AND TREATMENT

INITIAL CARE: GENERAL CONSIDERATIONS

The spectrum of disease caused by HIV infection varies, from those coming to the ED with asymptomatic infection for symptoms unrelated to HIV disease, to symptomatic patients seeking care from involvement of virtually any organ system and with multiple coexisting symptoms.

Maintain confidentiality regarding HIV-related diagnoses in the ED. Begin care without discrimination and without assuming any illness trajectory unless advance directives, including cardiopulmonary resuscitation, are already in place. If friends or family accompany the patient to the ED, first ask the patient about privacy issues before beginning any conversations.

Always use blood and body fluid precautions during care (in some hospitals, this is termed *universal* or *standard precautions*). Healthcare workers can be exposed to the blood and body fluids of HIV-infected patients or patients at high risk of harboring the HIV virus. ED-based studies show that many patients have unsuspected HIV infection and that seropositivity cannot be predicted accurately, even after assessment of risk factors. See Chapter 163, "Occupational Exposures, Infection Control, and Standard Precautions."

A basic history and physical examination help to identify the clinical stage of disease and to direct attention to the most likely complications. Obtain a thorough report detailing past and current medications including ART, previous infections, and the patient's ability to perform activities of daily living. The exam seeks findings of organ involvement related to the chief complaint and features that might assist with staging such as oral candidiasis, skin lesions, temporal wasting, and dementia.

Diagnosis and initial care seek to recognize infection (when not previously diagnosed), assess the severity of disease, identify specific organ(s) involved, and institute therapy. Consultation with an infectious disease specialist and others with expertise in HIV infection is often necessary to provide proper therapy and disposition. Disposition decisions are based on the need for inpatient evaluation or management and the patient's ability to function as an outpatient, the latter often being driven by oral intake and ambulation ability and the availability of appropriate medical follow-up. Healthcare, family resources, and case management can aid decision making about appropriate site for care.

Systemic symptoms such as fever, weight loss, and malaise are common in HIV-infected patients and account for the majority of HIV-related ED presentations. In the ED, look for systemic infection, malignancy, drug toxicity, or metabolic abnormalities. Often, this includes assessing serum electrolytes with renal function, CBC, liver function studies, blood cultures, urinalysis and urine culture, hepatic function tests, and chest radiograph; use serologic testing for syphilis, cryptococcosis, toxoplasmosis, cytomegalovirus infection, and coccidioidomycosis more selectively. Lumbar puncture occurs after

neuroimaging if headache, altered sensorium, visual change, or other focal neurologic symptoms or signs are present.

When treating the febrile ill-appearing HIV patient, provide fluid resuscitation and prompt empiric antibiotics, and admit for further evaluation and management. Outpatient evaluation and treatment are indicated only when all of the following conditions are met: the source of the fever does not dictate admission, the patient is able to function adequately at home (e.g., can maintain sufficient oral intake), and timely medical follow-up can be arranged.

HIV STAGE AND CAUSES OF FEVER

Infections are the most common cause of hospitalization among HIV-infected persons. In HIV-infected persons without obvious localizing signs or symptoms, sources of fever vary by stage of disease. Patients with **CD4+ T-cell counts of >500 cells/mm^3** generally have causes of fever similar to those in nonimmunocompromised patients, whereas those with **CD4+ T-cell counts between 200 and 500 cells/mm^3** are more likely to have infections that are associated with early immune compromise, including bacterial pneumonia, herpes zoster, and tuberculosis. For patients with **CD4+ T-cell counts of <200 cells/mm^3**, the most common causes of fever without obvious localizing findings are early *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii*); central line infection; infection with *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, or cytomegalovirus; drug fever; and sinusitis. Other causes of fever include endocarditis, lymphoma, and infection with *Histoplasma capsulatum* or *Cryptococcus neoformans*.

Disseminated *M. avium* Complex Infection Disseminated *M. avium* complex infection occurs predominantly in patients with CD4+ T-cell counts of ≤100 cells/mm^3 who are not on ART or azithromycin prophylaxis. Persistent fever and night sweats are typical symptoms. Associated symptoms include weight loss, diarrhea, malaise, and anorexia. Dissemination to the bone marrow, liver, and spleen results in anemia and elevated alkaline phosphatase levels. Diagnose this with acid-fast stain of stool or other body fluids or by blood culture. Cultures using the lysis-centrifugation method are more sensitive for *M. avium* complex (and histoplasmosis) and aid diagnosis in patients with late-stage disease and fever of unknown origin. Treatment for *M. avium* complex reduces bacteremia and improves symptoms but does not eradicate disease; therapy starts with clarithromycin combined with ethambutol and rifabutin. Azithromycin is an alternative therapy.

Immune Reconstitution Inflammatory Syndrome Immune reconstitution inflammatory syndrome mimics an autoimmune event, with lymphadenitis, fever, and other symptoms starting weeks to months after beginning ART, often during tuberculosis therapy. There is no definitive diagnostic test for this condition. Treatment guidelines advise continuing ART; use nonsteroidal anti-inflammatory agents for mild to moderate cases; in severe cases, use corticosteroids (prednisone 1 to 2 milligrams/kg or equivalent for 1 to 2 weeks). Add the appropriate antimicrobials if there is a known or suspected infection.

Cytomegalovirus Cytomegalovirus is a common cause of serious opportunistic viral disease in HIV-infected patients. Disseminated disease involves the GI, pulmonary, and central nervous systems. The most important manifestation is retinitis (see later section, "Cytomegalovirus Retinitis"). Treatment is with foscarnet or ganciclovir. Oral ganciclovir is a prophylaxis agent (**Table 155-2**).

Endocarditis Fever in injection drug users should trigger suspicion for infective endocarditis, which often has a nonspecific presentation in the ED (see Chapter 156, "Endocarditis"). Most ED physicians admit febrile injection drug users while awaiting the results of blood cultures and echocardiography given the high morbidity and mortality coupled with the difficulties encountered with outpatient follow-up in the drug user population.

Neoplasm and Drug Fever Noninfectious causes of fever in HIV patients include neoplasm and drug fever. Non-Hodgkin's lymphoma is the most frequently occurring neoplasm, characterized by high-grade, rapidly growing mass lesions. New CNS symptoms, particularly a change in mental status in the presence of fever, require neuroimaging. Definitive diagnosis of non-Hodgkin's lymphoma requires biopsy. Radiotherapy and chemotherapy are effective treatment regimens. Drug fever may be secondary to injection drug abuse or adverse drug reactions (see later discussion).

NEUROLOGIC COMPLICATIONS

Neurologic disease in HIV patients may be related to opportunistic infections, neoplasms, impact of HIV infection on CNS, or HIV treatment itself. Presenting symptoms may include seizures, altered mental status, headache, meningismus, and focal neurologic deficits.

Patients with HIV presenting to the ED with headache, seizure, altered mental status, or focal neurologic deficits with or without fever should have neuroimaging, especially in patients with CD4 count <200 cells/mm^3. Although noncontrast CT is typically the first imaging modality used in the ED, contrast-enhanced CT and MRI may be needed if CT findings are equivocal or negative. If no mass lesion exists, lumbar puncture follows to assess or obtain the following: CSF pressures, WBC count and differential, protein and glucose concentrations, Gram staining, India ink staining, bacterial culture, mycobacterial culture, fungal culture, toxoplasmosis and cryptococcosis antigen assays, coccidioidomycosis titer, and polymerase chain reaction assays for JC virus, Epstein-Barr virus, cytomegalovirus, *Toxoplasma gondii*, herpes simplex virus types 1 and 2, and varicella-zoster virus. Save additional CSF in case further testing needs arise later. Consider toxoplasmosis serology and QuantiFERON tuberculosis testing too. Even if the ED evaluation is unrevealing, admit all patients with new or changed neurologic signs or symptoms.

HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

HIV-associated neurocognitive disorder (also referred to as *HIV encephalopathy*, *HIV-associated dementia, or AIDS dementia complex*) is a progressive, subacute disorder heralded by subtle impairment of recent memory, cognitive deficits, and behavioral disturbances. Up to 50% of patients on ART have some form of HIV-associated neurocognitive disorder.[16] Many patients may exhibit only mild deficits. However, inadequately treated patients may progress to the most advanced form of HIV-associated neurocognitive disorder, HIV-associated dementia, and demonstrate moderate to severe cognitive impairment with behavioral changes.[17] HIV-associated dementia is a diagnosis of exclusion, once MRI and lumbar puncture have ruled out other pathologies. New signs or symptoms in a patient with known HIV-associated dementia should prompt workup for other CNS processes. ART is the most effective treatment for HIV-associated dementia.

TOXOPLASMIC ENCEPHALITIS

Since the introduction of ART, toxoplasmosis encephalitis remains the most commonly reported neurologic opportunistic infection.[18] It occurs most commonly in patients with CD4+ cell counts <100 cells/mm^3 as latent bradyzoites acquired early in life reactivate. Symptoms may include headache, fever, focal neurologic deficits, altered mental status, seizures, and behavioral changes. On unenhanced CT scan, toxoplasmosis typically appears as multiple subcortical lesions with a predilection for the basal ganglia and corticomedullary junction. Contrast-enhanced CT scan typically shows multiple ring-enhancing lesions with surrounding areas of edema. MRI is more sensitive than contrast-enhanced CT scan in detecting toxoplasmosis. Consider primary CNS lymphoma as another potential cause or mimic. CSF may not be available since many patients are at risk for herniation; polymerase chain reaction, although highly specific (100%), is not sufficiently sensitive (50% to 80%) to detect *T. gondii* in CSF. Patients with positive serology (immunoglobulin G) in combination with symptoms and imaging suggestive of *T. gondii* should be treated.

Admit patients with suspected toxoplasmosis and treat with a combination of IV pyrimethamine plus sulfadiazine plus leucovorin (folinic acid). Clindamycin is a substitute for sulfadiazine. Some trials show trimethoprim-sulfamethoxazole may have equal efficacy[19] (Table 155-2). Corticosteroids can aid in treating any mass effect, but discontinue these as soon as possible. For patients responsive to toxoplasmosis therapy, use chronic suppressive therapy with oral sulfamethoxazole-trimethoprim;

TABLE 155-2 Treatment Recommendations for Common Human Immunodeficiency Virus–Related Infections

Organ System	Infection	Therapy
Systemic	*Mycobacterium avium-intracellulare*	Clarithromycin, 500 milligrams PO twice a day *and* Ethambutol, 15 milligrams/kg PO once a day *and* Rifabutin, 300 milligrams/kg PO once a day (addition may improve survival and decrease risk of macrolide resistance)
	CMV infection (GI)	Ganciclovir, 5 milligrams/kg IV twice a day for 3–4 wk *or* Foscarnet, 90 milligrams/kg every 12 h for 3–4 wk
Pulmonary	*Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia	Trimethoprim-sulfamethoxazole (TMP-SMZ), 5 milligrams/kg (of TMP component) every 8 h for 21 d *or* Clindamycin 600 milligrams every 8 h plus primaquine 15–30 milligrams once daily for 21 d *Note:* Other second-line options are available for those who are allergic. If partial pressure of arterial oxygen is <70 mm Hg or alveolar-arterial gradient is >35 mm Hg, then add: Prednisone, 40 milligrams twice a day for 5 d, then 40 milligrams once a day for 5 d, then 20 milligrams once a day for 11 d
	Mycobacterium tuberculosis infection*	Isoniazid, 5 milligrams/kg PO once a day *and* Rifampin, 10 milligrams/kg (600 milligrams max) PO once a day *or* rifabutin 5 milligrams/kg PO once a day (for person on PIsw, NNRTIs, integrase inhibitors, or methadone) *and* Pyrazinamide, 15–30 milligrams/kg (2 grams max) PO once a day *and* Ethambutol, 15–20 milligrams/kg (1.6 grams max) PO once a day *and* Pyridoxine (vitamin B_6) 60 milligrams PO once daily *Note:* Treatment duration determined by site of disease and response to therapy.
CNS	Toxoplasmosis†	Pyrimethamine, 200-milligram loading dose PO followed by 50–75 milligrams PO once a day for 6–8 wk *and* Sulfadiazine, 1–1.5 grams PO every 6 h for 6–8 wk *and* Leucovorin, 10–25 milligrams once a day
	Cryptococcosis‡	Amphotericin B, 0.7 milligram/kg IV once a day for 2 wk *and* Flucytosine, 25 milligrams/kg IV four times a day for 2 wk *then* Fluconazole, 400 milligrams/d PO for 8–10 wk
Ophthalmologic	CMV infection (retinitis)§	Valganciclovir, 900 milligrams PO twice a day for 14–20 d of induction therapy, then 900 milligrams PO daily for maintenance therapy IV ganciclovir and foscarnet are now rarely used because of need for permanent indwelling catheter and availability of safer options (valganciclovir)
GI	Candidiasis (thrush—limited to mouth)	Clotrimazole, 10-milligram troches 5 times a day for 7–14 d *or* Nystatin, 500,000 units 5 times a day, gargle for 7–14 d
	Esophagitis (primarily *Candida*)	Fluconazole, 200–400 milligrams/d PO
	Salmonellosis†	Ciprofloxacin, 500 milligrams PO twice a day for 2–4 wk *Note:* Modify according to susceptibilities when available.
	Cryptosporidiosis	No known effective cure; best results with highly active antiretroviral therapy and symptomatic treatment
Cutaneous	Herpes simplex	Acyclovir, 400 milligrams PO 3 times a day for 7–10 d *or* Famciclovir, 500 milligrams 3 times a day for 7–10 d *or* Valacyclovir, 1 gram PO twice a day for 7 d *or* for severe disease Acyclovir, 5–10 milligrams/kg IV every 8 h for 7 d

(*Continued*)

TABLE 155-2 Treatment Recommendations for Common Human Immunodeficiency Virus–Related Infections (*Continued*)

Organ System	Infection	Therapy
	Herpes zoster	Acyclovir, 800 milligrams PO 5 times a day for 7–10 d *or* Famciclovir, 500 milligrams PO 3 times a day for 7–10 d *or* Valacyclovir, 1 gram PO 3 times a day for 7–10 d *or* for ocular or disseminated disease Acyclovir, 5–10 milligrams/kg PO every 8 h for 5–7 d
	Candida or *Trichophyton* infection	Topical clotrimazole 2 or 3 times a day for 3 wk *or* Nystatin, 500,000 units 5 times a day, gargle for 7–14 d *or* Fluconazole 100–200 milligrams PO every day for 7–14 d

Note: Medication dose and duration may need to be adjusted based on drug–drug interactions, renal and/or liver functions based on individual patient, and concomitant medications. Please check with your local pharmacist prior to using these doses.

Abbreviations: CMV = cytomegalovirus; NNRTIs = nonnucleoside reverse transcriptase inhibitors.

*Specific drug regimen must be adjusted if patient is receiving highly active antiretroviral therapy.

†Maintenance therapy required.

‡Maintenance therapy required; may be discontinued if CD4+ T-cell count is >150 cells/mm^3 for >16 wk.

§Maintenance therapy required until CD4+ T-cell count is >150 cells/mm^3.

this can also be prophylaxis in patients with positive toxoplasmosis serologic test results and CD4+ T-cell counts of <100 cells/mm^3.

CRYPTOCOCCAL MENINGITIS

Cryptococcal infection occurs most commonly in patients with CD4+ counts of <50 cells/mm^3. The most common presenting signs are fever and headache, followed by nausea, altered mentation, and focal neurologic deficits. Presentation may be subacute, and meningismus is uncommon. Although communicating hydrocephalus with high intracranial pressure may develop, CT imaging may be normal or nonspecific.

Diagnosis of CNS cryptococcal infection in HIV patients relies on CSF cryptococcal antigen testing (92% sensitive and 83% specific), fungal culture (95% to 100% sensitive), or staining with India ink (60% to 80% sensitive). Serum cryptococcal antigen testing helps but has lower sensitivity than CSF testing (approximately 95%). The expected CSF WBC count elevation is often absent in patients with AIDS, although increased opening pressure is common and drainage aiming to reduce pressure by 50% or to less than 20 cm H_2O is best.

Patients with CNS cryptococcosis require hospital admission and IV amphotericin B and oral flucytosine for 14 days, followed by fluconazole for 8 weeks to clear the CSF (Table 155-2). Long-term maintenance therapy follows initial treatment.

OTHER NEUROLOGIC DISORDERS

Cytomegalovirus may cause encephalitis, radiculomyelitis, or mononeuritis multiplex, with nonspecific periventricular enhancement on neuroimaging and highly sensitive and specific CSF polymerase chain reaction. Evaluate patients with cytomegalovirus encephalitis for concurrent retinitis. Ganciclovir is a mainstay of treatment. Reactivation of the JC virus may lead to progressive multifocal leukoencephalopathy, with focal neurologic deficits developing over weeks, although acute cases may mimic stroke, and initiation of ART is key to management. Multifocal demyelinating lesions exist on imaging; sensitivity of CSF polymerase chain reaction for JC virus is variable.

The incidence of primary CNS lymphoma has declined since the introduction of ART; once diagnosed, prognosis is poor, with a median survival of 2 months. CNS lymphoma may present with nonspecific symptoms or focal deficits, without fever. Postcontrast imaging may demonstrate a ring-enhancing lesion, and presence of Epstein-Barr virus in CSF is highly sensitive. Other considerations in the presence of neurologic symptoms include bacterial meningitis, herpes simplex virus infection, neurosyphilis, tuberculosis (tuberculoma or meningitis, treated as systemic tuberculosis), cerebrovascular accidents, and metabolic encephalopathies. Neuropsychiatric disturbances may occur from HIV therapies including ART, such as efavirenz, or drugs to treat opportunistic infections, such as ganciclovir.

Peripheral neuropathies are common in HIV patients, either because of chronic HIV infection, known as HIV-associated distal sensory polyneuropathy, or treatment-related toxicity related to ART; change in treatment regimen may address the latter. Reserve opioids for short durations and severe pain; topical capsaicin or lamotrigine aid often. Autonomic neuropathies and inflammatory demyelinating polyneuropathies may also occur.[20]

PSYCHIATRIC DISORDERS

HIV infection may cause CNS and metabolic disturbances that can produce psychiatric symptoms. HIV infection is also a psychosocial stressor and may contribute to social isolation, poverty, and hopelessness. In the ED, search for underlying organic causes, such as delirium, dementia, neurologic infection or mass, electrolyte abnormality, medication adverse effect, trauma, or other organic etiology of depression. Patients with AIDS psychosis typically develop hallucinations, delusions, or other behavioral changes.

Depression is common during all phases of HIV infection.[21-23] Antidepressant therapy is often started if symptoms of depression continue for >2 weeks and with close monitoring for side effects. Patients with suicidal ideation or profound dysfunction may require inpatient psychiatric management.

An increased incidence of mania occurs in both the early and late stages of HIV infection. Late-stage mania is closely associated with dementia and carries a poor prognosis. If danger exists, use physical restraints or acute pharmacologic intervention. Other psychiatric manifestations may occur with increased incidence in the HIV-infected population, including schizophrenia, bipolar disorder, posttraumatic stress disorder, and personality disturbance.

Nearly 50% of those with HIV infection also have a history of substance abuse.[24] Depression and psychotic symptoms are more prevalent among patients with substance abuse. ED management includes identification and outpatient referral to integrated substance abuse and psychiatric resources. Some antiretroviral agents have interactions with buprenorphine and methadone requiring dosage modifications of the latter two agents.

OPHTHALMIC COMPLICATIONS

Cytomegalovirus retinitis and herpes zoster ophthalmicus must be recognized by the emergency physician and have specialty consultation sought. Other manifestations include HIV retinopathy, characterized by non–vision-threatening retinal cotton-wool spots (seen in >50% of patients with advanced HIV), retinal hemorrhages, and microaneurysms. Syphilis may lead to ocular complications, and *Toxoplasma* retinochoroiditis (whitish retinal lesions without hemorrhage), *Cryptococcus* chorioretinitis (multiple discrete yellowish spots on choroid and retina), and pneumocystis choroiditis (multiple pale yellow-white choroidal spots) may also occur. Treatment for these entities is the same as for systemic infection.

CYTOMEGALOVIRUS RETINITIS

Cytomegalovirus retinitis (**Figure 155-1**) is the most serious ocular opportunistic infection and is the leading cause of blindness in AIDS patients. Since the advent of newer ART, the incidence of cytomegalovirus infection has decreased.[25] Retinitis may be asymptomatic early but may present with changes in visual acuity, visual field cuts, photophobia, flashes, floaters, eye redness, or eye pain. Findings on indirect ophthalmoscopy are fluffy white perivascular lesions with areas of hemorrhage, which may be confused with benign cotton-wool spots. Request emergent ophthalmologic consultation early in suspected cytomegalovirus retinitis. Systemic treatment, often with oral valganciclovir, is a first-line treatment; those with sight-threatening lesions near the optic nerve or macula also need intravitreal ganciclovir.

HERPES ZOSTER OPHTHALMICUS

Herpes zoster ophthalmicus (see Chapter 241, "Eye Emergencies") usually presents with paresthesia and discomfort in the distribution of cranial nerve V_1 (ophthalmic branch), followed by the appearance of the typical zoster skin rash. Ocular complications include conjunctivitis, episcleritis, iritis, keratitis, secondary glaucoma, and, rarely, retinal necrosis. Early recognition and treatment can prevent ocular damage.

PULMONARY COMPLICATIONS

Pulmonary abnormalities in HIV-infected patients include a wide variety of conditions including community-acquired bacterial pneumonia, *P. jirovecii* pneumonia (PCP), tuberculosis, cytomegalovirus infection, cryptococcosis, histoplasmosis, chronic obstructive pulmonary disease, lymphoid interstitial pneumonia, and neoplasms. The most common cause of pneumonia in HIV-infected patients in the United States and Western Europe is *Streptococcus pneumoniae,* followed by PCP and tuberculosis.[26] Pulmonary radiographic findings are helpful in determining likely causes (**Table 155-3**). Admit patients with new-onset or profound pulmonary symptoms, especially in the presence of hypoxemia or altered mental status. In patients with known existing pulmonary involvement, disposition and care decisions are based on change from baseline, the effectiveness of ongoing or previous treatment, ability to adhere to therapy, and the ability to obtain outpatient follow-up.

TABLE 155-3 Chest Radiographic Abnormalities: Differential Diagnosis in the Patient With Acquired Immunodeficiency Syndrome

Finding	Causes
Diffuse interstitial infiltration	*Pneumocystis jirovecii* infection
	Cytomegalovirus infection
	Mycobacterium tuberculosis infection
	Mycobacterium avium-intracellulare complex infection
	Histoplasmosis
	Coccidioidomycosis
	Lymphoid interstitial pneumonitis
Focal consolidation	Bacterial pneumonia
	Mycoplasma pneumoniae infection
	P. jirovecii infection
	M. tuberculosis infection
	M. avium-intracellulare complex infection
	Malignancy
Nodular lesions	Lymphocytic interstitial pneumonitis
	Kaposi's sarcoma
	M. tuberculosis infection
	M. avium-intracellulare complex infection
	Fungal infection
	Toxoplasmosis
Cavitary lesions	*P. jirovecii* infection
	M. tuberculosis infection
	Bacterial infection
	Fungal infection
Adenopathy	Kaposi's sarcoma
	Lymphoma
	M. tuberculosis infection
	Cryptococcosis
Normal radiograph	Upper respiratory infection
	Bronchiolitis
	P. jirovecii infection

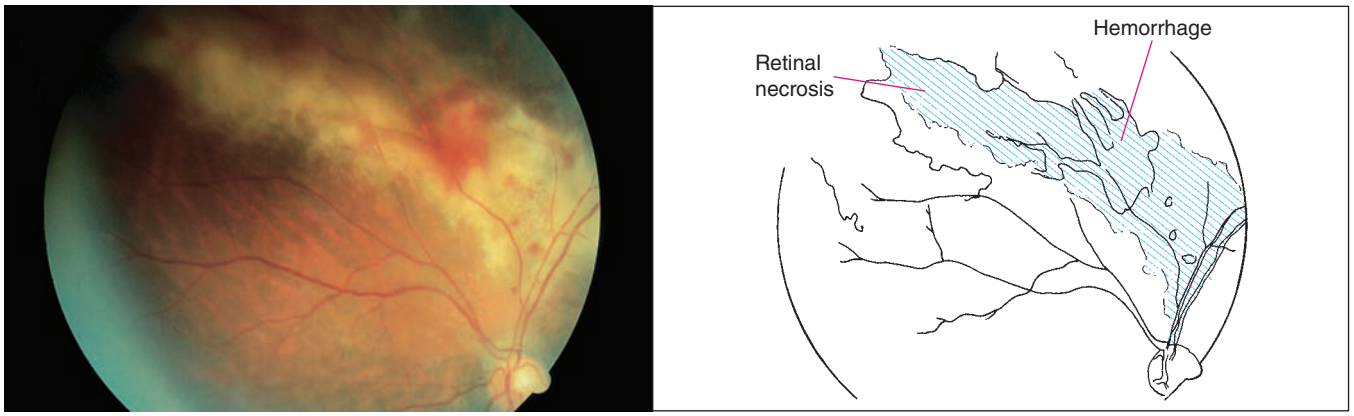

FIGURE 155-1. Cytomegalovirus retinitis. "Pizza pie" or "cheese and ketchup" appearance is demonstrated by hemorrhages and the dirty white granular-appearing retinal necrosis adjacent to major vessels. [Photograph contributed by Richard E. Wyszynski, MD. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine*, 3rd ed, © 2009 by McGraw-Hill, Inc., New York.]

PNEUMOCYSTIS PNEUMONIA

PCP is the most common opportunistic infection among AIDS patients.[27] The causal agent is known as *P. jirovecii* (previously known as *P. carinii*), previously classified as a protozoan but now reclassified as a fungus. Approximately 70% of HIV-infected patients acquire PCP at some time during their illness, and PCP is often the initial opportunistic infection that establishes the diagnosis of AIDS. This infection is the most frequent serious complication of HIV infection in the United States and the most common identifiable cause of death in patients with AIDS. The incidence of PCP has decreased among patients on ART but remains a high trigger for morbidity and mortality.[28] PCP pneumonia typically occurs in patients with a low CD4 count of <200 cells/mm^3. The classic presenting symptoms of PCP are fever, cough (typically nonproductive), and shortness of breath (progressing from being present only with exertion to being present at rest).

Symptoms are often insidious and accompanied by fatigue. Chest radiographs most often show diffuse interstitial infiltrates (Table 155-3), but negative radiographic findings exist in 15% to 25% of patients with PCP.[29] The lactate dehydrogenase level may be elevated in patients with PCP, but this test has low sensitivity and specificity, impairing utility. Arterial blood gas analysis usually demonstrates hypoxemia and an increase in the alveolar-arterial gradient. Suspect early PCP if a patient demonstrates a decrease in pulse oximetric values with exercise; even an ED "walk" can detect this exercise desaturation. Presumptive diagnosis of PCP is possible in the ED if there is hypoxemia without any other explanation. Inpatient diagnostics include bronchoscopy with specimen analyses.

The preferred therapy is trimethoprim-sulfamethoxazole (Table 155-2).[30-32] Use body mass–based dosing, 15 to 20 milligrams/kg/d PO or IV; a typical PO dose is two double-strength tablets three times daily for 21 days. For moderate to severe disease, use IV trimethoprim-sulfamethoxazole (15 to 20 milligrams/kg of trimethoprim and 75 to 100 milligrams/kg of sulfamethoxazole per day). Adverse reactions, including rash, fever, and neutropenia, occur in up to 65% of AIDS patients. Alternative regimens include trimethoprim-dapsone, clindamycin-primaquine, or atovaquone. Pentamidine is an alternative IV agent (Table 155-2). Add systemic steroids in patients with a partial pressure of arterial oxygen of <70 mm Hg or an alveolar-arterial gradient of >35 mm Hg. Oral prednisone, starting at 40 milligrams twice daily and tapering over 21 days (Table 155-2), is a common approach.[33] Start ART or continue any existing regimen.

Seventy percent of patients have reinfection within 18 months, which is why prophylactic therapy is key. Oral trimethoprim-sulfamethoxazole, one double-strength tablet daily, is preferred. Prophylaxis for all patients with CD4+ T-cell counts of <200 cells/mm^3 is another common approach to mitigate PCP. Repeat PCP infections are often less responsive to therapy.

TUBERCULOSIS

Clinical manifestations of tuberculosis in HIV-infected patients vary according to the severity of immunosuppression. Typical presentations of tuberculosis occur in patients with CD4+ T-cell counts of >200 to 500 cells/mm^3. Those with tuberculosis and advanced HIV infection, with CD4 cell counts <100 cells/mm^3, often have extrapulmonary or disseminated disease.[34,35] Classic manifestations include cough with hemoptysis, night sweats, prolonged fevers, weight loss, and anorexia. With worsening immunosuppression, patient presentation becomes less classic; in addition, upper lobe involvement and cavitary lesions are less common as patients become more immunosuppressed, particularly among patients with late-stage AIDS.[36] Negative purified protein derivative skin tuberculosis test results are frequent among AIDS patients due to immunosuppression. Definitive diagnosis of tuberculosis usually occurs with stain and culture of expectorated sputum, although some cases require bronchoscopy. Later stage HIV is also associated with increased frequency of extrapulmonary tuberculosis with clinical manifestation associated with the involved sites of infection. Frequent sites of dissemination are peripheral lymph nodes, bone marrow, CNS, GI system, and urogenital system.

In the ED, think of tuberculosis in any HIV-infected patients with pulmonary symptoms, and begin precautions to avoid transmission. Place the patient in an isolation room and with an appropriate mask immediately and until the diagnosis is excluded. Current treatment guidelines recommend a four-drug initial empirical therapy to include a combination of isoniazid, rifampin, ethambutol, and pyrazinamide (Table 155-2; see Chapter 67, "Tuberculosis").[37-39] Multidrug-resistant tuberculosis remains a concern, increasing the need for suspicion and early isolation. All HIV-infected patients with positive purified protein derivative skin tests should receive isoniazid plus pyridoxine for 9 to 12 months; alternatives include rifampin or rifabutin for 4 months. In addition, give empiric treatment to HIV-infected persons in close contact with another patient with active tuberculosis. Start ART or continue a regimen, regardless of CD4 count.[40]

OTHER PNEUMONIAS

Bacterial pneumonia is the most common pulmonary infection in HIV-infected patients. Morbidity and mortality are high, with an inpatient mortality rate of 10%.[41] Common pathogens are *S. pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*. Productive cough, leukocytosis, and the presence of a focal infiltrate suggest bacterial pneumonia. Risk factors and prognosis for bacterial pneumonia among HIV-infected persons on newer ART are similar to those of the general population.[42]

Patients with severe immunosuppression are predisposed to disseminated fungal infections such as those caused by *C. neoformans, H. capsulatum,* and *Aspergillus fumigatus*. Cytomegalovirus or *M. avium* complex infections can occur in patients with extremely low CD4 cell counts (<50 cells/mm^3).

NONINFECTIOUS PULMONARY DISORDERS

Lymphocytic interstitial pneumonia may present with dyspnea and hypoxia. Typical radiographic findings include ground-glass opacities and/or nodules. Treat lymphocytic interstitial pneumonia with a systemic antiretroviral regimen. Chronic obstructive pulmonary disease and asthma are seen with increasing frequency and are managed with traditional therapies.[43] HIV-infected persons are at increased risk for lung cancer, which may include Kaposi's sarcoma and lymphoma.[44,45] Increased incidence of pulmonary hypertension may be related to HIV infection, injecting drug use, and/or ART.[46] Pulmonary hypertension may present with dyspnea, cough, or chest pain and should be treated with ART.

CARDIOVASCULAR COMPLICATIONS

Cardiovascular disease is one of the most common causes of death.[47] HIV-infected individuals are at increased risk of cardiovascular disease.[48-51] Cardiovascular complications may be related to opportunistic infections, structural defects, or drug toxicity. HIV-associated cardiovascular conditions include ischemic heart disease, cardiomyopathy, infective endocarditis, pericardial effusion, congestive heart failure, or dysrhythmias. Cardiotoxicity may result from illicit substances, such as cocaine and methamphetamine, or therapeutic agents, such as pentamidine and zidovudine.

RENAL COMPLICATIONS

Monitor renal function during care for those with HIV infection, because renal insufficiency secondary to HIV-associated nephropathy, HIV immune complex disease, prerenal azotemia, drug nephrotoxicity, and arterionephrosclerosis are possible.[52,53] Risk factors for HIV-associated nephropathy include African descent, low CD4 count, and high viral load.[54] Nephrotoxicity may rise from ART, including agents such as atazanavir, tenofovir, acyclovir, foscarnet, indinavir (associated with nephrolithiasis), trimethoprim, and other agents. In the ED, check serum creatinine, estimated glomerular filtration rate, and urinary sediment.[55] Many medications, including antiretroviral agents, have renal metabolism and require dosage adjustment for patients with renal insufficiency.

GI COMPLICATIONS

GI disorders compose some of the most common complaints in patients with HIV. Frequent presenting symptoms include odynophagia, abdominal pain, and diarrhea. ED evaluation seeks to identify the severity of symptoms and perform appropriate initial diagnostic studies. Therapy starts with volume and electrolyte repletion, with antimicrobial therapy

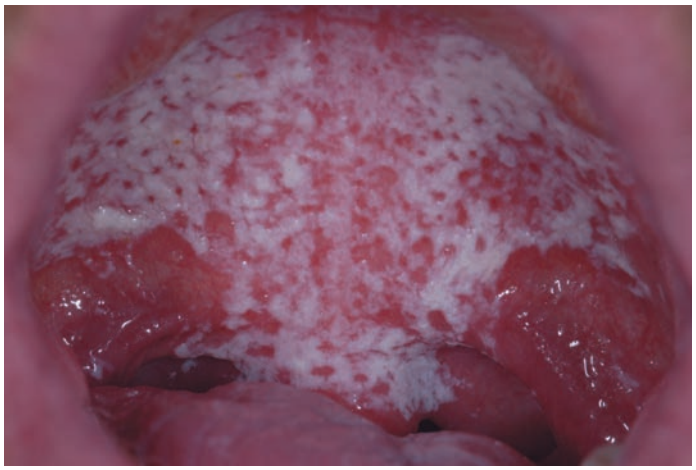

FIGURE 155-2. Oral candidiasis (thrush). Extensive thrush is seen on the hard and soft palate of this immunocompromised patient. [Photograph contributed by Lawrence B. Stack. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine*, 3rd ed, © 2009, McGraw-Hill, Inc., New York.]

when appropriate. Disposition is based on degree of immunosuppression, the duration of symptoms, the clinical appearance of the patient, and the response to ED therapy.

ORAL AND ESOPHAGEAL COMPLICATIONS

Oral Candidiasis/Thrush Oral lesions are common in HIV-infected patients, frequently contributing to malnutrition. The appearance of oral lesions in HIV patients serves as a potential clinical marker for degree of immunodeficiency, with increased rates of thrush occurring with CD4 counts of <500 cells/mm^3. Oral candidiasis ("thrush"; **Figure 155-2**) affects >80% of AIDS patients. The tongue and buccal mucosa are commonly involved, and the plaques are easily scraped from the erythematous base. Differentiation from hairy leukoplakia (adherent, white, thickened lesion[s] on the lateral tongue border) is challenging, but microscopic examination of a potassium hydroxide smear can confirm the diagnosis. Oral fluconazole, 100 mg once daily for 7 to 14 days, is first-line treatment; clotrimazole and nystatin are second-line treatments.

Other Oral Lesions Other causes of painful oral and perioral lesions include hairy leukoplakia, which is associated with the Epstein-Barr virus, leads to epithelial thickening on the lateral borders of the tongue, and is adherent. Herpes simplex virus infection usually has painful oral and perioral vesicular lesions, with diagnosis confirmed by identification of multinucleated giant cells in scrapings or by culture. Both herpes simplex virus infection and hairy leukoplakia are responsive to oral acyclovir. Oral Kaposi's sarcoma appears as a nontender, well-circumscribed, slightly raised violaceous lesion. Diagnosis requires biopsy, with topical treatments being palliative and started outside the ED.

Esophageal involvement may occur with *Candida*, herpes simplex virus, and cytomegalovirus infection. Complaints of odynophagia, dysphagia, or chest pain may be indicative of esophagitis and be debilitating. In those with CD4+ T-cell counts of <200 cells/mm^3, *Candida* is responsible for the majority of bouts. Treatment for esophagitis is presumptive in the ED with oral fluconazole (Table 155-2). IV amphotericin B is a second-line therapy and used when oral treatment fails. Endoscopy, histologic staining and culture of lesions, and biopsy should be done for patients who fail to respond to therapy or have atypical presentations. Cytomegalovirus and herpes simplex virus infections discovered by endoscopy are treated with ganciclovir and acyclovir, respectively.

DIARRHEA

Diarrhea is the most frequent GI complaint of patients with HIV. Infectious causes include bacteria (*Shigella*, *Salmonella*, enteroadherent *Escherichia coli*, *Entamoeba histolytica*, *Campylobacter*, *M. avium-intracellulare* complex, *Clostridium difficile*, and others), parasites (*Giardia lamblia*, *Cryptosporidium*, *Cystoisospora belli* [previously *Isospora belli*], and others), viruses (cytomegalovirus, herpes simplex virus, HIV, and others), and fungi (*H. capsulatum*, *C. neoformans*, and others). In those with CD4 <200 cells/mm^3, consider *Cryptosporidium* and microsporidia; if CD4 is <50 cells/mm^3, patients are at risk for cytomegalovirus and MAC. Sexual transmission of shigellosis and lymphogranuloma venereum is increasing and may contribute to etiology of diarrhea in men who have sex with men. In many cases, a pathogen is never identified.

In the ED, exclude dietary causes and medication effects first; then, obtain stool culture for enteric bacteria, a specimen for *C. difficile* toxin (in the setting of antibiotic use), and multiple stool specimens for ova and parasite examination (including acid-fast bacilli and trichrome stain). Bacterial infections generally follow a more acute and fulminant course, whereas parasitic infections are frequently indolent. If suspecting bacterial infection in a patient with CD4 count <200 cells/mm^3 and clinically severe diarrhea (six or more episodes or bloody stools and/or fevers/chills), start empiric treatment with ciprofloxacin by mouth.

Cryptosporidium and *Cystoisospora* infections are common parasitic causes associated with profuse watery diarrhea; both are detected by modified acid-fast staining of a stool specimen. *Cystoisospora* infection is usually responsive to trimethoprim-sulfamethoxazole, but relapse is common. Cryptosporidiosis is difficult to treat; ART is the mainstay of treatment, coupled with supportive care, including rehydration and electrolyte repletion. The efficacy of paromomycin and nitazoxanide and other agents is unclear.

In patients with CD4 <50 cells/mm^3, the most common diarrheal pathogens are cytomegalovirus and *M. avium-intracellulare* complex, each requiring biopsy for diagnosis. Use prolonged antimicrobial therapy; relapse is frequent for both infections.

About 15% of patients with late-stage AIDS experience severe, high-volume watery diarrhea absent a clear pathogen, with the presumed diagnosis of AIDS-related enteropathy. Octreotide may aid some of these patients. Crofelemer may reduce symptoms of noninfectious diarrhea in patients with HIV.[56] Diarrhea can also be a side effect of protease inhibitors; non-Hodgkin's lymphoma and Kaposi's sarcoma can also present with diarrhea if GI tract involvement is present. Pancreatic insufficiency may represent a treatable cause of chronic diarrhea.

ED management consists of repletion of fluid and electrolytes and treatment of targeted pathogens, as noted earlier; admit those with suspected bacteremia, AIDS, significant dehydration, malnutrition, or electrolyte imbalance. Patients who appear nontoxic and can tolerate liquids are eligible for outpatient care and follow-up to obtain test results. In the absence of bloody diarrhea or systemic complaints, treat patients symptomatically with antimotility agents (e.g., loperamide, diphenoxylate).

OTHER GI COMPLICATIONS

Coinfection with hepatitis B virus and hepatitis C virus is common, especially among injection drug users. Opportunistic infection with cytomegalovirus, *Cryptosporidium*, *M. avium-intracellulare* complex, and *M. tuberculosis* also may cause hepatitis. *Cryptosporidium* may also cause cholangiopathy. Drug-related hepatitis and hypersensitivity are other possibilities.

Anorectal disease is common in AIDS patients. Proctitis presents with painful defecation, rectal discharge, or tenesmus. Common causative organisms include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, lymphogranuloma venereum, and herpes simplex virus. Proctocolitis includes the same symptoms plus diarrhea, and multiple bacterial organisms may be responsible (most commonly *Shigella*, *Campylobacter*, and *E. histolytica*). Evaluation includes anoscopy with microscopic examination, Gram staining, and culture of pus and/or stool.

CUTANEOUS COMPLICATIONS

Noninfectious cutaneous disorders are common in HIV and can include xerosis, eczema, seborrheic dermatitis, psoriasis, and drug reactions.[57] Pruritus is common, and ED evaluation includes history, physical examination, removal of offending agents, and treatment of the underlying condition. Symptomatic treatment with emollients and antipruritic agents can be effective.[58]

CUTANEOUS INFECTIONS

Skin and soft tissue infections occur in the HIV-infected population, and often are signs of disseminated disease or bacteremia. Methicillin-resistant *S. aureus* colonization and infection are prevalent and are associated with low CD4+ cell counts, men who have sex with men, anal intercourse, previous methicillin-resistant *S. aureus* infections, and illicit drug use.[59,60] Human papillomavirus infections manifesting as condyloma acuminata or warts are common; treatment is cosmetic or symptomatic and includes cryotherapy, topical therapy, or laser therapy. Intertriginous infections with *Candida* or *Trichophyton* are frequent in HIV-positive patients. Treatment is with topical clotrimazole, miconazole, or ketoconazole. Molluscum contagiosum presents as CD4 counts decrease to <100 cells/mm^3 with pearly flesh-colored papules with central umbilication; the goal of localized treatment is primarily cosmetic. Scabies occurs in about 20% of HIV-infected patients, with scaly, persistent pruritic eruptions. Treat with permethrin 5% cream or oral ivermectin. Atypical presentations, such as papular or crusted scabies, may also occur. Cutaneous cytomegalovirus, tuberculosis, syphilis, coccidioidomycosis, histoplasmosis, and cryptococcosis are other considerations and may mandate systemic treatment.

HERPES SIMPLEX VIRUS

Herpes simplex virus infections are common and either localized or systemic. In patients with immunosuppression, infection may become progressive and chronic (see Chapter 153, "Sexually Transmitted Infections"). IV acyclovir is the therapy for extensive disease (Table 155-2).

VARICELLA-ZOSTER VIRUS INFECTION

Reactivation of varicella-zoster virus is more common in patients with HIV infection and AIDS than in the general population. The clinical course is prolonged, and complications are more frequent. In HIV-positive patients, oral acyclovir, famciclovir, and valacyclovir are options for treatment for those with limited involvement in absence of significant immunosuppression (Table 155-2). Patients with disseminated disease or ophthalmic involvement should receive IV acyclovir.

KAPOSI'S SARCOMA

Kaposi's sarcoma appears more often in men who have sex with men than in other risk groups. Clinically, it consists of firm, painless, raised, brown-black or purple patches, plaques, or nodules (see Figure 251-30).

Common sites are the face, chest, genitals, and oral cavity, but widespread dissemination involving internal organs may occur. Biopsy confirms the diagnosis. Radiotherapy treats localized disease; widespread disease may be responsive to chemotherapy in combination with ART.[61]

BACILLARY ANGIOMATOSIS

In patients with CD4 count <100 cells/mm^3, *Bartonella* may cause vascular proliferations of the skin, although any organ may be involved. Firm, red or violaceous nodules are painful and may resemble pyogenic granulomas or Kaposi's sarcoma. Treatment typically consists of doxycycline or erythromycin, and patients should be referred for biopsy.

SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections, HIV, and viral hepatitis share common routes of transmission and may coexist.[62-64] Genital ulcers caused by diseases such as herpes, chancroid, and syphilis are portals of entry for HIV. There is more frequent HIV seropositivity in patients with genital ulcers, gonorrhea, and chlamydial infections. The prevalence of sexually transmitted infections, including syphilis, is increasing and warrants enhanced surveillance.[65] See Chapter 153 for details.

IMMUNIZATION OF HIV-INFECTED PATIENTS

HIV-infected persons should not receive live-virus or live-bacteria vaccines.[66] The exception to this rule is the measles-mumps-rubella vaccine.

Killed or inactivated vaccines pose no danger to immunosuppressed patients.[67] Because symptomatic HIV-infected persons have a suboptimal response to vaccines, all single-dose vaccines are best given early in the course of HIV infection. **Table 155-4** summarizes recommendations for common immunizations.

TABLE 155-4 Immunization Recommendations for Adult Human Immunodeficiency Virus–Infected Patients

Recommended Vaccines	Recommendation
Tetanus, diphtheria, and pertussis (Tdap)	One booster in adulthood
Tetanus-diphtheria toxoid (Td)	Every 10 y
Pneumococcal	One dose
Influenza (inactivated)	One dose annually
Hepatitis B	Three doses over a 2-y period
Withhold in Severe Immunodeficiency	
Measles-mumps-rubella	Avoid in patients with CD4+ T-cell count <200 cells/mm^3
Varicella	Avoid in patients with CD4+ T-cell count <200 cells/mm^3
Contraindicated Vaccines	
Oral polio vaccine	
Smallpox vaccine	
Live attenuated influenza vaccine	

ANTIRETROVIRAL THERAPY

After the introduction of ART, sharp declines in AIDS incidence and mortality occurred, transforming HIV therapeutics into long-term management of a chronic infection. General therapeutic goals include: (1) prolonging and improving the quality of life; (2) reducing viral load as much as possible to halt disease progression and prevent or reduce the development of resistant variants; (3) promoting immune reconstitution, both quantitative (CD4+ T-cell count) and qualitative (pathogen-specific immune response); and (4) reducing side effects and maintaining therapeutic options. A complete drug list and up-to-date guide for the general classes of antiretroviral drugs, principles for initiating therapy, and common adverse reactions are on the Centers for Disease Control and Prevention website (https://www.cdc.gov/hiv/guidelines/index.html).

The five main classes of antiretroviral drugs are (1) nucleoside reverse transcriptase inhibitors, which interfere with the action of reverse transcriptase (e.g., zidovudine); (2) nonnucleoside reverse transcriptase inhibitors, which bind to reverse transcriptase and block RNA- and DNA-dependent DNA polymerase activity (e.g., efavirenz); (3) protease inhibitors, which block HIV protease, a key enzyme in establishing HIV infectivity (e.g., indinavir); (4) entry inhibitors, which prevent HIV entry into cells by targeting specific viral surface proteins or their corresponding receptors (e.g., enfuvirtide); and (5) integrase inhibitors, which work by blocking integrase, a protein that HIV needs to insert its viral genetic material into the genetic material of an infected cell (e.g., raltegravir).

Preferred initial treatment regimens include at least three drugs—two nucleoside reverse transcriptase inhibitors *plus* one of the following classes: nonnucleoside reverse transcriptase inhibitor, protease inhibitor (boosted with ritonavir), or integrase strand transfer inhibitor. The newest guidelines recommend that all HIV-infected patients, regardless of CD4+ cell count, start ART in order to reduce morbidity and mortality associated with HIV infection and to prevent HIV transmission.[68] Education and counseling are considered an integral part of ART initiation regarding risk and benefits as well as developing strategies to optimize adherence.[69] For these reasons, decisions regarding initiation of and changes in ART should be made in consultation with the primary care physician and an infectious disease consultant.

DRUG INTERACTIONS AND ADVERSE EFFECTS IN HIV-INFECTED PATIENTS

Current ART programs include a standard three-drug regimen that may cause a range of changes in metabolic or physiologic functions and be toxic. **Table 155-5** shows the currently available antiretroviral

TABLE 155-5 Antiretroviral Medications, Major Adverse Effects, and Interacting Drug Effects[70]

Antiretroviral Medications*	Adverse Effects	Interacting Drugs	Effects of Interaction
Nucleoside reverse transcriptase inhibitors			
Abacavir	Stevens-Johnson syndrome, hypersensitivity reaction		
Didanosine	Peripheral neuropathy, lactic acidosis, pancreatitis, retinal changes, insulin resistance/diabetes mellitus		
Emtricitabine	Skin hyperpigmentation/discoloration, acute exacerbation of hepatitis may occur in HBV/HCV patients who discontinue drug		
Lamivudine	Acute exacerbation of hepatitis may occur in HBV/HCV patients who discontinue drug		
Stavudine	Pancreatitis, lactic acidosis/hepatic steatosis (rare), peripheral neuropathy, ascending muscle weakness (rare), dyslipidemia, lipoatrophy		
Tenofovir	Pancreatitis, headache, renal insufficiency, diarrhea, nausea, vomiting, osteomalacia, acute exacerbation of hepatitis may occur in HBV/HCV patients who discontinue drug		
Zidovudine	Bone marrow suppression, nausea, vomiting, headache, lactic acidosis/hepatic steatosis (rare), hyperlipidemia, insulin resistance/diabetes mellitus, lipoatrophy, myopathy		
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)		Anticonvulsants, rifampin	Anticonvulsants: decreased concentration of antiretrovirals (some contraindicated), rifampin: decreased NNRTI (contraindicated with some NNRTIs)
Delavirdine	Transaminitis, rash, headache		
Efavirenz	Depression, psychosis, suicidal ideation, rash, serum transaminase elevation, hyperlipidemia, QT prolongation	Midazolam	Increased concentration of midazolam (oral administration contraindicated)
Etravirine	Rash (including Stevens-Johnson syndrome, hypersensitivity reaction), nausea		
Nevirapine	Rash (including Stevens-Johnson syndrome), hepatic failure		
Rilpivirine	Rash, depression, insomnia, headache, hepatoxicity, QT prolongation	Proton pump inhibitors	Decreased concentration of antiretroviral (contraindicated)
Protease inhibitors	Hyperlipidemia, hyperglycemia, fat maldistribution	Antiarrhythmics, anticonvulsants, anticoagulants and antiplatelet agents, midazolam, rifampin, HMG-CoA reductase inhibitors	Antiarrhythmics: increased levels of both drugs (some contraindicated); anticonvulsants: decreased concentration of antiretroviral and varying concentration of the interacting drug (some contraindicated); anticoagulants: varying impact on anticoagulant concentration (monitoring needed with warfarin, coadministration not recommended with others); midazolam: increased midazolam (do not administer orally); rifampin: decreased concentration of antiretroviral (contraindicated); HMG-CoA reductase inhibitors: increased risk of rhabdomyolysis
Amprenavir	Toxicity from propylene glycol diluent		
Atazanavir	Indirect hyperbilirubinemia, prolonged PR interval, cholelithiasis, nephrolithiasis, renal insufficiency, serum transaminase elevations, rash	Antacids, H_2-receptor antagonists, proton pump inhibitors	Decreased absorption of atazanavir; space use of antacids/H_2-receptor antagonists; proton pump inhibitors contraindicated in some situations
		Diltiazem	Increased concentration of diltiazem (decrease diltiazem dose by half)
Darunavir	Headache, nausea, diarrhea, rash (including Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.), hepatotoxicity, serum transaminase elevation, increase in serum creatinine		
Fosamprenavir	Rash, diarrhea, nausea, vomiting, headache, serum transaminase elevation, possible increased bleeding episodes in patients with hemophilia, nephrolithiasis		
Indinavir	Nephrolithiasis, nausea, hepatitis, nephrotoxicity, indirect hyperbilirubinemia, headache, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, hemolytic anemia, possible increased bleeding episodes in patients with hemophilia		
Nelfinavir	Secretory diarrhea, possible increased bleeding episodes in patients with hemophilia, serum transaminase elevation		

(*Continued*)

TABLE 155-5 Antiretroviral Medications, Major Adverse Effects, and Interacting Drug Effects[70] (*Continued*)

Antiretroviral Medications*	Adverse Effects	Interacting Drugs	Effects of Interaction
Ritonavir	Nausea, vomiting, diarrhea, paresthesia (circumoral and extremities), hepatitis, taste perversion, possible increased bleeding episodes in patients with hemophilia		
Ritonavir/lopinavir	Nausea, vomiting, pancreatitis, serum transaminase elevation, insulin resistance/diabetes mellitus, possible increased bleeding episodes in patients with hemophilia, PR interval prolongation	Digoxin	Increased digoxin concentration (monitor levels)
Saquinavir	Nausea, diarrhea, headache, serum transaminase elevation, possible increased bleeding episodes in patients with hemophilia, PR interval prolongation, QT interval prolongation, torsades de pointes		
Tipranavir	Intracerebral hemorrhage, hepatotoxicity, rash, possible increased bleeding episodes in patients with hemophilia	Proton pump inhibitors	Decreased absorption of proton pump inhibitors; coadministration not recommended
Entry and fusion inhibitors			
Enfuvirtide	Bacterial pneumonia, injection site reaction, hypersensitivity reaction		
CCR-5 antagonist			
Maraviroc	Abdominal pain, postural hypotension, cough, dizziness, pyrexia, rash, upper respiratory tract infection, hepatotoxicity		
Integrase inhibitors		Anticonvulsants	Decreased antiretroviral concentrations (some contraindicated)
Dolutegravir	Hypersensitivity reaction, insomnia, headache, depression and suicidal ideation (rare)		
Raltegravir	Increased creatine phosphokinase, rhabdomyolysis, muscle weakness, nausea, diarrhea, headache, rash (including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis), pyrexia, insomnia, depression, and suicidal ideation (rare)		

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

*Some antiretroviral agents have interactions with buprenorphine and methadone, requiring modifications of the latter two agents.

Source: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. (Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services.) Accessed October 17, 2018.

medications, their major adverse effects, and their interacting drug effects. Concomitant antibiotic prophylaxis can compound adverse effects from antiretrovirals.

Drug interactions are pharmacokinetic (changes in the level of one or more drugs) or pharmacodynamic (changes in effect, therapeutic response, or side effect of one or more drugs).[71,72] Consultation with a hospital pharmacologist and an infectious disease specialist helps manage those with a suspected drug reaction.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 156

Endocarditis

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INTRODUCTION AND EPIDEMIOLOGY

Endocarditis patients often have nonspecific signs and symptoms, but endocarditis has the potential for multiorgan involvement. The clinical course of endocarditis can be indolent or fulminant. The majority of endocarditis is infective; diagnosis relies on a set of explicit criteria (see later Tables 156-3 and 156-4 in "Diagnosis" section). Unrecognized endocarditis has frequent complications and high mortality.

In developed countries, the incidence of infective endocarditis ranges from 2 to 11.6 cases per 100,000 patient-years[1-7] and is higher in urban settings (likely reflecting the impact of injection drug use). Pediatric endocarditis is uncommon and is primarily associated with structural heart disease, postoperative congenital heart disease, rheumatic heart disease, or catheter-related bacteremia.[8] Overall, men are more commonly affected than women, and in-hospital mortality rate ranges from 18% to 32%.[1,2,9] Short-term mortality in medically managed endocarditis increases with severe comorbid illnesses, abnormal mental status, congestive heart failure, or a bacterial etiology other than *Streptococcus viridans*.[10]

Most cases of endocarditis occur in those with a predisposing structural abnormality (congenital or acquired), prosthetic valve, or a risk factor for disease (e.g., injection drug use, intravascular device, poor dental hygiene, chronic hemodialysis, human immunodeficiency virus infection). Although the mitral valve is the most commonly affected site (followed by the aortic, tricuspid, and pulmonic valves), the incidence of tricuspid valve endocarditis has steadily increased, attributed principally to increased rates of injection drug use.[11]

For native valve endocarditis in the developed world, mitral valve prolapse is a common predisposing lesion. Other underlying structural factors include congenital defects (e.g., bicuspid aortic valve), degenerative cardiac lesions (calcific aortic stenosis), and rheumatic heart disease. In developing countries, rheumatic heart disease–related valvulopathy remains the leading risk factor.

The estimated risk in injection drug users is 2% to 5% per year, with a mean age of diagnosis of 30 years old. Injection drug use–associated endocarditis often involves the tricuspid valve, has an increased susceptibility to recurrence (approximately 40%), and has increased mortality

in human immunodeficiency virus–positive patients with CD4+ count of <200/mm^3. Large vegetation size and fungal organism are also associated with poor outcome.[12]

Indwelling vascular devices create increased risk that microorganisms will attach to valves during bacteremia. Healthcare-associated endocarditis occurs when diagnosis is made >72 hours after admission without evidence of endocarditis on admission, endocarditis develops within 6 months after hospital discharge, or endocarditis develops within 6 months of cardiovascular manipulations including central venous catheter use, arteriovenous fistula for hemodialysis, invasive intravascular techniques, or intracardiac devices such as pacemakers and left ventricular assist devices.[13,14]

Prosthetic valve endocarditis occurs in 1% to 4% of recipients during the first year following replacement and in approximately 1% per year thereafter. There is no difference in infection risk between mechanical or bioprosthetic valves. Cases with onset within 60 days after surgery are termed *early* prosthetic valve endocarditis and are usually nosocomial. Cases starting beyond 60 days after surgery are termed *late* prosthetic valve endocarditis and are usually community acquired. Hospital mortality rates are highest for those with early (30% to 80%) versus late (20% to 40%) prosthetic valve endocarditis, attributable to the greater virulence of the causative organisms involved.

PATHOPHYSIOLOGY

The normal endothelium is resistant to infection and thrombus formation. Injury from high-pressure gradients and turbulent flow, as occurs with preexisting valvular or congenital cardiac lesions, lessens the natural defense. With injection drug use, endothelial damage occurs from repetitive bombardment with particulate matter (i.e., talc) present in injected material or from ischemia brought on by drug-induced vasospasm (cocaine use is particularly associated with endocarditis). The resultant endothelial damage promotes platelet/fibrin deposition and the formation of sterile vegetations (nonbacterial thrombotic endocarditis). Nonbacterial thrombotic vegetations (also called *marantic* endocarditis) can result from hypercoagulable states, malignancy, or systemic lupus erythematosus (Libman-Sacks endocarditis) and in areas surrounding foreign bodies (vascular catheters or prosthetic valves).

Transient bacteremia (as little as 10 organisms per milliliter of blood for <30 minutes) may colonize and convert to infective endocarditis. Triggers include skin trauma or endogenously colonized surfaces of the oropharynx or GI or GU tract. Endocarditis can occur in the absence of trauma, and in normal hosts, it can be related to spontaneous bacteremia arising from brushing teeth, dental procedures, and both minor or systemic infections.[15-19]

Coexistence of bacteremia and nonbacterial thrombotic endocarditis does not uniformly result in infective endocarditis. The infecting organism must be able to adhere to the nonbacterial thrombus on the endothelium. Adherent organisms stimulate further deposition of platelets and fibrin, leading to generation of a "protected site" that phagocytic cells cannot easily penetrate. Although nonbacterial thrombotic endocarditis often precedes infective endocarditis, it not a prerequisite because highly invasive organisms (*Staphylococcus aureus*) can directly invade the endocardium. As the disease progresses, fragments from vegetation spread into the circulation and cause sustained bacteremia.

MICROBIOLOGY

A wide range of pathogens cause infective endocarditis. Bacteria are the predominant cause, with a small number of species responsible for most of the cases (**Table 156-1**). *Staphylococcus* is the single most common cause, followed by streptococci (including viridans group streptococci) and enterococci.[1,3,20-23] Other rarer causes of infectious endocarditis include *Rickettsia, Chlamydophila*, *Bartonella*, *Coxiella burnetii*, *Legionella*, *Candida*, and *Aspergillus*.[23]

The increase in staphylococcal endocarditis is linked to the increase in healthcare-associated endocarditis and increasing IV drug use. *S. aureus* is associated with rapid valve destruction, infection of structurally normal heart valves (particularly tricuspid valves in patients who are IV drug abusers), and increased risk of in-hospital death.[1] The incidence of staphylococcal endocarditis related to pacemaker lead infection is also increasing and associated with severe morbidity and mortality.[24] In contrast, streptococcal endocarditis tends to be indolent. Enterococcal endocarditis is associated with underlying valvular disease and risk factors (diabetes mellitus, manipulation of the GU or lower GI tract). Early prosthetic valve endocarditis is most commonly caused by perioperative colonization from *Staphylococcus epidermidis, Aspergillus,* or *Candida albicans*.

Blood cultures are the best method for detection of endocarditis but are negative in about 5% of patients; 33% to 50% of culture-negative endocarditis is attributed to prior antibiotic administration. For culture-negative cases without prior antibiotic administration, infection is most often due to fastidious organisms (usually from the HACEK group—*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella*—and also *Bartonella* and *Coxiella burnetii*).[25]

CLINICAL FEATURES

The clinical manifestations of endocarditis range from acute/fulminant to insidious/indolent.[20] Common presenting symptoms include fever, chills, weakness, and dyspnea. The most common complications are

TABLE 156-1 Microbiology of Infective Endocarditis (IE)

Native Valve IE (% of cases)			Intracardiac Device IE (% cases)		
	Normal Host	Injection Drug Use		Prosthetic Valve IE	Other Devices*
Staphylococcus aureus	28	68	*S. aureus*	23	35
Coagulase-negative *Staphylococcus*	9	3	Coagulase-negative *Staphylococcus*	17	26
Viridans group streptococci	21	10	*Viridans* group streptococci	12	8
Other streptococci	14	3	*Streptococcus bovis*	10	7
Enterococcus species	11	4	*Enterococcus* species	12	6
HACEK	2	0	HACEK	2	1
Fungus	1	1	Fungus	4	1
Polymicrobial	1	3	Polymicrobial	1	0
Others	4	5	Others	7	6
Culture negative	9	3	Culture negative	12	10

Abbreviation: HACEK = *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* group.

*Including pacemakers and implantable cardioverter-defibrillators.

TABLE 156-2 Clinical Features of Infective Endocarditis

Symptoms	%	Signs	%
Fever	80	Fever	90
Chills	40	Heart murmur	85
Weakness	40	New murmur	3–5
Dyspnea	40	Changing murmur	5–10
Anorexia	25	Skin manifestations	18–50
Cough	25	Osler nodes	10–23
Malaise	25	Splinter hemorrhages	15
Skin lesions	20	Petechiae	20–40
Nausea/vomiting	20	Janeway lesions	<10
Headache	20	Splenomegaly	20–57
Stroke	20	Embolic phenomena	>50
Chest pain	15	Septic complications	20
Abdominal pain	15	Mycotic aneurysm	20
Mental status change	10–15	Renal failure	10
Back pain	10	Retinal lesions	2–10

congestive heart failure (44%), CNS findings (30%), and peripheral arterial embolization (22%).[22]

FEVER

Early bacteremia produces nonspecific signs and symptoms (**Table 156-2**), usually beginning within 2 weeks of infection. Symptoms include fever, chills, nausea, vomiting, fatigue, and malaise.[15] Fever (>38°C [100.4°F]) is present in almost all patients (>90% overall, >98% with injection drug use).[5,14,20,21] Fever may be absent in the elderly, those using antibiotics or antipyretics, and those with congestive heart failure, renal failure, or immunosuppression.

CARDIAC MANIFESTATIONS

Congestive heart failure occurs in up to 70% of patients from distortion or perforation of valvular leaflets, rupture of the chordae tendineae or papillary muscles, or perforation of cardiac chambers. Heart murmurs are common, heard in 50% to 85% of patients, although less so in right-sided endocarditis (<50%). Valvular abscesses and pericarditis can result from local extension. Other cardiac complications include heart blocks and dysrhythmias that result from extension of infection through the interventricular septum to the conduction system.

NEUROLOGIC MANIFESTATIONS

About 20% to 40% of patients develop neurologic symptoms, including embolic cerebral ischemic events (often in multiple areas, a clinical clue), CNS abscess, intracranial hemorrhage, mycotic (or infected) aneurysm, meningitis, or seizures.[26] Rupture of a cerebral mycotic aneurysm results in subarachnoid hemorrhage. Embolic stroke involving the middle cerebral artery is the most common CNS complication.[1]

ARTERIAL EMBOLIZATION

Embolization of vegetation fragments is common (20% to 50% of patients),[27] resulting in infarction or abscess in remote tissues. Pulmonary complications include pulmonary infarction, pneumonia, empyema, or pleural effusion; multifocal pneumonia, like multifocal cerebral infarction, often is a clue to septic embolization. Coronary artery emboli usually arise from the aortic valve and may cause acute myocardial infarction or myocarditis. Embolic splenic infarction causes left upper quadrant abdominal pain with radiation to the left shoulder. Renal emboli result in flank pain and hematuria. Emboli to the mesenteric arteries cause acute abdominal pain, melena, or bowel ischemia. Emboli to arteries of the extremities may produce acute limb ischemia. Retinal artery embolism may cause acute monocular blindness.

CUTANEOUS FINDINGS

Cutaneous embolic phenomena are less common due to early detection and treatment. Cutaneous findings may occur in 5% to 10% of cases and may include petechiae, splinter or subungual hemorrhages of digits, Osler nodes (small, tender subcutaneous nodules on the pads of the digits), and Janeway lesions (small hemorrhagic painless plaques on the digits).[28,29] Digital clubbing is infrequent, and occurs only in those with long-standing disease. Cutaneous signs are not specific and occur in other types of vasculitis or bacteremia.

DIAGNOSIS

Suspicion of endocarditis usually requires hospital admission for culture, echocardiography, and assessment of the clinical course.[1] Prolonged unexplained fever, malaise, or other constitutional symptoms should prompt evaluation for endocarditis. Thoroughly evaluate and admit febrile injection drug users since the prevalence of endocarditis is high (10% to 15%), follow-up is often challenging, and clinical findings cannot reliably exclude the diagnosis. Admit patients with a cardiac prosthetic valve and fever (or persistent malaise, vasculitis, or new murmur) given the high morbidity and mortality associated with prosthetic valve infections. In stable patients with a low suspicion of endocarditis who were initially discharged, admit immediately once positive blood cultures result.

The **Duke criteria**[30,31] aid diagnosis of infective endocarditis (**Tables 156-3** and **156-4**). A more recent study demonstrated excellent negative predictive value for the Prediction Rule for Endocarditis in Injection Drug Users, which assesses risk based on tachycardia, cardiac murmur, and absence of skin infection.[32] This latter tool requires more research before wider use in ED treatment and disposition decisions.

BLOOD CULTURES

Obtain blood cultures (at least 10 mL per culture bottle) before beginning antibiotics. Draw three sets from separate sites because fewer collections may not detect bacteremia. Those receiving any antibiotic therapy recently often require additional sets of blood cultures. Ideally, wait at least 1 hour between the first and last blood culture. Although administration of antibiotics prior to culture acquisition reduces recovery rate of

TABLE 156-3 Duke Criteria* for Infective Endocarditis

Major Criteria

- Positive blood culture for IE
- Typical microorganism consistent with IE from two separate blood cultures* as noted below:
- *Streptococcus bovis,* viridans streptococci, HACEK group

  or
- Community-acquired *Staphylococcus aureus* or enterococci in the absence of a primary focus

  or
- Microorganisms consistent with IE from persistently positive blood cultures defined as:
  - At least two positive cultures of blood samples drawn >12 h apart

    or
  - All of three or a majority of four or more separate blood cultures (with first and last sample drawn at least 1 h apart)
- Single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer of >1:800
- Evidence of echocardiographic involvement
- Positive ECG for IE defined as:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation

    or
  - Abscess

    or
  - New partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

- Predisposition: predisposing heart condition or injection drug use
- Fever: temperature >38°C (100.4°F)
- Vascular phenomena: major arterial emboli, septic pulmonary conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid fever
- Microbiologic evidence: positive blood culture but does not meet a major criterion as noted in Table 156-4* or serologic evidence of active infection with organism consistent with IE
- Echocardiographic minor findings were eliminated in the modified Duke criteria

Abbreviations: HACEK = *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella*; IE = infective endocarditis.

*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause IE.

TABLE 156-4 Modified Duke Criteria for Infective Endocarditis

Definite Infective Endocarditis

- Pathologic criteria
- Microorganisms demonstrated by culture or histologic examination of a vegetation or in a vegetation that has embolized or in an intracardiac abscess

  or
- Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Clinical Criteria, Using Specific Definitions Listed in Table 156-3

- Two major criteria

  or
- One major and three minor criteria

  or
- Five minor criteria

Possible infective endocarditis

- One major criterion and one minor criterion
- Three minor criteria

Rejected

- Firm alternate diagnosis for manifestations of endocarditis

  or
- Resolution of manifestations of endocarditis with antibiotic therapy for 4 d or less

  or
- No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for 4 d
- Does not meet criteria for possible infective endocarditis

bacteria by 35% to 40%,[33] in critically ill patients, do not withhold antibiotics to obtain cultures.[34] In patients with confirmed endocarditis, repeat blood cultures every 48 to 72 hours to assess treatment progress.[23,35]

For patients at risk for culture-negative infective endocarditis, advise the laboratory of the suspected diagnosis to prompt specialized testing for fastidious organisms. Polymerase chain reaction techniques aid pathogen detection.

OTHER DIAGNOSTIC TESTS

There are no definitive laboratory tests that diagnose endocarditis. Common findings are anemia (70% to 90%), hematuria, and elevation of erythrocyte sedimentation rate (>90%), C-reactive protein, or procalcitonin.

ECG findings are also nonspecific but can identify conduction abnormalities resulting from infection. Prolonged PR interval, new left bundle branch block, or new right bundle branch block with left anterior hemiblock suggests spread of infection into the conduction system. Junctional tachycardia, Wenckebach block, or complete heart block may indicate extension of infection from the mitral annulus into the atrioventricular node or proximal bundle of His.

Chest radiographs may demonstrate pulmonic emboli (often in multiple areas) in patients with right-sided valvular involvement or may show acute heart failure in those with left-sided valvular involvement.

ECHOCARDIOGRAPHY

Echocardiographic abnormalities represent one of the two major criteria for definitive diagnosis. Two-dimensional transthoracic echocardiography is the first choice for those with native valves.[35,36] The specificity of transthoracic echocardiography for vegetations is excellent (98%), although sensitivity varies according to patient population. Sensitivity of transthoracic echocardiography is highest in injection drug users (88% to 94%), who more often have larger vegetations, right-sided lesions, and favorable acoustic windows. For those with chest wall deformities, obesity, or chronic obstructive pulmonary disease, transthoracic echocardiography is less sensitive.

Transesophageal echocardiography is more sensitive and specific in detecting valvular abnormalities than transthoracic echocardiography due to improved image resolution but is less immediately available in the emergency setting. Use transesophageal echocardiography in patients with prosthetic valves or intracardiac devices, patients with inadequate transthoracic echocardiography imagery, and those with intermediate or high clinical probability of endocarditis.[35,36] Transesophageal echocardiography is of particular value for assessing suspected complications such as myocardial abscess and perivalvular extension.

TREATMENT

INITIAL STABILIZATION

Patients with endocarditis may present with hemodynamic instability, respiratory compromise, pulmonary edema, diminished pulmonary capacity, altered mental status, and acidosis. Emergency stabilization with airway management and hemodynamic monitoring and support are priority interventions. Intra-aortic balloon counterpulsation aids the

emergency management of unstable mitral valve rupture but is contraindicated for aortic valve rupture.

Definitive management requires a team approach, and that often includes experts from cardiology, infectious disease, and cardiac surgery.

Systemic clot lysis or anticoagulation for treatment of endocarditis-associated stroke is controversial (concern of worsening underlying event) and best managed together with a stroke expert. Current guidelines for native valve endocarditis recommend withholding anticoagulation for at least 2 weeks after a CNS embolic event to reduce the risk of hemorrhagic transformation.[23,37,38]

Patients with prosthetic valves being treated with anticoagulants may be maintained on established regimens as long as there is no evidence of bleeding. Patients with prosthetic valve endocarditis and evidence of embolic strokes should have anticoagulation and antiplatelet therapy withheld for at least 2 weeks to reduce the risk of hemorrhagic transformation.[23,39]

EMPIRIC TREATMENT OF SUSPECTED ENDOCARDITIS OF NATIVE VALVES

Antibiotic selection is based on patient characteristics and local resistance patterns. **Table 156-5** lists sample empiric treatment regimens.[23,39-41] Although some recommend awaiting culture results before antibiotic therapy for patients with subacute bacterial endocarditis, we recommend ED initiation of antibiotic therapy targeting the most common organisms for all patients suspected of endocarditis **after** obtaining blood cultures. For patients with suspected native valve infection, empiric antibiotic therapy includes a penicillinase-resistant penicillin, a cephalosporin, or daptomycin.[42] Gentamicin is no longer recommended for native valve staphylococcal infective endocarditis due to minimal benefit and significant nephrotoxicity.[23,41,43] For patients with complications (injection drug use, congenital heart disease, nosocomial infection, endocarditis developed while taking oral antibiotics, or suspected methicillin-resistant *S. aureus*), add vancomycin.

TABLE 156-5 Empiric Therapy of Suspected Bacterial Endocarditis*

Patient Characteristics	Recommended Agents, Initial Dose
Uncomplicated history	Ceftriaxone, 1–2 grams IV *or* Nafcillin, 2 grams IV *or* Oxacillin, 2 grams IV *or* Cefepime, 1 gram IV *and* Vancomycin, 15 milligrams/kg (if anaphylactic to penicillins) *or* Tobramycin, 1 milligram/kg IV
Injection drug use, congenital heart disease, hospital-acquired, suspected methicillin-resistant *Staphylococcus aureus,* or already on oral antibiotics	Nafcillin, 2 grams IV *plus* Vancomycin, 15 milligrams/kg IV *or* Daptomycin 8–10 milligrams/kg IV
Concern for vancomycin-resistant *Enterococcus* infection	Daptomycin 8–10 milligrams/kg *or* Linezolid 600 milligrams
Prosthetic heart valve	Nafcillin 2 grams IV (if oxacillin-susceptible) *or* Vancomycin, 15 milligrams/kg IV (if oxacillin resistance is suspected) *plus* Gentamicin, 1–2 milligrams/kg IV *plus* Rifampin, 300 milligrams PO

*Based on American Heart Association, endorsed by the Infectious Diseases Society of America (http://www.idsociety.org/Organ_System/, accessed April 1, 2014). Because of controversy in the literature regarding the optimal regimen for empiric treatment, antibiotic selection should be based on patient characteristics, local resistance patterns, and current authoritative recommendations.

EMPIRIC TREATMENT OF SUSPECTED PROSTHETIC VALVE ENDOCARDITIS

For patients with suspected artificial valve endocarditis, empiric therapy includes an antistaphylococcal β-lactam agent or vancomycin, with consideration of adding gentamicin and rifampin.[23,41]

DEFINITIVE TREATMENT OF ENDOCARDITIS

Base definitive antibiotic treatment on culture and sensitivity results. Most patients will require 4 to 6 weeks of antibiotic therapy. Surgical management is indicated in patients with severe valvular dysfunction, congestive heart failure, relapsing prosthetic valve endocarditis, major embolic complications, fungal endocarditis, new conduction defects or dysrhythmias, or persistent bacteremia after appropriate therapy.[23,39,44] Surgical risk increases in those >65 years old, on inotropes, with sepsis, or with cerebral emboli.[45] Patients with concern for pacemaker lead infection may require removal of infected hardware in order to achieve source control.[24]

ENDOCARDITIS PROPHYLAXIS

Because every day dental activities (brushing, flossing, chewing) cause bacteremia, dental hygiene is critical. Give **antibiotic prophylaxis to those at risk (Table 156-6)** prior to manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.[35,39,46] **Prophylaxis is *not* needed in those at risk for nondental procedures**, such as local injections, laceration suturing, IV placement, blood drawing, endotracheal intubation, endoscopy, vaginal delivery, oral trauma, urethral catheterization, or uterine dilation and curettage. Some experts recommend prophylaxis for body art, such as tattooing and piercing, but this is not a standard practice.[35,47]

Prophylaxis is *not* routinely indicated for patients with mitral valve prolapse, pacemakers, hypertrophic cardiomyopathy, physiologic murmurs, coronary artery bypass surgery or angioplasty, or surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus.[46]

Recommendations for procedures that manipulate infected skin structures or musculoskeletal tissue are Class IIb (consider but usefulness not established); it is reasonable to administer antibiotics before the procedure for the highest-risk groups identified in Table 156-6. Choose an antibiotic active against staphylococci and β-hemolytic streptococci; vancomycin and clindamycin are options for those unable to tolerate a β-lactam or those suspected to have an infection caused by a methicillin-resistant strain of *Staphylococcus*. The incidence of bacteremia with abscess incision and drainage is very low, which is one reason why many do not prophylaxis in this setting.

A simplified strategy for antibiotic prophylaxis is provided in **Table 156-7**. With the endorsement of the National Institute for Health and Clinical Excellence of London,[48] the European College of Cardiology does not recommend prophylaxis before respiratory tract procedures, GI or GU procedures, or uncomplicated dermatologic or musculoskeletal procedures.[49]

TABLE 156-6 Highest-Risk Conditions for Endocarditis[31]

- Prosthetic heart valves
- Prosthetic material used for valve repair
- History of previous infective endocarditis
- Unrepaired cyanotic congenital heart disease
- Repaired congenital heart defect with prosthetic material or device
- Repaired congenital heart disease with residual defects
- Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve

TABLE 156-7 Prophylaxis Against Endocarditis for Highest-Risk Patients

Procedure	Patient Characteristics	Antibiotic Agent	Dose
Dental procedures involving manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa	Able to take oral antibiotics	Amoxicillin	2 grams PO, 30–60 min before procedure
		or	
	Unable to take oral medication	Ampicillin	2 grams IM or IV, 30–60 min before procedure
		or	
		Cefazolin or ceftriaxone	1 gram IM or IV, 30–60 min before procedure
	Allergic to penicillins or ampicillin	Cephalexin	2 grams PO, 30–60 min before procedure
		or	
		Clindamycin	600 milligrams PO, 30–60 min before procedure
		or	
		Azithromycin or clarithromycin	500 milligrams PO, 30–60 min before procedure
	Unable to take oral medication and allergic to penicillins or ampicillin	Cefazolin or ceftriaxone	1 gram IM or IV, 30–60 min before procedure
		or	
		Clindamycin	600 milligrams IM or IV, 30–60 min before procedure
Procedures on infected skin, skin structure, or musculoskeletal tissue	Non–methicillin-resistant strain of *Staphylococcus* or β-hemolytic *Streptococcus* suspected	Dicloxacillin	2 grams PO, 30–60 min before procedure
		or	
		Cephalexin	2 grams PO, 30–60 min before procedure
	Patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by a methicillin-resistant strain of *Staphylococcus*	Vancomycin	1 gram IV, 30–60 min before procedure
		or	
		Clindamycin	600 milligrams IM or IV, 30–60 min before procedure
Other procedures (respiratory; GI; GU; noninfected dermatologic or musculoskeletal procedures)		Prophylaxis not indicated	

With good aseptic technique, prophylactic antibiotics are not recommended prior to invasive procedures such placement of as central lines.[35]

RISK OF ENDOCARDITIS RECURRENCE

Nearly 5% of patients with a single episode of endocarditis have repeat or relapse of endocarditis. Risk factors for repeat endocarditis include IV drug use and hemodialysis.[50] Repeated episodes of endocarditis may require valvular repair or replacement.[39]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 157

Tetanus

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INTRODUCTION AND EPIDEMIOLOGY

Tetanus is uncommon in the United States, but worldwide estimates are approximately 100,000 cases per year, with a mortality rate of 35% to 40%.[1,2] The Centers for Disease Control and Prevention defines tetanus as a syndrome of acute onset of hypertonia and/or painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause.[3] In the United States, tetanus is a reportable disease, aggregated through the National Notifiable Diseases Surveillance System.

Improved childbirth practices, widespread immunization programs for children, decennial tetanus boosters for adults, mechanization of agriculture, and use of chemical fertilizers rather than animal manure have all resulted in a >95% decline in the annual incidence of tetanus in the United States since 1947.[4] From 2009 to 2015, 197 tetanus cases were reported in the United States, with 16 deaths.[4] Most patients who develop tetanus have inadequate immunity to the disease. Due to waning immunity and failure to receive routine boosters, only 31% of Americans >70 years old have adequate tetanus immunity.[5] Tetanus among children and neonatal tetanus are uncommon. The case fatality rate is approximately 8%, and patients >55 years of age account for all deaths.[3,4]

Most cases of tetanus in the United States are associated with an acute wound. Puncture, contaminated, infected, or devitalized wounds account for approximately 70% of tetanus cases. Although less common, chronic wounds and dental abscesses are also associated with the disease. Diabetics and injection drug users have an increased risk of contracting tetanus.[3,6]

Two thirds of patients who develop tetanus do not seek medical care for their initial wound. Of those who do seek initial treatment and later develop tetanus, up to 95% do not receive appropriate therapy.[3]

PATHOPHYSIOLOGY

Clostridium tetani is a motile, nonencapsulated, anaerobic gram-positive rod; it produces toxins that cause tetanus. *C. tetani* exists in either a vegetative or spore-forming state. The spores are ubiquitous in soil and animal feces and can survive on environmental surfaces for years.

In agricultural areas, adults may harbor the organism; spores are found in many places, including on skin or in contaminated heroin.[6,7] *C. tetani* is usually introduced into a wound in the spore-forming, noninvasive state but can germinate into the toxin-producing, vegetative form if tissue oxygen tension is reduced. **Crushed or devitalized tissue, a foreign body, or the development of infection favors the growth of the toxin-producing form of *C. tetani*.**[7,8]

C. tetani produces two exotoxins: tetanolysin, which facilitates growth of the bacterial population; and tetanospasmin, a powerful neurotoxin responsible for all of the clinical manifestations of tetanus. Tetanospasmin reaches the nervous system by hematogenous spread of the exotoxin to peripheral nerves and by retrograde intraneuronal transport. Tetanospasmin does not cross the blood–brain barrier, but retrograde intraneuronal transport of the exotoxin enables tetanospasmin to gain access to the CNS.[8]

Tetanospasmin prevents the release of the inhibitory neurotransmitters glycine and γ-aminobutyric acid from presynaptic nerve terminals, releasing the nervous system from its normal inhibitory control. Loss of inhibition may also affect the preganglionic sympathetic neurons, resulting in sympathetic overactivity and high circulating catecholamine levels.[7-10]

CLINICAL FEATURES

Tetanus results in generalized muscular rigidity, violent muscular contractions, and autonomic nervous system instability.[8] Wounds that become contaminated with toxin-producing *C. tetani* are often puncture wounds, but contaminated wounds range from deep lacerations to minor abrasions.[3] **No wound exists in up to 10% of patients with tetanus.** Tetanus can also develop after surgical procedures, otitis media, or abortion and can develop in injection drug users from contaminated heroin and in neonates through infection of the umbilical stump.[6,11] **The incubation period for tetanus ranges from <24 hours to >1 month.** Short incubation periods are associated with severe disease and a poor prognosis. Clinical tetanus comes in three forms: generalized, cephalic, and local.

Generalized tetanus accounts for about 80% of cases. The most frequent presenting complaints of patients with generalized tetanus are pain and stiffness in the masseter muscles ("lockjaw"). Nerves with short axons are first involved, with symptoms in the facial muscles; later, descending progression to the muscles of the neck, trunk, and extremities occurs. The transition from muscle stiffness to rigidity leads to the development of trismus and the characteristic facial expression called risus sardonicus (sardonic smile). Reflex convulsive spasms and tonic muscle contractions are responsible for the development of dysphagia, opisthotonic flexing of the arms, clenching of the fists, and extension of the lower extremities. Spasms can last for 3 to 4 weeks. Recovery depends on regrowth of axonal nerve terminals and may take months.[8] Complications of tetanus include rhabdomyolysis and long-bone fractures secondary to violent muscle contractions. The mental status is normal, an important consideration in differentiating tetanus from other disorders (**Table 157-1**). Patients remain conscious and alert unless laryngospasm or contraction of respiratory muscles results in respiratory compromise. Aspiration pneumonia is present in 50% to 70% of autopsied cases.[7,8]

Autonomic dysfunction and a hypersympathetic state including tachycardia, labile hypertension, profuse sweating, hyperpyrexia, and increased urinary excretion of catecholamines occur during the second week of clinical generalized tetanus.[8-10] **Neonatal tetanus**, a form of generalized tetanus, develops in infants born to inadequately immunized mothers, frequently after unsterile treatment of the umbilical cord stump.[11] Infants with neonatal tetanus are weak, irritable, and have an inability to suck. Symptoms are evident by the second week of life.[11]

Cephalic tetanus follows injuries to the head or occasionally otitis media and results in dysfunction of the cranial nerves, most commonly the seventh. It has a poor prognosis.

Local tetanus displays muscle rigidity in proximity to the site of injury and usually resolves completely after weeks to months. Local tetanus may progress to the generalized form of the disease. Approximately 1% of these cases are fatal.[7,8]

TABLE 157-1 Differential Diagnosis of Tetanus

Disorder	Comments
Strychnine poisoning	See Chapter 201, "Pesticides."
Dystonic reaction (phenothiazines, metoclopramide)	See Chapter 180, "Antipsychotics."
Hypocalcemic tetany	See Chapter 17, "Fluids and Electrolytes."
Malignant neuroleptic syndrome	See Chapter 180, "Antipsychotics."
Serotonin syndrome	See Chapter 178, "Atypical and Serotonergic Antidepressants."
Stiff person syndrome	Centrally mediated motor hyperexcitability with persistent and intense spasms, particularly of the proximal lower limbs and lumbar paraspinal muscles.
Peritonsillar abscess	See Chapter 246, "Neck and Upper Airway."
Peritonitis	See Chapter 71, "Acute Abdominal Pain."
Meningeal irritation (bacterial meningitis, subarachnoid hemorrhage)	See Chapter 174, "Central Nervous System and Spinal Infections," and Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage."
Rabies	See Chapter 158, "Rabies."
Temporomandibular joint disease	See Chapter 243, "Face and Jaw Emergencies."

DIAGNOSIS

Tetanus is a clinical diagnosis. In the United States, 96% of tetanus cases occur in those with unknown or inadequate immunization history.[3] The elderly, those on hemodialysis, and the immunocompromised often have inadequate immunity.[12,13] There are no laboratory tests to diagnose tetanus, although serum antitoxin titers of >0.01 IU/mL are usually protective. An immunochromatographic dipstick test allows rapid assessment of immunity, with an 88% sensitivity and 98% specificity; it may be useful in regions with high disease incidence.[14] However, tetanus can occur in patients with protective levels of antitetanus antibodies.[15] Wound culture is of limited value because *C. tetani* may be cultured from wounds in the absence of clinical disease and may not be recovered in patients with documented tetanus.

Table 157-1 provides the differential diagnosis of tetanus. **Strychnine poisoning** most closely mimics the clinical picture of generalized tetanus.

TREATMENT

Treatment is supportive (**Table 157-2**). Identify and debride the wound to improve the oxidation-reduction potential of infected tissue, remove spores, and prevent further toxin production. Provide tetanus immunization because the disease does not result in immunity.

Admit patients with tetanus to the intensive care unit. Respiratory compromise requires immediate neuromuscular blockade and intubation. Minimize environmental stimuli to prevent the precipitation of reflex convulsive spasms.

TETANUS IMMUNOGLOBULIN

Human tetanus immunoglobulin neutralizes circulating tetanospasmin and toxin in the wound but not toxin already fixed in the nervous system. Even though tetanus immunoglobulin does not reduce clinical symptoms of tetanus, it may reduce mortality.[16] For postexposure prophylaxis, a single dose of 250 units (4 units/kg in children) IM given in the anterolateral thigh or deltoid is recommended. For the treatment of clinical tetanus, the optimal dose of tetanus immunoglobulin is unknown, but 3000 to 6000 units IM is the usual recommended dose, administered in a separate syringe and opposite the site of tetanus toxoid administration. A portion of the dose is optimally given in and around the wound.[7] Intrathecal administration of tetanus immunoglobulin does not appear to have advantages over standard IM delivery.[17] Give **tetanus immunoglobulin before wound debridement because exotoxin may**

TABLE 157-2 Treatment of Tetanus

Respiratory management	Sedation and neuromuscular blockade with succinylcholine or vecuronium for intubation and ongoing mechanical ventilation
Immunotherapy	Tetanus immunoglobulin, 3000–6000 units IM opposite side of the body from tetanus toxoid, with at least a portion around the wound site *and* Tetanus toxoid (DTaP or Td/Tdap depending on age), 0.5 mL IM at presentation, and 6 wk and 6 mo after presentation
Wound care	Wound debridement
Antibiotic therapy	Metronidazole, 500 milligrams IV every 6 h. **Penicillin can theoretically potentiate the effects of tetanospasm.**
Muscle relaxation	Diazepam preferred
Management of autonomic dysfunction	Magnesium sulfate, 40 milligrams/kg IV loading, then 2 grams/h (1.5 grams/h if ≤45 kg) continuous infusion to maintain blood level of 2.0–4.0 mmol/L *or* Labetalol, 0.25–1.0 milligram/min continuous IV infusion Morphine sulfate, 0.5–1.0 milligram/kg/h Clonidine, 300 micrograms every 8 h by nasogastric tube

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; Tdap = tetanus toxoid with lower doses of diphtheria and acellular pertussis than DTaP; Td = tetanus-diphtheria.

be released during wound manipulation. Repeated doses of tetanus immunoglobulin are unnecessary because the half-life is 28 days.

ANTIBIOTICS

Antibiotics have limited utility; when used, **metronidazole**, 500 milligrams IV every 6 to 8 hours, is the antibiotic regimen of choice.[18-20] Penicillin can theoretically potentiate the effects of tetanospasmin, but no clinical data show an adverse effect in use.[21]

MUSCLE RELAXANTS

Tetanospasmin prevents neurotransmitter release at inhibitory interneurons, so tetanus therapy aims at restoring normal inhibition. The benzodiazepines are centrally acting inhibitory agents used for this purpose. Diazepam is the preferred benzodiazepine for treatment of tetanus because of cost and availability. **Another option is midazolam, a water-soluble agent, administered as a continuous infusion in cases that require large doses of benzodiazepines.[21]** Intrathecal baclofen has some effect in the treatment of tetanus but is not recommended as routine therapy.[17,21]

NEUROMUSCULAR BLOCKADE

Prolonged neuromuscular blockade aids in control of ventilation, muscular spasms, secondary fractures, and rhabdomyolysis. Succinylcholine can be given early for emergency airway control, whereas vecuronium is a good option for prolonged blockade because of minimal cardiovascular side effects.[19]

TREATMENT OF AUTONOMIC DYSFUNCTION

One randomized controlled trial in 256 patients with severe tetanus demonstrated that magnesium sulfate reduced autonomic instability and muscle spasm in the disease.[9] Magnesium sulfate also reduces urinary catecholamine excretion in patients with severe tetanus.[10] However, a meta-analysis failed to show a benefit of magnesium sulfate on tetanus mortality, and the effect of the drug on duration of intensive care unit and hospital stay and need for ventilatory support was unclear.[22]

Adrenergic blocking agents may reduce the autonomic dysfunction of severe tetanus. A short-acting β-blocker such as esmolol, or a combined α- and β-adrenergic blocking agent such as labetalol, are options.

Morphine sulfate reduces sympathetic α-adrenergic tone and central sympathetic efferent discharge and produces peripheral arteriolar and venous dilatation.[8] Clonidine, a central α_2-receptor agonist, may reduce the sympathetic hyperactivity that causes autonomic dysfunction and thereby provide better control of crises.[23]

TETANUS IMMUNIZATION

Patients who recover from tetanus must receive active immunization, because infection does not confer immunity and vaccination is the only means of disease prevention. Give adsorbed tetanus toxoid (0.5 mL) IM at the time of presentation and at 6 weeks and 6 months after injury.

In patients with incomplete vaccinations, with tetanus-prone wounds and more than 5 years from previous vaccination, or with any wounds more than 10 years from vaccination, use tetanus-diphtheria if ≥7 years old.[24] Use diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) for patients <7 years of age.[25] Because of the recent increase in the incidence of pertussis, adults should receive a single lifetime dose of Tdap (tetanus toxoid with lower doses of diphtheria and acellular pertussis than DTaP) to replace one tetanus-diphtheria booster.[25] Adolescents should also receive a single dose of Tdap, preferably at 11 to 12 years of age.[26] An inadvertent dose of DTaP in an adult would count as the single lifetime dose of Tdap.

The revised Advisory Committee on Immunization Practices guidelines recommend administering a dose of Tdap during each **pregnancy**, irrespective of the patient's prior history of receiving Tdap or interval since last injection, to maximize the maternal antibody response and passive antibody levels in the newborn.[27] Tdap may be given at any point during pregnancy, with optimal timing between 27 and 36 weeks of gestation unless treating a specific wound. For women who have never received Tdap, it should be given to the mother immediately postpartum.

Table 157-3 summarizes the guidelines for tetanus immunization and tetanus prophylaxis in wound management.[25] Patients with human immunodeficiency virus infection or severe immunodeficiency who have contaminated wounds should also receive tetanus immunoglobulin, regardless of their tetanus immunization history.[28] **Only about 60% of patients with an acute injury who seek medical care receive appropriate tetanus wound prophylaxis.[3]** Table 157-2 summarizes the management of tetanus.

Adverse reactions following tetanus immunization include erythema, induration, and pain at the injection site. Local reactions are common and usually self-limited. Exaggerated local reactions (Arthus reactions) occur occasionally and involve extensive pain and swelling of the entire

TABLE 157-3 Summary Guide to Tetanus Prophylaxis in Wound Management

	Clean, Minor Wounds		All Other Wounds*	
History of Adsorbed Tetanus Toxoid (doses)	Tdap or Td† IM	TIG, 250 units IM	Tdap or Td†	TIG, 250 units IM
Unknown or less than 3	Yes‡	No	Yes	Yes
3 or more§	No¶	No	Yes#	No

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; DT = diphtheria-tetanus toxoids; Td = tetanus-diphtheria; Tdap = tetanus toxoid with lower doses of diphtheria and acellular pertussis than DTaP; TIG = tetanus immunoglobulin.

*For example, wounds >6 hours old, contaminated with soil, saliva, feces, or dirt; puncture or crush wounds; avulsions; wounds from missiles, burns, or frostbite.

†DTaP for children <7 years of age (DT if pertussis vaccine is contraindicated); Td for persons ≥7 years of age. A single booster dose of Tdap is recommended for adolescents and adults to replace 1 Td booster.

‡The primary immunization series should be completed. Three doses total are required, with the second dose given at least 4 weeks after the first dose and the third dose given 6 months later.

§If only three doses of fluid toxoid have been received, then a fourth dose of *absorbed* toxoid should be given.

¶Yes, if >10 years since last dose.

#Yes, if >5 years since last dose. Boosters more frequent than every 5 years may predispose to side effects.

extremity. Arthus reactions occur most often in adults with high serum tetanus antitoxin levels who have received frequent doses of tetanus toxoid, which is the reason this therapy is limited to 10-year intervals.

Contraindications to tetanus-diphtheria or Tdap include a history of serious allergic reaction (respiratory compromise or cardiovascular collapse) to vaccine components. History of encephalopathy (e.g., coma or prolonged seizures) not attributable to an identifiable cause within 7 days of administration of a pertussis vaccine is a contraindication to Tdap. Reasons to defer tetanus-diphtheria or Tdap include Guillain-Barré syndrome ≤6 weeks after a previous dose of tetanus toxoid-containing vaccine, moderate to severe acute illness, unstable neurologic condition, or history of an Arthus reaction to a tetanus toxoid–containing vaccine administered <10 years previously.[25] If tetanus toxoid is contraindicated, consider passive immunization with tetanus immunoglobulin.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 158

Rabies

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INTRODUCTION AND EPIDEMIOLOGY

This chapter reviews the pathophysiology and epidemiology of rabies, pre- and postexposure rabies prophylaxis, and clinical presentation and treatment of rabies. Current information is available from the Centers for Disease Control and Prevention (http://www.cdc.gov/rabies/).

More than 3 billion people are at risk of rabies in over 100 countries.[1] Rabies is responsible for approximately 60,000 fatalities annually worldwide, with India accounting for approximately one third of cases.[2,3] The World Health Organization estimates that more than 15 million people receive a postexposure preventive regimen annually.[4]

Rabies is primarily a disease of animals.[5-7] The epidemiology of human rabies reflects both the distribution of the disease in animals and the degree of human contact with these animals. A summary of major rabies vectors is provided in **Table 158-1**.

In the United States, rabies is endemic in many wild animal populations, with more than 5500 rabid animals reported in 2015.[8] Although human rabies is rare in the United States, postexposure rabies prophylaxis is provided to between 40,000 and 50,000 persons each year.[9] The cost of rabies prevention in the United States is greater than $300 million, most of which is spent on dog vaccinations.[10] From January 2003 to September 2016, 38 cases of human rabies were reported in the United States, of which 12 cases were contracted in other countries. **Bats** represent the most common exposure for human rabies cases in the United States.[8] **Worldwide, greater than 99% of human rabies cases are acquired by dog bite**.[2]

TABLE 158-1 Major World and U.S. Rabies Vectors

Vector	Region
Dogs	Asia, Latin America, Africa
Foxes	Europe, Arctic, North America
Skunks	Midwest United States, Western Canada
Coyotes	Asia, Africa, North America
Mongooses	Asia, Africa, Caribbean
Bats	North America, Latin America, Europe
No rabies	Hawaii, United Kingdom, Australasia, Antarctica

PATHOPHYSIOLOGY

Rabies virus is the prototype member of the genus *Lyssavirus*.[11,12] All lyssaviruses are adapted to replicate in the mammalian CNS, are transmitted by direct contact, and are not associated with transmission by or natural replication in insects.

Viral infection of the salivary glands of the biting animal is responsible for the infectivity of saliva.[5-7,13] After a bite, saliva containing infectious rabies virus is deposited in muscle and subcutaneous tissues. The virus remains close to the site of exposure for the majority of the **long incubation period (typically 20 to 90 days)**. Rabies virus binds to the nicotinic acetylcholine receptor in muscle, which is expressed on the postsynaptic membrane of the neuromuscular junction. Subsequently, the virus spreads across the motor end plate and ascends and replicates along the peripheral nervous axoplasm to the dorsal root ganglia, the spinal cord, and the CNS. Following CNS replication in the gray matter, the virus spreads outward by peripheral nerves to virtually all tissues and organ systems.

Histologically, rabies is an encephalitis, resulting in infiltration of lymphocytes, polymorphonuclear leukocytes, and plasma cells, and focal hemorrhage and demyelination in the gray matter of the CNS, the basal ganglia, and the spinal cord. Negri bodies, in which CNS viral replication occurs, are eosinophilic intracellular lesions found within cerebral neurons and are highly specific for rabies. Negri bodies are found in about 75% of proven cases of animal rabies. Although their presence is pathognomonic for rabies, their absence does not exclude it.

Transmission of rabies virus usually begins when the contaminated saliva of an infected host is passed to a susceptible host, usually by the bite of a rabid animal. Of note, the bite of a bat may escape notice; human rabies cases with no known animal exposure are most commonly attributed to bats.[2] Other, less common routes of documented transmission include contamination of mucous membranes (i.e., eyes, nose, mouth), aerosol transmission during spelunking (caving) in bat-infested caves, exposure while working in the laboratory with rabies virus, and infected organ transplantation (e.g., cornea, liver, kidney, vascular graft, lung).

PREEXPOSURE PROPHYLAXIS

Preexposure prophylaxis with rabies vaccine is highly recommended for persons whose recreational or occupational activities place them at risk for rabies (**Tables 158-2** and **158-3**).[14-16] Although the initial rabies preexposure vaccine regimen is similar for all risk groups, the need for booster doses, the timing of booster doses, and the need for and timing of serologic tests to confirm immunity differ based on the degree of individual risk for exposure to rabies. Preexposure prophylaxis may be obtained from the local health department or from a local physician or veterinarian. Preexposure vaccination does not eliminate the need for additional therapy after a rabies exposure but simplifies postexposure prophylaxis by eliminating the need for human rabies immunoglobulin (HRIG) and by decreasing the number of doses of vaccine required (see later section "Postexposure Prophylaxis in Special Populations"). Individuals receiving preexposure prophylaxis should be counseled regarding the continued need for postexposure prophylaxis following an exposure.

POSTEXPOSURE PROPHYLAXIS

RISK ASSESSMENT

The risk of developing rabies following a bite or scratch by a rabid animal depends on whether the wound was a bite, scratch, or nonbite exposure; the number of bites; the depth of the bites; and the location of the wounds (**Table 158-4**).[17]

Risk assessment for postexposure prophylaxis includes determining the epidemiology of animal rabies in the area where the contact occurred; knowing the species of animal involved; understanding the type of exposure (e.g., bite vs. nonbite); clarifying the circumstances of the exposure incident; and determining if the animal can be safely captured and tested for rabies (**Table 158-5**).[18] **The distinction between a "provoked" and "nonprovoked" attack should not be used for risk**

TABLE 158-2 Rabies Preexposure Risk Assessment and Recommendations

Risk Category	Nature of Risk	Typical Population	Preexposure Recommendations
Continuous	Virus present continuously, often in high concentrations; specific exposures likely to go unrecognized; bite, nonbite, or aerosol exposure	Rabies research laboratory workers,* rabies biologicals production workers	Primary course: serologic testing every 6 months; booster immunization if antibody titer is below acceptable level†
Frequent	Exposure usually episodic with source recognized, but exposure also might be unrecognized; bite, nonbite, or aerosol exposure	Rabies diagnostic laboratory workers,* cavers, veterinarians and staff, and animal-control and wildlife workers in rabies-endemic areas; all persons who regularly handle bats	Primary course: serologic testing every 2 years; booster immunization if antibody titer is below acceptable level†
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized; bite or nonbite exposure	Veterinarians and animal-control and wildlife workers working with terrestrial animals in areas where rabies is uncommon or rare, veterinary students, travelers visiting areas where rabies is endemic and immediate access to appropriate medical care, including biologicals, is limited	Primary course: no serologic testing or booster immunization
Rare (population at large)	Exposure always episodic with source recognized; bite or nonbite exposure	U.S. population at large, including persons in rabies-endemic areas	No immunization necessary

*Judgment of relative risk and extra monitoring of immunization status of laboratory workers is the responsibility of the laboratory supervisor.

†Minimum acceptable antibody level is complete virus neutralization at 1:5 serum dilution by the rapid fluorescent focus inhibition test. A booster dose should be administered if the titer falls below this level.

assessment. Most animal bites are "provoked" from the standpoint of the animal (e.g., interfering with the animal's food, offspring, feeding habits). In addition, approximately 15% of animals with rabies do *not* exhibit aggressive behavior but are apathetic ("dumb rabies"). The local health department can provide information about the epidemiology of animal rabies in the area. **Evaluation for postexposure prophylaxis is indicated for persons bitten by, scratched by, or exposed to saliva from a wild or domestic animal that could be rabid (Figure 158-1).**

Give postexposure prophylaxis as soon as possible after exposure to rabies-prone wildlife (Tables 158-5 and **158-6**).

Bites For the purpose of rabies postexposure prophylaxis, **a bite exposure is defined as any penetration of the skin by the teeth of an animal.**[14] Bites to the face and hands carry the highest risk, but the site of the bite does not influence the decision to begin therapy.

Nonbite Exposures A **nonbite exposure** is contamination of scratches, abrasions, open wounds, or mucous membranes with saliva or brain tissue from a rabid animal. For example, animal licks to nonintact skin have transmitted rabies. Nonbite exposures from animals very rarely cause rabies. If the material containing the virus is dry, the virus can be considered noninfectious. Petting a rabid animal or contact with blood, urine, or feces (e.g., guano) of a rabid animal does not constitute an exposure and is not an indication for prophylaxis.[14]

Exposures to Animals Previously Vaccinated for Rabies A fully vaccinated dog or cat (i.e., two vaccinations) is unlikely to become infected with rabies. No documented vaccine failures have been reported

TABLE 158-3 Rabies Preexposure Prophylaxis Schedule—United States (2008)

Type of Immunization	Route	Regimen
Primary	Intramuscular*	HDCV or PCECV; 1.0 mL (deltoid area), one dose on days 0,† 7, and 21 or 28
Booster‡	Intramuscular*	HDCV or PCECV; 1.0 mL (deltoid area), one dose on day 0† only

Abbreviations: HDCV = human diploid cell vaccine; PCECV = purified chick embryo cell culture vaccine.

*Use deltoid area for adults and older children. For young children, use anterolateral thigh. Do not administer vaccine in the gluteal area.

†Day 0 is the day the first dose of vaccine is administered.

‡Persons in the continuous risk category should have a serum sample tested for rabies neutralizing antibody every 6 months, and persons in the frequent risk category should be tested every 2 years. An IM booster dose of vaccine should be administered if the serum titer falls to maintain the value of at least complete neutralization at a 1:5 serum dilution by rapid fluorescent focus inhibition test. See recommendations by the Centers for Disease Control and Prevention[14] for more details.

TABLE 158-4 Risk of Rabies in the Absence of Postexposure Prophylaxis After Exposure to a Rabid Animal

- Multiple severe bites around the face: 80%–100%
- Single bite: 15%–40%
- Superficial bite(s) on an extremity: 5%
- Contamination of a recent wound by saliva: ~0.1%
- Contact with rabid saliva on a wound older than 24 hours: 0%
- Transmission via fomites (e.g., tree branch): theoretical*
- Indirect transmission (e.g., raccoon saliva on a dog): theoretical*

*Literature review revealed no cases due to this theoretical method of transmission.

TABLE 158-5 Rabies Postexposure Risk Assessment and Recommendations (2012)[18]

Animal Type	Evaluation and Disposition of Animal	Postexposure Prophylaxis Recommendations
Dogs, cats, and ferrets	Healthy and available for 10 d of observations	Persons should not begin vaccination unless animal develops clinical signs of rabies.*
	Rabid or suspected rabid	Immediate immunization.
	Unknown (e.g., escaped)	Consult public health officials.
Skunks, raccoons, foxes, and most other carnivores; bats†	Regard as rabid unless animal proven negative for rabies virus by laboratory tests‡	Consider immediate immunization.
Livestock, horses, rodents, rabbits and hares, and other mammals	Consider individually	Consult public health officials; bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, mice, rats, rabbits, hares, and other small rodents almost never require rabies postexposure prophylaxis.

*During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

†Provide postexposure prophylaxis immediately.

‡The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended.

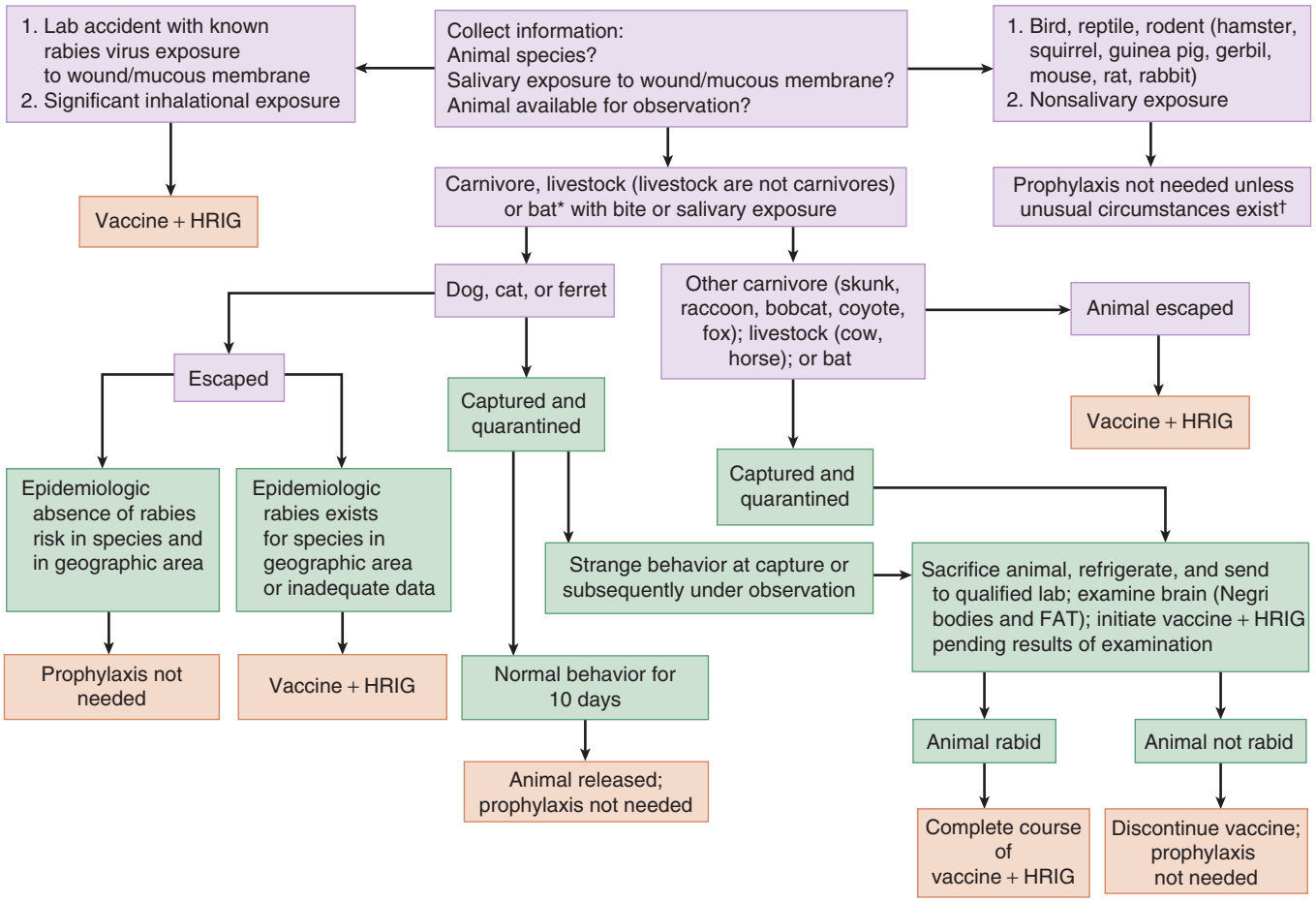


FIGURE 158-1. Clinical guidelines for administration of postexposure prophylaxis. (*) Consider postexposure prophylaxis for persons who were in the same room as a bat and who might be unaware that a bite or direct contact had occurred. (†) The small mammals listed here have never been reported to transmit rabies to humans in the United States, but theoretically, such animals could acquire and transmit rabies. Therefore, postexposure prophylaxis following a bite or scratch from one of these mammals would be indicated only if such an animal had signs typical of rabies or a positive laboratory test for rabies. Consult with local public health officials for reports of rabies in atypical animals. FAT = fluorescent antibody testing; HRIG = human rabies immune globulin.

TABLE 158-6 Summary of Risk of Acquiring Rabies in the United States

Risk	Exposures
Moderate to high	Bite by skunk, raccoon, fox, and other wild carnivores (unless animal tested negative for rabies) Bite or direct contact with bat (unless animal tested negative for rabies) Exposure by percutaneous injury, mucous membrane exposure, or inhalation to live rabies virus in a laboratory Dog bite in a country with endemic rabies and inadequate immunization of dogs (or bite by feral dog)
Very low to low	Bite by inadequately vaccinated cat or dog that has access to the outdoors (or feral cat or dog) Contamination of open wound or abrasion (including scratches) with, or mucous membrane exposure to, saliva or other potentially infectious material (e.g., neural tissue) from a possibly rabid animal (skunk, raccoon, fox, and other wild carnivores, bat) Awakening in a room with a bat present
No risk identified	Contact of animal fluids (e.g., saliva, blood, neural tissue) with intact skin Indirect contact with saliva from a wild animal (e.g., by cleaning a dog or cat that has had contact with a wild animal)

in the United States among dogs or cats that received two vaccinations. Rare cases have been reported among animals that had received only a single dose of vaccine. In the United States, animals other than dogs, cats, and ferrets that can transmit rabies and are the source of an animal bite or scratch to a human should be euthanized and tested for rabies *even if the animals have been vaccinated*.

Exposures to Bats Any direct contact between a human and a bat should be evaluated for a rabies exposure. **Seeing a bat does not constitute an exposure.** Postexposure prophylaxis is not indicated if the person can be *certain* that a bite, scratch, or mucous membrane exposure did not occur or if the bat is available for testing and results are negative for the presence of rabies virus. All bats that might be a source of exposure, if available, should be sent to the public health department and tested for rabies, because approximately 94% of submitted bats in the United States have tested negative for rabies.[19] **The Advisory Committee on Immunization Practices recommends consideration of postexposure prophylaxis for persons who were in the same room as a bat and who were unaware if a bite or direct contact had occurred** (e.g., a sleeping person awakens to find a bat in the room, or an adult witnesses a bat in a room with an unattended child, mentally disabled person, or intoxicated person).[14,18] One article calculated the incidence of rabies following bedroom exposure with contact as 0.6 cases per billion person-years,[19] whereas another article reported that the number needed to treat to prevent a single case of rabies in this context would be 314,000 to 2.7 million persons.[20]

Bites From Healthy-Appearing Animals The Centers for Disease Control and Prevention recommends that a healthy dog, cat, or ferret that bites a person be confined and observed for 10 days.[14,18] At the first sign of illness during confinement, such animals should be evaluated by a veterinarian and a report immediately made to the local health department. If signs suggestive of rabies develop, the animal should be euthanized and its head removed and shipped under refrigeration (not frozen) for examination of the brain by a qualified laboratory designated by the local or state health department.

Bites From Stray Animals Any stray or unwanted dog, cat, or ferret that bites a person may be euthanized immediately and the head submitted for rabies examination. Animals that might have exposed a person to rabies should be reported immediately to the local health department. **An animal other than a dog, cat, or ferret that received prior vaccination** may still require euthanasia and testing if the period of virus shedding is unknown for that species.

Person-to-Person Transmission There are anecdotal reports of person-to-person transmission of rabies. Fluids from the upper and lower respiratory tracts of humans frequently test positive for rabies virus. Despite the lack of proven healthcare-associated transmission, about 30% of healthcare personnel who have had contact with a human diagnosed with rabies have received postexposure prophylaxis. Given the mechanism of disease transmission and concern among healthcare workers, contact isolation precautions should be used for patients with known or suspected rabies, and healthcare workers who care for such patients should wear either masks and eye protection or face shields.[14] **Healthcare personnel with nonintact skin or mucous membrane exposure to infective saliva or neural tissue from patients with rabies should receive postexposure prophylaxis.**

Patients Concerned About Rabies For unusual exposures, the state veterinarian or local public health agency can be contacted for more information. However, for patients who voice concern about rabies exposure even if the risk assessment is virtually nil (Table 158-6), vaccination can be offered, along with an explanation of the risks and benefits of vaccination. If the risk of rabies is virtually nil, we discourage the administration of HRIG.

WOUND CARE

First, assess wounds for the presence of a life-threatening condition, such as arterial laceration or pneumothorax.[21] Provide proper wound care, including **tetanus prophylaxis, wound cleansing with soap and water and (if available) a dilute solution of povidone-iodine (1 mL povidone-iodine in 9 mL of water or normal saline)**, antibiotics (if indicated) to prevent bacterial infection (see Chapter 46, "Puncture Wounds and Bites"), and **rabies prophylaxis** as indicated.[15]

POSTEXPOSURE PROPHYLAXIS TREATMENT

In the United States, postexposure prophylaxis consists of a regimen of one dose of HRIG and four doses of rabies vaccine over a 14-day period, **except for immunocompromised persons**, who should receive a five-dose series of vaccine over a 28-day period (**Table 158-7**).[15,18] The shift from a five-dose to a four-dose series of rabies vaccine occurred in 2010 and is based on rabies virus pathogenesis, experimental animal studies, clinical trials, epidemiologic surveillance, and economic analyses.[15] No other aspects of postexposure prophylaxis were altered from the 2008 recommendations (e.g., use of HRIG, site of injection). HRIG and the first dose of rabies vaccine should be given as soon as possible after exposure, preferably within 24 hours. If HRIG was not administered when vaccination was begun, it can be administered up to 7 days after administration of the first dose of the vaccine.

Follow the Centers for Disease Control and Prevention recommendations for postexposure prophylaxis *exactly* (Table 158-7). Note that rabies vaccine should **never** be administered in the gluteal area; only the deltoid or anterolateral thigh (for younger children) is acceptable. Although no postexposure prophylaxis vaccine failures have been reported in the United States since the licensing of human diploid cell vaccine in 1980, several persons outside the United States have contracted rabies after postexposure prophylaxis with tissue culture–derived vaccine.[5] Most of these cases involved deviation from the recommended protocol; wounds were not cleansed, passive immunization with HRIG was not provided, or rabies vaccine was injected into the gluteal rather than the deltoid area. A small number of failures of apparently properly administered postexposure prophylaxis have been reported; however, such cases are rare and factors such as use of HRIG of inadequate potency cannot be definitively ruled out.[22] Nonetheless in the context of the worldwide burden of human rabies exposure, the efficacy of timely, properly administered postexposure prophylaxis is very nearly 100%.

Rabies Vaccines Rabies vaccines available in the United States include human diploid cell vaccine (produced in human diploid cells; Imovax®, Sanofi Pasteur, Lyon, France) and purified chick embryo cell culture vaccine (produced in chick embryo cells; RabAvert®, Novartis Vaccines, Emeryville, CA). **The active antibody response requires approximately 7 to 10 days to develop, and detectable rabies virus–neutralizing antibodies generally persist for several years.** All currently used vaccines are produced in cell cultures and are significantly less toxic than older vaccines that were produced in neural tissue. Side effects of human diploid cell vaccine, including mild erythema, swelling, and pain at the injection site, have been reported in 10% to 90% of vaccine recipients. Systemic reactions, such as headache, nausea, abdominal pain, muscle aches, and dizziness, have been reported in 5% to 40% of recipients. Serum sickness–like reactions (type III hypersensitivity) have been

TABLE 158-7 Rabies Postexposure Prophylaxis Schedule—United States, 2010

Immunization Status	Treatment	Regimen*
Not previously immunized	Wound cleansing	Cleanse all wounds with soap and water; irrigate wounds with 9:1 diluted solution of povidone-iodine (if available).
	HRIG	Administer **20 IU/kg actual body weight**. If anatomically feasible, infiltrate the *full dose* around the wound(s) and give any remaining volume IM at an anatomic site distant from vaccine administration; do not give HRIG in the same syringe as vaccine. HRIG may partially suppress active production of rabies virus antibody, so **do not give more than the recommended dose**.
	Vaccine	HDCV or PCECV 1.0 mL (deltoid area†), one dose on days 0,‡ 3, 7, and 14.#
Previously immunized[f]	Wound cleansing	Cleanse all wounds with soap and water; irrigate wounds with 9:1 povidone-iodine solution.
	HRIG	HRIG should *not* be administered.
	Vaccine	HDCV or PCECV 1.0 mL (deltoid area†), one dose on days 0‡ and 3.

Abbreviations: HDCV = human diploid cell vaccine; HRIG = human rabies immunoglobulin; PCECV = purified chick embryo cell culture vaccine.

*These regimens are appropriate for all age groups, including children.

†The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh (anterolateral aspect) may be used. Vaccine should never be administered in the gluteal area.

‡Day 0 is the day the first dose of vaccine is administered.

#Day 28 vaccine dose no longer recommended by the Advisory Committee on Immunization Practices, **unless the patient is immunocompromised** (see later section, Immunocompromised Persons). See http://www.cdc.gov/rabies/resources/acip_recommendations.html.

[f]Any persons with a history of preexposure prophylaxis with HDCV or PCECV; prior postexposure prophylaxis with HDCV or PCECV; or previous immunization with any other type of rabies vaccine and a documented history of antibody response to the prior immunization.

noted in approximately 6% of persons receiving booster doses of human diploid cell vaccine and occur 2 to 21 days after administration of the booster dose. Such reactions have not been life threatening and have not been reported with purified chick embryo cell culture vaccine. Anaphylaxis and neurologic symptoms have only rarely been associated with the current rabies vaccines. **Severe egg allergy is a contraindication to the use of purified chick embryo cell culture vaccine.**

Rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine.[21] Usually such reactions can be successfully managed with anti-inflammatory and antipyretic agents. When a person with a history of serious hypersensitivity to rabies vaccine must be revaccinated, antihistamines may be given. Epinephrine should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination (as after any other injection given in a healthcare setting).

Human Rabies Immunoglobulin HRIG is administered only once, at the beginning of antirabies prophylaxis, to provide immediate antibodies until the patient responds to rabies vaccine by producing antibodies. A passive antibody titer is evident in 24 hours. Failure to administer HRIG has led to rabies despite appropriate postexposure prophylaxis with human diploid cell vaccine. If HRIG was not given when vaccination was begun, it can be given through the seventh day after administration of the vaccine.[15] **Beyond the seventh day after vaccination is begun, HRIG is not indicated**, because an antibody response is presumed to have occurred. The Centers for Disease Control and Prevention recommends that as much as possible of the full dose be infiltrated around the wound. **HRIG should never be administered in the same syringe or into the same anatomic site as the vaccine**, as the antibody and vaccine will neutralize each other. Even if the wound has to be sutured, it should be infiltrated locally with HRIG. This practice is safe and does not create an additional risk of infection. However, caution is needed when injecting into a tissue compartment, such as the finger pulp, because excessive HRIG can increase compartment pressure and lead to necrosis.[23] Any remaining HRIG that cannot be administered into the local wound area should be injected intramuscularly at a site distant from vaccine administration. HRIG is prepared from plasma of hyperimmunized donors and screened for known viruses (e.g., human immunodeficiency virus, hepatitis). No cases of virus transmission from HRIG that is commercially available in the United States or Australia have been reported. HRIG should not be given to those with immunoglobulin A deficiencies and known antibodies of immunoglobulin A, because small amounts of immunoglobulin A may be present in HRIG and can cause a severe allergic reaction.

WORLD HEALTH ORGANIZATION POSTEXPOSURE PROPHYLAXIS GUIDELINES

In the United States, only regimens recommended by the Advisory Committee on Immunization Practices should be used. The World Health Organization has provided recommendations for rabies postexposure prophylaxis that also consider the cost and availability of vaccines and HRIG.[24,25] Per the World Health Organization, the indication for postexposure prophylaxis depends on the contact with the suspected rabid animal:

- Category I: touching or feeding animals, licks on intact skin (i.e., no exposure)
- Category II: nibbling of uncovered skin, minor scratches or abrasions without bleeding
- Category III: single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, licks on broken skin, exposure to bats

For category I exposures, no prophylaxis is required. For category II, immediate vaccination is recommended. For category III, immediate vaccination and administration of rabies immunoglobulin are recommended. Per the World Health Organization, factors that should be taken into consideration when deciding whether to initiate postexposure prophylaxis include the epidemiologic likelihood of the implicated animal being rabid, the category of exposure (i.e., I, II, or III), and the clinical features of the animal, as well as its availability for observation and laboratory testing. In most situations in developing countries, the vaccination status of the implicated animal alone should not be considered when deciding whether to give or withhold prophylaxis.

For IM administration, the World Health Organization recommends the following postexposure regimens. The postexposure vaccination schedule is based on injecting 1 mL or 0.5 mL (volume depends on the type of vaccine) into the deltoid muscle (or anterolateral thigh in children <1 year of age) of patients with category II and III exposures. Rabies vaccine should **never** be injected in the gluteal area. The recommended regimen consists of either a five- or a four-dose schedule:

- The five-dose schedule consists of one dose on each of days 0, 3, 7, 14, and 28.
- The four-dose schedule consists of two doses on day 0 (one dose in each of the two deltoid or thigh sites) followed by one dose on each of days 7 and 21.

An alternative for healthy, fully immunocompetent, exposed persons who receive wound care plus high-quality rabies immunoglobulin plus World Health Organization–prequalified rabies vaccines is a postexposure regimen consisting of four doses administered IM on days 0, 3, 7, and 14 (consistent with current U.S. recommendations).

Intradermal administration requires a smaller dose and is used to reduce the cost of vaccine in some countries. However, intradermal administration is technically more demanding and requires appropriate staff training. For intradermal administration, the World Health Organization recommends the following postexposure regimen: The two-site regimen prescribes injection of 0.1 mL at two sites (deltoid and thigh) on days 0, 3, 7, and 28. This regimen may be used for people with category II and III exposures in countries where the intradermal route has been endorsed by national health authorities.

POSTEXPOSURE PROPHYLAXIS IN SPECIAL POPULATIONS

Persons With Prior Rabies Immunization If exposed to rabies, persons previously vaccinated should receive two intramuscular doses (1 mL each) of vaccine, one immediately and one 3 days later.[15,18] "Previously vaccinated" refers to persons who have received one of the recommended preexposure or postexposure prophylaxis regimens of human diploid cell vaccine or purified chick embryo cell culture vaccine, or those who have received another vaccine and had a documented acceptable rabies antibody titer. HRIG is unnecessary and should not be given in these cases, because an anamnestic antibody response will follow the administration of a booster regardless of the prebooster antibody titer.

Immunocompromised Persons Immunization of immunocompromised persons presents special challenges. First, vaccines may represent a danger to the immunocompromised individual. Second, the immune response to vaccination may be insufficient. Higher doses or additional immunizations may be required, and even with these modifications, the immune response may be suboptimal. The severely immunocompromised are those who have congenital immunodeficiency, human immunodeficiency virus infection, leukemia or lymphoma, aplastic anemia, or generalized malignancy, or who are being treated with alkylating agents, antimetabolites, radiation, or large amounts of corticosteroids.[15]

Because rabies vaccine is formulated with inactivated virus, it does not represent a danger to immunocompromised persons and may be administered to such persons using the standard recommended doses and schedule (Table 158-7). However, a five-dose schedule should be used in immunocompromised persons.[15]

The recommendations for the use of HRIG are the same for immunocompromised and immunocompetent persons. However, corticosteroids, antimalarials, other immunosuppressive agents, and immunosuppressive illnesses can interfere with the development of active immunity and predispose the patient to developing rabies. **Immunosuppressive agents should not be administered during postexposure prophylaxis, unless they are essential for the treatment of other conditions.** When rabies postexposure prophylaxis is administered to persons receiving steroids or other immunosuppressive therapy, it is especially important that serum be tested for rabies antibody to ensure that an adequate response has developed.[14] To confirm the adequacy of the immune response, serum collected 1 to 24 weeks after the postexposure prophylaxis course

should completely neutralize challenge virus at a 1:5 serum dilution, as measured by a rapid fluorescent focus inhibition test.[14] If no acceptable antibody response is detected, consult an infectious disease expert and appropriate public health officials.

Travelers Preexposure prophylaxis is recommended for certain international travelers based on the local incidence of rabies in the countries to be visited, the availability of appropriate antirabies biologicals, and the intended travel activity.[26,27] Such persons include veterinarians, animal handlers, field biologists, spelunkers, missionaries, and certain laboratory workers. It is recommended to consult the CDC Yellow Book (https://wwwnc.cdc.gov/travel/page/yellowbook-home) prior to travel for updated guidance. **Chloroquine phosphate** (and possibly other structurally related antimalarials such as mefloquine, which is administered for malaria chemoprophylaxis) **may interfere with the antibody response to intradermal rabies vaccine administered for preexposure prophylaxis.** The IM route, not the intradermal route, should be used for people taking chloroquine concurrently (the intradermal route is not approved for use in the United States); ideally, the rabies preexposure vaccination series should be completed before beginning chloroquine.

Between 2003 and September 2016, nine persons died in the United States from rabies after having been exposed (most often via dog bite) while visiting a foreign country.[8] For this reason, all persons who have returned from abroad should be questioned regarding whether they received an animal bite or scratch in an area with endemic rabies. Persons bitten or scratched by an animal in an area with endemic rabies should receive appropriate postexposure prophylaxis if the injury has occurred within the known incubation period (which may rarely extend up to 5 or more years).

U.S. citizens and residents who are exposed to rabies while traveling in countries where rabies is endemic may sometimes receive postexposure prophylaxis with regimens or biologicals that are not used in the United States. If postexposure prophylaxis is begun outside the United States using a regimen or biological of nerve tissue origin not approved by the U.S. Food and Drug Administration, it may be necessary to provide additional treatment when the patient reaches the United States.[14] State and local health departments should be contacted for specific advice in such cases. The major modification used abroad, usually in an attempt to reduce cost, is the substitution of various schedules for intradermal injection or the use of vaccines not approved by the U.S. Food and Drug Administration.

Pregnant Women **Adverse pregnancy outcomes or fetal abnormalities have not been associated with rabies vaccination.** Because of the potential consequences of inadequately treated rabies exposure and because adverse events have not been associated with rabies postexposure prophylaxis during pregnancy, pregnancy is not considered a contraindication to rabies postexposure prophylaxis or HRIG.[14] If there is substantial risk of exposure to rabies, preexposure prophylaxis may also be indicated during pregnancy.

Children The dose of rabies vaccine for preexposure and postexposure prophylaxis is the same in infants and children as in adults (Table 158-7).[14] The dose of HRIG for postexposure prophylaxis is based on actual body weight. For small children with multiple bites, the calculated dose of HRIG may be insufficient to infiltrate all wounds. However, sterile saline can be used to dilute the volume twofold or threefold to permit thorough infiltration.[26]

CLINICAL RABIES

Rabies virus causes **acute encephalitis** in all warm-blooded hosts, including humans, and the outcome is almost always fatal. Although patients with rabies may manifest a variety of clinical symptoms and signs, the disease tends to follow a characteristic course (**Table 158-8**).

Most commonly, the incubation period after a bite ranges from 20 to 90 days.[5] However, incubation periods have been reported that are as short as 4 days and as long as 6 years. For patients who died from rabies in the United States between 1980 and 1996 and in whom a definite animal bite occurred, the median incubation period was 85 days (range, 53 to 150 days).[28] The incubation period is shorter when the site of the bite is on the head than when it is on an extremity.[5]

TABLE 158-8 Natural History of Clinical Rabies in Humans After Incubation Period

Clinical Stage	Defining Event	Usual Duration	Common Symptoms and Signs*
Prodrome	First symptom	2–10 d	Pain or paresthesia at site of bite Malaise, lethargy Headache Fever Nausea, vomiting, anorexia Anxiety, agitation, depression
Acute neurologic phase	First neurologic sign	2–7 d	Anxiety, agitation, depression Hyperventilation, hypoxia Aphasia, incoordination Paresis, paralysis Hydrophobia, pharyngeal spasms Confusion, delirium, hallucinations Marked hyperactivity
Coma	Onset of coma	0–14 d	Coma Hypotension, hypoventilation, apnea Pituitary dysfunction Cardiac arrhythmia, cardiac arrest
Death or recovery (extremely rare)	Death or initiation of recovery	Months (recovery)	Pneumothorax Intravascular thrombosis Secondary infections

*Not every symptom or sign may be present in each case.

CLINICAL FEATURES

During the prodrome, the symptoms and signs are nonspecific. Early in the course, some patients may report symptoms suggestive of rabies such as limb pain, limb weakness, and paresthesias at or near the presumed exposure site. The prodrome merges into the acute neurologic phase, which begins when the patient develops objective signs of CNS disease.

There are two clinical forms of rabies: an encephalitic form in 80% and a paralytic form in 20%.[13] In encephalitic rabies, there are often episodes of generalized arousal or hyperexcitability, disorientation, hallucinations, and bizarre behavior, often separated by lucid intervals. Autonomic dysfunction is common and includes hypersalivation, hyperthermia, tachycardia, hypertension, piloerection, cardiac arrhythmias, and priapism. Paralytic rabies generally begins with paresis in the bitten extremity with spread to quadriparesis and bilateral facial weakness. There is progression of paralytic rabies to coma and organ failure, typically with a longer clinical course than in encephalitic rabies.[13] About 50% of patients have classic hydrophobia, in which attempts to drink fluids result in severe spasms of the pharynx, larynx, and diaphragm.

Coma almost always occurs within 10 days of the onset of symptoms. Death occurs due to a variety of complications, including pituitary dysfunction, seizures, respiratory dysfunction with progressive hypoxia, cardiac dysfunction with dysrhythmias and arrest, autonomic dysfunction, renal failure, and secondary bacterial infections.

Only 14 patients are known to have survived rabies; most survivors have had severe neurologic sequelae. In all but three cases, the patient had received postexposure prophylaxis with rabies vaccine (e.g., duck embryo, suckling mouse brain) before the onset of symptoms.[2]

DIAGNOSIS AND TREATMENT

Rabies should be included in the differential diagnosis of any patient with unexplained acute, rapidly progressive encephalitis, especially in the presence of anatomic instability, dysphagia, hydrophobia, paresis, or parasthesias.[29-32] Diseases that may be confused with rabies include tetanus, poliomyelitis, Guillain-Barré syndrome, botulism, transverse myelitis, postvaccinal encephalomyelitis, intracranial mass lesions,

cerebrovascular accidents, poisoning with atropine-like compounds, and infectious causes of viral encephalitis (e.g., herpes simplex, varicella zoster, arthropod-borne viral encephalitis such as eastern equine encephalitis). Emerging diseases that can be confused with rabies include West Nile virus (United States, Europe, Middle East, Africa), Toscana virus (Europe), Japanese encephalitis (Asia), enterovirus 71 (Asia), human herpes virus 6 (worldwide), chikungunya fever (Asia, Africa, Europe), Nipah virus (Asia), and Hendra virus (Asia).[33,34]

The diagnosis of rabies is frequently made postmortem. This occurs because of the rarity of the disease, the increasing number of persons without an obvious exposure, and clinical confusion with other disorders. Important clues to diagnosis include a history of an animal bite or bat exposure and the development of the pathognomonic signs of hydrophobia and aerophobia (precipitating grimacing and other signs by blowing air on the patient's face).

During the incubation period of rabies, no diagnostic test is available for animals or humans that will indicate infection. Once symptoms become evident, antigen detection in biopsy specimens from highly innervated skin (i.e., nuchal skin), antibody detection in serum (if unvaccinated) or CSF (all people), isolation of virus from saliva, or detection of nucleotide sequences in saliva, skin, or other tissues can detect evidence of the disease.[7,35] Serum antibodies may be present as early as day 5 of clinical illness, but antibodies may be absent after 10 to 14 days or longer. CT of the brain is only useful to exclude other diseases. MRI of the brain may be normal or may show lesions in gray matter areas of the brain parenchyma, including the brainstem. Cerebrospinal fluid analysis often shows a mild mononuclear pleocytosis.

No specific therapy has been of demonstrated benefit in clinical rabies.[7] Treatment with rabies vaccine, rabies immunoglobulin, IV ribavirin, or interferon is not effective.[36] In animal models, use of corticosteroids shortens the incubation time and increases mortality, and for this reason, **steroids are contraindicated**. Survival with normal neurologic function was reported for a 15-year-old girl in whom coma was induced and treatment with ketamine, midazolam, ribavirin, and amantadine was provided.[37] However, similar regimens have been used for more than 30 other patients without success.[38] Most documented cases of rabies survival have occurred since 2000, suggesting that modern supportive care increases the likelihood of survival, particularly in resource-rich settings. Currently, treatment is directed at the clinical complications of the disease. Although rabies is not treatable, every attempt should be made to achieve rapid diagnosis, because it justifies public health measures to limit contacts with the patient and permits reconstruction of a history to identify others who may have been exposed to the same infective source.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 159

Malaria

Malcolm E. Molyneux

INTRODUCTION

Malaria, a protozoan disease transmitted by the bite of the *Anopheles* mosquito, is one of mankind's most feared and serious afflictions. It is a leading cause of morbidity and mortality in many tropical areas of the world, especially in Africa. Approximately 55% of the world's population is exposed to the infection, which exerts its toll mainly on the young and the pregnant. Malaria is endemic or sporadic throughout most of the tropics and subtropics below an altitude of 1500 m, excluding the Mediterranean littoral, the United States, and Australia. Malaria is perhaps the most significant disease acquired through international travel to the tropics.

Five species of the genus *Plasmodium* infect humans: *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium falciparum*, and *Plasmodium knowlesi.* In 2016, there were an estimated 216 million cases of symptomatic malaria worldwide (88% of which occurred in Africa), with about 445,000 deaths, 90% of which occurred in Africa, with nearly 77% of those occurring in young children.[1] The great majority of malaria deaths are due to *P. falciparum* infections, although both *P. vivax* and *P. knowlesi* can also cause fatal disease. *P. knowlesi* is a zoonosis. Macaques (old world monkeys) are the natural host, and the transmitting mosquito's habitat is limited to the forest fringe—a fact that may limit the spread of this species of parasite.[2]

The global incidence of malaria (both cases and deaths) has decreased dramatically in recent years. In many countries, however, transmission has remained unchanged or even increased.[1] Obstacles to successful reduction of malaria worldwide include human factors (poverty, war, inadequate international cooperation), capacities of the mosquito vector (changing temperatures, insecticide resistance), and parasite characteristics (antimalarial drug resistance).

EPIDEMIOLOGY

Malaria transmission occurs in large areas of Central and South America, the Caribbean, sub-Saharan Africa, the Indian subcontinent, Southeast Asia, the Middle East, and Oceania. Certain species may predominate in a given geographic area.[3] For example, *P. vivax* is more common in the Indian subcontinent, whereas *P. falciparum* is the most prevalent form in Africa, Haiti, and New Guinea. *P. knowlesi* has been found in several countries in southeast Asia, including Malaysia, Myanmar (Burma), Thailand, the Philippines, and Singapore.[4]

The risk of contracting malaria varies considerably between regions. In 2014, the Centers for Disease Control and Prevention reported 1724 cases of malaria among persons in the United States.[3] Of 1605 imported cases where the region of acquisition was known, 1383 (82%) were acquired in Africa (70% of these in West Africa), 160 (9.5%) in Asia (62% of these in India), and 54 (3.4%) in Central and South America and the Caribbean. *P. falciparum* accounted for 66% and *P. vivax* for 13% of all cases (although in many cases, the parasite species was not identified). Thus >60% of all cases of malaria identified in the United States in 2014, including the majority of cases due to *P. falciparum,* were acquired from travels in West Africa, despite the fact that for every traveler to sub-Saharan Africa, at least 10 travelers visit potential malarious areas of Asia and South America each year.

Resistance of *P. falciparum* to chloroquine has been widespread for many years.[5] Strains of *P. falciparum* have since become resistant to other chemotherapeutic agents, including pyrimethamine-sulfadoxine (no longer recommended as first-line treatment; can be used in pregnancy), quinine, mefloquine, and doxycycline.[5] Widespread mefloquine-resistant strains of *P. falciparum* have been seen in parts of Thailand, Myanmar (Burma), Cambodia, and China. Of greatest current concern is the observation in Cambodia and other parts of southeast Asia that parasites have become slower to respond to artemisinin therapy and that some artemisinin combination therapies have begun to fail.[6] Worldwide vigilance is required to track the continuing efficacy of this important class of drugs. Resistance of *P. vivax* to chloroquine has also been identified in Southeast Asia.[7]

PATHOPHYSIOLOGY

The organism is transmitted primarily by the bite of an infected female *Anopheles* mosquito, which requires a blood meal every 3 to 4 days to nourish its eggs. This vector is most frequently found in tropical and subtropical regions below 1500 m (5000 ft) above sea level. Plasmodial sporozoites are injected into the host's bloodstream during the mosquito's blood meal and are carried through the bloodstream to the liver. Within hours, the hepatic parenchymal cells are invaded, and asexual reproduction of the parasite begins (pre-erythrocytic schizogony or exoerythrocytic stage). After thousands of daughter merozoites have

been formed within a hepatocyte (amplification cycle), the cell ruptures, releasing daughter merozoites into the circulation, where they rapidly invade erythrocytes to begin the erythrocytic stage of the asexual cycle. In *P. vivax* and *P. ovale* infection, a portion of the intrahepatic forms are not released, but remain dormant as **hypnozoites**, which can reactivate after months or years to cause clinical relapses.

A merozoite matures within the erythrocyte, feeding on hemoglobin and enlarging until it divides into about a score of daughter-merozoites to form a schizont. Eventually, the infected erythrocyte lyses, merozoites are released, and these invade uninfected red blood cells, continuing and amplifying the infection. Once merozoites enter the erythrocytic stage, they do not reinvade the liver.

A portion of the merozoites develop into sexual forms (gametocytes). Upon ingestion by another feeding *Anopheles* mosquito, male and female gametocytes undergo sexual reproduction within the vector's gut and migrate as infective sporozoites to her salivary glands. To maximize her blood meal, the mosquito injects her next victim with saliva containing an anticoagulant, which introduces the malarial infection. The rate at which parasites replicate and migrate in the mosquito is temperature dependent; at average environmental temperatures below about 15°C (59°F), the cycle does not complete before the death of the mosquito, and malaria transmission cannot occur.

The clinical signs of malaria first appear during the erythrocytic stage. The rupture of schizont-containing erythrocytes triggers an array of host cytokine responses, giving rise to fever and other features of the malarial illness. Because fever slows the rate of schizont formation, early-stage parasites tend to catch up with more mature stages, and therefore over time, schizont rupture may become synchronous, giving rise to the periodic fever characteristic of untreated malaria. Such periodicity rarely has time to develop when malaria is treated promptly with efficacious drugs.

Each species of *Plasmodium* has specific characteristics, including typical morphologic forms and selective red blood cell tropism (**Table 159-1**). Many of these characteristics are responsible for important pathophysiologic consequences.

Anemia can develop rapidly with *P. falciparum* infection because the percentage of erythrocytes parasitized can be overwhelming (erythrocytes of all ages are susceptible to invasion) and because the life span of uninfected erythrocytes is also reduced, while bone marrow erythropoiesis is slowed or halted. *P. falciparum* asexual parasites transport to the red cell surface proteins that can adhere to host endothelial receptors, resulting in the sequestration of mature parasites in the microvasculature of many tissues and organs. Sequestration may be enhanced by the impaired deformability of infected erythrocytes and consequent slowing of blood flow through microvessels. Sequestration benefits parasites by keeping them away from the spleen, but additional consequences for the host include metabolic deprivation and/or impaired perfusion of tissues, processes that are believed to contribute to many of the syndromes characteristic of severe falciparum malaria. Acidosis, for example, results from tissue hypoxia, to which sequestration, hypotension, and severe anemia may all contribute. Hypoglycemia is largely due to impaired hepatic gluconeogenesis, possibly enhanced by the consumption of glucose by actively metabolizing parasites and the diversion of glucose for the host's anaerobic glycolysis. Sequestration accounts for the paucity of observed mature parasites in the peripheral smear of patients infected with *P. falciparum.*

Although nearly all malaria transmission is mediated by mosquito vectors, plasmodia of any species may also be transmitted by transfusion of infected blood, by needlestick accident, or across the placenta from mother to fetus. In these cases, an exoerythrocytic phase is absent, and hypnozoites of *P. vivax* or *P. ovale* cannot develop.

Untreated, inadequately treated, or frequent malaria may lead to sequelae mediated by immunologic mechanisms, including massive splenomegaly with consequent hypersplenism, and glomerulonephritis leading to a nephrotic syndrome (attributed, without strong evidence, mainly to *P. malariae* infection). Thrombocytopenia (rarely sufficient to cause bleeding) is invariable in acute symptomatic malaria.

INCUBATION PERIOD

The incubation period between inoculation and symptoms varies with the species of parasite (Table 159-1). In the nonimmune, symptoms begin after an incubation period ranging from 7 days to several weeks or more. Incomplete suppression of disease by partially active chemoprophylaxis and partial immunity can prolong the incubation period to months or even years. For U.S. residents who developed malaria associated with travels abroad during 2014, 95% of those with *P. falciparum* infections reported symptom onset before or within 29 days of arrival in the United States. By contrast, in 41% of patients with *P. vivax* and in 66% of patients with *P. ovale* infections, symptoms began ≥30 days after arrival in the United States. Ninety-nine percent of infections with any species presented within 1 year of arrival in the United States.[3]

TABLE 159-1 Characteristics of Malaria-Causing *Plasmodium* Species

	P. Falciparum	*P. Vivax*	*P. Ovale*	*P. Malariae*	*P. Knowlesi*
Clinical Characteristics					
Incubation period	8–25 d	8–27 d	9–17 d	15–30 d	Uncertain
Chloroquine resistance	Yes	Rare	No	No	No
Fatal attack	Yes	No	No	No	No
Relapse	No	Yes	Yes	No	No
Histologic Characteristics					
Asexual erythrocytic cycle	48 h	48 h	48 h	72 h	Uncertain
RBC preference	Reticulocytes (but can infect RBCs of all ages)	Reticulocytes	Reticulocytes	Older cells	All RBCs
Degree of parasitemia	High (multiple rings per RBC)	Low	Low	Low	Can be high
Ring forms and early trophozoites	Ring forms predominate; threadlike cytoplasm with double-chromatic dots	Amoeboid cytoplasm	Compact cytoplasm	Compact cytoplasm	Ring forms sometimes seen
Mature trophozoites	Rarely seen	Observed	Observed	Observed	Observed
Schizonts	Rarely seen	Observed	Observed	Observed	Observed
Gametocytes	Banana shaped	Round	Round	Round	Round
Circumference of infected red cell	Normal	Enlarged	Oval, with ragged (fimbriated) ends	Normal	Normal
Appearance of red cell cytoplasm	Normal	Stippled (fine Schuffner's dots)	Larger Schuffner's dots	Normal	Normal

Abbreviation: RBC = red blood cell.

CLINICAL FEATURES

In an area of intense transmission, most malaria infections occur in children, who gradually acquire a considerable degree of immunity. In such areas, a high percentage of children may have asymptomatic parasitemia (**malaria infection**), and illness due to malaria (**malaria disease**) is commonly mild and only occasionally severe or life threatening. Nevertheless, the absolute burden of mortality is large because nearly all children are infected. Adults in such areas rarely develop severe or fatal disease.

By contrast, malaria due to *P. falciparum* is a medical emergency in a nonimmune host of any age, because the infection, if untreated, is likely to progress and to become life threatening. Once a *P. falciparum* infection has reached the stage of severe disease, there is a 5% to 30% risk of a fatal outcome, even if optimal treatment is then begun. The early clinical features of malaria are nonspecific, and malaria can mimic many other infections. A diagnosis of malaria must be considered in any person returning from the tropics with an unexplained febrile illness and must be considered in any resident in the tropics who develops a fever.

UNCOMPLICATED MALARIA

The clinical hallmark of malaria is fever, with a prodrome of malaise, myalgia, headache, and chills.[8] In some patients, chest pain, cough, abdominal pain, or arthralgias may be prominent. Early symptoms are nonspecific and can easily be confused with a viral syndrome such as influenza or hepatitis or with bacterial sepsis. In a nonimmune individual, the illness usually progresses to include chills, followed by high-grade fever accompanied by nausea, orthostatic dizziness, and extreme weakness. After several hours, the fever abates and the patient develops diaphoresis and becomes exhausted. If the infection is untreated, the paroxysms of malaria—chills and fever followed by diaphoresis—may over time begin to occur at nearly regular intervals that correspond to the length of the asexual erythrocytic cycles (Table 159-1). The classic paroxysms of malaria are often lacking in malaria due to *P. falciparum* or in persons who received some form of chemoprophylaxis. The findings upon physical examination are also not specific for malaria. Most patients appear acutely ill with high fever, tachycardia, and tachypnea. Splenomegaly and abdominal tenderness are common. The liver may or may not be enlarged. Clinical signs that point to a diagnosis other than (or in addition to) malaria include lymphadenopathy and a maculopapular or petechial rash.

In children growing up in a malarious area, attributing an illness to malaria is particularly difficult because many children carry parasites without being unwell and because symptoms and signs of both mild and severe malaria are nonspecific.[9] In these circumstances, the higher the parasite density in the peripheral blood, the greater is the likelihood that malaria is the cause of the illness.

SEVERE (COMPLICATED) MALARIA

Malaria is described as severe or complicated when it includes one or more of the following syndromes in the context of a plasmodial infection, usually due to *P. falciparum*: coma with or without seizures ("cerebral malaria"), prostration, severe anemia, acidosis, hypoglycemia, acute renal failure, acute respiratory distress syndrome, pulmonary edema, jaundice, intravascular hemolysis, shock, and disseminated intravascular coagulation. Of 1724 malaria cases reported in the United States in 2014, 293 (17%) became severe, and five patients died (1.7% of the 293 severe cases).[3]

Complications of malaria can develop rapidly in untreated *P. falciparum* infection or may supervene early in the course of treatment. Occasionally, one or more complications may constitute the presenting illness, when correct diagnosis may be both difficult and critically important. A patient with severe malaria is at risk of dying even with optimal case management. Case fatality rates range between 5% and 30% in patients receiving treatment for severe malaria according to the complications present and their intensity.

When cerebral malaria is suspected, meningitis or encephalitis must be either excluded or treated, and the clinician must decide whether a lumbar puncture is safe. At lumbar puncture, the opening pressure is usually raised in children and normal in adults. The fluid is normal in appearance and on routine tests. In children in *P. falciparum*–endemic areas, asymptomatic parasitemia is common, so it is difficult to be sure that an illness is due to malaria. In a child with coma and parasitemia, the presence of a recently identified retinopathy (**Figure 159-1**) greatly strengthens confidence that malaria is the cause of the syndrome.[10] Among those who recover from cerebral malaria, up to 1 in 3 children and up to 1 in 20 adults may be left with, or may later develop, neurologic sequelae.



FIGURE 159-1. Retinal examination in a child with cerebral malaria. Note the patches of whitening around the fovea (dark area 2.5 disc diameters from the disc, right of field). Note also scattered white-centered hemorrhages. [Photo contributed by Ian McCormick, MD.]

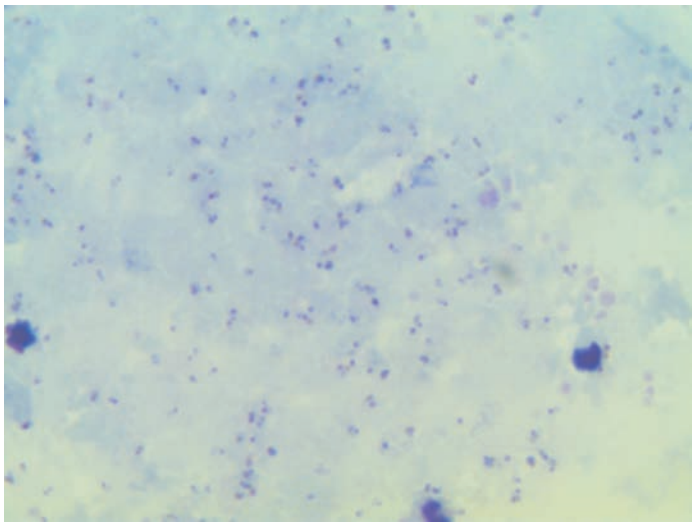
Infections caused by any species of *Plasmodium* can result in hemolysis, some degree of anemia, splenic enlargement, and, occasionally, traumatic rupture of the enlarged spleen.

The very young, the elderly, and pregnant women are at greatest risk of developing complications when infected with *P. falciparum*.[11] Additional risk factors for severe malaria include an immunocompromised state, asplenia, failure to take appropriate chemoprophylaxis, refusal of or delay in seeking medical care, and late or erroneous diagnosis.[12]

DIAGNOSIS

The diagnosis of malaria rests on a history of potential exposure in a malarious area, clinical symptoms, signs, and competent microscopic examination of well-prepared thick and thin blood films (**Figure 159-2**). Diagnosis based on clinical features alone has very low specificity and results in overtreatment.[1]

The three major questions to be answered by the blood smear are as follows: (1) Is there evidence of malaria? (2) If so, what is the density of parasitemia (correlates with prognosis)? (3) What species of malaria is responsible for the infection, and in particular, is *P. falciparum* present? Clues to the diagnosis of *P. falciparum* infection include the presence of small ring forms with double-chromatin dots within the erythrocyte, multiple infected rings in individual red blood cells, a paucity (usually absence) of mature trophozoites and schizonts on smear, and infected



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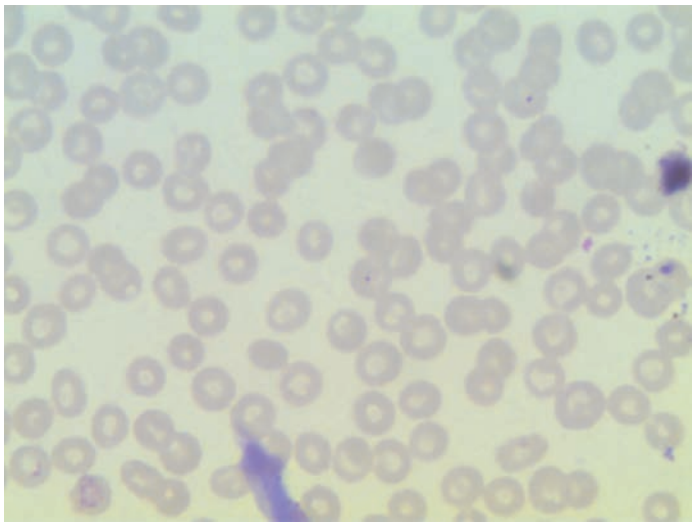

B

FIGURE 159-2. **A.** Thick and **B.** thin blood microscopy films from different children with malaria. The thick film shows numerous parasite nuclei, each with a faint blush of cytoplasm, seen either as a ring or as a smudge beside the nucleus. The thin film shows a single early ring stage of *Plasmodium falciparum* (center of field). The absence of dots in the erythrocyte cytoplasm and the normal size and shape of the erythrocyte distinguish this from *Plasmodium vivax* and *Plasmodium ovale*.

erythrocytes that are not enlarged and that have cytoplasm without basophilic stippling. In some (but not all) cases, gametocytes may be seen; in *P. falciparum* infection, these have a diagnostic crescent shape (banana shape). Parasite densities above 4% of erythrocytes are rare in malaria due to non-falciparum species. Obtain smears daily to assess the efficacy of drug treatment.

P. knowlesi is usually misdiagnosed as the less aggressive *P. malariae*, because the two are identical under light microscopy and require polymerase chain reaction for differentiation. Any patient coming from Asia with a high parasite burden resembling *P. malariae* should be assumed to be harboring *P. knowlesi*.[2]

THICK BLOOD FILM

Place a small drop of blood (5 µL) on a microscope slide, spread it evenly to a diameter of approximately 1 cm, allow it to dry, and then stain, without initial fixation, with Field's or Giemsa stain. Record the result as the number of parasites seen per oil-immersion field (for an approximate indication of density) or per 200 white cell nuclei counted (a more accurate density of parasites can then be calculated once the WBC count is known). A thick blood film contains several layers of red cells (which are lysed by the staining procedure), allowing parasitemias down to approximately 40/µL to be detected by an expert microscopist.

THIN BLOOD FILM

A standard hematologic blood smear (fixed with methanol and stained with Giemsa) allows a single sheet of intact red cells to be scrutinized for the percentage of red cells parasitized, from which the number of parasites per microliter can be calculated when the red cell count is known. Because the red cells are not destroyed, a thin film allows both parasite and red cell morphology to be examined, enabling more confident identification of the species of plasmodium. A thin film may fail to detect a parasitemia with a density below approximately 1000/µL, but it is more useful than a thick film for counting very heavy infections.

A long and careful search for parasites is necessary before a film is declared "negative." In early infection, especially infection due to *P. falciparum*, in which mature-stage parasitized erythrocytes are sequestered from the bloodstream, parasitemia may be undetectable even in a competently read thick blood film. **In highly suspicious cases, failure to detect parasitemia is not an indication to withhold therapy.** If parasites are not seen in the stained thin smear, a thick smear must be done. If parasites are not seen on the first thick film, obtain repeat thick smears at least twice daily for as long as malaria remains a suspected diagnosis or until the patient is better. The first smear is positive in >90% of cases.[13]

ADDITIONAL DIAGNOSTIC TECHNIQUES

Rapid diagnostic tests now make an important contribution to immediate diagnosis where facilities are limited. Rapid diagnostic tests detect parasite antigens (BinaxNOW®, ParaSight-F®) or the parasite enzyme lactate dehydrogenase (OptiMal®).[14] The sensitivity of rapid tests is close to that of thick blood films, especially for *P. falciparum* malaria. Antigen-detecting rapid tests remain positive for up to a month after a malarial infection, even if the infection has been successfully treated.

Polymerase chain reaction–based techniques to detect parasite DNA are more sensitive than microscopy and are valuable for research studies, but are rarely available for routine clinical purposes.

ADDITIONAL LABORATORY STUDIES

Nonspecific laboratory features of malaria include normochromic normocytic anemia with findings suggestive of hemolysis, a normal or mildly depressed total leukocyte count, thrombocytopenia, an elevated erythrocyte sedimentation rate, and mild abnormalities in liver and renal functions. In severe *P. falciparum* malaria, there may be hypoglycemia, severe anemia, hyperlactatemia, electrolyte disturbances, or evidence of acute renal failure or disseminated intravascular coagulation.

TREATMENT

Treatment decisions are based on the severity of the illness and the species of the infecting parasite determined by microscopic examination of thick and thin blood films. Treatment guidelines in this section are based on the most current information available as of this writing.[15] The World Health Organization[15] and the Centers for Disease Control and Prevention[16,17] update and publish practice guidelines at intervals for the diagnosis and treatment of malaria.

UNCOMPLICATED (NONSEVERE) MALARIA DUE TO *P. FALCIPARUM*

Admit the patient to the hospital because severe disease can develop rapidly, even after the start of specific therapy. Give analgesia if required (e.g., acetaminophen, 500 milligrams every 6 hours PO) and oral fluids. If the patient can take and retain drugs by mouth, begin a full course of oral antimalarial drugs without delay (**Table 159-2**). Artemisinin-containing combination therapies are considered the drugs of choice by the World Health Organization.[1,15] If a dose is vomited, the dose may be repeated; if it is vomited again, switch to parenteral therapy as for severe disease (see

TABLE 159-2 Drug Options for Therapy of Uncomplicated *Plasmodium falciparum* Malaria

Drug	Adult Dose	Pediatric Dose
Treatment of Choice Is an Artemisinin-Containing Combination Therapy (ACT)		
Artemether-lumefantrine (Coartem®; each tablet contains artemether 20 milligrams and lumefantrine 120 milligrams)	4 tablets twice daily for 3 d (the first 2 doses should be about 8 h apart)	5–15 kg: 1 tab initially, 1 tablet in 8 h, then 1 tablet every 12 h × 2 d 15–25 kg: 2 tablets initially, 2 tablets in 8 h, then 2 tablets every 12 h × 2 d 25–35 kg: 3 tablets initially, 3 tablets in 8 h, then 3 tablets every 12 h × 2 d >35 kg: follow adult dosing
Artesunate-amodiaquine (where available; not available in the United States; each adult tablet contains artesunate 100 milligrams and amodiaquine hydrochloride salt 270 milligrams)	2 tablets once daily for 3 d	5 to <9 kg: 1 tablet/d of artesunate (AS) 25 milligrams/amodiaquine (AQ) 67.5 milligrams 9 to <18 kg: 1 tablet/d of AS 50 milligrams/AQ 135 milligrams 18 to <36 kg: 1 tablet/d of AS 100 milligrams/AQ 270 milligrams ≥36 kg: 2 tablets/d of AS 100 milligrams/AQ 270 milligrams (adult dose)
Alternatives to ACT		
Drug	**Adult Dose**	**Pediatric Dose**
Atovaquone-proguanil (Malarone®; each adult tablet contains atovaquone 250 milligrams and proguanil 100 milligrams; each pediatric tablet contains atovaquone 62.5 milligrams and proguanil 25 milligrams)	4 tablets once daily for 3 d. Do not use for treatment if atovaquone-proguanil has been taken as chemoprophylaxis and the patient's current illness is a suspected treatment failure.	5–8 kg: 2 pediatric tablets × 3 d 9–10 kg: 3 pediatric tablets × 3 d 11–20 kg: 1 adult tablet × 3 d 21–30 kg: 2 adult tablets × 3 d 31–40 kg: 3 adult tablets × 3 d >41 kg: adult dose
Quinine sulfate (plus doxycycline or clindamycin)	650 milligrams PO every 8 h for 3–7 d	10 milligrams sulfate salt/kg, up to adult dose PO every 8 h for 3–7 d
Plus		
Doxycycline	100 milligrams PO every 12 h for 7 d	2.2 milligrams/kg (up to adult dose of 100 milligrams) PO every 12 h for 7 d
Or in children under age 8 y		
Clindamycin		7 milligrams/kg PO every 8 h for 7 d

Table 159-3) until able to resume treatment by mouth. Maintain regular checks for the development of any complications (listed earlier under "Clinical Features"). Check blood daily for parasite density and for hemoglobin concentration. When stable, the patient may be discharged to complete the course of oral drugs at home; stress the importance of completing the course and of reporting back with any recurrence of symptoms.

The World Health Organization does not recommend chloroquine for the treatment of *P. falciparum* malaria, owing to changing resistance patterns and the superiority of artemisinin-containing combination therapies.[1,15] As of July 2017, the Centers for Disease Control and Prevention recommends chloroquine for *P. falciparum* malaria imported from areas of low chloroquine resistance including Central America west of the Panama Canal, Haiti, the Dominican Republic, and parts of the Middle East.[16,17] Dose options are listed at the Centers for Disease Control and Prevention malaria website (http://www.cdc.gov/malaria/).

UNCOMPLICATED MALARIA DUE TO *P. VIVAX, P. MALARIAE, P. OVALE,* OR *P. KNOWLESI*

Admission to the hospital should not be necessary in most cases; however, if *P. knowlesi* is suspected, hospital admission is recommended. Dual infection with *P. falciparum* and any of the other species is possible.

TABLE 159-3 Antimalarial Drug Options for Severe (Complicated) Malaria

Drug	Adult Dose	Pediatric Dose
Artesunate* (available from the CDC if quinidine fails to provide improvement; call 770-488-7788)	2.4 milligrams/kg IV at 0, 8, and 24 h, then daily. Artesunate can be given IM if necessary.	2.4 milligrams/kg IV at 0, 8, and 24 h, then daily. Artesunate can be given IM if necessary.
Quinidine gluconate (plus doxycycline or clindamycin)†	6.25 milligrams base (= 10 milligrams salt)/kg IV load over 2 h (maximum, 600 milligrams), follow with 0.0125 milligram base (= 0.02 milligram salt)/kg/min continuous infusion.	6.25 milligrams base (= 10 milligrams salt)/kg IV load over 2 h (maximum, 600 milligrams), follow with 0.0125 milligram base (= 0.02 milligram salt)/kg/min continuous infusion.
Plus		
Doxycycline	2.2 milligrams/kg IV (up to adult dose of 100 milligrams) every 12 h for 7 d.	2.2 milligrams/kg IV (up to adult dose of 100 milligrams) every 12 h for 7 d.
Or in children under age 8 y		
Clindamycin		10 milligrams base/kg loading dose IV followed by 5 milligrams base/kg IV every 8 h for 7 d.

Abbreviation: CDC = Centers for Disease Control and Prevention.

*Artesunate is considered the drug of choice by World Health Organization guidelines.

†Quinine dihydrochloride is an alternative to quinidine gluconate (20 milligrams [salt]/kg infused IV over 2–4 hours, then 10 milligrams/kg every 8 hours, can be given IM if necessary, as 50 milligrams/mL solution).

Make sure that the initial and subsequent slides are carefully scrutinized for evidence of *P. falciparum*, because severe disease may then develop even while on treatment. Give simple analgesia and fluids as required. Treat nonfalciparum malaria with chloroquine (each tablet contains 250 milligrams of salt = 150 milligrams of base); the adult dose is four tablets initially, then two tablets after 6 hours, then two tablets daily for 2 days. The pediatric dose is 16.7 milligrams (salt)/kg PO immediately, followed by 8.3 milligrams (salt)/kg PO at 6, 24, and 48 hours. A preferable alternative is an artemisinin combination therapy (Table 159-3 for dosage). *P. vivax* malaria acquired from an area with chloroquine resistance should be treated with artemisinin-containing combination therapy.[1]

Patients with *P. vivax* or *P. ovale* malaria require additional treatment to eradicate hypnozoites from the liver. This treatment can be given after full recovery from the initial illness; the most common agent used is primaquine phosphate. The adult dose is 30 milligrams of base per day for 14 days. First check the patient for glucose-6-phosphate dehydrogenase deficiency (glucose-6-phosphate dehydrogenase–deficient persons are at risk of hemolysis when treated with primaquine; an alternative management of relapsing malarias is chloroquine base 300 milligrams weekly for 6 months). Treatment with primaquine is not needed in patients with *P. falciparum* or *P. malariae* malaria because there are no dormant asexual forms in the liver. *P. vivax* or *P. ovale* infections that have been acquired by needlestick accident, blood transfusion, or transplacental infection do not need treatment with primaquine for the same reason. However, primaquine is recommended after completion of treatment for *P. falciparum* in areas where onward transmission of the parasite must be prevented (e.g., in countries approaching elimination).[18]

SEVERE (COMPLICATED) MALARIA

Severe malaria is usually due to *P. falciparum*, but occasionally, it is due to *P. vivax* or *P. knowlesi*. The patients should be admitted to an appropriate level of intensive care. Both supportive and specific antimalarial therapies are urgent and critical to the patient's survival. Monitor the patient frequently; new complications may develop after the start of treatment.

Supportive Management Initial resuscitation may require oxygen for hypoxia, fluid replacement, IV glucose for hypoglycemia, blood or platelet transfusion for severe anemia or for disseminated intravascular coagulation, and occasionally intubation for severe respiratory distress or suspected raised intracranial pressure with altered mental status. Additional treatments for septic shock may be necessary (see Chapter 151, "Sepsis"). Monitor to identify and treat seizures, hyperpyrexia, acute respiratory distress syndrome, or acute renal failure. Culture blood samples for bacterial infections, and give immediate parenteral antibiotics, because a bacterial coinfection cannot be ruled out by clinical assessment initially.

Specific Antimalarial Chemotherapy Initiate parenteral therapy with an efficacious antimalarial drug without delay. Options are listed in Table 159-3.

With any of the regimens in Table 159-3, continue the treatment by a parenteral route for at least 24 hours; thereafter, as soon as the patient is well enough to take drugs by mouth, switch to a complete course of the best available oral therapy (Table 159-2). If the patient remains unable to take oral therapy, the chosen parenteral therapy should be continued for a maximum of 7 days.

Do not delay treatment while awaiting laboratory confirmation, because the initial smear for *P. falciparum* may be negative, even on microscopy of a thick blood film, in a nonimmune individual. An unstable patient (abnormal vital signs or any systemic complication) with a clinical or travel history suggesting malaria should be started on artesunate (if available) or quinidine gluconate (Table 159-3) until a diagnosis of malaria can be ruled out.

In the United States, parenteral quinine should be reserved for individuals who develop, or who are considered to be at high risk of developing, cardiotoxicity while receiving IV quinidine.

To initiate a patient with severe malaria in the Centers for Disease Control and Prevention treatment protocol (United States only) using artesunate, contact the Centers for Disease Control and Prevention Malaria Hotline: 770-488-7788 (Monday–Friday, 9 a.m.–5 p.m., Eastern time), or after hours, call 770-488-7100 and request to speak with a Centers for Disease Control and Prevention Malaria Branch clinician.[19]

IV artesunate is the drug of choice for severe malaria, according to the World Health Organization. Artesunate is rapidly effective and extremely potent against all erythrocyte stages. It does not cause cardiac toxicity or hypoglycemia. It is effective and is superior to IV quinine or quinidine in both adults[19] and children.[20] Prompt treatment for severe malaria is critical, and artesunate's major limitation at present in the United States is its lack of timely availability.

RATES OF PARASITE CLEARANCE

With correct treatment, the parasite load in the peripheral blood should decrease rapidly during the first few days. This decrease is significantly faster with artemisinin drugs than with all other therapies, because artemisinin drugs kill early-stage as well as late-stage parasites. With artemisinin treatment, the parasite count usually decreases significantly within the first 12 hours, whereas with other drugs, this decrease may take 24 to 48 hours. In a patient treated with quinidine or quinine, the density of asexual parasites may be unchanged or even increased after 24 hours of therapy, but this is rarely the case in a person treated with an artemisinin therapy. Asexual forms of the parasite should not be detectable within 5 days of the start of any effective treatment course. Gametocytes, the sexual forms, which do not cause disease in the human host, may persist for several weeks after treatment and do not indicate treatment failure.

COMPLICATIONS OF TREATMENT

Complications of treatment are listed in **Table 159-4**.

Glucocorticoids are of no proven benefit for cerebral malaria and should not be used. Other unproven or harmful adjunctive therapies include heparin, iron chelators, pentoxifylline, and dichloroacetate.

Quinine and quinidine are potent inducers of insulin release and may cause severe hypoglycemia, especially during pregnancy. Sudden changes in orientation, sweating, tremor, tachycardia, or anxiety should prompt bedside glucose measurement and treatment accordingly. Cinchona alkaloids are myocardial depressants, so cardiac monitoring is needed during administration of quinidine or quinine. At least partial resistance to quinine has been reported in Southeast Asia, but it has not yet been identified in Africa.

DISPOSITION AND FOLLOW-UP

Many patients feel better after the first day or two of treatment for uncomplicated malaria. Emphasize the importance of completing the treatment, because partial therapy may fail to eliminate parasites and may be followed by recrudescence of infection. Advise the patient to report any recurrence of symptoms, because even completed treatment may fail or an unrecognized additional infection may emerge. An episode of malaria is an opportunity to advise an individual about how to prevent further infections. After severe malaria, review the patient at intervals for any sequelae. Survivors of acute kidney injury, acute respiratory distress syndrome, or severe anemia usually recover fully, but cerebral malaria may be followed by neurologic sequelae in a proportion of cases, especially in children.[21]

SPECIAL CONSIDERATIONS

PREGNANCY

Among nonimmune adults, those who are pregnant are at greater risk of developing severe disease than others. Pregnant women are at particular risk of anemia, hypoglycemia, and, especially in the third stage of labor, fluid overload. Artemisinin drugs are probably safe in pregnancy but are still subject to restriction in the first trimester. Quinidine and quinine can be used in pregnancy but carry a greater risk of causing hypoglycemia through stimulation of insulin secretion from hypertrophied pancreatic β-cells.

TABLE 159-4 Adverse Effects, Precautions, and Contraindications of Antimalarial Drugs

Drug	Minor Toxicity	Major Toxicity	Precautions/Contraindications
Chloroquine	Nausea/vomiting, diarrhea, pruritus, postural hypotension, rash, fever, headache, dizziness	Rare; hypotension and shock after parenteral therapy Retinopathy after prolonged use	Avoid in patients with severe psoriasis and some types of porphyria. Caution with decreased liver function.
Quinine or quinidine	Cinchonism (nausea and vomiting, headache, tinnitus, dizziness, visual disturbance)	Hypotension, cardiac dysrhythmias, hypoglycemia, Coombs-positive hemolysis, abortions, neuromuscular paralysis (myasthenia)	Contraindicated in cardiac disease. Caution in pregnancy, myasthenia gravis.
Mefloquine	Nausea/vomiting, cramps, diarrhea, anorexia, dizziness, headaches, nightmares, and bradycardia	Rare unless underlying heart disease with bradycardia or the patient is on selected cardiotoxic medications (dysrhythmias, arrest); acute toxic confusional states may occur, as can seizures	Precaution during pregnancy and in children weighing <10 kg. Avoid if the patient is receiving quinidine. Avoid if the patient has heart conduction disturbance or if underlying seizure or major neuropsychiatric disorders.
Doxycycline	GI disturbances, phototoxicity, vaginal candidiasis	Rare; esophageal ulcerations if not taken with fluids	Avoid during pregnancy and in children <8 y of age unless alternatives not available. May depress prothrombin time in patients receiving anticoagulants.
Artemether-lumefantrine (Coartem®)	Headache, dizziness, anorexia, and asthenia	Rare; severe skin rash, QT prolongation	Avoid use with other drugs that may prolong QT interval. Drug interactions with cytochrome P450 3A4 and cytochrome P450 2D6.
Atovaquone-proguanil (Malarone®)	Nausea, vomiting, cramps, oral ulcers, headaches, dizziness	Rare serious allergic reactions and alopecia reported	Contraindicated in pregnancy and in children <5 kg (no safety data) and in patients with creatinine clearance <30.
Primaquine*	Nausea, vomiting, diarrhea, cramps, methemoglobinemia	Massive hemolysis in patients with G6PD deficiency Exacerbation of systemic lupus erythematosus or rheumatoid arthritis	Contraindicated in G6PD deficiency, pregnancy.

Abbreviation: G6PD = glucose-6-phosphate dehydrogenase.

*Terminal treatment for *Plasmodium vivax* and *Plasmodium ovale* infections only.

PREVENTION

Both the Centers for Disease Control and Prevention and World Health Organization publish information regarding prevention of malaria for residents of endemic areas and for travelers who are considering visiting those countries. These recommendations are updated at regular intervals.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 160

Food and Waterborne Illnesses

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FOODBORNE ILLNESSES

INTRODUCTION AND EPIDEMIOLOGY

Foodborne illness occurs after consumption of a food contaminated with bacteria, viruses, or protozoans. Outbreaks from contaminated food are often widespread due to advances in modern food logistics. International travel contributes to foodborne illnesses as travelers are exposed to new pathogens and migrants may introduce diseases, making foodborne disease a global public health concern.[1]

The Centers for Disease Control and Prevention estimates that foodborne diseases affect 9 million Americans each year, leading to 128,000 hospitalizations and 3000 deaths.[2,3] Children have the highest frequency of foodborne illness. Viruses are the most common cause of foodborne disease, with the norovirus causing more than half all cases and 26% of all admissions.[2] Other viral sources of infection include rotavirus, astrovirus, and enteric adenovirus.

Although less frequent, bacterial causes tend to be more severe, with nontyphoidal *Salmonella* and *Listeria* most often resulting in fatality.[2,3] Other common bacterial causes of foodborne illness include *Clostridium perfringens*, *Campylobacter* spp., *Toxoplasma gondii*, *Shigella*, *Staphylococcus aureus*, and Shiga toxin–producing *Escherichia coli* (STEC). The most common foods associated with foodborne illness outbreaks from any pathogen reported in the United States are poultry, leafy vegetables, and fruits/nuts.[2,3] For further discussion, see Chapter 73, "Disorders Presenting Primarily With Diarrhea."

PATHOPHYSIOLOGY

There are three basic mechanisms by which microbes cause illness. First, some pathogens such as *S. aureus*, *Bacillus cereus*, and *Clostridium botulinum* (botulism) produce toxins causing illness. These toxins are present in the food before ingestion and result in the rapid onset (1 to 6 hours) of symptoms. Preformed toxins such as staphylococcal enterotoxin stimulate the host immune system to release inflammatory cytokines within the intestine.[4] These cytokines trigger the accompanying nausea and vomiting.

The second method involves toxin production after ingestion, which interacts with intestinal epithelium; this occurs with *Vibrio*, *Shigella*, and STEC. These cause diarrhea (sometimes bloody) and lower abdominal cramping, with onset at approximately 24 hours after exposure. Some toxins produced by *Vibrio* and enterotoxigenic *E. coli* alter chloride and sodium transport across intestinal mucosal surfaces without destroying

TABLE 160-1 Etiologic Agents for Foodborne Diseases and Usual Incubation Periods

1–6 Hours	6–24 Hours	24–48 Hours	2–6 Days	1–2+ Weeks
Astrovirus	*Bacillus cereus* diarrhea toxin	*Clostridium botulinum*	*Campylobacter*	*Brucella*
B. cereus preformed toxin	*C. perfringens*	Enterotoxigenic *Escherichia coli*	*Shigella*	*Cryptosporidium*
Ciguatoxin	*Vibrio parahaemolyticus*	*Salmonella*	Enterohemorrhagic *E. coli*	*Entamoeba*
Heavy metals		*Trichinella*	*Vibrio cholerae*	*Giardia*
Monosodium glutamate			*Yersinia*	Hepatitis A
Norovirus				*Listeria*
Scombroid toxin				*Salmonella typhi*
S. aureus toxin				
Tetrodotoxin				

cells.[5] The resulting osmotic gradient produces a large fluid shift into the intestinal lumen, which overwhelms the absorptive capacity of the colon causing watery diarrhea. Other toxins produced disrupt host cell protein production, which causes death of the intestinal epithelium, resulting in bloody diarrhea and extraintestinal symptoms.[6]

Finally, direct invasion of the intestinal epithelium is a mechanism for the enteric viruses, notably *Salmonella*, enteroinvasive *E. coli*, and *Campylobacter*. These pathogens enter host cells and destroy intestinal epithelium.[7] This causes diarrhea due to transient malabsorption that is frequently bloody and accompanied by fever. Illness requires ingestion of just a few pathogens to cause disease. The upper and lower GI symptoms from invasive organisms last from 24 hours to weeks (**Table 160-1**).

The normal human digestive system defends against illness in many ways. The low gastric pH of 1 to 3 kills many ingested pathogens, whereas the intestinal flora competitively inhibits pathogens and secretes bactericidal fatty acids and other chemicals.[8,9] Intestinal motility prevents pathogens from having prolonged contact with mucosal surfaces and mixes organisms with mucus-containing protective glycoproteins. Immunologic cells also directly attack pathogens attempting transmural migration.[9]

Alteration of these protective mechanisms can increase susceptibility to foodborne disease. For example, proton pump inhibitors, histamine-2 blockers, and antacids reduce gastric acid production and increase susceptibility in foodborne illnesses.[8,9] Recent antibiotic use, chemotherapy or radiation therapy, and recent surgery alter the intestinal flora. Decreased intestinal motility from opioids, antiperistaltic drugs, or surgery encourages pathogen growth and migration.[9]

CLINICAL FEATURES

Suspect a foodborne disease when two or more people in a household or close association (e.g., the same workplace or communal eating arrangement) develop GI symptoms at or near same onset time. The most common symptoms are nausea, vomiting, diarrhea, and abdominal cramping. Systemic symptoms of fever, dehydration, and malaise also occur. Neurologic symptoms of seizures and altered mental status are seen in approximately 10% of pediatric patients with *Shigella* and are associated with worse outcomes.[10]

Question patients about the types of food they have recently ingested, frequency of restaurant meals, consumption of public-vended or street-vended foods, ingestion of seafood, and consumption of raw foods. Ask about recent travel or camping, contact with food handlers, and diaper changing. Children who attend day care centers and residents of long-term care facilities are at increased risk for foodborne diseases. Individuals working in the food industry are other frequent victims or sources; ask them about their personal hygiene and food-handling practices. Finally, seek a history of comorbid conditions or influencing therapies, including human immunodeficiency virus (HIV) infection or immunosuppressive drug use.

On exam, look for dehydration and systemic findings. Carefully look for blood in the stool and for alternative causes of symptoms such as appendicitis. The clinical features of specific foodborne infections are listed in **Table 160-2**.

TABLE 160-2 Clinical Features of Foodborne Infections

Clinical Presentation	Foodborne Pathogens
Gastroenteritis with vomiting as the primary symptom	Viral pathogens: norovirus, rotavirus, and astrovirus; preformed toxins: *Staphylococcus aureus* and *Bacillus cereus*
Noninflammatory diarrhea (watery nonbloody)	Can be any enteric pathogen, but classically: ETEC *Giardia* *Vibrio cholerae* Enteric viruses *Cryptosporidium* *Cyclospora*
Inflammatory diarrhea (grossly bloody, fever)	*Shigella* *Campylobacter* *Salmonella* EIEC Shiga toxin–producing *Escherichia coli* 0157:H7 and non-0157:H7 *Vibrio parahaemolyticus* *Yersinia* *Entamoeba*
Persistent diarrhea (>14 d)	Parasites: *Giardia* *Cyclospora* *Entamoeba* *Cryptosporidium*
Neurologic manifestations	Botulism (*Clostridium botulinum* toxin) Scombroid fish poisoning Ciguatera fish poisoning Tetrodotoxin Toxic mushroom ingestion Paralytic shellfish poisoning Guillain-Barré syndrome *Shigella* (pediatric seizures, encephalopathy, and rarely coma)
Systemic illness	*Listeria monocytogenes* *Brucella* *Salmonella typhi* *Salmonella paratyphi* *Vibrio vulnificus* Hepatitis A, E

Abbreviations: ETEC = enterotoxigenic *E. coli*; EIEC = enteroinvasive *E. coli*.

DIAGNOSIS

Most patients with foodborne diseases do not require diagnostic testing; illnesses are usually self-limited. Routine stool testing is not indicated for uncomplicated, watery diarrhea.[11] However, electrolytes and a CBC aid in patients with systemic illness findings, serious comorbid conditions, or those with prolonged symptoms. Obtain a stool test in those with:

- Watery diarrhea with signs of hypovolemia
- Bloody diarrhea
- Fever ≥38.5°C (101.3°F)
- Duration of illness >1 week
- Severe abdominal pain or tenderness
- Hospitalized patients or recent antibiotic use
- Elderly (≥70 years of age) or the immunocompromised
- Pregnant women or those with comorbid conditions such as inflammatory bowel disease

Diagnostic testing for a specific pathogen uses either stool staining/culture or multipathogen molecular panel. Routine stool cultures will identify *Salmonella*, *Campylobacter*, and *Shigella* but may not detect enterotoxigenic *E. coli*, vibrios, fungi, and viruses. Newer molecular panels using polymerase chain reaction are sensitive and less dependent on sample quality than routine stool cultures and help identify a wide array of pathogens.[12] These assays have become the test of choice at most institutions since they can detect bacterial, viral, and parasitic infections in a single stool sample. Indirect tests for bacterial causes of diarrhea such as fecal leukocytes or lactoferrin are not recommended.[11]

Add testing for ova and parasites selectively (e.g., in the immunocompromised, travelers, patients with symptoms lasting longer than 2 weeks, community waterborne outbreaks, or men who have sex with men).[11] The newer multipathogen molecular panels are sensitive and specific for these parasites.

Elderly patients, young children, and the immunocompromised are more likely to have severe illness, atypical presentations, and long-term sequelae. Patients with acquired immunodeficiency syndrome or other immunocompromised states can rapidly develop life-threatening symptoms and should undergo additional testing for *Cryptosporidium, Cyclospora, Microsporidia, Mycobacterium avium* complex, and *Cytomegalovirus*.

TREATMENT

Most episodes of acute gastroenteritis require adequate hydration and supportive care. The World Health Organization recommends initial oral hydration with a glucose-containing fluid (i.e., Pedialyte® or equivalent).[13] Reserve parenteral rehydration for patients with severe dehydration or with continued vomiting and inability to tolerate oral fluids. Antiemetics may reduce vomiting, ED length of stay, and need for admission.[14,15] Antimotility medications, such as loperamide, may decrease illness duration for mild to moderate nonbloody diarrhea in adults without fever; avoid these in children and patients with dysentery (fever and bloody diarrhea) due to concerns of prolonging the illness.[16]

Empiric antibiotics do not dramatically alter the course of illness since most cases are viral or self-limited bacterial in origin. The 2017 Infectious Diseases Society of America guidelines recommend empiric treatment for patients with bloody diarrhea under the following circumstances[11]:

- Infants less than 3 months of age
- Immunocompromised patients with severe illness
- Ill immunocompetent people with documented fever, abdominal pain, bloody diarrhea, and bacillary dysentery presumptively due to *Shigella*
- Recent international travelers with fever ≥38.5°C or signs of sepsis

Avoid empiric antibiotics if you believe illness is from STEC O157 and other STEC that produce Shiga toxin due to increased risk of hemolytic-uremic syndrome (HUS). Empiric antibiotics are an option for well-appearing patients with watery diarrhea and a history of international travel, but these are not needed for most with other diarrheal illnesses, even when prolonged more than 14 days. A common bacterial enteritis regimen is oral ciprofloxacin, 500 milligrams twice daily, or levofloxacin, 500 milligrams once a day, each for 3 to 5 days. Azithromycin, 500 milligrams once daily for 3 days, is an alternative.[11] See **Tables 160-3, 160-4, 160-5,** and **160-6** for detailed treatment recommendations.

DISPOSITION AND FOLLOW-UP

Admit or observe for prolonged intervals those who have systemic symptoms, comorbid conditions, or severe dehydration with inability to tolerate oral fluids. Have a low threshold for admitting immunocompromised patients. Pregnant patients have increased risk of complications, especially with *Listeria* infection, and may require further monitoring.[11]

Discharged patients should receive instructions on proper hygiene, notably frequent hand washing to protect non-ill family members and contacts. Patients discharged with pending stool culture or other studies should have a clear plan for follow-up.

SPECIAL CONSIDERATIONS

ENTEROHEMORRHAGIC *E. COLI* AND HEMOLYTIC-UREMIC SYNDROME

Enterohemorrhagic *E. coli* that produces Shiga toxin is the most common cause of HUS in children.[17] The STEC strain O157:H7 is most commonly associated with pediatric HUS, but other organisms such as O104:H4, O111, and *Shigella* are also associated with adult HUS-like illnesses.[10] The Shiga toxin produced by these organisms halts protein synthesis in renal glomerular cells as the precipitating event in HUS. Toxin binding to the glomerular endothelium produces a thrombogenic environment, leading to microangiopathic hemolysis through multiple cellular mechanisms.[18] Antibiotics may promote Shiga toxin release, which increases the incidence of HUS; for this reason, avoid antibiotics when suspecting this pathogen. In addition, avoid antimotility agents. Treatment of HUS is supportive, although eculizumab, a monoclonal antibody to complement factor C5 that blocks complement activation, shows promise in severe cases.[19] Approximately 50% of pediatric patients with HUS require dialysis, and dehydration at the time of admission increases the frequency and duration of renal support.[20]

SCOMBROID AND CIGUATERA POISONING

Scombroid fish poisoning occurs after ingestion of fish of the family Scombridae (tuna, mackerel, and bonito). Other non-Scombridae fish such as mahi-mahi, bluefish, herring, and sardines are triggers. The disease occurs when histidine is metabolized by bacteria into histamine and other bioactive amines.[21] Improper temperature control allows high concentrations of these substances to accumulate in the fish. Symptoms usually begin 30 minutes to 24 hours after ingestion and include flushing, headache, abdominal cramping, vomiting, and diarrhea. Symptoms are usually self-limited for 12 to 48 hours. However, severe cardiac and respiratory symptoms may occur in the elderly or patients with comorbid conditions. Treatment is with antihistamines (H_1 and H_2 blockers) such as diphenhydramine and cimetidine. Laboratory testing is not indicated in most cases.[21]

Ciguatera poisoning is caused by eating reef fish contaminated with the dinoflagellate *Gambierdiscus toxicus,* which produces ciguatoxin. The toxin is heat resistant and accumulates in large predatory fish such as grouper, snapper, amberjack, and barracuda. Ciguatoxin acts on sodium channels, resulting in membrane depolarization. Nausea, vomiting, and diarrhea occur 1 to 24 hours after ingestion, followed by hypesthesias, paresthesias, numbness, malaise, generalized weakness, and sensitivity to temperature extremes. Bradycardia and hypotension are possible.[22] The GI symptoms typically resolve over a few days, whereas the neurologic symptoms may persist in a waxing and waning pattern

TABLE 160-3 Clinical Features, Diagnosis, and Management of Bacterial Foodborne Illness

Etiology	Signs and Symptoms	Duration of Illness	Associated Foods	Laboratory Testing	Treatment
Bacillus anthracis	Nausea, vomiting, bloody diarrhea, abdominal pain, malaise	Weeks	Poorly cooked meat	Blood	Ciprofloxacin or doxycycline IV + PCN, vancomycin, rifampin, or clindamycin
Bacillus cereus (preformed toxin)	Sudden onset of nausea, vomiting; can have diarrhea	24 h	—	Clinical diagnosis; assay must be ordered specifically	Supportive care
B. cereus (diarrheal toxin)	Watery diarrhea, cramping, nausea	1–2 d	Meats, gravies, stew, vanilla sauces	Not necessary	Supportive care
Brucella	Fever, chills, myalgias, arthralgias, weakness, bloody diarrhea	Weeks	Raw milk, unpasteurized goat's milk or cheese, contaminated meat	Serology, blood culture	Doxycycline 100 milligrams PO twice daily + streptomycin 1 gram IM for 14–21 d
Campylobacter	Diarrhea, cramping, nausea, vomiting, fever, often bloody diarrhea	2–10 d	Contact with raw poultry, undercooked poultry, unpasteurized milk, contaminated water	Routine stool culture on special media and temperature; MMP	Ciprofloxacin 750 milligrams PO twice daily or levofloxacin 500 milligrams PO daily or azithromycin 500 milligrams daily for 3–5 d
Clostridium botulinum (preformed toxin)	Vomiting, diarrhea, blurred vision, diplopia, dysphagia, descending muscle weakness, paralysis	Days to months	Canned foods, canned fish, foods kept warm in dishes, herbed oils, cheese sauce	Stool, serum, or food assay for toxin; stool culture	Supportive care (may require intubation), botulism antitoxin
C. botulinum—infants	Infants <12 mo, lethargy, weakness, poor feeding, head control, and suck	Variable	Honey, home canned vegetables, corn syrup	Stool, serum, or food for toxin; stool culture	Botulism immunoglobulin; antitoxin not recommended in infants
Clostridium perfringens	Watery diarrhea, nausea, cramping	1–2 d	Meat, poultry, dried or precooked foods, poor temperature control	Stools for enterotoxin, stool culture	Supportive care
Enterohemorrhagic *Escherichia coli* and Shiga toxin–producing *E. coli*, 0157:H7	Severe, often bloody diarrhea; abdominal pain; vomiting; little or no fever	5–10 d	Undercooked beef (hamburger), unpasteurized milk, juices, raw fruits and vegetables	Stool culture; may require special media; toxin assay; MMP	Supportive; avoid antibiotics due to risk of hemolytic-uremic syndrome
Enterotoxigenic *E. coli*	Watery diarrhea, cramping, vomiting	3–7 d	Water or food contaminated with human feces	Stool culture; MMP	Supportive; ciprofloxacin 500 milligrams PO twice per day or levofloxacin 500 milligrams PO once daily for 3 d
Listeria monocytogenes	Fever, myalgias, nausea, diarrhea; premature delivery if pregnant; meningitis	Variable	Fresh soft cheeses, poorly pasteurized dairy products, deli meats, hot dogs	Blood or cerebrospinal fluid culture; listeriolysin O antibody assay	Supportive care; ampicillin or penicillin G; TMP-SMX for PCN allergic
Salmonella	Diarrhea, vomiting, abdominal pain, fever, myalgia	4–7 d	Eggs, poultry, unpasteurized dairy products, raw fruits and vegetables, street-vended food	Routine stool culture; MMP	Supportive care; ciprofloxacin 500 milligrams PO twice daily or levofloxacin 500 milligrams once daily for 3–5 d; ceftriaxone IV for severe disease or immunocompromised; vaccine for *Salmonella typhi*
Shigella	Abdominal cramping, fever, diarrhea with blood and mucus	4–7 d	Fecal contamination of any food or water, person to person, prepared food	Routine culture; MMP	Supportive care; ciprofloxacin 500 milligrams PO twice per day or levofloxacin 500 milligrams once per day for 3–5 d or azithromycin 500 milligrams PO daily for 3 d
Staphylococcus aureus (preformed toxin)	Sudden-onset severe nausea, vomiting, diarrhea, fever	1–2 days	Improperly refrigerated meats, potato or egg salad; left out pastries	Clinical diagnosis; assay for toxin; culture if indicated	Supportive care only
Vibrio cholerae	Profuse watery diarrhea and vomiting; life-threatening dehydration	3–7 d	Contaminated water, fish, shellfish, street-vended foods	Specifically ordered stool culture; MMP	Aggressive PO or IV fluid replacement, azithromycin 1 gram PO once or doxycycline 300 milligrams once or ciprofloxacin 1 gram PO once
Vibrio parahaemolyticus	Watery diarrhea, cramping, vomiting	2–5 d	Undercooked or raw fish or shellfish	Stool culture (special media required); MMP	Supportive care; antibiotics in severe illness: ciprofloxacin 500 milligrams PO twice daily or TMP-SMX double strength PO twice daily or doxycycline 100 milligrams PO twice daily for 3 d
Vibrio vulnificus	Vomiting, abdominal pain, diarrhea, skin infections; can be fatal in liver disease or immunocompromised patients	2–8 d	Undercooked or raw fish or shellfish	Specifically ordered stool, blood, or wound cultures; MMP	See Table 160-8
Yersinia	Pseudoappendicitis, fever, abdominal pain, vomiting, diarrhea, rash	1–3 wk	Undercooked pork products, tofu, contaminated water	Stool, blood, or vomitus cultures (special media); MMP	Supportive care; antibiotics usually not required; if septic: gentamicin, 5 milligrams/kg IV daily + ceftriaxone 2 grams IV daily

Abbreviations: MMP = multipathogen molecular panel; PCN = penicillin; TMP-SMX = trimethoprim-sulfamethoxazole.

TABLE 160-4 Clinical Features, Diagnosis, and Management of Viral Foodborne Illness

Etiology	Signs and Symptoms	Duration of Illness	Associated Foods	Laboratory Testing	Treatment
Hepatitis A	Diarrhea, jaundice, dark urine, flulike illness, abdominal pain	2 wk to 3 mo	Shellfish, raw produce, contaminated water, infected contacts	Liver profile, bilirubin, positive immunoglobulin, and antihepatitis A antibodies	Supportive care; prevention with immunization
Norovirus, rotavirus, and other enterovirus	Nausea, vomiting, abdominal cramping, diarrhea; sometimes fever, malaise, headache	12 h to 9 d	Fecal contaminated foods; foods touched by infected workers (salads, sandwiches, produce); shellfish	Clinical diagnosis; multipathogen molecular panel	Supportive care, good hygiene, adequate fluid replacement

for 3 months to years.[23] Acute treatment is supportive. A consensus review of nine articles reported that IV mannitol may aid severe acute cases, but the evidence is conflicting and mannitol doses were not well described.[24]

CHRONIC SEQUELAE OF FOODBORNE ILLNESS

Approximately 2% to 3% of patients with foodborne diseases have longer sequelae thought to be related to autoimmunity.[25,26] Protein virulence factors (superantigens) can initiate extreme immune responses. *Salmonella, Shigella,* and *Campylobacter* result in a seronegative reactive arthritis in approximately 2% of those infected.[27] *Campylobacter* infection is associated with Guillain-Barré syndrome, with a reported rate as high as 30.4 per 100,000 cases.[26] Symptoms of Guillain-Barré syndrome typically occur 7 to 21 days after the GI symptoms resolve.[25,26] Other autoimmune disorders potentially related to superantigens from foodborne pathogens include multiple sclerosis, rheumatoid arthritis, psoriasis, and Graves' disease.[25,27] Infections with *Salmonella, Yersinia,* and *Campylobacter* may increase short- and long-term risk of death, even after accounting for comorbid diseases.[28]

WATERBORNE ILLNESSES

INTRODUCTION AND EPIDEMIOLOGY

Waterborne illnesses occur from ingestion or contact with contaminated water found in swimming pools, hot tubs, spas, and naturally occurring freshwater and saltwater during recreational use.[29] Numerous bacteria, viruses, and protozoans arrive in the water by fecal contamination and cause infections. However, some species of bacteria are indigenous aquatic organisms such as *Pseudomonas aeruginosa, Vibrio, Aeromonas,* nontuberculous *Mycobacterium*, and *Legionella*.[30]

Physiologic mechanisms intended to prevent infection from waterborne pathogens are the same as those discussed earlier for foodborne diseases in the pathophysiology section.

There were 493 recreational waterborne disease outbreaks in the United States reported to the Centers for Disease Control and Prevention in 2000 to 2014, which resulted in at least 27,219 cases of disease and eight deaths.[29] The majority of these outbreaks started in treated water sources (such as swimming pools) or from chlorine-tolerant organisms such as *Cryptosporidium* (which accounted for more than half of all cases). *Legionella* caused 16% of illnesses and 75% of deaths.[29]

BACTERIA AND WATERBORNE ILLNESS

Implementation of water disinfection and filtration treatments reduced waterborne outbreaks from enteric bacteria.[30] Waterborne infections from *V. cholerae* and *S. typhi* are now extremely rare in the developed world, but both remain a major cause of illness in developing nations.[31]

Several enteric bacteria are commonly implicated in waterborne disease outbreaks in the United States. ***Campylobacter*** is found in virtually all surface waters due to contamination from wild bird feces and is the most common bacteria associated with recreational waterborne disease outbreaks.[29] Several outbreaks of human campylobacteriosis came from contaminated drinking water.[32] STEC can also be transmitted from ingestion or contact with water contaminated by farm animal feces.[33] *Shigella* species, *Salmonella* species, and *Yersinia enterocolitica* are other enteric bacteria that can cause waterborne outbreaks.[30] Most enteric bacteria, including *E. coli* O157:H7 and *Campylobacter*, are susceptible to chlorination.

Although *V. cholerae* is an enteric organism acquired from water with fecal contamination, many other *Vibrio* species are endemic in marine and estuarine waters. *Vibrio* species can cause diarrheal illnesses or skin

TABLE 160-5 Clinical Features, Diagnosis, and Management of Parasitic Foodborne Illness

Etiology	Signs and Symptoms	Duration of Illness	Associated Foods	Lab Testing	Treatment
Cryptosporidium	Watery diarrhea, cramping, fever	Weeks to months—may be relapsing	Any contaminated uncooked food, water	Specific stool examination; MMP	Supportive care and HAART in HIV infected; nitazoxanide 500 milligrams PO twice daily for 3 d + azithromycin in patient with HIV and severe symptoms
Cyclospora	Watery diarrhea, weight loss, cramping, vomiting, fatigue	Weeks to months, relapsing	Various types of fresh produce	Specific stool examination; MMP	TMP-SMX-DS PO twice per day or ciprofloxacin 500 milligrams twice daily for 7–10 d; nitazoxanide 500 milligrams PO twice daily for 7 d In HIV patients: TMP-SMX-DS PO 4 times a day for 21 d
Entamoeba histolytica	Bloody diarrhea, frequent stools, lower abdominal pain	Weeks to months	Any contaminated uncooked food, water	Examination of stool for cysts and parasites; serology; MMP	Metronidazole 750 milligrams PO 3 times daily for 5–10 d or paromomycin 500 milligrams PO 3 times daily for 7 d or tinidazole 2 grams PO for 3 d or nitazoxanide 500 milligrams PO twice daily for 3 d
Giardia	Diarrhea, cramping, copious flatus	Months	Any contaminated uncooked food	Examination of stool for ova and parasites; MMP	Metronidazole 250 milligrams PO 3 times daily for 7–10 d or tinidazole 2 grams PO once or nitazoxanide 500 milligrams PO twice daily for 3 d or paromomycin 500 milligrams PO 3 times daily for 7 d or albendazole 400 milligrams PO once daily for 5 d

Abbreviations: HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; MMP = multipathogen molecular panel; TMP-SMX-DS = trimethoprim-sulfamethoxazole double strength.

TABLE 160-6 Clinical Features, Diagnosis, and Management of Toxinogenic Foodborne Illness

Etiology	Signs and Symptoms	Duration	Foods	Lab Tests	Treatment
Ciguatera toxin	Abdominal pain, vomiting, diarrhea, paresthesias, reversal of hot and cold sensation, weakness, hypotension, bradycardia	Days to months	Large reef fish (barracuda most common)	Clinical diagnosis	Supportive care; high-dose atropine for bradycardia; IV mannitol for severe neurologic symptoms
Tetrodotoxin (puffer fish)	Paresthesias, headache, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure, death	Death in 4–6 h	Puffer fish	Detection of tetrodotoxin in fish	Emergent supportive care; anticholinesterases such as neostigmine and edrophonium
Scombroid (histamine)	Flushing, rash, burning sensation, dizziness, paresthesias	3–6 h	Pelagic fish—tuna, mackerel, swordfish, mahi-mahi	Clinical diagnosis, can assay for histamine in fish	Antihistamines, supportive care
Shellfish toxins	Diarrhea, vomiting, abdominal pain, fever, numbness, dizziness, myalgias, confusion, memory loss, coma	2 h to 3 d	Shellfish, mussels, clams	Detection of toxin in shellfish	Supportive care, self-limited

infections.[34] ***Vibrio vulnificus*** is associated with life- and limb-threatening necrotic wound infections. The organism is found predominantly along the Gulf Coast and is acquired by patients with open wounds that are exposed to seawater. The wound infections are associated with a high rate of sepsis and amputation. Cirrhosis and high iron levels are associated with worse outcome.[34]

Found in fresh and marine waters, ***Aeromonas*** species can cause gastroenteritis and wound infections.[35] The majority of wound infections are simple cellulitis, but necrotizing infections and septic arthritis occur.[36,37] In addition, immunocompromised patients may progress to develop peritonitis, cholangitis, and meningitis.[35]

P. aeruginosa is an opportunistic pathogen found in freshwater, with immunocompromised patients at particular risk. In normal hosts, *Pseudomonas* can cause otitis externa, keratitis in contact lens wearers, and folliculitis.[38] Although *Pseudomonas* can contaminate drinking water, it does not cause a diarrheal illness in normal hosts.

Nontuberculous *Mycobacterium* exists in saltwater and freshwater and can cause illness.[39] ***Mycobacterium marinum*** is associated with granulomatous skin infections, also called **fish tank or aquarium granuloma** (**Figure 160-1**).[40] *Mycobacterium avium* complex is associated with GI, pulmonary, or disseminated disease in immunocompromised patients, particularly patients with HIV.[39]

Legionella is a common inhabitant of freshwater, including water that meets the standards for drinking.[29] Infection occurs from inhalation of contaminated aerosols, resulting in one of two syndromes: **Legionnaires disease** and **Pontiac fever**. Pontiac fever is a flulike illness contracted by breathing mist that comes from a water source (e.g., air conditioning cooling towers, whirlpool spas, and showers) contaminated with the bacteria. Further discussion of Legionnaires disease is available in Chapter 65, "Community-Acquired Pneumonia, Aspiration Pneumonia, and Noninfectious Pulmonary Infiltrates."



FIGURE 160-1. Skin infection from *Mycobacterium marinum* (fish tank or aquarium granuloma). A painful indurated plaque is noted on the dorsal surface of the proximal thumb. (Reproduced with permission from Wolff K, Johnson RA: *Color Atlas and Synopsis of Clinical Dermatology*, 5th ed, © 2005, McGraw-Hill, Inc., New York.)

PROTOZOA AND WATERBORNE ILLNESS

Giardia lamblia is a common protozoal cause of waterborne disease in the United States and accounts for 16,000 cases of diarrheal disease annually.[41] It is frequently found in surface waters from mountain streams to municipal reservoirs and is resistant to common chlorination.

A form of giardiasis, often called "**beaver fever,**" can result from contamination of natural waters by animals such as beavers. Backpackers, campers, and travelers to disease-endemic areas are at high risk for waterborne giardiasis, as are children under 5 years of age.[41] Community outbreaks often start out as a waterborne disease, but subsequent transmission commonly occurs from person to person. *Giardia* is associated with acute and chronic forms of gastroenteritis, although many patients infected with *Giardia* remain asymptomatic.

Cryptosporidium is an intracellular protozoan parasite and the most common cause of recreational waterborne GI illness in the United States.[29] The Centers for Disease Control and Prevention estimates 748,000 cases of cryptosporidiosis occur each year and result in hospital admissions costing $45.8 million.[42] The inoculum required to cause infection is low, and large numbers of oocysts are excreted in the feces of infected hosts.[43] Standard doses of chlorine and zonation used in water treatment are not effective against *Cryptosporidium,* which explains its association with recreational water sources.[42] Water filtration reduces the number of oocysts, but occasionally enough remain to be infective. Infection with *Cryptosporidium* in a normal host results in a self-limited diarrheal illness, and many exposures are asymptomatic. Immunocompromised patients may experience chronic diarrhea or life-threatening complications.[43] *Cyclospora, Isospora,* and *Microspora* are other protozoan parasites that can cause severe disease in immunocompromised patients.[44]

Entamoeba histolytica is a protozoan that causes intestinal amebiasis. It is a significant waterborne pathogen in developing countries, but in the United States, it is most commonly seen in migrants, travelers to endemic areas, men who have sex with men, and institutionalized patients.[45,46] Symptoms range from asymptomatic infection to severe dysentery.[45] Fulminant colitis with bowel necrosis and perforation occurs in <1% of cases but has a mortality rate >40%.[47] Seeding of the liver or brain can occur, particularly in men with underlying liver disease, resulting in the formation of amoebic hepatic abscesses.[45]

Naegleria fowleri is a thermophilic organism found in warm and hot freshwater ponds that is responsible for rare but often fatal primary amoebic meningoencephalitis.[48] Human disease occurs after inhalation of the trophozoites that invade the nasal cribriform plate, later digesting neurons. Symptoms begin after a 1- to 7-day incubation and include

fever, headache, and altered mental status. Mortality rates approach 95% even with treatment.[49]

ENTERIC VIRUSES AND WATERBORNE INFECTION

More than 100 enteric viruses are pathogenic in humans, many of which can be transmitted by drinking water and recreational water.[50] Several enteric viruses, including the Norwalk virus and rotaviruses, are chlorine resistant.[29] Outbreaks can happen with contamination of private wells and community water systems.[50]

Hepatitis A and E trigger epidemic and sporadic infections from contaminated water. Infection from the hepatitis A virus typically results in an acute self-limited hepatitis, rarely leading to fulminant hepatic failure. Several outbreaks attributed to contaminated food led to an increased incidence of hepatitis A after a period of decline.[51] Once considered a disease confined to tropical regions, the incidence of hepatitis E in developed countries is rising.[52] In endemic and underdeveloped countries, morbidity and mortality from hepatitis E associated with pregnancy or preexisting liver disease are high due to hepatic failure.

Noroviruses, including the Norwalk virus, are the leading cause of acute gastroenteritis across all age groups.[53] Outbreaks are often linked to contaminated drinking and recreational water, including on cruise ships.[54] Rotavirus and enteric adenoviruses are other important waterborne enteric viruses. Noroviruses, rotaviruses, and enteric adenoviruses typically cause a self-limited gastroenteritis, although dehydration from these infections can be severe in children.

CLINICAL FEATURES OF WATERBORNE INFECTIONS

The majority of patients with waterborne disease present with nausea, vomiting, and diarrhea. Think of this cause in symptomatic patients with recent travel, outdoor activities such as camping or backpacking, recent recreational water use, or those using a private drinking water supply rather than municipal drinking water or bottled water. Patients with severe or chronic gastroenteritis symptoms may have immune deficiency caused by HIV or immunosuppressive drugs. In patients with bloody diarrhea, suspect invasive enteric organisms.[11] Suspect *Giardia* and other protozoan parasites in patients with diarrhea lasting 2 or more weeks.[11] Consider invasive amoebic organisms in patients presenting with altered mental status, meningeal signs, or peritonitis after recreational water exposure.

Physical examination seeks to identify signs of dehydration and any open skin wounds acquired in fresh or marine waters. The waterborne skin infections range in severity from simple cellulitis to necrotizing fasciitis. Patients with *V. vulnificus* present after recent exposure to saltwater with hemorrhagic bullae or signs of necrotizing infection (**Figure 160-2**).[33] Clinical features of waterborne pathogens are summarized in **Table 160-7**.



FIGURE 160-2. Skin infection from *Vibrio vulnificus*. *V. vulnificus* was cultured from the bulla aspirates from this patient with hemorrhagic and bullous skin lesions of the lower legs. (Reproduced with permission from Wolff K, Johnson R: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th ed, © 2009 McGraw-Hill, Inc., New York.)

TABLE 160-7 Type of Transmission and Clinical Features Associated With Waterborne Pathogens

Pathogen	Drinking Water	Recreational Water	Clinical Features
Campylobacter	+	+	Gastroenteritis; can be associated with Guillain-Barré syndrome
Escherichia coli O157H7	+	+	Gastroenteritis; can be associated with hemolytic-uremic syndrome
Salmonella species	+	+	Gastroenteritis, typhoid fever
Shigella species	+	+	Gastroenteritis
Yersinia species	+	+	Gastroenteritis
Vibrio species	+	+	Gastroenteritis; skin infections
Aeromonas species	+	+	Gastroenteritis; skin infections
Pseudomonas	–	+	Skin infections; nosocomial infections
Nontuberculous *Mycobacterium*	+/–	+	Skin infections; disseminated disease in immunocompromised
Giardia	+	+	Acute and chronic gastroenteritis; asymptomatic carriage
Cryptosporidium	+	+	Acute and chronic gastroenteritis, severe among immunocompromised
Entamoeba	+	+	Acute and chronic gastroenteritis; rare fulminant colitis; liver or rare brain abscess
Naegleria fowleri	+/–	+	Acute meningoencephalitis
Hepatitis A	+	+	Acute hepatitis; rare liver failure
Hepatitis E	+	+	Acute hepatitis; fulminant and severe in pregnancy
Enteric viruses	+	+	Gastroenteri

DIAGNOSIS

Criteria for testing are the same as noted in foodborne illness and usually not needed. Viral antigen tests for rotavirus may be helpful in children with severe or persistent symptoms to distinguish viral from bacterial pathogens. Testing with a multipathogen molecular panel is indicated in patients with recent travel to endemic countries, immunocompromised status, or diarrheal illness of 2 or more weeks; during community-wide waterborne outbreaks; or in men who have sex with men.[11,30] Because parasite excretion may not be continuous, three specimens separated by at least 24 hours may be needed to identify the causative pathogen when performing stool microscopic inspection.

The diagnosis of waterborne skin infections is based primarily on the patient's physical examination findings and history of water exposure. Identification of the causative agent can be attempted by Gram stain and wound culture (acid-fast staining if *M. marinum* is suspected). Reserve blood cultures for systemically ill patients and children less than 3 months of age.[11]

TREATMENT

In most cases of acute gastroenteritis from waterborne pathogens, treatment is rehydration. Use empiric antibiotic therapy for patients with moderate to severe disease, recent travel history, or symptoms lasting more than 1 week; those needing hospitalization; and immunocompromised hosts.[11] **Avoid antibiotics in cases of suspected *E. coli* O157:H7 due to an increased risk of development of HUS.** Appropriate antibiotic regimens are 3 to 5 days of oral ciprofloxacin 500 milligrams twice daily, levofloxacin 500 milligrams once daily, or double-strength trimethoprim-sulfamethoxazole twice daily.[11]Azithromycin 500 milligrams orally once daily for 3 to 5 days is used in pregnant women,

TABLE 160-8 Treatment of Waterborne Skin Infections

Pathogen	Clinical Features of Skin Infection	Treatment
Vibrio vulnificus	Cellulitis with hemorrhagic bullae, septicemia	Doxycycline 100 milligrams IV twice per day plus fourth-generation cephalosporin; necrotizing infections require emergent surgical debridement
Aeromonas species	Cellulitis, necrotizing wound infections	Mild infections: ciprofloxacin 500 milligrams PO twice per day; severe infections: ciprofloxacin 400 milligrams IV twice per day plus an IV antipseudomonal penicillin or fourth-generation cephalosporin; necrotizing infections require emergent surgical debridement
Pseudomonas aeruginosa	Hot-tub folliculitis, cellulitis in immunocompromised/diabetics	Hot-tub folliculitis is usually self-limited. Severe infection: ciprofloxacin 400 milligrams IV twice per day plus an IV antipseudomonal penicillin or fourth-generation cephalosporin
Mycobacterium marinum	Granulomatous skin infections	Clarithromycin 500 milligrams PO twice per day or doxycycline 100 milligrams PO twice per day for 3 mo; severe cases: combine with rifampin or ethambutol

children, and patients with travel to areas with fluoroquinolone-resistant *Campylobacter* (Thailand).[11]

Antimotility agents can be given to adults without signs of invasive bacterial infection (bloody stools or fever).[16] Probiotics, such as lactobacilli, may shorten the duration of diarrheal illnesses in adults and children.[55]

Metronidazole is a common first-line treatment for infections from *Giardia* and *Entamoeba*. However, tinidazole is more effective and better tolerated for *Giardia* treatment[56] (Table 160-5). Parenteral metronidazole is still used initially for invasive disease from *Entamoeba*. Paromomycin is an alternative to metronidazole and tinidazole in pregnant women.[57] Other alternatives for *Giardia* and *Entamoeba* treatment include nitazoxanide and furazolidone.[57] Albendazole is also effective for giardiasis, but not amebiasis.

Infections from *Cryptosporidium* are generally self-limited and usually do not require specific treatment in immunocompetent patients. However, use nitazoxanide or paromomycin in patients with prolonged infections, children, and the immunocompromised.[58] For immunocompromised patients with *Cryptosporidium*, nitazoxanide or paromomycin alone or in combination with azithromycin is used. Initiation of highly active antiretroviral therapy is the first priority for *Cryptosporidium* treatment in patients with HIV.[59] Treatment of meningoencephalitis from *Naegleria fowleri* includes amphotericin B (including intrathecal), rifampin, fluconazole, miltefosine, and azithromycin.[49]

Treatment of waterborne skin infections includes empiric antibiotic administration (**Table 160-8**) and tetanus vaccination if needed. Consensus is that initial empiric antibiotic therapy is broad spectrum, including clindamycin in combination with a fourth-generation cephalosporin, an extended-spectrum fluoroquinolone (i.e., moxifloxacin), or an antipseudomonal penicillin (i.e., piperacillin-tazobactam).[60] If *V. vulnificus* is suspected, treat with doxycycline and a fourth-generation cephalosporin.[34] Use clarithromycin or doxycycline for most *M. marinum* infections, adding rifampin or ethambutol if severe.[40] Patients with evidence of necrotizing infections need surgical consultation for operative debridement.[60]

DISPOSITION AND FOLLOW-UP

Most episodes of acute gastroenteritis secondary to waterborne pathogens are self-limited. Patients with systemic symptoms, severe dehydration, or comorbid illnesses or patients unable to tolerate oral fluids are bedded (admission or longer observation). Admit those with waterborne skin infections accompanied by systemic illness, suspected necrotizing findings, or comorbid conditions such as immunocompromised states.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 161

Zoonotic Infections

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INTRODUCTION

Zoonoses are diseases caused by bacteria, viruses, parasites, or fungi transmitted from vertebrate animals or insects to or from humans. Ticks are one of the most important vectors of human infectious diseases in the world. Exposures or occupations that involve animal contact are risk factors for disease (**Table 161-1**). Recent travel, particularly in spring, summer, and early fall, or history of habitation in an underdeveloped country are additional risk factors. Zoonoses can occur at any time of the year, but in temperate climates, most zoonoses happen in the spring and summer. A patient with a zoonotic infection has signs and symptoms similar to many acute infections: fever, headache, myalgias, malaise, and weakness (**Table 161-2**).

This chapter focuses on the most important tick-borne diseases, upper and lower respiratory zoonoses, and parasitic zoonoses. Many of the parasitic, bacterial, and viral organisms responsible for gastroenteritis share a zoonotic source in addition to a human source. These are discussed in Chapter 73, "Disorders Presenting Primarily With Diarrhea." Life-threatening zoonoses such as rabies, malaria, and serious viral infections are discussed in separate chapters.

TICK-BORNE INFECTIONS

Ticks parasitize vertebrates in virtually every part of the world. Saliva of some tick species contains anesthetic and inflammatory factors, and some species contain a toxin that paralyzes the host. Ticks feed for several days on the host, and their presence often goes unnoticed for a time; many affected patients do not recall a history of a tick bite.[1] Tick-borne

TABLE 161-1 Risk Factors for Zoonotic Infection

Risk Category	Examples
Agricultural workers	Farmers, cattle ranchers, sheep ranchers, and migrant workers
Animal processing workers	Slaughterhouse workers, animal hide processors, and workers in manufacturing who deal with animal products
Outdoor enthusiasts	Forestry workers, lumbermen, surveyors, park rangers, hunters, spelunkers, and fishermen
Pet owners	Those living alongside a dog, cat, bird, rodent, rabbit, reptile, or fish
Professionals	Veterinarians, animal researchers, and animal handlers
Immunocompromised patients	Those with congenital immunodeficiencies, diabetes mellitus, alcoholism, renal failure, liver failure, cancer, splenectomy, or human immunodeficiency virus

TABLE 161-2 Common Systemic Zoonotic Infections

Agent	Animal Reservoir	Physical Findings	Diagnostic Tests	Treatment
Aeromonas species	Fish, reptiles	Nonspecific fever, severe crepitant cellulitis with systemic toxicity, gastroenteritis	—	See Chapter 160, "Food and Waterborne Illnesses"
Brucella canis	Dogs	Nonspecific fever	Serologic testing, blood culture	Doxycycline plus gentamicin or rifampin. TMP-SMX plus gentamicin in children
Capnocytophaga	Dogs and cats	Fever, septic shock, and meningitis from infected bite	Culture of bite wound	Amoxicillin-clavulanate or clindamycin. Pip-Tazo or a carbapenem plus clindamycin/vancomycin for shock
Chlamydophila psittaci	Birds	Fever, flulike illness, pneumonia, endocarditis, sepsis	Serologic testing and sputum culture	Doxycycline. Azithromycin and levofloxacin are alternatives
Coxiella burnetii	Cattle, sheep, goats, and occasionally cats	Fever, pneumonia, hepatitis, meningitis, endocarditis	Serologic testing, PCR	Doxycycline, with the possible alternative of a fluoroquinolone or macrolide
Ehrlichia species	Ticks	Nonspecific fever, sepsis, meningitis, hepatitis	Clinical diagnosis, serologic testing, peripheral blood smear, immunocytologic testing, PCR	Doxycycline recommended for all patients (even children and pregnancy). Rifampin is alternative
Leptospira species	Birds, dogs, rodents	Fever, pneumonia, conjunctivitis, lymphadenopathy	Darkfield microscopic examination of body fluids, serologic testing	Penicillin G IV. Ceftriaxone IV alternative. Mild disease: oral doxycycline or amoxicillin or azithromycin
Francisella tularensis	Rabbits, cats, wild animals, biting insects	Fever, sepsis, meningitis, pneumonia, hepatitis, rash	Serologic testing (poses hazards to laboratory staff)	IV aminoglycosides. Alternative: Doxycycline or ciprofloxacin
Rickettsia rickettsii	Ticks	Fever, diarrhea, or typical presentation of Rocky Mountain spotted fever	Clinical diagnosis, rise in antibody titer between acute and convalescent serum, skin biopsy	Doxycycline or chloramphenicol
Salmonella enterica	Dogs, cats (rarely), reptiles (turtles)	Fever, abdominal pain, sepsis, cellulitis, meningitis, endocarditis, septic arthritis	Blood or stool culture	Fluoroquinolones or third-generation cephalosporins
Streptococcus iniae cellulitis	Fish, seafood	Fever, cellulitis	Wound culture, blood culture	β-Lactams except aztreonam. Alternatives: azithromycin, clindamycin, fluoroquinolones
Yersinia pestis	Dogs, cats, rodents	Bubonic: fever, headache, buboes; or pneumonic: cough, chills, dyspnea, shock	Blood culture, culture of suspected sites	Doxycycline, fluoroquinolone, gentamicin, streptomycin, or chloramphenicol

Abbreviations: PCR = polymerase chain reaction; Pip-Tazo = piperacillin-tazobactam; TMP-SMX = trimethoprim-sulfamethoxazole.

diseases are often accompanied by a rash. Tick-borne zoonoses have a geographic distribution (**Table 161-3**) and seasonal variation.

TICK REMOVAL, PROPHYLACTIC TREATMENT, AND PREVENTION OF TICK BITES

The most effective way to remove an embedded tick is manual extraction with tweezers or blunt angled forceps to grasp the tick as close to the skin surface as possible. Avoid puncturing or grasping the body of the tick because this can lead to rupture of the tick and release of an infectious pathogen. Pull perpendicular to the skin with gentle traction, avoiding twisting or breaking the tick. Remove all residual body parts to limit any granulomatous reaction and infection. After complete removal of the tick, cleanse and disinfect the skin surface. Do not use topical or injected lidocaine or pass sutures through the tick, and avoid the use of gasoline, kerosene, petroleum jelly, or fingernail polish, which all can increase infection or impair complete tick removal. Commercially available tick removal devices exist, although tweezers are effective.[2] Save the removed tick in alcohol to aid in identification, which is helpful if later illness occurs.

Use prophylactic treatment of a tick bite in select circumstances.[3] Prophylactic indications include the ability to easily identify the tick as *Ixodes scapularis*, tick attachment for >36 hours or with obvious tick engorgement, and a local tick bite in an area with *Borrelia burgdorferi* carrier rate of >20%.[4] In such cases, use a *one-time dose* of doxycycline 200 milligrams for adults or 4 milligrams/kg in children for Lyme disease prophylaxis.

The best method to avoid tick bites is the application of topical DEET (*N,N*-diethyl-m-toluamide) to exposed skin and treatment of clothing with permethrin. Optimal DEET concentration is 15% to 33%, with less effectiveness if the DEET concentration is >35%. Apply to skin according to label directions.

ROCKY MOUNTAIN SPOTTED FEVER

The human disease-causing rickettsioses—the spotted fevers—include a number of different species identified in the Americas, Europe, Southwest Asia, Africa, Siberia, western Russia, and Australia. Disease names are based on species and geography: Mediterranean spotted fever, Israel spotted fever, Astrakhan fever, Siberian tick typhus, Queensland tick typhus, African tick bite fever, and so on.

Rocky Mountain spotted fever is one of the most severe of the tick-borne illnesses in the United States, with peak occurrence occurring in June and July. The fatality rate for Rocky Mountain spotted fever is <0.5%. More than 60% of reported U.S. cases originate from five states: North Carolina, Tennessee, Oklahoma, Missouri, and Arkansas.[5] The causative organism is *Rickettsia rickettsii*, a pleomorphic, obligate intracellular organism, and the vectors are the very small *Dermacentor* (*D. variabilis* and *D. andersoni*, the American dog tick) and *Rhipicephalus sanguineus* ticks (the brown dog tick, found in the American Southwest). Deer, rodents, horses, cattle, cats, and dogs are zoonotic hosts, with higher incidence in communities with free-roaming dog presence.[5] *Rickettsia parkeri* and other members of the family can possibly cause Rocky Mountain spotted fever and may be responsible for an increase in incidence.

TABLE 161-3 Tick-borne Infections

Disease	Primary Vector	Animal Reservoir	Clinical Features	Geographic Distribution
Babesiosis	*Ixodes dammini*, *I. scapularis*, and *I. pacificus*	Cattle, horses, dogs, cats, rodents, deer	Fatigue, malaise, anorexia, nausea, headache, sweats, rigors, abdominal pain, emotional lability, depression, dark urine, hepatomegaly, fever, petechiae, ecchymosis, occasional rash, and occasionally, pulmonary edema	Northeast and north-central United States
Colorado tick fever	*Dermacentor andersoni* (wood tick)	Deer, marmots, porcupines	Fever, chills, headache, myalgias, nausea, vomiting, photophobia, abdominal pain, and occasional sore throat; also may have conjunctivitis, lymphadenopathy, hepatosplenomegaly, stiff neck, retro-orbital pain, weakness, and lethargy	Western and northwestern United States and southwestern Canada
Anaplasmosis	*I. scapularis, I. pacificus*	Dogs, deer, other mammals	Fevers, chills, malaise, headache, nausea, muscle aches, cough, sore throat, and pulmonary infiltrates (especially in children)	Japan, Malaysia, and the eastern, northeastern, and north-central United States
Ehrlichiosis	*Amblyomma americanum* (lone star tick)	Dogs, deer, other mammals	Fevers, chills, malaise, headache, nausea, muscle aches, cough, sore throat, and pulmonary infiltrates (especially in children)	Japan, Malaysia, Europe, and southeastern and south-central United States
Lyme disease (*Borrelia burgdorferi*)	*I. dammini*	Deer, sheep, deer mice	Erythema migrans, meningitis, encephalitis, neuropathy, and joint and heart symptoms	Atlantic central and north-central United States, Europe
Rocky Mountain spotted fever (*Rickettsia rickettsii*)	*D. andersoni* and *Dermacentor variabilis* (dog tick)	North American mammals	Petechiae, purpura, pulmonary infiltrates, jaundice, myocarditis, hepatosplenomegaly, meningitis, encephalitis, and lymphadenopathy	Most of the continental United States, although more prevalent in the southeast and south-central United States
Relapsing fever (*Borrelia* species)	*Ornithodoros* species	Human body lice, wild rodents, humans	Fever, chills, headache, myalgias, and arthralgias; pain, nausea, vomiting, and hypotension	Worldwide
Southern tick-associated rash illness	*A. americanum*	Ticks; unclear if other reservoir exists	Erythema migrans, fever, headache, myalgias	Eastern, southeastern, and south-central United States
Tularemia (*Francisella tularensis*)	*Dermacentor* spp. and *Amblyomma* spp.	Rabbits, deer, dogs	Pneumonia, regional lymphadenopathy and headache, cough, myalgias, arthralgias, nausea, vomiting, ulceration at inoculation site, and ocular findings	Northern hemisphere, North America, northern Asia, Europe

CLINICAL FEATURES

The diagnosis relies on epidemiologic features and the clinical exclusion of other diseases. Early signs and symptoms of Rocky Mountain spotted fever are fever, headache, myalgia, and malaise. Additionally, other nonspecific findings include lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, and headache. Late in the disease course, confusion, meningismus, renal failure, respiratory failure, and myocarditis may occur. The classic clinical picture is the triad of fever, rash, and tick bite, but only about half of patients can recall a tick bite.

The rash occurs on days 2 to 4 after the onset of fever but is absent in approximately 20% of patients. Most patients do not have a petechial rash when they seek initial medical care.[1] The rash occurs earlier in children than in adults and begins as small blanching erythematous to pink macules and becomes petechial later. This characteristic maculopapular rash begins on the hands, feet, wrists, and ankles, and then spreads centripetally up the trunk. The *rash is not pathognomonic* and may occur in other illnesses. Additionally, the rash is easily overlooked early in infection and in those with dark skin. Another feature to recognize is the possibility of a nonexudative conjunctival injection with bilateral periorbital edema, resembling that found in toxic shock syndrome or Kawasaki's disease. Abdominal distention and organomegaly may exist on physical exam.[6]

DIAGNOSIS AND TREATMENT

Immunoglobulin G– or immunoglobulin M–specific antibodies are not detectable in acute-phase serum. Laboratory abnormalities are usually nonspecific, but the **combination of normal white and red cell counts, thrombocytopenia, mild elevation of liver enzymes (aspartate aminotransferase and alanine aminotransferase), and hyponatremia suggests Rocky Mountain spotted fever**, especially if the disease is advanced. Hypoalbuminemia may be present and is the cause of edema.[6] In addition to clinical patterns, diagnosis confirmation with a rise in antibody titer between acute and convalescent serum, skin biopsy with immunofluorescent testing, or culture is possible, although none of these are useful for ED diagnosis.

Preferred treatment is doxycycline (**Table 161-4**). Given the long half-life of doxycycline (18 to 21 hours), several days of a higher dose regimen may be required to achieve rapid therapeutic response in the critically ill patient. The risk of cosmetically perceptible tooth staining is small for a single course of treatment. **Use doxycycline therapy as the treatment of choice for all rickettsial diseases, including Rocky Mountain spotted fever, in children of all ages.**[1]

TICK PARALYSIS

Many tick species secrete neurotoxic substances from salivary glands of attached ticks. Tick paralysis occurs worldwide, in Australia, Africa, Europe, and North America, and is more common in children than adults. Prolonged tick attachment (5 to 7 days) can result in host paralysis. Symptoms are ascending weakness, beginning in the lower extremities, and moving upward to the trunk, upper extremities, and head over hours to days. Cerebrospinal fluid analysis is normal. Diagnosis is made upon finding a tick on the body. Tick removal leads to recovery in 24 hours.

LYME DISEASE

The first reports of Lyme disease were in Europe about 100 years ago based on descriptions of the rash, erythema chronicum migrans. Lyme disease is the most common vector-borne zoonotic infection in the United States, with approximately 30,000 annual cases reported. Based on public health data and insurance information, the actual number of patients diagnosed with Lyme disease may be closer to 300,000 per year.[7] Lyme disease is reported in Europe, China, Japan, Australia, parts of Russia, and in all U.S. continental states, with 96% of the reported cases

TABLE 161-4 Tick-borne Zoonotic Infections and Specific Treatment

Tick-borne Zoonotic Infection	Specific Treatment
Rocky Mountain spotted fever	Doxycycline 100 milligrams PO or IV twice a day for 7 d, or for 2 d after temperature normalizes. Some recommendations exist for an initial loading dose of 200 milligrams. For children weighing <45 kg, the dose is 2.2 milligrams/kg twice daily. Although doxycycline is contraindicated for use in pregnancy, it may be warranted in life-threatening situations. Chloramphenicol is an alternative; however, it has multiple toxic effects and contraindications and may be difficult to obtain. Dosing is 50 milligrams/kg/d divided into 4 doses for 7 d.
Lyme disease	Primary stage or mild secondary: 14–21 d of doxycycline (100 milligrams PO twice a day), amoxicillin (500 milligrams PO 3 times a day in adults, 50 milligrams/kg/d divided 3 times a day in children), or cefuroxime (500 milligrams PO twice a day in adults, 30 milligrams/kg/d divided 3 times a day in children). Macrolides possible but less effective. Severe illness, CNS positive, or high-degree heart block: ceftriaxone 2 grams IV for 14–30 d. A single 200-milligram oral dose of doxycycline given within 72 h of a high-risk deer tick bite is effective in preventing Lyme disease.
Tick-borne relapsing fever	Doxycycline (100 milligrams PO/IV twice a day for 7–10 d). Alternative: erythromycin (500 milligrams PO/IV 4 times a day for 7–10 d). Chloramphenicol is an alternative.
Colorado tick fever	Treatment is supportive.
Southern tick-associated rash illness	Treatment is supportive, often treated cautiously as Lyme with doxycycline as above.
Tularemia	Adults: streptomycin, 1 gram IM/IV twice a day, or gentamicin/tobramycin, 5 milligrams/kg IV divided every 8 h. Treat for 10 d. Children: streptomycin, 15 milligrams/kg IM twice daily (should not exceed 2 grams/d). Mild disease: ciprofloxacin, 750 milligrams PO twice a day, or doxycycline, 100 milligrams PO twice a day. Treat for 21 d. Prophylaxis for lab exposures: doxycycline, 100 milligrams PO twice a day, or ciprofloxacin, 500 milligrams PO twice a day. Treat for 14 d.
Babesiosis	Atovaquone (750 milligrams PO every 12 h) plus azithromycin (500 milligrams PO on day 1, then 250 milligrams daily). Treat for 10 d. If relapse occurs, treat for the longer duration: 6 weeks or 2 weeks after negative blood smear. Severe disease in adults: clindamycin (1200 milligrams IV twice a day or 600 milligrams PO 3 times a day) + quinine (650 milligrams PO 3 times a day). Treat for 7–10 d.
Ehrlichiosis and anaplasmosis	Doxycycline, 100 milligrams PO twice a day for 7–14 d. For children weighing <45 kg, the dose is 2.2 milligrams/kg twice a day.

originating from 14 states clustered in the northeast and upper midwest. Peak transmission occurs in May through August. The responsible organism is *B. burgdorferi*, a spirochete, and the vector is the *Ixodes* deer tick, also known as the black-legged tick. The overall risk of Lyme disease after a deer tick bite is low, about 3% in endemic areas. However, the risk of infection is proportional to the length of time the tick feeds on the host, with minimal to no risk associated with tick attachment duration of <36 hours.[4,8]

CLINICAL FEATURES

Lyme disease has three stages. The **first stage** is local and often with **erythema migrans**: an erythematous plaque with central clearing, seen in approximately 60% to 80% of cases.[1] It develops within 2 to 30 days at the site of the tick bite and is a result of a vasculitis. There may be accompanying fever, chills, fatigue, myalgias, arthralgias, and lymphadenopathy. The rash may persist for up to 1 month and recur in the secondary stage of Lyme disease. Untreated erythema migrans resolves spontaneously in 3 to 4 weeks. This rash causes few symptoms and may go unnoticed by the patient.

The **second stage**, early disseminated disease, develops with the reproduction and spread of the *Borrelia* spirochete, occurring within a few days to months of the initial infection. This stage has fever, adenopathy, neuropathies, cardiac abnormalities, arthritic complaints, and skin lesions. Multiple annular/target-shaped skin findings occur in up to 50% of the patients infected and are the most characteristic component of the secondary stage of illness.

The most common neurologic symptom in the secondary stage of illness is the development of cranial neuritis, most often **unilateral or bilateral facial nerve palsy**. Facial palsy can also occur along with the initial rash of erythema migrans. Neuroborreliosis occurs in 15% of the untreated cases and can consist of periodic headache, neck stiffness, difficulty in mentation, cerebellar ataxia, myelitis, encephalitis, motor or sensory radiculoneuritis, mononeuritis multiplex, and facial palsy.[9] Asymmetric oligoarticular arthritis of the large joints, with a particular predilection for the knees, is another complication. Brief attacks of asymmetric oligoarticular arthritis are common in the untreated patient in the secondary stage of illness. Attacks are characteristically separated by months of remission. Cardiac abnormalities occur in up to 8% of patients and present as varying degrees of atrioventricular block, sometimes requiring the insertion of a temporary pacemaker for stabilization. Additionally, myopericarditis may also be a manifestation on initial presentation.

The **late disseminated stage** of illness occurs months to years after the initial infection and is characterized by chronic arthritis, myocarditis, subacute encephalopathy, axonal polyneuropathy, and leukoencephalopathy.[9] The advanced, chronic neurologic forms of Lyme disease can persist for over 10 years. Additionally, between 10% and 20% of patients treated with antibiotics have persistent symptoms, usually muscle and joint aches with fatigue and perhaps an autoimmune response persistent after the initial infection.

DIAGNOSIS AND TREATMENT

Diagnosis is clinical early in disease when erythema migrans is present; testing diagnoses later stages of Lyme disease.[8] For the latter, use polymerase chain reaction testing, polyvalent fluorescence immunoassay, or Western immunoblot testing,[9] because *B. burgdorferi* is difficult to culture.

Treatment of Lyme disease is with doxycycline (preferred agent) or amoxicillin. Neurologic symptoms or other persistent manifestations require ceftriaxone therapy (Table 161-4). A previously marketed vaccine no longer exists, because it conferred no ongoing immunity.

EHRLICHIOSIS AND ANAPLASMOSIS

Ehrlichiosis is a group of zoonotic diseases caused by the *Ehrlichia* genus, gram-negative pleomorphic coccobacilli that will infect circulating leukocytes.[1] Infection due to *Ehrlichia chaffeensis* is also called *human monocytic ehrlichiosis*. The disease vector is the lone star tick, *Amblyomma americanum*. The major animal reservoir in North America is the white-tailed deer in the southeastern United States, with dogs and mice carrying several less common species of the pathogen.[10] Disease incidence rose from 0.8 to 3 cases per million in the United States in 2000 to 2007, partly attributed to increased recognition. It also exists in Europe. The mortality rate in confirmed cases varies between 1% and 3% depending on causative agent.[10]

Symptoms usually develop within 1 to 2 weeks of a tick bite.[11] Clinical signs and symptoms are fever, headache, malaise, nausea, vomiting, diarrhea, abdominal pain, and arthralgias. Fever is present in the vast

majority of cases (97%). Rash is present in 30% of adults and has no pathognomonic features.[12] With disease progression, a minority of patients develop renal failure, respiratory failure, and encephalitis. The acute phase of illness lasts <4 weeks, with the majority of patients recovering and proceeding on to a convalescent phase. Laboratory studies can demonstrate leukocytopenia, thrombocytopenia, and elevation of hepatic enzymes.

DIAGNOSIS AND TREATMENT

Diagnosis is made clinically but can be confirmed by laboratory testing once treatment has begun. Peripheral blood smear may show colonies of ehrlichiae in the WBCs in 20% of infected patients. Polymerase chain reaction is specific but not sensitive and is best done in the first week of illness. Antibody tests are negative in 85% of patients during initial infection. The reference criterion test is immunofluorescence assay.[11]

Treatment is with doxycycline until 3 to 5 days after fever resolution or 10 to 14 days after resolution of CNS symptoms in severe disease. Rifampin is an alternative in those with contraindications to doxycycline.[12]

Anaplasmosis is a tick-borne disease caused by the bacteria *Anaplasma phagocytophilum*.[13] Older terms for the disease are *human granulocytic ehrlichiosis* and *human granulocytic anaplasmosis*. The vector is the black-legged tick, *I. scapularis*, as well as the western black-legged tick, *Ixodes pacificus*. The clinical presentation of this disease is similar to ehrlichiosis, with geography of tick prevalence as the key difference between the two. Testing is similar, and treatment is also with doxycycline.

TICK-BORNE RELAPSING FEVER

Relapsing fever is caused by several varieties of gram-negative *Borrelia* spirochetes. It was first described in West Africa and is now worldwide. Within the United States, it is rarely found east of Texas.[14] *Ornithodoros* ticks (soft ticks that can survive for years between meals) are the vectors, and the principal zoonotic reservoirs are wild rodents, specifically tree squirrels and chipmunks.[15] The classic risk factor is sleeping in rustic mice-infested structures in the wilderness of the western United States. The initial presentation may be that of a rash or a 2- to 3-mm pruritic eschar at the site of a tick bite. An average incubation period of 7 days precedes the onset of fever, chills, cephalgia, myalgia, arthralgia, abdominal pain, and general malaise. Headache and myalgia occur in >90% of cases.[15] Characteristically, the 3-day-long febrile episodes are interspersed with 7-day-long afebrile periods, which may cycle one to four times before resolution.[15] Untreated, the disease is usually self-limited, with deaths occurring mostly at the extremes of age. Leukocytosis and thrombocytopenia are the typical laboratory findings.

DIAGNOSIS AND TREATMENT

Diagnosis confirmation is with the appearance of spirochetes on dark-field microscopy or Wright-Giemsa–stained peripheral blood smears, with a 70% sensitivity if obtained during a febrile period. Patients with relapsing fever may test false positive on Lyme disease assays due to protein cross-reactivity.[15] Treatment is with tetracycline or erythromycin. Use IV ceftriaxone for 10 to 14 days if any CNS involvement exists.[15] Patients in an endemic area with a confirmed tick bite can receive post-exposure doxycycline for prophylaxis.[16]

COLORADO TICK FEVER

Colorado tick fever is caused by an RNA virus of the genus *Coltivirus* in the family Reoviridae.[17] The principal vector is the wood tick, *D. andersoni*, and the zoonotic reservoirs are deer, marmots, and porcupines. The disease is endemic to the western mountainous regions of the United States with elevations between 4000 and 10,000 ft. Transmission to humans can occur with short periods of tick attachment. The incubation period is 3 to 5 days, and the onset of illness has fever, chills, headache, myalgias, and photophobia. There may be a macular or petechial rash in a minority of patients. The disease is self-limited, and complications are rare, although some patients may experience recurrent fever after 1 to 2 days of improvement.

DIAGNOSIS AND TREATMENT

Diagnosis is most often based on history, clinical findings, and geography. Treatment is supportive.[17]

SOUTHERN TICK-ASSOCIATED RASH ILLNESS (STAR)

Southern tick-associated rash illness (STAR) is an illness that clinically presents in a manner nearly identical to Lyme disease.[18] This disease has the typical target-shaped rash of primary Lyme and may be accompanied by nonspecific symptoms such as fever, myalgias, headache, and fatigue. This illness is transmitted by the lone star tick, *A. americanum*, which is endemic to the eastern, southeastern, and south-central United States.[19] Unlike Lyme disease, southern tick-associated rash illness is not known to cause delayed presentations of illness, nor does it cause cardiac or CNS involvement. The disease is thought to be transmitted directly by the tick, but no animal reservoirs or causative bacteria have been discovered. Although it is thought to be a benign and self-limited disease requiring only supportive care, southern tick-associated rash illness's clinical mimicry of Lyme disease leads many providers to empirically treat for the latter.

TULAREMIA

Tularemia is caused by a small, gram-negative, nonmotile intracellular coccobacillus, *Francisella tularensis*. The disease is found in North America, northern Asia, and Europe. The zoonotic vectors are ticks of the *Dermacentor* species (wood tick, dog tick) and the *Amblyomma* species (lone star tick), as well as various flies. The principal zoonotic reservoirs are rabbits, hares, and deer.[17] Tularemia is contracted through tick/fly bites, by inhalation, or through open wounds while in contact with an infected zoonotic host. Incubation is often between 3 and 6 days but may range from 2 hours to 3 weeks. The clinical presentation depends on the method of inoculation, and the clinical forms are called *ulceroglandular, glandular, typhoidal, pneumonic, oculoglandular,* and *oropharyngeal*. The **ulceroglandular form** is the most common, occurring in 80% of cases,[17] with a maculopapular skin lesion that ulcerates, followed by painful regional adenopathy and systemic symptoms. The **glandular form** consists of painful adenopathy without ulcerations. The **typhoidal form**, occurring in 20% to 30% of cases, consists of high fever, chills, cephalgia, and abdominal pain with an absence of skin and lymph involvement. Typhoidal tularemia has a slower tachycardia than would be expected given the fever magnitude. It is the form of the disease with highest morbidity, complications, and organ failure. The **oculoglandular form** and **pneumonic form** are the result of deposition into the eyes or inhalation of the *F. tularensis* bacterium. Pneumonic tularemia has up to a 50% mortality rate and is the most lethal form of the disease. Laboratory findings are nonspecific.

DIAGNOSIS AND TREATMENT

Confirmatory testing is difficult and poses health risks to laboratory staff. First-line treatment is with streptomycin; gentamicin, ciprofloxacin, imipenem, doxycycline, and chloramphenicol are alternative therapies. Prevention of exposure and early treatment are key measures to prevent adverse outcomes. Think of this infection in endemic areas. Due to the ease of transmission and lethality, *F. tularensis* is a possible agent of biologic warfare/terrorism (Table 9-1).

BABESIOSIS

Babesiosis is a malaria-like disease transmitted by ticks, with the etiologic agents being protozoan parasites. *Babesia microti* is the most common causative organism in the United States, with sporadic cases caused by *Babesia duncani* on the Pacific coast.[20] The major zoonotic reservoirs are domesticated mammals, rodents, and deer. *Ixodes* ticks function as the principal vector globally. Babesiosis is also transmitted through blood transfusions, with about 160 cases reported since 1979.[20] Clinically, the presentation occurs 1 to 4 weeks after exposure with

generalized malaise, anorexia, fever, and chills that can progress to intermittent sweats, myalgia, headache, and hemolytic anemia. Splenectomy and immunosuppression are risk factors. Laboratory tests demonstrate hemolysis, liver dysfunction, anemia, thrombocytopenia, and renal failure. Coinfection with Lyme disease or anaplasmosis/ehrlichiosis is common; patients with severe disease or disease refractory to treatment should be considered for alternative etiologies of illness.

DIAGNOSIS AND TREATMENT

Diagnose this infection by finding intraerythrocytic ring forms resembling malaria on a Giemsa- or Wright-stained peripheral blood smear, although false-negative results can occur when the level of parasitism is low. Treatment duration is typically for 7 to 10 days with atovaquone plus azithromycin or clindamycin, with quinine added for severely ill patients (Table 161-4).

ZOONOTIC ENCEPHALITIS AND MENINGITIS

Zoonotic encephalitis is most often an arboviral infection transmitted hematologically by an arthropod or insect vector from an animal host.[21] There are multiple distinct arboviruses that cause zoonotic encephalitis in the United States and Canada. Furthermore, encephalitis may be seen in the nonviral zoonotic infections of *Bartonella henselae, Brucella canis*, borreliosis, *Coxiella burnetii, Ehrlichia* species, listeriosis, leptospirosis, Lyme disease, Rocky Mountain spotted fever, psittacosis, and toxoplasmosis.[21] See Chapter 174, "Central Nervous System and Spinal Infections," for additional discussion.

The first clinical signs and symptoms are nonspecific: malaise, myalgia, and fever. Next often comes headache and a sudden decline in mental status. Head CT scan is usually normal. The cerebrospinal fluid is often abnormal, showing a slightly elevated opening pressure, normal to slightly elevated protein concentration, normal glucose levels, and predominance of lymphocytes. The infectious agent is rarely isolated from the cerebrospinal fluid. Enzyme-linked immunosorbent assay of serum can detect most arboviral infections causing encephalitis.

Treatment is supportive. **Consider treatable causes of encephalitis, such as herpes simplex or varicella, in the differential diagnosis.**

The West Nile virus is an arbovirus that can cause a flulike illness, West Nile fever or **West Nile virus encephalitis**. Infected mosquitoes transmit the virus to humans and other animals through bites. Approximately 20% of patients infected develop symptomatic illness, with <1% having severe or potentially fatal infection.[22] Although antibody responses can confirm disease, lab testing is usually not specific. Treatment for West Nile virus encephalitis is supportive (**Table 161-5**).

Powassan disease is an arbovirus similar to West Nile but is transmitted by the deer tick rather than mosquitos. The infection begins with a nonspecific prodrome of fever and chills, but often progresses to a viral encephalitis.[23] Diagnosis is by specialty tests at national laboratories, but the disease should be suspected in areas prone to Lyme disease.

Zoonotic meningitis can be caused by brucellosis, listeriosis, plague, salmonellosis, tularemia, leptospirosis, Lyme disease, ehrlichiosis, Q fever, Rocky Mountain spotted fever, or psittacosis. Cerebrospinal fluid is almost always abnormal, showing a slightly elevated opening pressure, normal to slightly elevated protein concentration, normal glucose levels, and predominance of lymphocytes. Treatment is directed toward the specific organism cultured from the cerebrospinal fluid. However, empiric antibiotic coverage should be administered immediately in any presumptive case of meningitis in an effort to reduce mortality and morbidity (see Chapter 174, "Central Nervous System and Spinal Infections").

TABLE 161-5 Selected Zoonotic Infections and Specific Treatment

Selective Zoonotic Infections	Specific Treatment
West Nile/Powassan encephalitis	Supportive care.
Brucellosis (*Brucella* species)	Mild disease: doxycycline, 100 milligrams PO twice a day for 6 weeks, + gentamicin, 5 milligrams/kg IV daily for 7 d. Alternative: doxycycline, 100 milligrams PO twice a day, + rifampin, 600–900 milligrams PO daily for 6 weeks. Joint involvement: doxycycline, 100 milligrams PO twice a day, + rifampin, 600–900 milligrams PO daily for 3 months, + gentamicin, 5 milligrams/kg IV once daily for first 7 d. Neurologic involvement: doxycycline, 100 milligrams IV/PO twice a day, + rifampin, 600–900 milligrams PO daily, + ceftriaxone, 2 grams IV twice a day. Treat until cerebrospinal fluid normalizes.
Psittacosis (*Chlamydophila psittaci*)	Doxycycline, 100 milligrams PO for 5–7 d. Alternative: azithromycin dose pack or levofloxacin, 750 milligrams PO for 5–7 d.
Q fever (*Coxiella burnetii*)	Doxycycline, 100 milligrams PO twice a day for 2–3 weeks. Alternative: consider 2–3 weeks of a fluoroquinolone or a macrolide.
Pasteurellosis (*Pasteurella multocida*)	Amoxicillin-clavulanate, 875/125 milligrams PO twice a day for 7–10 d. Alternative therapies based on culture data and presence of *Staphylococcus* coinfection. Often resistant to cephalexin, clindamycin, and macrolides.
Plague (*Yersinia pestis*)	Gentamicin, 5 milligrams/kg IV daily for 10 d. Alternative: streptomycin, 15 milligrams/kg IV/IM twice a day for 10 d. Postexposure prophylaxis: doxycycline, 100 milligrams PO twice a day, or ciprofloxacin, 500 milligrams PO twice a day. Treat for 7 d.
Hantavirus	Treatment consists of supportive care with attention to adequate oxygenation.
Toxocariasis (*Toxocara canis*)	Moderate to severe disease: albendazole, 400 milligrams PO twice a day, with/without prednisone, 60 milligrams/d for allergic response. Treat for 5 d. Alternative: mebendazole, 100–200 milligrams PO twice a day for 21 d.
Dipylidiasis (dog tapeworm)	Praziquantel, 5–10 milligrams/kg PO, one-time dose. Alternative: niclosamide, 2 grams PO, one-time dose
Leptospirosis	Mild disease: doxycycline, 100 milligrams PO twice a day for 5–7 d. Alternative: azithromycin, 500 milligrams PO daily for 3 d. Severe disease: penicillin G, 1.5 million units IV every 6 h for 7 d, or ceftriaxone, 2 grams IV daily for 7 d. Alternative: doxycycline, 100 milligrams IV for 7 d.

UPPER RESPIRATORY ZOONOTIC INFECTIONS

Recurrent pharyngitis in a household member can have a zoonotic source, sometimes the household pet. Case reports exist where domestic animals in cohabitation with humans were associated with group A streptococcal pharyngitis recurrence; however, current practice guidelines on infection can find no causal link.[24] **Prolonged exudative pharyngitis raises the suspicion of a zoonotic origin or atypical pharyngitis, particularly if the exudative pharyngitis includes systemic symptoms and leukocytosis, and is refractory to standard antistreptococcal therapy.** Dogs and domesticated farm animals can be the source of *Streptococcus* species, *Corynebacterium ulcerans, Yersinia* species, and viral vesicular stomatitis. All of these zoonoses can present as an exudative pharyngitis. Nondomesticated animals can be a source of exudative pharyngitis as a result of *Bordetella* species, *F. tularensis, Streptobacillus moniliformis,* and *Yersinia pestis*. Birds carry *Chlamydophila psittaci*, which can cause an atypical exudative pharyngitis in humans.

LOWER RESPIRATORY ZOONOTIC INFECTIONS

Zoonotic pneumonia presents as an atypical, community-acquired pneumonia with systemic symptoms. Most often, the presentation is productive or nonproductive cough, fever, chills, headache, myalgias, and a nonspecific rash. Symptoms can progress very rapidly. Ask about animal exposure, occupation, and recent travel. Consider zoonotic pneumonia as a source of gram-negative community-acquired pneumonia and in any case of atypical pneumonia with systemic symptoms (**Table 161-6**).

ANTHRAX

Inhalation anthrax (*Bacillus anthracis*) is acquired most often from handling unsterilized, imported animal hides or imported raw wool; anthrax is generally fatal. Inhalation anthrax is a mediastinitis without alveolar involvement rather than pneumonia. Initial symptoms are similar to influenza with a slightly higher propensity for dyspnea. Illness can progress to respiratory failure in 2 to 3 days, with marked mediastinal and hilar edema. **Anthrax vaccination** is available primarily for populations at high risk of exposure to aerosolized *B. anthracis* spores such as military personnel and laboratory workers.[25]

A 60-day antibiotic course combined with a three-dose vaccination course used in postexposure prophylaxis may aid in preventing anthrax postexposure, although this regimen is not presently approved by the U.S. Food and Drug Administration.[26] Antibiotics typically used in inhalation anthrax are doxycycline or ciprofloxacin, plus an additional one or two agents for synergy, including penicillin G, vancomycin, rifampin, or other agents for which the strain is suspected to be sensitive. Cephalosporins are contraindicated due to resistance.[26]

BRUCELLOSIS

Brucellosis (*Brucella* species) occurs most often from the consumption of unpasteurized dairy products. Reports of slaughterhouse workers exposed to aerosols containing *Brucella* bacteria becoming ill exist.[27] In the rare inhalation form of *Brucellosis*, patients have the appearance of an upper respiratory infection with a cough, productive sputum, hoarseness of voice, dyspnea, and wheezing. There are no pathognomonic signs on chest radiograph, and a variety of findings may be present including pneumonia, adenopathy, effusion, granulomas, and effusion. With long-standing resolution, calcified granulomas may remain.[28] Doxycycline combined with rifampin is effective therapy; the recommended duration is 6 weeks to prevent recurrence[27] (Table 161-6).

PSITTACOSIS

Psittacosis (parrot fever, parrot disease) is caused by *Chlamydophila psittaci*, an organism common to most birds and domesticated fowl. *Psittacosis* is the term for disease contracted from parrots, and *ornithosis* is the term for disease contracted from pigeons, sparrows, ducks, hens, and many other birds. This disease is rare, with few cases reported annually in the United States, although underreporting is likely due to the often mild unrecognized form of disease.[29] Human acquisition is from the inhalation of dust from dried bird feces, feather dust, aerosolized avian respiratory secretions, or direct bird contact.[29] Psittacosis is characterized by an incubation period of 5 to 14 days followed by abrupt onset of fever, chills, cephalgia, myalgia, and generalized malaise. Pneumonia is atypical, with a nonproductive cough and lobar or interstitial infiltrates on chest radiograph. Extrapulmonary manifestations including endocarditis, hepatitis, cranial nerve palsies, and acute interstitial nephritis are possible. Diagnosis is based on clinical suspicion for the disease and confirmation of isolation of *C. psittaci* from respiratory secretions or by immunoglobulin M immunoassay. Doxycycline is the mainstay of treatment, with most patients responding rapidly to therapy. Tetracycline is also an option along with macrolides[29] (Table 161-6).

Q FEVER

Q fever (*Coxiella burnetii*) is a rickettsial infection acquired by aerosol inhalation primarily; however, arthropod vector transmission is possible.[30] The primary reservoirs are cattle, sheep, and goats, with bacterial shedding in urine, afterbirth products, and feces. The organism is highly resistant to environmental degradation. The disease is often self-limited, with variable pulmonary manifestations and extrapulmonary findings. In addition to pulmonary infiltrates, severe headache, pericarditis, myocarditis, endocarditis, and a nonjaundiced hepatitis can occur. The majority of patients have nonspecific infiltrates on chest radiograph.[30] Doxycycline is the treatment of choice for acute Q fever and is most effective in reducing duration of symptoms and risk of complications when initiated within the first 3 days of illness. Q fever may rarely progress to a chronic infective state with fatigue and extrapulmonary manifestations being predominant findings[30] (Table 161-6).

PASTEURELLOSIS

Pasteurellosis (*Pasteurella multocida*) is endemic to the normal oral flora of cats and most dogs. Classically, infection is associated with necrotizing cellulitis from bite wounds. Rarely bronchitis, bronchopneumonia, and suppurative pleural effusion occur as a result of pulmonary infection. Treatment is with amoxicillin-clavulanate, doxycycline, penicillin, or a third-generation cephalosporin (Table 161-6).

PULMONIC PLAGUE

Between 1000 and 2000 cases of plague are reported each year to the World Health Organization, with mortality rates of approximately 10%. Most human cases today are in sub-Saharan Africa. In the United States, pulmonary plague (*Yersinia pestis*) is most often found in rock squirrels and ground rodents of the Southwest. Cats can be carriers of plague, whereas dogs are resistant to the disease. The principal vector is the rodent flea, with the majority of infected fleas globally found on black rats or brown sewer rats.[31] Humans and household pets become infected when bitten by a harboring flea or by consuming other infected animals. Humans may also be infected by inhalation of animal secretions. Incubation period from a flea bite to disease ranges from 2 to 10 days. Often an eschar develops at the site of the flea bite, followed by the development of a bubo, an enlarged, suppurative, proximal lymph node. Sepsis and pneumonia from hematologic spread occur following the bubo appearance. The disease is rapidly fatal if not aggressively treated.

Start treatment when plague is suspected, using parenteral streptomycin or gentamicin. Transition to oral therapy with doxycycline,

TABLE 161-6 Zoonotic Pneumonias

Disease	Organism	Reservoirs	Treatment
Inhalation anthrax	*Bacillus anthracis*	Imported animal hides, raw wool, sick domestic animals	Adult initial treatment: ciprofloxacin, 400 milligrams IV every 12 h (alternative: doxycycline, 100 milligrams IV every 12 h or levofloxacin, 500 milligrams every 24 h), + clindamycin, 900 milligrams IV every 8 h, + rifampin, 300 milligrams IV every 12 h. Plus one-time infusion raxibacumab, 40 milligrams/kg diluted over 2.25 h. When clinically stable: ciprofloxacin, 500 milligrams PO twice a day, + clindamycin, 450 milligrams PO every 8 h, + rifampin, 300 milligrams PO twice a day. Treat for 60 d.
Brucellosis	*Brucella* species	Food animals and product handling, ingestion, inhalation	Mild disease: doxycycline, 100 milligrams PO twice a day for 6 weeks, + gentamicin, 5 milligrams/kg IV daily for 7 d. Alternative: doxycycline, 100 milligrams PO twice a day, + rifampin, 600–900 milligrams PO daily for 6 weeks. Joint involvement: doxycycline, 100 milligrams PO twice a day, + rifampin, 600–900 milligrams PO daily for 3 months, + gentamicin, 5 milligrams/kg IV once daily for first 7 d. Neurologic involvement: doxycycline, 100 milligrams IV/PO twice a day, + rifampin, 600–900 milligrams PO daily, + ceftriaxone, 2 grams IV twice a day. Treat until cerebrospinal fluid normalizes.
Psittacosis, ornithosis	*Chlamydophila psittaci*	Bird exposure—pet and pet shop, veterinarians, turkey farms	Doxycycline, 100 milligrams PO for 5–7 d. Alternative: azithromycin dose pack or levofloxacin, 750 milligrams PO for 5–7 d.
Q fever	*Coxiella burnetii*	Inhaled endospores from animal-contaminated soil; cat afterbirth, ticks	Doxycycline, 100 milligrams PO twice a day for 2–3 weeks. Alternative: consider 2–3 weeks of a fluoroquinolone or a macrolide.
Tularemia	*Francisella tularensis*	Aerosol from dead birds, animals; bacteremic spread from bubo; ticks and biting flies	Adults: streptomycin, 1 gram IM/IV twice a day, or gentamicin/tobramycin, 5 milligrams/kg IV divided every 8 h. Treat for 10 d. Children: streptomycin, 15 milligrams/kg IM twice daily (should not exceed 2 grams/d). Mild disease: ciprofloxacin 750 milligrams PO twice a day or doxycycline 100 milligrams PO twice a day. Treat for 21 d. Prophylaxis for lab exposures: doxycycline 100 milligrams PO twice a day or ciprofloxacin 500 milligrams PO twice a day. Treat for 14 d.
Leptospirosis	*Leptospira interrogans*	Domestic and wild animals, contaminated water, veterinarians, farmers	Mild disease: doxycycline, 100 milligrams PO twice a day for 5–7 d. Alternative: azithromycin, 500 milligrams PO daily for 3 d. Severe disease: penicillin G, 1.5 million units IV every 6 h for 7 d, or ceftriaxone, 2 grams IV daily for 7 d. Alternative: doxycycline, 100 milligrams IV for 7 d.
Pasteurellosis	*Pasteurella multocida*	Underlying respiratory disease; contact with cat, dog in home	Amoxicillin-clavulanate, 875/125 milligrams PO twice a day for 7–10 d. Alternative therapies based on culture data and presence of *Staphylococcus* coinfection. Often resistant to cephalexin, clindamycin, and macrolides.
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick-associated, typical rash	Doxycycline 100 milligrams PO or IV twice a day for 7 d, or for 2 d after temperature normalizes. Some recommendations exist for an initial loading dose of 200 milligrams. For children weighing <45 kg, the dose is 2.2 milligrams/kg twice daily. Although doxycycline is contraindicated for use in pregnancy, it may be warranted in life-threatening situations. Chloramphenicol is an alternative; however, it has multiple toxic effects and contraindications, and may be difficult to obtain. Dosing is 50 milligrams/kg/d divided into 4 doses for 7 d.
Toxoplasmosis	*Toxoplasma gondii*	Contact with domestic food animals and pets, ingestion of cysts, pneumonia in immunocompromised persons	Severe disease: Pyrimethamine, 200 milligrams PO on d 1, followed by 50–75 milligrams PO every 24 h, + sulfadiazine, 1–1.5 grams PO every 6 h, + leucovorin, 5–20 milligrams 3 times weekly. If ocular involvement, treat as above and add prednisone, 0.5 milligrams/kg PO twice a day. Treat until 1–2 weeks after symptoms resolve, continue leucovorin for 1 week past that.
Plague	*Yersinia pestis*	Contact with mammals and fleas; veterinarians; outdoor activities in endemic area; cats	Gentamicin, 5 milligrams/kg IV daily for 10 d. Alternative: streptomycin, 15 milligrams/kg IV/IM twice a day for 10 d. Postexposure prophylaxis: doxycycline, 100 milligrams PO twice a day, or ciprofloxacin, 500 milligrams PO twice a day for 7 d.
Hantavirus pulmonary syndrome	Bunyaviridae	Rodent feces, urine, and saliva	Extracorporeal membrane oxygenation or consideration of ribavirin

ciprofloxacin, or chloramphenicol occurs after improvement, although these agents can be used as initial therapy in those who cannot tolerate the preferred choice. Continue any therapy for at least 10 days or 2 days after resolution of fever[31] (Table 161-6).

HANTAVIRUS

Hantavirus, identified in 1977, is from the Sin Nombre virus, which belongs to the Bunyaviridae family of viruses. The deer mouse (*Peromyscus maniculatus*) is the primary vector in the southwestern United States.[32] Infected rodents excrete hantavirus in feces, urine, and saliva. Human infection occurs with the inhalation of dried, particulate feces, by contact with urine, or by a rodent bite. In Asia, hantaviruses can cause hemorrhagic fever with renal syndrome—acute renal failure with concurrent thrombocytopenia, ocular abnormalities, and flulike symptoms. In the United States, the presentation of this zoonosis is that of a cardiopulmonary syndrome,[32] which consists of an initial flulike prodromal illness of 3 to 4 days in duration, rapidly followed by pulmonary edema, hypoxia, hypotension, tachycardia, and metabolic acidosis. Dizziness, nausea, vomiting, absence of cough, and thrombocytopenia are common and may help to differentiate hantavirus pulmonary syndrome from acute respiratory distress syndrome, bacterial pneumonia, and influenza pneumonia. Hantavirus pulmonary syndrome carries a very high mortality rate, initially estimated around 60%, but that has now improved to 30% with efforts toward recognition and early aggressive care.[33] Diagnosis is with an immunofluorescent or immunoblot assay. Treatment is supportive.[34]

SELECTED DERMATOLOGIC ZOONOTIC INFECTIONS

Dermatologic findings are common in zoonotic infections because the skin is often the site of inoculation. Ulcerations at the site of inoculation (chancres), typically on the hands or forearms, can result from zoonotic infection caused by bacteria, mycobacteria, fungi, or viruses.

BACTERIAL AND VIRAL ZOONOTIC SKIN INFECTIONS

The most well-described bacterial chancriform zoonotic lesions are *B. anthracis* (anthrax), *B. henselae* (cat-scratch disease), *Erysipelothrix rhusiopathiae* (erysipeloid), *F. tularensis* (tularemia), *Listeria monocytogenes* (listeriosis), *Mycobacterium marinum* (aquarium granuloma), and *Burkholderia mallei* (glanders).[35] Most chancriform zoonotic infections occur in livestock workers, cattle ranchers, veterinarians, stable workers, horse trainers, slaughterhouse workers, poultry workers, and farmers. Significant zoonotic fungal infection is principally from *Blastomyces dermatitidis* (cutaneous blastomycosis) and *Sporothrix schenckii* (sporotrichosis). Dog and cat owners, along with veterinarians, are most at risk of contracting these two fungal zoonoses.

Viral zoonotic dermatoses include *Vaccinia* species (cowpox), *Paravaccinia* species (pseudocowpox), and bovine papular stomatitis. These cutaneous viral zoonoses often occur on the hands and forearms of patients who work closely with cattle, sheep, goats, or horses. Systemic zoonoses can be accompanied by a nonspecific generalized maculopapular rash, which does not facilitate the diagnosis.

CUTANEOUS ANTHRAX

Cutaneous anthrax, also known as *woolsorter's disease*, accounts for 95% of all anthrax infections.[36] Cutaneous anthrax is most common in groups dependent on and in close contact with livestock and in agriculture-based societies. Recently, localized outbreaks occurred in injection drug users.[36] The hands and fingers are the most commonly infected areas of the body, but arms, lower legs, and feet can also be involved. After deposit of anthrax spores in a skin wound, a painless or pruritic macule develops 1 to 5 days later at the inoculum site. The macule evolves into an ulcerative site with multiple serosanguinous vesicles. Vesicles contain the anthrax bacillus and are infectious. Gram stain or culture of the vesicular fluid is often diagnostic. The ulcer progresses to a painless black eschar and falls off within 2 weeks. If purulence is present, suspect secondary bacterial superinfection. Untreated, mortality is between 5% and 20% with progression to shock possible. If the disease is acquired naturally (i.e., bioterrorism not a concern), penicillin or amoxicillin for 3 to 7 days is the primary treatment.[37] Other patients are treated with oral ciprofloxacin for 60 days, with doxycycline as an alternative option.

ZOONOSES ACQUIRED FROM HOUSEHOLD PETS

Dogs and cats are the two most common household pets in North America and account for the majority of these zoonotic infections. Small rodents, pet birds, reptiles, and aquarium fish account for only a fraction of the zoonotic infections in the United States[38] (**Table 161-7**). A growing trend of individuals owning small flocks of chickens and other poultry led to >70 outbreaks of *Salmonella* since 2000.[39] Although hand washing is often key to prevention, the number of outbreaks has increased as residential livestock have become more common.

HELMINTHS (WORMS)

Up to 50% of dogs are infected with at least one intestinal parasite, and 15% of adult dogs actively excrete *Toxocara canis*, the source of **toxocariasis** and visceral larva migrans.[38] Despite its prevalence in dogs, human toxocariasis is infrequently diagnosed, probably because infection is often subclinical. Typically, the only indication of infection is eosinophilia. Children may display fever, cough, nonspecific rash, and failure to thrive. Rarely, pulmonary infiltrates, hepatosplenomegaly, and seizures may occur. Diagnosis is by either biopsy of infected tissue or by enzyme-linked immunosorbent assay. Treatment in the symptomatic patient consists of albendazole or mebendazole (Table 161-5). Corticosteroids can be used to control the allergic component.

Other intestinal parasites transmitted to humans from household pets include *Ancylostoma caninum* or *braziliense* (cutaneous larva migrans), *Echinococcus granulosus* (echinococcosis), and *Dipylidium caninum* (dipylidiasis or dog and cat tapeworm).[38]

Cutaneous larva migrans is often a self-limiting, pruritic, erythematous serpiginous rash caused by a migrating hookworm larva in the skin acquired from fecally contaminated soil. Single-dose ivermectin is the preferred treatment in patients over 5 years of age. Multiple-dose albendazole is another option, as is topical thiabendazole. Although dogs and other carnivores are the definitive hosts for *E. granulosus*, echinococcosis is most common in areas of cattle and sheep ranching. This zoonosis involves multiple organ systems: liver, lung, muscle, bone, kidney, and brain. Typically, there is a unilocular cyst containing multiple larvae that enlarge over time. Definitive treatment is surgical; however, leakage of the cystic fluid can spread the infection and cause an anaphylactic reaction. Should the lesion not be anatomically favorable for unruptured excision, pharmacotherapy with benzimidazoles can be used, but recurrence is high.[40]

TABLE 161-7 Pet-Associated Zoonotic Infections

- Dog: anthrax, brucellosis, campylobacteriosis, cryptosporidiosis, dipylidiasis, echinococcosis, histoplasmosis, leptospirosis, pasteurellosis, rabies, Rocky Mountain spotted fever, salmonellosis, toxocariasis, tularemia, yersiniosis
- Cat: anthrax, campylobacteriosis, cryptosporidiosis, histoplasmosis, pasteurellosis, plague, Q fever, rabies, salmonellosis, toxocariasis, tularemia
- Bird and fowl: *Cryptococcus*, erysipeloid, listeriosis, *Mycobacterium*, psittacosis/ornithosis (*Chlamydophila psittaci*), salmonellosis, tularemia, viral encephalitis
- Rodent: leptospirosis, listeriosis, lymphocytic choriomeningitis, murine typhus, plague, rat-bite fever (*Streptobacillus moniliformis*), salmonellosis, tularemia, yersiniosis
- Fish and reptiles: erysipeloid, *Mycobacterium marinum*, salmonellosis, *Streptococcus iniae*, vibriosis

TABLE 161-8 Zoonotic Infections in Immunocompromised Patients

Infection	Source	Clinical Findings	Antibiotic Treatment
Cat-scratch disease, *Bartonella henselae*	Cats	Pyogenic granulomas, regional lymphadenopathy, and fever	Azithromycin Add rifampin for severe disease
Bordetella bronchiseptica	Dogs	Fever, pharyngitis, and cough	TMP-SMX, fluoroquinolones, azithromycin if *Bordetella pertussis* suspected
Campylobacter species	Dogs, cats	Gastroenteritis and diarrhea	See Chapter 160, "Food and Waterborne Illnesses"
Cryptococcus neoformans	Bird droppings and cats	Flulike symptoms early, photophobia, headache, cranial nerve symptoms, and meningeal irritation later	Mild disease: fluconazole Severe: amphotericin B + flucytosine followed by fluconazole
Cryptosporidium	Dogs	Diarrhea	Immunocompetent host: nitazoxanide HIV positive: HAART only
Giardia lamblia	Dogs, cats	Gastroenteritis and diarrhea	See Chapter 160.
Listeria monocytogenes	Livestock and dairy products	Sepsis and meningitis	Severe disease: ampicillin + gentamicin Gastroenteritis in at-risk population: amoxicillin or TMP-SMX
Mycobacterium			
M. avium	Pet birds	Pneumonia and gastroenteritis	Clarithromycin or azithromycin + ethambutol + rifampin
M. marinum	Fish	Cutaneous granulomas, skin ulcerations at distal extremities	Clarithromycin, minocycline, doxycycline, TMP-SMX, or rifampin + ethambutol
Rhodococcus equi	Farm animals	Pneumonia and cavitating lung lesions	Two of the following agents: levofloxacin, rifampin, azithromycin, ciprofloxacin, imipenem, vancomycin
Salmonella, *Salmonella* species	Dogs, cats, reptiles, poultry, livestock	Gastroenteritis, diarrhea, and sepsis	See Chapter 160.
Toxoplasmosis, *Toxoplasma gondii*	Cats	Pneumonia, brain abscesses, encephalitis, and ocular disease	Pyrimethamine + sulfadiazine + folinic acid

Abbreviations: HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; TMP-SMX = trimethoprim-sulfamethoxazole.

PROTOZOA

Cats are the host of the intracellular protozoan *Toxoplasma gondii*, which causes **toxoplasmosis**. Human toxoplasmosis can occur in three ways: by ingestion of uncooked or raw meat, especially pork or mutton containing the *Toxoplasma* cysts; by ingestion of the oocysts from cat and wild-animal feces; and transplacentally.[38] Transplacental transmission can result in fetal abnormalities including retinochoroiditis, hydrocephalus, hepatosplenomegaly, and thrombocytopenia. Pregnant women should limit their contact to only indoor cats, avoid changing cat litter, and wear gloves when gardening or in contact with soil or sand that could be contaminated with toxoplasma. The encysted trophozoite can become reactivated in a previously infected host if the host becomes immunocompromised. Treatment of acute chorioretinitis, of severely symptomatic patients, or in certain pregnancy conditions is with pyrimethamine (25 to 100 milligrams/d PO for 3 to 4 weeks) plus sulfadiazine (1.0 to 1.5 grams PO four times a day for 3 to 4 weeks) and folinic acid.[38,41]

IMMUNOCOMPROMISED PATIENTS

Immunocompromised patients include those with congenital immunodeficiencies, diabetes mellitus, chronic renal failure, or liver failure; splenectomized patients; chronic alcoholics; cancer patients; transplanted patients; and human immunodeficiency virus–positive patients. Of all of these patients, those undergoing chemotherapy and those with acquired immunodeficiency syndrome have the greatest risk of acquiring a zoonotic infection.[41] *Salmonella* and *Campylobacter* are the two most common infections acquired by immunocompromised patients from their pets, but the overall risk of transmission of *Salmonella* and *Campylobacter* from contact with pets is low. Other acquired zoonotic infections in immunocompromised patients are listed in **Table 161-8**.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 162

Global Travelers

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INTRODUCTION

Of returning travelers who become ill, many have neither serious nor exotic illnesses.[1] In a study evaluating 82,825 returning travelers seen in global travel clinics between 1996 and 2011, only 4.4% (3655) of the cases involved acute, tropical, potentially life-threatening causes of illness.[2] The initial task is to separate the more common causes of symptoms, such as upper respiratory infections, diarrheal illnesses, reactions to stress, fatigue, or new medications, from more ominous causes of illness in travelers.

Key points for the initial ED care are as follows:

1. Isolate and use personal protective precautions early when evaluating patients with suspected travel-related infections.
2. Identify red flag symptoms such as hemorrhage and altered mental status and initiate isolation and treatment prior to diagnostic confirmation.
3. Consider malaria in the febrile patient returning from travel, even in the presence of prophylaxis, and initiate treatment promptly.
4. Report suspected reportable illnesses.

TABLE 162-1 Risk of Infectious Exposure

- High risk (1 in 10 travelers): diarrhea, upper respiratory illness, and noninfectious illnesses such as injuries and exacerbation of preexisting chronic diseases
- Moderate risk (1 in 200 travelers): dengue fever, chikungunya, enteroviral infection, gastroenteritis, giardiasis, hepatitis A, malaria, salmonellosis, sexually transmitted diseases, shigellosis
- Low risk (1 in 1000 travelers): amebiasis, ascariasis, measles, mumps, enterobiasis, scabies, tuberculosis, typhoid, hepatitis B
- Very low risk (1 in >1000 travelers): human immunodeficiency virus, anthrax, Chagas' disease, hemorrhagic fevers, pertussis, plague, typhus, hookworm

INITIAL EVALUATION OF THE RETURNING TRAVELER

Illness before and after travel is common[3] (**Table 162-1**). Start by evaluating the travel destination. Diseases such as malaria are uncommon in the United States, but are leading causes of mortality overseas. Other parasitic agents, such as helminths and rickettsia, also occur with increased frequency and severity in the tropics (see Chapters 159 and 161, "Malaria" and "Zoonotic Infections"). Although both tuberculosis and human immunodeficiency virus are endemic to the United States, consider these in patients presenting from areas with a higher disease burden.

HISTORY

Once imported disease in recent travelers is suspected, direct the history (**Tables 162-2, 162-3**, and **162-4**.). Immunosuppression, age <5 years, advanced age, pregnancy, and diabetes often render the patient less tolerant of tropical infections.

Ask about the duration of travel and timing of return (Table 162-2). For example, if fever begins >21 days after return from travel, yellow fever, viral hemorrhagic fevers (including Ebola, covered elsewhere), and other arboviruses (e.g., dengue fever) are unlikely, irrespective of the exposure history (Table 162-2). In comparison, schistosomiasis may cause symptoms 4 to 8 weeks after exposure. Incubation periods may vary somewhat depending on host factors such as immune status and the use of chemoprophylaxis.

Other important considerations are the specific locales of the traveler, as rural versus urban areas have different infectious disease risks, types of accommodation (e.g., tents or beds without bed nets), and travel-related activities (e.g., exposure to jungles, farm animals), and high-risk behaviors (e.g., eating jungle meat, drinking untreated water) (**Table 162-5**).

Review any pretravel immunizations and preventive medications. Proper vaccination against hepatitis A, hepatitis B, and yellow fever can effectively rule these out as causes of illness. Although chemoprophylaxis reduces the risk of acquiring malaria, it does not eliminate the possibility. Because of increasing malaria resistance and variable adherence to chemoprophylaxis regimens, consider malaria in the febrile returning traveler even with reported chemoprophylaxis.

A history of medications, herbs, and traditional medicines is also useful. These may contain antipyretics and other components that can alter disease presentation.

If altered mental status and the appropriate travel history exist, suspect cerebral malaria or meningitis and provide prompt empiric treatment. In the context of fever and hemorrhagic symptoms with travel to affected areas, initiate infection control practices until Ebola and other hemorrhagic viruses are excluded. In the case of suspected bioterrorism, initiate infection control and decontamination immediately. It is important to identify diseases that may be rapidly fatal, easily treatable, and/or potentially contagious. Do not await confirmatory testing to initiate decontamination, isolation, and treatment.

TABLE 162-2 Typical Incubation Periods for Selected Tropical Infections

Incubation Period	Infections Likely
<10 d (short incubation)	Traveler's diarrhea Dengue fever and arboviral infections Chikungunya Yellow fever Anthrax Diphtheria Malaria Typhoid fever Meningococcal infections Plague Tularemia Typhus (louse- and flea-borne)
<21 d (intermediate incubation)	Leptospirosis Viral hemorrhagic fevers Malaria Enteric fevers (typhoid, paratyphoid) Typhus African trypanosomiasis Rabies Zika
>21 d	Viral hepatitis (A, B, C, D, E) Malaria Acute HIV infection Amebic liver abscess Schistosomiasis (Katayama fever) Visceral leishmaniasis Filariasis
>Months	Tuberculosis Malaria Filariasis Viral hepatitis B, C HIV Visceral leishmaniasis Rabies Syphilis African and American (Chagas' disease) trypanosomiasis

Abbreviation: HIV = human immunodeficiency virus.

PHYSICAL EXAMINATION AND DIAGNOSTIC TESTING

Evaluate the abdomen for hepatosplenomegaly or focal abdominal discomfort. Examine for lymphadenopathy and inspect the skin for rashes, lesions, or pallor. Ophthalmologic examination should look for scleral icterus, conjunctival injection, and petechiae. Remain alert for subtle neurologic signs and altered mental status.

Suspect an imported disease in the presence of high fever, signs of hemorrhage, diarrhea, shortness of breath, skin lesions, and neurologic disturbances. **Table 162-6** lists other signs of tropical illness.[4]

Usually one or more hallmark symptoms or signs are associated with specific infections, guiding diagnostic testing and categorization. These include fever, CNS complaints, abdominal pain, diarrhea, skin and eye complaints, and respiratory symptoms. Initial studies include a CBC with differential, hepatic function tests, and urinalysis; thick and thin blood smears for malaria with rapid antigen detection test if available; blood cultures, urine cultures, stool cultures, and stool analysis for WBCs, ova, and parasites; and chest radiograph.

TABLE 162-3 Travel-Specific Aspects of the Medical History

Pretravel information

- Previous medical condition
- Pediatric patient, diabetes, pregnancy, immunosuppression (especially human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome or steroid use)
- Pretravel consultation and preparation (self-treatment medications, vaccination history, prophylaxis, etc.)
- Type and compliance with chemoprophylaxis, particularly malaria
- History of routine childhood immunization (DPT, polio, MMR, HiB, etc.)
- Nation of birth and citizenship

Travel information

- Exact itinerary of departure and arrival (within the last 3–5 y may be relevant)
- Season of travel (monsoon, dry season)
- Destinations visited (including locations of transit or stopovers)
- Urban or rural, altitude
- Purpose of travel and activities in country
- General purpose of visit or travel (e.g., "adventure travel" with high exposure to remote, natural elements)
- Contacts and their health
- Habitat and location of lodging (bed nets, window screens, thatched roof, mud walls)
- Crowded living or sleeping conditions
- High-risk activities (e.g., medical care of displaced populations, spelunking in caves)
- Opioid use or injection drug use
- Sexual intercourse with high-risk sexual contacts (unprotected with anyone; with high-risk populations, e.g., commercial sex workers, in areas with high prevalence of HIV); dates and nature of sexual contact
- Exposure to environment (swimming in freshwater or saltwater, hiking, trekking, digging, or soil contact, e.g., open-toed shoes or bare feet)
- Consumption of high-risk foods (wild game or bush meat, raw or undercooked meats or fish, unpasteurized milk products, food from street vendors, natural sources of water, salads)
- Exposure to dogs, birds, or rodents
- Adverse incidents
- Insect or animal bites
- Saliva from animals to open wounds
- Assault or trauma
- Status and health of fellow travelers
- Possible ill contacts
- In-country medical consultations sought, remedies used, and procedures (injections, acupuncture, transfusions, dental procedures, body piercing, or tattooing)

Abbreviations: DPT = diphtheria, pertussis, and tetanus; HiB = *Haemophilus influenzae* type b; MMR = measles, mumps, and rubella.

TABLE 162-4 Regional Tropical Illnesses

- Africa: malaria, human immunodeficiency virus, TB, hookworm, tapeworm, roundworm, brucellosis, yellow fever (and other hemorrhagic fevers such as Lassa fever or Ebola), relapsing fever, schistosomiasis, tick typhus, filariasis, strongyloidiasis, Zika, chikungunya
- Central and South America: malaria, relapsing fever, dengue fever, filariasis, TB, schistosomiasis, Chagas' disease, typhus, Zika, chikungunya
- Mexico and the Caribbean: dengue fever, hookworm, malaria, cysticercosis, amebiasis, Zika
- Australia, New Zealand: dengue fever, Q fever, Murray Valley encephalitis, Japanese encephalitis
- Middle East: hookworm, malaria, anthrax, brucellosis, middle eastern respiratory virus
- Europe: giardiasis, Lyme disease, tick-borne encephalitis, babesiosis, chikungunya (southern Europe)
- China and East Asia: dengue fever, hookworm, malaria, strongyloidiasis, hemorrhagic fever, Japanese encephalitis, Zika, chikungunya

Abbreviation: TB = tuberculosis.

In a clinically well-appearing patient in whom malaria treatment is suspected, obtain blood for smear every 12 to 24 hours. Use other specific serologic tests selectively, such as erythrocyte sedimentation rate, purified protein derivative, syphilis testing, human immunodeficiency virus testing, and serology for arboviruses or rickettsiae.

Infectious disease consultation early in the evaluation can optimize testing and follow-up. Obtain an extra vial of serum in a red-top tube (for serology and immunology) during the initial evaluation for follow-up testing.

DISEASES COMMONLY ASSOCIATED WITH FEVER

Although fever is nonspecific, it raises the suspicion for a serious infection and is present in up to about 90% of serious travel-related illnesses (**Table 162-7**).[2,5-7] **Treat patients with fever after tropical travel as if they have malaria until proven otherwise.** Other common serious infections are listed in **Table 162-8**.[8,9]

MALARIA

The classic clinical triad for all species of malaria is fever, splenomegaly, and thrombocytopenia.[10,11] Fever is typically irregular for the first week and later may be periodic. Patients usually have continuous symptoms initially followed by episodic pyrexia every 2 to 3 days, depending on the infecting species. Periodicity is unusual with falciparum malaria. Serious malaria infections occur primarily in young children, pregnant women, the elderly, individuals who are immunologically naive or who have lost their acquired immunity through prolonged absence from an endemic country, and patients with comorbid medical problems. Because associated symptoms such as headache, cough, and GI problems mimic other conditions, malaria should be a consideration in all febrile travelers. If a patient has the appropriate travel history and altered mental status, suspect cerebral malaria and initiate treatment promptly.

Diagnosis is based on clinical presentation then confirmed with laboratory evidence of bloodborne protozoa. Patients with fever >38.5°C (101.4°F) of unclear origin and recent or past travel to an endemic area should be screened by blood smears and rapid antigen detection tests when available. Refer to Chapter 159, "Malaria," for a detailed discussion of malaria diagnosis and treatment.

DENGUE FEVER

The World Health Organization reports a 30-fold increase in incidence of dengue in the past 30 years, becoming a leading cause of morbidity and mortality in the tropics.[12] Suspect dengue fever among travelers with fever developing within 2 weeks of travel. Dengue may be contracted more than once, and subsequent infections may be progressively more severe.[13]

Dengue is transmitted by the day-biting *Aedes aegypti* mosquito. Dengue fever presents after a typically short incubation period of 4 to 7 days with sudden high fever, headache, nausea, vomiting, severe myalgias (hence the term "break bone fever"), and rash usually lasting several days. Facial flushing, conjunctival injection (although uncommon), and retro-orbital pain can occur. After defervescence, a fine, pale, morbilliform rash develops on the trunk and spreads to the extremities and face. Small children may only present with a mild upper respiratory infection. Dengue may be confused with influenza, measles, or rubella. West Nile fever can also present similarly, but also causes lymphadenopathy, which is usually absent in dengue. **Dengue can cause petechial hemorrhages indistinguishable from meningococcemia.**

Severe dengue, previously known as dengue hemorrhagic fever, preferentially occurs among infants of immune mothers, children >1 year old, and those with second and subsequent infections. It begins with fever and myalgias. After 2 to 7 days, as pyrexia improves, lassitude, fatigue, and shock develop with an ensuing mortality that is >10%. Clinical features include pleural effusions and bleeding diathesis with

TABLE 162-5 Specific Exposures and Associated Tropical Infections

Contact/Exposure	Possible Infections
Untreated water, unpasteurized dairy products	Salmonellosis, shigellosis, hepatitis, amebiasis, brucellosis, listeriosis, TB
Raw or undercooked shellfish	Clonorchiasis, paragonimiasis, *Vibrio*, hepatitis A
Raw or undercooked animal flesh	Trichinosis (e.g., pig, horse, bear), *Salmonella*, enterohemorrhagic *Escherichia coli*
Raw vegetables, water plants (e.g., watercress)	Fascioliasis
Animal contact (and animal products)	Rabies, Q fever, tularemia, brucellosis, echinococcosis, anthrax, plague, Nipah virus, toxoplasmosis, herpes B encephalitis
Rodent contact	Hantavirus, viral hemorrhagic fevers, murine (endemic) typhus, Lassa fever, plague, leptospirosis
Arthropod vectors	
Mosquitoes	Malaria, dengue fever, chikungunya, filariasis, yellow fever, Zika, and other arboviral infections
Ticks or mites	Rickettsioses, tularemia, scrub typhus, Crimean-Congo hemorrhagic fever, African tick bite fever
Reduviid (kissing) bugs	American trypanosomiasis (Chagas' disease)
Tsetse flies	African trypanosomiasis (African sleeping sickness)
Fleas	Typhus, plague
Sandflies	Leishmaniasis, sandfly fever
Freshwater exposure	Schistosomiasis, leptospirosis
Barefoot exposure	Strongyloidiasis, cutaneous larva migrans, hookworm
Sexual contacts	Human immunodeficiency virus, hepatitis B, syphilis, gonorrhea, chlamydia, herpes simplex, Zika
Infected persons contact	Viral hemorrhagic fever, enteric fever, meningococcal infection, TB

Abbreviation: TB = tuberculosis.

epistaxis, purpura, petechia, and marked thrombocytopenia with elevated hematocrit because of vascular permeability. Severe dengue may rapidly evolve and is often fatal. Severe dengue exhibits abdominal pain, severe emesis, mental status changes, and alternating severe pyrexia and hypothermia.

Diagnosis of dengue is based on clinical findings. Although serology is confirmatory, cross-reactivity often occurs with other flaviviruses. Enzyme-linked immunosorbent assay provides rapid confirmation of infection by day 6 of the illness. Laboratory abnormalities include leukopenia, thrombocytopenia, and hepatic dysfunction. In uncomplicated dengue fever, treatment is supportive and consists of fluids and analgesics. Only acetaminophen is recommended for managing pain and fever because **aspirin and other NSAIDs are contraindicated due to anticoagulant properties.**

TYPHOID FEVER

Enteric fever, or typhoid fever, is a serious infection diagnosed in roughly 400 travelers annually returning to the United States, with an additional 100 cases of paratyphoid.[14] Typhoid and paratyphoid are caused by *Salmonella typhi* and *Salmonella paratyphi*, respectively. **Once malaria is excluded, typhoid fever is commonly the cause of a febrile illness lasting >10 days.**[15] Typhoid fever is endemic in countries with poor sanitation and unsafe drinking water in Africa, the Americas, Southeast Asia, and the Western Pacific regions.[16] Vaccination before travel helps prevent illness, although protection wanes with time and revaccination is required.

TABLE 162-6 Physical Findings in Selected Tropical Infections

Physical Finding	Likely Infection or Disease
Rash	Dengue fever, typhus, syphilis, gonorrhea, Ebola fever, brucellosis, chikungunya, HIV seroconversion
Jaundice	Hepatitis, malaria, yellow fever, leptospirosis, relapsing fever
Lymphadenopathy	Rickettsial infections, brucellosis, HIV, Lassa fever, leishmaniasis, Epstein-Barr virus, cytomegalovirus, toxoplasmosis, trypanosomiasis
Hepatomegaly	Amebiasis, malaria, typhoid, hepatitis, leptospirosis
Splenomegaly	Malaria, relapsing fever, trypanosomiasis, typhoid, brucellosis, kala-azar, typhus, dengue fever, schistosomiasis
Eschar	Typhus, borreliosis, Crimean-Congo hemorrhagic fever, anthrax
Hemorrhage	Lassa, Marburg, or Ebola viruses; Crimean-Congo hemorrhagic fever; meningococcemia, epidemic louse-borne typhus

Abbreviation: HIV = human immunodeficiency virus.

The disease is transmitted in a dose-related fashion after food contamination by feces or urine from actively infected cases or healthy disease carriers. Incubation times and disease severity vary from 1 to 3 weeks. Most pathology occurs in the gut because of inflammation, necrosis, and ulceration. Typhoid fever classically begins with fever and headache and then progresses to high fever with chills, headache, cough, abdominal distention, myalgias, constipation, and prostration. In epidemics, patients can present with acute diarrhea and vomiting, headache, and meningeal signs. However, 30% of patients present with constipation rather than diarrhea.[17] **Bradycardia relative to fever is classic** (but may be absent); after several days of fever, a pale red macular rash may appear on the trunk (**rose spots**) among fair-skinned individuals. As the disease progresses, splenomegaly develops. Patients may develop leukopenia and elevated liver enzymes, although most cases have nonspecific laboratory values. Complications include small bowel perforation, anemia, disseminated intravascular coagulopathy, mycotic aneurism, pneumonia, meningitis, septic arthritis, myocarditis, cholecystitis, and renal failure. Sequelae include deafness, and other neurologic involvement including psychosis, ataxia, and seizures can occur.[18]

Diagnosis is clinical, confirmed by culturing blood, urine, or stool (during the second week) or by rapid antigen testing. Although most cultures have a moderate yield, bone marrow culture is most sensitive, and organism identification is possible after antibiotic treatment.

Current treatment recommendations for typhoid fever include **fluoroquinolones** (ciprofloxacin), **cephalosporins** (cefixime and ceftriaxone), or **azithromycin**, with duration of treatment dependent on severity of illness. Currently, fluoroquinolone resistance is increasing, especially in travelers returning from South and Southeast Asia, associated with nalidixic acid–resistant *S. typhi* strains.[19] Ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol are unreliable due to resistance. If the patient is severely ill with suspected typhoid meningitis/encephalitis or shock, administer dexamethasone in addition to antibiotics.[20] Supportive treatment includes IV rehydration and blood transfusion (if needed from GI losses). Relapses can occur after clinical improvement. Untreated, mortality is 10% to 20%, mostly in young children.[21]

TABLE 162-7 Tropical Infectious Diseases Causing Fever Among International Travelers

Disease	Distribution	Mode of Transmission
INCUBATION <2 WEEKS		
Undifferentiated fever		
Malaria, Zika	Most tropical and subtropical areas	Infected mosquito bite
Dengue	Tropics and subtropics, including urban areas	Infected mosquito bite
Chikungunya	Africa, Asia, Latin America, US, southern Europe, and Caribbean	Infected mosquito bite
Spotted fever	Worldwide	Infected tick or mite bite
Scrub typhus	Asia, Australia	Infected mite bite
Leptospirosis	Widespread, mostly tropics	Percutaneous contact with animal urine or contaminated soil and water; ingestion
Typhoid fever	Developing countries, especially Indian subcontinent	Contaminated food/water ingestion
Acute HIV infection	Worldwide	Permucosal or percutaneous exposure to infective blood or fluids
African trypanosomiasis	East African form found in East and South Africa. West African form found in central and West Africa	Infective tsetse fly bite
Shigellosis	Widespread, most common in developing countries	Contaminated food/water ingestion
Salmonellosis	Widespread, most common in developing countries	Contaminated food/water ingestion
Campylobacteriosis	Widespread, most common in developing countries	Contaminated food/water ingestion
Fever with hemorrhage		
Meningococcemia	Widespread, highly prevalent in sub-Saharan meningitis belt in dry season from December to June	Via respiratory and oral secretions
Leptospirosis	Widespread, most common in tropical climate	Freshwater exposure
Crimean-Congo hemorrhagic fever	East and West Africa, Eurasia	Infected tick bite
Viral hemorrhagic fever	Worldwide	Contact with an infected patient, rodent, bat, tick, or mosquito
Other bacterial infection		
Fever with CNS involvement		
Meningococcemia	See listing above	See listing above
Rabies	Common in Africa, Asia, and Latin America	Infected animal saliva exposure
Malaria	See listing above	See listing above
Many viral and bacterial forms		
Arboviral encephalitis (Japanese encephalitis, tick-borne encephalitis, dengue, West Nile, Murray Valley)	Worldwide	Infected mosquito or tick bite
Angiostrongyliasis	Widely scattered, most common in East Asia and Southeast Asia	Ingestion of contaminated food/water with snail or slug slime
Poliomyelitis	Primarily Africa and parts of Asia	Ingestion of feces-contaminated food/water
Fever with respiratory findings		
Influenza	Widespread; outbreaks on cruise ships	Direct or airborne droplet transmission
Severe acute respiratory syndrome	China, Hong Kong, other regions in East Asia	Direct or airborne droplet transmission
Legionellosis (legionnaires' disease)	Widespread; outbreaks in hotels and cruise ships	Inhalation or aspiration of infected droplets
Q fever	Worldwide	Inhalation of infective aerosol from animal source
INCUBATION 2–6 WEEKS		
Malaria	See listing above	See listing above
Typhoid fever	See listing above	See listing above
Hepatitis A and E	Widespread; most common in developing countries	Contaminated food/water ingestion
Acute schistosomiasis	Africa, Middle East, Southeast Asia, and Brazil	Penetration of skin by larval cercaria during freshwater exposure
Amebic liver disease	Widespread; developing countries	Ingestion of cysts usually in feces-contaminated food/water
Leptospirosis	See listing above	See listing above
African trypanosomiasis	See listing above	See listing above
Q fever	See listing above	See listing above
Acute HIV infection	Worldwide, increased risk in developing countries	Sexual exposure

(*Continued*)

TABLE 162-7 Tropical Infectious Diseases Causing Fever Among International Travelers (*Continued*)

INCUBATION >6 WEEKS		
Malaria	See listing above	See listing above
Tuberculosis	Worldwide	Inhalation
Hepatitis B	Widespread	Permucosal or percutaneous exposure to infective blood or fluids
Visceral leishmaniasis	Many parts of Africa, Asia, South America, and Mediterranean basin	Infective sand fly bite
Lymphatic filariasis	Widespread in tropical areas	Infected mosquito bite
Schistosomiasis	See listing above	See listing above
Amebic liver abscess	See listing above	See listing above
Rabies	Worldwide	Infected animal saliva exposure
African trypanosomiasis	See listing above	See listing above

Abbreviation: HIV = human immunodeficiency virus.

RICKETTSIAL SPOTTED FEVERS

Rickettsial spotted fevers are transmitted by the bite, body fluid, or feces of ixodid arthropod ticks, which are widely distributed globally. Fleas and mites can also transmit rickettsial infections. Among the eight major rickettsial infections, there is variation in severity. Mortality without treatment approaches 25%, which drops to 5% with treatment (see Chapter 161, "Zoonotic Infections").

Scrub Typhus and African Tick Typhus Suspect scrub typhus (*Rickettsia orientalis*) after rural travel in the Asia-Pacific region and maritime Russia and African tick typhus (*Rickettsia conorii* var. *pijperi*) after travel to sub-Saharan Africa or the West Indies. The mite bite, in the case of scrub typhus, or tick bite, with African tick typhus, may go unnoticed. After 3 to 14 days of incubation, patients develop fever, malaise, myalgias, severe headache, rash, nausea, and vomiting. The rash may be absent. Scrub typhus is characterized by a papule at the bite site. The papule later becomes necrotic and forms a crusted black "tache noire" eschar. As organisms disseminate, patients develop fever, malaise, headache, lymphadenopathy, and splenomegaly. African tick typhus presents like scrub typhus, but with less severe symptoms and localized lymphadenopathy associated with an eschar. Diagnosis is clinical, and serologic tests are confirmatory. Doxycycline is the empirical treatment of choice; azithromycin and chloramphenicol are alternatives.[22] African tick typhus requires only 3 days of therapy and is often self-limited even without treatment. In severe cases of scrub typhus, death occurs from a multiorgan toxemia within 1 to 2 weeks of illness onset if untreated. Continue treatment for at least 5 days and for 48 hours after defervescence.

Typhus (Epidemic Louse-Borne Typhus) Typhus is a rickettsial louse-borne disease caused by *Rickettsia prowazekii*. Typhus is a different disease from typhoid fever, the bacterial disease due to *S. typhi* (see earlier). Epidemic louse-borne typhus is transmitted by the arthropod body louse. Typhus is widespread and found in Central Africa, Asia, and Central, North, and South America. It is also common in rainy seasons and in cold regions affected by famine, war, or mass population movement, where clothing and blankets harbor the lice. Louse-borne disease occurs after louse body fluids and feces are rubbed into abrasions or after bites. Infection results in high fevers after an 8- to 12-day incubation period. Severe headache is common, and a maculopapular rash appears between days 4 and 7, generally sparing palms and soles. The rash may be hemorrhagic. Diagnosis starts on clinical grounds and is confirmed with serologic testing. Treatment is **doxycycline** or chloramphenicol until 48 hours after defervescence.[23] Treatment also includes delousing the patient's clothing. Mortality in severe cases is as high as 24%.[24]

TABLE 162-8 Most Common Causes of Fever After Travel to Tropical Regions

- Malaria
- Respiratory tract infections (upper respiratory tract infections, pneumonia, legionnaires' disease, and influenza)
- Diarrheal disease
- Urinary tract infection
- Dengue fever
- Enteric fever (typhoid, paratyphoid fever)
- Rickettsial infection
- Infectious mononucleosis
- Pharyngitis

LEPTOSPIROSIS (WEIL'S DISEASE)

Leptospirosis, or Weil's disease, follows mucous membrane or percutaneous exposure to freshwater contaminated by *Leptospira interrogans*. Infected animals include many wild and domesticated animals, especially rodents, which excrete the spirochete in their urine. Infected patients typically have had contact with dogs; swam, rafted, or waded in contaminated surface water; or farmed or gardened in contaminated areas. Outbreaks commonly occur after flooding.[25] Although the risk to most routine travelers is low, recent ecotourists and adventure travelers have become infected after intense water exposure.[26]

The clinical course can be asymptomatic, but often symptoms illustrate a biphasic pattern. After an incubation of 2 days to 4 weeks, symptoms may include high fever, severe headache, chills, myalgias, hepatitis (with or without jaundice), and nonspecific influenza-like complaints. **Notable is conjunctival injection without purulent discharge.** Symptoms resolve in 4 to 7 days, followed several days later by the severe, icteric Weil's disease caused by circulating antibodies. The second phase lasts for up to 4 weeks and can include aseptic meningitis, renal failure, uveitis, rash, and, rarely, circulatory collapse. Isolation of leptospires from blood, urine, or cerebrospinal fluid is diagnostic, although sensitivity varies with duration of symptoms. Serology is most often used to confirm the diagnosis. Treatment reduces the severity and duration of symptoms and may prevent the second disease phase. Mild disease can be treated within the first 3 days of illness with PO amoxicillin or doxycycline, whereas more severe cases require IV penicillin, ceftriaxone, or ampicillin. Treatment duration is 7 to 14 days. Consider empiric therapy with PO doxycycline or IV penicillin (or ampicillin) when suspecting leptospirosis.

ZIKA VIRUS

Transmitted by the *Aedes* mosquito, Zika virus (a member of the Flaviviridae family) is transmitted in a wide range of tropical areas in the world. In addition to mosquitos, Zika may be transmitted through sexual intercourse, from mother to fetus in utero and mother to child through breastfeeding, and through blood transfusion. Symptoms may include conjunctivitis, headache, joint pain, fever, and malaise. Although Zika does not commonly pose a serious threat to those infected, it has been associated with Guillain-Barré syndrome. Zika infection of a pregnant woman can cause multiple serious birth defects including severe microcephaly. Offer testing to any pregnant women traveling from Zika-affected regions exhibiting signs of Zika; counsel men and women with suspected Zika infection or exposure of the risk of sexual transmission.

The Centers for Disease Control and Prevention currently recommends that men returning from places at risk of Zika virus wait 3 months before having unprotected sex and that women wait 2 months, even if they have not been symptomatic. Treatment is supportive.[27]

CHIKUNGUNYA FEVER

A self-limited arboviral infection with epidemic potential also spread through the *Aedes* mosquito species, chikungunya has become a significant cause of illness, especially in the Caribbean and South America.[28] The incubation period is 1 to 12 days (usually 2 to 3 days), and it presents with fever, severe myalgias, fatigue, headache, morbilliform rash, and occasional thrombocytopenia. Hemorrhagic complications are rare. Diagnosis is through increases of immunoglobulin M antibodies either in serum or the cerebrospinal fluid. Treatment is supportive, and long-term arthralgia sequelae are not uncommon.[29]

RELAPSING FEVER

Relapsing fever is a bacterial infection caused by the spiral-shaped *Borrelia* species (*Borrelia* species not including *Borrelia burgdorferi,* the causative organism of Lyme disease) transmitted by lice or tick bites. It is rare among travelers yet should be suspected in those who have contact with refugee and displaced populations. After being introduced by a louse or tick bite, *Borrelia* reproduces in body fluids and produces endotoxins affecting the liver, spleen, and capillaries. After incubation of 3 to 10 days, patients develop fever, chills, headache, and myalgias. In rare severe cases, acute respiratory distress syndrome, CNS involvement, and liver failure occur. After spontaneous abatement, fever may relapse several times. Diagnosis is made by clinical suspicion and confirmed by identifying spirochetes in blood peripheral smear, cerebrospinal fluid, or bone marrow. Spirochetes are best seen when blood is sampled during a febrile period. Louse-borne and tick-borne relapsing fever is treated with tetracycline, doxycycline, or erythromycin. Ceftriaxone can also be given with CNS involvement.[30]

DISEASES COMMONLY ASSOCIATED WITH FEVER AND HEMORRHAGE

Among the most feared tropical diseases are viral hemorrhagic fevers. However, viral hemorrhagic fevers are rare when compared with other febrile hemorrhagic infections such as malaria, dengue fever, meningococcemia, leptospirosis, plague, bacterial sepsis, and rickettsial fevers. ***Neisseria meningitidis* is the most common cause of acute hemorrhagic fever in temperate climates.** Among travelers, several treatable infections, including Lassa fever, meningococcemia, leptospirosis, and rickettsial infection, can cause fever associated with hemorrhage. Most people with viral hemorrhagic fevers, such as dengue, hantavirus (Chapter 161), Lassa, Ebola, Marburg, and Rift Valley, develop fever within 3 weeks after exposure. Viral hemorrhagic fever usually follows the bite of infected mosquitoes and ticks, close contact with rodent/bat excreta, or direct contact with infected, symptomatic individuals (the latter notably for Ebola).

In the event of a suspected viral hemorrhagic fever of tropical origin, institute control measures, including isolation in a negative-pressure room, the use of high-efficiency particulate-arresting respirators, and the use of gloves and gowns. **Immediately notify local public health officials for suspected contagious viral hemorrhagic fevers such as Marburg, Lassa, Ebola, or Crimean-Congo hemorrhagic fever.** If intentional bioterrorism is suspected, notify local law enforcement officials, the Federal Bureau of Investigation, and the Centers for Disease Control and Prevention.

YELLOW FEVER

Yellow fever, an acute zoonotic flavivirus, has a jungle monkey reservoir present in the tropics of South America and Africa, where vaccination is mandatory. Outbreaks are common near tourist areas and may occur among nonimmunized adventure travelers who travel to endemic areas. With the increase in global travel and because the day-biting mosquito vector *A. aegypti* (which also transmits dengue) is endemic in a wide global distribution, including North and Central America, the Caribbean, as well as parts of Asia, yellow fever outbreaks can appear outside of traditionally endemic areas, as evidenced by a recent outbreak in Brazil.[31,32]

Yellow fever ranges in severity from an undifferentiated self-limited flulike illness to a hemorrhagic fever that is fatal in 20% to 50% of patients who develop severe disease (15% of infected persons).[32,33] After an incubation of 3 to 6 days, patients develop fever, headache, myalgias, conjunctival injection, abdominal pain, prostration, facial flushing, and relative bradycardia. In most cases, patients recover, but in others, fever remission lasts a few hours to several days, followed by renewed high fever, jaundice, vomiting, shock, multiorgan failure, and bleeding diathesis. **The classic presentation is a triad of jaundice, black emesis, and albuminuria.** Confusion, seizures, and coma are common in the late stages of the illness, and death can occur within 7 to 10 days after onset. The diagnosis is primarily clinical, although confirmation is possible through virus identification or rising antibody titers in recovering patients. Leukopenia and albuminuria are typical, direct bilirubin levels rise, and liver enzymes are elevated for several days, during which time azotemia and oliguria ensue. Treatment is supportive, with fluid replacement and management of hematologic complications.

EBOLA AND MARBURG VIRUSES

Periodic outbreaks of Ebola virus disease have existed since 1976. Transmission is thought to occur via human contact with infected animals, either primates or fruit bats.[34] The most recent large outbreak in multiple West African countries had >11,000 associated deaths by 2016.[35,36] Four Ebola species cause disease in humans. Disease transmission is by direct contact with infected blood or body fluids, contaminated needles or syringes, or infected bats or primates. The virus is stable, with little mutation in current species compared to that in the epidemic of 1976.

Symptoms begin 2 to 21 days after exposure with fever, myalgia, malaise, diarrhea, abdominal pain, and vomiting, and progress to hemorrhage, shock, and end-organ failure. Mortality is high, but those who recover have an antibody response that lasts about 10 years. Diagnosis is by enzyme-linked immunosorbent assay serology, polymerase chain reaction, culture, or immunochemistry and, in the United States, is performed at the U.S. Centers for Disease Control and Prevention *after* consultation and acceptance of specimens (770-488-7100). Treatment is supportive with no proven effective antiviral therapy; however, investigational therapies including convalescent serum and antibody treatments have been used. Vaccines remain under development, although at the time of this writing (November 2018), an investigational vaccine is being deployed in the Democratic Republic of Congo, which is combating an ongoing outbreak. Epidemic containment focuses on avoidance of exposure and, for healthcare workers, the use of personal protective equipment. Hospital preparedness consists of the identification of potential exposed contacts by identifying travel and direct exposure history, determining disease signs and symptoms, and then isolating individuals with possible disease.[37]

Similar to Ebola, episodic outbreaks of Marburg virus infection exist in sub-Saharan Africa, and the virus has been found in African fruit bats.[38] Clinical presentation is similar to Ebola.[36]

CRIMEAN-CONGO HEMORRHAGIC FEVER

This tick-borne viral disease is common in Africa, Eastern Europe, Asia, and the Middle East, especially in Turkey. Mortality ranges from 3% to 30%.[39] The prehemorrhagic period is characterized by the sudden onset of fever, headache, myalgia, dizziness, and, possibly, altered mental status. The hemorrhagic period is short (2 to 3 days), develops rapidly, and usually begins between the third and fifth day of disease. The most common bleeding sites are the nose, GI system (hematemesis, melena, and intra-abdominal), uterus (menometrorrhagia) and urinary tract (hematuria), and the respiratory tract (hemoptysis). Thrombocytopenia is common. Patients may have

leukopenia and elevated liver enzymes, lactate dehydrogenase, and creatinine. Prothrombin time and activated PTT can be prolonged.

Diagnosis is clinical and confirmed with serology. Treatment is primarily supportive, including treatment of coagulopathy and respiratory support in severe cases. Oral or IV forms of **ribavirin** are available and used in more severe cases; treat for 10 days.[39]

LASSA FEVER

Lassa fever is spread by contact with bush rat excreta or body fluid exposure from an infected person. Although found in rural parts of West Africa, it has been exported to Europe and North America by infected patients, and in endemic areas, impact is high, with up to 16% of admitted patients in hospitals having Lassa fever.[40]

After an incubation period of 3 to 16 days, the disease presents as a viral syndrome with insidious onset of fever, malaise, headache, sore throat, retrosternal chest pain, back pain, abdominal pain, and myalgias. Varied and nonspecific symptoms persist for 4 to 6 days, at which time the patient suddenly deteriorates and becomes gravely ill. Among those infected, approximately 80% have mild symptoms and 20% will have severe multiorgan disease. Pregnant women and their fetuses are at elevated risk of severe disease and death. The main features are high fever, prostration, severe sore throat with dysphagia and yellow-white exudates, abdominal pain, diarrhea, and vomiting. Only one third of patients experience bleeding, which may include oozing from the gums, hematemesis, melena, hematochezia, hemoptysis, hematuria, or brain hemorrhage. Diagnosis is made by enzyme-linked immunosorbent assay serology, culture, or immunohistochemistry. Strict patient isolation and use of personal protection by healthcare workers are necessary. Treatment is largely supportive, but patients with severe disease may benefit from early treatment with ribavirin IV or PO. Survivors will defervesce within 10 days of disease onset and, except for sensorineural deafness, can make a complete recovery.[41]

DISEASES COMMONLY ASSOCIATED WITH FEVER AND CNS INVOLVEMENT

Fever with acute mental status changes, headache (**Table 162-9**), nuchal rigidity, and focal neurologic signs is associated with a number of serious infections. **CNS involvement with fever in travelers returning from malaria-endemic regions requires emergency presumptive treatment for both malaria and bacterial meningitis (see Chapters 159 and 174, "Malaria" and "Central Nervous System and Spinal Infections," respectively).** The differential diagnosis for fever with CNS involvement includes malaria, meningitis, tuberculosis, typhoid fever, rickettsial infections, and rabies. Other causes are viral encephalitides, including Japanese and West Nile encephalitis, which often present similarly.

Patients with altered mental status suspected of tropical illness may demonstrate coma, decreased level of consciousness, meningeal signs, or seizures. Although seizures should arouse suspicion of cerebral malaria, suspect **cysticercosis** in those with long-term residence in Latin America and a first-time seizure. **Meningococcal meningitis** (caused by *Neisseria meningitidis*) occurs with regularity in sub-Saharan Africa along the "meningitis belt" running from Senegal to Ethiopia, and pilgrims attending the Hajj in Saudi Arabia are also at risk of *Neisseria* meningitis (Chapter 174). Aseptic meningitis may be caused by enteroviruses or, less commonly, typhoid fever, leptospirosis, or rickettsiae. Encephalitis may be caused by an arboviral infection, such as Japanese encephalitis.

TABLE 162-9 Tropical Infectious Diseases Causing Severe Headache and Fever

- Malaria
- Rickettsial disease
- Dengue fever
- Typhoid fever
- Human African trypanosomiasis

JAPANESE ENCEPHALITIS

Japanese encephalitis is a vaccine-preventable flavivirus infection that occurs in an epidemic or sporadic pattern over large areas of Asia and the western Pacific. It is rarely transmitted to U.S.-bound travelers because the *Culex* mosquito vector breeds primarily in rural rice fields. Approximately 25% of infected patients will have severe symptoms, presenting with a sudden high fever, headache, nuchal rigidity, vomiting, and seizures (especially infants) after the incubation time of 5 to 15 days. A variety of pyramidal and extrapyramidal signs may develop soon after fever. If the outcome is fatal, it usually occurs in the first 10 days. Diagnosis is based on clinical suspicion, although virus can be isolated from cerebrospinal fluid, and antibody titers can rise. Treatment is supportive. Recovery may take months, and varying degrees of residual neurologic damage may persist indefinitely. Immunization is recommended for travelers to rural, endemic regions in Asia.[42]

CYSTICERCOSIS

Cysticercosis is a systemic illness caused by dissemination of the larval form of the pork tapeworm, *Taenia solium*. The disease affects an estimated 50 million people worldwide. Endemic areas include Mexico, Latin America, sub-Saharan Africa, India, and East Asia. The incidence in the United States is increasing due to increased immigration from endemic areas and increased travel to endemic areas. Humans are definitive *T. solium* hosts and can carry the intestinal adult tapeworm. An intermediate host, usually a pig, ingests fecally shed egg-containing proglottids or *T. solium* eggs. Humans develop cysticercosis when they inadvertently ingest eggs from contaminated food or soil, not from eating undercooked pork, which can result in tapeworm infection only.[43]

Infestation can occur in almost any tissue. Involvement of the CNS, *neurocysticercosis*, is the most clinically important manifestation of the disease. Neurocysticercosis is the most common cause of CNS infection globally and the leading cause of adult-onset seizures worldwide.[44] Other symptoms of neurocysticercosis include obstructive hydrocephalus, meningoencephalitis, stroke-like focal deficits, headache, and visual or mental status changes. Noncontrast CT scan shows calcifications of inactive disease and can reveal mass effect or hydrocephalus. Antihelminthic agents (albendazole or praziquantel) are the mainstay of treatment. Use steroids in those with encephalitis, hydrocephalus, or vasculitis to avoid inflammation as cysts involute. In nonendemic areas, check stool studies of household contacts of confirmed cases.[45]

DISEASES COMMONLY ASSOCIATED WITH CHRONIC FEVER

Evaluate patients with chronic or relapsing fever lasting beyond 3 weeks after travel initially for non–travel-related infections, inflammatory diseases, and noninfectious disorders. Tropical illnesses that cause chronic fever include protozoal infections (e.g., trypanosomiasis, leishmaniasis, amebiasis, and malaria), typhoid or paratyphoid fever, and tuberculosis (**Table 162-10**).

HUMAN AFRICAN TRYPANOSOMIASIS (AFRICAN SLEEPING SICKNESS)

Sleeping sickness is caused by the two nearly identical endemic protozoan subspecies, *Trypanosoma brucei gambiense* (responsible for most clinical cases) and *Trypanosoma brucei rhodesiense*, transmitted by the tsetse fly found in rural East and West Africa. Large animal game is the main reservoir. After a bite, a localized inflammatory reaction occurs, followed in 2 to 3 days by a painless chancre (more common in East African than West African sleeping sickness) that increases in size for 2 to 3 weeks and then gradually regresses. Trypomastigotes mature and divide in the blood and lymph and cause intermittent fever unresponsive to antimalarials and occasional rash. In later stages, CNS involvement occurs, causing behavioral and neurologic changes, encephalitis, coma, and death. Disease categorization depends on whether or not the CNS

TABLE 162-10 Selected Causes of Chronic and Relapsing Fevers

Etiologic Organism	Organism Species
Bacterial	Bartonellosis
	Brucellosis
	Leptospirosis
	Q fever
	Relapsing fever
	Syphilis
	Tuberculosis
	Tularemia
	Typhoid fever
Fungal	Blastomycosis
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
Protozoan	Amebic liver disease
	Visceral leishmaniasis
	Malaria
	Human African and human American trypanosomiasis
Viral	Human immunodeficiency virus
Helminthic	Angiostrongyliasis
	Fascioliasis
	Schistosomiasis
	Toxocariasis
	Trichinosis

has been invaded. Other complications include hemolysis, anemia, pancarditis, and meningoencephalitis.[46,47]

Diagnosis is made by rapid evaluation of blood smears for the mobile parasite. Organisms can also be identified by aspiration of lymph nodes, chancres, or bone marrow or by CSF examination. The treatment of sleeping sickness varies according to the stage of illness. If the disease has not invaded the CNS, treat with pentamidine or suramin. If the CNS is invaded, treatment requires eflornithine, a combination of nifurtimox and eflornithine, or melarsoprol.[46,47] A newly approved 10-day regimen of oral fexinidazole (given once daily at a dose of 1800 milligrams on days 1 to 4, and then 1200 milligrams on days 5 to 10) eases the treatment difficulty with similar success to IV regimens that are much more challenging.

AMERICAN TRYPANOSOMIASIS (CHAGAS' DISEASE)

The protozoan *Trypanosoma cruzi* is spread by the reduviid "kissing bug" or "assassin" bug. Among travelers, it is rare; it causes an acute illness and, commonly, an asymptomatic infection with complications arising years later in the heart and GI tract. It is transmitted during a blood meal when the bug defecates trypanosome-infected feces around the meal site, causing a local inflammatory reaction and trypanosome inoculation after the host rubs the organism into the bite wound or into adjacent mucous membranes or conjunctiva. Infection can also be acquired by blood transfusion, by laboratory accidents, congenitally, and by oral transmission.[48,49]

Unilateral periorbital edema (Romaña sign) or painful cutaneous edema at the site of skin penetration (chagoma) is followed by a toxemic phase with parasitemia causing lymphadenopathy and hepatosplenomegaly. The acute phase generally lasts 2 to 4 weeks but may last up to 3 months. Next is a long, asymptomatic, latent phase when nerve ganglion cells are gradually destroyed, leading to depressed cardiac and GI function. Cardiac complications include myocarditis, dysrhythmias, cardiomyopathy, and sudden death. Chagas-induced heart disease is the leading form of congestive heart failure in much of Latin America. GI complications are also due to the nervous system damage, most commonly in the form of megaesophagus or megacolon.[50]

The acute-phase diagnosis occurs by detecting motile parasites on blood smears, by blood culture, or by muscle biopsy. In the chronic phase, serologic tests and tissue biopsy aid. Treatment is available for acute, reactivated, or chronic cases. The two medications used are nifurtimox and benznidazole.[51]

LEISHMANIASIS (VISCERAL)

Leishmania is an intracellular protozoan transmitted by sandflies. The disease occurs sporadically in rural Africa, Asia, the Mediterranean basin, and Central/South America, and additional global outbreaks occasionally occur. Suspect *Leishmania* in military personnel and their families living proximal to jungles, adventure travelers, field biologists, and emigrants from endemic zones.[52]

The infecting species determines the pathology, ranging from a localized self-healing lesion to widespread, persistent, and potentially destructive disease. Four major clinical syndromes exist.

The most important diagnostic information is patient origin and travel itinerary because endemic areas suggest the infection type. Definitive diagnosis requires reference laboratory expertise to isolate motile extracellular parasites aspirated from bone marrow, spleen, or lymph nodes, or on smears or sections taken from the ulcer edge by punch biopsy.

Treatment is with liposomal amphotericin B.[53]

DISEASES COMMONLY ASSOCIATED WITH ABDOMINAL AND URINARY COMPLAINTS

Illnesses causing abdominal pain and diarrhea are common among world travelers because of infecting bacteria, viruses, soil-transmitted helminths, and other parasites. Most infections are caused by the consumption of undercooked or fecal-contaminated foods and are preventable by adequate hygiene, potable water, and careful food preparation.

SCHISTOSOMIASIS (BILHARZIA OR SNAIL FEVER)

Schistosomiasis, infection with a blood fluke found in Africa, the Middle East, South America, and Asia, infects >200 million people worldwide, with 20 million people suffering severe consequences. For most short-term travelers, the risk is low, although significant outbreaks now occur among adventure tourists, longer-term visitors such as missionaries and volunteers, and those who swim in infested streams and lakes. The larvae are released into freshwater by snails, which are intermediate hosts. Infection occurs by tiny, free-swimming cercariae that penetrate wet, unbroken skin or are ingested from slow-moving freshwater. After inoculation, an immediate cercarial allergic and pruritic dermatitis may occur. When Katayama syndrome occurs, fever is accompanied by headache, cough, urticaria, diarrhea, hepatosplenomegaly, and eosinophilia. Worms mature into adults in the venous blood and, for the next 30 to 40 years, deposit eggs into selective body tissues (*Schistosoma haematobium* in the bladder and *Schistosoma mansoni* and *Schistosoma japonicum* in the GI tract). Eggs are deposited throughout the brain, skin, liver, and GI tract. Eggs stimulate a vigorous immune response that results in clinical symptoms.[54]

CNS symptoms include seizures, paralysis, and acute transverse myelitis. *S. haematobium* infection causes dysuria, frequency, and terminal hematuria, and can cause bladder scarring, calcification, and squamous cell carcinoma. *S. japonicum* and *S. mansoni* infections can cause diarrhea, abdominal cramps, and acute abdominal pain and, late in the disease course, can lead to hepatosplenomegaly, hepatic granulomas, periportal fibrosis, and portal hypertension.

Diagnosis is suspected by detecting eosinophilia, confirmed by microscopic identification of ova in midday urine or stool samples or in a biopsy specimen. Serologic antibody detection methods are accurate and are usually positive in light infections missed by egg detection. Praziquantel treatment is active against adult worms only; thus, it cannot be used for postexposure prophylaxis, and re-treatment may be required.[55]

DISEASES COMMONLY ASSOCIATED WITH ABDOMINAL PAIN AND DIARRHEA

Diarrhea and gastroenteritis are the most common travel ailments, affecting up to one half of travelers (**Table 162-11**). Traveler's diarrhea is especially common after travel to Africa, Asia, the Middle East, South and Central America, and Mexico. Diarrhea is typically accompanied by fever, flatulence, nausea, emesis, and abdominal pain, which is usually spasmodic and colicky. *Campylobacter jejuni* may cause severe and constant pain, and cholera may cause somatic muscle cramps. Nonbloody gastroenteritis and diarrhea are usually caused by bacteria or bacterial toxins, whereas dysentery usually results from toxigenic and invasive bacteria such as *Shigella*, *Salmonella*, *Campylobacter*, *Aeromonas*, *Escherichia coli*, or *Entamoeba histolytica* (**Table 162-12**). Traveler's diarrhea is less commonly due to viruses.

Acute abdominal pain among travelers is usually caused by nontravel causes with an expanded travel-based differential diagnosis. Mild traveler's diarrhea can be treated with bismuth or loperamide alone. For moderate to severe traveler's diarrhea (significant pain or blood in stool), treat empirically with azithromycin or fluoroquinolones (ciprofloxacin or levofloxacin), although resistance to fluoroquinolones is rising. Regional resistance can occur and should be verified (see Chapter 160, "Food and Waterborne Illnesses").[56]

TABLE 162-11 Common Infectious Diseases Causing Diarrhea in Travelers

Cause	Organism	Comments
Acute (duration <2 wk)		
Viral	Norwalk-like virus Rotaviruses Enteroviruses	Often not diagnosed; may account for 5%–10% of acute traveler's diarrhea
Bacterial	*Escherichia coli* (enterotoxigenic or enteroaggregative) *Campylobacter jejuni* *Salmonella* *Shigella* *Vibrio* *Clostridium difficile*	Most common identified cause of acute traveler's diarrhea; 50%–70%
Parasitic	*Giardia lamblia* *Cryptosporidium parvum* *Entamoeba histolytica* *Cyclospora cayetanensis* *Isospora belli* *Balantidium coli* *Trichinella spiralis*	Accounts for <1%–5% of acute traveler's diarrhea
Chronic or persistent (duration >2–4 wk)		
Bacterial	See above	Rare cause of chronic diarrhea
Parasitic		
Microsporidial	*Enterocytozoon bieneusi* *Encephalitozoon intestinalis*	Almost exclusively in immunocompromised
Protozoal	*G. lamblia* *E. histolytica*	Most commonly identified cause Bloody diarrhea with fever; fecal WBCs are rare
Helminthic	*Trichuris trichiura* *Strongyloides stercoralis* *Fasciolopsis buski* *Schistosoma*	Rarely associated with chronic diarrhea; usually in persons with heavy parasite burdens

TABLE 162-12 Causes of Diarrhea With and Without Fever or Blood

	With Fever	Without Fever
With blood	Bacillary dysentery *Campylobacter enterocolitis* *Salmonella enterocolitis* *Escherichia coli*	Amebiasis *Balantidium coli* *Schistosoma* *Trichuris*
Without blood	*Salmonella enteritis* Malaria (especially *Plasmodium falciparum*) Mild shigellosis *Campylobacter* infections Almost any infections in a child	*Staphylococcus aureus* *E. coli* (enterotoxigenic) *Clostridium perfringens* Viral infections of the gut Food toxins

AMEBIASIS

Pathogenic species such as *E. histolytica* are found worldwide and disproportionately infect those living in low-income settings. Amebiasis is typically spread by asymptomatic carriers whose excrement contains the encysted organism and is the leading cause of diarrhea globally. Travelers who are traveling for >6 months are at higher risk. Incubation times are typically 1 to 3 weeks for colitis and 2 weeks to several months for liver abscesses. Once cysts are ingested, amebic trophozoites invade the colon wall, lyse tissues, and cause necrotic abscesses.

Most infected people are asymptomatic. Symptoms range from alternating constipation and diarrhea over 1 to 3 weeks, to abdominal pain, bloody diarrhea, fever, dehydration, and weight loss. Extraintestinal metastases can infect the liver and, rarely, pericardium, lung, and brain. Colitis can lead to intestinal perforation and peritonitis. Complications such as liver abscesses may cause fever, right upper quadrant pain, or chronic, vague abdominal pain accompanied by weight loss.[57]

It can be difficult to differentiate pathogenic organisms (*E. histolytica*) from benign organisms (*Entamoeba dispar*) on stool microscopy without use of stool antigen detection tests or, preferably, stool polymerase chain reaction. Serology for elevated antibody titers helps identify systemic disease. Ultrasonography or CT scans may be useful to identify hepatic abscesses.[58]

Treatment of asymptomatic cyst passers includes iodoquinol, paromomycin, or diloxanide furoate. For symptomatic disease, choices include metronidazole, or tinidazole followed by either iodoquinol or paromomycin. For liver abscess, severe intestinal disease, or extraintestinal disease, treat with metronidazole or tinidazole followed by iodoquinol or paromomycin.[59]

GIARDIASIS

Giardia lamblia is a flagellated protozoan infecting the small intestine and biliary tree. It is globally endemic and is food- or waterborne by fecal contamination with encysted parasites and can be transmitted through person-to-person contact. It is a common cause of chronic traveler's diarrhea and can be contracted at camping sites and rural swimming areas. It can be differentiated from other causes of traveler's diarrhea by the slow onset of symptoms and incubation period of typically longer than 1 week.[60]

Ingested parasites reside in the duodenum and may lead to malabsorption because of duodenal microvilli obstruction. Symptoms include abdominal cramping, flatulence, and foul-smelling, watery diarrhea without blood or mucus. Chronic infections cause weight loss and anemia, and a common complication is lactose intolerance. Diagnosis is by duodenal sampling and stool ova and parasites showing either motile trophozoites or cysts. *Giardia* antigen detection in stool has good sensitivity and specificity. Treatment is with metronidazole, tinidazole, quinacrine, nitazoxanide, paromomycin, or furazolidone. Treatment is not always successful regardless of drug used, and combination therapy may be necessary.[60,61]

CHOLERA

Cholera is an acute diarrheal disease caused by the bacterium *Vibrio cholerae*. It is endemic and epidemic to many tropical nations. It is reported in Africa, Asia, Latin America, and more recently, Haiti and Mexico. Epidemics occur after flooding or acute population displacement with disruption of the water-sanitation system. Transmission is by fecal contamination of water or food (including raw or poorly cooked seafood and shellfish). Significant bacterial ingestion is required to cause symptoms. The incubation time is 2 to 3 days, and symptoms result from sodium pump inhibition in the GI tract by the cholera toxin. Infection is usually mild but can be life threatening, particularly among vulnerable populations, such as malnourished children, migrants, and those with chronic illness. Another group at risk are individuals with achlorhydria or those using medications decreasing gastric acidity. There is an asymptomatic carrier state.[16]

Severe disease is characterized by profuse, usually painless, watery diarrhea ("rice water stools"), severe dehydration, vomiting, leg cramps, and, occasionally, fever. Rapid fluid loss (up to 15 L/d) leads to extreme dehydration and shock. Aggressive rehydration can prevent death. Without proper fluid resuscitation, death can occur within hours, and mortality rates reach 50% to 75%.[62] Diagnosis is clinical, and when suspected, a rectal swab or stool specimen can be sent to a reference laboratory for culture confirmation. Rapid dipstick testing of stool is possible but should be followed by confirmatory testing.

The cornerstone of treatment is aggressive fluid resuscitation with PO rehydration solution or IV fluids, coupled with correction of metabolic acidosis and hypokalemia. For those with severe illness, antibiotics can shorten the illness course, diminish vomiting, lessen volume resuscitation needs, and ensure that bacteria are eradicated from stool. Doxycycline is the antibiotic of choice, followed by azithromycin, tetracycline, erythromycin, or ciprofloxacin. Secondary transmission is rare, and close contacts should not be given antibiotics as prophylaxis.[62]

PARASITIC HELMINTH (WORM) INFECTIONS

Major infestations are discussed here, and diagnosis and treatment are presented in **Table 162-13**.

In the patient in whom empirical therapy is chosen due to the appearance of a worm in fecal matter, treatment for nematodes can be considered. **By treating the adult patient empirically with albendazole for 3 days with a single repeat dose in 2 weeks, a number of pathologies can be treated** (roundworm, pinworm, whipworm, and hookworm). Send stool samples for laboratory analysis to provide more focused treatment. Diagnosis and treatment of these worms are provided in Table 162-13.

ASCARIASIS (ROUNDWORM)

The risk of infection with *Ascaris lumbricoides* to short-term travelers is low, and infection is suspected following ingestion of street vendor foods or vegetables fertilized by "night soil" (human feces) or animal feces. Eggs survive for years in moist soil, and transmission is typically fecal–oral or through poorly cooked food. Symptoms are usually

TABLE 162-13 Common Parasitic Helminth (Worm) Infestations

Name	Source of Contamination	Human Symptoms	Diagnosis	Treatment
Ascaris lumbricoides (roundworm)	Fecal–oral contamination or poorly cooked food	Minimal symptoms; or pneumonia, malnutrition, biliary or bowel obstruction, hepatic abscess, appendicitis, etc.	Stool examination, serology.	Albendazole, 400 milligrams single dose *or* Mebendazole, 100 milligrams twice a day for 3 d or 500 milligrams single dose *or* Ivermectin, 150–200 micrograms/kg single dose
Enterobiasis (pinworm, seatworm)	Fecal–oral and from contaminated objects	Intense perianal itching	Visual inspection, cellophane tape swab of anus upon waking.	Albendazole, 400 milligrams single dose and repeat in 2 wk *or* Mebendazole, 100 milligrams single dose and repeat in 2 wk *or* Pyrantel pamoate, 11 milligrams/kg (up to 1 gram) single dose and repeat in 2 wk
Trichuris trichiura (whipworm)	Fecal–oral contamination	Asymptomatic; or bloody diarrhea, rectal prolapse	Stool examination.	Albendazole, 400 milligrams daily for 3 d *or* Mebendazole, 100 milligrams daily for 3 d or 500 milligrams single dose
Ancylostoma duodenale and *Necator americanus* (hookworm)	Contaminated soil, larvae penetrate the skin	Severe anemia; cutaneous larva migrans	Stool examination, may require serial exams.	Albendazole, 400 milligrams single dose *or* Albendazole, 400 milligrams twice a day for 3 d *or* Pyrantel pamoate, 11 milligrams/kg (maximum, 1 gram) daily for 3 d
Taenia solium (pork tapeworm), *T. saginata* (beef tapeworm), and *Diphyllobothrium latum* (fish tapeworm)	Raw or undercooked pork or beef or fish	Asymptomatic, abdominal pain, bowel obstruction; *Taenia* cysts in skin, eye, brain, heart (see "Cysticercosis" section, above)	Stool examination or serology. Serology may be negative if cysts are calcified.	Praziquantel, 5–10 milligrams/kg single dose
Strongyloides stercoralis (threadworm)	Contaminated soil, larvae penetrate skin	Cough, pneumonia, and wheezing; abdominal pain, bloody diarrhea	Stool examination or stool concentration methods; serology or sputum examination.	Ivermectin, 100 micrograms/kg/d for 2 d *or* Albendazole, 400 milligrams twice a day for 7 d

minimal; a dry cough or eosinophilic pulmonary infiltrates may occur as young worms are expectorated and migrate from the lungs to the esophagus and gut. A large worm burden can lead to malnutrition and weakness, as well as bowel obstruction. Wandering *Ascaris* also traverse internal organs, rarely leading to biliary obstruction, hepatic abscess, acute pancreatitis, acute appendicitis, or hypersensitivity pneumonitis.[63]

ENTEROBIASIS (PINWORM)

Enterobiasis vermicularis is a common tropical disease caused by a small intestinal parasite transmitted by the fecal–oral route and is often acquired from contaminated objects such as toys, utensils, and bedding. It is a common disease among U.S. children and is more likely to be peridomestic rather than occur after tropical travel; hence, treatment of all housemates is recommended. The disease is characterized by intense perianal itching. Occasionally, worms may migrate to cause appendicitis, or via perianal migration, they may ultimately migrate to fallopian tubes and endometrium, causing inflammation and obstruction.[64]

TRICHURIS (WHIPWORM DISEASE)

Whipworm (*Trichuris trichiura*) is a nematode parasite of the large intestine distributed globally but most heavily in the tropics. Long-term travelers, former tropical residents, and visitors from the tropics are at high risk. It is obtained by ingesting contaminated soil or vegetables and is not transmissible from person to person. Light infestations are asymptomatic, and heavy infestations cause nonspecific abdominal symptoms, bloody diarrhea, and rectal prolapse.[65]

HOOKWORM

Hookworm is a common chronic nematodal infection caused by *Ancylostoma duodenale* and *Necator americanus*, which are globally distributed but are most heavily found in the tropics and subtropics. Because symptoms require large worm burdens, it is a low risk among short-term travelers. Hookworm causes chronic, severe anemia, especially in children. The cutaneous form is called *cutaneous larva migrans* (see later section, "Diseases Commonly Associated With Eye or Skin Complaints"). Transmission is by direct skin contact with soil contaminated by human feces, often in children with poor footwear exposed to raw sewage. Filariform larvae penetrate the skin. Microscopic examination of stool for eggs is the usual means of diagnosis.[66,67]

CESTODES (TAPEWORMS)

Among the cestodes, taeniasis and cysticercosis are the most pathologic. Infections occur worldwide, but especially in the tropics, and risk is high among children, the mentally disabled, and immigrants or visitors from endemic nations. Risk to travelers is low but is increased with consumption of undercooked pork, fish, or beef.

Taenia solium* and *Taenia saginata* (Pork and Beef Tapeworm)** ***T. solium (**pork tapeworm**) is encountered in the United States in immigrants or visitors to or from Central America and the Middle East. *T. saginata* (beef tapeworm) is seen more often, especially in those who consume raw beef (e.g., steak tartare), particularly in Latin America, Eastern Europe, Africa, and Russia. Adult worms live in the small intestine. Infected patients can be asymptomatic or present with nausea and vomiting, headache, abdominal pain, pruritus, constipation, diarrhea, and intestinal obstruction. The larval stage of *T. solium* can cause clinical disease (cysticercosis), which can sometimes be fatal. *Taenia* cysts may be found in subcutaneous tissue, the eye, brain, and heart and can cause seizures and hydrocephalus. Radiographs of the soft tissues may reveal curvilinear calcifications indicative of cysts, and cysts can be seen in the meninges and brain parenchyma on CT scanning. For discussion of neurocysticercosis see the earlier "Cysticercosis" section. *Dipylidium caninum* is discussed in Chapter 161.[68]

Diphyllobothrium latum* (Fish Tapeworm)** ***Diphyllobothrium latum (fish tapeworm) is encountered in those consuming raw fish (e.g., sushi and sashimi) or gefilte fish. *Diphyllobothrium* can compete with the host for vitamin B_{12}, and patients can develop pernicious anemia. Most patients are asymptomatic, but some develop intestinal or biliary obstruction.[69]

STRONGYLOIDES

Strongyloides stercoralis infects the small intestine. Distribution is worldwide, but infection is most common in humid tropics. Infection can develop in overseas military personnel, refugees, or immigrants. The risk is low in short-term travelers. Most infections cause minimal GI symptoms, occasional dyspnea, or hemoptysis with migration, or no symptoms. However, severe disseminated disease may occur in immunocompromised patients and cause hyperinfection with multiorgan symptoms, including meningitis, and septic shock. An upper GI series may reveal a deformed duodenal bulb, and *Strongyloides* may be confused with ulcer disease.[70]

DISEASES COMMONLY ASSOCIATED WITH EYE OR SKIN COMPLAINTS

Skin complaints among travelers are common and nonspecific and have many causes. **Travel-related skin disease is generally caused by one of the following: (1) exacerbations of previous conditions (e.g., atopic dermatitis, psoriasis); (2) environmental conditions (e.g., photosensitivity, contact allergies); or (3) infective organisms causing infestations or infections.**[16] The distribution and timing of the dermatosis may aid diagnosis of rashes associated with systemic illness (**Table 162-14**).[71] Among rashes reported by travelers, most are minor problems, such as sunburn, phototoxic/sensitivity reactions, insect bites, and prickly heat, and are often self-limiting and necessitate symptomatic care. **The most common tropical travel dermatoses in ill individuals requiring therapy are cutaneous larva migrans, insect bites including bites with bacterial superinfections, abscesses, and allergic reactions.**[72] The risk of serious conditions tends to increase with the amount of time spent overseas, and thus short-term travelers rarely contract dermatoses such as filariasis, Buruli ulcer, yaws, and leprosy (Hansen's disease). To further aid diagnosis, travelers with dermatoses can fit into five syndromic and morphologic categories (**Table 162-15**).

Management includes arranging biopsy for patients with chronic ulcerative lesions. Beware of the rare patient presenting with anxiety of parasitosis regardless of travel history. The following are select dermatoses associated with tropical exposures.

TABLE 162-14 Cutaneous Manifestations of Selected Infections

Appearance of Lesion	Possible Diagnosis
Maculopapular rash	Dengue fever Viral hemorrhagic fevers Leptospirosis Acute human immunodeficiency virus infection
Erythema chronicum migrans	Lyme disease
Rose spots	Typhoid fever
Pustules	Disseminated gonococcal infection
Petechiae, ecchymoses, hemorrhage	Meningococcemia Dengue fever Viral hemorrhagic fevers Yellow fever Rocky Mountain spotted fever Epidemic louse-borne typhus Leptospirosis
Eschar	Tick or scrub typhus Anthrax
Ulcer	Tularemia Cutaneous diphtheria
Urticaria	Helminthic infections

TABLE 162-15 Syndromic Categories of Travel-Related Dermatoses With Select Examples

- Fever and rash (petechial or hemorrhagic): dengue fever, arboviruses, rickettsial infections (e.g., scrub typhus), chikungunya, meningococcemia, leptospirosis, malaria, and erythema multiforme caused by drug reaction or common infection
- Papular eruptions: insect bites, persistent lesions (chiggers), scabies, allergic drug reactions, cercarial dermatitis (swimmers), *Pseudomonas* folliculitis (hot-tubbing), onchocerciasis (long-term travel)
- Persistent nodules: furunculosis, myiasis (movement within the lesion), chancroid, syphilis, systemic parasites/fungi
- Migratory swellings or skin lesions: cutaneous larva migrans, strongyloidiasis (fast moving and often on the buttocks), urticaria from various causes, and *Loa loa* (rarely)
- Ulcerative lesions: pyodermas, spider bites, chancroid and syphilis, cutaneous leishmaniasis

FILARIASIS: ONCHOCERCIASIS AND *LOA LOA*

ONCHOCERCIASIS (RIVER BLINDNESS)

River blindness is a chronic, nonfatal filarial disease leading to subcutaneous skin changes and blindness. It is caused by *Onchocerca volvulus*, a nematode transmitted by the female black fly, *Simulium* species, found near fast-moving rivers predominantly in sub-Saharan Africa as well as small foci in Yemen, Venezuela, and Brazil. Symptoms may take up to 18 months to appear and include intractable pruritus, altered skin pigmentation, skin nodules, lymphadenitis, and gradual visual impairment leading to blindness. Adult female worms reside in 2- to 3-cm painless nodules in skin and bones near joints, and release microfilariae that migrate through the skin, causing intense pruritus when they die, leading to chronic dermatitis, edema, and skin atrophy. Skin pigment changes result in "leopard skin," whereas loose pelvic skin is called "hanging groin." Blindness is a result of microfilariae migrating to the eye, invading it, and causing permanent damage when they die. Diagnosis is made by identification of microfilariae from a fresh skin biopsy, from nodule biopsies, or in the urine. Slit-lamp examination may reveal microfilariae in the cornea, anterior chamber, or vitreous. Treatment of choice is ivermectin, which kills microfilariae but does not kill the adult worm, thus requiring repeated dosing, suppressing microfilariae release from adults and preventing spread to eyes and skin.[73]

LOA LOA (EYE WORM)

Loiasis is caused by a filarial nematode confined to the rain forests of western and central Africa in a distribution that overlaps with that of onchocerciasis. It is a low risk to short-term travelers but should be suspected among immigrants, refugees, visiting nationals, and expatriates living several months or more in endemic zones. Among travelers, worm burden is usually low, and symptoms are related to hypersensitivity syndromes and not serious disease. The adult worms inhabit subcutaneous tissues, move about freely, and can live for up to 18 years after the patient's last possible exposure. They are spread from the bite of the *Chrysops* fly. Infections are usually asymptomatic; however, at times, infections cause painful or itchy subcutaneous swellings near the face and extremities known as Calabar swellings. Occasionally a worm passes across the eye under the conjunctiva, causing intense irritation, pain, and swelling of the periorbital tissues.[74]

Diagnosis is made by clinical presentation and by evaluating daytime-drawn blood for distinctively sheathed microfilariae and high-grade eosinophilia. Treatment for microfilariae and adult worms is **diethylcarbamazine citrate**. Screen for coinfection with onchocerciasis, which requires treatment first, given that diethylcarbamazine citrate is contraindicated in the treatment of onchocerciasis due to an inflammatory response that could induce blindness. In patients with very high microfilariae counts, diethylcarbamazine citrate may induce a sudden severe hypersensitivity and encephalitic syndrome, so treatment is begun with a very small dose, or a test-and-not-treat strategy for individuals with high microfilarial loads can be employed.[75] Albendazole can also be used to treat loiasis. Surgical excision is not recommended because multiple worms may not be visible. Subconjunctival worms, however, can be removed from the eye with analgesia and fine tweezers.[76]

CREEPING ERUPTION (CUTANEOUS LARVA MIGRANS)

Erythematous "creeping eruption" commonly occurs among tropical travelers and beach resort vacationers who walk barefoot or sit in beach sand contaminated by dog feces harboring the parasite *Ancylostoma braziliense*.[77] The lesions are typically slow moving, tracking, and serpiginous and are a result of an inflammatory reaction from the worm, which is unable to complete its growth cycle in humans (it is only an effective parasite of dogs or cats). Pruritus causes sleeplessness and restlessness. Bacterial superinfection is not uncommon. Diagnosis is based on clinical presentation, and no serology is available. Treatment consists of **albendazole** or ivermectin.[78]

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis is the most important cause of chronic skin ulceration in the world and is spread by sandflies in tropical and subtropical regions of Latin America, Africa, the Middle East, and Asia. This should be suspected among travelers such as military personnel, biologists, ecotourists, and adventure travelers, and should be part of the differential diagnosis of nonhealing cutaneous ulcers among travelers, foreign visitors, and immigrants from endemic areas. Although there are a variety of subtypes causing varying infections, the common presentation is of a small papule slowly enlarging and forming a painless shallow skin ulcer with a noticeable rolled edge like a volcano, with a raised edge and central crater, often with a scab. Diagnosis is made by tissue biopsy of the indurated ulcer margin or scraping of the base with material placed on a slide followed by Giemsa stain. Many forms are self-limiting; often observation alone is preferred, or lesions can be treated with heat application or paromomycin topical ointment. More serious forms can be treated with liposomal amphotericin B or sodium stibogluconate. Treatment response may vary with involved species and geographic distribution.[52]

LYMPHATIC FILARIASIS

Lymphatic filariasis is caused by nematodes (*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*) residing in the subcutaneous tissues and lymphatics. It is common to South America, Africa, and Asia. The risk to short-term travelers is low, although cases have been imported by long-term travelers. It is transmitted by flies or mosquitoes permitting larvae to enter the puncture wound during their blood meal. Adult filariae then reside in lymphatics and produce microfilariae that migrate to the bloodstream at night. First, symptoms develop after 6 months to 5 years. The most common symptom is recurrent bouts of "filarial fevers" lasting 2 to 3 weeks, associated with warmth and tenderness overlying a lymphatic vessel, followed by retrograde lymphangitis. The most frequently affected sites are extremities, breasts, and spermatic cord. As more attacks occur, lymphatics are chronically damaged, and the consequence is elephantiasis. "Nocturnal asthma" can occur with associated tropical pulmonary eosinophilia. Diagnosis depends on finding the sheathed microfilariae in a nocturnal peripheral blood smear. Serology is often useful in mild infections. Treatment is diethylcarbamazine citrate, which can cause hypersensitivity reactions with antigen liberation. Because of this, testing for coinfection with onchocerciasis and *Loa loa* is important to prevent adverse effects. Symptoms can be reduced by starting with a small dose. Repeated treatment may be necessary.[79,80]

DISEASES COMMONLY ASSOCIATED WITH PULMONARY COMPLAINTS

Returning travelers frequently develop respiratory complaints such as persistent cough, sinus congestion, and fever. Common local respiratory pathogens including viral causes such as influenza and bacterial infections are the most common etiologies. Risk factors for pulmonary

disease include prolonged air travel with recirculation of dry cabin air and exposure to fellow travelers with infectious agents. Long-term travelers are at increased risk for tuberculosis that may manifest many years after travel. In the ED, isolate the patient because contagious infections, such as tuberculosis, influenza, or coronaviruses (e.g., severe acute respiratory syndrome or Middle East respiratory syndrome), are possible. Also, have healthcare workers use personal protective devices.

Once public health threats are reasonably excluded, the evaluation is similar as for any nontravel patients. Additionally, ask about travel-related risk factors because a variety of pathogens such as viruses (viral hemorrhagic fevers), helminths (*Strongyloides*, *Schistosoma*, *Paragonimus*, *Ascaris*), and protozoa (*E. histolytica*, *Trypanosoma*, *Leishmania*) produce pulmonary symptoms or radiographic infiltrates.

CORONAVIRINAE: SEVERE ACUTE RESPIRATORY SYNDROME AND MIDDLE EAST RESPIRATORY SYNDROME

Coronaviruses are the causative agents of a diverse set of respiratory illnesses, ranging from the common cold to severe acute respiratory syndrome. As such, symptoms range from benign upper respiratory symptoms of cough, sinus congestion, and malaise to severe respiratory distress, pneumonia, multiorgan failure, and death.

Preventive measures target reduced close contact with infected persons and lessening nosocomial transmission. Place patients on airborne precautions, and healthcare providers should use gowns, gloves, eye protection, and respiratory protection with a minimum of a N95 mask.[81] Promptly notify local and state health departments of the case. Treatment of a respiratory syndrome caused by a coronavirus is supportive, although other therapies, including interferon-alfa, ribavirin, and steroid treatments, are often attempted absent strong data.[82,83]

SEVERE ACUTE RESPIRATORY SYNDROME FROM CORONAVIRUS

First reported in 2002 in China, severe acute respiratory syndrome from coronavirus is a poorly understood coronavirus. The reservoir is not certain, but the transmission cycle is thought to include bats and civet cats. Human-to-human transmission is most common. In 2002 to 2003, an outbreak occurred with the spread of severe acute respiratory syndrome to 26 countries with >8000 cases. Symptoms start with dry cough and diarrhea and progress to fulminant respiratory failure. At present, there are no known epidemics occurring.[84]

MIDDLE EAST RESPIRATORY SYNDROME FROM CORONAVIRUS

Middle East respiratory syndrome from coronavirus is an emerging coronavirus first reported in 2012. Between September 2012 and November 2018, the World Health Organization reported a total of 2260 cases of the Middle East respiratory syndrome coronavirus infection with >800 deaths[85]; approximately 80% of cases have been reported in Saudi Arabia, but cases have been reported in 27 countries, including the United States.

Although not certain, Middle East respiratory syndrome is likely to be spread by "droplet infection." Dromedary camels are thought to be a reservoir, but exact transmission mechanisms are not understood. Polymerase chain reaction can be used to detect Middle East respiratory syndrome coronavirus.[86]

TUBERCULOSIS

One fourth of the world is infected with tuberculosis, and in 2017, there were 1.3 million tuberculosis-related deaths worldwide.[87] The risk of tuberculosis in travelers is about 1% per year of stay in most areas of the world; however, individual risk factors and highly endemic settings can result in an increased risk.[88] High-risk sites for multidrug-resistant mycobacteria are Russia, Eastern Europe, Southeast Asia, China, southern Africa, and South America. Refugees and immigrants or expatriate workers (especially healthcare workers) returning from endemic areas are at higher risk of clinical tuberculosis (e.g., Eastern Europe, Africa, Asia). The initial ED management of suspected tuberculosis after respiratory isolation is discussed elsewhere (see Chapter 67, "Tuberculosis").

PARAGONIMIASIS (LUNG FLUKE DISEASE)

Paragonimus species cause trematode infections primarily affecting the lungs. It is widely distributed but is mostly found in the Far East and Southeast Asia (China is the major endemic site). It is uncommon in short-term travelers, but should be considered among immigrants or long-term residents of Asia who are also at risk for tuberculosis and among travelers indulging in local exotic foods. Cases in the United States have also been reported.[89] Humans are infected by swallowing larvae contaminating raw or pickled crustaceans. Incubation lasts 6 to 12 weeks, as larvae migrate from the duodenum to the lungs, where they cause purulent and bloody effusions, productive cough (eggs are expectorated), pleuritic chest pain, and hemoptysis. Chest pain is often present, and fever with night sweats may occur during early infections, causing tuberculosis to be incorrectly diagnosed.[90]

Chest radiographs demonstrate diffuse segmental infiltrates, nodules, ring cysts, or pleural effusions. Suspect paragonimiasis when no sputum smear acid-fast bacilli are found. Less commonly, parasites do not reach the lung, and diverse symptoms develop depending on fluke location. Symptoms include abdominal pain, diarrhea, migrating subcutaneous swelling, blindness, epididymis, testicular inflammation, and a variety of cerebral symptoms. Seizures can occur from intracranial encysted adults. Diagnosis is made by finding the characteristic eggs in sputum, urine, or stool, or by serologic tests. The treatment of choice is praziquantel or triclabendazole.[91]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 163

Occupational Exposures, Infection Control, and Standard Precautions

Charissa B. Pacella

INTRODUCTION

The U.S. Occupational Safety and Health Administration defines *occupational exposure* as a "reasonably anticipated skin, eye, mucous membrane, or parenteral contact with blood or other potentially infectious materials that may result from the performance of the employee's duties."[1] Blood covers "human blood, blood products, or blood components."[1] *Other potentially infectious materials* are "human body fluids, such as saliva, semen, and vaginal secretions; cerebrospinal, synovial, pleural, pericardial, peritoneal, and amniotic fluids; any body fluids visibly contaminated with blood; unfixed human tissue or organs; HIV [human immunodeficiency virus] or HBV [hepatitis B virus] containing cell or tissue cultures, culture mediums, or other solutions; and all body fluids where it is difficult or impossible to differentiate between body fluids."[1] **Healthcare workers should treat all bodily secretions, fluids, and tissues as potentially infectious.**

The Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention lists select infections and conditions that may be encountered in the ED, along with recommended occupational exposure precautions.[2-4] The concept of *standard precautions* is built on the premise that healthcare workers cannot readily identify patients who are infected or at risk for infection. Using infection control practices and personal protective equipment during all patient care activities is key.

U.S. Occupational Safety and Health Administration federal regulations prescribe safeguards to protect workers and reduce risk of exposure to blood and body fluids.[5] The Centers for Disease Control and Prevention and U.S. Occupational Safety and Health Administration websites provide the most up-to-date information regarding current regulations and standards.

PORTALS FOR EXPOSURE

Portals for infectious disease entry are percutaneous, mucous membrane (oral, ocular, nasal, vaginal, or rectal), respiratory, and dermal. The risk of infection in an exposed healthcare provider depends on (1) the route (portal) of exposure, (2) the concentration (number of organisms) of the pathogen in the infectious material, (3) the infectious characteristics (virility) of the pathogen, (4) the volume (dose) of infectious material, and (5) the immunocompetence (susceptibility) of the exposed individual.

Percutaneous exposures pose the highest risk of transmission for bloodborne disease. Needle sticks and lacerations by sharp objects account for most percutaneous injuries. Phlebotomy, initiation of IV access, manipulation of access devices, suturing, and medication injection all put workers at risk.

Mucous membrane exposures result from splatters, splashes, and sprays of blood and body fluids. Tasks associated with risk of mucous membrane exposure include wound management (hemorrhage control, exploration, irrigation, debridement), airway suctioning, nasogastric or orogastric tube placement, intubation, and specimen handling.

Respiratory exposures occur through inhalation of airborne or droplet particulate materials. Exposure risk grows when an individual is confined with an expectorating, coughing, or sneezing patient for prolonged periods or in a poorly ventilated environment.

Dermal exposure involves skin contact with patients, environmental surfaces, or objects contaminated with infectious material. The risk of infection increases if the contact involves a large surface area or nonintact skin (abraded, chapped, or excoriated). Drug-resistant organisms (e.g., methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci) and parasites of the integument (e.g., scabies, lice) are transmitted by dermal exposure. Many workplace activities risk dermal exposure including patient examination, moving patients, and changing linens and wound dressings. Healthcare workers are also at risk for hypersensitivity reactions to specific inert substances, notably latex, after prolonged or repeated dermal exposure.

INFECTION CONTROL

Infection control practices seek to prevent transmission of microbial agents and to provide a wide margin of safety for healthcare workers. **These practices include hand hygiene; use of personal protective equipment; cleaning, disinfecting, and sterilizing patient care equipment and environmental surfaces; decontamination and laundering of soiled uniforms, clothing, and linens; disposal of needles, sharps, and infectious waste; and patient location.** Infection control measures that are simple, easily accessible, and uniform across all situations have the greatest likelihood of compliance.

A complete infection control program includes administrative controls, equipment engineering, work practice controls, workforce education, and medical management.

Administrative controls organize, define, and direct infection control activities. The written infection control (exposure) plan defines policies, procedures, and activities related to the education, prevention, and management of infectious diseases in the workforce.

Equipment engineering reduces employee exposure by removing hazards or isolating healthcare workers from exposure. Examples include self-sheathing needles, needleless drug administration devices, sharps containers, disposable airway equipment, and personal protective equipment.

Personal protective equipment is "specialized clothing or equipment which does not permit blood or potentially infectious substances to pass through or reach worker clothing, skin, eyes, mouth, or other mucous membranes under normal conditions of use."[1] Personal protective equipment includes examination gloves, facemasks, eye protection, face shields, and impervious gowns, leggings, and shoe covers. Personal protective equipment reduces but does not eliminate exposure risk. Recommendations for specific personal protective equipment use appear under "Standard Precautions."

Work practice controls modify the performance of a task to minimize exposure to blood and blood-containing body fluids and infectious materials. Work practice controls include policies to guide disposal of needles and sharps containers (i.e., avoid shearing, bending, recapping, or breaking); disposal of contaminated linens, clothing, and infectious waste; disinfection of reusable equipment; and restriction of employee activities (i.e., eating, drinking, applying cosmetics) in work areas where there is a reasonable likelihood of exposure to blood and body fluids.

Workforce education includes information about the agents of infectious disease, epidemiology, disease transmission, signs and symptoms, risky work activities, risk reduction strategies, and postexposure management. Education must occur at the time of initial employment and at specified intervals thereafter.

Medical management practices include preexposure preventive vaccinations, postexposure medical evaluation, testing, infectious disease counseling, disease prophylaxis, and referral. The U.S. Occupational Safety and Health Administration mandates preexposure vaccines at initial employee training and within 10 days of employment for all personnel at risk of exposure.[1]

EXPOSURE TO HEPATITIS B, HEPATITIS C, AND HUMAN IMMUNODEFICIENCY VIRUS

Once an infectious exposure has occurred, healthcare workers should have access to a plan for postexposure prophylaxis (PEP) medical management 24 hours a day. The plan should include immediate medical assessment, risk analysis, counseling, treatment and prophylaxis, and follow-up appropriate to the type and source of the exposure.[6-11] A standardized initial approach is shown in **Table 163-1**.[8]

The medical record of care for the exposed person (the occupational exposure report) should contain specific information relative to the exposure incident. Key elements include the circumstances of exposure, medical history of the exposure source, and medical history of the exposed person per Centers for Disease Control and Prevention recommendations (**Table 163-2**).[7]

INITIAL TREATMENT AND ASSESSMENT

Thoroughly wash exposed wounds and skin sites with soap and water, and then irrigate mucous membranes with water. **Do not apply** caustics (bleach), antiseptics, or disinfectants directly to the wound.

TABLE 163-1 Outline for Management of Exposures to Blood or Body Fluids

- Expedite medical evaluation.
- Irrigate exposed areas with water; wash wounds with soap and water.
- Obtain history regarding exposure circumstances, source patient, and vaccination history of exposed person (Table 163-2).
- Obtain blood samples for laboratory studies (using consents when required) from exposed person; consider urine pregnancy test for women of childbearing potential.
- Order laboratory studies from source patient if known (using consents when required).
- Determine need for tetanus immunization.
- Determine need for hepatitis B PEP (Table 163-5).
- Determine need for human immunodeficiency virus PEP (Table 163-6) and mechanism for dosing as rapidly as possible.
- Counsel exposed person regarding risk of specific bloodborne pathogens and discuss risks/benefits of available treatment options.
- Review dosing and side effects of recommended treatments (Table 163-7).
- Arrange follow-up through employee health clinic within 72 h. Obtain expert consultation in appropriate cases (Table 163-8).

Abbreviation: PEP = postexposure prophylaxis.

TABLE 163-2 Recommendations for the Contents of the Occupational Exposure Report

- Date and time of exposure.
- Details of the procedure being performed, including where and how the exposure occurred; if related to a sharp device, the type and brand of device and how and when in the course of handling the device the exposure occurred.
- Details of the exposure, including the type and amount of fluid or material and the severity of the exposure (e.g., for a percutaneous exposure, depth of injury and whether fluid was injected; for a skin or mucous membrane exposure, the estimated volume of material and the condition of the skin [e.g., chapped, abraded, intact]).
- Details about the exposure source (e.g., whether the source material contained hepatitis B virus, hepatitis C virus, or HIV; if the source is HIV infected, the stage of disease and prognosis, history of antiretroviral therapy, viral load, and antiretroviral resistance information, if known).
- Details about the exposed person (e.g., hepatitis B vaccination and vaccine-response status).
- Details about counseling, postexposure management, and follow-up.

Abbreviation: HIV = human immunodeficiency virus.

TABLE 163-4 Evaluation of Occupational Exposure Source

Known sources

- Test known source for hepatitis B surface antigen, anti–hepatitis C virus, and HIV antibody.
- Direct virus assays for routine screening of source patients are *not* recommended.
- If possible, a rapid HIV-antibody test.
- If the source person is *not* infected with a bloodborne pathogen, baseline testing or further follow-up of the exposed person is *not* necessary.
- For source whose infection status remains unknown (e.g., the source person refuses testing), consider medical diagnoses, clinical symptoms, and history of high-risk behaviors.
- Do not test needles or instruments for bloodborne pathogens.

Unknown source

- For unknown source, evaluate the likelihood of exposure to a source at high risk for infection.
- Consider likelihood of bloodborne pathogen infection among patients in the exposure setting.

Abbreviation: HIV = human immunodeficiency virus.

Evaluate the exposure event for the potential to transmit hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV) based on the type of exposure and the amount and type of fluid or tissue (**Table 163-3**).[7] Blood, fluid containing visible blood, human tissue, and other potentially infectious materials may transmit bloodborne viruses. Percutaneous injury or mucous membrane contact with these substances conveys risk for virus transmission. Dermal contact with these substances does not convey risk of virus transmission unless the skin is *not* intact (abraded, chapped, excoriated, open wound). Saliva, sweat, tears, vomit, urine, feces, and respiratory secretions do not transmit HIV unless visibly bloody. The risk of hepatitis B and C virus transmission from nonbloody saliva is negligible.

TESTING FOR EXPOSURE

Perform diagnostic testing to determine the hepatitis B virus, hepatitis C virus, and HIV infection status of an exposure source as soon as possible and with consent when required (**Table 163-4**).[7] If possible, obtain a rapid HIV-antibody test on the exposure source. Direct viral assays (HIV p24 antigen enzyme immunoassay, HIV RNA, hepatitis C virus RNA) are not recommended. Testing of needles or sharps instruments for contamination is also not recommended. If the exposure source is HIV positive, obtain additional information as available, including CD4+ T-cell count, viral load, current and previous antiretroviral therapy, and history of antiretroviral resistance to help identify optimal PEP regimen. Do not delay the initiation of PEP awaiting additional information; changes in the regimen may be made upon follow-up within 72 hours after exposure.[7]

TABLE 163-3 Factors to Consider in Assessing Healthcare Workers After Occupational Exposures

Type of exposure

- Percutaneous injury
- Mucous membrane exposure
- Nonintact skin exposure
- Bites resulting in blood exposure to either person involved

Type and amount of fluid/tissue

- Blood
- Fluids containing blood
- Potentially infectious fluid or tissue (semen; vaginal secretions; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids)
- Direct contact with concentrated virus

Infectious status of source

- Presence of hepatitis B surface antigen
- Presence of HCV antibody
- Presence of HIV antibody

Susceptibility of exposed person

- Hepatitis B vaccine and vaccine response status
- HBV, HCV, and HIV immune status

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

HEPATITIS B VIRUS EXPOSURE AND POSTEXPOSURE PROPHYLAXIS

Factors in the management of hepatitis B virus exposure include the hepatitis B surface antigen status of the source and the hepatitis B vaccination and vaccine response status of the exposed person. Following a percutaneous exposure, the estimated risks of hepatitis in unvaccinated healthcare workers are 22% to 31% (exposure source positive for hepatitis B surface antigen and hepatitis B e antigen) and 1% to 6% (exposure source positive for hepatitis B surface antigen and negative for hepatitis B e antigen). The estimated risk of transmission is lower after mucous membrane exposure, nonintact skin exposure, or an exposure involving nonbloody fluids or tissues.[7] Every unvaccinated healthcare worker exposed to blood or body fluids should receive the hepatitis B vaccine series. For vaccinated workers, recommendations for PEP following hepatitis B virus exposure vary according to the hepatitis B surface antigen status of the exposure source and the vaccination/vaccine-response status of the exposed person (**Table 163-5**).[7] If choosing hepatitis B immunoglobulin therapy, give it as soon as possible after the exposure, ideally within 24 hours; after 7 days, the effectiveness of hepatitis B immunoglobulin is unknown.

HEPATITIS C VIRUS EXPOSURE

For occupational hepatitis C virus exposures, the Centers for Disease Control and Prevention recommends anti–hepatitis C virus testing of the source patient. Test the exposed person for anti–hepatitis C virus and alanine aminotransferase at baseline and follow-up (at 4 to 6 months), and testing for hepatitis C virus RNA may be performed at 4 to 6 weeks after exposure if needed to aid early diagnosis of hepatitis C virus. Confirm all positive anti–hepatitis C virus tests by enzyme immunoassay with supplemental testing (i.e., recombinant immunoblot assay). If the source patient is hepatitis C virus infected, the mean estimated risk of transmission is 1.8% after a percutaneous exposure (range, 0% to 7%). Estimated risk of transmission is lower following mucous membrane exposure, nonintact skin exposure, or exposure to nonbloody fluids or tissues.[7] Immunoglobulin and antivirals are not recommended for PEP after exposure to hepatitis C virus–positive blood.

Healthcare workers exposed to hepatitis B virus– or hepatitis C virus–infected blood do not need to take any precautions to prevent secondary transmission during the follow-up period; however, they should not donate blood, plasma, organs, tissue, or semen.

TABLE 163-5 Postexposure Prophylaxis for Percutaneous and Mucous Membrane Exposure to Hepatitis B Virus

Vaccination and Antibody Response Status of Exposed Workers	Treatment		
	Source Is HBsAg Positive	Source Is HBsAg Negative	Source Is Unknown or Not Available for Testing
Unvaccinated/nonimmune	HBIG* × 1 and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated			
Previously vaccinated known responder†	No treatment	No treatment	No treatment
Previously vaccinated known nonresponder‡	HBIG × 1 and initiate revaccination or HBIG × 2#	No treatment	If known high-risk source, treat as if source were HBsAg positive
Previously vaccinated antibody response unknown	Test exposed person for anti-HBsƒ	No treatment	Test exposed person for anti-HBsƒ
	1. If adequate,† no treatment is necessary 2. If inadequate,‡ administer HBIG × 1 and vaccine booster		1. If adequate,† no treatment is necessary 2. If inadequate,‡ administer vaccine booster and recheck titer in 1–2 mo

Note: Ideally, HBIG and first vaccination should be initiated within 24 hours of exposure. Persons who have previously been infected with hepatitis B virus are immune to reinfection and do not require postexposure prophylaxis.

Abbreviations: HB = hepatitis B; HBIG = hepatitis B immunoglobulin; HBsAg = hepatitis B surface antigen.

*Dose is 0.06 mL/kg IM.

†A responder is a person with adequate levels of serum antibody to HBsAg (i.e., anti-HBs ≥10 mIU/mL).

‡A nonresponder is a person with inadequate response to vaccination (i.e., serum anti-HBs <10 mIU/mL).

#The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second three-dose vaccine series. For persons who previously completed a second vaccine series (≥6 doses) but failed to respond, two doses of HBIG are preferred given 1 month apart.

ƒAntibody to HBsAg.

HIV EXPOSURE AND POSTEXPOSURE PROPHYLAXIS

Healthcare workers potentially exposed to HIV should receive expedited evaluation and baseline testing for HIV. Factors in the management of HIV exposure include the type of exposure (percutaneous, mucous membrane, or dermal), the volume of the exposure (small or large), and the HIV status of the source. Risk of HIV transmission following percutaneous exposure increases with exposure to a larger quantity of blood as indicated by (1) a device visibly contaminated with blood, (2) a needle placed in the source patient's artery or vein, (3) a large-bore hollow needle, or (4) a deep injury.[12,13] **If the source patient is HIV infected, the estimated risk of transmission is 0.3% after a percutaneous exposure and 0.09% after a mucous membrane exposure.** Estimated risk of transmission following a nonintact skin exposure or an exposure involving nonbloody fluids or tissues is even lower.[11]

If the source patient has a negative HIV antibody test, baseline testing and further follow-up of the exposed person are not normally necessary. If the source patient has a positive HIV antibody test, consider the source to be HIV positive *regardless of viral load* for the purpose of PEP and follow-up testing. Exposure to a source patient with an undetectable viral load does not eliminate the possibility of HIV transmission. If the source patient is suspected to have acute retroviral syndrome, consider the source to be HIV positive regardless of HIV test result.

Initiate PEP as soon as possible after the exposure; if later testing determines the source to be HIV negative, discontinue prophylaxis. PEP is less effective if started more than 24 to 36 hours after exposure. The interval after which no benefit is gained is unknown, so start PEP even when the postexposure interval exceeds 36 hours.

The U.S. Public Health Service provides guidelines for PEP following occupational exposure to HIV.[11] Guidelines recommend three (or more) tolerable antiretroviral drugs for all occupational exposures to HIV (**Tables 163-6** and **163-7**). Anticipate side effects and consider preemptive prescribing of ameliorating medications to improve PEP regimen adherence.[11] Also, consult with a local expert or with the National Clinician Consultation Center (1-888-448-4911; 11 am to 8 pm daily) for the more complex situations listed in **Table 163-8**. Do not delay initiation of postexposure therapy awaiting expert consultation; PEP may be started immediately and discontinued later based on new information or consultation. The optimal duration of PEP is unknown, but the Centers for Disease Control and Prevention recommends 4 weeks of treatment.[7]

Following an exposure to HIV, advise healthcare workers to be reevaluated within 72 hours to assess information about the source patient. Also, emphasize the importance of adherence to the PEP regimen for the duration of treatment. Similarly, recommend that all exposed healthcare personnel prevent potential secondary transmission, especially during the first 6 to 12 weeks after exposure, by doing the following: use condoms or exercise sexual abstinence; refrain from donating blood, plasma, organs, tissue, or semen; avoid pregnancy; and, if possible, avoid breastfeeding. Advise exposed workers to seek medical evaluation for any acute illness that occurs during the follow-up period, as this may signal the onset of acute retroviral syndrome. Follow-up testing includes HIV testing at baseline and at 6 weeks, 12 weeks, and 6 months after exposure, usually concluded 4 months after the exposure if a newer fourth-generation HIV p24 antigen–HIV antibody test is negative.

RESOURCES FOR POSTEXPOSURE PROPHYLAXIS

The National Clinician Consultation Center offers telephone consultation for providers managing occupational exposures to bloodborne

TABLE 163-6 Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Regimens

Preferred HIV PEP Regimen

Truvada® (tenofovir DF 300 milligrams + emtricitabine 200 milligrams once daily) ***PLUS*** raltegravir (400 milligrams twice daily) ***or*** dolutegravir (50 milligrams once daily)

Duration: 28 days

Alternative Regimens

May combine 1 drug or drug pair from the left column with 1 drug or drug pair from the right column. Prescribers unfamiliar with these agents/regimens should consult with a physician familiar with these agents and their toxicities.

Raltegravir	Tenofovir disoproxil fumarate + emtricitabine (Truvada®)
Dolutegravir	Tenofovir disoproxil fumarate + lamivudine
Darunavir + ritonavir	Zidovudine + lamivudine (Combivir®)
Etravirine	Zidovudine + emtricitabine
Rilpivirine	
Atazanavir + ritonavir	
Lopinavir/ritonavir (Kaletra®)	

Other alternative antiretroviral regimens should be used for PEP only with expert consultation.

TABLE 163-7 Drugs Commonly Used for Human Immunodeficiency Virus Postexposure Prophylaxis (PEP)

Drug (Trade Name; Abbreviation)	Dosage	Advantages/Disadvantages
Tenofovir DF (Viread®; TDF)	300 milligrams once daily Also component of fixed-dose combinations: Atripla®, Complera®, Stribild®, Truvada®	Well tolerated. Asthenia, headache, diarrhea, nausea, vomiting Nephrotoxicity; should not be administered to individuals with acute or chronic kidney injury, or estimated glomerular filtration rate <60 mL/min/1.73 m^2 Withdrawal may cause acute hepatitis exacerbation in the setting of chronic hepatitis B
Emtricitabine (Emtriva®; FTC)	200 milligrams daily Also component of fixed-dose combinations: Complera®, Stribild®, Truvada®	Well tolerated, minimal toxicity Skin discoloration, withdrawal may cause acute hepatitis exacerbation in the setting of chronic hepatitis B
Raltegravir (Isentress®; RAL)	400 milligrams twice daily	Well tolerated, minimal toxicity Insomnia, nausea, fatigue, headache, severe skin and hypersensitivity reactions
Dolutegravir (Tivicay®; DTG)	50 milligrams once daily	Well tolerated Headache, insomnia
Zidovudine (Retrovir®; ZDV, AZT)	300 milligrams twice daily Also component of fixed-dose combinations: generic lamivudine/zidovudine, Combivir®, Trizivir®	Side effects common and may impact adherence: nausea, vomiting, headache, insomnia, fatigue Anemia, neutropenia
Lamivudine (Epivir®; 3TC)	150 milligrams twice daily Also component of fixed-dose combinations: generic lamivudine/zidovudine, Combivir®, Epzicom®, Trizivir®	Well tolerated, minimal toxicity Rash Withdrawal may cause acute hepatitis exacerbation in the setting of chronic hepatitis B
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	LPV/RTV 200/50 milligrams = 2 tablets twice daily	GI intolerance, diarrhea, nausea, and vomiting are common PR and QT prolongation reported Potential for serious or life-threatening drug interactions

Note: For more information regarding dosing, side effects, drug–drug interactions, toxicity, and monitoring, see "Antiretroviral Drug Tables" in the Pharmacy section of the National Clinician Consultation Center website (http://nccc.ucsf.edu/clinical-resources/hiv-aids-resources/pharmacy/).

pathogens (1-888-448-4911; 11 am to 8 pm daily). Additional resources and recommendations are available on the center's website (http://www.nccc.ucsf.edu).

OTHER COMMON OCCUPATIONAL EXPOSURES

Other infectious diseases require special precautions, preventive measures, and postexposure care to minimize the risk of occupational exposure. Common sources of other occupational exposures are listed in **Table 163-9**. Maintain high suspicion for disease in populations at risk, and institute isolation precautions promptly when disease is considered.

TABLE 163-8 Situations for Which Expert Consultation for Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Is Recommended

- Delayed exposure report (>72 h after exposure)
- Unknown source (e.g., needle in a sharps disposal container or laundry)
  - Decide PEP case by case based on epidemiologic likelihood of HIV exposure.
  - Do not test needles or instruments.
- Known or suspected pregnancy or breastfeeding in the exposed person
  - Provision of PEP should not be delayed awaiting expert consultation.
- Toxicity of the initial PEP regimen
  - Symptoms are often manageable without changing regimen by prescribing antimotility or antiemetic agents. Counseling and support are encouraged because anxiety may worsen side effects.
- Serious medical illness in the exposed person
  - Significant underlying illness (e.g., renal disease) or an exposed person already taking multiple medications may increase the risk of toxicity and drug interactions.
- Expert consultation can be made with local experts or by calling the National Clinician Consultation Center at 1-888-448-4911.

INFECTION PRECAUTIONS

The Centers for Disease Control and Prevention's Hospital Infection Control Practices Advisory Committee promulgates two tiers of precautions: standard and transmission based. Standard precautions assume a broad approach to healthcare personnel and patient protection by including agents transmitted by routes other than blood. Transmission-based precautions are designed for patients with documented or suspected transmissible pathogens for which additional protection beyond standard precautions is required. Transmission-based precautions are of three types: airborne, droplet, and contact. Transmission-based precautions are to be used in addition to, not in place of, standard precautions.[2-4]

STANDARD PRECAUTIONS

Standard precautions are exercised when caring for *all* patients and include hand hygiene (washing or sanitizing), gloves, mask and eye protection or face shield, gowns, handling of patient care equipment and linens, environmental controls, workplace controls, and patient location or placement depending on the indication.

Hand hygiene with soap and water or alcohol-based hand sanitizer is one of the most important ways to prevent the spread of infection. The World Health Organization recommends that healthcare workers clean their hands: (1) before touching a patient, (2) before a clean/aseptic procedure, (3) after body fluid exposure/risk, (4) after touching a patient, and (5) after touching a patient's surroundings.[26] Using sterile or nonsterile gloves does not eliminate the need for hand hygiene; hand hygiene should be performed both before and after gloves are used. It may also be necessary to clean hands between procedures on the same patient to prevent cross-contamination. Alcohol-based gel and foam products are recommended for most routine hand hygiene due to lesser time burden (which may increase adherence) and greater reduction in bacterial counts as compared with regular and antimicrobial soap.[27] However, some pathogens, such as *Clostridium difficile*, are not eradicated by alcohol-based antiseptics. Scrubbing and rinsing with soap and

TABLE 163-9 Other Common Occupational Exposures

Disease	Infective Material	Infection Control and PPE*	Vaccine Availability and Efficacy	Employee Vaccination and Testing	Postexposure Management
Tuberculosis	Aerosolized bacilli and respiratory secretions	Airborne precautions	Yes (BCG) Limited efficacy Widely used outside U.S. Not recommended in U.S.	Vaccine not recommended in U.S. Routine testing (PPD) for those in high-risk areas every 6–12 mo	Approximately 20% of exposed people become infected. CDC recommended prophylactic treatment after exposure, but research does not support that practice.[14]
Measles (rubeola)	Respiratory secretions and droplet nuclei	Airborne precautions	Yes Highly effective Monovalent or combination	Primary immunization recommended 2 doses >4 wk apart	Previously unvaccinated individuals: Vaccine may prevent disease if given within 72 h of exposure. IG conveys temporary immunity and may prevent or modify disease if given within 6 d of exposure.[15,16]
Mumps	Respiratory secretions	Droplet precautions	Yes Highly effective Monovalent or combination	Primary immunization recommended 2 doses >4 wk apart	Previously unvaccinated individuals: Vaccine is unlikely to prevent disease but is not harmful and may protect in case of future exposure. IG is not effective and not recommended.[15]
Rubella	Respiratory secretions and contact	Droplet and contact precautions	Yes Highly effective Monovalent or combination	Primary immunization recommended 2 doses >4 wk apart	Previously unvaccinated individuals: Vaccine is unlikely to prevent disease but is not harmful and may protect in case of future exposure. IG is not effective and not recommended.[15]
Varicella zoster (herpes zoster, chickenpox, shingles)	Respiratory secretions and aerosols from vesicular fluid	Airborne and contact precautions†	Yes Highly effective	Immunization (or evidence of immunity) recommended[17,18]	Previously unvaccinated individuals: Vaccine may prevent infection. VZIG conveys temporary immunity and may prevent or modify disease if given within 4 d. Employee should be on furlough from day 10–21 following exposure.[17]
Influenza	Respiratory secretions	Droplet precautions Recommend exclusion or reassignment of employees who are ill with fever and respiratory symptoms	Yes Efficacy varies annually	Annual immunization recommended[19,20]	Individuals not vaccinated within the past year: Vaccine will not prevent disease but is not harmful and may protect in case of future exposure. Consider oseltamivir or zanamivir for chemoprophylaxis in higher-risk employees who experience a significant influenza exposure.[21]
Meningococcus	Respiratory secretions	Droplet precautions	Yes Not recommended without specific indication[22]	None recommended	Chemoprophylaxis should be reserved for individuals who performed mouth-to-mouth, intubated, or suctioned the patient without a mask in the setting of confirmed meningococcus.[23,24] Rifampin 10 milligrams/kg (max 600 milligrams/dose) every 12 h for 2 d Ceftriaxone 250 milligrams in single dose Ciprofloxacin 500 milligrams in single dose
Severe acute respiratory syndrome[25]	Respiratory secretions and droplet nuclei	Airborne and contact precautions Eye shield	None available	None recommended	No disease-specific recommendations
Scabies (mites)	Direct and indirect contact	Contact precautions	None	None available	No disease-specific recommendations
Pediculosis (lice)	Direct and indirect contact	Contact precautions	None	None available	No disease-specific recommendations

Abbreviations: BCG = bacillus Calmette-Guérin; CDC = Centers for Disease Control and Prevention; IG = immunoglobulin; PPD = purified protein derivative; PPE = personal protective equipment; VZIG = varicella zoster immunoglobulin.

*Standard precautions should always be applied in addition to other recommended precautions.

†If all skin lesions can be covered completely, then contact precautions alone are acceptable.

water is recommended whenever there is visible soiling of the hands or concern for *C. difficile*.

Gloves Use clean, nonsterile gloves whenever there is a chance of touching blood, body fluids, secretions, excretions, and contaminated items. Change gloves between tasks and procedures involving blood or other potentially infectious materials. Remove gloves and clean hands before touching noncontaminated items or environmental surfaces (e.g., phones, light switches, writing implements) or other patients.

Masks and Shields Facemasks, eye protection, and face shields that are fluid resistant are worn to protect mucous membranes of the eyes, nose, and mouth during patient care activities and procedures likely to generate splashes or sprays of blood, body fluids, secretions, excretions, and infectious materials. Examples of tasks for which masks or shields are recommended include hemorrhage control, airway management, needle decompression, childbirth, and nasogastric tube placement.[28] Replace masks that are soiled, moistened by the user's exhaled vapor, or contaminated by fluids as soon as possible. Protective function may be lost when the barrier device is saturated.

Gowns Clean, nonsterile gowns that are fluid resistant protect the worker's skin and clothing during patient care activities and procedures likely to generate splashes or sprays of blood, body fluids, secretions, and excretions. Sample tasks for which impervious gown is recommended include profuse GI bleeding, hemorrhage control, trauma resuscitation, and childbirth. Replace soiled gowns as soon as possible because barrier protection is lost if the garment is saturated. Use sleeve protectors, booties, and leggings when exposure to a large volume of contamination is anticipated.

Disposal Handle patient care equipment and linens soiled with blood, body fluids, secretions, and excretions specifically to avoid skin and mucous membrane exposure, contamination of clothing, and transfer of microorganisms to other patients and environments. Reusable items should be cleaned and reprocessed to eliminate infectivity. Promptly discard single-use items.

ENVIRONMENTAL AND WORK PRACTICE CONTROLS

Environmental controls include hospital procedures for the decontamination of objects in patient care areas. Clean and disinfect environmental surfaces, beds, bed rails, bedside equipment, and frequently touched surfaces between patient uses.

Workplace controls (work practice controls) include proper disposal of needles and other sharp instruments. Avoid recapping, excessive handling, and manipulation of sharp devices. Use safety devices when available, and replace sharps containers before they overflow. Patients who contaminate the environment or cannot assist in their own hygiene should be located in a private room when possible.

AIRBORNE PRECAUTIONS

In addition to standard precautions, use airborne precautions for patients known to be infected or suspected of being infected with microorganisms transmitted by airborne droplet nuclei. Airborne precautions also apply to small-particle (<5 μm) residue of evaporated droplets containing microorganisms that remain suspended in the air and can be widely dispersed by air currents. Examples of infectious agents spread by this method are listed in **Table 163-10**.[2]

ISOLATION

Isolate ED patients requiring airborne precautions in an **airborne infection isolation room** with (1) monitored negative air pressure in relation to surrounding areas, (2) 6 to 12 air changes per hour, and (3) discharge of the room air to the outdoors or high-efficiency filtration of the air before it is circulated to other areas in the hospital. The patient must remain in the isolation room with the door closed. Limit the movement in and out of the room and transportation of the patient. When movement is unavoidable, the patient should wear respiratory protection to avoid contamination of other areas within the hospital. Healthcare workers entering the room must wear respiratory protection, such as a personalized, fitted mask with efficient filters (approved particulate respirator).

TABLE 163-10 Airborne-Spread Infectious Diseases

- Rubeola (measles)
- Varicella (including disseminated zoster)
- Tuberculosis

TABLE 163-11 Droplet-Spread Infectious Diseases

- Invasive *Haemophilus influenzae* type B (including meningitis, pneumonia, epiglottitis, sepsis)
- Invasive *Neisseria meningitidis* (including meningitis, pneumonia, sepsis)
- Serious bacterial respiratory infections
- Diphtheria (pharyngeal)
- *Mycoplasma* pneumonia
- Pertussis
- Pneumonic plague
- Streptococcal pharyngitis, pneumonia, scarlet fever
- Serious viral infections
- Adenovirus
- Influenza (including H1N1)
- Mumps
- Parvovirus B19
- Rubella

DROPLET PRECAUTIONS

In addition to standard precautions, use droplet precautions for patients known to have or suspected of having serious illnesses transmitted by large particle droplets (>5 μm). Droplets are generated during talking, sneezing, or coughing and during the performance of procedures. Examples of infectious agents spread by this method are listed in **Table 163-11**.[2,4]

ISOLATION AND FACEMASKS

Place the patient in a private room when possible. Prioritize patients with excessive cough and sputum production to available single-patient rooms. Special air handling and ventilation are not required, and the door may remain open. If a private room is not available, the patient may be placed in a room with other patients who have active infections with the same microorganism (i.e., cohorting). If cohorting is also not possible, place a mask on the patient and maintain a spatial separation of at least 3 ft (1 m) between the infected patient and other patients and visitors. Avoid placing patients with droplet precautions in the same room with patients at increased risk for adverse outcomes from infection. Limit the movement and transportation of patients with droplet precautions. When movement is required, place a facemask on the patient. Healthcare workers should wear facemasks when working within 3 ft (1 m) of the patient. Healthcare workers should wear respiratory protection equivalent to a fitted N95 filtering respirator or higher level of protection during aerosol-generating procedures such as suctioning. Change protective attire and perform hand hygiene between contacts with all patients.

CONTACT PRECAUTIONS

In addition to standard precautions, use contact precautions when patients are known to have or suspected of having serious illnesses transmitted by direct patient contact or contact with items in the patient's environment. Examples of such infectious diseases are listed in **Table 163-12**.[2,4]

Change gloves whenever the examination and care of a patient result in contact with infectious materials and a high concentration of microorganisms (wound drainage or fecal material). When expecting contact with infectious materials (incontinence, dressing changes, attention to colostomy), wear a clean, nonsterile gown and gloves. Remove the gown

TABLE 163-12 Contact-Spread Infectious Diseases

- Multidrug-resistant infections or colonization (GI, respiratory, skin, wound sites)
- Enteric infections with low infective dose or prolonged environmental survival
- *Clostridium difficile*
- Enterohemorrhagic *Escherichia coli* 0157:H7
- *Shigella*
- Hepatitis A
- Rotavirus
- Respiratory syncytial virus
- Parainfluenza virus
- Enteroviral infections
- Skin infections that are highly contagious or that may occur on dry skin:
  - Diphtheria (cutaneous)
  - Herpes simplex virus (neonatal or mucocutaneous)
  - Impetigo
  - Major, noncontained abscesses, cellulitis, decubiti
  - Pediculosis
  - Scabies
  - Staphylococcal furunculosis
  - Herpes zoster (disseminated or in an immunocompromised host)
  - Viral hemorrhagic conjunctivitis
  - Viral hemorrhagic infections (Ebola, Lassa, Marburg, Crimean-Congo hemorrhagic fever)

and gloves before leaving the care area. Wash hands with an antimicrobial agent or waterless antiseptic after removal of gloves, and avoid contact with potentially contaminated environmental surfaces or items in the room after hand washing.

Limit transportation and movement of the patient. When movement is required, cover contaminated areas with large, bulky dressings. Bulky, adsorbent, leakproof dressings contain contaminated secretions and limit spread of disease.

Durable, multiuse medical equipment (e.g., blood pressure cuffs, stethoscopes, bedside commodes) should be dedicated to a single patient (or cohort of similarly infected patients). Personal and departmental medical equipment (e.g., stethoscopes, US machines) should be thoroughly cleaned between patient contacts to avoid contamination.

LATEX ALLERGY

Rubber latex is a manufactured polymer that exhibits excellent tensile strength, elasticity, and barrier capacity.[29] Rubber latex is in many medical products, including gloves (for surgery, examination, and housekeeping and cleaning), intravascular devices (balloon catheters, IV tubing, and ports), airway devices (nasopharyngeal airways, endotracheal tubes, and oxygen masks), tourniquets, blood pressure cuffs, ECG leads, tape, and dressings.

REACTIONS TO LATEX

Immune reactions to latex products may take three forms: irritant, contact dermatitis (type IV), and immunoglobulin E (type I).

Irritant reactions are nonimmune in nature and result in dry dermal erythema limited to the site of contact.

Contact dermatitis occurs as a result of dermal exposure to chemicals used in the manufacturing of latex products. This type IV reaction, which may extend beyond the site of contact, results in a dry dermal erythema, pruritus, weeping, and vesiculation. Such loss of skin integrity permits the access of latex proteins to the immune system and may result in an immunoglobulin E–mediated response.

An immunoglobulin E (type I) response is an immunologic reaction to protein allergens contained in latex. Clinical manifestations of such reactions include urticaria, asthma, rhinitis, angioedema, laryngeal edema, and anaphylaxis. Immunoglobulin E reactions may occur because of mucosal, dermal, contact, or inhalational exposure to lubricant powder.

At highest risk of developing immunoglobulin E–mediated latex allergy are those with repeated or chronic exposure to latex and those who are atopic. Healthcare workers are at increased risk of developing latex allergy due to high-intensity exposure.

LATEX-FREE PRODUCTS AND MINIMIZING LATEX ALLERGY

Many latex-free medical products are available to substitute for common latex products. Prevention of disease in healthcare workers is critical and requires the use of synthetic or low-allergen powder-free gloves.[29,30] Healthcare personnel may also use nonlatex gloves for workplace activities that do not involve contact with infectious materials; use synthetic or low-allergen powder-free gloves when handling infectious materials; avoid oil-based hand lotions or creams when wearing latex gloves (to prevent glove deterioration); wash hands with soap and water thoroughly upon removal of latex gloves; frequently clean work areas and equipment contaminated with latex-containing dust; obtain education and training regarding latex allergy; and recognize the symptoms of latex allergy. Hypoallergenic latex gloves do not reduce the risk of latex allergy but do reduce reactions to chemical additives in latex.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 14

Neurology

CHAPTER 164

Neurologic Examination

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INTRODUCTION

In most patients, the physical examination confirms thoughts formulated during history taking that are often the key to patient evaluation. Time of onset, symptom progression, associated complaints, and exacerbating factors are important historical points to guide appropriate examination and testing. The neurologic examination does not exist in isolation from the general physical examination or imaging procedures, and it is unusual for the neurologic examination to delineate a problem not already suggested by the patient's history or general physical examination. Few findings of the neurologic examination are pathognomonic of clinical conditions or are sufficiently specific that examination alone secures the diagnosis. Further complicating the value of the neurologic examination is that the sensitivity and specificity of different examination techniques have not been rigorously investigated, and the degree of interobserver variability is not known. The uncooperative patient or the patient with altered mental status presents additional challenges in performing a detailed examination.

The idea of performing a "complete" examination in the ED is impractical, because a "complete" examination frequently is neither appropriate nor required. An adequate examination is one that is sufficient for the task at hand. Examination of children follows the same framework as that for adults, but even more information is gathered indirectly by observation. For example, interacting with a child while playing with a toy or other object allows the examiner to assess vision, extraocular motion, coordination, and strength as the child reaches for and grasps the toy.[1] Traditional neurologic formulation follows a three-tiered approach: (1) Is there a lesion of the nervous system? (2) Where is the lesion? (3) What is the lesion? The examination detailed in this chapter is arbitrarily divided into eight sections with basic and advanced levels described for each section.

ORGANIZATIONAL FRAMEWORK

Organization of the neurologic examination into a framework of subsections is a convenient technique. Some of the tests grouped in a section assess several aspects of nervous system function, and listing of tests in a particular section is for organizational convenience. For example, visual field testing, although technically a test of higher cortical function, is listed with cranial nerve testing because the examining physician may find it easier to evaluate visual fields during that portion of the examination assessing cranial nerve function. One organizational scheme divides the examination into eight elements:

1. Mental status testing
2. Higher cerebral functions
3. Cranial nerves
4. Sensory examination
5. Motor system
6. Reflexes
7. Cerebellar testing
8. Gait and station

MENTAL STATUS TESTING

A mental status examination is part of every patient encounter. The observation may be brief and descriptive, such as, "The patient is awake, alert, and conversant," or it may be quite detailed. Mental status assesses the emotional and intellectual functioning of the patient. It is important to make some assessment of mental status since the patient with an abnormal mental status cannot be relied on for an accurate medical history.

Major elements of mental status testing are assessment of appearance, mood, and insight; assessment for thought disorders or abnormal thought content such as hallucinations; and testing of the sensorium. *Sensorium* is a term for the appropriate awareness and perception of consciousness. Mental status testing is covered more fully in Chapter 168, "Altered Mental Status and Coma."

One key element in mental status testing is assessment of attention and memory. Attention testing is easily performed with digit repetition. The average adult of normal intelligence should be able to repeat six or seven digits forward and four or five digits backward. Failure to do so may suggest confusion, delirium, or a problem with language perception. Often this represents a problem with attention rather than with memory. Memory is a complex process but is often simply broken into long-term and short-term activities. *Long-term memory* is recall of events of some months or years ago. *Short-term memory* is assessed by asking about events of the day or by three-object recall at 5 minutes. State three items and ask the patient to repeat; reassess at 5 minutes to obtain a gross assessment of short-term memory function. Failure to repeat the items immediately after presentation is likely an indication of an attention problem rather than of a memory problem.

Evaluation by screening tools is described in Chapter 168. Other screening tests for depression, substance abuse, or other problems are outside the scope of this chapter.

In general, patients with abnormal mental status, especially attention problems or disorientation, are more likely to have medical problems rather than functional or psychiatric causes. If a patient suffers from significant inattention, it is unlikely that the examiner will truly be able to determine whether the primary problem is one of cognition or attention.

HIGHER CEREBRAL FUNCTIONS

Assessment of higher cerebral functions tests neurologic tasks that are thought to be processed in the cerebral cortex. Language function defines the dominant hemisphere. The majority of the population is right-handed; for 90% of these patients, the left hemisphere is where language functions reside; hence, they are referred to as *left-hemisphere dominant*. Even in left-handed patients, most will be left-hemisphere dominant for language. Thus, a large cortical stroke affecting the cortex of the dominant hemisphere (the left hemisphere in most patients, whether they are left- or right-hand dominant) likely will affect language functions.

The nondominant hemisphere is the right hemisphere in most people. The nondominant hemisphere is concerned with spatial relationships. Often a nondominant hemispheric problem is suspected in the ED when the patient has consistent visual inattention to a care provider approaching from one side (usually the patient's left side).

Higher cerebral function pragmatically involves the assessment of language. For a patient with speech that is difficult to understand, a fundamental distinction must be made between *dysarthria* and a *dysphasia*

(aphasia and dysphasia are often used interchangeably in clinical practice). Dysarthria is a mechanical disorder of speech resulting from difficulty in the production of sound from weakness or incoordination of facial or oral muscles; this may result from a motor system problem (cortical, subcortical, brainstem, cranial nerve, or cerebellar), but it does not represent a disorder of higher cerebral function. Dysphasia is a problem of language resulting from cortical or subcortical damage; the portion of the brain concerned with comprehension, processing, or producing language is impaired.

There are many different types of aphasias, but a simplified scheme is sufficient for assessment in the ED.[2] A description of aphasia into fluent, nonfluent, or mixed patterns is adequate for initial testing and for communicating with other physicians.

BASIC

Normal conversation monitoring for correct responses is the common screening examination for a language disorder. If suspicion of a language disorder exists, a series of assessments allows categorization of the aphasia.

Test comprehension initially by the ability to follow simple commands. Asking the patient to identify common objects may also be part of the assessment. Use commonly available objects, such as a watch or a pen, as a stimulus. Query the patient regarding the names of different parts of the objects. Ask the patient to demonstrate how an object is used. The inability to show how an object is used, assuming hearing and motor functions are intact, may represent an apraxia, which is defined as the inability to perform a willed act.

In a nonfluent aphasia (a rough synonym is motor or expressive aphasia), the speed of language and the ability to find the correct words may be impaired. A common type of nonfluent motor aphasia is known as *Broca's aphasia*. Speech may be halting and slow, with stops between words or word fragments.

In a fluent aphasia (a rough synonym is auditory or receptive aphasia), the quantity of word production is normal or even increased. Sentences may have normal grammatical structure with normal rhythm, and intonation may be clearly articulated. However, language is impaired, and the listener may be struck by peculiarities of conversation that lack appropriate content. Incorrect words may be substituted within sentences that may be sound-alike words or words with similar yet incorrect meanings. A global or mixed aphasia involves elements of fluent and nonfluent aphasias and is the most common type encountered in clinical practice.

Nondominant hemisphere problems may show problems of auditory inattention, visual inattention, or sensory inattention.

ADVANCED

Testing of mental status and cognitive function requires an appreciation of cultural context and language barriers. Further assessment of comprehension may involve showing the patient a picture and asking for the patient's interpretation of the picture while noting if the content is correctly described and if the sentence structure and word selection of the descriptions are correct.

Assessing the ability of the patient to repeat a phrase may be a key point in delineating some types of fluent aphasias. Typically, the ability to repeat short words is more impaired than the ability to repeat longer words. A classic test involves asking the patient to repeat the phrase, "No ifs, ands, or buts." In one type of fluent aphasia, *Wernicke's aphasia*, comprehension is impaired, as is repetition.

Paraphasic errors may be further characterized in patients with fluent aphasia. Literal paraphasic errors are ones in which parts of words are replaced by incorrect sounds. The use of *spool* when *spoon* is meant is an example of a literal paraphasic error. At times, the errors may reach the point where the substitutions are not understandable, and neologisms (meaningless collections of syllables that take the place of a words in conversation) are produced. Verbal paraphasic errors involve substitutions of correct words for others; for example, a patient may wish to use *spoon* in a sentence and substitute *fork* or even *bike*; the word is a correct word, but the meaning of the sentence is transformed erroneously. A patient aphasic in speaking will also be aphasic in written communication.

A sequence of simple commands such as requesting the patient to draw a circle and then placing numbers like the numbers on a clock may reveal constructional errors. A response consistent with dysfunction of the nondominant hemisphere might be numbering half the clock face and stopping or placing all the numbers around one half of the circle.

Impairment of sensory perception on the cortical level may involve the inability to distinguish objects by touch alone. Implied in this testing is that the primary sensory modalities (sharp, light touch, etc.) are intact. In cases of nondominant hemisphere lesions, the ability to identify objects placed in a hand, such as coins, may be impaired.

SPECIAL CIRCUMSTANCES

A fluent aphasia may so severely impair communication that the patient is thought to be intoxicated or psychotic. Pay attention to the pattern of speaking—this may give the first indication of a language problem, and further constructional or language testing may demonstrate the presence of an aphasia.

CRANIAL NERVES

BASIC

A survey of the cranial nerves is often an integral part of neurologic assessment. Much information may be gathered informally. Look for facial asymmetry (cranial nerve VII) at rest or with movement. Lingual movement (XII) and other facial movements may be inferred during conversation if articulation is good. However, a more formal approach often is used in examination. Most examiners start with cranial nerve II in testing; cranial nerve I (olfactory) testing has infrequent application in emergency medicine.

Cranial nerve II is the optic nerve active in the afferent function of light and visual perception. Common tests for optic nerve function include visual acuity and stimulation for pupillary reactivity. The response to bright light stimulation involves direct and indirect (consensual) pupillary responses. This is a reflex arc, with the afferent limb being cranial nerve II and the efferent limb of the arc being cranial nerve III, which carries the pupilloconstrictors. A bright light directed into one eye should cause a brisk constriction of equal magnitude in both pupils. In the swinging flashlight test, observe the pupils as the light is slowly moved from one pupil to the other. A seemingly paradoxical dilation of one pupil as the light is moved onto that pupil may indicate optic nerve dysfunction of that eye; this is referred to as an *afferent pupillary defect* (see Chapter 241, "Eye Emergencies").

Cranial nerves III, IV, and VI are concerned with extraocular eye movements (see Chapter 241). Tracing an object through a full-H pattern allows assessment of the different cranial nerves. Cranial nerve VI innervates the lateral rectus muscle, which abducts the globe, moving it laterally away from the midline; this lateral movement will be impaired or lost in the case of cranial nerve VI palsy. In fact, the unopposed adduction movement of medial rectus muscle innervated by cranial nerve III may result in the globe being medially deviated. Cranial nerve III innervates the extraocular muscles that adduct each eye and those that elevate and depress the globe. Impairment of cranial nerve III will reveal several abnormalities of extraocular movement, reflecting weakness in the innervated muscles. A complete paresis of cranial nerve III will show a dilated pupil in a globe deviated downward and outward. An isolated cranial nerve IV weakness may be hard to detect; cranial nerve IV supplies the superior oblique muscle that elevates and intorts the globe.

Cranial nerve III also carries the parasympathetic pupilloconstrictors to the eye; a lesion of cranial nerve III may impair those fibers, resulting in unopposed dilatation and a pupil larger than in the unaffected eye. Ptosis from levator muscle paralysis may be another finding of cranial nerve III paresis.

Cranial nerve V has motor and sensory functions. It supplies the muscles of mastication and is assessed by appreciating the masseter

bulk. The sensory component of cranial nerve V supplies the cornea; the corneal reflex is a reflex arc involving cranial nerves V and VII. Cranial nerve VII supplies the muscles for facial movement as well as facial proprioception.

Cranial nerve VIII has auditory and vestibular afferent components. Cranial nerves IX and X are tested by observing pharyngeal musculature and gag reflexes. Cranial nerve XI is assessed by a shoulder shrug. Cranial nerve XII controls lingual movement and can be assessed by asking the patient to stick out the tongue and observing for any asymmetry of motion.

ADVANCED

In approximately 20% of the population, some degree of physiologic anisocoria on the order of 1 to 2 mm may be present. Small differences in pupillary size in otherwise asymptomatic patients likely represent this normal variant. A peripheral lesion of cranial nerve VII will cause complete facial paralysis on the same side as the lesion ("peripheral VIIth pattern"). A cortical lesion (often stroke) results in weakness of the lower and midface on the opposite side of the injury with preservation of motor function in the upper face ("central VIIth pattern"). This is due to the bilateral cortical upper motor neuron innervation of the forehead musculature present in most patients.

SPECIAL CIRCUMSTANCES

In the comatose patient, a **unilaterally dilated pupil** that is unreactive or reacts sluggishly to light may represent third nerve dysfunction or paresis from impingement of the oculomotor (III) nerve at the tentorium; this finding is consistent with the uncal herniation syndrome.

Vertigo often is a symptom from a vestibular system dysfunction but may result from a CNS disorder such as posterior circulation stroke. Observe the patient for nystagmus while looking ahead; if nystagmus is present while simply looking ahead, especially if vertical or direction-changing, a central cause of vertigo is likely. If **vertical skew gaze** is present or is provoked by alternately covering each eye with the patient looking directly ahead, a central cause may also be present.

The horizontal head impulse test (HIT) is a bedside maneuver to detect peripheral vestibular disease.[3] Assess the HIT by rapidly rotating the head to one side then the other while asking the patient to continue to look at a target; normally the vestibular-ocular reflex involuntarily moves the eyes while maintaining visual fixation on the target. With peripheral vestibular problems, the inability to maintain visual fixation during head rotation results in a rapid corrective jerking (saccade) back to the target; this is an abnormal HIT. In patients with acute persistent vertigo from stroke (central cause of vertigo), a normal finding with the HIT (visual fixation maintained, no rapid saccadic movement observed) reliably identified patients with a central cause of acute persistent vertigo. However, an abnormal test (positive saccadic movement observed) occurred in patients with both peripheral and central causes of vertigo.[4] Two additional maneuvers were advocated to be used in conjunction with the HIT to reliably exclude central causes of vertigo. Examination for nystagmus and assessment for skew gaze were added to HIT; this was termed HINTS testing (head impulse, nystagmus type, test of skew).[4,5] Nystagmus that changes direction with gaze to either side is predictive of a central lesion, as is spontaneous vertical or multidirectional nystagmus.[6] Skew deviation refers to misalignment of the eyes. Although subtle at times, it may be unmasked by alternately covering each eye while the patient fixes gaze on the examiner.[7] The HIT and HINTS exams have not been extensively analyzed in the ED setting.

SENSORY EXAMINATION

BASIC

The sensory evaluation can be key in some patients with sensory complaints. The primary sensory modalities are light touch, pinprick, position, vibration, and temperature sense. Because of variability in neuroanatomy, at times, dissociation of these modalities occurs and allows localization of problems to anatomic areas within the CNS.

Practically establishing that touch or pinprick is perceived in all extremities is often the only sensory assessment needed in a screening examination. However, if touch or pinprick is not intact or if peripheral nerve or spinal cord injury is suspected, additional detailed examination is usually necessary.

Position testing is best used for the detection of peripheral neuropathy or posterior column spinal cord disease. Position and vibration sensations are conveyed in the posterior columns of the spinal cord, so that there is no need to test both position and vibration—just test one.

ADVANCED

Spinal cord dermatome levels are illustrated in **Figure 164-1**. If sensory alteration conforms to a level or selectively involves specific dermatomes, further localization to the peripheral nerve or nerve root may be possible.

If primary sensory modalities are intact, then testing of higher sensory functions may be pursued; these are covered in the section on higher cerebral functions.

SPECIAL CIRCUMSTANCES

A few patterns of sensory loss are worthy of special mention. In cervical spinal cord injury or compression, an area of apparent sensory demarcation often appears to be just above the nipples. This transverse sensory level suggests a spinal cord lesion in the low cervical to high thoracic area. Most cervical dermatomes are represented in the upper extremity and not in the trunk (see Figure 164-1), and further testing is necessary to delineate the sensory level.

With suspected spinal cord injury, test the area of the perineum for sensation. The sacral dermatomes are distributed in an onion skin pattern around the perineum and are represented only in that region. The demonstration of a preserved island of sensation around the perineum may be the only sign of an incomplete spinal cord injury, which has a different prognosis than a complete spinal cord injury.

Some general comments may be made about patterns of sensory alterations. In general, a half-body sensory loss or alteration suggests cortical or subcortical lesions. A localized problem in one limb suggests a peripheral nerve or nerve root problem, although there are other possible locations of abnormalities in the CNS.[8]

MOTOR SYSTEM

There is more to evaluation of the motor system than simple assessment of strength. Muscle bulk and muscle tone are basic areas of assessment.

BASIC

Muscle tone may be characterized as normal, decreased, or increased. Assess tone by movement of muscle groups and appreciating any resistance to movement. Ask the patient to relax and not resist. Increased tone is greater than normal resistance to passive motion. **Cogwheeling** is transient increase or catching in resistance followed by release to the movement. Assess axial or truncal tone by standing behind the patient, grasping the shoulders, and gently moving the shoulders back and forth in a gentle rotation. A patient with normal tone will offer little resistance to repeated motions, and some spontaneous swing of the arms will be noted. A patient with increased axial tone (e.g., Parkinson's disease) may turn without the arm swing.

Simply having the patient hold the arms outstretched with palms upward and observing for any inward rotation or downward drift is a very sensitive sign for upper extremity weakness (**pronator drift**); this also may be assessed in unresponsive patients (**Figure 164-2**). If both arms are held outright at the same time, comparison is easy, with observation of the upper extremity of one side as opposed to the other. A similar maneuver may be performed in the lower extremities. Another sensitive test for a subtle hemiparesis is the forearm-rolling technique.

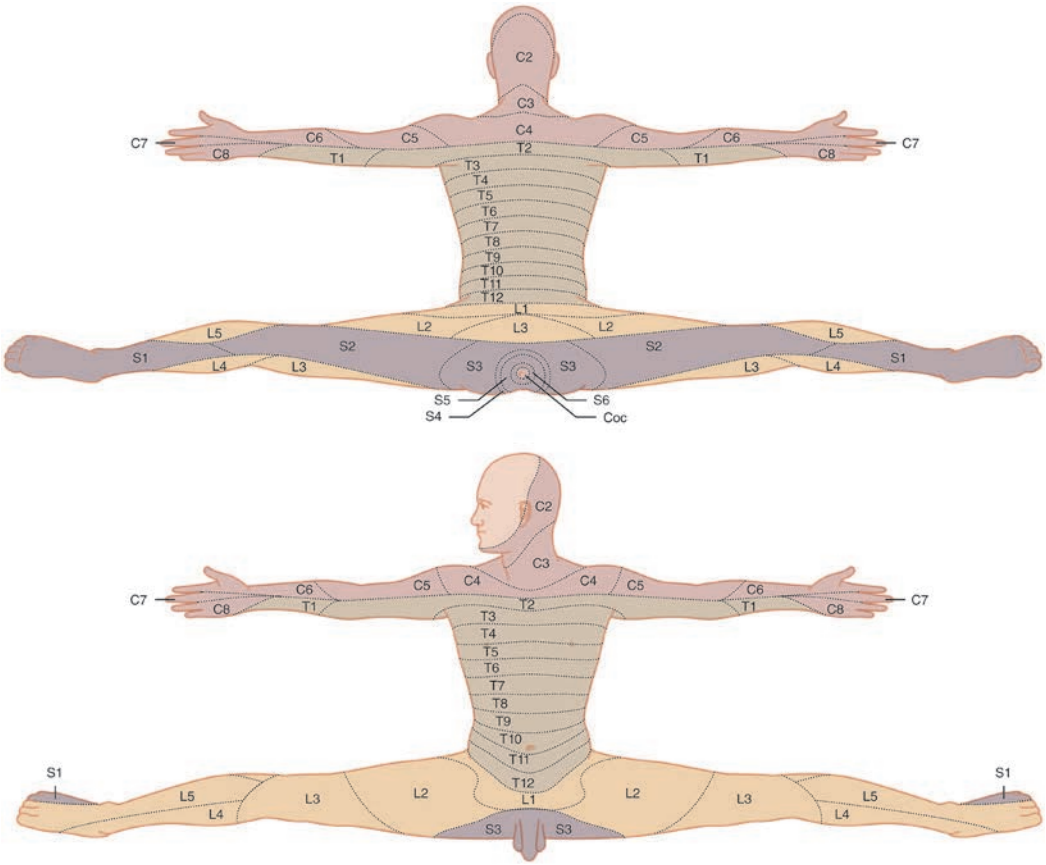

FIGURE 164-1. Sensory dermatomes.

With the forearms outstretched, ask the patient to make tight circles with each arm. The movements should be small and rapid. Asymmetry or slowness with one arm suggests a weak limb.[9] Decreased speed of foot tapping also may suggest weakness and an upper motor neuron problem.[10]



FIGURE 164-2. Testing for weakness in the comatose patient; diagram illustrates assessment of muscular tone in a patient with a right hemiplegia. A similar maneuver may be used in the conscious patient.

Tremor can be difficult to characterize, and there are many types of tremor. Action tremors, those that are absent at rest but evident with action or sustained limb position, include those from caffeine, hyperthyroidism, and alcohol or sedative withdrawal. Essential familiar tremor is also an action tremor. Rest tremors characterize **Parkinson's disease**, with tremor present during rest, diminishing with willed movement, and then resuming with the new position.

Assessment and recording of other motor strength are best done by description of the stimulus and response. For example, the fact that the patient is able to strongly resist elbow extension or elbow flexion against the examiner is an appropriate notation.

ADVANCED

Compare muscle mass or bulk of the affected area with muscle groups of the unaffected areas. If weakness or paralysis has been present for some time, muscle wasting or atrophy may be present. Brief, rapid twitches of small parts of a muscle may represent fasciculations, which may indicate a process involving the lower motor neurons.

A formal rating scale for muscle strength exists but is not straightforward to apply. A rating of 5 is assigned for normal strength, and a rating of 4 indicates weakness and the ability to contract the muscle against some resistance. Thus, a tremendous range of strength is covered within the range of the 4 rating. A rating of 0 represents complete paresis, and a rating of 1 indicates a minimal flicker of contraction. A rating of 2 is assigned for active movement of a muscle with gravity eliminated by limb repositioning (e.g., so that elbow flexion and contraction are demonstrated by a horizontal rather than by a vertical movement). A value of 3 is assigned to a muscle able to voluntarily demonstrate full motion against gravity only. It is better for the examiner to describe the strength of a muscle by noting the amount of resistance than by invoking what may be a little-used scale and erroneously applying a rating.

Listings of some muscle innervations, actions to test, and dermatomal representations are found in **Tables 164-1** and **164-2**.

TABLE 164-1 Muscle Innervation: Shoulder and Upper Extremity

Nerve	Action to Test	Muscle*
Long thoracic	Forward shoulder thrust	Serratus anterior
Dorsal scapular	Elevate scapula	Levator scapulae
Suprascapular	Arm external rotation	Infraspinatus; C5, C6
Axillary	Abduct arm (>90 degrees)	Deltoid; C5
Musculocutaneous	Flex and supinate arm	Biceps brachii
Ulnar	Ulnar flexion of hand	Flexor carpi ulnaris; C7, C8,† T1
	Flex DIP of fingers 4 and 5	Flexor digitorum profundus
	Thumb adduction	Adductor pollicis; C7, C8†
	Abduction of finger 5	Abductor digitorum minimi
	Opposition of finger 5	Opponens digitorum minimi
	Flexion of finger 5	Flexor digitorum minimi brevis
	Finger abduction and adduction	Interossei; C8, T1†
	Flex PIP and extend DIP of fingers 4 and 5	Lumbricals 3 and 4
Median	Forearm pronation	Pronator teres
	Radial hand flexion	Flexor carpi radialis; C7, C8, T1
	Hand flexion	Palmaris longus
	PIP flexion of fingers 2–5	Flexor digitorum superficialis
	Abduct thumb at the metacarpophalangeal	Abductor pollicis brevis
	Flex proximal phalanx thumb	Flexor pollicis brevis; C7, C8†
Anterior interosseous	Flex DIP fingers 2–5	Flexor digitorum profundus (radial)
	Flex thumb interphalangeal	Flexor pollicis longus
	Oppose thumb	Opponens pollicis; C8, T1†
	Flex PIP and extend DIP of fingers 2 and 3	Lumbricals 1 and 2
Posterior interosseous	Extension of digits 2–5	Extensor digitorum
	Ulnar hand extension	Extensor carpi ulnaris
	Thumb abduction	Abductor pollicis longus
	Thumb extension	Extensor pollicis longus and brevis
	Index finger extension	Extensor indicis proprius
Radial	Forearm extension	Triceps brachii; C6, C7,† C8
	Forearm flexion	Brachioradialis; C5, C6
	Radial hand extension	Extensor carpi radialis
	Forearm supination	Supinator

Abbreviations: DIP = distal interphalangeal joint; PIP = proximal interphalangeal joint.

*Dermatomal representations are listed after some muscles.

†Predominant dermatome.

TABLE 164-2 Muscle Innervation: Hip and Lower Extremity

Nerve	Action to Test	Muscle*
Femoral	Hip flexion	Iliopsoas; T12, L1,† L2, L3
	Leg extension	Quadriceps femoris; L2, L3,† L4
Obturator	Thigh adduction	Pectineus
		Adductor longus, brevis, magnus; L2, L3, L4
		Gracilis
Superior gluteal	Thigh abduction	Gluteus medius and minimus
	Thigh flexion	Tensor fascia lata
	Lateral thigh rotation	Piriformis
Inferior gluteal	Thigh abduction	Gluteus maximus
Sciatic (trunk)	Leg flexion	Biceps femoris; L5,† S1, S2
		Semitendinosus
		Semimembranosus
Deep peroneal	Foot dorsiflexion and supination	Tibialis anterior; L4, L5
	Toes 2–5 and foot extension	Extensor digitorum longus/brevis
	Great toe and foot dorsiflexion	Extensor hallucis longus
Superficial peroneal	Plantar flexion foot and eversion	Peroneus longus/brevis; L5, S1
Tibial	Plantar flexion and inversion	Posterior tibialis
	Flex distal phalanx toes 2–5	Flexor digitorum longus
	Flex distal phalanx great toe	Flexor hallucis longus
	Flex middle phalanx toes 2–5	Flexor digitorum brevis
	Flex proximal phalanx great toe	Gastrocnemius; L5, S1,† S2
	Knee flexion and ankle plantar flexion	Flexor hallucis brevis
	Ankle plantar flexion	Plantaris, soleus
Pudendal	Voluntary pelvic floor contraction	Perineal and sphincters; S3, S4

*Dermatomal representations are listed after some muscles.

†Predominant dermatome.

SPECIAL CIRCUMSTANCES

Although not classically described as part of the motor system examination, information regarding bladder tone and function is at times vital to the examiner. In patients with complaints of incontinence and low back pain, for example, discovery of a probable neurogenic bladder by demonstrating large US-assessed or postcatheterization **residual urine volume** might be a key to diagnosis of spinal cord compression. What is an abnormal postvoid residual bladder volume is difficult to say with certainty, and the literature is not clear on this point, but **in general, a volume of >100 mL, or certainly 200 mL, is cause for concern**.

REFLEXES

Muscle stretch reflexes are the least important part of the neurologic examination and offer little value when used in isolation. Correctly termed *muscle stretch reflexes*, the jerk or involuntary motor movement follows the stretching of muscle spindle fibers by the strike of the reflex hammer and the involuntary muscle contraction that follows. Muscle stretch reflexes serve mainly to confirm evidence collected in other parts of the history or physical examination.

Depending on the force of the reflex hammer strike and local impact factors, an elicited reflex may seemingly change from moment to moment. Make sure the patient and the muscle tested are relaxed. Often several reflex strikes are performed. Record the best response.

BASIC

Muscle stretch reflexes are graded on a scale from 1 to 4 that is not rigorously defined, with 0 representing the absence of reflex, 2 or 3 being normal, and 4 representing hyperactive reflexes. Patterns of reflex abnormalities (e.g., upper vs. lower extremity, left vs. right) may suggest a location of a problem within the CNS or peripheral nervous system.

The **Babinski response** is observation of the great toe moving upward in response to a mildly noxious stimulation applied to the lateral plantar or lateral aspect of the foot. The application of stimuli should not be hard or forceful. In adults, the normal response of the toe is to move downward to plantar stimulation. The presence of a **Babinski's sign**—that is, the abnormal reflex with movement of the great toe upward and perhaps fanning of the other toes—is the classic indicator of an upper motor neuron lesion. The reliability and accuracy of a Babinski's sign have been called into question.[10]



FIGURE 164-3. Method for eliciting ankle clonus.

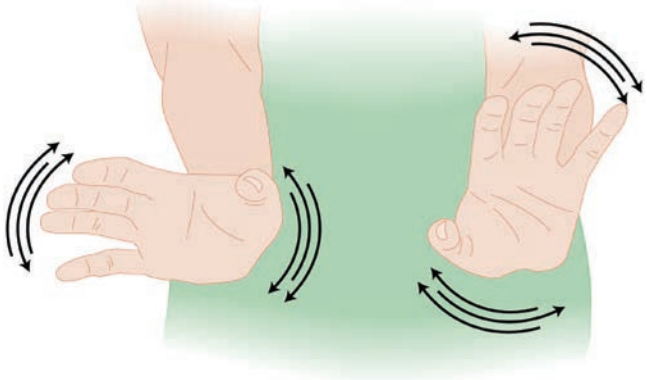

FIGURE 164-4. Pronation and supination test: cerebellar testing.

ADVANCED

Clonus is the rhythmic oscillation of a body part, typically the ankle, elicited by a brisk stretch (**Figure 164-3**). It is one sign of spasticity, in addition to a Babinski response (or slowing of foot tapping), increased muscle tone, and hyperactive muscle stretch reflexes. It may be seen in conditions of metabolic disturbance and primary neurologic dysfunction.

SPECIAL CIRCUMSTANCES

Disease processes involving upper motor neurons or their processes (cortical or spinal cord injuries) result in hyperactive reflexes, a Babinski response, and clonus. Processes injuring lower motor neurons, their axons, peripheral nerve roots, peripheral nerves, or the muscles themselves may result in hypoactive reflexes. However, in spinal cord injury or stroke, reflexes may take several hours or even days to become hyperactive, so the absence of these signs is not valuable in excluding acute spinal cord injury.

Spinal cord emergencies are high-risk clinical scenarios. Although the presence of a Babinski's sign and hyperreflexia are cardinal signs of upper motor neuron syndrome, the absence of these signs does not reliably exclude a diagnosis of spinal cord compression; pursue the diagnosis if historical or other physical examination findings suggest the possibility of this critical diagnosis.[11,12]

CEREBELLAR TESTING

The cerebellum is concerned with involuntary activities of the CNS and is a structure that helps with smoothing muscle movements and aiding with movement coordination. Very simply, the central cerebellar structures may be thought of as controlling coordination of posture and truncal movements (**axial coordination**). The lateral cerebellar structures are more coordinated with movements of the extremities (**appendicular coordination**).

BASIC

Rapidly alternating movements may be assessed by a variety of maneuvers. Hand-slapping tests, asking the patient to rapidly pronate and then supinate the forearm, and slapping the thigh with each movement is a commonly used test. The movements are normally small, and the hand slapping should be symmetric. Rapid pronation and supination of the hands is another test for dystaxia and dysmetria; the movements should be equal with both hands (**Figure 164-4**).

ADVANCED

Although usually included in cranial nerve testing, eye movements are useful in assessing cerebellar function, and abnormalities in their movements may suggest cerebellar dysfunction. Tracking an object slowly should show smooth, slow eye movements; breakup of the smooth movement may be evident and is analogous to the decompensation of movements that may occur in isolated cerebellar impairment. Similarly, if a patient is asked to look back and forth between two objects (finger-to-nose testing involves the patient looking back and forth quickly between the examiner's outstretched finger and nose), the eyes should quickly and conjugately look at the target without overshoot. These faster movements are, at least in part, reflective of intact cerebellar function. **Nystagmus** is rapid involuntary movements of the eyes that may be present with primary (straight-ahead) gaze or provoked by looking at extremes of gaze. Coarse nystagmus or other abnormalities of eye movements are at times present with cerebellar problems (see discussion above under cranial nerve testing, or see Chapter 170, "Vertigo," for more discussion of nystagmus).

GAIT AND STATION

It has been said that, if only one neurologic test could be performed, observation of the patient walking would be the most informative. The posture that the patient assumes when stationary defines the station of the patient. A variety of abnormal gaits and postures are discussed further in Chapter 169, "Ataxia and Gait Disturbances," as are different techniques of physical examination.

One feature common in many patients with cerebellar hemorrhage is the sudden inability to walk. Keep the possibility of cerebellar injury in mind when evaluating a patient with sudden onset of symptoms that include the inability to walk. Patients with cerebellar hemorrhage may also have severe nausea and vomiting. Their clinical condition is such that fine neurologic examination is simply not possible.

Acknowledgments: The authors would like to acknowledge the work of Dr. Greg Henry and Dr. Hugh S. Mickel, authors of chapters on this topic in previous editions of the study guide. Their chapters served as a check for completeness and provided some tabular information. J. Stephen Huff would like to acknowledge the influence of the late Dr. William DeMyer of Indiana University, whose instruction in the neurologic examination years ago stimulated an interest in this area.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 165

Headache

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INTRODUCTION AND EPIDEMIOLOGY

Headache is the fourth most common symptom presenting to the ED in the United States, accounting for close to 3% of total ED visits.[1] Overall, headaches affect people across all ethnic, geographic, and economic levels, with an estimated global prevalence of 47% in adults.[2]

In the ED, the approach to headache focuses on identifying patients at risk for rapid deterioration, morbidity, and mortality; rapidly identifying high-risk headache syndromes; and providing appropriate headache therapy.

PATHOPHYSIOLOGY

The brain parenchyma has no pain sensors.[3] Early theories postulating vasoconstriction and rebound vasodilatation as the cause of migraine have been refuted.[4] Numerous physiologic mechanisms play a role in the development of the various clinical headache syndromes. For example, occipital nerve irritation may lead to the development of occipital neuralgia.[5] Similarly, headaches associated with disturbances in intracranial pressure (high and low) are related to compression of, or traction on, pressure-sensitive structures in the meninges.[6] The pathophysiologic mechanisms of other headache syndromes, such as migraine headaches, cluster headaches, and toxic and metabolic headaches, are less clear. Discussion of these mechanisms is beyond the scope of this chapter.

TABLE 165-1 High-Risk Features for Headache: Clinical "Red Flags"

Onset	Sudden
	Trauma
	Exertion
Symptoms	Altered mental status
	Seizure
	Fever
	Neurologic symptoms
	Visual changes
Medications	Anticoagulants/antiplatelets
	Recent antibiotic use
	Immunosuppressants
Past history	No prior headache
	Change in headache quality, or progressive headache worsening over weeks/months
Associated conditions	Pregnancy or postpregnancy status
	Systemic lupus erythematosus
	Behçet's disease
	Vasculitis
	Sarcoidosis
	Cancer
Physical examination	Altered mental status
	Fever
	Neck stiffness
	Papilledema
	Focal neurologic signs

CLINICAL FEATURES

Although headaches are typically classified as **primary headaches** when there is no underlying cause (such as migraine, tension, or cluster headaches) and **secondary headaches** if associated with an underlying cause (such as tumor, meningitis, or subarachnoid hemorrhage), this distinction is not clinically useful in the ED setting. Rather, the emergency physician should focus on evaluating for and ruling out secondary causes of headache. Most patients with headache have conditions that are painful but benign in etiology. Identifying those at high risk for a secondary headache is the first step in management (**Table 165-1**). A high-risk cause for headache accounts for only 4% of all headaches but 10% to 14% of acute-onset ("thunderclap") headaches.[7,8] Improvement of the patient's pain with treatment does not predict benign cause of headache.

HISTORY

Features associated with high-risk headaches are as follows:

Patient Age Patients >50 years of age, with a new or worsening headache, represent a high-risk group.[9] The incidence of migraine, cluster, and tension headaches decreases with age, raising the likelihood of ominous pathology for older patients.[10] Close to 15% of patients over age 65 will have a dangerous secondary headache on neuroimaging,[11] and those over 50 have four times the rate of pathology.[7]

Onset of Symptoms The abrupt onset of severe headache, or **"thunderclap" headache**, requires immediate and thorough evaluation.[12] A thunderclap headache is defined by pain that reaches 7 out of 10 in less than 1 minute.[13] Thunderclap headache associated with intracerebral aneurysmal leak ("sentinel hemorrhage" or "herald bleed") may precede catastrophic aneurysmal rupture by days to weeks. Associated symptoms may include neck stiffness, nausea, vomiting, loss of consciousness, neurologic deficit, or altered mentation.[14] Onset of thunderclap headache during periods of exertion raises suspicion for subarachnoid hemorrhage or **arterial dissection** of the carotid or vertebrobasilar circulation. A headache with seizure, altered mental status, visual disturbance, or focal neurologic deficit may be due to posterior reversible encephalopathy syndrome[15] or reversible cerebral vasoconstriction syndrome.[16] Headaches associated with the Valsalva maneuver may herald an intracranial abnormality.[17] Rarely, spontaneous intracranial hypotension and acute hydrocephalus associated with third ventricular colloid cyst may present with thunderclap headache.[18] Other causes for thunderclap headache are listed in **Table 165-2**.

Headache Quality A change in pattern, frequency, quality, or intensity of a preexisting headache syndrome needs the same evaluation as a new-onset headache syndrome.

Fever Fever raises concern for CNS infection, such as meningitis, encephalitis, or brain abscess. However, the absence of fever does not exclude a CNS infection, especially in patients at the extremes of age and with immunocompromised states, such as human immunodeficiency virus. Headaches in patients with human immunodeficiency virus and CD4 count less than 200 cells/μL have a higher risk of intracranial pathology.[19,20]

TABLE 165-2 Causes of Thunderclap Headache

Hemorrhage	Intracranial hemorrhage
	"Sentinel" aneurysmal hemorrhage
	Spontaneous intracerebral hemorrhage
Vascular	Carotid or vertebrobasilar dissection
	Reversible cerebral vasoconstriction syndrome (RCVS)
	Cerebral venous thrombosis
	Posterior reversible encephalopathy syndrome (PRES)
Other causes	Coital headache
	Valsalva-associated headache
	Spontaneous intracranial hypotension
	Acute hydrocephalus (e.g., colloid cyst obstructing third ventricle)[18]
	Pituitary apoplexy
	Acute angle-closure glaucoma

TABLE 165-3 Clinical Features Suggestive of Migraine

Prior history of migraine	Moderate/severe intensity
Younger age	Unilateral
Multiple prior episodes	Throbbing
Aura and prodrome	Nausea/vomiting
Familiar triggers	Photophobia/phonophobia
Family history	Lasts hours
History of motion sickness	

Past Medical History The past medical history is essential in determining risk of secondary etiology for headache. A history of immunocompromised state (including human immunodeficiency virus, vasculitis, diabetes, among others) may prompt need for further evaluation. History of malignancy, trauma, current pregnancy, and recent pregnancy are suggestive of a secondary cause of headache.

Medication History Inquire about over-the-counter medications, anticoagulants, antiplatelet agents, chronic steroids, immunomodulatory agents, or antibiotics (prescribed or not) to identify patients at high risk for infection (e.g., eculizumab and its elevated risk for meningococcal infection). Chronic use of analgesic and anti-inflammatory agents may result in **rebound or withdrawal headaches**. Medication overuse is defined as use >10 times a month and is notable for ergots, triptans, and opioids.[17] Anticoagulants and antiplatelet agents increase the risk for hemorrhage, both spontaneous and traumatic.[21] The recent use of antibiotics may present with a falsely reassuring clinical appearance due to partial treatment of a potentially dangerous CNS infection.

Prior Headache History A prior history suggestive of migraine, tension, or cluster-type headaches and response to specific therapy may obviate the need for extensive ED evaluation (**Tables 165-3** and **165-4**).

Substance Use History Use of adrenergic agents such as cocaine, amphetamine, or derivative compounds such as methamphetamine increases risk of intracranial hemorrhage or the less common entity of reversible cerebral vasoconstriction syndrome.[22] Patients with a history of alcohol abuse are at increased risk of intracranial bleeding due to falls, interpersonal violence, and the potential for liver dysfunction associated with prolonged coagulation times and thrombocytopenia.

Family History Known aneurysm or sudden death in first-degree relatives raises the suspicion for intracranial aneurysm.[23] The incidence of aneurysm in patients with a family history is three to five times higher than in those without a family history. A personal or family history of autosomal dominant polycystic kidney disease also increases the risk for intracranial aneurysm. In patients with autosomal dominant polycystic kidney disease, aneurysmal rupture is more likely to occur at a younger age. The presence of migraine in a first-degree relative is associated with a two- to fourfold increased risk of developing migraine.[24]

PHYSICAL EXAMINATION

Vital Signs Headache is a common symptom associated with fever, as headache is seen in up to 60% of patients with upper respiratory tract infection symptoms.[7,25] The persistence of headache in the presence of a normalized temperature suggests consideration for further evaluation of a possible CNS infection. The presence of fever in association with neck stiffness and altered mental status represents the classic triad of meningitis. Close to 95% of patients with bacterial meningitis present with at least two of the four findings (classic triad plus headache).[26]

Severe hypertension can be associated with headache and the development of acute changes in mental status and neurologic function. Consider posterior reversible encephalopathy syndrome[27] and hypertensive emergency in such patients (see "Posterior Reversible Encephalopathy Syndrome" section).

TABLE 165-4 Clinical Features Suggestive of Cluster Headache

At least 5 attacks that meet the following criteria:	Associated **ipsilateral symptoms** (at least one):
• Severe	• Lacrimation
• Unilateral	• Conjunctival injection
• Lasts 15–180 min (untreated)	• Nasal congestion or rhinorrhea
• Circadian/circannual pattern	• Ptosis and/or miosis
	• Edema of the eyelid and/or face
	• Sweating of the forehead and/or face

Examination of the Head and Neck **Meningismus** is an important clinical clue to the presence of infection or hemorrhage.[26] Examine the ears, nose, and throat to identify otitis media and sinusitis, both of which may cause headache and contribute to the extension of infection to the CNS. Palpate for scalp tenderness and tenderness over the temporal arteries to assess for possible temporal arteritis.

Examination of the Eye Headache can occur with acute angle-closure glaucoma, scleritis, and endophthalmitis. Visual complaints require consideration of secondary etiology. Consider **acute angle-closure glaucoma** even when there is no focal ocular complaint, as the pain can be so severe the patient may fail to localize pain to the eye. Measure intraocular pressure to exclude glaucoma. Check visual acuity and visual fields and examine the pupils and eyelids, checking for signs of Horner's syndrome.

Funduscopic Examination **Papilledema** can be seen in the presence of raised intracranial pressure. However, there is typically a delay in the onset of papilledema once intracranial pressure begins to elevate, and papilledema can persist once intracranial pressure returns to normal.[28] The ability to recognize papilledema by routine direct ophthalmoscopy alone (particularly with nondilated pupils) is limited, but a panoptic ophthalmoscope provides a more reliable view of the retina.[29] Bedside US of the optic nerve sheath can also assess for papilledema.[30,31] The presence of papilledema requires CT imaging before lumbar puncture.[32]

Neurologic Examination A baseline neurologic assessment includes the following: mental status assessment; cranial nerve examination, including pupillary examination (for asymmetry or ptosis, which may suggest third nerve compression by posterior communicating artery aneurysms); assessment for other cranial neuropathies (which may raise suspicion for carcinomatous meningitis); motor examination to detect extremity weakness (particularly subtle weakness with pronator drift); reflex examination for subtle asymmetry or a Babinski reflex; and gait and coordination testing (which may be impaired in cerebellar lesions). Any neurologic deficit, including altered mental status, possesses the highest predictive value for CNS pathology.[33]

DIAGNOSIS

There are many causes of headache, each of which is diagnosed and managed differently.

LABORATORY TESTING

Routine blood testing is of limited utility in the diagnosis of acute headache and should be guided by the patient's age, history, relevant comorbidities, and medication history.

The laboratory evaluation of patients with high-risk headaches may include basic metabolic profile, CBC, coagulation panel, erythrocyte sedimentation rate, C-reactive protein, and blood cultures for possible infection.

IMAGING

Selecting an appropriate imaging study depends on the history, physical examination findings, and differential diagnosis of headache,[34-36] as well as the resources available to the emergency provider. **Table 165-5** summarizes some of the American College of Radiology and American College of Emergency Physicians recommendations for appropriate imaging. When MRI is immediately unavailable and diagnostic

TABLE 165-5 Choice of Imaging Modality

American College of Radiology

Noncontrast Head CT	MRI of Brain With and Without Contrast
• Trauma • Thunderclap headache • New headache *plus* focal neurologic deficit or papilledema • Chronic headache *plus* change in clinical features	• New-onset headache *plus* focal neurologic deficit/papilledema • Possible encephalitis • Possible vertebral/carotid dissection • Horner's syndrome • Valsalva or coital headache • Immunocompromised individual • Patient with cancer history/current cancer • Suspected temporal arteritis • Intracranial hypotension (low-pressure headache) • Headache with suspected intracranial complication of sinusitis/mastoiditis/oromaxillofacial origin • New-onset headache in pregnant woman (without contrast) • Headache of trigeminal autonomic origin • Chronic headache with *new* feature or focal deficit (CT can be first step)

American College of Emergency Physicians 2008 Clinical Policy: Which patients with headache require neuroimaging in the ED?

Patient Presentation	Recommendation
Headache and new abnormal findings in neurologic examination (focal deficit, altered mental status, altered cognitive function)	Level B (emergent noncontrast head CT)
New sudden-onset severe headache	Level B (emergent noncontrast head CT)
HIV-positive patients with a new type of headache	Level B (emergent noncontrast head CT)
Age >50 with new headache but with normal neurologic examination	Level C (urgent noncontrast head CT)

uncertainty regarding the possibility of an underlying lesion prevails, further imaging may be necessary, the timing of which will depend on the clinical circumstances and likelihood of the patient being able to follow up in a reliable fashion.[34]

If the patient presents with a typical history of headache that responds to typical measures and a normal neurologic examination, avoid neuroimaging to reduce radiation exposure. When appropriate, a noncontrast head CT is the fastest and most appropriate initial imaging study, as well as the most sensitive for detecting acute intracranial hemorrhage.[36,37]

Gadolinium-based magnetic resonance contrast agents are contraindicated for patients with renal insufficiency due to risk of nephrogenic systemic fibrosis, and intravenous contrast for CT should be carefully considered in patients with renal insufficiency, although literature suggests no association of contrast with renal injury.[38,39] Gadolinium is relatively contraindicated in pregnancy and breastfeeding women. **MRI** can be limited by claustrophobia. A discussion with the radiologist and/or radiology technical staff can clarify the safety of MRI in patients with devices or foreign bodies.

Magnetic resonance angiography is useful in detecting arterial disease (stenosis, congenital anomalies, dissection, CNS vasculitis) and should be considered in any case where there may be arterial pathology underlying the patient's symptoms. Discuss concerns for dissection with the radiologist to determine the most appropriate MRI method.

If MRI is unavailable or not clinically feasible, consult radiology regarding other appropriate imaging modalities.

LUMBAR PUNCTURE

After the clinical assessment, blood work, and imaging, the next step is to determine whether to perform a lumbar puncture (LP) and, if so, the timing of LP. LP can serve as both a diagnostic tool (as in meningitis, subarachnoid hemorrhage, intracranial hypotension, carcinomatous meningitis) and therapeutic tool (as in idiopathic intracranial hypertension).

Ideally, perform the LP with the patient in the lateral decubitus position to allow for the accurate measurement of opening pressure. Seated LP does not allow for accurate assessment of opening pressure. Opening pressure provides critical information about the patient's intracranial pressure and should be considered a routine procedure when performing LP.

The possibility of herniation in association with LP is a frequent concern of emergency providers. There is no randomized controlled trial assessing the question of when it is safe to perform an LP. **The cumulative evidence suggests that in patients with normal sensorium, no focal neurologic deficit, and without a history of immunosuppression, it is safe to proceed with LP without imaging prior to the procedure.**[40,41]

In the evaluation of patients with suspected acute bacterial meningitis, clinical signs of "impending" herniation are the best predictors of when to delay an LP because of the risk of precipitating herniation. Risk of an abnormal CT scan is elevated in patients with any of the following clinical features: a deteriorating or altered level of consciousness (particularly a Glasgow Coma Scale score of ≤11), brainstem signs (including pupillary changes, posturing, or irregular respirations), focal neurologic deficit, history of recent seizure, history of a preexisting neurologic disorder, or history of immunocompromised state. In patients with these clinical features, imaging prior to LP is appropriate, but never delay antibiotic administration while imaging is obtained. In patients without such findings, it is usually safe to perform LP without obtaining a CT scan in cases of suspected bacterial meningitis.[42]

DISPOSITION AND FOLLOW-UP

Most patients with headache can be treated and released from the ED with an appropriate follow-up plan. Identification of potential barriers to follow-up is an important step in ensuring that proper follow-up will be available to all patients, particularly for patients with limited resources or other barriers to accessing medical care. For some patients, inpatient care or observation may be warranted until symptoms improve or until testing is completed. A follow-up plan is important for patients with high-risk conditions, such as temporal arteritis or idiopathic intracranial hypertension. Follow-up is similarly important for patients with chronic headaches, given the potential for substance abuse, overutilization of resources, and repeated unnecessary imaging with potentially harmful radiation.[35]

SPECIFIC CAUSES OF HEADACHE

MENINGITIS/ENCEPHALITIS

Consider meningitis and encephalitis in patients with headache and the classic triad of fever, altered mentation, and neck stiffness.[26] Meningitis is due to the meningeal infection and inflammation, while encephalitis results from infection and inflammation of the underlying neural tissue. The combination of headache, fever, and neck stiffness is present in 44% of cases of meningitis, although 99% of patients will have at least one of these symptoms.[26] The source of infection in meningitis can be viral, bacterial, and less commonly, fungal or parasitic, with similar etiologies in encephalitis, although viral causes are most common. Have a high index of suspicion for meningitis in those with immunosuppression (particularly acquired immunodeficiency syndrome, human immunodeficiency virus, cancer history, chemotherapy, chronic steroids), which may be associated with more insidious types of meningitis such as *Cryptococcus*. An LP is indicated for suspected meningitis. **If the LP is delayed (e.g., CT, coagulopathy, thrombocytopenia, agitation) and meningitis is strongly suspected, administer antibiotics without**

delay.[32,43] For many patients who are awake and alert without evidence of papilledema or focal neurologic deficit and who have no history to suggest immunocompromised state or new-onset seizure, the head CT can be delayed until after the LP.[32]

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage resulting from rupture of an intracranial aneurysm carries only a 50% 30-day survival rate.[44,45] Approximately half of survivors have some degree of neurologic impairment. Early detection and appropriate management lead to improved clinical outcome. Only 1% of patients presenting to the ED with headache have subarachnoid hemorrhage. However, 10% to 14% of those complaining of the "worst headache of their life" have subarachnoid hemorrhage.[7,8] **Acute onset of a severe headache is subarachnoid hemorrhage until proven otherwise**.[12,14] Neck pain on history and stiffness on exam are suggestive.[46] Inquire about a family history as outlined above.[23] Obtain a noncontrast head CT as the first step in evaluation.[47] With third-generation CT equipment, CT scan done within 6 hours of headache onset is reported to have a sensitivity approaching over 99% and specificity over 99%, with a negative predictive value of 99.4% and positive predictive value of 100%.[46,48] If head CT is negative for blood but suspicion for subarachnoid hemorrhage is strong, or if the patient presents beyond 6 hours of headache onset, the next step is LP to detect blood or xanthochromia in the cerebrospinal fluid.[49] For further discussion, see Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage." Consultation with a neurologist or neurosurgeon may be appropriate if the history is highly suggestive of subarachnoid hemorrhage, because both the CT and LP can be normal.[50-52] CT angiogram, magnetic resonance angiogram, MRI with fluid-attenuated inversion recovery/susceptibility-weighted images,[53,54] or four-vessel cerebral angiogram may be reasonable.[34]

SUBDURAL HEMATOMA AND INTRACEREBRAL HEMORRHAGE

Intracranial hemorrhage may occur with or without a history of trauma, in the context of new or progressive headache, and with or without associated neurologic deficit. This is particularly important in the elderly, those with chronic alcohol and substance abuse, and patients using antiplatelet and anticoagulant agents. The antiplatelet agent clopidogrel increases the risk of acute intracranial bleeding immediately after trauma, so patients receiving antiplatelet agents and anticoagulants should be screened using head CT, regardless of symptoms. In a prospective trial of patients with blunt head trauma, 12% of those taking clopidogrel and 5.1% of those taking warfarin had acute intracranial hemorrhage noted on their initial CT scan. The risk of delayed intracranial hemorrhage was small in both groups (0 of 296 patients taking clopidogrel and 4 of 687 patients taking warfarin).[21]

Acute headache with associated vestibular symptoms (vertigo or ataxia) should be considered a cerebellar hemorrhage until proven otherwise. Cerebellar hemorrhages make up approximately 10% of all intracerebral hemorrhages and may require prompt surgical evacuation of the hematoma to prevent rapid progression to severe disability or death.[55]

BRAIN TUMOR

Headache in the setting of brain tumor is caused, at least in part, by cerebrospinal fluid flow obstruction and intracranial hypertension.[56]

Headache alone is a rare presentation of brain tumor.[57] Clinical signs and symptoms suggesting brain tumor include abnormal neurologic examination, headache worsened by Valsalva maneuver, headache causing awakening from sleep, seizures, recent cancer diagnosis, or mental status change. The absence of these features does not exclude the possibility of a brain tumor. In adults, nausea, vomiting, and neurologic deficit are more common than morning or nocturnal headache.[58,59] MRI with and without gadolinium is the study of choice for detecting brain tumors, but cost and limited access make it unfeasible in many settings. A noncontrast CT will identify large masses and edema associated with large masses, but may fail to identify smaller masses. However, noncontrast CT can diagnose hemorrhage secondary to malignancy, accounting for up to 11% of intracerebral hemorrhages.[60] Evaluate for potential barriers to access of medical care in clinical decision making, because additional imaging may be needed at follow-up.

CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis is a rare, but dangerous, cause of headache, with mean age of 39 years. Consider the diagnosis in patients presenting with new headache symptoms, especially in the presence of certain risk factors. Cerebral venous thrombosis is more common in women, especially in the peripartum period, and in patients with a recent surgical history. It is associated with hypercoagulable states such as use of oral contraceptives, hematologic disorders, factor V Leiden homozygous mutation, protein S or protein C deficiency, and anti–thrombin III deficiency.[61] The presentation can vary widely, from a progressive headache developing over days to weeks to, in some instances, a "thunderclap" headache. Similarly, the patient's clinical appearance can be quite benign, especially early in the course of the illness, or in more severe cases, patients may present with signs of elevated intracranial pressure, seizures (40%), stroke symptoms, and even coma (14%).[62,63] Approximately one third will develop intracerebral hemorrhage.[64]

In the presence of abnormal imaging (CT, MRI), focal neurologic deficit, or altered mental status, the diagnosis is made definitively with magnetic resonance venography. Given the rare nature of this diagnosis, patients suffering from cerebral venous thrombosis may be undergoing evaluation for other causes of severe headache. An elevated LP opening pressure should raise suspicion of cerebral venous thrombosis in the appropriate clinical setting and prompt further imaging with magnetic resonance venography or consultation with a neurologist.[65,66] LP can safely be performed in patients with cerebral venous thrombosis.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Patients with posterior reversible encephalopathy syndrome can present with severe headache, visual changes, seizures, and encephalopathy in the setting of marked blood pressure elevation (usually rapidly developing). It is most common in patients undergoing active treatment with immune-suppressing or -modulating medications or chemotherapeutic agents, as well as in patients with end-stage renal disease. Imaging with MRI typically shows evidence of symmetrical vasogenic edema in the occipital area of the brain, although other areas of the brain can be involved. Treatment involves blood pressure control and supportive care.[67]

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME

This condition can mimic subarachnoid hemorrhage (see Table 165-2). Characterized by the occurrence of one or more "thunderclap" headaches, the diagnosis should be considered only when the evaluation for subarachnoid hemorrhage has proven negative. The underlying pathophysiology of the syndrome is poorly understood, but it appears to coexist with a number of other cerebral angiopathies (including posterior reversible encephalopathy syndrome) that are characterized by diffuse cerebral vasospasm. The incidence is greater in women, and the peak age of onset is in the early 40s. Most patients will have more than one thunderclap headache over the course of a few weeks. Severe headache may be the only presenting feature, although some patients can present with seizure or focal neurologic deficit. The key diagnostic feature (multiple areas of cerebral vasoconstriction on cerebral angiography) is most commonly found on follow-up angiography between 2 and 3 weeks after symptom onset.[22] In three published series, the rate of permanent neurologic disability was between 6% and 20%. Reversible cerebral vasoconstriction syndrome, although not widely known among nonneurologists, does not appear to be that rare. One prospective case series included 67 patients diagnosed at a single hospital over a 3-year period of data collection.[68]

Initial neuroimaging in these patients may show evidence of nonaneurysmal subarachnoid hemorrhage, ischemic stroke, or intracranial hemorrhage. However, head CT is most commonly normal in these patients. Ultimately, there will be magnetic resonance angiography evidence of cerebral vasoconstriction in all patients, but this may be delayed in appearance. As such, the clinical presentation of thunderclap headache

TABLE 165-6 American College of Rheumatology Criteria for Diagnosis of Temporal Arteritis

Clinical Features	Comments
Age at disease onset ≥50 years	
New headache	Onset or type
Temporal artery abnormality	Tenderness to palpation of temporal arteries Decreased pulsation of temporal arteries
Erythrocyte sedimentation rate ≥50 mm/h	Westergren method
Abnormal artery biopsy (can be done after initiating steroids)	Vasculitis Predominance of mononuclear cell infiltration or granulomatous inflammation Multinucleated giant cells

without evidence of subarachnoid hemorrhage should be the main prompt to making this diagnosis or consulting with a neurologist.

TEMPORAL ARTERITIS

Temporal arteritis, also known as giant cell arteritis, is an inflammatory condition affecting the small and medium-sized intracranial and extracranial vessels. Primarily a disease of those >50 years old, its incidence increases with age. In addition to headache (over 80% of patients), associated symptoms may include fatigue, fever, proximal muscle weakness, jaw claudication, or transient ischemic attack symptoms, especially transient visual loss. Sedimentation rate may be elevated, as may C-reactive protein. Check intraocular pressure to exclude glaucoma. Diagnosis is made by the presence of three of the five criteria listed in **Table 165-6**, with sensitivity of 93.5% and specificity of 91.2%.[69] Begin treatment with prednisone, 60 milligrams PO daily, to minimize morbidity from visual impairment and stroke. Consult with an ophthalmologist to determine optic nerve function and a rheumatologist. It is important to ensure rapid and appropriate follow-up for patients discharged from the ED, ideally with their primary care provider.

MIGRAINE

The most common non–life-threatening headache in the ED is **migraine** (see Table 165-3). Migraine is defined as a headache of moderate to severe intensity that lasts hours (4 to 72 hours on average) and is usually unilateral, pulsatile in quality, typically associated with both photophobia and phonophobia, and generally made worse with physical activity. The POUND mnemonic (see Table 165-3) can be beneficial, as a patient who meets four of five criteria possesses a positive likelihood ratio of 24 for diagnosis of migraine.[70] Migraine can be episodic or chronic and can occur with or without aura. The characteristics of migraine aura vary widely. Among the most common aura symptoms are lightheadedness and visual changes (scotoma and scintillations). Migraines usually start in childhood and peak around age 40 years, with gradual decline thereafter. Prevalence is approximately 5% for males and 15% to 17% for females.[9]

Chronic migraine is defined as 5 or more migraine headache days per month over the past 3 months. Migraine sufferers who present to the ED are more likely to be chronic headache sufferers.[71,72]

There are many effective treatment options for management of migraine headache, based on randomized controlled trials. Triptans are considered first-line abortive therapy for migraine at home. However, in the ED setting, most patients have failed abortive therapy and require rescue therapy.

ED Treatment of Migraine Initial treatment includes IV treatment with dopamine receptor antagonist (droperidol, metoclopramide, prochlorperazine)[73] and NSAIDs (**Table 165-7**). Many combinations are effective. **Combination with antihistamine (usually diphenhydramine 25 to 50 milligrams IV) is helpful to treat** akathisias from antiemetics, although data suggest antihistamines alone are not helpful.[74,75]

Steroids may be useful to reduce the risk for headache recurrence after ED discharge.[76,77]

Opiates and barbiturate-containing compounds should not be used routinely for abortive migraine therapy unless other standard treatments fail. Not recommended for routine use are ergotamine and codeine- and tramadol-containing medications, as well as butorphanol and butalbital-containing medications.[78,79]

In **pregnancy**, there are scant data on treatment of migraine. In general, triptans are contraindicated; acetaminophen, opioids, or corticosteroids can be used. Metoclopramide (U.S. Food and Drug Administration category B) may be used. NSAIDs may be also used until the third trimester. Ergotamines and combination agents with caffeine and isometheptene are absolutely contraindicated in pregnant women.

Upon discharge from the ED, more than half of patients will have some residual headache, and there is an increased rate of recurrence of headache within the first 3 days after discharge.[76,77,80] A prescription for abortive medications should form part of the discharge plan for patients discharged from the ED with a diagnosis of migraine. Providers should be familiar with one or two fast-acting triptans (such as sumatriptan, sold as Imitrex® in the United States, and rizatriptan, sold as Maxalt® in the United States), as well as combinations of triptans, such as sumatriptan/naproxen (sold as Treximet® in the United States), or combination drugs, such as Midrin® (acetaminophen, 325 milligrams/dichloralphenazone, 100 milligrams/isometheptene, 65 milligrams).

OCCIPITAL NEURALGIA

Occipital neuralgia is characterized by paroxysms of lancinating pain at the back of the head, in the distribution of the greater and/or lesser occipital nerve. Patients describe the pain as stabbing or electric shock–like in quality, with hypersensitivity in the distribution of the affected nerve. Most cases are attributed to chronic neck tension or unknown causes. However, the condition can be associated with osteoarthritis or degenerative disease of the upper cervical spine. Occipital nerve block typically results in marked improvement of symptoms, and the results can persist for weeks after the injection. The procedure is both diagnostic and therapeutic. The procedure can be performed with ease in any setting and requires minimal expertise.

IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOR CEREBRI SYNDROME)

Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is most common in obese women. The incidence is 19.3 per 100,000 obese women between the ages of 20 and 44 years and has increased with the obesity epidemic. The most prominent symptoms include headache (84%), transient visual obscurations (68%), back pain (53%), and pulsatile tinnitus (52%). Only 32% of patients report visual loss. Untreated, idiopathic intracranial hypertension can lead to permanent visual impairment if not recognized and treated appropriately.[81]

The diagnostic criteria include papilledema with an otherwise normal neurologic examination and elevated opening pressure on LP (>25 cm H_2O in adults and >28 cm H_2O in children), in the setting of normal cerebrospinal fluid composition and normal imaging (having excluded other causes of raised intracranial pressure). Treatment is focused on preservation of vision. A variant of pseudotumor has been identified that does not present with papilledema but may present with the other clinical features of pseudotumor cerebri, along with abducens nerve palsy (unilateral or bilateral). In the absence of either papilledema or abducens nerve palsy, the diagnosis of pseudotumor without papilledema can be made if at least three of the following neuroimaging findings are present: empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve, and transverse venous sinus stenosis.[82]

LP is necessary to make the diagnosis of idiopathic intracranial hypertension, and concomitant removal of a volume of cerebrospinal fluid can provide temporary relief of symptoms. However, subjective improvement of symptoms after LP is not reliable in establishing the diagnosis.[82] Perform the LP with the patient in the lateral decubitus position, without sedation (which may cause mild hypercapnia and, subsequently, an elevated cerebrospinal fluid pressure measurement). The knees should be extended for measurement of cerebrospinal fluid

TABLE 165-7 Treatment Options for Migraine Headache

Drug	Dosing	Contraindications	Precautions and Pregnancy Category	Notes
Ketorolac	10–30 milligrams IV or IM	History of peptic ulcer disease (especially in elderly)	Pregnancy category B Avoid in third trimester	10, 15, and 30 milligrams are equivalent in pain relief
Prochlorperazine	5–10 milligrams IV or PR		Pregnancy category C Drowsiness Dystonic reactions	**Antiemetic** Concurrent: diphenhydramine
Metoclopramide	10 milligrams IV		Pregnancy category B Drowsiness Dystonic reactions	**Antiemetic** Concurrent: diphenhydramine
Droperidol	2.5 milligrams IV slow, or 2.5 milligrams IM		Pregnancy category C QT interval prolongation and/or torsades de pointes	Concurrent: diphenhydramine
Chlorpromazine	7.5 milligrams IV		Pregnancy not classified Hypotension Drowsiness Dystonic reactions	**Antiemetic** Pretreat with: normal saline bolus to minimize hypotension Concurrent: diphenhydramine
Magnesium sulfate	2 grams IV over 30 min		Pregnancy category D but effective in preeclampsia and eclampsia	Nonvalidated
Methylprednisolone	125 milligrams IV or IM		Rescue therapy	Nonvalidated
Dexamethasone	6–10 milligrams IV		Rescue therapy	Adjunctive therapy to reduce recurrence
Sumatriptan	6 milligrams SC	Ischemic heart disease Uncontrolled hypertension Basilar or hemiplegic migraine	Pregnancy category C	
Dihydroergotamine (DHE)	1 milligram IV over 3 min	Pregnancy Uncontrolled hypertension Ischemic heart disease Recent sumatriptan use (within 24 h) Basilar or hemiplegic migraine	Pregnancy category X Nausea Vomiting Diarrhea Abdominal pain	Pretreat with antiemetic
Valproate	500 milligrams IV	Pregnancy	Pregnancy category X	Nonvalidated
Ketamine	0.1–0.3 milligram/kg IV		Hypertension, tachycardia Emergence reaction Pregnancy category B	May be used in patients with head trauma, as it does not increase intracranial pressure

pressure, and the base of the manometer should be level with the right atrium. Elevated cerebrospinal fluid pressures can occur in the setting of the Valsalva maneuver, such as breath holding and crying, and if the pressure is measured in the sitting position. Cerebrospinal fluid can be removed in multiple aliquots, measuring cerebrospinal fluid pressure after each removal, until a target pressure of 15 to 20 cm H_2O is achieved. Determine the opening pressure. **In general, removal of 1 mL of cerebrospinal fluid will lower the cerebrospinal fluid pressure by about 1 cm H_2O.**[83] To avoid lowering the pressure excessively, first remove 1 mL for every 1 cm H_2O reduction desired, and then remeasure cerebrospinal fluid pressure. Excess cerebrospinal fluid removal can result in intracranial hypotension and a "low-pressure headache," which may require epidural blood patch for relief.

Ultrasound assessment of the optic nerve sheath is helpful when considering the diagnosis of idiopathic intracranial hypertension as a cause of headache. Literature suggests US is sensitive for detection of increased ICP, with sensitivity over 90% and specificity ranging from 67% to 85%. A disadvantage is the lack of a uniform cut-off level for the diagnosis of increased ICP. Optic nerve sheath diameter < 5 mm diameter is considered normal and > 6 mm abnormal, but the significance of measurements between 5-6 mm are controversial. However, a normal sheath diameter does not exclude a life-threatening disease, and US should be used in conjunction with other clinical assessments.

Oral acetazolamide can be effective in lowering intracranial pressure and decreasing symptoms of idiopathic intracranial hypertension. Treatment is typically started at 250 to 500 milligrams twice a day.[84] The dose can be increased to as much as 4 grams/d, but dose escalation is associated with significant side effects (paresthesias, fatigue, decreased libido, metallic taste) and should be done under the supervision of a neurologist or ophthalmologist for ongoing monitoring of papilledema and visual field testing to minimize the risk of visual loss.[85] Long-term interventional management may include cerebrospinal fluid shunting and optic nerve sheath fenestration for failing vision. For obese patients, weight loss is recommended.[85]

INTRACRANIAL HYPOTENSION

The headache of intracranial hypotension (low-pressure headache) is most commonly associated with recent dural penetration, either during LP, epidural anesthesia, or any operative procedure that involves opening the dura. Using a noncutting needle reduces the risk of post-LP headache.[86] Rarely, intracranial hypotension can occur spontaneously or in association with head or spine trauma.[87-89] Clinical features include headache that increases in severity with upright posture but improves or resolves in the supine position. Associated symptoms, such as alterations in hearing or vision, nausea, vomiting, diplopia, and visual changes, may occur. MRI, with and without contrast, confirms the diagnosis by showing diffuse enhancement of the meninges. The LP, if performed, should have an opening pressure <6 cm H_2O. Most patients experience spontaneous resolution of their symptoms. Evidence to support treatments such as IV fluid resuscitation and IV caffeine is limited. The most effective therapy for low-pressure headache is an epidural blood patch, typically performed by anesthesiologists.[87,90]

CARCINOMATOUS MENINGITIS

About 5% to 10% of patients with cancer develop leptomeningeal metastases. In addition to headache, cranial nerve abnormalities (typically more than one) and other neurologic findings may be present. Risk factors for carcinomatous meningitis include aggressive lymphoma subtypes and uncontrolled systemic disease. In suspected patients, the appropriate testing would include MRI with and without contrast (to evaluate for meningeal enhancement). Obtain MRI before LP, as MRI evidence of meningeal enhancement is common after LP and may confound the diagnosis. LP may reveal an elevated opening pressure (>20 cm H_2O). Cerebrospinal fluid analysis should include cytology (solid tumors) or flow cytometry (hematologic tumors). Malignant cells degrade quickly, so timely review of cerebrospinal fluid is important.[91]

CLUSTER HEADACHE

Cluster headaches (Table 165-4) occur in about 0.4% of the general population and can mimic dental pain. More common in men, cluster headaches typically start in adulthood and tend to occur in "clusters," with a circadian and circannual pattern, recurring daily for more than a week and remitting for at least 4 weeks. Episodes are typically unilateral and excruciating, but brief and self-limited. Up to 10% of patients will experience a more chronic form, with fewer episodes of remission. Associated **ipsilateral symptoms are common** (Table 165-4), and a distinguishing feature of this headache is the need for the patient to "pace," in contrast to the patient with migraine, who prefers to lie still in a quiet and dark room. Treatment consists of 100% oxygen administered at 12 L/min for 15 minutes through a nonrebreathing facemask.[92,93] Sumatriptan, 6 milligrams SC, can also be used, as can single-dose intranasal lidocaine 10% solution (effective in over one third of patients).[94]

HYPERTENSIVE HEADACHE

There is no compelling evidence linking mild to moderate **hypertension** with headache. Several studies using ambulatory blood pressure monitoring have found no association between mild to moderate high blood pressure (systolic blood pressure <180 mm Hg and/or diastolic blood pressure <120 mm Hg) and patient self-reported headache.[95] Uncontrolled hypertension can be associated with headache, especially in conditions where there is a rapid and marked rise in blood pressure, such as pheochromocytoma, posterior reversible encephalopathy syndrome,[27] hypertensive crisis, preeclampsia, and eclampsia.[95]

METABOLIC CAUSES OF HEADACHE

Metabolic headaches are hallmarked by deterioration in the setting of a disorder of homeostasis and typically improve after resolution of the disorder of homeostasis (**Table 165-8**).[95]

TABLE 165-8 Metabolic Causes of Headache

History	Examples	Treatment
Hypoxia/hypercapnia	High altitude	Acetaminophen/ibuprofen Acetazolamide 125–250 milligrams twice a day Steroids (dexamethasone) Prophylaxis: acetylsalicylic acid, 320 milligrams at 4-h intervals, starting 1 h prior to ascent; repeat 3 times
	Air travel	Nonsteroidal anti-inflammatory drugs (NSAIDs), pseudoephedrine, and nasal decongestants
	Pulmonary disease Congestive heart failure Sleep apnea	
Dialysis		Analgesics during dialysis
Autonomic dysreflexia (typical in quadriplegia)		Seated position Remove/loosen clothing Scrutinize for bladder distention/bowel impaction
Other	Hypothyroidism Fasting Cardiac cephalgia (associated with myocardial ischemia)	

CAROTID AND VERTEBRAL ARTERY DISSECTION

Cervical artery dissection, including both the carotid and vertebral arteries, is an important diagnosis, although it can be difficult to make in the ED. Cervical artery dissection accounts for 2% of all strokes and up to one quarter of strokes in young adults.[96,97] Cervical trauma, including coughing, sneezing, and physical activity, is associated in close to 40% of cases. Headache is the predominant symptom, although some patients may present with neck or facial pain. Delayed onset of neurologic symptoms by several days is common.[98-100]

Internal carotid dissection will present with anterior circulation symptoms, while vertebral artery dissection more commonly presents with posterior circulation symptoms. Other symptoms include cranial nerve palsies, vision changes, Horner's syndrome, and pulsatile tinnitus. Diagnosis requires CT with IV contrast or MRI/magnetic resonance angiography.[101-103]

CARBON MONOXIDE TOXICITY

Carbon monoxide toxicity is a dangerous etiology of headache. Smoke inhalation, heating sources with inadequate ventilation, and engine exhaust exposure are the most common etiologies. Symptoms include headache, myalgias, nausea/vomiting, and dizziness, although confusion, loss of consciousness, focal neurologic deficit, and death can result from severe exposure. Carbon monoxide toxicity should be suspected in the setting of multiple household members and pets with similar symptoms including headache and concerning exposure.[104,105] Pulse oximetry should not be relied on for screening or diagnosis, and co-oximetry is required.[106] Treatment includes oxygen supplementation, although hyperbaric oxygen therapy may be required in specific circumstances.[107]

PITUITARY APOPLEXY

Pituitary tumor apoplexy is a rare clinical diagnosis that is usually due to spontaneous hemorrhage or infarction of a preexisting pituitary adenoma.[108] Pregnancy, head trauma, pituitary radiation, and dopamine agonist therapy are other risk factors.[108-110] The earliest symptom is sudden, severe headache. The headache location tends to be retro-orbital, bifrontal, or suboccipital. Between 63% and 100% of patients will experience headache.[108] Associated symptoms may include ophthalmoplegia, reduced visual acuity, visual field defects (up to 75% of patients), altered consciousness, meningismus, and nausea and vomiting. CT (noncontrast) and MRI may show a sellar mass and hemorrhage. In the first 1 to 2 hours, the hyperacute hemorrhage may be easier to see on CT than MRI. MRI should be pursued after negative CT. Pituitary adenomas and cerebral aneurysms have a co-occurrence rate of 7.4%.[108] Pituitary tumor apoplexy requires immediate treatment with corticosteroids and urgent neurosurgical consultation. The treatment usually requires consultations from endocrinology, ophthalmology, and neurology with intensive care monitoring.

THIRD VENTRICLE COLLOID CYSTS

Colloid cysts of the third ventricle are a rare cause of acute neurologic deterioration and sudden death. The colloid cyst is usually congenital, slow growing, and benign, accounting for about 0.2% to 2% of all intracranial tumors, but it is the most common tumor of the third ventricle.[111] The usual clinical presentation is a history of severe paroxysmal and episodic attacks of (typically frontal) headache associated with nausea

and vomiting. The presumptive cause is the intermittent obstruction of cerebrospinal fluid flow through the foramina of Monro with associated rapid increase in intracranial pressure.[112]

ACUTE ANGLE-CLOSURE GLAUCOMA

Acute angle-closure glaucoma results from obstruction of aqueous humor flow due to narrow anterior chamber angle. This leads to increased intraocular pressure. Peak incidence occurs over age 70, and pupillary dilatation can precipitate an attack. Presentation includes abrupt eye pain, vision changes, and headache, although nausea and vomiting may occur. Decreased visual acuity, mid-fixed dilated pupil, and an edematous cornea may be found on exam. Diagnosis includes ocular pressure greater than 21 mm Hg, although this is usually greater than 30 mm Hg.[113-115]

PREECLAMPSIA

Preeclampsia may present with headache and should be considered in a female after 20 weeks of gestation up to 6 weeks postpartum with blood pressure greater than 140/90 mm Hg in combination with proteinuria or end-organ damage. Proteinuria is not required for diagnosis, and hypertension with thrombocytopenia, renal insufficiency, impaired liver function, cerebral or visual disturbance, or pulmonary edema is diagnostic.[116]

OTHER CAUSES

Other etiologies of headache include sinusitis, Valsalva-associated headache, and coital headache.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 166

Spontaneous Subarachnoid and Intracerebral Hemorrhage

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INTRODUCTION

Although hemorrhagic strokes, including nontraumatic subarachnoid hemorrhages and intracerebral hemorrhages, account for a relatively small portion of ED visits, a missed diagnosis can produce devastating results. Early recognition and aggressive management may improve outcomes. Hemorrhagic stroke accounts for 15% of all strokes and is classified according to the anatomic location of the bleed; nearly one third of hemorrhagic strokes are the subarachnoid type, whereas two thirds are from intracerebral hemorrhage.[1]

Subarachnoid hemorrhage is the leakage of blood into the subarachnoid space and classically presents as a sudden, severe headache. Intracerebral hemorrhage, bleeding into the brain parenchyma itself, typically presents as an acute neurologic deficit, often accompanied by headache. The features and treatment of subarachnoid and intracerebral hemorrhage are discussed in this chapter. Management of intracerebral hemorrhage is very different from the management of ischemic stroke. Ischemic stroke is discussed in Chapter 167, "Stroke Syndromes."

SUBARACHNOID HEMORRHAGE

EPIDEMIOLOGY

About 75% of atraumatic subarachnoid hemorrhages are caused by a ruptured aneurysm. In about 20% of cases a cause is not identified.[2] The remaining causes are related to a variety of miscellaneous conditions, including arteriovenous malformations, sympathomimetic drugs, and other less common causes. About 20% of patients with one aneurysm will have an additional aneurysm, which makes identification of the initial aneurysm important.

Two percent of family members of patients with subarachnoid hemorrhage will develop the same disease. This risk rises with increasing number of family members involved or with a family history of adult polycystic kidney disease.[2] Hypertension and smoking increase risk as well. Additional risk factors are listed in **Table 166-1**.

PATHOPHYSIOLOGY

Cerebral aneurysms are focal arterial pouches typically located in areas of bifurcation of the circle of Willis. While the precise pathophysiology is not known, many factors have been associated with aneurysmal development and rupture. Such factors include genetic predisposition, cellular aberrations in vascular wall repair or remodeling, and aberrations in local blood flow.[3] While it is not possible to predict rupture risk of a particular aneurysm, larger aneurysms (>5 to 10 mm) are more likely to rupture than smaller aneurysms.[3,4]

CLINICAL FEATURES

Patients with subarachnoid hemorrhage classically present to the ED with a severe headache of acute onset (termed a "thunderclap" headache) that reaches maximal intensity within seconds. Typically, the headache persists for several days but may resolve in a shorter period of time.[2] Subarachnoid hemorrhage is diagnosed in 11% to 25% of patients who present to the ED with a thunderclap headache.[5,6] **Even if a patient is not experiencing the "worst headache of their life," a headache that is different in intensity or quality from past headaches should raise concern for subarachnoid hemorrhage**. Headaches associated with loss of consciousness, seizure, diplopia or other neurologic signs, or nuchal rigidity also require clinical investigation.[7] Less frequently, patients may present with nausea and vomiting, altered mental status, photophobia, or symptoms suggestive of ischemic stroke. Approximately 20% of patients develop their symptoms while engaged in activities that cause increased blood pressure, such as exercise, sexual intercourse, or defecation.

DIAGNOSIS

Consider subarachnoid hemorrhage in the differential diagnosis for all patients presenting with a concerning headache. Subarachnoid hemorrhage can be ruled out with 100% sensitivity with implementation of the **Ottawa Subarachnoid Hemorrhage Rule** for headache evaluation. Although inclusion criteria are stringent, **subarachnoid hemorrhage may be excluded in patients under 40 years of age, without neck pain**

TABLE 166-1 Risk Factors for Subarachnoid Hemorrhage

- Hypertension
- Smoking
- Excessive alcohol consumption
- Polycystic kidney disease
- Family history of subarachnoid hemorrhage
- Coarctation of the aorta
- Marfan's syndrome
- Ehlers-Danlos syndrome type IV
- α_1-Antitrypsin deficiency

TABLE 166-2 Differential Diagnosis of Subarachnoid Hemorrhage

- Vascular pathology (other intracranial hemorrhage, ischemic stroke or transient ischemic attack, arterial dissection, venous thrombosis)
- Drug toxicity
- Infection (meningitis, encephalitis)
- Intracranial tumor
- Intracranial hypotension
- Metabolic derangements
- Primary headache syndromes (benign thunderclap headache, migraine, cluster headache)
- Hypertensive disorders

or stiffness, without a witnessed loss of consciousness, without onset during exertion, without a thunderclap headache, and without limited neck flexion.[8-10] Misdiagnosis is associated with normal mental status (present in about half of patients with subarachnoid hemorrhage) and smaller size of hemorrhage.[11] Up until recently, patients were believed to have worse outcomes if misdiagnosed, but this might not always be the case, and a careful evaluation for subarachnoid hemorrhage for patients who cannot be ruled out with the Ottawa subarachnoid hemorrhage rule is still important.[11-14] Complications of missed diagnosis include repeat hemorrhage and obstructive hydrocephalus. Symptomatic improvement following analgesics does not exclude life-threatening causes of headache.[15] **Table 166-2** lists the differential diagnosis of subarachnoid hemorrhage.

IMAGING

The initial diagnostic modality of choice when subarachnoid hemorrhage is suspected is a noncontrast CT of the head (**Figures 166-1** and **166-2**). **The sensitivity of CT in diagnosing subarachnoid hemorrhage is highest shortly after symptoms begin and is estimated to be 98% within 6 to 12 hours of symptom onset**. In patients who are neurologically intact who present with a thunderclap headache, a normal head CT within 6 hours of headache onset is extremely sensitive in ruling out aneurysmal subarachnoid hemorrhage.[16] Sensitivity decreases to about 91% to 93% at 24 hours and continues to decline rapidly thereafter, reaching 50% at 1 week.[7,15] Newer-generation CT scanners are even more sensitive for detecting subarachnoid hemorrhage, especially in the setting of (1) patients presenting within 6 hours of symptom onset, and (2) greater availability of a timely interpretation by a neuroradiologist.[17-19]

CT angiography and MRI or magnetic resonance angiography are options after a negative head CT, when these studies are clinically appropriate and available.[20] In a small study, two of 116 patients had an aneurysm discovered by CT angiography after normal findings on both CT and lumbar puncture.[21] The probability of correctly excluding a subarachnoid hemorrhage following CT/CT angiography is about 99.4%.[22] One of the consequences of this diagnostic pathway is the detection of incidental aneurysms that may prompt unnecessary intervention, with the background incidence of aneurysms in the population (2% to 6%) exceeding that of the morbidity and mortality associated with subarachnoid hemorrhages, as well as the ionizing radiation.[23] Current clinical practice has moved toward ruling out subarachnoid hemorrhages in patients with a normal CT/CT angiography so long as they present within 6 hours of symptom onset. The option for obtaining a lumbar puncture in patients in whom there is still a strong suspicion of subarachnoid hemorrhage, despite negative imaging studies, remains a method for complete evaluation.

The usefulness of MRI, particularly fluid-attenuated inversion recovery MRI sequences, is limited.[24] A negative MRI result still needs to be followed by a lumbar puncture.[25]

LUMBAR PUNCTURE

Most authorities recommend cerebrospinal fluid (CSF) analysis when a patient with suspected subarachnoid hemorrhage has a normal head CT.[26,27] Another advantage of lumbar puncture is the ability to identify other causes of headache, such as meningitis or idiopathic intracranial hypertension. The main disadvantage of lumbar puncture includes post–lumbar puncture headache and other discomfort for the patient; a lumbar puncture may be contraindicated in the patient with coagulopathy or thrombocytopenia.

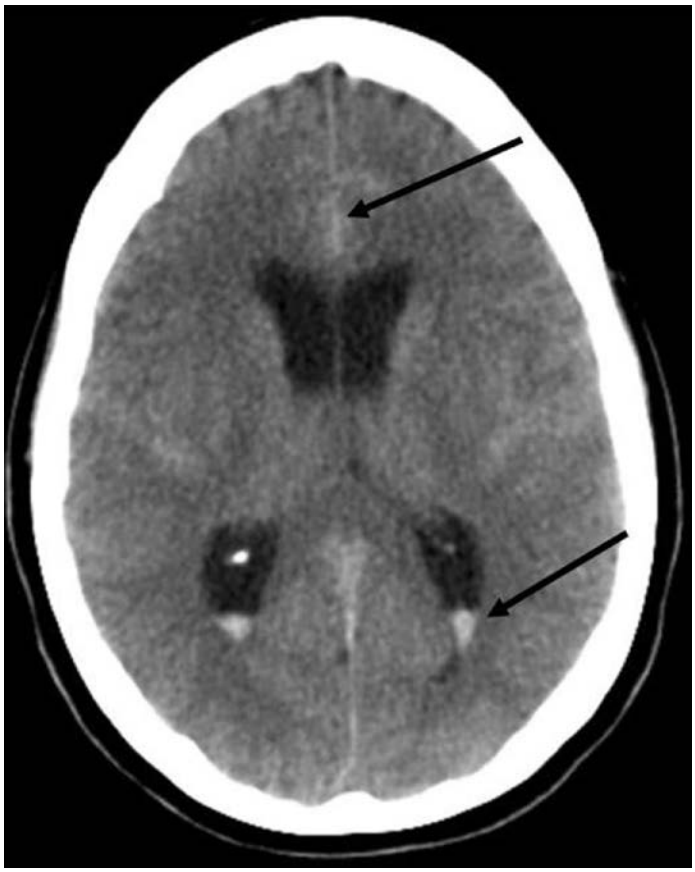

FIGURE 166-1. Diffuse subarachnoid hemorrhage with associated ventricular hemorrhage. *Top arrow* indicates blood in interhemispheric fissure. *Bottom arrow* indicates blood in lateral ventricle. [Image used with permission of James Anderson, MD, Department of Radiology, Oregon Health & Science University.]

The two CSF tests of greatest interest are the presence of xanthochromia and red blood cell (RBC) count. Xanthochromia is a yellow appearance of the CSF due to the enzymatic breakdown of blood releasing bilirubin. Any exposure of the CSF to light prior to interpretation can increase the rate of bilirubin degradation, which decreases any xanthochromia present.[2] Similarly, a delay in processing the CSF specimen may result in the development of xanthochromia following a traumatic lumbar puncture. CSF is evaluated for xanthochromia with visual inspection, the standard technique in most U.S. laboratories, or by spectrophotometry, which may have superior sensitivity but only 75% specificity, resulting in false positives.[28] The utility of the test is further limited in that it takes approximately 12 hours from hemorrhage onset for xanthochromia to develop in CSF.[29]

The RBC count in the third or fourth tube of CSF is commonly used to identify subarachnoid hemorrhage. The number of RBCs that constitutes a positive lumbar puncture result has never been clearly defined, nor has the number of RBCs that may be attributed to a traumatic lumbar puncture. One study demonstrated that approximately 10% to 15% of lumbar punctures are traumatic, using cutoffs of 400 and 1000 RBCs, respectively.[30] A comparison of cell counts between consecutive tubes or between tubes 1 and 4 is sometimes used to differentiate subarachnoid hemorrhage from a traumatic lumbar puncture. One small study, however, demonstrated that a 25% reduction in RBCs between tubes 1 and 4 may occur even in cases of confirmed subarachnoid hemorrhage.[31] Another small study found that RBCs <100 in the final tube effectively ruled out subarachnoid hemorrhage, whereas an RBC count of >10,000



FIGURE 166-2. Scattered subarachnoid hemorrhages (*arrows*). [Image used with permission of James Anderson, MD, Department of Radiology, Oregon Health & Science University.]

in the final tube was associated with an increase in the odds of subarachnoid hemorrhage by a factor of 6.[32] **Unfortunately, the literature remains unclear on the precise threshold number of RBCs needed in the CSF to be considered diagnostic of subarachnoid hemorrhage**.

In general, normal findings on head CT, the absence of xanthochromia, and zero or few RBCs ($<5 \times 10^6$ RBCs/L) in the CSF help reliably exclude subarachnoid hemorrhage.[33] A normal head CT result with a positive finding of xanthochromia or elevated RBC count in tube 4 should be considered diagnostic of subarachnoid hemorrhage.

SUBARACHNOID HEMORRHAGE GRADING SCALES

Many different subarachnoid hemorrhage grading scales exist. Those most widely used include the Hunt and Hess scale and the World Federation of Neurosurgical Societies scale (**Table 166-3**). A higher grade on either scale indicates a higher likelihood of poor outcome.

TABLE 166–3 Grading Scales for Subarachnoid Hemorrhage

Grade	Hunt and Hess Scale	World Federation of Neurosurgical Societies Scale
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS of 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS of 13 or 14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS of 13 or 14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS of 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS of 3–6, with or without motor deficits

Abbreviation: GCS = Glasgow Coma Scale score.

Source: Reproduced with permission from Hemphill JC: Neurologic critical care, in Fauci AS, Braunwald E, Kasper DL, et al (eds): *Harrison's Principles of Internal Medicine*, 17th ed. © McGraw-Hill, Inc., New York, 2008.

TREATMENT

Medical management of the subarachnoid hemorrhage patient in the ED should occur in a monitored critical care area and should target the prevention of complications. Reassess the Glasgow Coma Scale and pupillary responses regularly because a decrease of 1 Glasgow Coma Scale point may indicate the onset of complications.[2] Intracerebral and extracerebral complications of subarachnoid hemorrhage include rebleeding, vasospasm, cerebral infarction, cerebral edema, hydrocephalus, intracranial hypertension, fluid status and electrolyte abnormalities, respiratory failure, myocardial dysfunction, thromboembolism, and sepsis.[34]

The risk of rebleeding is greatest in the first 2 to 12 hours and can be reduced by adequate blood pressure control. Control blood pressure with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure. While target pressures have not yet been established, a decrease in systolic blood pressure to a range of 120 to 160 mm Hg is reasonable.[16] Because blood pressure may fluctuate through the course of the disease, a titratable IV antihypertensive is preferred. **Labetalol** and **nicardipine** are often used, with neither demonstrating clear superiority. **Avoid nitroprusside and nitroglycerin** because they increase cerebral blood volume and intracranial pressure.[35-37] There is debate regarding the use of antifibrinolytics to prevent rebleeding after subarachnoid hemorrhage, with weak evidence supporting short- but not long-term use in the first 7 days.[38] Generally, antifibrinolytics are not used because there is a risk of increased cerebral ischemia, as well as other dangerous complications.[38] However, in scenarios where there is an unavoidable delay in aneurysm obliteration, significant risk of rebleeding, and no major contraindications, initiation of tranexamic acid or aminocaproic acid in the ED is reasonable to reduce the risk of early aneurysm rebleeding, but should be done only in consultation with the accepting neurosurgeon given high complication rates.[16] Pain medications and antiemetics are also critical adjuncts in maintaining the alert patient's comfort and blood pressure.

Vasospasm is most common 2 days to 3 weeks after subarachnoid hemorrhage. A modest protective benefit is seen with administration of nimodipine, 60 milligrams PO every 4 hours, and this therapy should be initiated within 96 hours of symptom onset unless contraindicated due to allergy, nonfunctioning GI tract, or hepatic disease. Clinical trials of other novel treatments, including statins, magnesium, and endothelin receptor antagonist, have not demonstrated significant reductions in mortality.[39-43]

Delayed cerebral ischemia is associated with hypothermia, hyperthermia, and hyperglycemia. Prevent these conditions with the appropriate use of warming or cooling blankets, antipyretics, or insulin as indicated.

Approximately 5% to 20% of patients with subarachnoid hemorrhage have at least one seizure. Consideration of seizure prophylaxis is currently supported by several clinical guidelines; however, this topic remains controversial and should be determined in conjunction with the intensivist or neurosurgeon who will manage the patient.[44]

DISPOSITION AND FOLLOW-UP

Admit all patients diagnosed with subarachnoid hemorrhage to an intensive care unit in consultation with a neurosurgeon. In patients with normal findings on head CT and CSF analysis within 2 weeks of occurrence of initial headache symptoms, another explanation for symptoms should be pursued; these patients may be safe for discharge from the ED.[2,45] Consider consultation with a neurosurgeon for patients who present >2 weeks after the sudden onset of a severe headache causing

suspicion for subarachnoid hemorrhage if the initial workup yields normal findings.[2]

INTRACEREBRAL HEMORRHAGE

EPIDEMIOLOGY

Spontaneous intracerebral hemorrhage causes 8% to 11% of all acute strokes and is twice as common as subarachnoid hemorrhage. Like subarachnoid hemorrhage, intracerebral hemorrhage carries a high morbidity and mortality. Seven-day mortality is approximately 30%, 1-year mortality about 55%, and 10-year mortality approximately 80%.[46] Among those who survive, only one in five will be functionally independent at 1 year. Intracerebral hemorrhage occurs greater than two times more frequently in blacks than in whites, which may be related to the higher prevalence of hypertension in blacks.[47] Additionally, intracerebral hemorrhage occurs in approximately 3% to 9% of patients treated with tissue plasminogen activator for acute ischemic stroke.[35]

The effect on intracerebral hemorrhage of both novel oral anticoagulants and vitamin K antagonists such as warfarin when used for atrial fibrillation to prevent ischemic stroke has been at the center of much debate and research. Overall, poorer outcomes have been observed in patients taking anticoagulants, whether novel oral anticoagulants or vitamin K antagonists, who develop intracerebral hemorrhage.[43,48] Importantly, novel oral anticoagulants are associated with reduced risk of intracerebral hemorrhage when compared to warfarin when used for stroke prevention in atrial fibrillation.[49] Anticoagulation with warfarin is a significant risk factor for intracerebral hemorrhage, with an annual intracerebral hemorrhage incidence of 0.3% to 0.6% in those taking the drug, and warfarin plays a role in 6% to 16% of all cases of intracerebral hemorrhage. Among patients taking warfarin, the risk of intracerebral hemorrhage nearly doubles for each 0.5 increase in international normalized ratio above 4.5.

When comparing novel oral anticoagulant–associated intracerebral hemorrhage with vitamin K antagonist–associated intracerebral hemorrhage, more research is needed. One pooled analysis reports that intracerebral hemorrhage volume, 90-day mortality, and functional outcomes are similar following both novel oral anticoagulant– and vitamin K antagonist–associated intracerebral hemorrhage,[50] whereas another prospective review and meta-analysis demonstrated that novel oral anticoagulant–associated intracerebral hemorrhage is associated with smaller baseline hematoma volume and lesser neurologic deficit at time of hospital admission when compared to vitamin K antagonist–associated intracerebral hemorrhage.[51] As more patients are being transitioned to novel oral anticoagulants, one study demonstrated that of patients who sustain intracerebral hemorrhage, in-hospital mortality is lower for those on novel oral anticoagulants as compared with those on vitamin K antagonists.[52,53]

PATHOPHYSIOLOGY

Risk factors for intracerebral hemorrhage include long-standing hypertension, arteriovenous malformations, arterial aneurysm, anticoagulant therapy, use of sympathomimetic drugs (particularly cocaine and phenylpropanolamine), intracranial tumors, and amyloid angiopathy in the elderly. Current smoking and increased frequency of smoking also raise the risk of intracerebral hemorrhage, but the etiology of this increased risk is not as well defined as in ischemic stroke.[54]

CLINICAL FEATURES

Intracerebral hemorrhage may be clinically indistinguishable from cerebral infarction, subarachnoid hemorrhage, and ischemic stroke. In intracerebral hemorrhage, headache, nausea, and vomiting often precede the neurologic deficit, and in contrast to subarachnoid hemorrhage, the headache onset is usually more insidious. In hypertensive intracerebral hemorrhage, bleeding is usually localized to the putamen, thalamus, pons, or cerebellum (in decreasing order of frequency), and clinical examination findings may be relatable to those areas. Cerebellar hemorrhage is commonly associated with dizziness, vomiting, marked truncal ataxia, gaze palsies, and depressed level of consciousness. Patients with cerebellar hemorrhage are more likely to have rapidly progressive symptoms and may require more aggressive intervention than patients with other forms of intracerebral hemorrhage.

DIAGNOSIS AND IMAGING

The differential diagnosis of intracerebral hemorrhage is similar to that of subarachnoid hemorrhage. The history, rapidity of progression of symptoms, and other clinical features may suggest that intracerebral hemorrhage is more likely than subarachnoid hemorrhage or ischemic stroke, but these features are not adequate alone to make a clinical diagnosis. CT and MRI each have areas of superiority in evaluating a patient for intracerebral hemorrhage. **CT is optimal for demonstrating hemorrhage extension into the ventricles, whereas MRI is superior for demonstrating underlying structural lesions**. Either modality is considered acceptable as the initial study for diagnosing intracerebral hemorrhage.[35] Widespread availability of CT and its short scan time make a noncontrast CT the initial study of choice in most EDs (**Figure 166-3**). The addition of contrast may allow identification of masses or aneurysms.

Cerebral angiography may be useful in selected patients in stable condition who do not require urgent surgery, particularly those in whom no obvious cause of bleeding is identified and those younger than 45 years of age without hypertension.[55]



FIGURE 166–3. Large right-sided parietal intraparenchymal hemorrhage (*arrow*). [Image used with permission of James Anderson, MD, Department of Radiology, Oregon Health & Science University.]

TABLE 166-4 Suggested Guidelines for Treating Elevated Blood Pressure in Spontaneous Intracranial Hemorrhage[58]

Clinical Circumstances	Management
SBP >220 mm Hg	Consider aggressive reduction of blood pressure with continuous IV infusion.
SBP 150–220 mm Hg	Acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome.

Abbreviation: SBP = systolic blood pressure.

TREATMENT

Treat patients with intracerebral hemorrhage in a monitored critical care area. Patients with cerebellar hemorrhage are at particularly high risk of rapid deterioration and may require rapid intervention for surgical evacuation of hemorrhage.[56,57] Maintain close attention to the patient's airway and neurologic status. Reduce hyperthermia with antipyretics, administer antiepileptic medications if seizures occur, aggressively manage hypo- or hyperglycemia (>160 milligrams/dL or 8.9 mmol/L), manage blood pressure, and reverse coagulopathy (if present). Manage elevated intracranial pressure by raising the head of the bed 30 degrees and providing appropriate analgesia and sedation. If more aggressive reduction of intracranial pressure is required—such as administration of osmotic diuretics or intubation with neuromuscular blockade and mild hyperventilation—invasive intracranial pressure monitoring is generally indicated. Corticosteroids should not be given for treatment of elevated ICP in intracerebral hemorrhage.[58]

Current guidelines for blood pressure management are listed in **Table 166-4**.[58] Importantly, the Antihypertensive Treatment of Acute Cerebral Hemorrhage II study demonstrated **treatment of participants with intracerebral hemorrhage to achieve a target systolic blood pressure of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg.**[59]

REVERSE COAGULOPATHY

Given the complexity and variety of antiplatelet and anticoagulation agents in current use, institutional protocols should be available with clear algorithms listing the indications for, and dosing of, reversal agents (**Table 166-5**). If the coagulopathy is related to heparin use, administer protamine at approximately 1 milligram per 100 units of heparin, adjusting based on the time since the heparin was last given. For patients taking warfarin, provide reversal no matter what the value of the international normalized ratio. For further discussion, see Chapter 239, "Thrombotics and Antithrombotics." Several options exist for reversing warfarin-induced coagulopathy: vitamin K, fresh frozen plasma, recombinant factor VIIa, and prothrombin complex concentrates. Vitamin K, 5 to 10 milligrams IV, can fully reverse warfarin-induced anticoagulation, but the full effect takes 12 to 24 hours to achieve, during which time the hematoma may continue to expand.[60] Fresh frozen plasma has a faster onset, but contains variable amounts of clotting factors, and the dose of 15 mL/kg requires a large volume infusion that many patients cannot tolerate. **Fresh frozen plasma can be available for rapid administration as universal donor (AB+) without the need for type and cross-match**. One common clinical issue has centered on the advisability of platelet transfusion after spontaneous primary intracerebral hemorrhage in patients who are taking antiplatelet therapy. A multicenter, randomized controlled trial found that administering platelets to this subset of patients who sustained a spontaneous intracerebral hemorrhage **resulted in higher rates of mortality** and serious adverse events compared to a group who received standard care. **As a result, perform standard care without platelet transfusion for patients who are taking antiplatelet therapy.**[61]

Recombinant factor VIIa does not improve survival or functional outcome after intracerebral hemorrhage.[62] **Prothrombin complex concentrates are effective and rapidly reverse oral anticoagulants; however, morbidity and mortality remain high even when the coagulopathy is reversed.**[63] Manage intracerebral hemorrhage related to fibrinolytic therapy with standard intracerebral hemorrhage treatment along with platelet and cryoprecipitate infusions, although little evidence exists to guide therapy in these cases.[35]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

TABLE 166-5 Reversal of Anticoagulation for Intracerebral Hemorrhage

Anticoagulant	Reversal Agent	Comment
Warfarin	Vitamin K 5–10 milligrams IV	Onset of action of IV vitamin K is 2 h, with maximal effect at 6–24 h. PCC and IV vitamin K act synergistically in INR reduction.
	Fresh frozen plasma 2 units IV	Full dose 15 mL/kg limited by volume.
	Prothrombin complex concentrate (PCC) 50 IU/kg IV	Dose-related risk of thromboembolism; available as 3-factor (II, IX, X) and 4-factor (II, VII, IX, X) PCC; use what is available in your institution. Onset of action of PCC is about 30 min with a half-life of 4–6 h.
Aspirin and adenosine diphosphate receptor agonists	Obtain consultation if available when considering platelet infusion	**CAUTION: Platelet reversal may cause coronary or arterial thrombosis and worsen outcome.**
Unfractionated heparin (UFH)	1 milligram protamine/100 units of UFH; maximum dose, 50 milligrams; calculate last 3 h of heparin dose to determine protamine dose because heparin has short half-life	Infusion rate ≤5 milligrams/min; risk of hypersensitivity in patients with fish allergy or prior protamine exposure: premedicate with hydrocortisone 500 milligrams IV and diphenhydramine 50 milligrams IV.
Low-molecular-weight heparin (LMWH)	If last dose within 8 h, give 1 milligram protamine/1 milligram LMWH; maximum dose, 50 milligrams	See above protamine cautions. Infusion rate ≤5 milligrams/min; higher infusion rates can cause hypotension or bradycardia.
	If last dose 8–12 h ago, give 0.5 milligram protamine/1 milligram LMWH	
	If last dose ≥12 h ago, do not give protamine	
Direct thrombin inhibitor or factor Xa inhibitors	Idarucizumab 5 grams IV to reverse dabigatran[62]	

CHAPTER 167

Stroke Syndromes

Steven Go

INTRODUCTION AND EPIDEMIOLOGY

In the United States, 795,000 people experience strokes annually (one stroke every 40 seconds and one death from stroke every 4 minutes).[1] Of these events, 77% are primary strokes, whereas 23% represent recurrent strokes.[1] In addition to the human costs, the financial implications of stroke are enormous—strokes accounted for an estimated $33.9 billion of total expenditures in the United States in 2012 to 2013.[1] Despite these grim statistics, from 2004 to 2014, the age-adjusted stroke death rate fell 28.7%.[1] With the growing use of stroke units, thrombolysis, mechanical retrieval, and the ever-expanding treatment time window, there is potential for improving patient outcomes.

PATHOPHYSIOLOGY AND ANATOMY

Stroke is generally defined as any disease process that interrupts blood flow to the brain. Injury is related to the loss of oxygen and glucose substrates necessary for high-energy phosphate production and the presence of mediators of secondary cellular injury. Subsequent factors, such as edema and mass effect, may exacerbate the initial insult.

An understanding of the diagnosis and treatment of stroke begins with a working knowledge of the relevant vascular supply and neuroanatomy of the brain. The arterial supply to the brain is illustrated in **Figures 167-1** and **167-2**.

The vascular supply is divided into anterior and posterior circulations. Clinical findings in stroke are determined by the location of the lesion(s) (**Table 167-1**), but the degree of collateral circulation may cause variations in the specific clinical symptoms and their severity.

Stroke results from two major mechanisms: ischemia and hemorrhage. Ischemic strokes account for 87% of all strokes and are categorized by cause: thrombotic, embolic, or hypoperfusion related. Hemorrhagic strokes are subdivided into intracerebral (accounting for 10% of all strokes) and nontraumatic subarachnoid hemorrhage (accounting for 3% of all strokes)[1] (**Table 167-2**). The final common pathway for all of these mechanisms is altered neuronal perfusion. Neurons are exquisitely sensitive to changes in cerebral blood flow and die within minutes of complete cessation of perfusion—hence, the current treatment emphasis on rapid reperfusion strategies.

PREHOSPITAL CARE

The early detection of stroke must begin with the general public. In general, stroke knowledge among laypersons remains suboptimal, especially in the elderly,[2] the poorly educated,[2] and minority populations.[3] This has led to mass media initiatives to raise stroke awareness[4]; however, the effectiveness of these initiatives is often short lived.[4-6]

Three of the more commonly used prehospital tools are the Cincinnati Prehospital Stroke Scale,[7] the Los Angeles Prehospital Stroke Screen,[8] and the Melbourne Ambulance Stroke Screen[9] (**Table 167-3**).

With the increasing usage of endovascular thrombectomy for **emergent large-vessel occlusion**, numerous attempts have been made to derive prehospital tools to detect emergent large-vessel occlusion in order to aid in patient routing to comprehensive stroke centers.[10-16] However, at this time, no published scale has demonstrated both high specificity and sensitivity for detection of emergent large-vessel occlusion,[17,18] and the assessment of these scales in actual prehospital use has been limited.[18] Therefore, routine use of these emergent large-vessel occlusion scales in the prehospital setting awaits further validation.

Time is a critical component in the care of stroke patients. EMS personnel should quickly ascertain the time of onset of the patient's symptoms, giving particular attention to bystander accounts to clarify details, because stroke patients may be difficult historians. Family members and/or witnesses to the event should be urged to come to the ED as soon as possible to provide further medical information to the treating physician. Time at the scene should be limited. EMS personnel should rapidly stabilize the patient's condition and transport the patient to the closest facility best able to emergently and properly treat the patient's stroke.[19] In some cases, it may be necessary to bypass closer, but less capable, facilities in order to increase the chances of the patient receiving the best

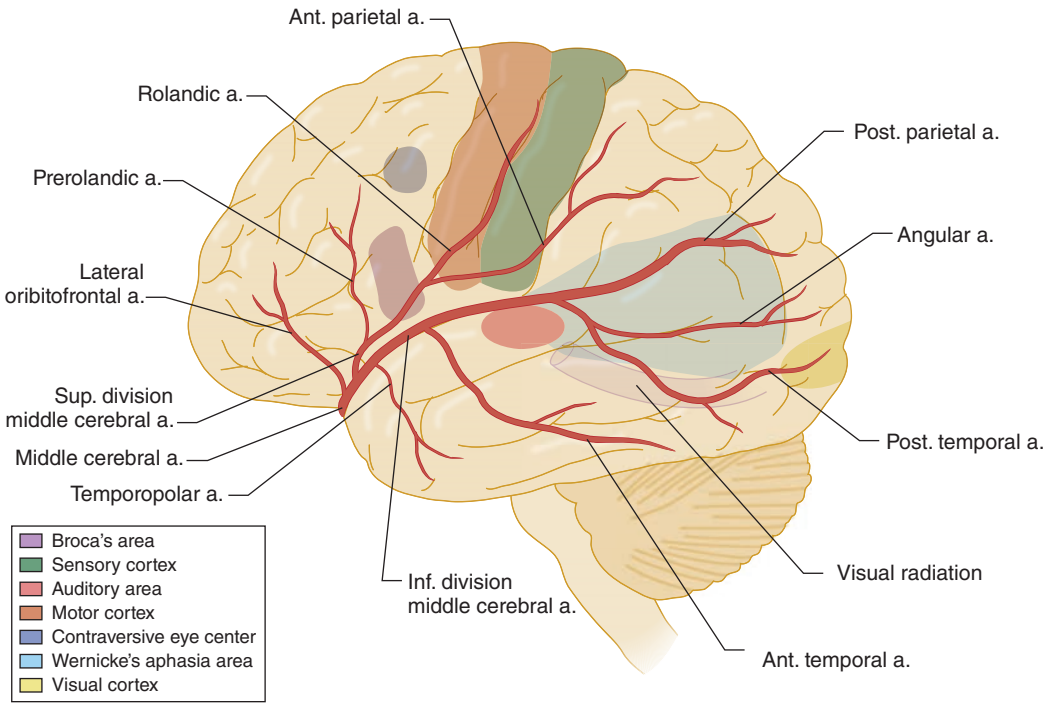

FIGURE 167-1. Cerebral hemisphere, lateral aspect. Note the branches and distribution of the middle cerebral artery and the principal regions of cerebral localization. The middle cerebral artery bifurcates into a superior and inferior division. a. = artery; ant. = anterior; inf. = inferior; post. = posterior; sup. = superior. [Modified with permission from Fauci AS, Braunwald E, Kasper DL, et al: *Harrison's Principles of Internal Medicine,* 17th ed. New York: McGraw-Hill Professional; 2008.]

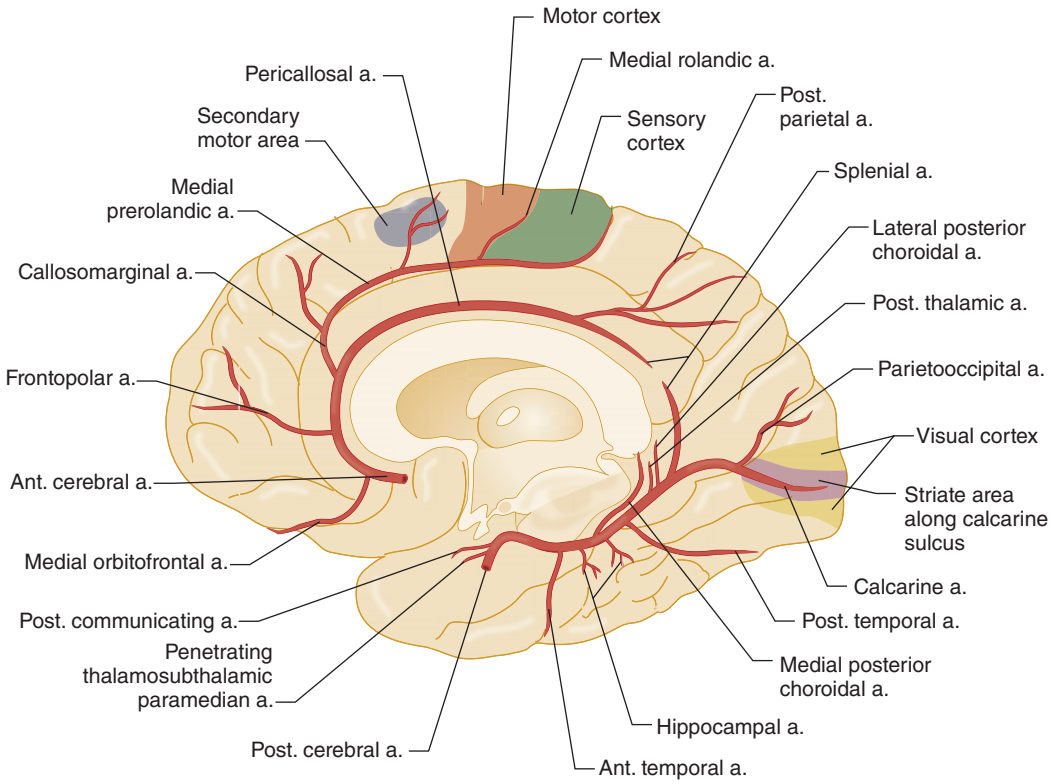

FIGURE 167-2. Cerebral hemisphere, medial aspect. Note the branches and distribution of the anterior cerebral artery, posterior cerebral artery, and the principal regions of cerebral localization. a. = artery; ant. = anterior; post. = posterior. [Reproduced with permission from Fauci AS, Braunwald E, Kasper DL, et al: *Harrison's Principles of Internal Medicine,* 17th ed. New York: McGraw-Hill Professional; 2008.]

possible care, especially if a patient may be a candidate for endovascular therapy. However, the decision-making process for determining the ideal destination remains complex. For example, one must weigh the known harms from delays in administration of IV thrombolytics[20] if a patient bypasses a primary stroke center versus the potential harm from delays in thrombectomy[21] that can be caused by the "drip and ship to a comprehensive stroke center" approach in patients who turn out to have an emergent large-vessel occlusion. At the time of this writing, the 2018 American Heart Association (AHA)/American Stroke Association (ASA) acute ischemic stroke recommendations[19] are being modified to better address this difficult issue.[22] Therefore, the development of local EMS stroke routing policies should involve EMS directors, ED medical directors, stroke center directors, and healthcare policy officials to determine how best to utilize the specific resources available in that particular community.

TABLE 167-1 Anterior and Posterior Circulation of the Brain

Circulation	Major Arteries	Major Regions of Brain Supplied
Anterior (internal carotid system)	Ophthalmic	Optic nerve and retina
	Anterior cerebral	Frontal pole
		Anteromedial cerebral cortex
		Anterior corpus callosum
	Middle cerebral	Frontoparietal lobe
		Anterotemporal lobe
Posterior (vertebral system)	Vertebral	Brainstem
	Posteroinferior cerebellar	Cerebellum
	Basilar	Thalamus
	Posterior cerebral	Auditory/vestibular structures
	Medial temporal lobe	Visual occipital cortex

CLINICAL FEATURES

The diagnosis of stroke in the ED rests on the bedrock of a focused, accurate history and physical examination.[23] The clinical presentation of stroke can range from the obvious (facial droop, arm drift, abnormal speech) to the subtle (generalized weakness, lightheadedness, vague sensory changes, altered mental status). Women account for slightly more than half of strokes in the United States,[24] and very modest gender differences exist in terms of presenting signs and symptoms.[25-27] In general, women tend to report more severe, but diffuse, nontraditional symptoms compared to the more traditional symptoms typically reported by men,[26] but evidence of these distinctions is limited (**Table 167-4**).

HISTORY

The timing of symptom onset, the presence of associated symptoms, and the medical history may point toward a particular mechanism of stroke. For example, sudden onset of symptoms suggests an embolic or hemorrhagic stroke, whereas a stuttering or waxing and waning deficit suggests a thrombotic or hypoperfusion-related stroke. A history of Valsalva maneuver immediately preceding a thunderclap headache or sudden onset of symptoms suggests a ruptured cerebral aneurysm, whereas a recent history of neck trauma or manipulation suggests cervical artery dissection. Risk factors for vessel thrombus include hypertension, diabetes mellitus, and coronary atherosclerotic disease. In contrast, atrial fibrillation, valvular replacement, or recent myocardial infarction suggests embolism. Transient neurologic deficits occurring in the same vascular distribution suggest underlying vascular disease consistent with a thrombotic stroke, whereas transient deficits involving different vascular distributions suggest embolism. Although adjunctive history can be helpful in determining the type of stroke, exhaustive or unduly prolonged attempts to elicit nonessential history should not delay therapy.

Accurately determine the time of symptom onset. Time of onset is frequently misreported as the time a patient was *discovered* with symptoms or the time of awakening (if symptoms were noted upon awakening).

TABLE 167-2 Stroke Classification

Stroke Type	Mechanism	Major Causes	Clinical Notes
Ischemic			
Thrombotic	Narrowing of a damaged vascular lumen by an in situ process—usually clot formation	Atherosclerosis Vasculitis Arterial dissection Polycythemia Hypercoagulable state Infection (human immunodeficiency virus infection, syphilis, trichinosis, tuberculosis, aspergillosis)	Symptoms often have gradual onset and may wax and wane. Common cause of transient ischemic attack.
Embolic	Obstruction of a normal vascular lumen by intravascular material from a remote source	Valvular vegetations Mural thrombi Paradoxical emboli Cardiac tumors (myxomas) Arterial-arterial emboli from proximal source Fat emboli Particulate emboli (IV drug use) Septic emboli	Typically sudden in onset. Account for 20% of ischemic strokes.
Hypoperfusion	Low–blood flow state leading to hypoperfusion of the brain	Cardiac failure resulting in systemic hypotension	Diffuse injury pattern in watershed regions. Symptoms may wax and wane with hemodynamic factors.
Hemorrhagic			
Intracerebral	Intraparenchymal hemorrhage from previously weakened arterioles	Hypertension Amyloidosis Iatrogenic anticoagulation Vascular malformations Cocaine use	Intracranial pressure rise causes local neuronal damage. Secondary vasoconstriction mediated by blood breakdown products or neuronal mechanisms (diaschisis) can cause remote perfusion changes. Risks include advanced age, history of stroke, and tobacco or alcohol use. More common in those of Asian or African descent.
Nontraumatic subarachnoid	Hemorrhage into subarachnoid space	Berry aneurysm rupture Vascular malformation rupture	May be preceded by a sentinel headache ("warning leak").

The time of onset is defined as the last known time when the patient's condition was at their baseline (i.e., "last known well" time).[19]

Quickly exclude as many **stroke mimics** as possible (**Table 167-5**).[28-30] After likely stroke mimics are excluded, if acute stroke is still the most likely diagnosis and if the symptom onset is within the recommended time limits for thrombolytic therapy, elicit information pertaining to inclusion and exclusion criteria for the administration of thrombolytics in acute ischemic stroke.[19,31]

PHYSICAL EXAMINATION

Assessment of airway, breathing, and circulation is the top priority. Next, the goals of examination are to confirm the diagnosis of stroke, exclude stroke mimics, and identify comorbidities. Fever should prompt an investigation for potential infection. CNS infections (meningitis, encephalitis) may mimic a stroke, or an infection such as aspiration pneumonia or a urinary tract infection may be a complication of the stroke. Evaluate for

TABLE 167-3 Prehospital Stroke Scales

Cincinnati Prehospital Stroke Scale (If *any* of the three items are abnormal, sensitivity = 66%, specificity = 87% for acute stroke.)	1. Facial droop (abnormal: one side of face does not move as well as other side) 2. Arm drift (abnormal: one arm does not move or one arm drifts down compared with the other) 3. Speech (abnormal: slurred, inappropriate words or mute)
Los Angeles Prehospital Stroke Screen (If answers to *all* items 1–6 are "Yes" or "Unknown," sensitivity = 91% [95% confidence interval (CI) 76%–98%], specificity = 97% [95% CI 93%–99%] for acute stroke.)	1. Age >45 y 2. No history of seizure disorder 3. New onset of neurologic symptoms in last 24 h 4. Patient ambulatory at baseline (prior to event) 5. Blood glucose level of 60–400 milligrams/dL 6. Obvious asymmetry in *any* of the following examinations: facial smile/grimace, grip, arm strength
Melbourne Ambulance Stroke Screen (If answers to *all* items 1–4 are "Yes" PLUS at least one of 5–8 is present, sensitivity = 90% [95% CI 81%–96%], specificity = 74% [95% CI 53%–88%] for acute stroke.)	1. Age >45 y 2. No history of seizure/epilepsy 3. Not wheelchair-bound/bedridden at baseline 4. Blood glucose 50–400 milligrams/dL 5. Unilateral facial droop 6. Unilateral hand grip weakness 7. Unilateral arm drift 8. Abnormal speech

TABLE 167-4 Selected Stroke Symptoms

Traditional symptoms	Sudden numbness or weakness of face, arm, or leg—especially unilateral*
	Sudden aphasia
	Sudden dysarthria*
	Sudden memory deficit or spatial orientation or perception difficulties
	Sudden visual deficit or diplopia*
	Sudden dizziness, gait disturbance, or ataxia*
	Sudden severe headache with no known cause
Nontraditional symptoms	Impaired consciousness or syncope†
	Generalized weakness†
	Altered mental status†
	Dysphagia†
	Shortness of breath
	Sudden pain in the face, chest, arms, or legs
	Seizure
	Falls or accidents
	Sudden hiccups
	Sudden nausea
	Sudden fatigue
	Sudden palpitations

*More common in men.

†More common in women.

meningismus, signs of emboli (Janeway lesions and Osler nodes), and bleeding diatheses (ecchymoses or petechiae). A funduscopic examination may identify signs of papilledema (suggesting a mass lesion, cerebral vein thrombosis, or hypertensive crisis) or preretinal hemorrhage (consistent with subarachnoid hemorrhage). Assess for findings suggestive of possible cardiac or vascular disease, such as rales, an S_3 gallop, or carotid bruit.

Use a validated stroke severity scale to assess the neurologic status of the patient. **The National Institutes of Health Stroke Scale (NIHSS)[32] is the most widely used scale for documenting the severity of a stroke**. The **NIHSS** is an 11-category (15-item) neurologic evaluation (score range of 0 to 42) that is rapid (5 to 10 minutes), has a high interrater reliability,[33,34] and provides a baseline score that is useful in predicting patient outcomes[35,36] (**Table 167-6**). An Adobe Acrobat (pdf) file of the NIHSS, as well as detailed instructions for its use, are readily available for download from the National Institute of Neurological Disorders and Stroke (NINDS) website (https://www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale.pdf). In addition, NIHSS calculators are available on the internet[37] and for use with mobile devices.[38,39] An important caveat is that **the NIHSS is weighted toward the detection of anterior circulation strokes** as opposed to posterior circulation strokes.[40,41] This is because common symptoms of posterior strokes (cranial nerve deficits and ataxia) receive fewer points, and ataxia is often scored as absent by raters if weakness is present. In addition, the NIHSS has a bias toward detection of left hemisphere strokes.[42] A modified NIHSS, which omits the redundant and least reliable items, produces clinical results similar to those for the full NIHSS[43] and is easier to use (score range of 0 to 31); however, this scale has not been as widely validated as the full NIHSS and is not in common use. Important scoring rules for proper use of the NIHSS[44] are as follows: **Score what you see, not what you think; score the first response, not the best response**, except item 9 (best language); and **do not coach**. (See Video: NIH Stroke Scale.)

TABLE 167-5 Stroke Mimics

Disorder	Distinguishing Clinical Features
Seizures/postictal paralysis (Todd's paralysis)	Transient paralysis following a seizure, which typically disappears quickly; can be confused with transient ischemic attack. Seizures can be secondary to a cerebrovascular accident.
Syncope	No persistent or associated neurologic symptoms.
Meningitis/encephalitis	Fever, immunocompromised state may be present, meningismus, detectable on lumbar puncture.
Complicated migraine	History of similar episodes, preceding aura, headache.
Brain neoplasm or abscess	Focal neurologic findings, signs of infection, detectable by imaging.
Epidural/subdural hematoma	History of trauma, alcoholism, anticoagulant use, bleeding disorder; detectable by imaging.
Subarachnoid hemorrhage	Sudden onset of severe headache.*
Hypoglycemia	Can be detected by bedside glucose measurement, history of diabetes mellitus.
Hyponatremia	History of diuretic use, neoplasm, excessive free water intake.
Hypertensive encephalopathy	Gradual onset; global cerebral dysfunction, headache, delirium, hypertension, cerebral edema.
Hyperosmotic coma	Extremely high glucose levels, history of diabetes mellitus.
Wernicke's encephalopathy	History of alcoholism or malnutrition; triad of ataxia, ophthalmoplegia, and confusion.
Labyrinthitis	Predominantly vestibular symptoms; patient should have no other focal findings; can be confused with cerebellar stroke.
Drug toxicity (lithium, phenytoin, carbamazepine)	Can be detected by particular toxidromes and elevated blood levels. Phenytoin and carbamazepine toxicity may present with ataxia, vertigo, nausea, and abnormal reflexes.
Bell's palsy	Neurologic deficit confined to isolated *peripheral* seventh nerve palsy; often associated with younger age.
Ménière's disease	History of recurrent episodes dominated by vertigo symptoms, tinnitus, deafness.
Demyelinating disease (multiple sclerosis)	Gradual onset. Patient may have a history of multiple episodes of neurologic findings in multifocal anatomic distributions.
Conversion disorder	No cranial nerve findings, nonanatomic distribution of findings (e.g., midline sensory loss), inconsistent history or examination findings.

*Although subarachnoid hemorrhage is a type of stroke, it has special considerations in terms of diagnosis and management. See Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage."

ISCHEMIC STROKE SYNDROMES

ANTERIOR CEREBRAL ARTERY INFARCTION

Occlusion of the anterior cerebral artery is uncommon (0.5% to 3% of all strokes[45]), but when unilateral occlusion occurs, it can cause contralateral sensory and motor symptoms in the lower extremity, with sparing of the hands and face. In addition, a left-sided lesion is typically associated with akinetic mutism and transcortical motor aphasia (a nonfluent aphasia with greatly reduced spontaneous speech, but with retained auditory comprehension and repetition ability), whereas right-sided infarction can result in confusion and motor hemineglect. Bilateral occlusion can cause a combination of the above symptoms but was particularly associated with mutism, incontinence, and poor outcome in one small series.[46]

MIDDLE CEREBRAL ARTERY INFARCTION

The middle cerebral artery is the vessel most commonly involved in stroke, and clinical findings can be quite variable, depending on exactly where the lesion is located and which brain hemisphere is dominant. (In right-handed patients and in up to 80% of left-handed patients, the left hemisphere is dominant.) A middle cerebral artery stroke typically presents with hemiparesis, facial plegia, and sensory loss contralateral to the affected cortex. These deficits variably affect the face and upper extremity more than the lower extremity. If the dominant hemisphere is involved, aphasia (receptive, expressive, or both) is often present. If the nondominant hemisphere is involved, inattention, neglect, extinction on double-simultaneous stimulation, dysarthria without aphasia, and constructional apraxia (difficulty in drawing complex two-dimensional

TABLE 167-6 National Institutes of Health Stroke Scale (NIHSS)

Instructions	Scale Definition
1a. Level of consciousness (LOC)* The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, or orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or is totally unresponsive, flaccid, and areflexic.
1b. LOC questions The patient is asked the month and his or her age. The answer must be correct—there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions are given a score of 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a score of 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or nonverbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC commands The patient is asked to open and close the eyes and then to grip and release the nonparetic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime) and the result scored (i.e., follows no, one, or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best gaze Only horizontal eye movements are tested. Voluntary or reflexive (oculocephalic) eye movements are scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score is 1. If a patient has an isolated peripheral nerve paresis (cranial nerve III, IV, or VI), the score is 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, preexisting blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If the patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a score of 1, and the results are used to respond to item 11.	0 = No vision loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial palsy* Ask—or use pantomime to encourage—the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or noncomprehending patient. If facial trauma/bandages, orotracheal tube, tape, or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetric movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor arm The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 s. (Count out loud and use fingers to show the patient the count.) The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the nonparetic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. 5a. Left arm 5b. Right arm	0 = No drift; limb holds 90 (or 45) degrees for full 10 s. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 s; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement.
6. Motor leg The limb is placed in the appropriate position: hold the leg at 30 degrees (the patient is always tested supine). Drift is scored if the leg falls before 5 s. (Count out loud and use fingers to show the patient the count.) The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the nonparetic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. 6a. Left leg 6b. Right leg	0 = No drift; leg holds 30-degree position for full 5 s. 1 = Drift; leg falls by the end of the 5-s period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 s, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement.

(*Continued*)

TABLE 167-6 National Institutes of Health Stroke Scale (NIHSS) (*Continued*)

Instructions	Scale Definition
7. Limb ataxia* This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with the patient's eyes open. In case of visual defect, ensure that testing is done in the intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. In case of blindness, test by having the patient touch the nose from an extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.
8. Sensory† Sensation or grimace to pinprick when tested, or withdrawal from a noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal, and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to check accurately for hemisensory loss. A score of 2, "severe or total sensory loss," should be given only when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a score = 3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on affected side, or there is loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched on face, arm, and leg.*
9. Best language A great deal of information about comprehension is obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the test picture, to name the items on the test naming sheet, and to read from the test list of sentences. Comprehension is judged from responses here as well as responses to all of the commands in the preceding general neurologic examination. If vision loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a score = 3) automatically scores 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. However, reduction of speech and/or comprehension makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient's response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria* If the patient is thought to be normal, an adequate sample of speech must be obtained by asking the patient to read or repeat words from the test list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN) and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.
11. Extinction and inattention Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe vision loss preventing visual double simultaneous stimulation and the responses to cutaneous stimuli are normal, the score is 0. If the patient has aphasia but does appear to attend to both sides, the score is 0. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Because the abnormality is scored only if present, the item is never scored as untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction in more than one modality; patient does not recognize own hand or orients to only one side of space.

*Items not included in the modified NIHSS.[43]

†Scale for item 8 is compressed to two elements (0 = normal; 1 = abnormal) for modified NIHSS.[43]

Source: National Institute of Neurological Disorders and Stroke (NINDS) website (https://www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale.pdf). Accessed September 11, 2018.

or three-dimensional figures) may occur. A homonymous hemianopsia and gaze preference toward the side of the infarct may also be seen, regardless of the side of the infarction.

POSTERIOR CEREBRAL ARTERY INFARCTION (DISTAL POSTERIOR CIRCULATION)

The classic symptoms and signs of posterior circulation strokes include ataxia, nystagmus, altered mental status, and vertigo, but presentation can sometimes be rather subtle.[47] Crossed neurologic deficits (e.g., ipsilateral cranial nerve deficits with contralateral motor weakness) may indicate a brainstem lesion. According to an analysis of a large stroke registry,[48] symptoms of posterior cerebral artery involvement include unilateral limb weakness, dizziness, blurry vision, headache, and dysarthria. Common presenting signs include visual field loss, unilateral limb weakness, gait ataxia, unilateral limb ataxia, cranial nerve VII signs, lethargy, and sensory deficits.[48] Visual field loss, classically described as contralateral homonymous hemianopsia and unilateral cortical blindness, is thought to be specific for distal posterior circulation stroke because the visual centers of the brain are supplied by the posterior cerebral artery. Light-touch and pinprick sensation deficits, loss of ability to read (alexia) without agraphia, inability to name colors, recent memory loss, unilateral third nerve palsy, and hemiballismus have also been reported. Motor dysfunction, although common, is typically minimal, which can keep some patients from realizing they have had a stroke.

BASILAR ARTERY OCCLUSION (MIDDLE POSTERIOR CIRCULATION)

Occlusion of the basilar artery most commonly presents with symptoms of unilateral limb weakness, dizziness, dysarthria, diplopia, and headache.[48] The most common presenting signs are unilateral limb

weakness, cranial nerve VII signs, dysarthria, Babinski sign, and oculomotor signs.[48] Dysphagia, nausea or vomiting, dizziness, and Horner's syndrome are positively correlated with basilar artery occlusion.[48] Basilar artery occlusion can also rarely cause locked-in syndrome, which occurs with bilateral pyramidal tract lesions in the ventral pons and is characterized by complete muscle paralysis except for upward gaze and blinking. Basilar artery occlusions have a high risk of death and poor outcomes.[49,50]

VERTEBROBASILAR INFARCTION (PROXIMAL POSTERIOR CIRCULATION)

Patients with vertebrobasilar infarction most commonly present with symptoms of dizziness, nausea or vomiting, headache, dysphagia, unilateral limb weakness, and unilateral cranial nerve V symptoms.[48] Common presenting signs include unilateral limb ataxia, nystagmus, gait ataxia, cranial nerve V signs, limb sensory deficit, and Horner's syndrome.[48] For further discussion of vertigo, see Chapter 170, "Vertigo."

CEREBELLAR INFARCTION

Patients with cerebellar infarction can present with very nonspecific symptoms and can present with dizziness (with or without vertigo), nausea and vomiting, gait instability, headache, limb ataxia, dysarthria, dysmetria, nystagmus, hearing loss, and intractable hiccups.[51] Mental status may vary from alert to comatose. Because up to 25% of noncontrasted head CTs can be normal in cerebellar infarction,[52] if the initial noncontrasted head CT is unremarkable, **obtain an emergent diffusion-weighted MRI when this diagnosis is suspected**. A CT angiogram or magnetic resonance angiogram is useful to characterize any vascular lesion once the diagnosis is made. The clinical presentation and course of cerebellar infarction can be frustratingly difficult to predict, but the clinician must remain vigilant to the possibility of rapid deterioration secondary to increased brainstem pressure caused by cerebellar edema. Therefore, extremely close serial examinations (especially looking for gaze palsy and altered mental status) and prompt neurologic and neurosurgical bedside consultations are needed. **Obtain early neurosurgical consultation for patients with cerebellar infarction.** Cerebellar edema can lead to rapid deterioration with herniation, and consultation is required to determine the need for emergency posterior fossa decompression in these patients. Acute **obstructing hydrocephalus or symptomatic mass effect** requires rapid treatment of elevated intracranial pressure with hyperosmolar therapy (mannitol or hypertonic saline) and emergent surgical decompression.[51]

LACUNAR INFARCTION

Lacunar infarcts are pure motor or sensory deficits caused by infarction of small penetrating arteries and are commonly associated with chronic hypertension and increasing age. The presentation is variable based on the location and size of the lesions. The prognosis is generally considered more favorable than for other stroke syndromes.

CAROTID AND VERTEBRAL ARTERY DISSECTION

Carotid or vertebral artery dissection (**collectively referred to as "cervical artery dissection**") is an uncommon entity (2.6 to 2.9 per 100,000 annually in the general population) that is a major cause of stroke (up to 20% prevalence) in young adults and the middle-aged.[53] A history of neck trauma in the days to weeks prior to presentation is a prominent risk factor. The trauma is usually minor[54] (e.g., manipulative therapy of the neck[55-57] or sport-related trauma[58]). Other associated conditions include hypertension,[59] large-vessel arteriopathies,[60] history of migraine,[61] and heritable connective tissue disease.[62]

The typical first symptom of patients with carotid or vertebral artery dissection is unilateral **headache** (68%), neck pain (39%), or face pain (10%),[63] which can precede other symptoms by hours to days (median, 4 days).[64] New-onset headache or neck pain of unclear etiology is such an important symptom that imaging of the neck vessels is recommended by some as part of initial evaluation.[65] **Symptoms may be transient or persistent.** The median time between an initial presentation of neck pain and the development of other neurologic symptoms is 14 days, but if headache is the first symptom, other neurologic symptoms follow within a median time of 15 hours.[64]

CAROTID ARTERY DISSECTION

The headache is most commonly in the frontotemporal region and, due to its variable quality and severity, may mimic subarachnoid hemorrhage (i.e., "thunderclap" headache), temporal arteritis, or preexisting migraine. A partial Horner's syndrome (miosis and ptosis) has traditionally been linked to carotid artery dissection, but in reality, it occurs in only about 25% of patients and is a sign accompanying other disorders besides stroke.[66] Associated cranial nerve palsies have been reported in 12% of carotid artery dissections.[67] Carotid dissection can progress to cause cerebral ischemia or, rarely, retinal infarction.

VERTEBRAL ARTERY DISSECTION

Vertebral artery dissection commonly presents with dizziness/vertigo (58%), headache (51% to 65%), and neck pain (46% to 66%).[63,68] Both headache and neck pain can be unilateral or bilateral.[63] The headache is typically occipital, but can rarely present with pain on an entire side of the head or in the frontal region.[69] Other symptoms and signs may include unilateral facial paresthesia, dizziness, vertigo, nausea/emesis, diplopia and other visual disturbances, ataxia, limb weakness, numbness, dysarthria, and hearing loss. Cervical radiculopathy (typically a peripheral motor deficit at the C5 level) is a rare presentation (1%) and can also involve multiple levels and sensory findings.[70] Untreated vertebral artery dissection may result in infarction in regions of the brain supplied by the posterior circulation.

CT/CT angiography and MRI/magnetic resonance angiography are the diagnostic modalities of choice for suspected carotid, vertebral, or basilar artery dissection and have similar test performance characteristics.[71] The choice of study is usually determined by immediate availability and patient stability. The sensitivity of color duplex US for the detection of cervical artery dissection is comparatively low (approximately 92%) and may miss important vascular lesions.[72,73]

TREATMENT OF CAROTID AND VERTEBRAL ARTERY DISSECTION

Cervical artery dissection can cause ischemic stroke via a thromboembolic process, or a decreased blood flow secondary to the vascular lesion itself, or from a mixed mechanism.[74] If a patient with cervical artery dissection presents with the symptoms of acute ischemic stroke, **treat them similarly to any other stroke patient.** Although no large-scale randomized trials regarding systemic thrombolysis in cervical artery dissection have yet been published, a meta-analysis of 10 observational studies (n = 846) concluded that thrombolysis was equally efficacious in stroke from cervical artery dissection as in stroke from other causes.[75] Furthermore, the study determined that thrombolysis in cervical artery dissection caused no increased incidence of harm when compared to its use in stroke from other causes.[75] Therefore, **consider the administration of IV thrombolytic therapy in all eligible patients with stroke from cervical artery dissection**. The efficacy of endovascular therapy for cervical artery dissection–related stroke is unclear because the benefits of endovascular therapy have been shown only for the anterior circulation (see later section "Endovascular Therapy"), and there is a paucity of published data to direct care in these patients. For example, after excluding many studies for low quality, a 2017 meta-analysis studying this issue was able to include only 16 retrospective case reports or small case series, which had "an overall high risk of bias."[76] Although the outcome trend in the included data was favorable for endovascular therapy, the lack of high-quality randomized data makes drawing definitive conclusions difficult. Therefore, if a patient with cervical artery dissection–related stroke qualifies for consideration of endovascular therapy, discuss with a stroke neurointerventionalist at a comprehensive stroke center to help determine the best course of action.

In cervical artery dissection patients who are not candidates for thrombolysis or endovascular therapy, the two major medical choices

for treatment are **anticoagulation or antiplatelet therapy**. Historically, carotid and vertebral artery dissection has been traditionally treated with IV heparin followed by warfarin (to maintain an INR of 2.0 to 3.0). This treatment has persisted despite the absence of high-quality randomized controlled trials comparing anticoagulation with other potentially more effective treatment modalities.[77] In 2012 and 2015, meta-analyses of nonrandomized trials found no difference in patient outcomes between antiplatelet therapy and anticoagulation.[78,79] In 2015, the Cervical Artery Dissection in Stroke Study was published.[80] The Cervical Artery Dissection in Stroke Study was the first randomized trial comparing antiplatelet agents (aspirin, dipyridamole, or clopidogrel alone or in combination [determined by the individual clinician]) to anticoagulation (heparin [either unfractionated heparin or therapeutic low-molecular-weight heparin] followed by warfarin) in acute cervical artery dissection. **The Cervical Artery Dissection in Stroke Study found no difference in patient outcomes between the two treatment modalities**. An important caveat is that based on previous estimates of recurrent stroke prevalence, the planned study size was small (n =250). However, during the trial, it was discovered that the prevalence of recurrent stroke in both the control and study groups was far lower than expected and there were no deaths. Based on these data, the authors determined the study lacked the power to detect a difference between the two treatment modalities and that the revised sample size to do so (n = 10,000) made further investigation unfeasible.[81] Therefore, pending the availability of new randomized controlled trial data, **administer either anticoagulant or antiplatelet therapy in the ED if the patient is not a candidate for IV thrombolysis**. Select the specific therapy in conjunction with appropriate specialist consultation.

HEMORRHAGIC STROKE SYNDROMES

Spontaneous **intracerebral hemorrhage** may be clinically indistinguishable from ischemic infarction, but the two conditions are distinct clinical entities in terms of management, with higher levels of morbidity and mortality for hemorrhage than for ischemic infarction.[82,83] Therefore, perform CT to differentiate between the two. Headache, nausea, and vomiting often precede the neurologic deficit, and the patient's condition may quickly deteriorate (see Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage").

Cerebellar hemorrhage may be clinically indistinguishable from cerebellar infarction. The same clinical presentation and management considerations detailed earlier in this chapter apply (see earlier section "Cerebellar Infarction").

Subarachnoid hemorrhage is typically characterized by a severe occipital or nuchal headache. Patient history includes the recent sudden onset of a maximal-intensity headache in many cases. Careful history taking may reveal activities associated with a Valsalva maneuver, such as defecation, sexual activity, weight lifting, or coughing, at stroke onset. For further information, see Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage."

STROKE DIAGNOSIS

Mimics (Table 167-5)[28-30] can often be distinguished from stroke by careful history taking and physical examination, bedside tests, observation, and appropriate imaging. However, it can be difficult to distinguish conditions with focal transient symptoms (e.g., seizure) from transient ischemic attack (TIA).

INITIAL DIAGNOSTIC EVALUATION

The classic mantra, "**time is brain**,"[84] explains the current AHA/ASA stroke guidelines Class IB recommendation to enact "an organized protocol for the emergency evaluation of patients with suspected stroke" in which the primary goal is to achieve a door-to-needle time of ≤60 minutes of ED arrival in ≥50% of acute ischemic stroke patients who are treated with thrombolytics.[19] Based on performance data in hospitals participating in the "Get with the Guidelines—Stroke" initiative (i.e., median door-to-needle time 56 minutes; 30% treated in ≤45 minutes),[85] it seems likely that the recommended door-to-needle time goal will decrease in the future. Creation of a multidisciplinary stroke team is recommended, along with implementation of quality improvement initiatives to "safely increase IV thrombolytic treatment."[19] The culture of the institution should be aligned to encourage rapid diagnosis and treatment of stroke. Train triage personnel to suspect stroke and to quickly activate a stroke critical pathway that includes specific standing orders and procedures. Implement the critical pathway immediately upon that patient's arrival, beginning in the triage area. Notify the emergency physician, the ED charge nurse, and the CT and laboratory technicians immediately when acute stroke is suspected. Do not delay the workup because ED beds are overcrowded or the emergency physician is currently otherwise engaged. ED core interventions are listed in **Table 167-7**.[19,86-98]

Nonessential testing and procedures (including IV starts and blood draws) should ***not*** delay performing brain imaging **within 20 minutes of the patient's arrival. A summary of time goals is listed in Table 167-8**.[19]

BRAIN IMAGING

Obtain emergency non–contrast-enhanced CT for suspected acute stroke upon arrival. **Most acute ischemic strokes are not visualized by a noncontrast brain CT in the early hours of a stroke.**[23] Therefore, the utility of the first brain CT is primarily to exclude intracranial bleeding, abscess, tumor, and other stroke mimics, as well as to detect current contraindications to thrombolytics (e.g., "extensive regions of clear hypoattenuation").[19]

The CT scan should be interpreted by the most expert interpreter available as soon as it is completed. The identification of subtle hemorrhage and early cerebral infarction requires expertise. In hospitals without on-site experts, telemedicine consultation is an option. Studies have shown fair to excellent interobserver agreement in CT readings between telemedicine stroke neurologists and neuroradiologists,[99,100] and telemedicine was associated with faster head CT interpretation in a cohort of 19 rural critical access hospitals.[101] In one retrospective study (n = 1659), even when there were differing CT interpretations between telemedicine stroke neurologists and overreading neuroradiologists in patients who received thrombolytics, there was no association with thrombolysis-related symptomatic intracranial hemorrhage.[99]

Diffusion-weighted MRI is superior to non–contrast-enhanced CT or other types of MRI (T1/T2 weighted, fluid-attenuated inversion recovery) in the detection of acute infarction.[102,103] However, CT's superior rapid availability, MRI's patient-specific contraindications (lack of cooperation, claustrophobia, metallic implants or pacemakers, and diminished access to the patient), the relative inexperience in some practitioners in interpreting MRI scans in acute stroke, and cost-effectiveness[102] work in CT's favor for this indication. Therefore, **in the vast majority of EDs, a non–contrast-enhanced CT is the most readily available imaging study and is the *only* imaging study necessary prior to administration of thrombolytics**.[19] An emerging exception to this general rule is in the case of patients in whom time of stroke symptom onset is uncertain. One trial found that patients with ischemic stroke seen with diffusion-weighted MRI, but no hyperintensity of the parenchyma seen on fluid-attenuated inversion recovery, benefited from IV thrombolytic therapy[104] (see later section "Thrombolysis: Indications, Exclusions, Dosage, and Complications"). Nevertheless, even in these patients, non–contrast-enhanced CT is still the imaging mode of first choice.

VASCULAR IMAGING

With the advent of endovascular therapies, identifying the presence of intracranial large-vessel stenosis or occlusion is important for therapeutic decisions. CT angiography or magnetic resonance angiography can detect these lesions. If a patient is a possible candidate for endovascular therapy, vascular imaging (typically CT angiography of the head and neck) is recommended concurrently with the initial head CT; however, these additional studies **should not delay thrombolytic administration**.[19] In other words, if a patient is a candidate based on the initial CT, **do not delay thrombolytic administration while waiting to perform CT angiography or to receive the results of CT angiography**. Therefore, if an

TABLE 167-7 Core ED Interventions for Suspected Acute Stroke

Intervention/Evaluation	Rationale/Discussion
All patients	
Assessment of airway, breathing, circulation	Immediate life threats must be addressed before other interventions are undertaken. Actively manage airway if necessary.
Establish IV access	IV access is necessary for possible thrombolytic therapy. (**Do not delay brain imaging for prolonged IV access attempts.**)
Pulse oximetry	To detect hypoxia.
Oxygen administration (if hypoxia is present)	Routine oxygen supplementation is not indicated in stroke[86] and should be given only to keep oxygen saturation >94%.
Cardiac monitoring	Dysrhythmias, especially atrial fibrillation, are not infrequent in acute stroke and may predict 3-month mortality.[87,88] Prophylactic administration of antiarrhythmic agents is not indicated.
Bedside glucose determination	To rapidly rule out hypoglycemia mimicking stroke. Treat hypoglycemia (<60 milligrams/dL) with IV dextrose. **This is the only laboratory test result required prior to thrombolytic therapy**[19] *unless* the patient is taking oral anticoagulation therapy or heparin, or if there is a strong suspicion of thrombocytopenia or other bleeding diatheses[19] (see Table 167-11).
Noncontrasted brain CT or MRI	To exclude intracerebral hemorrhage, other contraindications to IV thrombolytics, or stroke mimics. (See discussion in "Brain Imaging" section of this chapter.)
ECG	Acute coronary syndrome, dysrhythmias (especially **atrial fibrillation**), ECG changes, and abnormal cardiac biomarkers are frequently associated with acute stroke.[89,90] ECG abnormalities and abnormal troponin T levels may also predict short-term and 3-mo mortality.[87,91] A large study (n = 9180) of consecutive stroke patients revealed that 2.3% suffered a subsequent myocardial infarction, with 64.9% morbidity/mortality compared with 35.8% in the entire cohort.[92] A 2016 meta-analysis (n = 52,098) determined that one third of ischemic stroke patients with no previous cardiac history had >50% coronary stenosis. There was also a 3% overall risk of having an myocadiac infarction within a year of an acute stroke.[93]
CBC including platelet count	To detect polycythemia, thrombocytosis, or thrombocytopenia.
Coagulation studies	To detect preexisting coagulopathy in hemorrhagic stroke or when thrombolytics are being considered in circumstances where there is a strong suspicion of the possibility of a coagulopathy (see Table 167-11).
Electrolyte levels	To detect electrolyte-imbalance stroke mimics (particularly Na^+ and Ca^{2+}).
Cardiac biomarker levels	See "ECG" earlier in this table. A 2018 study also found that an elevated B-type natriuretic peptide within 48 hours was associated with a pure cardiac stroke mechanism (odds ratio 4.35; 95% confidence interval 2.59–7.29; $P < .5$) and may be useful in detecting cardiac etiologies of ischemic stroke.[94]
Nothing by mouth (NPO) order	To protect against aspiration.
Strict bed rest in the ED	To protect against falls and seizures (in the period immediately after stroke). In patients who can maintain oxygenation, supine position has been suggested to possibly improve patient outcomes by enhancing cerebral blood flow[95]; however, a large (n = 11,093) cluster-randomized, crossover trial found no difference in stroke patient outcomes between lying flat for 24 hours and head of bed elevation to at least 30 degrees.[96] However, significant methodologic concerns about this study have been raised, and optimal head positioning for stroke remains controversial.[97] That said, it is probably reasonable to consider raising the head of the bed to 15 to 30 degrees in patients at risk for hypoxia, airway compromise, aspiration, or suspected increased intracranial pressure.
Selected patients	
Chest radiograph	Routine chest radiography in asymptomatic patients is *not* recommended and should be reserved only for situations where a cardiopulmonary contraindication to thrombolytics is suspected or if immediate management would be significantly impacted by chest radiograph findings.[98]
Urinalysis	To detect infectious stroke mimics or stroke-associated infections.
Pregnancy test (if female of childbearing age)	Pregnancy influences diagnosis and management considerations.
Toxicology screen and/or blood alcohol level (if ingestion suspected)	To detect stroke mimics as well as potential causes of stroke such as ingestion of a sympathomimetic (e.g., cocaine, methamphetamine, phencyclidine).
Lumbar puncture (if infection or subarachnoid hemorrhage suspected)	To detect stroke mimics. 2018 American Heart Association/American Stroke Association guidelines recommend that based on consensus expert opinion (Class IIb; Level of evidence: C-EO), IV thrombolysis may be considered in patients who have undergone lumbar puncture in the preceding 7 d.[19]

indicated CT angiography is not done with the initial head CT, it is reasonable to administer thrombolytics after the noncontrasted CT and then return the patient to the CT scanner for CT angiography to minimize door-to-needle time.[19] It is important to realize that in patients with no history of renal insufficiency, it is **not** necessary to have a serum creatinine result prior to performing contrasted studies for stroke, because these studies are not associated with significantly increased risk of acute kidney injury.[105-107]

TABLE 167-8 AHA/ASA Time Recommendations for Acute Ischemic Stroke Presenting to the ED

Intervention	Time Goal (from ED arrival)
Activation of stroke team	Immediately upon arrival
Start of brain imaging	≤20 minutes
Administration of IV thrombolytics	≤60 minutes (secondary goal ≤45 minutes)

Abbreviation: AHA/ASA = American Heart Association/American Stroke Association.

PERFUSION STUDIES

In acute ischemic stroke, the area of irreversible brain infarct (**core**) is surrounded by ischemic tissue that may potentially be salvageable, regardless of the time of onset of symptoms. The size of this **penumbra region** cannot be ascertained clinically, so perfusion CT and diffusion-weighted MRI/fluid-attenuated inversion recovery can be used to measure the size of the penumbra and to guide further therapy for patients who fall outside the time ranges for thrombolysis or where the time of symptom onset is unclear.[108] However, to date, there are only two major positive studies in these particular patients that used perfusion

studies to select candidates for endovascular therapy in their protocols (see later section "Endovascular Therapy"): the Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial[109] and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution trial (DEFUSE 3).[110] Therefore, the current AHA/ASA guidelines **do not recommend routine use of perfusion studies in *all* stroke patients**. Rather, they primarily advocate using perfusion studies in the context of strict adherence to DAWN and DEFUSE 3's inclusion and exclusion criteria when treating patients outside of clinical trials.[19] This point has become an issue of debate because of the publication of positive studies on patients who awaken with stroke symptoms ("wake-up strokes") that used CT perfusion to aid in selecting patients for thrombolytic therapy.[104,111,112] These studies and clinician feedback caused the AHA/ASA to withdraw the portion of their 2018 guidelines that suggested using perfusion studies in selecting patients for endovascular therapy in <6 hours was **not** beneficial.[22] **Therefore, at this time, the best use of perfusion studies in acute stroke remains somewhat unsettled**, but it is likely to be pivotal in the management of patients with unknown or prolonged last known well times[113] and in patients with TIA (see later section "TIA Risk Stratification and Disposition").

GENERAL TREATMENT OF ACUTE ISCHEMIC STROKE

STANDARD TREATMENT

Initial ED stabilization and interventions are listed in Table 167-7.[19,86-98] Many of these interventions are consensus based. Not all patients will be eligible for thrombolytics, so it is important to follow general treatment principles for all patients.

Dehydration can contribute to worsened outcomes in ischemic stroke patients secondary to increased blood viscosity, hypotension, renal impairment, and venous thromboembolism.[114,115] However, routine volume expansion and hemodilution do not improve outcomes in stroke patients.[116] Therefore, correct dehydration if present with IV crystalloid fluids, but do not overcorrect. For euvolemic patients, provide maintenance fluids.

Routine oxygen supplementation is not indicated in stroke[86] and should be given only if necessary to **keep oxygen saturation >94%**. Hyperbaric oxygenation treatment is of no benefit.[117]

Fever is associated with increased morbidity and mortality in stroke,[118] possibly due to fever-related inflammatory response,[118] increased metabolic demands, and free radical production.[119] Identify the source of fever and treat the underlying cause (e.g., infection). While it is traditional to treat the fever itself with acetaminophen, strong evidence of favorable outcomes as a result of doing this remains elusive.[120,121] Avoid ibuprofen for temperature regulation, as it has been shown to not lower temperature in these patients[122] and may be associated with risk of bleeding. In addition, physical cooling measures should be considered second-line therapies only,[123] as their benefit has not been established.[124]

Admit all acute stroke patients to monitored care units familiar with the care of stroke patients, preferably to specialized stroke units at designated stroke centers. The use of stroke units has been associated with decreased complications and length of stay, improved daily function, decreased rate of discharge to long-term care facilities, and increased likelihood of being able to live at home in the long term—with the benefit being independent of thrombolytic use.[125-127] If a patient with acute stroke presents to a facility that lacks these resources, consider transferring the patient to a higher level of care after the patient's condition has stabilized and IV thrombolytics have been given, as indicated—the "drip and ship" model. Emergent, early consultation with an experienced stroke physician at the accepting institution is desirable in these circumstances.

BLOOD PRESSURE CONTROL IN STROKE

The optimal blood pressure for acute ischemic stroke victims is unknown; however, based on consensus opinion, the current AHA/ASA acute stroke guidelines[19] recommend that hypotension and hypovolemia be corrected with either colloids or crystalloids[128] to maintain organ perfusion; however, there is no specific target blood pressure for patients not eligible for reperfusion therapy.

Conversely, based on the blood pressure guidelines used in randomized controlled trials of thrombolytics, blood pressure control is considered essential prior to, during, and after thrombolytic therapy. A systolic blood pressure >185 mm Hg or a diastolic blood pressure >110 mm Hg is a contraindication to the use of thrombolytics[19] because elevated blood pressure (both before and after thrombolysis)[129,130] is associated with increased risk for hemorrhagic transformation of ischemic stroke. Elevated pretreatment blood pressure is common (20%),[131] and a strategy of active management of elevated blood pressure as opposed to watchful waiting may increase the proportion of patients able to receive thrombolysis.[131,132] **Therefore, if a patient is a candidate for thrombolytics, lower blood pressure to meet these entry parameters.** An approach to management of arterial hypertension is detailed in **Table 167-9**[19] and **Table 167-10**.[19] If the target arterial blood pressures cannot be reached with these measures, **then the patient is no longer a candidate for thrombolytic therapy**. Similarly, based on randomized controlled trials of intra-arterial therapy, the same blood pressure goal of ≤185/110 mm Hg is recommended for those who are candidates for intra-arterial therapy.[19] Preliminary studies also suggest that less favorable outcomes after thrombectomy are also associated with elevated baseline blood pressures.[133]

TABLE 167-9 Management of Hypertension Before Administration of Recombinant Tissue Plasminogen Activator (rtPA) or in Patients Awaiting Thrombectomy

If the patient is a candidate for rtPA therapy, the target arterial blood pressures are **systolic blood pressure ≤185 mm Hg and diastolic blood pressure ≤110 mm Hg.**

Drug	Comments
Labetalol, 10–20 milligrams IV over 1–2 min, may repeat ×1	Use with caution in patients with severe asthma, severe chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, myasthenia gravis, concurrent calcium channel blocker use, hepatic insufficiency. May cause dizziness and nausea.
or	
Nicardipine infusion, 5 milligrams/h, titrate up by 2.5 milligrams/h at 5- to 15-min intervals; maximum dose: 15 milligrams/h; when desired blood pressure attained, reduce to 3 milligrams/h	Use with caution in patients with myocardial ischemia, concurrent use of fentanyl (hypotension), congestive heart failure, hypertrophic cardiomyopathy, portal hypertension, renal insufficiency, hepatic insufficiency (may need to adjust starting dose). Contraindicated in patients with severe aortic stenosis. Can cause headache, flushing, dizziness, nausea, reflex tachycardia.
or	
Clevidipine infusion, 1–2 milligrams/h, titrate up by doubling dose every 2–5 min; maximum dose: 21 milligrams/h	Use with caution in patients with congestive heart failure. Can cause reflex tachycardia atrial fibrillation, and systemic hypotension. Contraindicated in patients with severe aortic stenosis, allergies to soy or eggs, and lipid metabolism disorders (e.g., pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis with hyperlipidemia).
Alternative agents such as hydralazine or enalaprilat may be considered if clinically appropriate.	
If the target arterial blood pressures for rtPA administration cannot be reached with these initial measures, then ***the patient is no longer a candidate for rtPA therapy***.	

HYPERGLYCEMIA

The current AHA/ASA guidelines recommend the maintenance of blood glucose between 140 milligrams/dL (7.77 mmol/L) and 180 milligrams/dL (9.99 mmol/L).[19] Avoid and treat hypoglycemia (<60 milligrams/dL

TABLE 167-10 Management of Hypertension During and After Administration of Thrombolytics or Other Acute Reperfusion Therapy

Blood Pressure Monitoring Frequencies	
Time After Start of rtPA Infusion	**Frequency of Blood Pressure Monitoring**
0–2 h	Every 15 min
3–8 h	Every 30 min
9–24 h	Every 60 min
Drug Treatment of Hypertension During and After Administration of Thrombolytics or Other Acute Reperfusion Therapy	
If systolic blood pressure is >180–230 mm Hg or diastolic blood pressure is >105–120 mm Hg	Labetalol, 10 milligrams IV followed by infusion at 2–8 milligrams/min. *or* Nicardipine infusion, 5 milligrams/h, titrate up by 2.5 milligrams/h at 5- to 15-min intervals; maximum dose 15 milligrams/h. *or* Clevidipine infusion, 1–2 milligrams/h, titrate up by doubling dose every 2–5 min; maximum dose 21 milligrams/h.
If blood pressure is not controlled by above measures or if diastolic blood pressure >140 mm Hg	Consider sodium nitroprusside infusion (0.5–10 micrograms/kg/min). Continuous arterial monitoring advised; use with caution in patients with hepatic or renal insufficiency. Increases intracranial pressure. Pregnancy category C.

[3.33 mmol/L]). Remember that both hypoglycemia and hyperglycemia are important stroke mimics.

Hyperglycemia is common in acute stroke,[134,135] and glycemic control has been recommended based on data that associate less favorable outcomes with hyperglycemia.[136-138] However, data to support improved outcomes with tight glycemic control are lacking,[139,140] and hypoglycemia must be avoided because it is associated with brain dysfunction.[140]

ANTIPLATELET THERAPY

The current AHA/ASA guidelines recommend the administration of oral (or by rectum if swallowing impairment is present) aspirin within 24 to 48 hours after stroke onset unless thrombolytics have been given within the prior 24 hours.[19] No antiplatelet agent (including aspirin) should be given within 24 hours of receiving thrombolytic therapy. When the results of the International Stroke Trial[141] and the Chinese Acute Stroke Trial[142] are combined (40,000 patients), these studies demonstrate significant reduction in mortality and morbidity rates (at 4 weeks and 6 months) when aspirin (dose 160 to 300 milligrams) is administered to acute ischemic stroke patients within 48 hours.[143] The benefit seems due mainly to reduction of recurrent stroke. Aspirin is cost-effective and adds no risk to the outcome of ischemic stroke.[143] In eligible patients with aspirin contraindications, it might be reasonable to consider alternative antiplatelet drugs, but evidence for their efficacy is limited.[19] In terms of combination antiplatelet therapy, the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial found that mild stroke patients who received clopidogrel along with aspirin within 24 hours had fewer recurrent strokes (hazard ratio 0.68; 95% confidence interval [CI], 0.57 to 0.81; number needed to treat = 29)[144,145] and better functional outcomes (1.7% absolute reduction of poor functional outcome; 95% CI, 0.03% to 3.42%; number needed to treat = 59)[146] in 90 days than patients who received aspirin alone. However, the CHANCE study patients had mild, nondisabling strokes or TIAs, and the study was performed entirely in China. Therefore, these results await wider external validation before they can be recommended routinely. **Antiplatelet therapy is contraindicated in acute hemorrhagic stroke.**

THROMBOLYSIS BACKGROUND

NINDS STUDY

The National Institutes of Health/NINDS study[147] was a randomized double-blind trial comparing IV alteplase with placebo. The drug was administered within 3 hours of symptom onset, with approximately one half of patients treated within 90 minutes. Outcomes were measured using four different neurologic outcome scales (including the NIHSS) and a global statistic. Although there was no difference in the treatment and control groups at 24 hours, at 3 months, the odds ratio (OR) for a favorable outcome in treated patients was 1.7 (95% CI, 1.2 to 2.61; $P = .008$), an 11% to 13% absolute risk reduction benefit (number needed to treat = 8 to 9 for tPA <3 hours). Put another way, 31% to 50% of the patients receiving alteplase (depending on the scale used) had a favorable outcome at 3 months compared with 20% to 38% of patients given placebo. Benefit was found regardless of ischemic stroke subtype and was sustained 1 year after therapy. Symptomatic intracerebral hemorrhage attributable to thrombolytics occurred in 6.4% of patients in the alteplase group (45% mortality), whereas symptomatic intracerebral hemorrhage occurred in 0.6% of those in the placebo group (50% mortality). Despite this increased rate of intracerebral hemorrhage, the mortality rate at 3 months was not significantly different for the treatment and placebo groups (17% vs. 21%, respectively; $P = .30$), and the percentage of patients left severely disabled was lower among those receiving thrombolytics.[147] The NINDS trial represented the first randomized placebo-controlled trial that showed benefit of IV alteplase in acute stroke. Prior trials using different thrombolytic agents, different dosing of thrombolytics, or different treatment windows failed to show benefit or showed harm. **Based largely on the NINDS data, in 1996, the U.S. Food and Drug Administration approved the use of IV alteplase in acute ischemic stroke within 3 hours of stroke onset.**

Concerns have been raised about the NINDS trial results.[148,149] The NINDS trial, although well designed, was relatively small and studied 624 patients total, 312 of whom received alteplase. As a result of chance, there existed an imbalance in baseline stroke severity between the two groups that apparently favored the thrombolytic group. Therefore, the NINDS investigators commissioned an independent reanalysis of the data[150] in 2004 that took this imbalance into account. This reanalysis found that, despite the imbalance, the originally described benefit of alteplase held. The authors concluded that "these findings support the use of alteplase to treat patients with acute ischemic stroke within 3 hours of onset."[150] However, they did concede the need to collect further data to determine which particular stroke subgroups would benefit or be harmed. In 2009, a graphic reanalysis of the NINDS trial data set was published,[151] which showed very small differences in the treatment and placebo group outcomes, with a slight favoring of thrombolytic treatment. Therefore, the authors concluded that the reported NINDS results could have resulted from confounding alone. However, the methodology of this reanalysis was challenged in a subsequent graphic reanalysis of the NINDS data that supported the original results,[152] although these critiques have also been challenged in turn.[153] Finally, the reliability of one of the primary measures of stroke disability in NINDS and subsequent trials, the modified Rankin scale, has been questioned.[154]

SUBSEQUENT THROMBOLYTIC TRIALS

The European Cooperative Acute Stroke Study III (ECASS III) demonstrated efficacy with an expansion of the treatment window to 4.5 hours.[31] The OR favored treated patients (OR 1.34; 95% CI, 1.02 to 1.76), and the post hoc analysis, which adjusted for confounding variables, yielded similar statistical results (OR 1.42; 95% CI, 1.02 to 1.98). Although the incidence of intracerebral hemorrhage was higher in the treated group than the placebo group (27% vs. 17%) and the incidence of symptomatic hemorrhage was also higher in the treated group (2.4% vs. 0.2%; 7.9% vs. 3.5% when the NINDS definition of symptomatic hemorrhage was used), mortality was similar in both groups (7.7% in the rtPA group and 8.4% in the control group). Based on these data, AHA/ASA issued a 2009 scientific advisory[155] that recommended **thrombolytics should be administered to eligible patients who present between 3 and 4.5 hours of an acute stroke, as long as they meet the ECASS III criteria** (see **Table 167-11**). However,

TABLE 167-11 Summary of American Heart Association (AHA)/American Stroke Association (ASA) 2018 Inclusion/Exclusion Criteria for IV Alteplase in Acute Ischemic Stroke

Inclusion Criteria	
Onset of symptoms <3 h prior to thrombolytic administration	Defined as the time the patient was last known well or last known to be at their neurologic baseline.
Measurable diagnosis of acute ischemic stroke	Use of NIHSS score recommended. There is no upper or lower limit of NIHSS score for thrombolytics, as benefit may be seen with both mild but disabling stroke symptoms[170] as well as in very severe strokes.[158] Early improvement with residual moderate impairment and potential disability is not a contraindication.
Age ≥18 y	No upper age limit for <3 h last known well time administration.
Onset of symptoms from 3 to 4.5 h prior to rtPA administration	Must meet the above inclusion criteria, *plus* these additional inclusion criteria: Age ≤80 y No history of diabetes mellitus and prior stroke NIHSS score ≤25 Not taking oral anticoagulants No brain imaging evidence of ischemic injury involving greater than one third of the middle cerebral artery territory
Exclusion Criteria	
Last known well time >3 or 4.5 hours	
Acute intercranial hemorrhage or history of intracranial hemorrhage	
Symptoms and signs suggestive of subarachnoid hemorrhage	
CT brain imaging that exhibits extensive regions of clear hypoattenuation (obvious hypodensity)	
Prior ischemic stroke or severe head trauma within 3 months	
Acute posttraumatic brain infarction that occurs during acute in-hospital phase	
Intracranial/intraspinal surgery within 3 months	
GI malignancy or GI bleeding within 21 days	
Pretreatment systolic blood pressure >185 mm Hg *or* diastolic blood pressure >110 mm Hg **despite therapy** (see Table 167-9)	
Platelet count <100,000/mm^3	If patient has no history of thrombocytopenia, thrombolytics may be given before this lab result is available; however, stop thrombolytics if the platelet count is <100,000/mm^3.
INR >1.7 or activated PTT >40 s, or prothrombin time >15 s	If patient is not taking oral anticoagulant or heparin, thrombolytics may be given before this lab result is available; however, stop thrombolytics if these lab tests come back elevated above normal limits. Oral anticoagulant use in and of itself is not a contraindication, but these labs should be checked prior to administration of thrombolytics if the patient is taking oral anticoagulants or heparin.
Use of low-molecular-weight heparin within preceding 48 h	
Current use of **direct thrombin inhibitors** or **direct factor Xa inhibitors** with elevated sensitive laboratory tests (such as activated PTT, INR, platelet count, and ecarin clotting time [ECT]; thrombin time; or appropriate factor Xa activity assays)	Thrombolytics may be given before coagulopathy labs results available if the patient has not received a dose of these agents for >48 h *and* if renal function is normal. Thrombolytics may be given if the appropriate coagulopathy laboratory tests are not elevated.
Current use of glycoprotein IIb/IIIa receptor inhibitors	
Current infective endocarditis	
Known or suspected aortic arch dissection	
Intra-axial intracranial neoplasm	
Blood glucose level <50 milligrams/dL (2.7 mmol/L)	The glucose level should be normalized prior to thrombolytic administration.
Selected Additional Recommendations for Various Conditions	
Arterial puncture of noncompressible artery <7 d	The safety and efficacy of thrombolytics in this condition are unclear.
Arteriovenous malformation	The safety and efficacy of thrombolytics with this condition are unclear; however, thrombolytics may be considered in the case of severe stroke with unruptured/untreated intracranial arteriovenous malformation.
Dural puncture	Dural puncture (<7 d) is not a contraindication.
Eye hemorrhage	Diabetic retinal hemorrhage or other ophthalmologic hemorrhage is not a contraindication, but the benefits of thrombolytics must be weighed against the potential threat to sight.
Major surgery or major trauma (not involving the head) within preceding 14 d	rtPA may be carefully considered if the benefits outweigh risks.
Malignancy	Extra-axial intracranial neoplasm is not a contraindication. The safety and efficacy of thrombolytic administration in systemic malignancy are unclear.
Menstruation	Menstruation and menorrhagia without clinically significant anemia are not contraindications. Clinically significant anemia due to these processes mandates an emergent consultation with a gynecologist prior to thrombolytic administration

(*Continued*)

TABLE 167-11 Summary of American Heart Association (AHA)/American Stroke Association (ASA) 2018 Inclusion/Exclusion Criteria for IV Alteplase in Acute Ischemic Stroke (*Continued*)

Myocardial infarction	Acute myocardial infarction is not a contraindication to rtPA. Recent (<3 months) non–ST-segment elevation myocardial infarction is not a contraindication to rtPA. Recent (<3 months) ST-segment elevation myocardial infarction involving the left anterior, right, or inferior myocardium is not a contraindication to rtPA.
Other cardiac conditions	Consult a cardiologist prior to rtPA administration for other cardiac conditions such as pericarditis, heart chamber thromboses, and cardiac tumors.
Pregnancy	rtPA may be considered for pregnant women with moderate to severe stroke. The administration of rtPA at <14 d postpartum remains controversial.
Seizure at onset	Seizure at onset is not a contraindication to rtPA if residual impairments are thought secondary to stroke and not postictal phenomenon.
Unruptured intracranial aneurysm	An aneurysm <10 mm in size is not a contraindication to rtPA. rtPA administration with an aneurysm ≥10 mm size is controversial.

Abbreviation: NIHSS = National Institutes of Health Stroke Scale.

based on trial data and unpublished data from the U.S. manufacturer of alteplase (Genentech), the U.S. Food and Drug Administration has denied approval for this indication[156]; therefore, alteplase administration >3 hours after symptom onset is still considered off label in the United States.[157] In contrast, the European Medicines Agency has approved use from 3 to 4.5 hours after symptom onset.

In 2012, the third International Stroke Trial (IST-3)[158] was published, making it the largest (n = 3035 patients) randomized controlled trial for ischemic stroke to date. Patients in the treatment group were given the standard dose of thrombolytics up to 6 hours after stroke onset, with 72% of patients receiving thrombolytics after 3 hours. The exclusion criteria were loosened, including eliminating any upper age limit and the broadening of the acceptable blood pressure range prior to thrombolytics (systolic 90 to 220 mm Hg; diastolic 40 to 130 mm Hg).[159] The trial showed no difference at 6 months in the primary outcome measure, Oxford Handicap Score (0 to 2; alive and independent): 37% versus 34% (OR 1.13; 95% CI, 0.95 to 1.35; $P = .181$) in the treatment versus control groups, respectively. However, a secondary ordinal analysis showed a favorable shift in Oxford Handicap Scores (indicating less disability) in the treatment group at 6 months. Although symptomatic intracranial hemorrhage occurred in 7% of treated patients versus 1% of controls (P <.0001) and 11% of deaths occurred within 7 days in treated patients versus 7% in controls (P <.001), mortality at 6 months was the same (27%) in both treatment and control groups. The favorable shift in Oxford Handicap Score in treated patients appeared to last at least 18 months and was associated with higher overall self-reported health, with no increased mortality.[160] Interestingly, a subgroup analysis in the IST-3 revealed that patients receiving thrombolytics between 3 and 4.5 hours after symptom onset actually had a nonstatistical trend toward a *worse* functional outcome compared with controls than patients receiving thrombolytics less than 3 hours and from 4.5 to 6 hours after symptom onset.[158]

In 2014, a Cochrane systematic review and meta-analysis (27 trials, 10,187 patients) concluded that thrombolytic-treated stroke patients were less likely to be dead or dependent than controls, and that early treatment was better than late treatment, with possible benefit up to 6 hours after symptom onset.[161] This benefit held despite increased symptomatic intracranial hemorrhage and more early and late deaths. In 2016, a group of nonneurologists and nonemergency physicians published a systematic review and meta-analysis (26 trials, 10,431 patients) that concluded that although thrombolysis was associated with marginally improved functional outcomes, it also increased early mortality and symptomatic intracranial hemorrhage rates.[154,162] These authors urgently called for further randomized controlled trials to be performed to help resolve this continuing controversy.

In 2015, the American College of Emergency Physicians gave a Level B (moderate clinical certainty) recommendation for IV thrombolytics both in the below 3 hour and in the 3 to 4.5 hour treatment windows.[163] Subsequently, although the Canadian Association of Emergency Physicians "strongly recommended" IV thrombolytics in the below 3 hour window, as a result of data from the IST-3[158] and other data,[164] the Canadian Association of Emergency Physicians issued a conditional recommendation **against** the use of thrombolytic therapy beyond 3 hours of symptom onset.[165] Others recently raised similar concerns,[149,166] some of which prompted a review of alteplase for ischemic stroke by the United Kingdom Medicines and Healthcare Products Regulatory Agency. This review eventually upheld the decision to endorse the use of IV alteplase for stroke up to 4.5 hours.[167]

THROMBOLYSIS: INDICATIONS, EXCLUSIONS, DOSAGE, MONITORING, AND COMPLICATIONS

Indications **The decision to administer thrombolytics must be made rapidly and accurately.** There must be careful identification of the time of symptom onset, defined as the **last moment the patient was known to be at baseline (i.e., last known well time)**. Taking the patient and family chronologically through the events immediately prior to the stroke is particularly helpful in unclear cases. **Thrombolytic use in stroke is not currently recommended by AHA/ASA when the time of onset cannot be reliably determined**.

As of this writing, the **AHA/ASA recommend that strokes recognized upon awakening (up to approximately 25% to 30% of strokes[168,169]) should be clocked from the time at which the patient was last known to be without symptoms**. However, after the current AHA/ASA guidelines[19] were published, the landmark Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial results were published.[104] WAKE-UP was a randomized controlled multicenter European trial that recruited patients who awoke with stroke symptoms or who were not considered candidates for IV thrombolysis with a last known well time of >4.5 hours. These patients underwent MRI with diffusion-weighted imaging and fluid-attenuated inversion recovery. If in the judgment of the treating physician, there was evidence of an acute ischemic stroke on diffusion-weighted MRI, but no parenchymal hyperintensity on fluid-attenuated inversion recovery, the patients were considered to have a **diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch** consistent with a recent stroke and the patients were offered enrollment into the study. A total of 503 patients were randomly assigned to either a standard dose of alteplase or placebo, and there were no significant differences in demographic qualities, stroke severity (median NIHSS of 6), or median time of thrombolysis to symptom onset between the groups. Average last known well time for both groups was about 10 hours, and the average time from symptom recognition to treatment was about 3 hours for both groups. At 90 days after treatment, 53.3% of the alteplase group had minimal disability (modified Rankin scale score of 0 or 1) compared with 41.8% of the placebo group (adjusted OR 1.61; 95% CI, 1.09 to 2.36; $P = .02$). The median 90-day modified Rankin scale score of the alteplase group was 1, whereas in the placebo group, it was 2 (adjusted common OR 1.62; 95% CI, 1.17 to 2.23; $P = .003$). However, 4.1% of patients who received alteplase died within 90 days compared with 1.2% of patients in the control group (OR 3.38; 95% CI, 0.92 to 12.52; $P = .07$), with 50% of the deaths in the treatment group being unrelated to the acute stroke. In a similar vein, 2.0% of the alteplase patients suffered a symptomatic

intracerebral hemorrhage compared with 0.4% in the placebo group (OR 4.95; 95% CI, 0.57 to 42.87; $P = .15$). This trial had several limitations, including the exclusion of patients eligible for mechanical thrombectomy, adults >80 years old, and patients with NIHSS score of >25 and/or large middle cerebral artery lesions. In addition, the trial was stopped early (about 300 patients short of planned enrollment) due to cessation of funding. Had these limitations not been present, the numerical trends toward increased harm in the treatment group may well have been statistically significant. Although these important results await further confirmation by larger trials, WAKE-UP is a landmark trial that has the potential to change practice in the near future, especially when mechanical thrombectomy is not a viable option; however, its results **should be considered preliminary at this time**.

To achieve optimal outcomes, the patient must be evaluated carefully for indications and exclusions for IV thrombolytic therapy (Table 167-11), and the findings must be documented meticulously, preferably on computerized or preprinted assessment forms. The decision to administer thrombolytics is made by assessing multiple factors, including the numerical NIHSS score. A score between 4 and 22 is commonly used as one of the criteria for thrombolytic administration. However, some patients may have a lower NIHSS score, yet have a potentially disabling condition (e.g., aphasia, hemianopia, gait disturbance). Some studies have also shown benefit with thrombolysis in minor strokes,[170,171] but further data are needed to be conclusive.[172,173] Nevertheless, interpret an NIHSS score in the total context of the individual patient when making treatment decisions.

A bedside blood glucose is required prior to thrombolysis; however, do not withhold thrombolysis because other laboratory results are still pending unless there is reason to suspect a pathologic or iatrogenic coagulopathy. Administer thrombolytic therapy to eligible patients even if endovascular therapies are being considered.[19]

Exclusions In the previous AHA/ASA stroke guidelines,[155,174] the exclusion criteria hewed very closely to the conservative criteria used by the NINDS and ECASS III trials. However, in the current recommendations,[19] several of the previous exclusion/relative exclusion criteria from the 2013 guidelines[156] have been eliminated or modified based on recent data and expert consensus.[157] In addition, the practical clinical validity of the ECASS III criteria for administration of thrombolytics from 3 to 4.5 hours has been challenged, because positive outcomes have been demonstrated in patients who would not have qualified for treatment in ECASS III.[157] However, the current AHA/ASA guidelines still list them as part of the inclusion criteria for thrombolytics from 3 to 4.5 hours (Table 167-11), but they note the ongoing controversy. Therefore, carefully consider the treatment risks versus anticipated benefits of proposed rtPA therapy, especially if any of the relative contraindications are present prior to administration of the drug. When faced with such patients, obtain emergency consultation with a physician with acute stroke expertise, whether on-site or via telemedicine, because local expert treatment varies and patient care decisions should be individualized.

Dosage As of this writing, only alteplase is FDA approved for treatment of acute ischemic stroke. However, the treatment options may include tenecteplase in some situations, especially outside the US. Alteplase and tenecteplase have different dosages. Therefore, use the full brand or generic name (alteplase, tenecteplase) when ordering. Do not use abbreviations (rtPA, TNK, etc) to avoid medication errors. As doses also vary for the clinical indication (stroke, STEMI, PE), make sure the dose you select is the dose appropriate for the clinical indication.[175] **The standard total dose of alteplase is 0.9 milligram/kg IV, with a maximum dose of 90 milligrams; administer 10% of the dose as a bolus over 1 minute, with the remaining amount infused over 60 minutes.** Recent data from Asian trials have suggested that low-dose alteplase in acute ischemic stroke results in comparable patient outcomes, with less morbidity and mortality.[176] However, at the time of this writing, these preliminary results await large-scale confirmation in non-Asian populations; therefore, the above standard alteplase dose remains recommended.

The dose of **tenecteplase** is weight-based,: <60 kg: 30 milligrams; 60-70 kg: 40 milligrams; 80-90 kg 45 milligrams; >90 kg, 50 milligrams for patients > 90 kg. The maximum dose is 50 milligrams. Tenecteplase is given as a single IV bolus over 5-10 seconds.

Monitoring and Complications Perform blood pressure and neurologic checks every 15 minutes for 2 hours after starting the infusion. Table 167-10 outlines the emergent management of hypertension during and after administration of thrombolytics. Admit patients to a specialized stroke unit (if available) or an intensive care unit familiar with the use of thrombolytic drugs and neurologic monitoring. If post-rtPA bleeding is suspected, halt drug administration and perform an emergent CT. Order a CBC with platelet count, coagulation studies, fibrinogen level, and typing and cross-match for packed red blood cells, cryoprecipitate or fresh frozen plasma, and platelets. Emergent neurology, neurosurgery, and hematology consultations, as needed, are appropriate. **Be prepared to treat the possible side effect of orolingual angioedema** (reported incidence approximately 0.2% to 17%).[177-179] Patients taking angiotensin-converting enzyme inhibitors appear to be at higher risk for this complication (adjusted OR 3.9; 95% CI, 1.6 to 9.7).[180] Middle cerebral artery infarction has also been previously reported to be a risk factor, but this has been challenged by more recent data.[181] If orolingual angioedema occurs, discontinue thrombolysis[19] and treat angioedema similarly to other causes of angioedema (see Chapter 14, "Allergy and Anaphylaxis"). Consider administration of icatibant, which has been reported to be efficacious in thrombolytic-associated angioedema in a handful of case reports.[182,183] Administration of plasma-derived C1 esterase inhibitor has also been suggested to be of value, given its efficacy in angiotensin-converting enzyme inhibitor–associated angioedema.[19,184] The role of angioedema prophylaxis in this setting is unknown, but there has been at least one reported case of successful IV thrombolysis for recurrent stroke in a patient with history of previous thrombolytic-associated angioedema, using simultaneous administration of prednisolone, ranitidine, and clemastine.[185] History of angioedema to thrombolytics and use of angiotensin-converting enzyme inhibitors are not designated by the ASA/AHA as explicit contraindications to IV thrombolysis[19]; however, if these factors are present, **specifically discuss them as part of informed consent**.

ENDOVASCULAR THERAPY

There is intense interest in endovascular therapies, primarily intra-arterial thrombolysis and mechanical clot disruption/extraction. Potential advantages of endovascular therapies include an expanded treatment window, a treatment for patients with non–time-based contraindications to IV thrombolysis, an ability to specifically evaluate the occluded vascular territory, use of lower total doses of thrombolytic drugs, and the possibility of mechanical clot disruption. However, early randomized trials of mechanical endovascular therapy with primarily intra-arterial thrombolysis or first-generation endovascular devices did not show benefit.[186-189]

Subsequently, in 2015, five pivotal multicenter trials regarding intra-arterial thrombectomy in acute ischemic stroke were published. The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN),[190] the Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) trial,[191] the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial,[192] the Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial,[193] and the Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT) trial[194] were the first prospective, randomized trials to demonstrate the efficacy of intra-arterial thrombectomy with IV thrombolysis with second-generation devices in acute ischemic stroke. In 2016, an additional randomized trial, Thrombectomie des Artères Cerebrales (THRACE),[195] was published, the results of which were consistent with those of the previous studies.

MR CLEAN[190] was the largest trial (n = 502) and the only trial of this group that was not stopped prematurely for efficacy. It compared intra-arterial treatment (thrombolysis, thrombectomy, or both) with usual medical therapy for patients with anterior circulation proximal occlusions within 6 hours of stroke onset (91% of the control group received IV rtPA). The inclusion criteria included adults >18 years old (no upper

age limit) and an NIHSS score ≥2. Major findings included significant 90-day functional benefit in treatment versus controls (90-day modified Rankin scale score of 0 to 2: 32.6% vs. 19.1%, respectively [OR 2.16; 95% CI, 1.39 to 3.38]; number needed to treat = 7). With intra-arterial treatment, there was no significant increase in symptomatic ICH (7.7% vs. 6.4%), but there was a higher incidence of vessel perforation (0.9%) and dissection (1.7%), and 5.6% of patients had an ischemic stroke in a different vascular distribution within 90 days versus 0.4% in controls. However, despite these findings, there was no statistical difference in mortality (18.9% vs. 18.4%). An important limitation of this study is that although the disease severity was similar in the treatment and control groups, the control group had relatively poor outcomes in terms of the modified Rankin scale. This reflects the rather broad inclusion criteria of the study, which may allow greater generalizability of the results.

The results of the other five trials cited are largely consistent with MR CLEAN, and these trials were all stopped early during interim safety analyses because of efficacy of the treatment arm (**Table 167-12**).

Based on the data from the previously discussed six trials, in 2015, the AHA/ASA issued a new Class IA recommendation[196] that patients receive endovascular therapy with a stent retriever if they meet all of the inclusion criteria in **Table 167-13.**

A subsequent pooled analysis (n =1287) for the first five randomized positive trials found that a modified Rankin scale score of 0 to 2 at 90 days was present in 46% of patients in the endovascular treatment group versus 26.5% of controls (number needed to treat = 5.1), with no significant difference in 90-day mortality or symptomatic intracranial hemorrhage.[197] A 2016 Cochrane systematic review and meta-analysis of 10 trials of endovascular therapy, including the previous negative trials, concluded the following: "Moderate to high quality evidence suggests that compared with medical care alone in a selected group of patients endovascular thrombectomy as add-on to intravenous thrombolysis performed within six to eight hours after large vessel ischaemic stroke in the anterior circulation provides beneficial functional outcomes, without increased detrimental effects."[198]

TABLE 167-12 Results of Eight Positive Randomized Trials of Mechanical Intra-Arterial Treatment in Acute Anterior Stroke

Trial	No.	Upper Age Limit (y)	Endovascular Treatment	Time Inclusion Criteria	mRS (0–2) at 90 d* (treatment vs. controls)	Mortality† (treatment vs. controls)	Symptomatic Intracranial Hemorrhage† (treatment vs. controls)
MR CLEAN[190]	502	None	Retrievable stent +/– intra-arterial thrombolysis or intra-arterial thrombolysis alone	Ability to undergo endovascular treatment within 6 h	32.6% vs. 19.1% OR = 2.16 (95% CI, 2.39–3.38) NNT = 8	18.9% vs. 18.4%	7.7% vs. 6.4%
EXTEND-IA[191]	70	None	Solitaire FR stent retriever	IV thrombolysis <4.5 h of stroke onset	71% vs. 40% OR = 4.2 (95% CI, 1.4–12) NNT = 4	9% vs. 20%	0% vs. 6%
ESCAPE[192]	316	None	Retrievable stent	Within 12 h of stroke onset	53% vs. 29.3% Rate ratio = 1.8 (95% CI, 1.4–2.4) NNT = 5	10.4% vs. 19%	3.6% vs. 2.7%
SWIFT PRIME[193]	196	80	Solitaire stent retriever	Within 6 h of stroke onset	60% vs. 35% Risk ratio = 1.70 (95% CI, 1.23–2.33) NNT = 4	9% vs. 12%	0% vs. 3%
REVASCAT[194]	206	80	Solitaire stent retriever	Within 8 h of stroke onset	43.7% vs. 28.2% OR = 2.1 (95% CI, 1.1–4.0) NNT = 7	18.4% vs. 15.5%	1.9% vs. 1.9%
THRACE[195]	414	80	Various stent retriever devices	IV thrombolysis within 4 h and thrombectomy within 5 h of stroke onset	53% vs. 42% OR = 1.55 (95% CI, 1.05–2.30) NNT = 9	12% vs. 13%	2% vs. 2%
DAWN[109]	206	None	Trevo stent retriever	Within 6–24 h of last known well time	49% vs. 13% OR = 6.25 (95% CI, 3.11–12.54) NNT = 3	19% vs. 18%	6% vs. 3%
DEFUSE 3[110]	182	90	Various FDA-approved thrombectomy devices	Within 6–16 h of last known well time	45% vs. 17% OR = 4.01 (95% CI, 2.02–8.02) NNT = 4	14% vs. 26%	7% vs. 4%

Abbreviations: CI = confidence interval; DAWN = Diffusion-Weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention; DEFUSE 3 = Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; ESCAPE = Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; FDA = U.S. Food and Drug Administration; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin scale; NNT = number needed to treat; OR = adjusted odds ratio; REVASCAT = Randomized Trial of Revascularization with Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset; SWIFT PRIME = Solitaire FR with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; THRACE = Thrombectomie des Artères Cerebrales.

*Treatment efficacy differences in each trial are statistically significant.

†Differences in mortality and symptomatic intracranial hemorrhage in each trial were not statistically significant.

TABLE 167-13 AHA/ASA Indications for Endovascular Therapy With a Stent Retriever[196]

- Prestroke mRS score 0 to 1
- Acute ischemic stroke receiving IV rtPA within 4.5 h of onset according to guidelines from professional medical societies
- Causative occlusion of the ICA or proximal MCA (M1)
- Age ≥18 y
- NIHSS score of ≥6
- ASPECTS of ≥6
- Treatment can be initiated (groin puncture) within 6 h of symptom onset

***All* 7 criteria need to be met for stent retriever endovascular therapy to be indicated.**

Abbreviations: AHA/ASA = American Heart Association/American Stroke Association; ASPECTS = Alberta Stroke Program Early CT Score; ICA = internal carotid artery; MCA (M1) = sphenoidal (horizontal) segment of the middle cerebral artery; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; rtPA = recombinant tissue plasminogen activator.

In 2018, two important studies, the DAWN trial[109] (n = 206) and the DEFUSE 3 trial[110] (n = 182) compared endovascular therapy plus standard treatment with standard treatment alone in patients with late presenting stroke (6 to 24 hours and 6 to 16 hours last known well time, respectively) and evidence of potentially reversible ischemia (a mismatch between clinical symptoms and infarct size and a penumbra of ≥15 mL, respectively; Table 167-12). Both trials were multicenter, randomized, open-label trials with blinded outcome assessment, and both were stopped early because of the loss of clinical equipoise in favor of the treatment group. DAWN found that the percentage of patients with functional outcome at 90 days (modified Rankin scale score of 0 to 2) with thrombectomy was 49% compared with 13% in the control group (an adjusted difference of 33% [95% CI, 21% to 44%]; posterior probability of superiority >0.999). Similarly, DEFUSE 3 found that thrombectomy patients had a better distribution of disability scores at 90 days than controls (OR 2.77; 95% CI, 1.63 to 4.70; P <.001). The percentage of thrombectomy patients compared with controls who had a modified Rankin scale score of 0 to 2 at 90 days was 45% versus 17%, respectively (risk ratio 2.67; 95% CI, 1.60 to 4.48; P <.001). In both trials, the mortality and morbidity outcomes in both the treatment and control groups were statistically equal. Although these results support the notion of extending the window for acute treatment of stroke, an important caveat is that the AHA/ASA recommends thrombectomy in the >6 hour window **only if the strict inclusion/exclusion criteria for DAWN or DEFUSE 3 are followed**. The inclusion and exclusion criteria of both trials are complex and lengthy but are readily available online.[199,200]

Despite the encouraging results of all of these recent endovascular therapy trials, the current availability of endovascular treatment modalities remains rather limited at most primary stroke centers, which may circumscribe widespread use.[201]

Nevertheless, **although all eligible stroke patients should be considered for IV thrombolysis as a first-line therapy, also consider emergent consultation with a neurointerventionalist for adjunctive endovascular therapy in patients who meet the criteria listed in Table 167-13[196]** and in patients who meet the DAWN or DEFUSE 3 criteria.[199,200]

OTHER TREATMENT MODALITIES

Therapeutic hypothermia, induced hypertension, endovascular therapies, carotid endarterectomy/stenting, and emergency hemicraniectomy for massive infarcts are modalities that are being studied, but as of this writing, benefits are unproven.

Mild **therapeutic hypothermia** is associated with improved neurologic outcomes in comatose patients who survive cardiopulmonary arrest.[202] Consequently, there is much interest in the potential benefit of induced hypothermia in acute stroke, both alone and in combination with neuroprotective strategies[203] and endovascular therapy.[204] However, hypothermia's efficacy has not been firmly established, and it may be associated with increased risk of pneumonia.[205] Therefore, its use is considered experimental at this time.[19]

Animal data[206] and preliminary trials have suggested that implementing **drug-induced hypertension** in an effort to increase blood flow to the ischemic penumbra may benefit outcomes from acute ischemic stroke,[207-209] with recent increased interest given penumbra-based endovascular interventions.[210] However, there are insufficient data to recommend this modality outside of clinical trials at this time.[19]

Patients with a massive middle cerebral artery infarct are less favorable candidates for thrombolytic therapy and have an 80% mortality rate. Massive middle cerebral artery infarct is commonly associated with space-occupying cerebral edema and may be amenable to decompressive craniectomy. A 2007 pooled analysis of data from three European trials (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery [DECIMAL],[211] Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery [DESTINY],[212] and Hemicraniectomy After Middle Cerebral Artery Infarction With Life-Threatening Edema Trial [HAMLET])[213] showed that decompressive hemicraniectomy was associated with better outcomes than medical therapy.[214] However, the overall efficacy of this approach remains in question. For example, in 2014, the Hemicraniectomy and Durotomy upon Deterioration Infarction-Related Swelling (HeADDFIRST) pilot trial[215] found no statistical difference in the 180-day mortality between the medically managed patients in this trial (40%) and the patients who underwent hemicraniectomy plus medical treatment (34%). Ultimately, several recent meta-analyses of hemicraniectomy versus medical treatment for large middle cerebral artery infarction concluded that although decompressive craniectomy results in reduced mortality, most survivors are left with severe or very severe disability.[216-218] Therefore, the decision to perform surgery must be made on an individual case-by-case basis.

TRANSIENT ISCHEMIC ATTACK

TIA is defined as follows: "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction."[219] This tissue-based definition recognizes that although TIA symptoms typically last <1 to 2 hours, duration of symptoms is an unreliable discriminator between TIA and infarction because about 33% of TIAs have signs of infarction on MRI.[220] **View a TIA as analogous to unstable angina**—that is, an ominous harbinger of a potential future vascular event. In fact, the adjusted OR for stroke <1 month after TIA is 30.4 (95% CI, 10.4 to 89.4),[221] and the overall 90-day stroke risk after TIA is about 9.2% to 9.5%.[136-138] Some data suggest that 50% of these subsequent events occur within 2 days after presentation to the ED.[136] Published risk factors associated with increased risk for subsequent stroke include hypertension, diabetes mellitus, symptom duration of ≥10 minutes, weakness, and speech impairment.[136] A study of admitted patients found increased risk with male sex, age ≥65 years, hyperlipidemia, and dysarthria.[139]

TIA DIAGNOSIS

The initial considerations and workup of TIA are very similar to those of acute stroke (see earlier section "Stroke Diagnosis"), including the emphasis on seeking mimics that can simulate TIA (Table 167-5). Pay particular attention to performing an ECG in these patients to detect atrial fibrillation, given its association with cardioembolic stroke and the fact its associated stroke risk can be mitigated in many patients. An unsettled issue in the initial workup involves brain imaging. Although a noncontrasted CT is still the initial imaging study of choice (primarily to rule out stroke mimics), it cannot reliably predict risk of subsequent stroke.[222] However, it has been shown that positive findings on diffusion-weighted MRI have predictive value for subsequent early stroke risk in TIA patients,[223] as does cervical vascular imaging by magnetic resonance angiography.[224] Furthermore, a large meta-analysis[225] of 41 studies (n = 2541) determined that although Doppler US has test characteristics slightly inferior to magnetic resonance angiography in detecting 70% to 99% carotid stenosis (sensitivity of 89% [95% CI, 85% to 92%] and 94%

[95% CI, 88% to 97%] and specificity of 84% [95% CI, 77% to 89%] and 93% [95% CI, 89% to 96%], respectively),[225] Doppler US still performs well enough (negative likelihood ratio of 0.13, compared to 0.06 for MRA)[225] to be useful in helping to risk-stratify TIA patients in the ED.[226] Due to its relatively low specificity (84%), **confirm any positive Doppler US findings with magnetic resonance angiography or CT angiography**. As a screening test, CT angiography lagged behind the other two modalities in detecting extracerebral carotid stenosis in TIA patients (sensitivity 77% [95% CI, 68% to 84%], specificity 95% [95% CI, 91% to 97%], negative likelihood ratio 0.24),[225] despite its utility in detecting intracranial vascular lesions.[227] Based on these and similar data, in 2016, the American College of Emergency Physicians recommended[226] that suspected TIA patients should receive a noncontrasted head CT in the ED, and **when feasible,** physicians should obtain diffusion-weighted MRI and cervical vascular imaging. These recommendations reference a growing trend to attempt to use clinical characteristics plus imaging to selectively manage some TIA patients as outpatients (see later section "TIA Risk Stratification and Disposition").

TIA TREATMENT

Treatment of TIA primarily focuses on prevention of subsequent stroke.

ANTIPLATELET AGENTS

After TIA, the use of aspirin to prevent future vascular events is historically well accepted. Current practice includes dipyridamole plus aspirin (reasonable as a first choice), clopidogrel, and aspirin alone. The selection of a particular antiplatelet regimen is a multifactorial decision based on comorbid conditions, bleeding risk, prior drug use, and cost.

A very large meta-analysis (>88,000 patients)[228] concluded that aspirin plus dipyridamole was superior to aspirin alone for prevention of vascular events after stroke or TIA. Aspirin plus dipyridamole was associated with more hemorrhagic events than dipyridamole (relative risk 1.83; 95% CI, 1.17 to 2.81) but was associated with fewer hemorrhagic events than aspirin and clopidogrel (relative risk 0.38; 95% CI, 0.25 to 0.56). However, the previously mentioned CHANCE trial (n = 5170) found that the combination of clopidogrel and aspirin was superior to aspirin alone for reducing the risk of stroke in the first 90 days without increasing the risk of hemorrhage.[144] These positive outcomes were found to have persisted at 1-year follow-up.[145] The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial is currently in progress to investigate this comparison as well.[229]

ANTICOAGULATION

Adjusted-dose oral anticoagulation with warfarin has been the historical therapy of choice for stroke prevention in patients with nonvalvular atrial fibrillation and TIA; however, an assessment of warfarin anticoagulation for stroke prevention in the United States demonstrated a dismal rate of optimal anticoagulation control.[230] This has led to multiple randomized controlled trials of novel anticoagulants, which have been shown to have equivalent efficacy but with less risk of intracranial hemorrhage compared to warfarin.[231] The risk of recurrent stroke in the presence of atrial fibrillation without anticoagulation is low, probably <5% over the next 48 hours; moreover, the risk of hemorrhagic transformation of an acute stroke is also greatest in the first 48 hours. Consequently, **in the setting of acute atrial fibrillation, anticoagulation therapy typically should not be started in the ED but should be initiated in the inpatient setting.**

Multiple studies have demonstrated that, although unfractionated heparin may help prevent recurrent stoke, its potential benefits are outweighed by the increased risk of intracranial hemorrhage. Multiple studies of low-molecular-weight heparin and heparinoids have found similarly disappointing results. A Cochrane systematic review of 24 randomized trials (23,748 patients) found no net benefit of anticoagulants in acute stroke.[232] In addition, a meta-analysis of seven trials focused specifically on anticoagulant use in acute cardiothrombotic stroke and found no overall benefit.[233] **Therefore, the use of unfractionated heparin, low-molecular-weight heparin, or heparinoids for emergent treatment of a specific stroke subtype or TIA cannot be recommended based on available evidence, even in the presence of atrial fibrillation.[234]**

ENDARTERECTOMY

In TIA patients with medically treated high-grade internal carotid artery lesions, **carotid endarterectomy** should be performed promptly, because surgical benefit is greatest within 2 weeks of the TIA.[235] The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[236] and the International Carotid Stenting Study (ICSS)[237] suggest that **carotid stenting** may be a viable alternative to endarterectomy, with similar functional outcomes up to 10 years,[237,238] despite a small increase in nondisabling stroke in stented patients in the ICSS trial.[237] Carotid stenting may be especially useful in patients <70 years old[236] or in patients with higher surgical risks.[239] On the other hand, the evidence-based role of emergent or urgent carotid endarterectomy/stenting in acute stroke is still not conclusively defined.[19]

TIA RISK STRATIFICATION AND DISPOSITION

Because TIAs frequently precede acute strokes, much work has been done in attempting to develop TIA risk stratification tools in an effort to identify which low-risk patients may safely be discharged from the ED and worked up as outpatients. The most frequently studied of these tools is the **A**ge, **B**lood pressure, **C**linical characteristics, **D**uration, and **D**iabetes ($ABCD^2$) scoring system.[240] In 2007, the $ABCD^2$ scoring system was developed to incorporate and replace two previous scoring scales (California score and ABCD score).[240] Johnston et al[240] initially reported 2-day risks of subsequent stroke as 1% ($ABCD^2$ score 0 to 3), 4.1% (score 4 to 5), and 8.1% (score 6 to 7). The 7-day stroke risks were 1.2% ($ABCD^2$ score 0 to 3), 5.9% (score 4 to 5), and 11.7% (score 6 to 7).

Despite these initial promising data, subsequent published studies produced conflicting conclusions as to the $ABCD^2$ score's utility for predicting subsequent stroke after TIA.[241-243] The interrater reliability and accuracy of the $ABCD^2$ score have been challenged, especially with nonspecialists in actual use.[244-247] A large meta-analysis (>16,000 patients)[248] found inadequate positive and negative likelihood ratios (1 to 2 and 0.5 to 1, respectively) to be of practical use when deciding stroke risk in a given patient. Overall, the $ABCD^2$ score identified high-risk patients poorly and had only modest success in predicting low-risk patients, and the study authors cautioned against solely relying on the $ABCD^2$ score to risk-stratify patients.[248] In an attempt to improve accuracy of $ABCD^2$, the presence of two or more TIA events at 7 days ($ABCD^3$) and diffusion-weighted MRI ($ABCD^3$-I) have been added to the original scoring system. One study did demonstrate the superiority of these new scales to predict stroke.[249] However, the addition of these two data points limits the usefulness of these scales in the ED during initial presentation.

Although use of the $ABCD^2$ score had been recommended previously by major guidelines,[219] based on the most current literature, the American College of Emergency Physicians issued an updated clinical policy[226] in 2016. **This clinical policy recommends that current risk stratification instruments such as $ABCD^2$ should not be used to identify TIA patients who can be safely discharged home.[226]** Specifically, "the $ABCD^2$ does not sufficiently identify the short-term risk for stroke to use alone as a risk-stratification instrument."[226]

A 13-factor Canadian TIA score[250] has been developed that has shown initial promising results; however, it has yet to be validated for general use.

In light of the difficulty in precisely identifying TIA patients who are safe to send home from the ED, some experts have recommended that most TIA patients be hospitalized to monitor and educate them, begin antiplatelet therapy (unless contraindicated), rapidly treat subsequent stroke, assess stroke risk factors, implement preventive measures, and perform endarterectomy in appropriate patients.[219]

However, as a result of cost resource utilization concerns, there is great interest in developing ED-based strategies for safely managing TIAs as outpatients as opposed to standard admission. Numerous studies have been published exploring this issue.[226] Although these studies have largely shown that the use of special ED-directed TIA protocols results in decreased resource use with no increased risk of subsequent stroke, most have compared admission with extensive ED observation

protocols or prompt referral to dedicated TIA clinics. A representative example is a 2007 randomized controlled trial[251] (n = 151) that demonstrated that lower-risk patients (i.e., those **without** the following factors: abnormality on initial head CT, abnormal ECG, abnormal lab values, known possible embolic source [atrial fibrillation, cardiomyopathy, or valvulopathy], known carotid stenosis, previous large stroke, or crescendo TIAs) can be safely discharged after a 12-hour ED observation period that includes continual cardiac and serial clinical monitoring, coupled with a thorough initial evaluation (including neurology consultation, carotid imaging, and echocardiography). More recent studies have also included diffusion-weighted MRI in their protocols.[252] Many of these studies lack sufficient controls and are relatively small, and there is no consensus on which specific protocol or approach is optimal. In addition, many of the proposed algorithms require resources that are not readily available in most EDs. However, there is general support for the use of these types of protocols by the American College of Emergency Physicians.[226] The approach to the disposition of a specific patient must be individualized and may depend not only on medical factors, but also the patient's social situation, as well as the healthcare resources available at the particular treating institution.

SPECIAL POPULATIONS

STROKE OR TIA WITH CONCURRENT ACUTE MYOCARDIAL INFARCTION

The co-occurrence of acute myocardial infarction and acute stroke has implications for acute treatment in the ED, but strong evidence-based treatment recommendations are lacking. Troponin elevation in acute ischemic stroke is not uncommon (prevalence, 0% to 34%[253]), is associated with multiple disease processes (e.g., acute coronary syndrome, congestive heart failure, renal failure, myopericarditis, chronic obstructive pulmonary disease, pulmonary embolism, sepsis, atrial fibrillation[254,255]), and is independently associated with worse all-cause mortality.[256] Troponin elevation in acute stroke is most probably secondary to acute coronary syndrome if other obvious causes are excluded, especially if typical ECG findings for acute coronary syndrome are present.[257] Concomitant acute stroke and acute myocardial infarction due to paradoxical embolus traversing a patent foramen ovale has been well described in the literature.[258,259] Type A aortic dissection has also been reported to present with simultaneous stroke and myocardial infarction.[260]

Simultaneous acute ischemic stroke and myocardial infarction can be therapeutically problematic because treating one condition with a procedure may delay a time-dependent indicated procedure for the other. In addition, there are some therapies for acute myocardial infarction (e.g., heparin) that are contraindicated in acute stroke. There are no published controlled trials directly addressing these complex patients. Nonetheless, based on expert consensus, the 2018 AHA/ASA guidelines gave a Class IIa (moderate) recommendation: **"For patients presenting with concurrent AIS [acute ischemic stroke] and acute MI [myocardial infarction], treatment with IV alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated is reasonable."**[19] Regardless of the treatment strategy chosen, the risks and benefits of the various therapeutic approaches must be carefully weighed in this situation in order to prioritize the various proposed interventions, depending on the clinical condition of the patient.[261] Obtain emergent neurology and cardiology consults on these patients, **but do not delay thrombolysis for stroke if the patient qualifies**.

SICKLE CELL DISEASE

Stroke afflicts both adults and children with sickle cell disease, with an overall prevalence of 3.8%[262] compared to the overall prevalence of 2.7% (age ≥20 years) in the general population in the United States.[1] Sickle cell disease is the most common cause of ischemic stroke in children. Patients homozygous for hemoglobin S have the highest incidence of stroke (0.61 in 100 patient-years), but all genotypes are at increased risk.[262] The highest incidence of hemorrhagic stroke in these patients occurs from ages 20 to 29.[262]

Cerebral aneurysms and arterial abnormalities also occur with increased frequency in patients with sickle cell disease, and careful evaluation for subarachnoid hemorrhage is mandated for patients presenting with headache and neurologic findings. Initial management is similar to that for stroke patients without sickle cell disease, but care should also be taken to treat the underlying sickle cell disease with oxygen administration, hydration, and pain control, if necessary.

The presence of sickle cell disease has not been found to significantly affect safety or outcomes in stroke patients treated with IV thrombolysis[263] and is not considered a contraindication to thrombolytic therapy in eligible patients.[19] Therefore, **if patients with sickle cell disease otherwise qualify, administer IV thrombolysis**.

Despite a paucity of high-quality evidence, expert consensus also recommends emergent **exchange packed red blood cell transfusion** in sickle cell patients with acute ischemic stroke, with the goal of reducing hemoglobin S levels to <30%,[264] along with a target goal to achieve a total hemoglobin level of 10 grams/dL (but no higher in order to avoid hyperviscosity).[265-267] The same therapy has been recommended in hemorrhagic stroke in order to reduce vasospasm and secondary ischemic infarction.[264] Exchange transfusion appears to reduce the incidence of subsequent ischemic stroke in children compared with simple transfusion.[268] However, if exchange transfusion is not readily available, consider a simple packed red blood cell transfusion in these patients while preparations for exchange transfusion are being made.

Emergent consultation with a hematologist and a stroke neurologist is in order for these patients, and admission to a comprehensive stroke center is indicated.

YOUNG ADULTS

Strokes in young adults (age 18 to 50 years) are increasing in incidence.[269,270] Possible causes include an increasing prevalence of some traditional cardiovascular risk factors[271] (e.g., hyperlipidemia,[272] diabetes,[273,274] obesity[275]), increasing rates of recreational drug use,[276] and better awareness and diagnosis of stroke in this age group.[269,277] In this group, **cervical arterial dissection** accounts for 20% of all ischemic strokes and may often be preceded by only minor trauma. The young adult with a cardioembolic event may have mitral valve prolapse, rheumatic heart disease, or paradoxical embolism[259] as the originating cause. Migrainous stroke (infarction associated with typical migraine attack among those with established recurrent migraines) is also a possibility in this age group. Some members of this population are at risk for ischemic stroke from substance abuse. Heroin, cocaine, amphetamines, and other sympathomimetic drugs are often implicated.[276] Patients who have human immunodeficiency virus and a recent CD4 cell count <200 cells/mm^3 are also at increased risk for ischemic stroke (rate ratio 2.5; 95% CI, 1.3 to 4.6),[278] as are young adults who survive cancer.[279] Studies suggest that younger stroke victims have more favorable morbidity and mortality rates than elders after undergoing stroke treatments such as IV thrombolysis,[280] thrombectomy,[281] and decompressive surgery for large middle cerebral artery strokes.[282] Therefore, **treat these patients aggressively**.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 168

Altered Mental Status and Coma

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INTRODUCTION

Altered mental status and coma are broad clinical categories used to describe disorders of arousal and content of consciousness. Arousal behaviors include wakefulness and basic alerting. Content of consciousness includes awareness, memory, language, reasoning, spatial relationship integration, emotions, complex attention, and the myriad integration processes that make us human. Delirium, dementia, and coma may each affect consciousness, but their clinical presentations are distinct. Prompt and accurate differentiation between the three conditions is essential for appropriate management in the ED setting. Coma is characterized by failure of both arousal and content functions of consciousness. The altered states of delirium and dementia have multiple effects on neuropsychological function to varying degrees. While delirium refers to an acute state of fluctuating attention and change in cognition, dementia is a chronic disorder of deteriorating cognition, with or without behavioral disturbances. Psychiatric disorders and altered mental states may share features such as hallucinations or delusions. Some distinctions between the different states are summarized in **Table 168-1**.

DELIRIUM

INTRODUCTION

Delirium, acute encephalopathy, and other synonyms all refer to an abrupt disorder characterized by impairment of attention and cognition. While delirium may present at any age, it is much more prevalent in older adults. The literature suggests that at least 1 out of 10 elderly ED patients and at least 1 out of 4 elderly hospitalized patients have delirium at the time of admission.[1-4] Emergency physicians may fail to recognize delirium in three out of four of such cases.[3,4] Given evidence that delirium in ED patients is associated with an increase in morbidity, mortality, and hospital length of stay, the Society for Academic Emergency Medicine Geriatric Task Force has recommended that formal cognitive assessment should be a quality indicator in emergency care of the elderly.[3,5-7]

PATHOPHYSIOLOGY

The pathologic mechanisms leading to delirium are complex and are thought to involve impairments in neuronal connectivity and plasticity, leading to "acute brain failure."[3,8] There are five general causes[9]:

1. Primary intracranial disease
2. Systemic diseases secondarily affecting the CNS
3. Exogenous toxins (including prescribed pharmacotherapies)
4. Drug withdrawal and pain
5. Major trauma or surgery

TABLE 168-1 Features of Delirium, Dementia, and Psychiatric Disorder

Characteristic	Delirium	Dementia	Psychiatric Disorder
Onset	Over days	Insidious	Sudden
Course over 24 h	Fluctuating	Stable	Stable
Consciousness	Reduced or hyperalert	Alert	Alert
Attention	Disordered	Normal	May be disordered
Cognition	Disordered	Impaired	May be impaired
Orientation	Impaired	Often impaired	May be impaired
Hallucinations	Visual and/or auditory	Often absent	Usually auditory
Delusions	Transient, poorly organized	Usually absent	Sustained
Movements	Asterixis, tremor may be present	Often absent	Absent

CLINICAL FEATURES

Delirium typically develops over days. Disordered attention and acute fluctuating course are the hallmarks of the condition, which may also affect cognition, level of consciousness, language, and perception. Activity levels may be either increased or decreased. The patient may fluctuate rapidly between hypoactive and hyperactive states. **Symptoms may be intermittent, and it is not unusual for different caregivers to witness completely different behaviors within a brief time span.** Sleep-wake cycles are often disrupted. Tremor, asterixis, tachycardia, sweating, hypertension, or emotional outbursts may be present. Hallucinations tend to be visual, although auditory hallucinations can also occur.[1,2,10]

DIAGNOSIS

Since delirium is a clinical diagnosis, a thorough history and physical examination are key for obtaining findings indicative of possible delirium. Eliciting a history from caregivers, spouse, or other family members is the primary method for diagnosing delirium.[1,2,10] **Compared to the patient's baseline, the acute onset of attention deficits and cognitive abnormalities, fluctuating in course, is virtually diagnostic of delirium.**

One important tool for detecting delirium is the mental status examination and other cognitive screening instruments.[11,12] The Mini-Mental State Examination is historically the standard against which many shorter and less cumbersome tools have been tested.[12] The Geriatric Emergency Department Guidelines recommend a combination of screening tests: the highly sensitive **Delirium Triage Screen** (incorporates the Richmond Agitation-Sedation Scale) and the highly specific **Brief Confusion Assessment Method**[13] **(Figure 168-1).**

Evaluate medication history, including both over-the-counter medications and prescribed medications, in detail. Check for drug interactions. Assess for an underlying process, such as infection, metabolic derangement, or trauma. Basic ancillary testing should include serum electrolyte levels, hepatic and renal studies, urinalysis, CBC, and a chest radiograph. Order a head CT if a mass lesion such as subdural hematoma is suspected; follow this by performing a lumbar puncture if meningitis or subarachnoid hemorrhage is considered.

Depression may resemble hypoactive delirium, with withdrawal, slowed speech, and poor results on cognitive testing present in both conditions. However, rapid fluctuation of symptoms is common in delirium but generally absent in depression. **Patients with depression are oriented and able to perform commands**.

An unusual cause of an altered mental state, but one suspected to be underrecognized, is **nonconvulsive status epilepticus**, or **complex partial status epilepticus**. This twilight state may persist for hours or even months. Suspicion and electroencephalography are required for recognition. (See Chapter 171, "Seizures and Status Epilepticus in Adults," for further discussion of nonconvulsive status epilepticus.)

TREATMENT

Direct treatment toward the underlying cause(s). Common medical causes of delirium are listed in **Table 168-2**. Multiple causes may be present in a given patient.

Nonpharmacologic approaches to delirium are the standard of care. Environmental manipulations such as adequate lighting, psychosocial support, re-orientation activities, and mobilization may be helpful in enhancing the patient's ability to interpret the surroundings correctly.[2,9,10,13] In the elderly, physical restraints are inadvisable except as a last resort and are associated with worse outcomes.[14] In circumstances of risk of harm to self or others, the use of antipsychotics may be indicated. However, the efficacy of antipsychotics in treating delirium

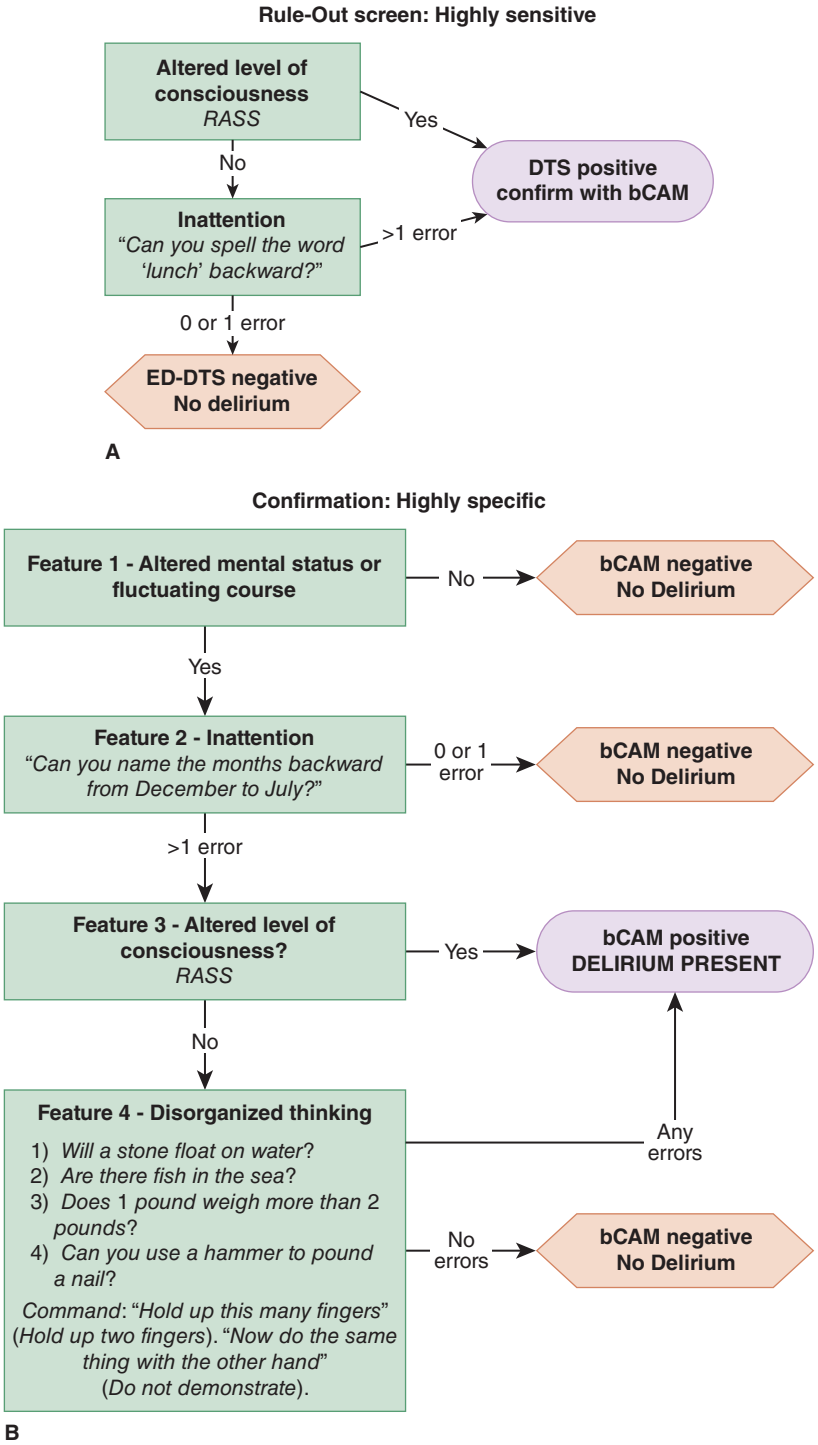

FIGURE 168-1. Delirium Triage Screen (DTS) and Brief Confusion Assessment Method (bCAM). RASS = Richmond Agitation-Sedation Scale. [Reproduced with permission from XOS Technologies, Inc. dba XOS Digital, Atlanta, GA.]

in older adults remains controversial.[15] Haloperidol is a frequent initial choice at a dose of 5 to 10 milligrams PO, IM, or IV, with reduced dosing of 1 to 2 milligrams in older adults. Repeat at 20- to 30-minute intervals as needed. In younger patients, benzodiazepines, such as lorazepam, 0.5 to 2.0 milligrams PO, IM, or IV, may be used in combination with haloperidol. Guidelines recommend avoiding benzodiazepines in the elderly.[14,16] Chapter 287, "Acute Agitation," provides further discussion on management of agitation.

DISPOSITION AND FOLLOW-UP

Admit the patient with delirium to the hospital for further treatment and additional diagnostic testing, unless a readily reversible cause for the acute mental status change is discovered and treatment initiated. This decision is individualized with consideration of patient characteristics, the resources in the home or healthcare facility, and the patient's safety.

DEMENTIA

INTRODUCTION

Dementia is a chronic, major neurocognitive disorder entailing a gradual loss of mental capacity. Executive, social, and cognitive abilities deteriorate, and behavioral problems can develop. The most frequent causes of dementia include Alzheimer's disease and vascular dementia. Dementia with Lewy bodies is the second most common neurodegenerative

TABLE 168-2 Important Medical Causes of Delirium

Infectious	Pneumonia
	Urinary tract infection
	Meningitis or encephalitis
	Sepsis
Metabolic/toxic	Hypoglycemia
	Alcohol ingestion
	Electrolyte abnormalities
	Hepatic encephalopathy
	Thyroid disorders
	Alcohol or drug withdrawal
Neurologic	Stroke or transient ischemic attack
	Seizure or postictal state
	Subarachnoid hemorrhage
	Intracranial hemorrhage
	CNS mass lesion
	Subdural hematoma
Cardiopulmonary	Congestive heart failure
	Myocardial infarction
	Pulmonary embolism
	Hypoxia or carbon dioxide narcosis
Drug related	Anticholinergic drugs
	Alcohol or drug withdrawal
	Sedatives—hypnotics
	Narcotic analgesics
	Selective serotonin or serotonin-norepinephrine reuptake inhibitors
	Polypharmacy

TABLE 168-3 Classification of Dementia by Cause

Degenerative
- Alzheimer's disease
- Dementia with Lewy bodies
- Huntington's disease
- Parkinson's disease

Vascular
- Multiple infarcts
- Hypoperfusion (cardiac arrest, profound hypotension, others)
- Subdural hematoma
- Subarachnoid hemorrhage

Infectious
- Meningitis (sequelae of bacterial, fungal, or tubercular)
- Neurosyphilis
- Viral encephalitis (herpes, human immunodeficiency virus), Creutzfeldt-Jakob disease

Inflammatory
- Systemic lupus erythematosus
- Demyelinating disease, others

Neoplastic
- Primary tumors and metastatic disease
- Carcinomatous meningitis
- Paraneoplastic syndromes

Traumatic
- Traumatic brain injury
- Subdural hematoma

Toxic
- Alcohol
- Medications (anticholinergics, polypharmacy)

Metabolic
- Vitamin B_{12} or folate deficiency
- Thyroid disease
- Uremia, others

Psychiatric
- Depression (pseudodementia)

Hydrocephalic
- Normal-pressure hydrocephalus (communicating hydrocephalus)
- Noncommunicating hydrocephalus

dementia after Alzheimer's. However, other, more treatable disorders may cause or simulate dementia.

The typical course of dementia involves insidious symptom onset. The abrupt onset of symptoms or rapidly progressive symptoms should prompt a search for other diagnoses, including delirium. Presentation to the ED is usually precipitated by a sentinel event. Hallucinations, delusions, repetitive behaviors, depression, and anxiety are all common.

PATHOPHYSIOLOGY

Most cases of dementia in the United States are due to Alzheimer's disease, a neurodegenerative disorder of imprecise etiology. The pathophysiology is complex, with neuritic or amyloid plaques of tau protein and neurofibrillary tangles. However, the relationship between these findings and the clinical syndrome of Alzheimer's disease is incompletely understood.[17] Other neurodegenerative diseases have their own unique pathologies. Vascular dementia accounts for the next largest number of dementia cases. The pathology is that of cerebrovascular disease with multiple infarctions, not all of which may have been clinically apparent. A listing of different types of dementia is provided in **Table 168-3**.

CLINICAL FEATURES

Clinical features of dementia vary depending on etiology. Whereas visual hallucinations are a cardinal feature of dementia with Lewy bodies, perceptual disturbances may or may not be present in Alzheimer's or vascular dementia. In many dementias, impairment of short-term memory is gradual and progressive, with relative preservation of remote memories. Language function can be affected in any dementia subtype, but is most common in frontotemporal dementia and later stages of Alzheimer's disease. Generally, dementia is staged according to degree of decline in global function. Individuals with mild cognitive impairment often have intact activities of daily living and instrumental activities of daily living, whereas those who meet criteria for dementia have some measure of functional deficit.

Patients with vascular dementia often show similar neurocognitive symptoms but may have chronic neurologic physical deficits from prior cerebrovascular accidents. Furthermore, vascular dementia often coexists with Alzheimer's disease.[18]

DIAGNOSIS

General physical examination does not determine the diagnosis of dementia but may be helpful in identifying associated causes.[19] The presence of focal neurologic signs may suggest vascular dementia or a mass lesion. Increased motor tone, rigidity, or a shuffling gait may suggest Parkinsonian-related dementia. Consider normal-pressure hydrocephalus if urinary incontinence and gait disturbance develop early in the disease process. The recommended screening method by the Geriatric Emergency Department Guidelines is to first screen for delirium with the Delirium Triage Screen and Brief Confusion Assessment Method combined, and then screen for dementia using the Short Blessed Test.[13,20]

Laboratory assessment in the ED may include a CBC, comprehensive metabolic profile, urinalysis, and possibly thyroid function tests and chest radiography. Outpatient evaluation may include serum vitamin B_{12} level, serologic testing for syphilis (in patients at risk), erythrocyte sedimentation rate, serum folate level, and human immunodeficiency virus testing.[21] Consider CT or MRI imaging in the ED when clinically

indicated (e.g., if there is concern for normal pressure hydrocephalus or new stroke).

Diagnosis of probable vascular dementia requires signs of cerebrovascular disease. The relationship between stroke and cognitive decline are usually temporally related. A fluctuating, stepped course suggests vascular dementia.

The possibility of a concurrent medical condition suddenly causing cognitive functioning to deteriorate should be strongly considered and often is the thrust of investigation in the ED. Urinary tract infection, congestive heart failure, and hypothyroidism are just a few of the conditions that may cause a patient with mild dementia to show rapid decline. The symptoms overlap with those of delirium, as discussed earlier in the "Clinical Features" section under "Delirium," and the two conditions may overlap.[2,10] In the differential diagnosis, consider the so-called treatable causes of dementia (included in Table 168-3) and impairment in cognitive function caused by depression (pseudodementia). Additionally, behavioral and psychiatric symptoms of dementia (e.g., depression, anxiety, agitation, hallucination) may prompt a visit to the ED.

TREATMENT

The behavioral and psychiatric symptoms of dementia are ideally managed by nonpharmacologic measures. There are three main categories to consider when targeting with interventions: (1) unmet needs, such as unrecognized pain; (2) learned behaviors, such as a behavior that elicits a desired response; and (3) environmental vulnerability and stress sensitivity, such as an aggressive behavior due to fear from a new situation.[22]

Atypical and conventional antipsychotic drugs carry a black box warning against use for behavioral and psychiatric symptoms of dementia, due to an increased risk in mortality. Reserve consideration of antipsychotic use for patients with significant risk of harm to self and others. Coordinate treatment with caregivers who are in a position to monitor the patient's behavior patterns over time.

Treatment of vascular dementia is limited to treatment of risk factors, including hypertension.

Normal pressure hydrocephalus is suggested by the presence of excessively large ventricles on head CT and can prompt consideration of a trial of lumbar puncture with cerebrospinal fluid drainage or ventricular shunting.

DISPOSITION AND FOLLOW-UP

A new diagnosis of dementia may be entertained in the ED, but the depth of the required diagnostic evaluation usually exceeds the time available during the ED visit. A decision to admit or to arrange an outpatient diagnosis should occur after the major and urgent differential diagnostic possibilities have been eliminated. Direct attention toward the presence of delirium or a treatable cause of dementia. Consider hospital admission if comorbid medical problems, a rapidly progressive or atypical clinical course, or an unsafe or uncertain home situation exists.

COMA

INTRODUCTION

Coma is a state of reduced alertness and responsiveness from which the patient cannot be aroused.[23,24] The Glasgow Coma Scale (**Table 168-4**; see also Chapter 257, "Head Trauma") is a widely used clinical scoring system for alterations in consciousness. Advantages are the simplicity of the scoring system and assessment of separate verbal, motor, and eye-opening functions. Disadvantages include lack of acknowledgment of hemiparesis or other focal motor signs and lack of testing of higher cognitive functions. Interrater variability has been noted in assessments using the **Glasgow Coma Scale**.[25] Another coma scale, the FOUR (Full Outline of Unresponsiveness) score, has been used in intensive care units and has the advantages of assessing simple brainstem functions and respiratory patterns, as well as eye and motor responses.[26] Causes of coma likely to be encountered in the ED are noted in **Table 168-5**.

PATHOPHYSIOLOGY

The pathophysiology of coma is complex. Coma can result from deficiency of substrates needed for neuronal function (as with hypoglycemia or hypoxia). With systemic causes, the brain is globally affected, and signs that localize dysfunction to a specific area of the brainstem or cortex are usually lacking. With primary CNS causes, coma may result from a brainstem disorder such as hemorrhage or from bilateral cortical dysfunction. Signs localizing to specific areas of CNS dysfunction such as hemiparesis or cranial nerve abnormalities may be present. Unilateral hemispheric disease, such as stroke, should not alone result in coma. The function of the brainstem and/or both hemispheres must be impaired for unresponsiveness to occur.

The herniation syndromes are models for alterations of consciousness, but their mechanisms are unknown. In **uncal herniation syndrome**, the medial temporal lobe shifts to compress the upper brainstem, which results in progressive drowsiness followed by unresponsiveness.[24,27] The ipsilateral pupil is sluggish, eventually becoming dilated and nonreactive as the third cranial nerve is compressed by the medial temporal lobe. Hemiparesis may develop ipsilateral to the mass from compression of the descending motor tracts in the opposite cerebral peduncle. **Central herniation syndrome** is characterized by progressive loss of consciousness, loss of brainstem reflexes, decorticate posturing, and irregular

TABLE 168-4 Glasgow Coma Scale

Component	Score	Adult	Child <5 y	Child >5 y
Motor	6	Follows commands	Normal spontaneous movements	Follows commands
	5	Localizes pain	Localizes to supraocular pain (>9 mo)	
	4	Withdraws to pain	Withdraws from nail bed pressure	
	3	Flexion	Flexion to supraocular pain	
	2	Extension	Extension to supraocular pain	
	1	None	None	
Verbal	5	Oriented	Age-appropriate speech/vocalizations	Oriented
	4	Confused speech	Less than usual ability; irritable cry	Confused
	3	Inappropriate words	Cries to pain	Inappropriate words
	2	Incomprehensible	Moans to pain	Incomprehensible
	1	None	No response to pain	
Eye opening	4	Spontaneous	Spontaneous	
	3	To command	To voice	
	2	To pain	To pain	
	1	None	None	

TABLE 168-5 Differential Diagnosis of Coma

Coma from causes affecting the brain diffusely

- Encephalopathies
  - Hypoxic encephalopathy
  - Metabolic encephalopathy
  - Hypertensive encephalopathy
- Hypoglycemia
- Hyperosmolar state (e.g., hyperglycemia)
- Electrolyte abnormalities (e.g., hypernatremia or hyponatremia, hypercalcemia)
- Organ system failure
  - Hepatic encephalopathy
  - Uremia/renal failure
- Endocrine (e.g., Addison's disease, hypothyroidism, etc.)
- Hypoxia
- Carbon dioxide narcosis
- Toxins
- Drug reactions (e.g., neuroleptic malignant syndrome)
- Environmental causes—hypothermia, hyperthermia
- Deficiency state—Wernicke's encephalopathy
- Sepsis

Coma from primary CNS disease or trauma

- Direct CNS trauma
  - Diffuse axonal injury
  - Subdural hematoma
  - Epidural hematoma
- Vascular disease
  - Intraparenchymal hemorrhage (hemispheric, basal ganglia, brainstem, cerebellar)
- Subarachnoid hemorrhage
  - Infarction
  - Hemispheric, brainstem
- CNS infections
- Neoplasms
- Seizures
  - Nonconvulsive status epilepticus
  - Postictal state

respiration.[24] Because midline shift without herniation, as demonstrated by neuroimaging, seems to correlate with a decreased level of consciousness, vascular compression due to local cerebral edema or local increased intracranial pressure (ICP) may be an underlying mechanism for these syndromes.

A diffuse increase in ICP can cause diffuse CNS dysfunction. Cerebral blood flow is constant at mean arterial pressures of 50 to 100 mm Hg due to the process of cerebral autoregulation. At mean arterial pressures outside this range, cerebral blood flow may be reduced, and diffuse ischemia may develop. **Cerebral perfusion pressure is equal to the mean arterial pressure minus the ICP (cerebral perfusion pressure = mean arterial pressure – ICP).** In extreme uncontrolled elevation of the ICP, cerebral perfusion pressure is diminished as the ICP approaches the mean arterial pressure, which causes brain ischemia.

Particularly in unresponsive patients with a history of seizures, the possibility of ongoing nonconvulsive seizures must be considered. Subtle status epilepticus or ictal coma may represent transformed generalized convulsive status epilepticus. Electrical seizures may continue in the absence of clinical seizures.[28]

CLINICAL FEATURES

The clinical features of coma vary with both the depth of coma and the cause. For example, a patient in a coma with a hemispheric hemorrhage and midline shift may have decreased muscle tone on the side of the hemiparesis. The eyes may conjugately deviate toward the side of the hemorrhage. **With expansion of the hemorrhage and surrounding edema, increase in ICP, or brainstem compression, unresponsiveness may progress to a complete loss of motor tone and loss of the ocular findings as well.**

A variety of abnormal breathing patterns may be seen in the comatose patient.[24] They offer little information in the acute setting. Pupillary findings, the results of other cranial nerve evaluation, hemiparesis, and response to stimulation are all parts of the clinical picture that need assessment. These findings can assign the cause of the coma into a probable general category—diffuse CNS dysfunction (toxic-metabolic coma) or focal CNS dysfunction (structural coma). A further division of structural coma into hemispheric (supratentorial) or posterior fossa (infratentorial) coma is often possible at the bedside.

Toxic-Metabolic Coma Many different toxic and metabolic conditions cause coma. The diffuse CNS dysfunction is reflected by the lack of focal physical examination findings that point to a specific region of brain dysfunction. For example, in toxic-metabolic coma, if the patient demonstrates either spontaneous movements or reflex posturing, the movements are symmetric without evidence of hemiparesis. Muscle stretch reflexes, if present, are symmetric. Pupillary response is generally preserved in toxic-metabolic coma. Typically, the pupils are small but reactive. If extraocular movements are present, they are symmetric. If extraocular movements are absent, however, this sign is of no value in differentiating toxic-metabolic from structural coma. A notable exception is severe sedative poisoning as from barbiturates; the pupils may be large, extraocular movements absent, muscles flaccid, and the patient apneic, which simulates the appearance of brain death.

Coma From Supratentorial Lesions Coma caused by lesions of the hemispheres, or supratentorial masses, may present with progressive hemiparesis or asymmetric muscle tone and reflexes. The hemiparesis may be suspected with asymmetric responses to stimuli or asymmetric extensor or flexor postures. Uncal herniation syndrome, as described earlier in "Pathophysiology," is an example of a supratentorial syndrome. Frequently, however, large acute supratentorial lesions are seen without the features consistent with temporal lobe herniation. Coma without lateralizing signs may result from decreased cerebral perfusion secondary to increased ICP. Reflex changes in blood pressure and heart rate may be observed with increased ICP or brainstem compression. Hypertension and bradycardia in a comatose patient may represent the Cushing reflex from increased ICP.

Coma From Infratentorial Lesions Posterior fossa or infratentorial lesions compose another structural coma syndrome. **An expanding lesion, such as cerebellar hemorrhage or infarction, may cause abrupt coma, abnormal extensor posturing, loss of pupillary reflexes, and loss of extraocular movements.** The anatomy of the posterior fossa leaves little room for accommodating an expanding mass. Early brainstem compression with loss of brainstem reflexes may develop rapidly. Another infratentorial cause of coma is pontine hemorrhage, which may present with the unique signs of pinpoint-sized pupils.

Pseudocoma Pseudocoma or psychogenic coma is occasionally encountered and may present a perplexing clinical problem. Adequate history taking and observation of responses to stimulation reveal findings that differ from those in the syndromes described in the previous sections. Pupillary responses, extraocular movements, muscle tone, and reflexes are shown to be intact on careful examination. Tests of particular value include responses to manual eye opening (there should be little or no resistance in the truly unresponsive patient) and extraocular movements. Specifically, if avoidance of gaze is consistently seen with the patient always looking away from the examiner, or if nystagmus is demonstrated with caloric vestibular testing, this is strong evidence for nonphysiologic or feigned unresponsiveness.

DIAGNOSIS

In the approach to the comatose patient, perform stabilization, diagnosis, and treatment actions simultaneously. Examination, laboratory procedures, and neuroimaging allow differentiation between structural and metabolic causes of coma in almost all patients in the ED. History and physical examination findings allow that initial assignment in many

patients, but liberal use of CT scanning is encouraged because exceptions to the tentative clinical diagnosis are frequent.[29]

Address airway, breathing, and circulation immediately. Consider reversible causes of coma, such as hypoglycemia or opiate overdose. Access all available historical sources (EMS personnel, caregivers, family, witnesses, medical records, etc.) to aid in diagnosis.

The tempo of onset of the coma is of great diagnostic value. Abrupt coma suggests abrupt CNS failure with possible causes such as catastrophic stroke or seizures. A slowly progressive onset of coma may suggest a progressive CNS lesion such as tumor or subdural hematoma. Metabolic causes, such as hyperglycemia, may also develop over several days.

Address general examination and measurement of vital signs (including oxygen saturation and temperature) following stabilization and resuscitation. General examination may reveal signs of trauma or suggest other diagnostic possibilities for the unresponsiveness. For example, a toxidrome may be present that suggests diagnosis and treatment, such as the opiate syndrome with hypoventilation and small pupils.

Neurologic testing deviates from the standard examination. Fine tests of weakness, such as testing for pronator drift of the outstretched upper extremities, are not possible in the unresponsive patient. However, asymmetric findings on examination of cranial nerves through pupillary examination, assessment of corneal reflexes, and testing of oculovestibular reflexes may suggest focal CNS lesions. Abnormal extensor or flexor postures are nonspecific for localization or cause of coma but suggest profound CNS dysfunction. Asymmetric muscle tone or reflexes raise the suspicion of a focal lesion. **The goal of the physician is to rapidly determine if the CNS dysfunction is from diffuse impairment of the brain or if signs point to a focal (and perhaps surgically treatable) region of CNS dysfunction.**

CT is the neuroimaging procedure of choice. Acute hemorrhage is readily identified, as is midline shift and mass lesions. Consider lumbar puncture if CT scan findings are unremarkable and subarachnoid hemorrhage or CNS infection is suspected. Suspect basilar artery thrombosis in a comatose patient with "normal" results on head CT, in which the only finding may be a hyperdense basilar artery.[30] MRI or cerebral angiography is needed to make the diagnosis of basilar artery thrombosis.

SPECIAL CONSIDERATIONS IN COMA

If trauma is suspected, maintain stabilization of the cervical spine during assessment. If protection of the airway is in doubt or the coma state is likely prolonged, then protect the airway by intubating the patient. Rapid-sequence intubation techniques are discussed at length in Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation." **For children, consider ingestions, infections, and child abuse in the appropriate clinical setting.**

Patients who have had generalized seizures and remain unresponsive may be in a continuing state of electrical seizures without corresponding motor movements. This is called **nonconvulsive status epilepticus** or **subtle status epilepticus** and can be described as electromechanical dissociation of the brain and body. **If the motor activity of the seizure stops and the patient does not awaken within 30 minutes, then consider nonconvulsive status epilepticus.** Obtain neurologic consultation and electroencephalography.[28]

TREATMENT

Treatment of coma involves identification of the cause of the brain failure and initiation of specific therapy directed at the underlying cause. Attend to airway, ventilation, and circulation. Evaluate and treat for readily reversible causes of coma, such as hypoglycemia and opioid toxicity.

Antidotes Rapid point-of-care glucose determination can identify the need for dextrose. Although thiamine should be administered before glucose infusion in patients with a suspected history of alcohol abuse or malnutrition, thiamine is not necessary for all patients. Routine use of flumazenil in coma of unknown cause is not recommended.[31] Naloxone, an opiate antagonist, may be useful in diagnosis and treatment of coma of unknown cause, given that the miosis of the opiate toxidrome can be absent with some opioids and mixed ingestions.

Increased Intracranial Pressure If history, physical examination, or neuroimaging findings suggest increased ICP, specific steps can reduce or ameliorate any further rise in ICP. Any noxious stimulus, including "bucking" the ventilator, can increase ICP, so use paralytic and sedative agents. A general recommendation is to keep the head elevated about 30 degrees and at midline to aid in venous drainage. **Mannitol** (0.5 to 1.0 gram/kg IV) can decrease intravascular volume and brain water and may transiently reduce ICP. Hypertonic saline infusion has also been found to be effective in reducing ICP. In cases of brain edema associated with tumor, dexamethasone, 10 milligrams IV, reduces edema over several hours. Hyperventilation with reduction of partial pressure of arterial carbon dioxide can reduce cerebral blood volume and transiently lower ICP. Current recommendations are to avoid excessive hyperventilation (partial pressure of arterial carbon dioxide ≤35 mm Hg) during the first 24 hours after brain injury. Brief hyperventilation may be necessary for refractory intracranial hypertension. Data to recommend specific therapy are lacking, and preferences among individuals and institutions vary greatly, so communicate early with consultants and admitting physicians.

DISPOSITION AND FOLLOW-UP

Patients with readily reversible causes of coma, such as insulin-induced hypoglycemia, may be discharged if home care and follow-up care are adequate and a clear cause for the episode is suspected. Admit patients with persistent altered consciousness. Most institutions depend on emergency physicians to stabilize the patient's condition and correctly assign a tentative diagnosis so that the patient may be admitted to the proper specialty service. If the appropriate service is not available, then consider transfer to another hospital after patient stabilization.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 169

Ataxia and Gait Disturbances

J. Stephen Huff

INTRODUCTION

Ataxia and gait disturbances may be symptoms of many disease processes and generally are not in themselves diagnoses. **Ataxia** is uncoordinated movement. A **gait disorder** is an abnormal pattern or style of walking. The presenting problem may be articulated by the patient or family as weakness, dizziness, stroke, falling, or another nonspecific chief complaint. Such symptoms must always be viewed in the context of the patient's overall clinical picture. This chapter reviews the more common causes of acute ataxia and gait disorders (**Table 169-1**).

PATHOPHYSIOLOGY

Clinicians often erroneously think that ataxia and gait disorders result primarily from cerebellar lesions. However, such ataxia and gait problems may result from systemic conditions that affect different elements of the central or peripheral nervous systems. Cerebellar lesions may indeed cause ataxia, but isolated lesions of the cerebellum are not the most common cause of these complaints. Ataxias may be classified as either motor (cerebellar) or sensory.

TABLE 169-1 Common Etiologies of Acute Ataxia and Gait Disturbances

Systemic conditions
- Intoxications with diminished alertness
  - Ethanol
  - Sedative—hypnotics
- Intoxications with relatively preserved alertness (diminished alertness at higher levels)
  - Phenytoin
  - Carbamazepine
  - Valproic acid
  - Heavy metals—lead, organic mercurials
- Other metabolic disorders
  - Hyponatremia
  - Inborn errors of metabolism
  - Wernicke's disease

Disorders predominantly of the nervous system
- Conditions affecting predominantly one region of the CNS
  - Cerebellum
    - Hemorrhage
    - Infarction
    - Degenerative changes
    - Abscess
  - Cortex
    - Frontal tumor, hemorrhage, or trauma
    - Hydrocephalus
  - Subcortical
    - Thalamic infarction or hemorrhage
    - Parkinson's disease
    - Normal pressure hydrocephalus
  - Spinal cord
    - Cervical spondylosis and other causes of spinal cord compression
    - Posterior column disorders
- Conditions affecting predominantly the peripheral nervous system
  - Peripheral neuropathy
  - Vestibulopathy

MOTOR ATAXIAS

Motor ataxias (also referred to as **cerebellar ataxias**) are usually caused by disorders of the cerebellum. The sensory receptors and afferent pathways are intact, but integration of proprioceptive information is faulty. Involvement of the lateral cerebellum (one of the cerebellar hemispheres) may lead to a motor ataxia of the ipsilateral limb. Lesions affecting primarily the midline portion of the cerebellum often cause problems with axial muscle coordination, which is reflected in difficulty maintaining a steady upright standing or sitting posture.

There are many reports of CNS lesions producing motor ataxia in what intuitively seem unlikely locations. Supratentorial infarctions, particularly small, deep infarctions, and lacunae of the posterior limb of the internal capsule have been reported to cause isolated hemiataxia. It is postulated that interruption of either ascending or descending cerebellar to cortical pathways are the cause of this motor-type ataxia.[1] Small infarctions or hemorrhages in thalamic nuclei may produce a clinical picture of motor- or cerebellar-like ataxia with hemisensory loss. These effects are seen contralateral to the lesion.[2] Lesions affecting the frontal lobe, such as tumors or cystic masses, may cause a motor ataxia of the contralateral extremities through poorly understood mechanisms.[3] Nontraumatic spinal cord compression may present with gait ataxia or abnormality.[4]

SENSORY ATAXIAS

Sensory ataxias are due to failure of transmission of proprioception or position sense information to the CNS. Failure may arise from disorders affecting the peripheral nerves, spinal cord, or cerebellar input tracts. Coordinated motor performance is faulty, even though motor systems and the cerebellum are intact. Sensory ataxias may be somewhat compensated by visual sensory information. Loss of visual information leads to the observation that sensory ataxias often worsen in poor lighting conditions.

GAIT DISORDERS

No organized classification scheme exists for gait disorders, and different authors categorize abnormal gaits in descriptive terms. A **cerebellar or motor ataxic gait** is wide-based with unsteady and irregular steps, and compensation for environmental barriers may be lacking. The **gait of sensory ataxia** resulting from loss of proprioception is notable for abrupt movement of the legs and slapping impact of the feet with each step. A variety of other terms are used to describe abnormal gaits.

An **apraxic gait** is one in which the patient seemingly has lost the ability to initiate the process of walking, an "ignition failure." This may occur with right or nondominant hemispheric lesions. Frontal lobe dysfunction may result in a similar gait and may be seen in normal pressure hydrocephalus.[5]

The term **festinating gait** is used to describe narrowly based miniature shuffling steps and is common in Parkinson's disease. An abnormal gait with outward swinging or circumabduction of the leg suggests a mild **hemiparesis** reflecting the asymmetric weakness of the proximal lower extremity muscles. Bilateral weakness of the trunk and pelvic girdle muscles may result in a **waddling gait** from failure to maintain the normal position of the pelvis relative to the lower extremities.

A functional gait disorder is one in which the patient is unable to walk normally, although all motor pathways, sensory pathways, and cerebellar functions may be demonstrated to be functioning normally. The underlying problem is often a conversion disorder. Functional gaits may be bizarre, at times resembling a person balancing on a tightrope and seemingly threatening to fall but not falling. A dramatic functional gait with flailing movements without falling actually demonstrates that strength, balance, and coordination are intact.

A unifying concept defines gait disorders according to the level of processing of neurologic information (**Table 169-2**).[6,7] The classification scheme is not ideal but does allow a thoughtful approach to patient diagnosis.

Low-level gait disturbance refers to disorders of proprioception or dysfunction of the musculoskeletal system. **Middle-level gait disturbance** causes distortion of appropriate interaction of postural and motor processes or synergies. This might include stroke with paralysis, cerebellar dysfunction, or diseases of the basal ganglia such as Parkinson's disease. **High-level gait disturbances** seemingly involve structures or processes

TABLE 169-2 Classification of Gait Disorders

Low-level gait disorders
- Musculoskeletal problems
  - Arthritic gait or other joint or skeletal problems
  - Muscle weakness
- Peripheral sensory problems
  - Sensory ataxic gait
  - Vestibular problems

Middle-level gait disorders
- Hemiplegia
- Paraplegia
- Motor or cerebellar ataxia
- Parkinson's disease
- Dystonia, chorea, other movement disorders

High-level gait disorders
- Senile gait (cautious gait)
- Frontal ataxic gait
- Apraxic gait (gait ignition failure)
- Frontal disequilibrium

that choose the appropriate responses for the support surface, body position in space, and intention of the patient. Cautious gait, apraxic gait, and the frontal gait disorder conceptually fall into this group with pathology that correlates with lesions in the frontal cortex or thalamus. This latter group is the least understood and often the source of clinical confusion.

CLINICAL FEATURES

HISTORY

Collect historical information about the entire symptom constellation including presence of headache, nausea, fever, weakness, or numbness. A history of fever, review of medication history, or family history of ataxia may lead to the diagnosis in individual cases. The nature of onset of symptoms and the time course of the process guide the pace of investigations. For example, abrupt onset of gait difficulty in a patient with severe headache, drowsiness, nausea, and vomiting should suggest an acute process within the CNS, possibly a hemorrhage into the cerebellum. The possible consequences of that diagnosis are severe and may require immediate attention. At the other extreme, a patient without significant medical history who is brought to the ED with a stumbling gait after an episode of binge drinking requires examination and may need nothing other than observation unless history or physical examination suggests trauma or some alternative cause for the symptoms.

PHYSICAL EXAMINATION

The following discussion of the neurologic examination assumes that the gait disorder is the dominating abnormality. Physical examination including testing of cranial nerves, mental status, sensation, and the motor system is necessary and may yield findings that lead to an unanticipated diagnosis. An approach to the neurologic examination is presented in Chapter 164.

General physical examination of a patient with ataxia or gait disturbance should include determination of orthostatic vital signs. Orthostatic hypotension may be present in hypovolemia, diabetic neuropathy, and other neurologic syndromes. Especially in the elderly, fluid replacement for simple hypovolemia may often correct symptoms of unsteadiness.

Gait testing is one of the most important parts of the directed neurologic examination. Observe the patient sitting upright in the stretcher, and then have the patient rise, stand, walk, and turn around. The patient should be asked to walk at a normal speed, then walk on the heels, and then the toes. Tandem gait is toe-to-toe walking and tests many elements of the nervous system. **Do not assume a normal examination without observing ambulation.**

Cerebellar functions are tested by asking the patient to perform smooth voluntary movements and rapidly alternating movements. Dyssynergia (breakdown of movements into parts), dysmetria (inaccurate fine movements), or dysdiadochokinesia (clumsy rapid movements) may indicate a lateral cerebellar lesion. The rapid thigh-slapping test particularly examines rapidly alternating movements. This is correctly performed by asking the patient to pat the thigh with the palm then the back of the same hand in alternating fashion, making a sound with each rapid slap. The maneuver is performed with each hand in turn. The finger-to-nose test may be helpful in distinguishing between cerebellar and posterior column (proprioceptive) lesions. Performing this test with the eyes closed tests proprioception in the upper extremities. A test for cerebellar function that emphasizes the lower extremities is the heel-to-shin test. In cerebellar disease, the heel may initially overshoot the other shin or knee, and the action is done with a series of jerky movements. In posterior column disease, there may be difficulty locating the knee with the heel, and the movement down the shin typically weaves from side to side or falls off. Another test commonly used for cerebellar function is checking for abnormal rebound; with sudden release of a flexed forearm against resistance, the individual fails to check further excessive flexion. Another example of rebound phenomena is when a tapped outstretched arm excessively oscillates back and forth for several seconds.

The Romberg test is primarily a test of sensation, and if positive, it may distinguish sensory from motor ataxia. While standing with arms outstretched and eyes open, observe the patient for signs of unsteadiness. The feet should be narrowly spaced, and the posture should be easily maintained. The inability to maintain a steady standing posture (or, in extreme cases, a seated position) confirms that an ataxia is present but does not yet give any information about the type of ataxia. Then ask the patient to close his or her eyes, which eliminates visually orienting information. If the ataxia worsens with the loss of visual input, then the Romberg sign is present or positive, suggesting sensory ataxia with a problem of proprioceptive input (posterior column, vestibular dysfunction) or a peripheral neuropathy. Further neurologic examination is indicated to confirm the suspicion of sensory ataxia. In patients who show little or no change in unsteadiness with eye closure (Romberg test–negative), a motor ataxia is suggested, with possible localization of that problem to the cerebellum. Note that many normal individuals will have some small increase in unsteadiness with eye closure.

Historically, tabes dorsalis (neurosyphilis) was a common cause of sensory ataxia. In tabes dorsalis, the posterior columns and posterior spinal roots degenerate primarily in the lumbosacral region. The loss of proprioceptive information from the lower extremities renders the patient dependent on visual cues for correct gait. The classic description depicts a patient walking slowly with wide gait while staring at the ground. In darkness or with interruption of vision, the patient is unable to walk. The gait in this condition appears peculiar, with the foot first raised and then slapped to the ground with each step. These abnormalities reflect the loss of proprioceptive information from the posterior roots and posterior columns. Consider the possibility of vitamin B_{12} deficiency in patients with evidence of posterior column disease. If the deficiency is left untreated, an initial unsteady gait may progress to weakness, spasticity, and ataxia. The finding of a megaloblastic anemia may be a clue, but the neuropathy may precede the anemia.

Sensory examination in a patient with unsteady gait or ataxic movements should include position or vibration testing (posterior columns), as well as testing sensation to pinprick. Testing of the deep tendon reflexes will serve largely to discover asymmetry or spasticity that might suggest an alternative diagnosis. Acute cerebellar injury may result in muscle hypotonia for a few days or weeks.[8]

Nystagmus is seen in many different disorders due to lesions in a variety of different locations of the CNS, but the presence of nystagmus does suggest that a pathologic process is intracranial (CNS or vestibular) and not in the spinal cord or peripheral nervous system (see Chapter 170, "Vertigo").

DIAGNOSIS

Assuming a primary complaint of ataxia, the first task is to determine whether the ataxia is sensory or motor, and whether the primary process is systemic or within the nervous system. If the ataxia is thought to result from problems within the nervous system, the next question is one of localization to the peripheral nervous system or the CNS and then perhaps to a more specific anatomic location. Finally, the tempo of the illness, comorbid diseases, and other clinical findings guide investigations and may allow a disease-specific diagnosis.

A patient with acute gait failure over hours to days needs thorough evaluation in the ED, often requiring neuroimaging and lumbar puncture if cerebrospinal fluid infection is suspected. Acute ataxia or gait disturbance may also be evaluated by consultation if available, and possible admission, in contrast to a patient with gradual loss of abilities over weeks or months where outpatient referral and evaluation may be more appropriate.

SPECIAL POPULATIONS

THE GERIATRIC PATIENT

The gait changes with advancing age. A typical constellation includes gait slowing, shortening of the stride, and widening of the base. This results in the appearance of a guarded gait—that is, the gait of someone about to slip and fall. Many patients are aware of the loss of speed and adaptive balance and acknowledge the need to be careful. The nature of the senile gait is not fully understood but may represent a mild degree of neuronal loss, failing proprioception, slowing of corrective responses, or

weakness of the lower extremities. Senile gait disorder is thought to exist in up to one fourth of the elderly population. Some authorities divide this disorder into components of gait ataxia with mild truncal instability and widened gait, and gait slowing with diminished spontaneous arm swing and bradykinesia.[9] However, elements of the senile gait are also found in neurologic diseases, so consider the possible presence of a disorder such as Parkinson's disease or normal pressure hydrocephalus in elderly patients with gait impairment.[9] Patients unable to walk or care for themselves, or with increasing falls at home, need admission for diagnosis and supportive care planning.

THE ALCOHOLIC PATIENT

A history of alcoholism or malabsorption problem in the patient with ataxia or gait disorder raises the possibility of a potentially remedial nutritional problem. If acute motor ataxia is present with confusion or eye movement abnormalities, consider **Wernicke's disease** and administer IV thiamine.[10] The entity of alcoholic cerebellar degeneration (sometimes referred to as rostral vermis syndrome, because a portion of the cerebellar vermis is preferentially affected) may represent the same nutritional deficiency and not the direct toxic effects of alcohol.

CHILDREN

In evaluating children with acute ataxia or gait disorder, examination must exclude weakness and musculoskeletal disorders. The child may be awake, alert, and playful but is visibly unsteady or wobbly sitting on a stretcher. The differential diagnosis is extensive (**Table 169-3**). Acute or deteriorating presentation generally mandates an aggressive search for the underlying cause and will likely need inpatient management.[11]

Intoxications are a cause of ataxia in children, and ingestions may be surreptitious. History should include queries about any medications in the household. Acute ataxia may follow immunizations, viral illnesses, or varicella, which has been rarely reported in the preeruptive phase of varicella.[12] Most children are in the 2- to 4-year-old range. Acute cerebellar ataxia of childhood is thought to be a postinfectious demyelinating disorder. The onset of gait ataxia is abrupt, and only occasionally is fever present at the time ataxia begins. The latency from the prodromal illness to the onset of ataxia is from 2 days to 2 weeks. Other neurologic findings encountered included truncal ataxia, dysmetria, and, uncommonly, cranial nerve abnormalities. Patients with ataxia following varicella appear to have uniform excellent recovery compared with patients with acute cerebellar ataxia of other causes who may have some residual problems.[13] Little workup is needed if the ataxia occurs in the convalescent phase of varicella, and antiviral medications are not indicated. Otherwise, neuroimaging, lumbar puncture, and consultation are advisable. One study showed that although roughly half of the patients had cerebrospinal fluid inflammatory changes with pleocytosis or elevated immunoglobulin G index, in only a minority of cases did MRI identify inflammatory changes in the cerebellum.[12] Another small report noted MRI abnormalities not only in the cerebellum but also in other areas of the CNS. This "syndrome" may in fact consist of several subgroups, some of which involve transient demyelination.[14]

Posterior fossa mass lesions and other CNS masses may present with ataxia, although usually some additional abnormalities of cranial nerves or strength will be discovered with careful examination. Attention is needed to exclude abnormalities on physical examination that might suggest problems not localized to the cerebellum. Abnormal ocular movements should increase the suspicion of a mass lesion. Acute ataxia associated with rapid chaotic eye movements (opsoclonus) and myoclonic jerks of the head and extremities is the striking syndrome of opsoclonus-myoclonus. This may be a postviral syndrome but is often a paraneoplastic syndrome associated with a neuroblastoma located in the abdomen or chest.[10]

Unusual metabolic disorders such as pyruvate decarboxylase complex deficiency may present with ataxia. Family history may or may not suggest a metabolic disorder. Typically, the onset is gradual, but abrupt decompensations may occur. Other systemic or CNS abnormalities will be present.

TABLE 169-3 Causes of Acute Ataxia in Children, Roughly in Order of Frequency

Cause	Example
Drug intoxication	Ethanol Isopropyl alcohol Phenytoin Carbamazepine Sedatives Lead, mercury
Idiopathic	Acute cerebellar ataxia of childhood
Infection and inflammation	Varicella Coxsackievirus A and B Mycoplasma Echovirus Postinfectious inflammation Postimmunization
Neoplasm	Neuroblastoma Other CNS tumors
Paraneoplastic	Opsoclonus-myoclonus syndrome
Trauma	Subdural or epidural posterior fossa hematoma
Congenital or hereditary	Pyruvate decarboxylase deficiency Friedreich's ataxia Hartnup disease
Hydrocephalus Cerebellar abscess Labyrinthitis/vestibular neuronitis Transverse myelitis Meningoencephalitis	

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 170

Vertigo

Brian Goldman
Peter Johns

INTRODUCTION AND EPIDEMIOLOGY

Vertigo is defined as the sensation of self-motion when no motion is occurring. Vestibular disorders are conditions that affect the vestibular sensory organs in the inner ear or the cerebellum and brainstem and the connections between them.

Some patients have difficulty describing the sensation of vertigo.[1] Dizziness is a nonspecific word patients use to describe vertigo, but is also used by some patients to describe the symptoms of presyncope, imbalance, lightheadedness, and other sensations. Assess patients for nonvestibular causes of dizziness such as orthostatic hypotension, presyncope, and new medications such as antihypertensives.

Vertigo is a diagnostic challenge because it has many potential causes (**Table 170-1**).

TABLE 170-1 Peripheral and Central Causes of Vertigo

Peripheral Causes	Relative Frequency of Presentation to the ED	Key Points	Clinical Course
Benign paroxysmal positional vertigo	The most common cause of vertigo	Less than 2-minute episodes of vertigo, initiated by head movement. Dix-Hallpike test shows vertical upward and rotatory nystagmus.	Benign, particle repositioning maneuvers is first-line treatment. Medications rarely indicated.
Vestibular neuritis	Common	Hours/days of continuous, constant vertigo. Use HINTS plus exam if nystagmus present.	Spontaneous improvement over days/weeks.
Labyrinthitis	Less common	Ear pain, tinnitus, and hearing loss onset 1 or more days before vertigo; otherwise similar to vestibular neuritis.	A complication of otitis media. Serious if bacterial (rare).
Ménière's disease	Less common	Recurrent episodes of vertigo, hearing loss, tinnitus, and ear fullness.	Slowly progressive; can lead to profound hearing loss.
Perilymph fistula	Rare	Vertigo and hearing loss after head trauma or pressure changes to middle ear (flying/diving/nose blowing).	Can benefit from surgical correction.
Superior canal dehiscence	Rare	Vertigo brought on by loud sounds, coughing, and straining.	Surgery for severe cases.
Vestibular schwannoma	Rare	Slow onset of hearing loss, tinnitus, and less commonly, vertigo.	Slowly growing; amenable to surgery if growing and symptomatic.
Central Causes			
Vestibular migraine	Most common central cause of vertigo, but much underdiagnosed.	Recurrent attacks in patients with migraine, including episodes of isolated vertigo. About half the episodes have migrainous features.	Most experts recommend treatment as per migraine headache.
Cerebellar/brainstem stroke	Less common	Often presents with other neurologic signs or symptoms, but can present with symptoms similar to vestibular neuritis; use HINTS plus exam if nystagmus is present. Hearing loss can occur at onset of stroke.	Admit to hospital, as patients can develop edema and/or hydrocephalus, leading to coma/death.
Posterior circulation transient ischemic stroke	Less common	Usually presents with other neurologic signs or symptoms.	Can present shortly before stroke.
Cerebellar hemorrhage	Less common	Significant ongoing headache; possibly decreased level of consciousness.	Neurosurgical consult; tonsillar herniation or hydrocephalus can occur.

Abbreviation: HINTS = head impulse test, nystagmus, test of skew.

Three of the most common vestibular disorders are featured prominently in this chapter. These are **benign paroxysmal positional vertigo (BPPV)**, **vestibular neuritis**, and **cerebellar/brainstem stroke.** The term Acute Vestibular Syndrome (AVS) is sometimes used to describe the entities of vestibular neuritis and cerebellar/brainstem stroke.

BPPV is the most common cause of vertigo in all clinical settings including the ED. The condition occurs when otoconia (which normally reside in the utricle) are displaced spontaneously or by trauma or infection into the semicircular canals. As a result, when patients move their head in certain positions, they experience vertigo and nystagmus, sometimes very intense, for less than 2 minutes, often around 20 seconds. BPPV can be diagnosed easily with a bedside test and is highly responsive to treatment with the Epley or other particle repositioning maneuvers.

Vestibular neuritis is the second most common peripheral cause of vertigo. Sometimes erroneously mislabeled as labyrinthitis by some clinicians, the condition is believed to be caused by a deficit in one of the vestibular nerves. The likely cause is a virus. The patient develops a prolonged, continuous bout of vertigo that is intense for several days and then resolves over days, weeks, or months. There is no associated ear pain, hearing loss, or tinnitus in vestibular neuritis.

Labyrinthitis, a complication of acute otitis media, is less common than vestibular neuritis but can present in a similar manner, with days of ongoing, continuous vertigo and nystagmus. Unlike vestibular neuritis, patients with labyrinthitis complain of ear pain, hearing loss, or tinnitus as well as vertigo.

Cerebellar/brainstem stroke (hereafter referred to as cerebellar stroke) is the most feared cause of vertigo. Patients with cerebellar stroke may develop edema causing acute hydrocephalus or brainstem compression that leads to increased disability or death. Many patients present with neurologic symptoms such as limb weakness or paresthesia, diplopia, or dysarthria, but some present without these features; as such, the condition may resemble vestibular neuritis.

When patients are discharged from the ED with a diagnosis of peripheral vestibular disorder, the frequency of missed strokes is very low, about .41%(2).

The fear of missing a stroke can lead the clinician to pursue advanced diagnostic imaging in patients with benign peripheral conditions. Fortunately, the most common peripheral causes of vertigo presenting to the ED, BPPV and vestibular neuritis, can often be differentiated from cerebellar stroke by history, physical examination, and focused bedside testing.[3]

PATHOPHYSIOLOGY

The CNS coordinates and integrates sensory input from the visual, vestibular, and proprioceptive systems. Vertigo arises from a mismatch of information from two or more of the involved senses, caused by dysfunction in the sensory organ or its corresponding pathway.

Visual inputs provide spatial orientation. Proprioceptors help relate body movements and indicate the position of the head relative to that of the body. The vestibular system (via the otoliths) establishes the body's orientation with respect to gravity. The cupula's sensors track rotary motion. The three semicircular canals sense orientation to movement and head tilts and are filled with a fluid called *endolymph.* The movement of fluid in the semicircular canals causes specialized hair cells inside the canals to move, causing afferent vestibular impulses to fire. Sensory input from the vestibular apparatus travels to the nucleus of the eighth cranial nerve (**Figure 170-1**).

The medial longitudinal fasciculus, the red nuclei, the cerebellum, the parietal lobes, and the superior temporal gyrus of the cerebral cortex integrate the various sensory inputs. Connections between these

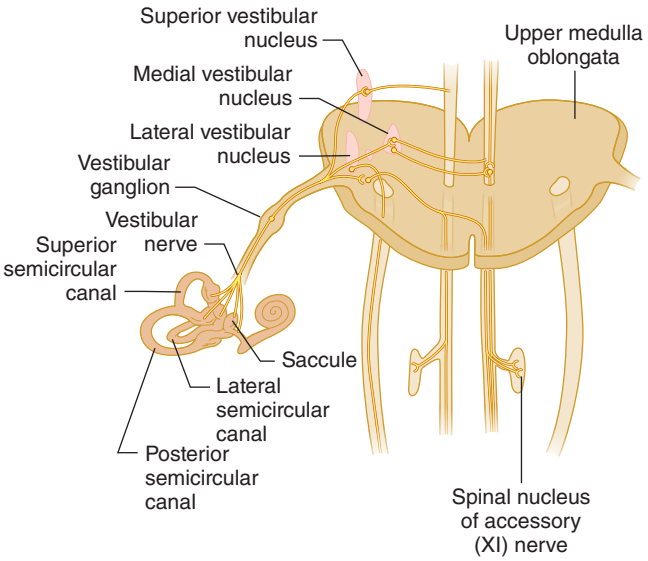

FIGURE 170-1. Vestibular innervation.

structures and the oculomotor nuclei that drive the vestibulo-ocular reflex complete the system. The vestibulo-ocular reflex prevents visual blurring from head movements and body sway.

Balanced input from the vestibular apparatus on both sides is the norm. Unilateral lesions of the vestibular apparatus as well as excessive unilateral firing due to abnormal motion of the endolymph produce imbalanced activity and vertigo. Rapid head movements accentuate the imbalance. Symmetric bilateral damage does not usually produce vertigo but may lead to truncal or gait instability.

The prevalence of dizziness increases with age and is due to decreases in visual acuity, proprioception, and vestibular input, plus an increase in free-floating otoconia within the semicircular canals that cause BPPV. Older patients are also more likely to take medications that cause dizziness.

CLINICAL FEATURES

OVERVIEW

If the presenting complaint points to true vertigo, the history and physical should then focus on a central cause of vertigo. Such neurologic signs and symptoms include focal weakness of the face or limbs, sensory changes, dysmetria (limb or truncal), diplopia, dysarthria, and dysphagia and dysphonia. Spontaneous vertical nystagmus (seen in primary gaze, with the patient looking straight ahead) is also indicative of central vertigo but is seen less commonly than other types of nystagmus, even in cerebellar and brainstem lesions. Short episodes of vertical upward nystagmus with a rotatory component during the Dix-Hallpike test are diagnostic of the most common form of BPPV.

Patients who are unable to stand unaided should have a central cause of vertigo ruled out. This is in contrast to the patient with peripheral vertigo; they may be very reluctant to stand or walk but are able in general to do so.

A significant and persistent headache that accompanies vertigo suggests the possibility of a cerebellar hemorrhage, and neck pain suggests vertebral artery dissection.

Patients with current or recent transient vertigo who screen positive for the neurologic symptoms mentioned previously should have diagnostic imaging as well as referral to a specialist. This method of screening will identify the majority of ischemic or hemorrhagic cerebellar and brainstem strokes causing vertigo, as well as posterior circulation transient ischemic attacks and vertebral artery dissections. Many of the vestibular disorders that cause peripheral and central vertigo are found in Table 170-1.

HISTORY AND PHYSICAL

An initial approach to diagnosing acute vertigo, focusing on BPPV, vestibular neuritis, and cerebellar stroke, is shown in the flow chart in **Figure 170-2**.

BPPV comes on abruptly with quick head movements, getting in or out of bed, or rolling over in bed. Patients with orthostatic hypotension complain of dizziness when they stand up but not when they resume the supine position or roll over in bed. If the patient with BPPV remains still, the vertigo usually goes away in less than 1 or 2 minutes. However, the associated nausea and vomiting may persist, prompting the patient to state that the dizziness lasts longer than 2 minutes. In addition, between bouts of vertigo, the patient with BPPV may feel slightly "off" but without ongoing vertigo or spontaneous nystagmus. This is contrasted with the presentations of vestibular neuritis and cerebellar stroke in which the patient has persistent and continuous vertigo lasting many hours or days **and whose vertigo is made worse by position change.** Note that head movements can worsen both central and peripheral vertigo.

Assess the patient carefully for nystagmus. The direction of the nystagmus is defined as the direction of the fast component of the nystagmus. Nystagmus can be horizontal, vertical, rotatory, or a combination. Since nystagmus may be suppressed by visual fixation, avoid having the patient stare at your finger or light source when observing for nystagmus. Observe for spontaneous nystagmus, which can be seen when the patient is looking straight ahead (primary gaze). Also observe for gaze-evoked nystagmus by having the patient look approximately 30 degrees from primary gaze to the left and right. To avoid fixation, place a blank piece of paper close to the side of the patient's head and ask the patient to look through the paper as if it is not there.

BEDSIDE TESTING FOR BPPV

PATIENTS WITH EPISODES OF VERTIGO LASTING LESS THAN 2 MINUTES AND INITIATED BY HEAD POSITION CHANGE BUT NO SPONTANEOUS OR GAZE-EVOKED NYSTAGMUS

Dix-Hallpike Test The Dix-Hallpike test (DHT) (See Video: Dix Hallpike Maneuver) is used to confirm the diagnosis of posterior canal BPPV, which is the most common form of BPPV. It is appropriate to perform a DHT if a patient has dizziness brought on by head movements only (such as rolling over in bed, lying down, or getting out of bed) that lasts 15 to 30 seconds **and** has no spontaneous or gaze-evoked nystagmus.

Consider pretreatment with an antiemetic only if the patient is having trouble tolerating positional testing or therapeutic maneuvers; it should not be given routinely.[4]

Have the patient seated on a stretcher or bed and positioned so that when supine, the patient's neck can be extended 20 degrees. To observe for nystagmus, instruct the patient to keep the eyes open throughout the test, even if vertigo occurs. To test the left ear, have the patient turn the head 45 degrees to the left. The examiner then quickly brings the patient from a sitting position to a supine position, with the neck extended 20 degrees and head turned 45 degrees to the left. Wait 15 seconds, and if no vertigo or nystagmus occurs, sit the patient up. Test the right side in the same manner, with the head turned 45 degrees to the right (See Video: Performing the Dix-Hallpike Test).

A positive DHT consists of a few seconds (up to 15) of latency, in which the patient is asymptomatic, followed by the onset of vertigo with a crescendo-decrescendo pattern of nystagmus that typical lasts roughly 15 to 30 seconds.

The nystagmus is a combination of **vertical** upward and rotatory, with the upper poles of the eyes beating toward the downward ear. When the patient looks more toward the upward ear, the nystagmus becomes more vertical and more rotatory when looking toward the downward ear.[5,6] The downward ear is the affected ear. Otoconia that originate in the utricle have been displaced and are now in the posterior semicircular canal (See Video: Positive Dix-Hallpike Test).

Note that HINTS (head impulse test, nystagmus, test of skew) plus testing should not be performed on patients with brief episodes of vertigo or who do not have spontaneous or gaze-evoked nystagmus because lack of nystagmus is a key component of a central cause of Acute Vestibular Syndrome.[7]

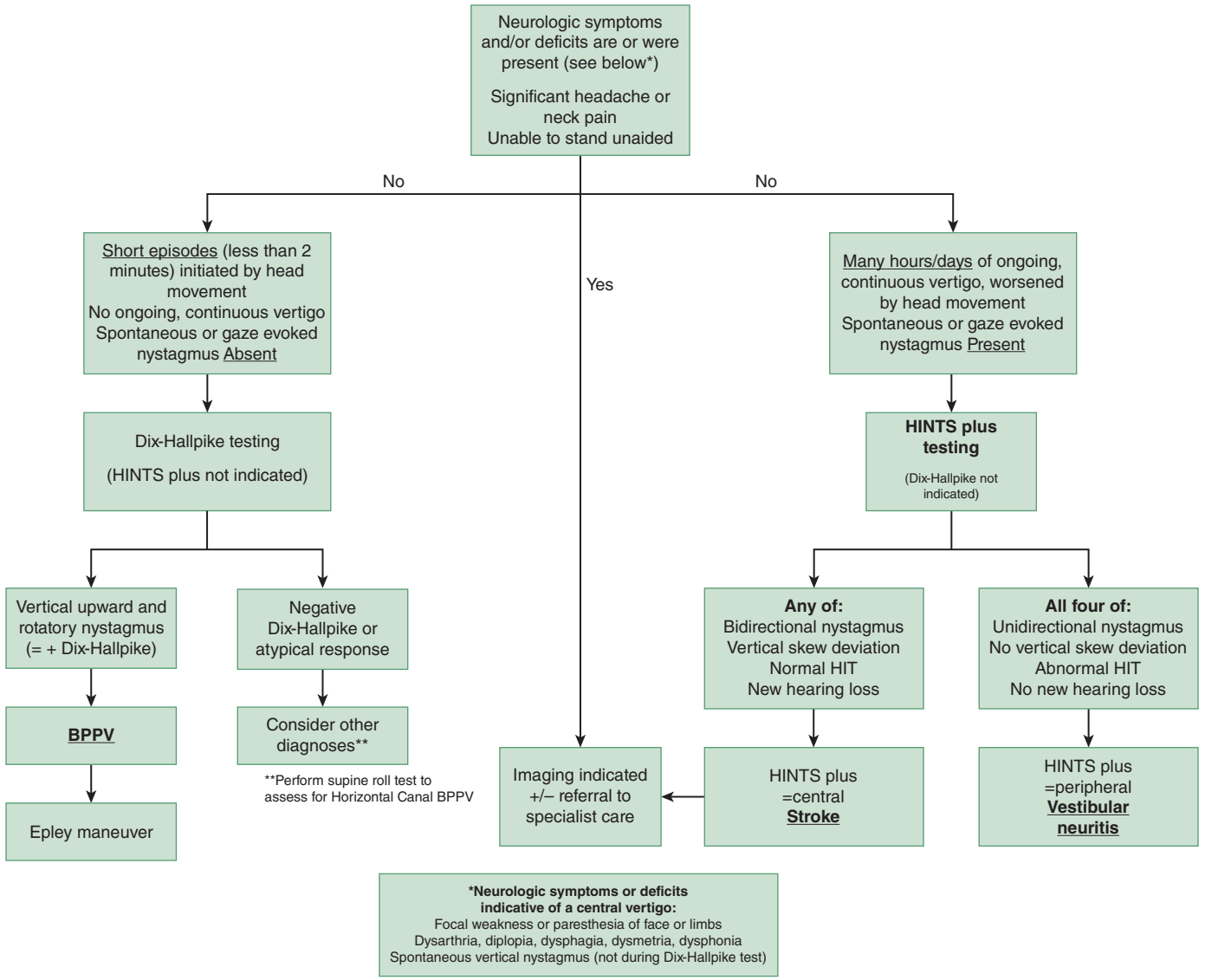

FIGURE 170-2. Flow chart of the initial approach to the diagnosis of acute vertigo. BPPV = benign paroxysmal positional vertigo; HINTS = head impulse test, nystagmus, test of skew; HIT = head impulse test.

TREATMENT OF POSTERIOR CANAL BPPV

Patients who are diagnosed with BPPV can be treated with the Epley maneuver during their ED visit.[8] The Epley maneuver should be considered first-line treatment for posterior canal BPPV. The affected ear is the downward ear when the patient has a positive DHT. Since BPPV can occur in either ear, there is a left and right Epley maneuver (**Figure 170-3** and See Video: The Epley Maneuver).

In Figure 170-3, the left ear Epley maneuver is shown. Hold each position for the length of time the patient is having vertigo, plus another 30 seconds. The first position is the same as the positive DHT position. Then, without sitting the patient up, the head is rotated 90 degrees to the negative DHT side, the second position. For the third position, the patient is asked to roll on his or her side and the head is rotated another 90 or more degrees in the same direction as the previous step, so that the patient is now looking toward the stretcher or straight down at the floor. In the final step, the patient is asked to move the legs forward off the bed, and the patient is brought to the sitting position, while keeping the head turned in the same direction as in the third position. In the final position, the patient should sit with head upright and looking forward.

After 10 minutes, repeat the DHT. If the post-Epley DHT produces no vertigo or nystagmus, the patient can be discharged without any restrictions on activity. It is not unusual for patients whose vertigo and nystagmus have resolved to feel slightly "off" for a day or two after being treated successfully. However, there should be no further episodes of positional nystagmus. If the post-Epley DHT is still positive, the Epley maneuver can be repeated. If the second Epley maneuver is unsuccessful, instruct the patient to perform subsequent trials of the maneuver at home twice a day until symptoms resolve. Such patients should have follow-up to ensure clinical improvement.

Since the episodes of BPPV typically last 15 to 30 seconds, do not prescribe vestibular suppressants.

If the DHT is negative on both sides or purely horizontal nystagmus is seen, then perform the supine roll test to determine whether the patient is suffering from a less common variant of BPPV—horizontal canal BPPV.

TREATMENT OF HORIZONTAL CANAL BPPV

If the patient has pure horizontal nystagmus when testing both left and right sides with the supine roll test, then the patient has horizontal canal BPPV and will not benefit from the Epley maneuver. Such patients can be treated with another particle repositioning maneuver called the Gufoni maneuver (See Video: Horizontal Canal BPPV).

Horizontal canal BPPV is rarer, resolves spontaneously more quickly, and is more difficult to assess and treat than posterior canal BPPV. Thus, it is reasonable to refer the patient with suspected horizontal canal BPPV to a clinician familiar with the diagnosis for further management.

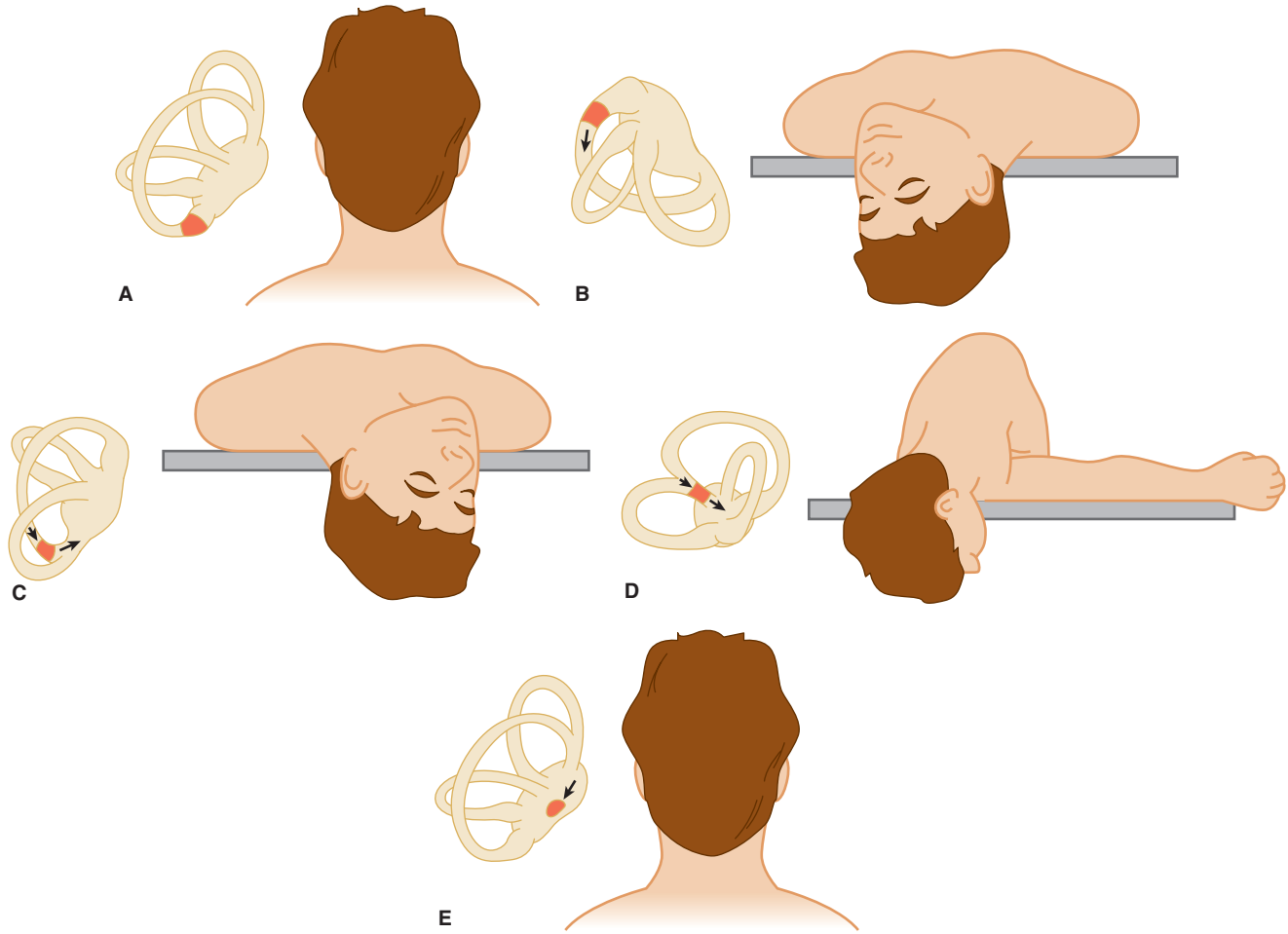

FIGURE 170-3. Left-sided Epley maneuver.

ANTERIOR CANAL BPPV

Should the patient experience downward vertical nystagmus during the DHT, the patient may be suffering from the least common form of BPPV, anterior canal BPPV. It can be treated using the deep head hanging maneuver (See Video: Anterior Canal BPPV).

Patients with a positive DHT are invariably suffering from posterior canal BPPV and do not need imaging. Rarely, patients with purely horizontal or down-beating nystagmus on positional testing may have a central cause of vertigo such as cerebellar degeneration, strokes, or tumors.

If the appropriately selected maneuver fails to resolve the episode of BPPV, the patient should have follow-up for further assessment and treatment.

BEDSIDE HINT+ TESTING TO DISTINGIUISH VESTIBULAR NEURITIS FROM CEREBELLAR/ BRAINSTEM STROKE

PERSISTENT CONTINUOUS ONGOING VERTIGO FOR HOURS OR DAYS WITH SPONTANEOUS NYSTAGMUS AND/OR GAZE-EVOKED NYSTAGMUS

These patients are suffering from acute vestibular syndrome with vertigo, nausea, and vomiting. Symptoms of acute vestibular syndrome worsen with head movement. Patients may also present with difficulty with gait. The majority of patients seen with acute vestibular syndrome are suffering from vestibular neuritis, but some will have a cerebellar stroke. Many, but not all, patients with stroke will have features suggestive of central vertigo (Figure 170-2). If these features are present, the patient should have neurodiagnostic imaging. Less commonly, multiple sclerosis can also present with acute vestibular syndrome.

HINTS Exam and HINTS Plus Exam The HINTS plus exam is a series of four bedside tests: **h**ead **i**mpulse test, **n**ystagmus, and **t**est of **s**kew, plus a bedside test for new hearing loss. This battery of tests is used to distinguish patients with continuous vertigo (lasting hours to days) and nystagmus who have a peripheral disorder (most likely vestibular neuritis) from those who have a central disorder (most likely cerebellar stroke). The original HINTS study selected patients with at least two risk factors for stroke, and the majority had strokes. The HINTS exam was performed by a single neuro-ophthalmologist. The HINTS exam was more sensitive and specific than early MRI.[9]

A study of acute vestibular syndrome patients (two thirds of whom had vestibular neuritis) who had HINTS performed in the ED by neurology residents showed almost identical results, with 100% sensitivity and 94% specificity for the HINTS exam in identifying stroke from vestibular neuritis.[10] (See Video: The HINTS Plus Exam in Vertigo.)

Nystagmus Examine the patient first for spontaneous or gaze-evoked nystagmus and note the direction and type. **Only patients with persistent ongoing vertigo and spontaneous or gaze-evoked nystagmus should undergo HINTS testing.**[7] In vestibular neuritis, the nystagmus (typically horizontal with a rotatory component) becomes more intense when the patient gazes in the direction of the nystagmus and lessens when looking away from the direction of the nystagmus. The affected ear in vestibular neuritis is the ear opposite to the direction of the nystagmus. Note that in vestibular neuritis, the fast component of the nystagmus does not change direction when gazing left and right. In central causes of nystagmus, the direction of the nystagmus *may* change direction depending on the direction of gaze (bidirectional nystagmus). When the patient looks to the left, the fast component of the nystagmus is to the left, and when looking to the right, the fast component is to the right. Although this is not always seen in central causes of vertigo, it is a highly specific sign for central vertigo.

Test of Skew Test of skew is accomplished by the cover-uncover test. While the patient looks at the examiner's nose, the examiner covers one eye and then covers the other eye. Any vertical or diagonally upward or downward movement of the eyes as they are uncovered indicates a central cause of vertigo.

Head Impulse Test Next, the head impulse test is used to demonstrate an abnormal vestibulo-ocular reflex on the side of the affected ear, a finding in patients with vestibular neuritis. To perform a head impulse test, hold the patient's head gently but firmly. Ask the patient to look at the examiner's nose, and gently move the head left and right around 20 degrees from the midline. The patient should be sufficiently relaxed so that the examiner can then move the patient's head from 20 degrees left or right of the midline quickly back to the midline. This should be done in a random fashion so that the patient does not anticipate in which direction the quick movement will occur.

In normal subjects, the eyes remain fixated on the examiner's nose, indicating an intact vestibulo-ocular reflex. In patients with vestibular neuritis, when the head is moved quickly toward the affected ear (spontaneous nystagmus is in the direction of the unaffected ear), the eyes will move with the head and thus overshoot the target (the examiner's nose). The examiner sees a "catch up saccade" in the same direction as the spontaneous nystagmus that is noticeably larger in amplitude.

Since most patients with stroke do not have a nerve deficit, a **normal** head impulse test is concerning for a central cause of vertigo in patients with persistent vertigo and spontaneous nystagmus. This counterintuitive finding bears emphasis, as it is open to misinterpretation.

Hints Plus Finally, the "plus" component of the HINTS plus exam has the examiner check for acute hearing loss by rubbing thumb and fingers together just lateral to the patient's left and right ear and asking whether the patient can hear it. **New hearing loss is suggestive of a central cause.** In particular, patients with an anterior inferior cerebellar artery stroke may have an abnormal head impulse test due to infarction of the labyrinth, as well as part of the cerebellum. The labyrinth contains the sensory end organs of balance and hearing. Thus, these patients will have both an abnormal head impulse test and new hearing loss.

Table 170-2 outlines the clinical characteristics of BPPV, vestibular neuritis, and cerebellar stroke and details the indications for and interpretation of DHT and HINTS plus testing.

TREATMENT OF VESTIBULAR NEURITIS

The majority of patients with constant vertigo lasting hours to days who undergo HINTS plus testing in the ED will be diagnosed with vestibular neuritis. The treatment is largely symptomatic, with short courses of antiemetic medications to ease vomiting.[11]

TREATMENT OF CEREBELLAR/BRAINSTEM STROKE

Admission is indicated to allow monitoring for complications such as cerebral edema and hydrocephalus. Secondary stroke prevention and rehabilitation should also be instituted during hospitalization.

It should be emphasized that the DHT should be performed only on patients with brief episodes of vertigo who have **no** spontaneous or gaze-evoked nystagmus. HINTS plus testing should be performed only on patients with hours or days of continuous constant vertigo and who **have** nystagmus. Since the two clinical presentations are easy to distinguish, there is no rationale for performing both the DHT and the HINTS plus exam in the same patient.

Patients who have vertigo that lasts between 2 minutes and many hours could have other diagnoses, most commonly vestibular migraine, Ménière's syndrome, or transient ischemic attack.

POSTERIOR CIRCULATION TRANSIENT ISCHEMIC ATTACK

Posterior circulation transient ischemic attack may present with transient vertigo and focal neurologic symptoms typical of cerebellar or brainstem stroke, such as weakness of the face or limbs, sensory changes, dysmetria (limb or truncal), diplopia, dysarthria, dysphagia, or dysphonia. Such patients should be triaged, investigated, and treated similar to patients with anterior circulation transient ischemic attacks. Since HINTS plus testing should be performed only on patients with ongoing vertigo and nystagmus, HINTS plus testing is **not** appropriate for transient ischemic attack patients whose vertigo and/or other posterior circulation symptoms have resolved.

Patients with posterior circulation stroke often experience transient neurologic attacks prior to the stroke. However, only 4% of patients with posterior circulation stroke seek medical attention for what seems to them to be nonspecific symptoms.[12] In one study of 169 patients with isolated vertigo, just one patient had a transient ischemic attack.[13] A study of 3900 patients with transient ischemic attack found that isolated vertigo was negatively associated with having an impending stroke.[14]

TABLE 170-2 Clinical Presentation and Guide to Bedside Testing for BPPV, Vestibular Neuritis, and Cerebellar Stroke

	BPPV	Vestibular Neuritis	Cerebellar Stroke
Vertigo when still	No	Yes	Yes
Able to stand unaided	Yes	Yes	May not be able to
Spontaneous and/or gaze-evoked nystagmus	No	Yes	Yes
Typical spontaneous or gaze-evoked nystagmus seen	Not present	Unidirectional horizontal/rotatory Not purely vertical	Various, including bidirectional horizontal/rotatory, sometimes vertical
Worse when moves head	Yes	Yes	Yes
Other neurologic symptoms or findings	No	No	Often but not always present
New hearing loss	No	No	Can occur
Appropriate to perform Dix-Hallpike test	Yes	No	No
Nystagmus produced during Dix-Hallpike test	Vertical upward and rotatory	Do not perform Dix-Hallpike test	Do not perform Dix-Hallpike test
Appropriate to perform HINTS plus exam	No	Yes	Yes
Results from HINTS plus exam	Do not perform HINTS plus testing	All four findings: Unidirectional nystagmus No vertical skew Abnormal HIT No hearing loss HINTS plus = peripheral	ANY of: Bidirectional nystagmus Vertical skew present Normal HIT New hearing loss HINTS plus = central
Imaging indicated	No	No	Yes
Primary treatment	Epley maneuver	Supportive treatment	Treatment for stroke

Abbreviations: BPPV = benign paroxysmal positional vertigo; HINTS = head impulse test, nystagmus, test of skew; HIT = head impulse test.

TABLE 170-3 Approach to Diagnostic Imaging in Vertigo

BPPV and vestibular neuritis: none required if findings are typical and bedside testing is confirmatory

Cerebellar/brainstem stroke:

- CT angiography if in rare case the stroke score deficit indicates potential benefit for thrombolysis or endovascular clot retrieval
- Emergent MRI if acute intervention not indicated or HINTS plus indicates central cause **and** more than 48 hours of vertigo
- Admit to hospital and perform delayed MRI in 2–3 days if acute intervention not indicated; HINTS plus indicates central cause **and** symptoms less than 48 hours

Vestibular migraine: none required if clinical history and presentation are diagnostic for vestibular migraine

Suspected vertebral artery dissection (significant ongoing neck pain): CT angiography or MRI/MRA of head and neck

TIA with neurologic symptoms or signs beyond vertigo and nystagmus: CT angiography or MRI/MRA

Suspected TIA without neurologic symptoms (isolated vertigo): consider CT angiography or MRA if patient has significant risk factors for stroke/TIA; a optimal diagnostic strategy has yet to be defined

Ménière's disease: none for typical presentation

Suspected cerebellar hemorrhage (significant ongoing headache or decreased level of consciousness): CT of the head

Multiple sclerosis: MRI

Postconcussive vertigo: CT of the head if intracranial hemorrhage suspected

Labyrinthitis:

- **Viral:** none
- **Bacterial:** MRI

Superior canal dehiscence syndrome: CT of temporal bone

Vestibular schwannomas: MRI

Abbreviations: BPPV = benign paroxysmal positional vertigo; HINTS = head impulse test, nystagmus, test of skew; MRA = magnetic resonance angiography; TIA = transient ischemic attack.

The optimal diagnostic approach for patients who present with spontaneous transient isolated vertigo remains uncertain.

DIAGNOSTIC IMAGING

See Table 170-3 for a condition-specific approach to diagnostic imaging.

TREATMENT

SYMPTOMATIC TREATMENT FOR PERIPHERAL VERTIGO

Short-term treatment with antiemetic and vestibular suppressant pharmacotherapy is a mainstay for patients with peripheral vertigo other than BPPV[15] (**Table 170-4**). Withdraw symptomatic treatments as soon as possible to facilitate central vestibular compensation.[16]

DRUG THERAPY

Pharmacotherapy is used to treat specific conditions, reduce symptoms, or enhance vestibular compensation. Drugs with anticholinergic effects can be quite effective for vertigo. Transdermal scopolamine is a time-honored remedy. H_1 antihistamines are commonly prescribed drugs for their anticholinergic effects. H_2 antihistamines are not effective. Calcium channel blockers (Table 170-4) are indicated for the symptomatic relief of vertigo in patients not responding to scopolamine or antihistamines. Neuroleptics such as promethazine and metoclopramide reduce nausea and vomiting by blocking brainstem dopaminergic receptors. They too are indicated as second-line treatment. Do not use prochlorperazine and chlorpromazine in dizziness caused by orthostatic hypotension. Ondansetron, a serotonin 5-HT_3 receptor antagonist, is an antinauseant that has been used to treat intractable vertigo in brainstem disorders as well as vertigo due to multiple sclerosis.

Small doses of benzodiazepines may be used sparingly to relieve symptoms of acute vestibular neuritis. However, these agents may impair vestibular compensation and thus should not be used for more than 3 days.

Betahistine is a strong H_3 and weak H_1 antagonist that increases cochlear blood flow and decreases peripheral vestibular inputs. A dosage of 48 milligrams/d is effective in treating vertigo, and may facilitate vestibular compensation.[17]

Gabapentin is indicated for dizziness associated with multiple sclerosis.

Antihistamines can cause sedation and anticholinergic adverse effects. Antidopaminergic neuroleptic agents can induce or exacerbate orthostatic hypotension. These drugs also cause somnolence and acute dystonia and can exacerbate anticholinergic adverse effects. Avoid using medications with overlapping anticholinergic and antidopaminergic effects in combination. Do not treat patients with nonvertiginous dizziness and disequilibrium of aging with antivertigo medications.

OTHER SPECIFIC CONDITIONS

VESTIBULAR MIGRAINE

Vestibular migraine is the most common central cause of vertigo. After BPPV, it is the second most frequent cause of vertigo in the ED. It has a 1-year prevalence of 0.89%.[18] **In patients who are referred to a tertiary vertigo clinic, 25% of the patients have vestibular migraine, but the diagnosis was suspected by the referring physician in less than 10% of cases.**[19]

Vestibular migraine is a common cause of vertigo in children. For some postmenopausal women with a long-standing history of migraine, episodic vertigo may replace the typical headache. Thirty percent of patients have no headache before, during, or after the episode of vertigo. The diagnosis of vestibular migraine is made clinically (**Table 170-5**). Currently, there is no proven specific therapy for prophylaxis of vestibular migraine.[20] **Expert opinion suggests the use of the medications that are commonly used for migraine headache.**

MÉNIÈRE'S SYNDROME

Ménière's syndrome is a disorder associated with an increased endolymph within the cochlea and labyrinth. It tends to occur in older men and women with equal prevalence. The disease is usually unilateral but may become bilateral over time. The precise pathogenesis is unknown, but evidence suggests that patients have difficulty regulating the volume, flow, and composition of endolymph. The onset is usually sudden, with associated nausea, vomiting, and diaphoresis, with attacks lasting from 20 minutes to 12 hours. The frequency of attacks varies from several times per week to several times per month. Other associated symptoms include tinnitus, diminished hearing, and fullness in one ear. Between attacks, the patient is usually well, although decreased hearing may persist.

Ménière's syndrome is managed symptomatically with antihistamines and betahistine; combination therapy with triamterene and hydrochlorothiazide is also recommended in confirmed cases. Calcium channel blockers may also be used (Table 170-4). None of these drug treatments improves hearing.

Refer patients for treatment to an otolaryngologist, because intratympanic injections of corticosteroids or gentamicin are increasingly used to control the frequency of attacks in patients not responding to standard therapy.[21]

PERILYMPH FISTULA

A perilymph fistula is an opening in the round or oval window that permits pneumatic changes in the middle ear to be transmitted to the vestibular apparatus. Trauma, infection, or a sudden change in the pressure inside the ventricular system may cause the tear. The diagnosis is suggested by the sudden onset of vertigo and hearing loss associated with head trauma, flying, scuba diving, severe straining, heavy lifting, coughing, or sneezing. Associated symptoms may include hearing loss.

Perilymph fistula is managed with symptomatic treatment and bed rest and referral to an ear, nose, and throat specialist for surgical repair (emergent referral for patients with acute associated hearing loss).

VESTIBULAR GANGLIONITIS

Vestibular ganglionitis is believed to be caused by a neurotrophic virus such as varicella-zoster reactivated years following initial infection. Herpes zoster oticus, also known as the Ramsay Hunt syndrome, is a

TABLE 170-4 Pharmacotherapy of Vertigo and Dizziness

Category	Drug	Dosage	Indications	Advantages	Disadvantages
Anticholinergics	Scopolamine	0.5 milligram transdermal patch (behind ear) three to four times a day	Vertigo, nausea	Useful if patient is vomiting	Sometimes difficult to obtain
Antihistamines	Dimenhydrinate	50–100 milligrams IM, IV, or PO every 4 h	Vertigo, nausea	Inexpensive	Drowsiness/anticholinergic effect
	Diphenhydramine	25–50 milligrams IM, IV, or PO every 4 h	Vertigo, nausea	Inexpensive	Drowsiness/anticholinergic effect
	Meclizine	25 milligrams PO two to four times a day	Vertigo, nausea		Drowsiness/anticholinergic effect
Antiemetics	Hydroxyzine	25–50 milligrams PO four times a day	Vertigo, nausea	Inexpensive	Drowsiness/anticholinergic effect
	Metoclopramide	10–20 milligrams IV, PO three times a day	Vertigo, nausea	Effective, versatile	Occasional extrapyramidal effect
	Ondansetron	4 milligrams IV two to three times a day; 8 milligrams PO twice a day			
	Promethazine	25 milligrams IM, PO, or PR three to four times a day	Vertigo, nausea	Useful if vomiting	Occasional extrapyramidal effect
Benzodiazepines	Diazepam	2–5 milligrams PO two to four times a day	Central vertigo, anxiety related to peripheral vertigo	Inexpensive	Dependency, may impair vestibular compensation
	Clonazepam	0.5 milligram PO two times a day	Central vertigo, anxiety related to peripheral vertigo	Inexpensive	Dependency, may impair vestibular compensation
Calcium antagonists	Cinnarizine	25 milligrams PO two to three times a day	Peripheral vertigo, vestibular migraine	Nonsedating	Lesser clinical experience
	Nimodipine	30 milligrams PO two times a day	Peripheral vertigo, vestibular migraine	Nonsedating	Lesser clinical experience
	Flunarizine	20 milligrams PO two times a day	Ménière's syndrome	Well tolerated	Not available in the United States
Vasodilators	Betahistine	48 milligrams PO three times a day for up to 6–12 mo	Ménière's syndrome	Well tolerated	Little evidence of efficacy for other causes of peripheral vertigo
Corticosteroids	Methylprednisolone	100 milligrams/d tapered by 20 milligrams/d every fourth day	Vestibular neuronitis	Well tolerated	Efficacy largely unproven; adverse effects associated with corticosteroids
Antivirals	Valacyclovir	1000 milligrams three times a day for 7 d	Vestibular neuronitis	Well tolerated	Efficacy largely unproven
Anticonvulsants	Carbamazepine	200–600 milligrams/d	Vestibular paroxysmia	Inexpensive	Monitor CBC and liver function tests
	Topiramate	50–100 milligrams/d	Vestibular migraine prophylaxis	Well tolerated	Not well evaluated; does not abort acute vertigo
	Valproic acid	300–900 milligrams/d	Vestibular migraine prophylaxis	Well tolerated	Not well evaluated; does not abort acute vertigo
	Gabapentin	300 milligrams four times per day	Multiple sclerosis–associated dizziness	Reduces acquired pendular nystagmus of multiple sclerosis	Known adverse effect profile
β-Blockers	Metoprolol	100 milligrams/d	Vestibular migraine prophylaxis	Long experience	Known adverse effect profile

neuropathic disorder thought to be associated with vestibular ganglionitis. It is characterized by deafness, vertigo, and facial nerve palsy. **The diagnosis is confirmed by the presence of grouped vesicles on an erythematous base inside the external auditory canal.** Treat this disorder with antiviral therapy started within 72 hours of the appearance of vesicles along with symptomatic treatments.

OTOTOXICITY

Various drugs have been found to be ototoxic (**Table 170-6**). Aminoglycoside antibiotics produce hearing loss and peripheral vestibular dysfunction by accumulating inside the endolymph, causing the death of cochlear and vestibular hair cells. However, because both inner ears are affected, vertigo is uncommon. Clinical manifestations include ataxia and oscillopsia (defined as the inability to maintain visual fixation while moving). The damage is usually irreversible but is dose and duration dependent. Loop diuretics (furosemide and ethacrynic acid) also cause irreversible vestibular toxicity and ototoxicity. Cytotoxic agents such as vinblastine and cisplatin cause vestibular damage; however, newer platinums, such as carboplatin, are less likely to do so. The antiarrhythmic drug quinidine and antimalarial drugs derived from quinine, such as chloroquine and mefloquine, also can cause vestibular symptoms that may be irreversible.

Reversible causes of vestibular damage and ototoxicity include NSAIDs, salicylates, minocycline, erythromycin, and some fluoroquinolones.

TABLE 170-5 Diagnostic Criteria for Vestibular Migraine

- Moderate or severe episodes of vertigo lasting **5 minutes to 72 hours**
- Past or current **history of migraine**
- **5 or more episodes of vertigo, at least 50%** of which **have one of following three migrainous** features: visual aura, photophobia or phonophobia, or typical migraine headaches
- Typical migraine headaches should have at least two of the following four qualities: unilateral, pulsating, moderate or severe intensity, or aggravated by routine activity
- In addition, the patient's clinical presentation should not better accounted for by another headache or vestibular problem

TABLE 170-6 Ototoxic and Vestibulotoxic Agents

Agent	Dose Dependent	Reversible
Aminoglycosides	Yes	Usually not; possible improvement with *N*-acetylcysteine
Erythromycin	No	Yes
Minocycline	No	Yes
Fluoroquinolones	No	Yes
NSAIDs; salicylates	Yes	Yes
Loop diuretics	No	Can be irreversible
Cytostatic drugs	Yes	No
Antimalarials	No	Yes
Anticonvulsants	Yes	Yes

Isolated cases of unsteady gait have been observed with antiviral drugs such as abacavir as well as antiparasitic agents. Solvents and other chemicals such as propylene glycol, toluene, mercury, and hydrocarbons can cause both peripheral and central vestibular symptoms.

Drugs that sometimes induce a central vestibular syndrome include tricyclic antidepressants, neuroleptics, opiates, and alcohol. Anticonvulsants cause dizziness and ataxia, especially in older patients. Phenytoin, toluene, and cancer chemotherapy agents can cause irreversible cerebellar toxicity. Phencyclidine is a recreational drug that causes central vestibular symptoms, including nystagmus and ataxia.

In general, most patients adapt to chronic vertigo by relying on intact proprioception and vision. However, benzodiazepines and neuroleptics that are often used as antivertigo therapy may exacerbate symptoms by delaying or inhibiting such compensation. Thus, avoid using this therapy on a long-term basis. Refer patients with suspected ototoxicity to an otolaryngologist.

POSTTRAUMATIC VERTIGO

Acute posttraumatic vertigo and unsteady gait are caused by a direct injury to the labyrinthine membranes. The onset of vertigo is immediate and is accompanied by nausea and vomiting. There may be a concomitant fracture of the temporal bone. Vertigo associated with a closed head injury warrants CT or MRI to exclude an intracranial hemorrhage. Vertigo due to direct labyrinthine trauma tends to resolve within several weeks. Closed head trauma also can displace otoconia from the utricular maculae, precipitating an attack of BPPV. Postconcussive syndrome can be associated with unsteadiness of gait and a vague sense of dizziness. These patients may be treated symptomatically, with referral to an appropriate clinic if symptoms fail to resolve.

WALLENBERG'S SYNDROME

A lateral medullary infarction (Wallenberg's syndrome) of the brainstem can cause vertigo as part of its clinical presentation. **Classic ipsilateral findings include facial numbness, loss of corneal reflex, Horner's syndrome, and paralysis or paresis of the soft palate, pharynx, and larynx (causing dysphagia and dysphonia).** Contralateral findings include loss of pain and temperature sensation in the trunk and limbs. Occasionally, lesions of the sixth, seventh, and eighth cranial nerves can occur, causing vertigo, nausea, vomiting, and nystagmus. These patients require emergent MRI and neurologic consultation.

MULTIPLE SCLEROSIS

Demyelinating disease can present with vertigo that lasts several hours to several weeks and is usually not recurrent. The vertigo is mild, with nystagmus the most prominent finding on physical examination. Such patients require confirmatory testing with MRI as well as vestibular evoked myogenic potentials and referral to a neurologist.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 171

Seizures and Status Epilepticus in Adults

Josh Kornegay

INTRODUCTION AND PATHOPHYSIOLOGY

A seizure is an episode of abnormal neurologic function caused by inappropriate electrical discharge of brain neurons. Neuronal electrical discharge, in its most simple form, can be thought of as the homeostasis of glutaminergic (excitatory) and γ-aminobutyric acid (inhibitory) activity. The seizure is the clinical attack in the setting of inappropriate excitatory activity. Some patients with "epileptic" electroencephalographic (EEG) discharges may not experience any overt clinical symptoms. Some seizure-like episodes may be due to causes other than abnormal brain electrical activity, but such attacks are not true seizures.

Epilepsy is a clinical condition in which an individual is subject to recurrent seizures. It implies a fixed, excitatory condition of the brain with a lower seizure threshold. The term *epileptic* does not refer to an individual with recurrent seizures caused by reversible conditions such as alcohol withdrawal or metabolic derangements.

Primary or *idiopathic* seizures are those in which no evident cause can be identified. *Secondary* seizures are a consequence of an identifiable neurologic condition, such as a mass lesion, previous head injury, or stroke. Electrical stimulation of the brain, convulsant potentiating drugs, profound metabolic disturbances, or significant head trauma all may cause *reactive seizures* in otherwise normal individuals. Reactive seizures are generally self-limited and not considered to be a seizure disorder or epilepsy.

Additional definitions of seizures are based on clinical factors or duration: **status epilepticus** is seizure activity ≥5 minutes, or two or more seizures without regaining consciousness between seizures[1]; **refractory status epilepticus** is persistent seizure activity despite the IV administration of adequate amounts of two antiepileptic agents.

SEIZURE CLASSIFICATION

The International League Against Epilepsy recommends dividing seizures into two major groups: *generalized seizures* and *partial seizures* (**Table 171-1**). When there are inadequate data to categorize the seizure, the seizure is considered *unclassified.*

GENERALIZED SEIZURES

Generalized seizures are thought to be caused by near simultaneous activation of the entire cerebral cortex, perhaps caused by an electrical discharge originating deep in the brain and spreading outward. The attacks begin with abrupt loss of consciousness, and this may be the only clinical manifestation of the seizure (as in absence attacks), or there may be a variety of motor manifestations (tonic posturing, clonic jerking of the body and extremities).

Generalized tonic-clonic seizures are the most familiar and dramatic of the generalized seizures. **In a typical attack, the patient suddenly becomes rigid (tonic phase), trunk and extremities are extended, and the patient**

TABLE 171-1 Classification of Seizures

- Generalized seizures (consciousness always lost)
- Tonic-clonic seizures (grand mal)
- Absence seizures (petit mal)
- Others (myoclonic, tonic, clonic, or atonic seizures)
- Partial (focal) seizures
  - Simple partial (no alteration of consciousness)
  - Complex partial (consciousness impaired)
  - Partial seizures with secondary generalization (Jacksonian march)
- Unclassified (inadequate information)

falls to the ground. As the tonic phase subsides, there are increasing coarse movements that evolve into a symmetric, rhythmic (clonic) jerking of the trunk and extremities. Patients are often apneic during this period and may be cyanotic. They often urinate and may vomit. As the attack ends, the patient is left flaccid and unconscious, often with deep, rapid breathing. Typical attacks last from 60 to 90 seconds; bystanders generally overestimate the duration of the seizure. Consciousness returns gradually, and postictal confusion, myalgias, and fatigue may persist for several hours.

Absence seizures are very brief, generally lasting only a few seconds. **Patients suddenly develop altered consciousness but no change in postural tone. They appear confused or detached, and current activity ceases.** They may stare or have twitching of the eyelids. They may not respond to voice or to other stimulation, exhibit voluntary movements, or lose continence. Attacks cease abruptly, and the patients typically resume previous activity without postictal symptoms. Patients and witnesses may be unaware that anything has happened. Classic absence seizures occur in school-aged children and are often attributed by parents or teachers to daydreaming or inattention. The attacks can occur as frequently as 100 or more times daily and may result in poor school performance. They usually resolve as the child matures. Similar attacks in adults are more likely to be minor complex partial seizures and should not be termed absence. The distinction is important because the causes and treatment of the two seizures are different.

PARTIAL (FOCAL) SEIZURES

Partial seizures are due to electrical discharges beginning in a localized region of the cerebral cortex. The discharge may remain localized or may spread, involving nearby cortical regions or the entire cortex. Focal seizures are more likely to be secondary to a localized structural lesion of the brain.

In simple partial focal seizures, the seizure remains localized, and consciousness is not affected. It is possible to deduce the likely location of the initial cortical discharge from the clinical features at the onset of the attack. For example, unilateral tonic movements limited to one extremity suggest a focus in the contralateral motor cortex, whereas visual symptoms suggest an occipital focus. Olfactory or gustatory hallucinations suggest a focus in the medial temporal lobe. Such sensory phenomena, known as *auras,* are often the initial symptoms of attacks that then become more widespread, termed *secondary generalization.*

Complex partial seizures are focal seizures in which consciousness or mentation is affected. They are often caused by a focal discharge originating in the temporal lobe and are sometimes referred to as *temporal lobe seizures*. Complex partial seizures are commonly misdiagnosed as psychiatric problems because symptoms can be so bizarre. **Symptoms may include automatisms, visceral symptoms, hallucinations, memory disturbances, distorted perception, and affective disorders.** Common automatisms include lip smacking, fiddling with clothing or buttons, or repeating short phrases. Visceral symptoms often consist of a sensation of "butterflies" rising up from the epigastrium. Hallucinations may be olfactory, gustatory, visual, or auditory. There may be complex distortions of visual perception, time, and memory. Affective symptoms may include intense sensations of fear, paranoia, depression, elation, or ecstasy. Because such seizures result in alterations of thinking and behavior, they were previously referred to as *psychomotor seizures,* but to avoid confusion with psychiatric illness, the term *complex partial seizure* is preferred.

Focal seizures may spread to involve both hemispheres, mimicking a typical generalized seizure. For the purpose of classification, diagnosis, and treatment, such attacks are still regarded as focal seizures. In some patients, the discharge may spread so rapidly that no focal symptoms are evident, and the correct diagnosis may depend entirely on demonstration of the focal discharge on an EEG recording.

CLINICAL FEATURES

HISTORY

When a patient presents after the event, the first step is to determine whether the episode was truly a seizure. Obtain a careful history of the details of the attack from the patient and any bystanders who witnessed the attack. Inquire about the physical description of the attack, as witnesses may mislabel the activity and mistake nonseizure activity as a seizure.

Important avenues of inquiry include the presence of a preceding aura, abrupt or gradual onset, progression of motor activity, loss of bowel or bladder control, presence of oral injury, and whether the activity was localized, generalized, symmetric, or asymmetric. Ask about the duration of the episode, and determine the presence of postictal confusion or lethargy.

Next, determine the clinical context of the episode. If the patient is a known epileptic, clarify the baseline seizure pattern. If the attack is consistent with the previous seizure pattern, identify precipitating factors of the current seizure. **Common precipitating factors include missed doses of antiepileptic medications; recent alterations in medication, including dosage change or conversion from brand name; sleep deprivation; increased strenuous activity; infection; electrolyte disturbances; and alcohol or substance use or withdrawal.**

If there is no previous history of seizures, a more detailed inquiry is needed. Symptoms such as unexplained injuries, nocturnal tongue biting, or enuresis suggest previous unrecognized seizures. Ask about a history of recent or remote head injury. Persistent, severe, or sudden headache suggests intracranial pathology. Pregnancy or recent delivery raises the possibility of eclampsia. A history of metabolic or electrolyte abnormalities, hypoxia, systemic illness (especially cancer), coagulopathy or anticoagulation, exposure to industrial or environmental toxins, drug ingestion or withdrawal, and alcohol use may point to predisposing factors (**Table 171-2**).

PHYSICAL EXAMINATION

Immediately obtain a complete set of vital signs and a point-of-care glucose. In the postseizure setting, focus the initial exam on checking for injuries, especially head or spine trauma, as a result of the seizure. A posterior shoulder dislocation is an injury that is easy to overlook. Lacerations of the tongue and mouth, dental fracture, and pulmonary aspiration are also frequent sequelae.

Perform a directed, complete neurologic examination and subsequent serial examinations. Follow the patient's level of consciousness and mentation closely to avoid missing nonconvulsant status epilepticus (see below). **A transient focal deficit (usually unilateral) following a**

TABLE 171-2 Common Causes of Provoked (Secondary) Seizures

- Trauma (recent or remote)
- Intracranial hemorrhage (subdural, epidural, subarachnoid, intraparenchymal)
- Vascular lesion (aneurysm, arteriovenous malformation)
- Mass lesions (primary or metastatic neoplasms)
- Degenerative neurologic diseases
- Congenital brain abnormalities
- Infection (meningitis, encephalitis, abscess)
- Hypo- or hyperglycemia
- Hypo- or hypernatremia
- Hyperosmolar states
- Uremia
- Hepatic failure
- Hypocalcemia, hypomagnesemia (rare)
- Cocaine, lidocaine, antidepressants, theophylline, isoniazid
- Mushroom toxicity (*Gyromitra* spp.)
- Hydrazine (rocket fuels)
- Alcohol or drug withdrawal
- Eclampsia of pregnancy (may occur up to 8 weeks postpartum)
- Hypertensive encephalopathy
- Anoxic-ischemic injury (cardiac arrest, severe hypoxemia)

simple or complex focal seizure is referred to as *Todd's paralysis* and should resolve within 48 hours.

DIAGNOSIS

Clinical features that help to distinguish seizures from other nonseizure attacks include the following:

- Abrupt onset and termination. Some focal seizures are preceded by auras that can last 20 to 30 seconds, but most attacks begin abruptly. Episodes reported to develop over several minutes or longer should be regarded with suspicion. Most seizures last only 1 or 2 minutes, unless the patient is in status epilepticus.
- Lack of recall. Except for simple partial seizures, patients usually cannot recall the details of an attack.
- Purposeless movements or behavior during the attack.
- Most seizures are followed by a period of postictal confusion and lethargy.

DIFFERENTIAL DIAGNOSIS

Many episodic disturbances of neurologic function may be mistaken for seizures (seizure mimics). A complete review of these conditions is too lengthy for inclusion here, but several important entities are mentioned.

Syncope usually presents with prodromal symptoms, such as lightheadedness, diaphoresis, nausea, and "tunnel vision." However, cardiac syncope may occur suddenly without any prodromal warning. Syncope may be associated with injury, incontinence, or even brief tonic-clonic activity. Recovery is usually rapid, with no postictal-like symptoms. For further discussion, see Chapter 52, "Syncope."

Pseudoseizures can be difficult to distinguish from true seizures and may occur in a patient who also has a documented seizure disorder. Pseudoseizures are psychogenic in origin and are often associated with a conversion disorder, panic disorder, psychosis, Munchausen syndrome, or malingering. Suspect this diagnosis when seizures occur in response to emotional upset or occur only with witnesses present. Pseudoseizures are often bizarre and highly variable. Patients often are able to protect themselves from noxious stimuli during the attack. Characteristic movements include side-to-side head thrashing, pelvic thrusting, and clonic alternating extremity motions rather than symmetric. Incontinence and injury are uncommon, and there is usually no postictal confusion. Patients will often stop the seizure-like activity on command. Accurate diagnosis of pseudoseizures may require prolonged EEG or video monitoring to demonstrate normal EEG activity during an attack. The lack of a lactic acidosis or elevated prolactin level within 10 to 15 minutes of the cessation of seizure-like activity makes true seizures much less likely.[2,3]

Hyperventilation syndrome can be misdiagnosed as a seizure disorder. A careful history will reveal the gradual onset of the attacks with shortness of breath, anxiety, and perioral numbness. Such attacks may progress to involuntary spasm (especially carpopedal) of the extremities and even loss of consciousness, although postictal symptoms are rare. Asking the patient to hyperventilate often reproduces the episodes.

Movement disorders, such as dystonia, chorea, myoclonic jerks, tremors, or tics, may occur in a variety of neurologic conditions. Consciousness is always preserved during these movements, and the patient can often temporarily suppress the movements.

Migraine headaches may be preceded by an aura similar to that seen in some partial seizures. The most common migraine aura is the scintillating scotoma. Migraine headaches may also be accompanied by focal neurologic symptoms, such as homonymous hemianopsia or hemiparesis. However, active movement disorders are inconsistent with migraine.

LABORATORY TESTING

Individualize the use of laboratory studies. **In a patient with a well-documented seizure disorder who has had a single unprovoked seizure, the only tests that may be needed are a glucose level and pertinent anticonvulsant medication levels.**

In the case of an adult with a first seizure or unclear seizure history, more extensive studies are usually needed and depend on the clinical context. Obtain serum glucose, basic metabolic panel, lactate, calcium, magnesium, a pregnancy test, and toxicology studies. Consider assays for anticonvulsant drug levels. A seizure may result in a lactate-driven, wide anion gap metabolic acidosis.[2] Most lactate abnormalities will clear within 30 minutes. The prolactin level may also be elevated for a brief period (15 to 60 minutes) immediately after a seizure.[3] These tests can prove helpful in distinguishing true seizures from a pseudoseizure.

Interpret the results of anticonvulsant levels with caution. If patient history is limited, a positive serum assay for anticonvulsant drugs suggests (but does not prove) the presence of a chronic seizure disorder. The usual therapeutic and toxic levels indicated in laboratory reports are helpful only as rough guides. **The therapeutic level of a drug is the level that provides adequate seizure control without unacceptable side effects.** A marked change in previously stable drug levels may indicate noncompliance, a change in medication, malabsorption of a drug, or ingestion of a potentiating or competing drug. A very low serum anticonvulsant drug level suggests medication noncompliance and is the most common cause of a breakthrough seizure.

IMAGING

Obtain a CT scan of the head in the ED for patients with a first-ever seizure or a change in established seizure patterns to evaluate for a structural lesion. A noncontrast CT is an appropriate screening tool.[4,5] Obtain a CT scan if there is any concern for an acute intracranial process based on history, comorbidities, or findings on physical examination. **Concern for an acute intracranial process is an important indication for obtaining CT imaging, even if there is a coexistent metabolic process.**

Because many important processes, such as tumors or vascular anomalies, may not be evident on noncontrast studies, a follow-up contrast-enhanced CT or MRI is often needed. Almost one quarter of adults with new-onset seizure will have visualized pathology on follow-up MRI, with rates increasing to as high as 53% in those with onset of a focal seizure.[6] The timing of further imaging studies can be discussed with the consulting neurologist.

Obtain other radiographic studies as indicated by the clinical presentation to avoid missing other sequela as a result of the seizure. These may include chest radiographs, cervical spine radiographs, or musculoskeletal imaging if aspiration or injuries are suspected. Special examinations, such as cerebral angiography, are rarely part of the ED evaluation.

LUMBAR PUNCTURE

Lumbar puncture in the setting of an acute seizure is indicated if the patient is febrile or immunocompromised or if subarachnoid hemorrhage is suspected and the noncontrast head CT is normal. For further discussion, see Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage," and Chapter 174, "Central Nervous System and Spinal Infections."

ELECTROENCEPHALOGRAPHY

Although EEG is helpful, it is often not readily available in most EDs. Emergent EEG can be considered in the evaluation of a patient with persistent, unexplained altered mental status to evaluate for nonconvulsive status epilepticus, subtle status epilepticus, paroxysmal attack when a seizure is suspected, or ongoing status epilepticus after chemical paralysis for intubation. Emergent EEG is normally performed in consultation with a neurologist.

TREATMENT OF UNCOMPLICATED SEIZURES

PATIENTS WITH ACTIVE SEIZURES

Typically, little is required during the course of an active seizure other than supportive and patient protective measures. If possible, turn the patient to the side to reduce the risk of aspiration. It is usually not necessary or even possible to ventilate a patient effectively during a

seizure, but once the attack subsides, clear the airway. Suction and airway adjuncts should be readily available. **It is not necessary or recommended to give IV anticonvulsant medications during the course of an uncomplicated seizure, although the practitioner should be ready to administer these medications if seizures do not terminate.** Most seizures will self-resolve within 5 minutes. Any unnecessary sedation at this point will complicate the evaluation and result in a prolonged decrease in level of consciousness.[7] Seizures that fail to abate after 5 minutes are considered status epilepticus and require more aggressive medical interventions (see "Status Epilepticus," below).

PATIENTS WITH A HISTORY OF SEIZURES

Proper management of a patient with a well-documented seizure disorder who presents after one or more seizures depends on the particular circumstances of the case. Identify and correct potential precipitants that may lower the seizure threshold. Many seizures occur due to medication nonadherence. Some anticonvulsants have very short serum half-lives, and missing a single dose may result in a sharp drop in serum levels. If anticonvulsant levels are very low, supplemental doses are appropriate, and the regular regimen can be restarted or adjusted. A loading dose is frequently provided. Without a loading dose, the patient may not achieve anticonvulsant effects for days to weeks and is at risk for subsequent seizures. Because there are no data comparing parenteral versus oral replacement, route is left to the discretion of the medical provider[8] and should be based on knowledge of pharmacology. For example, the oral loading dose of phenytoin is 20 milligrams/kg given in three divided doses every 2 to 4 hours—a time frame not acceptable for a typical ED stay—so the IV route is needed to achieve the proper loading dose.

In the noncompliant patient, obtain a serum anticonvulsant level before administering a supplemental or loading dose to avoid drug toxicity. **If anticonvulsant levels are adequate and the patient has had a single seizure, specific treatment may not be needed if the seizure pattern and frequency fall within the expected range for the patient.** If anticonvulsant levels are not available (i.e., levetiracetam or lacosamide) and there is a missed dose or noncompliance, give the usual dose in the ED before discharge.

Even well-controlled patients may have occasional breakthrough seizures. Attempt to identify any precipitants that have lowered the seizure threshold. If none is found, a change or adjustment of medication may be needed and should be made in consultation with the patient's primary care physician or neurologist along with follow-up in 1 to 3 days. There are no specific guidelines for the duration of ED observation in the situation of an individual with a prior history of seizures. Some clinicians discharge patients with seizures resulting from nontherapeutic anticonvulsant levels after administration of a loading dose of an anticonvulsant, if vital signs are normal and the mental status has returned to baseline. Ideally, discharge patients with a reliable family member or friend and with medical follow-up arranged.

PATIENTS WITH A FIRST UNPROVOKED SEIZURE

Guidelines do not recommend hospital admission or initiation of anticonvulsant therapy in the patient with a first unprovoked seizure, as long as the patient has returned to neurologic baseline.[1,8] The most important predictors of seizure recurrence are the underlying cause of the seizure and the results of the EEG. The decision to begin outpatient treatment with antiepileptics depends on the risk of recurrent seizures weighed against the risk-benefit ratio of anticonvulsant therapy. In general, patients with a first unprovoked seizure who have a normal neurologic examination, no acute or chronic medical comorbidities, normal diagnostic testing including noncontrast head CT, and normal mental status can safely be discharged from the ED. Initiation of antiepileptic medication may be deferred to the outpatient setting where further studies, including an EEG and MRI, can be performed.[1,4,8] Consider consultation and/or admission for patients who do not meet the above criteria.

Patients with secondary seizures due to an identifiable underlying condition (Table 171-2) often require admission and should generally be treated to minimize seizure recurrence.

The ideal initial antiepileptic regimen is a single-drug therapy that controls seizures with minimum toxicity. If treatment is initiated, drug selection is based on the type of seizure and should be done in consultation with a neurologist. Antiepileptic agents, such as valproate, lamotrigine, topiramate, levetiracetam, and oxcarbazepine, are options for adults with new-onset seizures.[5,9] Consider developing common protocols between emergency medicine and neurology when treatment of new-onset seizures is initiated from the ED.

Instruct discharged patients to take precautions to minimize the risks of injury from further seizures. Swimming, working with hazardous tools or machines, and working at heights should be avoided. Driving is prohibited until cleared by the neurologist or primary care physician. Driving privileges should conform to state law, and it may be up to the emergency physician to document seizure activity with the Department of Motor Vehicles.

SPECIAL POPULATIONS

HUMAN IMMUNODEFICIENCY VIRUS

Mass lesions, encephalopathy, herpes zoster, toxoplasmosis, *Cryptococcus*, neurosyphilis, and meningitis are all seen more frequently in this population and can all provoke seizure activity.[10,11]

Perform an extensive investigation for the cause of the seizure. If no space-occupying lesion is identified on noncontrast head CT scan and there is no evidence of increased intracranial pressure, perform a lumbar puncture to exclude CNS infection. If no explanation for seizures is found, then obtain a contrast-enhanced head CT or MRI.

NEUROCYSTICERCOSIS

Neurocysticercosis is caused by a CNS infection with the larval stage of the tapeworm *Taenia solium* and is the most common cause of provoked (secondary) seizures in the developing world.[12] The most common form of disease is parasitic invasion of brain parenchyma and cyst formation. Over 1 to 2 years, the cyst degenerates and becomes fibrotic, leaving a focal area of scar and calcification. Seizures are the most common clinical manifestation of neurocysticercosis and most frequently occur as the parasite is degenerating. In 80% to 90% of cases, the lesions resolve within 3 to 6 months, leaving the patient free of seizures. Up to 20% of patients will continue to have seizures and require ongoing therapy with antiepileptic medications.[12]

In most cases, neuroimaging in neurocysticercosis is nondiagnostic. CT or MRI may demonstrate a 1- to 2-cm cystic lesion with thin walls and a 1- to 3-mm mural nodule (the parasite), a localized area of ring-like enhancement with surrounding edema, a calcified lesion, or hydrocephalus. Definitive diagnosis relies on a combination of the patient's clinical picture, exposure history, serologic testing, and neuroimaging.

Seizures in neurocysticercosis are typically controlled by antiepileptic monotherapy. Definitive treatment of neurocysticercosis is controversial and highly variable, depending on the number, location, and viability of the parasites within the CNS.[13,14] Antiparasitics (praziquantel and albendazole) and steroids are best initiated in consultation with an infectious disease specialist or neurologist.

PREGNANCY

The management of seizures (or control of epilepsy) during pregnancy requires a multidisciplinary approach. Most seizures in pregnancy are not first-time seizures, and initial evaluation is generally as discussed above, with the addition of an obstetric evaluation to determine gestational age and fetal well-being.

When a woman beyond 20 weeks of gestation develops seizures in the setting of hypertension, edema, and proteinuria, the diagnosis is *eclampsia*. Magnesium sulfate is the treatment. In eclampsia, magnesium sulfate infusion compared to diazepam and phenytoin resulted in a >50% reduction in recurrence of seizures and a lower incidence of pneumonia, intensive care unit admission, and assisted ventilation.[15-17] Detailed discussion of seizures in pregnancy is provided in Chapter 100,

"Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period."

ALCOHOL ABUSE

Seizures and alcohol use are associated through missed doses of medication, sleep deprivation as an epileptogenic trigger, increased propensity for head injury, toxic coingestions, electrolyte abnormalities, and withdrawal seizures. Benzodiazepines in doses sufficient to manage withdrawal symptoms will usually afford adequate protection from acute seizures. These doses are often very large and need to be given in an escalating fashion.[18] Evaluate and treat the alcohol-abusing patient with a first seizure as any other patient with a first-time seizure. Detailed discussion of alcohol withdrawal seizures is provided in Chapter 292, "Substance Use Disorders."

STATUS EPILEPTICUS

Status epilepticus can occur in patients with a history of seizures or can be a first epileptic event. The most common causes of status epilepticus include subtherapeutic antiepileptic levels; preexisting neurologic conditions, such as prior CNS infection, trauma, or stroke; acute stroke; anoxia or hypoxia; metabolic abnormalities; and alcohol or drug intoxication or withdrawal.[19]

Status epilepticus is a single seizure ≥5 minutes in length or two or more seizures without recovery of consciousness between seizures.[1,20,21] After 5 minutes, seizures are less likely to spontaneously terminate, less likely to be controlled with antiepileptic drugs, and more likely to cause neuronal damage. **Status epilepticus is a neurologic emergency, and treatment should be initiated in all patients with continuous seizure activity lasting more than 5 minutes.**

As seizures surpass the 5-minute mark, dramatic changes occur at the cellular level. Decreased expression and internalization of γ-aminobutyric acid receptors, coupled with increased expression of both glutamine and *N*-methyl-D-aspartate receptors, lead to a greatly diminished seizure threshold.[22,23] The blood–brain barrier is also compromised, leading to CNS penetration of potassium and albumin, both of which are hyperexcitatory CNS chemicals.[24] After 20 minutes, hypotension, hypoxia, metabolic acidosis, hyperthermia, hypoglycemia, cardiac dysrhythmias, and pulmonary edema frequently develop.[25] This hyperexcitatory milieu makes standard antiseizure therapies much less effective in seizure termination.

In **nonconvulsive status epilepticus**, the patient is comatose or has fluctuating abnormal mental status or confusion, but no overt seizure activity is present. The diagnosis is challenging and is typically made by EEG. Findings suggestive of nonconvulsive status epilepticus include a prolonged postictal period after a generalized seizure; subtle motor signs such as twitching, blinking, and eye deviation; fluctuating alterations in mental status; or unexplained stupor and confusion.[25]

TREATMENT OF STATUS EPILEPTICUS

Early recognition and treatment of status epilepticus are critically important. Mortality dramatically increases with delayed diagnosis or initiation of treatment, particularly with nonconvulsive status epilepticus, age greater than 60 years, and in patients with no documented seizure disorder.[26] The goal of treatment is seizure control as soon as possible and within 30 minutes of presentation (**Figure 171-1**). Examination, identification of potential causes, application of the ABCs (airway, breathing, and circulation), and treatment all begin simultaneously. Direct a focused history and physical examination toward possible causes and subsequent injuries.

Establish large-bore IV access and determine a bedside glucose. Administer normal saline, avoiding IV fluids containing glucose as phenytoin is not compatible with glucose-containing solutions. Place the patient on oxygen, a cardiac monitor, pulse oximeter, and end-tidal capnography.

In established status epilepticus, consider endotracheal intubation for airway protection, oxygenation, and ventilation. Use a short-acting

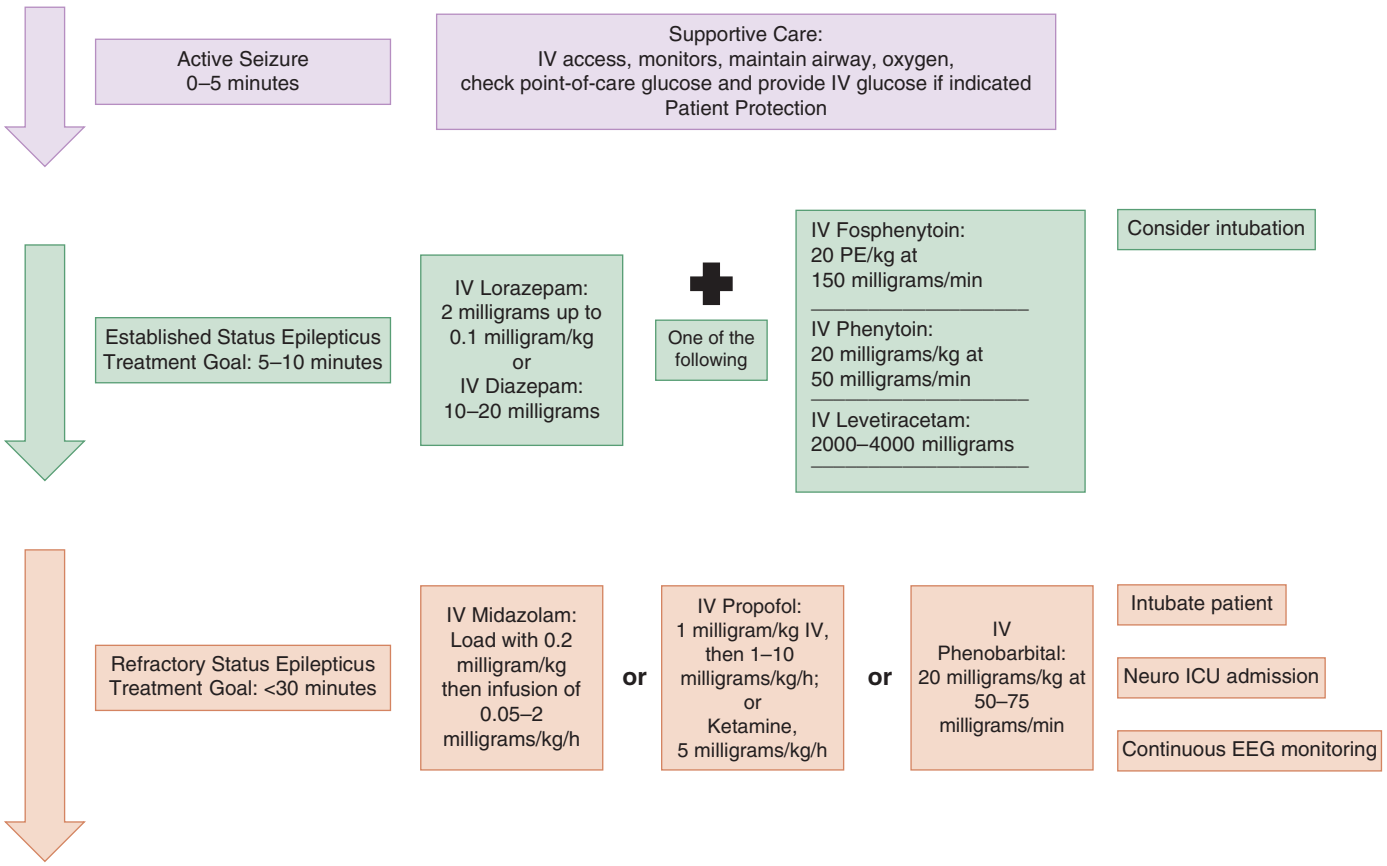

FIGURE 171-1. Guidelines for management of active seizures and status epilepticus. EEG = electroencephalogram, ICU = intensive care unit, PE = phenytoin equivalent.

paralytic agent in order not to mask ongoing seizure activity. Arrange for continuous EEG monitoring as soon as possible after paralytic agents have been used.

Initial laboratory evaluation includes blood glucose, a metabolic panel including calcium and magnesium, lactate, and if appropriate, a pregnancy test, a toxicology screen, and anticonvulsant levels.

Administer glucose IV if hypoglycemia is suspected or confirmed. Monitor temperature continuously, and treat hyperthermia with passive cooling. Place a urinary catheter to monitor urine output and insert a nasogastric tube to help prevent aspiration.

If toxic ingestion is suspected as the cause of seizures, proceed with GI decontamination (as appropriate). Do not attempt lumbar puncture during status epilepticus. **If bacterial meningitis or encephalitis is suspected clinically, then immediately start empiric antibiotic or antiviral therapy.** Radiographic studies, such as a CT scan, will usually need to be delayed until seizures are controlled.

ANTICONVULSANT DRUGS IN STATUS EPILEPTICUS

The drugs most often used in the therapy of status epilepticus are the benzodiazepines (lorazepam, midazolam, or if not available, diazepam) and phenytoin or fosphenytoin (Figure 171-1). Benzodiazepines are used in patients with continuous or very frequent seizures to temporarily control the seizures until more specific agents can be given. IV lorazepam (2 to 4 milligrams) and IV diazepam (5 to 10 milligrams) have equal efficacy in controlling status epilepticus.[8] Compared to diazepam, lorazepam has a slightly slower onset (3 vs. 2 minutes) but a significantly longer duration of action (12 to 24 hours vs. 15 to 60 minutes) and is associated with fewer seizure recurrences. In one prehospital study, IM midazolam demonstrated decreased seizure time and fewer intensive care unit admissions when compared to lorazepam if no IV access was available,[27] and in an additional noninferiority prehospital trial, IM midazolam was determined to be as safe and effective as IV lorazepam.[28] However, **IV lorazepam is still considered the initial agent of choice if IV access is available.** Lorazepam is also more effective than phenytoin or phenobarbital as a first-line agent.[29] Respiratory depression and hypotension may occur, especially in young children and in patients taking alcohol, barbiturates, narcotics, or other sedatives. In patients with difficult IV access and emergent need for seizure control, there may be a role for rectal diazepam gel or buccal midazolam. Although there have been no trials in adults, rectal diazepam has been used by EMS providers in children with good success for years, and recent trials of buccal midazolam (0.5 milligram/kg, up to 10 milligrams) show more efficacy than rectal diazepam in the pediatric population.[30,31]

In established status epilepticus, follow benzodiazepines with longer-acting antiepileptic agents: fosphenytoin or phenytoin; levetiracetam; valproate; or lacosamide. One of these antiepileptic agents should be started within 20 minutes of diagnosis.[1] The most updated consensus guidelines do not currently recommend one second-line agent over another.[32] Multicenter trials are currently under way to help determine which of these antiepileptic agents are the most effective in helping terminate status epilepticus.[33]

Fosphenytoin is a water-soluble prodrug of phenytoin that is converted to phenytoin in the plasma. Fosphenytoin has similar time of onset, effectiveness, and cardiac effects as phenytoin. It has much fewer infusion-site reactions due to the lack of propylene glycol and ethanol as the diluents. Fosphenytoin may be infused quickly, and for that reason, it is preferred over phenytoin. Fosphenytoin dosing is expressed as phenytoin equivalents to prevent confusion. The loading dose is 20 phenytoin equivalents/kg, which can be infused at 150 phenytoin equivalents/min over 10 to 15 minutes.[9] Fosphenytoin can also be given IM, which may be useful if the patient does not have IV access.

The loading dose for **phenytoin** is 20 milligrams/kg IV. Doses in excess of the usual 1000 milligrams are often required. Due to myocardial depression from its propylene glycol diluent, phenytoin is typically infused no faster than a rate of 25 milligrams/min (taking about 1 hour to administer). The rate may be increased to 50 milligrams per minute during status epilepticus as long as hypotension does not develop. Place patients on a cardiac monitor, with blood pressure assessments every 5 to 15 minutes during the infusion and every 15 minutes for 1 hour after infusion.[34] Phenytoin should not be mixed with any glucose-containing IV fluid and should not be given IM due to erratic absorption. Adverse effects include infusion-site reactions, hypotension, and cardiac dysrhythmias, and it is contraindicated in patients with second- or third-degree atrioventricular blocks. If side effects develop, stop the infusion and restart at a lower rate after side effect resolution.

Valproic acid is effective but has serious side effects compared to the agents listed above; the Food and Drug Administration has issued a black-boxed warning for hepatic failure and pancreatitis, and valproic acid should not be administered along with phenytoin. The dose is 20 to 40 milligrams/kg IV.[1,9,22,35,36]

Levetiracetam is very effective, is quick to administer, and has few interactions and side effects. The precise mechanism of action is unknown, but it may inhibit voltage-dependent calcium channels and facilitate γ-aminobutyric acid inhibitory transmission. The dose is 20 to 60 milligrams/kg IV. While it is not yet approved by the Food and Drug Administration for status epilepticus, it is rapidly gaining favor as a first-line drug for established status epilepticus.[1,9,37-39]

Lacosamide is a potential alternative for status epilepticus with limited availability and limited data on its use. The dose is 200 milligrams IV given over 15 minutes.[1,40]

REFRACTORY STATUS EPILEPTICUS

Refractory status epilepticus is defined as persistent seizure activity despite the IV administration of adequate amounts of two antiepileptic agents and usually exceeds 60 minutes.[1] One study found up to 31% of patients with status epilepticus developed refractory status epilepticus.[41]

Various approaches to refractory status epilepticus have been advocated (Figure 171-1).[1,7,9,22,36-47] Overall, there are few controlled trials that strongly support a single agent or combination of agents. Recommendations include propofol, midazolam, and barbiturates such as phenobarbital or pentobarbital given as infusions.[1] All of these agents can lead to hypotension, sometimes requiring concomitant vasopressor use, and frequently require intubation. Ideally, treatment is in consultation with a neurologist and in an intensive care setting, as advanced respiratory support, cardiovascular support, and EEG monitoring are all needed.

Propofol is a widely used, lipophilic, general anesthetic that has come into favor for refractory status epilepticus. It can be started as an infusion at typical rates of 2 to 10 milligrams/kg/h and titrated up to effect of seizure cessation. Propofol has the added benefit of a short half-life allowing for quicker neurologic recovery after seizure control is achieved. At higher doses (>40 milligrams/kg/h), patients are at increased risk for hemodynamic instability including hypotension as well as propofol infusion syndrome.[1,7,9,22,43]

Midazolam is an easily titrated, infusible benzodiazepine that can also be used in the ongoing treatment of refractory status epilepticus. Midazolam can be started at 0.05 to 0.4 milligram/kg/h and is titrated up to seizure cessation.[1,9,44] Midazolam can accumulate in peripheral soft tissues, particularly with renal insufficiency, leading to a much prolonged recovery period.

Barbiturates, such as **phenobarbital** (up to 20 milligrams/kg IV) or **pentobarbital**, may be considered as third-line drugs in patients whose seizures are not controlled despite full loading doses of benzodiazepines and other agents. However, **patients in refractory status epilepticus may not respond to barbiturates.** One study found no added seizure control with phenobarbital.[36] A subsequent meta-analysis showed improved seizure control with pentobarbital compared to propofol or midazolam, but no differences in mortality.[42] Respiratory depression and hypotension are more common when using barbiturates, especially at higher doses or when diazepam or lorazepam is also given.[1,9,22] Additionally, midazolam and propofol have the advantage over barbiturates of having a shorter half-life and rapid clearance, allowing for earlier extubation and clinical assessment.[1] For these reasons, current recommendations are to use propofol and midazolam infusions as first- and second-line agents, respectively, in refractory status epilepticus with barbiturates as a third-line agent.[1,9,22,43,44]

Finally, **ketamine** may also be considered as a third-line agent in refractory status epilepticus. Ketamine is an *N*-methyl-D-aspartate receptor antagonist and helps block the hyperexcitatory pathway,

which is thought to be a greater culprit in refractory status epilepticus. Ketamine can be administered as a bolus dose of 0.5 to 4.5 milligrams/kg or as an infusion up to 5 milligrams/kg/h. Multiple case reports and one retrospective study have demonstrated its increased utilization, safety, and likely benefit in terminating refractory status epilepticus.[22,44-48]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 172

Acute Peripheral Neurologic Disorders

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INTRODUCTION

Acute peripheral neurologic lesions are a diverse group of disorders. By definition, they involve injury or disease in sensory and motor fibers outside of the CNS extending to the neuromuscular junction. The peripheral nervous system (PNS) serves sensory, motor, and autonomic functions. Thus, the patient with a peripheral nerve lesion may have deficits in any combination of these functions. **Exclude central processes, such as stroke or spinal cord injury, before considering an acute peripheral lesion.**

DISTINGUISHING CENTRAL AND PERIPHERAL LESIONS

Use CNS and PNS neuroanatomy principles to distinguish lesions. Peripheral nerves contain varying amounts of motor, sensory, and autonomic fibers and follow well-described paths that make them prone to typical injuries. Thus, peripheral nerve lesions are more likely to be confined to one limb and to present with the involvement of multiple sensory modalities and motor symptoms. A typical example would be a nerve compression syndrome presenting with weakness, numbness, and tingling that developed after the arm was held in an unusual position for a prolonged period. However, weakness and numbness can be seen in both peripheral and central disorders. Hyporeflexia sometimes occurs with acute central lesions, but hyperreflexia and spasticity invariably develop with time. PNS disorders, like CNS diseases, can affect bulbar structures, resulting in diplopia, dysarthria, or dysphagia. Despite the overlap, CNS disorders have other features not seen in peripheral disease. For example, aphasia, apraxia, and vision loss are hallmarks of cortical disease. Most CNS lesions will result in upper motor neuron signs: hyperreflexia, hypertonia (spasticity), and extensor plantar (Babinski) reflexes. Although there can be many similarities between patients with CNS and PNS lesions, the distinctions are clear (**Table 172-1**). Lateralization of weakness, hyperreflexia, positive Babinski's sign, or any other CNS finding requires further investigation for a central rather than peripheral disorder.

TABLE 172-1 Differentiating CNS From Peripheral Nervous System Disorders

	CNS	Peripheral Nervous System
History	Cognitive changes Sudden weakness Nausea, vomiting Headache	Weakness confined to one limb Weakness with associated pain Posture- or movement-dependent pain Weakness after prolonged period in one position
Physical Examination		
Reflexes	Brisk reflexes (hyperreflexia) Babinski's sign Hoffman's sign	Hypoactive reflexes Areflexia
Motor	Asymmetric weakness of ipsilateral upper and lower extremity Facial droop Slurred speech	Symmetric proximal weakness
Sensory	Asymmetric sensory loss in ipsilateral upper and lower extremity	Reproduction of symptoms with movement (compressive neuropathy) All sensory modalities involved
Coordination	Discoordination without weakness	Loss of proprioception

LOCALIZING PERIPHERAL NERVE LESIONS

Patients with peripheral nerve disorders frequently require diagnostic evaluation unavailable during the initial ED encounter.

HISTORY

The elements required to localize the process will usually include the following: symmetry; proximal versus distal symptoms; sensory, motor, or autonomic involvement; and mono- versus polyneuropathy. Sensory symptoms may include numbness, tingling, dysesthesias, pain, or ataxia. Motor symptoms manifest as weakness. Autonomic disability may present as orthostasis, bowel or bladder dysfunction, gastroparesis, or sexual dysfunction. Associated findings will frequently narrow the differential diagnosis or suggest a specific diagnosis. For example, in the setting of a recent viral infection or vaccination, consider Guillain-Barré syndrome. Is there a history of diabetes or subacute trauma? Does the patient with thrush or wasting and undiagnosed immunodeficiency have a human immunodeficiency virus (HIV)-associated neuropathy? Patients with an attached tick may have tick paralysis.

PHYSICAL EXAMINATION

Perform a comprehensive neurologic examination on patients with peripheral nerve disorders, paying particular attention to the specific area and distribution involved. Evaluate for hypotonia, muscle wasting, fasciculations, and hyporeflexia. Is there focal weakness? What is the perception of light touch, vibration, and position sense? If there are sensory deficits, what spinal nerve levels do they involve?

DIAGNOSIS

Many patients with peripheral nerve disorders will require electromyography and nerve conduction velocity studies. Electromyography is used to differentiate primary muscular or neuromuscular junction problems from peripheral nerve disorders. Nerve conduction velocity studies, which measure the speed of conduction by observing the response to nerve stimulation by distally placed electrodes, can differentiate between axonal loss and demyelination. Combined with the history and physical examination, these tests allow the consultant to better localize the lesion and make a firm diagnosis. Lumbar puncture and cerebrospinal fluid analysis are frequently required to confirm the diagnosis in acute or subacute inflammatory and infectious processes. In certain cases, nerve biopsy may be required. In cases where biopsy is considered, MRI can direct the biopsy site to the area of greatest utility.

TREATMENT

Management of PNS disorders depends on the specific diagnosis; however, a few general principles apply. Initiate supportive care for

severe, life-threatening neuromuscular diseases in the ED. Monitor patients with the potential for respiratory failure, aspiration, and cardiac dysrhythmias. **For patients at risk for diaphragmatic failure, measure baseline forced vital capacity or negative inspiratory pressure in the ED to assess whether there is an immediate need for respiratory support or admission to an intensive care unit.** Admit patients with acute peripheral neurologic conditions if there is potential respiratory or autonomic compromise, or if they present with severe or rapidly progressing weakness. If a peripheral disorder is suspected and the patient does not require admission, arrange for neurologic follow-up within 7 to 10 days.

ACUTE PERIPHERAL NEUROPATHIES

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is an acute polyneuropathy characterized by immune-mediated peripheral nerve myelin sheath or axon destruction. The prevailing theory is that antibodies directed against myelin sheath and axons of peripheral nerves are formed in response to a preceding viral or bacterial illness. Symptoms are at their worst in 2 to 4 weeks, and recovery can vary from weeks to a year.

Clinical Features Classically, Guillain-Barré syndrome is preceded by a viral illness, followed by **ascending symmetric weakness or paralysis and areflexia or hyporeflexia**. Paralysis may ascend to the diaphragm, compromising respiratory function and requiring mechanical ventilation in one third of patients. Autonomic dysfunction may be present as well.

The classic Guillain-Barré syndrome is a demyelinating disorder of the peripheral nerves. It is sometimes preceded by a viral or bacterial illness. Common infectious precipitants include *Campylobacter jejuni*, Zika virus, Cytomegalovirus, Epstein-Barr virus, or *Mycoplasma pneumoniae*. The cause is unknown but thought to be associated with antiganglioside antibodies.

There are many variants of Guillain-Barré syndrome. The demyelinating form (lymphocytic infiltration of the myelin sheath of peripheral nerves) is common in the US and the axonal form (motor paralysis with sensory function intact) in Asia. The **Miller-Fisher syndrome** variant is characterized by ophthalmoplegia, ataxia, and areflexia. Severity of symptoms and duration of illness depend upon the form of the disease.

Diagnosis The diagnosis is mostly historical, but lumbar puncture and electrodiagnostic information can improve confidence in the diagnosis. **Table 172-2** lists the specific diagnostic criteria.

TABLE 172-2 Diagnostic Criteria for Classic Guillain-Barré Syndrome

Required

- Progressive weakness of more than one limb
- Areflexia

Suggestive

- Progression over days to weeks
- Recovery beginning 2–4 weeks after cessation of progression
- Relative symmetry of symptoms
- Mild sensory signs and symptoms
- Cranial nerve involvement (Bell's palsy, dysphagia, dysarthria, ophthalmoplegia)
- Autonomic dysfunction (tachycardia, bradycardia, dysrhythmias, wide variations in blood pressure, postural hypotension, urinary retention, constipation, facial flushing, anhydrosis, hypersalivation)
- Absence of fever at onset
- Cytoalbuminologic dissociation of cerebrospinal fluid (high protein and low white cell count)
- Typical findings on electromyogram and nerve conduction studies

Cerebrospinal fluid analysis shows high protein levels (>45 milligrams/dL) and WBC counts typically <10 cells/mm^3, with predominantly mononuclear cells. When there are >100 cells/mm^3, other considerations include HIV, Lyme disease, syphilis, sarcoidosis, tuberculous or bacterial meningitis, leukemic infiltration, or CNS vasculitis. Electrodiagnostic testing demonstrates demyelination. Nerve biopsy reveals a mononuclear inflammatory infiltrate. If MRI is performed to rule out alternative diagnoses, it will show enhancement of affected nerves.

Treatment The first step in management is assessment of respiratory function. Airway protection in advance of respiratory compromise decreases the incidence of aspiration and other complications. A well-established monitoring parameter is vital capacity, with normal values ranging from 60 to 70 mL/kg. A simple bedside assessment of respiratory status is obtained by trending values reached when the patient counts from 1 to 25 with a single breath. **Avoid depolarizing neuromuscular blockers like succinylcholine for intubation in Guillain-Barré syndrome due to the risk of a hyperkalemic response.**

Both IV immunoglobulin and plasma exchange shorten the time to recovery.[1,2] Neither has been shown to be superior to the other, nor are they more efficacious when used together. There are adverse effects seen with both modalities of treatment. IV immunoglobulin has been associated with thromboembolism and aseptic meningitis; plasma exchange is associated with hemodynamic instability and a small increase in the rate of relapse, though full recovery is still more likely. In general, IV immunoglobulin is more widely available and less cumbersome to administer. Corticosteroids are of no benefit and may be harmful.[3]

Disposition Admit patients with acute Guillain-Barré syndrome to a unit where cardiac, respiratory, and neurologic functions can be monitored. Even if a patient does not initially meet the criteria for intubation, intensive care unit admission may still be indicated in order to avoid sudden, unmonitored respiratory failure (**Table 172-3**).[2]

BELL'S PALSY

Bell's palsy is the most common cause of unilateral facial paralysis. There are 23 to 25 cases per 100,000 population annually, affecting men and women equally. Cranial nerve VII, the facial nerve, supplies motor innervation to the muscles of expression of the face and scalp and the stapedius muscle and taste to the anterior two thirds of the tongue. The cause of Bell's palsy is not clear. Herpes simplex virus DNA and antigens have been discovered around the facial nerve of affected patients, leading to the suspicion that the herpes simplex virus may be the culprit.

Clinical Features Idiopathic Bell's palsy may be preceded by pain around or behind the ear. Onset of facial paralysis is acute, with maximal symptoms in 2 to 3 days. Facial numbness or hyperesthesia can

TABLE 172-3 Managing Respiratory Failure in Guillain-Barré Syndrome

Indications for intubation

- Vital capacity <15 mL/kg
- Declining one breath count
- Pa_{O_2} <70 mm Hg on room air
- Bulbar dysfunction (difficulty with breathing, swallowing, or speech)
- Aspiration

Indications for admission to intensive care unit

- Patients with 4 or more of the following findings: inability to stand, inability to lift the head, inability to lift the elbows, insufficient cough, time from symptom onset to hospital admission <7 days, or elevated liver enzymes
- Autonomic dysfunction
- Bulbar dysfunction
- Initial vital capacity <20 mL/kg
- Initial negative inspiratory force less than −30 cm of water
- Decrease of >30% of vital capacity or negative inspiratory force
- Inability to ambulate
- Treatment with plasmapheresis

Abbreviation: Pa_{O_2} = partial pressure of arterial oxygen.

accompany paralysis. Subtle dysfunction of cranial nerves V, VIII, IX, and X may be associated; for example, patients may also complain of decreased taste or hyperacusis due to paralysis of the stapedius muscle. On exam, patients will have facial droop, effacement of wrinkles and forehead burrows, and inability to completely close the eye. Recurrent idiopathic Bell's palsy occurs in a small number of patients.

Diagnosis Diagnosis of idiopathic Bell's palsy is based on the history and physical exam and is a diagnosis of exclusion of other conditions that can cause facial palsy. **The most important alternative diagnoses to exclude are ear infections and stroke.** Always perform an ear examination to identify otitis media and malignant otitis, and palpate the mastoids for tenderness, because infections of the ear and mastoids can affect the mastoid, tympanic, labyrinthine, or meatal segments of the cranial nerve VII (**Figure 172-1**).

When a central process causes facial paralysis, the forehead will be spared, as the forehead is supplied by cranial nerve VII arising near the pontomedullary junction, with crossed innervation. Peripheral facial nerve palsies will manifest as weakness throughout the facial nerve distribution, including the forehead. **Middle cerebral artery ischemia or stroke** consists of hemiparesis, facial plegia sparing the forehead, and sensory loss all contralateral to the affected cortex. Rarely, a brainstem stroke may mimic Bell's palsy if the stroke affects the area where the facial nerve wraps around the abducens (cranial nerve VI) nucleus. Brainstem stroke findings include peripheral facial nerve palsy and ipsilateral gaze palsy due to ischemia of the abducens nucleus. So, **test extraocular muscle function in all patients suspected of having Bell's palsy. Any patient with facial paralysis sparing the forehead or inability to abduct an eye should undergo neuroimaging to assess for stroke.** No imaging or laboratory testing is needed in patients with high suspicion of Bell's palsy unless further studies are required to exclude alternative diagnoses.

Treatment and Disposition Treatment with corticosteroids has shown significant benefit in the treatment of Bell's palsy.[4] Evidence from randomized controlled trials suggests a benefit when giving antiviral medications in combination with steroids over steroid therapy alone. The combination also was associated with reduced sequelae of Bell's palsy. Importantly, no significant increase in adverse events was noted when adding antivirals. As such, prescribe antivirals in conjunction with steroids.[5]

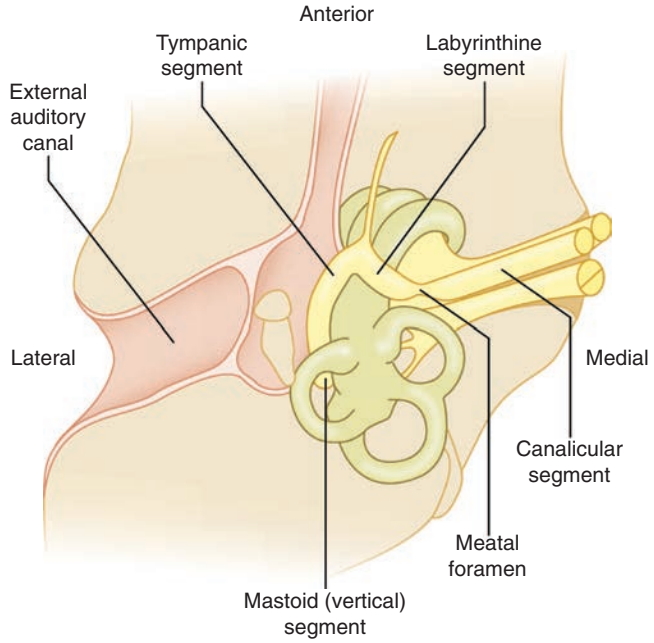

FIGURE 172-1. Relationships of cranial nerve VII to the inner and middle ear. [Adapted with permission from Lalwani AK (ed): *Current Diagnosis & Treatment in Otolaryngology-Head & Neck Surgery*, 3rd ed. New York: McGraw-Hill, Inc.; 2012. Sect XVI Facial Nerve Chapter 70. Figure 70-3, Part A.]

Patients with facial paralysis are at risk for corneal abrasions and keratitis due to eyelid weakness and incomplete eye closure. Patients can use a patch to close the affected eye if there is incomplete closure. Prescribe ocular lubricants, such as an artificial tear replacement, to prevent the eye from drying out. Most patients begin to recover within 3 weeks, but about 15% will have permanent paralysis. Ensure follow-up within 7 days with a primary care physician or otolaryngologist.

RAMSEY HUNT SYNDROME (HERPES ZOSTER OTICUS)

Ramsey Hunt syndrome is a herpes zoster infection of the geniculate ganglion. Signs and symptoms include unilateral facial nerve palsy, severe pain, and a vesicular eruption on the face or in the auditory canal. Ramsey Hunt syndrome may be indistinguishable from Bell's palsy if paralysis precedes the vesicular eruption. Cranial nerve VIII may also be involved with associated vertigo, nausea, and hearing loss. When active herpes zoster is suspected, prescribe both steroids and antivirals.[6]

ACUTE NEUROPATHIES OF LYME DISEASE

Lyme disease may cause a broad range of nervous system disease, both peripheral and central, as well as acute and chronic. Consider Lyme disease as the causative agent in patients who have facial palsy with erythema migrans, tick bite, or arthritis. Some patients will have bilateral facial palsy. Multifocal Lyme polyradiculopathy may occur in the acute phase of Lyme infection. Signs and symptoms include burning and painful neuropathy, plexopathy, and other mononeuropathies.

Diagnosis is based on history of tick bite and a physical examination that uncovers an attached tick or erythema chronicum migrans rash (see Figure 251-18). If cerebrospinal fluid is obtained, it will show the mononuclear pleocytosis typical of Lyme infection. Treatment is with doxycycline 100 milligrams twice daily for 14 to 21 days. Facial nerve palsies in Lyme disease represent the secondary stage of illness and require 1 month of treatment with doxycycline (100 milligrams PO twice a day) or amoxicillin, cefuroxime, ceftriaxone, or azithromycin.

FOCAL MONONEUROPATHIES

Focal mononeuropathies are most likely due to focal nerve compression, although systemic processes may also lead to mononeuropathy. Diabetes is the most common systemic cause of noncompressive focal neuropathy. Focal mononeuropathy can occur at any point of compression along the course of a peripheral nerve, but most commonly occurs along the ulnar, median, radial, lateral femoral cutaneous, and peroneal nerves.

MEDIAN MONONEUROPATHY (CARPAL TUNNEL SYNDROME)

The most common form of any focal mononeuropathy is median mononeuropathy, or carpal tunnel syndrome. Carpal tunnel syndrome results from compression of the median nerve at the wrist where it traverses the carpal tunnel. The boundaries of the carpal tunnel are the carpal bones and the flexor retinaculum. The most common etiology is injury due to repetitive use, but other causes include diabetes mellitus, pregnancy, amyloidosis, obesity, renal failure, rheumatoid arthritis, hypothyroidism, trauma, and edema.

Clinical Features The classic signs of carpal tunnel syndrome are pain, paresthesias, and numbness in the distribution of the median nerve—the palmar aspect of the thumb, index, middle, and radial aspect of the fourth finger. Patients may report symptoms in the entire hand, but careful examination will reveal preserved sensation in the fifth and ulnar fourth digits. Symptoms are worsened by extension and flexion of the wrist and are worse at night. Weakness and wasting of the muscles of the thenar eminence may be noted on exam.

Diagnosis Provocative testing, such as Tinel's sign and Phalen's maneuvers, can confirm the diagnosis of carpal tunnel syndrome. **Tinel's sign** detects irritated nerves by percussing over the nerve and eliciting tingling. Tapping on the palmar aspect of the wrist will result in an electric shock sensation shooting into the hand when there is compression of the median nerve. **Phalen's maneuver** is positive for carpal tunnel syndrome when holding the wrists in flexion for 60 seconds evokes

or worsens symptoms. Electrodiagnostic testing demonstrates slowing of nerve conduction across the carpal tunnel. Testing is typically performed on an outpatient basis to confirm the diagnosis or to aid in the decision for operative repair.

Treatment and Disposition The initial treatment of carpal tunnel syndrome is conservative. Encourage evaluation of workplace ergonomics. Provide a neutral wrist splint, which can be worn at night only. Evidence shows short-term benefit from oral steroids, ultrasound, yoga, and carpal bone mobilization. NSAIDs have not been shown to be better than placebo for symptom improvement.[7] Refer the patient to a hand surgeon if not improving with these treatments for consideration of surgical release.

ULNAR MONONEUROPATHY (CUBITAL TUNNEL SYNDROME AND GUYON'S CANAL SYNDROME)

The ulnar nerve extends from the medial cord of the brachial plexus and courses through the cubital tunnel behind the medial epicondyle at the elbow before entering the forearm. At the wrist, it passes through Guyon's canal, bounded by the hamate and pisiform bones and the ligament connecting them. It supplies cutaneous innervation to the medial palm via the superficial terminal branch and to the fifth and medial fourth fingers via the deep terminal branch and innervates the palmaris brevis muscle. The ulnar nerve is most vulnerable to repetitive stress, inflammation, and trauma in the cubital tunnel and at Guyon's canal.

Cubital tunnel syndrome is the most common ulnar mononeuropathy and the second most common compressive mononeuropathy. It results from pressure on the ulnar nerve at the medial epicondyle.

Guyon's canal syndrome is caused by entrapment of the ulnar nerve in Guyon's canal of the wrist. It is also called **"handlebar palsy,"** because it occurs in cyclists from prolonged compression of the wrist against the handlebars.

Clinical Features The classic symptoms of ulnar mononeuropathy include tingling in the fifth and lateral fourth fingers. With time, numbness and weakness of the intrinsic muscles of the hand develop. In severe cases, paralysis and wasting of the intrinsic muscles of the hand may occur.

Diagnosis Provocative testing is useful. Ulnar compression is possible if tapping on the cubital tunnel at the elbow provokes symptoms. A positive elbow flexion sign is seen when symptoms recur within 3 minutes of the elbow being held in flexion with the wrist in extension. **Froment's sign** is an inability of the thumb to oppose or put pressure against the index finger. To perform this test, ask the patient to hold a piece of paper between thumb and index finger. If you can pull the paper away or the thumb flexes at the interphalangeal joint to compensate for weakness of the adductor pollicis brevis, the test is positive. In the patient with suspected **cubital tunnel syndrome**, consider C8 entrapment and thoracic outlet syndrome. C8 entrapment can be differentiated by the presence of neck pain and worsening symptoms with neck flexion. Thoracic outlet syndrome worsens with shoulder abduction. Electrodiagnostic testing serves to precisely localize the lesion. In Guyon's canal syndrome, or handlebar palsy, compression of the ulnar nerve is more likely to spare sensory fibers that branch off before the canal. It presents as intrinsic weakness without sensory symptoms. Diagnosis of Guyon's canal syndrome is difficult, and MRI can sometimes aid in diagnosis.

Treatment and Disposition In most cases of ulnar nerve mononeuropathy, the goal of treatment in the ED is to initiate conservative treatment and to ensure proper diagnosis and appropriate follow-up, usually with an orthopedist. Pain is not a common component of this syndrome, but anti-inflammatory medication may alleviate symptoms. Reduce repetitive use at work and home, and eliminate habits that cause pressure on the elbow or wrist.

DEEP PERONEAL NERVE ENTRAPMENT

The deep peroneal nerve may become entrapped at three locations along its course: the fibular head, anterior to the ankle joint as it passes beneath the extensor retinaculum (anterior tarsal tunnel syndrome), and distal to this point. Compression of the deep peroneal nerve may result from proximal fibular fracture or habitual crossing of the legs. Patients develop foot drop or numbness of the web between the great and second toes. Conservative treatment is recommended initially—provide a splint or brace to maintain the foot at a right angle with the leg. Prompt follow-up with a neurologist is important because nerve conduction studies should be performed to differentiate this syndrome from lumbar root or motor neuron disease.

MERALGIA PARESTHETICA

Meralgia paresthetica is entrapment of the lateral femoral cutaneous nerve in the inguinal canal. Entrapment causes numbness and pain of the anterolateral thigh. The cause can be pelvic (pregnancy, enlarging mass, aneurysm), extrapelvic (trauma, tight garment or belt, obesity), or systemic (diabetes). On examination, the patient may complain of hyperesthesia in the area of pain, and Tinel's sign may be evident when percussing over the anterior superior iliac spine. The **pelvic compression test** also supports this diagnosis: turn the patient on his or her side, compress the pelvis, and if the patient's symptoms are relieved after 30 seconds of lateral compression of the pelvis, the diagnosis is confirmed.

Conservative management with NSAIDs, weight loss, relief from tight garments, and physiotherapy is usually successful. Local injection of lidocaine and corticosteroid near the insertion of the inguinal ligament into the anterior superior iliac spine provides relief. Surgical decompression or nerve resection may be required for relief of symptoms.

PLEXOPATHIES

The cervical, brachial, and lumbosacral plexuses are formed by the convergence of nerve roots, which then branch into peripheral nerves. In the case of the brachial plexus (**Figure 172-2**), the process of mixing and dividing is repeated in the stages of trunks and cords before peripheral nerves take off. Plexopathies share many of the same causes, the most common being trauma, surgery, neoplasm, and radiation therapy. Despite this similarity, plexopathies differ significantly in diagnosis and management.

BRACHIAL PLEXOPATHY

The brachial plexus, formed by the C5-T1 nerve roots, is the most common site of plexopathy. The brachial plexus is made complex by the nerve roots merging into upper middle and lower trunks, which split and merge into lateral posterior and medial cords that split again

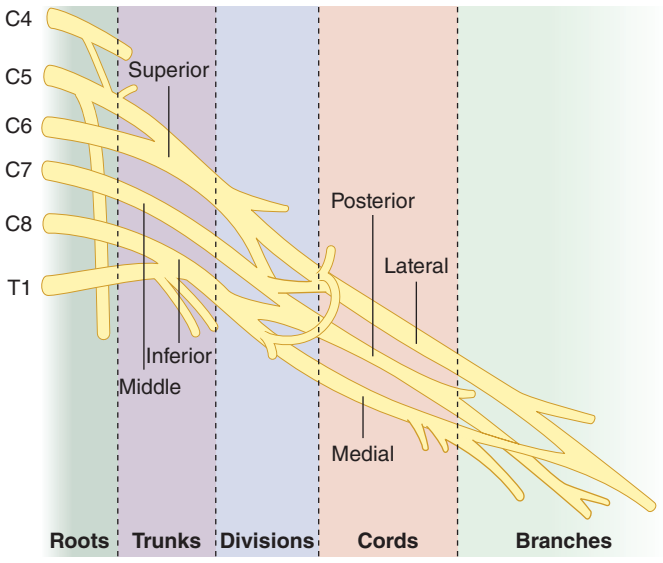

FIGURE 172-2. The anatomy of the brachial plexus. [Reproduced with permission from Reichman EF, Tolson DR: Regional nerve blocks, in Reichman EF, Simon RR (eds): *Emergency Medicine Procedures*. New York: McGraw-Hill, Inc.; 2004.]

and form five peripheral nerves (see Figure 172-2). Injury at each of these anatomic locations will result in differing symptoms. Brachial plexopathies generally manifest as weakness first, but pain and paresthesias may also develop. On examination, the patient has weakness in various distributions of the brachial plexus. The upper trunk is the more common site of involvement, affecting strength of proximal arm and shoulder musculature. Infraclavicular plexopathy due to trauma is frequently associated with injury to the axillary vessels. Causes of brachial plexopathy include trauma (penetrating trauma, humeral neck fracture, severe traction injury, or dislocation), shoulder reduction, neoplasm (Pancoast tumor), radiation, or surgery. A **"burner"** is burning pain involving one upper extremity, sometimes with numbness, paresthesias, or weakness, occurring after trauma to the neck and shoulder. It can occur in football players and other athletes during sports. A burner can be a brachial plexopathy, caused by traction to the shoulder or an injury to the cervical nerve roots caused by neck flexion-hyperextension. Brachial plexopathies can also result from cervical rib compression, midshaft clavicular fracture, or penetrating trauma. Assessment consists of careful neurologic examination, spine imaging, and consultation with neurology, neurosurgery, or orthopedics, depending on the specific injury identified.

LUMBOSACRAL PLEXOPATHY

The L1-S4 nerve roots form the lumbosacral plexus. Causes of lumbosacral plexopathy are less likely traumatic and more likely to include radiation, diabetic amyotrophy, aortic aneurysm, retroperitoneal hemorrhage, or compression from arteriovenous malformations. The differential diagnosis also includes the **cauda equina and conus medullaris syndromes**. Lesions affecting the lumbar portion of the plexus result in weakness of hip adduction and flexion and knee extension, decreased sensation at the top and inner thigh, and decreased patellar reflexes. Lesions affecting the sacral portion of the plexus result in inability to abduct the thigh at the hip joint, weakness of hip extension and knee flexion, and decreased sensation of the back of the thigh and below the knee. Plain radiographs of the lumbar spine are useful to screen for spine compression from degenerative or neoplastic disease. Perform MRI when cord injury or compression is considered. See Chapter 279, "Neck and Back Pain," for detailed discussion of epidural compression syndromes, cauda equina syndrome, and conus medullaris syndrome. CT of the abdomen will exclude aortic aneurysm, psoas muscle masses, and retroperitoneal hemorrhage, which also present with asymmetric lower extremity weakness. Management of plexopathies is usually directed at the underlying cause.

CERVICAL PLEXOPATHY

The cervical plexus, formed by the C1-C4 nerve roots, is the least common plexopathy. Apart from trauma or neoplasm, the condition is occasionally seen postoperatively due to positioning during surgery. Patients may have few symptoms. Neoplastic lesions may cause a deep boring and constant pain. Due to anatomic parameters, electrodiagnostic assessment is difficult and unreliable. Order a CT or MRI scan if a neoplastic process is considered. The management of cervical plexopathy is usually nonoperative.

NEUROMUSCULAR JUNCTION DISORDERS

BOTULISM

Botulism is a toxin-mediated neuromuscular junction disorder that causes acute weakness leading to respiratory failure. In 2015, the Centers for Disease Control and Prevention reported 199 cases of confirmed botulism. Of these, 71% were infantile botulism, 20% were foodborne, and 8% were wound botulism.[8] Botulism affects infants between the ages of 1 week and 11 months and has been implicated as a cause of sudden infant death syndrome. The causative organism, *Clostridium botulinum*, is an anaerobic spore-forming bacterium found in soil and honey. In suitable environments, these spores germinate and release toxin that irreversibly binds the presynaptic membrane of peripheral and cranial nerves, inhibiting the release of acetylcholine at the peripheral nerve synapse. Three of the eight known toxins, types A, B, and E, produced by *C. botulinum* cause human disease. The most commonly implicated is toxin A, which is also used cosmetically in injection form. Most cases of botulism are isolated events associated with improperly preserved canned foods. In adults, botulism results from ingestion of preformed toxin. Infantile botulism occurs due to ingestion of spores that germinate in the higher pH of the infant GI tract. Botulism can result from wound infections, mostly occurring in injection drug users. In 2015, there were 15 reported case of wound botulism, with 14 occurring in people who inject drugs.[8] Toxin type E is associated with preserved or fermented fish and marine mammals, and the latter are the most important sources of botulism in Alaska, Japan, Russia, and Scandinavia. *C. botulinum* is classified as a category A bioweapon by the Centers for Disease Control and Prevention, among the most lethal.[9]

Clinical Features Onset of symptoms occurs 6 to 48 hours after the poisoning with toxin. Patients experience nausea, vomiting, abdominal cramps, and diarrhea or constipation, which may easily be misdiagnosed as an acute gastroenteritis. **Classically, botulism produces a descending, symmetric paralysis**. Since the disorder is at the neuromuscular junction, there is no sensory deficit and no pain. The muscles first affected are the cranial nerves and bulbar muscles. The patient presents with diplopia, dysarthria, and dysphagia and may report blurred vision. Deep tendon reflexes are normal or diminished. Toxin-mediated decrease in cholinergic output causes anticholinergic symptoms, such as constipation, urinary retention, dry skin and eyes, and hyperthermia. **Pupils are often dilated and nonreactive to light.** Pupillary findings provide an important point of differentiation from myasthenia gravis, which does not affect the pupil. Infantile botulism presents as constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be in the differential of the "floppy" infant.

Diagnosis The diagnosis of botulism is made based on clinical findings and exclusion of other processes. The toxin can be identified in both serum and stool, but the assay is not commonly available. If the suspected food source is available, it should be tested for toxin.

Treatment and Disposition Initial treatment is supportive. Secure the airway if there is respiratory compromise. Severe botulism may necessitate mechanical ventilation for months. For infant intestinal botulism, human-derived botulinum immune globulin significantly reduces time of hospitalization and time on mechanical ventilation.[10,11] For children older than 1 year of age and adults, equine serum botulism antitoxin similarly has been shown to reduce length of time in the hospital and on the ventilator. Administer antitoxin as soon as the diagnosis is made to prevent worsening of symptoms and shorten the time of recovery. If contaminated food is still in the GI tract, consider administering an enema. Wounds may require surgical treatment to remove the source of toxin-producing bacteria.[12] Report suspected cases to the local health department so that further exposures can be prevented.

TICK PARALYSIS

Tick paralysis, or tick toxicosis, is an uncommon disease caused by a poorly defined neurotoxin secreted in the saliva of several tick species. It is most common in spring and summer and in the Pacific Northwest, western, and southeastern states. Most cases are in children.

Clinical Features Initially, 4 to 7 days after tick attachment, patients experience nonspecific influenza-like symptoms including malaise and weakness. These symptoms progress to ataxia and then an **ascending weakness and paralysis** without sensory involvement. Infants and children may be listless or irritable. When the bulbar nerves and diaphragm become involved, respiratory failure ensues.

Diagnosis Tick paralysis is diagnosed based on typical symptoms and when the culprit tick is located. **Perform a complete body search for ticks before initiating treatment for other possible diagnoses.** The most common tick attachment site is the scalp. If no tick is found, the differential diagnosis of acute ataxia and ascending flaccid paralysis without sensory involvement includes Guillain-Barré syndrome, botulism, spinal cord tumor, and poliomyelitis.

Misdiagnosis of tick paralysis can lead to failure to find and remove the tick and unnecessary therapies such as central venous access, plasma exchange, and IV immunoglobulin. Tick paralysis and Guillain-Barré syndrome are indistinguishable even with nerve conduction studies.[13]

Treatment and Disposition Treatment involves complete removal of the attached tick. Remove ticks by taking hold of the very head of the tick with tweezers and applying gentle steady traction. If a tick is not found on the skin, use a fine-tooth comb to look through hair.

Admit patients with respiratory distress to the intensive care unit, and admit all patients to the hospital to ensure symptoms do not progress. Local wound care and supportive care (including intubation and mechanical ventilation if necessary) result in excellent recovery within hours to days.[13]

INFLAMMATORY MYOPATHIES

Although not acute peripheral neurologic lesions, polymyositis and dermatomyositis present with similar symptoms to many peripheral neuropathies. These diseases are rare inflammatory myopathies causing symmetric weakness that progresses over weeks to months.

Clinical Features Patients develop weakness of the proximal limbs, trunk, and neck. Some experience dysphagia, myalgias, and rarely dyspnea when the respiratory muscles become involved. Sensation and reflexes are normal, and the ocular muscles are usually spared. Occasionally cardiac muscle may be involved with cardiomyopathy, heart failure, and conduction disturbances. The findings of dermatomyositis are similar with the addition of a diffuse violaceous rash often on the face and trunk.

Diagnosis Diagnosis is mainly clinical, but certain laboratory findings are characteristic such as elevated erythrocyte sedimentation rate, elevated creatine kinase, and leukocytosis. The differential diagnosis includes Lambert-Eaton syndrome, endocrinopathies, toxic myopathies, and infectious myopathies.

Treatment and Disposition To prevent irreversible muscle damage, both polymyositis and dermatomyositis require treatment with systemic corticosteroids or other immunosuppressants.

Admit patients with rhabdomyolysis, respiratory distress, or profound weakness. Otherwise, patients may be discharged with neurology or rheumatology follow-up within 7 days.

SUBACUTE AND ACUTE-ON-CHRONIC PERIPHERAL NERVE LESIONS

Neuropathies can also be associated with an underlying medical disorder, such as HIV and diabetes.

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED PERIPHERAL NEUROLOGIC DISEASE

HIV infection, its complications, and its pharmacologic treatments are associated with a number of peripheral neurologic disorders. The most common of these, HIV neuropathy and antiretroviral drug–induced neuropathy, are chronic processes that do not cause sudden disability or symptoms. HIV-infected patients have a high rate of mononeuritis multiplex and an inflammatory myopathy resembling polymyositis. In late-stage acquired immunodeficiency syndrome, almost all patients manifest neuropathy. Patients in the early stages of HIV infection have greater susceptibility to Guillain-Barré syndrome. The presentation is similar to that of the non–HIV-infected patient. Treatment is the same as in non-HIV Guillain-Barré syndrome, with an emphasis on identifying patients who are likely to need intubation and mechanical ventilation early in the ED stay followed by close monitoring of respiratory function.

CYTOMEGALOVIRUS RADICULITIS

In the latter stages of acquired immunodeficiency syndrome, cytomegalovirus may acutely infect the lumbosacral nerve roots, causing a polyradiculopathy or cauda equina syndrome. Evidence of systemic cytomegalovirus infection, including retinitis, is almost always present. As opposed to the more common chronic neuropathy of HIV, patients with cytomegalovirus radiculitis become acutely weak, with primarily lower extremity involvement, and may have variable degrees of bowel and bladder dysfunction. The examination shows primarily lower extremity weakness and hyporeflexia, with decreased sensation in the lower extremities and groin. Rectal tone may be impaired. Lumbar puncture reveals a pleocytosis with predominantly polymorphonuclear cells and modestly increased protein. Viral DNA is detected by polymerase chain reaction in most patients and is highly specific. MRI of the lumbosacral spine demonstrates swelling and clumping of the cauda equina. Imaging is recommended to exclude mass lesions of the lower spine or nerve roots. Early identification is important, as antiviral treatment is effective. The treatment of cytomegalovirus radiculitis is IV ganciclovir, started at 5 milligrams/kg every 12 hours for 3 to 6 weeks. Treatment can be initiated before definitive diagnosis.

DIABETIC PERIPHERAL NEUROPATHY

Diabetes mellitus remains the most common cause of noncompressive focal neuropathy. A variety of mechanisms contribute to the pathophysiology of diabetic neuropathy. Chronic hyperglycemia and glycemic variability lead to oxidative stress and neuroinflammatory processes that result in a variety of neuropathic syndromes.

Diabetic peripheral neuropathy is the term used for any neuropathy in a type 1 or type 2 diabetic patient. The most common manifestation of diabetic peripheral neuropathy is a distal symmetric polyneuropathy, but it may also lead to focal neuropathies and mononeuropathy multiplex. Diabetic peripheral neuropathy is an example of a distal axonopathy resulting in length-dependent, centripetal "dying back" of the affected nerves. This phenomenon produces the typical stocking and glove distribution of diabetic neuropathy.

Hyperglycemic neuropathy is seen in newly diagnosed diabetics and normally improves with glycemic control. Insulin neuritis is a reversible condition characterized by acute limb pain and paresthesias associated with rapid glycemic control with insulin. Painful diabetic neuropathy is usually intermittent and worse at night. It can be experienced variably as pins and needles, throbbing, burning, aching, or cramping. Duration is less than 6 months. After 6 months, the same process is termed chronic painful diabetic neuropathy. Diabetic neuropathic cachexia is a rare syndrome causing weight loss and painful dysesthesias of the limbs and trunk.

Diabetic amyotrophy is a lumbosacral plexopathy seen in patients with a long-standing history of diabetes and presents with back pain followed by weakness. Patients report the acute onset of ipsilateral back pain, followed within days by progressive leg weakness. Sensory findings are absent. The examination reveals decreased leg power in a variety of patterns reflecting impairment of plexus function with relatively symmetric sensation. There may be muscle wasting in affected limbs in long-standing disease. Deep tendon reflexes may be diminished on the affected side. Bowel and bladder functions are not affected.

Glucose control has been linked to a reduction in the development of neuropathy.[14] The Diabetes Control and Complications Trial demonstrated a 60% reduction in risk of developing neuropathy with tight glycemic control, which persisted for 8 years.[15] Emphasize strict foot care to the diabetic who has already developed neuropathy. Neuropathy-associated anesthesia may result in inadvertent trauma and subsequent development of ulcers, cellulitis, fasciitis, osteomyelitis, and eventual amputation. Symptomatic management is an ED patient's most immediate concern. NSAIDs are ineffective in treating neuropathic pain and are relatively contraindicated in the diabetic patient due to their renal and cardiac effects. There is strong evidence for pregabalin in the treatment of painful diabetic neuropathy. Moderate evidence also exists for gabapentin, sodium valproate, amitriptyline, venlafaxine, duloxetine, opiates, capsaicin, and percutaneous electrical nerve stimulation.[16,17]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 173

Chronic Neurologic Disorders

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AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), often referred to as *Lou Gehrig's disease*, causes rapidly progressive muscle atrophy and weakness resulting from the degeneration of both upper and lower motor neurons. ALS leads to varying degrees of spasticity, hyperreflexia, and muscle paralysis, eventually resulting in pulmonary complications and the need for mechanical ventilatory support. Because there is no cure, clinicians attempt to slow disease progression and preserve function as much as possible. Medical management focuses on preventing pulmonary infections and forestalling terminal respiratory failure.

PATHOPHYSIOLOGY

Since 2009, 13 genes and loci have been identified that are associated with the disease.[1] Inclusions in the TAR DNA-binding protein-43 have been found in both ALS and frontotemporal dementia.[2] Environmental exposures are suspected to increase the risk of ALS, but no specific ones have been identified to date.[3]

Gross CNS pathology includes frontal cortical atrophy, degeneration of both the corticospinal and spinocerebellar tracts, a reduction in large cervical and lumbar motor neurons, and cranial nerve nuclei degeneration. Both motor and sensory peripheral nerves undergo axonal degeneration and segmental demyelination, including motor end plate and axon terminal involvement.

CLINICAL FEATURES

Upper motor neuron demyelination and dysfunction cause limb spasticity, hyperreflexia (including Babinski sign and a brisk jaw-jerk reflex), and emotional lability. Limb weakness, a lower motor neuron dysfunction, is the presenting symptom in 65% of patients.[4] Other associated lower motor neuron dysfunctions include atrophy, cramps, fasciculations, dysarthria, dysphagia, and difficulty in mastication. At the time of initial presentation, asymmetric extremity cramping, fatigue, weakness, and atrophy can be seen, most prominently in the upper extremities.[5] Facial weakness, dysarthria, tongue weakness, and atrophy can be seen with bulbar lower motor neuron dysfunction. Despite these profound motor findings, sensory and cognitive function is usually spared. Significant extremity atrophy occurs, as do fasciculations, hyperreflexia, foot drop, and claw deformity of the hand. Patients also may develop monotonal speech caused by tongue atrophy, despite the relative sparing of facial and eye movements. Parkinsonian dementia may occur in up to 15% of patients. Other cognitive problems, such as apathy, poor attention, decreased motivation, and altered social skills, can be present. **Regardless of the initial symptoms, widespread motor and respiratory dysfunction progress within weeks to months.**

DIAGNOSIS

Patients with ALS typically present to the ED with their diagnosis firmly established. There are multiple diagnostic criteria of ALS, including El Escorial, Airlie House, and the Awaji-Shima criteria, all of which include upper and lower motor neuron dysfunction in the same anatomic distribution. **Patients present with rapidly progressing weakness, muscle atrophy, fasciculations, and hyperreflexia but without other CNS dysfunction, such as cerebellar ataxia, autonomic dysfunction, or involuntary movements.**[6] Given the variation and complexity of symptoms, diagnosis of ALS can be challenging. The median time to diagnosis is 14 months.[1] ALS-like symptoms can be seen with other systemic illnesses, such as diabetes, dysproteinemia, thyroid and parathyroid dysfunction, vitamin B_{12} deficiency, heavy metal toxicity, and vasculitis, as well as CNS and spinal cord tumors. Additional differential diagnoses include other neuropathies, such as myasthenia gravis or compressive radiculopathies. ALS is often diagnosed only after significant muscle wasting that is consistent with motor neuron dysfunction develops.[7] The Amyotrophic Lateral Sclerosis Functional Rating Scale (revised) is a sensitive and reliable tool for diagnosis of ALS.[7] Electromyography, nerve conduction velocity studies, spinal fluid analysis, and neuromuscular biopsies are also useful diagnostic studies. MRI excludes other disease processes but does not confirm the diagnosis of ALS. Definitive diagnosis of ALS should be made by a neurologist.[8]

TREATMENT

Emergency management is required for acute respiratory failure, aspiration pneumonia, choking episodes, or trauma related to extremity weakness. Blood gas determination does not reliably predict impending respiratory failure because mild hypoxia and hypercarbia may already be present from the course of the disease. **A forced vital capacity <25 mL/kg or a 50% decrease from predicted normal increases the risk of aspiration pneumonia and respiratory failure**. If the patient presents with respiratory complaints, emergency management should focus on improving pulmonary function (e.g., nebulized medications, steroids, antibiotics, assisted ventilation, and intubation).

Therapy is designed to enhance muscle function to avoid malnutrition, recurrent aspiration, and choking. Riluzole, a preferential tetrodotoxin sodium channel blocker, modulates excitotoxin glutamate and has been shown to prolong time to ventilator dependence and possibly increase survival by 2 to 3 months.[9-11] It is most useful in patients with a clear diagnosis of ALS whose symptoms have been present for <5 years, who have a forced vital capacity >60% of predicted, and who do not have a tracheostomy.

Optimizing pulmonary function, including the eventual use of long-term assisted ventilation, is an important part of enhancing the quality of life as diaphragm weakness progresses.[12] Many ALS patients will find some benefit from regular progressive resistance exercises, which may provide an anti-inflammatory effect, a neuroendocrine effect, or beneficial effects on CNS plasticity and myofiber remodeling, just as they would in healthy patients.[13]

DISPOSITION

Because the need for long-term ventilatory assistance is rarely reversible, establish or confirm the patient's preference regarding intubation through patient and family conversation, a living will, or power of attorney for health care. Hospital admission is indicated with impending respiratory failure, pneumonia, the inability to control secretions, or a worsening overall status that requires social service intervention for long-term placement.

MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disease characterized by muscle weakness and fatigue, made worse after repetitive use of voluntary muscles. Acetylcholine receptor antibodies impair receptor function at the neuromuscular junction, causing muscle weakness, most often in proximal muscles. Weakness is generally reversible in the short term by rest and immunotherapy. The early recognition and aggressive management of cholinergic or myasthenic crises in patients with myasthenia gravis are essential to provide optimal care for these patients in the emergency setting.

PATHOPHYSIOLOGY

In the normal neuromuscular junction, acetylcholine release by the nerve fiber causes a localized end-plate potential that leads to muscle fiber contraction. In myasthenia gravis, **there is a marked decrease in the number and function of the muscle fiber acetylcholine receptors,** despite normal nerve anatomy and function. Failure to respond to acetylcholine stimulation causes decreased muscle fiber potential amplitudes, leading to decreased muscle strength. Acetylcholine receptor

autoantibodies are seen in approximately 80% of patients.[14] These antibodies react with the acetylcholine receptor. The autoantibodies cause accelerated acetylcholine receptor degradation, dysfunction, and blockade. Disease severity can be correlated with acetylcholine receptor autoantibody levels.

It is believed that either the dysfunction of the **thymus gland** or an immune response to exogenous infectious antigens causes the pathologic autoimmune response in myasthenia gravis. The thymus is abnormal in most patients with myasthenia gravis, presenting as thymic hyperplasia or a thymoma. Thymectomy resolves or improves the symptoms in most patients, especially those with a thymoma. It is also possible that the acetylcholine receptor autoantibodies arise after exposure to viral or bacterial antigens, such as the herpes simplex virus or Epstein-Barr virus, which causes an autoimmune response to acetylcholine receptor proteins.

CLINICAL FEATURES

The symptoms of myasthenia gravis can mimic the symptoms seen in many other chronic neurologic disorders; hence, it has been named "the great imitator." **Most myasthenia gravis patients have generalized weakness that is most pronounced in the extremity muscle groups, neck extensors, and facial and bulbar muscles.** Although ptosis and diplopia are the most common presenting symptoms, limb weakness and oropharyngeal symptoms, such as dysphagia, dysarthria, dysphonia, and dyspnea, can also be seen initially or occur over time. Ocular signs can include Cogan lid twitch (in which the eyes are lowered for 10 to 20 seconds, then droop or twitch when the patient attempts to raise them); ptosis; cranial nerve III, IV, or VI weakness; gaze palsies; internuclear or complete ophthalmoplegia; and end-gaze nystagmus.[15] Symptoms can fluctuate throughout the day, usually worsening as the day progresses or with prolonged muscle group use, such as with prolonged reading or prolonged chewing during a meal. Despite the presence of profound muscle weakness, there usually is no deficit in sensory, reflex, or cerebellar functioning. **Elderly patients with myasthenia gravis can be misdiagnosed as a having a cerebral vascular accident if new-onset facial weakness or dysarthria is seen.**[16]

Although weakness is typically focal and mild to moderate in severity, rarely, undiagnosed patients with myasthenia gravis may present with extreme weakness in the muscles of respiration, resulting in respiratory failure. **This life-threatening situation, termed *myasthenic crisis*, can be seen before diagnosis or as a result of inadequate drug therapy or drug tolerance.**

DIAGNOSIS

Consider the diagnosis of myasthenia gravis in any patient who complains specifically of ocular disturbances or proximal limb muscle weakness not associated with systemic causes of generalized fatigue. Involvement of the ocular, bulbar, and extremity muscle groups may suggest myasthenia gravis, as well as the observations that the symptoms fluctuate, often worsening as the day progresses, and are alleviated by rest.[17] The differential diagnosis includes congenital myasthenia gravis, Lambert-Eaton syndrome (seen with small-cell lung tumors), drug-induced myasthenia (e.g., penicillamine, procainamide, quinines, aminoglycosides), botulism, thyroid disorders, and other causes of ocular disorders, such as intracranial mass lesions.

The diagnosis is established through the administration of edrophonium chloride (an acetylcholinesterase inhibitor); electromyography, which demonstrates a postsynaptic neuromuscular junctional dysfunction with repetitive nerve stimulation; and serologic testing for acetylcholine receptor antibodies. **In the presence of abnormal neuromuscular transmission, edrophonium or neostigmine is expected to improve muscle strength in objectively weak limb, ocular, and pharyngeal muscles.** Because these drugs can cause profound weakness in the presence of other disorders that impair neuromuscular transmission, be prepared to provide ventilatory support or perform endotracheal intubation as a complication of pharmacologic testing. Electromyographic testing with repetitive nerve stimulation demonstrates a rapid reduction in the size of the muscle action potential, a finding that correlates with the clinical observation of enhanced weakness with prolonged or repetitive muscle use.

TREATMENT

Treatment includes administration of the acetylcholinesterase inhibitors (pyridostigmine or neostigmine), thymectomy, chronic immune suppression with corticosteroids or azathioprine, and acute immune modulation using plasma exchange or IV immunoglobulin when indicated.[18-20] Patients who undergo thymectomy have lower rates of complications due to immunosuppressive medications and decreased distress related to symptoms.[21] Most patients show improvement with oral corticosteroids in the short term, although high-dose steroids sometimes result first in more weakness before improvement. Azathioprine or mycophenolate[22] can supplement chronic oral steroid therapy and lowers the steroid dose. Prednisone with or without azathioprine is the most effective treatment for controlling symptoms and preventing myasthenic crisis.[23,24] Severe symptoms, such as those that would require hospital admission, might require the use of IV immunoglobulin or a combination of high-dose steroids and plasma exchange.[25,26]

The severity of muscle weakness can vary in response to physical insults such as asthma exacerbations, infections, menstruation, pregnancy, emotional stress, hot weather, and other disorders that alter the response to medication, such as pulmonary, renal, and GI disease. Even with immunomodulatory treatment, muscle weakness will unlikely resolve completely.

Many drugs used in the ED can affect neuromuscular function. Antibiotics worsen muscle weakness and can cause respiratory failure due to fatigue (**Table 173-1**). Maintain myasthenia gravis patients with their usual dose of cholinergic inhibitors, such as pyridostigmine, while being treated for other conditions in the ED. The suggested pyridostigmine dose is 60 to 90 milligrams PO every 4 hours. **If a dose is missed, the next dose is usually doubled. If the patient cannot take oral medications or is intubated, administer one-thirtieth of the PO dose (2 to 3 milligrams) of pyridostigmine by slow IV infusion. The usual IV dose for neostigmine is 0.5 milligram.** Consult a neurologist to

TABLE 173-1 Drugs to Avoid in Myasthenia Gravis

Steroids	Adrenocorticotropic hormone,* methylprednisolone,* prednisone*
Anticonvulsants	Phenytoin, ethosuximide, trimethadione, paraldehyde, magnesium sulfate, barbiturates, lithium
Antimalarials	Chloroquine,* quinine*
IV fluids	Sodium lactate solution
Antibiotics	Aminoglycosides, fluoroquinolones,* neomycin,* streptomycin,* kanamycin,* gentamicin, tobramycin, dihydrostreptomycin,* amikacin, polymyxin A, polymyxin B, sulfonamides, viomycin, colistimethate,* lincomycin, clindamycin, tetracycline, oxytetracycline, rolitetracycline, macrolides, metronidazole
Psychotropics	Chlorpromazine,* lithium carbonate,* amitriptyline, droperidol, haloperidol, imipramine
Antirheumatics	D-Penicillamine, colchicine, chloroquine
Cardiovascular	Quinidine,* procainamide,* β-blockers (propranolol, oxprenolol, practolol, pindolol, sotalol), lidocaine, trimethaphan, magnesium, calcium channel blockers (verapamil)
Local anesthetics	Lidocaine,* procaine*
Analgesics	Narcotics (morphine, hydromorphone, codeine, meperidine)
Endocrine	Thyroid replacement*
Eyedrops	Timolol,* echothiophate
Others	Amantadine, diphenhydramine, emetine, diuretics, muscle relaxants, central nervous system depressants, respiratory depressants, sedatives, procaine,* phenothiazines
Neuromuscular blocking agents	Tubocurarine, pancuronium, rocuronium, gallamine, dimethyl tubocurarine, succinylcholine, decamethonium

Note: See also discussion on eMedicine from WebMD by William D. Goldenberg, MD, available at: http://emedicine.medscape.com/article/793136-overview#a1.

*Case reports implicate drugs in exacerbations of myasthenia gravis.

TABLE 173-2 Edrophonium Testing in Myasthenia Gravis

	Myasthenic Crisis	Cholinergic Crisis
Pathology	Undermedication, decrease in acetylcholine receptor causes decreased stimulation by ACh	Overmedication, excess anticholinesterase drugs, overstimulation by ACh
Finding after edrophonium administration	Visible improvement in muscle contractibility, fusion of diplopia, or resolution of ptosis	Worsening of symptoms, muscle weakness, and possible respiratory paralysis
Implication of edrophonium test finding	Patient positive for myasthenia gravis, undermedication of anticholinesterase drugs	Overmedication has occurred, possibly due to insufficient effect from anticholinesterase drugs
Clinical treatment required based on test results	Increase in anticholinesterase drugs, such as pyridostigmine and neostigmine	Treat with atropine; if respiratory paralysis occurs, assist with ventilation

Abbreviation: ACh = acetylcholine.

determine the optimal IV dose, rate of infusion, and timing of repeat pyridostigmine or neostigmine dosing.

The most significant ED complication of myasthenia gravis is respiratory failure, which is usually precipitated by infection, surgery, or the rapid tapering of immunosuppressive drugs. Although intubation should be considered in patients with a low forced vital capacity or in the presence of abnormal blood gas analysis, this decision is made primarily on clinical grounds. Patients may have increased sensitivity to nondepolarizing agents based on their concurrent use of acetylcholinesterase inhibitors. Additionally, they can have either resistance or prolonged duration from depolarizing agents. Because of the increased sensitivity of myasthenia gravis patients to neuromuscular junction inhibitors and an unpredictable reaction to succinylcholine in particular, **avoid the administration of depolarizing or nondepolarizing paralytic agents** in preparation for intubation.[27] Patients with myasthenia are extremely sensitive to these agents, and the paralytic effects can be expected to persist at least two to three times longer than in normal patients. Consider using short-acting agents such as fentanyl or propofol in smaller doses, as it is important to avoid further respiratory depression. Sugammadex may be used to reverse rocuronium if necessary.[28] If paralytic agents are absolutely necessary, consider using one with a shorter half-life, such as etomidate, at one half the dose of these agents, although this recommendation is anecdotal.

As many as 20% of myasthenia gravis patients will experience a myasthenic crisis requiring acute emergency intervention.[29] Myasthenic crisis, which occurs either because of disease exacerbation or inadequate drug therapy, must be distinguished from cholinergic crisis, which is caused by excessive cholinergic effects of the drugs used to treat the disease. This differentiation can be made in the ED by the use of edrophonium chloride testing, a test that can also be used to diagnose myasthenia (**Table 173-2** and **Figure 173-1**). Edrophonium is used for this purpose because of its rapid onset (30 seconds) and the short duration of effects (5 to 10 minutes). **A positive result is characterized by the resolution of muscle weakness within a few minutes, and thus suggests that the symptoms are caused by a myasthenia exacerbation.** The development of muscle fasciculations, respiratory depression, or cholinergic symptoms within a few minutes of administering edrophonium suggests that the baseline muscle weakness is related to a cholinergic crisis, rather than a myasthenic crisis, and further edrophonium administration is contraindicated. If there is no evidence of adverse cholinergic effects after a small dose (such as 1 milligram IV), up to 10 milligrams of edrophonium can then be given in order to demonstrate benefit in the face of a presumed myasthenic crisis. If edrophonium is being used solely for diagnostic purposes, it is administered in similar aliquots looking for improvement in ocular symptoms. Neostigmine can then be given IM or SC in 0.5- to 2.0-milligram doses, with clinical effectiveness by 30 minutes and lasting for up to 4 hours. Alternatively, 15-milligram neostigmine tablets can be given PO, each having a clinical effect comparable to that of a 0.5-milligram parenteral neostigmine injection.

In children, the total edrophonium IV dose is 0.15 milligram/kg, not to exceed 10 milligrams. To test adverse cholinergic effects with a test dose in children, give an initial IV edrophonium dose one tenth that of the total dose. For children weighing <75 lb (34 kg), a test dose of 1 milligram is appropriate, and a total dose of 5 milligrams can be used in 1-milligram increments. In infants, or when IV access is not available in children <75 lb (34 kg), the IM edrophonium test dose is 0.5 to 2.0 milligrams.

Edrophonium may cause bradycardia, atrioventricular block, atrial fibrillation, and cardiac arrest. Place all patients receiving edrophonium on a cardiac monitor and pulse oximetry, with special caution in those with a cardiac disease. Place a cardiopulmonary resuscitation cart containing atropine and intubation equipment at the bedside. Although atropine will counteract the muscarinic effects (miosis, lacrimation, salivation, bradycardia) of edrophonium, it will not reverse the nicotinic effects (skeletal muscle paralysis) of a cholinergic crisis. Acute respiratory failure can result from either acute myasthenic crisis or acute cholinergic crisis. Patients with a cholinergic crisis who worsen with edrophonium test dose administration may require immediate intubation and management of excessive secretions and acute bronchospasm.

DISPOSITION

Admit patients who demonstrate clinical signs of respiratory compromise to the intensive care unit setting. When admitting the patient, consider other complications of muscle weakness in patients with myasthenia gravis, such as impaired swallowing, aspiration, dehydration, and decubitus ulcer formation. It is generally accepted in the neurology community that cyclosporine and cyclophosphamide significantly improve myasthenia gravis, whereas azathioprine, mycophenolate, and tacrolimus have not been found to provide significant benefit.[30]

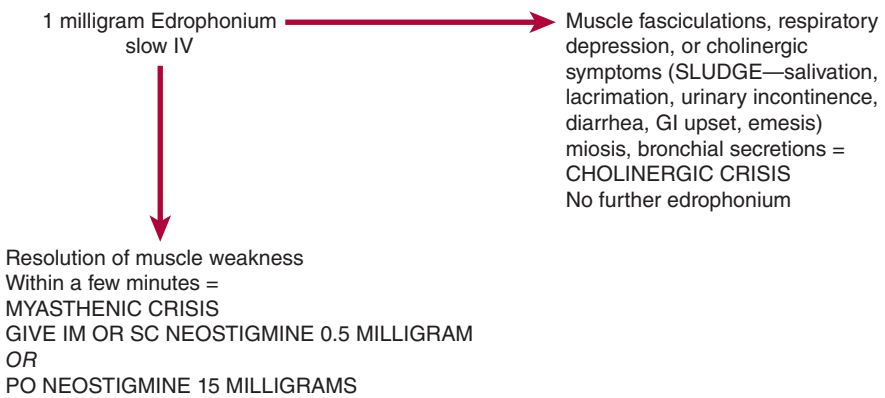

FIGURE 173-1. Edrophonium test for myasthenic versus cholinergic crisis.

Corticosteroids are known to be useful short term, and these additional modalities should be considered in an effort to lower the dose.[31]

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a neurologic disorder that causes varying degrees of motor, sensory, visual, and cerebellar dysfunction as a result of multifocal areas of CNS myelin destruction. Paresthesias, gait difficulty, extremity weakness, poor coordination, and vision disturbances often occur with a relapsing and remitting clinical course. Despite the lack of a definitive cure, immunosuppression and immunomodulation provide adequate symptomatic relief in the majority of patients, such that most have only mild to moderate lifetime morbidity, resulting in a reduction in overall life expectancy of only 5 to 10 years.[32]

Three clinical courses are noted in patients with MS. Up to 90% have a relapsing and remitting course, with relapses lasting weeks to months. The remaining patients have either a relapsing and progressive course or a chronically progressive clinical course, the latter of which is more common with advanced age.

PATHOPHYSIOLOGY

The disease process of MS is best described as an inflammatory disorder resulting in scattered neuron demyelination, but the cause is unknown. There is no risk of MS from vaccinations.[33] MS causes a dysfunction in oligodendrocytes such that the axonal myelin sheaths are damaged, slowing nerve impulse conduction. Scattered cerebral and spinal plaques cause gliosis primarily in the white matter, with relative axon sparing.

Plaques occur in multiple areas, including the cerebrum, brainstem, spinal cord, and cranial nerves. Lesions in the corticospinal tracts, posterior columns, and spinothalamic tracts will cause upper motor neuron, proprioception/vibration, and pain/temperature dysfunction, respectively. Cranial nerve lesions result in optic neuritis, as well as facial motor and sensory deficits.

CLINICAL FEATURES

Suspect multiple sclerosis in a young person who presents with multiple episodes of transient neurologic symptoms during which each episode suggests pathology from a different area of the brain. For most patients, lower extremity symptoms are more prominent than upper extremity symptoms. **The physical examination may reveal generalized decreased strength, increased tone, hyperreflexia, clonus, a positive Babinski reflex, a decrease in both vibration sense and joint proprioception, and a reduction in pain and temperature sensation.** Although sensory and motor deficits are present initially in only one third of patients, all patients will experience these findings at some point during the disease course. Patients may describe these deficits as a heaviness, weakness, stiffness, or extremity numbness. **Lhermitte sign** is commonly experienced during the course of MS and is defined as an electric shock sensation, vibration, or pain radiating down the back and often into the arms or legs resulting from the flexion of the neck. Rarely, patients with established MS will present with acute transverse myelitis that manifests as complete or near-complete loss of motor function. Cerebellar lesions may cause a kinetic tremor, dysmetria, or truncal ataxia. Vertigo may develop as a result of brainstem lesions.

Optic neuritis, which usually causes acute or subacute central vision loss, may be the initial diagnosis of MS in up to 30% of patients. Vision loss, which occurs over several days and is usually unilateral, is often preceded by retrobulbar pain or extraocular muscle pain that may be reproduced with periorbital palpation. Optic neuritis may cause an afferent pupillary defect, or **Marcus Gunn pupil**. This is found when a light directed into the affected eye causes pupil dilation instead of constriction (see Chapter 241, "Eye Emergencies"). Although ocular pain most often resolves over several days, it may take months for the vision disturbances to resolve. Most patients experience blurred vision, compromised color vision, and/or eye pain due to optic neuritis at some point during the course of the disease. Nystagmus, diplopia, and internuclear ophthalmoplegia are also often seen. Internuclear ophthalmoplegia usually causes abnormal eye adduction bilaterally and horizontal nystagmus. When bilateral internuclear ophthalmoplegia is seen acutely in an otherwise healthy young person, it is highly suggestive of MS.

Dysautonomias can cause vesicourethral dysfunction, resulting in urinary retention, urgency, frequency, detrusor–external sphincter dyssynergia, and stress or overflow incontinence. GI dysfunction can cause constipation and fecal incontinence. Sexual dysfunction, especially in males, may be a presenting symptom and correlates with other types of urologic dysfunction. Cognitive and emotional changes, including dementia, decreased motivation, depression, and bipolar mood disorders, occur in many patients. Cerebral MS, which affects 5% of MS patients, can cause a severe decrease in intellect and seizures. Simple partial seizures are twice as common in patients with MS as in the general population. Of note, the treatment for MS can cause seizures, and antiepileptic drugs used to treat the seizures may further exacerbate MS.[34]

MS symptoms can worsen with activities or changes that increase body temperature. Examples include exercise, fever, or hot baths. Visual acuity may worsen with increases in body temperature. Most initial attacks or exacerbations of MS will progress over several days, peak at about 1 week, and resolve over several weeks to months. Complete recovery from an acute exacerbation occurs more commonly early in the course of the disease than it does in later years.

DIAGNOSIS

Consider multiple sclerosis when a patient has either two or more episodes of neurologic dysfunction that suggest distinct white matter pathology or spinal cord dysfunction in two or more separate locations. Findings on MRI can aid in the diagnosis to allow for earlier recognition and treatment.[35] Optic, cerebrospinal fluid, and neuroimaging findings, as well as typical features such as dysautonomias, all suggest the diagnosis. Symptoms that mimic MS are seen with systemic lupus erythematosus, Lyme disease, neurosyphilis, human immunodeficiency virus disease, and Guillain-Barré syndrome, which are all associated with peripheral nervous system demyelination. MS progression is often monitored with the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite scores, which are standardized scales used to grade the degree of disability across multiple organ systems to accurately evaluate those affected by the varied clinical expression of multiple sclerosis.[36] These scales are then used to measure progression of disease and guide therapy.

Nearly all patients will demonstrate some nervous system pathology on MRI neuroimaging. T2-weighted scans demonstrate multiple discrete lesions in the supratentorial white matter, homogeneous borders surrounding the ventricles, or infratentorial or spinal cord lesions.[37] Although CT is not as sensitive as MRI, it may show cerebral atrophy, ventricular enlargement, and low-density focal lesions in the cerebrum, brainstem, or optic nerves. Lumbar punctures are performed as part of the diagnostic workup. Cerebrospinal fluid protein and gamma-globulin concentrations can be elevated, and a slight increase in the cerebrospinal fluid WBCs (up to 25/mm^3), most of which are T-lymphocytes, can also be seen.

TREATMENT

Consult a neurologist for guidance in management options. Treatment modalities include mitoxantrone, glucocorticoids, natalizumab, alemtuzumab, interferon-β, fingolimod, dimethyl fumarate, teriflunomide, and glatiramer.[38] Mitoxantrone has been associated with bone marrow, hepatotoxicity, and cardiac toxicity.[39] High-dose methylprednisolone therapy, given either IV or PO, shortens the duration of exacerbations.[40,41] There is a 1:1000 incidence of progressive multifocal leukoencephalopathy with natalizumab treatment.[42] IV immunoglobulin is suggested for postpartum exacerbations and for patients with relapsing-remitting disease in whom other therapies such as interferon-β and glatiramer are not tolerated.[43]

DISPOSITION

Focus ED management on early diagnosis and treatment of acute exacerbations. Patients with respiratory distress, optic neuritis, pulmonary infections, severe constipation, and worsening muscle weakness should be managed expeditiously due to the propensity of these patients to deteriorate rapidly. Use rapid sequence induction and the Sellick maneuver for endotracheal intubation because of an increased aspiration risk as a consequence of decreased gastric motility. Also, because many patients with MS have labile autonomic nervous system function, be prepared to treat hypotension in the setting of rapid sequence induction, emergency intubation, mechanical ventilation, and surgical anesthesia. Treat seizures with standard anticonvulsant medications and management protocols. Reduce fever to minimize the weakness associated with elevated temperature. **Test for urinary tract infections and pyelonephritis, especially in patients with residual urine volumes >100 mL.** Obtain a postvoid residual urine volume and a urine culture, and initiate antibiotic therapy whenever there is clinical evidence of a urinary tract infection or significant bacteriuria. When feasible, discharged patients should manage elevated residual urine volumes with intermittent sterile catheterization as opposed to chronic placement of a urinary drainage catheter. **Admit for a disease exacerbation or for IV antibiotic or steroid therapy.**

The American Academy of Neurology has published guidelines describing the use of MRI in MS diagnosis, treatment with natalizumab and mitoxantrone, and the utility of the measurement of interferon-β antibody levels. These guidelines conclude the following: The use of natalizumab reduces clinical features such as relapse rate and disease severity but is associated with adverse effects.[44] Mitoxantrone has modest beneficial clinical effects that must be balanced against adverse effects.[45] The presence of MRI-identifiable lesions at the time of symptom onset is associated with later definitive MS diagnosis.[44] The Cochrane Collaboration has published reviews outlining the use of amantadine, azathioprine, corticosteroids, cyclophosphamide, mitoxantrone, and dietary interventions, as well as the treatment of ataxia. These reviews conclude the following:

1. The use of amantadine to reduce fatigue in MS patients is not substantiated.[46]
2. Azathioprine is a useful alternative to interferon-β in patients who frequently relapse and require steroid therapy.[47]
3. There is no clear benefit to the use of PO or IV steroids in the treatment of optic neuritis in MS patients, although quicker recovery of vision may occur with IV therapy.[48]
4. Cyclophosphamide does not prevent the progression of MS symptoms, and its use is associated with significant adverse effects.[49]
5. Mitoxantrone modestly reduces MS patient disease progression and relapse frequency and should be considered for patients with worsening disability caused by MS.[50]
6. Dietary regimens and vitamin supplementation have yet to demonstrate clinical benefit for MS patients.[51]
7. There are insufficient data to support any specific therapies for the treatment of ataxia and/or tremors that occur in MS patients.[52]

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome is an autoimmune disorder that causes fluctuating weakness and fatigue, most notably in the proximal limb muscles, that improves with sustained or repeated exercise (in contrast to myasthenia gravis where repeated exercise causes worsening fatigue). Lambert-Eaton myasthenic syndrome is predominantly a disease associated with older men with a history of cigarette smoking and lung cancer. The syndrome can precede detection of malignancy by several years. Approximately 40% to 62% of patients with Lambert-Eaton myasthenic syndrome are found to have concurrent small-cell lung cancer.[53] Diagnosis is confirmed by electromyography. Small-cell lung cancer correlates strongly with more rapid disease progression. Electromyography is abnormal as a result of diseased calcium channels at the cholinergic nerve terminals. Reduced compound muscle action potentials that increase by >100% following maximal voluntary action on electrophysiologic testing help to confirm the diagnosis.[54]

The etiology of Lambert-Eaton myasthenic syndrome is likely from an autoimmune response of P/Q-type voltage-gated calcium channels on axon nerve terminals.[55,56] These channels are integral to the release of acetylcholine during the action potential. If there is any impairment in the calcium ion flow, it results in muscle weakness. In seronegative Lambert-Eaton myasthenic syndrome, there is an absence of the anti-P/Q–type voltage-gated calcium channel antibodies. It is hypothesized that seronegative Lambert-Eaton myasthenic syndrome is also incited by autoantibodies.[57] Patients often complain of myalgias, muscle stiffness (especially in the hip and shoulders), paresthesias, metallic taste in their mouth, and autonomic symptoms (e.g., dry mouth and impotence) caused by muscarinic cholinergic insufficiency. Although eye movements are unaffected, pupillary reflexes can be abnormal. Motor reflexes may be diminished. The sensory examination can be normal, but because the disease is associated with malignancy, paraneoplastic or chemotherapy-induced neuropathy can lead to a superimposed sensory deficit.

TREATMENT

Treatment is supportive. Progression to respiratory or bulbar failure is rare. Neuromuscular transmission can also be enhanced by a neuromuscular transmission enhancer, 3,4-diaminopyridine, which is considered first-line treatment.[58,59] Immunosuppression with corticosteroids, IV immunoglobulin, guanidine, aminopyridines, and azathioprine also can be used to reduce symptom severity.[60,61] Hospital admission is indicated when infectious complications occur or when severe disability requires inpatient immunotherapy.

PARKINSON'S DISEASE

Parkinson's disease is an extrapyramidal movement disorder characterized by a resting tremor, cogwheel rigidity, bradykinesias or akinesias, and impaired postural reflexes. The disease is associated with a reduced number of functional dopaminergic receptors in the substantia nigra. Drug therapy is designed to enhance central dopaminergic activity, thus decreasing the relative excess in central cholinergic activity. Even though multiple drug and surgical therapies can be used to minimize symptoms, the disease still progresses without symptom remission in most patients.

PATHOPHYSIOLOGY

Parkinson's disease is characterized by the presence of cellular cytoplasmic inclusions, termed *Lewy bodies*. In the pigmented areas of the midbrain, especially the substantia nigra, there is depigmentation, dopaminergic neuron loss, and gliosis. These cellular changes result in the loss of functional dopaminergic receptors, causing a decrease in the overall level of striatal dopamine.

CLINICAL FEATURES

The clinical diagnosis of Parkinson's disease is based on the presence of one or more of four hallmark neurologic signs identified in the mnemonic ***TRAP:* resting *tremor*, cogwheel *rigidity*, bradykinesia or *akinesia*, and impairment in *posture* and equilibrium**. Patients may also present with facial and postural changes, voice and speech abnormalities, depression, and muscle fatigue. Initial symptoms can be insidious with vague symptoms such as a feeling of slow, stiff, or decreased manual dexterity progressing over months to years. Due to this slow disease progression with nonspecific symptoms, diagnosis is often delayed. The first stage of the disease is the premotor phase that includes reduced olfaction and constipation. This is followed by the motor phase, which responds to L-dopa in the honeymoon phase of the disease. In late-stage disease, patients experience motor disabilities, freezing of their gait, falls, incontinence, orthostatic hypotension, and dementia.[62]

Early in the disease, patients can present with a unilateral resting tremor of the upper extremity. The tremor is a repetitive, low-amplitude movement that involves the fingers and thumb, but can also affect the legs or face, that occurs five or more times per minute. This repetitive movement is described as **"pill rolling."** Tremors can dissipate when intentional movement is performed, which differentiates it from the kinetic tremor of other neurologic disorders. For example, on physical examination, the resting tremor of Parkinson's disease will become less prominent as the patient performs the finger-to-nose test, and tremor resumes once this purposeful movement is ended and the limb is at rest and supported. Cogwheel rigidity, a common feature in Parkinson's disease, is rigidity and tremor that causes jerky resistance to passive movements. Bradykinesia, the general sense of slowness of voluntary movement, is often felt to be the most debilitating symptom. In severe cases of Parkinson's disease, patients may develop marked akinesia that limits their ability to perform activities of daily living, such as turning in bed, rising from a seated position, or ambulating. When the disorder impairs postural reflexes, patients may have an impaired ability to turn or change direction while walking or may lose their balance and fall. Patients are also commonly affected by impulse control disorders.[63]

DIAGNOSIS

The clinical diagnosis of Parkinson's disease follows an algorithm based on the TRAP symptoms. There is no definitive laboratory or neuroimaging study that is pathognomonic for diagnosis. CT and MRI most often only show CNS atrophy. While the diagnosis of Parkinson's disease is based on recognition of the TRAP symptoms and response to dopaminergic therapy, there is a broader group of neurologic disorders that fall under parkinsonism. Parkinsonism is characterized by tremors, rigidity, and bradykinesia and is often associated with other disorders such as postencephalitis, neurosyphilis, subacute spongiform encephalopathy, and acquired immunodeficiency syndrome. Parkinsonism can also occur as a result of street drugs, toxins, neuroleptic drugs, hydrocephalus, head trauma, and more rare and complex neurologic disorders.

In **drug-induced Parkinson's disease**, akinesia is the most common sign, with resting tremor less commonly observed. Other characteristics of drug-induced parkinsonism include a history of drug ingestion known to interfere with central dopamine activity, short interval between symptom onset and maximal disability, bilateral presentation of motor dysfunction, and the presence of other drug-related motor abnormalities. In cases of parkinsonism, there is no specific treatment. By treating the underlying disorder and removing any offending agents, the process can sometimes be halted or occasionally reversed.

TREATMENT

The goal of all currently available therapies is symptom reduction. Therapies include anticholinergic agonists, such as trihexyphenidyl and benztropine; drugs that increase central dopamine levels, such as amantadine, levodopa, and carbidopa; and dopamine receptor agonists, such as bromocriptine and pergolide. Ergot agonists are no longer recommended, as newer agents have replaced them.[64] When symptoms cause severe motor dysfunction, the monoamine oxidase inhibitor selegiline and the catechol methyltransferase inhibitors entacapone and tolcapone may be effective.

Levodopa, an amino acid precursor to neurotransmitters including dopamine, can cause symptoms such as anorexia, nausea, and vomiting due to increases in peripheral dopamine levels. When levodopa is combined with carbidopa, a peripheral decarboxylase inhibitor, smaller doses of levodopa are required for effectiveness, reducing side effects. Over time, the effectiveness of levodopa will diminish, requiring the additional use of dopamine receptor agonist therapy. Individuals who are fully mobile, in the "on" state, can suddenly convert to the "off" state and become akinetic, especially in the morning shortly after rising and before taking the initial daily dose. This "on-off" phenomenon is treated by the use of controlled-release preparations of the combined carbidopa-levodopa therapy. Human aromatic L-amino acid decarboxylase allows for more effective levodopa conversion to dopamine without the adverse effects of high doses of levodopa.[65] Other dopamine agonists that have been found to be effective as monotherapy included piribedil, pramipexole, ropinirole, rotigotine, and cabergoline.[66]

When drug effectiveness diminishes over time or when significant motor or psychiatric complications occur, a "drug holiday" lasting approximately 1 week can be attempted. Despite the fact that withdrawal of dopaminergic therapy can worsen symptoms, functioning may improve once therapy is resumed, with improvement lasting weeks to months. Deep brain stimulation can treat advanced disease with motor disabilities and can improve quality of life.[67]

The treatment for drug-induced parkinsonism is termination of the causative agents. Patients who are refractory to optimal drug therapy for all types of Parkinson's disease may benefit from pallidotomy, a stereotactic neurosurgical procedure that enhances medical therapy effectiveness and reduces dyskinesia severity.[68,69] Thalamic stimulation or thalamotomy is useful for patients with severe tremor.

SPECIAL CONSIDERATIONS

Although most patients with Parkinson's disease present to the ED with an established diagnosis, some might present undiagnosed with motor or sensory symptoms that may not be attributed immediately to the disorder. Patients may experience motor symptoms such as freezing episodes, dysphagia, or abnormalities of whole-body movement. Sensory complaints may include akathisias, paresthesias, muscles aches, or extremity pain. Although severe pain is usually related to the loss of medication efficacy, it can be a prominent symptom of undiagnosed Parkinson's disease. Complications related to motor, gait, and truncal disabilities include deep venous thrombosis, pulmonary embolism, aspiration pneumonia, compressive neuropathies, and trauma from frequent falls. Autonomic disturbances, such as orthostatic hypotension, intestinal motility disorders, and bladder dysfunction, can occur, as well as facial seborrhea. Behavior abnormalities caused by frontal lobe dysfunction and dementia also are seen.

Dyspnea, respiratory distress, and pneumonia are more likely during the "off" periods, when drug efficacy is reduced. Adjust chronic therapies in consultation with the patient's primary care physician or neurologist, who can often help to determine which symptoms reflect dopaminergic excess and whether prior drug holidays have improved the patient's symptoms. The most common cause of death in severe Parkinson's disease is respiratory failure.

Dopaminergic therapy toxicities can include cardiac dysrhythmias, orthostatic hypotension, dyskinesias, and dystonias. Psychiatric and sleep disturbances, including nightmares, auditory and visual hallucinations, paranoia, and psychosis, are related to the treatment dose and duration and can be improved by a reduction in dosage or a drug holiday. Depression and panic attacks are common and can occur in patients independent of dopaminergic therapy. Psychotropics (such as haloperidol) that can cause tardive dyskinesia must be used carefully, if at all, in patients with Parkinson's disease.

In the ED setting, continue a patient's Parkinson's medication and consult with a pharmacist if they are unable to take medications by mouth. There have been cases of patients developing life-threatening parkinsonism-hyperpyrexia syndrome in the setting of abrupt withdrawal of dopamine and amantadine.[70] This syndrome is similar to neuroleptic malignant syndrome (NMS) with hyperthermia, rigidity, dysautonomia, and altered mental status.

POLIOMYELITIS AND POST-POLIO SYNDROME

Poliomyelitis is a neurotropic enterovirus that causes paralysis through motor neuron destruction, muscle denervation, and atrophy. Indigenously acquired wild poliovirus was eradicated from the United States in 1979 and from the Western Hemisphere in 1991. While 80% of the world's population lives in polio-free areas, the disease is still endemic in Pakistan, Afghanistan, and Nigeria.[71]

Mass immunization with the inactivated poliovirus vaccine or attenuated oral poliovirus vaccine has dramatically reduced the incidence of polio, but polio outbreaks still occur in populations that are not consistently or adequately immunized. Immunocompromised patients are at greater risk for contracting polio, most often after exposure to children

who were vaccinated with the attenuated oral poliovirus vaccine. With the use of attenuated oral poliovirus vaccine, there is a one in 1.4 to 2.8 million risk of developing polio, with a higher rate in immunocompromised recipients. Additionally, one in 6.7 million people who are exposed to children who have been vaccinated with the attenuated oral poliovirus vaccine may develop polio as well. In developing countries, recent intramuscular injections, tonsillectomy, and strenuous exercise are associated with increased polio infection severity.

Post-polio syndrome is expected to affect up to 100,000 of the 250,000 U.S. adults with a history of polio. Post-polio syndrome, also called *post-poliomyelitis progressive muscular atrophy*, is an important sequela of acute poliomyelitis. This disorder is characterized by the recurrence of motor symptoms, following a latent period of several decades, after the resolution of the motor symptoms caused by the initial infection. Because most cases of polio occurred before mass immunization, patients diagnosed now with post-polio syndrome most likely will be >50 years old. Disease onset is 20 to 35 years after the initial infection. Although post-polio syndrome most often occurs after a stable, disease-free period of at least 15 years by definition,[71] there are risk factors that predict an earlier onset of post-polio syndrome. These include advanced age at the time of initial polio infection, greater residual motor disability, residual bulbar or respiratory signs, and the occurrence of recent injuries that require limb immobilization. Post-polio syndrome is a diagnosis of exclusion.[72]

PATHOPHYSIOLOGY

In developed countries, the viral transmission of polio is oral to oral, whereas in developing countries, where the sanitation is poor, the transmission is fecal to oral. Acutely, the polio enterovirus enters the body through the GI tract and reproduces in the GI lymphoid tissue, termed *gut-associated lymphoid tissue*. Oral secretion of the virus takes place for several days, whereas stool excretion can last for several weeks.

At a critical concentration, the virus spreads to the large motor nuclei of the spinal cord, the brainstem, and the reticular formation. The vestibular and brainstem motor nuclei, hypothalamus, thalamus, cerebellum, and precentral motor cerebral cortex also can be infected by the poliovirus. There is loss of infected neurons. Neuron loss then causes a cycle of muscle denervation and reinnervation, resulting in loss of muscle function.

The cause of the post-polio syndrome is unknown. The motor neuron degeneration is thought to be a result of dysfunction in the individual nerve axons in surviving motor neurons.

CLINICAL FEATURES

Acute Poliomyelitis Polio infection is asymptomatic in >90% of cases. The majority of **symptomatic polio infections** involve only a minor viral illness that causes no paralysis, termed *abortive polio.* After an incubation period of a few days, symptoms may include fever, malaise, headache, sore throat, and GI symptoms. Some of the patients who experience the minor viral illness, especially young children, may develop aseptic meningitis as the infection resolves. Only 1% to 2% of all poliovirus infections result in the major illness associated with neurologic involvement. Often there is resolution of the minor viral illness symptoms before development of neurologic symptoms, making it difficult to identify the preceding minor viral illness. Muscle pain, stiffness, and weakness during the early viral syndrome may be predictive of later paralysis.

When the major illness occurs, most commonly the spinal cord anterior horn cells are affected, causing asymmetric proximal limb weakness, especially in the lower extremities. **Flaccid and weak muscles, absent tendon reflexes, and fasciculations characterize spinal polio.** Although polio patients note pain, paresthesias, and transient sensory abnormalities, sensory deficits are usually not found on clinical examination. Maximal paralysis usually occurs within 5 days, and muscle wasting then occurs over several weeks. Autonomic dysfunction, including sweating disturbances, urine retention, delayed gastric emptying, and constipation, is commonly found. Most spinal polio patients will demonstrate improved motor function, with resolution of the paralysis occurring within the first year after the acute infection.

Up to 20% of polio patients with paralysis will develop bulbar polio, which can cause speech, swallowing, facial muscle, and extraocular muscle dysfunction. Acute polio infection also can cause encephalitis and can disturb the reticular formation, resulting in cardiac dysrhythmias, blood pressure alterations, hypoxia, and hypercarbia. Patients who survive the acute episode of encephalitis normally recover without residual effects.

Consider **acute paralytic poliomyelitis** whenever an at-risk patient develops an acute febrile illness, aseptic meningitis, and asymmetric flaccid paralysis associated with the loss of deep tendon reflexes and normal sensation. As with other causes of aseptic meningitis, the cerebrospinal fluid reveals pleocytosis during the first week after paralysis onset. The cerebrospinal fluid WBC count can elevate into the hundreds, with a predominance of neutrophils early in the disease course. Although the poliovirus can be cultured from the cerebrospinal fluid early in the disease course, throat and rectal swabs provide a greater yield. When a particular viral serotype is identified, serial serum antibody titers can be used to verify the cultures.

The most important cause of paralysis on the differential diagnosis that must be considered and excluded is Guillain-Barré syndrome, which, unlike the acute polio infection, causes more symmetric muscle weakness. Acute paralysis can result from peripheral neuropathies caused by infectious mononucleosis, Lyme disease, or porphyria. Paralysis also can result from inflammatory myopathies, electrolyte abnormalities, toxins, or other viruses, such as coxsackie viruses, mumps, echoviruses, and nonpolio enteroviruses. Paralysis also can result from acute spinal cord compression, vascular lesions, and transverse myelitis, all of which should produce a sensory level and sphincter disturbances. In children, it is necessary to exclude spinal muscular atrophy, which can be undiagnosed until it is manifested by dramatic limb weakness caused by an acute febrile illness.

Post-Polio Syndrome Patients with **post-polio syndrome** complain of muscle fatigue, joint pain, worsening of skeletal deformities, or weakness in muscles that were spared during the initial viral infection. When muscle weakness is observed, atrophy, pain, paresthesias, and fasciculations may be noted both in previously unaffected muscle groups and in those previously involved.[73] Patients may also develop new bulbar, respiratory, or sleep difficulties. For example, laryngeal muscle weakness can cause progressive dyspnea, dysphagia, and/or hoarseness. Some patients complain of abnormal movements in sleep that disturb normal sleep, requiring therapy with benzodiazepines or dopaminergic drugs.[74] These symptoms occur independently of any concurrent neurologic, orthopedic, psychiatric, or systemic medical illness.

To diagnose post-polio syndrome, the patient should have a history of acute paralytic poliomyelitis with stable recovery of motor function associated with residual muscle atrophy, weakness, and areflexia with normal sensation in at least one limb. Additionally, there should be new muscle symptoms or weakness not attributable to an acute injury, neuropathy, radiculopathy, or systemic, neurologic, or psychiatric illness.

Treatment of the new muscle weakness seen with post-polio patients is primarily symptomatic, with the use of analgesic and anti-inflammatory medications. Most patients with post-polio syndrome benefit from muscle training[75] and daily exercise.[76] An additional therapeutic option is lamotrigine (Lamictal®). When used in conjunction with an exercise routine, lamotrigine may improve the quality of life in post-polio patients by reducing pain and fatigue.[77]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 174

Central Nervous System and Spinal Infections

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CENTRAL NERVOUS SYSTEM INFECTIONS

BACTERIAL MENINGITIS

INTRODUCTION AND EPIDEMIOLOGY

Bacterial meningitis is a life-threatening emergency that affects about 1.2 millions individuals worldwide each year.[1] The incidence and major pathogens vary by region, country, age group, and immunization status.[2-4] For example, although meningococcal meningitis occurs worldwide in epidemic and sporadic form, the highest incidence is in the meningitis belt of sub-Saharan Africa, from Senegal to Ethiopia.[5] In the United States, the most common causes of bacterial meningitis are *Streptococcus pneumoniae* (58.0%), group B *Streptococcus* (18.1%), *Neisseria meningitidis* (13.9%), *Haemophilus influenzae* (6.7%), and *Listeria monocytogenes* (3.4%).[6] *Escherichia coli* in the neonatal population and *Mycobacterium tuberculosis* in immunocompromised hosts are also important considerations.[7]

PATHOPHYSIOLOGY

Organisms enter the cerebrospinal fluid (CSF) either through hematogenous or direct contiguous spread. In hematogenous spread, bacteria colonize the upper airway and invade the bloodstream, gradually making their way to the subarachnoid space. The subcapsular components of *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis* induce an inflammatory cascade, and leukocyte toxins cause cellular swelling and inflammation of the brain and meninges.[8] Blood–brain barrier permeability increases, allowing protein and water to enter and leading to vasogenic edema. CSF drainage is inhibited by reduced absorption of the arachnoid granules with resultant obstruction and hydrocephalus, and CSF is forced into the periventricular parenchyma, causing interstitial edema. Disruption of cell membrane homeostasis causes cytotoxic edema. As the brain and meninges rest in a fixed-volume skull, this leads to an elevation in intracranial pressure. Vasculitis decreases cerebral blood flow and can cause ischemia and thrombosis. Additionally, neurons are directly injured by free radicals from granulocytes and endothelial cells.[9]

In direct contiguous spread, organisms gain entry into the CSF from adjacent infections such as sinusitis, brain abscess, or otitis media. Organisms can also enter directly with penetrating traumatic injury, through congenital defects, or during neurosurgical procedures. In these cases, the organisms and their pathophysiologic effects vary.

Important risk factors for bacterial meningitis are listed in **Table 174-1**.

TABLE 174-1 Important Risk Factors for Bacterial Meningitis

- Acute or chronic otitis media
- Sinusitis
- Immunosuppression/splenectomy
- Alcoholism
- Pneumonia
- Diabetes mellitus
- Cerebrospinal fluid leak
- Pneumonia
- Endocarditis
- Neurosurgical procedure/head injury
- Indwelling neurosurgical device/cochlear implant
- Advanced age
- Malignancies
- Liver disease
- Unvaccinated to *Haemophilus influenzae* type b, *Neisseria meningitidis*, or *Streptococcus pneumoniae*

CLINICAL FEATURES

The presentation of fever, headache, stiff neck, and altered mental status is commonly seen in patients with bacterial meningitis. Most patients have at least two of four of these symptoms, but their absence does not exclude meningitis. Headache is the most common symptom and is seen in more than 85% of patients.[9] Fever is the second most common symptom. Seizures and focal neurologic deficits are seen in 25% to 30% of patients.[9]

HISTORY

Assess historical data in order to elicit risk factors suggestive of certain pathogens. *N. meningitidis* is associated with close living quarters, such as in military barracks and college dormitories. Unvaccinated patients are at risk for *H. influenzae*. Consider *L. monocytogenes* in older adults and alcoholics.[10] Penetrating head trauma makes *S. pneumoniae* more likely. *Staphylococcus aureus*, coagulase-negative staphylococci, and streptococci are commonly implicated organisms after craniotomy, whereas coagulase-negative staphylococci are commonly seen after ventriculoperitoneal shunt and spinal surgery.[4] Immunocompromised patients, such as those with human immunodeficiency virus, on chronic steroids, or with a history of splenectomy, are susceptible to meningitis with encapsulated organisms.

PHYSICAL EXAMINATION

Evaluate for focal neurologic dysfunction such as hemiparesis, visual field deficits, or disordered eye movements. Increased intracranial pressure can cause papilledema or cranial nerve palsy especially involving cranial nerves 3, 4, 6, and 7. Assess for meningeal irritation with gentle neck flexion and extension, or Brudzinski sign (flexion of hips and knees in response to passive neck flexion) and Kernig sign (contraction of the hamstrings in response to knee extension while the hip is flexed). Examine the skin for cutaneous stigmata such as petechiae, splinter hemorrhages, and pustules.[11] Percuss the sinuses and examine the ears for signs of primary infection.

DIAGNOSIS

LUMBAR PUNCTURE

The diagnosis of meningitis is based on CSF results obtained by lumbar puncture (LP). Withhold LP if there is coagulopathy, as evidenced by thrombocytopenia or anticoagulant or antithrombotic use, until coagulopathy is corrected. In general, a platelet count ≤20,000/μL (and some prefer ≤50,000/μL) or INR ≥1.5 is a contraindication to performing an LP on an emergent basis.[12] The risk of bleeding complications such as epidural hematoma resulting from LP in the presence of anticoagulants, antiplatelet agents, and NSAIDs is not known, and risks and benefits of LP must be considered in such circumstances.[13,14] Send CSF for studies including Gram stain and culture, cell count with differential, glucose, and protein.[9] Typical CSF findings for bacterial, viral, fungal, and neoplastic meningitides are listed in **Table 174-2**,[15-18] but there is considerable overlap.

LABORATORY TESTING

Bacterial meningitis is associated with an elevated opening pressure >170 mm H_2O, and WBCs are elevated greater than 1000/mm^3 with a neutrophilic predominance. CSF protein is often elevated above

TABLE 174-2 Cerebrospinal Fluid (CSF) Diagnostic Evaluation of Meningitis and Encephalitis

	Opening Pressure (<170 mm H_2O)*	Color (clear)	Gram Stain (negative)	Cell Count (<5 WBC, 0 PMN)	Glucose (>40 milligrams/dL)	Protein (<50 milligrams/dL)	Cytology (negative)
Bacterial	Elevated	Cloudy, turbid	Positive (60%–80% before antibiotic, 7%–41% after antibiotic)	>1000–2000/mm^3 WBC, neutrophilic predominance, >80% PMN	<40 milligrams/dL, CSF/blood glucose ratio <0.3–0.4	>200 milligrams/dL	Negative
Viral	Normal	Clear or bloody	Negative	<300/mm^3 WBC, lymphocytic predominance, <20% PMN	Normal	<200 milligrams/dL	Negative
Fungal	Normal to elevated	Clear or cloudy	Negative	<500/mm^3	Normal to slightly low	>200 milligrams/dL	Negative
Neoplastic	Normal	Clear or cloudy	Negative	<300/mm^3	Normal to slightly low	>200 milligrams/dL	Positive

*Normal values and findings are in parentheses.

Abbreviation: PMN = polymorphonuclear lymphocyte.

200 milligrams/dL, and glucose is often decreased below 40 milligrams/dL or the glucose serum–to–CSF ratio is <0.4.[15-17]

Sterilization of the CSF is possible within 2 hours of initiating parenteral antibiotics in meningococcal and 6 hours in pneumococcal meningitis, highlighting the importance of timely LP.[19] Without antibiotics, Gram stain is positive in 60% to 80% of cases, but in patients treated with antibiotics, the Gram stain is positive in 7% to 41%.[17] CSF is positive in 80% to 90% of cases if analysis is performed before antibiotics are initiated, although results are not available during the course of the ED stay. **When bacterial meningitis is considered, never withhold empiric antibiotic therapy in order to collect the CSF sample.[20]**

Rapid latex agglutination tests can be used to detect bacterial antigens and improve bacterial identification. These tests are available for *S. pneumoniae*, group B streptococci, *H. influenzae*, *E. coli*, and *N. meningitidis*, but are associated with false-positive and false-negative results and limited sensitivity and specificity. Polymerase chain reaction testing is highly sensitive for organisms such as *S. pneumoniae, N. meningitidis*, group B streptococci, *H. influenzae, L. monocytogenes*, and *M. tuberculosis* but does not provide information on antimicrobial susceptibility.[9] Serum procalcitonin, C-reactive protein, and CSF lactate concentrations have been studied as adjuncts to diagnosis of bacterial meningitis with negative CSF examinations, but are not a substitute for decision making in the treatment of an individual patient.[18,21] Recent studies suggest that serum procalcitonin may demonstrate a similar specificity to CSF markers of meningitis while offering a higher sensitivity, making it a useful adjunct for diagnosis.[22] If suspicion is great despite negative initial CSF results, admit for empiric antibiotic treatment and consider repeat LP.[15]

CT SCAN BEFORE LUMBAR PUNCTURE

Perform the LP as soon as possible to secure the diagnosis of meningitis. Concern about the complication of cerebral herniation from LP has led to controversy in determining which patients require a CT scan of the brain prior to the procedure.[17]

Order a head CT prior to LP in patients with high-risk criteria for herniation (**Table 174-3**). Although a CT scan can help identify contraindications for an LP, a normal CT scan does not imply that there is no risk of herniation with LP if a patient exhibits clinical predictors of impending herniation such as deteriorating mental status, posturing, irregular respirations and pupillary changes, or seizures.[23]

TABLE 174-3 Criteria for Obtaining Head CT Before Lumbar Puncture[8,17,23]

- Altered mental status or deteriorating level of consciousness
- Focal neurologic deficit
- New-onset seizure
- Papilledema
- Immunocompromised state
- Malignancy
- History of focal CNS disease (stroke, focal infection, tumor)
- Concern for mass CNS lesion
- Age >60 y

TREATMENT

After addressing airway, breathing, and circulation status, immediately initiate empiric antibiotic therapy if bacterial meningitis is clinically suspected. **Never delay administration of empiric antibiotic therapy for neuroimaging or to perform LP, because antibiotic treatment takes precedence over definitive diagnosis.[8]** Obtain blood cultures to assist in identification of the organism and to help guide inpatient therapy if it will not delay time to antibiotics. Base antibiotic selection on the clinical scenario including age, immunization status, living conditions, and past medical history. See **Table 174-4** for general recommendations.

EMPIRIC TREATMENT FOR PRESUMPTIVE BACTERIAL MENINGITIS

The empiric antibiotic regimen for adults between 18 and 49 years of age is a third-generation cephalosporin, such as cefotaxime 2 grams IV or ceftriaxone 2 grams IV, plus vancomycin 15 to 20 milligrams/kg IV to achieve serum trough concentrations of 15 to 20 micrograms/mL, to cover the common pathogens *S. pneumoniae* and *N. meningitidis*. For adults 50 years and older or those who may be immunocompromised, add ampicillin 2 grams IV to cover *L. monocytogenes*.[8] If patients have a severe allergy to penicillin, options include replacing ceftriaxone with meropenem or moxifloxacin and replacing ampicillin with trimethoprim-sulfamethoxazole. Add acyclovir 10 milligrams/kg IV if herpes simplex virus (HSV) encephalitis is suspected.[15] Use a third- or fourth-generation cephalosporin, such as ceftazidime or cefepime, plus

TABLE 174-4 Guidelines for Treatment of Meningitis Based on Patient Characteristics[8]

Patient Characteristic	Primary Empiric Therapy	Presumed Bacteria
Immunocompetent	Cefotaxime 2 grams IV or ceftriaxone 2 grams IV, plus vancomycin 15–20 milligrams/kg IV If severe penicillin allergy, can replace ceftriaxone with meropenem 2 grams IV or moxifloxacin 400 milligrams IV	*S. pneumoniae* and *N. meningitidis*
Age >50 y Immunocompromised	Cefotaxime 2 grams IV or ceftriaxone 2 grams IV, plus vancomycin 15–20 milligrams/kg IV PLUS ampicillin 2 grams IV If severe penicillin allergy, can replace ampicillin with trimethoprim-sulfamethoxazole 15–20 milligrams/kg/d divided 4 times daily	*L. monocytogenes*

vancomycin for patients who have recently undergone a neurosurgical procedure.[16] Initiate antibiotics as soon as possible in order to increase survival and reduce morbidity.[3,9]

Administration of dexamethasone to patients with presumptive pneumococcal meningitis before or with the first dose of antibiotics can reduce CSF inflammation, reduce the risk of morbidity and mortality in adults, and reduce hearing loss and other neurologic sequelae in children.[10,24] The recommended dosage of dexamethasone is 10 milligrams IV every 6 hours for 3 days for adults.[24]

Current guidelines provide no recommendation for the most common ED situation, in which the first dose of empiric antibiotics is given before LP is performed or before results of LP are received. However, delayed initiation of antibiotic treatment in bacterial meningitis patients is associated with death or poor clinical outcomes.[25] Common sense suggests that dexamethasone could be administered just before, or concurrently with, empiric antibiotics to patients with strong suspicion for bacterial meningitis or to patients in whom grossly purulent CSF is obtained at the time of LP. One expert consensus panel opined that dexamethasone treatment can be administered up to 4 hours after initiation of antibiotic treatment.[25]

SPECIAL SITUATIONS

BACTERIAL MENINGITIS RESULTING FROM SINUSITIS OR OTITIS

The prevalent use of antibiotics has decreased the frequency of suppurative intracranial complications from sinusitis and otitis, but bacterial meningitis resulting from these diseases still occurs. The virulence of the affecting organism and host factors, such as immunocompromised state, influence spread to the CNS. In the ear, bacteria can spread through endolymphatic channels, bony erosions, or osteothrombophlebitis of small vessels. Thrombophlebitis of veins is a common mechanism by which bacteria disseminate from the sinuses; this may result in cavernous sinus thrombosis or empyema.[26] CT imaging is very sensitive for sinusitis and permits earlier diagnosis with demonstration of air-fluid levels in the involved sinuses. CT is nonspecific, however, and should be interpreted with the clinical background in mind (**Figure 174-1**). Infections are often polymicrobial. Initiate empiric antibiotic therapy with fluoroquinolones, such as levofloxacin or moxifloxacin, or with a third-generation cephalosporin, such as ceftriaxone, plus metronidazole.[27]

ADDITIONAL ADJUNCTIVE TREATMENT FOR BACTERIAL MENINGITIS

Monitor patients with meningitis closely for complications or signs of clinical deterioration, especially evaluating their respiratory and neurologic status.[10] Treat fever, and manage seizures with anticonvulsants. Avoid hypotonic fluids, and monitor serum sodium level serially to detect syndrome of inappropriate antidiuretic hormone or cerebral salt wasting.[9,24] Closely evaluate for signs of increased intracranial pressure and vasculopathy that may lead to brain ischemia. If signs of elevated intracranial pressure are detected, elevate the bed to 30 degrees, use 25% mannitol or hypertonic 3% saline for diuresis, and consider a trial of mild hyperventilation.[9] Measurement of intracranial and systemic arterial pressure may be useful in severe cases to monitor cerebral perfusion pressure. Consider admission to the intensive care unit to ensure proper level of care.[10]

CHEMOPROPHYLAXIS FOR THOSE EXPOSED TO BACTERIAL MENINGITIS

Bacterial meningitis is spread by droplets, and risk for developing bacterial meningitis after exposure is estimated to be 500 to 800 times higher than the general population.[16] Chemoprophylaxis can decrease transmission of *N. meningitidis* by 89% in close contacts.[11] Chemoprophylaxis is recommended for individuals who have been exposed to patients diagnosed with *N. meningitidis* and *H. influenzae*.[11] It is not recommended for patients diagnosed with pneumococcal meningitis.[16] Close contacts include housemates, individuals exposed to secretions (shared utensils or toothbrushes, kissing, mouth-to-mouth resuscitation), and individuals who intubated the patient without a facemask. To be most effective, initiate chemoprophylaxis within 24 hours of contact. Risk of infection after a period of 2 weeks from exposure is considered rare, and prophylaxis is not recommended after this time period. Treatment options for high-risk contacts include rifampin 10 milligrams/kg to a maximum of 600 milligrams per dose every 12 hours for four doses, ciprofloxacin 500 milligrams orally once, or ceftriaxone 250 milligrams IM once.[11] Instruct all patients who receive chemoprophylaxis to seek

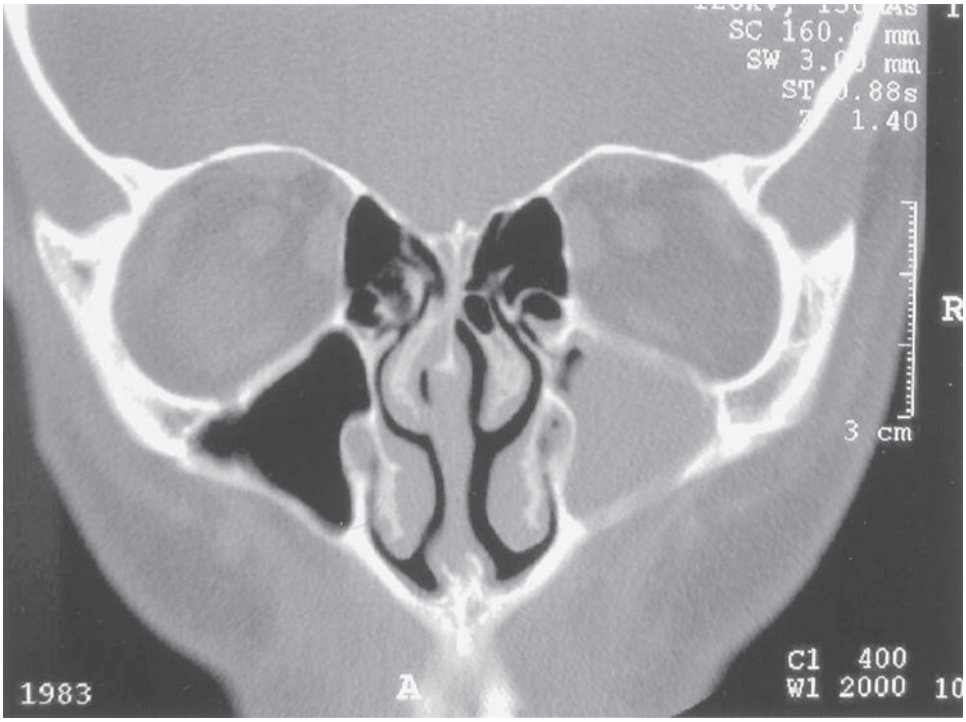

FIGURE 174-1. Acute sinusitis with opacification of the maxillary sinus. [Reproduced with permission from Brunicardi FC, Andersen D, Billiar T, et al: *Schwartz's Principles of Surgery*, 8th ed. New York, McGraw-Hill, Inc.]

medical attention immediately if they develop any symptoms of illness or meningitis.

Admit all patients diagnosed with bacterial meningitis and those highly suspected of having meningitis to the hospital on droplet isolation.

VIRAL MENINGITIS

INTRODUCTION

Viral meningitis typically presents with subacute headache, fever, and findings of meningeal irritation, such as nuchal rigidity. Several viruses can cause viral meningitis, including nonpolio enteroviruses, HSV, varicella-zoster virus, cytomegalovirus, adenovirus, and human immunodeficiency virus. Specific diagnosis depends on isolation of the virus or positive results on immunoassay of the CSF. Nonpolio enteroviruses (echovirus, coxsackievirus, and enterovirus) typically are seen in summer through fall and account for more than 90% of all cases of viral meningitis.[4]

LABORATORY TESTING

Viral meningitis is associated with normal opening pressures and a negative Gram stain (Table 174-2). WBCs are <300/mm^3 with a lymphocytic predominance, and usually less than 20% polymorphonuclear lymphocytes.[15] Protein is often slightly elevated, but not typically above 200 milligrams/dL, and CSF glucose is normal. The percentage of polymorphonuclear cells may be higher in early viral meningitis, and in some cases, glucose levels may be decreased.[15] Consider partially treated bacterial meningitis if a patient with symptoms consistent with meningitis had previously been treated with antibiotics and the LP suggests aseptic meningitis. Viral culture is insensitive, so if a viral etiology is suspected, send for molecular testing by polymerase chain reaction from the CSF.[4] Polymerase chain reaction testing is available for HSV, enterovirus, and other viral organisms.

DISPOSITION AND FOLLOW-UP

There can be overlap of CSF findings with early bacterial meningitis and partially treated bacterial meningitis, making the specific diagnosis for some cases of viral meningitis difficult in the ED. Although supportive care is the mainstay of treatment for viral meningitis, it is appropriate to admit the toxic-appearing patient to the hospital for empiric antibiotic therapy until culture results return in situations of diagnostic uncertainty. HSV-2 meningitis can cause necrotizing encephalitis and neurologic deficits.[4] Admit patients with diagnosed or suspected HSV-2 meningitis after beginning treatment with acyclovir 10 milligrams/kg IV every 8 hours.[10]

FUNGAL CNS INFECTIONS

Over the past 30 years, the incidence of fungal CNS infections has been increasing, likely due to acquired immunodeficiency syndrome as well as an increase in patients on immunosuppressants due to stem cell and organ transplants.[28] The most common cause of fungal meningitis is *Cryptococcus neoformans*, followed by *Coccidioides immitis*, which can be seen in immunocompetent hosts as well as the immunocompromised.[4,28] *Aspergillus* and *Candida* are most often discovered in immunocompromised hosts. Mucormycoses can be seen especially in diabetics from direct extension of sinus infection.

LABORATORY TESTING

The CSF analysis of fungal meningitis shows lymphocytic predominance, an elevated opening pressure, low glucose, and slightly increased protein (Table 174-2).[7,29] Significant elevations in opening pressure are often seen in cryptococcal meningitis. Gram stain is negative, and WBC is usually <500/mm^3. Consider fungal testing especially for immunocompromised patients in whom fungal etiologies are suspected, including India ink staining and serum cryptococcal antigen testing, cytology, and histopathology.[7] Send CSF for *Borrelia* antibodies in patients with suspected Lyme disease and for acid-fast stain and culture for suspected mycobacteria in tuberculous meningitis.

Patients often have a prolonged symptom course. Use fungal stain and culture for diagnosis if a fungal etiology is suspected, and look for elevated opening pressure during LP. Consider CT or MRI to search for intracranial complications such as granulomas or abscesses.

TREATMENT

Treatment for fungal infections is dependent on diagnosis through LP. Liposomal amphotericin B is the agent of choice in cryptococcal meningitis. Use fluconazole or itraconazole for *C. immitis*. Treat *Candida* meningitis with liposomal amphotericin B often combined with flucytosine.[7]

VIRAL ENCEPHALITIS

Viral CNS infections can also cause viral encephalitis, which is an infection and inflammation of the brain parenchyma.[4] Viral encephalitis is clinically distinguished from viral meningitis with presence of neurologic findings such as altered level of consciousness, focal weakness, or seizures, although the two often coexist.

The causes of viral encephalitis vary year to year and across geographical locations, with an incidence of 3.5 to 7.5 per 100,000 people.[30] Immune status, exposure to insects or animals, and travel history play a key role in determining the etiology. An underlying cause, however, is found in only about a third of cases.[29] HSV accounts for 40% to 50% of cases where a cause is determined.[30] HSV-1 is responsible for most cases of HSV encephalitis; HSV-2 frequently causes aseptic meningitis but is not usually associated with development of encephalitis.[30] Other viral pathologic agents in North America include Epstein-Barr virus, cytomegalovirus, and rabies. Common arboviral encephalitides include La Crosse encephalitis, St. Louis equine encephalitis, Western equine encephalitis, and West Nile virus.

PATHOPHYSIOLOGY

Immunocompromised patients such as those with organ or stem cell transplants are susceptible to new or reactivated infections with HSV and varicella-zoster virus. Impaired immune status also plays a role in cytomegalovirus encephalitis. The arboviruses are transmitted by mosquitoes and ticks. Rabies is transferred by the bite of an infected animal and leads to severe encephalitis and a very high mortality rate.[4] Common to all is preliminary viral invasion of the host at a site where replication takes place that is outside the CNS. Most viruses then reach the nervous system hematogenously during viremia. However, at least three important viruses—rabies, HSV, and herpes zoster virus—reach the spinal cord and eventually the brain by traveling backward within axons from a distal site, where they gain access to nerve endings. Once in the brain, disruption of neural cell functions by the virus and by the effects of the host's inflammatory responses ensues. Gray matter is predominantly affected, resulting in cognitive and psychiatric signs, lethargy, and seizures.

CLINICAL FEATURES

Consider encephalitis in patients exhibiting behavioral changes, new psychiatric symptoms, cognitive deficits, or seizures.[29] The triad of headache, fever, and altered mental status may be seen but is not invariably present. Rash or skin vesicles suggest herpes zoster, and skin vesicle culture may be useful for diagnosis. Lymphadenopathy or splenomegaly points to Epstein-Barr virus, which can be picked up on serologic testing. New onset of psychiatric symptoms and behavioral changes may be attributable to HSV. MRI, electroencephalogram, and polymerase chain reaction of the CSR could assist in making the diagnosis.

PHYSICAL EXAMINATION

Examine for signs of meningeal irritation and increased intracranial pressure and for neurologic findings that reflect the areas of involvement. Carefully assess mental status and cognition. Encephalitis may

show regional tropism. HSV involves limbic structures of the temporal and frontal lobes with prominent psychiatric features, memory disturbance, and aphasia. Some arboviruses predominantly affect the basal ganglia, causing choreoathetosis and parkinsonian movements. Involvement of the brainstem nuclei that control swallowing leads to the hydrophobic choking response characteristic of rabies encephalitis.[31]

DIAGNOSIS

Neuroimaging studies such as MRI or CT and electroencephalography are important in ruling out mass occupying lesions and making the diagnosis of encephalitis. MRI is more sensitive than CT. Obtain an MRI to help exclude lesions such as brain abscesses, and examine for findings suggestive of HSV encephalitis, such as involvement of the gray matter in the medial temporal and inferior frontal lobes (**Figure 174-2**). Electroencephalogram findings are generally nonspecific but can be useful in cases such as HSV encephalitis where an almost pathognomonic picture of periodic, asymmetric sharp waves is seen in the setting of acute febrile encephalopathy.[29] LP is the most useful diagnostic procedure in the ED, and CSF should be sent for Gram stain and culture, cell count with differential, glucose, and protein. Viral polymerase chain reaction can be helpful in detecting viral pathogens and has a 95% sensitivity and specificity for HSV.[9,32] CSF findings are similar to those in viral meningitis, with a lymphocytic pleocytosis, modestly elevated protein, and normal glucose.[32]

Consider bacterial meningitis in the differential diagnosis when fever and meningeal symptoms predominate. A late-summer encephalopathy suggests the possibility of arbovirus encephalitis, and an animal bite for which no antirabies treatment was administered has relevance for rabies. Suspect subarachnoid hemorrhage with acute onset of severe headache as the presenting sign. Lyme disease, tuberculosis, and fungal and neoplastic meningitis are in the differential diagnosis in less fulminant cases. If focal neurologic signs are present, consider brain abscess, empyema, or cavernous sinus thrombosis as possible causes.

TREATMENT

The antiviral of choice for HSV encephalitis is high-dose acyclovir at 10 milligrams/kg per dose IV every 8 hours.[10,30] Initiate treatment as soon as possible because the prognosis of HSV encephalitis is correlated with neurologic condition at the time antivirals are initiated. Treat varicella-zoster virus with acyclovir, 10 to 15 milligrams/kg per dose IV every 8 hours. Patients with herpes zoster virus encephalitis may also benefit from acyclovir therapy. Treat patients with cytomegalovirus encephalitis with ganciclovir, 5 milligrams/kg per dose IV every 12 hours.[31] There are no known treatments for arbovirus encephalitis; consider initiating treatment with acyclovir empirically until a CSF diagnosis is made.[10] Rabies encephalitis is rare but neurologically devastating, and once symptomatic, it is usually fatal.

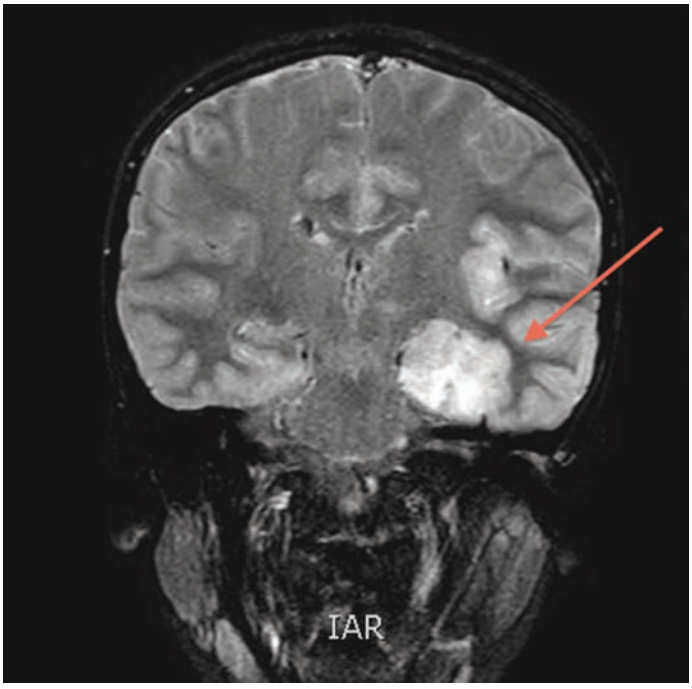

FIGURE 174-2. Fluid-attenuated inversion recovery hyperintensity in the left temporal lobe and left insula (*arrow*) suggests the diagnosis of herpes encephalitis. [Photo contributed by Elizabeth Yutan, Department of Radiology, Oregon Health & Science University.]

DISPOSITION AND FOLLOW-UP

Prognosis of viral encephalitides depends on the causative virus and host factors. Older adults and those who are immunocompromised are more likely to have an adverse outcome. Admit patients with encephalitis to the hospital. Patients may require intensive care unit care if they have signs of altered mental status or coma.

BRAIN ABSCESS

INTRODUCTION

A brain abscess begins as a focal area of cerebritis, which develops into a central pus-filled cavity ringed by a layer of granulation tissue and an outer fibrous capsule in a period of about 14 days.[33] It is surrounded by edematous brain tissue infiltrated with inflammatory cells. A brain abscess is a pathologic response typical of a relatively competent immune system against a bacterial invader. Focal brain infections from other organisms, such as granulomas due to tuberculosis, necrotic lesions of toxoplasmosis in immunocompromised patients, or cystic lesions of cysticercosis, are not abscesses in the pathologic sense.

PATHOPHYSIOLOGY

Organisms reach the brain hematogenously, from direct contiguous infection, or by direct seeding by neurosurgery or penetrating trauma. Hematogenous spread accounts for 15% to 30% of cases, direct spread from infection accounts for 25% to 50%, and trauma or surgery for 8% to 20%, while the route is unknown in 15% to 20% of cases.[33,34] Direct spread usually results in an isolated brain abscess, whereas hematogenous seeding results in multiple abscesses.

Investigate for the source of the brain abscess in order to determine the likely bacterial etiology and to treat the source itself. Otogenic brain abscesses are often caused by gram-negative rods and are located adjacent to the temporal lobe or cerebellum. Sinogenic or odontogenic abscesses are often caused by anaerobic and microaerophilic streptococci and are commonly located in the frontal lobes. Abscesses formed from hematogenous spread are usually polymicrobial, with anaerobic and microaerophilic streptococci commonly represented. Direct implantation or traumatic injuries yield staphylococci, with gram-negative rods also seen in cases related to neurologic surgery.[29]

CLINICAL FEATURES

HISTORY

Presenting features of brain abscess are nonspecific, and patients generally appear nontoxic. Headache is the most common feature, with fever as a close second. Although most patients present with one or more findings of headache, fever, altered mental status, focal neurologic symptoms, seizures, or balance changes, the classic triad of headache, fever, and focal neurologic deficit is present in <25% of all patients.[33,34] The nonspecific presentation contributes to both severity and outcome of brain abscesses because diagnosis and treatment are often delayed.[35] Symptoms reflect the infectious and neurologic (focal and mass effect producing) aspects of the disease and are often present for 1 to 8 weeks.[33] The presentation may be dominated by the origin of the infection (e.g., ear or sinus pain). Seizure occurs in 25% to 34% of patients.[36]

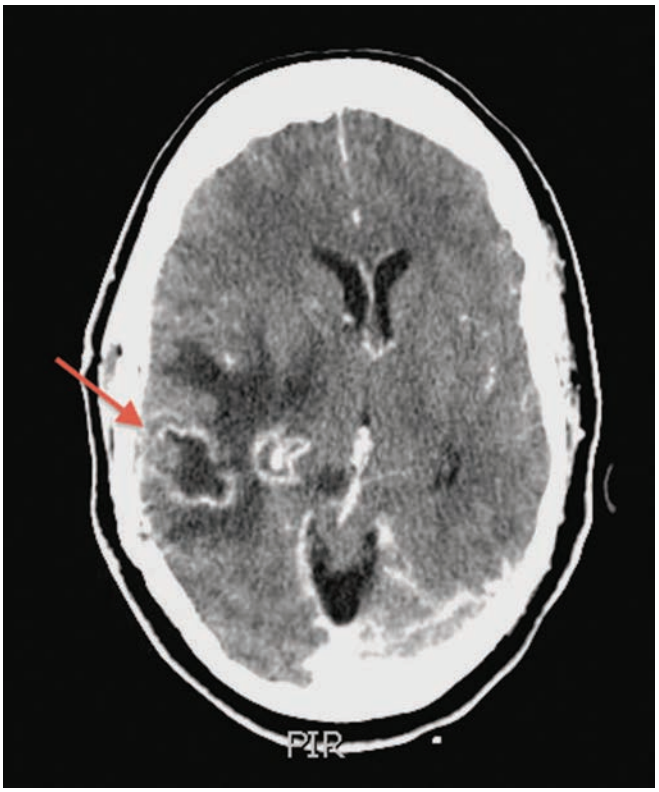

FIGURE 174-3. Ring-enhancing brain abscess with surrounding edema (*arrow*). [Photo contributed by David Peterson, Department of Radiology, Oregon Health & Science University.]

PHYSICAL EXAMINATION

Examine for focal neurologic signs that demonstrate the site of the lesion. Focal signs are present in approximately 60% of patients.[9,37] Assess for potential sites of origin, which may raise suspicion of brain abscess when the presentation is otherwise nonspecific in a patient with subacute headache and lethargy.

DIAGNOSIS

Neuroimaging is essential to the diagnosis of brain abscess and is one instance where a contrast-enhanced head CT scan is preferred over a noncontrast study in the ED. A noncontrast CT scan may only show a hypodense low-attenuation abnormality with mass effect, but later in the course, may show a peripheral ring.[33] A head CT with IV contrast shows one or several thin, smooth rings of enhancement surrounding a low-density central area and surrounded by edema (**Figure 174-3**). MRI usually demonstrates a ring whether or not gadolinium enhancement is used. Both CT and MRI are highly sensitive; CT is often more readily available in the ED. Avoid LP if clinical suspicion is high or focal neurologic deficits are present to prevent potential herniation in the case of increased intracranial pressure. If possible, obtain cultures of blood and other sites of infection to guide future management.

The differential diagnosis is broad because of the nonspecific symptoms of brain abscess. A sudden onset with focal features may suggest cerebrovascular disease. Prominent fever, stiff neck, and altered mental status may suggest meningitis or encephalitis. A protracted course with features of increased intracranial pressure may suggest neoplasm. Brain neoplasm, subacute brain hemorrhage, and other focal brain infections, such as toxoplasmosis, may mimic the imaging findings of brain abscess.

TREATMENT

Early combination empiric antibiotic therapy is important (**Table 174-5**). A multidisciplinary approach with neurosurgery and infectious disease consultations will help guide treatment selection. Aminoglycosides, macrolides, and first-generation cephalosporins are not effective treatment for brain abscess. Treatment with steroids is controversial.

DISPOSITION AND FOLLOW-UP

Neurosurgery involvement is paramount in treatment and management decisions. Patients with small abscesses <2.5 cm, with a Glasgow coma score >12, and who have an etiology that is known may be treated with IV antibiotics alone.[38] Aspiration may be done by the neurosurgical team to elucidate the causative organism. Total excision is less necessary with improved imaging, although it is performed in the setting of increased intracranial pressure or after failed medical management or aspiration.[7]

SPINAL INFECTIONS

EPIDURAL ABSCESS

INTRODUCTION AND EPIDEMIOLOGY

Spinal epidural abscess is a collection of pyogenic material that accumulates in the epidural space between the dura and vertebral periosteum and often leads to devastating neurologic outcomes.[39,40] The incidence of spinal epidural abscess has doubled in the past two decades, largely attributed to factors such as an increasing proportion of immunocompromised patients, more prevalent IV drug use, an increasing number of spinal procedures, and improved imaging modalities for detection.[41,42] Despite improvement in diagnosis and treatment, mortality remains high at 2% to 20%.[39] *S. aureus* is the most commonly involved bacteria and is

TABLE 174-5 Guidelines for Empiric Treatment of Brain Abscess Based on Presumed Source

Presumed Source	Primary Empiric Therapy	Alternative Therapy
Otogenic	Cefotaxime 2 grams IV every 4–6 h or ceftriaxone 2 grams IV every 12 h PLUS metronidazole 500 milligrams IV every 8 h	Piperacillin/tazobactam 4.5 grams IV every 6 h
Odontogenic	Penicillin G 4 million units IV every 4 h	Ceftriaxone 2 grams IV every 12 h PLUS metronidazole 500 milligrams IV every 6 h
Sinogenic	Cefotaxime 2 grams IV every 6 h or ceftriaxone 2 grams IV every 12 h PLUS metronidazole 500 milligrams IV every 8 h	No recommendation
Penetrating trauma	Cefotaxime 2 grams IV every 6 h or ceftriaxone 2 grams IV every 12 h PLUS metronidazole 500 milligrams IV every 8 h ± rifampin 10 milligrams/kg every 24 h	No recommendation
After neurosurgical procedure	Vancomycin loading dose 25–30 milligrams/kg IV loading dose or linezolid 600 milligrams IV every 12 h PLUS ceftazidime 2 grams IV every 8 h ± rifampin 10 milligrams/kg every 24 h	Can substitute linezolid 600 milligrams IV every 12 h instead of vancomycin. Can substitute meropenem 2 grams IV every 8 h OR piperacillin/tazobactam 4.5 grams IV every 6 h OR cefepime 2 grams IV every 8 h for ceftazidime.
Unknown source	Cefotaxime 2 grams IV every 6 h PLUS metronidazole 500 milligrams IV every 6 h	No recommendation

Note: See also http://www.hopkins-abxguide.org.

responsible for 70% of cases, with a higher proportion of methicillin-resistant *S. aureus* seen in patients with implantable devices.[39,42] Other pathogens include *Staphylococcus epidermidis*, streptococcal species, and gram-negative bacilli, which is especially prevalent in IV drug users. Mycobacteria and fungi causing spinal epidural abscess are rare. Tuberculosis spinal epidural abscess, also known as Pott's disease, is seen in areas where tuberculosis remains endemic and in the immunocompromised population.[43]

PATHOPHYSIOLOGY

Spinal epidural abscess can arise from hematogenous spread through blood circulation with soft tissue, urine, and respiratory infections contributing in the majority of cases. In general, hematogenously spread epidural abscesses are more likely to be found in the posterior epidural space.[42] Less commonly, spinal epidural abscesses are caused by direct extension from infected adjacent tissue, such as vertebral spondylodiscitis or vertebral osteomyelitis, which occurs when areas of slow blood flow in the vertebral body end plates are occluded by venous or arterial septic emboli, causing osteonecrosis.[44] Direct extension typically infects the anterior portion of the spinal column.[39,45] Fifteen to 22% of spinal epidural abscesses are caused iatrogenically from neurosurgical procedures, including percutaneous diagnostic and therapeutic techniques.[42] Trauma contributes to a small proportion of spinal epidural abscesses, with the remainder of cases without an identifiable source.[41,42]

Most spinal epidural abscesses affect the thoracic and lumbar spine, where the epidural space is wider with a larger venous plexus. The cervical spine is affected only 5% to 20% of the time, although morbidity and neurologic devastation are much greater than in thoracic or lumbar locations.[46]

Mechanisms for spinal cord neurologic sequelae are uncertain and are thought to be from a combination of direct compression from the abscess itself, ischemia due to compression of spinal veins and arteries, and septic thrombophlebitis.[39]

CLINICAL FEATURES

Back pain is the most common presenting complaint and is seen in the majority of cases. Fever is another common symptom, followed by the presence of a neurologic deficit. However, the classic triad of back pain, fever, and neurologic symptoms is seen in a minority of patients (8% to 37%).[39,42] Typically, patients with spinal epidural abscess progress through four stages in a period ranging from hours to days. Stage 1 consists of back pain, fever, and localized spinal tenderness. Stage 2 is composed of spinal irritation, including radicular pain, hyperreflexia, and nuchal rigidity. Stage 3 involves the bowel and bladder, with symptoms of fecal or urinary incontinence, as well as focal neurologic deficits such as motor weakness. Finally, in stage 4, paralysis ensues.[39,42] Patients with tuberculosis as an etiology may also endorse night sweats and weight loss.[47]

HISTORY

Screen any patient presenting with back pain, fever, or neurologic complaint for spinal epidural abscess. Patients may have a history of chronic back pain or may offer a mechanism of mild trauma, which can distract from a diagnosis of spinal epidural abscess. Similarly, neck pain or stiffness is often thought to be meningitis or encephalitis, causing cervical spinal epidural abscess to be overlooked.

Carefully search for back pain red flags in the patient's history, including immunocompromised states and immunosuppressant medications. Elicit a history of recent systemic illness or infection. Inquire about travel and history of tuberculosis. Ask about any current or former IV drug use, which can make patients higher risk for spinal epidural abscess development from *Pseudomonas* species. Solicit information about prior spinal surgeries or procedures, including LPs, epidurals, spinal injections, or epidural anesthesia. Ask about any changes in bowel or bladder habits, specifically episodes of bladder fullness or urinary or fecal incontinence.[42,48]

PHYSICAL EXAMINATION

Perform a thorough physical examination starting with a general assessment of sources of infection. Palpate the spine, searching for tenderness to palpation, especially in the midline, which may suggest spinal epidural abscess. Complete a full neurologic examination, including sensory dermatome testing and motor evaluation including ambulation. Check reflexes for hyper- or areflexia. Evaluate for symptoms of cauda equina syndrome. Perform a rectal examination looking for decreased rectal tone, which has a sensitivity of 60% to 80%, and an evaluation of perianal sensation for saddle anesthesia, which has a sensitivity of 75%.[49]

DIAGNOSIS

Diagnosis is delayed in many patients with spinal epidural abscess due to nonspecific presenting symptoms and the rarity of diagnosis. Send blood for laboratory studies including blood culture, CBC, erythrocyte sedimentation rate, and C-reactive protein. Leukocytosis is seen in only 60% to 78% of patients and is not sensitive or specific enough for a diagnosis of spinal epidural abscess.[42] Erythrocyte sedimentation rate is much more sensitive and, in one study, was elevated in 110 of 117 patients diagnosed with spinal epidural abscess.[42] C-reactive protein has the advantage of rising faster than erythrocyte sedimentation rate and returns to normal sooner as well, but some labs have a delay in resulting C-reactive protein. Do not withhold further diagnostics and treatment pending C-reactive protein.[42] Blood cultures are positive in up to 60% of cases and may be helpful for inpatient teams.[42] Do not perform LP if there is suspicion for spinal abscess. CSF culture is positive less than a quarter of the time, and LP poses the risk of traversing an abscess and causing meningitis or a subdural infection.[42]

MRI with gadolinium is the gold standard imaging study for the diagnosis of spinal epidural abscess and has a sensitivity and specificity greater than 90%.[45] If MRI is not available, consider emergent transfer to an appropriate referral center. In patients with contraindications to MRI, CT with myelography can be useful to localize epidural compression but is limited in its ability to distinguish abscess from other compressive lesions.[42] Plain radiographs are not sensitive or specific for diagnosis of spinal epidural abscess.[45]

TREATMENT

Once diagnosis has been established, prompt treatment is essential to reduce morbidity and enhance survival. Immediate consultation with a spine surgeon is paramount, and if a spine surgeon is not available, transfer to a referral center.[42] Neurologic outcome is correlated with degree of neurologic deficit prior to treatment.

There are no conclusive data regarding surgery versus conservative antibiotic therapy, and practices vary considerably from immediate operative therapy to conservative IV antibiotic therapy.[45] Patients with neurologic deficits usually require evacuation of the abscess with decompressive laminectomy, debridement, and long-term IV antibiotics, and some studies have shown improved outcomes with emergent surgery.[41] Patients who are neurologically intact or who have had neurologic deficits for >72 hours may be candidates for conservative treatment or CT-guided aspiration depending on the spinal surgeon's practice, with the understanding that if they develop neurologic deficits or decompensate, immediate surgical therapy is likely required.[41]

Start empiric antibiotic therapy if there will be an unavoidable delay for surgery or if the patient exhibits neurologic dysfunction or signs of sepsis. Appropriate empiric antibiotics can include a combination of

vancomycin, 15 to 20 milligrams/kg IV loading dose, to cover methicillin-resistant *S. aureus* along with an antipseudomonal β-lactam such as ceftazidime, 2 grams IV every 8 hours, cefepime, 2 grams IV every 8 hours, or meropenem, 2 grams IV every 8 hours.[39,50] Once cultures return, an infectious disease consult may be helpful to determine long-term antibiotic choice and duration.

Admit patients diagnosed with spinal epidural abscess for spinal surgery. If the patient will receive conservative therapy, admit to the intensive care unit for close monitoring, neurologic checks, and further management in conjunction with the spinal surgery team.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 175

Central Nervous System Procedures and Devices

Jay G. Ladde

LUMBAR PUNCTURE

Lumbar puncture is considered the gold standard diagnostic procedure to assist clinicians with the evaluation of subarachnoid hemorrhage, meningitis, encephalitis, and other neurologic conditions. Anxiolytics, such as benzodiazepines, may be administered to improve patient comfort, relaxation, and cooperation. Contraindications to lumbar puncture are listed in **Table 175-1**.

If an anxiolytic is used, administer a short-acting agent to avoid clouding subsequent clinical assessment. Antiseptic technique should be strictly observed. Scrub the site with a disinfecting agent and allow to dry thoroughly to avoid introduction of the chemical and the subsequent production of chemical arachnoiditis.

In adults, a transverse line drawn between the iliac crests crosses the spine at the L4 spinous process. The L4-L5 interspace is the most commonly used interspace for lumbar puncture, although one can also select the L3-L4 interspace. Palpate the L4-L5 interspace while the patient is curled as tightly as possible in a fetal position. Alternatively, the patient may be seated on the edge of a bed or cart leaning over a tray stand. This latter technique is particularly useful when landmarks are uncertain due to body habitus.

Use a $3^1/_2$-inch atraumatic 22-gauge needle in adults. Use of a needle larger than 20 gauge may double the incidence of post–lumbar puncture headache compared with a smaller needle. The use of an atraumatic or pencil-point needle (such as a Whitacre or Sprotte needle) is associated with fewer post–lumbar puncture headaches than a conventional cutting needle[1,2] (**Figure 175-1**). Also, a smaller needle size using the stylet is associated with reduced frequency of post–lumbar puncture headaches.[1]

TABLE 175-1 Contraindications to Lumbar Puncture

- Skin infection near the site of lumbar puncture
- CNS lesion causing increased intracranial pressure, or spinal mass
- Platelet count <20,000 mm^3 is an absolute contraindication; platelet counts >50,000 mm^3 are safe for lumbar puncture*
- International normalized ratio ≥1.5*
- Administration of unfiltrated heparin or low-molecular-weight heparin in past 24 h*
- Hemophilia, von Willebrand's disease, other coagulopathies*
- Trauma to lumbar vertebrae

*Correct clotting factor and/or platelet levels before lumbar puncture.

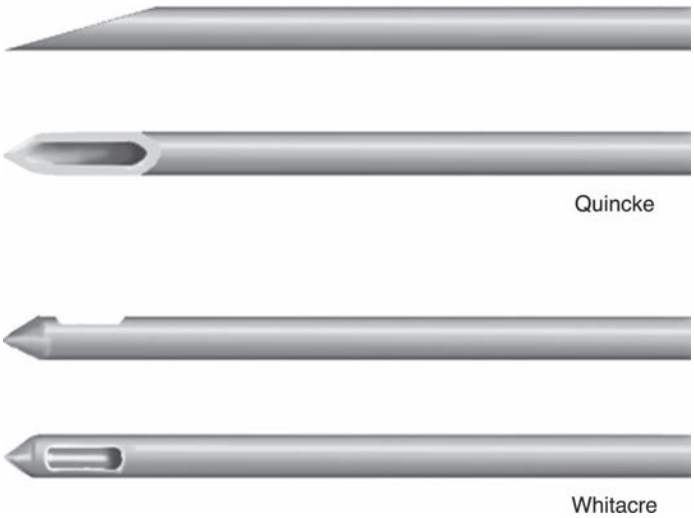

FIGURE 175-1. Two types of needle for lumbar puncture. The Quincke is a bevel-type needle, and the Whitacre is a pencil-point needle.

TECHNIQUE

Assemble all equipment. Then properly position the patient and identify the patient's L4-L5 interspace. Now put on sterile gown, mask, and gloves. Next, apply povidone-iodine to the area and let it dry. Apply sterile drapes. Anesthetize the skin with 1% lidocaine by raising a skin bleb, then directing the needle toward the umbilicus, and injecting the anesthetic in a fan-shaped area around the proposed lumbar puncture site. Make sure to pull back on the plunger to check for blood return before injecting to avoid intravascular injection. Recheck the patient's position, making sure the patient is perpendicular to the horizontal and not slanted. Check the needle and make sure that it is the correct size and that the stylet is easily removed and reinserted. Identify that the needle bevel (Quincke needle) or notch (Whitacre needle) is facing the ceiling. Put together the manometer, making sure you know how the stopcocks work. Assuming you are right-handed, identify the interspinous space with your left hand and position the needle at the L4-L5 interspace, parallel to the horizontal, and direct it firmly and slowly toward the patient's umbilicus. As the needle advances, you may feel a slight "pop," indicating that you have pierced the ligamentum flavum and dura mater. Remove the stylet, note draining cerebrospinal fluid (CSF), and attach the manometer to measure the opening pressure. After collecting at least 1 mL in each of four tubes, disconnect the manometer and replace the stylet before withdrawing the spinal needle (**Figure 175-2**). Do not aspirate because slight negative pressure may facilitate herniation.[1] (See Videos: Lumbar Puncture Decubitus Position; Lumbar Puncture with Ultrasound; and Lumbar Puncture Sitting Position.)

If unable to penetrate the subarachnoid space, it is best to withdraw the needle completely out of the skin, and direct the needle again. In some patients (e.g., those who are extremely obese, have scoliosis, or have degenerative disease of the spine), it is particularly difficult to successfully perform a lumbar puncture.

US imaging of the interspinous processes is superior to palpation with regard to fewer failed attempts.[3] A 5- to 10-MHz linear probe is applied in the sagittal plane to identify the dorsal spinous processes, and the midline is then marked with a sterile marking pen. Lumbar puncture is then performed as outlined above. If attempts fail, consultation for lumbar puncture with fluoroscopic guidance may be necessary.

Measure the opening pressure with the patient lying extended on his or her side. Pressures measured with the patient still curled in extreme flexion or sitting may be artificially elevated. Normal pressure

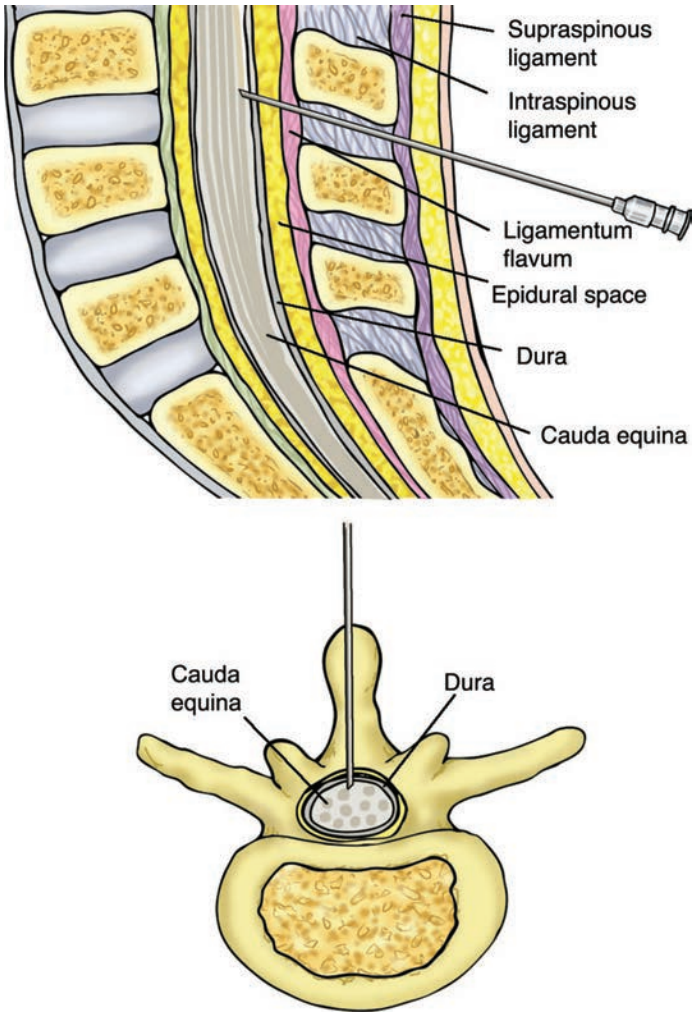

FIGURE 175-2. Anatomy of the lumbar spinal interspaces for lumbar puncture.

is <170 mm H_2O. Careful repositioning (straightening the curled patient or helping the seated patient to a lying position on his or her side) can be safely performed with the needle in place. Obtain accurate pressure readings only when the patient is in a calm state if possible. Shouting, crying, or coughing can elevate the pressure falsely.[1]

Obtain four tubes, each containing at least 1 mL of CSF. Obtain red and white blood cell counts with differential for tubes 1 and 4. Tube 4 may also be used for culture and Gram staining. Tube 2 is sent for determination of protein and glucose levels. Save tube 3 for other studies that may be required. **Table 175-2** lists normal CSF findings. See Chapters 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage," and 174, "Central Nervous System and Spinal Infections," for further discussion of CSF interpretation.

TABLE 175-2 Normal Cerebrospinal Fluid Values

Parameter	Value
Opening pressure	50–170 mm H_2O
Appearance	Clear (can be clear with up to 400 cells/mm^3)
Xanthochromia	None
Red blood cells	≤5/mm^3
WBCs	≤5/mm^3 (no polymorphonuclear leukocytes)
Glucose level	>40 milligrams/dL or 60%–70% of serum glucose level
Protein level	<50 milligrams/dL
Gram stain and culture results	Negative

COMPLICATIONS OF LUMBAR PUNCTURE

Local discomfort is to be expected; radicular pain indicates that the needle is too lateral, which necessitates repositioning. Spinal hematoma is a particularly ominous complication. The development of severe or persistent back pain after the procedure, radicular pain, new neurologic symptoms, or sphincter disturbance indicates that a spinal hematoma may be present. Most present within the first 6 hours.[1] Management includes MRI of the spine and neurosurgical consultation.

In emergent situations, it may be necessary to proceed with lumbar puncture even in patients who are anticoagulated with one or more medications. Assess platelet counts and review anticoagulation history. The decision process should take into account the risk of bleeding, thrombosis if anticoagulants are reversed, the benefit of lumbar puncture, and any alternative strategies. Antiplatelet drugs, such as aspirin and clopidogrel, offer such a low added risk to an emergent procedure that it is recommended to proceed without delay.[4,5] IV heparin has a short half-life, thus allowing for discontinuation for 4 hours prior to the procedure.[5] Warfarin may be reversed if the risk of thrombosis from reversal is low, to an international normalized ratio of less than 1.5.[5] The novel oral anticoagulants have not been studied well in this scenario, but carefully consider risks and benefits before proceeding.

Post–lumbar puncture headache is the most common complication of lumbar puncture. The cause is thought to be continuous CSF leakage from the dural puncture site. Traction on bridging vessels, dura, and nerves causes headache. Post–lumbar puncture headache usually begins 24 to 48 hours after the procedure and is located in the frontal or occipital area. It is pressure-like and throbbing, with variable intensity. It is intensified when the patient is sitting or standing upright and with Valsalva maneuvers such as coughing. The headache improves or resolves when the patient is supine. It can be associated with nausea, vomiting, and even vertigo and tinnitus. Risk factors for post–lumbar puncture headache include use of a large needle size (>22 gauge), use of a cutting (Quincke) needle, multiple attempts, and failure to replace the stylet when withdrawing the needle.[1,2] Post–lumbar puncture headache does not seem to be related to the opening pressure, the volume of CSF removed, or bed rest after the procedure. Postprocedural bed rest does not prevent this complication.[6] Diagnosis is clinical. Most headaches resolve with rest in the supine position, maintenance of hydration, and administration of antiemetics and analgesics.[1] IV caffeine (500 milligrams IV of caffeine sodium benzoate) is commonly administered, but whether or not it improves headache is controversial.[7] Persistent headache (>24 hours) can be treated with an epidural blood patch. In this procedure, usually performed by an anesthesiologist, a needle is introduced into the epidural space, and 20 to 30 mL of the patient's blood is injected into the epidural space.

CEREBROSPINAL FLUID SHUNTS

Mechanical shunting is the primary treatment for hydrocephalus. Placement of a CSF shunt is the most common pediatric neurosurgical procedure performed in the United States (**Figure 175-3**). It is also the neurosurgical procedure with the highest incidence of postoperative complications.[8] Many types of CSF shunt systems exist. Most systems consist of three components, beginning with a silastic tube passed into the ventricle via a burr hole. This tubing is tunneled subcutaneously to a valve chamber. The valve chamber, the second component, establishes a pressure gradient that ensures drainage of fluid away from the ventricle. The valve chamber, or in some cases a separate reservoir, allows access to the shunt system for patency testing, pressure measurement, CSF sampling, medication injection (e.g., chemotherapy, antibiotics), or contrast administration. Distal tubing, which is the third component, connects the valve chamber to a drainage point. The most common drainage site is the peritoneal cavity. Other drainage sites include the right atrium, gallbladder, pleural cavity, and ureter.

Programmable shunt valves allow for easier control of flow rates, which is particularly useful in previously difficult cases that required frequent adjustments. The valve can be adjusted and tested using a locator and indicator tool to determine the pressure programmed into the valve. An adjustment tool can then be used to increase or decrease the valve's

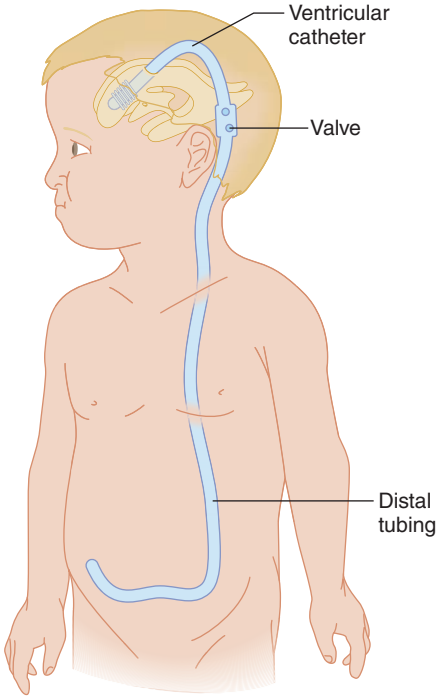

FIGURE 175-3. Ventriculoperitoneal shunt system.

pressure or performance as needed. Typical nonadjustable pressure-type valves are available with low, medium, and high settings. These valves open at a pressure gradient of 2 to 4, 4 to 6, and 8 to 10 cm H_2O for the low, medium, and high settings, respectively. The adjustable valves typically have five preset pressure settings that can be selected or adjusted as clinically warranted. The patient (or family) should have been given a card that documents initial settings and any subsequent adjustments. Pressure setting can also be confirmed by radiography using the radiopaque dials on the valve.

Exposure to strong magnetic fields and some MRI units can change the valve pressure setting, so all patients should have the setting verified after any exposure to strong magnetic fields. Controversy still exists as to whether programmable valves offer an advantage over traditional valves in reducing the number of revisions and extending shunt life.[9-11]

CSF SHUNT MALFUNCTION

Shunt malfunctions are the most common complications encountered with CSF shunts. Shunt malfunction can be due to obstruction, mechanical failure, overdrainage, loculation of ventricles, or abdominal complications.

Obstruction Obstruction is the most common type of shunt malfunction. The most frequent location of obstruction is the proximal tubing, followed by the distal tubing, and then the valve chamber. Proximal obstructions usually occur within the first years after shunt insertion. **Table 175-3** lists the common causes of CSF shunt obstruction.

Distal obstruction is the most frequently encountered obstruction in shunts in place for >2 years.[8] **Shunt obstruction usually manifests with signs and symptoms of increased intracranial pressure.** Infants generally present with vomiting, irritability, and a bulging fontanelle.[12] Older children and adults may present with cephalgia, nausea, vomiting, lethargy, ataxia, and cranial nerve palsies.[12]

Mechanical Failure Mechanical failure of shunts can be secondary to fracture, disconnection, migration, or misplacement. Typically, fractures appear in distal tubing many years after shunt placement; this is due to both degradation of tubing and stress from the growth of the patient.[8] The most common location for a fracture is along the clavicle or lower ribs.[13] Patients present with mild symptoms of increased intracranial

TABLE 175-3 Causes of CSF Shunt Obstruction

Proximal obstruction
- Tissue debris
- Choroid plexus
- Clot
- Infection
- Catheter tip migration
- Localized immune response to the tubing

Distal obstruction
- Kinking or disconnection of the tube
- Pseudocyst formation
- Infection

pressure. Local symptoms of pain, mild erythema, and edema over the affected area are not uncommon. In fact, it not unusual for a fracture to be found incidentally because the shunt tract often serves as a conduit between the fractured segments.[8] Disconnection often occurs shortly after insertion and manifests as increased intracranial pressure and fluid at the skin site around the disconnection. Migration occurs when a properly placed catheter migrates to a position in which drainage is compromised partially or completely. Misplacement entails the placement of the catheter into brain parenchyma, the choroid plexus, or the temporal horns; it usually manifests postoperatively with evidence of failure.

Overdrainage Overdrainage and the slit ventricle syndrome are seen in approximately 10% of patients with shunts.[8] Because of overdrainage, the tissues actually occlude the orifices of the proximal shunt apparatus. As intracranial pressure increases, the same occluding tissue is disengaged, which allows drainage to resume. This phenomenon is cyclical and is responsible for the episodic or waxing and waning aspect of the presenting complaint. Patients present with episodes of elevated intracranial pressure caused by a transient obstruction of the ventricular catheter from a collapsed ventricle. Decreased cerebral compliance may prevent the ventricles from fully expanding as intracranial pressure and volume increase, which further contributes to ventricular collapse. Antisiphon devices, antigravitational valves, and programmable shunt valves are devices used to reduce overdrainage; more recently, lumboperitoneal shunts have shown promise in reducing the rate of this complication.[8,14]

Loculation Separate, noncommunicating CSF accumulations may develop within a ventricle so that the shunt device is not able to drain the entire ventricular system, leaving behind enlarging pockets of fluid that may have compressive sequelae. Trapped fourth ventricle syndrome occurs when the fourth ventricle becomes loculated, presumably from closure of the sylvian aqueduct.[11] Patients present with typical symptoms of increased intracranial pressure as well as symptoms of brainstem compression, including poor feeding, disconjugate gaze, and difficulty swallowing.

Abdominal Complications Several abdominal processes can secondarily result in shunt malfunction. Any increase in abdominal pressures, even when caused by constipation, can increase effective resistance to CSF flow.[8] The most commonly encountered serious complication is malfunction due to pseudocyst formation. Pseudocysts are localized abdominal fluid collections that form around the peritoneal catheter. Infection is the major cause.[8] They often are asymptomatic until they enlarge substantially enough to cause abdominal pain.

CLINICAL PRESENTATION

Symptoms of CSF shunt malfunction usually develop over several days, although rapid deterioration within 24 hours has been reported. **Clinical features include mental status changes, headache, nausea, vomiting, abdominal pain, lethargy, decreased intellectual performance, ataxia, coma, and autonomic instability.** Often, the presenting complaint is vague. No single sign or symptom is accurate in predicting shunt

malfunction, although a decrease in level of consciousness may have the highest correlation with shunt malfunction.[13] As intracranial pressure increases, paralysis of upward gaze, dilated pupils, and papilledema may develop. Paralysis of upward gaze (or sundowning) is caused by impingement on the brainstem by the third ventricle as it engorges. Symptoms of slit ventricle syndrome are exacerbated or precipitated when the patient stands or exercises due to excessive CSF drainage and are relieved when the patient lies down or is in the Trendelenburg position.

SHUNT EVALUATION

Identification of shunt type is important, although frequently difficult. Many different types exist, and appropriate assessment depends on the apparatus implanted. For example, many flow control valves have a high set resistance so that flow is quite slow but steady. Conversely, such a flow pattern might indicate obstruction in a low-resistance shunt. Evaluate shunt function by manual testing and radiologic studies. Palpation of the shunt allows the physician to locate the valve chamber. Shunt patency is evaluated somewhat differently for each type of device depending on features such as the presence of valves or dome- or cylinder-shaped reservoirs. Generally, testing follows intuitive expectations but still may prove perplexing to inexperienced clinicians. For a simple device, once the chamber is located, it is gently compressed and observed for refill. **Difficulty compressing the chamber indicates distal flow obstruction, whereas slow refill, defined as refill requiring >3 seconds after compression, generally indicates a proximal obstruction.** Compression is inaccurate for identifying shunt obstruction because up to 40% of obstructed shunts show normal refill during manual palpation.[14] Furthermore, positive predictive value has been found to be as low as 12% for shunt pumping.[15] In any case, further evaluation is required.

A **shunt series** of plain radiographs includes anteroposterior and lateral radiographs of the skull and an anteroposterior view of the chest and abdomen (for ventriculoperitoneal shunts). Although plain radiography will identify kinking, migration, or disconnection of the shunt system, CT is required to evaluate ventricular size (**Figures 175-4** and **175-5**).

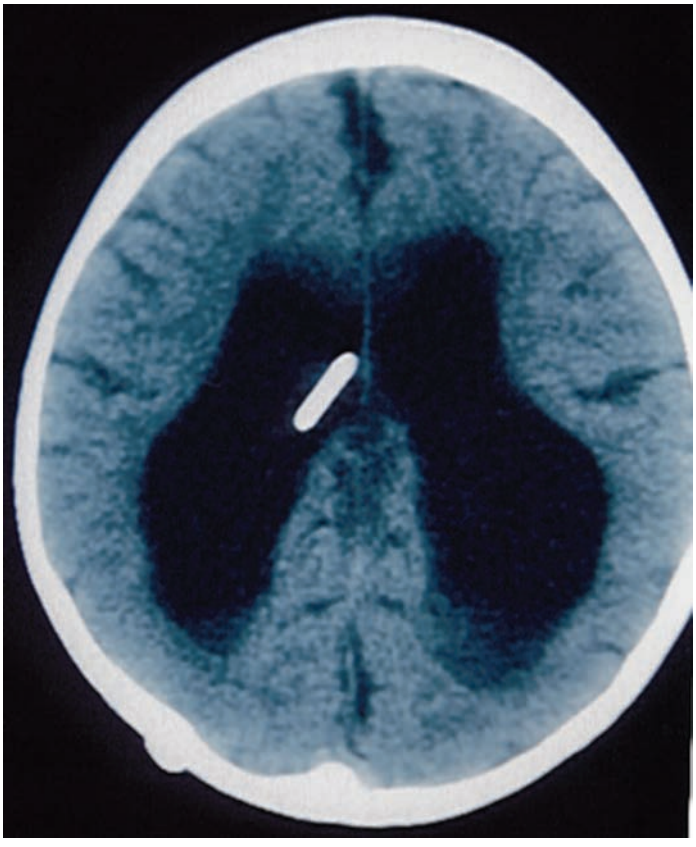

FIGURE 175-4. CT may reveal a persistent hydrocephalus despite the presence of a shunt, which suggests a malfunction. Comparison CTs are helpful when available.



FIGURE 175-5. Slit ventricle syndrome often presents with waxing and waning symptoms. The CT is often helpful in distinguishing it from other causes of malfunction.

Compare with previous CT scans because many patients with shunts have an abnormal baseline ventricular size. In one series using either CT or both CT and plain radiography, 24% of patients with documented shunt malfunction showed no radiologic evidence of the malfunction.[16] Between 9% and 15% of pediatric patients will have profound alterations in brain compliance leaving ventricular size unchanged even in profound shunt failure with high intracranial pressures.[8] Therefore, in patients with suggestive clinical features, unremarkable findings on CT and/or radiographic shunt series cannot be relied on to exclude shunt obstruction. Thus, **obtain neurosurgical consultation whenever shunt malfunction is suspected**.

Perform a shunt tap to make the diagnosis of shunt malfunction, exclude infection, or alleviate life-threatening increased intracranial pressure. (See Video: Ventriculoperitoneal Shunt Aspiration.) Unless a CNS emergency exists, the shunt tap should be performed by a neurosurgeon to avoid damage to the valve apparatus. Emergency physicians should be prepared to perform a shunt tap if a neurosurgeon is unavailable or if a shunt tap is needed to control life-threatening increased intracranial pressure.

To perform a shunt tap, locate and sterilely prepare the site over the valve system or reservoir of the shaved scalp. A 23-gauge needle or butterfly attached to a manometer is inserted into the reservoir. If no fluid returns or flow ceases, a proximal obstruction is likely. Measure the opening pressure while the reservoir outflow is occluded. An opening pressure of ≥20 cm H_2O indicates a distal obstruction, whereas low pressures indicate a proximal obstruction. The normal basal intracranial pressure is 12 ± 2 cm H_2O.

Flash MRI has assumed a growing role in serial examination for shunt function to obviate some of the radiation exposure associated with CT. In certain institutions, single-shot T2-weighted MRI has become the initial imaging modality of choice. With the advent and widespread use of programmable shunts, the concern over shunt failure after MRI exists. The MRI magnetic field can change the valve-pressure setting in programmable valves. Newer programmable valves do not reprogram even at a 3-T magnetic field.[11] In general, the settings of a programmable valve should be checked by the neurosurgeon after a patient undergoes MRI.

TREATMENT OF SHUNT MALFUNCTION

Surgical intervention is generally required in cases of shunt obstruction. As a temporizing measure, intracranial pressure can be lowered by standard methods of hyperventilation and osmotic diuresis (mannitol). **If these measures fail and surgical intervention is not immediately available, intracranial pressure can be lowered by removing CSF via the reservoir if the malfunction is distal.** To prevent choroid plexus bleeding, remove CSF slowly, and discontinue the process when intracranial pressure reaches 10 to 20 cm H_2O. Stable patients in whom obstruction is suspected require admission and neurosurgical consultation. Observe patients for any neurologic changes, abdominal complaints, or fever.

SHUNT INFECTION

Infection rates range between 3% and 20% per procedure.[17-19] The highest infection rates are found in the very young and old, and in patients who have had multiple shunt revisions. There is a 12% to 26% recurrence rate of shunt infection.[17] Patients who develop shunt infections demonstrate impairment in intellectual development compared with those who do not develop infection. Half of all shunt infections present within the first 2 weeks of placement, 70% present within 2 months, and 80% present within 6 months of placement. Up to 10% of shunt infections present >1 year after surgery.

CSF shunt infections can be categorized into internal and external infections. External infections involve the subcutaneous tract around the shunt, which on exam is usually tender, and there is often an associated fluid collection within the skin. An internal infection involves the shunt and the CSF contained within that shunt. Patients with CSF shunts have a higher risk of developing meningitis from typical pathogens than the general population. This increased risk may be due to disruption of the blood–brain barrier by foreign material. Shunt infections may be reduced with the use of antibiotic-impregnated catheters.[20]

The mortality is low if shunt infection is diagnosed and treated in a timely fashion. However, if ventriculitis develops, mortality is high, underscoring the need for prompt diagnosis and aggressive management.

BACTERIOLOGY

CSF shunt infections are typically caused by low-virulence organisms. In adults, the most commonly cultured agent is *Staphylococcus epidermidis*, which accounts for nearly half of all shunt infections, followed by *Staphylococcus aureus* and *Propionibacterium acnes*.[21,22] The only change in the microbiology of shunt infections over the past decade has been the emergence of methicillin-resistant strains of *Staphylococcus*.[18] Gram-negative, anaerobic, and mixed infections account for approximately 5% to 10% of shunt infections. Gram-negative infections are associated with the highest mortality. *Candida* accounts for a small number of infections and should be considered in premature newborns, immunosuppressed patients, and patients on long-term, broad-spectrum antibiotics. It is associated with a 5.8% mortality rate.[21]

CLINICAL FEATURES

The clinical presentation varies with the virulence of the organism and the severity of the infection. Typically, patients present with symptoms of obstruction and meningeal symptoms, including mental status changes, headache, nausea, vomiting, neck stiffness, and irritability. Fever and abdominal pain may also be present. These signs are not universally noted. In fact, the finding of fever is highly variable, and meningismus may be present in only one third of patients with shunt infection. Abdominal pain may be the predominant symptom in patients with ventriculoperitoneal shunts. Swelling, erythema, and tenderness along the site of the shunt tubing are highly suggestive of external shunt infection.[15]

Shunt nephritis is a chronic complication of vascular shunts. Typically, patients develop a chronic bacteremia from coagulase-negative *Staphylococcus* leading to an immune response. The patient presents with a nephritic syndrome with fever episodes and increased urinary sediment. It is most commonly seen with ventriculoatrial shunts. Treatment of the underlying infection leads to complete resolution of the renal disorder.[8]

DIAGNOSIS

A shunt tap is required to exclude CSF shunt infection. **A traditional lumbar puncture often misses CSF shunt infection** and has no meaningful role in the evaluation when shunt infection is suspected.

Analysis of fluid from infected CSF shunts usually reveals an elevated leukocyte count, elevated protein level, and normal glucose level. Almost one fifth of patients evaluated for shunt malfunction have positive CSF culture results despite normal results on CSF analysis. Other (non-CSF) laboratory values are rarely helpful in diagnosing CSF shunt infection. CT and plain radiographs of the shunt (shunt series) are required to exclude mechanical shunt malfunction, which often coexists with shunt infection.[22] Abdominal US or CT is indicated if an abdominal fluid collection, pseudocyst, or abscess is suspected. In patients with ventriculoatrial shunts, blood cultures are helpful in identifying the offending organism. In most other cases, hematogenous dissemination of infection is rare, thus rendering blood cultures of limited value.[19]

TREATMENT

Patients with CSF shunt infection or suspected shunt infection require emergent neurosurgical consultation and admission. Until the infecting agent is identified, therapy with broad-spectrum antibiotics effective against typical pathogens (e.g., ceftriaxone and vancomycin) is recommended. Rifampin has been given along with vancomycin for treatment of recurrent gram-positive infections because it easily penetrates the CSF. Early removal of the colonized device is important.

HALO DEVICES

The halo vest provides one of the most rigid types of cervical immobilization available. The halo vest consists of a lightweight radiolucent ring attached to a lightweight adjustable vest. Current vests allow adjustment of the cervical spine in multiple planes. Titanium pins that do not interfere with MRI are stronger, lighter, and more expensive than older stainless steel pins. Pins are usually tightened to 8 lb of pressure (**Figure 175-6**).[23,24]

Halo devices are indicated for stabilization of an unstable cervical spine, including stabilization of fractures, dislocations, and subluxations, and alignment of severe kyphotic and scoliotic spines.

COMPLICATIONS

Pin loosening is the most common complication encountered in the ED.[23,24] Obtain neurosurgical consultation and exclude infection of the pin site. **If pin loosening has caused movement of the halo device, assume that the cervical spine is unstable, immobilize the cervical spine using an alternative technique, and obtain radiographs to assess for proper alignment.** Tangential plain radiography, CT, or MRI can be used to exclude penetration of a pin through the inner table of the skull. Pin-site infection is the second most frequently encountered complication. It occurs in approximately 10% to 20% of patients with halo devices.[24] Nearly 50% of infections occur in the first 4 weeks after halo placement, and 60% involve the anterior pins. Careful examination is required to differentiate a localized pin-site infection from less common, more serious infections (<1% of cases), such as cellulitis, osteomyelitis, and abscess formation.[24] Consider these more serious infections if there is persistent pain, continued drainage despite antibiotic therapy, clear drainage, or a history of a fall. Patients with cellulitis often present with fever and systemic signs and symptoms of infection. Patients with osteomyelitis usually have a prolonged infection, pin-site loosening, and radiologic abnormalities. Patients who develop an abscess usually have neurologic changes and evidence of intertable penetration (CSF leak, trauma).



FIGURE 175-6. Demonstration of halo device application by emergency medical technicians at a high school assembly. [Reproduced with permission from North Carolina SAFETeens, Inc.]

Local pin-site infections are commonly managed with local wound care. The skin around the pin site must be pulled away to allow thorough cleaning of the skin beneath the pin and the skin–pin interface with soap and water four times a day. Obtain culture specimens from the wound site and administer antibiotics effective against skin pathogens (e.g., *Staphylococcus* and *Streptococcus* species). If local infection does not respond to treatment or if cellulitis, osteomyelitis, or abscess is suspected, obtain neurosurgical consultation for admission, IV antibiotics, and possible surgical intervention.

Pin-site discomfort occurs in up to 20% of patients.[23,24] It is most commonly a result of local inflammation. However, consider infection (localized or systemic) in each case. Sensory and motor deficits or paresthesias indicate nerve damage or pressure, whereas painful mastication indicates temporalis muscle inflammation, which often indicates too lateral a placement of pins. If infection is excluded, a short course of analgesics is recommended. Neurosurgical consultation is required if pain continues or a serious complication is suspected.

Ring migration or loss of immobilization occurs in 10% to 13% of patients. Suspect loss of immobilization in patients complaining of neck pain and change in fit or position of the ring or vest. Immediately immobilize the cervical spine using an alternative technique (e.g., hard collar plus backboard) and obtain radiographs to assess for changes in alignment. Obtain neurosurgical consultation for reapplication of the halo device.

Skin breakdown and pressure sores occur in 11% to 30% of patients. If either is present, inspect the vest for adequate padding and strap position. Urgent referral to a neurosurgeon for refitting may be required.

Dysphagia occurs in 1% to 2% of patients with halo devices.[23-25] Immobilization that holds the head in exaggerated extension is the usual cause of the dysphagia. Halo adjustment will remedy this problem. Alternatively, dysphagia can occur following anterior displacement of a bone graft. This diagnosis can be made by plain radiography or a swallowing study, and emergency surgical intervention is required.

Dural punctures occur in 1% to 2% of patients and are a result of halo system trauma.[23-25] This is rarely attributable to postapplication trauma because newer pin tighteners are designed to fail when torque exceeds 8 lb. Symptoms include headache, malaise, or visual changes. Physical examination may reveal a CSF leak or evidence of skull fracture. All patients with dural punctures require admission and neurosurgical consultation. Treatment includes elevation of the head, IV antibiotics, and pin removal.

In rare cases, CPR is required in patients with halo devices. To perform chest compressions, remove the anterior portion of the vest. Instructions for removing the halo vest are printed on the front of most vests. Intubation is performed with the halo in place. Emergent or semi-emergent intubation was required 13% of the time in one series.[25] If orotracheal intubation is unsuccessful, other airway management options include nasotracheal intubation, laryngeal mask airway, and cricothyrotomy.

SPECIAL POPULATIONS

Use of halo devices carries a special risk in the elderly patient. A mortality rate of 21% is reported in patients >79 years of age.[25] Rates of serious complications, such as respiratory depression (8% of cases) and dysphagia (11% of cases), are much higher in elderly patients.[25]

OTHER CENTRAL NERVOUS SYSTEM DEVICES

INTRATHECAL BACLOFEN INFUSION DEVICES

Generalized dystonia occurs in 15% to 25% of patients with cerebral palsy. Baclofen, a γ-aminobutyric acid agonist that acts at the level of the spinal cord by impeding the release of excitatory neurotransmitters, decreases spasticity. Oral baclofen offers patients only mild relief because of its inability to cross the blood–brain barrier and its poor lipid solubility. Intrathecal administration (**Figure 175-7**) is more effective, requires lower dosages, and leads to higher CSF levels. Intrathecal baclofen reduces spasticity and improves gait, sitting ability, and upper extremity function in most patients.[26] Intrathecal baclofen pumps are also used to treat spasticity related to spinal cord injury, multiple sclerosis, brain injury, cerebrovascular accidents, and perinatal infection sequelae.[26,27] Complications observed in patients receiving continuous intrathecal baclofen can be divided into medication-related, mechanical, and infection-related complications and are listed in **Table 175-4**.

When a complication occurs disrupting the administration of baclofen, withdrawal symptoms can be severe and life threatening, including extreme hypertonicity and spasms that may lead to rhabdomyolysis. The apparent accelerated spasticity should signal to the provider that a potential complication has arisen. Oral baclofen, dantrolene, and oral or parenteral benzodiazepines may be used to alleviate these symptoms. Infectious complications occur more frequently in children, revised pumps, and those placed subcutaneously.[27,28] Infection rate is 10%, with most infections presenting during the first month after placement.[27] Most infections are caused by *Staphylococcus* species, with a recent increase in methicillin-resistant *S. aureus*.[27] Serious infections and meningitis may arise even without local symptoms. The majority of infections require neurosurgical consultation and IV/intrathecal

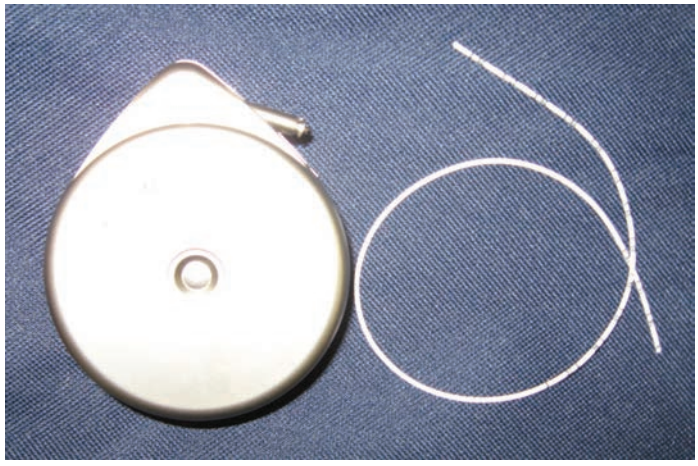

FIGURE 175-7. Typical baclofen pump.

TABLE 175-4 Complications of Intrathecal Baclofen Infusion

Medication related
- Hypotension
- Bradycardia
- Apnea
- Oversedation
- Respiratory depression

Mechanical
- Pump pocket effusions
- Pump failure
- Catheter extrusion
- Catheter dislodgement

Infection
- Local infection
- Meningitis
- Cerebrospinal fluid fistula formation

antibiotics. Direct concerns about baclofen pumps to the neurosurgeon, or other specialists who are expert in programming the pump.

IMPLANTABLE CENTRAL NERVOUS SYSTEM STIMULATORS

The pathogenesis of Parkinson's disease is thought to involve unregulated activity of the subthalamic nucleus and globus pallidus interna. High-frequency stimulation with implantable CNS devices is being used for suppression of parkinsonian and essential tremors. Neurostimulation is typically used if drug therapy has failed to control tremors. Neurostimulation is as efficient at controlling tremors as classic thalamotomy but is less invasive. Deep brain stimulation studies have shown a 40% to 75% improvement in motor scores as well as improvement of rigidity, bradykinesia, and postural instability.[29] Reported complication rates range from 7% to 65%, with a decline in the number of reported complications as physician experience increases.[29] Infection rates approach 3% to 10%.[29] Patients may present to the ED with varied complaints, including problems related to the subcutaneous pulse generator, temporary or permanent paresthesias, dysarthria, disequilibrium, or failure of the neurostimulator to suppress tremors. Neurosurgical consultation is needed because these complaints may represent lead displacement or migration requiring surgical correction or replacement. If the diagnosis remains uncertain, observation with the stimulator in the off position may be required to help differentiate mechanical failure from an acute neurologic deficit.[29]

SPINAL CORD STIMULATION

Spinal cord stimulation is an established modality for treating chronic back pain, multiple sclerosis pain, complex regional pain syndromes, phantom pain, diabetic neuropathy, postherpetic neuralgia, angina pectoris, intractable pain associated with some malignancies, and the pain syndromes associated with vascular disease. Multicontact electrodes are placed in the epidural space, and the distal end of the electrode is connected to an internalized pulse generator. The therapeutic response is thought to be a result of stimulation of one of several dorsal tracts as well as activating the release of inhibitory neurotransmitters.[30,31] Complications include dural puncture, spinal cord compression, CSF leak, hemorrhage, infection, abscess, epidural fibrosis, migration, interruption of wires, corrosion of contacts, and battery failure. The most frequent complication is device failure, accounting for 17% to 25% of complications.[32] The rate of infection is reported between 2.5% and 5%.[31] Patients with these devices should not undergo MRI.

PERIPHERAL NERVE STIMULATION

Peripheral nerve stimulators are used to treat neuropathic pain disorders in patients with chronic intractable pain such as with occipital neuralgia. The device is similar to other stimulators except that the electrodes are placed in the subcutaneous tissue overlying the peripheral nerves. Case reports of interference of stimulators causing pauses in cardiac pacemakers exist and thus must be considered in patients with both a pacemaker and stimulator and a new conduction abnormality.[33]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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CHAPTER 176

General Management of Poisoned Patients

Shaun Greene

INTRODUCTION

Poisoning is a worldwide problem that consumes substantial healthcare resources and causes many premature deaths. The burden of serious poisoning is carried by the developing world[1,2]; however, poisoning-related morbidity and mortality are also a significant public health concern in the developed world.[3-7]

Unintentional poisoning deaths in the United States are increasing, especially as a result of prescription analgesics. This increase has been ascribed to increasing prescription rates and aging of the baby-boom population.[8-10] Prevention is the key to reducing unintentional poisoning deaths. Pharmacists can ensure that medications are labeled correctly, anticipate potential drug interactions, and educate patients to use medications safely. Parents have the responsibility to ensure that poisons are placed in childproof, labeled containers stored in adult-only accessible nonfood storage areas to reduce pediatric exposures. Teachers and healthcare providers can provide age-appropriate education to children about the dangers of poisons. After an exposure, poison control centers staffed by highly trained individuals can provide customized advice to healthcare providers and the public. Poison control centers also participate in prevention, education, and toxicosurveillance activities.

Exposures occur most commonly by ingestion; other routes include inhalation, insufflation, cutaneous and mucous membrane exposure, and injection.[10] Some exposures have minimal risk. The criteria used to determine whether the exposure is nontoxic are as follows: (1) an unintentional exposure to a clearly identified single substance, (2) an estimate of the dose is known, and (3) a recognized information source (e.g., a poison control center) confirms the substance as nontoxic in the reported dose. Asymptomatic patients with nontoxic exposures may be discharged after a short period of observation, providing they have access to further consultation and a safe discharge destination.

Serious clinical effects occur in <5% of acutely poisoned patients presenting to developed-world hospitals, and in-hospital mortality rates are <1%.[10]

RESUSCITATION

Resuscitation is the first priority in any poisoned patient. After resuscitation, a structured risk assessment is used to identify patients who may benefit from an antidote, decontamination, or enhanced elimination techniques. Most patients only require provision of good supportive care during a period of observation in an appropriate environment.

Treatment of cardiac arrest in poisoned patients follows Advanced Cardiac Life Support guidelines with the addition of interventions potentially beneficial in toxin-induced cardiac arrest (**Table 176-1**).[11] Prolonged resuscitation is generally indicated, as patients are often young with minimal preexisting organ dysfunction. Utilization of extracorporeal cardiac and respiratory assist devices until organ toxicity resolves may be lifesaving.

Stabilization of airway, breathing, and circulation represents initial priorities. Compromised airway patency or reduced respiratory drive may lead to inadequate ventilation; provision of a mechanical airway and assisted ventilation is vital in these circumstances. IV crystalloid bolus (10 to 20 mL/kg) is first-line treatment of hypotension. Since most patients without toxin-induced fluid loss are generally not fluid depleted, avoid administration of excess fluid. Persisting hypotension despite an adequate volume infusion may respond to a specific antidote. Otherwise, cautious administration of an inotropic agent is indicated. Inotrope choice is guided by knowledge of the toxin's toxicodynamic properties and assessment of circulatory status (e.g., cardiac pump failure vs. vasodilatory shock). Extracorporeal membrane oxygenation should be considered for cases of cardiovascular failure refractory to other treatment modalities.[12]

ANTIDOTES

Stabilization of airway, breathing, and circulation allows further assessment of blood glucose concentration, temperature, and conscious state. Although the proper use of antidotes (**Table 176-2**) is important, only a few are indicated before cardiopulmonary stabilization (e.g., naloxone for opiate toxicity, cyanide antidotes for cyanide toxicity, and atropine for organophosphate poisoning).

HYPOGLYCEMIA

Treat hypoglycemia with IV dextrose (glucose). Patients at risk of Wernicke's encephalopathy also require thiamine, but do not require that it be administered before the dextrose.[13] Altered mental status when hypoglycemia cannot be excluded is an indication for IV dextrose. Supplemental oxygen, thiamine, glucose, and naloxone are often administered empirically as a cocktail in cases of altered mental status. Although relatively safe and affordable in the developed world, this approach may not be cost effective in developing countries. The decision to administer an antidote should be made after a rapid collateral history is obtained and targeted examination completed. Altered mental status not responding to an antidote or not consistent with exposure history requires further investigation. Metabolic, infective, and surgical (e.g., intracranial injury) causes of altered mental status should be considered.

CARDIAC ARRHYTHMIAS

In general, antidysrhythmic drugs are not first-line treatment for toxin-induced dysrhythmias, as most antidysrhythmic drugs have prodysrhythmic and negative inotropic properties. Most toxin-induced dysrhythmias respond to correction of hypoxia, metabolic/acid-base abnormalities, and administration of an antidote (e.g., digoxin Fab). Sodium bicarbonate is administered for sodium channel–blocker toxicity with cardiovascular complications, such as wide QRS complex tachydysrhythmias. Ventricular tachydysrhythmias may respond to overdrive pacing.

SEIZURES

Drug-induced seizures are treated with titrated doses of IV benzodiazepines, with the exception that isoniazid-induced seizures require pyridoxine. Metabolic disorders, such as hypoglycemia and hyponatremia, can also produce seizures and should be rapidly excluded. Propofol and barbiturates are second-line agents for benzodiazepine-resistant seizures (once isoniazid-induced seizures are excluded).[14] A small study provided evidence for the safety of levetiracetam for treatment of toxin-induced

TABLE 176-1 Potential Interventions in Toxin-Induced Cardiac Arrest[11]

Toxin or Toxin/Drug Class	Intervention
Toxins with a specific antidote (examples)	Antidote
Digoxin	Digoxin Fab
Organophosphates	Atropine
Envenomation	Antivenom
Sodium channel blocker or wide-complex tachycardia	Sodium bicarbonate
Calcium channel blocker or beta-blocker	High-dose insulin infusion
Local anesthetic agents Lipophilic cardiotoxins	IV lipid emulsion
Other Therapies to Consider	
Cardiac pacing Intra-aortic balloon pump Extracorporeal membrane oxygenation	

seizures; however, larger studies are required to evaluate efficacy.[15] **There is no role for phenytoin in the treatment of toxin-induced seizures; it has neither theoretical nor proven efficacy, and it may worsen toxicity.**[16]

AGITATION

Agitation is treated with titrated doses of benzodiazepines. See Figure 287-1, Acute Agitation. Large doses may be required and are appropriate in monitored settings where advanced airway interventions are available if required. Although antipsychotic agents are often used as second-line agents for toxin-induced agitation, they have theoretical disadvantages, including anticholinergic and extrapyramidal effects.[17,18] First generation antipsychotics, such as haloperidol have been associated with QT-interval prolongation and cardiac dysrhythmias; however, the incidence of adverse effects appears to be very low.

HYPERTHERMIA AND HYPOTHERMIA

Patients with core temperatures of >39°C (>102.2°F) require aggressive active cooling measures to prevent complications such as

TABLE 176-2 Common Antidotes Used in Resuscitation of the Acutely Poisoned Patient

Antidote	Initial Pediatric Dose*	Initial Adult Dose*	Indication
Calcium chloride 10% 27.2 milligrams/mL elemental Ca	0.15 mL/kg IV	10 mL IV	Calcium channel blockers
Calcium gluconate 10% 9 milligrams/mL elemental Ca	0.5–0.45 mL/kg IV	10–30 mL IV	Hypermagnesemia Calcium channel blockers
Cyanide antidote kit Amyl nitrite	Not typically used	Crack vial and inhale over 30 seconds, or place in chamber of ventilation bag and use 30 s on/30 s off	Cyanide
Sodium nitrite (3% solution)	Dosed according to hemoglobin level. If unknown, assume hemoglobin level is 12 g/dL (120 g/L) and dose with 0.33 mL/kg IV	10 mL IV	Cyanide Hydrogen sulfide (use only sodium nitrite)
Sodium thiosulfate (25% solution)	1.65 mL/kg IV	50 mL IV	Cyanide
Dextrose (glucose)	0.5–1.09 gram/kg IV	1 gram/kg IV	Insulin Oral hypoglycemics
Digoxin Fab Acute toxicity	5–10 vials IV	10 vials	Digoxin and other cardioactive steroids
Flumazenil	0.01 milligram/kg IV	0.2 milligram IV	Benzodiazepines
Glucagon	30 micrograms/kg IV over 1–2 min for CCB toxicity and 30–150 micrograms/kg IV over 1–2 min for BB toxicity	5 milligrams IV	Calcium channel blockers Beta-blockers
Hydroxocobalamin	70 milligrams/kg (maximum 5 grams) IV over 15 min	5 grams IV over 15 min	Cyanide Nitroprusside
IV lipid emulsion 20%	1.5 mL/kg IV bolus over 1 min (may be repeated 2 times at 5-min intervals), followed by 0.25 mL/kg per min IV infusion for 20 min	100-mL IV bolus over 1 min (may be repeated 2 times at 5-min intervals), followed by 18 mL/min IV infusion for 20 min	Local anesthetic systemic toxicity Rescue therapy for lipophilic cardiotoxins
Methylene blue	1 milligram/kg IV Neonates: 0.3–1.0 milligram/kg IV	1 milligram/kg IV	Oxidizing toxins (e.g., nitrites, benzocaine, sulfonamides)
Naloxone	As much as required Start: 0.01 milligram IV	As much as required Start: 0.1–0.4 milligram IV	Opioids Clonidine
Pyridoxine	Gram for gram if amount of isoniazid ingested is known, otherwise:		Isoniazid
	70 milligrams/kg IV (maximum 5 grams)	5 grams IV	
Sodium bicarbonate	1–2 mEq/kg IV over 1–2 min followed by 0.3 mEq/kg per hour IV infusion		Sodium channel blockers Urinary alkalinization
Thiamine	5–10 milligrams IV	100 milligrams IV	Wernicke's syndrome Wet beriberi

*See specific chapter for details regarding use.

Abbreviations: BB = beta-blockers; CCB = calcium channel blocker.

rhabdomyolysis, organ failure, and disseminated intravascular coagulation. Sedation, neuromuscular paralysis, and intubation are required if active measures are ineffective. Several toxidromes associated with hyperthermia are treated with specific pharmaceutical agents: sympathomimetic (benzodiazepines), serotonin (cyproheptadine[19]), and neuromuscular malignant syndrome (bromocriptine[20]).

Drug-induced coma with subsequent immobility and environmental exposure or inherent drug toxicity (opioids, phenothiazines, ethanol) may produce hypothermia. A core temperature <32°C (<90°F) is an indication for active rewarming.

NALOXONE

Naloxone is a nontoxic, diagnostic, and therapeutic antidote. It is a competitive opioid antagonist administered IV, IM, or intranasally[21] to reverse opioid-induced deleterious hypoventilation. Naloxone can be used as a diagnostic agent when history and/or examination findings (respiratory rate of <12 breaths/min is a predictor of response to naloxone) suggest possible opioid exposure. Naloxone is titrated to clinical effect using bolus doses, typically 0.1 to 0.4 milligram. Large initial bolus doses may precipitate vomiting and aspiration, acute opioid withdrawal, or an uncooperative, agitated patient. Miosis is an unreliable indicator of naloxone's adequate clinical effect, as some opioids do not affect pupil size. Doses are titrated to achieve desirable ventilation and conscious state (adequate respiratory rate, normal arterial oxygen saturations on room air, and verbal or motor response to voice). Although naloxone may reverse the effects of opioids for 20 to 60 minutes, the effect of many opioids will outlast this time frame with possible return of respiratory depression. Patients should be observed for 2 to 3 hours after administration of IV naloxone.

IV LIPID EMULSION

IV lipid emulsion has been postulated to provide an intravascular "lipid sink," sequestrating lipophilic toxins and preventing target receptor interaction. IV lipid emulsion should be used as part of management of cardiac arrest in bupivacaine toxicity.[22] Current evidence does not support IV lipid emulsion as first-line treatment of life-threatening toxicity associated with other drugs, including amitriptyline, calcium channel antagonists, non–lipid-soluble beta-receptor antagonists, cocaine, diphenhydramine, lamotrigine, bupropion, malathion, and cocaine.[22] IV lipid emulsion therapy may affect common laboratory analyses, which may potentially lead to unintentional treatment errors.[23] IV lipid emulsion therapy may cause fat deposition in extracorporeal membrane oxygenation circuits and increase blood clot formation.[24] **Currently, IV lipid emulsion can be considered as a potential rescue therapy in life-threatening cardiotoxicity caused by lipophilic cardiotoxins that is resistant to conventional therapies.**

ASSESSMENT

Following initial resuscitation and stabilization, a risk assessment is performed to predict course of clinical toxicity, interventions required, and patient disposition. Risk assessment is formulated using history, examination, and ancillary test results. Acute poisoning is a dynamic process; therefore, risk assessment may change with time and requires ongoing review.

HISTORY

Patients may not provide a clear history due to psychiatric illness, clinical effects of exposure, and fear of arrest or repercussions from family or friends. Information including identity of substances, doses, and route of exposure is crucial in formulating a risk assessment. Obtain collateral information from family, friends, previous medical records, and usual healthcare provider. Prehospital emergency services can provide information regarding empty medication containers or the scene environment (smells, particular materials or substances present). If possible, obtain knowledge of hobbies, occupation, presence of a suicide note, and recent changes in patient behavior.

TABLE 176-3 Examination of the Poisoned Patient

Organ System	Examination	Example of Finding (Possible Significance)
General	Mental state and dress Signs of injury Odors Nutritional state Vital signs	Unkempt (psychiatric illness) Scalp hematoma (intracranial injury) Malnourished (IV drug use, human immunodeficiency virus infection) Smell of bitter almonds (cyanide toxicity)
CNS	Conscious state Pupil size and reactivity Eye movements Cerebellar function/gait	Miosis (opioids, organophosphates, phenothiazines, clonidine intoxication) Nystagmus/ataxia (anticonvulsant and ethanol toxicity)
Cardiovascular	Heart rate/blood pressure Cardiac auscultation	Murmur (endocarditis/IV drug use)
Respiratory	Oxygen saturation Respiratory rate Chest auscultation	Fever/crepitations/hypoxia (aspiration pneumonia) Bronchorrhea/crepitations/hypoxia (organophosphate toxicity)
GI	Oropharynx Abdomen Bladder	Urinary retention (anticholinergic toxicity) Oral cavity burns (corrosive ingestion) Hypersalivation (cholinergic toxidrome)
Peripheral nervous	Reflexes Tone Fasciculations Tremor Clonus	Tremor/fasciculations (lithium toxicity) "Lead pipe" rigidity (neuromuscular malignant syndrome) Clonus/hyperreflexia (serotonin toxicity)
Dermal/peripheral	Bruising Cyanosis Flushing Dry/moist skin Injection sites Bullae	Bruising (coagulopathy, trauma, coma) Flushing/warm, dry skin (anticholinergic toxicity) Warm, moist skin (sympathomimetic toxicity) Bullae (prolonged coma, barbiturates)

EXAMINATION

A systematic physical examination can yield important clues to the nature and potential severity of an exposure (**Table 176-3**). Examine the skin folds, body cavities if appropriate, and clothing for retained tablets or substances.

TOXIDROMES

Substances belonging to a particular pharmaceutical or chemical class often produce a cluster of symptoms and signs, or "toxidrome" (**Table 176-4**), enabling the identification of potential toxins when a clear history is unavailable.

DIAGNOSTIC TESTING

A serum acetaminophen concentration is a routine screening test in poisoned patients because early acetaminophen poisoning is often asymptomatic and does not have a readily identifiable toxidrome at the time when antidotal treatment is most efficacious. Acetaminophen screening is especially important in patients presenting with altered

TABLE 176-4 Common Toxidromes

Toxidrome	Examples of Agents	Examination Findings (most common in bold)
Anticholinergic	Atropine, *Datura* spp., antihistamines, antipsychotics	Altered mental status, mydriasis, dry flushed skin, urinary retention, decreased bowel sounds, hyperthermia, dry mucous membranes Seizures, arrhythmias, rhabdomyolysis
Cholinergic	Organophosphate and carbamate insecticides Chemical warfare agents (sarin, VX)	Salivation, lacrimation, diaphoresis, vomiting, urination, defecation, bronchorrhea, muscle fasciculations, weakness Miosis/mydriasis, bradycardia, seizures
Ethanolic	Ethanol	CNS depression, ataxia, dysarthria, odor of ethanol
Extrapyramidal	Risperidone, haloperidol, phenothiazines	Dystonia, torticollis, muscle rigidity Choreoathetosis, hyperreflexia, seizures
Hallucinogenic	Phencyclidine Psilocybin, mescaline Lysergic acid diethylamide	Hallucinations, dysphoria, anxiety Nausea, sympathomimetic signs
Hypoglycemic	Sulfonylureas, insulin	Altered mental status, diaphoresis, tachycardia, hypertension Dysarthria, behavioral change, seizures
Neuromuscular malignant	Antipsychotics	Lead-pipe muscle rigidity, bradyreflexia, hyperpyrexia, altered mental status Autonomic instability, diaphoresis, mutism, incontinence
Opioid	Codeine, heroin, morphine	Miosis, respiratory depression, CNS depression Hypothermia, bradycardia
Salicylate	Aspirin Oil of wintergreen (methyl salicylate)	Altered mental status, respiratory alkalosis, metabolic acidosis, tinnitus, tachypnea, tachycardia, diaphoresis, nausea, vomiting Hyperpyrexia (low grade)
Sedative/hypnotic	Benzodiazepines Barbiturates	CNS depression, ataxia, dysarthria Bradycardia, respiratory depression
Serotonin	SSRIs MAOIs Tricyclic antidepressants Amphetamines Fentanyl St. John's wort	Altered mental status, hyperreflexia and hypertonia (>lower limbs), clonus, tachycardia, diaphoresis Hypertension, flushing, tremor
Sympathomimetic	Amphetamines Cocaine Cathinones	Agitation, tachycardia, hypertension, hyperpyrexia, diaphoresis Seizures, acute coronary syndrome

Abbreviations: MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

mental status or a self-harm ingestion, for whom an accurate history may not be available.

An ECG is a useful test to detect cardiac conduction abnormalities and identify patients at increased risk of toxin-induced adverse cardiovascular events.[25]

Measurement of drug or toxin concentrations in body fluids is not required in most poisonings, but in some exposures, measurement of serum drug concentrations does influence management (**Table 176-5**).

TABLE 176-5 Drug Serum Measurements That May Assist Patient Assessment or Management

Acetaminophen	Methemoglobin
Carbamazepine	Methotrexate
Carbon monoxide	Paraquat
Digoxin	Phenobarbital
Ethanol	Phenytoin
Ethylene glycol	Salicylate
Iron	Theophylline
Lithium	Valproic acid
Methanol	

Toxicologic screening tests of urine can be done in a central laboratory or performed with point-of-care assays.[26] Urine drug screens most often use enzyme-immunoassays to detect typical drugs within each class. Cross-reactivity is common and some drugs within the class may not be detected (**Table 176-6**). Dilute urine can make it difficult to detect low levels. Because some drugs are present in urine for an extended period of time, the positive test may not be related to the current clinical condition. Urine drug screen results seldom influence patient management in most adult overdoses and poisoning.

Toxicologic screening may be appropriate for medicolegal reasons, especially in pediatric cases when inappropriate drug administration or nonaccidental injury is suspected. A positive urine drug screen for an illicit substance is an indication to involve local child protection services.

DECONTAMINATION

Decontamination is required for toxic exposures affecting large dermal areas. Healthcare providers wearing personal protective equipment (if indicated) or observing universal precautions (gown, gloves, eye protection) should assist with undressing and washing the patient using copious amounts of water. Contaminated clothing is collected, bagged, and properly disposed. Decontamination ideally occurs in a separate area adjacent to the ED, minimizing cross-contamination.

TABLE 176-6 Standard Enzyme-Immunoassay Urine Drug Screens

Class (drugs typically tested)	Drugs not in this class possibly detected (false positives)+	Drugs in this class possibly not detected (false negatives)	Comments
Amphetamine and Methamphetamine	Amantadine **Bupropion** Chlorpromazine Desipramine **Dimethylamylamine** **Ephedrine** Fluoxetine Isoxsuprine **Labetalol** **Metformin** Phentermine Phenylephrine Phenylpropanolamine Promethazine **Pseudoephedrine** **Ranitidine** **Selegiline** Thioridazine Trazodone Trimethobenzamide Trimipramine	Methylenedioxymethylamphetamine [MDMA]	Detectable up to 48 h after single use
Barbiturates	Ibuprofen Naproxen	N/A	Detectable up to: Short-acting: 24 h Long-acting: 21 d
Benzodiazepines (oxazepam, nordiazepam)	**Oxaprozin** **Sertraline**	Alprazolam Clonazepam Flunitrazepam Lorazepam Triazolam	Detectable up to: Short-acting: 3 days Long-acting: 30 d
Cannabinoids (delta-9-tetracannabinol-9-carboxylic acid)	**Efavirenz** Ibuprofen Naproxen Pantoprazole Promethazine	Nabilone Synthetic cannabinoids (e.g., "K2" or "spice")	Detectable up to: Single use: 3 d Moderate use: 5–7 d Daily use: 10–15 d Long-term use: > 30 d
Cocaine (benzoylecgonine)	*	*	Detectable 2–4 d after single use
Methadone	Chlorpromazine Clomipramine **Diphenhydramine** **Doxylamine** Ibuprofen Quetiapine Thioridazine **Verapamil**	N/A	Detectable up to 3 d
Opiates (morphine, 6-acetylmorphine)	Dextromethorphan Diphenhydramine Fluoroquinolones (ciprofloxacin, levofloxacin, **ofloxacin**) Poppy seed and oil **Rifampin** Quinine	Buprenorphine Fentanyl Meperidine Methadone Oxycodone Oxymorphone Tramadol	Detectable 2–4 d depending on specific drug
Phencyclidine	Dextroamphetamine **Dextromethorphan** **Diphenhydramine** Doxylamine Ibuprofen Ketamine Lamotrigine Meperidine **Methylendioxyprovalerone** Thioridazine **Tramadol** **Venlafaxine**	N/A	Detectable up to 8 d after single use
Tricyclic Antidepressants	**Carbamazepine** **Cyclobenzaprine** Cyproheptadine Diphenhydramine Hydroxyzine Oxcarbazepine Promethazine **Quetiapine** Thioridazine	Clomipramine	Detectable 2–7 days

Abbreviation: N/A = not applicable.

*Cocaine immunoassay is highly specific with low cross-reactivity.

+Agents with strongest evidence for false-positive results noted in **bold**.

OCULAR DECONTAMINATION

Eye exposures may require local anesthetic (e.g., 0.5% tetracaine) instillation and lid retractors to facilitate copious irrigation with crystalloid solution. Alkalis produce greater injury than acids due to deep tissue penetration via liquefaction so that prolonged irrigation (1 to 2 hours) may be required. Ten minutes after irrigation (allowing equilibration of crystalloid and conjunctival sac pH), conjunctival sac pH is tested. Irrigation continues until pH is between 7.2 and 7.4. Ophthalmologic consultation is indicated for all ocular alkali injuries.

GI DECONTAMINATION

Gastric decontamination is not a routine part of poisoned patient management; there is minimal evidence demonstrating positive benefit, and there are associated complications (**Table 176-7**). Gastric decontamination may be considered in individual patients after a three-question risk-benefit analysis: (1) Is this exposure likely to cause significant toxicity? (2) Is GI decontamination likely to change clinical outcome? (3) Is it possible that GI decontamination will cause more harm than good?[27,28]

Emesis Traditionally, ipecac syrup was administered to induce vomiting, theoretically emptying the stomach of poisons. No published evidence supports the induction of emesis, and adverse outcomes associated with emesis are documented.[29] **There is no role for the induction of emesis in the ED in the poisoned patient.**[30]

Orogastric Lavage Once a widely practiced intervention, attempted removal of ingested toxin from the stomach by aspiration of fluid placed via an orogastric tube is now rarely indicated. No published evidence demonstrates that orogastric lavage changes outcome in the majority of poisoned patients, and the procedure has numerous complications.[31]

TABLE 176-7 Indications, Contraindications, and Complications of GI Decontamination Procedures

Orogastric Lavage	
Indications	Rarely indicated Consider for recent (<1 h) ingestion of life-threatening amount of a toxin for which there is no effective treatment once absorbed
Contraindications	Corrosive/hydrocarbon ingestion Supportive care/antidote likely to lead to recovery Unprotected airway Unstable, requiring further resuscitation (hypotension, seizures)
Complications	Aspiration pneumonia/hypoxia Water intoxication Hypothermia Laryngospasm Mechanical injury to GI tract Time consuming, resulting in delay instituting other definitive care
Activated Charcoal	**Adults 50 grams orally, children 1 gram/kg orally**
Indications	Ingestion within the previous hour of a toxic substance known to be adsorbed by activated charcoal, where the benefits of administration are judged to outweigh the risks
Contraindications	Nontoxic ingestion Toxin not adsorbed by activated charcoal Recovery will occur without administration of activated charcoal Unprotected airway Corrosive ingestion Possibility of upper GI perforation
Complications	Vomiting Aspiration of the activated charcoal Impaired absorption of orally administered antidotes
Whole-Bowel Irrigation	**Polyethylene glycol 2 L/h in adults, children 25 mL/kg per hour (maximum 2 L/h)**
Indications (potential)	Iron ingestion >60 milligrams/kg with opacities on abdominal radiograph Life-threatening ingestion of diltiazem or verapamil Body packers or stuffers Slow-release potassium ingestion Lead ingestion (including paint flakes containing lead) Symptomatic arsenic trioxide ingestion Life-threatening ingestions of lithium
Contraindications	Unprotected airway GI perforation, obstruction or ileus, hemorrhage Intractable vomiting Cardiovascular instability
Complications	Nausea, vomiting Pulmonary aspiration Time consuming; possible delay instituting other definitive care

Gastric lavage may be considered in cases of ingestion of a life-threatening amount of poison within the previous hour where institution of supportive care and antidotal therapy would not ensure full recovery. Adherence to best-practice principles can minimize complications from orogastric lavage (**Table 176-8**).

TABLE 176-8 Principles to Minimize Complications From Orogastric Lavage

- Ensure a protected airway if consciousness level is reduced.
- Use a 36F- to 40F-gauge orogastric tube (22F to 24F in children).
- Position the patient on the left side with the head down 20 degrees.
- Pass lubricated tube down the esophagus a distance equal to that between chin and xiphoid process.
- Confirm tube position by insufflation of air.
- Gently lavage with 200 mL (10 mL/kg in children) of warm tap water, allowing drainage after each aliquot.
- Continue until returned fluid is clear.
- Consider administration of activated charcoal via orogastric tube before removal.

Single-Dose Activated Charcoal Super-heating carbonaceous material produces activated charcoal, a highly porous substance, which is suspended in solution and given PO as a slurry. Toxins within the GI lumen are adsorbed onto the activated charcoal and carried through the GI tract, limiting absorption.[32] Activated charcoal does not effectively adsorb metals, corrosives, and alcohols. The decision to give activated charcoal requires individual patient risk assessment and is not considered routine management.[28]

Activated charcoal may be effective when given >60 minutes after ingestion of substances known to slow GI motility (e.g., anticholinergics)[33] or after massive ingestion of a substance associated with bezoar formation (e.g., salicylates). Activated charcoal mixed with ice cream improves palatability for children. Activated charcoal can be administered to intubated patients using an orogastric or nasogastric tube.

Whole-Bowel Irrigation Polyethylene glycol is an osmotically balanced electrolyte solution. Administration in large quantities mechanically forces substances through the GI tract, limiting toxin absorption.[34] Polyethylene glycol can be administered orally to cooperative, awake patients, but consider formal airway control if consciousness is likely to deteriorate. Minimize risk of pulmonary aspiration during whole-bowel irrigation by patient positioning (head up 30 degrees), ensuring bowel sounds are present during fluid administration, 1:1 nursing with suctioning of the oral cavity during infusion, and utilization of cuffed endotracheal tubes.

Evidence supporting whole-bowel irrigation is limited to volunteer studies and case reports[34] from which potential indications have been developed (Table 176-7). Nonsurgical treatment of asymptomatic body drug packers using whole-bowel irrigation is increasingly common, although no randomized clinical trials exist.[34] An antiemetic such as the prokinetic agent metoclopramide may be required to control polyethylene glycol–induced gastric distention and vomiting. The end point of whole-bowel irrigation treatment is clear rectal effluent and imaging demonstrating absence of foreign bodies.

ENHANCED ELIMINATION

MULTIDOSE ACTIVATED CHARCOAL

Multidose activated charcoal increases elimination of toxins with enteroenteric, enterohepatic, or enterogastric recirculation. Lipophilic drugs with low volume of distribution, protein binding, and molecular weight may pass down a concentration gradient between intravascular space and activated charcoal in the gut lumen. Multidose activated charcoal may also adsorb residual intraluminal toxins; this is more likely for substances slowing gastric motility or forming bezoars (**Table 176-9**). Although animal studies, volunteer studies, case reports, and case series demonstrate increased elimination rates (in some cases comparable to those of hemodialysis or charcoal hemoperfusion) of carbamazepine, dapsone, phenobarbital, phenytoin, quinine, and theophylline, there is limited evidence that multidose activated charcoal changes clinical outcome.[35]

Multidose activated charcoal may be administered by an orogastric or nasogastric tube to intubated patients. Regular aspiration of stomach contents helps avoid gastric distention. Multidose activated charcoal should not be given when bowel sounds are absent. Continued requirement for further multidose activated charcoal should be reviewed regularly during therapy.

TABLE 176-9 Indications, Contraindications, and Complications of Enhanced Elimination Procedures

Multidose Activated Charcoal	**Initial dose: 50 grams (1 gram/kg children), repeat dose of 25 grams (0.5 gram/kg children) every 2 hours**
Indications	Carbamazepine coma (reduces duration of coma) Phenobarbital coma (reduces duration of coma) Dapsone toxicity with significant methemoglobinemia Quinine overdose Theophylline overdose if hemodialysis/hemoperfusion unavailable
Contraindications	Unprotected airway Bowel obstruction Caution in ingestions resulting in reduced GI motility
Complications	Vomiting Pulmonary aspiration Constipation Charcoal bezoar, bowel obstruction/perforation
Urinary Alkalinization	
Indications	Moderate to severe salicylate toxicity not meeting criteria for hemodialysis Phenobarbital (multidose activated charcoal superior) Chlorophenoxy herbicides (2-4-dichlorophenoxyacetic acid and mecoprop): requires high urine flow rate of 600 mL/h to be effective Chlorpropamide: supportive care/IV dextrose normally sufficient
Contraindications	Preexisting fluid overload Renal impairment Uncorrected hypokalemia
Complications	Hypokalemia Volume overload Alkalemia Hypocalcemia (usually mild)

URINARY ALKALINIZATION

Alkaline urine favors ionization of acidotic drugs within renal tubules, preventing resorption of the ionized drug back across the renal tubular epithelium and enhancing elimination through the urine.[36] Urinary alkalinization is most effective for weak acids primarily eliminated by the renal tract that are also readily filtered at the glomerulus and have small volumes of distribution. Hypokalemia will reduce the effectiveness of urinary alkalinization (**Table 176-10**). The primary indication for urinary alkalinization is moderate to severe salicylate toxicity when criteria for hemodialysis have not been met.

Although urinary acidification can enhance the elimination of weak bases including amphetamines and phencyclidine, associated risks (e.g., rhabdomyolysis) outweigh potential benefit. Forced diuresis has no indication for any poisoning, with the exception of chlorophenoxy herbicides (see Chapter 201, "Pesticides").

TABLE 176-10 Protocol for Urinary Alkalinization in Adults With Normal Renal Function

- Correct existing hypokalemia.
- Administer a 1 to 2 mEq/kg IV sodium bicarbonate bolus.
- Infuse 100 mEq of sodium bicarbonate mixed with 1 L of D_5W at 250 mL/h.
- 20 mEq of potassium chloride may be added to the solution to maintain normokalemia.
- Monitor serum potassium and bicarbonate every 2–4 h to detect hypokalemia or excessive serum alkalinization.
- Check urine pH regularly (every 15–30 min); goal is a pH of 7.5–8.5.
- A further IV bolus of 1 mEq/kg of sodium bicarbonate may be necessary if sufficient alkalinization of the urine is not achieved.

Abbreviation: D_5W = 5% dextrose in water.

EXTRACORPOREAL REMOVAL

Extracorporeal removal techniques, including hemodialysis, hemoperfusion, and continuous renal replacement therapies, have limited indications in poisoned patients (**Table 176-11**). These procedures require a critical care setting, are expensive and invasive, are not always available, and have complications. Extracorporeal removal techniques were used in 0.13% of cases reported to U.S. poison control centers in 2016.[10]

TABLE 176-11 Indications, Contraindications, and Complications of Extracorporeal Removal Techniques

Hemodialysis	**Movement of solute down a concentration gradient across a semipermeable membrane**
Toxin requirements	Low volume of distribution, low protein binding, low endogenous clearance, low molecular weight
Indications	**Life-threatening poisoning by:** Lithium Phenobarbital Salicylates Valproic acid Methanol/ethylene glycol Metformin-induced lactic acidosis Potassium salts Theophylline
Contraindications	Hemodynamic instability Infants (generally) Poor vascular access Significant coagulopathy
Hemoperfusion	**Movement of toxin from blood, plasma, or plasma proteins onto a bed of activated charcoal (or other adsorbent)**
Toxin requirements	Low volume of distribution, low endogenous clearance, bound by activated charcoal
Indications	**Life-threatening poisoning caused by:** Theophylline (high-flux hemodialysis is an alternative) Carbamazepine (multidose activated charcoal or high-efficiency hemodialysis also effective) Paraquat (theoretical benefit only if instituted early after exposure)
Contraindications	Hemodynamic instability Infants (generally) Poor vascular access Significant coagulopathy Toxin not bound to activated charcoal
Continuous Renal Replacement Therapies	**Movement of toxin and solute across a semipermeable membrane in response to hydrostatic gradient. Can be combined with dialysis.**
Indications (potential)	Life-threatening ingestions of toxins when hemodialysis or hemoperfusion is indicated but is unavailable or hemodynamic instability precludes their utilization
Contraindications	Hemodialysis or hemoperfusion is available Poor vascular access Significant coagulopathy
Complications of Extracorporeal Removal Techniques	
Fluid/metabolic disruption Removal of antidotes Limited availability	Limited by hypotension (not continuous renal replacement therapy) Infection/bleeding at catheter site Intracranial hemorrhage secondary to anticoagulation

A toxin must possess a number of properties to be effectively removed by an extracorporeal technique in a clinically meaningful time frame: low volume of distribution (<1.0 L/kg), low molecular weight (<500 Da), relatively low protein binding, and low endogenous clearance.[37] In general, extracorporeal removal must improve endogenous clearance rate by >30% to be clinically beneficial. Hemoperfusion uses a charcoal (or other adsorbent) filter, which comes into direct contact with blood, partially overcoming molecular weight and protein-binding limitations.

Continuous renal replacement therapies (including venovenous hemofiltration and venovenous hemodiafiltration) are widely available and easily instituted in most hospitals. However, there is sparse evidence demonstrating any benefit in poisoning, primarily due to slow clearance rates.[37] A patient who requires extracorporeal removal should undergo hemodialysis or hemoperfusion, if available. Continuous renal replacement therapy can be used if hemodialysis or hemoperfusion is unavailable or will not be tolerated (e.g., due to hypotension).[37] Extracorporeal removal techniques including high-flux hemodialysis are constantly evolving, so discussion with an intensivist or nephrologist may be beneficial when this approach is considered. Expert consensus advice regarding optimum extracorporeal elimination techniques for individual toxins have been published by the Extracorporeal Treatments in Poisoning group.[38]

DISPOSITION

Planning for patient disposition from the ED should be part of initial risk assessment. Admission is indicated if the patient has persistent and/or severe toxic effects or will require a prolonged course of treatment. In most cases, a 6-hour observation period is sufficient to exclude the development of serious toxicity. Onset of clinical toxicity can be delayed after a number of exposures, including (but not limited to) modified-release preparations of calcium channel blockers, selective norepinephrine reuptake inhibitors (tramadol, venlafaxine), and newer antipsychotics (amisulpride); hence, a period of extended observation is indicated. In the developed world, toxicity will resolve within 24 hours in most poisoned patients requiring noncritical care inpatient management, and so these patients can be efficiently and safely managed in a toxicology or short-stay ward, if available. Patients who have deliberately self-poisoned require appropriate mental health assessment before disposition.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 177

Cyclic Antidepressants

Frank LoVecchio

INTRODUCTION

Cyclic antidepressants were the first generation of drugs developed to treat depression. Their use for treating depression has declined greatly as safer agents have been developed. Cyclic antidepressants are now occasionally used to treat obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, panic and phobia disorders, and anxiety disorders.

Cyclic antidepressants have the highest ratio of deaths to exposures for antidepressants reported to U.S. Poison Control Centers.[1] Roughly half of all cyclic antidepressant exposures involve other drugs as well, and most co-ingestants increase the incidence and severity of cyclic antidepressant overdose toxicity.

Eight cyclic antidepressants are currently available in the United States (**Table 177-1**), with more agents available in other countries. Two related antidepressants, amoxapine and maprotiline, have structural differences from traditional cyclic antidepressants but have similar toxicity in overdose. Cyclobenzaprine is a muscle relaxant that is almost structurally identical to amitriptyline but lacks antidepressant activity, and serious toxicity from overdose is rare.[2]

Cyclic antidepressants possess a narrow therapeutic index, and toxicity can occur at therapeutic dosages (**Table 177-2**).

PHARMACOLOGY

The cyclic antidepressants are named after their chemical structure, which consists of a three-ring central structure plus a side chain—thus the common term *tricyclic antidepressants*. Maprotiline is a tetracyclic (also termed a *heterocyclic*), with a four-ring central structure plus a side chain. Cyclic antidepressants are subdivided into two categories: tertiary and secondary amines. Tertiary amines have two methyl groups at the end of the side chain. The five tertiary amines—amitriptyline, clomipramine, doxepin, imipramine, and trimipramine—are generally more potent in blocking reuptake of serotonin compared to blocking reuptake of norepinephrine. Tertiary tricyclics also cause more anticholinergic side effects (e.g., constipation or blurred vision) and are also highly sedating because of their central effects on histamine receptors.

Secondary amines—desipramine, nortriptyline, and protriptyline—have one methyl group at the end of the side chain and are more potent in blocking reuptake of norepinephrine. The tetracyclic maprotiline has a side chain identical to that of the secondary amines; thus, it is more potent in blocking reuptake of norepinephrine.

Amoxapine has a three-ring central structure and a side chain that differs from the other tricyclics. It is a potent norepinephrine reuptake inhibitor and also blocks postsynaptic dopamine receptors. Thus, it is the only antidepressant that has antipsychotic effects and can produce seizures with minimal warning and normal QRS complex.

Cyclic antidepressants are nonselective agents with multiple pharmacologic effects (**Table 177-3**) with considerable variation in potency at therapeutic dosages.[3-5] However, these differences become less important at the higher plasma levels typically seen in overdose. Inhibition of amine reuptake (norepinephrine, serotonin) and antagonism of postsynaptic serotonin receptors are believed to produce the therapeutic effects of these agents. The remaining pharmacologic actions are seemingly without therapeutic benefit in treating major depression, but significantly contribute to cyclic antidepressant–related adverse effects and overdose toxicity.

Cyclic antidepressant–induced cardiotoxicity is the most important factor contributing to patient mortality.[6] Cardiac conduction abnormalities occur during cyclic antidepressant poisoning because inhibition of the fast sodium channels in the His-Purkinje system and myocardium decreases conduction velocity, increases the duration of repolarization, and prolongs absolute refractory periods. Fast sodium channel blockade produces changes in the QRS complex. Severe sodium channel blockade culminates in depressed myocardial contractility, hypotension, various types of heart blocks, cardiac ectopy, bradycardia, widening of the QRS complex, and/or the Brugada pattern. Cyclic antidepressants also block myocardial potassium channels and inhibit the efflux of potassium during repolarization.[6] This effect is seen on the ECG as QT interval prolongation, which is more pronounced at slower heart rates.[7,8]

PHARMACOKINETICS

All cyclic antidepressants share similar pharmacokinetic properties.[3] They are highly lipophilic, readily cross the blood–brain barrier, and achieve peak plasma levels between 2 and 6 hours after ingestion at therapeutic doses. In overdose, GI absorption can be prolonged because of the antimuscarinic effect on gut motility. Bioavailability is only 30% to 70% because of extensive first-pass hepatic metabolism. Cyclic antidepressants are highly protein bound to α_1-acid glycoproteins, with a large apparent volume of distribution, ranging from 10 to 50 L/kg. Tissue cyclic antidepressant levels are commonly 10 to 100 times greater than plasma levels, and only 1% to 2% of the total body burden of cyclic antidepressants is found in the blood. These pharmacokinetic properties explain why it is

TABLE 177-1 Cyclic Antidepressants and Related Drugs

Generic Name	Typical Adult Outpatient Daily Dose (milligrams)	Recommended Maximum Adult Outpatient Daily Dose (milligrams)	Elimination Half-Life (h)	Active Metabolites
Amitriptyline	75–150	300	10–26 (amitriptyline) 18–44 (nortriptyline)	Nortriptyline
Amoxapine*	50–300	400	8 (amoxapine) 30 (8-hydroxyamoxapine)	7-Hydroxyamoxapine (minor) 8-Hydroxyamoxapine (major)
Clomipramine	25–50	250	32 (clomipramine) 69 (desmethylclomipramine)	Desmethylclomipramine
Cyclobenzaprine*	15–30	30	18	None
Desipramine	75–200	300	12–27	None
Doxepin	75–300	300	15 (doxepin) 31 (desmethyldoxepin)	Desmethyldoxepin
Imipramine	75–200	300	11–25	Desipramine
Maprotiline*	75–150	225	43 (maprotiline) 60–90 (desmethylmaprotiline)	Desmethylmaprotiline
Nortriptyline	75–150	150	18–44	None
Protriptyline	15–60	60	67–89	None
Trimipramine	75–200	300	9–11	Desmethyltrimipramine

*See text for clarification.

unproductive to attempt removal of cyclic antidepressants by hemodialysis, hemoperfusion, peritoneal dialysis, or forced diuresis.[9]

Cyclic antidepressants are eliminated almost entirely by hepatic oxidation, which consists of *N*-demethylation of the amine side-chain groups and hydroxylation of ring structures. The removal of a methyl group from the tertiary amine side chain usually produces an active metabolite designated by the desmethyl prefix (Table 177-1). **Clinical toxicity from cyclic antidepressants usually lasts longer than explained by the activity of the parent drug because of the production of active metabolites.**

TOXICITY

Ingestions of <1 milligram/kg are generally nontoxic.[10] Life-threatening symptoms usually occur with ingestions of >10 milligrams/kg in adults, and fatalities are commonly associated with ingestions of >1 gram. Children are particularly susceptible to antimuscarinic effects and show clinical toxicity at lower dosages.[4] The majority of adult intentional ingestions and pediatric accidental exposures of >2.5 milligrams/kg are expected to result in some clinical toxicity based on the low therapeutic index of cyclic antidepressants.[10] In addition, patients at higher risk for cyclic antidepressant toxicity include patients who have co-ingested cardiotoxic or sedative-hypnotic medications, geriatric patients, and patients with underlying heart or neurologic disease.

Desipramine is the most potent sodium channel blocker among the cyclic antidepressants and is able to precipitate severe cardiotoxicity (e.g., wide QRS complex, hypotension) without producing significant antimuscarinic symptoms. It is associated with a higher case-fatality rate than the other cyclic antidepressants.[11] Amoxapine and maprotiline have historically been associated with greater toxicity than other cyclic antidepressants, especially in regard to causing seizures.[11]

Quantitative measurement of plasma levels of cyclic antidepressants (parent and metabolite) is helpful in monitoring long-term drug therapy, with therapeutic levels of 75 to 300 nanograms/mL (300 to 1000 nmol/L) for most agents. Patients with a combined plasma level of parent cyclic antidepressant and metabolite of >1000 nanograms/mL (>3500 nmol/L) are at greater risk for developing seizures and cardiotoxicity, but the severity of clinical toxicity does not always correlate with plasma cyclic antidepressant level.[6]

TABLE 177-2 Mechanisms for Cyclic Antidepressant Drug Toxicity at Therapeutic Dosages

- Administration of high therapeutic dosages to naive individuals
- Drug interactions with medications sharing similar pharmacologic actions
- Elevated levels of cyclic antidepressants due to genetically slow hepatic metabolism
- Drug interactions with other medications that inhibit hepatic metabolism (cytochrome P450 system)
- Additional toxicity from other active ingredients (e.g., antipsychotics) contained in some combination cyclic antidepressant formulations
- Preexisting cardiovascular or CNS disease that predisposes patients to toxicity
- Development of serotonin syndrome, usually in combination with serotoninergic medications

TABLE 177-3 Pharmacologic Profile of Cyclic Antidepressants

Pharmacologic Activity	Clinical Presentation
Antagonism of postsynaptic histamine receptors	Sedation, depressed consciousness
Antagonism of postsynaptic muscarinic receptors (both central and peripheral)	Central antimuscarinic: agitation to delirium, confusion, amnesia, hallucinations, slurred speech, ataxia, sedation, and coma Peripheral antimuscarinic: dilated pupils, blurred vision, tachycardia, hyperthermia, hypertension, decreased oral and bronchial secretions, dry skin, ileus, urinary retention, increased muscle tone, and tremor
Antagonism of postsynaptic α-adrenergic receptors (α_1-adrenergic > α_2-adrenergic receptors)	α_1-Adrenergic receptor: sedation, miosis, orthostatic hypotension, reflex tachycardia α_2-Adrenergic receptor: mild hypertension
Inhibition of norepinephrine reuptake	Agitation, mydriasis, diaphoresis, tachycardia, early hypertension
Inhibition of serotonin reuptake	Sedation, mydriasis, myoclonus, hyperreflexia (see Chapter 178, "Atypical and Serotonergic Antidepressants")
Inhibition of voltage-gated sodium channels	Impaired conduction, wide QRS complex, other conduction abnormalities; impaired cardiac contractility; wide-complex tachycardia, Brugada pattern, ventricular ectopy Hypotension
Inhibition of voltage-gated rectifier potassium channels	Prolongation of QT interval, ventricular ectopy, torsades de pointes

CLINICAL FEATURES

The clinical presentation of cyclic antidepressant toxicity varies from mild antimuscarinic symptoms to severe cardiotoxicity secondary to sodium channel blockade. Antimuscarinic symptoms commonly serve as markers for cyclic antidepressant toxicity (e.g., dry mouth and axillae, sinus tachycardia), but they alone are rarely responsible for fatalities. Moreover, antimuscarinic symptoms are not uniformly present in cyclic antidepressant toxicity. Altered mental status is the most common symptom reported after cyclic antidepressant exposure.[4,12-14] A Glasgow Coma Scale score of <8 in the ED is a strong predictor of serious complications such as seizures and cardiac dysrhythmia.[5,6] Sinus tachycardia is the most frequent dysrhythmia noted in cyclic antidepressant toxicity, occurring in up to 70% of symptomatic patients.[6,12-14]

Mild to moderate cyclic antidepressant toxicity presents as drowsiness, confusion, slurred speech, ataxia, dry mucous membranes and axillae, sinus tachycardia, urinary retention, myoclonus, and hyperreflexia. Antimuscarinic syndrome is classically associated with decreased bowel sounds and ileus, but bowel function is fairly resistant to inhibition, so the presence of active bowel sounds does not exclude antimuscarinic syndrome. Mild hypertension is occasionally present and rarely requires treatment. Overflow urinary incontinence may be mistaken for normal micturition in diaper-dependent children or older adults.

Most cyclic antidepressant overdose fatalities occur within the initial hours after ingestion, often before the patient reaches the hospital. **If serious toxicity is going to occur, it almost always is seen within 6 hours of ingestion and consists of the following features: coma, cardiac conduction delays, supraventricular tachycardia, hypotension, respiratory depression, ventricular tachycardia, and seizures.**[11]

Secondary complications from serious toxicity include aspiration pneumonia, pulmonary edema, anoxic encephalopathy, hyperthermia, and rhabdomyolysis. Seizures are more commonly reported in maprotiline and trimipramine overdoses.[15] Seizures are usually generalized, are of brief duration, and occur with other signs of serious toxicity.[5] **The exception to this rule is amoxapine overdoses; this agent can cause status epilepticus without warning or QRS complex widening.** Cyclobenzaprine overdoses are usually characterized by prolonged CNS sedation and antimuscarinic toxicity with minimal cardiotoxicity compared to amitriptyline.[2]

DIAGNOSIS

Cyclic antidepressant toxicity is diagnosed using a combination of four criteria: history of exposure, clinical symptomatology, characteristic ECG findings, and positive cyclic antidepressant urine drug screen results. Other toxic exposures may produce similar symptoms, signs, and ECG changes; the essential point is that the initial treatment for toxicity due to any of these medications is identical and should not be delayed until definitive drug test results become available. At least half of all cyclic antidepressant exposures involve co-ingestion of other substances, which can significantly increase or alter toxic manifestations.

False-positive results on qualitative cyclic antidepressant urine drug screens occur with carbamazepine, cetirizine, cyclobenzaprine, cyproheptadine, diphenhydramine, hydroxyzine, quetiapine, and phenothiazines (e.g., thioridazine).[16] The false-positive cyclic antidepressant screen result is generally dose dependent and is more common following a supratherapeutic dose of these medications. Most of these medications are structurally similar to cyclic antidepressants, producing the same ECG abnormalities and clinical toxicity in overdose as cyclic antidepressants. Conversely, false-negative results on cyclic antidepressant drug tests are extremely unusual with clinical toxicity.

ECG abnormalities are common with cyclic antidepressant toxicity and are useful in identifying patients at increased risk for seizures and ventricular dysrhythmias.[17] The classic ECG with cyclic antidepressant toxicity shows sinus tachycardia, right axis deviation of the terminal 40 milliseconds, and prolongation of the PR, QRS, and QT intervals (**Figure 177-1**). Right axis deviation is demonstrated as a positive terminal R wave in lead aVR and a negative S wave in lead I (Figure 177-1). **This classic ECG pattern is seen frequently in moderate to severe cyclic antidepressant toxicity, but its absence does not eliminate the possibility of toxicity, and life-threatening complications can occur in the absence of significant ECG abnormalities, especially following amoxapine ingestion.** Less common ECG abnormalities include right bundle branch block and high-degree atrioventricular blocks. The Brugada pattern is seen in roughly 10% to 15% of patients with cyclic antidepressant poisoning who require intensive care unit admission but is rarely seen in other overdoses.[18,19] Torsades de pointes is rarely seen in cyclic antidepressant overdoses in the presence of sinus tachycardia, which is partially protective against severe QT interval prolongation and afterpotential generation.

The risk of seizures increases if the QRS complex is >100 milliseconds, and ventricular dysrhythmias are more common if the QRS duration is >160 milliseconds.[6,17] Widening of the QRS complex from baseline and positive deflection of the terminal QRS complex in lead aVR are usually seen together but can occur independently of each other. The development of right axis deviation of the terminal 40 milliseconds and/or QRS complex widening appear to be less predictive of cyclic antidepressant–induced cardiotoxicity in young children because pediatric ECGs tend to have a wider range of acceptable variant features, and this complicates the identification of cyclic antidepressant toxicity on the ECG.

ECG abnormalities develop within 6 hours of ingestion and typically resolve over 36 to 48 hours.[6] Although these ECG abnormalities in isolation are not 100% specific for cyclic antidepressant toxicity, they should be assumed to be attributable to cyclic antidepressant exposure and managed accordingly in appropriate clinical circumstances.

TREATMENT

Evaluate patients for alterations of consciousness, hemodynamic instability, and respiratory impairment. Establish an IV line, initiate continuous cardiac rhythm monitoring, and obtain serial ECGs. Suggested laboratory studies include serum electrolytes, creatinine, and glucose. To identify co-ingestants, obtain serum acetaminophen and salicylate levels. Blood gas measurement is recommended for symptomatic patients. In patients with antimuscarinic symptoms, urinary catheterization may be required to prevent urinary retention, and a nasogastric tube may be needed if ileus is present. **Patients who are initially asymptomatic may deteriorate rapidly and therefore should be monitored closely for 6 hours.** Treatment recommendations (**Table 177-4**) are based primarily on cohort or case-control studies resulting in only moderate strength of evidence for those measures discussed in the following sections.[20]

GI DECONTAMINATION

Do not use ipecac syrup or gastric lavage.[9,21-23] **Give a single 1 gram/kg dose of activated charcoal PO** if patients are awake, have a patent airway, and arrive within 1 hour of ingestion.[9,24] Activated charcoal effectively binds cyclic antidepressants and decreases absorption. Neither multidose activated charcoal nor whole-bowel irrigation is warranted.[21,25] Asymptomatic patients with reliable histories of minimal cyclic antidepressant ingestion can be treated with activated charcoal alone and observed for toxicity.

SODIUM BICARBONATE

Sodium bicarbonate is used to treat cardiac conduction abnormalities, ventricular dysrhythmias, or hypotension refractory to IV fluid.[20,26] **Administer sodium bicarbonate as an initial IV bolus of 1 to 2 mEq/kg,** and repeat until patient improvement is noted or until blood pH is between 7.50 and 7.55 (**Figure 177-2**). Additional alkalization beyond this point can be deleterious to oxygen extraction and serum electrolytes.

As an alternative of repeat boluses, continuous infusions of sodium bicarbonate can be administered as 150 mEq added to 1 L of 5% dextrose in water (or 100 mEq added to 5% dextrose in 0.45% saline, creating a slightly hypertonic solution with the sodium bicarbonate added) and infused IV at a rate of 2 to 3 mL/kg per hour. Adjustments in the IV rate are made based on blood pH measurements and clinical response

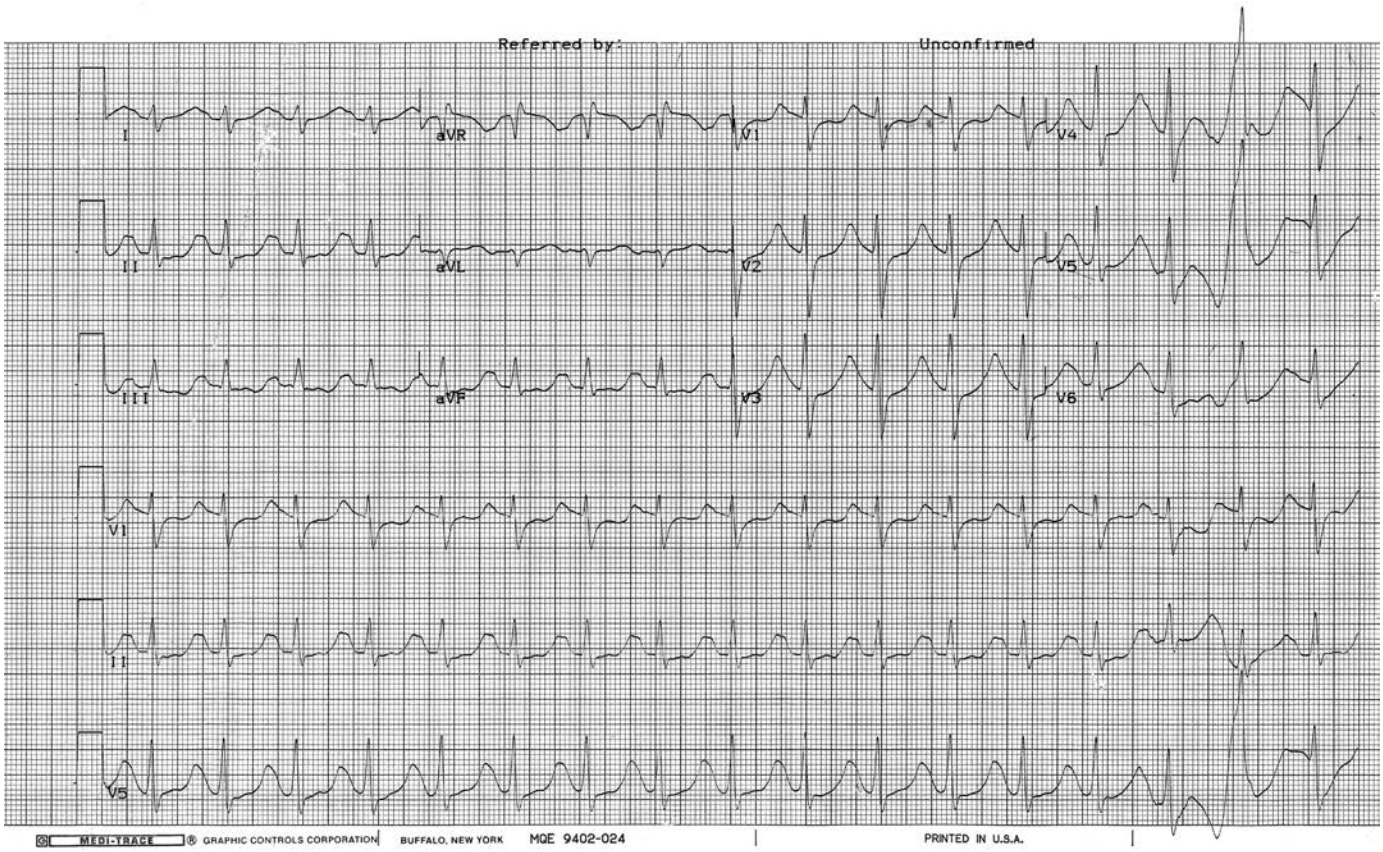

FIGURE 177-1. Twelve-lead ECG showing classic cyclic antidepressant ECG abnormalities: sinus tachycardia; prolonged PR, QRS, and QT intervals; and right axis deviation of the terminal 40 milliseconds of the QRS complex.

to therapy. Monitor serum electrolytes during the sodium bicarbonate infusion. Hypernatremia is not of particular concern using this dose of sodium bicarbonate.[13] Serum potassium will decrease during sodium bicarbonate therapy, and IV potassium supplementation may be required.[13]

ALTERED LEVEL OF CONSCIOUSNESS

Antagonism of postsynaptic muscarinic, histaminic, and α-adrenergic receptors contributes to the development of depressed mentation in cyclic antidepressant overdose. Coma from cyclic antidepressant toxicity typically is rapid in onset and is a predictive factor for cardiotoxicity and/or seizures.[5] Pulmonary aspiration is common among comatose cyclic antidepressant overdose patients. Agitation is observed commonly prior to the onset of coma, as well as during awakening. Agitation is best controlled with reassurance, decreased environmental stimulation, and benzodiazepines. **Do not give flumazenil or physostigmine for mixed cyclic antidepressant–benzodiazepine or cyclic antidepressant–anticholinergic overdoses, respectively.**

SEIZURES

Most seizures occur within the first 3 hours following ingestion and are typically generalized and of brief duration.[5] Multiple seizures are reported

TABLE 177-4 Treatment of Cyclic Antidepressant Overdose

Treatment	Dose	Indication	Comments
GI decontamination	Activated charcoal 1 gram/kg PO	Within 1 h of ingestion as long as airway is stable and patient is awake	Do not give multidose charcoal; do not perform whole-bowel irrigation
Initial treatment of hypotension or dysrhythmias	Sodium bicarbonate, 1–2 mEq/kg IV bolus; repeat bolus or add 150 mEq to 1 L 5% dextrose in water at 2–3 mL/kg per hour	For dysrhythmias, conduction abnormalities (QRS >100 ms), or hypotension refractory to IV fluid	Keep blood pH 7.50–7.55
Hypokalemia	Replace potassium as needed	Serum potassium <3.5 mEq/L	Bicarbonate will decrease potassium level
Seizures or agitation	Benzodiazepines for seizures or agitation	Phenobarbital 10–15 milligrams/kg for seizures refractory to benzodiazepines; watch for hypotension; secure airway with intubation	Do not give physostigmine, flumazenil, or phenytoin
Hypotension	Treat hypotension with normal saline, up to 30 mL/kg	Use norepinephrine or epinephrine if refractory to IV normal saline	Case reports suggest effectiveness of glucagon, 1 milligram IV bolus
Torsades de pointes and refractory dysrhythmias	Magnesium sulfate 2 grams IV; 3% saline 1–3 mL/kg IV over 10 min; overdrive pacing	Consider lipid emulsion for refractory dysrhythmias, but no convincing evidence of effectiveness	**Do not give** class I antiarrhythmics (i.e., procainamide, lidocaine, phenytoin, flecainide), β-blockers, calcium channel blockers, or class III antiarrhythmics (i.e., amiodarone, sotalol, ibutilide)

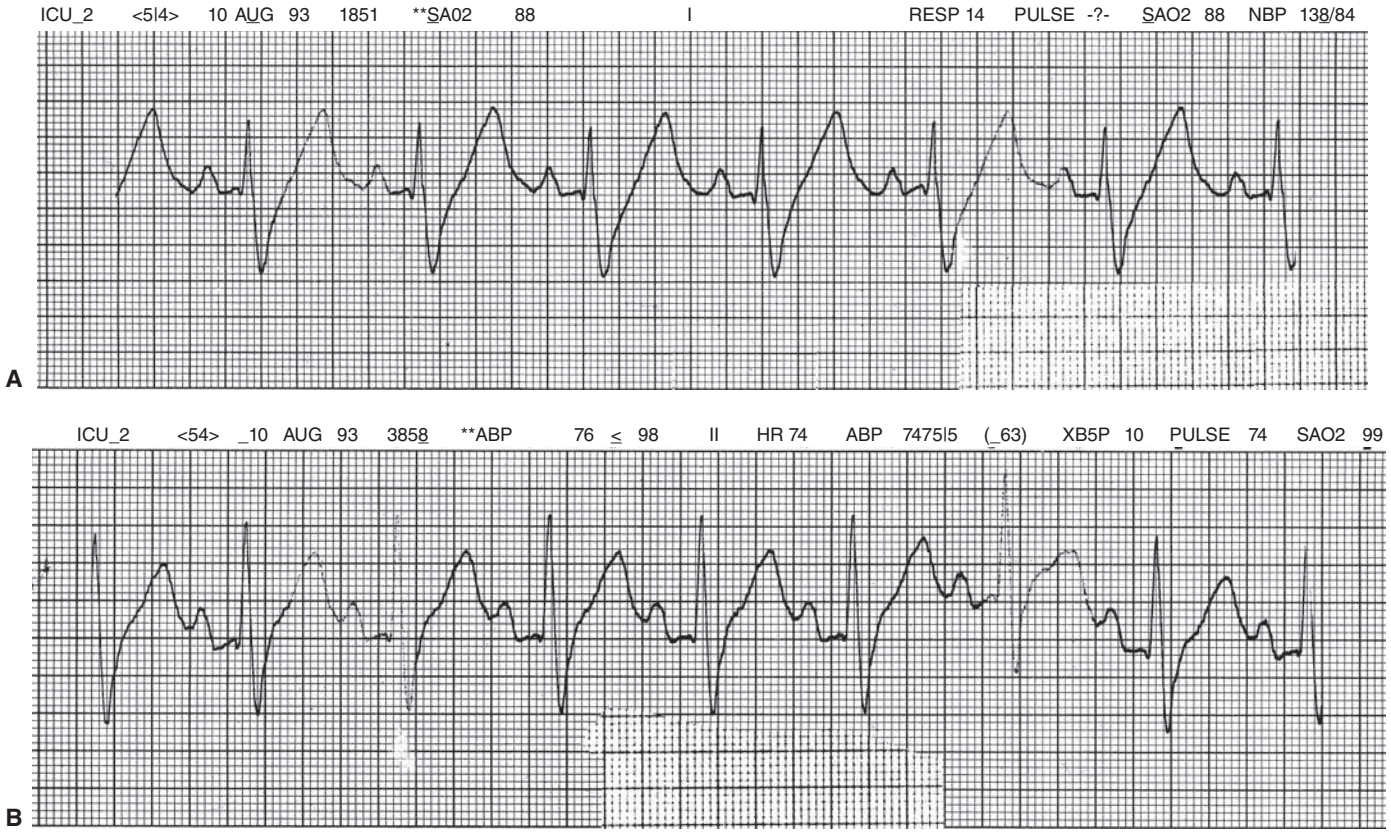

FIGURE 177-2. ECG before and after bicarbonate treatment. **A.** Cardiac rhythm strip of a patient with a wide QRS complex recorded 3 hours after ingestion of amitriptyline. **B.** Narrowing of the QRS complex in the same patient after administration of an IV bolus of sodium bicarbonate.

in approximately 10% to 30% of cases of cyclic antidepressant overdose. Focal seizures and status epilepticus are atypical and should prompt further neurologic evaluation. Seizures are especially common with maprotiline and amoxapine ingestions and require aggressive management, because status epilepticus is frequently associated with these two particular antidepressants.[11] **Benzodiazepines (e.g., diazepam, lorazepam) are the anticonvulsants of choice to stop seizure activity.** Barbiturates (e.g., phenobarbital) are indicated to treat seizures resistant to benzodiazepines. The initial IV dose of phenobarbital is 10 to 15 milligrams/kg, but this can be increased in patients with continued seizure activity and adequate blood pressure. Other therapy for refractory seizures includes continuous-infusion midazolam or propofol. Hypotension is a major side effect of IV phenobarbital administration.

Endotracheal intubation and respiratory support may be needed. **Phenytoin, sodium bicarbonate, and physostigmine do not stop cyclic antidepressant–induced seizures.** Neuromuscular blockers will stop the physical manifestations of seizures and their secondary effects, which include metabolic acidosis, hyperthermia, rhabdomyolysis, and renal failure, but they do not stop brain seizure activity. Therefore, following the induction of muscle paralysis, continue anticonvulsant therapy and consider electroencephalographic monitoring.

HYPOTENSION

Hypotension should be treated initially with isotonic crystalloid fluids in IV boluses in increments of 10 mL/kg to a maximum of 30 mL/kg.[20] With impaired cardiac contractility, pulmonary edema can develop if excessive fluids are administered. Hypotension that does not improve with appropriate fluid challenges should be treated with sodium bicarbonate (regardless of QRS complex duration). Vasopressors should be used when hypotension is unresponsive to fluids and sodium bicarbonate therapy, although response may be inconsistent.[27] **Norepinephrine and epinephrine are expected to be the most effective vasopressors because they directly compete with the cyclic antidepressants at the α-adrenergic receptors.** Start the IV infusion at 1 microgram/min and titrate according to blood pressure. Vasopressin can be tried if there is no response to norepinephrine or epinephrine.[28] Dopamine is less effective than norepinephrine in reversing cyclic antidepressant–induced hypotension because it has primarily indirect α-adrenergic agonist activity and, at lower dosages, promotes vasodilation through its β-adrenergic and dopaminergic actions.

Placement of a pulmonary artery catheter for monitoring in patients whose hypotension is refractory to fluid, sodium bicarbonate, and vasopressor therapy may precipitate life-threatening conduction abnormalities and ventricular dysrhythmias as the catheter passes through the right ventricle. Mechanical support of the circulation with cardiopulmonary bypass, overdrive pacing, or aortic balloon pump assistance may be warranted in patients with refractory hypotension, although no studies document the effectiveness of these measures. There are case reports suggesting that glucagon administered as 1-milligram IV boluses might be effective in patients with refractory cyclic antidepressant–induced hypotension.[29]

CARDIAC CONDUCTION ABNORMALITIES AND DYSRHYTHMIAS

Cyclic antidepressants frequently alter cardiac rate, conduction, and contractility. These negative cardiac effects are increased with acidosis, which occurs in patients with respiratory depression or seizures. Asymptomatic patients with sinus tachycardia, isolated PR interval prolongation, or first-degree atrioventricular block do not require specific pharmacologic therapy. Conduction blocks greater than first-degree atrioventricular block are worrisome because they can progress rapidly to complete heart block secondary to impaired infranodal conduction.

The controversial issue is whether asymptomatic or mildly toxic patients with isolated QRS complex prolongation should be treated with sodium bicarbonate therapy.[20] There are no controlled human trials demonstrating benefits in otherwise asymptomatic patients with QRS complex prolongation. Nonetheless, many physicians use sodium bicarbonate therapy in asymptomatic or minimally toxic patients with cyclic antidepressant overdose if the QRS duration is

>100 milliseconds. Hyperventilation represents a reasonable alternative to sodium bicarbonate therapy in the setting of renal failure, pulmonary edema, or cerebral edema, although hyperventilation is less effective in reversing toxicity.[30]

Ventricular dysrhythmias should be treated with sodium bicarbonate. Consider 3% hypertonic saline, 1 to 3 mL/kg IV over 10 minutes, to decrease ventricular ectopy or dysrhythmia in a patient with cardiotoxicity refractory to sodium bicarbonate therapy.[31]

Torsades de pointes should be treated initially with 2 grams of IV magnesium sulfate. Identify and treat electrolyte disorders that are associated with torsades de pointes. Overdrive pacing may be considered for refractory tachydysrhythmias. Older case reports indicate that IV isoproterenol may be of some benefit when overdrive pacing is not available. **The following medications are contraindicated in the treatment of cyclic antidepressant–induced dysrhythmias: all class I antiarrhythmic agents, β-blockers, calcium channel blockers, and all class III antiarrhythmic agents. Lidocaine, a sodium channel blocker, has unclear benefits in cyclic antidepressant–induced dysrhythmias, and there are no convincing data to support its effectiveness.**

LIPID EMULSION

Cyclic antidepressants are highly lipid soluble, and it has been postulated that IV lipid emulsion creates a "lipid sink" that sequesters the drug and prevents toxicity.[32] Case descriptions of lipid emulsion therapy for cyclic antidepressant overdoses report benefit,[33-39] no benefit,[40] and complications.[32,41] Currently, there is no consensus or convincing evidence for the use of lipid emulsion in cyclic antidepressant toxicity.[20,42-44] In patients with cardiotoxicity refractory to other measures, it seems reasonable to infuse a 20% lipid emulsion in an amount based on that recommended for local anesthetic systemic toxicity: 100 mL IV bolus (1.5 mL/kg) over 2 to 3 minutes, followed by an infusion of 18 mL (0.25 mL/kg) per minute to a total dose of 10 mL/kg.[44]

DISPOSITION AND FOLLOW-UP

Patients who remain asymptomatic after 6 hours of observation do not require hospital admission for toxicologic reasons.[10] All symptomatic patients require hospital admission to a monitored bed. Patients demonstrating signs of moderate to severe toxicity should be admitted to an intensive care unit. Hospitalized patients can be cleared medically after they are asymptomatic, with a normal or baseline ECG, normal mental status, and resolution of all antimuscarinic symptoms. Patients with an intentional overdose require mental health evaluation.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 178

Atypical and Serotonergic Antidepressants

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Erik G. Mattison

INTRODUCTION

Atypical and serotonergic antidepressants are commonly referred to as *newer* or *second-generation antidepressants* to distinguish them from the first-generation monoamine oxidase inhibitors and cyclic antidepressants. As a group, these antidepressants are the most popular form of psychopharmacologic therapy for the treatment of major depression, obsessive-compulsive disorder, panic disorders, and eating disorders.[1] These antidepressants produce less severe toxicity in overdose and are associated with fewer fatalities than either cyclic antidepressants or monoamine oxidase inhibitors.[2-4] This favorable overdose profile is tempered by the U.S. Food and Drug Administration black box warning regarding the use of some agents by patients <24 years old due to increased suicidal ideation and behavior.

This group of antidepressants is a heterogeneous collection of drugs that differ significantly in chemical structure, mechanism of action, pharmacokinetic characteristics, and adverse effect profile.[1] Nonetheless, they also share many important similarities.

Most possess serotonergic activity and, especially in combination with other serotonergic agents, have the potential to produce serotonin syndrome. These agents have negligible affinity for acetylcholine, dopamine, γ-aminobutyric acid, glutamate, and β-adrenergic receptors. These agents do not inhibit monoamine oxidase activity and are not associated with tyramine-like reactions. Most of these antidepressants do not significantly inhibit cardiac sodium, calcium, or potassium ion channels. Although their exact mechanism of action remains poorly understood, it is traditionally attributed to inhibition of neurotransmitter reuptake or interruption of negative feedback loops.

These antidepressants are metabolized primarily by hepatic enzyme systems (cytochrome P450 pathways). If two drugs are given that interact with a common metabolic pathway, drug levels can increase or decrease depending on the interaction. In addition, hepatic dysfunction can lead to elevated drug levels and subsequent drug toxicity. These antidepressants are not detected by routine hospital serum and urine drug screens. Specialty laboratories can measure parent drug and metabolite plasma levels, but this information is useful only for the confirmation of suspected drug overdose and does not affect patient management.

SPECIFIC AGENTS

ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants have chemical structures different from each other and from the other antidepressant classes (**Table 178-1**). They possess some unique clinical features at therapeutic doses and with overdoses.

BUPROPION

Bupropion has a monocyclic phenylaminoketone chemical structure that resembles the phenylethylamines (e.g., amphetamine), but does not produce stimulant effects or drug-addictive behavior at therapeutic dosages. The therapeutic mechanism of action of bupropion is primarily inhibition of neuronal reuptake of norepinephrine and dopamine with very minimal serotonergic activity.[5]

Bupropion is absorbed rapidly after oral administration, with peak plasma levels within 2 hours for regular-release tablets and within 3 hours for sustained-release preparations. Bupropion undergoes extensive first-pass hepatic metabolism, is highly protein bound, has an extremely large volume of distribution, and readily crosses the blood–brain barrier. The active metabolite, hydroxybupropion, although less potent than bupropion, preferentially inhibits norepinephrine reuptake and may contribute to seizure development.

Bupropion antidepressant therapy is well tolerated. The most commonly reported adverse effects at therapeutic dosages are mild and include dry mouth, dizziness, agitation, nausea, headache, constipation, tremor, anxiety, confusion, blurred vision, and increased motor activity.[6] Bupropion infrequently produces catatonia, hallucinations, psychosis, and paranoia, which are likely related to its dopaminergic activity. Abrupt discontinuation of bupropion has not been associated with withdrawal symptoms, but as a dopamine agonist, it may pose a slight theoretical risk of precipitating neuroleptic malignant syndrome after discontinuation.

Clinical Features Bupropion differs from other atypical antidepressants in that it has a narrow therapeutic index and possesses high morbidity and mortality indices after exposure.[4,7] Toxicity can occur

TABLE 178-1 Atypical Antidepressants

Agent	Recommended Maximum Daily Adult Dose (milligrams)	Elimination Half-Life Parent Compound (h)	Major Active Metabolite
Bupropion	450	10–21	Hydroxybupropion
Mirtazapine	45	20–40	Desmethylmirtazapine
Nefazodone	600	2–4	Hydroxy-nefazodone
Trazodone	400	3–6 (first phase) 5–9 (second phase)	*Meta*-chlorophenylpiperazine
Vilazodone	40	25	None
Vortioxetine	20	66	None

at dosages equal to or just slightly greater than the maximum therapeutic dose of 450 milligrams/d. **Conversely, significant toxicity is not expected in pure bupropion overdose with adult ingestions of <450 milligrams.** The most commonly reported symptoms in pure bupropion overdose include agitation, dizziness, tremor, nausea and vomiting, drowsiness, and tachycardia.[8,9] Mild hyperthermia is reported occasionally. Sinus tachycardia is the most common ECG abnormality seen following overdose, but QRS widening and QT interval prolongation have been reported.[10,11] Hypotension is unexpected in pure bupropion overdoses but has been reported in mixed-drug overdoses. Hypertension may occur but is usually of only mild to moderate severity. Coma and cardiac arrest have been reported in severe bupropion overdoses.

Seizures are more common with bupropion toxicity than with other atypical antidepressants[9,12] and usually are accompanied by other signs such as sinus tachycardia or altered mental status.[8,9,13] **Seizures can develop suddenly in otherwise asymptomatic patients.** Seizures usually occur within the first 1 to 4 hours after ingestion of immediate-release bupropion, but their appearance may be delayed for up to 8 hours.[8] Ingestions of extended-release preparations may predispose patients to seizures up to 24 hours after exposure.[13]

Treatment Establish a peripheral IV line, initiate cardiac rhythm monitoring, and obtain an ECG (**Table 178-2**). GI decontamination with activated charcoal is recommended provided it can be done within 1 hour of ingestion.[9] There is no evidence to support multidose activated charcoal or whole-bowel irrigation, even in overdoses of sustained-release products. Ipecac syrup is contraindicated due to the risk of seizures. Early onset of generalized seizures should be anticipated in all cases of bupropion ingestion and treated with benzodiazepines followed by phenobarbital, if necessary.

Hospital admission is recommended for all patients with seizures, persistent sinus tachycardia, or lethargy. Asymptomatic patients who have ingested only regular-release bupropion should be observed for 8 hours before discharge. **Adult patients ingesting >450 milligrams of extended-release bupropion require monitoring for approximately 24 hours.[13]**

MIRTAZAPINE

Mirtazapine is a tetracyclic compound that, in contrast to other atypical antidepressants, does not inhibit neuronal amine uptake.[1] Instead, it blocks central presynaptic α_2-adrenergic receptors and the postsynaptic serotonin 5-HT_2 and 5-HT_3 receptors. This has the therapeutic effect of increasing central norepinephrine and serotonin neurotransmission. Mirtazapine has a high affinity for blocking histamine-1 receptors and a moderate affinity for blocking muscarinic receptors. These effects commonly produce somnolence, especially in overdose.

Mirtazapine has a pharmacokinetic profile similar to other atypical antidepressants. It is absorbed rapidly with peak plasma levels within 2 hours after ingestion. Bioavailability is approximately 50% due to significant first-pass hepatic metabolism. The elimination half-life for mirtazapine is shorter in males than females, attributed to decreased cytochrome P450 metabolism in females. Mirtazapine is highly protein bound (85%) and has a large volume of distribution (5 L/kg). Agranulocytosis is a rare but potentially serious complication of chronic mirtazapine use.

Clinical Features Mirtazapine produces limited toxicity in overdose; the most common features are sedation, confusion, sinus tachycardia, and mild hypertension.[14-16] The risk of coma and respiratory depression is greatest at larger doses or when mirtazapine is combined with other sedative drugs.[16] Cardiac abnormalities such as sinus tachycardia or QT interval prolongation are rarely of clinical significance.[14-16]

Treatment Isolated mirtazapine overdose is managed with supportive care alone in the majority of ingestions.[14-16] Administer single-dose activated charcoal if the ingestion has occurred within the past hour. Ipecac syrup is contraindicated, and multidose activated charcoal or whole-bowel lavage is unnecessary. Symptomatic patients should be admitted to a monitored bed, but significant cardiac toxicity is very unlikely. Asymptomatic patients can be discharged after 6 hours of observation.

TABLE 178-2 Treatment of Bupropion Overdose

- IV access, cardiac rhythm monitor, and ECG
- Anticipate seizures; be prepared to treat with benzodiazepines
- Single-dose activated charcoal if ingestion within 1 h, especially if extended-release formulation
- Sodium bicarbonate for QRS complex prolongation >110 ms
- Magnesium sulfate for QT_c interval prolongation >500 ms
- Consider IV lipid emulsion therapy for refractory cardiovascular instability (case reports only)

NEFAZODONE

Nefazodone overdose is relatively benign; the most common symptom is drowsiness.[17] Hypotension, mild bradycardia, and prolonged QT interval can be seen in rare cases.[17,18] In general, symptoms occurred within 2 hours of ingestion and resolved with time and minimal supportive care.[17,18]

TRAZODONE

Trazodone is a triazolopyridine derivative with an antidepressant action believed to be due to a combination of serotonin reuptake inhibition and antagonism of postsynaptic serotonin 5-HT_2 receptors.[1] Trazodone is a moderately potent nonselective α-adrenergic receptor blocker with at least five times greater affinity for α_1-adrenergic than α_2-adrenergic receptors. Consequently, trazodone is frequently associated with orthostatic hypotension, which is maximal within the first 6 hours after ingestion, so the harmful consequences can be minimized by taking the medication at bedtime. Sedation, which is a common side effect of trazodone therapy, is believed to be secondary to inhibition of central α-adrenergic and histamine receptors.

Trazodone is absorbed rapidly and completely, with peak plasma levels occurring between 1 and 2 hours following oral administration. It is highly protein bound (89% to 95%) and has a moderate volume of distribution (1.2 L/kg). Trazodone primarily undergoes hepatic oxidation by the cytochrome P450 isoenzyme system producing one active metabolite, *meta*-chlorophenylpiperazine, which has a complex pharmacologic profile, including inhibition of serotonin uptake, stimulation and inhibition of multiple postsynaptic serotonin receptors, and interactions with other neurotransmitter systems.

The adverse effect profile for trazodone during therapeutic use is very favorable except that **trazodone is one of the most common causes of drug-induced priapism,** with an estimated incidence ranging from 1 to 10 per 10,000 patients. Trazodone should be discontinued immediately in any patient with a history of increased frequency of, increased duration of, or inappropriate penile or clitoral engorgement. Trazodone has been reported occasionally to be arrhythmogenic during therapeutic use, especially in patients with underlying cardiac risk factors such as conduction abnormalities or ischemic heart disease.

Clinical Features The most common symptom of acute trazodone poisoning is CNS depression. Other neurologic symptoms include ataxia

TABLE 178-3 Treatment of Trazodone Overdose

- IV access, cardiac rhythm monitor, and ECG
- Single-dose activated charcoal if ingestion within 1 h
- Treat seizures with IV benzodiazepines
- IV fluids for hypotension
- Direct-acting vasopressor (norepinephrine) for persistent hypotension and circulatory shock
- Magnesium sulfate for QT_c interval prolongation and/or torsades de pointes

and dizziness, and rarely, coma and seizures. Coma and seizures are more common when another epileptogenic drug is co-ingested. Pupils are usually of normal size and remain reactive. Trazodone-induced neurologic symptoms show marked improvement within 6 to 12 hours after ingestion and almost always resolve by 24 hours. Orthostatic hypotension is the most frequently reported cardiovascular abnormality noted in trazodone overdose and usually responds to fluid administration. The most common ECG abnormality is moderate prolongation of the QT interval.[17] Polymorphic ventricular tachycardia (torsades de pointes) has been reported in rare cases.[19] Commonly reported GI complaints include nausea, vomiting, and nonspecific abdominal pain.

Treatment Establish IV access, initiate cardiac rhythm monitoring, and obtain an ECG (**Table 178-3**). GI decontamination with single-dose activated charcoal can be used in appropriate patients who present within 1 hour. Patients who ingest >2 grams of trazodone or co-ingest other substances are at increased risk for serious toxicity with coma, seizures, respiratory arrest, cardiac dysrhythmias, and cardiac arrest.

Hypotension is treated initially with isotonic IV fluid administration. For persistent hypotension, use a direct-acting vasopressor (e.g., norepinephrine). Drugs with β-adrenergic receptor activity (e.g., dopamine) theoretically can worsen the hypotension in the presence of trazodone-induced α-adrenergic receptor antagonism. Treat QT interval prolongation and/or torsades de pointes arrhythmia with IV magnesium sulfate, followed by cardiac pacing as needed.[19]

Patients who have remained asymptomatic for at least 4 to 6 hours can be discharged safely from the ED, provided that necessary psychiatric evaluation has been completed or arranged. Patients with neurologic and/or cardiac symptoms require hospital admission to a monitored bed.

VILAZODONE

Vilazodone is an antidepressant with selective serotonin reuptake inhibition and partial serotonin $5\text{-}HT_{1A}$ agonism. Following overdose, the most common clinical features are drowsiness, vomiting, tachycardia, and agitation.[20] Most patients have symptoms for between 2 and 24 hours, although some remain symptomatic for more than 24 hours. Serotonin syndrome rarely occurs in isolated vilazodone overdoses.[20]

VORTIOXETINE

Vortioxetine selectively inhibits serotonin reuptake; antagonizes serotonin $5\text{-}HT_3$, $5\text{-}HT_{1D}$, and $5\text{-}HT_7$ receptors; stimulates the serotonin $5\text{-}HT_{1A}$ receptor; and is a partial agonist at the serotonin $5\text{-}HT_{1B}$ receptor.[17] Common side effects with therapeutic use include nausea, constipation, and vomiting. Clinical features in overdose are limited but appear to be minimal.[21] Serotonin syndrome would be a risk based on the mechanism of action.[17]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) are a structurally heterogeneous group of drugs that share selective affinity for inhibiting presynaptic serotonin reuptake without significantly affecting norepinephrine or dopamine reuptake (**Table 178-4**).[1] SSRIs are essentially devoid of direct presynaptic or postsynaptic receptor interactions. Thus, they are associated with fewer unwanted pharmacologic actions, in contrast with cyclic antidepressants.

TABLE 178-4 Selective Serotonin Reuptake Inhibitors

Agent	Recommended Maximum Daily Adult Dose (milligrams)	Elimination Half-Life Parent Compound (h)	Active Metabolite
Citalopram	40	35	Monodesmethylcitalopram Didesmethylocitalopram
Escitalopram	20	27–32	Desmethylcitalopram
Fluoxetine	80	96–144	Norfluoxetine
Fluvoxamine	300	16	None
Paroxetine	50	21	None
Sertraline	200	26	Desmethylsertraline

SSRIs are the most common form of pharmacotherapy for depression in the United States.[1] This class of antidepressants is the most frequently reported to be involved in drug overdoses, but fatalities are uncommon due to the high therapeutic index of these drugs.[2-4]

The SSRIs have similar pharmacokinetic profiles, including rapid and complete oral absorption, peak plasma levels occurring 4 to 8 hours after ingestion (except citalopram and escitalopram, which achieve peak plasma levels at 2 to 4 hours), significant first-pass hepatic metabolism, a high degree of protein binding (except citalopram and escitalopram), and a large volume of distribution. Fluoxetine is unique in that the active metabolite, norfluoxetine, is as potent as the parent compound. The half-life of norfluoxetine is 7 to 14 days, so the clinical effects of fluoxetine may last for up to 5 weeks after the last fluoxetine dose.

The SSRIs are metabolized almost entirely by the hepatic cytochrome P450 isoenzyme system, and these agents can inhibit the metabolism of other drugs dependent on that system. **The most serious drug-related adverse effect of SSRI psychopharmacotherapy is serotonin syndrome** (see later section, "Serotonin Syndrome").

Adverse effects with therapeutic doses include hyponatremia, which is believed to be secondary to inappropriate secretion of antidiuretic hormone.[1] Priapism has been reported but is extremely rare. A withdrawal syndrome consisting of nonspecific neurologic, psychiatric, and GI symptoms has been described in conjunction with abrupt discontinuation. It is less likely to occur with fluoxetine due to its long-acting metabolite.

Other neurologic adverse effects associated with SSRIs include headache, sedation, insomnia, dizziness, weakness or fatigue, tremor, and nervousness.[1] Seizures are uncommon but have been reported with all of these agents, with citalopram associated with the highest incidence of seizures among the SSRIs.[1] Serotonin has varying effects on the dopaminergic system. In many cases, extrapyramidal symptoms such as dystonic reactions, akathisia, dyskinesia, hypokinesia, and parkinsonian symptoms have been reported in association with SSRI therapy.[20] Consequently, SSRIs should be used cautiously with antipsychotic agents because they can potentiate antidopaminergic activity. Patients taking SSRIs commonly report GI complaints, such as nausea, diarrhea, constipation, vomiting, and anorexia. Other adverse effects less commonly reported include dry mouth, increased sweating, and blurred vision.

CLINICAL FEATURES

The greatest amount of human SSRI overdose experience has been with fluoxetine.[22] Information from case series involving the other SSRIs is consistent with the information accumulated on fluoxetine.[23,24] Fortunately, all of the SSRIs are characterized by a high therapeutic index, and fatalities are uncommon with pure overdoses.[2-4] Most adult and pediatric patients remain asymptomatic following SSRI overdose. The most common clinical features in symptomatic patients from overdose include nausea, vomiting, sedation, tremor, and sinus tachycardia. Less frequently observed are mydriasis, seizures, diarrhea, agitation, hallucinations, hypertension, and hypotension.

Sinus bradycardia is observed more frequently in fluvoxamine overdoses than in overdoses of other SSRIs. **Prolongation of the QRS complex and QT interval occurs in association with significant**

TABLE 178-5 Treatment of Selective Serotonin Reuptake Inhibitor Overdose

- IV access, cardiac rhythm monitor, and ECG
- Single-dose activated charcoal if ingestion within 1 h
- Treat seizures with IV benzodiazepines
- Sodium bicarbonate for prolonged QRS complex
- Magnesium sulfate for QT_c interval prolongation and/or torsades de pointes

citalopram and escitalopram ingestions.[25-30] In most cases, the ECG abnormalities gradually resolve over 24 hours. Tachycardia, mild hypotension, and lethargy are seen more commonly when SSRIs are combined with ethanol. Mixed-drug ingestions can produce a wide variety of additional symptoms depending on the toxicity of the co-ingestant. **About 10% of reported instances of serotonin syndrome occur as a consequence of acute overdose.**

TREATMENT

In patients who intentionally overdose, establish a peripheral IV line, initiate cardiac rhythm monitoring, and obtain an ECG (**Table 178-5**). Pure SSRI overdoses are associated with limited toxicity except for the infrequent development of life-threatening complications such as generalized seizures and serotonin syndrome. Based on the high therapeutic index and unlikelihood of serious toxicity, treatment with single-dose activated charcoal is logical for patients presenting within 1 hour of ingestion. Gastric lavage, ipecac syrup, multidose activated charcoal, and whole-bowel irrigation are not recommended.

Benzodiazepines are recommended as initial anticonvulsant therapy, followed by phenobarbital if seizures persist. Prolonged QRS or QT intervals are usually seen with citalopram or escitalopram but have been reported with other SSRIs in polydrug ingestions.[31] Delayed-onset serotonin syndrome, extrapyramidal reactions, and torsades de pointes are possibilities, especially with sustained-release compounds.[31,32]

Patients should be observed for 6 hours, during which time supportive care is generally adequate. Hospital admission with continuous cardiac rhythm monitoring is recommended for all patients who remain tachycardic, have altered mental status, ingested citalopram or escitalopram, demonstrate cardiac conduction abnormalities, or have features of the serotonin syndrome.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

The serotonin/norepinephrine reuptake inhibitors (SNRIs) are primarily nonselective inhibitors of serotonin and norepinephrine reuptake with a very small amount of dopamine reuptake inhibition (**Table 178-6**).[1] These drugs have no significant direct effect on presynaptic or postsynaptic neurotransmitter receptors. The SNRIs differ in their degree of protein binding and apparent volume of distribution, from venlafaxine with 27% protein binding and 6 to 7 L/kg volume of distribution, to duloxetine with 95% protein binding and a 1640 L/kg volume of distribution. Venlafaxine is absorbed the fastest after ingestion, achieving peak levels at 2 hours, whereas duloxetine reaches peak blood levels 6 to 10 hours after ingestion.

TABLE 178-6 Serotonin/Norepinephrine Reuptake Inhibitors

Agent	Recommended Maximum Daily Adult Dose (milligrams)	Elimination Half-Life (h)	Major Active Metabolites
Desvenlafaxine	100	11	None
Duloxetine	120	12	None
Levomilnacipran	120	12	None
Venlafaxine	375	5	Desmethylverlafaxine

TABLE 178-7 Treatment of Serotonin/Norepinephrine Reuptake Inhibitor Overdose

- IV access, cardiac rhythm monitor, and ECG
- Single-dose activated charcoal if ingestion within 1 h
- Consider whole-bowel irrigation with large (>4000 milligrams) venlafaxine overdoses
- Treat seizures with IV benzodiazepines
- IV fluids for rhabdomyolysis
- Sodium bicarbonate for prolonged QRS complex
- Magnesium sulfate for QT_c interval prolongation
- IV fluids and direct-acting vasopressors for hypotension

The adverse effect profile during therapeutic use for these medications is similar to that for SSRIs.[33] Venlafaxine is a notable exception and is able to produce mild to moderate hypertension when dosages exceed 225 milligrams/d, probably secondary to inhibition of norepinephrine reuptake. Duloxetine appears to have more GI side effects, such as nausea, dizziness, and vomiting, but causes less hypertension than venlafaxine.[34]

CLINICAL FEATURES

All SNRIs cause sympathetic nervous system stimulation via inhibition of norepinephrine reuptake, which predisposes patients to tachycardia, hypertension, diaphoresis, tremor, and mydriasis. Most of these effects are of moderate severity and can usually be managed with supportive care alone.[35] Patients may display alterations in level of consciousness, with mild to moderate sedation being fairly common and progressing to coma on rare occasions. Generalized seizures tend to occur early after ingestion and are more common after overdose with venlafaxine than after most SSRI exposures.[12] Subclinical rhabdomyolysis has been observed in about 25% of patients without seizures and 60% of patients with seizures following a venlafaxine overdose.[36] Large overdoses of venlafaxine can produce severe global impairment of left ventricular systolic contraction with a markedly reduced ejection fracture.[37]

ECG abnormalities are common following intentional SNRI overdoses. Sinus tachycardia is the most common ECG abnormality observed, but QRS widening and QT interval prolongation have also been reported.[10] Mortality is low in isolated overdose.[4,38]

TREATMENT

Establish a peripheral IV line, initiate cardiac rhythm monitoring, and obtain an ECG (**Table 178-7**). Single-dose activated charcoal is logical therapy for most SNRI overdoses if seen within an hour after ingestion.[39] Gastric lavage and ipecac syrup are contraindicated due to the potential for seizures and aspiration. Consider whole-bowel irrigation with a large venlafaxine ingestion.[39] Benzodiazepines are the anticonvulsants of choice. Hypertension and sinus tachycardia rarely require specific pharmacologic therapy, and β-blockers have the theoretical disadvantage of allowing unopposed α-adrenergic receptor stimulation. Treat hypotension with fluids and direct-acting α-agonists.

Asymptomatic patients should be observed for 6 hours. Symptomatic patients should be admitted to a monitored bed. Patients ingesting extended-release preparations require additional observation for at least 24 hours due to the possibility of delayed onset of toxicity.

SEROTONIN SYNDROME

Serotonin syndrome is a potentially life-threatening adverse drug reaction to serotonergic medications. It can be produced by any drug or, more commonly, by a combination of drugs that increase central serotonin neurotransmission (**Table 178-8**).[40-44] Antidepressants are the drug class most commonly associated with serotonin syndrome. Serotonin syndrome is characterized by a combination of alterations in cognition and behavior, autonomic nervous system function, and

TABLE 178-8 Serotonergic Drugs

Antidepressants

- Monoamine oxidase inhibitors: phenelzine, tranylcypromine, isocarboxazid, pargyline, rasagiline, and selegiline
- Selective serotonin reuptake inhibitors: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram
- Serotonin/norepinephrine reuptake inhibitors: venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine
- Cyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine
- Atypical antidepressants: trazodone (moderate potency), bupropion (low potency), and vilazodone (moderate potency)

Other Agents (potency to cause serotonin syndrome)

Amantadine (low potency)	Lysergic acid diethylamide (moderate potency)
Amphetamines (moderate potency)	Meperidine (high potency)
Bromocriptine (low potency)	Mescaline (moderate potency)
Buspirone (moderate potency)	Metoclopramide (low potency)
Carbamazepine (low potency)	Pentazocine (low potency)
Cocaine (moderate potency)	Pergolide (low potency)
Codeine (low potency)	Reserpine (low potency)
Dextromethorphan (high potency)	St. John's wort (moderate potency)
Fentanyl (moderate potency)	Sumatriptan and related triptans (high potency)
Levodopa (moderate potency)	Tramadol (high potency)
Linezolid (high potency)	
Lithium (high potency)	
L-Tryptophan and 5-hydroxytryptophan (high potency)	

neuromuscular activity.[40-44] The degree of abnormality in any one area is highly variable. The stimulation of specific postsynaptic serotonin receptors is required for full expression of this syndrome, primarily the serotonin 5-HT_{1A} and 5-HT_{2A} receptors, but other receptor subtypes may contribute. Drugs that block postsynaptic serotonin receptors are incapable of inducing this syndrome and are often used as a form of treatment.

CLINICAL FEATURES

The triad of cognitive, autonomic, and neuromuscular effects is a classic feature of the serotonin syndrome (**Table 178-9**). The vast majority of serotonin syndrome cases occur in patients taking serotonergic drugs at therapeutic dosages, but approximately 10% of cases develop after an overdose of serotonergic medication. **Serotonin syndrome usually occurs within 2 to 24 hours after the dosage of a serotonin agonist** (e.g., a monoamine oxidase inhibitor or an SSRI) has been increased or after a second serotonergic agent (e.g., dextromethorphan) has been added.

TABLE 178-9 Clinical Features of Serotonin Syndrome

	Major	Minor
Cognitive	Altered level of consciousness Agitation	Insomnia Restlessness Anxiety
Autonomic	Hyperthermia Diaphoresis	Tachycardia Hypertension or hypotension Tachypnea Mydriasis
Neuromuscular	Muscle rigidity Hyperreflexia Myoclonus Tremor	Akathisia Incoordination

TABLE 178-10 Comparison of Serotonin Syndrome, Neuroleptic Malignant Syndrome, and Anticholinergic Toxicity

	Serotonin Syndrome	Neuroleptic Malignant Syndrome	Anticholinergic Toxicity
Precipitating event	Addition of serotonergic agent	Addition of dopamine antagonist or withdrawal from dopamine agonist	Addition of anticholinergic agent
Onset	Usually within 24 h	Usually within days to weeks	Usually within 1–2 h
Distinguishing features	Myoclonus, tremor	Bradyreflexia (sluggish reflex response) and bradykinesia (motor slowing or psychomotor retardation)	Dry skin and mucous membranes
	Hyperreflexia	Lead pipe rigidity	Normal muscle tone and reflexes

The importance of serotonin syndrome in emergency practice is twofold. First, the diagnosis of serotonin syndrome is very challenging because of its nonspecific symptomatology.[45,46] Mild cases of serotonin syndrome frequently are misinterpreted as other psychiatric and medical disorders, and **severe cases are often misdiagnosed as neuroleptic malignant syndrome** because the two disorders share some features such as hypertension, tachycardia, tachypnea, fever, hypersalivation, and diaphoresis (**Table 178-10**).[47,48] Without proper recognition of patients at risk for serotonin syndrome, one may inadvertently precipitate serotonin syndrome by administering serotonergic agents (e.g., meperidine, tramadol, dextromethorphan). To prevent iatrogenic precipitation of the serotonin syndrome, use drug databases and other resources to evaluate for potential drug interactions.

The severity of serotonin syndrome varies (**Table 178-11**). The most commonly reported signs and symptoms associated with serotonin syndrome are altered mental status, hyperthermia, and increased muscle tone.[40-44] **Myoclonus is a common finding in serotonin syndrome and is an important distinguishing feature, because myoclonus is rarely seen in other conditions that mimic serotonin syndrome** (see Chapter 179, "Monoamine Oxidase Inhibitors," Chapter 180, "Antipsychotics," and Chapter 202, "Anticholinergics").[47-50]

Muscle rigidity, when present, is especially prominent in the lower extremities, which serves as another valuable clinical marker for serotonin syndrome. Patients with ataxia should be examined carefully for lower extremity hypertonia. Unilateral muscle rigidity and focal neurologic findings are not expected. Seizures are always generalized and usually short lived. Hyperthermia is usually of moderate severity, but temperatures >41°C (106°F) have been reported and are a marker of a poor prognosis. Hypertension is twice as common as hypotension and is associated with a more favorable prognosis.

There are no confirmatory laboratory tests for serotonin syndrome. Therefore, the diagnosis of serotonin syndrome is based entirely on clinical assessment and exclusion of other psychiatric and medical conditions. Published diagnostic criteria for serotonin syndrome emphasize exposure to a known serotonergic drug and the presence

TABLE 178-11 Severity Pattern of Serotonin Syndrome

Category	Clinical Features
Mild	Mild agitation, mild fever (<40°C), tremor, myoclonus, hyperreflexia, diaphoresis, mydriasis, elevated blood pressure and heart rate
Moderate	Marked agitation, hyperthermia (>40°C), myoclonus, hyperreflexia, ocular clonus, increased bowel sounds
Severe	Hyperthermia (>41.1°C), delirium, marked muscle rigidity, marked swings in blood pressure and heart rate

TABLE 178-12 Treatment of Serotonin Syndrome

- Stop all serotonergic therapy
- Initiate cardiopulmonary monitoring, establish peripheral IV access, and obtain ECG
- IV fluid rehydration; evaluate for rhabdomyolysis
- External cooling measures for hyperthermia
- Benzodiazepines for agitation
- Use short-acting IV antihypertensives (nitroprusside or esmolol) for severe hypertension
- Use direct-acting IV vasopressors (norepinephrine, epinephrine, or phenylephrine) for hypotension resistant to IV fluid resuscitation
- Cyproheptadine has been suggested in the past, but clinical evidence of benefit is lacking

of muscle clonus alone or at least one or two of the other common features.[40-44]

TREATMENT

The cornerstone of treating serotonin syndrome is discontinuing all serotonergic drugs and providing appropriate supportive care (Table 178-12).[40-44,50-52] All patients with serotonin syndrome should be admitted to the hospital until their symptoms have completely resolved. Severely ill patients require admission to an intensive care unit. Approximately 25% of patients require endotracheal intubation and ventilatory support. Most patients show dramatic improvement within 24 hours of symptom onset. Mortality varies according to the severity of the syndrome and aggressiveness of care.[41-44] The most common cause of death is severe hyperthermia.

Benzodiazepines are nonspecific serotonin antagonists and can be used to decrease patient discomfort and promote muscle relaxation.[52] Patients with severe serotonin syndrome should be sedated, undergo neuromuscular blockade with a nondepolarizing agent, have an endotracheal tube placed, be started on mechanical ventilation, and be admitted to the intensive care unit.

Cyproheptadine, is an antihistamine and serotonin antagonist with anticholinergic effects.[41-44] It can be used (off-label) for serotonin syndrome, but is only available in PO form. The initial dose is 12 milligrams, with repeat doses of 2 milligrams every 2 hours until clinical improvement is seen. However, benefits of, and indications for, cyproheptadine are not known due to lack of supportive clinical evidence.[50]

Chlorpromazine is an antagonist of 5-HT_{2A} receptors and there are reports of successful treatment of serotonin syndrome.[41,43] The advantage of chlorpromazine is that it is available in a parenteral form, but a potential disadvantage is that it can cause hypotension. It also blocks dopamine receptors, which can promote muscle rigidity, lower seizure threshold, and exacerbate neuroleptic malignant syndrome.[50] The use of dopamine agonists (e.g., bromocriptine) has no accepted role in treating patients with serotonin syndrome.[42] Dantrolene is a nonspecific muscle relaxant that is used occasionally in the management of serotonin syndrome, but clinical benefit is unproven.[42]

Patients with muscle rigidity, seizures, or hyperthermia should be monitored closely for rhabdomyolysis and/or metabolic acidosis. Clinical features of the serotonin syndrome usually resolve within 24 hours after the inciting drug is stopped, with an exception being fluoxetine due to its long half-life and that of the active metabolite. Once a patient recovers from serotonin syndrome, avoid future exposure to serotonergic drugs (Table 178-4), although the risk of recurrence is unknown.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 179

Monoamine Oxidase Inhibitors

Frank LoVecchio

INTRODUCTION

Monoamine oxidase inhibitors (MAOIs) were the first class of antidepressants, but current use of these agents is primarily limited to treating atypical and refractory cases of depression (**Table 179-1**).[1] Newer antidepressants have a more favorable side effect profile, less overdose toxicity, and no dietary restrictions. The declining popularity of oral MAOIs for the treatment of depression is partially offset by their increasing use for the treatment of Parkinson's disease.[2] In addition, a transdermal method of selegiline administration, approved for use in major depression, appears to avoid some of the worrisome aspects associated with traditional oral therapy.[3-5]

Safety and effectiveness of MAOIs in children have not been established, and the four agents used for treatment of depression have the identical U.S. Food and Drug Administration–mandated black box warning stating that patients <24 years old may have increased suicidal thinking and behavior while taking any type of antidepressant medication.

MAOIs are associated with tyramine reactions, serotonin syndrome, and medication incompatibilities that are unique to this class of antidepressants. Overdoses of MAOIs are considered life-threatening emergencies, and **even one pill could potentially kill a toddler**. The onset of clinical toxicity is often delayed to between 6 and 24 hours after ingestion, which can lead to misdiagnosis and mismanagement.

MAOI antidepressants with improved safety and tolerability, such as moclobemide, are available in Canada, Australia, and Europe, but not the United States. **St. John's wort (*Hypericum perforatum*)** contains many active ingredients, some of which have the ability to inhibit monoamine oxidase (MAO) and block serotonin reuptake.[6] St. John's wort is considered generally safe when taken at recommended dosages, but even modest MAO inhibition may become clinically significant in overdose, contribute to serotonin syndrome, or participate in a drug–drug interaction.

Medications with MAO inhibition as a pharmacologic action unrelated to their clinical indication (e.g., linezolid, procarbazine, furazolidone, and methylene blue) can precipitate serotonin syndrome when combined with other serotonergic agents.[7,8]

PHARMACOLOGY

MAO is an intracellular enzyme bound to the outer mitochondrial membrane.[9,10] It has been identified in most human cells except erythrocytes (which do not contain mitochondria). MAO removes amine groups from both endogenous and exogenous biogenic amines. This oxidative deamination process is the primary mechanism by which endogenous biogenic amines, such as norepinephrine, dopamine, and serotonin, become inactivated. A second important function of MAO is to decrease the systemic availability of absorbed dietary biogenic amines (e.g., tyramine) via hepatic and intestinal metabolism. Thus, inhibition of MAO leads to the accumulation of neurotransmitters in presynaptic nerve terminals (both centrally and peripherally) and increased systemic availability of dietary amines. MAO has a negligible role in metabolizing circulating catecholamines, either secreted endogenously (e.g., by the adrenal gland) or administered parenterally (e.g., epinephrine). Circulating catecholamines are metabolized by the enzyme catechol-O-methyltransferase that is located extraneuronally and is not affected by MAOIs.

MAO exists as two different isoenzymes, designated *monoamine oxidase isoenzyme A* (MAO-A) and *monoamine oxidase isoenzyme B* (MAO-B). Each isoenzyme has its own relative preference for different neurotransmitters, dietary amines, and inhibitory drugs.[9] During normal physiology, MAO-A is primarily responsible for the breakdown of serotonin and norepinephrine, whereas MAO-B preferentially metabolizes phenylethylamine; MAO-A and MAO-B have equal ability to metabolize dopamine or tyramine. These preferences are entirely dose

TABLE 179-1 U.S. Food and Drug Administration Approved Monoamine Oxidase Inhibitors

Agent	Indication	Formulation	Average Daily Therapeutic Dose	Maximum Daily Therapeutic Dose	Selectivity
Isocarboxazid	Major depression	10-milligram tablet	10–40 milligrams	60 milligrams	Nonselective
Phenelzine	Major depression	15-milligram tablet	45–75 milligrams	90 milligrams	Nonselective
Tranylcypromine	Major depression	10-milligram tablet	20–40 milligrams	60 milligrams	Nonselective
Selegiline	Major depression	6 milligrams, 9 milligrams, and 12 milligrams per 24-h patch	6 milligrams per 24-h patch	12 milligrams per 24-h patch	Nonselective (as a skin-patch formulation)
Rasagiline	Parkinson's disease	0.5- and 1.0-milligram tablets	0.5–1.0 milligram	1 milligram	MAO-B
Selegiline	Parkinson's disease	5-milligram tablet	10 milligrams	10 milligrams	MAO-B (as an oral formulation)
		1.25-milligram oral disintegrating tablet	1.25 milligrams	2.5 milligrams	MAO-B (as an oral formulation)
Moclobemide*	Major depression, social anxiety	150- and 300-milligram tablets	300 milligrams	600 milligrams	MAO-A

Abbreviations: MAO-A = monoamine oxidase isoenzyme A; MAO-B = monoamine oxidase isoenzyme B.

*Not available in the United States.

dependent and can be overcome at higher substrate concentrations or inhibitor doses (e.g., selegiline).

Overall, the human brain contains more MAO-B, and this predominance increases with advancing age. Dopaminergic neurons lack MAO-B activity and have limited MAO-A activity,[2] but significant MAO-B activity is present in surrounding astrocytes and glial cells. Thus, dopamine inactivation depends on astrocyte and glial cell metabolism. Serotonergic neurons exclusively contain MAO-B, which allows more serotonin to be recycled intact while metabolizing other nonserotonin neurotransmitters. Intestinal MAO activity is mostly due to MAO-A, whereas approximately equal proportions of both isoenzymes are found in the liver, affording the body protection against ingested exogenous amines that can cause toxicity (e.g., tyramine reaction).

Blockade of MAO-A in the GI tract is responsible for a severe hypertensive crisis that can occur after patients on MAOIs ingest foods containing the sympathomimetic tyramine, and the use of transdermal formulations may avert these side effects. Tyramine is usually metabolized in the GI tract, but the blockade of MAO-A allows it to flow into the general circulation. Although the accepted "MAOI diet" has been liberalized in recent years,[11] there are still several dietary restrictions to which patients on these medications must adhere.

MAOIs share structural similarities with endogenous amines that allow them to act as potential substrates for the enzyme. The antidepressant activity of phenelzine, tranylcypromine, isocarboxazid, and transdermal selegiline has been primarily attributed to their ability to increase norepinephrine and serotonin neurotransmission by increasing presynaptic concentrations of both amines. Their antidepressant effect correlates with >80% MAO-A inhibition. Additional mechanisms by which they exert their therapeutic effects are probably related to delayed postsynaptic receptor modifications (e.g., downregulation), indirect release of neurotransmitters, and inhibition of neurotransmitter reuptake.

The therapeutic benefit of selective MAO-B inhibitors in Parkinson's disease is related to increased striatal dopamine neurotransmission and protection against neuronal damage from oxidative stress.[2] MAO-B inhibition of >80% correlates with the observed therapeutic effect of selegiline and rasagiline in Parkinson's disease. At therapeutic doses, there is limited inhibition of MAO-A with modest effects on norepinephrine and serotonin metabolism.[2] However, at large doses (e.g., selegiline >20 milligrams/d), increasing MAO-A inhibition increases presynaptic norepinephrine and serotonin concentrations and thus has the potential to produce drug-related toxicity similar to that of the nonselective agents (phenelzine, tranylcypromine, and isocarboxazid).

Traditional MAOIs, such as isocarboxazid, phenelzine, tranylcypromine, rasagiline, and selegiline, form irreversible covalent bonds with the enzyme, rendering it permanently inactive. Once an irreversible inhibitor drug has been discontinued, it takes approximately 2 weeks before new enzyme synthesis restores activity to 50% of normal and up to 40 days to regain 100% activity.[10] Reversible inhibitors, on the other hand, competitively inhibit enzyme activity. After the reversible inhibitor drug is stopped, MAO function recovers over a period of hours as the drug–enzyme complex spontaneously dissociates. Moclobemide and toloxatone are reversible MAOIs available in most of the world, but not in the United States.

PHARMACOKINETICS

MAOI tablets are absorbed rapidly and completely from the GI tract but have relatively low bioavailability because of a large first-pass effect of hepatic metabolism.[10] The skin patch form of selegiline allows for more parent drug to bypass first-pass liver metabolism; this results in elevated blood levels with nonselective MAO inhibition and antidepressant activity.[4] The oral form of selegiline has lower blood levels secondary to first-pass effects, retains its MAO-B selectivity, and does not have antidepressant qualities. Metabolism by hepatic cytochrome P450 predisposes MAOIs to potential interactions with other drugs requiring similar hepatic enzyme pathways. Peak drug levels usually occur within 1 to 3 hours of ingestion. These drugs are highly protein bound and have relatively large volumes of distribution. Elimination half-life is relatively short, and an **important feature of clinical toxicity is that it is usually delayed until well after most of the drug has already been metabolized. Hence, blood levels do not correlate with clinical toxicity.**

Selegiline has many active metabolites, including desmethylselegiline, amphetamine, and methamphetamine.[5,12] Tranylcypromine does not produce amphetamine metabolites at normal therapeutic doses, but amphetamine has been noted in the serum following tranylcypromine overdose. Phenelzine metabolism results in multiple active metabolites such as β-phenylethylamine, which is metabolized by MAO-B. Rasagiline does not have any active metabolites.[2] Transdermal selegiline offers the advantage of continuous absorption over a 24-hour period without any peak effects. However, its absorption can be drastically increased by external heat application (e.g., sauna, heating pad).[4,5] The pharmacokinetic profile of most MAOIs indicates that attempts at extracorporeal removal (e.g., hemodialysis) or administration of repeat doses of activated charcoal would be unsuccessful in significantly reducing plasma drug levels.

DRUG INTERACTIONS

Long-term MAOI therapy predisposes to many potentially significant drug–drug interactions; some have been well established, whereas others are based on single case reports or solely on theoretical considerations.[11] Controlled human studies are impossible due to the life-threatening nature of these reactions, and animal studies often have limited applicability to human toxicity. **Therefore, emergency physicians should never administer new medications to patients taking MAOIs unless absolutely necessary.** Compatibility should always be confirmed before a new drug is administered, and the lowest effective dose should be used.

Drug–drug interactions involving MAOIs can be grouped into two categories: pharmacodynamic or pharmacokinetic. The most common

TABLE 179-2 Medications Considered Safe in Combination With Monoamine Oxidase Inhibitors*

Direct-Acting Sympathomimetics	Miscellaneous Drugs
Albuterol aerosol	Acetaminophen
Dobutamine	Antibiotics (except linezolid and furazolidone)
Epinephrine	Barbiturates
Isoproterenol	Benzodiazepines
Methoxamine	Calcium channel blockers
Norepinephrine	Corticosteroids
Terbutaline	Lidocaine
Vasopressin	Morphine
	Nitroglycerin
	Nitroprusside
	NSAIDs
	Phentolamine
	Procainamide

*Always use the lowest effective dosage.

pharmacodynamic reaction involves indirect-acting sympathomimetics. They have the potential to produce a hyperadrenergic condition similar to the tyramine reaction and can be found in over-the-counter preparations, drugs of abuse, and some prescription products. Pharmacokinetic interactions have been noted between certain drugs and MAOIs because these drugs are metabolized through the cytochrome oxidase enzyme system and thus can inhibit the metabolism of each other. A notable example of this type of drug interaction is the ability of ciprofloxacin and cimetidine to inhibit the metabolism of rasagiline, which can double its serum concentration.[2] Tranylcypromine and phenelzine have been shown to increase insulin release and predispose to hypoglycemia, especially in patients taking oral sulfonylurea agents.

SEROTONIN SYNDROME

Serotonin syndrome (see Chapter 178, "Atypical and Serotonergic Antidepressants") is a potentially life-threatening, often iatrogenic reaction. With MAOIs, serotonin syndrome most commonly occurs when combined with other serotonergic agents. **The important principle for emergency physicians is not to use meperidine, dextromethorphan, tramadol, linezolid, propoxyphene, a selective serotonin reuptake inhibitor, or a selective serotonin-norepinephrine reuptake inhibitor in a patient on MAOI therapy.** Patients should be warned about concomitant use of illicit drugs in general but especially cocaine, 3,4-methylenedioxymethamphetamine (MDMA; popularly known as ecstasy), and methamphetamine. Even after a patient discontinues MAOI therapy, 2 weeks are required before 50% of MAO enzyme activity returns. In general, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors should be discontinued for 2 weeks prior to using an MAOI with the exception of fluoxetine, which should be stopped 4 weeks before using an MAOI. **Consequently, there should be at least a 2-week abstinence period between the time an MAOI is discontinued and when any contraindicated drug is started; this recommendation is particularly important to prevent the development of serotonin syndrome.**

Awareness of which medications are generally considered safe for patients taking MAOIs is useful (**Table 179-2**). **Aspirin, acetaminophen, ibuprofen, morphine, and most antibiotics have been used in combination with MAOIs without complications.**

CLINICAL FEATURES

MAOIs have a low ratio of toxic to therapeutic dose. This characteristic predisposes patients to significant drug toxicity with ingestions just slightly larger than normal therapeutic doses. For isocarboxazid, phenelzine, or tranylcypromine, acute ingestions of 1 to 2 milligrams/kg may produce mild to moderate toxicity, ingestions of more than 2 to 3 milligrams/kg can be life threatening, and the lethal dose is estimated to be between 4 and 6 milligrams/kg.[13] Selegiline overdose experience is extremely limited, but because selectivity is lost after a 30-milligram ingestion, it should be assumed to produce toxicity similar to that of the traditional nonselective MAOIs.[12] Rasagiline is a far more selective MAO-B inhibitor than selegiline. It was given to healthy volunteers at doses 20 times the normal therapeutic dose without any significant toxicity. However, as of this writing, there are no published cases of rasagiline overdose, so prudence dictates that it should be subject to the same precautions as other agents in this class. Toxicity from moclobemide overdose alone is usually mild, even with large ingestions. But when combined with a serotonergic agent, serotonin syndrome is common and can be severe.[14]

An important clinical aspect of MAOI overdose is that the appearance of toxic symptoms is characteristically delayed to between 6 and 12 hours after ingestion, and the delay can be as long as 24 hours. The delayed onset of toxicity is attributed to the gradual accumulation of norepinephrine and serotonin in the brain and peripheral sympathetic neurons. Symptoms of MAOI overdose are most consistent with a hyperadrenergic state secondary to excessive stimulation of α-adrenergic and β-adrenergic receptors, but symptoms related to excessive serotonin receptor activity are also seen. Patients receiving long-term therapy may show earlier signs of toxicity due to preexisting enzyme inhibition. In severe cases, the hyperadrenergic state can be followed rapidly by hypotension and CNS depression resembling a sympatholytic condition. Toxicity usually persists for 1 to 4 days after ingestion.

Published descriptions of MAOI toxicity indicate tremendous variation in presentation: **there is no "typical" presentation of MAOI toxicity and no orderly progression of symptoms.**[12,13,15,16] The initial symptoms of overdose are reported to include headache, agitation, irritability, nausea, palpitations, and tremor. The earliest signs of toxicity include sinus tachycardia, hyperreflexia, hyperactivity, fasciculations, mydriasis, hyperventilation, nystagmus, and generalized flushing. In cases of moderate toxicity, opisthotonus, muscle rigidity, diaphoresis, chest pain, hypertension, diarrhea, hallucinations, combativeness, confusion, marked hyperthermia, and trismus may become evident. A peculiar ocular finding described as "ping-pong gaze" has been observed in some cases of MAOI toxicity and refers to bilateral wandering horizontal eye movements.[17] The cause for this gaze disorder is unknown, and it resolves gradually as the patient improves.

Severe toxicity is accompanied by coma, seizures, bradycardia, hypotension, hypoxia, and worsening hyperthermia. Hypotension is an ominous finding and is commonly resistant to therapy. Fetal death, intracranial hemorrhage, and cerebral or pulmonary edema have been reported in association with MAOI overdoses. The most common ECG abnormality seen with toxicity is sinus tachycardia, but T-wave abnormalities are occasionally seen. Moclobemide overdose may produce QT-interval prolongation but without associated dysrhythmias.[18] Death is usually secondary to multiorgan failure.

DIAGNOSIS

MAOI overdose is a clinical diagnosis based solely on history. Plasma drug levels do not correlate with clinical toxicity, nor are such tests routinely available in most hospital laboratories. Routine urine drug screens do not detect drugs of this class. Selegiline is likely to produce amphetamine metabolites, which can be detected on most urine drug screens. Tranylcypromine has the potential to produce amphetamine metabolites in overdose, but these are rarely detected. Laboratory tests can assist in the differential diagnosis and identify possible complications, including hypoxia, rhabdomyolysis, renal failure, hyperkalemia, metabolic acidosis, hemolysis, and disseminated intravascular coagulation. Leukocytosis and thrombocytopenia are seen commonly with toxicity.

The differential diagnosis includes drugs and medical conditions capable of producing a hyperadrenergic state, altered mental status, and/or muscle rigidity (**Table 179-3**). In addition, toxicity can be associated with a sympatholytic presentation. As noted, MAOI toxicity is difficult to diagnose without a history of exposure to the drug.

TABLE 179-3 Differential Diagnosis of Monoamine Oxidase Inhibitor Overdose

Intoxications	Medical conditions	Adverse drug reactions
Amphetamines	Heatstroke	Dystonic reactions
Antimuscarinics	Hypoglycemia	Malignant hyperthermia
Cathinone	Hyperthyroidism	Serotonin syndrome
Cocaine	Pheochromocytoma	Tyramine reaction
Methylphenidate	**Withdrawal states**	Spontaneous hypertensive crisis
MDMA (3,4-methylene-dioxymethamphetamine)	Ethanol (delirium tremens)	Neuroleptic malignant syndrome
	Sedative-hypnotics	Malignant catatonia
Phencyclidine	Clonidine	**Infectious diseases**
Phenylpropanolamine	β-Blockers	Encephalitis
Strychnine		Meningitis
Theophylline		Rabies
Tricyclic antidepressants (early)		Sepsis
		Tetanus

An elevated blood pressure in a patient receiving long-term MAOI therapy presents a dilemma. At therapeutic doses, hypertension can result from tyramine reactions, spontaneous hypertensive crisis, or serotonin syndrome.[9] Tyramine reactions are likely to occur in close relation to ingestion of food or drugs containing indirect sympathomimetics. Spontaneous hypertensive crisis is a rare condition, usually occurring in relation to recent drug dosing.[9] Serotonin syndrome most commonly occurs shortly after exposure to other serotonergic agents and usually is associated with significant cognitive-behavioral and neuromuscular abnormalities.

TREATMENT

GENERAL CARE

There are no known antidotes for MAOI toxicity. ED management is therefore directed toward supportive care and early treatment of complications. Place at least one (preferably large-bore) peripheral IV line and a cardiac monitor. Obtain laboratory studies, especially to identify hyperkalemia, metabolic acidosis, and rhabdomyolysis. Onset of toxicity is usually gradual and delayed, sometimes up to 24 hours after ingestion. However, the abrupt development of seizures, coma, respiratory insufficiency, hyperadrenergic storm, and cardiovascular collapse is possible. For any given dose of inhibitor, toxicity is predicted to be greater for children, the elderly, and patients with co-ingestants or significant underlying medical problems.

There is no accepted need or best method for GI decontamination in an MAOI overdose.[19] Ipecac syrup is contraindicated.[20] Gastric lavage is generally not recommended.[19,21] MAOIs are absorbed rapidly, so delayed gastric lavage or whole-bowel irrigation is unlikely to be of clinical benefit.[22] **If presentation is within 1 hour, consider activated charcoal administered as a single dose**; however, multidose administration is not expected to be useful.[23] Hemodialysis, hemoperfusion, and peritoneal dialysis have no established role in the treatment of MAOI poisoning. Urinary acidification is not recommended because it is ineffective in enhancing MAOI elimination and predisposes to acute renal failure secondary to myoglobin precipitation within renal tubules.

HYPERTENSION

Treat hypertension only with short-acting IV antihypertensive agents because of the potential for development of precipitous hypotension. In many cases, an intra-arterial catheter is required for accurate blood pressure monitoring. The recommended antihypertensive agents are phentolamine and nitroprusside. Phentolamine is a nonspecific α-adrenergic receptor blocker usually administered in 2.5- to 5.0-milligram IV boluses every 10 to 15 minutes until the blood pressure is controlled. It also can be given as a continuous infusion (0.2 to 0.5 milligram/min) for maintenance therapy. Phentolamine use is commonly associated with reflex tachycardia.

Nitroprusside is as effective as phentolamine. It is given as a continuous IV infusion starting at a rate of 1 microgram/kg per minute and is then titrated according to blood pressure response. Prolonged administration of high doses of nitroprusside can predispose to cyanide toxicity, but this potential complication is not relevant to initial treatment. Nitroglycerin is indicated for the relief of anginal chest pain and in patients with signs of myocardial ischemia. β-Blockers pose a theoretical risk of increasing blood pressure (through unopposed vasoconstriction) and are relatively contraindicated.

HYPOTENSION

Hypotension indicates a poor prognosis after MAOI overdose. Give IV normal saline fluid boluses initially. **When vasopressors are required, a direct-acting agent such as norepinephrine is preferred, and all indirect-acting agents such as dopamine should be avoided.** Patients receiving long-term MAOI therapy usually demonstrate an increased sensitivity to vasopressors, so use low initial dosages.

DYSRHYTHMIAS

Sinus tachycardia rarely calls for specific drug therapy unless it is producing cardiac ischemia. Lidocaine and procainamide are the most effective antiarrhythmics for treating the ventricular dysrhythmias seen with toxicity. Bradycardia may degrade quickly into asystole in the later stages of toxicity and requires pacemaker placement. Pharmacologic treatment of bradycardia includes atropine, isoproterenol, and dobutamine.

SEIZURES

Benzodiazepines such as lorazepam and diazepam are the anticonvulsants of choice in treating MAOI-induced seizures. Barbiturates such as phenobarbital are as effective as benzodiazepines but may cause hypotension, especially at higher dosages. Phenytoin is generally ineffective in stopping drug-induced seizures. General anesthesia and muscle paralysis may be necessary in cases of status epilepticus to prevent the metabolic acidosis, hyperthermia, and rhabdomyolysis that commonly accompany persistent seizure activity. Muscle paralysis is best accomplished using nondepolarizing neuromuscular blocking agents, because the action of succinylcholine may be enhanced by these MAOIs. **Vecuronium is preferred to pancuronium** because of the latter's propensity to produce elevations in heart rate and blood pressure. Electroencephalographic monitoring is required when muscle paralysis is used to control the peripheral manifestations of seizure activity.

HYPERTHERMIA

Antipyretics are not effective in lowering drug-induced fever. Benzodiazepines such as lorazepam or diazepam are useful first-line agents to reduce muscle hyperactivity and thus decrease secondary heat production. Increasing evaporative and conductive heat loss is essential for the successful treatment of drug-induced hyperthermia. This is best accomplished by using cool mist sprays and evaporative fans or cooling blankets. Hyperthermia is often resistant to treatment as long as there is persistent muscle rigidity. Muscle paralysis (using nondepolarizing agents) should be considered when diffuse rigidity is refractory to benzodiazepine therapy. Anecdotally, dantrolene is an effective relaxant in resistant cases of muscle rigidity, given at a dose of 0.5 to 2.5 milligrams/kg IV every 6 hours, but should only be used when other measures have failed to relieve muscle rigidity.[24,25]

DISPOSITION AND FOLLOW-UP

All patients with intentional MAOI overdoses or accidental ingestions of isocarboxazid, phenelzine, or tranylcypromine >1 milligram/kg require admission to an intensive care unit or equivalent. Patients with accidental exposures of <1 milligram/kg still require hospital admission but, because they are less likely to develop life-threatening complications, can be admitted to a bed with less frequent monitoring. Consultation with a medical toxicologist and regional poison control center is strongly recommended.

Asymptomatic patients should be monitored for at least 24 hours before discharge. Dietary and medication restrictions should be

followed meticulously during the hospitalization. All patients should be instructed to avoid contraindicated foods and medications for a minimum of 2 weeks after MAOI drug exposure. Patients who require transfer to hospitals with intensive care units should be transferred as soon as possible to avoid the problems anticipated with delayed onset of toxicity. All patients being transferred should be accompanied by medical personnel capable of performing advanced life support and airway management. **Even a single MAOI tablet may produce life-threatening drug interactions under the right circumstances.**

TYRAMINE REACTION

Tyramine is an exogenous dietary amine that is normally metabolized by intestinal and hepatic MAO.[11,26,27] Tyramine can be found in small amounts in many foods but is present at much higher levels in aged, cured, smoked, pickled, or fermented dietary products. The body normally has multiple levels of protection to prevent tyramine and other similar exogenous amines from entering the systemic circulation, but this protection is lost once the normal activity of MAO-A is inhibited by >80%. Therefore, all nonselective inhibitors predispose to tyramine reactions; however, tranylcypromine is associated more frequently with tyramine reactions than either phenelzine or isocarboxazid. Selective MAO-B inhibitors and reversible inhibitors are associated with a much lower incidence of tyramine reactions because they leave intestinal and hepatic MAO-A unaffected to metabolize tyramine. Selegiline (MAO-B selective) is unlikely to produce a tyramine reaction if taken in oral form at therapeutic doses, but at elevated doses, its selectivity is lost and it functions the same as the nonselective inhibitors. Dietary restrictions are unnecessary with rasagiline because of its greater selectivity for MAO-B at therapeutic dosages and transdermal preparations of MAOIs.[2]

Tyramine is structurally similar to amphetamine and is classified as an indirect sympathomimetic. Like most indirect sympathomimetics, tyramine enters the presynaptic neuron through amine uptake pumps. Once inside the neuron, indirect sympathomimetics are capable of releasing presynaptic stores of norepinephrine and, to a lesser degree, serotonin and dopamine. Tyramine also can displace epinephrine from the adrenal gland. A similar effect occurs with ingestion of foods that contain large amounts of dopamine, such as broad (fava) beans. It has been reported that <30% of patients taking MAOIs adhere to the recommended tyramine-restricted diet. In addition, approximately 4% to 8% of adherent patients experience a tyramine reaction during their course of therapy. Many of the previously restricted food sources are no longer considered dangerous, and newer guidelines call for avoiding only a few high-risk food groups such as meats or fish that are not fresh, sauerkraut, aged meats and cheeses, alcohol (tap or unpasteurized beers), pickled fish (herring), concentrated yeast extracts, banana peels, soy sauce, tofu, and broad beans.[11,26,27]

CLINICAL FEATURES

The tyramine reaction is typically of rapid onset, occurring within 15 to 90 minutes of ingestion of the dietary amine. The severity of this reaction is highly variable and is partially related to the total amount of tyramine ingested. **The hallmark symptom of the tyramine reaction is a severe occipital or temporal headache.** Other associated symptoms include hypertension, diaphoresis, mydriasis, neck stiffness, pallor, neuromuscular excitation, palpitations, and chest pain. Most symptoms resolve gradually over 6 hours without specific therapy, but fatalities have been reported in rare cases, usually due to intracranial hemorrhage or myocardial infarction.

TREATMENT

An ECG should be obtained for all patients with tyramine-associated chest pain. Focal neurologic findings or a persistent, severe headache warrants investigation with a CT scan.

In cases of severe hypertension, the recommended drug is phentolamine, given as 2.5- to 5.0-milligram IV doses every 5 to 15 minutes until the blood pressure is controlled. The half-life of phentolamine is approximately 20 minutes, and its duration of action is <1 hour. Nitroprusside is another rapidly acting direct vasodilator that is administered as a continuous IV infusion (1 to 4 micrograms/kg per minute). In cases of moderate hypertension, nifedipine and prazosin have been reported to be effective. β-Adrenergic blockers are contraindicated because of unopposed α-receptor stimulation.

DISPOSITION

Hospital admission should be strongly considered for patients whose symptoms do not resolve completely within 6 hours of onset. Patients who are asymptomatic after 4 hours of observation can safely be discharged home.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 180

Antipsychotics

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ANTIPSYCHOTICS

INTRODUCTION

The first-generation (typical) antipsychotics, introduced in the 1950s, were effective against the positive features of psychosis (e.g., delusions, hallucinations, disorganized thought) but provided no treatment for the negative features (e.g., avolition, alogia, social withdrawal). In addition, numerous adverse side effects associated with these agents led to poor patient compliance. The second-generation (atypical) antipsychotics were introduced in the 1990s, and the third generation followed in the 2000s. These second- and third-generation drugs work on both the positive and negative symptoms and, when taken at therapeutic doses, are associated with fewer extrapyramidal effects than the first-generation antipsychotics (**Table 180-1**).

Antipsychotics were historically referred to as *major tranquilizers* or neuroleptics. With the advent of the atypical antipsychotics, it became clear that antipsychotic properties do not necessarily parallel neuroleptic properties. For this reason, the preferred term is *antipsychotics*. These drugs are sometimes administered to treat other conditions, such as agitation, nausea and vomiting, and headache conditions; to suppress hiccups; and to control involuntary motor disorders, such as Tourette's syndrome, Huntington's chorea, and basal ganglia disorders.

PATHOPHYSIOLOGY

More than 50 different antipsychotics are available worldwide. Their pharmacologic effect is mediated by binding to CNS dopaminergic, α-adrenergic, muscarinic, histaminergic, and serotoninergic receptors.[1] **In overdose, the clinical toxicity is primarily an exaggerated effect of the pharmacologic activity.**

Virtually all antipsychotics bind to (and inhibit) presynaptic and postsynaptic dopamine-2 (D_2) receptors in the CNS.[2] Blockade of dopamine receptors in different regions of the brain produces varying effects. Blockade of D_2 receptors in the mesocortical and mesolimbic system is associated with antipsychotic efficacy, whereas D_2 receptor blockade in the area postrema (chemotactic trigger zone) is responsible for antiemetic activity.

The third-generation agents, such as aripiprazole, are also partial D_2-agonists, with effects dependent on the concentration of dopamine. At low levels of dopamine, they will stimulate the D_2 receptors, and at high levels of dopamine, they will inhibit the D_2 receptors.

TABLE 180-1 Common Antipsychotics

Generic Name	Brand Name in the United States	Typical Adult Maintenance Dose (milligrams)	Maximum Adult Daily Dose for Psychosis (milligrams)	Elimination Half-Life (oral dosing)
First-generation or typical antipsychotics				
Chlorpromazine	Thorazine®*	50–100 orally 3 or 4 times day	1000	23–37 h (parent drug) 10–40 h (active metabolite)
Fluphenazine	Prolixin®*	1–2.5 orally 3 or 4 times a day	40	15 h
Haloperidol	Haldol®*	0.5–2 orally 2 to 3 times a day	100	21–24 h
Loxapine	Loxitane®	15–25 orally 2 to 4 times a day	250	3–4 h
Perphenazine	Trilafon®*	8–16 orally 2 to 4 times a day	64	9–12 h
Pimozide	Orap®	2–10 orally once or twice a day	10	55 h
Prochlorperazine#	Compazine®*	5–10 orally 3 or 4 times a day	150	3–5 h
Promethazine#	Phenergan®	6.25–25 orally 3 to 4 times a day	100	7–14 h
Thioridazine	Mellaril®*	50–100 orally 3 to 4 times a day	800	24 h
Thiothixene	Navane®*	2–5 orally 2 to 3 times a day	60	34 h
Trifluoperazine	Stelazine®*	2–5 orally twice a day	40	18 h
Second-generation or atypical antipsychotics				
Amisulpride†	Solian®	200 orally twice a day	1200	12 h
Asenapine	Saphris®	5–10 SL twice a day	20	24 h
Brexpiprazole	Rexulti®	2–4 orally once a day	4	91 h
Cariprazine	Vraylar®	1.5–6 orally once a day	6	2–4 d (parent drug) 1–3 wk (active metabolite)
Clozapine	Clozaril®	150–300 orally twice a day	900	8 h (single dose) 12 h (steady state)
Iloperidone	Fanapt®	6–12 orally twice a day	24	18 h (extensive metabolizers) 33 h (poor metabolizers)
Lurasidone	Latuda®	4–160 orally once a day	160	18 h
Olanzapine	Zyprexa®	10 orally once a day	20	21–54 h
Paliperidone	Invega®	6 orally once a day in the morning	12	23 h
Pimavanserin	Nuplazid®	34 orally once a day	34	57 h (parent drug) 200 h (active metabolite)
Quetiapine	Seroquel®	50–100 orally 2 or 3 times a day	800	6–7 h
Risperidone	Resperidal®	1–2 orally once or twice a day	16	20 h
Sulpiride†	Dogmatil®	200–400 orally twice a day	1200	11 h
Ziprasidone	Geodone®	20 orally twice a day	160	7 h
Third-generation antipsychotics				
Aripiprazole	Abilify®	10–15 orally once a day	30	75 h (extensive metabolizers) 146 h (slow metabolizers)
Brexpiprazole	Rexulti®	2–4 orally once a day	4	91 h
Cariprazine	Vraylar®	1.5–6 orally once a day	6	2–4 d (parent drug) 1–3 wk (active metabolite)

Note: Several of these drugs are used for other conditions, such as nausea/vomiting, allergic disorders, and hiccups.

Abbreviation: SL = sublingual.

*Brand name formulation has been discontinued in the United States.

†Not available in the United States.

#Promethazine and prochlorperazine have low antipsychotic potency.

Blockade of the D_2 receptors in other regions of the brain produces many of the adverse effects associated with antipsychotics. Antagonism of the D_2 receptors in the tuberoinfundibular region is associated with hyperprolactinemia, which can cause galactorrhea, gynecomastia, and sexual dysfunction. Blockade of the D_2 receptors in the nigrostriatal region is associated with the development of extrapyramidal symptoms. Agents with greater D_2 receptor affinity (e.g., haloperidol or fluphenazine) have higher likelihood of inducing extrapyramidal symptoms, whereas agents with less receptor affinity (e.g., clozapine) are less likely to cause extrapyramidal symptoms. Blockade of the D_2 receptors in the anterior hypothalamus (preoptic area) can produce alterations in body temperature.

In addition to blocking dopamine receptors, many antipsychotics have activities at the α-adrenergic, muscarinic, histaminergic, and serotoninergic receptors. Antagonism of the α_1-adrenergic receptors leads to orthostatic hypotension and reflex tachycardia. Antagonism of the muscarinic receptors can produce hyperthermia, tachycardia, mydriasis, dry mucosal membranes, and urinary retention. Blockade of the histaminergic receptors primarily results in sedation. A consistent feature of the second- and third-generation antipsychotics is their potent blockade

of serotonin subtype 2A, which is greater than D_2 receptor inhibition. This intense antagonism of serotonin subtype 2A actually increases dopaminergic transmission in the nigrostriatal pathway, reducing the risk of extrapyramidal symptoms, and enhances the ability to treat negative features of psychosis.[3,4]

PHARMACOKINETICS

Most antipsychotics have similar pharmacokinetic profiles. After oral administration, absorption occurs rapidly, the drugs undergo significant first-pass metabolism, and peak plasma concentrations typically occur within 1 to 6 hours. Following intramuscular injection, peak plasma concentrations typically occur within 60 minutes for immediate-release products but can be delayed up to 1 day with depot preparations. Nearly all antipsychotics have high protein binding and a large volume of distribution. Metabolism is primarily through the cytochrome P450 enzyme system. Because of the near-complete hepatic metabolism of these drugs, renal impairment rarely requires dosage adjustments.

CLINICAL FEATURES

Isolated overdose of antipsychotics is rarely fatal, and most patients develop only mild to moderate symptoms.[5-7] Toxicity is largely a function of the dose ingested, habituation, comorbid conditions, and age. Following overdose, CNS depression is frequent but is less severe in patients receiving long-term therapy, because tolerance to the sedative effects develops after days to weeks of regular use. CNS effects range from lethargy, ataxia, dysarthria, and confusion to coma with respiratory depression in cases of severe overdose.[6,7] The ingestion of a single pill of some antipsychotics can cause significant CNS and respiratory depression in young children. Respiratory depression in adults is more common in multidrug overdoses.

Paradoxical agitation and delirium may occur in mixed overdoses, especially those involving agents with antimuscarinic properties. **Seizures** occur in approximately 1% of individuals after overdose, with the incidence higher for loxapine and clozapine. Gastric pharmacobezoars have been reported with quetiapine extended-release overdose.[8]

Many of the antipsychotics have antimuscarinic properties, especially clozapine, olanzapine, quetiapine, and thioridazine. Thus, patients can manifest signs or symptoms that are consistent with **antimuscarinic toxicity**, including tachycardia, dry mucous membranes, dry skin, decreased bowel sounds, urinary retention, agitation, delirium, and hyperthermia. However, due to the concurrent α-adrenergic antagonism of many of these agents, miosis, rather than mydriasis, is frequently observed.

The most common cardiovascular manifestations of antipsychotic overdose are **sinus tachycardia and orthostatic hypotension**. ECG changes also include QT prolongation (highest rate with amisulpride and thioridazine), QRS widening (usually with large ingestions), and nonspecific T-wave abnormalities.[9,10] Ventricular dysrhythmias are rare,[11] with the exception of amisulpride overdoses.[12]

DIAGNOSIS

Routine laboratory analysis should include basic chemistry tests and a pregnancy test for women of childbearing age. Test for co-ingestants, including acetaminophen and salicylate levels, in all intentional overdoses. Perform an ECG to assess the conduction intervals. Obtain complete blood counts for patients who develop a fever while taking clozapine or chlorpromazine.

TREATMENT

Treatment for patients with antipsychotic poisoning is largely supportive.[5-7] For patients who are known to have ingested or are suspected of having ingested a significant amount, establish IV access and monitor cardiac rhythm. Ventilatory support should be provided to patients with respiratory depression. Patients with depressed consciousness should receive oxygen supplementation, continuous pulse oximetry, assessment of blood glucose, and consideration for administration of naloxone and thiamine. Seizures should be treated with a benzodiazepine such as lorazepam.

Treat hypotension with IV fluid resuscitation; adults without previously known or suspected cardiac disease should receive at least 1 to 2 L of crystalloid and children should receive 20 to 40 mL/kg. If hypotension persists, direct-acting α-adrenergic agonists, such as **phenylephrine or norepinephrine**, are the preferred vasopressors for treatment. Dopamine, an indirect-acting vasopressor, is not recommended as a first-line agent for treatment of hypotension following an antipsychotic overdose.

Patients with a QT_c interval of >500 milliseconds are at increased risk for **torsades de pointes**.[13,14] Assuming there are no contraindications to magnesium supplementation and regardless of the serum magnesium level, adults with a QT_c interval of >500 milliseconds should receive **magnesium sulfate**, 2 grams IV over 10 minutes.[6] Patients with torsades de pointes should receive 2 grams of magnesium sulfate as a bolus, followed by an infusion of 2 to 4 milligrams/min, regardless of the magnesium concentration. Overdrive pacing can also be useful, especially in cases that prove refractory to magnesium.[15]

Patients with an intraventricular conduction delay (e.g., prolonged QRS complex) and ventricular dysrhythmias should be treated with **sodium bicarbonate**, 1 to 2 mEq/kg IV bolus, followed by intermittent boluses or a continuous infusion. Lidocaine is an acceptable alternative or second-line agent for ventricular dysrhythmias. Avoid using class Ia (e.g., quinidine, procainamide), Ic (e.g., propafenone), III (e.g., amiodarone), and IV antiarrhythmics in patients with cardiac conduction disturbances or ventricular dysrhythmias who are concurrently taking an antipsychotic because these antiarrhythmics may potentiate such cardiotoxicity.

DISPOSITION AND FOLLOW-UP

Following ingestion, observe the patient for at least 6 hours. Obtain orthostatic pulse and blood pressures and observe successful ambulation prior to discharge. The patient can be judged to be free of toxicity if there are no mental status changes, pulse and blood pressure abnormalities, orthostatic hypotension, and QT_c interval prolongation after 6 hours of observation from the time of ingestion.[16,17] Patients with evidence of toxicity (e.g., sinus tachycardia or QT interval prolongation) should be admitted to a monitored bed for observation. Patients who develop severe symptoms (e.g., seizure, respiratory depression, hypotension, acidosis) during the observation period in the ED should be admitted to an intensive care unit.

ADVERSE EFFECTS OF THERAPEUTIC DOSING

CARDIOVASCULAR

Antipsychotics can affect myocardial conduction and repolarization. At therapeutic dosages, this is usually evidenced by prolongation of the QT interval. Of the typical agents, thioridazine, pimozide, and IV haloperidol cause the greatest degree of QT prolongation.[13,18] Among the atypical antipsychotics, ziprasidone, sertindole, and amisulpride are associated with the greatest degree of QT prolongation in therapeutic dosing.[13,18]

EXTRAPYRAMIDAL SYMPTOMS

Although high-potency typical agents cause the highest rate of extrapyramidal symptoms, all antipsychotic agents are capable of producing these symptoms.[2] The four extrapyramidal syndromes include acute dystonia, akathisia, drug-induced parkinsonism, and tardive dyskinesia.

Acute dystonias manifest as hyperkinetic movements characterized by intermittent, uncoordinated, involuntary contractions of the muscles of the face, tongue, neck, trunk, or extremities. Although distressing to patients, these effects are not life threatening. Akathisias are a subjective sensation of motor restlessness. Occasionally, akathisia can be misinterpreted as increasing agitation related to an underlying psychiatric condition and can thereby prompt additional medication administration.

Acute dystonic reactions and akathisia are typically encountered early after starting therapy (or increasing the dose of a drug) and can be reversed with diphenhydramine (25 to 50 milligrams IV) or benztropine (1 to 2 milligrams IV). Diphenhydramine, 25 to 50 milligrams PO three or four times a day, or benztropine, 1 to 2 milligrams PO twice a day, should be continued for 2 to 3 days after parenteral treatment because of the prolonged effects of the dystonia-inducing agent.

Tardive dyskinesia and drug-induced parkinsonism typically develop after prolonged therapeutic use and are unlikely to be reversible.

OTHER ADVERSE EFFECTS

Therapeutic use of atypical antipsychotics is linked with the development of type 2 diabetes mellitus and diabetic ketoacidosis.[2,19-21] There is some suggestion that the risk is greatest with olanzapine.[22] Phenothiazines are associated with leukopenia in up to 0.8% and agranulocytosis in 0.05% of patients.[23] Several atypical antipsychotics have also been associated with agranulocytosis, with the highest incidence in patients taking clozapine, in whom leukopenia occurs in 3% and agranulocytosis in 0.8%. Due to these adverse effects, clozapine can only be prescribed within a strictly monitored program. Seizures have been associated with several antipsychotics, primarily chlorpromazine, loxapine, and clozapine.[24-26] The risk of seizure appears to be dose dependent. If they occur, seizures, should be treated with benzodiazepines (e.g., lorazepam, 1 to 2 milligrams IV bolus).

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome is a rare but potentially fatal idiosyncratic complication of antipsychotic drug therapy and not the result of an overdose.[27-29] Neuroleptic malignant syndrome most often occurs shortly after the start of therapy or after a dosage adjustment, and the antipsychotic serum concentration is usually within the therapeutic range. Neuroleptic malignant syndrome is associated with all the typical antipsychotics and most of the commonly available atypical antipsychotics, including aripiprazole, clozapine, olanzapine, risperidone, and ziprasidone.[30,31] Neuroleptic malignant syndrome patients are more commonly adult males, with peak incidence in the 20- to 25-year age range.[32] The incidence is about 1 to 2 cases per 10,000 patients treated.[28]

CLINICAL FEATURES

Neuroleptic malignant syndrome typically develops over a period of 1 to 3 days and is characterized by the tetrad of altered mental status, muscular rigidity, fever, and sympathetic nervous system lability. The rigidity is typically described as lead pipe and cogwheel rigidity, similar to that observed with parkinsonism. The majority of patients present first with altered mental status, followed by rigidity, then fever, and lastly sympathetic nervous system lability. Fever can be delayed for more than 24 hours after the first symptom.

In addition to the tetrad, two other features embody important concepts about this syndrome: recent dopamine antagonist exposure or dopamine agonist withdrawal and negative evaluation for other causes (**Table 180-2**).[33,34] Common laboratory abnormalities include elevated creatine kinase level, leukocytosis, elevated levels of hepatic transaminases, hypernatremia or hyponatremia, metabolic acidosis, myoglobinuria, elevated BUN and creatinine levels, and decreased serum iron level.[35]

All antipsychotics have been associated with neuroleptic malignant syndrome, but the clinical features of reported cases associated with second- and third-generation agents differ somewhat from the classic presentation induced by the first-generation drugs. Fever and sympathetic liability are less common in neuroleptic malignant syndrome induced by second- and third-generation antipsychotics.[36]

The differential diagnosis of neuroleptic malignant syndrome includes infectious, endocrine, toxicologic, and metabolic disorders. The most common disorder creating diagnostic confusion is **serotonin syndrome** (see Chapter 178, "Atypical and Serotonergic Antidepressants"). Clinical features more indicative of serotonin syndrome include a more rapid onset (2 to 24 hours), shivering, hyperreflexia, myoclonus, nausea, vomiting, diarrhea, and less intense muscle rigidity and fever.

TABLE 180-2 Diagnostic Criteria for Neuroleptic Malignant Syndrome

Major features	Fever >38°C (100.4°F), measured orally on at least two occasions
	Lead-pipe muscle rigidity
	Psychomotor slowing and altered mental status
	Sympathetic nervous system lability (2 or more features) • Elevated blood pressure • Blood pressure fluctuation • Diaphoresis • Urinary incontinence
	Recent dopamine antagonist exposure or dopamine agonist withdrawal
Minor features	Increased creatine kinase level (> 4 × upper limit) or myoglobinuria
	Tachycardia
	Tachypnea
	Hypersalivation (more prominent with clozapine or amisulpride)
	Tremor
	Muscle cramps
Exclusionary criteria	No other infectious, toxic, metabolic, or neurologic cause identified

TREATMENT

Treatment is primarily supportive (**Table 180-3**).[27,28,37,38] Withdraw any antipsychotics and potentiating drugs. Consider and evaluate for other medical conditions that can present in a similar manner, including CNS infection, other drug-induced hyperthermic syndromes, serotonin syndrome, anticholinergic poisoning, and sympathomimetic toxicity.[37,38] Reduce the patient's temperature with external cooling measures; pharmacologic antipyretics such as acetaminophen are not beneficial in lowering the temperature associated with this syndrome. Sedation is very important to decrease agitation and sympathetic activity; a benzodiazepine, such as lorazepam, is recommended.[27,37,38]

Airway and breathing difficulties should be anticipated, and patients with excessive secretions, dysphagia, decreased airway reflexes, acidosis, or hypoxia should be intubated. In addition, strongly consider intubating patients with fever and rigidity, because neuromuscular paralysis reduces the muscle contraction and thereby reduces the fever. **When patients with neuroleptic malignant syndrome are intubated, nondepolarizing agents (e.g., rocuronium) are preferred over depolarizing agents (e.g., succinylcholine)**.

TABLE 180-3 Treatment of Neuroleptic Malignant Syndrome

- Withdraw any antipsychotics and potentiating drugs, such as anticholinergics, antihistamines, or lithium
- IV hydration to restore circulating volume and maintain urine output
- Reduce the patient's temperature with external cooling measures
- Sedation with a benzodiazepine, such as lorazepam, 1–2 milligrams IV every 2–4 h as needed
- Airway protection: consider early intubation, especially if hypersalivation is present
- Nondepolarizing neuromuscular blocking agents
- Consider agents to reduce severe muscle rigidity
  - Dantrolene, 1.0–2.5 milligrams/kg IV load, followed by 1 milligram/kg IV every 6 h
  or
  - Bromocriptine, starting with 2.5 milligrams PO 3 to 4 times a day
  or
  - Amantadine, 100 milligrams PO 3 times a day

Complications from profound muscle rigidity are responsible for most deaths in neuroleptic malignant syndrome. Prompt reduction in muscle rigidity can be expected to minimize the occurrence of complications such as rhabdomyolysis, renal failure, respiratory failure, disseminated intravascular coagulation, and cardiovascular collapse. **The role of specific pharmacotherapy is unclear**; no treatment has been shown to be superior to supportive care alone.[27,37,38]

Pharmacologic therapies described in case reports and series include dantrolene, bromocriptine, benzodiazepines, and amantadine.[39] **Dantrolene** is a direct-acting skeletal muscle relaxant that is primarily used for more severe cases of neuroleptic malignant syndrome in which the rigidity is pronounced. Dantrolene should not be used concurrently with calcium, because this increases the risk of cardiovascular collapse.[7] **Bromocriptine** is a centrally acting dopamine agonist that can reduce fever and muscle rigidity in neuroleptic malignant syndrome and possibly shorten the duration.[40] This drug is only available in an oral preparation and may require administration by a nasogastric tube. Adverse side effects of hypotension, vomiting, and worsening of psychosis are limiting factors to the routine use of bromocriptine.[38] **Amantadine** is similar to bromocriptine in activity and only available in enteral form but is less likely to cause hypotension.

Patients with neuroleptic malignant syndrome should be admitted to the intensive care unit for monitoring and treatment. Most patients recover in 2 to 14 days.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 181

Lithium

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INTRODUCTION

Lithium is one of the most effective medications for the continuous treatment of bipolar disorder. It is particularly useful for the treatment of acute manic episodes and reduces rates of suicide associated with affective disorders.[1,2] Among agents used to treat depression, lithium is associated with high morbidity and mortality indices (events per 1000 exposures).[3]

PHARMACOLOGY

Lithium is a simple ion with a complex mechanism of action that is not fully understood. It is postulated to involve primary monoamine neurotransmission, via a direct interaction between the lithium ion and cellular enzymes, influencing the secondary signaling pathways of dopamine, serotonin, and norepinephrine.[1,4] Lithium competes with other similar cations, including sodium, potassium, magnesium, and calcium, and displaces them from intracellular and extracellular sites. Interference with sodium ions at the sodium channel and the sodium-potassium pump on the cell membrane is responsible for lithium's adverse effect on myocardial electrical activity. Lithium inhibits arginine vasopressin, an effect that is responsible for polyuria and nephrogenic diabetes insipidus seen during lithium therapy. Other pharmacologic effects include interference with the release and reuptake of norepinephrine at the nerve terminal site. Lithium may enhance serotonin release, particularly from the hippocampus, and has been implicated in serotonin syndrome when combined with other medications that alter serotonin metabolism. Lithium is handled by the kidney similar to sodium; anything that may increase sodium absorption, such as medications that reduce glomerular function, has the potential to contribute to lithium toxicity.[5]

PHARMACOKINETICS

After oral ingestion of therapeutic doses, lithium is rapidly and almost completely absorbed, although delayed absorption may occur with sustained-release products and after ingestion of a large number of tablets.[6] Lithium is not bound to plasma proteins and has an initial volume of distribution between 0.6 and 0.9 L/kg. Ingestion of a single tablet of lithium carbonate 300 milligrams containing 8.12 mEq of lithium ion is expected to increase the lithium concentration by approximately 0.1 to 0.3 mEq/L (assuming a normal volume of distribution in a patient with a weight of 50 to 100 kg).

Lithium exhibits a prolonged redistribution phase and tissue burden. Lithium distribution into and out of the brain is slower, resulting in neurologic effects that do not correlate with serum levels. The lithium concentrations in the brain and in the serum may differ by two- to threefold.[7] Continuation of toxic effects, even after hemodialysis, can be due to the drug's slow movement out of the CNS and redistribution. **Serum concentrations can serve as a marker of exposure but are poor predictors for severity of toxicity**. Thus, clinical signs and symptoms provide a more accurate indicator of CNS lithium concentrations compared to serum concentrations.

The elimination half-life after a single dose of lithium is about 18 to 24 hours in young adults and almost twice that in the elderly.[6] After continued therapy of longer than a year, the lithium elimination half-life increases, up to almost 60 hours in all ages. Lithium is not metabolized and is excreted unchanged, primarily in the urine. Like other cations of similar size, lithium is reabsorbed in the proximal tubule. The therapeutic index of lithium is narrow, and risk factors for the accumulation of lithium and the development of toxicity include NSAIDs, diuretics, angiotensin-converting enzyme inhibitors, advanced age, low-output heart failure, and states that result in decreased sodium intake such as GI loss.[1,5,8]

CLINICAL FEATURES

TOXIC EFFECTS

Lithium toxicity can be divided into three types: acute toxicity, chronic toxicity, and acute-on-chronic toxicity.[9-12]

Acute ingestions of lithium produce findings similar to that of other metal salts, consisting primarily of GI symptoms of abdominal pain, nausea, vomiting, and diarrhea, which may result in significant volume depletion. The resulting hypovolemia decreases renal clearance of lithium, further increasing serum concentration. Acute lithium overdoses present with more GI toxicity and less neurologic toxicity because of the slower accumulation into the brain after ingestion and distribution in body water. Patients with acute overdose may have markedly elevated serum concentrations that do not correlate well with either symptom severity or prognosis. As lithium distributes from the serum into the CNS, neurologic symptoms of confusion, seizures, and coma become apparent. Cardiac abnormalities such as hypotension, bradycardia, atrioventricular block, and ventricular dysrhythmias have been described but are very uncommon, and co-ingestions should be considered before attributing abnormalities solely to lithium toxicity.[13,14] Rare cases of adult respiratory distress syndrome have been associated with acute lithium toxicity.[15]

Lithium is a neurotoxin, and neurologic symptoms predominate in chronic toxicity. Common symptoms include postural tremor (exaggerated physiologic tremor), muscle fasciculation, clonus, choreoathetoid movements, ataxia, muscle weakness, dysarthria, nystagmus, agitation, and lethargy.[1,16-19] Although most patients present with a slowing of cognitive function, cases of lithium toxicity presenting with mania or auditory, visual, or tactile hallucinations have been reported. As toxicity worsens, confusion, lethargy, stupor, seizures, and finally coma develop. Less common toxic effects include hyperthermia, hypothermia, peripheral neuropathy, and severe leukopenia. Recognizing chronic lithium toxicity is difficult because it predominantly causes neurologic

TABLE 181-1 Clinical Features of Lithium Toxicity

Category	Features
Mild	Nausea, vomiting, fatigue, lethargy, fine tremor
Moderate	Confusion, agitation, dysarthria, ataxia, hypertonia, hyperreflexia, nystagmus, muscular weakness
Severe	Coma, seizures, myoclonus, hyperthermia, ventricular dysrhythmias, atrioventricular block, cardiovascular collapse

symptoms that are indistinguishable from organic causes of delirium, and symptoms do not reliably correlate with serum levels.[11,17,20,21]

Most patients recover from chronic toxicity as the body burden of lithium decreases. The syndrome of irreversible lithium-effectuated neurotoxicity describes the persistent neurologic dysfunction caused by lithium that persists for >2 months after cessation of the drug in patients without prior neurologic illness. Cerebellar dysfunction is the key finding with syndrome of irreversible lithium-effectuated neurotoxicity, manifested by truncal ataxia, unsteady gait, tremor of the hands and head, scanning speech, and diffuse incoordination.[22]

Acute-on-chronic toxicity results from a disruption in the balance of serum lithium concentrations in patients with a stable body burden from chronic therapy, most often precipitated by decreases in glomerular filtration or intravascular volume depletion or when a patient intentionally or unintentionally ingests an increased amount of lithium.[16] The resulting lithium load in the presence of already saturated tissue leads to toxicity, with clinical symptoms mimicking both acute (GI symptoms) and chronic (neurologic symptoms) toxicity (**Table 181-1**).

ADVERSE EFFECTS OF CHRONIC THERAPY

Adverse effects during therapeutic lithium use are common, occurring in up to 90% of treated patients. **The most frequent adverse effects include fine postural hand tremor, fatigue, polyuria due to loss of urinary concentration ability, hypothyroidism, and hyperparathyroidism with hypercalcemia.**[23-25] Worsening of a baseline tremor and development of ataxia or dysarthria are important signs of developing toxicity and may signal a need to decrease the dose of lithium.

Lithium is a common cause of drug-induced nephrogenic diabetes insipidus, which is prevalent in up to 40% of patients receiving long-term lithium treatment.[26,27] The decreased urinary concentrating ability is usually compensated in patients by increased thirst. The ability of the distal nephron to acidify the urine can be impaired, causing an incomplete distal renal tubular acidosis without acidemia. Long-term lithium treatment can lead to a progressive nephropathy, with a mild reduction in glomerular filtration[25,28] and approximately a 1% absolute risk of requiring renal replacement therapy.[28-30] Maintaining serum lithium levels <0.8 mEq/L (0.8 mmol/L) may reduce long-term renal damage.[31]

ECG abnormalities commonly reported with lithium use include QT interval prolongation, T-wave flattening or inversion, and significant bradycardia.[32] Hypothyroidism is the most prevalent endocrine dysfunction, occurring at a rate almost six times that in the general populace.[25,33] Hyperparathyroidism and hypercalcemia are frequently reported and can be associated with stimulation of hyperplasia or adenomas.[34]

DIAGNOSIS

The patient's history, symptoms, and signs should guide therapy, as opposed to a lithium concentration, which primarily serves as a marker of an exposure.[12] **Blood samples should be sent in lithium-free tubes because the use of lithiated heparin tubes can lead to falsely positive results up to 4 mEq/L (4 mmol/L).**[32] Therapeutic lithium levels are considered to be 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L), and most patients manifesting toxic effects have levels >2 mEq/L (>2 mmol/L). Additional tests to obtain if acute toxicity is suspected include a CBC where leukocytosis can be seen and a metabolic panel to evaluate kidney function. In chronic toxicity, consider assessing thyroid function (thyroid-stimulating hormone and thyroid hormone levels) and renal concentrating ability (simultaneous serum and urine sodium, creatinine, and osmolality). In acute overdose, additional tests may be useful (see Chapter 176, "General Management of Poisoned Patients").

TREATMENT

Initial stabilization of the patient's condition includes protection of the airway and provision of respiratory and hemodynamic support. Establish IV access, initiate cardiac rhythm monitoring, and obtain an ECG. Information regarding the lithium formulation can aid in further treatment, such as immediate- versus sustained-release tablets, doses, and quantity of ingestion. Subsequent treatment depends on clinical severity (**Table 181-2**).

GI decontamination has a limited role in lithium toxicity. Activated charcoal does not readily bind with lithium. Gastric lavage has no role in most cases of lithium overdose because the sustained-release preparations are often too large to fit through the lavage tubes and the immediate-release preparations are too rapidly absorbed in the GI tract.[35] Whole-bowel irrigation with polyethylene glycol solution at 2 L/h is the only method of GI decontamination that has shown some efficacy in removing lithium in the setting of acute ingestion of the sustained-release formulation provided there is no evidence of airway compromise or intestinal obstruction.[36]

The critical principle of lithium poisoning treatment is assessment of volume status and restoration of intravascular volume. IV administration of normal saline is required in nearly all patients with significant toxicity because of sodium and volume deficits.[12,37] Typical adult dosing is an IV bolus of normal saline 20 mL/kg, followed by continuous infusion at 1.5 to 2 times the maintenance rate. Volume repletion reestablishes normal renal elimination kinetics of lithium. Diuretic-induced diuresis does not enhance lithium elimination, and in fact, loop and thiazide diuretics promote water loss, which is followed by lithium retention.

Lithium is amenable to extracorporeal removal.[1,12] Consensus recommendations from the Extracorporeal Treatment in Poisoning Workgroup are to use extracorporeal treatment, such as dialysis, for severe lithium toxicity (coma, seizures, life-threatening dysrhythmias) or a serum lithium level >4.0 mEq/L (>4 mmol/L) in the presence of renal insufficiency.[38] Intermittent hemodialysis is the preferred modality, with continuous renal replacement being an acceptable alternative.[38] The goal of hemodialysis is to reduce the total body burden of lithium, but because the molecule is primarily intracellular and slowly diffuses across the cell membrane, removal of extracellular lithium through intermittent hemodialysis results in redistribution from the intracellular to extracellular compartments, causing a postdialysis rebound increase in serum lithium concentrations. Therefore, it is essential to monitor serum lithium levels for up to 8 hours after hemodialysis, and if symptoms recur or serum levels rise significantly, consider repeat hemodialysis. Peritoneal dialysis is no longer recommended because the clearance rates are approximately the same as through normal renal clearance with potential for complications such as bowel perforation.

Treat seizures with IV benzodiazepines, such as lorazepam, because phenytoin is ineffective in controlling drug-induced seizures. Consultation with a medical toxicologist is recommended for patients with serious toxicity.

TABLE 181-2 Management of Lithium Toxicity

IV saline infusion	Used in essentially all patients with toxicity Reestablishes euvolemia and normal lithium renal elimination
Whole-bowel irrigation	Used in awake patients who ingest sustained-release lithium preparations
Hemodialysis	Used for patients with severe toxicity Also used for patients with renal failure, patients who cannot tolerate IV saline infusion, and patients with high elevated serum lithium levels (>4.0 mEq/L in any type of overdose and >2.5 mEq/L in chronic toxicity)
IV benzodiazepines	Used for seizures seen in severe toxicity

DISPOSITION

Admission decisions are made by considering acuity of the toxicity and the circumstances that led to the toxicity.[39] Asymptomatic patients with acute ingestions should be monitored for 4 to 6 hours, with measurement of serial serum lithium levels. Admit patients with serum lithium levels of >1.5 mEq/L (>1.5 mmol/L) after an acute ingestion. **Any patient with an *acute* ingestion of a sustained-release preparation should be admitted regardless of serum lithium level and observed for signs and symptoms of lithium toxicity.**

Patients with mild toxicity who have no additional risk factors may be managed with IV saline treatment for 6 to 12 hours, often in an observation unit. Once repeated serum lithium levels decrease to <1.5 mEq (<1.5 mmol/L), patients can be discharged after psychiatric evaluation, if needed. Patients with moderate toxicity require admission, and patients with severe toxicity require intensive care and consideration for extracorporeal removal.

Patients taking lithium may seek care in the ED for conditions not related to mental health or lithium toxicity. Take care to avoid prescribing any drugs that negatively impact glomerular filtration and renal function. Thiazide diuretics, loop diuretics, NSAIDs, angiotensin-converting enzyme inhibitors, and angiotensin receptor II blockers are common agents with potential for lithium interaction promoting toxicity.[5]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 182

Barbiturates

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Frank LoVecchio

INTRODUCTION

Barbiturates are still the most common class of antiepileptic drugs used in developing countries, but their use is declining due to the introduction of safer, less toxic sedative-hypnotics (e.g., benzodiazepines) and second-generation anticonvulsants.[1] Status epilepticus,[2] severe ethanol and sedative withdrawal syndromes,[3-5] and toxicologic seizures[6] are typically managed with benzodiazepines, but barbiturates have a useful role as second-line agents. They are still used in combination drugs (e.g., butalbital) and alone (e.g., secobarbital) for the treatment of tension and migraine headaches[7-9] and for refractory intracranial hypertension from focal and diffuse brain injury.[10]

PHARMACOLOGY

Barbiturates are generally classified according to their duration of action, which is primarily dependent on lipid solubility and tissue distribution rather than the elimination half-life (**Table 182-1**).

Barbiturates readily distribute throughout the body to most tissues, crossing the blood–brain barrier and placenta, and are excreted in breast milk. Fetal blood barbiturate concentrations closely reflect maternal plasma levels, creating the potential for fetal withdrawal syndrome. Most barbiturates are metabolized in the liver to inactive metabolites, primarily through routes involving the cytochrome P450 system. The elimination half-life of barbiturates can be greatly shortened in infants and children and very prolonged in the elderly and in patients with liver or renal disease. Chronic barbiturate use induces activity of the cytochrome P450 enzymes and may accelerate the metabolism of concurrently taken therapeutic drugs such as oral contraceptives, anticoagulants, and corticosteroids.

Barbiturates' main action is the depression of activity in the CNS and musculoskeletal system. In the CNS, this is accomplished by enhancing the action of the primary inhibitory neurotransmitter γ-aminobutyric acid at its receptor.[11] When γ-aminobutyric acid binds to its chloride channel receptor, it causes it to open, resulting in a depolarization; the depolarization temporarily stabilizes the resting membrane potential and inhibits the firing of new action potentials. Barbiturates bind to the α subunit of the γ-aminobutyric acid receptor, causing an increase in the duration of opening of the cell membrane chloride channel; this results in prolonged depolarization and prolonged inactivity.

Benzodiazepines bind to a different site on the α subunit of the γ-aminobutyric acid receptor and increase the frequency with which the chloride channel opens. Increased duration, as opposed to increased frequency, is one of the reasons cited for increased morbidity and mortality with barbiturate overdoses compared to benzodiazepines.

Barbiturates inhibit both the activity of the excitatory neurotransmitter glutamate at the glutamate receptor and calcium-mediated excitatory neurotransmitter release at the presynaptic terminal. Blockade of the calcium channel may contribute to the cardiac contractility impairment seen with barbiturate overdoses. Barbiturates also have effects on voltage-dependent sodium and potassium channels, but in concentrations typically far above the therapeutic range.[12] These effects may contribute to the toxicity or paradoxical actions seen with some barbiturate drugs in overdoses.

CLINICAL FEATURES

Mild to moderate barbiturate intoxication closely resembles alcohol intoxication and toxicity of other sedative-hypnotics. Drowsiness, disinhibition, ataxia, slurred speech, and mental confusion are common features that escalate with increasing dose. The progressive neurologic depression seen with *severe* barbiturate intoxication predictably manifests as a range from stupor to coma to complete neurologic unresponsiveness, including the absence of a corneal reflex, deep tendon reflexes, and even brainstem reflexes (in patients who ultimately completely recover).[13]

TABLE 182-1 Selected Properties of Commonly Used Barbiturates in Adults

	Long Acting*	Intermediate Acting*		Short Acting*		Ultrashort Acting*	
Agent	Phenobarbital†	Amobarbital	Butalbital	Pentobarbital	Secobarbital	Thiopental	Methohexital
Duration of action (hours)	>6	3–6	3–4	<3	<3	5–10 min	5–7 min
Elimination half-life (hours)	24–96	14–42	35–88	21–42	20–28	6–26	1–2
Hypnotic dose PO (milligrams)	300–500	100–200	50–200	100–200	50–100	100–200	50–100 IV
Fatal dose, approximate (grams)‡	5	3–6	2–5	3–6	3–6	ND	ND

Abbreviation: ND = no data.

*This classification scheme is a convention only; it preceded the discovery that the elimination half-lives do not conform to the apparent duration of action.

†Only drug responsive to extracorporeal removal.

‡In nontolerant individuals.

The most common vital sign abnormalities seen in overdose are respiratory depression, hypothermia, and hypotension, with respiratory depression usually occurring first. Abnormal temperature control and respiratory depression are centrally mediated phenomena, whereas hypotension is primarily a result of decreased vascular tone. Pulse rate, pupil size, light reactivity, and nystagmus are variable. GI tract motility is slowed, resulting in delayed gastric emptying and ileus. Skin bullae, sometimes referred to as "barb blisters" or "coma blisters," are uncommon and may indicate nothing more than the effects of local skin pressure, although hypoxia has been implicated as well.[14] Coma blisters are not specific to sedative-induced coma; they have been reported after surgery,[15] from other causes of coma,[16] and even without coma.[17]

Early deaths in barbiturate overdose result from respiratory arrest and cardiovascular collapse. Common complications include hypoglycemia (perhaps due to starvation), pulmonary edema, aspiration pneumonia, and acute lung injury. Current mortality rates range between 1% and 3%; death usually results from multiple organ system failure. Lethal doses are estimates (Table 182-1), but **severe poisoning can be assumed if more than 10 times the hypnotic dose has been ingested in a single exposure in a nontolerant patient.**[18] As with other sedative-hypnotics, the toxic properties of barbiturates may be enhanced in the presence of benzodiazepines or alcohol. Conversely, the depressive effects may be protective in a mixed-stimulant overdose.[19]

DIAGNOSIS

Laboratory evaluation in barbiturate overdose should include determination of glucose levels, blood chemistries, CBC, blood gas (if indicated), toxicology screen for co-ingestants, chest radiograph, and an ECG. Urine drug screens most commonly use the immunoassay methodology, and a false-positive result on the barbiturate screen has been reported with ibuprofen and naproxen.[20] If important, confirm a positive urine screen using a more accurate method, such as gas chromatography–mass spectrometry.

Barbiturate serum levels are useful in establishing the diagnosis of a comatose patient; however, acute treatment decisions should be clinically based. Serum barbiturate levels reported in lethal overdoses vary widely, and measurements are not reliable in predicting clinical course after an overdose because they do not reflect brain barbiturate concentrations and may underestimate the clinical condition of a patient in the setting of polydrug exposure.[21] Barbiturate levels are also invalid in chronic barbiturate abusers who have developed physiologic tolerance and in patients with renal or hepatic disease who have decreased clearance.[18]

TREATMENT

In a barbiturate overdose, the initial priorities are airway management and supportive care. Once pulmonary and cardiovascular function has been stabilized, options for increasing drug clearance are considered.

AIRWAY ASSESSMENT AND INITIAL STABILIZATION

Assess the patient's mental status and airway stability. Intubation with mechanical ventilation in severe sedative-hypnotic overdose is often required. Barbiturate toxicity results in decreased cardiac output and vascular tone, often resulting in profound hypotension. Volume expansion with IV crystalloids is the mainstay for circulatory support in the absence of cardiac failure. If fluid resuscitation fails to correct hypotension, administer vasopressors such as dopamine or norepinephrine. Hypothermia between 30°C (86°F) and 36°C (96.8°F) is common and should be monitored via continuous core temperature and treated with rewarming measures.

ACTIVATED CHARCOAL

A single dose of activated charcoal should be given to cooperative, clinically stable patients who present within 1 hour of acute oral overdose.[22] Current consensus guidelines are to consider multidose activated charcoal if a patient has ingested a life-threatening amount of phenobarbital.[23] A typical adult regimen for multidose activated charcoal is an initial dose of 50 to 100 grams PO followed by 12.5 to 25 grams PO every 4 hours. Concurrent administration of cathartic agents remains unproven and is discouraged (see Chapter 176, "General Management of Poisoned Patients"). Careful attention to and monitoring of the patient's airway is important to decrease the risk of aspiration or bowel obstruction.

FORCED DIURESIS AND URINARY ALKALIZATION

Forced diuresis is not recommended because of the risks of sodium and fluid overload and lack of proven efficacy.

Urinary alkalization (see Chapter 176) does enhance the clearance of phenobarbital and primidone (which is metabolized to phenobarbital). This treatment is less effective than multidose activated charcoal in reducing serum levels, does not improve clinical outcomes, and **is not effective for shorter-acting barbiturates.**[24] In barbiturate poisoning, urinary alkalization is not a first-line treatment and has only a minor, if any, role.[25,26]

EXTRACORPOREAL ELIMINATION

Hemodialysis, hemoperfusion, and hemodiafiltration can enhance elimination of phenobarbital, but are reserved for patients who are deteriorating despite aggressive supportive care.[26-28] **These modalities are not useful for poisoning from barbiturates other than phenobarbital.** Exchange transfusion has also been reported to be useful in neonatal phenobarbital toxicity.[29]

DISPOSITION AND FOLLOW-UP

Mild to moderate barbiturate intoxication responds well to general supportive care, including a single dose of activated charcoal, as long as potential benefits outweigh aspiration risk. Improvement in neurologic status and vital signs over 6 to 8 hours signals eventual patient discharge or transfer. When indicated, obtain mental health assessment. For a long-acting agent such as phenobarbital, serial serum levels should be obtained during the initial 6 hours after an overdose before concluding the patient can be safely discharged or transferred. Evidence of toxicity after 6 hours will require hospital admission, and patients with severe toxicity should go to the intensive care unit. Consult with a medical toxicologist or local poison center to assist in the care of severe barbiturate-poisoned patients.

BARBITURATE WITHDRAWAL SYNDROME

Abrupt discontinuation of barbiturates in a chronically dependent user will produce withdrawal symptoms similar to alcohol or benzodiazepine withdrawal. Clinical manifestations will range from anxiety and restlessness to hallucinations, delirium, and/or generalized seizures. Severe symptoms in the ED can be treated with benzodiazepines or barbiturates, but due to the associated mortality, gradual in-hospital detoxification is needed.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 183

Benzodiazepines

Dan Quan

INTRODUCTION

Benzodiazepines, to varying degrees, have in common six major pharmacologic effects: sedative, hypnotic, anxiolytic, amnestic, anticonvulsant, and muscle relaxant.[1] Benzodiazepines are commonly used for the short-term treatment of anxiety, insomnia, seizures, and withdrawal

TABLE 183-1 Benzodiazepines

Generic Name	Time to Peak Effect (hours)†	Elimination Half-Life (hours)‡	Duration of Action (hours)	Active Metabolite Half-Life (hours)	Oral Dose Equivalents in Milligrams to Diazepam 10 Milligrams
Short Acting					
Alprazolam*	1–2	6–12	4-7	No	0.5
Midazolam*	IV 1–2 min IM 10–15 min PO 0.5–1	3–6	IV 2 IM 4–6 PO 4–6	Yes	5
Oxazepam*	0.3–0.5	5–10	3–6	No	20
Tetrazepam	1–3	15	6–8	No	50–100
Triazolam*	0.25–0.5	2–5	6–7	No	0.25–0.50
Intermediate Acting					
Bromazepam	1–3	10–20	<12	Yes	5–6
Cinolazepam	0.5–2	9	9	No	40
Estazolam*	1	10–24	<12	No	1–2
Flunitrazepam	0.25–0.3	18–24	4–6	Yes (36–200)	1
Loprazolam	0.5–4	6–12	<12	No	1–2
Lorazepam*	IV 5–20 min IM 20–30 min PO 0.5–1	9–16	6–8	No	1
Lormetazepam	0.5–2	10–12	<12	No	1–2
Nimetazepam	0.25–0.5	14–30	<12	No	5
Nitrazepam	0.5–5	16–48	<12	No	10
Premazepam	2	10–13	<12	No	3.75
Temazepam*	1.5	9–12	5–20	No	20
Long Acting					
Chlordiazepoxide*	2	5–30	5–30	Yes (36–200)	25
Clonazepam*	0.3–0.5	20–80	<12	No	0.5
Clorazepate*	1–2	48	8–24	Yes (36–200)	15
Cloxazolam	2–5	65	18–50	No	1–2
Diazepam*	IV 1–5 min PO 15–45 min PR 5–45 min	20–50	IV 0.25–1 PO 12–24	Yes (36–200)	10
Flurazepam*	0.5–1	2	12	Yes (50–100)	15–30
Flutoprazepam	0.5–2	60–90	24	Yes	2–3
Halazepam	1–3	—	12–24	Yes (30–100)	20–40
Ketazolam	2.5–3	30–100	12–24	Yes (36–200)	15–30
Medazepam	—	36–150	10–12	Yes (36–200)	10
Nordazepam	2	40–50	12–14	Yes (50–120)	10
Phenazepam	1.5–4	60	12	Yes	1
Pinazepam	1–2	20–25	12–24	Yes (40–100)	20
Prazepam	2–6	40–80	12–24	Yes (36–200)	10–20
Quazepam*	0.5–2	27–41	12–24	Yes (28–80)	20

*Available in the United States.

†After oral ingestion, unless otherwise specified.

‡Parent compound.

from alcohol or sedative-hypnotic agents.[2-5] The long-term benefits of benzodiazepines for psychiatric disorders are controversial.[6,7] Midazolam, a benzodiazepine with a short duration of action, is also used for procedural sedation and general anesthesia (**Table 183-1**).

Isolated benzodiazepine overdose has low mortality, and death is rare.[8] However, increased rates of morbidity do result from mixed overdose, especially in combination with opioids. **Isolated overdose with high-potency short-acting agents, such as alprazolam, temazepam, and triazolam, is associated with higher incidences of intensive care unit admissions, coma, and mechanical ventilation with toxicity compared to other benzodiazepines, such as diazepam.**[9] A review of suicide by self-poisoning found that temazepam was 10 times more toxic (fatal toxicity index) and 13 times more lethal (case fatality index) than diazepam.[10] In the ED, parenteral administration of benzodiazepines may result in significant complications, particularly respiratory depression and hypotension, especially when combined with opioids or other sedatives.

PHARMACOLOGY

Benzodiazepines stimulate the α subunit of the postsynaptic γ-aminobutyric acid ($GABA_A$) receptor in the CNS. Stimulation of this receptor affects the ligand-gated chloride channel on the cell membrane,

altering the transmembrane resting potential to below stimulation threshold and rendering the postsynaptic neuron less excitable. Stimulation of this $GABA_A$ receptor leads to inhibitory effects throughout the neuraxis, producing the typical clinical effects of sedation, anxiolysis, anticonvulsant activity, and striated muscle relaxation.

In general, benzodiazepines are well absorbed from the GI tract. The onset of action after oral ingestion is limited more by the rate of absorption from the GI tract than by the relatively rapid passage from the bloodstream into the brain. With the exception of lorazepam and midazolam, IM injection of benzodiazepines results in unpredictable absorption. IV administration of midazolam and lorazepam has an onset of action in 1 to 5 minutes. Diazepam may be administered rectally, and midazolam may be administered intranasally or intrabuccally, with variable rates of absorption by those routes.

Benzodiazepines are relatively lipid soluble, with some variation among the agents. Increased lipid solubility is associated with more rapid diffusion across the blood–brain barrier. After single doses, the more highly lipophilic benzodiazepines have a shorter onset of action but also a shorter duration of activity. This short duration of activity occurs because of rapid egress of the drug from the brain and bloodstream into inactive tissue storage sites. For this reason, the serum half-life is not a good indicator of the duration of action in an acute ingestion.

Benzodiazepine derivatives undergo hepatic metabolism through different pathways depending on the agent. Hepatic biotransformation occurs through either oxidation or conjugation; both pathways may be used by some derivatives. Oxidation often produces active metabolites that prolong the pharmacologic effects of the parent compounds. Oxidation is more susceptible to impairment by such factors as disease states (chronic liver disease), demographic characteristics (advanced age), and concurrent treatment with drugs that affect metabolism (estrogen, isoniazid, ethanol, ketoconazole, cimetidine, and phenytoin). Conjugation is a rapid process that generally produces inactive metabolites. Examples of agents that undergo conjugation primarily include lorazepam, oxazepam, and temazepam. These agents may be safer in susceptible groups such as patients with hepatic dysfunction.

There is conflicting evidence on how benzodiazepines affect fetal development.[11-13] In general, cohort studies have not found an increase in congenital malformations, whereas case-control studies show a small increase (especially for cleft lip and palate). This difference is ascribed to the higher sensitivity of case-control studies in identifying an association with specific conditions. The effect on fetal outcome of large doses of benzodiazepines taken for suicide attempts by pregnant women is not clear. Retrospective reviews of overdose with four different benzodiazepines, albeit with relatively small numbers, did not find an increased incidence of congenital abnormalities in the offspring.[14-18] Nearly all benzodiazepines enter breast milk, and therefore, caution should be exercised in patients taking benzodiazepines.[11,12]

Administration of benzodiazepines in the elderly or in patients with comorbid conditions (such as hepatic dysfunction) may be associated with more complications. Those with hepatic dysfunction can have impaired metabolism, causing increased clinical effects. Elderly patients taking benzodiazepines are at increased risk for falls, cognitive impairment, delirium, fractures, and motor vehicle accidents.[13,19]

Drug–drug interactions with benzodiazepines occur mainly with drugs that affect the **cytochrome P450 pathway**, specifically CYP3A4 and CYP2C19. For example, drugs such as ketoconazole or cimetidine are CYP3A4 inhibitors and may increase benzodiazepine blood levels, increasing their duration of action and/or clinical effect. Benzodiazepines themselves have not been implicated in affecting cytochrome P450 enzymes and, therefore, are unlikely to interfere with metabolism of other agents.

CLINICAL FEATURES

The clinical presentation of benzodiazepine intoxication is nonspecific and may be highly variable because of the frequent co-ingestion of other agents. Except for additive effects, drug interactions of benzodiazepines with other sedative-hypnotics are unusual.

The predominant manifestations of benzodiazepines are neurologic and are characterized by somnolence, dizziness, slurred speech, confusion, ataxia, incoordination, and general impairment of intellectual function. Prolonged coma is atypical and should prompt suspicion of intoxication with other agents or a nontoxicologic explanation. Neurologic effects of benzodiazepines may be prolonged or enhanced in the elderly, the young, and in those with protein deficiency or hepatic disease.

Paradoxical reactions, including excitement, anxiety, aggression, hostile behavior, rage, and delirium, have been reported but are quite uncommon. Paradoxical reactions may occur more with hyperactive children and in psychiatric patients. Benzodiazepines may have a disinhibiting effect, which, in the presence of various extrinsic factors, can lead to such actions as aggressive or hostile behavior. Other effects that have been reported and that have unclear etiologies include headache, nausea, vomiting, chest pain, joint pain, diarrhea, and incontinence.

Benzodiazepines may cause short-term anterograde amnesia; this effect may be desired, especially in procedural sedation.[13] Agents most often associated with anterograde amnesia are lorazepam, midazolam, and triazolam, although this may occur with the other benzodiazepines.

Uncommonly, respiratory depression and hypotension may occur, generally with either parenteral administration or in the presence of co-ingestants. IV administration is more likely to cause serious cardiorespiratory effects with rapid administration. In addition, the elderly and those with underlying cardiorespiratory disease are more susceptible to adverse effects of IV administration.

Propylene glycol as a diluent in parenteral preparations of diazepam and lorazepam may cause severe metabolic acidosis (lactic acidosis), nephrotoxicity, and hyperosmolar states when infused at doses >1 milligram/kg per day for an extended period of time.[20,21] During such treatment, an osmolar gap >10 is predictive of elevated propylene glycol concentrations.[21] Treatment of propylene toxicity is generally supportive but may require hemodialysis.[22]

Extrapyramidal reactions have been associated with the use of midazolam. Various allergic, hepatotoxic, and hematologic reactions also have been reported, but they are infrequent. In general, benzodiazepines have no long-term organ system toxicity other than that which can be ascribed to indirect effects from neurologic or cardiorespiratory depression.

DIAGNOSIS

Toxicologic testing in benzodiazepine ingestion is of limited value. Serum benzodiazepine levels do not correlate well with the clinical state, so serum level measurement is not routinely indicated. Qualitative testing with urine drug screens is typically designed to identify major metabolites of most benzodiazepines, such as oxazepam, temazepam, or nordiazepam, and not the parent compound.[23] Depending on the antibody specificity used in the immunoassay, a false-negative test can occur and is commonly seen with midazolam and flunitrazepam. A urine benzodiazepine screen can usually detect a short-acting agent (e.g., lorazepam) up to 3 days and a long-acting agent (e.g., diazepam) up to 30 days after ingestion. Thus, detection of a benzodiazepine agent taken in the recent past may not correctly identify the toxicologic cause of the patient's current condition. False-positive benzodiazepine urine drug screens have been reported with oxaprozin and sertraline, although improved immunoassay techniques have reduced this potential interference.[24,25]

TREATMENT

GENERAL MEASURES

Benzodiazepines often are ingested with other agents, and the history is frequently inaccurate. Therefore, in patients with depressed or altered mental status, other metabolic and toxicologic possibilities should be considered (see Chapter 176, "General Management of Poisoned Patients"). Do not induce emesis in benzodiazepine overdose because mental status depression may develop and increase the risk for pulmonary aspiration. Activated charcoal binds benzodiazepines effectively and may be considered. Aspiration risk should be weighed against the benefits of treatment for an ingestion that rarely causes major morbidity in isolated overdose.

The combination of rapid absorption and high level of protein binding render gastric lavage, elimination enhancement by forced diuresis,

hemodialysis, and hemoperfusion ineffective. Monitor neurologic and respiratory status and provide mechanical ventilation if necessary. Aspiration pneumonitis may be caused by severe respiratory and neurologic depression.

BENZODIAZEPINE ANTAGONIST

Flumazenil is a unique selective antagonist of the central effects of benzodiazepines, although there have been inconclusive claims that it may be effective in reversing the neurologic toxicity from other drugs.[26] Potential clinical applications include the reversal of coma in benzodiazepine overdose and reversal of iatrogenic benzodiazepine-induced sedation during procedural sedation.[23,27] Its use in benzodiazepine toxicity may obviate the need for tracheal intubation and respiratory support.[28,29]

However, some toxicologists advocate that flumazenil has limited utility in the ED, noting it is useful mainly in reversing the effects of short-acting benzodiazepines administered for diagnostic and therapeutic procedures.[30] Even in such cases, management is usually accomplished safely and easily by allowing the effects of the benzodiazepine to subside without antidotal administration.[29] Although the plasma elimination half-life of flumazenil is approximately 1 hour, its duration of action is variable and depends on the dose of flumazenil and the benzodiazepine administered. **Recurrent benzodiazepine toxicity may result once the effects of flumazenil have worn off.**[29] This is less likely for a benzodiazepine with a short duration of action, such as midazolam. The dose of **flumazenil is 0.2 milligram IV**, which can be repeated every minute, titrated according to response or to a total dose of 3 milligrams.

Several considerations should limit the empiric administration of flumazenil to a poisoned patient (**Table 183-2**). There is a higher incidence of side effects, albeit generally minor (agitation, nausea, vomiting, abdominal pain), when flumazenil is administered to an unconscious patient presenting to the ED.[28,31] Of greater importance, generalized seizures have occurred in patients given flumazenil after co-ingestions of benzodiazepines and seizure-inducing agents, particularly cyclic antidepressants.[31,32] Seizure activity after flumazenil administration also has occurred in patients physically dependent on benzodiazepines and in patients receiving benzodiazepines for control of a seizure disorder. The putative explanation for this convulsive activity is either the reversal of the cerebroprotective and anticonvulsive effects of benzodiazepines or the precipitation of a benzodiazepine withdrawal syndrome.

Flumazenil-precipitated seizures in patients who are chronically taking benzodiazepines should be treated aggressively with another $GABA_A$ receptor agonist because the benzodiazepine site on the receptor is antagonized. **Anticonvulsants such as phenobarbital or propofol are recommended for flumazenil-induced seizures.** Careful monitoring of the patient's respiratory and mental status is necessary during treatment and may require securing the airway.

Another reason to avoid empiric administration of flumazenil in overdose patients is that the history is often unreliable or unavailable. The apparent overdose may be caused instead by an intracranial mass lesion. **Flumazenil is contraindicated in patients with a suspected elevation of intracranial pressure, such as in severe head injury, due to its adverse effect on cerebral hemodynamics.**

DISPOSITION AND FOLLOW-UP

Indications for observation or hospital admission include significant alterations in mental status, respiratory depression, and hypotension. If mental status depression persists or is profound, other agents or conditions must be considered. Although many clinicians use the 6-hour principle for observation of stable patients after ingestion, there is insufficient evidence to recommend a specific duration for an appropriate ED observation period.

TABLE 183-2 Contraindications to Flumazenil

- Overdose of unknown agents
- Suspected or known physical dependence on benzodiazepines
- Suspected cyclic antidepressant overdose
- Co-ingestion of seizure-inducing agents
- Known seizure disorder
- Suspected increased intracranial pressure

TABLE 183-3 Clinical Features of Benzodiazepine Withdrawal

Psychiatric	Anxiety and nervousness*
	Restlessness and irritability*
	Insomnia and nightmares*
	Paranoia
	Hallucinations
	Delirium
Neurologic	Muscle twitching and tremors*
	Cognition and memory impairment*
	Perceptual distortions
	Hyperacusis and photophobia*
	Seizures*
Autonomic	Tachycardia*
	Hypertension
	Diaphoresis
	Nausea and vomiting
	Headache

*Common features.

BENZODIAZEPINE WITHDRAWAL

Benzodiazepine dependence can develop after long-term use—usually 6 to 12 months—and typically develops without tolerance (e.g., the absence of needing to increase dose to obtain the same effect).[33] Such patients are at risk for withdrawal upon sudden cessation. Withdrawal symptoms usually start within 2 to 3 days for short-acting benzodiazepines and 5 to 10 days for longer-acting ones. Benzodiazepine withdrawal is characterized by nervous system hyperactivity (**Table 183-3**). **Seizures are common in benzodiazepine withdrawal upon sudden discontinuation**. Withdrawal symptoms tend to be more severe with short-acting agents. Alprazolam withdrawal has some unique features compared with other benzodiazepine withdrawal syndromes.[34] Delirium and psychosis are more common, and hyperadrenergic states characterized by intermittent episodes of hypertension with sinus tachycardia have been reported.

To prevent withdrawal, benzodiazepine dosing should be slowly reduced over 4 to 6 weeks, or even longer when a patient is tolerant to a long-acting agent such as diazepam.[33] Dose reduction is guided by the patient's ability to tolerate symptoms.

Treatment of benzodiazepine withdrawal can obviously be done by reinstituting the drug and then embarking on a slow taper. Most benzodiazepines can be substituted by others for treatment of withdrawal symptoms with the apparent exception of alprazolam withdrawal, in which cases clonazepam is recommended since lorazepam, diazepam, and chlordiazepoxide are ineffective.[34] Alternative nonbenzodiazepine treatment includes antidepressants (e.g., trazodone), mood stabilizers (e.g., carbamazepine), anxiolytic agents (e.g., pregabalin or gabapentin), and β-blockers (e.g., propranolol).[35,36] Antihistaminic agents may be useful, and diphenhydramine, hydroxyzine, or promethazine have been effective.[33]

Patients with severe benzodiazepine withdrawal (i.e., experiencing seizures, delirium, and psychosis) should be admitted for stabilization on appropriate medications.[37,38] For patients with less severe withdrawal, reinstituting the benzodiazepine is recommended, with a suggestion to switch to a long-acting agent at an equivalent dose.[38] Outpatient follow-up with taper can then be done.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 184

Nonbenzodiazepine Sedatives

Frank LoVecchio

INTRODUCTION

The term *sedative-hypnotic* refers to any drug designed to produce sedation and sleepiness. These drugs can be divided into the benzodiazepines (see Chapter 183, "Benzodiazepines") and nonbenzodiazepines (**Table 184-1**).

One is most likely to encounter toxicity from these sedative drugs as part of accidental or nonaccidental overdose, as well as after an assault or trauma. Many nonbenzodiazepines were developed and are marketed for the treatment of insomnia, anxiety, and sedation.[1] Other agents with sedative effects, including antihistamines (e.g., diphenhydramine, doxylamine), antidepressants (e.g., amitriptyline, trazodone, mirtazapine), and antipsychotics (e.g., quetiapine), are also used to promote sleep.

Three sedative agents used in the past have been removed from the legal U.S. and Canadian markets: ethchlorvynol, glutethimide, and methaqualone. However, via Internet sites, these drugs are available to North American customers from locations in Eastern Europe, Africa, Asia, and South America.[2]

BUSPIRONE

Buspirone is approved by the U.S. Food and Drug Administration for treatment of anxiety disorders.[3] Off-label uses include treatment of depression and nicotine dependence. Buspirone is a partial agonist at the serotonin-1A receptor and an antagonist of the dopamine-2 receptor. The resultant effect on serotonin and dopamine neurotransmitter levels is complex, depending on the concentration of the drug and specific brain location, but overall effects are primarily suppression of CNS serotonergic activity and enhancement of dopaminergic and, possibly, noradrenergic activity.

Following ingestion, absorption is rapid and nearly complete, with significant first-pass metabolism in the liver (primarily via oxidation) resulting in a low bioavailability. Metabolism of buspirone (by cytochrome P3A4) produces several metabolites, including one active metabolite. Primary elimination is renal, with additional substantial fecal elimination.

Common adverse effects seen with buspirone include sedation, GI discomfort, vomiting, and dizziness. In therapeutic dosing, buspirone does not appear to cause psychomotor depression, and the drug has not been associated with any potential for abuse or withdrawal.[4]

The effects observed with a buspirone overdose are an exaggeration of adverse effects observed during therapeutic dosing. In general, the drug is well tolerated in overdose, and the treatment is largely supportive.[5] Animal toxicity studies indicate the potential for buspirone to provoke seizures, and one human case report noted the occurrence of a generalized tonic-clonic convulsion approximately 36 hours after a buspirone overdose (**Table 184-2**).[6] **Because of its serotonergic properties, buspirone has been associated with serotonin syndrome, although the true occurrence is exceedingly rare.**[7]

CARISOPRODOL AND MEPROBAMATE

Carisoprodol and its primary active metabolite meprobamate have been used since the 1950s. Carisoprodol is marketed as a centrally acting muscle relaxant, whereas meprobamate is marketed as an anxiolytic drug.

The exact mechanism of action of carisoprodol is not known; animal data demonstrate its ability to block interneuronal activity within the spinal cord and descending reticular formation. Other evidence suggests that the primary mechanism of action is simply related to sedation.[8] Carisoprodol may also have direct γ-aminobutyric acid activity, independent of its metabolite meprobamate.[9]

Following ingestion, carisoprodol is rapidly absorbed, with an onset of action within 30 minutes and a duration of action between 2 and 6 hours. Several formulations are marketed, sometimes combined with aspirin, caffeine, or codeine. Following metabolism in the liver, the carisoprodol metabolites are renally excreted.

Following ingestion, meprobamate is rapidly absorbed, with a duration of action of 6 to 10 hours. Following metabolism in the liver, the metabolites and 10% to 20% of the unchanged drug are eliminated by the kidneys.

With a carisoprodol overdose, there may be serious toxicity with sedation, coma, cardiovascular collapse, and pulmonary edema.[10] **Myoclonic jerks are frequently seen with carisoprodol toxicity, so suspect this ingestion in sedated or comatose patients with occasional jerking of the extremities.** Serotonergic features of carisoprodol intoxication have been noted, but the mechanism by which these symptoms and signs are produced is not understood.[11] Treatment of carisoprodol overdose and toxicity is supportive.

With meprobamate overdose, sedation, coma, and cardiopulmonary depression are seen, but there are no myoclonic jerks as described earlier with carisoprodol. **Ingestion of a large number of meprobamate tablets has been reported to form a gastric bezoar, and prolonged coma has been attributed to such retained drug within the stomach.**[12] If this

TABLE 184-1 Nonbenzodiazepine Sedative-Hypnotics

Name	Recommended Initial Adult Dose (oral; milligrams)	Recommended Maximum Adult Daily Dose (milligrams)	Time to Peak Plasma Levels	Elimination Half-Life
Buspirone	5 three times a day	60	40–90 min	2–3 h
Carisoprodol	250–350 four times a day	1400	1.5 h	2 h
Chloral hydrate	500–1000	Typically single dose 30 minutes before procedure	30 min	4 min for chloral hydrate and 6–10 h for trichloroethanol
γ-Hydroxybutyrate	See text	See text	30–60 min	0.3–1 h
Melatonin	0.2–5 qhs	5-10	30–60 min	40–50 min
Meprobamate	400 TID or QID	2400	3.6 h	10 h
Ramelteon	8 qhs	8	45 min	1–2.6 h
Tasimelteon	20 qhs	20	0.5–3 h	1.3 h
Zaleplon	5 qhs	20	0.7–1.4 h	0.9–1.2 h
Zolpidem	5 qhs	10	1–2 h	1.4–4.5 h
Zopiclone*	7.5 qhs	7.5	1.5–2 h	5–6 h
Eszopiclone	1 qhs	3	1–1.5 h	6–7 h

Abbreviations: qhs = at bedtime; QID = four times per day; TID = three times per day.

*Not available in the United States.

TABLE 184-2 Selected Aspects of Nonbenzodiazepine Overdose

Agent	Features Commonly Seen With Overdose	Unique Toxicologic Effects
Buspirone	Sedation	Generalized seizures (rare) Serotonin syndrome
Carisoprodol	Sedation, coma, cardiovascular collapse, pulmonary edema	Myoclonic jerks
Meprobamate	Sedation, coma, cardiopulmonary depression	Gastric bezoar with prolonged coma
Chloral hydrate	Coma	Cardiac instability, ventricular dysrhythmias, sensitivity to catecholamines, GI distress, hemorrhagic gastritis
γ-Hydroxybutyrate	Amnesia, sedation, seizure, coma, cardiac and respiratory depression	Steep dose–response curve Sudden awakening
Melatonin	Sedation, disorientation	None observed
Ramelteon	Sedation	None observed
Tasimelteon	Unknown	Limited experience, headache (possible)
Zolpidem	Sedation, coma possible	Limited experience, vomiting
Zaleplon	Sedation, incoordination	Limited experience, headache (possible)
Zopiclone and eszopiclone	Sedation	Limited experience, methemoglobinemia and hemolytic anemia (large overdoses)

occurs, multidose activated charcoal or endoscopic removal of the mass may be useful.

Carisoprodol withdrawal mimics ethanol and benzodiazepine withdrawal in that they are all γ-aminobutyric acid type A agonists.[13] Treatment of withdrawal is reinstitution of the carisoprodol or administration of other γ-aminobutyric acid type A agonists.

CHLORAL HYDRATE

Chloral hydrate was first marketed as a sedative in 1869, making it the oldest sedative-hypnotic agent still available. It remained quite popular until the early 1900s, when barbiturates largely supplanted its use. Chloral hydrate is primarily used as a sedative for painless procedures in young children because of its relatively wide therapeutic index, the lack of significant respiratory depression, and the ability for oral administration,[14] but the agent is not without risk.[15]

Following ingestion, chloral hydrate is quickly absorbed and rapidly reduced (by alcohol dehydrogenase) to the active metabolite trichloroethanol. Trichloroethanol is further oxidized to trichloroacetic acid, which is an inactive compound. Renal excretion of chloral hydrate is minimal.

Co-ingested chloral hydrate and ethanol have a synergistic effect. The metabolism of ethanol results in increased amounts of the reduced form of nicotinamide adenine dinucleotide, which, in turn, promotes the conversion of chloral hydrate to trichloroethanol. In addition, because of competition by chloral hydrate for alcohol dehydrogenase, there is decreased metabolism of ethanol. These interactions result in more elevated levels of both trichloroethanol and ethanol than would be seen if either was ingested alone. The resultant profound sedation yields the terms "**knock-out drops**" or "**Mickey Finn**" for this combination.

At therapeutic doses, chloral hydrate results in mental status depression, but airway and respiratory reflexes are not impaired. Paradoxical hyperactivity occurs in 1% to 2% and vomiting is seen in 3% to 10% of children given doses of 50 to 100 milligrams/kg PO.[16]

With an overdose, chloral hydrate can produce coma. **An important feature of chloral hydrate overdose is cardiovascular instability, manifested by decreased cardiac contractility, myocardial electrical instability, and increased sensitivity to catecholamines.**[17] Commonly encountered cardiac dysrhythmias include premature ventricular contractions, ventricular fibrillation, torsades de pointes, and asystole. GI irritation, manifesting as nausea, vomiting, or hemorrhagic gastritis, has also been observed. A diagnostic clue is the common presence of a pear-like odor.

Treatment of chloral hydrate overdose and toxicity is largely supportive. With coma, endotracheal intubation may be necessary. **IV β-adrenergic blockers should be used to treat ventricular dysrhythmias seen with chloral hydrate overdose.**[18] Torsades de pointes should be managed with IV magnesium sulfate or ventricular overdrive pacing.

γ-HYDROXYBUTYRATE (GHB)

γ-Hydroxybutyrate (GHB) is an endogenous molecule as well as a drug. GHB was originally used as an IV anesthetic, primarily in several European countries. In recent years, it has been marketed as a drug for body builders to improve body mass and reduce fat, as well as for use as a hypnotic, antidepressant, anxiolytic, and cholesterol-lowering drug.[19] GHB has been found in drug-facilitated sexual assaults.[20] Sodium oxybate (the sodium salt of GHB) is currently approved only for use within a highly regulated setting for the treatment of narcolepsy.[21] In some European countries, GHB or sodium oxybate is used as a treatment for alcohol dependence and withdrawal.[22] GHB can be formulated as a clear liquid or in solid form as a capsule, tablet, or white powder. GHB has many vernacular names, including **"liquid ecstasy," "Georgia Home Boy," "G,"** and **"Grievous Bodily Harm."**

Sodium oxybate is categorized a Schedule III drug by the U.S. Food and Drug Administration when used to treat narcolepsy, but GHB used for any purpose is considered a Schedule I drug. To circumvent laws, GHB precursors, namely γ-butyrolactone and 1,4-butanediol, have been introduced into the drug scene.[23] Following ingestion, lactonase enzymes in the blood convert γ-butyrolactone into GHB. Depending on the level of lactonase enzyme activity, this conversion can be rapid and produce a faster onset of symptoms compared with GHB. The conversion of 1,4-butanediol to GHB is a two-step process: conversion via alcohol dehydrogenase to γ-hydroxybutyraldehyde, with subsequent conversion via aldehyde dehydrogenase to GHB.

GHB undergoes metabolism via GHB dehydrogenase to succinic acid semialdehyde, which in turn can either be converted to succinic acid (to enter the Krebs cycle, yielding carbon dioxide and water) or to γ-aminobutyric acid, a primary inhibitory neurotransmitter. A small percentage of GHB will be excreted unchanged in the urine.

Following ingestion, GHB is rapidly absorbed from the GI tract, with peak plasma concentration occurring within an hour.[23] GHB has a relatively low oral bioavailability due to significant first-pass metabolism. After absorption, GHB follows a two-compartment model, in which the initial serum levels decline due to redistribution. There is a subsequent slower decline in the serum concentrations following metabolic degradation. Because of its short half-life, GHB is difficult to detect in the urine >6 hours after ingestion and is virtually nondetectable >12 hours after ingestion.[24] GHB has minimal protein binding and readily crosses the blood–brain barrier and placenta.

The body produces some endogenous GHB, both as a precursor and a breakdown product of γ-aminobutyric acid. At physiologic concentrations, GHB binds to a unique receptor that is distinct from γ-aminobutyric acid receptors. When the concentration of GHB in the brain exceeds the physiologic micromolar concentration, GHB can bind to (and activate) the γ-aminobutyric acid subunit B receptors.

GHB has a steep dose–response curve with a narrow therapeutic ratio; doses of 10 milligrams/kg result in short-term amnesia, doses of 20 to 30 milligrams/kg result in sedation and drowsiness, and doses exceeding 50 milligrams/kg result in seizure, coma, respiratory depression, and cardiac depression.[25,26] Bradycardia, hypothermia, and either miosis or mydriasis can occur.[23] During recovery, patients often wake up surprisingly quickly, as opposed to the more prolonged awakening phase seen after an overdose with other sedatives. Despite co-ingestants being commonly encountered, most patients fully regain consciousness within 3 to 4 hours.[27] The co-ingestion of ethanol can worsen hypoxia, increase the elimination half-life of GHB,[28] and prolong duration of toxicity.[27,29]

Treatment is largely supportive.[23] Intubation may be unnecessary, even in patients with severely depressed consciousness (Glasgow Coma

Scale score ≤8) because patients are usually able to protect their airway and maintain ventilation.[30] Once the patient is awake and alert, assuming no co-ingestants or secondary complications such as aspiration, the patient can be medically discharged or transferred. **Physostigmine or neostigmine are not recommended for reversal of known or suspected GHB intoxication.**[31] Fomepizole (a competitive antagonist of alcohol dehydrogenase) has little benefit in 1,4-butanediol overdoses because preventing metabolism of the ingested drug into GHB is of little benefit due to the short expected duration of symptoms.

Toxicologic detection of GHB can be difficult because of its short half-life,[26] the complexity of assay methodology, and the presence of the endogenous compound. If needed, toxicologic confirmation should be performed with blood or urine collected as soon as the individual arrives in the ED.[24,32]

MELATONIN

Melatonin is an endogenous hormone that is normally secreted by the pineal gland and is believed to be involved with the circadian sleep–wake cycle.[33] Melatonin is available without prescription in tablets or capsules at doses ranging from a physiologic dose of 0.2 milligram up to pharmacologic doses of 5 to 10 milligrams.

Two primary melatonin receptor subtypes are found in the human CNS.[33] The MT_1 receptor is located primarily in the hypothalamic suprachiasmatic nucleus and is involved in the effect melatonin has on circadian rhythm. The MT_2 receptor is found primarily in the retina, presumably involved in the interaction between incoming light, melatonin, and the circadian cycle. The MT_2 receptor is also found in the hypophysial pars tuberalis and is possibly responsible for the effects of melatonin on reproduction.

Following ingestion, peak plasma melatonin concentrations occur within 40 to 50 minutes. Melatonin has a short plasma half-life and a short duration of action in therapeutic doses. Melatonin is metabolized by initial conversion to O-desmethylmelatonin and 6-hydroxymelatonin. Both are subsequently conjugated as either a glucuronide or a sulfate before renal excretion.

At therapeutic dosing, side effects from melatonin include fatigue, headache, dizziness, and irritability.[34] Data on melatonin overdoses are limited, but overdose would be expected to result in an exaggeration of therapeutic effects, primarily sedation and disorientation, without any significant life-threatening effects.[35]

RAMELTEON

Ramelteon is a highly selective agonist at the melatonin MT_1 and MT_2 receptors, marketed for the treatment of insomnia.[36] Ramelteon has no significant activity at the γ-aminobutyric acid, dopamine, serotonin, norepinephrine, or opiate receptor sites. An active metabolite does have weak activity at the serotonin-2B receptor but is thought to be clinically insignificant.

Ramelteon is rapidly absorbed following oral administration, but oral bioavailability is <2% due to extensive first-pass metabolism. Hepatic metabolism of ramelteon yields four metabolites, one of which is active. Metabolism is primarily through the cytochrome P1A2 enzyme, with minor contributions via P2C and P3A4. The coadministration of P1A2 inhibitors such as fluoroquinolones and verapamil has been shown to increase ramelteon concentrations. Protein binding is extensive, the volume of distribution is large, and excretion is primarily renal.

In overdose, sedation would be expected, and treatment is supportive.[37] Ramelteon has not been associated with any potential for abuse and has minimal risk for producing withdrawal symptoms or rebound insomnia.[36]

TASIMELTEON

Tasimelteon is an agonist at melatonin MT_1 and MT_2 receptors used for treatment of non–24-hour sleep–wake disorder, a syndrome characterized by insomnia or excessive sleepiness from abnormal synchronization between the 24-hour light–dark cycle and the endogenous circadian rhythms of sleep and wakefulness.[38] The majority of patients with this syndrome are totally blind. Ramelteon and tasimelteon may have benefit in sleep disorders associated with comorbid psychiatric, neurologic, and cardiovascular conditions.[39]

After ingestion, peak concentrations occur within 0.5 to 3 hours. There is a large volume of distribution, high protein binding, and extensive metabolism with an elimination half-life of 1.3 hours.

There is no reported experience with tasimelteon overdose. Adverse effects reported during clinical trials suggest headache may occur. There have been no observed findings suggestive of abuse potential, physical dependence, or withdrawal during clinical trials.[40]

ZOLPIDEM, ZALEPLON, AND ZOPICLONE

Zolpidem, zaleplon, and zopiclone are three nonbenzodiazepine sedative-hypnotics used to treat insomnia.[1,34] All three promote sleep by enhancing CNS γ-aminobutyric acid activity but differ in their pharmacodynamic and pharmacokinetic profiles.

All three drugs bind to the benzodiazepine binding site on the postsynaptic γ-aminobutyric acid subtype A1 receptor, although they have different binding affinities to the α-1 and α-2 subunits.[41] Zaleplon has a very short half-life (about 1 hour), as opposed to the somewhat longer half-lives of zolpidem and zopiclone (Table 184-1).

All three drugs were initially promoted as an improvement upon benzodiazepines for the treatment of insomnia. They were to be safer, produce less psychomotor impairment with therapeutic doses, and not be addictive or associated with a withdrawal state. With experience, all three drugs have been found to impair psychomotor function,[42,43] create tolerance and dependence, and be associated with withdrawal states characterized by insomnia, anxiety, agitation, and delirium.[41] **Zaleplon, presumably because of its shorter elimination half-life, appears to produce less tolerance and withdrawal symptoms than zolpidem or zopiclone.**[44]

Zolpidem undergoes hepatic metabolism into three inactive metabolites, so dosage restrictions are recommended for those with hepatic impairment and those with chronic renal insufficiency. Common adverse effects include somnolence and nausea. Because of occasional psychomotor impairment, individuals should not drive or engage in hazardous activity the day following use of zolpidem. There are numerous reports of sleepwalking or vivid dreams after its consumption. Following overdose, sedation (including coma) and vomiting can occur.[45] Fatalities usually occur in the setting of co-ingestants, rather than with zolpidem by itself.[46]

Zaleplon absorption occurs rapidly (Table 184-1) but can be delayed if zaleplon is co-ingested with a high-fat meal. Following absorption, zaleplon undergoes extensive first-pass metabolism in the form of oxidation via aldehyde oxidase to form inactive metabolites. Elimination is primarily renal, with some fecal elimination as well. In therapeutic doses, zaleplon is not associated with any dependence or withdrawal state when taken for up to 5 weeks.[47] At doses up to 10 milligrams, no psychomotor or memory impairment is observed, but a dose of 20 milligrams is associated with some impairment. Reports of overdose with zaleplon are limited, but expected findings include sedation, incoordination, and possibly headache.

Zopiclone is not currently available in the United States, but **eszopiclone**, the *S*-configuration and active isomer of zopiclone, is marketed. Zopiclone is rapidly absorbed and hepatically metabolized into active (*N*-oxide metabolite) and inactive (*N*-dimethyl metabolite) compounds. Nearly half of the parent drug is excreted in the lungs following decarboxylation. Reports of zopiclone or eszopiclone overdose indicate sedation to be the primary observed effect.[48] Prolonged coma was reported in an elderly patient who ingested a large amount of eszopiclone.[49] Rare cases of methemoglobinemia and mild hemolytic anemia have been reported after large zopiclone overdoses.[50]

HISTORICAL SEDATIVES

Ethchlorvynol was marketed during the 1950s as an alternative to barbiturates. In 1999, the remaining U.S. manufacturer stopped production and sales of the drug, but availability elsewhere in the world persists.

Following ingestion, ethchlorvynol is rapidly absorbed from the GI tract. A biphasic distribution process is characterized by an initial phase of adipose tissue deposition followed by a redistribution out of adipose stores and back into the plasma. Ethchlorvynol has a plasma half-life of 10 to 25 hours, undergoes hepatic metabolism, and is renally excreted. At therapeutic dosing, sedation and nystagmus can occur. Overdose can be characterized by prolonged deep coma, hypothermia, hypotension, bradycardia, and cardiovascular collapse. Similar to other severe coma states, bullous lesions have been seen with ethchlorvynol overdose. Abusers have been reported to inject the drug, sometimes producing acute pulmonary edema. Ethchlorvynol overdose may produce a vinyl-like odor that can be a useful diagnostic clue. Treatment is largely supportive, but charcoal hemoperfusion has been used in massive overdoses.[51]

Glutethimide was withdrawn from the market in 1999 when the remaining U.S. manufacturer stopped production and sales. Availability overseas is suggested by listings on the Internet for sales of this drug. A unique aspect of this drug was that the combination of oral glutethimide with codeine produced a euphoria considered similar to that induced by heroin. In overdose, glutethimide produces a deep coma with periods of cyclic responsiveness. The cause of these cycles has been ascribed to an active metabolite, but evidence is not convincing. Following ingestion, absorption is variable and plasma half-life is 10 to 12 hours. Glutethimide possesses antimuscarinic properties, so toxic patients may have tachycardia, hypertension, mydriasis, urinary retention, and intestinal ileus. Treatment is primarily supportive.

Methaqualone was withdrawn from the U.S. market in 1984 when the remaining manufacturer stopped production. Continued use and abuse of methaqualone in South Africa is a significant problem, where the drug is often mixed with cannabis and smoked. As with the other two sedatives of historical interest, availability in other countries is suggested by Internet sites. A unique feature of a methaqualone overdose is muscular hyperactivity, with hyperreflexia and clonus and a lower rate of respiratory depression and hypotension compared with other sedatives. In severe overdoses, prolonged supportive treatment is often required.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 185

Alcohols

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INTRODUCTION

All alcohols cause clinical inebriation, with the strength of the inebriating effects directly proportional to the alcohol's molecular weight; hence, at the same concentration, isopropanol is more intoxicating than ethanol (**Figure 185-1**).

Primary toxicity can be due to the parent compound (ethanol and isopropanol) or to toxic metabolites (ethylene glycol and methanol). **Ethanol** and **isopropanol** are the most common alcohols ingested; their principal effects are GI irritation and intoxication, and they do not in themselves produce a clinically relevant metabolic acidosis. **Methanol** and **ethylene glycol** are toxic alcohols because they cause serious multisystem damage and metabolic acidosis.

ETHANOL

INTRODUCTION

Ethanol (CH_3CH_2OH, molecular weight 46.07) is a colorless, volatile liquid that is the most frequently used and abused drug in the world. Morbidity from acute ethanol intoxication is usually related to secondary injuries rather than direct toxic effects. Intoxication most commonly occurs from ingestion, but ethanol may also be absorbed via inhalation or percutaneous exposure.

Ethanol is usually consumed as an alcoholic beverage, such as 12 oz (355 mL) of beer (2% to 6% ethanol by volume), 5 oz (148 mL) of wine (10% to 20% ethanol by volume), or 1.5 oz (44 mL) of 80-proof spirits (40% ethanol by volume), each serving containing about 15 grams of ethanol. Ethanol may be found in high concentrations in many other common household products such as mouthwash (may contain up to 75% ethanol by volume) and colognes and perfumes (up to 40% to 60%), and as a diluent or solvent for medications (concentration varies widely between 0.4% and 65%). Such products are often flavored or brightly colored and may be attractive to children.

PATHOPHYSIOLOGY

Ethanol is rapidly absorbed after oral administration, and blood levels peak about 30 to 60 minutes after ingestion. The presence of food in the stomach prolongs absorption and delays the peak blood level. High concentrations of ethanol in the stomach may cause pylorospasm, delaying gastric emptying. Some ethanol is broken down in the stomach by gastric alcohol dehydrogenase, which lowers the amount available for absorption. This enzyme is present at higher levels in men than in women, which may account for the fact that women usually develop a higher blood ethanol level than men after consuming the same dose per kilogram of body weight.

Ethanol is a CNS depressant[1] that enhances the inhibitory neurotransmitter γ-aminobutyric acid receptors and blockade of excitatory *N*-methyl-D-aspartic acid receptors. Modulation of these systems leads to the development of tolerance, dependence, and a withdrawal syndrome when ethanol intake ceases in dependent individuals.

Because of the phenomenon of tolerance, blood ethanol levels correlate poorly with degree of intoxication. Although death from respiratory depression may occur in nonhabituated individuals at concentrations of 400 to 500 milligrams/dL (87 to 109 mmol/L), some alcoholic individuals can appear minimally intoxicated at blood concentrations as high as 400 milligrams/dL (87 mmol/L).[2] Although Canada, Mexico, and the United States have adopted 80 milligrams/dL (17 mmol/L) as the legal definition of intoxication for the purposes of driving a motor vehicle, impairment may occur with levels as low as 50 milligrams/dL (11 mmol/L), especially in nonhabituated individuals.[3]

Ethanol is predominantly eliminated by hepatic metabolism, with about 10% excreted in the urine, exhaled breath, and sweat. **Alcohol dehydrogenase** (**Figure 185-2**) is the major enzyme involved in the metabolism of ethanol, producing acetaldehyde. At low ethanol concentrations, this process follows first-order kinetics,[4] but as concentrations rise, alcohol dehydrogenase becomes saturated and metabolism switches

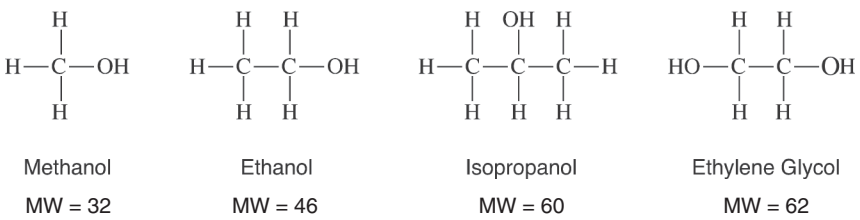

FIGURE 185-1. Chemical structures of the common alcohols.

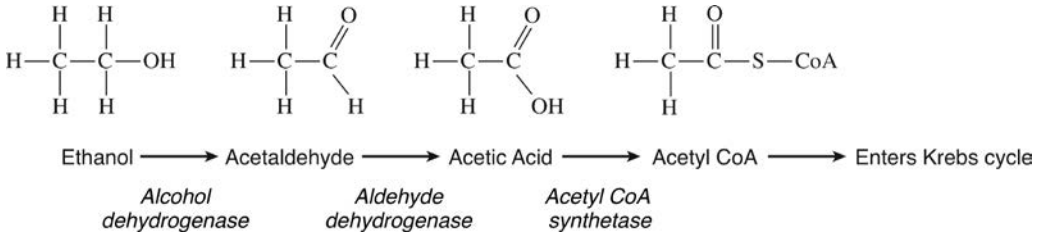

FIGURE 185-2. Metabolism of ethanol. CoA = coenzyme A.

to zero-order kinetics—a fixed amount is metabolized per unit of time. Also, as ethanol concentrations rise, the hepatic microsomal oxidizing system (specifically, cytochrome P450 2E1 [CYP2E1]) plays a more important role in metabolism.

Both alcohol dehydrogenase and CYP2E1 are inducible and thus are more active in chronic ethanol users. Therefore, rates of ethanol elimination from the blood vary from about 20 milligrams/dL per hour (4 mmol/L per hour) in nonhabituated individuals to up to 30 milligrams/dL per hour (6 mmol/L per hour) in individuals with chronic alcoholism.

CLINICAL FEATURES

The hallmark of ethanol toxicity is clinical inebriation.[5] Behavioral disinhibition may initially appear as euphoria or agitation and combativeness. As intoxication becomes more severe, slurred speech, nystagmus, ataxia, and decreased motor coordination develop. Severe intoxication may cause respiratory depression and coma. Nausea and vomiting often occur in conjunction with neurologic depression.

Ethanol causes peripheral vasodilation and flushed, warm skin, enabling loss to the environment and promoting hypothermia. Vasodilation may also lead to orthostatic hypotension and reflex tachycardia. Ethanol-induced hypotension is usually mild and transient, so significant or persistent hypotension warrants investigation for alternative causes.

Ethanol ingestion may cause hypoglycemia, usually in children and malnourished individuals due to low glycogen stores and reduced gluconeogenesis. The metabolism of ethanol by alcohol dehydrogenase requires the presence of the oxidized form of nicotinamide adenine dinucleotide (NAD^+), which is then converted into its reduced form (NADH). The metabolism of a significant amount of ethanol increases the NADH/NAD^+ ratio, which then promotes the conversion of pyruvate to lactate, diverting pyruvate away from the gluconeogenesis pathway (**Figure 185-3**).

When a chronic alcoholic suddenly stops consuming calories in the form of either ethanol or food, the body uses alternative fuel sources and begins to break down adipose tissue. This metabolism of fatty acids results in ketoacidosis (see Chapter 226, "Ketoacidotic Syndromes").

DIAGNOSIS

Ethanol-intoxicated patients often have other disease processes, such as infections and traumatic injuries, so perform a detailed physical examination, looking especially for evidence of trauma, and obtain as much history as possible. Uncomplicated ethanol intoxication improves over a few hours. **If depressed mental status fails to improve or deteriorates, consider other causes of altered mental status and evaluate appropriately.**

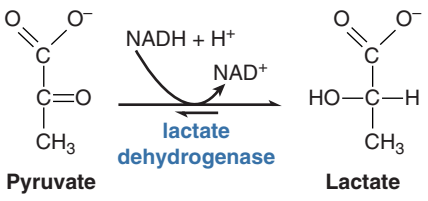

FIGURE 185-3. Conversion of pyruvate to lactate. LDH = lactate dehydrogenase; NAD^+ = oxidized form of nicotinamide adenine dinucleotide; NADH = reduced form of nicotinamide adenine dinucleotide.

The clinical assessment guides the selection of laboratory tests. For altered levels of consciousness, obtain a point-of-care glucose level. Ethanol levels are not necessarily required in cases of mild or moderate intoxication when no other abnormality is suspected, but measure serum alcohol levels in patients with altered mental status of unclear cause. Estimation of ethanol level is unreliable, particularly around levels of 100 milligrams/dL (22 mmol/L)[6,7] or in alcohol-tolerant patients.[8] In isolated ethanol intoxication, the presence of horizontal gaze nystagmus has a sensitivity of 70% to 80% for a blood ethanol level of 80 milligrams/dL (17 mmol/L) and a sensitivity of 80% to 90% for blood ethanol levels >100 milligrams/dL (22 mmol/L).[9-11]

Ask about concomitant drug use, especially cocaine. The attraction of abusing these drugs together may relate to the formation of the active cocaine metabolite cocaethylene, which, although less potent than the parent compound, has a half-life that is three to five times longer.[12] The risk of sudden death among users of both drugs simultaneously is higher than that among cocaine users alone.

Ethanol ingestion is the most common cause of an osmolar gap on serum electrolyte analysis (see Chapter 17, "Fluids and Electrolytes") and may be associated with a mild metabolic acidosis,[13] but a significant anion gap metabolic acidosis suggests the presence of lactic acidosis, ketoacidosis, or methanol or ethylene glycol toxicity.

TREATMENT

Management is observation until sobriety.[5] Activated charcoal is not useful since ethanol is rapidly absorbed; consider activated charcoal only if toxic adsorbable substances have been co-ingested within the past hour.

Treat hypoglycemia with IV dextrose 0.5 to 1 gram/kg. Although acute **Wernicke's encephalopathy** can be precipitated by prolonged sustained administration of IV carbohydrate, there is no evidence that a single dose of IV glucose can cause this syndrome.[14,15] The prevalence of vitamin deficiencies in acutely intoxicated ED patients is low and does not justify the routine use of IV vitamin-containing fluids.[16] Long-term drinkers may be vitamin deficient and are sometimes treated with IV fluids containing magnesium, folate, thiamine, and multivitamins, termed a ***banana bag*** because of the yellow color imparted by the multivitamin mixture.

Wernicke's encephalopathy is characterized by abnormal mental status, ataxia, and nystagmus, and requires daily treatment with thiamine, 100 milligrams, until normal diet is resumed. **Fluid administration does not hasten alcohol elimination**, so establishment of IV access for fluid administration alone is unnecessary in uncomplicated mild to moderate intoxication.[17]

Metadoxine, which is not currently available in the United States but is available in Latin America, Mexico, Asia, Africa, and Eastern Europe, enhances the metabolism of ethanol and accelerates recovery.[18,19] Metadoxine 900 milligrams IV is reported to double the rate at which ethanol blood levels decrease with time compared with the patient's own metabolism.[19,20]

DISPOSITION AND FOLLOW-UP

Patients with acute ethanol intoxication as the only clinical problem require ED observation until sober. Prior to discharge, reassess for an underlying mental health disorder, such as suicidal or homicidal ideation, that requires further care or hospital admission. Screening for alcohol use disorder prior to discharge with brief intervention and referral to appropriate outpatient services is recommended to reduce future

harm.[21] Clinical judgment, rather than a serum ethanol level, determines the appropriateness of discharge. Discharge the patient in the care of a responsible companion. Patients treated for alcohol intoxication should not be responsible for their own transportation home.

ALCOHOL WITHDRAWAL SYNDROMES

INTRODUCTION

Alcohol withdrawal symptoms develop in individuals with a history of heavy and prolonged consumption of alcohol who abruptly stop or reduce their drinking. The spectrum of alcohol withdrawal symptoms includes hand tremors, headache, loss of appetite, nausea and vomiting, diaphoresis, insomnia, tachycardia, hypertension, fever, psychomotor agitation, hyperarousal, craving, and anxiety, as well as the more serious manifestations of seizures, hallucinations, and delirium.[22] The abrupt withdrawal of alcohol from the brain of chronic heavy drinkers is thought to reduce inhibitory neurotransmission through γ-aminobutyric acid and enhance excitatory neurotransmission through glutamate, but not all heavy drinkers experience withdrawal when stopping or cutting back their consumption.

Alcohol withdrawal symptoms exist on a continuum from uncomplicated to moderate and severe, may begin as early as 2 to 6 hours after reduction in alcohol consumption, and can persist for up to 2 weeks (**Table 185-1**). Convulsions occur in 5% to 15%, and delirium tremens occurs in <5% of patient undergoing alcohol withdrawal; those with a prior history are at greater risk. Deaths from delirium tremens among patients receiving early and aggressive treatment have declined from 35% in the early 20th century to <5% in the current period.[22-24]

The first step in successful treatment is to identify alcohol withdrawal early and distinguish withdrawal from mimics. The most common mimics include toxic-metabolic abnormalities (hyponatremia, hypoglycemia, hypomagnesemia, diabetic ketoacidosis, Wernicke's encephalopathy), toxic alcohol ingestions (ethylene glycol, methanol), opioid or sedative withdrawal, prescription or illicit drug ingestions (anticholinergic drugs, stimulants), neurologic abnormalities (primary generalized seizures, withdrawal seizures), and sepsis.

Gastritis, peptic ulcer disease, and pancreatitis are comorbidities with symptoms that often require abrupt cessation of alcohol consumption, leading to withdrawal. The gathering of collateral history, thorough serial examinations of the undressed patient, repeated monitoring of vital signs, measurement of oxygen saturation and point-of-care testing for blood glucose, laboratory assessment of metabolic conditions, and imaging as clinically indicated can detect most comorbidities.

TABLE 185-1 Alcohol Withdrawal Continuum

Time	Manifestations	Comments
6–24 h	**Minor Symptoms** Anxiety Insomnia Anorexia, nausea and vomiting Headache Palpitations Tremor	Can be mild and patients may not require medical care
24–48 h	**Alcohol Withdrawal Hallucinations** Tactile most common Occasionally auditory or visual	Occur in 7%–8% Usually resolve in 48 h
36–60 h	**Withdrawal Seizures** Generalized tonic-clonic Can be single or multiple Status epilepticus uncommon	Occur in 5%–10% May occur as early as 6 h after alcohol cessation
60+ h	**Delirium Tremens** Agitation Disorientation Hallucinations Fever Diaphoresis Hypertension Tachycardia	Peaks at 5 d and may last up to 7 d

WITHDRAWAL HALLUCINOSIS

About a quarter of patients in alcohol withdrawal experience transient alterations in perception or illusions, such as tactile (paresthesias), visual (zooscopies or hallucinations of animals), or auditory (voices) illusions. Persistence of these symptoms, usually tactile or visual, is termed *alcohol withdrawal hallucinations*. Patients generally recognize these hallucinations as not real and maintain a clear sensorium. Tremors and other signs of alcohol withdrawal may not be present.

ALCOHOL WITHDRAWAL SEIZURES

Alcohol withdrawal seizures are diffuse tonic-clonic seizures that can occur as early as 6 hours after the decrease or cessation of alcohol ingestion, and 90% occur within 48 hours.[25] Alcohol withdrawal seizures can be single or multiple, and a few percent of patients can progress to status epilepticus.[22] More than half of withdrawal seizures are associated with underlying epilepsy, brain lesions, or substance use.[22] Focal seizures suggest a focal cerebral lesion. About one third of patients with alcohol withdrawal seizures develop delirium tremens, with the seizures terminating before the development of delirium. An alcohol withdrawal seizure may be brief, with a short or no postictal period.[25] The diagnosis of alcohol withdrawal seizures requires the exclusion of traumatic brain injury, hypoxia, hypoglycemia, structural lesions, infections, use of illicit drugs, idiopathic epilepsy, withdrawal from other recreational drugs, withdrawal from prescription sedatives, and noncompliance with antiseizure medications.[25]

DELIRIUM TREMENS

Alcohol withdrawal delirium tremens is characterized by acute and fluctuating disturbances in consciousness, confusion, psychomotor agitation, inattention, and impairment in cognitive and perceptual function (hallucinations) unrelated to preexisting or established dementia.[22] Patients often develop life-threatening fluid, metabolic, and electrolyte imbalances. Autonomic instability is generally present. Among the risk factors associated with delirium tremens are past withdrawal seizure and delirium tremens, severe dependence and prior detoxification history, high and long duration of alcohol intake, older age, use of other drugs, genetic polymorphism, and comorbidities.[22]

ALCOHOL-INDUCED PSYCHOTIC DISORDER

Alcohol-induced psychotic disorder is a separate entity from the more common withdrawal hallucinations seen as part of an acute alcohol withdrawal syndrome. In contrast to alcohol withdrawal hallucinations, auditory hallucinations predominate over visual and tactile hallucinations. They are often of a persecutory nature.[26] Psychosis, paranoia, and agitation may last from days to weeks. Diagnostic criteria require that symptoms start within 2 weeks of alcohol consumption and persist for 48 hours or greater beyond the withdrawal state.[27] Clouding of sensorium should be minimal. Treatment may require short- or long-term use of antipsychotics.[27] Alcohol-induced psychotic disorder has a high risk for suicide and co-occurs with other psychiatric diagnoses. Patients with hallucinations lasting for >6 months have the worst prognosis; however, the prognosis is more favorable if abstinence can be maintained.[26]

TREATMENT

The goals of therapy for alcohol withdrawal are to alleviate autonomic hyperactivity and agitation, halt progression to delirium tremens, and if possible, provide motivation for and access to detoxification to promote long-term abstinence.[22-24,28] Initial therapy is usually with benzodiazepines; no specific agent is superior to the others (**Table 185-2**).[22,24,28] IV administration works the fastest, with an onset of action of 1 to

TABLE 185-2 Treatment of Alcohol Withdrawal Syndromes

Condition	Treatment (see text)
Uncomplicated alcohol withdrawal (no seizures, no delirium)	Lorazepam 2 milligrams PO *or* Diazepam 10–20 milligrams PO *or* Oxazepam 15–30 milligrams PO *or* Chlordiazepoxide 50–100 milligrams PO *If vomiting:* Diazepam 10–20 milligrams IV *or* Lorazepam 2–4 milligrams IV *and* Ondansetron 4 milligrams IV
Alcohol withdrawal seizures	Lorazepam 2 milligrams IV
Alcohol withdrawal delirium tremens	Lorazepam 2–4 milligrams IV; double the dose and repeat every 15–20 min until light somnolence *or* Diazepam 10–20 milligrams IV over 2 min; double the dose and repeat every 5–10 min until light somnolence *If refractory to benzodiazepines:* Phenobarbital 65 milligrams IV every 15–30 min to maximum of 260 milligrams[7] (respiratory depression more common than with benzodiazepines; typically requires intubation) *or* Propofol 5 micrograms/kg per minute (or 0.3 milligram/kg per hour) titrated to effect; typically requires intubation (unlabeled use, primarily case reports of effectiveness)
Alcohol-induced psychotic disorder	Abstinence from alcohol Antipsychotics until symptoms remit

5 minutes for diazepam, 2 to 5 minutes for midazolam, and 5 to 20 minutes for lorazepam in alcohol withdrawal.[24] Intramuscular absorption of lorazepam and midazolam is adequate, but absorption of IM diazepam is erratic, and therefore, IM diazepam is not recommended. Both diazepam and chlordiazepoxide are metabolized by the liver, producing long-acting active metabolites with a 20- to 30-hour duration of action.

Individualized symptom-triggered therapy is recommended; such an approach results in less drug administration and shorter duration of treatment than fixed-drug dosing.[29] The Clinical Institute Withdrawal Assessment for Alcohol–Revised is the most commonly used instrument for guiding continuing treatment once a diagnosis of alcohol withdrawal is established (**Table 185-3**).[30] Symptom-triggered therapy uses hourly assessments of the Clinical Institute Withdrawal Assessment for Alcohol–Revised score to time repeat benzodiazepine doses. If the score is >15, successive doses are given every hour until the score is <15, and if the score is 8 to 14, successive doses are given every 2 hours until the score is <8. The Clinical Institute Withdrawal Assessment for Alcohol–Revised has been critiqued because 7 of the 10 components require accurate communication with the patient, so language barriers, comorbid conditions, and medications may make it difficult to score.[31] Alternatives to the Clinical Institute Withdrawal Assessment for Alcohol–Revised have been developed, but most have not been validated.[32]

Drug Therapy for Uncomplicated Alcohol Withdrawal For patients meeting criteria for uncomplicated alcohol withdrawal without seizures, or delirium, the recommended first-line treatment is a benzodiazepine (Table 185-2).[22-24,28] Because no specific benzodiazepine is more effective than the others, physician choice, institutional availability, cost, and patient factors are taken into consideration.

Drug Therapy for Alcohol Withdrawal Seizures Benzodiazepines are effective in protecting against seizures and reducing recurrent seizures in alcohol withdrawal.[33,34] The recommended dose is lorazepam 2 milligrams IV.[35] Phenytoin is not recommended for prevention of further alcohol-related seizures, and loading of phenytoin may, in fact, lower the seizure threshold.[36]

Drug Therapy for Alcohol Withdrawal Delirium Alcohol withdrawal delirium is treated with sedative-hypnotics in high enough doses to quickly control agitation, minimize adverse events, and achieve light somnolence with arousal when stimulated.[24,28] A benzodiazepine is the initial treatment of choice (Table 185-2). An approach using escalating doses, doubled each time until light somnolence, is recommended.[28] After that, patients can be placed on maintenance therapy with periodic boluses or continuous infusions.

Some patients may have continued symptoms unresponsive to adequate doses of benzodiazepines. The amount of benzodiazepine administered after which the patient is considered refractory is not well defined; failure to achieve an adequate response with 50 to 100 milligrams of diazepam or 10 to 20 milligrams of lorazepam administered in the first hour suggests that additional agents, such as phenobarbital, propofol, or dexmedetomidine, will be required.[37-42] The use of phenobarbital or propofol typically requires intubation. Adverse effects of propofol include hypotension, and prolonged use >48 hours at a dose of >5 milligrams/kg per hour can cause propofol infusion syndrome, with dysrhythmias, heart failure, hyperkalemia, lipemia, metabolic acidosis, and rhabdomyolysis.[39,40]

Patients with delirium require thorough diagnostic assessment, aggressive treatment of co-occurring illnesses, supportive care, prevention of aspiration, and treatment of hyperthermia, dehydration, hypoglycemia, and electrolyte imbalance. Thiamine 100 milligrams daily and folate 1 milligram daily should be considered. Use magnesium sulfate only if hypomagnesemia is present; benefit from magnesium therapy in the absence of hypomagnesemia is not established.[43] Physical restraints may be temporarily needed until chemical restraint is achieved; a quiet, calm, supportive environment with low stimuli contributes to successful management.[22-24]

Drug Therapy for Alcohol-Induced Psychotic Disorder Antipsychotic therapy with alcohol abstinence is the recommended treatment. Because patients with active alcohol-induced psychotic disorder are at risk for suicide, mental health assessment is recommended.[27]

DISPOSITION

Patients with mild or moderate uncomplicated alcohol withdrawal that responds well to initial ED treatment, without trauma or major medical comorbidities, with no suicidal or homicidal ideation, and without a seizure disorder can be managed successfully in a detoxification unit or discharged to a supportive family with referral to an outpatient program. Indications for admission include advanced age, mild or moderate withdrawal that does not respond well to ED treatment, the presence of active medical comorbidities, a prior history of delirium tremens, and alcohol withdrawal seizures. Consider intensive care unit admission for moderate withdrawal with comorbid conditions or severe withdrawal in which sedative requirements necessitate close monitoring to monitor respiratory status.

ISOPROPANOL

INTRODUCTION

Isopropanol (CH_3CHOCH_3, molecular weight 60.10), also known as ***isopropyl alcohol*** and ***2-propanol***, is a colorless, volatile liquid with a bitter, burning taste and an aromatic odor. It is found in many common, inexpensive household products, such as **rubbing alcohol** (usually 70% isopropanol). Isopropanol is widely used in industry as a solvent and disinfectant and is a component of a variety of skin and hair products, jewelry cleaners, detergents, paint thinners, and deicers.

Poisoning usually results from ingestion,[44,45] but may also occur after inhalation or dermal exposure in poorly ventilated areas or during alcohol sponge bathing. **Isopropanol is approximately twice as potent as ethanol in causing CNS depression, and its duration of action is two**

TABLE 185-3 Clinical Institute Withdrawal Assessment for Alcohol–Revised Scale*

Nausea and Vomiting Ask "Do you feel sick to your stomach? Have you vomited?" *Observation:* 0 no nausea and no vomiting 1 mild nausea with no vomiting 2 3 4 intermittent nausea with dry heaves 5 6 7 constant nausea, frequent dry heaves and vomiting	**Tactile Disturbances** Ask "Do you have any itching, pins and needles sensations, any burning, or any numbness, or do you feel bugs crawling on or under your skin?" *Observation:* 0 none 1 very mild itching, pins and needles, burning or numbness 2 mild itching, pins and needles, burning or numbness 3 moderate itching, pins and needles, burning or numbness 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
Tremor Arms extended and fingers spread apart. *Observation:* 0 no tremor 1 not visible, but can be felt fingertip to fingertip 2 3 4 moderate, with patient's arms extended 5 6 7 severe, even with arms not extended	**Auditory Disturbances** Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" *Observation:* 0 not present 1 very mild harshness or ability to frighten 2 mild harshness or ability to frighten 3 moderate harshness or ability to frighten 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
Paroxysmal Sweats *Observation:* 0 no sweat visible 1 barely perceptible sweating, palms moist 2 3 4 beads of sweat obvious on forehead 5 6 7 drenching sweats	**Visual Disturbances** Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" *Observation:* 0 not present 1 very mild sensitivity 2 mild sensitivity 3 moderate sensitivity 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations
Anxiety Ask "Do you feel nervous?" *Observation:* 0 no anxiety, at ease 1 mild anxious 2 3 4 moderately anxious, or guarded, so anxiety is inferred 5 6 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions	**Headache, Fullness in Head** Ask "Does your head feel different? Does it feel like there is a band around your head?" *Observation:* 0 not present 1 very mild 2 mild 3 moderate 4 moderately severe 5 severe 6 very severe 7 extremely severe
Agitation *Observation:* 0 normal activity 1 somewhat more than normal activity 2 3 4 moderately fidgety and restless 5 6 7 paces back and forth during most of the interview, or constantly thrashes about	**Orientation and Clouding of Sensorium** Ask "What day is this? Where are you? Who am I?" *Observation:* 0 oriented and can do serial additions 1 cannot do serial additions or is uncertain about date 2 disoriented for date by no more than 2 calendar days 3 disoriented for date by more than 2 calendar days 4 disoriented for place or person

*Total score ranges from 0 to 67. A score <8 represents mild withdrawal, no medication necessary; a score of 9 to 15 indicates moderate withdrawal, dose medication every 2 h; and a score >15 indicates severe withdrawal, dose medication every hour.

to four times that of ethanol. As a result, it is often used as a substitute intoxicant by alcoholics as well as in suicide attempts.

PATHOPHYSIOLOGY

Isopropanol is rapidly absorbed from the GI tract. Its peak blood levels occur 30 to 120 minutes after ingestion, and its volume of distribution is similar to that of ethanol. The major pathway for the metabolism of isopropanol is in the liver by alcohol dehydrogenase (50% to 80%), with the remainder excreted unchanged in the urine. Isopropanol is metabolized to a ketone, not an acid (**Figure 185-4**).

Ketosis and an osmolar gap without acidosis are the hallmarks of isopropanol toxicity.[43,44] The principal metabolite, acetone, does not cause eye, kidney, cardiac, or metabolic toxicity, although high levels of acetone may contribute to CNS depression. Acetone is excreted primarily by the kidneys, with some excretion through the lungs. It takes about 30 to 60 minutes after isopropanol ingestion for acetone to appear in the serum and about 3 hours for it to be detectable in the urine.[46]

Isopropanol metabolism most closely follows concentration-dependent (first-order) kinetics. The elimination half-life of isopropanol in the absence of ethanol is 6 to 7 hours, whereas the elimination half-life of acetone is 17 to 27 hours.[47] The long half-life of acetone may contribute to the prolonged mental status depression often associated with isopropanol poisoning. The toxic dose of 70% isopropanol is approximately 1 mL/kg, although as little as 0.5 mL/kg may cause symptoms. The minimum lethal dose for an adult has been reported as approximately 2 to 4 mL/kg, but survival has been reported following ingestions of up to 1 L. **Children are especially susceptible to toxic effects and may develop symptoms after as little as three swallows of 70% isopropanol.**[48]

CLINICAL FEATURES

The primary clinical toxicities of isopropanol are CNS depression caused by both the parent compound and acetone, and gastric irritation from isopropanol itself.[43,44] Onset of symptoms occurs within 30 to 60 minutes after ingestion, with peak effects in a few hours and duration of symptoms for many hours longer, possibly due to the contribution of acetone. As with the metabolism of any alcohol by alcohol dehydrogenase, the increased NADH/NAD^+ ratio may produce hypoglycemia.

Gastric irritation appears early and is a striking feature of isopropanol ingestions. GI symptoms range from nausea, vomiting, abdominal pain, and acute pancreatitis to hemorrhagic gastritis and upper GI bleeding. Severe poisoning is marked by early onset of coma, respiratory depression, and hypotension; rhabdomyolysis and renal failure have also been reported.

Massive ingestion may cause hypotension secondary to peripheral vasodilation. In infants and small children, if isopropanol is used to clean the skin, chemical burns can result and systemic symptoms can occur from dermal absorption.

DIAGNOSIS

Obtain point-of-care glucose testing and other testing as directed by the history and physical examination. Assess for upper and lower GI bleeding. Suspect isopropanol poisoning if the fruity odor of acetone or the smell of rubbing alcohol is present on the breath. Other signs are elevated osmolar gap, ketonuria, and ketonemia without acidosis. An increased anion gap or metabolic acidosis is not due to isopropanol intoxication, so if either is present, investigate for another cause. A spurious increase in serum creatinine level as a result of acetone's interference with the colorimetric creatinine assay is sometimes seen.[49]

Serum isopropanol and acetone levels may be assessed, although isopropanol levels may not be readily available from hospital laboratories. Isopropanol levels of 50 milligrams/dL (8 mmol/L) are often associated with intoxication in individuals who are not habituated to ethanol, but alcoholic patients may be considerably more resistant to the CNS effects of isopropanol.

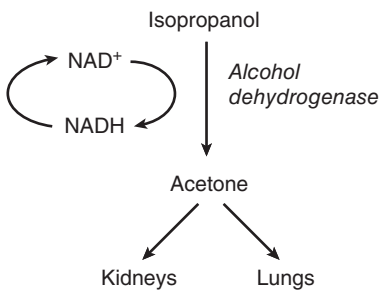

FIGURE 185-4. Metabolism of isopropanol. NAD^+ = oxidized form of nicotinamide adenine dinucleotide; NADH = reduced form of nicotinamide adenine dinucleotide.

TREATMENT

Treatment is supportive. Do not administer activated charcoal or perform gastric lavage unless indicated by recent co-ingestion of an additional toxic substance. **Do not administer fomepizole or ethanol**, because the metabolite (acetone) is no more toxic than isopropanol itself, and preventing isopropanol metabolism may prolong CNS toxicity.

Monitor for respiratory depression, and intubate and ventilate as needed. Hypotension usually responds to IV fluids. Obtain blood for type and cross-match if needed to treat GI bleeding. Hemodialysis eliminates both isopropanol and acetone. Consider hemodialysis if hypotension is refractory to conventional therapy or when the isopropanol level is >400 milligrams/dL (>66 mmol/L).[43,44]

DISPOSITION AND FOLLOW-UP

Patients with lethargy or prolonged CNS depression should be admitted to the hospital. Those who remain asymptomatic for 4 to 6 hours after ingestion may be discharged with referral for substance abuse counseling or mental health evaluation as indicated.

METHANOL AND ETHYLENE GLYCOL

INTRODUCTION

Methanol and **ethylene glycol** are similar in that the parent compounds possess minor toxicity (both causing inebriation and some direct gastric irritation), but the major toxicity occurs when the liver metabolizes these compounds to substances that cause metabolic acidosis and end-organ damage (**Table 185-4**).[44,50-52] Treatment is primarily directed toward halting the formation of these toxic metabolites.

Methanol, the simplest alcohol (CH_3OH, molecular weight 32.05), is a colorless, volatile liquid with a distinctive "alcohol" odor. Methanol is used in the synthesis of other chemicals and may be found in automotive windshield cleaning solution, solid fuel for stoves and chafing dishes, model airplane fuel, carburetor cleaner, gas line antifreeze, photocopying fluid, and solvents.

Most cases of methanol poisoning occur by ingestion, and most contemporary exposures in the United States occur from unintentional ingestion of windshield washer fluid and other automotive cleaning products.[53] Worldwide, there are outbreaks of poisoning from contaminated alcoholic beverages.[54,55] Persons who wish to consume ethanol but have no access to it for financial or other reasons may consume methanol as an alternative, either intentionally or unintentionally (due to improper or confusing labeling containing the word *alcohol*). Methanol may be systemically absorbed after inhalation or dermal exposure, but this rarely causes significant clinical toxicity. **Hence, extensive evaluation or observation is not required after minor skin or inhalational exposures.**

Ethylene glycol [$CH_2CH_2(OH)_2$, molecular weight 62.07] is a colorless, odorless, sweet-tasting liquid. Ethylene glycol has many contemporary uses as a glycerin substitute, preservative, component of hydraulic brake fluid, foam stabilizer, component for chemical synthesis, and most commonly an automotive coolant (antifreeze).

Virtually all ethylene glycol toxicity results from ingestion, because the chemical has a low vapor pressure and does not penetrate skin well.[56] Its sweet taste renders ethylene glycol an attractive ingestant for children

TABLE 185-4 Features of Methanol and Ethylene Glycol Toxicity and Treatment

	Methanol	Ethylene Glycol
Sources	Windshield cleaners, gas line antifreeze, solvents, solid fuel for stoves, adulterated alcoholic beverages, moonshine	Glycerin substitute, hydraulic fluid, antifreeze, adulterated alcoholic beverages, adulterated toothpaste (diethylene glycol)
Absorption	30–60 min	1–4 h
Metabolism (untreated)	Decreases 8.5 milligrams/dL per hour (2.7 mmol/L per hour)	Elimination half-life ≈ 3–8 h
Minimum lethal dose without treatment	1 gram/kg or about 100 mL in an adult	1.1–1.7 grams/kg or about 100 mL in an adult
Metabolism	Methanol → formaldehyde → formic acid	Ethylene glycol → glycoaldehyde → glycolic acid → glyoxylic acid → oxalic acid
Toxic effects	Formic acid blocks oxidative phosphorylation; metabolic acidosis from formic and lactic acids	Metabolic acidosis and tissue toxicity from glycolic acid and calcium oxalate crystals
Clinical features	Inebriation from parent compound, then 12–14 h later: metabolic acidosis; blurred or snow field vision; nausea, vomiting, abdominal pain	Inebriation from parent compound, then 4–12 h later: CNS effects, hypocalcemia, metabolic acidosis; 12–24 h: multisystem organ failure; 24–72 h: renal failure
Diagnosis	Methanol level >20 milligrams/dL (>6 mmol/L) Early: unexplained osmolal gap >10 mOsm/kg H_2O Later: elevated anion gap metabolic acidosis	Ethylene glycol level >20 milligrams/dL (>3.2 mmol/L) Early: unexplained osmolal gap >10 mOsm/kg H_2O Later: elevated anion gap metabolic acidosis and calcium oxalate crystals in urine
Treatment	Fomepizole 15 milligrams/kg IV over 30 min and then 10 milligrams/kg IV over 30 min every 12 h *or* Ethanol 10 mL/kg of 10% IV ethanol at 100 milligrams/kg per hour to keep ethanol level 100–150 milligrams/dL (22–33 mmol/L)	Fomepizole 15 milligrams/kg IV over 30 min and then 10 milligrams/kg IV over 30 min every 12 h *or* Ethanol 10 mL/kg of 10% IV ethanol at 100 milligrams/kg per hour to keep ethanol level 100–150 milligrams/dL (22–33 mmol/L)
	Folinic or folic acid 1 milligram/kg IV every 4–6 h (up to 50 milligrams per dose), continue until toxicity resolved	Pyridoxine 50–100 milligrams IV every 6 h for 24–48 h Thiamine 100 milligrams IV every 6 h for 24–48 h Magnesium sulfate 2 grams IV (once)
	IV sodium bicarbonate to maintain serum pH >7.30	IV sodium bicarbonate to maintain serum pH >7.20
	See text for indications for hemodialysis	See text for indications for hemodialysis

and pets. Other common exposure scenarios include ingestion as an ethanol substitute when ethanol is unavailable and intentional suicidal ingestions.[53]

PATHOPHYSIOLOGY

METHANOL

Methanol is rapidly absorbed and metabolized in the liver by alcohol dehydrogenase to formaldehyde, and then by aldehyde dehydrogenase to formic acid (**Figure 185-5**). First-order kinetics is present at very low methanol concentrations, with an elimination half-life of 1.8 to 3.0 hours.[57] At higher methanol concentrations, metabolism switches to zero-order kinetics, and blood methanol level decreases at a fixed rate, roughly 8.5 milligrams/dL per hour (2.7 mmol/L per hour).[58]

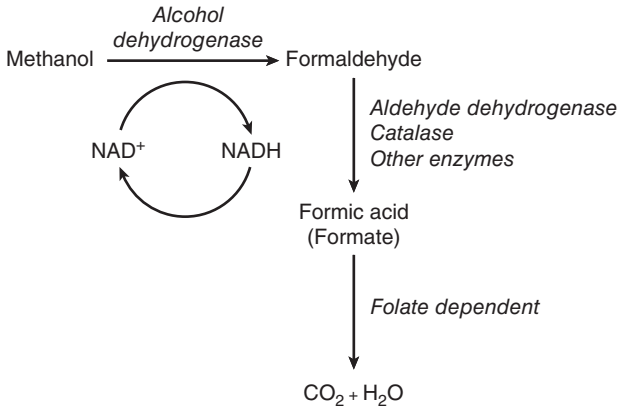

FIGURE 185-5. Metabolism of methanol. NAD^+ = oxidized form of nicotinamide adenine dinucleotide; NADH = reduced form of nicotinamide adenine dinucleotide.

Formic acid is the metabolite responsible for the toxicity and metabolic acidosis that occur with methanol poisoning. Acidosis correlates well with formic acid levels both in its magnitude and in the timing of its development. Formic acid's main mechanism of toxicity is its binding to cytochrome oxidase and blockade of oxidative phosphorylation. This leads to anaerobic metabolism and development of lactic acidosis. In addition, metabolism of methanol increases the NADH/NAD^+ ratio, which favors the conversion of pyruvate to lactate and thereby worsens lactic acidosis. Early in the course of methanol poisoning, more of the acidosis is due to formic acid itself, whereas later on, as cellular aerobic respiration is blocked and more lactate builds up, the contribution of lactate becomes more significant.[59]

Formic acid's inhibition of cytochrome oxidase increases with decreasing pH, so acidemia worsens the blockade of aerobic metabolism. Falling pH also favors the undissociated form of formic acid (as opposed to formate ion), which moves more readily across tissue barriers. Therefore, at lower pH, more formic acid can enter the brain and ocular tissues, worsening CNS depression as well as causing retinal and optic nerve injury. Lower pH may also prolong formic acid elimination by increasing tubular reabsorption.[60]

ETHYLENE GLYCOL

Like methanol, ethylene glycol itself has minor toxicity (it is a stronger inebriant than both methanol and ethanol and causes gastric irritation), but it is the hepatic oxidation of ethylene glycol that creates the toxic metabolites responsible for metabolic acidosis and end-organ damage. The liver metabolizes about 80% of an ingested dose, whereas the other 20% is excreted unchanged in the urine. When metabolism is unblocked, ethylene glycol has first-order metabolic kinetics with an elimination half-life of roughly 3 to 8 hours.

Like the other alcohols, ethylene glycol is metabolized sequentially by alcohol dehydrogenase to glycoaldehyde, followed by metabolism with aldehyde dehydrogenase to glycolic acid (**Figure 185-6**). The subsequent

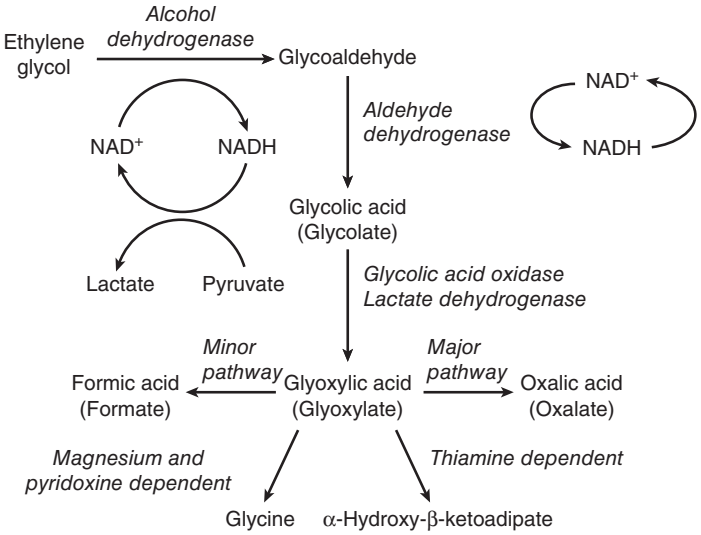

FIGURE 185-6. Metabolism of ethylene glycol. NAD^+ = oxidized form of nicotinamide adenine dinucleotide; NADH = reduced form of nicotinamide adenine dinucleotide.

conversion of glycolic acid to glyoxylic acid is the rate-limiting step for the elimination of ethylene glycol. Glycolic acid is the toxic metabolite, and its buildup is responsible for most of the metabolic acidosis. Once glycolic acid is converted to glyoxylic acid, it can be metabolized by one of several pathways. The major pathway is the conversion of glyoxylic acid to oxalic acid. Oxalic acid can complex with calcium, which leads to hypocalcemia and precipitation of calcium oxalate crystals in tissues and urine.[61] **End-organ damage from ethylene glycol poisoning is thought to be due to direct cytotoxicity of glycolic acid (although the exact mechanism of this is unclear) and tissue damage from precipitation of calcium oxalate crystals.**[61,62]

CLINICAL FEATURES

METHANOL

Methanol poisoning is characterized by CNS depression, metabolic acidosis, and visual changes.[44,52] However, multiple other organ systems are also affected. Coma, seizure, and severe metabolic acidosis on presentation predict a poor outcome in methanol poisoning.[63,64] Severity of poisoning correlates more with the level of acidosis than with the methanol level.

Clinical signs and symptoms may be significantly delayed after exposure, often by 12 to 24 hours, because metabolism to formic acid is required for tissue damage. Because ethanol competes for alcohol dehydrogenase, formation of the toxic metabolites from methanol will be delayed if ethanol has also been ingested.

Methanol is only a mild inebriant, and patients with tolerance to ethanol also demonstrate tolerance to methanol's intoxicating effects. Neurologic symptoms seen with methanol toxicity include headache, vertigo, dizziness, and seizures. Retinal and optic nerve tissue seems to be especially sensitive to the toxic effects of formic acid. **Ocular toxicity may present as photophobia or blurred or "snow field" vision**, with clinical findings including papilledema, nystagmus (rare), and nonreactive mydriasis once permanent damage has occurred.[65]

Head CT may demonstrate bilateral putamen necrosis, subcortical white matter damage, intracranial hemorrhage, and other patterns of brain injury from methanol poisoning.[66-68] Obtain a noncontrast head CT before administering anticoagulants. **Delayed parkinsonism and polyneuropathies can occur.**[69]

Cardiovascular toxicity includes tachycardia and hypotension, which may progress to shock. Initially, patients often demonstrate tachypnea and shortness of breath while attempting to compensate for the metabolic acidosis, but over time, this may progress to respiratory failure.

Methanol is irritating to the GI tract and may cause abdominal pain, anorexia, nausea, vomiting, pancreatitis, or gastritis. Transaminitis is usually mild and transient.[59] Rhabdomyolysis, renal failure, coma, and shock can occur in severe cases.

ETHYLENE GLYCOL

Ethylene glycol poisoning is characterized by CNS depression, metabolic acidosis, and renal failure.[44,52] However, multiple other organ systems may be affected. Clinical poisoning has historically been divided into three stages, although timing may vary and stages may overlap.

The first or "neurologic" stage typically begins 30 minutes to 12 hours after ingestion due to the intoxicating effects of the ethylene glycol parent compound and may range from mild depression to seizure and coma. Patients with tolerance to the depressant effects of ethanol may also exhibit relative tolerance to the inebriating effects of ethylene glycol. Patients are often described as appearing intoxicated (with ataxia, confusion, and slurred speech) but without an ethanol odor on the breath. Ethylene glycol is directly irritating to the GI tract, so abdominal pain, nausea, and vomiting may be present.

The generation of toxic metabolites generally takes 4 to 12 hours, or more if ethanol was co-ingested. CNS tissue effects of glycolic acid and calcium oxalate crystals include cerebral edema, basal ganglia hemorrhagic infarction, and meningoencephalitis.[70] Hypocalcemia, which occurs when calcium combines with oxalate, may contribute to seizures. Metabolic acidosis appears as toxic metabolites are generated.

The second or "cardiopulmonary" stage begins 12 to 24 hours after ingestion and is characterized by tachycardia and possibly hypertension. Tachypnea compensates for metabolic acidosis. Glycolate and oxalate crystal deposition in tissues leads to multiorgan system failure, including heart failure, acute lung injury, and myositis. Hypocalcemia, if present during any stage, may cause prolongation of the QT interval, myocardial depression, and dysrhythmias. Most deaths occur during this stage.

The third or "renal" stage is often delayed 24 to 72 hours after ingestion and is characterized by renal failure due to calcium oxalate crystal deposition in the proximal tubules, the most common major complication of serious ethylene glycol poisoning. Short-term hemodialysis is often required, and it may take weeks to months for the kidneys to recover. Delayed neuropathies may occur 5 to 20 days after ethylene glycol poisoning.[69,71,72]

DIAGNOSIS OF METHANOL OR ETHYLENE GLYCOL POISONING

Laboratory tests for a patient with suspected methanol or ethylene glycol poisoning should include blood ethanol levels, arterial blood gas analysis, chemistry panel, calculation of anion and osmolar gaps, serum osmolarity, and creatine kinase level. Serum ketone, β-hydroxybutyrate (if available), and lactate levels are helpful if a metabolic acidosis or an osmolar gap is present. Falsely elevated lactate results have been seen with some point-of-care analyzers in patients with severe ethylene glycol poisoning.[73] Check point-of-care glucose level. Measure serum acetaminophen and salicylate levels in patients with an intentional overdose. **Consider methanol or ethylene glycol poisoning in a patient with an unexplained acidosis** (see Chapter 15, "Acid-Base Disorders").

Acidosis will not be present immediately after exposure. The parent compounds must be converted to toxic metabolites before the acidosis develops; this may be delayed by hours to over a day, especially if ethanol is co-ingested.

METHANOL AND ETHYLENE GLYCOL LEVELS

The best laboratory test for diagnosing methanol or ethylene glycol poisoning is measurement of the specific serum level of the alcohol.[51]

Asymptomatic individuals following methanol ingestion usually have levels of <20 milligrams/dL (<6 mmol/L), and CNS symptoms may appear as levels rise above that. Ocular problems are associated with methanol levels of >50 milligrams/dL (>16 mmol/L), and the risk of fatality rises with levels >150 to 200 milligrams/dL (>47 to 62 mmol/L). However, toxicity associated with a given level depends greatly on how long after ingestion the level was measured. A level of 50 milligrams/dL (16 mmol/L) obtained 3 hours after ingestion implies a much smaller

TABLE 185-5 Substances That Contribute to the Osmolar Gap

Substance	Molecular Weight	mOsm/kg H_2O With a Serum Concentration of 100 milligrams/dL	Conversion Factor
Ethanol	46	22	4.6
Isopropanol	60	17	6.0
Methanol	32	31	3.2
Ethylene glycol	62	16	6.2

Notes: Calculated serum osmolarity = 2 × sodium + (BUN/2.8) + (glucose/18) + (ethanol/4.6) + (isopropanol/6.0) + (methanol/3.2) + (ethylene glycol/6.2)

Osmolar gap = measured serum osmolarity – calculated serum osmolarity

ingestion and less toxicity than if the same value was obtained 12 hours after ingestion.[74]

Asymptomatic individuals following ethylene glycol ingestion usually have peak levels <20 milligrams/dL (<3.2 mmol/L). As with methanol, toxicity associated with a given level depends greatly on how long after ingestion the level was measured. More useful are factors indicating metabolic dysfunction such as acidosis.

OSMOLAR GAP

In many hospital and clinical laboratories, methanol and ethylene glycol levels are not available in a timely manner to assist with initial medical decision making. In such circumstances, the **osmolar gap** may be used as a surrogate marker for toxic alcohol levels (**Table 185-5**).[75] This calculation determines the difference between the measured serum osmoles and the calculated osmoles. Methanol and ethylene glycol, but not their metabolites, are osmotically active and will contribute to the measured serum osmolarity.

For accurate calculation of the osmolar gap, obtain simultaneous blood samples for a basic serum chemistry panel (including BUN, glucose, and sodium levels), measurement of ethanol level, and measurement of serum osmolarity. **Using a previously obtained specimen to measure serum osmolarity ("add-on" tests) is not acceptable, because any toxic alcohols present may have volatilized since the sample was obtained.** In addition, the freezing point depression method must be used to measure serum osmolarity, rather than the vapor pressure method, which can miss volatile substances such as toxic alcohols. There is considerable variation in baseline osmolar gap in healthy subjects depending on the formula used for calculation,[76] so the reference range may differ among clinical laboratories. In general, an osmolar gap of more than 10 to 15 mOsm/kg H_2O raises concern and >50 mOsm/kg H_2O is highly suggestive of either methanol or ethylene glycol poisoning and is associated with increased mortality.[77]

The osmolar gap is highest when the parent toxic alcohol level is at its peak (roughly 30 to 60 minutes after ingestion), before significant metabolism has occurred (**Figure 185-7**). As the time since ingestion increases and the parent compound is metabolized, the osmolar gap will decrease. Hence, later-presenting patients may not have significant osmolar gaps. As metabolism occurs, acid metabolites build up and an anion gap metabolic acidosis develops as the osmolar gap narrows. There may be a time period in the middle range when the patient has both an osmolar gap and an anion gap.[78]

Although the osmolar gap may be helpful in conjunction with the rest of the clinical picture, it has many shortcomings and cannot be relied on to definitively diagnose or exclude a toxic alcohol poisoning.[75,79,80] Other conditions such as ketoacidosis, shock, and sepsis may cause an elevated osmolar gap.[81] Also, forgetting to account for ethanol is a common error when calculating the osmolar gap.

As noted, the range of normal variation in osmolar gap is wide and dependent on the formula used for calculation, so a toxic concentration of methanol or ethylene glycol may be present with an osmolar gap in the normal range.[79-81] For example, 1 milligram/dL (0.3 mmol/L) of methanol will raise serum osmolarity by 0.34 mOsm/kg H_2O.[81] Therefore, a methanol concentration of 50 milligrams/dL (15 mmol/L)—generally accepted to be toxic—will raise serum osmolarity 17 mOsm/kg H_2O. If a given patient's baseline was low to begin with, this methanol concentration would not create an abnormal osmolar gap.

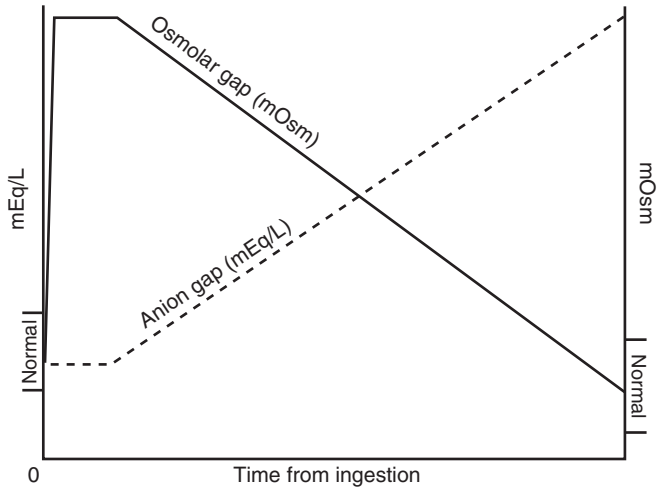

FIGURE 185-7. Relative changes in anion and osmolar gaps over time from ingestion of a toxic alcohol.

ANION GAP

The positively charged cations in the serum are electrically balanced by the negatively charged anions. In the clinical laboratory, not all cations and anions are routinely measured, and the level of measured cations is usually greater than that of measured anions; the difference is termed **unmeasured anions**. The predominant serum cation measured is sodium, which is almost completely balanced by the measured charged chloride and bicarbonate anions; the difference is termed the **anion gap**, consisting mostly of serum proteins, phosphate, sulfate, organic acids, and conjugate bases of ketoacids (see Chapter 15, "Acid-Base Disorders").

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

The normal anion gap varies according to the methodology used, and the physician should use the values established by the clinical laboratory. **In most clinical settings, an anion gap >15 mEq/L should be considered abnormal.** As noted, it takes time for the acidotic metabolites to become present, as much as 12 to 16 hours following methanol ingestion, so a normal anion gap does not exclude the diagnosis.

URINARY FLUORESCENCE

Urinary fluorescence under an ultraviolet or Wood's lamp has been anecdotally taught to be a helpful sign of ethylene glycol poisoning because most antifreeze products contain sodium fluorescein as an additive to aid in the detection of radiator leaks. Not all ethylene glycol products contain fluorescein; the fluorescence may be short-lived (lasting about 4 hours after ingestion); and the ability of the physician to detect fluorescence is affected by many technical factors.[82] Thus, the absence of urinary fluorescence cannot exclude an ethylene glycol ingestion. In addition, false-positive results occur, because many types of glass or plastic containers fluoresce on their own, and numerous foods, medications, toxins, and endogenous substances may cause urinary fluorescence.[83,84]

CALCIUM OXALATE CRYSTALS FOR ETHYLENE GLYCOL

Approximately half of patients poisoned with ethylene glycol demonstrate either monohydrate or dihydrate calcium oxalate crystals on urinalysis.[85] These are often misread as hippurate crystals. If present, they start to appear 4 to 6 hours after ingestion and may persist for days, especially in patients with renal failure. The monohydrate form is more common, and the dihydrate form is more specific for ethylene glycol poisoning.

TREATMENT

The basic principles of treatment for both methanol and ethylene glycol poisoning are performing initial resuscitation, providing cardiopulmonary support, correcting acidosis, preventing formation of toxic metabolites, and enhancing the clearance of the parent compound and toxic metabolites.[52] Because toxic alcohols are absorbed so rapidly, gastric decontamination is unlikely to be of benefit, and there is no evidence to support its routine use.[59,86,87] Activated charcoal may be used if there is a recent co-ingestant known to adsorb to charcoal.

CORRECT ACIDOSIS

Correcting acidosis may improve the outcome in patients poisoned with methanol because acidosis worsens the toxicity of formate; rapid improvement in visual and other systemic symptoms has been reported with correction of acidosis. In addition, alkalinization may help increase formic acid clearance by decreasing reabsorption in the proximal renal tubules.[60] However, the benefits of alkalinization may be equivocal if the patient is treated with metabolic blockade and hemodialysis. When used in methanol poisoning, give IV sodium bicarbonate infusions to maintain a serum pH of >7.30.[59] There is no evidence that alkalinization is specifically beneficial in ethylene glycol poisoning, but it seems reasonable to use sodium bicarbonate IV if there is a severe metabolic acidosis with pH <7.20.

METABOLIC BLOCKADE

Because laboratory confirmation may take time and because prompt treatment is important to prevent the formation of toxic metabolites, the decision to block metabolism often must be made before the diagnosis is secure (**Table 185-6**).[88] Start treatment while sorting out the clinical picture to protect the patient from serious toxicity, such as blindness or renal failure. Treatment with either ethanol or fomepizole greatly slows the elimination of methanol and ethylene glycol. Because hepatic oxidation is inhibited, elimination is determined by first-order renal excretion, and the elimination half-life averages 52 hours (range, 22 to 87 hours) for methanol (compared to an elimination half-life without metabolic blockade of 1.8 to 3 hours) and 13 to 20 hours for ethylene glycol (compared to an elimination half-life without metabolic blockade of 3 to 8 hours).[60,87,89,90]

The initial step in the metabolism of methanol (Figure 185-5) or ethylene glycol (Figure 185-6) is performed by alcohol dehydrogenase. This enzyme is competitively inhibited by either ethanol or fomepizole (4-methyl-1H-pyrazole).[89] Both ethanol and fomepizole have a much higher affinity for alcohol dehydrogenase than does methanol or ethylene glycol. Although ethanol was traditionally administered for metabolic blockade in methanol and ethylene glycol poisonings, fomepizole has supplanted ethanol for this purpose in many institutions.

Metabolic Blockade With Fomepizole The primary advantage of fomepizole is the lack of side effects such as CNS depression, GI irritation, and hypoglycemia caused by ethanol therapy.[91-93] Fomepizole is less susceptible to dosing errors than ethanol.[94] The primary limiting factor to fomepizole use is the increased cost of the drug relative to ethanol, which may reduce availability in resource-poor locations.

Fomepizole is continued until the toxic alcohol level is <20 milligrams/dL (methanol <6 mmol/L or ethylene glycol <3 mmol/L) and the metabolic acidosis has resolved. Fomepizole is believed to induce its own metabolism, so it is recommended that the dose be increased to 15 milligrams/kg every 12 hours if treatment lasts >48 hours.[59,95] More frequent dosing (every 4 hours) is required during hemodialysis because fomepizole is removed during this procedure. Fomepizole does not require frequent monitoring of serum levels or dosage adjustments necessary with ethanol treatment.

Adverse effects from fomepizole are rare; mild and transient nausea, headache, dizziness, and injection site irritation are most commonly reported.[89] The safety of fomepizole in pregnancy is unknown, so the risks and benefits to fetus and mother of fomepizole therapy should be weighed against those of the alternative treatments. Reports show good efficacy of fomepizole therapy in children.[96]

Metabolic Blockade With Ethanol If fomepizole is not available or its use is contraindicated (e.g., the patient has a known allergy), ethanol may be used to inhibit toxic alcohol metabolism, administered PO or IV.[97] Although ethanol may prevent toxic alcohol metabolism at blood levels as low as 30 milligrams/dL (7 mmol/L), the general recommendation is to maintain a target ethanol level of 100 to 150 milligrams/dL (22 to 33 mmol/L).[59] Extremely elevated toxic alcohol levels may reduce the effectiveness of alcohol dehydrogenase inhibition by ethanol, and ethanol levels of >150 milligrams/dL (>33 mmol/L) may be required to effectively block production of the toxic metabolites. Achieving the desired ethanol level may be difficult because individual response to ethanol administration varies considerably depending on baseline ethanol consumption.

While the loading dose of ethanol produces reasonably predictable blood levels, maintenance dosing varies depending on the patient's baseline ethanol use. If IV ethanol is not available, an oral ethanol protocol can be used with a loading dose (PO or via nasogastric tube) using 80-proof liquor of 1.5 to 2 mL/kg followed by maintenance dosing of 0.2 to 0.5 mL/kg per hour. **Do not use oral ethanol preparations via the IV route.** For both the IV and PO routes, serum ethanol concentrations should be monitored every 1 to 2 hours. All maintenance doses need to be doubled for patients undergoing hemodialysis.

With severe adult poisoning and when fomepizole therapy may be delayed or transport time to the hospital may be long, administration of three or four 1-oz (30-mL) "shots" of 80-proof liquor should raise blood ethanol concentrations sufficiently to block toxic alcohol metabolism in a 70-kg adult.[96] Maintenance dosages are approximately one to two shots per hour.

Ethanol treatment is continued until the toxic alcohol level is <20 milligrams/dL (methanol <6 mmol/L or ethylene glycol <3 mmol/L) and the metabolic acidosis has resolved. The disadvantage of using ethanol is the induction of a state of inebriation, so patients require close monitoring for neurologic and respiratory depression. Individual metabolic variations make dosing complicated, and frequent serum level monitoring and dosage adjustments are required. Children and malnourished individuals are particularly at risk for the development of hypoglycemia, although with careful monitoring, this complication is rare.[92] Administration of the 10% ethanol solution IV requires central venous access because it is hyperosmolar and irritating to peripheral veins. Use of less concentrated solutions, such as 5% IV ethanol solutions, may require administration of large fluid volumes.

Hemodialysis Hemodialysis can rapidly clear the toxic alcohols and metabolites, as well as correct acid-base disorders, thereby shortening the duration of metabolic blockade treatment.[59,87,98-100] Conversely, with fomepizole, patients can receive prolonged treatment with few side effects and without the need for hemodialysis and attendant risks.[101]

Hemodialysis may be required emergently for patients with severe acidosis, visual changes, hemodynamic instability, or renal failure (**Table 185-7**).[59,87,102,103] A serum level of ≥50 milligrams/dL (methanol ≥15 mmol/L or ethylene glycol ≥7.5 mmol/L) is considered an indication for hemodialysis, but this criterion has been questioned because many patients with high methanol or ethylene glycol levels have been effectively treated without hemodialysis.[101,104-106] Consider the entire clinical picture, rather than making a decision based only on a serum

TABLE 185-6 Indications for Metabolic Blockade With Fomepizole or Ethanol

- Elevated plasma levels: methanol >20 milligrams/dL (>6 mmol/L) or ethylene glycol >20 milligrams/dL (>3 mmol/L)
- If methanol or ethylene glycol level not available:
  - Documented or suspected significant methanol or ethylene glycol ingestion with ethanol level lower than approximately 100 milligrams/dL (22 mmol/L)*
  - Coma or altered mental status in patient with unclear history and:
    - Unexplained serum osmolar gap of >10 mOsm/L

      or
    - Unexplained metabolic acidosis *and* ethanol level of <100 milligrams/dL (<22 mmol/L)*

*If serum ethanol level is >100 milligrams/dL (>22 mmol/L), the patient will be protected from the formation of toxic metabolites by co-ingestion of ethanol, and specific metabolic blockade treatment can be delayed until toxic alcohol level is available. If the ethanol level is likely to fall to <100 milligrams/dL before the toxic alcohol results are back, then initiate metabolic blockade.

TABLE 185-7 Indications for Hemodialysis After Methanol or Ethylene Glycol Ingestion

- Refractory metabolic acidosis: pH <7.25 with anion gap >30 mEq/L and/or base deficit <−15
- Visual abnormalities*
- Renal insufficiency
- Deteriorating vital signs despite aggressive supportive care
- Electrolyte abnormalities refractory to conventional therapy
- Serum methanol or ethylene glycol level of >50 milligrams/dL†

*Applies only to methanol; visual abnormalities may not resolve immediately, so their persistence in the absence of other indications once hemodialysis is started is *not* an indication for continued hemodialysis.

†Although previously considered an indication for hemodialysis, there are reports of patients with levels of ≥50 milligrams/dL (methanol ≥15 mmol/L or ethylene glycol ≥7.5 mmol/L) being successfully treated with fomepizole with or without bicarbonate and no hemodialysis.

level. Some rebound in toxic alcohol levels may occur after hemodialysis is stopped, so metabolic blockade therapy should be continued for several hours after cessation of dialysis, with blood level rechecked to ensure that the toxic alcohol level remains low.[59,87]

Vitamin Therapy Adjunctive treatment with B vitamins (including folate) is recommended to help clear the toxic metabolites of methanol and ethylene glycol more quickly, although no solid evidence exists to indicate that this treatment is necessary or even helpful.[107]

In methanol poisoning, high doses of folate or folinic acid may facilitate breakdown of formic acid into carbon dioxide and water (Figure 185-5). Experimental animals with very large folate stores do not develop acidosis and toxicity from methanol poisoning unless they are artificially depleted of folate. Theoretically, increasing folate stores should hasten the detoxification of formate and prevent it from accumulating and causing end-organ damage. Folinic acid, the activated form of folic acid, is preferred, but folic acid may be used if the former is not available. Recommended dosing is 1 milligram/kg (up to 50 milligrams) IV every 4 to 6 hours.[59]

In ethylene glycol poisoning, adjunctive therapy with pyridoxine, thiamine, and magnesium may be used to facilitate metabolism of glyoxylate to nontoxic glycine and α-hydroxy-β-ketoadipoic acid (Figure 185-6). Magnesium can be given as a one-time dose of magnesium sulfate 2 grams IV. The two B vitamins are given in large doses: thiamine 100 milligrams IV and pyridoxine 50 to 100 milligrams IV, both every 6 hours for 2 days.[108]

Visual impairment can be a permanent complication of methanol poisoning.[109,110] Although treatment with fomepizole or ethanol and bicarbonate can prevent ocular toxicity, there is no other proven therapy to restore established visual damage.[109]

DISPOSITION AND FOLLOW-UP

Because of the complex management decisions required with methanol or ethylene glycol poisoning, consultation with a medical toxicologist or a regional poison control center is strongly recommended. Symptoms of methanol or ethylene glycol intoxication may be delayed, particularly if ethanol has been co-ingested. A patient with suspected ethylene glycol ingestion should be observed and monitored for 6 hours. If no ethanol is present, the patient remains completely asymptomatic, there is no osmolar gap, and no metabolic acidosis develops, the patient can be discharged. Methanol toxicity may be delayed longer, so a patient with suspected methanol ingestion should be observed for 12 hours using the same criteria.

Patients with significant signs and symptoms should be admitted to an intensive care setting. Patients seen at facilities unable to provide hemodialysis or intensive care should be transferred as soon as possible, if in sufficiently stable condition, to institutions capable of providing such care. Suicidal patients should receive a psychiatric evaluation when their condition improves and prior to discharge.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 186

Opioids

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INTRODUCTION

Opioids refers broadly to all compounds related to opium that possess analgesic and sedative properties. **Opiate** describes the alkaloids codeine and morphine found naturally in the opium poppy plant, *Papaver somniferum*. **Narcotic** refers to a broader group of soporific drugs, a term predominantly used by law enforcement to refer to controlled substances with abuse or addictive potential; use of this term in medical practice is discouraged.

Opioid abuse is a significant public health issue in the United States with a dramatic increase in ED visits related to opioids in the past 20 years.[1,2] Opioids were responsible for 66% of drug overdose deaths in the United States during 2016.[3] The majority of prescription opioid overdose deaths were associated with diversion, doctor shopping, and nonmedical use.

PHARMACOLOGY

Opioids modulate nociception at the terminals of afferent nerves in the CNS, peripheral nervous system, and GI tract. Opioids are agonists at the three primary opioid receptors: μ (mu), κ (kappa), and δ (delta). Opioid receptors are similar to other G protein-coupled receptors; transmembrane proteins that undergo conformation change when activated by external molecules that then alters some aspect of intracellular function. Opioid receptors vary widely in morphology and distribution. In addition, the specificity and affinity of an opioid for a particular receptor are variable. For example, tramadol possesses 1/6000th the affinity of morphine at the μ-receptor site.

Stimulation of the μ-receptors results in analgesia, sedation, miosis, respiratory depression, cough suppression, euphoria, and decreased GI motility. Stimulation of κ-receptors results in weaker analgesia, sedation, miosis, decreased intestinal motility, dysphoria, and hallucinations. Stimulation of the δ-receptors results in some analgesia and antidepressant effect. **All currently available opioid agonists possess μ-receptor activity and result in some degree of respiratory depression.**

Opioids can be categorized as naturally occurring compounds (termed *opiates*), chemical modifications of natural compounds (semisynthetic), and the synthetic derivatives (**Table 186-1**). Some opioids are agonists at all opioid receptors (e.g., morphine and hydromorphone), whereas others are partial agonists–antagonists (e.g., pentazocine, butorphanol, nalbuphine, and buprenorphine) at the opioid receptors.

PHARMACOKINETICS

Opioids are readily absorbed, achieving peak blood levels 30 to 60 minutes after ingestion of standard oral formulations. But other pharmacokinetic elements can vary depending on whether the opioid is a short-acting, long-acting, or sustained-release formulation. Long-acting opioids, such as methadone, reach peak blood levels in 30 to 60 minutes, but have a long duration of effect and half-life. Sustained-release forms take longer to achieve peak blood levels; for example, morphine sulfate controlled-release tablets reach peak blood levels at 90 minutes compared with 30 minutes for standard morphine tablets. As the name implies, sustained-release forms also have a long duration of effect compared to the immediate-release formulations.

After GI absorption, most opioids undergo first-pass hepatic metabolism, so bioavailability can vary from as low as 10% to as high as 80% after PO administration. Thus, at equal doses, most opioids are more potent given parenterally than PO. The opioids with good oral bioavailability are codeine, oxycodone, methadone, hydromorphone, and tapentadol.

TABLE 186-1 Classification and Characteristics of Major Pharmaceutical Opioids

	Oral Dose Equianalgesic to Morphine 10 milligrams SC (milligrams)	Parenteral Dose Equianalgesic to Morphine 10 milligrams SC (milligrams)	Duration of Analgesic Action* (h)	Elimination Half-Life* (h)
Opiate				
Codeine	200	120	4–6	2.5–4
Morphine	30	10	3–4	2–4
Semisynthetic				
Buprenorphine	4 SL	0.3	6–24	20–44
Hydrocodone	30	Not available	4–6	8
Hydromorphone	7.5	1.5	2–4	2–3
Oxycodone	20	Not available	3–6	3–4
Oxymorphone	6	1.5	4–6	7–11
Synthetic				
Diphenoxylate	2.5	Not available	Not applicable	2 h for diphenoxylate and 12–14 h for difenoxin†
Fentanyl	0.125	0.100	1	3–4
Meperidine	300	100	1–3	3–4 h for meperidine and 15–30 h for normeperidine†
Methadone	20	10	8–12	12–18
Tapentadol	75	Not available	4–6	4–5
Tramadol	100	100	4–6	5–7

Abbreviation: SL = sublingual.

*Initial doses in therapeutic amounts.

†Active metabolite.

The metabolism of codeine, meperidine, methadone, morphine, and oxycodone is primarily hepatic and subject to drug interactions and genetic variations. For example, antiretroviral medications can enhance the metabolism of methadone, which results in lower plasma methadone concentrations. As another example, codeine is metabolized to morphine via cytochrome P450 isoenzyme 2D6, an enzyme with genotypic and phenotypic variability. Patients with rapid cytochrome P450 enzyme 2D6 metabolism produce more morphine after a fixed dose of codeine. These interactions and genetic variations may influence the therapeutic effect of opioids (see Chapter 35, "Acute Pain Management").

In drug misuse, unconventional routes of administration (insufflating or injecting ground opioid tablets, heating fentanyl patches or applying multiple patches to the skin) may alter the drug's pharmacokinetics and often increase the rate of opioid absorption. Similarly, in opioid overdoses resulting in high plasma levels, the pharmacokinetics are altered due to enzymatic saturation. This may increase the severity of poisoning, delay the onset, and prolong the duration of action, as compared with the expected therapeutic actions.

OPIOID INTOXICATION

CLINICAL FEATURES

The brief descriptor of the widely recognized opioid toxidrome would include the triad of miosis, lethargy, and respiratory depression. The full effects associated with opioid intoxication also can include orthostatic hypotension, nausea and vomiting (especially in opioid-naive patients), histamine release resulting in localized urticaria (Figure 186-1) bronchospasm, ileus secondary to decreased GI motility, and urinary retention secondary to increased vesical sphincter tone.[4,5] The depression in mental status can be profound. The respiratory depression is characterized by slow and shallow respirations that can produce hypercarbia, hypoxia, and cyanosis. Miosis is not universally present from intoxication with every opioid; normal or even enlarged pupils have been documented secondary to pentazocine and meperidine toxicity. Mydriasis may also signal severe cerebral hypoxia or result from co-ingestants (diphenoxylate, heroin, scopolamine).



FIGURE 186-1. Urticaria on a forearm from local histamine release due to IV morphine. [Photo used with permission of J. S. Stapczynski, MD.]

Other possible findings in opioid toxicity include hypothermia, rhabdomyolysis, compartment syndrome, myoglobinuric renal failure, and seizures associated with overdoses of tramadol and meperidine.

Opioid-induced acute lung injury, previously known as *noncardiogenic pulmonary edema*, is an uncommon complication associated with opioid overdose.[5,6] Acute lung injury can occur immediately or be delayed up to 24 hours after overdose and presents with tachypnea, rales, decreased oxygen saturation, and bilateral pulmonary infiltrates with a normal cardiac silhouette on chest radiograph.[7] The incidence of acute lung injury is 10% in patients with severe overdose requiring naloxone.[8] The pathophysiology of opioid-induced acute lung injury is poorly understood and may be multifactorial. Pulmonary edema may result from direct alveolar injury from hypoxia, opioid-induced histamine release, capillary leak due to negative inspiratory pressure, or neurogenic injury.[4,9] Treatment includes oxygen supplementation and ventilatory support, with either noninvasive or invasive modalities. Additional naloxone, diuretics, and digoxin are not indicated.

The combination of meperidine, tramadol, or dextromethorphan with monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, or linezolid can result in **serotonin syndrome** (see Chapter 178, "Atypical and Serotonergic Antidepressants").[10] Serotonin syndrome is characterized by a spectrum of altered mentation from anxiety to delirium, hyperthermia, autonomic instability, hyperreflexia, and muscle rigidity, especially in the lower extremities. Although uncommon, deaths have been reported. Naloxone is not effective in treating opioid-induced serotonin syndrome.[10,11]

DIAGNOSIS

The triad of lethargy, miosis, and respiratory depression strongly suggests opioid intoxication, and in many clinical scenarios, specific evidence of opioid use is present. The combination of a respiratory rate of <12 breaths/min, miosis, and circumstantial evidence of opioid use (drug paraphernalia, needle marks, presence of a tourniquet, bystander corroboration) was highly sensitive for opioid overdose in the prehospital setting.[12]

Physical examination should be thorough: patients should be undressed completely yet carefully because drug use paraphernalia including needles and syringes may be hidden within clothing. Look for evidence of injection drug use, concealed opioids, or fentanyl patches on all parts of the body, including mucous cavities. Listen for auscultatory findings suggestive of pulmonary edema; palpate muscle groups to detect signs of compartment syndrome.

The differential diagnosis of opioid intoxication includes toxicologic exposure to drugs and compounds that produce similar findings, such as clonidine, organophosphates and carbamates, phenothiazines and atypical antipsychotic medications, sedative-hypnotic medications, and carbon monoxide. Clonidine overdoses are characterized by coma, bradycardia, hypotension, miosis, and periods of apnea that respond to tactile or auditory stimulation. Organophosphate and carbamate overdoses cause the cholinergic toxidrome: miosis, muscle fasciculations, profuse vomiting and diarrhea, and sweating. Phenothiazines, olanzapine, and risperidone cause neurologic depression and miosis from decreased adrenergic tone.[13] Gamma-hydroxybutyrate intoxication is associated with profound CNS depression, bradypnea, and, occasionally, miosis. Sedative-hypnotic agents and carbon monoxide cause profound neurologic depression but are not usually associated with miosis. Hypoglycemia, hypoxia, CNS infections, postictal states, and pontine and intracranial hemorrhages should also be considered in the differential diagnosis.

OPIOID SCREENS

A qualitative urine opioid screen may aid in the diagnosis, but available tests have limitations. The assay in most commercially available urine opioid screens recognizes morphine.[14] Opioids that are metabolized to morphine, such as codeine and heroin, as well as hydromorphone are detected by this urine assay as opiates. Specific immunoassay screens are available for oxycodone, fentanyl, or methadone.[15,16] Confirmation of a positive immunoassay screen requires gas chromatography/mass spectroscopy testing. Some common medications will produce false-positive results on opioid drug screens (**Table 186-2**).

TABLE 186-2 Medications Causing False-Positive Results on Urine Opioid Screens[14]

False-Positive Urine Opioid Screen	False-Positive Urine Methadone Screen
Poppy seeds	Chlorpromazine
Rifampin, rifampicin	Clomipramine
Quinine	Diphenhydramine
Diphenhydramine	Doxylamine
Fluoroquinolones	Ibuprofen
Dextromethorphan	Quetiapine
	Thioridazine
	Verapamil

A urine opioid screen can be positive up to 2 to 4 days after a single use of codeine, morphine, or heroin. The oxycodone, fentanyl, and methadone-specific screens can be positive up to 3 days after ingestion. As with most urine drug screening in the ED, detection of a drug taken in the recent past may not correctly identify the toxicologic cause of the patient's current condition. Serum acetaminophen concentration should be obtained in all suicidal ingestions and all cases of combination opioid–acetaminophen ingestions.

TREATMENT

Airway protection and ventilatory assistance are the most important treatment steps for opioid intoxications, because respiratory depression is the major morbidity and the cause of mortality.[4,5] Use bag-valve mask ventilatory support as needed to initially maintain adequate oxygenation and ventilation. After adequate ventilation is ensured, administer naloxone (**Table 186-3**). Endotracheal intubation may be necessary in some cases of opioid or polysubstance overdose with respiratory depression unresponsive or poorly responsive to naloxone or in cases in which acute lung injury is suspected.[4,5] Intubation offers the advantages of airway protection, easy access for suctioning, and provision of an alternate route of administration for some medications.

Single-dose activated charcoal (1 gram/kg PO) may be indicated in some patient populations, such as pediatric oral ingestion, if the patient is fully awake, or after the airway is protected with an endotracheal tube. Under special circumstances, delayed and multiple doses of activated charcoal may be useful, as in diphenoxylate hydrochloride–atropine sulfate overdoses and in cases of large ingestions of sustained-release preparations.[17]

TABLE 186-3 Naloxone

Drug	Route	Initial Dose*	Onset of Action	Duration of Action†
Naloxone	IV	0.04 milligrams if breathing spontaneously and suspected of chronic opioid use 0.4 milligrams if breathing spontaneously and opioid naive 2 milligrams if apneic or cyanotic	1–2 min	20–90 min
	IM or SC	2 milligrams	5–6 min	
	Intranasal	2 milligrams (1 milligram in each nostril)	6–8 min	
	Nebulized	2 milligrams in 3 mL normal saline	5 min	

*See text regarding subsequent dosing.

†Duration dependent on amount of opioid agonist present.

OPIOID ANTAGONISTS

Naloxone, a derivative of oxymorphone, is a pure competitive antagonist at all opioid receptors, with particular affinity for μ-receptors. Therefore, naloxone fully reverses all the effects of opioids, including respiratory depression, sedation, miosis, and analgesia. The elimination half-life of naloxone is 60 to 90 minutes, but the duration of action is as short as 20 minutes if a large amount of opioid agonist is present.

Naloxone has poor oral bioavailability but is well absorbed when given by injection (IV, SC, or IM), inhaled, or deposited on mucosa (intratracheally or intranasally, but not sublingual). Inhaled naloxone by nebulization is reasonably effective in reversing depressed mental status and respirations in opioid toxicity, with about 10% requiring additional rescue parenteral naloxone.[18-20] Intranasally administered naloxone provides a pharmacokinetic profile similar to that of IM or SC naloxone and is used by EMS personnel and in bystander naloxone administration programs.[21-24]

Naloxone effectiveness is dependent on the dose administered and the amount of opioid that needs to be reversed, balanced against the risk of precipitating withdrawal. There is wide variation in recommended naloxone doses to treat opioid toxicity.[25] It is prudent to use a small starting dose of naloxone, 0.04 milligram IV, in opioid-dependent patients who present with mental status depression and modest respiratory depression, because larger doses can induce opioid withdrawal symptoms in these individuals.[26] An initial dose of naloxone, 0.4 milligram IV, is recommended in non–opioid-dependent patients who present with mental status depression and modest respiratory depression. Subsequent doses of naloxone of 0.04 milligram to 0.4 milligram IV are administered every 2 to 3 minutes until the desired effect is reached. Incremental dosing of naloxone mitigates the precipitation of acute opioid withdrawal.[27]

For patients presenting with apnea or near-apnea and cyanosis, a large starting dose of naloxone, 2 milligrams IV, should be administered regardless of drug use history. Repeated doses of 2 milligrams IV every 3 minutes are recommended until a maximum of 10 milligrams IV is reached or respiratory depression is reversed. Exposures to fentanyl, novel synthetic opioids, and sustained-release preparations may require these larger-than-ordinary doses. Toxicity from leaking opioid-containing packets in the intestinal tract (i.e., in "body packers") can be extremely severe, and such patients require large and sustained naloxone doses until the drug-containing packets are expelled or removed.

The duration of action of naloxone may be shorter than that of the offending opioid, so naloxone infusions are occasionally required to support respiration over several hours as the opioid is metabolized. This is especially true for certain long-acting opioids, such as buprenorphine and methadone; for exposures to sustained-release preparations; and for ingestions of transdermal fentanyl patches. A continuous infusion should be considered only if the patient responded to the initial naloxone bolus and subsequently required repeat administration. **To calculate the naloxone continuous infusion dose, determine the "wake-up dose" and administer two thirds of that dose per hour by IV infusion.** Adjustments may be required if the patient develops respiratory depression (by repeating a bolus and increasing infusion rates) or withdrawal symptoms (by decreasing infusion rates). It is recommended that patients on naloxone infusions be admitted to a monitored unit.

Naloxone has a remarkable safety profile. When administered to opioid-naive patients, naloxone has no adverse effects. Although adverse effects are seen in about one third of patients who receive it for a suspected opioid overdose, serious complications are rare.[28] The most common adverse effects associated with naloxone are anxiety, nausea, vomiting, diarrhea, abdominal cramps, piloerection, yawning, and rhinorrhea, which are expected signs and symptoms of opioid withdrawal. Careful dosing of naloxone can prevent the precipitation of opioid withdrawal symptoms.[27,29]

Naltrexone, an oral opioid antagonist, is primarily used to maintain opioid abstinence after detoxification. Naltrexone, compounded into an extended-release monthly injection (Vivitrol®), is available to treat alcohol or opioid abstinence. **Nalmefene,** both an oral and parenteral opioid antagonist, has not been available in the United States since August 2008 but is available in Europe. Both naltrexone and nalmefene are long-acting reversal agents, so opioid-dependent patients who receive either of these reversal medications intentionally or inadvertently may require protracted management of withdrawal symptoms.

DISPOSITION AND FOLLOW-UP

The optimal observation period after an opioid intoxication is determined by the history and clinical picture. Patients with presumed heroin intoxication who respond to naloxone can be safely discharged 1 hour after administration of naloxone if they have independent mobility, normal vital signs, and normal mental status.[30-32]

In cases of exposure to opioids other than heroin, an observation period of 4 to 6 hours in the ED is recommended after the last naloxone administration. In long-acting opioid overdose, observation should be extended for a minimum of 8 hours.[4] Moderate to severely symptomatic patients usually require hospital admission to monitored settings and may require continued administration of naloxone. A behavioral health evaluation is needed in cases with suicidal intent.

SPECIAL CONSIDERATIONS

BUPRENORPHINE

Buprenorphine is a mixed opioid agonist–antagonist, with partial agonist activity at μ-receptors and antagonist activity at κ- and δ-receptors. Because buprenorphine is only a partial agonist at μ-receptors, it has decreased intrinsic activity that causes its clinical effects to plateau at higher dosages.[33] Buprenorphine has high affinity for and slow dissociation from the μ-receptor, which results in a long duration of action. Furthermore, other opioid agonists (such as heroin) or antagonists (such as naloxone) cannot easily displace buprenorphine from the μ-receptor. Buprenorphine has poor oral bioavailability because of extensive first-pass metabolism and is therefore administered using sublingual films or tablets or parenterally. The most frequently prescribed sublingual buprenorphine formulation is in combination with naloxone in a 4:1 ratio. Because naloxone has poor bioavailability from PO or sublingual administration, it was introduced into the preparation to discourage and limit parenteral abuse of the buprenorphine portion while not interfering with therapeutic use in the form of the sublingual film.

Buprenorphine can be associated with three distinct clinical scenarios. First, the opioid-naive patient who overdoses on buprenorphine will experience mental status depression, nausea, vomiting, miosis, and respiratory depression (usually with a plateau). In this situation, low-dose naloxone may not be fully effective in reversing mental status and respiratory depression.[34] **Because of the long duration of action of buprenorphine, naloxone infusions are necessary, and admission to the hospital is necessary in symptomatic patients.** The second possible scenario is buprenorphine exposure in the opioid-dependent patient. In this case, buprenorphine will precipitate opioid withdrawal symptoms, because the partial agonist buprenorphine behaves like an antagonist in the presence of an agonist. Buprenorphine-induced withdrawal is best managed with symptom-driven therapy, including antiemetics, nonopioid analgesics, antidiarrheal medications, and nonbenzodiazepine sedatives. The third possible clinical scenario is buprenorphine exposure in the opioid-dependent patient who is suffering from opioid withdrawal, in whom buprenorphine will act as a partial agonist and alleviate the symptoms of opioid withdrawal. Thus, **buprenorphine is unique in that it can both induce and treat opioid withdrawal, depending on the timing of its administration.** Buprenorphine can be used in the ED to alleviate opioid withdrawal[35] and be prescribed upon ED discharge to transition patients with opioid use disorder to medication-assisted treatment.[36]

METHADONE

Methadone is a synthetic opioid used as opioid replacement therapy in opioid dependence and can be prescribed as an analgesic for chronic pain. The initial analgesic duration is 8 to 12 hours with an elimination half-life of 12 to 18 hours. With repetitive dosing, analgesic action duration and elimination half-life increase to approximately 22 to 36 hours and up to 59 hours, respectively. The long duration of activity enables once-a-day dosing during chronic therapy. Methadone has a higher risk for overdose-related deaths than other opioids, often with co-ingestants.[37,38] Acute methadone overdoses present similarly to other

opioid intoxications, but the duration can be much longer, requiring naloxone infusions with close neurologic and respiratory monitoring.[39]

Methadone has several drug–drug interactions that can precipitate toxicity or withdrawal in patients on chronic therapy.[40] Interactions between methadone and human immunodeficiency virus medications are common and complex, creating potential for both increased toxicity and withdrawal. The relevant interactions for emergency physicians include ciprofloxacin, fluconazole, ketoconazole, and omeprazole, which can increase toxicity. Drug–methadone interactions that have potential to precipitate withdrawal include macrolides (especially clarithromycin), phenobarbital, phenytoin, spironolactone, and verapamil.

Methadone prolongs the QT interval in acute overdose or during long-term methadone treatment, providing the potential for cardiac dysrhythmias, such as torsades de pointes.[41] In patients with acute methadone overdose resulting in QT interval prolongation, serum electrolytes should be optimized and the patient should be admitted to a monitored unit until the condition resolves. Patients on long-term methadone therapy who develop a QT_c interval between 450 and 500 milliseconds do not require a dosage adjustment, but electrolyte imbalances should be corrected if present, and patients should be followed on an outpatient basis with frequent ECGs. Patients who develop a QT_c interval of >500 milliseconds should be considered for methadone dosage reduction or discontinuation.[42]

TRAMADOL

Tramadol is being increasingly prescribed in the United States for chronic pain. Tramadol binds norepinephrine and serotonin reuptake inhibitors to contribute to its analgesic effects. Tramadol has no direct opiate-binding capacity, but after it is metabolized by cytochrome P450 enzymes, the active metabolite, O-desmethyltramadol, binds the μ-opioid receptor. Tramadol's opioid effects can vary widely because of genetic variation, liver disease, renal disease, and co-prescribed drugs that affect cytochrome P450 metabolism capacity.[43,44]

Tramadol overdoses are associated with lethargy, nausea, tachycardia, and seizures.[45,46] At doses exceeding 500 milligrams, coma, hypertension, respiratory depression, and apnea are seen.[11,47] Features consistent with serotonin syndrome have been seen in isolated tramadol overdoses.[48] Tramadol-induced seizures are common, and naloxone is ineffective in preventing them. Fortunately, tramadol-induced seizures are usually single, and anticonvulsants are not necessary.[49,50] Tramadol has also been associated with higher rates of hypoglycemia compared to codeine, especially within the first 30 days of use.[44,51] Dependence during chronic therapy and withdrawal symptoms upon discontinuation have been reported with tramadol.[52]

MIXED AGONISTS–ANTAGONISTS

The mixed agonists–antagonists include pentazocine, butorphanol, and nalbuphine. These agents have variable but mostly antagonist activity at the μ-receptor and agonist effects at the κ-receptor. They may cause significant respiratory depression in overdose, and naloxone will reverse this respiratory depression. Mixed agonists–antagonists usually precipitate withdrawal when taken by an opioid-dependent individual, which reduces their potential for abuse. Pentazocine overdose can cause seizures.[53]

DIPHENOXYLATE HYDROCHLORIDE–ATROPINE SULFATE

Diphenoxylate hydrochloride–atropine sulfate is a frequently prescribed antidiarrheal agent. The medication is formulated as a combination tablet or liquid, containing diphenoxylate, 2.5 milligrams, and atropine, 0.025 milligram, in each tablet or 5 mL of liquid. In an overdose, initially the anticholinergic toxidrome dominates the clinical picture (see Chapter 202, "Anticholinergics"). The second phase of intoxication is characterized by the opioid toxidrome. Children <6 years of age can be symptomatic after ingestion of a single tablet. In pediatric patients, absorption can be delayed up to 6 to 12 hours in some cases because of the effect of atropine on GI motility. Admission and observation for 24 hours are recommended for children <6 years of age after ingestion of a combination tablet of diphenoxylate and atropine. Older children and adults should be observed in the ED for 6 hours. Administration of activated charcoal is recommended unless contraindicated.

FENTANYL AND NOVEL SYNTHETIC OPIOIDS

Fentanyl and novel synthetic opioids have contributed to rising opioid overdose deaths since 2016.[54] Novel synthetic opioids include both fentanyl analogs (acetylfentanyl, butyrlfentanyl, furanylfentanyl, carfentanil) and nonfentanyl μ-opioid agonists (U47700), all with varying and usually high potencies.[55-57] Illicitly manufactured fentanyl is 50 to 100 times more potent than morphine and has been detected in >50% of opioid overdose deaths in some states.[54] Illicitly manufactured fentanyl has been found as a contaminant in opioids, benzodiazepines, and cocaine.[55] Due to their ultrapotency, overdoses of illicitly manufactured fentanyl and novel synthetic opiods may require rapidly escalating and higher doses of naloxone, up to 10 to 20 milligrams IV, to reverse respiratory depression related to overdose.[55,56]

MIXED DRUGS AND CONTAMINANTS

Heroin is often mixed with other compounds, such as cocaine, scopolamine, clenbuterol, and fentanyl, which may contribute to varied opioid toxidromes. Adulterants found in illicit heroin may include strychnine, quinine, lactose, and talc. Scopolamine is an antimuscarinic agent that produces the anticholinergic toxidrome. Clenbuterol is a long-acting β-adrenergic agonist similar to albuterol and is used in veterinary medicine. A potent neurotoxin, 1-methyl-4-phenyl-1,2,3-tetrahydropyridine, has been used as a meperidine adulterant, producing parkinsonism in users.[58]

Starting in Russia in 2010, episodes of deaths and gangrene were reported associated with IV desomorphine or **"Krokodil,"** a synthetic alternative to heroin crudely made from codeine tablets with a high concentration of tissue-toxic impurities. The colloquial name is derived from the appearance of the skin after it is injected.[59]

KRATOM

Kratom (*Mitragyna speciosa*) has mitragynine as its principal alkaloid, with stimulating effects at low doses (cocaine-like effect) and sedative effects (opioid-like effect) at high doses.[60] Kratom has been used since the early 1930s in Africa and Southeast Asia for medicinal purposes and more recently to prevent opioid withdrawal symptoms by smoking, consuming, brewing, or mixing into drinks.[61] There has been growing use of kratom in Western countries due to its availability in smoke shops and on the Internet.[62] Since 2010, there has been a 10-fold increase in reported use in the United States.[63]

Kratom is used in the United States for three distinct indications: (1) to help manage chronic pain, (2) to mitigate withdrawal symptoms from opioids or alcohol, and (3) for acute euphoric effects.[64] Daily kratom use can lead to dependence, craving, and withdrawal symptoms.[64,66] Kratom can produce seizures,[67] serious toxicity, or even death, often associated with other drug use, such as decongestants, antidepressants, and benzodiazepines.[68] Krypton, a combination containing kratom, O-desmethyltramadol, and caffeine, has also been associated with fatalities.[69]

LOPERAMIDE

Loperamide, also known as "the poor man's methadone," has seen rising rates of misuse, abuse, and suicide ingestion since 2010.[70,71] At high doses (between 50 and 300 milligrams, 20 to 150 times the therapeutic dose of 2 milligrams), loperamide binds the μ-opioid receptor and has greater CNS penetration, leading to euphoria and mental depression. It can also cause severe cardiotoxic effects, including QT_c prolongation, QRS widening, ventricular tachycardia, ventricular fibrillation, and other cardiac dysrhythmias, due to both sodium and potassium channel blockade.[71,72]

Treatment of loperamide overdose should target three modes: GI decontamination, respiratory depression, and cardiotoxicity. Activated charcoal may be used for GI decontamination and repeated because loperamide inhibits peristalsis. Standard doses of naloxone (0.04 to 0.4 milligram) should be used to reverse respiratory depression. Cardiotoxicity due to sodium channel blockade potential with widened QRS

TABLE 186-4 Clinical Features of Opioid Withdrawal

Initial Features	Additional Features About 12 h After Onset	Subsequent Features About 12–24 h After Onset
Peak effects: 36–72 h	Peak effects: 72 h	Peak effects: 72 h
Anxiety	Irritability	Insomnia
Yawning	Tremor	Muscle spasms
Drug craving	Piloerection	Abdominal pain
Lacrimation	Mydriasis	Nausea, vomiting, diarrhea
Rhinorrhea		
Diaphoresis		
Myalgias		

complex is treated with sodium bicarbonate 1 to 2 mEq/kg IV, along with potassium and magnesium replacement. For patients with torsades de pointes, case reports have demonstrated success with cardiac overdrive pacing and isoproterenol IV infusions at 2 to 10 micrograms/min.[72,73] Other advanced therapies including intravenous lipid emulsion therapy and extracorporeal membrane oxygenation have had limited success in individual cases.[72]

OPIOID WITHDRAWAL

Downregulation of endogenous endorphins, dynorphins, and opioid receptors occurs with long-term use of opioids. Abrupt cessation of opioid use does not allow time for upregulation of receptors and results in increased neuronal firing and the opioid withdrawal syndrome.

Opioid withdrawal typically starts 6 to 12 hours after last use of short-acting opioids and 30 hours after abstinence from long-acting opioids. Opioid withdrawal can be abruptly precipitated by the administration of antagonists such as naloxone or naltrexone or the administration of partial agonist–antagonists such as buprenorphine. Opioid withdrawal usually starts with anxiety and progresses with development of additional symptoms over the next 12 to 24 hours (**Table 186-4**).[74] Opioid withdrawal symptoms usually peak on the third day of abstinence and resolve by the fifth or sixth day. Opioid withdrawal symptoms are very uncomfortable but are not life-threatening and rarely fatal. Vomiting and aspiration of gastric contents can cause pneumonitis and dehydration.

Clinical scoring tools have been developed to assist in the assessment of opioid withdrawal.[75] The commonly used Clinical Opiate Withdrawal Scale calculates a score based on the severity of 11 symptoms and can be used to assess appropriateness for buprenorphine or methadone and to monitor response to treatment (**Table 186-5**).[76]

TABLE 186-5 Clinical Opiate Withdrawal Scale (COWS)

Resting Pulse Rate (beats/min)
Measured after patient is sitting or lying for 1 min
0 – Pulse rate ≤80
1 – Pulse rate 81–100
2 – Pulse rate 101–120
4 – Pulse rate >120

Sweating
Over past 1/2 h not accounted for by room temperature or patient activity
0 – No report of chills or flushing
1 – Subjective report of chills or flushing
2 – Flushed or observable moistness on face
3 – Beads of sweat on brow or face
4 – Sweat streaming off face

Restlessness
Observation during assessment
0 – Able to sit still
1 – Reports difficulty sitting still, but is able to do so
3 – Frequent shifting or extraneous movements of legs/arms
5 – Unable to sit still for more than a few seconds

Pupil Size
0 – Pupils smaller or normal size for room light
1 – Pupils possibly larger than normal for room light
2 – Pupils moderately dilated
5 – Pupils so dilated that only the rim of the iris is visible

Bone or Joint Aches
If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored
0 – Not present
1 – Mild diffuse discomfort
2 – Patient reports severe diffuse aching of joints/muscles
4 – Patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny Nose or Tearing
Not accounted for by cold symptoms or allergies
0 – Not present
1 – Nasal stuffiness or unusually moist eyes
2 – Nose running or tearing
4 – Nose constantly running or tears streaming down cheeks

GI Upset
Over last 1/2 h
0 – No GI symptoms
1 – Stomach cramps
2 – Nausea or loose stool
3 – Vomiting or diarrhea
5 – Multiple episodes of diarrhea or vomiting

Tremor
Observation of outstretched hands
0 – No tremor
1 – Tremor can be felt, but not observed
2 – Slight tremor visible
4 – Gross tremor or muscle twitching

Yawning
Observation during assessment
0 – No yawning
1 – Yawning once or twice during assessment
2 – Yawning 2 or more times during assessment
4 – Yawning several times per minute

Anxiety or Irritability
0 – None
1 – Patient reports increasing irritability or anxiousness
2 – Patient obviously irritable or anxious
4 – Patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh Skin
0 – Skin is smooth
3 – Piloerection of skin can be felt or hairs standing up on arms
5 – Prominent piloerection

Total Score is the sum of all 11 items
Assessment: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; >36 = severe withdrawal.

Patients with mild opioid withdrawal are treated with symptomatic therapy, usually antiemetics and antidiarrheals as needed. Symptoms of moderate opioid withdrawal can be rendered more tolerable by the administration of the central α_2-agonist clonidine.[77] Clonidine should not be used if the patient is hypotensive or bradycardiac. A test dose of clonidine 75 to 100 micrograms PO should be given first with reassessment of the patient after 30 minutes. If there is no drop in the blood pressure and the patient is not dizzy, then treatment with 150 micrograms PO three times a day is begun, continued for 3 days and then tapered and discontinued after the fifth day.[78]

Opioid replacement therapy, usually with buprenorphine or methadone, should be considered for moderately severe withdrawal and is recommended for severe withdrawal.[78] To treat withdrawal, standard doses of buprenorphine or methadone are initiated, titrated over with next 2 to 3 days as withdrawal symptoms peak, and then tapered.[78,79]

The management of opioid-dependent individuals hospitalized for medical or surgical reasons can be challenging. Detoxification from opioids during the course of an acute medical illness is usually unsuccessful, so alleviation of withdrawal symptoms with opioid replacement is generally the goal. For patients already enrolled in an outpatient buprenorphine or methadone program, daily administration of the verified dose is recommended to inhibit withdrawal symptoms and reduce craving. A patient who uses high doses of opioids but who is not enrolled in methadone maintenance therapy can be given methadone 20 to 30 milligrams PO or 10 milligrams IM; this dose should inhibit withdrawal symptoms but not induce euphoria. Buprenorphine, 0.3 to 1.2 milligrams IV or IM every 6 hours or 2 to 4 milligrams sublingual, can safely be administered to a medically ill opioid-dependent patient experiencing withdrawal who is being admitted to the hospital.[79] **No methadone or buprenorphine should be administered to an opioid-dependent patient until withdrawal symptoms appear.**

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 187

Cocaine and Amphetamines

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INTRODUCTION

Historical records of indigenous cultures in South America describe early stimulant use by chewing leaves of the *Erythroxylum coca* plant, a practice that continues today. Cocaine was first used therapeutically in 1884 for ophthalmologic procedures, accompanied closely by reports of severe toxicity. Amphetamines were synthesized in 1887, and in 1932, they were marketed medicinally in an inhaler form as a bronchodilator. Use of methamphetamine to enhance physical and intellectual performance began in the 1930s. Amphetamines were widely used as an alertness aid for troops by both Allied and Axis powers during World War II. Today, cocaine and amphetamines have limited therapeutic roles but are widely used as drugs of abuse. Clinical effects and toxicity are due to sympathetic nervous system stimulation.

PHARMACOLOGY

COCAINE

Cocaine is the naturally occurring alkaloid found in *E. coca*, a plant indigenous to South America. The water-soluble hydrochloride salt is absorbed across all mucosal surfaces, including oral, nasal, GI, and vaginal epithelium; cocaine can thus be topically applied, swallowed, or injected IV. The hydrochloride salt (powder) form is most often insufflated (snorted) or dissolved in water and injected IV; it degrades rapidly when pyrolyzed. Freebase cocaine can be smoked because it melts at a much lower temperature and can be prepared in many ways. A common method uses an alkali, such as sodium bicarbonate, to produce "crack cocaine," which, when smoked, produces the popping sound that characterizes its name. The onset and duration of action vary with the route of administration (**Table 187-1**).

TABLE 187-1 Pharmacokinetics of Cocaine

Route of Exposure	Onset of Action	Peak Action	Duration of Action
IV	<1 min	3–5 min	30–60 min
Nasal insufflation (snorting)	1–5 min	20–30 min	60–120 min
Inhalation (smoking)	<1 min	3–5 min	30–60 min
GI	30–60 min	60–90 min	Unknown

Source: Reproduced with permission from Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR: *Goldfrank's Toxicologic Emergencies,* 10th ed. © 2015 by McGraw-Hill, Inc., New York.

When cocaine is insufflated nasally, the delayed and prolonged effect is a result of vasoconstrictive properties that limit mucosal absorption followed by swallowing a portion of the insufflated cocaine, which is then absorbed from the stomach. GI absorption is also prolonged by vasoconstriction, producing delayed peak effect.

Cocaine is primarily metabolized to ecgonine methyl ester by plasma cholinesterase. Relative deficiency of this enzyme may predispose affected patients to life-threatening toxicity.[1] Benzoylecgonine is the other major metabolite excreted in the urine and is the target compound detected in routine urine toxicology screens. Cocaethylene is a long-acting metabolite formed when cocaine is used in combination with ethanol. Cocaethylene has vasoconstrictive properties similar to those of cocaine.

Cocaine is both a CNS stimulant and a local anesthetic.[2,3] Central effects are mediated by enhancement of excitatory amino acids and blockade of presynaptic reuptake of norepinephrine, dopamine, and serotonin. The excess of neurotransmitters at postsynaptic receptor sites leads to sympathetic activation, producing the characteristic physical findings of mydriasis, tachycardia, hypertension, and diaphoresis, and predisposing to dysrhythmias, seizures, and hyperthermia. Cocaine use produces a euphoria associated with enhanced alertness and a general sense of well-being. It is thought that the psychological addiction, drug craving, and withdrawal effects are mediated by interference with dopamine and serotonin balance in the CNS. Subsequent dopamine depletion at the nerve terminals may account for the dysphoria and depression associated with long-term abuse.

Like other local anesthetics, cocaine inhibits conduction of nerve impulses by blocking fast sodium channels in the cell membrane. In cardiac myocytes, cocaine inhibits rapid inward sodium channels causing QRS prolongation and can also block potassium channels resulting in QT_c prolongation. Thus, in large doses, cocaine may exert a direct toxic effect on the myocardium, resulting in negative inotropy and wide-complex dysrhythmias.

AMPHETAMINES

Amphetamines compose a broad class of structurally similar derivatives of phenylethylamine. The derivative methamphetamine, also known as "ice," is abused by ingestion, IV injection, inhalation, or nasal insufflation. Absorption and peak effects vary with the route (**Table 187-2**). Modification of the basic amphetamine structure produces substances with additional psychoactive properties.[4,5] More than 50 such "designer" amphetamines have been created (**Table 187-3**), primarily for hallucinogenic effects (see Chapter 188, "Hallucinogens"). Methamphetamine and the designer amphetamines may have effects that persist for up to 12 hours or longer.

Amphetamines enhance the release and block the reuptake of catecholamines at the presynaptic terminal and may also directly stimulate

TABLE 187-2 Pharmacokinetics of Methamphetamine

Route of Exposure	Onset of Action	Peak Action	Duration of Action
IV	15–30 s	30 min	10–12 h
Nasal insufflation (snorting)	3–5 min	1–2 h	10–12 h
Inhalation (smoking)	10–30 s	5–10 min	8–12 h
GI	15–20 min	2–3 h	10–12 h

catecholamine presynaptic and postsynaptic receptors.[6] Some amphetamine metabolites inhibit monoamine oxidase, increasing cytoplasmic concentrations of norepinephrine. Certain amphetamine derivatives can also induce release of serotonin and affect central serotonin receptors.[7] These serotonergic effects account for the hallucinogenic properties of some amphetamine derivatives such as MDMA (3,4-methylenedioxymethamphetamine) and mescaline (3,4,5-trimethoxyphenethylamine). Downregulation of dopamine receptor activity with long-term use may contribute to the withdrawal phenomenon. Mortality from amphetamine toxicity is a result of hyperthermia, dysrhythmias, seizures, hypertension (intracranial hemorrhage or infarction), and encephalopathy.

Stimulants such as methylphenidate, ephedrine, pseudoephedrine, and phenylpropanolamine produce toxic syndromes similar to but generally less severe than those caused by cocaine and amphetamines.[8-13] The U.S. Food and Drug Administration–approved prescription stimulant medications for attention-deficit/hyperactivity disorder, such as methylphenidate and dextroamphetamine, are available in both immediate- and extended-release formulations. Abusers may crush the extended-release tablet to separate the active agent from the extended-release matrix to achieve a rapid onset of action after insufflation or injection.[14]

Synthetic (or substituted) cathinones, often termed "**bath salts**," are designer drugs derived from naturally occurring amphetamine analogs found in the *Catha edulis* plant. Cathinones stimulate the release and block the reuptake of norepinephrine, dopamine, and serotonin at synapses in the brain, producing stimulant effects similar to cocaine and amphetamines.[15-17] Commonly abused substituted cathinones include mephedrone, methylenedioxypyrovalerone, and methylone, although the composition in bath salts sold for abuse varies widely.

CLINICAL FEATURES

The clinical features of cocaine and amphetamine toxicity are the result of their sympathomimetic, vasoconstrictive, psychoactive, and local anesthetic properties affecting a variety of organ systems.[2-4,6]

CARDIOVASCULAR

Cocaine induces dysrhythmias, myocarditis, cardiomyopathy (including takotsubo), and acute coronary syndromes.[18] Other vascular complications include aortic rupture and aortic and coronary artery dissection. Even at relatively low doses, cocaine induces vasoconstriction in coronary arteries, contributing to cocaine-induced chest pain.[19] Coronary vasoconstriction is exacerbated by β-adrenergic blockade and antagonized by phentolamine, which suggests mediation through stimulation of α-adrenergic receptors.[20] This effect is potentiated by cigarette smoking, and risk is heightened in patients with preexisting coronary artery disease.[21,22] In addition to promoting vasospasm and causing increased myocardial oxygen demand, cocaine predisposes to acute coronary syndrome by increasing atherogenesis through increased platelet aggregation, thrombogenesis, and accelerated atherosclerosis.

Most patients who suffer cocaine-associated acute coronary syndrome are nonwhite men between the ages of 20 and 40 years who smoke cigarettes and regularly use cocaine. These demographic characteristics encompass the majority of patients presenting with cocaine-associated chest pain, making it difficult to predict those at greatest risk for myocardial infarction.[23-25] However, a recent study of a nationwide inpatient sample of 363,143 admissions for cocaine-induced chest pain suggests female sex, age >50 years, history of heart failure, supraventricular tachycardia, endocarditis, tobacco use, dyslipidemia, coronary artery disease, or renal failure as predictors of myocardial infarction.[26] All routes of cocaine administration are associated with chest pain, acute coronary syndrome, ST-segment elevation myocardial infarction, and non–ST-segment elevation myocardial infarction. Atypical chest pain is common.

Acute coronary syndromes and aortic dissection are also reported in association with ephedrine, phenylpropanolamine, and amphetamine use.[27] Mitral and aortic valve abnormalities associated with use of the amphetamine combination phentermine-fenfluramine prompted a voluntary recall of these appetite-suppressant drugs. Cardiopulmonary toxicity from other amphetamine diet aids has also been reported.

Dysrhythmias induced by cocaine can result from sympathomimetic stimulation, blockade of the sodium channel during depolarization, inhibition of the potassium channel during repolarization, and effects on calcium channel current.[18,28] Sympathomimetic-induced dysrhythmias are tachycardias, such as sinus tachycardia, reentrant supraventricular tachycardia, and atrial fibrillation and flutter. Sodium channel blockade produces a rightward shift of the terminal portion of the QRS complex as seen on the frontal plane ECG leads (aVr with terminal R wave >3 mm and R/S ratio >0.7), a pattern similar to that of cyclic antidepressants.[29] Progressive toxicity may induce a complete right bundle branch block or a prolonged QRS >120 milliseconds that, when combined with sinus tachycardia, produces a wide-complex tachycardia. Cocaine can induce the ECG appearance of the **Brugada** pattern, although it is not clear whether this is strictly a toxic effect or if the sodium channel–blocking effect of cocaine unmasks an underlying genetic predisposition to the Brugada syndrome.[30]

Potassium channel blockade impairs repolarization, prolonging the QT interval on the ECG.[29] The effects of cocaine on calcium channel current are dose dependent and complex, but at concentrations associated with clinical toxicity, prolongation of both depolarization and repolarization is seen, as well as enhanced dispersion in repolarization.[28] Delayed repolarization and enhanced dispersion promote early afterpotentials that can trigger reentrant dysrhythmias, such as ventricular tachycardia and a variant, torsades de pointes.

Takotsubo syndrome, transient apical ballooning of the left ventricle, has been associated with cocaine use. The physiology is not clearly understood, but has been attributed to the effects of a sympathomimetic surge on the myocardium after cocaine use.[31,32]

TABLE 187-3 Commonly Abused Designer Amphetamines

Abbreviation	Chemical Name
MDMA	3,4-Methylenedioxymethamphetamine
MDA	3,4-Methylenedioxyamphetamine
MDEA	3,4-Methylenedioxyethamphetamine
PMA	Paramethoxyamphetamine
DOB	4-Bromo-2,5-dimethoxyamphetamine
2CB	4-Bromo-2,5-dimethoxyphenylethylamine
STP or DOM	4-Methyl-2,5-dimethoxyamphetamine
Fenethylline (Captagon®)	Amphetaminoethyltheophylline

CNS

Neurologic syndromes associated with cocaine abuse include seizures, cerebral infarctions, and hemorrhages. Hyperadrenergic tone induces severe transient hypertension, hemorrhage, or focal vasospasm, and, sometimes, exacerbation of underlying abnormalities of cerebral blood vessels. Cerebral vasoconstriction following cocaine administration has been observed using magnetic resonance angiography.[33]

Other CNS manifestations reported after cocaine use include spinal cord infarctions, cerebral vasculitis, and intracranial abscesses. Choreoathetosis and repetitive movements (termed "crack dancing") are associated with cocaine and amphetamine intoxication and appear related to dopamine dysregulation. Acute dystonic reactions following cocaine use and withdrawal are also observed. Unilateral blindness has

been reported secondary to central retinal artery occlusion, and bilateral blindness can be caused by diffuse vasospasm. A syndrome of corneal abrasions and ulcerations secondary to smoke and irritation is known as "crack eye." Keratitis caused by methamphetamine use has been described as well.

"Cocaine washout" is a syndrome that may occur in patients after a prolonged crack binge and results from depletion of neurotransmitters. Patients have a depressed level of consciousness but can be aroused to normal with stimulation. Resolution of lethargy can take up to 24 hours.

Amphetamine, phenylpropanolamine, and ephedrine use are associated with intracranial hemorrhage, infarction, encephalopathy, and seizures.[4,6] Amphetamines can also cause a CNS vasculitis, resulting in focal neurologic deficits. A profound paranoid psychosis can be seen with long-term amphetamine abuse and withdrawal.

PULMONARY

Respiratory effects of cocaine use are more common in patients who smoke crack cocaine. Pulmonary hemorrhage, barotrauma, pneumonitis, asthma, and pulmonary edema have been observed.[34] Pneumomediastinum, pneumothorax, and pneumopericardium result from barotrauma secondary to performance of the Valsalva maneuver after inhalation or nasal insufflation in an attempt to enhance drug effect. Pneumonitis, asthma, and bronchiolitis may be an immunologic phenomenon or may result from numerous adulterants in illicit preparations.

Inhalation of crack cocaine is associated with new-onset bronchospasm, likely the result of local airway irritation.[35,36] Acute lung injury associated with cocaine use is multifactorial and may be catecholamine mediated. A similar syndrome has been described in patients with adrenergic excess from pheochromocytoma and intracranial hemorrhage. Upper airway irritation and a "thermal" uvulitis can occur in patients smoking crack cocaine.

GI

Cocaine-induced mesenteric vasospasm may produce intestinal ischemia, bowel necrosis, ischemic colitis, and splenic infarctions. In addition, GI ulceration, bleeding, and perforation occur in association with cocaine use. Advanced tooth decay (termed "meth mouth") is common in habitual methamphetamine users. The reasons are presumably multifactorial and are related to poor oral hygiene, persistent dry mouth, jaw clenching, and tooth grinding. The belief that contamination with acidic or corrosive substances from the manufacturing process is responsible for this condition is not supported by analysis of illicitly produced methamphetamine.

ENDOCRINE

MDMA users may develop hyponatremia due to drug-induced secretion of vasopressin in the setting of overhydration with water, which has been associated with several deaths. There is limited evidence suggesting that synthetic cathinones may cause similar effects.

RENAL

Cocaine or amphetamine use may cause traumatic and nontraumatic rhabdomyolysis.[37-39] In cocaine-induced rhabdomyolysis, up to one third of patients develop acute kidney failure.[39] Risk factors for rhabdomyolysis include altered mental status, seizures, dysrhythmias, and hemodynamic instability. Stimulants may further exacerbate renal injury by producing hyperthermia, vasoconstriction, hypotension, and hypovolemia. Renal infarction has been described following IV cocaine use.

PREGNANCY

Cocaine is a potent vasoconstrictor that affects uteroplacental blood flow. Cocaine abuse during pregnancy is associated with an increased incidence of spontaneous abortions, abruptio placentae, fetal prematurity, and intrauterine growth retardation.[40-43] Both spontaneous abortions and abruptio placentae appear to occur from placental vasoconstriction and increased uterine contractility, with concomitant maternal hypertension. A breastfed infant can become intoxicated secondary to maternal cocaine use. Methamphetamine abuse during pregnancy has detrimental effects on fetal growth.

DIAGNOSIS

Cocaine or amphetamine intoxication can usually be suspected based on the symptoms and signs of the sympathomimetic toxidrome: agitation, mydriasis, diaphoresis, tachycardia, tachypnea, hypertension, and possibly hyperthermia. Mental status can range from normal to severely agitated and paranoid. Lethargy or coma suggests a postictal state or intracranial hemorrhage. Symptoms such as chest pain, palpitations, dyspnea, headache, or focal neurologic complaints suggest end-organ toxicity. Without a history of cocaine or other stimulant use, it may be difficult to distinguish this presentation from other conditions with catecholamine excess, such as withdrawal from alcohol or sedative-hypnotic drugs (**Table 187-4**). Lactic acidosis may be present following seizures or as a result of vasoconstriction and hypoperfusion. As with all intoxicated patients, consider occult trauma and hypoglycemia.

Concomitant use of alcohol and other drugs frequently alters the clinical presentation. For example, a patient using both opioids and stimulants may present with a decreased level of consciousness and few, if any, other diagnostic features of catecholamine excess. When the opioid effects are reversed with naloxone, the stimulant effects are unmasked, often with impressive findings.

LABORATORY EVALUATION

Laboratory studies and imaging are directed by clinical findings. Obtain a chemistry panel and creatine kinase level in a patient with agitation or elevated temperature to evaluate for possible metabolic acidosis, renal failure, or rhabdomyolysis. Hyponatremia, often with altered mental status, occasionally occurs after the use of hallucinogenic amphetamines such as MDMA or mescaline. For chest pain, obtain an ECG and serum levels of cardiac biomarkers. If the patient is hyperthermic (>104°F or 40°C), coagulation and liver function studies should be performed. Altered mental status typically requires neuroimaging.

Urine drug screens to confirm cocaine or amphetamine use are readily available, but interpretation requires knowledge of pharmacology and the testing method.[44] Most of the rapid urine screening tests for cocaine are highly specific for cocaine metabolites (such as benzoylecgonine) and

TABLE 187-4 Differential Diagnosis of Cocaine or Amphetamine Toxicity

Toxicologic	Phencyclidine toxicity
	Hallucinogen toxicity
	Anticholinergic toxicity
	Sedative-hypnotic withdrawal
	Serotonin syndrome
	Neuroleptic malignant syndrome
CNS	Ischemic stoke
	Intracranial hemorrhage
	Traumatic brain injury
	Encephalitis or meningitis
	Cerebral vasculitis
	Neoplasm
Endocrine	Hypoglycemia
	Pheochromocytoma
	Hyponatremia
	Thyrotoxicosis
Psychiatric	Acute psychosis
Other	Heatstroke
	Hypoxia

exhibit little cross-reactivity to the parent compound or other metabolites. Commonly available urine drug screens for the cocaine metabolite benzoylecgonine are sensitive at very low levels, and cocaine use within the past 24 to 72 hours is typically detected, depending on dose. Cocaine can be detected in habitual users by more sensitive techniques (radioimmunoassay, gas chromatography) for up to 2 weeks after last use of the drug.

Most urine amphetamine screens detect amphetamine, dextroamphetamine, methamphetamine, and, with decreasing sensitivity, 3,4-methylenedioxymethamphetamine, MDMA, and 3,4-methylenedioxyamphetamine. Synthetic cathinones may be detected, but results are too variable to be clinically useful due to variation in both laboratory analyzers as well as "bath salt" preparations. Commercial urine drug screens for amphetamine are sensitive to 1000 nanograms/mL, and amphetamine use within the past 48 hours is usually detected. However, interfering substances and other phenylethylamine compounds cross-react with amphetamine immunoassays, which limits their specificity. For example, excessive use of certain nasal inhalers that contain cross-reacting stimulant-class drugs may lead to positive results on immunoassays. Patients who take the nonprescription decongestants pseudoephedrine or phenylephrine or use prescription stimulants for attention-deficit/hyperactivity disorder or narcolepsy can have a positive urine amphetamine result. Many drugs, such as bupropion, chlorpromazine, promethazine, thioridazine, trazodone, desipramine, and doxepin, have metabolites that react with the amphetamine immunoassay. Other drugs, such as labetalol, isometheptene, ranitidine, ritodrine, and trimethobenzamide, possess enough structural similarity to the basic amphetamine form to react with the immunoassay as well.

TREATMENT

Follow the standard protocol for poisoned patients (see Chapter 176, "General Management of Poisoned Patients"). Establish IV access, and provide oxygen administration for hypoxia. The cornerstone of therapy is monitoring of vital signs, treatment of complications, supportive care, and adequate sedation to prevent self-harm and allow for testing and imaging (**Table 187-5**).[45] Treat hyperthermia with an ice bath or cooling blankets (see Chapter 210, "Heat Emergencies").[46] Aggressive IV hydration is the primary treatment for rhabdomyolysis (see Chapter 89, "Rhabdomyolysis"). Seizures are initially treated with benzodiazepines, and status epilepticus requires aggressive treatment (see Chapter 171, "Seizures and Status Epilepticus in Adults"). Obtain a head CT to identify intracranial pathology as the cause of seizures.

SEDATION

Benzodiazepines are the cornerstone of therapy for sedation. Lorazepam, 2 milligrams IV, or diazepam, 5 milligrams IV, can be administered and titrated with repeated doses to decrease the excess autonomic and neural stimulation. Antipsychotics such as haloperidol, droperidol, and chlorpromazine are not first-line therapy because they may lower the seizure threshold, contribute to hyperthermia, and increase QT prolongation and the risk of ventricular dysrhythmias. However, if benzodiazepines are ineffective, antipsychotics may be necessary to control agitation and dangerous behavior.

TABLE 187-5 Management of Sympathomimetic Toxicity

- Vital signs and continuous cardiac monitoring
- Supportive care and prevent self-harm
- Benzodiazepines for sedation
- Aggressive cooling for hyperthermia
- IV fluid for rhabdomyolysis
- Benzodiazepines for seizures
- Evaluate chest pain and treat ACS
- Phentolamine for uncontrolled hypertension
- Targeted therapy for dysrhythmias

Abbreviation: ACS = acute coronary syndrome.

CHEST PAIN

Chest pain characteristics in cocaine users are no different than in patients with atherosclerotic heart disease. Question chest pain patients about the use of cocaine.[47] Cocaine users with suspected acute coronary syndrome are managed with aspirin and nitroglycerin (see Chapter 49, "Acute Coronary Syndromes").[47,48] Additional therapy is guided by the ECG.

IV calcium channel blockers (diltiazem, 5 to 20 milligrams IV) are recommended as adjunctive therapy for patients with ST-segment elevation or depression.[47] Use of β-adrenergic antagonists ("β-blockers") in the management of cocaine-associated myocardial ischemia or infarction is controversial.[47-50] Case reports suggested that β-blockers may create the potential for unopposed stimulation of α-adrenergic receptors that worsens coronary and peripheral vasoconstriction, hypertension, and possibly ischemia.[47,48] Conversely, large observational studies of patients with cocaine-related chest pain did not find an increased incidence of adverse effects in patients who received a β-blocker in the ED.[51-53] Labetalol (a mixed α-adrenergic and β-adrenergic antagonist) has been suggested for use by some in cocaine-associated chest pain because it does not appear to induce coronary artery vasoconstriction, even though β-adrenergic–blocking activity predominates over α-adrenergic–blocking activity.[50,54-57] **The 2014 American Heart Association/American College of Cardiology guidelines recommend that β-blockers not be administered to patients with signs of acute cocaine intoxication.**[48] Although there are no definitive data to guide treatment of tachycardia in the setting of cocaine-related chest pain, available evidence from the emergency medicine literature supports use of labetalol when clinical judgment dictates a need for heart rate reduction.

Emergent coronary angiography is recommended if ST segments remain elevated despite nitroglycerin and calcium channel–blocker therapy.[47] Fibrinolytics may be used for cocaine-induced ST-segment elevation myocardial infarction if no other contraindications exist and coronary angiography is not available.[47] Based on limited observational data demonstrating cardiac toxicity and similarities in pathophysiology between cocaine and amphetamines, the current American Heart Association/American College of Cardiology guidelines recommend therapy similar to that of cocaine-induced chest pain for chest pain in the setting of amphetamine use.[48,56]

For patients without evidence of acute cocaine intoxication or ST-segment elevation on ECG and a negative initial troponin, risk stratification using the HEART Pathway (history, ECG, age, risk factors, and troponin) or other risk stratification tools including serial ECGs and a minimum of two troponin assessments is reasonable.[58]

DYSRHYTHMIAS

Target antidysrhythmic therapy according to the probable pathogenesis of the dysrhythmia.[21,59,60] Sinus tachycardia is generally responsive to sedation, cooling, and IV fluid rehydration; β-blocker therapy should be avoided if possible, and labetalol should be used if β-blockade is judged necessary. Use a calcium channel blocker to treat reentrant supraventricular tachycardia as well as to control the ventricular rate in atrial fibrillation or flutter.

A wide-complex tachycardia with clinical evidence of cocaine toxicity can be assumed to be due to sodium channel blockade and treated with sodium bicarbonate, a 1 to 2 mEq/L IV bolus followed by either intermittent boluses or an infusion.[60,61] The frequency of boluses or the rate of infusion is guided by clinical response and serum pH; do not alkalinize the serum above a pH of 7.55 with sodium bicarbonate. Lidocaine in standard doses can be used in refractory cases of wide-complex tachycardia; theory and animal models suggest harmful interaction, but clinical experience has documented safety.[60]

Magnesium, lidocaine, and overdrive pacing have all been reported to be successful in cocaine-induced torsades de pointes. It seems reasonable, although of unproven benefit, to administer magnesium in an attempt to prevent torsades in patients with a prolonged corrected QT interval >500 milliseconds or who fall above the QT–heart rate pair nomogram.[62]

HYPERTENSION

Severe hypertension not responding to sedation with benzodiazepines should be treated with phentolamine (initial dose, 2.5 to 5.0 milligrams IV),

nitroglycerin, nicardipine, or a sodium nitroprusside infusion (initial dose, 0.3 microgram/kg per minute). Blood pressure may be lowered aggressively if the patient does not have chronic hypertension. Treatment for refractory hypertension is similar to that for hypertensive emergencies except that β-adrenergic blockers are not used (see Chapter 57, "Systemic Hypertension").

BODY STUFFERS AND BODY PACKERS

Cocaine and other drugs can be internally concealed.[63] Patients who swallow cocaine following police pursuit to conceal the evidence are termed "body stuffers." The swallowed packets are often poorly wrapped and can leak or perforate.[64] "Body packers" swallow a large number of well-sealed packets in order to smuggle drugs across international borders. Both methods can result in severe toxicity and death.[45,64]

Management of an asymptomatic cocaine body packer brought in by police or customs officials is a treatment dilemma.[63] CT is the best imaging modality to identify the packets.[65-67] If the patient shows no signs of toxicity, give single-dose activated charcoal and institute whole-bowel irrigation with polyethylene glycol electrolyte solution to gently hasten packet elimination.[45,68] Continue whole-bowel irrigation until passage of the last packet, and then obtain a confirmatory CT to ensure that all containers have passed. For symptomatic patients, provide sedation and symptomatic care, and obtain immediate surgical consultation for operative removal of the packets. Do not consult for endoscopy or colonoscopy because endoscopic manipulation may rupture the packets.[63,64]

DRUG INTERACTIONS

Because cocaine is metabolized by plasma cholinesterase, coadministration of drugs such as succinylcholine and mivacurium that are also metabolized by plasma cholinesterase may lead to unpredictable rates of metabolism, leading to foreshortened or prolonged effects.

Both lidocaine and cocaine are local anesthetics and act as sodium channel antagonists. It is thought that the neurotoxic effects of both occur by similar mechanisms. Despite theoretical risk in treating cocaine-induced dysrhythmias with lidocaine, it has been used safely in patients with cocaine-associated myocardial infarction.

Monoamine oxidase inhibitors block the degradation of intracellular catecholamines, increasing adrenergic neurotransmitters in the presynaptic terminals. Amphetamines are indirect-acting sympathomimetic amines that induce the release of stored catecholamines and are also weak inhibitors of monoamine oxidase. Thus, patients taking monoamine oxidase inhibitors who subsequently use amphetamines or phenylpropanolamine (and to a lesser extent cocaine) may precipitate an acute syndrome of excessive catecholamine release that results in severe hypertension, tachycardia, hyperthermia, agitation, tremors, and possible severe neurotoxicity.

DISPOSITION AND FOLLOW-UP

Disposition depends on initial patient presentation, response to therapy, the nature of the stimulant involved, and expected duration of effect. Patients demonstrating resolution of toxicity and clear sensorium in the absence of focal complaints or end-organ damage should be advised of the medical risks of drug abuse and referred to appropriate detoxification, counseling, and social support services.

Patients who present with adrenergic excess following recent cocaine use and who respond to initial sedation may be expected to improve completely during a period of observation in the ED because of the relatively limited duration of cocaine effects. In contrast, amphetamines have a longer duration of effect and produce prolonged toxicity, which necessitates observation or hospitalization.

WITHDRAWAL

Cocaine withdrawal is characterized by irritability, paranoid ideation, and depression.[69] Although symptoms during cocaine withdrawal are generally milder than those during amphetamine withdrawal, psychological addiction may be particularly strong. Methamphetamine withdrawal is characterized by drowsiness, lethargy, hunger, tremor, and chills. There is considerable potential for long-term depression and suicide. Symptoms of withdrawal are strongest during the first 48 hours, but milder symptoms can last up to 2 weeks. Although pharmacologic adjuncts (e.g., antidepressants, adrenergic antagonists, dopaminergic agents) are sometimes used during cocaine or amphetamine withdrawal, there are no data confirming efficacy.[69-71]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 188

Hallucinogens

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INTRODUCTION

The term *hallucinogen* is misleading. Hallucinogenic compounds rarely produce true hallucinations. Instead, users experience profound distortions in body image, sensory perception, and time perception, in addition to rapid, intense alterations in mood, increased intensity of any emotions, and heightened suggestibility. *Hallucinogen* is sometimes used interchangeably with the term *psychedelic*.

Hallucinogens are widely perceived as safe by the public and thus continue to be widely used. In fact, about 32 million Americans have used a psychedelic drug at least once in their lifetimes, or approximately 17% of all Americans between the ages of 21 and 64 years.[1] In addition, hallucinogens account for approximately 7% of U.S. ED visits involving illicit drugs.[2] However, these substances can cause dangerous physiologic effects resulting in serious health consequences.[3-5] The identity, purity, and amount of hallucinogenic compound are usually uncertain, and individual response can be unpredictable.

Hallucinogens in current use consist of both natural and synthetic compounds.[6] The proliferation of "designer drugs"—chemical analogs or derivatives of illicit drugs marketed to circumvent existing drug laws—is a growing problem. Manufacturers of designer drugs try to circumvent U.S. federal drug laws by stamping their product with advisories such as "not intended for human consumption" or by identifying the products as plant food, bath salts, or potpourri. Prosecution through the Federal Analog Act, a section of the Controlled Substance Abuse Act, can occur only if the drug is "intended for human consumption." Because of this limitation in federal law, some states have moved to ban the sale of such agents.

In the past decade, there has been a renewed interest in studying the potential therapeutic effects of hallucinogens. Clinical studies have demonstrated efficacy of hallucinogens such as psilocybin and lysergic acid diethylamide (LSD) in treating depression, anxiety, and substance addiction, but this area of research is in its infancy.[7]

Conditions that mimic hallucinogen intoxication include sedative-hypnotic withdrawal, anticholinergic poisoning, thyrotoxicosis, CNS infections, structural brain lesions, acute psychosis, hypoglycemia, and hypoxia.[8] Some prescription and nonprescription medications can cause hallucinations. The identity of street drugs is often misrepresented, and substitution or adulteration of product is common.[9,10]

Drug-induced psychosis may be difficult to distinguish from primary psychotic disorders.[11,12] A patient with substance-induced psychosis is more likely to have a diagnosis of dependence on any drug, report visual hallucinations, and have a history of parental drug abuse.[12]

GENERAL APPROACH TO TREATMENT

ASSESSMENT

The assessment of the hallucinogen-intoxicated patient should begin with assessment of vital signs and general clinical stability. Although severe vital sign abnormalities are rare with hallucinogens, the most common disturbances are hypertension and tachycardia resulting from sympathomimetic surge. A core temperature should also be obtained. While rare in isolated hallucinogen use, hyperthermia suggests severe poisoning and requires immediate intervention to avoid complications.

Hypoxia and hypoglycemia, both alternative explanations for altered mental status, should be quickly identified and corrected. Serum chemistries, a venous blood gas, and a creatine phosphokinase should be considered, particularly if there is a concern for co-ingestions causing metabolic derangement or rhabdomyolysis. An ECG will be necessary to identify QRS or QT interval prolongation related to co-ingestants. Qualitative urine immunoassays are readily available for some of the described hallucinogens such as amphetamine analogs, but these tests are hampered by so many limitations (inaccuracy and inability to pinpoint remote versus recent hallucinogen use) that they rarely contribute to the management of acutely poisoned patients. The use of urine immunoassays should not guide clinical management of patients with suspected hallucinogen poisoning.

TREATMENT

Supportive care is the mainstay of treatment in most situations. Creating a calm environment with few external stimuli and providing reassurance until the drug effects wear off are often sufficient in mild cases. Because most hallucinogens are rapidly absorbed and most patients with adverse events do not present until several hours after ingestion, gastric decontamination is rarely indicated.

In moderate to severe cases, benzodiazepines are the preferred choice for chemical sedation because they possess no significant drug interactions, have no dystonic or anticholinergic adverse effects, do not prolong the QT interval or promote arrhythmias, and are reversible by flumazenil if oversedation occurs (although risk of inducing withdrawal in the benzodiazepine-tolerant individual should be a consideration). In the moderately to severely agitated patient in whom IV access has not been obtained, IM midazolam 2 to 5 milligrams should be given. In patients with IV access, starting doses of benzodiazepines are as follows: 1 to 2 milligrams IV of midazolam or lorazepam and 2 to 5 milligrams IV of diazepam. If the patient is severely agitated or hypertensive, doubling these doses is reasonable provided that continuous monitoring and frequent reassessments are made. See Chapter 287, "Acute Agitation," for detailed discussion of agitation.

Antipsychotics such as haloperidol are frequently recommended as adjuncts for drug-induced delirium. Many antipsychotics (e.g., haloperidol) are potent dopamine receptor antagonists, which allows them to antagonize the psychiatric and psychomotor effects of select hallucinogens such as amphetamines. However, caution should be exercised when using antipsychotics because they can lower the seizure threshold, cause dystonia, precipitate dysrhythmias, and alter temperature regulation.[13]

Hypertension often responds to judicious use of sedation with a benzodiazepine, but in refractory cases, it can be treated with phentolamine or a calcium channel blocker. Provide active cooling for significant hyperthermia. Treatment of severe agitation, hyperthermia, or seizures may require neuromuscular paralysis, ice baths, and endotracheal intubation. Seizures are treated with benzodiazepines or propofol. Patients with rhabdomyolysis require aggressive IV hydration to maintain urine output. Dantrolene is a potential treatment option for hallucinogen-induced hyperthermia, but evidence is limited.[14]

DISPOSITION AND FOLLOW-UP

Compared with other abused psychoactive agents, hallucinogens have some of the largest acute safety ratios when lethal doses are measured against the doses customarily used to produce the desired effects.[15] Most patients seen in the ED due to adverse reactions from hallucinogen use can be discharged into the custody of family or friends if they are lucid and in medically stable condition after a period of observation. Patients with persistent psychotic symptoms or comorbid psychiatric illnesses require psychiatric evaluation.

COMMON HALLUCINOGENS

Common hallucinogens are listed in **Table 188-1**.

LYSERGIC ACID DIETHYLAMIDE

LSD is a potent psychoactive drug. As little as 25 micrograms produces psychedelic effects. The hallucinogenic effects are believed to be mediated through agonism at the serotonin type 2 (5-HT_2) receptor.[16,17]

LSD is a colorless, tasteless, odorless, water-soluble substance that is sold in various forms, but most commonly as small squares of dried blotter paper printed with colorful graphics and cartoons that have been perforated and soaked in liquid LSD solution. Each square typically delivers a dose of 20 to 80 micrograms. Other forms include "microdots" (tiny tablets), "windowpane" (gelatin sheets), impregnated sugar cubes or candy, and small bottles of "breath drops" (the drug in solution).

The psychedelic effects begin within 30 minutes of ingestion, peak within 4 hours, and last between 8 and 12 hours.[18,19] Sympathomimetic stimulation with mydriasis and elevations of pulse, blood pressure, and temperature usually precede the psychedelic effects.[18,19] While severe symptoms are uncommon in recreational use, marked facial flushing, mild gastric distress, piloerection, increased muscle tension, and hyperreflexia may occur. In massive overdoses (approximately >400 micrograms), coagulopathy, hyperthermia, seizure, coma, and respiratory arrest have been reported.[20] Although very rare, vasospasm resulting in peripheral ischemia and strokes has also been reported.[21]

The psychedelic effects of LSD depend on the user's prevailing mood, expectations, and surrounding environment. Effects may be perceived as pleasurable or horrifying. Predominant effects induced by LSD include visual hallucinations, audiovisual synesthesia, and derealization and depersonalization phenomena. Subjective well-being, happiness, and closeness to others are increased by LSD. However, profound distortions in perception of sensory stimuli, time, emotions, and memories also occur and may cause users to experience paranoia, depression, extreme panic, or an acute psychotic reaction known as a *dysphoric reaction* or "bad trip," which can result in serious physical trauma or suicide. Prolonged and sometimes permanent psychosis, known as "flashbacks" or "hallucinogen-persisting perception disorder," can result.[22]

Diagnosis is based on history of use, the presence of sympathomimetic signs, and reported psychedelic effects. LSD can be detected in the urine for several days after ingestion using specific radioimmunoassay and enzyme immunoassay techniques. Reassurance and observation in a quiet, safe environment are generally the only interventions required to manage a dysphoric reaction. Oral or parenteral benzodiazepines are indicated for patients with extreme agitation or signs of excessive sympathomimetic stimulation. Patients with paranoid or psychotic symptoms lasting longer than 8 to 12 hours may require hospital admission. Medical complications due to massive overdose are rare, and recovery is usually rapid and requires only supportive care.[18-20] An important consideration is that certain drugs may also be sold for use on blotting paper as LSD such as the 2C-series (2C-I) and *N*-2-methoxybenzylphenylethylamines (NBOMe). These agents are considered to be considerably more potent than LSD, and deaths have been reported.[23]

PSILOCYBIN

Psilocybin is a naturally occurring hallucinogenic compound found in at least six genera of mushrooms, but most notably the *Psilocybe* genus. Psilocybin is an indolealkylamine that is metabolized to the pharmacologically active compound psilocin. Both psilocybin and psilocin are believed to act as serotonin type 2 receptor agonists, similar to LSD.

Psilocybin-containing mushrooms grow naturally in the southern United States and Europe but can also be grown from kits sold over the Internet.[24] Most species of psilocybin-containing mushrooms turn bluish when bruised, but this is not a definitive method of identification or determination of potency. Psilocybin-containing mushrooms may

TABLE 188-1 Common Hallucinogens

Drug	Typical Hallucinogenic Dose	Duration of Action	Clinical Features	Complications	Specific Treatment
Lysergic acid diethylamide (LSD)	20–80 micrograms	8–12 h	Mydriasis Tachycardia Anxiety Muscle tension	Coma Hyperthermia Coagulopathy Persistent psychosis Hallucinogen persisting perception disorder	Reassurance Benzodiazepines
Psilocybin	5–100 mushrooms 4–6 milligrams of psilocybin	4–6 h	Mydriasis Tachycardia Muscle tension Nausea and vomiting	Seizures (rare) Hyperthermia (rare)	Reassurance Hydration Benzodiazepines
Mescaline	3–12 "buttons" 200–500 milligrams of mescaline	6–12 h	Mydriasis Abdominal pain Nausea and vomiting Dizziness Nystagmus Ataxia	Rare	Supportive Benzodiazepines
Methylenedioxymethamphetamine (MDMA, "ecstasy")	50–200 milligrams	4–6 h	Mydriasis Bruxism Jaw tension Ataxia Dry mouth Nausea	Hyponatremia Hypertension Seizures Hyperthermia Arrhythmias Rhabdomyolysis	Benzodiazepines Hydration Active cooling Dantrolene Specific serotonin antagonists
Synthetic cathinone derivatives ("bath salts")	50–300 milligrams of mephedrone	2–4 h	Agitation Tachycardia Hypertension Diaphoresis Mydriasis	Paranoia Panic reactions Hyperthermia Seizures Hyponatremia Rhabdomyolysis	Benzodiazepines Hydration Active cooling
Phencyclidine (PCP, "angel dust")	1–9 milligrams	4–6 h	Small or midsized pupils Nystagmus Muscle rigidity Hypersalivation Agitation Catatonia	Coma Seizures Hyperthermia Rhabdomyolysis Hypertension Hypoglycemia	Benzodiazepines Hydration Active cooling
Marijuana (cannabis)	5–15 milligrams of tetrahydrocannabinol (THC)	2–4 h	Tachycardia Conjunctival injection	Acute psychosis (rare) Panic reactions (rare)	Supportive Benzodiazepines
Synthetic cannabinoids ("K2," "spice")	2–5 milligrams of JWH-018*	3–4 h	Tachycardia Conjunctival injection	Acute psychosis Panic reactions Seizures (rare) Arrhythmias (rare)	Supportive Benzodiazepines
Bromo-benzodifuranyl-isopropylamine (Bromo-DragonFLY)	200–800 micrograms	10–14 h	Agitation Hallucinations	Seizures Vasoconstrictor with necrosis and gangrene	Supportive Benzodiazepines

*One of the first synthetic cannabinoids (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone, goes by the term JWH-018.

be dried or cooked without losing potency. Hallucinogenic mushrooms sold on the street are often nonpsychoactive mushrooms that have been adulterated with LSD or phencyclidine (PCP).[9] Because of the variation in mushroom size and concentration of psychoactive compounds, there is little correlation between the number of mushrooms ingested and the hallucinogenic effects. A user may ingest as few as five or as many as 100 mushrooms for a single "dose," but the typical recreational dose is 10 to 50 milligrams, which corresponds to 20 to 30 grams of fresh mushrooms or 1 to 2 grams of dried mushroom powder.

Hallucinogenic effects begin within 30 minutes of ingestion and last 4 to 6 hours.[25,26] The hallucinogenic effects are similar to, although less powerful than, those produced by LSD. Other common effects include mydriasis, tachycardia, nausea, and vomiting. Serious medical complications are extremely rare but include seizures, hyperthermia, rhabdomyolysis, and renal failure.[27] Mistaken identity and ingestion of highly toxic mushrooms are possible and can lead to serious outcomes.[28]

Management is supportive. There is no routinely available screening test for psilocybin or psilocin in the urine. If the patient's symptoms are not consistent with psilocybin ingestion, consider the possibility that a toxic mushroom (see Chapter 220, "Mushroom Poisoning") or other psychoactive substances were ingested.[28]

MESCALINE AND PEYOTE

Mescaline is found in many cacti, most notably the Mexican Peyote cactus (*Lophophora williamsii*) and the Peruvian San Pedro cactus

(*Trichocereus pachanoi*). Peyote is used in Native American religious ceremonies, and its legal use is restricted to the Native American Church. Mescaline is a phenylethylamine, structurally related to amphetamines, making it chemically distinct from LSD.[29] Mescaline is believed to act as a serotonin type 2 receptor agonist but is much less potent than LSD.

Peyote is most commonly sold as raw cactus or "buttons," 2- to 3-cm disks sliced off of the top of the cactus. Each button contains approximately 45 milligrams of mescaline. A typical hallucinogenic dose is 200 to 500 milligrams. Pills or capsules sold on the street as "mescaline" are unlikely to be genuine and may instead contain LSD or PCP.[9] Peyote exposures reported to poison control centers are relatively rare compared with other drugs of abuse. In 2007, for example, only 116 peyote or mescaline exposures were reported out of more than 2.4 million total drug exposures.[30]

Peyote is bitter tasting and within an hour of ingestion causes uncomfortable physical side effects—nausea, vomiting, abdominal discomfort, diaphoresis, dizziness, nystagmus, ataxia, and headache—that generally resolve after about 2 hours. Adrenergic stimulation causes mydriasis and mild elevations in pulse, blood pressure, and temperature. Hallucinogenic effects begin several hours after ingestion and persist for 6 to 12 hours. Significant morbidity or mortality caused by the physiologic effects of mescaline has not been observed, but death can result from aberrant behavior while under the influence of the drug.[31] Mescaline-intoxicated patients are managed supportively. Routine urine drug screens do not detect mescaline.

HALLUCINOGENIC AMPHETAMINES

More than 50 "designer" amphetamines have been created for their hallucinogenic properties. Very briefly, many amphetamine analogs share a phenylethylamine backbone. Phenylethylamines are chemical structures with an ethyl group that has an aromatic group and a terminal amine. Additions and substitutions of select groups occur to modify the pharmacologic properties and can help to predict toxicity from these substitutions. Best known is 3,4-**methylenedioxymethamphetamine (MDMA)**, a synthetic phenylethylamine derivative structurally related to both amphetamines and mescaline and commonly known by the street names "**ecstasy,**" "E", "Adam," "XTC," "Molly," and "MDM." Other amphetamines similar to MDMA include 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA or "Eve") and methylenedioxyamphetamine (MDA or "love drug"). MDMA is known for both its psychedelic properties and unique effects on mood and intimacy, which have led to its reputation as a "love drug" popular in dance clubs.[32] MDMA has complex effects, interacting with dopamine, norepinephrine, acetylcholine, and β_2-adrenergic and serotonin type 2A receptors and affecting the release of several hormones, including prolactin, oxytocin, adrenocorticotrophic hormone, dehydroepiandrosterone, and antidiuretic hormone.[33]

MDMA is usually ingested as tablets in doses of 50 to 200 milligrams. The drug is colorless and tasteless—properties lending to its use as a date-rape drug.[34] Symptoms occur within 30 minutes of ingestion and last about 4 to 6 hours. These include feelings of euphoria, inner peace, enhanced sociability, verbosity, and heightened sexual interest. The drug rarely causes actual hallucinations but can produce sensory effects such as alterations in the intensity of colors or sensation of textures. Other common effects include mydriasis, tachycardia, elevated blood pressure, nausea, jaw tension, bruxism, dry mouth, muscle aches, and ataxia. Current urinary amphetamine immunoassays incorporate a specific monoclonal antibody for MDMA and should routinely detect this drug.

MDMA and related amphetamines can produce serious complications and death.[35-38] As with other amphetamines, large-quantity overdoses can cause severe hypertension, intracranial hemorrhage, and ischemia in the heart or brain.[35] Fatal arrhythmias and sudden cardiac death have been reported, even in the absence of underlying heart disease.[35,36] The most frequently cited causes of death are hyperthermia and hyponatremia.[39-42] A syndrome of MDMA toxicity manifested by hyperthermia, seizures, disseminated intravascular coagulation, rhabdomyolysis, and hepatotoxicity has been described.[43] This pattern shares many features of the serotonin syndrome, and **combining MDMA with selective serotonin reuptake inhibitors (see Chapter 178, "Atypical and Serotonergic Antidepressants") or monoamine oxidase inhibitors (see Chapter 179, "Monoamine Oxidase Inhibitors") can precipitate serotonin syndrome**.[44] A purified or crystallized form of MDMA, known as Molly, is typically sold as a powder and is often taken orally. It is often viewed as a "safer form" of MDMA due to lack of adulterants, but it has been associated with adverse effects.[45]

Hyponatremia is predominantly due to excessive water consumption and inappropriate antidiuretic hormone secretion.[39,40] Excessive water drinking from thirst can occur if the drug is taken at hot and crowded club venues, with vigorous dancing and profuse sweating.[39,41] Chronic MDMA use results in permanent damage to serotonergic neurons.[46] Neuropsychiatric studies of habitual users demonstrate long-lasting cognitive impairment and mood dysfunction, including memory impairment, diminished learning ability, and depression.[47]

GI decontamination with activated charcoal may be useful if the drug was ingested within 60 minutes of ED arrival.[48] Weigh benefits of charcoal against risk of vomiting and aspiration. Hypertension and tachycardia often respond to benzodiazepines. Severe hypertension is treated with IV phentolamine or nitroprusside. Rapid IV titration with high doses of benzodiazepines or propofol may be required to control symptoms in patients with refractory agitation or seizures. Arrhythmias are managed with standard therapy.

Check serum electrolyte concentrations and anticipate and treat abnormalities, especially hyponatremia (see Chapter 17, "Fluids and Electrolytes"). Hyperthermia is managed with cooling measures and fluid resuscitation.[40,41] Patients with temperatures exceeding 40°C (104°F) have increased morbidity and mortality, so rapid cooling is important.[49] Due to the lack of supportive evidence from controlled studies and the potential harms of administration of dantrolene, including significant respiratory muscle weakness, expert opinion no longer supports use of dantrolene in amphetamine-induced hyperthermia.[14] Cyproheptadine has been suggested for treatment of the serotonin syndrome.[50] See Chapter 178, "Atypical and Serotonergic Antidepressants," for further discussion of serotonin syndrome.

SYNTHETIC CATHINONE DERIVATIVES: "BATH SALTS"

The abuse of cathinone is not new, as the young leaves and shoots of *Catha edulis* (khat) have been consumed for centuries in areas of Africa and the Arabian Peninsula in order to achieve stimulant effects. The use of synthetic cathinones, particularly in Europe and the United Kingdom, however, gained popularity in the late 2000s. Calls to U.S. poison control centers peaked in 2012, and use has slightly declined in the subsequent years, but this ingestant remains a public health concern, especially among "club-goers" and young adults.[51] Although cathinones were banned, manufacturers have frequently introduced new analogs; it has been estimated that nearly 250 such novel analogs are produced each year.[52] Cathinone and synthetic derivatives, including mephedrone, methylenedioxypyrovalerone, and methylone, are chemically similar to amphetamines. The synthetic cathinones differ structurally from other amphetamines by the addition of a ketone at the β position; this decreases penetration of the blood–brain barrier due to increased polarity. These drugs likely stimulate the release and inhibit the uptake of biogenic amines such as norepinephrine, dopamine, and serotonin.

Synthetic cathinone derivatives are abused by individuals seeking a "legal" high with stimulatory effects similar to those of cocaine or methylenedioxymethamphetamine. To avoid legal complications, synthetic cathinones are described as "not for human consumption" and are often intentionally mislabeled as "**bath salts,**" "**plant fertilizer,**" "**research chemicals,**" or "**plant food**." These drugs are given glamorous trade names such as "Bliss," "Ivory Wave," "Blue Silk," or "Vanilla Sky" and sell for approximately $25 to $35 per 500-milligram package.

Synthetic cathinones are most commonly insufflated ("snorted"), ingested, or inhaled, and less commonly injected or absorbed. Duration of effects depends on method of use—1 to 2 hours with nasal insufflation and up to 4 hours if ingested.[53] Users seek the subjective effects of increased alertness, openness, empathy, and libido. However, the adverse clinical effects can be very dangerous and are most commonly cardiac, psychiatric, and neurologic in origin. Due to the similarity to amphetamines, patients may exhibit a sympathomimetic toxidrome including agitation, psychosis, tachycardia, hypertension, and seizures.

Hyperthermia and hyponatremia may also be present. Other reported symptoms include sweating, nausea, headache, chest pain, palpitations, tremor, memory loss, and suicidal ideation. Repeated use in some can lead to the development of "excited delirium," a syndrome with symptoms of extreme agitation and violent behavior, which can rarely lead to cardiac arrest.[54] Synthetic cathinones are not detected on routine urine toxicology screens.

Treatment is primarily supportive and includes cardiovascular monitoring as well as the general approach outlined earlier. Admission to a monitored or intensive care unit setting is appropriate for patients with severe and persistent symptoms.

In September 2011, the U.S. Drug Enforcement Administration issued an emergency order to place three synthetic cathinones (mephedrone, methylenedioxypyrovalerone, and methylone) temporarily into Schedule I under the Controlled Substances Act. This rendered illegal the manufacture, sale, or possession of these agents; this administrative action subsequently became law. In subsequent years, additional synthetic cathinones have been similarly assigned Schedule I status.

PHENCYCLIDINE

PCP is a synthetic piperidine derivative that is structurally related to ketamine. PCP does not fit easily into a single classification, as the drug combines features of hallucinogens, depressants, and stimulants.[55] Unlike classic hallucinogens, PCP causes a clouding of the sensorium rather than heightened sensory awareness. The primary pharmacologic action is blockade of *N*-methyl-D-aspartate receptor channels. At high concentrations, PCP also interacts with other receptors and channels, including the opioid and acetylcholine receptors and voltage-gated electrolyte channels. PCP exhibits sympathomimetic effects by blocking reuptake of norepinephrine and dopamine.

PCP is easily and inexpensively synthesized. Powdered ("**angel dust**") or liquid ("**dippers**") drug is often combined with tobacco, marijuana, or other leafy materials and is usually smoked. PCP can also be ingested orally, snorted, or intravenously injected.[56] PCP may be unknowingly ingested, due to its being sold as another drug or used as an adulterant in another illicit drug product.[24] The onset of action depends on the mode of administration. With smoking, a rapid initial peak in plasma concentrations occurs in 5 minutes, with a second peak (likely due to absorption from the lungs) at about 20 minutes; effects generally last 4 to 6 hours. With large doses, effects can persist for days due to the drug's lipid solubility and accumulation in fat stores.[57,58]

Patients may experience CNS stimulation or depression, with clinical presentations ranging from physical violence to catatonic or comatose states.[56,59] A combination of cholinergic, anticholinergic, and sympathomimetic effects causes a confusing clinical toxidrome. PCP is often coadministered with other drugs such as crack cocaine ("**beam me up**"), marijuana ("**crystal supergrass**"), or ethanol, which also complicates the clinical picture.[57] The most common findings in PCP-intoxicated patients are altered mental status, hallucinations, multidirectional nystagmus, retrograde amnesia, hypertension (generally mild), and agitation.[57] Feelings of detachment (dissociation) from the environment and self may give the user feelings of strength, power, and invulnerability. Violent actions, agitation, bizarre and unpredictable behavior, and hallucinations or delusions are frequent. Diaphoresis, tachycardia, muscle rigidity, dystonic reactions, ataxia, and a decreased response to painful stimuli can occur. About 10% of patients are described as comatose.[58] Pupil size is variable; it is noteworthy that widely dilated pupils (which may be expected due to sympathomimesis) are uncommon with PCP toxicity.[57]

Medical complications from PCP toxicity are frequent.[55,59,60] Seizures occur in about 3% of patients, and up to 70% of cases exhibit rhabdomyolysis (occasionally producing acute renal failure).[58] Hypoglycemia, hypertension causing intracerebral hemorrhage, hyperthermia causing hepatic necrosis, and multiorgan failure can occur.[57,58,60,61] Violent behavior can result in self-injury.

Evaluate patients with suspected PCP toxicity for occult injury, hypoglycemia, and rhabdomyolysis.[55,56,59] PCP can be detected by commercially available urine drug screens up to 8 days after single use and up to several weeks after long-term use.[62] Cough and cold medications (dextromethorphan, diphenhydramine, and doxylamine), analgesics (ibuprofen, meperidine, and tramadol), and psychotropics (imipramine, mesoridazine, thioridazine, and venlafaxine) cross-react with the drug screen and produce false-positive results.

Sedation and physical restraints are frequently required to control violent and aggressive behavior. Parenteral benzodiazepines are preferable to physical restraints because fighting against restraints may contribute to rhabdomyolysis. Treatment is generally supportive and follows the general outline provided earlier. Patients exhibiting only minor clinical features of PCP intoxication and no medical complications can be discharged when behavior normalizes.[55,56,58,59] In a case series of 184 patients, 84% went home, 8% were admitted, and the rest were transferred to a crisis center.

MARIJUANA OR CANNABIS

Marijuana or cannabis consists of the dried leaves and flowers of the hemp plant *Cannabis sativa*. **Hashish** is prepared from the dried resin from the flower tops of this plant. The psychoactive ingredient in marijuana is tetrahydrocannabinol (THC).[63]

Marijuana is most often smoked[64] but can also be ingested. Symptoms persist for 2 to 4 hours after smoking, or longer if ingested. Clinical effects include drowsiness, euphoria, heightened sensory awareness, paranoia, and distortions of time and space. Hallucinations do not usually occur at usual doses. Common physiologic effects of marijuana are mild tachycardia, injected conjunctiva, bronchodilation, orthostatic hypotension, and impaired motor coordination.[65] Medical complications, which are rare, include panic reactions, brief toxic psychoses, pneumomediastinum, and pneumothorax. Reporting of acute cardiac events associated with marijuana use[66,67] is possibly the result of aging in the population of marijuana users and the increasing availability of medical marijuana. As of November 2017, 29 U.S. states, the District of Columbia, Puerto Rico, and Guam have authorized the medical use of marijuana, and as of January 2019, nine states and the District of Columbia have authorized its recreational use. Early studies in locations that have legalized marijuana have demonstrated increases in hospital admissions, ED visits, and calls to poison centers.[68] An unintentional and concerning consequence in states that have adopted legalization has also been a significant increase in the number of pediatric exposures and ingestions.[69]

Marijuana is used for treatment of medical conditions such as glaucoma and chemotherapy-related nausea and to promote weight gain in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. Chronic cannabis use is associated with psychiatric, respiratory, cardiovascular, and bone effects.[70] Cyclic vomiting syndrome, also called cannabinoid hyperemesis syndrome, is increasingly recognized as an entity associated with cannabinoid overuse; it is characterized by cyclical vomiting, diffuse abdominal pain, and relief with hot showers.[71-73] Symptoms are often misdiagnosed as gastroparesis or opiate withdrawal, and patients often undergo extensive laboratory testing and advanced imaging. Expert consensus recommends that treatment should focus on education on the need for cannabis cessation. Capsaicin as a topical preparation is reasonable as a first-line treatment.[74] Antipsychotics, including haloperidol and olanzapine, have been found to provide symptom relief in limited case studies.[75]

Acute psychiatric symptoms due to marijuana use can generally be managed with reassurance alone, but benzodiazepines can be used for severe symptoms. Standard urine drug screens are unreliable indicators of acute marijuana intoxication. High lipid solubility results in extensive deposition within body fat and slow excretion in the urine. After a single use, THC is detected by commercially available urine screens for up to 3 days. With long-term use, cannabinoids can be detected up to a month or longer after abstinence.[76] False-positive urine cannabinoid screening can occur due to use of ibuprofen, naproxen, pantoprazole, or efavirenz (a nonnucleoside reverse transcriptase inhibitor used to treat human immunodeficiency virus infection).

SYNTHETIC CANNABINOIDS

Around the world, there has been a dramatic increase in the demand, availability, and abuse of novel psychoactive drugs. This class includes synthetic cannabinoids, cathinone, and piperazine. Unlike THC,

synthetic cannabinoids (variably known as "K2," "spice," or "fake marijuana") are extremely potent. These synthetic agents are full agonists of the cannabinoid receptors, and as compared to THC, they cause more severe physiologic and psychological effects. One of the first synthetic cannabinoids, (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone, goes by the term JWH-018 for the initials of J.W. Huffman, who developed this compound to investigate drug–receptor interactions.[77]

After being produced in the laboratory, synthetic cannabinoids are dissolved in a solvent and then sprayed on an assortment of dried plant leaves (often with other preservatives and additives such as synthetic opioids and caffeine).[78] They are sold in shops and on the Internet and labeled as "incense" and "not for human consumption." The appeal of such products is driven by the desire for a legal "high" that is not detectable by current urine drug assays.

The product is usually rolled in paper and smoked in a manner similar to marijuana. Effects begin within minutes and may last for several hours, generally disappearing within 4 hours.[79] Most users will not seek or require medical attention, but some have experienced adverse reactions, with anxiety and tachycardia being the most common.[80] Other reported adverse effects include hypertension, diaphoresis, tremulousness, and agitation.[80,81] In 2018, there was an outbreak of unexplained and severe (including fatal) bleeding that was postulated to be due to contamination of synthetic cannabinoids with brodifacoum (a vitamin K antagonist).

In severe cases, patients may present in a semi-catatonic state and can be at risk for bradycardia, hypotension, renal failure, or secondary trauma.[82] Synthetic cannabinoids can precipitate psychosis in patients with prior mental illness.[83] Symptoms are usually self-limited and short lived, and treatment is supportive. Tachycardia, agitation, and anxiety can be treated with benzodiazepines titrated to effect. Patients with severe psychosis may be treated with antipsychotics if deemed necessary. Patients with severe and persistent symptoms may require admission, but the vast majority can be discharged once they are awake and have normal vital signs.

In 2012, the enactment of the Synthetic Drug Abuse Prevention Act permanently placed 26 types of synthetic cannabinoids and stimulants into Schedule I (most restrictive) of the Controlled Substances Act. However, effective regulation is difficult because new products (with unpredictable chemical formulas) are rapidly proliferating.

DESIGNER ALKALOIDS

Bromo-benzodifuranyl-isopropylamine, or **Bromo-DragonFLY**, is another phenylethylamine analog.[84] Bromo-DragonFLY stimulates serotonin receptors in the brain, similar to LSD. Bromo-DragonFLY was developed as a research chemical to study the relationship between molecular structure and psychedelic activity. The name comes from its chemical structure—two furanyl rings with double bonds and a side amphetamine arm—which gives it the appearance of a dragonfly. In 2005, Bromo-DragonFLY became available in human experimental markets and was soon diverted to hallucinogenic use.

Bromo-DragonFLY is sold as a white to pink powder that can be snorted, smoked, or injected. Bromo-DragonFLY may also be sold on blotter paper, similar to LSD, which has led to confusion in users seeking LSD and mistakenly consuming Bromo-DragonFLY instead. Bromo-DragonFly is often used in combination with other drugs in an effort to enhance or prolong effects. The hallucinogenic dose of Bromo-DragonFLY ranges from 200 to 800 micrograms, with the onset of action within 20 to 90 minutes and a typical duration of hallucinogenic effects up to 10 to 14 hours. However, accounts of experiences lasting 2 to 3 days after consumption of a single dose have been reported.[85] Toxicity includes agitation, hallucinations, and tonic-clonic seizures that may be delayed in onset.[86] Bromo-DragonFLY acts as a long-acting vasoconstrictor that can cause necrosis and gangrene several weeks after use. Bromo-DragonFLY has been associated with fatalities in several countries.[87] Two similar compounds, 2C-B-FLY and 3C-B-FLY, are also abused as hallucinogens.

Benzylpiperazine and trifluoromethylphenylpiperazine are synthetic phenylpiperazine analogs used as substitutes for amphetamine-derived designer drugs.[79,88] These two compounds are usually combined and sold as "**Legal X**" in attempt to mimic the effects of MDMA. These drugs are legally available in many countries. Clinical findings include sympathomimetic effects such as palpitations, agitation, anxiety, confusion, dizziness, headache, tremor, mydriasis, insomnia, urinary retention, vomiting, and seizures.[79,89]

Across Europe and the United States, Bromo-DragonFLY has been associated with deaths and delayed complications due to severe peripheral vasoconstriction and limb ischemia. Such complications are likely due to the agent's potent serotonergic properties.[85]

LESS COMMONLY ABUSED HALLUCINOGENS

Other drugs with hallucinogenic properties (**Table 188-2**) are enjoying increasing popularity due to Internet promotion of these "natural" psychoactive agents.[79,90]

TABLE 188-2 Less Commonly Abused Hallucinogens

Hallucinogen	Typical Route of Use	Onset of Action	Duration of Action	Additional Features of Acute Toxicity
Salvia divinorum: salvinorin A	Smoking of dried leaves Chewed leaves held in sublingual (SL) or buccal location	20–60 s (smoking) 10–20 min (SL or buccal)	20–30 min (smoking) 30–90 min (SL or buccal)	Headache
Toad venom or eggs: bufotoxins	Ingestion of toad venom extract or food made with toad eggs	30–60 min (nausea and vomiting)	1–3 d (untreated)	Abdominal pain, vomiting Sympathomimetic effects Features similar to cardiac glycoside toxicity
Ipomoea species (morning glory): lysergic acid amide	Ingestion of seeds	1–2 h	6–10 h	None
Nutmeg: myristicin	Ingestion of seeds or ground spice	3–6 h	6–24 h	Some features resemble anticholinergic toxicity
Datura species (Jimson weed and angel's trumpet): scopolamine, atropine, and hyoscyamine	Ingestion of seeds Smoking dried plant parts	1–3 h (ingestion) 5 min (smoking)	24–48 h	Anticholinergic effects
Ketamine	Snorting dried powder or smoking of powder admixed with marijuana or tobacco	5–15 min (nasal insufflation) 1–3 min (smoking)	45–60 min (nasal insufflation) 30–45 min (smoking)	Sympathomimetic effects
Dextromethorphan	Ingestion of liquid Nasal insufflation of powder	20–60 min (ingestion)	4–6 h (ingestion)	Nausea, vomiting, and diarrhea

SALVIA

Salvia divinorum ("**salvia**," "**Sally**," "**magic mint**") is a perennial herb in the mint family.[91] Salvia is sold as seeds, plant cuttings, whole plants, fresh and dried leaves, and liquid extracts purported to contain the active ingredient salvinorin A. Although salvia and salvinorin A are not currently regulated under the U.S. Controlled Substances Act, a number of states have placed controls on the plant and extract. When chewed, the leaf mass and juice are retained within the mouth, and absorption of the active ingredient is rapid, causing clinical effects within 5 to 10 minutes. Dried leaves, as well as extract-enhanced leaves, can be smoked. Smoking pure salvinorin A at a dose of 200 to 500 micrograms results in effects that begin within 30 seconds and last up to 30 minutes. Desired effects include perceptions of bright lights, vivid colors and shapes, body movements, and object distortions.[79,92,93] Adverse effects may include dysphoria, incoordination, dizziness, and slurred speech.[94] Treatment is supportive.

BUFOTOXINS

Bufotoxins (bufotenine and 5-methoxy-dimethyltryptamine) are hallucinogenic tryptamines found in the venom, skin, and eggs of many toads (e.g., *Bufo alvarius*, *Bufo marinus*).[95] Toad venom has also been used as an aphrodisiac ("**love stone**" or "**rock hard**") and in some traditional Chinese medicines (*chan su* and *kyushin*). Venom can be obtained by "milking" the toad's parotid glands and drying the liquid venom to form an extract. 5-Methoxy-dimethyltryptamine is a powerful psychedelic, whereas bufotenine has weaker effects. In addition to psychoactive substances, the venom contains cardioactive steroids (bufagins or bufadienolides), catecholamines (epinephrine and norepinephrine), and noncardiac sterols (e.g., cholesterol). Bufagins are **cardioactive steroids** that can cause cardiac toxicity similar to digoxin.[96] Toxicity from toad venom varies considerably depending on the toad species and its geographic location.

Symptoms of toad venom poisoning occur almost immediately. Effects may be restricted to local GI irritation, with copious salivation, nausea, vomiting, and abdominal discomfort persisting for hours. Systemic toxicity may develop due to sympathomimetic effects. Cardiac toxicity is similar to acute digoxin poisoning, with hyperkalemia, bradycardia, atrioventricular conduction block, ventricular tachycardia, ventricular fibrillation, and cardiac arrest.[97,98]

Serum digoxin immunoassay often yields a positive result. Bradyarrhythmias are initially treated with atropine and may require pacemaker placement. Antiarrhythmic drugs should be used for ventricular arrhythmias. Digoxin-specific Fab antibody treatment has been effective in animal models and human cases.[99,100]

MORNING GLORY SEEDS AND *IPOMOEA* SPECIES

Morning glory seeds (*Ipomoea violacea*, *Ipomoea tricolor*, and others) contain lysergic acid amide (ergine), a compound closely related to LSD. The seeds can be ingested for their hallucinogenic effects; typically, several hundred seeds are ingested as one "dose." Physical and psychological manifestations closely resemble the effects of LSD, and patients are managed similarly.

MYRISTICIN

Nutmeg is the dried seed from the tropical *Myristica fragrans* tree. Accidental or intentional ingestion of large amounts of nutmeg can cause delirium with hallucinations.[101] Misuse of nutmeg is more commonly encountered among college students, adolescents, and prisoners, often when ethanol or other recreational drugs are not available.[102] The hallucinogenic properties of nutmeg may be due to the component myristicin, but the mechanism is not well understood. Ingestion of one to three nutmeg seeds (or 5 to 15 grams of the ground spice) produces psychological effects that begin 3 to 6 hours later and last for 6 to 24 hours. Symptoms include tachycardia, flushing, dry mouth, nausea, and abdominal pain. Signs and symptoms may resemble anticholinergic poisoning, but pupils are usually small or midsized. Management is supportive care.

DATURA SPECIES

Jimson weed (*Datura stramonium*) and **angel's trumpet** (*Datura candida*) are plants that originated in the United States and Mexico but have spread worldwide throughout areas with warm and temperate climates. All *Datura* species contain the anticholinergic alkaloids atropine, scopolamine, and hyoscyamine. Seeds or other parts of the plant can be ingested or smoked and produce delirium, hallucinations, and seizures along with other classic anticholinergic effects, such as mydriasis, tachycardia, dry mouth and skin, blurred vision, urinary retention, and hyperthermia (see Chapter 202, "Anticholinergics").[103,104] Gastric emptying is often delayed, and the small, plentiful seeds can become trapped among the GI folds after ingestion; thus, **GI decontamination can be considered in select cases.** Whole-bowel irrigation is recommended for patients who have ingested a large number of seeds. Medications with anticholinergic properties, such as phenothiazines, should be avoided. Physostigmine, a reversible acetylcholinesterase antagonist, is a potential treatment for severe anticholinergic poisoning.[104] For further discussion, see Chapter 202, "Anticholinergics."

KETAMINE AND DEXTROMETHORPHAN

Ketamine and dextromethorphan are chemically related to PCP. Ketamine and PCP are described as dissociative drugs because they distort perceptions of sight and sound and produce feelings of detachment from the environment and self.[56,105] Ketamine, known by the street names "**vitamin K**" and "**special K**," can be abused by SC or IM injection, nasal insufflation of the dried powder, or smoking of the dried power admixed with marijuana or tobacco.[106] Ketamine abusers may come to the ED because of anxiety, palpitations, and chest pain.[107] Ketamine is thought to be psychologically addictive. Chronic abuse can cause GI toxicity including epigastric pain, hepatic dysfunction, and impaired gallbladder activity; urinary tract effects include ketamine cystitis.[108]

Dextromethorphan, available in over-the-counter cough suppressants, has become popular among adolescents.[109,110] A large quantity must be ingested for the user to experience hallucinogenic effects. Abuse among youths has prompted many states to enact restrictions regarding the buyer age and the maximum amount that can be purchased; most retailers and pharmacists keep dextromethorphan-containing cough medicines behind the counter. Since dextromethorphan-containing symptomatic relief products often contain other ingredients (e.g., antihistamines, acetaminophen), investigate for toxic amounts of a co-ingestant in any patient who has ingested hallucinogenic doses of dextromethorphan. Medical care is primarily supportive with treatment as outlined earlier in the general approach section.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 189

Salicylates

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INTRODUCTION

The widespread availability of aspirin or acetylsalicylic acid in prescription and over-the-counter preparations can lead to both accidental and intentional toxicity. Morbidity and mortality increase significantly when the condition is not rapidly identified, if there is a delay to starting treatment, or if poisoned patients are not treated aggressively.

In additional to aspirin oral preparations, numerous forms of salicylate are available as karyolitic agents, liniments, flavoring agents, and combination products. These products may contain salicylate, methyl salicylate, or acetylsalicylic acid, but regardless of the product, all formulations are rapidly converted to salicylate once ingested.[1] Five milliliters of oil of wintergreen contain 7 grams of aspirin and can be deadly to a toddler. Liniments and products used in hot vaporizers have high concentrations of methyl salicylate, and an ingestion of 5 to 10 mL can be lethal for an infant or a toddler.[2] Even though salicylate is poorly absorbed after ingestion of bismuth subsalicylate (Pepto-Bismol®), significant exposures can occur from massive ingestions, such as in patients with human immunodeficiency virus/acquired immunodeficiency syndrome taking this medication for chronic diarrhea.[3]

PATHOPHYSIOLOGY

After ingestion of therapeutic doses in standard tablet formulation, absorption is variable and dependent on dosage form, presence of food, and gastric pH, with peak salicylate levels usually occurring in 1 to 2 hours. In overdose, peak serum salicylate concentrations may not be reached for hours. Enteric-coated aspirin exhibits erratic absorption in therapeutic doses, and peak levels may also be delayed for hours after an overdose.[4] Salicylate itself impairs gastric emptying, which can result in delayed absorption.[5] There is potential for formation of gastric bezoars that can serve as a source of ongoing absorption.[6] Ingestion of methyl salicylate or other liquid formulations may have much more rapid absorption and achieve peak levels more rapidly. Limited information on powder forms of salicylates (common in the southeastern United States and the Middle East) suggests these forms follow the liquid salicylate pattern of low risk of prolonged absorption.[7]

After absorption, aspirin is hydrolyzed to salicylic acid (salicylate) and is distributed throughout body tissues, with 50% to 80% being bound to serum proteins. As salicylate concentrations increase and saturate protein-binding sites, free (unbound) concentrations of salicylate increase. In solution, salicylate exists in equilibrium between the ionized and nonionized state; only the unbound, nonionized salicylate can readily cross cell membranes. At physiologic pH (7.40), almost all salicylate is ionized, but acidemia will increase the nonionized fraction, enabling more salicylate to cross cell membranes and, importantly, substantially increase brain salicylate concentration.[8] Patients with identical total salicylate serum concentrations may vary greatly in their degree of toxicity depending on their tissue burden, plasma protein concentrations, pH, and other factors.

Salicylate undergoes hepatic metabolism in a process that rapidly becomes saturated even within the drug's therapeutic range. Thus, salicylate metabolism in the overdose situation follows zero-order kinetics (i.e., a set amount of salicylate is eliminated per unit of time).[9] Increased fraction of unbound salicylate also enhances renal clearance, making the kidney the major route of elimination during toxicity. Serum alkalinization can be used to keep salicylate in the plasma compartment and out of tissues, and urinary alkalinization can be used to enhance renal elimination. If the urine pH is above 7.5, more salicylate molecules in the urine will be ionized compared with the renal tubular cell pH of 7.4, and reabsorption across the urinary tubule will be reduced. This pH difference will also enhance secretion of nonionized salicylate down the concentration gradient.

Salicylate toxicity affects many physiologic systems (**Table 189-1**).

Salicylate directly stimulates the medullary respiratory center to produce tachypnea, hyperpnea, and respiratory alkalosis.[10] As toxicity worsens, inhibition of metabolism produces an acidosis that overwhelms the alkalosis. **Classically, the acid-base disturbance associated with salicylate poisoning is mixed: early respiratory alkalosis, followed by an elevated anion gap metabolic acidosis, and possibly late respiratory acidosis**. This respiratory alkalosis and metabolic acidosis are commonly mistaken for sepsis syndromes. Co-ingestion or administration of CNS depressants may blunt this initial respiratory stimulation. Salicylate stimulates skeletal muscle metabolism, which causes an increase in oxygen consumption and carbon dioxide production. Neurologic toxicity may impair ventilation so that it is unable to keep pace with increased carbon dioxide production, leading to respiratory acidosis—usually a late and ominous finding. Decreased ventilation can also be related to co-ingestions or iatrogenic medication.

TABLE 189-1 Pathophysiology of Salicylate Toxicity

- Local gastric irritation
- Reversible ototoxicity
- Stimulation of the chemoreceptor zone
- Stimulation of medullary respiratory center
- Stimulation of skeletal muscle metabolism
- Uncoupling of oxidative phosphorylation
- Enhancement of lipolysis
- Inhibition of Krebs cycle
- Increased vascular permeability
- Mobilization of glycogen stores
- Inhibition of gluconeogenesis

Salicylate affects both central and peripheral glucose homeostasis. Although salicylate causes mobilization of glycogen stores, resulting in hyperglycemia, it is also a potent inhibitor of gluconeogenesis. Therefore, normoglycemia is the most common finding in toxicity; hyperglycemia can be seen occasionally, and hypoglycemia is a rare finding.[11,12]

Salicylate can cause corrosive injury of the GI tract with abdominal pain, nausea, and vomiting with occasional hematemesis. These GI manifestations can lead to volume loss, metabolic alkalosis, and hypokalemia. Gastric perforation has been reported after a significant acute aspirin ingestion.[13] Salicylate-induced acute lung injury (noncardiogenic pulmonary edema) has been observed in humans. Although antiplatelet activity is a well-known, often desired effect of aspirin (but not other salicylate products), hemorrhage is a rare complication of acute (even massive) overdose. Large doses of all salicylates may cause significant hypoprothrombinemia resulting from inhibition of vitamin K–dependent functions.[14]

Salicylate ototoxicity is common, and tinnitus often occurs with levels in the therapeutic range (20 milligrams/dL [1.5 mmol/L]). Although classically described as tinnitus or "ringing in the ears," in practice, most patients will describe decreased sounds or that their hearing is "muffled." The exact mechanism causing this is unknown, and hearing effects are not permanent.

Cardiac arrhythmias are a rare complication of salicylate poisoning.[15]

CLINICAL FEATURES

Clinical manifestations of salicylate toxicity depend on the dose ingested, duration of exposure, and age and comorbidities of the patient.[8,16] In children and the elderly, end-organ toxicity can be seen with smaller doses and lower serum levels following an acute overdose. Chronic toxicity can produce insidious and severe neurologic changes that do not correlate well with dose or serum salicylate level. Patients with even a mild toxicity can become critically and severely ill if acidemia or dehydration develops.

INTOXICATION IN CHILDREN

In general, when the duration of salicylate intoxication is between 12 and 24 hours, metabolic acidosis and acidemia (pH <7.35) occur primarily in children <4 years old, and nearly all children <1 year old have acidosis. Young children can have a respiratory alkalosis, but this is often transient and missed because of their smaller ventilatory reserves.[17] In older children (>4 years old), the acid-base disturbance is usually a mixed disturbance with respiratory alkalosis, increased anion gap metabolic acidosis, and alkalemia (pH >7.45).

Chronic or "therapeutic" (repeated dose) pediatric salicylate poisonings are more serious and are associated with a higher mortality than acute salicylism.[8,16,18] Often, several days may elapse between the initial salicylate administration and the onset of symptoms. There is frequently a concurrent illness that prompted salicylate administration, and children usually appear more ill than those with acute intoxication. The

presenting features are usually fever, hyperventilation, and altered mental status with volume depletion, acidosis, and severe hypokalemia.[16] Young children are prone to hyperpyrexia, which indicates a worse prognosis.[18] Renal failure may be a significant complication, but pulmonary edema is unusual in the pediatric population.[16,18] Chronic salicylism is often mistaken for an infectious process, and the resultant delay in diagnosis may account for the more severe clinical picture. The diagnosis can be particularly difficult due to the proscription against aspirin use for fever in children (Reye's syndrome risk). Aspirin may have been given by family members rather than by a physician.

The diagnosis may be delayed if a history of salicylate ingestion is not available. The differential diagnosis includes diabetic ketoacidosis, sepsis, iron intoxication, and toxic alcohol poisoning.

TABLE 189-2 Severity Grading of Salicylate Toxicity in Adults

	Mild	Moderate	Severe
Acute ingestion (dose)	<150 milligrams/kg	150–300 milligrams/kg	>300 milligrams/kg
End-organ toxicity	Tinnitus Hearing loss Dizziness Nausea/vomiting	Tachypnea Hyperpyrexia Diaphoresis Ataxia Anxiety	Abnormal mental status Seizures Acute lung injury Renal failure Cardiac arrhythmias Shock

INTOXICATION IN ADULTS

Acute salicylate intoxication in adults is often due to intentional ingestion. The typical clinical presentation includes nausea, vomiting, tinnitus, hearing loss, sweating, and hyperventilation. Patients with tinnitus or hearing loss following an acute ingestion usually have an elevated serum salicylate value.[19]

Most adult patients with acute salicylate overdose have a mixed acid-base disturbance of alkalemia with respiratory alkalosis and metabolic acidosis. As toxicity progresses, acidosis worsens. CNS dysfunction manifests as agitation, lethargy, confusion, seizure, or coma. CNS dysfunction leading to cerebral edema is an ominous development and a sign of severe toxicity, requiring rapid and aggressive treatment.[8,20] Despite treatment and decreasing serum salicylate levels, patients may worsen and die from progressive neurologic impairment, possibly because of increasing CNS salicylate levels.

Salicylate-induced vomiting can produce a metabolic alkalosis. Other rare complications of salicylate toxicity include rhabdomyolysis, gastric perforation, and GI hemorrhage. Poor prognostic factors for acute salicylate toxicity include coma, fever, respiratory acidosis, seizure, and cardiac dysrhythmias. In adults with acute salicylate poisoning, independent predictors of severe outcome were older age, tachypnea, and initial lactate concentration. Initial salicylate concentration alone was not predictive.

Chronic salicylate intoxication (from repeated excessive dosing) in adults often presents with neurologic abnormalities such as lethargy, altered mental status, irritability, and hallucinations, particularly in the elderly.[21] Toxicity can develop even with small increases in doses due to saturable kinetics. Clinical features of chronic intoxication include hyperventilation, tremor, papilledema, agitation, paranoia, bizarre behavior, memory deficits, confusion, and stupor. Nausea and vomiting are less common than in acute salicylate toxicity, whereas increased liver function tests and increased prothrombin time are more common. Neurologic abnormalities in chronic salicylate poisoning may be nonspecific and may often mislead physicians. Chronic salicylism should be considered in a patient with unexplained neurologic or behavioral dysfunction, especially in the presence of a mixed acid-base disturbance, tachypnea, dyspnea, or unexplained pulmonary edema.[22] Compared with acute toxicity, adults with chronic salicylate toxicity have a higher tissue burden of salicylate, leading to more significant toxicity at a lower serum concentration.

The distinction between acute and chronic salicylate toxicity may not always be clear. A patient may present many hours after an acute severe salicylate overdose, when altered mental status, acidosis, elevated prothrombin time, and a "therapeutic" serum salicylate concentration appear more consistent with a chronically poisoned patient. Significant toxicity may be evident despite declining or "therapeutic" serum salicylate concentrations. In these situations, the patient's clinical status is most important when assessing the severity of toxicity (**Table 189-2**).

Chronic salicylism may develop in patients taking carbonic anhydrase inhibitors for treatment of glaucoma. The normal anion gap (hyperchloremic) metabolic acidosis produced by carbonic anhydrase inhibitors increases the volume of distribution for salicylate and facilitates its entry into the CNS, causing toxicity at a "therapeutic" serum salicylate concentration.

The differential diagnosis of a triple-mixed acid-base disturbance of increased anion gap acidosis, metabolic alkalosis, and respiratory alkalosis seen in salicylate toxicity is limited. Salicylates uncouple oxidative phosphorylation, which results in abnormal cellular energy production, and patients become dependent on anaerobic metabolism, resulting in accumulation of lactate. Thus, a significant salicylate poisoning will lead to an elevated serum lactate concentration, further broadening the differential diagnosis.

In clinical practice or at early stages of toxicity, this classic three-part acid-base disturbance may be difficult to appreciate. The differential is broad and includes (but is not limited to) sepsis, diabetic ketoacidosis, renal and hepatic failure, alcoholic ketoacidosis, and poisoning by iron, theophylline, caffeine, methanol, or ethylene glycol.

DIAGNOSIS

Diagnosis of salicylate toxicity is made by correlating a careful history, physical examination, and thoughtful ancillary testing. Supportive laboratory findings include an anion gap metabolic acidosis and elevated serum salicylate levels. **The Done nomogram is misleading and can grossly underestimate toxicity; *it should not be used*.**

TOXICOLOGIC TESTING

A pitfall in treating salicylate toxicity is reliance on a single serum level.[23] Significant toxicity has been reported to develop even in cases in which salicylates were undetectable on an initial assay approximately 4 hours after ingestion.[24] Salicylate toxicity can evolve rapidly. In patients with moderate or severe poisoning, it is prudent to obtain serial serum salicylate concentrations approximately every 1 to 2 hours, until the concentrations are declining and the patient's clinical status stabilizes.[25,26] Enteric-coated or modified-release preparations are formulated to remain intact in the acidic gastric environment, dissolving in the alkaline intestinal fluids. Drug release is therefore primarily a function of gastric emptying, and peak levels may not be reached until up to 60 hours after ingestion in an overdose.[4]

Commercially available tests for serum salicylate concentration are very accurate; the only reported significant interference has been with diflunisal (a NSAID), which produces false-positive results for significantly high serum salicylate concentrations.[27] Therapeutic salicylate concentrations are 150 to 300 micrograms/mL (or 15 to 30 milligrams/dL [1086 to 2172 micromole/L]). A pitfall is that units for measuring salicylate are not universal; measurement units can vary by institution, with the potential for patients to be mistakenly diagnosed as "salicylate toxic" if the physician mistakenly assumes the unit of measurement used.

ADDITIONAL ANCILLARY TESTING

Essential laboratory tests include electrolytes, glucose, BUN, and creatinine. Blood gases, chest and abdominal radiograph, ECG, CBC, serum calcium level, and urinalysis with urine pH determination should be obtained as clinically indicated. As in any ingestion, consider testing for acetaminophen as well, especially considering the number of combination products available in the market. Some enteric-coated medications are radiopaque and may be visible on an abdominal radiograph.[28]

A normal anion gap does not exclude salicylate toxicity in patients with an unknown ingestion. Mixed ingestions that include aspirin and the timing of exposure can alter "classic" metabolic disturbances. A negative

anion gap metabolic acidosis may be noted in salicylate toxicity due to aberrant reading of salicylate ions as chloride ions by analyzer electrodes.[29]

TREATMENT

GENERAL MEASURES

Treatment priorities are (1) immediate resuscitation with stabilization of airway, breathing, and circulation; (2) correction of volume depletion and metabolic derangements; (3) GI decontamination; and (4) reduction in body salicylate burden.[25,26] Salicylate absorption is reduced by the administration of activated charcoal both for regular and modified-release formulations. A single dose of activated charcoal, 1 to 2 grams/kg, should be administered to appropriate patients who have ingested potentially toxic amounts of salicylate.[25,30,31] There are no convincing data to support the use of repeated or multiple doses of activated charcoal in salicylate overdose.[32]

Patients with severe salicylate intoxication are usually significantly volume depleted, have serious acid-base disturbances, and require aggressive IV volume and electrolyte replacement. Careful assessment of a patient's volume and electrolyte status is important, particularly in the elderly or in patients with a history of cardiac disease. Volume replacement is initially undertaken with normal saline or lactated Ringer's with administration of an initial bolus of 20 mL/kg. The average adult who presents several hours after ingestion is dehydrated by at least 4 to 6 L.

ALKALINIZATION

Systemic and urinary alkalinization are beneficial for salicylate toxicity, although the precise mechanism is debated.[26,33] As initial fluid resuscitation is undertaken, patients should undergo treatment with sodium bicarbonate with a goal of a serum pH of approximately 7.5. Hypokalemia is common, and potassium should be added to the infusion after adequate urine output has been established. Serum potassium should be maintained in the 4.0 to 4.5 mEq/L range.

Urinary salicylate clearance is directly proportional to urine flow rate, but, more importantly, it is logarithmically proportional to urine pH.[33] Urine alkalinization is more effective in enhancing salicylate elimination than forced diuresis. Urinary alkalinization also avoids the potential complication of fluid overload that is risked (particularly in those with marginal cardiac output or limited reserve) from the large IV volume given to increase urine flow. Urinary alkalinization should be considered as first-line treatment for patients with moderately severe salicylate poisoning.[25,34]

Hydration and alkalinization should be initiated simultaneously in patients with severe salicylate intoxication. A common approach is to volume restore patients with normal saline or lactated Ringer's to a target urine output of 1 to 2 mL/kg per hour. Concurrently, in a second IV line, an IV bolus of sodium bicarbonate (1 to 2 mEq/kg) is given followed by a continuous infusion (three ampules of either 44 or 50 mEq per ampule of sodium bicarbonate added to 1 L of 5% dextrose in water). Unless there is a contraindication, potassium should be added to the bicarbonate fluid as well. The infusion is run at two to three times maintenance and adjusted to maintain the urine pH >7.5 (**Figure 189-1**).

In moderate and severe overdoses, the patient's cardiopulmonary and neurologic status should be assessed frequently. Serum salicylate, urine pH, and electrolyte concentrations should be checked every 1 to 2 hours.[25,26] Once the serum salicylate concentration peaks and begins to decrease on serial measurement, repeat measurement can be obtained every 4 to 6 hours.

OTHER MEASURES

Patients with salicylate-induced acute lung injury (noncardiogenic pulmonary edema) should be managed the same as patients with acute lung

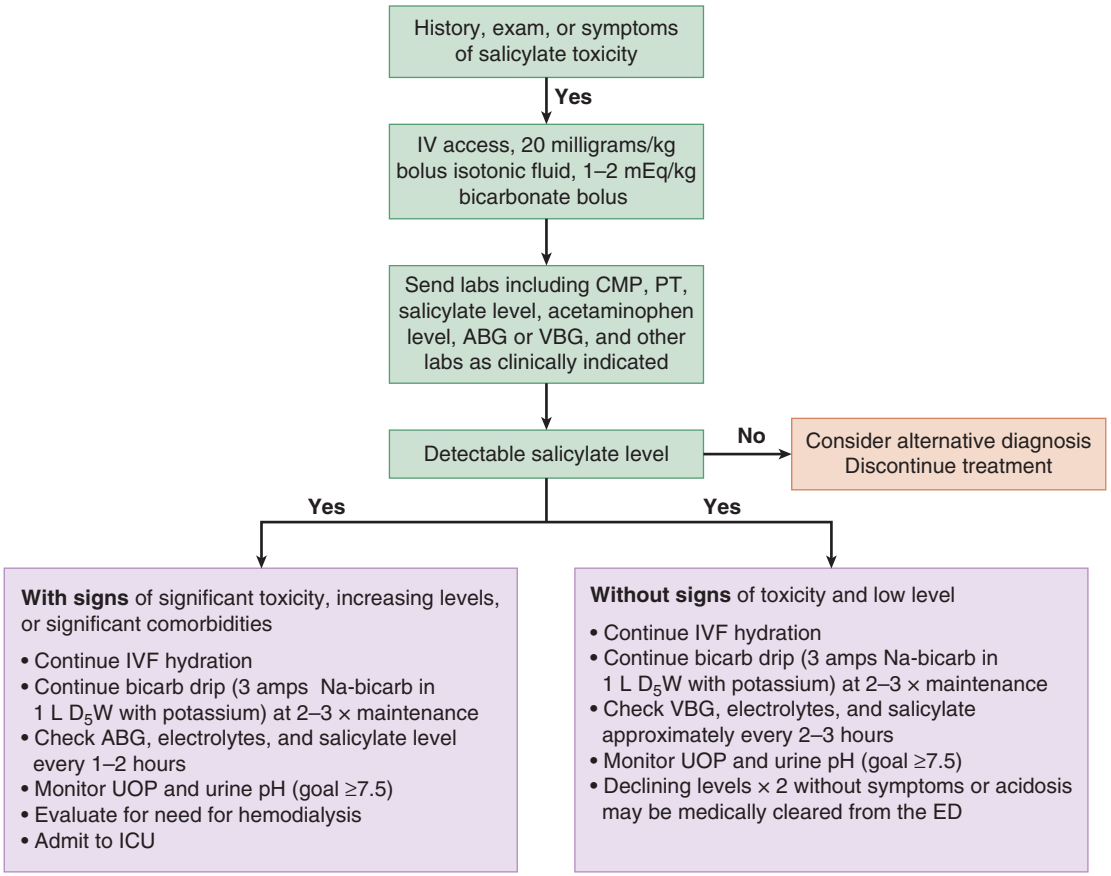

FIGURE 189-1. Management of salicylate poisoning. ABG = arterial blood gas; bicarb = bicarbonate; CMP = comprehensive metabolic panel; D_5W = 5% dextrose in water; ICU = intensive care unit; IVF = intravenous fluids; PT = prothrombin time; UOP = urinary output; VBG = venous blood gas.

injury from other causes. Pulmonary edema begins to improve concomitantly with the lowering of serum salicylate concentrations. Aggressive efforts toward rapid elimination by hemodialysis may be beneficial in this subset of patients. Hemodialysis enables removal of salicylate without the volume infusion that accompanies sodium bicarbonate administration; hemodialysis thus avoids the risk of volume-mediated aggravation of lung injury.[35]

When a patient with severe salicylate toxicity requires endotracheal intubation, mechanical ventilation, and sedation, it is important to maintain hyperventilation; ventilator settings should not be based on standard age- and weight-based nomograms. Before intubation and mechanical ventilation, most patients with severe salicylate toxicity have a respiratory alkalosis. Controlling the ventilatory rate and volume to "normal" ranges produces a decrease in serum pH and causes a rapid shift of salicylate into the CNS. It is important to maintain respiratory alkalosis during mechanical ventilation. Use the minimal amount of safe sedation that allows a patient to continue over-breathing the ventilator. Consider one to two ampules (88 to 100 mEq) of bicarbonate bolus immediately prior to intubation as a basic buffer for the transient decrease in ventilation that occurs during rapid-sequence induction intubation.

Hemorrhagic complications are rarely seen following single massive salicylate overdoses, but chronic administration of large doses may cause significant hypoprothrombinemia. Even in this circumstance, hemorrhage is rarely seen in clinical practice. When bleeding does occur, it rarely appears to be a contributing factor in mortality from salicylate toxicity. Patients with clinically significant bleeding should be treated with fresh frozen plasma. Observations in animals and humans indicate that administering large doses of vitamin K after the development of hypoprothrombinemia has little or no effect on the prothrombin time when serum salicylate concentration is high.

HEMODIALYSIS

Hemodialysis is considered the extracorporeal technique of choice for the treatment of serious salicylate toxicity because hemodialysis can correct acid-base and electrolyte abnormalities while rapidly reducing the body salicylate burden.[36,37] The inherent delays in implementing hemodialysis underline the importance of early consideration of this intervention; thoughtful planning and prompt consultation with the nephrology service are strongly advised. **Indications for hemodialysis include clinical deterioration or failure of improvement despite intensive supportive care, lack of success in alkalinizing serum and urine, renal insufficiency or failure, severe acid-base disturbance, altered mental status, and acute lung injury. Consider hemodialysis for salicylism requiring respiratory and ventilatory support.**[37]

Serum salicylate concentration should not be the sole determinant in the decision to initiate hemodialysis; however, patients with acute toxicity and serum salicylate concentrations >100 milligrams/dL (>7.2 mmol/L), patients with chronic toxicity with concentrations >60 milligrams/dL (>4.3 mmol/L), and symptomatic patients with lower serum salicylate concentrations should be considered candidates for hemodialysis. Consider the early use of hemodialysis in patients who are elderly, have chronically ingested aspirin, have altered mental status, have acidemia, or have comorbidities (e.g., coronary artery disease or chronic obstructive pulmonary disease).[23]

Emergency hemodialysis places a significant demand on the cardiovascular system, and hypotensive patients or those with underlying cardiac disease may not be able to tolerate the hemodynamic intensity of 4-hour hemodialysis treatments. A less demanding but more prolonged therapy, such as hemofiltration, hemodiafiltration, or sustained low-efficiency dialysis, may be used until hemodialysis can be tolerated. Once initiated, extracorporeal elimination techniques should be continued until the serum salicylate level is <20 milligrams/dL (<1.4 mmol/L).

DISPOSITION AND FOLLOW-UP

A patient may be discharged from the ED once it can be determined that the patient had an inconsequential salicylate overdose; this requires demonstration of serial declining salicylate levels. Patients who have overdosed on enteric-coated or modified-release preparations of aspirin should be treated regardless of initial serum salicylate concentrations and be observed for approximately 24 hours with serial serum salicylate measurements until a declining level is confirmed. Salsalate overdoses may warrant an even longer period of observation.[38] Although the determination of serial salicylate concentrations offers valuable information regarding the effectiveness of the treatment implemented, it is not a substitute for clinical evaluation of a patient, and management decisions should not be solely based on a particular serum salicylate concentration. Early consultation with a clinical toxicologist or the regional poison control center is recommended.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 190

Acetaminophen

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INTRODUCTION

Acetaminophen (*N*-acetyl-*p*-aminophenol or paracetamol) is the most popular over-the-counter analgesic and is one of the most common toxic exposures reported to poison centers. Acetaminophen (sometimes abbreviated APAP) is available as a sole agent or combined with a variety of other medications prepared in different forms, such as tablets, capsules, gels, and liquids. Although most serious poisonings involve intentional self-harm, poisonings often occur because of the erroneous belief that this medication is benign or because the victim was unaware that acetaminophen was an ingredient in the ingested preparation.[1,2] In the United States, acetaminophen is the most common cause of drug-induced liver failure and accounts for almost half of all cases of acute liver failure.[3,4] Acetaminophen–opioid combination products have been implicated in chronic overuse, likely due to an increasing opioid requirement leading to concomitantly increasing acetaminophen exposure.[5] In response to these safety concerns, in 2011, the U.S. Food and Drug Administration limited the prescription acetaminophen–opioid combination preparation strength to 325 milligrams per dosage unit and now requires a boxed warning to notify consumers of the potential risk for serious liver toxicity.[6]

PHARMACOLOGY

ORAL ACETAMINOPHEN

The recommended maximum total daily dose is 3900 milligrams in adults using 325-milligram acetaminophen (regular strength) and 3000 milligrams when using the 500-milligram acetaminophen (extra strength) preparation. Adults should not use acetaminophen for more than 10 consecutive days unless directed by their physician. **For children, the recommended acetaminophen dose is 10 to 15 milligrams/kg every 4 to 6 hours as needed, with a maximum daily dose of 75 milligrams/kg or five doses in a 24-hour period.**

Patients with insufficient glutathione stores (e.g., alcoholics and acquired immunodeficiency syndrome patients) and patients with induced cytochrome P450 (CYP450) enzymatic activity (e.g., alcoholics and those taking concurrent anticonvulsant or antituberculous medications) may be at greater risk for developing acetaminophen-induced hepatotoxicity following overdose (as opposed to therapeutic dosing described earlier). Despite the limited evidence, it may be prudent to reduce acetaminophen dosage and duration of therapy for

this population. In contrast, children, because of their greater ability to metabolize acetaminophen through hepatic sulfation, may be at decreased risk for developing hepatotoxicity following a moderate overdose.[7-9]

After ingestion of therapeutic doses, acetaminophen is rapidly absorbed from the GI tract, and peak serum concentrations are usually achieved within 30 minutes to 2 hours. Following an overdose, peak serum concentrations are usually achieved within 2 hours. Delayed absorption can occur especially after overdose of acetaminophen preparations combined with opioid or antimuscarinic medications, as well as those with altered-release kinetics such as extended-release preparations.[10-12] In therapeutic amounts, acetaminophen has nearly 100% bioavailability, is approximately 20% bound to serum proteins, has a volume of distribution around 0.85 L/kg, and has an elimination half-life of approximately 2.5 hours. The therapeutic concentration for the antipyretic effect of acetaminophen is between 10 and 20 micrograms/mL (66 to 132 micromole/L), but therapeutic concentrations for analgesia are not established. Oral acetaminophen appears to be nontoxic when administered following therapeutic dosing guidelines.

IV ACETAMINOPHEN

The recommended dosing of IV acetaminophen for adults or children weighing more than 50 kg is 650 milligrams every 4 hours or 1000 milligrams every 6 hours, with a maximum total daily dose of 4 grams. For adults or children weighing less than 50 kg, the recommended dosing is 12.5 milligrams/kg every 4 hours or 15 milligrams/kg every 6 hours (maximum individual dose of 750 milligrams), with a maximum total daily dose of 75 milligrams/kg or 3750 milligrams, whichever is less. Peak concentrations following IV administration occur at the end of the 15-minute infusion period.[13] Compared to a similar dose of oral acetaminophen, IV acetaminophen achieves a 70% greater maximum concentration but provides a similar total drug exposure.[13]

ACETAMINOPHEN METABOLISM

Acetaminophen metabolism after therapeutic ingestion is primarily by glucuronidation and sulfation (**Figure 190-1**).

In overdose, normal pathways for acetaminophen metabolism are saturated and a larger proportion is oxidized by the CYP450 system to

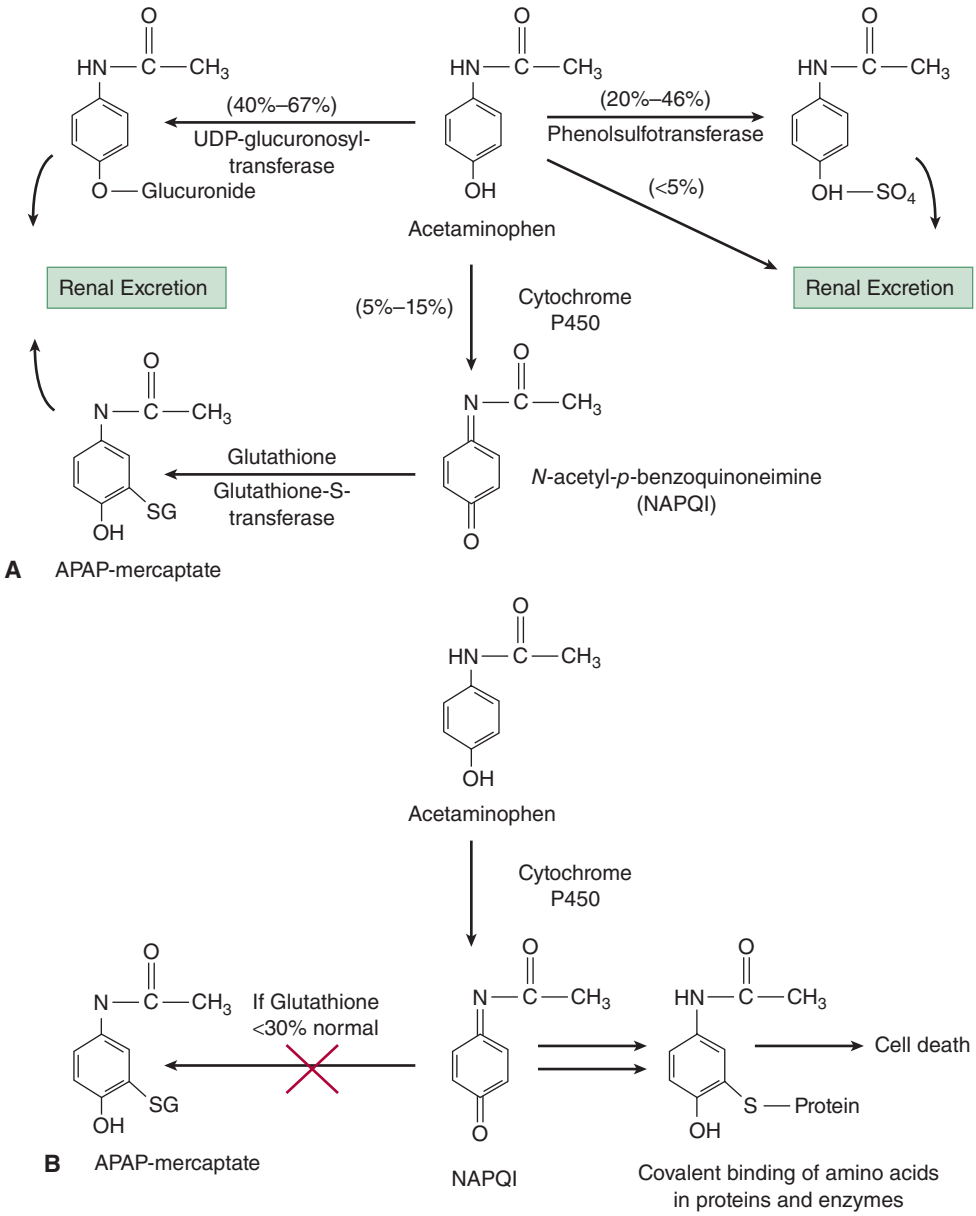

FIGURE 190-1. Acetaminophen metabolism. **A.** After ingestion of therapeutic amounts, predominant metabolism is via glucuronidation and sulfation. The small amount of *N*-acetyl-*p*-benzoquinoneimine (NAPQI) generated is conjugated with glutathione to a nontoxic compound. **B.** After ingestion of large amounts, glucuronidation and sulfation are saturated, and an increased amount of NAPQI is generated. Detoxification of NAPQI to a nontoxic compound soon depletes glutathione stores, leaving excess NAPQI to bind to intracellular proteins, causing cell death. APAP = *N*-acetyl-*p*-aminophenol (acetaminophen).

a reactive metabolite, *N*-acetyl-*p*-benzoquioneimine (NAPQI). NAPQI is detoxified by hepatic glutathione to a nontoxic compound that can be renally eliminated. However, when hepatic stores of glutathione decrease to <30% of normal in the setting of overdose, NAPQI binds to hepatic macromolecules, resulting in a centrilobular hepatic necrosis. Observed hepatocyte damage typically progresses with cell lysis on the second day after an acute toxic exposure, releasing hepatic enzymes (such as transaminases) and NAPQI-hepatic protein adducts into the circulation where they are detectable in the serum. This corresponds generally to the development of overt clinical toxicity.

CLINICAL FEATURES

FOUR STAGES OF ACETAMINOPHEN TOXICITY

The clinical presentation of human acetaminophen poisoning can be roughly divided into four stages (**Table 190-1**). During the first 24 hours after exposure (stage 1), patients may be asymptomatic or have minimal and nonspecific clinical effects of toxicity, such as anorexia, nausea, vomiting, and malaise. By days 2 to 3 (stage 2), findings seen in stage 1 often improve, but clinical signs of hepatotoxicity (including right upper quadrant pain and tenderness) may occur and serum transaminases may be elevated. Even without treatment, most patients with mild to moderate hepatotoxicity recover without sequelae. However, by days 3 to 4 (stage 3), some patients will progress to fulminant hepatic failure.[14,15] Characteristic stage 3 findings include metabolic acidosis, coagulopathy, renal failure, encephalopathy, and recurrent GI symptoms. Patients who survive the complications of fulminant hepatic failure begin to recover over the next 2 weeks (stage 4), with complete resolution of hepatic dysfunction in survivors after 1 to 3 months.

Acetaminophen may also cause acute, extrahepatic toxic effects, presumably because of the presence of CYP450 or similar enzymes (e.g., prostaglandin H synthase) in other organs. In rare cases, isolated renal injury, cardiac toxicity, and pancreatitis may occur.[16,17]

Ingestion of massive doses of acetaminophen (e.g., >500 milligrams/kg or peak plasma acetaminophen concentration >750 micrograms/mL or >5000 micromole/L) can cause early-onset metabolic acidosis with an elevated lactate and altered sensorium even in the absence of either liver failure or hypotension. Likely mechanisms for this finding include depletion of liver glutathione stores resulting in generation of 5-oxoproline and metabolite-induced inhibition of mitochondrial respiration.[18,19]

DIAGNOSIS

A toxic exposure to acetaminophen is suggested when a patient ≥6 years old ingests (1) >10 grams or 200 milligrams/kg as a single ingestion, (2) >10 grams or 200 milligrams/kg over a 24-hour period, or (3) >6 grams or 150 milligrams/kg per 24-hour period for at least 2 consecutive days. For children <6 years old, ingestion of 200 milligrams/kg or more of acetaminophen as a single ingestion or over an 8-hour period, or of 150 milligrams/kg per 24-hour period for the preceding 48 hours is considered a toxic exposure. These values are empiric and not validated in human trials, but they are widely used as recommendations for emergency evaluation.

Due to the widespread availability of acetaminophen-containing products, limited accuracy of the medical history, the delayed nature of clinical manifestations after overdose, and the serious complications of acute toxicity without antidotal therapy, **measurement of a serum acetaminophen concentration is recommended for all patients presenting to the ED with an intentional overdose**.[20,21] Potentially toxic acetaminophen concentrations are occasionally identified in patients who overdose but deny ingesting acetaminophen.[22,23] Therefore, empirical testing of all patients with presumed intentional or chronic acetaminophen overdose may be cost-effective, as the estimated cost of treating a single patient for complications of acetaminophen-induced hepatotoxicity is judged to outweigh the cost of routine laboratory testing all intentional overdose patients.

THE RUMACK-MATTHEW NOMOGRAM

The implication of a measured acetaminophen concentration is determined by plotting the value on the Rumack-Matthew nomogram (**Figure 190-2**).[24] This nomogram was derived from a retrospective analysis of oral acetaminophen overdose patients and their clinical outcomes. The original nomogram line separating possible toxicity from unlikely toxicity was based on a 4-hour acetaminophen concentration of 200 micrograms/mL (1300 micromole/L), but was subsequently modified by moving the line to a 4-hour acetaminophen concentration of 150 micrograms/mL (1000 micromole/L) to increase the safety margin for treatment decisions. **The nomogram only directly applies to an acetaminophen concentration obtained after a single oral exposure and during the window between 4 hours and 24 hours after ingestion.** Outcome prediction using this nomogram cannot be applied to acetaminophen concentrations obtained outside this window or following chronic or recurrent exposures. Obtaining multiple acetaminophen concentrations following acute overdose is rarely indicated in the absence of hepatotoxicity.[25,26] An initial concentration below the nomogram line may rarely "cross the line" in patients who ingest acetaminophen preparations known to have prolonged absorption kinetics.[12] However, the clinical significance of "crossing the line" in this fashion is unknown. Similarly, because the nomogram was constructed and verified by using only a single serum concentration, the clinical implications of a concentration above the line that falls below it on repeat analysis are unknown.

Based on data obtained before the widespread use of antidotal therapy, patients with serum acetaminophen concentrations above the original line (4-hour postingestion concentration >200 micrograms/mL or >1300 micromole/L) were observed to have a 60% risk of developing hepatotoxicity (defined as alanine aminotransferase >1000 IU/mL), a 1% risk of renal failure, and a 5% risk of mortality.[27] In addition, patients with extremely high serum acetaminophen concentrations (above a parallel line coinciding with a 4-hour postingestion concentration of

TABLE 190-1 Clinical Stages of Acute Acetaminophen Toxicity

	Stage 1	Stage 2	Stage 3	Stage 4
Approximate timing	First 24 h	Days 2–3	Days 3–4	After day 5
Clinical manifestations	Anorexia Nausea Vomiting Malaise	Improvement in anorexia, nausea, and vomiting Abdominal pain Hepatic tenderness	Recurrence of anorexia, nausea, and vomiting Encephalopathy Anuria Jaundice	Clinical improvement and recovery (7–8 d) *or* Deterioration to multiorgan failure and death
Laboratory abnormalities		Elevated serum transaminases Elevated bilirubin and prolonged prothrombin time if severe	Hepatic failure Metabolic acidosis Coagulopathy Renal failure Pancreatitis	Improvement and resolution *or* Continued deterioration

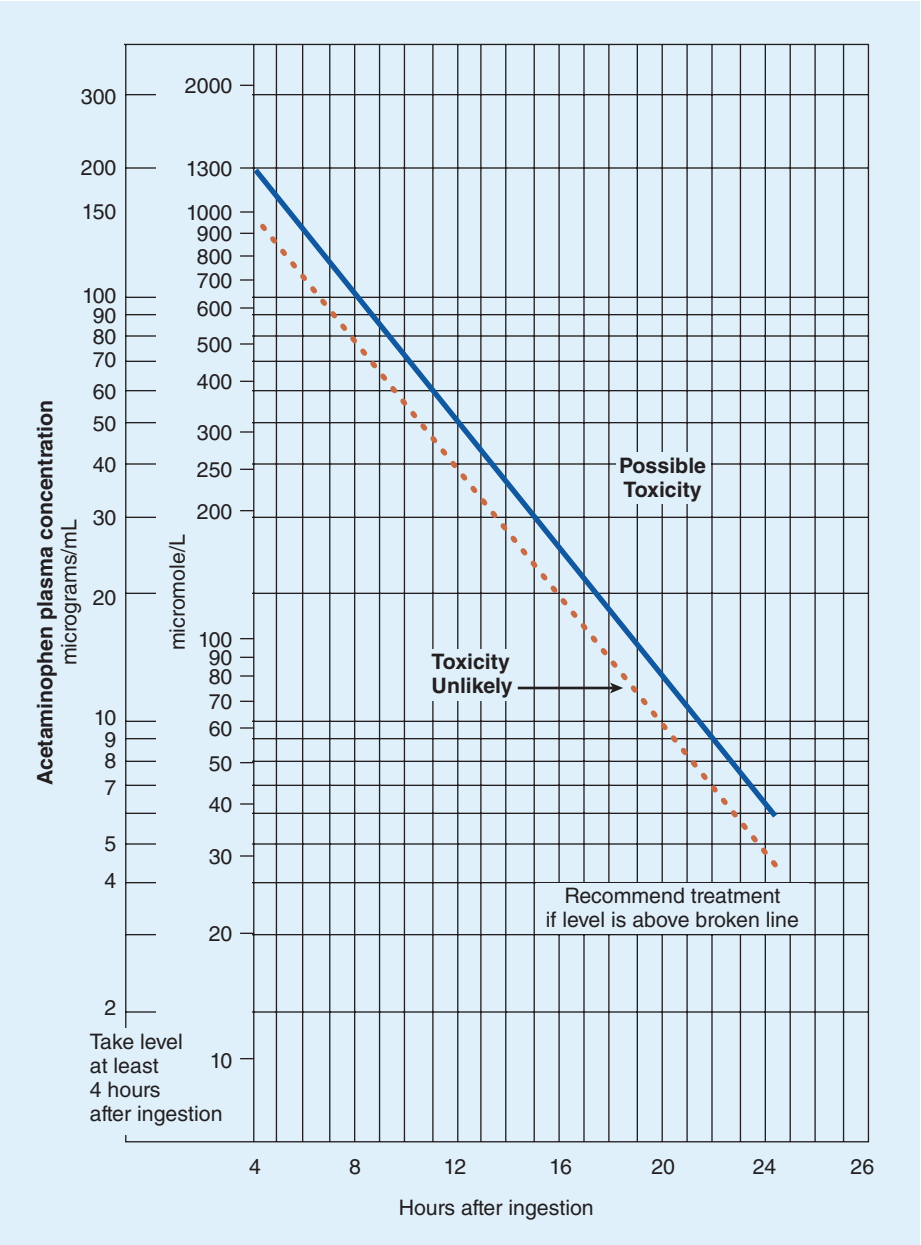

FIGURE 190-2. Rumack-Matthew nomogram.

300 micrograms/mL or 2000 micromole/L) were observed to have a 90% risk of developing hepatotoxicity. The prediction of a safe outcome below the nomogram line corresponding to a 4-hour postingestion concentration of 150 micrograms/mL (1000 micromole/L) was confirmed in patients who did not receive antidotal therapy; the incidence of hepatotoxicity in patients with acetaminophen concentrations below this nomogram line was 1%, and all patients recovered without complications.[26]

A validated method to determine potential toxicity from IV acetaminophen overdose has not been established. Fortunately, the European experience with IV acetaminophen suggests that these overdoses appear to be rare in-hospital occurrences that are likely to occur following an error in calculating the acetaminophen dose in pediatric patients.[28-30] The available clinical data for evaluating IV acetaminophen overdose remain limited to several published case reports.[28,30,31] Based on these data, the United Kingdom published revised precautionary guidelines recommending empiric acetylcysteine for any single IV acetaminophen dose above 60 milligrams/kg or acetaminophen concentrations above 50 micrograms/mL on the nomogram at 4 hours. The Rumack-Matthew nomogram was, however, derived solely from oral acetaminophen overdose patients, and the effectiveness of application to determine toxicity following IV acetaminophen overdose is unknown.

TREATMENT

GI DECONTAMINATION

For most cases of acetaminophen poisoning, adequate GI decontamination consists of the early administration of activated charcoal orally or through a nasogastric tube.[32,33] More aggressive forms of decontamination, such as gastric lavage or whole-bowel irrigation, are unnecessary because of the rapid GI absorption of acetaminophen and the reliable success of treating acetaminophen poisoning with acetylcysteine.

ACETYLCYSTEINE

The mainstay for the prevention or treatment of acetaminophen toxicity is the administration of acetylcysteine.[34-36] The current "standard" acetylcysteine protocols were developed primarily from

observational trials, and it is not clear if they represent the most effective regimens.[37]

Although its mechanisms of action are not fully understood, acetylcysteine is thought to have two important beneficial effects.[36,37] In early acetaminophen poisoning (<8 hours after ingestion), acetylcysteine averts toxicity by preventing the binding of NAPQI to hepatic macromolecules. Acetylcysteine may do this by acting as a glutathione precursor or substitute, or a sulfate precursor, or it may directly reduce NAPQI back to acetaminophen. In established acetaminophen toxicity or >24 hours after acetaminophen ingestion, acetylcysteine diminishes hepatic necrosis by acting as an antioxidant, decreasing neutrophil infiltration, improving microcirculatory blood flow, or increasing tissue oxygen delivery and extraction.

If acetylcysteine is given within 8 hours of an acute acetaminophen ingestion, it is nearly 100% effective in preventing the development of hepatotoxicity.[27] The longer the initiation of acetylcysteine therapy is delayed beyond 8 hours after ingestion, the greater is the risk of developing hepatotoxicity.[38] Even if administration is delayed up to 24 hours, acetylcysteine reduces risk of hepatotoxicity compared to historical controls.[27]

Clinical experience suggests that patients with poor glutathione reserves, such as alcoholics and the chronically ill, have similar excellent clinical outcomes when the standard treatment guidelines are applied to their care. As such, there is no need to alter the use of the acetaminophen treatment nomogram or modify the dosing of acetylcysteine for these patients.

The weight of evidence suggests that **acetylcysteine therapy is both safe and efficacious during pregnancy** and that the approach to treating a pregnant patient following an acetaminophen overdose should remain the same. Acetylcysteine treatment has never been associated with fetal malformations in humans, but fetal demise and malformations have been described following a delay in acetylcysteine treatment after acetaminophen overdose in first-trimester pregnant women.[39]

IV Acetylcysteine IV acetylcysteine has supplanted oral administration due to its greater ease of administration, greater patient acceptance, equivalent efficacy, and shorter duration of treatment for many cases of acetaminophen poisoning.[40-43] The major limitation of IV acetylcysteine is the occurrence of drug-related anaphylactoid reactions, which occur in 4% to 17% of patients (most during the first 2 hours of administration).[44,45] Mild cases are treated with diphenhydramine, and severe cases are treated by temporarily slowing or stopping the acetylcysteine infusion. Unfortunately, fulminant liver failure requiring transplant has occurred after discontinuation of *N*-acetylcysteine due to anaphylactoid reaction.[4,46] IV *N*-acetylcysteine infusion can be reinitiated at a slower rate after administration of diphenhydramine in asymptomatic patients.[47] Asthmatics appear to have a greater risk of anaphylactoid reactions during IV acetylcysteine therapy, whereas high acetaminophen concentrations are protective from developing anaphylactoid reactions.[45,46,48-50]

The standard regimen for IV acetylcysteine uses a 21-hour protocol including a loading dose of 150 milligrams/kg over 1 hour, followed by a first maintenance dose of 50 milligrams/kg infused over 4 hours, and then followed by a second maintenance dose of 100 milligrams/kg infused over 16 hours (**Table 190-2**). Because the three-phase dosing regimen for IV acetylcysteine may result in dosing errors and produce side effects due to the initial high infusion rate, alternative dosing regimens are being explored.[51-55]

IV acetylcysteine is commercially available as a 20% solution and requires dilution to a 2% solution for infusion into a peripheral vein. Both 5% dextrose in water and half-normal saline can be used as diluents.[56] **Given the volume and hypotonicity of fluid required, specific acetylcysteine weight-based fluid volume guidelines should be followed for children and small adults (<40 kg), and these patients should be carefully monitored to avoid fluid overload and hyponatremia during treatment. A dose calculator and detailed pediatric dilution directions for IV acetylcysteine are available at Acetadote.com.**[40]

Despite the lack of randomized direct comparisons, IV acetylcysteine is as effective and safe as oral therapy for patients with early acetaminophen poisoning, as compared with retrospective cohorts and historical controls.[42,57-60] IV acetylcysteine is the route of choice for patients with acetaminophen-induced fulminant hepatic failure because oral acetylcysteine has not been adequately studied in this setting.[61]

Oral Acetylcysteine The standard 72-hour oral acetylcysteine regimen used in the United States consists of a loading dose of 140 milligrams/kg followed by maintenance doses of 70 milligrams/kg every 4 hours for 17 additional doses (Table 190-2). It may still be appropriate in certain patients, such as those at high risk for anaphylactoid responses to the IV formulation and asthmatics. The taste is disagreeable, and some patients with persistent nausea and vomiting may require concomitant antiemetics such as ondansetron.

TABLE 190-2 Acetylcysteine Dosing Regimens

	PO	IV Adult	IV Pediatric (21–40 kg)	IV Pediatric (5–20 kg)
Preparation	Available as 10% and 20% solutions. Dilute to 5% solution for PO administration.	Available as 20% solution. Dilution required.	Available as 20% solution. Dilution required.	Available as 20% solution. Dilution required.
Loading dose	140 milligrams/kg	150 milligrams/kg in 200 mL 5% dextrose in water infused over 60 min	150 milligrams/kg in 100 mL 5% dextrose in water infused over 60 min	150 milligrams/kg in 3 mL/kg 5% dextrose in water infused over 60 min
Maintenance dose	70 milligrams/kg every 4 h for 17 doses	50 milligrams/kg in 500 mL 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour) *followed by* 100 milligrams/kg in 1000 mL 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour)	50 milligrams/kg in 250 mL 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour) *followed by* 100 milligrams/kg in 500 mL 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour)	50 milligrams/kg in 7 mL/kg 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour) *followed by* 100 milligrams/kg in 14 mL/kg 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour)
Duration of therapy	72 h*	21 h*	21 h	21 h
Comments	Dilute with powdered drink mix, juice, or soda. Serve chilled. Drink through a straw to reduce disagreeable smell.	Monitor for drug-related adverse effects and anaphylactoid reactions.	Monitor for drug-related adverse effects and anaphylactoid reactions.	Monitor for drug-related adverse effects and anaphylactoid reactions.

*Check with your institution or poison control center for alternative dosing protocols and for management of adverse effects.

EXTRACORPOREAL ELIMINATION

Recent guidelines recommend extracorporeal treatment (extracorporeal membrane oxygenation) in addition to acetylcysteine **only** in the setting of altered mental status, metabolic acidosis, an elevated lactate, **and** an acetaminophen level of >900 milligrams/L. In all other instances, extracorporeal treatment would only be recommended in the rare clinical scenario where acetylcysteine was unavailable or could not be administered.[62] Acetylcysteine is dialyzable, and a dose increase to account for acetylcysteine removal during hemodialysis (50%) or continuous renal replacement therapy (25%) is recommended.[63,64]

TREATMENT GUIDELINES BASED ON TIME TO ED PRESENTATION

Treatment guidelines for oral acetaminophen poisoning are based on the time to presentation to the ED after ingestion: <4 hours, between 4 hours and 24 hours, and unknown time or >24 hours before presentation (Figure 190-3).[25] The risk of hepatotoxicity increases with the lag time between ingestion and initiation of acetylcysteine therapy.[38] The optimal outcome with acetylcysteine therapy is achieved when it is administered within 8 hours after ingestion, so the optimal "decision-time window" for treatment is between the 4-hour acetaminophen concentration measurement and 8-hour goal to initiate acetylcysteine.[27] No further acetaminophen serum measurements are necessary once the need for acetylcysteine therapy has been determined until the completion of the course of therapy.

Presentation Within 4 Hours of Ingestion For patients who present to the ED within 4 hours and are likely to have a significant acetaminophen overdose, treatment begins with GI decontamination (usually activated charcoal) while awaiting the 4-hour postingestion acetaminophen concentration. If the clinical laboratory can report the acetaminophen concentration within the 8-hour postingestion window, wait for the serum acetaminophen concentration and plot the result on the nomogram to determine whether acetylcysteine therapy is necessary. If the acetaminophen concentration will not be available by 8 hours after ingestion, empirically initiate acetylcysteine therapy, by either route, without waiting for the result. Subsequently, when the acetaminophen concentration is determined, the need for acetylcysteine therapy can be determined with the use of the nomogram.

Presentation >4 and <24 Hours After Ingestion For patients who present >4 hours but <24 hours following acetaminophen ingestion, determine the serum acetaminophen concentration as soon as possible. GI decontamination may be performed, particularly for suspected co-ingestants, but it may have limited effectiveness because of the delay in presentation. If the laboratory can determine the acetaminophen concentration within 8 hours after ingestion, await the acetaminophen concentration and plot the result on the nomogram to determine if acetylcysteine therapy is necessary. Otherwise, empirically administer acetylcysteine.

Presentation >24 Hours After Ingestion or Time of Ingestion Unknown For patients in whom the time of acetaminophen ingestion remains unknown or is >24 hours or for those with suggestive clinical findings of acetaminophen poisoning, a serum acetaminophen concentration and serum transaminase, bilirubin, and prothrombin time tests should be determined. Initiate acetylcysteine therapy as soon as possible while awaiting laboratory results. In this scenario, a detectable acetaminophen concentration (>10 micrograms/mL or >66 micromole/L) suggests that the patient may be at risk for developing hepatotoxicity. Similarly, elevated serum transaminases suggest

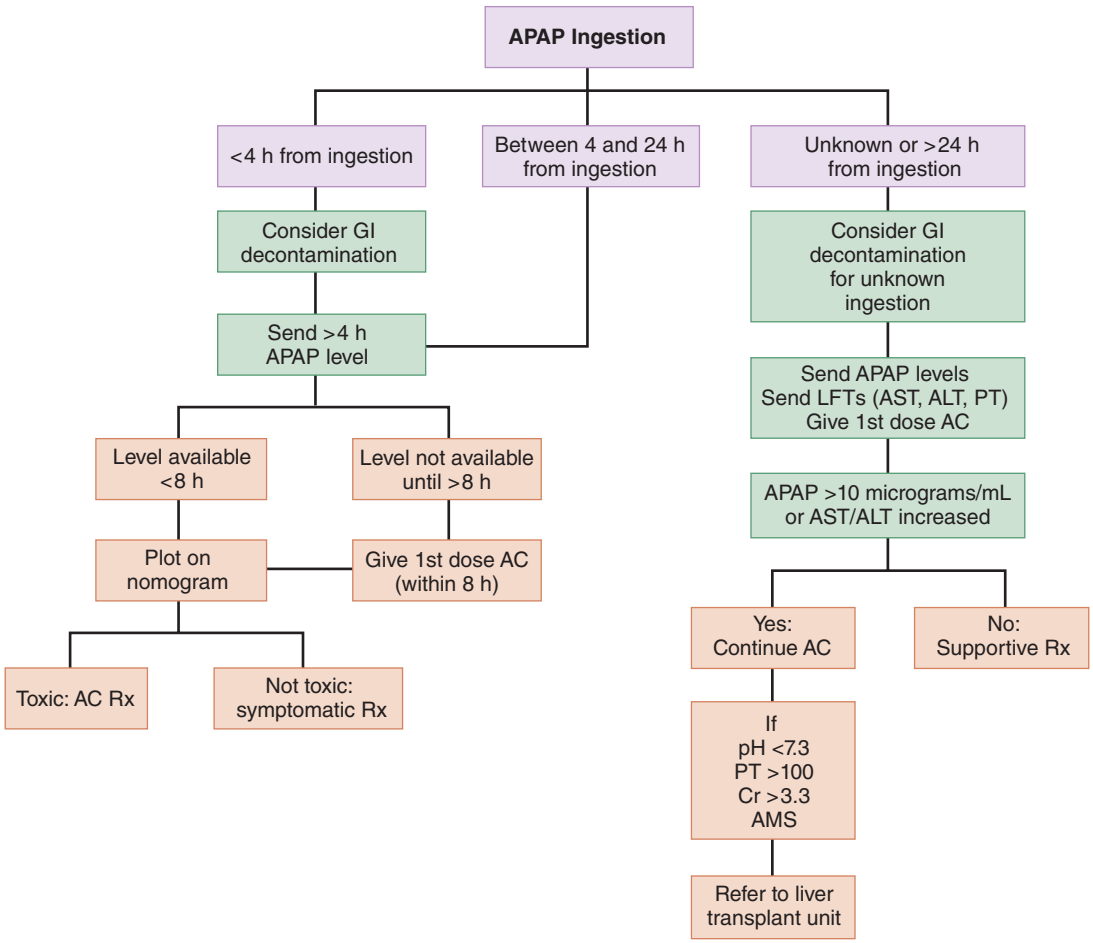

FIGURE 190-3. Treatment guidelines for acetaminophen (APAP) ingestion. All times noted are after ingestion. AC = acetylcysteine; ALT = alanine aminotransferase; AMS = altered mental status; AST = aspartate aminotransferase; Cr = creatinine; LFTs = liver function tests; PT = prothrombin time; Rx = treatment.

the possibility of ongoing hepatic toxicity. Therefore, continued acetylcysteine therapy is indicated if the acetaminophen concentration is measurable or if the serum transaminases are elevated. If serum acetaminophen concentration is <10 micrograms/mL (<66 micromole/L) and the serum transaminases are not elevated, the acetylcysteine can be discontinued.

DISPOSITION AND FOLLOW-UP

Recheck serum acetaminophen and transaminase levels at the completion of acetylcysteine therapy with continuation of acetylcysteine infusion at the rate of 6.25 milligrams/kg per hour. If serum acetaminophen concentration is not detectable or is <10 micrograms/mL (66 micromole/L) and transaminase concentrations are normal, the acetylcysteine therapy can be discontinued.[37,43] If either the serum acetaminophen concentration or liver function tests are elevated, the acetylcysteine should be continued until the serum acetaminophen concentration is undetectable and the patient has demonstrated clearly downtrending transaminases (at least two values) and there are no signs of synthetic liver dysfunction.

All patients requiring acetylcysteine therapy should be admitted to the hospital until the completion of the therapy. In general, admission to a hospital floor bed is adequate unless the co-ingestant is of concern, hepatotoxicity is severe, or the patient is suicidal and 24-hour direct observation cannot be arranged. Patients who are not at risk for developing acetaminophen-induced hepatotoxicity (e.g., acetaminophen concentration below the nomogram or unmeasurable acetaminophen concentration with normal hepatic transaminase concentrations) should be observed in the ED for 4 to 6 hours to exclude potentially toxic co-ingestants before disposition. Psychiatric evaluation should be considered for patients with intentional acetaminophen overdoses. Cases of acetaminophen ingestion or toxicity should be reported to the regional poison control center for both data collection purposes and assistance with management.

SPECIAL CONSIDERATIONS

FULMINANT HEPATIC FAILURE

Unfortunately, a small percentage of patients who overdose with acetaminophen will develop fulminant hepatic failure. The mortality rate for patients with acetaminophen-induced fulminant hepatic failure without acetylcysteine therapy is significant. Most fatalities occur on days 3 to 5 after overdose and are attributed to hepatic complications such as cerebral edema, hemorrhage, shock, acute lung injury, sepsis, and multiorgan failure. Patients who survive fulminant hepatic failure generally begin to show evidence of recovery by days 5 to 7. Survivors will eventually develop complete hepatic regeneration without any persistence of hepatic impairment.

Acetylcysteine treatment decreases the incidence of cerebral edema, reduces vasopressor requirements, and improves survival in acetaminophen-induced fulminant hepatic failure.[61,65] Acetylcysteine also appears to be beneficial in the treatment of other forms of hepatic failure, including viral hepatitis and alcoholic cirrhosis.[66-68]

Prognostic indicators (aka King's College Criteria) associated with the highest risk of mortality from acetaminophen-induced fulminant hepatic failure include metabolic acidosis (arterial pH <7.30) despite fluid and hemodynamic resuscitation, or a combination of coagulopathy (prothrombin time >100 seconds), renal insufficiency (serum creatinine >3.3 milligrams/dL or >292 micromole/L), and grade III or IV hepatic encephalopathy.[69] Other predictors of a poor prognosis individually include an Acute Physiology and Chronic Health Evaluation II score >15, elevated serum lactate (>26 milligrams/dL or >3.0 mmol/L) after fluid resuscitation, hypoglycemia, and elevated serum phosphate (>3.71 milligrams/dL or >1.2 mmol/L) on the second day after ingestion.[70-73]

Treatment for acetaminophen-induced fulminant hepatic failure includes acetylcysteine therapy; correction of coagulopathy and acidosis; monitoring for and aggressive treatment of cerebral edema, hypoglycemia, and electrolyte abnormalities; and early patient referral to a liver specialty or transplant center. Unlike the treatment of early acetaminophen toxicity, IV acetylcysteine therapy should be continued past the 21-hour standard regimen and until the patient recovers, receives a liver transplant, or dies.

MULTIPLE-DOSE AND EXTENDED-RELEASE ACETAMINOPHEN INGESTIONS

Patients with staggered acetaminophen ingestions and liver injury often have delayed presentation to the hospital and a higher rate of adverse outcomes.[74] **Multiple closely spaced acetaminophen ingestions and extended-release acetaminophen ingestions represent two unique aspects of acetaminophen poisoning for which the Rumack-Matthew nomogram cannot be applied because a single time of ingestion does not exist.** A conservative approach is to assume that a single ingestion occurred at the earliest possible time stated by the patient, with the acetaminophen concentration plotted on the Rumack-Matthew nomogram based on this artificial time and treatment decisions made accordingly. For example, if the patient ingests five doses of 50 milligrams/kg of acetaminophen over a 4-hour period beginning 8 hours ago, a single acetaminophen ingestion is assumed to have occurred 8 hours ago, and the serum concentration is accordingly plotted on the nomogram.

Extended-release acetaminophen formulations consist of a bilayered tablet containing a 325-milligram immediate-release outer layer and a 325-milligram slow, continuous-release, highly compressed inner layer. Because there are few clinical data concerning overdose with these preparations, treatment guidelines remain conservative, and the manufacturer recommends obtaining a second acetaminophen concentration 4 to 6 hours after the first concentration in those situations in which the first measured concentration (4 to 8 hours after ingestion) is elevated, but below the nomogram line.[10,75,76] A full course of acetylcysteine therapy should be instituted (or continued if already started) if the second acetaminophen concentration is above the nomogram line. If the initial concentration is above the nomogram line, standard therapy should be administered, and there is no need to obtain a second concentration.

MASSIVE ACETAMINOPHEN OVERDOSE

Patients presenting after massive (>40 grams or 500 milligrams/kg) acetaminophen overdose are at high risk of hepatotoxicity, even with early acetylcysteine administration.[63,77-79] The standard 21-hour protocol relies on empiric dosing, and this model may prove inadequate for patients with massive acetaminophen overdose. At this time, no data demonstrate superiority of an **alternative** regimen, but in patients with massive acetaminophen overdose, enhanced therapeutic measures should be considered. Options include the addition of oral acetylcysteine to the standard IV protocol, increasing the third infusion dose to 200 milligrams/kg over 16 hours as opposed to the dose of 100 milligrams/kg over 16 hours used in the standard IV acetylcysteine protocol, or reloading the standard acetylcysteine regimen at completion of the 21-hour protocol if serum acetaminophen concentration remains significantly elevated.[80,81]

IV ACETAMINOPHEN OVERDOSE

Accepted guidelines for treatment of IV acetaminophen overdose do not currently exist in the United States. The United Kingdom has published revised precautionary guidelines recommending empiric acetylcysteine for any single IV acetaminophen dose >60 milligrams/kg or acetaminophen concentrations >50 micrograms/mL on the nomogram at 4 hours. The local poison center should be contacted for guidance following any suspected IV acetaminophen overdose.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 191

Nonsteroidal Anti-Inflammatory Drugs

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Rana Biary

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutic agents in the United States. All share inhibition of the cyclooxygenase enzyme as a mechanism of action. NSAIDs are effective antipyretics, analgesics, and anti-inflammatory agents. Because of their large therapeutic window, acute ingestion with overdoses rarely produces serious complications.[1,2] The morbidity from NSAIDs in acute overdose is far overshadowed by complications of NSAIDs at therapeutic doses, which include GI bleeding, drug-induced renal failure, and atherosclerotic heart disease.[3-6]

PHARMACOLOGY

NSAIDs are structurally varied compounds with common therapeutic effects (**Table 191-1**). NSAIDs reversibly inhibit COX, which is responsible for the production of prostaglandins from arachidonic acid. The anti-inflammatory effect of NSAIDs is through the inhibition of prostaglandin production and neutrophil migration.[7] NSAIDs are antipyretics via inhibition of prostaglandin E_2 in the hypothalamus. Analgesia is mediated by attenuation of prostaglandin-mediated hyperalgesia and local pain fiber stimulus.

CYCLOOXYGENASE

Two isoforms of COX (COX-1 and COX-2) vary in presence and distribution.[8] COX-1 is present with a steady level of activity and is found primarily in blood vessels, kidneys, and the stomach. In contrast, COX-2 is found in low levels in human tissue unless induced by proinflammatory mediators.[8]

COX inhibitors can be categorized as nonselective, partially selective, or selective regarding their inhibition of COX enzyme isoforms (Table 191-1). Most NSAIDs nonselectively inhibit both COX-1 and COX-2. COX-1 inhibition is responsible for most of the unwanted GI side effects of NSAIDs. Drugs such as etodolac and meloxicam were created to inhibit COX-2 preferentially, theoretically reducing the unwanted GI effects. Unfortunately, the COX-2–selective compounds do not appear to be more effective mediators of inflammation or analgesia and are still associated with GI side effects.[9,10]

PHARMACOKINETICS

All NSAIDs are rapidly absorbed from the GI tract, and most achieve peak serum levels within about 2 hours. They are highly protein bound, have low volumes of distribution (approximately 0.2 L/kg), and cross the blood–brain barrier. NSAIDs undergo metabolism mainly in the liver.

TABLE 191-1 Nonsteroidal Agents Available in the United States

Class and Agent	Half-Life With Therapeutic Doses of Standard Oral Tablets or Capsules* (h)	Typical Initial Adult Oral Dose (milligrams)	Maximum Recommended Adult Daily Oral Dose (milligrams)
Nonselective NSAIDs			
Acetic acids			
Diclofenac	2	35 TID	150
Indomethacin	2.6–11.2	25 BID or TID	200
Ketorolac	5	10 QID	120
Meclofenamate	1–2 (15†)	50 QID	400
Mefenamic acid	2	250 QID	1000
Nabumetone	<1 (22–26†)	1000 daily	2000
Sulindac	8 (16†)	150 BID	400
Tolmetin	5	400 TID	1800
Propionic acids			
Fenoprofen	3	300 TID	3200
Flurbiprofen	5–8	50 BID	300
Ibuprofen	2	400 QID	2400 (pain, dysmenorrhea) 3200 (osteoarthritis)
Ketoprofen	2–4	50 TID	300
Naproxen	12–17	250 BID	1000 (pain) 1500 (osteoarthritis)
Oxaprozin	16–45 (38–57‡)	1200 daily	1800
Oxicams			
Piroxicam	50	20 daily	20
Partially selective COX-2 inhibitors			
Etodolac	6–8	200 TID	1000
Meloxicam	20–24	5 daily	15
Selective COX-2 inhibitors			
Celecoxib	11	200 BID	400

Abbreviations: BID = twice per day; COX-2 = cyclooxygenase 2; QID = four times per day; TID = three times per day.

*Not sustained-release or enteric-coated preparations.

†Half-life of active metabolite.

‡Half-life of protein-bound drug.

Plasma half-lives of NSAIDs range from 2 hours for ibuprofen to greater than 50 hours for the long-acting agents piroxicam and phenylbutazone (Table 191-1). Creation of active metabolites may prolong the therapeutic effect beyond that of the parent compound.

Ingestion of large amounts of some drugs, such as ibuprofen and naproxen, results in slower absorption, with 3 to 4 hours required to achieve peak plasma levels. As greater amounts of NSAIDs are absorbed in large overdoses, greater fractions of free drug become available for toxicity in a nonlinear manner because protein binding is limited.

Topical NSAIDs Topical NSAIDs are well absorbed through the skin and reach therapeutic levels in synovial fluid. According to the most recent Cochrane review, topical diclofenac and ketoprofen provide good relief in acute muscular injuries but have limited efficacy in chronic conditions such as osteoarthritis.[11]

SIGNIFICANT DRUG–DRUG INTERACTIONS

Aspirin Daily aspirin therapy reduces the incidence of recurrent myocardial infarction and stroke by impairment of platelet aggregation. Ibuprofen administered three times per day competitively inhibits this aspirin effect on platelets by its interaction with the thromboxane pathway, thus undermining aspirin's cardioprotective effect.[12,13] Ketorolac and diclofenac, unlike other NSAIDs, do not alter aspirin's inhibition of platelet aggregation and thromboxane synthesis.[14]

Antihypertensive Agents NSAIDs decrease the effectiveness of antihypertensive drugs through inhibition of prostaglandin synthesis.[15] NSAIDS can also aggravate preexisting hypertension or raise blood pressure through their renal effects.

Anticoagulants When combined with warfarin or non–vitamin K oral anticoagulants, NSAIDs increase risk for upper GI bleeding,[16,17] although the risk may vary with specific agents. A recent meta-analysis demonstrated a small increase in risk of bleeding with the use of warfarin and NSAIDs,[18] while other studies demonstrate that the risk is NSAID specific, with meloxicam being the only NSAID to increase INR with warfarin therapy.[19] Concomitant therapy with COX-2 inhibitors and warfarin still incurs some risk of GI bleeding, but the risk is less with nonselective NSAID–warfarin combinations.[20,21] Due to the drug–drug interactions and risk of GI bleeding, avoid chronic NSAID use in patients on warfarin or novel oral anticoagulants.[22,23]

Decreased Renal Clearance of Drugs NSAIDs may also decrease renal clearance by inhibition of renal synthesis of prostaglandins (which serve as vasodilators) and by decreasing renal blood and glomerular filtration rate. NSAIDs increase concentrations of drugs such as lithium, methotrexate, and metformin. NSAIDs are a potential risk factor in the development of metformin-associated lactic acidosis.[24]

TOXICITY AT THERAPEUTIC DOSES

NSAIDs are generally safe drugs but have a number of well-reported side effects at therapeutic doses (**Table 191-2**). **Indomethacin, piroxicam, and diclofenac are responsible for a greater proportion of side effects,** whereas the propionic acid agents (e.g., ibuprofen) are associated with fewer problems.[25,26]

CNS CNS adverse effects at therapeutic doses include headache, cognitive difficulties, behavioral change, and aseptic meningitis.[27,28] Acute psychosis has been reported with indomethacin and sulindac—agents with structural similarity to serotonin—and is more commonly in the elderly.[29]

Patients with NSAID-induced aseptic meningitis may experience symptoms of headache, fever, and neck stiffness occurring within hours of a therapeutic dose.[27,30,31] Cerebrospinal fluid analysis of these patients finds elevated WBC counts and protein levels with normal or decreased glucose levels. Symptoms resolve after NSAID use is stopped and may recur with repeat NSAID challenges.[31] This phenomenon, most often seen in patients who have underlying autoimmune diseases such as systemic lupus erythematosus, is thought to be a hypersensitivity reaction. Exclude infection before assuming NSAID-induced aseptic meningitis. Agents associated with aseptic meningitis include celecoxib, diclofenac, ibuprofen, ketoprofen, naproxen, rofecoxib, sulfasalazine, sulindac, and tolmetin.

TABLE 191-2 NSAID Toxicity at Therapeutic Doses

Organ System	Clinical Toxicity
CNS	Behavioral changes, cognitive difficulties, headache, psychosis, aseptic meningitis, seizures
Cardiovascular	Increased risk of myocardial infarction and risk of sudden death following myocardial infarction
Pulmonary	Bronchospasm, hypersensitivity pneumonitis, pulmonary edema
GI	Dyspepsia,* nausea,* heartburn,* gastritis, gastric and duodenal erosions, mucosal bleeding,* gastric and duodenal perforation
Hepatic	Spectrum of hepatic injury ranging from asymptomatic elevation of serum transaminases to fulminant hepatic failure
Renal	Sodium and water retention,* hyperkalemia, azotemia,* acute tubular necrosis, interstitial nephritis, renal failure
Hematologic	Increased risk of bleeding, bone marrow suppression, aplastic anemia, agranulocytosis, red cell aplasia, hemolytic anemia, thrombocytopenia
Dermatologic	Maculopapular rashes, photosensitivity reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis
Bone	Delayed wound and fracture healing
Reproductive	Slowed uterine contractions, premature closure of ductus arteriosus, fetal intracranial hemorrhage, necrotizing enterocolitis, oligohydramnios

*Common side effects.

Cardiovascular Increased cardiovascular events, including myocardial infarction, can result from long-term use of both nonselective NSAIDs and selective COX-2 agents.[32,33] Risk depends on drug, drug dose, and duration and is also more profound in patients with established coronary artery disease.[32,34] The greatest risk for myocardial infarction occurs within the first month of any NSAID use and at higher doses.[33,35] Begin therapy with medications not associated with increased cardiovascular effects, such as acetaminophen, and progress to nonselective NSAIDs, or for patients over 75 years of age, use a topical rather than oral NSAID.[35-39] If NSAIDs are administered in patients with high cardiovascular risk, give short courses of the lowest dose.[40,41]

Pulmonary NSAIDs have been associated with adverse pulmonary reactions, including bronchospasm in asthmatics, hypersensitivity pneumonitis, eosinophilic pneumonia, and rarely pulmonary edema.[42-44] Cessation of NSAID use resolves the symptoms.

NSAIDs and aspirin can trigger bronchospasm in patients with reactive airway disease.[42] The spectrum of this reaction ranges from rhinitis to severe bronchospasm with laryngeal edema.[45] Patients with underlying reactive airways disease and nasal polyps are at greater risk for these complications. Hypersensitivity reaction to NSAIDs is due to increased proinflammatory cysteinyl leukotrienes and decreased prostaglandin E_2 from COX-1 inhibition.[42]

GI GI effects from NSAIDs include dyspepsia, heartburn, nausea, and GI bleeding.[10] These effects derive from inhibition of cytoprotective gastric prostaglandins resulting in injuries ranging from mild ulceration to life-threatening bleeding.[5] NSAIDs' inhibition of gastric prostaglandins also increases permeability of the GI barrier.[46]

Hepatic Clinically apparent liver injury caused by NSAIDs is idiosyncratic and rare.[47] Diclofenac and sulindac are the two NSAIDs most commonly linked to hepatotoxicity. Drug withdrawal should lead to complete recovery.

Renal COX inhibition decreases prostaglandin synthesis and causes renal vasoconstriction. Continued NSAID use may lead to acute tubular necrosis. Interstitial nephritis and glomerular injury may result from NSAID-associated activation of inflammatory cells.[5,6,48]

Hematologic Nonselective NSAIDs inhibit platelet formation of thromboxane A_2, a potent stimulator of platelet aggregation. The new COX-2 inhibitors have far fewer antiplatelet effects than traditional NSAIDs. Most NSAIDs decrease platelet aggregation only when significant concentrations of the drug are present, and therefore, increased bleeding tendencies from NSAIDs are not widely reported.

Bone marrow suppression and aplastic anemia are rare hematologic complications of almost all NSAIDs, with indomethacin, diclofenac, and phenylbutazone responsible for most reported cases. NSAID use has also resulted in agranulocytosis, hemolytic anemia, red cell aplasia, and thrombotic thrombocytopenic purpura.[49-51]

Dermatologic Rash, angioedema, and urticaria are the most common manifestations of hypersensitivity reactions to NSAIDs.[52] The agents most frequently involved in dermatologic complications include benoxaprofen, phenylbutazone, and piroxicam. Drug reactions to NSAIDs range from benign maculopapular rashes to Stevens-Johnson syndrome and toxic epidermal necrolysis. NSAIDs are among the most commonly implicated drugs in cases of toxic epidermal necrolysis, accounting for up to one third of drug-related cases. NSAIDs of all types (oral and topical) can cause photosensitivity reactions including increased sensitivity to sun exposure (phototoxic) and true photoallergic reactions (see Chapter 249, "Generalized Skin Disorders"). Ketoprofen and piroxicam are the most frequently involved in photoallergic reactions.

Bone Bone healing is a complex cascade of events that involves prostaglandins' influence on the balance between bone formation and resorption.[53,54] The most recent guidelines by the American Pain Society recommend the use of NSAIDs for postoperative pain in fractures because there is not sufficient evidence against its use in humans.[55]

Reproductive Prostaglandins are found in high concentration in the uterus at term and have a stimulatory effect on normal labor. NSAIDs will impair uterine motility through inhibition of prostaglandin synthesis. They may be associated with increased risk of miscarriage when used around conception.[56] One of the most significant effects of fetal exposure to NSAIDs is premature constriction of the ductus arteriosus that may result in fetal pulmonary hypertension.[57] The many other reported effects of in utero exposure to NSAIDs have resulted in the U.S. Food and Drug Administration recommendation against the use of NSAIDs after 29 weeks of pregnancy.[57]

TOXICITY WITH ACUTE OVERDOSE

Although the vast majority of patients with acute overdoses suffer little morbidity, with massive NSAID ingestions, some fatalities can occur; these cases may present with altered mental status, metabolic acidosis, and shock.[58-61] Historically, phenylbutazone was most commonly associated with severe toxicity following an overdose, and although it was withdrawn from the U.S. market in the 1970s, it is still available from veterinary sources and in other countries. By a wide margin, ibuprofen is the most common agent currently reported in NSAID overdoses. Patients who develop symptoms following an ibuprofen overdose usually ingest more than 100 milligrams/kg. Initial symptoms predominantly include abdominal pain, nausea, and vomiting, all beginning within 4 hours of ingestion (**Table 191-3**). Most patients who manifest severe toxicity, including apnea, coma, and metabolic acidosis, ingest more than 400 milligrams/kg. There is limited published experience concerning acute overdose of COX-2 inhibitors, but they are assumed to have similar profiles as the nonselective NSAIDs.

CNS CNS manifestations of acute NSAID overdose are usually minimal, although patients with significant overdose may have headache, diplopia, nystagmus, and altered mental status including coma.[27] Mefenamic acid has high potential for seizures in overdose.[62] Muscle twitching and seizures that are responsive to benzodiazepines have been reported.[63]

Cardiovascular Acute NSAID overdose can be associated with hypotension and dysrhythmias ranging from bradycardia to ventricular tachycardia and fibrillation. NSAIDs are not known to be a primary cause of dysrhythmias, but fluid and electrolyte abnormalities provoked by NSAID toxicity may induce cardiac rhythm abnormalities.

TABLE 191-3 NSAID Toxicity After an Acute Overdose

Initial symptoms within 4 h after ingestion	Abdominal pain, nausea, vomiting
CNS	Headache, nystagmus, diplopia, altered mental status, coma, muscle twitching, and seizures (mefenamic acid)
Cardiovascular	Hypotension, shock, bradydysrhythmia, ventricular tachycardia or fibrillation and QT prolongation
Metabolic	Hyperkalemia, hypocalcemia, hypomagnesemia
GI and hepatic	Continued abdominal pain, nausea, vomiting, hepatic injury, pancreatitis (rare)
Renal	Acute kidney injury

Cardiovascular dysfunction from acute NSAID overdose is responsive to conventional critical care management.

Metabolic Electrolyte and acid-base abnormalities may occur in acute NSAID overdoses. Alterations in serum electrolytes may develop secondary to decreased prostaglandin synthesis or from NSAID-induced renal failure. Sodium and water retention may lead to volume overload in patients with preexisting cirrhosis, heart failure, or renal failure. Hyperkalemia, hypocalcemia, and hypomagnesemia have been reported in NSAID overdoses complicated by acute renal failure.

Increased anion gap metabolic acidosis has been observed with large overdoses of ibuprofen and naproxen, which may be due to these NSAIDs and their metabolites being weak acids. Concurrent lactic acid production in the setting of NSAID-induced seizures or shock may exacerbate the acidosis.

GI and Hepatic Patients presenting after acute NSAID overdose may have abdominal pain, nausea, and vomiting, but life-threatening GI hemorrhage is not a typical finding after acute overdoses. Overdose may also result in hepatic injury, as measured by cholestasis and elevated transaminase levels. Rare cases of pancreatitis have been reported after overdoses of ibuprofen, naproxen, and indomethacin.[64-66]

Renal NSAID overdose rarely causes acute kidney injury, but may place a stressed renal system at risk for failure. The clinical presentation may include hematuria and oliguria. Most patients with acute renal failure due to an NSAID overdose have eventual recovery of renal function, but some may need long-term dialysis.

TREATMENT

Most patients who present following an NSAID overdose will be asymptomatic. Follow the general principles for managing the poisoned patient (see Chapter 176, "General Management of Poisoned Patients"). Determine if the amount of drug ingested was less than 100 milligrams/kg (unlikely to result in toxicity) or more than 400 milligrams/kg (significant risk for toxicity).

Asymptomatic NSAID ingestions usually require minimal laboratory evaluation and supportive care (**Figure 191-1**). Activated charcoal is recommended for the majority of patients with NSAID overdose who have an intact mental status and are protecting their airway. IV fluids and an H_2 blocker or proton pump inhibitor can be given empirically. Replace electrolytes. Screen for potentially dangerous co-ingestants by measuring the serum acetaminophen and salicylate levels and obtaining a 12-lead ECG.

Patients who are symptomatic with altered mental status, seizures, shock, respiratory distress, or cardiac dysrhythmias require aggressive resuscitation and stabilization (Figure 191-1). Establish an airway as needed, institute mechanical ventilation when necessary, treat hypotension with fluid boluses and/or vasopressors, and manage seizures initially with IV benzodiazepines. Activated charcoal is recommended in all symptomatic patients with a protected airway. Consider gastric lavage for recent ingestions involving mefenamic acid or phenylbutazone.

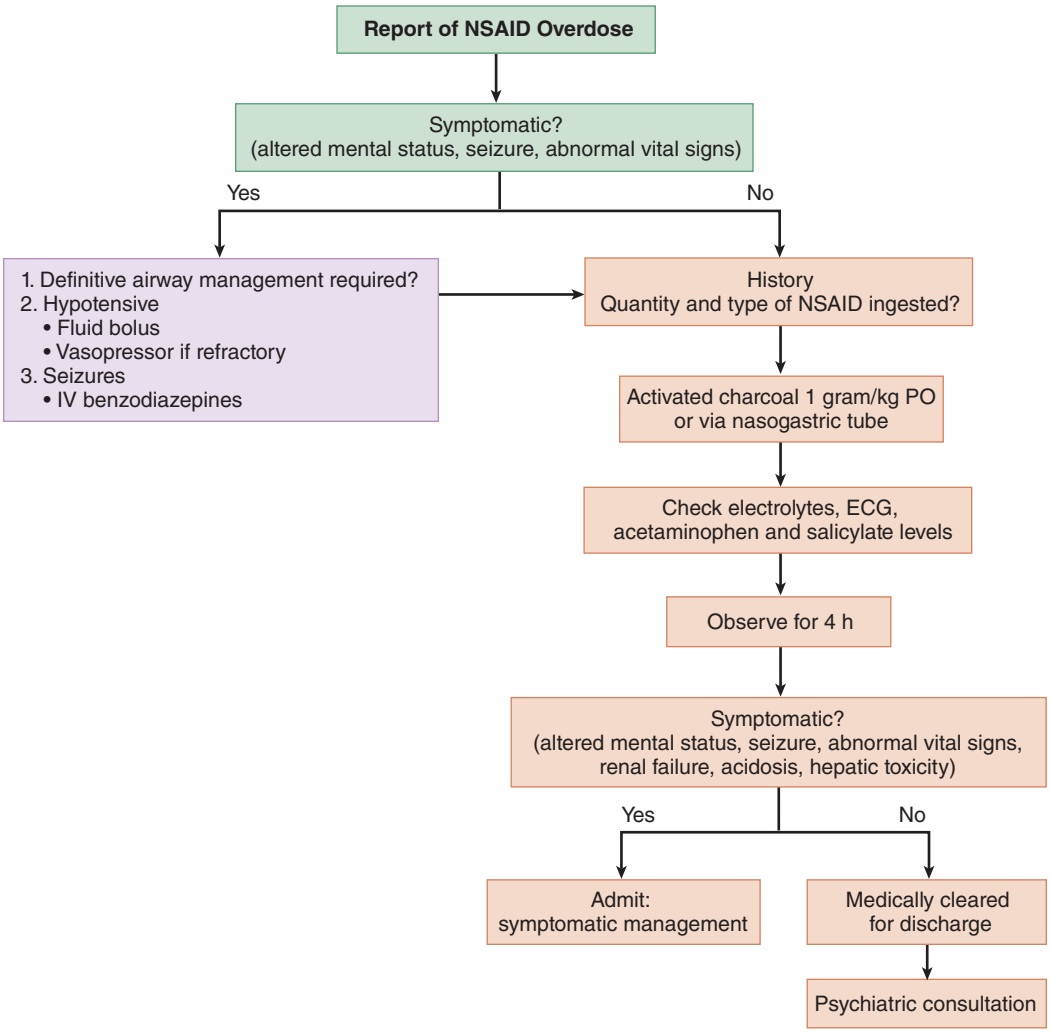

FIGURE 191-1. Approach to treatment of acute NSAID overdose.

Whole-bowel irrigation can be considered for severe overdose with enteric-coated formulations.[67] Hemodialysis, hemofiltration, and charcoal hemoperfusion are not effective in enhancing elimination because NSAIDs are highly protein bound. Likewise, manipulation of serum and urine pH through IV alkalinization is not beneficial in enhancing renal elimination. Hemodialysis may be needed for severe metabolic derangements or renal failure not responsive to conservative therapies.

Patients with symptomatic NSAID overdoses should have a serum chemistry panel, hepatic profile, CBC, and coagulation profile. Serum NSAID levels do not correlate with observed toxicity or outcomes, so serum levels for specific NSAIDs are not indicated.

DISPOSITION AND FOLLOW-UP

Most patients with asymptomatic NSAID ingestions can be safely discharged after a 4-hour period of observation. Patients with a symptomatic overdose (altered mental status, abnormal vital signs, electrolyte abnormalities, or acute renal failure) should be admitted for observation and supportive care. All overdoses should be reported to the regional poison control center both for management assistance and for statistical tracking. The majority of NSAID overdoses will not cause significant sequelae, and even patients with major symptoms have a good prognosis if they overcome the initial insult.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 192

Methylxanthines and Nicotine

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INTRODUCTION

Methylxanthines include **caffeine**, **theophylline**, **theobromine**, and **nicotine**. These agents are plant-derived alkaloids with ubiquitous use in beverages (caffeine in coffee and soda), foods (theobromine in chocolate), tobacco products (nicotine), and medications (theophylline and caffeine). Newer methylxanthine derivatives include pentoxifylline (improves peripheral blood flow) and doxofylline (a bronchodilator).[1,2] All methylxanthines have shared pharmacologic properties and very similar pharmacodynamic effects.

METHYLXANTHINES

EPIDEMIOLOGY

Caffeine (1,3,7-trimethylxanthine), a structural analog of adenosine, is found with varying amounts in beverages and "energy-enhanced" foods, such as candy bars, potato chips, and oatmeal (**Table 192-1**).[3] Many "energy drinks" contain guarana, a plant whose seeds contain

TABLE 192-1 Caffeine Content of Various Products

Source	Caffeine Content (milligrams)
Coffee (8 oz or 240 mL, brewed)	60–120
Tea (8 oz or 240 mL, brewed)	20–90
Colas, caffeinated (8 oz or 240 mL)	20–40
Dark chocolate (1 oz or 30 mL)	5–35
"Higher caffeine energy drinks" (8–24 oz)	70–505
Acetaminophen-aspirin-caffeine tablet	65
Nonprescription antidrowsiness tablet	200
Caffeine powder (via online sources)	Varies; up to 1700 per 5 mL

high concentrations of caffeine and other methylxanthines. Drinks with guarana may not list caffeine as an ingredient.[4] Other uses for caffeine include apnea of prematurity, analgesic adjuncts, postdural puncture headache, appetite suppression for weight loss, sleep prevention, and diuresis.

Theophylline (1,3-dimethylxanthine) and its water-soluble salt, **aminophylline**, were used extensively in the past for the treatment of asthma and chronic obstructive pulmonary disease. However, theophylline's use has declined due to its narrow therapeutic window and the development of safer agents. Theophylline is still used in patients with debilitating bronchospastic disease, particularly outside the United States.

Theobromine (3,7-dimethylxanthine) is found in the seeds of *Theobroma cacao*, from which chocolate and cocoa are derived, and *Camellia thea*, from which teas are steeped, and is an ingredient in numerous "energy drinks" in addition to caffeine. There are very few cases of human toxicity, but theobromine has been associated with atrial fibrillation.[5]

PHARMACOLOGY

Caffeine is most commonly consumed orally; however, it can be administered rectally or parenterally. Theophylline is usually taken orally as an elixir or as an extended-release or controlled-release tablet, although its absorption may be affected by food. Controlled-release tablets can result in erratic or delayed absorption. Theophylline can also be administered IV as aminophylline.

All methylxanthines are rapidly absorbed with early peak levels, cross the blood–brain barrier and placenta, and are excreted in breast milk (**Table 192-2**). Half-lives are only accurate at therapeutic concentrations and vary according to drug level, age extremes, smoking, organ system dysfunction (e.g., cirrhosis), infection, and cytochrome P450 inhibition (**Table 192-3**).

TABLE 192-2 Pharmacokinetics of Methylxanthines

Parameter	Caffeine	Theophylline
Therapeutic serum concentration	5–20 micrograms/mL (25–100 micromole/L)	8–20 micrograms/mL (44–110 micromole/L)
Bioavailability (oral)	~100%	~100%
Oral peak absorption (h) (delayed in overdose)	0.5–1.0	1–2 (up to 8 h with sustained-release preparations)
Volume of distribution (L/kg)	~0.6	~0.5
Protein binding	~35%	~60%
Major active metabolites	Paraxanthine Theobromine Theophylline	Caffeine (only if <6 mo old)
Clearance	Hepatic	<1 y old: 50% hepatic and 50% renal >1 y old: 90% hepatic and 10% renal
Half-life (accurate only at therapeutic concentrations)	Neonates: >50 h <1 y old: 20 h >1 y old: 5 h	Neonates: 20–30 h Children and adults: 5 h >60 y old: 10 h

TABLE 192-3 Factors Affecting Theophylline Clearance

	Increase Theophylline Clearance	Decrease Theophylline Clearance
Medications	Barbiturates Benzodiazepines (suspected) Carbamazepine Phenytoin St. John's wort	Cimetidine Ethanol (coingested) Erythromycin (all macrolides suspected) Oral contraceptives Propranolol (metoprolol suspected) Fluoroquinolones (most) Verapamil
Medical conditions		Cirrhosis Heart failure Pneumonia (other infections suspected)
Other	Hyperthyroidism Tobacco Marijuana (cannabis)	Pregnancy Obesity Fever (suspected)

Methylxanthines exhibit Michaelis-Menten kinetics; that is, metabolism changes from first-order to zero-order kinetics at increased concentrations such that a fixed amount, not percentage, of drug is eliminated per unit of time, making accurate half-life predictions impossible following an overdose. This also explains why patients who chronically use theophylline may develop a large increase in serum theophylline concentration with only a small increase in dose. Methylxanthines are metabolized in the liver by the cytochrome P450 1A2 pathway. Theophylline undergoes significant enterohepatic recirculation, so toxic serum levels can be maintained longer than anticipated.

CLINICAL FEATURES OF TOXICITY

Theophylline has the most potential for significant toxicity, followed by caffeine and then theobromine. The underlying pathophysiology involves adenosine antagonism, increased endogenous adrenergic stimulation, and, at toxic levels, phosphodiesterase inhibition (**Table 192-4**).

The main organ systems involved in methylxanthine toxicity are GI, neurologic, cardiovascular, and metabolic (**Table 192-5**).

GI Toxic Effects Nausea and vomiting are reported in >70% of acute overdoses.[6] Theophylline can also induce esophageal reflux by decreasing lower esophageal sphincter pressure.

Neurologic Toxic Effects Methylxanthine-induced seizures can be severe and refractory to treatment. First-time seizures in the setting of heavy caffeinated "energy drink" consumption have been reported.[7,8] In theophylline toxicity, incidence of seizures is approximately 50% when serum levels are >40 micrograms/mL (>200 micromole/L) during chronic therapy and >120 micrograms/mL (>600 micromole/L) after an acute ingestion.[6] Seizures during chronic therapy are seen with lower serum concentrations due to relatively higher tissue levels. In chronic toxicity, seizures can occur without prior neurologic symptoms of tremor or agitation.

Cardiovascular Toxic Effects Methylxanthines induce the release of endogenous catecholamines, stimulating β-adrenergic receptors and resulting in increased inotropy and chronotropy, vasodilation, hypotension, and reflex tachycardia. Sinus tachycardia is the most common cardiac manifestation of both caffeine and theophylline use and toxicity. Both atrial and ventricular tachydysrhythmias are described with excessive caffeine intake.[9,10] Theophylline toxicity may result in atrial dysrhythmias such as multifocal tachycardia and fibrillation or flutter. Ventricular ectopy is more common with chronic toxicity and in patients with advanced age or underlying cardiac dysfunction.[11] Ventricular fibrillation and tachycardia are rare.

TABLE 192-4 Methylxanthine Mechanisms of Action and Toxicity

	Adenosine Antagonism	Increased Catecholamines	Inhibition of Phosphodiesterase
Mechanism	Inhibition of adenosine-1 and adenosine-2 > adenosine-3 receptors	Increased circulating catecholamines (epinephrine and norepinephrine)	Phosphodiesterase inhibition (at toxic levels)
Effect	Decreased adenosine activity Increased excitatory neurotransmitters activity	Stimulation of β_1 and β_2 receptors	Increased concentration of cyclic adenosine monophosphate and catecholamine effects
Therapeutic effect	Bronchodilation	Bronchodilation	No role at therapeutic doses
Clinical toxicity	Vasoconstriction Dysrhythmias Seizures	Tachycardia Vasodilation Hypotension	Enhanced β-adrenergic effects

Metabolic Toxic Effects Methylxanthine toxicity is associated with hypokalemia, hyperglycemia, and metabolic acidosis. Hypokalemia is most common in acute overdose, due to increased catecholamines.[12] Rhabdomyolysis has been reported in caffeine and theophylline overdoses, presumably due to the hypermetabolic state, agitation, and seizures.[13,14]

Tolerance and Withdrawal Chronic use of methylxanthines, particularly caffeine, can lead to tolerance, dependence, or withdrawal. Caffeine withdrawal syndrome has a varied course depending on use. Withdrawal symptoms typically start at 6 to 24 hours after the last dose, peak at about 36 hours, and can last for several days. Headache and fatigue are the most common symptoms and are seen after either chronic use or short-term, high-dose exposures. **Caffeine withdrawal headaches** can be debilitating and should be included in the differential diagnosis of ED patients with headache.

DIAGNOSIS OF TOXICITY

Caffeine Toxicity There is no clearly defined toxic dose or level of caffeine. Following a single ingestion of 120 milligrams of caffeine, an average peak serum concentration of 3 micrograms/mL (15 micromole/L) results at 1 hour. Caffeine doses around 120 milligrams enhance arousal and performance of both cognitive and psychomotor skills.[15]

Ingestions of 100 to 150 milligrams/kg or serum levels >100 micrograms/mL (>500 micromole/L) are likely to cause life-threatening toxicity, and an acute ingestion of >200 milligrams/kg can be lethal.[4,16] Serum caffeine concentrations are not readily available in most clinical settings and offer little in terms of clinical decision making, so management of caffeine toxicity is guided by clinical findings.

TABLE 192-5 Clinical Manifestations of Methylxanthine Toxicity

Organ System	Manifestation
GI	Nausea Vomiting Gastritis
Neurologic	Headache Tremor Agitation Seizure
Cardiovascular	Tachycardia Hypotension Atrial dysrhythmias Ventricular ectopy
Metabolic	Hypokalemia Hyperglycemia Metabolic acidosis Hyperthermia Rhabdomyolysis

Theophylline Toxicity Although there is an established therapeutic serum concentration for theophylline, clinical effects are determined by the amount of free drug in tissue, not the serum. **The best predictor of major theophylline toxicity after an acute overdose—seizures, hypotension, or cardiac dysrhythmias—is the peak serum concentration. In chronic toxicity, although serum levels are elevated, the level itself does not necessarily predict major toxicity.** In an acute ingestion, monitor serial theophylline levels to establish a trend in absorption and document a declining concentration to assist in the medical clearance of patients, because peak levels may be delayed many hours following a massive, acute overdose (**Table 192-6**). Management decisions should be based on symptoms and the patient's clinical condition, not on drug levels alone.

TREATMENT

The three main components to caring for a patient with methylxanthine toxicity are resuscitation (stabilizing cardiovascular and pulmonary function), GI decontamination to interrupt continued absorption (when appropriate), and minimizing end-organ effects. Supportive care and an appropriate observation period are required to prevent secondary sequelae. Monitor patients in a high-acuity setting. Treatments specific to methylxanthines, particularly theophylline, include use of activated charcoal, treatment of dysrhythmias and seizures, and enhanced elimination.

Initial ancillary studies should include ECG, serum electrolytes, creatinine, urea, glucose, and total creatine kinase. Other laboratory tests may be required based on patient presentation, available medications, and comorbidities. After an intentional ingestion, consider comorbid poisonings, such as with acetaminophen (paracetamol) or salicylate. Consult with a medical toxicologist or a regional poison control center to discuss case-specific treatment.

GI Decontamination Consider GI decontamination with a potentially life-threatening **theophylline** poisoning provided there are no contraindications, such as an unprotected airway, intractable nausea or vomiting, ileus, bowel obstruction, or need for emergent endoscopy (**Table 192-7**).[17] In **caffeine** ingestion, there is little benefit to GI decontamination because of the rapid absorption and associated nausea.

Ondansetron is the preferred antiemetic to control associated nausea or vomiting. Do not use phenothiazines (i.e., promethazine) because these agents lower the seizure threshold. Ranitidine can be used to decrease gastric acid hypersecretion. **Do not give cimetidine as it can prolong methylxanthine half-life.**

Multidose activated charcoal can enhance theophylline elimination by interrupting enterohepatic recirculation.[18] Consult with a toxicologist or poison center regarding the use of whole-bowel irrigation for the ingestion of sustained-release preparations.[19] Endoscopic removal of a slow-release, theophylline-containing bezoar may be necessary. Ipecac syrup, cathartics, and gastric lavage after theophylline ingestion are without proven benefit, have potential adverse effects, and are not recommended.[20-22]

Seizures Due to adenosine antagonism, seizures may be difficult to control, particularly with theophylline toxicity. Benzodiazepines, such as lorazepam 2 to 4 milligrams IV or diazepam 5 to 10 milligrams IV in adults, are first-line agents. Repeated, larger doses may be necessary.

TABLE 192-6 Methylxanthine Toxicity Classifications

	Acute Toxicity	Acute on Chronic Toxicity	Chronic Toxicity
Clinical scenario	Acute exposure: one-time ingestion of a bottle of theophylline or caffeine tablets	Acute exposure in a person chronically using that methylxanthine: an acute ingestion of a bottle of theophylline in a patient taking theophylline	An ongoing exposure to a stable amount with bioaccumulation; typically, due to decreased clearance: a newly prescribed medication inhibits theophylline metabolism, leading to slowly increasing tissue concentrations
Risk of clinical effects	Variable, depends on amount	High, depends on amount ingested and comorbidities	High, depends on tissue level of drug, age, and comorbidities
Timing of peak serum concentration	Often delayed for many hours	Usually delayed	Often immediately available
Correlation of peak serum concentration with clinical effects	Moderate correlation	Moderate correlation	Weak correlation

Barbiturates, such as phenobarbital 10 to 20 milligrams/kg IV in adults, should be used if escalating doses of benzodiazepines are ineffective. At high doses, benzodiazepines and barbiturates can compromise the airway or lead to respiratory depression, so maintain a low threshold for endotracheal intubation. Phenytoin is not useful or recommended.[23]

Patients who fail to respond to anticonvulsant therapy should be sedated, intubated, and paralyzed with a neuromuscular blocking agent; general anesthesia may be required. Paralyzed patients should have an electroencephalogram to monitor for continued seizure activity. Due to the severity of theophylline-induced seizures, some toxicologists recommend prophylactic use of a γ-aminobutyric acid agonist (e.g., lorazepam) to raise seizure threshold in patients presenting with markedly elevated theophylline levels, although this approach has not been validated in human studies.

Cardiovascular Support Manage hypotension initially with IV fluids. The most commonly reported methylxanthine-induced tachydysrhythmias are atrial fibrillation and supraventricular tachycardia, managed using cardioselective β-blockers (esmolol or metoprolol). Ventricular dysrhythmias are uncommon.[24]

Enhanced Elimination Enhanced elimination techniques can prevent or help treat significant toxicity following methylxanthine poisonings. Multidose activated charcoal is recommended for toxic or potentially toxic theophylline ingestions.[18]

Hemodialysis is safe and is as efficacious as hemoperfusion for the treatment of theophylline toxicity.[25] Hemodialysis is also effective for massive caffeine ingestions and pentoxifylline toxicity.[26,27]

Hemodialysis enhances methylxanthine clearance and provides fluid and electrolyte correction. Most experts suggest that a methylxanthine-induced life-threatening event, such as seizures or intractable dysrhythmias, is an indication for hemodialysis. **In addition, we suggest that dialysis should be considered if (1) after an acute ingestion, a symptomatic patient has a serum theophylline level >100 micrograms/mL (>555 micromole/L) or (2) a chronic toxicity patient has a serum theophylline level >60 micrograms/mL (>333 micromole/L) with significant symptoms or comorbidities.**[28] Published experience suggests that most patients who receive hemodialysis **after** a methylxanthine-induced life-threatening event, such as a seizure or dysrhythmia, will continue to have them, whereas as few as 5% of patients who received hemodialysis **before** manifesting severe toxicity will go on to develop a life-threatening event.[29]

TABLE 192-7 GI Decontamination for Methylxanthine Toxicity

GI Decontamination Technique	Indication*	Dosing
Activated charcoal (single dose)	Acute ingestion	<12 y old: 0.5–1.0 gram/kg PO >12 y old: 25–100 grams PO
Multidose activated charcoal (requires close observation)	Acute ingestion	Normal activated charcoal loading dose, followed by: 0.25–0.5 gram/kg PO every 2–4 h for 12 h (frequency and duration may vary)
Whole-bowel irrigation using iso-osmolar polyethylene glycol electrolyte solution	Acute ingestion of sustained-release preparations	9 mo–6 y: 25 mL/kg per hour 6–12 y old: 1000 mL/h >12 y old: 1500–2000 mL/h Duration: 4–6 h or until clear rectal effluent

*Consider contraindications; for details see http://www.clintox.org/resources/position-statements.

Supportive Care Treat vomiting with antiemetics, and correct volume depletion with isotonic fluids. Hypokalemia may not require treatment unless there are clinical findings such as ECG changes, cardiac ectopy, or muscle weakness because potassium is shifted intracellularly and total-body potassium is only mildly depleted. Provide continuous cardiac monitoring until toxicity has resolved. Assess for hyperthermia, rhabdomyolysis, and compartment syndrome, and provide specific treatment. Patients who are sedated and paralyzed should undergo continuous electroencephalographic monitoring to evaluate for occult sustained or recurrent seizures.

DISPOSITION AND FOLLOW-UP

Following an intentional or accidental methylxanthine ingestion, patients are judged nontoxic when they are asymptomatic, have a normal physical examination and vital signs, and, if available, have normal or decreasing serum concentrations. Patients who remain asymptomatic for at least 6 hours after an acute ingestion of immediate-release tablets can be considered nontoxic. Patients with an ingestion of sustained-release medication should be monitored for 12 hours or longer. Patients with intentional ingestions should receive a behavioral health or psychiatric evaluation to assist with appropriate disposition and follow-up.

NICOTINE

EPIDEMIOLOGY

Nicotine is the primary alkaloid in tobacco, a product produced from the dried leaves of plants in the genus *Nicotiana*. Tobacco is consumed as smoke (i.e., cigarettes) or smokeless (i.e., chewing tobacco) products.[30] A typical cigarette contains approximately 20 milligrams of nicotine, but only about 1 milligram is absorbed during smoking. Nicotine gums usually contain 2 or 4 milligrams per piece; formulation and mastication assist in higher absorption compared to smoking a cigarette.

Liquid nicotine used in **electronic (E)-cigarettes** contains up to 36 milligrams/mL of nicotine. Calls to poison centers for pediatric ingestion of liquid nicotine are increasing,[31,32] with more serious toxicity seen with liquid nicotine exposure compared to cigarettes,[31] and deaths have been reported.[33,34]

Other nicotine sources include smoking cessation products (gums, patches, nasal inhalers), pesticides, traditional remedies, and plants, including dermal exposures during tobacco harvest causing "green-tobacco sickness."[35]

PHARMACOLOGY

Nicotine is rapidly absorbed in the lungs, as well as across mucous membranes, the intestinal tract, and intact skin. Smoking tobacco

leads to a peak serum nicotine concentration of 40 nanograms/mL (250 micromole/L), depending on depth of inhalation. Nicotine crosses the blood–brain barrier and affects the CNS within seconds of smoking. Absorption across mucous (oral) membranes is slower than absorption from smoking and is further delayed by gastric acids. Therapeutic use of a 4-milligram piece of nicotine gum leads to a peak nicotine concentration of about 10 nanograms/mL (60 micromole/L) at 45 minutes.[36] The half-life of nicotine is variable, averaging about 2 hours in adults. Metabolism is by the liver, mainly by cytochrome P450 2A6, with 85% being converted to **cotinine**.

Once absorbed, nicotine binds to nicotinic acetylcholine receptors throughout the body, including the central nervous, autonomic, and neuromuscular systems. Early in toxicity, nicotine acts as an agonist, activating these ion channels and leading to increased neuronal firing with release of neurotransmitters, including acetylcholine, dopamine, glutamate, norepinephrine, and serotonin. At higher concentrations and/or as toxicity persists, the acetylcholine receptors are inhibited by persistent membrane depolarization, ultimately leading to receptor inactivation.

CLINICAL FEATURES

In overdose, nicotine mainly affects the GI, cardiovascular, neurologic, and respiratory systems (**Table 192-8**). Nausea and vomiting are the most common effects and can limit absorbed amounts following ingestion. Early effects are due to acetylcholine receptor activation and include tremor, dizziness, tachycardia, and bronchorrhea. Delayed effects, manifesting after larger exposures, occur due to receptor inactivation and include bradycardia, dysrhythmias, hypoventilation, and coma. Seizures are possible and are due to centrally mediated actions.

Nicotine poisoning in children usually results from the ingestion of tobacco or nicotine-containing products, such as E-cigarette liquid. There is no consensus on the estimated lethal dose of nicotine, and accidental ingestion of cigarettes or chewing tobacco in children rarely results in serious outcomes.[37]

A child who ingests one or more intact cigarettes, or three or more cigarette butts, has a 90% chance of becoming symptomatic, usually within 30 minutes.[38] More severe poisonings, such as ingestion of nicotine-containing pesticides, self-harm attempts with nicotine-containing E-cigarette liquid, or abuse of dermal patches, can result in seizures, respiratory failure, hypotension, dysrhythmias, and death.[33] Because nicotine freely crosses the placenta and is found in small concentrations in breast milk, neonatal withdrawal is possible.[39]

Green-tobacco sickness is characterized by nausea, vomiting, weakness, dizziness, and headaches, due to the dermal absorption of nicotine during tobacco harvesting.[35] Onset of symptoms may be delayed for several hours. Patients with significant comorbidities, particularly underlying cardiovascular or seizure disorders, are theoretically at higher risk for morbidity.

Chronic nicotine use has been associated with insulin resistance in diabetics, increased cardiovascular risks, dysrhythmias, and the potential for withdrawal.[40] Nicotine withdrawal manifests with irritability, depression, drowsiness, trouble sleeping, increased appetite, and headaches, with symptoms peaking at 2 to 3 days after last use. Withdrawal can occur in smokers as well as smokeless tobacco and nicotine gum users.

TABLE 192-8 Clinical Effects of Nicotine Toxicity

Organ System	Signs and Symptoms of Nicotine Toxicity*	
	Immediate (<1 h)	Delayed (>1 h)
GI	Hypersalivation Nausea Vomiting	Diarrhea
Cardiovascular	Tachycardia Hypertension	Dysrhythmias Bradycardia Hypotension
Neurologic	Tremor Headache Ataxia	Hypotonia Seizure Coma
Respiratory	Bronchorrhea	Hypoventilation Apnea

*Onset of toxicity is varied and can be delayed for hours following dermal exposure.

TABLE 192-9 Treatment of Nicotine Toxicity

Clinical Condition	Intervention	Considerations
Nausea, vomiting, gastritis	Antiemetics Proton pump inhibitors	Ondansetron, 4 milligrams IV Pantoprazole, 40 milligrams IV
Tremor, seizures	Benzodiazepines	Lorazepam, 1–2 milligrams IV Diazepam, 5–10 milligrams IV
Hypotension	Fluid resuscitation	Monitor and replace serum electrolytes
Hypoventilation	Intubation and mechanical ventilation	—
Withdrawal	Nicotine replacement therapy	Requires outpatient follow-up

DIAGNOSIS

The diagnosis of acute nicotine toxicity is based on reliable history and physical examination, with laboratory analysis being of little value. Qualitative toxicologic screening assays can detect nicotine and cotinine in the urine but may only reflect exposure.

TREATMENT

The treatment of nicotine toxicity is symptomatic. Fortunately, because nicotine has a short half-life, symptoms typically resolve rapidly. Cardiovascular and ventilatory support may be required in severe toxicity (**Table 192-9**). Benzodiazepines may be used for seizures, and endotracheal intubation and mechanical ventilation may be required if significant neuromuscular weakness or respiratory depression develops. Ipecac syrup or activated charcoal is not recommended. Decontamination with soap and water should be done following dermal exposures. There is no role for enhanced elimination or urine acidification.

Nicotine withdrawal can be distressing but is not life threatening. Treatment options include the use of nicotine replacement therapy and antidepressants.

DISPOSITION AND FOLLOW-UP

Monitor patients with known or suspected nicotine toxicity; the length of observation depends on the type of product ingested. Patients who remain asymptomatic with normal vital signs after 3 hours from an acute ingestion of nicotine-containing product (except intact transdermal patches) can be discharged from medical care. **Those who ingest intact transdermal patches should be observed longer, at least 6 hours.** Patients with intentional ingestions should receive a behavioral health or psychiatric evaluation to assist with appropriate disposition and follow-up.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 193

Digitalis Glycosides

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INTRODUCTION

The medicinal benefits of cardiac glycosides have been recognized for centuries. Even with development of alternative medications, digitalis preparations such as digoxin are still used for the treatment of atrial fibrillation and symptomatic congestive heart failure.[1] In addition to availability as pharmaceuticals, cardiac glycosides are also found in plants such as foxglove, oleander, red squill, and lily of the valley. Similar cardioactive steroids are also found in the skin of toads in the Bufonidae family and in some herbal medications. Although intentional overdoses of cardiac glycosides are relatively uncommon, adverse drug reactions and chronic toxicity continue to cause morbidity.[2,3]

PATHOPHYSIOLOGY

Digoxin is a cardiac glycoside available for PO or IV use. Following oral absorption, digoxin reaches a maximal serum concentration 1 to 3 hours after ingestion. It is approximately 25% protein bound and has a large volume of distribution (6 to 7 L/kg). The drug is primarily eliminated through the kidneys.

Digoxin, like other cardiac glycosides, inhibits sodium-potassium adenosine triphosphatase (ATPase).[4] This inhibition results in increased intracellular sodium and increased extracellular potassium. As a result of the increased intracellular sodium, the sodium-calcium antiporter is not able to effectively remove calcium from the myocyte. Consequently, there is an increase in intracellular calcium, which augments inotropy. The increased intracellular calcium can contribute to delayed afterdepolarizations, which may lead to premature ventricular contractions and arrhythmias. In addition, there is a decreased refractory period of the myocardium, which increases automaticity and hence is associated with an increased risk of arrhythmias. Furthermore, cardiac glycosides shorten atrial and ventricular repolarization, thereby decreasing the refractory period and thus increasing automaticity.

Cardiac glycosides also increase vagal tone via action at the carotid body, thereby reducing conduction through the sinoatrial and atrioventricular nodes. In toxic concentrations, cardiac glycosides can increase sympathetic tone. Digoxin can reduce plasma renin concentrations.[5] In patients with advanced heart failure, digoxin can cause vasoconstriction. However, in patients without heart failure, cardiac glycosides can cause vasoconstriction. This difference is likely due to increased sensitivity of the carotid baroreceptors in patients with advanced, chronic heart failure.[6]

CLINICAL FEATURES

Digoxin has a narrow therapeutic index, and toxicity results from an exaggeration of its pharmacologic activity. The timing and clinical presentation of acute versus chronic digoxin toxicity differ significantly (**Table 193-1**).[7] In addition to cardiac manifestations such as syncope and arrhythmia, digoxin toxicity may present with GI distress, dizziness, headache, weakness, malaise, delirium, or confusion. Thus, an elderly patient taking digoxin who presents with mental status changes should be evaluated for toxicity.

ACUTE TOXICITY

Patients with acute digoxin toxicity tend to have more abrupt onset of symptoms than those with chronic toxicity. In acute cardiac glycoside poisoning, there may be an asymptomatic period of several hours before the onset of symptoms. Nausea, vomiting, anorexia, and vague abdominal pain are often the earliest manifestations of acute toxicity. Increased central vagal tone typically produces cardiac manifestations such as bradyarrhythmias or atrioventricular block. Neurologic manifestations such as weakness or confusion can occur independently of hypotension. The classic description of digoxin toxicity includes viewing yellow-green halos around objects, termed *xanthopsia*. However, patients more frequently describe nonspecific changes in color vision.[8]

Hyperkalemia is an important finding in acute toxicity and may develop due to inhibition of sodium-potassium ATPase. Digoxin levels obtained within the first 6 hours following an acute ingestion may be falsely elevated; the level represents a predistribution level rather than reflecting the amount ingested. **Overall, the severity of acute toxicity correlates most closely with the degree of hyperkalemia and correlates poorly with the early serum digoxin levels.**[9]

TABLE 193-1 Clinical Presentation of Digitalis Glycoside Toxicity

	Acute Toxicity	Chronic Toxicity
Clinical history	Intentional or accidental ingestion	Typically elderly cardiac patients taking diuretics; may have renal insufficiency.
GI effects	Nausea and vomiting, abdominal pain, anorexia	Nausea, vomiting, diarrhea, abdominal pain.
CNS effects	Headache, dizziness, confusion, coma	Fatigue, weakness, confusion, delirium, and coma are often prominent features.
Cardiac effects	Bradyarrhythmias or supraventricular tachyarrhythmias with atrioventricular block	Almost any ventricular or supraventricular arrhythmia can occur; ventricular arrhythmias are common.
Electrolyte abnormalities	Hyperkalemia	Normal, decreased, or increased serum potassium, hypomagnesemia.
Digoxin level	Marked elevation (if obtained within 6 h)	Minimally elevated or within "therapeutic" range.

CHRONIC TOXICITY

Chronic toxicity occurs most typically in the elderly and is often the result of drug–drug interactions or declining renal function. Some of the more common drug interactions that predispose to chronic digoxin toxicity involve calcium channel antagonists, amiodarone, β-receptor antagonists, diuretics, indomethacin, procainamide, or erythromycin. A common scenario involves a patient being prescribed a diuretic, which results in mild dehydration and hypokalemia; dehydration reduces the clearance of digoxin, and hypokalemia increases susceptibility to digoxin, with the combination effect resulting in chronic toxicity.

Decreases in renal function and lean body mass associated with aging may alter the pharmacokinetics of digoxin, leading to toxicity at normally therapeutic doses.[10] Older patients may also be at higher risk due to coexisting diseases and polypharmacy.[10,11]

As compared to cases with acute digoxin toxicity, patients with chronic toxicity often have vague and nonspecific signs and symptoms. GI symptoms may occur with chronic toxicity, but they may be less pronounced than seen in the acutely toxic patient. **Neurologic manifestations, such as weakness, fatigue, confusion, or delirium, are more prominent features in chronic toxicity.**[7]

DIAGNOSIS

The diagnosis of digoxin toxicity is a composite picture, using history, physical examination, and laboratory studies; no single element excludes or confirms the diagnosis. In patients with heart failure and normal renal function, daily digoxin doses are usually between 125 and 250 micrograms. Digoxin toxicity can occur with a single ingestion of 1 to 2 milligrams in an adult, and fatalities have been reported following an acute ingestion of 10 milligrams in an adult and 4 milligrams in a child.

Differential diagnosis includes other bradyarrhythmia-inducing agents such as calcium channel antagonists, β-receptor antagonists, class

IA antidysrhythmics (procainamide and quinidine), class IC antidysrhythmics (flecainide and encainide), clonidine and other imidazolines, and organophosphate or carbamate insecticide poisoning. Glycoside-containing and other cardiotoxic plants should also be considered (e.g., foxglove, squill, lily of the valley, oleander, rhododendron, monkshood, tobacco, false hellebore, and yew berry). Sick sinus syndrome, with its combination of supraventricular arrhythmias and cardiac conduction blocks, can also mimic digoxin toxicity. Hyperkalemia from any cause may produce bradycardia and abnormal cardiac conduction and should be considered in the differential diagnosis.

ECG

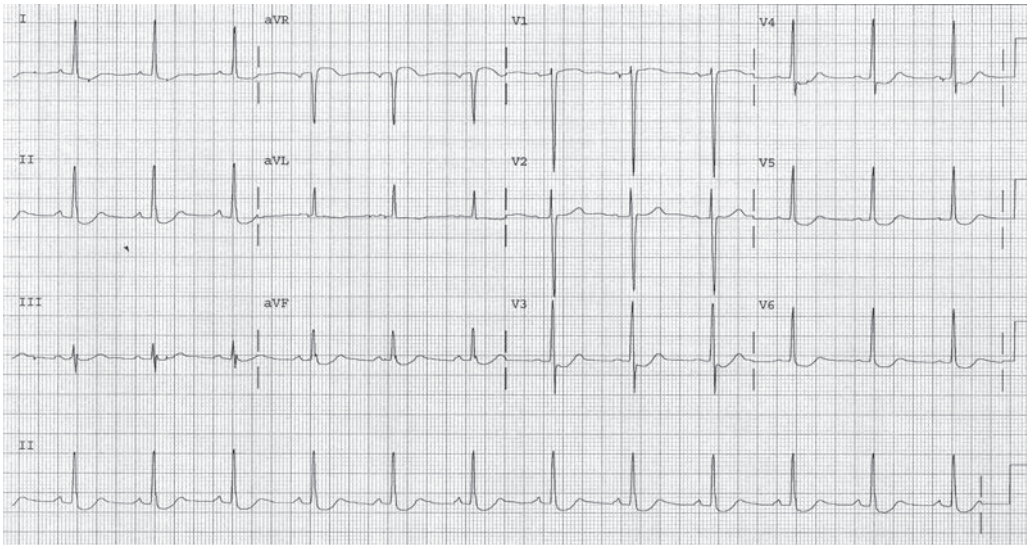
In digoxin toxicity, almost any cardiac arrhythmia may be observed, with the exception of rapidly conducted atrial arrhythmias.[12,13] **The most common arrhythmias in digoxin toxicity are premature ventricular contractions and bradycardic rhythms.**[12] Ventricular arrhythmias occur more frequently in chronic than in acute poisonings. Although rare and not pathognomonic for digoxin toxicity, bidirectional ventricular tachycardia should be investigated for possible toxicity because only a few xenobiotics (digoxin included) are known to produce this unique arrhythmia.

Digoxin-toxic patients may have four specific ECG findings that are typically seen with therapeutic drug levels; presence of these findings does not indicate toxicity. The four findings are T-wave changes (such as flattening or inversion), QT-interval shortening, "scooped" depression of the ST segment, and increased U-wave amplitude (**Figure 193-1**).[14]

LABORATORY

In acute poisonings, the serum potassium and digoxin levels can provide useful diagnostic information.[15] As noted, acute poisoning of the sodium-potassium ATPase pump may result in markedly elevated serum potassium levels. In this circumstance, the serum potassium level is a better indicator of end-organ toxicity (and a better prognostic indicator) than the serum digoxin level.[9]

With chronic toxicity, in contrast to acute poisoning, the serum potassium and digoxin levels are less useful. In these patients, the serum potassium is usually normal or low due to concomitant diuretic therapy, but it may be elevated due to renal insufficiency. Thus, in the setting of chronic toxicity, measured serum potassium is more reflective of underlying comorbidities than the degree of inhibition of sodium-potassium ATPase by digoxin. Also, the serum digoxin level does not correlate with



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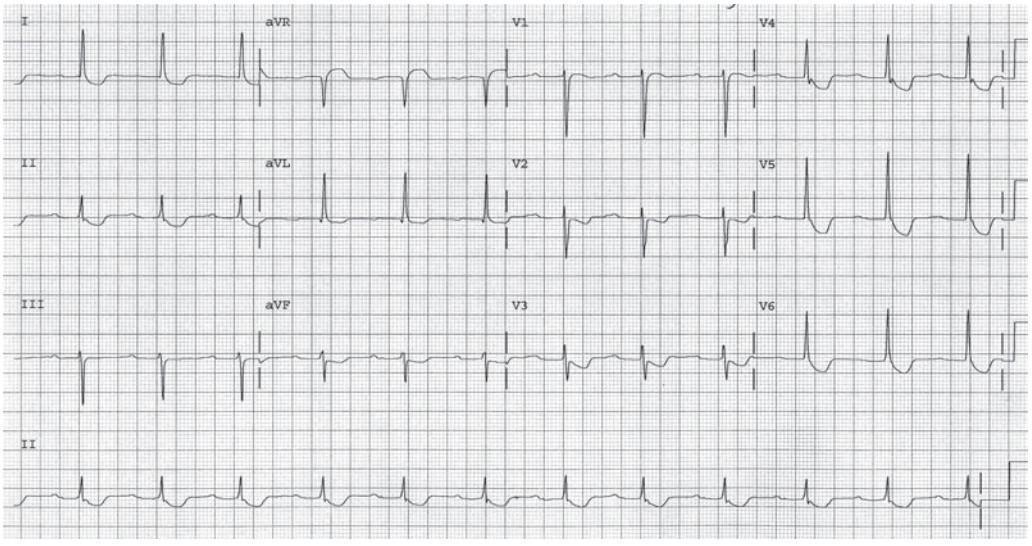

B

FIGURE 193-1. ECG demonstrating findings seen with digoxin use. **A.** ECG shows scooping of ST segments and small U waves with a serum digoxin level of 0.9 nanogram/mL (1.15 nmol/L). **B.** ECG shows scooping of ST segments, flattening of T waves, and first-degree atrioventricular block with a serum digoxin level of 1.2 nanograms/mL (1.54 nmol/L).

the clinical manifestations and *may be within therapeutic ranges* despite significant cardiac toxicity.

Serum digoxin level should be interpreted in the overall clinical context and not relied upon as the sole indicator of the presence or absence of toxicity. Generally accepted therapeutic digoxin levels are 0.5 to 2.0 nanograms/mL (1.0 to 2.6 nmol/L), with corresponding toxic levels above 2.5 nanograms/mL (above 3.2 nmol/L). Due to a relatively slow distribution phase, high digoxin levels sampled from the serum following a recent acute ingestion are not always an accurate indicator of concentration at receptor sites. Serum levels are most reliable when obtained 6 hours after ingestion, when distribution is complete.[15] Despite the limitations as just noted, it is generally true that higher serum digoxin levels are associated with greater likelihood of toxicity. **Importantly, the serum digoxin level should not be the sole factor in establishing the diagnosis of digoxin toxicity, so do not wait for a digoxin level before implementing therapy in an unstable patient.**

Some individuals have digoxin-like immunoreactive substances that cross-react with the digoxin assay, artificially elevating the serum digoxin levels even in the absence of cardiac glycosides. Digoxin-like immunoreactive substances may be found in neonates, third-trimester pregnant women, patients with subarachnoid hemorrhage, and patients with renal or hepatic dysfunction. In addition, naturally occurring cardiac glycosides and cardioactive steroids from plants and animals may cross-react with digoxin assays. The degree of cross-reactivity is variable, and no reproducible correlation has been established between these substances' serum levels and toxicity.[16]

TREATMENT

Management of a digoxin-poisoned patient includes general supportive care, treatment of specific complications of toxicity, prevention of further drug absorption, enhancement of drug elimination, antidote administration (when indicated), and safe disposition (**Table 193-2**).[7] Although patients with intentional or accidental ingestions may present with no symptoms, life-threatening complications of toxicity should be anticipated. Management of the asymptomatic patient should focus on preventing drug absorption and closely monitoring for the development of toxicity. Continuous cardiac monitoring, IV access, and frequent reevaluations should be provided for any patient with a potentially toxic ingestion of digoxin.

For the patient with life-threatening arrhythmias, identify and rapidly correct conditions such as hypoxia, hypoglycemia, hypovolemia, and electrolyte abnormalities. IV magnesium may counteract ventricular irritability seen with cardiac-glycoside toxicity.[18] Use atropine and/or transvenous cardiac pacing as a temporizing treatment for bradyarrhythmias while preparing or obtaining digoxin-specific antibody fragments.[19]

Digoxin-specific antibody fragments (digoxin-Fab) are the treatment of choice in acute poisoning with hyperkalemia (potassium >5.0 mEq/L) and in acute or chronic toxicity with any life-threatening arrhythmia.[20,21] Hyperkalemia is not typically the cause of the death; it is instead a predictor of severe poisoning and increased mortality. Treatment of digoxin-induced hyperkalemia with insulin, dextrose, sodium bicarbonate, or exchange resins does not reduce mortality.[9]

Administration of calcium salts in cardiac glycoside–induced hyperkalemia is controversial. Older literature indicated an increased incidence of ventricular arrhythmias and a higher mortality when calcium was administered to digoxin-toxic patients. However, data from an animal model and retrospective review of a limited number of human patients with digoxin toxicity who received IV calcium found no increase in ventricular arrhythmias or mortality.[22-24] Given that hyperkalemia is not typically the cause of death in digoxin toxicity, calcium salts are best avoided in cases of recognized digoxin toxicity. **In summary, hyperkalemia in acute digoxin poisoning is an indicator of severe toxicity and digoxin-Fab should be given to reduce mortality.**

In chronic toxicity, hypokalemia and hypomagnesemia should be corrected, because both predispose to digoxin toxicity.

TABLE 193-2 Overview: Treatment of Digitalis Glycoside Poisoning

Asymptomatic patients

- Obtain accurate history.
- Secure IV access.
- Initiate continuous cardiac monitoring.
- GI decontamination: Activated charcoal, 1 gram/kg PO, can be considered in an awake, alert, cooperative patient who presents within 1 h of ingestion.
- Frequent reevaluation.

Symptomatic patients

- Obtain accurate history.
- Secure IV access.
- Initiate continuous cardiac monitoring.
- GI decontamination: Activated charcoal, 1 gram/kg PO, in an awake, alert, cooperative patient who presents within 1 h of ingestion.
- *Bradyarrhythmias*
  - Atropine: 0.5–1.0 milligram IV as a temporizing measure for bradyarrhythmias while awaiting digoxin-specific antibody fragments
  - Transcutaneous pacing while awaiting digoxin-specific antibody fragments for symptomatic bradycardia that does not respond to atropine
  - Digoxin-specific antibody fragments: IV infusion (see later discussion for dose)
- *Cardiac arrest*
  - CPR with current advanced cardiac life support protocols (prolonged CPR may be appropriate)[17]
  - Digoxin-specific antibody fragments: IV bolus (10 vials if amount ingested is unknown)

GI DECONTAMINATION AND ENHANCED ELIMINATION

Administrating activated charcoal may have utility in early acute ingestion of digoxin.[21] Activated charcoal may be of benefit following the acute ingestion of yellow oleander, although results of large, randomized trials have been mixed.[25] Gastric lavage is not recommended; asystole during lavage has been reported in a digoxin-toxic patient, presumably from vagal stimulation during the procedure, and no clinical benefit has been demonstrated. Cathartics, forced diuresis, hemodialysis, and hemoperfusion have no role in enhancing elimination of digitalis glycosides. In patients with chronic renal failure who develop digoxin toxicity, there are limited data supporting use of binding resins such as cholestyramine to help enhance elimination.[26]

DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS (DIGOXIN-FAB)

Digoxin-Fabs are derived from ovine antibodies to digoxin. Following IV infusion, the antibody fragments bind digoxin in the plasma and distribute widely throughout the body, removing digoxin from tissues. In severely poisoned patients after digoxin-Fab administration, 90% will show reversal or significant improvement in life-threatening arrhythmia; in most cases, clinical improvement occurs within 1 hour. Patients in cardiac arrest had a 50% survival when receiving digoxin-Fab during the resuscitation, which is significantly better than historical survival with treatment with conventional therapies.[27] Because of cross-reactivity with other cardiac glycosides, digoxin-Fabs are also beneficial in treating digitoxin, foxglove, and oleander poisonings, although large doses have sometimes been required.[16,25] Indications for digoxin-Fab are life-threatening arrhythmias (including hemodynamically significant arrhythmias) and hyperkalemia in excess of 5 mEq/L associated with acute poisoning.

Digoxin-Fab administration is associated with few adverse effects.[20,27] Cardiogenic shock has been reported in patients dependent on digoxin for inotropic support. In addition, ventricular response to atrial fibrillation may be increased. Hypokalemia may develop rapidly as digoxin toxicity is reversed. There have been reports of mild acute hypersensitivity reactions, manifesting as rash, flushing, or facial swelling.

A full neutralizing dose of digoxin-Fab is based on an estimation of the total-body load of digoxin, which can be calculated from either the

TABLE 193-3 Calculation of Digoxin-Specific Antibody Fragment (Fab) Full Neutralizing Dose

Based on suspected amount ingested	Digoxin body load (milligrams) = 0.8 × suspected ingested amount (milligrams) Digoxin body load (milligrams) = serum digoxin concentration (nanograms/mL) × 5.6 L/kg × weight (kg)/1000 One vial (about 40 milligrams) of digoxin-Fab neutralizes 0.5 milligram of digoxin ingested
Based on total serum digoxin concentration	Number of vials = serum concentration (nanograms/mL) × patient weight (kg)/100

dose ingested or a steady-state serum digoxin level (**Table 193-3**). In an acute poisoning, each vial of digoxin-Fab reverses approximately 0.5 milligram of ingested digoxin. In hemodynamically stable patients, half the calculated total neutralizing dose is infused initially, and the other half is given if an adequate clinical response is not seen in 1 to 2 hours.[28] Observational studies report that a total of 200 to 480 milligrams of digoxin-Fab (5 to 12 vials) were required to effectively treat severely digoxin-toxic patients.[27] When the ingested dose is unknown and serum level is unavailable, 10 vials are recommended as initial treatment in life-threatening situations. Digoxin-Fab is administered IV through a 0.22-mm filter over 30 minutes, except in cardiac arrest, when the dose is given as an IV bolus.

Calculations of a full neutralizing dose may overestimate the amount of digoxin-Fab necessary, and smaller doses may adequately eliminate digoxin from the central compartment.[29] In chronic toxicity, an acceptable approach in the hemodynamically stable patient without clear life-threatening arrhythmias is to administer half of the dose calculated by level. If instability develops, the remainder of the full calculated dose can be administered. One to three vials (40 to 120 milligrams) of digoxin-Fab are often adequate in reversing chronic toxicity.[29]

Total serum digoxin levels obtained following digoxin-Fab administration have little correlation with clinical toxicity. Because most laboratory assays do not distinguish between antibody-bound and unbound digoxin, total serum levels obtained following digoxin-Fab administration may increase 10- to 20-fold.[27] However, because the Fab-digoxin complex is not pharmacologically active, this increased level does not correlate with clinical toxicity. In the presence of renal failure, the Fab-digoxin complex may persist in the circulation for prolonged periods.[30] Recurrent toxicity can occur up to 10 days after digoxin-Fab administration in patients with renal failure as the complex degrades. Due to the large molecular weight of the Fab-digoxin complex (45,000 to 50,000 Da), hemodialysis does not enhance its elimination, although plasma exchange may be of benefit.[31,32] New liver support devices incorporating albumin-based dialysis and plasma filtration may be expected to be able to clear the Fab-digoxin complex based on molecular weight alone; some devices have been reported to clear substances up to 100 kDa.[33] However, there is no experience using this technique with digoxin-poisoned patients.

DISPOSITION AND FOLLOW-UP

Extended observation with serial digoxin and potassium levels is recommended for anyone with a confirmed acute ingestion. Asymptomatic patients should be observed until the serum digoxin level is decreasing on serial measurements and the potassium level has remained normal. Patients with signs of toxicity should be admitted to a monitored unit. Consultation with a medical toxicologist or the regional poison control center is recommended. Patients receiving digoxin-Fab require intensive care unit observation for 6 to 12 hours.[28] Patients in renal failure who receive digoxin-Fab may be at risk of delayed toxicity, as the Fab-digoxin complex can dissociate several days later. Finally, patients with suspected suicidality should undergo behavioral health or psychiatric evaluation before discharge.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 194

Beta-Blockers

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INTRODUCTION

β-Adrenergic receptor antagonists (β-blockers) are medications used in the treatment of various cardiovascular, neurologic, endocrine, ophthalmologic, and psychiatric disorders. Among all drug-related fatalities reported to poison control centers nationwide in 2016, β-blockers were involved in 8% of all cases and were responsible for 2% of single-agent fatal exposures.[1]

PHARMACOLOGY

The β-adrenergic receptors are membrane glycoproteins present as three subtypes in various tissues (**Table 194-1**). These receptors play a critical role in cardiovascular physiology by modulating cardiac activity and vascular tone.

During times of stress (i.e., catecholamine release), β-adrenergic receptor stimulation increases myocardial and vascular smooth muscle cell activity through a sequence of intracellular events (**Figure 194-1**).[2,3]

The β-receptor is coupled to a stimulatory G_s protein. This G_s protein stimulates adenylate cyclase, which in turn catalyzes the formation of cyclic adenosine monophosphate (cAMP), the so-called *intracellular second messenger*. Increased cAMP ultimately phosphorylates the L-type calcium channel, which leads to channel opening and calcium entry into the cell. This increase in cytosolic calcium acts at the ryanodine receptor, a calcium channel on the sarcoplasmic reticulum, causing it to release its stored calcium into the cytosol. This process is termed *calcium-induced calcium release*. Stored calcium becomes available to participate in mechanical contraction via the actin and myosin complex. Like the cardiac myocyte, the vascular smooth muscle uses L-type calcium channels to regulate intracellular calcium and subsequently coordinate vascular tone. Phosphodiesterase breaks down cAMP to adenosine 5'-monophosphate, which removes the stimulus for calcium channel opening, and the contractile process ceases.

The β-blockers modulate the activity of cardiac myocytes and vascular smooth muscle contraction by decreasing calcium entry into the cell.[2,3] Therapeutically, β-blockade lessens the work performed by diseased or injured myocardium and lowers elevated blood pressure. In toxicity, excessive β-blockade may lead to bradycardia, decreased contractility, hypotension, and ultimately cardiogenic shock.[2]

TABLE 194-1 Location and Activity of β-Adrenergic Receptors

β-Receptor Type	Location	Agonism	Antagonism
β_1	Myocardium	Increases inotropy Increases chronotropy	Decreases inotropy Decreases chronotropy
	Kidney	Stimulates renin release	Inhibits renin release
	Eye	Stimulates aqueous humor production	Inhibits aqueous humor production
β_2	Bronchial smooth muscle	Causes bronchodilation	Causes bronchospasm
	Visceral smooth muscle	Relaxes uterus Causes ileus	—
	Skeletal muscle	Increases force of contraction Stimulates glycogenolysis	—
	Liver	Stimulates glycogenolysis and gluconeogenesis	Inhibits glycogenolysis and gluconeogenesis
	Vascular	Vasodilation	Minimal vasoconstriction
β_3	Adipose tissue	Stimulates lipolysis	Inhibits lipolysis
	Skeletal muscle	Stimulates thermogenesis	Inhibits thermogenesis

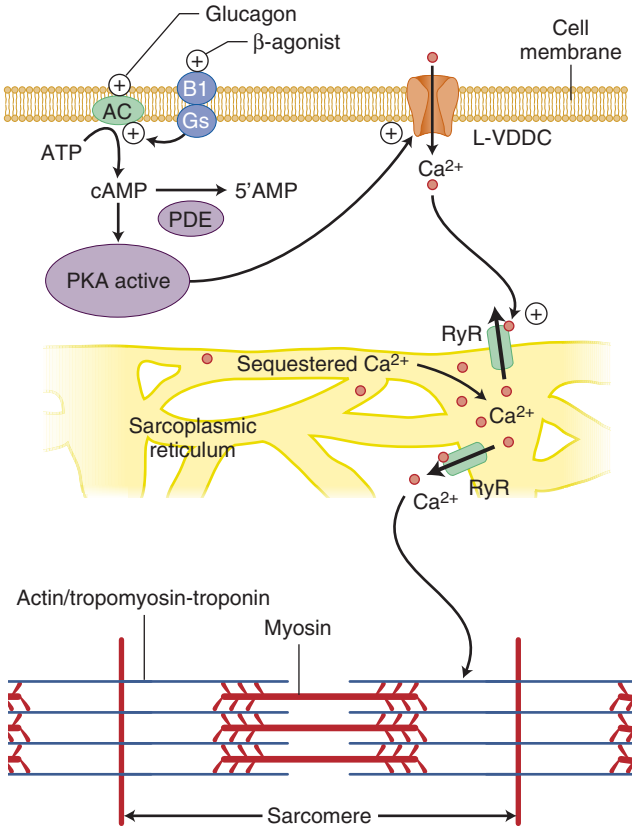

FIGURE 194-1. Cardiac myocyte β_1-receptor and calcium signaling. Following myocyte depolarization, extracellular calcium (Ca^{2+}) enters the cell via the L-type or voltage-gated calcium channel (L-VDCC) and binds to the ryanodine receptor (RyR) in the sarcoplasmic reticulum, causing an efflux of sequestered Ca^{2+} out of the sarcoplasmic reticulum into the cytosol. Free Ca^{2+} binds to troponin that allows the myosin and actin interaction, resulting in contraction of the cardiac myocyte. Binding of a β-agonist to the β_1-adrenergic receptor (B1) on the cell surface activates the Gs protein. The Gs protein then activates adenylate cyclase (AC), which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). The increased cAMP activates protein kinase A (PKA). Activated PKA serves as further stimulus for the L-VDCC opening. Glucagon independently activates adenylate cyclase. cAMP is metabolized by phosphodiesterase (PDE) into inactive adenosine 5′-monophosphate (5′AMP).

The pharmacologic properties of various β-blockers influence their spectrum of action, adverse drug reactions, and toxicity (**Table 194-2**).[4,5] These properties include receptor selectivity, sodium channel blockade (also known as *membrane-stabilizing activity*), lipid solubility, protein binding, and partial agonist activity (also known as *intrinsic sympathomimetic activity*). For example, highly lipid-soluble agents (such as propranolol) readily cross the blood–brain barrier and achieve high concentrations in brain tissue.[2,3] This may contribute to the more severe CNS manifestations of mental status depression, seizures, and coma seen after an overdose of such agents.[2,3] In addition to β-antagonism, several β-blockers also inhibit myocardial sodium channels (similar to quinidine and cyclic antidepressants), rendering these drugs potentially more cardiodepressant following overdose.[3] However, in massive overdoses, all β-blockers can be severely cardiodepressive.[6]

Although β_1 cardioselective medications have less risk of unwanted β_2 effects, such as bronchospasm, selectivity is often lost following large overdoses.[3] Several β-blockers, such as pindolol, have partial agonist activity, causing weak stimulation of the β-receptor, with a lesser tendency for bradycardia during therapeutic use.[4] Some β-blockers, such as labetalol and carvedilol, are also antagonists at α_1-adrenergic receptors, which can result in exaggerated hypotension during therapeutic use. Sotalol is unique among β-blockers in its action as a Vaughan-Williams class III agent, causing blockade of inward rectifier potassium channels involved in cardiac repolarization.[2-4]

In addition to cardiopulmonary effects, β-blockers alter metabolism in the liver, skeletal muscle, and adipose tissue. Under normal conditions, the heart uses free fatty acids as its primary energy source, but during times of stress, it switches to carbohydrate metabolism. The inhibition of glycogenolysis and gluconeogenesis in β-blocker overdose reduces the availability of carbohydrates for use by metabolically active cells. Although hypoglycemia can occur as a consequence of β-blocker toxicity, it is actually uncommon.[2] In the presence of adequate glucose stores, euglycemia and even hyperglycemia are more common than hypoglycemia.

Clinically relevant pharmacokinetic characteristics include drug formulation (regular or extended release), rate of drug absorption, protein binding, lipid solubility, elimination (mostly by hepatic metabolism), and volume of distribution. These properties determine onset of symptoms, duration of symptoms, target organ toxicity, and potential treatment modalities.

CLINICAL FEATURES

Toxicity due to β-blockers can produce a spectrum of clinical symptoms (**Table 194-3**).[2,3,7] The timing of symptom appearance depends upon the formulation. Absorption of regular-release β-blockers occurs rapidly, often with peak effects within 1 to 4 hours. However, delays of up to 6 hours following acute ingestion have occurred.[8] Experience is limited regarding onset of symptoms with poisoning following an ingestion of sustained-release β-blocker formulations, but based on other sustained-release cardiac drugs, it is assumed that symptoms may be delayed for >6 hours after ingestion.[2,3] Co-ingestants that alter gut function, such as opioids and antimuscarinic drugs, may affect absorption of β-blockers and subsequent onset of symptoms.[2]

The primary target of β-blocker toxicity is the cardiovascular system, and the hallmark of severe toxicity is bradycardia with shock.[2,3,7,9] Bradycardia due to sinus node suppression or conduction abnormalities occurs in virtually all significant β-blocker intoxications, although ingestion of β-blockers with partial agonist activity may initially present with hypertension and tachycardia.[9] The β-blockers with sodium channel antagonism can cause conduction abnormalities, leading to a wide-complex bradycardia that can worsen hypotension and shock (especially when the QRS interval is >100 milliseconds).[9]

The cardiotoxic profile of sotalol is different from that of other β-blockers due to its blockade of potassium channels, causing QT prolongation.[3] Thus, sotalol is more often associated with ventricular dysrhythmias, including premature ventricular contractions, bigeminy, ventricular tachycardia, ventricular fibrillation, and torsades de pointes.[3]

β-Blockers also affect the CNS and pulmonary system. Neurologic manifestations include depressed mental status, coma, and seizures.[2] These symptoms most likely occur due to a combination of hypoxia secondary to poor perfusion, sodium channel antagonism, and direct neuronal toxicity.[2] More lipophilic β-blockers, such as propranolol, cause greater neurologic toxicity than the less lipophilic agents.[9] Seizures are generally brief, and status epilepticus is rare.[2] Antagonism of the β_2-receptor in bronchial smooth muscle can cause bronchospasm, both in the setting of nonselective β-blockers and in large ingestions of cardioselective β-blockers, where β_1 selectivity may be lost.

DIAGNOSIS

The diagnosis of β-blocker toxicity is primarily made on clinical grounds, including patient history, physical examination findings, and results of basic diagnostic testing. Patients commonly present with a history of intentional overdose or therapeutic misadventure. The diagnosis may be more challenging in cases of polypharmacy, multidrug overdose, or chronic drug toxicity. In addition to β-blockers, multiple other drugs and toxins can present with bradycardia and hypotension; however, there are several features that can help to differentiate these exposures (**Table 194-4**).

Laboratory testing is recommended to assess renal function, glucose level, oxygenation, and acid-base status. Although specific β-blocker drug levels might be of value for later confirmation of an ingestion, these levels are not helpful initially because they do not correlate with the degree of toxicity and are generally not available in a timely fashion to affect acute management.[2,3,7] False-positive amphetamine results can

TABLE 194-2 β-Blocker Pharmacologic Profiles

Agent	β_1 Selectivity	Lipophilicity	Partial Agonism	Protein Binding (%)	Sodium Channel Blockade	Half-Life (h)	Maximum Recommended Adult Daily Dose (milligrams)
Acebutolol	+	Moderate	+	25	+	3–4	1200 (800 in elderly)
Atenolol	+	Weak	0	6–16	0	6–9	100 (HTN) 200 (angina)
Betaxolol	+	High	0	55	±	14–22	40
Bisoprolol	++	Moderate	0	30–40	0	9–12	20 (HTN) 10 (HFrEF)
Carvedilol	0	Moderate	0	>95	±	7–10	50 (IR) 80 (ER)
Esmolol	+	Weak	0	55	±	9 min	NA
Labetalol	+	Weak	0	50	±	3–4	2400
Metoprolol	++	Moderate	0	12	±	3–4	450 (HTN) 400 (angina)
Nadolol	0	Weak	0	30	0	12–24	320 (HTN) 240 (angina)
Nebivolol	+++	Moderate	0	98	0	8–27	40
Oxprenolol	0	Moderate	++	80	+	1–2	
Pindolol	0	High	++	40–60	±	3–4	60 (HTN) 40 (angina)
Penbutolol	0	High	+	80–98	0	5–20	80
Propranolol	0	High	0	>90	++	3–4	640 (HTN) 320 (angina)
Sotalol	0	Weak	0	Minimal	0	12	640
Timolol	0	High	±	10–60	0	4–5	60

Abbreviations: + = some activity; ++ = strong activity; ± = possible activity; 0 = no activity; ER = extended-release form; HTN = hypertension; HFrEF = heart failure with reduced ejection fraction; IR = immediate-release form; NA = not applicable.

be seen on urine drug screens from labetalol, because one of its metabolites is structurally similar to amphetamine.[10] Cardiac function may be evaluated with a 12-lead ECG, rhythm monitor, and bedside cardiac US.[11] A drug-induced Brugada pattern has been reported in propranolol overdose, a β-blocker that also blocks cardiac sodium channels.[12]

TREATMENT

GENERAL MANAGEMENT

Patients with suspected β-blocker overdose should be evaluated in a critical care area of the ED with appropriate monitoring because they may experience abrupt cardiovascular collapse or neurologic depression. If orotracheal intubation is performed, the drugs used for sedation and paralysis may worsen hypotension in the setting of an already depressed myocardium (see Chapter 29A, "Tracheal Intubation").[2,3,7]

No one particular treatment is consistently effective in the management of β-blocker toxicity, and multiple simultaneous treatment measures may be required to resuscitate the critically ill patient. Therapy should be tailored to each individual case based on exposure history, ECG, bedside cardiac US, and/or central hemodynamic monitoring. The goal of resuscitation is to improve hemodynamics and organ perfusion. Specific end points of therapy may include a cardiac ejection fraction of 50% or greater, a reduction of the QRS interval to <120 milliseconds, a heart rate of >50 to 60 beats/min, a systolic blood pressure of >90 to 100 mm Hg (12.0 to 13.3 kPa) in an adult, urine output of 1 to 2 mL/kg per hour, and improved mentation.

TABLE 194-3 Common Findings With β-Blocker Toxicity

Cardiovascular	Hypotension Bradycardia Conduction delays and blocks (first-degree atrioventricular block) Ventricular dysrhythmias (sotalol) Asystole Decreased contractility
CNS	Depressed mental status Coma Psychosis Seizures Respiratory arrest
Pulmonary	Bronchospasm
Electrolytes	Hypoglycemia (uncommon) Hyperkalemia

TABLE 194-4 Toxicologic Causes of Bradycardia and Hypotension

Cause	Differentiating Features
Calcium channel blockers	Elevated lactate level and possible hyperglycemia
Naturally occurring cardioactive steroids (oleander, foxglove, lily of the valley, rhododendron, and *Bufo* toads)	Ventricular ectopy May cross-react with digoxin immunoassay
Class IC antiarrhythmic drugs (propafenone)	Wide-complex bradycardia
Clonidine	Opioid-like manifestations: coma, miosis, decreased respirations
Cyanide	Profound metabolic acidosis and elevated lactate level
Digoxin (acute)	Hyperkalemia Elevated level on digoxin immunoassay
Organophosphates	Cholinergic toxidrome

GI DECONTAMINATION

Although there is little evidence to support routine GI decontamination following overdose of most substances, ingestion of a significant quantity of β-blockers with the risk of severe toxicity is a circumstance in which early decontamination should be considered.[13] Activated charcoal may be of benefit if it can be given within 1 hour after ingestion in a patient without airway compromise.[14,15] There may be an additional window of opportunity for activated charcoal therapy following ingestion of extended-release β-blockers. After airway protection, consider gastric lavage in recent, large ingestion. Ipecac syrup and cathartic agents are not recommended.[16] Gastric lavage is not recommended.[13] Whole-bowel irrigation may be beneficial and should be considered after a large ingestion of an extended-release product.[17]

PHARMACOLOGIC TREATMENT

Specific pharmacologic therapies are directed at restoring perfusion to critical organ systems by improving myocardial contractility, increasing heart rate, or both.[2,3,7] This is done through fluid resuscitation and administration of glucagon, adrenergic agonists, high-dose insulin, calcium, and phosphodiesterase inhibitors (**Figure 194-2**). Individual pharmacologic therapies have variable effectiveness and are often used simultaneously.[7] Aggressive measures such as hemodialysis, hemoperfusion, cardiac pacing, placement of intra-aortic balloon pumps, and extracorporeal circulatory support have also been used when patients are refractory to pharmacologic therapy.[18]

Treatment of **sotalol toxicity** may require the use of additional pharmacologic measures due to its potassium channel effects. In addition to the therapies discussed earlier, magnesium supplementation, lidocaine, and cardiac overdrive pacing may be of specific benefit if there is QT prolongation or torsades de pointes.

GLUCAGON

Glucagon is a first-line agent in the treatment of acute β-blocker–induced bradycardia and hypotension.[2,19] Glucagon, produced in the pancreatic α-cells from proglucagon, independently activates myocardial adenylate cyclase, bypassing the impaired β-receptor and increasing intracellular cAMP (Figure 194-1). Glucagon has demonstrated positive inotropic and chronotropic effects in both animal models and human studies.[20] Effects from an IV bolus of glucagon are seen within 1 to 2 minutes, reach a peak in 5 to 7 minutes, and have a duration of action of 10 to 15 minutes.[2,3] Due to the short duration of effect, a continuous infusion is often necessary after bolus administration. The initial bolus dose of glucagon is 3 to 10 milligrams (30 to 150 micrograms/kg in children), and if no response is seen within 15 minutes, a repeat bolus can be given. If a beneficial effect is seen from the glucagon bolus, a continuous infusion of 1 to 5 milligrams/h (20 to 70 micrograms/kg per hour in children) can be used to maintain this effect. Titrate the glucagon infusion to achieve adequate hemodynamic response. There is no identified maximum therapeutic dose or duration of treatment.[19]

The amount of glucagon required to treat a significant β-blocker overdose may exceed the total amount available at any given hospital.[19] The positive inotropic and chronotropic effects of glucagon may not be maintained for a prolonged period due to tachyphylaxis. Nausea and vomiting are commonly reported side effects of high-dose glucagon therapy and may be related to esophageal sphincter relaxation. Antiemetics can be given prior to glucagon administration. Check QT_c interval before giving ondansetron. Intubation prior to glucagon administration may be warranted in any patient with altered mental status in order to limit the risk of aspiration.[2,3,7]

Prior to 1998, glucagon was derived from porcine and bovine pancreas and contained other pancreatic compounds such as insulin and phenol as a preservative.[2] The contribution of this insulin content to the original glucagon's overall efficacy is unclear (see discussion later in "High-Dose Insulin Therapy"). Since 1998, glucagon has been produced via recombinant technology and is devoid of insulin or phenol.

ADRENERGIC RECEPTOR AGONISTS

The β-adrenergic receptor agonists—such as norepinephrine, dopamine, epinephrine, and isoproterenol—are routinely used to treat β-blocker toxicity.[2,19] However, results have been variable even when dosages far exceed those recommended in standard guidelines for cardiac resuscitation.[3] The most effective adrenergic receptor agonists may be norepinephrine and epinephrine due to their chronotropic and vasopressor effects. Phenylephrine may also be beneficial as a vasopressor. Although isoproterenol may increase heart rate, it does so at the expense of vasodilation. Dobutamine has a similar downside: potential improvement in inotropy but worsening of hypotension due to vasodilation.

HIGH-DOSE INSULIN THERAPY

High-dose insulin (HDI) therapy, also referred to as hyperinsulinemia-euglycemia therapy, is an important treatment modality for β-blocker toxicity.[17,21-23] Insulin acts as an inotrope by facilitating myocardial utilization of glucose (the energy substrate employed during stress), in contrast to glucagon, epinephrine, and calcium, which promote free fatty acid utilization.[21-24] In animal models, HDI improved survival in severe β-blocker overdose compared with glucagon, epinephrine, or vasopressin administration.[25,26] The most consistent cardiodynamic effect in these models was an increase in contractility.

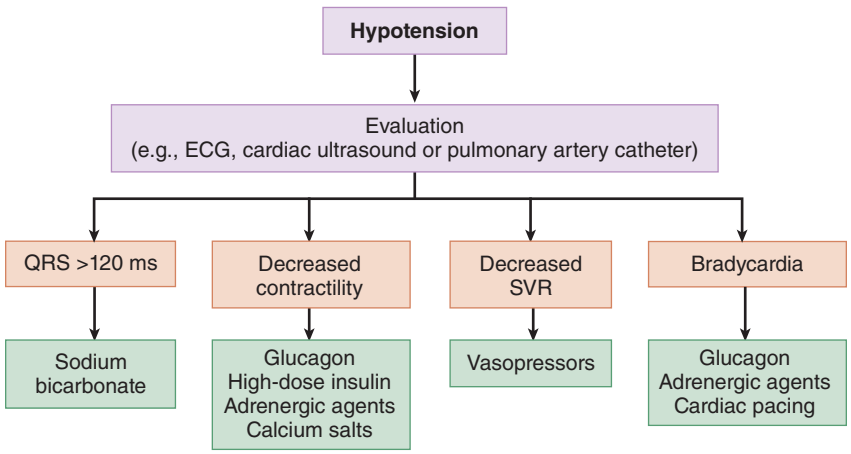

FIGURE 194-2. Management strategies in β-blocker toxicity. Cardiac function is evaluated using ECG, cardiac US, and/or central hemodynamic monitoring. For wide QRS interval, consider sodium bicarbonate therapy. For impaired myocardial contractility, consider glucagon, high-dose insulin, adrenergic agents, and calcium therapy. For decreased systemic vascular resistance, consider vasopressors, such as norepinephrine, epinephrine, dopamine, and phenylephrine. For bradycardia, consider glucagon, adrenergic agents, and cardiac pacing. (See text for details.) SVR = systemic vascular resistance.

TABLE 194-5 Protocol for High-Dose Insulin Therapy in Severe β-Blocker Overdose

- Check serum glucose, and if <200 milligrams/dL (<11 mmol/L), administer 50 mL of 50% dextrose (0.5 gram/mL) in water IV (children 1 mL/kg of 25% dextrose).
- Administer regular insulin 1 unit/kg IV bolus.
- Begin regular insulin infusion at 1.0 unit/kg per hour along with dextrose 10% (0.1 gram/mL) in water at 200 mL/h (adult) or 5 mL/kg per hour (pediatric).
- Titrate infusion rate up to 10 units/kg per hour according to the hemodynamic goal of HR >50 beats/min and SBP >100 mm Hg (>13.3 kPa).
- Monitor serum glucose every 15–20 min.
- Titrate dextrose infusion rate to maintain serum glucose level between 100 and 200 milligrams/dL (5.3 and 10.7 mmol/L).
- Once dextrose infusion rates have been stable for 60 min, glucose monitoring may be decreased to hourly.
- Monitor serum potassium level and start IV potassium infusion if serum potassium level is <2.8 mEq/L (<2.8 mmol/L).
- Maintain serum potassium between 2.8 and 3.2 mEq/L (2.8 and 3.2 mmol/L).

Abbreviations: HR = heart rate; SBP = systolic blood pressure.

HDI dosing used for treatment of β-blocker toxicity is much higher than that used for traditional glucose control in diabetes (**Table 194-5**). The initial dose is regular insulin 1 unit/kg IV bolus and is followed by a continuous infusion of 1 unit/kg per hour that is titrated to the desired hemodynamic response of a heart rate at least 50 beats/min and systolic blood pressure of at least 100 mm Hg (13.3 kPa).[21-23] The maximum dose has not yet been established, although an animal model of propranolol overdose found that cardiac output increased in a dose-response manner when the insulin dose was raised from 1 to 10 units/kg per hour,[27] and human case reports and case series have reported doses this high.[23,28]

The onset of action with HDI is reported to be 15 to 45 minutes, but a delayed response of several hours has been noted.[21] HDI is continued until there is resolution of toxicity; the duration of HDI infusion described in case reports ranges from 9 to 49 hours.[23] The insulin infusion can be gradually weaned or abruptly halted, and should be reinstituted if heart rate or blood pressure falls after cessation of HDI. Supplemental dextrose is needed for several hours after insulin infusion is stopped.

Potential adverse effects from HDI are hypoglycemia and lowered serum potassium. Dextrose infusion is used to prevent hypoglycemia and often required during the duration of therapy.[23] Hypoglycemia tends to occur more often in the treatment of β-blocker toxicity when compared to the treatment of calcium channel–blocker overdose. In a large case series, 41% of patients with single-agent β-blocker overdose treated with HDI developed hypoglycemia.[28] Serum potassium is monitored, and supplemental replacement is given if the level is below 2.8 mEq/L (2.8 mmol/L).[21,23] An increase in the dextrose infusion rate required to maintain serum glucose between 100 and 200 milligrams/dL (5.3 and 10.7 mmol/L), along with signs of clinical improvement, may be an indication that metabolic status is normalizing; that is, that the stress response is diminishing, the heart is reverting back to basal energy substrates, and extra insulin is no longer needed.

IV LIPID EMULSION THERAPY

IV lipid emulsion (ILE) therapy, also known as fat emulsion therapy or lipid rescue, is extremely effective in treating toxicity from local anesthetics and has also been used with mixed results in the treatment of toxicity from calcium channel blockers, typical and atypical antipsychotics, cyclic and other antidepressants, and some β-blockers.[29-32] The exact mechanism is not fully understood, but the likely explanation is that lipid emulsion acts as a pharmacologic sink, sequestering lipophilic drugs into a separate lipid compartment, and the amount of free drug available to target tissues is reduced ("lipid sink" model).[33] Other potential mechanisms may include supplying the myocardium with free fatty acids and phospholipids, increasing myocardial contractility by increasing myocyte calcium concentration, and elevating blood pressure by central sympathetic activation.

Animal models suggest that ILE, if effective, may be most beneficial in the treatment of toxicity from lipophilic β-blockers (Table 194-2), such as propranolol and carvedilol, rather than the more hydrophilic agents, such as metoprolol and atenolol.[34]

The dosing regimen for ILE is based on treatment of local anesthetic systemic toxicity. The standard 20% lipid emulsion is given as a 1.5 mL/kg bolus over 1 minute, followed by an infusion at 0.25 mL/kg per minute.[33] If the blood pressure remains low, an additional 1.5 mL/kg bolus may be repeated followed by an increase in the infusion rate to 0.5 mL/kg per minute. The recommended upper limit is 10 mL/kg over the initial 30 minutes. If the patient's hemodynamic stability is dependent on continued lipid infusion, the treatment may be continued beyond this level. Duration of therapy has not been fully established. If cardiac arrest occurs, a bolus dose can be given during the resuscitation.

Adverse effects reported with the use of ILE for the treatment of overdose and toxicity include lipemia causing interference with laboratory analysis, hypertriglyceridemia, pancreatitis, hypersensitivity, allergic reaction, acute lung injury, acute renal failure, venous thromboembolism, fat embolism, increased susceptibility to infection, and cardiac arrest.[35-38] Lipid emulsion may clog the hemofiltration filter, precluding renal replacement therapy and other methods of extracorporeal support during the infusion and until the lipid has been cleared from the blood.[39] Overall, the effect of ILE in various non–local anesthetic poisonings is heterogenous, and the quality of evidence remains low to very low.[32] Given the potential for adverse effects and the lack of strong supporting evidence for use of ILE in the treatment of β-blocker toxicity, ILE should be reserved for refractory shock after other treatment modalities have failed.

ATROPINE

Atropine, a muscarinic blocker, is unlikely to be effective in the management of β-blocker–induced bradycardia and hypotension, although its use is unlikely to cause harm.[3,4,7] It may be beneficial for the treatment of other co-ingestants.

CALCIUM

Canine studies and limited case reports suggest that calcium therapy may reverse depression of the myocardium via positive inotropic action, although with few chronotropic effects.[2,3] Calcium administration is not routinely recommended in β-blocker overdose, but may be considered in patients with refractory shock unresponsive to other therapies. Calcium for IV administration is available in two forms, gluconate and chloride, both in a 10% solution. A 10-mL dose of 10% calcium chloride solution contains three times more elemental calcium, 13.6 mEq (6.8 mmol), than 10 mL of 10% calcium gluconate solution, 4.5 mEq (2.23 mmol). Thus, one 10-mL ampule of 10% calcium chloride equals three 10-mL ampules of 10% calcium gluconate.

Potential adverse effects of calcium therapy include hypercalcemia, conduction blocks, worsening bradycardia, and inefficient cardiac energetics during shock (see earlier "High-Dose Insulin Therapy" section). Most patients tolerate transient increases in total calcium level without difficulty, and conduction blocks are rare. Severe soft tissue injury associated with inadvertent IV infiltration of the chloride formulation is the most concerning adverse event. Thus, calcium chloride is ideally given via central access. Calcium gluconate is only rarely associated with tissue injury and is the preferred form for peripheral administration.

The optimum dose of calcium in β-blocker toxicity is unknown. Animal studies and limited human studies suggest that large amounts of calcium are needed to treat drug-induced cardiac toxicity, but these data come from experience derived from treating calcium channel–blocker toxicity.[2,3] The recommended dose of 10% calcium gluconate is 0.6 mL/kg given over 5 to 10 minutes, followed by a continuous infusion of 0.6 to 1.5 mL/kg per hour.[2,3] The equivalent dosage of 10% calcium chloride is 0.2 mL/kg given via central line over 5 to 10 minutes, followed by a continuous infusion of 0.2 to 0.5 mL/kg per hour. Ionized calcium levels should be checked every 30 minutes initially and then every 2 hours to achieve an ionized calcium level of twice the normal value.[2]

PHOSPHODIESTERASE INHIBITORS

Phosphodiesterase inhibitors such as milrinone have been used to treat β-blocker toxicity. These agents inhibit the breakdown of cAMP, thereby sustaining intracellular calcium levels (Figure 194-1).[2,3] In animal models, phosphodiesterase inhibitors produce positive inotropic effects without increasing myocardial oxygen demand but have no appreciable effect on heart rate. Compared with glucagon, phosphodiesterase inhibitors do not provide any additional benefit and therefore have no advantage over glucagon. However, if glucagon is not available or pharmacy stores have been exhausted, a phosphodiesterase inhibitor is a reasonable alternative. In the setting of a β-blocker overdose, milrinone is administered as a continuous IV infusion, starting with a 50 micrograms/kg IV bolus, followed by an IV infusion of 0.375 to 0.75 microgram/kg per minute for milrinone.[40]

SODIUM BICARBONATE

Sodium bicarbonate is used to treat severe acidosis and wide QRS interval dysrhythmias secondary to sodium channel blockade. β-Blockers with sodium channel antagonism (e.g., propranolol; Table 194-2) can interfere with ventricular depolarization, predisposing to cardiac dysrhythmias. When the QRS interval is longer than 120 milliseconds, it is reasonable to administer sodium bicarbonate.[2] The suggested dose is a rapid bolus of 2 to 3 mEq/kg over 1 to 2 min.[2,3,6] Thus, a 70-kg adult receives a bolus of 140 to 210 mEq of sodium bicarbonate, or three to four ampules (50 mL each) of 8.4% sodium bicarbonate. Repeat boluses or an infusion may be required to maintain the QRS interval at <120 milliseconds.

CARDIAC PACING

Internal or external pacing may be considered to treat bradycardia in the setting of β-blocker toxicity.[2,3] Electrical capture and restoration of blood pressure are not always successful, potentially due to the lack of intracellular calcium needed for contraction.[2,3] Cardiac pacing may be most beneficial in treating torsades de pointes associated with sotalol toxicity.

EXTRACORPOREAL ELIMINATION (HEMODIALYSIS)

The high degree of protein binding and lipid solubility of β-blockers, as well as their large volume of distribution, renders extracorporeal drug removal useless for most drugs in this class. Acebutolol, atenolol, nadolol, and sotalol may be amenable to removal through hemodialysis owing to their lower protein binding, water solubility, and lower volume of distribution.[41]

EXTRACORPOREAL CIRCULATION

Occasionally, extreme means of resuscitation, including extracorporeal circulation (extracorporeal membrane oxygenation) and intra-aortic balloon pumps, have been successful when pharmacologic measures have failed to reverse cardiogenic shock.[42,43]

DISPOSITION AND FOLLOW-UP

Patients who develop altered mental status, bradycardia, conduction delays, or hypotension should be managed in an intensive care unit. A patient who ingests a sustained-released β-blocker product warrants admission and monitoring for the development of delayed toxicity.[2,3,9] Patients ingesting an overdose of immediate-release β-blocker tablets who remain asymptomatic and have normal vital signs at 6 hours after time of ingestion can be deemed medically safe for discharge or admission to a psychiatric facility.[9]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 195

Calcium Channel Blockers

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Christian Tomaszewski

INTRODUCTION

Calcium channel blockers (CCBs) are commonly used for the treatment of hypertension and angina pectoris and for ventricular rate control in supraventricular dysrhythmias. Less common uses include migraine prophylaxis and treatment of esophageal spasm, pulmonary hypertension, or arterial vasospasm due to Raynaud's disease.[1]

PHARMACOLOGY

Understanding the physiology of calcium in the cardiovascular system is crucial to understanding the effects of CCBs. Influx of calcium is regulated by L-type calcium channels, which are found predominantly in the heart, vascular smooth muscle, and pancreatic β islet cells. Intracellular calcium facilitates sinoatrial node depolarization and propagation of the electrical signal through the atrioventricular node. Additionally, myocytes rely on L-type channels to allow intracellular calcium influx during the plateau phase (phase 2) of the action potential, which signals the release of stored calcium from the sarcoplasmic reticulum, allowing myocardial contraction. Calcium influx is also necessary for the release of insulin. Therefore, CCBs have multiple effects by blocking the entry of calcium required for normal pacemaker activity, atrioventricular nodal conduction, myocardial contraction, and insulin release.[2]

At therapeutic concentrations, CCBs bind to the α_1 subunit of the L-type calcium channel, causing the channel to favor the closed state and thereby decreasing calcium entry. At very high concentrations, some CCBs (notably verapamil) may occupy the channel canal and completely block calcium entry. The results are profound smooth muscle relaxation, weakened cardiac contraction, blunted cardiac automaticity, and intracardiac conduction delay.[1] Clinically, these effects produce hypotension and bradycardia. Animal data suggest that verapamil overdose also impairs myocardial carbohydrate intake, which contributes to the negative cardiac inotropy.[3] All CCBs undergo hepatic metabolism through CYP3A4.

The three main pharmacologic classes of CCBs are phenylalkylamines, benzothiazepines, and dihydropyridines (which is the class that includes most newer CCB agents) (**Table 195-1**). It is easiest to think of CCBs as dihydropyridines (all CCBs with generic names ending in "pine") and nondihydropyridines.

All CCBs relax vascular smooth muscle, reduce pacemaker activity, and decrease cardiac contractility. However, these effects occur at different dose ranges for each drug. All three CCB classes increase coronary blood flow in a dose-dependent fashion.[4] Each group binds a different region of the calcium channel and has different affinities for calcium channels in various tissues. Verapamil is the most potent negative inotrope of all CCBs. At any concentration, it causes at least as much depression of heart contraction as it does vascular smooth muscle dilatation.[5] The combined cardiovascular effect may be one reason that verapamil overdose causes more deaths than all other CCBs combined.[6]

Dihydropyridines bind more selectively to vascular smooth muscle calcium channels than to cardiac calcium channels and therefore relax smooth muscle at concentrations producing almost no negative inotropy. The difference in the effects of these agents is the reason for preferential use of specific agents in particular clinical situations.[7] The nondihydropyridines, verapamil and diltiazem, are used to manage hypertension, achieve rate control in atrial flutter and atrial fibrillation, and abolish supraventricular reentrant tachycardias. Dihydropyridines are typically used to treat diseases with increased peripheral vascular tone, such as hypertension, Prinzmetal's angina, and vasospasm after subarachnoid hemorrhage.[1]

The original three CCBs—verapamil, nifedipine, and diltiazem—all have relatively short serum half-lives (Table 195-1). Consequently,

TABLE 195-1 Oral Calcium Channel Blockers

Class	Standard Preparation (IR) Half-Life (h)	Maximum Adult Daily Dose (milligrams)	Comments
Nondihydropyridines			More cardioselective
Phenylalkylamines			
Verapamil	2–5	480 for IR and ER	Most potent negative inotrope of all CCBs
Benzothiazepines			
Diltiazem	3–5	480 for IR and 540 for ER	
Dihydropyridines (most newer calcium channel blockers fall into this class)			More selective for vasculature
Nifedipine	2	180 for IR and 90 for ER	
Amlodipine	30–50	10	
Nicardipine	8–14	120 for IR and ER	
Felodipine	8	10	
Isradipine		10	
Nimodipine	Early: 1–2; terminal: 8–9	360	
Nisoldipine	7–12	34	

Abbreviations: ER = extended release; IR = immediate release.

extended-release (ER) formulations have been developed for all three. Because ER formulations prolong drug absorption, onset of effect may be delayed and toxicity may be prolonged following overdose.[8,9] Several of the newer dihydropyridines have prolonged duration of action and, therefore, are generally not formulated as ER products. Because newer formulations are released frequently, it is helpful to consult with the ED pharmacist or contact a regional poison control center for help in determining if a given product ingested in an overdose is formulated as an immediate-release (IR) or ER preparation.

CLINICAL FEATURES

The most prominent and life-threatening effects are an extension of the therapeutic effects on the cardiovascular system, particularly decreased cardiac output and peripheral vasodilation. Hypotension is the most common physiologic abnormality after overdose.[10,11] Patients with moderate verapamil or diltiazem (nondihydropyridines) poisoning often have sinus bradycardia, varying degrees of atrioventricular block, and hypotension. Atrioventricular block occurs more often with verapamil than with diltiazem or nifedipine.[12] Mild or moderate dihydropyridine overdoses usually cause peripheral vasodilatation with resultant hypotension and reflex tachycardia.[12] Like all CCBs, dihydropyridines lose their selectivity in large overdoses and may present with sinus bradycardia or normal rate in severe toxicity. All CCBs may cause complete heart block, depressed myocardial contractility, and vasodilatation that ultimately results in cardiovascular collapse.

Pulmonary and CNS effects are generally secondary to decreased myocardial function and impaired organ perfusion. Cardiogenic pulmonary edema is sometimes observed in severe overdoses, especially if large volumes of crystalloid are infused during resuscitation. Acute lung injury (noncardiogenic pulmonary edema) has also been reported.[13,14] Seizures, delirium, stroke, and coma have been described and are presumed to be secondary to cerebral hypoperfusion. Alteration in consciousness in the absence of hypotension should not be attributed to CCB toxicity; in such a scenario, evaluate for other causes of mental status alteration. Nausea and vomiting are common.[15] Life-threatening GI complications include bowel necrosis and ischemia, even without hypotension. ER products can cause development of bezoars.

DIAGNOSIS

POTENTIAL TOXICITY

Adults receiving long-term therapy with CCBs can develop hypotension, bradycardia, or cardiac conduction abnormalities if they ingest as little as twice their regular daily dose.[16] It is hypothesized that patients receiving long-term CCB therapy have comorbidities and may be taking additional medications, such as other antihypertensives, that render these patients sensitive to adverse effects from relatively small increases over their usual CCB regimen. Children may be sensitive to CCB toxicity, and deaths have been reported after even single-tablet ingestion.[6,17] **Therefore, all pediatric CCB ingestions should be referred for medical attention and observation.**

ER preparations complicate overdose management by delaying the onset of toxicity. IR CCBs generally display toxicity within 1 to 2 hours and up to 6 hours after ingenstion.[12] ER preparation may delay toxicity to 6 to 12 hours after ingestion, with reports up to 16 hours after ingestion.[8,12,15,18] It is therefore important to determine the exact formulation of the ingested agent to guide management decisions. **If the history cannot identify the exact formulation, the clinician should assume it is ER and modify treatment conservatively**. In addition to the exact formulation ingested, other important aspects in the history are the time of ingestion and the possibility of co-ingestants that may contribute to toxicity.

ECG findings include sinus bradycardia, varying degrees of atrioventricular block, and slowing of intraventricular conduction. Because dihydropyridines initially have greater effects on smooth muscle dilation then they do on myocardium, reflex tachycardia is commonly seen with low to moderate toxic ingestions of these agents. In contrast, significant overdoses of verapamil or diltiazem are frequently associated with junctional and ventricular escape rhythms.

Laboratory testing and imaging are done to assess the overall metabolic state of the patient and to identify systemic complications of ingestion. Review all patient medications, and obtain digoxin levels if there is access to, or the patient is taking, digoxin. Determine if β-blockers are part of the patient's therapy or are also ingested as part of the overdose. Hyperglycemia is often noted after CCB ingestion, which differentiates it from β-blocker ingestion, which typically results in euglycemia or sometimes hypoglycemia. CCBs inhibit calcium-mediated insulin secretion from the β islet cells in the pancreas, impeding the use of carbohydrates; CCBs also increase insulin resistance by unclear mechanisms.[19] Hyperglycemia in the setting of a CCB overdose is considered a poor prognostic indicator.[20]

Systemic hypoperfusion may cause a lactic acidosis with an elevated anion gap and low serum bicarbonate level. Hypokalemia may be observed in severe overdoses. Serum calcium levels are usually normal. Ionized serum calcium levels may be followed during treatment with IV calcium preparations, but the optimum serum calcium level for patients with severe CCB poisoning is unknown. CCB serum concentrations are not routinely available and are not used in management. Screen blood and urine for other potential toxins after suicidal overdose.

DIFFERENTIAL DIAGNOSIS

A few conditions and other drug toxicities can produce bradycardia, atrioventricular block, and hypotension (**Table 195-2**). Hypothermia should be detected during vital sign assessment. Myocardial infarction may be evident on the initial or subsequent ECG. Suspect hyperkalemia in patients with renal failure.

TABLE 195-2 Differential Diagnosis of Bradycardia, Atrioventricular Block, and Hypotension

- Hypothermia
- Acute coronary syndrome
- Hyperkalemia
- Hypothyroidism
- Cardiac glycoside toxicity
- β-Blocker toxicity
- Antiarrhythmic drugs class IA and IC toxicity
- Central α_2-adrenergic agonist (clonidine or tetrahydrozoline) toxicity
- Large overdoses of sedative-hypnotics and muscle relaxants

It may be difficult to distinguish CCB toxicity from cardiac glycoside toxicity; patients may be taking these drugs for the same indications and at the same time (see Chapter 193, "Digitalis Glycosides"). In general, patients with chronic digoxin poisoning have greater ventricular excitation, including rate and ectopy, than patients with CCB toxicity. In acute overdose, digoxin toxicity may be distinguished by hyperkalemia. However, because the main manifestations of acute cardiac glycoside poisoning are heart block and bradycardia, bedside differentiation may be difficult.

Toxicity from β-adrenergic antagonists may be clinically indistinguishable from CCB toxicity (see Chapter 194, "Beta-Blockers"). In general, β-blocker toxicity is not as severe, and patients tend to have low to normal glucose and normal to elevated serum potassium levels. On physical exam, a patient with β-blocker toxicity may appear "cool and clammy" as compared to a patient with CCB toxicity who may be warmer with flushed skin (due to arteriolar vasodilation). However, these findings are not consistent enough to have reliable diagnostic value. Fortunately, the treatment for these two poisonings is similar, with calcium, adrenergic agonists, glucagon, insulin, and pacing considered useful therapy for both.[21]

TREATMENT

Begin resuscitation, obtain an ECG, and institute cardiopulmonary monitoring (**Table 195-3**). Evaluate all patients, especially those with altered mental status, for hypoglycemia and opioid toxicity. Decreased level of consciousness following CCB ingestion is a result of cerebral hypoperfusion or co-ingestion. Administer oral activated charcoal if within 1 hour of ingestion of IR and ER preparations, provided patient can protect his or her airway, or intubate as needed as mental status deteriorates. Provide early airway management in patients with mental status change or hemodynamic instability.[2] Endotracheal intubation may minimize the risk of aspiration associated with GI decontamination. Vomiting is not just associated with decontamination; glucagon administration may also precipitate vomiting.

Following airway management, provide cardiovascular stabilization. Give IV crystalloids for hypotension, but overaggressive fluid administration may produce or worsen pulmonary edema. The goal of treating bradycardia is to increase end-organ perfusion rather than restore a specific heart rate; some patients with heart rates of 30 to 40 beats/min can maintain adequate blood pressure and perfusion and therefore require only monitoring. Conversely, patients may respond to cardiac pacing with an increase in heart rate to 90 to 100 beats/min without improvement in blood pressure or perfusion; they may require additional therapy to improve inotropy.

Therapies to increase heart rate include medications and cardiac pacing. Atropine alone is rarely effective for CCB-induced bradycardia, but administration is commonly recommended.[12] Calcium salts may improve both heart rate and blood pressure, but the response is variable.

TABLE 195-3 General Treatment for Calcium Channel–Blocker Overdose*

Treatment	Comments
Monitoring	Initiate cardiopulmonary monitoring and obtain ECG.
CBC; serum electrolytes and metabolic panel; magnesium, calcium, and phosphorus; VBG and serum lactate; glucose; digoxin level as indicated	For all patients with potentially toxic overdose. Follow glucose levels.
Naloxone	If signs of opioid toxicity.
Single-dose activated charcoal; protect airway	If ingestion within 1 h and no vomiting or altered mental status; for children even if one tablet ingested.
Multidose activated charcoal; protect airway	For ER preparations.
IV crystalloid for hypotension	Overaggressive treatment can cause pulmonary edema.
Endotracheal intubation	Early intubation if altered mental status or hemodynamic instability.

Abbreviations: ER = extended release; VBG = venous blood gas.

*See Figure 195-1 for treatment of severe toxicity.

Transvenous or transcutaneous pacing is indicated for hypotensive patients with severe bradycardia (heart rate <30 beats/min), and may improve rate but may not correct hypotension.

Persistent hypotension after infusion of crystalloids, administration of calcium salts, and treatment of bradycardia should be treated with adrenergic vasopressors, high-dose insulin (HDI), or both. Recommendations for HDI and additional therapies are based on animal data and human case reports or series, with the caution that case reports often document the use of multiple therapies simultaneously.[21-23] In critically ill patients, it is helpful to have early consultation with a toxicologist or the poison control center to assist with the administration of infrequently used treatments.

GI DECONTAMINATION

Activated Charcoal Given the lethality of CCBs and lack of an effective antidote, perform GI decontamination with activated charcoal. CCBs bind well to activated charcoal, and activated charcoal should be given to adults following any potentially significant IR or ER exposure, especially if presentation is within an hour of ingestion.[24] Give activated charcoal after accidental ingestion of verapamil in children, because life-threatening toxicity has occurred from a single tablet. Give multiple-dose activated charcoal after ingestion of an ER preparation.

Ipecac Ipecac syrup to induce emesis is not recommended.[24]

Gastric Lavage Routine gastric lavage is not recommended because risks outweigh benefits. Late gastric lavage is recommended by some toxicologists for a patient who presents within an hour of ingesting an amount significantly in excess of toxic exposure or for any patient who requires intubation after CCB ingestion.

Whole-Bowel Irrigation Given the potential for severe toxicity, consider whole-bowel irrigation (WBI) with polyethylene glycol for patients with large ingestions of ER products.[18] A large amount of medication may be removed through WBI. Monitor closely, because complications from WBI may contribute to hemodynamic instability.[25]

CALCIUM SALTS

Exogenous calcium increases the extracellular calcium concentration and increases the transcellular gradient, driving calcium intracellularly through unblocked calcium channels. Administration of calcium salts has improved blood pressure in animal models and in human case reports of CCB toxicity.[18,26-29] However, the effects are variable, and patients with significant toxicity may not respond to calcium therapy alone.

Calcium chloride (13.6 mEq per 1-gram ampule) is preferred to calcium gluconate (4.5 mEq per 1-gram ampule) because it provides triple the amount of calcium per volume. Use a central line for infusion of calcium chloride to avoid soft tissue necrosis that can be associated with extravasation. The dose of calcium chloride is a 1-gram (10 mL of 10% solution) IV bolus over 5 minutes in adults (pediatric dose is 15 milligrams/kg or 0.15 mL/kg of the 10% solution). Calcium gluconate can be given at three times this amount. **The effects of calcium administration may be transient, and repeat dosing up to every 10 to 20 minutes is commonly required. Alternatively, a continuous infusion of calcium chloride 2 to 6 grams/h may also be used in adults (pediatric dose is 10 to 40 milligrams/kg per hour).** Measure ionized serum calcium levels every 30 minutes after the initial infusion is started and every 1 to 2 hours thereafter. A calcium concentration goal of approximately 1.5 to 2 times normal should be achieved. However, for patients who do not respond to other therapies, it is reasonable to continue calcium administration even when serum calcium levels are considerably elevated.

An acceptable level for hypercalcemia has not been defined. Published case reports of CCB poisoning describe survival following administration of 30 grams of calcium chloride over 12 hours resulting in a serum calcium level of 23 milligrams/dL (5.94 mmol/L)[18] and death from iatrogenic hypercalcemia with a serum calcium level of 32.3 milligrams/dL (8.07 mmol/L).[30] A safe but effective dose of calcium salts to use in the treatment of CCB toxicity is unclear. If repeat dosing or continuous infusions are used, hypercalcemia and/or hypophosphatemia can occur. Although monitoring of serum ionized calcium and phosphorus concentrations during repeated or prolonged calcium therapy is recommended, it is unclear if such electrolyte abnormalities have clinical

consequence or should be treated. Consultation with toxicology can assist with this management.

ADRENERGIC AGENTS

Patients who do not respond to calcium administration or who require repeated doses require adrenergic agonists, typically epinephrine or norepinephrine, titrated to a mean arterial pressure of 65 mm Hg (Figure 195-1).[21-23]

No single adrenergic vasopressor is consistently effective. A response may occur with dopamine, epinephrine, norepinephrine, vasopressin, dobutamine, or isoproterenol.[31-33] Patients with decreased contractility and peripheral vasodilatation, especially in the face of relative bradycardia, may benefit from an agent with both α- and β-agonist effects, such as epinephrine or norepinephrine (Figure 195-1). Methylene blue, a nitric oxide scavenger and guanylate cyclase inhibitor used for vasoplegia, and phosphodiesterase inhibitors such as amrinone, milrinone, and enoximone have been reported to improve blood pressure in animal studies and human case reports.[34-39]

When standard doses are inadequate, it is reasonable to use high doses or multiple agents titrated to achieve a mean arterial blood pressure of 65 mm Hg, although there is risk of ischemic complications.[33] Alternatively, another approach, such as HDI, glucagon, or lipid emulsion, can be considered.

HIGH-DOSE INSULIN THERAPY

HDI is a promising treatment for the myocardial suppression associated with CCB poisoning.[40-47] Potential mechanisms of action include positive inotropic effects of insulin, increased calcium entry, and improved myocardial use of carbohydrates as an energy source.[19] Insulin increases intracellular transport of glucose into cardiac and skeletal muscle and has inotropic properties.[42] There are no clinical trials comparing HDI therapy directly to other treatments, but multiple human case reports show that HDI improves perfusion in CCB poisoning unresponsive to other therapies, with a therapeutic response noted within 15 to 30 minutes.[42-48] The main adverse effect is potential hypoglycemia, which is easily detected with point-of-care glucose testing and treated with dextrose. Hypokalemia is also seen from intracellular potassium shifts. Replace potassium if potassium falls to <2.8 mEq/L (<2.8 mmol/L).

TABLE 195-4 Protocol for High-Dose Insulin Therapy in Severe Calcium Channel Blocker Overdose

- Check serum glucose, and if <200 milligrams/dL (<11 mmol/L), administer 50 mL of 50% dextrose (0.5 gram/mL) in water IV (children, 1 mL/kg of 25% dextrose).
- Administer regular insulin 1 unit/kg IV bolus.
- Begin regular insulin infusion at 1 unit/kg per hour along with dextrose 10% (0.1 gram/mL) in water at 200 mL/h (adult) or 5 mL/kg per hour (pediatric).
- Titrate insulin infusion rate up to 10 units/kg per hour according the hemodynamic goal of HR >50 beats/min and SBP >100 mm Hg (>13.3 kPa).
- Monitor serum glucose every 15–20 min.
- Titrate dextrose infusion rate to maintain serum glucose level between 100 and 200 milligrams/dL (5.3 and 10.7 mmol/L).
- Once dextrose infusion rates have been stable for 60 min, glucose monitoring may be decreased to hourly.
- Monitor serum potassium level and start IV potassium infusion if serum potassium level is <2.8 mEq/L (<2.8 mmol/L).
- Maintain serum potassium between 2.8 and 3.2 mEq/L (2.8 and 3.2 mmol/L).

Abbreviations: HR = heart rate; SBP = systolic blood pressure.

Given benefit seen in animal models and clinical reports, begin HDI for hypotensive patients, especially if they do not respond to vasopressor therapy (Figure 195-1).

Doses of insulin used for HDI are greater than those for diabetic treatment (**Table 195-4**).[49] An initial insulin bolus is followed by a continuous infusion along with a dextrose infusion to prevent hypoglycemia (Table 195-4). Although traditional infusion doses were started at 1 unit/kg per hour, several protocols use a higher dose of up to 10 units/kg per hour, which is considered high-dose therapy.[50,51] A recent randomized

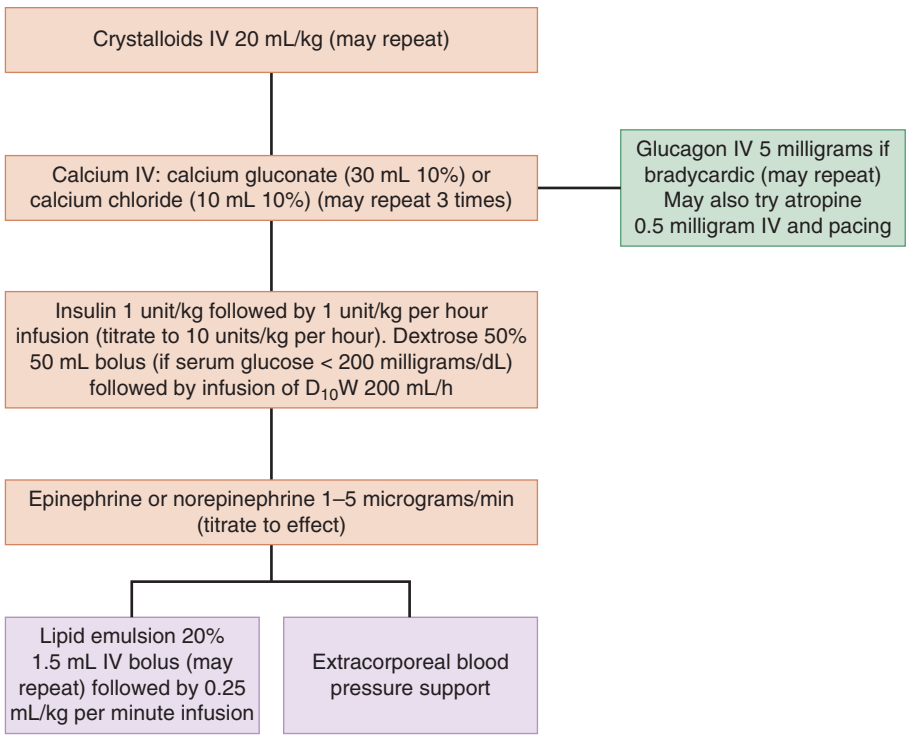

FIGURE 195-1. Treatment algorithm for severe toxicity. After giving fluids and calcium, if inadequate response, give glucagon for hypotension. Give atropine and institute cardiac pacing for bradycardia. Consider pretreatment with an antiemetic when giving glucagon. When a patient is refractory to these treatments, high-dose insulin (HDI) and vasopressors are the next treatments recommended. HDI can be given in lieu of vasopressors; however, the recommendation is to give in concert with vasopressors because HDI response takes 15 to 30 minutes. Once there is a response, wean vasopressors first. Extracorporeal membrane oxygenation (ECMO) or lipid emulsion therapy is usually warranted if the previous modalities fail, with the authors' preference being ECMO. If patient is to start ECMO, discuss the use of lipids with managing team before starting. If patient is not at an ECMO facility and patient cannot be transferred, lipid emulsion therapy can be started. See also Table 195-4.

controlled trial of pigs poisoned by propranolol showed a dose response over time, with improvements of cardiac output with increasing HDI doses up to 10 units/kg per hour. No ceiling dose has yet been established.[52] Page et al[50] showed no significant increase in complications between use of lower- and higher-dose insulin in a retrospective study. The hemodynamic response to HDI is usually seen in 15 to 45 minutes, so begin the infusion at 1 unit/kg per hour, and increase the infusion rate if there is no clinical improvement within 30 minutes. Monitor the serum glucose concentrations and adjust the dextrose infusion to maintain an acceptable glucose range. Maintain the HDI infusion until toxicity has resolved; durations of 9 to 49 hours may be necessary. The insulin infusion may be reinstituted if toxicity recurs. Due to persistent elevated insulin concentrations, dextrose supplementation may be required for up to 24 hours after the infusion is discontinued.

GLUCAGON

Glucagon, a hormone synthesized by the pancreas, is the therapy of choice for β-adrenergic blocker poisoning because of its ability to bypass the β-adrenergic receptor and stimulate cardiac activity via activation of adenylate cyclase (see Chapter 194, "Beta-Blockers"). In CCB poisoning, the inhibition is downstream from glucagon's binding site; therefore, glucagon theoretically offers no advantage over other agents. Nevertheless, glucagon administration improves blood pressure in animal models, and several case reports have also noted improvement in hemodynamics after glucagon therapy.[53-56] However, failure to respond has also been reported.[43]

The recommended glucagon dose is an initial IV bolus of 5 milligrams in adults and 0.03 milligram/kg in children given over 1 to 2 minutes (Figure 195-1). A response is usually seen within 15 minutes. If there is no response, the bolus dose may be repeated. If there is hemodynamic improvement, a maintenance infusion should be initiated at 5 milligrams/kg per hour in adults and 0.05 milligram/kg per hour in children.

The main adverse effects of glucagon are vomiting and hyperglycemia; empirically give ondansetron, once it is determined that there is no QT_c prolongation, hypokalemia, or hypomagnesemia. Because of the large amounts of glucagon required, hospital supplies of the drug are often rapidly depleted; plan ahead and consider making arrangements (e.g., with nearby centers) for additional glucagon.

IV LIPID EMULSION THERAPY

Lipid emulsion therapy was first described in the management of local anesthetic toxicity. Lipid emulsions appear to create a pharmacologic sink for fat-soluble drugs.[57] Therapy may also provide fatty acid substrate for cardiac energy supply and improve myocyte function by increasing intracellular calcium levels. Lipid emulsion therapy prolonged survival in an animal model of verapamil poisoning,[58] and several case reports described benefit in CCB ingestions unresponsive to standard therapy.[59,60] There are many different commercial lipid emulsion preparations, with the major components typically being soybean oil, egg yolk phospholipids, and glycerin.

The recommended dose is a 20% lipid emulsion given as a 1.5 mL/kg bolus over 2 to 3 minutes, followed by a 0.25 mL/kg per minute infusion. If the blood pressure remains low, an additional 1.5 mL/kg bolus may be repeated followed by an increase in the infusion rate to 0.5 mL/kg per minute. The recommended upper limit for lipid emulsion infusion is about 10 mL/kg over the initial 30 minutes. If the patient's hemodynamic stability is dependent on continued lipid infusion, the treatment may be continued.[61] Case reports suggest that if sudden cardiac arrest occurs in the setting of overdose, a bolus can be given in the hope of restoring spontaneous circulation. In addition to interference with laboratory parameters (e.g., blood cell count, electrolytes, liver transaminases), there are rare adverse effects such as hypertriglyceridemia, hypoxemia (with high doses), and hyponatremia.[23]

EXTRACORPOREAL CIRCULATORY SUPPORT

With lack of response to aggressive medical therapy, consider circulatory support measures, such as the placement of intra-aortic balloon pumps, the use of left ventricular assist devices, and even extracorporeal membrane oxygenation, which may provide adequate blood pressure to allow clearance of the drug and resolution of symptoms.[23,62,63] Lipid emulsion therapy can cause complications with extracorporeal membrane oxygenation.[64] Contact the extracorporeal membrane oxygenation team before starting lipid emulsion, if extracorporeal membrane oxygenation is to be used. Due to CCB's large volume of distribution and high affinity for protein binding, hemodialysis and hemoperfusion are not beneficial in the treatment of CCB overdoses.[65]

DISPOSITION AND FOLLOW-UP

In general, patients usually manifest toxicity within 6 hours of ingestion of IR products. Therefore, those who are asymptomatic and who have normal vital signs and normal ECG after a 6-hour observation period can be discharged after appropriate psychiatric evaluation.[24] Toxicity may be delayed for up to 12 hours after ingestion of ER products.[8,9] **As a rule, patients who ingest potentially toxic amounts of ER products should be monitored for at least 24 hours.** Contact the regional poison control center for assistance with management.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 196

Antihypertensives

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Dan Quan

INTRODUCTION

An estimated 29% of adults in the United States have hypertension; thus, antihypertensives are commonly found in patient homes.[1] Several classes of drugs used to treat hypertension are discussed in this chapter: diuretics, sympatholytic agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and vasodilators (**Table 196-1**). Calcium channel blockers and β-blockers, also used in the treatment of hypertension, are discussed elsewhere (see Chapter 195, "Calcium Channel Blockers," and Chapter 194, "Beta-Blockers").

For most of these agents, life-threatening toxicity is not expected in acute overdose.[2] In nearly all cases, good supportive care is adequate. The initial approach to the patient with potential overdose of an antihypertensive drug is fairly uniform. Secure the airway as necessary, establish IV access, provide continuous cardiac monitoring, and obtain an ECG. A bolus of crystalloid solution is first-line treatment for hypotension. If a vasopressor is required, a direct-acting drug such as norepinephrine is preferred. If pulmonary aspiration is not a concern, activated charcoal can be given within the first hour. Although there is usually no specific therapy for initial management of these drugs in overdose, the different classes of antihypertensives are distinct in their potential for causing metabolic derangements and adverse effects.

DIURETICS

Diuretics initially control hypertension by increasing elimination of salts, but their mechanism of action in long-term blood pressure control is not clear. All diuretics cause increased sodium elimination, which results in the potential for hyponatremia, hypokalemia, hyperkalemia, hypomagnesaemia, and hypovolemia.

Thiazides, like **hydrochlorothiazide**, inhibit sodium chloride reabsorption in the renal distal convoluted tubule. Decreased sodium reabsorption leads to increased excretion of potassium and the possibility of hypokalemia. Calcium regulation is also affected by thiazide diuretics via two separate mechanisms: (1) inhibition of vitamin D synthesis and thus decreased calcium absorption from the GI tract, and (2) increased

TABLE 196-1 Summary of Antihypertensive Drugs

Class	Drug	Mechanism of Action	Clinical Presentation With Toxicity	Comments
Diuretics	Chlorothiazide Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	Inhibition of distal tubule sodium chloride absorption	Hypovolemia Hypokalemia Hypercalcemia	Metabolic complications, such as hypokalemia, glucose intolerance, and hyperuricemia seen with increased therapeutic thiazide doses.
	Bumetanide Furosemide	Inhibition of sodium-potassium-chloride symporter in renal loop of Henle	Hypovolemia Hypocalcemia Hypokalemia Hypomagnesemia	
	Amiloride Triamterene	Inhibition of sodium absorption and potassium elimination in renal distal collecting duct	Hypovolemia Hyperkalemia	
	Eplerenone Spironolactone	Mineralocorticoid antagonist	Hypovolemia Hyperkalemia	
Sympatholytics	Doxazosin Prazosin Tamsulosin Terazosin	α_1-Adrenergic receptor antagonist	Hypotension	Phenylephrine may be used for refractory hypotension.
	Clonidine Guanabenz Guanfacine	α_2-Adrenergic receptor agonist Imidazoline receptor agonist μ-Receptor opioid agonist	Hypotension Bradycardia Neurologic depression	Dopamine considered agent of choice for hypotension. Phenylephrine may be used for refractory hypotension.
	Oxymetazoline Tetrahydrozoline	Imidazoline receptor agonist	Hypotension Bradycardia Neurologic depression	
	Guanadrel Methyldopa Reserpine	Decreased norepinephrine release	Hypotension Bradycardia Hemolytic anemia (idiosyncratic reaction to methyldopa)	
Angiotensin-converting enzyme inhibitors	Benazepril Captopril Enalapril Fosinopril Moexipril Perindopril Quinapril Trandolapril	Inhibition of ACE Inhibition of bradykininase	Hypotension Hyperkalemia Angioedema (idiosyncratic) Cough (idiosyncratic)	Epinephrine, corticosteroids, and antihistamines have no proven benefit in ACEI-induced angioedema. Icatibant 30 milligrams SC or C1 esterase inhibitor [human] 1000 U IV appear effective in ACEI-induced angioedema.
Angiotensin receptor blockers	Candesartan Eprosartan Irbesartan Losartan Telmisartan Valsartan	Angiotensin II receptor antagonist	Hypotension Hyperkalemia Angioedema (less common than with ACE inhibitors)	Epinephrine, corticosteroids, or antihistamines have no proven benefit in ARB-induced angioedema.
Vasodilators	Hydralazine	Arteriolar vasodilation	Hypotension Lupus-like syndrome (idiosyncratic reaction to hydralazine)	
	Minoxidil	Arteriolar vasodilation	Tachycardia Increased myocardial oxygen demand	
	Sodium nitroprusside	Arteriolar and venous vasodilation (via nitric oxide release)	Hypotension Tachycardia Thiocyanate toxicity (after prolonged infusion) Cyanide toxicity (very rare)	Thiosulfate should be administered if cyanide toxicity is considered. Many pharmacies mix sodium nitroprusside and thiosulfate to avert cyanide toxicity.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ACEI = angiotensin-converting enzyme inhibitors.

renal absorption of calcium. The net result, however, is calcium retention and potentially hypercalcemia.[3] Glucose intolerance is noted at higher doses.

Loop diuretics, such as **furosemide** and **bumetanide**, are used more frequently for control of edema and pulmonary congestion than for hypertension. Loop diuretics inhibit the activity of the sodium-potassium-chloride symporter (a type of cotransporter that facilitates transport across a plasma membrane) in the renal loop of Henle, where 25% of the filtered sodium load is typically reabsorbed. A secondary effect of the inhibition of this symporter is decreased calcium and magnesium reabsorption, which results in hypocalcemia, hypokalemia, and hypomagnesemia.

Triamterene, **amiloride**, **spironolactone**, and **eplerenone** are referred to as potassium-sparing diuretics for their ability to cause a sodium chloride diuresis without increased potassium secretion. Triamterene and amiloride inhibit sodium channels in the distal renal tubule and collecting duct, which play a role in both reabsorbing sodium and secreting potassium. These drugs may be used in conjunction with other stronger diuretics for management of hypertension. Triamterene has been associated with rare cases of crystalline nephropathy.[4]

Spironolactone and eplerenone are antagonists of mineralocorticoids such as aldosterone. Mineralocorticoid antagonists increase elimination of sodium and retention of hydrogen and potassium. Spironolactone is typically used to treat heart failure and hepatic cirrhosis. In the acute overdose setting, hyperkalemia and hypotension are the most serious clinical manifestations of these drugs.

Clinical manifestations of excessive diuresis include tachycardia, hypotension (orthostatic or supine), electrolyte abnormalities, and generalized weakness. The ECG may show changes caused by these electrolyte abnormalities (see Chapter 17, "Fluids and Electrolytes"). A widened QRS interval or peaked T waves may suggest hyperkalemia, such as from a potassium-sparing diuretic. A prolonged QT interval may indicate hypokalemia, hypomagnesemia, or hypocalcemia, which may be caused by a loop diuretic.

The first priority of therapy is restoration of plasma volume. Administer an isotonic crystalloid solution bolus, such as 0.9% saline. Treat electrolyte abnormalities, such as hyperkalemia, hypokalemia or hypocalcemia, with standard management and fluid resuscitation (see Chapter 17, "Fluids and Electrolytes").

In addition to causing direct toxicity, diuretics may potentiate toxicity from other medications. Mechanisms include decreased renal clearance of drugs or creation of a metabolic state that changes a particular drug's effect. **Diuretics and ACEIs can increase the risk of lithium toxicity** by reducing lithium elimination (see Chapter 181, "Lithium").[5] Hypokalemia from diuretics may exacerbate arrhythmias seen in chronic digoxin poisoning or other antiarrhythmics (see Chapter 193, "Digitalis Glycosides").

SYMPATHOLYTIC AGENTS

Catecholamines produced by the sympathetic nervous system play a key role in maintaining blood pressure. Drugs with action at α-adrenergic receptors are used to diminish peripheral sympathetic tone in order to decrease blood pressure. There are two subtypes of α-adrenergic receptors. Stimulation of the α_1-adrenergic receptors causes vasoconstriction of arterioles and veins, increasing peripheral vascular resistance and elevating blood pressure. Stimulation of the α_2-adrenergic receptors produces different effects in the peripheral and central nervous systems. In the peripheral nervous system, stimulation of the α_2-receptors produces vasoconstriction and increases blood pressure. In the CNS, stimulation of the α_2-receptors at presynaptic sympathetic terminals inhibits the release of catecholamines, thereby decreasing sympathetic tone, promoting peripheral vasodilation, and decreasing blood pressure.

DOXAZOSIN, PRAZOSIN, AND TERAZOSIN

Doxazosin, **prazosin**, and **terazosin** antagonize α_1-adrenergic receptors, reducing peripheral vascular resistance. Although the aforementioned drugs are used for the treatment of hypertension, other members of this class, such as **tamsulosin**, are used exclusively for management of benign prostatic hyperplasia and as an adjunct in nephrolithiasis management. Because an increase in peripheral vascular resistance is required to maintain blood pressure when changing from a supine to an upright position, it is not surprising that the most typical adverse effect observed with α_1-adrenergic antagonists is orthostatic hypotension, particularly within 30 to 90 minutes after ingestion, and is most prominent after taking the first dose.[6]

Although orthostatic hypotensive episodes may be associated with lightheadedness and adverse events such as falls resulting in hip fracture, patients rarely come to the ED with prolonged hemodynamic instability. Patients who do present with hypotension associated with α_1-adrenergic antagonist use should be placed supine and receive a crystalloid bolus. Based on the mechanism of action of these drugs, α_1-adrenergic agonists should be used if blood pressure does not improve with IV fluids.[7]

CLONIDINE

Clonidine is the most commonly used α_2-adrenergic agonist. Clonidine is available in an oral formulation and as a transdermal patch. This class of drugs, which also includes guanabenz and guanfacine, stimulates α_2-adrenergic receptors in the CNS, inhibiting release of catecholamines in the periphery, which results in decreased heart rate, contractility, and peripheral vascular resistance. Clonidine shares the imidazoline functional group with the nasal spray decongestant oxymetazoline and topical eye vasoconstrictor medication tetrahydrozoline. **Inappropriately ingesting oxymetazoline or tetrahydrozoline can result in toxicity similar to clonidine poisoning.**[8,9] In addition to hemodynamic effects, clonidine also possesses opioid agonist properties at the μ receptor.[10] For this reason, clonidine is used in some opioid-dependent patients to ameliorate symptoms of withdrawal.

Clonidine poisoning typically results from either intentional overdose or exploratory pediatric poisoning.[11,12] **Even a single tablet may cause significant symptoms in a child.**[13,14] Toxicity can develop from ingesting clonidine patches.[15,16] Compounded ointments used for chronic pain may contain clonidine; application of these patches to small children (or to adults in excessive quantity) may produce toxicity.[17-19]

Shortly after an ingested overdose of clonidine, the peripheral α_2-adrenergic stimulation may cause hypertension.[12,20] By the time of presentation, however, the clinical manifestations of central α_2-adrenergic stimulation and imidazoline toxicity are present with bradycardia, CNS depression, and hypotension.[11,21] Clonidine may produce miotic pupils in a manner similar to opioids.[22] Hypothermia may occur as a result of opioid or adrenergically mediated pathways. Somnolence is typical and may progress to apnea in severe cases.[8,11,23] Although clonidine is intended to be dosed twice daily, symptoms may last days with an overdose.

Focus on ventilatory and hemodynamic support in clonidine toxicity.[21,24] Clonidine-induced respiratory and neurologic depression has variable response to naloxone, and its use is unlikely to be helpful in adults[21,25-29]; however, it is considered to be more effective in children.[28] Bradycardia may be treated with atropine. When encountered, hypertension should be treated only if it is severe and prolonged, because hypertension may unpredictably give way to hypotension. If it is necessary to treat clonidine-associated hypertension, use a short-acting drug that can be quickly discontinued (e.g., nitroprusside). Hypotension associated with clonidine typically responds well to crystalloid fluid resuscitation.

METHYLDOPA

Methyldopa is also a centrally acting antihypertensive, although it has a unique mechanism. Methyldopa is a dopamine analog that, in the CNS, is converted in two steps to α-methylnorepinephrine, which in turn substitutes for norepinephrine in adrenergic neuron secretory vesicles. In the CNS, α-methylnorepinephrine stimulates presynaptic α_2-adrenergic receptors, reducing peripheral sympathetic tone. In therapeutic dosing, the peak effect of methyldopa is delayed for 6 to 8 hours, because time is required for methyldopa to pass into the brain and be converted to its active form. Methyldopa use is also associated with an autoimmune hemolytic anemia, which can occur during long-term therapeutic use.[30,31] If symptomatic hypotension is encountered in association with methyldopa, IV crystalloid solution should be administered. In cases

of refractory, severe hypotension, a direct-acting vasopressor such as norepinephrine should be administered.[32]

GUANADREL AND RESERPINE

Guanadrel and **reserpine** are antihypertensives that interfere with the release of catecholamines from synaptic terminals. Guanadrel, which has no intrinsic sympathetic activity, substitutes for norepinephrine in presynaptic storage vesicles. Reserpine inhibits formation of biogenic amine storage vesicles in central and peripheral neurons. In each case, there is a decreased capacity to release catecholamines in response to a sympathetic stimulus. Sympathetic tone is diminished, and peripheral vascular resistance decreases. There is little experience with these drugs in overdose. However, because the common mechanism of both drugs is a decrease in circulating catecholamines, it would seem reasonable to administer boluses of crystalloid as first-line therapy and to use a direct-acting vasopressor, such as norepinephrine or phenylephrine, to treat refractory hypotension.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin II raises blood pressure by several mechanisms, including triggering aldosterone release, increasing response to catecholamines, and acting as a direct vasoconstrictor. Angiotensin II is created in a two-step process. In the first step, renin, released by the kidneys, cleaves angiotensinogen, forming angiotensin I. The second step uses angiotensin-converting enzyme, which separates the carboxy terminus off angiotensin I, forming angiotensin II. Inhibition of this conversion at either step results in decreased blood pressure.

ACEIs are thought to slow the progression of diabetic glomerulopathy and have been shown to improve mortality and left ventricular function when administered after myocardial infarction. Members of this large class of drugs can be identified by their shared "-pril" suffix: **benazepril**, **captopril**, **enalapril**, **fosinopril**, **moexipril**, **perindopril**, **quinapril**, and **trandolapril**. Inhibition of angiotensin-converting enzyme results in decreased production of angiotensin II, which causes vasodilation. Despite their widespread use, these medications have not been associated with significant morbidity in overdose. ACEIs can cause hyperkalemia in therapeutic dosing. If hypotension is encountered, initial therapy focuses on basic management, including administration of boluses of crystalloid and vasopressors for refractory cases.

Captopril, and possibly other ACEIs, are thought to inhibit the metabolism of the enkephalins, a group of endogenous opioids. Naloxone, a μ-opioid antagonist, may reverse captopril-associated hypotension[33] but is not universally effective.[34]

ARBs produce vasodilatation and increase renal salt elimination. Members of this class end with the suffix "-artan" and include **losartan**, **candesartan**, **irbesartan**, **valsartan**, **telmisartan**, and **eprosartan**. When they are taken therapeutically, the peak antihypotensive effect of agents in this class is not observed for 4 weeks. Typically, these drugs are not associated with significant morbidity in overdose. There are no reported cases of isolated ARBs overdose causing life-threatening hypotension. Like ACEIs, ARBs can cause hyperkalemia, which results from decreased aldosterone production. This effect is typically seen in patients with renal insufficiency.[27]

Persistent dry cough occurs in 5% to 20% of patients treated with ACEIs.[35] Cough typically develops within a few weeks after ACEI therapy is started and is more common in women, and the rate of occurrence or severity does not correlate with dose. Cough will usually resolve in 1 to 4 weeks after the drug is stopped, although resolution may take up to 3 months for some patients. The only effective treatment is discontinuing the ACEI, substituting a different antihypertensive. ARBs are not associated with an increased incidence of chronic cough and may be used in patients with ACEI-induced cough.[36]

Angioedema is the most consequential adverse effect associated with ACEIs and ARBs (see Chapter 14, "Allergy and Anaphylaxis").[37-39] Angioedema is an idiopathic reaction that occurs in 0.1% to 0.7% of patients prescribed these drugs.[38,40] Because these agents are widely used, this small percentage represents a large number of events. Patients present with swelling of the lips, larynx, pharynx, tongue, or vocal cords, which can range in severity from mild to airway compromise. Symptoms develop over several hours and may not resolve for 24 hours or longer.[39] **The absence of urticaria, abdominal swelling, and genitourinary swelling differentiates ACEI-induced angioedema from histamine-mediated causes.**[41] The mechanism is thought to be related to inhibition of ACE-mediated degradation of bradykinin, a peptide associated with vasodilatation and tissue edema, and accumulation of substance P and other prostaglandins.[39,41] ARBs do not inhibit bradykinin, so the exact pathophysiology of angioedema associated with drugs from this class is not clear. **The mean time from first use to development of angioedema has been reported as about 2 years,**[42] **but angioedema can occur at any time during therapy,** with 12% of patients developing this reaction in the first week of ACEI use.

Management of ACEI-induced angioedema begins with evaluation of the airway. If the patient has difficulty breathing, stridor, or lingual or oropharyngeal edema, secure the airway, usually by intubation.[43] Fiberoptic-guided laryngoscopy is recommended because it requires minimal sedation and provides direct visualization in an edematous airway. **Regardless of the method employed, a skilled operator should secure the airway early because angioedema can progress rapidly and anatomic landmarks may become obscured.**

Allergic-reaction drugs, such as epinephrine, antihistamines, and corticosteroids, are often given but not likely beneficial because ACEI-induced angioedema is not mediated by histamines or immunoglobulins.[38] Agents reported beneficial in ACEI-induced angioedema include icatibant, a bradykinin-2 antagonist, at a dose of 30 milligrams SC[44]; C1 esterase inhibitor (human) 1000 units IV[45]; and fresh frozen plasma 2 units,[46,47] but the overall quality of evidence is mixed.[48,49]

Patients with milder symptoms should be observed and managed medically. There is no consensus regarding the disposition of patients with ACEI-associated angioedema who do not require ED airway intervention. Patients with milder swelling only around the lips or face should be observed for 6 to 12 hours and considered for discharge when swelling begins to regress.[41] Patients should be instructed that angioedema can recur if they continue to take the same agent or switch to another agent of the same class.[50,51] **After an episode of angioedema, the safest and recommended course of action is to discontinue all ACEIs and ARBs.**

VASODILATORS

HYDRALAZINE AND MINOXIDIL

Hydralazine is an antihypertensive agent most commonly used during pregnancy. Hydralazine relaxes arteriolar smooth muscle but does not affect venous smooth muscle or epicardial coronary arteries. Hydralazine is metabolized to an inactive compound by hepatic acetylation. Roughly half of Americans are fast acetylators and therefore require a higher dose to achieve a given clinical effect. The peak effect of the drug is seen 30 to 120 minutes after ingestion, although effects may last as long as 12 hours. The most common adverse effects of hydralazine overdose result from vasodilatation, but serious events are rare. Patients with hydralazine overdose with mild hypotension may develop ST-segment depression on ECG.[52] This myocardial ischemia is thought to result from a steal syndrome in which peripheral vasodilatation is accompanied by reflex tachycardia without an increase in epicardial blood flow, so that myocardial demand increases while coronary perfusion does not. Because of this reflex tachycardia, hydralazine should not be used for treatment of acute coronary syndrome or cocaine-associated chest pain.

Patients on continuous treatment with hydralazine are at risk for development of a lupus-like syndrome. The mechanism is thought to be formation of autoantibodies, but it is not known how hydralazine contributes to this process. Risk factors include high dose, female gender, slow-acetylator phenotype, and white ethnic background. Symptoms of this syndrome include arthralgia, arthritis, fever, and pericardial

effusion. Management includes administration of anti-inflammatories and discontinuation of the drug.

Minoxidil is a potent antihypertensive generally used only for resistant cases of hypertension. Minoxidil is better known for its topical formulation as a treatment for male pattern baldness. Minoxidil is metabolized to minoxidil sulfate, which in turn relaxes smooth muscle by opening potassium channels and causing hyperpolarization. Like hydralazine, minoxidil has little effect on venous smooth muscle. Peripheral vasodilatation results in reflex tachycardia and increased cardiac output. Reduced renal perfusion causes fluid retention. For this reason, minoxidil is usually prescribed with a β-blocker and diuretic. Overdose of minoxidil is associated with hypotension, common reflex tachycardia, and occasional myocardial ischemia in a manner similar to hydralazine.[53-56]

Hypotension from either hydralazine or minoxidil is treated with IV crystalloid fluids. Vasopressors should be avoided if possible, because severely poisoned patients may have coronary ischemia. If blood pressure is refractory to fluid resuscitation, an α_1-adrenergic agonist, such as phenylephrine or midodrine,[55] is preferable to a β-adrenergic agonist, in order to minimize tachycardia and prevent increased myocardial oxygen demand.

SODIUM NITROPRUSSIDE

Sodium nitroprusside is administered IV for hypertensive emergencies.[57,58] Nitroprusside derives its activity from the release of nitric oxide, an endogenous mediator of vasodilation, which stimulates smooth muscle guanylyl cyclase to produce cyclic guanosine monophosphate. The onset of action is roughly 30 seconds, and the offset is 3 minutes. Nitroprusside dilates both arteriolar and venous smooth muscle. In the ED, hypotension is the adverse effect most likely to be observed. If hypotension occurs, the infusion should be stopped immediately. If signs of cerebral hypoperfusion are present, place the patient supine or possibly in the Trendelenburg position. Because of the very brief duration of action of the drug, little else is generally necessary after discontinuing the drug.

When nitric oxide is released from nitroprusside, cyanide is produced as well. As long as the nitroprusside infusion rate is not above 2 to 5 micrograms/kg per minute, the cyanide is usually of little consequence, because it is immediately metabolized by rhodanese to thiocyanate, a much less toxic metabolite. At higher infusion rates over several days, the ability of rhodanese to detoxify cyanide may become overwhelmed.[59] Administration of sodium thiosulfate, which serves as a substrate for rhodanese, can be protective for patients requiring a high rate of nitroprusside administration. Cyanide toxicity may manifest as confusion, lactic acidosis, and progression to cardiovascular collapse. If the clinician is concerned about cyanide toxicity, the infusion should be discontinued, and sodium thiosulfate should be administered.

Over time, the thiocyanate generated by detoxification of cyanide can itself cause toxicity manifesting as nausea, fatigue, and CNS depression. Thiocyanate toxicity, although much more common than cyanide toxicity during nitroprusside treatment, is unlikely to occur in the ED. Thiocyanate, which is eliminated by the kidney with a half-life of 3 to 7 days, usually does not accumulate until infusion has continued for several days.[60] The most important predictors of toxicity are rate of production (nitroprusside infusion rate) and rate of elimination (renal function).

FENOLDOPAM

Fenoldopam is a selective dopamine-1 agonist used for hypertensive emergencies, although its clinical utilization in the United States has remained low.[61,62] Fenoldopam is administered parenterally and acts as a vasodilator and diuretic.[57,58] Fenoldopam has a half-life of approximately 5 minutes, and after infusion is instituted, steady-state serum levels are reached in about 30 to 60 minutes. If hypotension is encountered after fenoldopam administration, the infusion should be stopped immediately and a fluid bolus administered.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 197

Anticonvulsants

Frank LoVecchio

INTRODUCTION

Anticonvulsants, or antiepileptics, are used to treat acute seizures and prevent convulsions in patients with epilepsy. The first generation of antiepileptics was developed between 1938 and 1978 (**Table 197-1**). Since 1993, over 20 additional agents, termed the *second and third generations* of antiepileptic drugs, have been introduced into clinical use. In general, these new anticonvulsants have fewer serious adverse side effects and fewer drug interactions than the first-generation agents.

The first-generation drugs have an established therapeutic range for serum levels that can guide therapy during long-term management and that roughly correlate with acute toxicity from an overdose. Consistent therapeutic levels have not been established for the second- and third-generation anticonvulsants, and serum levels are not a useful guide to therapy.

The toxicity of two benzodiazepines used to treat seizures—clonazepam and clobazam—is discussed elsewhere (see Chapter 183, "Benzodiazepines")

This chapter reviews the pharmacology, clinical features, and treatment for toxicity of commonly used anticonvulsants. Disposition recommendations depend on the resolution of clinical toxicity, but patients with intentional overdose need mental health evaluation in the ED before discharge.

PHENYTOIN AND FOSPHENYTOIN

Phenytoin is a primary anticonvulsant for partial and generalized tonic-clonic seizures. In conjunction with rapidly acting anticonvulsants, it is useful in the treatment of non–drug-induced status epilepticus.[1] Phenytoin has been used to prevent seizures due to head trauma (in the immediate posttraumatic period) and in the management of some chronic pain syndromes. Serious complications are extremely rare after intentional phenytoin overdose if supportive care is provided. Most phenytoin-related deaths have been associated with rapid IV administration or hypersensitivity reactions.

Phenytoin is available in oral and injectable forms. Phenytoin has poor solubility in water, so the vehicle for the parenteral formulation is 40% propylene glycol and 10% ethanol, adjusted to a pH of 12 with sodium hydroxide. The acute cardiovascular toxicity seen with IV phenytoin infusion is usually ascribed to the propylene glycol diluent. Other limitations with parenteral phenytoin are the irritating nature of the vehicle and a tendency to precipitate in IV solutions. **Fosphenytoin** (a disodium phosphate ester of phenytoin) is a prodrug that is converted to phenytoin by phosphatases in the body with a conversion half-life of 10 to 15 minutes. **The advantage of parenteral fosphenytoin is that it is soluble in aqueous solutions, is buffered to a pH of 8.8, is nonirritating to the tissues, and can be given by IM injection.**[2]

PATHOPHYSIOLOGY

Mechanism of Action Phenytoin exerts its anticonvulsant effects by blocking neuronal voltage-sensitive and frequency-dependent sodium channels, suppressing repetitive neuronal activity, and preventing the spread of a seizure focus.[3]

Pharmacokinetics Phenytoin is a weak acid with a pK_a of 8.3. In the acid milieu of the stomach and even at physiologic pH, most of the drug is nonionized and its aqueous solubility is limited. Absorption after oral ingestion is slow, variable, and often incomplete, especially after an overdose. Different phenytoin preparations can have major differences in bioavailability. **Consequently, it may be necessary to obtain serial measurements of serum level in suspected overdose to determine peak levels.** Peak levels typically occur between 3 and 12 hours after a *single therapeutic* oral dose.

TABLE 197-1 First-Generation Anticonvulsant Drugs

Drug	Typical Oral Adult Dose (milligrams)	Maximum Oral Daily Dose (milligrams)	Elimination Half-Life With Therapeutic Doses (h)
Carbamazepine	800–1200 per day divided BID to QID	1600	25–65 (initial doses) 12–17 (repeated doses)
Ethosuximide	250–750 BID	1500	56–60
Methsuximide	300–1200 once daily	1200	1–3 (parent drug) 28–34 (active metabolite)
Phenobarbital	60 BID or TID	200*	79
Phenytoin	300–400 per day divided BID or TID	600*	7–42
Primidone	250 TID or QID	2000	10–12 (parent drug) 75–126 (phenobarbital)
Valproic acid	30–60 per kilogram per day divided BID or TID	60 per kilogram	16

Abbreviations: BID = twice a day; QID = four times a day; TID = three times a day.

*Approximation: Individualize dosage based on serum drug concentrations and clinical parameters.

Protein Binding Phenytoin is extensively (about 90%) bound to plasma proteins, especially albumin. The free, unbound form is the biologically active moiety responsible for the drug's clinical effect and toxicity. The unbound fraction of the drug is greater in neonates, the elderly, and pregnant women; unbound fractions are also higher in the settings of renal failure, hypoalbuminemia (cirrhosis, nephrosis, malnutrition, burns, trauma, or cystic fibrosis), or hyperbilirubinemia. Drugs that displace phenytoin from binding sites (salicylate, valproate, phenylbutazone, tolbutamide, and sulfisoxazole) also result in an increased unbound fraction.

Metabolism Ninety-five percent of phenytoin is metabolized by hepatic microsomal enzymes, and it is primarily hydroxylated through a series of inactive compounds. The metabolism of phenytoin is capacity limited (dose dependent). At plasma concentrations of <10 micrograms/mL, elimination is by **first-order kinetics** (a fixed *percentage* of drug is metabolized per unit of time). At higher concentrations, including those in the therapeutic range of 10 to 20 micrograms/mL (40 to 80 micromole/L), the metabolic pathways may become saturated and the elimination may change to **zero-order kinetics** (a fixed *amount* is metabolized per unit of time). With zero-order kinetics, small increases in maintenance doses may saturate the enzyme systems, markedly prolonging phenytoin's half-life and resulting in a disproportionate increase in the plasma level. **Thus, incremental dose increases should be limited to 30 to 50 milligrams at a time, and levels should be carefully monitored when it is necessary to raise phenytoin doses above 300 milligrams (or above 5 milligrams/kg) per day.**

Concomitant use of drugs that inhibit or enhance hepatic microsomal activity may result in an increase or decrease of phenytoin level, respectively. Phenytoin also affects the metabolism of various other agents (**Table 197-2**).

Propylene Glycol and Ethanol Diluents Propylene glycol is a potent myocardial depressant and vasodilator and also enhances vagal tone. This chemical can cause coma, seizures, circulatory collapse, ventricular dysrhythmias, atrioventricular node depression, and hypotension in experimental animals.[4] Other toxic effects from propylene glycol include hyperosmolality, hemolysis, and lactic acidosis.[5] The ethanol diluent fraction of parenteral phenytoin may precipitate a reaction in patients taking disulfiram.

CLINICAL FEATURES

CNS Toxicity As toxic phenytoin levels are reached, inhibitory cortical and excitatory cerebellar and vestibular effects begin to occur. The initial sign of toxicity is usually nystagmus, which is seen first on forced lateral gaze and later becomes spontaneous (**Table 197-3**).[6] Vertical, bidirectional, or alternating nystagmus may occur with severe intoxication. A decreased level of consciousness is common and may be seen with initial sedation, lethargy, ataxic gait, and dysarthria.[6] This may progress to confusion, coma, and even apnea in a substantial overdose. Nystagmus may disappear as the level of consciousness decreases, and complete ophthalmoplegia and loss of corneal reflexes may occur. Therefore, absence of nystagmus does not exclude severe phenytoin toxicity. Nystagmus returns as serum drug levels decrease and coma lightens.

Paradoxically, very high levels of phenytoin may be associated with seizures, although this is a rare occurrence, and such phenytoin-induced seizures are usually brief and generalized; they are almost always preceded by other signs of toxicity, especially in acute overdose.[7]

Cerebellar stimulation and alterations in dopaminergic and serotonergic activity levels may cause acute dystonias and movement disorders such as opisthotonos and choreoathetosis. Hyperactive deep tendon reflexes, clonus, and extensor toe responses also may be elicited. Chronic neurologic toxicity includes peripheral neuropathy and cerebellar degeneration with ataxia.

TABLE 197-2 Phenytoin Drug Interactions (Partial List)

Phenytoin increases serum levels of	Phenytoin levels are increased by
Acetaminophen	Amiodarone
Acetazolamide	Chloramphenicol
Amiodarone	Cimetidine
Oral contraceptives	Disulfiram
Primidone	Fluconazole
Zidovudine	Isoniazid
Phenytoin increases toxicity of	Oral anticoagulants
Carbamazepine	Phenylbutazone*
Oral anticoagulants	Salicylate (high dose)*
Phenytoin decreases serum levels of	Trimethoprim
Cyclosporine	Phenytoin levels are decreased by
Disopyramide	Antineoplastic drugs
Doxycycline	Calcium
Ethanol (chronic use)	Ethanol
Furosemide	Diazepam
Glucocorticoids	Diazoxide
Levodopa	Folic acid
Methadone	Phenobarbital
Mexiletine	Rifampin
Quinidine	Sucralfate
Theophylline	Sulfonamides*
Valproate	Theophylline
	Tolbutamide*
	Valproate*

*These drugs displace phenytoin from its protein-binding sites, thus increasing the free phenytoin fraction, although the total phenytoin level may decrease.

TABLE 197-3 Clinical Features of Phenytoin Toxicity

CNS	Dizziness, tremor (intention), visual disturbance, horizontal and vertical nystagmus, diplopia, miosis or mydriasis, ophthalmoplegia, abnormal gait (bradykinesia, truncal ataxia), choreoathetoid movements, irritability, agitation, confusion, hallucinations, fatigue, coma, encephalopathy, dysarthria, meningeal irritation with pleocytosis, seizures (rare)
Peripheral nervous system	Peripheral neuropathy, urinary incontinence
Hypersensitivity (anticonvulsant hypersensitivity syndrome)	Eosinophilia, rash, pseudolymphoma (diffuse lymphadenopathy), systemic lupus erythematosus, pancytopenia, hepatitis, pneumonitis
GI	Nausea, vomiting, hepatotoxicity
Dermatologic	Hirsutism, acne, rashes (including Stevens-Johnson syndrome)
Other organs	Fetal hydantoin syndrome, gingival hyperplasia, coarsening of facial features, hemorrhagic disease of the newborn, hyperglycemia, hypocalcemia
Parenteral toxicity	May cause hypotension, bradycardia, conduction disturbances, myocardial depression, ventricular fibrillation, asystole, and tissue necrosis from infiltration

Cardiovascular Toxicity **Cardiovascular complications have been almost entirely limited to cases of IV administration, in large part due to the constituents of the parenteral vehicle or, in rare cases, with chronic oral toxicity.**[8] Cardiac toxicity after acute oral phenytoin overdose in an otherwise healthy patient has not been reported and, if observed, is due to other causes (e.g., hypoxia, other drugs).[9]

Reported cardiovascular complications include hypotension with decreased peripheral vascular resistance, bradycardia, conduction delays progressing to complete atrioventricular nodal block, ventricular tachycardia, primary ventricular fibrillation, and asystole. ECG changes include increased PR interval, widened QRS interval, and altered ST segments and T waves. Cardiovascular toxicity is more common in the elderly, those with underlying cardiac disease, and the critically ill. Guidelines for parenteral phenytoin administration stress a slow rate of infusion and constant monitoring. Even though fosphenytoin does not contain the propylene glycol diluent, cardiovascular toxicity can occur with IV administration. Hypotension is seen in about 8%, and rare cases of bradycardia, atrioventricular nodal block, and asystole have been observed.[2,10,11]

Vascular and Soft Tissue Toxicity IV extravasation can produce skin and soft tissue necrosis, compartment syndrome, and limb gangrene. There are reports of delayed bluish discoloration of the affected extremity ("purple glove syndrome") followed by erythema, edema, vesicles, bullae, and local tissue ischemia.[12]

Hypersensitivity Reactions Hypersensitivity reactions usually occur within 1 to 6 weeks of beginning phenytoin therapy and can present as a febrile illness with skin changes (erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis) and internal organ involvement (hepatitis, rhabdomyolysis, acute interstitial pneumonitis, renal failure, lymphadenopathy, leukopenia, and/or disseminated intravascular coagulation). **Patients with a history of previous hypersensitivity reactions should not receive phenytoin, and because of similar reactions to phenobarbital, lamotrigine, felbamate, and carbamazepine, these anticonvulsants should also be avoided.**

DIAGNOSIS

The therapeutic phenytoin serum level is 10 to 20 micrograms/mL (40 to 80 micromole/L), which generally corresponds to a free phenytoin level of 1 to 2 micrograms/mL.[13] Although 50% of patients achieve reduction in seizure frequency below these levels, some patients require levels as high as 20 micrograms/mL for adequate control. The ratio of toxic dose to therapeutic dose for phenytoin is rather low, and there is wide individual variability in the levels required to cause adverse effects. In general, toxicity is correlated with increasing plasma levels (**Table 197-4**).

TABLE 197-4 Correlation of Plasma Phenytoin Level and Toxic Effects

Total Plasma Phenytoin Level (micrograms/mL [micromole/L])	Toxic Effects
<10 (<40)	Usually none
10–20 (40–80)	Occasional mild nystagmus
20–30 (80–120)	Nystagmus
30–40 (120–160)	Ataxia, slurred speech, nausea and vomiting
40–50 (160–200)	Lethargy, confusion
>50 (>200)	Coma, seizures

TREATMENT

The initial treatment of severe oral phenytoin overdose is similar to that for ingestion of other drugs. Correct acidosis (respiratory or metabolic) to decrease the active free phenytoin fraction. Multidose activated charcoal may decrease drug half-life, but does not decrease time to recovery and does not change outcome in overdose patients.[14] Seizures may be treated with IV benzodiazepines or phenobarbital, with the caution that seizures are uncommon in phenytoin overdose. **For patients with severe and persistent toxicity, hemodialysis and hemoperfusion can produce substantial improvement in neurologic toxicity.**[15-17]

Cardiac monitoring after isolated oral ingestion is unnecessary. Atropine and temporary cardiac pacing may be used for symptomatic bradyarrhythmias associated with IV phenytoin. Hypotension that occurs during IV administration of phenytoin or fosphenytoin usually responds to discontinuation of the infusion and administration of isotonic crystalloid.

DISPOSITION AND FOLLOW-UP

Phenytoin has a long and erratic absorption phase after oral overdose, so the decision to discharge or medically clear a patient for psychiatric evaluation cannot be based on one serum level. After acute ingestions, serum level should be measured every few hours. Patients with oral ingestion who have serious complications (seizures, coma, altered mental status, or significant ataxia) should be admitted for further evaluation and treatment. Those with mild symptoms should be observed in the ED and discharged once their levels of phenytoin are declining and they are clinically well. Mental health or psychiatric evaluation should be obtained, as indicated, in cases of intentional overdose.

Patients with symptomatic chronic intoxication should be admitted for observation unless signs are minimal, adequate care can be obtained at home, drug levels are decreasing, and 6 to 8 hours have elapsed since the patient's last therapeutic dose. Phenytoin therapy should be stopped in all cases, and if toxicity continues to resolve, serum level may be reassessed in 2 to 3 days to guide resumption of therapy.

CARBAMAZEPINE

Carbamazepine is a primary anticonvulsant used in the treatment of partial and tonic-clonic seizures. Other uses include trigeminal neuralgia, chronic pain disorders, manic disorder, and bipolar disorder.

PATHOPHYSIOLOGY

Carbamazepine inhibits sodium channels and interferes with muscarinic acetylcholine receptors, nicotinic acetylcholine receptors, *N*-methyl-D-aspartate receptors, and CNS adenosine receptors.[3] It has central antidiuretic effects, which may lead to the syndrome of inappropriate antidiuretic hormone secretion. Carbamazepine is a potent cytochrome P450 (CYP450) enzyme inducer and enhances its own metabolism over time.

Carbamazepine is an iminostilbene derivative that is chemically and structurally similar to imipramine. GI absorption is slow, and peak serum concentrations usually occur within 8 hours but may occur as late as 12 hours after ingestion. A therapeutic carbamazepine concentration is 8 to 12 micrograms/mL (34 to 51 micromole/L).[18]

Carbamazepine has a protein binding of about 80% and is metabolized by liver CYP450 isoenzymes to an active metabolite (10,11-epoxide) responsible for much of the neurotoxicity seen in overdose. Autoinduction of the enzymes that metabolize carbamazepine occurs after about 1 month of continuous use, decreasing the elimination half-life (Table 197-1).[17]

CLINICAL FEATURES

After an overdose, the delayed and erratic absorption due to anticholinergic properties (which delay GI motility) and low water solubility can cause delayed clinical deterioration or a crescendo-decrescendo clinical course.[19] Manifestations of acute toxicity include mental status depression, ataxia, nystagmus, ileus, hypertonicity with increased deep tendon reflexes, dystonic reactions, and an anticholinergic toxidrome.[19-21] Paradoxical seizures can occur in patients with high carbamazepine concentrations and an underlying seizure disorder. There are sporadic reports of left ventricular dysfunction with heart failure and transient heart block (without hemodynamic compromise). **Cardiac arrhythmias are rarely seen, but carbamazepine is one of the few drugs that can potentially cause both a wide QRS interval and seizures.** Laboratory abnormalities seen with acute overdose include hyponatremia, hyperglycemia, and transient elevation of serum liver enzyme levels.

DIAGNOSIS

Serum carbamazepine concentrations are not linearly correlated with poisoning severity. However, serum concentrations of >40 micrograms/mL (>170 micromole/L) are associated with an increased risk of serious complications such as seizures, respiratory failure, coma, and cardiac conduction defects.[22] Serum concentrations higher than 60 to 80 micrograms/mL (250 to 340 micromole/L) may be fatal. The seriousness of toxicity should be judged by the clinical status of the patient, not by the serum concentration.[20-22]

Because the chemical structure of carbamazepine is related to imipramine, **carbamazepine can cause a false-positive tricyclic antidepressant result on a urine drug screen.**[23] Both carbamazepine and epoxide metabolite are measured by the standard enzyme-multiplied immunoassay to determine serum levels.

TREATMENT

Because delayed absorption is possible, activated charcoal may be considered if the patient is not obtunded and presents within 1 hour of ingestion.[14] Multidose activated charcoal may decrease drug half-life but does not decrease time to recovery or change outcome in overdose patients.[24] **In patients with severe toxicity and multiorgan dysfunction, hemodialysis, hemoperfusion, and hemodiafiltration are effective.**[25-31] Although cardiac conduction delays are rare, if conduction delay is noted on the ECG, sodium bicarbonate treatment is reasonable.

DISPOSITION AND FOLLOW-UP

Patients can be medically cleared from the ED if at least two carbamazepine measurements obtained a few hours apart show decreasing levels (preferably <15 micrograms/mL or 63 micromole/L) and the patient is awake, ambulatory, and free of cardiac conduction abnormalities.

VALPROIC ACID

Valproic acid (oral preparation) or valproate sodium (IV form) is used to treat tonic-clonic seizures, absence seizures, partial complex seizures, and posttraumatic epilepsy. Valproic acid is also used in migraine headache prophylaxis, to control manic episodes in bipolar disorder, and in the treatment of neuropathic pain.

PATHOPHYSIOLOGY

Valproic acid affects neurotransmitters and the function of electrically excitable cells.[3] Valproic acid increases γ-aminobutyric acid concentrations, reduces release of γ-hydroxybutyrate, and blocks *N*-methyl-D-aspartate receptors.[32] Valproic acid prolongs recovery of inactivated sodium channels, enhances potassium conductance, and reduces T-type calcium current firing.

With standard preparations at therapeutic doses, peak serum concentrations occur within 4 hours after ingestion. If the enteric-coated or controlled-release formulation has been ingested, peak serum concentration may be delayed for 12 to 17 hours.[33]

Valproic acid is metabolized by the liver by glucuronic acid conjugation and mitochondrial beta oxidation. Valproic acid enters mitochondria by using L-carnitine as a cofactor. Protein binding is extensive and influenced by serum concentration, with 90% of the drug protein bound at concentrations of 40 micrograms/mL (277 micromole/L). The half-life of valproic acid may be two or three times longer after overdose.[33-36]

CLINICAL FEATURES

After an overdose with acute toxicity, the most frequent sign is CNS depression, ranging from drowsiness to coma.[35] Other findings include respiratory depression, hypotension, hypoglycemia, hypocalcemia, hypernatremia, hypophosphatemia, and anion gap metabolic acidosis that may persist for days. Toxicity to the liver produces elevated serum levels of aminotransferases, ammonia, and lactate. Pancreatitis may occur, and thrombocytopenia may be clinically significant and severe.[35]

Valproic acid increases renal ammonia production and blocks hepatic ammonia metabolism, thus producing hyperammonemia following valproate overdose and during long-term therapy.[37,38] Cerebral edema has been seen in acute overdose.[34,35] Valproic acid–induced hepatotoxicity may be either intrinsic and benign (reversible, reproducible, and dose dependent) or idiosyncratic and fatal (unpredictable, not dose dependent, with a long latent period).[39-41] Children <3 years of age who are receiving multiple antiepileptic agents and have additional medical problems are at highest risk for fatal hepatotoxicity, with an incidence of about 1 in 500. Serum levels of transaminases and ammonia should be checked in children on valproate therapy who demonstrate somnolence or lethargy.

DIAGNOSIS

Therapeutic valproic acid concentrations are 50 to 100 micrograms/mL (346 to 693 micromole/L). Although serum concentration does not correlate well with either seizure control or toxicity, adverse side effects increase as concentrations rise above 150 micrograms/mL (1040 micromole/L), and coma may occur with levels above 800 micrograms/mL (5547 micromole/L). Serum ammonia and glucose concentrations should be measured with suspected valproic acid toxicity. **Valproic acid is eliminated partly as ketone bodies and may cause a positive test result for ketones in the urine or blood.**

TREATMENT

Single-dose activated charcoal alone is sufficient for the vast majority of patients with a valproic acid overdose. Consider multidose activated charcoal and/or whole-bowel irrigation after ingestion of enteric-coated, delayed-release preparations to prevent the ongoing absorption that may occur from delayed capsule or tablet dissolution.[14,42] Because of delayed peak serum levels after an overdose, serial concentrations should be measured.

Overdose patients have been given **L-carnitine** in an attempt to increase valproic acid metabolism by beta oxidation, and this therapy appears to hasten the resolution of coma, prevent hepatic dysfunction, and reverse mitochondrial metabolic abnormalities in patients with acute intoxication.[43-45] Administration of L-carnitine 100 milligrams/kg IV initially followed by infusions of 50 milligrams/kg every 8 hours is

recommended in cases of valproic acid toxicity with lethargy, coma, hyperammonemia, and hepatic dysfunction.[44]

Hemoperfusion and hemodiafiltration have been used to treat severe valproic acid overdose.[46-50] Although valproic acid should not be amenable to dialysis due to significant protein binding, unbound (free) drug is markedly increased in overdose, and removal of valproic acid from this pool appears beneficial. During hemoperfusion and hemodiafiltration treatment, elimination half-life is decreased by two- to sevenfold. Universal use of hemodiafiltration cannot be recommended for all patients. Clinical comparison of extracorporeal detoxification with supportive care reports a benefit with extracorporeal removal.[51]

DISPOSITION AND FOLLOW-UP

Patients can be medically cleared from the ED if valproic acid levels measured every few hours demonstrate a decline and the patient is asymptomatic.

OTHER FIRST-GENERATION ANTICONVULSANTS

ETHOSUXIMIDE AND METHSUXIMIDE

Ethosuximide and **methsuximide** are used to treat absence seizures. Therapeutic serum concentrations for ethosuximide are 40 to 100 micrograms/mL (280 to 700 micromole/L). Therapy with methsuximide is monitored by measuring the metabolite normethsuximide, with a therapeutic range of 10 to 40 micrograms/mL (53 to 212 micromole/L). Acute toxicity from ethosuximide or methsuximide overdose is characterized by CNS depression (ataxia, confusion, slurred speech, decreased level of consciousness), respiratory depression, and nausea and vomiting. Treatment is supportive.

PRIMIDONE AND PHENOBARBITAL

Primidone and **phenobarbital** are used to treat a variety of seizure types. Primidone is metabolized into phenobarbital; both the parent drug and its active metabolite act on γ-aminobutyric acid receptors, producing synaptic inhibition. Therapeutic serum concentrations for primidone are 5 to 12 micrograms/mL (23 to 55 micromole/L). The therapeutic serum concentrations for phenobarbital are 15 to 40 micrograms/mL (65 to 172 micromole/L). Urinary alkalinization somewhat enhances the clearance of phenobarbital and primidone. See Chapter 182, "Barbiturates," for further discussion.

SECOND- AND THIRD-GENERATION ANTICONVULSANTS

As a group, the second- and third-generation anticonvulsants are less toxic in acute overdose than the first-generation agents, and most of the serious complications reported have occurred in cases of mixed ingestion.[52] Some specific acute toxic effects are notable (**Table 197-5**).

BRIVARACETAM

Brivaracetam is used as monotherapy or adjunct therapy for partial seizures.

TABLE 197-5 Second- and Third-Generation Anticonvulsants

Drug	Usual Oral Adult Dose (milligrams)	Maximum Oral Adult Daily Dose (milligrams)	Elimination Half-Life in Adults With Therapeutic Doses (h)	Unique Effects Seen With Overdose
Brivaracetam	25–100 BID	200	9	
Eslicarbazepine acetate	800–1600 once daily	1600	13–20	Vertigo, ataxia, hemiparesis
Ezogabine or retigabine*				Agitation, irritability, aggressive behavior
Felbamate	2400–3600 per day divided TID or QID	3600	20–23	Crystalluria, hematuria, aplastic anemia, liver failure
Gabapentin	300–1200 TID	3600	5–7	Drowsiness, ataxia, nausea, vomiting
Lacosamide	150–200 BID	400	7–15	Limited experience; serious toxicity unlikely
Lamotrigine	200 once daily	200	25	Drowsiness, vomiting, ataxia, and dizziness; serious neurologic and cardiovascular toxicity with co-ingestants; Stevens-Johnson syndrome
Levetiracetam	500–1500 BID	3000	6–8	Lethargy, coma, respiratory depression
Oxcarbazepine	600 BID	2400	2 (parent drug) 9 (active metabolite)	Little toxicity from isolated oxcarbazepine overdose
Perampanel	8–12 every night at bedtime	12	105	
Pregabalin	160–600 per day divided BID or TID	600	6	Drowsiness and depressed level of consciousness
Rufinamide	1600 BID	3200	6–10	Limited experience; serious toxicity unlikely
Stiripentol*				No information
Tiagabine	32–56 per day divided BID to QID	56	7–9	Rapid onset of lethargy, coma, seizures, and status epilepticus; myoclonus, muscular rigidity, and delirium
Topiramate	200 BID	400	21	Somnolence, vertigo, agitation, and mydriasis; seizures and status epilepticus; metabolic acidosis
Vigabatrin†	1500 BID	3000		Drowsiness, unconsciousness, coma
Zonisamide	100–600 per day divided once daily or BID	600	63	Little toxicity from isolated zonisamide overdose

Abbreviations: BID = twice a day; QID = four times a day; TID = three times a day.

*Not available in the United States as of March 2018.

†Restricted distribution in the United States.

ESLICARBAZEPINE ACETATE

Eslicarbazepine acetate is a prodrug for eslicarbazepine, an anticonvulsant that stabilizes sodium-dependent channels in their inactivated state and is used to treat partial seizures.[53,54] Eslicarbazepine possesses modest and possible clinically relevant drug interactions with phenytoin, carbamazepine, and oral contraceptives.[53-55] Symptoms of vertigo, ataxia, and hemiparesis have been observed after accidental overdose.

EZOGABINE

Ezogabine (generic name in the United States), known in Europe as **retigabine**, activates voltage-gated potassium channels in the brain, a unique mechanism among the anticonvulsants.[53,54,56] Ezogabine has drug interactions with phenytoin, carbamazepine, and lamotrigine.[53-55] Side effects seen with ezogabine therapy include dizziness, fatigue, confusion, tremor, and ataxia.[56] Increased rate of urinary retention and slight increase in QT interval have been reported. There is limited experience with overdose, but agitation, irritability, and aggressive behavior have been noted. This drug is no longer distributed in the United States.

FELBAMATE

Felbamate was the first of the second-generation antiepileptics.[52] However, shortly after its introduction in 1993, it received a "black box warning" because of the association with aplastic anemia (with an incidence 100 times higher than in the general population) and hepatic failure. Hence, it is only recommended when other treatment regimens have failed to control seizures. The proposed mechanism of action of felbamate is inhibition at γ-aminobutyric acid receptors and excitation at *N*-methyl-D-aspartic acid receptors. Felbamate has drug interactions with the first-generation anticonvulsants and oral contraceptives. In overdose, the symptoms are usually mild, but in large ingestions, felbamate can crystallize in the kidney, producing crystalluria, hematuria, and possibly acute renal failure.[57-59] Treatment is supportive.

GABAPENTIN

Gabapentin, as its name suggests, increases γ-aminobutyric acid levels in the brain. It also has indirect effects on calcium channels located on the postsynaptic terminal. Gabapentin is used to treat partial seizures. Gabapentin has drug interactions with cimetidine and antacids. With an overdose, gabapentin produces little toxicity, usually being associated with drowsiness, ataxia, nausea, and vomiting that resolve in about 10 hours.[60] Depressed level of consciousness has been described in a patient with end-stage renal disease who ingested multiple doses of gabapentin over 2 days without intervening hemodialysis; hemodialysis was associated with rapid recovery.[61] The only reported suicide from gabapentin overdose is controversial.[62]

LACOSAMIDE

Lacosamide affects voltage-gated sodium channels in the CNS and is used to treat partial seizures.[63] Lacosamide has no significant drug interactions.[54,55] During therapeutic use, adverse reactions are usually mild to moderate and typically include dizziness, headache, nausea, and diplopia.[63] There is limited clinical experience with lacosamide overdose, but serious toxicity after an isolated overdose would not be expected to occur.

LAMOTRIGINE

Lamotrigine inhibits sodium channels in CNS neurons and likely has the same effect in the heart.[53] Lamotrigine is used to treat partial and generalized seizures. Lamotrigine interacts with the first-generation antiepileptics.[55] Autoimmune reactions, such as Stevens-Johnson syndrome, have occurred during therapeutic use. With an overdose, the clinical course is usually benign, and the most common effects are drowsiness, vomiting, ataxia, and dizziness.[64,65] Serious neurologic and cardiovascular toxicity is rare, but has been reported after lamotrigine overdose (although sometimes with co-ingestants).[66-70] Neurologic toxicity includes oculogyric crisis,[71] provoking of seizures,[68,72-75] status epilepticus, and coma. Cardiac toxicity includes QRS complex widening,[76] atrioventricular nodal block,[77] and cardiovascular collapse.[70,75] Acute pancreatitis has been reported in association with a lamotrigine overdose.[78] Treatments used in lamotrigine overdose include **activated charcoal** to reduce absorption,[79] **sodium bicarbonate for QRS complex widening, magnesium sulfate for QT interval prolongation, and IV lipid emulsion** to remove active drug from binding sites and sequester it in a lipid sink.[80,81]

LEVETIRACETAM

The mechanism of action of **levetiracetam** is not known. The drug binds to a synaptic vesicle glycoprotein and inhibits presynaptic calcium channels, reducing neurotransmitter release. This is believed to impede impulse conduction across synapses. Levetiracetam is used to treat partial and generalized seizures. During therapeutic use, the major side effect is somnolence, and mood disorders are usually seen during the initial 4 weeks of therapy.[82] There are few reports of levetiracetam overdose, and the most common symptom is lethargy that can progress to coma and rarely respiratory depression.[83-86] Recovery is usually rapid with supportive care alone.

OXCARBAZEPINE

Oxcarbazepine inhibits voltage-sensitive sodium channels in the nervous system and is used to treat partial seizures.[87] Oxcarbazepine interacts with phenytoin, lamotrigine, and oral contraceptives.[54,55] During therapeutic use, hyponatremia and drug rash can be seen. Hyponatremia is a common adverse effect of both oxcarbazepine and carbamazepine, due in part to increased responsiveness of collecting tubules to antidiuretic hormone. There appears to be little toxicity from isolated oxcarbazepine overdose; most of the serious neurologic depression has been seen with mixed ingestions.[88-91]

PERAMPANEL

Perampanel is used to treat partial-onset seizures and generalized seizures in those >12 years old, mostly as an adjunctive agent. The half-life is about 100 hours. It is a possible agent of abuse, because high doses can produce euphoria. It is a U.S. Food and Drug Administration Schedule III drug because abuse can lead to dependence. Dose-related effects include hostility, aggression, and agitation.[92,93] There are almost no reports describing overdose. It is best to discuss management with your toxicologist or poison control center.

PREGABALIN

Pregabalin has a mechanism of action similar to that of gabapentin, increasing γ-aminobutyric acid levels in the brain in addition to having indirect effects on calcium channels located on the postsynaptic terminal. Pregabalin is used as adjunct therapy for partial seizures. Pregabalin has drug interactions with ethanol, lorazepam, and oxycodone.[54,55] During long-term therapeutic use, the most commonly reported side effects are somnolence and dizziness; serious adverse effects are rare. There is little reported experience with pregabalin overdose. Depressed level of consciousness appears to be the major symptom.[94,95] Similar to the experience with gabapentin, toxicity from pregabalin has been reported in patients with end-stage renal failure but resolves with dialysis.[96]

RUFINAMIDE

Rufinamide inhibits the activity of sodium channels, prolonging their inactive state and is used as adjunct therapy in Lennox-Gastaut syndrome.[97] Rufinamide has drug interactions with other anticonvulsants—phenytoin, carbamazepine, valproate, phenobarbital, and lamotrigine—as well as with oral contraceptives.[54,55] During long-term therapy, commonly reported adverse reactions include headache, dizziness, fatigue, and somnolence. There is limited clinical experience with rufinamide overdose, but given the lack of symptoms seen with doses of more than six times the recommended amount, toxicity would not be expected after an isolated overdose.

STIRIPENTOL

Stiripentol inhibits the reuptake of γ-aminobutyric acid into the presynaptic neuron, thereby increasing γ-aminobutyric acid concentrations in the synaptic cleft and promoting γ-aminobutyric acid activity. Stiripentol possesses modest drug interactions with valproate and clobazam.[54,55] Side effects during therapeutic use include drowsiness, ataxia, tremor, anorexia, nausea, and vomiting. Transient aplastic anemia and leukopenia have occurred. There is no information on clinical overdose with this medication. Stiripentol, first used in Europe and Canada, was approved in 2018 by the Food and Drug Administration for use in the United States.

TIAGABINE

Tiagabine inhibits the reuptake of γ-aminobutyric acid into the presynaptic neuron, thereby promoting γ-aminobutyric acid activity. Tiagabine is used as adjunct therapy to treat partial seizures. Tiagabine interacts with most of the first-generation antiepileptics, including phenytoin, valproate, carbamazepine, phenobarbital, and primidone.[54,55] In overdose, tiagabine can cause the rapid onset of neurologic toxicity, including lethargy, coma, and seizures.[98-101] Tiagabine overdose can provoke status epilepticus, even in patients without an underlying seizure disorder.[102-105] Other signs seen in tiagabine overdose include myoclonus, muscular rigidity, and delirium.[98] Recovery usually occurs in about 24 hours.

TOPIRAMATE

Topiramate inhibits γ-aminobutyric acid receptors in addition to affecting sodium channels in the brain and is used to treat partial and generalized seizures. Topiramate possesses drug interactions with other anticonvulsants—phenytoin, valproate, carbamazepine, phenobarbital, and primidone—as well as with oral contraceptives.[54,55] Adverse effects observed during therapeutic use include promotion of renal stone formation and glaucoma. In overdose, topiramate can produce somnolence, vertigo, agitation, and mydriasis.[106-108] Seizures and status epilepticus have been reported.[109,110] **A unique aspect of topiramate overdose is the production of a non–anion gap metabolic acidosis.**[111-113] The cause is inhibition of renal carbonic anhydrase, and because of the long half-life of topiramate, metabolic acidosis can last up to 7 days. However, this effect is completely reversible, and no permanent sequelae have been seen.

VIGABATRIN

Vigabatrin is a structural analog of γ-aminobutyric acid that increases brain concentrations of this neurotransmitter. Vigabatrin has a modest drug interaction with phenytoin.[54,55,114] Vigabatrin is used to treat refractory complex partial seizures, and because of the potential to induce permanent vision loss, it is only available in the United States via a restricted distribution program. During chronic therapy, vigabatrin may worsen mood and exacerbate psychosis. Sedation, headache, and weight gain are common side effects. After acute overdose, drowsiness, unconsciousness, and coma are described in the majority of cases.[115]

ZONISAMIDE

Zonisamide inhibits voltage-sensitive sodium channels in CNS neurons and is used to treat partial seizures.[116] Zonisamide has drug interactions with most of the first-generation antiepileptics, including phenytoin, valproate, carbamazepine, phenobarbital, and primidone.[54,55] Serious adverse effects during therapeutic use include the promotion of renal stone formation and a drug-induced rash. Isolated zonisamide overdose is associated with lethargy.[117,118] A death ascribed to zonisamide overdose was actually a mixed ingestion that included mirtazapine, diphenhydramine, and caffeine.[119]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 198

Iron

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INTRODUCTION

Iron supplements are widely available, particularly in homes with small children and young women. Women of childbearing age with iron available at home are at risk of intentional iron overdose due to the impact of maternal stress. The attractiveness of the brightly colored sugar-coated tablets and improper storage of iron make children susceptible to ingestion, serious toxicity, and death.[1] The 1997 federal requirement that all preparations containing >30 milligrams of elemental iron be distributed only in blister packs and the implementation of mandated warning labels from the U.S. Food and Drug Administration coincided with the reduction of pediatric iron poisonings and deaths.[2,3] Despite the rescindment of the blister pack requirement in 2003, serious iron poisonings in children have remained low.[4]

PHARMACOLOGY

Excess iron in overdose may saturate the body's mechanisms for iron homeostatis, allowing for unbound ("free") iron to cause organ toxicity. Due to its reactivity with oxygen, iron is always bound to a carrier molecule under normal circumstances. Carrier molecules include transferrin (serum protein), ferritin (intracellular storage), and iron-containing proteins (hemoglobin, myoglobin, cytochromes, and other enzymes and cofactors). The body cannot directly excrete iron, so regulation of GI iron uptake and limitation of absorption by sloughing of mucosal cells containing surplus iron are the principal mechanisms for maintaining physiologic iron concentrations.

The oral bioavailability of iron depends on the formulation ingested (**Table 198-1**) along with body iron stores (increased with iron deficiency anemia) and ingestion with food or fasting (increased in fasting state). The bioavailability of ionic iron preparations is low, about 10% to 15% for ferrous (Fe^{2+}) salts and about 5% for ferric (Fe^{3+}) salts. Most dietary iron is in the ferric form chelated to a heme moiety. Following ingestion, the ferric ion is separated from heme and reduced to ferrous iron by a brush border ferrireductase. Iron chelated with heme, such as that found in meat, is more readily absorbed than tablets of ionic iron or nonheme iron in plants. Commercially available formulations of iron chelated with amino acids (e.g., glycinate) mimic dietary meat, with bioavailability about twice that of ferrous sulfate.

Ferrous iron is transported into enterocytes of the GI tract, oxidized to ferric iron, which binds to transferrin, and transported from the enterocytes into the circulation throughout the body. The serum total iron-binding capacity assay primarily measures the amount of serum transferrin and is generally two to three times the normal serum iron concentration (50 to 170 micrograms/dL or 9 to 30 micromol/L). Iron is stored within the body in the form of ferritin, a large intracellular storage protein that can reversibly bind as many as 4500 molecules of iron. In adults, about 0.5 to 1 gram of elemental iron is stored as ferritin and hemosiderin, primarily in the bone marrow, spleen, and liver, and mobilized from these stores in times of iron deficiency.[5]

PATHOPHYSIOLOGY

Iron, as a transition metal, is a potent catalyst for the production of oxidants such as free radicals.[6] Through this mechanism, iron is a direct GI tract irritant causing vomiting, diarrhea, abdominal pain, mucosal ulceration, and bleeding soon after a significant ingestion. As the mucosal surface is injured, the regulatory enterocyte barrier is compromised, and free iron passes unimpeded into the blood, becoming systemically available.

Free iron disrupts critical cellular processes and induces acidosis and widespread organ toxicity. In acute iron poisoning, with the appearance of free iron, a multifactorial metabolic acidosis with an elevated lactate appears due to inhibition of oxidative phosphorylation by disruption of the mitochondrial electron transport chain, production of toxic hydroxyl

TABLE 198-1 Iron Formulations and Elemental Iron Composition

	Iron Formulation	Elemental Iron Composition	Typical Dose Size	Amount of Elemental Iron
Ionic	Ferrous fumarate (PO)	33%	324-milligram tablet	106 milligrams/tablet
	Ferrous sulfate (PO)	20%	325-milligram tablet	65 milligrams/tablet
			220 milligrams/5 mL solution	8.8 milligrams/mL
	Ferrous gluconate (PO)	12%	324-milligram tablet	38 milligrams/tablet
	Sodium ferric gluconate (IV)	1.25%		12.5 milligrams/mL
	Ferric citrate (PO)	21%	1-gram tablet	210 milligrams/tablet
Nonionic	Carbonyl iron (PO)	98%	1 caplet proprietary mixture	45 milligrams/caplet
	Iron polysaccharide (PO)	46%	1 capsule proprietary mixture	150 milligrams/capsule
	Iron dextran (IV)			50 milligrams/mL
	Iron sucrose (IV)	2%		20 milligrams/mL
Chelated	Ferrous bisglycinate (PO)	20%	125-milligram capsule	25 milligrams/capsule
	Iron glycinate (PO)	27%	185-milligram capsule	50 milligrams/capsule

radicals, induction of membrane lipid peroxidation, liberation of hydrogen ions from reduction of ferrous iron, and hypotension. Hepatotoxicity occurs as the portal blood supply delivers a large amount of iron to the liver. In addition, coagulopathy unrelated to hepatotoxicity may occur through inhibition of thrombin formation and the effect of thrombin on fibrinogen. Myocardial and vascular dysfunction result from vasodilation, negative ionotropic effect, and direct myocardial iron deposition.

TOXICITY

The amount of ingested elemental iron in ionic form correlates with the potential for toxicity (**Table 198-2**). **In general, moderate toxicity occurs at doses of 20 to 60 milligrams/kg of elemental iron, and severe toxicity can be expected following ingestion of >60 milligrams/kg of elemental iron.** The most commonly prescribed formulation, a ferrous sulfate 325-milligram tablet (20% elemental iron by weight), contains 65 milligrams of elemental iron, and approximately 20 tablets would be expected to produce moderate toxicity after an acute ingestion in an average-size (65-kg) adult. Pediatric multivitamins typically contain less elemental iron per tablet (10 to 18 milligrams) and thus are associated with less fatality compared to adult iron supplements.[7] Ferric chloride poisoning can occur with occupational inhalation, accidental ingestion through mislabeling, and suicidal ingestion.[8] Ingestion of commercially available chemical hand warmers, containing 95 to 120 grams of reduced elemental iron (not an iron salt), may cause corrosive injury of the esophagus and stomach[9] and result in significant iron absorption with potential toxicity.[10,11]

Exceptions to the correlation of ingested dose and toxicity include chelated iron and carbonyl iron. Despite their increased iron content, chelated sources of supplemental iron are less toxic than nonchelated iron in overdose, because the ligand sterically limits the iron from participating in redox reactions.[12] Similarly, carbonyl iron is a nonionic iron molecule that does not participate in redox reactions, and the limited experience with overdose of carbonyl iron suggests a lower incidence of toxicity compared with ingestion of an equivalent amount of ionic iron.[13]

TABLE 198-2 Predicted Toxicity of Ionic Iron Ingestion

Predicted Clinical Effects	Elemental Ionic Iron Dose*	Serum Iron Concentration†
Mild GI effects; low risk for systemic toxicity	<20 milligrams/kg	<300 micrograms/dL (<54 micromol/L)
Significant GI effects: moderate to severe systemic toxicity	20–60 milligrams/kg	300–500 micrograms/dL (54–90 micromol/L)
Severe systemic toxicity and increased morbidity	>60 milligrams/kg	>500 micrograms/dL (>90 micromol/L)

*Elemental iron dose by history.

†Serum iron concentration obtained within 4–6 h of ingestion; hourly measurement until peak.

CLINICAL FEATURES

Five stages of clinical toxicity are traditionally described, although in more practical terms, acute iron toxicity can be considered to manifest in two clinical stages: local GI tract toxicity and systemic toxicity.

Stage 1 is characterized by abdominal pain, vomiting, and diarrhea.[14] Iron is directly irritating and corrosive to the GI tract and typically induces vomiting within the first few hours following ingestion. Vomiting is the clinical sign most consistently associated with acute iron toxicity. Patients with symptoms of gastric irritation may either recover over several hours or progress to systemic toxicity. **The absence of GI symptoms within 6 hours of ingestion essentially excludes a significant iron ingestion.**

Stage 2, or the "latent" stage, occurs in more severe poisonings that progress to systemic toxicity within the 6- to 24-hour interval following ingestion. Resolution of GI symptoms may falsely reassure the patient and physician as this is not a truly quiescent phase. In severe poisonings, the latent stage is marked by ongoing clinical illness and progressive systemic deterioration secondary to volume loss and worsening metabolic acidosis. Alternatively, the resolution of GI findings may signal the end of mild poisoning, and in such a circumstance, the results of the patient's laboratory studies should be normal.

Stage 3 is characterized by systemic toxicity from iron-induced disruption of cellular metabolism with resultant shock and lactic acidosis. Iron-induced coagulopathy may worsen bleeding and hypovolemia. The coagulopathy may be biphasic, with prolonged prothrombin time and partial thromboplastin time within the first 24 hours. This initial coagulopathy appears to be reversible with chelation therapy, because free iron initially interferes with the activity of factors in the coagulation cascade. Subsequent coagulopathy is from iron-induced hepatic injury that reduces coagulation factor production. During stage 3, renal failure, cardiomyopathy, and failure of other critical organ systems may also occur.

Stage 4, the hepatic stage, develops 2 to 5 days following ingestion.[15] It results from iron uptake by the reticuloendothelial system with local lipid peroxidation; it manifests as elevation of aminotransferase levels and may progress to acute fulminant hepatic failure.

Stage 5 refers to delayed sequelae, including gastric outlet obstruction secondary to the corrosive effects of iron on the pyloric mucosa. Delayed sequelae are rare and occur 4 to 6 weeks after ingestion.[14]

As noted earlier, patients who develop GI effects that resolve and who continue to look well clinically and have near normal laboratory findings will not develop significant systemic toxicity.

DIAGNOSIS

LABORATORY TESTING

Laboratory tests should include CBC, determination of serum electrolyte levels, renal and liver function studies, coagulation function tests, serum glucose, and serum iron levels, with the understanding that these



FIGURE 198-1. A large number of radiopaque tablets in the left upper quadrant are visible on abdominal radiograph. [Used with permission from the Fellowship in Medical Toxicology, New York University School of Medicine, New York City Poison Control Center.]

results are to assess the overall condition of the patient, because **iron toxicity is largely a clinical diagnosis.**

Arterial blood gas analysis and serum lactate determination are usually unnecessary in mild cases, because determination of serum electrolyte levels (anion gap evaluation) usually yields all the important information. However, in patients with moderate to severe toxicity or in those with respiratory compromise, arterial blood gas results yield useful information. With moderate to severe ingestions, the blood bank should perform blood typing and screening in anticipation of potential need.

Interpret serum iron levels to assess toxicity and direct management with caution. **In general, serum iron levels measured within 4 to 6 hours after an acute ingestion correlate with the severity of toxicity** (Table 198-2), **but low serum iron levels do not exclude toxicity**. Serum iron levels may be low because of variable times to peak level following ingestions of different iron preparations, and treatment with deferoxamine can artificially lower serum iron levels. **Serum total iron-binding capacity has little value in the assessment of iron-poisoned patients.** It becomes falsely elevated in the presence of elevated serum iron levels or deferoxamine, and significant organ damage occurs despite exceeding the serum iron level.

IMAGING

Standard ferrous sulfate tablets and reduced iron are radiopaque and frequently visible on routine radiographs,[10] and this may help guide GI decontamination when present (**Figure 198-1**). However, many iron preparations are not routinely detected, including pediatric chewable and liquid preparations, and absence of radiopaque material on radiographs does not exclude iron ingestion.[3]

TREATMENT

Iron poisoning is a clinical diagnosis. Signs and symptoms consistent with iron poisoning should guide treatment, rather than serum iron concentrations alone (**Figure 198-2**). Patients who are asymptomatic on ED arrival, have not ingested a potentially toxic dose, and have normal findings on physical examination can be observed and do not require specific medical treatment. Patients who vomit once or twice from the gastric irritant effects of iron but who are otherwise asymptomatic, hemodynamically stable, and without metabolic acidosis can also be observed and may require no specific treatment.

Patients with clinical toxicity should first be stabilized with attention to airway, breathing, and circulation, after which GI decontamination and chelation therapy with deferoxamine may proceed.[3,16] Antiemetics such as metoclopramide or ondansetron should be used for repetitive vomiting. Patients with persistent vomiting and abnormal vital signs or other signs of poor perfusion or shock should undergo aggressive fluid resuscitation and treatment with deferoxamine. Coagulopathy should be treated with parenteral vitamin K_1 and/or fresh frozen plasma, as indicated. Significant blood loss may require transfusion.

GI DECONTAMINATION

Do not give ipecac syrup, activated charcoal, cathartics, oral sodium bicarbonate, or phosphosoda. Ipecac syrup may obscure the initial signs of clinical toxicity and is no more effective at gastric emptying than is iron-induced vomiting.[17] Activated charcoal does not adsorb significant amounts of iron, while vomiting charcoal may be aspirated, and its use may complicate endoscopy if that becomes necessary.[17] Orogastric lavage may not be effective if the ingested tablets are large or if several hours have elapsed since ingestion, but it may be useful in rare cases if performed shortly after large ingestion, prior to significant vomiting, or if a modified-release formulation was ingested.[3,18] There are no data to support the efficacy of oral sodium bicarbonate or phosphosoda in forming insoluble iron salts and preventing absorption.[3,17]

Radiopaque tablets visible on radiography indicate potential for progressive toxicity and can guide decontamination measures (Figure 198-1). Whole-bowel irrigation with a polyethylene glycol solution may be effective in patients with large iron ingestions.[3,19] Administration of 250 to 500 mL/h in children or 2 L/h in adults by nasogastric tube may clear the GI tract of iron pills before absorption can occur.[19] Endoscopy can remove large iron loads or an iron-containing gastric bezoar.[20,21] Laparoscopic gastrotomy is a rarely used option for removal of an iron-containing gastric bezoar in profoundly ill patients when other measures are unsuccessful or impractical.[22]

DEFEROXAMINE

Deferoxamine is a chelating agent derived from *Streptomyces pilosus* used to treat iron toxicity. Deferoxamine binds free iron, iron from plasma, and iron from inside cells and mitochondria, but not iron bound to organic molecules. Upon binding, it forms the complex ferrioxamine, which is renally excreted. Deferoxamine can be safely administered to children and pregnant women. Although deferoxamine binds only a small amount of iron (9 milligrams of elemental iron for each 100 milligrams of deferoxamine) and thus chelates only a small fraction of the total amount of iron ingested, this generally proves clinically effective in restoring cellular function.[23]

Administration of deferoxamine is indicated in the iron-poisoned patient with systemic toxicity, persistent emesis, metabolic acidosis, progressive toxicity, or a serum iron level predictive of moderate to severe toxicity (Figure 198-2).[3,16] The manufacturer recommends IM administration for all patients not in shock,[23] but most toxicologists advise IV administration rather than IM administration because of the unreliability of IM absorption and enhanced iron excretion following IV administration.[3,16]

The initial deferoxamine adult dose is 1000 milligrams (children 50 milligrams/kg) IV. Begin the infusion slowly, starting at 5 milligrams/kg per hour to avoid producing a rate-related hypotension. Aggressive volume resuscitation may be required in the volume-depleted, hypotensive, iron-toxic patient who is in need of deferoxamine. **Hypotension is not a contraindication to IV deferoxamine administration.**

The infusion rate of deferoxamine IV can be titrated to 15 milligrams/kg per hour as tolerated. The recommended amount of deferoxamine for an acute iron overdose is a total of 360 milligrams/kg or 6 grams in an adult during the first 24 hours, typically ordered as 500-milligram infusions over 4 to 8 hours after the initial 1000-milligram dose.[16,23] Amounts larger than this and/or administered longer than 24 hours are associated with complications, including renal insufficiency or failure[24] and pulmonary toxicity.[25]

As ferrioxamine is excreted, the urine color changes to what is classically called "vin rosé" but is more typically a brown or rusty hue.[26] The disappearance of the "vin rosé" color suggests there is no more free iron available to be complexed with deferoxamine and excreted. False-negative results, color-change latency, and difficulty in visualizing a color change can limit the utility of this test.[16]

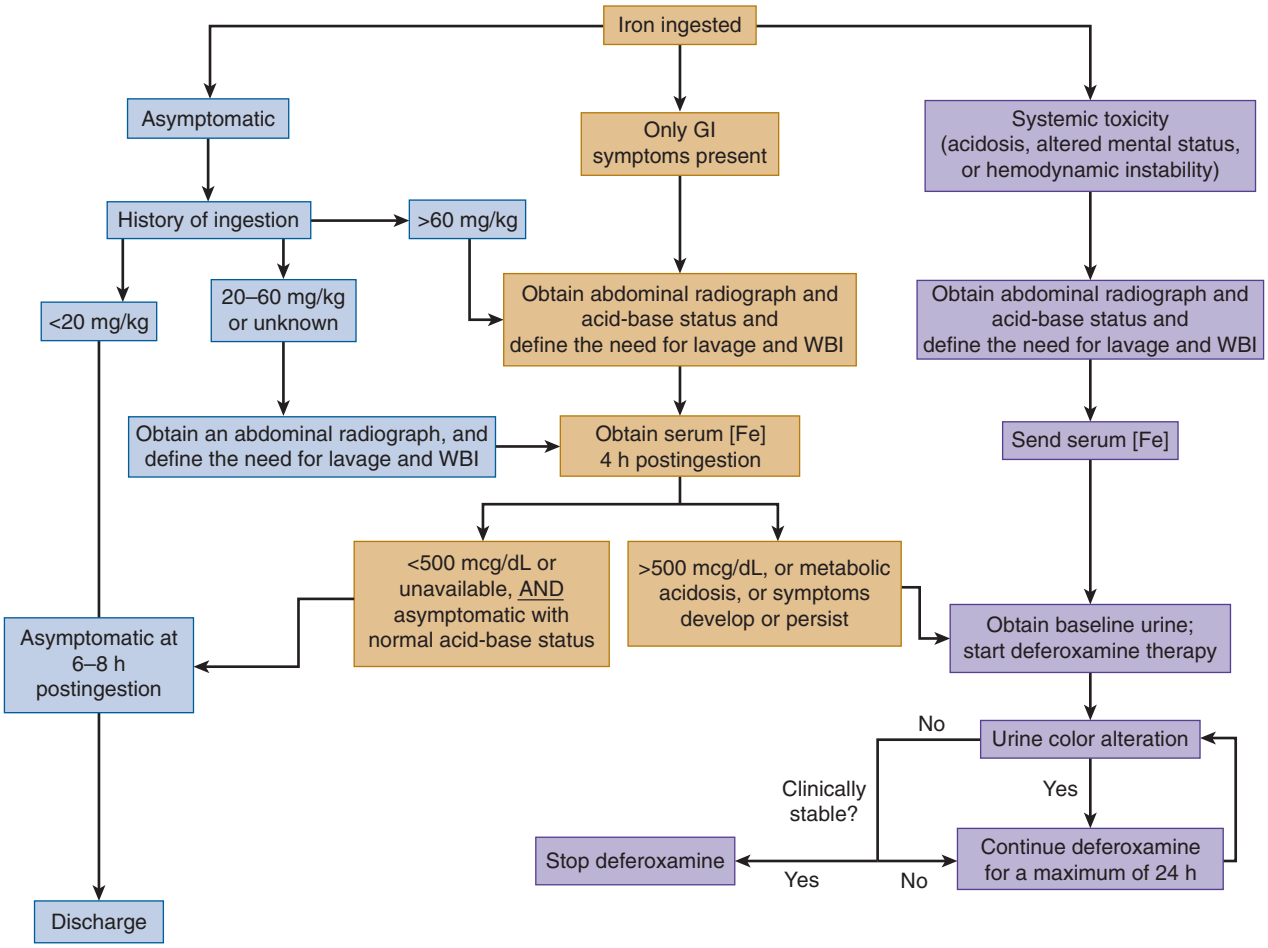


FIGURE 198-2. Algorithm for clinical management of iron salt ingestion. Fe = iron; mcg = microgram. [Reproduced with permission from Nelson LS, Howland MA, Lewin NA, et al: *Goldfrank's Toxicologic Emergencies*, 11th ed. New York, NY: McGraw-Hill Education; 2019. Figure 45-3, Pg 673.]

There is uncertainty regarding the duration of deferoxamine therapy.[3,16,23] **Clinical recovery of the patient is the most important factor guiding the decision to terminate deferoxamine therapy** because measured iron levels are artificially depressed by the presence of deferoxamine and urine color change can be unreliable. Continue deferoxamine therapy in patients who continue to exhibit severe iron toxicity after 24 hours of treatment, using a decreased rate to avoid the associated risks mentioned earlier.

OTHER THERAPIES

Oral iron chelators—**deferiprone** and **deferasirox**—reduce iron absorption when administered simultaneously or within 1 hour of iron ingestion.[27] However, there is no evidence of benefit in human overdoses, and oral chelation therapy would theoretically be of use only when taken promptly after the iron ingestion; thus, their use is limited by the time to presentation for treatment and the significant vomiting expected with clinical iron toxicity. **Oral iron chelating agents should *not* replace IV deferoxamine when chelation is indicated in clinical iron toxicity.**

Although hemodialysis and hemofiltration do not remove iron, such treatment may be necessary to remove the deferoxamine–iron complex in patients with renal failure who are unable to excrete the complex in their urine.[16,28,29] Severe iron poisoning can be treated with exchange transfusion in addition to deferoxamine therapy.[30]

In patients with rapidly rising liver transaminases, coagulopathy, and acute kidney injury, there should be timely assessment for liver transplantation. Progression to fulminant hepatic failure may be precipitous, and with delay, there is increased risk of clinical deterioration precluding liver transplant.[31]

DISPOSITION AND FOLLOW-UP

Patients who have not ingested a potentially toxic amount of iron, who remain asymptomatic (other than transient vomiting from the gastric irritant effects of iron), and who have normal findings on physical and laboratory evaluation for a period of 4 to 6 hours can be safely discharged or transferred for appropriate mental health evaluation. Patients who receive deferoxamine therapy should be admitted. The regional poison control center or a medical toxicologist should be contacted for assistance with management.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 199

Hydrocarbons and Volatile Substances

C. William Heise
Frank LoVecchio

INTRODUCTION

Hydrocarbons are a diverse group of organic compounds consisting primarily of carbon and hydrogen atoms. The two basic forms of hydrocarbons are aliphatic (straight- or branched-chain carbon arrangement)

TABLE 199-1 Common Products That Contain Hydrocarbons

Hydrocarbon and State at Room Temperature	Commercial Use
Aliphatic–linear structure, toxicity varies depending on volatility	
Gasoline (petrol)–liquid	Motor fuel
Kerosene (paraffin)–liquid	Stove and lamp fuel
Mineral seal oil–liquid	Furniture polish
Petroleum ether–liquid	Industrial solvent
Diesel fuel–liquid	Motor fuel
n-Hexane–liquid	Plastic cement, rubber cement
Methane, butane, propane, and ethane–gas	Fuel
Mineral spirits (white spirits)–liquid	Solvent, paint thinner
Turpentine–liquid	Solvent, paint thinner
Mineral oil (liquid paraffin)–liquid	Lubricant, laxative
Paraffin wax–solid	Industrial uses, candles
Petroleum jelly (petrolatum or soft paraffin)–solid	Skin lotion
Aromatic–ring structure, high toxicity	
Benzene–liquid	Chemical intermediate, gasoline (small amount, 0.8% on average)
Toluene–liquid	Airplane glue, plastic cement, acrylic paint
Xylene–liquid	Solvent, cleaning agent, degreaser
Halogenated–high toxicity	
Carbon tetrachloride–liquid	Solvent, refrigerant, aerosol propellant
Chloroform–liquid	Solvent, chemical intermediate
Methylene chloride–liquid	Paint stripper, varnish remover, aerosol paint, degreaser
Trichloroethylene–liquid	Spot remover, degreaser, typewriter correction fluid
Trichloroethane–liquid	Spot remover, degreaser, typewriter correction fluid
Tetrachloroethylene (perchloroethylene)–liquid	Dry cleaning agent, degreaser

or aromatic (carbon arranged in a ring). Hydrocarbons are in many household and occupational products (**Table 199-1**). While all hydrocarbons can be toxic, aromatic and halogenated hydrocarbons are associated with the most severe systemic toxicity. Volatile agents are associated with the highest aspiration risk. Identification of the specific hydrocarbon or class can help anticipate specific potential toxicity and guide management.

Chain length and branching determine the phase of the hydrocarbon at room temperature. Short-chain aliphatic compounds (up to 4 carbons), such as methane, ethane, propane, and butane, are gases; intermediate-chain aliphatic compounds (5 to 19 carbons), such as solvents, lamp oil, lighter fluid, and gasoline, are liquid; and long-chain aliphatic compounds (>19 carbons), such as waxes, are solids. Liquid hydrocarbons account for most exposures seen in the ED.[1]

Most hydrocarbon exposures occur as liquid ingestions or inhalations and usually have a benign clinical course.[1,2] Serious toxicity and deaths associated with hydrocarbon exposure are usually due to ingestions rather than inhalation. Symptoms and signs of pulmonary injury develop in up to 50% of children who ingest hydrocarbons,[3,4] and hydrocarbon aspiration can produce acute respiratory distress syndrome.[5] Suicidal injection of gasoline or kerosene with severe multiorgan toxicity has been reported.[6,7]

Volatile substances, usually hydrocarbon solvents contained in household or commercial products, can be inhaled for their euphoric effects (**Table 199-2**).[8] Abusers are typically teenagers and younger adults, especially those in lower socioeconomic groups.[9] Inhalation occurs by three different methods: (1) in "huffing," the individual soaks a rag with the inhalant and then places it over the mouth and nose; (2) in "bagging," the individual puts the hydrocarbon in a bag (usually a plastic bag) and repeatedly inhales deeply from the bag; and (3) in "sniffing," the hydrocarbon is directly inhaled via the nostrils.[10] In addition to causing deaths, abuse of volatile agents is associated with crimes such as homicide, sexual assault, and child abuse.[11] The most commonly abused volatile hydrocarbons are paints, solvents, and gasoline.

TABLE 199-2 Commonly Abused Volatile Substances

Product	Volatile Agent
Acrylic spray paint	Toluene
Adhesives, glue	Toluene, trichloroethylene
Aerosol propellants	Propellants and butane
Cigarette lighter refills	Butane
Degreasing agents	Trichloroethylene
Dry cleaning agents	Tetrachloroethylene
Fire extinguishers	Bromochlorodifluoromethane
Inhalational anesthetics	Nitrous oxide, halothane
Lighter fluid	Naphtha
Motor fuel	Gasoline (petrol)
Nitrites ("poppers")	Isobutyl nitrite, amyl nitrite
Paint stripper	Methylene chloride
Plastic modeling cement	Methyl ethyl ketone, toluene
Spot removers	Trichloroethylene, trichloroethane
Typewriter correction fluid	Trichloroethane, trichloroethylene

PATHOPHYSIOLOGY

The toxic potential of hydrocarbons depends on their physical characteristics (viscosity, surface tension, and volatility), chemical characteristics (aliphatic, aromatic, or halogenated), presence of toxic additives (pesticides or heavy metals), routes of exposure, concentration, and dose. The physical characteristics contribute the most to aspiration risk.

Viscosity refers to the general "thickness" of a liquid; fluids with a lower viscosity flow more easily than ones with high viscosity. Viscosity is measured in Saybolt universal seconds (SUS); fluids such as gasoline, kerosene, mineral seal oil, and turpentine have low viscosity (<60 SUS), whereas diesel fuel, grease, mineral oil, paraffin wax, and petroleum jelly have high viscosity (>100 SUS).[12] Surface tension refers to the property where liquid molecules tend to cohere to each other. Liquids with high surface tension in contact with a solid surface tend to ball up, creating the smallest surface area rather than spreading out. Volatility refers to the ability of the liquid or solid to vaporize and is inversely related to the boiling point; highly volatile liquids have a low boiling point. **Ingestion of liquids with low viscosity and surface tension and high volatility increases the risk for aspiration because these substances flow easily, spreading out widely on the oral mucosa, and vaporize at body temperature**. **Inhalation of aromatic hydrocarbons or halogenated hydrocarbons can result in systemic absorption and the potential for significant toxicity.**

CLINICAL FEATURES

Ingestion or aspiration of hydrocarbons mainly impairs the pulmonary system, but depending on the specific compound, the central nervous, peripheral nervous, GI, cardiovascular, renal, hepatic, dermal, and/or hematologic systems may be affected (**Table 199-3**).[13,14]

PULMONARY TOXICITY

Hydrocarbon aspiration causes chemical pneumonitis by direct toxicity to the pulmonary parenchyma and alteration of surfactant function.

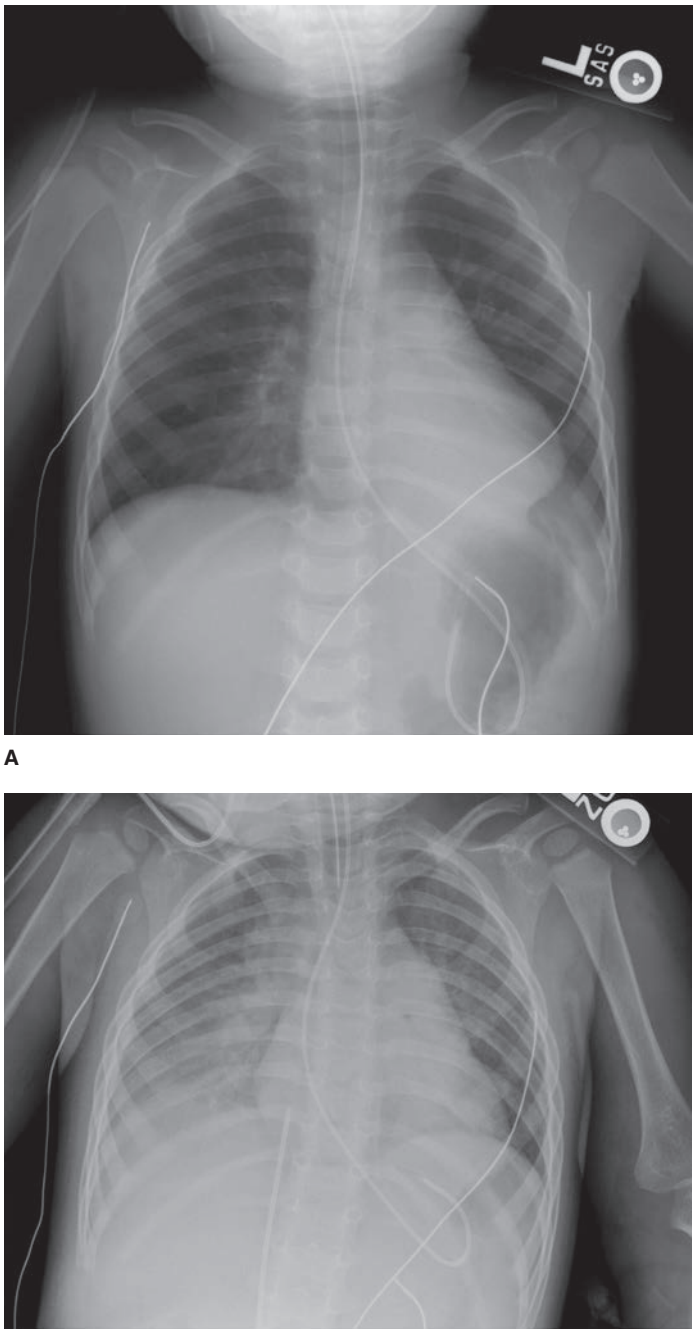
TABLE 199-3 Clinical Manifestations of Hydrocarbon Exposure

System	Clinical Manifestations
Pulmonary	Tachypnea, grunting respirations, wheezing, retractions
Cardiac	Ventricular dysrhythmias (may occur after exposure to halogenated hydrocarbons and aromatic hydrocarbons)
Central nervous	Slurred speech, ataxia, lethargy, coma
Peripheral nervous	Numbness and paresthesias in the extremities
GI and hepatic	Nausea, vomiting, abdominal pain, hepatotoxicity, loss of appetite (mostly with halogenated hydrocarbons)
Renal and metabolic	Muscle weakness or paralysis secondary to hypokalemia in patients who abuse toluene
Hematologic	Lethargy (anemia), shortness of breath (anemia), neurologic depression/syncope (carbon monoxide from methylene chloride), cyanosis (methemoglobinemia from amine-containing hydrocarbons)
Dermal	Local erythema, papules, vesicles, generalized scarlatiniform eruption, exfoliative dermatitis, "huffer's rash," cellulitis

Destruction of alveolar and capillary membranes results in increased vascular permeability and edema. The clinical manifestations of pulmonary aspiration are usually apparent soon after exposure from irritation of the oral mucosa and tracheobronchial tree. Symptoms include coughing, choking, gasping, dyspnea, and burning of the mouth. Patients with these symptoms should be assumed to have aspirated.

Signs include tachypnea, grunting respirations, wheezing, or retractions depending on the severity of aspiration. An odor of the hydrocarbon may be noted on the patient's breath. Hyperthermia of ≥39°C (≥102.2°F) is likely and may occur initially or 6 to 8 hours after exposure. The fever is usually an inflammatory response due to pneumonitis. Necrotizing pneumonitis and hemorrhagic pulmonary edema may develop within minutes to hours in patients with severe aspiration. In most fatalities, these complications occur rapidly. With less severe damage, symptoms usually subside within 2 to 5 days, except in the case of pneumatoceles and lipoid pneumonias, the symptoms of which may persist for weeks to months.

In most patients with clinically significant aspiration, chest radiography results are eventually abnormal, but the time course of radiographic changes varies and correlation with physical examination findings may be poor. Changes may be seen as early as 30 minutes after aspiration, but **the initial radiograph in a symptomatic patient may be deceptively clear. Conversely, an asymptomatic patient can still have abnormal chest radiographic findings.** Radiographic changes usually appear by 2 to 6 hours; if they are going to occur, they are almost always present by 24 hours (**Figure 199-1**). The most common radiologic finding is bilateral infiltrates at the bases. Multilobar involvement is more common than single-lobe involvement, and right-sided involvement is more common than left-sided involvement.[15-17] Hydrocarbon-induced aspiration pneumonitis can lead to lung necrosis and the creation of a pneumatocele.[18]



A

B

FIGURE 199-1. Two chest radiographs of a child who aspirated lamp oil and developed aspiration pneumonitis. **A.** Day 1: intubated, left lower lobe infiltrates. **B.** Day 3: intubated, worsening perihilar and bibasilar patchy infiltrates and new right small pleural effusion.

CARDIAC TOXICITY

Life-threatening dysrhythmias, such as ventricular tachycardia and ventricular fibrillation, may occur with systemic absorption. Dysrhythmias occur most commonly after exposure to halogenated hydrocarbons and aromatic hydrocarbons. Exposure to short-chain aliphatic hydrocarbons occasionally causes dysrhythmias (mainly ventricular fibrillation).[10] The most worrisome acute complication found in solvent abusers is "**sudden sniffing death syndrome,**" which occurs within minutes of exposure.[8] The mechanism of toxicity is believed to be catecholamine sensitization of the heart by hydrocarbons (especially halogenated hydrocarbons), resulting in ventricular dysrhythmias.[8,10,19] Other mechanisms for sudden death include simple asphyxia, respiratory depression, and vagal inhibition. Ventricular akinesia and polymorphic ventricular dysrhythmias have also been described after overdose of chloral hydrate (a halogenated aliphatic hydrocarbon).[19]

CNS TOXICITY

CNS effects, primarily depression of consciousness, result from a combination of: (1) direct toxic response to the systemic absorption of the hydrocarbon, (2) indirect result of severe hypoxia secondary to aspiration, (3) simple asphyxiation due to the displacement of oxygen by the volatile hydrocarbon, or (4) volatile substance abuse with a plastic bag that prevents adequate oxygenation. Systemic effects occur through GI absorption, the inhalation of highly volatile petroleum distillates, or direct dermal penetration.

Signs of neurologic toxicity include slurred speech, ataxia, lethargy, and coma.[13] Although hydrocarbons are central neurologic depressants, they often have an initial excitatory effect manifested as hallucinations, tremor, agitation, and convulsions. Individuals who abuse volatile

solvents or workers who experience long-term hydrocarbon exposure may present to the ED complaining of recurrent headaches, ataxia, emotional lability, cognitive impairment, or psychomotor impairment.

PERIPHERAL NERVOUS SYSTEM TOXICITY

Exposure to *n*-hexane, methyl *n*-butyl ketone, and other six-carbon aliphatic hydrocarbons is associated with the development of a characteristic peripheral polyneuropathy caused by demyelinization and retrograde axonal degeneration.[20] Onset of symptoms may be delayed for weeks, and toxicity is attributed to a metabolite, 2,5-hexanedione, produced by the cytochrome P450–mediated biotransformation of the parent compounds. This neurotoxic metabolite is thought to inhibit glutaraldehyde-3-phosphate dehydrogenase, which supplies energy for axonal transport.

Clinically, the patient may complain of chronic numbness and paresthesias in the extremities. The key component in making the diagnosis is a history of exposure to solvents, usually through occupations and hobbies. The compound *n*-hexane is found in gasoline, quick-drying glues, rubber cement, and various solvents used in the printing, shoemaking, textile, and furniture industries.[21]

GI AND HEPATIC TOXICITIES

Most hydrocarbons are GI irritants. Vomiting, which occurs in many patients with aliphatic hydrocarbon ingestions, increases the risk of pulmonary aspiration. Gastric perforation has been reported after accidental ingestion of chlorofluorocarbons.[22]

Hepatic damage resulting from ingestion of halogenated hydrocarbons is well described.[23,24] **Chlorinated hydrocarbons, such as carbon tetrachloride (CCl_4), methylene chloride, trichloroethylene, and tetrachloroethylene, are especially hepatotoxic.** For example, CCl_4 causes centrilobular liver necrosis similar to acetaminophen toxicity. Free radical metabolites of these agents that cause lipid peroxidation are responsible for hepatocellular destruction. The time course of hepatic dysfunction with acute exposures appears to be similar to that of acetaminophen hepatotoxicity—within 24 to 48 hours after ingestion.

Clinically, patients may come to the ED complaining of nausea, vomiting, abdominal pain, or loss of appetite. Depending on the severity, the physical examination may reveal a patient with jaundice, lethargy, and/or abdominal tenderness, especially in the right upper quadrant. Results of serum transaminase tests and other hepatic synthetic function tests may be abnormal within 24 hours after ingestion.

RENAL AND METABOLIC TOXICITIES

Solvent abuse and occupational exposure to hydrocarbons may result in renal dysfunction. **Chlorinated hydrocarbons, such as chloroform, CCl_4, and trichloroethylene, are also nephrotoxic.** Toluene, an aromatic hydrocarbon that is commonly abused, may cause renal tubular acidosis in patients who inhale toluene-containing substances.[8,25] The mechanism of toluene-induced renal tubular acidosis is not clear. The typical metabolic profile of renal tubular acidosis is a normal anion gap hyperchloremic acidosis with hypokalemia and a urine pH of >5.5. The metabolites of toluene (hippuric acid and benzoic acid) can be the cause of an elevated anion gap metabolic acidosis.[26]

Clinically, habitual toluene abusers may complain of muscle weakness caused by hypokalemia.[27] The serum potassium level may be so low (<2 mEq/L) that severe weakness develops, occasionally resulting in muscle paralysis. Significant rhabdomyolysis may also result.[28] **Toluene abuse should be considered in individuals (especially young patients) who come to the ED with symptoms similar to hypokalemic periodic paralysis.**[25,27]

HEMATOLOGIC TOXICITY

Hydrocarbon-induced hemolysis rarely occurs after the acute ingestion of gasoline, kerosene, and tetrachloroethylene, and after inhalation of mineral spirits. Exposure to benzene (an aromatic hydrocarbon) is associated with an increased incidence of hematologic disorders, including aplastic anemia, acute myelogenous leukemia, and multiple myeloma.[29] Naphthalene exposure is associated with hemolytic anemia. Delayed methemoglobinemia is associated with occupational exposure to hydrocarbons containing amine functional groups such as aniline (see Chapter 207, "Dyshemoglobinemias").[30] Delayed carboxyhemoglobinemia is associated with **methylene chloride** exposure due to its metabolism to carbon monoxide, which takes a few hours.[31] This is unlike ordinary carbon monoxide exposure from exogenous sources in which the maximum carboxyhemoglobin level occurs at the time of the exposure. **Clinically, patients may come to the ED with malaise, headache, dyspnea, or cyanosis depending on the exposure and the severity of the toxicity.**

DERMAL TOXICITY

Dermal toxicity from exposure to hydrocarbons is most often associated with the short-chain aliphatic, aromatic, and halogenated hydrocarbons. These agents act as primary irritants and as sensitizers. Occasionally, highly permeable hydrocarbons can penetrate the skin, resulting in systemic toxicity. Skin findings can range from local erythema, papules, and vesicles to a generalized scarlatiniform eruption and an exfoliative dermatitis (Table 199-3). A "huffer's rash" may be noted over the face of patients who habitually abuse the volatile hydrocarbons.[8] Frostbite of the face may develop during the inhalational abuse of fluorinated agents. A defatting dermatitis, similar to chronic eczematoid dermatitis, may occur.

Cellulitis and sterile abscesses have been associated with the injection of hydrocarbons, and even a small amount of injected hydrocarbon can cause significant injury.[32] Hydrocarbon-induced soft tissue necrosis has recently been seen in patients using "**krokodil**," which is desomorphine synthesized from codeine using hydrocarbon solvents.[33] Dermal exposure to heated high-viscosity, long-chain aliphatics, such as tar, asphalt, or bitumen, presents a particularly challenging problem because of their association with thermal burns, hyperthermia, and difficulty with decontamination.[34] Tar burns are discussed in the Chapter 218, "Chemical Burns."

DIAGNOSIS

Diagnosis of hydrocarbon toxicity incorporates the findings of the history, physical examination, bedside cardiac and pulmonary monitoring, laboratory tests, and chest radiography. Determine the specific hydrocarbon-containing product, because identification can help anticipate specific potential toxicity and guide management. Pulse oximetry is useful to evaluate oxygenation status, and blood gas analysis can be used to assess ventilation and acid-base status. Cardiac rhythm monitoring and an ECG are indicated in symptomatic patients and patients who ingest halogenated hydrocarbons. A chest radiograph is indicated in a symptomatic patient after hydrocarbon aspiration. Chest radiography is not required in asymptomatic patients.

There are no specific quantitative hydrocarbon tests for standard use when evaluating suspected hydrocarbon intoxication. A basic metabolic panel is indicated in patients with a history of toluene abuse or in whom electrolyte abnormalities and renal insufficiency are suspected. Obtain hepatic function studies, serum ammonia, and prothrombin time in patients who ingest or inhale halogenated hydrocarbons. A CBC is indicated if anemia, bleeding disorder, hemolysis, or leukemia is considered. Measure carboxyhemoglobin level in patients with exposure to methylene chloride; repeat measurements may be necessary. Determination of methemoglobin level is indicated in patients with exposure to hydrocarbons containing amine functional groups. Abdominal radiographs may show evidence of ingestion of chlorinated hydrocarbons such as CCl_4 or chloroform because of the radiopaque nature of polyhalogenated substances.[23]

TREATMENT

Securing the airway and maintaining ventilation are the critical maneuvers in patients who present with respiratory depression and/or significant neurologic depression (**Table 199-4**). Swelling of the lips and tongue due to irritant effect or freeze injuries can complicate airway

TABLE 199-4 Management of Hydrocarbon Exposures

Airway and breathing	Secure airway. Antidotes: Administer oxygen for carboxyhemoglobinemia and methylene blue for methemoglobinemia. Provide supplemental oxygen. Administer inhaled β_2-agonists. Ventilatory support: Provide positive end-expiratory pressure or continuous positive airway pressure as needed to achieve adequate oxygenation.
Cardiac	Circulation: Administer IV crystalloid fluid for initial volume resuscitation of hypotensive patients. Do not use catecholamines in cases of halogenated hydrocarbon exposure. Consider propranolol, esmolol, or lidocaine for ventricular dysrhythmias induced by halogenated hydrocarbon exposure. Consult the poison control center, toxicologist, and other appropriate specialists as needed.
Decontamination	Dermal: Remove hydrocarbon-soaked clothes, decontaminate skin with soap and water, and decontaminate eyes with saline irrigation. GI: Not indicated. See discussion below.
Other	Laboratory tests: Order CBC, basic metabolic panel, liver function tests (serum transaminase, bilirubin, albumin levels), prothrombin time, partial thromboplastin time, carboxyhemoglobin level, methemoglobin level, and/or radiologic studies as indicated (see text). Correct electrolyte abnormalities. Do not give steroids. Administer blood products as needed.

management. Administer oxygen to correct hypoxia. Inhaled β_2-agonists may also be useful, especially in the setting of bronchospasm, but their role in the treatment of hydrocarbon pneumonitis has not been studied. Positive end-expiratory pressure or continuous positive-pressure airway ventilation may sometimes be required to maintain oxygenation, but may increase potential for further (barotrauma) injuries such as pneumothorax or pneumatocele. In cases of severe pulmonary aspiration resulting in refractory hypoxemia, there are case reports of successful treatment with high-frequency jet ventilation or extracorporeal membrane oxygenation.[35,36] Surfactant therapy has been used to treat acute lung injury from hydrocarbon aspiration.[37-40]

Treat hypotension with aggressive fluid resuscitation. **Avoid administration of catecholamines such as dopamine, norepinephrine, and epinephrine. Catecholamines may cause dysrhythmias, especially after exposure to halogenated hydrocarbons and aromatic hydrocarbons.** Hydrocarbon-induced dysrhythmias are generally seen shortly after the exposure, especially with inhalational use. Continuous cardiac monitoring should be initiated, and an ECG should be obtained. For hydrocarbon-induced ventricular dysrhythmias, class IA (procainamide) or class III (amiodarone, bretylium, and sotalol) antiarrhythmics should be avoided because of the risk of QT interval prolongation.[19] Propranolol, esmolol, and lidocaine have all been reported to successfully treat these ventricular dysrhythmias in case reports.[10,19,41]

There is no indication for gastric lavage because risks of aspiration far outweigh any theoretical benefits.[42] Activated charcoal is not recommended; it does not adsorb hydrocarbons well and poses a risk for vomiting and aspiration. In the rare case where a recent (<1 hour) exposure has occurred with a highly toxic hydrocarbon (e.g., aromatic or halogenated chemical) or in which a hydrocarbon has been combined with another highly toxic substance (e.g., pesticide), consultation with a poison center may result in recommendation for gastric lavage; even in these cases, benefit from gastric lavage is unproven.

There is no clear evidence that corticosteroids are helpful in hydrocarbon-induced pneumonitis.[13] One meta-analysis advocating low-dose steroids for acute lung injury and respiratory distress[43] has been criticized because the patients were not generally treated with current lung-protective ventilation strategies.[44] Antibiotics are not indicated unless there is clinical suspicion of superimposed bacterial pneumonitis.

In summary, exogenous catecholamines (e.g., epinephrine), prophylactic antibiotics, and corticosteroids should be avoided.

In dermal exposures, decontamination is preferably done at the scene or before entering the ED to avoid spreading fumes to patient treatment areas. The patient needs to be fully undressed to prevent ongoing contamination from hydrocarbon-soaked clothes. Make sure staff wear protective gloves and aprons to prevent secondary exposure, especially to organophosphate-containing mixtures. Dermal decontamination with soap and cold water and eye decontamination with saline irrigation should be performed.

DISPOSITION AND FOLLOW-UP

If feasible, consult a medical toxicologist or regional poison control center for symptomatic hydrocarbon exposures and asymptomatic exposures to aromatic hydrocarbons or hydrocarbons with toxic additives. In cases of inhalation or aspiration of **nonhalogenated aliphatic hydrocarbons**, asymptomatic patients may be discharged home after about 6 to 8 hours of observation with instructions to return if delayed symptoms develop.

Further observation or hospitalization is required for patients who are symptomatic after hydrocarbon exposure. For pediatric hydrocarbon ingestions, the presence of wheezing, altered consciousness, or tachypnea within 2 hours predicts the need for further treatment.[45] Hospitalization is also recommended for those who ingest hydrocarbons capable of producing delayed complications (e.g., halogenated hydrocarbons causing hepatic toxicity) or hydrocarbons with toxic additives (organophosphates and organic metal compounds). Patients with suicidal intent or with complications of solvent abuse need behavioral health evaluation.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 200

Caustic Ingestions

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Wallace A. Carter

INTRODUCTION

Caustics are substances that cause both functional and histologic damage on contact with body surfaces. Many household and industrial chemicals have caustic potential. Caustics are broadly classified as alkalis (pH >7) or acids (pH <7). In developed nations, increased education and product regulation (especially of acids) have decreased morbidity and mortality from caustic exposures in both adults and children. However, in underdeveloped parts of the world, exposure to caustics remains a significant problem.[1-3] Alkaline ingestions predominate in the developed world,[4] whereas acid ingestions are more common in developing countries.[5]

Caustic exposures tend to fall into three distinct groups: (1) intentional adolescent or adult ingestions with suicidal ideation; (2) unintentional ingestions (the majority of which are by curious children in the toddler age group); and (3) other incidental, often occupational or industrial contact exposures. The majority of reported exposures are unintentional or accidental, but intentional ingestions account for the majority of serious injuries.[1] The geographic variation in caustic ingestion circumstances, such as involved substances, intention, age of the patient, and extent of evaluation, make it important to base treatment decisions on each particular patient's presentation.

TABLE 200-1 Common Caustic Compounds

Compound	Found In
Alkalis	
Sodium hydroxide	Industrial chemicals, drain openers, oven cleaners
Potassium hydroxide	Drain openers, batteries
Calcium hydroxide	Cement, hair relaxers, perm products
Ammonium hydroxide	Hair relaxers and perm products, dermal peeling/exfoliation, toilet bowl cleaners, glass cleaners, fertilizers
Lithium hydroxide	Photographic developer, batteries
Sodium tripolyphosphate	Detergents
Sodium hypochlorite	Bleach
Acids	
Sulfuric acid	Automobile batteries, drain openers, explosives, fertilizer
Acetic acid	Printing and photography, disinfectants, hair perm neutralizer, pickling solution
Hydrochloric acid	Cleaning agents, metal cleaning, chemical production, swimming pool products
Hydrofluoric acid	Rust remover, petroleum industry, glass and microchip etching, jewelry cleaners
Formic acid	Model glue, leather and textile manufacturing, tissue preservation
Chromic acid	Metal plating, photography
Nitric acid	Fertilizer, engraving, electroplating
Phosphoric acid	Rust proofing, metal cleaners, disinfectants

Many chemicals used in industry have caustic potential (**Table 200-1**). Household caustics are often less concentrated forms of industrial-strength cleansers.

PATHOPHYSIOLOGY

The degree to which a caustic substance produces tissue injury is determined by a number of factors: pH, concentration, duration of contact, volume, and titratable acid or alkaline reserve. Acids tend to cause significant injuries at a pH <3 and alkalis at a pH >11. The physical properties of the product formulation (i.e., liquid, gel, granular, or solid) can influence the nature of the contact with tissue. Following ingestion, solid or granular caustics often injure the oropharynx and proximal esophagus, whereas liquid alkali ingestions are characterized by more extensive esophageal and gastric injuries. *Titratable acid or alkaline reserve* refers to the amount of acid or base required to neutralize the agent; the greater this value, the greater is the potential for tissue injury.

Esophageal mucosal burns from caustic ingestions are classified by a visual endoscopic grading system, which correlates with risk of future complications: **Grade 1 burns** involve tissue edema and hyperemia; **grade 2 burns** include ulcerations, blisters, and whitish exudates, which are subdivided into grade 2A (noncircumferential) and 2B (deeper or circumferential) lesions; and **grade 3 burns** are defined by deep ulcerations and necrotic lesions.[6] Following the initial mucosal injury, tissue remodeling occurs over roughly 2 months. In mild cases, normal esophageal function is restored, but in severe cases, dense scar tissue forms, resulting in stricture formation. Esophageal strictures are a source of significant morbidity and may require long-term treatments with dilations, stenting, or surgery. Early phases of remodeling, particularly days 2 to 14 after exposure, are associated with increased tissue friability and higher risk of perforation, both spontaneous and iatrogenic.

ALKALI INJURIES

Following caustic alkali exposures, the hydroxide ion easily penetrates tissues, causing immediate cellular destruction via protein denaturation and lipid saponification. This is followed by thrombosis of local microvasculature that leads to further tissue necrosis. Alkali injuries induce a deep tissue injury called **liquefaction necrosis**. Severe intentional alkali ingestion may cause deep penetration into surrounding tissues with resultant multisystem organ injuries, including esophageal injury, gastric perforation, and necrosis of abdominal and mediastinal structures. Severe injuries to the pancreas, gallbladder, small intestine, and mediastinum after intentional ingestion have been reported. Solid alkali ingestions, such as some lye preparations, have a greater potential for oropharyngeal and proximal esophageal tract injury and less for distal injury.

The most common household alkali is **bleach**, a 3% to 6% sodium hypochlorite solution with a pH of approximately 11. Household liquid bleach is minimally corrosive to the esophagus and rarely causes significant injury beyond grade 1 esophageal burns. Esophageal stricture was not observed as a complication of household bleach ingestion in a series involving almost 400 patients.[7] However, ingestion of industrial-strength bleach containing much higher concentrations of sodium hypochlorite may result in gastric and esophageal necrosis. Bleach ingestion may cause emesis secondary to gastric irritation and/or pneumonitis after aspiration. Pulmonary irritation related to chlorine gas production in the stomach or when mixed with other substances may also occur.[8,9] A common reaction is the production of the highly irritating **chloramine gas** when bleach and ammonia household cleaners are combined.[10]

ACIDS

Injuries by strong acids produce **coagulation necrosis**. Dissociated hydrogen ions and their associated anions penetrate tissues, leading to cell death and eschar formation. This process is believed to limit continued hydrogen ion penetration and protect against deeper injury. When ingested acids settle in the stomach, gastric necrosis, perforation, and hemorrhage may result. Although it was previously thought that acids were esophagus sparing with most tissue injury concentrated in the stomach, endoscopy following an acid ingestion finds a similar incidence of gastric and esophageal injury.[11-13] Acid ingestion may be complicated by systemic absorption of acid with associated metabolic acidosis, hemolysis, and renal failure.[14] Hydrofluoric acid is a unique ingestion discussed in Chapter 218, "Chemical Burns" (see "Hydrofluoric Acid").

CLINICAL FEATURES

The cardinal features of caustic ingestion are a chemical burn to the GI mucosa,[15] sometimes associated with chemical burns to the skin or eyes from splashes or dribbling (see Chapter 217, "Thermal Burns," and Chapter 241, "Eye Emergencies"). Pharyngeal burns from ingestion produce pain, odynophagia, drooling, and vocal hoarseness. Dyspnea may be caused by edema of the upper airway, aspiration of the caustic substance into the tracheobronchial tree, or inhalation of fumes, particularly acids. Esophageal burns produce dysphagia, odynophagia, and chest pain. Ocular burns are painful, reduce visual acuity, and produce visible damage to the anterior structures of the eye.

HISTORY

The key priority is rapid airway assessment and stabilization. Following that, obtain a directed history to determine the type, amount, and timing of the ingested caustic and the presence of co-ingestants. Determine if the ingestion was intentional or unintentional.

PHYSICAL EXAMINATION

Look for signs of respiratory distress or circulatory shock. With ingestions, look for signs of oropharyngeal injury (mucosal burns, drooling), respiratory injury (dysphonia, coughing, stridor, wheezing), and gastric injury (vomiting, epigastric tenderness) (**Figure 200-1**).[4,15-20] Streaks of caustic burns on the face or chest are called "dribble burns" (**Figure 200-2**).

DIAGNOSIS

Conflicting data exist on the reliability of presenting signs and symptoms to predict upper GI injuries.[21-25] **Intentional ingestions are associated with higher grades of GI tract injury, with or without clinically obvious signs.**[26] The incidence of serious GI injury after pediatric



A



B

FIGURE 200-1. Acid ingestion. **A.** Moderate intraoral burns on buccal mucosa and tongue. **B.** Lingual burns.

unintentional ingestions has been the focus of many studies.[4,21-23,25,27,28] Although serious esophageal injury can occur in the absence of oral burns, essentially all children with serious esophageal injuries (grade 2 or 3) after accidental caustic ingestion have some initial signs of injury, such as stridor, drooling, or vomiting.[22,23,25] Pain alone is an inconsistent predictor of severity of injury.

Assess for hemodynamic instability. Causes of shock include GI bleeding, complications of GI perforation, volume depletion, and toxicity from co-ingestants. Examine for peritoneal signs due to hollow viscous perforation. Consider mediastinitis in patients complaining of chest discomfort, and palpate the chest wall and neck for signs of subcutaneous emphysema. Inspect the eyes for ocular burns and the skin for splash and dribble burns.

LABORATORY TESTING

For children who unintentionally ingest common household alkalis (e.g., bleach) or acids (e.g., toilet bowl cleaner), the need for ancillary testing is only necessary in those with signs or symptoms of significant injury (e.g., drooling, respiratory distress, or vomiting). For an intentional ingestion or ingestion of a strong acid or alkali, laboratory evaluation should include a venous or arterial blood gas, electrolyte panel, hepatic profile, complete blood count, lactate, and blood type and screen. Caustic ingestions can cause an **anion gap acidosis** based on lactate production due to direct tissue injury or shock. Strong acid ingestions may be associated with both severe anion gap (e.g., sulfuric acid) and nongap acidoses (e.g., hydrochloric acid). In suicidal patients, obtain acetaminophen and salicylate levels to screen for potential co-ingestants. An ECG is indicated following a hydrofluoric acid exposure to check for QT interval prolongation from hypocalcemia.



FIGURE 200-2. Acid ingestion. Dermal dribble burns on upper chest.

IMAGING

Obtain a chest radiograph in patients with chest pain, dyspnea, or vomiting to check for peritoneal and mediastinal air. In 2015, the World Society of Emergency Surgery consensus conference recommended the use of IV contrasted thoracoabdominal CT scans in caustic ingestion management.[29] Although endoscopy has been the traditional gold standard for grading esophageal injury and predicting stricture rates, recent evidence suggests CT scans outperform endoscopy in the prediction of stricture and the need for surgical esophageal reconstruction due to the greater ability to determine the depth of injury,[30,31] although conflicting results are noted and some authors see CT as a useful adjunct to endoscopy but not a replacement.[32] US can be used to evaluate and follow up corrosive gastric injury if there is perforation or severe edema preventing endoscopy.[33]

ENDOSCOPY

Endoscopy is the traditional gold standard for evaluating the location and severity of injury to the esophagus, stomach, and duodenum after caustic ingestion. The controversy has been who needs endoscopy and when should it be performed.[24,25,28,34,35] **Regardless of symptoms, patients with intentional caustic ingestions should undergo early endoscopy because ingestions with suicidal intent carry the highest risk of clinically important injury.**

In unintentional ingestions, particularly by children, the decision to perform endoscopy is less clear cut.[24,25,28,34,35] Most children with serious caustic esophageal injury will be symptomatic,[28] and although there is a correlation between clinical findings and corrosive severity, lack of symptoms is judged by some authors not to be an adequate predictor of no injury.[27,36,37] **Early endoscopy is recommended after unintentional caustic ingestions in adults and children with signs or symptoms of serious injury such as stridor or significant oropharyngeal burns and/or vomiting, drooling, or food refusal, with or without oropharyngeal burns.**[22,24,25,28,34,35,37]

The primary purpose of endoscopy is diagnosis,[6,38-40] with high accuracy for grade 3 injuries and less so for grade 2 damage when compared to biopsy.[41] Early endoscopy permits grading of injuries, helps guide treatment, and predicts future morbidity (**Table 200-2**). Early endoscopy is safe, improves clinical course, and reduces costs of admission.[42]

TABLE 200-2 Correlation of Esophageal Injury Grade With Morbidity and Interventions

Endoscopic Injury Grade	Grade 1 Esophageal Injury	Grade 2A Esophageal Injury	Grade 2B or 3 Esophageal Injury
Future morbidity	No risk of strictures or carcinoma	Strictures tend not to occur	At risk for hemorrhage and perforation (early), strictures (delayed), and carcinoma (late)
Nutritional support	Diet as tolerated	If unable to tolerate PO, provide nutritional support via nasogastric, orogastric, or percutaneous feeding tube *or* Total parenteral nutrition	Initiate early percutaneous feeding tube *or* Total parenteral nutrition
General interventions	Supportive care	Admission recommended, supportive care	Intensive care unit admission recommended; may require additional imaging or surgical exploration for gastric injuries

An additional benefit of endoscopy is endoscopic guidance of an orogastric or nasogastric tube past injured areas of esophagus or stomach to allow enteral feeding while healing occurs.[43] This is particularly important in children with low glycogen stores or with high-grade injuries, in whom caloric requirements will be high.

Tissue friability after a caustic burn increases significantly at 24 to 48 hours after injury and is maximal between days 5 and 14, although endoscopy has been performed safely 5 days after exposure.[44] **Experts recommend that endoscopy should be performed early after ingestion, within 12 to 24 hours from the time of ingestion, to avoid iatrogenic perforation.**[43,45-47] Traditionally, endoscopists have terminated their examination at the first sign of severe esophageal injury (grade 2B or 3). Experienced operators using modern, smaller, and flexible endoscopes with minimal insufflation of air can usually obtain more distal visualization documenting all injuries to the esophagus, stomach, and duodenum, an important point in pediatric acid ingestions where gastric and duodenal burns are common.[48]

TREATMENT

AIRWAY

The first priority is airway protection. Patients with respiratory distress may have significant oral, pharyngeal, and/or laryngotracheal injuries that require emergent airway management. Respiratory injuries from caustic ingestion can cause significant morbidity and mortality, especially in elderly patients.[49] Approach caustic ingestions as difficult airways. Ideally, patients with potential airway injuries should have fiberoptic evaluation of the airway before intubation to determine the extent of the damage, but this may not always be possible.

Oral intubation with direct visualization is the first choice for definitive airway management. For potential airway compromise, establish a secure endotracheal airway early rather than risk greater difficulty later when secondary effects of injury, such as edema, complicate the situation. Cricothyrotomy may be needed if oropharyngeal edema, tissue friability, and bleeding make intubation difficult or impossible. Blind nasotracheal intubation is contraindicated due to the potential for exacerbating airway injuries. If possible, avoid laryngeal mask airways, combination tubes with pharyngeal and tracheal balloons, retrograde intubation, and bougies because these devices and techniques can increase tissue damage or cause perforation.

DECONTAMINATION, NEUTRALIZATION, AND DILUTION

The ED staff should take precautions to prevent ongoing injury to the patient and staff from continued caustic exposure. ED staff involved should wear protective gowns, gloves, and masks with face shields. Standard decontamination, with removal of soiled or soaked clothing and copious irrigation with towels and soap (as needed), is adequate in most cases. Vomiting may reexpose the patient and staff to the caustic agent.

Gastric decontamination with activated charcoal is contraindicated if a caustic is the only ingestion. Charcoal does not adhere well to most caustics and will impede visualization when endoscopy is performed. **Ipecac syrup is contraindicated**, because vomiting will result in repeat exposure of the airway and GI mucosa to the caustic agent and could precipitate perforation.[50]

In general, do not insert nasogastric tubes until after endoscopic evaluation. With high-grade esophageal burns, feeding tubes may be inserted under endoscopic guidance if clinically indicated. Dilution and neutralization therapy are not recommended in the prehospital setting or ED because there is no proven human benefit and because of the potential risk of gastric distention, vomiting, and perforation.[51-54]

FLUID RESUSCITATION

Establish large-bore IV access and resuscitate with crystalloids. Coingestants, bleeding, and third spacing, as well as metabolic disarray from acid-base derangements, can lead to shock. Central venous access may be required for monitoring of resuscitation.

SYSTEMIC STEROIDS AND PROPHYLACTIC ANTIBIOTICS

There is controversy concerning the benefit of systemic steroids in caustic ingestions.[55-63] The ability of steroids to inhibit the inflammatory response led to the hypothesis that steroids may decrease stricture formation after caustic ingestion, and animal models have suggested benefit. One prospective human trial found statistically significant protection against the development of stricture formation in grade 2B lesions, and corticosteroids are recommended by some international treatment guidelines.[45,63] A subsequent pooled meta-analysis has not shown benefit for injury, and steroids may increase the risk of infection, perforation, and hemorrhage.[62] Use has been discouraged by other experts.[29,57] One criticism of pooled meta-analysis data is that some individual studies did not clearly distinguish between grade 1 and 2A lesions, which do not typically lead to strictures, and grade 2B and 3 injuries, which might theoretically benefit from steroids.[60]

There is no current evidence to support the ED administration of prophylactic antibiotics after caustic ingestions in humans. However, in protocols in which steroids are used or in grade 2B or 3 injury, addition of penicillin or another antibiotic that covers oral flora has been part of the treatment regimen.[57,64]

SURGERY AND ESOPHAGEAL STENTING AND DILATION

Major ingestions of caustic agents may result in perforation of the GI tract or extensive tissue necrosis requiring emergency surgery.[65-70] Laparotomy is generally preferred over laparoscopic evaluation for posterior gastric visualization. The indications for emergency surgery include esophageal perforation, peritoneal signs, or free intraperitoneal air. Large-volume ingestions (>150 mL), signs of shock, respiratory distress, persistent lactic acidosis, ascites, and pleural fluid may be other indications for surgical exploration.[65]

For grade 2B and 3 injuries without obvious perforation, recommendations include a period of esophageal rest,[71] early gastrostomy for enteral feeding,[37,72] and dilation therapy (in the first 3 weeks) with or without stenting.[73-76] Once strictures form, they may be difficult to treat and require stenting and/or multiple balloon dilatations or bouginage.[77] Controversy exists about the most appropriate treatment for esophageal stricture (i.e., long-term repetitive dilation therapy versus surgery).[75-78]

TREATMENT OF SYSTEMIC TOXICITY

Morbidity or death from alkali injuries usually results from the complications of direct tissue necrosis, but acid ingestions may result in additional systemic toxicity from absorption of the acid.[14] Acid-base disorders (increased anion gap or normal anion gap acidosis depending on acid ingested), hemolysis, coagulopathy, and renal failure may result. Acute lung injury (noncardiogenic pulmonary edema) may follow caustic ingestions as a complication of local or systemic effects.

NUTRITIONAL SUPPORT

Nutritional support is often necessary following a severe caustic injury to the esophagus or stomach. Support can be achieved by percutaneous (usually jejunostomy) feeding, nasoenteral feeding, or total parenteral nutrition.[64,79]

EXPERIMENTAL THERAPIES

Animal experiments have found that drugs affecting collagen deposition, including interferon-α-2b, octreotide, β-aminopropionitrile, colchicine, *N*-acetylcysteine, D-penicillamine, and polaprezinc, can prevent or treat esophageal strictures after caustic ingestion.[77,80,81] Pentoxifylline, a local inflammatory and microcirculation mediator, has experimental benefit. Mitomycin C, a fibroblast proliferation inhibitor, has been used topically on strictures with some success.[82] Oral agents to coat and protect the GI tract from insult, including sucralfate, bismuth subsalicylate, and sodium polyacrylate, are beneficial in animal experiments. None of these agents have been evaluated in controlled human clinical trials, and no specific recommendation can be made regarding their use. H_2 blockers and proton pump inhibitors are often used in the treatment protocols,[64] but no evidence supports or refutes their use.

COMPLICATIONS AND PROGNOSIS

Short-term prognosis is worse with grade 3 GI injury, systemic complications, and age >65 years.[47,83] Most long-term sequelae from caustic exposure are related to injuries to the GI tract. Acid ingestions may scar the pylorus and result in gastric outlet obstruction. Caustic alkali ingestions may cause esophageal strictures that may result in dysphagia, odynophagia, and malnutrition. Persistent drooling, reluctance to eat, severe oropharyngeal burns, and persistent fever correlate with the development of esophageal stricture after unintentional caustic ingestion in children.[84]

Patients with grade 3 caustic injuries to the esophagus have about a 1000-fold increased risk for squamous cell cancer of the esophagus, which can occur decades after the initial ingestion and resulting esophageal injury.[85] Because cancer can develop if a portion of the esophagus remains after reconstructive surgery for esophageal stricture, total removal of the esophagus is recommended.[86]

DISPOSITION AND FOLLOW-UP

Asymptomatic patients with low-risk ingestions and no signs of drooling, stridor, or vomiting and who tolerate food or drink may be discharged from the ED after a period of observation. Admit all patients with symptomatic caustic ingestions. Patients with grade 1 injuries can be discharged from hospital after endoscopy, provided they can tolerate oral fluids and food. Grade 2A injuries warrant hospitalization to ensure that symptoms and injury do not progress. Grade 2B and 3 injuries are significant, require enteral or parenteral nutrition, and have an early risk for bleeding or perforation; admit these patients to an intensive care unit.[64] Contact the regional poison control center for data collection purposes and assistance with management.

SPECIAL CONSIDERATIONS

LAUNDRY DETERGENT POD INGESTIONS

Laundry detergent pods, also known as capsules, liquitabs, or sachets, have long been available in Europe and were introduced to the U.S. market in 2010.[87,88] Each pod contains concentrated detergent within a dissolvable plastic membrane. An individual pod may have internal chambers that contain a stain remover and brightener separate from the detergent. Exposure to the concentrated preparation in these pods is more likely to produce symptoms than exposure to traditional laundry detergent products.[89,90]

Dermal or ocular exposure to the contents can produce irritation of the skin, conjunctiva, or cornea. **Ingestion by young children can produce serious toxicity with profuse vomiting, respiratory distress, and neurologic depression.**[91,92] The etiology of these systemic symptoms is unknown. Caustic injury to the pharynx and esophagus can produce difficulty swallowing with drooling and aspiration during recovery.[93] Treatment is supportive with airway protection and mechanical ventilation. In severe cases, ventilation may be required for days.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 201

Pesticides

Shaun Greene

Pesticides include insecticides, herbicides, and rodenticides.[1] Pesticide toxicity results from intentional, accidental, and occupational exposures. More than 150,000 pesticide poisoning deaths occur each year worldwide, with insecticides accounting for the majority of the mortality.[2] **Pesticides are marketed as multiple formulations, often under shared brand names. Therefore, complex clinical syndromes can result from exposure to both active and other ingredients.** Human toxicity can occur from many ingredients in proprietary formulations, including solvents and surfactants. Pesticides have class-specific toxicities, with many having both local and systemic effects. Management often includes consultation with a hazardous materials and toxins database or with a poison control center. Cornerstones of management are meticulous supportive care and early identification of exposures that may benefit from administration of an antidote.

The World Health Organization classifies pesticides according to toxicity based on rodent median lethal oral and dermal exposures. However, human case-fatality rates display large variation for compounds within the same chemical and/or World Health Organization toxicity classification.[3] **Toxicity classification should not be used to predict severity after human exposure.**

INSECTICIDES

Chemical insecticides are toxic to the human nervous system, producing acute and chronic manifestations, as well as delayed sequelae after acute exposure. Six major classes of insecticides are in common use (**Table 201-1**). Other compounds used to control insects include repellents.

TABLE 201-1 Insecticides and Repellents

Insecticides	Repellents
Organophosphates	Amitraz
Carbamates	*N*,*N*-diethyl-3-methylbenzamide (DEET)
Organochlorines	
Pyrethrins/pyrethroids	
Neonicotinoids	
Nereistoxin analogs	

ORGANOPHOSPHATES

Commonly used organophosphates include diazinon, acephate, malathion, parathion, and chlorpyrifos. Organophosphate and carbamate compounds are the insecticide exposures most commonly resulting in healthcare facility attendance in the United States.[4] Potency among organophosphates varies; highly potent compounds, such as parathion, are used primarily in agriculture, whereas those of intermediate potency, including coumaphos and trichlorfon, are used in animal care. Diazinon and chlorpyrifos were phased out from household use in the United States in 2000 due to neurotoxicity, particularly on the developing brains of children, but they continue to be used in many other parts of the world.[2] The organophosphate structure can be modified into chemical agents of mass destruction (see Chapter 8, "Chemical Disasters").

Globally, organophosphate poisoning results most commonly from deliberate self-poisoning.[2,5] Accidental exposures occur in agricultural and industrial settings through use of pesticide spray applicators or spills during transport.[6] Inadvertent exposure can occur from flea-dip products in pet groomers and children and from contaminated food. Systemic absorption of organophosphates occurs by inhalation and after mucous membrane, transdermal, transconjunctival, or GI exposure.

Consultation with a poison control center or medical toxicologist can be useful to assist in patient management and to collect data for surveillance reports. When consulting, precise communication of the specific product name from the container label is essential to identify both active and inert ingredients. As noted, confusion can arise because similar brand names are used for more than one agent.

Pathophysiology Organophosphate and carbamate compounds inhibit the enzyme cholinesterase.[3] Acetylcholinesterase (true or red blood cell acetylcholinesterase) is found primarily in erythrocyte membranes, nervous tissue, and skeletal muscle. Plasma cholinesterase (pseudocholinesterase or butyrylcholinesterase) is found in the serum, liver, pancreas, heart, and brain. Inhibition of cholinesterase leads to acetylcholine accumulation at nerve synapses and neuromuscular junctions, resulting in overstimulation of acetylcholine receptors. This initial overstimulation is followed by paralysis of cholinergic synaptic transmission in the CNS, in autonomic ganglia, at parasympathetic and some sympathetic nerve endings (e.g., sweat glands), and in somatic nerves. Excess acetylcholine results in a ***cholinergic crisis*** that manifests as a central and peripheral clinical toxidrome.

Organophosphate compounds bind irreversibly to acetylcholinesterase, thus inactivating the enzyme through the process of phosphorylation. The term *aging* describes the permanent, irreversible binding of the organophosphorus compound to the cholinesterase. The time to aging is highly variable among different agents and can range from minutes to a day or more. **Once aging occurs, the enzymatic activity of cholinesterase is permanently destroyed,** and new enzyme must be resynthesized over a period of weeks before clinical symptoms resolve and normal enzymatic function returns. **Antidotes are more effective if given before aging occurs.**

Clinical Features Clinical presentations depend on the specific agent involved, the quantity absorbed, route of exposure, and the amount and character of additives (including solvents) in any preparation.[7,8] Organophosphate insecticide poisoning can have substantial variability in clinical course, response to treatment, and outcome.[8,9] Four clinical syndromes are described following organophosphate exposure: **acute poisoning, intermediate syndrome, chronic toxicity, and organophosphate-induced delayed neuropathy**.[10]

In **acute organophosphate poisoning**, most poisoned patients are symptomatic within the first 8 hours and nearly all within the first 24 hours. Organophosphate agents such as malathion are associated with local irritation of the skin (dermatitis) and respiratory tract (wheezing) without evidence of systemic absorption.

Acute organophosphate poisoning results in CNS, muscarinic, nicotinic, and somatic motor manifestations (**Table 201-2**). In mild to moderate poisoning, symptoms occur in various combinations. In severe exposures, nicotinic features may be observed first. Time to symptom onset varies according to exposure route, occurring within minutes of massive ingestion. Symptom onset is most rapid with inhalation and least rapid with transdermal absorption; however, dermatitis or skin excoriation may hasten this.

TABLE 201-2 Clinical Effects of Cholinergic Excess Secondary to Organophosphorus Insecticide Poisoning

Mnemonics for the Muscarinic Effects of Cholinesterase Inhibition	
S	Salivation
L	Lacrimation
U	Urinary incontinence
D	Defecation
G	GI pain
E	Emesis
D	Defecation
U	Urination
M	Miosis
B	Bradycardia, bronchorrhea, bronchospasm
E	Emesis
L	Lacrimation
S	Salivation
"Killer Bs"	Bradycardia, bronchorrhea, bronchospasm

Nicotinic Effects of Cholinesterase Inhibition

- Muscle fasciculations, cramps, and weakness (including diaphragm)
- Mydriasis, pallor
- Tachycardia, hypertension

CNS Effects of Cholinesterase Inhibition

- Anxiety, restlessness, emotional lability
- Tremor, headache, dizziness
- Confusion, delirium, hallucinations
- Seizures, coma

Acetylcholine is the presynaptic neurotransmitter at nicotinic receptors in the sympathetic ganglia and adrenal medulla. Inhibition of acetylcholinesterase at these locations results in sympathetic stimulation, producing pallor, mydriasis, tachycardia, and hypertension. In most patients, parasympathetic stimulation usually predominates, but mixed autonomic effects are common.

Nicotinic stimulation at neuromuscular junctions results in muscle fasciculations, cramps, and muscle weakness. This syndrome may progress to paralysis and areflexia, making it difficult to detect seizure activity. Respiratory muscle paralysis can lead to ventilatory failure. Death is often due to respiratory failure caused by bronchorrhea and respiratory muscle weakness.

Abdominal pain is common, with rare cases of pancreatitis and peritonitis.[11] The clinical course may be complicated by aspiration of gastric contents and hydrocarbon solvents within insecticide preparations; this causes lipoid pneumonia and contributes to respiratory failure. Myocardial ischemia can occur in the early stages of severe toxicity.[12]

More lipid-soluble organophosphates may not produce immediate symptoms of toxicity, but instead produce delayed sequelae. Low-grade chronic organophosphate exposures occur among farmworkers, pesticide manufacturing plant workers, exterminators, and patients taking cholinergic ophthalmologic preparations.[13] Symptoms and signs are often less dramatic and nonspecific and occur without the cholinergic syndrome.

An **intermediate syndrome** occurring 1 to 5 days after an organophosphate exposure is reported in up to 40% of patients following ingestion.[14] Clinical features include paralysis of neck flexor muscles, muscles innervated by the cranial nerves, proximal limb muscles, and respiratory muscles (respiratory support may be needed). Symptoms or signs of cholinergic excess are absent in this syndrome. Electromyography may assist in making the diagnosis.[15] Aggressive, early antidote therapy and supportive measures may prevent or ameliorate the severity

of this syndrome. Symptoms usually resolve within 7 days. Nerve gas poisoning has not been reported to cause the intermediate syndrome.

Chronic toxicity, seen primarily in agricultural workers with daily exposure, manifests as symmetrical sensorimotor axonopathy.[16] This mixed sensorimotor syndrome may begin with leg cramps and progress to weakness and paralysis, mimicking features of the Guillain-Barré syndrome.

Organophosphate-induced delayed neuropathy is characterized by cognitive dysfunction, impaired memory, mood changes, autonomic dysfunction, peripheral neuropathy, and extrapyramidal signs.[13] Chronic fatigue syndrome and multiple chemical sensitivity have been reported in some (predominantly female) patients after exposure to very low doses of organophosphate insecticides.[17] Children are at greater risk of toxicity when exposed, due to smaller body size and lower baseline levels of cholinesterase activity.

Chemical warfare nerve agents, such as soman, sarin, tabun, and VX, are organophosphate compounds that inactivate acetylcholinesterases. They are rapid acting and extremely potent; death can occur within minutes of inhalation or dermal exposure, as was reported during the 2013 Syrian conflict.[18] Soman ages within minutes; thus, there is little time to administer antidotes.

Diagnosis **Diagnosis and treatment are based on history and the presence of a suggestive toxidrome; laboratory cholinesterase assays and reference laboratory testing for specific compounds take time and have limitations, and waiting for results delays administration of potentially lifesaving therapy.** Diagnosis is often difficult due to a constellation of clinical findings that can be variable in both acute and chronic poisonings.

Noting a characteristic hydrocarbon or garlic-like odor may assist in diagnosis. The cholinergic toxidrome may vary depending on the intoxication's severity and the predominance of muscarinic, nicotinic, and CNS manifestations. **The majority of patients severely poisoned with an organophosphorus insecticide will have altered mental status, pinpoint pupils, excessive sweating, and difficulty breathing.[8]**

Plasma butyrylcholinesterase and red cell acetylcholinesterase enzyme activity are both quantifiable but serve only as markers of cholinesterase activity at the synaptic junction. Red cell acetylcholinesterase is a more accurate indicator of synaptic cholinesterase inhibition, but plasma butyrylcholinesterase is easier to assay and more available. Baseline cholinesterase activity varies among individuals, and the degree of cholinesterase inhibition necessary to produce symptomatic illness is variable. In addition, there is poor standardization of normal ranges between laboratories.

Plasma butyrylcholinesterase activity may be decreased by up to 50% following exposure in asymptomatic patients not requiring treatment. Red cell acetylcholinesterase is typically reduced to 10% to 20% of normal activity in moderate poisoning and to <10% in severe cases. Plasma butyrylcholinesterase activity usually decreases first following a significant exposure and takes 28 to 42 days to normalize in cases where an oxime (e.g., pralidoxime) has not been administered. Red cell acetylcholinesterase requires regeneration of red blood cells to recover, and following a severe exposure, full activity may not be restored for up to 120 days.

Plasma butyrylcholinesterase levels may be depressed in patients with genetic variants, chronic disease states, liver dysfunction, hypersensitivity reactions, infection, pregnancy, and low serum albumin states and by drugs (succinylcholine, codeine, morphine), neoplasms, and malnutrition. Red blood cell acetylcholinesterase measurements are factitiously lowered by hemoglobinopathies, pernicious anemia, oxalate-containing blood containers, and concurrent antimalarial treatment.

Routine laboratory test abnormalities are nondiagnostic but may include evidence of pancreatitis, hypo- or hyperglycemia, leukocytosis, and abnormal liver function.[10] In severe cases, a chest radiograph may show pulmonary edema. Common abnormalities include torsades de pointes, ventricular tachycardia, and ventricular fibrillation. ECG changes include ST-segment changes, peaked T waves, atrioventricular block, and prolongation of the QT interval.[10] Electromyography may identify and quantify acetylcholinesterase inhibition at neuromuscular junctions.[16]

TABLE 201-3 Treatment for Organophosphate Poisoning

Decontamination	Protective clothing must be worn to prevent secondary poisoning of healthcare workers. Handle and dispose of all clothes as hazardous waste. Wash patient with soap and water. Handle and dispose of water runoff as hazardous waste.
Monitoring	Cardiac monitor, pulse oximeter, 100% oxygen
Gastric lavage	No proven benefit
Activated charcoal	No proven benefit
Atropine	Initial bolus of 1.2–3.0 milligrams IV in an adult depending on severity of symptoms (doses in children should start at 0.05 milligram/kg IV). Double the dose of IV atropine every 5 min to achieve adequate atropinization: • Clear chest on auscultation • Heart rate >80 beats/min • Systolic blood pressure >80 mm Hg Follow with continuous infusion of 10%–20% per hour of the initial dose of atropine that was required to achieve adequate atropinization (typical infusion rates vary from 0.4 to 4 milligrams/h IV in adults). Adjust infusion rate to maintain adequate atropinization and avoid atropine toxicity (absent bowel sounds, hyperthermia, delirium).
Pralidoxime	Give as soon as possible, may even be given 24–48 h after exposure 30 milligrams/kg IV in adults (30 milligrams/kg up to 1 gram in children), mixed with normal saline and infused over 5–10 min Followed by continuous infusion: 8 milligrams/kg per hour for 24–48 h
Seizures	Benzodiazepines IV

Treatment Treatment consists of airway control, intensive respiratory support, general supportive measures, decontamination, prevention of absorption, and the administration of antidotes (**Table 201-3**).[8,19] **Death occurs in untreated patients through a combination of bronchorrhea, respiratory muscle paralysis, and CNS depression. Therefore, immediate priorities following decontamination are airway protection, provision of ventilation, reduction of bronchorrhea via adequate atropinization, and reversal of respiratory muscle paralysis through administration of an oxime. Therapy should not be withheld pending determination of cholinesterase levels.**

In cases of acute cutaneous exposure, protective clothing must be worn to prevent secondary poisoning of healthcare workers.[20] Neoprene or nitrile gloves should be used instead of latex. Patients with suspected exposure must be removed from the contaminated environment and transported to the ED, in a manner that is safe for patients and healthcare workers (e.g., no transport by helicopter). All clothes and accessories must be removed completely, placed in plastic bags, and disposed of as hazardous materials.[21] The patient should be immediately decontaminated externally with copious amounts of a mild detergent such as dishwashing liquid and water. Decontamination includes the scalp, hair, fingernails, skin, conjunctivae, and skin folds. Body fluids should be treated as contaminated. Abrasion or irritation of the skin should be avoided. Contaminated runoff water should be contained and disposed of as hazardous material. Instruments used can be decontaminated using chlorine bleach.

Patients with acute exposures should be placed on oxygen, a cardiac monitor, and pulse oximeter. A 100% nonrebreather mask will optimize oxygenation in the patient with excessive airway secretions and bronchospasm; however, atropine administration should not be delayed or withheld if oxygen is not immediately available.[22] Gentle suction will assist in clearing airway secretions resulting from hypersalivation, bronchorrhea, or emesis. Coma, seizures, respiratory failure, excessive respiratory secretions, or severe bronchospasm necessitates endotracheal intubation. Establish an IV line with baseline blood sampling that can include determination of cholinesterase levels. **A nondepolarizing**

agent should be used when neuromuscular blockade is needed. Succinylcholine is metabolized by plasma butyrylcholinesterase; therefore, prolonged paralysis may result. Hypotension is initially treated with fluid boluses of isotonic crystalloid.

There is no published evidence demonstrating that gastric lavage improves outcome following organophosphate ingestion.[23] Gastric lavage undertaken within 1 hour of a very large ingestion (following airway protection via endotracheal intubation) may be beneficial, but its performance should not delay timely administration of antidotal therapy. Activated charcoal is sometimes recommended because organophosphates do bind in vitro, although there is no evidence that single or multiple doses of activated charcoal improve patient outcome.[24] Hemodialysis, hemofiltration, and hemoperfusion are of no proven value.

Atropine is the antidote for significant organophosphate poisonings (Table 201-3).[8,25-27] As a competitive antagonist of acetylcholine at central and peripheral muscarinic receptors, atropine will reverse the effects secondary to excessive cholinergic stimulation. Pinpoint pupils, excessive sweating and secretions, and respiratory distress are triggers for treatment with atropine. In adults, an initial dose of 1.2 to 3.0 milligrams is given depending on severity of symptoms. **The dose is doubled every 5 minutes until the following are achieved: chest clear on auscultation, heart rate >80 beats/min, and systolic blood pressure >80 mm Hg. Large amounts of atropine, on the order of hundreds of milligrams, may be necessary in massive ingestions.** Proactive contact with the hospital pharmacy (or even other centers) may be necessary to ensure access to adequate amounts of atropine.

Pupillary dilatation is not a therapeutic end point. **Tachycardia is not a contraindication to the use of atropine in organophosphorus poisoning because tachycardia can occur secondary to bronchospasm or bronchorrhea with hypoxia, which can be reversed with atropine.**

The initial atropine should be IV when possible, but 2 to 6 milligrams IM should be considered when IV access is not possible. Normally, this initial dose of atropine should produce clinically obvious antimuscarinic symptoms; absence of anticholinergic symptoms after an initial dose is thus consistent with organophosphate poisoning. Once an effective amount of atropine has been given, an infusion of 10% to 20% per hour of the initial dose of atropine that was required to achieve adequate atropinization should be started in order to maintain an anticholinergic state. **Importantly, atropine reduces respiratory tract secretions but does not reverse muscle weakness. Respiratory support through endotracheal intubation and artificial ventilation is required in severe poisoning.**

Glycopyrrolate, an alternate anticholinergic agent that does not produce CNS toxicity, may be used. However, its dosing is not well defined, and there is no proven benefit compared to atropine. The need for glycopyrrolate is unclear because adequate atropinization (using atropine) without significant CNS toxicity can be achieved via monitoring for anticholinergic effects (e.g., absent bowel sounds, hyperthermia, delirium) and adjusting the atropine infusion rate as needed.[8]

Compounds called *oximes* are used to displace organophosphates from the active site of acetylcholinesterase, thus reactivating the enzyme.[8,25,28] Pralidoxime is the oxime in common use and ameliorates muscarinic, nicotinic, and CNS symptoms. Importantly, pralidoxime reverses muscle paralysis if given early, before aging occurs. If possible, blood samples for acetylcholinesterase levels are obtained before administration of pralidoxime, but it is **important that pralidoxime be administered as soon as possible before permanent and irreversible aging occurs.** Although pralidoxime is more effective in acute than in chronic intoxications, it is recommended for use even later than 24 to 48 hours after exposure.

The pralidoxime dose recommended by the World Health Organization is a 30-milligram/kg IV bolus followed by an IV infusion of 8 milligrams/kg per hour.

Pralidoxime should be continued for 24 to 48 hours while monitoring acetylcholinesterase levels. Despite theoretical and experimental benefit and worldwide clinical use, current evidence is inadequate to show that oximes reduce mortality or the complication rate in acute organophosphate poisoning.[28-30] **Pralidoxime is not recommended for asymptomatic patients or for patients with known carbamate exposures presenting with minimal symptoms.**

Seizures are treated with airway protection, oxygen, atropine, and benzodiazepines.[8] **Atropine may prevent or abort seizures (due to cholinergic overstimulation) that occur within the first few minutes of exposure.** Pulmonary edema and bronchospasm are treated with oxygen, intubation, positive-pressure ventilation, atropine, and pralidoxime. Succinylcholine, ester anesthetics, and β-adrenergic blockers may potentiate poisoning and should be avoided.

Although there is some evidence for the benefit of magnesium sulfate and calcium channel blockers in the treatment of organophosphate poisoning, they are not yet recommended for routine clinical use.[31]

Disposition and Follow-Up Minimal exposures may require only decontamination and 6 to 8 hours of observation in the ED to detect delayed effects. Reexposure should be avoided because sequential exposures can result in cumulative toxicity. Patients returning to work should be limited from further exposure.

Admission to the intensive care unit is necessary for significant poisonings. Most patients respond to pralidoxime therapy with an increase in acetylcholinesterase levels within 48 hours. If there is no post-hypoxic brain damage and if the patient is treated early, symptomatic recovery occurs in 10 days. If toxins are fat soluble, the patient may be symptomatic for prolonged periods of time and may be dependent on continuous pralidoxime infusion. During this period, which may last weeks while awaiting resynthesis of new enzyme, supportive care and respiratory support may be needed. The end point of therapy is determined by the absence of signs and symptoms on withholding of pralidoxime.

CARBAMATES

The carbamate insecticides—aldicarb, carbofuran, carbaryl, ethienocarb, fenobucarb, oxamyl, methomyl, pirimicarb, propoxur, and trimethacarb—are cholinesterase inhibitors that are structurally related to the organophosphate compounds.[10] These agents are primarily used as insecticides, but illegally imported rodenticides may contain aldicarb.[32]

Pathophysiology Carbamates can be toxic after dermal, inhalation, and GI exposure. Carbamates transiently and reversibly bind to and inhibit the cholinesterase enzyme. Regeneration of enzyme activity by dissociation of the carbamate–cholinesterase bond occurs within minutes to a few hours and involves rapid, spontaneous hydrolysis of the carbamate–cholinesterase bond. Therefore, aging does not occur, and as a major difference from organophosphate poisoning, in carbamate poisoning, restoration of normal function does not require generation of new enzyme.

Clinical Features **In adults, symptoms of acute carbamate poisoning are similar to the cholinergic syndrome observed with organophosphate agents but are of shorter duration.** Because carbamates do not effectively penetrate the CNS in adults, less central toxicity is seen, and seizures do not occur. However, in children, presentation of acute carbamate poisoning differs, with a predominance of CNS depression and nicotinic effects. Carbamates can also produce the intermediate syndrome.[14]

Diagnosis Diagnosis is based on clinical history and findings. Measurement of acetylcholinesterase activity is generally not helpful because enzymatic activity may spontaneously return to normal 4 to 8 hours after a carbamate exposure.

Treatment Initial treatment of carbamate poisoning is the same as for organophosphorus compounds. Atropine is the antidote of choice and is administered for muscarinic symptoms. Atropine is usually all that is necessary while waiting for the carbamylated acetylcholinesterase complex to dissociate spontaneously and recover function (usually within 24 hours). Therapy is usually not needed for more than 6 to 12 hours.

The use of pralidoxime in carbamate poisoning is controversial. The carbamate-binding half-life to cholinesterase is approximately 30 minutes, and irreversible binding does not occur; therefore, there is little need for pralidoxime. Human case reports and some (but not all) animal studies suggest that pralidoxime may potentiate the toxicity of carbamates such as carbaryl.[33] Pralidoxime should be avoided in known single-agent carbaryl poisonings. However, pralidoxime should be considered in mixed poisonings with an organophosphorus compound and a carbamate or if the type of insecticide is unknown.

Disposition and Follow-Up Because carbamate poisonings have transient cholinesterase inhibition and rapid enzyme reactivation, the clinical course tends to be more benign than seen with organophosphates. Most patients recover completely within 24 hours. However, patients with depressed levels of consciousness have a significant mortality,[34] and methomyl poisoning is associated with a high risk of cardiac arrest at presentation as well as subsequent death after resuscitation.[35]

In mild poisonings, observation suffices, and the patient may be discharged with follow-up. Moderate poisonings necessitate 24 hours of observation that includes evaluation for possible concomitant exposure to (and toxicity from) inactive ingredients or vehicles such as hydrocarbons.

ORGANOCHLORINES

Dichlorodiphenyltrichloroethane (DDT) is the prototype insecticide of these chlorinated hydrocarbons. Chlordane, heptachlor, dieldrin, and aldrin are compounds used for termite and roach control. Most have been restricted or banned in the United States, Europe, and many other countries because of their toxicity as well as their persistence in the environment and long half-life in the human body. Worldwide, these insecticides continue to be used. Hexachlorocyclohexane (lindane) is a general garden organochlorine insecticide that is also used in some countries to treat scabies and head lice infestations. This compound is well absorbed by ingestion and inhalation. Dermal absorption occurs, particularly if the skin is abraded or repeated applications are used. Children and the elderly can develop neurotoxicity and seizures with therapeutic use of lindane.[36]

Pathophysiology Organochlorines are central neurologic stimulants that can be toxic after dermal, inhalation, and GI exposures. Transdermal absorption is affected by the type of vehicle and the agent's (liquid or solid) physical state. Organochlorines antagonize γ-aminobutyric acid–mediated inhibition of the central neurons, leading to hyperexcitability with repetitive neuronal discharges following the action potential. Organochlorines are highly lipid soluble and accumulate in human tissues. Most are capable of inducing the hepatic microsomal enzyme system. Presence of organochlorines therefore reduces therapeutic efficacy of drugs that are inactivated by this system.

Clinical Features **Neurologic symptoms predominate in acute organochlorine intoxication.**[37,38] Mild poisoning presents with dizziness; ataxia; fatigue; malaise; headache; neurologic stimulation with hyperexcitability, irritability, and delirium; apprehension; tremulousness; myoclonus; and facial paresthesias. More severe exposures may result in seizures, hyperthermia, coma, renal injury, and death.[37-39] Seizures may occur early, without prodromal syndromes, and are usually short lived (although status epilepticus may occur). Organochlorines are marketed dissolved in hydrocarbon solvents that, by themselves, can cause sedation, coma, and aspiration pneumonitis. Either the organochlorines or the solvents can sensitize the myocardium to endogenous catecholamines, posing risk for cardiac dysrhythmia.

Chlorfenapyr is a prodrug insecticide that is converted into the active form after absorption by the insect. Chlorfenapyr manifests biphasic neurotoxicity.[40] Initial symptoms are nonspecific and include headaches, body aches, drowsiness, and weakness. A latent period of apparent recovery is followed, on the seventh day after ingestion, by rapidly progressive paralysis leading to coma with a fatal outcome. No treatment is effective once the delayed symptoms start.

Diagnosis History is important, and valuable information can be obtained from the package label regarding the product and vehicle involved. Laboratory evaluation generally is not helpful, but organochlorines can be detected in the serum and urine by specialty laboratories.

Treatment Decontamination with removal of clothes and washing of the skin with mild detergent and water should occur following dermal exposure. Treatment includes administration of oxygen, with intubation indicated to treat hypoxia secondary to seizures, aspiration, and respiratory failure. Benzodiazepines are indicated for seizure control. Dysrhythmia control may be indicated, but epinephrine should be avoided because both organochlorines and the associated co-ingested organic solvents can sensitize the myocardium to endogenous catecholamines. Hyperthermia is managed by external cooling. Activated charcoal and possibly gastric lavage (in large, recent ingestions) may be useful. The exchange resin cholestyramine is potentially useful for symptomatic patients exposed to chlordecone.

Disposition and Follow-Up Exposed patients should be observed for 6 hours and admitted to the hospital if signs of toxicity develop or if ingestion involved a hydrocarbon.

PYRETHRINS AND PYRETHROIDS

Pyrethroid use and poisonings have increased since the phaseout of organophosphate insecticides for use in human dwellings. Pyrethrins are naturally occurring active extracts derived from the chrysanthemum plant. Pyrethroids are synthetic analogs of the pyrethrins with greater potency and environmental persistence, but they are considered safer than organochlorine and organophosphate insecticides.[41] Pyrethroids are used commonly as aerosols in automated insect sprays in public areas; therefore, inhalation is the most common source of exposure. These agents are available as dusts and liquids in a hydrocarbon base. Pyrethrins are common ingredients in over-the-counter household insecticides, pediculicides, and scabicides. They are rapidly hydrolyzed by mammals and therefore pose low risk of human toxicity.

Pathophysiology Toxicity results from dermal absorption, inhalation, or ingestion. Pyrethroids block the sodium channel at the neuronal cell membrane, causing repetitive neuronal discharge.[42] Additional effects include inhibition on γ-aminobutyric acid receptors, increased nicotinic cholinergic transmission, norepinephrine release, and interference with sodium–calcium exchange across cell membranes. Pyrethrin antigens are cross-antigenic with ragweed pollen, so allergic reactions are common after exposure.

Clinical Features These compounds can cause dermal, pulmonary, GI, and neurologic illness. **Allergic hypersensitivity reactions are the most common effects of pyrethrins and manifest as dermatitis, bronchospasm, rhinitis, hypersensitivity pneumonitis, or anaphylaxis.**[41,43] Skin contact may lead to paresthesias and burning within 30 minutes of exposure that usually dissipates within 24 hours.

Systemic toxicity can occur from occupational poisonings and following large intentional ingestions. Features of systemic toxicity include fatigue and lethargy, nausea and vomiting, paresthesias, hyperexcitability, tremors, muscle fasciculations, pulmonary edema, respiratory failure, and seizures.[44]

Diagnosis Diagnosis is dependent on a history of exposure. Differential diagnosis includes allergic reactions and ingestions with neurologic stimulants. Laboratory tests have no diagnostic value.

Treatment Treatment includes removal from exposure; dermal, ocular, and GI decontamination; treatment of allergic manifestations; and supportive care.

Disposition and Follow-Up Disposition is usually related to the severity of asthmatic and allergic manifestations. The clinical course is usually benign, and hospitalization is not necessary for most accidental exposures.

NEONICOTINOIDS

Neonicotinoids are structurally similar to nicotine, acting as agonists at the postsynaptic acetylcholine receptor. Neonicotinoids have high affinity for insect CNS nicotinic acetylcholine receptors, producing paralysis and death. Commercially available agents from this family include imidacloprid, thiamethoxam, clothianidin, acetamiprid, thiacloprid, dinotefuran, and nitenpyram.

Data regarding human toxicity are limited to case reports. Toxicity from imidacloprid poisoning is relatively mild to moderate in most cases, with symptoms of nausea, emesis, diarrhea, and headache. However, uncommon cases of respiratory failure, encephalopathy, hypotension, rhabdomyolysis, and renal failure have occurred.[45,46] Toxicity from acetamiprid poisoning has been associated with severe nausea and vomiting, muscle weakness, hypothermia, convulsions, and hypothermia.[47] Treatment is supportive.

NEREISTOXIN ANALOGS

Analogs of nereistoxin are considered low-toxicity insecticides and include bensultap, cartap, thiocyclam, and thiosultap. These insecticides induce neurotoxicity by promoting extracellular calcium influx and stimulating the release of intracellular calcium from the sarcoplasmic reticulum.

Occupational skin exposure can produce nausea, vomiting, muscle tremors, dyspnea, and mydriasis. Intentional ingestions are associated with depressed level of consciousness, muscle fasciculations and spasms, seizures, hypotension, hypoxia, and death.[48-50]

Animal studies suggest that sulfhydryl-containing compounds including L-cysteine, acetylcysteine, D-penicillamine, and dimercaprol, may be effective antidotes, but human data are lacking. Treatment is supportive.

AMITRAZ

Amitraz is an insect repellent, topical insecticide, and acaricide used as a spray on agricultural crops and as a wash solution to treat ectoparasites found on domesticated animals. Amitraz possesses agonist activity at the postsynaptic α_2-adrenergic receptor, interacts with the neuromodulator octopamine, inhibits monoamine oxidase, and impairs prostaglandin synthesis.

The clinical manifestations following human overdose include mental status depression, bradycardia, respiratory depression, miosis, hypotension, and hypothermia.[51,52] Mechanical ventilation may be required, but with supportive therapy, recovery is expected.

N,N-DIETHYL-3-METHYLBENZAMIDE (DEET)

DEET is used extensively as an over-the-counter insect repellent, formulated within products at concentrations from 5% to 100%. When used as directed, these products are generally safe. Toxicity can occur with ingestion or prolonged exposure on covered or damaged skin. DEET is a neurotoxin that causes seizures after large ingestions or extensive dermal exposures of high-concentration products. Small children are most susceptible to systemic toxicity from skin absorption. Dermal absorption occurs within 2 hours of topical application, but peak concentrations may be delayed several hours.

Systemic toxicity is rare but manifests as restlessness, insomnia, altered behavior, confusion, neurologic depression, slurred speech, ataxia, tremors, muscle cramps, hypertonia, and seizures occurring with or without prodrome. Hypotension and bradycardia have been reported with large dermal or oral exposures. Treatment includes benzodiazepines for seizures, skin decontamination with mild detergent and water, and activated charcoal for recent ingestions. Most patients recover with supportive care.

HERBICIDES

Herbicides are used to kill weeds. Mechanisms of toxicity to plants include inhibition of photosynthesis, respiration, protein synthesis, or growth stimulation (by mimicking plant hormones called *auxins*). Some classes pose a health hazard to humans (**Table 201-4**). Herbicidal formulations contain multiple ingredients such as organic solvents, surfactants, and preservatives that may have their own toxic effects; these may not always be disclosed on the product label.

CHLOROPHENOXY HERBICIDES

Chlorophenoxy herbicides are synthetic plant hormones that disrupt transport of nutrients and growth, leading to plant death.[53] The most commonly used compounds are 2,4-dichlorophenoxyacetic acid and 4-chloro-2-methylphenoxy-acetic acid. 2,4,5-Trichlorophenoxy acetic acid has been banned throughout much of the world because of its contamination with 2,3,7,8,-tetrachlorodibenzo-*p*-dioxin. These compounds are effective against broadleaf plants and are used as weed killers on lawns and grain crops.

TABLE 201-4 Selected Herbicide Classes That Pose Potential Harm to Humans

- Chlorophenoxy compounds
- Bipyridyls: paraquat and diquat
- Urea substituted herbicides
- Organophosphates
- Glyphosate

Pathophysiology Mechanisms leading to human toxicity following chlorophenoxy herbicide exposure include cell membrane damage, disruption of neuronal transport mechanisms, formation of false neurotransmitters acting at muscarinic and nicotinic receptors, and uncoupling of mitochondrial oxidative phosphorylation.[53] Oral absorption of chlorophenoxy herbicides is rapid. Dermal and inhalational absorption is poor and rarely results in systemic toxicity.

Clinical Features Local exposure leads to eye and mucous membrane irritation that may last for days. After ingestion, nausea, vomiting, and diarrhea occur. Pulmonary complications may include dyspnea, hemoptysis, and pulmonary edema. Cardiovascular findings include hypotension, tachycardia, and dysrhythmias. Mental status changes and seizures may occur. Muscle toxicity manifests as muscle tenderness, fasciculations, myotonia, and rhabdomyolysis. Metabolic acidosis and hyperthermia may occur secondary to uncoupling of oxidative phosphorylation; hypercapnia and ventilatory failure can follow. Peripheral neuropathy and myopathy have been described in the recovery phase after acute and chronic exposure.

Diagnosis Diagnosis is based on a history of exposure. Ancillary tests generally are nonspecific but may demonstrate a metabolic acidosis, rhabdomyolysis, or evidence of hepatorenal dysfunction. Toxin levels are not immediately available.

Treatment Treatment is supportive and includes decontamination measures, respiratory support for myopathic-related respiratory failure, and maintenance of adequate urine output for rhabdomyolysis.[53,54] Although urinary alkalinization will increase the elimination of these compounds and is recommended for severely poisoned patients, it should be used with caution in cases of hyperthermia since bicarbonate administration will increase carbon dioxide production.[54,55] Hemodialysis can also be used to enhance chlorophenoxy herbicide clearance.

Disposition and Follow-Up Severe toxicity and serious complications are not common following exposure to chlorophenoxy herbicides. Because toxic effects usually appear within 4 to 6 hours, patients with mild symptoms can be observed and discharged after that time.

BIPYRIDYL HERBICIDES

The bipyridyl compounds, **paraquat and diquat**, are nonselective contact herbicides. Both are used widely and are responsible for significant morbidity if ingested.[57] Paraquat is a fast-acting, nonselective herbicide. It is used for killing grass and weeds and is manufactured as a liquid, granules, or as an aerosol. Paraquat is commonly combined with diquat and other herbicides. Most products contain a blue dye, a stenchant, and an emetic. Ingestion is responsible for the majority of paraquat deaths,[56] although deaths have been reported after transdermal exposure. Inhalation of and exposures to sprays can be very irritating to conjunctivae and the airway but are unlikely to cause systemic toxicity. Diquat poisoning is less commonly reported than paraquat poisoning, but clinical features of toxicity are similar. Management of diquat toxicity is considered the same as for paraquat.

Pathophysiology Paraquat is a severe local irritant and devastating systemic toxin.[57] There is minimal transdermal absorption of paraquat in the absence of preexisting skin lesions. Ingested paraquat is absorbed rapidly, particularly if the stomach is empty. Plasma concentration peaks within minutes to 2 hours after ingestion. Paraquat is then distributed to most organs, with the highest concentrations found in the kidneys and lungs. A lethal oral dose of the 20% concentrate solution is about 10 to 20 mL in an adult and 4 to 5 mL in a child.

Paraquat actively accumulates in the alveolar cells of the lungs, where it is transformed into a reactive oxygen species, the superoxide radical.[58] This anion is responsible for lipid peroxidation that leads to degradation

of cell membranes, cell dysfunction, and necrosis. Lung injury has two phases. An initial destructive phase is characterized by loss of type I and type II alveolar cells, infiltration by inflammatory cells, and hemorrhage. These changes may be reversible. The later, proliferative phase is characterized by fibrosis in the interstitium and alveolar spaces. Paraquat and oxygen enhance each other's toxicity by sustaining the redox cycle. Myocardial injury and necrosis of the adrenal glands may occur.

Diquat's structure and action mechanism are similar to those of paraquat. Formulations containing diquat do not contain the dye, stenching agent, or emetic usually added to paraquat. The lethal dose for diquat is similar to that of paraquat, but there is less occurrence of pulmonary injury and fibrosis because of diquat's lower affinity for pulmonary tissue. Diquat is caustic to the skin and GI tract, and exposure can result in renal and liver necrosis.

Clinical Features Clinical features depend on both the amount and route of exposure. Paraquat's severe caustic effects produce local skin irritation and ulceration of epithelial surfaces. Severe corrosive corneal injury may result from eye exposure. Upper respiratory tract exposure may result in mucosal injury and epistaxis. Inhalation may lead to cough, dyspnea, chest pain, pulmonary edema, epistaxis, and hemoptysis. Respiratory symptoms may persist for several weeks after inhalation exposure.

Ingestion causes GI irritation and mucosal damage with ulcerations (**Table 201-5**). A burning sensation of the lips or mouth may occur within a few minutes to hours, followed by ulceration 1 to 2 days later. Nausea, vomiting, diarrhea, buccopharyngeal pain, esophageal pain, and abdominal pain may develop. Hypovolemia occurs from GI fluid losses and decreased oral intake.

Multisystem effects include GI tract corrosion, acute renal failure, cardiac failure, hepatic failure, and extensive pulmonary injury. The effects can be evident within a few hours following large ingestions, but more typically, manifestations of renal failure and hepatocellular necrosis develop between the second and fifth days; progressive pulmonary fibrosis leading to refractory hypoxemia occurs 5 days to several weeks after exposure. Metabolic (lactic) acidosis is common as a result of pulmonary effects (e.g., hypoxemia) combined with multisystem failure.

TABLE 201-5 Paraquat Toxicity From Ingestion

Category	Clinical Features	Approximate Amount Ingested
Mild	Asymptomatic or nausea, vomiting, and diarrhea. Renal and hepatic injury minimal or absent. Decreased pulmonary diffusion capacity may be present. Complete recovery expected.	<20 milligrams/kg or <7.5 mL of 20% concentrated solution in average adult
Severe	Initially nausea, vomiting, diarrhea, abdominal pain, and mouth and throat ulceration. Positive colorimetric test for paraquat in the urine. 1–4 d: renal failure, hepatic impairment, hypotension. 1–2 wk: cough, hemoptysis, pleural effusion, pulmonary fibrosis. Survival possible, but majority of cases die within 2–3 wk from pulmonary failure.	Between 20 and 40 milligrams/kg or between 7.5 and 15 mL of 20% concentrated solution in average adult
Fulminant	Initially nausea, vomiting, diarrhea, and abdominal pain. Rapid development of renal and hepatic failure, GI ulceration, pancreatitis, toxic myocarditis, refractory hypotension, coma, convulsions. Death from cardiogenic shock and multiorgan failure within 1–4 d.	>40–50 milligrams/kg or >15–20 mL of 20% concentrated solution in average adult

Diagnosis Early diagnosis, prognostication, and subsequent therapy are important. Obtain details of the exposure, including its timing, route, accidental or intentional nature, and amount and concentration of the product. The quantity of paraquat ingested is directly related to outcome. Age over 50 years and a history of renal disease are associated with worse prognosis.[58,59] A sensation of generalized skin burning is associated with increased risk of death.[60]

Laboratory abnormalities generally reflect the consequences of vomiting, diarrhea, and multiorgan failure. Acute kidney injury is common and is associated with increased mortality. Creatinine increase is driven by paraquat-induced oxidative stress as well as acute kidney injury; thus, it is not an accurate marker of glomerular filtration rate in the setting of paraquat toxicity. An increase in creatinine of <0.034 milligram/dL (3 micromole/L) per hour over 5 hours is associated with recovery. An increase in creatinine of >0.049 milligram/dL (4.3 micromole/L) per hour over 6 hours or an increase in serum cystatin C concentration of >0.009 milligram/L over 6 hours is associated with death.[61]

Serum lactate may aid with prognosis.[62] Two retrospective studies assessed lactate levels associated with death. One identified a lactate of >3.35 mmol/L (30 mg/dL) as having 74% sensitivity for mortality, whereas the other found an 82% sensitivity for death associated with a lactate level exceeding 4.4 mmol/L (40 mg/dL).[63,64]

Radiographic abnormalities of diffuse pulmonary infiltrates may indicate aspiration or direct paraquat-induced parenchymal injury. Radiographic extent of pulmonary involvement is related to outcome. Chest radiographs may also show pneumomediastinum or pneumothorax due to corrosive rupture of the esophagus; these findings are associated with increased mortality risk.[65]

A urinary dithionite test can be performed to detect paraquat within a few hours after ingestion and has some prognostic value; a clear test color between 6 and 24 hours after paraquat exposure favors survival. The test is semiquantitative; patients with a darker blue color change have a worse prognosis.[66,67] A commercially available semiqualitative colorimetric test (Paraquat Test Kit®; Syngenta CTL, Surrey, United Kingdom) is available for detecting paraquat in urine or plasma.

Quantitative analyses for paraquat in blood can assist in the diagnosis.[57] Nomograms are used for predicting survival based on plasma paraquat concentration and time of ingestion, but require availability of specific analytical methods that may not always be available.[65] A predictive nomogram based on plasma concentration has not been developed for diquat poisoning.

Consult with gastroenterology about the need for endoscopy to identify the extent and severity of mucosal lesions.

Treatment **The goal of early and vigorous decontamination is to prevent absorption and thus reduce pulmonary toxicity.** Any exposure to paraquat is a medical emergency, with hospitalization indicated even if the patient is asymptomatic. Commencement of treatment should never be delayed to wait for the results of diagnostic testing. **The outcome for patients with evidence of severe poisoning is extremely poor, despite best available treatments instituted in advanced critical care settings.** In some cases, the most humane approach will be to provide analgesia and supportive care, rather than invasive interventions. Early treatment is mainly supportive but is an important determinant of survival. **Do not administer supplemental oxygen unless the patient is severely hypoxic because added oxygen stimulates superoxide radical formation and promotes oxidative stress.**

Remove clothing and decontaminate skin with mild detergent and water. Take care to avoid skin abrasions that may increase absorption. If there is conjunctival irritation, irrigate with copious amounts of water or saline. Replace fluid and electrolytic losses and maintain intravascular volume and urine output. Treat pain with opioids. Gastric lavage is contraindicated due to the high likelihood of paraquat-induced corrosive injury. Consult with GI for consideration of potential esophageal corrosive injury and need for endoscopy.[57]

In patients presenting within 2 hours of ingestion, GI decontamination with absorbents that bind paraquat should be undertaken as a matter of urgency, either via oral ingestion or via a nasogastric tube. A single dose of activated charcoal (1 to 2 grams/kg), diatomaceous fuller's earth (1 to 2 grams/kg in 15% aqueous suspension), or bentonite (1 to 2 grams/kg in a 7% aqueous slurry) should be used.[57]

Hemoperfusion can remove paraquat and has been recommended to be started as soon as possible. Limited evidence suggests a possible survival benefit when hemoperfusion is commenced within 4 hours of paraquat exposure.[68,69] If hemoperfusion is not available, then other extracorporeal elimination therapies including intermittent hemodialysis may be beneficial.[70-72] Although continuous venovenous hemodialysis removes paraquat, it is unlikely to provide rapid reductions in paraquat concentrations and therefore should not be used if other therapies are available. Continuous venovenous hemodialysis may be used as a therapy in the event of acute kidney injury.

Small methodologically limited studies suggested a benefit from repeated pulse doses of glucocorticoids and cyclophosphamide, but a large randomized controlled trial demonstrated no benefit.[73,74] Dexamethasone may be beneficial and should be administered at a dose of 8 milligrams IV every 8 hours for the first 72 hours.[75] Dexamethasone has relatively low toxicity and, in severe poisoning, may provide benefit if continued for weeks following exposure when there is the possibility of progression of pulmonary injury. Acetylcysteine may provide benefit and is of low toxicity. It should be administered continuously while there is evidence of acute toxicity in the inpatient setting.[76]

Serial pulmonary function tests, chest radiographs, renal function tests, and blood gas determinations may be used to monitor progression of toxicity.[62]

Treatment for diquat poisoning is similar to that for paraquat. Despite the lower toxicity for diquat, mortality approaches 50% after intentional diquat ingestion.

Disposition and Follow-Up All patients should be observed for at least 12 hours following exposure. Clinically well patients with a negative urine dithionite test at this time are unlikely to develop toxicity. Patients with evidence of severe toxicity and prognostic markers indicating a fatal outcome should receive appropriate supportive and palliative care. Patients with clinical toxicity and an unclear prognosis are admitted to a critical care environment.

UREA-SUBSTITUTED HERBICIDES

Urea-substituted herbicides such as chlorimuron, diuron, fluometuron, and isoproturon are inhibitors of photosynthesis and have low systemic toxicity. In humans, methemoglobinuria may occur with ingestion.[77] Treatment includes decontamination, supportive care, and as-needed treatment for methemoglobinemia (with methylene blue) (see Chapter 207, "Dyshemoglobinemias").

ORGANOPHOSPHATE HERBICIDES

In addition to their use as insecticides, some organophosphate compounds are effective herbicides. Butiphos is used commonly as a cotton defoliant applied prior to mechanical harvesting. Treatment is identical to that for organophosphate insecticides.

GLYPHOSATE

Glyphosate is the active ingredient in many widely used preparations available for consumer use on lawns and gardens. **Some lawn and garden products sold using a common or group brand name may contain different active ingredients; a common brand name may contain either glyphosate or the more toxic herbicide diquat.**

Glyphosate can produce severe toxicity with massive ingestions of the diluted product or smaller-volume ingestions of solutions that are concentrated (>10%).[78] Ingestion of >150 mL of a 36% glyphosate solution is associated with severe multiorgan toxicity. Preparations may contain the toxic surfactant polyoxyethyleneamine, which is a corrosive, and the combination is more toxic than glyphosate alone. Inhalational exposures cause respiratory irritation. Dermal absorption is poor, so symptomatic poisonings are generally from ingestion.

Clinical effects include mucous membrane irritation and erosions with nausea, vomiting, abdominal pain, and diarrhea.[79] Severe toxicity is characterized by airway burns, GI corrosive injury, metabolic acidosis, acute kidney injury, hyperkalemia, coma, refractory cardiovascular collapse, and potentially death.

Early airway evaluation is important in order to detect burns and edema. Airway protection may be required via endotracheal intubation. Treatment is primarily supportive. Along with oxygenation and ventilation, priorities include supporting circulation, treating hyperkalemia, and ameliorating complications due to corrosive GI effects. Hemodialysis may be supportive when severe acidosis and acute kidney injury are present.[80]

Patients with small, asymptomatic ingestions can be discharged after 6 hours of observation. Significant GI symptoms, altered level of consciousness, hypoxemia, metabolic acidosis, and cardiovascular abnormalities indicate admission to an intensive care unit.

RODENTICIDES

A number of agents with distinct toxicities are used as rodenticides. Rodenticides are commonly classified based on whether they are anticoagulants or nonanticoagulants. Although intentional ingestions are often associated with significant morbidity and mortality, most unintentional exposures occur in young children and result in minimal or no toxicity.

NONANTICOAGULANTS

A number of nonanticoagulant rodenticides have been used throughout history. Many have been discontinued, although poisonings still occur from old products stored in garages, barns, and homes (**Table 201-6**).

ANTICOAGULANTS

Warfarin-type anticoagulants were the first generation of anticoagulant rodenticides and distributed commonly disguised as yellow corn meal or rolled oats.[87] **Most one-time warfarin rodenticide ingestions are insignificant accidental poisonings and do not cause any bleeding problems. Significant coagulopathy requires large amounts in a single exposure or a repetitive exposure over several days.** Following a single large ingestion, onset of the anticoagulant effect takes place within 12 to 48 hours. Warfarin's biologic half-life is approximately 42 hours.

Therapy is not necessary for ingestion of a single mouthful of a warfarin rodenticide. For potentially toxic recent ingestion, consider activated charcoal. Obtain a baseline prothrombin time and INR determination and repeat it in 12 to 24 hours. Vitamin K_1 (phytonadione) administration is indicated if the INR is >2.0. The suggested total PO daily dose is 1 to 5 milligrams in children and 20 milligrams in adults, administered in two to four divided doses.

Second-generation superwarfarins and the indandione derivatives were introduced when rodent resistance to warfarin began to appear.[87] They are currently responsible for approximately 80% of human rodenticide exposures reported in the United States. Their mechanisms are the same as that of warfarin, but they are more potent, have more prolonged anticoagulant activity, and therefore have the potential to be highly toxic. Poisonings involving the indandione derivatives pindone, diphacinone, chlorophacinone, and valone have toxic and clinical characteristics similar to those of the superwarfarins.

The **superwarfarins** include the 4-hydroxy-coumarins brodifacoum, difenacoum, coumafuryl, and bromadiolone. These are readily available over the counter as grain-based bait. After intentional ingestions, adults often develop a coagulopathy within 24 to 48 hours. **Because the biologic half-life of brodifacoum is approximately 120 days, a single ingestion may result in marked anticoagulation effects for weeks to months.**[88] Intentional repeated ingestions can cause severe bleeding.

The diagnosis may not be readily apparent. Some patients may not report an intentional ingestion. Small children and depressed patients with an unexplained coagulopathy or bleeding should raise suspicion of superwarfarin poisoning. Although the prothrombin time and INR are usually monitored, large doses of warfarin can also cause prolongation of the activated partial thromboplastin time. **Superwarfarins are not detected by warfarin assays, but specific serum assays are available in reference laboratories.**

Unintentional superwarfarin ingestions in the pediatric patient are unlikely to result in significant toxicity.[89] Obtain a baseline INR and repeat 24 and 48 hours after ingestion. For acute intentional ingestions, gastric lavage is indicated for early presentations, and activated charcoal should be administered. Obtain a baseline INR and repeat in 12 and 24 hours. If the INR is elevated but there is no active hemorrhage, oral

TABLE 201-6 Selected Non-anticoagulant Rodenticides

Rodenticide	Toxicity	Mechanism	Clinical Effects	Treatment
Arsenic	Severe	Binds sulfhydryl groups on proteins	Dysphagia, muscle cramps, nausea and vomiting, bloody diarrhea, dysrhythmias (QT prolongation), cardiovascular collapse, altered mental status, seizures, and late peripheral neuropathies.	Activated charcoal in conjunction with airway protection, supportive care, chelation therapy using succimer, and dimercaprol.
Barium carbonate and other soluble forms such as barium chlorides, hydroxides, and sulfides	Severe	Inhibits potassium channels, leading to hypokalemia. Acts as depolarizing neuromuscular blocker.	Onset occurs within 1–8 h with nausea, vomiting, diarrhea, abdominal pain, dysrhythmias, respiratory failure, muscular weakness, paresthesias, and paralysis.	Gastric lavage with sodium or magnesium sulfate added to lavage solution to convert carbonate to less toxic sulfate; potassium replacement.
Elemental or yellow phosphorus	Severe, early cardiac and neurologic toxicity is a poor prognostic sign.	Caustic. Possible mitochondrial toxin.	Skin irritation, cutaneous burns, oral burns, abdominal pain, hematemesis, possible "smoking" luminescent vomitus and stool, garlicky odor, direct toxic effects on the myocardium, kidney, and peripheral vessels, cardiovascular collapse; late neurologic depression with multisystem toxicity and hepatorenal syndrome.	Supportive care, cardiac monitoring, correction of electrolyte abnormalities. Maintenance of serum glucose concentration may reduce cellular injury.
Sodium fluoroacetate (SFA)[81]	Severe	Blocks Krebs cycle	Nausea, vomiting, apprehension, lactic acidosis, seizures, coma, respiratory depression, cardiac dysrhythmias, and pulmonary edema; ECG abnormalities include ST-segment and T-wave changes, tachycardia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation; hyperkalemia and hypocalcemia are common.	Activated charcoal, seizure and dysrhythmia control, and supportive care; experimental regimens include glycerol monoacetate, calcium gluconate, sodium succinate, and ethanol loading; consultation with a toxicologist is recommended.
Strychnine	Severe	Competitive antagonism of the inhibitory neurotransmitter glycine at the postsynaptic brainstem and spinal cord motor neuron	Restlessness, muscle twitching, painful extensor spasms, opisthotonos, trismus, inability to swallow, and facial grimacing; medullary paralysis and death can follow.	Airway control, quiet environment (minimize sensory stimulation), and activated charcoal; avoid lavage (may precipitate seizures); benzodiazepines, barbiturates, analgesia; neuromuscular blockage if necessary.
Tetramine[82]	Severe	Blocks γ-aminobutyric acid receptors in the CNS	Rapidly acting; initial features include headache, nausea, dizziness, fatigue, anorexia, numbness, and listlessness; severe symptoms include loss of consciousness, seizures, and coma; death is usually caused by respiratory failure.	The median lethal dose for tetramine is ~0.1 milligram/kg; 6–12 milligrams sufficient to kill an adult; no antidote; supportive care; benzodiazepines or barbiturates for seizures.
Thallium sulfate[83]	Severe	Combines with mitochondrial sulfhydryl groups, interfering with oxidative phosphorylation	Early GI symptoms: nausea, vomiting, and abdominal pain; after 2–5 d, painful paresthesias, myalgias, muscle weakness, headache, lethargy, tremors, ataxia, delirium, seizures, and coma; death from respiratory failure and dysrhythmias; alopecia after approximately 2 wk; chronic neurologic sequelae.	Supportive care; multiple doses of activated charcoal or Prussian blue (potassium ferric hexaniacinate) to interrupt enterohepatic circulation and increase elimination in stool; hemodialysis.
Zinc or aluminium phosphide[84,85]	Severe	Combines with water and stomach acid to produce phosphine gas; cellular toxicity and necrosis to the GI tract, kidney, and liver if ingested and to the lungs if inhaled	Immediate nausea, vomiting, epigastric pain, phosphorous or fishy breath, black vomitus, and GI irritation or ulceration; myocardial toxicity, shock, and acute lung injury; agitation, coma, seizures, hepatorenal injury, metabolic acidosis, hypocalcemia, tetany.	Treat acidosis and hypocalcemia; consider acetylcysteine[86]; supportive care.
Cholecalciferol (vitamin D_3)	Moderate	Mobilization of calcium from bones	Hypercalcemia, osteomalacia, and systemic metastatic calcifications.	Treat hypercalcemia with IV normal saline, furosemide, steroids, calcitonin, and biphosphates as needed.
Red squill	Low (limited toxicity in humans due to early onset of emesis with gastric emptying)	Blocks sodium-potassium adenosine triphosphatase (similar to digoxin poisoning)	Nausea, protracted vomiting, diarrhea, abdominal pain; massive ingestion causes hyperkalemia, atrioventricular block, ventricular irritability with dysrhythmias, and death.	Treat as digoxin toxicity (atropine, external pacing, digoxin-specific antibody fragments, activated charcoal).

vitamin K_1 is recommended. Forms of vitamin K other than vitamin K_1 are ineffective because the conversion of these other forms to the active form is blocked by superwarfarins. Because of the extended half-life of the anticoagulant, prolonged therapy with high doses of vitamin K_1 may be required to maintain hemostasis.[90,91] Initial daily doses of 1 to 5 milligrams in children and 20 milligrams in adults are recommended with titration to maintain a normal INR. Doses up to 100 milligrams per day for 10 months have been reported. Upon discontinuation of vitamin K_1 therapy, serial INR determinations are required to ensure that further therapy is not needed.

Patients with acute hemorrhage may require repletion of volume losses with normal saline or blood transfusions. Vitamin K_1, 10 milligrams, should be administered by slow IV infusion to minimize the risk of a hypotensive reaction. Replacement of coagulation factors should be

achieved using four-factor prothrombin complex concentrate or three-factor prothrombin complex concentrate and fresh frozen plasma.

For asymptomatic patients who have accidentally ingested a super-warfarin, follow-up in 24 and 48 hours for coagulation studies should be arranged. Prevention measures should be emphasized.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 202

Anticholinergics

Frank LoVecchio

INTRODUCTION

Anticholinergic properties are present in over 600 compounds, including prescription drugs, over-the-counter medications, and plants (**Table 202-1**). Many of these substances possess anticholinergic activity as either a direct therapeutic effect or as an adverse effect in addition to their primary or predominant pharmacologic effect. Atropine (D,L-hyoscyamine), hyoscyamine, and scopolamine (L-hyoscine) are natural alkaloids that represent prototypical anticholinergic compounds.

Antihistamine (particularly diphenhydramine) overdose is the most common overdose that produces anticholinergic toxicity.[1] Toxicity in children may result from accidental ingestion of an anticholinergic medication, oral administration of hyoscyamine-containing agents to treat colic, topical use of diphenhydramine-containing salves, or therapeutic application of a transdermal hyoscine patch.[2-5] In the elderly, therapeutic doses of one or multiple medications with anticholinergic properties may produce anticholinergic symptoms, or they may simply cause ileus without other anticholinergic findings.[6,7] Ophthalmologic instillation of anticholinergic mydriatics can cause toxicity, especially in the elderly or young children; patients are therefore instructed to lie down and apply 5 minutes of gentle pressure on the nasolacrimal duct when instilling these agents.[8]

Atropine is the antidote for cholinergic syndromes produced from nerve agents or organophosphate insecticides.[9] Administration of high-dose atropine to someone without cholinesterase poisoning can result in anticholinergic toxicity. This occurred in Israel during the first Gulf War in 1991, when frightened civilians dosed themselves with atropine fearing an incoming Scud missile chemical weapon attack.

Plant poisonings may result in an anticholinergic toxidrome. In Taiwan, the anticholinergic toxidrome is most commonly associated with plant exposures.[10] Belladonna alkaloid-containing plants have potent anticholinergic effects and produce toxicity 1 to 4 hours after ingestion (sooner if smoked). Alkaloid plants are abused for their hallucinogenic effects.[11,12] Group poisonings with anticholinergic plants are common in adolescents seeking psychoactive hallucinogenic effects.[13,14] Inadvertent poisoning from the ingestion of belladonna-contaminated herbal teas and Chinese traditional medicines has been reported.[15,16] Ingestion of seeds and berries, sometimes due to mistaken identity, can produce anticholinergic toxicity.[17,18] Anticholinergics have been substituted for other abused psychoactive drugs and then sold to unwitting customers.[19] Adulteration of commonly abused drugs (e.g., heroin, cocaine) with scopolamine or atropine has been observed.[20-22]

TABLE 202-1 Major Groups of Substances With Anticholinergic Activity

Class and Subclass	Prototypical Agent(s)
Cyclic antidepressants	Amitriptyline hydrochloride, imipramine hydrochloride, doxepin hydrochloride
Antihistamines	
Ethanolamines	Diphenhydramine, dimenhydrinate
Ethylenediamines	Tripelennamine
Alkylamines	Chlorpheniramine
Piperazines	Loratadine, meclizine, cetirizine
Phenothiazines	Prochlorperazine, promethazine
Antiparkinson drugs	
Tropanes	Benztropine mesylate
Piperidines	Trihexyphenidyl
Antipsychotics	
Phenothiazines	Chlorpromazine, thioridazine, perphenazine
Nonphenothiazines	Clozapine, olanzapine, molindone, loxapine, quetiapine
Antispasmodics	
Cyclohexane carboxylic acids	Dicyclomine
Quaternary ammonium	Methantheline bromide
Belladonna alkaloids	
Tropanes	Atropine, homatropine, scopolamine hydrobromide
Pyrrolidines	Glycopyrrolate
Mydriatics	
Phenylacetates	Cyclopentolate hydrochloride
Pyridines	Tropicamide
Skeletal muscle relaxants	
Tricyclics	Cyclobenzaprine hydrochloride
Ethylamines	Orphenadrine citrate
Plants	
Datura species	*Datura stramonium* (Jimson weed), *Datura candida* (angel's trumpet)
Mandragora species	*Mandragora officinarum* (mandrake)
Brugmansia species	*Brugmansia suaveolens* (angel's tear, maikoa, or white angel's trumpet), *Brugmansia versicolor* (angel's tear or angel's trumpet)
Mushrooms	
Amanita species	*Amanita muscaria, Amanita pantherina*

PHARMACOLOGY

Anticholinergic drug absorption can occur after ingestion, smoking, or ocular use. With oral ingestion, the onset of anticholinergic toxicity usually occurs within 1 to 2 hours. Because muscarinic blockade slows gastric emptying and decreases GI motility, absorption and peak clinical effects are often delayed. An example is diphenoxylate-atropine (e.g., Lomotil®), an antidiarrheal agent that may present with toxicity up to 12 hours after ingestion.

Cholinergic receptors exist as two major subtypes: muscarinic receptors and nicotinic receptors. Muscarinic receptors are found predominantly on autonomic effector cells that are innervated by postganglionic parasympathetic nerves, on some ganglia, and in the brain, particularly the hippocampus, cortex, and thalamus. Nicotinic receptors are found at peripheral autonomic ganglia, at neuromuscular junctions, and also in the brain. Acetylcholine is the neurotransmitter that modulates both receptor types. Genes encode for five muscarinic receptors through G-protein receptor activation; four seem to be physiologically active (**Table 202-2**).

The structure of nicotinic receptors is complex, composed of several subunits that are encoded by multiple genes. The subunits are combined into four main families of nicotinic receptors: the muscle type, found at the neuromuscular junction; the ganglion type, found in autonomic ganglia; and two brain types found in the CNS.

Anticholinergic drugs and plant toxins competitively inhibit or antagonize the binding of the neurotransmitter acetylcholine to muscarinic acetylcholine receptors. The term *anticholinergic* is technically

TABLE 202-2 Muscarinic Receptors

Receptor	Target Organ	Receptor Action When Stimulated
M_1	Autonomic ganglia Brain Salivary glands Stomach	Decreases activity in autonomic ganglia Increases salivary and gastric acid secretion
M_2	Heart	Decreases sinus node rate and slows conduction through the atrioventricular node Decreases the force of atrial contraction and possibly ventricular contraction
M_3	Smooth muscle Endocrine/exocrine glands Iris	Bronchospasm Mild vasodilation Increases saliva and gastric acid production Constricts the pupil
M_4	CNS	Multiple actions
M_5	Has not been elucidated	

a misnomer. A more accurate term is *antimuscarinic* agents, because anticholinergic agents do not antagonize effects at nicotinic acetylcholine receptors such as those at the neuromuscular junction. Clinical manifestations from these drugs are modulated through disturbances in the CNS (central effects) and the parasympathetic nervous system (peripheral effects) (**Table 202-3**).

The signs and symptoms of anticholinergic toxicity are a result of both central and peripheral cholinergic blockade. The *central anticholinergic syndrome* refers to the clinical state when there is predomination of the central effects (fever, agitation, delirium, coma) of muscarinic receptor antagonism. The *peripheral anticholinergic syndrome* refers to peripheral muscarinic antagonism's constellation of findings: tachycardia, flushed dry skin, dry mouth, ileus, and urinary retention.

TABLE 202-3 Muscarinic and Antimuscarinic Effects

Organ	Stimulation or Muscarinic Effect	Antagonism or Antimuscarinic Effect
Brain	Complex interactions Possible improvement in memory	Complex interactions Impairs memory Produces agitation, delirium, and hallucinations Fever
Eye	↓ Pupil size (miosis) ↓ Intraocular pressure ↑ Tear production	↑ Pupil size (mydriasis) ↑ Intraocular pressure Loss of accommodation (blurred vision)
Mouth	↑ Saliva production	↓ Saliva production Dry mucous membranes
Lungs	Bronchospasm ↑ Bronchial secretions	Bronchodilation
Heart	↓ Heart rate Slows atrioventricular conduction	↑ Heart rate Enhances atrioventricular conduction
Peripheral vasculature	Vasodilation (modest)	Vasoconstriction (very modest)
GI	↑ Motility ↑ Gastric acid production Produces emesis	↓ Motility ↓ Gastric acid production
Urinary	Stimulates bladder contraction and expulsion of urine	↓ Bladder activity Promotes urinary retention
Skin	↑ Sweat production	↓ Sweat production (dry skin) Cutaneous vasodilation (flushed appearance)

The full range of clinical manifestations associated with anticholinergic overdose may be only partly explained by muscarinic receptor blockade. Many of these anticholinergic agents possess activity at other cell membrane receptors, and toxicity after overdose can be a mixture of pharmacologic mechanisms. For example, the clinical findings associated with cyclic antidepressant overdose are only partly characterized by anticholinergic effects that vary considerably among different cyclic antidepressants. The most life-threatening complications of cyclic antidepressant overdose do not result from anticholinergic effects, but are rather a result of myocardial sodium channel–blocking effects and wide-complex tachydysrhythmias.

IV injection of antihistamines, particularly of those (e.g., diphenhydramine) affecting H_1 histamine receptor antagonists, seems to cause euphoria in some patients; this translates to abuse potential. The effect may be attributed to the drug's increasing dopamine levels in the brain's nucleus accumbens area (which stimulates the reward and motivation system).[23]

CLINICAL FEATURES

The classic features of the anticholinergic toxidrome can be stated as:

- **Dry as a bone**
- **Red as a beet**
- **Hot as a hare**
- **Blind as a bat**
- **Mad as a hatter**
- **Stuffed as a pipe**

Dry skin (especially dry axillae) and dry mucous membranes (e.g., dry mouth) are the typical peripheral clinical manifestations, the result of impaired sweat gland and salivary gland secretions, respectively. The skin may be warm and flushed (red) from cutaneous vasodilatation. Other typical peripheral features of muscarinic blockade include hypoactive or absent bowel sounds secondary to decreased peristalsis and GI motility. A palpable bladder or enlargement on bedside US secondary to urinary retention may be seen.

Sinus tachycardia is usually present. More malignant dysrhythmias are less common. Ingestions of large amounts of diphenhydramine have been associated with wide-complex tachydysrhythmias from a sodium channel–blocking effect (not from an anticholinergic effect).[24,25] Diphenhydramine overdose has been reported to cause QT-interval prolongation.[26,27] Dilated pupils are often a delayed clinical finding (12 to 24 hours) that may not be observed despite the presence of other anticholinergic signs.

The **delirium** of the central anticholinergic syndrome is characterized by restlessness, irritability, disorientation, confusion, agitation, auditory and visual hallucinations, and incoherent speech. The anticholinergic toxic patient has great difficulty interacting appropriately with environmental stimuli. Lilliputian ("little people") hallucinations have been described in this setting. Repetitive picking at the bed clothes or imaginary objects is also characteristic. A characteristic feature of anticholinergic delirium is dysarthria, manifested by a staccato speech pattern and difficult-to-comprehend speech. This may be exacerbated by severe dysphasia from decreased mucous secretion. High-pitched cries may sometimes be heard. Patients may also exhibit jerking movements of the extremities and seizures.

Although this delirium is usually accompanied by the peripheral manifestations discussed earlier, clinical presentations vary. Tachycardia without delirium or delirium without tachycardia may occur. "Agitated depression" can occur from both central excitation and depression. Depression is usually associated with higher doses; features include lethargy, somnolence, and coma. Overdose with olanzapine, an atypical antipsychotic with significant anticholinergic properties, produces unpredictable mental status fluctuations that can range from somnolence to agitation lasting for hours.[28]

Agitation-induced hyperthermia is a worrisome complication of anticholinergic toxicity, and its development may be significantly potentiated by decreased sweating, movement, and the inability to dissipate heat. A markedly elevated body temperature may lead to multisystem organ dysfunction and rhabdomyolysis, resulting in coagulopathy as well as liver, kidney, and brain injury. Fatalities associated with anticholinergic overdose are characterized by severe agitation, status epilepticus, hyperthermia, wide-complex tachydysrhythmias (usually from sodium channel–blocker effect), and cardiovascular collapse.[29]

The risk of toxicity for most anticholinergic agents is typically dose related. For example, severity of diphenhydramine overdose correlates with the amount ingested, with moderate symptoms occurring after ingestion of 300 milligrams[30] and 7.5 milligrams/kg in children,[31] and severe symptoms seen only after ingestions of 1000 milligrams or more in adults.[30]

DIAGNOSIS

DRUG SCREENING

In patients with altered mental status, obtain routine laboratory evaluation, including measurement of electrolytes, glucose, creatine kinase, and pulse oximetry. In most cases of isolated anticholinergic toxicity, these tests should be normal. Limited urine drugs-of-abuse screening generally does not detect anticholinergic agents, although some rapid screens may produce positive results for cyclic antidepressants due to the structural similarities of some anticholinergic compounds, particularly diphenhydramine and hydroxyzine. Comprehensive urine drug screens, usually performed by thin layer chromatography or mass spectrometry, may detect most antihistamines and phenothiazines, although such testing does not usually detect plant alkaloids, scopolamine, or atropine and, in general, is cost prohibitive and insufficiently timely to assist in care. A positive drug screen for an anticholinergic agent only indicates exposure, such as a therapeutic dose, and does not necessarily imply an overdose or supratherapeutic ingestion.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anticholinergic toxicity includes life-threatening presentations such as viral encephalitis, Reye's syndrome, head trauma, alcohol and sedative-hypnotic withdrawal, postictal state, other intoxications, neuroleptic malignant syndrome, and acute psychotic disorders. The difference between anticholinergic toxicity and sympathomimetic toxicity (e.g., cocaine toxicity, delirium tremens) can be subtle, because patients with either may develop tachycardia, mydriasis, and delirium. The presence of red dry skin and the absence of bowel sounds suggest anticholinergic poisoning.[32] At times, patients presenting with acute psychotic disorders may have an abnormal mental status, suggesting anticholinergic toxicity, but true delirium and attention deficits are much more characteristic of the latter condition. Other CNS disorders, such as viral encephalitis, may also affect cholinergic outflow and produce similar anticholinergic clinical signs not related to a toxic exposure.[33]

TREATMENT

Treatment of anticholinergic toxicity primarily includes observation, monitoring, and supportive care (**Table 202-4**). Temperature monitoring and treatment of hyperthermia are essential. GI decontamination with activated charcoal may be warranted to decrease absorption if the ingestion occurred within 1 hour of presentation. Although the benefit of activated charcoal is equivocal after 1 hour from ingestion, the decreased gut motility associated with anticholinergic ingestions may warrant charcoal administration beyond this 1-hour window.[34-36] Multidose activated charcoal is not recommended in patients with impaired GI motility, such as occurs with anticholinergic toxicity.[37] Ipecac syrup, which has no indication in any overdose patient, is contraindicated in anticholinergic toxicity.[31,38] A rare case of pharmacobezoar has been reported with diphenhydramine overdose; this should be a consideration if the toxidrome continues longer than expected.[39]

TABLE 202-4 Treatment of Anticholinergic Toxicity

Action	Agent	Comments
GI decontamination	Activated charcoal	May be more effective due to the decreased GI motility
Sedation	Benzodiazepines	Decreases the risk of hyperthermia, rhabdomyolysis, and traumatic injuries
Wide-complex tachyarrhythmias	Sodium bicarbonate	Arrhythmia due to sodium channel blockade; avoid class IA antiarrhythmics (procainamide)
Cholinesterase inhibition	Physostigmine	Use for cases of severe agitation or delirium; avoid when cardiac conduction abnormalities are present (see "Treatment" section)

The major therapeutic challenge in the treatment of moderate to severe anticholinergic poisoning involves obtaining adequate control of the agitated individual. Inadequate sedation may lead to worsening or prolonged hyperthermia, rhabdomyolysis, and traumatic injury. Although physical restraints may be required to gain initial control, **pharmacologic sedation is strongly recommended**, because prolonged use of physical restraints in the struggling and agitated patient may lead to further complications.

Pharmacologic sedation should begin with IV administration of a benzodiazepine, such as lorazepam or diazepam. Benzodiazepines are not a specific antidote, and some patients may be refractory to large doses. Phenothiazines should be avoided because of their own anticholinergic effects. In severe cases of agitation when adequate sedation cannot be achieved without impairing respiration, mechanical ventilation and deep sedation may be necessary.

IV sodium bicarbonate should be used to treat wide-complex tachydysrhythmias.[24,25] Class IA antiarrhythmic agents should be avoided because of their own sodium channel blockade properties.

Physostigmine is a reversible acetylcholinesterase inhibitor (mechanistically related to the carbamate insecticides) that crosses the blood–brain barrier due to its lipophilic tertiary ammonium properties. Acetylcholinesterase inhibition results in acetylcholine accumulation that reverses both central and peripheral anticholinergic effects. Using physostigmine to reverse anticholinergic toxicity is controversial.[40,41]

The major adverse effects of physostigmine—profound bradycardia and seizures—were historically touted as common, but evidence for this belief is lacking.[42] Importantly, **the risk of these adverse effects appears greater in patients without anticholinergic toxicity, so accurate diagnosis of anticholinergic toxicity is important before administering physostigmine.**[41,42]

Evidence for benefits of physostigmine in anticholinergic toxicity is mixed. Retrospective analysis of 52 patients[43] and case reports[44-46] found that physostigmine was significantly better in controlling agitation and reversing delirium compared with benzodiazepines and was associated with fewer complications and a shorter recovery time. There was no difference in adverse effects between the two groups. Conversely, a different case series did not find that physostigmine use reduced complications or shortened length of stay in 17 patients with severe agitation and delirium after Jimson weed ingestion.[47] However, no adverse effects or complications were observed from physostigmine use.

Physostigmine can be used in cases of severe agitation and delirium from pure anticholinergic toxicity, especially in cases necessitating physical restraints and manifesting resistance to benzodiazepines.[48] The adult dose of physostigmine is 0.5 to 2 milligrams (pediatric dose is 0.02 milligram/kg with a maximum dose of 2 milligrams) by slow IV administration over 5 minutes. When physostigmine is effective, a significant decrease in agitation should be apparent within 15 to 20 minutes. Provide continuous cardiac monitoring before and during administration of physostigmine to assess for potential bradycardia. Monitor the patient for signs of cholinergic excess, such as diarrhea, urination, miosis, bradycardia, bronchospasm, bronchorrhea, emesis, lacrimation, and salivation. **In cases of uncertain anticholinergic poisoning, a diagnostic challenge with physostigmine is *not* recommended because**

of the small but increased risk of adverse effects in patients *without* anticholinergic toxicity.[41,42]

Physostigmine may be repeated in the same dose if required. Patients who remain asymptomatic for more than 6 hours after the first dose of physostigmine will not require repeat physostigmine dosing.[49] Contraindications to physostigmine use include asthma, nonpharmacologically mediated intestinal or bladder obstruction, cardiac conduction disturbances, and suspected concomitant sodium channel antagonist poisoning.

DISPOSITION AND FOLLOW-UP

Patients with mild symptoms of anticholinergic toxicity that resolve after 6 hours of ED observation may be medically cleared. Because the duration of action of physostigmine is generally shorter than the duration of action of many anticholinergic agents, the reversal effect may dissipate, resulting in recurrent toxicity.

Patients with more than mild symptoms, as well as those who have received physostigmine, require hospital observation until symptoms resolve or approximately 12 hours after the last dose of physostigmine.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 203

Metals and Metalloids

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Lewis S. Nelson

INTRODUCTION

Acute metal and metalloid toxicity can cause significant morbidity and mortality if unrecognized and inappropriately treated. **Metals** are chemical elements that possess three general properties: (1) they are a good conductor of heat and electricity, (2) they are able to form cations, and (3) they can combine with nonmetals through ionic bonds. The terms *heavy metal* and *toxic metals* have a historical tradition in clinical medicine, but lack precise definition and scientific merit. In order of ascending atomic weight, the following metals are toxic to humans: beryllium, vanadium, cadmium, barium, osmium, mercury, thallium, and lead. **Lead and mercury produce the most clinically significant cases of human metal poisoning**.

Metalloids are chemical elements with properties intermediate to those of metals and nonmetals. Although there is no precise definition, metalloids tend to have these two general properties: (1) they are semiconductors of electricity, and (2) they form amphoteric oxides. In order of ascending atomic weight, the following metalloids are considered toxic to humans: boron, silicon, germanium, arsenic, antimony, tellurium, and polonium, with **arsenic being the most clinically significant toxic metalloid**.

Exposure to either metals or nonmetals can be from (1) the pure element, (2) an organic compound containing the toxic element (defined as those compounds that contain carbon), or (3) an inorganic compound containing the element (defined as those that do not contain carbon). Depending on the metal or metalloid, potential toxicity is affected by which chemical form is responsible for the exposure.

Because of their effects on numerous enzymatic systems in the body, patients with metal or metalloid poisoning often present with protean manifestations primarily affecting five systems: neurologic, cardiovascular, GI, hematologic, and renal. Effects on the endocrine and reproductive systems are less clinically apparent. **It is important to recognize an initial "index case" of metal poisoning to prevent others from being exposed or poisoned (Table 203-1)**.

TABLE 203-1 Sources of Lead, Arsenic, and Mercury Exposure

Element	Source
Lead	
Elemental, inorganic	Soldering; battery burning/reclamation; bronzing; brass-making; glassmaking; ingesting ceramic lead glaze; stripping old paint; lead abatement; "moonshine"; liquids in improperly glazed pottery; contaminated herbal medications and cosmetics; indoor shooting ranges; ingestion of paint chips, lead-laden floor dust, lead foreign bodies; lead bullets in abdomen or joint spaces; contaminated municipal water supplies Workers at risk: jewelers, painters, lead smelters, stained glass designers, pipe cutters, pigment makers, printers, welders, pottery makers, radiator repair personnel, battery reclamation workers, construction workers
Organic	Leaded gasoline (tetraethyl lead) [no longer legally produced]
Arsenic	
Inorganic (arsenite [trivalent] or arsenate [pentavalent])	Insecticides, rodenticides, herbicides, mining, smelting/refining, Ayurvedic and homeopathic medicines, well water contaminated by leaching mineral ores and/or industrial waste; wood preservatives
Organic	Seafood, parasitical medicines
Gas (arsine)	Mining smelting/refining, semiconductor industry; made by mixing acids with arsenic-containing insecticides
Mercury	
Elemental	Battery and thermometer manufacture; sphygmomanometer repair; dentistry; jewelry and lamp manufacture; photography; mercury mining; manufacture of scientific instruments
Inorganic (mercury salts)	Cosmetic products, especially skin-lightening products; taxidermy; fur processing; tannery work; chemical laboratories; manufacture of explosives, fireworks, disinfectants, button batteries, inks, and vinyl chloride
Organic (methyl mercury, ethyl mercury, and phenyl mercury)	Contaminated seafood; embalming; manufacture of drugs, fungicides, bactericides; handling of insecticides; pesticides, coated seeds; use of chlor-alkali process

LEAD

EPIDEMIOLOGY

Lead is the most common cause of chronic metal poisoning and remains a major environmental contaminant, especially in developing countries. Exposure to lead can occur from inhalation or ingestion, and both inorganic and organic forms of lead produce clinical toxicity. Nonpaint sources include foreign medications, herbal and dietary supplements, Ayurvedic medications, traditional remedies, metallic charms, and cosmetics, especially products from Asia and Africa.[1]

Chronic lead exposure and toxicity in children is considered a public health concern because of the potential impact on intellectual development.[2] Most industrialized countries have banned lead in household paints, gasoline, plumbing systems, food, and drink cans; created lead abatement programs; and enforced standards for industrial use of lead.[2-4] In the United States, continued lead exposure is associated with residence in urban dwellings, residence in dwellings built before 1974 (especially before 1946), poverty, non-Hispanic black race or ethnicity, and higher population density.[5,6] The town of Flint, Michigan, became the focus of national attention in 2014 when a change in water supply resulted in a 5% incidence of elevated blood lead levels in children <6 years old from a prior baseline of 3.1%.[7]

Elevated lead levels in children are common in low-income countries where substandard or marginal living conditions exist near landfills and industries such as smelters, mines, and refineries.[2,5] In developing countries, informal recycling of used lead-acid batteries and processing of gold ore rich in lead have caused mass lead poisonings.[8,9]

PHARMACOLOGY

Absorption of inorganic lead is usually via the respiratory and GI tracts; skin absorption is negligible. Dietary deficiencies in calcium, iron, copper, and zinc may contribute to increased GI absorption in children. Absorption of lead from bullets or shot lodged in bone or muscle is typically minimal, but increased absorption and toxicity have been reported when these are in contact with body fluids, such as synovial fluid or cerebrospinal fluid. Absorption of organic lead, such as tetraethyl lead from "leaded gasoline," can occur after inhalation, ingestion, and dermal exposure. After absorption, tetraethyl lead is metabolized to inorganic lead and triethyl lead; the latter is responsible for the acute neurotoxicity from leaded gasoline.

Greater than 90% of the total body lead is stored in bone, where it easily exchanges with the blood. Lead can be transferred across the placenta, a process exacerbated by increased bone turnover during pregnancy. Excretion of lead occurs slowly; the biologic half-life of lead in bone has been estimated to be 30 years.

PATHOPHYSIOLOGY

Lead toxicity primarily affects the nervous, cardiovascular, hematopoietic, and renal systems. Toxic effects of lead in the CNS include (1) injuries to astrocytes, with secondary damage to the microvasculature and resultant disruption of the blood–brain barrier, cerebral edema, and increased intracranial pressure; (2) decreases in cyclic adenosine monophosphate and protein phosphorylation, which contribute to memory and learning deficits; and (3) alteration with calcium homeostasis, which leads to spontaneous and uncontrolled neurotransmitter release.[10] In the peripheral nervous system, lead causes primary segmental demyelination, followed by secondary axonal degeneration, mostly of the motor nerves.[11]

In the cardiovascular system, increases in the prevalence of hypertension and atherosclerotic vascular disease are found in individuals with elevated blood lead levels. Worldwide, it is estimated that chronic lead toxicity contributes to 2.5% of ischemic heart disease and 3.1% of stroke.[12]

In the hematopoietic system, lead interferes with porphyrin metabolism, which contributes to lead-induced anemia. Coexisting iron deficiency may act synergistically with lead toxicity to produce a more profound anemia. Hemolytic anemia also occurs as a result of inhibition of red blood cell pyrimidine 5′-nucleotidase, an enzyme responsible for clearing cellular RNA degradation products.

In the kidney, lead affects the proximal tubule, producing Fanconi's syndrome with aminoaciduria, glycosuria, phosphaturia, and renal tubular acidosis.[13] Chronic interstitial nephritis and increased uric acid levels are due to increased tubular reabsorption of urate. Chronic lead toxicity has been linked to gout and chronic renal failure.

Lead adversely affects osteoblast and osteoclast function in bone. With chronic lead exposure, increased calcium deposition at growth plates may be seen as "**lead lines**" on radiographs of long bones. Lead-induced adverse effects on the reproductive system include increased fetal demise, premature rupture of membranes, depressed sperm counts, abnormal or nonmotile sperm, and sterility.

CLINICAL FEATURES

Signs and symptoms of lead poisoning vary according to the type of exposure (acute vs. chronic) and, to a lesser extent, according to the age of the individual and type of lead (inorganic vs. organic) involved (**Table 203-2**). Young children are more susceptible than adults to the CNS effects of lead. Delayed cognitive development can occur in infants and children whose blood lead levels are 5 micrograms/dL (0.24 micromol/L) or higher.[14] Encephalopathy due to lead poisoning typically occurs in toddlers age 15 to 30 months old with blood lead levels >100 micrograms/dL (4.8 micromol/L), but may occur with lower blood lead levels. Encephalopathy may begin dramatically with seizures or coma or may develop indolently over weeks to months with decreased alertness and memory progressing to delirium.[15]

GI and hematologic manifestations occur more frequently with acute than with chronic poisoning, and the colicky abdominal pains may be associated with concurrent hemolysis. Patients may complain of a metallic taste and, with long-term exposure, have bluish-gray gingival lead lines. Lead poisoning also causes constitutional symptoms, including arthralgias, generalized weakness, and weight loss. Conversely, adult and pediatric patients may appear asymptomatic in the face of significantly elevated blood lead levels.

TABLE 203-2 Clinical Features of Lead Poisoning

System	Clinical Manifestations
CNS	Acute toxicity: encephalopathy, seizures, altered mental status, papilledema, optic neuritis, ataxia Chronic toxicity: headache, irritability, depression, fatigue, mood and behavioral changes, memory deficit, sleep disturbance
Peripheral nervous system	Paresthesias, motor weakness (classic is wrist drop), depressed or absent deep tendon reflexes, sensory function intact
GI	Abdominal pain (mostly with acute poisoning), constipation, diarrhea, toxic hepatitis
Renal	Acute toxicity: Fanconi's syndrome (renal tubular acidosis with aminoaciduria, glucosuria, and phosphaturia) Chronic toxicity: interstitial nephritis, renal insufficiency, hypertension, gout
Hematologic	Hypoproliferative and/or hemolytic anemia; basophilic stippling (nonspecific)
Reproductive	Decreased libido, impotence, sterility, abortions, premature births, decreased or abnormal sperm production

With organic lead poisoning, neurologic abnormalities predominate. Findings range from behavioral changes, with irritability, insomnia, restlessness, and nausea and vomiting, to tremor, chorea, convulsions, and mania.

DIAGNOSIS

A detailed history, including potential occupational, environmental, travel-related, or recreational exposures, is the most important part in making a diagnosis of lead toxicity. Focus on clinical findings, the age of the home as well as any remodeling, and work, school, or day care locale. Ask adults about medication, dietary supplements, cosmetics, and hobbies and evaluate children who may be secondarily exposed to lead from adult activities. Additionally, screen children for abnormal development and the presence of pica or excessive hand-to-mouth behavior. Toxicity due to retained lead bullets may manifest several decades after being shot. Hyperthyroidism, pregnancy, fever, reinjury, or immobilization of the affected extremity can promote lead release from these retained objects after years of dormancy. **The combination of abdominal pain or neurologic dysfunction with anemia should raise suspicion for lead toxicity. Consider the diagnosis in all children presenting with acute encephalopathy.**

The definitive diagnosis of lead poisoning rests on finding an elevated blood lead level. Fingerstick capillary blood may be used as screening, but results maybe be misleading due to the potential for environmental lead contamination. Elevated concentrations always should be confirmed using a venous blood sample.[16] The reference value for an elevated blood lead level per the Centers for Disease Control and Prevention has decreased from 60 micrograms/dL (2.88 micromol/L) in the 1960s to its current value of 5 micrograms/dL (0.24 micromol/L).[3,17]

Although it is important to order a blood lead level for confirmatory diagnosis and assistance in monitoring therapy, the laboratory turnaround time for results may be days. **Diagnostic studies in the ED should therefore focus on evaluation for anemia and examination of radiographs for evidence of lead exposure.**

The anemia from lead toxicity can be normocytic or microcytic, with or without evidence of hemolysis. Basophilic stippling in red blood cells from impaired clearing of cellular RNA degradation products is sometimes seen in lead-poisoned patients. This finding is nonspecific for lead poisoning; it is also found in arsenic toxicity, sideroblastic anemia, and

the thalassemias. **Anemia and basophilic stippling occur variably, and their absence does not exclude lead toxicity.**

Following acute or subacute ingestion of lead, abdominal radiographs may show radiopaque material in the GI tract. In children with chronic lead poisoning, radiographs of long bones, especially of the knee, may reveal horizontal, metaphyseal "lead lines," which represent failure of bone remodeling rather than deposition of lead.

The differential diagnosis of lead poisoning includes Wernicke's encephalopathy; withdrawal from ethanol and other sedative-hypnotic drugs; meningitis; encephalitis; human immunodeficiency virus infection; intracerebral hemorrhage; hypoglycemia; severe fluid and electrolyte imbalances; hypoxia; arsenic, thallium, and mercury toxicity; and poisoning with cyclic antidepressants, anticholinergic drugs, ethylene glycol, or carbon monoxide. The abdominal pains of lead poisoning can mimic sickle cell crisis, the hepatic porphyrias, or appendicitis. Chronic lead poisoning can mimic major depression, hypothyroidism, polyneuritis, gout, iron deficiency anemia, and learning disability.

TREATMENT

Patients with appropriate signs and symptoms and an elevated blood lead level are classified as lead poisoned and should be treated.

For acute encephalopathy, provide standard life support measures and treat seizures with benzodiazepines. If lead encephalopathy is suspected, initiate chelation therapy promptly (i.e., in the ED) without waiting for the results of a blood lead level (**Table 203-3**). If abdominal films demonstrate GI foreign bodies consistent with lead, institute whole-bowel irrigation with a polyethylene glycol electrolyte solution. Larger lead bodies, such as fishing sinkers and jewelry, may require endoscopic or surgical removal.

Chelation therapy for lead toxicity uses **dimercaprol** (previously known as *British anti-Lewisite* or *BAL*), **edetate calcium disodium** (sometimes abbreviated *$CaNa_2$-EDTA*), and **succimer** (also known as *dimercaptosuccinic acid* or *DMSA*) (Table 203-3).[18,19] **Penicillamine**, another chelating agent, is not approved by the U.S. Food and Drug Administration for treatment of lead toxicity, but penicillamine is used in Europe for lead poisoning. **The chelation dosing schedules are guided by the blood lead levels, the presence or absence of findings, and the age of the patient.**[20,21] Adverse side effects from chelation therapy are common, and consultation with a medical toxicologist or other lead poisoning expert is recommended to assist in management.

TABLE 203-3 Guidelines for Chelation Therapy in Lead-Poisoned Patients*

Severity and Blood Lead Level	Dose
Encephalopathy	Dimercaprol, 75 milligrams/m^2 (or 4 milligrams/kg) IM every 4 h for 5 d *and* Edetate calcium disodium, 1500 milligrams/m^2 per day via continuous infusion or in 2–4 divided doses IV for 5 d; max 3 grams/d; start 4 h after dimercaprol
Symptomatic and/or severe poisoning Adults: blood lead >100 micrograms/dL (4.8 micromol/L) Children: blood lead >70 micrograms/dL (3.4 micromol/L)	Dimercaprol *and* Edetate calcium disodium (as described above) *or* Edetate calcium disodium (alone) *or* Succimer (as described below)
Asymptomatic Adults: blood lead 70–100 micrograms/dL (3.4–4.8 micromol/L) Children: blood lead 45–69 micrograms/dL (2.2–3.3 micromol/L)	Succimer, 350 milligrams/m^2 (or 10 milligrams/kg) PO every 8 h for 5 d, then every 12 h for 14 d
Asymptomatic Adults: blood lead <70 micrograms/dL (3.4 micromol/L) Children: blood lead <45 micrograms/dL (2.2 micromol/L)	Routine chelation not indicated; remove patient from source of exposure

*General guidelines. Consult with medical toxicologist or regional poison center for specifics and dosing.

Dimercaprol crosses the blood–brain barrier and is indicated when neurotoxicity or high blood lead levels are present. Dimercaprol is administered IM and is typically used with edetate calcium disodium to prevent lead from being transported into the brain. **The diluent for dimercaprol includes peanut oil, and therefore, anticipate an allergic reaction and provide careful monitoring for patients with peanut allergy.** Side effects of dimercaprol include hypertension; fever, pain, and sterile abscess at injection site; nausea; vomiting; diarrhea; abdominal pain; headache; lacrimation; rhinorrhea; and hemolysis in glucose-6-phosphate dehydrogenase–deficient patients. Side effects with dimercaprol are dose dependent and occur in up to 65% of treated patients using recommended doses.

Edetate calcium disodium can be used as a single agent in the treatment of lead toxicity, but because this agent does not cross the blood–brain barrier, dimercaprol should be given before and during the entire course of edetate calcium disodium when there are CNS symptoms. **An important precaution: do not confuse this product with edetate disodium, which is used to treat hypercalcemia.** Side effects from edetate calcium disodium include renal toxicity, dermatitis, headache, fever, chills, and myalgias.

Succimer, an oral analog of dimercaprol, effectively chelates lead. Although succimer does not cross the blood–brain barrier, its use as a sole agent is not associated with exacerbation of lead-induced encephalopathy.[22] Some toxicologists consider succimer the preferred chelator for lead poisoning in all but the most severe cases. Its advantages include oral administration without increasing lead absorption from the GI tract, no serious adverse effects, and minimal chelation of essential metals. Side effects from succimer include nausea, vomiting, diarrhea, abdominal pain, rash, pruritus, sore throat, rhinorrhea, drowsiness, paresthesias, transient elevations in serum transaminases and alkaline phosphatase, thrombocytosis, and eosinophilia.

Chelation was not associated with any increased risk of birth defects in the few published cases, and pregnant women with elevated blood lead levels should be chelated following the same guidelines (Table 203-3).[23] Neonatal blood lead levels may be elevated despite maternal chelation, and neonates may require chelation following birth.

Abdominal colic usually subsides within days after beginning chelation therapy, and other acute manifestations clear within 1 to 16 weeks with therapy. Lead-induced nephropathy may be partly reversible with chelation therapy. Approximately 85% of patients who suffer lead encephalopathy develop permanent central neurologic damage, including seizures, mental retardation in children, and cognitive deficits in adults.

DISPOSITION AND FOLLOW-UP

Removal of the source of lead is the most important action for lead poisoning, and patients should not be returned to the home environment until lead decontamination and abatement measures have been addressed. Family members and coworkers should be evaluated for occult lead toxicity. Hospital admission is recommended for (1) children with symptoms or with a blood lead level >70 micrograms/dL (>3.4 micromol/L), (2) adults with central neurologic symptoms, and (3) patients with suspected lead toxicity when returning to the environment is considered dangerous.

ARSENIC

EPIDEMIOLOGY

Arsenic is a nearly tasteless, odorless metalloid that causes significant acute and chronic toxicity worldwide.[24] Arsenicals are found in a variety of compounds and industries (Table 203-1) and continue to be used as

a means for homicide and suicide. Chronic arsenic toxicity from unsafe drinking water has the potential to threaten the health of millions of people worldwide, particularly in Bangladesh.[25]

Arsenic exists in elemental, inorganic salts, organic salts, and gaseous forms. Elemental and organic forms have limited toxicity, whereas inorganic compounds, including arsenite (trivalent or As^{3+}) and arsenate (pentavalent or As^{5+}), are highly toxic.

PHARMACOLOGY

Arsenic is well absorbed by GI, respiratory, and parenteral routes and may be absorbed through nonintact skin. Due to its water solubility, pentavalent arsenic (arsenate) is more readily absorbed across mucous membranes, such as the GI tract, than is trivalent arsenic (arsenite), which penetrates the skin more readily due to its increased lipid solubility. Within 24 hours, inorganic arsenic redistribution into the liver, kidney, spleen, lung, GI tract, muscle, and nervous tissues occurs, with subsequent integration into hair, nails, and bone. Elimination from the blood is rapid, and excretion is predominantly renal. Toxicity of the various forms is partly determined by excretory rates, with the more toxic arsenite being excreted at a slower rate than arsenate or the organic arsenical compounds. Arsenic crosses the placenta and is teratogenic in animals and humans.

PATHOPHYSIOLOGY

Arsenic reversibly binds with sulfhydryl groups found in many tissues and enzyme systems. Acute exposure produces dilatation and increased permeability of small blood vessels, resulting in GI mucosal and submucosal inflammation and necrosis, cerebral edema and hemorrhage, myocardial tissue destruction, and fatty degeneration of the liver and kidneys. Subacute or chronic exposure can cause a primary peripheral axonal neuropathy with secondary demyelination. Inhaled arsine attaches to sulfhydryl groups of hemoglobin, producing an acute hemolytic anemia with resulting jaundice, abdominal pain, and hemoglobinuria-induced acute renal failure.[26]

CLINICAL FEATURES

The signs and symptoms of toxicity vary with the form, amount, and concentration ingested and the rates of absorption and excretion of the various arsenical compounds (**Table 203-4**).

Following ingestion of inorganic arsenic, clinical effects usually develop within minutes to hours of ingestion. Severe gastroenteritis with nausea, vomiting, and cholera-like diarrhea is the hallmark of acute poisoning and may last several days to weeks, frequently necessitating hospitalization. Patients may complain of a metallic taste. Hypotension and tachycardia secondary to volume depletion, capillary leak, and myocardial dysfunction occur in moderate to severe cases. The ECG may demonstrate nonspecific ST-segment and T-wave changes with a prolonged QT interval, although these findings are more common in chronic intoxication. Ventricular tachycardia with a torsades de pointes morphology may occur.[27] Acute encephalopathy, acute respiratory distress syndrome, acute kidney injury, and rhabdomyolysis may ensue.

Survivors of acute poisonings and patients who are poisoned slowly may develop subacute toxicity, typically presenting with weakness, muscle aches, abdominal pain, memory loss, personality changes, periorbital and extremity edema, or skin rash, often with a history of gastroenteritis occurring 1 to 6 weeks earlier.[28] Central neurologic symptoms include headache, confusion, delirium, and personality changes, which may become chronic. Peripheral neuropathy develops in a stocking-glove distribution and is initially sensory, with motor symptoms developing later. Rarely, an ascending paralysis mimicking Guillain-Barré syndrome may develop. Dermatologic manifestations vary and include morbilliform rash, alopecia, and desquamation. **Mees lines** (1- to 2-mm–wide transverse white lines in the nails) due to disrupted keratinization of the nail matrix may be seen 4 to 6 weeks after an acute exposure.

Chronic toxicity from arsenic occurs with ongoing low-level occupational or environmental exposure and has been linked to the development of hypertension, peripheral vascular disease, diabetes mellitus, epidermoid cancer, respiratory tract cancer, hepatic angiosarcoma, and, possibly, leukemia. Dermatologic findings are prominent and include hyperpigmentation, hyperkeratosis of the palms and soles, Bowen's disease, and squamous and basal cell carcinomas. Perforation of the nasal septum has been found in workers exposed occupationally to arsenic.

TABLE 203-4 Clinical Features of Inorganic Arsenic Toxicity

Onset of Symptoms	Clinical Features
Acute toxicity (10 min to several hours)	GI: nausea, vomiting, cholera-like diarrhea Cardiovascular: hypotension; tachycardia; dysrhythmias, including torsades de pointes; secondary myocardial ischemia Pulmonary: acute respiratory distress syndrome Renal: acute renal failure Central neurologic: encephalopathy
Subacute toxicity (1–3 wk after acute exposure or with chronic exposure)	Central neurologic: headache, confusion, delirium, personality changes Peripheral neurologic: sensory and motor neuropathy Cardiovascular: QT interval prolongation Pulmonary: cough, alveolar infiltrates Dermatologic: rash, alopecia, Mees lines
Chronic toxicity (ongoing low-level occupational or environmental exposure)	Dermatologic: hyperpigmentation, keratoses, Bowen's disease, squamous and basal cell carcinoma Cardiovascular: hypertension, peripheral arterial disease Endocrine: diabetes mellitus Oncologic: lung and skin cancer

DIAGNOSIS

The diagnosis is easily missed without a history of exposure to arsenic, and physicians rarely encounter arsenic toxicity. **Consider acute arsenic poisoning in a patient with hypotension that was preceded by severe gastroenteritis with no apparent explanation**. Chronic arsenic toxicity should be considered in a patient with a peripheral neuropathy, typical skin manifestations, or recurrent bouts of unexplained gastroenteritis.

An abdominal radiograph may demonstrate intestinal radiopaque metallic flecks following ingestion. The ECG often reveals a prolonged QT interval, especially in subacute poisoning. The CBC may reveal a normocytic, normochromic, or megaloblastic anemia, and/or a thrombocytopenia. The WBC count may be elevated in acute toxicity and decreased in chronic toxicity. A relative eosinophilia and red cell basophilic stippling may be observed. Elevated reticulocyte counts are found in cases with a component of hemolytic anemia.

Definitive diagnosis of acute poisoning is made by finding elevated arsenic levels in a 24-hour urine collection. All urinary measurements of metals should be collected in metal-free containers after a 5-day seafood-free diet (there is a large amount of organic arsenic in seafood). Normal urinary arsenic level is <50 micrograms/L (0.67 micromol/L), and total urinary arsenic excretion in an unexposed patient typically does not exceed 100 micrograms/d (1.3 micromol/d). If the baseline urinary level is within normal limits and arsenic intoxication is still suspected, hair and nail clippings should be harvested for laboratory analysis. **Due to the rapid distribution of arsenic in tissues, blood arsenic levels are often unreliable.**

Include arsenic toxicity in the differential diagnosis for shock of unknown cause, encephalopathy, peripheral neuropathy (including Guillain-Barré syndrome), Addison's disease, hypo- and hyperthyroidism, patients with the previously mentioned dermatologic manifestations, Korsakoff's syndrome, persistent gastroenteritis and/or cholera-like diarrhea, porphyria, other metal toxicities such as thallium and mercury, and unexplained, prolonged malaise and weakness.

TREATMENT

Acute arsenic toxicity is a life-threatening illness requiring aggressive management. Hypotension and dysrhythmias are the most common causes of death. Hypotension, usually due to volume depletion, should be managed initially with crystalloid volume replacement, and vasopressor therapy with dopamine or norepinephrine may be required. Avoid overhydration because pulmonary and cerebral edema can occur. Ventricular tachycardia and fibrillation may be treated with lidocaine, amiodarone, and electrical defibrillation as necessary. Magnesium sulfate, isoproterenol, and overdrive pacing therapies should be considered for torsades de pointes. Monitor and correct potassium, calcium, and magnesium levels.

Institute gastric lavage with a large-bore orogastric tube for acute ingestion. Activated charcoal poorly adsorbs arsenic but may be effective for co-ingestants. Whole-bowel irrigation should be considered if abdominal radiographs reveal intestinal radiopaque materials consistent with arsenic.

Chelation therapy for arsenic toxicity uses dimercaprol or succimer (**Table 203-5**). Treat patients with acute arsenical poisoning or severe, life-threatening toxicity with dimercaprol until the clinical condition stabilizes and succimer, the less toxic oral chelating agent, can be substituted.[29] **Do not delay chelation in severely ill patients until laboratory confirmation because chelation is most effective when given within minutes to hours of exposure.** Conversely, hold chelation therapy in clinically stable patients with suspected chronic arsenic toxicity pending diagnosis. Chelation with the oral agent succimer may lower the tissue content of arsenic and speed urinary excretion but does not appear to decrease morbidity or mortality in chronic arsenic poisoning.[29] Obtain early consultation with a regional poison control center or medical toxicologist for treatment. For chronic toxicity, prevent further arsenic absorption and, if appropriate, GI decontamination. Dermatologic manifestations of chronic toxicity are unresponsive to chelation.[29]

DISPOSITION AND FOLLOW-UP

Hospitalization is recommended for (1) patients with acute or life-threatening known or suspected arsenic poisoning, (2) chronically poisoned patients requiring dimercaprol therapy, and (3) patients in whom suicidal or homicidal intent is suspected. In patients with acute arsenic poisoning, prognosis may be influenced favorably by the rapid institution of dimercaprol therapy. Recovery from arsenical neuropathy appears to be related more to the initial severity of symptoms than to chelation therapy, although in patients who do recover, dimercaprol appears to significantly shorten the duration of illness. Often, neurologic recovery occurs slowly over months to years.

ARSINE GAS

Arsine is a colorless, nonirritating toxic gas encountered in the semiconductor industry, ore smelting, and refining processes and is produced when arsenic-containing insecticides are mixed with acids.

Arsine gas is highly toxic and extremely flammable. It has a garlic or fishy odor, but there may be no odor detectable with toxic exposure. Exposure is by inhalation. Malaise, dizziness, nausea, and abdominal pain occur within a few hours. Intravascular hemolysis and renal failure then develop. Arsine gas does not cause acute arsenic poisoning. Treatment is supportive, with blood transfusions, exchange transfusion to remove the nondialyzable arsine, and hemodialysis for the acute kidney injury.[30] Chelation therapy has no role in the management of arsine toxicity.

TABLE 203-5 Guidelines for Chelation Therapy in Arsenic-Poisoned Patients

Chelator	Dose
Dimercaprol	3–5 milligrams/kg deep IM every 4 h for 2 d, followed by 3–5 milligrams/kg IM every 6–12 h until able to switch to succimer, up to 10 d total
Succimer	10 milligrams/kg PO every 8 h for 5 d, followed by 10 milligrams/kg PO every 12 h for 14 days; children <5 years old: 350 milligrams/m^2 PO on adult schedule

Note: These are general guidelines. Consult with medical toxicologist or regional poison center for specifics and dosing.

MERCURY

EPIDEMIOLOGY

Mercury occurs in elemental (quicksilver), inorganic, and organic forms. Inorganic mercury compounds are subdivided largely into mercurous (Hg^+) (e.g., mercurous chloride or calomel) and mercuric (Hg^{2+}) salts (e.g., cinnabar or mercuric sulfide). Organic mercurials exist as short- and long-chained alkyl and aryl compounds. The short-chained alkyls, such as methyl mercury and ethyl mercury, are more toxic to humans, with dimethyl mercury being lethal in small amounts. All forms of mercury are toxic but differ in the means of exposure, routes of absorption, constellations of clinical findings, and responses to therapy (Table 203-1).[31]

PHARMACOLOGY

Elemental mercury is absorbed primarily by vapor inhalation or transdermally. For example, attempting to clean up elemental mercury from a broken thermometer with a vacuum causes volatilization due to both the heat and the airflow through the canister. Absorption by the GI tract is usually negligible so that **swallowing elemental mercury contained in a glass thermometer does not produce adverse effects unless the mucosa is damaged**. IM injections of mercury can induce abscess and granuloma formation. IV injections have produced mercury pulmonary and systemic emboli.[32] Elemental mercury crosses the blood–brain barrier, where it is ionized and trapped in the CNS.

Inorganic mercury salts are absorbed primarily through the GI tract, but they may also be slowly absorbed across intact skin.[33] Mercuric salts deposit in the ionized form primarily in the kidney, liver, and spleen. Mercury salts do not enter the CNS in consequential amounts nor do they cross the placenta.

Organic mercury compounds are also primarily absorbed by the GI tract. The highly lipid-soluble short-chained alkyls easily cross membranes, accumulating in red blood cells, the CNS, liver, kidney, and fetus. Longer chained alkyl and the aryl compounds are biotransformed into inorganic mercuric ions in the body; thus, their toxicity more closely resembles inorganic mercury toxicity.

Inorganic and the aryl organic mercurials are eliminated in the urine and feces. The short-chained alkyl compounds are excreted primarily in the bile, where they undergo significant enterohepatic circulation.

PATHOPHYSIOLOGY

Mercury binds with sulfhydryl groups, affecting a diverse number of enzyme and protein systems in the various organs in which they deposit. For example, mercuric salts produce proximal renal tubular necrosis.[31]

CLINICAL FEATURES

The clinical effects of mercury poisoning depend on the form and, in some cases, the route of exposure.[31] In general, the neurologic, GI, and renal systems are predominantly affected.

Elemental Mercury Acute symptoms following inhalation of elemental mercury vapor include shortness of breath, fever/chills, cough, nausea, vomiting, diarrhea, metallic taste, headaches, weakness, and blurry vision. In severe cases, patients may develop acute respiratory distress syndrome. Following metabolism of absorbed elemental mercury to inorganic salts, patients may also develop signs of inorganic mercury toxicity, including tremor and renal failure.

Inorganic Mercury Mercury salts are highly irritating, and an acute ingestion produces a severe hemorrhagic gastroenteritis with abdominal pain often associated with a characteristic graying of the oral mucosa

and metallic taste. Shock and cardiovascular collapse may rapidly ensue. Acute kidney injury results from both direct toxicity of the mercury ions and from decreased renal perfusion due to shock.

GI findings of chronic inorganic mercury toxicity include metallic taste, burning sensation in the mouth, loose teeth, mucosal lesions and fissures, excessive salivation, and nausea. Hallmarks of chronic neurologic toxicity include tremor, neurasthenia, and erethism.[31] *Neurasthenia* is characterized by fatigue, depression, headaches, and difficulty concentrating. *Erethism* refers to behavioral changes characterized by shyness, emotional lability, irritability, insomnia, and delirium. Chronic renal toxicity ranges from reversible proteinuria to the nephrotic syndrome. Acrodynia, also known in small children as *pink disease*, is an immune-mediated reaction to mercury characterized by a generalized rash; edema and erythema of the palms, soles, and face; excessive sweating; fever; irritability; splenomegaly; and generalized hypotonia with particular weakness of the pelvic and pectoral muscles.

Organic Mercury The short-chained alkyl compounds, methyl, dimethyl, and ethyl mercury, have the most devastating effects on the CNS. After a latent period of weeks to months, orofacial paresthesias are a common initial symptom, followed by headache, tremor, and fatigue. In severe cases, patients may develop ataxia, muscle rigidity and spasticity, blindness, hearing deficits, and dementia.[31] Mild GI, renal, and pulmonary abnormalities may develop with organic mercury poisoning.

DIAGNOSIS

An exposure history in either the patient or a household member, along with typical physical findings, especially tremor or those of erethism or acrodynia, suggests mercury poisoning. Ingestion of mercuric chloride can produce a rapidly fatal course and should be considered in a patient presenting with a corrosive gastroenteritis.[34] Often, however, the diagnosis of mercury toxicity is subtle and only made after many other diagnoses have been investigated.

For all forms of mercury, except short-chained alkyls, a 24-hour urinary measurement of mercury should be performed after a 5-day seafood-free diet. A seafood meal (which contains organic mercury) can temporarily elevate the mercury level to the toxic range until the mercury is eliminated. Most unexposed individuals will have 24-hour urine mercury levels <10 to 15 micrograms/L (<0.05 to 0.075 micromol/L). A level >20 micrograms/L (>0.1 micromol/L) may indicate meaningful exposure, but does not diagnose poisoning without an appropriate exposure and clinical syndrome.

Short-chained alkyl mercury compounds are excreted predominantly by the bile, rendering urinary measurements invalid to assess toxicity from these agents. Laboratory diagnosis after this exposure rests on finding elevated whole-blood mercury levels, because these compounds concentrate in erythrocytes. Whole-blood mercury levels are normally <5 micrograms/L (<0.025 micromol/L).

Although elevated blood or urine values are necessary to confirm the diagnosis, levels correlate poorly with toxicity and do not distinguish asymptomatic exposure from mercury poisoning. Furthermore, blood or urine levels do not represent total-body burden. Levels are most useful in confirming exposure and in following the effects of chelation therapy (see following section, "Treatment").

MRI findings in methyl mercury toxicity from ingestion of contaminated seafood include marked atrophy of the visual cortex, cerebellar vermis and hemispheres, and postcentral cortex.[35]

Behavioral changes or tremor similar to those caused by mercury can be seen with hypothyroidism, apathetic hyperthyroidism, metabolic encephalopathy, senile dementia, adverse effects of therapeutic drugs, Parkinson disease, delayed neuropsychiatric sequelae of carbon monoxide poisoning, lacunar infarction, cerebellar degenerative disease or tumor, and ethanol or sedative-hypnotic drug withdrawal. Corrosive gastroenteritis can be caused by iron, arsenic, phosphorus, acids, or alkali ingestion. Cerebral palsy, intrauterine hypoxia, and teratogenic effects of therapeutic and illicit drugs and environmental contaminants should be considered when evaluating an infant thought to be affected in utero by short-chained alkyl mercury compounds.

TREATMENT

General therapeutic measures include removal from exposure and supportive therapy. Hemodialysis does not enhance mercury clearance but may be indicated for treatment of acute kidney injury.

For **elemental mercury**, the severe respiratory failure following inhalation of volatilized elemental mercury or aspiration of elemental mercury may require endotracheal intubation and positive-pressure ventilation.

For ingestion of **inorganic mercury salts**, treat with aggressive IV hydration and GI decontamination, including gastric lavage if the patient has not had significant emesis, and consider activated charcoal unless contraindicated (e.g., bleeding).

For **organic mercury** toxicity, institute gastric decontamination in the setting of acute ingestion, and supportive care. Chelation is indicated if it can be given within several hours after ingestion of mercury salts.[29] Chelation therapy for patients with chronic poisoning, especially to organic mercury, is less effective. A history of significant mercury exposure, signs and symptoms consistent with mercury poisoning, and substantially elevated blood or urine mercury levels may assist in the decision making and help determine duration of treatment for chronic mercury toxicity. Dimercaprol and succimer are Food and Drug Administration approved for mercury poisoning (**Table 203-6**). In Germany, the chelator dimercapto-propane sulfonate is widely used to treat mercury poisoning.[19,31,36]

The chelation regimen is adjusted according to clinical response and development of adverse reactions. Adverse reactions with dimercaprol increase with dose and include nausea, vomiting, headache, paresthesias, and diaphoresis. Fever is frequently seen in children during dimercaprol therapy. The dimercaprol–mercury complex is dialyzable, and hemodialysis may be helpful in patients receiving dimercaprol who have diminished renal function. Plasma exchange transfusion also was beneficial in a case of mercuric chloride ingestion.[34] **Dimercaprol is contraindicated in methyl mercury poisoning due to the potential for exacerbation of central neurologic symptoms.** Succimer is generally well tolerated. Consultation with a poison control center or medical toxicologist is recommended for further assistance with chelation treatment.

DISPOSITION AND FOLLOW-UP

Hospital admission is recommended for (1) patients known or suspected to have ingested mercury salts, (2) patients known or suspected to have inhaled elemental mercury vapor with pulmonary injury, and (3) patients requiring dimercaprol therapy.

Outcome depends on the form of mercury and the severity of toxicity. Mild cases of elemental and mercury salt poisoning and very mild cases of organic mercury toxicity may have complete recovery. Death can occur in severe cases of mercuric chloride poisoning and with

TABLE 203-6 Guidelines for Chelation Therapy in Mercury-Poisoned Patients

	Elemental and Inorganic Mercury	Organic Mercury
Severe acute poisoning	Dimercaprol, 75 milligrams/m^2 (5 milligrams/kg) IM every 4 h for 2 d, followed by 2.5 milligrams/kg IM every 6 h for 2 d, followed by 2.5 milligrams/kg IM every 12–24 h until clinical improvement occurs or until able to switch to succimer therapy, for up to 10 d total	Succimer, 10 milligrams/kg PO every 8 h for 5 d, then every 12 h for 14 d; children <5 years old: 350 milligrams/m^2 orally on adult schedule
Mild acute poisoning and chronic poisoning	Succimer, 10 milligrams/kg PO every 8 h for 5 d, then every 12 h for 14 d	No proven benefit for chelation therapy

Note: These are general guidelines. Consult with medical toxicologist or regional poison center for specifics and dosing.

TABLE 203-7 Source, Manifestations, and Treatments for Patients Poisoned by Less Common Metals

Metal	Poisoning Source	Acute Clinical Manifestations	Chronic Clinical Manifestations	Specific Treatment
Bismuth	Antidiarrheals (bismuth subsalicylate), impregnated surgical packing paste	Abdominal pain, acute renal failure	Myoclonic encephalopathy	Dimercaprol (limited evidence)
Cadmium	Contaminated soil in cadmium-rich areas; alloys used in welding, soldering, jewelry, and batteries	Ingestion: hemorrhagic gastroenteritis Inhalation: pneumonitis, acute respiratory distress syndrome	Proteinuria, osteomalacia (itai-itai or ouch-ouch disease), lung cancer (questionable)	Ingestion: succimer (limited evidence; not generally indicated) Pneumonitis: chelation not indicated
Chromium	Corrosion inhibitors (e.g., heating systems), pigment production, leather tanning, metal finishing, dietary supplements, prosthetic joints	Skin irritation and ulceration, contact dermatitis; GI irritation, renal and pulmonary failure	Mucous membrane irritation, perforation of nasal septum, chronic cough, contact dermatitis, skin ulcers ("chrome holes"), lung cancer	Acetylcysteine (animal studies suggest efficacy as chelator)
Cobalt	"Hard metal dust" (tungsten–cobalt mixture), flexible magnets, drying agents, prosthetic joints	Contact dermatitis, asthma	Metal lung disease (spectrum ranging from alveolitis to fibrosis), cardiomyopathy, thyroid hyperplasia	Acetylcysteine (animal studies suggest efficacy as chelator)
Copper	Leaching from copper pipes and containers; fungicide (copper sulfate); welding (copper oxide)	Ingestion: resembles iron poisoning; blue vomitus (copper salts), hepatotoxicity, hemolysis, methemoglobinemia Inhalation: metal fume fever (self-limited fever, chills, cough, dyspnea)	Hepatotoxicity (childhood cirrhosis or idiopathic copper toxicosis)	Dimercaprol for hepatic or hematologic toxicity Succimer in mild poisoning
Silver	Colloidal (metallic) silver used for medicinal purposes as oral solutions, aerosols, and douches; cauterizing and antiseptic agent (silver nitrate); jewelry, wire	Mucosal irritation (silver oxide and nitrate)	Argyria (permanent skin discoloration due to silver deposition and melanocyte stimulation)	Selenium (possible role)
Thallium	Rodenticides (use prohibited in the United States); contaminated herbal products; medical radioisotope (minuscule dose); most poisonings related to homicide	Early: nausea, vomiting, abdominal pain, tachycardia Intermediate (>24 h): painful ascending neuropathy, cardiac dysrhythmias, altered mental status Delayed (2 wk): alopecia	Sensorimotor neuropathy, psychosis, dermatitis, hepatotoxicity	Multidose activated charcoal Prussian blue, 125 milligrams/kg PO every 12 h (usually dissolved in 50 mL of 15% mannitol)
Zinc	Smelting, electroplating, military smoke bombs, zinc lozenges, welding/galvanizing (zinc oxide)	Ingestion: nausea, vomiting, abdominal pain (resembles iron poisoning) Inhalation: mucosal irritation, metal fume fever (zinc oxide)	Copper deficiency, sideroblastic anemia, neutropenia	Edetate calcium disodium Supportive care for metal fume fever

dimethyl mercury exposure. Most patients with symptomatic organic mercury poisoning are left with residual neurologic deficits. Environmental decontamination and removal of the patient, family members, and coworkers from a site of ongoing contamination play a critical role in preventing injury to others.

OTHER METALS AND METAL SALTS

Other metals and their salts may cause toxicity (**Table 203-7**). Metal salts typically cause early GI irritation (nausea, vomiting, diarrhea, cramping, and hemorrhage) with subsequent neurologic, renal, hematologic, and cutaneous abnormalities. Symptoms are often vague, and without an explicit history of metal salt exposure, patients are usually misdiagnosed.[37] **Metal fume fever** is the clinical syndrome of fever, chills, body ache, headache, and fatigue resulting from inhalation of dust or fumes containing zinc, aluminum, or magnesium oxide.

Treatment universally involves removal of the patient from the source, topical decontamination, administration of activated charcoal (if exposure involves ingestion), and supportive care, including aggressive fluid and electrolyte repletion and hemodialysis, if required. Indications for chelation and its efficacy in treating metal toxicity vary with the specific metal (Table 203-7).[18,19,36,38] Consult with a medical toxicologist or a regional poison control center for specific indications and drug doses.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 204

Industrial Toxins

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Frank LoVecchio

INTRODUCTION

A **hazardous chemical** is defined by the U.S. Occupational Safety and Health Administration as any chemical that has been scientifically shown to be a health hazard (causes acute or chronic health effects) or a physical hazard (e.g., combustible liquid, explosive, flammable). The Occupational Safety and Health Administration estimates that there are 575,000 chemicals in the workplace, with 53,000 being potentially hazardous.[1] Considering that unplanned exposures and contamination can occur at any time during manufacturing, transport, storage, usage, or disposal of these chemicals, inevitably, emergency physicians can expect to occasionally be responsible for the management and care of a hazardous materials patient (see Chapter 5, "Disaster Preparedness").[2]

When managing a patient exposed to an industrial chemical, it is helpful to refer to the Material Safety Data Sheet and adhere to the recommendations regarding decontamination. Although the Material Safety Data Sheet will also include "first aid" recommendations (**Table 204-1**), the provider should also consult with a medical toxicologist or a regional poison control center to discuss case-specific hazards, optimal treatments, and dispositions. Although many exposures produce immediate effects, some agents may result in delayed onset of symptoms that require at least 24 hours of observation (**Table 204-2**).

TABLE 204-1 Agents Absorbed Through Intact Skin That May Result in Systemic Toxicity*

Acrylamide	Methyl bromide
Acrylonitrile, acetonitrile, propionitrile	Methylene chloride (slow)
Aniline	Nerve agents
Chlordane	Nitrates
Dinitrophenol	Nitrobenzene
Hydrocarbons: benzene, gasoline, toluene, xylene (all slowly absorbed)	Pesticides
Hydrogen cyanide, cyanide salts	Phenol
Hydrogen fluoride (hydrofluoric acid)	T2 toxin (biologic)
Metals (organic mercury, thallium)	

*Many toxins may be absorbed through abraded skin.

Children are more sensitive to chemical exposures; higher minute volumes, smaller airway diameters, and lesser ability to clear secretions make them more susceptible to inhaled toxins, and thinner, more permeable skin with a larger body surface-to-mass ratio increases the potential for dermal absorption.[3-5] A pregnant woman should be treated as any other adult patient.[6]

This chapter discusses industrial toxins that produce primarily respiratory toxicity (**Table 204-3**) or metabolic toxicity. Toxic chemicals discussed elsewhere include nerve agents and vesicants (see Chapter 8, "Chemical Disasters"); hydrocarbons (see Chapter 199, "Hydrocarbons and Volatile Substances"); acids and alkalis (see Chapter 200, "Caustic Ingestions"); organophosphates and carbamates (see Chapter 201, "Pesticides"); metals (see Chapter 203, "Metals and Metalloids"); oxidants (see Chapter 207, "Dyshemoglobinemias"); and carbon monoxide (see Chapter 222, "Carbon Monoxide").

TABLE 204-3 Toxic Industrial Exposures That Cause Respiratory Symptoms

Agent	Irritant	Signs/Symptoms/ Findings	Treatment
Phosgene	Mild/none	I—Eye and upper airway irritation; possibly none D—Dyspnea, noncardiogenic pulmonary edema	Supplemental oxygen only if hypoxemic (Sa_{O_2} <92%) Respiratory supportive care Consider nebulized β-agonists Mandatory rest Ocular care
Chlorine	Yes	I—Eye and upper airway irritation, nausea and vomiting (low-level exposure) D—Pulmonary edema (high-level exposure)	Humidified oxygen Respiratory supportive care Consider nebulized β-agonists Consider nebulized sodium bicarbonate Ocular care
Nitrogen dioxide	Yes	I—Dyspnea with transient improvement D—Worsening dyspnea due to pulmonary edema 24–72 h after exposure; methemoglobinemia	Humidified oxygen Respiratory supportive care Consider early corticosteroid treatment
Ammonia	Yes	I—Coughing, hoarseness, bronchospasm, eye and upper airway irritation	Humidified oxygen Consider nebulized β-agonists Consider nebulized anticholinergics Respiratory supportive care Ocular care

Abbreviations: D = delayed; I = immediate; Sa_{O_2} = arterial oxygen saturation.

RESPIRATORY TOXINS

Determinants of airborne agent toxicity primarily include factors such as concentration of the inhaled toxin, duration of exposure, and whether the exposure occurred in an enclosed space (Table 204-3). Other influential factors include vapor density, allergic or nonallergic bronchospastic response, exertional state or metabolic rate of the victim, and unique host susceptibility such as underlying reactive airway disease, history of smoking, or extreme age. Aspiration of gastric contents may cause further pulmonary insult.

General management of the patient with toxic inhalation injury begins with removal from the source and supplemental oxygen for hypoxemia. Irrigate the eyes and skin as appropriate. Toxin-specific treatments are discussed later in this chapter, although in general, inhaled bronchodilators and steroids for bronchospasm may be considered, especially if the patient has underlying reactive airway disease. Prophylactic antibiotics are not indicated.

The physical examination should include inspection of the upper airway for evidence of singed nasal hair, soot in the oropharynx, facial or oropharyngeal burns, stridor, hoarseness, dysphagia, cough, carbonaceous sputum, tachypnea, retractions, accessory muscle use, wheezing, or cyanosis. Copious airway secretions, hypoxia, bronchospasm, and pulmonary edema indicate lower airway injury, and with the potential for sudden deterioration in patients with upper airway injury, there should be a low threshold for endotracheal intubation.

Pertinent laboratory studies include arterial blood gas analysis with carboxyhemoglobin, methemoglobin, and lactate levels; whole-blood cyanide levels if persistent acidosis occurs (although this will not change immediate management); ECG monitoring; and chest radiography. The role for diagnostic or therapeutic bronchoscopy in inhaled toxin exposure is controversial.

TABLE 204-2 Toxins With Delayed Onset of Symptoms or Requiring Prolonged Monitoring

Agent	Potential Delayed Toxicity
Acrylonitrile, acetonitrile, propionitrile	Cyanide toxicity
Aniline	Methemoglobinemia
Arsine	Hemolysis
Ethylene oxide	Pulmonary edema and neurotoxicity
Methyl bromide	Pulmonary edema
Methylene chloride	Carbon monoxide toxicity, dysrhythmias
Phosphine	Pulmonary edema
Zinc phosphide	Pulmonary edema

PHOSGENE

Phosgene was first used as a chemical agent of warfare in World War I, where it was responsible for 80% of all chemical gas fatalities. Phosgene is no longer stockpiled by the U.S. military; however, it has widespread use in manufacturing and industry as a chemical precursor in the production of plastics, pharmaceuticals, dyes, polyurethane, and pesticides.[7,8] The heating of chlorinated fluorocarbons (Freon®) will also form phosgene gas and has caused poisonings in the refrigerator/air conditioner manufacturing and repairing industry.[9]

Phosgene release and contamination can be insidious. The gas is relatively water insoluble and therefore has poor warning properties. Only mild initial eye, nose, throat, and upper airway irritation are expected, and these may be entirely absent.[7] Classically, when released, phosgene forms a white cloud with a characteristic odor of newly mown hay. The major injury is an acid burn to lower airways as phosgene reaches the alveoli and hydrolyzes to carbon dioxide and hydrochloric acid.[10] Acylation of alveolar capillary membranes results in diffuse capillary leak and noncardiogenic pulmonary edema, which may be delayed for up to 24 hours.[10,11]

Symptoms are typically dyspnea and chest tightness. If the exposure is massive, immediate dyspnea and mucous membrane and eye irritation

may occur. The onset of dyspnea or pulmonary edema within 4 hours of exposure suggests a very poor prognosis.[10]

Recovery usually occurs with respiratory supportive care and management of acute lung injury (noncardiogenic pulmonary edema).[12] Do not provide supplemental oxygen until symptoms and signs of hypoxia develop or arterial oxygen saturation falls, and then administer at the lowest fraction of inspired oxygen to maintain arterial oxygen saturation above 94%.[13]

Pharmacologic therapy recommendations, based on case reports and animal models, include early corticosteroids and nebulized β-agonists, nebulized *N*-acetylcysteine, and NSAIDs.[12,14,15]

Exertion increases pulmonary edema from phosgene, so rest is mandatory.[11] If patients require intubation and mechanical ventilation for respiratory failure, a protective ventilation strategy with low tidal volume, low plateau pressures, and high positive end-expiratory pressure should be used.[16,17] Observe and monitor even asymptomatic patients for 24 hours after acute exposure.

CHLORINE

Chlorine is widely available in the industrial sector, in the setting of laboratories, paper manufacturing, swimming pool maintenance, and municipal water treatment.[18-21] Chlorine gas also has potential for use as an unconventional weapon.[22] When dispersed, this dense green-yellow gas has an acrid, pungent odor and, unlike phosgene, has excellent warning properties. Chlorine gas has intermediate water solubility, which is consistent with the observation that moderately exposed World War I soldiers exhibited both central airway damage and pulmonary edema.[23]

Early inflammatory injury results from the formation of hydrochloric and hypochlorous acids and oxidants upon contact with moist membranes.[24] Immediate ocular and upper airway irritation along with nausea and vomiting are common following mild exposures.[18,25,26] More significant exposure results in coughing, hoarseness, and pulmonary edema, usually within 6 hours, with some exposures leading to acute respiratory distress syndrome.[19,27] Severe exposures may produce pulmonary infiltrates or edema visible on radiographs or CT scan.[28]

Care is primarily supportive, with the use of humidified oxygen and bronchodilators as needed.[26] Prophylactic antibiotics are not recommended. Nebulized sodium bicarbonate as a neutralizing therapy may improve pulmonary function during the initial 4 hours of treatment, but the long-term benefits are unproven.[20,29,30] Uncontrolled studies of both parenteral and inhaled steroids show improvement in airway resistance and arterial oxygenation but no improvement in the outcome with severe lung injury.[31] Chlorine causes dermal injury at high concentration, and skin decontamination may be required. In patients with ocular symptoms, the cornea should be evaluated for a chemical burn. A moderately symptomatic patient should be observed for 24 hours, monitoring for delayed onset of respiratory complications.

NITROGEN DIOXIDE

Nitrogen dioxide and other **nitrogen oxides** are encountered in the form of silo gas (**"silo filler disease"**), as products of combustion, in industrial processes, or as components of military blast weapons, smokes, and obscurants.[32,33] These oxides have limited water solubility that results in primarily lower airway toxicity.[34] Initial exposure may produce only very mild initial discomfort, but slow conversion of nitrogen dioxide to nitric acid in the alveoli results in delayed alveolar injury and pulmonary edema.[32,35-37] Thus, a triphasic illness typically is seen with initial dyspnea and flulike symptoms, transient improvement, and then worsening dyspnea, which heralds the onset of pulmonary edema 12 hours after exposure.[33,35,37-39] Treatment is supportive. Case reports describe benefit with early corticosteroid treatment for acute lung injury following nitrogen dioxide exposure,[39] although overall evidence is inconclusive.[31]

AMMONIA

Ammonia is widely available; it is found in household and industrial chemicals and fertilizers and used in the synthesis of plastics and explosives.[40] Ammonia is a highly water-soluble, colorless, alkaline, corrosive gas with a characteristic pungent odor that rapidly reacts with wet surfaces to form ammonium hydroxide. Ammonia has good warning properties due to its odor and immediate symptoms of mucous membrane, eye, and throat irritation. Lower airway involvement resulting in bronchospasm, pulmonary edema, residual reactive airway disease, and even permanent lung injury has been described following massive exposures, especially in those who were entrapped in enclosed spaces.[41]

Treatment is supportive with humidified oxygen and bronchodilators. The use of anticholinergics to control airway secretions has been reported.[42] Concentrated ammonia, such as 8.4% ammonia hydroxide, is hazardous to the eyes, and symptomatic patients should undergo ocular irrigation followed by evaluation for corneal burns.

METABOLIC TOXINS

CYANIDE

Cyanide has an infamous history. It was the agent used by Nazi Germany (Zyklon B) in the gas chambers during the Holocaust, by Jim Jones in the mass cult suicide at the People's Temple in Guyana (commonly called "Jonestown"), for murder in over-the-counter drug-tampering incidents, and at the World Trade Center bombing in 1993.[43,44] Cyanide can be generated through natural and industrial processes and house and structure fires (**Table 204-4**).

PATHOPHYSIOLOGY

Cyanide inhibits many metabolic processes, with its most toxic effect from binding with very high affinity to the ferric ion cytochrome a_3 portion of cytochrome oxidase within the mitochondria, resulting in an abrupt cessation of electron transport and oxidative phosphorylation, thus inhibiting aerobic metabolism.[44] Thus, following an acute exposure, organs and tissues with high oxygen consumption are the first and most severely affected.

Cassava, a tropical root that is the food staple in many countries, contains the cyanogenic glycosides *linamarin* and *lotaustralin* that liberate cyanide when metabolized in the body.[45] Chronic exposure to **dietary cyanide** is linked to tropical ataxic neuropathy and is endemic in countries where cassava consumption is high.[46,47]

The primary mechanism for detoxification of cyanide is its metabolism in the liver by rhodanese to thiocyanate, a nontoxic compound that is renally excreted. Toxicity occurs when this mechanism is rapidly overwhelmed.

CLINICAL FEATURES

Clinical presentation of the cyanide-poisoned patient depends on the cyanide-containing compound, the route, concentration and duration of

TABLE 204-4 Sources of Cyanide

- Burning of: wool, nylon, silk, acrylic, polyurethane, melamine, polyacrylonitrile, polyamide plastics
- Industries: fabrication of plastics, electroplating, mining, photography, precious metal reclamation, solvents, hair removal from hides
- Fumigants and fertilizers
- Vermin extermination: cyanide spread into burrows and dens
- Chemistry laboratories
- Medicinal: laetrile (amygdalin),* sodium nitroprusside
- Plants: seeds from *Prunus* species (apricots, cherries, plums, peaches), cassava, bamboo shoots
- Illicit phencyclidine manufacturing
- Cigarette smoke
- Vehicle exhaust

*No longer available in the United States, but widely available via the Internet and sold outside the United States.

TABLE 204-5 Signs and Symptoms of Acute Cyanide Toxicity

Cardiovascular	
Tachycardia	Mild
Hypertension	↓
Bradycardia	
Hypotension	
Cardiovascular collapse	
Asystole	Severe
CNS	
Headache	Mild
Drowsiness	↓
Seizures	
Coma	Severe
Pulmonary	
Dyspnea	Mild
Tachypnea	↓
Apnea	Severe

exposure, and the time since exposure. The onset of symptoms following inhalational exposure to hydrogen cyanide gas is immediate.[48] Exposure to concentrations <50 parts per million causes restlessness, anxiety, palpitations, dyspnea, and headache.[49] Higher concentrations of hydrogen cyanide gas cause severe dyspnea, loss of consciousness, seizures, and cardiac dysrhythmias. Coma, cardiovascular collapse, and death may occur immediately on exposure to very high levels. The median lethal dose for humans from hydrogen cyanide gas is estimated to be 200 parts per million for a 30-minute exposure and 600 to 700 parts per million for a 5-minute exposure.[49] The onset of symptoms following ingestion of a cyanide salt typically occurs within minutes. The median lethal dose of potassium or sodium cyanide in an untreated adult is estimated at 140 to 250 milligrams, but death has been reported with ingestion of as little as 50 milligrams, and survival has been reported with much larger ingestions when antidotes are used.[49]

The typical seriously poisoned patient has an altered level of consciousness and is hyperventilating, hypotensive, and bradycardic (**Table 204-5**).[43,50] Cutaneous manifestations vary, but, importantly, the patient is not initially cyanotic, as cyanide does not significantly alter the oxygen-carrying capacity of hemoglobin. However, cyanosis does follow if there is significant respiratory compromise or arrest. The smell of **bitter almonds** and a **cherry-red skin color** (attributed to an increased venous hemoglobin oxygen saturation) are often used in describing cyanide poisoning; however, these findings are unreliable and should not be used to exclude cyanide poisoning.[51]

Severe unexplained metabolic acidosis is a consistent clinical feature (Table 204-6).[51] In victims of smoke inhalation, toxic cyanide levels correlate with plasma lactate levels >90 milligrams/dL (>10 mmol/L), independent of the carbon monoxide level.[52] The decision to institute antidotal treatment of cyanide poisoning must be made long before confirmatory laboratory studies can be obtained. Although cyanide levels are not closely correlated with toxicity, they can be used to retrospectively confirm a clinical diagnosis or for forensic purposes. A variety of methods are available to measure cyanide in the environment and in biologic fluids, but whole-blood cyanide level is the most commonly available test.[49]

Symptoms of poisoning are delayed following the ingestion of compounds that require metabolic activation to release free cyanide, such as **acetonitrile**, a solvent sold commercially as a cosmetic nail remover,[53] and **amygdalin** from apricot pits.[54] The slow release of cyanide by the spontaneous degradation of **sodium nitroprusside**, which is increased by exposure to sunlight, also results in delayed toxicity, particularly during prolonged or high-dose infusions.[55]

TREATMENT

Good supportive care with 100% oxygen along with crystalloids and vasopressors for hypotension is paramount.[56] There are multiple

TABLE 204-6 Anticipated Laboratory Findings in Cyanide Poisoning

Test	Result	Cause
Serum electrolytes	Elevated anion gap	Lactic acidosis from anaerobic metabolism
Arterial blood gases	Metabolic acidosis Normal Pa_{O_2}	Oxygenation initially normal
Lactate	>90 milligrams/dL (>10 mmol/L)	Correlates with toxic cyanide level
Measured oxygen saturation by co-oximetry	Normal	Hemoglobin retains normal oxygen-carrying capacity
Measured arterial-mixed venous oxygen difference	Decreased	Decreased tissue oxygen consumption
Whole-blood cyanide level	Toxic >0.5 microgram/mL (>12 mmol/L) Fatal >2.5 micrograms/mL (>60 mmol/L)	Note: plasma cyanide levels are roughly one tenth of the whole-blood cyanide levels
Fire victims	Elevated carboxyhemoglobin level	Carbon monoxide generated by incomplete combustion Synergistic toxicity with cyanide

Abbreviation: Pa_{O_2} = partial pressure of arterial oxygen.

antidotes for cyanide poisoning with variation in regional availability.[50,57-59] The two antidotes most commonly used in the United States are **hydroxocobalamin** (Cyanokit®) and the **cyanide antidote kit** (containing nitrites and thiosulfate). While their efficacy is similar, their mechanisms of action vary greatly and are described in further detail later in this chapter. Due to the production of methemoglobin by the nitrites in the cyanide antidote kit, **hydroxocobalamin should be considered the first-line therapy in cyanide poisoning if exposure involves fire smoke or any other potential source of concomitant carbon monoxide poisoning.**[60-64]

The decision to administer a cyanide antidote is straightforward when faced with a critically ill patient with clear history of cyanide exposure. More difficult management decisions arise in patients with smoke inhalation who may have carbon monoxide exposure as well as suspected cyanide exposure and in patients who are critically ill and acidotic without any known history of cyanide exposure. Consultation with a toxicologist or the regional poison control center is advised. However, there are some cases that should be treated empirically without delay. Patients who have been exposed to smoke and/or fire and present with a Glasgow Coma Scale score of <10 with signs of end-organ damage (i.e., cardiac arrest, seizures, respiratory distress) should be empirically treated with hydroxocobalamin or thiosulfate; a carboxyhemoglobin level >10% and/or lactate level of >8 mmol/L strengthen this decision.[62,65]

Hydroxocobalamin (vitamin B_{12a}) is a metalloprotein with a cobalt center that binds cyanide, removing it from cytochrome oxidase and forming cyanocobalamin, which is then eliminated via the kidneys. The dose of hydroxocobalamin in an adult patient is 5 grams IV over 15 minutes (**Table 204-7**). A second dose of 5 grams IV may be repeated once (for a total of 10 grams) if the patient's condition warrants.[66] The pediatric dose is 70 milligrams/kg (maximum dose of 5 grams) IV over 15 minutes and may be repeated once if the patient's condition warrants.[67] Hydroxocobalamin has a low toxicity profile; side effects include transient hypertension, a reddish discoloration of the skin and mucous membranes,

TABLE 204-7 Treatment of Cyanide Poisoning With Hydroxocobalamin

100% oxygen	
IV crystalloids and vasopressors for hypotension	
+/– Sodium bicarbonate for acidemia	
And	
Hydroxocobalamin	Adults: 5 grams IV over 15 min. If needed, may repeat 5 grams for a total of 10 grams. Children: 70 milligrams/kg (maximum, 5 grams) IV over 15 min. If needed, may repeat once.

TABLE 204-8 Treatment of Cyanide Poisoning With Cyanide Antidote Kit

100% oxygen IV crystalloids and vasopressors for hypotension +/– Sodium bicarbonate for acidemia *And*	
Adults	**Amyl nitrite** inhaler; crack vial and inhale over 30 s.* **Sodium nitrite** 3% solution: 10 mL (300 milligrams) IV given over no less than 5 min.† **Sodium thiosulfate** 25% solution: 50 mL (12.5 grams) IV. Repeat sodium thiosulfate once at half dose (25 mL) if symptoms persist.
Children	**Amyl nitrite** inhaler; crack vial and hold in front of nose for 15–30 s.*† **Sodium nitrite** 3% solution: adjusted according to hemoglobin level, given IV over no less than 5 min† (monitor methemoglobin level <30%).
Hemoglobin (grams/100 mL)	**Sodium Nitrite 3% Solution (mL/kg)**
7	0.19
8	0.22
9	0.25
10	0.27
11	0.30
12	0.33
13	0.36
14	0.39
Sodium thiosulfate 25% solution: 1.65 mL/kg IV. Repeat sodium thiosulfate once at half dose (0.825 mL/kg) if symptoms persist.	

*Not necessary if IV is in place.

†Avoid nitrites in the presence of severe hypotension if diagnosis is unclear or there is potential concomitant carbon monoxide poisoning; use sodium thiosulfate only.

and rare anaphylactic reactions. Due to the discoloration of body fluids caused by hydroxocobalamin, interference with chemistry and co-oximetry tests as well as hemodialysis machines has been reported; therefore, blood samples should be collected prior to administration.[68-71]

The **cyanide antidote kit** has been well established for cyanide poisoning, although its use is declining and it has been removed from the commercial market in some countries.[72-74] The antidotes contained in the cyanide treatment kit include ampules of amyl nitrite for inhalation, 10-mL vials of 3% sodium nitrite (300 milligrams), and 50-mL vials of 25% sodium thiosulfate (12.5 grams) (**Table 204-8**). Treatment of profound acidemia with sodium bicarbonate appears to enhance the effect of the nitrites and thiosulfate.[75]

The rationale for using nitrites is based on their ability to form methemoglobin, which binds cyanide more avidly than the ferric iron of cytochrome oxidase, thus removing cyanide from the cytochrome and enabling the mitochondria to reactivate electron transport and oxidative metabolism.[76] Inhaled amyl nitrite is a temporizing measure when IV access has not been established, but **amyl nitrite is not needed when sodium nitrite can be given IV**. Nitrites do have significant side effects, including hypotension and the development of excessive methemoglobinemia, which will further decrease oxygen delivery with concomitant carbon monoxide poisoning.[57,75,77] However, hypotension is not a contraindication to nitrite therapy in severe cyanide poisoning. In children, the sodium nitrite dose is adjusted according to the hemoglobin level to keep the methemoglobin level less than 30% (Table 204-8).[49,77] If hemoglobin values are not available, the empiric dose of sodium nitrite for a child less than 25 kg is based on the 10-gram hemoglobin concentration.[77]

Sodium thiosulfate, given after the administration of sodium nitrite, enhances the activity of the enzyme rhodanese, which catalyzes the transfer of sulfate from sodium thiosulfate to cyanide to form thiocyanate, a less toxic form that is excreted by the kidneys.[57,72,75] Animal studies using lethal doses of cyanide demonstrate that the therapeutic effects of sodium nitrite and sodium thiosulfate are synergistic.[72,73,75] However, sodium thiosulfate has very limited toxicity in comparison with nitrites and should be used as a sole therapy for victims of cyanide poisoning from inhalation injury if there is a concern for concomitant carbon monoxide exposure if hydroxocobalamin is unavailable.[78,79]

The fetus is sensitive to the adverse effects of methemoglobinemia, so nitrate therapy should be avoided. Animal models have shown that sodium thiosulfate does not cross the placenta and appears to protect the fetus from nitroprusside in cyanide toxicity[80]; if available, it should be considered first in early pregnancy.[62] There are limited data on the safety of hydroxocobalamin in pregnancy, but its benefits outweigh the risk in significant cyanide poisoning and should be administered if it is the only antidote available.[62]

Two other antidotes are available, which are primarily used in Europe. **Dimethylaminophenol** is a rapid methemoglobin inducer developed in Germany for the treatment of cyanide poisoning.[57-59,75] Clinical efficacy is similar to sodium nitrite. The adult dose is 250 milligrams (5 mL of 5% solution) IV over 1 minute, used in combination with sodium thiosulfate. **Dicobalt edetate** is a cobalt compound with a high affinity for cyanide. Although highly effective as a cyanide antidote, the toxicity of dicobalt edetate is greater when cyanide is not present, limiting its use to cases where the presence of cyanide is unequivocal.[43,44,57-59,75] The adult dose for dicobalt edetate is 300 milligrams IV over approximately 1 minute. If there is inadequate clinical response after 5 minutes, a second dose of 300 milligrams IV may be given.

The data on hyperbaric oxygen for treatment of cyanide poisoning are conflicting, because studied patients also received multiple therapies, so improvement cannot be contributed solely to hyperbaric oxygen.[81-83] The lack of supportive evidence and impracticality make hyperbaric oxygen therapy an unproven endeavor in acute cyanide toxicity.

DISPOSITION AND FOLLOW-UP

Patients who receive cyanide antidotal therapy should be admitted for observation. Patients who have ingested a substance that may result in delayed toxicity (up to 6 hours) should also be admitted. Full recovery is anticipated in many cases of severe poisoning in which treatment is initiated rapidly and cardiac arrest has not yet occurred. Recovery despite cardiac arrest also has been reported, but anoxic encephalopathy may ensue.

HYDROGEN SULFIDE

Hydrogen sulfide is a colorless, flammable gas that may be encountered in industries such as oil and gas or as a natural product of organic decomposition, such as sewer or manure gas.[84,85] Hydrogen sulfide can be made by mixing common household products, a method well documented in suicides.[86] Regardless of its source, it is among the most common causes of fatal gas inhalation exposures. Fatal exposures usually occur in enclosed spaces that may claim additional victims as would-be rescuers are poisoned upon entering.[87] Large industrial or natural releases of hydrogen sulfide may produce fatalities in unconfined spaces.[88]

PATHOPHYSIOLOGY

The mechanism of toxicity is similar to that of cyanide, with disruption of oxidative phosphorylation through inhibition of cytochrome oxidase a_3, except this impairment reverses rapidly when hydrogen sulfide exposure ceases.[89] Cellular asphyxia and impaired adenosine triphosphate production promote anaerobic metabolism with lactate accumulation and metabolic acidosis.

CLINICAL FEATURES

Hydrogen sulfide is one of the few chemical asphyxiants that also possesses irritative properties, such that respiratory and ocular irritation are common following exposure.[85,90] However the characteristic odor of "rotten eggs" may not be noticed due to olfactory fatigue from persistent low-level exposures or from acute olfactory paralysis seen at high hydrogen sulfide levels. In high concentrations, rapid loss of consciousness, seizures, and death

occur after only a few breaths.[91] Delayed pulmonary edema and corneal injury should be anticipated in survivors of massive exposures.

TREATMENT

Treatment begins with removal from the source, administration of high-flow oxygen, and decontamination of the skin and eyes, as appropriate.[92] For patients still conscious, symptoms resolve with this treatment alone. For patients with altered sensorium or impaired cardiovascular function after hydrogen sulfide exposure, administration of **sodium nitrite** 300 milligrams IV over 2 to 4 minutes can produce rapid improvement, but only when given within minutes of exposure.[85,92] The concept behind this treatment is that low-level methemoglobin formation may enhance conversion of sulfide to the less toxic sulfmethemoglobin. An animal model of lethal hydrogen sulfide toxicity found benefit with both cobinamide and hydroxocobalamin, but human treatment experience is needed before this agent can be recommended.[93,94] Hyperbaric oxygen therapy for hydrogen sulfide toxicity has been described in multiple published case reports, but there is no evidence that it is superior to standard oxygen therapy.[82,95]

DISPOSITION AND FOLLOW-UP

Patients who receive cyanide antidotal therapy should be admitted for observation. Full recovery is anticipated in many cases of severe poisoning in which treatment is initiated rapidly and cardiac arrest has not yet occurred.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 205

Vitamins and Herbals

Michael Levine

INTRODUCTION

Vitamins and herbal preparations, particularly those sold in health food stores, are considered by many to be innocuous but may have potential toxicity, especially when taken in excessive amounts over a period of time. Also, herbal preparations may contain toxic contaminants that can cause poisoning.

VITAMINS

Hypervitaminosis from the fat-soluble vitamins A, D, E, and K can produce subacute toxicity (after days to a few weeks) or chronic toxicity (after weeks to months of excessive ingestion). Of the water-soluble vitamins, niacin, pyridoxine, and ascorbate are associated with toxicity (**Table 205-1**).

TABLE 205-1 Clinical Features of Hypervitaminosis

Vitamin	Symptoms
Vitamin A	Subacute toxicity: red peeling rash, headache, and vomiting. Chronic toxicity: blurred vision, appetite loss, abnormal skin pigmentation, hair loss, dry skin, pruritus, long-bone pain, bone fractures, liver failure, pseudotumor cerebri, and hypercalcemia.
Vitamin D	Subacute toxicity: hypercalcemia, anorexia, nausea, abdominal pain, lethargy, weight loss, polyuria, constipation, confusion, and coma.
Vitamin E	Chronic toxicity: coagulopathy in patients on warfarin, nausea, fatigue, headache, weakness, and blurred vision.
Vitamin K	Acute toxicity: anaphylactoid reactions if given rapidly in the parenteral form (rare). Interferes with warfarin, resulting in subtherapeutic coagulation.
Vitamin B_1 (thiamine)	No toxicity observed with ingestion of large doses.
Vitamin B_2 (riboflavin)	No toxicity observed with ingestion of large doses.
Vitamin B_3 (niacin)	Acute toxicity: "niacin flush" (redness, burning, and itching of the face, neck, and chest). Hypotension a rare possibility. Chronic toxicity: Abnormalities of liver function, impaired glucose tolerance, hyperuricemia, skin dryness, and discoloration.
Vitamin B_6 (pyridoxine)	Subacute and chronic toxicity: peripheral neuropathy with unstable gait, and marked loss of position and vibration senses.
Vitamin B_{12}	No toxicity observed with ingestion of large doses. With large IV doses: erythema of skin, mucous membranes, serum, and urine. Rare anaphylactoid reactions. Possible interference with serum colorimetric lab studies.
Folate	No toxicity observed with ingestion of large doses. Masking of macrocytic anemia from vitamin B_{12} deficiency with large doses of folate.
Vitamin C (ascorbate)	Chronic toxicity: nephrolithiasis (controversial), intrarenal deposition of oxalate crystals with renal failure; large doses can produce diarrhea and abdominal cramps.

VITAMIN A

Dietary vitamin A is present in two forms: preformed vitamin A (retinol and retinyl palmitate [an ester] from animal sources) and provitamin A (carotenoids) found in plants. After ingestion, the ester form is hydrolyzed in the GI tract to retinol. Retinol is then absorbed into intestinal mucosal cells, where it then combines with a fatty acid to again become a retinyl ester. Carotenoids are dark-colored compounds found in plants. β-Carotene is the carotenoid most efficiently converted to retinol by duodenal mucosal cells. The recommended daily allowance (RDA) for preformed vitamin A (retinol) is 900 micrograms (3000 IU) for adolescents and adult men, and 700 micrograms (2400 IU) in adult women.[1] The liver contains approximately 95% of body vitamin A stores.

Vitamin A forms part of the visual pigments of the retina (rhodopsin and iodopsin), is important for the formation of mucus-secreting cells in the columnar epithelium, maintains bone growth, and maintains cellular membrane stability.

Hypervitaminosis A is usually due to excessive supplement use,[2] although there have been case reports of acute toxicity due to ingestion of mammal organs (e.g., fish liver).[3] There is variability among patients in the amounts necessary to develop hypervitaminosis; for example, it is much more common in children with chronic kidney disease who take supplements compared to those not on supplements.[4] The minimum dose that may cause toxicity in humans is not established.

Symptoms of hypervitaminosis A include blurred vision, appetite loss, abnormal skin pigmentation, loss of hair, dry skin, pruritus, long-bone pain, and an increased incidence of bone fractures. **Rarely, hypervitaminosis A can result in pseudotumor cerebri, hypercalcemia, and hepatic failure.**[5] The treatment of hypervitaminosis A includes discontinuation of the vitamin and supportive care.

β-Carotene, a provitamin A, does not cause hypervitaminosis. In diabetic patients and patients with hypothyroidism, however, large doses of β-carotene can cause a yellowish discoloration of the skin, which fades once β-carotene is stopped. This phenomenon is occasionally seen in infants and toddlers who consume large amounts of carrots and other pigmented vegetables.

Vitamin A deficiency can result in anemia, numerous ocular symptoms, and immune suppression with subsequent increased risk of infection. Young children and pregnant women are some of the groups at highest risk of developing vitamin A deficiency.[6]

VITAMIN D

Dietary vitamin D is ingested as a provitamin, either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3); both forms are essentially bioequivalent. These provitamins are then converted to calcitriol (1,25-dihydroxycholecalciferol), the physiologically active form of vitamin D. The major function of calcitriol is to elevate plasma calcium and phosphorus levels, enabling normal bone mineralization.

The RDA for vitamin D is 15 micrograms (600 IU) for adults,[7] with therapeutic doses sometimes exceeding 125 micrograms (5000 IU) daily. Patients at the extremes of age are at higher risk for toxicity, as are those on supplementations.[8,9] Prolonged exposure to vitamin D may result in hypercalcemia, hypercalciuria, and hyperphosphatemia.[10] However, the **primary symptoms of hypervitaminosis D relate to hypercalcemia** and include anorexia, nausea, abdominal pain, lethargy, weight loss, polyuria, constipation, confusion, and rarely, coma.

Treatment of hypervitaminosis D includes discontinuation of vitamin D, reduction of the calcium intake, and reduction of serum calcium levels. IV hydration, calcitonin, and bisphosphonates can be used in the management of hypercalcemia. Vitamin D deficiency may result in **rickets** and osteomalacia.

VITAMIN E

There are eight unique, fat-soluble, naturally occurring alcohols (called tocopherols and tocotrienols) that possess vitamin E activity, with *d*-α-tocopherol the most active form. Because it is rapidly oxidized, α-tocopherol protects other molecules from being oxidized and thus is termed an antioxidant.[11] Foods high in vitamin E include wheat germ, corn, soybean, sunflower seed, almonds, peanuts, spinach, and broccoli.

The RDA for vitamin E is 15 milligrams (22.4 IU) for adults.[12] Vitamin E is thought to be nontoxic at daily doses of up to 400 milligrams (600 IU). With daily doses greater than 670 milligrams (1000 IU) taken for a long time, vitamin E has the ability to antagonize the effects of vitamin K,[13] specifically acting as a competitive inhibitor of vitamin K–dependent γ-carboxylation. In addition, through the production of thromboxane, high levels of vitamin E inhibit platelet aggregation. Thus, patients on warfarin therapy are at risk for bleeding, whereas it is rare for patients not on warfarin to bleed from large amounts of vitamin E. Patients on tamoxifen or cyclosporine may also have drug–nutrient interactions at high doses of vitamin E.[14] Other effects in adults who take large doses for a long period of time include nausea, fatigue, headache, weakness, and blurred vision.[15] These symptoms resolve weeks after discontinuation of the vitamin.

VITAMIN K

Vitamin K activity is found in several compounds of varied origin: phylloquinone or vitamin K_1, which is naturally produced by plant sources; menaquinone or vitamin K_2, which is produced by bacterial sources; and menadione or vitamin K_3, a synthetic chemical that is a vitamin precursor of vitamin K_2. Because large doses of menadione are toxic, the use of menadione supplements is banned in the United States for human use but can still be found in animal feed.

The GI absorption of vitamin K requires the presence of bile and pancreatic juice, with between 10% and 80% of ingested vitamin K being absorbed. It is thought that most of the vitamin K used in the body is derived from plant sources (K_1). Furthermore, if one has an adequate dietary intake of vitamin K_1, eradication of the gut bacteria will not lead to a deficiency of vitamin K.[16] In contrast to the other fat-soluble vitamins, vitamin K is not stored in the body to any significant extent. Vitamin K deficiency is uncommon because the normal American diet contains vitamin K substantially in excess of the RDA, which is 120 micrograms in adult men and 90 micrograms in adult women.[17]

Vitamin K is required for the production of six factors involved in the coagulation cascade: factors II, VII, IX, and X, along with proteins C and S. Warfarin inhibits vitamin K activity, thereby producing a coagulopathy.

The main concern about vitamin K toxicity is the adverse reactions seen with the IV form. The only recommended form of vitamin K for both oral and parenteral use is K_1. Because vitamin K is fat soluble, it is given parenterally in a lipid-soluble form. Historically, rates of anaphylactoid reactions were more common due to a different colloidal suspension.[18] With current preparations, anaphylactoid reactions to IV vitamin K occur at a rate of 0.03% (3 per 10,000).[19] Absorption of IM vitamin K_1 is erratic, and absorption from SC administration is relatively ineffective, whereas PO absorption is reliable and effective. Thus, vitamin K should be administered orally when feasible or intravenously for life-threatening hemorrhage or in cases where absorption from the GI tract is questionable.

Toxicity from oral vitamin K is rare, although daily doses exceeding 500 micrograms are associated with skin rashes.

VITAMIN B_1 (THIAMINE)

Vitamin B_1, or thiamine, is converted by the body to thiamine pyrophosphate, which acts as a cofactor for several metabolic reactions, including transketolations. Food sources of thiamine include fruits, grain, meats, fish, and milk, among others.

Intestinal absorption of thiamine is greatest in the jejunum. Thiamine is not stored in the body to any significant extent. Because of renal excretion (water solubility), there is no toxicity to the ingestion of large doses of thiamine over prolonged periods. The RDA for thiamine is 1.2 milligrams in adult men and 1.1 milligrams in adult women.[20]

Historically, there was concern about the ability of thiamine to precipitate Wernicke's encephalopathy if glucose was not administered prior to the thiamine.[21] There are no clear data to support that theory, and IV glucose is unlikely to precipitate Wernicke's encephalopathy in patients with altered mental status. Thiamine supplementation prior to glucose administration is not required.

Rarely, IV thiamine may precipitate anaphylactoid reactions. This event is likely related to the diluent and contaminants, as the current pure aqueous forms of thiamine for IV use very rarely result in anaphylactoid adverse reactions.[22] Therefore, IV use of thiamine is both safe and clinically efficacious. Conversely, PO and IM thiamine is absorbed unpredictably in the emergency setting.

Thiamine deficiency may result in **beriberi,** which is characterized by anorexia, weight loss, and neuropathy. In addition, thiamine deficiency can result in **Wernicke's syndrome** or **Korsakoff's psychosis**. Wernicke's syndrome is characterized by confusion, ataxia, and ophthalmoplegia, whereas Korsakoff's psychosis is characterized by confusion, confabulations, and psychosis.[23]

VITAMIN B_2 (RIBOFLAVIN)

The RDA for riboflavin is 1.3 milligrams in adult men and 1.1 milligrams in adult women.[24] Riboflavin is excreted through the urine, and toxicity has not been reported regardless of the amount ingested.[25]

VITAMIN B_3 (NIACIN)

There are two active forms of niacin—nicotinic acid and nicotinamide—which, in conjunction with thiamine and riboflavin, function as coenzymes in energy metabolism. Niacin becomes part of the coenzymes nicotinamide-adenine dinucleotide and nicotinamide-adenine dinucleotide phosphate; both are required in all major metabolic pathways where there is oxidative breakdown of amino acids, fatty acids, and other compounds, including the oxidation of ethanol.

Niacin is found primarily in poultry, meat, and fish, with lesser amounts in plants. The RDA for niacin is 16 milligrams for adult men and 14 milligrams for adult women.[26]

Nicotinic acid in the range of 1 to 3 grams per day lowers serum cholesterol and β-lipoprotein, but nicotinamide does not. Large niacin doses can also deplete cardiac muscle glycogen and can cause liver toxicity. Some patients experience a frightening "niacin flush" when taking a dose of >100 milligrams. **The niacin flush, caused by prostaglandin D_2 and E_2 release with subsequent vasodilation, is characterized by face, neck, and chest burning, itching, and erythema.[27] Rarely, hypotension may occur.[28]** The use of aspirin before or at the time niacin is consumed may reduce the prevalence of niacin-induced flushing.[29] Higher niacin doses may additionally cause nausea, abdominal cramping, diarrhea, and headache. Extremely high doses of niacin for a prolonged period may produce abnormalities of liver function, impaired glucose tolerance, hyperuricemia, and skin changes such as dryness and discoloration. These subacute and chronic symptoms resolve within days to weeks after stopping treatment.

Niacin deficiency can result in **pellagra**, which is characterized by dermatitis, diarrhea, and dementia.

VITAMIN B_6 (PYRIDOXINE)

Vitamin B_6 is a necessary cofactor for many enzymatic processes. The active form of pyridoxine is pyridoxal-5-phosphate, which serves as a cofactor for the formation of γ-aminobutyric acid. The RDA for vitamin B_6 is 1.3 milligrams for adults aged 19 to 50 years.[30]

Chronic administration of high doses of pyridoxine may result in peripheral sensory neuropathy, and sometimes with autonomic and motor nerve impairment. After withdrawal of the vitamin, recovery occurs within several months, although some patients may have residual neurologic impairment. **There is no evidence that a single 5-gram IV dose of pyridoxine will cause any type of nerve damage.**[31]

Vitamin B_6 also can cause intestinal inactivation of levodopa in patients receiving that medication for Parkinson's disease. Tell patients not to take this vitamin at the same time as the medication.

Pyridoxine deficiency primarily manifests as seizures. The deficiency can be congenital or acquired (e.g., decreased γ-aminobutyric acid production as a result of isoniazid or hydrazines). In addition, anemia (caused by impaired synthesis of heme), xanthurenic aciduria (as a result of reduced formation of hydroxyanthranilic acid), cystathioninuria (as a result of decreased cleavage of cystathionine to cysteine and homoserine), and homocystinuria (due to impaired formation of cystathionine) may result.

VITAMIN B_{12} (CYANOCOBALAMIN)

Due to the size and complexity of the vitamin B_{12} molecules, deficiencies of this water-soluble vitamin result more from absorption problems than from dietary insufficiencies.[32] Absorption depends on the production of intrinsic factor by the parietal cells of the stomach. Vitamin B_{12}–intrinsic factor complexes are initially formed in the stomach. The complexes pass to the ileum, where the intrinsic factor attaches to the intestinal epithelium, facilitating the absorption of the vitamin B_{12}. Vitamin B_{12} is stored in the liver in such quantities that it takes several years for pernicious anemia to develop in an individual who is a strict vegetarian and ingests little B_{12} or in someone unable to produce intrinsic factor.[32] Dietary vitamin B12 is primarily obtained from animal sources. The RDA for vitamin B_{12} is 2.4 milligrams in adults.[33]

Until recently, it was believed that vitamin B_{12} had a wide therapeutic index for harm. With the advent of the use of the vitamin B_{12} precursor, hydroxocobalamin, as an antidote for cyanide poisoning, there have been a few case reports of direct vitamin B_{12} toxicity. These cases are characterized by erythema of the skin, mucous membranes, urine, and serum.[34] Rare cases of anaphylactoid reactions have also been reported. Hydroxocobalamin can also interfere with colorimetric lab tests, including those that test for carbon monoxide.[35]

Vitamin B_{12} deficiency can result in hematologic, neurologic, and psychiatric effects.[32] The common hematologic disorders include megaloblastic anemia and pancytopenia. The neurologic disorders commonly observed include paresthesias, peripheral neuropathies, and dorsal spinal cord column demyelination. Psychiatric symptoms include depression, dementia, and psychosis.

FOLATE

Folate, or folic acid, is essential for the production of DNA, RNA, and proteins. Folate is found in fresh leafy green vegetables, yeasts, and liver. After ingestion, folate is actively absorbed in the small and large intestine. The RDA for folate is 400 micrograms in adults.[36]

Both deficiencies of vitamin B_{12} and folate can result in megaloblastic (macrocytic) anemia. Large doses of folic acid given to an individual with an undiagnosed vitamin B_{12} deficiency could correct megaloblastic anemia, but leave the individual at risk of developing irreversible neurologic damage. Such cases of neurologic progression in vitamin B_{12} deficiency have been mostly seen at folate doses of 5 milligrams and above.[37]

VITAMIN C (ASCORBATE)

The major form of vitamin C, ascorbate or ascorbic acid, is a strong reducing agent that participates in hydroxylation reactions such as those necessary for the formation of collagen. Vitamin C, which is found primarily in fruits and vegetables, is absorbed through the jejunum and ileum. The RDA for vitamin C is 90 milligrams in adult men and 75 milligrams in adult women.[38]

Chronic high-dose ascorbate ingestion has been reported to cause renal failure due to intrarenal deposition of oxalate crystals.[39] Large doses of vitamin C may produce diarrhea and abdominal cramps, which subside with discontinuation. Limited data suggest that vitamin C in doses exceeding 1000 milligrams may result in false-negative guaiac testing for fecal occult blood.[40]

Scurvy is due to vitamin C deficiency and results in collagen, protein, and lipid metabolism abnormalities. In addition, the presence of vitamin C in the intestines increases the absorption rate of iron, so those with a vitamin C deficiency will also be iron depleted.

HERBAL OR BOTANICAL DIETARY AGENTS

Herbal preparations have long been used by traditional cultures, and their use appears to be increasing in developed countries.[41] In developed countries, herbal preparations have been looked upon as a natural and inexpensive alternative to common Western pharmaceuticals. However, studies funded by the National Center for Complementary and Alternative Medicine have not supported the use of herbal medications for treatment of depression (St. John's wort),[42] dementia (*Ginkgo biloba*),[43] prostatic hypertrophy (saw palmetto),[44] osteoarthritis (glucosamine and chondroitin),[45] and the common cold (*Echinacea*).[46] There is also a false belief that because herbal products are "natural" that they must be "safe."

Because herbal products are classified as dietary supplements by the Dietary Supplemental Health and Education Act of 1994,[47] the U.S. Food and Drug Administration does not have authority to require testing for safety and effectiveness before marketing. However, since 2007, the Food and Drug Administration has required that manufacturers guarantee the identity, purity, strength, and composition of their dietary supplements.[48] The Food and Drug Administration can restrict sales or remove a supplement from the market if it is proven to be potentially unsafe or harmful. Herbal agents can be classified as generally safe, potentially toxic, or toxic (**Table 205-2**).[49-52] Many herbal agents have specific liver, eye, and cardiovascular toxicities.[53-58]

TABLE 205-2 Some Generally Safe Herbal Supplements or Agents

Agent	General Use	Rare Adverse Effect
Chamomile	Antispasmodic	Anaphylaxis if patient allergic to ragweed
Chondroitin	To treat arthritis	May cause GI upset
Echinacea	To treat or prevent upper respiratory or urinary tract infections	Anaphylaxis if patient allergic to daisies May deplete vitamin stores
Feverfew	To prevent migraines	Suddenly discontinuing may precipitate migraine If chewed, may cause mouth sores If applied to skin, may cause dermatitis
Garlic	To treat hypertension, colic, and hyperlipidemia	Hypotension, rash, nausea, vomiting, diarrhea; death has been reported in massive doses in children
Ginkgo	To treat dementia, vertigo, and Raynaud's disease	May inhibit platelet aggregation and interact with warfarin May cause GI upset
Ginseng	To treat impotence, fatigue, ulcers, and stress	May interact with warfarin Lowers blood glucose May cause insomnia, nervousness
Glucosamine	To treat arthritis	Allergic reaction
Kava	Used for sedation and to relieve sore throat pain	Hepatotoxicity
St. John's wort	To treat depression	Phototoxicity May interact with serotonin reuptake inhibitors; avoid tyramine-containing foods
Valerian	Used for sleep and sedation	Interacts with other sedating drugs May have paradoxical stimulant effect

TABLE 205-3 Some Potentially Toxic Herbal Supplements or Agents

Agent	General Use	Adverse Effect
Black cohosh	To delay or treat menopause	Nausea, vomiting, dizziness, weakness
Chaparral (creosote bush)	Antioxidant effects, analgesia	Potentially hepatotoxic and nephrotoxic
Comfrey	Bone and teeth building, variety of other uses	Potentially hepatotoxic
Ephedra	Weight loss	Hypertension; contraindicated for patients with hypertension, diabetes, or glaucoma
Hawthorn	Congestive heart failure	Additive toxicity with prescribed cardioactive steroids
Juniper	Diuretic	Hallucinogenic; may also cause renal toxicity, nausea, and vomiting
Lobelia	As an expectorant or for treatment of asthma	Anticholinergic syndrome
Nutmeg	Dyspepsia, muscle aches, and arthritis	Hallucinations, GI upset, agitation, coma, miosis, and hypertension
Pennyroyal	Rubefacient, delaying menses, abortifacient	Hepatotoxicity
Pyrrolizidine alkaloids	Pulmonary ailments	Hepatic veno-occlusive disease
Wormwood	Dyspepsia	Absinthism: restlessness, vertigo, tremor, paresthesias, delirium
Yohimbe	Aphrodisiac	Hallucinations, weakness, hypertension, and paralysis

Although herbal preparations can cause direct toxicity from the herb itself, it is much more common that the patient becomes ill from the contamination, misuse, overuse, or misidentification of the herbal preparation.[59] Herbal preparations can cause either direct toxicity (**Table 205-3**) or indirect toxicity from herb–drug interactions (**Table 205-4**).[52] Reported contaminants in herbal preparations include lead, selenium, and cyanide.[60-64]

Much of the available literature on herb–drug interactions is anecdotal and nonreproducible, but there are some herb–drug interactions that, because of numerous clinical reports, animal studies, and/or

TABLE 205-4 Some Likely Herb–Drug Interactions

Herb	Herb Used For	Drug	Effect of Interaction
Cayenne (*Capsicum*)	Arthritis, neuralgia, analgesic	Angiotensin-converting enzyme inhibitors Theophylline sustained-release	Increased cough Increased absorption
Dan shen (*Salvia*)	Reduction of lactation	Warfarin	Decreased warfarin metabolism
Ephedra	Energizer, weight loss, asthma, sinus congestion	Monoamine oxidase inhibitors Sympathomimetics	Increased toxicity Additive effect
Ginkgo	Dementia, peripheral arterial disease, tinnitus	Aspirin Warfarin	Increased risk of bleeding
Grapefruit juice	For vitamin C activity	Amiodarone Benzodiazepines Calcium channel blockers Carbamazepine Clomipramine Cyclosporine Dextromethorphan Ethinyl estradiol 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors ("statins") Phosphodiesterase type 5 inhibitors (erectile dysfunction drugs) Quinidine Sertraline	Increased drug availability of any one of these drugs because of inhibition of intestinal CYP3A4
Kava	Sedative/anxiolytic	Caffeine Fluvoxamine Theophylline	Increased levels from inhibition of CYP1A2
Licorice in chronic, high doses	Respiratory disorders, hepatitis, inflammatory diseases, infections	Antihypertensives Diuretics Prednisolone	Decreased effect (can cause pseudohyperaldosteronism by inhibiting 11-β-dehydrogenase) Increased potassium loss, myopathy Increased drug levels
St. John's wort	Depression	Cyclosporine Digoxin Indinavir	Decreased serum levels; transplant rejection Decreased serum level Decreased serum level
Yohimbine	Erectile dysfunction, sexual potency	Clonidine Cyclic antidepressants	Decreased effect Enhanced autonomic and central effects of yohimbe

Abbreviation: CYP = cytochrome P450.

controlled clinical studies, can be deemed to be "likely" (Table 205-4).[65] Although not usually of clinical relevance, certain herbals may also interfere with assays for therapeutic drugs.[66-68]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 206

Antimicrobials

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INTRODUCTION

Adverse effects associated with antimicrobials occur primarily in three circumstances: side effects with therapeutic dosing, subacute to chronic effects from sustained therapeutic use, and acute toxicity resulting from excessive dosing. Side effects can be immunologic (allergic) or nonimmunologic (pharmacologic or idiosyncratic) in nature. Antibiotics cause more reported allergic reactions than other drugs, possibly due to their high frequency of use often in a repeated and interrupted fashion. Sometimes a diluent or other chemical constituent in the formulation of a drug causes the adverse effect.

Most patients who sustain an acute antimicrobial overdose remain asymptomatic, and observation is generally all that is required. Measurement of drug levels is neither helpful nor readily available to affect management but may be confirmatory. Levels are available for several antibiotics such as chloroquine, isoniazid, and quinine. Ancillary testing should be based on the substance ingested and the clinical condition of the patient, such as methemoglobin concentrations for patients with dapsone or chloroquine toxicity.[1] Some antimicrobials are associated with specific, significant toxicities following an acute ingestion and may require directed therapy (**Table 206-1**).

Consider GI decontamination for patients suspected of ingesting a toxic amount of a potentially dangerous antimicrobial agent. Single-dose activated charcoal without sorbitol given orally or via nasogastric tube is most beneficial within 1 hour of the ingestion.[2,3] Multidose activated charcoal is indicated in symptomatic patients who have ingested dapsone or quinine.[4] Hemodialysis or hemoperfusion is effective at reducing concentrations of dapsone,[5,6] chloramphenicol,[7] cefepime,[8,9] and possibly pentamidine.[10]

Ask women of childbearing age about pregnancy and lactation when prescribing antimicrobials. LactMed is a National Library of Medicine and National Institutes of Health database of drugs that describes maternal and infant levels of drugs and effects on breastfed infants and on lactation. Effective June 30, 2015, the U.S. Food and Drug Administration published the Pregnancy and Lactation Labeling Rule, which removed pregnancy letter categories (A, B, C, D, and X) and allows for considerations of risk and benefit when prescribing medication to pregnant and nursing women. Also, see Chapter 99, "Comorbid Disorders in Pregnancy," for more detailed discussion of drugs in pregnancy.

TABLE 206-1 Select Antimicrobial Toxicities and Their Specific Treatments

Drug	Acute Toxicity	Special Therapy for Symptomatic Overdose
Antibacterials		
Penicillin	Seizures (50 million units or more IV)	Benzodiazepines
Amoxicillin	Crystalluria, hematuria, acute renal failure	IV fluid
Cephalosporins	Encephalopathy, seizures	Benzodiazepines
Chloramphenicol	Cardiovascular collapse	Hemodialysis
Fluoroquinolones	Seizures	Benzodiazepines
Macrolides	Prolonged QT interval, torsades de pointes arrhythmia	Magnesium sulfate
Sulfonamides	Methemoglobinemia	Methylene blue
Vancomycin	"Red man syndrome" (anaphylactoid response)	Slow or stop infusion, antihistamines
Antimalarials		
Chloroquine	Seizures, QRS-complex and QT-interval prolongation, hypotension, hypokalemia	Epinephrine, diazepam
Quinine (quinidine)	Sodium-potassium channel blockade, α-adrenergic antagonism, hypoglycemia, ototoxicity, ophthalmic toxicity	Multidose activated charcoal, sodium bicarbonate, dextrose, octreotide
Primaquine	Methemoglobinemia, hemolysis	Methylene blue
Antituberculous medications		
Isoniazid	Inhibition of γ-aminobutyric acid synthesis and functional deficiency of pyridoxine, seizures	Benzodiazepines, high-dose pyridoxine

ANTIBACTERIALS

PENICILLINS, CEPHALOSPORINS, AND OTHER β-LACTAM AGENTS

Acute overdoses of penicillins and cephalosporins mainly produce nausea, vomiting, and diarrhea but are rarely life threatening. Large doses of penicillins or cephalosporins may produce seizures through γ-aminobutyric acid inhibition, and seizures are managed by administration of benzodiazepines or barbiturates.[11] Seizures resulting from intrathecal doses of penicillins or cephalosporins may require cerebral spinal fluid exchange for treatment.[12] Imipenem may cause seizures in overdose or at therapeutic doses, and these are treated in the same manner. Agitation, encephalopathy, absence seizures, and nonconvulsive status epilepticus have been reported with cefazolin, ceftazidime, cefuroxime, and cefepime.[9,13,14] Patients most at risk for adverse neurologic effects from β-lactams are those with renal failure, those with underlying CNS abnormalities, and those receiving high-dose therapy.[14,15] Amoxicillin overdose may produce crystal-induced interstitial nephritis, hematuria, and renal failure; treatment is supportive with IV fluids.[16-19]

Amoxicillin-clavulanate can cause rare cases of cholestatic hepatitis (1 to 6 weeks after initiation) and pancreatitis.[20] Treat with supportive care and discontinuation of the drug. Penicillins are associated with bone marrow suppression, hemolysis, interstitial nephritis, and vasculitis.[21] Cephalosporins are associated with serum sickness and can cause acute hemolytic crisis.[22] Cephalosporins with the *N*-methylthiotetrazole side chain, such as cefazolin and cefotetan, can produce a disulfiram-like reaction as the side chain is released.[23]

Two unique acute adverse reactions to procaine penicillin G are the Jarisch-Herxheimer reaction and Hoigne's syndrome. The **Jarisch-Herxheimer reaction** can begin within a few hours following antibiotic treatment of Lyme disease or early syphilis. This reaction is characterized by headache, fever, myalgias, and rash; is usually limited to 24 hours; and results from antigen released from lysed bacteria.[24] **Hoigne's syndrome** begins within minutes after an intramuscular or intravascular injection of procaine penicillin G. This syndrome is characterized by extreme apprehension, fear, hallucinations, illusions, hypertension and tachycardia, and seizures. The cause of this reaction is unclear, but the effects occur in the absence of other signs of anaphylaxis.[25] Amoxicillin and ceftriaxone have been reported to produce a similar reaction.[26]

CLINDAMYCIN

The lincosamide class includes clindamycin and lincomycin, and its main acute toxicities are nausea, vomiting, and diarrhea. Although all

antibiotics have been associated with depletion of normal gut flora that allows for proliferation of *Clostridium difficile*, clindamycin is among those antibiotics that carry a higher risk for this infection and the potential complications of pseudomembranous colitis and toxic megacolon.[27] Clindamycin is also associated with two forms of liver injury: (1) transient elevations of serum aminotransferases and (2) acute idiosyncratic liver injury characterized by jaundice, alanine transaminase levels 2 to 12 times over baseline, fever, and rash. This latter form of injury usually shows minimal cell injury on liver biopsy and is not associated with liver failure.[28]

FLUOROQUINOLONES

Acute overdose of fluoroquinolones rarely produces life-threatening effects. Seizures are a rare consequence of fluoroquinolone use, possibly due to γ-aminobutyric acid inhibition or through sequestration of magnesium.[11] There is also an association with prolongation of the QT interval and subsequent torsades de pointes.[29] Fluoroquinolones are associated with acute renal failure, possibly through a hypersensitivity reaction where risk factors include concomitant use of renin-angiotensin–blocking agents.[30] Crystal-induced nephropathy has been reported with therapeutic doses of ciprofloxacin.[31] Caution is advised when these antibiotics are used in children due to potential musculoskeletal abnormalities with developing cartilage and bone, although data suggest the risk is very low.[32] In adults, tendon rupture has been attributed to fluoroquinolone use, with levofloxacin accounting for more than all others combined.[33] Discontinue the antibiotic in those who complain of painful or swollen tendons. Fluoroquinolones are also associated with dysglycemia, rash, serum sickness, and tinnitus.[14]

LINEZOLID

The first member of a new class of antibiotic, synthetic oxazolidinones, linezolid inhibits monoamine oxidase and can lead to serotonin syndrome when used concurrently with other serotonergic medications such as selective serotonin reuptake inhibitors.[34]

Chronic therapy longer than 28 days is associated with peripheral neuropathy and optic neuropathy with loss of central vision and loss of color and visual acuity. Lactic acidosis can occur, especially in patients with numerous comorbidities including sepsis and cirrhosis. Linezolid is also associated with anemia, thrombocytopenia and pancytopenia, and cholestatic hepatitis.[35]

MACROLIDES AND KETOLIDES

Although the most common adverse reaction to macrolide use is GI distress, QT-interval prolongation with potential for torsades de pointes is the most important.[36,37] The mechanism for this effect is blockade of the delayed rectifier potassium currents and has been noted after use of erythromycin, clarithromycin, telithromycin, and, to a lesser extent, azithromycin. Erythromycin and clarithromycin, but not azithromycin, also inhibit cytochrome P450 3A4, potentially causing drug interactions. Macrolides are also associated with high-frequency sensorineural hearing loss, cholestatic hepatitis, and rarely pancreatitis.[38]

TRIMETHOPRIM-SULFAMETHOXAZOLE

These two antimicrobials work together for their antibiotic effect and are associated with many commonly reported adverse effects. Among them are allergic reactions, hematologic disorders, hypoglycemia, methemoglobinemia, rhabdomyolysis, and psychosis. Trimethoprim-sulfamethoxazole is also associated with idiosyncratic acute liver injury with a clinical pattern suggestive of a drug allergy or hypersensitivity mechanism that is particularly common among human immunodeficiency virus–infected patients.[39]

VANCOMYCIN

Red man syndrome is an anaphylactoid response related to the rate of IV vancomycin infusion that can include angioedema, chest pain, dyspnea, flushing, pruritus, and urticaria. Rarely, this syndrome can also cause seizures and cardiovascular collapse. Most symptoms resolve within 15 minutes when the infusion is stopped. Continuing the infusion at a slower rate or with increased dilution can help decrease recurrence. Pretreatment with diphenhydramine is also helpful.[40]

ANTIFUNGALS

TRIAZOLES

Antifungal agents such as fluconazole, clotrimazole, and miconazole are not expected to produce severe toxicity in acute overdose settings. Uncommon adverse reactions such as hepatotoxicity can occur, rarely leading to liver failure and death. Liver injury is hepatocellular and can be accompanied by eosinophilia, fever, and rash. Recovery begins with stopping the drug and may take as long as 3 to 4 months. These antifungals are also associated with neutropenia and thrombocytopenia, and they inhibit cytochrome P450 3A4, potentiating toxicity from other pharmaceuticals.[41]

AMPHOTERICIN B

Amphotericin B is used for progressive, life-threatening fungal infections and is rarely encountered in the ED. Acute overdoses are associated with fever, headache, nausea, vomiting, rigors, hypotension and tachycardia, anemia, dysrhythmias, electrolyte wasting, nephrotoxicity, neuropathy, and cardiac arrest.[42]

ANTIMALARIALS

ATOVAQUONE-PROGUANIL

Atovaquone-proguanil (generic Malarone) is most often associated with GI distress and headache. It is quite well tolerated and is considered safe during pregnancy and breastfeeding.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Chloroquine toxicity usually begins within 3 hours of ingestion with nausea, vomiting, and diarrhea.[43] Cardiovascular collapse may be precipitous, with QRS-complex prolongation and atrioventricular nodal blockade. Hypotension may be more severe than that seen with quinine overdose and is accompanied by respiratory depression and hypokalemia.[44] Neurologic toxicity may include headache, obtundation, and seizures.

Aggressive supportive care is needed. A decreased mortality rate has been demonstrated in chloroquine overdose treated with early intubation, gastric lavage, deep sedation with benzodiazepines, and vasoactive pressor support with epinephrine to maintain a systolic blood pressure of 100 mm Hg (13.3 kPa).[45-47]

MEFLOQUINE

Mefloquine is used for prophylaxis or treatment of drug-resistant malaria and is associated with a variety of complications. In addition to GI distress, mefloquine is a rare cause of cardiac depression and severe CNS events, including seizures, hallucinations, and psychosis. Milder CNS effects, such as headache, insomnia, and vivid dreams, occur in up to 25% of patients. Mefloquine is not recommended as first-line therapy and is contraindicated in patients with seizures or psychiatric disorders.[48]

PRIMAQUINE

Primaquine is associated with GI distress and may cause hemolytic anemia and methemoglobinemia, especially in a glucose-6-phosphate dehydrogenase–deficient population. Granulocytosis, granulocytopenia, hypertension, dysrhythmia, and neurologic depression are rare complications associated with overdose.[49,50]

QUININE

The cardiac toxicity of quinine includes both sodium and potassium channel antagonism, which may result in widened QRS-complex

intervals, QT prolongation and torsades de pointes, hypotension, syncope, and sudden death.[51] Quinine also has significant ocular toxicity in acute overdose, and blindness may result from serum levels >10 to 15 micrograms/mL (31 to 46 micromol/L).[52,53] Quinine-induced ototoxicity can produce symptoms that range from tinnitus to deafness.[54] Hypoglycemia may also result from hyperinsulinemia.

Sodium bicarbonate to maintain a serum pH of 7.55 is the mainstay of treatment for quinine-induced cardiac toxicity while avoiding class IA, IC, and III antidysrhythmic agents. **Quinine overdose is one of the few drugs for which multiple-dose activated charcoal is truly indicated.**[4]

ANTIPARASITICS

Most antiparasitics, such as albendazole, mebendazole, and thiabendazole, have minimal toxicity following an acute overdose, usually only producing abdominal pain, nausea, and vomiting. Levamisole, an antihelminthic that was discontinued in the United States in 1999 due to agranulocytosis, has been a common adulterant in illicit cocaine. Complications found among cocaine users stemming from the levamisole contaminant include leukocytoclastic vasculitis, cutaneous necrotizing vasculitis, and thrombotic vasculopathy without vasculitis.[55]

ANTITUBERCULOUS MEDICATIONS

ISONIAZID

First-line medications used to treat both latent and active tuberculosis include isoniazid, rifampin, ethambutol, and pyrazinamide. Of these, isoniazid is associated with high morbidity and mortality in overdose.[56,57] At therapeutic doses, adverse effects from isoniazid include neuropathy and hepatic injury.

The clinical symptoms of acute isoniazid overdose typically begin with nausea, mental status changes, and ataxia, which may be seen as early as 30 minutes after ingestion. These symptoms may progress to **the three classic features of acute isoniazid overdose: seizures, metabolic acidosis, and protracted coma**.[58,59] Seizures typically follow acute isoniazid ingestions of greater than 20 to 30 milligrams/kg. Isoniazid-induced seizures are generalized tonic-clonic in nature and are often refractory to standard anticonvulsive therapy with benzodiazepines and barbiturates. The mechanism for isoniazid-induced seizures is a functional deficiency of pyridoxine (vitamin B_6) and inhibition of the synthesis of γ-aminobutyric acid, the primary CNS inhibitory neurotransmitter. Seizures with therapeutic doses of isoniazid have been reported,[60] presumably due to very low vitamin B_6 levels.[61] Although the metabolic acidosis that accompanies isoniazid-induced seizures is likely due to motor activity, the lactic acidemia may not resolve as rapidly as with other more typical epileptic seizures.

Consider isoniazid overdose in patients with refractory seizures.[56] Isoniazid-induced seizures are treated with a combination of benzodiazepines and pyridoxine. The dose of **pyridoxine** is a gram-for-gram equivalent to the amount of isoniazid ingested.[62] For patients who ingest an unknown quantity of isoniazid, the recommended dose of pyridoxine is 5 grams IV in adults and 70 milligrams/kg (maximum 5 grams) in pediatric patients. Pyridoxine should be administered at a rate of approximately 1 gram IV every 2 to 3 minutes until the seizures stop or the maximum dose has been given. After the seizures have ceased, the remainder of the pyridoxine dose should be given over the following 4 to 6 hours to limit recurrent seizures. If seizures persist after the full dose has been given, it may be repeated.

Adequate single-dose therapy of pyridoxine should be effective to stop most seizures, but patients who do not receive adequate pyridoxine dosing may have repeat seizures. Pyridoxine may also assist in reversing isoniazid-induced coma. Hospitals where tuberculosis is endemic should ensure that an adequate supply of IV pyridoxine is maintained to treat overdoses.[63] If only pyridoxine tablets are available, they may be crushed and administered by nasogastric tube.

Phenytoin has no role in treating seizures originating from isoniazid overdose, and there is little role for sodium bicarbonate treatment of the metabolic acidosis resulting from isoniazid toxicity. Because most isoniazid-induced toxicity occurs within 2 hours of ingestion, patients who remain asymptomatic for 6 hours after ED presentation are safe for medical clearance.

OTHER ANTITUBERCULOSIS AGENTS

Other antituberculous medications are associated with a variety of adverse reactions of a milder nature. **Ethambutol** toxicity is also primarily GI in nature but additionally may cause unilateral or bilateral ocular toxicity including blurred vision, disruption of color perception, and loss of peripheral vision.[64] **Rifampin** infrequently causes severe toxicity and is most often associated with GI symptoms. Acute toxicity has been associated with flushing, angioedema, and neurologic effects including numbness, extremity pain, ataxia, and weakness. Rifampin has been presumptively implicated in producing acute kidney injury with proteinuria.[65] **Pyrazinamide** is not associated with any toxic effects following an acute overdose.

ANTIVIRAL/RETROVIRAL MEDICATIONS

Common side effects from oseltamivir, used for the treatment of influenza, are nausea, vomiting, diarrhea, dizziness, and headache. Oseltamivir is associated with QT prolongation,[66] but there is no evidence the drug causes torsades de pointes or should be avoided in patients with congenital long QT syndrome.[67] Oseltamivir can cause acute neuropsychiatric effects including depression, agitation, and hallucinations within 24 hours of the first dose.[66,68]

In the treatment of human immunodeficiency virus, protease inhibitors as a class can cause QT prolongation[69] and nephrolithiasis,[70] whereas reverse transcriptase inhibitors can cause lipodystrophy[71] and lactic acidosis.[72] For patients being induced to or taking buprenorphine, the University of California, San Francisco (http://hivinsite.ucsf.edu/) maintains a list of antiretrovirals that affect buprenorphine levels.

Methadone also has important interactions with antiretrovirals, mostly requiring methadone dose increases. Check available databases or infectious disease specialists for specific information.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 207

Dyshemoglobinemias

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INTRODUCTION

Dyshemoglobinemias are disorders in which the hemoglobin molecule is functionally altered and prevented from carrying oxygen. The most clinically relevant dyshemoglobinemias are carboxyhemoglobin, methemoglobin, and sulfhemoglobin.[1] Carboxyhemoglobin is created following carbon monoxide exposure and, because of its unique importance and prevalence, is discussed separately (see Chapter 222, "Carbon Monoxide").

METHEMOGLOBINEMIA

PATHOPHYSIOLOGY

The iron moiety within deoxyhemoglobin normally exists in the ferrous (bivalent or Fe^{2+}) state. Ferrous iron avidly interacts with compounds seeking electrons, such as oxygen or other oxidizing agent, and in the process is oxidized to the ferric (trivalent or Fe^{3+}) state. Hemoglobin

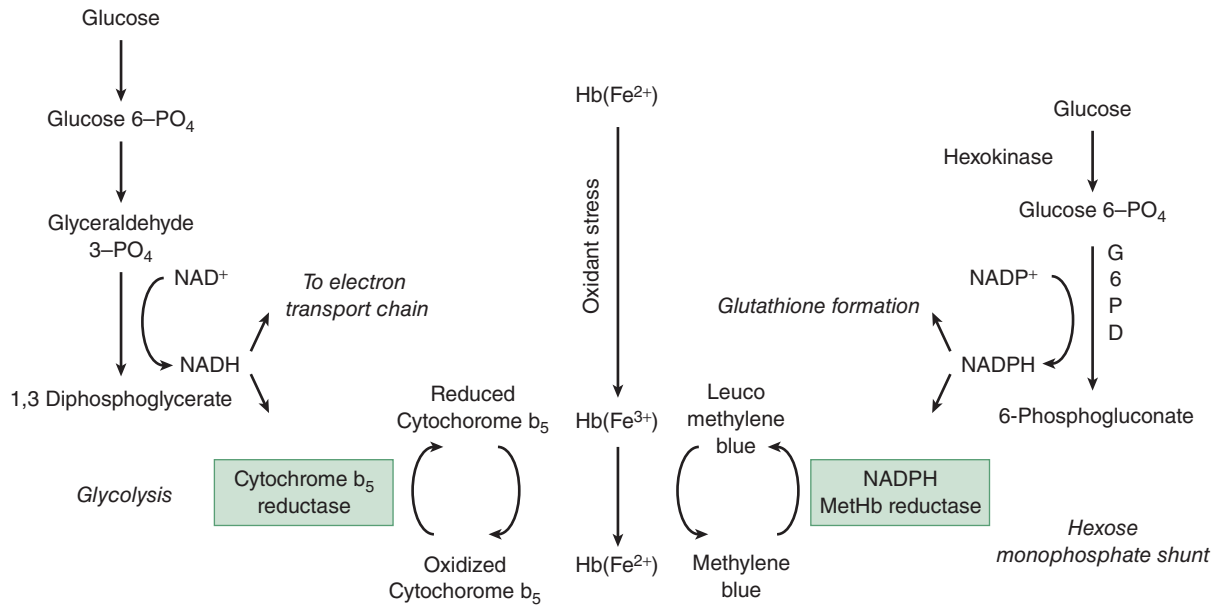

FIGURE 207-1. Methemoglobin formation and mechanism of action of methylene blue. G6PD = glucose-6-phosphate dehydrogenase; $Hb(Fe^{2+})$ = hemoglobin; $Hb(Fe^{3+})$ = methemoglobin; NAD^+ = oxidized nicotinamide adenine dinucleotide; NADH = reduced form of nicotinamide adenine dinucleotide; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; PO_4 = phosphate.

in the ferric form is unable to bind oxygen for transport and is termed *methemoglobin*. Normally, <1% to 2% of circulating hemoglobin exists as methemoglobin; higher concentrations define the condition of *methemoglobinemia*.

Methemoglobin accumulation is enzymatically prevented by the rapid reduction of the ferric iron back to the ferrous form. Cytochrome b_5 reductase is primarily responsible for this reduction, in which reduced nicotinamide adenine dinucleotide donates its electrons to cytochrome b_5, which subsequently reduces methemoglobin to hemoglobin (**Figure 207-1**). This pathway is responsible for reducing nearly 95% of methemoglobin produced under typical circumstances. Methemoglobinemia occurs when this enzymatic reduction is overwhelmed by an exogenous oxidant stress, such as a drug or chemical agent (**Table 207-1**).

Methemoglobin can also be reduced by a second enzymatic pathway using the reduced form of nicotinamide adenine dinucleotide phosphate (or NADPH) and NADPH-methemoglobin reductase.[2] This pathway is normally of minimal importance and is responsible for <5% of total reduction under typical circumstances. However, this enzyme and pathway are crucial for the antidotal effect of methylene blue (Figure 207-1).

The limited role for NADPH partially explains why patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with a resultant deficit of NADPH are **not** at increased risk of developing methemoglobinemia, although they are at risk of developing hemolysis following exposure to an oxidant stress. To a very limited extent, nonenzymatic reduction systems, such as vitamin C and glutathione, may participate in the reduction of methemoglobin to hemoglobin.

The primary adverse clinical effect of methemoglobin is the reduction in the oxygen content of the blood. Because hemoglobin-bound oxygen accounts for the vast majority of an individual's oxygen-carrying capacity, as the methemoglobin concentration rises, oxygen-carrying capacity falls. Patients with methemoglobinemia are often more symptomatic than patients with a simple anemia that produces an equivalent reduction in oxygen-carrying capacity. This is caused by a leftward shift in the oxyhemoglobin dissociation curve, the consequence of which is a reduced release of oxygen from the erythrocyte to the tissue at a given partial pressure of oxygen (**Figure 207-2**).[2]

The oxyhemoglobin dissociation curve of blood with a 50% reduction in erythrocytes (i.e., anemia) follows a curve similar to that of nonanemic blood; although the oxygen content is lower, unbinding of half of the oxygen (50% oxygen saturation) occurs at the same partial pressure of oxygen. With 50% methemoglobin, the leftward shift of the oxyhemoglobin dissociation curve means that hemoglobin is less willing to give up its oxygen, so that tissue hypoxia is more severe than in those with a 50% anemia.

Acquired Methemoglobinemia Drugs in conventional doses rarely produce clinically significant methemoglobinemia (Table 207-1). Benzocaine is the local anesthetic most commonly associated with methemoglobinemia.[3-6] Methemoglobin induction with sodium nitrite is a therapeutic goal in the management of patients suffering from

TABLE 207-1 Drugs Causing Methemoglobinemia

Oxidant	Comments
Analgesics	
Phenazopyridine	Commonly reported
Phenacetin	Rarely used
Antimicrobials	
Antimalarials	Common
Dapsone	Hydroxylamine metabolite formation is inhibited by cimetidine
Sulfamethoxazole	Uncommon
Local Anesthetics	
Benzocaine	Most commonly reported of the local anesthetics
Lidocaine	Rare
Prilocaine	Common in topical anesthetics
Dibucaine	Rare
Nitrates/Nitrites	
Amyl nitrite	Cyanide antidote kit and used to enhance sexual encounters
Isobutyl nitrite	Used to enhance sexual encounters
Sodium nitrite	Cyanide antidote kit
Ammonium nitrate	Cold packs
Silver nitrate	Excessive topical use
Well water	Problem in infants, due to nitrate fertilizer runoff
Nitroglycerin	Rare
Other	
Rasburicase	Treatment for hyperuricemia in tumor lysis syndrome

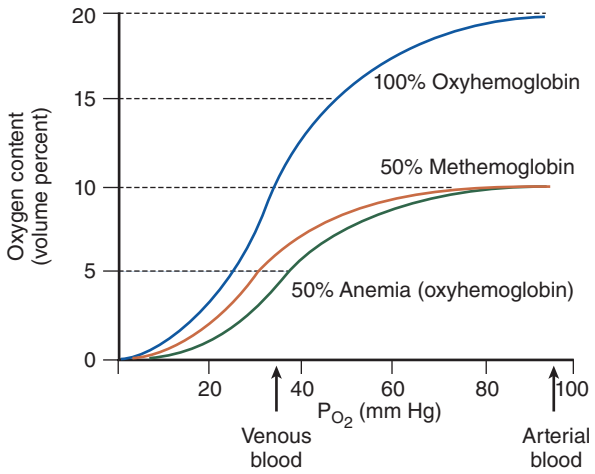

FIGURE 207-2. Oxyhemoglobin dissociation curve.

cyanide poisoning (see Chapter 204, "Industrial Toxins"). With certain compounds, particularly dapsone, metabolism to the "active" oxidant is required before induction of methemoglobinemia, so there may be substantial delay until toxicity is evident.[7] Occupational methemoglobinemia usually involves exposure to aromatic compounds, primarily amino- and nitro-substituted benzenes.[8] Routes of absorption are typically dermal or inhalational due to the high lipophilicity and volatility of these compounds, respectively.

Neonates and infants are more susceptible to methemoglobin accumulation because of undeveloped methemoglobin reduction mechanisms. This accounts for the relatively common development of methemoglobinemia in infants given certain nitrogenous vegetables (e.g., spinach), who consume well water that contains high nitrate levels (generally from fertilizer use), or who experience gastroenteritis where GI flora can convert nitrate to the nitrite form.[9,10]

Hereditary Methemoglobinemia Hereditary methemoglobinemia results from either an enzymatic deficiency (i.e., cytochrome b_5 reductase) or from the presence of an amino acid substitution within the hemoglobin molecule itself, termed *hemoglobin M*.[1] Patients with cytochrome b_5 reductase deficiency develop methemoglobin levels of 20% to 40%. Cyanosis in these individuals begins at birth, but they remain asymptomatic and develop normally.

Hemoglobin M, an abnormal form of hemoglobin, has altered tertiary structure so that the heme iron exists in an environment favoring the ferric form. This disorder only occurs in the heterozygous form, because the homozygous form is incompatible with life. As with cytochrome b_5 reductase deficiency, patients develop profound cyanosis but tolerate the elevated methemoglobin concentrations well due to compensatory mechanisms.

CLINICAL FEATURES

Healthy patients who have normal hemoglobin concentrations do not usually develop clinical effects until the methemoglobin level rises above 20% of the total hemoglobin.[11,12] At methemoglobin levels between 20% and 30%, anxiety, headache, weakness, and lightheadedness develop, and patients may exhibit tachypnea and sinus tachycardia. Methemoglobin levels of 50% to 60% impair oxygen delivery to vital tissues, resulting in myocardial ischemia, dysrhythmias, depressed mental status (including coma), seizures, and lactate-associated metabolic acidosis. Levels above 70% are largely incompatible with life.

Cyanosis associated with methemoglobin is often described as a gray discoloration of skin, with a detection threshold for methemoglobin of 1.5 grams/dL, corresponding to methemoglobin levels between 10% and 15% in a nonanemic individual. **Anemic patients may not exhibit cyanosis until the methemoglobin level rises well above 10% because cyanosis detection is dependent on the concentration of methemoglobin, not the percentage.** Anemic patients may likewise develop clinical features at lower methemoglobin concentrations because the relative percentage of hemoglobin in the oxidized form is greater.

Patients with preexisting cardiopulmonary diseases that impair oxygen delivery will also manifest abnormalities with lesser elevations in their methemoglobin levels. Conversely, compensatory mechanisms that shift the oxyhemoglobin dissociation curve to the right, such as acidosis or elevated 2,3-diphosphoglycerate, may result in somewhat better tolerance of methemoglobin.

DIAGNOSIS

Consider methemoglobinemia in patients with cyanosis, particularly if cyanosis does not improve with supplemental oxygen (**Figure 207-3**).[4,5,7,11,12] A useful clue is that patients with methemoglobin-associated cyanosis generally are less symptomatic than equivalently appearing patients with hypoxemia-induced cyanosis. This is due to the more deeply pigmented color of methemoglobin compared with deoxyhemoglobin; it takes about 5 grams/dL of deoxyhemoglobin to cause cyanosis, which equates to an oxygen-carrying capacity of approximately 67% of normal (in someone with a total hemoglobin of 15 grams/dL), compared with the cyanosis visible with a methemoglobin concentration of 1.5 grams/dL, which equates to an oxygen-carrying capacity of 90% of normal. Blood containing more than 20% methemoglobin has a characteristic "chocolate brown" color when phlebotomized. A color reference chart has been developed to estimate methemoglobin levels from drops of blood on white absorbent paper.[13,14]

Pulse oximetry results are not accurate in patients with methemoglobinemia.[15] The standard pulse oximeter uses two wavelengths of light, 660 nm and 940 nm, to calculate the percentage of oxyhemoglobin. Methemoglobin is also detected by these wavelengths, so light absorption by methemoglobin confounds the calculation for the oxyhemoglobin

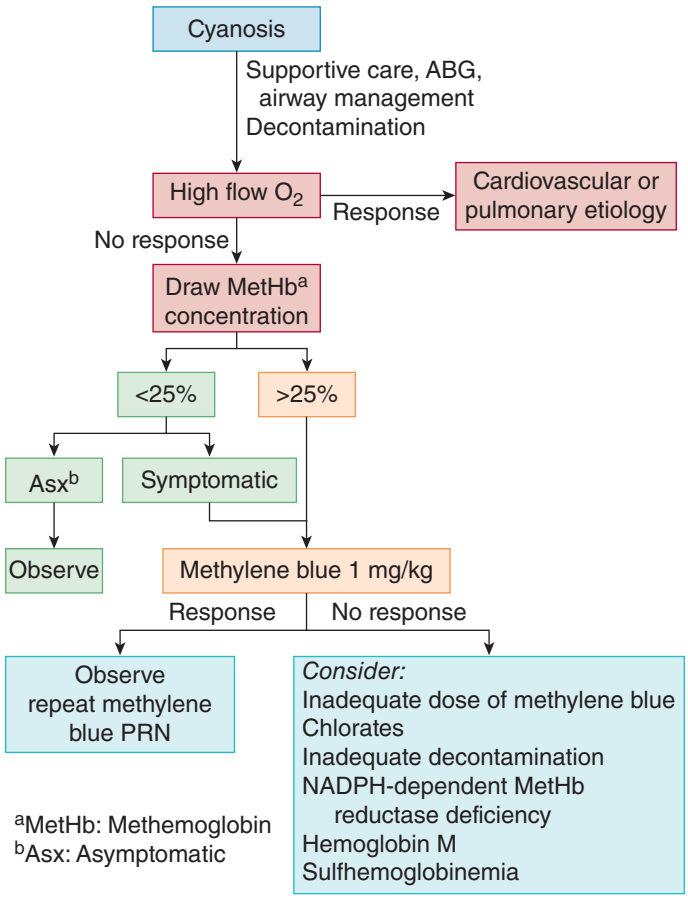

FIGURE 207-3. Toxicologic approach to the cyanotic patient. ABG = arterial blood gas; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate. [Reproduced with permission from Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS, (eds): *Goldfrank's Toxicologic Emergencies*, 11th ed. New York: McGraw-Hill, Inc., 2019; Figure 124-7.]

percentage. **In patients with methemoglobinemia, the pulse oximeter will report a falsely elevated value for arterial oxygen saturation percentage.** The specific values vary by oximeter, but typically report approximately 85%.[15]

Commercially available pulse co-oximeters and pulse spectroscopy use additional wavelengths of light to measure the total hemoglobin concentration and percentages of carboxyhemoglobin and methemoglobin.[16-18] Their accuracy for detecting methemoglobinemia has improved with additional wavelengths, improved probes, and more robust software.

Definitive identification of dyshemoglobinemias requires co-oximetry, a spectrophotometric method capable of differentiating oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin species.[11,12] This widely available test can be performed on a venous or arterial specimen.

Arterial blood gas results may be initially deceptive because the partial pressure of oxygen, a measure of dissolved, not bound, oxygen, is normal. Thus, calculation of oxygen saturation from measured partial pressure by the blood gas analyzer will produce a falsely elevated result.

TREATMENT

Patients with methemoglobinemia require supportive measures to ensure oxygen delivery and administration of appropriate antidotal therapy, if indicated (**Table 207-2**).[11,12] Gastric decontamination is of limited value, because there often is a substantial time interval between exposure to the toxic agent and the development of methemoglobin. If a source of continuing GI exposure is suspected, decontamination is indicated, and in most stable patients, a single dose of activated charcoal is likely sufficient. Dermal decontamination should be used as indicated. **Antidotal therapy with methylene blue is reserved for symptomatic patients or for those asymptomatic patients with methemoglobin levels >25%.**

Methylene blue indirectly accelerates the enzymatic reduction of methemoglobin by NADPH-methemoglobin reductase. NADPH-methemoglobin reductase reduces methylene blue to leucomethylene blue, which is then capable of directly reducing the oxidized iron (Fe^{3+}) back to the ferrous state (Fe^{2+}) (Figure 207-1). **The initial dose of methylene blue is 1 milligram/kg (0.1 mL/kg of the 1% solution or approximately 7 mL in an adult) IV slowly over 5 minutes**. The infusion should be slow because rapidly administered doses of methylene blue are painful. Clinical improvement should be seen within 20 minutes, and as the methemoglobin level falls, the most severe signs and symptoms will resolve first. Resolution of the cyanosis occurs later only after the methemoglobin concentration falls below 1.5 grams/dL. Repeat dosing of methylene blue is acceptable if cyanosis has not cleared in 1 hour. Serotonin syndrome is a rare risk when methylene blue is administered to patients on serotonergic drugs such as antidepressants.[19,20]

Treatment failures may result if the patient has G6PD deficiency, because this enzyme is critical for the production of NADPH by the hexose monophosphate shunt (Figure 207-1). Hemolysis may impede a response to methylene blue, which requires an intact erythrocyte to be effective. Oxidant drugs with long serum half-lives, such as dapsone, with a half-life of approximately 50 hours, produce prolonged oxidant stress to the red blood cell. Therefore, **dapsone-exposed patients may require repetitive dosing of methylene blue.**[21] Because the hydroxylamine metabolite of dapsone is responsible for the production of methemoglobin, inhibition of its formation by cytochrome P450 with cimetidine, in standard doses, is generally recommended.[7]

In rare instances, patients may be deficient in NADPH-methemoglobin reductase, the required enzyme for methylene blue activation. Treatment failure may occur in patients with sulfhemoglobinemia, which is clinically indistinguishable from methemoglobinemia but which is not responsive to methylene blue. Methemoglobinemia due to chlorate poisoning is responsive to methylene blue when used early in mild cases, but less responsive in severe poisonings when hemolysis is present. Patients who do not respond to methylene blue should be treated supportively. If clinically unstable, the use of packed red cell transfusions or exchange transfusions may be indicated.

TABLE 207-2 Management of Methemoglobinemia

- Assess airway, breathing, and circulation; exclude other causes of cyanosis.
- Insert an IV line.
- Administer oxygen.
- Attach the patient to a cardiac monitor and pulse oximeter or co-oximeter.
- Obtain an ECG as indicated.
- Decontaminate the patient as needed.
- Administer methylene blue if symptomatic or methemoglobin >25%.
- Consider cimetidine for patients taking dapsone.

SULFHEMOGLOBINEMIA

PATHOPHYSIOLOGY

Sulfhemoglobinemia is a rare condition that occurs when a sulfur atom irreversibly binds to the porphyrin ring of the heme moiety and induces the permanent oxidation of iron to the ferric (Fe^{3+}) state.[1] Many of the agents responsible for sulfhemoglobinemia are identical to those associated with methemoglobin. Because many of these drugs or chemicals do not contain sulfur, the origin of sulfur is speculative; hypotheses include alteration of intestinal flora with production of hydrogen sulfide and/or glutathione from bacteria such as *Morganella morganii*.[22,23] Historically, sulfhemoglobinemia was most often associated with acetanilide, phenacetin, sulfonamide, and a proprietary mixture that contained sodium bromide. Because these drugs are rarely used and the sodium bromide component in the proprietary mixture was removed in 1975, contemporary cases of drug-induced sulfhemoglobinemia are now most often reported with phenazopyridine, dapsone, metoclopramide, and sumatriptan.[24,25] Sulfhemoglobinemia has been associated with industrial chemicals, such as trinitrotoluene, hydroxylamine sulfate, dimethyl sulfoxide, and hydrogen sulfide.[26]

CLINICAL FEATURES

Patients with sulfhemoglobinemia can have a clinical presentation similar to those with methemoglobinemia.[27] However, the disease process itself is substantially less concerning because, although the reduction in the patient's oxygen-carrying capacity is quantitatively similar, the sulfhemoglobin oxygen dissociation curve is shifted rightward, not leftward as in methemoglobinemia, favoring the release of hemoglobin-bound oxygen to the tissue with sulfhemoglobinemia. Because of the milder symptoms, it is likely that cases of sulfhemoglobinemia are often missed.[28]

DIAGNOSIS

The pigmentation of the blood by sulfhemoglobin is substantially more intense than other colored hemoglobin species; only 0.5 gram/dL of sulfhemoglobin is needed to produce a cyanosis equivalent to that produced by 1.5 grams/dL of methemoglobin or 5 grams/dL of deoxyhemoglobin. The color of blood drawn from a patient with sulfhemoglobinemia has been described as dark green-black. **In sulfhemoglobinemia, standard pulse oximetry tends to report a falsely low value for arterial oxygen saturation percentage.**[29] The diagnosis of sulfhemoglobinemia may be difficult to confirm as special settings for laboratory co-oximetry are required to reliably measure sulfhemoglobin concentration.[30]

TREATMENT

Sulfhemoglobin persists for the life of the red cell and the level is not reduced by treatment with methylene blue. Most patients require only supportive care, although exchange transfusion or packed red cell transfusion is occasionally recommended for patients with severe toxicity.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 16

Environmental Injuries

CHAPTER 208

Cold Injuries

Michael T. Paddock

INTRODUCTION

The occurrence of cold-related injuries depends on the degree of cold exposure, as well as environmental and individual factors. Frostbite is the prototypical freezing injury and is seen when ambient temperatures are well below freezing. Nonfreezing cold injuries occur as a result of exposure to wet conditions when temperatures are above freezing. The most common nonfreezing cold injuries are trench foot and chilblains. Although frostbite is likely to result in permanent tissue damage, nonfreezing cold injuries are characterized by usually mild but uncomfortable inflammatory lesions of the skin. This chapter describes the occurrence, risk factors, and treatment of the nonfreezing cold injuries—trench foot and immersion foot, chilblains or pernio, panniculitis, and cold urticaria—and freezing injury—frostbite.

NONFREEZING COLD INJURIES

TRENCH FOOT

Trench foot, or immersion foot, was first identified during military operations. Homelessness, alcoholism, substance abuse, and psychiatric disorders are risk factors for trench foot.[1,2] The pathophysiology of trench foot is multifactorial, but involves direct injury to soft tissue and peripheral nerves sustained from prolonged cooling, accelerated by wet conditions.[3]

Early symptoms progress from subjective tingling to numbness of the affected tissues. On initial examination, the foot may appear pale, mottled, anesthetic, pulseless, and immobile, with no immediate change after rewarming. A hyperemic phase begins within hours after rewarming and is associated with severe burning pain and reappearance of proximal sensation. As perfusion returns to the foot over 2 to 3 days, edema and bullae may form. Anesthesia frequently persists for weeks and may be permanent. In more severe cases, tissue sloughing and gangrene may develop. Hyperhidrosis and cold sensitivity are common late features and may persist for months to years. Severe cases may be associated with prolonged convalescence and permanent disability.[4] Treatment is supportive, but vasodilator drugs may be tried, such as oral prostaglandin E_1, limaprost, a vasodilator that increases blood flow and inhibits platelet aggregation. Limaprost, 20 micrograms orally three times daily, has been shown to increase skin temperature, which suggests improved circulation.[5] Feet should be kept clean and warm and be dryly bandaged, elevated, and closely monitored for early signs of infection. Prophylaxis for trench foot includes keeping warm, ensuring good boot fit, changing out of wet socks several times a day, never sleeping in wet socks and boots, and, once early symptoms are identified, maximizing efforts to warm, dry, and elevate the feet.

CHILBLAINS OR PERNIO

Chilblains, or pernio, are characterized by mild but uncomfortable inflammatory lesions of the skin caused by long-term intermittent exposure to damp, nonfreezing ambient temperatures. Symptoms are precipitated by acute exposure to cold.[6] The most common areas affected are the feet (toes), hands, ears, and lower legs. Chilblains are primarily a disease of women and children, and although rare in the United States, the disease is common in the United Kingdom and other countries with a cold or temperate, damp climate.[6] In addition, young females with Raynaud's phenomenon and other immunologic abnormalities such as lupus erythematosus, as well as those in households with inadequate heating and lack of warm clothing, are at greatest risk. Some studies suggest that a low body mass index may be associated with increased risk.[6,7]

Early symptoms progress from tingling to numbness of the affected tissues. The cutaneous manifestations, which appear up to 12 to 24 hours after acute exposure, include localized edema, erythema, cyanosis, plaques, nodules, and, in rare cases, ulcerations, vesicles, and bullae. Patients may complain of pruritus and burning paresthesias. Rewarming may result in the formation of tender blue nodules, which may persist for several days.

Management is supportive. The affected skin should be rewarmed, gently bandaged, and elevated. Additional recommended therapy includes nifedipine, 10 to 20 milligrams PO three times daily for vasodilatation; pentoxifylline, 400 milligrams PO three times daily to decrease blood viscosity; or an oral analog of prostaglandin E_1, limaprost, 20 micrograms orally three times daily for vasodilatation.[5,8,9] Topical corticosteroids (e.g., 0.1% triamcinolone cream) are beneficial.[9] Smoking cessation should be advised.[9]

PANNICULITIS

Panniculitis is characterized by mild degrees of necrosis of subcutaneous fat tissue that develops during prolonged exposure to temperatures just above freezing. It is observed in children exposed to local or topical cold objects (e.g., "popsicle panniculitis" of the cheeks) and on the thighs and buttocks of young women involved in equestrian activities due to tight clothing and cold ambient temperatures.[10] During resolution of the mild inflammation, adipose fibrosis may result in cosmetic defects, such as unevenness of the skin. There is no effective treatment for the injury.

COLD URTICARIA

Cold urticaria is a distinctive example of hypersensitivity to cold air or water, which in rare cases may lead to anaphylaxis.[11] Most cases are idiopathic,[12] but they can also be associated with increased affinity of immunoglobulin E to mast cells and viral infections.[12] The diagnosis can be confirmed with the cold water test during outpatient follow-up. Young adults and children and those with atopy or other forms of inducible urticaria are most commonly affected.[11,13]

Cold urticaria is treated similarly to urticarial lesions from other causes. Antihistamines (H_1) are recommended for acute cases, although up to four times the standard dose may be required (avoid elevated doses in patients with chronic kidney disease). Suggested medications include desloratadine (start at 5 milligrams daily, up to 20 milligrams daily for 7 days) or loratadine (start at 10 milligrams daily, up to 40 milligrams PO daily for 7 days).[14] Consensus recommends escalating the dose of nonsedating antihistamines before initiating other medications,[15,16] typically at outpatient follow-up. Other potential therapies include leukotriene receptor antagonists (zafirlukast, montelukast),[17,18] mast cell stabilizers, and immunomodulators.[16] Epinephrine autoinjectors are available for patients with a history of cold-induced anaphylaxis.

FROSTBITE

EPIDEMIOLOGY

Risk factors for frostbite include activities or occupations with increased cold exposure time such as military personnel, winter sports enthusiasts, outdoor workers, the elderly, the homeless, people who abuse drugs or alcohol, and those with psychiatric disorders. Individual attributes, such as physiology, behavior, and general health, affect an individual's likelihood of developing cold-related injuries (**Table 208-1**).[19-24] Wind markedly increases the cooling rate by increasing convective heat loss and reducing the insulation value of clothing, thus increasing the risk of frostbite. Skin temperature is <0°C (<32°F) when frostbite occurs. Frostbite can develop within 2 to 3 seconds when metal surfaces that are at or below –15°C (5°F) are touched.[24]

The areas most commonly affected by frostbite are the head (31% to 39.1% of cases), hands (20% to 27.9%), and feet (15% to 24.9%).[21,25] Studies vary regarding which of these sites is most commonly affected, with military personnel reporting higher incidences of foot and hand involvement than civilians.[25] Although most cases of frostbite are mild (frostnip), 12% of cases are more severe (**Table 208-2**).[19]

PATHOPHYSIOLOGY

Frostbite is tissue injury secondary to freezing. It is generally agreed that freezing alone is usually not sufficient to cause tissue death, and the consequences of thawing contribute markedly to the degree of injury.[26] The depth of tissue freezing depends on the temperature, the duration of exposure, and the velocity of freezing.

TABLE 208-1 Factors Increasing the Likelihood of Frostbite

Environmental
- Lower temperatures (especially <20°C, –4°F)
- Higher wind speed (>4.5 m/s, 10 mph)
- Increased wetness
- Contact with cold objects (metal) or liquids (petroleum, oil)
- Duration of cold exposure
- Hypoxia
- Altitude (>5182 m, 17,000 ft)

Physical/anthropometric characteristics
- Male gender
- Increasing age in men
- Activity that increases cold or wind exposure
- Prolonged stationary posture
- Poor cold acclimatization
- Alcohol use
- Fatigue
- Dehydration
- Smoking
- Use of moisturizing ointments on exposed skin
- Inappropriate or wet clothing
- Constrictive clothing (e.g., tight boots)

Health-related/physiologic
- Raynaud's phenomenon
- Vibration-induced white finger
- Cold-induced vasodilation reactivity
- Other peripheral vascular diseases
- Diabetes
- Peripheral neuropathies
- Certain medications (e.g., vasoconstrictive drugs)
- Previous cold injury
- Psychiatric disorders or altered mental status

TABLE 208-2 Body Parts Affected by Frostbite (Lifetime Cumulative Incidence)

	Number of Frostbite Episodes			
Degree of Frostbite	All	Head	Hands	Feet
All frostbite cases	2555 (44%)	1668 (31%)	1154 (20%)	810 (15%)
First degree	2333 (41%)	1462 (28%)	1064 (19%)	738 (14%)
Higher than first degree, deep	671 (12%)	459 (9%)	213 (4%)	174 (3%)

Notes: Study population, N = 5839. Some persons had multiple locations and degrees of frostbite.

Endothelial damage, beginning at the point of thaw, is the likely critical event in frostbite. Immediately after freezing and thawing, an arachidonic acid cascade forms and promotes vasoconstriction, platelet aggregation, leukocyte sludging, and erythrostasis, which results in venule and arterial thrombosis and subsequent ischemia, necrosis, and dry gangrene.[27] The necrosis of tissue following frostbite either is due to cellular injury or is secondary to a vascular lesion.[26]

Frostbite injury can be divided into three zones. The zone of coagulation is the most severe and is usually distal, and the damage is irreversible. The zone of hyperemia is the most superficial, is typically proximal, has the least cellular damage, and generally recovers without treatment in <10 days. The zone of stasis is the middle ground and is characterized by severe, but possibly reversible, cell damage. It is this middle zone for which treatment may have benefit if the circulation in the frozen area can be restored.

Tissue susceptibility to frostbite varies. The least to most sensitive tissues are, in order, cartilage, ligament, blood vessel, cutis, epidermis, bone, muscle, nerve, and bone marrow.

CLINICAL FEATURES AND DIAGNOSIS

Frostbite injuries are frequently classified by the depth of injury and amount of tissue damage based on appearance after rewarming (**Table 208-3**). Visual determination of tissue viability is difficult during the first few weeks after the injury, and viable tissue can often be identified only after gangrenous tissue has demarcated and sloughed.

First-degree injury (frostnip) is characterized by partial skin freezing, erythema, mild edema, lack of blisters, and occasional skin desquamation several days later. The patient may complain of stinging and burning, followed by throbbing. Prognosis is excellent. Second-degree injury is characterized by full-thickness skin freezing, formation of substantial edema over 3 to 4 hours, erythema, and formation of clear blisters filled with fluid rich in thromboxane and prostaglandins (**Figure 208-1**). The blisters form within 6 to 24 hours, extend to the end of the digit, and usually desquamate and form hard black eschars over several days. The patient complains of numbness, followed later by aching and throbbing. Prognosis is good. Third-degree injury is characterized by damage that extends into the subdermal plexus. Hemorrhagic blisters form and are associated with skin necrosis and a blue-gray discoloration of the skin (**Figure 208-2**). The patient may complain that the involved extremity feels like a "block of wood," which is followed later by burning, throbbing, and shooting pains. Prognosis is often poor. Fourth-degree injury is characterized by extension into subcutaneous tissues, muscle, bone, and tendon. There is little edema. The skin is mottled, with nonblanching cyanosis, and eventually forms a deep, dry, black, mummified eschar. Vesicles often present late, if at all, and may be small, bloody blebs that

TABLE 208-3 Classification of Frostbite Injuries

First degree	Numbness, central pallor with surrounding erythema and edema, desquamation, dysesthesia
Second degree	Blisters of the skin with surrounding edema and erythema
Third degree	Tissue loss involving the entire thickness of the skin; hemorrhagic blisters
Fourth degree	Tissue loss involving the entire thickness of the part, including deep structures, resulting in the loss of the part



FIGURE 208-1. Second-degree frostbite in the hand with blisters. [Photo contributed by Scott Sherman, MD.]



FIGURE 208-3. Third- and fourth-degree frostbite of bilateral feet. [Photo contributed by Edward Lew, MD.]

do not extend to the digit tips. The patient may complain of a deep, aching joint pain. Prognosis is extremely poor (**Figures 208-3** and **208-4**).

DIAGNOSIS

The diagnosis of frostbite is clinical. Frostbite may occur anywhere on the skin, but is generally limited to the distal part of the extremities, face, nose, and ears. The injured area looks pale and waxy and feels hard and cold. Patients frequently complain of stinging and numbness.

Because it is initially difficult to estimate the depth of the cold injury, early injuries are best classified simply as either superficial or deep. Prognostic considerations of ultimate tissue loss should take into account duration of exposure, environmental conditions (temperature, wind, and precipitation), type of clothing worn, level of physical activity, possible contact with metal or moisture, and associated use of recreational drugs, alcohol, or tobacco in addition to physical findings. Patients with frostbite may have concomitant cold-related problems such as hypothermia and dehydration, and conversely, patients with hypothermia may also have frostbite.

Although some chemical liquids and burn injuries may cause blister formation, a history of cold exposure differentiates chemically induced blisters from cold-induced injuries.



FIGURE 208-2. Second- and third-degree frostbite in the hand with blisters. [Photo contributed by Edward Lew, MD.]

No specific laboratory tests are indicated when treating patients with frostbite, and specific laboratory evaluation should be guided by the clinical situation including associated trauma or medical illness, as well as guiding the safety of therapeutic agents. Imaging prior to rewarming is not helpful, either for diagnostic or prognostic purposes. The use of technetium-99 scintigraphy (bone scan) has prognostic value and may guide subsequent therapy.[28,29] Angiogram of the affected extremity



A



B

FIGURE 208-4. **A.** Fourth-degree frostbite 1 month after injury. Note the clear demarcation line in the fingers. **B.** The same hands 2 months after surgical treatment.

may have prognostic and therapeutic value after initial rewarming has been performed. A retrospective case review of 114 patients in a single burn center undergoing protocolized diagnostic angiogram assessment reported both positive and negative predictive value in determining need for amputation of the affected extremities.[30] Patients who demonstrated flow abnormalities within 24 hours of rewarming underwent immediate intra-arterial thrombolysis.[30] Patients should not receive angiograms at institutions unable to provide therapeutic intervention.

TREATMENT

Prehospital Care Initial field management of frostbite includes prevention of further cold injury, hypothermia, and dehydration. Remove wet and constrictive clothing, cover with dry clothing, and protect against wind. Do not heat the frozen area, because dry heat may cause further injury. Do not attempt rewarming until the risk of refreezing is eliminated.[31,32] Refreezing will cause even more severe damage and is an important concern when initiating prehospital care. Provide analgesia, as the rewarming process is very painful. Immobilize and elevate frozen extremities, and handle gently. The patient should not ambulate on edematous or blistered feet. Home remedies such as rubbing the affected area or rubbing snow on frostbitten tissue increase tissue damage and should not be performed.[31,32] Topical agents such as creams or lotions should not be applied in the field.

ED Management Rapid rewarming is the first definitive step of frostbite therapy and should be initiated as soon as the risk of refreezing injury can be avoided.[31,32] Place the injured extremity in gently circulating water heated to a temperature of 37°C to 39°C (98.6°F to 102.2°F), for approximately 20 to 30 minutes, until the distal extremity is pliable and erythematous.[31,32] Frostbitten faces can be thawed using moistened compresses soaked in warm water. Some patients may tolerate immersion of the ears in a bowl or pool of warmed water. Anticipate severe pain during rewarming and treat with parenteral opiates prior to initiating rewarming therapy.

Local care is directed toward tissue preservation and infection prevention. Management of clear blisters and the use of prophylactic antibiotics are somewhat controversial. The blister fluid is rich in destructive thromboxane and prostaglandins. Although removal theoretically limits damage from these chemicals and enables access to the underlying tissue for topical therapy, not all experts agree that removal is indicated. Hemorrhagic blisters should not be debrided, because this often results in tissue desiccation and worse outcome. However, there is some controversy as to whether aspiration is helpful. Both blister types should be treated with topical aloe vera cream every 6 hours, which helps to combat the arachidonic acid cascade and may provide some symptom relief.[31,32] Affected digits should be separated with soft padding and wrapped with sterile, dry gauze. Other affected areas should be dressed in bulky, loose-fitting dry gauze dressings to allow room for the expected subsequent edema. Elevation of the involved extremities may help decrease edema and pain. Ibuprofen, 600 milligrams orally every 6 hours as needed, is recommended due to its prostaglandin effects.[33]

Tetanus immunization status should be assessed and appropriate vaccination administered if needed, as frostbite is a tetanus-prone wound (see Chapter 157, "Tetanus").

Management of Pulse Deficits After Rewarming Management of pulse deficits after rewarming requires coordination of multiple specialists and is best facilitated by institutional protocols to guide and expedite management, as therapy is time sensitive.[34] Pulse deficits should be confirmed by Doppler. If the institution of patient presentation is unable to provide advanced therapies or imaging to direct management, consider transfer to a center with expertise managing severe frostbite, if advanced treatment options can be implemented within 24 hours of rewarming. If contemplating intervention, the vasculature of the involved extremity should be imaged, most commonly with technetium-99 scintigraphy or angiography, depending on institutional protocol and anticipated intervention.

Because microvascular thrombosis plays a role in tissue injury, systemic thrombolytic therapy has been advocated for use in cases at risk for proximal or multiple-digit amputations[35,36] and, when given within 24 hours after rapid rewarming, appears to reduce digit amputations.[31,37-39]

TABLE 208-4 Treatment of Frostbite

Core Treatment

- Immersion in or application of water at 37°C to 39°C (98.6°F to 102.2°F) until affected area is pliable and erythematous; do not begin rewarming until risk of refreezing is eliminated
- Parenteral narcotics for pain management
- Topical aloe vera cream every 6 h
- No blister or soft tissue debridement acutely
- Meticulous local care
- Tetanus immunization
- Ibuprofen, 600 milligrams, or 10 milligrams/kg/dose every 6 hours as needed

Managing Post-rewarming Pulse Deficits

- Prevent refreezing
- Assess local frostbite management expertise; consider transfer to facility with frostbite expertise if advanced treatment can be implemented within 24 hours or rewarming
- Image affected extremity vasculature using institutional protocol
- Consider IV or intra-arterial thrombolytic therapy by institutional protocol
- Consider IV iloprost infusion where available

The evidence in support of IV or intra-arterial tissue plasminogen activator is limited to retrospective studies, and bleeding risks must be weighed against potential benefit.[30] However, thrombolytic therapy is recommended by multiple experts from several specialties.[30,31,40-44] Both IV administration (most commonly tissue plasminogen activator, 0.15 milligram/kg bolus, followed by 0.15 milligram/kg over 6 hours up to a total dose of 100 mg) and intra-arterial administration (with papaverine to reduce vasospasm), using an agent and dose determined by institutional protocol, have been used with success; neither route has been shown to be superior. Heparin should be continued for 24 to 72 hours after thrombolysis is complete. Alternatively, in countries where available (not available in the United States), the prostacyclin iloprost has been shown to be as effective as thrombolytic therapy.[45] Start iloprost at 0.5 nanogram/kg/min IV to a maximum dose of 2 nanograms/kg/min for 5 days, and titrate the dose down if the patient experiences facial flushing with intolerable headache. **Table 208-4** presents the core treatment of frostbite.

Therapies of Uncertain Benefit The role of prophylactic antibiotics is unclear. The edema that is present on the first several days after injury appears to predispose to infection. However, the historical recommendation for penicillin G, 500,000 units IV every 6 hours for 48 to 72 hours, is not evidenced based.[33] Topical antibiotics such as bacitracin or silver sulfadiazine cream are not currently recommended[32,33] and may complicate the concurrent use of aloe vera cream, which may be therapeutic. In contrast to prophylactic antibiotics, suspected infections should be investigated with wound culture and treated empirically. Heparin has not been shown to have benefits outside of being an adjunct to thrombolytic therapy. Hyperbaric oxygen therapy appears to be of limited value, although it can be added after thrombolytic or prostacyclin therapy has been initiated.[46,47]

Early surgical intervention is not indicated in the management of frostbite. Premature surgery has been an important contributor to unnecessary tissue loss and poor results in the past. This is due primarily to the inability to assess the depth of frostbite at early stages and the fact that the blackened, mummified carapace protects the underlying regenerating tissue. Limited early escharotomy may be indicated if the eschar is preventing adequate range of motion or circulation. Fasciotomy is rarely, if ever, indicated.

Austere Environment Treatment Considerations Management of patients in austere environments, such as those in expedition base camps, can be particularly difficult based on environmental conditions, limited access to resources, and reduced ability to transfer patients to more definitive levels of care. Consideration should be given for providing core treatment measures in a field clinic or base camp including rewarming therapy, wound management, and oral prostaglandins.[48] If treatment is to occur at altitude where expected oxygen saturations are

below 90% (>4000 m or 13,000 ft), the use of supplemental oxygen or a portable hyperbaric device should be considered.[48] Recent case series proposed the use of systemic thrombolytic therapy and/or prostacyclin therapy in these environments if transfer is not possible in time to provide potentially definitive management.[48] These cases include severe frostbite of the digits, when amputation risk is high (significant peripheral cyanosis that extends proximally above metacarpophalangeal joints after rewarming), if unable to transfer to higher levels of care within 24 hours.[48] The field use of IV prostacyclin therapy (iloprost) has also been proposed and may be less risky for lower grades of frostbite and if the patient cannot be transferred to a higher level of care within 48 hours.[48]

Sequelae Up to 65% of persons with frostbite injuries experience sequelae from their injuries.[4] Sequelae may be seen in patients with mild injuries but are generally more intense with more severe frostbite. The most typical sequelae are hypersensitivity to cold, pain, ongoing numbness, and increased risk for developing future frostbite injury. The clinical and functional limitations associated with late sequelae are dependent on the type and severity of the frostbite injury and the related anatomic deformities and amputations.

Disposition and Follow-Up Because it is difficult to determine the extent of frostbite on initial examination, it is best to be conservative when contemplating admission. Consider age and social and medical issues when planning disposition. Undomiciled patients should not be discharged back into subfreezing temperatures with an active injury, and a special consideration for admission or discharge to a local shelter is warranted. If the frostbite is extensive and the hospital and staff are not equipped to treat injury of that degree of severity, consider transfer to a tertiary hospital after initial rewarming and treatment.

Patients with only superficial local frostbite may be discharged home if social circumstances allow. Patients with deeper frostbite injuries should be hospitalized. At discharge from the ED, patients must be provided with sufficient guidelines for self-care as well as clear instructions for short-term and long-term follow-up, preferably with local burn center or plastic surgery providers. Patients who are discharged from the ED should be treated with topical aloe vera cream and oral ibuprofen and encouraged not to smoke or drink alcohol to maximize healing potential.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 209

Hypothermia

Douglas J.A. Brown

INTRODUCTION AND EPIDEMIOLOGY

Accidental hypothermia is an involuntary drop in core temperature below 35°C (<95°F) and can often be associated with significant morbidity and mortality.[1] **Therapeutic hypothermia**, also called targeted temperature management, is a purposeful drop in core temperature usually performed with the hope of ameliorating tissue damage associated with an ischemic event.[2,3]

Accidental hypothermia can be subclassified as primary, due to simple environmental exposure, or secondary, due to impaired thermoregulation (**Table 209-1**). Primary accidental hypothermia is commonly seen in cold climates, whereas secondary accidental hypothermia can be seen worldwide. The true incidence of accidental hypothermia and its related morbidity and mortality remains unknown,[4] but estimates suggest it is 0.1 to 5 cases per 100,000 inhabitants in nontropical climates.[5]

TABLE 209-1 Causes of Secondary Hypothermia

Predominantly Increased Heat Loss
- Burns
- Iatrogenic (i.e., blood transfusions and other cold infusions, cooling blankets, inadequate insulation)
- Recent birth

Predominantly Impaired Thermogenesis
- Impaired shivering (i.e., advanced or very young age, malnutrition, physical exhaustion, neuromuscular disease)

Multifactorial
- Medications and toxins (i.e., alcohol, anesthetic agents, narcotics, sedatives, vasodilators)
- Metabolic and endocrine disorders (i.e., alcoholic or diabetic ketoacidosis, hypoadrenalism, hypoglycemia, hypopituitarism, hypothyroidism lactic acidosis, Wernicke's encephalopathy)
- Neurologic (i.e., space-occupying lesion, stroke, spinal cord injury)
- Sepsis (small subset of sepsis cases, more common in the elderly or cachectic patient)
- Shock
- Trauma

HYPOTHERMIA CLASSIFICATION

Historically, hypothermia has been classified as mild, moderate, severe, and profound, based on core temperature, shivering, level of consciousness, and vital signs.[6-8] Unfortunately, there is considerable variation in clinical features at any given temperature, and a reliable core temperature is sometimes unavailable during initial assessment. Shivering is particularly unreliable because it may be present or absent across a wide temperature range. The modified staging system (mild, moderate, severe, and hypothermic cardiac arrest)[6-8] described in **Table 209-2** is a hybrid of the Swiss[8] and classical systems[6] that is based primarily on level of consciousness, the presence or absence of vital signs, and core temperature (when available).

PATHOPHYSIOLOGY

Body temperature is tightly regulated by a combination of behavioral, neuroendocrinologic, and cardiovascular responses to cold stress. Core temperature will fall when the amount of heat lost to the environment exceeds the amount of heat produced.

HEAT LOSS

Heat is lost from a warm body by conduction, convection, evaporation, and radiation. Conduction occurs when a warm body makes direct contact with a cold object. Conductive heat loss can be minimized by avoiding contact with cold or poorly insulated objects (e.g., metal backboards or stretchers). Convective cooling occurs when a fluid (usually air or water) comes in contact with a warm body. The amount of heat lost via convection can be considerable and is proportional to the amount of fluid that flows around the body, the specific heat capacity of the fluid, and the temperature difference between the fluid and the body. Practically, the emergency physician needs to understand that exposure to cool air or water will result in heat loss, that water can absorb a large amount of heat in a short period of time, and that windy conditions or flowing water can significantly increase the rate of cooling. Evaporative heat loss occurs due to the energy required for water to phase change from a liquid to a gas. The amount of heat lost to evaporation is proportional to the temperature difference between the body and the air and the wind speed over the body and is inversely proportional to the humidity. Therefore, a warm, moist body exposed to cold, dry, windy air will lose a significant amount of heat. A vapor barrier (e.g., a plastic bag or sheet) placed around the patient effectively prevents evaporative cooling but is often not practical when repeated access to the patient's skin is required. Radiant cooling occurs because all warm bodies "radiate" heat in the form of electromagnetic waves. Increasing the temperature

TABLE 209-2 Staging and Treatment of Accidental Hypothermia

Stage	Clinical Symptoms	Typical Core Temperature	Treatment
Mild (HT I)	Conscious, shivering	35–32°C	Warm environment and clothing, warm sweet drinks, and active movement (if possible) HT I patients with significant trauma or comorbidities or those suspected of secondary hypothermia should receive HT II treatment
Moderate (HT II)	Impaired consciousness* (may or may not be shivering)	<32–28°C	Active external and minimally invasive rewarming techniques (warm environment; chemical, electrical, or forced air heating packs or blankets; warm parenteral fluids) Cardiac and core temperature monitoring Minimal and cautious movements to avoid dysrhythmias Full-body insulation, horizontal position, and immobilization
Severe (HT III)	Unconscious*, vital signs present	<28°C	HT II management plus: Airway management as required Preference to treat in an ECLS center, if available, due to the high risk of cardiac arrest Consider ECLS in cases with cardiac instability that is refractory to medical management Consider ECLS for comorbid patients who are unlikely to tolerate the low cardiac output associated with HT III
Hypothermic cardiac arrest (HT IV)	Vital signs absent	Cardiac arrest is possible below 32°C; the risk increases substantially below 28°C and continues to increase with ongoing cooling	CPR and up to three doses of epinephrine and defibrillation (further dosing guided by clinical response) Airway management Transport to ECLS† Prevent further heat loss (insulation; warm environment; do not apply heat to head) Active external and minimally invasive rewarming (see HT II) during transport is recommended but controversial; do not apply heat to head

Abbreviations: ECLS = extracorporeal life support; HT = hypothermia.

*Consciousness may be impaired by comorbid illness (e.g., trauma, CNS pathology, toxic ingestion) independent of core temperature.

†Transfering an HT IV patient to an ECLS center may reduce mortality by 40% to 90% (number needed to treat, ~2); if ECLS is not available within a few hours of transport,[7,9] consider on-site rewarming with hot packs or forced air blankets, warm IV fluid, ± warm thoracic lavage, ± warm bladder lavage, and ± warm peritoneal lavage; do not apply heat to the head.

of the room can minimize radiant heat loss, and some losses can be recovered using special reflective fabrics (likely low yield in most clinical situations). In summary, it is important to minimize heat loss in the hypothermic patient, and a basic understanding of the physics of heat transfer can be helpful. Practically, heat loss can be minimized by heating the room, removing wet clothes, drying the patient (or wrapping the patient in a vapor barrier), providing insulation, and protecting the patient from wind.

HEAT CONSERVATION AND PRODUCTION

The most important responses to cold include behavior (e.g., putting on warm clothing, seeking a warm environment), peripheral vasoconstriction, increased metabolic rate, and muscular thermogenesis (voluntary or shivering). Shivering is a remarkably efficient method of heat production, and care is required to preserve this important source of heat. Unfortunately, shivering can be suppressed by medications (e.g., analgesics, sedatives), by the application of warming devices (e.g., hot packs, forced air blankets, warm humidified air), if energy stores are exhausted, or if the core temperature drops below a critical level (~31°C).[6] The suppression of shivering by various warming methods is one of the reasons why the rewarming literature is so controversial.

CONTINUED CORE COOLING

Core temperature may continue to drop after a patient is removed from the cold environment,[10,11] a process often referred to as afterdrop. The amount of continued core cooling will depend on the stage of hypothermia, the degree of thermoregulatory dysfunction, the ongoing cold stress (often significant in the prehospital care environment), and the physics of heat transfer (heat from the relatively warmer core will be transferred to the cooler periphery by direct conduction or by convection from blood flow). Careful experimental studies have demonstrated an approximately 1°C drop in core temperature during minimally invasive rewarming when shivering is inhibited with narcotics[12] or during exercise,[13] but case series have not demonstrated any clinically significant afterdrop or morbidity when minimally invasive rewarming is used.[7,14] In general, healthy uninjured patients who are able to shiver and have adequate fuel reserves (or can drink warm sweet drinks) will be able to self-rewarm once removed from further cold stress. In contrast, patients who have lost the ability to shiver are at significant risk of further temperature decline unless active rewarming is used.[7,15,16] The use of aggressive immersion rewarming techniques such as hot baths or showers should likely be avoided due to the potential risks of vasodilatory hypotension or convective cooling.[17]

SECONDARY HYPOTHERMIA

Cases of secondary hypothermia can be conveniently organized into those caused predominantly by increased heat loss, those caused predominantly by impaired thermoregulation, and those caused by multiple factors (Table 209-1). This classification is somewhat arbitrary, but in general, the multifactorial cases have a higher risk of missed diagnosis and are less likely to fully resolve with rewarming and supportive care. Iatrogenic causes of hypothermia deserve special attention, particularly in trauma patients, where the loss of just a few degrees of core temperature can create a profound coagulopathy and more than double patient mortality.[18] Massive transfusion and large-volume crystalloid resuscitation are common iatrogenic causes of hypothermia unless proper fluid warmers are used. Inadequate insulation, repeated or prolonged exposure to the cool air of the resuscitation or operating room, and inadequate core temperature monitoring all contribute to iatrogenic heat loss, which may increase morbidity and mortality.

COLD PHYSIOLOGY

The body attempts to preserve normothermia through mechanisms such as increased metabolic rate, peripheral vasoconstriction, increased preshivering muscle tone, or shivering. As the core temperature drops

below approximately 35°C, progressive impairment occurs, affecting all of the body's organ systems. CNS impairment can progress from poor judgment, amnesia, and dysarthria to ataxia, apathy, unconsciousness, areflexia, and eventually electroencephalographic arrest.[6] Paradoxical undressing is a potentially deadly behavior that occurs in up to 30% of fatal hypothermia cases.[19] Below approximately 29°C, the pupils may become dilated and fixed, and below approximately 23°C, corneal reflexes may be absent; neither is reliable for neurologic prognosis in hypothermia.[6]

Cardiorespiratory Responses Cardiovascular responses to cold include profound peripheral vasoconstriction and an initial increase in heart rate and blood pressure, usually followed by progressive bradycardia, hypotension, and myocardial irritability. Below approximately 32°C, the risk of cardiac arrest increases as malignant cardiac dysrhythmias become more common, particularly below 28°C.[20] The term ***rescue collapse*** is used to describe cardiac arrest that can commonly occur during extrication, transport, or treatment of a deeply hypothermic patient. The cause of rescue collapse is multifactorial, but ultimately related to the profound irritability of the cold myocardium. Atrial fibrillation and flutter are expected dysrhythmias and not necessarily markers of cardiac instability.[7] ECG changes in hypothermia are variable but classically include bradycardia with prolonged PR, then QRS widening, and then prolonged QT_c. ECGs are often complicated by muscle tremors or shivering, and hypothermia can cause almost any heart block or atrial or ventricular dysrhythmias. The classic **Osborn J waves** (**Figure 209-1**) usually occur below 32°C, can be misdiagnosed as ST-elevation myocardial infarction, and can also be caused by intracranial pathology or sepsis.[6] Occasionally patients may be in a low-flow state, with a very difficult to detect pulse that may provide some oxygen delivery. Asystole is the common final dysrhythmia, but in accidental hypothermia, it does not exclude the possibility of a successful resuscitation.[7]

Respiratory changes include initial tachypnea, followed by a progressive decrease in minute ventilation and eventual respiratory arrest. Pulmonary edema is an inconsistent complication of hypothermia, but is common after resuscitation from stage IV hypothermia. The gradient between end-tidal carbon dioxide ($ETCO_2$) and uncorrected partial pressure of arterial carbon dioxide increases variably in severe hypothermia, making the interpretation of $ETCO_2$ and titration of ventilation parameters challenging in the absence of blood gas measurements.[21]

Metabolic Responses The renal response to hypothermia is termed *cold diuresis* and is a response to vasoconstriction-induced hypervolemia. It results in significant fluid losses, which may be further increased in patients with a history of cold water immersion or alcohol intoxication.[6] Rhabdomyolysis is a potential complication of hypothermia[22]; however, the clinician should always exclude a missed compartment syndrome or extensive frostbite when an elevated creatine kinase is detected. Hypothermia can also cause muscle rigidity, termed *pseudo-rigor mortis*; hence, rigor mortis cannot be used as a reliable marker of death in the cold patient. Hypothermia has a somewhat dramatic impact on coagulation and blood viscosity, and these effects are often underrecognized by clinicians because blood samples are heated to 37°C prior to analysis. Coagulopathy is a concern below 34°C, particularly in trauma patients in whom hypothermia can compromise the chance for a surgical cure and exponentially increase mortality,[18] partly due to poor activity of clotting factors and platelet dysfunction.[23] Hypothermic patients can also be hypercoagulable from a combination of increased viscosity, hemoconcentration, and an inflammatory cascade similar to disseminated intravascular coagulation; these factors can put hypothermic patients at an increased risk for venous thromboembolic disease as well as coronary and cerebral artery occlusion.[6]

Cellular oxygen consumption decreases as core temperature drops and, in an otherwise healthy patient who has adequate oxygen delivery prior to cooling, may provide protection against ischemia. It is estimated that cerebral oxygen requirements are approximately 50% at 28°C, 19% at 18°C, and 11% at 8°C.[6,24] This neuroprotective effect of hypothermia is exploited in certain cardiac surgeries. The most dramatic technique is deep hypothermic circulatory arrest, where patients are cooled to approximately 18°C and cardiac arrest is induced and maintained for up to approximately 30 minutes.[25] The combination of the potential to survive prolonged periods of ischemia, with the uncertainty of knowing if a patient has been in a low-flow state (difficult to detect cardiac activity that provides some oxygen delivery) versus cardiac arrest, increases the complexity of termination of resuscitation decisions for hypothermic patients unless the history clearly indicates death prior to cooling.

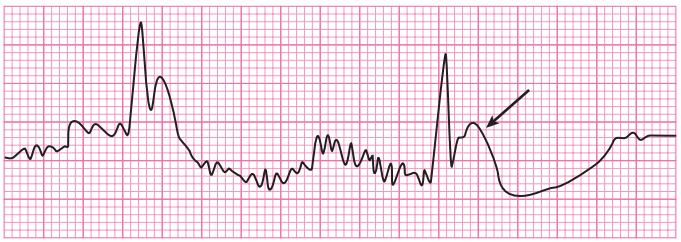

FIGURE 209-1. ECG strip from a patient with a temperature of 25°C (77°F) showing atrial fibrillation with a slow ventricular response, muscle tremor artifact, and Osborn (J) wave (***arrow***).

CLINICAL FEATURES

Patients with hypothermia will feel cold to touch; they will have a core temperature less than 35°C and may have a history of cold exposure or a history of a condition associated with secondary hypothermia (Table 209-1). Hypothermia can be staged clinically using level of consciousness and vital signs (Table 209-2). Measure the core temperature as soon as possible. If the core temperature deviates significantly from the clinical features of the stage, then consider alternative diagnoses. For example, if a patient has a core temperature of 33°C but is unconscious, hypothermia is unlikely the main cause of coma.

CORE TEMPERATURE MEASUREMENT

Make sure that the device being used to measure core temperature is capable of extreme measurements and is properly calibrated (thermistor devices are usually preferred). Temperature measurement at different body sites will yield different readings depending on local perfusion and environmental conditions. In the intubated patient, the lower third of the esophagus (~24 cm below the larynx in an adult) is the preferred site for core temperature measurement, because it closely mirrors the cardiac temperature.[6] In the absence of an esophageal probe, a rectal probe inserted to a depth of 15 cm or a bladder probe is adequate, but realize that these temperatures often lag behind true core temperature during rewarming and that bladder or peritoneal lavage may falsely elevate the reading. Oral and infrared tympanic temperature measurements do not correlate well with core temperature and should not be used. When an accurate core temperature measurement is not available, management decisions should be made based on clinical staging (Table 209-2). Ongoing core temperature monitoring should be implemented as soon as possible for all moderate to severe hypothermia patients (stages II to IV).

DIAGNOSIS

Hypothermia causes dysfunction of every organ system, so the potential list of differential diagnoses is broad. A practical approach is to focus the differential diagnosis using a combination of history, physical exam, and expected degree of dysfunction for the clinical stage and measured core temperature. For the patient with absent vital signs, if the history indicates normothermic cardiac arrest prior to cooling, then hypothermia can be excluded as the cause of cardiac arrest, regardless of the patient's core temperature (**Figure 209-2**). Similarly, in the patient with absent vital signs, asystole, and an accurate core temperature above 32°C, accidental hypothermia is ***not*** the cause of cardiac arrest. Classic diagnostic dilemmas in relation to accidental hypothermia often revolve around impaired cognitive function, level of consciousness, or declaration of death. Intoxication, head injury, and CNS infection are three

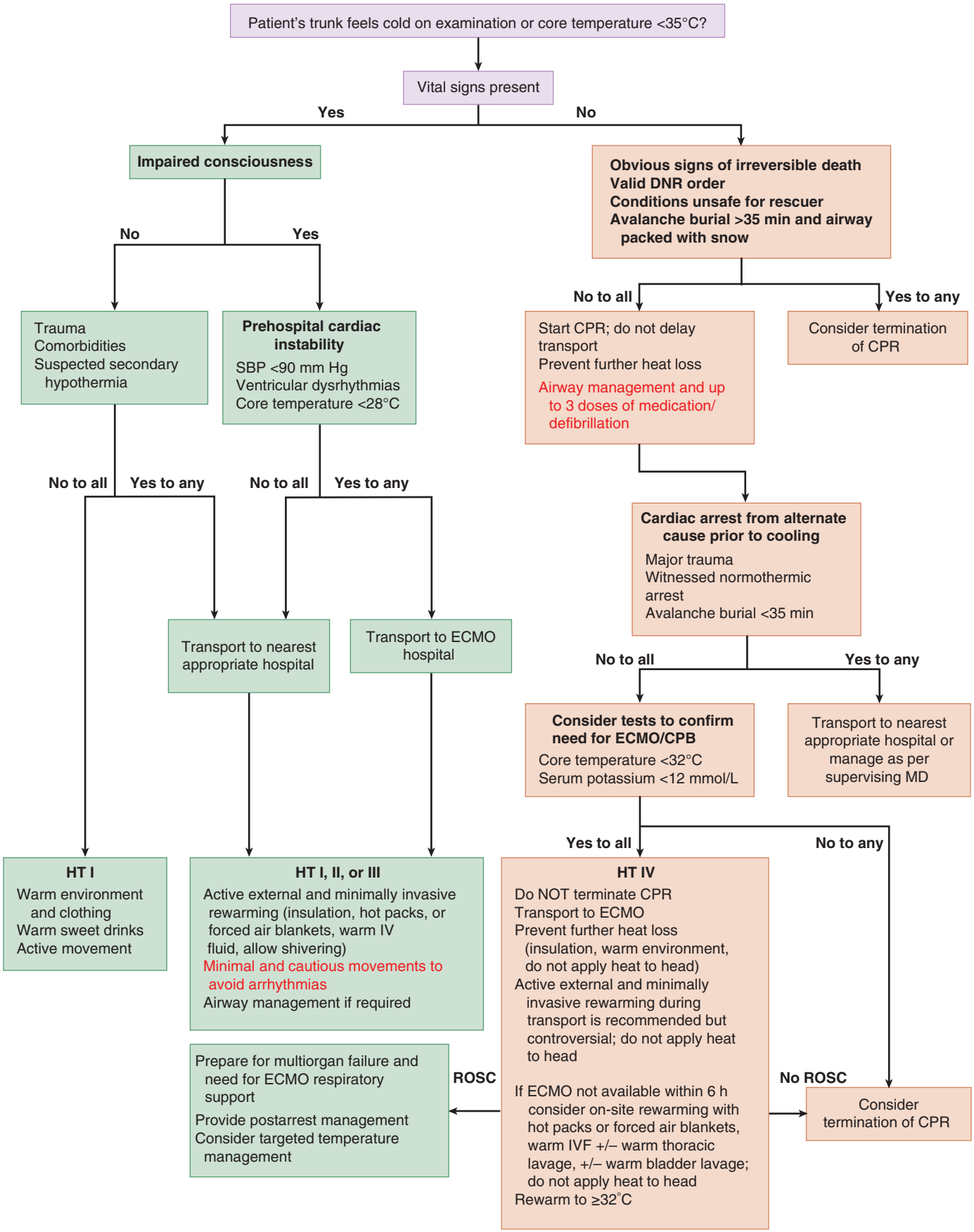

FIGURE 209-2. Transport and management of accidental hypothermia.[7] CPB = cardiopulmonary bypass; DNR = do not resuscitate; ECMO = extracorporeal membrane oxygenation; HT = hypothermia; MD = physician; ROSC = return of spontaneous circulation; SBP = systolic blood pressure.

examples of conditions that impair neurologic function directly, but can also cause secondary hypothermia and cold-related neurologic dysfunction. Vigilance is required with any decreased level of consciousness, particularly if the degree of neurologic impairment does not match the stage of hypothermia. Areflexia or paralysis should not be attributed to hypothermia until spinal injury has been ruled out.

Carefully consider secondary causes of accidental hypothermia, particularly if the measured core temperature is lower than expected based on the cold exposure history or the patient is slow or fails to rewarm with appropriate therapy. Tachycardia or tachypnea can be a marker of secondary pathology in moderate and severe hypothermia (stages II and III), because bradycardia with or without bradypnea is the normal response to hypothermia below a core temperature of approximately 32°C. Intoxication and sepsis are two common causes of secondary hypothermia, and depending on the patient presentation, routine screening and, in some cases, empiric therapy may be reasonable. Classic causes such as adrenal failure and myxedema coma are comparatively rare, and empiric testing or therapy is likely unwarranted in the absence of good historical or laboratory evidence. Hyperglycemia that persists after rewarming may indicate secondary pathology such as diabetic ketoacidosis or pancreatitis. The appropriate breadth of workup will vary considerably depending on the particular patient and the degree of clinical uncertainty.

DECLARATION OF DEATH

Declaration of death in the presence of hypothermia is particularly challenging due to the ability of hypothermia to mimic death (can cause fixed and dilated pupils, stiffness resembling rigor mortis, absent reflexes, or respiratory arrest) or cause death that may be reversible. **Figure 209-3** provides a triage tool for stage IV (absent vital signs) patients to assist with clinical decision making. In general, patients with obvious signs of irreversible death or who are frozen solid, have a history of normothermic arrest with subsequent cooling, or have a potassium level >12 mmol/L are extremely unlikely to benefit from resuscitative efforts, and death can be declared without rewarming.[7] An exception to the above statement is the child with simultaneous normothermic cardiac arrest and very rapid accidental cooling (e.g., a child pinned underwater in an icy creek); in such a case, prolonged resuscitation and expert consultation may be appropriate (see "Children" under the "Special Considerations/Special Populations" section).[26]

LABORATORY TESTING AND IMAGING

Laboratory testing and imaging studies should be targeted based on history, physical examination, and the differential diagnosis. It seems reasonable that every hospitalized hypothermia patient undergo point-of-care glucose testing, but additional routine tests are not necessarily required. An ECG should be obtained for moderate and severe hypothermia (stages II and III) patients, and a chest radiograph is likely reasonable depending on the suspicion for conditions such as aspiration or pulmonary edema. For cases where secondary hypothermia is suspected, measuring CBC, serum electrolytes, creatinine, glucose, lactate, lipase, thyroid-stimulating hormone, random cortisol level, osmolality, and levels of potential intoxicants (e.g., ethanol, aspirin, acetaminophen) and calculation of the anion and osmolar gap may be reasonable depending on clinical suspicion. Patients with suspected sepsis may benefit from blood culture. For patients with suspected compartment syndrome, frostbite, or prolonged immobility, measure serum creatine kinase. Severe hypothermia (stages III and IV) patients should be considered critically ill, and therefore, expanded laboratory testing including CBC, electrolytes, pH, lactate, blood gas levels, and creatine kinase may be considered. For patients in cardiac arrest (stage IV), a serum potassium level ≥12 mmol/L is strongly associated with nonsurvival.[7]

HYPOTHERMIA EFFECTS ON LABORATORY VALUES

Laboratory results from hypothermic patients can be difficult to interpret due to the fact that high, low, or "normal" values may be appropriate in different patients. In an otherwise healthy patient with primary hypothermia, most laboratory values will normalize with rewarming; therefore, treat the patient, not the numbers. For complex cases or those that do not respond to usual therapy, it may be helpful to have a sense of the "expected" abnormalities associated with hypothermia. Hematocrit classically increases approximately 2%/°C, secondary to decreased circulating plasma volume.[6] WBC counts may be normal or decreased due to sequestration or secondary causes such as sepsis. Electrolyte abnormalities are inconsistent, and cold blood may be prone to sampling hemolysis; hence, rewarming and ongoing monitoring are often the best strategy. Glucose levels are somewhat unpredictable, with an early rise being common secondary to catecholamine-induced gluconeogenesis and hypothermia-induced insulin resistance. This increase is classically followed by a drop with the onset of resource depletion and metabolic failure.[6] Acid-base disturbances in hypothermia are complex; some hypothermic patients will be acidotic, whereas others may be alkylotic, and both conditions may be an appropriate physiologic response to cooling[6] or may be a marker of secondary pathology. Blood gas analyzers rewarm samples to 37°C, and in rewarmed samples, the partial pressure of gases increases and the pH is lower, compared with the cold in vivo sample (correction usually not required; see stage III treatment for details). It is also important to note that the coagulopathy of hypothermia (see earlier section, "Cold Physiology") will not be apparent on laboratory results due to the warming of samples prior to testing.

TREATMENT

Treatment of accidental hypothermia varies depending on the clinical stage, but the general principles include basic or advanced life support, prevention of further heat loss, transport to an appropriate facility if indicated,[27] rewarming (Table 209-2 and Figure 209-2), and in secondary hypothermia, treatment of the underlying cause.

MILD HYPOTHERMIA (STAGE I)

Otherwise healthy stage I patients (conscious, shivering, core temperature ≥32°C) can often be rewarmed locally using a warm environment, provision of dry clothes, warm sweet drinks, and active movement. Stage I patients with traumatic injuries or significant medical comorbidities or in whom secondary hypothermia is suspected should be transported to the nearest appropriate hospital and managed as per stage II guidelines.

MODERATE HYPOTHERMIA (STAGE II)

Stage II patients (impaired consciousness, may or may not be shivering, core temperature ~28°C to 32°C) require careful handling, prevention of further heat loss, active external and minimally invasive rewarming (warm environment; forced air, electrical, or chemical warming blankets; warm parenteral fluids), cardiac monitoring, and core temperature monitoring (**Figure 209-4**). Careful handling to decrease the risk of cardiac dysrhythmia becomes important for stage II and III patients, due to the increasing irritability of the cold myocardium. For all stages of hypothermia, warmed crystalloids (38°C to 42°C) should be titrated based on clinical volume status. Significant volume might be required during rewarming. Warmed IV fluids do not provide significant heat, but do prevent iatrogenic cooling. Atrial fibrillation, atrial flutter, and bradycardia are common in accidental hypothermia, do not usually require specific therapy, and typically resolve with rewarming. **Vasopressors are usually not indicated in early resuscitation** because hypothermia already provides maximal vasoconstriction and the addition of vasopressors may increase the risk of dysrhythmia. Vasopressors may be indicated later in resuscitation if rewarming-induced vasodilation cannot be managed with fluids and is contributing to significant hypotension. Special care is required when assessing the risk-to-benefit ratio of sedatives and analgesics. Many medications will inhibit shivering, decrease sympathetic tone, and/or cause vasodilatation, all of which can contribute to a further drop in core body temperature.[13] Depending on the stage of hypothermia, the degree of thermoregulatory dysfunction,

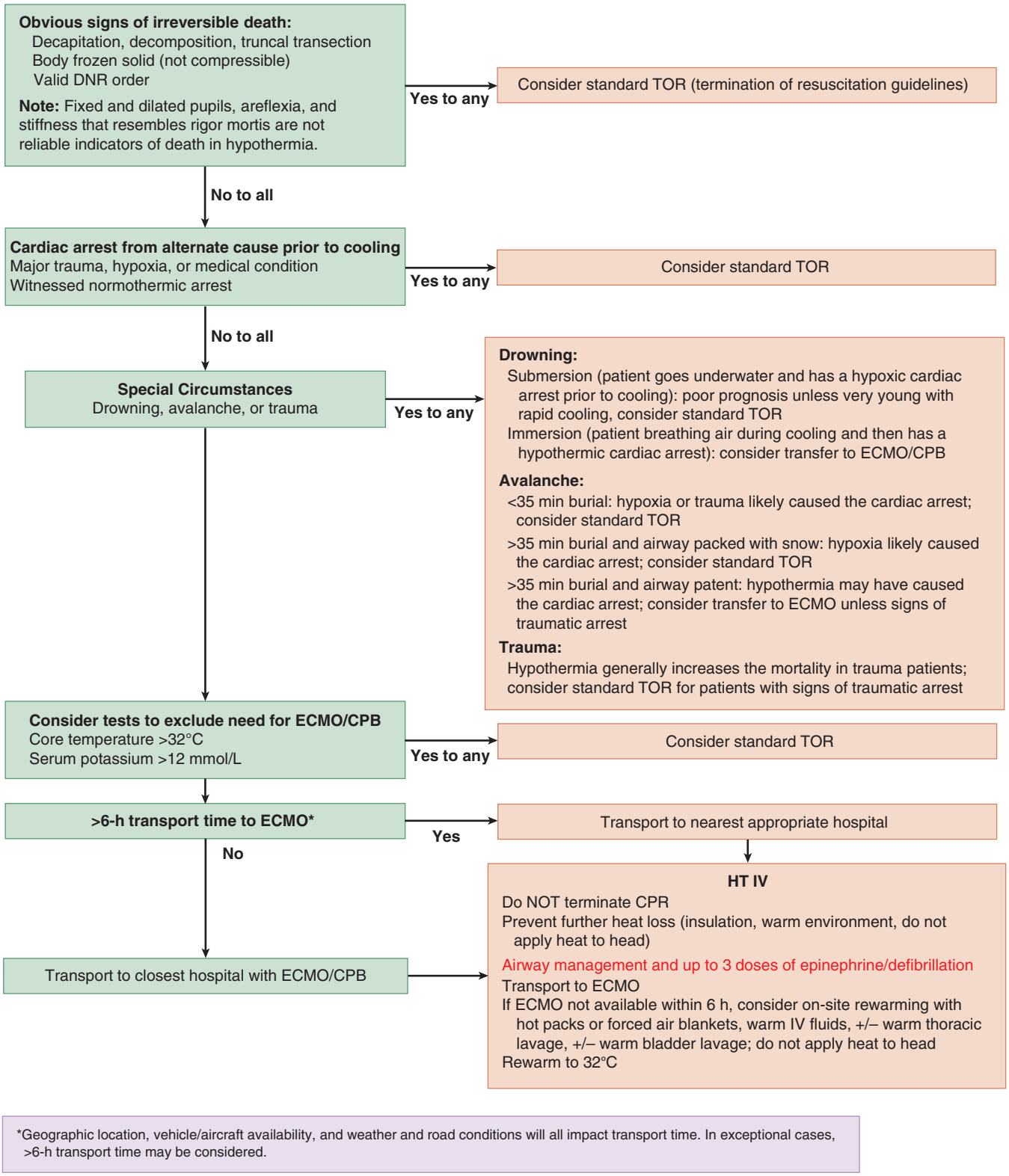

FIGURE 209-3. Triage tool for hypothermia (HT) patients with absent vital signs. CPB = cardiopulmonary bypass; DNR = do not resuscitate; ECMO = extracorporeal membrane oxygenation. [© Doug Brown, MD, FRCPC.]

the cold stress, and the physics of heat transfer, continued core cooling is possible despite appropriate treatment, particularly in the prehospital care setting. Such a failure to rewarm should trigger the clinician to reconsider secondary causes of hypothermia and ensure that ongoing heat losses have been ameliorated (uninsulated backboard, wet clothing, cool or windy environment) and that rewarming techniques are actually delivering significant heat.

SEVERE HYPOTHERMIA (STAGE III)

Stage III (unconscious, vital signs present, core temperature <~28°C) patients require the same treatment as stage II patients and may require intubation for airway protection (Table 209-2). The role of invasive vascular rewarming methods that do not support circulation (dialysis, venovenous extracorporeal membrane oxygenation (ECMO), and

Hospital Resuscitation Checklist:

- ☐ Cardiac monitor and careful handling
- ☐ Core temperature monitoring (esophageal, rectal, or bladder)
- ☐ If cardiac arrest, ventricular dysrhythmia, core temp <28°C, or unstable:
  - Do not stop resuscitation; seek expert consultation
  - Potential for good outcome despite prolonged resuscitation; ideally transfer to ECMO center if indicated
- ☐ Minimally invasive rewarming:
  - ☐ Hypothermia burrito (see below; preference for forced air warming blankets)
  - ☐ +/– Bladder lavage
    (3-way Foley, 40°C saline, 2–4 L/h by gravity)
    [confirm volume in = volume out, will invalidate bladder and rectal temperature measurements]
- ☐ IV fluid resuscitation (crystaloid, 38–42°C):
  - ☐ Titrate fluids to clinical volume status (avoid overresuscitation)
  - ☐ 10–20 mL/kg (~1 L) to start (may be reasonable)
  - ☐ Additional 10–20 mL/kg per ~3°C core temp increase (may be required)
- ☐ Hypothermia is NOT a contraindication to airway management
- ☐ Avoid hyperoxia (titrate Fio_2 to 92%–98%)
- ☐ If central venous access is required, keep the tip of the catheter (and guidewire) far from the heart (femoral, shallow internal jugular, or shallow subclavian)
- ☐ Avoid vasopressors during early resuscitation (relative hypotension may be physiologic depending on core temperature; consider expert consultation)

Minimally Invasive Rewarming: (hypothermia burrito)

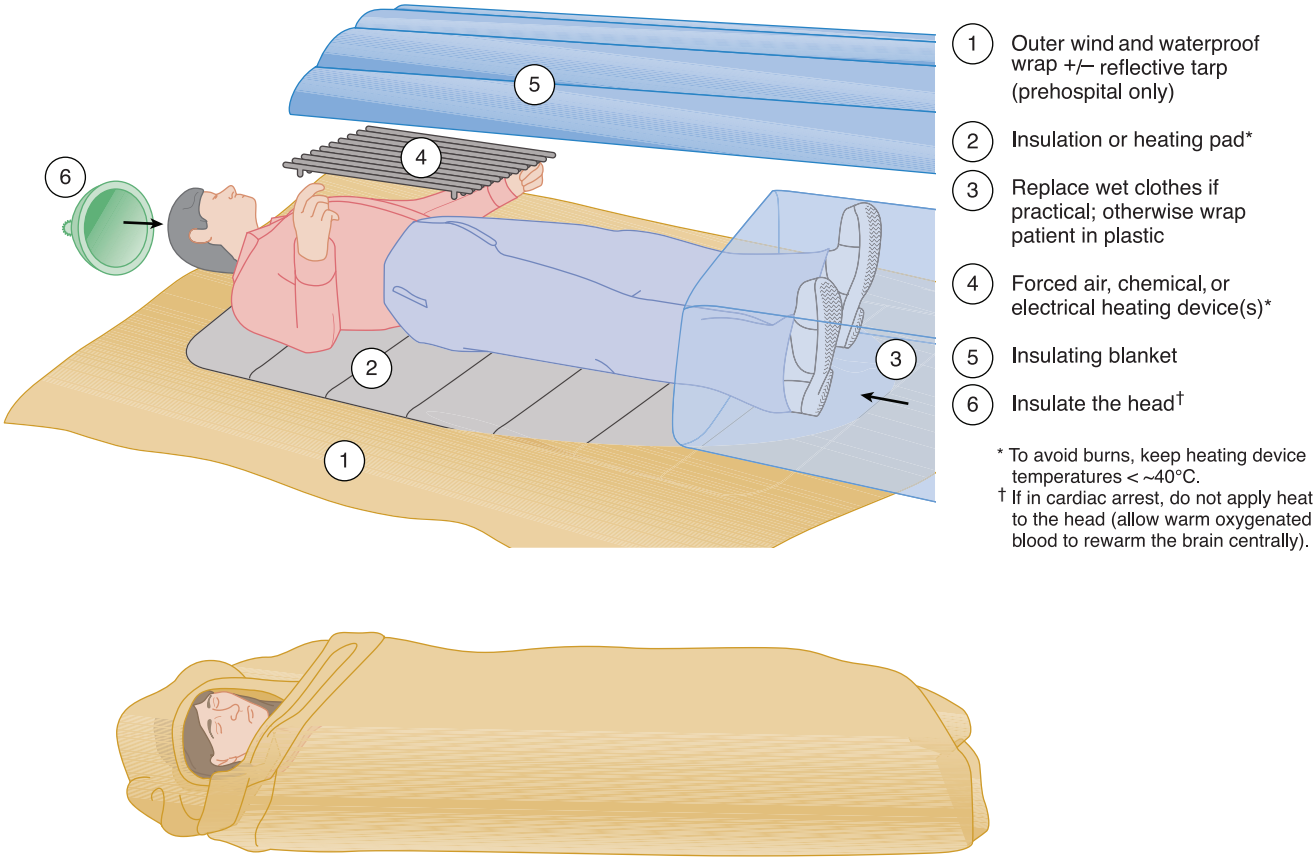

FIGURE 209-4. Practical tips for rewarming patients with moderate and severe hypothermia. ECLS = extracorporeal life support. [© Doug Brown, MD, FRCPC.]

commercial temperature management systems) remains uncertain due to unproven benefits and the potential for procedure- and device-related morbidity.[28] The use of body cavity lavage rewarming has mostly been replaced by minimally invasive rewarming methods for stable patients and by extracorporeal life support (ECLS), where available, for unstable patients or those in cardiac arrest.[7] For stable patients who are slow to rewarm, it is reasonable to use warm saline (38°C to 42°C) bladder lavage because the potential for morbidity is very low, particularly when compared with peritoneal, thoracic, gastric, or rectal lavage. The use of warm humidified gases for ventilation is recommended; however, it does not contribute significantly to rewarming.[29,30] Other invasive interventions, such as advanced airway management and central line placement, should be performed if required, despite the slight risk of triggering a malignant dysrhythmia (avoid guidewire or catheter tip contact with the heart).[7]

Stage III patients are at high risk for cardiac arrest, so patients with a core temperature <28°C, hypotension out of proportion to the degree of hypothermia, or ventricular dysrhythmias should be transferred to an ECLS center if one is available within a few hours of transport[7,9] unless comorbidities, such as major trauma, necessitate transfer to an alternate center. For stage III patients with vital signs, the minimum sufficient circulation is unknown, and there is no accepted threshold to transition a potentially unstable patient with vital signs onto ECLS. In studies

TABLE 209-3 Criteria for ECLS Rewarming in Severe Hypothermia (HT III) Endorsed by the International Commission for Mountain Emergency Medicine[32]

- Failure to improve with external active and minimally invasive rewarming methods
- Life-threatening dysrhythmia
- Hypotension (systolic blood pressure <90 mm Hg)
- Respiratory failure
- Refractory acidosis

Abbreviations: ECLS = extracorporeal life support; HT III = hypothermia stage III.

involving mostly healthy young people, patients with stable vital signs do well with minimally invasive rewarming,[31] but in older comorbid populations (who may have poor tolerance for low cardiac output), there is emerging evidence that ECLS may be beneficial for certain patients with a core temperature <28°C (**Table 209-3**).[32,33]

Treat acid-base disturbances in hypothermic patients primarily by rewarming and reassessment. For the intubated patient, respiratory parameters should target an uncorrected partial pressure of carbon dioxide of 40 mm Hg (this is known as an alpha-stat strategy, where correction factors are ***not*** applied to account for the temperature difference between patient temperature and blood gas analysis temperature).[6,34,35] In situations where blood gas measurement is not possible, the role of $ETCO_2$ measurements to guide ventilation is unclear. Some authors suggest the values should not be used,[21] while others suggest targeting normal $ETCO_2$.[7,32] Further research is ongoing, and this author's current practice is to use blood gas results when available and, in their absence, to follow the recommendations for hypothermic cardiac surgery and titrate ventilation to a temperature-corrected $ETCO_2$.[36,37] Do not give bicarbonate to correct pH, unless there is a clear alternate indication, as in certain toxic ingestions.

HYPOTHERMIC CARDIAC ARREST (STAGE IV)

Because hypothermia induces a low-flow state, it can be challenging to detect a pulse in a hypothermic patient, so perform a careful check for signs of life. If any breathing, movement, or pulse is detected, watchful waiting and supportive care are recommended; otherwise, start CPR. High-quality CPR, prevention of further heat loss, and transfer to an ECLS center when possible are the most important priorities for stage IV patients. When transfer to ECLS is definitely not available and the patient is in cardiac arrest, thoracic lavage with normal saline (38°C to 42°C) using a single or dual chest tube method may be the second-best rewarming strategy when combined with ongoing CPR.[38]

Controversy exists regarding the use of epinephrine and defibrillation in hypothermic cardiac arrest. The European Resuscitation Council 2010 guidelines recommend up to three defibrillation attempts, to withhold epinephrine until the core temperature exceeds 30°C, and to double the dose frequency until the temperature is above 35°C.[29] In contrast, the American Heart Association 2010 guidelines state that it may be reasonable to use vasopressors during cardiac arrest.[30] Given the conflicting animal and human data that each recommendation is based on, a reasonable approach is to use standard advanced cardiac life support protocols for up to three cycles and, in the absence of clinical response, defer further defibrillation or epinephrine until core temperature increases significantly or the patient's clinical status changes.

One of the major challenges with stage IV hypothermia is to select the patient with cardiac arrest caused by hypothermia for prolonged resuscitation while avoiding futile resuscitation for patients with normothermic cardiac arrest and subsequent cooling. Measuring a serum potassium >12 mmol/L or a core temperature >32°C can help to avoid futile resuscitation, but in their absence, the clinician is dependent on the history and physical to select the patients who may benefit from prolonged resuscitation (Figure 209-3).

Stage IV patients with return of spontaneous circulation should be rewarmed to ≥32°C and receive standard postarrest management[30] with consideration given to targeted temperature management[3] or therapeutic hypothermia[2] based on institutional preference. Patients rewarmed to ≥32°C without return of spontaneous circulation who are in asystole can be considered for termination of resuscitation in the absence of other causes of reversible cardiac arrest.

DISEASE COMPLICATIONS

Early complications are those that develop during the rewarming process, whereas late complications occur after rewarming. Most early complications have been described in the previous "Cold Physiology" section and can be minimized by handling patients carefully and using minimally invasive or extracorporeal rewarming techniques. Early ECLS-related complications are mostly related to cannulation and include bleeding, vessel perforation, dissection, and distal limb ischemia.[33] Possible late complications are numerous and can affect most organ systems. Common respiratory complications include pulmonary edema and infection. Common cardiac complications include prolonged hypotension or dysrhythmias. A variety of neurologic injuries, such as seizure disorders, peripheral neuropathy, impaired cognitive function, or persistent vegetative state, are possible in cases of severe or prolonged ischemia. Similar to other critically ill patients, multiorgan failure is possible, including, but not limited to, acute respiratory distress syndrome, renal failure, liver failure, rhabdomyolysis, disseminated intravascular coagulopathy, bowel ischemia, and adrenal insufficiency.[1] With stage IV hypothermia, colder core temperatures and longer durations of CPR generally predict increased complications. Cardiac stunning[39] and respiratory failure are two important potential late complications of stage IV hypothermia due to the potential need for prolonged ECLS or ECMO.[27]

DISPOSITION AND FOLLOW-UP

Patients suffering from primary hypothermia who are rewarmed in the ED can be discharged home with routine follow-up by a primary care provider. Patients suffering from secondary hypothermia may require admission or specialized follow-up depending on the nature and severity of the underlying condition. Patients who are unable to be rewarmed within a reasonable period of time will require admission with cardiac and core temperature monitoring (stage III and IV patients require a critical care setting).

SPECIAL CONSIDERATIONS/SPECIAL POPULATIONS

CHILDREN

Pediatric stage IV hypothermia patients require special consideration, and in general, expert consultation is warranted prior to termination of resuscitation. They have a larger surface area–to–body mass ratio, which means they have the potential to cool more rapidly than adults. Additionally, children may have an increased ability to tolerate and recover from hypoxic brain injury. Therefore, prolonged resuscitation may be indicated, even in cases of normothermic hypoxic cardiac arrest, if there is simultaneous very rapid cooling. The classic outlier in the literature is the case of a 2.5-year-old girl who went immediately under the water of a 5°C creek and suffered a normothermic hypoxic cardiac arrest but was rapidly cooled (pinned against a rock under fast-flowing cold water); 66 minutes later, she was removed from the water in cardiac arrest, received 3 hours of CPR, had a core temperature of 19°C, was successfully resuscitated using ECLS, and had a good neurologic outcome.[26]

EXTRACORPOREAL LIFE SUPPORT OR EXTRACORPOREAL MEMBRANE OXYGENATION

The use of ECLS/ECMO for the management of stage IV hypothermia can dramatically improve survival for patients, with a number needed to treat of approximately 2 (absolute risk reduction of death, 50% to 90%).[7,9] Well-selected patients treated in an ECLS/ECMO center have an approximately 50% to 100% survival rate, compared with a rate of approximately 10% to 30% if treated in a center without extracorporeal rewarming.[7,40] Hypothermic patients have tolerated prolonged periods of CPR (≥5 hours) with a good neurologic outcome.[9,41,42] The combination

of improved outcomes with extracorporeal rewarming and the prolonged patient tolerance for CPR argue for the early identification of stage III and IV patients and priority transfer to an ECLS/ECMO center. Unfortunately, many physicians are not aware of this benefit, and many healthcare systems are not prepared to transfer patients in cardiac arrest. The creation of critical care pathways that outline triage, initial management, transport destinations, and care goals within a given healthcare system has the potential to improve outcomes, in a similar manner to cardiovascular care pathways.[43] A *New England Journal of Medicine* current concepts article[7] provides a preliminary framework, but considerable local and regional work is still required to create a functional system. The provincial health authority in British Columbia, Canada, has implemented a regional clinical practice guideline and care pathway,[44] and Poland has improved patient outcomes by creating the world's first dedicated centralized severe hypothermia treatment center.[45]

DROWNING, AVALANCHE, AND TRAUMA

Drowning, avalanche burial, and trauma are three situations that warrant special consideration in the context of hypothermia. Patients removed from cold water should be extracted in a horizontal position in an effort to decrease the risk of orthostatic and hydrostatic changes triggering rescue collapse. The majority of drowning is **submersion**, where the patient immediately goes under the water, suffers a hypoxic cardiac arrest, and then develops hypothermia. With the exception of children, who may undergo simultaneous hypoxic cardiac arrest and rapid cooling,[26] most submersion patients are unlikely to benefit from prolonged resuscitation (normothermic hypoxic cardiac arrest with brain death prior to cooling). The less common **immersion** patient may benefit from prolonged resuscitation; this patient is initially immersed in cold water but able to breathe air, cooling ensues, and the patient eventually suffers a presumed hypothermic cardiac arrest and may or may not become secondarily submerged. A case series of survival in adolescents with prolonged CPR after cold water immersion has been reported.[40] See Chapter 215, "Drowning," for detailed discussion of drowning.

With **avalanche** burial, most episodes of cardiac arrest are caused by asphyxia or trauma.[46] Avalanche burial results in much slower cooling than cold water exposure, and it will take from 35 minutes to several hours for the patient's core temperature to drop below 32°C (assuming initial normothermia). Therefore, if the patient is recovered in cardiac arrest after less than 35 minutes of burial, hypothermia is not the cause of cardiac arrest. For patients recovered after 35 minutes of burial, in the absence of obvious traumatic death, an airway packed with snow, or an accurate core temperature >32°C, accidental hypothermia may be the cause of cardiac arrest and prolonged resuscitation may be indicated. Cardiac arrest secondary to blunt trauma has a dismal prognosis (<1% survival),[47] and a core temperature <35°C further increases the odds of death by at least 2.4.[18] Therefore, it is reasonable to apply normothermic termination of resuscitation guidelines to patients suspected of blunt traumatic arrest, even in the presence of hypothermia.

AUSTERE ENVIRONMENTS

In the rare circumstances of stage IV hypothermia in an austere environment, when ongoing CPR during transport is not possible, it may be reasonable to transport without CPR (particularly if the patient has pulseless electrical activity) until such a time as CPR can be maintained or a definitive care center is reached. The decision to not perform CPR in an austere environment may be risky given that prehospital CPR is performed in the vast majority of stage IV hypothermia literature; however, there are two published cases that have shown good outcomes despite CPR interruptions[41,48] and one case where CPR was not performed at all during transport.[49] There is considerable controversy about whether or not to perform CPR for stage IV patients with pulseless electrical activity.[50,51] It is this author's opinion that the benefits of CPR far outweigh the risks for the patient with absent vital signs, regardless of the ECG findings.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 210

Heat Emergencies

Frank LoVecchio

INTRODUCTION AND EPIDEMIOLOGY

Heat emergencies represent a continuum of disorders from heat cramps to heat stress that, when severe, culminate in heat stroke. The incidence of heat-related emergencies varies with the weather, although other factors may have a greater impact.[1] During heat waves and severe droughts, fatality rates spike.[1] Physiologic acclimatization and cultural adaptation provide protection from heat stroke for people who live in warmer climates. From 1999 to 2010, there were 8081 heat-related deaths in the United States.[1] The heat wave during the summer of 2003 is estimated to have caused 14,800 deaths in France.[2] In the Russian heat wave in July/August 2010, there were an estimated 15,000 deaths, with additional morbidity from associated forest fires and smoke injury.[3]

PATHOPHYSIOLOGY

MECHANISMS OF HEAT TRANSFER

Controlled by the hypothalamus, body temperature is regulated through the delicate balance of heat production, accumulation, and dissipation. Heat is generated by cellular metabolism and the mechanical work of skeletal muscle. Heat accumulates from radiation from the sun and contact with hot objects. Heat is absorbed when the ambient temperature rises above body temperature. As core temperature rises, the autonomic nervous system is stimulated to promote sweating and cutaneous vasodilatation.

The body has several mechanisms for dissipating heat to the environment, including radiation (the transfer of heat by electromagnetic waves from a warmer object to a colder object), conduction (heat exchange between two surfaces in direct contact), convection (heat transfer by air or liquid moving across the surface of an object), and evaporation (heat loss by vaporization of water, or sweat). Evaporation is the principal mechanism of heat loss in a hot environment, but this becomes ineffective above a relative humidity of 75%. Radiation and evaporation dissipate most body heat at lower ambient temperatures (<35°C [<95°F]).

The effect of wind on heat loss depends on wind velocity. Wind moves heat away from the skin by convection, but above 32.2°C (90°F) and 35% humidity, convection does not remove heat well.[4] This is why the use of fans alone is not effective in preventing heat stroke during periods of high environmental temperature and humidity.

When the ambient temperature rises to >35°C (>95°F), the body can no longer radiate heat to the environment and becomes dependent on evaporation for heat transfer. As humidity increases, the potential for evaporative heat loss decreases. The combination of high temperature and high humidity essentially blocks the two main physiologic mechanisms that the body uses to dissipate heat. Elevations of temperature are accompanied by an increase in oxygen consumption and metabolic rate, resulting in hyperpnea and tachycardia.

RESPONSE TO HEAT STRESS

Controlled by the hypothalamus, the body maintains a core temperature between 36°C and 38°C (96.8°F and 100.4°F). Native thermal regulation mechanisms begin to fail at core temperatures of <35°C (<95°F) and >40°C (>104°F).[5] It is possible to maintain core temperatures of 40°C to 42°C (104.0°F to 107.6°F) for short periods without adverse effect.[5]

The physiologic response to heat stress consists of four primary mechanisms: dilatation of blood vessels, particularly in the skin; increased sweat production; decreased heat production; and behavioral heat control.

During exercise in hot environments, the heart rate increases to compensate for the decrease in stroke volume from the cutaneous vascular dilation and to maintain cardiac output.[6] Patients with underlying cardiovascular disease or pharmacologic or physiologic impairment of

these mechanisms may not be able to elevate cardiac output. Heat stress may also result in arrhythmias, myocardial ischemia, and exacerbation of congestive heart failure.[7]

Elevated cholinergic stimulation to the skin results in increased sweat production. Sharp increases in the rate of sweat production normally occur with core temperature elevations above 37°C (98.6°F).[7] Cutaneous vascular dilation and sweating increase as the body temperature rises until a homeostatic stall of heat production is reached when the rate of heat production in response to exercise equals heat loss.[8] Interestingly, sweating activation in older adults requires a greater rise in skin temperature (1.5°C, or 2.7°F) compared to younger adults.[9]

EFFECT OF MEDICATIONS

Medications often interfere with heat-removal mechanisms. Notable drugs are anticholinergic agents, diuretics, phenothiazine, β-blockers, calcium channel blockers, and sympathomimetic agents.[10] Anticholinergic agents impair sweating and the cardiovascular response to heat. Diuretics lead to volume depletion and decreased cardiac output. Phenothiazines have anticholinergic properties and deplete central stores of dopamine, which interfere with the hypothalamic thermoregulatory center. Medications such as β-blockers and calcium channel blockers decrease the cardiovascular response to heat and reduce peripheral blood flow and the ability to sweat. Sympathomimetics cause cutaneous vasoconstriction and inhibit sweating. Alcohol inhibits secretion of antidiuretic hormone, which leads to dehydration, and blunts the psychological heat-avoidance response. Heroin, cocaine, and amphetamines disrupt the function of endogenous endorphins and adrenocorticotropic hormones that are involved in heat adaptation mechanisms. Amphetamines and cocaine increase muscle activity and lead to heat production. Lysergic acid diethylamide and phencyclidine act on the CNS to induce a hypermetabolic state.[10]

RISK FACTORS

In addition to patients on the medications discussed in the previous section, populations at higher risk of developing heat emergencies include the elderly, young children, athletes, persons with limited mobility, and alcoholics.[7,8] Other risk factors for exertional heat emergencies include obesity, dehydration, and vigorous exertion in the heat without proper training and acclimatization. Lack of air-conditioning and social isolation are also risk factors for nonexertional heat emergencies.[7,8] Individuals with a history of heat stroke are at greater risk for another episode. Patients with congenital absence of sweat glands, progressive systemic scleroderma, hyperthyroidism, and pheochromocytoma are also at increased risk for heat stroke.

ACCLIMATION

Acclimation is the adaptation of the body to environmental changes. It involves a number of physiologic and biochemical adjustments that allow an individual to withstand heat stresses that would otherwise result in substantial morbidity and mortality.

Acclimation lowers the thermal set point in the hypothalamus, which triggers the onset of sweating at lower core temperatures, and the rate of sweating may double in the acclimated human. Aldosterone secretion is boosted, and sodium conservation results from more efficient reabsorption from the sweat. Plasma volume expands, heart rate decreases for any given heat load, and exercise tolerance improves. Dilation of cutaneous blood vessels occurs at a lower core temperature to promote earlier cooling. In most individuals, acclimation can be achieved over 7 days to several weeks.[11] Once removed from the hot environment, the body will de-acclimate to the original physiologic parameters within 1 to 2 weeks.[12,13]

MODELS OF HEAT INJURY

The pathology of heat stroke is not completely understood, and although heat stroke is triggered by hyperthermia, there is evidence that secondary endotoxemia triggers a systemic inflammatory response, coagulopathy, and multiorgan failure.[14,15]

Heat exhaustion and heat stroke occur when the body's thermoregulatory responses are impaired or overwhelmed and are no longer capable of maintaining homeostasis. Excessive heat is directly toxic to cells, causes an acute-phase reaction with release of inflammatory cytokines, and damages vascular endothelium. Nearly all cells respond to sudden heating by producing heat stress proteins, whose mechanism of action is still not completely understood.[14,15]

Escalating cellular temperature results in denaturation of proteins, interruption of cellular processes, and cell death. Temperatures of >41.6°C (>106.9°F) can produce cellular injury in hours. As temperature rises, cellular damage occurs more quickly and extensively. Temperatures >49°C (>120.2°F) typically result in immediate cell death and tissue necrosis.[15] The enhanced vascular permeability due to damaged vascular endothelium results in activation of the coagulation cascade and disseminated intravascular coagulation.

Classic Classic heat injury occurs during periods of high environmental heat stress. Physical exertion is not required if the heat gain occurs at environmental temperatures and humidity levels that overwhelm the native heat loss mechanisms. The increase in core temperature seen in this setting is often slow, occurring over a period of hours to days. Because of this slow rise in heat burden, volume and electrolyte abnormalities are common. High-risk populations include the elderly, the young, and those with psychological, physiologic, and pharmacologic impairments of heat loss mechanisms (e.g., diabetes; Raynaud's disease; drugs such as anticholinergics, diuretics, antipsychotics, cocaine). Epidemiologic studies of classic heat injury typically identify the elderly, living alone or without social support and without air-conditioning.[16]

Exertional Exertional heat injury usually affects individuals who are participating in athletic events or performing jobs under conditions of high heat stress. Risk factors include dehydration, concurrent illness, obesity, wearing too much clothing, and poor cardiovascular fitness. In this setting, heat production and heat gain from the environment exceed the capacity of heat removal processes. Physical exercise is the most common single source of internal heat production. Without an efficient cooling mechanism, progressive dehydration and hyperpyrexia continue to the level of cardiovascular and metabolic failure.

Confinement Hyperpyrexia Confinement hyperpyrexia is a special category of nonexertional hyperpyrexia and can occur in several circumstances, such as when children are left inside cars, when stowaways are abandoned inside closed vehicles or railroad cars, and when workers are occupationally exposed to heat inside enclosed spaces. Between January 1990 and December 2014 in the United States, 3115 nonfatal heat injuries and 729 fatalities were reported in children who were left intentionally in motor vehicles during hot days.[17] Nonventilated vehicle compartments in a hot environment may reach temperatures of 54°C to 60°C (129.2°F to 140.0°F) in <10 minutes.[17] In the August 2003 heat wave in France, a risk factor for heat stroke mortality was heat exposure at home or in a non–air-conditioned healthcare facility.[18]

SPECIFIC TYPES OF HEAT ILLNESS

Heat emergencies comprise a range of disorders from minor (heat edema, prickly heat, heat cramps, and heat exhaustion) to major (heat stroke). Minor heat emergencies are primarily diagnosed and differentiated from heat stroke on clinical grounds.

HEAT EDEMA

Heat edema is a self-limited process manifested by mild swelling of the feet, ankles, and hands that appears within the first few days of exposure to a hot environment. Heat edema is due to the cutaneous vasodilatation and orthostatic pooling of interstitial fluid in gravity-dependent extremities. An increase in the secretion of aldosterone and antidiuretic hormone in response to the heat stress contributes to the mild edema. In general, heat edema is found in elderly nonacclimatized individuals who are physically active after a period of sitting while traveling in a vehicle or airplane. Occasionally, heat edema occurs after prolonged standing. The edema is mild and does not impair or interfere with normal activities. Very rarely, pitting edema of the ankles may develop but does not progress to the pretibial region.



FIGURE 210-1. Miliaria rubra (prickly heat). [Image used with permission of Peter Lio, MD.]

History and physical examination are usually sufficient to exclude systemic causes of edema in healthy patients. In the elderly, new pedal edema from heat should be differentiated from early congestive heart failure or deep venous thrombosis. Heat edema usually resolves spontaneously in a few days. Elevation of the legs and the use of support hose facilitate removal of the interstitial fluid; diuretics have no role.[8]

PRICKLY HEAT

Prickly heat is a pruritic, maculopapular, and erythematous rash over normally clothed areas of the body. Also known as ***lichen tropicus***, ***miliaria rubra***, or ***heat rash***, it is an acute inflammation of the sweat ducts caused by blockage of the sweat pores by macerated stratum corneum (**Figure 210-1**). The sweat ducts become dilated under pressure and ultimately rupture, producing superficial vesicles in the malpighian layer of the skin on a red base. Itching is the predominant clinical feature during this phase and can be treated successfully with antihistamines. Wearing clean, light, and loose-fitting clothing and avoiding sweat-generating situations can prevent prickly heat. Calamine lotion, topical steroids, and oral vitamin C can be of benefit.[19] Chlorhexidine in a light cream or salicylic acid cleaning solution may provide some relief.

With prolonged or repeated heat exposure, a keratin plug fills the sweat duct, causing obstruction in the stratum malpighian layer. When the duct ruptures a second time, the resultant vesicle will be driven deeper into the dermis. This vesicle simulates the white papules of piloerection and is not pruritic. This is known as the *profunda* stage of prickly heat (miliaria profunda) and can readily advance into a chronic dermatitis. Infection with *Staphylococcus aureus* or methicillin-resistant *S. aureus* is a common complication. The skin can be desquamated by applying 1% salicylic acid to the affected area three times a day.

HEAT CRAMPS

Heat cramps are painful, involuntary, spasmodic contractions of skeletal muscles, usually those of the calves, although they may involve the thighs and shoulders. These cramps usually occur in individuals who are sweating profusely and replace fluid losses with water or other hypotonic solutions. Heat cramps may occasionally occur during exercise or, more commonly, during a rest period following several hours of vigorous physical activity. Nonacclimated or unconditioned individuals who are just starting manual labor in a hot environment are at risk for heat cramps. Although heat cramps are self-limited and do not cause significant morbidity, the pain associated with them can precipitate an ED visit. In general, heat cramps are short in duration, are limited to a definitive group of muscles, and almost never involve enough muscle mass to cause rhabdomyolysis.

The pathogenesis of heat cramps is believed to involve a relative deficiency of sodium, potassium, or magnesium and fluid at muscle level. Patients with severe heat cramps may have hyponatremia and hypochloremia.[20] Rhabdomyolysis is rare and occurs secondary to diffuse and protracted muscle spasm.[15]

Treatment consists of fluid and salt replacement (PO or IV) and rest in a cool environment. For mild cases, or if an overwhelming number of patients require treatment, a 0.1% to 0.2% saline solution can be given PO. Two 650-milligram salt tablets dissolved in a quart of water provide a 0.1% saline solution.[13,20] Many electrolyte solution drinks (sports drinks) are commercially available and are much more palatable. Patients with more severe symptoms require IV rehydration with normal saline. Heat cramps can be prevented by maintaining adequate dietary salt intake or by drinking commercial electrolyte beverages. Salt tablets by themselves should not be used, because the tablets are a gastric irritant and cause nausea and vomiting.

HEAT STRESS

CLINICAL FEATURES AND DIAGNOSIS

Heat stress is part of the continuum of heat illness but does not meet criteria for heat stroke. Heat stress can result from either water or sodium depletion, but is typically a combination of both. Water depletion tends to occur in the elderly and in persons working in hot environments with inadequate water replacement. Salt depletion tends to occur in nonacclimatized individuals who replace fluid losses with large amounts of hypotonic solutions.

Heat stress presents with symptoms that include headache, nausea, vomiting, malaise, dizziness, and muscle cramps as well as signs of dehydration, such as tachycardia and orthostatic hypotension or near-syncope. Rhabdomyolysis may be present on rare occasions (see Chapter 89, "Rhabdomyolysis"). Because of the ill-defined and nonspecific symptoms, heat exhaustion is often a diagnosis of exclusion.

On physical examination, the temperature may be normal or elevated, usually not above 40°C (104°F). Patients with heat exhaustion (stress) do not manifest signs of CNS impairment (**Table 210-1**).

Laboratory studies almost universally demonstrate hemoconcentration, although the specific electrolyte abnormalities seen depend on the ratio of fluid and electrolyte losses to intake. Patients who have had no fluid intake of any kind exhibit hypernatremia, whereas those who partly rehydrate with salt-containing fluids develop isotonic hypovolemia with normal sodium and chloride levels. Serum potassium and magnesium levels are variable.

TREATMENT

Heat stress is treated with volume and electrolyte replacement and rest. Removal from the heat-stressed environment is essential. Patients with mild heat stress may be treated with oral electrolyte solutions. Rapid infusion of moderate amounts of IV fluids (1 to 2 L of normal saline) may be necessary in patients who demonstrate significant tissue hypoperfusion. Ideally, the choice of IV solution should be guided by

TABLE 210-1 Signs and Symptoms of Heat Emergencies

Heat Cramps	Heat Stress (Exhaustion)	Heat Stroke
Muscle cramps	Symptoms seen in heat cramps plus:	Symptoms seen in heat stress (exhaustion) plus:
Normal to mildly elevated temperature	Normal to elevated temperature (<40°C [<104°F])	**Elevated temperature (>40°C [>104°F])**
Sweating	Nausea, vomiting, headache, malaise, dizziness	**Neurologic abnormalities:** inappropriate behavior, confusion, delirium, ataxia, coma, seizures
	Orthostatic hypotension	
		Anhidrosis or sweating

laboratory determinations, but isotonic salt solutions may be used until specific electrolyte abnormalities are identified. In general, hospitalization is not required. Patients with congestive heart failure or severe electrolyte disturbances may require admission, because of the time needed to correct fluid and/or electrolyte deficits.

Heat stress with an elevated temperature can progress to heat stroke even after the patient is removed from the hot environment. Therefore, patients with heat stress who do not respond to approximately 30 minutes of fluid replacement and removal from the hot environment should be cooled until the core temperature drops to ≤39°C (102°F). Patients should not be prematurely labeled as having heat stress without observation and reassessment.

HEAT STROKE

Heat stroke is an acute life-threatening emergency with high mortality and is fatal if left untreated.

CLINICAL FEATURES

The cardinal features of heat stroke are hyperthermia (>40°C [>104°F]) and altered mental status. See also symptoms listed in Table 210-1. Although patients presenting with classic (nonexertional) heat stroke may exhibit anhidrosis, the absence of sweat is not considered a diagnostic criterion because sweat is present in over half of patients with heat stroke.[15]

The CNS is particularly vulnerable in heat stroke. The cerebellum is highly sensitive to heat, and ataxia can be an early neurologic finding. Virtually any neurologic abnormality may be present in heat stroke, including irritability, confusion, bizarre behavior, combativeness, hallucinations, plantar responses, decorticate and decerebrate posturing, hemiplegia, status epilepticus, and coma. Seizures are quite common, especially during cooling. Neurologic injury is a function of the maximum temperature reached and the duration of exposure.[15]

The distinction between exertional and classic (nonexertional) heat stroke is not clinically important, because immediate cooling and support of organ system function are the therapeutic goals for both. A delay in cooling increases the mortality rate.

DIAGNOSIS

There are no diagnostic tests for heat stroke, and the differential diagnosis is extensive. Therefore, the diagnosis of heat stroke is determined by history and clinical presentation, and exclusion of other processes (**Table 210-2**).

Laboratory Evaluation Diagnostic studies are directed toward detecting end-organ damage and excluding other diseases. Helpful studies include a CBC, comprehensive metabolic panel with arterial blood gas analysis, coagulation profile, creatine phosphokinase level, myoglobin level, urinalysis, ECG, and chest radiograph. CT of the head and lumbar puncture may be indicated to rule out other causes of altered mental status. The partial pressure of arterial carbon dioxide is often <20 mm Hg due to hyperventilation. Patients with exertional heat stroke often have lactic acidosis, and hypoglycemia may occur.

TABLE 210-2 Differential Diagnosis of Heat Stroke

Infection	**Neurologic**
• Sepsis syndrome	• Hypothalamic bleeding or infarct
• Meningitis	• Cerebrovascular accident
• Encephalitis	• Status epilepticus
• Malaria	**Toxicologic**
• Typhoid	• Anticholinergic toxidrome
• Tetanus	• Sympathomimetic overdose
Endocrine	• Salicylate overdose
• Thyroid storm	• Serotonin syndrome
• Pheochromocytoma	• Malignant hyperthermia
• Diabetic ketoacidosis	• Neuroleptic malignant syndrome
	• Withdrawal syndromes—alcohol and benzodiazepine withdrawal

PREHOSPITAL CARE

Remove the patient from the hot environment immediately, and perform standard resuscitation measures. Check point-of-care glucose if there is altered mental status. Start cooling by removing clothing and implementing one of the following methods: spray the patient with water and provide airflow over the patient (ideal method but not always practical during transportation); place wet towels or sheets over the patient's body; or place ice on the patient. Administer a bolus of normal saline (1 to 2 L) if hypotension is present.[15] Online medical direction is helpful when transport times are long and when EMS personnel in the given region rarely encounter heat stroke.

ED RESUSCITATION

The goals of therapy are immediate cooling and aggressive support of organ system function.

Continue standard resuscitation measures. Administer IV fluids at a rate that ensures adequate urine output. In elderly patients or patients with cardiovascular disease, consider invasive monitoring. Check glucose levels. Monitor core temperature with an electronic rectal thermometer, temperature probe–equipped urinary drainage catheter, or esophageal thermometer.

COOLING TECHNIQUES

Currently, only physical methods of cooling are recommended, and there is no evidence to support one particular approach over another. In clinical practice, the primary physical cooling procedure is one that allows easy patient access, is readily available, is tolerated well by the patient, and is effective (**Table 210-3**). With all cooling methods, the goal is to reduce the core temperature to approximately 39°C (102.2°F) and to avoid overshoot hypothermia.[7] No method has been proven superior.[7] If the initial cooling method used does not lower temperature quickly, try another method.[15,21]

Evaporative Cooling Cooling by evaporation is practical and comfortable for the patient compared with other methods. Remove patient clothing and spray cool water (~15°C [59°F]) on most of the patient's body surface. Directing a fan over the patient facilitates evaporation. If the skin temperature is reduced <30°C (86°F), shivering will result in more heat production, and peripheral vasoconstriction will impair evaporation. To prevent hypothermic overshoot, some recommend using either tepid water warmed to 40°C (104°F) or exposing the patient to hot air (45°C [113°F]) with the fan.[21] This method is the foundation of several cooling units such as the **Makkah cooling unit**, which is widely used in the Middle East to treat pilgrims traveling to Mecca who succumb to heat stroke. The Makkah cooling unit is composed of a large hammock with built-in sprinklers that spray cool water (15°C [59°F]) over the patient's body and powerful fans that blow warm air (45°C [113°F]) over the patient. The main problems with the Makkah cooling method are cost, portability, and the fact that evaporation rates are reduced in very humid environments.

The two main difficulties associated with evaporative cooling are shivering and the inability of cardiac electrodes to adhere to the skin. Shivering is treated primarily with short-acting benzodiazepines and secondarily with phenothiazines. Phenothiazines may lower the seizure threshold and cause hypotension, and their anticholinergic properties impair sweating.

Immersion Cooling Immersion cooling is performed by placing the undressed patient into a tub of ice water deep enough to cover the trunk and extremities, while keeping the patient's head out of the water. Problems associated with immersion cooling include shivering, displacement of monitoring leads, and inability to perform defibrillation or resuscitative procedures. Also, a tub or receptacle large enough to accommodate the patient may not be readily available. The efficiency of immersion cooling has been documented primarily in young, healthy

TABLE 210-3 Summary of Cooling Techniques

Cooling Method	Advantages	Disadvantages	Recommendations
Evaporative cooling	Provides effective cooling Readily available Practical Well tolerated	Can cause shivering Less effective in humid environments Makes it difficult to maintain electrode positions	Strongly recommended
Immersion cooling	Provides effective cooling	Can cause shivering Poorly tolerated Not compatible with resuscitation settings	Recommended
Ice packs on neck, axillae, and groin	Practical Can be added to other cooling methods	Cooling times longer than other modalities Poorly tolerated	Can be used as adjunct cooling method
Cardiopulmonary bypass	Provides fast and effective cooling	Invasive Not readily available Setup is labor intensive	Recommended in severe or resistant cases when available
Cooling blankets	Easy to apply	Have limited cooling efficacy Impede use of other cooling methods	Not recommended when other methods available
Cold water gastric, urinary bladder, rectal, or peritoneal lavage	Advocated to cool the core when cardiopulmonary bypass not desirable or possible, however, efficacy not validated	Invasive Labor intensive May lead to water intoxication Human experience is limited	Effectiveness and safety not established

patients without comorbid diseases. The efficacy and safety of immersion in patients with classic (nonexertional) heat stroke and patients with significant comorbid diseases (e.g., coronary artery disease) have not been established.

Massage with ice water is an alternative for patients who cannot tolerate immersion, although its effectiveness as a single modality for cooling remains unclear.[21]

Invasive Cooling Measures When evaporation or immersion methods are not sufficient, invasive cooling may be considered. The most rapid method of cooling a heat stroke victim is cardiopulmonary bypass, although lack of availability and logistical problems are major disadvantages. Cold water gastric lavage, cold water urinary bladder lavage, and cold water rectal lavage are other adjunctive measures that can be performed in the ED but require patient cooperation, are labor intensive, have the potential for inducing water intoxication, and are of questionable efficacy. Cold water peritoneal lavage is yet another option, but its effectiveness has not been validated.

Other Cooling Measures Cooling blankets work slowly and should not be a sole treatment for heat stroke. IV infusion of cold fluids alone is not considered effective treatment. Applying ice packs to the neck, axillae, and groin does not lower temperature quickly enough to be used alone. There are no studies on the effectiveness of antipyretics. Dantrolene is not indicated for treatment of heat stroke.[21]

COMPLICATIONS OF HEAT STROKE

Heat stroke causes both early and late complications (**Table 210-4**).[7,15] Hypotension is a common initial finding. Usually the blood pressure will rise in response to fluid bolus and body cooling. The combination of low cardiac output and elevated central venous pressure warrants the use of vasoactive catecholamines such as dopamine or dobutamine if a 20 mL/kg fluid bolus does not result in improvement. Once the central venous pressure reaches 12 to 14 mm Hg and cooling is initiated, dopamine or dobutamine may be used to maintain a normal blood pressure. Inotropes that cause severe vasoconstriction by α-adrenergic stimulation, such as norepinephrine, may impede cooling by redirecting blood flow away from the skin.

Fluid and electrolyte abnormalities vary depending on the type of onset and duration of the disorder, any underlying disease (especially cardiovascular disease), and any prior use of medications, such as diuretics. Hypokalemia due to total-body depletion of potassium may be noted, and hyperkalemia may result from acute renal failure and rhabdomyolysis. Hypernatremia is seen in severely dehydrated patients, whereas hyponatremia occurs in patients who hydrate with oral hypotonic solutions.

Hematologic disorders may be apparent clinically and on laboratory evaluation. Findings of abnormal hemostasis include purpura, petechiae, and conjunctival, GI, renal, or pulmonary hemorrhage. Coagulation studies may show thrombocytopenia, hypoprothrombinemia, and hypofibrinogenemia. Thermal injury to the vascular endothelium can cause increased platelet aggregation, changes in capillary permeability, thermal deactivation of plasma proteins resulting in a decreased level of clotting factors, disseminated intravascular coagulation, and fibrinolysis.[15,22]

Thermal injury to the liver is a common finding in heat stroke, although jaundice does not always develop. Delayed elevation of hepatic enzyme levels, peaking 24 to 72 hours after the thermal insult, is attributed to centrilobular necrosis. Glucose homeostasis is affected. Hepatic damage is almost always reversible, with a full recovery.

TABLE 210-4 Complications of Heat Stroke

	Early	Late
Vital signs	Hypotension	
	Hypothermic overshoot	
	Hyperthermic rebound	
Muscular	Rhabdomyolysis	
Neurologic	Delirium/coma	Cerebral edema
	Seizure	Encephalopathy
		Persistent neurologic deficit
Cardiac	Heart failure	Myocardial injury
Pulmonary	Pulmonary edema	Acute respiratory distress syndrome
Renal	Oliguria	Renal failure, rhabdomyolysis
GI		Intestinal ischemia or infarction
		Pancreatic injury
		Hepatic dysfunction
Metabolic	Hypokalemia	Hyperkalemia
	Hypernatremia	Hypocalcemia
	Hyponatremia	Hyperuricemia
Hematologic		Thrombocytopenia
		Disseminated intravascular coagulation

Renal failure results from direct thermal injury to the kidney, rhabdomyolysis, or volume depletion. Clinically, this is manifested by oliguria, microscopic hematuria, proteinuria, myoglobinuria, and granular or red cell casts in the urine. Early volume expansion decreases the detrimental renal effects of heat stroke.

Adult respiratory distress syndrome requires ongoing respiratory support. Myocardial injury may also occur. The presence of hypotension, low cardiac output, and a falling cardiac index is associated with a poor prognosis.

Seizures may occur during cooling and can be controlled with benzodiazepines.

Mortality correlates with the degree of temperature elevation, time to initiation of cooling measures, and the number of organ systems affected. In one prospective cohort study, the risk of death increased substantially in patients who presented with anuria, coma, or cardiovascular failure.[23]

DISPOSITION AND FOLLOW-UP OF HEAT EMERGENCIES

Patients with minor heat emergency syndromes (heat edema, heat cramps, or heat stress) require only ED treatment along with clear discharge instructions and outpatient follow-up. However, patients with underlying diseases, such as congestive heart failure or renal failure, and patients with severe electrolyte imbalance may require hospital admission. No decision rules exist to guide disposition decisions.

Patients with heat stroke require admission to a unit providing care at a level appropriate to the patient's condition. Patients who are intubated, are in hemodynamically labile condition, require invasive hemodynamic monitoring, or need continued cooling should be admitted to the intensive care unit. If the receiving healthcare facility is unable to provide the services needed for quality care, then transfer the patient to a higher-level facility.

SPECIAL POPULATIONS

The elderly have a higher mortality rate and suffer more complications with heat stroke.[7,8,15] Elderly persons who lack mobility, have preexisting medical illness, take medications that may affect thermoregulation or ambulation, live in housing that is without thermal insulation, or sleep on the top floor are particularly susceptible to heat stress.[18]

Young children lack adequate thermoregulatory and sweating capabilities, do not instinctively replace their fluid losses or limit exercise in extreme heat, and may be unable to remove themselves from risky environments such as a closed car in the sun. Teenagers and preadolescents are at risk because they may use poor judgment when exercising in high heat and humidity and may push themselves to the limit. Early season high school heat stroke deaths are most likely to occur during the first 4 days of practice; children require 10 to 14 days to achieve an appropriate acclimatization response.

PREVENTION

The Centers for Disease Control and Prevention has tips for the prevention of heat illness,[24] and the National Athletic Trainers' Association published a position statement that details prevention strategies.[13]

General recommendations for the individual include (1) decreasing or rescheduling strenuous activity for cooler parts of the day; (2) wearing light and loose-fitting clothing; (3) increasing carbohydrate intake and decreasing protein intake to decrease endogenous heat production; (4) drinking plenty of fluids, even when not thirsty; (5) avoiding alcoholic beverages; (6) using salt tablets as well as fluids; (7) avoiding direct sunlight; and (8) taking advantage of the shade. Community health officials and governmental leaders should recognize the need to educate the public, coordinate and plan the implementation of these measures in advance, and avoid resorting to crisis management.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 211

Bites and Stings

Aaron Schneir
Richard F. Clark

INTRODUCTION AND EPIDEMIOLOGY

The phylum Arthropoda is the largest division of the animal kingdom. The phylum includes insects (bees, wasps, hornets, flies, mosquitoes, bedbugs, fire ants, caterpillars, fleas), arachnids (spiders, scorpions, chiggers, ticks), and crustaceans (shrimp, lobsters, crabs). Venomous bites and stings from arthropods are a significant worldwide problem. In the United States, anaphylactic reactions to Hymenoptera stings account for the most fatal arthropod envenomations, although exposures to all arthropods can result in potential emergencies. This chapter discusses the most common and serious arthropod bites, stings, and envenomations. Tick bites are discussed in Chapter 161, "Zoonotic Infections."

WASPS, BEES, AND ANTS (HYMENOPTERA)

Wasps, bees, and ants belong to the order Hymenoptera. More fatalities result from stings by these insects than by stings or bites by any other insect. There are three major subgroups or "superfamilies" of medical importance: (1) Apidae, which includes the honeybee and bumblebee; (2) Vespidae, which includes yellow jackets, hornets, and wasps; and (3) Formicidae, or ants.

BEES AND WASPS

Honeybees and bumblebees are usually docile, stinging only when provoked. A female honeybee is capable of stinging only once (male bees have no stinger) because its stinger has multiple barbs that cause the sting apparatus to detach from the bee's body, leading to evisceration and eventual death.

Africanized honeybees, or so-called "killer bees," are now found in many of the southern and warmer regions of the United States, including Arizona, California, Nevada, New Mexico, and Texas. These bees are hybrids of African bees that escaped from laboratories in Brazil during the 1950s and have successfully spread northward along the coasts and temperate regions of the continent. Their venom is no more toxic than that of their American counterpart, but Africanized hybrid honeybees are much more aggressive and more likely to attack in swarms. An attack from Africanized bees can lead to massive stinging, resulting in multisystem damage and death from severe venom toxicity.[1,2]

Most of the allergic reactions reported each year due to Hymenoptera occur from wasp, hornet, and yellow jacket stings. These arthropods typically nest in the ground (yellowjackets) in trees and shrubs (hornets) or in walls (wasps). They have volatile tempers and may be disturbed by work taking place around the nest. As with bees, only the females have adapted a stinger from the ovipositor on the posterior aspect of the abdomen. Although vespids also possess barbed stingers, they can withdraw their stingers from the victim, which permits multiple stings.

Hymenoptera venom contains several components.[3] Although histamine is one component, other substances are now recognized as more important. Melittin, a known membrane-active polypeptide that can cause degranulation of basophils and mast cells, constitutes >50% of the dry weight of bee venom. Protein enzymes such as phospholipase and hyaluronidase may account for most systemic reactions.[4,5] Because all Hymenoptera share many of these components, cross-sensitization may occur in individuals allergic to one species.

CLINICAL FEATURES

The most common response to a Hymenoptera sting is a transient local reaction that can last up to several days and generally spontaneously resolves. Localized itching, pain, erythema, and swelling are common.

Large local reactions can increase in size over 1 to 2 days and may take 3 to 10 days to resolve, and lymphangitis may develop even in the absence of infection.[6] A local reaction occurring in the mouth or throat can produce airway obstruction. Stings around the eye or on the lid may result in the development of an anterior capsule cataract, atrophy of the iris, lens abscess, globe perforation, glaucoma, or refractive changes.

Anaphylaxis Symptoms range on a continuum. Most reactions develop within the first 15 minutes, and nearly all occur within 6 hours. Initial mild symptoms may progress swiftly to shock. There is no correlation between systemic allergic reaction and the number of stings. Symptoms include nausea, vomiting, and diarrhea; lightheadedness and syncope; involuntary muscle spasms; edema without urticaria; and, rarely, seizures. Respiratory distress and cardiac arrest can result. Urticaria and bronchospasm do not need to be present. In general, the shorter the interval between the sting and the onset of symptoms, the more severe is the reaction. Fatalities that occur within the first hour after the sting usually result from airway obstruction or hypotension.

Organ System Effects Renal and hepatic failure and disseminated intravascular coagulation can result from massive bee stings. Creatine phosphokinase concentrations can reach 100,000 IU/L or greater in cases in which rhabdomyolysis occurs from direct venom toxicity.[2] Toxic reactions are believed to occur due to a direct multisystem effect of the venom. Symptoms usually subside within 48 hours, but may last for several days in severe cases, and some effects, such as rhabdomyolysis, can be delayed. We recommend hospital admission or observation for victims with large numbers of stings, for those with substantial comorbidities, and for those at extremes of age.

Delayed Reaction A delayed reaction may appear 5 to 14 days after a sting and consist of serum sickness–like signs and symptoms of fever, malaise, headache, urticaria, lymphadenopathy, and polyarthritis.[7] Frequently, the patient has forgotten about the encounter and is puzzled by the sudden appearance of symptoms. This reaction is believed to be immune complex mediated.

Unusual Reactions Infrequently, a reaction to Hymenoptera venom produces neurologic, cardiovascular, and urologic symptoms, with signs of encephalopathy, neuritis, vasculitis, and nephrosis. Guillain-Barré syndrome has been reported as a possible consequence of a Hymenoptera sting. Identification of the offending insect can be difficult, except for the honeybee, which predictably leaves its stinger with venom sac attached in the lesion. In general, definitive insect identification is unnecessary, because signs and symptoms of envenomation are similar for all species of Hymenoptera. If edema persists at the sting site, then consider secondary cellulitis. Severe local reactions on the foot or ankle can be misdiagnosed as gout if the insect sting is not visible.

GENERAL TREATMENT

If the bee stinger is present in the wound, remove it. Although conventional teaching suggested scraping the stinger out to avoid squeezing remaining venom from the retained venom gland into the tissues, involuntary muscle contraction of the gland continues after evisceration, and the venom contents are quickly exhausted. Immediate removal is the important principle, and the method of removal is irrelevant. Wash the sting site thoroughly with soap and water to minimize the potential for infection. For local reactions, intermittent application of cold compresses at the site may diminish pain and swelling. Oral analgesics, including NSAIDs and antihistamines may limit discomfort and pruritus, respectively. If edema is significant, elevation and rest of the affected limb may be beneficial. Although physicians often prescribe corticosteroids for large local reactions, it is not clear there is benefit of doing so. The natural course of large local reactions is to increase in size over 1 to 2 days, take 3 to 10 days to resolve, and potentially be associated with lymphangitic streaks; associated infections are uncommon.[6]

ANAPHYLAXIS TREATMENT

Although the initial signs and symptoms of a systemic reaction may be mild, the victim's condition can deteriorate rapidly in a matter of minutes. Administer IM epinephrine, 0.3 to 0.5 milligram (0.3 to 0.5 mL of 1:1000 concentration) in adults and 0.01 milligram/kg in children (up to 0.3 milligram). **To avoid mishaps in dosing, many EDs now stock adult and pediatric EpiPens®, which provide a standard adult or pediatric dose (EpiPen®, 0.3 milligram epinephrine; EpiPen-Jr®, 0.15 milligram epinephrine for children <30 kg).** Provide aggressive fluid resuscitation with crystalloids. Antihistamines, histamine-2 receptor antagonists, and steroids are also commonly given. See Chapter 14, "Allergy and Anaphylaxis," for detailed discussion. Antivenoms have been studied for the treatment of mass bee attacks but are not yet commercially available.[8]

LONG-TERM MANAGEMENT AND PREVENTIVE CARE

Generally, referral to an allergist/immunologist and further testing are not recommended for localized dermal reactions, including large ones. Patients who have had an anaphylactic reaction to any stinging insect, including Hymenoptera, should (1) be educated on avoidance; (2) be prescribed, be instructed on the indications for self-administration of, and carry epinephrine; (3) be referred to an allergist/immunologist who can perform skin testing and consider initiation of venom immunotherapy; and (4) consider carrying medical identification (e.g., medical alert tag) for stinging insect hypersensitivity. Venom immunotherapy is extremely effective in decreasing the risk and degree of subsequent systemic reactions.[6]

ANTS

There are five known species of fire ants (*Solenopsis*) in the United States: the native species *Solenopsis aurea*, *Solenopsis geminata*, and *Solenopsis xyloni*, and at least two imported species, *Solenopsis invicta* and *Solenopsis richteri*. The two imported species entered the United States in the 1930s, have now become well established throughout the Gulf Coast states, and are spreading throughout the Southwest.[9] Fire ants inhabit loose dirt and breed 9 to 10 months of the year. One mature nest can produce 200,000 ants during a 3-year period, which accounts for rapid spread. The venom of the fire ant is almost entirely an insoluble alkaloid. There is possible cross-reactivity between the venoms of fire ants and those of other Hymenoptera, and individual stings may produce systemic toxicity in sensitized individuals.

Fire ants are characterized by their tendency to swarm when provoked, and they may attack in great numbers. Fire ants in a swarm most often position themselves on their victim and sting simultaneously in response to an alarm pheromone released by one or several individuals. Immobilized or elderly patients can become rapidly covered by swarms, with multiple severe stings or death.[10] Reactions to the sting include local, large local, and systemic (anaphylaxis). An immediate local reaction typically consists of a wheal and flare and characteristically exhibits a pustule at the sting site. A large local reaction involves extension of edema, erythema, and induration from the bite site and may last several days. Intense pruritus may occur with local reactions.[11] Rarely, a systemic reaction manifested by urticaria and angioedema can occur. Fatalities and other severe reactions have been reported to occur rapidly following single stings from ants, but most occur in patients with a history of prior venom allergy and prior cardiopulmonary disease, in whom injectable epinephrine was not given.[12,13] Rhabdomyolysis and renal failure have also been reported after massive fire ant stings.[14]

Estimated hypersensitivity to fire ant venom occurs in 16% of the general population, with some crossover with those sensitized to the stings of other Hymenoptera. Treatment of fire ant stings consists of local wound care. In systemic reactions, treat for anaphylaxis. Desensitization may be necessary in patients exhibiting potentially life-threatening reactions to these arthropods. The wearing of socks or cotton tights seems to provide more protection from fire ant stings than the use of insect repellents.[15]

SPIDERS (ARANEAE)

Although nearly 40,000 species of spiders have been described worldwide, medically significant envenomations have been described in only a few dozen. Spiders are carnivores, and venom probably evolved for

TABLE 211-1 Medically Important Spider Bites and Treatment

Spider	Bite Features	Complications	Treatment
Loxosceles: brown recluse spider, corner spider (worldwide distribution)	Painless bite, usually firm erythematous lesion that heals with little or no scar over days to weeks	Occasional hemorrhagic blister at 24 h; dermatonecrosis; systemic effects rare, mostly in children, at 24–72 h	No validated treatments
Widow spider: black widow, redback, button spider (worldwide distribution)	Pinprick bite; pain can spread to entire extremity; target lesion 1–2 cm	Acetylcholine and norepinephrine release; muscle cramps extending to trunk, back, and abdomen; hypertension, tachycardia	*Latrodectus* antivenom (Merck & Co), species specific; derived from horse serum; Fab antivenom available in Australia and Mexico; Analatro® antivenom in clinical trials in United States
Armed spider: banana spider (Central and South America)	Intense pain at bite site	Severe pain, sympathetic and parasympathetic effects; priapism; vertigo, visual disturbances	Antivenom available in Brazil
Funnel-web spider (Australia)	Severe pain, with wheal and erythema at site; very rapid envenomation	Parasympathetic effects, muscle fasciculation; myocardial damage and pulmonary edema; cerebral edema; death can occur within minutes	Compressive elastic bandage; funnel-web spider antivenom
Tarantula (worldwide)	Painful bite with local erythema and edema	Barbed hairs can penetrate cornea and conjunctivae; contact dermatitis from hairs	Ophthalmology consult for red eye and pain

paralyzing prey. The vast majority of spiders pose little harm to humans because their venom-injecting fangs are too small to penetrate human skin, the amount of venom injected is too little to produce toxicity, or the venom itself has little effect on mammalian cells. Even if a reaction is elicited, it is often local, and systemic toxicity is confined to a few specific species (**Table 211-1** and **Figure 211-1**).

SPIDERS CAUSING NECROTIC ARACHNIDISM (*LOXOSCELES*)

Loxosceles are brown spiders that have a worldwide distribution. The highest density is shown in Figure 211-1, and of these, *Loxosceles reclusa* (the brown recluse spider) occupies the largest geographic area and accounts for the majority of significant envenomations. In South America, particularly Brazil, *Loxosceles laeta* and *Loxosceles intermedia* account for most significant envenomations. Envenomation outside of endemic areas is very uncommon.[16] Nocturnal *Loxosceles* spiders are found indoors or outdoors in dark, dry areas (e.g., basements, closets, woodpiles); they are shy but may bite when threatened. A pigmented, violin-shaped pattern on the cephalothorax of the brown recluse is often present (**Figure 211-2**). However, this characteristic is considered unreliable and often misinterpreted. *Loxosceles* species are most accurately identified by their eye pattern, which consists of six paired eyes (one anterior pair and two lateral pairs); paired eyes are very close together which can give the appearance of three (rather than six) black dots.[16] Most other U.S. spiders have eight eyes arranged in two rows of four. The venom of the brown recluse contains multiple enzymes, including hyaluronidase and sphingomyelinase D, which is the major enzyme responsible for necrosis. Significant necrotic wounds are rare but possible through neutrophil activation, platelet aggregation, and thrombosis. Although both local and systemic complications of *Loxosceles* envenomation have been well described, the perceived threat of the brown recluse far exceeds its actual danger. For more information about recluse spiders, see the University of California, Riverside, Spider Research site (http://spiders.ucr.edu).

CLINICAL FEATURES

Bites by *Loxosceles* spiders are described as initially painless, which often prohibits possible identification of the spider. The most common manifestation of a bite is a mild erythematous lesion that may become firm and heal with little or no scar within several days or weeks. Occasionally, a more severe local reaction occurs, beginning with mild to severe pain several hours after the bite, accompanied by localized erythema, pruritus, and swelling. A hemorrhagic blister then forms, surrounded by vasoconstriction-induced blanched skin (**Figure 211-3**). By day 3 or 4, the hemorrhagic area may become ecchymotic, which leads to the "red, white, and blue" (erythema, blanching, and ecchymosis) sign. The ecchymotic area may become necrotic, with eschar formation by the end of the first week. The necrotic, slowly healing ulcers may not reach maximum size for many weeks after envenomation and

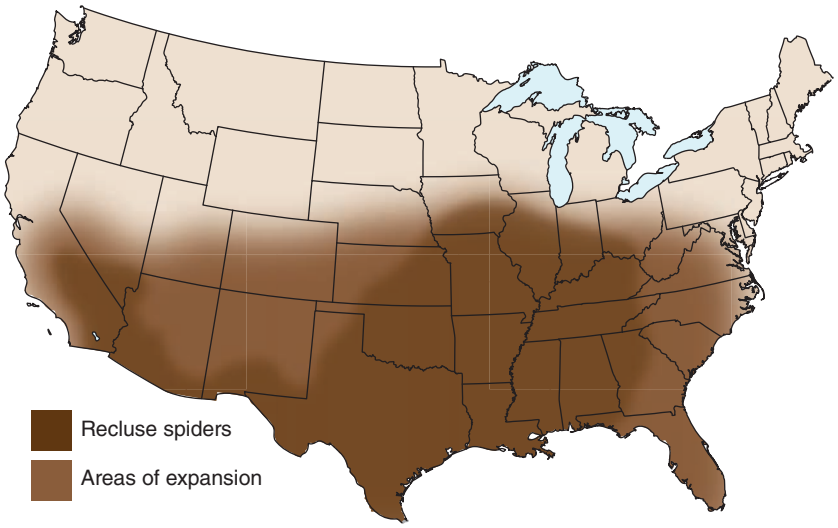

FIGURE 211-1. Highest density range of recluse (genus *Loxosceles*) spiders in the United States.

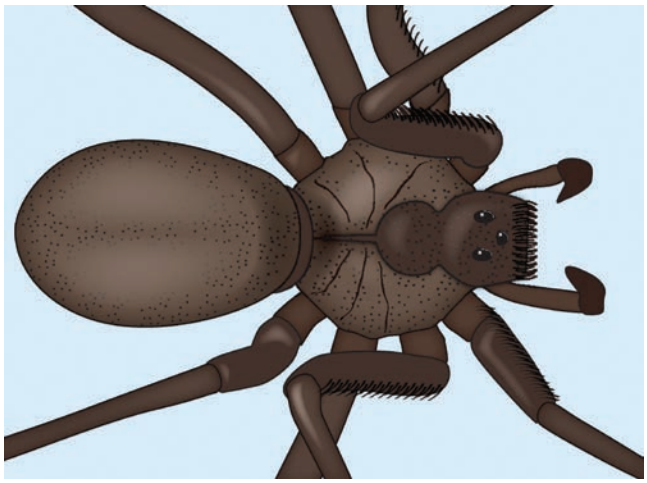

FIGURE 211-2. Close-up look at the characteristic fiddle-shaped back marking on the brown recluse spider (*Loxosceles reclusa*). Note the eyes, which are distributed as a single anterior pair and two lateral pairs; the paired eyes are very close together.

can occasionally result in a significant cosmetic defect requiring skin grafting.

Although significant systemic effects are not uncommon after bites of *L. laeta*, the predominant South American species, they rarely occur after bites of the brown recluse, the predominant U.S. species. Systemic effects, the hallmark of which is hemolysis, are seen more often in children and typically occur 24 to 72 hours after the bite. Other effects include nausea, vomiting, fever, chills, arthralgias, thrombocytopenia, rhabdomyolysis, hemoglobinuria, and renal failure. Disseminated intravascular coagulation and death are extremely rare.

Correct diagnosis of a brown recluse envenomation without definitive spider identification is difficult. Although the presence of a consistent clinical picture in an endemic area is suggestive, it is likely that a myriad of infectious and noninfectious conditions are misdiagnosed as brown recluse bites.[16] In patients who are suspected of having been bitten and who exhibit signs and symptoms of envenomation, obtain a CBC, BUN and creatinine, and coagulation profile. Assays to detect envenomation have been used in research, but a commercial test is not currently available.

TREATMENT

Treatment of a possible necrotic spider bite should include the usual supportive measures. Antibiotics are indicated if signs of infection exist, although secondary infections are uncommon. Various treatments have been advocated for brown recluse spider bites, including antihistamines, antivenom, colchicine, dapsone, hyperbaric oxygen, surgical excision, steroids, and topical nitroglycerin. None of these therapies have clear benefit, and most wounds from the brown recluse are self-limiting and heal without any medical intervention. Administration of the leukocyte inhibitor dapsone continues to be advocated by some despite lack of supporting research and known adverse effects, including hemolysis and methemoglobinemia. Early antivenom administration after envenomation is efficacious in animal models.[17] However, antivenom's potential utility is limited by delayed post-bite presentation, inability to identify an envenomation, and difficulty of prognosticating the (rare) development of dermatonecrosis. An equine-derived antivenom is commonly used in Brazil, but its efficacy is unclear. In the United States, there is no commercially available *Loxosceles* antivenom. Arranging follow-up for serial wound evaluation is appropriate. If ulceration develops, referral to a surgeon is indicated. Surgical debridement should be delayed until clear margins are established, often 2 to 3 weeks after the bite. Patients with systemic symptoms following a bite warrant hospitalization.

HOBO SPIDER (*ERATIGENA AGRESTIS*; FORMERLY *TEGENARIA AGRESTIS*)

A native of Europe and Central Asia, the hobo or northwestern brown spider is now found in the Pacific Northwest of the United States and southern British Columbia. Hobo spiders are brown with gray markings and have a 7- to 14-mm body length and a 27- to 45-mm leg span. They live in moist, dark areas such as woodpiles and basements.

Little documentation supports the occurrence of necrosis from hobo spider bites.[16] In its native European habitat, it is not considered poisonous to humans, and venom analysis comparing European to U.S. species has confirmed no unique differences. Confirmed bites have demonstrated localized erythema, itching, pain, and swelling.[18]

There is no diagnostic test for hobo spider envenomation and no proven treatment.

WIDOW SPIDERS (*LATRODECTUS*)

Latrodectus or "widow" spiders have a worldwide distribution. In the United States, the black widow is the most well-known, although of the five *Latrodectus* species found commonly in the United States, only three (*Latrodectus mactans*, *Latrodectus variolus*, and *Latrodectus hesperus*) are actually black. Other varieties may be predominantly brown (*Latrodectus geometricus*) or red (*Latrodectus bishopi*). An orange-red hourglass-shaped marking characterizes many of the *Latrodectus* species (**Figure 211-4**). Female spiders are relatively large,

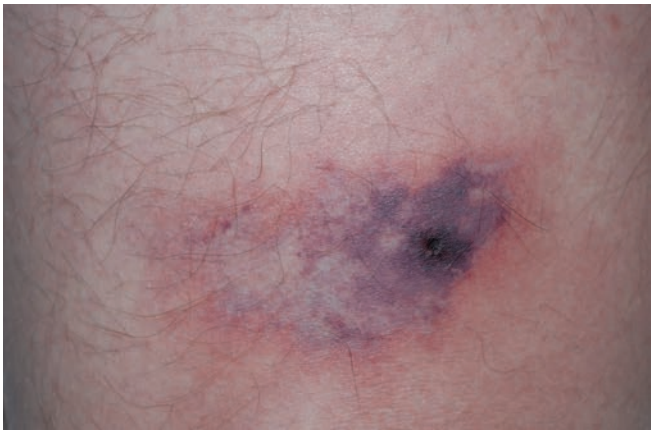

FIGURE 211-3. Early brown recluse spider bite (approximately 8 hours old) with a violaceous center surrounded by a faint spreading erythema. [Photograph by Lawrence B. Stack, MD. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine*, 3rd ed, © 2009 by McGraw-Hill, Inc., New York.]



FIGURE 211-4. Black widow spider (*Latrodectus mactans*) with offspring. Note characteristic hourglass marking on abdomen. [Photograph by Lawrence B. Stack, MD. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine*, 3rd ed, © 2009 by McGraw-Hill, Inc., New York.]

with a body size ranging up to 1.5 cm in length and leg spans of 4 to 5 cm. The male spider is approximately one third the size of the female and lighter in color, and his bite cannot penetrate human skin. Black widow spiders are found most often in woodpiles, basements, garages, and sheds. *Latrodectus* will aggressively defend her web, particularly when guarding her eggs. Most black widow bites in the United States occur between April and October and are usually seen on the hands and forearms.

The black widow spider injures its victim and its prey with highly potent venom. The most active component of the venom is α-latrotoxin, which acts through both calcium-dependent and calcium-independent pathways leading to receptor stimulation, pore formation, and ultimately massive release of neurotransmitters (predominantly acetylcholine and norepinephrine).[19] Acetylcholine release accounts for neuromuscular manifestations, and norepinephrine release accounts for the cardiovascular manifestations.

CLINICAL FEATURES

The severity and features of *Latrodectus* envenomation may vary for different widow spiders from different regions. However, in all cases, the most prominent feature of envenomation is local, regional, or generalized pain which may be associated with systemic symptoms and autonomic effects. Most *Latrodectus* bites are felt immediately as a pinprick sensation at the bite site, followed by increasing local pain that may spread quickly to include the entire bitten extremity. Erythema appears approximately 20 to 60 minutes after the bite. In some bites, a small, <5-mm erythematous macule develops that may evolve into a larger target lesion with a blanched center and surrounding erythema (**Figure 211-5**). The clinical syndrome of envenomation is referred to as latrodectism. Victims frequently complain of cramp-like spasms in large muscle groups, although physical examination of the "cramping" extremity rarely reveals rigidity. The pain often increases progressively, becomes generalized, and can involve the trunk, back, and abdomen. Localized diaphoresis near the site of envenomation can be seen. Severe abdominal wall musculature pain and cramping are well described, and in the absence of a known bite, the clinical picture can be confusing. Hypertension and tachycardia are common. Systemic symptoms include headache, nausea, vomiting, diaphoresis, photophobia, and dyspnea. Rarely reported complications include atrial fibrillation, myocarditis, priapism, and death. The pain with envenomation can be severe and intermittent and, if untreated, often lasts for a day. Occasionally, symptoms may persist for several days.

Because the initial bite is typically painful with most *Latrodectus* species, it is common for the offending spider to be identified. In the absence of a witnessed bite, a clinical diagnosis can be made based on characteristic symptoms and signs. There is no confirmatory laboratory test.

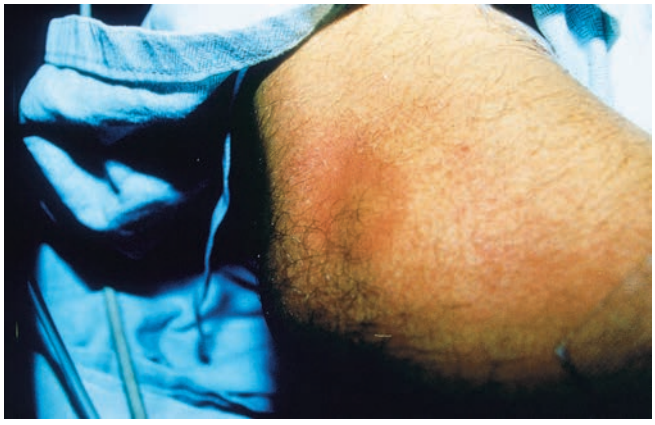

FIGURE 211-5. Black widow spider bite on the knee. [Photograph by Gerald O'Malley, DO. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine*, 3rd ed, © 2009 by McGraw-Hill, Inc., New York.]

TREATMENT

Cleansing of the bite site is reasonable. The optimal management of latrodectism remains controversial.[20] IV calcium had been recommended in the past, but a retrospective study did not demonstrate efficacy.[21] Opioid administration is appropriate to treat pain, and benzodiazepines may also be considered. For severe envenomations, admission may be necessary to achieve adequate pain control. Case reports, retrospective series, and anecdotal experience from those knowledgeable in managing these bites suggest efficacy of antivenom administration.[21,22] From this experience, rapid resolution of symptoms with antivenom administration and ability to discharge patients from the ED after a short observation period are possible.[21] Successful treatment of latrodectism with antivenom has been described even with administration 90 hours after envenomation.[23] Additionally, case reports have detailed successful use in pregnant patients, in whom envenomation could theoretically induce preterm labor and mimic preeclampsia.[24] However, the efficacy of antivenom administration has been recently questioned based on two studies that, to date, are the only randomized, prospective, placebo-controlled studies using *Latrodectus* antivenom. In both studies, antivenom administration did not demonstrate efficacy for the primary pain endpoint chosen, although in one study, pain was more rapidly reduced than with placebo.[25,26]

Latrodectus antivenom is produced in at least three countries with specificity for indigenous species: Redback (*Latrodectus hasselti*) Spider Antivenom® (CSL Ltd., Melbourne, Australia), Button Spider Antivenom® (South African Vaccine Producers Institute, Edenvale, South Africa), and Antivenin *Latrodectus mactans*® (Merck & Co., Inc., Whitehouse Station, NJ). It is likely that the antivenom to one species would be clinically effective in treating the bites of the others. Indications, amount, and route of administration vary according to product. Antivenin *Latrodectus mactans* and Button Spider Antivenom are administered IV, and Redback Spider Antivenom is typically administered by IM injection. An Australian-based study using Redback Spider Antivenom found minimal clinical difference between IV and IM routes.[27]

Anaphylaxis From Antivenom In the early years of its use, whole immunoglobulin G Antivenin *Latrodectus mactans*® use in the United States was considered safe. The only death was ascribed to administration via undiluted IV push to an asthmatic patient with known multiple medication allergies; slow administration of diluted antivenom was recommended to minimize risk.[28] However, in the past decade two additional cases of anaphylaxis to Antivenin *Latrodectus mactans*® have been described despite dilution and slow administration.[29,30] In one of these cases, the anaphylaxis resulted in cardiac arrest, and despite initial successful resuscitation, the patient later died.[29] Such reactions have not been described with the Australian product that is a purified $F(ab)_2$ antivenom. The current U.S. antivenom is available from Merck (Table 211-1). Antivenin *Latrodectus* Equine Immune $F(ab)_2$ (Analatro®), which is expected to be less immunogenic and safer than whole-antibody products, is currently commercially available in Mexico and was used in one of the randomized, placebo-controlled, double-blind studies mentioned earlier.[25] It is currently in phase III clinical trials in the United States. The recent questions of antivenom efficacy and potential for fatal reactions, particularly with the current U.S. product, should be considered, particularly since envenomation from a *Latrodectus* bite is rarely life threatening itself. A thorough discussion of risk and benefits should occur with the patient.

ARMED SPIDERS (*PHONEUTRIA*)

The armed spiders are found throughout South America and Costa Rica. The majority of clinically important bites have been described in Brazil. The spiders are solitary, nocturnal, do not construct a web, and possess potent neurotoxic venom. They have been reported to hide in banana bunches during shipping and can bite workers handling these bananas at their destination. When threatened, they assume a characteristic aggressive position by raising their four front legs, displaying their fangs, bristling their leg spines, and moving to continually face their threat. The best-known armed spider, *Phoneutria nigriventer* (banana spider), is large, with a body size up to 3.5 cm and leg length up to 6 cm. *P. nigriventer*

venom contains a mixture of potent neurotoxins that produce CNS, spinal cord, and autonomic effects.

Most *P. nigriventer* bites produce no significant symptoms. Significant envenomation produces local symptoms (severe pain) followed by sympathetic stimulation (tachycardia, hypertension), parasympathetic hyperactivity (nausea, vomiting, diaphoresis, salivation), spinal cord impairment (priapism), and CNS effects (vertigo, visual changes). Children and the elderly are at highest risk for serious envenomation. Pulmonary edema, shock, and death are rare.[31] Most healthy adults recover in 1 to 2 days.

In most cases, supportive care is adequate. Local anesthetic infiltration at the bite site can control pain. A polyvalent antivenom (Instituto Butantan, São Paulo, Brazil) is available for cases of severe envenomation from *P. nigriventer*.

FUNNEL-WEB SPIDERS (*ATRAX/HADRONYCHE*)

Funnel-web spiders are the deadliest spiders in the world. Fortunately, they only exist in a localized geographical location in eastern Australia, envenomations are rare (median of two per year), and no fatalities have been reported since the introduction of antivenom in 1981.[32] The spiders are so named because they construct a cylindrical web that extends into a recess, such as a burrow in the ground or a hole in a tree.

Funnel-web spiders have a shiny black body and long fangs, and females can grow up to 4 cm in body length. Females stay close to their webs, but the smaller and more aggressive males tend to wander, especially during the summer following a rain. *Atrax* venom contains atracotoxin, which (like scorpion venom) binds to sodium channels and causes release of neurotransmitters leading to both autonomic and neuromotor effects.

CLINICAL FEATURES

Atrax bites may result in local reaction with immediate pain, followed by wheal formation and surrounding erythema. Later, localized sweating and piloerection may be observed. The vast majority of *Atrax* bites do not result in significant envenomation or systemic toxicity. The onset of severe envenomation is rapid and unlikely to begin after 2 hours.[32] Symptoms and signs of systemic toxicity include perioral paresthesias, cholinergic excess (nausea, vomiting, diaphoresis, salivation, lacrimation, bronchorrhea), neuromuscular stimulation (muscle fasciculation, tremors, spasms, weakness), and CNS toxicity (altered level of consciousness). Myocardial damage with pulmonary edema may occur early after envenomation and is thought to be from massive catecholamine release.[33] Death after *Atrax robustus* envenomation has been reported as a result of cardiac arrest, hypotension, or pulmonary failure occurring between 15 minutes and 3 days after a bite.

TREATMENT

To reduce venom absorption and systemic toxicity from a bite on an extremity, apply a compressive elastic bandage to the entire length of the limb, and splint the extremity to prevent movement.[34] Immobilize the victim and transport promptly to the hospital.

The specific treatment for systemic toxicity is Funnel-Web Spider Antivenom® (CSL Ltd., Melbourne, Australia). If the patient has signs of systemic toxicity upon arrival or develops them after the compressive elastic bandage is carefully removed, antivenom should be administered until symptoms improve. Antivenom appears effective in reversing many of the manifestations of envenomation and appears to improve mortality. It does not appear effective in reversing cardiac damage.[33] Supportive therapy for hypotension (IV fluid), bronchorrhea (atropine), tremors and agitation (benzodiazepines), and hypertension and tachycardia (β-blockers) may be necessary.

TARANTULAS (THERAPHOSIDAE)

Tarantulas are large, hairy spiders belonging to the family Theraphosidae that are popular as pets. The hairs found on the abdomen of most species of tarantulas in North and South America resemble a velvety covering and are used defensively. When threatened, tarantulas may flick these hairs a short distance with their two back legs. Although North American tarantula hairs rarely penetrate human skin, the hairs can imbed deeply into the conjunctiva and cornea and can cause inflammation in all levels of the eye, from conjunctiva to retina. **Patients who manifest a red eye and pain after handling a tarantula should be examined to determine if offending barbed hairs are present in the cornea or conjunctiva.** Although hairs are sometimes easily seen on slit-lamp examination, they may at times be very difficult to detect. Therapy includes surgical removal of the hairs and topical application of steroids to control inflammation. Ophthalmia nodosa is a granulomatous, nodular reaction that can occur in cases of ocular exposure to tarantula hairs.[35] Patients may also develop a diffuse contact dermatitis from indirect exposure to hairs while cleaning a tarantula cage. Tarantula bites occasionally occur from North and South American species, leading to localized pain and swelling. Systemic symptoms from these species are rare. Certain Old World tarantulas in Africa and Asia, which may lack protective urticating hairs, can cause severe and persistent pain from envenomation.[36]

OTHER SPIDERS

Yellow sac spiders (*Cheiracanthium*) are medium-sized, typically yellow spiders that have a worldwide distribution. A few species are commonly found in homes. The most common symptom of a bite is local sharp pain. Minor erythema, swelling, and pruritus may occur at the bite site. Dermatonecrotic lesions are rare.[37]

Wolf spiders (*Lycosa*) are small- to medium-sized (3- to 5-mm body length) ground-dwelling spiders with a worldwide distribution. The venom produces local pain and occasionally induration and erythema, but no systemic symptoms and no skin necrosis.

Jumping spiders (family Salticidae) are typically small (<15 mm), brightly colored, and very active spiders with a worldwide distribution. A bite may produce pain, swelling, pruritus, and erythema with resolution in 2 days.

Daddy long-legs spiders (family Pholcidae) are common cellar and outbuilding dwellers along the Pacific coast and in southwestern deserts. There are no case reports of human envenomation.

SCORPIONS (SCORPIONIDAE)

Scorpions have a worldwide distribution, and highly toxic species are found in Africa, India, Mexico, North Africa, South America, the Middle East, and the Caribbean island of Trinidad. The toxins of the *Centruroides* and *Parabuthus* scorpions exhibit primarily neuromuscular effects, but toxins of the *Androctonus*, *Buthus*, and *Mesobuthus* scorpions exhibit cardiovascular effects.[38] Several species of scorpions are found in the warmer parts of the southern United States, but most species cause little more than localized pain. In the United States, only *Centruroides sculpturatus* (bark scorpion), found throughout Arizona, New Mexico, and parts of Texas and California, possesses venom potent enough to cause systemic toxicity.

CLINICAL FEATURES

Most stings cause localized pain at the bite site, and systemic toxicity occurs in <10% of stings. Scorpion venom contains many toxins, but the toxins with the most serious medical effects can open neuronal sodium channels and cause prolonged and excessive depolarization. Somatic and autonomic (parasympathetic and sympathetic) systems are affected (**Table 211-2**). **Infants and young children are at highest risk for severe systemic symptoms**, which can be life threatening. Motor hyperactivity is nearly universal when symptoms are systemic and may present as restlessness or uncontrollable jerking of the extremities that appears to be seizure-like activity. Peripheral nervous system toxicity includes abnormal oculomotor function, loss of pharyngeal muscle control, uncoordinated neuromuscular activity with respiratory compromise, and tongue fasciculations. Hypersalivation is common and, combined with cranial nerve dysfunction, can threaten airway integrity. Cardiovascular toxicity from systemic envenomation includes tachycardia, hypertension, pulmonary edema, and cardiogenic shock.

TABLE 211-2 Scorpion Sting Effects and Treatment

Clinical Effect	Pathophysiology	Treatment	Comments
Local effects only	Pain at sting site	Acetaminophen, NSAID, local lidocaine without epinephrine at sting site	
Dermatonecrosis over hours or days	Local necrosis, in 20% systemic features, myoglobinuria; similar to *Loxosceles* spider envenomation		*Habromys lepturus* of Iran
Tachycardia, hypertension, mydriasis	Excess catecholamines	Antivenom*; prazosin	
Agitation and anxiety	Neuromuscular agitation	Benzodiazepines	
Pulmonary edema	Catecholamine-induced cardiac injury, myocardial depression; cardiogenic shock	Antivenom*; nitroglycerin or prazosin†; dobutamine† for cardiogenic shock	*Androctonus*, *Buthus*, *Mesobuthus*, and *Tityus* scorpions
Hypotension, bradycardia, salivation, sweating, abdominal pain, diarrhea, pancreatitis	Cholinergic effects	Atropine	*Tityus* species
Oculomotor abnormalities, uncoordinated neuromuscular activity, muscle spasms	Neuromuscular excitation	Antivenom*; benzodiazepines	*Centruroides* scorpions, also *Parabuthus* and *Tityus*
Multiorgan failure			Supportive care

*Role of antivenom not clear once systemic toxicity established, as antivenom binds toxin but does not reverse established injury.

†Role of vasodilators not clear; concern if using vasodilators with dobutamine.

DIAGNOSIS AND TREATMENT

Diagnosis is clinical. Laboratory studies are needed in severe envenomation to identify organ system involvement.

Treatment is described in Table 211-2. Administer opioids for pain control and short-acting benzodiazepines for sedation as needed. Scorpion antivenom directed against different species has been produced for research or clinical use in many other countries. Recommendations for use and dosing of these products vary widely. Like all animal-derived antivenom, both immediate and delayed allergic reactions, including serum sickness, are possible. A randomized, double-blind study from Arizona in children suffering from significant neurotoxic effects of *Centruroides* stings demonstrated that an equine-derived IV scorpion-specific antibody $F(ab')_2$ resolved the clinical syndrome within 4 hours and significantly reduced the need for concomitant sedation.[39] The antivenom used, Anascorp®, is available for use in the United States but is currently quite expensive, and therefore, use should be restricted to patients with severe systemic symptoms. The most dangerous clinical manifestation of scorpion envenomation worldwide is acute heart failure and pulmonary edema. It remains unclear whether an initial massive catecholamine release and myocardial stunning is universally responsible for this.[40,41] It may be that in certain species, direct cardiotoxic effects of the venom can occur. Administration of the vasodilator prazosin is advocated to counteract the initial adrenergic response, and dobutamine administration may be appropriate to support cardiac dysfunction.

CHIGGERS (TROMBICULIDAE)

Chigger infestations result from mite larvae feeding on host skin cells. Mites are found in almost every habitat and are 0.3 to 1.0 mm in length. The larvae attach themselves to host skin with mandibular structures. They tend to attach in areas where an obstacle such as tight-fitting clothing is met, such as at the tops of socks, the leg bands of underwear, the waistband, or the edges of a bra. Once attached, the larvae release digestive enzymes to liquefy epidermal cells. The combination of digestive enzymes secreted by the mite and subsequent host immune response produces the "chigger bite."

CLINICAL FEATURES

Although diseases such as rickettsialpox and scruff typhus have been spread by mite vectors, the major clinical manifestation of chigger infestation is most often intense pruritus. The attached chigger may be seen initially as a bright red fleck on the skin, and it, along with the larvae, may be easily scratched off. Lesions are intensely pruritic and often appear as grouped papules or papulovesicles. The localized allergic response may last for weeks, and significant excoriation may occur at the site from intense scratching. A summer penile syndrome in children has been attributed to chiggers that manifests with acute swelling of the penis, often accompanied by pruritus.[42] The diagnosis of chigger infestation may be difficult, because many other arthropods cause similar clinical manifestations. The history of outdoor exposure combined with the presence of signs and symptoms localized to areas of snug-fitting clothing may be helpful.

TREATMENT

Treatment is primarily symptomatic to control the itching and consists of oral antihistamines and topical steroids. Oral steroids may be helpful in severe cases. Chiggers themselves may be killed with permethrin and other topical scabicides. If secondary infection occurs, antibiotics are indicated.

MOSQUITOS, FLIES, FLEAS, AND LICE

MOSQUITOES

Mosquitoes penetrate skin with the piercing motion of a bayonet-like proboscis. The actual puncturing of the skin surface causes minimal trauma and frequently is not felt by the host. A local anesthetic is injected into the wound that causes local tissue damage and local hypersensitivity. Bites can lead to both immediate and delayed reactions. An immediate skin reaction includes redness, a wheal, and itching. A delayed reaction can occur and usually consists of edema and pruritus. The immediate reaction tends to be of short duration, whereas a delayed reaction may persist for hours, days, and even weeks. Severe local reactions with skin necrosis are possible. Patients can acquire allergy to mosquito saliva constituents and develop symptoms consisting of an escalating reaction to seasonal exposures with increasingly pronounced edematous and pruritic lesions, sometimes accompanied by fever, malaise, generalized edema, severe nausea and vomiting, and necrosis with resulting scarring. Treatment is symptomatic with antihistamines and NSAIDs.

The greatest danger from mosquitoes is the transmission of disease. Even with extensive pest control programs, arbovirus infections and malaria are epidemic in many parts of the world. Chikungunya virus, dengue, Japanese B encephalitis, yellow fever, Zika virus, and various types of equine encephalitis are among the many viruses transmitted by mosquitoes. In addition, West Nile virus can be found across North America. Malaria is also encountered frequently in patients in the United States after travel and in immigrant populations from areas where malaria is endemic. Insect repellents offer some protection from mosquito bites.

FLIES (DIPTERA)

Bloodsucking flies range in size from the tiny sand fly, approximately 1 to 3 mm in length, to horseflies, which can be >2 cm. All flies stab and pierce the skin, causing some degree of pain and pruritus. Several species, such as deerflies, blackflies, horseflies, and sand flies, can produce allergic reactions, although these are rarely as severe as those produced by Hymenoptera venom. There is also the possibility of myiasis (infestation of tissue with fly larvae, e.g. botfly). Although rarely acquired in the United States, patients may present with cutaneous myiasis after travel to Africa and Central and South America.

The diagnosis of fly bite depends chiefly on the patient's history and knowledge of the arthropods that frequent the area of encounter. In the case of botfly, a travel history combined with recognition of a cystic-like skin lesion on exposed skin with a central pore through which the larva breathes and excretes exudate is essential to making the proper diagnosis. Treatment for most local reactions to Diptera bites is symptomatic, and treatment of systemic reactions is the same as for reactions to Hymenoptera venom. Application of cold compresses may alleviate localized edema. Secondary infection of Diptera bites can occur, and antibiotics may be necessary in some cases. Oral antihistamines may be helpful in relieving pruritus from fly bites, but topical steroids can be used when local reactions are severe, and oral steroids are indicated when systemic hypersensitivity symptoms are present. Although **botfly** infestation is generally a self-limited condition as the larvae will eventually exit the skin spontaneously, removal is appropriate. Application of various topical agents such as petroleum jelly that suffocate the larva may entice it to leave. Incision and removal of the entire larva is also effective.[43]

FLEAS (SIPHONAPTERA)

Bites of fleas, lice, and scabies mites produce lesions so similar that diagnosis is often difficult. Flea bites are frequently found in zigzag lines, especially on the legs and in the waist area. The lesions most often have a hemorrhagic-appearing center surrounded by erythematous and urticarial patches. Flea bites are usually quite pruritic, and red spots can persist at bite sites for some time.

The main concern in the treatment of these bites is the possibility of secondary infection. Children may develop impetigo as a complication. The lesions should be washed thoroughly with soap and water. Children with flea bites should have their fingernails cut short to prevent scratching. To relieve discomfort and itching, local application of calamine, cool soaks, and oral or topical antihistamines may be helpful. For severe discomfort, application of a topical steroid cream or spray may be necessary. If secondary infection develops, topical or oral antibiotics may be needed.

KISSING BUGS AND BED BUGS (HEMIPTERA)

The order Hemiptera includes two bloodsucking families of arthropods with medical importance. These are Reduviidae (reduviids, or "kissing" bugs) and Cimicidae ("bed bugs" and their relatives). Various species of kissing bugs are found predominantly in the southern United States and Central and South America. The common name "kissing bugs" derives from their habit of feeding at night on any exposed surface of a sleeping victim, commonly the face. Bed bugs are also nocturnal feeders, and their distribution is worldwide. Recently, there has been a worldwide major resurgence in bed bug infestations, particularly in developed countries. This has been attributed to immigration, international travel, and insecticide resistance.[44] Both bugs are attracted to warm bodies and hide near beds. Bed bugs are found in nearby cracks and crevices. Kissing bugs of Central and South America are vectors of Chagas disease (trypanosomiasis). Current evidence does not support transmission of diseases to humans by bed bugs.[45]

CLINICAL FEATURES

Bites from both bugs are typically painless. Erythematous papules, bullae, and wheals may develop. A linear bite pattern on the skin is well described with bed bugs, and telltale brown or black patterns of excrement may be found on bed linen. A thorough search of bedding and nearby cracks and crevices will often reveal the bugs. Bed bugs are notoriously difficult to eradicate. One study demonstrated the potential for ivermectin (oral antiparasitic drug) administration to help eradicate bed bugs that are feeding on the patient.[46]

TREATMENT

Treatment of both types of bites is symptomatic. Cool compresses, topical steroids, and antihistamines can be used to relieve associated pruritus. Some individuals become highly sensitive to kissing bugs and react with systemic allergic symptoms following a bite. They should be treated as previously outlined for Hymenoptera envenomation.

CATERPILLARS AND MOTHS (LEPIDOPTERA)

Lepidopterism refers to the adverse effects resulting from contact with butterflies, moths, or their caterpillars. Caterpillars, the larval stage of moths and butterflies, are responsible for most symptomatic exposures. For protection, they may have either hairs or spines that can be attached to venom glands. The spines and hairs may cause mechanical irritation, whereas the venom can produce additional symptoms. Although isolated exposures are most common, particularly in children who may be attracted to the colored or "furry" appearance of caterpillars, there are multiple species that under the right conditions can cause "epidemics" of cutaneous or systemic exposures. A couple of moth species, most notably the *Hylesia* genus in Venezuela (responsible for the "Caripito itch"), can cause local irritant or allergic reactions.

CLINICAL FEATURES

Most reactions to Lepidoptera are mild and self-limited. Most caterpillars are harmless to humans. Pruritus from localized "caterpillar dermatitis" and occasional diffuse urticaria are the predominant symptoms of exposures to the hairs and venom. The puss caterpillar (*Megalopyge opercularis*) is found in the southeastern United States and accounts for most of the serious envenomations in this country. After initial contact, intense local burning pain, rather than pruritus, is typical. A grid-like pattern of hemorrhagic papules may be seen within 2 to 3 hours of these exposures and may last for several days. Regional lymphadenopathy is common, and the affected limb can swell. Other potential symptoms include headaches, fever, hypotension, and convulsions. No deaths have been reported. Ingestions of the hickory tussock caterpillar (*Lophocampa caryae*), found in the eastern United States, have been reported, with symptoms ranging from drooling to diffuse urticaria. Spines have been visualized in the oropharynx and even the esophagus in some of these patients, requiring endoscopy to aid in removal.[47] Two species of *Lonomia* caterpillars, found primarily in Brazil and Venezuela, are capable of causing potentially fatal coagulation defects.

TREATMENT

Treatment is symptomatic and supportive. Spines can be removed using adhesive tape. Antipruritic or topical anesthetic preparations, topical steroids, and oral antihistamines are typically used. For symptomatic ocular and oral exposures, removal of hairs may be necessary, and endoscopy has been described. Anaphylaxis is rare but would be treated in the typical manner. An antivenom specifically for *Lonomia obliqua* is available in Brazil to reverse coagulopathy.[48]

BLISTER BEETLES (COLEOPTERA)

Although the order Coleoptera includes a large number and variety of beetles, clinically significant envenomation occurs only from those that contain a vesicant (blister beetles). Blister beetles are found worldwide, including the United States. The most well-known blister beetle is the "Spanish fly" (*Cantharis vesicatoria*), found in Spain.

CLINICAL FEATURES

Blister beetles contain a highly potent vesicant (either cantharidin or pederin) that can be exuded or released if the beetle is brushed against, pressed, or crushed on the skin. **For this reason, a blister beetle should be removed from the skin by blowing or flicking.** Cantharidin-containing preparations are used medicinally for wart removal. Application of these substances in low concentration is without adverse effect.[49] However, higher concentrations or contact with the beetle's venom may cause local inflammation, leading to bullae formation. Severe conjunctivitis may also occur if cantharidin or pederin contacts the eyes from contaminated hands. Most described cases of blister beetle dermatosis are from seasonal outbreaks due to pederin-containing beetles.[50] At least one outbreak has been described in the United States. Topical exposure to blister beetles can cause a vesiculobullous eruption typical of a vesicant. Pederin-containing dermal exposures result in a more delayed (up to 36 to 72 hours) but more painful and symptomatic eruption than those from cantharidin-containing beetles. Due to the delay in onset of symptoms and signs, misdiagnosis is common. High concentrations of cantharidin preparations may result in dermal absorption and systemic toxicity. Systemic toxicity is well described following ingestion, either of the whole beetle or of cantharidin-containing preparations. Severe vomiting, hematemesis, abdominal pain, and diarrhea may occur, followed by dysuria, hematuria, oliguria, and renal failure. Although the exact mechanism by which cantharidin produces systemic toxicity is unknown, the vesicant action likely explains most of the findings. Direct cardiac toxicity with large ingestions of cantharidin is possible, and deaths have been reported. Fortunately, most preparations sold as "Spanish fly" for their purported aphrodisiac properties have very low concentrations of cantharidin. The local vascular congestion and urethral inflammation that occur following ingestion may be interpreted by some as enhanced sexuality.

TREATMENT

Treatment is supportive. The skin should be irrigated thoroughly after topical exposure to remove any persistent vesicant, followed by local wound care. Patients who are symptomatic after ingestion should be admitted and treated supportively.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 212

Snakebite

Richard C. Dart
Julian White

INTRODUCTION AND EPIDEMIOLOGY

Venomous snakes account for an annual estimated 1.5 million to 3 million bites and possibly greater than 100,000 deaths worldwide.[1] The American Association of Poison Control Centers reports an annual average of 6000 bites, approximately 2000 of them by venomous snakes. Because of underreporting, the true number of snakebites in the United States is possibly as high as 45,000 per year, with 7000 to 8000 by venomous snakes.[2] The major venomous snakes of the world can be divided into three groups: Viperidae (vipers and pit vipers), Elapidae (includes Hydrophiinae, or sea snakes; see Chapter 213, "Marine Trauma and Envenomation"), and the diverse group of non–front-fanged colubrid snakes (former family Colubridae, now split into several families).

In the United States, most snakebites occur in the warm summer months, when snakes and victims are most active. In the past, it was estimated that mortality from venomous snakebite approached 25%. Because of the availability of antivenom and advances in emergency and critical care, mortality rates today are <0.5%; approximately five deaths occur per year.[2]

Except for bites by imported species, North American venomous snakebites involve the pit vipers (Crotalinae subfamily of Viperidae) or coral snakes (Elapidae family). The crotaline snakes are represented by the rattlesnakes (*Crotalus* species), pygmy rattlesnakes, and massasauga (*Sistrurus* species), as well as the copperheads and water moccasins (*Agkistrodon* species). Venomous snakebites from imported exotic species are infrequent, but may occur in zoo personnel as well as in amateur herpetologists. A regional poison control center can provide information on snake identification, expected toxicity, and location of antivenom.

CROTALINAE (PIT VIPER) BITES

The crotaline snakes are called pit vipers because of bilateral depressions or pits located midway between and below the level of the eye and the nostril (**Figure 212-1**). The pit is a heat receptor that guides strikes at warm-blooded prey or predators. Crotaline snakes are also distinguished by the presence of two fangs that fold against the roof of the mouth, in contrast to the coral snakes, which have shorter, fixed, erect fangs. Within the pit viper group, the rattle distinguishes the rattlesnake from other crotaline snakes. The mistaken belief that rattlesnakes always rattle before striking has persisted for centuries. In truth, many strikes occur without a warning rattle.

PATHOPHYSIOLOGY

Crotaline venom is a complex enzyme mixture that causes local tissue injury, systemic vascular damage, hemolysis, fibrinolysis, and neuromuscular dysfunction, resulting in a mixture of local and systemic effects. Crotaline venom quickly alters blood vessel permeability; this leads to loss of plasma and blood into the surrounding tissue, which causes hypovolemia. Crotaline venom activates and consumes fibrinogen and platelets, causing a coagulopathy. In some species, specific venom fractions block neuromuscular transmission, which leads to cranial nerve weakness (e.g., ptosis), respiratory failure, and altered sensorium.

CLINICAL FEATURES

Up to 25% of crotaline snakebites are dry bites: venom effects do not develop. The manifestations of crotaline envenomation involve a complex interaction of the venom and the victim. The species and size of the snake, the age and size of the victim, the time elapsed since the bite, and characteristics of the bite or bites (location, depth, and number; the amount of venom injected) all affect the clinical evolution. The severity of envenomation following a crotaline bite is therefore variable. An

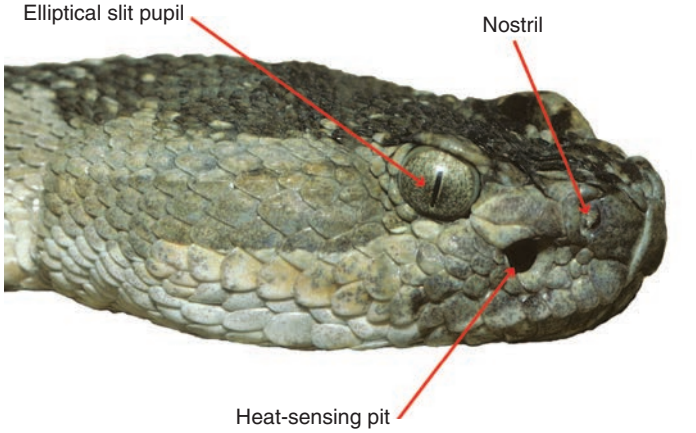

FIGURE 212-1. Pit viper.

initially minimal bite may evolve into a more serious bite and require large amounts of antivenom.

The cardinal manifestations of crotaline envenomation are the presence of one or more fang marks, localized pain, and progressive edema extending from the bite site. Other early symptoms and signs are nausea and vomiting, weakness, oral numbness or tingling of the tongue and mouth, dizziness, and muscle fasciculation. Systemic effects include tachypnea, tachycardia, hypotension, and altered level of consciousness. In general, local swelling at the bite site becomes apparent within 15 to 30 minutes, but in some cases, swelling may not start for several hours. In severe cases, edema can involve an entire limb within an hour. In less severe cases, edema may progress over 1 to 2 days. Edema near an airway or in a muscle compartment may threaten life or limb without causing systemic effects. Rapid onset of angioedema may occur.

Progressive ecchymosis may also develop because of leakage of blood into subcutaneous tissue. Ecchymoses may appear within minutes or hours, and hemorrhagic blebs may be seen within several hours. Hemoconcentration often develops as a result of fluid extravasation into subcutaneous tissue; it can be followed by a decrease in hemoglobin level over several days as intravascular volume is restored.

DIAGNOSIS

The diagnosis of snakebite is based on the presence of fang marks and a history consistent with exposure to a snake (e.g., walking through a field). **Snake envenomation involves the presence of a snakebite plus evidence of tissue injury. Clinically, the injury may be manifest in three ways: local injury (swelling, pain, ecchymosis), hematologic abnormality (thrombocytopenia, elevated prothrombin time, hypofibrinogenemia), or systemic effects (e.g., oral swelling or paresthesias, metallic or rubbery taste in the mouth, hypotension, tachycardia).** Abnormalities in any one of these areas indicate that venom effect is developing. The absence of any of these manifestations for a period of 8 to 12 hours following the bite indicates a dry bite.

TREATMENT

FIRST AID

First aid measures should never substitute for definitive medical care or delay the administration of antivenom (**Table 212-1**). Take all patients bitten by a pit viper to a healthcare facility. **Avoid dangerous first aid treatments such as suction and incision.** Do not use kits that contain suction cups; the cups produce little suction and seal poorly on digits. The blade in the kit, or any method of incision, can injure digital nerves, arteries, and tendons. The Sawyer Extractor® (Sawyer Products, Inc., Safety Harbor, FL) suction pump is said to remove venom without incision, but safety and efficacy of the product are questioned.[3] Electric shock treatment of the bite site is dangerous and ineffective and can cause electrical injuries. Ice water immersion worsens the venom injury.

Do not use tourniquets because they obstruct arterial flow and cause ischemia. Constriction bands may be useful, especially when immediate medical care is not available. A constriction band is an elastic bandage or Penrose drain, thick rope, or piece of clothing wrapped circumferentially above the bite and applied with enough tension to restrict superficial venous and lymphatic flow while maintaining distal pulses and capillary filling. **Apply the band snugly but loose enough to avoid arterial compromise.** It should be easy to insert one or two fingers under the band. A constriction band can delay venom absorption without causing increased swelling.[4] In distinction to a constriction band, a pressure immobilization bandage is a compression pad placed over the bite site combined with a snug elastic bandage wrap and extremity immobilization. This technique is recommended for coral snake and other elapid snake bites but is generally discouraged for crotaline bites because it may increase pain at the site.

TABLE 212-1 Recommended First Aid Measures for Snakebite

- Retreat well beyond striking range. Many victims are bitten again while trying to capture the snake.
- Remain calm. Movement will increase venom absorption.
- Immobilize the extremity in a neutral position below the level of the heart.
- Ensure prompt transport to a medical facility whether or not there are signs of envenomation.
- Constriction bands (see text) can be applied if there is no nearby medical facility.

PREHOSPITAL MANAGEMENT

In the prehospital phase, immobilize the limb, establish IV access in another limb, administer oxygen, and transport the victim to a medical facility. Do not remove tourniquets or constricting bands until antivenom is available, except where there is clear arterial vascular compromise threatening limb viability; in this latter situation, anticipate possible rapid development of systemic envenomation upon removal of first aid.

Institute advanced life support measures as indicated. If the patient is hypotensive, rapidly administer IV isotonic fluids. Immobilize the limb in a neutral position during transport to reduce further venom absorption. Consult with a physician or poison control center familiar with the management of snake envenomation.

ED MANAGEMENT

Antivenom is the mainstay of therapy for venomous snakebites[1,5] (Table 212-2). Antivenom is composed of heterologous antibodies derived from the serum of animals immunized with the appropriate snake venoms. The antibodies bind and neutralize the venom molecules.

Crotalidae Polyvalent Immune Fab (Ovine) (FabAV) is used in the United States. Crotalidae Immune F(ab')2 (Equine) (Fab_2AV) is now commercially available. The serum half-life of **Fab_2AV** is longer, and a prospective trial reported that the incidence of recurrent coagulopathy was reduced. The relative effectiveness and safety of each product are unknown. Each antivenom is produced by immunizing sheep or horses with crotaline snake venoms, which vary by the product. The immune serum is harvested from the host animals and then digested with papain (FabAV) or pepsin (Fab_2AV) to produce antibody fragments. In both cases, the more immunogenic Fc portion of the antibody is eliminated during purification.

All snakebite patients who develop progressive signs and symptoms should be treated promptly with antivenom. **Progression is defined as worsening of local injury (e.g., pain, ecchymosis, swelling), abnormal laboratory results (e.g., worsening platelet count, prolonged coagulation times, decreased fibrinogen level), or systemic manifestations (e.g., unstable vital signs, abnormal mental status) (Table 212-3).**

Administer antivenom IV to establish "initial control" (**Figure 212-2**). **Initial control is cessation of progression of three clinical evaluation parameters: local effects, systemic effects, and hematologic**

TABLE 212-2 Clinical Features and Treatment of Reptile Envenomation

Reptile	Clinical Findings	Antivenom
Crotaline snake (pit viper)	Fang marks Local tissue injury Fibrinolysis Thrombocytopenia Systemic effects	Crotalidae Polyvalent Immune Fab Crotalidae Immune F(ab')2 (Equine)
Coral snake	Neurologic dysfunction	Antivenom (*Micrurus fulvius*)
Elapid snake	Coagulopathy for some species Systemic effects, primarily neurologic dysfunction Cardiac arrhythmias and dysfunction Local injury for some species	Each species has monovalent or polyvalent antivenoms

TABLE 212-3 Laboratory Evaluation in Crotaline or Elapid Snakebite

- CBC*
- INR or prothrombin time*
- PTT*
- Fibrinogen level*
- Fibrin degradation product levels
- Serum electrolyte levels
- Glucose level
- BUN level
- Platelet count
- Creatine kinase level
- ECG†
- Arterial blood gas analysis‡

*Should be performed as soon as possible and repeated within 12 h.

†Suggested for patients >50 y of age and patients with a history of heart disease.

‡Should be performed if any signs or symptoms of respiratory compromise are evident.

TABLE 212-4 Management of Compartment Syndrome Caused by Crotalinae Snake Envenomation*†

- Determine intracompartmental pressure.
- If pressure is not elevated, continue standard management.
- If signs of compartment syndrome are present and compartment pressure is >30 mm Hg:
  - Elevate limb.
  - Administer mannitol, 1–2 grams/kg IV over 30 min.
  - Simultaneously administer *additional* antivenom over 60 min.
- If elevated compartment pressure persists another 60 min, consider fasciotomy.

*Elevated compartment pressure is caused by the action of the venom on the tissues, and thus management of compartment syndrome due to snakebite is unique; therefore, the most effective treatment is to neutralize the venom, which may reduce the compartment pressure.

†The mannitol and antivenom deliver a high osmotic load, and fluids and electrolyte levels need careful monitoring. The administration of mannitol and antivenom must be completed promptly so that, if ever needed, fasciotomy may be performed as early as possible.

abnormalities. It is crucial to document initial control because the most common error in management is insufficient dosing early in treatment.

After reconstitution, dilute each dose of antivenom in crystalloid and infuse over 1 hour. After initial control has been established, two-vial maintenance doses are recommended (Figure 212-2) for FabAV. Fab_2AV will be introduced in 2019[6]; dosing schedules are different, and the healthcare provider should be careful to use antivenom according to the product label and in consultation with a poison center. **In children, the total volume, but not the number of vials, may be reduced.[7] If IV access is unavailable, the IO route may be used.**

Do not inject antivenom IM or directly into a digit, because venom-induced hypovolemia may retard absorption of antivenom. Hospital pharmacies in regions where venomous snakes are prevalent should maintain adequate stocks of antivenom. Unfortunately, many hospitals stock insufficient amounts of antivenom, even in endemic areas.[8]

The package insert is useful as a guide for antivenom preparation. Give antivenom in a critical care facility such as an ED or intensive care unit, under direct physician supervision, and with resuscitative drugs (including epinephrine) and equipment immediately available. The incidence of acute reactions to modern antivenoms is low.[9] If an acute allergic reaction occurs, stop the infusion immediately and administer antihistamines (both histamine-1 and histamine-2 receptor blockers). Epinephrine should be readily available and administered for anaphylaxis.

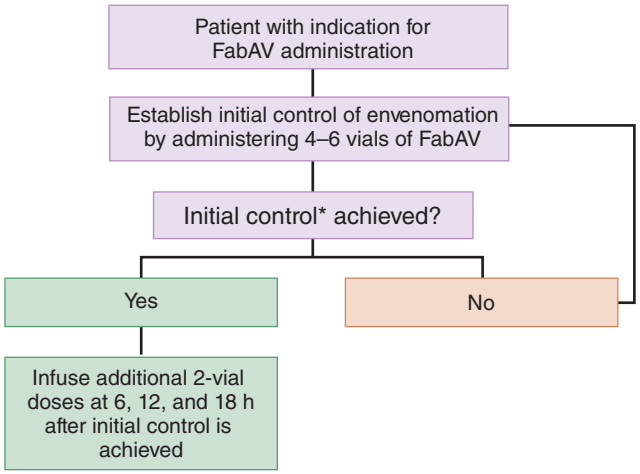

FIGURE 212-2. General strategy for administration of pit viper antivenoms in the United States. Both antivenoms use the same strategy of establishing initial control followed by additional antivenom as needed. However, the dosage varies; the package insert should be consulted for dosing recommendations. *Initial control is cessation of progression of all components of envenomation: local effects, systemic effects, and coagulopathy. FabAV = Crotalidae Polyvalent Immune Fab (Ovine).

Continue to observe for progression of edema and systemic signs of envenomation during and after antivenom infusion. Measure limb circumference at several sites above and below the bite, and outline the advancing border of edema with a pen every 30 minutes. These measures serve as an index of the progression as well as a guide for antivenom administration. Repeat laboratory determinations every 4 hours or after each course of antivenom therapy, whichever is more frequent. Additional doses of antivenom may be warranted if the patient's condition worsens. The use of crotaline antivenom for copperhead envenomation is controversial, but recent studies indicate effectiveness of FabAV.[10] It should be administered in copperhead bites where progression occurs over time. The value of aggressive supportive care cannot be overemphasized. Administer isotonic fluid resuscitation followed by vasopressor agents for hypotension. **Antivenom is the best treatment for hematologic abnormalities, but if active bleeding occurs, blood component replacement may be necessary after antivenom has been given.**

Compartment syndrome is another complication of snakebite. Increased compartment pressure may occur when venom is injected or spreads into a compartment; this is often manifested by severe pain that is localized to a compartment and usually resistant to opiate analgesia. **Table 212-4** presents the suggested treatment of compartment syndrome.[11] The use of fasciotomy is controversial, and there is no firm evidence supporting its use.

Clean the bite wound and determine the need for tetanus immunization. Obtain wound specimens for culture and administer antibiotics if signs of infection are present. Although antibiotic prophylaxis is recommended by some authors, the data available do not support its use.[12] Steroids are not effective and could be harmful. Steroids should be reserved for the treatment of allergic reactions or serum sickness.

Serum sickness is uncommon after antivenom treatment. The symptoms are fever, rash, and arthralgias. Start prednisone, 1 milligram/kg PO once daily, and taper over 1 to 2 weeks.

DISPOSITION AND FOLLOW-UP

It cannot be overemphasized that one can easily be deceived by a bite that initially appears innocuous. Unremarkable physical examination and laboratory test results at presentation do not reliably exclude significant envenomation. **Observe patients for at least 6 to 8 hours in the ED before determining disposition.**

Discharge patients with dry bites who have been observed for 6 to 8 hours with instructions to return if pain, swelling, or bleeding develops. Admit patients with severe or life-threatening bites and patients receiving antivenom to an intensive care unit; the general ward is appropriate for patients with mild or moderate envenomations who have completed or do not require further antivenom therapy.

Patients are ready for discharge from the hospital when swelling begins to resolve, coagulopathy has been reversed, and the patient is ambulatory. Physical therapy for the bitten part (particularly the hand) is recommended after swelling has lessened and coagulopathy has resolved. Patients should return if symptoms recur or if they develop bruising or other signs of recurrent coagulopathy. Outpatient follow-up is necessary to monitor for infection and serum sickness. The patient should be instructed about serum sickness symptoms and advised to report if such symptoms develop.

ELAPID SNAKEBITE

U.S. CORAL SNAKEBITES

U.S. coral snakes include the eastern coral snake (*Micrurus fulvius*), the Texas coral snake (*Micrurus tener*), and the Arizona (Sonoran) coral snake (*Micruroides euryxanthus*). The eastern coral snake is found primarily in the southeastern United States. The Texas and Arizona coral snakes are found primarily in their eponymous states. Coral snakes account for 20 to 25 bites a year.

All coral snakes are brightly colored with black, red, and yellow rings. The red and yellow rings touch in coral snakes, but they are separated by black rings in nonvenomous snakes, which led to the well-known rhyme, **"Red on yellow, kill a fellow; red on black, venom lack." This rule is not always true outside of the United States.**

Coral snake venom is primarily composed of neurotoxic components that do not cause marked local injury (Table 212-2). Admit potential victims of coral snakebite to the hospital for observation, because venom effects may develop hours after a bite and are not easily reversed. Administer three to five vials of antivenom, Antivenin® (*M. fulvius*), IV to patients who have definitely been bitten, because it may not be possible to prevent further effects or reverse effects once they develop.[13] Additional doses of coral snake antivenom are reserved for cases in which symptoms or signs of coral snake envenomation appear. Because respiratory failure may result from clinical effects of the neurotoxin, baseline and serial measurement of pulmonary function parameters (e.g., inspiratory pressure and vital capacity), in addition to intensive care observation, may be useful. Prolonged ventilatory support may be required in severe cases. Observe the patient closely for signs of respiratory muscle weakness and hypoventilation. Bites by the Sonoran coral snake are mild, and antivenom is not usually needed.

ELAPID BITES WORLDWIDE

Elapids are found throughout the world in warm climates. Elapids occur in Australia, New Guinea, Asia, Africa, and the Americas. All sea snakes are elapids (subfamily Hydrophiinae). Medically significant groups include some venomous snakes of Australia (tiger snakes [*Notechis*], brown snakes [*Pseudonaja*], taipans [*Oxyuranus*], death adders [*Acanthophis*], "black" snakes [*Pseudechis*], pygmy copperheads [*Austrelaps*], rough-scaled snake [*Tropidechis carinatus*], broad-headed snakes [*Hoplocephalus*]) and, in other areas, cobras (*Naja*; Asia and Africa), mambas (*Dendroaspis*; Africa), kraits (*Bungarus*; Asia), coral snakes (*Micrurus*; Americas), and a variety of less common genera and species.[14]

Elapid bites produce systemic effects, particularly neurologic effects: tremor, salivation, dysarthria, diplopia, bulbar paralysis with ptosis, fixed and constricted pupils, dysphagia, dyspnea, and seizure.[14] Some groups (e.g., cobras) also produce pain, local injury, and necrosis, which may be more clinically prominent than systemic effects.[14] The immediate cause of death is usually paralysis of respiratory muscles. Australian elapids produce coagulopathy; some cause rhabdomyolysis, as do some kraits. Signs and symptoms may be delayed 12 or more hours. Some cobras in Africa and Asia ("spitting cobras") can spit venom several feet. If spit into the eye, this venom can cause **venom spit ophthalmia,** a very painful acute corneal injury rendering the victim temporarily blind, but systemic envenomation does not occur. In general, a spitting cobra bite causes moderate to severe local effects, including necrosis, with paralytic effects uncommon in most species.

PATHOPHYSIOLOGY

The Elapidae possess nonretractile small- to medium-sized paired fangs that have grooved, often enclosed venom channels rather than hollow venom ducts.[14] It is thought that the Elapidae exert voluntary control over the injection of venom, hence the frequent occurrence of a dry bite.

The venom of the Australian elapids contains several important components.[14,15] Neurotoxins (tiger snake, taipan, death adder, and others) act at the neuromuscular junction and cause descending symmetric flaccid paralysis. Signs usually develop within 2 to 12 hours after the bite and may include ptosis, partial ophthalmoplegia (diplopia), dysarthria, loss of facial expression, loss of airway control, and respiratory paralysis. The procoagulant toxins (seen in brown snake, tiger snake, taipan, and others) act as prothrombin converters, leading to a venom-induced consumptive coagulopathy with fibrinogen depletion and variable thrombocytopenia. Intracranial hemorrhage is a recognized complication.

Brown snake envenomation can cause rapid collapse and death.[15,16] Renal impairment or failure may also result from snakebite. The mechanisms are poorly understood and may include hypotension, myoglobinuria, coagulopathy, and direct renal toxicity.[14,15] Myolysins (tiger snake, taipan, and mulga snake) are structurally related to the neurotoxins but instead produce rhabdomyolysis, which may result in muscle pain, weakness, myoglobinuria, secondary renal failure, and hyperkalemia.[14,15] Rarely, a venom-induced thrombotic microangiopathy may complicate brown and tiger snake envenomation.[16-18] Local tissue destruction is uncommon with the bite of any Australian species, although mild to moderate ecchymosis and swelling may occur. This likely accounts for the popularity of pressure bandages and immobilization in Australia.[15]

CLINICAL FEATURES

The severity of elapid envenomation cannot be estimated by the clinical appearance of the bite site or by initial symptoms.[14-17] Even with severe envenomation, patients may initially feel well and manifest few clinical features. Early symptoms include nausea, vomiting, headache, abdominal pain, diplopia, dysphonia, progressive muscle weakness, discolored urine, and seizures.[15] Young children may not provide a history of snakebite; if a child develops toxicity in a region populated with elapids, envenomation should be suspected.[15] In Australia, the most common cause of snakebite fatality is a prehospital cardiac arrest, inadequately resuscitated, as a result of a brown snake (*Pseudonaja* spp.) bite.

DIAGNOSIS

The diagnosis requires correlation of history, clinical features, and laboratory investigations. Laboratory tests often determine if the patient requires antivenom treatment.[14-17] Key tests include prothrombin time (PT), INR, activated PTT, D-dimer, fibrinogen, fibrin degradation products, hemoglobin, platelet count, electrolytes, renal function test, and creatine kinase. These tests should be performed prior to removal of first aid, 1 hour after removal of first aid, and at 6 and 12 hours after bite (earlier if clinical abnormalities develop).[15,19] Look for evidence of procoagulant coagulopathy (prolonged PT and activated PTT, high INR, raised D-dimer/fibrin degradation products, low fibrinogen), anticoagulant coagulopathy (abnormal PT and activated PTT with high INR, but normal fibrinogen and D-dimer/fibrin degradation products), platelet effects, rhabdomyolysis (grossly elevated creatine kinase, myoglobinuria), renal damage (abnormal renal function tests, reduced urine output), hyponatremia, and a syndrome similar to hemolytic-uremic syndrome (thrombocytopenia, anemia, intravascular hemolysis).[15] A Snake Venom Detection Kit® (SVDK; bioCSL, Parkville, Victoria, Australia) is available to identify snake venom at the bite site or in the urine, correlated to venom immunotype (which corresponds to "monovalent" antivenom type), for use exclusively with Australian and New Guinea snakes.[15] Positive SVDK identification of venom at the bite site or in the urine assists in selecting a "monovalent" antivenom, but does not

represent an indication for antivenom therapy, because of the significant rate of "dry bites" by some Australian elapids.[15] World Health Organization guidelines on treating snakebite in Asia and Africa are a useful online resource on diagnosis and treatment for these regions.[20,21]

TREATMENT

FIRST AID

In Australia and New Guinea, pressure bandaging and immobilization of the involved limb are used. The principle is to contain the venom locally and prevent venom transport by lymphatic vessels. Wrap an elastic bandage firmly over the bite site and then extend it to cover the entire limb (bandage pressure similar to that used for sprains: firm, but not tourniquet tight).[15] Limb splinting to prevent movement is an essential part of the method. Examination of lymphatic flow rates with simulated venom has demonstrated that, even if the upper or lower limb is appropriately bandaged and immobilized, walking will hasten systemic envenoming.[22] **Use of tourniquets is contraindicated.** In the rare circumstance that a bite is inflicted on the trunk, apply firm pressure to the affected area without restricting breathing.

Outside of Australia and New Guinea, the choice of first aid is more nuanced. If the bite is from an elapid that causes predominantly local tissue damage (e.g., a spitting cobra) or an unidentified snake, then pressure bandaging and immobilization may potentially increase local tissue injury.[14] The risk from potentially increased local tissue damage caused by pressure bandaging and immobilization must be balanced against the risk of progressive neurotoxicity, if neurotoxic snakes are present locally. Consider omitting pressure bandaging and immobilization but splinting the bitten part if likely snake species do not include neurotoxic snakes.

ED MANAGEMENT

Any history suggestive of snakebite should prompt appropriate first aid and transport to a medical facility with appropriate medical expertise, laboratory facilities, and antivenom supplies. Maintain pressure bandaging and immobilization (or immobilization only) until envenomation is excluded or until the patient can receive antivenom.[15] If the patient deteriorates immediately after removal of first aid measures, reapply and give antivenom. Once antivenom is infusing, remove the pressure bandage so that antivenom can reach the envenomed area. There is no evidence that venom is inactivated by being trapped at the bite site.[15]

Antivenom should be given only in cases in which there is clear clinical or laboratory evidence of systemic envenomation. Clinical indications for immediate antivenom therapy include evidence of neurotoxic effects (ptosis, cranial nerve involvement, progressive muscle weakness, or diaphragmatic involvement), coagulopathy, rhabdomyolysis, renal failure, cardiac collapse, significant local tissue injury, or vomiting unresponsive to antiemetics.[14,15] If evidence of systemic envenomation is not present, remove the first aid measures and observe the patient for at least 12 hours, or longer for some species.[15,19] Repeat laboratory tests 1 hour after removing the first aid measures and at intervals thereafter dictated by the patient's condition.

For Australian elapid snakebites, there is only one manufacturer (Seqirus/CSL Ltd, Melbourne, Australia) that produces five "monovalent" antivenoms corresponding to the five venom immunotypes, a polyvalent antivenom that covers all of the five venom immunotypes, plus a sea snake antivenom that is effective for all sea snake species globally.[14,15] The initial dose of antivenom is controversial, but simply following the product instructions is prudent. Similarly, the initial dose of antivenom for non-Australian snakes should be based on manufacturer recommendations. For patients presenting with severe envenomation, higher initial doses may be warranted. Always administer antivenom IV. **If IV access is unavailable, consider IO administration.** IM administration is strongly discouraged due to slow absorption and potential complications of anticoagulation. Dilute antivenom about 1:10 in normal saline (lower dilution in small children or cardiac-compromised adults), then commence the infusion slowly, looking for evidence of adverse reaction (rash, wheeze, hypotension, angioedema); gradually increase the rate to give the entire dose over 20 to 30 minutes (longer if high-volume antivenom).[14,15] Give the same dose to children as adults. Skin testing before antivenom administration is not recommended,[14,15] and equipment for treatment of anaphylaxis should be at the bedside. Hypersensitivity is an uncommon complication of antivenom therapy in Australia.[23-25] Elsewhere, antivenoms may have high rates of adverse reactions. A 5-day course of steroids (e.g., prednisone, 1 milligram/kg PO once daily) may be prescribed to reduce the incidence of serum sickness, but clear evidence of efficacy is lacking.[15]

Antivenom cannot reverse some venom effects, such as established presynaptic neurotoxic paralysis, renal failure, and rhabdomyolysis. It is therefore important to give antivenom as soon as indicated. If this is not possible, support respiration and renal function as clinically required. Advanced flaccid paralysis usually requires protection of airway and respiratory support for periods of days to months.

When indicated, give monovalent or polyvalent antivenom immediately in sufficient doses to improve coagulation values. Pregnancy is not a contraindication to antivenom therapy.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 213

Marine Trauma and Envenomation

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Kevin J. Knoop

MARINE TRAUMA

Human contact with the marine environment is becoming more frequent as recreational and commercial use of the world's oceans increases. In addition to the hazards of drowning and cold exposure, the marine environment provides the habitat for dangerous marine fauna. Many marine animals have evolved sharp teeth and spines or venom glands for defense and predation. Encounters with marine life may result in traumatic injury or envenomation, requiring emergency medical management. Providing care for these conditions may be further complicated by the marine environment's geographic isolation from locations with definitive health care.

EPIDEMIOLOGY

The most common reported U.S. exposures are to jellyfish (31%), stingrays (16%), venomous fish (including lionfish, catfish, and others) (28%), and gastropods (6%).[1] However, data likely favor the reporting of more severe injuries and the exclusion of common minor injuries. Human impact may be altering the geographic distribution of marine fauna as climate change affects migration patterns and artificial waterways connect previously separated bodies of water and their ecosystems.[2,3]

The International Shark Attack File recorded 2944 unprovoked shark attacks between 1958 and 2017, with the United States reporting the most attacks. Within the United States, 56% of attacks occur in the waters off Florida, with Hawaii, California, and the Carolinas rounding out the top five states reporting unprovoked shark attacks.[4] Despite the public perception, the risk of shark attack is extremely small compared with almost any other injury, with only 70 to 100 shark attacks worldwide each year, resulting in only 5 to 15 deaths.[4,5] Although the incidence of shark attacks has steadily risen since 1900, the mortality has fallen from 40% in the 30 years following World War II to current rates of approximately 10% to 20%.[6] Death is usually a result of a lack of prehospital resuscitation, hemorrhagic shock, or drowning.

Other marine creatures implicated in traumatic injuries to humans include barracuda, giant groupers, sea lions, seals, crocodiles, alligators, and piranhas. Some fish with sharp spines and fins (needlefish, wahoo, and triggerfish) can inadvertently injure humans. Wounds resulting from interactions with such creatures are a combination of crush injury, abrasion, puncture, and/or laceration.

BACTERIOLOGY OF MARINE SOFT TISSUE INFECTIONS

Marine soft tissue infections are often polymicrobial, halophilic, gram-negative infections that may be resistant to first- and second-generation penicillins and cephalosporins.[7] Infecting bacteria are numerous and can vary with the environment, type of injury, and marine organism. Bacteria include staphylococci, streptococci, *Aeromonas hydrophilia*, *Escherichia coli*, *Pseudomonas* species, *Erysipelothrix* species, *Chromobacterium*, *Edwardsiella*, *Shewanella*, *Mycobacterium* species, *Mycoplasma* species, and *Vibrio* species.[8-10] Marine-associated infections are frequently diagnosed late because the history of marine exposure or injury is poorly recalled, and patients are often initially given inappropriate antibiotics, which potentially increases the morbidity of an already virulent infection. Patients with underlying conditions such as liver disease, immunosuppression, and diabetes are more susceptible to halophilic *Vibrio* infections.[11] *Vibrio* skin infections can progress rapidly from initial contact and local painful inflammation, through subepidermal bullae containing hemorrhagic fluid and vasculitis, to necrosis and small-vessel thrombosis, bacteremia, and septicemia.[8,11]

MAJOR MARINE TRAUMA

Encounters with sharks, skates, stingrays, barracuda, moray eels, and giant groupers can result in major trauma. Of these animal-related injuries, shark bites are the best characterized.[12,13] Shark attacks can result in neurovascular injury and significant tissue loss. Sharks typically attack the appendages (in either seals or humans), which tend to dangle lower than the head and torso while the victim is swimming on the surface. In 70% of surface swimmers, only the lower limb is involved. The upper limb can be subsequently injured when the victim tries to fend off the attacker. Sharks are unable to chew their prey and so sequentially strip and tear the prey to eat it.[5] In more serious attacks, substantial tissue loss and extremity amputation are common. However, 98.6% of shark attacks in the United States are nonfatal.[4]

Stingrays possess spined tails that reflexively whip upward when the animal is stepped on or startled. These encounters typically result in foot and ankle injuries. However, serious thoracoabdominal injuries have been reported. Morbidity and mortality result from penetrating trauma to internal organs.[14-16] Imaging should be obtained to rule out a rare retained spine tip.

Victims of marine animal–associated trauma should be removed sufficiently from the water to allow immediate resuscitation. As in trauma settings, place a tourniquet on limbs with evidence of uncontrolled arterial hemorrhage, because the survival benefit after tourniquet placement outweighs the low risk of neurologic injury from compression.[17] At the hospital, manage injuries according to institutional trauma protocols.[12]

There are two trauma caveats with respect to marine injuries. First, teeth and spines may be retained in bone and soft tissue and be a source of infection. Obtain plain radiographs of all injured regions to identify fractures, periosteal stripping, and retained foreign bodies. If radiographs are unremarkable but there is still a high clinical suspicion for a retained foreign body, US may be helpful. US may be particularly helpful in identifying radiolucent fragments of sea urchin spines and stingray barbs.[18,19] The second trauma caveat is that the mouths and integument of marine fauna can be heavily colonized with marine bacteria. Swab wounds and send specimens for culture. Many marine microorganisms require special selective media for culture and sensitivity testing, so alert the microbiology laboratory that a marine-acquired organism might be present. Infections from marine microorganisms can be more serious than usual soft tissue infections. Irrigate open wounds and debride devitalized tissue. **Do not suture lacerations or puncture wounds sustained in marine environments. Provide early antibiotic treatment** (usually antibiotic combinations) for wounds from major trauma, in those at risk for infection, in the immunocompromised or those with hepatic disease, and for established infection (**Tables 213-1** and **213-2**).[8,9,11,20,21] Provide postexposure tetanus prophylaxis.[22] Obtain early surgical consultation for thorough debridement for suspected *Vibrio vulnificus* infections or any necrotizing infection. Regardless of the antibiotic choice, close clinical follow-up is essential to identify treatment failures early.

TABLE 213-1 Recommendations for Antibiotic Treatment of Marine-Associated Wounds

No Antibiotic Indicated	Prophylactic/ Outpatient Antibiotics	Hospital Admission for IV Antibiotics
Healthy patient	Late wound care	Predisposing medical conditions
Prompt wound care	Large lacerations or injuries	Long delays before definitive wound care
No foreign body	Early or local inflammation	Deep wounds, significant trauma
No bone or joint involvement		Wounds with retained foreign bodies
Small or superficial injuries		Progressive inflammatory changes Penetration of periosteum, joint space, or body cavity Major injuries associated with envenomation Systemic illness

MINOR MARINE TRAUMA

Most marine injuries and stings do not cause serious injury. Treatment depends on the agent and the seriousness of injury (Table 213-2). Coral cuts are probably the most common injuries sustained underwater and usually involve the hands, forearms, elbows, and knees (**Figure 213-1**). The initial reaction to a coral cut is stinging pain, erythema, and pruritus. Within minutes, the break in the skin may be surrounded by an erythematous wheal, which fades over 1 to 2 hours. With or without treatment, the local reaction of red, raised welts and local pruritus may progress to cellulitis with ulceration and tissue sloughing. The wounds heal slowly over 3 to 6 weeks.

Promptly and vigorously irrigate cuts to remove all foreign matter. Fragments that remain can become embedded and increase the risk of infection or foreign-body granuloma. Instruct patients to clean superficial wounds daily, and to return to the ED for any signs of inflammation. Give antibiotics if infection develops (Tables 213-1 and 213-2).

TABLE 213-2 Antibiotics for Marine-Associated Wound Infections*

For All: Staphylococci and Streptococci Coverage	Seawater Associated: *Vibrio* Species Coverage	Freshwater Associated: *Aeromonas* Species Coverage
First-generation cephalosporin *or* Methicillin-resistant *Staphylococcus aureus* coverage depending on prevalence	Fluoroquinolone *or* Third-generation cephalosporin	Fluoroquinolone *or* Trimethoprim-sulfamethoxazole *or* Carbapenems

*Patients should receive both an antibiotic from the first column and a second agent from either the second or third column. Most marine bacteria are resistant to cephalosporins and antibiotic combinations are needed for serious infections. Antibiotic choices have not been robustly investigated. Antibiotic sensitivities vary, and in vitro antibiotic susceptibility data and clinical outcomes may not relate. Marine infections are polymicrobial.



FIGURE 213-1. These injuries occurred when the swimmer was thrown up against coral by wave action. Coral wounds should be evaluated for retained foreign body. [Photo contributed by Kaitlin Pala, MD.]

MARINE ENVENOMATIONS

Venomous marine animals produce venom in specialized glands. The venom can then be applied to or injected parenterally into other organisms using a specialized venom apparatus. Venom is not a pure substance but a mixture of mainly protein and peptide toxins. The effect of a specific toxin depends on its site of action; it may be neurotoxic, hemotoxic, dermatotoxic, cytotoxic, or myotoxic. Unlike thermostable ingestible seafood poisons, marine venoms are typically high-molecular-weight, heat-labile proteins.[23]

STINGRAYS AND VENOMOUS FISH

STINGRAYS

All stingrays' tails house venomous spines.[15] Inflicted lacerations allow the injection of venom. Stingray injuries cause immediate intense local pain that may radiate and last for many hours. There is often significant bleeding depending on the site of injury, and the wound may be erythematous or dusky. Systemic effects are uncommon, but have been reported and relate more to the systemic response to severe pain. Submerging the affected extremity in **hot water between 110°F (43.3°C) and 114°F (45.6°C)** can denature the venom protein and provide pain relief within 10 to 30 minutes.[24,25] Topical lidocaine can be applied for additional pain relief, and systemic analgesics can blunt the pain of hot water submersion.

VENOMOUS FISH STINGS

Venomous fish are found in tropical and, less commonly, temperate oceans and private aquariums. The important venomous fish include stonefish, weeverfish, scorpionfish, and lionfish. The effects of the stings range from severe with stonefish to minimal with some types of catfish and other fish with nonvenomous spines.[16,26]

Stonefish (*Synanceia* species) and scorpionfish (Scorpaenidae) occur throughout tropical and warmer temperate oceans from the central Pacific, west through the Indo-Pacific, to the East African coastline. They are a diverse group of fish, with differing habitats, swimming patterns, and ability to camouflage.[16,26] The venom apparatus varies among species, but most have 5 to 15 dorsal spines. Stonefish are stationary bottom dwellers usually frequenting shallow water.

Clinical effects are characterized by immediate severe and increasing local pain, which may radiate proximally. Untreated, the pain typically peaks at 30 to 90 minutes and persists for 4 to 6 hours, but this varies considerably for different fish. The wound site usually has significant local edema and erythema. Nonspecific systemic effects such as sweating, nausea, vomiting, and even syncope may occur. Extensive tissue necrosis is not seen unless a secondary infection develops.

Weeverfish (or weaverfish) are all saltwater fish and are the most venomous fish in the temperate zone. They are found in the Mediterranean and European coastal areas and are bottom dwellers that sting when stepped on. Their five to seven envenoming dorsal spines can penetrate leather boots, producing pain severity similar to stonefish injuries. Wounds may eventually necrose.

TREATMENT OF VENOMOUS FISH AND STINGRAY INJURIES

Irrigate the wound immediately, and remove any visible pieces of the spine or integumentary sheath. Control bleeding and immerse in hot water as soon as possible (**Table 213-3**). During the hot water soak, the wound can be explored and foreign material removed. Provide oral or parenteral analgesics as needed. The wound can also be infiltrated with lidocaine **without epinephrine,** or a regional nerve block can be applied to help control pain.

Once pain is controlled, cleanse the wound using an aseptic technique, reexplore and remove foreign material, and debride necrotic tissue. Obtain soft tissue imaging when possible to visualize retained foreign material.

The conclusions of the few study series involving venomous fish stings and the experience of aquarium workers are that most injuries are minor and do not require antibiotics.[26] Although some authors routinely recommend antibiotic prophylaxis, the majority do not unless the wound is large or there is considerable foreign material. This situation is more likely with stingray wounds, which have the greatest potential to cause necrosis and infection. Prevention of infection by careful cleaning of the wound and debridement, if required, is more important. An **antivenom exists for stonefish envenomation** (CSL Ltd., Melbourne, Australia) and should be used in cases of severe systemic reactions to stonefish and possibly other venomous fish.[27,28] Although it is registered for IM and IV administration, IV is more likely to be effective, based on experience with other antivenoms. Like other marine antivenoms, stonefish antivenom is prepared from horse serum, so be prepared to treat anaphylaxis and serum sickness.

SEA SNAKES

There are numerous species of sea snakes that are closely related to terrestrial elapids, all of which are venomous. They occur in the tropical warm temperate Indian and Pacific Oceans (including Hawaiian waters). None are found in the Atlantic Ocean, the Carribbean, or North American coastal waters. Probably the most important species medically is the beaked sea snake (*Enhydrina schistosa*), which has caused fatalities in Southeast Asia.

Sea snakes can be distinguished from land snakes by their flat tails and valve-like nostril flaps, and from eels by the presence of scales and the absence of gills and fins. The venom apparatus consists of two to four short, hollow maxillary fangs, and a pair of associated venom glands. About 20% of bites cause significant envenomation, and up to 40% of these are potentially fatal without treatment. The venom of sea snakes contains neurotoxins and myotoxins; one tends to dominate the clinical features. However, there are no toxins that affect coagulation.

Bites are typically painless and may go unnoticed. Symptoms typically become apparent 30 minutes to 4 hours after the bite. The first complaint is usually related to myotoxicity, with severe myalgia and nonspecific muscle weakness. Other symptoms include nausea, vomiting, and malaise. The muscle pain may become so severe that movement is limited, which is typified by trismus that develops in the jaw. Immobility secondary to pain should be distinguished from weakness or paralysis caused by neurotoxicity. Rhabdomyolysis and secondary renal failure develop in more severe cases, which may be complicated by hyperkalemia. Neurotoxicity without myotoxicity has been reported in some

TABLE 213-3 Early Treatment of Marine Envenomations

Organism	Detoxification	Further Treatment
Penetrating Envenomations		
Catfish, lionfish, scorpionfish, stingray	Hot water immersion*, topical lidocaine	Usual wound care†; irrigate with seawater or normal saline (NS) Observe for development of systemic symptoms **Assess for deep penetration from stingray spines;** consider surgical consultation
Stonefish, weeverfish	Hot water immersion*, topical lidocaine	Usual wound care†; irrigate with seawater or NS **Stonefish antivenom** for severe systemic reaction (CSL Ltd., Melbourne, Australia); be prepared to treat anaphylaxis
Sea snake	—	Pressure immobilization **Polyvalent sea snake antivenom** (CSL Ltd., Melbourne, Australia) for systemic reaction; be prepared to treat anaphylaxis Supportive care; observe for 8 h for myotoxicity and neurotoxicity; may need intensive care unit (ICU) care
Blue-ringed octopus	—	Pressure immobilization; flaccid paralysis and respiratory failure can develop in minutes Provide respiratory support and ICU care
Cone snail	Consider hot water immersion*	Pressure immobilization; observe for paralysis and respiratory failure; supportive care
Sea urchin and starfish	Hot water immersion*, topical lidocaine	Explore wound and remove any spines, tufts, or pincers
Fireworms	Topical 5% acetic acid (vinegar)	Consider topical corticosteroids Remove bristles
Nonpenetrating Envenomations		
Fire coral, hydroids	Irrigate with seawater or saline	Topical corticosteroids for itching
Portuguese man-of-war, bluebottle jellyfish	Irrigate with seawater or saline Remove tentacles and nematocysts‡ Hot water immersion* Topical lidocaine	Topical corticosteroids for itching Observe for development of systemic symptoms Supportive care
Box jellyfish (Indo-Pacific *Chironex* species, *Carybdea alata* [Hawaiian box jellyfish] and Australian *Carukia* species)	Remove tentacles and nematocysts‡ Topical 5% acetic acid (vinegar)§ Topical lidocaine Consider hot water immersion*	Topical corticosteroids for itching Observe for development of systemic symptoms Supportive care
Irukandji syndrome (Australian *Carukia* species)	Remove tentacles and nematocysts‡ Hot water immersion*	Administer ***Chironex* antivenom**; be prepared for anaphylaxis Magnesium for cardiac arrest Parenteral opioids for pain

*Hot water immersion = 111°F (43.3°C) to 114°F (45.6°C) water until pain is relieved.

†Usual wound care = Irrigate, explore, debride, consider antibiotics and analgesics, update tetanus immunization, elevate extremity.

‡Remove tentacles and nematocysts = scrape, sticky tape, seawater or saline irrigation.

§Controversial; depends on species. Treatment of life-threatening *Carybdea* species stings is recommended.

sea snake envenomations, with ascending flaccid or spastic paralysis accompanied by ophthalmoplegia, ptosis, facial paralysis, and pupillary changes. Death is most commonly a result of respiratory failure.

Diagnosis of a sea snake bite is based on the combination of snake identification and the presence of a puncture bite wound that was initially painless and occurred in a marine setting. Suspect envenomation if severe myalgia develops. The presence of myoglobinuria and an elevated creatine kinase level is also typical, indicating rhabdomyolysis. Neurotoxic symptoms are rapid in onset and usually appear within 2 to 3 hours. If no symptoms develop by 6 to 8 hours, envenomation is unlikely to have occurred.

First aid treatment is pressure immobilization of the affected limb.[29] Elastic bandages are preferred.[30] Administer **polyvalent sea snake antivenom (CSL Ltd., Melbourne, Australia)** for systemic envenomation.[28] The antivenom is made from horse serum, so be prepared to treat anaphylaxis and delayed serum sickness. Intensive supportive care and monitoring of renal, metabolic, and respiratory functions are critical.

OCTOPUS INJURIES

Injuries from the octopus or squid are unusual. All octopuses have venom, but the only dangerous octopus is the blue-ringed octopus. The venom tetrodotoxin, introduced by a bite, causes respiratory arrest within minutes. Treatment is supportive. Pressure immobilization at the bite area is the recommended first aid treatment.

The bite of the Australian blue-ringed octopus (*Hapalochlaena* species) has caused at least two deaths. The saliva of the octopus contains tetrodotoxin and produces effects clinically identical to those of tetrodotoxin poisoning seen most commonly with puffer fish ingestion.[31,32] Octopus bites typically occur on the upper extremity, almost always when the animal is picked up (**Figure 213-2**). The bite causes small, painless puncture marks, and many go unnoticed. In most cases, no symptoms develop or only mild local numbness and paresthesia occur. In more severe envenomations, vomiting and progressive flaccid paralysis with eventual respiratory failure may begin within 10 minutes of envenomation.[33] Wrap the limb with a lymphatic occlusive bandage to provide pressure immobilization until definitive care is reached. Treatment is supportive, with mechanical ventilation as required, and full recovery usual occurs over 1 to 5 days. No antivenom or antidote is available.

CONE SNAIL INJURIES

Cone snails have intricate shell patterns, making them attractive to handle. Cone snails are predators that feed by injecting a potent mixture of neurotoxins using detachable, dart-like radicular teeth. Stings



A



B

FIGURE 213-2. This acute octopus bite (**A**) was initially treated with ciprofloxacin, but persisted with a scab (**B**) and regional adenopathy for several months. After treatment with doxycycline, adenopathy resolved, but a chronic nonhealing ulcer remained. [Photo contributed by Steven Whelpley, MD.]

by cone snails are rare. Most stings occur after prolonged contact with the shell or when breaking the shell. With significant envenomation, local pain is followed immediately by local numbness, which quickly spreads from the extremity to the trunk and then to the head and neck region. Partial paralysis develops within 30 minutes, progressing to complete voluntary muscle paralysis and respiratory failure. Mortality following *Conus geographus* envenomation may be as high as 65%.[34] Less severe envenomations cause muscle pain, partial paralysis, or ataxia, or in mild cases only local effects. Treatment is pressure immobilization with a lymphatic-occlusive bandage until definitive care is reached.

SEA URCHINS AND STARFISH

Sea urchins with blunt tips generally have solid nontoxic spines, whereas those with sharp spines tend to have venom in the spine. Injury from the spines causes localized pain, which is exacerbated by pressure, even if there are no retained spines in the wound[35] (**Figure 213-3**). If a spine enters a joint, it may cause severe synovitis. Wounds from black sea urchin spines may leave a black discoloration of the skin. Contact with venomous spines causes immediate, intense burning pain, with erythema, swelling, and often bleeding of the skin surrounding the puncture sites. The acute pain usually subsides over hours. Secondary infection and granuloma formation from remaining spine fragments are well-described delayed effects. Systemic features have been reported rarely, often when multiple spines are involved, but may be due to severe pain.

Some starfish have surface spines, tufts, or pincers. The crown-of-thorns starfish (*Acanthaster planci*) can be found on most reefs in the Indo-Pacific region and has caused outbreaks of envenomation in Japan and Australia.[1] Crown-of-thorn starfish are covered with sharp, rigid spines that can passively deliver a variety of substances when they penetrate skin. Introduced substances can include venom (produced in special glandular tissue), mucus, bacteria, or dermal tissue. Injury by the spines produces 1 to 2 hours of severe burning pain that is often greater than expected for the degree of mechanical injury. Other local effects include bleeding, erythema, and mild edema. In more severe cases, particularly with multiple punctures, the wound may become dusky or discolored. Pruritus and persisting edema can occur, perhaps as a result of allergy. Systemic effects are uncommon but may include paresthesias, nausea, vomiting, lymphadenopathy, and muscular paralysis.[1,6]

Treatment is immediate immersion in hot water to tolerance (45°C [113°F]) for 30 to 90 minutes or until pain is relieved. Topical or locally injected lidocaine can provide additional pain relief. Give analgesics; IV analgesia is often needed. Remove retained spines or tufts as well as possible, without causing more tissue injury. Soft tissue radiographs, US, or MRI may be helpful in locating retained spines. US may be particularly helpful in identifying radiolucent fragments of sea urchin spines.[19] Arrange follow-up, because further surgical removal of spines may be required if there are ongoing symptoms. Spines in joints require immediate orthopedic consultation.



FIGURE 213-3. Sea urchin sting in the foot showing the entry sites. [Used with permission of Vidal Haddad Jr., MD, PhD.]

FIREWORMS OR BRISTLEWORMS

Fireworms, or bristleworms, are segmented worms covered with cactus-like bristles that can penetrate the skin. These bristles easily detach in the skin and can be difficult to remove. Envenomation causes intense inflammation with a burning sensation and erythema. Untreated, the pain generally resolves within a few hours, but erythema may last for 2 to 3 days. Bristles should be removed with forceps or adhesive tape. Vinegar (5%) may be applied topically. The inflammatory response may require a course of corticosteroids.

HYDROIDS AND FIRE CORAL

Hydroids are colonies of tiny jellies attached to a feather-like or seaweed-like base. They are abundant on seaweed, reefs, pilings, floating docks, or lines. Coastal storms can break off feather hydroid branches and cause infestation of a local swimming area. Fire corals look like corals, are often mistaken for seaweed, and are small brush-like growths on rocks and coral itself. Contact with nematocysts or stinging threads results in an immediate sting after even a superficial brush contact, followed by itching pain, associated with the development of painful wheals and urticaria after 30 minutes. The welts may last for up to a week but leave no permanent mark. With more extensive exposure, blistering and a hemorrhagic and zosteriform reaction can occur. Lesions crust over after a few days. Vinegar can inhibit nematocyst discharge. Pain relief can be provided with analgesics. Treat itching with topical steroids.

JELLYFISH

There are many types of jellyfish, but the most important groups affecting humans are the Portuguese man-of-war or bluebottle jellyfish, the box jellyfish, and those jellyfish causing Irukandji syndrome.

Jellyfish are characterized by their unique stinging nematocysts,[34] which number in the thousands and are found mainly on the tentacles, but also in lesser numbers on the body or bell. The nematocyst contains a minute dose of venom, in some cases highly potent, and a harpoon-like mechanism. A physical or chemical stimulus triggers the rapid release of a hollow, sharply pointed, threadlike tube from the nematocyst, which penetrates the skin and delivers venom subcutaneously. There are a number of genera worldwide causing local and systemic reactions, all with similar toxic effects.

The clinical features of jellyfish envenomation vary in severity. The severity depends on the venom dose, the marine species, and the victim (age and size). Mild envenomation results in bothersome acute skin reactions, with immediate stinging pain and erythema or wheal formation at the site. Lesions usually resolve spontaneously over days to a couple of weeks, with occasional postinflammatory hyperpigmentation.

Treatment of jellyfish stings is not well studied. A treatment helpful for one species may worsen effects from another species. Irrigation with seawater to remove nematocysts and hot water immersion and application of topical lidocaine appear to be the most universally beneficial treatments. Do not irrigate with freshwater because the hypotonic solution is thought to stimulate nematocyst discharge. Other applications, such as sodium bicarbonate or vinegar, may worsen stinging from some species.

PORTUGUESE MAN-OF-WAR AND BLUEBOTTLE JELLYFISH

This group of jellyfish (*Physalia* species) has a large gas-filled float, which suspends multiple tentacles. The nematocysts are found on the tentacles but not on the float. *Physalia* species are the most widely distributed jellyfish and are responsible for thousands of human envenomations in Florida, parts of Asia and Africa, Australia, and Western Europe.[1,2,36] All species occur in swarms in shallow water and usually cause stings in the surf or are washed up on the shore. Nematocysts from fractured tentacles may remain active for months.

The Portuguese man-of-war is technically a siphonophore (colony of specialized organisms) rather than a true jellyfish. However, from a medical perspective this marine hydrozoan can be considered with the jellyfish. The Portuguese man-of-war has multiple tentacles that can be as long as 30 m (**Figure 213-4**). The bluebottle jellyfish is smaller and single-tentacled and found commonly in Australia and Hawaii.



FIGURE 213-4. Portuguese man-of-war. This specimen was discovered washed up on a Florida beach. Tentacles are capable of stinging for days after washing ashore. Application of vinegar (4% to 5% acetic acid) has been found to trigger nematocyst discharge in this species. [Photo contributed by John J. Devlin, MD.]

Stings from *Physalia* species cause immediate, intense pain that often fades over an hour but may persist for many hours, particularly with larger specimens. The sting causes a characteristic linear erythematous eruption, classically referred to as a "string of pearls" pattern.[35] Respiratory distress and death have been reported following *Physalia* envenomation, and delayed effects have been reported in rare instances.[36,37]

Treatment is to first wash the area with seawater and then immerse in hot water, as the venom is heat labile. Vinegar is not recommended for *Physalia* stings. Remove tentacles and nematocysts by scraping the skin with a sharp object (e.g., razor or credit card) or by applying adhesive tape.[38] If adhesive tape is used, the adherent nematocysts can later be identified.

There is no specific antidote for *Physalia* envenomation, and care is supportive.

BOX JELLYFISH AND IRUKANDJI SYNDROME

The box jellyfish is the most dangerous jellyfish and includes two important members: the Indo-Pacific box jellyfish (*Chironex fleckeri*) and the Australian jellyfish (*Carukia barnesi*) that causes Irukandji syndrome.[39,40] Box jellyfish are also found in the Philippines, Japan, and the U.S. Atlantic coast. The Hawaiian box jellyfish (*Carybdea alata*) causes numerous stings to beachgoers in Hawaii, although no deaths have been confirmed from this organism.[41]

The Indo-Pacific box jellyfish (*Chironex*) has been described as the world's most venomous animal.[42] It has caused over 80 deaths in the past century.[43] The exact mechanism of toxicity and toxins involved in death—which can occur rapidly, within 1 to 2 minutes—remains unclear, but a primary cardiotoxic role is likely.[42] Severe reactions or death can occur following skin contact with tentacles, especially in children.[39,44] However, the vast majority of stings are mild to moderate, consisting of skin welts and immediate, sometimes severe pain.[39] The toxic skin reaction may be quite intense, with rapid formation of wheals, vesicles, and a darkened reddish brown or purple whip-like flare pattern with stripes 8 to 10 mm wide. With more severe stings, blistering occurs, and superficial necrosis develops after 12 to 18 hours. Severe box jellyfish stings cause a pathognomonic crosshatched pattern, classically referred to as a "frosted ladder" pattern (**Figure 213-5**). Following the acute toxic reaction, a delayed hypersensitivity reaction occurs in approximately 60% of cases, with papular urticaria at the sting sites.[39,45]

The Australian jellyfish (*Carukia barnesi*) causes the **Irukandji syndrome**.[40] The sting initially causes mild local effects with localized



FIGURE 213-5. Box jellyfish sting. This 24-year-old woman was snorkeling off of Koh Tao, Thailand, when she was stung by a box jellyfish 15 minutes prior to this photograph being taken. She presented with severe extremity pain and chest tightness. [Photo contributed by Sittidet Toonpirom, MD, and Rittirak Othong, MD.]

pain and erythema. Approximately 20 to 30 minutes later, severe generalized pain in the abdomen, back, chest, head, and limbs develops. The pain is usually associated with systemic signs of catecholamine excess, including tachycardia, hypertension, sweating, piloerection, and agitation. In severe cases, cardiogenic shock with pulmonary edema and serum troponin elevation occur.[40,44]

Treatment consists of deactivation of attached nematocysts, tentacle removal, reversal of venom effects if possible, and symptomatic and pain relief. All victims with systemic signs or symptoms should be observed for ongoing envenomation or delayed reactions (Table 213-3).

Irrigate with seawater or normal saline to remove and deactivate undischarged nematocysts. Remaining visible tentacles can then be removed. Do not irrigate with freshwater because the hypotonic solution is thought to stimulate nematocyst discharge. Best methods for removal are scraping the skin with a sharp object (e.g., razor or credit card) or application of adhesive tape.[38] If adhesive tape is used, the adherent nematocysts can later be identified. Treat with hot water immersion (111°F [43.3°C] to 114°F [45.6°C]) and apply topical lidocaine.[46]

Effective topical decontaminants appear to be species specific.[46,47] Because the species is often unknown, the geographic location of the envenomation guides decontamination. In Indo-Pacific waters, **particularly those surrounding Australia,** nematocyst deactivation therapy with 5% acetic acid (vinegar) is recommended,[43,48] and 5% acetic acid is the first-line management recommendation by the Australian Resuscitation Council.[43,49,50]

Treatment for severe *Chironex* envenomation consists of standard resuscitative measures and administration of sheep-derived antivenom specific for *C. fleckeri* (CSL Ltd., Melbourne, Australia).[39] Be prepared to treat anaphylaxis. Fatalities despite antivenom administration may be related to the rapidity of onset of cardiovascular collapse after *Chironex* envenomation.[27] Therefore, antivenom should be administered IV as early as possible. The initial dose may be repeated if there is no clinical response, and some clinicians recommend three or more doses in severe envenomations associated with cardiovascular collapse.[44] Magnesium improves outcome in animal studies and should be considered in refractory cases of severe *Chironex* envenomation with cardiac arrest.[40,45]

Severe generalized pain in Irukandji syndrome requires titrated IV opioid analgesia, often with large and repeat doses. Magnesium bolus and infusion have been used for treatment of the pain and hypertension associated with Irukandji syndrome.[45,51] However, adverse effects due to hypermagnesemia have been reported, and the treatment has not been as effective as originally suggested.[51,52] A recent systematic review of magnesium sulfate administration in the management of Irukandji syndrome found no clear evidence of benefit, and its use is not recommended.[53]

Obtain an ECG and troponin testing on admission; echocardiography is useful in patients with myocardial involvement. Manage pulmonary edema with oxygen supplementation, positive-pressure ventilation, and inotropes.

CONTROVERSIES IN JELLYFISH ENVENOMATION MANAGEMENT

The application of topical commercial vinegar (4% to 5% acetic acid solution) in the treatment of jellyfish and stinging hydroid envenomation is controversial. A 2012 systematic review and a 2013 Cochrane review both found no benefit from the intervention.[46,47] Further, an in vivo study observed increased jellyfish nematocyst discharge after application of vinegar, particularly from *Physalis physalis* tentacles.[54] Similarly, in a randomized controlled trial of multiple topical treatments for *Chrysaora chinesis* stings in 96 human subjects, application of 5% acetic acid failed to improve pain as compared to placebo.[55] This appears to contradict field observations and recommendations by authorities in wilderness medicine.[56-58] It is possible that nematocysts from different jellyfish species respond differently to vinegar, and the intervention is a subject of ongoing scientific investigation. However, at this time, topical application of vinegar for jellyfish envenomation cannot be universally recommended as standard care. For jellyfish stings, "hot water and lidocaine appear more universally beneficial in improving pain symptoms and are preferentially recommended."[46] The venoms are heat labile, and heat reduces toxicity in most jellyfish envenomations.[36,41,47] *Chironex* stings are the exception. Recent evidence suggests hot water immersion is "no more effective than icepacks for reducing the acute pain of box jellyfish stings."[59] In waters surrounding the United States, application of 5% acetic acid solutions to tentacles from *Chrysaora* species appears to increase nematocyst discharge.[54,60] For *Chrysaora* (e.g., sea nettle) or *Cyanea* (e.g., lion's mane) jellyfish, a slurry of baking soda (sodium bicarbonate) is thought to be effective.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 214

Diving Disorders

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INTRODUCTION

Millions of recreational, commercial, and scientific dives are logged annually, and the vast majority of dives are completed without incident. However, there are physiologic effects and injuries relatively unique to the underwater environment. Generally, these effects and injuries are secondary to pressure changes on the submerged human body and the breathing of compressed gas.[1] This chapter outlines the most common diving injuries: barotrauma of descent (otic, sinus, and pulmonary), barotrauma of ascent (pulmonary overinflation syndromes and arterial gas embolism), decompression sickness, immersion pulmonary edema, oxygen toxicity, and nitrogen narcosis.

THE GAS LAWS

Understanding diving injuries requires familiarity with the three relevant gas laws most pertinent to diving: Boyle's law, Dalton's law, and Henry's law.

Boyle's law states that given a constant temperature, the pressure and volume of an ideal gas are inversely related. That is, if pressure is doubled, the volume of gas is halved. This law is stated as: $P_1V_1 = P_2V_2$.

Pressure can be measured in a variety of units. The International System of Units defines pressure using the pascal (Pa). Other commonly used units of pressure include millimeters of mercury (mm Hg), torr, pounds per square inch (psi), bar, or atmosphere (atm):

1 atm = 760 mm Hg = 760 torr = 14.7 psi = 1.013 bar = 101,325 Pa = 101.325 kPa. Additionally, pressure in diving settings is often described using feet of seawater (fsw) or meters of seawater (see below). In this chapter, we use atm, mm Hg, and fsw for pressure units.

Because of the high density of water, a relatively small change in depth causes a great change in pressure. The weight of seawater produces a change of 1 atm for each 33 ft of depth. For freshwater, pressure increases 1 atm for each 34 ft of depth. Therefore, the pressure exerted on a diver at a depth of 33 ft in seawater = 1 atm for the seawater + 1 atm for the atmosphere above the water = 2 atmospheres absolute (ATA). A diver at 165 ft of seawater would experience 6 ATA of pressure (1 atm for each 33 ft of seawater = 5 atm + 1 atm for atmospheric pressure at sea level).

Thus, **Boyle's law** dictates that as a diver descends in the water column, the volume of air-containing structures will decrease. For example, if the lungs contain volume V at the surface, a diver who descends to 33 ft of seawater holding his or her breath would have a lung volume of $^1/_2V$. If the diver then breathes compressed air at this depth (from scuba equipment or from a surface-supplied source of gas), lung volume would return to V. If the diver then ascends to the surface without exhaling, lung volume would be $2V$ at the surface. This pressure–volume relationship governed by Boyle's law is important in the etiology of injuries due to barotrauma and produces the volume changes of bubbles in the tissues and circulation that are associated with recompression (hyperbaric) therapy.

Dalton's law states that the total pressure exerted by a mixture of gases is the sum of the partial pressures of each gas. Therefore, the partial pressure of a given component of a gas mixture will increase as the ambient pressure increases, although the proportion of gas in the mixture remains constant. The partial pressure of nitrogen in air at sea level is approximately 600 mm Hg or 0.79 ATA (the fraction of nitrogen in air, 0.79 × 760 mm Hg or 1 ATA). At a depth of 99 fsw, the partial pressure of nitrogen in air would be 4 × 600 = 2400 mm Hg (or 3.16 ATA).

Henry's law, which states that at equilibrium the quantity of a gas dissolved in a liquid is proportional to the partial pressure of the gas, along with Dalton's law, explains the uptake of inert gas into tissues when breathing compressed air at depth. It is the uptake of inert gas that is intrinsic to the development of decompression sickness.

EVALUATION OF THE DIVER

History There are several aspects of the history that are specific to the diver that need to be obtained. Ask the diver for their complete dive profile, including time, depth, number of dives done that day, and type of breathing gas used. Additionally, obtain history regarding the dive itself, including level of exertion, difficulty with equalization, any equipment difficulty, any history of rapid ascent, or if the dive buddy witnessed anything unusual. If there is a dive computer, it may be useful to see if there were any omitted decompression stops or evidence of rapid ascent. It is also very important to get an exact history regarding timing and onset of symptoms. For example, vertigo that occurs on descent with ear equalization is likely due to barotrauma and not inner ear decompression sickness. Chest pain and shortness of breath that occur at depth are unlikely to be due to an arterial gas embolism and may be due to immersion pulmonary edema (see below) or other primary pulmonary or cardiac disease.

Physical Exam All divers should undergo a thorough physical examination. Particular attention should be paid to the neurologic examination, including a full cerebellar and mental status exam. The patient may even be unaware of subtle cognitive abnormalities that may otherwise go undetected.[2] It is also important to note that neurologic signs may not present like other neurologic illnesses and may not localize to any one identifiable lesion or spinal cord level. Urinary retention may be an early sign of severe spinal cord decompression sickness, and ability to void should always be evaluated.

BAROTRAUMA OF DESCENT

The clinical conditions resulting from barotrauma of descent are barotitis (ear squeeze), external ear squeeze, sinus barotrauma, inner ear barotrauma, and face, tooth, or dry-suit squeeze (**Table 214-1**).

PATHOPHYSIOLOGY

During descent, the volume of gas in all air-containing body cavities decreases. The air space in the middle ear makes the tympanic membrane the tissue most commonly affected by this phenomenon, if active measures such as "clearing the ears" with a Valsalva or other maneuvers are not successful.[3] As the volume of gas decreases, the tympanic membrane is bent inward, causing a feeling of fullness or pain in the ear. Forcing air through the Eustachian tube with a Valsalva maneuver will equalize the pressure between the middle ear and external ear canal by filling the middle ear with additional gas. Generally, divers who experience pain in an ear during descent will attempt to clear the ear and, if unsuccessful, will ascend to decrease the pressure differential and attempt equalizing again. If the diver is unsuccessful in equalizing and continues the descent, prolonged pain and injury to the tympanic membrane may result, known as barotitis or "ear squeeze."

BAROTITIS (EAR SQUEEZE)

Barotitis can range from symptoms of pain or fullness without otoscopic changes, to hemorrhage within the tympanic membrane or hemorrhage

TABLE 214-1 Summary of Barotrauma of Descent and Ascent

Barotrauma	Clinical Features	Treatment
Barotrauma of descent		
Otic barotrauma ("ear squeeze")	Pain, fullness, vertigo, conductive hearing loss from inability to equalize middle ear pressure	Decongestants, consider antibiotics
Sinus barotrauma ("sinus squeeze")	Pain over affected sinus, possible bleeding from nares	Decongestants, consider antibiotics
Inner ear barotrauma	Sudden onset of sensorineural hearing loss, tinnitus, severe vertigo after forced Valsalva	Head of bed up, no nose blowing, antivertigo medications, and urgent otolaryngology consultation as some surgeons advocate early exploration
Barotrauma of ascent		
Pulmonary overinflation syndromes (pulmonary barotrauma)	Dyspnea, chest pain, subcutaneous air, extra-alveolar air on radiograph; usually occurring secondary to rapid or uncontrolled ascent	Pneumomediastinum requires only symptomatic care and does not require recompression Pneumothorax requires drainage and does not require recompression (if recompression is instituted for treatment of arterial gas embolism, then the pneumothorax must be drained before recompression)
Arterial gas embolism	Neurologic symptoms occurring immediately after uncontrolled or rapid ascent or neurologic symptoms in the setting of pulmonary barotrauma	Airway, breathing, circulation, high-flow oxygen, IV hydration, immediate recompression (hyperbaric oxygen), consider adjunctive lidocaine Any neurologic symptom in the setting of documented pulmonary barotrauma must be treated as an arterial gas embolism

into the middle ear with hemotympanum. Ultimately, the tympanic membrane may rupture, resulting in relief of the pain but also possibly causing an influx of water into the middle ear. This, in turn, might cause calorically induced vertigo and potential panic, drowning, or other injury.

Barotitis is treated conservatively with analgesics and decongestants. If tympanic membrane rupture occurs, antibiotics can be prescribed, especially if the diving occurred in contaminated water. Divers with perforated tympanic membranes should refrain from diving until the perforation heals. Most such perforations heal without difficulty, but referral to an otolaryngologist is appropriate for individuals with larger perforations or when healing does not occur. Divers with barotitis without perforation should refrain from diving until the diver is again able to equalize the pressure in the affected middle ear.

EXTERNAL EAR SQUEEZE

If the external canal is occluded by cerumen or an ear plug, the inability to equalize pressure between the external canal and the tympanic membrane causes the bending of the tympanic membrane outward, producing an injury called "external ear squeeze" that produces pain and tympanic membrane hemorrhage.

SINUS BAROTRAUMA

If the ostia to the sinuses are occluded, air cannot enter the sinuses during descent to equalize the increasing pressure. This causes pain and mucosal edema and can lead to submucosal hemorrhage and stripping of the sinus mucosa from bone, hemorrhage (often causing bleeding from the nose into the mask), and, rarely, paresthesias in the infraorbital nerve distribution. A similar traumatic neuropathy can occur to the facial nerve with middle ear barotrauma. Sinus barotrauma is treated with conservative measures, including decongestants and, possibly, antibiotics.

INNER EAR BAROTRAUMA

The inner ear is also susceptible to barotrauma, occasionally causing significant long-term damage. If a diver attempts a forceful Valsalva maneuver to equalize the middle ear against an occluded Eustachian tube, the pressure differential between the cerebrospinal fluid, transmitted through the vestibular and cochlear structures and the middle ear air space, can cause rupture of the oval or round window, fistulization of the window, tearing of the vestibular membrane, or a combination of such injuries. Additionally, if the diver is able to open the Eustachian tube in this situation, a rapid increase in middle ear pressure may occur. This pressure wave is transmitted to the inner ear and can also cause a similar injury. Divers with inner ear barotrauma will generally present with unilateral roaring tinnitus, sensorineural hearing loss, and profound vertigo. A "fistula test" may be positive—that is, insufflation of the tympanic membrane on the affected side causes the eyes to deviate to the contralateral side and reproduction of the vertigo. Because this injury usually occurs on descent and divers will provide a history of difficulty clearing the ears, this condition can usually be easily differentiated from other causes of vertigo, such as inner ear decompression sickness, cerebral arterial gas embolism, or alternobaric vertigo (discussed below).

Immediate complications of inner ear barotrauma are potential panic or disorientation, leading to possible drowning or a rapid ascent that predisposes the diver to pulmonary barotrauma. Divers with barotraumatic injuries to the inner ear require urgent otolaryngologic evaluation. Treatment is controversial, with some authors advocating immediate exploration and others suggesting a trial of bed rest (head upright), medications to control vertigo, and mechanical measures to reduce cerebrospinal fluid pressure spikes (e.g., stool softeners, no nose blowing). These authors reserve exploration for patients whose symptoms do not respond to conservative therapy or patients with severe hearing defects or significant abnormalities on an oculo-nystagmogram. Divers with potential inner ear barotrauma who will be treated with hyperbaric oxygen for decompression sickness or cerebral arterial gas embolism require emergent tympanostomy because hyperbaric treatment will re-create the same pressure differentials that caused the injury, potentially causing more perilymph leakage and, possibly, worsening the injury, as well as the symptoms.[3]

FACE SQUEEZE, TOOTH SQUEEZE, AND DRY-SUIT SQUEEZE

Other air-containing structures can be compressed during descent, producing "squeeze" symptoms. A face squeeze occurs when air is not added to the facemask during descent, causing the face and eyes to be forced into the collapsing mask. This can produce facial bruising, conjunctival injection or hemorrhage, changes in vision, and, rarely, retrobulbar hemorrhage. The latter could be a true ophthalmologic emergency. A tooth squeeze occurs when air spaces inside a tooth—due to decay, a filling, or an abscess—become compressed during descent. A dry-suit squeeze occurs when suit folds are compressed into the underlying skin, producing local trauma manifested by painful red streaks.

BAROTRAUMA OF ASCENT

The clinical conditions of barotrauma of ascent are alternobaric vertigo, pulmonary barotrauma, arterial gas embolism, and decompression sickness (Table 214-1).

ALTERNOBARIC VERTIGO

During ascent, the physics of gas in air-containing organs is, of course, opposite that of descent—that is, air will expand as the pressure decreases. Air will flow through the ostia of the sinuses, and the expanding air in the middle ear will open the Eustachian tube (much like during takeoff in an airplane). Should air be trapped temporarily in one middle ear cavity, the pressure differential may cause unequal vestibular impulses to the brain, resulting in vertigo (alternobaric vertigo). This is usually transient and generally requires no specific treatment. Symptoms should resolve shortly after surfacing. Prolonged symptoms of vertigo should prompt one to look for another cause of vertigo.

PULMONARY BAROTRAUMA

Air also expands within the lungs with ascent. If a diver breathing compressed air ascends with a closed glottis (holds breath, coughs, vomits), most frequently seen in a rapid, panicked, out-of-air ascent, the expanding air may cause parenchymal lung injury. This can occur even in shallow water (e.g., a swimming pool). Pulmonary barotrauma, also called *pulmonary overinflation* or *burst lung syndrome*, can lead to pneumomediastinum. This generally only requires symptomatic treatment and may be subtle on the chest radiograph.[4] Mediastinal air can track superiorly into the neck, resulting in subcutaneous air on physical examination or air on a cervical spine radiograph. Pulmonary overinflation injury can cause pneumothorax, requiring aspiration of air or tube thoracostomy. If air enters the pulmonary venous circulation, embolization of the gas through the arterial system occurs. The most sensitive end-organ to such embolization is the brain, and *cerebral arterial gas embolism* is the term applied to this condition, although the air emboli distribute to other tissues and organs.[5] **Any neurologic symptom or sign referable to the circulation to the CNS in the setting of barotrauma associated with ascent should be considered to be secondary to cerebral arterial gas embolism.** The symptoms, signs, and treatment are discussed below in the section "Arterial Gas Embolism." Isolated pneumomediastinum can be treated with surface oxygen, observation, and serial chest radiographs.

Pulmonary barotrauma (**Figure 214-1**) can occur without a rapid ascent or closed glottis in divers with congenital cysts, obstructive pulmonary disease, or other processes that cause air trapping.

OTHER BAROTRAUMAS OF ASCENT

An air pocket underneath a tooth may equilibrate with ambient pressure while diving, only to expand during ascent. This produces severe pain and may dislodge a filling or fracture a tooth. Swallowed air during diving may expand during ascent, rarely producing gastric distention and abdominal cramps.

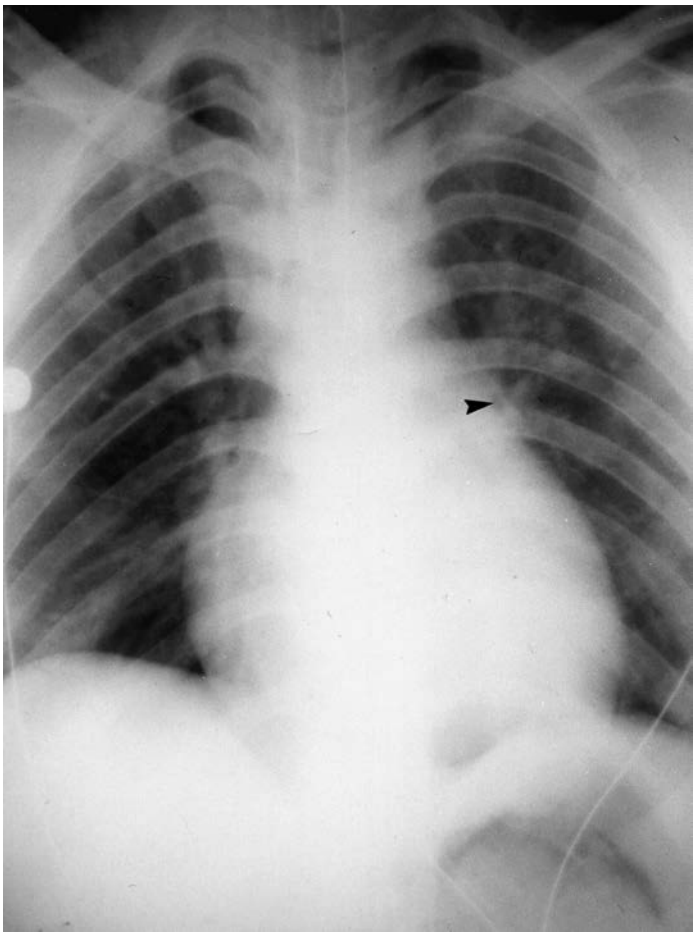

FIGURE 214-1. Pulmonary barotrauma. Note the air in the mediastinum in this radiograph (*arrow*). There is also air in the soft tissues of the neck.

DECOMPRESSION SICKNESS

PATHOPHYSIOLOGY

The pathophysiology of decompression sickness is related to the obstructive and inflammatory effects of inert gas bubbles in tissues and the vascular system.[5] Decompression sickness may occur in divers breathing compressed air, caisson workers, high-altitude pilots, or astronauts. Bubbles may form when a body with additional inert gas in solution experiences a decrease in ambient pressure that causes liberation of the gas. Uptake of inert gas occurs at different rates in different tissues.

The U.S. Navy publishes dive tables to provide the limits to a dive (measured by bottom depth and time) that can be undertaken without a decompression stop ("no decompression" or "no stop" dives). Other Navy tables provide a variety of decompression schedules for longer dives. A multitude of dive computers, often using proprietary mathematical models, provide divers with relatively safe diving limits. Decompression sickness is less likely to occur if the limits of the dive tables or dive computer are followed, but compliance with dive table limits or a dive computer does not completely eliminate risk.[6]

Bubbles are necessary but not sufficient by themselves to cause decompression sickness; bubbling occurs after many dive profiles that do not lead to decompression sickness. Obviously, there must be a threshold at which the bubble load causes symptoms. The exact mechanism of bubble formation is not known, although preexisting gas micronuclei in the circulation likely form a nidus for gas accumulation.[7] Bubbles may form directly in tissues or the circulation (usually the low-pressure venous circulation). Classically, it is thought that bubbles directly obstruct blood flow, leading to direct ischemia. Also, the air–blood and air–endothelial interfaces initiate a variety of inflammatory and thrombotic processes; activate the endothelium, leading to neutrophil adhesion and activation; and change the permeability of the endothelium, resulting in third spacing of fluid. In addition, decompression stress induces the production of microparticles, which are lipid bilayer–enclosed membranous vesicles extruded from vascular endothelial and other cells. Injection of these microparticles in animal models creates a clinical condition consistent with decompression sickness.[8] In humans, a positive relationship between microparticles and surface proteins associated with neutrophil activation and the occurrence of decompression sickness has been observed.[9]

CLINICAL FEATURES OF DECOMPRESSION SICKNESS

The most commonly used classification divides decompression sickness into two (or sometimes three) main groups (**Table 214-2**). We focus on types I and II for clarity. **Type I** is also called "pain-only" decompression sickness and involves the joints, extremities, and skin ("cutis marmorata"). Lymphatic obstruction can occur in type I, causing lymphedema, which usually takes days to resolve despite recompression therapy. **Type II** involves the CNS (mainly the spinal cord in compressed air divers and the brain in high-altitude decompressions), vestibular symptoms ("staggers"), and cardiopulmonary symptoms ("chokes"). To further complicate the nomenclature and classification of decompression sickness, it can also occur when an arterial gas embolism (see "Artificial Gas Embolism") causes inert gas to come out of solution after a dive profile that would otherwise not be expected to cause decompression sickness (called type III).[10] Some advocate the use of the alternate term

TABLE 214-2 Classification of Decompression Sickness (DCS)

Classification	Clinical Features	Comments
Type I: "pain-only" DCS	Deep pain in joints and extremities, unrelieved but not worsened with movement	Usually single joint, most commonly knees and shoulders
	Skin changes—mottling, pruritus, and color changes	Lymphatic obstruction can occur and takes days to resolve despite recompression therapy
Type II: "serious" DCS	Pulmonary ("chokes")—cough, hemoptysis, dyspnea, and substernal chest pain	
	Cardiovascular collapse can occur	
	Neurologic—sensation of truncal constriction, ascending paralysis, usually rapid in onset	More commonly affects the lower cervical and thoracic regions; may see scattered lesions
		Autonomic dysfunction may be seen
	Vestibular ("staggers")—vertigo, hearing loss, tinnitus, and disequilibrium	Usually occurs after deep, long dives
Type III: combination of DCS and arterial gas embolism	Symptoms of DCS II noted above plus a variety of stroke syndromes, symptoms, and signs	Symptoms occur on ascent or immediately upon surfacing
		Symptoms of arterial gas embolism may spontaneously resolve

decompression illness, instead of differentiating between decompression sickness and cerebral arterial gas embolism, to encompass all pathologic syndromes following a reduction in ambient pressure.[1]

Generally, the symptoms of decompression sickness occur minutes to several hours after surfacing, but in rare cases, symptoms can occur days after diving. Symptoms occurring between dives may improve during a subsequent dive (as recompression has occurred), but get worse upon resurfacing (as the inert gas load has increased and ambient pressure has decreased). Flying with the resultant decrease in ambient pressure may precipitate or worsen symptoms. For this reason, divers are generally advised to refrain from flying for at least 12 to 24 hours after the last dive depending on the nature of the diving exposure.[11]

Pain Divers with type I decompression sickness typically describe a deep pain, unrelieved but not worsened with movement. This pain can be attributed to or confused with pain caused by injury, potentially making accurate diagnosis difficult. Pain is thought to be due to distention from bubbles in ligaments or fascia, intramedullary bubbles at the ends of long bones, or the activation of stretch receptors caused by bubbles in tendons. The mechanism of simple distention of tissues is supported by the rapid improvement of symptoms with recompression. Common pain locations are knees and shoulders, and most often, only a single joint is involved. Decompression sickness in commercial and military divers, caisson workers, and aviators tends to manifest most often as joint pain. Sport divers, who usually perform multiple dives often over a period of days, are more prone to spinal cord effects. Poorly localized and difficult-to-describe back or abdominal pain may herald the more serious signs of spinal cord involvement.

Pulmonary Symptoms Pulmonary symptoms, generally seen usually only after more prolonged exposures, are caused by large numbers of pulmonary artery bubbles and include symptoms of cough, hemoptysis, dyspnea, and substernal chest pain. Cardiovascular collapse can occur.

Neurologic Symptoms The classic description of divers with neurologic decompression sickness (type II) can begin with a sensation of truncal constriction or girdle-like pain. Often a wooly feeling begins in the feet, developing into an ascending paralysis, producing symptoms of transverse myelitis. This form is usually rapid in onset and tends to affect the lower cervical and thoracic regions. However, in type II decompression sickness, neurologic deficits do not necessarily cause distinct spinal cord syndromes (i.e., an anterior or posterior spinal artery syndrome), nor will a definitive level necessarily be found, as lesions may be scattered throughout the spinal cord.[12] Autonomic involvement, with resulting incontinence and sexual dysfunction, is not uncommon. The pathophysiology of spinal cord decompression sickness seems to be initial bubbling in the low-pressure venous plexus system that first impedes and then obstructs venous outflow from the cord. Decreasing venous blood flow prevents dissolved nitrogen in spinal cord tissues from egressing, and in situ bubbles within the spinal cord develop (called *autochthonous bubbles*).

Vestibular Symptoms Vestibular decompression sickness usually occurs after deep, long dives, although it has been reported in sport divers. Signs are vertigo, hearing loss, tinnitus, and disequilibrium. The vestibular syndrome can be differentiated from inner ear barotrauma mainly by the history, because patients with inner ear barotrauma develop symptoms in the water and, generally, immediately after a forced Valsalva maneuver to equalize the middle ear pressure.[13]

Other nonspecific symptoms such as headache, nausea, dizziness, or unusual fatigue are also reported. It may be difficult to differentiate fatigue from decompression sickness from the expected fatigue from the exertion of diving.

Patent Foramen Ovale The association between decompression sickness and patent foramen ovale is unclear. There appears to be an increased prevalence in patients with inner ear and cutaneous decompression sickness. It is reasonable to screen divers with recurrent, unexplained decompression sickness for a patent foramen ovale. Closure of a large defect will reduce arterialization of venous gas emboli, although it has yet to be shown if such closure will reduce the incidence of subsequent decompression sickness.[14]

ARTERIAL GAS EMBOLISM

Arterial gas embolism occurs when air enters the left side of the vascular system. In the setting of diving, this most often results from pulmonary barotrauma. Arterial gas embolism can also occur as a complication of certain medical procedures, such as central vascular catheterization and cardiac bypass. Air inadvertently introduced into the venous circulation can cross from the right side of the circulation from intracardiac or pulmonary arteriovenous shunts. Air bubbles may also arterialize through these same shunts, sometimes making the source of arterial bubbles difficult to determine.[15] Whatever the source, when air embolizes systemically, distribution depends mainly on blood flow and not gravity.

Clinical Features of Arterial Gas Embolism The most dramatic effect of arterial gas embolism is on the brain, resulting in a variety of stroke syndromes, symptoms, and signs, depending on the part of the brain affected. Rarely, diving-related arterial gas embolism from pulmonary barotrauma causes immediate apnea and cardiac arrest. The mechanism of cardiovascular collapse appears to be air in the entirety of the large arteries and veins of the central vascular bed.[16] The effects of arterial gas embolism secondary to pulmonary barotrauma usually occur on ascent or immediately upon surfacing. If the victim does not die immediately, the symptoms of cerebral arterial gas embolism often include loss of consciousness, seizure, blindness, disorientation, or hemiplegia. Symptoms may spontaneously improve as the gas enters the venous cerebral circulation after a spike in blood pressure. Sometimes, by the time the patient reaches the clinician, the only signs that remain are subtle defects. In particular, parietal lobe signs and symptoms are easily overlooked. A cascade of inflammatory processes also occurs in air embolism, just as in decompression sickness.[5]

DIAGNOSIS OF DECOMPRESSION SICKNESS AND ARTERIAL GAS EMBOLISM

Diagnosis is clinical, based on history and physical exam, with limited laboratory testing. There are no current definitive diagnostic criteria for decompression sickness. The San Diego Diving and Hyperbaric Organizations criteria uses a point system to identify dive injuries resulting in decompression sickness with a high degree of specificity (90%),[17] but a sensitivity of only 53%. This is helpful to create databases of divers with decompression sickness to study outcomes and allow study of adjunctive therapies. The San Diego Diving and Hyperbaric Organizations criteria for arterial gas embolism have been shown in a small study to be useful. Using a cut point of ≥2 points, the score has a 94.7% sensitivity (95% confidence interval, 71.9% to 99.7%) and 85.7% specificity (95% confidence interval, 42.0% to 99.2%) for the diagnosis of arterial gas embolism (**Table 214-3**).[18]

TABLE 214-3 San Diego Diving and Hyperbaric Organizations Criteria for Arterial Gas Embolism

Time Criteria		Points*
Any of the following signs or symptoms within 5 min of surfacing	Disorientation Sudden loss of consciousness Aphasia Hemiplegia	3 points
Any of the following signs or symptoms within 5 min of surfacing	Hemiparesis or monoparesis Seizures (new onset) Cortical blindness	2 points
With resurfacing or discovered during ED evaluation	A rapid uncontrolled ascent, or any ascent with panic and the onset of symptoms Hemoptysis Presence of barotrauma on chest radiograph (pneumomediastinum, pneumopericardium, or pneumothorax) Creatine phosphokinase greater than 2 times normal in the absence of musculoskeletal trauma	1 point

*Requires 2 or more points to suggest a diagnosis of arterial gas embolism.

Using these criterial may be helpful to the clinician; however, until a larger study can validate this study, physician clinical judgment should supersede this scoring system.

Laboratory Testing Laboratory testing is not always indicated in cases of very mild symptoms or presentations. If labs are obtained for evaluating either decompression sickness or arterial gas embolism, it is useful to obtain a CBC, creatine phosphokinase, liver enzymes, and possibly cardiac enzymes (if any chest pain or shortness of breath present). The hematocrit may increase due to hemoconcentration and third spacing of fluids. The creatine phosphokinase (and other enzymes such as lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) will become elevated secondary to the systemic distribution of bubbles. The degree of elevation of creatine phosphokinase corresponds to the embolism severity. Cardiac troponins may also be elevated and most likely do not represent occlusive coronary artery disease.[5] However, arterial gas embolism and decompression sickness are clinical diagnoses and cannot be ruled in or out based on laboratory testing.

Imaging Routine imaging is not indicated in all cases of decompression sickness or arterial gas embolism. If the patient is having any chest pain or shortness of breath, a chest radiograph is recommended to evaluate for possible pneumothorax, pneumomediastinum, or other possible causes of symptoms. An untreated pneumothorax is an absolute contraindication to hyperbaric therapy. A head CT scan may be obtained in patients with neurologic symptoms, particularly if the cause of symptoms is unclear, to rule out other causes such as a hemorrhagic stroke or subarachnoid hemorrhage. Although there may be gas bubbles seen in cases of arterial gas embolism, a negative CT does not rule out the diagnosis. Findings from decompression sickness and arterial gas embolism may both be seen on MRI; however, there may be discrepancy between the timing of the appearance of the lesions on MRI and what is clinically observed—either worsening of lesions on MRI with clinical improvement or improvement on MRI with worsening symptoms.[19] Obtaining an MRI should not delay hyperbaric oxygen therapy.

TREATMENT OF DECOMPRESSION SICKNESS AND ARTERIAL GAS EMBOLISM

Treatment includes administering 100% oxygen, increasing tissue perfusion with IV fluids, and rapid recompression. A supine position—not Trendelenburg position—is recommended for patients with arterial gas embolism. Patients may improve on surface oxygen and even have complete resolution of symptoms. However, it is imperative that these patients still be treated with hyperbaric oxygen due to risk of recurrence or relapse of symptoms.

Recompression therapy with hyperbaric oxygen treats these conditions through several mechanisms. See Chapter 21, "Hyperbaric Oxygen Therapy," for detailed discussion. The administered pressure decreases the size of bubbles, and the high partial pressure of oxygen in solution increases inert gas washout from bubbles and tissue. Mass action dictates a gas will travel down pressure gradients; therefore, nitrogen will move from bubbles with a high partial pressure of nitrogen into plasma, where it will travel to the lungs and be exhaled. Conversely, oxygen from plasma with a high partial pressure of oxygen will enter bubbles, but ultimately will diffuse into cells and be metabolized, further reducing bubble size. Hyperbaric oxygen also decreases tissue edema and increases oxygen delivery to ischemic tissues. Additionally, it attenuates ischemia reperfusion injury by reducing neutrophil activation and adhesion to the endothelium.[20]

Recompression using U.S. Navy Treatment Table 6 is a commonly used method of management for decompression sickness, employing a maximal treatment pressure of 2.8 ATA (60 fsw). Table 6 is also used for air embolism, although some advocate an initial pressurization to 6 ATA (165 fsw) to maximize bubble compression, then continuation at 2.8 ATA (U.S. Navy Table 6A). Different treatment tables are used in other parts of the world, and there is some experience using lower treatment pressures for decompression sickness in monoplace chambers with reportedly comparable results.[21] Some patients may benefit from repeated treatments if symptoms do not fully resolve. Recompression should occur as soon as possible, and it should not be withheld in cases with delayed presentation.[5] Additionally, for divers who have missed needed decompression stops because of an emergency ascent or nonadherence to appropriate diving tables, it may be appropriate for them to undergo recompression therapy **even if asymptomatic.** U.S. Navy Table 5 recompression would usually be adequate in such a circumstance.

The administration of IV lidocaine as a therapeutic adjunct for cerebral arterial gas embolism has been advocated because it appears to decrease neuropsychiatric deficits when given during anesthesia for cardiac procedures requiring bypass,[22-24] since bypass operations commonly cause the entry of air into the arterial system. Dosing of lidocaine in this setting is not standardized, although typical cardiac dosing is commonly used.[25] NSAIDs may also be helpful.[22]

The **Divers Alert Network Emergency Hotline** (telephone: 1-919-684-9111; website: http://www.diversalertnetwork.org) has staff available 24 hours a day to provide assistance to divers and to help clinicians treat patients with decompression sickness or arterial gas embolism. The Divers Alert Network can provide information and the location of the nearest recompression facility around the world.

SPECIAL CONSIDERATIONS

IMMERSION PULMONARY EDEMA

Pulmonary edema can occur while diving or swimming. Because the first reported cases occurred in cold water, this condition was first described as "cold water" or "cold-induced" pulmonary edema. However, many cases have subsequently been reported in warm water, up to 27°C (80.6°F).[26] Typical symptoms of pulmonary edema (dyspnea, chest discomfort, coughing up pink frothy secretions) occur at depth and usually improve over time or with standard treatments for pulmonary edema. The cause is unknown despite human studies.[27] Initially, it was thought that there was no significant incidence of underlying cardiac disease, as many of these cases were initially reported in military trainees and triathletes who were significantly exerting themselves. However, as more cases are reported, it seems that there may be a relationship to underlying cardiac and pulmonary disease, particularly in middle-aged and older divers without significant exertion. It is possible that the mechanism of disease may be different in these patients, though with a common final pathway of disease. It may be prudent, particularly in older divers, to pursue a cardiac workup, including an ECG, cardiac markers, echocardiogram, and possible stress testing.[28-30] Interestingly, some divers will experience repeated episodes, whereas others may never experience another episode.

NITROGEN NARCOSIS

Inert gas narcosis occurs when air is breathed at a depth of 100 fsw or greater. Symptoms include loss of fine motor skills and high-order mental processes and can cause divers to engage in dangerous or foolish activities during deep dives. At depths greater than 300 fsw, unconsciousness may occur from the anesthetic effect of nitrogen.

OXYGEN TOXICITY

Oxygen toxicity usually affects the lungs or brain, depending on the partial pressure of oxygen delivered and duration of exposure. Pulmonary oxygen toxicity generally occurs at lower partial pressures of oxygen but with longer exposures, whereas cerebral oxygen toxicity occurs at high partial pressures with generally short exposures. Pulmonary oxygen toxicity is unusual in diving due to the long exposure required to develop symptoms.

Cerebral oxygen toxicity most often occurs with partial pressures of oxygen >1.4 ATA in the water. Some divers may breathe "nitrox" or **oxygen-enriched air** with fractions of oxygen of 32% to 36%. Therefore, cerebral oxygen toxicity can occur at lesser depths and actually is the factor that limits diving depth with nitrox. Additionally, there are rebreather systems (closed-circuit systems), with the diver breathing within a continuous circuit of gas that has a very high fraction of oxygen (>95%), with carbon dioxide being scrubbed out. With these systems, cerebral oxygen toxicity can occur at depths as little as 25 ft.

Signs and symptoms of cerebral oxygen toxicity include twitching, nausea, paresthesias, dizziness, and seizures. High partial pressures of

oxygen are used clinically in hyperbaric chambers (2.4 ATA, 2.8 ATA, and sometimes 3.0 ATA), but cerebral oxygen toxicity in this setting is rare, reported in <1 per 1000 patients. Cerebral oxygen toxicity is also affected by partial pressure of arterial carbon dioxide and cerebral blood flow and may be caused by an increase in nitric oxide production, although this is still an area of active investigation.[31]

Besides nitrogen narcosis and oxygen toxicity, other gas-related conditions important in diving medicine are toxicity from carbon monoxide and the adverse effects of elevated partial pressures of carbon dioxide. Additional issues, especially with very deep dives, include heat loss from breathing helium and the high-pressure nervous syndrome, characterized by tremor and loss of fine motor function caused by the direct effects of pressure.

OTHER CONDITIONS

Injuries and medical conditions occurring during and immediately after compressed air diving are often misattributed as decompression sickness or cerebral arterial gas embolism. Be aware that any medical condition can occur under the water. Acute myocardial infarction, pulmonary embolism, stroke, seizure, encephalitis, and even appendicitis have been erroneously attributed to diving. True diving accidents or cardiac sudden death can be misattributed to drowning—a common final pathway of submersion.[32]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 215

Drowning

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INTRODUCTION AND EPIDEMIOLOGY

Drowning is submersion in a liquid medium resulting in respiratory difficulty or arrest.[1] As with other causes of accidental death, drowning injury typically involves otherwise healthy, young individuals, but can involve individuals of any age or background.

Worldwide, drowning accounts for >370,000 deaths annually and is the leading cause of injury death among children <15 years of age.[1] In the United States, there are >500,000 drowning events each year and 1100 deaths, which makes drowning the second leading cause of unintentional death of individuals from birth to age 19 years old.[2,3] Although the rate of drowning deaths has decreased over the past 40 years, it remains high in low- and middle-income countries, which account for 91% of unintentional drowning deaths worldwide annually.[4] The vast majority of victims survive submersion events, with effects ranging from minimal or transient injury to profound neurologic insult.

Drowning incidence peaks in three age groups: The highest is in children <5 years old,[2,3] the second peak is in those aged 15 to 24 years,[2,3] and the third peak is in the elderly.[5] Toddlers drown primarily after falling into swimming pools or open water, but they also drown in bathtubs and buckets in the home. Physicians also need to evaluate for intentional drowning (child abuse) or factitious disorder by proxy (formerly Munchausen's by proxy). In teenagers and adults, suicide, homicide, and domestic violence can be causes of drowning. In this age group, drowning is also more likely if alcohol or drugs are involved.[6] The elderly also have an increased risk of bathtub drowning, often related to comorbid medical conditions or medications. Even in coastal areas, most drownings take place in warm, freshwater bodies of water, especially swimming pools.

Additional injuries or disorders that either precipitate or are associated with drowning events are shown in **Table 215-1**.

TABLE 215-1 Disorders and Injuries Associated With Drowning

Disorders Associated With Drowning
• Alcohol or other intoxicants
• Syncope (e.g., due to hyperventilation prior to underwater diving)
• Seizures
• Cardiac conditions (e.g., dysrhythmias including prolonged QT syndromes, Brugada's syndrome, ischemic heart disease)
• Dementia
• Intentional (suicide, homicide, child abuse or neglect in young children)
Injuries Associated With Drowning
• Spinal cord injuries due to diving into shallow water, significant falls from heights, or boating/personal watercraft mishaps
• Hypothermia
• Aspiration
• Respiratory failure, insufficiency, or distress

PATHOPHYSIOLOGY

After submersion, the degree of hypoxic insult to the CNS determines the ultimate outcome. It was previously thought that parasympathetic activation of the **diving reflex** (i.e., bradycardia, apnea, peripheral vasoconstriction, and central shunting of blood flow) provided transient protection during submersion. However, in most cases, the diving reflex is overwhelmed by the stimulation of the sympathetic nervous system, yielding no meaningful protection.[5] Cerebral protection in cold water submersions most likely results from rapid CNS cooling before significant hypoxic damage occurs.

Physiologic scoring systems[6,7] to predict drowning outcome have been devised but are not clinically helpful. The vast majority of patients who arrive at the hospital with stable cardiovascular signs and awake, alert neurologic function survive with minimal disability, whereas those who arrive with unstable cardiovascular function and coma do poorly because of the hypoxic-ischemic insult. Predictors are not accurate for the 15% to 20% of drowning victims whose condition on arrival is between these two extremes. However, patients who had a low Glasgow Coma Scale score upon arrival to the ED (average of 3.2 for nonsurvivors vs. 11.6 for survivors), who required CPR, who were intubated, or for whom presser support was initiated all had a lower survival than those who did not have or require any of these.[8]

End organs can also be affected by hypoxemia and metabolic acidosis. Aspiration of substances such as contaminated foreign material, particulate matter, bacteria, vomitus, or chemical irritants can affect eventual pulmonary recovery. **Electrolyte abnormalities are seldom significant and are usually transient unless there is significant hypoxia, CNS depression, renal injury from hemoglobinuria, or myoglobinuria.**[8,9] Hematologic values are usually normal unless there has been massive hemolysis. Disseminated intravascular coagulation can be a complicating factor in drowning outcome but usually occurs following severe hypoxic insult.

TREATMENT

PREHOSPITAL CARE

Rapid resuscitation of a drowning victim (quickly restoring ventilation and oxygenation) optimizes outcome. After safe removal of the victim from the water, CPR should be initiated as quickly as possible. Trauma as a cause of drowning is uncommon, and most injured drowning patients have a history of trauma or signs of injury on examination.[10] Cervical spine injury is rare (0.5%) in drowning unless there is a history of diving, falling from a significant height, or motorized vehicle crash.[11] Use cervical spine precautions if the history warrants it.

Administer high-flow oxygen by facemask if the patient is breathing or by positive-pressure bag-valve-mask ventilation if the patient is not breathing. For patients who do not recover spontaneous respiratory effort, endotracheal intubation and positive-pressure ventilation are necessary.

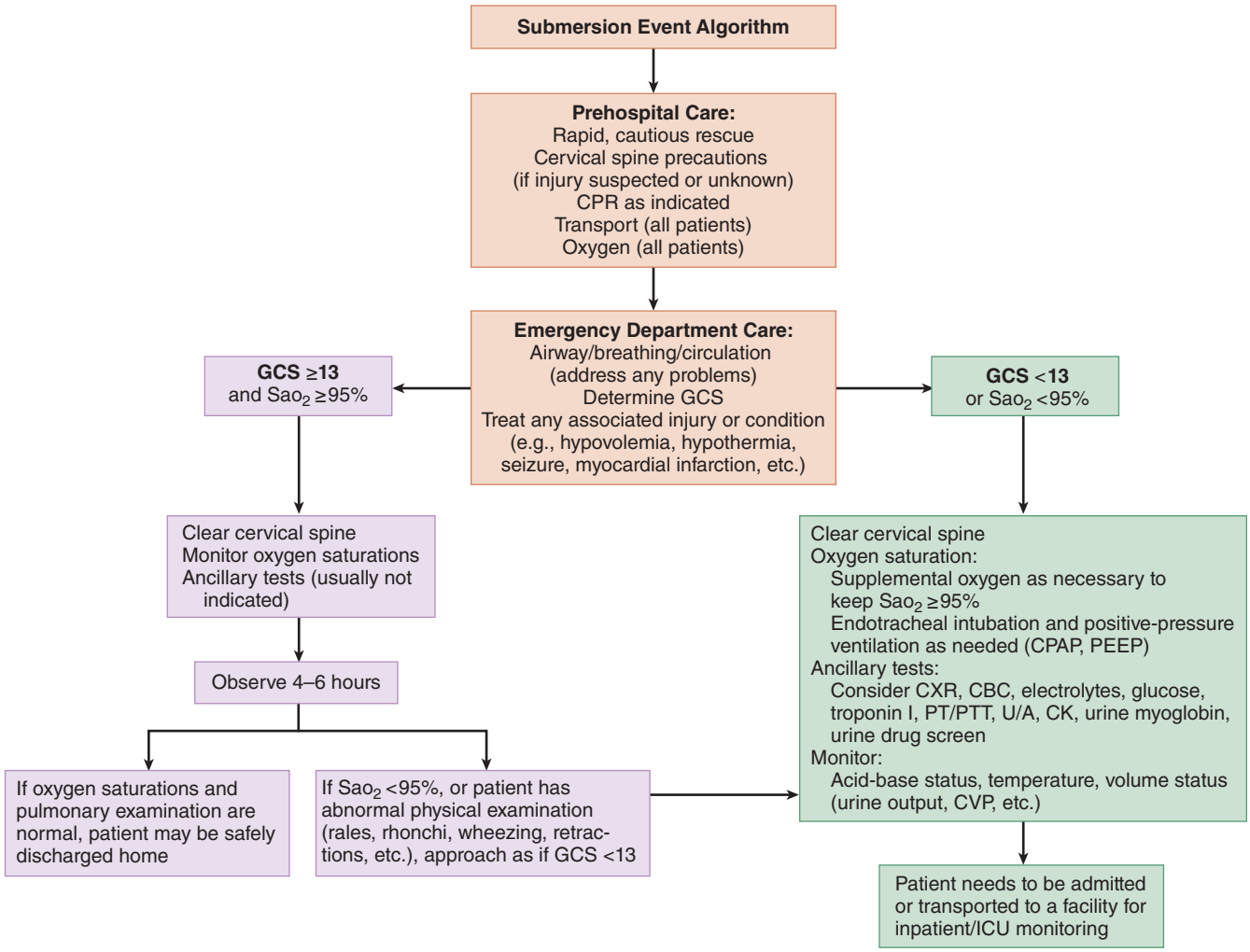

FIGURE 215-1. Drowning event algorithm. CBC = complete blood count; CK = creatine kinase; CPAP = continuous positive airway pressure; CVP = central venous pressure; CXR = chest radiograph; GCS = Glasgow Coma Scale score; ICU = intensive care unit; PEEP = positive end-expiratory pressure; PT = prothrombin time; PTT = partial thromboplastin time; Sao_2 = oxygen saturation (via pulse oximetry); U/A = urinalysis.

All patients with amnesia for the drowning event, loss of or depressed consciousness, or an observed period of apnea, as well as those who require a period of artificial ventilation, should be transported to an ED for evaluation, even if they are asymptomatic at the scene. The patient should be warmed and monitored, and IV access should be established (**Figure 215-1**).

PRIMARY ED TREATMENT

Upon the patient's arrival at the ED, **assess and secure the airway, provide oxygen, determine core temperature, and assist ventilation as necessary**. If the patient is hypothermic, administer warmed isotonic IV fluids and apply warming adjuncts (e.g., blankets, overhead warmers, warming devices). Address any associated injuries. **Because cervical injury is rare without a history of diving or associated trauma, routine cervical immobilization and CT of the brain are not necessary.**[11]

Patients who present to the ED with a Glasgow Coma Scale score of >13 and an oxygen saturation of ≥95% are at low risk for complications (Figure 215-1) and should be observed for 4 to 6 hours. If the pulmonary examination does not reveal rales, rhonchi, wheezing, or retractions and arterial oxygen saturation on room air remains ≥95%, the patient can be safely discharged home. Laboratory studies and radiographs are unnecessary and are not predictive of discharge.[9,12] The patient should be told to return if fever, mental status changes, or pulmonary symptoms occur. If, after 4 to 6 hours, the patient develops an oxygen requirement, the findings on pulmonary examination are abnormal (rales, rhonchi, wheeze, retractions, etc.), or the patient's condition deteriorates, reassessment and admission or transfer to a monitored bed are needed.[9,12]

Patients who present to the ED with a Glasgow Coma Scale score of <13 should be maintained on supplemental oxygen and ventilatory support as needed. If high-flow oxygen (fraction of inspired oxygen of 40% to 60%) cannot maintain an adequate partial pressure of arterial oxygen (>60 mm Hg in adults, >80 mm Hg in children), then intubate the patient and provide positive-pressure ventilation. Chest radiography and laboratory studies should be done to evaluate for pulmonary aspiration and other complications (Figure 215-1). Although aspiration is common, prophylactic antibiotics have not been shown to improve outcome and may be associated with resistant infections.[13] Continuous cardiac monitoring, pulse oximetry, temperature monitoring, and frequent reassessments should be performed for all patients. Hypothermia is a concern in patients who have been submerged in cold water (see Chapter 209, "Hypothermia").

If the patient is normothermic upon arrival in the ED and in cardiopulmonary arrest or asystole, serious thought should be given to discontinuing resuscitation efforts because recovery without profound neurologic complications is rare.[14,15]

SECONDARY TREATMENT

Hospital management of drowning victims is largely supportive.[16] All drowning victims who require ED resuscitation should be admitted to an intensive care unit for continuous cardiopulmonary and frequent

neurologic monitoring. Most victims of significant submersion injury benefit from mechanical ventilation. Supernormal levels of positive end-expiratory pressure may be used to recruit fluid-filled lung units and aid oxygenation. Most patients demonstrate rapid improvement in oxygenation in the first 24 hours. Patients presenting with a significant aspiration pattern or cardiovascular collapse are predisposed to develop acute respiratory distress syndrome. Although prophylactic antibiotics lack supporting evidence, delayed pulmonary infection, particularly among patients requiring mechanical ventilation, is a risk, and unusual organisms, including ***Aeromonas*** species, should be considered if treatment is initiated. Care should be taken to avoid lung overdistention and ventilator-associated barotrauma.

For patients who have been resuscitated from cardiac arrest, the hemodynamic response to exogenously administered epinephrine is frequently short lived, and most require a continuous infusion of dopamine or epinephrine in the ED or intensive care unit. Invasive (pulmonary artery catheter) or noninvasive (echocardiogram) measurement of ventricular function is often instructive. Hemodynamic recovery, when it occurs, can be expected within 48 hours. Patients demonstrating no hemodynamic recovery after 48 hours may slowly improve over the first week but are more likely to have long-term neurologic damage.[17]

Results of "brain resuscitation" after significant warm water drowning have been disappointing.[9,16] The degree of cerebral edema is largely determined by the duration of the anoxic or ischemic insult at the time of submersion. Efforts to control cerebral edema, including the use of mannitol, loop diuretics, hypertonic saline, fluid restriction, and mechanical hyperventilation, have not shown benefit.[16] Controlled hypothermia, barbiturate "coma," and intracranial pressure monitoring do not improve outcome in pediatric drowning victims.[9] Although rare, complete or near-complete neurologic recovery after asystole has been reported in both children and adults after icy water submersion episodes.

PROGNOSIS, DISPOSITION, AND FOLLOW-UP

Family members should be counseled about likely outcome. Based on initial presentation, resuscitation, laboratory data, and serial examinations, experienced practitioners should be able to provide accurate predictions of outcomes in most cases.[17] There are no standardized terms for describing drowning incidents.[18] This chapter uses the terms *asymptomatic* and *symptomatic drowning*.

ASYMPTOMATIC DROWNING

Drowning victims who are asymptomatic or mildly symptomatic can be observed for 4 to 6 hours. If the findings of pulmonary examination and oxygen saturation on room air remain normal, patients can be discharged home. If deterioration is going to occur, it will do so within the 4- to 6-hour observation period.[12,19-21] No data are available regarding long-term outcomes, but it is unlikely that there are any measurable adverse effects. Patients and/or parents should be advised to seek medical care for any respiratory complaints or fever.

SYMPTOMATIC DROWNING

Because submersion duration is frequently unknown or only estimated, the extent of required resuscitation is often the most objective measure of the degree of anoxic or ischemic insult (Table 215-2). Details of initial presentation and resuscitation are frequently strong prognostic indicators.

For patients who require hospital admission, if the submersion victim does not require cardiopulmonary resuscitation at the scene or in the ED, complete recovery within 48 hours is expected. A small fraction of patients with significant aspiration may develop severe, even life-threatening acute respiratory distress syndrome.

Victims requiring bystander CPR at the scene have a guarded prognosis. Of scene-resuscitated pediatric victims, about 20% later die in the hospital, and about 5% are left with severe hypoxic-ischemic encephalopathy.[15,22] Those victims who demonstrate continuous neurologic and cardiovascular improvement after hospital admission generally make a good recovery. Frequently, neurologic and cardiovascular examinations are normal within 24 hours of the drowning event. Victims who later die in the hospital usually demonstrate deteriorating cardiovascular and neurologic status.

Victims undergoing CPR in the ED have a poor prognosis. Prolonged (>30 minutes) CPR in drowning victims indicates significant anoxic or ischemic insult to the heart, brain, and other vital organs. Complete neurologic recovery is rare, with only anecdotal reports of neurologic recovery after ED CPR of pediatric drowning victims. Asystole, whether noted at the scene or in the ED, is a near-universal sign of poor prognosis in both adult and pediatric drowning injury.[16,23]

For the emergency physician, the answers to the questions of whom and how vigorously to resuscitate remain challenging.[16,22] **Complete or near-complete neurologic recovery after asystole has been reported in both children and adults after drowning in icy water, although such occurrences are rare** and documented mostly in case reports or small series (see also Chapter 209, "Hypothermia"). A large series of 1377 open-water drowning victims found *no* intact survivors among the group submerged for more than 15 minutes, whether in warm or cold water, and there were no survivors of submersion greater than 60 minutes.[24] There was also no difference in survival for children compared with adults in several studies, which contradicts the common belief that pediatric patients do better than adults.[7,23] For asystolic victims of drowning with short submersion durations (i.e., a few minutes) and short transport times who receive CPR en route, a vigorous resuscitation attempt is reasonable.[25] CPR should be abandoned if no response is noted. Conversely, because of the poor prognosis for intact neurologic survival, ED resuscitation attempts can reasonably be withheld from asystolic victims of drowning with longer submersion and transport times.[15,22]

TABLE 215-2 Factors Associated With Poor Resuscitation Prognosis in Near-Drowning

- Need for bystander CPR at scene
- CPR in the ED
- Asystole at scene or in ED after warming

PREVENTION

The American Academy of Pediatrics' Committee on Injury, Violence, and Poison Prevention has released a technical report on drowning prevention detailing information that can instruct local prevention programs.[26,27] The World Health Organization and the Centers for Disease Control and Prevention have online information to guide parents and the lay public for drowning prevention.[1,28]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 216 High-Altitude Disorders

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INTRODUCTION

Millions of people annually visit mountainous areas of the western United States at altitudes of >2440 m (>8000 ft). In addition, tens of thousands travel to high-altitude regions in other parts of the world. Physicians working or traveling in or near these locations are likely to encounter high-altitude illness or preexisting conditions that are exacerbated by altitude. Although the focus of this chapter is hypoxia-related problems,

patients in the mountain environment may require care for associated illnesses such as hypothermia (see Chapter 209, "Hypothermia"), frostbite (see Chapter 208, "Cold Injuries"), dehydration, and lightning injury (see Chapter 219, "Electrical and Lightning Injuries").

High altitude (>2440 m [>8000 ft]) is a hypoxic environment. Because the concentration of oxygen in the troposphere remains constant at 21%, the partial pressure of oxygen (P_{O2}) decreases as a function of the barometric pressure. Two locations in the U.S. western state of Colorado are illustrative. In Denver, at 1610 m (5280 ft), air pressure is 17% less than at sea level; Aspen, at 2440 m (8000 ft), has 26% less oxygen than sea level. At 5490 m (18,000 ft), there is half the oxygen available at sea level, whereas on top of Mount Everest (8848 m or 29,029 ft), there is only one third. Oxygen supplementation prevents symptoms of altitude illness during hypobaric exposure. Symptoms of acute mountain sickness (AMS) are due primarily to hypoxia, not hypobaria.

Altitude may be divided into stages according to physiologic effects. *Intermediate altitude*, 1520 to 2440 m (5000 to 8000 ft), produces decreased exercise performance and increased alveolar ventilation without major impairment in arterial oxygen transport. AMS occurs at and above 2130 to 2440 m (7000 to 8000 ft) and sometimes at lower altitudes in particularly susceptible individuals. Patients who have limitations in ventilatory response (e.g., patients with some neuromuscular diseases or those with preexisting hypoxemia) may become more symptomatic in this range of altitude. *High altitude,* 2440 to 4270 m (8000 to 14,000 ft), is associated with decreased arterial oxygen saturation (Sa_{O2}); marked hypoxemia may occur during exercise and sleep. Most cases of altitude-related medical problems occur in this elevation range, because of the availability of overnight tourist facilities located at these heights.

Very high altitude, 4270 to 5490 m (14000 to 18,000 ft), is uncommon in the United States, but is encountered by visitors to the mountainous regions of South America and the Himalayas. Abrupt ascent can be dangerous, and a period of acclimatization is required to prevent illness. *Extreme altitude,* >5490 m (>18,000 ft), experienced only by mountain climbers, is accompanied by severe hypoxemia and hypocapnia. At this height, progressive physiologic deterioration eventually outstrips acclimatization, and sustained human habitation is impossible. **Because hypoxemia is maximal during sleep, sleeping altitude is the critical driver of altitude illness.**

PHYSIOLOGY AND PATHOPHYSIOLOGY OF ALTITUDE ACCLIMATIZATION

Acutely hypoxic individuals become dizzy, faint, and rapidly unconscious if hypoxic stress is sufficient (Sa_{O2} <65%). However, if given days to weeks to acclimatize, individuals can tolerate surprising degrees of hypoxemia. Although the fundamental process of acclimatization takes place in cellular and mitochondrial metabolism, acute "stress" responses enable temporizing homeostasis while allowing cells time to truly acclimatize.

VENTILATION

The primary initial adaptation to hypoxemia is defense of alveolar P_{O2} through increased ventilation. The hypoxic ventilatory response is modulated by the carotid body, which senses a decrease in arterial oxygenation and signals the central respiratory center in the medulla to increase ventilation. Individuals with a more vigorous inborn response show more successful acclimatization and improved exercise performance. Respiratory stimulants increase the ventilation response; respiratory depressants and chronic hypoxia weaken it. A low hypoxic respiratory drive may allow significant hypoxemia to develop during sleep.

With ascent, initial hyperventilation is attenuated quickly by respiratory alkalosis, which acts as a brake on the respiratory center. As renal excretion of bicarbonate increases to compensate for the respiratory alkalosis, pH returns toward normal and ventilation continues to increase. The process of maximizing ventilation, termed *ventilatory acclimatization*, culminates after 4 to 7 days at a given altitude. With continuing rise to higher altitudes, the central chemoreceptors reset to progressively lower values of partial pressure of CO_2, and the completeness of acclimatization can be gauged by the partial pressure of arterial CO_2.

TABLE 216-1 Normal Blood Gas Concentrations at Various Altitudes

Altitude	Pa_{O2} (mm Hg)	Sa_{O2} (%)	Pa_{CO2} (mm Hg)
Sea level	90–95	96	40
5000 ft (1520 m)	75–81	95	35.6
7500 ft (2290 m)	69–74	92–93	31–33
15,000 ft (4570 m)	48–53	86	25
20,000 ft (7000 m)	37–45	76	20
25,000 ft (7620 m)	32–39	68	13
29,000 ft (8840 m)	26–33	58	9.5–13.8

Abbreviations: Pa_{CO2} = partial pressure of arterial carbon dioxide; Pa_{O2} = partial pressure of arterial oxygen; Sa_{O2} = arterial oxygen saturation.

Acetazolamide, which induces bicarbonate diuresis, greatly facilitates this process through its inhibition of carbonic anhydrase (thus counteracting ascent-related respiratory alkalosis).[1] An appreciation of the normal values for blood gases and acid-base status with acclimatization at various altitudes is necessary to distinguish abnormalities (**Table 216-1**).

BLOOD

Within hours of ascent to altitude, serum erythropoietin level increases, resulting in increased red cell mass over days to weeks. This adaptation has no importance during initial acclimatization when acute altitude illness develops. However, excessive red cell mass may develop over a period of weeks to months, leading to chronic mountain polycythemia. Shifts in the oxyhemoglobin dissociation curve are thought to be minimal at altitude because of balancing physiologic effects. Hypoxia causes an increase in the level of 2,3-diphosphoglyceric acid and shifts the curve to the right, which has the effect of facilitating unloading of oxygen to the tissues. Respiratory alkalosis shifts the curve to the left, which has the opposite effect (i.e., facilitating oxygen loading in the lungs).

FLUID BALANCE

Peripheral venous constriction on ascent to altitude causes an increase in central blood volume that triggers baroreceptors to suppress secretion of antidiuretic hormone and aldosterone; diuresis results. Combined with the bicarbonate diuresis from the respiratory alkalosis, the result is decreased plasma volume and a hyperosmolality that results from a reset of the osmolar center of the brain. Hemoconcentration increases oxygen-carrying capacity of the blood. Clinically, diuresis and hemoconcentration are considered healthy responses, whereas antidiuresis is associated with AMS and may contribute to peripheral edema.

CARDIOVASCULAR SYSTEM

Stroke volume decreases initially, and increased heart rate is required to maintain cardiac output. Maximum exercising heart rate at altitude declines in proportion to the decrease in maximum oxygen consumption (Vo_2max). Cardiac muscle in healthy persons can withstand extreme levels of hypoxemia (partial pressure of arterial oxygen [Pa_{O2}] of <30 mm Hg) without evidence of ST-segment changes or ischemic events. Blood pressure typically increases mildly on ascent, secondary to increased sympathetic tone, but labile blood pressures are also possible.

The pulmonary circulation constricts with exposure to hypoxia. Pulmonary vasoconstriction is advantageous during some conditions of regional alveolar hypoxia (e.g., pneumonia). However, it poses a disadvantage during the global hypoxia of altitude exposure by increasing overall pulmonary vascular resistance and pulmonary artery pressure. A hyperreactive response increases susceptibility to high-altitude pulmonary edema (HAPE). This is the underpinning of sildenafil therapy for HAPE.[2]

Cerebral blood flow transiently increases on ascent to altitude (despite the respiratory alkalosis), increasing oxygen delivery to the brain. This response is limited by the increase in cerebral blood volume, which may increase intracranial pressure and aggravate symptoms of altitude illness.

EXERCISE CAPACITY

Exercise capacity, as measured by Vo_2 max, drops dramatically on ascent to altitude, by approximately 10% for each 1000-m (3280-ft) altitude gain above 1500 m (4920 ft). During acclimatization, submaximal endurance increases appreciably after 10 days, but Vo_2 max does not. The mechanism of this decrement might be lack of adequate oxygen supply to the muscle cells due to the low driving pressure for transcapillary oxygen diffusion. Another theory suggests that the CNS limits muscle activity to preserve its own oxygenation.

LIMITATIONS TO ACCLIMATIZATION

There are limits to acclimatization. Even those who are by nature good acclimatizers cannot tolerate the hypoxia of extreme altitude for long. Miners in South America report that they cannot live at altitudes >5800 m (>19,000 ft) because of weight loss, lethargy, poor-quality sleep, weakness, and headache. High-altitude mountaineers cannot survive for more than a few days at >8000 m (>26,200 ft) without supplemental oxygen because of rapid deterioration of physiologic functioning. Considerable weight loss due to loss of fat and lean body mass is unavoidable.

SLEEP AT HIGH ALTITUDE

Frequent nighttime awakenings are a common nuisance at high altitude but are innocuous and improve with acclimatization. These awakenings are typically seen above 2700 m (8860 ft) and are driven by periodic breathing (Cheyne-Stokes respiration). Awakenings consist of 6- to 12-second apneic pauses interspersed with cycles of vigorous ventilation. Intervals of apnea of >20 seconds can be observed at extreme altitudes. Both sleep quality and arterial oxygenation during sleep improve with acclimatization and with acetazolamide.

HIGH-ALTITUDE SYNDROMES

High-altitude syndromes are those attributed directly to hypoxia: acute hypoxia, AMS, HAPE, high-altitude cerebral edema (HACE), retinopathy, peripheral edema, sleeping problems, and a group of neurologic syndromes. **Each of these clinical syndromes has a distinctive pattern and phenotype, but all share the fundamental etiology of hypoxia, all are seen in the same setting of rapid ascent in unacclimatized persons, and all respond to the same essential therapies: descent and oxygen.** Other syndromes occurring at high altitude, which are not necessarily related to hypoxia, include thromboembolic events, high-altitude pharyngitis, and bronchitis.

ACUTE HYPOXIA

The syndrome of acute hypoxia occurs in the setting of sudden and severe hypoxic insult, such as occurs with accidental decompression of a pressurized aircraft cabin or failure of the oxygen system used by a pilot or high-altitude mountaineer. Relatively acute hypoxia can also occur due to abrupt overexertion (precipitating arterial desaturation), acute onset of pulmonary edema, carbon monoxide poisoning, or sleep apnea. Unacclimatized persons become unconscious at an Sa_{O2} of 50% to 60%, a Pa_{O2} of less than approximately 30 mm Hg, or a jugular venous P_{O2} of <15 mm Hg. Acute hypoxia reverses with immediate administration of oxygen, rapid descent, and correction of the underlying cause. The sensitivity of the CNS to acute hypoxia is reflected in the entity's symptom progression: dizziness, lightheadedness, and dimmed vision leading to loss of consciousness.

ACUTE MOUNTAIN SICKNESS

AMS is a syndrome characterized by headache along with some combination of nausea or vomiting, dizziness, fatigue, or sleep disturbance (Table 216-2). AMS occurs in the setting of more gradual and less severe hypoxic insult than acute hypoxia syndrome. Its incidence varies by location, ease of access to the high-altitude environment, rate of ascent, and sleeping altitude. One study found a 25% incidence of AMS in physicians attending a continuing education meeting held at 2100 m (6900 ft) in Colorado. Other studies at resorts between 2220 and 2700 m (7280 and 8860 ft) in elevation claim an incidence between 17% and 40%; a sleeping altitude of 2740 m (9000 ft) seems to be a threshold for a marked increase in AMS incidence.[3] Approximately 40% of trekkers in Nepal on the path to Mount Everest experience AMS, and climbers on Mount Rainier have a very high incidence of 70% (probably due to rapidity of ascent).

In addition to sleeping altitude and rate of ascent, genetic predisposition determines individual susceptibility to AMS largely through a phenotype of blunted ventilatory response to hypoxia. Cardiovascular training status and sex have little influence on attack rates. Age has little influence on incidence, with children being as susceptible as adults, although those >50 years of age tend to have less AMS. Obesity appears to increase the risk of AMS, possibly due to greater nocturnal oxygen desaturation.[4] Susceptibility to AMS generally is reproducible in an individual on repeated exposures. Persons living at intermediate altitudes of 1000 to 2000 m (3300 to 6600 ft) already are partially acclimatized and do much better than lowlanders on ascent to higher altitudes.

TABLE 216-2 Lake Louise Acute Mountain Sickness (AMS) Self-Questionnaire*

Headache	Score
No headache—0	
Mild headache—1	
Moderate headache—2	
Severe headache, incapacitating—3	
GI symptoms	Score
No symptoms—0	
Poor appetite or nausea—1	
Moderate nausea or vomiting—2	
Severe nausea and vomiting, incapacitating—3	
Fatigue/weakness	Score
Not tired or weak at all—0	
Mild fatigue or weakness—1	
Moderate fatigue or weakness—2	
Severe fatigue or weakness, incapacitating—3	
Dizzy/lightheadedness	Score
No dizziness/lightheadedness—0	
Mild dizziness/lightheadedness—1	
Moderate dizziness/lightheadedness—2	
Severely light-headed, fainting/passing out—3	
Difficulty sleeping	Score
Slept well—0	
Did not sleep as well as usual—1	
Woke many times, poor night's sleep—2	
Could not sleep at all—3	
Total symptom score	

*Diagnosis of AMS requires headache plus 1 or more of the above symptoms.

Mild AMS: score of 2–4

Moderate AMS: score of 5–9

Severe AMS: score of 10–15

Source: Reproduced with permission from Roach RC, Bartsch P, Hackett PH, Oelz O; the Lake Louise AMS Scoring Consensus Committee: The Lake Louise Acute Mountain Sickness Scoring System, in Sutton J, Houston C, Coates G (eds): *Hypoxia and Mountain Medicine: Proceedings of the 8th International Hypoxia Symposium.* Burlington, VT: Pergamon Press; 1992, p. 272.

PATHOPHYSIOLOGY

AMS is due to hypobaric hypoxia, but the exact sequence of events leading to illness remains unclear. Cerebral vasodilation appears to be the initiating event. Vasodilation occurs in the brain in all persons

ascending to high altitude, thus increasing cerebral blood flow and blood volume. Whether this is solely sufficient to cause the symptoms of mild AMS is unclear. However, in persons who progress to HACE, vasogenic edema is evident as increased T2 signal on MRI.[5] The leaky blood–brain barrier in HACE is due either to loss of autoregulation leading to overperfusion or to increased permeability caused by inflammatory mediators. A robust anti-inflammatory response leading to less disruption of the blood–brain barrier may be a key factor in those individuals' resistance to AMS.[6] A combination of these two processes is also possible. The fact that dexamethasone so effectively treats AMS supports the hypothesis that vasogenic edema is critical to its development.

CLINICAL FEATURES

The diagnosis of AMS is based on characteristic symptoms within the context of a recent ascent to an altitude above 2000 m (6560 ft). On arrival, the person typically feels lightheaded and slightly breathless, especially with exercise. Characteristic symptoms develop between 1 and 6 hours later, but sometimes are delayed for 1 or 2 days, and may be worst upon awakening. Symptoms of mild AMS are similar to those of an ethanol hangover. Headaches are usually bifrontal and worsen with exertion, bending over, or performing a Valsalva maneuver. GI symptoms include anorexia, nausea, and sometimes vomiting (especially in children). The chief constitutional symptoms are lassitude and weakness. The person with AMS can be irritable and often wants to be left alone. Sleepiness and a deep inner chill also are common. The Lake Louise AMS self-report questionnaire can be helpful in following the severity of the illness (Table 216-2).

Physical findings in mild AMS are nonspecific. Heart rate and blood pressure are variable and usually in the normal range, although postural hypotension may be present. **Sa_{O2} can be normal or slightly low for a given altitude. The percent Sa_{O2} correlates poorly with the diagnosis of AMS.** Localized rales are detectable in up to 20% of persons with AMS. Fundoscopy reveals venous tortuosity and dilatation, and retinal hemorrhages are common at altitudes >5000 m (>16,400 ft) and in those with pulmonary and cerebral edema. Facial and peripheral edema sometimes accompanies AMS. With ascent, optic nerve sheath diameter increases due to edema but does not correlate with AMS development.[7]

As the illness progresses, headache becomes more severe while vomiting and oliguria develop. Lassitude may progress so that the victim requires assistance in eating and dressing. **The onset of ataxia or altered level of consciousness heralds progression to HACE. Coma may ensue within 12 hours if treatment is delayed.** The diagnosis of AMS can be difficult in preverbal children; in these cases, AMS should be a diagnosis of exclusion.[8]

The differential diagnosis in this setting includes carbon monoxide poisoning, dehydration, migraine, hypothermia, viral illness, and exhaustion. Carbon monoxide poisoning may have a presentation very similar to that of AMS and is not uncommon in mountain towns in the winter. Reduced oxyhemoglobin levels complicate hypoxia from high altitude, and the effects are additive. Hypoxia may trigger a migraine headache in patients with a personal or family history of migraine.[9,10] Unlike headaches from non-AMS causes (e.g., migraine), cephalalgia from AMS often dissipates within 10 to 15 minutes of supplemental oxygen administration.

The average duration of AMS at a Colorado resort (3000 m or 9840 ft) was 15 hours, with a range of up to 94 hours. Half of those affected with AMS chose to self-medicate.[3] At higher sleeping altitudes, the illness may last much longer (up to weeks if untreated) and is more likely to progress to pulmonary or cerebral edema. Eight percent of those with AMS at 4270 m (14,000 ft) in Nepal developed HAPE, HACE, or both.[11]

TREATMENT

The goals of treatment (**Table 216-3**) are to prevent progression, treat symptoms, and hasten acclimatization. Early diagnosis is essential. Initial clinical presentation does not predict eventual severity, and all persons with AMS must be observed carefully for progression of illness. **The three principles of treatment are (1) do not proceed to a higher sleeping altitude in the presence of symptoms, (2) descend if symptoms do not abate or become worse despite treatment, and (3) descend and treat immediately in the presence of symptoms of HACE or HAPE.** Descent is the definitive treatment for all forms of altitude illness. However, descent is not always an option, nor is it always necessary.

TABLE 216-3 Suggested Treatment Options for High-Altitude Illness

Mild AMS	No further ascent Descent to lower altitude or acclimatization at same altitude Acetazolamide, 125–250 milligrams PO twice a day, to speed acclimatization Symptomatic treatment as necessary with analgesics and antiemetics
Moderate/severe AMS	Immediate descent for worsening symptoms Low-flow oxygen if available Acetazolamide, 250 milligrams PO twice a day, and/or dexamethasone, 4 milligrams PO every 6 h Hyperbaric therapy
High-altitude cerebral edema	Immediate descent or evacuation Oxygen 2–4 L/min or titrated to Sa_{O2} >90% Dexamethasone, 8 milligrams PO, IM, or IV, then 4 milligrams every 6 h Hyperbaric therapy if patient cannot descend
High-altitude pulmonary edema	Immediate descent or evacuation Oxygen 4 L/min or titrated to Sa_{O2} >90% Nifedipine, 30 milligrams PO extended-release every 12 h, or tadalafil, 10 milligrams PO every 12 h if no oxygen or descent* Hyperbaric therapy if patient cannot descend Measures to minimize patient exertion and keep patient warm Dexamethasone if cerebral signs present, 4 milligrams PO every 6 h
Periodic breathing/ insomnia	Acetazolamide, 62.5–125.0 milligrams PO at bedtime as needed

Abbreviations: AMS = acute mountain sickness; Sa_{O2} = arterial oxygen saturation.

*Drug therapy is unnecessary if oxygen is available.

Descent and Oxygen Mild AMS is self-limited and generally improves with an extra 12 to 36 hours of acclimatization if ascent is halted. Remarkably, a drop in altitude of only 300 to 1000 m (980 to 3280 ft) is usually effective in ameliorating symptoms. Evacuation to a hospital or to sea level is unnecessary except in the most severe cases. To simulate descent, portable hyperbaric bags can be used to treat high-altitude illness (Gamow® bags). The patient is inserted into the fabric chamber, and a pressure of 0.9 kg/2.5 cm^2 (2 lb/in^2) is achieved by means of a manual or automated pump, equivalent to a drop in altitude of 1500 m (4920 ft). A valve system creates sufficient ventilation to avoid CO_2 accumulation or oxygen depletion.

Oxygen effectively relieves symptoms, but to conserve supplies in the field, it is generally unavailable or reserved for those with moderate to severe AMS. Oxygen supplementation quickly relieves headache and dizziness. Nocturnal administration of low-flow oxygen (0.5 to 1 L/min) is particularly helpful. The combination of oxygen and descent provides optimal therapy, especially in more severe illness.

Medical Therapy Pharmacologic treatment offers an alternative to descent or oxygen in patients with mild to moderate AMS. Acetazolamide acts by inhibiting the enzyme carbonic anhydrase. Acetazolamide reduces renal reabsorption of bicarbonate, causing a bicarbonate diuresis and metabolic acidosis that stimulates ventilation. As a result, Pa_{O2} rises and the deleterious effects of hypobaric hypoxia are reduced. The drug also maintains cerebral blood flow despite greater hypocapnia.

The treatment regimen for AMS varies: a dose of 125 milligrams PO twice daily is effective for most individuals, whereas others may

require 250 milligrams PO twice daily. Side effects occur more commonly with higher doses, including peripheral paresthesias and sometimes nausea or drowsiness. Although acetazolamide contains a sulfhydryl moiety, cross-reactivity in those with sulfa antibiotic allergy is uncommon.[12] Nevertheless, individuals with a history of anaphylaxis to sulfa antibiotics should avoid acetazolamide. Treatment should be continued until symptoms of AMS resolve. It can always be restarted if symptoms return. Because the drug inhibits carbonic anhydrase on the tongue, carbonated beverages such as soda or beer may have an altered or "flat" taste.

Although acetazolamide remains the standard of care for the treatment of AMS, a targeted approach focused on symptomatic treatment is a reasonable alternative, especially in those with intolerance or allergy to acetazolamide. Acetaminophen (650 to 1000 milligrams), ibuprofen (600 to 800 milligrams), and aspirin (650 milligrams) are all effective for altitude-related headache. Ondansetron, 4 to 8 milligrams as orally disintegrating tablets every 4 to 6 hours, effectively treats nausea and vomiting associated with AMS and should be the first-line antiemetic in this setting.

Dexamethasone, 4 milligrams PO, IM, or IV every 6 hours, is quite effective for mountain sickness, but is best reserved for cases of moderate to severe AMS because of potential side effects. Given that dexamethasone does not aid acclimatization, some rebound symptoms may follow discontinuation. A short taper period may prevent rebound. It is often clinically useful to provide simultaneous therapy with acetazolamide (to speed acclimatization) and a brief course of dexamethasone (to treat symptoms). Another useful treatment regimen, but one that is not yet validated, is a one-time dose of dexamethasone followed by a course of acetazolamide. Dexamethasone is not useful for prophylaxis, however.[13]

Frequent nighttime awakening is a common nuisance at high altitude. Before bedtime, acetazolamide, 62.5 to 125 milligrams, improves sleep oxygenation and reduces apneic periods, thereby improving sleep quality. Other safe sleep aids that do not cause respiratory depression include zolpidem, eszopiclone, and diphenhydramine (**Table 216-4**).

PREVENTION

Graded ascent with adequate time for acclimatization is the best prevention. A recommendation for those visiting moderate-altitude resorts in the western United States is to spend a night at an intermediate altitude of 1500 to 2000 m (4920 to 6560 ft) (Denver or Salt Lake City) before sleeping at altitudes >2500 m (>8200 ft). Mountaineers and trekkers should avoid abrupt ascent to sleeping altitudes over 3000 m (9840 ft) and allow two nights for each 1000-m (3230-ft) gain in camp altitude starting at 3000 m (9840 ft). Other preventive measures include avoiding overexertion, alcohol, and respiratory depressants.

Graded ascent is not always possible or practical. In such cases, a pharmacologic approach aimed at prevention of AMS may be warranted. The ideal prophylactic drug for AMS would be safe, cheap, and available over the counter given the millions of individuals at risk for AMS. Unfortunately, such a drug does not exist, and each approach has trade-offs.

Prophylactic acetazolamide benefits those with a history of AMS and those with forced rapid ascent to sleeping altitude above 2500 m. It remains the standard of care for prevention. Because acetazolamide prevents AMS by enhancing ventilatory acclimatization, fear of masking serious illness is unwarranted. For prophylactic use, acetazolamide should be started 24 hours before the ascent and should be continued for the first 2 days at altitude. It can be restarted if illness develops. Acetazolamide reduces the symptoms of AMS by approximately 75% in persons ascending rapidly to sleeping altitudes of >2500 m (>8200 ft). The downsides of acetazolamide include the commonly experienced paresthesias and, in rare cases, development of Stevens-Johnson syndrome.[14] An alternative for those with anaphylaxis to sulfa is dexamethasone, 4 milligrams PO every 12 hours, starting the day of ascent and continuing for the first 2 days at altitude.

Several promising recent studies suggest that over-the-counter analgesics such as ibuprofen and acetaminophen are effective for AMS prevention. In one study of 80 individuals ascending above 3800 m (>12,000 ft), ibuprofen was shown to reduce the incidence of AMS from 69% to 43%.[15] One theoretical drawback to ibuprofen is that it may exacerbate high-altitude gastropathy found in some patients at high altitude, theoretically leading to GI bleeding.[16,17] When acetaminophen was compared to ibuprofen, both medicines performed similarly in reducing incidence of AMS.[18] Conflicting evidence exists on the use of *Ginkgo biloba* for AMS prevention. A few studies indicate that a regimen of 100 milligrams twice a day started 3 to 5 days before ascent is effective in preventing AMS, but other studies have shown no benefit.[19,20] Lack of standardization of gingko preparations may explain these conflicting results; the active ingredient is still unknown. Despite

TABLE 216-4 Medications for High-Altitude Illnesses

Agent	Indication	Dosage	Adverse Effects	Comments
Acetazolamide	Prevention of AMS	125–250 milligrams PO twice a day beginning 24 h before ascent and continuing during ascent and for at least 48 h after arrival at highest altitude	Common: paresthesias, polyuria, altered taste of carbonated beverages Less common: drowsiness, nausea	Can be taken episodically for symptoms (speeds acclimatization); no rebound effect; pregnancy category C, avoid in breastfeeding
	Treatment of AMS	250 milligrams PO every 8–12 h		
	Pediatric AMS	5 milligrams/kg/d PO in divided doses every 8–12 h		
	Periodic breathing	125 milligrams PO 4 h before bedtime		
Dexamethasone	Treatment of AMS	4 milligrams every 6 h PO, IM, or IV	Mood changes, hyperglycemia, dyspepsia	Rapidly improves AMS symptoms; can be lifesaving in HACE, may improve HACE enough to facilitate descent; no value in HAPE; pregnancy category C but preferably avoided in pregnancy or breastfeeding
	HACE	8 milligrams initially, then 4 milligrams every 6 h PO, IM, or IV		
	Pediatric HACE	0.15 milligram/kg every 6 h PO, IM, or IV, not to exceed 16 milligrams/d		
Tadalafil	Prevention of HAPE	10 milligrams PO twice a day starting 1 d prior to ascent and continuing for 2–4 d at maximum sleeping altitude	Headache, hypotension (less than with nifedipine), priapism (rare), visual/hearing change or loss (extremely rare)	More effectively blunts hypoxic pulmonary vasoconstriction than sildenafil; better tolerated than nifedipine; pregnancy category B
Nifedipine	Prevention of HAPE	20–30 milligrams extended-release PO every 12 h	Reflex tachycardia, hypotension (uncommon)	
	Treatment of HAPE	30 milligrams extended-release PO every 12 h		No value in AMS or HACE; not necessary if supplemental oxygen available; pregnancy category C

Abbreviations: AMS = acute mountain sickness; HACE = high-altitude cerebral edema; HAPE = high-altitude pulmonary edema.

the variable results, ginkgo is a safe option for those who desire a natural alternative. Neither iron nor budesonide is currently recommended for the prevention of AMS.[21-23]

Preacclimatization Although graded ascent is the most effective means of preventing altitude illness, this strategy is not always feasible. Numerous preacclimatization strategies have been proposed by commercial guiding services with the goal of reducing the incidence of altitude illness and to improve exercise performance while climbing. These preacclimatization protocols use intermittent exposure either to hypobaric hypoxia by use of hypobaric chambers or normobaric hypoxia through commercially available low-oxygen tents or breathing masks. These strategies vary considerably in their use of hypoxic "dose" (simulated altitude), duration of exposure, and overall number of exposures over a period of days. Although many of these strategies induce physiologic responses suggestive of acclimatization, only a few are able to demonstrate a significant decrease in AMS incidence.[24,25] An efficient and effective preacclimatization strategy has yet to be determined.

HIGH-ALTITUDE CEREBRAL EDEMA

HACE is defined by progressive neurologic deterioration or ataxia in an individual who has recently ascended to high altitude. Headache, nausea, and vomiting are common antecedents to HACE but are not always present. HAPE is concomitantly found in roughly half of cases of HACE. The diagnosis should be made clinically and is characterized by altered mental status, ataxia, stupor, and progression to coma if untreated. Raised intracranial pressure can lead to focal neurologic signs such as third or sixth cranial nerve palsies. HACE at intermediate altitudes is exceedingly rare, with reported cases precipitated by severe hypoxia associated with HAPE and/or a preexisting space-occupying cerebral lesion.

Treatment of HACE is oxygen supplementation, descent, and steroid therapy (Tables 216-3 and 216-4)**. Descent is the highest priority.** In acutely ill patients who cannot descend, a combination of steroids, supplemental oxygen, and a hyperbaric bag constitutes optimal therapy, but it is rare that all of these are available. Persons remaining ataxic or confused after descent should be admitted to hospital. The possibility of encephalitis or meningitis, stroke, or subarachnoid hemorrhage should be considered in patients whose condition does not improve with treatment. Typically, the partial pressure of arterial CO_2 is already low and the pH high; thus, further hyperventilation could exacerbate cerebral ischemia. Acetazolamide may be used as an adjunct for acute management in the field. Evidence is lacking for the use of hypertonic saline, loop diuretics, or mannitol in HACE. Coma may persist for days, even for weeks, after evacuation to lower altitude, yet the patient may still recover. Persistent coma is sufficiently unusual that its presence mandates exclusion of other causes of neurologic deterioration. MRI findings of HACE include reversible white matter edema evidenced by increased T2 signal, especially in the splenium of the corpus callosum (**Figure 216-1**).[5] Hemosiderin depositions in the corpus callosum may be detected by MRI for years after a case of HACE; this may be useful in the setting of diagnostic uncertainty.[26]

HIGH-ALTITUDE PULMONARY EDEMA

HAPE accounts for more altitude-related mortality than HACE, since it occurs more frequently. While treatable with the right resources, death occurs due to a failure of early recognition, misdiagnosis, or inability to descend to a lower altitude. The condition is easily reversible with descent and oxygen administration.

The incidence of HAPE varies from <1 in 10,000 skiers in Colorado to 2% to 3% of climbers on Mount Denali. Women appear less susceptible than men. Risk factors include heavy exertion, rapid ascent, cold, excessive salt ingestion, use of a respiratory depressant, a previous history indicating inherent individual susceptibility, and pulmonary hypertension. Genetic factors include diminished lung epithelial sodium channel activity, excessive hypoxic pulmonary hypertension, and immunogenetic factors.[27,28] Pulmonary hypertension from any cause greatly predisposes to HAPE. As a result, HAPE has been reported in patients with intracardiac

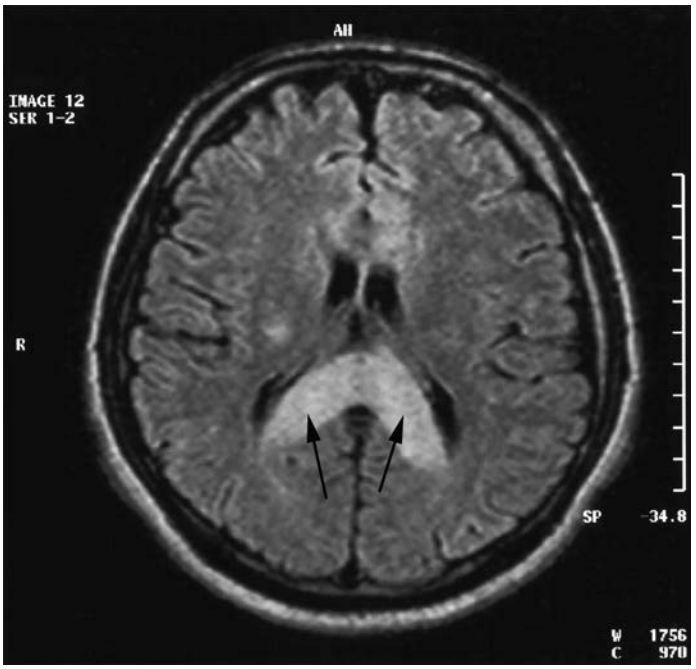


FIGURE 216-1. MRI of a 34-year-old male high-altitude mountaineer with high-altitude cerebral edema. The *arrows* indicate the markedly increased T2 signaling in the splenium of the corpus callosum indicating edema.

shunts (atrial septal defect, patent ductus arteriosus, patent foramen ovale), congenital absent pulmonary artery, drug-induced pulmonary hypertension (phentermine), and chronic venous thrombotic disease.[29,30] Preexisting respiratory infection may predispose children to HAPE.[31]

PATHOPHYSIOLOGY

HAPE is a noncardiogenic, hydrostatic edema; left ventricular function is normal. Left ventricular end-diastolic pressure, pulmonary artery wedge pressures, and left atrial pressures are low to normal, cardiac output is low, and pulmonary vascular resistance and pulmonary artery pressure are markedly elevated. The culprit in HAPE is high microvascular pressure. Pulmonary hypertension is an essential component, but not all persons with pulmonary hypertension develop HAPE. Predisposed individuals have a low hypoxic ventilatory response paired with exaggerated vasoconstriction within the microcirculation of the lung. These individuals tend to experience recurring HAPE on repeated exposures to high altitude. Inflammation is not present early in the course of HAPE, as measured by the chemical composition of bronchoalveolar lavage fluid, but appears as secondary finding as HAPE progresses.[32]

CLINICAL FEATURES

The differential diagnosis of shortness of breath at altitude is broad and includes pneumonia, pulmonary embolism, myocardial infarction, congestive heart failure, mucous plugging, hypoxia with mild exercise intolerance, and bronchitis. Early in the course of HAPE, the individual develops a dry cough, decreased exercise performance, dyspnea on exertion, and increased recovery time from exercise. Localized rales, usually in the right mid-lung field, are common. Resting percent Sa_{O2} is often 10 to 20 points lower than normal for a given altitude and will drop further with exertion. Comparing oxygen saturation of a symptomatic individual to others without dyspneic symptoms can be a useful test in the field and requires only a portable pulse oximeter.[33] Late in the course of the illness, tachycardia, tachypnea, dyspnea at rest, marked weakness, productive cough, cyanosis, and more generalized rales develop. As hypoxemia worsens, altered mental status progresses to coma.

Because early diagnosis is critical, decreased exercise performance or dry cough should raise the suspicion of early HAPE. Progression



FIGURE 216-2. Chest radiograph of an 11-year-old girl with reentry high-altitude pulmonary edema at 2670 m (8750 ft).

of dyspnea with exertion to dyspnea at rest is a hallmark of HAPE. The typical victim is strong and fit (which are factors that facilitate quick ascent) and may or may not have symptoms of AMS before the onset of HAPE. The condition typically worsens at night and is most commonly noticed on or after the second night at a new altitude. Rales are not audible in 15% of persons with HAPE at rest, but can be elicited immediately after a short bout of exercise. Low-grade fever is common, and tachycardia and tachypnea generally correlate with the severity of illness. On cardiac auscultation, a prominent P_2 and right ventricular heave may be appreciated. ECG may reveal right-axis deviation and a right ventricular strain pattern consistent with acute pulmonary hypertension. Chest radiographic findings progress from interstitial to localized alveolar to generalized alveolar infiltrates as the illness progresses from mild to severe (**Figure 216-2**). The absence of infiltrates should alert the clinician to the possibility of an alternative diagnosis. US is accurate to diagnose HAPE.[34]

TREATMENT

The key to successful treatment of HAPE (Tables 216-3 and 216-4) is early recognition; the condition in its early stage is easily reversible. The optimal therapy depends on the environmental setting, evacuation options, availability of oxygen or hyperbaric units, and ease of descent. **Immediate descent is the treatment of choice, but this is not always possible.** During descent, exertion by the patient must be minimized. Reports of patients dying during descent probably are related to overexertion that offsets the benefit of lower altitude. Oxygen supplementation produces excellent results and can completely resolve the pulmonary edema without descent to a lower altitude, but it may require 36 to 72 hours to do so. In settings such as Colorado ski resorts, for example, keeping the patient at altitude but on oxygen may be a practical option. However, the required quantities of oxygen are rarely available to trekking, mountaineering, and back-country skiing groups. Oxygen immediately lowers pulmonary artery pressure and improves arterial oxygenation. Its use is lifesaving when descent is not an option; in such cases, rescue groups should prioritize delivery of oxygen to the victim. As in the treatment of AMS and HACE, the portable hyperbaric bag is a useful adjunct to therapy when immediate descent is not possible.

Bed rest may be adequate for very mild cases, and bed rest with supplemental oxygen may suffice for moderate illness, as long as the safety of the patient can be ensured by the presence of a medical facility, adequate oxygen, or immediate descent capability should the patient's condition deteriorate.[35] Because cold stress elevates pulmonary artery pressure, the patient should be kept warm.

Because oxygen supplementation and descent are so effective, experience with drugs has been limited. Nifedipine, either as a 10-milligram capsule or 30-milligram extended-release formulation, can reduce pulmonary artery pressure by 30% to 50% but increases Sa_{O2} only slightly.[36] Nifedipine, 20 milligrams (slow-release preparation) every 8 hours while ascending, provides effective prophylaxis in those who have previously experienced HAPE.[37] The phosphodiesterase-5 inhibitors sildenafil and tadalafil blunt hypoxic pulmonary vasoconstriction through generation of nitric oxide.[38] Tadalafil, 10 milligrams PO twice a day 24 hours prior to ascent, effectively prevents HAPE in susceptible individuals.[39] These agents may also prove to be useful for treatment of HAPE when oxygen is unavailable. It should be noted that when oxygen is available, additional treatment with drugs such as nifedipine may be unnecessary.[40]

Inhaled salmeterol twice a day reduces the incidence of HAPE by 50% in persons with previous repeat episodes of HAPE.[41] The mechanism is presumed to be upregulation of the epithelial sodium channel and increased clearance of alveolar fluid. Although β-agonists have not yet been studied for the treatment of HAPE, their likely benefit and appealing safety profile make their use for treatment of HAPE reasonable. **However, none of these agents is as effective as oxygen administration or descent, which still remain the treatments of choice.**

Hospitalization is warranted for severe illness that does not respond immediately to descent, especially if cerebral edema is present. Intubation, oxygen supplementation with a high fraction of inspired oxygen (FIO_2), and positive end-expiratory pressure ventilation are rarely required. Antibiotics are indicated for coexisting infection when present. Measurement of brain natriuretic peptide level or echocardiography may be needed to exclude a cardiac component of edema in persons with potential heart failure. Patients with HAPE who do not make the usual rapid improvement or who develop the condition at <2500 m (<8200 ft) should be evaluated for pulmonary emboli or other anatomic abnormalities, such as congenital absence of a pulmonary artery or intracardiac shunt. Echocardiography with bubble contrast material can assess for the presence or absence of shunting from a patent foramen ovale or other cardiac abnormality.

Adequate discharge criteria are progressive clinical and radiographic improvement plus Pa_{O2} of 60 mm Hg or Sa_{O2} of >90%. Residual effects such as fibrosis or abnormal pulmonary function tests have not been reported. An episode of HAPE is not a contraindication to subsequent ascent. However, patients should be counseled regarding the importance of staged ascent and of recognizing early signs and symptoms; prophylaxis with acetazolamide along with tadalafil, sildenafil, or nifedipine may also be wise.

OTHER ALTITUDE SYNDROMES

PERIPHERAL EDEMA

Swelling of the face and distal extremities is common at high altitude. Peripheral edema was reported in 18% of trekkers at 4200 m (13,800 ft) in Nepal and was twice as common in women.[11] It often was associated with AMS but not in all cases. The presence of peripheral edema should raise suspicion of altitude illness and prompt a thorough examination for pulmonary and cerebral edema. The problem can be treated with diuretics but will resolve spontaneously with descent.

HIGH-ALTITUDE RETINOPATHY

Retinal abnormalities described at high altitude include retinal edema, tortuosity and dilatation of retinal veins, disc hyperemia, retinal

hemorrhage, and, rarely, cotton-wool exudates. Retinal hemorrhages are asymptomatic, except for rarely occurring macular hemorrhages, and are not considered an indication for descent unless vision changes are present. They resolve spontaneously in 10 to 14 days. Hemorrhages are common at sleeping altitudes of >5000 m (>16,400 ft) and occur at lower altitudes in persons with altitude illness.

HIGH-ALTITUDE BRONCHITIS

Many unacclimatized persons exercising at altitudes of >2500 m (>8200 ft) develop a dry, hacking cough. Breathing high volumes of dry, cold air may induce respiratory heat loss, secretions, and bronchospasm. As in cough-variant asthma, fast-acting β-agonists (e.g., albuterol) delivered by metered-dose inhaler may provide relief from these coughing spasms. Prophylactic use of long-acting β-agonists and inhaled steroids may be useful for prevention of debilitating cough. Humidification units may help indoors, while wearing a balaclava or a similar thin fabric layer over the mouth and nose may help keep the airway moist and reduce coughing fits.

CHRONIC MOUNTAIN POLYCYTHEMIA/CHRONIC MOUNTAIN SICKNESS

Monge's disease, also called *chronic mountain sickness*, has been recognized in all high-altitude locations of the world. Both long-term high-altitude residents and lowlanders who relocate to high altitude may develop this condition after variable lengths of residence. Males have a much higher incidence, and incidence also increases with age. The disease is characterized by excessive polycythemia for a given altitude, which causes symptoms such as headache, muddled thinking, difficulty sleeping, impaired peripheral circulation, drowsiness, and chest congestion. The diagnosis is based on presence of the characteristic symptoms and a hemoglobin value greater than expected for the altitude, generally >20 to 22 grams/dL.

Therapy includes phlebotomy, relocation to a lower altitude, or home oxygen use. Respiratory stimulants such as acetazolamide (250 milligrams PO twice a day) and medroxyprogesterone acetate (20 to 60 milligrams PO twice per day) also have been used successfully. The response to respiratory stimulants supports the role of hypoventilation in this disorder.

SPECIAL POPULATIONS

INDIVIDUALS WITH ILLNESSES AGGRAVATED BY HIGH ALTITUDE

Chronic Lung Disease Patients with chronic obstructive pulmonary disease ascending to altitude often report increased dyspnea and reduced exercise performance. Patients with hypoxemia, pulmonary hypertension, disordered control of ventilation, and sleep-disordered breathing at sea level may require supplemental oxygen at altitude because of greater alveolar hypoxia. Patients who are oxygen dependent at sea level will need to increase their F_{IO_2}. The required F_{IO_2} can be calculated by multiplying low-altitude F_{IO_2} by the ratio of low-altitude barometric pressure to high-altitude barometric pressure. This will ensure the delivery of the same P_{O_2} as at low altitude.

Cardiovascular Disease A healthy heart and cardiovascular system can tolerate even extreme hypoxia remarkably well. Examinations of numerous ECGs, echocardiograms, heart catheterization findings, and exercise test results demonstrate no cardiac ischemia or cardiac dysfunction in healthy persons at high altitude, even when Pa_{O_2} is <30 mm Hg. Those with atherosclerotic disease may not have the same adaptive capabilities and intuitively seem more likely to experience acute cardiac events. Epidemiologic data, however, do not support this supposition.[42] Long-term residence at high altitude reduces morbidity and mortality from atherosclerotic heart disease, and visitors apparently do not have increased risk of acute myocardial infarction.[43,44] Ischemia may be provoked with less exercise during the first few days at 2500 m (8200 ft) among persons with coronary artery disease; however, after 5 days of acclimatization, patients perform at their sea-level exercise capacity without increased or early-onset angina.[45]

Congestive heart failure may worsen in tourists arriving at the moderate altitude of ski resorts; this is related to fluid retention rather than depressed ventricular function from hypoxia. Therefore, patients with congestive heart failure should maintain or increase their diuretic dosage during travel to high altitude, and clinicians may consider administering low-flow oxygen during sleep to patients with congestive heart failure, at least for the first few nights after arrival at altitude.

Ascent to altitude produces a mild but variable increase in blood pressure in normotensive and hypertensive persons, secondary to increased sympathetic tone. Patients should continue hypertensive medications at altitude, monitor blood pressures, and, in some cases, temporarily adjust medication doses. No data suggest that hypertensive patients have a higher risk for any of the altitude illnesses. Hypertension is not a contraindication to altitude exposure.

Neurologic Syndromes of High Altitude Until recently, most neurologic events at high altitude were attributed to HACE or AMS. Clearly, this is oversimplification. Other syndromes now recognized as related to high altitude include altitude syncope, cerebrovascular spasm (migraine equivalent), cerebral arterial or venous thrombosis (infarct), transient ischemic attack, and cerebral hemorrhage. These syndromes are characterized by more focal neurologic findings than in cerebral edema, although differentiation in the field may be difficult. Previously asymptomatic conditions may be unmasked by exposure to altitude: Space-occupying lesions may be revealed as the brain volume increases; hyperventilation can reveal seizure disorders, and arteriovenous malformations may hemorrhage due to changes in cerebral blood flow. **Focal neurologic signs should be thoroughly evaluated and not attributed to altitude illness.**

Other symptoms may be due to exacerbation or unmasking of underlying disease, such as previously asymptomatic brain tumors and epilepsy. Presumably, space-occupying lesions become symptomatic because of increased brain volume at altitude. Hyperventilation (hypocapnic alkalosis), which is commonly used to induce seizure activity on electroencephalography, may explain unmasking of seizure disorder at altitude. Changes in cerebral blood flow may exacerbate preexisting vascular lesions such as aneurysm or arteriovenous malformation, leading to spontaneous intracerebral hemorrhage.

In the field, it is reasonable to treat neurologic events as if cerebral edema were present, with rapid descent to lower altitude, oxygen supplementation, administration of steroids, and evacuation to hospital if symptoms persist. It is prudent to avoid use of agents that may contribute to hypotension and decrease cerebral perfusion.

Sickle Cell Disease Even the modest cabin altitude of pressurized aircraft (1500 to 2000 m [5000 to 6600 ft]) may cause persons with hemoglobin SC and sickle cell–thalassemia disease to experience vaso-occlusive crisis. Exposure to high altitude thus requires oxygen supplementation for such individuals. At high altitudes, left upper quadrant pain should alert the physician to consider splenic infarction syndrome. Sickle cell trait is not considered a risk factor for most high-altitude conditions, although splenic infarction has been reported.

Pregnancy Pregnant women who live at high altitude have an increased prevalence of hypertension, delivery of low-birth-weight infants, and neonatal hyperbilirubinemia in their offspring. However, although data are limited, an increased incidence of pregnancy complications in lowlanders who visit high altitude has not been reported.[46] The normal Pa_{O_2} of the fetus is 29 to 33 mm Hg, and the mild maternal hypoxia induced by traveling to resort-type altitudes does not generate significantly more hypoxic stress. Few data exist regarding exercise in pregnancy at altitudes of >2500 m (>8200 ft), so a conservative approach should be used. Pregnant women should avoid altitudes—generally speaking, a sleeping altitude of 3000 m (10,000 ft)—at which Sa_{O_2} falls to <85%.[47] Perhaps of more concern than mild hypoxia is the fact that high-altitude locations are often remote from medical (and obstetric) facilities. Patients need to be aware that without access to sophisticated medical care, complications may be associated with more serious consequences. Patients with high-risk pregnancies should stay at low altitude.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 217

Thermal Burns

E. Paul DeKoning

EPIDEMIOLOGY

More than 450,000 individuals in the United States receive medical treatment each year for burn injuries, with 486,000 receiving treatment in 2016 alone.[1] Although 40,000 patients require hospitalization and >60% of those are treated at one of 128 specialized burn centers,[1] the vast majority of burn patients are treated in the acute setting by emergency physicians and discharged with outpatient follow-up.[2,3]

Nearly 70% of burn victims are male,[1] and risk is highest between the ages of 18 and 35 years. Seventy-seven percent of all injuries are accounted for by fire or scalding; 43% of scald injuries occur in children <5 years of age.[4] Although overall survival exceeds 96%, fire, burn, and smoke inhalation still account for approximately 3400 deaths each year in the United States.[1] Elderly patients understandably have a disproportionately higher death rate.[4-6] The risk of death from a major burn increases with larger burn size, older age, the presence of inhalation injury, and female sex.[6]

The Centers for Disease Control and Prevention lists the following groups as being at increased risk of fire-related injuries and death: children ≤4 years of age, adults ≥65 years of age, African Americans and Native Americans, persons living in rural areas, persons living in manufactured homes or substandard housing, and persons living in poverty.[7]

Care of the acute burn–injured patient has improved significantly over the past several decades.[8,9] The rate of hospital admissions has decreased owing to improvements in both the acute care provided in the ED and outpatient care at specialized burn centers. Indeed, over the past 50 years, dramatic improvements in survival after burn injury have been seen, in large part due to specialized burn care.[10] Only approximately 4% of those treated in specialized burn treatment centers die from their injuries or associated complications.[4,11] Additionally, survivors of high total body surface area (>20%) burns tend to have better 5-year survival than those with <20% total body surface area burns, because burn center survivors tend to be younger with fewer comorbidities.[12]

PATHOPHYSIOLOGY

Skin consists of two layers: the epidermis and the dermis (**Figure 217-1**). Skin thickness varies both by age and anatomic location: It is relatively thinner at extremes of age, whereas it is thicker on the palms, soles, and upper back. Thus, the depth and severity of thermal injury vary by both the age of the victim and the anatomic location exposed.

Skin functions as a semipermeable barrier to evaporative water loss, protects against environmental assault, and aids in the control of body temperature, sensation, and excretion. Partial-thickness thermal injury disrupts these barrier functions and contributes to free water deficits. This effect may be significant with moderate to large burns.

Thermal injury results in a spectrum of local and systemic homeostatic disorders that contribute to burn shock (**Table 217-1**). These include disruption of normal cell membrane function, hormonal alterations, acid-base disturbance, hemodynamic changes, and hematologic derangement.

The fluid and electrolyte abnormalities seen in burn shock are largely the result of alterations of cell membrane potential causing intracellular influx of water and sodium and extracellular migration of potassium, secondary to dysfunction of the sodium pump. In patients with burns >60% of total body surface area, depression of cardiac output results in a lack of response to aggressive volume resuscitation. Although disputed by others, Baxter and Shires[13] have explained this phenomenon to be due to circulating myocardial depressants. Systemic vascular resistance is increased. A significant metabolic acidosis may be present even in the early stages of a large burn injury. Massive thermal injury results in an

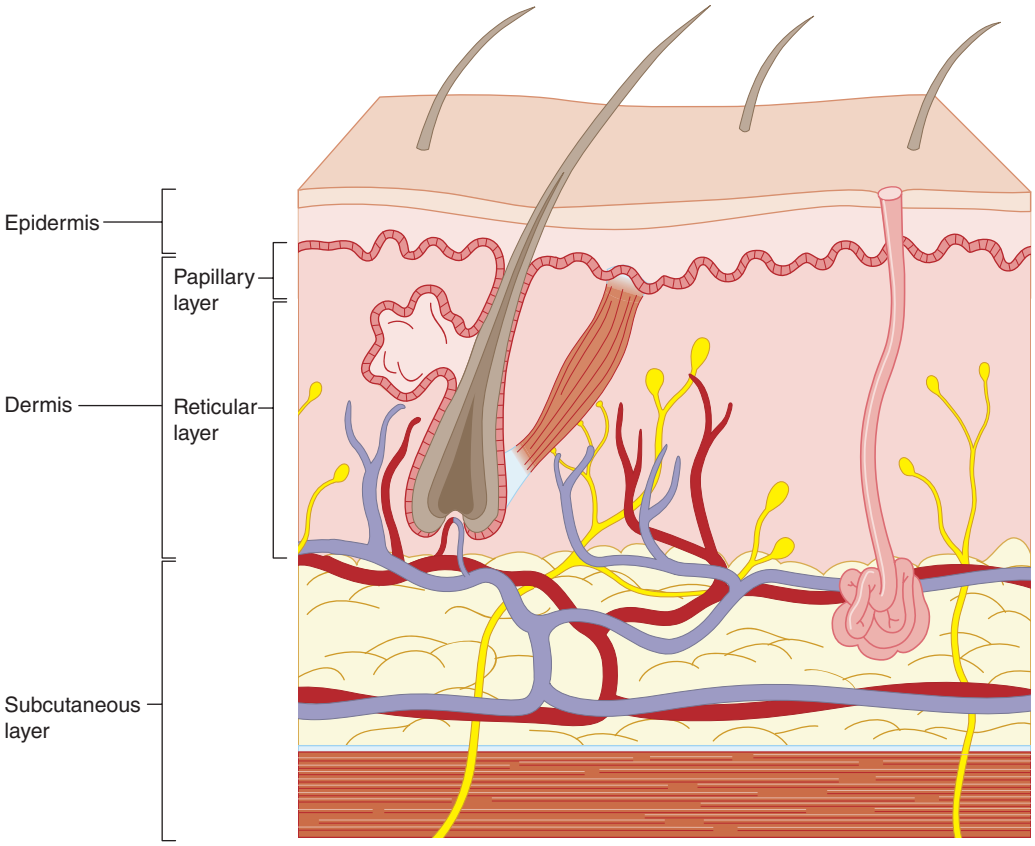


FIGURE 217-1. Layers of the skin.

TABLE 217-1 Physiologic Effects of Thermal Injury

- Disruption of sodium pump
- Intracellular influx of sodium and water
- Extracellular efflux of potassium
- Depression of myocardial contractility (>60% of body surface area burned)
- Increased systemic vascular resistance
- Metabolic acidosis
- Increase in hematocrit and increased blood viscosity
- Secondary anemia from erythrocyte extravasation and destruction
- Local tissue injury
- Release of histamines, kinins, serotonins, arachidonic acids, and free oxygen radicals

increase in hematocrit with increased blood viscosity during the early phase, followed by anemia from erythrocyte extravasation and destruction. Surprisingly, however, transfusion is seldom required for patients with isolated burn injury, and aggressive transfusion has been associated with increased morbidity and mortality.[14-16]

Thermal injury is progressive. Local effects of thermal injury include the liberation of vasoactive substances, disruption of cellular function, and formation of edema. The subsequent systemic response alters the neurohormonal axis and further extends the injury. Implicated in these events are histamine, kinin, serotonin, arachidonic acid metabolites, and free oxygen radicals. These substances exert their primary effects at the local level and cause progression of the burn wound. **Although many factors may influence prognosis, the severity of the burn, the presence of inhalation injury, associated injuries, the patient's age, comorbid conditions, and acute organ system failure are most important.**[5,6] Cell damage occurs at temperatures of >45°C (113°F) owing to denaturation of cellular protein. The size and depth of the resulting burn are functions of the burning agent, its temperature, and the duration of exposure. Burn wounds are described as having three zones: the zone of coagulation, in which tissue is irreversibly destroyed with thrombosis of blood vessels; the zone of stasis, in which there is *stagnation* of the microcirculation; and the zone of hyperemia, in which there is *increased* blood flow. The zone of stasis can become progressively more hypoxemic and ischemic if resuscitation is not adequate. In the zone of hyperemia, there is minimal damage to the cells and spontaneous recovery is likely.

CLINICAL FEATURES

BURN SIZE

Burn size determines fluid resuscitation needs and the majority of decisions for hospital transfer. Burn injury size is quantified as the percentage of body surface area involved.[9] The **Rule of Nines** is a simple and commonly used method to calculate burn size (**Figure 217-2**), It divides the body into segments that are approximately 9% or multiples of 9%, with the perineum forming the remaining 1%. Because of the proportionately larger heads and smaller legs of infants and children, this method must be modified in pediatric burn injury.

A second method assumes that **the area of the back of the patient's hand is approximately 1% of their total body surface area. The number of "hands" that equal the area of the burn can approximate the percentage of body surface area burned.** A third and more precise method uses the **Lund-Browder burn diagram** (**Figure 217-3**). This allows an accurate age-adjusted determination of burn size for a given depth, allowing for the anatomical differences of children.[17]

BURN DEPTH

The depth of a burn has historically been described in degrees: first, second, third, and fourth (**Table 217-2**). However, a classification of burn depth according to the need for surgical intervention has become the accepted approach in burn treatment centers: superficial partial-thickness, deep partial-thickness, and full-thickness burns[8]

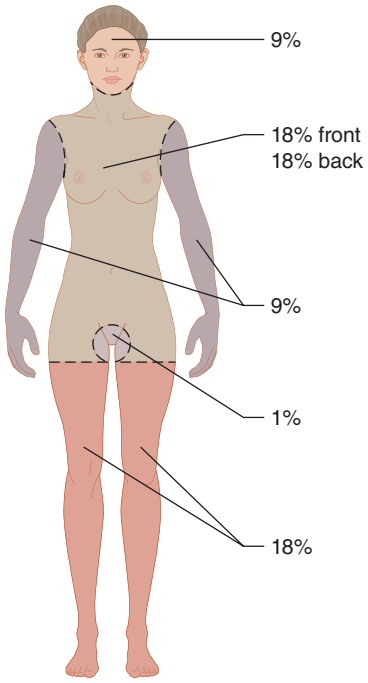
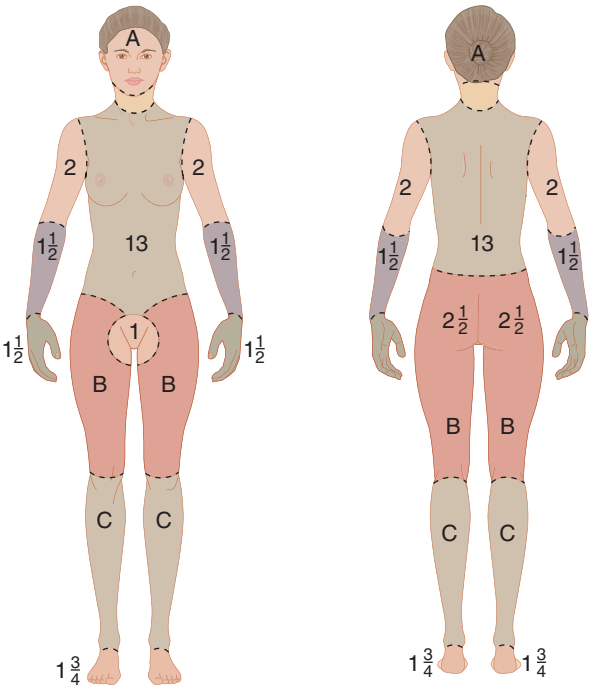


FIGURE 217-2. Rule of Nines diagram for estimation of adult burn size.



Relative percentages of areas affected by growth (age in years)

	0	1	5	10	15	Adult
A: half of head	9½	8½	6½	5½	4½	3½
B: half of thigh	2¾	3¼	4	4¼	4½	4¾
C: half of leg	2½	2½	2¾	3	3¼	3½

Second-degree _____ and

Third-degree _____ =

Total percent burned _____

FIGURE 217-3. Lund-Browder diagram for estimation of burn size.

TABLE 217-2 Burn Depth Features Classified by Degree of Burn

Burn Depth	Histology/Anatomy	Example	Healing
Superficial (first degree)	Epidermis	Sunburn	7 d
	No blisters, painful		
Superficial partial-thickness (superficial second degree)	Epidermis and superficial dermis	Hot water scald	14–21 d, no scar
	Blisters, very painful		
Deep partial-thickness (deep second degree)	Epidermis and deep dermis, sweat glands, and hair follicles	Hot liquid, steam, grease, flame	3–8 wk, permanent scar
	Blisters, very painful		
Full-thickness (third degree)	Entire epidermis and dermis charred, pale, leathery; no pain	Flame	Months, severe scarring, skin grafts necessary
Fourth degree	Entire epidermis and dermis, as well as bone, fat, and/or muscle	Flame	Months, multiple surgeries usually required

(**Table 217-3**). Determination of burn depth requires clinician judgment using commonly observed wound features. There is no objective method of measuring burn depth, and burn wound biopsy is not routine practice.

A superficial burn involves only the epidermal layer of skin. Sunburn is frequently given as an example, even though it is caused by ultraviolet light instead of thermal injury.[18] **The burned skin is red, painful, and tender without blister formation.** Superficial burns usually heal in about 7 days without scarring and require only symptomatic treatment (**Figure 217-4**).

Partial-thickness burns extend into the dermis and are subdivided into superficial partial-thickness (**Figure 217-5**) and deep partial-thickness burns (**Figure 217-6**).

In superficial partial-thickness burns, the epidermis and the superficial dermis (papillary layer) are injured, while the deeper layers of the dermis, hair follicles, and sweat and sebaceous glands are spared. Superficial partial-thickness burns are often caused by hot water scalding. **The skin is blistered, and the exposed dermis is red and moist.** These wounds are exceedingly painful to touch. The dermis is well-perfused with intact capillary refill. Healing typically occurs in 14 to 21 days, scarring is usually minimal, and there is full return of function.

Deep partial-thickness burns extend into the deep dermis (reticular layer) (Figure 217-6). Hair follicles and sweat and sebaceous glands are damaged, but their deeper portions usually survive. Hot liquids (e.g., oil or grease), steam, or flame usually cause this type of injury. **The skin may be blistered, and the exposed dermis is pale white to yellow in color. The burned area does not blanch; it has absent capillary refill and absent pain sensation.** Deep partial-thickness burns may be difficult to distinguish from full-thickness burns. Healing takes 3 weeks to 2 months; scarring is common and related to the depth of the dermal injury. Surgical debridement and skin grafting may be necessary to obtain maximum function.

TABLE 217-3 Burn Depth Features: American Burn Association Burn Classification

Burn Classification	Burn Characteristics	Disposition
Major burn	Partial-thickness >25% BSA, age 10–50 y Partial-thickness >20% BSA, age <10 y or >50 y Full-thickness >10% BSA in anyone Burns involving hands, face, feet, or perineum Burns crossing major joints Circumferential burns of an extremity Burns complicated by inhalation injury Electrical burns Burns complicated by fracture or other trauma Burns in high-risk patients	Burn center treatment
Moderate burn	Partial-thickness 15%–25% BSA, age 10–50 y Partial-thickness 10%–20% BSA, age <10 y or >50 y Full-thickness burns ≤10% BSA in anyone No major burn characteristics present	Hospitalization
Minor burn	Partial-thickness <15% BSA, age 10–50 y Partial-thickness <10% BSA, age <10 y or >50 y Full-thickness <2% in anyone No major burn characteristics present	Outpatient treatment

Abbreviation: BSA = body surface area.

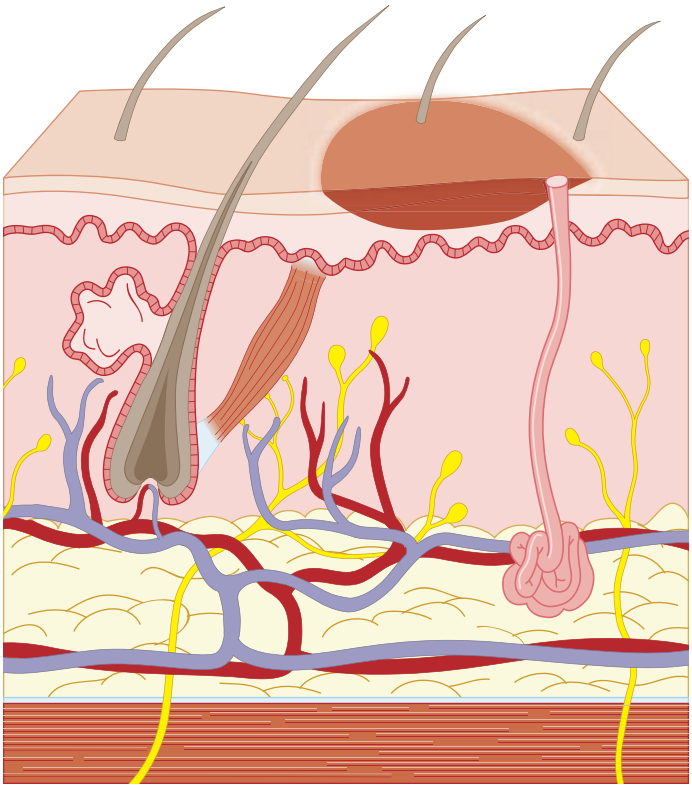


FIGURE 217-4. Superficial burn.

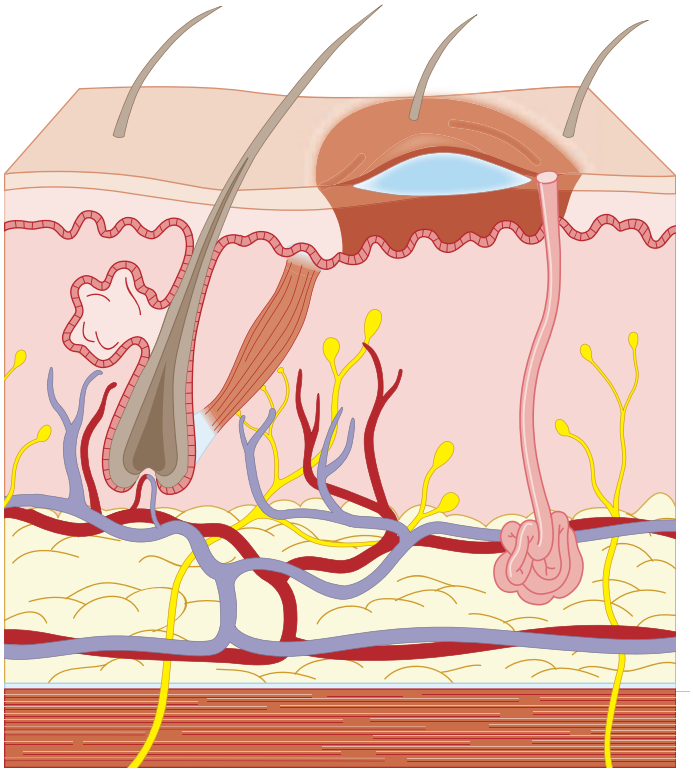


FIGURE 217-5. Superficial partial-thickness burn.

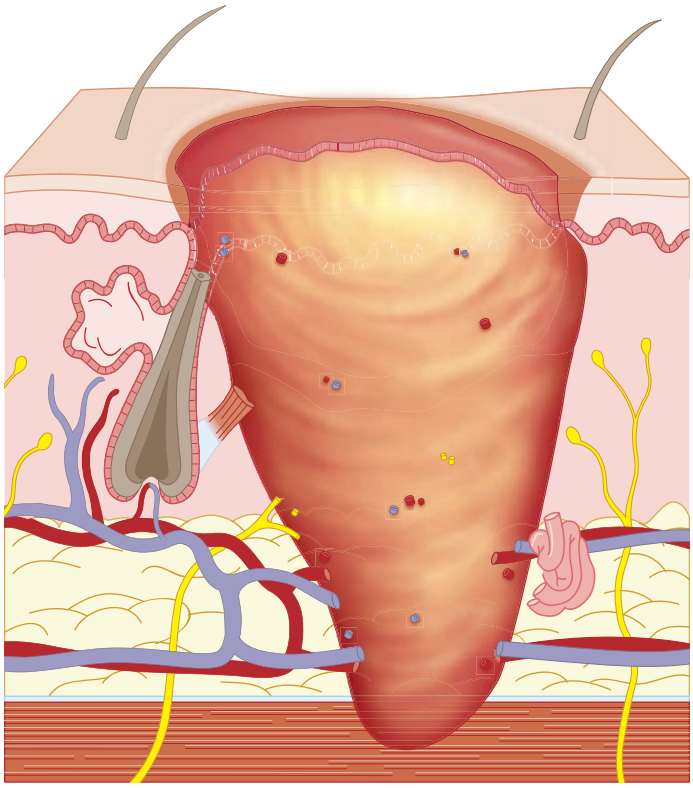


FIGURE 217-7. Full-thickness burn.

Full-thickness burns involve the entire thickness of the skin (**Figure 217-7**). All epidermal and dermal structures are destroyed. These injuries are typically caused by flame, hot oil, steam, or contact with hot objects. **The skin is charred, pale, painless, and leathery.** Because all dermal elements are destroyed, these injuries do not heal spontaneously. Surgical repair and skin grafting are necessary; significant scarring is the norm.

Fourth-degree burns are those that extend through the skin to the subcutaneous fat, muscle, and even bone. These are devastating, life-threatening injuries. Amputation or extensive reconstruction is sometimes required.

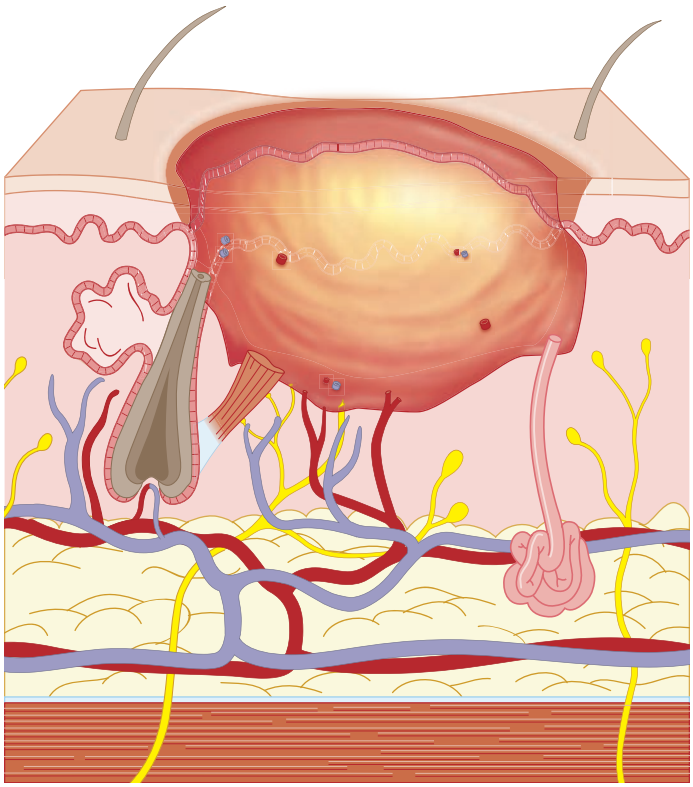


FIGURE 217-6. Deep partial-thickness burn.

BURN CENTER TRANSFER

The American Burn Association provides guidelines for referral to a burn center, in addition to indications based on burn depth (**Table 217-4**).[9,19] Children <10 years of age and adults >50 years are considered high-risk patients. Patients with significant comorbidities, such as heart disease, diabetes, or chronic pulmonary disease, are also likely to require

TABLE 217-4 American Burn Association Burn Unit Referral Criteria

- Full-thickness/third-degree burns in any age group
- Partial thickness burns >10% total body surface area
- Burns involving the face, hands, feet, genitalia, perineum, or major joints
- Electrical burns, including lightning injury
- Chemical burns
- Inhalation injury
- Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
- Burn injury in any patients with concomitant trauma (e.g., fractures) in whom the burn injury poses the greatest risk of morbidity or mortality
- Burn injury in children in hospitals without qualified personnel or equipment to care for children
- Burn injury in patients who will require special social, emotional, or long-term rehabilitative intervention
- Burn injury in children <10 y and adults >50 y of age

prolonged care and should be considered for transfer to a burn unit. Burn severity, underlying medical and social conditions, and the capabilities of the institution initially receiving the patient must all be considered in the decision to transfer the patient to a burn unit.

INHALATION INJURY

As treatment of burn shock and sepsis has improved, inhalation injury has become the main cause of mortality in burn patients. Most fire-related deaths are due to smoke inhalation.[5,6,11] Inhalation injury is associated with closed-space fires and conditions that decrease mentation, such as overdose, alcohol intoxication, drug abuse, and head injury. Exposure to smoke includes exposure to heat, particulate matter, and toxic gases.[20] Direct thermal injury is usually limited to the upper airway; thermal injuries below the level of the vocal cords can occur in cases of steam inhalation.

Smoke contains particulate matter, usually <0.5 μm in size, which is formed from incomplete combustion of organic material. Small particles may reach the terminal bronchioles, where they can initiate an inflammatory reaction that leads to bronchospasm and edema. Toxic inhalants are divided into three large groups: tissue asphyxiants, pulmonary irritants, and systemic toxins.[20] The two major tissue asphyxiants are carbon monoxide and hydrogen cyanide.

Carbon monoxide poisoning is a well-known consequence of smoke inhalation injury. Severe carbon monoxide poisoning produces brain hypoxia and coma. Comatose patients lose airway protective mechanisms, which may result in aspiration and further pulmonary injury. All patients with suspected carbon monoxide exposure should receive 100% oxygen by non-rebreather mask and should be evaluated for hyperbaric oxygen therapy (see Chapter 222, "Carbon Monoxide"). Hydrogen **cyanide** is formed by the combustion of nitrogen-containing polymers such as wool, silk, polyurethane, and vinyl. Cyanide binds to and uncouples mitochondrial oxidative phosphorylation, which leads to profound tissue hypoxia. Specific treatment for cyanide toxicity may be required (see Chapter 204, "Industrial Toxins").

Inhalation injury damages endothelial cells, produces mucosal edema of the small airways, and decreases alveolar surfactant activity, resulting in bronchospasm, airflow obstruction, and atelectasis. Although lower airway edema may not be clinically evident for up to 24 hours, upper airway edema can occur rapidly. Over time, tracheal and bronchial epithelial sloughing occurs. Approximately half of intubated burn patients admitted to burn centers develop acute respiratory distress syndrome.[21] The most recent international guidelines for the management of burn injuries suggest lung-protective strategies including using low tidal volumes in patients with acute respiratory distress syndrome. Specifically, maintaining plateau pressures below 31 cm H_2O and tidal volumes below 7 mL/kg is indicated. Prophylactic antibiotics and corticosteroids are not recommended in inhalation injury.[10] **Therefore, when inhalation injury is present, careful fluid resuscitation guided by hemodynamic monitoring can help avoid pulmonary edema and acute respiratory distress syndrome.**

The initial diagnosis of smoke inhalation is made from a history of exposure to fire in an enclosed space and physical signs that include facial burns, singed nasal hair, soot in the mouth or nose, hoarseness, carbonaceous sputum, and expiratory wheezing. No single method for diagnosing the extent of inhalation injury exists. Measurement of arterial carboxyhemoglobin is used to document prolonged exposure to products of incomplete combustion. The chest radiograph may be normal initially. Bronchoscopy and radionuclide scanning may also be helpful in evaluating the full extent of injury.

Treat suspected inhalation injury **prior to** definitive diagnosis. Provide humidified oxygen (100%) by facemask. Obtain arterial blood gas concentrations, **including carboxyhemoglobin levels**. Control of the upper airway is achieved by prompt endotracheal intubation. Indications for intubation include (1) full-thickness burns of the face or perioral region, (2) circumferential neck burns, (3) acute respiratory distress, (4) progressive hoarseness or air hunger, (5) respiratory depression or altered mental status, and (6) supraglottic edema and inflammation on bronchoscopy. Additionally, consider the patient's anticipated clinical course.

BURN TREATMENT

The management of patients with **moderate to major** burns can be divided into three phases: (1) prehospital care, (2) ED resuscitation and stabilization, and (3) admission or transfer to a specialized burn center.

PREHOSPITAL CARE

The basis of prehospital care of the burn-injured patient consists of the following: (1) stop the burning process; (2) assess and, if necessary, secure the airway; (3) initiate fluid resuscitation; (4) relieve pain; (5) protect the burn wound; and (6) transport the patient to an appropriate facility.

On-site assessment of a burned patient is divided into primary and secondary surveys. In the primary survey, identify and treat immediately life-threatening conditions. Initial management of the burn-injured patient is similar to that of any other trauma patient: airway, breathing, circulation, and cervical spine immobilization where appropriate. During the secondary survey, perform a thorough head-to-toe evaluation.

The patient must be extricated from the burning environment, and burning clothing must be immediately removed. The remainder of the clothing should be removed after the airway, breathing, and circulation are secured. Remove rings, watches, jewelry, and belts because they retain heat and produce a tourniquet-like effect on the extremity, causing ischemia. Give oxygen by facemask. **Pay close attention to the airway: rapid deterioration may occur even when the initial assessment judges the airway to be acceptable.** Consider prophylactic intubation in patients with perioral burns sustained in a closed-space fire. Give IV isotonic crystalloid. Cover the patient with clean sheets to protect the wound. While early cooling can reduce the depth of burn and reduce pain, uncontrolled cooling may result in hypothermia. Provide analgesia according to protocol or with direction of the online medical control physician. Transport the patient to the nearest ED capable of caring for a burn-injured patient or, if none is available, to the nearest ED for stabilization and subsequent transfer.

ED MANAGEMENT

INITIAL ASSESSMENT

Obtain a directed history from the patient and EMS personnel to determine the burning agent(s), involvement of chemicals, the duration of exposure, and if the injury was sustained in an open or enclosed space. Assess for loss of consciousness, risk of blast injury from explosion, contact with electricity, or other trauma. Assess the adequacy of, or need for, cervical immobilization. Obtain the general history, including past medical and surgical illnesses, chronic disease, allergies, medications, and tetanus immunization status.

Quickly assess the patient's respiration and circulation and initiate stabilization (**Table 217-5**). Examine the patient for signs of inhalation injury, as evidenced by respiratory distress, facial burns, carbonaceous sputum, singed nasal hair, and soot in the mouth. **If there is any evidence of airway compromise with swelling of the neck, burns inside the mouth, or wheezing, perform early endotracheal intubation.**

Assess the adequacy of circulation by noting the blood pressure, pulse rate, capillary refill time, mental status, and urinary output, keeping in mind that due to the catecholamine response associated with burn injury, a heart rate of 100 to 120 beats/min is considered within normal limits for adults.[10] Insert IV lines in unburned areas, but when this is not possible, a burned area can be used and resuscitation started according to a burn fluid resuscitation formula.

During the secondary examination, perform a head-to-toe assessment, including examination of the eye for corneal burns. Estimate and record the size and depth of the burn injury. In patients with partial-thickness burns of >20% of body surface area, nasogastric tube insertion is routinely required due to frequent development of ileus. Insert a urinary catheter to measure urinary output and to prevent urinary retention in patients with perineal burns.

TABLE 217-5 ED Care of Patients With Major Burns

Airway	Breathing	Circulation	Adjuncts
Reevaluation of airway	Continuous pulse oximetry with supplemental oxygen	Establishment of two large-bore peripheral IV lines in unburned skin	Placement of Foley catheter
Early intubation for any sign of breathing difficulty, airway burn, swelling, or suspected inhalation injury			Insertion of nasogastric tube
	Determination of carboxyhemoglobin level	IV administration of lactated Ringer's solution using Parkland or other burn resuscitation formula	Administration of tetanus booster
	Bronchoscopy if inhalation injury is a concern	Cardiac monitoring	Assessment for other trauma using Advanced Trauma Life Support guidelines
	Mechanical ventilation as needed		Pain control

Routine laboratory tests, including a CBC and measurement of electrolyte, BUN, creatinine, and glucose levels, should be performed. In patients with moderate or severe burns or suspected inhalation injury, obtain an arterial blood gas analysis, carboxyhemoglobin level, serum creatine kinase, urinalysis for myoglobin, chest radiograph, and ECG. Fiberoptic bronchoscopy is indicated in suspected inhalation injury and in intubated patients for both diagnostic and therapeutic purposes. Additional radiographs should be taken as indicated for other suspected trauma.

Treat suspected inhalation injury with humidified 100% oxygen, intubation and ventilation, bronchodilators, lung-protective vent settings,[10] and aggressive pulmonary toilet; hyperbaric oxygen may be necessary for severe carbon monoxide poisoning.

Burn injury in the pregnant woman is associated with significant morbidity to mother and child. The outcome of the pregnancy is determined by the extent of injury to the mother. Spontaneous termination of pregnancy is common in large–body surface area burns. Resuscitation requirements may exceed those estimated using common guidelines. Fetal monitoring and early consultation with the obstetrician and burn specialist are recommended.

FLUID RESUSCITATION

Although the importance of early fluid resuscitation is supported by clinical experience,[22,23] no consensus exists on the appropriate assessment of resuscitation and its effect on outcome.[22] Additionally, overresuscitation is not without consequence. In general, resuscitation should be guided by monitoring cardiorespiratory status and urine output rather than strict adherence to a formula. **The following formulas are a guide for fluid resuscitation of the burn-injured patient. Monitor and adjust according to individual patient response.**

The Baxter or Parkland formula is likely the most widely used thermal injury resuscitation regimen in North America.[8,9] This formula calls for 4 mL of lactated Ringer's solution multiplied by the percentage of body surface area burned (partial- and full-thickness burns only) multiplied by patient body weight in kilograms. Half of the total is administered in the first 8 hours after injury and the remainder during the following 16 hours (**Table 217-6**). Volumes may be large, and hemodynamic monitoring techniques should be used to protect against inadvertent volume overload.

TABLE 217-6 Parkland Formula for Fluid Resuscitation

Adults

- LR 4 mL × weight (kg) × % BSA burned* over initial 24 h
- Half over the first 8 h from the time of burn
- Other half over the subsequent 16 h
- Example: 70-kg adult with 40% second- and third-degree burns: 4 mL × 70 kg × 40 = 11,200 mL over 24 h

Children

- LR 3 mL × weight (kg) × % BSA burned* over initial 24 h plus maintenance
- Half over the first 8 h from the time of burn
- Other half over the subsequent 16 h

Abbreviations: BSA = body surface area; LR = lactated Ringer's solution.

*Partial- and full-thickness burns only.

Patients with thermal injury and concomitant multisystem trauma and those with inhalation injuries generally require fluid resuscitation in excess of calculated needs. Burn patients with preexisting cardiac or pulmonary disease require much greater attention to fluid management. Monitor fluid resuscitation closely by frequent assessment of vital signs, cerebral and skin perfusion, pulmonary status, and urinary output, as well as hemodynamic monitoring. Urine output should be 0.5 to 1.0 mL/kg/h.

Because the ED is primarily responsible for initial fluid resuscitation, early discussion with burn specialists may be helpful in avoiding under- or overresuscitation. Patients with major burns can quickly receive excessive IV fluid during the prehospital and ED phases, particularly if two large-bore peripheral catheters are in place with fluid infusing at a wide-open rate. Document total fluid infused and titrate infusion to the patient's response. Clear documentation of fluid resuscitation should accompany all patients transferred to burn centers.

There are several methods of calculating fluid resuscitation for infants and children. The Parkland formula can be modified to maintain a urinary output of 1 mL/kg/h. Alternatively, a pediatric maintenance rate for 24 hours can be calculated, and an additional 2 to 4 mL/kg multiplied by percentage of body surface area burned is then added to the total. The entire amount is infused over the first 24 hours. In children weighing <25 kg, a goal urine output of 1.0 mL/kg/h is necessary. Add 5% dextrose to maintenance fluids for children weighing <20 kg due to smaller glycogen stores.[8]

Two additions or modifications to isotonic crystalloid resuscitation have been studied: adjuvant colloid and hypertonic saline. However, neither improves patient outcome. Adjuvant colloid given along with isotonic crystalloid resuscitation is not beneficial and is associated with decreased glomerular filtration rate.[24] Discussion of the use of adjuvant colloid continues, but it is used very little in North America and the United Kingdom,[25] although Israeli investigators have reported favorable results with the addition of colloid to their burn formulas.[26] Use of hypertonic saline has been associated with an increased rate of renal failure and death.[27] In an effort to decrease burn edema, protein loss, and abdominal compartment syndrome, investigators have also studied the efficacy of *permissive hypovolemia* in reducing burn edema and the multiple organ dysfunction that follows.[28] This practice necessitates invasive monitoring and is of interest, but it is not standard of care and should not be used in ED resuscitation at this time.

Electrical injuries, incineration burns, and associated crush injuries may produce rhabdomyolysis and myoglobinuria, leading to renal failure. Acute renal failure occurs in approximately 15% of patients admitted to burn centers and is associated with severe burns (mean body surface area involvement of 48%).[29] Therapy to limit renal damage from myoglobinuria should be initiated as outlined in Chapter 89, "Rhabdomyolysis."

WOUND CARE

After evaluation and resuscitation of the patient, attend to burn wounds.[2] Initially, wounds are best covered with a clean, dry sheet. Later, small burns can be covered with a moist saline-soaked dressing while the patient is awaiting admission or transfer. The soothing effect of cooling on burns is most likely due to local vasoconstriction. Cooling stabilizes mast cells and reduces histamine release, kinin formation, and thromboxane B_2 production. For large burns, sterile drapes are



FIGURE 217-8. Escharotomy of the hand.

preferred, because application of saline-soaked dressings to a large area can cause hypothermia.

Consult the admitting service or burn center early. Avoid the use of antiseptic dressings in the ED, because the admitting service will need to assess the wound. Wound care for transferred patients should be discussed with the accepting burn center. Do not delay transfer for wound debridement. For transferred patients, the referring facility should follow the accepting regional burn center's treatment protocol if available.

Escharotomy Patients with circumferential deep burns of the limbs may develop compromise of the distal circulation, particularly after initiation of resuscitation. The distal vascular status of such patients must be monitored closely, including pulses, capillary refill, pulse oximetry, and skin temperature. Doppler flow testing may likewise be useful. If vascular compromise is evident, escharotomy is indicated. The eschar is incised with a scalpel to the level of the fat on the mid-lateral portion of the limb, using care to avoid incising the fascia (i.e., fasciotomy). Elevated compartment pressures can be clinically evident. The incision may be extended to the hand and fingers (**Figure 217-8**). Escharotomy may provoke substantial soft tissue bleeding. Consider consultation by phone with a burn surgeon.

If there are circumferential burns of the chest and neck, eschar may restrict ventilation. An escharotomy of the chest wall should be performed to allow adequate ventilation. Incisions are made at the anterior axillary line from the level of the second rib to the level of the twelfth rib. These two incisions should be joined transversely so the chest wall can expand (**Figure 217-9**).

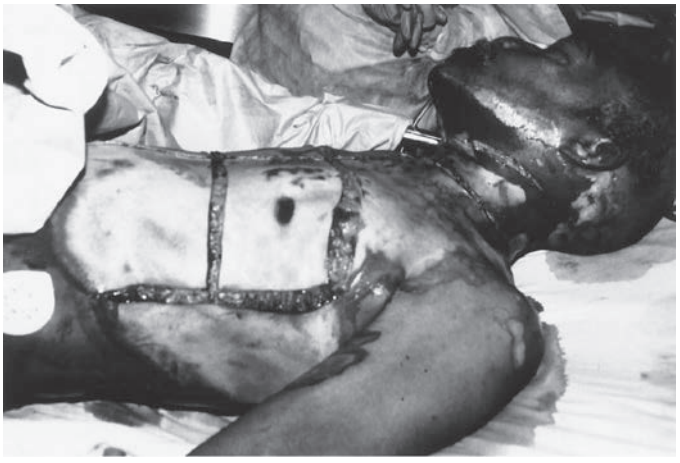


FIGURE 217-9. Escharotomy of the chest wall.

PAIN CONTROL

Burn injuries are exceedingly painful, and superficial partial-thickness burns are the most painful. Burn injury not only makes an otherwise already injured area and surrounding tissue more painful, but also causes hyperalgesia, chiefly mediated by A fibers. Local cooling may be soothing but does not provide pain control and can cause hypothermia;[30] additional pain management should be provided.

During the acute phase, the preferred route for most medication is IV. Opioids (e.g., morphine, fentanyl, hydromorphone) are the mainstay of treatment, and relatively large dosages may be required. Anxiolytic agents may also be given. Ensure adequate analgesia for patients being discharged. Achieving adequate pain control is required for patients being considered for discharge.

CARE OF MINOR BURNS

Minor burns typically qualify for ambulatory care. Minor burns should be isolated, should not cross joints or be circumferential, and should not meet criteria for burn center care. Treatment of minor burns is provided in **Table 217-7**. Even in patients with burn injury <10% of body surface area, patients at the extremes of age and/or patients with significant comorbidities, challenging social situations, or inadequate pain control may require inpatient care and possibly transfer to a burn center. Care of minor burns in discharged patients requires appropriate wound care instructions, adequate pain control, and coordination between the ED and the physician who will see the patient in follow-up.[2]

Because burns are painful, appropriate analgesia is required. After appropriate analgesia, clean the burn wound with mild soap and water or dilute antiseptic solution. Debride ruptured blisters. Also debride large intact blisters or those over very mobile joints. Small blisters on nonmobile areas should be left intact. Tetanus immunization status should be assessed, and tetanus toxoid and/or immunoglobulin should be administered as needed.

Topical antimicrobials (antiseptics or antibiotics) play an important role in reducing bacterial colonization and enhancing the rate of healing in burns.[8,9] A wide variety of topical agents and specialized dressings are commonly used for minor burns. A mainstay of treatment has traditionally been 1% silver sulfadiazine due to its easy application and minimal toxicity. However, three meta-analyses found delayed healing in burns treated with silver sulfadiazine compared to newer dressings.[32-34] Newer dressings require less frequent dressing changes and are associated with reduced pain.[32] Do not use silver sulfadiazine on the face because it can stain the skin gray. Silver sulfadiazine should not be used in infants less than 2 months of age.

For the face or other small minor burns, recommended topical agents include bacitracin and triple-antibiotic (neomycin, polymyxin B, and bacitracin zinc) ointments.[31] Although 8.5% mafenide acetate cream and 0.2% nitrofurazone ointment are available for topical application, these are not good choices for treatment of large burns in an outpatient setting. Mafenide penetrates the eschar well and is useful in treating patients with invasive infections, but it is a carbonic anhydrase inhibitor and can cause metabolic acidosis. Nitrofurazone is supplied in a polyethylene glycol vehicle that can be toxic if absorbed in patients with

TABLE 217-7 ED Care of Minor Burns

- Provide appropriate analgesics before burn care and for outpatient use
- Cleanse burn with mild soap and water or dilute antiseptic solution
- Debride wound as needed
- *Apply topical antimicrobial agent or dressing:
  - Bacitracin ointment
  - Triple-antibiotic ointment (neomycin, polymyxin B, bacitracin zinc)
- Consider use of synthetic, solid, or biological dressings
- Provide detailed burn care instructions with follow-up in 24–48 h

*Consider contacting the director of the local or regional burn center to identify the center's preferred topical antimicrobial agent and/or synthetic occlusive dressing to integrate local and tertiary burn care.

compromised renal function. Mafenide and nitrofurazone have little utility in the ED management of the acutely burn-injured patient. **Dressings should ideally be changed twice daily, gently removing residual ointment, for as long as the wounds continue to weep, then daily until healing is complete.**[31]

Synthetic occlusive, solid, or biological dressings are alternative methods of managing partial-thickness burns in outpatients. Wounds are cleansed and debrided prior to application of these dressings. Examples include clear occlusive synthetics, foam or hydro-fiber dressings impregnated with antiseptics, or treated biologic membranes. Consider contacting the director of the local or regional burn center to identify the center's preferred topical antimicrobial agent and/or specific burn dressing to integrate local and tertiary burn care. The goal is for the dressing to act as artificial skin. Wounds should be reevaluated at 24 to 48 hours. Wounds treated with synthetic solid, or biological dressings are well tolerated by patients, require few dressing changes, and heal with good appearance.[31]

Reassess burn wounds at 24 to 48 hours for depth and extent of burn. Explain the follow-up visit schedule and prescribe analgesics. Discharge instructions should include home burn care, pain control, and the symptoms and signs of infection. Burned extremities should be elevated for 24 to 48 hours to prevent edema. Advise patients to return to the ED with signs or symptoms of infection or if pain is inadequately controlled. Patients with deep partial-thickness, full-thickness, and mixed-thickness burns not requiring admission should be referred to a plastic surgeon or burn care specialist in 2 to 4 days for reevaluation and consideration for skin grafting. Patients with self-inflicted burns have additional social and psychological needs that must be addressed either during inpatient admission or prior to discharge from the ED. They have been associated with substance abuse and decreased likelihood of follow-up.[35] Consider psychiatric evaluation early if self-harm is suspected.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 218

Chemical Burns

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Michael Lynch

INTRODUCTION AND EPIDEMIOLOGY

More than 25,000 products can produce chemical burns. Most exposures occur occupationally, but home exposures are common as well. As few as 10% of all burn center admissions are the result of chemical burns; however, the morbidity and mortality are high and may account for as many as 30% of all burn deaths.[1,2] Burn injuries from corrosives, mostly to the face and neck, are unfortunately a common and growing method of assault in low- and middle-income countries. Long-term psychological and physical effects are debilitating.[3] Careful individual attention is required for chemical burn treatment due to the nature of concomitant tissue injury as well as chemical exposure.

PATHOPHYSIOLOGY

The skin is a barrier and transition zone between the internal and external environments. Although the outer stratum corneum layer of the skin functions as an excellent barrier against many chemicals, some penetrate it readily. Chemicals can produce burns, dermatitis, allergic reaction, thermal injury, and/or systemic toxicity.

Most chemicals produce tissue damage by their chemical reaction rather than by thermal injury. Certainly, some chemicals produce significant heat by means of an exothermic reaction. However, most skin damage is the result of the chemical's unique characteristics.

TABLE 218-1 Factors Influencing Tissue Damage

- Duration of contact
- Concentration of agent
- Quantity of agent
- Mechanism of action
- Extent of penetration

Unlike thermal burns, chemical burn injuries require tailored evaluations and treatments based on the specific agent involved. Multiple factors influence tissue damage and percutaneous absorption of chemicals (**Tables 218-1** and **218-2**).

Most chemical burns are caused by acids or alkalis. At similar volumes and manner of contact, alkalis usually produce far more tissue damage than acids. **Acids tend to cause coagulation necrosis with protein precipitation forming a tough leathery eschar.** The eschar typically limits deeper penetration of the agent. **Alkalis produce liquefaction necrosis and saponification of lipids.** The result is a poor barrier to chemical penetration allowing deeper burns and persistent tissue injury. Other chemical injuries occur by various pathophysiologic mechanisms. Some chemical agents cause injury by more than one mechanism (**Table 218-3**).

Death early after severe chemical burns is usually related to hypotension, acute renal failure, and hypovolemic shock. However, systemic toxicity and subsequent morbidity and mortality may also occur if chemicals are absorbed. Acidosis, hypotension, hyperkalemia, dysrhythmia, and shock can occur with systemic absorption of certain caustics (**Table 218-4**).

GENERAL APPROACH TO CHEMICAL BURNS

The initial goal of treatment is to remove the patient from the exposure and prevent any further chemical contact.[4] If not performed prior to arrival, remove all exposed clothing immediately. With few exceptions, aggressive large-volume irrigation with water is the cornerstone of initial treatment.[4] Chemical agents will continue to damage tissue until they are removed or inactivated. Dry chemical particles such as lime should be brushed away before irrigation.[5] Sodium metal and related compounds should be initially covered with mineral oil or excised, because water can cause a severe exothermic reaction.[6] Dilution of phenol (carbolic acid) with water may enhance penetration.[5] **For the most part, however, use of water or saline to irrigate a chemical burn should not be delayed while searching for other treatment agents and should ideally begin immediately at the scene of the accident.**[4,5] Almost universally, earlier irrigation means a better prognosis. New amphoteric and hypertonic chelating agents offer promise as more effective irrigation solutions for chemical burns as more evidence becomes available.[7]

Hospital personnel should maintain universal precautions while decontamination is ongoing. At the very minimum, mask, face shield, chemical-resistant gown, gloves, and water-impervious boots should be worn.

The amount of elapsed time to initiate dilution or removal of chemical agents is directly related to the eventual depth and degree of injury.[5] The time required for irrigation varies. Severe alkali burns may require

TABLE 218-2 Factors Influencing Percutaneous Absorption of Chemicals

Body site

- Areas of thin skin (i.e., genitalia, face, and skinfolds are particularly vulnerable)
- Amount of surface area

Integrity of skin

- Increased vulnerability: traumatized skin, elderly skin, dehydration, inflammation

Nature of the chemical

- Lipid solubility, pH, concentration

Duration of contact

- Poor irrigation, chemical-soaked garments, occlusive dressings

TABLE 218-3 Classification of Chemicals

Classification of Chemical Damage	Mechanism of Injury
Acids	Protein denaturation as proton donors
Alkalis	Protein denaturation as proton acceptors
Organic solvents	Disruption of cellular membranes
Inorganic solvents	Scavenge ions and salt production within tissues

several hours of irrigation. Use pH indicator paper to determine continued presence of alkali or acid in burn wounds and possible need for further irrigation. Irrigation should continue until pH is neutral or near neutral.

Although thermal energy is produced in an exothermic reaction when using water irrigation, copious amounts of water will decrease the rate and intensity of the chemical reaction and dissipate the heat.[8] Continue irrigation at a gentle flow to avoid continued skin contact with chemicals. After irrigation and debridement of remaining particles and devitalized tissue, apply topical antimicrobial agents to affected areas, and provide tetanus immunization as needed.[1] Other than measures specific for a particular chemical burn, treatment following initial therapy is similar to that of thermal burns (**Table 218-5**).[5] Aggressive fluid replacement is needed if extensive chemical burns are sustained. Analgesics may be needed, and in the case of allergic responses to chemicals, epinephrine, antihistamines, and steroids may be required.

ACID BURNS

Perform a complete examination of a patient with a significant chemical acid burn to the skin because acids may also cause respiratory and mucous membrane irritation. Furthermore, skin absorption of some compounds may occur and result in systemic illness.

Apart from hydrofluoric acid, strong acids produce coagulation necrosis from the denaturation of proteins in the superficial tissue. Injury severity is related to the physical characteristics of the acid. Most substances with a pH <2 are strong corrosives. Other important tissue-damaging properties of acids include concentration, molarity, and complexing affinity for hydroxyl ions. The higher each of these factors is, the greater is the tissue damage. **Contact time with the skin is the most important chemical burn feature that healthcare professionals may alter.** For example, instantaneous skin decontamination of 18M sulfuric acid will cause no burn, but a 1-minute exposure can cause full-thickness skin damage.

ACETIC ACID

The dilute (<40%) acetic acid solution found in hair-wave neutralizer solutions is perhaps the most common cause of chemical burns to the scalp in women. Prolonged contact, especially with an already damaged scalp, can cause a partial-thickness burn that heals slowly and is prone to infection. Initial treatment is copious water irrigation. Oral antibiotics should be prescribed if the scalp burn has created open skin lesions.

TABLE 218-4 Systemic Effects Associated With Chemical Burns

Chemical	Systemic Toxicity
Hydrofluoric acid	Hypocalcemia, hypomagnesemia, hyperkalemia, cardiac arrhythmias, sudden death
Tannic acid, chromic acid, formic acid, picric acid, phosphorus	Hepatic necrosis, nephrotoxicity
Cresol	Methemoglobinemia, massive hemolysis, multiple organ failure
Gasoline	Severe pulmonary, cardiovascular, neurologic, renal, and hepatic complications
Phenol (carbolic acid)	Cardiovascular and CNS toxicity
Sodium nitrate, potassium nitrate	Severe methemoglobinemia with refractory cyanosis
Dichromate solution	Liver failure, acute renal failure, death despite hemodialysis

CARBOLIC ACID (PHENOL)

Phenol (carbolic acid), a corrosive organic acid used widely in industry and medicine, denatures proteins and causes chemical burns characterized by a relatively painless white or brown coagulum. Paradoxically, dilute phenol penetrates tissue more readily than the concentrated form. Systemic absorption may result in life-threatening cardiac dysrhythmias or seizures. Although commercially available in concentrations up to 90%, even dilute solutions of 1% to 2% phenol may cause a burn if contact is prolonged or extensive. Chemically related phenolic compounds that induce skin damage include cresol, creosote, and cresylic acid.

Coagulation necrosis of the involved area is common. Necrotic tissue may delay absorption temporarily, but phenol may become entrapped under the eschar. Remove contaminated clothing and begin water irrigation immediately. Water lavage alone may not be totally effective, because the necrotic coagulum inhibits water penetration to the deeper layers.

Decontamination is more effective using an undiluted polyethylene glycol solution of molecular weight 200 to 400 or by a gentle wash with isopropyl alcohol. **An isopropyl alcohol rinse is equivalent to polyethylene glycol in removing phenol.**[5,9] Either irrigation solution reduces the extent of cutaneous corrosion and decreases systemic toxicity. If neither polyethylene glycol nor isopropyl alcohol is available in adequate supplies, large volumes of water should be used.

CHROMIC ACID

Chromium hexavalent compounds (Cr^{6+}) are powerful oxidizers. The chromate ion in chromic acid produces a chronic penetrating ulcerating lesion of the skin. Generalized exposure to powdered chromic acid can result in conjunctivitis, lacrimation, and ulceration of the nasal septum. Systemic chromium toxicity can cause liver or renal failure, GI bleeding, coagulopathy, and CNS disturbances. Significant symptoms may occur after only 1% to 2% body surface area burns. **A 10% body surface area cutaneous burn caused by chromic acid can be fatal due to systemic toxicity.** Any acute skin exposure to chromic acid should be treated with copious water irrigation and observation for systemic effects. Aggressive excision is the best method for prevention of systemic effects because depth of the burn is difficult to determine and absorption of chromium may continue after irrigation.[10]

FORMIC ACID

Formic acid in 60% solution is used by acrylate glue makers, cellulose formate workers, and tanning workers. Formic acid produces coagulation necrosis. Systemic effects, including decreased respiration, anion gap metabolic acidosis, and hemolysis, have been reported.[11] Treatment includes immediate decontamination and irrigation with water.[5] Systemic toxicity may require IV sodium bicarbonate for the metabolic acidosis or exchange transfusions for severe hemolysis.

HYDROCHLORIC AND SULFURIC ACIDS

The dermal toxicity of hydrochloric acid and sulfuric acid is so well recognized that early decontamination and water irrigation usually prevent severe burns to the skin. These acids can burn the skin dark brown or black. Toilet bowl cleaners may contain 80% solutions of sulfuric acid, and some drain cleaners may be 95% to 99% sulfuric acid solutions. Munitions, chemical, and fertilizer manufacturers commonly use 95% to 98% sulfuric acid solutions in their industrial processes. Automobile battery fluid is 25% sulfuric acid. Most household bleaches are only 3% to 6% hypochlorite solutions, which, although acidic, cause little damage unless they are in contact with skin for a prolonged time. Treatment is the same as for formic acid burns.

HYDROFLUORIC ACID

Hydrofluoric acid is used in the production of high-octane fuel, glass etching, semiconductors, microelectronics/microinstruments,

TABLE 218-5 Treatment of Select Chemical Burns

Chemical	Treatment	Comments
Acids		
All acid burns require prompt decontamination and copious irrigation with water.		
Acetic acid	Copious irrigation	Consider systemic antibiotics for extensive scalp burns.
Phenol (carbolic acid)	Copious irrigation Sponge with undiluted polyethylene glycol of molecular weight 200–400	Isopropyl alcohol may also be used.
Chromic acid	Copious irrigation	Observe for systemic toxicity.
Formic acid	Copious irrigation	Dialysis may be needed for severe toxicity.
Hydrofluoric acid	Copious irrigation 10% calcium gluconate intradermal for severe cases	Consider intradermal injection of 10% calcium gluconate or intra-arterial calcium gluconate for severe cases. Monitor serum calcium and magnesium in severe exposure.
	Topical calcium gluconate gel, 2.5% for mild cases	25 mL of 10% calcium gluconate in 75 mL of sterile water-soluble lubricant (K-Y jelly or US jelly)
Nitric acid	Copious irrigation	Consult with burn specialist.
Oxalic acid	Copious irrigation	Evaluate serum electrolytes and renal function.
	IV calcium may be required	Cardiac monitoring for serious dermal exposure
Alkalis		
All alkali burns require prompt decontamination and copious, prolonged irrigation with water.		
Portland cement	Prolonged copious irrigation	May need to remove cement particles with a brush, such as a preoperative scrubbing brush
Elemental Metals		
Water is generally contraindicated in extinguishing burning metal fragments embedded in the skin.		
Elemental metals (sodium, lithium, potassium, magnesium, aluminum, and calcium)	Cover metal fragments with sand, foam from a class D fire extinguisher, or mineral oil Excise metal fragments that cannot be wiped away	
Hydrocarbons		
Gasoline	Decontamination	
Tar	Cool before removal Remove using antibiotic ointment containing polyoxylene sorbitan (polysorbate)	Baby oil can be used.
Vesicants		
Mustards	Decontaminate Copious irrigation	If limited water supply, adsorbent powders (flour, talcum powder, fuller's earth) can be applied to the mustard and then wiped away with a moist towel.
Reducing Agents		
Alkyl mercury compounds	Copious irrigation Debride, drain, and copiously irrigate blisters	Blister fluid is high in metallic mercury content.
Lacrimators		
Tear gas	Copious irrigation	May cause respiratory symptoms if inhaled
Pepper spray	Copious irrigation	May cause respiratory symptoms if inhaled
Miscellaneous		
White phosphorus	Remove clothing Copious irrigation; keep exposed skin areas wet or submerged until all particles have been removed due to risk of ignition when exposed to air Debride visible particles	Systemic toxicity is a significant concern.
Air bag	Prolonged copious irrigation	

germicides, dyes, plastics, tanning, and fireproofing material and is used in cleaning stone and brick buildings. It is also a very effective rust remover.

Unlike other acids, hydrofluoric acid penetrates deeply and will cause progressive tissue loss. It produces burns in two ways. First, hydrogen ions cause direct cellular damage as other acids do through protein denaturation. Second, free fluoride ions scavenge intracellular cations, such as calcium and magnesium, disrupt cellular membranes, and inhibit the sodium/potassium/ATPase. This leads to systemic hypocalcemia, hypomagnesemia, and hyperkalemia. Locally, free fluoride ions cause spontaneous depolarization of nerve tissue and severe pain. Pain will persist until all free fluoride ions have been neutralized.

The dermal effects may not be immediately noted and are more related to the concentration of hydrofluoric acid than to the duration of exposure. Solutions >50% produce immediate pain and tissue destruction. Solutions <20% may not produce signs and symptoms until 12 to 24 hours after exposure. The skin often develops a blue-gray appearance with surrounding erythema.

The treatment of hydrofluoric acid burns consists of two phases. The first, immediate phase is copious water irrigation for 15 to 30 minutes. This may be the only treatment that is needed if the hydrofluoric acid solution is <20% concentration, the duration of exposure was very brief, and decontamination is begun immediately. Severe, persistent pain denotes a more serious injury requiring the second phase of treatment.

The second phase of treatment is aimed at replacing calcium and magnesium and detoxifying the enzyme-poisoning fluoride ion. Two ions—calcium (Ca^{2+}) and magnesium (Mg^{2+})[13]—bind the fluoride ion and curtail its toxic effects. However, the overwhelming clinical experience to date has been with calcium gluconate, so it is the agent of choice. Calcium gluconate can be administered as a topical preparation, subcutaneous/intradermal injection, or intra-arterial infusion. If commercial 2.5% gel is not available, a calcium gluconate gel can be made with a water-soluble lubricant and should be generously applied to the affected skin. **The topical preparation is made by mixing 3.5 grams of calcium gluconate powder in 5 oz of water-soluble lubricant, or 25 mL of 10% calcium gluconate in 75 mL of water-soluble lubricant.** Calcium chloride or calcium carbonate can be substituted if no calcium gluconate is available. The main limitation of topical therapy is the impermeability of the skin to calcium, and therefore, topical therapy is limited to use in mild, superficial burns. Most importantly, topical therapy should not delay intradermal or intra-arterial injections for severe burns.

Treatment with intradermal injection of a 10% calcium gluconate solution through a 27-gauge needle into the hydrofluoric acid–burned skin can be effective. **A typical dose of 0.5 mL of 10% calcium gluconate per square centimeter of burned skin is recommended.** Pain relief is nearly immediate, and, indeed, the elimination of pain may be used as a guide for further therapy. Unfortunately, injection therapy has several disadvantages: (1) only limited amounts of calcium are delivered to the tissue; (2) hyperosmolarity and inherent toxicity of free calcium ions cause more pain initially, and more tissue damage is possible if calcium is not bound to fluoride; (3) vascular compromise can result if too much fluid is injected, especially into digits; and (4) rapid penetration of hydrofluoric acid beneath the nail requires nail removal to administer the calcium gluconate into the nail bed adequately. **Acute hydrofluoric acid contamination of the hands, feet, digits, or nails requires consultation with a medical toxicologist and plastic surgeon.**

Intra-arterial infusion of calcium gluconate may be used to prevent tissue necrosis and stop the pain associated with hydrofluoric acid burns.[13] This should be performed as soon as possible after the initial burn, preferably within 6 hours of insult. Place an intra-arterial catheter in the appropriate vascular supply (the brachial artery if the entire hand is affected) and connect to a three-way stopcock to which is attached an arterial pressure-monitoring device and the infusion syringe of calcium gluconate. A 50-mL syringe may be filled with 10 mL of a 10% calcium gluconate solution and 40 mL of 5% dextrose in water and infused over 4 hours. The arterial pressure-monitoring device ensures that the catheter has not dislodged from the lumen of the cannulated artery. Repeat infusion may be needed if pain recurs within 4 hours. Intra-arterial infusion avoids the disadvantages of local infiltration therapy, but it has its own disadvantages: it is an invasive vascular procedure that (1) may result in arterial spasm or thrombosis, (2) requires more time and hospital resources, and (3) requires experience in the technique.

Inhalation of hydrofluoric acid can cause immediate or delayed pulmonary injury. All cases of suspected inhalation injury should be admitted for observation even if asymptomatic. Nebulized calcium gluconate may be attempted in these cases, but no controlled studies exist for its use. **The solution is made by adding 1.5 mL of 10% calcium gluconate solution into 4.5 mL of sterile water or saline and is administered by nebulizer.**

Ocular exposure to hydrofluoric acid requires water irrigation for at least 30 minutes and emergent ophthalmologic consultation. An animal study suggests that calcium-containing irrigation fluids for eye exposures may be harmful.[14] Therefore, standard eye irrigation practices should be used. The possibility of severe injury and eye necrosis should not be taken lightly. In severe ocular exposures, systemic absorption is possible as well.

TABLE 218-6 Options for Treatment of Hydrofluoric Acid Skin Burns

- Copious irrigation for 15–30 min immediately.
- Application of calcium gluconate gel; use commercial 2.5% gel or mix 25 mL of 10% calcium gluconate in 75 mL of water-soluble lubricant.
- Further treatment options as dictated by patient response:
  - Dermal injection of 10% calcium gluconate at the rate of 0.5 mL/cm^2 of skin surface using a small-gauge needle.
  - Arterial infusion over 4 h (40 mL of 5% dextrose in water with 10 mL of 10% calcium gluconate).
  - Consider supplemental magnesium and calcium IV.

Systemic toxicity from dermal and oral hydrofluoric acid exposure can result in ventricular fibrillation because of systemic acidosis, hyperkalemia, hypomagnesemia, and hypocalcemia. **In major hydrofluoric acid burns or oral exposures, immediately administer IV calcium and magnesium, using standard slow IV rates, before laboratory results are available.** Once patients develop hypocalcemia or hypomagnesemia, it is very difficult to restore these electrolyte deficiencies. Cardiac monitoring, IV access, and electrolyte monitoring should be performed in all cases of significant hydrofluoric acid dermal burns or oral exposures (**Table 218-6**).

METHACRYLIC ACID

Methacrylic acid, found in many artificial nail cosmetic products, can produce severe dermal burns, usually in preschoolers. Emergency treatment is copious water irrigation.

NITRIC ACID

Nitric acid is used in industry for casting iron and steel, electroplating, engraving, and fertilizer manufacturing. Upon contact with skin, nitric acid can produce tissue damage by oxidation and may turn the skin yellowish as it is burned. Emergency treatment consists of copious water irrigation and standard burn care (see Chapter 217, "Thermal Burns").

OXALIC ACID

Oxalic acid is used for leather tanning and blueprint paper. Oxalic acid binds calcium and prevents muscle contraction. The wounds should be irrigated with water, and IV calcium may be required. Serum electrolytes and renal function should be evaluated, and cardiac monitoring should be instituted after serious dermal exposure.

ALKALI BURNS

Alkalis penetrate skin deeper and longer than acids and present a greater danger of toxicity from systemic absorption. Wounds may initially look superficial only to become full-thickness burns in 2 to 3 days. Alkalis combine with protein and lipids in tissue to form soluble protein complexes and soaps that permit passage of hydroxyl ions deep into tissue. Soft, gelatinous, friable, brownish eschars are often produced (**Figure 218-1**). Strong alkalis have a pH >12.

LYES

Strong, corrosive alkalis ("lyes") include ammonium, barium, calcium, lithium, potassium (caustic potash), and sodium (caustic soda) hydroxides. Lyes are widely used in industry and are found in home products such as drain and toilet cleaners, detergents, and paint removers. The urine sugar reagent tablet Clinitest® (Bayer) contains anhydrous sodium hydroxide.[15] Ammonium hydroxide is used in the production of synthetic fibers and extensively in agriculture. Exposure to these



FIGURE 218-1. Deep alkali burn. [Reproduced with permission from http://www.burnsurgery.org/Modules/initial_mgmt/sec_6.htm.]

chemicals can result in severe toxicity including mucous membrane, ocular, dermal, GI, and inhalational/pulmonary injury. Suicidal ingestion of lye may result in rapid death from upper airway occlusion. Late morbidity related to esophageal and gastric necrosis may be minimized by early surgical intervention with esophagogastrectomy. The mainstay of treatment is immediate, voluminous, and persistent irrigation.[16] **Lyes are extremely corrosive and penetrating. Lye burns require copious irrigation for long periods of time.**

LIME

Lime (calcium oxide) is found in agricultural products and cements. There is considerable variability of lime content in different grades of cement, with fine to textured masonry cement having more lime than concrete. Lime is converted by water to the alkali calcium hydroxide. Upon skin contact, lime draws water out of the skin. **All dry lime particles should be brushed away before irrigation.[5] Even a small amount of water may generate an exothermic reaction resulting in calcium hydroxide formation and tissue injury.** Brisk irrigation with a large volume of water (taking care to avoid splashing in eyes) should be used and will permit dissipation of heat.

PORTLAND CEMENT

Portland cement, which accounts for a major proportion of the cement used in the United States, is a mixture of sand, lime, and other metal oxides. In the presence of water, calcium hydroxide, sodium hydroxide, and potassium hydroxide may all be formed. Workers who kneel in wet cement or get cement in their boots may discover burns hours after initial contact. In addition, skin may become irritated from gritty material, and a contact dermatitis may develop in individuals sensitive to the chromate contained in the material. Treatment of cement burns may require cleaning the wound with a brush, such as a preoperative scrubbing brush, to remove cement particles imbedded in the dermis.

METALS

Foundry workers are sometimes burned by molten metal, which may spill or splash on body parts and run down into the boots. Elemental metals, sodium, lithium, potassium, magnesium, aluminum, phosphorus, and calcium may all cause burns. When exposed to air, some elemental metals spontaneously ignite. **Water is generally contraindicated in extinguishing burning metal fragments embedded in the skin because the resultant explosive exothermic reaction can lead to significant tissue injury. Burning metal may be extinguished with a class D fire extinguisher, smothered with sand, or covered with mineral oil.** Wound debridement should include excision of metal fragments that cannot be wiped away. Metal fragments should be placed in mineral oil to prevent further ignition.[6]

HYDROCARBONS

GASOLINE

Hydrocarbons cause a fat-dissolving corrosive injury to the skin referred to as defatting dermatitis. Gasoline, a complex mixture of alkanes, cycloalkanes, and aromatic hydrocarbons, is the most common hydrocarbon burn treated in the ED.

A hydrocarbon chemical burn typically resembles a thermal scald or a partial-thickness burn, although full-thickness burns rarely result from prolonged contact with gasoline.[17] During extremely cold weather, topical gasoline exposure may lead to frostbite when rapid gasoline evaporation causes heat loss from the skin. Systemic effects of hydrocarbon absorption include neurologic, pulmonary, cardiovascular, GI, and hepatic injuries. For further discussion, see Chapter 199, "Hydrocarbons and Volatile Substances."

The primary treatment is decontamination by removing saturated clothing and irrigating exposed skin with soap and water. Otherwise, management is as for a thermal burn.

HOT TAR

Hot tar is derived from long-chain petroleum and coal hydrocarbons. Roofing tars and asphalt are heated to temperatures up to 500°F (260°C), and the burns sustained are usually more thermal than chemical. Although the surface area size of the burn is usually small, solidified material stuck to skin and hair is difficult to remove. **If hot, the tar should be cooled to prevent continued thermal injury.** Manual mechanical debridement can be painful and destructive to skin structures. Polyoxylene sorbitan (polysorbate), contained in many antibiotic ointments, is an emulsifying agent that can be used to remove tar. Industrial removal agents such as De-Solv-It®, a citrus and petroleum distillate, are also effective in tar removal. Baby oil is also effective for tar removal.

VESICANTS (DIMETHYL SULFOXIDE, CANTHARIDES, AND SULFUR MUSTARD)

Dimethyl sulfoxide, cantharides, and mustard gas are vesicant or drying agents. Skin burns present with edema and blister formation due to production of ischemia and anoxic necrosis at the site of contact. Dimethyl sulfoxide is a water-soluble organic solvent used in industry. It is available without prescription and is used topically for sprains, bruises, minor burns, and joint pain. Due to its chemical composition and solubility, dimethyl sulfoxide can penetrate barrier surfaces such as nitrile gloves. Cantharides ("Spanish fly") is occasionally used for its supposed aphrodisiac effects. Sulfur mustard is a vesicant historically used in chemical warfare. An alkylating agent, exposure results in inhibition of cellular enzymatic activity, leading to necrosis. For further discussion, see Chapter 8, "Chemical Disasters."

Skin damage following vesicant exposure is often severe and can result in deep skin penetration, edema, blisters, ulcers, and serious morbidity. Immediate, copious irrigation with water or saline may mitigate the extent of tissue injury. Skin can also be decontaminated by using adsorbent powders such as flour, talcum powder, and fuller's earth if the supply of water is limited. These powders adsorb the mustard from the skin and should be wiped away with a moist towel. Almost any material can be used to brush the vesicant away from skin. The military uses M258A1 kits for skin decontamination. These kits contain three sets of towelettes, one of each containing phenol, sodium hydroxide, and sodium benzene sulphonochloramine (chloramine). Chloramine produces "free" chlorine, which inactivates sulfur mustard. Povidone iodine shows great promise in the prevention and early treatment of skin damage caused by sulfur mustard. Human data are currently lacking, but in animal models, both prevention of burns and immediate (<10 minutes) treatment yielded impressive skin protection.[18]

POTASSIUM PERMANGANATE

Potassium permanganate is an oxidizing agent that is mildly irritating in dilute solution, but in concentrated solution, it can produce dermal burns with a thick, brownish purple eschar of coagulated protein. Burns should be copiously irrigated with water.

ALKYL MERCURY COMPOUNDS

Alkyl mercury compounds, which are reducing agents used in disinfectants, fungicides, and wood preservatives, can produce dermatitis or burn lesions. Lesions typically are erythematous with blister formation. The blister fluid is high in metallic mercury content. The burning process continues if the agent remains in contact with skin. Partial-thickness burns deepen if the blister fluid remains, so the blisters should be debrided, drained, and copiously irrigated. Repeated or prolonged exposure to topical mercury compounds may lead to systemic mercury toxicity.

LACRIMATORS OR TEAR GAS

Lacrimators, or tear gas, such as 2-chloroacetophenone, o-chlorobenzylidene malonitrile, and oleoresin capsicum (pepper spray), cause skin and mucosal irritation within 20 to 60 seconds of exposure and can lead to development of contact dermatitis. Although the skin injury is usually limited, inhalation and eye injuries may be severe. Treatment of skin exposure is rapid removal from the offending agent followed by irrigation. Ocular irritation is treated with copious water or saline irrigation, followed by slit-lamp examination for corneal damage. Arrange ophthalmology follow-up in 24 hours. Inhalation injuries are treated with respiratory support including oxygen and bronchodilators. There is no role for steroid therapy.[19]

WHITE PHOSPHORUS

White phosphorus is used as an incendiary in munitions and fireworks and as a component of insecticides, rodenticides, and fertilizers. It ignites spontaneously when exposed to air and is rapidly oxidized to phosphorus pentoxide. Burns caused by both its solid and liquid forms are seen in both the military and civilian populations. Death has been reported in burns covering <10% body surface area.

Flaming droplets of inorganic phosphorus may embed beneath the skin. The heat of the reaction causes tissue destruction. Particles continue to oxidize slowly until debrided, neutralized, or completely oxidized. If phosphorus is exposed to air, it will continue to burn. Remove contaminated clothing and visible particles, and copiously irrigate burns with normal saline or water. Skin exposed to white phosphorus must remain wet or immersed in water until completely debrided to prevent further injury.[5] **Wood's lamp** examination aids identification of remaining phosphorus as it fluoresces. **Copper sulfate solution should not be used despite its ability to detoxify phosphorus because it causes hemolysis and increases mortality.**

White phosphorus burns are characterized by slow healing and ongoing burning, necessitating early and aggressive treatment. Systemically absorbed phosphorus is a serious concern. Hypocalcemia, hyperkalemia, and hepatic and renal injury all have been reported. Even patients with small burns should be considered for admission or transfer to a burn center for aggressive hydration, monitoring, and further treatment.[20] Treatment providers should take care to wear protective equipment and avoid direct contact with the patient's clothing, feces, and emesis.

AIR BAG BURNS

Approximately 8% of individuals suffering injuries related to air bag deployment are burned. Air bags deploy by ignition of solid propellant—sodium azide and cupric oxide—that creates an exothermic reaction leading to rapid inflation of the air bag. Many other gases are created during activation, including corrosives such as sodium hydroxide, nitric oxide, ammonia, and multiple hydrocarbons. Burns associated with air bags include friction, thermal, and chemical burns.[21] Most frequently, burns are produced on the face, hands, and eyes. Full-thickness skin burns have been reported. Perform slit-lamp examination for eye irritation to detect keratitis. Treatment of air bag chemical burns is similar to any alkali burn: immediate and copious water irrigation.

OCULAR BURNS

After the hands, the eyes are the second most common site of chemical burns documented in a national insurance database in Asia.[22] **Chemical burns to the eyes are ocular emergencies requiring immediate treatment.**[23]

If the nature of the chemical is not known, use pH paper to determine the presence of acid or alkali. Acid quickly precipitates the superficial tissue proteins of the eye, producing the typical "ground glass" appearance of the cornea. Damage sustained secondary to acid burns is, in most cases, immediate and limited to the area of contact.

Alkali burns are generally more severe than acid burns, frequently with unsightly and disastrous results. **In a short period of time, strong alkalis can penetrate the cornea, anterior chamber, and retina, with destruction of all sensory elements, thus causing complete blindness** (see Figure 241-49 in Chapter 241, "Eye Emergencies"). **Begin with 1 to 2 L of normal saline for each eye for 30-minute continuous irrigation as the minimum treatment. Do not use neutralizing substances.**

Check the pH in the conjunctival sac to see whether it has returned to 7.0-7.3 to determine the need for further irrigation. Many many liters may be needed for irrigation. However, extended 2- to 3-hour irrigation, despite apparent conjunctival pH correction, is recommended in the setting of strong alkaline or hydrofluoric acid burns with obvious examination abnormality, to correct anterior chamber pH as well as conjunctival pH. **During irrigation, the eyelid may have to be held open manually or with retractors due to severe orbicularis spasm (see Chapter 241).** The eyelids should be everted. **Sweep the fornices with a wet cotton applicator to remove any particulate matter, especially if the pH is not responding well to irrigation.**

Pain control with topical anesthetics during evaluation and treatment is necessary. Systemic opioids may be necessary for severe pain or associated injuries. For additional discussion, see Chapter 241. **Obtain emergency ophthalmology consultation for corneal burns.**

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 219

Electrical and Lightning Injuries

Caitlin Bailey

INTRODUCTION

Electrical injuries are divided into high-voltage injuries (≥1000 V), low-voltage injuries (<1000 V), and electric arc flash burns, which by definition do not result in passage of current through the tissues. Lightning injury is an extreme and unique form of electrical injury. This chapter also discusses injuries caused by electronic control devices, such as the **Taser**®. Burns from electrical accidents can result from heating due to electric current flow through tissues, explosions, and burning of flammable liquids, clothes, and other objects. Burns are discussed in Chapter 217, "Thermal Burns."

EPIDEMIOLOGY

Approximately 6500 electrical injuries occur per year in the United States, accounting for 4% of total burns. Of these, the majority are work related (61%), mostly industrial injuries. The overall complication rate is 10.6%, with the fewest complications among children aged 1 to 5 years (2%).[1] There were 134 fatal electrical injuries reported by the Electrical Safety Foundation International in 2017, a slight decline from previous years.[2,3] The most common high-voltage injuries in the United States are also work related and include arc burns in electricians and high-voltage injuries in power line workers.[4] High-voltage power line injuries are particularly disabling because they often lead to deep muscle necrosis and the need for fasciotomy and amputation.[4]

BASICS OF CURRENT FLOW

Electric current is the movement of electrical charges. **Table 219-1** lists a few key terms related to electricity.

Current flow is measured in amperes. Current flow is driven by an electrical potential difference, which is measured in volts. Intervening material between two or more contact points resists electric current flow; this resistance is measured in ohms. Ohm's law describes the relationship between current (I), voltage (V), and resistance (R) and states that the *current* through a conductor between two points is directly *proportional* to the *potential difference* or *voltage drop* across the two points and inversely proportional to the *resistance* between them. For example, a person who grasps a grounded pipe in one hand and a metal cable connected to a 120-volt source in the other hand will experience a current flow through the body, the magnitude of which varies inversely with the resistance of the circuit. If the total resistance from the power source, through the person, and to the ground is estimated to be 1000 Ω, the current (I) would be calculated as follows: I = (120 V)/(1000 Ω) = 0.120 A = 120 mA.

Conductors are materials that allow electric current to flow easily. Insulators are materials that do not allow electric current flow. Tissues with high fluid and electrolyte content conduct electricity better than tissues with less fluid and electrolyte content. Bone is the biologic tissue with the greatest resistance to electric current, while nerves and vascular structures have low resistance. Dry skin has high resistance, but sweaty or wet skin has much less resistance.

Many of the physiologic effects of electric shock are related to the amount, duration, and type of current [alternating current (AC) or direct current (DC)], and the path of current flow (**Table 219-2**). DC current flows in a constant direction, whereas AC current alternates direction in a cyclical fashion. **Standard household electricity is AC. Electricity in batteries and lightning is DC. Low-frequency (50- to 60-Hz) AC can be more dangerous than similar levels of DC because the alternating current fluctuations can result in ventricular fibrillation.** The identification of electric shock as due to AC or DC is also important to reconstruct the mechanism of injury. AC current can produce muscular tetany, during which the victim cannot let go of the electrical source. Both AC and DC current can hurl the victim away from the current source, which results in severe blunt force injury.

TABLE 219-1 Electrical Terms and Units of Measure

Term	Unit of Measure
Electric current Movement of electrical charges	Amperes
Current flow Driven by voltage or electrical potential difference	Volts
Resistance Hindrance to flow of current	Ohms
Ohm's law (current = voltage/resistance) The current is proportional to voltage. The current is inversely proportional to resistance.	

TABLE 219-2 Effects of Current

Effect	Current Path	Minimum Current: 60 Hz AC (mA)*
Tingling sensation, minimal perception	Through intact skin	0.5–2.0
Pain threshold	Through intact skin	1–4
Inability to let go: tetanic contractions of hand and forearm tighten grasp, decreasing skin resistance	From hand through forearm muscles into trunk	6–22
Respiratory arrest: can be fatal if prolonged	Through chest	18–30
Ventricular fibrillation	Through chest	70–4000
Ventricular standstill (asystole): similar to defibrillation; if current stops, sinus rhythm may resume	Through chest	>2000

Abbreviation: AC = alternating current.

*Ranges are approximate and depend on various factors.

For current to flow through an individual, a complete circuit must be created from one terminal of a voltage source to a contact area on the body, through the subject, and then from another contact on the person to the other terminal of the voltage source (or to a ground that is connected to the voltage source). Current flows through a person from one contact area to another along multiple, somewhat parallel paths. For example, electrical power source contacts just on the left hand and left leg would result in current flow through those limbs and the trunk, including the heart, muscles of respiration, and other tissues in the trunk. Current would not flow through the other limbs or head, because they are not in an electrically conductive path between the two power source contacts. The pattern of current flow through the body, if known, can be used to raise or lower suspicion of injury to certain body parts; for instance, hand-to-hand flow involves crossing the thorax and heart.

ELECTRICAL INJURIES

MECHANISMS OF ELECTRICAL INJURY

HIGH- AND LOW-VOLTAGE INJURIES

The risk for serious and fatal electrical injury increases with voltage, especially >600 V (Table 219-2). **High voltage is usually defined as >1000 V.** Power lines in U.S. residential areas typically carry 7620 V AC. This is stepped down by transformers to 240 V AC before entering most residential and nonindustrial buildings. **In the United States, home outlets are 120 V, and in Europe and Australia, they are 240 V.** High-voltage injuries are more often associated with severe musculoskeletal, visceral, and nervous system injury than are low-voltage injuries.

Electricity-induced injuries can occur via several mechanisms: (1) direct tissue damage from the electrical energy, (2) tissue damage from thermal energy, and (3) mechanical injury from trauma induced by a fall or muscle contraction.

ELECTRICAL BURNS

Electrical burns are severe when high voltages are involved, because only a fraction of a second of current flow is necessary for severe damage to occur.[5] Burns are less common with low-voltage injuries, because low-voltage contact produces little heat energy in the skin and other tissues.[6]

ELECTRIC ARC INJURIES

Electricity arcing from one conductor to another may radiate enough heat to burn and even kill persons 10 or more feet from the arc. There can also be a blast force that throws the person. Arcs that do contact a

person directly will have heating due to current flow through the body, in addition to the flash burn and mechanical blast forces. Serious burns often result.[7] The voltages that create an electric arc are usually in the thousands of volts. Temperatures as high as 20,000°C (35,000°F) are created. Serious, and sometimes fatal, burns may result from heat radiated by the arc and clothing ignited by the arc.

TETANIC CONTRACTIONS

Electric current can induce sustained muscular contraction, or tetany. The overall effect varies according to type (AC or DC), frequency, voltage, and extent of contact.[5,8] For example, AC current flowing through the forearm can cause flexor tetany of the fingers and forearm that overpowers actions of the extensor muscles. Forceful muscle contractions can cause fractures and joint dislocations, especially around the shoulders.[9] If the hand and fingers are properly positioned, the hand will grasp the conductor tightly, leading to prolonged, low-resistance contact with the power source because the person cannot let go. This allows current to flow for many seconds or minutes.

The increased duration of contact and the decreased contact resistance caused by a tight sustained grasp greatly increase the heat-related damage to deep tissues. Heating due to electric current builds over time. Because heating is directly proportional to the duration of current flow and proportional to the square of the current amplitude (until burning and other tissue changes occur), a person who is unable to let go of a conductor for 30 seconds receives about 90 times as much tissue heating as a person who recoils from the voltage source in one third of a second. To make injury still more severe, a tight grasp on a conductor decreases contact resistance, which leads to an increase in current flow. Thus, heat-related injury to deep tissues is often more than a hundred times worse when there is a history of the patient's being unable to let go of the conductor.

Current flow through the trunk and legs may cause brief, but strong, opisthotonic (arching) posturing and leg movements. The person appears to be thrust from the voltage source due to these muscle contractions and may sustain mechanical trauma in addition to electrical injury. If a person does manage to hold on to a high-voltage source, severe tissue damage occurs.

CLINICAL FEATURES OF ELECTRICAL INJURY

Electric current can induce immediate cardiac dysrhythmias, respiratory arrest, and seizures. Current that traverses the chest vertically (hand to foot or head to toe) or horizontally (hand to hand) can produce arrhythmias and respiratory arrest.

CARDIAC INJURY

Arrythmias are the most common cardiac manifestation of electrical injury. Fatalities due to asystole or ventricular fibrillation usually occur prior to arrival in the ED.[6] **Asymptomatic patients with normal ECGs on arrival to the hospital do not develop later dysrhythmias after low-voltage (<1000 V) injuries.**[10-14] Myocardial injury can also occur from vascular damage (spasm, thrombosis, or dissection), resulting in ischemia. Conduction blocks can occur.[15]

CNS AND SPINAL CORD INJURY

Neurologic impairment is common in electrical injuries, occurring in approximately 50% of patients with high-voltage injuries.[4] Given the multisystem dysfunction present in many electrical injury patients, take care to perform and document a careful neurologic exam, if possible, before intubation and sedation.

Transient loss of consciousness is common after electrocution and may be followed by seizures. Victims may be confused and agitated or deeply comatose and require airway protection. Patients may also demonstrate focal neurologic deficits such as quadriplegia, hemiplegia, aphasia, or visual disturbances. Head and cervical spine CT should be performed to rule out traumatic etiologies for these deficits; MRI may be necessary for purely electrical damage. Electrical injury has been known to cause blindness[16] due to occipital lobe injury as well as direct injury to the optic nerve.[17,18] Neurologic deficits may be transient, but survivors may have persistent difficulties with attention, working memory, and learning.[19]

Spinal cord injury occurs in up to 8% of high-voltage electrical injuries.[20] Mechanisms include compressive vertebral fractures,[21] purely electrical damage, or vascular injury.[22] Initial MRI findings may be normal in electrical trauma patients with permanent spinal cord injury,[23-25] although newer MRI imaging protocols may detect abnormalities missed on standard MRI.[26]

Neurologic deterioration can occur days to months after the initial injury[27-29] and generally has incomplete resolution. There is a motor predominance in the deficit in most cases. Delayed onset of spinal cord dysfunction may be due to progressive vascular injury (especially to the spinal artery branch supplying the anterior horn cells) or delayed cell membrane damage via the cumulative effect of free radicals (electroporation), leading to progressive demyelination.[23,30] The clinical features may take the form of transverse myelitis, amyotrophic lateral sclerosis, or a Guillain-Barré–like illness.[31]

PERIPHERAL NERVE INJURY

Nerve tissue has the lowest resistance in the body, encouraging electrical passage through these tissues and causing associated damage. Peripheral nerve injuries often involve the hands after the individual touches a power source. Paresthesias may be immediate and transient or delayed in onset, appearing up to 2 years after injury.[4,32] Extensive peripheral nerve damage may occur with minimal thermal injury. Electrical contact with the palm produces median or ulnar neuropathy more often than radial nerve injury.[33] Brachial plexus lesions have also been reported, as well as a case of trigeminal neuralgia.[34] Persistent symptoms related to peripheral nerve damage can occur despite normal results on nerve conduction studies.[35]

CUTANEOUS BURNS

Cutaneous burns are often seen at the electrical contact areas (often referred to as *entry* and *exit wounds* in the case of DC current or *contact wounds* in the case of AC current). Many seriously injured patients have burns on either the arm or skull, paired with burns on the feet. These burns are typically painless, gray to yellow, depressed areas. Most patients with burns from electrical injury need admission and care by a burn specialist. See Chapter 217, "Thermal Burns," for management of cutaneous burns.

ORTHOPEDIC INJURY

Fractures may be caused by tetanic muscle contractions or associated falls. While fractures are more likely to result from high-voltage injury, fractures of the wrist, forearm, humerus, femoral necks, shoulders, and scapulae have been reported from exposure to household voltages (120 to 220 V AC) without associated trauma.[8,36,37] Posterior shoulder dislocations are commonly seen with electrical injury.

VASCULAR AND MUSCLE INJURY

Vascular and muscle injury occur most commonly in the setting of high-voltage injury, such as power line contact. Electric current passing along peripheral arteries may cause early spasm and persistent deficits in endothelial and smooth muscle function,[38] as well as subsequent thrombosis, stenosis, or aneurysm formation. Because of concomitant vascular and muscular destruction, **patients with high-voltage shocks are at significant risk for development of compartment syndrome, even if the contact (or arcing) lasted <1 second.** Compartment syndrome has also been noted in patients with injuries from ≥120 V AC who sustain contact for longer than a few seconds. Patients typically exhibit ongoing muscle pain with movement.[7]

Contact with >1000 V, prehospital cardiac arrest, crush injury, and full-thickness skin burns are associated with significant tissue damage requiring surgical intervention. Fasciotomy and amputation are frequent sequalae of high-voltage injuries, occurring in up to 29% and 41% of patients, respectively.[39,40] High-voltage electrical injury is associated

with rapid loss of body fluids into the areas of tissue damage, requiring aggressive resuscitation.

COAGULATION DISORDERS

Thermal injury or tissue necrosis from electric current can cause a variety of coagulation disorders. Low-grade disseminated intravascular coagulation may be a result of hypoxia, vascular stasis, rhabdomyolysis, and release of procoagulants from damaged tissue. Transient coagulopathies have also been reported with high-voltage injury, including acquired, transient factor X deficiency.[41] Electrical injury may unmask underlying vascular injury and has been reported in association with ischemic stroke at low voltage.[42]

BLAST INJURY

Electric arcs in the industrial environment or near a power line can produce a strong blast pressure, similar to those seen in other types of explosions.[43] Cognitive complaints following blast injury may resemble those that result from moderate mechanical head trauma. Mechanisms of brain injury include mechanical trauma related to the blast, as well as arterial air emboli associated with blast-related alveolar disruption (see Chapter 7, "Bomb, Blast, and Crush Injuries").

INHALATION INJURY

Chemical toxins such as ozone can be produced by coronas and arcs. Acute effects of ozone exposure include mucous membrane irritation, temporarily reduced pulmonary function, and pulmonary hemorrhage and edema. Fires and explosions associated with electrical incidents may lead to inhalation of carbon monoxide and other toxic substances.

OCULAR INJURY

Electrical shock can cause a wide range of ocular trauma, most commonly to the cornea (epithelial erosion/defect, keratitis, scarring), as well as uveitis, retinal detachment, macular edema, optic nerve damage, and intraocular bleeding and thrombosis.[17,44,45] Providers should have a low threshold for full ophthalmologic evaluation for any electric shock patient with an ocular complaint to document related injury. Cataract formation has been described weeks to years after electrical injury to head, neck, or upper chest.[8] Cataracts have also occurred after electric arc or flash burns.

AUDITORY INJURY

The auditory system may be damaged by current or by hemorrhage in the tympanic membrane, middle ear, cochlea, cochlear duct, and vestibular apparatus. Delayed complications include mastoiditis, sinus thrombosis, meningitis, and brain abscess. Hearing loss may be immediate or develop later as a result of complications. Hearing should be briefly checked in the ED, with follow-up formal testing arranged for any patient who appears to have a deficit.

GI INJURY

Pain due to bowel perforation and intra-abdominal hemorrhage may be attributed to more obvious coexisting injuries.[46] There are reports in the literature of lethal intra-abdominal injuries from electric current that were found only at autopsy. Ileus may develop in association with spinal cord injury.

SCENE AND PREHOSPITAL CARE

Table 219-3 outlines prehospital care of the patient with electrical injury.

RESCUER SAFETY

The recommendations in Table 219-3 should be followed strictly to protect rescuers while managing the patient. **Reapplication of voltage to downed lines sometimes occurs as circuit breakers automatically reset, which makes the lines jump many feet with great force. Be aware that support structures such as cables may be electrically alive.**

TABLE 219-3 Scene and Prehospital Care

- Stay at least 10 m (32 ft) from downed power lines, jumping power lines, and support structures.
- Turn off the source of electricity prior to rescue, if possible.
- If electrical source cannot be quickly turned off, take precautions to prevent electrical injury to the rescuer.
- Wear gloves and shoes rated for the power line voltage.
- Initiate rescue breathing and resuscitation efforts while injured person is still on pole, if no contact with source of electricity is ensured.
- Maintain spinal immobilization of injured person, if possible.

Victims still in contact with a source of voltage may transmit an electric current to would-be rescuers. With voltages above about 600 V, dry wood and other materials may conduct significant amounts of electric current and therefore cannot be used to remove the person from a voltage source. A rescuer standing on the ground touching any part of a vehicle that is in contact with a power line is likely to be killed or seriously injured. Electric shock is not prevented in this situation by the rescuer wearing rubber gloves and boots, unless these are designed for the voltage present and have been recently tested for insulation integrity.

SCENE RESUSCITATION AND STABILIZATION

Low-voltage AC can produce ventricular fibrillation by direct stimulation of the heart, or ventricular fibrillation can occur after several minutes of respiratory arrest resulting from paralysis of respiratory muscles (Table 219-2). **High-voltage AC and DC are more likely to produce transient ventricular asystole.** The asystole sometimes reverts spontaneously to normal sinus rhythm with pulses, but prolonged apnea may continue. **Apnea with pulses** sometimes occurs in linemen working above the ground near high-voltage lines. Supporting respirations above ground may be all that is needed to stabilize the patient's condition. Vigorous resuscitation efforts should be initiated in patients with cardiac arrest from electric shock, because there may be insignificant tissue damage despite the potentially lethal dysrhythmia.[47]

Maintain spinal immobilization during resuscitation to the extent possible, because spinal fractures can be caused by tetanic muscle contractions, falls, and other secondary trauma.

ED DIAGNOSIS AND TREATMENT

Provide the usual evaluation (airway, breathing, circulation) and resuscitation for major trauma victims. Maintain spinal immobilization during resuscitation until adequate imaging and examination can be done.

Cardiac arrhythmias can be treated according to standard protocols (see Chapter 23, "Defibrillation and Electrical Cardioversion," and Chapter 24, "Cardiac Resuscitation"). Maintain cardiac monitoring for patients with high-voltage injuries as well as all symptomatic patients.[10,11] Cardiac complications are more common in patients with high-voltage injuries and in those with loss of consciousness and include ventricular and atrial dysrhythmias, bradydysrhythmias, and QT-interval prolongation.[48-50] **Admission for cardiac monitoring is not needed for asymptomatic patients with normal ECG on presentation after a low-voltage electrical injury,** because the risk of developing a subsequent malignant rhythm requiring intervention is very low.[12,15,51]

Assess for tissue damage and identify associated complications. A careful vascular and neurologic examination of involved extremities is important. Normal findings on initial assessment do not exclude serious injury or the possibility of delayed spinal cord injury following high-voltage contact.

Focus next on systematic assessment and treatment, especially for injuries specific to or common in electrical injury, as outlined in **Table 219-4**. Laboratory and radiographic evaluation of high-voltage

TABLE 219-4 Assessment and Treatment of Complications Associated With Electrical Injuries

Organ or System	Assessment/Treatment/Comments
Circulatory	Start with Parkland fluid resuscitation formula.*
Renal	Initiate fluid resuscitation.
Myoglobinuria	Initiate fluid resuscitation.†
Central and peripheral nervous	Order head CT if mental status is abnormal; assess for spinal cord and peripheral nerve injury.
Skin	Assess and treat cutaneous burns.*
Musculoskeletal	Perform careful assessment of spine, pelvis, long bones, and joints. Assess for compartment syndrome and need for fasciotomy.
Vascular	Spasm may occur leading to delayed thrombosis, aneurysm formation, or muscle damage.
Coagulation	Treat coagulation disorders by eliminating the precipitating factor through early surgical debridement. If bleeding is present, replace coagulation factors.‡
Lungs	Assess for inhalation injury, carbon monoxide, or alveolar injury from blast.
Eyes	Document complete eye examination. Delayed cataracts may develop.
Ears	Assess for blast injury. Document hearing. Middle and inner ear disorders may occur.
GI	Intra-abdominal injury may occur from current or blast.
Lips and oral cavity	Watch for delayed bleeding.

*Refer to Chapter 217, "Thermal Burns."

†Refer to Chapter 89, "Rhabdomyolysis."

‡Refer to Chapter 254, "Trauma in Adults."

injuries should follow standard trauma guidelines (see chapters in Section 21, "Trauma," and Section 22, "Orthopedics").

In the case of **low-voltage injuries**, laboratory testing and imaging are usually not required unless the patient is symptomatic or has abnormal physical examination findings. Symptoms such as chest pain, palpations, loss of consciousness, altered mental status, confusion, weakness, dyspnea, abdominal pain, weakness, burn with subcutaneous damage, vascular compromise, or abnormal results on ECG require further testing.

FLUID RESUSCITATION

Fluid resuscitation guided by the Parkland formula (4 mL/kg multiplied by the percentage of body surface area burned, administered over 24 hours) is only a rough starting point in fluid management. Extensive deep tissue damage resulting from high-voltage injury may be present even when the cutaneous burn seems limited. Therefore, fluid requirements are often greater than predicted by external injuries using the Parkland formula.

MYOGLOBINURIA

Patients with suggestive symptoms or high-voltage injury should be monitored for the onset of compartment syndrome, rhabdomyolysis, and renal failure. If myoglobinuria is suspected, institute aggressive IV fluid resuscitation to maintain a urinary output of between 1 and 2 mL/kg/h, with attention to correction and prevention of electrolyte abnormalities. Maintain a high urine output until the serum creatine kinase level is less than five times normal or urine myoglobin measurements return to normal.

Prognostic factors associated with the need for a fasciotomy within 24 hours of injury are (1) myoglobinuria, (2) burns over 20% of total body surface area, or (3) a full-thickness burn over 12% body surface area.[39] Presence of any one of these three factors is predictive of development of the need for fasciotomy. The International Society for Burn Injuries 2018 guidelines recommend that patients with myoglobinuria should be transferred to a burn center with expertise in escharotomy and fasciotomy.[48]

DISPOSITION AND FOLLOW-UP

LOW-VOLTAGE INJURIES <600 V

Although there is no universally accepted protocol for management and disposition of patients with low-voltage injuries, **in general, asymptomatic patients who sustain an electric shock of ≤240 V AC can be discharged home if they have a normal ECG on presentation and normal examination findings.**[10,11] Patients who feel unwell or have any new ECG abnormality should be monitored and reassessed.[10,11]

HIGH-VOLTAGE INJURIES ≥600 V

All patients having contact with ≥600 V AC should be admitted for observation, even if there is no apparent injury. Routine cardiac monitoring is not required unless the patient is symptomatic or the initial ECG findings are abnormal. Low-voltage injury patients with symptoms beyond superficial skin injury or abnormal lab or ECG results may have systemic injury and require admission as well. Patients with extensive cutaneous burns should be transferred to a specialized burn center after initial trauma stabilization. This is especially true in children.[52] The International Society for Burn Injuries 2018 guidelines recommend that patients sustaining electric shock >1000 V AC should be transferred to a burn center for evaluation and management.[48]

SPECIAL POPULATIONS

PREGNANT WOMEN

In addition to the measures recommended earlier, in pregnant patients beyond 20 to 24 weeks of gestation, fetal heart rate and uterine activity should be monitored for at least 4 hours because of the possibility of mechanical trauma related to the electric shock and electrical discharge to the fetus.[48,53-55]

CHILDREN

Children are more likely to sustain household current electrical injury than high-voltage injury. Overall outcome appears to be better, including a lower incidence of amputation and fasciotomy than in adults, although skin grafts may be required (25% in one 10-year study of pediatric burn center referrals).[52]

Oral and Lip Burns Serious oral injury can occur in a child who places the end of a power cord in the mouth. The electric field and current flow created between the two wires near the end of the cord can produce high temperatures and significant tissue damage. Most injuries are unilateral, involving the lateral commissure, tongue, and/or alveolar ridge[5,56,57] (**Figure 219-1**). Systemic complications of oral burns are uncommon. **Vascular injury to the labial artery is not immediately apparent** because of vascular spasm, thrombosis, and overlying eschar. Severe bleeding from the labial artery occurs in up to 10% of cases when the eschar separates, usually after 5 days.[58] If the parents are reliable, can monitor the child, and can be shown how to control bleeding, outpatient management may be considered. Parents should be educated that bleeding may occur up to 2 weeks after injury. Prior to discharge, however, specialty consultation should be obtained and follow-up secured, because of the risk of deforming scar formation during the healing process, in which new cells tend to migrate medially, reducing the span of mouth opening. Splinting and other measures are often needed to prevent the development of this deformity and dysfunction. Home care includes saline or hydrogen peroxide rinses and gentle swabbing to debride necrotic tissue and promote formation of healthy granulation tissue. Topical application of petrolatum-based antibiotics may have a soothing effect.



FIGURE 219-1. Oral burn in a child from power cord. A 2-year-old boy sustained a third-degree burn to the commissure of the mouth after biting down on an electrical cord. This photograph was taken 3 days after initial treatment. [Reproduced with permission from Shah BR, Lucchesi M: *Atlas of Pediatric Emergency Medicine.* © 2006 by McGraw-Hill, Inc., New York.]

Hand Wounds Hand wounds are common electrical injuries in children.[59] Children who sustain hand wounds from electrical outlet injuries with no other injury and no evidence of cardiac or neurologic involvement can be discharged after local wound care is provided and careful follow-up is ensured.

LIGHTNING INJURIES

EPIDEMIOLOGY

Lightning causes approximately 500 injuries each year in the United States, with 20 to 50 deaths per year in the past decade.[60] Lightning fatalities constitute fewer than 3% of weather-related deaths, which are more commonly due to extreme heat or cold.[61] Lightning fatalities are most common in fishermen, but also occur in other outdoor recreational activities such as golf and camping.[62] Lightning injury reporting is inexact and biased toward the more severe and fatal events. Approximately 70% to 90% of persons struck by lightning survive, but as many as three quarters of these survivors have permanent sequelae.[63,64]

Lightning most often occurs during thunderstorms. However, approximately 10% of lightning occurs without rain and when the sky is blue.[65] In addition, lightning can occur during dust storms, sandstorms, tornados, hurricanes, snowstorms, and nuclear explosions, and in the clouds over volcanic eruptions. Lightning injuries can also occur while riding in airplanes. Lightning injury associated with indoor telephone use during lightning storms has been reported.[34] A study in Australia identified up to 80 such injuries yearly without any reported fatalities.[66]

Even though lightning is electrical energy, lightning injuries differ substantially from high-voltage electrical injuries seen in association with human-generated sources. There are differences in injury patterns, injury severity, and emergency treatment[53,67,68] (**Table 219-5**).

PATHOPHYSIOLOGY

Lightning often travels over the surface of the body in a phenomenon called *flashover* and is therefore less likely to cause internal cardiac injury or muscle necrosis than is human-generated electrical energy. Wet skin may actually decrease the risk of internal injury, helping the current travel along the outside of the body. Flashover explains how victims may survive a lightning strike with little or no injury. Lightning causes internal injury through blunt mechanical force, current flow through the body, and other mechanisms. The large current flow in lightning creates a pulsed magnetic field that can induce current flow in a nearby person.[69] This current can produce destructive effects.

Lightning emits brief but intense thermal radiation that produces rapid heating and expansion of the surrounding air. Tympanic membrane perforation and internal organ contusion may occur. Vaporization of sweat from the skin can occur with tearing of clothing, giving the appearance of an assault.[70] Lightning may inflict thermal injury as moisture on the victim's skin is transformed into steam, as electric current flows through deeper tissues, and through resistance heating of metal objects on the body or in clothing pockets. Lightning may melt metallic objects on the victim. Lightning can be conducted along metal fences, bleachers, plumbing pipes, and other structures. Intense photic stimulation may damage the retina or produce cataracts.

STUNNING (KERAUNOPARALYSIS)

Neurologic and muscular "stunning," referred to as *keraunoparalysis*, can follow lightning strike and may initially produce a variety of neurologic signs and symptoms.[71] Keraunoparalysis is associated with successful resuscitation after cardiorespiratory arrest. In cases of keraunoparalysis that resolve within an hour, there can be lower limb weakness that is greater than upper limb weakness. Other extremity-related signs and symptoms include sensory abnormalities, pallor, coolness, and diminished and absent pulses. Excessive autonomic nervous system stimulation may be responsible for these transient symptoms.[72] In some cases, keraunoparalysis persists for a longer time. In such cases, there is typically amnesia and "neurotic" behavior that slowly clears over a

TABLE 219-5 Comparison of Lightning and Electrical Injuries

Factor	Lightning	High-Voltage AC	Low-Voltage AC
Current duration	10 μs to 3 ms	Generally brief (1–2 s), but may be prolonged	0.3 s or many minutes
Typical voltage and current range	10 million to 2 billion V, 3000 to 200,000 A	600–200,000 V, <1000 A	<600 V, usually <20–30 A
Current characteristics	Unidirectional (DC)	Alternating (AC)	Alternating (AC)
Current pathway	Skin flashover; deeper pathways can result in burns	Horizontal (hand to hand), vertical (hand to foot)	Horizontal (hand to hand), vertical (hand to foot)
Tissue damage	Superficial and minor if no deep tissue pathway	Deep tissue destruction	Sometimes deep tissue destruction
Initial rhythm in cardiac arrest	Asystole	Asystole more than ventricular fibrillation	Ventricular fibrillation
Renal involvement	Myoglobinuria is uncommon, and renal failure is rare.	Myoglobinuria and renal failure are relatively common.	Myoglobinuria and renal failure occur occasionally.
Fasciotomy and amputation	Rarely necessary	Relatively common	Sometimes necessary
Blunt injury	Caused by explosive shock wave that can throw the person and cause eardrum rupture	Caused by falls, being thrown from current source, tetanic contractions	Caused by tetanic contraction, falls, being thrown from current source
Immediate cause of death	Prolonged apnea, blunt injury, deep tissue burns	Prolonged apnea, ventricular fibrillation, blunt injury, deep tissue burns	Ventricular fibrillation, prolonged apnea, blunt injury

Abbreviations: AC = alternating current; DC = direct current.

week. More persistent and sometimes permanent sequelae can include muscular weakness and pain, photophobia, and disturbances of neurologic control.[69]

TYPES OF LIGHTNING STRIKES

Lightning strikes in a number of different ways, some of which injure multiple victims. A *direct strike* occurs when the victim is struck directly by the lightning discharge. A *side flash* occurs when a nearby object is struck and current then traverses through the air to strike the victim. A side flash may injure multiple victims at once, as when a group huddles close to a structure that is struck. A *contact strike* occurs when lightning strikes an object the victim is holding and current is transferred from the object through the person to the ground. Lightning injury from indoor telephone use during a lightning storm is an example of contact strike. A *ground current* occurs when lightning hits the ground and current is transferred through the ground to nearby victims. The amount of electrical voltage and current decreases as the distance between the victim and strike point increases. This ground current can create a *stride potential* or step voltage between the victim's separated feet. The foot closer to the strike point will experience a higher electrical potential than the foot farther away. Therefore, electrical current can enter one foot, travel up that leg, through the torso, and down the other leg and exit the other foot. This can result in isolated neurovascular injury to the legs. Recently, a fifth mechanism, in which a weak *upward streamer* does not become connected to the completed lightning channel, was implicated in a fatal lightning injury.[73]

Immediate cardiac arrest from lightning strike results from depolarization of the myocardium and sustained asystole. Immediate respiratory arrest after lightning strike may be a result of depolarization and paralysis of the medullary respiratory center. **Both cardiac and respiratory arrest may be present without evidence of external injury.** Although cardiac automaticity may spontaneously return, concomitant respiratory arrest may persist and lead to a secondary hypoxic cardiac arrest.

CARE AT THE SCENE

Lightning can produce multiple victims because of multiple lightning strikes, stride potentials, and side flashes.[67] **In contrast to patients with cardiac arrest caused by mechanical trauma, persons with lightning injury who appear to be dead (in respiratory arrest, with or without cardiac arrest) should be treated first.** Such victims may have little physical damage, and they have a reasonable chance of successful resuscitation. Use of automated external defibrillators and other defibrillators along with CPR can be lifesaving. **Prolonged CPR is sometimes successful.**

During a storm, power lines may fall to the ground as a result of high winds, lightning-related damage to power lines and their support structures, and vehicular damage to power line support structures. Therefore, a person thought to have been hit by lightning may actually have been shocked by the stride potential related to a nearby power line lying on the ground. Physical findings suggestive of lightning injury may be subtle or nonexistent. Therefore, information about the scene of the accident may be just as informative as examination of the patient.

ED DIAGNOSIS AND TREATMENT

The usual advanced cardiac and trauma treatment principles apply, including assessment and stabilization of the airway, breathing, and circulation. Lightning victims in cardiac arrest have a better prognosis than those in cardiac arrest from coronary artery disease, so aggressive resuscitative efforts are indicated.[47] Hypotension is not an expected finding following lightning injury and warrants an investigation for hemorrhagic blood loss. Perform a careful secondary examination to detect occult injuries.[74] Cutaneous burns may help identify the current path and suggest potential organ injury. Initial ancillary studies include CBC, serum electrolyte levels, creatinine level, BUN level, glucose level, creatine kinase level, urinalysis, and ECG. Imaging studies (plain radiography, US, or CT) should be performed as dictated by suspected injuries. Other ancillary studies may be indicated depending on clinical circumstances.[75]

CARDIAC EFFECTS

In the victim with spontaneous circulation, hypertension and tachycardia are common findings, presumably because of sympathetic nervous system activation. Specific treatment is usually not necessary, because blood pressure and pulse rate will spontaneously decrease. Cardiac effects reported after lightning injury include global depression of myocardial contractility, coronary artery spasm, pericardial effusion, and atrial and ventricular arrhythmias. The ECG may show acute injury with ST-segment elevation and QT-interval prolongation. T-wave inversions may be seen, especially in the presence of neurologic injury. Myocardial infarction after lightning injury is unusual. CPR, automated external defibrillators, and other resuscitative measures should be used promptly.[47] Prolonged resuscitative efforts are sometimes successful. Therapeutic hypothermia can be considered as well.[76]

NEUROLOGIC INJURY

Many lightning-strike victims are rendered unconscious or have temporary lower extremity paralysis. Seizures may result from the passage of electric current through the brain or may be the result of mechanical brain injury or hypoxia. The most lethal neurologic injuries involve heat-induced coagulation of the cerebral cortex, development of epidural or subdural hematoma, and intracranial hemorrhage.

Autonomic dysfunction caused by lightning may produce pupillary dilation or anisocoria not related to brain injury, and these signs have no prognostic significance in comatose lightning-strike victims. Most neurologic injury related to lightning strike can be classified as immediate and transient or delayed and permanent, although some effects may be immediate and permanent. Transient effects that typically resolve in 24 hours include loss of consciousness, confusion, amnesia, and extremity paralysis. Delayed and often progressive disorders include seizures, muscular atrophy and amyotrophic lateral sclerosis, parkinsonian syndromes, progressive cerebellar ataxia, myelopathy with paraplegia or quadriplegia, and chronic pain syndromes.[30] Lightning can cause intracranial injury directly when passing through the head, as well as by secondary trauma. Therefore, CT scan is indicated in cases of coma, altered mental status, or persistent headache or confusion.

VASCULAR EFFECTS

Vasomotor spasm in an extremity is sometimes seen as a local response to lightning exposure. Possible mechanisms include sympathetic nervous stimulation, local arterial spasm, and ischemia of peripheral nerves. Skin color changes, from white to blue to red, may occur in extremities after lightning strike. Such changes are presumably from cycles of vasoconstriction and vasodilatation, with pallor and cyanosis followed by hyperemia. Severe vasoconstriction is thought to be responsible for loss of pulses, mottling of skin, coolness of extremities, loss of sensation, and paralysis due to ischemia of peripheral nerves. As vasoconstriction resolves spontaneously, these signs and symptoms often resolve. Because skeletal muscle injury is rare in lightning strike, compartment syndromes are less likely. If doubt exists, the presence of compartment syndrome and the need for fasciotomy may be confirmed by measurement of intracompartmental pressures and close clinical monitoring.

OCULAR INJURY

Ophthalmic injuries are common in lightning-strike victims, and lightning-induced cataracts are the most frequently observed ocular sequela.[77] Cataracts caused by lightning are usually bilateral. Cataract formation without evidence of current flow through the head or eyes, such as after brief exposure to an electric arc, has been described. Perhaps this is a result of damage of the lens by radiant energy. Cataracts may form weeks to years after the lightning injury. Lightning can affect any part of the eye, producing hyphema, vitreous hemorrhage, corneal abrasion, uveitis, retinal detachment or hemorrhage, macular holes,

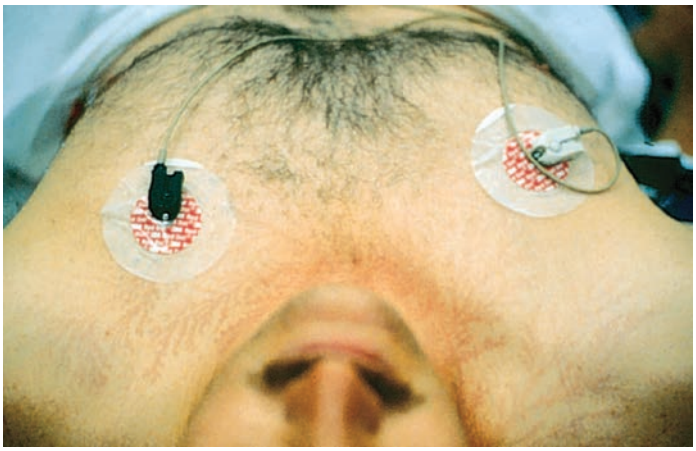

FIGURE 219-2. Lichtenberg figures with red lacy fern pattern seen on the upper chest. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB: *The Atlas of Emergency Medicine,* 2nd ed. © 2002 by McGraw-Hill, Inc., New York.]



FIGURE 219-3. Punctate lightning burns. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB: *The Atlas of Emergency Medicine,* 2nd ed. © 2002 by McGraw-Hill, Inc., New York.]

and optic nerve damage. A patient with discomfort or visual changes deserves a careful examination with follow-up.

AUDITORY INJURY

Blast effect producing tympanic membrane rupture is relatively common. Victims sustaining lightning strike via a conventional corded telephone are at higher risk for otologic injury, including persistent tinnitus, sensorineural deafness, ataxia, vertigo, and nystagmus.[66] In patients who are sleeping with an ear or eye on the ground near a lightning strike, temporary deafness or blindness can result.

MUSCULOSKELETAL INJURY

A variety of skeletal fractures can be seen from the blunt force injury associated with lightning strike. Intense myotonic contractions can produce shoulder dislocations. Rhabdomyolysis after lightning strike is unusual. Spinal fractures can be caused by tetanic muscle contractions, as well as by falls and other secondary trauma. Therefore, spinal immobilization should be maintained during resuscitation, to the extent possible under the circumstances, until spinal stability can be assessed. Because spinal fractures often occur at multiple levels in the same patient, the entire vertebral column should be imaged when a fracture is found at one level.

CUTANEOUS INJURY

There are six main dermatologic manifestations of lightning injury. *Lichtenberg figures* are considered pathognomonic for lightning strike and consist of a red superficial feathering or ferning pattern (**Figure 219-2**). These figures are the result of electron showering over the skin and are not true thermal burns; they disappear within 24 hours. *Flash burns* are similar to those found in arc welders, appearing as mild erythema, and may involve the cornea. *Punctate burns* (**Figure 219-3**) look similar to cigarette burns in that they are usually <1 cm and are full-thickness burns. *Contact burns* occur when metal close to the skin is heated from the lightning current. *Superficial erythema* and *blistering burns* have been described. *Linear burns*, <5 cm wide, occur in areas of skinfolds such as the axilla or groin. Contact wounds characteristic of electrical injury from human-produced sources are not commonly seen in lightning injuries. Cutaneous wounds are treated with customary wound or burn care, including tetanus prophylaxis, irrigation, debridement, and dressing.

DISPOSITION AND FOLLOW-UP

Patients should be carefully assessed for injuries. ECG and other monitoring are indicated as for any electric shock. Admission should be considered for most patients with persistent muscle pain, as well as those with persistent neurologic, cardiac rhythm, or vascular abnormalities. Follow-up is recommended to assess delayed effects of lightning, even for patients with no apparent injury.

SPECIAL POPULATIONS

In some cases, fetal injury and death have been noted to follow lightning strike with little or no maternal injury. One review reported that among 11 pregnant women who survived being struck by lightning, there were five cases of fetal death in utero, abortion, stillbirth, or neonatal death.[54] Abruptio placentae has also been reported. Monitoring of maternal uterine activity and fetal heart rate is recommended for at least 4 hours after a lightning strike to a pregnant woman. Such monitoring will alert the physician to the development of abruptio placentae, which can occur following any physical trauma.

INJURY DUE TO ELECTRONIC CONTROL DEVICES

PATHOPHYSIOLOGY

Electronic control devices (ECDs, also known as conductive energy devices or CEDs), such as the cattle prod, stun gun, and the Taser®, can lead to injuries. Approximately 11% of "legal intervention injuries" (i.e., injuries sustained while being taking into custody) are related to ECDs. The vast majority of ECD-injured patients are treated and released, but 6% are hospitalized.[78] TASER International, Inc. (Scottsdale, AZ) produces a series of devices that deliver high-voltage, low-amperage electrical pulses, typically at 10 to 20 cycles per second (subtetanic rate). The pulses are designed to induce involuntary muscle contraction, neuromuscular incapacitation, and/or pain. The likelihood of electrical injury is minimal[79-82]; however, reports have been published that attribute or associate cardiac arrest with these devices.[83,84] In addition, falls or other forceful movements resulting from electric current can lead to injury, as can use in flammable and other hazardous environments.[85] Some devices shoot wires with fishhook-like barbs on the ends that penetrate and hook into the skin; penetrating injuries can result from this mechanism. (See Video: Fishhook and Taser Removal.)

CLINICAL FEATURES

Most ECD injuries are limited to superficial punctures and minor lacerations and cutaneous burns. Reported significant injuries have included skull penetration,[86] eye perforation,[87,88] retinal detachment,[89]

testicular torsion,[90] miscarriage,[91] and pneumothorax,[90] as well as blunt trauma from falls and burns. Burns may occur when ECDs are used in flammable environments or when they are used to incapacitate someone on a hot surface.

Clinical evaluation should address the agitation underlying the use of the ECD. Patients may be agitated due to stimulant intoxication or other causes of medical delirium (including alcohol withdrawal or thyroid storm) and should be fully evaluated for both the underlying cause and the metabolic consequences of delirium, including hyperthermia, electrolyte abnormalities, rhabdomyolysis, and acidosis.[92]

TREATMENT AND DISPOSITION

A series of human studies (and some in healthy volunteers[93]) have suggested that ECDs do not cause or worsen hyperthermia, hyperkalemia, hypoxia, acidosis, and a variety of other problems often seen with in-custody deaths.[94-97] However, many underlying medical or mental health conditions may be at play in the patient who has required ECD discharge for restraint. Deaths reported after ECD use are typically in subjects with preexisting cardiac disease, history of agitation and long struggles with police, or acute substance use.[98] Determine why the ECD was used, obtain a past medical and mental health history, and obtain a good description of the patient's behavior before and after the incident. Careful evaluation and monitoring are needed in the patient with abnormal vital signs or who is ill-appearing, had prolonged struggle, may have mental health issues, or appears to be in agitated delirium. Assess for musculoskeletal injury. Because incidents involving the Taser or ECDs are likely to involve higher levels of overall scrutiny by police or legal officials, it seems most reasonable to be conservative in ED evaluation for symptoms other than burning at the skin site, and to obtain ECG, CBC, electrolytes, metabolic panel, total creatine phosphokinase, and other studies (perhaps toxicology) as suggested by the history or physical examination.

There are no reported guidelines or evidence-based studies relative to ED care. Patients who remain asymptomatic (i.e., have no symptoms other than burning at the skin site), have calmed down by the time of original assessment, have no history of loss of consciousness or significant cardiac disease or other comorbidities, have no signs of mental health issues, and appear well can usually be discharged. Patients who were severely agitated can be discharged if they have calmed down, maintained stable vital signs for 2 hours, have a normal physical and mental status exam, and have a normal 12-lead ECG and normal electrolytes and creatine phosphokinase. Those with abnormal vital signs, labs, or ECG, or with history of loss of consciousness or significant underlying cardiac disease, should be admitted for further observation.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 220

Mushroom Poisoning

Anne F. Brayer

INTRODUCTION AND EPIDEMIOLOGY

Mushrooms are a common toxic exposure, with an average of 7428 exposures per year from 1999 to 2016, with 62% of cases in children <6 years of age.[1] Approximately 40 exposures per year result in major harm, averaging three deaths per year.[1] Liver failure is the most common serious harm.[1]

Fortunately, the majority (86%) of reported mushroom exposures have a benign outcome.[1,2] There are no easily recognizable differences between nonpoisonous and poisonous mushrooms. Mushroom toxins are not heat labile and so are not destroyed or deactivated by cooking, canning, freezing, drying, or other means of food preparation.

Depending on the type of mushroom, adverse effects from ingestion range from mild GI symptoms to major cytotoxic effects resulting in organ failure and death. Toxicity varies based on the amount ingested, the age of the mushroom, the season, the geographic location, and the way in which the mushroom was prepared prior to ingestion. One person may show significant effects, whereas others may be asymptomatic after ingesting the same mushroom (**Table 220-1**). Mushroom toxicity is divided into early toxicity (within 2 hours after ingestion) and delayed toxicity (6 hours to 20 days later).

Mushroom poisoning occurs in four main groups of individuals: young children who ingest poisonous mushrooms inadvertently, wild mushroom foragers, individuals attempting suicide or homicide, and individuals looking for a hallucinatory "high." Identification of the mushroom ingested may be difficult and time consuming. Very often, foragers mix different species of mushrooms together, so it is not always clear that the species being identified is the same one that was ingested. Therefore, direct treatment by a patient's symptoms rather than by attempts at mushroom identification. **In a patient with a history of mushroom ingestion and ongoing symptoms, observe or admit the patient until symptoms and signs resolve and end-organ damage is excluded, or the mushroom has been clearly identified as nontoxic.** Treatment for mushroom poisoning is based on case reports and small series.[3]

Nearly all fatalities in the United States and Europe occur from ingestion of mushrooms of the *Amanita* species (*Amanita phalloides*, *Amanita virosa*, and *Amanita bisporigera*).[4] If *Amanita* ingestion is suspected, identification of the species may be helpful, but is difficult because there are many *Amanita* mushrooms that are nontoxic. *Amanita* species generally have warts on the cap (remnants of the membrane covering the emerging mushroom), which give it a spotted appearance. The gills are "free," ending before the stem begins. The stem characteristically has a membrane ring around it and widens as it enters the soil. In most cases, the stem of the mushroom is contained in a cup or volva, which may be underground (**Figures 220-1, 220-2,** and **220-3**).

EARLY-ONSET GI SYMPTOMS

PATHOPHYSIOLOGY

Most wild mushroom ingestions cause mild GI irritation, and mushrooms that cause GI irritation can be of many types. In North America and in almost every country, *Chlorophyllum molybdites* is particularly common and is sometimes mistaken for an *Amanita*.[3] Many little brown mushrooms found commonly in lawns, and often accidentally ingested by children, are in this category. *Omphalotus*, *Boletus*, *Entoloma*, *Gomphus*, *Hebeloma*, *Lactarius*, and *Verpa* genera are other examples for this group (**Figure 220-4**). The actual toxin varies with the species of mushroom, but most toxins are poorly described.

CLINICAL FEATURES

The majority of mushroom-induced intoxications are mild and do not prompt a visit to the ED.[1] *C. molybdites*, however, is an exception that may cause severe symptoms.[5] Typically, patients present with acute onset of vomiting and diarrhea <2 hours after ingesting the mushroom. There may be intestinal cramping, chills, headaches, and myalgias. Diarrhea is usually watery, but occasionally bloody with fecal leukocytes. Most commonly, symptoms are mild and self-limited. Symptoms usually resolve within 24 hours but may last up to several days. Vomiting and diarrhea can cause dehydration and electrolyte imbalance. The presentation may be confused with acute gastroenteritis or acute food poisoning if the patient does not offer the history of mushroom ingestion.

TREATMENT

Treat with activated charcoal, supportive care, and antiemetics. Give activated charcoal 0.5 to 1.0 gram/kg PO within the first hour of

TABLE 220-1 Mushrooms: Symptoms, Toxicity, and Treatment

Symptoms	Mushrooms	Toxicity	Treatment
GI symptoms			
Onset <2 h	*Chlorophyllum molybdites* *Omphalotus illudens* *Cantharellus cibarius* *Amanita caesarea*	Nausea, vomiting, diarrhea (occasionally bloody)	IV hydration Antiemetics
Onset 6–24 h	*Gyromitra esculenta* *Amanita phalloides* *Amanita bisporigera*	Initial: nausea, vomiting, diarrhea Day 2: rise in AST, ALT levels Day 3: hepatic failure	IV hydration, glucose; monitor AST, ALT, bilirubin, BUN, and creatinine levels, prothrombin time, partial thromboplastin time For *Amanita:* multiple-dose activated charcoal Consider *N*-acetylcysteine 150 milligrams/kg loading dose (see text) Consider penicillin G, 300,000–1,000,000 units/kg/d Silymarin, 20–40 milligrams/kg/d, where available Consider cimetidine, 4–10 grams/d Consider transfer to a center with active liver transplant program (see text)
Muscarinic syndrome Onset <30 min	*Inocybe* *Clitocybe*	SLUDGE syndrome (***s***alivation, ***l***acrimation, ***u***rination, ***d***efecation, ***G***I hypermotility, and ***e***mesis)	Supportive; atropine, 0.02 milligram/kg (minimum dose 0.1 milligram, maximum dose 1 milligram), repeated as needed for severe secretions
CNS excitement Onset <30 min	*Amanita muscaria* *Amanita pantherina*	Intoxication, dizziness, ataxia, visual disturbances, seizures, tachycardia, hypertension, warm dry skin, dry mouth, mydriasis (anticholinergic effects)	Supportive; sedation with benzodiazepines (e.g., lorazepam 0.05 milligram/kg, maximum dose 4 milligrams)
Hallucinations Onset <30 min	*Psilocybe* *Gymnopilus*	Visual hallucinations, ataxia	Supportive; sedation with benzodiazepines, external cooling
Disulfiram reaction 2–72 h after mushroom, and <30 min after alcohol	*Coprinus*	Headache, flushing, tachycardia, hyperventilation, shortness of breath, palpitations	Supportive; IV hydration, β-blockers for supraventricular tachycardia Norepinephrine for refractory hypotension
Renal compromise	*Cortinarius* spp *Amanitia smithiana*	GI symptoms initially, followed by flank pain, polyuria, anuria,	Supportive; monitor urine output, renal status, delayed renal transplant; IV hydration β-Blockers for supraventricular tachycardia Norepinephrine for refractory hypotension
Dermatitis 1–2 d after ingestion	Shiitake	Whip-like, linear, erythematous wheals, blanching erythematous patches, scattered petechiae, pruritus	Oral antihistamines, 0.1% triamcinolone ointment twice daily; spontaneously resolves within 1–3 wk

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.



FIGURE 220-1. *Amanita muscaria.* [Photo used with permission of Jilber Barutciyan.]



FIGURE 220-2. *Amanita pantherina.* [Photo used with permission of Jilber Barutciyan.]



FIGURE 220-3. *Amanita phalloides.* [Photo used with permission of Jilber Barutciyan.]

ingestion. There is no role for prophylactic decontamination therapy of asymptomatic patients.[6] Provide IV fluid and electrolyte replacement when necessary. Antiemetics can be given, but **do not give antidiarrheal agents**, because they may prolong exposure to the toxin.[2] In most cases, symptoms are self-limited, resolving within 12 to 24 hours. Some cases of *Amanita smithiana* ingestion present with early GI symptoms (between 30 minutes and 12 hours) and can progress to renal failure within 3 to 5 days.[7] Therefore, patients with toxicity or persistent symptoms should have laboratory evaluation for liver or renal dysfunction and observation for worsening.

Once vomiting has subsided and the patient is tolerating oral fluids, discharge from the ED is safe. Rarely, symptoms may persist and hospitalization may be needed for fluid and electrolyte replacement. Recommend outpatient follow-up within 5 days, and provide return precautions (urinary changes, lumbar or flank pain).[7]



FIGURE 220-4. *Omphalotus olearius.* [Photo used with permission of Jilber Barutciyan.]

EARLY-ONSET NEUROLOGIC SYMPTOMS

PATHOPHYSIOLOGY

Several classes of mushrooms cause neurologic symptoms. These include the hallucinogenic mushrooms ("magic mushrooms") that contain the chemical psilocybin, which is rapidly dephosphorylated by alkaline phosphatase to the more psychoactive chemical psilocin.[8] Psilocin acts on serotonergic neurons in the CNS, causing effects similar to those of lysergic acid diethylamide. Mushrooms of the *Psilocybe* genus, which are the most commonly ingested in this class, are small brown or gold mushrooms that commonly grow on dung in warmer climates throughout the Pacific Northwest and southeastern United States as well as warm regions of Central America, South America, Asia, and Australia.[9] They characteristically turn a greenish blue when bruised or cut. Nontoxic mushrooms may also be laced with phencyclidine or lysergic acid diethylamide and sold as hallucinogenic mushrooms.

Mushrooms containing the isoxazole derivatives ibotenic acid and muscimol also possess neurologic effects, which are thought to be mediated by γ-aminobutyric acid and anticholinergic activity. *Amanita muscaria* is the principle representative of this group of mushrooms and is easily identified (Figure 220-1). It has an orange or red cap with white warts (remnants of the universal veil present in young specimens), as well as a ring (annulus) and cup (volva) on the stem. *Amanita pantherina*, another member of the group, is 5 to 14 cm in length and diameter, with a white to brown cap, and has the ring and cup on the stem (Figure 220-2). Both specimens grow under trees in woodlands throughout North America.

CLINICAL FEATURES

Symptoms typically develop within 2 hours of ingestion of hallucinogenic mushrooms. Euphoria, a heightened imagination, a loss of the sense of time, and visual distortions or hallucinations are common. Tachycardia and hypertension may be noted because of the presence of phenylethylamine in psilocybin-containing mushrooms.[10] Fever and seizures have been reported in rare cases. Symptoms generally last 4 to 6 hours but can persist up to 12 hours.[11] There are infrequent reports of flashbacks for up to 4 months after ingestion, particularly in association with other substances that alter cognition such as alcohol or marijuana.[9]

Patients ingesting isoxazole-containing mushrooms usually present with symptoms within 30 minutes of ingestion. Signs of muscarinic poisoning are the first apparent (nausea, vomiting, diarrhea, vasodilation, diaphoresis, salivation). These are replaced by an atropine-like symptom complex about 30 minutes after ingestion (mydriasis, xerostomia, elevated temperature, increased blood pressure), along with drowsiness, amentia, dizziness, photosensitivity, euphoria, motor hyperactivity, ataxia, muscle jerking, hallucinations, and delirium with difficulty with perception of size, time, and place. Seizures have been reported in children. Draw laboratory studies to assess liver and kidney function. Symptoms are typically self-limited, resolving within 4 to 6 hours after ingestion. Headache and fatigue are reported to occur the day following ingestion, with headache lasting up to a few weeks.[9]

TREATMENT

Treatment for ingestion of hallucinogenic mushrooms is largely supportive. Place the patient in a darkened, quiet room, devoid of visual stimuli, and provide reassurance. If sedation is required, benzodiazepines such as diazepam or lorazepam are preferred. Do not give anticholinergic agents because they may aggravate delirium.

Treat symptomatic ingestion of isoxazole-containing mushrooms with activated charcoal. In patients with severe vomiting and diarrhea, replace fluids and electrolytes. Appropriately restrain patients who are agitated, and provide sedation as necessary with benzodiazepines (diazepam or lorazepam). Treat seizures with benzodiazepines.

Consider treatment with physostigmine only for patients with **severe** anticholinergic symptoms. Physostigmine can produce bradycardia, hypotension, and seizures. The dose is 1 to 2 milligrams IV in adults and 0.01 to 0.03 milligram/kg IV in children, administered slowly.

Monitor continuous cardiorespiratory effects and blood pressure during administration. Base the decision to discharge from the ED on duration of symptoms and need for ongoing pharmacologic sedation or intubation.

EARLY-ONSET MUSCARINIC SYMPTOMS

Muscarine was the first mushroom toxin to be identified.[12] Mushrooms of the *Inocybe* and *Clitocybe* genera are common causes of muscarinic poisoning (**Figure 220-5**). The *Inocybe* mushrooms are small brown mushrooms with conical caps, typically found under hardwoods and conifers. The *Clitocybe* mushrooms are usually found individually on lawns and in parks and are white to gray, with a cup-shaped cap. *A. muscaria*, despite its name, contains far less muscarine than these other groups and only rarely causes cholinergic poisoning symptoms. Isoxazole-containing mushrooms can cause transient muscarinic symptoms early after ingestion.

PATHOPHYSIOLOGY

Muscarine is a parasympathomimetic compound that is heat stable and acetylcholine like. It is not degraded by cholinesterase and, therefore, has a long duration of action.[13] Acetylcholine receptors on the heart, apocrine glands, and smooth muscle are activated by muscarine.[12] Mushrooms containing muscarine cause neurologic symptoms and muscarinic or cholinergic effects.

CLINICAL FEATURES

The symptoms of muscarinic intoxication are characterized by the **SLUDGE syndrome** (salivation, lacrimation, urination, defecation, GI hypermotility, and emesis). In addition to the SLUDGE syndrome, patients with muscarine ingestions can develop diaphoresis, muscle fasciculations, miosis, bradycardia, and bronchorrhea. Symptoms typically present within 30 minutes of ingestion and spontaneously resolve in 4 to 12 hours. Draw laboratory studies to assess for liver and kidney function.

TREATMENT

Treatment includes atropine and supportive care. In most cases, muscarinic symptoms are mild and self-limited. Supportive care is sufficient. Because emesis is a common presenting symptom, activated charcoal administration is often difficult. Patients with severe vomiting may require IV fluid and electrolyte replacement.

Atropine is an antidote for muscarinic symptoms and can be administered to patients with **severe** symptoms. It can be effective in treating bradycardia and hypotension unresponsive to IV fluid administration. Atropine is helpful in the treatment of diaphoresis, increased oral secretions, and bronchorrhea. It may also help reduce GI cramping, emesis, and diarrhea. The dose is 0.5 to 1.0 milligram IV for adults and 0.02 milligram/kg IV for children (minimum dose, 0.1 milligram; maximum dose, 1 milligram). The dose can be repeated as necessary to control bronchorrhea, bradycardia, or hypotension. Large doses may be necessary to treat severe toxicity. Patients should be carefully monitored during administration. Oxygen and inhaled β-agonists (albuterol) are recommended for the treatment of patients with increased pulmonary secretions and bronchospasm.

Symptoms of muscarinic poisoning frequently resolve within 12 hours of ingestion, and many patients can be safely discharged from the ED after observation when symptoms have subsided and clinical and laboratory parameters are normal.



FIGURE 220-5. *Clitocybe candicans.* [Photo used with permission of Jilber Barutciyan.]

DELAYED-ONSET GI SYMPTOMS

Mushrooms of two different genera, *Gyromitra* and *Amanita*, cause significant toxicity, which characteristically presents several hours after ingestion. *Gyromitra esculenta* (the false morel) is an uncommon cause of poisoning in North America, but is more common in Scandinavia and Europe.[4] *G. esculenta* has a brown convoluted top resembling a brain and is often mistaken for the highly sought-after morel mushroom. *A. phalloides* and *A. bisporigera* are common in the Northern Hemisphere and are found throughout the West Coast, Midwest, and parts of the Northeast of the United States. Immigrants may mistake these mushrooms for edible varieties common in eastern Asia. Mushrooms of the *Amanita* genus are responsible for 95% of deaths associated with mushrooms, primarily due to liver failure and acute kidney injury. Toxic ingestions in North America occur most commonly in the autumn.

PATHOPHYSIOLOGY

Gyromitrin (*N*-methyl-*N*-formylhydrazone) is a volatile heat-labile toxin and primarily responsible for symptoms. Gyromitrin concentration decreases significantly after boiling and desiccation.[14] Gyromitrin is hydrolyzed in the stomach to form *N*-methyl-*N*-formylhydrazine and *N*-methylhydrazine. *N*-Methylhydrazine binds to pyridoxine and interferes with enzymes that require pyridoxine as a cofactor. γ-Aminobutyric acid is lowered in the CNS, which may be a cause of associated seizures. *N*-Methyl-*N*-formylhydrazine is converted into a free radical in the liver and causes local hepatic necrosis by blocking the activity of the cytochrome P450 system, glutathione, and other hepatic enzyme systems.[14] These two chemicals explain the CNS and hepatic dysfunction characteristic of gyromitrin toxicity. The cause of the initial GI symptoms is not known.

A. phalloides contains several phallotoxins and amatoxins. Phallotoxin is a bi-cyclic peptide that alters the enterocyte cellular membrane, thereby causing early GI symptoms. Its effect is limited to the GI tract, because it is not absorbed by the intestine.[15] Amatoxins are bi-cyclic octapeptides that are rapidly absorbed through the intestinal mucosa. They are carried to the liver and undergo enterohepatic circulation, which results in prolonged toxin exposure after ingestion. Nine amatoxins have been identified, but α-amanitin (amanitin) appears the most physiologically active.[2] Kinetic studies in humans show that α-amanitin is cleared from the plasma within 48 hours.[16] Free radical formation may also be involved in toxicity.[17] α-Amanitin has the greatest effect on cells that undergo rapid protein synthesis and turnover, including cells of the GI tract mucosa, hepatocytes, and renal tubular epithelium.[18] In adults, the dose that causes 50% mortality is 0.1 milligram/kg of body weight, which is commonly contained in a single mushroom.[15]

Pathologic changes are noted in both gyromitrin and amatoxin toxicity. Patients who ingest gyromitrin-containing mushrooms show diffuse hepatocellular damage and interstitial nephritis. Patients who ingest amatoxin-containing mushrooms show fatty degeneration of the liver, with intranuclear collection of lipids and extensive hepatic necrosis. Electron microscopy shows vacuolization of the mitochondria and clumping of the chromatin in the nucleoli. There are extensive lipid peroxidation changes in both the nucleus and the cytoplasm.

CLINICAL FEATURES

The distinctive characteristics of gyromitrin-containing mushroom toxicity are intense GI signs and symptoms (nausea, vomiting, and watery diarrhea) that develop 6 to 24 hours after ingestion, typically between 6 and 8 hours.

Hypovolemia is common during this phase of toxicity. In severe cases, hepatic failure is evident on day 3 and may result in death as early as day 7. Serum transaminase levels may be significantly elevated. **Hypoglycemia** occurs during the GI phase and again in the acute hepatic failure phase.

Initial GI symptoms can be accompanied by dizziness, headache, seizures, incoordination, and muscle cramps. The initial GI symptoms resolve within 2 to 5 days.[5] In a mild ingestion, the neurologic symptoms persist for several days and resolve without sequelae.

Patients who ingest amatoxin-containing mushrooms also have delayed onset of GI symptoms (6 to 24 hours). The gastroenteritis is intense, often requiring fluid and electrolyte replacement. There are four stages in amatoxin poisoning. The first (latent) stage is characterized by the absence of any signs or symptoms and lasts up to 24 hours after ingestion. During the 12 to 24 hours of the second stage, GI symptoms such as intense cramping abdominal pain, nausea, vomiting, and diarrhea dominate the clinical picture. Both stools and vomitus may become bloody. Although right upper quadrant tenderness and hepatomegaly may be noted, results of liver function tests are usually normal. Patients who present during this stage are frequently misdiagnosed with gastroenteritis. The third, or convalescent, phase lasts 12 to 24 hours. During this stage, the patient feels and looks better, but levels of liver enzymes, such as aspartate aminotransferase, alanine aminotransferase, and bilirubin, begin to rise, heralding the onset of liver damage and need for continued monitoring. Renal function may also deteriorate. In the fourth and final stage, which begins 2 to 4 days after ingestion, transaminase levels rise dramatically, and liver and renal function deteriorate. Hyperbilirubinemia, coagulopathy, hypoglycemia, acidosis, hepatic encephalopathy, and hepatorenal syndrome are noted.[2]

In both *Gyromitra* and *Amanita* toxicity, prothrombin time may be elevated and unresponsive to administration of vitamin K or fresh frozen plasma. Amylase and lipase elevation suggests pancreatic damage, although symptomatic pancreatitis is rare. Abnormal laboratory findings in amatoxin poisoning include a decrease in neutrophils, lymphocytes, and platelets, and abnormal thyroid function results. Hypophosphatemia (primarily noted in children), hypocalcemia, and elevated insulin levels occur. None of these laboratory abnormalities correlates with clinical disease, and their cause is unknown.

The mortality from *Gyromitra* ingestion is estimated at 15% to 35% and is generally attributed to hepatic failure, renal failure, or fluid and electrolyte disorders.[5] More recently, mortality has been reduced to 10% to 15%, because of improved care for hepatic failure and liver transplantation. Patients who survive severe hepatic failure from amatoxin may develop signs of chronic active hepatitis with persistent elevation in liver transaminase levels, development of anti–smooth muscle antibodies, and presence of cryoglobulins. No prolonged effects from gyromitrin toxicity have been reported.

DIAGNOSIS

The diagnosis of gyromitrin toxicity is generally assumed from the clinical features and the identification of the mushroom ingested, either by the patient or from samples. Identification of *Amanita* species generally requires a trained mycologist. The **Meixner colorimetric test** is used to look for the presence of amatoxin. A drop of fresh mushroom pulp, methanol extract from dried mushrooms, or gastric material is placed on a high-lignin paper (e.g., newspaper) and allowed to dry. A drop of 10-N or 12-N hydrochloric acid is then applied to catalyze the reaction of the amatoxin with the lignin in the paper. The area will turn blue within 1 to 2 minutes if amatoxins are present, but the appearance of color may be delayed up to 30 minutes if the amatoxin concentration is low.[2] Although the test is sensitive, it is not very specific, and other nontoxic mushrooms may give a positive test result. Tests using thin-layer chromatography, high-performance liquid chromatography, and radioimmunoassay have been developed to detect amatoxin. Unfortunately, these assays are not generally available to clinicians and are used most often in research settings.[2] Amatoxin can be detected in plasma, urine, GI tract contents, and feces. However, its presence merely confirms amatoxin poisoning. Levels do not appear to correlate with clinical severity, and amatoxin is not detected in many patients, presumably because of rapid clearance.

TREATMENT

General treatment includes activated charcoal; continued monitoring for hypoglycemia, hepatic failure, renal failure, and coagulopathy; and supportive care. Administer activated charcoal to patients presenting with severe vomiting and diarrhea within a few hours of mushroom ingestion. Repeated doses of charcoal for at least the first 24 hours may be effective, particularly in the presence of amatoxin (because it undergoes enterohepatic circulation).[15] Fluid and electrolyte replacement is mandatory. Glucose level should be monitored and glucose replaced as needed. **Hypoglycemia is one of the most common causes of death in early mushroom toxicity.**

All patients who have ingested amatoxin- or gyromitrin-containing mushrooms (or suspected) should be closely monitored for 48 hours for the development of hepatic and renal failure. Electrolyte levels, liver enzyme levels, and prothrombin time should be monitored several times a day. Patients should be treated with a low-protein diet and should receive standard supportive therapy for hepatic failure. Fresh frozen plasma and vitamin K can be used for the treatment of prolonged prothrombin time, but in many cases, coagulopathy does not respond to treatment.

Patients who develop hepatic failure should be monitored closely, and in severe cases, preparations should be made for liver transplantation. Although no firm criteria exist, progressive coagulopathy, encephalopathy, and renal failure despite maximal medical therapy are frequently listed indications for emergency liver transplantation.[19] Consultation with a transplant center specialist is warranted for patients with aspartate aminotransferase level of ≥4000 IU/L.[20] Many patients have met these criteria and survived without transplantation, and many patients have died without meeting these criteria. Liver transplantation, however, does provide the only option for patients in fulminant hepatic failure and has been quite successful.

Gyromitrin-Specific Treatment Treat the neurologic symptoms associated with gyromitrin with high-dose pyridoxine. **Pyridoxine** provides the cofactor required for the regeneration of γ-aminobutyric acid. High doses of pyridoxine, 25 milligrams/kg IV over 30 minutes up to a maximum of 25 grams/d, are recommended, but doses of pyridoxine in excess of 40 grams are associated with severe peripheral neuropathy.[21,22] Pyridoxine does not affect the development or course of hepatic failure, and there is no specific therapy for gyromitrin-induced hepatic failure.

Amatoxin-Specific Treatment Although multiple modalities have been tried in the past with mixed results, **activated charcoal**, ***Silybum marianum,*** and ***N*-acetylcysteine** are emerging as the best-supported treatment modalities.[15,20,23] Early in the clinical course, repeated dosing of activated charcoal is thought to be beneficial by reducing the absorption of amatoxin as it undergoes enterohepatic circulation. *S. marianum,* a milk thistle isolate, is also thought to prevent toxicity by interfering with transmembrane transport during enterohepatic circulation and inhibiting the binding of α-amanitin to hepatocytes.[15,23] There is some evidence that *Silybum* has additional hepatoprotective effects that result from stimulating protein synthesis and inhibiting tumor necrosis factor-α release in damaged liver cells.[23] It is given as a loading dose of 5 milligrams/kg over 1 hour followed by 20 milligrams/kg/d for 6 days. This treatment is not currently approved by the U.S. Food and Drug Administration; it is available in Europe, and phase II/III clinical trials are in progress in the United States. *N*-Acetylcysteine is also beneficial as a means of reducing reactive metabolites by providing sulfhydryl groups for this purpose. It is given IV in three sequential doses of 150 milligrams/kg over 1 hour, 50 milligrams/kg over 4 hours, and 100 milligrams/kg over 16 hours.

Despite these therapies, amatoxin toxicity may lead to fulminant liver failure. In cases of amatoxin-induced liver failure, the amatoxin itself is rapidly absorbed and excreted, which limits the utility of hemoperfusion and/or hemodialysis. The Molecular Adsorbent Recirculation System® can support liver function while hepatocytes recover

or until transplantation becomes feasible.[24] Although randomized controlled trials are not available, numerous case reports have shown improved liver functioning coinciding with this device.[24] Orthotopic liver transplantation (the entire organ is replaced with a graft) and auxiliary partial orthotopic liver transplantation (a portion of the native liver is removed and replaced with a graft until recovery occurs) are both surgical options.[15]

High-dose penicillin G and ceftazidime have both demonstrated a capacity for decreasing the uptake of amanitin by hepatocytes.[18,25] However, these therapies appear to be less effective than using *Silybum* alone.[23] Thioctic acid is a free radical scavenger and has been used for many years but has not yet gained support in the literature.

Patients suspected of ingesting amatoxin- or gyromitrin-containing mushrooms should be admitted and monitored for 48 hours, with monitoring of hepatic and renal function.

DELAYED-ONSET RENAL FAILURE

Delayed-onset renal failure is seen after ingestion of *Cortinarius* (*Cortinarius orellanus*, *Cortinarius speciosissimus*, and *Cortinarius gentilis* and *A. smithiana* mushrooms.[26] ***Cortinarius*** species are found primarily in Europe. *A. smithiana* mushrooms are common in forest areas of western North America.[7]

PATHOPHYSIOLOGY

Orellanine and ortinarin A and B are the nephrotoxic compounds in species of *Cortinarius* (*C. orellanus*, *C. speciosissimus*, and *C. gentilis*). These toxins are heat stable, and their mechanisms of action are not well known. Orellanine and its derivatives are believed to inhibit protein synthesis in the kidneys. Histopathologic examination indicates interstitial nephritis with edema and leukocyte infiltration, tubular necrosis, basal membrane rupture, and fibrosis without glomerular injury in patients poisoned with orellanine-containing mushooms.[18,22,27]

Allenic norleucine (aminohexadienoic acid) and chlorocrotylglycine are the nephrotoxins found in *A. smithiana*.[26] Allenic norleucine has been shown to induce renal tubular epithelial necrosis and tends to exert its effect earlier than orellanine in cultured cell lines.[7]

CLINICAL FEATURES

Patients who ingest mushrooms containing nephrotoxins often present initially with GI symptoms, including nausea, vomiting, and nonbloody diarrhea. Symptoms begin several hours to days after ingestion and may persist for 3 days. Occasionally, paresthesias, abnormal taste, and cognitive dysfunction are reported. Symptoms of renal failure, including lumbar and flank pain, oliguria, or more rarely polyuria, begin between 3 and 20 days after ingestion. Patients who ingest *A. smithiana* tend to develop GI symptoms earlier, with a range of symptom onset between 30 minutes and 12 hours (median, 5 to 6 hours). Orellanine ingestion tends to present with GI symptoms later, with a range of 12 hours to 14 days after ingestion. Similarly, renal failure is noted to develop earlier in allenic norleucine cases (within 3 to 5 days) and occurs within 4 to 15 days of orellanine ingestion.[7] Many patients who ingest these mushrooms never develop renal dysfunction, which suggests variability in host sensitivity to their toxic effects. Consider allenic norleucine or orellanine toxicity from wild mushroom ingestion in a patient with unexplained acute renal failure.

TREATMENT

There is no specific treatment for patients who develop renal failure from ingestion of *Cortinarius* or *A. smithiana* mushrooms. Monitor urine output and electrolyte, calcium, magnesium, BUN, and creatinine levels. Hemodialysis is indicated for refractory hyperkalemia, refractory acidosis, uremic symptoms, or severe renal dysfunction. Supportive hemodialysis may be required, but many patients experience a spontaneous return of normal renal function. Because spontaneous improvement is reported, renal transplantation should be withheld for several months to monitor patient response. Renal transplantation has been used in several patients with good success.[28]

Monitor patients suspected of ingesting orellanine- or ortinarin-containing mushrooms for at least 72 hours for electrolyte abnormalities and renal failure.

DELAYED-ONSET DISULFIRAM REACTION

Perhaps most interesting, although clinically least important, is a mushroom toxin contained in the *Coprinus* genus. This mushroom, which is very common in North America, is known as "inky cap" or "shaggy mane." It is a tall, white, thin mushroom with a shaggy cap. As the mushroom ages, the cap liquefies and blackens, and black liquid drips from the necrosing cap. The mushroom contains coprine, which is chemically related to disulfiram.

PATHOPHYSIOLOGY

Coprine causes inhibition of alcohol dehydrogenase within 2 hours of ingestion, and activity may last up to 72 hours. If alcohol is consumed during this sensitive period, patients develop a typical disulfiram reaction. Mushrooms ingested at the same time as alcohol produce no toxicity.

CLINICAL FEATURES

Because of the delay between mushroom consumption and alcohol consumption, few patients link their symptoms to the ingestion of a mushroom. Symptoms include headache, paresthesias of distal extremities, metallic taste, flushing, palpitations, chest pain, nausea, vomiting, and diaphoresis and generally occur within minutes to several hours after alcohol consumption. Symptoms generally last for 2 to 4 hours but may last up to 2 days.[5] Most symptoms are mild. Diagnosis is made based on presence of the symptom complex and its association with alcohol consumption.

Because alcohol is readily absorbed from the GI tract, GI decontamination has no role and charcoal administration is not beneficial. Patients occasionally become hypotensive and respond to administration of IV fluids or, in refractory cases, norepinephrine. Excessive sympathetic activity can be inhibited by β-blockers.[5]

Most cases are self-limited, and patients can be discharged once they can tolerate oral fluids. Prior to discharge, educate patients about the link between alcohol consumption and mushroom ingestion.

SHIITAKE DERMATITIS

Shiitake dermatitis is a well-known entity in Japan, China, and Korea, and cases have been reported in Europe and the United States.[29,30] Shiitake dermatitis is a characteristic flagellate erythema appearing as whip-like, linear wheals that appear within 1 or 2 days of ingesting raw or cooked shiitake mushrooms. The rash tends to be pruritic and can also involve branching patches of erythema and scattered petechiae. The pathophysiology is not fully understood but is thought to be toxin-induced, involving the thermolabile polysaccharide lentinan that is found in the shiitake mushroom. Skin biopsy results are nonspecific.[29,30] Allergy testing in affected individuals is negative.[30]

Treat symptoms with 0.1% triamcinolone ointment twice daily and oral antihistamines. Regardless of treatment, the rash resolves spontaneously without hyperpigmentation in 1 to 4 weeks.[29,30]

The rash is self-limited, and no sequelae have been reported.

SPECIAL POPULATIONS

Toxic mushroom exposure during pregnancy has been reported.[28] In one series, a slightly lower birth weight was noted in infants born to mothers with toxic mushroom exposure than in infants of mothers with no such exposure. Most infants appeared to be healthy and developmentally normal, in keeping with the findings that amatoxins do not cross the placental barrier.[31,32]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 221

Poisonous Plants

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INTRODUCTION

Common poisonous and injurious plants number in the hundreds and have a wide variety of toxicities. This chapter focuses on the most important plant-related exposures clinically relevant to emergency medicine (**Tables 221-1** and **221-2**).[1,2] Individual plants are discussed in terms of their pathophysiology, clinical features (toxidromes), and treatment.[3] Highly poisonous plants (Table 221-1) are highlighted in depth below, and brief reviews are provided for other common poisonous plants. Table 221-2 organizes common poisonous plants according to toxin structure.

EPIDEMIOLOGY

In 2016, the American Association of Poison Control Centers received 47,793 reports of plant exposures. Of these cases, 28,636 involved children <5 years of age. There were an additional 1644 nonexposure calls that provided information about plants to callers.[2] The vast majority of exposures (96%) are unintentional ingestions. Cutaneous and ophthalmic exposures are common but generally go unreported. Although inhalational exposures are possible, they are rarely reported.

Unfortunately, obtaining an accurate plant exposure history can be difficult. Most exposures occur in children and are usually unwitnessed. Uncertainty typically surrounds these cases, particularly whether ingestion truly occurred. The timing and amount of exposure are also difficult to quantify in many of these situations. Furthermore, even when a plant is available, identification errors are common and a botanist's expertise may be required. In fact, data from the National Poison Data System demonstrate that medical providers and poison centers are unable to identify the plant approximately 15% of the time.[2] For photos of select toxic plants, the reader is referred to Lim et al[4] and Nelson and Balcik.[5]

GENERAL EVALUATION AND MANAGEMENT

CLINICAL FEATURES

Classification of plants and their toxicities is complex. The most straightforward approach for emergency physicians is to classify toxic plants by the mechanism of action of the toxin and then to further subclassify based on the specific toxin. This will help predict the toxicologic effects. The reverse process can be used if the patient presents with clinical findings (Table 221-2). Unfortunately, attributing one toxicologic syndrome per plant oversimplifies the complexity of plant chemistry. Plants often contain multiple toxic compounds, each of which produces its own toxicologic effects.

Moderate systemic effects as a consequence of plant-related exposures occur in about 1% of exposed patients. Severe life-threatening effects or disabling injuries are extremely uncommon and occur in only about 0.04% of exposed patients. Death occurs in <0.001% of exposed patients.

Dermatitis and GI irritation are the most commonly reported effects of plant toxicity. GI complaints occur commonly following ingestion, and additional toxic symptoms may accompany or follow. Although dermatitis is another commonly reported finding of plant toxicity, systemic toxicity rarely follows (see Table 221-3).

TABLE 221-1 Examples of Severely Poisonous Plants

- Poison hemlock (*Conium maculatum*)
- Yew (*Taxus* spp.)
- Foxglove (*Digitalis purpurea*)
- Oleander (*Nerium oleander*)
- Castor bean (*Ricinus communis*)
- Rosary pea (*Abrus precatorius*)
- Water hemlock (*Cicuta maculata*)
- Buckthorn (*Karwinskia humboldtiana*)

TREATMENT

Most plant-related exposures can be managed with supportive care. In patients able to tolerate oral administration and believed to have potentially concerning exposures, administer activated charcoal to prevent absorption of toxin from the GI tract. Because of the uncertainty surrounding plant exposures, observe asymptomatic or minimally symptomatic patients for 4 to 6 hours in the ED if the presumed toxin is believed to have a rapid onset of effect. Discharge asymptomatic patients and those with resolved minor toxicity after observation, with strict return precautions if symptoms develop. **Admit those with more than minimal findings because toxicity may continue to evolve in those patients exposed to toxins with delayed onset (e.g., cyanogenic glycosides, mitotic inhibitors, or toxalbumins).** This approach is generally applied to all patients with plant exposure because the scientific literature lacks adequate data to provide less conservative recommendations. There are few antidotes available to treat poisonings by plant toxins; none are unique to plant exposures but rather are generalized from use in other poisonings.

Report all exposures to the regional poison control center to obtain assistance with plant and toxin identification, to obtain assistance with patient management, and to enable collection of accurate data on toxic plant exposures. Unfortunately, data reported by the National Poison Data System do not require confirmation of exposure, and the incidence of consequential adverse effects is obscured by inconsequential or unconfirmed ingestions.

HIGHLY POISONOUS PLANTS AND COMMON TOXIC PLANTS

NICOTINIC AND NICOTINE-LIKE TOXINS (POISON HEMLOCK)

In *Phaedo*, Plato details the death of Socrates: After drinking a potion consisting of the extracts of **poison hemlock** (*Conium maculatum*), he slowly develops paralysis and dies. All parts of poison hemlock contain coniine and similar alkaloids that are structurally and functionally analogous to nicotine. Typically, ingestion of poison hemlock is due to misidentification because of its similarity in appearance to wild carrot or Queen Anne's lace (*Daucus carota*), parsley (*Petroselinum crispum*), parsnip (*Pastinaca sativa*) roots, or anise (*Pimpinella anisum*). Although most ingestions are unintentional, there are case reports of toxicity from intentional use by patients for a presumed opioid-like effect or for intentional self-harm.[6-8]

Clinical Features Overstimulation of nicotinic cholinergic receptors can rapidly progress from seemingly mild symptoms to death from respiratory failure. Clinical findings may appear within minutes. Mild effects include nervousness and tremor due to sympathomimetic stimulation. As toxicity progresses, patients exhibit more pronounced sympathomimetic features, parasympathetic findings, and paralysis from nicotinic receptor stimulation at the neuromuscular junction.

Treatment Management consists of GI decontamination with activated charcoal and supportive care, which may include respiratory support and administration of IV fluids, antidysrhythmics, and anticonvulsants.

SODIUM CHANNEL TOXINS (YEW, RHODODENDRON, LAUREL, MONKSHOOD, LARKSPUR)

A number of plants across different classifications cause sodium channel effects that result in cardiac, respiratory, GI, and CNS effects. **Yew** (*Taxus* spp.) contains taxine alkaloids in all parts of the shrub except

TABLE 221-2 Classification of Poisonous Plants

Toxin Structure	Examples
Alkaloids	
Solanine and chaconine	Green potato leaves, American nightshade, black nightshade (Solanaceae)
Anticholinergics	Deadly nightshade (*Atropa belladonna*) Angel's trumpet or jimson weed (*Datura* spp. and *Solandra* spp.) Henbane (*Hycoscyamus niger*) Mandrake (*Mandragora officinarum*)
Cholinergics	Calabar bean (*Physostigma venenosum*) Pilocarpus (*Pilocarpus* spp., often grouped and called jaborandi)
Nicotinic and nicotine-like	Tobacco (*Nicotiana* spp.) Poison hemlock (*Conium maculatum*) Golden chain (*Laburnum anagyroides*) Blue cohosh (*Caulophyllum thalictroides*) Lupin (*Lupinus* spp.)
Psychotropics	Peyote (*Lophophora williamsii*) Nutmeg and mace (*Myristica fragrans*) Morning glory (*Argyreia* spp. and *Ipomoea* spp.) Hawaiian baby woodrose seeds (*Argyreia nervosa*) Ayahuasca (*Banisteriopsis caapi*)
Hepatotoxic pyrrolizidines	Comfrey (*Symphytum officinale*) Sassafras (*Sassafras albidum*) Ragwort (*Heliotropium* spp.)
Sodium channel modulators	Monkshood (*Aconitum* spp.) Larkspur (*Delphinium* spp.) False or green hellebore (*Veratrum* spp.) Yew (*Taxus* spp.)
Antimitotic alkaloids and resins	Autumn crocus (*Colchicum autumnale*) Mayapple (*Podophyllum peltatum*) Wild mandrake (*Podophyllum emodi*) Glory lily (*Gloriosa superba*) Madagascar periwinkle (*Catharanthus roseus*)
Glycosides	
Cardioactive steroids or cardiac glycosides	Foxglove (*Digitalis purpurea*) Lily of the valley (*Convallaria majalis*) Oleander (*Nerium oleander*) Christmas rose (*Helleborus niger*) Milkweed (*Asclepias* spp.) Squill (*Urginea maritime* and *Urginea indica*) Yellow oleander (*Thevetia peruviana*)
Cyanogenic glycosides	Almond, apricot, and cherry pits (*Prunus* spp.) Tapioca plant, cassava (*Manihot esculenta*) Elderberry (*Sambucus canadensis*) Hydrangea (*Hydrangea macrophylla*)
Salicylates	Poplar species (*Populus* spp.) Willow species (*Salix* spp.)
Proteins, peptides, and lectins	
Toxalbumins	Castor bean (*Ricinus communis*) Rosary pea (*Abrus precatorius*) Pokeweed (*Phytolacca americana*) Black locust (*Robinia pseudoacacia*) American mistletoe (*Phoradendron flavescens*) European mistletoe (*Viscum album*) Black vomit nut (*Jatropha curcas*)
Hypoglycin	Ackee fruit (*Blighia sapida*) Litchi (or lychee) fruit (Sapindaceae spp.)
Carboxylic acids	
Calcium oxalate crystals	Dumbcane (*Dieffenbachia* spp.) Philodendron (*Philodendron* spp.) Caladium (*Caladium* spp.) Jack in the pulpit (*Arisaema triphyllum*) Elephant's ear (*Colocasia* spp.) Rhubarb (*Rheum raponticum*)
Alcohols	
Convulsants	Water hemlock (*Cicuta maculata*)
Phenols and phenylpropanoids	
Coumarins and derivatives	Sweet clover (*Melilotus* spp.) Tonka beans (*Dipteryx* spp.) Sweet-scented bedstraw (*Galium triflorum*) Red clover (*Trifolium pretense*)
Capsaicin	Cayenne pepper (*Capsicum* spp.)
Demyelination	Buckthorn or coyotillo (*Karwinskia humboldtiana*)
Terpenoids and resins	
Grayanotoxin (sodium channel blockers)	Azalea and rhododendron (*Rhododoendron* spp.), mountain laurel (*Kalmia latifolia*)
Kava lactones	Kava kava (*Piper methysticum*)
Thujone	Grand wormwood (*Artemisia absinthium*)
Anisatin	Star anise (*Illicum* spp.)
Tetrahydrocannabinol	Marijuana (*Cannabis sativa*)

the aril, which is the berry's red fleshy portion. The hard seed inside of the berry also contains taxine alkaloids that block sodium and calcium channels.[9,10] Few effects are to be expected if ingestions are small or if berries are consumed without crushing the central seed. However, large ingestions can lead to more serious adverse effects or death.

Grayanotoxins are a class of 18 terpenoids that either inhibit or open sodium channels depending on the specific toxin.[11] They are found in the leaves, flowers, and nectar of several plants such as **azaleas** and **rhododendron** (*Rhododendron* spp.). They are also found in the **mountain laurel** (*Kalmia latifolia*). Ingestion of the leaves, flower, or honey from the nectar of the flower can result in toxicity.[5]

Aconitine and other aconite alkaloids, found in **monkshood** (*Aconitum* spp.) and **larkspur** (*Delphinium* spp.), activate cardiac, and less so neuronal, sodium channels. Higher aconite alkaloid concentrations correlate with the development of ventricular dysrhythmias.[12] Monkshood is sometimes used in traditional Chinese medicine as an inotrope. False or **green hellebore** (*Veratrum* spp.) is often confused for leeks by foragers, and these plants contain veratridine and other assorted veratrum alkaloids, which function similarly to aconitine.

Clinical Features Regardless of the particular alkaloid or terpenoid and its specific mechanism of cardiac toxicity, findings after ingestion may variably include salivation, lacrimation, bradycardia or tachycardia, cardiac dysrhythmias, hypotension, hyperkalemia, paresthesias, muscle weakness, respiratory failure, seizures, and potentially death.[5,9,13]

Treatment Early after ingestion, activated charcoal may decrease absorption from the GI tract. No antidote is available, and symptomatic patients should receive supportive care such as IV fluids or vasopressors if hypotensive. Atropine is typically effective for bradycardia, although pacing has been used in refractory cases.[11] Antidysrhythmics, such as amiodarone, procainamide, or flecainide, may be needed for malignant dysrhythmias.[4,12] Cardioversion for wide-complex dysrhythmias can be

attempted in unstable patients with the understanding that instability may persist and dysrhythmias may recur given the underlying channelopathy. Case reports describe successful use of cardiopulmonary bypass or extracorporeal membrane oxygenation in treating critically ill patients with refractory cardiac toxicity from yew poisoning and aconite poisoning.[4,9,12,14,15]

CARDIOACTIVE STEROIDS (FOXGLOVE, OLEANDER)

Cardioactive steroids are found in many plants, including **foxglove** (*Digitalis* spp.), **oleander** (*Nerium* spp.), **dogbane** (*Apocynum cannabinum*), **lily of the valley** (*Convallaria majalis*), and **milkweed** (*Asclepias* spp.). Cardioactive steroids, sometimes called cardiac glycosides, inhibit the sodium/potassium–adenosine triphosphatase pump.

Clinical Features Acute toxicity closely resembles that from digoxin and includes early GI effects followed by cardiac dysrhythmias. Serum digoxin concentrations may be used to qualitatively confirm cardioactive steroid exposure due to cross-reaction with the laboratory assay, but the absolute value holds little clinical quantitative value.

Treatment Early after ingestion, oral activated charcoal may decrease systemic exposure by preventing absorption.[16] Assess serum potassium concentration and obtain an ECG to aid in prognosis and therapy. Administer digoxin immune Fab fragments to patients with a serum potassium >5 mEq/L after an acute overdose or any cardiac dysrhythmia.[17] Unlike with digoxin, antidote dosing should be empiric (10 vials as an initial dose), and the digoxin concentration should not be used to calculate dosing, because the assay is not an accurate reflection of toxin burden. Avoid transvenous pacing and calcium administration for the increased theoretical risks of inducing a dysrhythmia. Traditional treatments for hyperkalemia such as insulin, calcium, sodium bicarbonate, or hemodialysis are usually unnecessary if digoxin immune Fab is administered.

TOXALBUMINS (CASTOR BEAN, RICIN)

Ricin and abrin are examples of toxalbumins that can be extracted from the **castor bean** (*Ricinus communis*) and **rosary pea** (*Abrus precatorius*), respectively. Ricin, in particular, is a potential biologic weapon and has been implicated in a number of attempted assassinations.

These toxalbumins are proteins, peptides, or lectins, which exert their toxicity by entering cells and inhibiting protein synthesis.

Clinical Features The clinical syndrome associated with the toxalbumins depends on quantity as well as route of exposure. Although one castor bean contains enough ricin to kill, its toxicity is typically limited following ingestion. Even if the castor bean is chewed to break the protective hard shell that sequesters the toxin, the enteral absorption of ricin is poor, which tends to limit toxicity to diarrhea and abdominal pain.[18] Most unintentional toxalbumin ingestions reported to poison centers did not result in severe toxicity, but the small sample size and reporting bias associated with poison center data should not discourage providers from treating and observing potential ingestions for signs of toxicity.[18] Although delayed systemic toxicity is possible following large ingestions, this is more concerning following parenteral exposures. Systemic organ dysfunction includes cardiac, neurologic, hepatic, and renal sequelae. Inhalational exposures are rapidly progressive and can result in life-threatening respiratory failure, circulatory collapse, and death within 36 hours.[19]

Treatment Treat toxalbumin ingestion by administration of activated charcoal followed by a lengthy observation period. All routes of exposure can be fatal, but hydration and aggressive supportive care significantly reduce mortality. More information about ricin can be found at the Centers for Disease Control and Prevention website (http://www.emergency.cdc.gov/agent/ricin).

Toxalbumins are found in a number of other plants such as **American mistletoe** (*Phoradendron flavescens*) and **European mistletoe** (*Viscum album*). The leaves and stems contain phoratoxin and viscumin, both of which are less potent than ricin. The berries also contain low levels of toxins that may result in gastroenteritis following large doses. These berries are abundant in homes during the holiday season and are attractive to children. Fortunately, significant morbidity after berry ingestion is rare, although single incidents of seizure, gait instability, hepatotoxicity, and death have been reported.[20] Patients who remain asymptomatic for 6 hours after ingestion can be discharged with return precautions, while patients who develop GI symptoms typically do well with fluids and electrolyte monitoring.[21]

CONVULSANTS (WATER HEMLOCK)

Cicutoxin is a diol found in the **water hemlock** (*Cicuta maculata*), **western water hemlock** (*Cicuta douglasii*), and **hemlock water dropwort** (*Oenanthe crocata*). These plants are often mistaken for wild parsnip, turnip, or parsley, causing toxicity through dermal or enteric absorption. All parts of the plant are poisonous, with the highest concentration of cicutoxin in the tuber. Cicutoxin's mechanism of action is not fully understood. However, it may impair γ-aminobutyric acid receptor or potassium channel function.

Clinical Features Toxicity can manifest as early as 15 minutes following exposure. Mild effects include GI discomfort, followed by bradycardia, hypotension, respiratory distress, seizures, and death. Seizures may be severe and refractory to conventional anticonvulsant therapy. The mortality rate may be as high as 30%.[22]

Treatment Treatment consists of GI decontamination with activated charcoal and supportive care. Treat seizures with γ-aminobutyric acid agonists such as benzodiazepines or barbiturates.

DEMYELINATING ANTHRACENONES (BUCKTHORN)

Buckthorn or **coyotillo** (*Karwinskia humboldtiana*), which is found in the southwestern United States, Mexico, Central America, and the Caribbean, contains demyelinating anthracenones that lead to progressive muscle weakness that resembles Guillain-Barré syndrome. Weakness occurs weeks after ingestion, rendering GI decontamination futile in symptomatic patients. In severe cases, respiratory paralysis can lead to death without respiratory support. There is no antidote, and treatment is largely supportive until recovery.[5]

BELLADONNA ALKALOIDS (NIGHTSHADE, JIMSONWEED, HENBANE)

Deadly nightshade (*Atropa belladonna*), **jimsonweed** (*Datura* spp.), and **henbane** (*Hyoscyamus niger*) all contain atropine or atropine-like alkaloids such as hyoscyamine and scopolamine.

Clinical Features Ingestion or smoking results in antimuscarinic effects such as tachycardia, hyperthermia, mydriasis, decreased bowel sounds, urinary retention, altered mental status, and dry, flushed skin, although only some features of the toxidrome may be present.[23] Severe poisoning can include seizures, coma, and death. Onset of effects depends on route of exposure, but findings should be evident within 4 hours. Exposures most commonly are intentional, such as through experimentation with the plant's psychoactive properties.[24]

Treatment Treatment is largely supportive. Benzodiazepines are useful in calming patients, but avoid antipsychotics such as haloperidol to prevent further antimuscarinic activity. Physostigmine inhibits cholinesterase, resulting in increased synaptic concentrations of acetylcholine that can overcome the muscarinic antagonism. Physostigmine is generally indicated only for patients with moderate to severe clinical toxicity. Improvement in effect may be transient, and patients can require repeat dosing if toxicity recrudesces. Patients who receive physostigmine may improve faster and require shorter hospitalizations than patients receiving sedative-hypnotics.

ANTIMITOTIC ALKALOIDS (AUTUMN CROCUS, GLORY LILY, MAYAPPLE)

Colchicine is contained in all parts of the **autumn crocus** (*Colchicum autumnale*) and **glory lily** (*Gloriosa superba*). Colchicine halts cellular mitosis by inhibiting microtubule formation. Gastroenteritis, which may be delayed (2 to 24 hours), is followed by multisystem organ failure. Common effects include coagulopathy, bone marrow suppression with granulocytopenia and thrombocytopenia, cardiac dysrhythmias, cardiogenic shock, acute respiratory distress syndrome, hepatic failure,

delirium, seizures, coma, and death. If patients survive, alopecia and neuropathy may develop. Mild toxicity is expected if GI symptoms begin >9 hours after ingestion.[25,26]

Podophyllin is an extract of the roots of the **mayapple plant** (*Podophyllum peltatum*). This extract contains a mixture of toxins including podophyllotoxin, which inhibits topoisomerase II and microtubule formation. Toxicity is characterized by obtundation, coagulopathy, hematologic suppression, renal failure, GI irritation, hepatotoxicity, and death.[5]

Early after ingestion, pursue aggressive GI decontamination because there is no antidote and toxicity can be fatal due to multisystem organ involvement. Due to colchicine's potential for delayed onset of toxicity, observe exposed patients for a prolonged period. In addition to GI decontamination with activated charcoal, treatment usually requires aggressive fluid resuscitation and aggressive supportive care. Colchicine-specific Fab fragments have been used in colchicine-poisoned patients with some success experimentally but are not commercially available.

CALCIUM OXALATE (ELEPHANT'S EAR)

Many common household ornamental plants contain crystalline calcium oxalate. Examples include **dumbcane** (*Dieffenbachia* spp.), **elephant's ear** (*Colocasia* spp.), and **philodendron** (*Philodendron* spp.). The calcium oxalate crystals are needle shaped and are bundled in raphides that also contain proteolytic enzymes and other chemicals. The contents are extruded when the plant is injured, causing both direct trauma from the crystals and inflammation due to the chemicals' effects.

Clinical Features Ingestion of calcium oxalate–containing plants results in immediate oropharyngeal pain and swelling. This pain usually limits the amount of plant ingested. In serious cases, the swelling can involve upper airway structures and cause respiratory compromise due to obstruction.[27,28] Ocular exposures to the calcium oxalate–containing plants result in ocular pain, corneal injury, and conjunctivitis. Pain and swelling can last up to 8 days.

Treatment Patients with oropharyngeal swelling and pain following ingestion tend to improve with supportive care. Anti-inflammatories may decrease swelling and provide analgesia. Topical treatments such as ice, ice water, and ice cream are soothing and can be given in patients with stable, patent airways. Patients at risk of airway obstruction must be closely monitored and should be quickly intubated if progressing. Consider steroid administration; however, there are no trials demonstrating outcome improvement with steroid use.

CYANOGENIC PLANTS (*PRUNUS* SPECIES)

Several thousand plants, including many common vegetables and fruits, contain cyanogenic compounds such as amygdalin. Fortunately, the toxins are either sequestered in nonconsumed portions of the foods (e.g., seeds) or exist in quantities that are not clinically significant. Amygdalin is found in the leaves, bark, and seeds of those fruits of the ***Prunus* species**, including pears, apples, plums, peaches, and apricots. Although the aril (fruit portion) of these plants is nontoxic, ingestion of the other portions of the plants and their seeds can result in the liberation of hydrogen cyanide from amygdalin in the GI tract. Linamarin and lotaustralin are present in **cassava** (*Manihot esculenta*) and are similarly hydrolyzed to liberate hydrogen cyanide.[5,29] If prepared correctly, the cyanogenic glycosides are detoxified prior to consumption.[30,31] Initial GI irritation effects may be delayed; tissue hypoxia can follow. Rapid progression of toxicity can occur, and treatment for cyanide poisoning should be initiated immediately.

CAPSAICIN (PEPPERS)

Capsicum peppers contain capsaicin, a phenylpropanoid toxin that causes irritation, burning, and pain upon contact with skin and mucous membranes. This toxin enhances the release of substance P from small unmyelinated nerve fibers, which stimulate nociceptors that cause the sensation of burning or heat. Contact typically occurs as a result of self-inoculation while preparing peppers or exposure to spraying of pepper extracts in self-defense. Decontaminate affected areas by irrigation with copious amounts of water and gentle hand soap. Ocular exposures may require aggressive decontamination and ophthalmologic evaluation. Analgesics may be necessary.

MISCELLANEOUS GI TOXINS

Solanine and chaconine are glycoalkaloids that are present in many common plants and vegetables of the ***Solanum* species**. Unripe eggplant, green potatoes, and their sprouts contain a small amount of these heat-labile glycoalkaloids. Ingestion may cause GI effects such as vomiting, diarrhea, and abdominal pain, which can be delayed as long as 24 hours. CNS symptoms such as hallucinations, delirium, and obtundation are reported.[21,32] There is no specific antidote for solanine or chaconine poisoning, and supportive care is usually sufficient.

Pokeweed (*Phytolacca americana*) contains phytolaccatoxin and similar phytotoxins in the leaves and roots. The mature berries are less toxic. Exposures can occur when foragers mistake the roots for other nontoxics such as parsnips or horseradish. Pokeweed is often prepared in poke salad or pokeroot tea. Toxicity is avoided if prepared by parboiling young greens. Incorrect preparation results in GI upset from direct mucosal irritation. Nausea, vomiting, hemorrhagic gastritis, abdominal pain, and profuse diarrhea may last for 48 hours.[33] Severe intoxications may rarely result in coma and death. Treatment is supportive. A nonconsequential lymphocytosis develops approximately 3 days after ingestion and typically resolves within 2 weeks.

Ackee fruit grows on the *Blighia sapida* tree, and it is a common ingredient in West African and Jamaican cuisine. Unripe ackee fruit contains the heat-stable toxins hypoglycin A and B. Hypoglycin A inhibits free fatty acids from entering the mitochondria, impairs substrate formation for gluconeogenesis, and prevents conversion of glutamate to γ-aminobutyric acid. The resulting clinical syndrome, which is characterized by severe vomiting and hypoglycemia, is **Jamaican vomiting sickness**. Severe cases develop acidemia, seizures, and encephalopathy.[5,34] Administer IV dextrose or a carbohydrate-heavy meal to hypoglycemic patients. Treat seizures liberally with benzodiazepines. However, seizures may be refractory to benzodiazepines if γ-aminobutyric acid concentrations are critically low. Rarely, chronic toxicity from hypoglycin A can lead to cholestatic hepatitis or fulminant liver failure.[5,35] Admit symptomatic patients for close monitoring and treatment.

Hypoglycin A is also found in litchi or **lychee fruit** (*Sapindaceae* species). Since 1995, outbreaks of life-threatening hypoglycemic encephalopathy in India have been associated with litchi harvesting season. Recently, researchers and epidemiologists linked the presence of hypoglycin A and a structurally similar toxin, methylenecyclopropylglycine (MCPG), to these outbreaks. The ingestion of these toxin-containing litchi in malnourished children has led to fatal hypoglycemia. Since this discovery, incidence of this illness has fallen following recommendations to limit litchi consumption, provide consistent nightly meals, and ensure timely correction of hypoglycemia.[36,37]

Holly (*Ilex* spp.) exposures are among the top 10 plant exposures reported to poison control centers.[2] Although the leaves are nontoxic, the attractive berries contain a mixture of toxins. The most consequential of this mixture are saponins, glycosides that cause abdominal pain, vomiting, and diarrhea. If fewer than six berries are ingested, minimal toxicity should follow.[38] Large ingestions with severe GI upset may result in electrolyte abnormalities. For symptomatic patients, treatment is supportive.

PLANT-INDUCED DERMATITIS

Dermal exposure to a number of plants can result in dermatitis. These exposures are some of the most commonly reported plant-related concerns reported to poison control centers in the United States.[2] Classification by mechanism of action can guide therapy (**Table 221-3**), but often, exposure to a single plant can result in injury due to multiple mechanisms.

MECHANICAL INJURY

Specialized plant structures can injure the dermis and serve as a nidus for entry of toxins. Needle-shaped crystals, such as calcium oxalate

TABLE 221-3 Plant-Induced Dermatitis

Dermatitis Classification	Mechanism of Injury	Specific Plants
Mechanical injury		
	Calcium oxalate	Dumbcane (*Diffenbachia maculate*) Philodendron (*Philodendron* spp.)
	Raphides and trichomes	Stinging nettles (*Urtica dioica*) Velvet bean or cowhage (*Mucuna pruriens*) Pineapple (*Bromeliaceae* spp.)
Irritant dermatitis		
	Phorbol esters	Cow's horn (*Euphorbia grandicornis*) Poinsettia (*Euphorbia pulcherrima*) Manchineel tree (*Hippomane mancinella*)
	Other chemical irritants	Stinging nettles (*Urtica dioica*) Velvet bean or cowhage (*M. pruriens*) Pineapple (*Bromeliaceae* spp.)
Contact dermatitis		
	Urushiol oleoresins	Gingko (Ginkgoaceae) Poison ivy, oak, and sumac (*Toxicodendron* spp.) Mango (*Mangifera indica*) Pistachio (*Pistacia vera*) Cashew (*Anacardium occidentale*)
	Miscellaneous antigens	Peruvian lily (*Alstroemeria* spp.) Narcissus and daffodils (*Narcissus* spp.) Tulips (*Tulipa* spp.) Primroses (*Primula* spp.)
Phytophotodermatitis		
	Furocoumarins	Cow parsnip (*Heracleum lanatum*) Wild parsnip (*Pastinaca sativa*) Lime (*Citrus aurantiifolia*)

crystal bundles, are found in a number of common plants, including **dumbcane** (*Dieffenbachia* spp.) and **philodendron** (*Philodendron* spp.). Needles of **pineapples** (*Bromeliaceae* spp.) and the hairs of **stinging nettles** (*Urtica dioica*) directly pierce the dermis, and chemical irritants in these structures cause further dermal injury (see next section).

IRRITANT DERMATITIS

Phorbol esters found in the sap of plants of the **Euphorbiaceae** (spurge) can cause dermal irritation following contact. The phorbol esters can penetrate the dermis upon contact. Symptoms such as erythema and bullae may develop shortly after direct contact. Ocular injuries and GI injury can also occur upon exposure or ingestion. Occasionally, aerosolized irritants can cause dermatitis or respiratory distress. Exposures to **poinsettia** (*Euphorbia pulcherrima*) are typically well tolerated despite the widespread belief that poinsettia ingestion is potentially life threatening. Occasionally, these plants cause hypersensitivity reactions because several members of the *Euphorbia* family carry common allergens, including trees that produce natural latex.[21] **Pineapples** (*Bromeliaceae* spp.), **stinging nettles** (*U. dioica*), and **dumbcane** (*Dieffenbachia* spp.) all introduce irritants such as proteolytic enzymes and other proinflammatory chemicals such as histamine, acetylcholine, and 5-hydroxytryptamine.[39]

ALLERGIC CONTACT DERMATITIS

Many plants can cause allergic contact dermatitis after repeat exposure. Sensitization occurs after a resin binds to skin proteins and forms an antigen. Reexposure then stimulates a T-cell–mediated immune response.

Poison ivy, **poison oak**, and **poison sumac** (*Toxicodendron* spp.) are ubiquitous sources of the antigenic resin urushiol. **Ginkgo** (Ginkgoaceae), mango (*Mangifera indica*), pistachio (*Pistacia vera*), and cashew (*Anacardium occidentale*) are common foods with urushiol-like compounds. In sensitized individuals, reexposure can result in urticaria and pruritus. Over 12 to 48 hours, symptoms may progress to varying degrees of vesiculobullous formation. Treatment usually consists of drying agents and local topical steroids, but systemic steroids may be necessary in severe cases. Some exposures can result in type I hypersensitivity or anaphylaxis. See Chapter 253, "Skin Disorders: Extremities."

Tulips (*Tulipa* spp.) and **daffodils** (*Narcissus* spp.) contain the glycoside tuliposide A. After hydrolysis, an allergen causes tulip fingers or daffodil itch with chronic reexposure, a painful and pruritic condition.

PHYTOPHOTODERMATITIS

Phytophotodermatitis occurs when furocoumarins are activated by sunlight and produce symptoms that resemble sunburn in the acute phase; erythema and bullae are common. When these symptoms heal, hyperpigmentation persists for months. The mechanism is unknown. Exposure can be directly through the dermis, or furocoumarins can be deposited in the skin following ingestion and subsequent systemic circulation. Many plants, including common foods, can cause phytophotodermatitis, including numerous citrus fruits, celery, carrots, and herbs.[5]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 222

Carbon Monoxide

Gerald E. Maloney

INTRODUCTION AND EPIDEMIOLOGY

Carbon monoxide (CO) is one of the most common toxic exposures that emergency physicians will encounter. It is the second most common cause of fatal poisoning, either intentional (suicidal) or accidental, in the United States,[1] and is suspected to be the most common cause of fatal poisoning worldwide. Despite a great deal of clinical experience and several randomized trials, there is no clear consensus on the best approach to managing CO exposures.[2]

Exact statistics for CO poisoning are difficult to determine, mainly due to incomplete reporting. In 2016, the American Association of Poison Control Centers Toxic Exposure Surveillance System reported 13,620 exposures, with 48 deaths.[3] Deaths in the United States from both intentional and accidental exposures are over 1200 per year.[4] Decades ago, vehicular emissions were the major source of CO poisoning in U.S. adults. Currently, nonvehicular sources, such as heating systems, are more common, as modern exhaust systems reduce CO emissions.[5] **Table 222-1** lists the most common sources of CO exposures.[3,6-8]

Peak incidence occurs in the fall and winter months, generally due to use of space heaters, wood-burning stoves, charcoal burning for heat, or portable generators without adequate ventilation.[4] It is not uncommon for whole families to be affected. Exposures have been reported in persons riding in the back of pickup trucks, as well as persons riding in vehicles with exhaust pipes occluded by snow. It is believed that CO poisoning is probably the most pressing danger from smoke inhalation and is a major contributor to fire-related deaths.

An unusual source of CO is methylene chloride, which is found in varnishes and paint strippers and bubbling fluid in Christmas ornaments. Routes of exposure are inhalational or by ingestion. Methylene

TABLE 222-1 Sources of Carbon Monoxide

- Wood or coal-burning stoves or heaters
- Propane-fueled heaters
- Structure fires
- Natural gas–powered heaters/furnaces/generators
- Automotive exhaust
- Motorboat exhaust
- Gasoline-powered generators or motors
- Forklifts/ice resurfacing machines
- Methylene chloride

chloride is metabolized in the liver to CO. As a result of ongoing metabolism, persistent elevation of carboxyhemoglobin occurs despite oxygen therapy.[9] Time to peak CO levels may be ≥8 hours.

PATHOPHYSIOLOGY

CO is typically described as a colorless, odorless gas. It is normally present in air at 10 ppm or less, perhaps higher in urban areas. CO is also an endogenous substance, with production occurring in the body during normal breakdown of heme. Normal physiologic CO levels (as carboxyhemoglobin) from this process are approximately 1% in healthy nonsmokers. Physiologic production can be increased in hemolysis or sepsis. CO toxicity causes profound tissue hypoxia and activation of inflammatory mediators that may lead to permanent injury of the heart, the CNS,[8,10-14] and less commonly, the peripheral nervous system.[15]

TISSUE HYPOXIA

The most easily quantified physiologic effect is binding to hemoglobin to form carboxyhemoglobin (COHb). The binding affinity of normal adult hemoglobin for carbon monoxide is over 200 times that for oxygen (**Figure 222-1**).[8] CO affinity is higher for fetal hemoglobin, which may account for potentially severe fetal toxicity.[8] Approximately 85% of CO is bound to hemoglobin, with the rest dissolved in plasma or bound intracellularly, often to myoglobin. CO shifts the oxyhemoglobin dissociation curve to the left, impairing oxygen release to the tissues. The half-life of COHb on room air at normal atmospheric pressure ranges from 249 to 320 minutes.[8] On 100% oxygen at atmospheric pressure, half-life is about 74 to 80 minutes.[8] The exception to this is COHb generated by methylene chloride exposure, which can have a half-life of ≥8 hours due to ongoing metabolic production.[9]

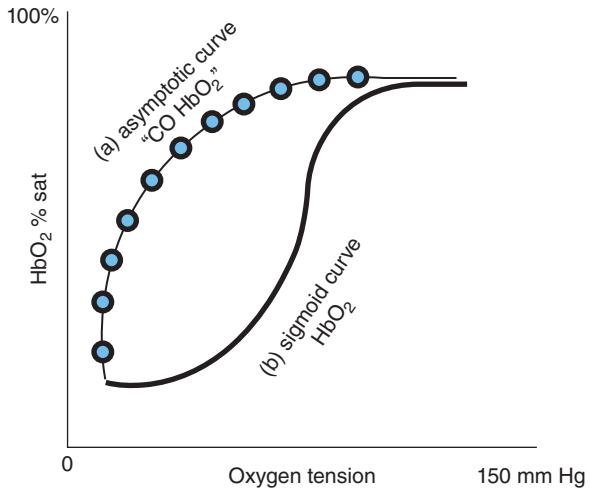

FIGURE 222-1. Carboxyhemoglobin "shift to the left" reshaping of the oxyhemoglobin (HbO_2) dissociation curve. (a) Carbon monoxide (CO)–affected HbO_2 dissociation curve (asymptotic) and (b) normal HbO_2 dissociation curve (sigmoid).

MITOCHONDRIAL INHIBITION

CO binds as ferrous heme a_3, disabling oxidative phosphorylation. Inhibition is more profound under the hypoxic conditions resulting from CO binding of hemoglobin. The net effect is decreased adenosine triphosphate production and production of free radicals, compromising tissues with the highest metabolic demand, the brain and heart, and generating lactic acidosis.

INFLAMMATORY AND PLATELET EFFECTS

CO activates platelets by displacing nitric oxide (NO) from platelet surface proteins; the displaced NO reacts with superoxide released from the effects of CO on the mitochondria to yield peroxynitrite, which further compromises mitochondrial function and stimulates platelet activation.[8,10] These combined effects stimulate neutrophils to degranulate, releasing myeloperoxidase and amplifying further degranulation and platelet adhesion.[14] The proinflammatory mediators catalyze lipid peroxidation of myelin basic proteins of nerve tissues, triggering lymphocyte and microglia activation in the brain[16] and causing neurologic injury and dysfunction, primarily of the CNS.[8,10] Cells in the basal ganglia are particularly sensitive to this neurotoxic effect and may be demonstrated by the globus pallidus lesions evident on CT or MRI. Platelet activation, endothelial injury, and cell apoptosis combine to yield several types of cardiac injury or dysfunction, including myocardial infarction, cardiomyopathy, and myocardial fibrosis.[8,10,11]

CARBOXYHEMOGLOBIN MEASUREMENT

Co-oximetry, which measures total hemoglobin as well as oxyhemoglobin, methemoglobin, and COHb saturation, is the only accurate measurement tool. There is excellent correlation between arterial and venous COHb levels, and so a **venous blood gas with co-oximetry** is sufficient in most cases.[17,18]

Standard pulse oximetry is unreliable in the diagnosis of CO poisoning. Routine arterial blood gas analyzers *without* co-oximetry calculate, rather than measure, saturation and add the contribution of dyshemoglobinemias to total oxygen saturation. The wavelengths for COHb fall into the same range as those for oxyhemoglobin, so standard pulse oximetry does not differentiate the two. As a result, in CO poisoning, the oxygen saturation obtained by standard pulse oximetry may appear artificially high[19,20] (Figure 222-1). When the pulse oximetry values, without co-oximetry, are compared to the oxygen saturation on an arterial blood gas, the oxygen saturation on the pulse oximeter will be higher than the saturation on the arterial blood gas. This is termed the **pulse oximetry gap.**

CLINICAL FEATURES

The clinical presentation of CO poisoning varies widely, leading to misdiagnosis in many cases (**Table 222-2**). An unconscious patient pulled from a house fire or from a running car in a closed garage does not represent a diagnostic dilemma; the patient with "flulike" symptoms, or the elderly person with syncope and ischemic ECG changes is difficult to correctly diagnose.

TABLE 222-2 Symptoms and Signs of Acute Carbon Monoxide Poisoning

Headache	Visual disturbances
Nausea/vomiting	Focal neurologic deficit
Ataxia	Dyspnea/tachypnea
Seizure	Bullous skin lesions
Syncope	Retinal hemorrhage
Chest pain/shortness of breath	ECG changes/dysrhythmias
Confusion	Cardiac arrest

HISTORY

History may be obviously suggestive, such as headache related to home propane heater use, with headache relief when leaving the home environment. Other situations, such as new-onset seizure, syncope, myocardial infarction, or cardiac arrest, are not as obvious. Concurrent symptoms in other members of the household, or even pets, may be a clue. However, even within a household, different persons may manifest symptoms differently, depending on age, comorbid disease, and proximity to the CO source. Occupational history may help, particularly in cases due to less common causes such as methylene chloride exposure. Exposure to any gas, propane-powered motors, or fumes from methylene chloride, especially if in a closed environment, may serve as a clue in nonspecific presentations. Consider CO poisoning in the differential diagnosis of coma, mental status changes, and elevated anion gap metabolic acidosis or lactic acidosis.

PHYSICAL EXAM

The classically touted finding of cherry red oral mucosa is rarely seen in living patients. Vital signs may reveal mild fever, tachycardia, tachypnea, hypertension, or hypotension. Severe poisoning can cause respiratory or cardiac arrest. Neurologic findings are variable, ranging from mild headache and confusion to irritability, seizures, focal neurologic deficits, ataxia, and coma. Retinal hemorrhages have been reported with severe poisoning. Skin findings include bullous lesions, generally seen in patients with prolonged immobility from pressure necrosis, although a direct toxic effect of CO on epidermal tissue is possible. Signs and symptoms of CO poisoning may be obscured by trauma or burns. A comatose patient removed from a fire scene should be assumed to have CO poisoning until proven otherwise, even in the absence of cutaneous or airway burns.

Although most discussions focus on an acute exposure, chronic poisoning, generally from occupational sources, also must be considered. Symptoms are usually more insidious, such as trouble concentrating, personality changes, neuropsychiatric problems, or memory loss, and can be difficult to diagnose.

INTERPRETING CARBOXYHEMOGLOBIN LEVELS

COHb levels are typically <1% to 2% in the nonsmoker and 4% to 10% in the active smoker.[21] Therefore, the diagnosis of CO poisoning is clinical: **an elevated COHb level along with a history of exposure and compatible symptoms or signs.** The COHb level is not an absolute indicator of clinical severity, nor is rapid clearance of an elevated level evidence of clinical improvement. When interpreting COHb levels, consider time and duration of exposure, time from exposure to presentation, treatment (such as high-flow oxygen) rendered in route, and clinical symptoms.[21] Although a markedly elevated COHb level, such as 50%, is a clear indicator of severe intoxication, a level of 10% in a patient with symptoms a few hours earlier can still be a marker of CO intoxication.

In one series, 30% of 163 patients with CO poisoning had a normal COHb level at ED presentation.[22] Even in the absence of an elevated COHb level, the diagnosis is still made by history of exposure and compatible symptoms or signs.

ANCILLARY TESTS

Obtain arterial blood gases and serum lactate levels. Elevated lactate from the interference in the electron transport chain, an unexplained elevated anion gap metabolic acidosis, elevated creatine phosphokinase, or elevated troponin may trigger an investigation for CO poisoning. Consider concomitant cyanide poisoning. Also consider additional toxicology testing for intentional CO poisoning.

ECG findings may range from entirely normal to ST-segment elevation myocardial infarction. There does not appear to be any classic CO ECG pattern. Of note, few patients with acute myocardial infarction due to CO poisoning have occlusive arterial lesions demonstrated by cardiac catheterization.[23] Patients diagnosed with CO poisoning have been reported to have an increased risk of subsequent myocardial infarction,[24] but this is controversial.[17] Poisoned patients appear to have an increased risk of future ischemic stroke.[25]



FIGURE 222-2. The scan shows characteristic bilateral symmetrical lucencies of the globus pallidus (*arrowheads*). [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *The Atlas of Emergency Medicine*, 4th ed. McGraw-Hill Education, Inc., 2016. Fig 17.53, p. 613. Photo contributor: Lawrence B. Stack, MD.]

IMAGING

Radiographic imaging is generally more helpful in establishing an alternative diagnosis. However, CO poisoning is associated with one specific radiographic finding, globus pallidus lesions (**Figure 222-2**). Lesions are generally bilateral, symmetric, and more common in severely poisoned patients.[10]

TREATMENT

Initial resuscitation is no different from initial resuscitation of any other critically ill patient. If CO poisoning is suspected, start 100% oxygen immediately. Identify risks for possible referral for hyperbaric oxygen treatment (**Table 222-3**).

ED TREATMENT OF CARBOXYHEMOGLOBIN WITH NO HIGH-RISK FEATURES

If there are no high-risk features and the patient has only mild symptoms such as headache, dizziness, or nausea/vomiting, continue 100% oxygen until symptoms have resolved and COHb is normal (<3%). An ED observation period of 6 hours, with 100% oxygen, is recommended

TABLE 222-3 Common Indications for Referral for Hyperbaric Oxygen Treatment

Loss of consciousness/syncope	Acute myocardial ischemia
Altered mental status/confusion	Cardiovascular dysfunction/dysrhythmia
Seizure	Hypotension
Coma	Severe metabolic acidosis
Focal neurologic deficit	Carboxyhemoglobin level ≥25%
Pregnancy carboxyhemoglobin level ≥15%	

by Hampson and colleagues[26] for those with mild symptoms. Methylene chloride exposure requires ≥8 hours of observation and oxygen treatment.

TREATMENT OF CARBOXYHEMOGLOBIN WITH HIGH-RISK FEATURES

American College of Emergency Physicians guidelines recommend that emergency providers "should use HBO_2 [hyperbaric oxygen] therapy or high-flow normobaric therapy for acute CO-poisoned patients."[20] However, two expert societies, the Undersea and Hyperbaric Medicine Society and the Tenth European Consensus Conference on Hyperbaric Medicine, recommend hyperbaric oxygen for the treatment of symptomatic CO poisoning.[27,28] The indications for hyperbaric oxygen therapy listed in Table 222-3 are based on these two sources.[27,28]

A Cochrane review from 2011 examined six clinical trials; two were positive trials showing decreased neurologic sequelae, and the remaining four trials failed to demonstrate a benefit.[29] However, all of the studies suffered from various degrees of methodologic flaws, and it was unclear whether hyperbaric oxygen improves long-term neurocognitive outcomes.[29] Two additional trials published since the Cochrane review were negative.[30,31] Taking into consideration the evidence, as well as the recommendations from experts, the clinician should review the severity of the patient's symptoms, the COHb level, the comorbid conditions (including pregnancy), and the location of the nearest center with emergency hyperbaric capabilities and consult with the referral center when considering the need for hyperbaric oxygen therapy.

DISPOSITION

Those without any high-risk features of CO intoxication may be discharged from the ED after symptom resolution and normalization of COHb as long as the exposure is not considered to be a suicide attempt and patients are returning to a safe environment. If there is a suspected source of environmental CO, other potentially exposed persons should be contacted and evaluated in the ED. Notify the fire department to measure ambient levels of CO at the source site. Once the safety of the discharge destination is established, the patient may be discharged.

Patients with accidental or inadvertent CO exposure should be referred for cognitive follow-up in 4 to 6 weeks.[26] Intentional CO poisoning requires emergency psychiatric consultation in the ED and eventual follow-up for cognitive dysfunction.[26]

For those with high-risk features of CO intoxication, prior to referral or transport for hyperbaric oxygen, secure the airway, stabilize vital signs, continue 100% oxygen, and identify and treat trauma or acute surgical or medical issues. Fulfill Emergency Medical Treatment and Labor Act requirements prior to transfer. Given the limitations in space inside a hyperbaric chamber, as well as the difficulties in rapidly extricating the patient once a "dive" has commenced, most hyperbaric specialists are hesitant to accept an unstable patient. See Chapter 21, "Hyperbaric Oxygen Therapy," for additional information.

SPECIAL SITUATIONS

DELAYED NEUROLOGIC SEQUELAE (OR ENCEPHALOPATHY)

Delayed neurologic sequelae can occur 4 days to 5 weeks after CO exposure. There are no widely established diagnostic criteria for delayed injury, so the reported incidence varies widely, from 3% to 40% of patients.[32] In a series of 347 patients diagnosed with CO exposure, 24% were diagnosed with delayed neurologic sequelae.[22] Risks include prolonged CO exposure (>6 hours), Glasgow Coma Scale score <9, seizures at the time of initial presentation, and leukocytosis. Reported neurologic effects include cognitive impairments and affective disorders.[22] The precise neuropathology is not known, but proposed mechanisms supported primarily by animal studies include apoptosis, immune-mediated injury, and delayed inflammation.[12,13,33,34]

Hyperbaric oxygen has been used anecdotally with success for the treatment of delayed neurologic sequelae of CO[35]; however, it has not been tested in a trial. A bundle therapy has been suggested for this indication using temperature control, hyperbaric oxygen, steroids, antioxidants, and sympatholytics.[36] The success of these therapies and the individual contribution of each component are yet to be determined.

INFANTS, PREGNANT WOMEN, AND THE ELDERLY

Infants may be more susceptible to the effects of CO due to the persistence of fetal hemoglobin for the first 6 months of life, as well as higher metabolic rates.[8] The indications for referral of children for hyperbaric oxygen therapy are similar to those for adults. Hyperbaric oxygen has been used in children with a good safety profile. There are no data on optimal therapy for exposure in neonates or young infants. Obtain consultation for this age group.

Pregnant women should be considered for referral or discussed with the admitting physician at a hyperbaric center at CO levels of 15% to 20% because fetal morbidity has been demonstrated at lower levels than usual due to the high affinity of CO for fetal hemoglobin.[8]

The elderly, particularly those with serious comorbid disease, are also at higher risk from CO poisoning. In patients with known coronary artery disease, even low levels of COHb (4% to 6%) can cause ECG changes and myocardial ischemia.[8] Some elderly may also be at risk due to use of alternative heating sources, particularly during the winter.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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CHAPTER 223

Type 1 Diabetes Mellitus

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Adam Schlichting

INTRODUCTION AND EPIDEMIOLOGY

Diabetes can be classified into type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes, and other specific types of diabetes based on the etiology (**Table 223-1**); however, many people with diabetes do not easily fit into a single class.[1] About 5% of people with diabetes are estimated to have T1DM, which is about 1.25 million American children and adults.[2,3]

PATHOPHYSIOLOGY

T1DM is characterized by an autoimmune, cellular-mediated destruction of β cells of the pancreas. These patients usually have almost no circulating insulin.[1] It is mostly diagnosed in children and young adults, but it can also develop in adults.[4] Spontaneous ketoacidosis almost always develops in untreated cases, and insulin is required for survival.

Chapter 224, "Type 2 Diabetes Mellitus," discusses T2DM in detail. Hyperglycemia is present in all types of diabetes mellitus and is the main factor responsible for chronic complications. Therefore, maintaining euglycemic control is the cornerstone of management.

DIAGNOSIS

The American Diabetes Association criteria for diagnosis are listed in **Table 223-2**.[1] Any one of these can be used to make the diagnosis. Patients with a fasting plasma glucose of 100 to 125 milligrams/dL (5.6 to 7.0 mmol/L), a hemoglobin A1C of 5.7% to 6.4%, or a 2-hour plasma glucose of 140 to 199 milligrams/dL (7.8 to 11.0 mmol/L) as part of an oral glucose tolerance test are classified as having *prediabetes*.[4] This should be viewed as an increased risk for diabetes and cardiovascular disease rather than a clinical diagnosis.

Glycated hemoglobin (hemoglobin A1C) represents the average blood glucose level over a 2- to 3-month period.[1] It is an indirect measure, and age, race/ethnicity, pregnancy, hemoglobinopathies, and recent transfusions may impact interpretation.[4]

In the ED, it is common to encounter isolated elevations of blood glucose with no established relationship to a meal. If patients have classic symptoms of hyperglycemia (polydipsia, polyuria) or are in hyperglycemic crisis, they may indeed be diagnosed with diabetes.

TREATMENT

T1DM is characterized by an absolute insulin deficiency, so some form of insulin is required for survival. Select patients with T1DM may also be treated with additional prandial injections of pramlintide, a synthetic form of the β-cell–produced hormone amylin.[5] Patients with T1DM may also benefit from β-cell transplantation or pancreas transplantation. Other noninsulin agents are useful in T2DM and are discussed separately in Chapter 224.

INSULIN

As of 2006, all U.S. Food and Drug Administration–approved insulin preparations are recombinant human insulin or an analog.[6] These insulins are highly pure and stable, and vials in use can be kept up to 28 days at room temperature.[7] The most common concentration of insulin is 100 units/mL ("U100"), but other concentrations including 200 units/mL ("U200"), 300 units/mL ("U300"), and 500 units/mL ("U500") are available, allowing a smaller volume to be injected. Although unmodified "regular" insulin was the first type of human-derived insulin used, many new insulin analogues have now become available (**Table 223-3**, **Figure 223-1**).[8,9] Regardless of the insulin analog, 1 unit of insulin can be substituted for a longer- or shorter-acting analog, as long as the total daily dose is equivalent (e.g., neutral protamine Hagedorn [NPH] 20 units twice daily can be converted to glargine 40 units daily).[7] There can be considerable variability in the onset and duration of action depending on the dose (e.g., regular insulin has a longer duration of action with larger doses), site of injection, degree of exercise, and presence of circulating anti-insulin antibodies.

A physiologic regimen of insulin generally starts with half of the daily requirement given as basal insulin (once-daily long-acting or twice-daily intermediate-acting insulin) and prandial doses of rapid-acting insulin administered 5 to 30 minutes before each meal (**Figure 223-2**).[8] Most patients with T1DM require a **total daily dose of insulin between 0.4 and 1 unit/kg/d,** with approximately half given as basal insulin such as insulin glargine and half to be given in divided doses preprandially.[10,11] This can provide a rough idea when a patient says, "I have no idea how much insulin I take."

Prandial dosing is most often based on the anticipated amount of carbohydrate about to be consumed, for example, 1 unit of insulin for each 15 grams of carbohydrate; this is known as "carb counting." Prandial dosing must also take into consideration the premeal measured glucose level. In this case, the patient adds an additional amount of insulin to correct for premeal hyperglycemia or reduces the prandial dose to account for premeal hypoglycemia. Some patients may be on a simplified, fixed amount of insulin for each meal.

Insulin can be given as intermittent subcutaneous dosing, IV infusion, inhalation, or continuous subcutaneous infusion using an insulin pump. Intramuscular injection of insulin is not approved by the U.S. Food and Drug Administration. Intermittent insulin doses are given subcutaneously with a syringe or pen. The syringe method is the least expensive but requires care and precision to give the correct dose. Pens provide more accurate dosing, and many patients consider these to be more convenient. Subcutaneous injection is the most common method of insulin administration. Absorption varies due to regional circulatory differences, and frequent use of a single site may lead to fibrosis or lipodystrophy. Patients are instructed to limit injections to one region of the body but rotate sites within that region. IV administration of regular insulin results in an onset of action within 10 to 15 minutes and rapid reductions in plasma glucose, and is the recommended method of administration in hyperglycemic crises—diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic state. See Chapters 225 and 227 for management of these conditions.

TABLE 223-1 Etiologic Classification of Diabetes Mellitus

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
- Immune mediated
- Idiopathic

Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

Other specific types, such as
- Genetic defects of β-cell function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas (pancreatitis, trauma, cystic fibrosis, etc.)
- Endocrinopathies (Cushing's syndrome, pheochromocytoma, hyperthyroidism, somatostatinoma, glucagonoma, etc.)
- Drug- or chemical-induced (interferon-α, β-adrenergic agonists, diazoxide, phenytoin, glucocorticoids, nicotinic acid, pentamidine, thiazides, thyroid hormone, pyrinuron, etc.)
- Infections (congenital rubella, cytomegalovirus, etc.)
- Uncommon forms of immune-mediated diabetes (anti-insulin receptor antibodies in conditions like lupus, etc.)
- Other genetic syndromes sometimes associated with diabetes (Down's syndrome, Klinefelter's syndrome, Turner's syndrome, etc.)

Gestational diabetes mellitus

INHALED INSULIN

In 2006, inhaled insulin was marketed in the United States but was discontinued by the manufacturer. The U.S. Food and Drug Administration approved a new formulation of inhaled regular insulin in 2014 for prandial use in adults without pulmonary disease.[12] This recombinant regular Technosphere insulin (Afrezza®) may be noninferior to injected prandial insulin combined with long-acting insulin injections, but there are minimal long-term data available.[13]

GLYCEMIC COMPLICATIONS IN INSULIN-DEPENDENT PATIENTS

The major hyperglycemic emergencies, hyperosmolar hyperglycemic state and diabetic ketoacidosis, are discussed in Chapter 227, "Hyperosmolar Hyperglycemic State," and Chapter 225, "Diabetic Ketoacidosis," respectively. Here we discuss the common ED presentation of an "abnormal lab value" (i.e., patients with no acute symptoms of hyperglycemia found to have elevated plasma glucose levels).

TABLE 223-2 American Diabetes Association Criteria for the Diagnosis of Diabetes

A1C ≥6.5%*	The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
Or Fasting plasma glucose ≥126 milligrams/dL (7.0 mmol/L)*	Fasting is defined as no caloric intake for at least 8 h.
Or Casual plasma glucose ≥200 milligrams/dL (11.1 mmol/L) **and** symptoms of hyperglycemia or hyperglycemic crisis	Classic symptoms of hyperglycemia include polyuria and polydipsia.
Or 2-h plasma glucose ≥200 milligrams/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)*	OGTT must be performed as described by the World Health Organization.

Abbreviations: A1C = glycated hemoglobin; DCCT = Diabetes Control and Complications Trial; NGSP = National Glycohemoglobin Standardization Project.

*Should be confirmed by repeat testing unless unequivocal hyperglycemia is present.

HYPERGLYCEMIA IN PREVIOUSLY DIAGNOSED T1DM

For patients with T1DM with hyperglycemia noted on multiple ED visits, refer to the primary physician for insulin dose adjustment. In the interim, ask patients to keep a daily record of every meal, every dose of insulin administered (along with type of insulin), and blood glucose levels four times a day (after rising in the morning, before lunch, before dinner, and at bedtime).

If an insulin dose adjustment is made in the ED, the basic regimen should conform to a once- or twice-daily dose of long- or intermediate-acting insulin, combined with prandial doses of rapid-acting insulin. The magnitude of increase in the basal insulin dose should be carefully tailored to the degree of hyperglycemia in the patient and duration of time since the last meal, but **typically should change by no more than 10%.** For example, if a patient has a measured glucose of 300 milligrams/dL (16.6 mmol/L) 1 hour after consuming a meal, increasing long-acting insulin may result in late hypoglycemia as the measured glucose is more attributable to recent carbohydrate ingestion; this episode of hyperglycemia may be better managed by recommending an increase in preprandial insulin dosing.

A conservative supplemental dose of rapid-acting insulin may be calculated as follows: 1 unit per 50 milligrams/dL (2.8 mmol/L) above target glucose level for T1DM, and 1 unit per 30 milligrams/dL (1.7 mmol/L) above target glucose level for T2DM.[11]

For example, to achieve a goal blood glucose of 100 milligrams/dL (5.5 mmol/L) in a patient with T1DM who has a glucose level of 350 milligrams/dL (19.5 mmol/L), administer 5 units of rapid-acting insulin. Anticipated carbohydrate consumption would require additional insulin.

If the patient is using neutral protamine Hagedorn (NPH or isophane) insulin, inspect the insulin vial; if frosting is noted on the sides of the bottle, this may indicate denaturation, which renders the insulin ineffective. Provide the patient with a new prescription, and discard the old vial.

Falsely Elevated Capillary Glucose Several substances can falsely elevate point-of-care and home blood glucose monitoring accuracy, including acetaminophen, ascorbic acid, and peritoneal dialysis solutions using icodextrin.[14-17] Falsely elevated point-of-care glucose reading and reflexive insulin administration have been responsible for several reports of severe hypoglycemia. Point-of-care test strips for both home and hospital use are also sensitive to temperature and humidity and thus may provide inaccurate glucose levels. **If the point-of-care glucose level does not fit the clinical presentation or if the patient receives peritoneal dialysis, obtain a laboratory plasma glucose level for treatment decisions.**

HYPOGLYCEMIA IN INSULIN-DEPENDENT PATIENTS

Hypoglycemia (plasma glucose <70 milligrams/dL [<3.9 mmol/L]) is the major adverse effect of tight glycemic control. Apart from insulin administration, patients with T1DM are prone to hypoglycemia because the surge of glucagon is absent and epinephrine secretion may be blunted due to neuropathy, age, or autonomic dysfunction from prior hypoglycemic episodes.

Older insulin regimens used once- or twice-daily injections of NPH, Lente insulin, or premixed combinations (70/30, 75/25, or 50/50) of basal insulin and regular insulin as the prandial dose. These schedules mandated fixed meal times and activity schedules, so it was not unusual to develop hypoglycemia with missed meals or unusual stress. Modern physiologic regimens of insulin administration (once-daily long-acting insulin with short-acting doses immediately before meals) have significantly reduced the incidence of hypoglycemia.[11] However, many patients remain on premixed dosing due to familiarity or financial limitations.

Determine the cause of hypoglycemia. Common causes include inadequate intake of food, inaccurate administration of insulin, infection, renal failure, acute coronary syndrome, and unusual physical or mental stress. Identify the timing and administration of insulin in relation to meals. Ask if the patient is measuring blood glucose

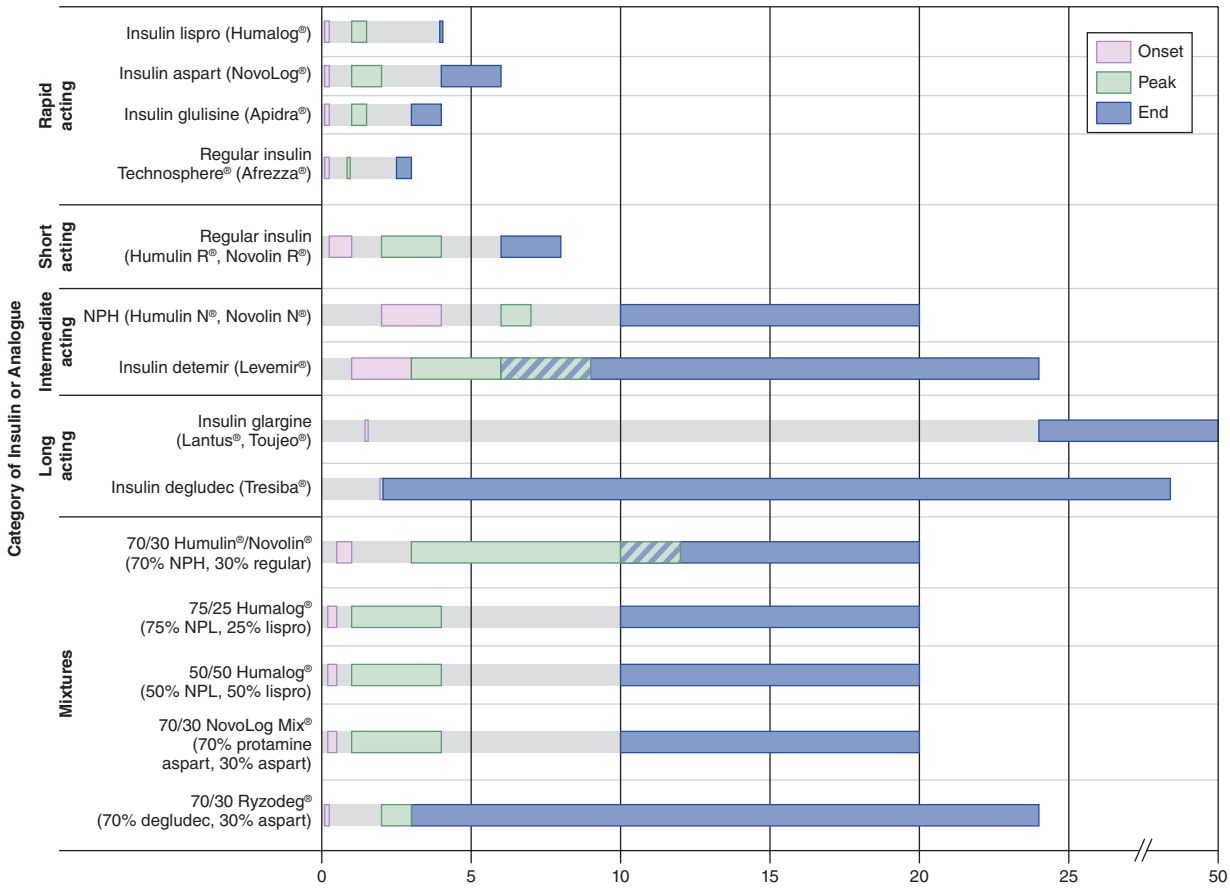
TABLE 223-3 Commonly Used Insulin Preparations, Their Pharmacokinetics and Unique Features*

Category of Insulin or Analogue	Name	Pharmacokinetics			Unique Properties
		Onset (hours)	Peak (hours)	End (hours)	
Rapid acting	Insulin lispro (Humalog®)	0.1–0.25	1.0–1.5	4	Fixed duration of action, regardless of dose
	Insulin aspart (NovoLog®)	0.1–0.25	1–2	4–6	More stable than other rapid-acting insulins
	Insulin glulisine (Apidra®)	0.1–0.25	1.0–1.5	3–4	Antiapoptotic; may counteract β-cell destruction
	Regular insulin Technosphere® (Afrezza®)	0.1–0.25	0.9	2.5–3	Inhaled insulin; contraindicated in chronic lung disease
Short acting	Regular insulin (Humulin R®, Novolin R®)	0.25–1.0	2–4	6–8	—
Intermediate acting	NPH (Humulin N®, Novolin N®)	2–4	6–7	10–20	Inexpensive
	Insulin detemir (Levemir®)	1–3	3–9	6–24	Action is relatively constant with gentle peak
Long acting	Insulin glargine (Lantus®, Toujeo®)	1.5	No peak	24+	Cannot be mixed with other insulins in same syringe
	Insulin degludec (Tresiba®)	2	No peak	>42	Allows variation in time of injection from day to day
Mixtures	70/30 Humulin®/Novolin® (70% NPH, 30% regular)	0.5–1.0	3–12	10–20	—
	75/25 Humalog® (75% NPL, 25% lispro)	0.2–0.5	1–4	10–20	—
	50/50 Humalog® (50% NPL, 50% lispro)	0.2–0.5	1–4	10–20	—
	70/30 NovoLog Mix® (70% protamine aspart, 30% aspart)	0.2–0.5	1–4	10–20	—
	70/30 Ryzodeg® (70% degludec, 30% aspart)	0.1–0.25	2–3	>24	—

Note: All brand names are copyrighted by their respective owners.

Abbreviations: NPH = neutral protamine Hagedorn (also called isophane insulin); NPL = neutral protamine lispro.

*Ultralente, Lente, and 50/50 insulin formulations are no longer available in the United States.



Note: All brand names are copyrighted by their respective owners.
Abbreviations: NPH = neutral protamine Hagedorn (also called isophane insulin); NPL = neutral protamine lispro.
*Ultralente, Lente and 50/50 insulin formulations are no longer available in the United States.

FIGURE 223-1. Insulins: onset, peak, and duration of action. NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro.

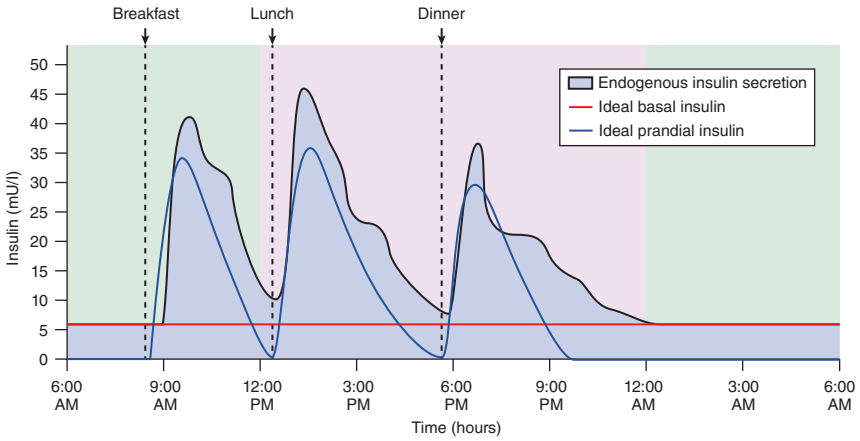


FIGURE 223-2. Representation of basal and prandial insulin dosing.

at home; at a minimum, it should be checked daily before breakfast and recorded in a diary. There is great variation in the pattern of hypoglycemic signs and symptoms from patient to patient; however, **individual patients tend to experience the same pattern from episode to episode**. Common neuroglycopenic symptoms may include headache, irritability, drowsiness, confusion, dizziness, tiredness, inability to concentrate, and difficulty speaking. These symptoms may mimic an acute ischemic stroke. Adrenergic symptoms such as tremor, sweating, anxiety, nausea, palpitations, feelings of warmth, and shivering are also seen, as are other symptoms such as hunger, weakness, and blurred vision.[18]

Hypoglycemic unawareness or hypoglycemia-associated autonomic failure occurs when diabetic patients have deficient counterregulatory hormone excretion, resulting in a lack of symptoms of hypoglycemia.[19] This results in frequent episodes of hypoglycemia and profound hypoglycemia. β-Blocker medication may also contribute to this condition by masking typical adrenergic symptoms of hypoglycemia.

Treatment of Hypoglycemia Glucose is the preferred treatment, although any glucose-containing carbohydrate may be used. The initial dose is 15 to 20 grams of glucose (PO, IV, or IO), which can be repeated if hypoglycemia persists after 15 minutes. Sublingual glucose (40% dextrose gel preferred; teaspoon of sugar may suffice) may also be effective in resource-limited situations.[20-22]

Pure fructose does not cross the blood–brain barrier and does not significantly improve blood glucose levels. Most sweet foods or drinks contain both glucose and fructose; they are labeled as containing "sugars," which includes glucose, fructose, or sucrose. Protein has a negligible contribution to serum glucose, so foods such as peanut butter or cheese are not recommended for hypoglycemia treatment. Once hypoglycemia has resolved, have the patient eat a meal or carbohydrate snack. **Table 223-4** lists the sugar content of commonly used oral agents.

Glucagon emergency kits are available for caregivers of patients with T1DM for emergency situations. One milligram of intramuscular glucagon stimulates glycogenolysis and is effective in 10 to 15 minutes. Preliminary data show that intranasal glucagon may also be effective.[23] Once the patient is alert enough to swallow, give oral glucose immediately. Glucagon is not effective in glycogen-depleted patients, and glucagon may induce nausea and vomiting, which can make it difficult to consume oral glucose subsequently.

Insulin Overdose Short-acting insulin may have delayed and prolonged absorption; patients with a significant accidental or intentional overdose should be monitored for several hours. Patients with a significant overdose of a long-acting insulin should be admitted for monitoring of glucose levels. Most patients may be discharged if caregivers and family members can monitor symptoms and capillary glucose levels.

INSULIN PUMPS (CONTINUOUS SC INSULIN INFUSION)

The use of an insulin pump (continuous SC insulin infusion) (See Video: The Insulin Pump) is common, but prevalence of pump use varies from 14% to 70% depending on demographics and country.[24-29] An insulin pump is a small device (about the size of a pager) that delivers *rapid-acting insulin* at a basal rate and boluses of insulin for prandial and hyperglycemia correction. Once programmed, the pump can automatically calculate dosing for a certain amount of carbohydrates about to be consumed and correct for premeal hyperglycemia or hypoglycemia. The insulin is pumped through a flexible tube and infused via a subcutaneous catheter. The pump is usually attached to the patient's waistband. The patient must refill the insulin reservoir and change the catheter every 2 to 3 days. **Table 223-5** lists manufacturers of insulin pumps available in the United States. Some insulin pumps do not use tubing but directly attach to the patient with adhesive.[30]

The basal rate of insulin (generally, 0.5 to 1.5 units/h) can be varied throughout the day; for example, increased to counteract an early morning cortisol surge or decreased before exercising. Continuous insulin delivery eliminates the need for long-acting insulin injection such that the pump delivers all insulin required by the patient in the form of rapid-acting insulin. Rarely, patients requiring exceptionally high doses of insulin using an insulin pump, patients who wish to be disconnected from their pump for extended periods of time, or patients at higher risk of hyperglycemia or diabetic ketoacidosis (e.g., young children) may inject an additional once- or twice-daily long-acting insulin.[31,32] The

TABLE 223-4 Sugar* Content of Agents Available at Home or Over the Counter

Agent	Dose/Route	Sugar Content
Fruit juice	1 cup PO	Variable depending on type of juice and manufacturer (mostly fructose) 8 oz Mott's® apple juice: 28 grams sugar
Honey	1 Tbsp PO	17 grams sugar (glucose and fructose)
Sugar-containing soda	12 oz (one can) PO	(Non-diet) Pepsi®: 41 grams sugar (mostly fructose) (Non-diet) Sprite®: 38 grams sugar (mostly fructose) (Non-diet) Coca-Cola (Coke)® Original: 39 grams sugar (mostly fructose)
Glucose tablets	4 tablets PO	16 grams glucose
Glucose gel	1 tube PO/SL	15 grams glucose

*"Sugar" may include glucose, fructose, galactose, sucrose, lactose, or maltose.

TABLE 223-5 Manufacturers of Insulin Pumps Available in the United States with Their 24-Hour Phone Numbers

Manufacturer	Website	Telephone Number
Animas*	http://www.animas.com	(877) 937-7867
Insulet OmniPod	http://www.myomnipod.com	(800) 591-3455
Medtronic MiniMed	http://www.medtronicdiabetes.com	(800) 646-4633
Roche Accu-Chek	https://www.accu-chek.com/support/insulin-pumps	(800) 688-4578
Sooil DANA	http://www.sooil.com	(866) 747-6645 ext. 102
Tandem Diabetes	https://www.tandemdiabetes.com	(877) 801-6901

*Animas insulin pump is no longer manufactured but is still in use. Telephone number is still active.

pump can be manually activated to deliver a bolus for hyperglycemia and for prandial dosing. Insulin pumps are most appropriate for motivated patients who are mechanically adept, well educated about diabetes and carbohydrate counting, and able to monitor their capillary glucose four to six times a day. Benefits of insulin pump therapy over multiple daily injections include average reduction in hemoglobin A1C of 0.5% and reduction in hypoglycemic episodes (See Video: The Insulin Pump).[24,33]

INSULIN PUMP COMPLICATIONS

Insulin pump delivery can fail for a variety of reasons (disconnection, empty reservoir, kinked catheter, priming errors), although modern pumps have built-in alarms to detect these conditions.[34] Because pumps use only rapid-acting insulin, **onset of ketoacidosis can be very rapid after pump failure**—an hour or less. **If the pump is defective or needs to be removed for a procedure such as MRI**, give the patient either a dose of rapid-acting insulin or long-acting insulin, especially if the insulin pump is to be interrupted for over an hour. **If a patient on an insulin pump needs to be nothing by mouth (NPO)**, the insulin pump should not be removed and glucose levels should be checked every 30 to 60 minutes. If the patient has hypoglycemic episodes, the pump basal rate can be reduced; consultation with an endocrinologist is recommended.

Patients being switched from multiple daily injections of insulin to insulin pumps are typically handled as outpatients and will require special attention if presenting to the ED during this transition period. Specific considerations for patients on insulin pumps presenting with hyperglycemia or hypoglycemia are discussed elsewhere in this chapter.

Other important complications of insulin pump therapy include cellulitis at the infusion site or lipodystrophy. If patients using insulin pumps are incidentally found to have hyperglycemia or hypoglycemia, they should be allowed to treat themselves either by administering an insulin bolus through their insulin pump or by consuming carbohydrates, respectively.[19,28,35] Their endocrinologist should have provided them instructions on how to address this.

CONTINUOUS INTERSTITIAL GLUCOSE MONITORING VERSUS POINT-OF-CARE (CAPILLARY) OR SERUM GLUCOSE MONITORING

Continuous glucose monitoring devices measure interstitial glucose concentrations with a subcutaneous sensor and then transmit glucose values to an insulin pump or other display device. Interstitial glucose values are adjuncts to capillary glucose monitoring and typically require manipulation of the insulin pump to administer insulin. An even newer technology, the hybrid closed-loop system, was approved by the U.S. Food and Drug Administration in 2016. The hybrid closed-loop system adjusts insulin dosing based on continuous glucose monitoring data. The system can maintain the target glucose for a longer period, reduce episodes of hyper- or hypoglycemia, and reduce hemoglobin A1C levels.[36,37]

Despite the substantial benefits of monitoring continuous interstitial glucose levels, it must be noted that interstitial glucose is a proxy, but not identical to, the more traditionally measured and validated serum glucose levels. There is about a 10-minute time lag for change between serum glucose and interstitial glucose levels.[38] Several common medications may result in inaccurate continuous interstitial glucose sensor readings, notably including acetaminophen.[39] **Measure capillary or serum glucose levels in the ED, and do not use interstitial glucose values (i.e., those displayed on the patient's continuous glucose monitor) for diagnostic purposes.**

HYPERGLYCEMIA IN PATIENTS USING INSULIN PUMPS

There are no widely accepted published guidelines for the ED management of patients with insulin pumps who present to the ED with hyperglycemia. Extrapolating from inpatient recommendations, we recommend that patients using insulin pumps who present to the ED with either hyperglycemia or hypoglycemia should be treated the same as patients who are on multiple daily doses of insulin, and the insulin pump should not be disabled.[19,28]

Once the patient has been stabilized, ask about dietary indiscretions and search for infections. Ask specific questions about the insulin pump: When was the insulin reservoir filled? When was the infusion set last changed? Is the insertion site of the infusion set periodically changed? When was the insulin reservoir last changed? Has the pump been submerged in water? Have any device alarms been sounding?[40] Examine the device thoroughly to ensure the pump is on, the reservoir is not empty, no alarms are indicated, the tubing is not kinked, and the infusion site is well attached to the skin. The patient or caregiver may provide useful information on pump operation, diagnostics, and how to disconnect it if necessary. All pumps have a telephone number for 24-hour technical support from the manufacturer (Table 223-5). If there is suspicion for pump malfunction, consult endocrinology for consideration of replacement of the insulin pump with long-acting basal insulin.

DIABETIC KETOACIDOSIS IN PATIENTS USING INSULIN PUMPS

In the case of diabetic ketoacidosis in a patient using an insulin pump, assume a problem with the pump, disconnect the pump, and start an IV insulin infusion following protocols for management of diabetic ketoacidosis. We recommend against bolus IV insulin prior to initiation of an insulin drip because this provides no clinical benefit.[41] Consider SC administration of long-acting insulin at the initiation of an insulin drip, particularly if re-initiation of insulin pump therapy is not expected after resolution of the diabetic ketoacidosis.[42] If the patient remains in the ED and their ketoacidosis resolves, ensure that a dose of long-acting insulin is administered at least 1 hour before stopping the insulin drip unless the insulin pump is to be re-initiated—in that case, restart pump therapy approximately 1 hour before stopping the IV insulin drip. To re-initiate pump therapy, make sure that the pump is working appropriately by running diagnostics on the device, checking that the insulin reservoir is filled with fresh insulin, and placing a new SC insulin infusion catheter. **Check serum glucose levels every 30 to 60 minutes.** See Chapter 225 for further discussion of transition of insulin dosing in diabetic ketoacidosis.

HYPOGLYCEMIA IN PATIENTS USING INSULIN PUMPS

Treat hypoglycemia just as in other patients. **Do not discontinue the pump, as diabetic ketoacidosis can rapidly develop.** If recurrent hypoglycemia develops after initial treatment, pump malfunction may be the cause. Please see the earlier section "Hyperglycemia in Patients Using Insulin Pumps."

SPECIAL CONSIDERATIONS

UNDIAGNOSED DIABETIC

A long asymptomatic period is common for T2DM, but T1DM typically has a short period before the disease becomes overt. If the patient is newly identified with severe and symptomatic hyperglycemia (>250 to 300 milligrams/dL [13.8 to 16.7 mmol/L]), insulin should be

administered in the ED. Insulin can be given even if it is not known at the time whether the patient has T1DM or T2DM. Patients with severe or symptomatic hyperglycemia should be admitted or placed in an observation unit for further glucose control and education.

For patients with hyperglycemia but without ketoacidosis, a low dose of regular or rapid-acting insulin (1 unit subcutaneously for every 30 to 50 milligrams/dL above glucose of 250 to 300 milligrams/dL) may be given to reduce hyperglycemia, and a long-acting insulin (e.g., 0.1 to 0.2 units/kg of insulin glargine) should be given in the ED to prevent diabetic ketoacidosis.

For patients without severe and symptomatic hyperglycemia, regular or rapid-acting insulin can be given to reduce the glucose to about 250 milligrams/dL. Then, most patients may be discharged with a prescription for metformin and referral to their physician or clinic within 24 hours for further evaluation and care.[19,43] For further discussion of T2DM care and noninsulin antidiabetic agents such as metformin, see Chapter 224.

GLUCOCORTICOID THERAPY

Patients with T1DM who are started on glucocorticoids before discharge from the ED will likely develop hyperglycemia. They should be informed about warning signs of hyperglycemia and advised to seek close follow-up with their primary physician, with frequent monitoring of blood glucose at home and additional bolus doses of insulin. **Routine increase in long-acting basal insulin dosage is not advised**, as both the duration of action of the insulin as well as the steroid must be carefully considered.

Although previously undiagnosed patients with diabetes may develop hyperglycemia while on glucocorticoid therapy, the hyperglycemia will often resolve spontaneously once the glucocorticoid course is completed. If hyperglycemia is persistent or symptomatic, medication may be required after failure of dietary modification and exercise.

PRAMLINTIDE

Patients with T1DM who are unable to achieve optimal glucose control may also be treated with injections of prandial pramlintide in addition to prandial or continuous SC insulin. Pramlintide, a synthetic form of the hormone amylin, is produced by β-cells. Amylin promotes satiety, slows gastric emptying, aids in suppressing postprandial glucagon secretion, and reduces hemoglobin A1C levels.[5,44,45] Despite these benefits, the necessity for injection of a second prandial medication, incidence of nausea, and severe hypoglycemia, especially during dose titration, prevent the great majority of patients with T1DM from using this medication.[46,47]

TRANSPLANTATION

There are three methods of pancreas transplantation: simultaneous pancreas and kidney (75% of transplants), pancreas after kidney (18%), and pancreas transplant alone (7%).[48] In 2016, 215 pancreas transplants and 798 combined kidney/pancreas transplants were performed in the United States.[49] Life-long immunosuppression is required. One-year graft survival with insulin independence approaches 86% (simultaneous pancreas and kidney), 80% (pancreas after kidney), and 78% (pancreas transplant alone); 10-year graft survival is 68% (simultaneous pancreas and kidney), 46% (pancreas after kidney), and 39% (pancreas transplant alone).[48,50]

Another promising modality is islet cell transplantation. The Edmonton protocol has led to insulin independence in T1DM.[51] Insulin independence is short lived, however; 2 years after transplantation, 76% of patients again required the use of exogenous insulin. Some longitudinal studies have demonstrated insulin independence 12 years after Edmonton protocol islet cell transplant.[52]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 224

Type 2 Diabetes Mellitus

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TYPE 2 DIABETES MELLITUS

EPIDEMIOLOGY

Type 2 diabetes mellitus (T2DM) is a complex, chronic metabolic disorder. It is a major public health issue and an important contributor to morbidity and mortality all over the world.[1,2] Diabetes reduces the life expectancy of its victims by approximately 10 years. Mortality and morbidity increase because of increased risk of cardiovascular disease, stroke, visual impairment, renal disease, and amputations.

According to the Centers for Disease Control and Prevention report on ED visits of ≥18-year-old adults in 2014, 14.2 million were reported with diabetes as any listed diagnosis. These included 245,000 visits for hypoglycemia and 207,000 for hyperglycemic crisis.[3]

PATHOPHYSIOLOGY

T2DM is a complex heterogeneous metabolic disorder, characterized by chronic elevation of plasma glucose levels. The pathogenesis is complex and involves interaction of genetic and environmental factors. The most important pathophysiologic features of T2DM are *decreased insulin sensitivity* (insulin resistance) and *impaired insulin secretion*

It is generally believed that, in T2DM, fasting hyperglycemia is caused by increased production of glucose by liver, which is not suppressed because of hepatic resistance to insulin action. Normally, after meals, glucose uptake in peripheral tissues increases and glucose production by gluconeogenesis and glycogenolysis decreases. Insulin acts both directly and indirectly to inhibit gluconeogenesis and glycogenolysis. In T2DM, owing to hepatic resistance to insulin, the liver is programmed to both overproduce and underuse glucose.

However, postprandial hyperglycemia results from several mechanisms: abnormal insulin secretion by pancreatic β cells in response to a meal, impaired regulation of hepatic glucose production, and reduced glucose uptake by peripheral tissues, particularly the skeletal muscle, that are insulin sensitive.[4]

Insulin resistance is the diminished tissue response to insulin at one or more sites in the complex pathways of hormone action and requires higher than normal plasma insulin levels to maintain normoglycemia. The major sites of insulin resistance in T2DM are the liver, skeletal muscle, and adipose tissue.

Insulin secretion is usually impaired and generally insufficient to compensate for insulin resistance.[5] The mechanism behind impaired insulin release in T2DM is complicated and includes glucotoxic and lipotoxic effects, as well as deposition of amyloid within islet cells. Glucotoxicity is the negative effect of prolonged and excessive glucose on β-cell function. Lipotoxicity is the exposure to increased levels of free fatty acid, which also impairs β-cell function.[6]

The **incretin hormones** *glucagon-like peptide-1* (GLP-1) and *glucose-dependent insulinotropic polypeptide*, secreted by intestinal L cells following glucose intake, stimulate pancreatic β cells and are responsible for 50% to 70% of total insulin secretion. In people with T2DM, the incretin system is functionally impaired,[7,8] leading to hyperglycemia.

Chronic hyperglycemia is the cornerstone of microvascular complications. Dyslipidemia and hypertension that often accompany T2DM play an important part in macrovascular complications.[9,10]

The increased prevalence of infection is primarily attributed to phagocyte dysfunction, including impaired adherence, chemotaxis, phagocytosis, bacterial killing, and respiratory burst.[11] Other abnormalities include nonenzymatic glycation of immunoglobulins and reduced T-lymphocyte populations.

CLINICAL FEATURES

The classic symptoms, which are usually mild and nonspecific, include fatigue, weakness, polyuria, polydipsia, polyphagia, and blurred vision. Most patients with T2DM are overweight, beyond their 30s, and suffer from other comorbid conditions such as hypertension, cardiovascular disease, dyslipidemia, or polycystic ovary syndrome. Clues in the patient's past medical history that are suggestive of diabetes mellitus include frequent superficial infections and slow healing of skin lesions after minor trauma.

Acute complications include diabetic ketoacidosis, hyperosmolar hypertonic nonketotic state, and hypoglycemia. Diabetic ketoacidosis and hyperosmolar hypertonic nonketotic state are covered elsewhere in this book (see Chapters 225 and 227), and hypoglycemia, which in most cases is actually a complication of the treatment of diabetes, is discussed separately at the end of this chapter in the "Hypoglycemia" section.

Chronic complications are categorized as microvascular (retinopathy, neuropathy, and nephropathy), macrovascular (coronary artery disease, cerebrovascular disease, peripheral vascular disease), and nonvascular (including infectious) complications. One of the chronic complications of diabetes may be the reason for the ED visit or may be found during review of systems and physical examination. A brief review of the manifestations of the involvement of various organ systems by diabetes is presented in **Table 224-1**.

CARDIOVASCULAR COMPLICATIONS

"Silent ischemia" (the absence of chest pain despite myocardial ischemia) is common in diabetic patients. It is also common for myocardial infarction to present with atypical or less impressive symptoms such as weakness, fatigue, and confusion. Patients may suffer from pain in unusual locations or with lower than expected severity. This may explain the increased incidence of medically unrecognized acute myocardial infarction in diabetics compared with nondiabetics (40% vs 25%).

NEUROLOGIC COMPLICATIONS

Diabetic neuropathy is a diagnosis of exclusion and should be labeled as such only after other forms of neuropathy, such as chronic inflammatory demyelinating polyneuropathy, vitamin B_{12} deficiency, hypothyroidism, and uremia, have been excluded. The most significant morbidity associated with diabetic neuropathy is foot ulceration.

It may be difficult in the ED to differentiate the signs and symptoms of diabetic mononeuropathy from a transient ischemic attack or stroke, and imaging and other modalities are needed for diagnosis.

FOOT AND LOWER EXTREMITY COMPLICATIONS

Diabetic foot ulceration results from interaction of many factors, including peripheral neuropathy, excessive plantar pressure, repetitive trauma, peripheral vascular disease, and wound-healing disturbances.[12-14] Ulcers act as a portal of entry for bacteria, resulting in cellulitis and abscess formation. Aerobic gram-positive cocci (especially *Staphylococcus aureus*) are the predominant pathogens. Gram-negative rods may be encountered in patients with chronic wounds or those who have recently received antibiotic therapy. Those with foot ischemia or gangrene may be infected with obligate anaerobic microorganisms.[14,15]

Foot complaints in a diabetic require a thorough foot examination. Ulcer characteristics, including dimensions, depth, appearance (erythema, swelling, and purulence), and location, should be described. Hair and nail growth, calluses, corns, foot deformities, sensation, and vascular status (palpation of pedal and popliteal pulses) should be assessed. It is sometimes difficult to distinguish between lower extremity ulcers resulting from vascular insufficiency and those due to diabetes. Venous ulcers are typically present above the malleoli with irregular borders. Arterial ulcers are often found on the toes or the shins, with pale, "punched-out" borders. These ulcers are typically painful in the absence of coexisting neuropathy. **Diabetic ulcers**, on the other hand, usually occur at areas of increased pressure (e.g., sole of the foot) or friction (due to footwear). **Any ulceration found should be unroofed and probed using a blunt-ended rigid sterile probe to determine the depth.** The ability to probe to bone through the ulcer suggests the strong possibility of osteomyelitis and deep-space soft tissue infection. Purulence or inflammation suggests infection, and both aerobic and anaerobic cultures should be taken from purulent drainage or material curetted from the base of the wound. Such specimens are preferable to wound swab specimens, which are often contaminated with colonizing bacteria and often do not identify the infected organism(s).

The diagnosis of osteomyelitis in patients with diabetic foot ulcer remains a challenge. When the wound can be probed to the underlying bone, presence of osteomyelitis is almost certain. Radiographs, although not very sensitive, should be obtained in patients with deep or long-standing ulcers to exclude osteomyelitis, subcutaneous gas, foreign bodies, and Charcot joints. MRI can identify osteomyelitis if radiographs are negative but clinical suspicion is high.[16,17] **Table 224-2** shows the diagnostic utility of physical examination, laboratory, and basic radiographic testing in the diagnosis of osteomyelitis in patients with diabetic foot ulcer.

OPHTHALMIC COMPLICATIONS

Although there are case reports of ocular hemorrhage after thrombolysis with streptokinase,[18,19] the risk of intraocular bleeding following thrombolytic therapy in patients with retinopathy is thought to be very low (0.05%).[20]

TABLE 224-1 Chronic Complications of Type 2 Diabetes Mellitus

Organ Complications	Disorders	Comments
Cardiovascular complications	Coronary artery disease	2- to 4-fold increase in risk and worse prognosis than in nondiabetics Atypical acute coronary syndrome symptoms
	Heart failure	2–5 times increased risk in diabetics Risk factor–adjusted hazard ratio of 1.82 in men and 3.73 in women
	Diabetic cardiomyopathy	Myocardium more susceptible to ischemia and less able to recover after an ischemic insult
	Peripheral vascular disease	2–4 times increased in diabetics Limb claudication, limb ischemia and tissue loss, and amputation Affects tibial and peroneal arteries, as well as femoral and popliteal arteries
Renal complications	Diabetic nephropathy	Affects 5%–40% of patients with type 2 diabetes Present in approximately 7% of the cases at the time of diagnosis Triad of hypertension, albuminuria, and progressive renal failure
	Renal papillary necrosis	Asymptomatic or symptoms similar to renal colic or acute pyelonephritis Urinalysis: necrotic fragments of renal papilla, red and white blood cells, bacteria

(*Continued*)

TABLE 224-1 Chronic Complications of Type 2 Diabetes Mellitus (*Continued*)

Organ Complications	Disorders	Comments
Neurologic complications	Stroke	3 times increased risk of stroke Increased risk of recurrent stroke and stroke-related dementia
	Chronic sensorimotor distal symmetric polyneuropathy	Burning pain, electrical or stabbing sensations, paresthesia, hyperesthesia, and deep aching pain Loss of vibration, pressure, pain, and temperature sense; commonly in the legs and feet with a symmetric stocking and glove pattern
	Proximal motor neuropathy	Weakness of the proximal muscles of the lower limbs Spontaneous or percussion-provoked muscle fasciculation Onset may be gradual or abrupt
	Mononeuropathies	May affect a large peripheral nerve or an isolated cranial nerve Usually sudden onset with pain Due to entrapment or microvascular infarct Increased incidence of carpal tunnel syndrome
	Autonomic neuropathy	May cause dysfunction of every part of the body Signs include resting tachycardia, orthostatic hypotension, gastroparesis, autonomic diarrhea (at least 3 weeks of increased stool frequency and/or liquidity), constipation, erectile dysfunction, neurogenic bladder
Infectious complications	Common infections (pneumonia, soft tissue infections, and urinary tract infections)	Infectious agents usually similar to nondiabetics Some organisms more common (*Staphylococcus aureus* and *Mycobacterium tuberculosis* in pneumonia, and *Candida* species in urinary tract infections)
	Malignant otitis externa	Frequently due to *Pseudomonas aeruginosa*, but staphylococci, fungi, and other gram-negative organisms also have been isolated Unilateral otalgia, decreased hearing, purulent ear discharge, tenderness of the pinna and periauricular area, swollen external auditory canal, and sometimes fever Tender, inflamed external auditory canal with a mass of granular-appearing tissue Can lead to osteomyelitis, meningitis, venous sinus thrombosis, or subdural empyema
	Emphysematous cholecystitis	Fever and abdominal pain Gas within the gallbladder and biliary tree on imaging Most frequently *Clostridium* species in addition to streptococci, *Escherichia coli*, and *Pseudomonas*
	Emphysematous pyelonephritis	Rare, life-threatening infection with gas production in renal parenchyma and around the kidney Fever, clinical toxicity, flank pain, and sometimes a palpable mass
	Rhinocerebral mucormycosis	Almost exclusively occurs in diabetics Invasive fungal infection of the nasal and paranasal sinuses, sometimes involving the palate and adjacent tissues Sudden and rapidly progressive onset Periorbital or perinasal pain, blood-tinged nasal discharge, unilateral headache, increased tearing, swelling of eyelids and conjunctiva, and decreased vision Signs can include black eschar on the nasal mucosa or hard palate due to ischemia, proptosis, and, if the infection progresses, cranial nerve involvement or seizures
Ophthalmologic complications	Retinopathy	Nonproliferative stage: • Hard exudates (accumulation of lipid in the outer plexiform layer) • Retinal hemorrhage (flame-shaped hemorrhage in the nerve fiber layer; dot-and-blot hemorrhage in deeper layers of the retina) • Soft exudates (cotton wool spots due to microinfarctions of the retina) • Venous tortuosity and beading Proliferative stage: • Neovascularization • Vitreous hemorrhage • Rubeosis iridis and the resultant glaucoma • Traction retinal detachment
	Eyelids and conjunctiva	Recurrent styes, blepharoconjunctivitis, and xanthelasma; fatty deposits in the subcutaneous tissue of the lids
	Cornea	Bacterial corneal ulcers, neurotropic ulcers, and difficulties with contact lenses
	Other	Cataracts and open- and narrow-angle glaucoma
Dermatologic complications	Noninfectious	Protracted wound healing, acanthosis nigricans, necrobiosis lipoidica, diabetic dermopathy, scleredema, and granuloma annulare
	Infectious	Cellulitis, furuncles and carbuncles, and candidiasis Necrotizing fasciitis: typically of mixed bacterial origin, most common organisms: *Streptococcus pyogenes, S. aureus,* anaerobic streptococci, and *Bacteroides.* Fournier's gangrene Erythrasma: pruritic red-brown patch in the axilla or groin; *Corynebacterium minutissimum*

TABLE 224-2 Diagnostic Accuracy of Physical Examination, Laboratory, and Imaging Investigations for Lower Extremity Osteomyelitis in Patients with Diabetic Foot Ulcers*

Finding	Positive LR (95% CI)	Negative LR (95% CI)
Ulcer area >2 cm^2	7.2 (1.1–49)	0.48 (0.31–0.76)
Positive "probe-to-bone" test	6.4 (3.6–11)	0.39 (0.20–0.76)
Erythrocyte sedimentation rate (with a cutoff of 70 mm/h)	11 (1.6–79)	0.34 (0.06–1.90)†
Plain radiograph	2.3 (1.6–3.3)	0.63 (0.51–0.78)
MRI	3.8 (2.5–5.8)	0.14 (0.08–0.26)

Abbreviations: CI = confidence interval; LR = likelihood ratio.

*Bone biopsy is considered the gold standard.

†95% CI crosses 1.0.

In neither the American College of Cardiology/American Heart Association[21] nor the European Society of Cardiology guidelines[22] for the management of patients with ST-segment elevation myocardial infarction has retinopathy been mentioned as the absolute or relative contraindications to intravenous fibrinolytic therapy. Therefore, retinopathy should not be considered a contraindication. The indications and potential complications of thrombolytic therapy should be discussed with the patient before its administration.

RENAL , DERMATOLOGIC, AND INFECTIOUS COMPLICATIONS

Renal, dermatologic, and infectious complications are listed in Table 224-1.

DIAGNOSIS

Look for diabetes in the presence of symptoms suggestive of hyperglycemia in the undiagnosed diabetic. It is reasonable to check the glucose level in patients with certain presentations such as unexplained cellulitis, foot ulcers, frequent candidal infections, and unexplained neuropathy.

When evaluating a patient with established diabetes mellitus in the ED, in addition to complaint-directed history and physical examination, give special attention to diabetes-related aspects. Assessment can include questions about prior diabetes care, presence or absence of diabetes complications and diabetes-related comorbidities, and assessment of the patient's knowledge about the disease. Elements of the history and physical examination relative to T2DM are presented in **Tables 224-3** and **224-4**.

TABLE 224-3 Elements of the Medical History in Patients with Type 2 Diabetes Mellitus

Key Elements of Medical History	
Past medical history	Cardiovascular disease, hypertension, dyslipidemia, foot lesions, ophthalmologic diseases, nephropathy, neuropathy, cerebrovascular disease
Prior diabetes care	Type of treatment and recent changes in the regimen; prior glycated hemoglobin A_{1c} levels; blood sugar self-monitoring results; frequency, severity, and cause of hyper- or hypoglycemic episodes; diet and exercise history
Drug history	Oral antidiabetic drugs, insulin, diuretics, β-adrenergic agonists, β-adrenergic blockers, aspirin, statins
Social history	Smoking, substance abuse
Review of systems	Skin: dryness, pruritus, color changes, ulcers Weight loss GI: constipation, diarrhea, nausea, gastric fullness GU: urine, and sexual dysfunction (impotence) Visual changes Numbness, dizziness, and weakness Chest pain

TABLE 224-4 Elements of the Physical Examination in Patients with Type 2 Diabetes Mellitus

Key Elements of Physical Examination	
General	Height, weight, and body mass index
Vital signs	Blood pressure (including orthostatic measurement)
Head, eye, ear, nose, and throat examination	Funduscopy (to look for hemorrhage or proliferative retinopathy); visual acuity; intraocular pressure; thyroid palpation
Skin	Intertriginous areas (to look for acanthosis nigricans), insulin injection sites, lancet puncture sites, nonhealing wounds, cellulitis, tinea
Cardiovascular	Auscultation of the carotid arteries and abdomen for bruits; assessment of peripheral pulses (especially dorsalis pedis and posterior tibial pulses)
Foot examination	Signs of skin breakdown on the feet, signs of infection, determination of proprioception and vibration, monofilament sensation, presence/absence of patellar and ankle reflexes, pinprick or temperature sensation

Diagnosis of diabetes can be done in four ways: fasting plasma glucose level; random glucose level; hemoglobin A_{1c} (HbA_{1c}) level; or 2-hour oral glucose tolerance test. An oral glucose tolerance test is reserved for patients in whom diabetes is strongly suspected despite a normal or impaired fasting glucose.[23] HbA_{1c} is often used to monitor the effectiveness of treatment.

Current criteria for the diagnosis of diabetes are summarized in **Table 224-5**. Impaired fasting glucose, impaired glucose tolerance, or an HbA_{1c} level between 5.7% and 6.4% is usually referred to as *prediabetes* and denotes hyperglycemia not sufficient to meet diagnostic criteria for diabetes but significant for being a risk factor for future diabetes and for cardiovascular disease.

TREATMENT

Treatment of T2DM can be discussed under three topics: the day-to-day prevention of hyperglycemia (long-term management of hyperglycemia); prevention and management of chronic complications; and acute therapy of severe hyperglycemia and life-threatening metabolic decompensation (i.e., hyperosmolar hypertonic nonketotic state and diabetic ketoacidosis). Diabetic ketoacidosis and hyperosmolar hypertonic nonketotic state are discussed elsewhere in this book (see Chapters 225 and 227, respectively).

TABLE 224-5 Diagnostic Criteria for Diabetes

Test	Impaired Fasting Glucose (milligrams/dL)	Impaired Glucose Tolerance (milligrams/dL)	Diabetes* (milligrams/dL)
Fasting plasma glucose†	100–125 (5.5–6.9 mmol/L)	—	≥126 (≥6.9 mmol/L)
2-h OGTT	—	140–199 (7.8–11 mmol/L)	≥200 (≥11 mmol/L)
Random‡ plasma glucose concentration	—	—	≥200 (≥11 mmol/L) plus symptoms of diabetes#
$HgbA_{1c}$	5.7–6.4%		≥6.5%

Abbreviations: $HgbA_{1c}$ = hemoglobin A_{1c}; OGTT = oral glucose tolerance test (75-gram glucose load).

*In the absence of unequivocal symptoms of hyperglycemia, these criteria should be confirmed on a subsequent day.

†Fasting is defined as no caloric intake for at least 8 hours.

‡Random is defined as any time of the day without regard to time since last meal.

#The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

TABLE 224-6 Glycemic Goals

Parameter	American Diabetes Association Recommended Target
Premeal plasma glucose	80–130 milligrams/dL (4.4–7.2 mmol/L)
Postprandial plasma glucose	<180 milligrams/dL (<10 mmol/L)
Hemoglobin A_{1c}	<7.0%

The American Diabetes Association recommends that the goal of treatment in nonpregnant adults should be an HbA_{1c} value <7%. Other guidelines, such as that of the American College of Endocrinology, have recommended lower levels.[24] With respect to fasting, premeal, and postprandial targets, the American Diabetes Association suggestions are summarized in **Table 224-6**.[25]

NEWLY DIAGNOSED DIABETIC IN THE ED

The consensus statement on management of T2DM by the American Diabetes Association and the European Association for the Study of Diabetes recommends metformin in combination with lifestyle changes, as well as timely augmentation of therapy with additional agents (including other oral antidiabetic agents and insulin) to achieve recommended levels of glycemic control. This should be done in conjunction with the control of the symptoms of acute hyperglycemia and treatment of the underlying or exacerbating conditions. **Metformin can be safely initiated at a dose of 500 milligrams per day for patients whose T2DM has been newly diagnosed in the ED, provided that the estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2.**[24] The dose can be increased as needed in 500-milligram increments each week to a maximum of 2 grams per day. If admission is not warranted and exacerbating factors have been sought and effectively addressed, however, the initiation of pharmacotherapy can also be left to the primary care physician at 24- to 48-hour follow-up.

ACUTE THERAPY OF SEVERE HYPERGLYCEMIA

Acute hyperglycemia is defined as a blood glucose level of >300 milligrams/dL (>16.7 mmol/L). In this situation, the patient may have excessive urine output, weight loss, fatigue, blurred vision, or prominent neuropathic symptoms. Older patients may develop volume depletion, with acute mental status changes, hypovolemic shock, and acute renal insufficiency. Common precipitants include drug interaction with glucose-altering medications (most commonly, corticosteroids, sympathomimetics, diuretics, anticonvulsants, salicylates, and β-adrenergic receptor agonists), infections, acute illnesses such as acute coronary syndrome or CNS ischemia, or changes in or noncompliance with the prescribed drug regimen. Volume repletion, IV regular insulin, correction of electrolyte imbalance, and specific therapies directed toward any identified underlying cause of hyperglycemia are the components of treatment.

Regular human insulin is administered IV because absorption of SC insulin in a volume-depleted patient can be erratic. SC administration of insulin in non–volume-depleted patients is acceptable. Insulin lispro is an excellent alternative to regular human insulin. However, insulin lispro does not currently have U.S. Food and Drug Administration approval for IV administration, although many clinicians do use it. Typically, an initial bolus dose of 0.1 to 0.15 unit/kg IV or SC of regular human insulin or insulin lispro is given, which may be repeated in 1 to 2 hours if glucose levels have not fallen at least 50 milligrams/dL (2.8 mmol/L).

Patients should have a rapid therapeutic response to insulin, and with improved glycemic control, many patients may become more responsive to oral therapies and may be able to switch to oral agents alone after using insulin initially. When initial therapy with insulin can be discontinued because of recovery from an acute illness or marked improvement of metabolic control, a standard oral therapy approach may be instituted.

MANAGEMENT OF HYPERGLYCEMIA IN ED OBSERVATION OR ED BOARDING

With many admitted patients boarding in the ED for longer periods, EPs frequently encounter patients with random blood glucose of 140 mg/dL (7.8 mmol/L) or higher on routine lab tests. The patient may or may not be a known diabetic. Stress and decompensation of diabetes may contribute to the pathophysiology of this problem, or it may be iatrogenic, resulting from either inadvertent cessation of antihyperglycemic medications or administration of hyperglycemia-inducing drugs such as glucocorticoids or vasopressors. Whatever the mechanism, emergency physicians may be called upon to control the patient's blood glucose. There is some evidence that in patients who are later admitted, paying careful attention to high blood glucose levels in the ED leads to better glycemic control in the hospital.

In critically ill patients, insulin infusion is usually required. The goal is to maintain blood glucose in the range of 140 to 180 mg/dL (7.8 to 10 mmol/L). More stringent control (with blood glucose <110 mg/dL [<6 mmol/L]) may actually increase mortality and is not recommended.

In patients who are not in a critical condition, subcutaneous insulin with a premeal glucose target of less than 140 mg/dL (7.8 mmol/L) and random blood glucose of less than 180 mg/dL (10 mmol/L) is recommended. In most patients with T2DM admitted for an acute illness, oral hypoglycemic agents should be discontinued and insulin substituted. However, writing orders for sliding scale insulin for admitted patients can lead to undesirable levels of hypoglycemia and hyperglycemia. **Sliding scale insulin should not be used for more than 12 to 24 hours,** and scheduled subcutaneous insulin therapy, consisting of basal (long- or intermediate-acting) insulin, in combination with bolus/prandial (rapid- or short-acting) insulin, should be substituted. A total dose of 0.2 to 0.5 unit/kg/day is usually required based on the age and renal function of the patient. Half of this dose is administered as basal once or twice a day, and the remaining is given as prandial doses in three equally divided doses before each meal (only if the patient is eating) or every 4 to 6 hours (in patients on enteral or parenteral nutrition). If the desired target blood glucose is not achieved, correction insulin should also be added to the scheduled insulin regimen.[26-28] In noncritical diabetic patients who are already on insulin therapy, the patient's current regimen should be adjusted based on the patient glycemic control status; the 0.2 to 0.5 unit/kg/day dose calculation may not be sufficient in these cases.

DISPOSITION AND FOLLOW-UP

Guidelines for admission considerations are listed in **Table 224-7**. Diabetic patients may need admission for conditions that in nondiabetics are usually treated on an outpatient basis.

Patients who present with new-onset T2DM without evidence of metabolic decompensation, acute hypoglycemia, or hyperglycemia and

TABLE 224-7 Disposition/Guidelines for Hospital Admission

Inpatient care for type 2 diabetes mellitus is generally appropriate for the following clinical situations:

- Life-threatening metabolic decompensation such as diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic state
- Severe chronic complications of diabetes, acute comorbidities, or inadequate social situation
- Hyperglycemia (>400 milligrams/dL [>22 mmol/L]) associated with severe volume depletion or refractory to appropriate interventions
- Hypoglycemia with neuroglycopenia (altered level of consciousness, altered behavior, coma, seizure) that does not rapidly resolve with correction of hypoglycemia
- Hypoglycemia resulting from long-acting oral hypoglycemic agents or hypoglycemia of unknown cause
- Fever without an obvious source in patients with poorly controlled diabetes

do not meet the aforementioned criteria for admission should see their primary care provider within the week, as a general rule, to arrange for education, dietary evaluation, and initiation or refinement of appropriate therapy for glycemic control.

ANTIDIABETIC PHARMACOTHERAPY

There are several classes of antidiabetic agents. Their classification is based on mechanism of action: agents that cause insulin sensitization primarily in the liver, agents that cause insulin sensitization primarily in peripheral tissues, agents that promote secretion of insulin, agents that block reabsorption of glucose by the kidney, and agents that slow the absorption of carbohydrates (**Table 224-8**). Combined formulations are available that mix drugs from different classes of antihyperglycemic agents (metformin plus a thiazolidinedione or a secretagogue).

METFORMIN

Metformin is the only biguanide available in the United States. Metformin activates adenosine monophosphate–activated protein kinase and hence reduces hepatic insulin resistance. The resulting effect is decreased gluconeogenesis and glucose production in the liver.[29,30] Some effect on improving insulin sensitivity in peripheral tissues has inconsistently been suggested. Metformin is usually started at a dose of 500 milligrams once daily (with a meal) and can be titrated upward slowly to a maximum dose of 2 grams per day. Due to its short duration of action, metformin is generally taken at least twice daily. Metformin bears a wide safety margin[31]; the most common adverse effects include nausea, diarrhea, crampy abdominal pain, metallic taste, and dysgeusia. **Another rare side effect of metformin is lactic acidosis, which almost exclusively occurs in patients with renal insufficiency. Metformin is eliminated by the kidney in unchanged form and so is contraindicated in patients with an estimated glomerular filtration rate of <30 mL/min.** Because metformin does not increase insulin levels, it is not associated with a significant risk of hypoglycemia. Other contraindications include hepatic insufficiency, any form of acidosis, severe hypoxemia, and alcohol abuse. **Take care when administering metformin simultaneously with nephrotoxic agents such as contrast dye. Withhold metformin for 48 hours *after* IV contrast administration.**

GLITAZONES

Glitazones (thiazolidinediones) work through binding and modulation of the activity of peroxisome proliferator–activated receptors. This nuclear receptor influences the differentiation of fibroblasts into adipocytes and lowers free fatty acid levels. Thus, thiazolidinediones improve insulin sensitivity and reduce free fatty acid levels. Pioglitazone and rosiglitazone have replaced the first drug of this class, troglitazone, because they are believed to be safer. Thiazolidinediones are well tolerated, and their only significant adverse effects are weight gain and fluid retention. This class of drugs is contraindicated in the presence of active hepatocellular disease. Thiazolidinediones can increase the risk of bone fractures in postmenopausal women and older males.[24,32]

SULFONYLUREAS

Sulfonylureas are the oldest class of oral antidiabetic agents. They bind to the sulfonylurea receptor, a subunit of the adenosine triphosphate–sensitive potassium channel on plasma membrane of pancreatic β cells, causing a series of reactions, thereby leading to insulin secretion (exocytosis of insulin granules). Drugs in this class can be divided into first- and second-generation agents. First-generation sulfonylureas include chlorpropamide, tolbutamide, tolazamide, and acetohexamide. The second generation of this class includes drugs with higher potency and fewer adverse effects and drug–drug interactions (namely, glipizide, glyburide, gliclazide, and glimepiride). **Hypoglycemia** and weight gain are the major adverse effects of sulfonylureas (highest risk of hypoglycemia seen with glyburide), and other side effects like allergic reactions, GI intolerance, hyponatremia, or alcohol flushing are very rare and drug dependent.

GLINIDES

Repaglinide is an insulin secretagogue, structurally distinct from the sulfonylureas. It binds to pancreatic β cells and stimulates insulin release. Repaglinide is absorbed more rapidly and thus produces faster and briefer stimulus to insulin secretion. However, it has a prolonged effect on fasting glucose. The maximum dose of this drug is 2 milligrams taken with each meal. Repaglinide has an almost completely biliary elimination, and therefore, can be used safely in patients with renal insufficiency.

TABLE 224-8 Some Properties of Classes of Antihyperglycemic Agents

Parameter	Biguanides	Sulfonylureas	Glinides	Glitazones (TZDs)	α-Glucosidase Inhibitors	GLP1 Receptor Agonists	SGLT2 Inhibitors	DPP4 Inhibitors	Amylin Mimetics
Mechanism of action	Suppress liver glucose production	Potentiate insulin secretion	Potentiate insulin secretion	Improve insulin sensitivity (fat, liver, and muscle)	Delay intestinal carbohydrate absorption	Potentiate insulin secretion, decrease glucagon secretion, and slow gastric emptying	Block glucose reabsorption by the kidney	Potentiate insulin secretion and decrease glucagon secretion	Decrease glucagon secretion, slow gastric emptying
Examples	Metformin	Glyburide, glipizide, glimepiride	Repaglinide, nateglinide	Pioglitazone, rosiglitazone	Acarbose, miglitol	Exenatide, liraglutide	Canagliflozin, dapagliflozin	Sitagliptin	Pramlintide
Efficacy	High	High	Modest	High	Modest	High	Intermediate	Intermediate	Modest
Adverse effects	Nausea, diarrhea, lactic acidosis (rare), vitamin B_{12} deficiency	Hypoglycemia, weight gain	Weight gain	Edema, congestive heart failure, weight gain	Flatulence, diarrhea	Nausea, vomiting, diarrhea	Genitourinary infections, euglycemic DKA	Angioedema, urticaria, pancreatitis	Nausea, vomiting
Nonglycemic effects	Limits weight gain	None	None	None	None	Weight loss	Weight loss, blood pressure reduction	None	Weight loss

Abbreviation: DKA = diabetic ketoacidosis; DPP4 = dipeptidyl peptidase 4; GLP1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter 2; TZD = thiazolidinediones.

Nateglinide, a phenylalanine derivative, has an even shorter duration of action than repaglinide. It has a specific effect on postprandial glucose and almost no effect on fasting glucose. This drug is used as 120-milligram tablets taken with each meal.

ALPHA-GLUCOSIDASE INHIBITORS

Acarbose and miglitol inhibit the final step of carbohydrate digestion at the brush border of intestinal epithelium through competitive inhibition of α-glucosidases. This action delays the absorption of carbohydrates and consequently decreases the postprandial glucose peak and insulin response to the meal. They have only a modest effect on blood glucose reduction and commonly cause flatulence and diarrhea. Their advantage is lowering postprandial glucose without increasing weight or hypoglycemic risk. They should be used cautiously in patients with chronic renal disease.

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS

In humans, *glucagon-like peptide 1* (GLP-1) mediates the process by which oral glucose has a greater stimulatory effect on endogenous insulin secretion than parenteral glucose (the so-called *incretin effect*). GLP-1 analogues (also referred to as *incretin analogues* or *incretin mimetics*) are available in several formulations and exert their HbA_{1c}-lowering and weight reduction effects through several mechanisms: they suppress glucagon secretion, slow gastric emptying, reduce food intake, and promote β-cell proliferation and secretion. GLP-1 analogues are used in the treatment of T2DM patients who do not achieve adequate glycemic control on metformin or the combination of metformin and another antidiabetic agent.[33-35] An important feature of GLP-1 analogues is that this class of drugs increases insulin secretion only in the presence of hyperglycemia resulting from oral intake, leading to a low risk of hypoglycemia. **Exenatide** (Byetta®) is a synthetic peptide with 53% amino acid similarity to GLP-1. Exenatide is administered at a dose of 5 to 10 micrograms twice daily as SC injection in the abdomen, thigh, or arm. Dose adjustment is necessary in patients with end-stage renal failure (creatinine clearance of <30 mL/min). **Liraglutide** (Victoza®) is a GLP-1 receptor agonist that is injected at a dose of 0.6 to 1.2 milligrams once a day, so some prefer it over exenatide. This class of drug is contraindicated in the presence of medullary thyroid cancer or in those with multiple endocrine neoplasia. Pancreatitis is a reported adverse effect, but the evidence is questionable. They should be withheld if the patient develops acute pancreatitis.

DIPEPTIDYL PEPTIDASE 4 INHIBITORS

Dipeptidyl peptidase 4 inhibitors prolong the action of native GLP-1 through inhibiting its metabolism by dipeptidyl peptidase 4. They are administered orally. Saxagliptin, sitagliptin, linagliptin, and vildagliptin are some of available preparations. Dipeptidyl peptidase 4 inhibitors (except linagliptin) need dose adjustment in renal dysfunction. A safety alert was issued for saxagliptin in February 2014 due to possible association with heart failure. This class should be used cautiously in patients with history of pancreatitis.

AMYLIN ANALOGUES

Amylin is a neuroendocrine peptide that is normally cosecreted with insulin from the pancreatic β cells. It has a complementary action for insulin in regulating plasma glucose. In T2DM, secretion of amylin diminishes and is delayed in advanced stages of the disease. Pramlintide is the synthetic analogue of amylin with several metabolic effects: It (1) suppresses endogenous secretion of glucagon, especially in the postprandial state, thereby decreasing postprandial hepatic glucose production; (2) reduces the rate of gastric emptying; (3) decreases appetite and induces satiety; and (4) reduces postprandial glucose levels.[36-38] **Pramlintide** is used as a 120-microgram SC injection at mealtime in patients with type 1 diabetes as well as patients with T2DM who are treated with insulin but who are very vigilant with insulin dosage and blood glucose monitoring. It carries a U.S. Food and Drug Administration black box warning; if given with insulin therapy, it can induce severe hypoglycemia, especially within 3 hours of insulin administration.

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

This group of drugs, through a mechanism that is independent of insulin, inhibits sodium-glucose cotransporter 2 in the proximal nephron, thereby decreasing reabsorption of glucose and increasing glucose and sodium excretion in the urine. This leads to the reduction of HbA_{1c} as well as systolic and diastolic blood pressure. Due to their mechanism of action, their effectiveness decreases at the estimated glomerular filtration rate of less than 45 to 60 mL/min/1.73 m^2. Canagliflozin, dapagliflozin, and empagliflozin are the available formularies in this group. Sodium-glucose cotransporter 2 inhibitors have been reported to be associated with euglycemic DKA.[39] Therefore, in diabetic patients taking sodium-glucose cotransporter 2 inhibitors, the presence of nausea, vomiting, malaise, or metabolic acidosis should prompt the clinician to look for the presence of urine and/or serum ketones.

INSULIN

Decreased secretion of insulin due to declining β-cell function eventually makes oral antidiabetic agents ineffective in achieving glycemic control and leads to the need for insulin therapy. Insulin can be used to supplement endogenous production of insulin both in the basal and postprandial state. Traditionally, insulin has been used for the treatment of T2DM when nutritional therapy and oral agents have failed to control blood glucose levels. There is, however, an increasing trend toward the initiation of insulin at an earlier stage of the disease. Besides when therapy with oral agents fails to achieve the glycemic target, insulin may be used in the treatment of T2DM in several other situations: during the perioperative period in a diabetic patient, for treatment of acute hyperglycemic crises, and even as the initial therapy in severe hyperglycemia (blood glucose ≥300 milligrams/dL or HbA_{1c} ≥10%). There are several formulations of insulin available, with different pharmacokinetics. See Chapter 223, "Type 1 Diabetes Mellitus," for detailed discussion of insulins.

PREVENTION AND MANAGEMENT OF CHRONIC COMPLICATIONS

Emergency physicians can reinforce patient education and provide access to additional resources as necessary. Interventions that may be initiated or augmented in the ED for chronic complications are presented in **Table 224-9, 224-10,** and **224-11** and are briefly discussed below.

LOWER EXTREMITY AND FOOT COMPLICATIONS

From a clinical standpoint, foot ulcers can be classified as non–limb-threatening, limb-threatening, or life-threatening infections. Non–limb-threatening infection is defined as one that is small (<2 cm of surrounding cellulitis or inflammation), does not involve deep structures or bone, and is the result of recent injury to a well-perfused limb. The patient has no signs of systemic toxicity or leukocytosis. Limb-threatening infections are characterized by the presence of >2 cm of surrounding cellulitis or inflammation, with associated ascending lymphangitis, deep full-thickness ulceration or abscess, a large area of necrotic tissue, involvement of deep structures or bone, gangrene adjacent to the ulcer, or critical lower extremity ischemia (i.e., absence of palpable pulses). Life-threatening infection has clinical signs of sepsis, including fever, leukocytosis, hypotension, tachycardia, tachypnea, altered mental status, and metabolic abnormalities ranging from hypoglycemia to diabetic ketoacidosis and hyperosmolar hypertonic nonketotic state (**Table 224-12**).

TABLE 224-9 Management of Diabetes Complications

Complication	Treatment
Hypertension	Lifestyle modification ACEI and ARB are the preferred agents if albuminuria is present Thiazide-like diuretics or dihydropyridine calcium channel blockers can also be used
Dyslipidemia	Lifestyle modifications Moderate to high-intensity statin therapy PCSK9 inhibitors in refractory cases Fibrates for extreme hypertriglyceridemia
Acute coronary syndrome	Same as in nondiabetic patients
Nephropathy	ACEI or ARB (if hypertensive)
Retinopathy	Optimize glucose and blood pressure control Prompt referral of patients with any level of macular edema, severe nonproliferative diabetic retinopathy, or any proliferative diabetic retinopathy Bleeding after thrombolytic therapy felt to be very low (0.05%); discuss risks/benefits before administration
Neuropathy	Improved glycemic control Pharmacologic treatment

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; PCSK9 = proprotein convertase subtilisin/kexin type 9.

TABLE 224-10 Drugs Used in the Treatment of Symptomatic Diabetic Autonomic Neuropathy

Class	Examples	Typical Dosages*
Tricyclic drugs	Amitriptyline	10–75 milligrams at bedtime
	Nortriptyline	25–75 milligrams at bedtime
	Imipramine	25–75 milligrams at bedtime
Anticonvulsants	Gabapentin	300–1200 milligrams twice a day
	Carbamazepine	200–400 milligrams twice a day
	Pregabalin†	100 milligrams twice a day
5-Hydroxytryptamine and norepinephrine uptake inhibitor	Duloxetine†	60–120 milligrams daily
Substance P inhibitor	Capsaicin cream	0.025%–0.075% applied twice a day or four times a day
Opioids	Tapentadol (extended release)†	50–250 milligrams orally twice a day

*Dose response may vary; initial doses need to be low and titrated up.

†Has U.S. Food and Drug Administration indication for treatment of painful diabetic neuropathy.

TABLE 224-11 Symptomatic Treatment of Selected Autonomic Neuropathies in Diabetic Patients

Manifestation of Autonomic Neuropathy	Treatment
Gastroparesis	Frequent small meals, prokinetic agents (e.g., metoclopramide), dietary modification
Diarrhea	Soluble fiber, anticholinergic agents, cholestyramine
Constipation	Dietary fiber supplementation, bulking agents, stool softener
Neurogenic bladder	Bethanechol, intermittent catheterization
Erectile dysfunction	Psychological counseling, phosphodiesterase inhibitors (e.g., sildenafil)
Postural hypotension	Increasing salt intake (in the absence of hypertension), elastic stockings, midodrine, or droxidopa
Anhydrosis	Scopolamine, emollients, skin lubricants

Management of foot ulcers requires a multidisciplinary approach. Principles of management include debridement of necrotic tissues, avoidance of pressure points, management of infection (**Table 224-13**) and/or ischemia, management of hyperglycemia and other medical comorbidities, proper wound handling, and surgery.

Treatment of noninfected chronic wounds mostly relies on avoidance of weight bearing and nonadherent padded dressings. Prophylactic antibiotics are not recommended. Refer to a specialist in diabetes-related foot care within a few days to consider the need for debridement, total contact casting, further evaluation of any bony deformity or neuropathy, and evaluation for peripheral vascular disease.

Non–limb-threatening infections can usually be managed in the outpatient setting with appropriate minor debridement and administration of oral antibiotic therapy (Table 224-13). Application of well-padded dressing and avoidance of pressure to the affected area are necessary for adequate wound healing.

Treatment of limb-threatening infections requires hospitalization, IV antibiotics (Table 224-13), and surgical debridement. Direct empiric antibiotics against the predominant pathogens, *Staphylococcus* and *Streptococcus* species. Include coverage for aerobic gram-negative and anaerobic bacteria for gangrenous, ischemic, or malodorous wounds. Topical antibiotics are generally not recommended. In the absence of palpable pedal pulses, vascular ultrasonography is needed. Further studies can include the ankle-brachial index, toe pressures, or measurement of transcutaneous oxygen tension. Immediate surgical consultation is indicated for incision and debridement, possible revascularization, or amputation.

HYPOGLYCEMIA

Hypoglycemia is often a complication of the treatment of diabetes mellitus. However, some cases of hypoglycemia encountered in the ED are spontaneous. Timely recognition of this diagnosis and prompt intervention, as well as initiating the workup for the etiology of the spontaneous hypoglycemic event, are important yet sometimes challenging tasks.[40]

Although there is no fixed laboratory definition of hypoglycemia, in a nondiabetic patient, **it is clinically defined as follows: (1) symptoms consistent with the diagnosis; (2) symptoms associated with a low glucose level; and (3) symptoms resolve with glucose administration**.[41-43] The definition of hypoglycemia in diabetics is more complex. Generally speaking, a plasma glucose concentration of ≤70 milligrams/dL (3.9 mmol/L) is often considered as a reasonable threshold to alert the patient to the possibility of developing hypoglycemia.[44]

PATHOPHYSIOLOGY

Although the human brain depends on glucose as its primary source of energy, it is unable to synthesize or store glucose, accounting for the common manifestation of hypoglycemia as altered mental status. Physiologic response to low blood glucose includes suppression of insulin secretion and release of the counterregulatory hormones (e.g., glucagon and epinephrine). These responses are modified with increasing age. Renal clearance of insulin decreases with age, and this may enhance the risk of hypoglycemia in the elderly. On the other hand, in subjects with T2DM, counterregulatory hormones are secreted at higher blood glucose levels (compared with nondiabetics and those with type 1 diabetes mellitus), resulting in some protection against hypoglycemia in patients with T2DM. Improved glycemic control through insulin therapy lowers the blood glucose level threshold for the counterregulatory response and offsets this protective effect of diabetes.

Hypoglycemia occurs most frequently with insulin and sulfonylureas. **Hypoglycemia is not a common side effect of treatment with glitazones, glinides, or α-glucosidase inhibitors.** Among sulfonylureas, the risk of hypoglycemia depends on the pharmacokinetic properties of each agent. Chlorpropamide, glyburide (glibenclamide), and long-acting glipizide are long-acting sulfonylureas and are associated with more episodes of hypoglycemia. Hypoglycemia is rarely, if ever, encountered in patients using only metformin. Risk factors for severe hypoglycemia in patients with T2DM include age, past history of vascular disease, renal

TABLE 224-12 Clinical Practice Pathways for Diabetic Foot Ulcer and Infection

Extent of Infection	Characteristics	Diagnostic Procedures	Treatment
Non–limb-threatening infection	<2 cm cellulitis	Cultures from base of ulcer (with tissue specimen if possible)	Outpatient management with follow-up in 24–72 h
	Superficial ulcer	Diagnostic imaging (radiography, MRI, nuclear scans as indicated)	Debridement of all necrotic tissue and callus
	Mild infection	Serologic testing	Wound care/dressing
	No systemic toxicity	CBC with differential	Empiric antibiotic coverage, modified by culture findings
	No ischemic changes	ESR	Appropriate off-loading of weight bearing
	No bone or joint involvement	Comprehensive metabolic panel	Wound care continued with packs, dressings, and debridement as needed
	Does not probe to bone		Hospital admission if infection progresses or systemic signs or symptoms develop
			Refer to podiatrist for follow-up care, special shoes, and prostheses as needed
Life- or limb-threatening infection	>2 cm cellulitis	Deep culture from base of ulcer/wound with tissue specimen if possible	Hospital admission
	Deep ulcer	Diagnostic imaging (radiography, MRI, nuclear scan, bone scan, leukocyte scan, arteriography)	Surgical debridement with resection of all necrotic bone and soft tissue
	Odor or purulent drainage from wound	Serologic testing	Exploration and drainage of deep abscess
	Fever	CBC with differential	Empiric antibiotic coverage, modified by culture findings
	Ischemic changes	ESR	Surgical resection of osteomyelitis
	Lymphangitis, edema	Comprehensive metabolic panel	Wound care continued with packs, dressings, debridement as needed
	Sepsis or septic shock	Blood cultures	Foot-sparing reconstructive procedures
			Refer to podiatrist for follow-up care, special shoes, and prostheses as needed

Abbreviation: ESR = erythrocyte sedimentation rate.

failure, decreased food ingestion, alcohol consumption, and drug interactions. In nondiabetics, other causes such as adverse effects of drugs (and alcohol), factitious hypoglycemia, tumors (insulinoma or non–islet cell), critical illness (e.g., sepsis or liver failure), and hormone deficiencies (adrenal insufficiency or hypopituitarism) should be considered.

CLINICAL FEATURES

The clinical manifestations of hypoglycemia are divided into two broad categories: *neuroglycopenic* and *autonomic*. Autonomic findings consist of adrenergic symptoms (including anxiety, nervousness, irritability, nausea, vomiting, palpitations, and tremor) and cholinergic symptoms (e.g., sweating, hunger, paresthesias, and sweating). **Neuroglycopenic** manifestations include alterations in consciousness, lethargy, confusion, combativeness, agitation, seizures, and focal neurologic deficits. The patient is commonly found pale and diaphoretic, with some levels of altered mental status. **Table 224-14** lists various medical conditions that may be mistaken for hypoglycemia.

DIAGNOSIS

Always consider hypoglycemia (in both the ED and the prehospital setting) as a potential cause of altered mental status. Failure to determine the blood glucose level early in the evaluation can result in a delayed or missed diagnosis with associated morbidity because of CNS injury or unnecessary invasive procedures and therapies. Confirm hypoglycemia with bedside glucose testing. The accuracy of bedside reflectance tests is acceptable although less reliable at extremely low and high glucose levels. Glucose values of whole blood are approximately 15% less than that of serum or plasma. This discrepancy is a result of the relatively low glucose concentration in red blood cells. Whenever possible, send a serum sample to the laboratory for confirmation. **In diabetic patients who develop hypoglycemia while taking the usual dose of sulfonylurea, suspect an underlying cause.** Drug interactions, decreased drug metabolism, and decreased drug excretion are common precipitating causes. In nondiabetic patients, without history of inadvertent or deliberate use of blood sugar–lowering agents, obtain a serum sample before initiation of dextrose therapy. This sample can later be sent to the laboratory for measuring serum insulin, pro-insulin, and C-peptide, at the discretion of the consultant endocrinologist. This simple measure obviates the need to perform a *fasting test* in order to diagnose the cause of hypoglycemia.

TREATMENT

Regardless of the cause, management of hypoglycemia in the ED includes prompt diagnosis and PO or IV administration of rapidly metabolized carbohydrates (i.e., glucose or dextrose). In patients with altered mental status, 50% dextrose in water is administered IV as a bolus dose of 50 mL, which provides 25 grams of glucose. This dose may be repeated after 15 minutes if hypoglycemia persists. When blood glucose reaches 70 milligrams/dL and the patient regains consciousness, continue carbohydrates to prevent recurrence of hypoglycemia. This can be accomplished through PO administration of long-acting carbohydrates. If blood glucose is normalized but the patient is still unconscious or receiving nothing by mouth, provide a continuous IV infusion of dextrose (5% dextrose in water at a rate to maintain the serum glucose >100 milligrams/dL [5.55 mmol/L]). Check blood glucose every 30 minutes for the first 2 hours, looking for rebound hypoglycemia. If hyperglycemia is maintained by slow administration of dextrose, the infusion may be reduced and eventually withdrawn.

Failure to respond to parenteral glucose administration should prompt consideration of other causes of hypoglycemia, such as sepsis, toxin, insulinoma, hepatic failure, or adrenal insufficiency. Hypoglycemia resulting from sulfonylureas is much more challenging than insulin-induced hypoglycemia. Hemodialysis and charcoal hemoperfusion, although mentioned in case reports, are not routinely recommended for sulfonylurea overdose.

Since sulfonylureas cause glucose-stimulated insulin secretion, glucose administration may potentially aggravate hypoglycemia in these cases. **Octreotide** is a somatostatin analog and is able to suppress insulin secretion immediately and negates the effects of the sulfonylurea. It can be used successfully for the treatment of sulfonylurea-induced hypoglycemia and is believed to be superior to glucose and diazoxide

TABLE 224-13 Antimicrobial Therapy in Infected Diabetes-Related Lower Extremity Ulcers

Non–limb-threatening*
- Cephalexin, 500 milligrams PO every 6 h, 10-d course
  Or
- Clindamycin, 300–450 milligrams PO every 6–8 h, 10-d course
  Or
- Dicloxacillin, 500 milligrams PO every 6 h, 10-d course
  Or
- Amoxicillin-clavulanate, 875/125 milligrams PO every 12 h, 10-d course
  Or
- Clarithromycin 500 milligrams PO every 12 h *(in severe penicillin allergy)*

Limb-threatening*

Oral regimen†:
- (Ciprofloxacin *or* levofloxacin *or* moxifloxacin) *plus* clindamycin
  Or
- Trimethoprim-sulfamethoxazole *plus* amoxicillin-clavulanate

IV regimens:
- Ampicillin-sulbactam, 3 grams every 6 h
  Or
- Piperacillin-tazobactam 4.5 grams every 6–8 h
  Or
- Clindamycin, 900 milligrams every 6 h *plus*
- (ciprofloxacin, 400 milligrams every 8–12 h
  Or
- Ceftriaxone, 1 gram every 12 h)

Life-threatening*

IV regimens:
- Imipenem-cilastatin, 500 milligrams every 6 h
  Or
- Meropenem 1 gram every 8 h
  Or
- Vancomycin, 15–20 milligram/kg every 12 h, *plus* metronidazole, 500 milligrams every 8 h, *plus* (aztreonam, 2 grams every 6–8 h
  Or
- Ciprofloxacin 400 milligrams every 8–12 h)
  (if MRSA coverage is warranted)

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus*.

Note: Adjust all dosages for renal/hepatic function and monitor blood levels where appropriate.

*See the section "Lower Extremity and Foot Complications" for definitions.

†This approach is acceptable under special circumstances with close follow-up.

TABLE 224-14 Differential Diagnosis of Hypoglycemia
- Stroke
- Transient ischemic attack
- Seizure disorder
- Traumatic head injury
- Brain tumor
- Narcolepsy
- Multiple sclerosis
- Psychosis
- Sympathomimetic drug ingestion
- Hysteria
- Altered sleep patterns and nightmares
- Depression

in preventing recurrent hypoglycemia. The ideal dosage and interval of octreotide are not well defined. Recommendations vary from a single 50- to 100-microgram SC injection after a single hypoglycemic episode, to serial SC injections (50 to 100 micrograms every 6 to 8 hours) or constant IV infusion (125 micrograms/h) after a second hypoglycemic episode. Some suggest that the addition of octreotide, 50 micrograms SC, to standard therapy may result in a decrease in frequency of hypoglycemic episodes and an increase in mean plasma glucose.[45,46] **Octreotide is only recommended after initial glucose therapy has been initiated for sulfonylurea-induced hypoglycemia and can be considered when the response to dextrose is inadequate. It is primarily used to reduce the risk of recurrent hypoglycemia.**

Glucagon is a U.S. Food and Drug Administration–approved alternative that may be used SC or IM in the absence of IV access. SC injection of this polypeptide hormone can cause an approximate 100 milligram/dL (5.55 mmol/L) increase in serum glucose of hypoglycemic patients. Response to glucagon therapy is generally slower when compared with IV dextrose, requiring 7 to 10 minutes for normalization of mental status. Additionally, the response to glucagon administration may be short lived. **In adults, glucagon is administered at the dose of 1 milligram as an SC or IM injection.** Intranasal glucagon has also been used safely in some studies for the treatment of hypoglycemia.[46] In patients who are thought to be glycogen-depleted (such as heavy alcohol users or marathon runners after the race), glucagon therapy is not recommended. Glucagon is not recommended for sulfonylurea-induced hypoglycemia.

Diazoxide has also been used in the treatment of refractory sulfonylurea-induced hypoglycemia. It acts by directly inhibiting insulin secretion from pancreatic β cells. Diazoxide may cause hypotension and so should be administered as a slow IV infusion (300 milligrams over 30 minutes every 4 hours).

DISPOSITION AND FOLLOW-UP

Patients who experience hypoglycemia due to sulfonylureas, non–short-acting insulins, or meglitinides should be admitted for serial glucose monitoring and treatment. A patient with an isolated episode of accidental hypoglycemia not resulting from oral hypoglycemic agents of long-acting insulins, who has reliable follow-up, may be discharged from the ED upon completion of an uneventful 4-hour observation period.[46]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 225

Diabetic Ketoacidosis

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INTRODUCTION AND EPIDEMIOLOGY

Diabetic ketoacidosis (DKA) is an acute, life-threatening complication of diabetes mellitus. DKA occurs predominantly in patients with type 1 (insulin-dependent) diabetes mellitus. The incidence of DKA in the United Kingdom, United States, and other developed countries is comparable, with an annual incidence between 13.4 and 14.9 cases per 1000 type 1 diabetics.[1] There has been an increased number of DKA cases in patients with newly diagnosed type 2 (non–insulin-dependent) diabetes mellitus, especially in African Americans and Hispanics. Ketosis-prone type 2 diabetics have significant impairment in insulin secretion and action that subsequently recovers after resolution of DKA.[1] Over the

past decade in the United States, the frequency of DKA has increased by 30%, with close to 140,000 hospitalizations per year.[2] A better understanding of the pathophysiology of DKA and an aggressive, uniform approach to its diagnosis and management have reduced mortality to <1% of reported episodes in experienced centers.[1] However, mortality is higher in patients from developing countries, those with comorbidities and the elderly.[3]

PATHOPHYSIOLOGY

Figure 225-1 illustrates the complex relationships between insulin and counterregulatory hormones. DKA is a response to cellular starvation brought on by relative insulin deficiency and counterregulatory or catabolic hormone excess (Figure 225-1). Insulin is the only anabolic hormone produced by the endocrine pancreas and is responsible for the metabolism and storage of carbohydrates, fat, and protein. Counterregulatory hormones include glucagon, catecholamines, cortisol, and growth hormone. Complete or relative absence of insulin and the excess counterregulatory hormones result in hyperglycemia (due to excess production and underutilization of glucose), osmotic diuresis, prerenal azotemia, worsening hyperglycemia, ketone formation, and an elevated anion gap metabolic acidosis.[4]

INSULIN

Ingested glucose is the primary stimulant of insulin release from the β cells of the pancreas. Insulin's main action occurs at the three principal tissues of energy storage and metabolism—the liver, adipose tissue, and skeletal muscle. Insulin acts on the liver to facilitate the uptake of glucose and its conversion to glycogen while inhibiting glycogen breakdown (glycogenolysis) and suppressing gluconeogenesis. The net effect of these actions is to promote the storage of glucose in the form of glycogen. Insulin increases lipogenesis in the liver and adipose cells by producing triglycerides from free fatty acids and glycerol while inhibiting the breakdown of triglycerides. Insulin stimulates the uptake of amino acids into muscle cells with subsequent incorporation into muscle protein while preventing the release of amino acids from muscle and hepatic protein sources.

Deficiency in insulin secretion due to loss of islet cell mass is the predominant defect in type 1 diabetes mellitus. In the initial stages of diabetes mellitus, the secretory failure of β cells impairs fuel storage and may be evident only during a glucose tolerance test. As levels of insulin decrease, fuel stores are mobilized during fasting, resulting in hyperglycemia. When pancreatic β-cell reserve is present, hyperglycemia may trigger an increase in insulin and a return to normal glucose concentration. With further disease progression, hyperglycemia can no longer trigger an increase in insulin activity. Despite the presence of elevated intravascular glucose, in the absence of insulin, cells are unable to use glucose as a fuel source. The body responds by breaking down protein and adipose stores to try to produce a usable intracellular fuel. Loss of the normal physiologic effects of insulin leads to secretion of catabolic (counterregulatory) hormones and resulting hyperglycemia and ketonemia.

KETOACIDOSIS

The response to cellular starvation seen with insulin insufficiency is increased levels of glucagon, catecholamines, cortisol, and growth hormone. Glucagon is the primary counterregulatory hormone. The catabolic effects of these hormones include increased gluconeogenesis and glycogenolysis, breakdown of fats into free fatty acids and glycerol, and proteolysis with increased levels of amino acids. Increased levels of glucogenic precursors, such as glycerol and amino acids, facilitate gluconeogenesis, worsening hyperglycemia.

Free fatty acids released in the periphery are bound to albumin and transported to the liver, where they undergo conversion to ketone bodies. The primary ketone bodies **β-hydroxybutyrate** (βHB) and **acetoacetic acid** (AcAc) account for the metabolic acidosis seen in DKA. The two are in equilibrium: **AcAc + NADH ⇌ βHB + NAD**. AcAc is metabolized to **acetone**, another major ketone body. Depletion of

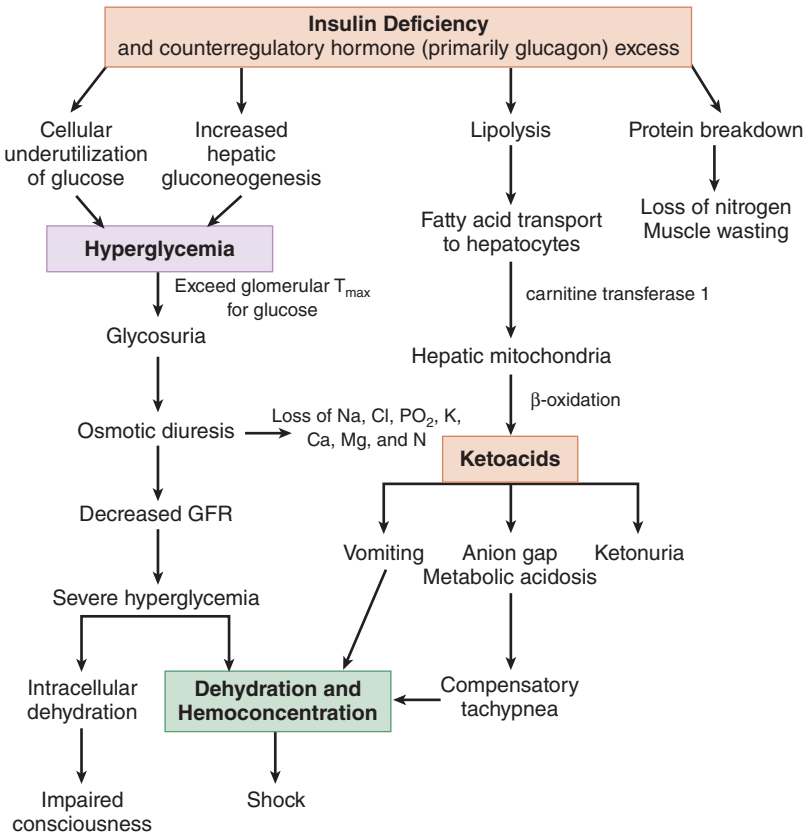

FIGURE 225-1. Insulin deficiency. Pathogenesis of diabetic ketoacidosis secondary to relative insulin deficiency and counterregulatory hormone excess. GFR = glomerular filtration rate.

TABLE 225-1 Important Causes of Diabetic Ketoacidosis

- Omission or reduced daily insulin injections
- Dislodgement/occlusion of insulin pump catheter
- Infection
- Pregnancy
- Hyperthyroidism, pheochromocytoma, Cushing's syndrome
- Substance abuse (cocaine)
- Medications: steroids, thiazides, antipsychotics, sympathomimetics
- Heat-related illness
- Cerebrovascular accident
- GI hemorrhage
- Myocardial infarction
- Pulmonary embolism
- Pancreatitis
- Major trauma
- Surgery

hepatic glycogen stores favors ketogenesis. Low or absent insulin levels decrease the ability of the brain and cardiac and skeletal muscle to use ketones as an energy source, increasing ketonemia. The persistently elevated serum glucose level eventually causes an osmotic diuresis. The resulting volume depletion worsens hyperglycemia and ketonemia.

The renin-angiotensin-aldosterone system, activated by volume depletion, exacerbates renal potassium losses already occurring from osmotic diuresis. In the kidney, chloride is retained in exchange for the ketoanions being excreted. The loss of ketoanions represents a potential loss of bicarbonate. In the face of marked ketonuria, a superimposed hyperchloremic acidosis is also present. As adipose tissue is broken down, prostaglandins I_2 and E_2 are produced. Both account for paradoxical vasodilation that occurs despite profound levels of volume depletion.

CAUSES OF DKA

Factors known to precipitate DKA are listed in **Table 225-1**.[4] Additional risk factors include poor economic background, lack of insurance or minority status, drug abuse, depression, and the presence of an eating disorder. In many patients, no clear precipitating cause is found.[4]

CLINICAL FEATURES

The clinical manifestations of DKA are related directly to hyperglycemia, volume depletion, and acidosis. The metabolic alterations of DKA tend to evolve within 24 hours.[4] Osmotic diuresis gradually leads to volume loss in addition to renal losses of sodium, chloride, potassium, phosphorous, calcium, and magnesium. Initially, patients may compensate by increasing fluid intake, and polyuria and polydipsia are usually the only symptoms until ketonemia and acidosis develop. As acidosis progresses, ventilation is stimulated physiologically by acidemia to diminish the P_{CO_2} and to counter metabolic acidosis. Acidosis combined with the effects of prostaglandins I_2 and E_2 leads to peripheral vasodilation despite profound levels of volume depletion. Prostaglandin release is also felt to play a role in unexplained nausea, vomiting, and abdominal pain that are seen frequently at presentation, especially in children. Vomiting, which may be a maladaptive physiologic response to diminish the acid load, unfortunately exacerbates potassium losses. As volume depletion progresses, poor absorption of SC insulin renders its administration less effective. Impaired mental status may develop and is most likely multifactorial, related to metabolic acidosis, hyperosmolarity, low extracellular fluid volume, and poor hemodynamics. **Alteration of consciousness seems to correlate better with elevated serum osmolality (>320 mOsm/L or >320 mmol/kg) than with severity of metabolic acidosis**.[5]

Tachycardia, orthostasis or hypotension, poor skin turgor, and dry mucous membranes result from volume depletion. **Kussmaul respirations**, increased rate and depth of breathing, may be observed. Acetone produces the characteristic fruity odor on the breath found in some patients. The absence of fever does not exclude infection. Hypothermia is present occasionally because of peripheral vasodilation.

Abdominal pain and tenderness associated with DKA generally correlate with the level of acidosis. Pain can be due to gastric dilatation, ileus, or pancreatitis, but any other acute abdominal disorder can also develop. Due to the frequency of abdominal pain and the presence of an elevated serum amylase or lipase level in both DKA and pancreatitis, distinguishing these two conditions may be difficult. An elevated serum lipase level is more specific to pancreatitis, but it may also be elevated in DKA.

DIAGNOSIS

A blood glucose level >250 milligrams/dL (13.9 mmol/L), an anion gap >10 to 12 mEq/L (>10 mmol/L), a bicarbonate level <15 mEq/L (<15 mmol/L), and a pH <7.3 with moderate ketonuria or ketonemia constitute the diagnosis of DKA.[1,4,6] Traditionally, DKA is divided into mild, moderate, and severe states based on total-body deficits of water and electrolytes. Mild DKA is defined as an arterial pH of 7.25 to 7.3, a serum bicarbonate of 15 to 18 mEq/L (15 to 18 mmol/L), and an anion gap >10 mEq/L, whereas moderate DKA is defined as arterial pH between 7.0 and 7.24, a serum bicarbonate of 10 to 15 mEq/L (10 to 15 mmol/L), and an anion gap >12 mEq/L in an alert to drowsy patient. Severe DKA is defined as a pH <7.00, bicarbonate <10 mEq/L (<10 mmol/L), and anion gap >12 mEq/L in a stuporous to comatose patient.[1]

EUGLYCEMIC DKA

In contrast to the above DKA criteria, **euglycemic ketoacidosis (euDKA)** (glucose <250 milligrams/dL or <13.9 mmol/L) can create a diagnostic challenge. Situations in which euDKA occurs include pregnant patients, young type 1 diabetics who are vomiting, patients who present just after receiving insulin, patients with impaired gluconeogenesis (alcohol abuse or liver failure), and patients with low caloric intake or starvation. Suspect euDKA in such patient populations even in the presence of relative normoglycemia (**Table 225-2**).[7,8] euDKA has also recently been described as a potential adverse side effect in patients taking sodium-glucose cotransporter 2 (SGLT-2) inhibitors (e.g., canagliflozin, dapagliflozin, or empagliflozin). Potential mechanisms include decreased insulin dose requirements and higher glucagon levels.[8] SGLT-2 inhibitors increase glucose secretion in the urine, thereby decreasing carbohydrate availability. The subsequent drop in insulin release inhibits gluconeogenesis in the liver, in turn resulting in ketogenesis and the lower serum glucose levels commonly seen in euDKA. A clinical suspicion for ketosis (nausea, vomiting, malaise) in this unique subset of patients combined with the measurement of serum βHB (generally >3 mEq/L [>3 mmol/L]) can aid in the prompt diagnosis of DKA.[7-9] As outlined below, treatment includes dextrose containing fluids coupled with insulin therapy until ketosis resolves.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of DKA (**Table 225-3**) includes any cause of a high anion gap metabolic acidosis. Patients with hyperosmolar, nonketotic

TABLE 225-2 Risk Factors for Diabetic Ketoacidosis Patients with Initial Glucose <250 milligrams/dL (13.9 mmol/L) (Euglycemic Ketoacidosis)

- Patients presenting shortly after receiving insulin
- Type 1 diabetics who are young and vomiting
- Patients with impaired gluconeogenesis (alcohol abuse or liver failure)
- Low caloric intake/starvation
- Depression
- Pregnancy
- SGLT2 inhibitors*

*SGLT2 inhibitors = inhibitors of sodium-glucose transport protein 2 (e.g., dapagliflozin, canagliflozin, empagliflozin).

TABLE 225-3 Differential Diagnosis for Diabetic Ketoacidosis

- Alcoholic ketoacidosis
- Starvation ketoacidosis
- Renal failure
- Lactic acidosis
- Ingestions
  - Salicylates
  - Ethylene glycol
  - Methanol

coma tend to be older, have a more prolonged course, and have prominent mental status changes. Serum glucose levels generally are much higher (>600 milligrams/dL or >33.3 mOsm/L), and there is little to no anion gap metabolic acidosis.[4] The ketosis in alcoholic ketoacidosis and starvation ketosis tend to be milder (βHB generally <3 mEq/L [<3 mmol/L], serum bicarbonate usually >18 mEq/L [>18 mmol/L]), and the serum glucose level is usually low or normal. βHB predominates in alcoholic ketoacidosis, so the urinary ketone test may be negative or trace positive.

Various toxic ingestions may also cause a high anion gap acidosis, so if a toxic ingestion cannot be excluded, serum osmolarity or drug-level testing is required. Renal failure, anion gap acidosis, and liver function abnormalities may be due to acetaminophen toxicity. Depending on the hemodynamic status, lactic acidosis (poor perfusion) may occur simultaneously with DKA; in these cases, determination of the serum lactate level is indicated. **Patients taking metformin with new-onset renal insufficiency are at risk for developing type B (aerobic) lactic acidosis.**

LABORATORY TESTING

Obtain a rapid bedside glucose level, urinalysis, and ECG to assess for evidence of hyperkalemia, and obtain a CBC, serum electrolytes, BUN and creatinine, urinalysis, venous blood gas, and phosphate, magnesium, and calcium levels. Calculate the anion gap [Na – (Cl + HCO_3)]. Blood cultures and other laboratory tests should be done as clinically indicated. Arterial blood gas determinations are optional but may be required for the diagnosis and monitoring of critically ill patients.

Ketone Bodies In DKA, elevated serum levels of βHB and AcAc cause acidosis and ketonuria. The **nitroprusside** reagent normally used to detect urine and serum ketones **only detects AcAc**; acetone is only weakly reactive and βHB not at all. Gas chromatography can be used to detect serum acetone but is expensive and time consuming.

NADH accumulation in mitochondria, as may occur with lactic acidosis or alcohol metabolism, favors the βHB side of equilibrium noted earlier (**AcAc + NADH ⇌ βHB + NAD**). Paradoxically, as the patient is being treated and clinically improves, ketone levels will increase as the body converts the more acidic βHB to AcAc. Therefore, the urine and/or blood ketone test (Acetest®) that uses the nitroprusside reaction is not a reliable measure for diagnosis or monitoring of DKA. Compared to a urine dipstick for ketones, a more reliable and preferred test for ketonemia in DKA is a quantitative βHB serum level. In general, during DKA, the βHB level is greater than 3 mEq/L (3 mmol/L), and this test should be obtained with other initial laboratory testing, as outlined above.[3] Drugs with a sulfhydryl group, such as the angiotensin-converting enzyme inhibitor captopril, interact with the reagent in the nitroprusside test, producing a potential false-positive urine test for ketones. Consider the clinical presentation and other biochemical markers when interpreting a positive urine nitroprusside test in this subset of patients.[1]

Acid-Base Abnormalities **DKA leads to a wide anion gap metabolic acidosis.** Hyperchloremic acidosis also occurs on the basis of ketoanion exchange for chloride in the urine and is especially common in patients who maintain good hydration status and glomerular filtration rate despite ketoacidosis. Metabolic alkalosis may occur secondary to vomiting, osmotic diuresis, and concomitant diuretic use. Rarely, some patients with DKA may present with normal-appearing [HCO_3^-] or even an elevated [HCO_3^-], if coexisting metabolic alkalosis is severe enough to mask the acidosis. In such situations, an elevated anion gap may be the only clue to the presence of an underlying metabolic acidosis otherwise masked by the concomitant volume contraction–related metabolic alkalosis.

Venous pH has essentially replaced arterial blood gases in the assessment of the acid-base status of the DKA patient. A strong correlation exists between venous and arterial pH in patients with DKA, and the arterial blood gas value does not impact therapy.[10] **Venous pH is about 0.03 lower than arterial pH.** Venous pH obtained during routine phlebotomy should be used to avoid arterial puncture, which is painful and may cause arterial vascular complications.

A low P_{CO_2} determination usually reflects respiratory compensation for metabolic acidosis. If it is lower than explained by the degree of acidosis, a primary respiratory alkalosis exists, which may be an early indication of pulmonary disease (e.g., pneumonia, pulmonary embolus) or sepsis as a possible trigger of DKA. Chapter 15, "Acid-Base Disorders," details how compensatory changes in P_{CO_2} can be distinguished from a primary respiratory alkalosis.

Potassium Total-body potassium is depleted by renal losses. **However, the measured serum potassium level is normal or elevated in most patients[4] because of two important factors**: extracellular shift of potassium secondary to acidemia and increased intravascular osmolarity caused by hyperglycemia. Although the actual incidence of initial hypokalemia on laboratory testing in DKA is not known, a few studies report an occurrence of 4% to 6%.[5,11,12] **The decrease in serum potassium during therapy is reported to be about 1.5 mEq/L (1.5 mmol/L) and parallels the drop in glucose and the dose of insulin.**[5,11]

ECG changes of hyperkalemia or hypokalemia may be seen. The ECG also should be evaluated for ischemia because myocardial infarction may precipitate DKA.

Sodium and Other Electrolytes Osmotic diuresis leads to excessive renal losses of sodium chloride in the urine. However, the presence of hyperglycemia tends to artificially lower the serum sodium levels. **Standard teaching is that 1.6 mEq (1.6 mmol) should be added to the reported sodium value for every 100 milligrams (5.55 mmol) of glucose >100 milligrams/dL (>5.5 mmol/L). However, the correction factor is probably 2.4, especially for blood glucose levels >400 milligrams/dL (>22.2 mOsm/L).**[13] Osmotic diuresis also causes urinary losses and total-body depletion of phosphorous, calcium, and magnesium. Hemoconcentration frequently leads to initially elevated levels of these electrolytes in serum. As therapy progresses, lower serum levels of each will be evident.

Other Laboratory Values **Serum creatinine frequently may be elevated factitiously if the laboratory assay for creatinine is interfered with by the nitroprusside assay.** Some elevation in creatinine is expected due to prerenal azotemia. Liver function studies may be elevated because of fatty infiltration of the liver, which gradually corrects as the acidosis is treated. Leukocytosis is often present because of hemoconcentration and stress. However, a WBC count >25,000 mm^3 and/or an absolute band count of 10,000 mm^3 or more is suggestive of infection.[2] Elevation of C-reactive protein may reflect the proinflammatory state found in DKA; elevated levels of cytokines may also be present.

TREATMENT

The diagnosis of DKA should be suspected at triage. Begin aggressive fluid therapy before receiving laboratory results[4] (**Figure 225-2**). The goals of therapy are (1) volume repletion, (2) reversal of the metabolic consequences of insulin insufficiency, (3) correction of electrolyte and acid-base imbalances, (4) recognition and treatment of precipitating causes, and (5) avoidance of complications. Place patients on a cardiac monitor and begin at least one large-bore (16- to 18-gauge) IV infusion of isotonic crystalloid. A second IV line with 0.45% normal saline at minimal rate to keep the IV line open can be considered. **The order of therapeutic priorities is volume first and foremost, correction of potassium deficits, and then insulin administration.** Metabolic disturbances should be corrected at the approximate rate of occurrence or over 24 to 36 hours.

Meeting the goals of safely replacing deficits and supplying missing insulin requires monitoring every 2 hours of electrolytes (glucose, potassium, and anion gap), vital signs, level of consciousness, and volume input/output until recovery. **The goal of treatment is glucose**

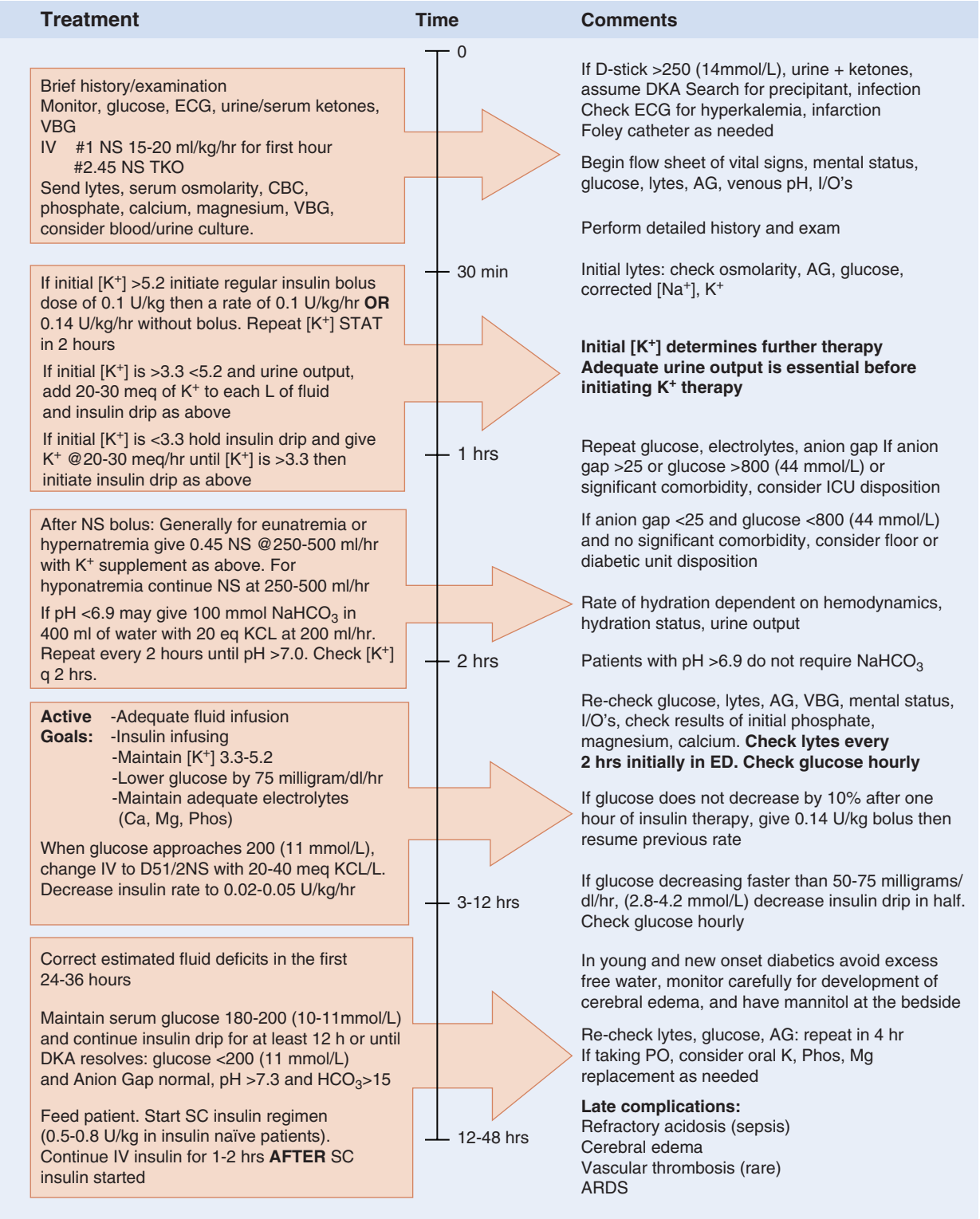

FIGURE 225-2. Timeline for the typical adult patient with suspected diabetic ketoacidosis (DKA). *IV insulin infusion <1.0 unit/kg/h may require a bolus dose of regular insulin (0.1 unit/kg).[4] AG = anion gap; ARDS = acute respiratory distress syndrome; BS = blood sugar; ICU = intensive care unit; I/Os = inputs/outputs; NS = normal saline; TKO = to keep vein open; VBG = venous blood gas.

<200 milligrams/dL (<11.1 mmol/L), bicarbonate ≥18 mEq/L (≥18 mmol/L), and venous pH >7.3.

VOLUME REPLETION

Fluid helps restore intravascular volume and normal tonicity, perfuse vital organs, improve glomerular filtration rate, and lower serum glucose and ketone levels.[4] Rehydration improves the response to low-dose insulin therapy.[4] The average adult patient has a water deficit of 100 mL/kg (5 to 10 L) and a sodium deficit of 7 to 10 mEq/kg (7 to 10 mmol/L/kg).[4] Normal saline is the most frequently recommended fluid for initial volume repletion even though the extracellular fluid of the patient is initially hypertonic.[14] Normal saline does not provide "free water" to correct intracellular fluid loss, but it does prevent an excessively rapid fall in

extracellular osmolarity and the potential devastating transfer of excessive water into the CNS. Large-volume resuscitation with normal saline may result in hyperchloremic metabolic acidosis, prolonging time to resolution of acidosis in DKA. Further, there is a possible association between normal saline resuscitation and increased mortality in septic shock patients when compared to balanced fluid resuscitation.[15] Replacing normal saline with lactated ringer's solution or another balanced electrolyte solution may help to slightly speed resolution of acidosis[16] and prevent hyperchloremic acidosis[17] without any reduction in mortality. Without clear evidence of superiority, **it is reasonable to select either normal saline, lactated ringer's, or a commercially available balanced crystalloid solution for volume replacement in DKA**. There is no consensus on the best fluid choice in DKA. A recent large randomized trial comparing outcomes with use of balanced crystalloid or normal saline was not specific to DKA patients, but supports the use of balanced crystalloids in critically ill patients.[18] After initial resuscitation with isotonic crystalloid, change fluids to 0.45% normal saline once the corrected serum sodium is normal or elevated.[6,7]

Based on clinical suspicion alone and before initial electrolyte results, **administer the initial fluid bolus of isotonic crystalloid at a rate of 15 to 20 mL/kg/h during the first hour** unless there are mitigating circumstances.[6] The rate of hydration should depend on hemodynamic stability, hydration status, urine output, and serum electrolytes. After the initial bolus, administer normal saline at 250 to 500 mL/h in hyponatremic patients, or give 0.45% normal saline at 250 to 500 mL/h for eunatremic and hypernatremic patients.[7] **In general, the first 2 L are administered rapidly over 0 to 2 hours, the next 2 L over 2 to 6 hours, and then an additional 2 L over 6 to 12 hours.** This replaces approximately 50% of the total water deficit over the first 12 hours, with the remaining 50% water deficit to be replaced over the subsequent 12 hours.

When the blood glucose level falls to about 250 milligrams/dL (13.9 mmol/L), change to 5% dextrose in 0.45% normal saline. Patients without extreme volume depletion can be managed safely with a more modest fluid replacement regimen such as 250 to 500 mL/h for 4 hours. Closely monitor the volume status in the elderly or in those with heart or renal disease. Excess fluid may contribute to the development of adult respiratory distress syndrome and cerebral edema.

POTASSIUM REPLACEMENT

Patients in DKA usually present with profound total-body potassium deficits in the range of 3 to 5 mEq/kg (3 to 5 mmol/kg).[4] This deficit is created by insulin deficiency, metabolic acidosis, osmotic diuresis, and frequent vomiting. Only 2% of total-body potassium is intravascular. The initial serum concentration is usually normal or high because of the intracellular exchange of potassium for hydrogen ions during acidosis, the total-body fluid deficit, and diminished renal function. **Initial hypokalemia indicates severe total-body potassium deficits, and large amounts of replacement potassium are usually necessary in the first 24 to 36 hours.**

Correction of the acidosis predicts the change in serum potassium concentration. **For each 0.1 decrease in pH, serum potassium concentration rises approximately 0.5 mEq/L (0.5 mmol/L)**, and the same relationship holds as the pH increases. This can be used as a guide for estimating the serum potassium concentration when pH balance is restored.

Hypokalemia During initial therapy for DKA, the serum potassium concentration may fall rapidly, primarily due to the action of insulin promoting reentry of potassium into cells and, to a lesser degree, the dilution of extracellular fluid, correction of acidosis, and increased urinary loss of potassium. If these changes occur too rapidly, precipitous hypokalemia may result in fatal cardiac arrhythmias, respiratory paralysis, paralytic ileus, and rhabdomyolysis. **The rapid development of severe hypokalemia is potentially the most life-threatening electrolyte derangement during the treatment of DKA.**[4]

As a general guideline, an initial serum potassium level >3.3 mEq/L (>3.3 mmol/L) but <5.2 mEq/L (<5.2 mmol/L) (before fluid resuscitation and insulin, coupled with urine output) calls for 20 to 30 mEq/L (20 to 30 mmol/L) for at least 4 hours to keep potassium between 4 and 5 mEq/L (4 and 5 mmol/L).[6] Because the most rapid changes occur during the first few hours of therapy, measure the plasma potassium level initially every 2 hours. If oliguria or renal insufficiency is present, withhold or decrease potassium replacement.

Initial hypokalemia (<3.3 mEq/L or <3.3 mmol/L) is uncommon but necessitates a more aggressive replacement before insulin therapy.[4] In this setting, give potassium IV at 20 to 30 mEq/h (20 to 30 mmol/h) and hold insulin until [K^+] is ≥3.5 mEq/L (≥3.5 mmol/L).[6,7] There is no advantage to using potassium phosphate (K_2PO_4) compared to potassium chloride because K_2PO_4 may result in hypocalcemia and metastatic precipitation of calcium phosphate in tissues. Oral potassium replacement is safe and effective and is the preferred route of replacement as soon as the patient can tolerate oral fluids. In DKA, initial potassium replacement is usually by an intravenous line. Each institution may have specific guidelines for potassium replacement, but a general approach is a rate no faster than 10 mEq/h (10 mmol/h) via peripheral IV or 20 mEq/h (20 mmol/h) via central line access. Continuous cardiac monitoring is generally recommended while replacing potassium in the severely hypokalemic patient. During the first 24 hours, 100 to 200 mEq (100 to 200 mmol) of KCl is usually required.

Hyperkalemia **Obtain an ECG immediately and check for signs of hyperkalemia once DKA is suspected.**

Giving potassium to a patient in a hyperkalemic potentiating state (e.g., acidemia, insulin deficiency, volume contraction, renal insufficiency) may dangerously increase the extracellular potassium level and precipitate fatal dysrhythmias. The initial measurement of serum electrolytes, ECG review for signs of hyperkalemia, and the presence of urine output determine initial potassium therapy. An initial serum potassium level >5.2 mEq/L usually reflects a more profound acidemia and volume depletion or renal insufficiency. Fluid and insulin therapy alone usually will lower the serum potassium level rapidly. Albuterol nebulization can provide an additional quick potassium-lowering effect. See Chapter 17, "Fluids and Electrolytes," for further treatment of hyperkalemia.

INSULIN

Low-dose regular insulin administration by an infusion pump is simple and safe, ensures a steady blood concentration of insulin, allows flexibility in adjusting the insulin dose, and promotes a gradual decrease in serum glucose and ketone body levels.[4] The half-life of IV insulin is 4 to 5 minutes, with an effective biologic half-life at the tissue level of approximately 20 to 30 minutes.

IV Insulin After the initial fluid bolus, or simultaneously in a second IV line, **administer insulin at a rate of 0.1 to 0.14 unit/kg/h with no insulin bolus once hypokalemia ([K+] <3.3 mEq/L [<3.3 mmol/L]) is excluded**. An alternative insulin regimen is 0.1 unit/kg bolus IM, if it is difficult to establish another IV line,[19] followed by a drip rate at 0.1 unit/kg/h.[7] An IV loading dose of insulin is not recommended in children and new-onset young adult diabetics and is optional in adults.[19,20] Plasma glucose concentration typically decreases by 50 to 75 milligrams/dL/h (2.8 to 4.2 mmol/L/h), but if the blood glucose fails to drop by 10% 1 hour after initial therapy, or 3 mmol/L/h, (assuming adequate hydration), give a 0.14 unit/kg bolus and resume insulin drip rate.[6,7] **Another option is to increase the insulin infusion rate by 1 unit/h.**[19] The incidence of nonresponse to low-dose continuous IV insulin administration is 1% to 2%, with infection being the primary reason for failure to respond.

Resolution of hyperglycemia usually occurs earlier than resolution of the anion gap, so **once the serum glucose is 250 milligrams/dL (11 mmol/L), add dextrose to the IV fluids and reduce the insulin drip rate to 0.02 to 0.05 unit/kg/h**. Maintain the serum glucose between 150 and 200 milligrams/dL (8.3 and 11 mmol/L) until the resolution of DKA.[7] Occasionally, a 10% dextrose solution may be needed to maintain glucose levels.[19] **Continue the insulin infusion until the resolution of DKA—glucose <200 milligrams/dL (<11 mmol/L) and two of the following: a serum bicarbonate level >15 mEq/L, a venous pH >7.3, and/or a normal calculated anion gap.**[1,7] Monitor laboratory values every 1 to 2 hours to ensure that insulin is being administered in the desired amount.

Transition from IV Insulin After DKA Correction **A transition from the IV insulin infusion to SC insulin is necessary to avoid relapse to hyperglycemia or DKA when the insulin infusion is stopped. Relapse can occur quickly, within an hour after IV insulin is stopped due to the short duration of action of IV insulin.** The method of insulin transition varies, and there is no set protocol. Once the patient eats, the glucose infusion can be stopped, but it is important to overlap the IV and SC insulin for 2 to 4 hours to avoid potential relapse to hyperglycemia or DKA. It is best to collaborate with the inpatient team or endocrinologist to develop a protocol for the transition to SC insulin. New-onset diabetics can be started on a total daily dose of 0.5 to 0.8 unit/kg/dL, whereas previously treated diabetic patients can be restarted on their previous insulin dosage. It is generally preferred to transition from IV to SC by using long-acting (glargine) and rapid-acting (lispro, glulisine) SC insulin regimens that mimic normal insulin physiology as opposed to intermediate-acting insulin (NPH) and regular human insulin. The long and rapid acting insulin analogs may have a lower incidence of hypoglycemia.[21] One method is to give 50% of the usual long-acting insulin dose 2 hours before the IV insulin infusion is stopped (see Figure 223-1 for onset and duration of action of long-acting insulins). Additional glucose coverage can be provided with short-acting insulin as needed. Continue glucose checks every hour for 2 hours. Further intervals for glucose checks and the need for additional SC regular insulin dosing depend on the patient's response and institutional protocols.

SC Insulin In carefully selected cases of uncomplicated mild to moderate DKA, the use of rapid-acting SC insulin may be another treatment option. Small studies have demonstrated no difference in terms of time to resolution of hyperglycemia or acidosis when comparing serial doses of SC short-acting insulins (lispro, aspart) with IV infusions of regular insulin.[22-26,] Suggested dosing regimens of SC lispro include an initial injection of 0.3 unit/kg followed by 0.1 unit/kg every hour,[2] or an initial dose of 0.3 unit/kg followed by 0.2 unit/kg every 2 hours until blood glucose is <250 milligrams/dL (<13.9 mmol/L).[25] Then, the insulin dose is decreased by half and administered every 1 or 2 hours until resolution of DKA.[2,26] This can avoid intensive care admissions and lower hospital costs but still requires close nursing monitoring that is difficult to accomplish in the ED or nonmonitored setting.

HYPOPHOSPHATEMIA

Serum phosphate levels often are normal or increased on presentation of DKA and do not reflect the total-body phosphate deficits secondary to enhanced urinary losses.[11] Phosphate (similar to glucose and potassium) reenters the intracellular space during insulin therapy, resulting in low phosphate concentrations. Hypophosphatemia is usually most severe 24 to 48 hours after the start of insulin therapy. Acute phosphate deficiency (<1.0 milligram/dL) can result in hypoxia, skeletal muscle weakness, rhabdomyolysis, hemolysis, respiratory failure, and cardiac dysfunction.

There is no established role for initiating IV K_2PO_4 for DKA in the ED.[4,7,11] In general, do not give IV phosphate unless the serum phosphate concentration is <1.0 milligram/dL (0.323 mmol/L). Significant hypophosphatemia tends to develop many hours into therapy, after the patient is already admitted. Undesirable side effects from IV phosphate administration include hyperphosphatemia, hypocalcemia, hypomagnesemia, metastatic soft tissue calcifications, hypernatremia, and volume loss from osmotic diuresis. If *absolutely* necessary (a phosphate level <1.0 milligram/dL early in therapy), IV phosphate replacement should be administered as IV K_2PO_4, 2.5 to 5 milligrams/kg (0.08 to 0.16 mmol/kg).[26] Monitor serum calcium level if giving supplemental phosphate.

HYPOMAGNESEMIA

Osmotic diuresis may cause hypomagnesemia and deplete magnesium stores from bone. Hypomagnesemia may inhibit parathyroid hormone secretion, causing hypocalcemia and hyperphosphatemia. If the serum magnesium concentration is <2.0 mEq/L (<1.0 mmol/L) or symptoms are suggestive of hypomagnesemia, give magnesium sulfate 2 grams IV over 1 hour. Obtain serum magnesium and calcium levels on presentation and 24 hours into therapy. Monitor levels every 2 hours if there is initial hypomagnesemia or hypocalcemia or if symptoms suggestive of hypomagnesemia or hypocalcemia occur.

BICARBONATE

Acidotic patients routinely recover from DKA without alkali therapy.[4] Although it may take hours, the slowing of ketoacid production from infused insulin allows the generation of bicarbonate ions as ketoacids are oxidized. This production in bicarbonate during DKA treatment may be decreased if the brain and kidney oxidize fewer ketoacids.[28] **Give bicarbonate if the initial pH is <6.9, but do not give bicarbonate if the pH is ≥6.9.**[1,3,7,29]

Severe metabolic acidosis is associated with numerous cardiovascular (impaired contractility, vasodilation, and hypotension) and neurologic (cerebral vasodilation and coma) complications. Theoretical advantages of bicarbonate include improved myocardial contractility, elevated ventricular fibrillation threshold, improved catecholamine tissue response, and decreased work of breathing. The disadvantages of bicarbonate include worsening hypokalemia, paradoxical CNS acidosis, worsening intracellular acidosis, impaired (shift to left) oxyhemoglobin dissociation, hypertonicity and sodium overload, delayed recovery from ketosis, elevation of lactate levels, and possible precipitation of cerebral edema.[3]

Although there is a lack of literature supportive of improved outcome measures with the use of bicarbonate in the severely acidotic DKA patient, the decision to use bicarbonate should be based on the clinical condition and pH of the patient.[1,30] Potential benefits of bicarbonate in the elderly with cardiovascular instability must be balanced against the potential disadvantages.[4] There may be selected patients who benefit from cautious alkali therapy, including those with decreased cardiac contractility and peripheral vasodilatation, and patients with life-threatening hyperkalemia and coma. Patients with severe acidosis may be at higher risk for clinical deterioration, so **adults with a pH <6.9 can be given 100 mEq (100 mmol) of sodium bicarbonate in 400 mL of water with 20 mEq (20 mmol) KCl at 200 mL/h for 2 hours until the venous pH >7.0**. If the pH remains <7.0 despite the infusion, repeat the infusion until pH >7.0.[6,7] Remember to check $[K^+]$ every 2 hours. Severe acidosis (pH <7.0) and worsening pH despite aggressive therapy for DKA should prompt investigation for other causes of metabolic acidosis (see Chapter 15).

DISEASE COMPLICATIONS

COMPLICATIONS RELATED TO ACUTE DISEASE

In general, the greater the initial serum osmolality, BUN, and blood glucose concentrations, and the lower the serum bicarbonate level (<10 mEq/L), the greater is the mortality.

Infection and myocardial infarction are the main contributors to mortality. Additional factors that increase morbidity include old age, severe hypotension, coma, and underlying renal and cardiovascular disease. Severe volume depletion leaves the elderly at risk for deep venous thrombosis.

COMPLICATIONS RELATED TO THERAPY

Major complications related to therapy of DKA are listed in **Table 225-4**. These include hypoglycemia, hypokalemia, hypophosphatemia, acute respiratory distress syndrome, and cerebral edema. Check QT_c intervals before giving symptomatic pharmacotherapy.

Acute respiratory distress syndrome is a rare complication of therapy but may develop particularly in the elderly and those with impaired myocardial contractility. Overly aggressive fluid therapy decreases plasma oncotic pressure and raises left atrial end-diastolic pressure, favoring a shift of fluid across the pulmonary capillary membrane.

In very young children, new-onset diabetics, and adolescents with DKA, **cerebral edema** remains the most common and feared cause of mortality[31-35] (see Chapter 147, "Diabetes in Children"). Young age and new-onset diabetes (particularly in young adolescents) are the only identified potential risk factors. There are no evidence-based recommendations for adults.[4] Cerebral edema usually develops within 4 to

TABLE 225-4 Potential Pitfalls During Treatment of DKA

Pitfall	Guideline (See Text for Details)
Delay in diagnosis	Blood glucose may be 250–300 milligrams/dL (13.9–16.6 mmol/L); urine ketones may initially be negative
Unrecognized precipitating illness	Check ECG for infarction; examine patient for site of infection
Inadequate fluids	Majority of adult patients tolerate 15–20 mL/kg/h normal saline for first hour (1–2 L normal saline), additional fluids by clinical condition/serum Na^+
Unrecognized low K^+	Check K^+ prior to insulin; K^+ supplement before insulin for $[K^+]$ <3.3
Overemphasis on insulin	Follow insulin guidelines
Hypoglycemia	Goal for glucose decrease 50–75 milligrams/dL/h (2.8–4.2 mmol/L); add dextrose when glucose <250 milligrams/dL (<13.9 mmol/L)
Unrecognized electrolyte derangements	During first 6 h of treatment, check glucose hourly and electrolytes every 2 h; check QT_c intervals
Overzealous use of bicarbonate and phosphate	$NaHCO_3$ not indicated for pH >6.9; no routine indication for phosphate supplementation
Recurrent DKA	Avoid stopping insulin drip before anion gap resolves. Give SC insulin, feed patient, then stop insulin drip 1–2 h later
Cerebral edema **NOT** recognized early	See **TABLE 225-5**. Very young and new-onset patients at risk; perform frequent neurologic checks for mental status change

12 hours but can present up to 24 to 48 hours after starting treatment and carries a high mortality.[2,33-35] One hypothesis is that the osmotic diuresis promotes loss of water and sodium from both intra- and extracellular spaces. Hyperglycemia leads to a hyperosmolar extracellular state. Brain cells enzymatically produce osmotically active particles that protect cells from further loss of water and shrinkage. During therapy with IV fluid and insulin, water moves into brain cells faster than osmotically active particles can dissipate, promoting cellular swelling.

There are no specific presentation or treatment variables that predict or contribute to the development of cerebral edema.[32,33] Monitor the relationship between the increase in sodium compared to the decrease in plasma glucose levels during the initial treatment phase of DKA. Gradual replacement of water and sodium deficits and slow correction of hyperglycemia may lessen the risk of cerebral edema by avoiding rapid changes in water movement between the intracellular and extracellular spaces.[26]

Premonitory symptoms are severe headache, incontinence, change in arousal or behavior, pupillary changes, blood pressure changes, seizures, bradycardia, or disturbed temperature regulation. Any change in neurologic function early in therapy is an indication for IV mannitol (1 to 2 grams/kg).[35] Mannitol should be given before respiratory failure or obtaining confirmatory CT scans because serious morbidity and mortality may be prevented. Hypertonic saline (3%), 5 to 10 mL/kg over 30 minutes, may be an alternative to mannitol.[2,29,33] Intubation and fluid restriction are generally necessary. There are no data supporting glucocorticoid use in DKA-related cerebral edema.

LATER COMPLICATIONS

Metabolic acidosis refractory to routine therapy may be secondary to unrecognized infection (lactic acidosis), rarely insulin antibodies, or improper preparation or administration of the insulin drip. Shock that is unresponsive to aggressive fluid therapy suggests gram-negative bacteremia or silent myocardial infarction. Hyperchloremic non–anion gap metabolic acidosis can develop during therapy due to rapid volume expansion in the face of reduced bicarbonate. In addition, bicarbonate equivalents are excreted in the urine as ketones and are replaced with chloride provided by the normal saline. This emphasizes the importance of monitoring the anion gap during therapy. The non–anion gap metabolic acidosis resolves during recovery as bicarbonate is regenerated and excess chloride is excreted in the urine.

Late vascular thrombosis may occur in any muscular artery, although the cerebral vessels appear to be most susceptible. Volume depletion, low cardiac output, increased blood viscosity, and underlying atherosclerosis may predispose the elderly to this complication. Thrombosis may occur several hours or days after institution of therapy and after resolution of ketoacidosis. Despite this increased risk, no studies support prophylactic anticoagulant use, although some experts suggest the use of heparin may be beneficial in DKA if there is no associated bleeding disorder.[7,14]

Mortality in DKA results mainly from sepsis or pulmonary and cardiovascular complications in the elderly and fatal cerebral edema in children and young adults (**Table 225-6**).

TABLE 225-5 Best Practice to Prevent Cerebral Edema

- Slow reduction of osmolality during treatment
- Avoid large volumes of hypotonic fluid
- Drop blood glucose slowly during treatment
- Do not allow plasma Na^+ to fall during treatment
- Avoid unnecessary bicarbonate during treatment
- Avoid hypoxia, hypo-K^+, PO_4, Mg

DISPOSITION AND FOLLOW-UP

The great majority of patients require hospitalization in a monitored setting where there is nursing experience with IV insulin infusions. In many institutions, patients are cared for initially in an intensive or intermediate care unit. A select group of patients with an anion gap of <25, a glucose level of <600 milligrams/dL (<33.3 mmol/L), and no comorbidity at the time of disposition decision may be managed safely on an inpatient unit with nursing expertise using insulin infusions and managing diabetic patients. Some institutions may have protocols for the use of SC rapid-acting insulin on a medical floor. Patients presenting early in the course of their illness who can tolerate oral liquids may be managed safely in the ED or observation unit and discharged after 6 to 12 hours of therapy.

SPECIAL POPULATIONS

RECURRENT DKA PATIENTS

Patients who present to the ED with recurrent episodes of DKA should have barriers to care access addressed while in the ED or during their

TABLE 225-6 Complications of Diabetic Ketoacidosis

Related to Acute Disease	Related to Therapy	Later Complications
Loss of airway	Hypokalemia	Recurrent anion gap metabolic acidosis
Sepsis	Hypophosphatemia	Non–anion gap metabolic acidosis
Myocardial infarction	Acute respiratory distress syndrome	Vascular thrombosis
Hypovolemic shock	Cerebral edema	Mucormycosis
	Hypoglycemia	

hospital stay. In urban settings, insulin noncompliance is a major trigger for recurrent DKA. Cocaine is an independent risk factor for DKA, and patients who use illicit drugs may benefit from drug rehabilitation.[6,7] Using social workers to assist patients with drug access and affordability, drug rehabilitation when indicated, and education provided by the diabetic care team can promote improved glycemic control.[36]

PATIENTS WITH INSULIN PUMPS

See Chapter 223 for a detailed discussion of insulin pumps (See Video: Insulin Pump). **Patients with insulin pumps who are suspected to have DKA should have their pumps disconnected and turned off and should be treated just like any other patient. Reinstitution of pump therapy should start in the same time frame as switching over to SC insulin in the non–pump user.**

DKA IN PREGNANCY

DKA in pregnancy is a leading cause of fetal loss, with a fetal mortality rate of approximately 30%.[36,37] Several physiologic changes make diabetic pregnant women prone to DKA. Maternal fasting serum glucose levels are normally lower than in the nonpregnant state, which leads to relative insulin deficiency and an increase in baseline free fatty acid levels in the blood.[38] DKA is triggered at lower sugar levels in pregnancy, so the provider should recognize signs and symptoms of DKA and check a serum βHB level.[35,38] Pregnant women normally have increased levels of counterregulatory hormones. In addition, the chronic respiratory alkalosis seen in pregnancy leads to decreased bicarbonate levels due to a compensatory renal response, resulting in a decrease in buffering capacity. Pregnancy is associated with vomiting and urinary tract infections, which can precipitate DKA.[38] Maternal hyperglycemia causes fetal hyperglycemia and osmotic diuresis. Maternal acidosis causes fetal acidosis, decreases uterine blood flow and fetal oxygenation, and shifts the oxygen-hemoglobin dissociation curve to the right. Maternal hypokalemia also can lead to fetal dysrhythmias and death. **Correcting maternal hyperglycemia, acidosis, and electrolyte balance is the first priority.**

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 226

Ketoacidotic Syndromes

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INTRODUCTION

Ketones form a viable energy source used daily by the body in response to variations in carbohydrate intake and energy demand. There are several conditions that may result in excessive production of ketoacids that can result in a significant metabolic acidosis. The challenge for the clinician is to differentiate states of excessive, uncontrolled ketoacidosis from physiologic ketonemia, from states where excessive ketones may be produced, or from conditions or a toxin altering normal metabolism.[1] The pathophysiology of ketoacidosis is poorly understood. Authors speculate about the hormonal milieu and pre-existing glycogen stores that, under some circumstances, will tip certain patients into pathologic ketoacidosis.

The benefits of controlled metabolic access to ketones (i.e., ketogenic diet) have been recently advocated for several conditions. Unfortunately, the timing and triggers for the exact tipping point from controlled to uncontrolled ketone production are not well understood. This chapter will discuss important conditions of uncontrolled ketone production and treatment of this pathologic state.

PATHOPHYSIOLOGY

Ketones may be produced through metabolism of long-chain fatty acids for energy within cells or made within the perivenous hepatocytes and then displaced into the serum for use by cells without mitochondria (i.e., red blood cells). Serum ketones are also used as an energy source for the brain because long-chain fatty acids cannot cross the blood–brain barrier and neurons cannot generate their own ketones. Once generated, ketones can be used as an additional energy source, entering the citric acid cycle as acetyl coenzyme A and taking the place of pyruvate generated through glucose metabolism. Ketone production is typically tightly regulated to prevent excessive ketoacid production and metabolic acidosis. Lower serum levels of insulin and ketones coupled with higher levels of cortisol and epinephrine may trigger an increase in ketone production.[2] Regulation of ketone production is complex and incompletely understood. Additionally, the rate of ketone consumption can vary over time (minutes, hours, days) for unknown reasons.[3] In general, with the exception of DKA, low levels of insulin are not found in ketoacidotic syndromes.

To understand ketone metabolism, first remember that ketones are made daily by the body for energy, and that production is tightly regulated to limit serum levels (**Figure 226-1**). The normal blood ketone level is about 1 milligram/dL. Ketones are metabolized as rapidly as they are formed. Pathologic states arise when production exceeds metabolism or consumption, resulting in metabolic acidosis. Second, it is important to understand the ketone forms normally present in the human body. Acetyl coenzyme A, an energy source that can enter the citric acid cycle for metabolism, is produced in the liver and then converted to the ketones β-hydroxybutyrate and acetoacetate. These ketones spontaneously decay to acetone, which is a volatile chemical and thus exhaled and detected on the breath. Finally, the ratio of ketone production may vary. Typically, in most conditions (pathologic or normal physiology), the balance of β-hydroxybutyrate and acetoacetate is relatively equal (1:1), with a little higher concentration of β-hydroxybutyrate. One notable exception is **alcoholic ketoacidosis**, where β-hydroxybutyrate exceeds acetoacetate (see below). In all other pathologic ketoacidosis conditions, urinary or serum ketones are present and are necessary to diagnosis pathologic ketoacidosis. Ketones are osmotically active, and an elevation may result in an increased osmolal gap.

Ethanol metabolism results in nicotinamide adenine dinucleotide depletion manifesting as a higher ratio of the reduced form of nicotinamide adenine dinucleotide to the nonreduced form. This high ratio also results in increased lactate production, so lactate levels are higher than normal in alcoholic ketoacidosis but not as high as seen in shock or sepsis.

COMMON KETOACIDOTIC SYNDROMES

Identifying the cause of excessive ketone levels producing metabolic acidosis may be complicated. **Table 226-1** lists several possible conditions associated with elevated serum ketones. DKA is discussed in detail in Chapter 225, "Diabetic Ketoacidosis," and toxins are discussed in their specific chapters.

ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis is a condition occurring in alcoholic patients who enter a period of fasting after a dramatic period of ethanol binging. Alcoholic ketoacidosis results in metabolic acidosis and dehydration, with variable levels of serum glucose, depending on the amount of glycogen stored in the liver. Serum glucose levels may even be elevated.[4]

Nausea, vomiting, abdominal pain, and constitutional complaints are common.[4] Notably, the ratio of β-hydroxybutyrate to acetoacetate is elevated in both DKA and alcoholic ketoacidosis. However, the ratio is much higher in alcoholic ketoacidosis and may approach 10:1. This is largely due to the presence of more acetoacetate in DKA. Since urine tests for ketones detect acetoacetate only, patients with alcoholic ketoacidosis may have dramatic ketoacidosis with low or even undetectable levels of urine ketones.[4] Point-of-care blood testing for ketones primarily measure β-hydroxybutyrate.

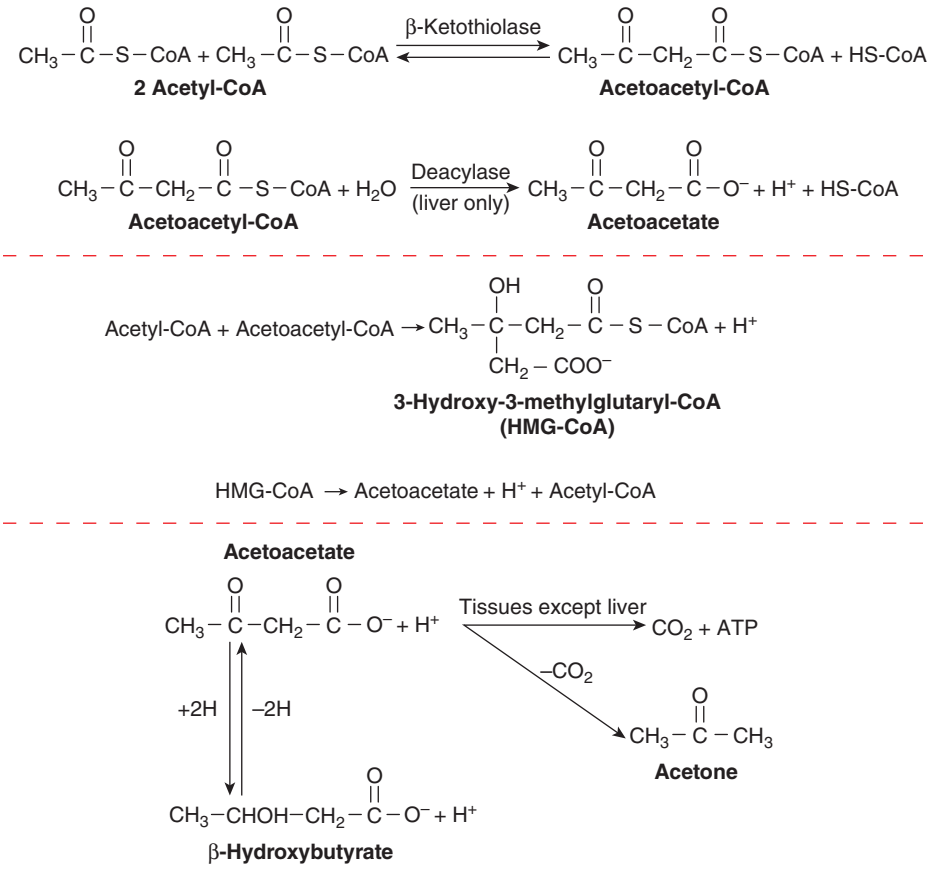

FIGURE 226-1. Formation and metabolism of ketone bodies. [Reproduced with permission from Barrett KE, Barman SM, Boitano S, Reckelhoff JF (eds.) *Ganong's Medical Physiology Examination & Board Review*. New York, NY: McGraw-Hill Education; 2018, Fig 1-13.]

TABLE 226-1 Differential Diagnosis of Ketosis with Metabolic Acidosis

Acidosis Due to Ketoacidosis	Acidosis from an Underlying Ketone-Producing Condition	Acidosis from Chemicals Other Than Ketones; However, Ketonemia May Be Present
DKA (see Chapter 225, "Diabetic Ketoacidosis")	Toxic ingestions: Acetone Isoniazid Isopropanol Propylene glycol Salicylic acid	Dehydration
Alcoholic ketoacidosis	Inborn errors of metabolism: Error in carbohydrate metabolism Error in fatty acid metabolism	Gastritis/upper GI bleeding Hepatitis Pancreatitis Pneumonia Seizures Sepsis Renal Failure
Starvation ketosis and eating disorders		
Nutritional ketosis		
Ketogenic diet		

STARVATION KETOSIS

The human body goes through various rates of ketone production throughout the normal course of daily activities. During periods of fasting (overnight) or increased energy demands (exercise), local ketone production increases.[3] As the duration of carbohydrate fasting increases, hepatic ketone production and intracerebral ketone utilization increase. Typically, prolonged fasts of 14 days are well tolerated in those with adequate endogenous insulin and no other coexisting condition that alters the serum hormonal milieu. "Well tolerated" in this context implies that ketone production does not dramatically exceed metabolic demand, limiting any resultant metabolic acidosis and/or ketonuria with dehydration.

Pregnancy is the most frequently described condition where starvation ketosis may result in excessive ketone production with metabolic acidosis, ketonuria, and dehydration. This can occur with only 24 to 48 hours of vomiting and inadequate oral intake.[5] Speculations regarding the increased susceptibility include the effect of additional maternal hormones as well as fetal/placental hormone secretion. However, conditions of higher metabolic demand have also been identified as triggers (e.g., breastfeeding, hyperthyroidism). There is a case report of a 16-year-old patient with Duchenne muscular dystrophy and severe pre-existing malnutrition who developed significant ketoacidosis.[6] In addition, bariatric surgery may pose a risk for pathologic ketoacidosis after brief episodes of inadequate intake, secondary to mechanical complications of surgery.[7]

NUTRITIONAL KETOSIS

There are recent suggestions in the medical literature that athletic performance, especially endurance performance, may be enhanced by the ingestion of nutritional supplements rich in ketones in an attempt to alter intracellular energy preference. The safety of this practice is

unclear, and it is not known if dietary supplements may contribute to pathologic acidosis.[8]

KETOGENIC DIET

The ketogenic diet may be desired for several medical conditions; weight control and seizures are the two most common. Additional conditions (Alzheimer's disease and Parkinson's disease) may warrant future trials of a therapeutic ketogenic diet. In healthy volunteers, the ketogenic diet does not routinely induce metabolic acidosis due to ketosis.[9]

TOXIC INGESTIONS

In some toxin ingestions, ketone production is a primary result of the toxin, rather than the cause of the patient's symptoms. Such ingestions include acetone, aspirin (salicylic acid), isoniazid, isopropanol , methanol, and propylene glycol. Thus, routinely consider toxic overdose as a cause of unexplained ketosis.

INBORN ERRORS OF METABOLISM

Consider inborn errors of metabolism in children with ketosis, especially if associated with hypoglycemia. Children who develop ketosis after a longer fast may have a fatty acid oxidation disorder.[10] See Chapter 146, "Metabolic Emergencies in Infants and Children," for detailed discussion of diagnosis and emergency treatment.

DIFFERENTIAL DIAGNOSIS

Urinary detection of ketones and an increased anion gap diagnose the presence of a ketoacidotic condition. History, physical examination, dietary review, and assessment of comorbidities are necessary to focus the diagnosis. As discussed earlier, lack of elevated urine ketone levels does not exclude the diagnosis in cases of alcoholic ketoacidosis.[4] Elevated glucose levels are most commonly described in cases of alcoholic ketoacidosis[4] and less commonly in other causes of pathologic ketoacidosis. There are no published large series of ketoacidotic conditions, so generalizations about serum glucose levels cannot be made.

The conditions listed in column 1 of Table 226-1 are often associated with significant dehydration and electrolyte disturbances, including hypokalemia, hyperkalemia, hypomagnesemia, and hypophosphatemia.[4] Patients with alcoholic ketoacidosis often have underlying liver disease and may have abnormal liver enzyme levels.

Column 2 of Table 226-1 lists toxic ingestions and inborn errors of metabolism associated with ketonuria and metabolic acidosis. Elevated serum ketones may result from ingestion of an alcohol other than ethanol. Methanol and ethylene glycol ingestions do not produce ketosis, but the acidosis tends to be severe. Isopropyl alcohol ingestion results in production of ketones. The presence of a large osmolal gap suggests acute isopropyl, ethanol, methanol, or ethylene glycol ingestion. If the blood alcohol level is known, then its contribution to any osmolal gap can be calculated. **Each 100 milligrams/dL (21.7 mmol/L) of ethanol raises the osmolal gap by 22**. Details of osmolal gap are discussed in Chapter 17, "Fluids and Electrolytes."

The presence of a mixed acid-base disturbance suggests a comorbid disorder (column 3 of Table 226-1) .

TREATMENT

Treatment of ketoacidosis is supportive.[4,5,7,11,12] Reestablish intravascular volume. Published series of patients with pathologic ketoacidosis report the need for isotonic volume expansion, and supplemental dextrose is required.

Monitor and correct electrolyte abnormalities. Correct hypomagnesemia. Hypophosphatemia can slow the resolution of acidosis as phosphorus is necessary for mitochondrial utilization of glucose and for oxidation of the reduced form of nicotinamide adenine dinucleotide. However, phosphate replacement generally is unwarranted unless levels are very low (<1.0 milligram/dL or <0.323 mmol/L).[13]

Administer supplemental dextrose. Insulin therapy is needed only for DKA, as brisk hypoglycemia can occur when insulin is given to patients with a starvation-type ketoacidotic syndrome.[13] In alcoholic or malnourished patients, some feel that thiamine supplementation prior to glucose administration should be given to prevent Wernicke's encephalopathy and Korsakoff's syndrome.

Serum ketone levels, correlated with clinical status, may be used to help guide therapy and will decrease as the ketoacidosis resolves, while an increasingly positive reaction in urinary ketones during treatment signifies improvement, as results lag behind clinical status. Acidosis should clear within 12 to 24 hours.

For severe ketoacidosis in a patient on a ketogenic diet for seizure control, obtain consultation to weigh the risks and benefits of all aspects of supportive therapy.

DISPOSITION AND FOLLOW-UP

Adults with an uncomplicated ED course may be safely discharged home if there is resolution of acidosis and the patient is able to tolerate oral fluids. When caring for complicated conditions (e.g., children with hypoglycemia, inborn error of metabolism, therapeutic ketogenic diet, toxic ingestions, medical comorbidities), coordinate care with the primary team treating the underlying disorder. Patients with alcoholic ketoacidosis should receive counseling on alcohol dependence, be encouraged to use multivitamins, and be offered treatment in an alcohol detoxification program. Patients with persistent acidosis or a complicated course will require hospital admission.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 227

Hyperosmolar Hyperglycemic State

Charles S. Graffeo

INTRODUCTION AND EPIDEMIOLOGY

The **hyperosmolar hyperglycemic state (HHS)** is characterized by progressive hyperglycemia and hyperosmolarity typically found in a debilitated patient with poorly controlled or undiagnosed type 2 diabetes mellitus, limited access to water, and commonly, a precipitating illness. Although most cases of HHS occur in the elderly, the incidence of HHS in children is increasing, with the common risk factors being obesity and African American race.[1]

PATHOPHYSIOLOGY

The basic pathophysiology of diabetes is discussed in Chapter 223, "Type 1 Diabetes Mellitus," and Chapter 224, "Type 2 Diabetes Mellitus," and is also outlined in **Figure 227-1**. The development of HHS is attributed to three main factors: (1) insulin resistance and/or deficiency; (2) an inflammatory state with marked elevation in proinflammatory cytokines (C-reactive protein, interleukins, tumor necrosis factors) and counterregulatory stress hormones (catecholamines, growth hormone, glucagon, cortisol) that cause increased hepatic gluconeogenesis and glycogenolysis; and (3) osmotic diuresis followed by impaired renal excretion of glucose.[2,3]

In patients with type 2 diabetes, physiologic stresses combined with inadequate water intake in an environment of insulin resistance or deficiency lead to HHS. As serum glucose concentration increases, an osmotic gradient develops, shifting water from the intracellular space into the intravascular compartment, causing cellular dehydration.

The initial increase in intravascular volume is accompanied by a temporary increase in the glomerular filtration rate. As serum glucose increases, the capacity of the kidneys to reabsorb glucose is exceeded, and an osmotic diuresis occurs with total body water losses that can

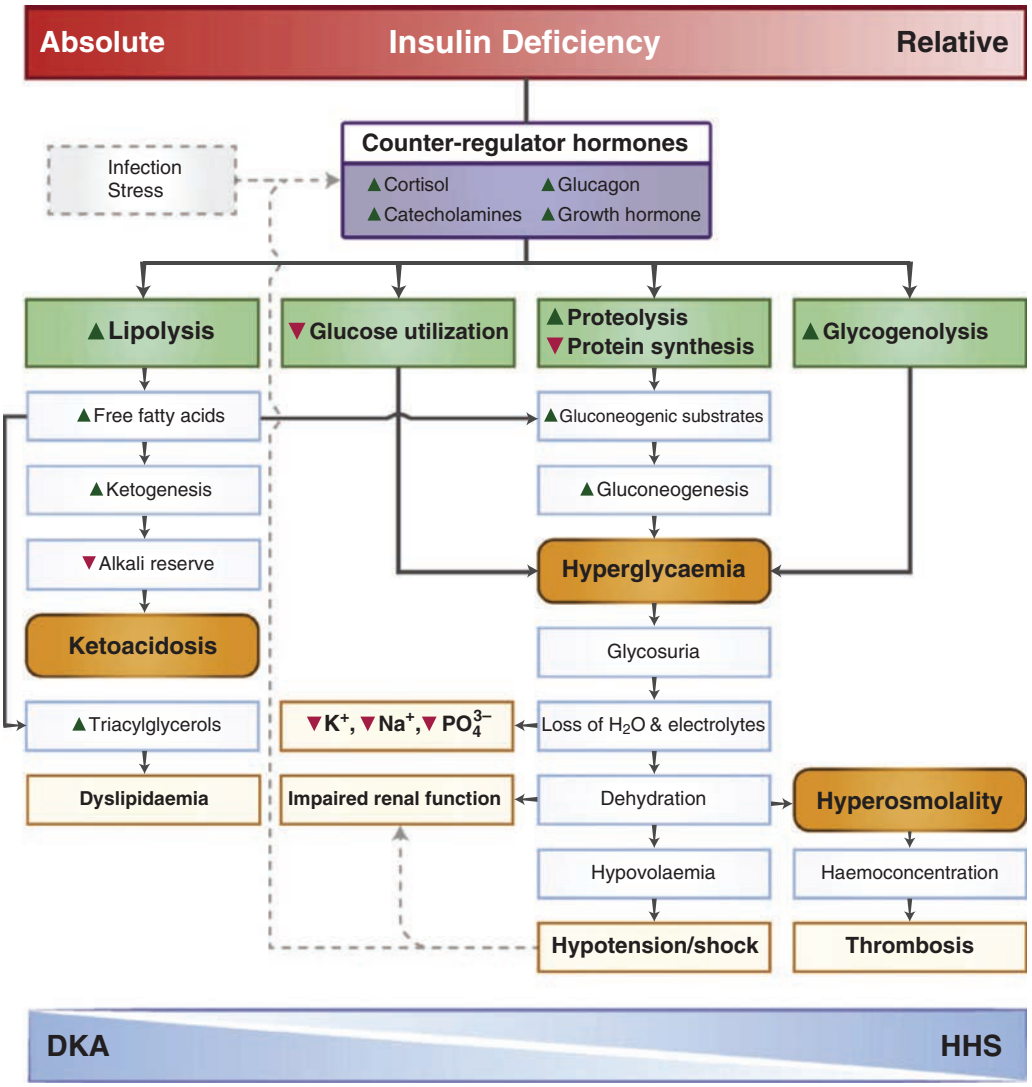

FIGURE 227-1. Pathophysiology of hyperglycemic emergencies. HHS = hyperosmolar hyperglycemic state. [Reproduced with permission from Cardoso L et al: Controversies in the management of hyperglycaemic emergencies in adults with diabetes. *Metabolism* 68: 43, 2017 [PMID: 28183452]. Fig. 1. Copyright Elsevier.]

exceed 20% to 25% of total body weight, or approximately 8 to 12 L in a 70-kg patient. During osmotic diuresis, significant urinary loss of sodium and potassium and more modest losses of calcium, phosphate, and magnesium occur. With ongoing volume losses, renal perfusion and glomerular filtration are reduced, and renal tubular excretion of glucose is further impaired.[4]

The relative lack of severe ketoacidosis in HHS is poorly understood and has been attributed to three possible mechanisms: (1) higher levels of endogenous insulin than are seen in DKA; (2) lower levels of counterregulatory "stress" hormones; and (3) inhibition of lipolysis by the hyperosmolar state itself. Evidence of significant ketoacidosis in a patient thought to have type 2 diabetes should bring into question the possibility of variants of type 1 diabetes, such as latent autoimmune diabetes in adults.[5] Additionally, a greater proportion of ketosis-prone type 2 diabetes has been described in African American, Hispanic, and Asian populations.[6]

CLINICAL FEATURES

HISTORY AND COMORBIDITIES

The typical patient with HHS is elderly and often institutionalized, with baseline cognitive impairment and comorbid medical illnesses, who is referred for abnormalities in vital signs, lab results, and/or mental status changes that have evolved over days to weeks. Patient complaints are often nonspecific and may include malaise, weakness, anorexia, fatigue, vomiting, and cognitive impairment. Up to 15% of patients may present with seizures, which are typically focal, although generalized seizures may occur. In other cases, HHS is noted in patients with no prior history of diabetes mellitus who present with acute illnesses such as stroke, myocardial infarction, pneumonia, abdominal emergencies, and sepsis. Patients taking antipsychotics or antidepressants may present a particular risk, and HHS should be considered as part of the medical screening process for psychiatric patients.

HHS is associated with a host of conditions (**Table 227-1**) and drugs (**Table 227-2**) that may predispose to hyperglycemia and volume depletion.[7]

PHYSICAL EXAMINATION

The physical findings in HHS generally include signs of severe volume depletion such as poor skin turgor, dry mucous membranes, sunken eyes, tachycardia, and hypotension. The degree of lethargy and coma has a linear relationship to serum osmolality. Patients with coma tend to be older and have higher osmolality, more severe hyperglycemia, acidosis, and greater volume contraction.[4]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

HHS is "defined" by severe hyperglycemia with serum glucose usually >600 milligrams/dL (>33.3 mmol/L), an elevated calculated plasma osmolality of >315 mOsm/kg (>315 mmol/kg), serum bicarbonate

TABLE 227-1 Conditions That May Precipitate Hyperosmolar Hyperglycemic State

- Diabetes
- Infection, especially pneumonia or urinary tract infection
- Myocardial infarction
- Renal insufficiency
- Cerebrovascular events
- Mesenteric ischemia
- GI hemorrhage
- Pulmonary embolism
- Pancreatitis
- Severe burns
- Parenteral or enteral alimentation
- Peritoneal or hemodialysis
- Heat-related illness
- Rhabdomyolysis
- Pregnancy
- Trauma

TABLE 227-3 Diagnostic Criteria for DKA and Hyperosmolar Hyperglycemic State (HHS)

	DKA	HHS
Plasma glucose	>250 milligrams/dL (>13.8 mmol/L)	>600 milligrams/dL (>33.3 mmol/L)
Serum bicarbonate	≤18 mEq/L (<18 mmol/L)	>15 mEq/L (>15 mmol/L)
Urine acetoacetate*	+	– or small
Serum beta hydroxybutyrate	+	– or small
Serum ketones†	+	– or small
Serum osmolality‡	Variable	>320 mOsm/kg (>320 mmol/kg)
Anion gap#	>12 mEq/L (>12 mmol/L)	<12 mEq/L (<12 mmol/L)
Arterial/venous pH	<7.30	>7.30

*Nitroprusside method.

†Gas chromatography method or nitroprusside method.

‡Osmolality calculation: 2(measured $[Na^+]$ + glucose (milligrams/dL or mmol/L)/18.

#Anion gap calculation: $[Na^+] - [Cl^-] + [HCO_3^-]$.

>15 mEq/L (>15 mmol/L), an arterial pH >7.3, and serum ketones that are negative to mildly positive. Metabolic acidosis or ketonemia associated with HHS is likely to be due to tissue hypoperfusion, starvation ketosis, and azotemia in various combinations, although there is growing evidence for ketosis-prone type 2 diabetic subgroups.[6] **It is important to recognize the potential for a variety of mixed acid-base patterns in patients with HHS.**

A comparison of the laboratory features of DKA and HHS is shown in **Table 227-3**.

LABORATORY TESTING AND IMAGING

Laboratory tests and diagnostic imaging should be tailored to the individual patient. Laboratory workup commonly includes a CBC with differential, comprehensive metabolic profile, magnesium and phosphate, urinalysis, serum and urine osmolality, lactate, β-hydroxybutyrate, and blood and urine cultures. In addition, cardiac markers, creatine phosphokinase, arterial or venous blood gas, thyroid function studies, procalcitonin, and coagulation profiles should be considered. Chest radiographs and ECGs are generally recommended. Diagnostic studies, such as CT, lumbar puncture, toxicologic studies, and echocardiography, should be patient specific.

In general, electrolyte abnormalities vary. Initially, contraction alkalosis due to a profound water deficit may occur. An anion gap metabolic acidosis is often attributable to sepsis, poor tissue perfusion, starvation ketosis, or renal impairment.

Sodium Serum sodium level varies and is not a reliable indicator of the degree of volume contraction. Hyperglycemia has a dilutional effect on measured serum sodium: **Standard teaching is that serum Na^+ decreases by approximately 1.6 mEq/L (1.6 mmol/L) for every 100 milligrams/dL (5.6 mmol/L) increase in serum glucose >100 milligrams/dL (5.6 mmol/L). For glucose > 400 milligrams/dL (22.2 mmol/L), a correction factor of 2.4 is more accurate.**

Formula for glucose 100-400 milligrams/dL (>5.55-22mmol/L)

$$\text{Corrected } [Na^+] = \text{Measured } [Na^+] + \frac{1.6 \times (\text{glucose in mg/dL} - 100)}{100}$$

Formula for glucose in mmol/L

$$\text{Corrected } [Na^+] = \text{Measured } [Na^+] + \frac{1.6 \times (\text{glucose in mmol/L} - 5.6)}{5.6}$$

Osmolality Serum osmolality correlates positively with severity of disease as well as mental status changes and coma. In the United States, many authors suggest using calculated **effective** serum osmolality, which excludes osmotically inactive urea. Although osmotically inactive, urea is known to be elevated in dehydration, shock, renal impairment, and catabolic states.[8] Recent guidelines from the United Kingdom suggest that including urea when calculating serum osmolality may more accurately reflect severity of dehydration and help protect against overzealous correction of osmolality, which can predispose patients to cerebral edema and osmotic demyelination syndrome.[9,10]

$$\textit{Osmolality}\ 2[Na^+] + \frac{\text{glucose}}{18} + \text{BUN}/2.8$$

$$\textit{Effective Osmolality}\ 2[Na^+] + \frac{\text{glucose}}{18}$$

TABLE 227-2 Some Drugs That May Predispose Individuals to the Development of HHS

- Diuretics
- Statins
- β-Blockers
- Chlorpromazine
- Cimetidine
- Glucocorticoids
- β-Agonists
- Antipsychotics
- Antidepressants
- Phenytoin
- Calcium channel blockers
- Pentamidine
- Immunosuppressive drugs (tacrolimus, cyclosporine)
- Diazoxide
- L-asparaginase
- Protease inhibitors
- Nicotinic acid
- Nucleoside reverse transcriptase inhibitors
- Interferons

The normal serum osmolality range is approximately 275 to 295 mOsm/kg. Values >300 mOsm/kg are usually indicative of significant hyperosmolality, and those >320 mOsm/kg are commonly associated with alterations in cognitive function. In general, serum osmolality correction should not exceed 3.0 Osm/kg/h.

Potassium On average, potassium losses range from 4 to 6 mEq/kg. Despite these total-body deficits, initial serum laboratory measurements may be normal or even high in the presence of acidosis when intravascular $[H^+]$ ions are exchanged for intracellular $[K^+]$ ions. As intravascular volume is replaced and acidosis is reversed, $[K^+]$ deficiency becomes more apparent.

Other Laboratory Testing Hypomagnesemia is common, and serum magnesium levels should be monitored and replaced. Consequences of hypophosphatemia, such as CNS abnormalities, cardiac dysfunction, and rhabdomyolysis, are uncommon and usually associated with serum phosphate levels below 1.0 milligram/dL. Routine replacement of phosphate, unless severe, is usually unnecessary. Prerenal azotemia is common, with plasma BUN-to-creatinine ratios often exceeding 30:1, indicating severity of dehydration and the catabolic state.[8]

TREATMENT

Improvement of tissue perfusion is the key to effective recovery in HHS. **Treatment includes correction of hypovolemia, identifying and treating precipitating causes, correcting electrolyte abnormalities, gradual correction of hyperglycemia and hyperosmolarity, and frequent monitoring.** The therapeutic plan must be carefully considered and adjusted for concurrent medical illnesses such as cardiac, renal, and pulmonary disease.

Overzealous resuscitation can result in significant harms and should be avoided. A protocol for treating severely ill patients likely requiring intensive care unit–level care is shown in **Figure 227-2.**

FLUID RESUSCITATION

Fluid resuscitation alone replenishes intravascular volume, improves tissue perfusion, and decreases serum glucose about 35 to 70 milligrams/dL/h. **Begin normal saline infusion before insulin therapy is started.**

The average fluid deficit in HHS is in the range of 20% to 25% of total body water, or 8 to 12 L. By using the patient's usual weight in kilograms, normal total body water and water deficit can be calculated. **One half of the fluid deficits should be replaced over the initial 12 hours and the balance over the next 24 hours when possible.** The actual rate of fluid administration should be individualized for each patient, based on the level of renal and cardiac impairment. **Begin fluid resuscitation with 0.9% normal saline at a rate of 15 to 20 mL/kg/h during the first hour, followed by rates from 4 to 14 mL/kg/h.** Limit the rate of volume repletion during the first 4 hours to <50 mL/kg of normal saline. Once hypotension, tachycardia, serum hyponatremia, and urinary output improve, 0.45% NaCl can be used to replace the remaining free water deficit. Hourly glucose, electrolyte, and osmolality measurements should be taken to monitor progress in the critically ill.

ELECTROLYTES

Hypokalemia is a risk for dysrhythmia and should be replaced during volume repletion and insulin administration. If the initial serum potassium measurement is <3.3 mEq/L, begin potassium supplementation and withhold insulin therapy until potassium is replenished.

In general, replace potassium at a rate of 10 to 20 mEq/h. For life-threatening hypokalemia, infusion rates of up to 40 mEq/h may be needed, and under these circumstances, central venous access is warranted. Monitor serum potassium levels every hour until a steady state has been achieved.

Sodium deficits are replenished fairly rapidly, considering the amount of normal saline given during IV fluid replacement. Replace **magnesium deficits** with 1 to 2 grams of magnesium given over 1 hour.

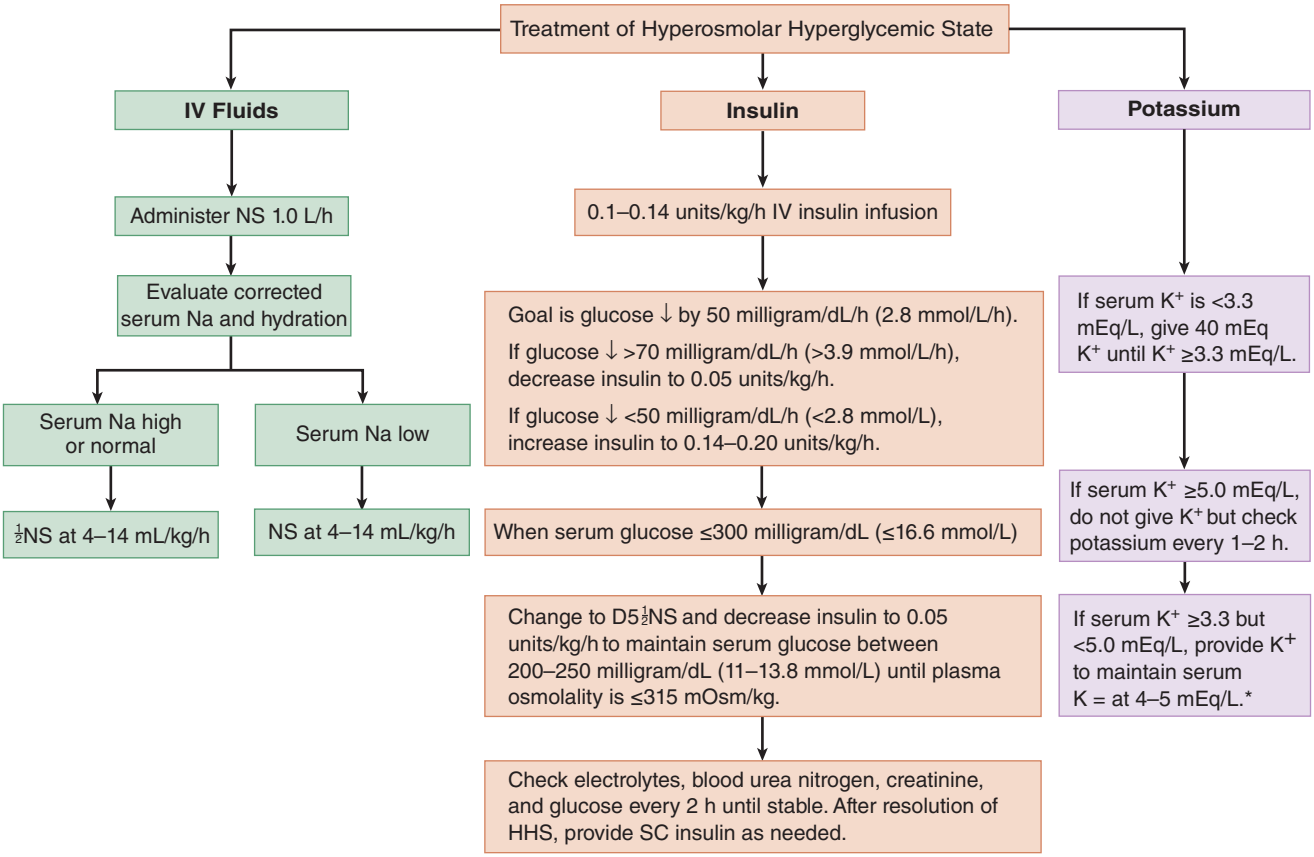

FIGURE 227-2. Protocol for the management of severely ill adult patients with hyperosmolar hyperglycemic state (HHS). *Concentrations of K^+ ≥20 mEq/L should be administered via central line. D5$^1/_2$NS = 5% dextrose in half-normal saline; NS = normal saline.

Phosphate should only be replaced if the phosphate level is <1.0 milligram/dL (<1.0 mmol/L). **Sodium bicarbonate** has been included in American Diabetes Association guidelines if serum pH is <7.0; however, more recent data suggest no benefit and potential harms in the pediatric population.[4,11]

INSULIN

Begin insulin after initial fluid resuscitation has been completed. If insulin is started too early, intravascular volume may be further depleted by shifting osmotically active glucose and fluids out of the intravascular space.

The absorption of insulin by the IM or SC route is unreliable in patients with HHS, and a continuous infusion of insulin is recommended. Initiation of insulin therapy should begin at 0.1 unit/kg/h.[4] With adequate hydration and insulin therapy, the goal of therapy is to maintain a steady rate of decline in the glucose concentration of 50 to 75 milligrams/dL/h (2.8–4.1 mmol/L/h). With adequate hydration, the insulin infusion may be adjusted every hour until a steady glucose decline is achieved. If glucose falls too rapidly, decrease the infusion rate by half, to 0.05 or 0.07 unit/kg/h. Once serum glucose decreases to <300 milligrams/dL (<16.6 mmol/L), change the IV solution to 5% dextrose in half-normal saline, and reduce the insulin infusion to 0.02 to 0.05 unit/kg/h until serum osmolality is <315 mOsm/kg and glucose is maintained between 200 and 300 milligrams/dL (11.1–16.6 mmol/L). Once the patient is mentally alert and able to eat and prior to discontinuing parenteral insulin, administration of long-acting SC insulin has demonstrated efficacy in preventing rebound hyperglycemia.[12]

DISEASE COMPLICATIONS

Despite cerebral edema representing >50% of fatalities in children with hyperglycemic emergencies, **cerebral edema is an uncommon complication in adults with HHS**. There are few data on the incidence of or clinical indicators that may predispose to cerebral edema in adults. A small case series suggests that rapid changes in osmolality in HHS can predispose to osmotic demyelination syndrome.[13] The current recommendation is to limit the rate of volume repletion during the first 4 hours to <50 mL/kg of normal saline, measure serum osmolality frequently, and monitor the patient's mental status during treatment. Stat head CT or MRI is indicated, as is early neurosurgical consultation, if cognitive deterioration develops. Although there are no evidence-based treatments for cerebral edema, osmotic agents remain the most practical option. Venous and arterial thromboses are a common complication in HHS, and unless contraindicated, all patients should receive prophylactic anticoagulation as part of the management plan.[14]

DISPOSITION AND FOLLOW-UP

When considering the patient population predisposed to developing HHS (debilitated patients with multiple comorbidities), intensive care unit monitoring for the initial 24 hours of care is usually the most appropriate course of action. Patients without significant comorbid conditions who demonstrate a good response to initial therapy may be considered for monitored step-down or non–intensive care unit admission. Patients with HHS are often chronically debilitated and may present in a premorbid state often late in the natural history of their disease processes. In this context, the patient's goals of care should be identified early and remain at the forefront of the ED management plan. In a retrospective study that looked at predictors of recurrent hospitalization for patients with DKA and HHS, age <35 years, history of depression or substance abuse, self-pay or publicly funded insurance, and HbA_{1c} level >10.6% were associated with higher odds of readmission.[15]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 228

Hypothyroidism and Myxedema Crisis

Alzamani Mohammad Idrose

INTRODUCTION AND EPIDEMIOLOGY

Hypothyroidism is a clinical syndrome caused by insufficient thyroid hormone production, which slows cell metabolism. The prevalence of overt hypothyroidism in the general population varies between 0.3% and 3.7% in the United States, and between 0.2% and 5.3% in Europe.[1-4] The prevalence of hypothyroidism increases with age (>65 years) and is higher among white individuals and women.[5] The disorder is nearly 10 times more common in females than in males. On the other hand, subclinical hypothyroidism is more prevalent than overt hypothyroidism in all age groups and can be seen in 4% to 15% of women, especially the elderly.[6] Myxedema coma mortality rates with current treatments are between 30% and 60%.[6]

PATHOPHYSIOLOGY

Thyroxine (T_4) and triiodothyronine (T_3) are the thyroid hormones. The ratio of thyroxine T_4 to triiodothyronine T_3 released in the blood is about 10:1. Peripherally, thyroxine T_4 is converted to the active triiodothyronine T_3, which is three to four times more potent than thyroxine T_4. The half-life of thyroxine T_4 is 7 days, and the half-life of triiodothyronine T_3 is about 1 day.

Primary hypothyroidism is caused by the intrinsic dysfunction of the thyroid gland. The most common cause is Hashimoto's thyroiditis. Primary hypothyroidism is also caused by surgical removal or radioactive ablation and can be a result of some drug effects.[7] Drugs such as lithium, α-interferon, interleukin, and tyrosine kinase inhibitors (e.g., sunitinib) can cause hypothyroidism. Amiodarone can cause hypothyroidism in up to 14% of patients.[8-10]

Secondary hypothyroidism is caused by a deficiency of thyroid-stimulating hormone (TSH) from the pituitary gland or deficiency of thyrotropin-releasing hormone from the hypothalamus. Some literature specifically refers to hypothalamic causes as tertiary hypothyroidism.[11,12] Nevertheless, both are central causes of hypothyroidism involving the hypothalamic-pituitary axis and shall be referred to as secondary hypothyroidism in this chapter.

Euthyroid sick syndrome is associated with low triiodothyronine T_3 or thyroxine T_4 levels and a normal or low TSH level in a patient who is clinically euthyroid. This condition is found in critically ill patients or those with severe systemic illness.

Table 228-1 lists common causes of hypothyroidism.

CLINICAL FEATURES OF HYPOTHYROIDISM

The common clinical features of hypothyroidism are listed in **Figure 228-1**. Additional cardiopulmonary findings include angina, bradycardia, distant heart sounds from pericardial effusion, low voltage on the ECG, pleural effusions, cardiomyopathy, or hypoventilation.[13] **Figure 228-2** shows an example of severe pretibial myxedema. **Table 228-2** describes the clinical differences between primary and secondary hypothyroidism.

CLINICAL FEATURES OF MYXEDEMA CRISIS

Myxedema crisis is a state of metabolic and multiorgan decompensation characterized by uncorrected hypothyroidism, mental status changes or coma, and hypothermia (usually <35.5°C [95.9°F]). In hypothyroid patients, myxedema crisis can be precipitated by a number of conditions, including infection, anesthetic agents, cold exposure, trauma, myocardial infarction or congestive heart failure, stroke, GI hemorrhage, surgery, burns, medications (e.g., β-blockers, sedatives, narcotics, phenothiazine, amiodarone), or thyroid medication noncompliance.

TABLE 228-1 Common Causes Primary and Secondary of Hypothyroidism

Primary Hypothyroidism (disorders of thyroid gland)	Secondary Hypothyroidism (disorders of hypothalamic-pituitary axis)
Autoimmune disease (e.g., Hashimoto's thyroiditis)	Panhypopituitarism
Thyroiditis	Pituitary adenoma, hypothalamic tumor
Iodine deficiency	Infiltrative disorders (hemochromatosis, sarcoidosis)
After ablation (surgery, radioiodine)	Brain irradiation
Infiltrative thyroid disease (lymphoma, sarcoid, tuberculosis)	CNS infection
Drugs directly affecting thyroid function	
• Valproate	
• Potassium perchlorate	
• Iodine	
• α-Interferon	
• Interleukin-2	
• Amiodarone	
• Lithium	
• Sunitinib	
• Antituberculosis drugs (ethionamide and para-aminosalicylic acid [PAS])	
• Retroviral agents	



FIGURE 228-2. Mysedema (non-pitting edema) in a patient with hypothyroidism. (Image courtesy of Dr. Zanariah Hussein.)

The characteristic hypothyroid habitus is evident (Figure 228-1), as well as bradycardia, hypotension, hypothermia, hypoventilation, and altered mental status or coma. Blood pressure is quite variable, but of patients in full myxedema crisis, half initially exhibit clinical shock with systolic blood pressure <100 mm Hg. The capillaries are "leaky," and this may contribute to hypotension. Infection may be present even though fever, tachycardia and sweating may not be evident, because bradycardia and hypothermia mask these signs. Altered mental status can result from CO_2 narcosis or hypoglycemia. Pleural effusions are frequently demonstrable. Other potential respiratory problems include upper airway obstruction from glottic edema, vocal cord edema, and macroglossia. Metabolism of tranquilizers, sedatives, and anesthetics is reduced in hypothyroidism, and the exaggerated effects of such medications can also contribute to altered mental status. **Hypothermia is so common in myxedema crisis that a normal temperature should suggest an underlying infection**. Hypothyroid habitus, absence of shivering, and pseudomyotonic reflexes (prolonged relaxation phase of deep tendon reflexes—at least twice as long as the contraction phase) may help distinguish myxedema crisis from accidental hypothermia.

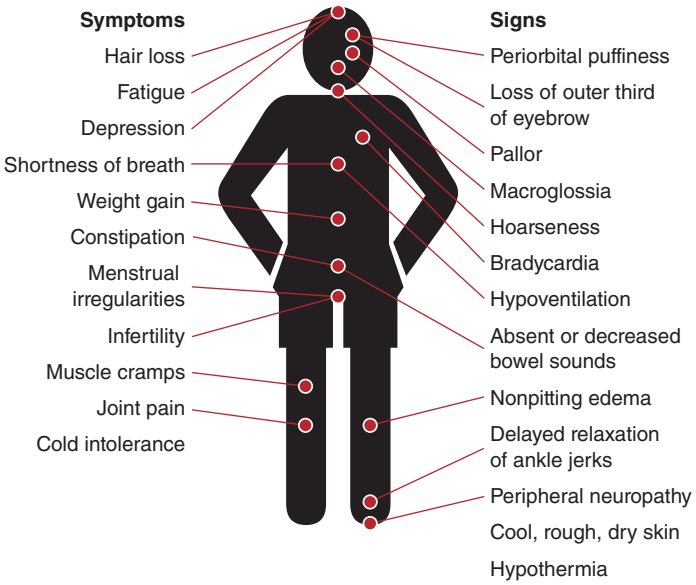

FIGURE 228-1. Signs and symptoms of hypothyroidism.

TABLE 228-2 Clinical Differentiation of Primary and Secondary Hypothyroidism

Features	Primary Hypothyroidism	Secondary Hypothyroidism
Previous thyroid operation	Yes	None
Obese	More obese	Less obese
Hypothermia	More common	Less common
Voice	Coarse	Less coarse
Pubic hair	Present	Absent
Skin	Dry and coarse	Fine and soft
Heart size	Increased	Normal
Menses and lactation	Normal	No lactation, amenorrhea
Sella turcica size	Normal	May be increased
Serum TSH	Increased	Decreased
Plasma cortisol	Normal	Decreased
Response to TSH	None	Good
Response to levothyroxine without steroids	Good	Poor response

Abbreviation: TSH = thyroid-stimulating hormone.

DIAGNOSIS

The diagnosis of hypothyroidism is based on laboratory testing. The diagnosis of myxedema crisis is clinical. The differential diagnoses include sepsis, depression, adrenal crisis, congestive heart failure, hypoglycemia, stroke, hypothermia, drug overdose, and meningitis.

LABORATORY EVALUATION AND IMAGING

Obtain baseline levels of TSH, thyroxine T_4, triiodothyronine T_3, and cortisol before initiating treatment. This facilitates eventual diagnosis as well as response to treatment.

High TSH, with low total or free thyroxine T_4 and triiodothyronine T_3, confirm primary hypothyroidism. Low TSH with low total or free thyroxine T_4 and triiodothyronine T_3 points toward secondary hypothyroidism (hypothalamic–pituitary etiology). The assays of free thyroxine T_4 and triiodothyronine T_3 are preferable to total thyroxine T_4 and triiodothyronine T_3, as results are more accurate and not affected by protein binding.

Thyroid hormone levels may also be altered as a result of drug interactions (Table 228-1), but thyroid function usually normalizes after discontinuation of these drugs. Ideally, thyroid function tests should be obtained before initiating therapy with these agents and periodically thereafter.

Menorrhagia can be a sign of hypothyroidism, and if menorrhagia is severe, microcytic anemia due to iron loss can develop. **Hyponatremia** due to increased antidiuretic hormone and impaired free water clearance is common. **Hypoglycemia** may be present due to decreased gluconeogenesis, decreased insulin clearance, and concomitant adrenal insufficiency or growth hormone deficiency. Arterial blood gases typically show hypoxemia, hypercapnia, metabolic acidosis from tissue hypoxia, and respiratory acidosis from hypoventilation due to muscle weakness.

Further laboratory assessment depends on the differential diagnosis, comorbidities, and search for precipitating factors. Obtain an ECG to identify myocardial infarction or heart block. Chest radiograph is needed to identify pneumonia, pleural effusion, or cardiomegaly. Bedside ultrasound can detect pericardial and pleural effusions.

TREATMENT OF SYMPTOMATIC HYPOTHYROIDISM

If a hypothyroid patient has symptoms of hypothyroidism and has been noncompliant with thyroid medication, or a newly diagnosed hypothyroid patient is confirmed by thyroid function tests done in the ED, oral levothyroxine may be started. The average starting dose for healthy adults younger than age 50 is 50 micrograms of oral levothyroxine once a day.[14] For those older than 50 years or with cardiac disease, the initial dose is lower, 12.5 to 25 micrograms once a day. For all adults, the dose is adjusted by 12.5- to 25-microgram increments at 4- to 6-week intervals. Instruct the patient to follow up with the primary care physician or endocrinologist for monitoring and further dose adjustments in a month.

TREATMENT OF MYXEDEMA CRISIS

Myxedema crisis treatment consists of supportive care, thyroid hormone replacement (supplementing with thyroxine T_4, triiodothyronine T_3, or a combination of both), and identification and treatment of precipitating factors (**Table 228-3**).

THYROID HORMONE REPLACEMENT FOR MYXEDEMA CRISIS

Administer thyroid hormone upon clinical suspicion of myxedema crisis, as confirmatory laboratory thyroid hormone levels will not be available initially. IV thyroxine (T_4) in the form of levothyroxine should be started as replacement. Alternatively, IV triiodothyronine (T_3) in the form of liothyronine (synthetic triiodothyronine T_3) can be given if it is available, but should be cautiously used in the elderly or those with cardiac disease as it is more potent. IV thyroxine T_4 and IV triiodothyronine T_3 can be given together if the patient has persistent hemodynamic instability or poor respiratory effort.

Thyroid hormone replacement should initially be given IV because severe or even mild hypothyroidism results in decreased intestinal motility and GI absorption. Once intestinal motility recovers, oral medication can be given.

Replacement with Intravenous Thyroxine (Levothyroxine) Levothyroxine is the synthetic form of thyroxine. The initial dose for myxedema crisis is 4 micrograms/kg IV, with the usual starting dose from 200 to 400 micrograms IV.[15] This is followed in 24 hours by 100 micrograms IV, then 50 micrograms IV until oral medication is tolerated. **Starting dose in the elderly is lower at 100 micrograms IV**. The advantages of levothyroxine are smooth, slow, and steady onset of action and its widespread availability. Disadvantages include the fact that extrathyroidal conversion of thyroxine T_4 to triiodothyronine T_3 may be reduced in myxedema crisis. The onset of action of thyroxine T_4 is longer than that of triiodothyronine T_3.

Replacement with Intravenous Triiodothyronine (Liothyronine) Liothyronine is the synthetic form of triiodothyronine T_3. In myxedema crisis, the loading dose of 20 micrograms can be given, followed by a maintenance dose of 10 micrograms every 8 hours until oral medication can be given.[15] The advantage of triiodothyronine T_3 over thyroxine T_4 is that the deiodinase conversion of thyroxine T_4 to the active hormone triiodothyronine T_3 is reduced in myxedema crisis. IV triiodothyronine T_3 also has a rapid onset of action, between 2 and 4 hours. triiodothyronine T_3 crosses the blood–brain barrier more readily than thyroxine T_4. However,

TABLE 228-3 ED Treatment for Myxedema Crisis

Supportive care

- Airway, breathing, and circulation: airway control, oxygen, IV access, and cardiac monitoring
- IV therapy: dextrose for hypoglycemia; water restriction for hyponatremia
- Vasopressors: if indicated (ineffective without thyroid hormone replacement)
- Hypothermia: treated with passive rewarming
- Steroids: hydrocortisone (due to increased metabolic stress; start with 100–200 milligrams IV)

Thyroid replacement therapy (see discussion of thyroid hormone replacement in text)

- **IV thyroxine (levothyroxine) at 4 micrograms/kg (typically between 200 and 400 micrograms as initial dose)**, followed in 24 h by 100 micrograms IV, then 50 micrograms IV until oral medication is tolerated. **Starting dose of thyroxine in the elderly is 100 micrograms IV.**

  OR

- **IV triiodothyronine (liothyronine) at a dose of 20 micrograms IV followed by 10 micrograms IV** every 8 h until the patient is conscious. **Start with no more than 10 micrograms IV for the elderly or those with coronary artery disease.** (Triiodothyronine is less preferred in patients with cardiac disease, as its potency could precipitate cardiac arrhythmias or infarction.)

Note: Start with IV levothyroxine first. IV liothyronine can be added if treatment with IV levothyroxine alone is not effective or in patients with persistent hemodynamic instability or poor respiratory effort.

Identify and treat precipitating and comorbid factors

- Infections
- Sedatives
- Cold exposure
- Trauma
- Myocardial infarction or congestive heart failure
- Cerebrovascular accident
- GI hemorrhage
- Hypoxia
- Hypercapnia
- Hyponatremia
- Hypoglycemia

the disadvantages of IV triiodothyronine T_3 are its more potent effect and fluctuating serum levels and its potency, which can cause cardiac arrhythmias or myocardial ischemia, especially in the elderly or those with cardiac disease. If IV triiodothyronine T_3 is given, provide continuous cardiac monitoring and obtain interval ECGs to identify myocardial ischemia.

Supportive Management Supportive measures should be directed at treating hypothermia, hypoventilation, and hyponatremia, volume depletion, and hypoglycemia. For myxedema crisis, give a stress dose of hydrocortisone (100 to 200 milligrams IV) at the start of therapy. Obtain serum cortisol levels prior to initiation of therapy, but it is not necessary to wait for results. If sepsis is possible or likely, give empiric broad-spectrum antibiotics.[15,16]

DISPOSITION AND FOLLOW-UP

Myxedema crisis carries a high mortality rate, ranging from 30% to 60% depending on comorbid diseases.[6] Factors such as advanced age, bradycardia, and persistent hypotension suggest a poor prognosis. All patients with myxedema crisis require intensive care unit admission. Milder hypothyroidism patients may only be discharged with a clear plan of management with follow-up by either an endocrinologist or primary care physician.

SPECIAL SITUATIONS

PREGNANT WOMEN

Overt hypothyroidism is seen in about 1% to 2% of pregnant women.[17] Subclinical hypothyroidism is seen in another 2.5%.[18]

Pregnancy increases the requirement of thyroid hormone because of the increased rate of metabolism in the mother and the transplacental transport of thyroid hormone, which is essential for the development and maturation of the different organs of the fetus. For women who are being treated for hypothyroidism, the dose of thyroxine T_4 should be increased by approximately 30% as soon as the pregnancy is confirmed.[19] The thyroid function should be checked every 8 weeks. Thyroid function test results during pregnancy may be difficult to interpret. This is because pregnant women may have a higher production of thyroid hormone from stimulation of the thyroid gland by human chorionic gonadotropin, which has a similar structure to that of TSH. In addition, increased estrogen during pregnancy results in higher levels of thyroid-binding globulin, which transports thyroid hormone in the blood. Therefore, a normal thyroid hormone level in a pregnant woman may not mean the patient is euthyroid, especially if the patient has symptoms of hypothyroidism. Thyroid hormone replacement may still be required in such a case.

Hypothyroidism is diagnosed in pregnancy if patients have symptoms and, in general, have high levels of TSH and low free thyroxine T_4. Subclinical hypothyroidism in pregnancy can be identified if the test results show high levels of TSH and normal free thyroxine T_4. Subclinical hypothyroidism should be treated to ensure a healthy pregnancy.

In myxedema crisis, IV levothyroxine is used for pregnant women. It is safe for the fetus.

ELDERLY/CARDIAC PATIENTS

Age and the presence of cardiac comorbidities are associated with a poor outcome in myxedema crisis. Standard doses of thyroxine T_4, and especially of triiodothyronine T_3, can precipitate cardiac arrhythmias. When required, start with no more than half the recommended dose of thyroxine T_4 or triiodothyronine T_3 for elderly patients.

THE ASYMPTOMATIC PATIENT WITH A PALPABLE NODULE IDENTIFIED IN THE ED

Solitary thyroid nodules are a common physical finding in the general population. Although most are benign colloid nodules that will disappear over time, a small percentage of solitary nodules are thyroid carcinomas. Refer for fine-needle aspiration biopsy.

THYROXINE HORMONE OVERDOSE

Levothyroxine is the most widely used agent for thyroid replacement. When taken in overdose, symptoms do not occur until 24 hours later as a result of metabolic conversion of thyroxine T_4 to triiodothyronine T_3. The symptoms may present earlier if triiodothyronine T_3 is ingested. Treatment is not standardized. For acute ingestion, activated charcoal can be given. Cholestyramine can increase fecal elimination, and propranolol can control tachycardia and anxiety.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 229

Hyperthyroidism and Thyroid Storm

Alzamani Mohammad Idrose

INTRODUCTION AND EPIDEMIOLOGY

Thyroid hormone affects virtually all organ systems and is responsible for increasing metabolic rate, heart rate, and ventricle contractility, as well as muscle and CNS excitability. The thyroid hormones are thyroxine (T_4) and triiodothyronine (T_3). The ratio of T_4 to T_3 released in the blood is 10:1. Peripherally, T_4 is converted to the active T_3, which is three to four times more potent than T_4.

Hyperthyroidism is an excessive amount of thyroid hormones in the body. The terms *hyperthyroidism* and *thyrotoxicosis* are often used interchangeably. Hyperthyroidism is a clinical syndrome with a variety of signs and symptoms, and **thyroid storm** is its extreme manifestation.

Thyroid storm is an acute, severe, life-threatening hypermetabolic state caused either by excessive release of thyroid hormones causing adrenergic hyperactivity or an increased peripheral response to thyroid hormone in response to one or more precipitants. The most common underlying cause is Graves' disease (85% of all hyperthyroidism cases in the United States). It is caused by thyroid-stimulating hormone (TSH) receptor antibodies that stimulate excess and uncontrolled thyroidal synthesis and secretion of thyroid hormones. It occurs most frequently in young women (10 times more common in women compared with men) at any age group.[1] The mortality of thyroid storm is in the range of 8% to 25%.[1,2] This chapter will focus primarily on the treatment of thyroid storm.

HYPERTHYROIDISM

Primary hyperthyroidism is caused by the excess production of thyroid hormones from the thyroid glands or from external factors. **Secondary hyperthyroidism** is caused by the excess production of thyroid-releasing hormones or TSH in the hypothalamus and pituitary, respectively (**Tables 229-1** and **229-2**).

CLINICAL FEATURES

The clinical features of hyperthyroidism are varied. The patient may only complain of constitutional symptoms such as generalized weakness and fatigue. Heat intolerance, diaphoresis, fever, voracious appetite but poor weight gain, anxiety, emotional lability, palpitations, diarrhea, and hair loss are common historical features. If there is a history of hyperthyroidism, ask about treatment and compliance with medication. The signs and symptoms of hyperthyroidism are as shown in **Table 229-3**. The severity of exophthalmos is not necessarily parallel with the magnitude of thyroid dysfunction but reflects the autoimmune process taking place. Not all hyperthyroidism patients present with goiter. A goiter is not present with exogenous administration of thyroid hormone and apathetic thyrotoxicosis. Likewise, the presence of a goiter does not necessarily

TABLE 229-1 Common Causes of Primary and Secondary Hyperthyroidism

Primary Hyperthyroidism	
Graves' disease (toxic diffuse goiter)	Most common of all hyperthyroidism (85% of all cases) Associated with diffuse goiter, ophthalmopathy, and local dermopathy
Toxic multinodular goiter	Second most common cause of hyperthyroidism
Toxic nodular (adenoma) goiter	An enlarged thyroid gland that contains a small rounded mass or nodules with overproduction of thyroid hormone
Thyroiditis	Inflammation of the thyroid gland
Hashimoto's thyroiditis	Initially gland is overactive (hyperthyroidism) but is typically followed by a state of hypothyroidism
Secondary Hyperthyroidism	
Thyrotropin-secreting pituitary adenoma	Thyroid gland stimulated to produce hormones

confirm the diagnosis of thyrotoxicosis. Thyroid gland tenderness can be found in inflammatory conditions such as subacute thyroiditis.

LABORATORY TESTING

Obtain a CBC, electrolytes, glucose, serum cortisol, renal and liver function tests, ECG, and chest radiograph. Obtain a pregnancy test in women of child-bearing age. Other general studies depend on clinical evaluation, comorbidities, and the differential diagnosis.

Serum TSH Level In **primary hyperthyroidism**, the TSH level is low as a result of the negative feedback mechanism toward a high thyroid hormone level. Nevertheless, a low TSH level by itself is not diagnostic, as serum TSH may be reduced as a result of chronic liver or renal disease or the effect of certain drugs such as glucocorticoids, which reduce TSH secretion.

In **secondary hyperthyroidism**, TSH is increased because of increased production in the pituitary.

TABLE 229-2 External Causes of Hyperthyroidism

Nonthyroidal Disease	
Ectopic thyroid tissue (struma ovarii)/ teratoma	A rare form of mature teratoma that contains thyroid tissue
Metastatic thyroid cancer	Production of extraglandular thyroid hormones
Human chorionic gonadotropin	Stimulates thyroid hormone secretion
Drug Induced or Iodine Intake	
Iodine	Iodine-induced thyrotoxicosis (called *Jod-Basedow phenomenon*): After treatment of endemic goiter patients with iodine or stimulation of thyroid hormones from use of iodine-containing agents such as radiographic contrast agents
Amiodarone	Contains iodine; may cause either thyrotoxicosis or hypothyroidism
Interferon-α, interleukin-2	During treatment for other diseases, such as viral hepatitis and human immunodeficiency virus infection
Thyrotoxicosis factitia	Accidental or Munchausen-like, whereby thyroid hormone is taken by patient to fake illness
Ingestion of meat containing beef thyroid tissue	Cow thyroid tissue contains thyroid hormones
Excessive thyroid hormone ingestion	

TABLE 229-3 Symptoms and Signs of Hyperthyroidism

Affected System	Symptoms	Signs
Constitutional	Lethargy Weakness Heat intolerance	Diaphoresis Fever Weight loss
Neuropsychiatric	Emotional lability Anxiety Confusion Coma Psychosis	Fine tremor Muscle wasting Hyperreflexia Periodic paralysis
Ophthalmologic	Diplopia Eye irritation	Lid lag Dry eyes Exophthalmos Ophthalmoplegia Conjunctival infection
Endocrine: thyroid gland	Neck fullness Tenderness	Thyroid enlargement Bruit
Cardiorespiratory	Dyspnea Palpitations Chest pain	Widened pulse pressure Systolic hypertension Sinus tachycardia Atrial fibrillation or flutter High-output heart failure
GI	Diarrhea Yellowish sclera	Hyperactive bowel sounds Jaundice
Reproductive	Oligomenorrhea Decreased libido	Gynecomastia Telangiectasia
Gynecologic	Menorrhagia Irregularity	Sparse pubic hair
Hematologic	Pale skin	Anemia Leukocytosis
Dermatologic	Hair loss	Pretibial myxedema* Warm, moist skin Palmar erythema Onycholysis

*Pretibial myxedema may be present in 5% of patients with Graves' disease.

Free Thyroid Hormone Levels: Free T_4 and Free T_3 A low TSH with an elevated free T_4 confirms primary hyperthyroidism. A high TSH with high free T_4 denotes secondary causes of hyperthyroidism. On the other hand, a low TSH with a normal free T_4 but elevated free T_3 is diagnostic of T_3 thyrotoxicosis. T_3 thyrotoxicosis occurs in <5% of patients who have thyrotoxicosis in North America. Thyroid hormone levels are not necessarily acutely elevated when the transition from uncomplicated thyrotoxicosis to thyroid storm occurs.

Total Thyroid Hormone Level of T_4 and T_3 Total serum T_4 and T_3 (bound and unbound) are increased in thyrotoxicosis. Eighty percent of circulating T_3 is derived from monodeiodination of T_4 in peripheral tissues, whereas 20% emanates from direct thyroidal secretion. Both T_4 and T_3 are then bound to proteins in the form of thyroxine-binding globulin, transthyretin, and albumin. Only a small fraction of the hormones are free and unbound. Laboratory measurement of total T_3 and total T_4 measures mainly protein-bound hormone concentrations. In thyroid storm, total thyroid hormone level may or may not be increased. Results also may be affected by conditions that affect protein binding. With the improved assays for free T_4 and free T_3, there is now little indication to measure total T_3 and total T_4.

Thyroid Antibody Titers Thyroid-stimulating antibodies are detected in Graves' disease. Thyroid antibody titers (to thyroid peroxidase or thyroglobulin) will help determine diagnosis.

TREATMENT AND DISPOSITION OF UNCOMPLICATED HYPERTHYROIDISM

Further evaluation, treatment, and disposition of patients with uncomplicated hyperthyroidism depend on the patient's age, comorbidities, disease severity, and identification of the underlying cause.

A thyroid sonogram with Doppler flow can be done to assess thyroid gland size, vascularity, and the presence of nodules. Typically, a thyroid gland secreting excessive hormones would be enlarged. However, in the setting of subacute postpartum thyroiditis, silent thyroiditis, or exogenous causes of hyperthyroidism, the thyroid gland is not expected to be enlarged. Nuclear medicine imaging with iodine-131 would reveal a greatly increased uptake of radioiodine as early as 1 or 2 hours after administration of the agent.

Ambulatory evaluation is usually appropriate for most patients. Consult with an endocrinologist or the patient's primary care physician about the next diagnostic and therapeutic steps.

For patients with features suggesting impending thyroid storm, see discussion below on thyroid storm.

THYROID STORM

Thyroid storm is a clinical diagnosis for patients with preexisting hyperthyroidism. Do not rely on lab results for diagnosis or to start treatment. In determining whether or not a patient has thyroid storm, the main systems to concentrate on are the **thermoregulatory system** (rise in temperature), **cardiovascular system** (ranging from tachycardia to atrial fibrillation and congestive cardiac failure), **CNS** (ranging from being agitated to seizure), and the **GI-hepatic system** (ranging from nausea to vomiting and jaundice) (**Figure 229-1**). Search for a precipitating event (**Table 229-4**).

PATHOPHYSIOLOGY

The pathophysiologic mechanisms underlying the shift from uncomplicated hyperthyroidism to thyroid storm are not entirely clear. However, they involve adrenergic hyperactivity either by increased release of thyroid hormones or increased receptor sensitivity. Many of the signs and symptoms are related to adrenergic hyperactivity. Patients with thyroid storm have relatively higher levels of free thyroid hormones as opposed to those with uncomplicated hyperthyroidism. The total thyroid hormone level may or may not be increased in those with uncomplicated hyperthyroidism.

When there is excess of thyroid hormones, circulating T_4 and T_3 are taken into the cytoplasm of cells. T_4 is converted to its active form, T_3. Within the cytoplasm, the T_3 then exerts its effect by passing into the nucleus and binding to thyroid hormone receptors or thyroid hormone–responsive elements to induce gene activation and transcription.[3,4] The receptors receiving the hormone will stimulate changes specific to the tissue.

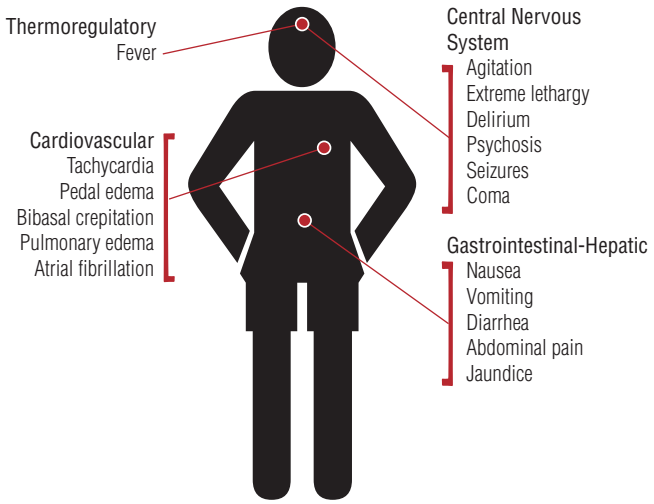

FIGURE 229-1. Clinical features of thyroid storm.

TABLE 229-4 Precipitants of Thyroid Storm

Systemic insult	**Cardiovascular insult**
Infection	Myocardial infarction
Trauma	Cerebrovascular accidents
General surgery	Pulmonary embolism
Endocrinal insult	**Obstetrics related**
Diabetic ketoacidosis	Labor and delivery
Hyperosmolar coma	Eclampsia
Drug or hormone related	**Radioactive iodine therapy**
Withdrawal of antithyroid medication	
Iodine administration	
Thyroid gland palpation	
Ingestion of thyroid hormone	
Unknown cause in up to 25% of cases	

In the pituitary gland, thyroid hormones exert negative regulation, resulting in TSH suppression.

During thyroid storm, precipitants such as infection, stress, myocardial infarction, or trauma will multiply the effect of thyroid hormones by freeing thyroid hormones from their binding sites or increasing receptor sensitivity.

PRECIPITANTS OF THYROID STORM

The precipitants of thyroid storm are as shown in Table 229-4. In some patients undergoing radioactive iodine therapy for hyperthyroidism, thyroid storm may ironically occur following treatment due to withdrawal of antithyroid drugs, release of thyroid hormones from damaged thyroid follicles, or the effect of radioactive iodine itself.

CLINICAL FEATURES OF THYROID STORM

The additional signs and symptoms of thyroid storm, apart from those evident in hyperthyroidism, are as shown in Figure 229-1. Fever is often present in thyroid storm. It may herald the onset of thyrotoxic crisis in previously uncomplicated disease. Palpitations, tachycardia, and dyspnea are common. A pleuropericardial rub may be heard. The direct inotropic and chronotropic effects of thyroid hormone on the heart cause increased stroke volume, contractility, and cardiac output. Enhanced contractility produces elevations in systolic blood pressure. Thyroid storm may also cause widened pulse pressure due to high cardiac output and reduced peripheral vascular resistance. Atrial fibrillation occurs in 10% to 35%.[4]

Table 229-5 provides the **Burch and Wartofsky Point Scale (BWPS)** for thyroid storm diagnosis. The system is practical because it is based on clinical and physical criteria and it is sensitive for thyroid storm, but it is not very specific.

Apart from this scoring system, in 2012, Akamizu et al[1] formulated diagnostic criteria for thyroid storm and clarified its clinical features, prognosis, and incidence based on nationwide surveys in Japan. After this, the Japanese Thyroid Association proposed diagnostic criteria of TS1 and TS2 for thyroid storm, taking into account laboratory evidence of increased free thyroid hormones with any CNS symptoms and non-CNS symptoms such as fever, tachycardia, heart failure presentation, or GI–hepatic derangement manifestations.[1] Nevertheless, a Burch and Wartofsky Point Scale score ≥45 appears more sensitive than a Japanese Thyroid Association classification of TS1 or TS2 in detecting patients with a clinical symptoms.[5-7]

The major differential diagnoses of thyroid storm are shown in **Table 229-6**.

LABORATORY TESTING, IMAGING, AND ECG

Obtain a CBC, electrolytes, glucose, and renal and liver function tests to identify comorbidities. Obtain a pregnancy test in women of childbearing age. Except for pregnancy testing (see later treatment section,

TABLE 229-5 Burch and Wartofsky Diagnostic Parameters and Scoring Points for Thyroid Storm

Diagnostic Parameters	Scoring Points
1. Thermoregulatory dysfunction	
Temperature °C (°F)	
37.2–37.7 (99–99.9)	5
37.7–38.3 (100–100.9)	10
38.3–38.8 (101–101.9)	15
38.9–39.4 (102–102.9)	20
39.4–39.9 (103–103.9)	25
≥40 (≥104.0)	30
2. CNS effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizures, coma)	30
3. GI-hepatic dysfunction	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
4. Cardiovascular dysfunction	
Tachycardia (beats/min)	
90–109	5
110–119	10
120–129	15
≥140	25
5. Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
6. Atrial fibrillation	
Absent	0
Present	10
7. Precipitating event*	
Absent	0
Present	10

*See Table 229-3.

Scoring system: Score of ≥45: highly suggestive of thyroid storm. Score of 25–44: suggestive of impending storm. Score of <25: unlikely to represent thyroid storm.

Source: Reproduced with permission from Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 22: 263, 1993.[3,5]

TABLE 229-6 Differential Diagnosis of Thyroid Storm

- Infection and sepsis
- Sympathomimetic ingestion (e.g., cocaine, amphetamine, ketamine drug use)
- Heat exhaustion
- Heat stroke
- Delirium tremens
- Malignant hyperthermia
- Malignant neuroleptic syndrome
- Hypothalamic stroke
- Pheochromocytoma
- Medication withdrawal (e.g., cocaine, opioids)
- Psychosis
- Organophosphate poisoning

"Inhibition of New Thyroid Hormone Synthesis," below), start treatment upon suspicion of the diagnosis without waiting for laboratory results. In thyroid storm, CBC typically shows leukocytosis with shift to the left. Hyperglycemia tends to occur because of a catecholamine-induced inhibition of insulin release and increased glycogenolysis and rapid intestinal absorption of glucose. Mild hypercalcemia and elevated alkaline phosphatase can occur because of hemoconcentration and enhanced thyroid hormone–stimulated bone resorption.[8]

Thyroid storm also induces liver enzyme metabolism, causing raised liver enzymes, so obtain baseline values. In 30% of patients, treatment with an antithyroid drug such as propylthiouracil can cause transient elevation of liver enzymes.[6] A high serum cortisol value is an expected finding. This should be the normal reaction of an adrenal gland to a body under stress. The finding of an abnormally low cortisol level should raise suspicion of coincidental adrenal insufficiency.

Imaging Chest radiograph should be done to rule out infection as a precipitant for thyroid storm. Bedside echocardiography would typically show tachycardia, enhanced left ventricular contractility, and a dilated inferior vena cava in the presence of high-output cardiac failure. CT of the brain may be necessary to exclude neurologic conditions if diagnosis is uncertain, because CNS abnormalities causing altered mental status may precipitate thyroid storm.

ECG ECG findings most commonly include sinus tachycardia and atrial fibrillation. Sinus tachycardia occurs in approximately 40% of cases.[4] Atrial fibrillation occurs in 10% to 35% of patients and more commonly in patients >60 years old with underlying structural heart disease.[4] Premature ventricular contractions and heart blocks may be present. Atrial premature contractions and atrial flutter may also occur. Institute cardiac monitoring.

TREATMENT OF THYROID STORM

The order of therapy in treating thyroid storm is very important with regard to the use of thionamide and iodine therapy. **Obtain pregnancy testing before beginning ED treatment, and obtain consultation for treatment if the patient is pregnant or breastfeeding.** If the patient is not pregnant, inhibit thyroid gland synthesis of new thyroid hormone with a thionamide (methimazole and propylthiouracil are thionamide drugs available in the United States) before iodine therapy is begun to prevent the stimulation of new thyroid hormone synthesis that can occur if iodine is given too soon.

Treatment aims are as follows:

- Supportive care
- Inhibition of peripheral adrenergic effects
- Inhibition of new hormone synthesis
- Inhibition of thyroid hormone release
- Preventing peripheral conversion of T_4 to T_3
- Preventing free thyroid hormone reabsorption
- Treating the precipitant
- Definitive care

The treatment recommendations are shown in **Table 229-7**, with specific comments in the following sections.

TREATMENT AIM 1: SUPPORTIVE CARE

Fluid losses could result from the combination of fever, diaphoresis, vomiting, and diarrhea. With high metabolic rate in thyroid storm, check blood glucose, and if blood sugar is relatively low, IV fluids with dextrose (isotonic saline with 5% or 10% dextrose) may be given to replenish glycogen stores.

TREATMENT AIM 2: INHIBITION OF PERIPHERAL ADRENERGIC EFFECTS

Thyroid storm is a hyperadrenergic state with the risk of high-output cardiac failure. Therefore, reducing afterload and heart rate with a

TABLE 229-7 Treatment for Thyroid Storm

1. **Supportive care**
   General: oxygen, cardiac monitoring
   Fever: external cooling with ice packs or cooling blankets; acetaminophen 325–650 milligrams PO/PR every 4–6 h (aspirin is contraindicated because it may increase free thyroid hormone)
   Dehydration: IV fluids, IV saline with 5% dextrose may be used to replace glycogen depletion if blood sugar is low
   Nutrition: glucose, multivitamins, thiamine, and folate can be considered (deficient secondary to hypermetabolism)
2. **Inhibition of peripheral adrenergic effects**
   Propranolol 0.5–1 milligrams IV over 10 minutes, then 1–2 milligrams every few hours adjusted to vital signs. For the less toxic patient, PO dose of 60–80 milligrams every 4 h (for reactive airway diseases, cardioselective β-blockers, such as atenolol or metoprolol, or calcium channel blockers can be considered)
   or
   Esmolol 250–500 micrograms/kg IV load, then 50–100 micrograms/kg/min titrated doses to vital signs
   or
   Reserpine 2.5–5.0 milligrams IM every 4–6 h, preceded by 1-milligram test dose while monitoring blood pressure (may consider if β-blocker is contraindicated but avoid in congestive heart failure or hypotension and cardiac shock)
   or
   Guanethidine 30–40 milligrams PO every 6 h (may consider if β-blocker is contraindicated but avoid in congestive heart failure, hypotension, and cardiac shock)
3. **Inhibition of new thyroid hormone synthesis**
   Methimazole 20 milligrams every 6 h PO
   (Avoid methimazole in pregnant women. Teratogenic risk is highest in first trimester. Methimazole is Food and Drug Administration pregnancy category D. Obtain consultation if patient is breastfeeding.)
   or
   PTU, a loading dose of 500–1000 milligrams given PO and followed by 250 milligrams every 4 h
   (PTU is used for pregnant women in first trimester. PTU also has a boxed warning issued by the U.S. Food and Drug Administration in 2010 regarding rare but severe hepatic dysfunction. There are case reports of hepatic failure in mother/fetus.) Obtain consultation if the patient is breastfeeding.
4. **Inhibition of thyroid hormone release (at least 1 h after step 3)**
   Lugol solution 8–10 drops PO every 6–8 h
   or
   Potassium iodide (SSKI) five drops (0.25 mL or 250 milligrams) PO every 6 h
   or
   IV iopanoic acid (Telepaque®), 1 gram every 8 h for first 24 h, then 500 milligrams twice a day (Food and Drug Administration pregnancy category C)
   or
   Ipodate (Oragrafin®), 0.5–3 grams/d PO (especially useful with thyroiditis or thyroid hormone overdose)
   or
   Lithium carbonate (if allergic to iodine or agranulocytosis occurs with thionamides), 300 milligrams PO every 6 h (1200 milligrams/d) and subsequently to maintain serum lithium at 1 mEq/L
   (Lithium is contraindicated for use in pregnant mothers; effects in breastfeeding uncertain, so obtain consultation.)
5. **Preventing peripheral conversion of T_4 to T_3**
   Hydrocortisone 300 milligrams IV initially, then 100 milligrams every 8 h until stable (also for adrenal replacement due to hypermetabolism)
   or
   Dexamethasone 2 milligrams IV every 6 h
6. **Prevention of free thyroid hormones reabsorption**
   Cholestyramine 4 grams every 6 h
7. **Treat precipitating event**
   All triggers of thyroid storm should be searched and treated accordingly (e.g., infection, myocardial infarct, diabetic ketoacidosis)
8. **Definitive therapy**
   Radioactive iodine ablation therapy or surgery may be necessary.

Note: Replacement therapy: dialysis and plasmapheresis are last resorts for patients who do not respond to treatments 1–5.

Abbreviation: PTU = propylthiouracil.

β-blocker is essential. Inotropic agents may have to be considered carefully as they may worsen the hyperadrenergic state.

Propranolol can be given IV in slow 1- to 2-milligram boluses, which may be repeated every 10 to 15 minutes until the desired effect is achieved (i.e., clinical improvement or heart rate <100 beats/min). Orally, propranolol therapy usually begins at 20 to 120 milligrams per dose or 160 to 320 milligrams/d in divided doses.[6,9]

Propranolol can be given IV at 0.5 to 1 milligram over 10 minutes. This can then be increased to 1 to 2 milligrams over 10 minutes each time, adjusting the dose every few hours to the patient's vital signs.[9] For the less toxic patient, a PO dose of 60 to 80 milligrams every 4 hours can be given.

Alternatively, a short acting β-blocker such as esmolol may be used by administering an IV load of 250 to 500 micrograms/kg, after which 50 to 100 micrograms/kg/min are given in a titrated dose based on the vital signs. A short-acting β-blocker is preferable for patients with cardiac failure because the drug's action could be curtailed if the patient deteriorates. Alternatively, IV landiolol or oral bisoprolol can be also be used.[9]

Propranolol seems to be better than esmolol, because propranolol has the beneficial effect of preventing T_4 to T_3 conversion as well as being a

nonselective β-blocker. Nevertheless, a recent study found evidence that, in severe thyroid storm, T_4 to T_3 conversion may already be reduced.[9]

For other conditions contraindicated to β-blockers such as reactive airway diseases, cardioselective β-blockers, such as atenolol or metoprolol, or calcium channel blockers can also be considered.

Alternatively, reserpine 2.5 to 5.0 milligrams IM can be given every 4 to 6 hours, preceded by 1-milligram test dose while monitoring blood pressure. Reserpine is an alkaloid agent that depletes catecholamine stores in sympathetic nerve terminals and the CNS. It can have CNS depressant effects. In severe asthmatics, IM reserpine, 2.5 milligrams every 4 hours, may be considered in lieu of peripheral blockade. Guanethidine, 30 to 40 milligrams PO every 6 hours, may also be an option. Guanethidine inhibits the release of catecholamines. These agents would be indicated only in rare situations in which β-adrenergic receptor antagonists are contraindicated and when there is no hypotension or evidence of CNS-associated mental status changes.[3] Side effects of both medications include hypotension and diarrhea. Avoid their use in congestive heart failure, hypotension, and cardiac shock as the blood pressure may drop.

The contraindications to peripheral blockade are the same as those for other medical conditions. Exercise caution in patients with congestive cardiac failure and thyrotoxic cardiomyopathy. Complicated patients with both a tachydysrhythmia and congestive heart failure can be managed first with rate control.

TREATMENT AIM 3: INHIBITION OF NEW THYROID HORMONE SYNTHESIS

Thionamides Thionamides used for the treatment of thyrotoxicosis are either methimazole or propylthiouracil (PTU). Thionamide therapy decreases the synthesis of new hormone production but also has immunosuppressive effects.[10] Thionamides inhibit synthesis of thyroid hormones by preventing organification and trapping of iodide to iodine and by inhibiting coupling of iodotyrosines.

Methimazole has a longer half-life than propylthiouracil, permitting less frequent dosing. It presents in free form in the serum, whereas 80% to 90% of propylthiouracil is bound to albumin.[10] Methimazole is U.S. Food and Drug Administration pregnancy category D and is especially teratogenic in the first trimester of pregnancy.

The dose for methimazole is 20 milligrams given PO every 6 hours.[6,9] The total daily dose that should be given is 60 to 80 milligrams/d. If given PR, similar dose can be crushed in aqueous solution. Although there are no commercially available parenteral formulations of the thionamides, there are case reports of methimazole being administered IV in circumstances in which the PO and PR routes of administration could not be used.[8] Methimazole was shown to have similar pharmacokinetics for both PO and IV use in normal subjects and in subjects with hyperthyroidism. In some centers, only carbimazole (which is the prodrug of methimazole) is available. If methimazole is not available, carbimazole can be used with the same potency.[9] The initial dose is 40 to 60 milligrams, followed by a maintenance dose of between 5 and 20 milligrams daily.

As for **propylthiouracil**, the dose for thyroid storm is 500 to 1000 milligrams given PO as a loading dose followed by 250 milligrams every 4 hours.[6] The drug can be given by nasogastric tube or PR. Outside the thyroid gland, only PTU, not methimazole, can inhibit conversion of T_4 to T_3, and this is the advantage of PTU.

Precautions on Use of PTU In 2009, the Food and Drug Administration notified healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of PTU in adults and children. There is an increased risk of hepatotoxicity with PTU when compared with methimazole. Since 2010, the Food and Drug Administration added a boxed warning to the prescribing information of PTU to include information about case reports of severe liver injury and acute liver failure, some of which had been fatal.[11] The Food and Drug Administration recommends that PTU be reserved for patients who cannot tolerate methimazole.

PTU is currently used as a second-line drug therapy for hyperthyroidism in general. Its use as a first-line agent is still considered in thyroid storm in view of its advantage of blocking T_4 to T_3 conversion. Nevertheless, there is recent evidence that this conversion may already be reduced in thyroid storm.[6] PTU is strictly preferred only in the case of pregnant patients during the first trimester, as methimazole use during this period had been associated with teratogenicity.[12] Nevertheless, methimazole is again suggested for use during the second and third trimesters of pregnancy.

If PTU is used, signs and symptoms of liver injury should be closely monitored, especially in the first 6 months of therapy initiation. PTU medication may cause increased liver enzyme levels. It should not be used as therapy if transaminase levels reach more than three times the upper limit of normal or if the levels are elevated at the onset of therapy.[6] PTU should not be used in children unless the patient is allergic to or intolerant of methimazole and no other treatment options are available.[6]

TREATMENT AIM 4: INHIBITION OF HORMONE RELEASE

Iodine Lugol solution, potassium iodide, ipodate (Oragrafin®), or lithium carbonate can be given to stop thyroid hormone release. **Thionamide therapy must be instituted first with these drugs only given at least 1 hour later**. Iodine therapy blocks the release of prestored hormone and decreases iodide transport and oxidation in follicular cells.

Lugol solution can be given as 8 to 10 drops PO initially and then every 6 to 8 hours. Lugol solution provides 8 milligrams of iodide per drop.

Iodinated radiographic contrast dyes that contain ipodate (Oragrafin®) 0.5 to 3 grams/d orally or IV iopanoic acid (Telepaque®) 1 gram every 8 hours for the first 24 hours followed by 500 milligrams twice a day have also been used to inhibit hormone release, and they also have the added property to effectively prevent conversion of T_4 to T_3 (Food and Drug Administration pregnancy category C).

All of the iodine-containing agents listed here lead to rapid decreases in both T_4 and T_3 levels.[13]

Nevertheless, iodine-containing solution should not be given to patients with iodine hypersensitivity, iodine overload, or iodine-induced hyperthyroidism or to those with amiodarone-induced thyrotoxicosis.

Alternative Drugs if Iodine Intake Is Contraindicated • **Potassium Perchlorate** Potassium perchlorate blocks thyroid uptake of iodine and thus interferes with the production of new hormones. The perchlorate anion, ClO_4^-, is a competitive inhibitor of iodide transport. The recommended dose is 0.5 gram of potassium perchlorate per day. It is used in amiodarone-induced thyrotoxicosis for which iodine replacement is contraindicated. However, it has side effects of aplastic anemia and nephrotic syndrome.

Lithium In severe thyroid storm conditions, lithium can also be used in combination with PTU or methimazole. Lithium inhibits thyroid hormone release from thyroid gland. Lithium also has added effects on the thyroid gland that decrease thyroid hormone synthesis, thereby increasing intrathyroidal iodine content and inhibiting coupling of iodotyrosine residues that form T_4 and T_3. In thyroid storm, the dosing for lithium is 300 milligrams every 8 hours. To avoid lithium toxicity, lithium level should be monitored regularly every day to maintain a concentration of approximately 0.6 to 1.0 mEq/L (0.6–1.0 mmol/L). Frequent monitoring of serum lithium levels is mandatory, especially because the serum lithium concentrations may change as the patient is rendered more euthyroid. Avoid lithium in pregnancy as it has teratogenic effects.[14]

TREATMENT AIM 5: PREVENTING PERIPHERAL CONVERSION OF THYROXINE TO TRIIODOTHYRONINE

The peripheral conversion of T_4 to T_3, which is responsible for 85% of T_3 present in the circulation, is blocked by PTU, propranolol, and glucocorticoid. Nevertheless, for PTU and propranolol, this effect is not quantitatively significant. Therefore, glucocorticoids such as hydrocortisone or dexamethasone are essential in treatment. Glucocorticoid use in thyroid storm also improves survival rates.[3] In patients who have severe thyrotoxicosis, especially in conjunction with hypotension, treatment with glucocorticoids is a standard practice because of the possibility of relative adrenal insufficiency. Hydrocortisone 300 milligrams IV is given

initially, followed by 100 milligrams every 8 hours until stable. Alternatively, dexamethasone 2 milligrams IV can be given every 6 hours.[9]

TREATMENT AIM 6: PREVENTING REABSORPTION OR REMOVAL OF THYROID HORMONES

Cholestyramine is used to inhibit thyroid hormone reabsorption. Thyroid hormone is metabolized mainly in the liver, where it is conjugated to glucuronides and sulfates. These conjugation products are then excreted in the bile. Free hormones are released in the intestine and finally reabsorbed, completing the enterohepatic circulation of thyroid hormone. In states of thyrotoxicosis, there is increased enterohepatic circulation of thyroid hormone. Cholestyramine is an anion exchange resin that decreases reabsorption of thyroid hormone from the enterohepatic circulation. Cholestyramine in combination with methimazole or PTU causes a more rapid decline in thyroid hormone levels than standard therapy with thionamides alone.[15] Its dosage is 4 grams every 6 hours.

Thyroid Hormone Removal In patients who have contraindications to PTU and methimazole, such as a prior severe reaction, direct removal of thyroid hormone has been described. Plasmapheresis, charcoal hemoperfusion, resin hemoperfusion, and plasma exchange may be effectively used to rapidly reduce thyroid hormone levels in thyroid storm patients who respond poorly to traditional therapeutic measures.[16]

TREATMENT AIM 7: IDENTIFY PRECIPITATING FACTORS

Search for infection in febrile thyrotoxic patients. Obtain an ECG to identify myocardial infarction, ischemia, or arrhythmia.

In cases of thyroid storm precipitated by DKA, myocardial infarction, pulmonary embolism, or other acute processes, appropriate management of the specific underlying problem should proceed along with the treatment of the thyrotoxicosis.[3]

TREATMENT AIM 8: DEFINITIVE THERAPY

Definitive therapy with radioactive iodine ablation or surgery may not be able to be done for several weeks or months after treatment with iodine for thyroid storm. Close follow-up and monitoring should continue, with plans for definitive therapy to prevent a future recurrence of life-threatening thyrotoxicosis.[2]

RAPID PREPARATION OF THYROTOXIC PATIENTS FOR EMERGENCY SURGERY

In the event that a patient has thyrotoxicosis and requires emergent surgery, the recommendation of drug supplementation is as shown in **Table 229-8**. The supplementation is important because surgery in a patient with hyperthyroidism may precipitate thyroid storm.[17,18]

DISPOSITION AND FOLLOW-UP

Thyroid storm patients typically require admission to the intensive care unit. Patients with thyroid storm often have concomitant diseases precipitating the attack and require close monitoring. Complete recovery may take 1 week until circulating levels of thyroid hormones are depleted. Stable hyperthyroid patients with minimal symptoms can only be discharged for follow-up either by an endocrinologist or primary care physician, if the patient is already on medication with a clear plan of follow-up.

SPECIAL SITUATIONS

PREGNANCY AND LACTATION

Avoid methimazole during the first trimester of pregnancy in thyrotoxic patients in view of its teratogenic effects. PTU should be used during the first trimester. This can be converted back to methimazole from the second trimester onward. Lithium is contraindicated in pregnancy. Effects on breastfeeding infants are not well documented. Obtain consultation.

ELDERLY PATIENTS

Older patients may present with "apathetic" thyrotoxicosis (i.e., with some atypical symptoms, including weight loss, palpitations, weakness, dizziness, syncope, memory loss, and physical findings of sinus tachycardia or atrial fibrillation). Signs and symptoms of this condition are few and subtle, and the initial appearance of disease may be single-organ failure (e.g., congestive heart failure), producing diagnostic confusion by pointing to diagnoses other than thyrotoxicosis.

TABLE 229-8 Rapid Preparation of Thyrotoxic Patients for Emergent Surgery

Drug Class	Recommended Drug	Dosage	Mechanism of Action	Continue Postoperatively?
β-Adrenergic blockade	Propranolol	40–80 milligrams PO 3 to 4 times a day	β-Adrenergic blockade; decreased thyroxine-to-triiodothyronine conversion (high dose)	Yes
	or			
	Esmolol	50–100 micrograms/kg/min	β-Adrenergic blockade	Change to PO propranolol
Thionamide	Propylthiouracil	200 milligrams PO every 4 h	Inhibition of new thyroid hormone synthesis; decreased thyroxine-to-triiodothyronine conversion	Stop immediately after near-total thyroidectomy; continue after nonthyroidal surgery
	or			
	Methimazole	20 milligrams PO every 4 h	Inhibition of new thyroid hormone synthesis	Stop immediately after near-total thyroidectomy; continue after nonthyroidal surgery
Oral cholecystographic agent	Iopanoic acid	500 milligrams PO twice a day	Decreased release of thyroid hormone; decreased thyroxine-to-triiodothyronine conversion	Stop immediately after surgery
Corticosteroid	Hydrocortisone	100 milligrams PO or IV every 8 h	Vasomotor stability; decreased thyroxine-to-triiodothyronine conversion	Taper over first 72 h
	or			
	Dexamethasone	2 milligrams PO or IV every 6 h	Vasomotor stability; decreased thyroxine-to-triiodothyronine conversion	Taper over first 72 h
	or			
	Betamethasone	0.5 milligram PO every 6 h, IM or IV	Vasomotor stability; decreased thyroxine-to-triiodothyronine conversion	Taper over first 72 h

Source: Reproduced with permission from Langley RW, Burch HB: Perioperative management of the thyrotoxic patient. *Endocrinol Metab Clin of North Am* 32: 519, 2003. Copyright Elsevier.

THYROTOXIC PATIENTS WITH ATRIAL FIBRILLATION

β-Blockers can provide rate control. Propranolol can be used if the patient is not in failure. Esmolol, with short-acting effect, is a safer choice. If β-blockers are contraindicated, digoxin can be used. Calcium channel blockers can also be cautiously considered but can induce severe hypotension and reduce systemic vascular resistance. Amiodarone can be considered, but note that it has 37% organic iodine in weight. Ensure thionamides have been given to avoid synthesis of new thyroid hormones. As in any atrial fibrillation, thrombosis may ensue and heparinization should be instituted. Thyrotoxic patients may require a lower maintenance dose of warfarin than euthyroid patients because of increased clearance of vitamin K–dependent clotting factors.

CONGESTIVE CARDIAC FAILURE IN THYROID STORM

Avoid vasodilators such as nitrates because thyrotoxicosis is associated with vasodilatation and decreased systemic vascular resistance. Avoid β-blockers when the cardiac failure is associated with underlying ischemic, hypertensive, or valvular heart disease. A short-acting β-blocker such as esmolol is a safer choice.

DRUG INTERACTIONS IN THYROTOXIC PATIENTS

Many drugs interfere with protein binding, including heparin, furosemide, phenytoin, carbamazepine, diazepam, salicylates, opiates, estrogens, and NSAIDs. Because of this interference with total thyroid hormone levels, free hormone concentrations are preferable in the diagnosis of thyrotoxicosis.[8]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 230

Adrenal Insufficiency

Alzamani Mohammad Idrose

INTRODUCTION

The adrenal gland synthesizes steroid hormones in the cortex and catecholamines in the medulla. **Primary adrenal insufficiency, or Addison's disease, is due to intrinsic adrenal gland dysfunction and results in decreased cortisol, aldosterone, and gonadotropin production.** About 90% of the gland must be destroyed for clinical adrenal insufficiency to develop.

Secondary adrenal insufficiency is due to hypothalamic–pituitary dysfunction with failure to secrete corticotropin-releasing hormone and/or adrenocorticotropic hormone (ACTH) and **results in cortisol deficiency only.**[1]

Adrenal crisis is a life-threatening exacerbation of adrenal insufficiency when an increased demand fails to increase hormone production. The risk of death is higher in those who are older, diabetic, or present with impaired consciousness.[2-4]

PHYSIOLOGY

The adrenal gland is made up of the cortex and medulla, which produce steroid hormones and catecholamines, respectively. The adrenal cortex produces three categories of steroids: the glucocorticoids (**cortisol**), mineralocorticoids (**aldosterone**), and gonadocorticoids (**sex hormones**). Glucocorticoids are produced in the zona fasciculata, and mineralocorticoids and gonadocorticoids are respectively produced in the zona glomerulosa and zona reticularis of the adrenal cortex. The adrenal medulla produces adrenalin, noradrenalin, and a small amount of dopamine in response to stimulation by sympathetic preganglionic neurons.

Cortisol is secreted in response to direct stimulation by ACTH. ACTH secretion is stimulated by corticotropin-releasing factor released from the hypothalamus. Secretion occurs in a diurnal rhythm, with higher levels secreted in the morning and lower levels in the evening. In normal circumstances, the daily cortisol equivalent is about 20 milligrams/d of hydrocortisone. Plasma cortisol suppresses the release of ACTH through negative feedback inhibition. Cortisol facilitates the stress response by affecting the heart, vascular bed, water excretion, electrolyte balance, potentiation of catecholamine action, and control of water distribution. It affects fat, protein, and carbohydrate metabolism by stimulating glycogenolysis and neoglycogenesis. It is involved in immunologic and inflammatory responses and affects calcium metabolism. It promotes growth and development but, in excess, interferes with the GI tract mucosa maintenance, leading to peptic ulcer.

Aldosterone secretion is controlled primarily by the renin–angiotensin system and serum potassium concentration. The renin–angiotensin system controls aldosterone levels in response to changes in volume, posture, and sodium intake. Serum potassium (hyperkalemia) influences the adrenal cortex directly to increase aldosterone secretion. Aldosterone maintains sodium and potassium plasma concentrations, regulates extracellular volume, and controls sodium and water balance.

Gonadocorticoids include androgen hormones and estrogen. Androgens produced include testosterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate, which are present in both men and women. In women, androgens are produced in the adrenal glands as well as the ovaries and promote the development of sex characteristics such as axillary and pubic hair and libido. In men, most androgens (testosterone) are produced in the testes. Androgens made by the adrenal glands are less important for normal sexual function.

PRIMARY ADRENAL INSUFFICIENCY

Causes of primary adrenal insufficiency (Addison's disease) are shown in **Table 230-1**. In the United States, autoimmune disorders are responsible for most cases.[1,3] Autoimmune disorders may occur as an isolated process or as a component of polyglandular autoimmune syndrome types I and II.

Drugs such as etomidate, aminoglutethimide, mitotane, and ketoconazole suppress cortisol synthesis by the adrenal gland. Etomidate can precipitate acute adrenal insufficiency in a dose-dependent manner.[5] Drugs such as phenytoin, phenobarbital, rifampicin, and thyroid hormone replacement may increase glucocorticoid metabolism.

In terms of infection, worldwide, tuberculosis is the most common cause of primary adrenal insufficiency. Human immunodeficiency virus may cause adrenal insufficiency through opportunistic infections (principally cytomegalovirus) or use of medications, such as ketoconazole. Secondary adrenal insufficiency can develop through inhibition of the hypothalamus–pituitary–adrenal axis.

Infiltrative diseases such as amyloidosis, hemosiderosis, and bilateral metastasis from cancer may also cause primary adrenal insufficiency. Thrombosis and/or hemorrhage of the adrenals may occur as a complication of anticoagulation therapy, sepsis, disseminated intravascular coagulation, meningococcemia (Waterhouse-Friderichsen syndrome), or antiphospholipid syndrome.

SECONDARY ADRENAL INSUFFICIENCY

Secondary adrenal insufficiency can develop through inhibition of the hypothalamus–pituitary–adrenal axis.[6,7] Causes are shown in **Table 230-2**. Secondary adrenal failure is usually characterized by depressed ACTH secretion, which reduces cortisol production, but aldosterone levels remain normal because of preserved stimulation by both the renin–angiotensin axis and potassium. Adrenal sex hormone production is also preserved. Intracranial disorders such as brain tumor, pituitary

TABLE 230-1 Causes of Primary Adrenal Insufficiency

Etiologies	Examples
Autoimmune	Isolated adrenal insufficiency or associated with polyglandular insufficiencies (polyglandular autoimmune syndrome type I or II)
Adrenal hemorrhage or thrombosis	Necrosis caused by meningococcal sepsis Coagulation disorders Overwhelming sepsis (Waterhouse-Friderichsen syndrome)
Drugs	Adrenal enzyme inhibitors (affect those with limited pituitary or adrenal reserve) Etomidate Aminoglutethimide (used by body builders) Mitotane (orphan drug used to treat adrenocortical carcinoma) Ketoconazole
Infections	Tuberculosis Fungal, bacterial sepsis Acquired immunodeficiency syndrome involving adrenal glands
Infiltrative disorders	Sarcoidosis Hemochromatosis Amyloidosis Lymphoma Metastatic cancer
Surgery	Bilateral adrenalectomy Bariatric surgery
Hereditary	Adrenal hypoplasia Congenital adrenal hyperplasia Adrenoleukodystrophy Familial glucocorticoid deficiency

disease, postpartum pituitary necrosis, or major head trauma may affect the hypothalamic–pituitary function, resulting in secondary adrenal insufficiency.[8]

The most common cause of secondary adrenal insufficiency is long-term therapy with pharmacologic doses of glucocorticoids.[9] Severity of adrenal suppression is variable and depends on the dose and potency of the glucocorticoid and the time of day the drug is taken (suppression is greater when taken in the evening). Recovery of the hypothalamus–pituitary–adrenal axis may take a few months to 1 year after steroid cessation. Although hypothalamus–pituitary–adrenal axis suppression is related to duration of treatment, steroid dose, and total cumulative dose, there is no strict correlation with any of these factors. Some critically ill patients demonstrate reduced cortisol clearance and suppression of ACTH release.[10]

TABLE 230-2 Causes of Secondary Adrenal Insufficiency

Etiology	Examples
Prolonged glucocorticoid therapy	Chronic use of steroids inhibits CRH and ACTH production
Pituitary necrosis or bleeding	Postpartum pituitary necrosis (Sheehan's syndrome)
Brain tumors	Pituitary/hypothalamic tumor Local invasion (craniopharyngioma)
Pituitary irradiation/surgery/head trauma	Disrupts CRH and ACTH production capacity in hypothalamic–pituitary axis
Infiltrative disorders of the pituitary or hypothalamus	Sarcoidosis Hemosiderosis Hemochromatosis Histiocytosis X Metastatic cancer Lymphoma
CNS infections involving hypothalamus or pituitary	Tuberculosis Meningitis Fungus Human immunodeficiency virus

Abbreviations: ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

ADRENAL CRISIS

Adrenal crisis is a life-threatening state caused by insufficient levels of cortisol. It can result from acute destruction of the hypothalamic–pituitary axis or the adrenal glands or from acute stressors in the setting of underlying primary or secondary adrenal insufficiency. Reported stressors include acute infection, especially GI infection; surgery; extreme physical activity; acute severe injury or burns; and cessation of chronic glucocorticoid replacement.[11] Infections are the most common precipitants.[9]

Acute adrenal crisis is characterized by severe hypotension refractory to vasopressors. Other symptoms include severe abdominal pain, nausea, and vomiting, mimicking an acute abdomen. CNS symptoms of confusion, disorientation, and lethargy may be present. There may be associated sepsis, even without fever. Consider adrenal crisis in situations of unexplained hypotension, especially in patients with a history of glucocorticoid therapy; those with acquired immunodeficiency syndrome, tuberculosis, autoimmune disease, or severe head trauma; those with a history of chronic fatigue and hyperpigmentation; and those with disorders known to cause acute adrenal crisis (as seen in Tables 230-1 and 230-2).

CLINICAL FEATURES

Primary and secondary adrenal insufficiency have dissimilar clinical presentations (**Table 230-3**). **Primary adrenal insufficiency** presents with symptoms of diminished cortisol, aldosterone, and gonadocorticoids, and increased ACTH, which causes skin hyperpigmentation. On the other hand, **secondary adrenal insufficiency** presents with symptoms of diminished cortisol and possibly with related symptoms of intracranial lesions (e.g., headache, visual changes, galactorrhea). **Cortisol deficiency symptoms** depend on the cause and can include weight loss, lethargy, weakness, mental status changes, and GI symptoms (anorexia, nausea, vomiting, abdominal pain, and diarrhea). **Mineralocorticoid (aldosterone) deficiency symptoms** include dehydration, syncope, salt craving, and hypotension (usually with orthostatic changes). **Gonadocorticoid deficiency symptoms** are observed more in women, who present with decreased axillary and pubic hair and decreased libido.

TABLE 230-3 Features of Primary and Secondary Adrenal Insufficiency

Features	Primary	Secondary
Volume depletion and hypotension	Marked	Not as severe unless crisis is present
Serum potassium	Hyperkalemia	Hypokalemia
Serum sodium	Hyponatremia	Hypernatremia (aldosterone present) or hyponatremia (due to water retention)
Cushingoid appearance	Absent	May be present (if due to long-term glucocorticoid use)
Symptoms of other pituitary hormone deficiencies (e.g., hypothyroidism and amenorrhea)	Absent	May be present (depends on the hypothalamic–pituitary site of lesion)
Skin pigmentation	Present (due to high ACTH level)	Absent
Serum glucose	Low	Low
ACTH	High	Low
Cortisol	Low	Low

Abbreviation: ACTH = adrenocorticotropic hormone.

LABORATORY STUDIES AND IMAGING

Obtain a bedside glucose determination to identify hypoglycemia. Obtain CBC, serum electrolyte and calcium levels, serum cortisol, hepatic function studies, ECG, and urinalysis.[12] Additional studies are determined by the presumptive underlying cause such as sepsis, hemorrhage, or CNS abnormality. Chest radiograph can assess for tuberculosis or bacterial pneumonia. An abdominal CT scan can identify adrenal gland hemorrhage or infarction. Head CT or MRI can assess CNS causes of secondary adrenal insufficiency.

Primary adrenal insufficiency is typically characterized by hyponatremia and hyperkalemia due to mineralocorticoid (aldosterone) deficiency. Reduced cortisol and aldosterone also cause increased antidiuretic hormone release, which causes hyponatremia. The serum potassium may also be affected by the dilutional effect, and thus sometimes the potassium level may be normal. **Secondary adrenal insufficiency** is characterized by either hypernatremia from functioning aldosterone causing renal sodium reabsorption or hyponatremia following water retention. In both primary and secondary adrenal insufficiency, cortisol deficiency can lead to hypotension or hypoglycemia. Mild metabolic acidosis is evident due to tissue hypoxia from hypovolemia and hypotension. ECG changes are generally related to potassium imbalances. Hypercalcemia can occur, from calcium mobilization from bone stores and calcium resorption in the proximal tubule.

Serum cortisol or ACTH levels are not usually readily available at ED presentation. If available, a serum cortisol >18 micrograms/dL generally rules out adrenal insufficiency.[13] A high ACTH level is seen in primary adrenal insufficiency, but ACTH is low in secondary adrenal insufficiency.[14] The ACTH stimulation test can also differentiate primary from secondary adrenal insufficiency. After obtaining a baseline cortisol level, 250 micrograms of cosyntropin (synthetic form of ACTH) is administered IV. Significant increase in serum cortisol (>18 micrograms/dL) confirms secondary adrenal insufficiency.[12-15] If an ACTH stimulation is contemplated and emergent steroids are necessary, give dexamethasone, as it has minimal cross-reactivity with cortisol.

TABLE 230-4 Treatment for Adrenal Crisis

Administer IV Fluids for Hypotension

Use dextrose-containing saline if hypoglycemic (begin with D5/NS).

↓

Give Steroids

Hydrocortisone, 100-milligram IV bolus, is the drug of choice for cases of adrenal crisis or insufficiency, especially for underlying primary insufficiency (provides both glucocorticoid and mineralocorticoid effects). If no IV access, 100 milligrams can be given IM. Follow with IV infusion of 200 milligrams/24 h of hydrocortisone or 100 milligrams IV every 6 h. Obtain consultation for further dosing.

or

Dexamethasone, 4-milligram bolus (preferred if rapid ACTH stimulation test is contemplated). However, if dexamethasone is given, add fludrocortisone 100 micrograms/d as dexamethasone does not have mineralocorticoid properties.

↓

Supportive Care

Maintain airway, breathing, and circulation; consider bolus glucose, thiamine, naloxone, etc., for altered mental status. Correct potassium, sodium, and calcium.

↓

Consider Vasopressors

Administer only after steroid therapy in patients unresponsive to aggressive fluid resuscitation (choice of norepinephrine, dopamine, or phenylephrine [Neo-Synephrine®]).

↓

Determine Underlying Cause

Investigate as appropriate—sepsis, adrenal hemorrhage, CNS abnormality.

↓

Optimize Maintenance Dosage of Steroids

Patients may require lifelong glucocorticoids ± mineralocorticoid ± androgen supplementation. During periods of stress, increase maintenance doss of chronic steroids up to 3 times the daily dose, to satisfy increased physiologic need for cortisol.[16]

Abbreviations: ACTH, adrenocorticotropic hormone; D5/NS, 5% dextrose/normal saline.

TREATMENT

ADRENAL INSUFFICIENCY

For **primary adrenal insufficiency**, treatment requires daily dosing of glucocorticoid and mineralocorticoid, usually for life. Mineralocorticoids are replaced with an oral, synthetic mineralocorticoid drug such as fludrocortisone (Florinef®). The dose is tailored to manage blood pressure and fluid balance. Androgen replacement may be recommended for women. For **secondary adrenal insufficiency**, only glucocorticoid replacement is required. Typical glucocorticoid dose is 20 milligrams/d of oral hydrocortisone or prednisolone equivalent. Dexamethasone is not used for maintenance because dose titration is difficult and cushingoid effects can be pronounced.[12]

For patients receiving chronic steroids, increase the maintenance dose during periods of stress (e.g., illness, surgery, trauma, GI upset) to satisfy the increased physiologic need for cortisol. Dosage recommendations vary and are based on expert opinion. **A typical stress dose is three times the daily maintenance dose of glucocorticoid**.[16] Mineralocorticoid dosage generally stays the same. Endocrinology consultation can be helpful for further recommendations.

ADRENAL CRISIS

Treatment is outlined in **Table 230-4**. Begin therapy immediately in any suspected case of adrenal crisis, because prognosis is related to the rapidity of treatment onset. Give IV fluids and steroids early. If hypoglycemia is present, give dextrose-containing solutions.

DISPOSITION AND FOLLOW-UP

Admit patients with adrenal crisis to an intensive care unit for careful clinical monitoring, IV steroid administration, and confirmation of diagnosis and identification of etiology. Discharge can only be considered for mild cases of adrenal insufficiency with identified etiologies and after a clear plan of management is established, often with endocrinology consultation.

SPECIAL POPULATIONS

PATIENTS ON CHRONIC CORTICOSTEROIDS

Hypothalamus–pituitary–adrenal axis function is inhibited with chronic use of steroids. Always consider adrenal insufficiency in patients with chronic steroid use presenting with any acute illness. Hypothalamus–pituitary–adrenal axis function should recover within about 1 month after the last dose of steroid intake but may be longer in some cases. Patients who receive steroids by topical, intranasal, inhalational, or PR routes are not at risk for hypothalamus–pituitary–adrenal axis suppression.

PATIENTS WITH CHRONIC ADRENAL INSUFFICIENCY WITH ACUTE ILLNESS OR INJURY

Patients with chronic adrenal insufficiency who present to the ED with a minor illness or injury require special attention to steroid dosing.[13] In normal circumstances, about 20 milligrams/d of hydrocortisone is equivalent to the daily production of cortisol. For a minor illness or injury, triple the daily glucocorticoid dose for 24 to 48 hours until symptoms improve.[16] Increasing the mineralocorticoid dose, if the patient is receiving one, is usually not necessary. Arrange follow-up care in 24 hours with the primary care physician or endocrinologist. Patients should return to the ED if nausea, vomiting, fever, weakness, or any other untoward symptoms develop or if they cannot retain their medications.

PREGNANCY WITH ADRENAL INSUFFICIENCY

Most women with primary adrenal insufficiency are able to undergo healthy pregnancy, labor, and delivery. During the third trimester, the glucocorticoid dose may require adjustment. Give hydrocortisone bolus, 100 milligrams, during labor. Women with hyperemesis gravidarum may need to switch from oral medication to parenteral medication until symptoms subside.

SEPSIS

Intravenous hydrocortisone is not necessary to treat septic shock if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability. Intravenous hydrocortisone at a dose of 200 milligrams/d is only recommended if these are not achievable.[17]

Etomidate, which is used in rapid sequence induction, suppresses adrenal synthesis of cortisol by inhibiting adrenal mitochondrial 11-β hydroxylase, the enzyme responsible for the final conversion of 11-deoxycortisol to cortisol.[5] Previous studies have evaluated the effect of etomidate on adrenocortical suppression in septic patients; however, none of the studies have been sufficiently powered to determine the effects on mortality. A single dose of etomidate does not increase mortality in patients with sepsis.[18,19]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 231

Anemia and Polycythemia

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ANEMIA

Anemia is a common medical problem, affecting approximately one quarter of the world's population, especially children, pregnant and premenopausal women, the elderly, and the chronically ill.[1-4] Anemia is not so much a disease as a sign or symptom. There are three broad causes of anemia: (1) blood loss, (2) decreased red blood cell production, and (3) increased red blood cell (RBC) destruction.

PATHOPHYSIOLOGY

Anemia is a reduced concentration of RBCs. In healthy persons, normal erythropoiesis ensures that the concentration of RBCs present is adequate to meet the body's demand for oxygen and that the destruction of RBCs balances the production. The average life of the circulating erythrocyte is approximately 110 to 120 days. Any process or condition that results in the loss of RBCs, that impairs RBC production, or that increases RBC destruction will result in anemia if the bone marrow cannot produce new cells to replace those lost (**Table 231-1**).

Quantification of the erythrocyte concentration is reflected in (1) RBC count per microliter, (2) hemoglobin concentration, and (3) hematocrit (percentage of RBC mass to blood volume). Reference RBC values for adults vary between genders, with smaller variations for ethnicity and age (**Table 231-2**).

Anemia reduces the oxygen-carrying capacity of a given volume of blood. The body responds to anemia in ways to minimize the effect of this reduction in oxygen-carrying capacity. Mechanisms vary depending on the rapidity of onset, the degree of anemia, and the underlying condition of the patient. The cardiovascular response typically manifests with vasoconstriction in the peripheral vasculature and vasodilation in the central vasculature to help preserve blood flow to vital organs. As anemia worsens, systemic small-vessel vasodilation will occur, increasing blood flow to tissues. These processes result in decreased systemic vascular resistance, increased cardiac output, and often tachycardia. In addition, RBCs enhance their ability to release oxygen to the tissues by a shift of the oxyhemoglobin dissociation curve. Finally, anemia will result in the stimulation of erythropoietin as a result of tissue hypoxia and breakdown products from RBC destruction. New, immature erythrocytes, known as reticulocytes, will appear in the blood within 3 to 7 days.

CLINICAL FEATURES

The severity of signs and symptoms depends on the rate of development of anemia; the degree of anemia; and the age, comorbidities, and general condition of the patient. Otherwise healthy patients may tolerate significant anemia with minimally altered vital signs until they become profoundly fatigued, whereas physiologic compensation will be more challenging in those with medical comorbidities. Most adults will be symptomatic when hemoglobin levels decrease below 7 grams/dL; however, some patients with chronic anemia may have no complaints even with hemoglobin levels as low as 5 grams/dL.

Patients with chronic anemia may note weakness, fatigue, dizziness, dyspnea with exertion, palpitations, and orthostatic symptoms. Additional manifestations may depend on comorbid illnesses, such as worsened chest pain in a patient with preexisting angina. Specific historical features can be helpful in the identification and diagnosis of anemia, such as recent trauma, hematochezia, melena, hemoptysis, hematemesis, hematuria, or menorrhagia. More subtle historical features include relevant comorbidities such as peptic ulcer disease, chronic liver disease, and chronic kidney disease. Query regarding the use of antiplatelet agents, anticoagulants, and NSAIDs.

Physical exam findings include tachycardia; skin, nail bed, and mucosal pallor; systolic ejection murmur; bounding pulse; and widened pulse pressure. Signs of easy bleeding or bruising suggest a coagulation disorder. Evidence of jaundice and hepatosplenomegaly suggests hemolysis. Unusual skin ulcerations, peripheral neuropathy, or neurologic signs such as ataxia or altered mental status may be evidence of nutritional deficiencies.

Patients who develop acute, severe anemia may have any of the signs and symptoms noted above. In addition, they may have resting dyspnea, diaphoresis, anxiety, or severe weakness that may progress to lethargy and altered mental status. Loss of >40% of blood volume from traumatic or spontaneous hemorrhage can lead to severe symptoms that are due more to intravascular volume depletion than to anemia.[5]

DIAGNOSIS

The diagnosis is established by a finding of decreased RBC count, hemoglobin, and hematocrit on the CBC. Further workup initiated in the ED can help expedite a diagnosis and should be started before the transfusion of packed RBCs whenever possible.

The initial evaluation of newly diagnosed anemia includes consideration for a source of bleeding, including the most common internal sites—GI or uterine bleeding. If there is no physical or historical evidence of bleeding, RBC indices, reticulocyte count, and peripheral blood smear should be reviewed (**Table 231-3**). The mean corpuscular volume is the most useful guide to the possible etiology of an anemia and classifies the anemia as microcytic, normocytic, or macrocytic.[6] Other useful diagnostic tests include the red cell distribution width and reticulocyte count. Serum ferritin is the most useful test for the diagnosis of iron deficiency anemia.[7] Following this initial classification, additional tests can lead to a specific diagnosis (**Figures 231-1, 231-2,** and **231-3**).[2-4,7-10]

The most common causes of macrocytosis are alcohol abuse, liver disease, vitamin B_{12} and/or folate deficiency, and hypothyroidism.[8] Medications that affect folate absorption or metabolism and produce macrocytosis include phenytoin, valproate, trimethoprim, sulfamethoxazole, and metformin. The reverse transcriptase inhibitors used to treat human immunodeficiency virus infection can also produce macrocytosis, but they do so without causing anemia. Reticulocytes are larger than mature RBCs, so automated blood cell counters can report a mean corpuscular volume value above the normal range when an increased reticulocyte count is present.

Sideroblastic anemia can be due to a congenital mutation (X-linked or autosomal recessive), a somatic mutation (as seen in myelodysplastic syndromes) or from an acquired condition.[10] The most common cause of acquired sideroblastic anemia is alcohol abuse. Pyridoxine deficiency, lead poisoning, copper deficiency, or zinc toxicity can cause

TABLE 231-1 Classification of Anemia

Mechanism	Example
Loss of red blood cells by hemorrhage	Acute GI bleeding
Increased destruction	Sickle cell disease Drug-induced autoimmune hemolytic anemia
Impaired production	Nutritional deficiency anemia (iron, folate) Aplastic or myelodysplastic anemia
Dilutional	Rapid IV crystalloid infusion

TABLE 231-2 Reference Range Red Blood Cell Values for Adults

	Male	Female
Red blood cell count (million/mm^3)	4.5–6.0	4.0–5.5
Hemoglobin (grams/dL)	14–17 (140–170 grams/L)	12–15 (120–150 grams/L)
Hematocrit or packed cell volume (%)	42–52	36–48
Mean corpuscular volume: MCV (fL)	78–100	78–102
Mean corpuscular hemoglobin: MCH (picograms/cell)	25–35	25–35
Mean corpuscular hemoglobin concentration: MCHC (grams/dL)	32–36 (320-360 g/L)	32–36 (320-360 g/L)
Red cell distribution width: RDW (%)	11.5–14.5	11.5–14.5
Reticulocytes (%)	0.5–2.5	0.5–2.5

Note: Normal values may vary depending upon the equipment used, patient's age, and the altitude of patient residence.

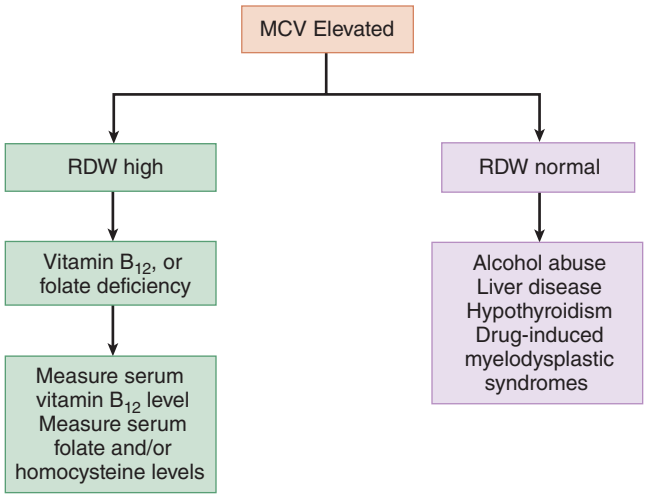

FIGURE 231-1. Evaluation of macrocytic anemia. MCV = mean corpuscular volume; RDW = red cell distribution width.

sideroblastic anemias. Antimicrobials associated with sideroblastic anemia include linezolid, chloramphenicol, isoniazid, and cycloserine.

TREATMENT

The treatment of anemia depends on the cause and clinical status of the patient. In the ED, anemia that requires the most urgent attention results from acute blood loss.[5] All patients with ongoing blood loss should have their blood typed and cross-matched for possible transfusion (see Chapter 238, "Transfusion Therapy"). The decision to transfuse the anemic patient is individualized, taking into account clinical symptoms, the patient's age and health, and the likelihood of further

TABLE 231-3 Laboratory Tests in the Evaluation of Anemia

Test	Interpretation	Clinical Correlation
Mean corpuscular volume (MVC)	Measure of the average red blood cell (RBC) size.	Decreased MCV (microcytosis) is seen in chronic iron deficiency, thalassemia, anemia of chronic disease, and lead poisoning. Increased MCV (macrocytosis) can be due to vitamin B_{12} or folate deficiency, alcohol abuse, liver disease, reticulocytosis, and some medications (see "Diagnosis" section).
Mean corpuscular hemoglobin (MCH)	Measure of the amount of hemoglobin in average red blood cell.	—
Red cell distribution width (RDW)	Measures the size variability of the RBC population.	In early deficiency anemia (iron, vitamin B_{12}, or folate), may be increased before the mean corpuscular volume becomes abnormal.
Mean corpuscular hemoglobin concentration (MCHC)	Measure of hemoglobin concentration in average RBC.	Low MCHC can be seen in iron deficiency anemia, defects in porphyrin synthesis, and hemolytic anemia.
Ferritin	Ferritin is a protein in the body that binds to iron. Serum levels serve as an indication of the amount of iron stored in the body.	Low serum ferritin is associated with iron deficiency anemia and helps differentiate this anemia from other causes.
Reticulocyte count	These RBCs of intermediate maturity are a marker of production by the bone marrow.	Decreased reticulocyte count reflects impaired RBC production. Increased counts are a marker of accelerated RBC production.
Peripheral blood smear	Allows visualization of the RBC morphology.	May guide to new diagnosis of diseases such as sickle cell disease.
	Allows evaluation for abnormal cell shapes.	Aids in the diagnosis of entities such as hemolytic anemia.
	Allows examination of the white blood cells and platelets.	May guide the diagnosis of other diseases that cause anemia.
Coombs test	Direct Coombs test is used to detect antibodies on RBCs.	Direct Coombs test is positive in autoimmune hemolytic anemia, transfusion reactions, and some drug-induced hemolytic anemia.
	Indirect Coombs test is used to detect antibodies in the sera.	Indirect Coombs test is routinely used in compatibility testing before transfusion.

Abbreviations: MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distribution width.

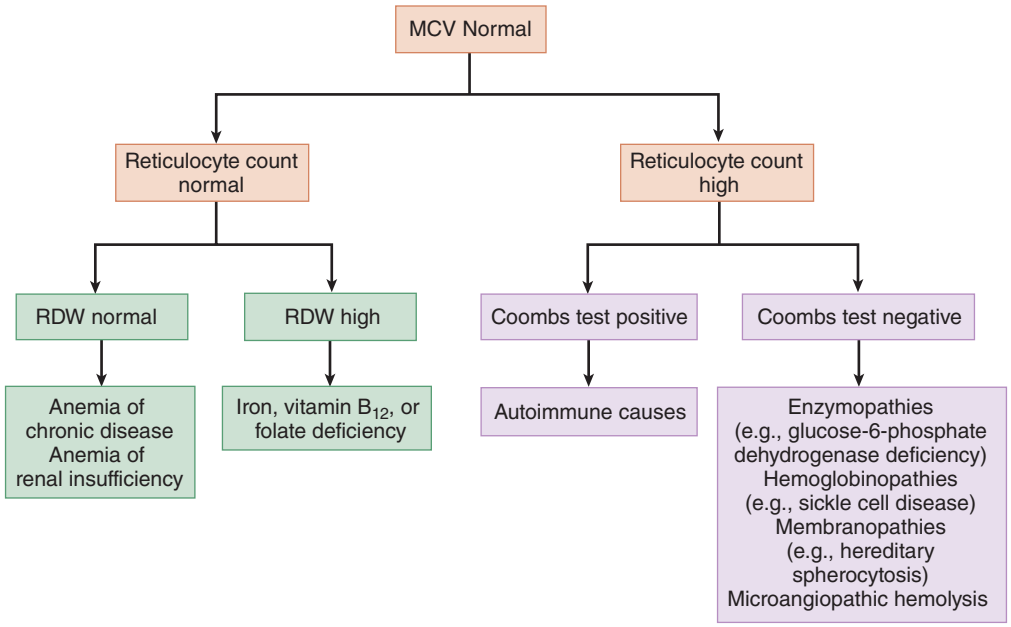

FIGURE 231-2. Evaluation of normocytic anemia. MCV = mean corpuscular volume; RDW = red cell distribution width.

blood loss.[11,12] In general, patients who are symptomatic at rest or are hemodynamically unstable and show evidence of tissue hypoxia and/or limited cardiopulmonary reserve should have RBCs transfused. In most settings, patients with anemia benefit when transfused at hemoglobin levels of ≤7 grams/dL (60 to 70 grams/L). Liberal transfusion strategy (defined as a hemoglobin threshold of 9.5 to 10 grams/dL or 95 to 100 grams/L) is not generally associated with clinical benefit.[12]

ED patients with lesser degrees of anemia who are hemodynamically stable and have no evidence of tissue hypoxia, typically with hemoglobin levels of ≥8 grams/dL (80 grams/L), do not require immediate transfusion, and outpatient follow-up is recommended for further hematologic evaluation.

Treatment for nutritional deficiency anemias usually produces a reticulocyte response in 4 to 7 days (**Table 231-4**). Standard therapy for iron or folate deficiency uses oral replacement. Vitamin B_{12} replacement has traditionally been IM because of concern that malabsorption of the vitamin would limit the effectiveness of oral replacement.[13] However, oral doses of 1000 micrograms of vitamin B_{12} per day are as effective as the IM route.[14,15]

DISPOSITION AND FOLLOW-UP

Patients with anemia from ongoing blood loss should be admitted to the hospital for further evaluation and treatment. Patients with isolated anemia not related to blood loss do not necessarily require hospital admission if they are asymptomatic and hemodynamically stable, they have minimal comorbid disease, and follow-up can be arranged. Patients newly diagnosed with anemia who also have abnormalities in the WBC or platelet count should have hematologic consultation and may require admission.

POLYCYTHEMIA

Polycythemia is suggested when an elevated hemoglobin or hematocrit (packed cell volume) is found on CBC testing (**Table 231-5**).[16] Since hemoglobin and hematocrit values on the CBC are ratios, an elevation can be due to either a decrease in plasma volume or an increase in RBC mass. The former is termed relative polycythemia and is most

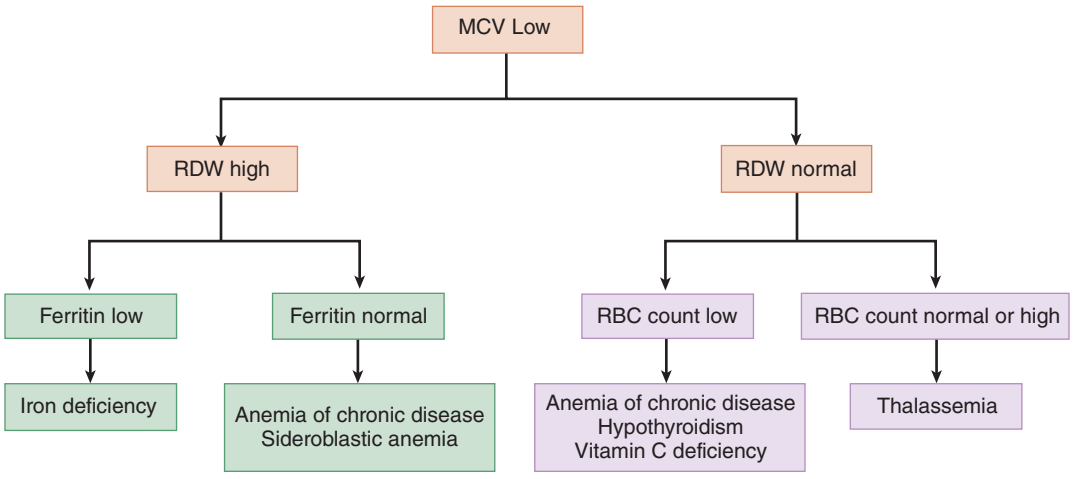

FIGURE 231-3. Evaluation of microcytic anemia. MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distribution width.

TABLE 231-4 Treatment for Specific Anemias

Anemia Type	Treatment (Adult Doses)
Iron deficiency anemia	Elemental iron, 200 to 300 milligrams/d (e.g., ferrous sulfate, 325 milligrams, three to four tablets taken on an empty stomach over the course of day); reticulocyte count should increase within 4–7 d and peak at 10 d; sustained treatment after correction of anemia is usually necessary to replenish iron stores.
Cyanocobalamin (vitamin B_{12}) deficiency anemia	Cyanocobalamin, 1000 micrograms IM per week for 8 wk and every month thereafter; reticulocyte count should increase within 4 d and peak at 7 d. Oral replacement with 1000 micrograms/d is as effective (see "Treatment" section).
Folate deficiency anemia	Folate, 1 milligram PO per day (doses up to 5 milligrams may be needed for patients with malabsorption); reticulocyte count should increase within 4 d with normalization of hemoglobin level in 1–2 mo.
Sideroblastic anemia	Evaluate for reversible causes. Discontinue any offending agents. Treatment is mainly supportive, consisting primarily of blood transfusions to maintain the hemoglobin level. A trial of pyridoxine at pharmacologic doses (500 milligrams PO daily) may be helpful, with response most commonly seen in cases resulting from ethanol abuse or isoniazid. Some patients with hereditary X-linked sideroblastic anemia also respond to pyridoxine. Improvement with pyridoxine is rare for sideroblastic anemia of other causes.
Aplastic anemia	Supportive care, including transfusion if appropriate.
Anemia of chronic disease	Supportive care, including transfusion if appropriate. Erythropoietic agents (patients with cancer, chronic kidney disease, human immunodeficiency virus). Omega-3 polyunsaturated fatty acids (patients with rheumatoid arthritis and diabetes mellitus).

commonly caused by dehydration from excessive fluid loss, decreased oral intake, and/or excessive diuresis.

Absolute polycythemia is an increase in the RBC mass. *Primary polycythemia* is due to an acquired or inherited mutation in erythroid cell lines and, less commonly, erythropoietin receptor mutations. This category includes polycythemia vera.[17] *Secondary polycythemia* usually results from increased circulating levels of erythropoietin, directly stimulating RBC production (Table 231-5).

TABLE 231-5 Polycythemia (Erythrocytosis)

Relative	Normal RBC numbers and mass, decreased plasma volume	Dehydration, diuretics
Absolute	Primary	Polycythemia vera (*JAK2* gene mutation) Congenital mutations in erythropoietin receptor
	Secondary–acquired	Central hypoxia: lung disease, high-altitude habitat, chronic carbon monoxide exposure Renal hypoxia: renal artery stenosis, polycystic kidney disease, post renal transplant Excess erythropoietin production: testosterone and anabolic steroids, paraneoplastic syndromes
	Secondary–congenital	Altered oxyhemoglobin affinity Disordered oxygen sensing
	Idiopathic	No identifiable cause

CLINICAL FEATURES

Symptoms of polycythemia are often vague and may include chest, abdominal, or muscle pain and generalized weakness. CNS manifestations may be present, from mild fatigue and headache, to focal neurologic signs and coma. Patients with polycythemia vera will classically present with pruritus when exposed to hot water and early satiety from splenomegaly. Physical exam may reveal splenomegaly in these patients. Additional findings may include plethoric facies and ruddy skin, as well as distal cyanosis and clubbing from microemboli.[16] Hyperviscosity syndrome is a life-threatening complication of polycythemia that presents with the triad of bleeding, visual disturbances, and focal neurologic deficits caused by thrombosis and microhemorrhage.[16-18] Patients with polycythemia vera are prothrombotic and at increased risk for venous thromboembolism.

DIAGNOSIS

The diagnosis of polycythemia is suggested by a higher than expected hemoglobin or hematocrit for the patient's demographics on CBC (a hemoglobin >18.5 grams/dL [>185 grams/L] or hematocrit >52% in a male and a hemoglobin >16.5 grams /dL [>165 grams/L] or a hematocrit >48% in a female). If relative polycythemia is not suspected, workup of absolute polycythemia should include urinalysis, renal and hepatic function tests, and pulse oximetry. Consider co-oximetry to assess for chronic carbon monoxide poisoning. Erythropoietin level, while not helpful in the acute setting, may guide further assessment. Chest radiograph or cardiopulmonary function testing may be indicated if secondary polycythemia is suspected. Polycythemia vera may be suggested by history, but formal diagnosis requires bone marrow biopsy or genetic testing in addition to an elevated hemoglobin level.[19]

TREATMENT AND DISPOSITION

The treatment of relative polycythemia is with correction of decreased plasma volume. The mainstay of treatment for patients with polycythemia vera is low-dose aspirin and phlebotomy to a hematocrit of 45%.[16,17] Pharmacotherapy, including hydroxyurea, interferon-α, systemic anticoagulation, and the JAK1/JAK2 inhibitor ruxolitinib may be initiated after risk stratification and hematology consultation.[15-17,19,20] Polycythemia with hyperviscosity syndrome should be managed aggressively, with IV hydration and early hematology consultation.[18]

The patient can usually be discharged when polycythemia is discovered as an incidental finding. Patients with clinical manifestations due to hyperviscosity syndrome require admission.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 232

Hemostasis

Stephen John Cico

THE BLEEDING PATIENT

Most bleeding seen in the ED is a result of trauma—local wounds, lacerations, or other structural lesions—and the majority of traumatic bleeding occurs in patients with normal hemostatic mechanisms. In these patients, specific assessment of hemostasis is unnecessary. However, some ED patients have abnormal bleeding due to impaired hemostasis. Identifying

these patients requires attention to the history and physical findings.[1-3] Generally speaking, when patients have spontaneous bleeding from multiple sites, bleeding from untraumatized sites, delayed bleeding several hours after trauma, and bleeding into deep tissues or joints, the possibility of a bleeding disorder should be considered.

Important historical data that aid in identifying a congenital bleeding disorder include the presence of unusual or abnormal bleeding in the patient and other family members and any occurrence of excessive bleeding after dental extractions, surgical procedures, or trauma. Many patients with abnormal bleeding have an acquired disorder, such as liver disease, renal disease, or drug use (particularly ethanol, aspirin, NSAIDs, antiplatelet drugs, oral anticoagulants, antibiotics, and other salicylate-containing products). Many supplements and herbal preparations, including garlic, ginseng, ginkgo biloba, ginger, and vitamin E, can also increase bleeding tendencies.

The site of bleeding may provide an indication of the hemostatic abnormality. Mucocutaneous bleeding, including petechiae, ecchymoses, epistaxis, GI or GU bleeding, or heavy menstrual bleeding, is characteristic of qualitative or quantitative platelet disorders. Purpura is often associated with thrombocytopenia and commonly indicates a systemic illness. Bleeding into joints and potential spaces, such as between fascial planes and into the retroperitoneum, and delayed bleeding are most commonly associated with coagulation factor deficiencies. Patients who demonstrate both mucocutaneous bleeding and bleeding in deep spaces may have disorders such as disseminated intravascular coagulation, in which both platelet abnormalities and coagulation factor abnormalities are present (see Chapter 233, "Acquired Bleeding Disorders," Chapter 234, "Clotting Disorders," and Chapter 235, "Hemophilias and von Willebrand's Disease").

Common laboratory tests for hemostasis have their limitations.[4,5] They are generally useful and reliable for identifying disorders of coagulation factor function and quantitative platelet availability. However, tests of qualitative platelet function show a significant biologic variation, so that standardization has been difficult to achieve.[5] In addition, liver disease and renal failure—two conditions that increase the potential for abnormal hemorrhage—may not give consistent and measurable abnormal results on routine tests of hemostasis.[6,7]

THE PATIENT WITH A THROMBUS

A patient with an intravascular thrombosis, such as a venous thromboembolism or pulmonary embolus (particularly if recurrent), suggests the potential for an underlying hypercoagulable state (see Chapter 234).[8] Premature coronary artery disease and acute coronary syndrome in individuals as young as teenagers have also been linked to hypercoagulable conditions. However, many, if not most, occurrences of intravascular thrombosis are not due to exaggerated hemostasis but rather are due to local conditions, with blood vessel wall injuries, local inflammation, or vascular stasis provoking the thromboembolic event.

The susceptibility to hypercoagulation may be acquired or genetically transmitted. Common acquired hypercoagulable disorders include essential thrombocythemia, polycythemia vera, paroxysmal nocturnal hemoglobinuria, antiphospholipid syndrome, and cancer (often occult at the time of acute thrombosis). Inherited hypercoagulable disorders include factor V Leiden, prothrombin mutations, hyperhomocysteinemia, and deficiencies of protein C, protein S, and antithrombin. Patients with inherited hypercoagulable conditions tend to have venous thrombosis, whereas those with acquired disorders can have both arterial and venous clots.

Proteins C and S are vitamin K–dependent antihemostatic factors made in the liver, and deficiencies of these proteins are inherited in an autosomal manner. Protein C is activated by thrombin and functions with protein S to stop fibrin formation and to stimulate the process of fibrinolysis. Antithrombin is also an antihemostatic protein that blocks activated coagulation factors. Elevated homocysteine level is also a known risk factor for thromboembolism.

Laboratory tests for a hypercoagulable diathesis show wide biologic variation, and standardization among laboratories has been difficult to achieve. The clinical utility of testing patients for suspected hypercoagulable conditions is dependent on the specific disorder.[8-10]

NORMAL COAGULATION

The normal hemostatic system consists of a complex process that limits blood loss through the formation of a platelet plug (primary hemostasis) and the production of cross-linked fibrin (secondary hemostasis), which strengthens the platelet plug.[11] These reactions are counterregulated by the fibrinolytic system, which limits the size of the fibrin clot that is formed and thereby prevents excessive clot formation. Congenital and acquired abnormalities occur in all these systems. The affected patient may have excessive hemorrhage, excessive thrombus formation, or both.[2]

PRIMARY HEMOSTASIS

Primary hemostasis is the platelet interaction with exposed vascular subendothelial collagen that results in the formation of a platelet plug at the site of injury. Required components for this to occur are normal vascular subendothelium (collagen), functional platelets, normal von Willebrand factor (connects the platelet to the endothelium via glycoprotein Ib), and normal fibrinogen (connects the platelets to each other via glycoprotein IIb/IIIa) (**Figure 232-1**). Primary hemostasis begins within 20 seconds of injury, is short lived, and requires secondary hemostasis for clot stabilization.[2]

SECONDARY HEMOSTASIS

Secondary hemostasis consists of the tightly regulated reactions of the plasma coagulation proteins. The final product is cross-linked fibrin, which is insoluble and strengthens the platelet plug formed in primary hemostasis (**Figure 232-2**).

Secondary hemostasis is also known as the *coagulation cascade*. The inactivated coagulation proteins (factors) are identified by Roman numerals, and after activation, the activated factor is designated by *a*. There are two independent activation pathways. The contact system is known as the *contact activation pathway* or *intrinsic pathway*, and the tissue factor system is known as the *tissue factor pathway* or *extrinsic pathway*.[2,11] The pathways merge at the point of activation of factor X. Medications such as rivaroxaban, apixaban, and edoxaban inhibit the activity of factor Xa. The combination of factor Xa, factor Va, phospholipid, and calcium ("thrombinase complex") more efficiently catalyzes the conversion of prothrombin to thrombin than free factor Xa. In turn, thrombin catalyzes the conversion of fibrinogen to fibrin monomer. Medications such as bivalirudin or dabigatran are direct thrombin inhibitors. The *common pathway* describes the steps from factor X activation to cross-linked fibrin formation.

THE FIBRINOLYTIC SYSTEM

The fibrinolytic system regulates the hemostatic mechanism by limiting the size of the fibrin clots that are formed (**Figure 232-3**). Tissue plasminogen activator, released from endothelial cells, is the principal physiologic trigger for the fibrinolytic process, converting plasminogen, synthesized in the liver and adsorbed in the fibrin clot, to plasmin. Plasmin degrades fibrinogen and fibrin monomer into low-molecular-weight fragments known as fibrin degradation products and degrades cross-linked fibrin into D-dimers.

Other physiologic inhibitors of hemostasis with clinical relevance include antithrombin and the protein C–protein S system. Antithrombin is a protein that forms complexes with all the serine protease coagulation factors (factors XIIa, XIa, Xa, and IXa and thrombin), thereby inhibiting their function. Heparin potentiates this interaction, which is the basis for its use as an anticoagulant. Proteins C and S are vitamin K–dependent factors that are produced in the liver. Activated protein C binds to the cell surface–bound protein S, and this complex is capable of inactivating the two plasma cofactors factors Va and

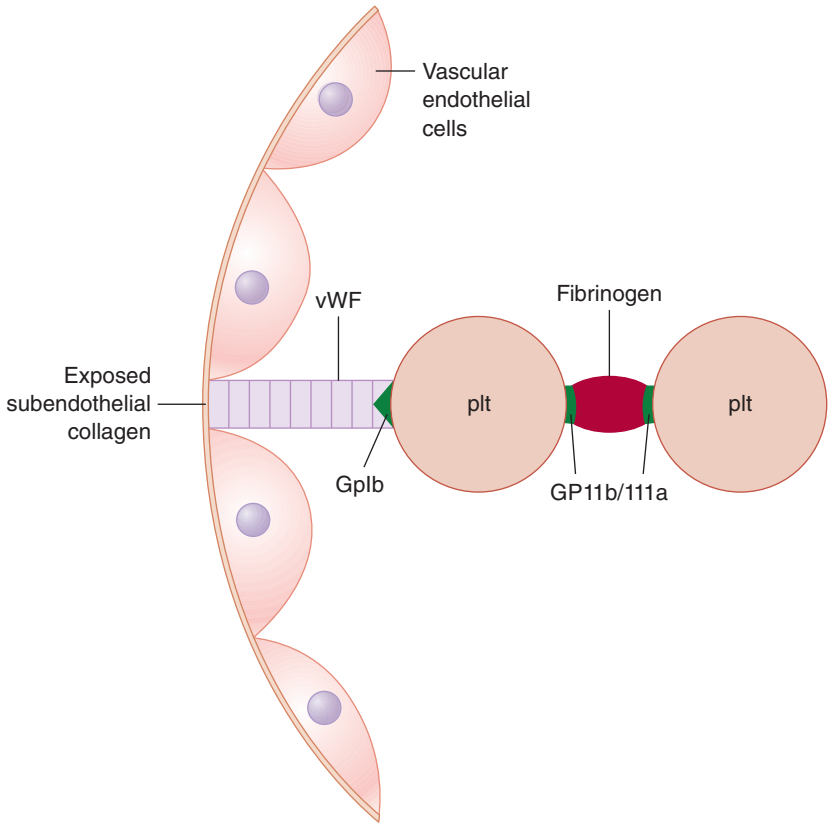

FIGURE 232-1. Primary hemostasis. GpIb = glycoprotein Ib; GpIIb/IIIa = glycoprotein IIb/IIIa; plt = platelet; vWF = von Willebrand factor.

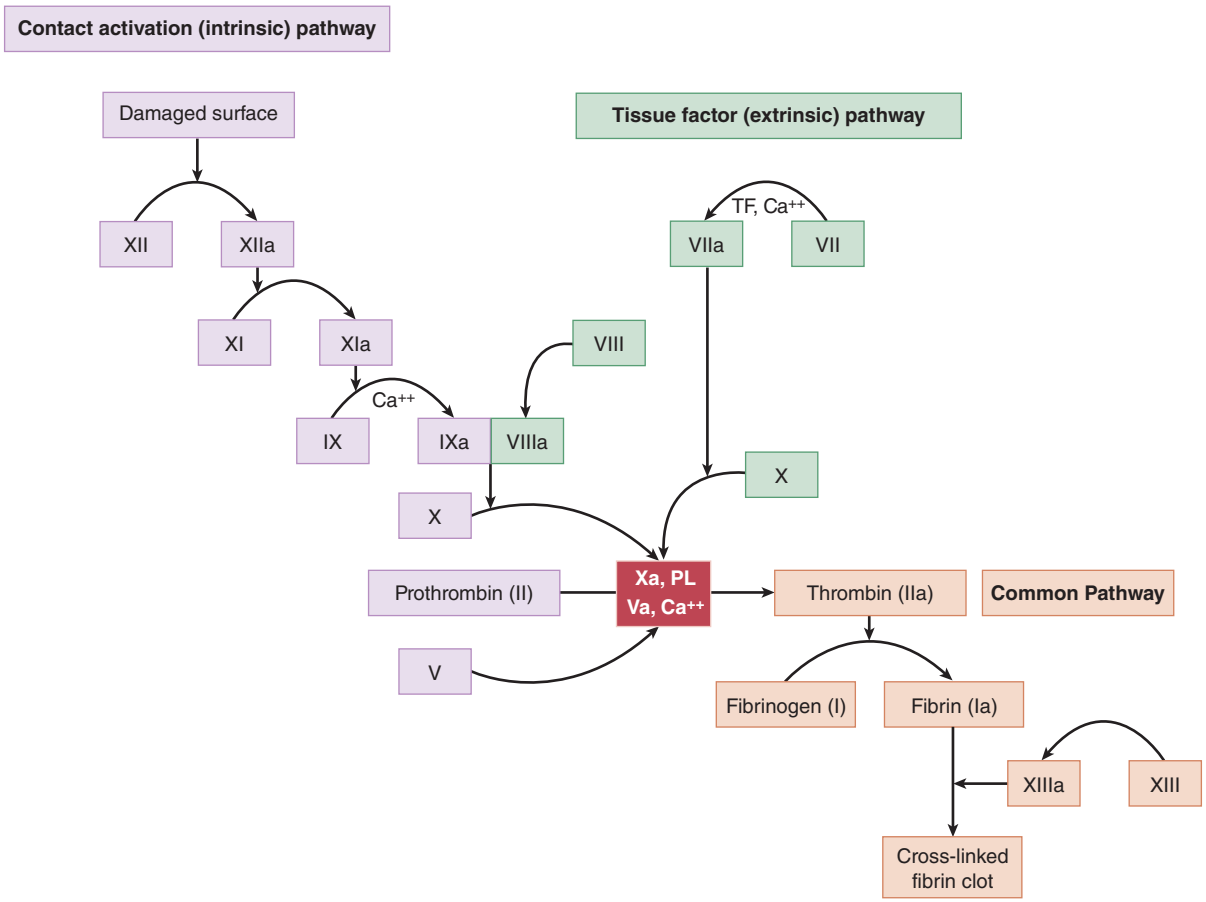

FIGURE 232-2. Secondary hemostasis. Ca^{++} = calcium; fibrinogen is factor I; PL = phospholipid surface (often platelets); prothrombin is factor II; TF = tissue factor.

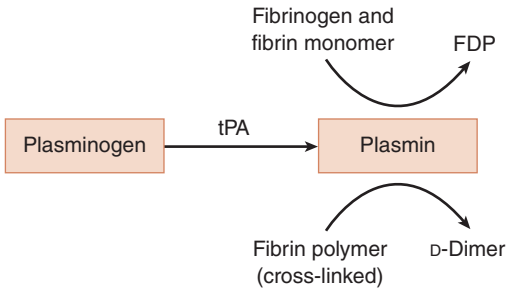

FIGURE 232-3. The fibrinolytic system. FDP = fibrin degradation product; tPA = tissue plasminogen activator.

VIIIa and inhibiting their participation in the coagulation cascade. A single amino acid substitution in factor V, a condition named factor V Leiden, prevents activated protein C from binding and inhibiting the activity of factor Va. Thus, patients with this inherited condition have prolonged thrombogenic factor Va activity. Factor V Leiden deficiency or defects in antithrombin, protein C, and protein S produce a potentially hypercoagulable condition and predispose the patient to venous thromboses.[8]

TESTS OF HEMOSTASIS

Before embarking on a sequence of hemostatic testing, evaluate the patient in three areas: (1) Is the bleeding abnormal? (2) Is there a current medical condition associated with increased hemorrhage? (3) Is there a structural cause that explains the bleeding?[1-3]

The basic laboratory tests obtained for a patient with a suspected abnormal bleeding disorder are a CBC and platelet count, prothrombin time, and activated partial thromboplastin time (**Table 232-1**). The results of these tests, coupled with clinical evaluation, should enable formulation of a differential diagnosis.[12,13] Additional studies are ordered as indicated (**Table 232-2**). Obtain hematologic consultation if the differential diagnosis or the laboratory approach is unclear. In patients with perioperative bleeding, the basic laboratory tests for coagulation are of little help in assessment or management.[14]

TABLE 232-1 Initial Tests of Hemostasis

Screening Tests	Reference Value	Component Measured	Clinical Correlations
Primary Hemostasis			
Platelet count	150–400,000/mm^3 (150–400 × 10^9/L)	Number of platelets per mm^3	*Decreased platelet count (thrombocytopenia)*: bleeding usually not a problem until platelet count is <50,000/mm^3 (50 × 10^9/L); high risk of spontaneous bleeding, including CNS bleeding, seen with count of <10,000/mm^3 (10 × 10^9/L); usually due to decreased production or increased destruction of platelets
			Elevated platelet count (thrombocytosis): commonly a reaction to inflammation or malignancy, and occurs in polycythemia vera; can be associated with hemorrhage or thrombosis
Bleeding time (BT)	Variable Typically 2.5–10.0 min using a BT template	Interaction between platelets and the subendothelium	*Prolonged BT* caused by: Thrombocytopenia (platelet count <50,000/mm^3 or 50 × 10^9/L) Abnormal platelet function (von Willebrand's disease, antiplatelet drugs, uremia, liver disease)
Secondary Hemostasis			
Prothrombin time (PT) and international normalized ratio (INR)	PT: 11–13 s; depends on reagent INR: 1.0	Extrinsic system and common pathway—factors VII, X, V, prothrombin, and fibrinogen INR = 1.7 corresponds to approximately 30% activity of coagulation factors as a whole	*Prolonged PT* most commonly caused by: Warfarin (inhibits production of vitamin K–dependent factors II, VII, IX, and X) Liver disease with decreased factor synthesis Antibiotics that inhibit vitamin K–dependent factors (moxalactam, cefamandole, cefotaxime, cefoperazone)
Activated partial thromboplastin time (aPTT)	22–34 s Depends on type of thromboplastin reagent used "Activated" with kaolin	Intrinsic system and common pathway—factors XII, XI, IX, VIII, X, V, prothrombin, and fibrinogen	*Prolonged aPTT* most commonly caused by: Heparin therapy Factor deficiencies (factor levels have to be <30% of normal to cause prolongation)
Fibrinogen level	Slightly variable according to specific test Typically 200–400 milligrams/dL (2–4 g/L)	Protein made in liver; converted to fibrin as part of normal coagulation cascade	Low levels seen in disseminated intravascular coagulation Elevated in inflammatory processes (acute-phase reactant)
Thrombin clotting time (TCT)	10–12 s	Conversion of fibrinogen to fibrin monomer	*Prolonged TCT* caused by: Low fibrinogen level Abnormal fibrinogen molecule (liver disease) Presence of heparin, fibrin degradation products, or a paraprotein (multiple myeloma); these interfere with the conversion Occasionally seen in hyperfibrinogenemia
"Mix" testing[15]	Variable	Performed when results on one or more of the above screening tests is prolonged; the patient's plasma ("abnormal") is mixed with "normal" plasma and the screening test is repeated	*If the mixing corrects* the screening test result: one or more factor deficiencies are present
			If the mixing does not correct the screening test result: a circulating inhibitor is present

TABLE 232-2 Additional Hemostatic Tests

Test	Reference Value	Component Measured	Clinical Correlations/Comments
Fibrin degradation product (FDP) and D-dimer levels	FDP: variable depending on specific test, typically <2.5–10 micrograms/mL (2.5–10 milligrams/L)	FDP test: measures breakdown products from fibrinogen and fibrin monomer	Levels are elevated in diffuse intravascular coagulation, venous thrombosis, pulmonary embolus, and liver disease, and during pregnancy
	D-Dimer: variable depending on specific test, typically <250–500 nanograms/mL (250–500 micrograms/L)	D-Dimer test: measures breakdown products of cross-linked fibrin	
Factor level assays	60%–130% of reference value (0.60–1.30 units/mL)	Measures the percent activity of a specified factor compared to normal	To identify specific deficiencies and direct therapeutic management
Protein C level	Variable Typically 60%–150% of reference value	Level of protein C in the blood	Vitamin K dependent Increases with age Values higher in males than females Deficiency associated with thromboembolism in people <50 y of age
Protein S level	Variable Typically 60%–150% of reference value	Level of protein S in the blood	Vitamin K dependent Increases with age Values higher in males than females Deficiency associated with thromboembolism in people <50 y of age
Factor V Leiden (FVL)	Variable	Screening test looks for activated protein C resistance, and confirmatory test analyzes DNA sequence of factor V gene	FVL not inactivated by activated protein C Heterozygotes have 7× and homozygotes have a 20× increased lifetime risk of venous thrombosis Mutation associated with thromboembolism in people <50 y of age
		Screening assay uses activated partial thromboplastin time with and without added activated protein C	
Antithrombin level	Variable depending on specific test Typically 20–45 milligrams/dL (200–450 milligrams/L)	Measures level of antithrombin in the blood	Not vitamin K dependent; patients with deficiency require higher dosages of heparin for anticoagulation therapy Deficiency associated with thromboembolism in people <50 y of age
Antiphospholipid antibodies	IgG <23 GPL units/mL and IgM <11 MPL units/mL	Tests for antibodies that bind to phospholipids Lupus anticoagulant Anticardiolipin antibody	*Lupus anticoagulant*: elevated in systemic lupus erythematosus (SLE) and other autoimmune diseases *Anticardiolipin antibody*: elevated in SLE, other autoimmune diseases, syphilis, and Behçet's syndrome Increased risk of spontaneous abortions, fetal loss, and fetal growth retardation
Anti–factor Xa activity	During LMWH therapeutic use: 0.5–1.1 IU/mL During LMWH prophylactic use: 0.2–0.5 IU/mL	Inhibition of factor Xa activity	Used to monitor LMWH therapy and determine levels of rivaroxaban, apixaban, and edoxaban using agent-specific calibration. May be elevated in renal dysfunction
Platelet function assay	88–183 s Variable	Tests for platelet adhesion and aggregation	Affected by uremia, anemia, thrombocytopenia, antiplatelet medications, and von Willebrand's disease
			Initial test done with epinephrine. A prolonged test is repeated using ADP, and if normal (<122 s), indicates probable aspirin effect
Peripheral blood smear	Qualitative and quantitative based on visualization	Estimates quantity and appearance of platelets, WBCs, and red blood cells	Allows identification of clumped platelets, abnormal cells interfering with coagulation (leukemia)
			Operator dependent
Dilute Russell viper venom time	23–27 s	Venom directly activates factor X and converts prothrombin to thrombin when phospholipid and factor V are present	Prolonged in the presence of antiphospholipid antibodies
Inhibitor screens	Variable	Verifies the presence or absence of antibodies directed against one or more of the coagulation factors	*Specific inhibitors*: directed against one coagulation factor, most commonly against factor VIII
			Nonspecific inhibitors: directed against more than one coagulation factor; example is lupus-type anticoagulant
Des-γ-carboxyprothrombin or PIVKA II (protein induced by vitamin K absence or antagonism) test	Variable	Measures inactive under-carboxylated form of prothrombin	Increased in vitamin K–deficient states, such as hemorrhagic disease of the newborn
			Increased in overdoses of warfarin or cholestatic liver diseases that can respond to vitamin K therapy

Abbreviations: ADP = adenosine diphosphate; GPL = 1 microgram of affinity-purified immunoglobulin G anticardiolipin antibody from an original index serum; IgM = immunoglobulin M; MPL = 1 microgram of affinity-purified immunoglobulin M anticardiolipin antibody from an original index serum; LMWH = low-molecular-weight heparin.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 233

Acquired Bleeding Disorders

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INTRODUCTION

Bleeding is regulated by a complex process involving platelets and the coagulation system (see Chapter 232, "Hemostasis"). Platelet defects typically manifest with petechiae and mucosal bleeding, whereas coagulation defects usually present as spontaneous or excessive hemorrhage. Management of significant acquired bleeding disorders should be discussed with a hematologist because there are often subtleties in diagnosis and treatment.

ACQUIRED PLATELET DEFECTS

Circulating platelets provide the initial defense against bleeding. Acquired platelet disorders may be quantitative (decreased number of circulating platelets) or qualitative (poorly functioning platelets). Both significant thrombocytopenia and qualitative platelet dysfunction are commonly manifested by the presence of nonpalpable petechiae, often most pronounced in the lower extremities and in areas where blood flow is restricted. Other typical findings may include purpura, mucosal bleeding (gingival, epistaxis), menorrhagia, hemoptysis, hematuria, and hematochezia, whereas deep tissue bleeding and hemarthrosis are less common.

Securing circulatory stability is the primary treatment priority in the bleeding patient. Once done, perform the history, physical examination, and directed laboratory testing to define the clinical syndrome. Recent illness, symptoms, and medications are potentially relevant in the patient who appears to have a platelet disorder. Physical examination should assess for additional bleeding sites and the type of bleeding. Assess for lymphadenopathy, splenomegaly, rash, pallor, or jaundice that suggests diagnoses such as leukemia, lymphoma, systemic lupus erythematosus, infectious mononucleosis, or hemolytic anemia.

THROMBOCYTOPENIA

Quantitative defects that result in thrombocytopenia are caused by decreased production, increased destruction, splenic sequestration, platelet loss, or a combination (**Table 233-1**).[1] The etiologies of thrombocytopenia are diverse, and the pathologic mechanism is not always initially clear. Viral infections may impair thrombopoiesis due to direct infection of the megakaryocyte, toxic effects of viral proteins or cytokines, hemophagocytosis, or production of antibodies that bind to platelets and enhance immune destruction.[2] A drug history is important, because many medications have been implicated in causing thrombocytopenia or impairing platelet function (**Table 233-2**).[3-5]

A CBC will establish the presence and degree of thrombocytopenia and also indicate whether other hematologic cell lines are affected. A peripheral smear can assess platelet morphology and evaluate other cell lines. Rarely, in vitro platelet agglutination occurs, which leads to spuriously low platelet counts reported by automated cell counters (pseudothrombocytopenia) when collected in ethylenediaminetetraacetic acid–coated blood tubes; this can be detected by the presence of platelet clumping on a peripheral smear. In this case, a correct platelet count may be obtained by using citrated or heparin-anticoagulated blood tubes.

Testing for human immunodeficiency virus, hepatitis C virus, and *Helicobacter pylori* is recommended in cases of isolated thrombocytopenia, as low platelets may be the only readily apparent manifestation in early infections.[6] If the etiology of low platelets remains unclear, further laboratory testing to evaluate for disorders such as hemolysis and disseminated intravascular coagulation (DIC) may be needed. Although usually not necessary in instances of isolated thrombocytopenia, bone marrow biopsy may be obtained when malignancy or other bone marrow pathologies are of concern.

When circulating platelet levels decrease to below 10,000 to 20,000/mm^3 (10 to 20 × 10^9/L), the risk of spontaneous bleeding becomes concerning, particularly for intracranial hemorrhage. Additional risk factors for bleeding include age, comorbid illness (e.g., renal disease, liver disease, connective tissue disease, peptic ulcer disease, hypertension), fall risk, and lifestyle activity. Platelet transfusion in the nonbleeding patient is usually considered when counts fall below 10,000/mm^3 (10 × 10^9/L).[7] The cause of the platelet deficiency may also influence the risk of bleeding. At a given platelet level, patients with immune thrombocytopenia (ITP) typically bleed less than patients with aplastic anemia, as the younger platelets present in ITP are more effective in hemostasis.[6]

Immune Causes of Thrombocytopenia ITP is an acquired immune-mediated disorder in which circulating platelets typically fall to very low levels.[3,8] ITP results from antiplatelet antibodies that attack platelet

TABLE 233-1 Pathophysiology of Acquired Thrombocytopenia

Mechanism	Associated Clinical Conditions
Decreased platelet production	Marrow infiltration (tumor or infection) Viral infections (rubella, HIV, hepatitis C, others) Drugs (Table 233-2) Radiation Vitamin B_{12} and/or folate deficiency
Increased platelet destruction	Immune thrombocytopenia Thrombotic thrombocytopenic purpura Hemolytic-uremic syndrome Disseminated intravascular coagulation Viral infections (HIV, mumps, varicella, Epstein-Barr virus) Drugs (Table 233-2)
Platelet loss	Excessive hemorrhage Hemodialysis, extracorporeal circulation
Splenic sequestration	Sickle cell disease, cirrhosis

Abbreviation: HIV = human immunodeficiency virus.

TABLE 233-2 Drugs That Produce Thrombocytopenia or Impair Platelet Function

Produce Thrombocytopenia*	Impair Function
Heparin	Aspirin
Gold salts	NSAIDs
Sulfa-containing antibiotics	Clopidogrel, prasugrel, and ticagrelor
Quinine and quinidine	Penicillins and cephalosporins
Ethanol (chronic use)	Calcium channel blockers
Vancomycin	β-Adrenergic blockers: propranolol
Ibuprofen	Nitroglycerin
Rifampin	Antihistamines
Abciximab and eptifibatide	Phenothiazines
Thiazides and furosemide	Cyclic antidepressants
Penicillins/cephalosporins	
Procainamide	
Cimetidine and ranitidine	
Valproate and carbamazepine	

*Many other drugs may also cause thrombocytopenia. The above list shows drugs with the most evidence.



A B

FIGURE 233-1. Two patients with primary immune thrombocytopenic purpura. **A.** Petechiae with platelet count of 3000/mm^3 (3 × 10^9/L). **B.** Gingival bleeding with platelet count of 5000/mm^3 (5 × 10^9/L). [Image used with permission of J. Stephan Stapczynski, MD.]

surface glycoproteins such as glycoprotein IIb/IIIa, leading to peripheral platelet destruction. There is evidence that the same antibodies lead to impaired platelet production by megakaryocytes.[9] Despite very low platelet counts, the circulating platelets are not functionally impaired.

ITP may be classified as primary (formerly known as *idiopathic thrombocytopenic purpura*) or secondary when associated with other medical conditions (autoimmune disorders, infections) or drug exposures.[8] This distinction is of clinical importance, as management of the underlying disorder or discontinuation of the drug in cases of secondary ITP may lead to normalization of the platelet count.

Primary ITP may occur at any age, with equal prevalence between genders, with the exception of those age 30 to 60 years, in which women predominate. Primary ITP is classified by duration of illness: newly diagnosed (diagnosis to 3 months), persistent (3 months to 12 months), and chronic (>12 months).[8] The majority of adults with primary ITP progress to chronic illness.

The most common presenting sign of ITP is a petechial rash (**Figure 233-1A**). Mild epistaxis, gingival bleeding (**Figure 233-1B**), and menorrhagia in women of childbearing age may also be seen. Except for petechiae and bruising, the patient should have a normal physical examination.

The CBC should demonstrate normal cell lines except for the platelets. A mild anemia may be seen if bleeding has been persistent. The peripheral smear should show large, well-granulated platelets, although they will be few in number. Bone marrow biopsy is not indicated unless clinical features are atypical. If the evaluation supports the diagnosis of primary ITP, then additional testing in the ED is not required.

Treatment for ITP is initiated based on the risk of bleeding (**Table 233-3**). Major bleeding is uncommon when platelets are >50,000/mm^3 (>50 × 10^9/L). As most fatal bleeding complications occur when platelet counts fall below 30,000/mm^3 (30 × 10^9/L), experts and guidelines recommend this level as the threshold for initiating treatment of ITP in adults.[6,7,9-11] Bleeding risk correlates with lower platelet counts and patient age greater than 60, a prior history of bleeding, chronic renal or liver illnesses, and use of medications that alter hemostasis. For all patients with primary ITP, minimize bleeding risk by avoiding use of antiplatelet medications when possible, maintaining good blood pressure control, optimizing control of comorbid conditions (e.g., liver disease, renal disease), and addressing fall risks.

About two thirds of children with primary ITP will have spontaneous resolution within 6 months of diagnosis.[11] An antecedent viral infection is commonly reported. Additionally, the measles-mumps-rubella vaccination has been associated with the development of acute ITP, although this is rare, occurring in less than 1 per 25,000 doses given.[12] The risk of severe bleeding complications appears to be rare in children, regardless of their absolute platelet count.[6,8,13] Children without signs of active bleeding and good psychosocial support typically do not require hospitalization or medical treatment. Good anticipatory guidance should be provided to the family, and the child should abstain from contact sports or activities that might place them at risk for head injury.

First-line treatment for primary ITP generally includes corticosteroids, typically prednisone for 4 weeks (shorter courses may be considered for children),[6,9-11,13] or alternatively high-dose dexamethasone IV pulse therapy.[6] Initial response may not be seen for 4 to 14 days, and peak effect can be expected between 7 and 28 days. IV immunoglobulin may also be considered, either alone or in combination with corticosteroids. Initial response to IV immunoglobulin is more rapid than corticosteroids, occurring between 1 and 3 days, with peak effect seen between 2 and 7 days. Side effects of IV immunoglobulin include aseptic meningitis, transient neutropenia, acute kidney injury, and transfusion reactions/hypotension.

Second-line treatment modalities include splenectomy and use of newer agents, such as the monoclonal antibody rituximab, which blunts the autoimmune destruction of platelets, and thrombopoietin receptor agonists, which stimulate platelet production (i.e., romiplostim, eltrombopag).

In the event of life-threatening hemorrhage where hemostasis must be achieved rapidly, IV corticosteroids (such as dexamethasone) and IV immunoglobulin should be administered concomitantly.[13] Platelet transfusions should be initiated, and doses two to three times the typical dose might be required due to persistent autoimmune destruction.[7] Platelet

TABLE 233-3 Treatment of Immune Thrombocytopenia

Platelet transfusion	<10,000–20,000/mm^3 (<10–20 × 10^9/L) prophylactically to prevent bleeding
	<50,000/mm^3 (<50 × 10^9/L) if actively bleeding
	<20,000–50,000/mm^3 (<20–50 × 10^9/L) if patient requires diagnostic puncture
	<50,000–100,000/mm^3 (<50–100 × 10^9/L) if patient requires invasive procedure
Corticosteroids	Prednisone, 1 milligram/kg PO per day for 21 days then tapered *or* Dexamethasone, 20 milligrams/m^2 IV per day for 4 d
IV immunoglobulin	1 gram/kg IV per day for 3 d
Splenectomy	Considered for refractory cases

transfusions may need to be repeated frequently until bleeding subsides or targeted treatment modalities take effect. Emergent splenectomy may be considered if all other treatment options are exhausted.

Drug-Induced Immune Thrombocytopenia Over 200 drugs have been implicated in causing immune-mediated suppression of platelet production, increased platelet destruction, or platelet aggregation (Table 233-2).[3-5] The clinical presentation is similar to ITP, and the thrombocytopenia may be severe. Drug-induced thrombocytopenia typically occurs 5 to 14 days following initiation of a drug but may occur sooner if there has been recent prior exposure. A careful history should include not only prescribed medications but also herbal remedies, foods, and beverages (e.g., quinine in tonic water, alcohol). Chronic alcohol use is a common cause of thrombocytopenia. Platelet counts typically normalize with cessation of the causative agent. Heparin-induced thrombocytopenia causes a significant drop in platelets, but patients are paradoxically hypercoagulable due to platelet activation (see Chapter 239, "Thrombotics and Antithrombotics").

Nonimmune Causes of Thrombocytopenia Thrombocytopenia may occur from non–immune-mediated causes (Table 233-1). Drugs may cause platelet aggregation as well as decreased production.[4] In thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, thrombotic microangiopathy occurs when vessel injury results in deposition of platelet-fibrin thrombi (see Chapter 144, "Hematologic Emergencies in Infants and Children," and Chapter 237, "Acquired Hemolytic Anemia"). DIC is also a well-described cause of platelet destruction. In patients with marked hemorrhage, large-volume fluid resuscitation may lead to a dilutional thrombocytopenia. Additionally, bacterial, rickettsial, and viral infections can cause direct toxic destruction of platelets. Thrombocytopenia specific to pregnancy may be a result of the hemolysis–elevated liver enzymes–low platelets (HELLP) syndrome, preeclampsia, gestational thrombocytopenia (see Chapter 100, "Maternal Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period"), or ITP. Finally, an enlarged spleen can sequester a significant portion of the platelet pool.

Thrombocytopenia is present in up to 70% of patients with chronic liver disease.[14] The etiology appears multifactorial. Patients often have underlying medical conditions related to their liver disease such as alcohol use, viral hepatitis, or nutritional deficiencies that impair platelet production. Thrombopoietin, which is produced by hepatocytes, may be decreased. Portal hypertension may lead to splenic sequestration. Endotoxemia from infection may promote platelet aggregation. Some patients also demonstrate platelet autoantibodies. The degree of quantitative thrombocytopenia may be mitigated by an increased level of circulating von Willebrand factor that is common in patients with chronic liver disease, which promotes platelet adhesion. For this reason, routine platelet transfusion is not recommended in the absence of clinically significant bleeding. However, a platelet count of >50,000/mm^3 (>50 × 10^9/L) should be achieved prior to invasive procedures (e.g., lumbar puncture, surgery, liver biopsy).[15]

FUNCTIONAL PLATELET DISORDERS

Several disease processes can cause acquired qualitative or functional abnormalities of platelets (**Table 233-4**).[16] In the myeloproliferative diseases, platelets are often dysfunctional, even if the platelet count is normal or elevated. Patients can have prolonged bleeding times and clinically significant bleeding. To control acute bleeding, transfusion should be considered to raise the level of normal platelets to 50,000/mm^3 (50 × 10^9/L). In macroglobulinemia and related disorders, the elevated level of viscous proteins interferes with platelet function. Patients with clinically significant bleeding may require plasmapheresis to reduce the protein level and correct hemostatic function.

TABLE 233-4 Clinical Conditions Associated With Qualitative Platelet Abnormalities

- Uremia
- Liver disease
- Disseminated intravascular coagulation
- Antiplatelet antibodies (immune thrombocytopenia, systemic lupus erythematosus)
- Cardiopulmonary bypass
- Myeloproliferative disorders (thrombocytosis, polycythemia vera, chronic myeloid leukemia, acute lymphocytic or myelogenous leukemia)
- Dysproteinemias (multiple myeloma, Waldenström's macroglobulinemia)
- von Willebrand's disease (congenital or acquired)

TABLE 233-5 Duration of Antiplatelet Drug Activity

Drug	Time to Full Effect	Time to Full Recovery of Platelet Function	Drug Elimination Half-Life
Aspirin 325 milligrams PO single dose or 100 milligrams PO daily	1 h	4 d	3 h
Ibuprofen 400 milligrams PO single dose	1 h	8 h	2 h
Naproxen 220 milligrams PO single dose	1 h	2 d	12–17 h
Clopidogrel 600 milligrams PO loading dose and 75 milligrams PO daily maintenance	2–4 h	7 d	6 h

Many drugs can influence platelet function (Table 233-2 and **Table 233-5**). Of these, the most commonly used are aspirin, which produces an irreversible impairment in platelet aggregation, and the NSAIDs, clopidogrel and prasugrel, which produce impairment in platelet adhesion and aggregation (see Chapter 239, "Thrombotics and Antithrombotics"). Desmopressin can be used to reduce perioperative bleeding if urgent surgery is necessary in patients on antiplatelet drugs.[17]

Thrombocytosis, a platelet count exceeding 500,000/mm^3 (500 × 10^9/L), can be seen in inflammatory reactions, malignancy, polycythemia, and postsplenectomy. Platelet function can be normal or abnormal depending on the underlying condition. Therefore, thrombocytosis can be associated with bleeding (mucosal) or thromboembolic (deep venous thrombosis, portal or mesenteric thrombosis, splenic vein thrombosis) manifestations. However, these events are unusual, even with platelet counts in excess of 1,000,000/mm^3 (1000 × 10^9/L).

ACQUIRED COAGULATION DISORDERS

Acquired coagulation disorders can result from underlying medical disease and autoimmune factor inhibitors.

LIVER DISEASE

Acute and chronic liver disease is commonly associated with laboratory tests demonstrating impaired coagulation. Hepatocytes synthesize all of the coagulation factors and related regulatory proteins, with the exception of factor VIII and von Willebrand factor. Diseases affecting the hepatic parenchyma may result in a decreased synthesis of these factors, including the vitamin K–dependent carboxylation of factors II (prothrombin), VII, IX, and X. Because vitamin K is a fat-soluble vitamin, malabsorption can occur with processes that interfere with the absorption of fat-soluble vitamins, including impaired bile acid metabolism (i.e., primary biliary cirrhosis), intrahepatic or extrahepatic cholestasis, and treatment with bile acid binders. Thus, prolonged prothrombin time (PT) is common in patients with decompensated hepatic function.

Despite marked prolongations of PT and activated partial thromboplastin time (aPTT) seen in advanced liver disease and cirrhosis, these tests poorly predict onset and severity of bleeding, including bleeding from esophageal varices or invasive procedures or surgery.[15,18-20] Although there may be marked reduction in procoagulant proteins in liver disease, there is typically a parallel decrease in the endogenous anticoagulant proteins such as protein C and antithrombin. Therefore, primary hemostasis may be relatively maintained. In fact, patients with liver disease may be

susceptible to thrombosis; patients with liver disease and cirrhosis are twice as likely to develop unprovoked deep venous thrombosis and have a relatively high incidence of portal venous thrombosis.[21]

In the actively bleeding patient with liver disease, attention to volume and circulatory status is paramount. Transfusion of packed red blood cells should be used to maintain an adequate hemoglobin and hemodynamic stability. Fresh frozen plasma transfusions or platelets should be transfused if significant hemorrhage (e.g., from esophageal varices) is associated with a coagulopathy or thrombocytopenia with a platelet count below 60,000/mm^3 (60 × 10^9/L).[15] Plasma transfusions should be used cautiously because they may incite thrombosis and expand intravascular volume, exacerbating portal hypertension and increasing the severity of variceal bleeding. There is no evidence that coagulation factor VIIa (recombinant) or prothrombin complex concentrate (human) provides benefit.[22] The benefit of vitamin K in these patients has also been called into question, and its routine use is not substantiated.[22,23] Treatment may be guided by whole-blood viscoelastic hemostasis assays.

Primary prevention of bleeding in patients with liver disease should focus on medical optimization of their risk factors, rather than treatment of abnormal tests of coagulation or thrombocytopenia.[15,18] These include management and prevention of portal hypertension, treatment of esophageal varices, management of primary causes for liver disease (i.e., alcohol use, hepatitis C), optimization of renal function, and management and prevention of sepsis or infection.

RENAL DISEASE

Patients with renal disease frequently manifest disorders of hemostasis. Early renal impairment has been associated with a tendency for thrombosis relating to increased production of procoagulant factors as well as decreased formation of tissue plasminogen activator.[24] In advanced renal disease, bleeding complications are of particular concern due to qualitative platelet dysfunction from decreased ability to adhere to damaged endothelium and aggregate. Patients with chronic kidney disease are at increased risk for minor bleeding (mucosal and cutaneous) and major bleeding (intracerebral and GI hemorrhage). Routine tests of hemostasis—PT, aPTT, and platelet counts—are often normal, although bleeding time will usually be prolonged. Abnormalities in platelet function can be due to direct effects of uremic toxins and impaired drug elimination. Anemia itself has been associated with platelet dysfunction. Thrombocytopenia can occur from dialysis, and the heparin used may also potentiate bleeding.

Desmopressin is the most common agent used to correct bleeding in patients with uremic platelet dysfunction, producing an increase in serum von Willebrand factor and enhancing the platelet's ability to aggregate.[25] The dose is 0.3 milligram/kg SC or IV, with a rapid onset and duration of action lasting at least 4 hours. Side effects are generally mild and include headache, flushing, minor hypotension, tachycardia, nausea, abdominal cramps, and local site reaction. Other strategies that improve platelet function include the use of cryoprecipitate, conjugated estrogens (0.6 milligram/kg IV daily), erythropoietin to improve anemia, and hemodialysis to remove toxins.[24] Platelet transfusions alone are generally ineffective because the infused platelets quickly acquire the platelet defect. Life-threatening bleeding in renal failure patients is treated using the combination of cryoprecipitate, platelet transfusions, packed red blood cell transfusions, desmopressin, and conjugated estrogens.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is an acquired syndrome characterized by inappropriate and widespread activation of the coagulation system resulting in intravascular thrombin generation, small vessel thrombosis, and consumption of clotting factors and platelets.[26] Concomitant activation of the fibrinolytic system also occurs, resulting in the breakdown of fibrin clots and subsequent bleeding. DIC is associated with a variety of precipitating disorders (**Table 233-6**).

TABLE 233-6 Common Conditions Associated With Disseminated Intravascular Coagulation (DIC)

Clinical Setting	Comments
Infection Bacterial Viral Fungal	Probably the most common cause of DIC; 10%–20% of patients with gram-negative sepsis have DIC; endotoxins stimulate monocytes and endothelial cells to express tissue factor; Rocky Mountain spotted fever causes direct endothelial damage; DIC more likely to develop in asplenic patients or patients with cirrhosis; septic patients are more likely to have thrombosis than bleeding.
Carcinoma Adenocarcinoma Lymphoma	Malignant cells may cause endothelial damage and allow the expression of tissue factor as well as other procoagulant materials; most adenocarcinomas tend to have thrombosis (Trousseau's syndrome), whereas prostate cancer tends to have more bleeding; DIC is often chronic and compensated.
Acute leukemia	DIC most common with promyelocytic leukemia; blast cells release procoagulant enzymes; there is excessive release at time of cell lysis (chemotherapy); more likely to have bleeding than thrombosis.
Trauma	DIC especially with brain injury, crush injury, burns, hypothermia, hyperthermia, rhabdomyolysis, fat embolism, hypoxia. Massive bleeding can occur.
Organ injury Liver disease Pancreatitis	May have chronic compensated DIC; acute DIC may occur in the setting of acute hepatic failure; tissue factor is released from the injured hepatocytes. Pancreatitis can activate the coagulation cascade.
Pregnancy	Placental abruption, amniotic fluid embolus, septic abortion, intrauterine fetal death (can be chronic DIC); can have DIC in hemolysis–elevated liver enzymes–low platelets (HELLP) syndrome.
Vascular disease	Large aortic aneurysms (chronic DIC can become acute at time of surgery), giant hemangiomas, vasculitis, multiple telangiectasias.
Envenomation	DIC can develop with bites of rattlesnakes and other vipers; the venom damages the endothelial cells; bleeding is not as serious as expected from laboratory values.
Acute lung injury (ALI) or adult respiratory distress syndrome	Microthrombi are deposited in the small pulmonary vessels; the pulmonary capillary endothelium is damaged; 20% of patients with ALI develop DIC, and 20% of patients with DIC develop ALI.
Transfusion reactions, such as acute hemolytic reaction	DIC with severe bleeding, shock, and acute renal failure.

Pathogenesis The common pathway of illnesses that precipitate DIC is an inappropriate loss of localization or compensated control with the intravascular activation of coagulation (**Figure 233-2**). Immune, inflammatory, and coagulant pathways are involved. Damaged endothelial cell walls trigger activation of the intrinsic clotting cascade, leading to thrombin generation and subsequent intravascular fibrin clot deposition. Increased thrombin generation leads to consumption of anticoagulant regulatory proteins (i.e., protein C, protein S, and antithrombin), further potentiating thrombosis and ischemic tissue damage. Production of thrombin and fibrin indirectly activates tissue plasminogen activator and the counterregulatory fibrinolytic system. When hyperfibrinolysis occurs, the hemostatic clots dissolve and bleeding ensues.

Clinical Features Clinical features of DIC vary with the underlying precipitating illness.[27] Hypercoagulation may predominate in certain conditions such as sepsis, where signs of ischemic end-organ failure are common, and physical findings in these patients may include cutaneous gangrene or thrombotic purpura. In other instances, such as DIC associated with leukemia, hyperfibrinolysis may predominate and clinical features may include petechiae, ecchymoses, oozing from catheter or venipuncture sites, or hematuria. Certain DIC-related disorders such as trauma and obstetric complications tend to have both strong hypercoagulation and hyperfibrinolysis elements and lead to major bleeding complications (e.g., wounds, intracranial, GI). Yet other conditions may

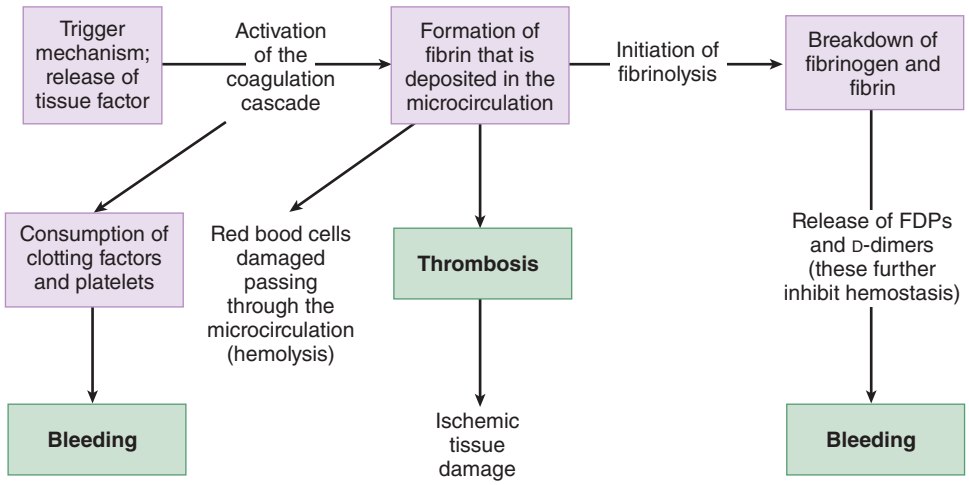

FIGURE 233-2. Pathophysiology of disseminated intravascular coagulation. Refer to "Pathogenesis" section under "Disseminated Intravascular Coagulation" for details. FDPs = fibrin/fibrinogen degradation products.

be associated with mild and compensated DIC in which signs of thrombosis and bleeding are subclinical.

Laboratory Findings The typical laboratory results in acute DIC (**Table 233-7**) include thrombocytopenia, prolonged PT, low fibrinogen level, and elevation of fibrin-related markers (i.e., D-dimer, fibrin degradation products, soluble fibrin). The most commonly observed abnormality is thrombocytopenia; a progressive drop in the platelet count is sensitive, although not specific, for DIC. Depletion of coagulation factors is reflected by a prolonged PT. Fibrinogen is an acute-phase reactant and may be normal or elevated in early DIC. Scoring systems have been developed and validated to aid in the diagnosis (**Table 233-8**).[27,28]

Differential Diagnosis Primary fibrinolysis is a rare syndrome where plasmin is generated and fibrinolysis occurs without the production of thrombin. Severe liver disease will also manifest with coagulation abnormalities and low platelets. These two entities can be differentiated from DIC based on clinical history and laboratory tests. The hematologic abnormalities in liver disease should be relatively stable in contrast to the worsening abnormalities associated with acute DIC. Additionally, the D-dimer assay will usually be normal or minimally elevated in both primary fibrinolysis and liver disease but is often significantly elevated in DIC.

Treatment Paramount to the management of DIC is the control of the underlying disorder whenever possible. Treatment strategies in DIC include blood product support and strategies to modulate thrombin formation (**Table 233-9**).[26,27,29] Generally speaking, blood products should only be administered when there is evidence of bleeding.

Platelet transfusions are recommended in actively bleeding patients who have platelet counts below 50,000/mm^3 (50 × 10^9/L) and may be considered in those considered to be at high risk for bleeding (such as DIC resulting from chemotherapy) when platelet counts fall below 20,000/mm^3 to 30,000/mm^3 (20 to 30 × 10^9/L).[29] Fresh frozen plasma should be administered in bleeding patients when PT/aPTT exceeds 1.5 times normal or when fibrinogen levels fall below 100 milligrams/dL (1 gram/L). The initial recommended dose is 15 mL/kg, although there is some evidence that 30 mL/kg may be superior when volume overload

TABLE 233-7 Laboratory Abnormalities Characteristic of Disseminated Intravascular Coagulation (DIC)[28]

Studies	Result
Most Useful	
Platelet count	Usually low, or dropping
Prothrombin time (PT)	Prolonged
Fibrinogen level	Usually low (fibrinogen is an acute-phase reactant, so may actually start out elevated), fibrinogen level <100 milligrams/dL (<1 gram/L) correlates with severe DIC
Fibrin degradation products and D-dimer*	Elevated
Helpful	
Activated partial thromboplastin time (aPTT)	Usually prolonged
Thrombin clotting time (TCT)	Prolonged (not sensitive)
Fragmented red blood cells	Should be present (not specific)
Specific factor assays	Extrinsic pathway factors are most affected (VII, X, V, and II)
Factor II, V, VII,† X	Low
Factor VIII (acute-phase reactant)	Low, normal, high
Factor IX	Low (decreases later than other factors)

*Levels may be chronically elevated in patients with liver or renal disease.

† Factor VII is usually low early because it has the shortest half-life.

TABLE 233-8 International Society on Thrombosis and Haemostasis Scoring System for Disseminated Intravascular Coagulation (DIC) When Associated Condition Known to Cause DIC Is Present[27]

Test	Points
Platelet count	
>100,000/mm^3 (>100 × 10^9/L)	0
50,000–100,000/mm^3 (50–100 × 10^9/L)	1
<50,000/mm^3 (<50 × 10^9/L)	2
Fibrin-related marker (D-dimer, fibrin degradation products)	
Normal	0
Mildly elevated (<5 times upper limit of normal)	2
Markedly elevated (>5 times upper limit of normal)	3
Prothrombin time prolongation	
<3 s	0
3–6 s	1
>6 s	2
Fibrinogen level	
>100 milligrams/dL (>1 gram/L)	0
<100 milligrams/dL (<1 gram/L)	1

Note. A score of ≥5 is compatible with overt DIC. A score <5 is suggestive (not affirmative) for nonovert DIC.

TABLE 233-9 Treatment of Disseminated Intravascular Coagulation (DIC)

- Treat underlying precipitating disorder: volume resuscitation, antibiotics, external cooling
- Platelet transfusions for thrombocytopenia <50,000/mm^3 (<50 × 10^9/L) and active bleeding
- Fresh frozen plasma for prolonged PT or aPTT (>2 times normal) or low fibrinogen (<100 milligrams/dL [1 gram/L]) and active bleeding
- Fibrinogen concentrate for persistent low fibrinogen <100 milligrams/dL (<1 gram/L)
- Vitamin K for prolonged PT
- Consider venous thromboembolism prophylaxis with LMWH
- Consider tranexamic acid for trauma-related DIC

Abbreviations: aPTT = activated partial thromboplastin time; LMWH = low-molecular-weight heparin; PT = prothrombin time.

is not of concern. Fibrinogen concentrate should be considered when hypofibrinogenemia persists despite use of plasma. Patients with a prolonged PT should receive parenteral vitamin K.

There is no proven benefit in DIC with other coagulation factor products, such as prothrombin complex concentrate (human) or coagulation factor VIIa (recombinant). Due to high risk of thrombosis in DIC, low-molecular-weight heparin is recommended in patients with DIC when bleeding is absent and platelet counts exceed 30,000/mm^3 (30 × 10^9/L).[29] Antifibrinolytic medications (e.g., tranexamic acid) should generally be avoided in patients with DIC. One notable exception is in trauma-related DIC, where their use reduces mortality.[30]

CIRCULATING INHIBITORS OF COAGULATION

Acquired inhibitors of blood coagulation, also known as *circulating anticoagulants*, are antibodies directed against one or more of the coagulation factors. Although inhibitors may develop spontaneously in previously healthy patients with normal hemostasis, most inhibitors develop in patients with hereditary bleeding disorders who receive transfusion of plasma products. Inhibitors have been described for most of the coagulation factors; the two most common inhibitors are factor VIII inhibitors and antiphospholipid antibodies. Factor VIII inhibitors are "specific" inhibitors, directed only against factor VIII, as opposed to antiphospholipid antibodies, including lupus anticoagulant and anticardiolipin antibodies, which are "nonspecific" inhibitors directed against several of the coagulation factors. Lupus anticoagulant and anticardiolipin antibodies often result in thrombosis (see Chapter 234, "Clotting Disorders").

Factor VIII Inhibitors Factor VIII inhibitors most commonly develop in patients with hemophilia A (see Chapter 235, "Hemophilias and von Willebrand's Disease") but can also develop spontaneously in patients with previously normal hemostasis, a condition termed *acquired hemophilia A*.[31] Although rare, it is important to recognize this clinical entity because the mortality rate is over 20%. Approximately 85% of acquired hemophilia A cases occur in the elderly. In about half of cases, inhibitors develop in association with malignancy, autoimmune disorders, pregnancy, drugs (interferon, clopidogrel), blood transfusions, or infections.

Patients who develop factor VIII inhibitors can present with massive spontaneous ecchymoses, hematomas, and hematuria. Laboratory studies classically show a normal PT, normal thrombin clotting time, and a greatly prolonged aPTT that does not correct with mixing. A factor VIII–specific assay will show very low or absent factor VIII activity.

A hematologist should direct the management of an acute, clinically significant bleeding episode. Treatment options include administration of factor VIII, prothrombin complex concentrate (human), FEIBA (anti-inhibitor coagulant complex), coagulation factor VIIa (recombinant), desmopressin acetate, and tranexamic acid.[31-33] Additionally, the use of aspirin, NSAIDs, and intramuscular injections should be avoided and conservative therapies should be considered, including compression and immobilization of the bleeding site.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 234

Clotting Disorders

Jessie G. Nelson

THROMBOPHILIA

INTRODUCTION

Most patients develop arterial or venous thromboses because of local factors (e.g., a focal atherosclerotic lesion producing a thrombus in a coronary artery) or major systemic events (e.g., trauma, surgery, or prolonged immobilization). However, several inherited genetic mutations and acquired conditions predispose patients to venous thromboembolism with some studies finding up to 50% of patients with unprovoked venous thromboembolism having a hypercoagulable disorder or thrombophilia (**Table 234-1**).[1] No specific risk factor or condition guarantees abnormal thrombosis. Rather, similar to seizures, patients have a varying threshold for clotting. Risks for clotting from genetic, acquired, and environmental factors are additive and, in some cases, multiplicative.[2]

PATHOPHYSIOLOGY

Several physiologic systems ensure that blood clots do not extend beyond the necessary area. The two most clinically important pathways involve antithrombin and protein C (**Table 234-2**). Antithrombin (also called antithrombin III) is a plasma-based protein that inhibits several activated coagulation factors, primarily thrombin, factor Xa, and factor IXa. Both unfractionated heparin and low-molecular-weight heparin possess anticoagulant activity by increasing the rate by which antithrombin inhibits these factors: approximately 2000- to 4000-fold for thrombin, about 500- to 1000-fold for factor Xa, and about a million-fold for factor IXa. Protein C is a vitamin K–dependent plasma protein that binds to the endothelial cell surface and is activated by thrombin. Activated protein C cleaves both factor Va and factor VIIIa, inhibiting both the common pathway and the intrinsic pathway. Protein S, another vitamin K–dependent plasma protein, is a cofactor that increases the inhibitory action of activated protein C by about 20-fold.

DIAGNOSIS

Thrombophilic disorders are rarely diagnosed in the ED. Instead, the emergency physician's primary responsibilities are to suspect the thrombophilia, recognize higher risk of thrombosis in patients with a known thrombophilia, obtain pertinent information to suspect an undiagnosed prothrombotic state, refer for evaluation, and appropriately manage acute thrombosis (**Table 234-3**).[3]

Laboratory testing specific for hypercoagulable conditions is not helpful in an ED setting.[4] Some factor levels cannot be reliably measured in

TABLE 234-1 Hypercoagulable States

Inherited	Acquired
Activated protein C resistance due to factor V Leiden mutation	Pregnancy
	Medications: Oral contraceptives/hormone replacement therapy, tamoxifen, lenalidomide
Prothrombin gene mutation 20210A	Malignancy
Protein C deficiency	Heparin-induced thrombocytopenia
Protein S deficiency	Antiphospholipid syndrome
Antithrombin deficiency	Warfarin-induced skin necrosis
Hyperhomocysteinemia, severe	Hyperviscosity syndromes
ABO blood type (non-O)	Human immunodeficiency virus (HIV)

TABLE 234-2 Functions of Coagulation Proteins in Protein C and Antithrombin Systems

Factor	Function	Pertinent Disorders
Prothrombin (factor II)	Precursor to thrombin, which converts fibrinogen to fibrin.	Prothrombin mutations, 20210A and others
Factor V, activated	Complexes with factor Xa, calcium, and phospholipid to convert prothrombin to thrombin.	Activated protein C resistance due to factor V Leiden mutation
Protein C, activated	Cleaves activated factors Va and VIIIa.	Congenital protein C deficiency Activated protein C resistance due to factor V Leiden mutation Neonatal purpura fulminans Warfarin-induced skin necrosis
Protein S	Cofactor for activated protein C. Cofactor for tissue factor pathway inhibitor (which inhibits extrinsic pathway of coagulation). Counteracts factor Xa's protection of factor Va from degradation.	Congenital protein S deficiency Neonatal purpura fulminans Warfarin-induced skin necrosis
Antithrombin	Inhibits thrombin, factor Xa, and factor IXa. Binds heparins, leading to increased antithrombin activity.	Antithrombin deficiency
Phospholipids	Present on cell membranes of endothelial cells that line blood vessels. The activity of several proteins in the coagulation cascade is enhanced when bound to phospholipids.	Antiphospholipid syndrome

the setting of acute thrombosis or while the patient is taking a vitamin K antagonist such as warfarin or direct oral anticoagulants.

The ED diagnostic approach to individual episodes of suspected thrombosis in a thrombophilic patient is site specific (e.g., cerebral arterial or venous circulation, coronary circulation, or peripheral venous system). Recorded characteristics in the derivation samples for the Wells Score[5] or Pulmonary Embolism Rule Out Criteria[6] excluded patients with known genetic causes for thrombophilia. Instead of risk stratification tools, use the patient's personal history of venous thromboembolism (phenotypic evidence of thrombophilia). **Using a normal serum D-dimer level to exclude venous thromboembolism in patients with known hypercoagulable disorders has not been validated.**

TREATMENT AND DISPOSITION

Initial management and disposition of individual episodes of confirmed thrombosis in a patient with thrombophilia are similar to those of a patient without known thrombophilia, with exceptions discussed in specific conditions.[7] Patients not currently on anticoagulation should consider prophylactic anticoagulants for high-risk situations such as surgery, pregnancy and the postpartum period, and prolonged travel. Estrogen-based oral contraceptive pills and hormone replacement therapy should be avoided in patients with known thrombophilia because of the thrombotic risk.

TABLE 234-3 Features Suggestive of Thrombophilia

- Early thrombosis (age 45 y and younger)
- Recurrent thrombotic events or fetal loss
- Family history of thrombosis or recurrent fetal loss
- Thrombosis in unusual location (mesenteric, cerebral, axillary, or portal veins)

SPECIFIC CONDITIONS ASSOCIATED WITH THROMBOPHILIA

INHERITED CLOTTING DISORDERS

ACTIVATED PROTEIN C RESISTANCE (FACTOR V LEIDEN)

Activated protein C resistance caused by the factor V Leiden mutation is the most prevalent inherited hypercoagulable disorder; approximately 5% of the U.S. population of European descent is heterozygous for this mutation.[8] In this disorder, the gene for factor V has a single point mutation that makes factor Va resistant to inhibition by activated protein C (factor V Leiden). This leads to overabundant conversion of prothrombin to thrombin. Factor V Leiden is inherited in an autosomal dominant pattern, with most patients being heterozygous for the mutation. Heterozygotes for factor V Leiden have a sevenfold increased risk of deep venous thrombosis compared with noncarriers, with homozygotes having a 20-fold increase in risk. Factor V Leiden is more highly associated with deep vein thrombosis than pulmonary embolism[9] and has been observed in up to 21% of patients with first-time deep venous thrombosis.[10] Activated protein C resistance also produces pregnancy complications such as severe preeclampsia, placental abruption, fetal growth restriction, and stillbirth.

PROTHROMBIN GENE MUTATION

The most common mutation of the prothrombin gene (20210A) leads to increased prothrombin biosynthesis with about a 30% increase in circulating prothrombin levels, creating a prothrombotic state. Prothrombin mutations are inherited in an autosomal dominant manner, with mutations in the prothrombin gene present in about 2% of Caucasians.[2] Heterozygotes account for up to 10% of patients with initial episodes of deep venous thrombosis.[10] Patients with prothrombin gene mutation present with increased risk of venous thromboembolism and pregnancy complications, similar to activated protein C resistance from factor V Leiden.

DEFICIENCIES OF CLOTTING INHIBITORS

Antithrombin Deficiency Several mutations to the antithrombin gene exist, many leading to antithrombin deficiency. Two percent of patients with a history of thrombosis have an antithrombin deficiency,[11] and it is more prevalent in Asian populations. Antithrombin deficiency is classified into two main groups. In type 1, the measured level of antithrombin is diminished, whereas patients with type 2 have a normal amount of antithrombin, but the function is greatly diminished due to conformational changes in the protein. Antithrombin deficiency is inherited in an autosomal dominant fashion. Heterozygous patients have a fivefold increased risk of thrombotic events, typically pregnancy complications and venous thromboembolism. Homozygous antithrombin deficiency is incompatible with life.

Protein C and Protein S Deficiencies Protein C and S deficiencies, like antithrombin deficiency, are transmitted in an autosomal dominant fashion, but with more varied clinical presentations. Prevalence can only be estimated, because not all patients with heterozygous defects develop inappropriate thrombosis. Heterozygous protein C deficiency is thought to be present in 1:250 to 1:500 people, and heterozygous protein S deficiency is estimated to occur in about 1:500 individuals.[12] Homozygous protein C or S deficiency is rare and presents as neonatal purpura fulminans. Patients with heterozygous protein C or S deficiency are at higher risk for venous thromboembolism, and like antithrombin deficiency, these disorders can be associated with either decreased total amount of protein C or S or decreased functional activity. In general, lower function is associated with higher risk and frequency of thrombotic events. Protein C and S deficiency, like antithrombin deficiency, is more prevalent in the Japanese and Chinese populations, with up to 32% percent of Japanese adults with venous thromboembolism having a deficiency of protein C, protein S, or antithrombin.[12]

Patients with heterozygous protein C or S deficiency are at higher risk for warfarin-induced skin necrosis because warfarin inhibits protein C

and S synthesis. Warfarin-induced skin necrosis is rare and is prevented by both avoiding loading doses of warfarin and continuing heparin products until the INR is therapeutic. Therefore, any patient who develops warfarin-induced skin necrosis should be evaluated for protein C or S deficiency. Early evidence suggests direct oral anticoagulants are not as efficacious for protein S deficiency compared to other inherited thrombophilias.[13]

OTHER INHERITED CONDITIONS

Hyperhomocysteinemia is associated with increased risk for various vascular diseases as well as venous thromboembolic disease, primarily through pathogenic effects of elevated homocysteine levels on vasculature.[14] In recent years, mounting evidence exists showing an association between non-O blood groups (i.e., A, B, and AB) and a modest but statistically significant increased risk of both venous and arterial thromboembolic events.[15] The pathogenesis of this interaction is incompletely understood.

ACQUIRED CLOTTING DISORDERS

PREGNANCY AND ESTROGEN USE

The coagulation changes in pregnancy (**Table 234-4**) represent an adaptive measure to prevent excessive hemorrhage with delivery.[16] Many of these changes are anatomic in nature, whereas some are related to the relatively high estrogen state. These changes promoting thrombosis are similar but less profound in women taking oral contraceptives and hormone replacement therapy.

The exact mechanism of how exogenous estrogen therapy leads to a hypercoagulable state is complex and not completely understood, but high doses of estrogen clearly confer a higher risk for clotting. The current low doses for estrogens in oral contraceptives are associated with a smaller but still clinically significantly increased risk of thrombosis. Estrogen use has been associated with modest increases in several procoagulant proteins (factors VII, VIII, and X, prothrombin, and fibrinogen) as well as decreases in anticoagulant proteins (antithrombin, protein S, protein C). Use of oral contraceptives or hormone replacement therapy in a patient with known heterozygosity for factor V Leiden puts the patient at an even higher risk for thrombosis, approximately a 15-fold increase.

MALIGNANCY

Malignancy is associated with increased risk for thrombus formation, but the exact mechanisms are not completely understood.[17,18] For patients with a new diagnosis of cancer, the risk of venous thromboembolism is highest in the first 3 months after diagnosis, with an odds ratio of about 50. Some types of cancers are more likely to promote thrombosis than others, with pancreatic, brain, acute myelogenous leukemia, gastric, esophageal, gynecologic, kidney, and lung cancers having the highest association with thrombosis. Cancer also increases the incidence of arterial thrombotic events, such as myocardial infarction and ischemic stroke.[17] Other manifestations of hypercoagulability in cancer patients include chronic disseminated intravascular coagulation, nonbacterial thrombotic endocarditis, migratory superficial thrombophlebitis, and thrombotic microangiopathy. Chemotherapy itself can also affect coagulation in many ways, such as downregulation of proteins C and S, induction of tissue factor production by endothelial cells, and direct cell damage.

Use low-molecular-weight heparin for the initial treatment of venous thromboembolism in patients with active cancer.[18,19] Long-term anticoagulation following the diagnosis of venous thromboembolism in these patients uses low-molecular-weight heparin for 6 months as opposed to warfarin.[18] Evolving data indicate the effectiveness of direct oral anticoagulants; however, because of their increased risk of GI bleeding, it is suggested to avoid these agents in patients with GI malignancies.[19,20] Prophylactic anticoagulation for primary prevention of venous thromboembolism in ambulatory medical oncology patients is not recommended.[18]

TABLE 234-4 Factors Contributing to Hypercoagulable State in Pregnancy

Anatomic	Hematologic
Venous occlusion from gravid uterus.	Increased thrombin generation from placental secretion of tissue factor
Trauma to pelvic veins during delivery.	
Tissue injury during surgical delivery.	Increased production of procoagulant proteins
Left iliac vein crosses over left iliac artery, leading to relative compression (left leg deep venous thrombosis is three times more likely than right in pregnant patients).	Decreased free and total protein C
	Increased platelet activation and platelet turnover

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia is a consumptive coagulopathy in which components of the clotting cascade are inappropriately activated, forming arterial and venous thrombus.[21] Platelet factor 4 is a cell-signaling molecule that plays a central role in this syndrome. Platelet factor 4 neutralizes heparin and heparin-like endogenous compounds, and the heparin–platelet factor 4 combination inhibits local antithrombin activity, thereby promoting coagulation. Heparin-induced thrombocytopenia develops when patients develop antibodies against the heparin–platelet factor 4 complex. A complex of heparin, platelet factor 4, and the antibody binds to platelets, activating them. The platelets then form small microparticles that initiate clot formation. The measured platelet count falls because platelets are bound in both small and large clots. Also, the heparin–platelet factor 4 antibody complex can stimulate endothelial cells and monocytes to release tissue factor, which further stimulates the coagulation cascade.

The typical presentation of heparin-induced thrombocytopenia has the platelet count falling to 50,000 to 70,000/mm^3 (50 to 70 × 10^9/L) within 5 to 15 days after starting heparin treatment. Despite the low platelet counts, the patient is hypercoagulable for days to weeks, even after heparin is stopped. Rarely, patients can develop a rapid-onset presentation within hours of initiation of heparin. Case reports of heparin-induced thrombocytopenia-like illness without prior exposure to heparin products exist.[21]

With more outpatients being treated with heparin products for venous thromboembolism or other thrombophilias, patients with heparin-induced thrombocytopenia may present to the ED with this syndrome. The diagnosis of heparin-induced thrombocytopenia hinges on laboratory findings and cannot be definitely diagnosed on clinical grounds alone.[21] Thrombocytopenia is almost universally present (with the exception being patients with preexisting thrombocytosis). Suspect the syndrome when platelets have dropped approximately 50% from a recent value in a patient currently or recently taking a heparin product. All heparin products, both unfractionated and low-molecular-weight, must be stopped. These patients need anticoagulation because the risk for thrombosis is highest in the first week after diagnosis.[21] Patients are typically treated with direct thrombin inhibitors (argatroban or bivalirudin) or indirect factor Xa inhibitors (danaparoid).[22] Hematology consultation should be sought.

WARFARIN-INDUCED SKIN NECROSIS

Warfarin inhibits the production of vitamin K–dependent coagulation factors, with the serum levels of the individual factors decreasing according to their half-life. Upon initiation of warfarin, protein C is decreased before most of the procoagulant proteins. This decrease in protein C leads to a transient relative protein C deficiency, which can lead to clinically significant hypercoagulability.

Warfarin-induced skin necrosis presents with painful, red lesions usually located over the extremities, breasts, trunk, or penis.[23] Lesions typically start with an initial central erythematous macule, extending

over hours to a localized edema, developing central purpuric zones and then necrosis. Thrombin inhibitors, such as low-molecular-weight heparin, are administered and continued until therapeutic anticoagulation is achieved with warfarin to prevent this complication.[23] Rarely, warfarin-induced skin necrosis occurs despite appropriate heparin treatment. When it does, approximately one third of patients will prove to have an inherited protein C deficiency.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is an autoimmune disorder defined by the development of venous and/or arterial thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies.[24] Many of the specific antibodies discovered have targets that are not phospholipids, but rather proteins that interact with phospholipids, such as prothrombin, protein C, and protein S. The most common specific antibodies associated with antiphospholipid syndrome are lupus anticoagulant, β_2-glycoprotein I, and anticardiolipin antibodies. Lupus anticoagulant was initially discovered in patients with systemic lupus erythematosus and prolongation of the activated thromboplastin time; hence, the name *lupus anticoagulant.* However, in vivo, the lupus anticoagulant acts as a procoagulant and is associated with thrombosis.[24]

Up to 5% of normal, healthy young people have antiphospholipid antibodies; this number increases with age and comorbid conditions, but only a minority of these patients develop antiphospholipid syndrome (40 to 50 per 100,000 persons). Antiphospholipid antibodies are positive in approximately 13% of patients with stroke, 11% with myocardial infarction, and 9.5% with deep venous thrombosis.[25] As with most autoimmune disorders, antiphospholipid syndrome is more common in women and is diagnosed from a combination of laboratory findings and clinical findings (**Table 234-5**).

Most patients with antiphospholipid syndrome have no predisposing conditions (primary antiphospholipid syndrome). A minority have conditions thought to be associated with their antiphospholipid syndrome (secondary antiphospholipid syndrome), such as rheumatologic or autoimmune disorders (systemic lupus), infections, and drug exposures (e.g., phenytoin, hydralazine, cocaine).

Although most patients with antiphospholipid syndrome present with isolated, recurrent thrombotic events, about 1% have a rapidly progressive form known as *catastrophic antiphospholipid syndrome,* representing acceleration in the pathophysiologic processes of antiphospholipid syndrome with widespread small-vessel occlusions in multiple organs.[24] Common triggers for the catastrophic course include infection, surgery, oral anticoagulant withdrawal, oral contraceptive use, obstetric complications, and cancer. However, 40% of the time, no obvious trigger can be found. Mortality of catastrophic antiphospholipid syndrome is approximately 50% despite treatment.

Obviously, antiphospholipid syndrome patients with recurrent thrombotic events need lifelong anticoagulation. Pregnant women with antiphospholipid syndrome need anticoagulation with subcutaneous unfractionated or low-molecular-weight heparin or low-dose aspirin therapy. Because many normal healthy patients have antiphospholipid antibodies, prophylaxis without a personal history of thrombosis is not recommended. In the rare event of catastrophic antiphospholipid syndrome, a multipronged approach involving anticoagulation, steroids, immunosuppressive therapy, plasmapheresis, and/or IV immunoglobulin is typically used.[26]

TABLE 234-5 Clinical Manifestations of Antiphospholipid Syndrome

System	Examples
Venous	Deep venous thrombosis: extremities, cerebral, portal, hepatic, renal, retinal
Arterial	Premature atherosclerosis Acute coronary syndrome Ischemic stroke Vascular stenosis or occlusion: extremities, aorta, renal, retinal
Obstetric	Fetal loss: often after 10-wk gestation Preterm labor Low birth weight Preeclampsia
Neurologic	Migraine Sneddon's syndrome—clinical triad of stroke, hypertension, and livedo reticularis Cognitive dysfunction Subcortical dementia Chorea Dysphagia Guillain-Barré syndrome Seizures Optic neuritis
Skin	Livedo reticularis
Cardiac	Valvular abnormalities (Libman-Sacks endocarditis) Syndrome X (angina-like chest pain, cardiac stress test positive for ischemia, normal coronary angiography)
Skeletal	Osteonecrosis
Renal	Thrombotic microangiopathy Renal artery or vein thrombosis Renal artery stenosis with hypertension
Pulmonary	Pulmonary embolus Pulmonary hypertension (from recurrent emboli)
GI	Budd-Chiari syndrome (hepatic vein thrombosis) Mesenteric ischemia Hepatic infarction Acalculous cholecystitis with gallbladder necrosis
Hematologic (other than thrombosis)	Bleeding diathesis (rare) Acquired hypoprothrombinemia Thrombocytopenia Hemolytic anemia
Catastrophic antiphospholipid syndrome	Fulminant multisystem organ failure

HYPERCOAGULABILITY ASSOCIATED WITH OTHER DISORDERS

Many other conditions are associated with increased risk of clotting. Patients with **nephrotic syndrome** have an increased risk of hypercoagulability for complex reasons. In several cases, this is simply a matter of increased urinary excretion of anticoagulant proteins. The nephrotic syndrome can also lead to increased endothelial injury and platelet aggregation. Patients with several forms of **vasculitis**, such as Behçet's syndrome, antineutrophil cytoplasmic antibody–associated vasculitis, and granulomatosis with polyangiitis, have a slightly increased risk of thrombosis. **Hyperviscosity syndromes,** such as essential thrombocythemia, polycythemia vera, Waldenström's macroglobulinemia, multiple myeloma, and sickle cell disease, also place patients at increased risk for thrombosis. Most risk factors for cardiovascular disease, such as obesity and diabetes, are also risk factors for venous thromboembolism to varying degrees.[27] **Diabetes** alone slightly increases the risk for thrombosis in younger patients without other obvious risks for thrombosis.[28] Patients with **human immunodeficiency virus** have a 2- to 10-fold increased risk for venous thromboembolism compared to the general population.[29]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 235

Hemophilias and von Willebrand's Disease

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INTRODUCTION

Hemophilias are bleeding disorders due to deficiency in clotting cascade factors (see Chapter 232, "Hemostasis").[1-3] The most common factor abnormalities are of factor VIII (**hemophilia A**) or factor IX (**hemophilia B**). **von Willebrand's disease** is a related defect of the von Willebrand factor.[4]

These hereditary bleeding disorders typically appear early in life, and adult patients will usually be able to relate a history of a bleeding problem. However, patients with mild forms of inherited disease may be unaware of a bleeding disorder until stressed by significant trauma or development of another hemostatic problem such as addition of antihemostatic medications.

Systemic bleeding disorders should be suspected in patients with severe bleeding related to trivial trauma or minor surgery, or spontaneous bleeding, particularly when the bleeding occurs in joints or muscle. Unusual bleeding or bruising at multiple areas should also raise concern about a coagulopathy. Medications can be responsible for unmasking a mild bleeding diathesis.

The pattern of bleeding can suggest a likely etiology. Patients with easy bruising, gingival bleeding, epistaxis, hematuria, GI bleeding, or heavy menses are more likely to have a deficiency or dysfunction of the platelets. Conversely, patients with spontaneous deep bruises, hemarthrosis, retroperitoneal bleeding, or intracranial bleeding are more likely to have a coagulation factor deficiency. In factor-deficient patients, bleeding associated with trauma may be delayed, due to defective fibrin clot formation that inadequately stabilizes the initial platelet thrombus. Patients with von Willebrand's disease may present with features of both platelet and clotting factor problems.

HEMOPHILIA

EPIDEMIOLOGY

The genes that encode factors VIII and IX are located on the long arm of the X chromosome. A genetic mutation in the factor VIII gene produces hemophilia A, occurring in about 1 in 5000 male births in the United States. A mutation in the factor IX gene causes hemophilia B, affecting approximately 1 in 25,000 male births in the United States. Together, these two forms of hemophilia make up about 99% of patients with inherited coagulation factor deficiencies. Hemophilia A and B are clinically indistinguishable from each other, and specific factor testing is required to identify the type.

Because hemophilia A and B are X-linked disorders, hemophilia is overwhelmingly a disease of men, with women typically being asymptomatic carriers, except in rare cases.[5] Although these disorders are genetic and usually inherited, approximately one third of new cases of hemophilia arise from a spontaneous gene mutation, and a family history may be absent.

PATHOPHYSIOLOGY

Bleeding manifestations in patients with all forms of hemophilia are directly attributable to the decreased plasma activity levels of either factor VIII or IX (**Table 235-1**). Those with factor activity levels of 0.3 to 0.4 IU/mL (30% to 40% of normal) may never be aware that they have hemophilia, or they might manifest unusual bleeding only after major surgery or severe trauma. Unless there is another underlying disease, patients with hemophilia do not have problems with minor cuts and abrasions, as hemostasis from these injuries is achieved by platelet activation and the formation of the primary hemostatic plug (see Chapter 232).

TABLE 235-1 Hemophilia Severity

Disease Severity	Factor VIII or IX Activity (% of normal)	Clinical Features
Severe	<0.01 IU/mL (<1%)	Severe spontaneous bleeding, difficult to control if traumatic
Moderate	0.01–0.05 IU/mL (1%–5%)	Usually bleeding from trauma; may bleed spontaneously
Mild	0.05–0.40 IU/mL (5%–40%)	Bleeding after trauma

Bleeding is the major complication of hemophilia, but as a result of frequent exposure to blood products, many hemophiliacs in the past were infected with viral hepatitis or human immunodeficiency virus. Fortunately, currently available factor replacement products have essentially eliminated the risk of seroconversion.

CLINICAL FEATURES

Depending on the severity of the disease, both hemophilia A and B are characterized by easy bruising and spontaneous recurrent bleeding primarily into the joints and muscles and less commonly into other areas (**Table 235-2**).[1-3] Trauma or a surgical procedure can result in prolonged and difficult-to-control bleeding.

DIAGNOSIS

For patients with established hemophilia, hemostatic testing (e.g., prothrombin time, activated partial thromboplastin time) is unlikely to yield new information and is not routinely indicated. In patients with a suspected bleeding disorder, hemophilia is suspected when the prothrombin time, which measures the extrinsic coagulation cascade, is normal, but the activated partial thromboplastin time, which measures the intrinsic coagulation cascade, is prolonged. However, patients with factor levels above 0.3 to 0.4 IU/mL (30% to 40% of normal) may have an activated partial thromboplastin time within the test reference range. **Bleeding time in both forms of hemophilia will be normal and therefore not helpful**. The diagnosis is confirmed by quantitative measurement of factor VIII or IX levels below 0.50 IU/mL (<50% normal). If mild hemophilia A is suspected, a variant of von Willebrand's disease characterized by abnormal binding of factor VIII and von Willebrand factor should be excluded by special binding tests or genetic analysis.

TABLE 235-2 Hemophilia Bleeding Manifestations

Site	Comments
Hemarthroses	Most common site, more frequent in hinged joints (elbows, knees, ankles) than in multiaxial joints.
Soft tissue	Bleeding into soft tissues or muscle; bleeding can dissect along fascial planes; most dangerous in the neck (airway compromise), limbs (compartment syndromes), eye (retro-orbital hematoma), spine (epidural hematoma), and retroperitoneum (circulatory shock).
Mucocutaneous bleeding	Delayed bleeding after dental extractions; spontaneous bleeding from the nose, pharynx, GI tract, or lungs is uncommon.
CNS	Intracranial bleeding is the most common cause of hemorrhagic death in hemophiliacs of all age groups; subdural hematomas occur spontaneously or with minimal trauma.
Hematuria	Common, usually not serious, and a specific bleeding site is rarely found.
Hemophilic pseudotumor	Unresolved or undertreated hematomas erode into adjacent bones resembling bone cysts or malignancy; may compress adjacent nerves and vessels.

TREATMENT

GENERAL PRINCIPLES

Initiate indicated resuscitation and hemorrhage control (**Table 235-3**).[6,7] Assess the patient's history. Many patients and their families administer factor concentrate therapy at home, and patients are taught to self-treat at the first symptom before little outward evidence develops. Patients may have an established management plan for acute bleeding episodes, and regional hemophilia foundations, associations, and centers often maintain a database that can be contacted for patient-specific information, especially if there is an uncertainty about the need for factor replacement.

Treatment of bleeding in patients with hemophilia primarily relies on either the early replacement of missing factors or, for those who have mild factor VIII deficiency, stimulating the body to secrete clotting factor from intracellular stores. **Begin replacement before or at the same time as other resuscitative and diagnostic maneuvers for intracranial, intrathoracic, intra-abdominal, retroperitoneal, ocular, or airway bleeding** (Table 235-2). Bleeding into the neck, tongue, or retropharynx can compromise the airway. Patients with suspected intracranial hemorrhage, either spontaneous with an acute severe headache or after blunt head injury, should receive immediate factor replacement therapy prior to head CT. Complaints of back, thigh, groin, or abdominal pain may be symptoms of retroperitoneal bleeding. An **iliopsoas muscle hemorrhage** is a common form of retroperitoneal bleeding seen in hemophiliacs, and patients may describe hip pain and have difficulty straightening their leg, preferring to keep it in a flexed, externally rotated position. An iliopsoas muscle hemorrhage can compress and damage the femoral nerve, cause anemia of blood loss, or produce circulatory shock.

The initial manifestations of bleeding can be subtle. Simple injuries, such as ankle and wrist sprains, may at first appear benign, and several hours may pass before hemarthrosis is apparent. **So, while there may not be physical signs of bleeding into a joint, patients will reliably report when bleeding is occurring.** Prompt treatment of hemarthroses with factor replacement and rest of the joint for 4 to 5 days can prevent or reduce the long-term sequelae of hemophilic arthropathy. If a large hemarthrosis is already present, consultation with an orthopedist for appropriate splinting, possible arthrocentesis, and rehabilitation may improve the outcome once the bleeding has been controlled.[8] **Compartment syndromes** can result from bleeds within the fascial compartments of the extremities. Compartment pressures can be safely measured **after** the patient has received factor replacement.

When treating patients with hemophilia for other reasons, some general principles apply. Do not place central venous access or arterial lines without factor replacement. Similar rules apply to arterial blood gases, lumbar puncture, and other invasive procedures. Do not give IM injections unless factor replacement is given and maintained for several days. If a patient with hemophilia requires interhospital transfer, initiate factor replacement **before** transfer, and do not delay factor replacement with attempts to obtain imaging.

TABLE 235-3 Approach to the Bleeding Hemophiliac Patient[6,7]

- Initial resuscitation and hemorrhage control
- Assess patient's history, home factor replacement therapy, and presence of inhibitors
  - Discuss with hematologist or contact hemophilia center
- Initiate replacement therapy as indicated
  - Prior to invasive procedures, central lines and further workup or intervention
- Imaging as indicated (e.g., head CT for head injury or neurologic findings, plain films for effusions, CT of abdomen/pelvis for retroperitoneal bleeding)
- Treat pain as indicated, primarily with acetaminophen or opioids
  - Avoid use of aspirin or NSAIDs; no IM injections
- Consultations as indicated (e.g., orthopedics for hemarthrosis)
- Admission or transfer for CNS, neck, pharyngeal, retropharyngeal, or retroperitoneal bleeding or possible compartment syndrome
  - Adequate factor replacement therapy should be initiated prior to transfer

FACTOR REPLACEMENT THERAPY

The two sources of factor replacement therapy for hemophilic patients are purification from human plasma and recombinant technology from hamster or human embryonic kidney cell lines (**Table 235-4**).[9-11] Opinions vary as to the preferred product,[12,13] and World Federation of Hemophilia guidelines do not express a preference.[2,9] In the United States, the National Hemophilia Foundation position is that recombinant factor concentrates are the preferred treatment for hemophilia.[11] **Where possible, use the product that the patient uses at home.**[6]

The dosing regimen used in the hemophilic patient is based on the clotting factor volume of distribution, the half-life of the factor, and the hemostatic level of factor required to control the bleeding (**Table 235-5**).[14] Clotting factor is dosed in units of activity; 1 IU of factor represents the amount present in 1 mL of normal plasma. In hemophilia A, 1 IU of factor VIII per kilogram of body weight raises the plasma level by approximately 0.02 IU/mL (2%). The half-life of factor VIII is approximately 8 to 12 hours. For hemophilia B, 1 IU of factor IX per kilogram of body weight will raise the plasma level by approximately 0.01 IU/mL (1%). The half-life of factor IX is approximately 16 to 24 hours.

Factor concentrates are supplied as lyophilized powder in single-use glass vials containing a range of amounts, from 250 to 4000 IU per vial. Calculation of the factor dose is done using the patient's weight and, to avoid wasting factor, rounding up doses to the next vial. For major

TABLE 235-4 Hemophilia Replacement Factor Products

Hemophilia Type	Available Products* (Manufacturer/Distributor)
Hemophilia A	**Recombinant Factor VIII Concentrates**
	Advate® (Baxter)
	Adynovate® (Shire)
	Afstyla® (CSL Behring)
	Eloctate® (Bioverativ)
	Helixate FS® (Bayer/CSL Behring)
	Kogenate FS® (Bayer)
	Kovaltry® (Bayer HealthCare)
	Novoeight® (Novo Nordisk A/S)
	Nuwig® (Octapharma USA)
	Recombinate® (Baxter)
	Xyntha® (Pfizer)
	Human Plasma–Derived Factor VIII Concentrates
	Corifact® (CSL Behring)
	Hemofil M® (Baxter)
	Koate-DVI® (Grifols Therapeutics)
	Monarc-M® (Baxter HealthCare)
	Monoclate-P® (CSL Behring)
	Human Plasma–Derived Factor VIII Concentrates That Contain von Willebrand Factor
	Alphanate® (Grifols Therapeutics)
	Humate-P® (CSL Behring GmbH)
	Wilate® (Octapharma USA)
Hemophilia B	**Recombinant Factor IX Concentrates**
	Alprolix® (Bioveratic)
	BeneFIX® (Pfizer)
	Idelvion® (CSL Behring)
	Ixinity® (Emergent BioSolutions)
	Rebinyn® (Novo Nordisk A/S)
	Rixubis® (Shire)
	Human Plasma–Derived Factor IX Concentrates
	Bebulin® (Shire)
	Mononine® (CSL Behring)

*Commercial trade names provided for ease of specific identification.

TABLE 235-5 Initial Factor Replacement Guidelines in Moderate and Severe Hemophilia

Severity and Site	Desired Factor Level to Control Bleeding	Hemophilia A Initial Dose (IU/kg)	Hemophilia B Initial Dose (IU/kg)	Comments
Minor: skin (deep laceration)	—	—	—	Skin abrasions and lacerations usually do not require factor replacement. Treat with pressure and topical thrombin.
Minor: early hemarthrosis, mild muscle bleeding, mild oral bleeding	0.2–0.4 IU/mL (20%–40%)	10–20	20–30	Repeat dose every 12–24 h for 1–3 d until bleeding episode is resolved. Typical duration of replacement is 1–3 d.
Moderate: definite hemarthrosis, moderate muscle bleeding, moderate oral bleeding	0.3–0.6 IU/mL (30%–60%)	15–30	25–50	Repeat dose every 8–24 h until resolution of bleeding episode. Orthopedic consult for hemarthrosis. Typical duration of replacement is 3–5 d.
Major: retropharyngeal, GI, intra-abdominal, intrathoracic, retroperitoneal	0.6–1.0 IU/mL (60%–100%)	30–50	30–50	Repeat dose every 8–24 h until resolution of bleeding episode. May require replacement for up to 10 d.
CNS	1.0 IU/mL (100%)	50	50–100	Treat before CT. Early neurosurgical consultation.

bleeding, high levels of factor replacement are required and continued until bleeding stops (Table 235-5). Repeat doses are usually given as repeat bolus therapy every 8 to 24 hours, or 6 to 12 hours in patients under 6 years of age.

For less severe bleeding in soft tissue, muscle, or joints, a lesser amount of factor replacement is necessary; usually three doses over 1 to 2 days are sufficient to control bleeding. In addition to factor replacement, extremity and joint bleeding may benefit from splinting followed by physical therapy.[4] Cryotherapy has no proven benefit in hemarthroses.[15]

SPECIAL CONSIDERATIONS

ORAL AND MUCOSAL BLEEDING

Oral bleeding from hemophilia is more common in children than in adults. For an oral bleed, the area should be identified and cleaned of inadequate clot and solution of **topical bovine thrombin** sprayed on to the site or applied in conjunction with a saturated absorbable gelatin sponge. Repeat doses should be limited because repetitive application of topical bovine thrombin can induce antibodies to factor V, resulting in a syndrome of severe bleeding and thrombosis, which can rarely be fatal. Factor replacement may be required, dosed according to the severity of bleeding. Antifibrinolytic agents, such as **aminocaproic acid** and **tranexamic acid**, are useful adjunctive therapies with a low rate of adverse effects.[2] For very superficial mucosal injuries, it may be possible to manage the bleeding with antifibrinolytic therapy alone. The adult dose of aminocaproic acid is 6 grams every 6 hours given PO or IV. The adult dose of tranexamic acid is 10 milligrams/kg IV three times per day for 2 to 8 days.

MILD HEMOPHILIA A

Patients with **mild hemophilia A** (factor levels of 5% of normal or greater) who have mild bleeding may not always require factor replacement.[1,2,16] Rather, they may be treated with **desmopressin**, which stimulates the release of von Willebrand factor from endothelial storage sites, promoting an increase of factor VIII in the plasma (**Table 235-6**).[16-18] A concentrated intranasal preparation is available and can be used at home. IV or intranasal desmopressin will increase the factor VIII level by two to four times. Desmopressin treatment can be repeated in 24 hours, but with repetitive use, the patient's stores of factor VIII will become depleted, and subsequently, the effect will be less. Desmopressin is an antidiuretic agent, so fluid restriction may be needed during use.

TABLE 235-6 Desmopressin Treatment of Mild Hemophilia A and von Willebrand Disease

Patient	IV Preparation	Nasal Preparation
<2 y	Not recommended	Not recommended
<50 kg weight	0.3 microgram/kg IV over 30 min	Single spray of 150 micrograms in one nostril
>50 kg weight	0.3 microgram/kg IV over 30 min; maximum dose, 20 micrograms	One spray of 150 micrograms in each nostril (total dose, 300 micrograms)

HEMATURIA

Hematuria is common in hemophilia but is typically not severe.[19] Rest and hydration are important to ameliorate bleeding and factor replacement is indicated for gross hematuria. Hemophiliacs are at increased risk for nephrolithiasis, suggesting that renal imaging is indicated for patients with symptoms of renal colic or new-onset hematuria.[19]

FACTOR INHIBITORS

Factor inhibitors, antibodies against replacement factors, tend to occur most commonly in severe hemophiliacs.[2] The incidence of inhibitor development is 30% in severe hemophilia A and 5% in severe hemophilia B.[20] Inhibitors not only interfere with the effectiveness of factor replacement therapy, but also can cause anaphylaxis during factor administration in patients with hemophilia B. The use of factor replacement in hemophilic patients with inhibitors is guided by the concentration of inhibitor and the type of response the patient has to factor concentrates. ED physicians should query hemophiliacs about whether they have known inhibitors.

The overriding principle in treating patients with inhibitors is close consultation with a hematologist. In patients with low levels of inhibitor antibodies (<5 Bethesda inhibitor assay units) who are not vigorous antibody responders, some hematologists may recommend giving an increased dose of factor in an attempt to overwhelm the existing antibody. Alternative therapies include anti-inhibitor coagulant complex (FEIBA®) and coagulation factor VIIa (recombinant) (**Table 235-7**).[21-23] Anti-inhibitor coagulant complex, derived from human plasma, contains factors II, IX, and X, mostly nonactivated, and factor VII, primarily in the activated form. Activated factor VII, either from human plasma or

TABLE 235-7 Replacement Therapy for Hemophilia A and B in Patients With Inhibitors

Product*	Initial Dose	Dosing Interval	Comments
Anti-inhibitor coagulant complex FEIBA® (Shire)	50–100 units/kg	6–12 h	Repeat until hemostasis is achieved. Total daily doses should not normally exceed 200 units/kg
Coagulation factor VIIa (recombinant) NovoSeven RT® (Novo Nordisk A/S)	90 micrograms/kg	2 h	Repeat until hemostasis is achieved or therapy is judged ineffective

*Commercial trade names provided for ease of specific identification.

recombinant, when complexed with tissue factor, activates factor X. Factor Xa, in concert with factor Va, calcium, and phospholipid, promotes the conversion of prothrombin to thrombin, which ultimately leads to the formation of a hemostatic plug composed of cross-linked fibrin.

ACQUIRED HEMOPHILIA

Acquired hemophilia occurs when autoantibodies are created against factor VIII, resulting in inactivation of this factor and a hemorrhagic tendency (see Chapter 233, "Acquired Bleeding Disorders").[24,25] The bleeding pattern in acquired hemophilia is usually widespread cutaneous purpura and internal bleeding, with hemarthroses being less common, a difference from congenital hemophilia. Treatment of acute bleeding uses factor products that bypass the inhibitor antibodies, such as anti-inhibitor coagulant complex or coagulation factor VIIa (recombinant).

POSTPARTUM ACQUIRED HEMOPHILIA

Postpartum acquired hemophilia is a rare condition with severe hemorrhagic potential.[26,27] The risk is highest with the first pregnancy, and presentation is typically 2 months after delivery, with persistent vaginal bleeding being the most common presenting symptom. Treatment for hemorrhage is with anti-inhibitor coagulant complex or coagulation factor VIIa (recombinant) (Table 235-7). Production of the autoantibodies will spontaneously cease over many months, achieving complete remission. Recurrence with subsequent pregnancies is uncommon.

DISPOSITION AND FOLLOW-UP

Many hemophilic patients are able to judge the severity of bleeding, self-administer replacement therapy, and monitor the response at home.[1,2,6,7] Such patients may likely be discharged after initial treatment in the ED for typical joint, soft tissue, or nasal hemorrhage. Relative indications for hospital admission include treatment requiring multiple factor replacement doses or necessity for parenteral pain management. Patients with bleeding in the CNS, neck, pharynx, retropharynx, or retroperitoneum or those with a potential compartment syndrome should be admitted. Given the complexity of treatment for this subset of patients, consultation or transfer to a hemophilia treatment center is recommended.

VON WILLEBRAND'S DISEASE

EPIDEMIOLOGY

von Willebrand's disease is the most common inherited bleeding disorder, present in 1% of the population.[4] Most patients have a mild defect, and clinically significant bleeding is rare. Congenital von Willebrand's disease is heterogeneously inherited and variably expressed, and although there are multiple variants, it can be classified into three major groups (**Table 235-8**). An acquired form of von Willebrand's disease occurs when autoantibodies develop against von Willebrand factor, resulting in rapid clearance of the antibody–von Willebrand factor complex from the circulation.

PATHOPHYSIOLOGY

von Willebrand factor is a glycoprotein that, unlike most other coagulation factors, is synthesized, stored, and then secreted by the vascular endothelial cells. von Willebrand factor serves two key roles in normal hemostasis: as a cofactor for platelet adhesion and as the carrier protein for factor VIII.[28] Circulating von Willebrand factor does not bind directly to platelets, but, when exposed to the subendothelial matrix, von Willebrand factor undergoes a structural change, allowing it to bind to platelet glycoprotein Ib. This interaction between von Willebrand factor and platelet glycoprotein Ib leads to platelet activation and adhesion to other platelets, as well as to the damaged endothelium. As a carrier protein, von Willebrand factor protects factor VIII from proteolytic degradation within the plasma. A defect in von Willebrand factor that diminishes factor VIII binding produces a clinical presentation similar to mild hemophilia A.

TABLE 235-8 von Willebrand's Disease Classification and Treatment

Type	Frequency	Defect	Treatment
1	70%–80% of cases	Normal vWF is present but in decreased quantity (approximately 20%–50% normal levels)	Desmopressin and, if no response, consider the measures below
2	10%–15% of cases	The vWF is abnormal and dysfunctional	Recombinant vWF, vWF-containing concentrate or cryoprecipitate (if vWF-containing product is not available)
3	<10% of cases	Almost no vWF is present	Recombinant vWF, vWF-containing concentrate or cryoprecipitate (if vWF-containing product is not available)

Abbreviation: vWF = von Willebrand factor.

CLINICAL FEATURES

Skin and mucosal bleeding is common in people with von Willebrand's disease, particularly in children and adolescents. Examples of bleeding include recurrent epistaxis, gingival bleeding, unusual bruising, GI bleeding, and menorrhagia in young women. Hemarthrosis is not typical unless severe disease is present. In mild cases of von Willebrand's disease, the patient may be unaware of the disease until after a surgical procedure or injury when unexpected bleeding occurs.

DIAGNOSIS

The common abnormalities seen in von Willebrand's disease include prolonged bleeding time, low or normal von Willebrand factor antigen, and low von Willebrand factor activity.[29] The prothrombin time should be normal, and about half of patients have a mildly prolonged activated partial thromboplastin time. Diagnostic testing can be complicated, and misdiagnosis can occur from errors in specimen handling, storage, processing, and laboratory testing proficiency. In addition, variability in von Willebrand factor levels can sometimes make von Willebrand's disease difficult to differentiate from mild hemophilia A.

TREATMENT

NONTRANSFUSIONAL THERAPY

Desmopressin is the primary therapy for many patients with type 1 von Willebrand's disease.[18,30] For other types of von Willebrand's disease, desmopressin may still work in conjunction with products that contain von Willebrand factor, but hematologists tend to recommend either one or the other. Desmopressin induces the release of von Willebrand factor from storage sites within the endothelium. In responsive individuals, it causes a transient two- to fourfold increase in von Willebrand factor. Desmopressin also has an effect on the endothelium that promotes hemostasis. IV and concentrated nasal spray preparations of desmopressin are available (Table 235-5). Desmopressin may be repeated in 24 hours, but the response to subsequent doses diminishes as vWF stores become depleted. Desmopressin also has antidiuretic properties, so fluid restriction for 24 hours after administration is important to prevent hyponatremia.[30]

TRANSFUSIONAL THERAPY

Transfusional therapy is used for type 1 patients who do not (or no longer) respond to desmopressin or have type 2 or 3 von Willebrand's disease.[11,31] A von Willebrand Factor (recombinant) (Vonvendi®, Baxalta US, Inc.) product became available in 2015. The initial dose is 40 to 50 IU/kg IV for

minor bleeding and 50 to 80 IU/kg for major bleeding, with subsequent doses every 8 to 24 hours as needed. Plasma derivatives that contain von Willebrand factor can also be used with an initial dose of 30 to 50 IU/kg (Table 235-4). Cryoprecipitate also contains von Willebrand factor, but because it does not undergo viral inactivation, cryoprecipitate should only be used in life-threatening emergencies when other products are not available.[11] Platelet transfusions may benefit patients with certain types of von Willebrand's disease (type 3) who do not respond to von Willebrand factor products.[32]

ADDITIONAL THERAPY

Avoid medications with known antiplatelet effects, including aspirin, NSAIDs, antiplatelet agents, heparin, and some antibiotics. Patients with von Willebrand's disease with significant epistaxis should be treated with desmopressin or transfusion therapy as needed to control bleeding. If unsuccessful, intranasal topical therapy or cauterization may be necessary (see Chapter 244, "Nose and Sinuses"). Menorrhagia is a common complaint in young women with von Willebrand's disease. Oral contraceptives can help raise von Willebrand factor levels and limit the degree of menstrual bleeding. For dental injury or planned procedures in the oral cavity, an antifibrinolytic agent can be used. **Aminocaproic acid** can be taken orally, and **tranexamic acid** can be made into a mouthwash, to be used for 5 to 10 days after the injury or surgical procedure.

DISPOSITION AND FOLLOW-UP

In most patients with von Willebrand's disease, the acute bleeding episodes can be controlled with local measures and desmopressin; such patients can usually be discharged. The unusual von Willebrand's disease patient with almost no von Willebrand factor activity is typically handled like a patient with hemophilia. Relative indications for hospital admission include treatment requiring multiple factor replacement doses or necessity for parenteral pain management. Patients with bleeding in the CNS, neck, pharynx, retropharynx, or retroperitoneum or those with a potential compartment syndrome should be admitted, with consideration of transfer to a hemophilia center.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 236

Sickle Cell Disease and Hereditary Hemolytic Anemias

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Alex Koyfman

INTRODUCTION

Hereditary anemias result from defects in hemoglobin production, abnormalities in red blood cell (RBC) metabolism, or changes within RBC membrane structure. Increased hemolysis occurs because the RBCs produced are either abnormal or sustain damage after release from the bone marrow and are removed from the circulation, primarily by the spleen. Depending on the compensatory rate of production, the concentration of circulating erythrocytes may decrease, resulting in anemia.

Inherited hemoglobin disorders are comprised of two main groups: disorders with abnormal hemoglobin structure (e.g., sickle cell disease) and disorders of abnormal hemoglobin production (e.g., the thalassemias). About 5% of the world's population are carriers of a clinically significant abnormal hemoglobin gene.[1] These genetic abnormalities result in hemoglobin that tends to gel or crystallize, possesses abnormal oxygen-binding properties, or is readily oxidized to methemoglobin, rendering the RBC susceptible to hemolysis.

SICKLE CELL DISEASE

Sickle cell disease (SCD) is a group of genetic RBC disorders that constitute a worldwide public health problem.[2,3] An estimated 250 million people (approximately 4.5% of the world population) are carriers of the sickle cell gene,[1] with an estimated >250,000 new individuals born each year with SCD.[1] SCD affects predominantly people of African Equatorial descent, although it is also found in persons of Mediterranean, Indian, and Middle Eastern origin.[1] SCD affects approximately 100,000 people in the United States, and about 2 million Americans are sickle cell gene carriers.[4] One of every 13 African Americans carries the sickle cell gene, and SCD occurs in 1 of every 365 African American births.[4]

Antenatal and neonatal screening, parental education about complications, monitoring in clinics and close follow-up, immunizations, prophylactic penicillin to prevent pneumococcal septicemia, and increased use of drugs such as hydroxyurea counteract the high mortality rate seen with untreated SCD. In the United States, survival to age 18 years approaches 94%, and the overall life expectancy is >50 years.[5,6]

PATHOPHYSIOLOGY

SCD is characterized by RBCs that contain at least one abnormal hemoglobin, hemoglobin S. Hemoglobin is made of iron (heme) and protein chains (globin). There are four types of globin molecule chains (alpha, beta, gamma, and delta), which determine the type of hemoglobin present.[7] Hemoglobin A, the normal constituent of adult hemoglobin (95% to 98%), consists of a pair of alpha and beta chains. HbSS, the hemoglobin of sickle cell anemia, consists of a pair of alpha chains and a pair of sickle beta chains. The hemoglobin of sickle cell trait, HbS, consists of two alpha chains, one normal beta chain, and one sickle beta chain.

The abnormal hemoglobin S results from an adenine-to-thymine DNA substitution in the beta-globin chain of hemoglobin.[3,8] RBCs with normal hemoglobin are donut shaped and flexible enough to move through arterioles and capillaries. RBCs containing hemoglobin S are stiff and sickle shaped. Sickling, or distortion of the RBC, results in premature RBC destruction (abnormal life span of about 20 days) and increases blood viscosity, leading to microvascular obstruction (**Figure 236-1**).[8-10] Vascular obstruction worsens hypoxia and causes acidosis in the microcirculation that contributes to further sickling. The sickling process is initially reversible when the HbS is reoxygenated, but with repeated episodes of sickling, the red cell membrane is permanently damaged, and the cell

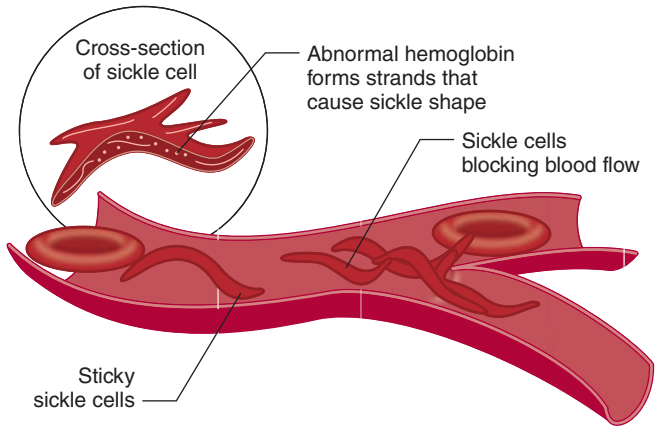

FIGURE 236-1. Intravascular blood flow of normal and sickle red blood cells (RBCs). Abnormal, sickled RBCs clumping and blocking blood flow in a blood vessel. (Other cells also may play a role in this clumping process.)

remains irreversibly sickled. Anywhere from 5% to 50% of the circulating erythrocytes in a patient with SCD can be irreversibly sickled cells. The overall effect is chronic, ongoing hemolysis and episodic periods of vascular occlusion, resulting in tissue ischemia affecting many organ systems.

SICKLE CELL ANEMIA (HbSS DISEASE)

CLINICAL FEATURES

Because newborn screening occurs in the United States and in most developed countries, patients usually know that they have the disease. HbSS disease can produce a wide spectrum of manifestations, but vaso-occlusive crises account for the majority of ED presentations.[3,8] Life- or organ-threatening complications should always be anticipated[11] (**Table 236-1**).

Vaso-Occlusive Pain Crisis The initiating event of the pain crisis may not be identifiable, but stressors such as infection, cold, dehydration, and altitude have been implicated. As a result of intravascular sickling and small-vessel occlusion, infarction of bone, viscera, and soft tissue occurs. This manifests as diffuse bone, muscle, and joint pain (back or extremity pain are most common) and, in some cases, symptoms related to a specific affected organ. **Initial management includes timely and aggressive pain management, appropriate hydration, identification of a treatable cause of the crisis, and a search for complications** (**Table 236-2**).[11,12]

The CBC and reticulocyte count assess the degree of anemia and whether the marrow is still producing red cells. If the reticulocyte count is not available, the presence of polychromasia in the peripheral blood smear can be used to provide evidence of continued RBC production. It is common for HbSS patients to have a low-grade temperature as well as a modestly elevated leukocyte count during a painful crisis, potentially confounding detection of an infection. A leukocyte count >20,000/mm^3 (>20 × 10^9/L) with an increased number of bands is not typical for sickle

TABLE 236-1 Complications of Sickle Cell Anemia

Neurologic	Ischemic or hemorrhagic stroke Cerebral aneurysm Chronic and neuropathic pain syndrome
Eye	Retinopathy
Pulmonary	Pulmonary hypertension Pneumonia Acute chest syndrome
Cardiac	Cardiomegaly
Abdominal, GI	Cholelithiasis Mesenteric ischemia Hepatic infarction Intrahepatic cholestasis Splenic sequestration
Renal, GU	Hematuria Urinary tract infection Renal infarction Papillary necrosis Renal failure Priapism
Musculoskeletal	Acute vaso-occlusive pain crisis; bone, joint, and muscle pain Osteomyelitis Avascular necrosis of femoral head
Dermatologic	Leg ulcers
Hematologic	Chronic hemolysis Acute hemolytic crisis Aplastic crisis Hypercoagulability: pulmonary embolism and venous thrombosis

TABLE 236-2 Guidelines for the Assessment and Management of Acute Vaso-Occlusive Crisis in Adults

History	Duration and location of pain History of fever Presence of focal swelling or redness Precipitation factors for acute episode Medications taken for pain relief Prior vaso-occlusive episodes and any differences/similarities to the current episode
Physical examination	Assess degree of pain Inspect sites of pain, looking for swelling, warmth, redness General: respiratory distress, pallor, hydration, jaundice, rash Vital signs: especially temperature, pulse oximetry Respiratory: lung sounds Heart: cardiomegaly and systolic murmur common with chronic anemia Abdomen: tenderness, organomegaly
Ancillary tests	CBC, leukocyte differential, electrolyte and renal function panel, urine dipstick (obtain if moderate to severe pain or focal pathology is present, or pain is atypical for acute episode) CBC, leukocyte differential, reticulocyte count, liver function, bilirubin, lactate dehydrogenase, electrolyte and renal function panel, urinalysis (if being admitted, concern for another condition or complication, toxic appearing) Chest radiograph, if signs of lower respiratory tract pathology are present Blood cultures and additional blood tests: as indicated by clinical condition
General management	Bed rest; provide warmth and a calm, relaxing atmosphere Distractions where appropriate: television, music, etc. Oral fluids: typically about 3 L/d IV fluids to correct dehydration or if reluctant to drink or vomiting is present (unnecessary if euvolemic) Oxygen: not routinely required unless hypoxemia is present (<92%) Encourage deep breathing, incentive spirometry
Pain management	Use analgesics appropriate to degree of pain Acetaminophen for mild pain NSAIDs for mild to moderate pain (avoid if renal insufficiency is present); conflicting results for opioid sparing, reduction in pain severity and duration Opioids for moderate to severe pain; typical initial doses include: Morphine, 20–30 milligrams PO or 6–10 milligrams IV Hydromorphone, 2–4 milligrams PO or 1–2 milligrams IV Reassess response in 15–30 min; may repeat with one fourth to one half of the initial dose Ketamine in subdissociative doses can be used for opioid sparing, reduction in treatment time, and reduced pain scores
Consider adjuvant therapy	Medication to prevent constipation Antiemetic Anxiolytic
Disposition and follow-up	Consider admission to the hospital if: Acute chest syndrome is suspected Sepsis, osteomyelitis, or other serious infection is suspected WBC count is >30,000/mm^3 (30 × 10^9/L) Hemoglobin level is <5 grams/dL (50 grams/L) Platelet count is <100,000/mm^3 (100 × 10^9/L) Pain is not under control after 2 to 3 rounds of analgesics in the ED
	Consider discharge if: Pain is under control and patient can take oral fluids and medications Appropriate oral analgesics are available Patient is able to comply with home care instructions Patient has resources for follow-up

crisis alone; this combination suggests a potential infection. Mild elevations in serum bilirubin and lactate dehydrogenase levels are common due to chronic hemolysis.

Supplemental oxygen is needed only for hypoxia (<92%).[11,13] During a painful crisis, HbSS patients may be hypovolemic due to their disease (deficient renal concentrating ability) or crisis (anorexia, vomiting, or fever), so PO or IV rehydration followed by maintenance hydration may be necessary. There are no published trials that have evaluated the safety and efficacy of different types of IV fluids for vaso-occlusive crises.[14] Euvolemic patients do not require IV hydration, and no hydration regimen shortens the duration or severity of a painful sickle cell attack.[15]

No reliable signs or tests can diagnose or exclude a vaso-occlusive pain crisis. Self-reported pain scores do not reliably correlate with vital sign abnormalities, and patient behavior (walking around, talking on phone) or appearance does not exclude significant pain. Laboratory values are not markers for pain.

Treatment of acute, severe pain typically requires parenteral opioids, such as morphine or hydromorphone,[8,11,12] although oral morphine may be effective. Meperidine is not recommended due to the potential for neurotoxicity (seizures and behavior changes) from accumulation of the metabolite normeperidine. Avoid IM injections because repeated injections can be associated with unpredictable absorption and muscle fibrosis. Some patients may require large opioid doses for adequate analgesia. Regular doses of analgesics for a few hours to several days typically are required. Continuous or demand patient-controlled analgesia, or both, is an effective method for pain control and can reduce opioid need and decrease opioid-related adverse events, and in general, it is well accepted by patients. NSAIDs can be used for their probable additive effect in pain management of sickle cell crisis, but use should be individualized based on patient risk factors, such as renal disease.[8,11,12,16] Low-dose ketamine by continuous IV infusion is a potential adjuvant analgesic in acute pain crisis and may reduce opioid medication requirements, time to analgesic treatment, and total pain.[17,18]

A recommended practice is to develop an individualized assessment and treatment protocol for specific patients who frequent the ED with painful crises.

Transfusion Practice RBC transfusion to reduce the concentration of HbS-containing erythrocytes does not shorten the duration or reduce the risk of complications of routine acute vaso-occlusive painful crisis. Furthermore, transfusion involves significant expense, the risk of bloodborne disease transmission, and the potential for iron overload and exposes the patient to the minor RBC antigens, with the potential to induce antibodies that prevent or complicate future transfusions (see Chapter 238, "Transfusion Therapy"). Transfusion for sickle cell crisis or complications is reserved for specific indications such as aplastic crisis, pregnancy, stroke, respiratory failure, and general surgery.[8,11-13] Transfusion protocols are categorized as aggressive (decreasing HbS to <30%) and conservative (increasing hemoglobin to >10 g/dL or 100 g/L); for most indications, there is no clinical difference between aggressive or conservative protocols.

Bone Pain Bone pain is common during a sickle cell crisis and is usually located in the back and the extremities. The pain is diffuse, without focal signs of inflammation; therefore, redness, warmth, or swelling suggests infection such as cellulitis or osteomyelitis. The femoral and humeral heads are most commonly affected, primarily due to pressure increases from vascular occlusion and increased RBC marrow. Localized hip pain with difficulty ambulating suggests aseptic necrosis of the femoral head; approximately 30% of HbSS patients develop femoral head damage by age 30 years old. Joint effusions are occasionally seen in painful sickle cell crisis, and arthrocentesis is often necessary to differentiate this complication from infection. Plain radiographs may show evidence of aseptic necrosis or osteomyelitis, whereas bone infarcts usually are not visible on radiographs. A radionuclide bone scan or MRI may be necessary to differentiate infection from infarction.

Acute Chest Syndrome **Acute chest syndrome** is defined as a new infiltrate on chest radiograph in association with one other new sign or symptom: fever >38.5°C (101.3°F), cough, wheezing, tachypnea, or chest pains.[19-21] In adults, acute chest syndrome occurs most commonly 1 to 3 days after hospitalization for an acute pain crisis. Acute chest syndrome is the leading cause of death in patients with HbSS in the United States, with a mortality up to 9% and 13% of patients requiring mechanical ventilation.[19] Although this phenomenon occurs most often as a single episode, some patients may experience multiple attacks, resulting in chronic lung disease.[22]

Acute chest syndrome has multiple potential precipitating etiologies, including pulmonary infections, pulmonary infarction, fat emboli, and rib infarction.[20-22] Acute chest syndrome may also result from iatrogenic causes. Opioid analgesics promoting hypoventilation can increase the risk of acute chest syndrome. It is not clear if excess hydration producing pulmonary edema increases the risk of acute chest syndrome.[23]

Up to 30% of cases of acute chest syndrome admitted to the hospital will have an infectious pathogen identified.[19] The two most common organisms identified are the atypical pneumonia pathogens *Chlamydia pneumoniae* (in adults) and *Mycoplasma pneumoniae* (in pediatric patients).[19] Other organisms associated with acute chest syndrome include *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, adenoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses, cytomegalovirus, and parvovirus B19.[19] Traditionally, *Streptococcus pneumoniae* was considered the most frequent cause of pulmonary infection, but this pathogen is now rare in cases of acute chest syndrome, presumably due to the use of pneumococcal immunization and prophylactic penicillin therapy.

Abundant evidence for fat embolism as a possible cause for acute chest syndrome includes bony slivers and marrow fat found in the pulmonary vasculature at autopsy, fat droplets within endothelial cells identified in lung biopsy specimens collected via bronchoscopy in living patients, and elevated serum levels of free fatty acids and circulating secretory phospholipase A_2, a potent inflammatory mediator originating from the bone marrow.[24] Pulmonary thrombosis has a high prevalence in sickle cell anemia and is common in acute chest syndrome (17% of cases).[25]

The acute chest syndrome is the final result of several pathogenic processes exerting their effects individually and collectively in a vicious cycle, creating regional hypoxia, acidosis, and lung injury (**Figure 236-2**).

Respiratory symptoms are usually present, including cough, shortness of breath, chest pain, and fever, although the clinical presentation may vary.[20,21] Fever occurs in 80%, followed by cough in up to 74% and chest pain in 44% to 57% (may be pleuritic due to pulmonary infarction). On physical examination, rales are the most common finding (48% to 76%).[23] Chest radiographs are important to identify the presence of a new patchy infiltrate; any lobe can be affected. The radiographic changes often lag behind the clinical features, so the radiograph may be initially normal, and the clinical severity of disease and the extent of hypoxia may not correlate with radiographs. Adults typically demonstrate lower lobe disease with effusion.[26]

Acute chest syndrome is treated with supportive care (oxygen, analgesics, hydration), antibiotics, and exchange transfusion (**Table 236-3**).[11,13,20-22] Give oxygen for hypoxemia. Pain control with parenteral opioids requires careful monitoring to prevent both oversedation and hypoventilation. Patients are often unable to adequate drink fluids to maintain hydration. Administer maintenance IV fluid therapy with 5% dextrose in half normal saline until the patient is able to adequately drink. Monitor closely to avoid volume overload.[27]

Antibiotics are recommended irrespective of cultures, and many experts believe that patients with acute chest syndrome should receive a full course of empirical broad-spectrum antibiotics to treat pathogens commonly associated with community-acquired pneumonia.[11,13,20,21] Typically a parenteral cephalosporin and macrolide are used to ensure coverage of *Mycoplasma* and *Chlamydia*.[13] Bronchospasm may accompany acute chest syndrome and can persist after recovery, indicating that bronchial hyperactivity can be a marker of lung injury in some patients. Inhaled β_2-adrenergenic agents can be used if wheezing occurs.[28] Incentive spirometry is recommended for prophylaxis and treatment.

Transfusion therapy is believed to be lifesaving in acute chest syndrome, but there are no firm evidence-based recommendations for its use,[29] and currently accepted indications for exchange transfusion in acute chest syndrome are based on empirical observations.[11,13,20-22] Significant increases in hemoglobin from transfusion may increase viscosity and the risk of complications.[23] Exchange transfusion appears more advantageous, particularly in patients with relatively high hemoglobin (>9.0 g/dL

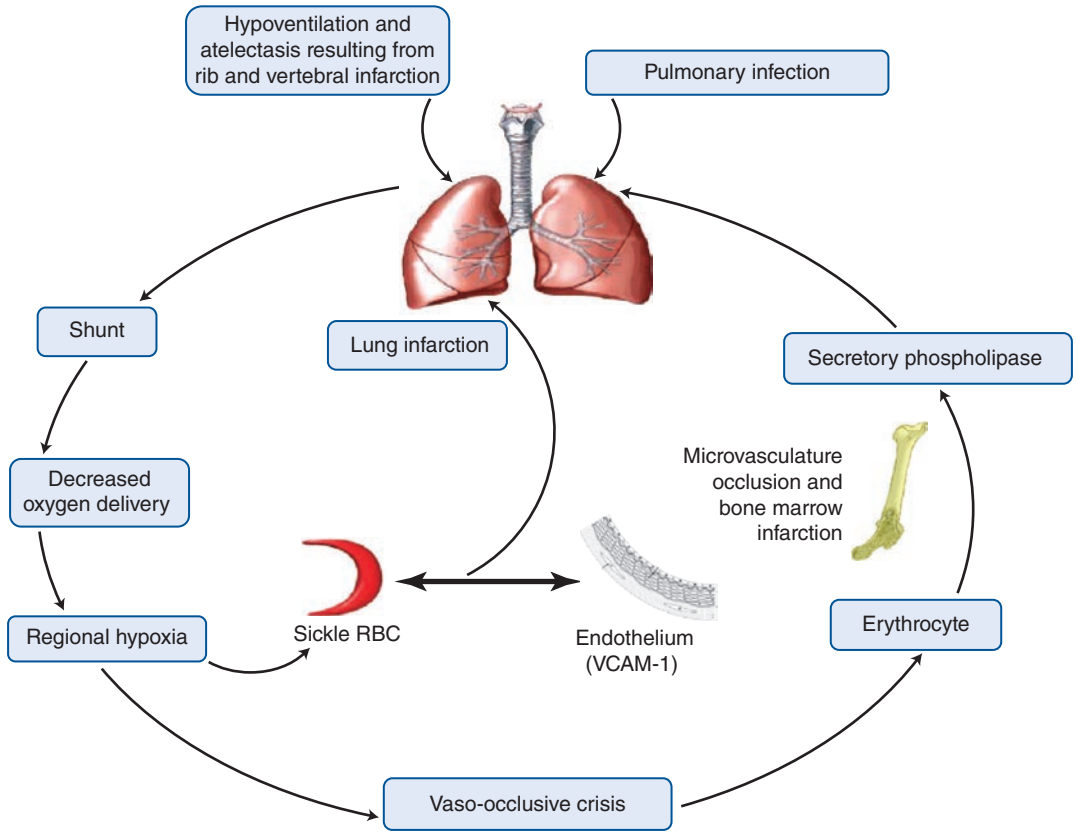

FIGURE 236-2. Pathogenesis of acute chest syndrome. RBC = red blood cell; VCAM-1 = vascular cell adhesion molecule-1.

or 90 g/L). Exchange transfusion decreases the concentration of sickled hemoglobin while maintaining an unchanged whole-blood viscosity and resulting in little iron gain. Exchange transfusion is usually reserved for severe crises signaled by deterioration of the patient's partial pressure of arterial oxygen to <60 mm Hg (<8 kPa) with the goal to decrease the HbS level to <30%; it is also used in the presence of neurologic abnormalities or multiorgan failure in the setting of acute chest syndrome.

Systemic corticosteroids to treat acute chest syndrome are controversial; they may prevent deterioration and decrease the need for transfusion but are associated with higher rates of readmission.[30-32]

Patient clinical status dictates disposition and level of care required. All patients with acute chest syndrome should be admitted to a monitored setting, although not necessarily an intensive care unit. Increasing age is associated with poor outcome, but the best predictors of poor outcomes include platelets <199,000/mm^3, comorbidity including cardiac disease, and extensive lung involvement.[33] Long-term complications include pulmonary hypertension, pulmonary fibrosis, and cor pulmonale.[26]

Abdominal Crisis Generalized and constant abdominal pain is a common complaint during an acute sickle cell crisis, and it may be difficult to distinguish from a focal abdominal problem, such as cholecystitis or appendicitis. **With a vaso-occlusive crisis, there should be accompanying musculoskeletal pain, the patient can frequently identify that the pain is similar to prior episodes, and there should not be physical evidence of peritonitis.** Repeated abdominal examinations should be done to assess for progression of tenderness and development of peritoneal signs.

Hepatic infarction may produce jaundice and abdominal pain, which can be difficult to distinguish from hepatitis or cholecystitis. Liver involvement is common in patients with vaso-occlusive pain crisis, with elevation in liver function tests due to sinusoidal vaso-occlusion. Hepatic sequestration is similar to splenic sequestration and results from hepatic congestion from sickle cells. Anemia with a brisk reticulocyte response, hepatomegaly, and right upper quadrant pain typically occur. Severe right upper quadrant pain and marked elevations of bilirubin may be due to intrahepatic cholestasis, which rarely may progress to shock liver and hepatic failure. Hepatic crises including hepatic sequestration and intrahepatic cholestasis require volume resuscitation and likely exchange transfusion. Biliary disease is common because pigment-related cholelithiasis occurs in 30% to 70% of sickle cell anemia patients from chronic hemolysis and increased bilirubin turnover.

GU System Vaso-occlusive events involving the kidneys are often asymptomatic and likely account for the frequent finding of microscopic hematuria.[34] Infarction in the renal medulla may cause flank pain, renal colic–type pain, and costovertebral angle tenderness, mimicking pyelonephritis.[35] Papillary necrosis may result in either gross or microscopic hematuria, but RBC casts are uncommon. Approximately 30% of adults with HbSS develop renal failure, with microalbuminuria and proteinuria common findings.[7] Renal imaging studies generally are necessary for correct diagnosis of renal infarction or papillary necrosis. Both are treated with IV fluids to maintain urine flow and close monitoring of hemoglobin levels to ensure that anemia does not worsen. Patients are often prescribed angiotensin-converting enzyme inhibitors prophylactically to reduce renal disease progression. The higher incidence of renal injury in this population warrants caution with NSAIDs.[8] Urinary tract infections are common, and routine urine dipstick is recommended with ED assessment.

Priapism occurs in up to 30% of males. Priapism is typically the low-flow variety due to stasis, hypoxia, and ischemia. Patients with stuttering priapism (recurrent episodes that last <3 hours often with a pattern of increasing frequency and severity) are treated with oral adrenergic agents or hormonal analogs.[36] Patients with a major episode (sustained erection lasting >4 hours) are treated with fluid hydration, pain control, corporal aspiration, and intracorporal installation of a dilute α-adrenergic agonist solution (see Chapter 93, "Male Genital Problems"). Transfusions, either simple or exchange, have no proven benefit for sickle cell–associated priapism.[36]

Splenic Infarction and Sequestration The spleen is particularly susceptible to the vaso-occlusive effects of sickled cells, and over time, microinfarctions result in a spleen that is essentially nonfunctional by

TABLE 236-3 Assessment and Treatment of Acute Chest Syndrome

History	Major presenting symptoms: dyspnea, fever, cough
	Accompanying chest, rib, bone, or joint pain
	Assess degree or severity of pain
	Recent or previous sepsis, infection, pneumonia, or hospitalization
	Prior history of acute chest syndrome, especially if required intubation and ventilatory support
	Potentially infectious contacts
	Current medications, especially daily prophylactic penicillin
	Immunization history, especially pneumococcal and *Haemophilus influenzae* type b
	Baseline hemoglobin level and arterial oxygenation saturation
Physical examination	General: respiratory distress, pallor, hydration, jaundice, rash
	Vital signs: especially temperature, pulse oximetry
	Respiratory: chest wall, lung sounds
	Heart: cardiomegaly and systolic murmur common with chronic anemia
	Abdomen: tenderness, organomegaly
Ancillary tests	CBC, leukocyte differential, reticulocyte count, serum electrolytes, liver function, renal function, urinalysis
	Cross-match sample: if red blood cell transfusion is contemplated
	Arterial blood gas: if moderate to severe respiratory distress and/or hypoxemia on pulse oximetry
	Chest radiography
	Blood cultures
	Additional blood tests: as indicated by clinical condition
Treatment	Oxygen: adjust according to pulse oximetry
	Oral hydration: preferable
	IV hydration: use Dextrose 5% in half-normal saline at rate 1 to 1.5 times maintenance (aggressive IV fluids can worsen acute chest syndrome)
	Analgesics: if needed, generally potent parenteral opioids are used, monitor for signs of respiratory suppression
	Incentive spirometry
	Antibiotics: empiric antibiotics recommended to cover community-acquired pneumonia pathogens
	Transfusion: use if severe acute anemia is present
Exchange transfusion	Consider when
	Severe acute chest syndrome on admission and past history of requiring ventilatory support: useful to prevent intubation
	Multiorgan dysfunction/multiorgan failure syndrome
	Neurologic abnormalities
	Deterioration despite above management: useful to prevent intensive care unit admission
	Patient already intubated and on ventilatory support: useful to shorten duration of ventilatory need
	Suspected or confirmed fat or bone marrow embolism

age 5.[37] This renders these patients at risk for serious infections and overwhelming sepsis from encapsulated organisms. Therefore, immunizations, prophylactic penicillin therapy, and parental education are critical to minimize the risk of infection and prompt early evaluation of fever in these patients. As HbSS patients grow into teenage years, the risk of overwhelming sepsis decreases, but they remain predisposed to infection.

Splenic sequestration is an important cause of significant morbidity and occasional mortality, with its occurrence being more common in children than in adults due to RBCs becoming trapped within the spleen and removed from circulation.[38] After ages 3 to 5 years, splenic sequestration is uncommon due to splenic autoinfarction.[39] However, it may occur in adults with persistent splenic tissue. This syndrome manifests by the sudden enlargement of the spleen with an acute decrease in the hemoglobin level (>2 g/dL or >20 g/L) due to sequestration of the blood volume within the spleen, along with reticulocytosis and splenomegaly. Left upper quadrant pain may or may not be present. Symptoms include tachycardia, hypotension, pallor, and lethargy, and the spleen is usually enlarged and firm. Platelets also may be sequestered, resulting in moderate thrombocytopenia. The reticulocyte count should remain elevated.

Therapy includes volume resuscitation, which may mobilize some of the RBCs trapped within the spleen. Simple RBC transfusion or exchange transfusion may be necessary. An investigation for a precipitating infection should be done. Rarely, splenectomy is necessary. Unfortunately, recurrence of this syndrome is common at a rate approaching 50%.

Hemolytic Anemia and Aplastic Crisis Patients with HbSS have a chronic hemolytic state due to the shape of the red cells. The baseline hemoglobin level is often between 6 and 9 g/dL (60 to 90 g/L), and the reticulocyte count is between 5% and 15%. With infections, the hemolytic process may worsen, and hemoglobin may drop from the previous baseline. Typically, erythrocyte production will increase in response to the increased RBC destruction, but it may not be enough to compensate for the increased hemolysis. Acutely, the patient may notice symptoms of worsening fatigue, shortness of breath, dyspnea on exertion, and scleral icterus. Symptoms may worsen if other comorbid diseases are present. It is uncommon for the hemolysis to be so severe as to require transfusion.

Aplastic crisis results when the production of RBCs declines significantly, producing a rapid decrease in the hemoglobin level with reticulocytopenia.[40] The most common cause of aplastic crisis appears to be infection, specifically from human parvovirus B19. Folate deficiency and bone marrow necrosis with fat embolism also may play a role.[41] Aplastic crisis is more common in children than in adults. Patients generally will present with increasing fatigue and pallor and no evidence of increased hemolysis. The hemoglobin level will be unusually low, and few or no reticulocytes will be present; reticulocyte count is typically <0.5%. The leukocyte and platelet levels are usually normal. This syndrome is usually self-limiting, lasting 7 to 10 days, and the marrow will begin producing RBCs spontaneously within 1 week. Transfusion may be required in the interim.

Acute Stroke Ischemic and hemorrhagic stroke, as well as subarachnoid hemorrhage, are common in patients with HbSS disease.[42] The risk of stroke in children with sickle cell anemia is >200 times greater than those without the disorder,[43] and approximately 10% of patients experience a stroke before age 20 years old. Stroke is more common in pediatric patients compared to adults with HbSS.[7,8] The cause of stroke in most patients is cerebral infarction due to occlusion or narrowing of large cerebral vessels.[44] Increased cerebral blood flow and oxygen extraction at rest accompany these anatomic changes.[45,46] Silent cerebral infarcts visible on MRI have been observed in over a third of patients by age 14 years and are associated with decreased intellectual ability, poor academic achievement, and risk of progression to overt stroke.[47] Hemorrhagic strokes and subarachnoid hemorrhage most commonly occur in the third decade of life and are the most common acute neurologic complication in adults.[43,48] Cerebral aneurysms are also more common, perhaps due to local vessel occlusion or ischemia.

Acute stroke in an sickle cell anemia patient is treated with emergent simple or partial exchange transfusion to maintain HbS <30%.[49] Unfortunately, children who suffer a stroke are at 70% to 90% risk for recurrence, so chronic transfusion therapy is indicated to prevent recurrent stroke after the initial event.[47] The 2018 American Heart Association/American Stroke Association guidelines state that tissue plasminogen activator in sickle cell anemia patients with acute ischemic stroke may be beneficial, and discussion with a neurologist and hematologist is recommended.[50]

Infections Patients with sickle cell anemia are functionally asplenic after early childhood and functionally immunocompromised due to altered complement activity and increased bone marrow turnover,

rendering them susceptible to infections from encapsulated organisms, such as *H. influenzae* and *S. pneumoniae*.[51,52] Other common infections associated with sickle cell anemia include pneumonia caused by these organisms as well as *M. pneumoniae*, meningitis, and osteomyelitis due to *Salmonella typhimurium*, *S. aureus*, and *Escherichia coli*. In addition to *H. influenzae* immunization, patients with sickle cell anemia should be encouraged to receive yearly influenza vaccinations and remain up to date with pneumococcal immunization, and children should be maintained on prophylactic daily oral penicillin.[53]

In patients with fever and sickle cell anemia, CBC, chest radiograph, and urinalysis are recommended, with further testing based on the suspected source. If no source is found on history, examination, or basic assessment, obtain blood/urine cultures and consider admission for empiric IV antibiotic therapy in those who have a high fever (>39.5°C [103.1°F]) or those who appear ill.[13]

Cardiovascular Complications Cardiomegaly is common and correlates with the degree of chronic anemia. Additionally, cardiac dysfunction may occur from microinfarcts and hemosiderin deposition from hemolysis and blood transfusion.[54] Cardiac contractility is enhanced to maintain adequate systemic oxygen delivery, producing a systolic ejection murmur. Although the literature suggests patients with HbSS have minimal atherosclerosis of the large coronary vessels,[55-57] acute coronary syndrome may result from vaso-occlusive events.[58-60] Thus, consider acute coronary syndrome and obtain an ECG and cardiac biomarkers in patients presenting with chest pain or dyspnea. Further testing and treatment are based on these results, with interventional treatment recommended if ST-elevation myocardial infarction is diagnosed.

HbSS patients have laboratory evidence of thrombophilia, and combined with endothelial dysfunction and impaired vascular flow, there appears to be a 50- to 100-fold increased risk for pulmonary embolism and venous thrombosis.[61-65] Pulmonary embolism may also increase the risk of chronic pulmonary hypertension.[65] Because baseline D-dimer levels are increased in the steady state and levels are much higher during pain crisis,[66] clinical decision tools for deep venous thrombosis or pulmonary embolism using published D-dimer thresholds are not reliable in HbSS patients.

Dermatologic Chronic, poorly healing leg ulcers around the malleoli are common in older sickle cell patients.[67] Minor injury, impaired microcirculation due to repeated sickling episodes and microinfarcts, and infections all contribute to the development and persistence of these ulcers. No systemic or topical therapy has proven superior to facilitate healing.[68]

Multiorgan Failure Syndrome A small proportion of patients with vaso-occlusive crises can progress to multiorgan failure syndrome,[26,69] a most ominous complication with high mortality. The syndrome most commonly occurs in the setting of brisk hemolysis, with hemodynamic compromise and acute deterioration of at least two of three major organs (lungs, liver, or kidneys).[69]

Laboratory findings typically include elevated serum lactate dehydrogenase, acute anemia, thrombocytopenia, and renal injury. Thrombotic thrombocytopenic purpura can develop.[70,71] Chest radiograph may reveal multilobar infiltrates, and acute lung injury is a complication in 25% of cases.[69] Consultation with hematology and nephrology with admission to the intensive care unit is recommended. Simple or exchange transfusion is recommended, although evidence supporting this is lacking.[13] If thrombotic thrombocytopenic purpura occurs, plasma exchange with exchange transfusion can be of benefit, and in the setting of acute lung injury, endotracheal intubation with lung-protective strategies may be needed.

SICKLE CELL TRAIT

People with **sickle cell trait** (HbAS, heterozygous with one gene for the sickle mutation) have a normal life span and usually are asymptomatic, although complications have been attributed to the trait, categorized as definite, probable, or possible.[72] Definite associations include renal medullary carcinoma, hematuria and renal papillary necrosis, hyposthenuria, splenic infarcts, and exercise-related deaths. Probable associations include venous thromboembolic events, pregnancy-related complications, and complicated hyphema. Possible associations include retinopathy, acute chest syndrome, and asymptomatic bacteriuria.[72] Many of the associations are seen only under conditions of severe tissue hypoxia, acidosis, dehydration, or hypothermia or with coexistent beta-thalassemia.[73]

OTHER VARIANTS OF SICKLE CELL DISEASE

SICKLE CELL–HEMOGLOBIN C DISEASE

HbC results from a single point mutation in the β-globin chain gene; lysine is substituted for glutamic acid at the sixth position. The prevalence of the *HbC* gene is approximately 1 per 5000 in African Americans but is as high as 16% in parts of West Africa.[74] Deoxygenated HbC has the tendency to precipitate inside the RBC, forming crystals that decrease cell deformability and increase blood viscosity. Patients with HbC trait (heterozygous for the *HbC* gene, or *HbAC*) are asymptomatic, and those with HbC disease (homozygous for the *HbC* gene, or *HbCC*) typically have a mild hemolytic anemia, abundant target cells,[75] and sporadic episodes of musculoskeletal pain, splenomegaly, dental infarctions, and angioid retinopathy.[76]

The heterozygous sickle cell variant, sickle cell–hemoglobin C (*HbSC*), results when the gene for HbS is inherited from one parent and the gene for HbC is inherited from the other parent. These individuals have almost equal amounts of HbS and HbC but no HbA. Because HbC does not polymerize as readily as HbS, HbSC disease generally has less severe clinical consequences than sickle cell anemia (HbSS).[77] HbSC patients have a milder chronic hemolytic anemia and, as a consequence, milder reticulocytosis. The peripheral smear shows abundant target cells and a few sickle cells.

The complications of HbSC disease are similar to HbSS disease, although usually less severe. As opposed to sickle cell anemia, adult patients with HbSC disease often have splenomegaly. HbSC disease patients are susceptible to a proliferative retinitis that is visible on fundoscopy as angioid streaks (jagged, reddish brown, subretinal lines that taper outward from the optic nerve), representing breaks in the brittle Bruch membrane.[76] Cracks in the membrane lead to impairment of the choriocapillaries, which may produce loss of photoreceptor cells and lead to impaired vision.

SICKLE CELL–HEMOGLOBIN O-ARAB DISEASE

Hemoglobin O-Arab is a hemoglobin variant resulting from substitution of lysine for glutamic acid at position 121 of the β-globin chain. Hemoglobin O-Arab is widespread in the Middle East, is present in the Balkans, and occasionally occurs in African Americans.[78] Patients heterozygous for hemoglobin O-Arab (*HbAO-Arab*) have no clinical problems. Patients homozygous for hemoglobin O-Arab (*HbOO-Arab*) or heterozygous for sickle cell–hemoglobin O-Arab (*HbSO-Arab*) are clinically similar to patients with sickle cell anemia, having severe hemolytic anemia and recurrent vaso-occlusive crises, and children have the potential to develop sickle cell dactylitis and splenic sequestration crises.

THALASSEMIA

The thalassemias are a diverse group of hereditary disorders caused by defective synthesis of globin chains, resulting in an inability to produce normal adult hemoglobin.[79-81] The hallmark of these disorders is a microcytic, hypochromic, hemolytic anemia. These disorders are most common in those of Mediterranean, Middle Eastern, African, and Southeast Asian descent and are thought to be protective against malaria.[82]

The thalassemia syndromes are categorized depending on the globin chain affected or the abnormal hemoglobin produced. Thus, β-globin gene mutations give rise to **β-thalassemia** and α-globin mutations cause **α-thalassemia**.[80]

Both forms of thalassemia are characterized by varying degrees of anemia depending on the amount of ineffective erythropoiesis and premature destruction of the circulating RBCs. The hypoxia associated with severe anemia triggers compensatory mechanisms in an attempt to increase RBC production. This causes enlargement of the

reticuloendothelial organs and expansion of the bone marrow cavity, leading to osteopenia.

α-THALASSEMIA CARRIER AND TRAIT

Patients who are α-thalassemia carriers and with α-thalassemia trait have no clinical symptoms or physical findings, and patients with α-thalassemia trait are detected by the finding of microcytic RBCs and a borderline to slightly low hemoglobin level.[79]

α-THALASSEMIA (HEMOGLOBIN H DISEASE)

This disorder is thought to be protective for malaria and consists of both ineffective erythropoiesis and increased hemolysis. The populations with highest incidences are found in Southeast Asia, the Mediterranean, the Middle East, northern Thailand, and southern China. There is marked phenotypic variation in the clinical picture, from intrauterine or fetal death to mild anemia in adulthood. Hemoglobin H can cause chronic hypochromic microcytic anemia and hemolysis, which worsens during oxidant stress. Treatment is supportive and includes avoidance of unnecessary iron therapy. **Table 236-4** lists drugs to avoid in patients with α Thalassemia (HbH disease) because the drugs may precipitate hemolysis.

β-THALASSEMIA MINOR (β-THALASSEMIA TRAIT)

Patients with β-thalassemia minor are heterozygous for the β-globin mutation and have only mild microcytic anemia.[78,79] Splenomegaly may be present. On blood smear, these patients may have microcytosis and hypochromia as well as basophilic stippling. An elevated hemoglobin A_2 level, typically 4% to 6%, confirms the diagnosis. These patients generally have no clinical manifestations and may only come to attention during an evaluation for a mild anemia.

β-THALASSEMIA INTERMEDIA

β-Thalassemia intermedia is the result of genetic combination of β-gene mutations producing microcytic moderate anemia (blood hemoglobin usually >7 g/dL), splenomegaly, and intense bone marrow hyperplasia. HbF levels are elevated.[83,84] Clinical symptoms tend to be milder and delayed compared to thalassemia major. Transfusion requirements are variable, and complications from iron overload are less extreme.

β-THALASSEMIA MAJOR (COOLEY'S ANEMIA)

In β-thalassemia major, both β-globin genes are defective, and production of β-globin chains is severely impaired. Newborn infants with β-thalassemia major are usually well because HbF is predominant during the first few months of life. Symptoms emerge during the second 6 months of life when β-globin production would be expected. The RBCs of these children show a low mean corpuscular volume with microcytic and hypochromic cells. Variation in size and shape of the RBCs will be notable (increased RBC distribution width), as will be the presence of nucleated cells. HbF levels remain elevated, often >90% in untransfused individuals. This diagnosis should be considered in any child with a severe microcytic anemia and the appropriate ethnic background.

Affected children develop hepatosplenomegaly, jaundice, and expansion of the erythroid marrow, causing bone changes and osteoporosis, and possess increased susceptibility to infection.[85] The anemia is severe and requires regular, lifelong blood transfusions, with resultant challenges of alloimmunization.[86] Transfusions and enhanced iron absorption eventually cause iron overload, which is the etiology of most of the morbidity and mortality associated with the thalassemia. Untreated iron overload results in hemochromatosis with cardiac, hepatic, and endocrine dysfunction.[78,79,85,87] Treatment is chelation, with parenteral (desferrioxamine)[88] or oral (deferiprone and deferasirox)[89,90] agents.[81]

For those with a known diagnosis who present to the ED with significant symptoms related to anemia or hemolysis, consider transfusion along with a search for precipitating events.

TABLE 236-4 Drugs That Produce Oxidative Stress on Red Blood Cells at Therapeutic Doses

	Definite Association	Possible Association
Sulfonamides	Sulfacetamide Sulfamethoxazole Sulfanilamide	Sulfasalazine Sulfadimidine Glibenclamide
Antimalarials	Primaquine Pamaquine	Chloroquine
Urinary agents	Nitrofurantoin Nalidixic acid Phenazopyridine	
Miscellaneous antibiotics	Dapsone	Ciprofloxacin Chloramphenicol
Mothballs	Naphthalene	
Miscellaneous drugs	Methylthionium chloride (methylene blue)	Vitamin K analogs Ascorbic acid

SICKLE CELL–β-THALASSEMIA DISEASE

Sickle cell–β-thalassemia disease, a heterozygous sickle cell variant, occurs when the gene for sickle hemoglobin is inherited from one parent and a gene for β-thalassemia is inherited from the other parent. The frequency of sickle cell–β-thalassemia disease is about 1 per 1600 African American births. The severity of the disease depends on the functionality of inherited β-thalassemia gene. Between 80% and 90% of affected individuals have a β-thalassemia gene that results in the production of some normal β-chains, yielding a modest amount of HbA. Such patients have a mild hemolytic anemia with near-normal hemoglobin levels, few crises, and minimal organ damage. Those 10% to 20% of patients who inherit a β-thalassemia gene that inhibits all β-globin production have severe hemolytic anemia and vaso-occlusive symptoms comparable with patients with sickle cell anemia.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy of RBCs in humans, affecting >400 million people worldwide,[91] mainly among persons of African, Asian, or Mediterranean ancestry, a distribution suggestive of an ability to protect against malaria.[92] The disease has >400 variants.[91,93]

G6PD deficiency is an X-linked inherited disorder that primarily affects males.[93] Females must have two defective genes to be severely affected, but because expression of this gene is variable, women with one abnormal gene may still show some symptoms. Most adults are usually asymptomatic, but some may have intermittent hemolytic anemia, and a few have chronic hemolysis.

G6PD is an enzyme that catalyzes the oxidation of glucose 6-phophogluconate while concomitantly being responsible for the production of nicotinamide adenine dinucleotide phosphate, a required cofactor for maintaining glutathione in its reduced state. Typically, multiple enzymes catalyze dehydrogenase reaction in cells, except in RBCs, where G6PD is the predominant producer of nicotinamide adenine dinucleotide phosphate. Glutathione in the reduced state acts as a scavenger for harmful oxidative cell metabolites and, with the help of the enzyme glutathione peroxidase, converts harmful peroxide to water. G6PD-deficient RBCs are therefore susceptible to oxidative stress; oxidization of the sulfhydryl groups causes hemoglobin to precipitate within the cell. The precipitated hemoglobin is recognized by the presence of **Heinz bodies** on the peripheral blood smear (**Figure 236-3**). The affected RBCs are removed from the circulation by the spleen. Oxidant damage also occurs at the RBC membrane, producing both extravascular and intravascular hemolysis.

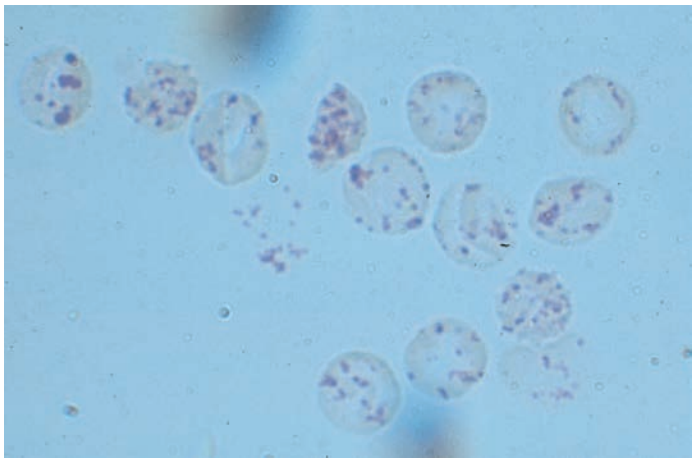

FIGURE 236-3. Heinz bodies. Blood mixed with hypotonic solution of crystal violet. Precipitates of denatured hemoglobin within the cells. [Reproduced with permission from Lichtman M, Beutler E, Kaushansky K, et al: *Williams Hematology*, 7th ed. Copyright © 2006, McGraw-Hill Inc., New York.]

CLINICAL FEATURES

The clinical expression of G6PD variants encompasses a spectrum of hemolytic syndromes. The likelihood of developing hemolysis and disease severity are determined by the degree of the enzyme deficiency (**Table 236-5**).

A serious complication of G6PD deficiency is neonatal jaundice occurring during the first week of life. The elevated bilirubin induces neurotoxicity that can result in permanent neurologic sequelae (kernicterus). Phototherapy is used to lower the serum bilirubin concentration.

Class III variants are the most prevalent G6PD mutations, with acute hemolytic events that are usually self-limited and well tolerated, so the variant condition may remain undetectable.[91]

Aside from favism and drug-induced hemolytic anemia, infection is the most common cause of hemolysis in G6PD-deficient individuals. There is also an increased incidence of pigmented gallstones and splenomegaly in patients with G6PD deficiency.

DIAGNOSIS

G6PD deficiency is established by the demonstration of decreased enzyme activity through quantitative assay. Evaluation of a blood film can reveal evidence of oxidative hemolysis. In societies with a high prevalence of G6PD deficiency, neonatal screening programs for this disorder are appropriate.

Patients with acute symptoms should be evaluated with a CBC and reticulocyte count (to evaluate level of anemia and bone marrow function), serum bilirubin levels, serum aminotransferases (to exclude other causes of jaundice), urinalysis (hemoglobinuria), and lactate dehydrogenase (elevated in hemolysis and a marker of hemolytic severity).

TABLE 236-5 World Health Organization Classification of Glucose-6-Phosphate Dehydrogenase (G6PD) Variants

- Class I variants: severe enzyme deficiency (<1% of normal activity) and have chronic hemolytic anemia.
- Class II variants, such as G6PD Mediterranean: severe enzyme deficiency (1%–10% normal activity), associated with acute intermittent hemolytic episodes.
- Class III variants, such as G6PD A–: moderate enzyme deficiency (10%–60% of normal activity) with intermittent hemolysis usually associated with stressors such as infection or drugs.
- Class IV variants: no enzyme deficiency (60%–150% normal activity), no hemolysis or other clinical significance.
- Class V variants: increased enzyme activity (>150% normal activity), no clinical significance.

TREATMENT

Treatment of the patient with G6PD deficiency is determined by the patient's overall clinical condition and removal of the offending agent, if present. If the illness is severe, then blood transfusion with packed RBCs may be warranted. Fluids are essential to prevent renal injury.

In patients with known G6PD deficiency, infections should be treated aggressively and oxidant drugs avoided. **There is solid evidence to implicate eight currently used medications as causing acute hemolysis in patients with G6PD deficiency: dapsone, phenazopyridine, nitrofurantoin, primaquine, rasburicase, pegloticase, methylthioninium chloride (methylene blue), and tolonium chloride (toluidine blue).**[94,95] Other oxidant drugs in therapeutic doses are not associated with increased hemolysis in G6PD-deficient patients.[94] Full recovery is typical after an acute hemolytic event.

HEREDITARY SPHEROCYTOSIS

Hereditary spherocytosis is the result of an erythrocyte membrane defect and is the most prevalent hereditary hemolytic anemia among people of northern European descent, affecting approximately 1 in 2000.[96] The disease typically is inherited in an autosomal dominant pattern, although a less common autosomal recessive variant exists, and up to 20% of hereditary spherocytosis patients develop the condition as a result of an apparent spontaneous mutation. The abnormal shape of the RBC results from molecular abnormalities in the cytoskeleton of the cell membrane, most commonly from mutations in the genes for the proteins spectrin and ankyrin.[97,98] These abnormalities result in RBCs with a microspherocytic shape that is not pliable enough to pass through the spleen. This results in an increased rate of destruction and a compensatory increase in RBC production.

CLINICAL FEATURES

The clinical spectrum of hereditary spherocytosis is divided into those with (1) mild disease, occurring in about 20% with an autosomal dominant inheritance; (2) moderate disease, occurring in about 75% with primarily autosomal dominant inheritance; and (3) severe disease, occurring in approximately 5% with an autosomal recessive inheritance.[99,100] The main complications include aplastic or megaloblastic crises, hemolytic crisis, cholecystitis or cholelithiasis, and neonatal hemolysis with jaundice.[99,100] The disease is primarily marked by anemia, jaundice, and splenomegaly.

Neonatal jaundice during the first week of life occurs in 30% to 50% of those with hereditary spherocytosis. After the neonatal period, the symptoms and signs depend on the severity of ongoing hemolysis. Patients with mild disease usually have a normal hemoglobin level and little or no splenomegaly but are susceptible to hemolytic or aplastic episodes triggered by infection. Patients with moderate disease have mild to moderate anemia, modest splenomegaly, periodic episodes of hemolysis with jaundice, and an increased incidence of pigmented gallstones. The rare patient with severe hereditary spherocytosis has significant hemolytic anemia requiring episodic blood transfusions, chronic jaundice, and an enlarged spleen.

DIAGNOSIS

The peripheral blood smear shows spherocytes with a normal to low mean corpuscular volume and increased mean corpuscular hemoglobin concentration (>36%). The diagnosis of hereditary spherocytosis is usually established by a combination of clinical history and examination, family history, and RBC indices and morphology.[101]

TREATMENT

Severe symptomatic anemia is acutely treated with RBC transfusions. In severe cases, splenectomy generally will reverse the anemia,[98,102] except in the unusual cases of autosomal recessive variants. After splenectomy, spherocytes are still present.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 237

Acquired Hemolytic Anemia

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INTRODUCTION

Acquired hemolytic anemias are disorders characterized by hemolysis of red blood cells (RBCs) not due to congenital or inherited disorders of hemoglobin synthesis or of the RBC membrane. Hemolysis of RBCs can take place within the intravascular space or in the extravascular spaces of the spleen and liver and can produce a spectrum of disease from mild, asymptomatic illness to severe hemodynamic compromise leading to critical ED encounters.

Clinical features of hemolytic anemia include those common to anemia in general: weakness, dizziness, shortness of breath, tachycardia, palpitations, chest pain, new or accentuated cardiac murmur, and pallor. RBC destruction generates free hemoglobin that is then broken down into bilirubin. Jaundice and darkened urine may develop when bilirubin production exceeds the liver's ability to conjugate it for biliary and fecal excretion. Splenic enlargement may promote the storage and extravascular breakdown of RBCs.

Characteristic laboratory findings of acquired hemolytic anemia demonstrate hemolysis of RBCs, hemoglobin breakdown, and compensatory RBC production (**Table 237-1**).

IMMUNE-MEDIATED ACQUIRED HEMOLYTIC ANEMIA

Immune-mediated acquired hemolytic anemia encompasses three main categories: autoimmune, alloimmune, and drug induced.

AUTOIMMUNE HEMOLYTIC ANEMIA

Individuals with autoimmune hemolytic anemia make antibodies against their own RBCs.[1,2] Diagnosis requires evidence of an antibody on the patient's RBCs, usually accompanied by an autoantibody in the plasma. The direct antigen test, also known as the **direct Coombs test**, is performed by combining the patient's anticoagulated, washed RBCs with anti–immunoglobulin G and anti-C3d (complement) antibodies to detect the presence of immunoglobulin G and/or complement on the RBC surface. A positive direct antigen test consists of the detection of either immunoglobulin G or complement on the RBC surface; it does not require the detection of both. A positive direct antigen test is not specific for a diagnosis of autoimmune hemolytic anemia (**Table 237-2**), nor does the presence of immunoglobulin G and/or complement on a patient's RBCs indicate the severity of disease; the direct antigen test is, however, a critical confirmatory screen. The **indirect Coombs test** looks for the presence of autoantibodies in the patient's serum, testing against a panel of RBCs bearing specific surface antigens.

TABLE 237-1 Basic Tests and Findings in the Evaluation of Hemolytic Anemia

Purpose	Test	Finding
Confirm anemia/blood loss	Hemoglobin	Decreased
	Hematocrit	Decreased
Confirm compensatory RBC production	Reticulocyte count	Increased
Confirm hemolysis	Peripheral smear	Spherocytes—extravascular hemolysis, RBC phagocytosis by macrophages
		Schistocytes—intravascular hemolysis, RBCs fragmented by shear mechanism
Confirm hemolysis	Lactate dehydrogenase	Increased, released by RBCs
Confirm hemolysis	Haptoglobin	Decreased, indicative of intravascular hemolysis
	Free hemoglobin	Increased, indicative of intravascular hemolysis
	Hemoglobinuria	Present
Confirm hemoglobin breakdown	Total bilirubin	Increased
	Indirect (unconjugated) bilirubin	Increased (hepatic conjugation of bilirubin overwhelmed)
	Urinary urobilinogen	Increased

Abbreviation: RBC = red blood cell.

TABLE 237-2 Differential Diagnosis of Positive Direct Antigen (Direct Coombs) Test

- Autoimmune hemolytic anemia
- Hemolytic transfusion reaction, acute or delayed
- Hemolytic disease of newborn
- Transplantation
- Drug-related hemolytic anemia
- IV immunoglobulin therapy
- Rh(D) immunoglobulin therapy
- Antilymphocyte globulin therapy
- Antithymocyte globulin therapy
- Sickle cell disease
- β-Thalassemia
- Renal disease
- Multiple myeloma
- Hodgkin's disease
- Systemic lupus erythematosus
- Human immunodeficiency virus/acquired immunodeficiency syndrome

Autoimmune hemolytic anemia can be categorized into primary and secondary disease.[1] Primary, or idiopathic, disease occurs without a known underlying etiology, whereas secondary disease is associated with an underlying disorder. Many cases initially designated as primary are later found to be associated with lymphoproliferative, autoimmune, or infectious diseases. Autoimmune hemolytic anemia is further divided into autoantibody type: warm type, cold type, and mixed type (**Table 237-3**).[2]

Warm Antibody Autoimmune Hemolytic Anemia Warm autoantibody–mediated hemolysis is predominantly extravascular, with antibody-coated RBCs consumed mostly by splenic macrophages and, to a lesser degree, by hepatic macrophages known as *Kupffer cells*.[3,4] Partial phagocytosis of the original RBC membrane structure leads to the formation of the more rigid, fragmentation-prone spherocyte. Increased spherocytosis found on peripheral blood smear correlates positively with severity of extravascular hemolysis.

Warm antibody autoimmune hemolytic anemia is initially treated with high-dose corticosteroids, typically oral prednisone, 1 to 1.5 milligrams/kg per day for 3 to 4 weeks, followed by lower doses for 3 to 4 months. Improvement is expected in 80% to 85% of patients, but complete remission occurs in only approximately 30% of patients.[3]

Monoclonal antibodies (e.g., rituximab) or immunosuppressive agents (e.g., azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide) are used to decrease autoantibody production.[2,3] Splenectomy removes both the main site of extravascular hemolysis in IgG-mediated disease and a major site of general autoantibody production, with clinical benefit in up to 60% of patients and potential for long-term remission or a complete cure.

A serious complication of splenectomy is **overwhelming postsplenectomy infection** due to encapsulated bacteria.[5,6] Prevention strategies include pneumococcal and meningococcal vaccinations and daily penicillin prophylaxis for the first few years after splenectomy. Overwhelming postsplenectomy infection should be treated early, often when symptoms and findings are mild, with both vancomycin and ceftriaxone IV.[7]

TABLE 237-3 Categories of Autoimmune Hemolytic Anemia (AIHA)

Warm antibody AIHA: Autoantibodies adhere most strongly to RBCs at 37°C (98.6°F).	65%–70% of AIHA cases 2:1 female predominance 50% primary (idiopathic) disease 50% secondary disease: lymphoproliferative, autoimmune disease, postinfection (transient) Usually immunoglobulin G (IgG) autoantibody against Rh(D) antigen Hemolysis usually extravascular Steroid responsive: 70%–80%
Cold antibody AIHA: Autoantibodies adhere most strongly to RBCs at 0–4°C (32–39.2°F).	20%–25% of AIHA cases **Cold agglutinin disease: IgM autoantibody against I antigen** Primary disease: older females Secondary disease: lymphoproliferative disorders, postinfection (transient) Raynaud's phenomenon, livedo reticularis, vascular occlusion Attacks precipitated by cold exposure Rarely intravascular hemolysis Not steroid responsive **Paroxysmal cold hemoglobinuria: IgG autoantibody against P antigen** Primary disease: rare, in adults Secondary disease: usually in children after upper respiratory infection Intravascular hemolysis during cold weather Usually not steroid responsive
Mixed-type antibody AIHA: Autoantibodies have variable temperature-dependent RBC adherence.	5%–10% of AIHA cases Primary disease: more common in older females Secondary disease: lymphoproliferative and autoimmune disorders Usually chronic course with severe exacerbations Usually steroid responsive

Abbreviation: RBC = red blood cell.

Severe hemolysis in cases of warm antibody autoimmune hemolytic anemia may be treated with plasma exchange as a transient stabilizing measure while waiting for steroids or immunosuppressive agents to take effect.

For a patient with life-threatening anemia, the goal is to transfuse allogeneic RBCs without producing potentially harmful transfusion reactions. To find compatible RBCs for transfusion, laboratory personnel must determine whether the patient's blood contains both alloantibodies (directed to antigens not present on the patient's RBCs) and autoantibodies (targeted to commonly occurring antigens present on the patient's RBCs).[8,9] The testing process can be both labor and time intensive, sometimes requiring 6 hours or longer. Once completed, antigen-free, compatible RBC units are the best approach for safe and effective transfusion. If emergently needed, transfusion of the *least incompatible* units may be administered slowly and in the smallest amounts necessary with close monitoring.[10]

Cold Antibody Autoimmune Hemolytic Anemia Cold autoantibodies lead to clumping or agglutination of RBCs on peripheral smear at cooler temperatures.[1,2] Cold antibody autoimmune hemolytic anemia is associated with complement fixation on the RBC surface and triggering of the complement cascade. Hemolysis occurs in both the extravascular and intravascular spaces. Instead of splenic macrophages, the hepatic macrophages known as *Kupffer cells* are responsible for most of the extravascular RBC destruction. The two major cold antibody disorders are **cold agglutinin disease** and **paroxysmal cold hemoglobinuria**. Fifty percent of secondary cold antibody cases are associated with lymphoproliferative disorders, with underlying infection as the next leading cause.

Cold agglutinin disease is exacerbated by the cold, so more episodes of acute hemolysis are seen during winter.[11] Because the peripheral circulation is typically cooler than the central circulation, secondary Raynaud's phenomenon and vascular occlusion can complicate cold agglutinin disease, leading to acrocyanosis and tissue necrosis/gangrene.[12] Painful discoloration and mottling of the skin (termed livedo reticularis) may be seen.[13] Primary cold agglutinin disease causes chronic, recurrent hemolysis in older adults, particularly females, with a peak incidence at age 70 years. As with all of the idiopathic autoimmune hemolytic anemias, an associated underlying disease process may be discovered well after initial presentation of cold agglutinin disease; in particular, an occult lymphoproliferative disorder may be the source of the aberrant cold autoantibodies.

Secondary cold agglutinin disease may present after infection with *Mycoplasma pneumoniae*, Epstein-Barr virus, infectious mononucleosis, adenovirus, cytomegalovirus, influenza, varicella-zoster virus, human immunodeficiency virus, *Escherichia coli*, *Listeria monocytogenes*, or *Treponema pallidum*. Hemolysis typically begins 2 to 3 weeks after the onset of illness, corresponding with peak antibody development against the infectious agent, and resolves about 2 to 3 weeks after resolution of the infectious illness. Many patients with *Mycoplasma* pneumonia and infectious mononucleosis will have measurable cold agglutinin titers, but far fewer will develop symptomatic hemolytic anemia. Conversely, cold agglutinin disease associated with lymphoproliferative diseases such as chronic lymphocytic leukemia and lymphoma produces high autoantibody levels with potential for significant hemolysis.

An important principle in treating cold agglutinin disease is keeping the extremities and appendages, particularly the nose and ears, warm in cold weather. Patients should take a daily folate supplement for healthy RBC production. Cold agglutinin disease is less likely to respond to steroids, with response rates as low as 35%.[11] Splenectomy is less effective in treating cold agglutinin disease because splenic macrophages play a lesser role in IgM-mediated cold antibody disease. Severe hemolysis has been treated successfully with immunosuppressive agents such as chlorambucil, cyclophosphamide, interferon-α, fludarabine, or rituximab.[11,14] Because immunoglobulin M autoantibodies have an intravascular distribution, plasmapheresis may assist by removing autoantibodies from the circulation when combined with immunosuppressive agents. Infection-related cold antibody disease does not require therapy because the hemolytic anemia is usually self-limited.

If RBC transfusion is necessary, transfused blood should be infused at 37°C (98.6°F) using a blood warmer. Transfusions should be limited as they may worsen ongoing hemolysis because most cold antibodies act against the I/i group antigens found on most donor RBCs. Donor complement in the transfused product also may exacerbate ongoing hemolysis.

Paroxysmal cold hemoglobinuria is caused by a biphasic hemolysin immunoglobulin G autoantibody called the *Donath-Landsteiner (D-L) antibody* that is directed against the P antigen system found on most RBCs.[15] This potent autoantibody binds to RBCs and fixes early complement cascade proteins at low temperatures, whereas terminal complement components adhere and produce intravascular lysis of RBCs at warmer, physiologic temperatures.

Bursts of cold weather–induced intravascular hemolysis lead to bouts of dark urine or hemoglobinuria for which the disease is named. Other presenting symptoms include attacks of high fever, chills, headache, abdominal cramps, nausea and vomiting, diarrhea, and leg and back pain, all exacerbated by cold weather. Cold urticaria may develop, as well as extremity paresthesias and Raynaud's phenomenon.

Primary paroxysmal cold hemoglobinuria is a rare, idiopathic, chronic condition occurring in adults, characterized by cold-induced episodes of massive hemolysis. Secondary disease occurs predominantly in children, usually seen after a preceding infection with adenovirus, influenza A, measles, mumps, Epstein-Barr virus, cytomegalovirus, varicella, *M. pneumoniae*, *Haemophilus influenzae*, or *E. coli*. Most pediatric cases are self-limited and nonrecurring, but severe cases may take weeks to resolve. With severe hemolysis, hemoglobinuria is common, and methemoglobinemia may be seen. Acute renal failure may develop as a complication. Adult patients with chronic, relapsing disease should be tested for syphilis, because cold-provoked hemolysis has been associated with tertiary or late syphilis as well as with congenital syphilis.

Patients with paroxysmal cold hemoglobinuria should be kept warm. Steroids can be considered in children with severe hemolytic anemia, but because infection-related disease tends to be self-limited, benefit is uncertain. Disease secondary to syphilis responds to effective antibiotic treatment. Splenectomy is not helpful, and plasmapheresis should be used only as a temporizing measure in life-threatening cases. RBC transfusion using a blood warmer should be limited to cases of severe anemia because most donor units are P antigen positive and may stimulate further production of antibodies.

Mixed Antibody Autoimmune Hemolytic Anemia Mixed-type autoimmune hemolytic anemia, with both warm and cold autoantibodies to RBCs, presents as either primary or secondary disease, with the latter most commonly associated with lymphoproliferative and autoimmune diseases, particularly systemic lupus.[1,2] The course of illness is usually chronic with severe exacerbations. Like the warm antibody disorder, the mixed type is usually steroid responsive, can be treated with splenectomy, and responds to immunosuppressive therapy.

ALLOIMMUNE HEMOLYTIC ANEMIA

Alloimmune hemolytic anemia requires exposure to allogeneic RBCs with subsequent alloantibody formation. In the laboratory, alloantibodies react specifically with the allogeneic RBCs that triggered their production and not against a patient's own RBCs. A well-known example of this is when the Rh(D)-negative maternal immune system develops immunoglobulin G alloantibodies upon exposure to Rh(D)-positive fetal RBCs. The maternal alloantibodies can then cross the placenta, leading to fetal RBC destruction in a condition known as ***hemolytic disease of the newborn.***[16] Anemia can range from mild to potentially fatal, producing intrauterine fetal death. The term ***hydrops fetalis*** has been used to describe the anasarca seen in severe cases. Transplacental or fetomaternal hemorrhage, the inciting stimulus for maternal alloantibody formation, may occur during amniocentesis, chorionic villus sampling, delivery, or abortion (threatened or otherwise). **Administration of anti-D immunoglobulin G following a fetomaternal hemorrhage event and soon after delivery will suppress maternal alloantibody formation and prevent subsequent hemolytic disease of the newborn.** Treatment of established hemolytic disease of the newborn employs intrauterine and intravascular fetal transfusion and may include plasma exchange and/or IV immunoglobulin therapy.

Most adults who develop alloimmune hemolytic anemia have a history of RBC transfusion, which sensitizes patients to allogeneic RBC antigens. A subsequent transfusion can result in immediate alloantibody production, resulting in the fever, chest and flank pain, tachypnea, tachycardia, hypotension, hemoglobinuria, and oliguria seen in the hemolytic transfusion reaction (see Chapter 238, "Transfusion Therapy"). In patients with high alloantibody titers, the hemolytic reaction can be immediate. Delayed alloantibody-mediated hemolysis is also possible, with hemolytic transfusion reaction symptoms presenting 3 to 7 days after transfusion.

DRUG-INDUCED HEMOLYTIC ANEMIA

Drug-induced hemolytic anemia is rare, estimated at 1 in 1,000,000 patients, where drug exposure induces antibody formation, leading to the destruction of RBCs.[17] More than 100 drugs are reported to induce autoantibody production against RBC antigens (**Table 237-4**).[18] Drug-induced hemolytic anemia can result in either a positive or negative direct antigen test and can be difficult to distinguish from autoimmune hemolytic anemia, so a careful review of current medications is important in patients with a new hemolytic anemia.

Stop the potentially offending agent when a drug-induced hemolytic anemia is suspected. Treatment is symptomatic, with carefully screened RBCs transfused as needed. Steroids can be used in cases of drug-related severe hemolysis.

TABLE 237-4 Drugs Most Often Cited as Inducing Hemolytic Anemia

Cephalosporins	Cefotetan Ceftriaxone Cephalothin
Chemotherapeutic agents	Fludarabine Interferon Oxaliplatin
NSAIDs	Diclofenac Mefenamic acid Phenacetin Tolmetin
Penicillins	Penicillin G Piperacillin
Miscellaneous	Catechin (antidiarrheal) Levodopa (antiparkinsonian) Methyldopa (antihypertensive) Nomifensine (antidepressant) Quinidine (antidysrhythmic) Rifampin (antibiotic)

MICROANGIOPATHIC SYNDROMES

The two classic syndromes associated with microangiopathic hemolytic anemia are thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS).[19,20] Both syndromes involve platelet aggregation in the microvascular circulation via mediation of von Willebrand factor. Microangiopathic hemolytic anemia or schistocyte-forming hemolysis occurs from fragmentation of RBCs during travel through these partially occluded arterioles and capillaries. Although TTP and HUS are clinical syndromes with characteristic features, overlap does occur, sometimes making differentiation difficult. TTP is more common in adults and induces more prominent neurologic effects, whereas HUS is more common in children with greater impairment on the renal system.

THROMBOTIC THROMBOCYTOPENIC PURPURA

The classic pentad for TTP includes CNS abnormalities, renal pathology, fever, microangiopathic hemolytic anemia, and thrombocytopenia. Untreated TTP carries a high mortality rate, but plasma exchange therapy can achieve remission of disease in >80% of patients.[20-22]

Pathophysiology The pathophysiology of TTP is connected to a specific metalloprotease ADAMTS-13 (*a d*isintegrin *a*nd *m*etalloproteinase with a *t*hrombospondin type 1 motif, member 13, also known as *von Willebrand factor–cleaving protease*). ADAMTS-13 is made by hepatic stellate cells, glomerular podocytes, and vascular endothelial cells. Its function is to cleave von Willebrand factor that has been unfolded by shear stress within the microvasculature of arterioles and capillaries. Without this cleavage function, unfolded von Willebrand factor monomers can form large multimers that lead to formation of intravascular microthrombi. TTP has been associated with ADAMTS-13 activity at levels <10% of normal.[23] However, severely deficient ADAMTS-13 activity alone does not reliably trigger TTP; often other precipitating or contributing factors are important, including pregnancy, infection, inflammation, and medication use.

ADAMTS-13 activity levels typically decrease by up to 30% during pregnancy, although not usually to the severely low levels associated with TTP.[23] It is hypothesized that the hypercoagulable state of pregnancy combined with the decreased ADAMTS-13 activity level may set the stage for TTP in pregnancy. TTP shares many clinical and laboratory features with preeclampsia–eclampsia, HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelet count), and acute fatty liver of pregnancy (see Chapter 100, "Material Emergencies After 20 Weeks of Pregnancy and in the Peripartum Period"), but symptoms of severe preeclampsia or HELLP syndrome before 24 weeks of gestation should raise suspicion for TTP.[20,24]

Human immunodeficiency virus infection, particularly with progression to acquired immunodeficiency syndrome, is associated with microangiopathic anemia and thrombocytopenia.[25] Influenza vaccination has

been implicated as a TTP trigger, leading to production of autoantibody against ADAMTS-13.[26] Acute pancreatitis, capable of inducing a systemic inflammatory response, has also been associated with TTP, although moderately rather than severely low ADAMTS-13 activity levels lead to uncertainty about a TTP diagnosis versus some other thrombotic microangiopathic process.[27,28]

Drugs associated with TTP include ciprofloxacin, ofloxacin, levofloxacin, quinine, sirolimus (when used with calcineurin inhibitors such as cyclosporine), risperidone, clopidogrel, lansoprazole, valacyclovir, mitomycin, infliximab, and ticlopidine.[20] Ticlopidine in particular is thought to induce autoantibody formation against ADAMTS-13 as well as microvascular endothelial cell injury in genetically susceptible individuals within 2 to 12 weeks of starting the medication. Ticlopidine has been associated with more severe thrombocytopenia and microangiopathic hemolysis than clopidogrel, whereas clopidogrel has produced more significant renal insufficiency not readily responsive to plasma exchange therapy.[29] Days to weeks may be required to achieve remission in ticlopidine- or clopidogrel-associated TTP cases.

Clinical Features Shearing of RBCs across these microthrombi produces the microangiopathic hemolytic anemia. Platelet aggregation in TTP leads to systemic platelet depletion or thrombocytopenia. When these microthrombi are concentrated in the CNS and renal arterioles and capillaries (though notably not found in venules), they promote tissue ischemia and necrosis, with resultant end-organ damage such as seizure, stroke, other focal neurologic deficits, coma, and acute renal injury.

Along with findings of severe anemia and thrombocytopenia of $<20{,}000/mm^3$ ($<20 \times 10^9/L$), serum and urine tests may corroborate ongoing intravascular hemolysis (Table 237-1) with renal injury or failure. Because TTP thrombi do not incorporate fibrin, **TTP can be distinguished from disseminated intravascular coagulation by normal coagulation studies**.[30]

Treatment Plasma exchange therapy is very effective in TTP with the goal to achieve a normal platelet count.[20,21] Daily plasmapheresis (plasma exchange) of 40 mL/kg or up to 1.0 to 1.5 times a patient's plasma volume is performed and then either weaned in frequency or stopped once normal platelet counts are reached for 2 to 3 consecutive days. Infusion of donor plasma replaces defective or insufficient ADAMTS-13, and removal of the patient's plasma rids the body of defect ADAMTS-13, autoantibodies, and large von Willebrand factor multimers.

If plasmapheresis cannot be performed immediately, fresh frozen plasma infusion can be initiated, with pheresis occurring later.[20] Infusion with factor VIII concentrate containing ADAMTS-13 activity can be considered for patients with plasma allergy after specialist consultation and review.

Severe TTP may require additional interventions such as RBC transfusion, anticonvulsants, antihypertensives, and hemodialysis. **Avoid platelet transfusions**, except in life-threatening bleeding or intracranial hemorrhage, because acutely worsened thrombosis can lead to renal failure and, potentially, death. **Aspirin** can exacerbate hemorrhagic complications in the setting of severe thrombocytopenia, but can still be used for cerebrovascular and cardiovascular indications in patients with adequate platelet counts. Heparin is not beneficial in TTP. Corticosteroids, rituximab, and cyclosporine may be used in the treatment of autoimmune TTP.[20,21] Discontinue the inciting drug in all cases of drug-associated TTP.

Outcome TTP relapse, defined as a new case onset >30 days after completion of remission-achieving plasma exchange therapy, is seen in 20% to 50% of cases, most often within 2 years after the initial episode. Patients with ADAMTS-13 activity levels <10% are at increased risk for relapse.[23] Triggers for relapse may be the same as those inciting original cases. Relapses may present with milder symptoms and less severe hematologic findings. Patients with multiple relapses may experience them farther and farther apart, and total volume and duration requirements for plasma exchange therapy are lessened in subsequent cases.[31]

The maternal mortality rate from TTP has been reduced significantly with the use of plasma exchange therapy, but fetal mortality has remained high secondary to placental microvascular occlusion, ischemia, and infarction. TTP may relapse with subsequent pregnancy, so affected women should be counseled accordingly.[24]

HEMOLYTIC-UREMIC SYNDROME

HUS, a common cause of acute renal failure in childhood, consists of **microangiopathic hemolytic anemia, acute nephropathy or renal failure, and thrombocytopenia**.[19,20,32] HUS can be classified as typical or atypical, with prognosis favoring typical cases.[32]

Typical HUS (>90% of cases) occurs in children, usually between age 1 and 4 years, presenting about 1 week into a case of infectious diarrhea that is often bloody and without associated fever. The causative agent of typical HUS is Shiga toxin (alternatively verocytotoxin)–producing *E. coli*, with serotype O157:H7 predominating in North America.[32,33] Other less common causes of diarrhea-associated HUS include *Shigella*, *Yersinia*, *Campylobacter*, and *Salmonella*. A variety of both fresh and processed foods have been implicated in *E. coli* O157:H7 infection outbreaks, with HUS occurring as a complication in each of the outbreaks.[33]

Atypical HUS (5% to 10% of cases) occurs in older children and adults and may be difficult to distinguish from TTP because of extrarenal involvement. Atypical HUS is associated with other infectious organisms, such as *Streptococcus pneumoniae* and Epstein-Barr virus, or it may have a noninfectious cause, such as bone marrow transplantation or the administration of immunosuppressant or chemotherapeutic agents.[32]

Pathophysiology Shiga toxin–producing *E. coli* O157:H7 possesses potent virulence factors that allow invasion of intestinal epithelial cells and subsequent transmural intestinal migration.[32] The ensuing colonic inflammation produces the characteristic hemorrhagic colitis associated with *E. coli* O157:H7 and other Shiga toxin–producing bacteria. Shiga toxin, once absorbed into the systemic circulation, binds with greatest affinity to receptors found on the surfaces of glomerular and renal tubular epithelial and endothelial cells and, to a lesser extent, to receptors lining cerebral and colonic epithelial and endothelial cells and pancreas. Molecular mimicry may exist between human CD36, an antigen found on endothelial cells and platelets, and Shiga toxin, so that antibody formed against the toxin may bind to CD36 and incite the pathologic processes leading to HUS.[34]

Toxin-mediated microvascular injury promotes platelet aggregation (and therefore, systemic depletion, leading to thrombocytopenia), thrombus formation at the injury site, and shearing of RBCs, contributing to tissue ischemia and necrosis. Microthrombi within the pancreas have been postulated to cause pancreatic β-cell death and subsequent deficits in insulin secretion. Thus, patients with HUS may present with hyperglycemia consistent with new-onset diabetes mellitus. Some may even go on to have chronic insulin requirements with increased morbidity and mortality rates.[35]

Clinical Features HUS typically presents 2 to 14 days after diarrhea develops, so patients may present during the diarrheal illness phase, with abdominal cramps, with or without bloody diarrhea, and often without fever. For the patient with nonbloody diarrhea, testing stool for fecal leukocytes can reveal occult inflammatory colitis, thereby prompting stool culture, specifically for *E. coli* O157:H7.[32] For the patient with bloody diarrhea, the results of stool testing for Shiga toxin–producing bacteria, including *E. coli* O157:H7, can guide medical treatment, alert providers that the complication of HUS should be anticipated, and aid in the cause of public health disease monitoring and outbreak prevention. In addition to the studies required for diagnosing hemolytic anemia, electrolyte and renal function panels should be obtained to detect nephropathy and associated electrolyte disturbances, whereas urinalysis should be examined for RBCs, RBC casts, protein, and other evidence of acute nephropathy.[32]

Treatment Typical HUS is treated with supportive care, with focus on hydration and RBC transfusion for significant anemia.[36,37] Hemodialysis may be required should acute renal failure develop. Infection with *E. coli* O157:H7 should not be treated with antimotility drugs because these agents appear to increase the risk of developing HUS.[37] Use of antibiotics for the treatment of *E. coli* O157:H7 diarrhea is controversial because in vitro studies have found that antibiotics may increase Shiga toxin expression from the bacteria, and case-control human studies have found that antibiotic treatment of the diarrheal illness may increase the risk of developing HUS.[37,38] Atypical HUS is treated with eculizumab.[39]

Outcome Acute renal failure occurs in 55% to 70% of patients with typical HUS, but most patients, up to 85%, recover kidney function.[32]

The mortality rate in typical HUS is about 5% to 15%. Historically, patients with atypical HUS had a poor outcome, with permanent renal failure or neurologic damage occurring in about half of patients and a morality rate approaching 25%. Aggressive treatment, including eculizumab, appears to significantly reduce the incidence of permanent renal failure and lower the death rate in atypical HUS.[39]

MACROVASCULAR HEMOLYSIS

A **prosthetic heart valve** may create turbulent blood flow with high shear stress across the valve. Older-generation mechanical heart valves were subject to deterioration that produced subsequent hemolysis, but hemolysis associated with current prosthetic heart valve models is most often attributed to paravalvular leak. Such leaks may occur at the time of valve placement or develop later in the life of the prosthetic valve if infection or calcification promotes dehiscence.[40] Particularly after mitral valve replacement, hemolysis may occur at both clinically insignificant and significant levels.

Macrovascular hemolysis can also occur after **intracardiac patch repair** or **aortofemoral bypass**; in patients with **coarctation of the aorta, severe aortic valve disease, or ventricular assist devices**; and in patients requiring the use of extracorporeal circulation such as during cardiopulmonary bypass, plasma exchange, or hemodialysis.[41,42] Mechanical sheer stress, chemical contaminant, and exposure to dialysis membranes are all factors contributing to hemolysis risk during hemodialysis, although technologic advances have made these events rare.[42]

Patients with ongoing mild macrovascular hemolysis should receive supplemental iron and folate to promote healthy reticulocytosis. By reducing the heart rate, β-blocker therapy may decrease RBC shear stress in the presence of a prosthetic valve and thereby mitigate hemolysis. Pentoxifylline, a xanthine derivative that reduces blood viscosity and improves RBC flexibility and deformability, can reduce hemolysis associated with prosthetic heart valves.[40] Hemolysis associated with extracorporeal circulation typically begins during the procedure, but such patients may or may not exhibit symptoms until hours afterward.

TABLE 237-5 Additional Causes of Hemolysis

Cause	Disorder	Comments
Infection		
	Malaria	Protozoan infects and damages RBCs, producing "blackwater fever" or hemoglobinuria
	Babesiosis	Protozoan infects and damages the RBC
	Clostridium perfringens	Toxin lyses RBCs
	Leptospirosis	Weil's syndrome; toxin lyses RBCs
Envenomation		
	Hymenoptera stings	Requires massive venom injection
	Brown recluse spider	Part of systemic loxoscelism
	Pit viper; Crotalinae; Elapidae; Viperinae	Intravascular RBC destruction
Chemical exposure		
	Arsine	Hemolysis can present 24 h after exposure[43,44]
	Naphthalene	Mothballs; well water contaminated by toxic dumps; can affect fetus in utero and neonates; patients with G6PD deficiency at higher risk
Direct impact trauma		
	March hemoglobinuria	Runners, soldiers, karate, conga drummers[45]; hemoglobinuria but usually not anemia[45-47]

Abbreviations: G6PD = glucose-6-phosphate dehydrogenase; RBC = red blood cell.

ADDITIONAL CAUSES OF HEMOLYSIS

Infection, envenomation, chemical exposure, and trauma can also result in hemolysis (**Table 237-5**).

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 238

Transfusion Therapy

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INTRODUCTION

Modern transfusion practice uses blood collected using a preservative–anticoagulant combination (usually citrate phosphate dextrose or citrate phosphate dextrose adenine-1). The collected whole blood is tested for transfusion-transmitted diseases and most often separated into specific components supplied as standardized preparations termed "units" (**Table 238-1**).[1] Transfusion in the ED typically is done for acute blood loss and/or circulatory shock using packed red blood cells (PRBCs), with increasing interest in using stored whole blood in severely bleeding patients.[2] Coagulation factors derived from human plasma or manufactured with recombinant technology are used to treat hemorrhage associated with a deficiency of one or more factors or to reverse the effect of antithrombotic medications (see Chapter 239, "Thrombotics and Antithrombotics") (**Table 238-2**).

Safe transfusion practice uses informed consent (patient is informed about the risks, benefits, and alternatives to transfusion) and steps to ensure that the correct blood product is delivered to the correct patient. A best practice is to use two individuals to verify the identification of the patient and the unit before transfusion. Bar code identification along with verification by one individual is an alternative to two-person verification.[3]

BLOOD TRANSFUSION

STORED WHOLE BLOOD

There is increasing interest in the practice of whole blood transfusion early in the resuscitation of patients with hemorrhagic shock, often before their ABO group is known.[4,5] The possible advantage is that whole blood as the initial resuscitation fluid efficiently provides treatment for blood loss, coagulopathy, and platelet hemostatic function to patients losing large volumes of blood. In addition, whole blood transfusion is simpler to administer since all three components (red cells, platelets, and plasma) are in one bag. Whole blood transfusion has been used by the military to treat traumatic hemorrhagic shock since the Korean War.[6] Based on this experience, several civilian trauma and EMS systems have started using whole blood transfusion. In response, the American Association of Blood Banks issued standards for whole blood transfusion in *Standards for Blood Banks and Transfusions*, 31st edition, effective April 1, 2018.[1]

Whole blood transfusion uses either stored or fresh whole blood.[7] Stored whole blood has a shelf life dependent on the anticoagulant used—21 days for citrate phosphate dextrose or 35 days for citrate phosphate dextrose adenine-1—although the hemostatic function of stored whole blood degrades after 2 weeks of storage. Fresh whole blood is collected via donation from prescreened donors ("walking blood donors") immediately before transfusion. Because fresh whole blood does not undergo testing before transfusion, it is used solely by the military for

TABLE 238-1 Blood Products

Component	Shelf Life	Approximate Volume/Unit (mL)	Approximate Content/Unit*	Initial Dose	Initial Dose Effect Without Ongoing Loss or Destruction of Red Cells or Platelets
Stored whole blood (type O, with low titer of anti-A and anti-B antibodies used for emergency unmatched transfusions)	21 d for CPD and 35 d for CPDA-1	500	Red cells 35%–38%, platelet count 150,000–200,000/mm^3 ($150–200 \times 10^9$/L), coagulation factors approximately 85% of predonation levels	Adult: 2 units	Raises hemoglobin concentration approximately 2 grams/dL (20 grams/L) or hematocrit by 6% in adults
Packed red blood cells	21–42 d	250–350	Red cells 65%–80% Plasma 10–20 mL	Adult: 2 units	Raises hemoglobin concentration approximately 2 grams/dL (20 grams/L) or hematocrit by 6% in adults
Platelets (apheresis-collected single-donor platelet concentrate)	5 d	250–300	Platelets $3–6 \times 10^{11}$	1 unit or 5 mL/kg	Raises platelet count by up to 50,000/mm^3 (50×10^9/L), but less in many cases
Platelets (pooled donor platelet concentrate, rarely used in the United States)	5 d	50–60	Platelets $8–9 \times 10^{10}$	6 units or 5 mL/kg	Raises platelet count by up to 50,000/mm^3 (50×10^9/L), but less in many cases

Abbreviations: CPD = citrate phosphate dextrose; CPDA-1 = citrate phosphate dextrose adenine-1.

*Unless specifically prepared, most blood-derived products contain small amounts of white blood cells, red blood cells, platelets, and plasma in addition to the specific component.

severely bleeding patients when stored blood or component therapy is not available (e.g., resuscitative care initiated in active combat zones). Fresh whole blood is not approved for civilian use by the American Association of Blood Banks or U.S. Food and Drug Administration.

Although transfused whole blood can be matched to the blood type of the recipient patient before use, the most urgent need for whole blood transfusion is in the severely bleeding patient before blood typing (e.g., in the ambulance, helicopter, or ED). It is important to note that while

TABLE 238-2 Coagulation Factor Products

Type of Product*	Initial Dose	Comments and Approved Indications
Fresh frozen plasma (FFP)	4 units or 15 mL/kg	Volume 200–250 mL/unit 1 unit contains about 200–250 units of each individual coagulator factor and 400–500 milligrams of fibrinogen Initial dose raises most coagulation factor levels approximately 20% Shelf life: 1 y frozen and up to 5 d after thawing Used for coagulation factor replacement
Cryoprecipitate	1 unit per 5–10 kg body weight; typically 10 units in an adult	Volume 30–40 mL/unit Each unit typically contains: factor VIII 80–140 units, fibrinogen 150–250 milligrams, von Willebrand factor 80–100 units, and factor XIII and fibronectin in variable amounts Initial dose increases fibrinogen 50–100 milligrams/dL (0.5–1.0 gram/L) Shelf-life: 1 y frozen and 4 h thawed Used for replacement of fibrinogen, factor XIII, factor VIII, or von Willebrand factor
Fibrinogen concentrate (human) RiaSTAP® (CSL Behring)	Dosed to increase fibrinogen level from baseline to >150 milligrams/dL (1.5 grams/L) If baseline fibrinogen level unknown, administer 70 milligrams/kg	Each vial contains 900–1300 milligrams of fibrinogen Used for acute bleeding episodes in patients with congenital fibrinogen deficiency
Factor IX complex Profilnine SD® (Grifols Biologicals) Bebulin VH® (Baxter Healthcare Corporation)	Dosed according to desired factor IX increase	Contains factors II, IX, and X Used in hemophilia B (factor IX deficiency)
Prothrombin complex concentrate (human) Kcentra® or Beriplex® P/N (CSL Behring) Octaplex® (Octapharma)	Dosed in factor IX units according to pretreatment INR	Contains factors II, VII, IX, and X and may also contain antithrombotic protein C and protein S Used for urgent reversal of bleeding due to vitamin K antagonist (e.g., warfarin) in adult patients
Anti-inhibitor coagulant complex FEIBA NF® (Baxter)	50–100 units/kg	Contains factors II, IX, and X, mainly nonactivated, and factor VII, mainly in activated form Used in hemophilia A or B patients with inhibitors
Coagulation factor VIIa (recombinant) NovoSeven® RT (Novo Nordisk)	90 micrograms/kg	Bleeding episodes and perioperative management in hemophilia A or B patients with inhibitors Congenital factor VII deficiency Glanzmann's thrombasthenia with refractoriness to platelet transfusions Bleeding episodes and perioperative management in adults with acquired hemophilia

*Commercial trade names provided for ease of product identification.

type O is the universal donor for red cells, it is **not** the universal donor for plasma (see later section "Fresh Frozen Plasma"). As a result, donated units of type O whole blood are tested for levels of anti-A and anti-B antibodies, and units with low titers of anti-A and anti-B antibodies are used in unmatched whole blood transfusion to decrease the risk of hemolytic transfusion reactions. Similar to unmatched PRBCs, men and women over age 50 years may receive Rh-positive blood, whereas women of childbearing age should receive Rh-negative blood. When unmatched stored whole blood transfusion is used, obtain a pretransfusion sample to establish the recipient's blood group as it may be difficult to determine after transfusion. The practice of whole blood transfusion in civilian hospitals and EMS systems is currently limited to a few locations in the United States, but further expansion is anticipated.

PACKED RED BLOOD CELLS

Adult total blood volume is approximately 2.5 L/m^2, 75 mL/kg, or about 5 L in a 70-kg person. Although whole blood would seem ideal to replace red cells, the platelets and plasma present are not usually necessary and could be separated and used for directed treatment of patients with thrombocytopenia or coagulopathy, respectively. Therefore, whole blood is most often fractionated to its components for storage and transfusion. PRBCs are prepared by the centrifugation of whole blood collected with the preservative and anticoagulant solution to remove approximately 80% of the plasma (Table 238-1).[8]

Emergency PRBC transfusion is usually performed for acute blood loss or profound anemia to restore intravascular oxygen-carrying capacity. A hemoglobin concentration of 7 grams/dL (70 grams/L) or greater is adequate to support oxygen delivery in most adults who are hemodynamically stable. Substantial evidence supports that the hemoglobin threshold of 7 grams/dL (70 grams/L) for PRBC transfusion—termed a *restrictive threshold*—is safe and effective.[9,10] For patients with preexisting cardiovascular disease or who are undergoing orthopedic or cardiac surgery, the recommended transfusion threshold is a hemoglobin concentration of 8 grams/dL (80 grams/L).[8-10] There is inadequate evidence for the threshold that should be used in patients with acute coronary syndrome, hematologic or oncologic conditions, chronic transfusion-dependent anemia, or severe thrombocytopenia (since anemia has been shown to reduce platelet effectiveness).

For actively bleeding patients, transfusion is based on clinically estimated blood loss rather than hemoglobin levels, because the fall in measured hemoglobin will lag behind the clinical impact of acute blood loss. A loss of about 30% blood volume (1500 mL in an adult) generally produces symptoms and signs, but young, healthy patients can tolerate this degree of loss, especially when treated with crystalloid. However, patients with chronic illness such as underlying anemia, cerebrovascular disease, or cardiac diseases; those with pacemakers; and those on β-blockers or similar medications may not tolerate blood loss. Consider emergency PRBC transfusion for unstable trauma patients based on an inadequate response to an initial 2-L bolus of IV crystalloid (see Chapter 13, "Approach to Traumatic Shock"). Use the anticipated clinical course to guide the decision to transfuse the patient with acute hemorrhage, with a lower threshold if the source of bleeding cannot be controlled immediately compared to a patient whose acute hemorrhage has stopped.

Use the minimum amount of PRBCs to accomplish the desired clinical outcome.[9] **A single PRBC unit will raise the hemoglobin by 1 gram/dL (10 grams/L) and hematocrit by 3% in adults. In children, 10 to 15 mL/kg of PRBCs will raise the hematocrit by 6% to 9% and the hemoglobin level by approximately 2 to 3 grams/dL (20 to 30 grams/L).**[11]

One unit of PRBCs, approximately 250 mL in volume, is generally transfused over 1 to 2 hours in stable patients, with faster infusion rates in patients with hemodynamic instability. Single-unit PRBC transfusions should not exceed 4 hours to prevent contamination. If a slow transfusion is desired (e.g., in a patient at risk for volume overload), the blood bank should be asked to split a unit so that the first half can be transfused over 4 hours while the second half waits in the blood bank refrigerator. During standard transfusions, the initial infusion rate is slower over the first 30 minutes so that if there is a transfusion reaction, the infusion may be stopped.

Type, Screen, and Cross-Match PRBC transfusion requires matching the recipient's and donor's red blood cells according to blood type (ABO and Rh) and screening the recipient's plasma for antibodies to the minor red blood cell antigens. Screening is done using a mixture of commercially available red blood cells that have all the important minor antigens. If the screen is positive for antibodies, then the recipient's plasma is cross-matched against the specific PRBC unit intended for transfusion. Blood type can be determined in approximately 15 minutes, whereas it takes about 45 to 60 minutes to perform a serologic cross-match. If an anti–red blood cell antibody is found in the recipient's plasma, cross-matching may take longer and require additional blood specimens from the patient.

Type O Rh-negative (universal donor) PRBC may be used in critical circumstances because these transfused red cells do not contain major blood group antigens (A or B). Type O Rh-positive blood may be used if type O Rh-negative is not available, but should be avoided in girls and women of childbearing potential. Approximately 20% of Rh-negative patients transfused with 1 unit of Rh-positive PRBCs will develop anti-Rh(D) antibodies, creating the risk for hemolytic disease of the newborn with subsequent pregnancies. This is usually clinically inconsequential for men or postmenopausal women.

Treated Red Blood Cells PRBCs may be further treated for specific clinical applications: leukocyte-reduced PRBCs, irradiated PRBCs, washed PRBCs, and frozen PRBCs.[8] Leukocyte-reduced PRBCs have 70% to 85% of the white cells removed in order to (1) decrease the occurrence of nonhemolytic febrile reactions due to cytokines from transfused white cells; (2) prevent sensitization to human leukocyte antigen antibodies found on white cells in patients who may be eligible for bone marrow transplantation; and (3) minimize the risk of intracellular virus transmission, such as cytomegalovirus. Irradiation of PRBCs eliminates the capacity of T lymphocytes to proliferate, thereby preventing the donor's T lymphocytes from reacting to the recipient's cells and thus reducing the risk for graft-versus-host disease. Irradiated cells are used in transplant patients, neonates, and immunocompromised patients, and with directed donations from relatives of the patient. Washed PRBCs are indicated in patients who have a hypersensitivity to plasma, such as those with immunoglobulin A deficiency or persistent febrile reactions. For rare blood types, red cells may be frozen and saved for up to 10 years for later use.

MASSIVE TRANSFUSION

Massive transfusion in adults is variously defined as either the replacement of one blood volume (approximately 10 units of PRBCs) within a 24-hour period, replacement of 50% of blood volume within 3 hours, or ongoing transfusion during a period of rapid bleeding, such as >150 mL/min.[12] If only PRBCs were used, platelets and coagulation factors lost or consumed would not be replaced, potentially increasing bleeding. Massive transfusion protocols using fixed ratios of PRBCs, platelets, and fresh frozen plasma (FFP) are in common use (see Chapter 13, "Approach to Traumatic Shock").[12] The optimal ratio of PRBCs to platelets to FFP is not established.[13] Some protocols include cryoprecipitate, fibrinogen concentrate, coagulation factor VIIa (recombinant), tranexamic acid, or prothrombin complex concentrate.[12] Although most research on massive transfusion protocols has been in trauma, many institutions use similar strategies for other causes of hemorrhagic shock, such as postpartum hemorrhage or massive GI bleeding.

Draw sufficient specimens early in the course from massive transfusion patients because once the patient has received close to one blood volume of transfused products, new blood specimens will contain so much donor blood that it will confuse further cross-matching of subsequent units. Hypothermia is a risk during massive transfusion, so blood and crystalloid should be warmed, in addition to instituting warming measures for the patient. Hypocalcemia from the preservative citrate chelating calcium may occur with a massive transfusion.

PLATELET TRANSFUSION

Platelet transfusions are used either prophylactically to prevent bleeding in thrombocytopenia or therapeutically when patients with thrombocytopenia are actively bleeding. One apheresis-collected, single-donor

TABLE 238-3 General Indications for Platelet Transfusion

- Platelet count <5000/mm^3 (<5 × 10^9/L)
- Platelet count <10,000/mm^3 (<10 × 10^9/L) for therapy-induced thrombocytopenia (e.g., chemotherapy)
- Platelet count <20,000/mm^3 (<20 × 10^9/L) with a coagulation disorder or low-risk procedure (including central line placement)
- Platelet count <50,000/mm^3 (<50 × 10^9/L) with active bleeding, lumbar puncture, or major surgery
- Platelet count <100,000/mm^3 (<100 × 10^9/L) with neurologic or ophthalmologic surgery, intracranial hemorrhage, or major multisystem trauma
- As part of a massive transfusion protocol
- Platelets are generally not indicated for ITP, TTP, or HIT, except in the context of ongoing severe bleeding

Abbreviations: HIT = heparin-induced thrombocytopenia; ITP = immune thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura.

platelet concentrate is the standard product in developed countries (Table 238-1). Platelets collected from six different donors can be pooled to create one unit for transfusion, but this practice is not recommended because this increases the risk of disease transmission and transfusion reaction.[14]

One apheresis single-donor platelet unit will increase the platelet count by up to 50,000/mm^3 (50 × 10^9/L), an amount sufficient to provide prophylaxis or stop spontaneous and minor traumatic bleeding in most situations. Check platelet levels at 1 and 24 hours after transfusion completion because the response is variable. Transfused platelets should survive 3 to 5 days; failure of platelets to rise appropriately may be due to increased consumption of platelets from an underlying process, active thrombosis due to ongoing hemorrhage, destruction due to platelet antibodies, or sequestration due to hypersplenism.

The decision to transfuse platelets depends on the severity of thrombocytopenia and clinical circumstances. Among the evidence-based guidelines issued by the American Association of Blood Banks in 2015 and by the British Committee for Standards in Hematology in 2016, the **indications most relevant to emergency medicine are a combination of thrombocytopenia and bleeding or risk of bleeding (Table 238-3).**[15-17] Consult with a transfusion medicine specialist or hematologist if uncertain about platelet transfusion in a specific situation.

There are variable recommendations concerning platelet transfusions in patients with nonfunctioning platelets, on antiplatelet medications, or with uremia, von Willebrand's disease, or hyperglobulinemia. In von Willebrand's disease, normal platelets may help deliver von Willebrand factor to the bleeding site. Conversely, in uremic patients, the transfused platelets may not function any better than native platelets. Platelets are of no benefit in patients with spontaneous cerebral hemorrhage associated with antiplatelet agents.[18]

Relative contraindications to the transfusion of platelets are disorders associated with platelet activation, such as thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia, in which transfusion may worsen thrombosis. In these conditions, ongoing bleeding or the need to perform procedures may necessitate platelet transfusion in consultation with the appropriate specialist.

Platelet transfusions are usually ABO-type specific because the platelets are bathed in plasma, although a serologic cross-match is usually not done. As a result, patients receiving platelets are subject to many of the same complications described for plasma transfusion. Depending on availability, non–type-specific platelets may sometimes be transfused. This practice is usually avoided in children or patients receiving multiple transfusions because they are at higher risk for complications. Transfusing non–type-specific platelets may also shorten the half-life of the transfused platelets.

As with PRBCs, platelets can be leukocyte reduced or washed. Patients who have had repeated transfusions may become alloimmunized and refractory to platelet transfusion, noted by the lack of expected rise in platelet count after transfusion. Such patients need human leukocyte antigen–matched or cross-matched platelets. Other factors may affect the efficacy of platelet transfusion, including bacterial sepsis in the recipient, antibiotics forming an antigen complex epitope with the platelet, disseminated intravascular coagulation, and splenomegaly.

COAGULATION FACTOR TRANSFUSION

FRESH FROZEN PLASMA

FFP is obtained after the cells are separated from whole blood and then frozen within 8 hours of collection.[19] FFP takes approximately 20 to 40 minutes to thaw, and this process cannot be sped up through artificial heating. Once thawed, FFP can be transfused up to 5 days later. Trauma centers and other specialty hospitals may keep prethawed units of FFP available.

Each unit of FFP has a volume of 200 to 250 mL and contains approximately 1 unit of each coagulation factor and 2 milligrams of fibrinogen per milliliter (Table 238-1). The increase in individual coagulation factors seen after FFP infusion varies with the specific factor. In general, 1 unit of FFP will increase most coagulation factors by 3% to 5% in a 70-kg adult. For clinically relevant correction of severe coagulation factor deficiencies, a dose of 15 mL/kg (or 4 units in a 70-kg adult) is often required (Table 238-1).

Transfused FFP should be ABO type compatible; however, Rh compatibility is unnecessary. It is a misconception that type O plasma is a universal donor, as it is for PRBCs. This is not the case, because type O plasma contains antibodies to A and B blood group antigens. **Type AB is the universal donor for FFP, and in emergencies, universal donor FFP can be given minutes after thawing.** Because it is hard to maintain a supply of type AB plasma, type A plasma can be used for emergencies if the recipient is type B or AB.[20]

FFP is used for bleeding from warfarin-induced overanticoagulation when prothrombin complex concentrate is not available, for replacement of multiple coagulation deficiencies, for deficiency of an individual coagulation factor when a specific replacement is not available, and during massive transfusion (**Tables 238-4** and **238-5**).[21] Other possible indications for FFP include hereditary angioedema if C1 esterase inhibitor is not available (see Chapter 14, "Allergy and Anaphylaxis").[22] FFP is used during plasma exchange for treatment of diseases such as thrombotic thrombocytopenic purpura and Guillain-Barré syndrome.[23] FFP is not recommended to reverse anticoagulation from direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban, or edoxaban (see Chapter 239, "Thrombotics and Antithrombotics").[24] There is no evidence to support the use of FFP in coagulopathic patients for procedures such as central venous line placement.[25]

Clinically adequate hemostasis is generally present with functional coagulation factor levels 30% to 40% of normal, which corresponds to an INR of about 1.7; thus, FFP administration to reverse coagulopathy should be restricted to patients with an INR of ≥1.8.[26]

CRYOPRECIPITATE

Cryoprecipitate is the cold-insoluble protein fraction of plasma containing primarily factor VIII and fibrinogen. There is significant variability in volume and content of cryoprecipitate units prepared from different centers.[27] With the development of recombinant factor VIII products for use in hemophilia and fibrinogen concentrates for use in hypofibrinogenemia, there is a lesser role for cryoprecipitate.[28] Cryoprecipitate may be used in bleeding patients with fibrinogen levels <100 milligrams/dL (<1 gram/L) due to severe liver disease, uremia, disseminated intravascular coagulation, and dilutional coagulopathy, although there is controversy

TABLE 238-4 General Indications for Fresh Frozen Plasma Transfusion

- Reversal of warfarin overanticoagulation when PCC not available
- Bleeding with multiple coagulation defects
- Correction of coagulation defects for which no specific factor is available
- As a component of a massive transfusion protocol
- As part of plasma exchange when treating thrombotic microangiopathies or neurologic disorders

Abbreviation: PCC = prothrombin complex concentrate.

TABLE 238-5 Replacement Therapy for Congenital Factor Deficiencies

Coagulation Factor	Approximate Incidence*	Replacement Therapy
Factor I (fibrinogen)	1 per million	Fibrinogen concentrate Cryoprecipitate (if fibrinogen concentrate unavailable)
Factor II (prothrombin)	1 per 2 million	PCC
Factor V	1 per million	FFP
Factor VII	1 per 500,000	PCC
		Coagulation factor VIIa (recombinant)
Factor VIII†	1 per 5000–10,000 males	Coagulation factor VIII (recombinant or human)
		Desmopressin for mild hemophilia
von Willebrand's disease‡	Up to 1 per 100 persons	Desmopressin von Willebrand factor (recombinant) or antihemophilic factor/von Willebrand factor complex (human); cryoprecipitate if either unavailable
Factor IX†	1 per 30,000 males	Coagulation factor IX (recombinant or human)
		Factor IX complex
Factor X	1 per million	FFP for minor bleeding episodes
		PCC for major bleeding
Factor XI‡	3 per 10,000 Ashkenazi Jews	FFP
	1 per million in general population	
Factor XII	25 per 1000	No bleeding manifestations; replacement not required
Factor XIII	1 per million	FFP or cryoprecipitate

Abbreviations: FFP = fresh frozen plasma; PCC = prothrombin complex concentrate; vWF = von Willebrand factor.

*Source: van Herrewegen F, Meijers JC, Peters M, van Ommen CH: Clinical practice: the bleeding child. Part II: disorders of secondary hemostasis and fibrinolysis. *Eur J Pediatr* 171: 207, 2012.

†See Chapter 235, "Hemophilias and von Willebrand's Disease."

‡Factor XI levels correlate poorly with bleeding complications; many patients have low levels but no bleeding complications.

over dosing and efficacy (**Table 238-6**).[27,29] The typical adult dose is 10 units, administered in two doses, each containing five pooled units.

FIBRINOGEN CONCENTRATE (HUMAN)

Fibrinogen concentrate is derived from pooled human plasma and is used to treat bleeding episodes in patients with congenital fibrinogen deficiency.[30] Fibrinogen has been investigated for benefit in other hemorrhagic conditions with an observed ability to reduce bleeding and transfusion requirements, but without a measurable effect on mortality.[31] The advantages over cryoprecipitate are minimal risk of disease transmission due to viral inactivation, accurate dosing because each vial is assayed for fibrinogen content, a lower volume for infusion, no need for thawing, no requirement of ABO testing and compatibility, and a rapid reconstitution for infusion.

Fibrinogen is dosed according the patient's baseline fibrinogen level, the target level (in most circumstances >150 milligrams/dL),[32] volume of distribution, and body weight. If the baseline fibrinogen level is unknown, the initial dose is 70 milligrams/kg. The most common adverse reactions include allergic reactions, fever, chills, nausea, and vomiting.

TABLE 238-6 General Indications for Cryoprecipitate Transfusion

- Bleeding with a fibrinogen level of <100 milligrams/dL (<1 gram/L)
- Dysfibrinogenemia
- Bleeding in some subtypes of von Willebrand's disease that are unresponsive to desmopressin, and factor VIII concentrates are unavailable

FACTOR IX COMPLEX (HUMAN)

Factor IX complex is derived from human plasma and primarily contains factors IX, X, and prothrombin. This product is typically used to treat hemophilia B (factor IX deficiency) and has been studied to treat hemorrhage caused by excessive warfarin effect, because this product contains three of the four vitamin K–dependent coagulation factors. Factor IX complex is often identified as three-factor prothrombin complex concentrate to differentiate it from the four-factor prothrombin complex concentrate product.

PROTHROMBIN COMPLEX CONCENTRATE (HUMAN)

Prothrombin complex concentrate is derived from human plasma and contains the four vitamin K–dependent clotting factors: prothrombin and factors VII, IX, and X. During development and introduction into clinical use, this product was usually identified as four-factor prothrombin complex concentrate to differentiate it from factor IX complex, or three-factor prothrombin complex concentrate. Some prothrombin complex concentrate formulations may also contain anticoagulant proteins C and S and antithrombin, as well as heparin.

Prothrombin complex concentrate is approved for urgent reversal of overanticoagulation from vitamin K antagonists (such as warfarin).[33] The prothrombin complex concentrate dose is calculated from pretreatment INR values and administered using factor IX units. Prothrombin complex concentrate can also be used as part of a protocol for reversal of direct oral anticoagulants such as rivaroxaban, apixaban, edoxaban, or dabigatran in the setting of life-threatening bleeding.[24,34]

Prothrombin complex concentrate does not require thawing, does not necessitate ABO-compatibility testing, and does not carry the risk of volume overload, all of which can hinder FFP use. Because the effects of prothrombin complex concentrate are transient, vitamin K should usually be coadministered for sustained warfarin reversal. Thrombosis is the major complication of prothrombin complex concentrate and is observed in approximately 2.5% of treated patients, although this incidence is less than in similar patients treated with FFP.[33]

ANTI-INHIBITOR COAGULANT COMPLEX

Anti-inhibitor coagulant complex is derived from human plasma and contains the four vitamin K–dependent factors: factors II, IX, and X (mainly in nonactivated form) and factor VII (mainly in activated form). This product is commonly known as FEIBA, an abbreviation for factor VIII inhibitor bypassing activity, and has also been termed activated prothrombin complex concentrate. Anti-inhibitor coagulant complex is approved for use in hemophilic patients with inhibitors and has been studied for reversal of direct oral anticoagulants[35] and for treatment of bleeding in acquired hemophilia.[36] The risk of adverse thromboembolic complications is low in patients with congenital hemophilia[37] but higher in other populations.

COAGULATION FACTOR VIIa (RECOMBINANT)

Coagulation factor VIIa (recombinant) is approved for use in the treatment of bleeding in hemophilia A and B patients who have developed inhibitor antibodies to factors VIII or IX, respectively. Other uses for this agent have been investigated, such as acquired hemophilia, coagulation support in liver failure, multisystem trauma, intracranial hemorrhage, and postpartum bleeding.[38-40] The major drawback to this product is risk of thrombosis (up to 4% in patients with acquired hemophilia).

COMPLICATIONS OF BLOOD TRANSFUSIONS

Up to 20% of all transfusions may result in some type of adverse reaction.[3,41] Most reactions are minor; serious reactions are uncommon, and life-threatening ones are rare (**Table 238-7**).[42] In critically ill patients,

TABLE 238-7 Transfusion Reactions

Reaction Type	Signs and Symptoms	Management	Evaluation
Acute intravascular hemolytic reaction	Fever, chills, low back pain, flushing, dyspnea, tachycardia, shock, hemoglobinuria	Immediately stop transfusion. IV hydration to maintain diuresis; diuretics may be necessary. Cardiorespiratory support as indicated.	Retype and repeat cross-match. Direct and indirect Coombs test. CBC, creatinine, prothrombin time, activated partial thromboplastin time. Haptoglobin, indirect bilirubin, lactate dehydrogenase, plasma free hemoglobin. Urine for hemoglobin.
Delayed extravascular hemolytic reaction	Often have low-grade fever but may be entirely asymptomatic	Usually presents days to weeks after transfusion. Rarely causes clinical instability.	Hemolytic workup as above to investigate the possibility of intravascular hemolysis.
Febrile nonhemolytic transfusion reaction	Fever, chills	Stop transfusion. Initially manage as in intravascular hemolytic reaction (above) because cannot initially distinguish between the two. Can treat fever and chills with acetaminophen. Usually mild but can be life threatening in patients with tenuous cardiopulmonary status. Consider infectious workup. Premedication with acetaminophen can mask this reaction.	Hemolytic workup as above because may not be able to initially distinguish febrile from hemolytic transfusion reactions.
Allergic reaction	Mild: urticaria, pruritus Severe: dyspnea, bronchospasm, hypotension, tachycardia, shock	Stop transfusion. If mild, reaction can be treated with diphenhydramine; if symptoms resolve, can restart transfusion. If severe, may require cardiopulmonary support; do not restart transfusion.	For mild symptoms that resolve with diphenhydramine, no further workup is necessary, although blood bank should be notified. For severe reaction, do hemolytic workup as above because initially may be indistinguishable from a hemolytic reaction.

transfusion reactions may be difficult to identify; therefore, watch for unexpected changes in patient status during a transfusion. **Two important first steps in any confirmed or suspected transfusion reaction are to (1) immediately stop the transfusion and (2) contact the blood bank that issued the transfusion product.**[8] The blood bank physician is an important resource for managing the suspected transfusion reaction.

A common error in management of a confirmed or possible transfusion reaction is to abandon all transfusion. Typically, transfusion reactions, such as hemolytic reactions or transfusion-related acute lung injury, are due to the interaction between a particular unit and a particular patient. Even patients with severe reactions can safely receive future blood products if they are appropriately matched to the patient. One of the first steps in management of a transfusion reaction is to draw a new specimen to retype and cross-match new units so that transfusion can resume as soon as possible.[8]

Premedication with acetaminophen and/or diphenhydramine is done to prevent febrile and/or allergic transfusion reactions[43]; however, the effects are limited,[44,45] and routine prophylactic premedication is not recommended in patients without prior reactions. However, premedication may be used for patients with previous febrile or allergic transfusion reactions.

HEMOLYTIC TRANSFUSION REACTIONS

Hemolytic transfusion reactions occur when the recipient's antibodies recognize and induce hemolysis of the donor's red blood cells.[8,46,47] The reaction is usually immediate when antibodies already exist as anti-A or anti-B immunoglobulin M antibodies or immunoglobulin G antibodies in very high titer. Reactions can be delayed when there is an amnestic response to a transfused red blood cell antigen to which the recipient has been previously sensitized.[8,10] Immediate transfusion reactions caused by ABO incompatibility are usually the result of technical errors made during the collection of blood, pretransfusion testing, or patient identification, and are responsible for the majority of transfusion fatalities.[10]

With acute hemolytic reaction, most of the transfused cells are destroyed, which may result in activation of the coagulation system, disseminated intravascular coagulation, and release of anaphylatoxins and other vasoactive amines. Clinical features of an acute hemolytic reaction include back pain, pain at the site of the transfusion, headache, alteration of vital signs (fever, hypotension, dyspnea, tachycardia), chills, bronchospasm, pulmonary edema, bleeding due to developing coagulopathy, and evidence of new or worsening renal failure.

Ongoing transfusion should be stopped immediately on first indication of potential problems. While laboratory confirmation is being performed, the sequelae of hemolysis are treated supportively. Check renal function, electrolytes, and coagulation status. Maintain renal blood flow and urine output with fluids, mannitol, and furosemide, as needed. Treat circulatory shock with IV infusions and vasopressors to support blood pressure.

The remaining donor blood should be sent, along with a posttransfusion blood specimen from the recipient, to the blood bank. The blood typing and cross-match are repeated, the patient's serum is tested for blood group alloantibodies, and the donor's plasma is tested for the presence of antibodies that react with the patient's blood. With intravascular hemolytic transfusion reactions, serum haptoglobin will be decreased, serum lactate dehydrogenase will be elevated, and a direct antigen (Coombs) test usually will be positive. The blood bank will be able to test the blood, review records, confirm blood types, and determine if the patient's syndrome is from a transfusion reaction.

Extravascular delayed hemolytic reactions occur in approximately 1 per 1000 to 6000 PRBC units transfused. Hemolysis most commonly occurs in the spleen and occasionally in liver and bone marrow. This type of reaction is less serious and rarely fatal.[8,10] It may be identified by a positive Coombs test, elevated unconjugated (indirect) bilirubin level, and less than expected increase in hemoglobin from the transfusion.

FEBRILE NONHEMOLYTIC TRANSFUSION REACTIONS

Febrile transfusion reactions are characterized by fever during or within 4 hours of a blood transfusion.[8,10,46,47] Febrile reactions occur in <0.5% of FFP transfusions, <1% of red blood cell transfusions, and ≤5% of platelet transfusions.[8,48] Febrile transfusion reactions are more common in patients who have been exposed to foreign blood antigens, such as multiparous women or multiply transfused patients. Febrile transfusion reactions result from a combination of recipient antibody against donor leukocytes and the release of cytokines that are produced during storage. Clinical presentation can range from a mild elevation in temperature to a high fever along with rigors, headache, myalgias, tachycardia, dyspnea,

and chest pain. A severe febrile reaction may be difficult to initially differentiate from the more serious hemolytic transfusion reaction or sepsis.

For a febrile reaction during a patient's first-time transfusion, or in any severe reaction, the transfusion should be stopped and the product returned to the blood bank for testing. Laboratory investigation similar to that done for possible hemolytic transfusion is done, and blood cultures should be obtained. The febrile transfusion reaction is usually self-limited and will respond to antipyretics. A mild fever in a patient who has been transfused before is usually not serious. In most cases, the transfusion can be restarted after consultation with the blood bank physician. For patients with recurrent febrile reactions, the use of leukocyte-reduced blood products and pretreatment with antipyretics may be helpful.

ALLERGIC TRANSFUSION REACTIONS

Allergic transfusion reactions typically manifest with urticaria and pruritus during the infusion.[8,10,46,47] A small percentage of patients will have more severe reactions, such as bronchospasm, wheezing, and anaphylaxis. These reactions are caused by an immune response to transfused plasma proteins. The incidence of allergic transfusion reactions varies widely.[49]

Antihistamine therapy usually will control urticaria and pruritus. The transfusion should be stopped, but can usually be restarted after evaluation. For anaphylaxis with severe symptoms, the transfusion should be stopped and treatment with epinephrine, steroids, H_2 blockers, and bronchodilators begun. Patients with immunoglobulin A deficiency may experience severe anaphylactic reactions in response to exposure from immunoglobulin A in donor products. Washing the plasma from the red blood cells minimizes this type of reaction.

INFECTIOUS COMPLICATIONS

Improved blood donor screening, serologic testing, safer handling of blood products, and viral inactivation of blood products have reduced the risk of infection from transfusion.[50-53] Despite screening donor blood for antibodies to the most concerning viral agents, there is still a small risk of viral transmission (**Table 238-8**). Most cases of transmission are thought to occur during the window period between infection and antibody production in the donor. This window can be reduced by antigen testing of donated blood for known viral antigens. In the United States, blood is tested for syphilis, hepatitis B and C, human immunodeficiency virus, human T-cell lymphotropic virus, West Nile virus, Chagas disease, and Zika virus.[8]

Prevalence for cytomegalovirus antibodies in the general population is between 50% and 80%; therefore, a transfusable unit is not tested routinely for cytomegalovirus unless the recipient is seronegative and either pregnant, a potential or present transplant candidate, immunocompromised, or a premature infant.[8] Leukocyte-reduced blood components further decrease the risk of cytomegalovirus transmission to susceptible populations because most of the virus resides in the leukocytes.

Other infections transmitted by blood transfusion include West Nile virus, variant Creutzfeldt-Jakob disease, babesiosis, and dengue.[49-51] Additionally, blood can become contaminated with bacteria during storage or processing. Transfusion-associated bacterial infection was more commonly reported with platelet concentrates than PRBC or FFP.[54] Evaluation of a possible septic reaction involves obtaining blood cultures from the patient and examination of material from the blood container by Gram stain with cultures of specimens from the container and the administration set.[8,47]

TABLE 238-8 Approximate Risk of Infection From Blood Product Transfusion

Etiology	Estimated Frequency: One Infection per Number of Units Transfused
HIV-1	1 per 6 million
Human T-cell lymphotropic virus types 1 and 2	1 per 640,000
Hepatitis B	1 per million
Hepatitis C	1 per 100 million
Parvovirus B19	1 per 10,000

Abbreviation: HIV = human immunodeficiency virus.

TRANSFUSION-RELATED ACUTE LUNG INJURY

Transfusion-related acute lung injury is an uncommon but life-threatening complication of transfusion characterized by the development of acute respiratory distress associated with noncardiogenic pulmonary edema occurring within 6 to 72 hours after receiving a blood transfusion. Transfusion-related acute lung injury is due to antileukocyte antibodies in the donor product that produce polymorphonuclear leukocyte degranulation within the lung.[55] Transfusion-related acute lung injury is more common after plasma transfusion than red blood cell transfusion. Mitigation strategies with blood donor screening have been partially successful in reducing the risk of transfusion-related acute lung injury.[56] Transfusion-related acute lung injury is self-limiting and generally resolves spontaneously with only supportive care, although severe, fatal cases can occur. Because the pulmonary edema is noncardiogenic, use care to distinguish transfusion-related acute lung injury from volume overload and avoid aggressive diuresis, which can cause rapid deterioration.

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD

Transfusion of blood products can cause rapid volume expansion when compared to similar volumes of crystalloid fluids, leading to transfusion-associated cardiovascular overload.[57] Patients with limited cardiovascular reserve, such as those with severe chronic compensated anemia and the elderly, are at the highest risk. Clinical features include dyspnea, hypoxia, and pulmonary edema. Recognize the potential for volume overload so that blood can be transfused slowly, the patient can be monitored carefully, and treatment with diuretics can be initiated when necessary. The usual rate of PRBC or FFP transfusion is 2 to 4 mL/kg per h, but it can be slowed to 1 mL/kg per h in more delicate patients. Blood product units may also be split, as described earlier.

ELECTROLYTE IMBALANCE

Large-volume transfusions may uncommonly cause hypocalcemia, hypokalemia, or hyperkalemia. The anticoagulant citrate is a component of many blood preservatives and chelates calcium, but the effect of infused citrate is clinically insignificant because patients with normal hepatic function metabolize the citrate to bicarbonate. Rarely with massive transfusions, hepatic metabolism is overwhelmed, and hypocalcemia can develop and/or the excess bicarbonate generated causes alkalemia, driving potassium into the cells and causing hypokalemia.[58] The potassium content in stored blood products increases during storage, and uncommonly, patients with renal insufficiency or neonates can develop hyperkalemia from transfusion.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 239

Thrombotics and Antithrombotics

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INTRODUCTION

Antithrombotic therapy (i.e., **anticoagulants, antiplatelet agents, and fibrinolytics**) is used to treat or reduce the risk of arterial and venous thromboembolic conditions, including acute coronary syndrome, deep venous thrombosis and pulmonary embolism (collectively, venous thromboembolic disease), transient ischemic attack, and ischemic stroke (**Table 239-1**). Moreover, antithrombotic agents help prevent occlusive

TABLE 239-1 Indications for Antithrombotic Therapy

Clinical Indication	Comments
Treatment of Deep Venous Thrombosis and Pulmonary Embolism	
Unfractionated heparin 80 units/kg IV bolus followed by 18 units/kg per h continuous IV infusion, with the aPTT checked after 6 h and the infusion adjusted to maintain anti-FXa activity 0.3–0.7 IU/mL or aPTT 1.5–2.5 times reference range (e.g., 68–106 s) *with* concurrent institution of warfarin	In most cases, heparin and warfarin started simultaneously, with an overlap of 3–5 d. Warfarin is monitored and dose adjusted to a target INR of 2.0–3.0 in most patients.
Enoxaparin 1 milligram/kg SC every 12 h or 1.5 milligrams/kg SC once a day	Laboratory monitoring not routinely required (see text) If CrCl <30 mL/min: 1 milligram/kg SC daily
Dalteparin 200 units/kg SC once daily or 100 units/kg SC twice daily	Not FDA approved for this indication
Fondaparinux weight-tiered regimen <50 kg: 5 milligrams SC once a day 50–100 kg: 7.5 milligrams SC once a day >100 kg: 10 milligrams SC once a day	Laboratory monitoring not routinely required Avoid in patients with CrCl <30 mL/min
Dabigatran 150 milligrams PO twice daily	Following 5–10 d of initial therapy with parenteral anticoagulant Avoid in patients with CrCl <30 mL/min or on hemodialysis
Rivaroxaban 15 milligrams PO twice daily for 21 d with food, followed by 20 milligrams PO once daily with food	Avoid use in patients with CrCl <30 mL/min
Apixaban 10 milligrams PO twice daily for 7 d, followed by 5 milligrams twice daily	Reduce dose by 50% if patient taking dual strong VYP3A4 and P-glycoprotein inhibitors. If Cr >1.5 milligrams/dL and either ≥80 years of age or body weight ≤60 kg: 2.5 milligrams twice daily
Edoxaban 30 milligrams PO daily (if ≤60 kg) or 60 milligrams PO daily (if >60 mg)	Following 5–10 d of initial therapy with parenteral anticoagulant If CrCl 15 to 50 mL/min: 30 milligrams PO daily If CrCl <15 mL/min: use not recommended
Streptokinase 250,000 units IV bolus, followed by 100,000 units/h continuous IV infusion for 1–3 d *or* Alteplase 100 milligrams IV infused over 2 h *or* Tenecteplase weight-tiered single IV bolus <60 kg: 30 milligrams ≥60–<70 kg: 35 milligrams ≥70–<80 kg: 40 milligrams ≥80–<90 kg: 45 milligrams ≥90 kg: 50 milligrams	Fibrinolytic treatment of deep venous thrombosis and pulmonary embolism is recommended only in carefully selected patients.
Prophylaxis for Deep Venous Thrombosis and Pulmonary Embolism	
Unfractionated heparin 5000 units SC every 8–12 h	Highest-risk patients for venous thromboembolism should receive every-8-h dosing. Recommend using in patients with renal dysfunction
Dalteparin 2500 to 5000 IU SC once a day	—
Enoxaparin 40 milligrams SC once daily (normal renal function), 30 milligrams SC twice daily (trauma), or 40 milligrams SC twice daily (obese patients)	—
Fondaparinux 2.5 milligrams SC once a day	—
Rivaroxaban 10 milligrams PO once a day with or without food	—
Apixaban 2.5 milligrams PO twice daily	For prophylaxis after hip and knee replacement surgery, initial dose taken 12–24 h after surgery
Betrixaban 160 milligrams PO first dose, then 80 milligrams PO daily. If CrCl 15–30 mL/min, start 80 milligrams PO first dose, then 40 milligrams PO daily.	Approved for VTE prophylaxis, not treatment
ST-Segment Elevation Myocardial Infarction	
Aspirin (non–enteric coated) 162–325 milligrams PO once a day *plus* Clopidogrel 300 milligrams PO loading dose (consider 600 milligrams if PCI is planned) followed by 75 milligrams PO once a day *or* Ticagrelor 180 milligrams PO loading dose, followed by 90 milligrams PO twice daily *or* Prasugrel 60 milligrams PO loading dose followed by 10 milligrams PO once a day (in patients ≤60 kg, the recommended maintenance dose is 5 milligrams PO once a day)	Dual therapy—aspirin plus another antiplatelet agent—is common. Prasugrel is contraindicated for patients with a previous stroke and not recommended in patients age ≥75 y.

(*Continued*)

TABLE 239-1 Indications for Antithrombotic Therapy (*Continued*)

Clinical Indication	Comments
Unfractionated heparin 60 units/kg IV bolus (maximum, 4000 units according to the ACC/AHA guidelines or 5000 units according to the ESC guidelines) followed by 12 units/kg per h (maximum, 1000 units) continuous IV infusion adjusted to anti-FXa activity 0.3–0.6 IU/mL or aPTT 1.5–2.5 times reference range (e.g., 68–96 s) *or* Enoxaparin 30 milligrams IV bolus, followed by 1 milligram/kg SC every 12 h (maximum, 100 milligrams for the first 2 doses only) for patients <75 y old or 0.75 milligram/kg SC every 12 h for patients >75 y old (no IV bolus is administered in this population) *or* Bivalirudin 0.75 milligram/kg IV bolus followed by 1.75 milligrams/kg per h continuous IV infusion (FDA approved for use in cardiac catheterization laboratory only)	Optimal anticoagulation strategies are not completely defined. Bivalirudin is recommended in patients with heparin-induced thrombocytopenia.
Streptokinase 1.5 million units IV over 60 min *or* Alteplase 15 milligrams IV bolus over 1–2 min followed by 0.75 milligram/kg IV over 30 min (maximum, 50 milligrams) and 0.50 milligram/kg IV over 60 min (maximum, 35 milligrams) *or* Reteplase 10 units IV bolus, then a second 10-unit dose at 30 min *or* Tenecteplase weight-tiered single IV bolus <60 kg: 30 milligrams ≥60–<70 kg: 35 milligrams ≥70–<80 kg: 40 milligrams ≥80–<90 kg: 45 milligrams ≥90 kg: 50 milligrams	Early administration is more important than choice of specific fibrinolytic agent.
Unstable Angina and Non–ST-Segment Myocardial Infarction	
Aspirin (non–enteric coated) 162–325 milligrams PO once a day	Optimal antiplatelet strategies are not completely defined.
Clopidogrel 300 milligrams PO loading dose (consider 600 milligrams if PCI is planned) followed by 75 milligrams PO once a day *or* Prasugrel 60 milligrams loading dose followed by 10 milligrams PO once daily (in patients ≤60 kg, the recommended maintenance dose is 5 milligrams PO once a day) *or* Ticagrelor 180 milligrams PO loading dose, followed by 90 milligrams PO twice daily	Dual therapy—aspirin plus another antiplatelet agent—is common. Prasugrel is contraindicated for patients with a previous stroke and not recommended in patients age ≥75 y.
Unfractionated heparin 60 units/kg IV bolus (maximum, 4000 units according to the ACC/AHA guidelines or 5000 units according to the ESC guidelines) followed by 12 units/kg per h (maximum, 1000 units) continuous IV infusion adjusted to anti-FXa activity 0.3–0.6 IU/mL or aPTT 1.5–2.5 times reference range (e.g., 68–96 s) *or* Enoxaparin 1 milligram/kg SC every 12 h *or* Glycoprotein IIb/IIIa inhibitor, depending on risk and whether PCI is planned *or* Bivalirudin 0.75 milligram/kg IV bolus followed by 1.75 milligrams/kg per hour continuous IV infusion (FDA approved for use in cardiac catheterization laboratory only)	Optimal anticoagulation strategies are not completely defined. Bivalirudin is recommended in patients with heparin-induced thrombocytopenia.
Peripheral Arterial Disease	
Aspirin 162–325 milligrams PO once a day	—
Cilostazol 100 milligrams PO twice a day	—
Acute Ischemic Stroke	
Alteplase 0.9 milligram/kg (maximum, 90 milligrams) with 10% of total dose given as an IV bolus over 1 min followed by the remainder as an IV infusion over 60 min	Use of fibrinolytics in acute ischemic stroke requires *strict* adherence to recommended guidelines and should be done with informed consent. Adjunctive use of anticoagulants should be avoided for 48 h.
Tenecteplace 0.25 milligrams/kg IV bolus	Not FDA approved for this indication (see text). Recommend informed consent. Adjunctive use of anticoagulants should be avoided for 48 h.
Postischemic Stroke	
Aspirin 81 milligrams PO once a day	—
Clopidogrel 75 milligrams PO once a day	Use clopidogrel if aspirin allergic.
Dipyridamole 200 milligrams extended-release PO twice a day	Usually combined with aspirin 25–50 milligrams PO twice a day

(*Continued*)

TABLE 239-1 Indications for Antithrombotic Therapy (*Continued*)

Clinical Indication	Comments
Transient Ischemic Attack	
Aspirin 81 milligrams PO once a day	Use clopidogrel if "aspirin failure" or aspirin allergic.
Clopidogrel 75 milligrams PO per day	—
Stroke Reduction in Nonvalvular Atrial Fibrillation	
Warfarin dose monitored and adjusted by INR	Target INR is 2.0–3.0 in most patients.
Dabigatran 150 milligrams PO twice daily (patients with CrCl >30 mL/min) or 75 milligrams PO twice daily (patients with CrCl 15–30 mL/min)	Routine laboratory monitoring not necessary
Rivaroxaban 20 milligrams PO once daily with evening meal (patients with CrCl >50 mL/min) or 15 milligrams once daily with evening meal (patients with CrCl 15–50 mL/min)	Routine laboratory monitoring not necessary
Apixaban 5 milligrams PO twice daily or 2.5 milligrams twice daily in patients with at least 2 of the following characteristics: age ≥80 y, body weight ≤60 kg, or serum Cr ≥1.5 milligrams/dL	Routine laboratory monitoring not necessary
Edoxaban 60 milligrams once daily (patients with CrCL between 50 and 95 mL/min) or 30 milligrams once daily (patients with CrCl 15–50 mL/min)	Avoid use if CrCl >95 mL/min. Routine laboratory monitoring not necessary

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; aPTT = activated partial thromboplastin time; Cr = creatinine; CrCl = creatinine clearance; ESC = European Society of Cardiology; FDA = U.S. Food and Drug Administration; FXa = factor Xa; PCI = percutaneous coronary intervention; VTE = venous thromboembolism.

vascular events in patients at risk for thrombosis due to atherosclerotic arterial disease, atrial fibrillation, medical illness with immobility, or surgical insult. These agents, however, can cause life-threatening complications, primarily serious or life-threatening hemorrhage. Detailed management strategies for thromboembolic disorders are discussed in their respective chapters (see Chapter 49, "Acute Coronary Syndromes"; Chapter 56, "Venous Thromboembolism Including Pulmonary Embolism"; and Chapter 167, "Stroke Syndromes").

Hemostasis—whether physiologic after accidental injury or pathologic after rupture of an atherosclerotic plaque—is initiated by platelet interaction with the vascular subendothelium and continues with a series of reactions among plasma coagulation proteins that generate the final product of cross-linked fibrin incorporated into the initial platelet plug (see Chapter 232, "Hemostasis"). Arterial thrombi, composed primarily of platelets bound by thin fibrin strands, develop under high-flow conditions, especially at sites of ruptured plaques. **Both anticoagulants and platelet-inhibiting drugs may effectively prevent and treat arterial thrombosis.** In contrast, venous thrombi tend to form in areas of sluggish blood flow and are composed mainly of red blood cells and large fibrin strands. **Anticoagulant drugs are more effective than antiplatelet drugs in preventing venous thromboembolism.**

Antithrombotic agents are classified by their mechanism of action. **Anticoagulants** block the synthesis or activation of clotting factors, interfering with the coagulation cascade at one or more steps. **Antiplatelet agents** interfere with platelet activation or aggregation. **Fibrinolytic agents** (often but inaccurately referred to as thrombolytic agents) stimulate the enzymatic dissolution of the fibrin component.

Thrombotics or hemostatic agents are used to diminish bleeding due to either an antithrombotic agent or an acquired or genetic bleeding disorder (see Chapter 233, "Acquired Bleeding Disorders," and Chapter 235, "Hemophilias and von Willebrand's Disease," respectively).

ORAL ANTICOAGULANTS

Oral anticoagulants are used to (1) stop further thrombosis when the condition already exists (e.g., venous thrombosis), (2) reduce the risk of embolism in patients with thrombotic disease (e.g., venous thrombosis or left ventricular mural thrombus), and (3) prevent thrombi from forming in patients with risk factors for their development (e.g., atrial fibrillation, prolonged immobilization, or prosthetic heart valve) (Table 239-1). Oral anticoagulants can be either indirect acting, such as the vitamin K antagonists (e.g., warfarin), or direct acting (termed *direct-acting oral anticoagulants*).

WARFARIN

PHARMACOLOGY

Warfarin, a hydroxy coumarin compound, is a widely used oral anticoagulant.[1,2] Warfarin is readily absorbed after ingestion, reaching peak blood concentrations in 2 to 4 hours, and has a circulating half-life of 20 to 60 hours. Warfarin is bound to albumin, metabolized by the liver, and excreted in the urine. Warfarin blocks activation of vitamin K and thereby interferes with hepatic carboxylation of coagulation factors II, VII, IX, and X. The decrease in these vitamin K–dependent cofactors impairs the extrinsic and common coagulation pathway. Warfarin also blocks the synthesis of proteins C and S. Activated protein C (with protein S and phospholipid as cofactors) proteolyses factors Va and VIIIa, thereby inhibiting the coagulation cascade. Thus, warfarin has both an antithrombotic effect (by inhibiting the synthesis of factors II, VII, IX, and X) and a prothrombotic effect (through inhibition of proteins C and S production), but during maintenance therapy, the overwhelming effect is one of anticoagulation.

Warfarin dosing is guided by measurement of the INR, a standardized measurement of prothrombin time, with a desired therapeutic range of 2.0 to 3.0 in most cases.[2] Drugs and food that interfere with warfarin absorption, bind to albumin, or alter hepatic metabolism can have a profound effect on warfarin activity (**Table 239-2**). Warfarin is generally

TABLE 239-2 Warfarin Interactions

Consideration	Effect on PT or INR*
Major	
Vitamin K malabsorption or dietary deficiency	↑
Excess vitamin K	↓
Reduced gut bacteria (antibiotics)†	↑
Decreased warfarin absorption	↓
Altered warfarin metabolism (cytochrome P450)	Variable
Drug effects†	Variable
Other	
Decreased clotting factor production (liver disease)	↑
Increased metabolism of clotting factors (fever)	↓
Confounding technical or laboratory factors (e.g., phlebotomy, handling in transport, thromboplastin reagents)	Variable

*↑ = prothrombin time (PT) or INR prolonged; ↓ = PT or INR decreased.

†Consult drug-interaction reference for any new medications.

contraindicated in pregnancy because it is teratogenic (especially during the 6th to 12th weeks of gestation) and can cause fetal hemorrhage.

Protein C has a short half-life (8 hours), and plasma levels quickly fall after starting warfarin. The vitamin K–dependent coagulation factors have half-lives that range from approximately 7 hours for factor VII to approximately 60 hours for prothrombin (factor II). **The phase delay between the fall in levels of protein C (an antithrombotic protein) and the fall in levels of the four affected coagulation factors (prothrombotic proteins) results in a transient state of increased thrombogenesis at the start of warfarin therapy that persists for 24 to 36 hours.** This hypercoagulable state is mitigated by providing sufficient overlap with a parenteral anticoagulant (typically, a heparinoid) during the first 3 to 5 days of warfarin treatment[1,2] and during any interruption of warfarin therapy for surgery or an invasive procedure.[3-5] Because factors X and II have relatively long half-lives, the parenteral anticoagulant should not be discontinued until the INR is in the desired therapeutic range for 2 consecutive days. **Thus, a noncompliant patient with the risk for catastrophic complications from sudden intravascular thrombosis—such as a patient with a mechanical prosthetic heart valve who has stopped oral anticoagulants—should be treated with a parenteral anticoagulant in addition to restarting warfarin.**

There is also a prothrombotic rebound during the first 4 days after cessation of warfarin therapy. However, there is no increased incidence of clinical episodes of thrombosis with termination of warfarin therapy, and thromboembolic events that occur in patients after warfarin discontinuation are most likely related to the underlying condition.

The two major complications of warfarin therapy are bleeding and, less commonly, skin necrosis. The most important factor influencing the risk of bleeding is the intensity of anticoagulant therapy. The risk of clinically significant bleeding is increased when the INR is >4.5 to 5.0.[1,2] Skin necrosis occurs primarily (but not exclusively) in patients with protein C deficiency. This complication usually develops 3 to 8 days after starting treatment and is caused by thrombosis of small cutaneous vessels. Treatment includes discontinuation of warfarin, administration of a parenteral anticoagulant to maintain desired anticoagulation, vitamin K_1 administration, and screening for protein C and S deficiencies.

Patient-specific risk factors for increased risk of bleeding during warfarin treatment include hypertension, anemia, prior cerebrovascular disease, GI lesions, and renal disease. The relationship between advanced age and warfarin-associated bleeding is controversial. Elderly individuals who are otherwise appropriate candidates for anticoagulant therapy should not have warfarin withheld solely because of their age, although elderly patients require more frequent and careful monitoring. Medications that increase warfarin activity and antiplatelet medications increase bleeding risk during warfarin therapy (Table 239-2).

Potential drug–drug and drug–food interactions with warfarin are numerous and complex. Carefully review medications prescribed on ED discharge. **In addition, it is recommended that drug–drug interaction references be used whenever adding a new medication to a patient on warfarin.** Drugs frequently prescribed upon ED discharge that should generally be avoided in patients on warfarin because of the increased risk of bleeding, include NSAIDs, sulfa-containing drugs (e.g., sulfamethoxazole), macrolides, and fluoroquinolones. Drugs that induce hepatic cytochrome P450 activity may increase the metabolism and reduce the effect of warfarin. Because the effect may take several days to manifest, the following agents should only be prescribed upon ED discharge after careful review and with close follow-up: barbiturates, anticonvulsants (e.g., phenytoin, carbamazepine, primidone), antibiotics (e.g., dicloxacillin, nafcillin, rifampin), and antipsychotics or sedatives (e.g., haloperidol, trazodone).

WARFARIN COAGULOPATHY

The two important principles when warfarin-treated patients bleed with a prolonged INR are as follows: (1) attempt to identify and attenuate the cause of bleeding, and (2) lower the intensity of the anticoagulant effect. In patients with a modestly elevated INR without clinically evident bleeding, cessation of warfarin, careful observation, and periodic monitoring compose the safest course (**Figure 239-1**).[2,6,7] Conversely, reversal is recommended when the INR is markedly elevated or there

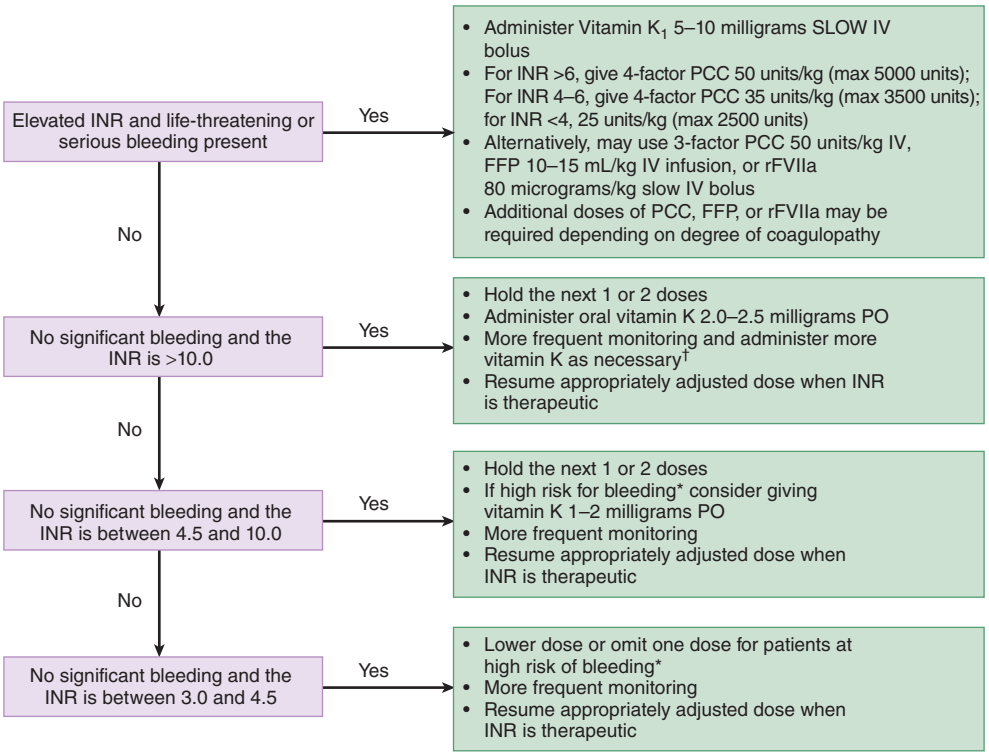

FIGURE 239-1. Management of prolonged INR (warfarin-induced coagulopathy). *High risk of bleeding: age >75 years, concurrent antiplatelet drug use, polypharmacy, liver or renal disease, alcoholism, recent surgery, or trauma. †There are no validated tools to predict risk of short-term major bleeding in patients with severe overanticoagulation. The decision to admit for observation relies on physician judgment. FFP = fresh frozen plasma; 4-factor PCC = prothrombin complex concentrate (human) containing coagulation factors 2, 7, 9, and 10; 3-factor PCC = coagulation factor IX complex containing coagulation factors 2, 9, and 10; rFVIIa = coagulation factor VIIa (recombinant).

is clinically significant bleeding.[2,7] The speed and extent of reversal should be balanced against the risk of recurrent thromboembolism in patients who require therapeutic anticoagulation.[8] For example, an overanticoagulated patient with a prosthetic mitral valve may develop fatal thrombosis if supratherapeutic anticoagulation is rapidly and fully reversed.

Three approaches used to reverse warfarin-induced coagulopathy are as follows: (1) stop warfarin therapy; (2) administer **vitamin K_1** (PO or IV); and (3) replace deficient coagulation factors using either **fresh frozen plasma, prothrombin complex concentrate (human), coagulation factor IX complex (human), or coagulation factor VIIa (recombinant)** (Figure 239-1).[2,9-12] In asymptomatic patients with an elevated INR of 4.5 to 10 due to warfarin, oral vitamin K_1 1.0 to 2.0 milligrams will produce a measurable reduction in INR by 16 hours, with a therapeutic level by the second day.[6,7] In asymptomatic patients with an INR >10, oral vitamin K_1 2 milligrams is also effective, although the reduction in INR takes longer. Although low-dose oral vitamin K_1 carries a small risk for patients who require therapeutic anticoagulation, it is reasonable to consult an appropriate specialist before using vitamin K_1 to reverse anticoagulation in stable patients.

IV vitamin K_1 carries a rare but serious, non–dose-dependent risk of anaphylaxis and should not be used for routine reversal of therapeutic overanticoagulation.[13] For patients who require continued anticoagulation, IV administration also carries the risk of overcorrection not associated with oral use. IV vitamin K_1 should be restricted to patients with life-threatening bleeding[2] and to symptomatic patients poisoned by an excessive ingestion of warfarin (e.g., suicidal overdose). Generally, overdose patients do not require long-term therapeutic anticoagulation, and reversal does not carry the risk of recurrent thrombosis.

Administration of vitamin K to a warfarin-treated patient should not be considered reversal of anticoagulation. Vitamin K simply restores the patient's ability to begin again to synthesize factors II, VII, IX and X, and reattaining physiologic levels and normal hemostasis may take hours to days to achieve.

The fastest method of reversing therapeutic overanticoagulation is with coagulation factor repletion by IV infusion, using either fresh frozen plasma, prothrombin complex concentrate (human) (PCC or four-factor PCC), or coagulation factor IX complex (human) (or three-factor PCC) with or without coagulation factor VIIa (recombinant).[9-12] For patients with intense anticoagulation (INR >10) who require only partial reversal, fresh frozen plasma 10 to 15 mL/kg would be expected to restore coagulation factors to about 30% of normal, corresponding to an INR of 1.7 to 1.8. Disadvantages of fresh frozen plasma include potential fluid overload, which can be difficult to reverse with furosemide. Some institutions provide **"universal donor" fresh frozen plasma**, which is derived from AB-Rh+ donors and thus contains no anti-A, anti-B, or anti-Rh antibodies. If available and indicated, it can be given without a type and cross-match of blood from the recipient and as soon as it is defrosted (20 to 30 minutes).

For patients with life-threatening hemorrhage who require rapid, complete reversal, such as those with warfarin-associated intracranial hemorrhage, **give vitamin K 10 milligrams IV and PCC 25 to 50 milligrams/kg IV** (Figure 239-1).[8,14,15] If factor IX complex (or three-factor PCC) is used, consider the addition of coagulation factor VIIa (recombinant) to make up for the minimal amount of factor VII in factor IX complex. Additional doses of these products may be required depending on the degree of coagulopathy. PCC reverses the INR within 30 minutes, with the degree of INR reduction depending on the initial INR. The half-life of PCC is about 4 to 6 hours. The onset of action of IV vitamin K is about 2 hours, with maximal effect at 6 to 12 hours, so PCC and IV vitamin K act synergistically in INR reduction.

DIRECT THROMBIN INHIBITORS

Dabigatran etexilate, an oral direct thrombin inhibitor, is used to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and the risk of recurrent deep venous thrombosis or pulmonary embolism after treatment of the acute episode.[1,16-19] After ingestion, dabigatran etexilate is converted to the active agent dabigatran by esterase, achieving peak serum concentrations in 2 hours with a terminal elimination half-life of 14 hours. Dabigatran is a reversible inhibitor of both circulating and clot-bound thrombin. Dabigatran has more predictable pharmacologic activity than warfarin, a broad therapeutic window, low interpatient variability, and no significant drug–drug (except for rifampin) or drug–diet interactions. Monitoring with standard coagulation tests during therapeutic use is not required. In routine use in patients with atrial fibrillation, dabigatran is generally safer than warfarin, with the notable exception of a higher risk of major GI bleeding. As with warfarin, the concomitant use of NSAIDs and other antiplatelet medications greatly increases the risk of bleeding for patients taking dabigatran.

Prothrombin time and the activated PTT are insensitive to the activity of dabigatran, whereas the thrombin clotting time is typically overly sensitive.[1,20] The ecarin clotting time has a linear dose response through the range of dabigatran concentrations seen during clinical use, but this test is not commonly available. **For practical purposes, a normal thrombin time excludes a significant coagulopathy due to dabigatran. If available, a diluted thrombin time is even more specific.**[1]

Only about 15% to 20% of absorbed dabigatran is metabolized, and the remainder is excreted unchanged in the urine. It is therefore important to maintain urinary output in patients with active bleeding while taking dabigatran to enhance drug elimination.

Idarucizumab (Praxbind®), a monoclonal antibody fragment that binds dabigatran, is U.S. Food and Drug Administration approved when reversal of the anticoagulant effects of dabigatran is needed for life-threatening or uncontrolled bleeding or for emergency surgery or urgent procedures (**Table 239-3**).[21,22] The recommended dose of idarucizumab is 5 grams, provided as two separate vials each containing 2.5 grams in 50 mL.[22] If bleeding continues, consider a repeat dose of 5 grams. If idarucizumab is not available, observational experience suggests that either anti-inhibitor coagulant complex (FEIBA NF or activated PCC) or prothrombin complex concentrate (four-factor PCC) may reverse the anticoagulative effect of dabigatran,[23] whereas fresh frozen plasma does not.[1] If idarucizumab is not available, hemodialysis can be effective with removal of 60% or more of the drug within 2 hours**; however, hemodialysis should be performed only if idarucizumab is not available.**[1,12,21]

TABLE 239-3 Reversal of Direct-Acting Oral Anticoagulants (DOACs)

Oral Direct Thrombin Inhibitors	
Dabigatran	Oral activated charcoal if recent or excessive ingestion Maintain urine output For severe bleeding or urgent reversal, idarucizumab 5 grams IV infusion or bolus (provided as two separate vials each containing 2.5 grams/50 mL) If idarucizumab not available and life-threatening bleeding is present, consider 50 units/kg IV (maximum dose 5000 units) of either aPCC or four-factor PCC
Oral Factor Xa Inhibitors	
Rivaroxaban Apixaban Edoxaban Betrixaban	Coagulant factor Xa (recombinant), inactivated (aka, andexanet alfa): Approved for major bleeding secondary to rivaroxaban or apixaban **Low dose:** (1) Last dose of rivaroxaban or apixaban was ≥8 h *or* (2) last dose was <8 h *and* rivaroxaban dose ≤10 milligrams or apixaban dose ≤5 milligrams; 400-milligram bolus IV over 30 min, followed by a continuous infusion of 4 milligrams/min for 120 min (total dose, 880 milligrams) **High dose:** Otherwise, 800-milligram bolus IV over 30 min, followed by a continuous infusion of 8 milligrams/min for 120 min (total dose, 1760 milligrams) **The infusion should be started within 2 min of the bolus.** Andexanet alfa not approved for use in edoxaban- or betrixaban-associated bleeding If andexanet alfa not available, for major bleeding, consider four-factor PCC 50 units/kg IV (maximum dose 5000 units)

Abbreviations: aPCC = anti-inhibitor coagulant complex, FEIBA, or activated prothrombin complex concentrate; four-factor PCC = prothrombin complex concentrate.

FACTOR Xa INHIBITORS

Rivaroxaban, apixaban, and edoxaban are oral direct factor Xa (FXa) inhibitors used for the treatment of venous thromboembolism and for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (**Table 239-4**).[1,24,25] Betrixaban is used for venous thromboembolism prophylaxis.[26] These FXa inhibitors have predictable pharmacologic properties and do not require routine laboratory monitoring.

The effect of the oral FXa inhibitors on standard coagulation tests is variable and not reliable for determining therapeutic effect or over-anticoagulation. The preferred most clinically available test is drug level using the anti–FXa activity assay calibrated for the specific oral FXa inhibitor used.[27] Drug level (anti-FXa activity) can be measured at either peak (3 to 5 hours after ingestion) or trough (1 to 2 hours before next dose). Levels associated with therapeutic doses have been published, but clinical laboratories have not established reference ranges, nor is there a consensus as to which levels denote inadequate anticoagulation or over-anticoagulation. The primary purpose of such assays is to determine drug presence prior to invasive procedures or thrombolytic therapy and assess compliance in cases of venous thromboembolism while on therapy.

Discontinuation of the drug for at least 24 hours could be sufficient when there is no imminent need for reversal, as in elective or nonurgent procedures. However, in patients with renal impairment and the elderly, additional time for clearance would be required before any surgical procedures are undertaken. There is an increased risk of stroke or other thrombotic event when rivaroxaban is suddenly discontinued in patients with nonvalvular atrial fibrillation.[28] When possible, another anticoagulant should be substituted.

Coagulant FXa (recombinant), inactivated (andexanet alfa), is a recombinant modified human FXa decoy protein that is U.S. Food and Drug Administration approved for treatment of life-threatening or uncontrolled bleeding due to rivaroxaban and apixaban.[29] The dose of andexanet alfa is determined by (1) the timing of the last dose and (2) the dose (Table 239-3). The low-dose regimen is used if (1) the last dose was taken ≥8 hours previously or (2) if the last dose was taken within 8 hours *and* the dose of rivaroxaban was ≤10 milligrams or the dose of apixaban was ≤5 milligrams. Otherwise, the high-dose regimen should be used. Two important potential complications were observed after andexanet alfa administration: thromboembolic events (18% of patients within 30 days of treatment, mostly related to non-reinstitution of therapeutic anticoagulation) and infusion-related reactions (e.g. flushing, feeling hot, cough, dyspnea, distorted taste, mild hives), which also occurred in 18% of patients.[29]

Due to high plasma protein binding, FXa inhibitors are not readily removed by dialysis. If andexanet alpha is not available, other options for the emergency reversal include activated anti-inhibitor coagulant complex (FEIBA NF or activated PCC) or PCC (four-factor PCC).[1,8,24,29]

Administration of **activated charcoal** within 2 hours of taking an oral anticoagulant may adsorb the drug from the intestines before it reaches the plasma. It would be reasonable to administer activated charcoal to a patient who has deliberately or accidentally ingested an inappropriate amount of dabigatran or an FXa inhibitor, and also in a patient with significant bleeding who has recently ingested even a therapeutic dose.

HEPARINS

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is a heterogeneous mixture of polysaccharides ranging in molecular weight from 3 to 30 kD, with most commercial preparations possessing a mean molecular weight of about 15 kD, corresponding to about 45 saccharide units.[30] The anticoagulant effect of UFH requires binding to antithrombin (previously named antithrombin III), and heparins are therefore "indirect" anticoagulants.[30] Although the UFH–antithrombin complex interferes with several activated factors in both the extrinsic and common coagulation pathways (factors Xa, IXa, XIa, and XIIa, and thrombin), the primary anticoagulant effect of heparin is due to thrombin and FXa inhibition. The majority of heparin's anticoagulant effect is dependent on a unique pentasaccharide sequence found in only about one third of heparin molecules. Variations in polysaccharide chain lengths found in UFH likely contribute to the unpredictable nature of heparin's dose–response relationship.

UFH is given parenterally with a half-life (30 to 150 minutes) that depends on the dose and route. Weight-based IV UFH dosing protocols are the most reliable approach for achieving a therapeutic effect and preventing further thrombosis during acute thromboembolic events.[29] Subcutaneous UFH is not recommended for the treatment of

TABLE 239-4 Oral Factor Xa Inhibitors

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Typical dose	20 milligrams PO once a day	5 milligrams PO twice a day	60 milligrams PO once a day	80 milligrams PO once a day
Oral bioavailability	Dose dependent: 10-milligram tablets: 80%–100% not affected by food 15- and 20-milligram tablets: about 66% without food and increases to >90% with food Peak serum concentrations 2–4 h	Approximately 50%, not affected by food Peak serum concentrations 3–4 h	Approximately 62%, not affected by food Peak serum concentrations 1–2 h	Approximately 34% Peak serum concentrations 3–4 h
Serum protein binding	92%–95%	87%	55%	60%
Metabolism	Oxidative degradation by hepatic cytochrome P450 isoenzymes CYP3A4, CYP3A5, and CYP2J2	About 25% with O-methylation and hydroxylation by hepatic cytochrome P450, primarily isoenzyme CYP3A4	Minimal, <15% via hydrolysis, conjugation, or oxidation	Hydrolysis extensively, minimal CYP450 metabolism
Elimination	About one third excreted unchanged in the urine, about one third excreted as inactive metabolites in the urine, and one third excreted as inactive metabolites in feces	About 30% in urine and 70% in feces	50% in urine and 50% in feces	Feces 85%, urine 11%
Elimination half-life	5–9 h	12 h	10–14 h	19–27 h
Drug concentration ranges with therapeutic doses (5th to 95th percentile), nanograms/mL	Peak: 189–419 Trough: 66–87	Peak: 91–321 Trough: 41–230	Peak: 120–250 Trough: 10–40	No published data

acute thromboembolic disease because the bioavailability via this route of administration ranges from 10% to 90%, depending on the dose. However, subcutaneous UFH can be used to prevent thromboembolism (Table 239-1). **Because UFH interferes with most laboratory investigations for hypercoagulable states, these tests should ideally be ordered before the patient is anticoagulated.** Neither UFH nor low-molecular-weight heparin crosses the placenta; consequently, both are safe to use in pregnancy.

UFH has an unpredictable anticoagulation effect, requires frequent monitoring, binds nonproductively to vascular endothelium and ubiquitous plasma proteins, and actually activates platelets by interacting with platelet factor 4. The unpredictable inhibition of thrombin by heparin is attributable to a low bioavailability from extensive nonspecific binding to serum proteins, macrophages, and endothelial cells. Therapeutic IV UFH therapy is monitored using either anti-Xa activity or the PTT (Table 239-1).[30,31] The therapeutic range for anti-FXa activity is 0.3 to 0.7 IU/mL for venous thromboembolism treatment, 0.3 to 0.6 IU/mL for acute coronary syndrome treatment, and 0.3 to 0.45 IU/mL for anticoagulation in the management of atrial fibrillation.[31] The therapeutic range for an activated PTT is 1.5 to 2.5 times the reference range value, typically 68 to 100 seconds. UFH can increase the prothrombin time by a variable amount, typically 1 to 5 seconds depending on the heparin concentration and the thromboplastin reagent used in the assay.

LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight heparins (LMWHs) are polysaccharide chains ranging in molecular weight from 2 to 9 kD, with commercial preparations (enoxaparin, dalteparin, and tinzaparin) possessing a mean molecular weight of approximately 4 to 5 kD, corresponding to about 15 saccharide units. LMWH possesses many clinical advantages compared to the parent compound (**Table 239-5**).[30] Both UFH and LMWH exert their anticoagulant effect by binding to and enhancing the activity of antithrombin. This interaction is mediated by a unique pentasaccharide sequence that induces a conformational change in antithrombin, enhancing binding to and inactivation of thrombin and factors Xa, IXa, XIa, and XIIa. Inhibition of thrombin is facilitated by an additional 13-saccharide group that brings the key binding regions of antithrombin and thrombin into contact. However, only the specific pentasaccharide sequence is necessary to bind to antithrombin for effective inhibition of FXa. UFH inhibits FXa and thrombin in roughly equal proportions (anti-FXa to antithrombin activity ratio of about 1) because chains of at least 18 saccharide units predominate. In contrast, more than half of LMWH molecules are smaller than 18 saccharide units, resulting in a reduced ability to inactivate thrombin and an enhanced affinity for inactivating FXa (anti-FXa to antithrombin activity ratio between 2:1 and 4:1).[30]

LMWH is cleared by the kidneys, so bleeding complications due to accumulation of the agent can occur in patients with significant renal impairment. Appropriate dosing of LMWH in patients with severe renal insufficiency (creatinine clearance <30 mL/min) is unclear. In patients with severe renal insufficiency, it is suggested that either a reduced dose of enoxaparin (50% of the usual amount) be used or UFH be administered instead.[29] Obese patients (body mass index >30) should receive weight-based LMWH dosing.[30]

TABLE 239-5 Advantages of Low-Molecular-Weight Heparin Over Unfractionated Heparin

Pharmacologic Effects	Clinical Benefit
Quick and predictable SC absorption	More reliable level of anticoagulation
More stable dose response	Eliminates need for monitoring
Resistance to inhibition by platelet factor 4	Decreased incidence of thrombocytopenia
Decreased antiheparin antibody production	Greater antithrombotic effects
Greater anti-FXa activity	Potential for reduced bleeding
Less antithrombin activity	Absence of "rebound"
Ease of administration	Outpatient therapy

The plasma half-life of LMWH is two to four times longer than UFH, allowing for once- or twice-daily dosing. LMWH has a decreased binding affinity for plasma proteins, endothelial cells, and macrophages, thus yielding a more predictable anticoagulant and dose–response relationship, allowing for SC administration at fixed dosages. There are greatly reduced interactions with the platelet factor 4 receptor, resulting in a much lower incidence of heparin-induced thrombocytopenia than that seen with UFH. Laboratory monitoring of the activity of LMWH is unnecessary in most patients,[32] but is suggested in high-risk patients (e.g., trauma, burns, critically ill) and those who experience recurrent thromboembolism while on therapy.[33] The gold standard for monitoring LMWH is the chromogenic anti-FXa assay,[33] drawn 3 to 4 hours after SC injection. The therapeutic level of LMWH for venous thromboembolism prophylaxis is 0.2 to 0.5 IU/mL,[34] and the therapeutic level for venous thromboembolism treatment is 0.5 to 1.1 IU/mL.

HEPARIN COMPLICATIONS

The two major complications of heparin are bleeding and heparin-induced thrombocytopenia.[35-37] Up to one third of patients receiving UFH develop some form of bleeding complication, with a 2% to 6% incidence of major bleeding.[30] An increased risk of up to 20% for major bleeding is associated with concomitant conditions, such as recent surgery or trauma, renal failure, alcoholism, malignancy, liver failure, and GI bleeding, as well as the concurrent use of warfarin, fibrinolytics, steroids, or antiplatelet drugs.

Bleeding in patients being treated with UFH is managed according to the clinical severity and less by activated PTT level **(Table 239-6)**.[2,30] Heparin-associated bleeding is not always reflected by a supratherapeutic activated PTT, so if bleeding develops during UFH therapy, heparin administration should be stopped immediately. **Although UFH half-life is dose dependent (30 to 150 minutes), its anticoagulation effect can last up to 3 hours.** Observation may be appropriate in less severe cases, with serial activated PTT used to determine when therapy may

TABLE 239-6 Reversal of Parenteral Antithrombotic Therapy

Agent	Management
Heparins	
Minor bleeding	Immediate cessation of heparin administration Supratherapeutic aPTT not always present Anticoagulation effect lasts up to 3 h from last IV dose. Observation with serial aPTT may be sufficient.
Major bleeding	Protamine dose: 1 milligram IV per 100 units of total amount of IV UFH administered within the past 3 h, maximum single dose 50 milligrams Protamine administration: IV slowly, maximum rate 5 milligrams/min Protamine has an anaphylaxis risk. Protamine does not completely reverse LMWH. Enoxaparin: Protamine 1 milligram IV (maximum dose, 50 milligrams) for every 1 milligram of enoxaparin given in the previous 8 h. If 8–12 h since last enoxaparin dose, give protamine 0.5 milligram IV for every 1 milligram of enoxaparin given. Dalteparin and tinzaparin: Protamine 1 milligram IV per every 100 units of dalteparin or tinzaparin given. If aPTT (measured 2–4 h after the protamine infusion) remains prolonged, give a second dose of protamine 0.5 milligram IV per 100 units of dalteparin or tinzaparin.
Pentasaccharides	
Fondaparinux	Antithrombotic effect of fondaparinux is 24–30 h. For life-threatening bleeding, anecdotal evidence suggests rFVIIa 90 micrograms/kg IV is effective.

Abbreviations: aPTT = activate partial thromboplastin time; LMWH = low-molecular-weight heparin; rFVIIa = coagulation factor VIIa (recombinant); UFH = unfractionated heparin.

be resumed. Although **protamine** can reverse the anticoagulant effect of UFH, adverse effects are common and include hypotension, bradycardia, dyspnea, nausea, vomiting, and urticaria. Protamine should be given slowly IV at a maximum rate of 5 milligrams/min. Monitor aPTT starting at 5–15 min after the protamine infusion; the onset of reversal is seen within 5 minutes and the duration of reversal activity is about 2 h. Additional doses may be required if bleeding persists or the aPTT remains elevated. Reversal of subcutaneously administered heparin may require repeated or prolonged protamine administration. Allergic reactions are common, and approximately 0.2% of patients receiving protamine develop anaphylaxis. Thus, protamine should be reserved for major bleeding complications.

Platelet count may fall in 10% to 20% of patients 2 to 3 days following initiation of UFH treatment due to nonimmunologic direct platelet aggregation. This process is sometimes termed "heparin-associated thrombocytopenia" and was previously termed "type I heparin-induced thrombocytopenia." The platelet nadir is typically no lower than 100,000/mm^3 (100 × 10^9/L), there is no risk for associated thrombosis, and platelet count recovers within 4 days despite continued heparin treatment.

Heparin-induced thrombocytopenia (HIT; previously termed "type II heparin-induced thrombocytopenia") is a syndrome due to the formation of immunoglobulin G or immunoglobulin M autoantibodies directed against both heparin and platelet factor 4 that activates platelets, producing both thrombocytopenia and a tendency for thrombosis.[35] Thrombosis may involve the skin (similar to warfarin-induced cutaneous necrosis), major arteries (e.g., ischemic limbs), or the veins (e.g., recurrent venous thrombosis or pulmonary embolism). The onset of HIT is usually 5 to 10 days after heparin treatment is started, but may be sooner for patients who developed an antibody from a previous heparin exposure. Although rare, one of the earliest clues is an anaphylactoid reaction within 30 minutes of receiving an IV bolus of heparin, often while the patient is in the ED. Patients who exhibit acute systemic reactions such as fevers, chills, hypertension, tachycardia, dyspnea, or chest pain should be evaluated for HIT by immediately obtaining a platelet count. Because a decrease in platelet count may be transient under these circumstances, the diagnosis can be missed if there is a delay in obtaining the platelet count.[35]

The incidence of HIT is variable and influenced by the specific heparin preparation used, dose, duration, and patient characteristics. In general, between 1% and 3% of postoperative patients treated with UFH for 4 to 14 days will develop HIT, compared with only 0.1% to 1.0% of medical or obstetric patients who receive UFH for a similar duration. HIT is approximately 10 times less frequent in patients treated with LMWH products. With HIT, the platelet count nadir is variable, typically 20,000 to 150,000/mm^3 (20 to 150 × 10^9/L). During treatment with UFH, it is recommended that a baseline platelet count be obtained and the count be repeated at 24 hours and every 2 to 3 days thereafter during the duration of therapy. A drop of 50% or more from baseline is considered evidence of HIT, even if the platelet count is within a normal range. It is recommended to assess for recent use of UFH or LMWH before instituting heparin therapy for a new venous thrombosis that may, in fact, be a thrombotic complication of HIT.

A scoring system (4Ts score) has been developed to assist in the diagnosis of HIT,[38] scoring the severity of thrombocytopenia; the timing of platelet count fall; the presence of new thrombosis, skin necrosis, or systemic reaction after IV heparin bolus; and the lack of other causes for thrombocytopenia.

With HIT, all heparin therapy (including "heparin lock" IVs and heparin-coated catheters) should be stopped. Protamine is not effective against the immune-mediated response. Platelet transfusion is not indicated because bleeding is not usually a manifestation of HIT and may precipitate thrombosis. The platelet count generally returns to normal in 4 to 6 days after heparin discontinuation. During the recovery phase, the risk of arterial or venous thrombosis is substantially elevated, and the potential complications include gangrene, stroke, and myocardial infarction. LMWH is not recommended to prevent thrombosis during this recovery period because of cross-reactivity between LMWH and the antiplatelet antibody. Additionally, warfarin should not be started until the platelet count has normalized and the patient is sufficiently anticoagulated by an alternative measure to avoid precipitating arterial or venous thrombosis or producing skin necrosis. **Anticoagulation with a non-heparin anticoagulant, such as danaparoid, lepirudin, fondaparinux, or bivalirudin, is recommended for strongly suspected or confirmed cases of HIT, even in the absence of symptomatic thrombosis.**[35,36,39]

In general, LMWH preparations cause less bleeding than UFH. Other reported side effects of LMWH include local skin reaction, pruritus, and rarely skin necrosis. Protamine will neutralize the inhibitory effect of LMWH on thrombin but not the inhibitory effect on FXa. Thus, protamine will not completely reverse the anticoagulant effect of LMWH (Table 239-6).

FONDAPARINUX AND HIRUDINS

FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and enhances its affinity for FXa, but not thrombin. It is not considered a heparin product and does not cause HIT. It is used in venous thromboembolism prophylaxis and treatment, and is typically recommended as one alternative antithrombotic that can be used in patients with a history of HIT.[17,30,40] Fondaparinux is administered by SC injection using fixed doses stratified according to the indication and body weight (Table 239-1). The drug has a terminal half-life of about 17 hours, which allows for once-daily dosing. Laboratory monitoring of the activity of fondaparinux is unnecessary in most patients. If required, adequacy of anticoagulation is measured using anti–FXa activity assay obtained 4 hours after drug administration, with a therapeutic range for venous thromboembolism treatment of 0.8 to 1.2 IU/mL. For fondaparinux-associated bleeding, limited data suggest that coagulation factor VIIa (recombinant) and anti-inhibitor coagulant complex (activated PCC) can reverse the coagulopathy.[23,41,42]

HIRUDINS

Hirudins (hirudin and lepirudin) and hirudin analogs (bivalirudin and argatroban) are polypeptides and parenteral direct thrombin inhibitors, possessing several potential advantages over heparin.[17,30] Unlike heparin, direct thrombin inhibitors are capable of inhibiting both circulating and clot-bound thrombin, do not inhibit other coagulation pathway or fibrinolytic enzymes, do not require antithrombin as a cofactor for activity, and do not interact with platelet factor 4 or plasma proteins. Therefore, direct thrombin inhibitors have a more predictable anticoagulant effect than UFH. Hirudin, lepirudin, and argatroban are used for anticoagulation in patients with heparin-induced thrombocytopenia.[35,36] Bivalirudin and argatroban are potential alternatives to UFH and LMWH for the treatment of acute coronary syndrome with percutaneous coronary intervention.[43,44]

The primary adverse effect of direct thrombin inhibitors is bleeding, and the majority of bleeding events occur at invasive sites. Because the half-life of hirudin and its analogs is relatively short (<1 hour) and an antidote is not currently available, management of hemorrhage may require only stopping the IV infusion and waiting. Coagulation factor replacement with fresh frozen plasma or PCC can be used if bleeding persists.

ANTIPLATELET AGENTS

ASPIRIN

Aspirin irreversibly blocks cyclooxygenase, an enzyme that in platelets catalyzes the conversion of arachidonic acid to thromboxane A_2 and in the blood vessel wall promotes prostacyclin synthesis (**Table 239-7**).[45,46] The net effect of aspirin in ischemic arterial beds depends on the balance between reduction in thromboxane A_2 (a vasoconstrictor and platelet-aggregation inducer) and reduction in prostacyclin (a vasodilator and platelet-aggregation inhibitor). Aspirin's antithrombotic effect can be seen with doses as low as 30 milligrams, but for reliable antiplatelet effect, an initial dose of 162 to 325 milligrams is recommended (Table 239-1).

TABLE 239-7 Oral Antiplatelet Agents

	Class/Mechanism of Action	Type of Inhibition	Time to Peak Effect	Elimination Half-Life	Duration of Antiplatelet Effect	Typical Dose
Aspirin	Nonselective cyclooxygenase inhibitor	Irreversible	30 min	15–30 min	Up to 7 d	325 milligrams PO initial dose for ACS Maintenance doses 81–162 milligrams PO once per day
Clopidogrel	ADP receptor inhibitor Prodrug; requires production of active metabolite	Irreversible	3–7 d	8 h	Up to 10 d	300 milligrams PO loading dose (consider 600 milligrams if PCI is planned) followed by 75 milligrams PO once per day
Prasugrel	ADP receptor inhibitor Prodrug; requires production of active metabolite	Irreversible	30 min	7 h	5–7 d	60 milligrams PO loading dose, followed by 10 milligrams (5 milligrams if <60 kg) PO once per day
Ticagrelor	ADP receptor inhibitor	Reversible	1.5 h	7 h	3–4 d	180 milligrams PO loading dose, followed by 90 milligrams PO twice per day
Dipyridamole	Multiple: reduces platelet aggregation, vasodilator, weak phosphodiesterase inhibitor	Reversible	N/A	Biphasic: 40 min and 10 h	1–2 d	200 milligrams extended-release PO twice per day (usually combined with low-dose aspirin)
Cilostazol	Phosphodiesterase inhibitor: reduces platelet aggregation, vasodilator	Reversible	N/A	11–13 h	3–4 d	100 milligrams PO twice per day

Abbreviations: ACS = acute coronary syndrome; ADP = adenosine diphosphate; N/A = not applicable; PCI = percutaneous coronary intervention.

Aspirin is quickly absorbed in the upper GI tract (unless consumed in an enteric-coated formulation), reaches peak blood concentrations in 20 to 40 minutes, and circulates with a half-life of 3 to 4 hours. However, cyclooxygenase inactivation is irreversible and lasts for the life span of the platelet. Only non–enteric-coated aspirin should be administered when prompt onset of action is necessary, as in patients with acute coronary syndrome.[46-48]

Side effects of aspirin use are mainly GI and are dose related. The side effects may be reduced in the maintenance therapy setting with concomitant use of antacids, enteric coating, and buffering agents. Aspirin should be avoided in patients with known hypersensitivity and used cautiously in those with bleeding disorders or severe hepatic disease. Active GI hemorrhage (e.g., bleeding peptic ulcer) is a contraindication to aspirin use. However, in acute coronary syndrome with occult GI bleeding (e.g., guaiac-positive stool), most experts favor aspirin use with careful monitoring. Daily aspirin therapy is advocated in the prevention of cardiovascular events in patients with known cardiovascular disease. The benefits in patients without cardiovascular disease (termed primary prevention) are modest and almost offset by the risk of hemorrhagic stroke and major bleeding.[48-50] In general, daily aspirin therapy does reduce recurrence of myocardial infarction, ischemic stroke, and sudden cardiovascular death (termed secondary prevention), with an increased risk of major bleeding events, primarily GI, and cerebral hemorrhage. The overall effect tends to be beneficial, although the magnitude of change with individual outcomes does vary with indication and between genders.

NSAIDs reversibly inhibit platelet cyclooxygenase and have the potential to reduce the antiplatelet efficacy of aspirin. Myocardial infarction patients have an increased risk of mortality, reinfarction, heart failure, and shock if taking NSAIDs within 7 days of presentation[51] and up to 90 days after the acute event.[52] Current acute coronary syndrome guidelines contain cautions about the use of NSAIDs.[52-55]

Upper GI irritation is the most common side effect of aspirin therapy.[46] Some patients are markedly sensitive to aspirin, such that even low doses lead to markedly prolonged bleeding times and risk of severe clinical hemorrhage, particularly related to surgery or trauma. Uremia and the combination of ethanol and aspirin are two circumstances where patients are especially sensitive to bleeding induced by aspirin.

Management of acute aspirin-induced or NSAID-induced hemorrhage involves the transfusion of enough normal platelets to increase the platelet count by 50,000/mm^3 (50 × 10^9/L), a level that will halt most bleeding (**Table 239-8**). While desmopressin can reverse the effect of aspirin on platelet function,[23] it is not a safe option as it can lead to arterial vasospasm. Because of the irreversible effect of aspirin on platelets, the hemostatic compromise might last for up to 7 days after aspirin has been discontinued, and platelet transfusions may have to be repeated daily.

ADENOSINE DIPHOSPHATE RECEPTOR AGENTS (CLOPIDOGREL, PRASUGREL, TICAGRELOR, TICLOPIDINE)

Clopidogrel, prasugrel, ticagrelor, and ticlopidine inhibit platelet activation by blocking the adenosine diphosphate receptor.[45,56] These agents are also termed "membrane-deforming" agents because by inhibiting the adenosine diphosphate receptor, the adjacent region of the platelet membrane containing the fibrinogen receptor is deformed and the fibrinogen receptor is rendered ineffective.

Clopidogrel is a prodrug that is metabolized into an irreversible adenosine diphosphate receptor inhibitor. Rapidly absorbed from the GI tract, oral doses of 600 milligrams result in a full antiplatelet effect by 2 hours that is sustained for up to 48 hours. Platelet function typically returns to normal 7 days after the last clopidogrel dose. Clopidogrel is used for the treatment of acute coronary syndrome[55,56] and established peripheral arterial disease,[57] as well as for secondary prevention of myocardial infarction[58] and ischemic stroke.[59] Although clopidogrel is generally well tolerated, adverse effects include dyspepsia, rash, and diarrhea. Clopidogrel can also be used in patients who have a history of aspirin hypersensitivity or major GI intolerance.

TABLE 239-8 Reversal of Oral Antiplatelet Agents

Aspirin and NSAIDs	Desmopressin 0.3–0.4 microgram/kg IV over 30 min Platelet transfusion to increase count by 50,000/mm^3 (typically requires one single donor apheresis-collected platelet concentrate or 6 units of random donor platelets) Aspirin-induced platelet inhibition may last for 7 d, so repeat platelet transfusions are sometimes required.
Other antiplatelet agents: clopidogrel, prasugrel, ticagrelor	Platelet transfusion to increase count by 50,000/mm^3 (typically requires one single donor apheresis-collected platelet concentrate or 6 units of random donor platelets) Desmopressin 0.3–0.4 microgram/kg IV over 30 min NSAID-induced platelet inhibition typically lasts <1 d. Clopidogrel-, prasugrel-, or ticagrelor-induced platelet inhibition may last up to 5–7 d.

The active metabolite is produced by the cytochrome P450 system, principally isoenzyme 2C19 (CYP2C19). Patients with a diminished CYP2C19 metabolizer status have a lessened antiplatelet response to clopidogrel. The reported frequency for poor CYP2C19 metabolizer status varies by ethnic background: approximately 2% for whites, 4% for blacks, and 14% for Chinese. A patient's CYP2C19 metabolizer status can be determined with genotype testing, and a higher dose regimen (600-milligram loading dose followed by 150 milligrams once daily) is suggested in poor metabolizers, although this dose regimen has not been validated in clinical outcome trials.[60] Omeprazole and esomeprazole are inhibitors of CYP2C19 and reduce the antiplatelet activity of clopidogrel if given within 12 hours of each other. While the effect on clinical outcome from this interaction is variable according to the patient's risk for cardiovascular events, it is prudent instead to give pantoprazole in the ED to patients receiving clopidogrel for acute coronary syndrome.[61]

Prasugrel, like clopidogrel, is a prodrug that is converted to the active metabolite that is an irreversible inhibitor of the adenosine diphosphate receptor on platelets.[55] Prasugrel is used in the treatment of acute coronary syndrome.[57] Compared to clopidogrel, prasugrel has an increased risk of bleeding and is less effective in patients with a history of a stroke or transient ischemic attack, patients >75 years of age, and patients with a body weight of <60 kg.

Ticagrelor is a reversible adenosine diphosphate receptor antagonist that does not need to be converted by the liver into an active metabolite.[55] Ticagrelor is used in a broad range of acute coronary syndrome patients.[55,62] Compared with clopidogrel, ticagrelor reduces the subsequent deaths from all cardiovascular causes or myocardial infarction.[63] There is a modest increase in the risk of major bleeding not related to coronary artery bypass graft surgery with ticagrelor and a trend toward more intracranial bleeding.

Ticlopidine is associated with significant risk for hematologic problems, such as neutropenia and thrombotic thrombocytopenic purpura. Therefore, ticlopidine is now rarely used in the United States.

Antiplatelet therapy is a risk factor for increased intracranial bleeding and worse outcome in closed head injury.[63] The observed risk is highest with clopidogrel.[63] Uncontrolled bleeding in patients on adenosine diphosphate receptor antagonist therapy should be treated with supportive therapy, and possibly platelet transfusions or desmopressin. (Table 239-8).[24]

PHOSPHODIESTERASE INHIBITORS (DIPYRIDAMOLE)

Dipyridamole is both a vasodilator and antiplatelet agent.[46,64] The specific antiplatelet effects are multiple and include reversible phosphodiesterase inhibition. Clinical efficacy of dipyridamole appears to be enhanced by formation into an extended-release preparation.[65] Current recommendations highlight the use of dipyridamole when combined with aspirin for the secondary prevention of stroke or transient ischemic attacks.[59,64] A fixed combination of aspirin, 25 milligrams, and extended-release dipyridamole, 200 milligrams PO twice a day, is commonly used for this indication. Dipyridamole is occasionally used in the standard formulation (not extended release) for angina prophylaxis and the prevention of prosthetic cardiac valve thrombosis when combined with warfarin or aspirin where doses of 50 to 100 milligrams PO three or four times a day are typical. Common adverse side effects include headache, dizziness, flushing, and abdominal pain.

Cilostazol is a strong reversible phosphodiesterase inhibitor in addition to having other effects on platelet metabolism.[65] Cilostazol is used to increase walking distance in patients with peripheral arterial disease[66] and reduce the incidence of stroke in patients with cerebrovascular disease.[59]

GLYCOPROTEIN IIB/IIIA ANTAGONISTS (ABCIXIMAB, EPTIFIBATIDE, TIROFIBAN)

During platelet aggregation, fibrinogen binds to the glycoprotein platelet-surface IIb/IIIa receptor. Thus, fibrinogen attached to glycoprotein IIb/IIIa receptors connecting adjacent platelets represents the final common pathway for platelet aggregation. Three parenteral glycoprotein IIb/IIIa receptor inhibitors are currently available (**Table 239-9**) for use in primary coronary angioplasty.[67] These agents are all administered as an initial IV loading dose (bolus for abciximab and eptifibatide and 30-minute infusion for tirofiban) followed by a continuous IV infusion. **Abciximab** is a noncompetitive glycoprotein IIb/IIIa inhibitor with a much longer platelet effect than its plasma half-life of 10 minutes; platelet function will take up to 48 hours to return to normal after discontinuing the infusion. Conversely, **eptifibatide** and **tirofiban** are competitive glycoprotein IIb/IIIa inhibitors, with a plasma half-life of approximately 2.5 and 2.0 hours, respectively, and functional platelet recovery is usually seen 3 to 5 hours after stopping either eptifibatide or tirofiban infusion.

Glycoprotein IIb/IIIa inhibitors produce the greatest benefit in acute coronary syndrome patients undergoing percutaneous coronary intervention.[68,69] Delaying initiation of eptifibatide to the time of percutaneous coronary intervention results in less bleeding with otherwise similar outcomes, suggesting that the preferred time for administration of glycoprotein IIb/IIIa inhibitors is in the cardiac catheterization laboratory, not in the ED.[69]

Patients receiving glycoprotein IIb/IIIa inhibitors have an increased risk for bleeding complications (often related to catheterization or coronary artery bypass surgery) but have no increased risk of intracranial hemorrhage. Treatment of major hemorrhage in patients on glycoprotein IIb/IIIa inhibitors requires red cell and platelet transfusions and replacement of coagulation factors as needed.

FIBRINOLYTICS

Although mechanisms vary, each fibrinolytic agent enhances the conversion of plasminogen to plasmin, which then enzymatically breaks apart the fibrin component of thrombi. Currently approved fibrinolytic agents include streptokinase, anistreplase, alteplase, reteplase, and tenecteplase.[70-72]

TABLE 239-9 Glycoprotein IIb/IIIa IV Antagonists

	Type	Mechanism of Action	Half-Life	Duration of Antiplatelet Effect	Loading Dose	Continuous Infusion
Abciximab	Monoclonal antibody fragment	Noncompetitive inhibition	10 min	24–48 h	0.25 milligram/kg IV bolus	0.125 microgram/kg per min (maximum, 10 micrograms/min) IV
Eptifibatide	Cyclic heptapeptide	Competitive inhibition	2.5 h	3–5 h	180 micrograms/kg IV bolus over 1–2 min (maximum, 22.6 milligrams)	2 micrograms/kg per min (maximum, 250 micrograms/min) IV CrCl <50 mL/min: 1 microgram/kg per min (maximum, 7.5 milligrams/h)
Tirofiban	Nonpeptide	Competitive inhibition	2 h	3–5 h	25 micrograms/kg per min IV for 30 min	0.15 microgram/kg per min CrCl ≤60 mL/min: 0.075 microgram/kg per min for up to 18 h

Abbreviation: CrCl = creatinine clearance.

STREPTOKINASE AND ANISTREPLASE (FIRST GENERATION)

Streptokinase, derived from β-hemolytic streptococci, binds to and activates circulating plasminogen, converting it to plasmin, which in turn attacks fibrin. Circulating fibrinogen also undergoes plasmin-induced lysis, producing a state of "systemic fibrinolysis." Streptokinase is administered as a slow infusion (usually 1.0 to 1.5 million units IV over 60 minutes) and has a serum half-life of approximately 23 minutes, but in most patients, the fibrinolytic effect persists for up to 24 hours. Because of the prolonged systemic fibrinolytic state and increased risk of hemorrhage, anticoagulation with heparin is usually delayed following treatment with streptokinase.

Anistreplase, a modified active plasminogen-streptokinase complex, has an effect similar to that of streptokinase, but its chief advantage is that it can be administered as a slow bolus (usually 30 units IV over 5 minutes) and has a serum half-life of approximately 90 minutes. Anistreplase has similar benefits and adverse effects compared to streptokinase.

Both streptokinase and anistreplase are antigenic, with allergic reactions occurring in approximately 6% of patients treated with streptokinase. Antibodies to streptokinase develop approximately 5 days after treatment and persist for 6 months, so re-treatment with streptokinase or anistreplase is not advised during this interval. In addition, streptokinase or anistreplase should not be administered within 12 months of a streptococcal infection.

ALTEPLASE, OR TISSUE PLASMINOGEN ACTIVATOR (SECOND GENERATION)

Alteplase, or tissue plasminogen activator, is a naturally occurring enzyme in vascular endothelial cells that directly cleaves a specific peptide bond in plasminogen, converting it to active plasmin. Alteplase has binding sites for fibrin, which would suggest specificity for activity in the thrombus and less systemic fibrinolysis.[72] Despite the in vitro clot specificity of alteplase, its clinical side effect profile is comparable to that of other fibrinolytics. The serum half-life of alteplase is <5 minutes, and it produces a shorter fibrinolytic state than streptokinase. Heparin is commonly administered shortly after the completion of alteplase infusion.[54,72] Unlike streptokinase and anistreplase, alteplase is not antigenic; allergic reactions occur in <2% of patients treated with alteplase and IV heparin. Depending on the indication, alteplase is given as a weight-based dose via an IV infusion over 60 to 90 minutes.

RETEPLASE AND TENECTEPLASE (THIRD GENERATION)

Both reteplase and tenecteplase are derived from modifications of the parent alteplase molecule, with the intent of improving both efficacy and safety.[72] Reteplase is a deletion mutant in which the fibronectin finger (high-affinity fibrin binding), epidermal growth factor, and kringle-1 (receptor binding) regions of the wild-type alteplase molecule have been deleted. These modifications prolong the half-life of reteplase to 13-16 minutes, nearly fourfold longer than alteplase, allowing for bolus administration of reteplase as opposed to infusion administration of alteplase.[55,71,72]

Tenecteplase is created using amino acid substitutions in four different regions of the alteplase molecule, with the intention of producing a product with a longer half-life, higher level of fibrin specificity, and extended duration.[72] The long half-life of tenecteplase (20-24 minutes) allows for weight-tiered bolus dosing. The specific amino acid substitutions produce a 14-fold greater fibrin specificity than alteplase and reduced systemic plasmin generation. Tenecteplase has a plasminogen activator inhibitor 1 resistance 80 times greater than alteplase, thus allowing for a longer association of tenecteplase with the fibrin-rich clot. In addition, tenecteplase does not stimulate an increase in thrombin-antithrombin complexes, in contrast to a fourfold increase following administration of streptokinase and a twofold increase after administration of alteplase, with the potential for reduced bleeding complications with tenecteplase.

Despite theoretical advantages associated with genetic modification, neither reteplase nor tenecteplase demonstrates an absolute mortality or safety benefit in the treatment of ST-segment elevation myocardial infarction. Although bolus-dose fibrinolytics result in fewer medication errors, when compared with more complicated regimens, this has not translated into improved patient outcomes.[73,74]

Tenecteplase is not FDA approved for acute ischemic stroke, but is used in other countries and the 2018 American Heart Association—American Stroke Association (AHA-ASA) Guidelines for the Early Management of Patients with Acute Ischemic Stroke contained a level IIb recommendation that tenecteplase might be considered as an alternative to alteplase.[75] Meta-analysis of five randomized controlled trials comparing tenecteplase to alteplase found equivalent rates of functional outcomes, mortality, and symptomatic intracranial hemorrhage.[76] A tenecteplase dose of 0.25 milligrams/kg was recommended based on benefits without the increased risk for intracranial hemorrhage seen with higher doses.[76]

CONTRAINDICATIONS TO FIBRINOLYTIC THERAPY

All available fibrinolytic agents have systemic antithrombotic effects and possess the potential for serious hemorrhage. Fibrinolytic-induced bleeding can be minor (such as oozing at IV sites), major (defined as hemodynamic compromise or significant drop in hemoglobin), or catastrophic (intracranial hemorrhage). The prevalence with which bleeding occurs varies according to the condition being treated. For example, intracranial hemorrhage typically occurs in <1% of patients treated with fibrinolytics for acute myocardial infarction[54] but is seen in approximately 6% of patients treated with alteplase for acute ischemic stroke.[77] Also, the risk of hemorrhage is increased according to patient characteristics and the use of concomitant drugs that also vary according to the condition under treatment.[77] General contraindications to fibrinolytic therapy are designed to reduce the risk of major and catastrophic bleeding (**Table 239-10**).

COMPLICATIONS OF FIBRINOLYTIC THERAPY

The most significant complications of fibrinolytic therapy are hemorrhagic, and the most catastrophic complication is intracranial hemorrhage. **Allergic reactions such as urticaria and angioedema are seen in 1% to 5% of patients treated with alteplase. Treatment includes stopping the infusion, evaluating the airway to determine the need for intubation, and administering antihistamine (e.g., diphenhydramine 50 milligrams IV) and corticosteroids (e.g., methylprednisolone 125 milligrams IV).** Hypotension occurs in up to 10% of patients

TABLE 239-10 General Contraindications to Fibrinolytic Therapy

Absolute

- Active or recent (<14 d) internal bleeding
- Ischemic stroke within the past 2–6 mo
- Any prior hemorrhagic stroke
- Intracranial or intraspinal surgery or trauma within the past 2 mo
- Intracranial or intraspinal neoplasm, aneurysm, or arteriovenous malformation
- Known severe bleeding diathesis
- Current anticoagulant treatment (e.g., warfarin with INR >1.7 or heparin with increased activated PTT)
- Current use of a direct thrombin inhibitor or direct factor Xa inhibitor with evidence of anticoagulant effect by laboratory tests
- Platelet count <100,000/mm^3 (<100 × 10^9/L)
- Uncontrolled hypertension (i.e., blood pressure >185/110 mm Hg)
- Suspected aortic dissection or pericarditis
- Pregnancy

Relative*

- Active peptic ulcer disease
- Cardiopulmonary resuscitation for longer than 10 min
- Hemorrhagic ophthalmic conditions
- Puncture of noncompressible vessel within the past 10 d
- Significant trauma or major surgery within the past 2 wk to 2 mo
- Advanced renal or hepatic disease

*Concurrent menses is not a contraindication.

TABLE 239-11 Reversal of Fibrinolytic-Induced Bleeding

Minor external bleeding	Manual pressure
Significant internal bleeding	Immediate cessation of fibrinolytic agent, antiplatelet agent, and/or heparin Reversal of heparin with protamine, as discussed earlier Typed and cross-matched blood ordered with verification of activated PTT, CBC, thrombin clotting time, and fibrinogen level Volume replacement with crystalloid and packed red blood cells as needed
Major bleeding or hemodynamic compromise	All measures listed for significant internal bleeding Fibrinogen concentrate 70 milligrams/kg IV, and recheck fibrinogen level; if fibrinogen level <100 milligrams/dL, repeat fibrinogen concentrate dose. If bleeding persists after fibrinogen concentrate or despite fibrinogen level >100 milligrams/dL, administer FFP 2 units IV. If bleeding continues after FFP, administer an antifibrinolytic such as aminocaproic acid 5 grams IV over 60 min followed by 1 gram/h continuous IV infusion for 8 h or until bleeding stops, or tranexamic acid 10 milligrams/kg IV every 6–8 h. Consider platelet transfusion.
Intracranial hemorrhage	All measures listed for significant internal and major bleeding with hemodynamic compromise Immediate neurosurgery consultation

Abbreviation: FFP = fresh frozen plasma

treated with either streptokinase or alteplase and is treated by slowing the fibrinolytic infusion rate and administering IV crystalloid, paying close attention to the patient's volume status.

To minimize the bleeding risks associated with fibrinolytic therapy, the following precautions should be observed: (1) avoid all unnecessary needle sticks; (2) avoid any arterial punctures; (3) limit venous access to easily compressible sites (e.g., avoid central venous lines, especially the jugular or subclavian veins); and (4) avoid both nasogastric tubes and nasotracheal intubation.

Careful monitoring of the patient is crucial. The hemoglobin level should be checked every 4 to 6 hours after fibrinolytic therapy is initiated. A fall in hemoglobin >1 to 2 grams/dL (0.6 to 1.2 mmol/L) should prompt a search for the source of blood loss. Most bleeding episodes (>70%) occur at vascular puncture sites, but intracranial, intrathoracic, retroperitoneal, GI, urologic, or soft tissue extremity hemorrhage may occur.

External bleeding at any site should be controlled with prolonged manual pressure (**Table 239-11**). Significant bleeding, especially from an internal site, mandates discontinuation of the fibrinolytic agent along with any antiplatelet agents and heparin. Volume replacement should be provided as necessary and supplemented with red blood cell transfusions if clinically indicated. The thrombin clotting time, activated PTT, platelet count, and fibrinogen level should be checked. Heparin administered within 4 hours of the onset of bleeding can be reversed with protamine.

Massive bleeding with hemodynamic compromise necessitates empiric coagulation factor replacement with fibrinogen concentrate (human) and/or fresh frozen plasma. If bleeding persists after appropriate fibrinogen and fresh frozen plasma replacement, an antifibrinolytic agent (e.g., aminocaproic acid or tranexamic acid) with or without platelets should still be administered. Fibrinolytic-associated intracranial hemorrhage requires an aggressive response with protamine (if the patient received heparin), fibrinogen concentrate (human), fresh frozen plasma, platelet transfusion, and an antifibrinolytic agent.

ANTIFIBRINOLYTIC AGENTS

Two hemostatic agents are used clinically to inhibit the enzymatic degradation of fibrin by plasmin: **tranexamic acid** and **aminocaproic acid** (**Table 239-12**). Both agents are derivatives of the amino acid lysine, have low molecular weight, can be administered both orally and IV, attach to several sites on plasminogen, prevent plasminogen from binding to fibrin, are minimally metabolized, and are primarily excreted by the kidney, but tranexamic acid has roughly eight times the antifibrinolytic activity of aminocaproic acid.

TABLE 239-12 Antifibrinolytic Agents

Agent	Suggested Initial Adult IV Dose for Emergent Indications*	Excretion	Elimination Half-Life
Tranexamic acid (TXA)	10 milligrams/kg IV over 10 min (maximum, 1 gram); repeat doses every 6–8 h	95% by kidney	3 h
Aminocaproic acid (ACA)	4–5 grams IV over 1 h, then 1 gram/h for 8 h or until bleeding stops (maximum, 30 grams/d)	65% by kidney	2 h

*Doses vary between indications and route; consult prescribing information for specifics.

INDICATIONS

These agents are used in hemorrhagic states to stop excessive bleeding and reduce perioperative blood transfusion requirements (**Table 239-13**).[78-99]

TABLE 239-13 Emergent Conditions Where Antifibrinolytic Agents Have Been Used

Condition	Comment*
Adult trauma with significant hemorrhage (BP <90 mm Hg or HR >110 beats/min) or considered at risk for significant hemorrhage	TXA IV reduces death from bleeding and all-cause mortality if administered prehospital or within 3 h.[81-85]
Postpartum hemorrhage	TXA IV may prevent and treat excessive postpartum hemorrhage after vaginal and cesarean delivery.[87-89]
Hemoptysis	TXA IV or PO may reduce the duration and volume of bleeding.[90,91]
Upper GI bleeding	TXA IV may reduce mortality and rebleeding rate; there is no effect on transfusion requirement.[92]
Aneurysmal subarachnoid hemorrhage	No proven benefit[93]
Traumatic intracranial hematoma	TXA decreased hematoma growth rate and total hemorrhage, but there was no change in mortality or neurologic outcome.[94]
GI and nasal bleeding due to hereditary hemorrhagic telangiectasia	ACA PO may reduce bleeding and transfusion requirements.[95,96]
Dental bleeding in hemophilia	FDA-approved indication for TXA PO
Prevent bleeding in hemophilia patients during surgery	TXA and ACA reduce bleeding and transfusion requirements.[80]
Traumatic hyphema	FDA-approved indication for TXA PO; both TXA and ACA prevent secondary hemorrhage.[97]
Epistaxis	Topical or PO TXA reduces rate of rebleeding.[98,99]
Heavy menstrual bleeding	FDA-approved indication for TXA PO; TXA available without prescription in Europe for menstrual bleeding.
When fibrinolysis contributes to bleeding	FDA-approved indication for ACA IV

Abbreviation: ACA = aminocaproic acid; BP = blood pressure; FDA = U.S. Food and Drug Administration; HR = heart rate; TXA = tranexamic acid.

*Not an FDA-approved indication unless otherwise noted.

Both agents had minimal use in emergency practice until a randomized clinical trial of the effect of tranexamic acid on mortality and vascular thrombotic events in 20,211 adult trauma victims was published in 2010.[82] This study found that tranexamic acid (1 gram IV over 10 minutes followed by 1 gram infused over 8 hours) reduced death due to bleeding and all-cause mortality, assessed at 4 weeks, with no observed increase in vascular thrombotic complications.[82] Mortality reduction was dependent on timing; efficacy was seen if administered within 3 hours, but not afterward.[83,84] Based on this study and additional analysis,[85] the World Health Organization added tranexamic acid to its List of Essential Medications in 2011. There is ongoing debate about the role of tranexamic acid in trauma care, with questioning about its value in the modern trauma care systems found in heavily resourced counties as opposed to the resource-limited hospitals that treated the bulk of patients in the CRASH-2 study.[86]

COMPLICATIONS OF ANTIFIBRINOLYTIC AGENTS

Both drugs have potential to cause vascular thrombosis, with reported rates that vary according to thrombus location and condition being treated.[100] The observed incidence of limb ischemia and myocardial infarction is low (<1%).[100] The incidence of deep vein thrombosis and pulmonary embolism is highest in patients with subarachnoid hemorrhage (2% and 3%, respectively).[100] In adult trauma, the observed incidence of deep vein thrombosis or pulmonary embolism after treatment with IV tranexamic acid was not significantly increased compared to the control group (about 1% for each thrombotic event).[82]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 240

Emergency Complications of Malignancy

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INTRODUCTION

The incidence of cancer is increasing as the general population ages and individual longevity grows. More patients with active malignancy are likely to come to the ED for care because of this increase, coupled with more intensive and varied treatments being applied in the outpatient setting.[1] Many conditions that prompt these patients to come to the ED will not be due to cancer.[2,3] Conversely, there are disorders often or uniquely related to malignancy that collectively are termed *oncologic emergencies*.[4-7] These malignancy-related emergencies are broadly categorized as: (1) those due to local tumor effects, (2) those secondary to biochemical derangement, (3) those that are the result of hematologic derangement, and (4) those related to therapy (**Table 240-1**).

TABLE 240-1 Emergency Complications of Malignancy

Related to local tumor effects	Malignant airway obstruction
	Bone metastases and pathologic fractures
	Malignant spinal cord compression
	Malignant pericardial effusion with tamponade
	Superior vena cava syndrome
Related to biochemical derangement	Hypercalcemia
	Hyponatremia due to inappropriate antidiuretic hormone secretion
	Adrenal insufficiency
	Tumor lysis syndrome
Related to hematologic derangement	Febrile neutropenia and infection
	Hyperviscosity syndrome
	Thromboembolism
Related to therapy	Chemotherapy-induced nausea and vomiting
	Chemotherapeutic drug extravasation
	Complications due to biologic therapy

EMERGENCIES RELATED TO LOCAL TUMOR EFFECTS

MALIGNANT AIRWAY OBSTRUCTION

Malignancy-related airway compromise is usually an insidious process that results from a mass originating in the oropharynx, neck, or superior mediastinum progressively obstructing airflow.[5,8] Acute compromise may occur with supervening infection, hemorrhage, or loss of protective mechanisms, such as muscle tone. Iatrogenic factors, such as radiation therapy, may create additional difficulties by producing local inflammation with tissue breakdown. It is helpful to classify airway impairment due to malignant tumor obstruction in two manners, as to location—from the lips and nares to the vocal cords (**upper airway**) versus those from the vocal cords to the carina (**central airway**)—and as to nature of the obstruction—**endoluminal**, **extraluminal**, or **mixed**. Almost regardless of the cause, airway obstruction usually presents with symptoms of shortness of breath and signs of tachypnea and stridor. The physical examination may show evidence of a mass in the pharynx, neck, or supraclavicular area.

Patients with airway obstruction due to a malignant tumor are evaluated with a combination of plain radiographs, CT, and endoscopic visualization.[5,8] Direct laryngoscopy is discouraged because injudicious manipulation of the upper airway may convert a partial obstruction into a complete one by provoking bleeding or edema.[9]

Emergency management includes the administration of supplemental humidified oxygen and maintenance of the best airway possible through patient positioning. Heliox—typically a 50:50 mixture of helium and oxygen—may provide symptomatic improvement in upper airway obstruction due to cancer when combined with other therapy.[10] High-flow nasal oxygen administration can also bide time to definitive airway management.

Mechanical intervention for critical airway obstruction from a tumor is rarely required in the ED. For patients with critical upper airway obstruction, emergency transtracheal jet ventilation or cricothyroidotomy could be lifesaving if the obstruction is above the vocal cords (see Chapter 30, "Surgical Airways"). However, the presence of an overlying tumor or swelling may render such procedures technically difficult. Alternatively, passage of the endotracheal tube beyond the area of obstruction is a consideration when the patient is progressing to complete airway occlusion.[5,9] This is best done using awake fiberoptic intubation with a 5-0 or 6-0 endotracheal tube that is wire reinforced, if possible. Placement of such a tube can provide symptomatic relief and time until procedures with more sustained benefit can be performed.

The various procedures to relieve malignancy-related airway obstruction include placement of an expanding stent at the stenotic site, neodymium-yttrium-aluminum-garnet laser photoradiation or argon plasma coagulation for vaporization of obstructing tissue, and mechanical tumor resection; these modalities are often combined.[11-13] Alternatively, variations of radiotherapy, such as endobronchial brachytherapy, photodynamic therapy, and external-beam radiation therapy, can be directed to the obstructing tumor, but the time for symptomatic response is longer than that of the mechanical approaches of laser photoradiation and stenting.

BONE METASTASES AND PATHOLOGIC FRACTURES

Anatomic disruption of bone weakened by preexisting conditions is termed a *pathologic fracture*. Pathologic fractures due to malignancy most commonly affect the axial skeleton (calvarium included) and the proximal aspect of the limbs. Most pathologic fractures are due to metastases from solid tumors (e.g., breast, lung, prostate) that localize in areas of bones with high blood flow, identified as containing red marrow.[14] Most patients with pathologic fractures have a known malignancy. Patients with bone metastases usually present with localized pain and a benign outward appearance of the involved area.[15]

Malignancy alters the normal radiographic appearance of bone, including loss of trabeculae with indistinct margins (osteolytic, or "moth eaten"), poorly demarcated areas of increased density (osteoblastic), and/or a periosteal reaction. Plain radiographs may identify only about half of metastatic bone lesions, and advanced imaging is often required for accurate detection.[16] CT with IV contrast, particularly when using reconstruction software, can visualize three-dimensional bone integrity and soft tissue extension, whereas MRI best detects small tumors and delineates soft tissue and bone marrow involvement. A total-body radionuclide bone scan can be used as a screening tool to identify areas of increased bone activity that could represent additional metastatic spread.[16] However, areas of radionuclide localization on the bone scan are not specific for cancer, and additional imaging studies of these areas are necessary for confirmation.

Treatment priorities are pain relief and restoration or salvage of function.[15] For acute pain or fracture, parenteral analgesics are recommended for rapid treatment. Patients with bone metastases often require long-acting oral opioids and other adjunctive medications for pain relief (see Chapter 38, "Chronic Pain"). Approximately 80% of painful bone metastases can be helped with palliative radiotherapy, although it may take several weeks after completion of a typical 5-day course of treatment to experience maximal benefit.[17] The majority of pathologic fractures require open surgical repair.[18]

MALIGNANT SPINAL CORD COMPRESSION

Up to 20% of cancer patients will develop neoplastic involvement of the vertebral column, and 3% to 6% will develop spinal cord compression.[4,5,7,19] Most cases of malignant spinal cord compression are due to metastases to vertebral bodies from solid organ tumors, with the thoracic vertebrae being the most common location for such metastases. Spinal cord compression occurs when these metastases enlarge, erode through the vertebral cortex into the spinal canal, and compress on the spinal cord. Less common causes of malignant spinal cord compression include local spread from paraspinal tumors through the intervertebral foramen or tumors (primary or metastatic) directly involving the spinal cord or meninges.

Approximately 90% of patients with malignant spinal cord compression will have back pain (**Table 240-2**).[19] Such pain is often described as unrelenting, progressive, worse when supine, and located in the thoracic vertebral area. Approximately 80% of patients with malignant spinal cord compression have a prior diagnosis of cancer, so individuals with known cancer and back pain should undergo radiographic imaging. Other symptoms of malignant spinal cord compression may include muscular weakness, radicular pain, and bladder or bowel dysfunction. Weakness is most apparent in the proximal extremity musculature and may progress to complete paralysis. Sensory changes initially may be confined to a band of hyperesthesia around the trunk at the involved spinal level and that eventually becomes anesthetic distal to the level. Urinary retention (with overflow incontinence), fecal incontinence, and impotence are late manifestations.

MRI preferably with contrast is the imaging modality of choice to localize the site, define the degree of cord compression, and identify additional vertebral lesions. The entire spinal column is imaged due to the potential for multiple level involvement. CT with or without myelography is used when MRI is contraindicated or inaccessible. Plain radiography may identify an abnormality in approximately 80% of patients with painful vertebral metastases. However, plain radiographs are less useful in patients with suspected malignant spinal cord compression, because radiographic findings do not always correlate with the level of spinal cord compression, and causes of malignant spinal cord compression other than vertebral body metastases will not produce visible changes in vertebral body radiographic appearance.

TABLE 240-2 Malignant Spinal Cord Compression

Suspect	Patient with known cancer: especially lung, breast, prostate Thoracic location: 70% Progressive pain and worse when supine Motor weakness: proximal legs Sensory changes: initially radicular, later distal anesthesia Bladder or bowel dysfunction: late findings
Imaging	Plain radiographs: may detect vertebral body metastases but less sensitive and specific for malignant spinal cord compression MRI: modality of choice, preferably with contrast; image entire vertebral column CT myelography: used when MRI not available or accessible
Corticosteroids	Dexamethasone, 10 milligrams IV followed by 4 milligrams PO or IV every 6 h Consider starting in ED if imaging is delayed
Radiotherapy	Standard approach, beneficial in approximately 70% No specific radiotherapy regimen proven superior Prognosis highly dependent on pretreatment neurologic function
Surgery	Consider in highly selected cases, such as the following: Patient in good general condition and able to undergo extensive surgery Appropriate prognostic life expectancy Rapidly progressive symptoms Clinical worsening during radiotherapy Unstable vertebral column

Use opioid analgesics for initial pain control. Consider administration of corticosteroids in the ED, especially if there will be a delay in MRI or CT myelography.[4,5,7,19] Typically dexamethasone, 10 milligrams IV bolus, followed by 4 milligrams PO or IV every 6 hours, is used. Further treatment, with continued corticosteroids, radiation therapy, surgery, or a combination of modalities, will depend on the life expectancy of the patient, extent of disease, and degree of motor impairment.[20] Radiation therapy has been the typical treatment for patients with malignant spinal cord compression, and a beneficial response is seen in approximately 70% of those treated.[20,21] The overall prognosis for those treated with radiotherapy is highly dependent on pretreatment functional ability; approximately 90% of those who can walk at the time of diagnosis remain ambulatory after radiation treatment, about half of those who have motor function but cannot walk will recover ambulatory ability with radiotherapy, but few patients with complete paraplegia at the time of diagnosis will recover lower extremity motor function.[22] Select patients with malignant spinal cord compression may benefit from surgical tumor resection, including those with neurologic impairment (Table 240-2).[19,20] Because of the complex decision making from among the therapeutic options, specialists in oncology, radiotherapy, and spinal surgery should be consulted early.

MALIGNANT PERICARDIAL EFFUSION WITH TAMPONADE

Pericardial involvement, often with effusion, occurs in up to 35% of patients with all types of cancer, although the effusions are often small and remain undiagnosed.[4,5,7,23] Symptomatic pericardial effusions occur less frequently and usually result from lung or breast cancer. Other etiologies for pericardial effusions in patients with malignant disease include other tumor types (such as melanoma, leukemia, or lymphoma) and a complication of treatment (radiotherapy or chemotherapy).

Symptoms and physical examination findings are a function of pericardial fluid accumulation rate and volume (see Chapter 55, "Cardiomyopathies and Pericardial Disease"). Large effusions can develop gradually and are surprisingly well tolerated. Symptoms of a pericardial effusion include dyspnea, orthopnea, chest pain, dysphagia, hoarseness, and hiccups. Physical findings include distant cardiac sounds, jugular venous distention, and a pulsus paradoxus.

A sudden increase in fluid between the nondistensible pericardium and compressible heart creates a cardiac tamponade: the low-pressure right heart is unable to accept vena caval return or pump forward to the pulmonary arteries, and the left ventricle cannot fill or produce a sustainable ejection fraction. Signs and symptoms include accentuation of those noted with pericardial effusion with additional manifestations of circulatory shock. There is usually tachycardia, hypotension, and a narrowed pulse pressure.

The ECG may demonstrate reduced voltage in the QRS complex throughout all leads, a reflection of the insulating characteristics of the effusion. Electrical alternans is a classic, although infrequent, finding with a large pericardial effusion. The cardiac silhouette on chest radiography may appear large, reflecting the gradually accumulated effusion in the stretched pericardial sac. **Echocardiography is the diagnostic tool of choice, being noninvasive, portable, and highly accurate in trained hands.** Echocardiography can not only detect the presence of a significant pericardial effusion, but also assess cardiac function and identify physiologic changes associated with cardiac tamponade.

Asymptomatic pericardial effusions do not require specific treatment. Patients with symptomatic effusions should undergo pericardiocentesis, ideally with echocardiographic guidance (see Chapter 34, "Pericardiocentesis"). Most often, this procedure can await the arrival of the specialist and transport of the patient to the appropriate procedural area. If patients with cardiac tamponade require emergent pericardiocentesis in the ED, use bedside US to guide needle direction during the procedure.

Malignant pericardial effusions are treated depending on the tumor type and overall patient condition.[23] Reduction in fluid production can be done by treating the tumor with appropriate systemic chemotherapy or radiotherapy. Intrapericardial chemotherapy may be useful in tumors sensitive to these agents. A pericardial window or partial pericardial resection can be done to prevent accumulation of fluid within the pericardial space. A percutaneous indwelling intrapericardial catheter can also prevent accumulation of fluid, but with the risks associated with percutaneous devices.[24] Malignant pericardial effusion typically indicates the presence of advanced disease, and most patients die within 1 year after diagnosis.

SUPERIOR VENA CAVA SYNDROME

The term *superior vena cava (SVC) syndrome* describes the clinical effects of elevated venous pressure in the upper body that result from obstruction of venous blood flow through the SVC.[4,5,7,25,26] This syndrome is classically caused by external compression of the SVC by an extrinsic malignant mass. The most common tumors associated with malignant SVC syndrome are lung cancer in 70% and lymphoma in approximately 20%. Benign conditions and intravascular thrombosis (precipitated by indwelling vascular catheters or pacemaker leads) currently account for about one third of all SVC syndrome cases. SVC syndrome rarely constitutes an emergency; the vast majority of patients do not materially deteriorate during the initial 1 to 2 weeks after diagnosis. The exception is when neurologic abnormalities are present due to increased intracranial pressure.

Symptom development correlates roughly with the severity of obstruction and the rate of narrowing. If compression occurs over weeks, collateral vessels dilate to compensate for impaired flow through the SVC. Most patients will describe symptoms developing a few weeks before seeking medical attention. Clinical manifestations correlate with a jugular venous pressure of 20 to 40 mm Hg (2.7 to 5.4 kPa), as compared with a normal range of 2 to 8 mm Hg (0.3 to 1.0 kPa). The most common symptoms are facial swelling, dyspnea, cough, and arm swelling.[25,26] Less common symptoms include hoarse voice, syncope, headache, and dizziness. In rare but extreme cases, venous obstruction can lead to increased intracranial pressure that produces visual changes, dizziness, confusion, seizures, and obtundation. Physical examination findings may show swelling of the face and arm, sometimes with a violaceous hue or plethora, and distended neck and chest wall veins.

The plain chest radiograph will usually show a mediastinal mass in cases of malignant SVC syndrome. CT of the chest with intravascular contrast is the recommended imaging modality to assess the patency of the SVC.[25,26] MRI is useful for patients who cannot receive IV contrast. Contrast venography is rarely needed, except in uncertain cases or as part of an intravascular interventional procedure. In patients with a known diagnosis of lung cancer, biopsy for pathologic confirmation of a malignancy is usually not required. For patients without a known intrathoracic cancer, tissue confirmation of a malignant cause is highly desirable before initiation of radiotherapy and required before initiation of chemotherapy.[26]

Initial management is with head elevation to decrease venous pressure in the upper body and supplemental oxygen to reduce the work of breathing. Corticosteroids and loop diuretics are commonly used, but there is no evidence that they contribute to clinical improvement, with the exception that corticosteroids would be expected to be helpful when the cause of the obstruction is lymphoma.

Radiation therapy is effective in reducing symptoms in approximately 75% of patients with SVC syndrome, reflecting the approximate incidence of radiosensitive tumors producing this disorder.[26] Many patients will experience a reduction in symptoms within 3 days after the start of radiation treatment.

Intravascular stents, with or without angioplasty, can be used to reduce obstruction to SVC flow.[26,27] These stents appear to produce a more rapid improvement in symptoms and signs compared with radiotherapy or chemotherapy, suggesting a preferential benefit in patients with severe manifestations who require urgent treatment.[26,27] Stent placement should also be considered for malignant causes that do not respond well to radiotherapy or chemotherapy (e.g., mesothelioma), for benign causes (e.g., fibrosing mediastinitis), or for intravascular thrombosis associated with an indwelling catheter.[26]

Chemotherapy is effective in producing symptomatic relief from SVC syndrome in approximately 80% of patients with lymphoma, 80% of patients with small-cell lung cancer, and 40% of patients with non–small-cell lung cancer.

Patients with SVC syndrome due to intravascular thrombosis can be treated with catheter-directed fibrinolytics.[26] Removal of an inciting intravascular object, such as a central venous catheter, should be considered. Postfibrinolytic anticoagulation is generally recommended to prevent recurrence, although there is no firm supporting evidence.[26] For cancer patients with an indwelling central venous catheter, prophylactic low-molecular-weight heparin decreases the incidence of symptomatic catheter-related venous thromboembolism for up to 3 months, but its use must be balanced by the potential harms of anticoagulation.[28]

Recurrence of SVC syndrome is seen in approximately 20% of lung cancer patients treated with radiotherapy and/or chemotherapy and 10% treated with intravascular stents.[26] For patients with malignant SVC syndrome, survival is dependent on the causative cancer; with lung cancer, median survival is approximately 6 to 12 months.

EMERGENCIES RELATED TO BIOCHEMICAL DERANGEMENT

HYPERCALCEMIA

Hypercalcemia is seen in 5% to 30% of patients with advanced cancer at some time during their disease course.[29] Breast cancer, lung cancer, and multiple myeloma are the malignancies most commonly associated with hypercalcemia. The three primary mechanisms whereby malignancy produces hypercalcemia are: (1) most commonly by production of a parathyroid hormone–related protein that is structurally similar to parathyroid hormone so that calcium is mobilized from bones and its renal reabsorption is increased; (2) by extensive local bone destruction associated with osteoclast-activating factors seen in lung and breast cancer and multiple myeloma; and (3) by production of vitamin D analogs, usually in lymphomas.

Classic symptoms of hypercalcemia include lethargy, confusion, anorexia, and nausea (see Chapter 17, "Fluids and Electrolytes"). Because most patients with hypercalcemia due to malignancy have advanced cancer, symptoms of general debility due to tumor may be difficult to distinguish from those caused by hypercalcemia. Hypercalcemia reduces intestinal motility, so constipation is common, although that symptom can be produced by concomitant opioid therapy for pain. Hypercalcemia produces an osmotic diuresis, so some of the nonspecific symptoms can be due to relative hypovolemia. **Clinical symptoms of hypercalcemia are most often correlated with the rate of rise in the serum calcium level, as opposed to the actual calcium level. Therefore, slow increases in serum calcium may be relatively asymptomatic until reaching high levels.**

Hypercalcemia does not always require treatment, especially if the patient is asymptomatic and well hydrated and the total serum calcium is less than 14 milligrams/dL (3.5 mmol/L). The initial treatment of symptomatic hypercalcemia is with IV isotonic saline according to the patient's initial volume status followed by a rate adjusted to the ability of the patient's cardiovascular system to tolerate a volume load (**Table 240-3**).[6,7] IV saline will result in clinical improvement and a modest decrease in the plasma calcium over 24 to 48 hours, but rarely normalizes the level. Furosemide is useful in patients with heart failure or renal insufficiency to prevent volume overload from normal saline infusion, but has little additive effect to the use of IV saline alone in the treatment of hypercalcemia in patients with normal cardiac and renal function. **Therefore, furosemide is not routinely recommended in the treatment of hypercalcemia due to malignancy.**

Because the initial priority is restoration of intravascular volume with IV saline, pharmacologic treatment of hypercalcemia is usually not initiated in the ED.[6,7] **Bisphosphonates, such as pamidronate or zoledronic acid, are the recommended agents to treat malignancy-associated hypercalcemia.**[6,7,29] Bisphosphonates are potent inhibitors of bone resorption and produce a sustained decrease in calcium 12 to 48 hours after administration, with the effect lasting for approximately 2 to 4 weeks. Bisphosphonates are given by slow IV infusion to prevent precipitation of bisphosphonate–calcium complexes in the kidney and subsequent renal failure.

Other agents have a limited role in the treatment of malignancy-induced hypercalcemia. Calcitonin lowers plasma calcium within 2 to 4 hours, but it may cause a hypersensitivity response, and tachyphylaxis develops within 3 days, so the beneficial effect is short lived. Calcitonin is only used when prompt reduction of calcium levels is needed.[7] Glucocorticoids, such as prednisone 60 milligrams PO daily, may be helpful with steroid-sensitive tumors, such as lymphomas and multiple myeloma.[6,7,29] Denosumab, a humanized monoclonal antibody that inhibits osteoclast activity and function, is approved for hypercalcemia refractory to bisphosphonate therapy.

Hemodialysis can be used to treat hypercalcemia and is indicated for those with profound mental status changes or renal failure or those unable to tolerate a saline load.

TABLE 240-3 Treatment of Cancer-Associated Hypercalcemia[7]

Intervention	Dosage	Comments
Normal saline	If hypovolemic: 1- to 2-L initial bolus over 1 h If euvolemic: 250–500 mL/h IV for 1 L, followed by 100–150 mL/h IV	Adjust the infusion rate according to the patient's cardiovascular status
Furosemide	20–40 milligrams IV	Use only for patients with volume overload after volume expansion
Pamidronate	60–90 milligrams IV over 2–4 h	Use with caution in renal insufficiency Onset of action may take days
Zoledronic acid	4 milligrams IV over 15 min	Use with caution in renal insufficiency Onset of action may take days Short infusion time is an advantage over pamidronate
Calcitonin	4–8 IU/kg SC or IV every 12 h	Rapid onset of action but short lived (about 3 d) Use when prompt reduction of calcium level is needed
Glucocorticoids	Prednisone 60 milligrams PO daily *or* Hydrocortisone 100 milligrams IV every 6 h	Used for hypercalcemia due to lymphomas and multiple myeloma
Denosumab	120 milligrams (or 0.3 milligram/kg) SC weekly for 4 wk, then every 4 wk	Used in hypercalcemia refractory to bisphosphonate therapy Can cause symptomatic hypocalcemia

HYPONATREMIA DUE TO INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Inappropriate secretion of antidiuretic hormone is most commonly associated with bronchogenic cancer, but may be seen in other malignancies and can also occur from chemotherapy, opioids, carbamazepine, and selective serotonin reuptake inhibitors.[6,30,31] Regardless of the etiology, the syndrome of inappropriate antidiuretic hormone consists of hyponatremia, decreased serum osmolality, and less than maximally dilute urine, all in the presence of euvolemia, absence of diuretic therapy, and normal renal, adrenal, and thyroid function (see Chapter 17). **Syndrome of inappropriate antidiuretic hormone secretion should be suspected if a patient with cancer presents with normovolemic hyponatremia.**

Signs and symptoms of hyponatremia are primarily neurologic and correlate with severity and with rapidity of development. Anorexia, nausea, and malaise are the earliest findings, followed by headache, confusion, obtundation, seizures, and coma. Seizures are usually generalized tonic-clonic in nature; focal seizures are uncommon from hyponatremia, and their occurrence suggests focal CNS lesions. Life-threatening symptoms are almost invariably associated with sodium concentrations <110 mEq/L (<110 mmol/L).

Water restriction is the mainstay of treatment in euvolemic asymptomatic patients. Patients with sodium levels >125 mEq/L (>125 mmol/L) are generally asymptomatic and can be managed with water restriction of 500 mL/d and close follow-up. More severe hyponatremia—serum sodium between 110 and 125 mEq/L with mild to moderate symptoms—may require furosemide 0.5 to 1.0 milligram/kg PO with concomitant IV normal saline to maintain euvolemia and effect a net free water clearance.

For severe hyponatremia—serum sodium <110 mEq/L, usually with coma or repetitive or sustained seizures—infuse 3% hypertonic saline (510 mEq/L) 100 mL over 10 to 15 minutes. Then reassess patient and measure serum sodium. If symptoms have not resolved or the serum sodium has not increased by 5 mEq/L, one or two additional doses of 3% hypertonic saline may be necessary (see Chapter 17).

ADRENAL INSUFFICIENCY

Adrenal insufficiency associated with malignancy may be secondary to adrenal tissue replacement by metastases, but is more commonly due to abrupt physiologic stress in the face of chronic glucocorticoid therapy with pharmacologic adrenal suppression (see Chapter 230, "Adrenal Insufficiency").[32,33] The subsequent vasomotor collapse may be sudden and severe.[32] Clues for acute adrenal insufficiency include mild hypoglycemia, hyponatremia, and hypotension refractory to volume loading and vasoconstrictor therapy.

Obtain a serum cortisol level, institute IV rehydration with normal saline, and administer stress doses of steroids, such as hydrocortisone

100 milligrams IV or dexamethasone 4 milligrams IV (see Chapter 230). The steroid-dependent patient will need increased doses of steroids during the acute illness, typically three times the daily maintenance dose of glucocorticoid.[32]

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is a metabolic crisis resulting from massive cytolysis and release of intracellular contents into the systemic circulation.[6,7,34] Of particular concern are the individual ions (potassium, phosphate, calcium), nucleic acids (which metabolize to uric acid), and intracellular proteins. Tumor lysis syndrome most commonly occurs with treatment of hematologic malignancies because of rapid cell turnover and growth rates, bulky tumor mass, and high sensitivity to antineoplastic agents. Tumor lysis syndrome is uncommon with solid tumors or without prior therapy ("spontaneous tumor lysis syndrome").

The manifestations of tumor lysis syndrome can be categorized by clinical effects (acute kidney injury, seizure, cardiac dysrhythmia, or arrest) and laboratory abnormalities (hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia). Renal failure is the strongest predictor of morbidity in tumor lysis syndrome and usually results from uric acid precipitation within the renal tubules. Phosphorus released from tumor cells may combine with calcium and precipitate in renal tubules and parenchyma as well. Hypovolemia may contribute to the renal impairment seen with tumor lysis syndrome. The release of intracellular potassium can produce acute hyperkalemia and provoke or contribute to cardiac dysrhythmias or cardiac arrest. Because malignant cells can contain fourfold the amount of phosphorus as normal cells, the abrupt release of extensive phosphate into the circulation may produce a decrease in serum calcium. The resultant hypocalcemia may induce tetany and seizures and contribute to dysrhythmias.

Recognize the potential for tumor lysis syndrome with treatment of hematologic malignancies. Prophylactic allopurinol and maintaining good hydration can reduce the risk of tumor lysis syndrome developing. Patients with established tumor lysis syndrome may experience sudden electrolyte changes and life-threatening complications, so admission to an intensive care unit with cardiac rhythm monitoring is indicated. Aggressive IV fluid administration to increase urinary excretion of the released intracellular solutes is the cornerstone for treatment of tumor lysis syndrome.[7,34] Increased urine flow will counteract the precipitation of urate and calcium phosphate crystals in the renal tubules.

Hyperkalemia is the most immediate life-threatening element with tumor lysis syndrome because of induced cardiac dysrhythmias and cardiac arrest.[6,34] Treatment is identical to other causes of hyperkalemia: β-adrenergic agonists, sodium bicarbonate, and dextrose-insulin therapy (see Chapter 17). Avoid calcium administration unless there is cardiovascular instability (ventricular dysrhythmias or wide QRS complexes) or neuromuscular irritability (seizures) because supplemental calcium may cause metastatic precipitation of calcium phosphate. Hyperphosphatemia is managed with phosphate binders (limited effect) or by the administration of dextrose and insulin. Hemodialysis can correct all biochemical abnormalities of tumor lysis syndrome, although a large phosphate burden may require repeat frequent and prolonged dialysis sessions or continuous renal replacement therapy.[6,34]

EMERGENCIES RELATED TO HEMATOLOGIC DERANGEMENT

FEBRILE NEUTROPENIA AND INFECTION

Infections are a common source of morbidity and mortality in patients with malignancies.[35,36] A common feature associated with the increased risk of infection in these patients is the presence of impaired immunity, especially neutropenia.[35,36] For clinical decision making, neutropenia is defined as an absolute neutrophil count <1000/mm^3 (<1.0 × 10^9/L), severe neutropenia is defined as an absolute neutrophil count <500/mm^3 (<0.5 × 10^9/L), and profound neutropenia is defined as an absolute neutrophil count <100/mm^3 (<0.1 × 10^9/L). Fever is defined for the purposes of clinical decision making as a temperature of 38.3°C (100.9°F) on one occasion or 38.0°C (100.4°F) persisting >1 hour.

Neutropenia in cancer patients is most commonly caused by chemotherapy, with the lowest neutrophil count typically seen 5 to 10 days after the last chemotherapeutic dose and recovery usually seen within 5 days afterward.[36-38] The risk of developing an infection primarily depends on the severity and duration of neutropenia. Comorbid conditions and other circumstances, such as indwelling devices, also contribute to the risk.[4,7,36,37]

Fever is the most common finding seen with bacterial infections in the neutropenic patient. Common symptoms and signs that usually localize the infectious source are often absent or muted in the neutropenic patient because the lack of neutrophils impairs the inflammatory response and diminishes the occurrence of expected findings.[36] Thus, a pulmonary infection may have minimal cough, have no productive phlegm, and lack radiographic infiltrates. A kidney infection may not produce pyuria.

Evaluation Perform a careful physical examination, with attention to three areas typically overlooked in routine examination: the oral cavity, the perianal area, and entry sites of intravascular catheters. **Digital rectal examination is relatively contraindicated in neutropenic patients—withhold until after initial antibiotic administration. Evaluate the entry sites of IV and tunneled catheters for evidence of infection.** Clotted catheters represent a high risk of infection due to bacterial colonization, and central venous catheters may cause endocarditis.

Because localizing signs and symptoms of a specific infection are often lacking, an evaluation for an occult infection is indicated.[36-39] Obtain two blood culture samples, with one from a central catheter, if present. A urinalysis, urine culture, and chest radiograph should be performed. Sputum, stool, and wound drainage Gram stain and culture should be obtained if productive cough, diarrhea, or wound drainage, respectively, are present. Assess serum electrolyte levels, renal function, and hepatic function.

Assessment If an infectious source is found, therapy and disposition are guided by the presumed pathogens and the expected clinical course. If, after assessment, no localized infection can be found, the two major clinical decisions are: (1) Does this patient require hospitalization, and (2) should empiric antibiotics be started? To assist in addressing both these questions, consult with the patient's oncologist.

Although hospitalization enhances the ability to reassess the patient and intervene early if a severe infection or clinical deterioration develops, hospitalization exposes the immunocompromised patient to hospital flora that is often drug resistant. Patients who appear well, have no abdominal pain, have no physical signs of infection, have a normal chest radiograph, and are expected to resolve their neutropenia within 7 days have a low risk of severe infection and can be considered for outpatient care.[36-38]

High-risk febrile neutropenic patients for whom hospitalization is recommended are defined by one or more of the following features: profound neutropenia expected to last >7 days, comorbid medical conditions, acute liver or renal injury, or non–low-risk scores by the Multinational Association for Supportive Care in Cancer Risk Index or Clinical Index of Stable Febrile Neutropenia tool.[35,36,40-42]

Treatment Empiric broad-spectrum antibiotics are used in febrile neutropenic patients when the benefits of early treatment are greater than the adverse side effects associated with such drugs.[36-39] **Clinical evidence consistently supports the benefits of empiric antibiotics when the absolute neutrophil count is ≤500/mm^3** (<0.5 × 10^9/L). There is little convincing evidence for empiric antibiotics when the absolute neutrophil count is >1000/mm^3 (>1.0 × 10^9/L). For neutrophil counts between 500 and 1000/mm^3 (0.5 and 1.0 × 10^9/L), use other risk factors for bacterial infection to make the decision regarding empiric antibiotics.[36-38]

Administer the initial empiric antimicrobial therapy to cover the range of potential bacterial pathogens (**Table 240-4**).[36-38,43] No specific antibiotic regimen has proven consistently superior in clinical trials, and monotherapy with an appropriate broad-spectrum agent is as effective as dual-agent treatment in most circumstances. If there is no known colonization with multidrug-resistant bacteria or colonization with vancomycin-resistant enterococci, initial treatment should be with a *Pseudomonas*-active β-lactam.[37] Add vancomycin in the following

TABLE 240-4 Empiric Antibiotic Therapy in Febrile Neutropenia

Situation	Drug (Adult Dose)	Comments
Outpatient	Ciprofloxacin 500 milligrams PO every 12 h *or* Levofloxacin 750 milligrams PO daily *plus* Amoxicillin/clavulanate 500/125 milligrams PO every 8 h or 1000/62.5 milligrams PO twice daily *or* Clindamycin 300 milligrams PO every 8 h	For low-risk patients with daily assessments by a medical provider for the initial 3 d
Monotherapy	Piperacillin/tazobactam 4.5 grams IV every 6 h *or* Cefepime 2 g IV every 8 h *or* Ceftazidime 2 g IV every 8 h *or* Imipenem/cilastatin 1 g IV every 8 h *or* Meropenem 1 g IV every 8 h	If no known colonization with multidrug-resistant bacteria or colonization with VRE, use piperacillin/tazobactam, cefepime, or ceftazidime If known colonization with ESBL-E, use imipenem/cilastatin or meropenem
Dual therapy	One of the monotherapy agents *plus* Vancomycin 1 gram IV every 12 hours *Or* Metronidazole 1 gram IV, followed by 500 milligrams IV every 6 h	Increased risk of adverse effects Add if hemodynamic instability, catheter-related infection, cellulitis, or known colonization with MRSA If abdominal symptoms are present

Abbreviations: ESBL-E = expended-spectrum β-lactamase–producing enterobacteria; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

situations: hemodynamic instability, catheter-related infection, skin or soft tissue infection, known colonization with resistant gram-positive organism, or severe mucositis when fluoroquinolone prophylaxis was recently used.[37] If there is a history of colonization with extended-spectrum β-lactamase–producing enterobacteria, initial treatment should be with imipenem or meropenem.[37]

The median duration of fever after initiation of empiric antibiotics is 2 days in low-risk patients and 5 to 7 days in high-risk patients. Therefore, continue initial empiric antibiotic therapy for 2 to 4 days before assessing clinical response and making therapeutic adjustments. Adjustments may be made earlier if clinical deterioration occurs or culture results become available. Continue empiric antibiotics until the documented infection has clinically resolved and/or the patient has been afebrile for 2 days and the absolute neutrophil count is >500/mm^3 (>0.5 × 10^9/L).[36-38]

HYPERVISCOSITY SYNDROME

Hyperviscosity syndrome is a pathologic condition in which blood is "thicker" than normal and its flow is impaired.[44] Blood viscosity depends on its plasma and cellular contents, and dehydration exacerbates hyperviscosity. Abnormal plasma contents that most commonly produce hyperviscosity are Waldenström's macroglobulinemia and immunoglobulin A–producing myeloma.[44] Hyperproduction of any cell line can lead to hyperviscosity. Polycythemia (with a hematocrit >60%) and leukemia (with a WBC count >100,000/mm^3 [>100 × 10^9/L] or a leukocrit >10%) are often are associated with clinically significant hyperviscosity.[45]

Initial symptoms are vague and may include fatigue, abdominal pain, headache, blurry vision, or, most commonly, altered mental status.[44,46] Cutaneous or mucosal bleeding is common. Intravascular thrombosis may occur, with the creation of focal or unusual findings. Patients with hyperleukocytosis often report dyspnea and fever. Funduscopic findings include retinal venous engorgement appearing as linked sausages, along with exudates, hemorrhages, and papilledema.

Laboratory findings suggesting hyperviscosity include rouleaux formation (red cells stacked like coins) on a peripheral blood smear and being unable to perform chemical testing due to serum stasis in the laboratory analyzers. Laboratory testing of blood viscosity is usually done on plasma or serum, and specific analytic methodology varies.[46] A common approach is to report the viscosity of the sample as a ratio to that of water; normal plasma viscosity is 1.7 to 2.1 and normal serum viscosity is 1.4 to 1.8, compared with water. Symptomatic patients usually have a serum viscosity >4.[46] **Laboratory measurement of plasma or serum viscosity will not identify hyperviscosity from polycythemia or leukemia.**

Initial therapy is intravascular volume repletion, early involvement of a hematologist, and emergency plasmapheresis or leukapheresis.[44-46] If coma is present and the diagnosis established, a temporizing measure can be a 2-unit (1000-mL) phlebotomy with concomitant volume replacement using 2 to 3 L of normal saline. Transfusion of red blood cells should be done with caution because such treatment may increase blood viscosity. Long-term management is appropriate chemotherapy.

VENOUS THROMBOEMBOLISM

Venous thromboembolism occurs with all tumor types and is the second leading proximate cause of death in cancer patients.[47-49] Symptomatic deep venous thrombosis occurs in approximately 15% of all patients with cancer and up to 50% of those with advanced malignancies.[47,48] Multiple factors contribute to an increased risk for venous thromboembolism.[49] The tumor may release procoagulant factors or inflammatory cytokines that directly activate the coagulation system. Large tumors may cause venous obstruction and promote thrombosis. Impaired production of proteins C and S and antithrombin can produce a hypercoagulable state. Surgery with attendant postoperative immobilization or long-term central venous catheterization can incite thrombosis. Chemotherapy or hormonal therapy for breast cancer increases the risk for thromboembolism. The angiogenesis inhibitors thalidomide, sunitinib, and bevacizumab are associated with significant thrombotic risks.[47,48]

Low-molecular-weight heparin is recommended as the initial treatment in cancer patients with venous thromboembolism, both deep venous thrombosis and pulmonary embolism.[50-53] Unfractionated heparin and fondaparinux are acceptable alternatives.[52,53] Continued treatment with low-molecular-weight heparin for at least 3 to 6 months is recommended because of better efficacy in preventing recurrent thromboembolic events compared to vitamin K antagonists.[51-54] **Direct-acting oral anticoagulants are not recommended for treatment of venous thromboembolism in patients receiving active treatment for their cancer,** but can be considered for use after the initial treatment with low-molecular-weight heparin of 10 days to 3 months in patients with stable cancer not receiving anticancer therapy.[53,55]

EMERGENCIES RELATED TO THERAPY

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting can be debilitating to an already compromised patient. Most IV chemotherapeutic agents are emetogenic, so antiemetics are commonly administered on the day of therapy and for 2 to 4 days afterward based on the emetogenic potential of the agent.[56,57] Antiemetics used for chemotherapy-induced vomiting include neurokinin-1 receptor antagonists, serotonin receptor antagonists, and corticosteroids (**Table 240-5**).[56-58] For refractory nausea and vomiting, benzodiazepines, dopamine receptor antagonists, or antipsychotic agents are added.[57,58]

TABLE 240-5 Antiemetic Agents for Chemotherapy-Induced Vomiting

Class and Agent	Adult Dose	Comments
Neurokinin-1 Receptor Antagonists		
Aprepitant	125 milligrams PO, followed by 80 milligrams PO on days 2 and 3	Half-lives: aprepitant = 9–13 h; fosaprepitant = 9–13 h; netupitant = 80 h; rolapitant = 169–183 h Common adverse effects: fatigue, neutropenia, abdominal pain, bradycardia, hypotension, headache, cough, decreased appetite, pruritus, and insomnia
Fosaprepitant	150 milligrams IV	
Netupitant	300 milligrams plus palonosetron 0.5 milligram PO	
Rolapitant	180 milligrams PO	
Serotonin Receptor Antagonists		
Granisetron	1 milligram IV	Common reactions: headache, abdominal pain Serious reactions: serotonin syndrome, QT interval prolongation Half-lives vary from 5 h for ondansetron, 9 h for granisetron, and 40 h for palonosetron
Ondansetron	8 milligrams IV	
Palonosetron	0.25 milligram IV	
Tropisetron*	5 milligrams IV	
Ramosetron*	0.3 milligram IV	
Corticosteroids		
Dexamethasone	8–12 milligrams IV	Mechanism unknown
Benzodiazepines		
Lorazepam	1–2 milligrams IV	Sedation, half-life 14 h
Midazolam	1 milligram IV or 5 milligrams IM	Sedation, half-life 2–3 h
Dopamine Receptor Antagonists		
Metoclopramide	10 milligrams IV or IM	Dose-related extrapyramidal side effects, half-life 5–6 h
Prochlorperazine	5–10 milligrams IV or IM	Extrapyramidal side effects, half-life 7 h
Antipsychotics		
Olanzapine	10 milligrams PO or IM	Not FDA approved for this indication, half-life 21–54 h

Abbreviation: FDA = U.S. Food and Drug Administration.

*Not available in the United States.

Chemotherapy-induced vomiting can be anticipatory, acute, or delayed.[58,59] Anticipatory vomiting is a conditioned reflex where vomiting occurs prior to administration of the chemotherapeutic agent. Acute vomiting occurs during the first 24 hours with maximal intensity at 5 to 6 hours after administration. Delayed vomiting has maximal intensity 48 to 72 hours after administration and can last up to 7 days.

For patients receiving highly emetogenic chemotherapy, the three-drug combination of a neurokinin-1 receptor antagonist (days 1 through 3 for aprepitant; day 1 only for fosaprepitant), a serotonin receptor antagonist (day 1 only), and dexamethasone (days 1 through 3 or 4) is recommended. For moderately emetogenic chemotherapy, the two-drug combination of palonosetron (day 1 only) and dexamethasone (days 1 through 3) is recommended. For low emetogenic agents, a single dose of dexamethasone 8 milligrams IV before chemotherapy is suggested.[57] For delayed chemotherapy-induced vomiting, the neurokinin-1 receptor antagonists are recommended.[59]

EXTRAVASATION OF CHEMOTHERAPEUTIC AGENTS

Most chemotherapeutic agents cause local tissue reaction when extravasated, but the agents associated with significant tissue damage are the vesicants primarily in the anthracycline, taxane, platin salt, and vinca alkaloid classes.[60-63] Clinical manifestations of chemotherapeutic drug extravasation include pain, erythema, and swelling, usually within hours of the infusion. Occasionally, clinical signs may be delayed if only a small amount of highly cytotoxic drug is extravasated. Serious injury produces blistering, induration, ulceration, and necrosis over a few days to weeks.

TABLE 240-6 Antidotes for Selected Extravasated Chemotherapeutic Drugs

Drug	Antidotes	Comments
Anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin)	Dry cooling	Initially 1 h, then 15 min several times per day Hold during dexrazoxane infusion
	Dexrazoxane	IV infusion within 6 h; repeat doses at 48 and 72 h
	Dimethyl sulfoxide	Apply over involved area; repeat 4–6 times per day for ≥7 d
Vinca alkaloids (vincristine and vinblastine)	Dry warming	Do not press or rub area
	Hyaluronidase	Inject in and around extravasated area
Mitomycin, cisplatin, mechlorethamine	Dry cooling	Initially 1 h, then 15 min several times per day
	Dimethyl sulfoxide	Apply over involved area; repeat 4–6 times per day for ≥7 d
Paclitaxel	Hyaluronidase	Inject in and around extravasated area

If extravasation happens to occur through an active peripheral line, the infusion is stopped and aspiration through the line is attempted and continued while the catheter is removed.[62,63] Aspirate palpable cutaneous blebs containing the extravasated chemotherapeutic agent. Elevate and immobilize the affected limb. Cooling or warming is beneficial for some agents (**Table 240-6**). Consult with the oncologist for treatment recommendations. Early referral to a plastic surgeon is suggested for anthracyclines and vinca alkaloids.

Antidotes are available for some chemotherapy drugs (Table 240-6).[62,63] Dexrazoxane is used for anthracycline extravasation at a dose of 1000 milligrams/m^2 IV infused over 1 to 2 hours within 6 hours of the extravasation event, with additional doses of 1000 milligrams/m^2 at 48 hours and 500 milligrams/m^2 at 72 hours.[64] Dimethyl sulfoxide and hyaluronidase are used to enhance absorption of the extravasated agent.[62] Dimethyl sulfoxide is applied as a generous trickle of the 99% solution over the involved area without pressing or rubbing and then covered with dry pads.[62] Hyaluronidase is reconstituted with normal saline to a concentration of 150 units/mL and then injected in and around the extravasation area via multiple punctures.[62] Inject about 0.2 mL per puncture site with a typical total dose of 1 mL, but up to 10 mL may be required. There are limited data supporting the use of sodium thiosulfate for reversal of alkylating agent toxicity.[62] **Intralesional injections of corticosteroids or bicarbonate are not effective.**

EMERGENCY COMPLICATIONS DUE TO BIOLOGIC THERAPY

Targeted antineoplastic agents and immunotherapeutic drugs are increasingly used for cancer therapy, and many patients have experienced substantially improved outcomes. However, these biologic cancer agents are associated with toxicities, some of which can be potentially life threatening.[65]

MONOCLONAL ANTIBODIES

Monoclonal antibodies are proteins produced by immune cells that specifically recognize a cell target. In targeted cancer therapy, specially engineered humanized or chimeric antitumor monoclonal antibodies are designed to bind to T cells, activating them to target and kill cancer cells (**Table 240-7**).[66]

Common adverse effects associated with monoclonal antibodies are fevers, chills, pruritus, and muscle pain, which can be managed using antipyretics, antihistamines, adequate IV fluids, along with cardiopulmonary monitoring and oxygen supplementation. A potentially serious

TABLE 240-7 Common Monoclonal Antibodies (MAB) and Their Applications in Cancer Therapy

MAB (origin)	Target	Indications	Serious Toxicities
Rituximab (human/murine)	CD20	Non-Hodgkin's lymphoma Lymphocytic leukemia	CRS
Ofatumumab (human IgG1 MAB)	CD20	Chronic lymphocytic leukemia unresponsive to chemotherapy	Immunodeficiency
Trastuzumab (humanized MAB)	HER2/neu	Breast cancer Metastatic GI cancers	Cardiac disease
Cetuximab (human MAB)	EGFR	Colon cancer Head and neck cancer	Diarrhea Exanthema
Bevacizumab (humanized IgG1 MAB)	VEGF	Metastatic colon cancer Breast cancer Renal cell cancer Non–small-cell lung cancer Glioblastoma	Hypertension GI bleeding or perforation Thromboembolism

Abbreviations: CD20 = B-leukocyte antigen CD20; CRS = cytokine release syndrome; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; IgG = immunoglobulin G; VEGR = vascular endothelial growth factor.

adverse reaction with monoclonal antibody therapy is cytokine release syndrome, where activated T cells release cytokines, with Il-6 as a key mediator.

CYTOKINE RELEASE SYNDROME

Cytokine release syndrome is a potentially life-threatening systemic inflammatory reaction observed after infusion of agents targeting different immune effectors.[65,67] Most commonly, affected patients develop fever, chills, tachycardia, and hypotension during or within 24 hours following drug administration. The syndrome may cause a broad spectrum of constitutional symptoms such as headache, myalgia, arthralgia, asthenia, and back or abdominal pain. Organ-related symptoms of cytokine release syndrome include bronchospasm, dyspnea, dysrhythmias, hypotension, confusion, oliguria, erythema, urticarial reaction, and pruritus. Symptoms of cytokine release syndrome that appear during or after first exposure to a "new" drug may be difficult to distinguish from anaphylaxis.[65] Treatment of cytokine release syndrome is guided by the severity, and all patients with cytokine release syndrome should be admitted to the hospital (**Table 240-8**).[67]

IMMUNE CHECKPOINT INHIBITOR THERAPY

Some tumor cells elaborate surface proteins that bind to receptors on T lymphocytes, inhibiting the ability of the T lymphocyte to kill the tumor cell. Immune checkpoint inhibitor therapy uses monoclonal antibodies that bind to either the tumor cell protein or the corresponding T-lymphocyte receptor, breaking the inhibition so that the T lymphocyte can kill the tumor cell. Current immune checkpoint inhibitors target either the cytotoxic T-lymphocyte–associated protein 4 (ipilimumab), the programmed cell death protein-1 on the tumor cell (pembrolizumab, nivolumab, or cemiplimab), or the programmed cell death ligand-1 on the T lymphocyte (atezolizumab, avelumab, or durvalumab). Most patients receive single-agent treatment with occasional use of combination therapy. Ipilimumab, nivolumab, and pembrolizumab have been in use for a longer time, so more instances of adverse effects arising from these drugs have been reported.[68]

Immune checkpoint inhibitor–induced immune-related adverse effects are defined as any toxicity with a potential immune-mediated cause. Although some immune-related adverse effects can present with potentially life-threatening symptoms, several immune-related endocrine adverse effects have an insidious onset and present with low-grade, nonspecific symptoms that are difficult to diagnose.[68] Immune checkpoint inhibitors can attenuate tolerance and cause overwhelming

TABLE 240-8 Recommendations for the Management of Cytokine Release Syndrome (CRS)

Grade	Clinical Features	Management
Grade 1	Fever or mild organ toxicity	• Treat fever with acetaminophen (ibuprofen is an alternative if not contraindicated) and hypothermia blanket (if needed) • Maintenance IV fluids to prevent dehydration • Assess for infection using blood and urine cultures and chest radiography • If neutropenic, start empiric broad-spectrum antibiotics and filgrastim
Grade 2	Hypotension, responds to IV fluids and/or low-dose vasopressors	• Initial IV fluid bolus with normal saline 500–1000 mL • Administer a second IV fluid bolus if systolic blood pressure remains <90 mm Hg • For hypotension refractory to two IV fluid boluses, administer anti–IL-6 therapy using tocilizumab 8 milligrams/kg IV or siltuximab 11 milligrams/kg IV • If hypotension persists after two fluid boluses and anti–IL-6 therapy, start vasopressors, transfer to intensive care unit, obtain echocardiogram, and initiate hemodynamic monitoring
	Hypoxia, responds to F_{IO_2} <40%	• Administer supplemental oxygen
	Organ toxicity	• Symptomatic management of organ toxicities
Grade 3	Hypotension, required high-dose or multiple vasopressors	• IV normal saline fluid boluses as needed • Tocilizumab and siltuximab as recommended for grade 2 CRS, if not previously administered • Vasopressors as needed • Transfer to intensive care unit, obtain echocardiogram, initiate hemodynamic monitoring • Dexamethasone 10 milligrams IV every 6 h
	Hypoxia, requiring F_{IO_2} >40%	• High–flow oxygen delivery and consider noninvasive positive-pressure ventilation
	Organ toxicity	• Symptomatic management of organ toxicities
Grade 4	Hypotension, life-threatening	• IV fluids, anti–IL-6 therapy, vasopressors, and hemodynamic monitoring • Methylprednisolone 1 gram IV daily
	Hypoxia, requiring ventilatory support	• Mechanical ventilation
	Organ toxicity	• Symptomatic management of organ toxicities

Abbreviations: F_{IO_2} = fraction of inspired oxygen; IL-6 = interleukin-6.

inflammation, tissue damage, and autoimmunity. The main target tissues are the GI tract, lungs, skin, pancreas, liver, and endocrine system.[65]

The adverse effects of immune checkpoint inhibitors vary with the specific agent and are more common with ipilimumab than nivolumab or pembrolizumab.[65,68] The most frequent complications of ipilimumab are diarrhea and enterocolitis.[68] Typically, the onset of GI symptoms is 6 weeks after start of treatment. Hypophysitis, inflammation of the pituitary gland, and thyroiditis are common adverse effects.[68,69] Pancreatitis is associated more with combination therapy and with nivolumab than ipilimumab and pembrolizumab. Other adverse effects of immune checkpoint inhibitors include pneumonitis, dermatitis, adrenalitis, nephritis, vasculitis, anemia, and uveitis.[68] Awareness of the distinct adverse effects of immune checkpoint inhibitor therapy is important to appropriately diagnose and manage these complications.[68] The American Society of Clinical Oncology has published guidelines for the management of immune-related adverse effects of immune checkpoint inhibitor therapy.[70] Mild toxicities can be controlled using topical regimens or oral antipruritics without use of systemic glucocorticoids.[70] For serious immune-related adverse effects (neurologic, pulmonary, and cardiac toxicities), systemic glucocorticoids are used and anti–tumor necrosis factor-α therapy may be needed by patients who do not respond adequately to glucocorticoid treatment.[70]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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SECTION 19

Eye, Ear, Nose, Throat, and Oral Disorders

CHAPTER 241

Eye Emergencies

Richard A. Walker
Srikar Adhikari

INTRODUCTION AND EPIDEMIOLOGY

The breadth of ocular emergencies seen in the ED requires solid examination skills and an understanding of basic differential diagnosis. An analysis of 1412 ED ocular emergencies presenting to a single center identified the four most common condition categories: ocular trauma in 27% (73% of trauma group had corneal abrasions), conjunctivitis in 15%, retinal problems in 3.6%, and glaucoma in 2%.[1]

This chapter reviews eye anatomy, the essential skills needed for the ED eye examination, and common ophthalmic medications. Common causes of the red eye, ocular infections and inflammation, trauma to the eye, acute visual reduction or loss, and acute cranial nerve palsies are discussed. The principles and advantages of ocular US are summarized.

EYE ANATOMY

The **orbit** is a pyramid of bony walls that converge to an apex posteriorly. The orbit is bordered superiorly by the frontal sinus, medially by the ethmoid sinus, inferiorly by the maxillary sinus, and laterally by the zygomatic bone. The ethmoid bone (lamina papyracea) is paper thin and is the most likely sinus wall to break in blunt eye trauma or to be perforated due to sinusitis with subsequent spread of infection to the orbit. The orbital contents include the ocular muscles, retroseptal fat, and the optic nerve, whereas the globe is considered a separate entity.

The anterior limit of the orbital cavity is the **orbital septum (Figure 241-1)**, which is a layer of fascia extending from the periosteum along the orbital rim to the levator aponeurosis of the upper eyelid and to the edge of the tarsal plate of the lower eyelid. Abnormalities, such as the accumulation of blood or infection, are referred to as "preseptal" or "postseptal." Postseptal conditions are extremely serious. **The septum is generally impervious to bacteria, which serves to limit spread of infection from the facial skin into the orbit.** All nerves and vessels of the eye enter through the apex of the orbit (posterior limit), which is also the site of origin for the extraocular muscles. The optic nerve is subject to compression from mass effect due to tumors, abscesses, or hematomas.

The arterial blood supply of the eye and orbit is the ophthalmic artery, the first major branch of the intracranial portion of the internal carotid artery, which enters the orbit beneath the optic nerve. The **central retinal artery** is the first intraorbital branch of the ophthalmic artery and courses through the optic nerve. The venous drainage of the eye and orbit is through the ophthalmic veins, which drain into the central retinal vein. The ophthalmic veins communicate directly to the cavernous sinus. This venous system has no valves, and this fact is the basis for the spread of facial and periorbital infections to the cavernous sinus.

The eye itself is composed of several different layers (**Figure 241-2**). The outermost layer is a thin, transparent mucous membrane (the **bulbar conjunctiva**) that continues onto the posterior surface of the eyelids (the **palpebral conjunctiva**). Deep to the conjunctiva is the **episclera**, a layer of thin, elastic tissue containing blood vessels that nourish the next deepest layer, the sclera. The **sclera** is the collagenous protective coating of the eye, which is the thinnest (and prone to rupture) at the insertion of the rectus muscles.

The **cornea** forms the anterior surface of the eyeball and is attached to the sclera at the limbus. From anterior to posterior, the cornea has five separate layers: epithelium, Bowman layer, stroma, Descemet membrane, and endothelium. The epithelium is five or six cell layers thick and is subject to damage from minor mechanical forces, resulting in corneal abrasion (**Figure 241-3**).

The iris, ciliary body, and choroid (the vascular pigmented layer of the eye between the sclera and retina) make up the **uveal tract**. The uveal tract supplies nutrition to the eye and assists in accommodation and pupillary constriction. The lens separates the aqueous humor in the anterior chamber from the vitreous humor in the remainder of the globe. (See the section titled "Acute Angle-Closure Glaucoma," under the section "Acute and Painful Vision Reduction or Loss," in this chapter for discussion of the production and flow of aqueous humor.) The retina is the sheet of neural tissue containing the rods and cones that lines the posterior two thirds of the inner surface of the globe, extending anteriorly as far as the ciliary body.

EYE EXAMINATION

HISTORY

A detailed history is as important in the patient with an eye complaint as it is for a complaint related to any other organ system. History should first categorize the symptom as vision loss, change in appearance of the eye, eye pain/discomfort, or trauma. The onset (gradual or sudden) of symptoms, duration of the symptoms, and circumstances surrounding the onset are important. Eye discomfort should be characterized as pain (aching, burning, throbbing, etc.), pruritus (associated with allergy), or a foreign body sensation as seen with corneal foreign bodies, abrasions, or ulcers. "Flashing lights" and a "curtain or veil" obstructing a portion of the visual field suggest a retinal detachment. In the case of trauma, ask about onset (traumatic iritis occurs 1 to several days after blunt trauma to the eye) and mechanism (globe penetration may occur in association with hammering, grinding, or use of other high-speed machinery). Document tetanus status and give tetanus toxoid as appropriate.

Past medical history can narrow the differential diagnosis. Previous surgery may be the cause of an irregular pupil. Absence of corrective lenses may account for decreased visual acuity and will require modification of the method for testing visual acuity. Use of contact lenses, especially the extended wear type, may be associated with bacterial corneal ulcers. Chronic use of certain ophthalmic medications may cause chemical conjunctivitis and inflammatory changes of the cornea. A history of diabetes or chronic hypertension and acute isolated sixth-nerve palsy suggests an ischemic cranial neuropathy. Monocular diplopia following trauma in a patient with an intraocular lens implant suggests dislocation of the intraocular lens. Ask about previous instances of similar symptoms and the associated diagnosis.

EXAMINATION

The eye examination typically proceeds in a sequential fashion unless the circumstances require otherwise (e.g., **chemical ocular injuries require irrigation *before* assessment of visual acuity**). The glossary of terms and abbreviations in **Table 241-1** is helpful when communicating with the ophthalmologist.

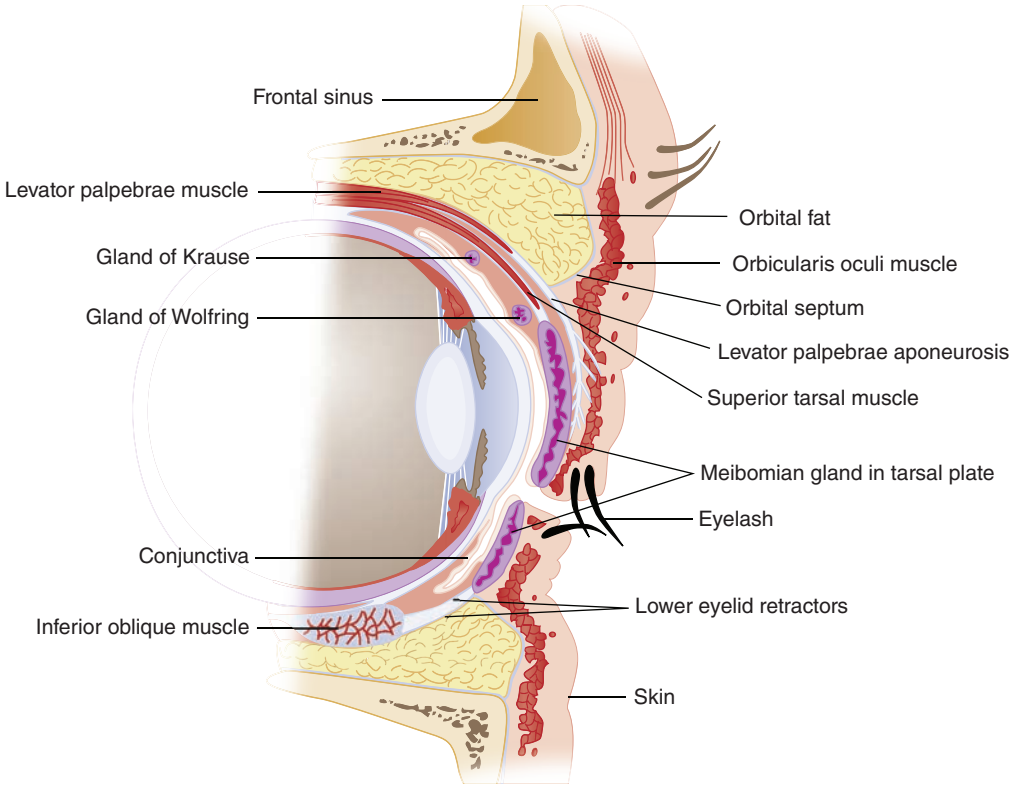


FIGURE 241-1. Cross-section of the anterior orbit. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology,* 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

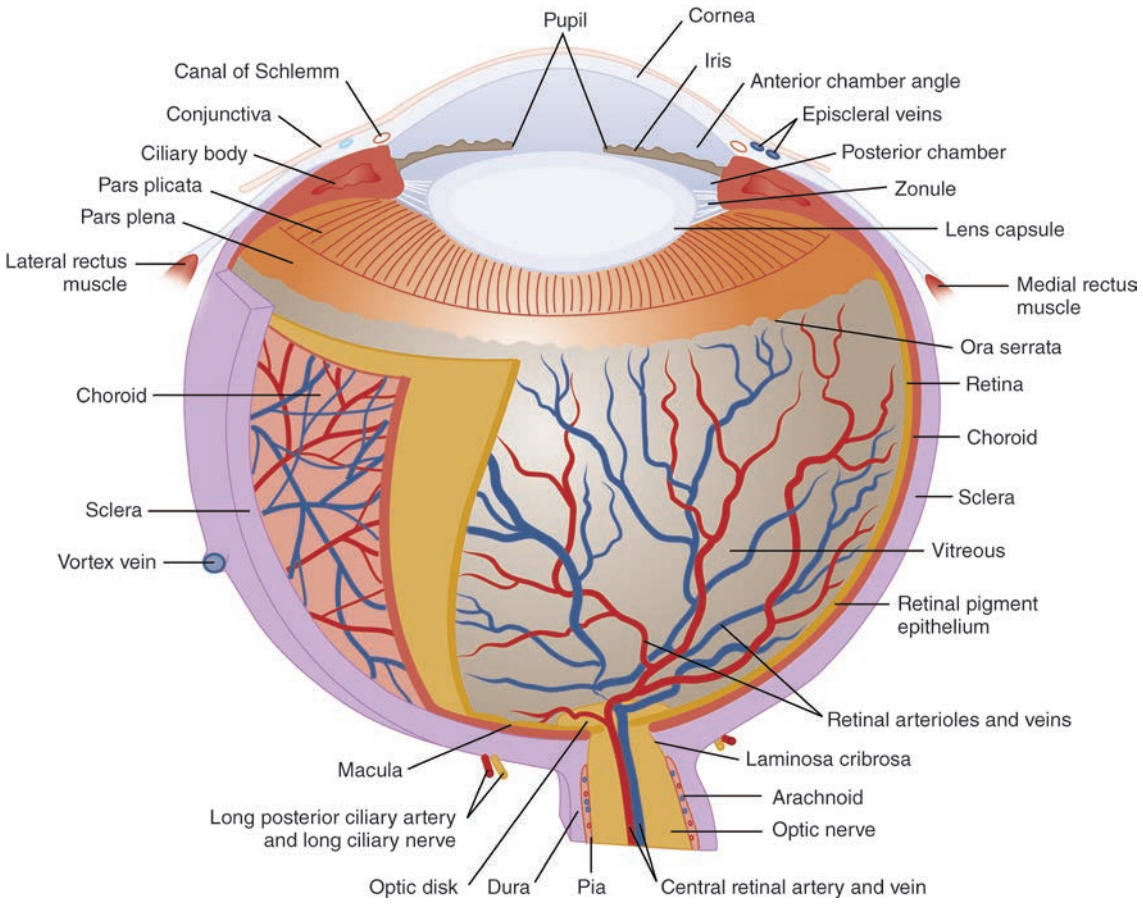


FIGURE 241-2. Internal structures of the human eye. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology,* 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

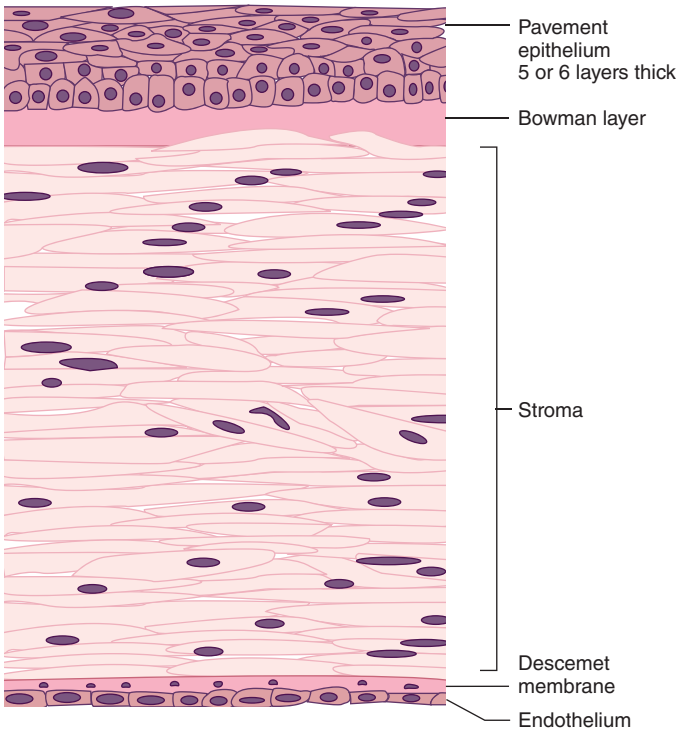


FIGURE 241-3. Transverse section of cornea. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology,* 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

TABLE 241-1 Glossary of Terms, Abbreviations, and Notations

AC	Anterior chamber, the first portion of the anterior segment.
Anisocoria	Unequal pupil size under equal lighting conditions.
Anterior segment	Consists of the anterior chamber and posterior chamber. Aqueous humor is produced in the posterior chamber of the anterior segment and circulates through the pupil into the anterior chamber of the anterior segment.
APD	Afferent pupillary defect (see Figure 241-8).
CF	Counting fingers (visual acuity assessment).
CVF	Confrontation visual fields.
EOM	Extraocular muscle. Extraocular movements.
HM	Hand motion (visual acuity assessment).
Hyphema	Red blood cells in the anterior chamber.
Hypopyon	WBCs in the anterior chamber.
INO	Internuclear ophthalmoplegia.
IOFB	Intraocular foreign body.
IOP	Intraocular pressure (mm Hg).
Limbus	Circumferential border where clear cornea ends and white sclera begins.
NLP	No light perception (blind).
OD	Oculus dexter (right eye).
OS	Oculus sinister (left eye).
OU	Oculus uterque (each eye).
PH	Pinhole visual acuity.
RD	Retinal detachment.
Tono-Pen® (Reichert, Inc., Depew, NY)	A hand-held, pen-shaped device for measuring IOP.
T_{tono}	Tension (IOP) with subscript representing method used: (tono = Tono-Pen®; S = Schiötz; A = applanation).*
V_{AC}	Visual acuity with correction (glasses or contact lenses).*
V_{AS}	Visual acuity without correction.*

*By convention, in documenting the visual acuity (V_A) or IOP, the right eye is listed above the left, as follows:

$T_{tono} < \begin{matrix}14\\15\end{matrix}$ This represents an IOP of 14 mm Hg in the right eye and 15 mm Hg in the left eye measured by Tono-Pen®.

$V_{AC} < \begin{matrix}20/20\\20/30\end{matrix}$ This represents a visual acuity *with* glasses/contacts of 20/20 right eye and 20/30 left eye.

$V_{AS} < \begin{matrix}20/400 \rightarrow 20/30\\CF \text{ at } 8 \text{ ft} \rightarrow 20/40\end{matrix}$ This represents a visual acuity *without* glasses/contacts of 20/400 in the right eye, improving to 20/30 with pinhole testing; counting fingers at 8 ft (2.4 m) in the left eye, improving to 20/40 with pinhole testing.

Full examination should include the following, generally in the order listed: visual acuity, confrontational visual fields, extraocular movements, pupillary reactions, lids and adnexa, conjunctiva and sclerae, cornea, anterior chamber, iris, lenses, vitreous, intraocular pressure, and funduscopic examination. Measurement of intraocular pressure is done toward the end of the examination because physical touching of the cornea is more irritating and invasive than the rest of the examination. Performance of a thorough funduscopic examination requires dilatation of the pupil, so this part of the examination is performed last. Not all parts of the examination need to be done on every patient. For example, testing visual fields adds little to the evaluation of a corneal foreign body but is essential to the evaluation of acute vision loss.

Visual Acuity Most vision-threatening disorders present with decreased visual acuity. **Visual acuity testing is the vital sign of the eye** and is the first step in any eye examination, even before shining a light in the eye; bright light can temporarily decrease visual acuity. The only exception to this rule is for chemical burns to the eye, where irrigation takes precedence above all else. Test visual acuity with contact lenses or glasses in place if possible. If the patient's glasses or contacts are unavailable, use **pinhole testing** of visual acuity. A commercial pinhole occluder may be used, or a note card perforated with an 18-gauge needle is an acceptable substitute. The pinhole allows only parallel light rays to fall on the macula, thereby reducing the refractive error and allowing an estimate of the person's corrected visual acuity. Visual acuity testing is ideally done with a standard wall-mounted visual acuity chart (**Snellen chart**) with the patient standing 20 ft (6 m) from the chart. Record the visual acuity as 20/x, where the numerator is the distance from which the patient can read the line (always 20) and the denominator is the distance from which a person with normal vision can read the same line. **The visual acuity is determined by the smallest line a patient can read with one half of the letters correct.** The number of incorrect letters is listed after the visual acuity as follows: 20/x-y (e.g., 20/40-2). Document best acuity in each eye and whether prosthetic devices were used in testing (glasses, pinhole).

Visual acuity can also be tested with a **near card** (**Rosenbaum chart**) held 14 in. (36 cm) from the patient. Patients in their mid-40s or older may require reading glasses or bifocals to read a near card because of presbyopia. If the bifocals are not available, use a pinhole occluder.

For patients with visual acuity <20/200, finger counting at a distance (e.g., finger counting at 3 ft or 1 m), perception of hand motion at 1 to 2 ft (0.3 to 0.6 m), and ultimately light perception can be used to document visual acuity. If the patient is unable to detect hand motion, turn off all the lights in the room, fully occlude the contralateral eye, and test for light perception. Illiterate patients can be tested using the direction of the letter **E** on the chart, and a verbal child may be tested with an **Allen chart** (pictures). Corneal abrasions or foreign bodies can cause severe photophobia, pain, and tearing, so a topical anesthetic can reduce discomfort sufficiently to allow a more accurate assessment of visual acuity. In recording the results of visual acuity testing, refer to Table 241-1.

When alternating black-and-white lines are passed from one side to another in front of a patient's eyes, **involuntary horizontal nystagmus**

(optokinetic nystagmus) will occur. The presence of optokinetic nystagmus excludes blindness in a patient with an otherwise normal examination who claims he or she cannot see (hysterical blindness). The test can be performed by placing thick black lines approximately 1 in. apart on a 2-ft strip of cardiac monitor paper, which is passed back and forth at eye level a distance of 1 ft from the patient.

Confrontation Visual Fields Test all four quadrants of the visual fields by having the patient cover one eye and look at the physician's nose. The examiner closes the opposite eye and holds a finger halfway between the patient and himself or herself. The finger is wiggled as it is moved medially toward the patient. The normal patient should see movement at approximately the same time as the physician does. A visual field defect may represent pathology anywhere from the occipital cortex to the optic nerve (**Figure 241-4**). Bitemporal hemianopia can occur in pituitary adenoma; homonymous hemianopia is associated with some cerebrovascular accidents; and monocular field cuts are sometimes seen with large retinal detachments.

Ocular Motility The normal patient can move the eye through the six cardinal positions of gaze, and the eye movements are controlled by the six extraocular muscles attached to each eye (**Figures 241-5** and **241-6**). Extraocular muscles are innervated by cranial nerves III, IV, and VI. **Cranial nerve IV controls the superior oblique muscle, cranial nerve VI controls the lateral rectus muscle, and all other extraocular muscles are controlled by cranial nerve III.** Extraocular movement can be impaired by restriction, interrupted or decreased innervation, or trauma. Examples of restriction include thyroid orbitopathy, myositis, and mechanical entrapment of a muscle secondary to an orbital blow-out fracture. Cranial nerve palsies or paresis may be caused by stroke, myasthenia gravis, diabetes, hypertension, tumors, aneurysms, infections, and trauma. Penetrating or blunt traumatic injury to an extraocular muscle also can result in motility disturbance.

Evaluate ocular alignment initially in *primary gaze* (looking straight ahead), and then test eye movements in all fields of gaze. Always ask

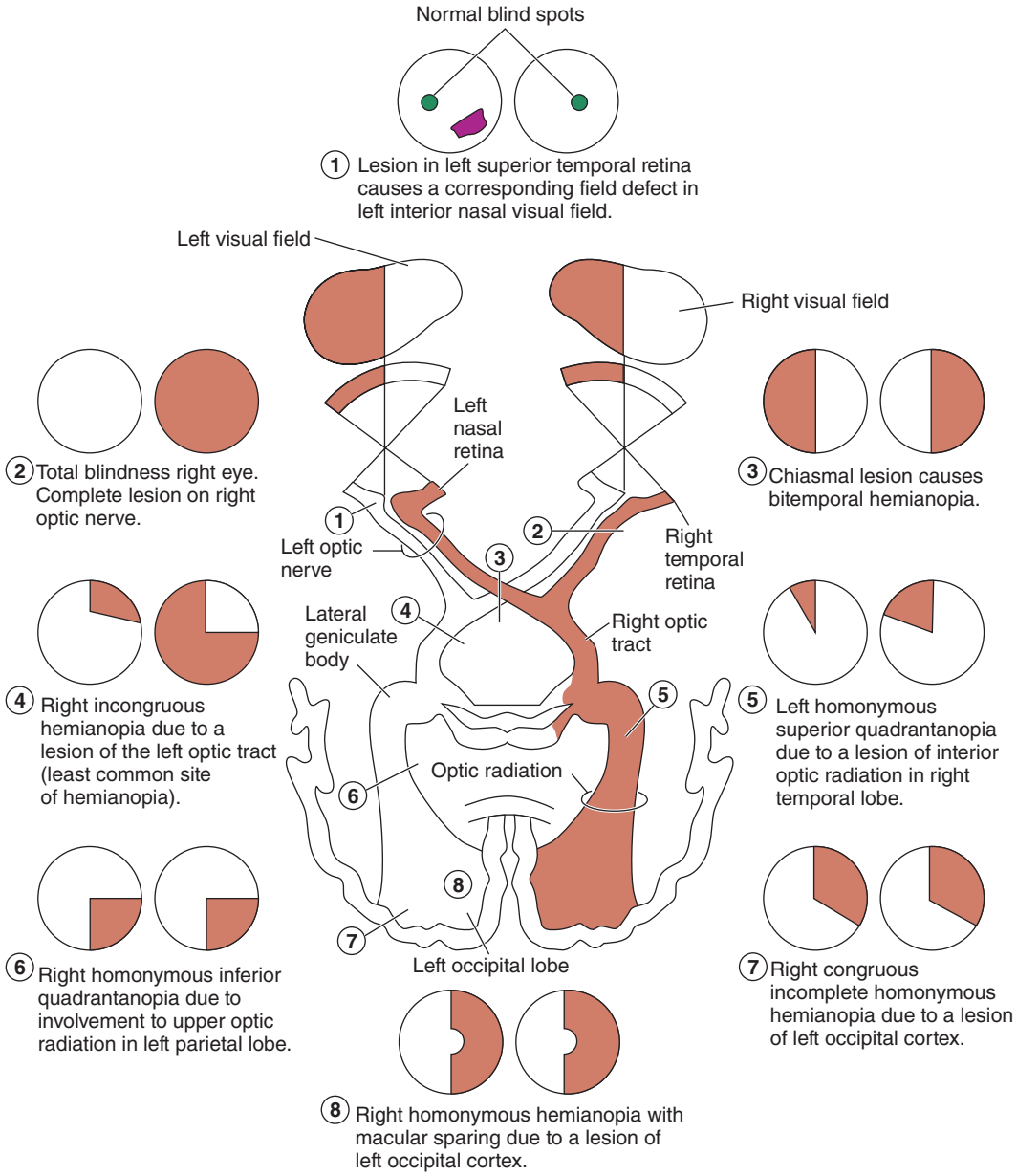


FIGURE 241-4. Visual field defects produced by lesions at various points along the optic pathways: (*1*) field defect caused by retinal lesion, (*2*) total blindness right eye, (*3*) bitemporal hemianopia, (*4*) right incongruous hemianopia, (*5*) left homonymous superior quadrantanopia, (*6*) right homonymous inferior quadrantanopia, (*7*) right congruous incomplete homonymous hemianopia, and (*8*) right homonymous hemianopia with macular sparing. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology*, 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

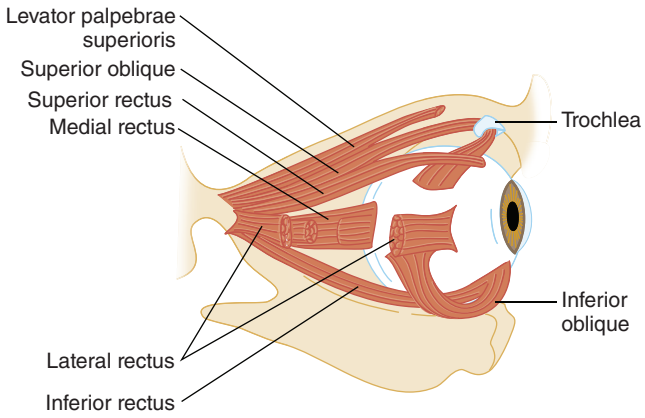


FIGURE 241-5. Extraocular muscles of the eye.

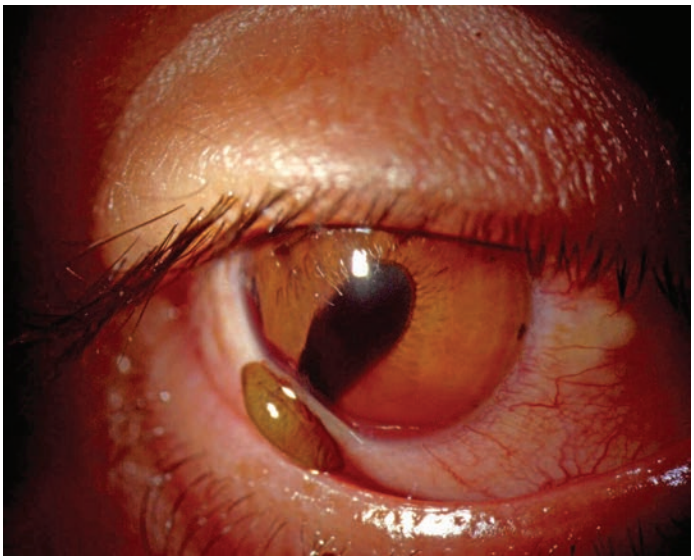


FIGURE 241-7. Prolapse of the iris with the classic teardrop-shaped pupil after penetrating trauma. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

the patient about diplopia, which may be a subtle sign of problems with extraocular muscles. Diplopia is usually worse when the patient is attempting to look in the direction of the malfunctioning muscle. Ask patients if diplopia persists when one eye is covered (monocular diplopia). **Monocular diplopia** can be caused by corneal irregularity, lens problems, or intraocular lens dislocation, or it can be a sign of malingering. Resolution of diplopia when one eye is covered represents pathology of an extraocular muscle or its innervation. Patients with lesions of the superior oblique muscle or the fourth cranial nerve may tilt their head to compensate for the diplopia.

Pupils Note the pupil size in millimeters and test shape and reaction to light. An irregular pupil may occur from prior surgery or remote trauma. The patient will usually be able to relate a previous history of irregular pupil. The classic irregular teardrop-shaped pupil may also be seen in acute blunt or penetrating trauma with rupture of the iris (**Figure 241-7**).

Assess pupils under slightly dim light to test for an afferent pupillary defect (**Figure 241-8**). **A positive afferent pupillary defect indicates an optic nerve disorder.** Any pathology that prevents light from getting to the CNS, such as opacification of the vitreous with blood, retinal pathology, or optic nerve pathology, will cause an afferent pupillary defect, also known as a ***Marcus-Gunn pupil***. The pupils will be equal in size *before* testing because of the consensual light response. Therefore, an afferent pupillary defect does *not* cause a baseline anisocoria and will be discovered only if specifically tested for. Perform the "swinging flashlight test" to detect an afferent pupillary defect. Shine a light in the pupil. The light causes constriction of the ipsilateral pupil and consensual constriction of the opposite pupil. The light is then shined/swung to the opposite pupil. The opposite pupil will dilate if an afferent pupillary defect is present, because the effect of light is not getting through to the CNS.

Causes of unequal pupils (**anisocoria**) can range from an acute emergency (posterior communicating artery aneurysm) to chronic baseline conditions such as previous intraocular trauma or surgery, or they can be idiopathic. **Physiologic anisocoria (benign chronic difference in pupil size) is the most common cause of asymmetric pupils.** The difference in size is usually <1 mm, and both pupils react normally by constricting to light and dilating in darkness. A single dilated pupil may represent impending **uncal herniation** (from pressure on the third nerve), but uncal herniation is accompanied by an altered level of consciousness and other focal neurologic signs. A single nonreactive dilated pupil may result from a topical cycloplegic agent (scopolamine, cyclopentolate, or atropine) or if an anticholinergic medication (such as ipratropium from a nebulization treatment for bronchospasm) is splashed into the eye. A careful history is important to determine whether anisocoria is preexisting. **It is not worthwhile to attempt to "reverse" a suspected chemically altered pupil in the ED as a diagnostic test because the results are not reliable.**

External Eye: Periorbital Skin, Lids, and Adnexa First, carefully examine the eyebrows, eyelids, lashes, palpebral and bulbar conjunctivae, lacrimal apparatus, cornea, and sclera. Look for follicles (seen with allergic and viral conjunctivitis), chemosis (subconjunctival edema fluid), injection/inflammation, discharge, trauma, hypopyon, hyphema, and foreign bodies. Apply drops of a fresh unused bottle of anesthetic if the eye is painful, and apply fluorescein to look for abrasions and lacerations.

Examine the periorbital skin and lids for trauma, infection, dysfunction, deformity, crepitus, or proptosis. Subcutaneous emphysema can be found with blow-out fractures of the medial orbital wall (ethmoid). Palpate the orbital rims for step-off deformities in trauma. Evert the upper eyelid to check for foreign bodies. Use of a cotton applicator is often recommended; however, this technique will only visualize the lower half of the inner upper eyelid (**Figure 241-9**). The edge of an eyelid retractor may be used to tent the upper lid while a second examiner looks under

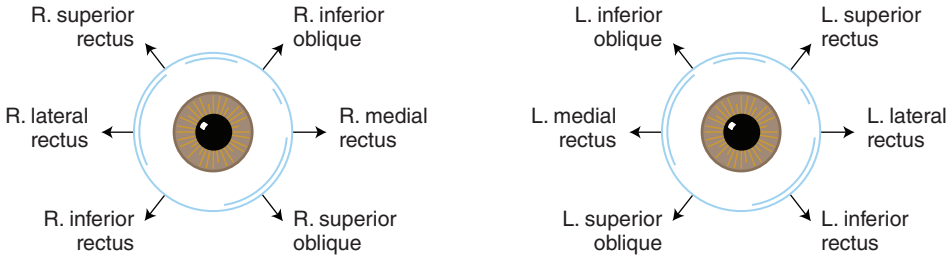


FIGURE 241-6. Arrows indicate direction of ocular movement by each muscle. Cranial nerve IV, superior oblique muscle; cranial nerve VI, lateral rectus muscle; cranial nerve III, superior rectus, inferior rectus, inferior oblique, and medial rectus muscles. L = left; R = right.

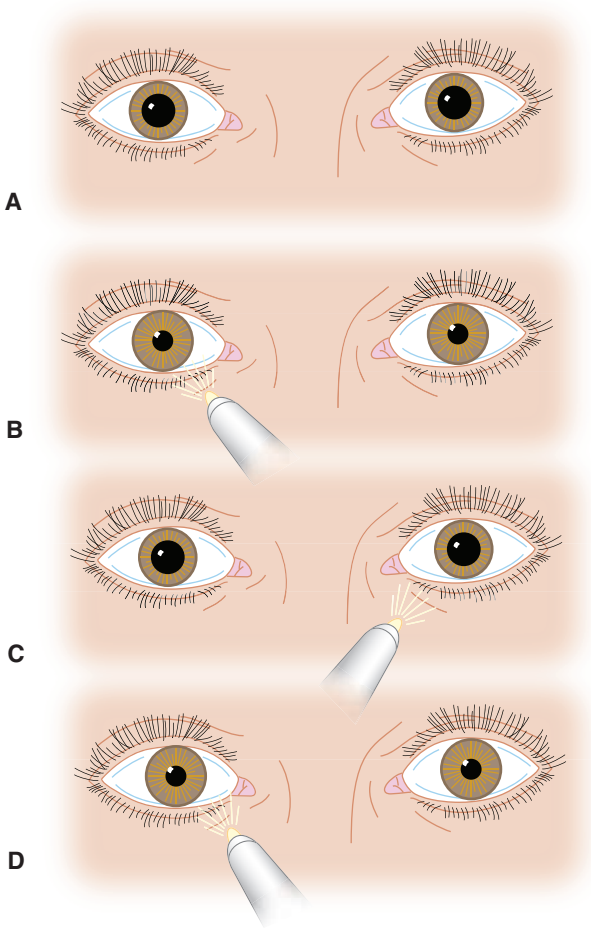


FIGURE 241-8. **A** and **B.** "Swinging flashlight test" revealing an afferent pupillary defect (Marcus-Gunn pupil) of the left eye. **A.** Pupils are normal and equal before light testing. **B.** Both pupils constrict when light is shined into the normal (right) eye. **C** and **D.** The test is positive when the affected pupil (left pupil) dilates in response to light. Conditions with an afferent pupillary defect include optic neuritis and central retinal artery occlusion.

the lid from a caudal direction, so-called *double eversion of the eyelid*. This will allow visualization of the upper half of the inner eyelid. A large paper clip may be bent into the shape of an eyelid retractor for this purpose (**Figure 241-10** and see **Figure 241-11**).

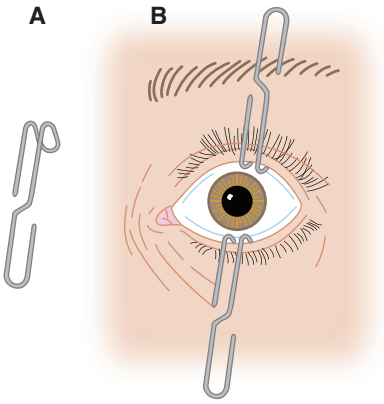


FIGURE 241-10. An alternative to an eyelid retractor. **A.** Unfold a paper clip and bend it into shape with a hemostat. **B.** Paper clips used to retract the eyelids. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD. McGraw-Hill Professional, Inc.]

Examine the Iris for Pupil Irregularity and Pupillary Dysfunction

Irregularity of the pupil will occur whenever one portion of the iris is tethered into place and may occur from posterior synechiae, where the iris is adhesed to the anterior lens capsule as seen in uveitis, or when any portion of the iris plugs a corneoscleral laceration causing a peaked pupil. Trauma may also cause the iris to tear at the root, termed *iridodialysis*. Assess the lens for opacities, lacerations, and subluxation.

Fluorescein Examination Fluorescein binds to damaged corneal epithelium and fluoresces green under a **Wood's lamp** or light through a cobalt blue filter. Using the slit lamp, **always remove contact lenses, as fluorescein will cause permanent staining of the lenses.** Touching the fluorescein strip directly to the cornea will cause staining mimicking a linear abrasion. The best way to apply fluorescein dye is to apply several drops of eye-irrigating solution or saline onto a paper fluorescein strip, and then lightly apply the moistened end of the fluorescein strip into the inferior conjunctival fornix. Ask the patient to blink several times to distribute the fluorescein. Then examine the cornea for streaming of fluorescein-tinged aqueous humor (positive Seidel test) seen in full-thickness laceration of the cornea (**Figure 241-12**). **The Seidel test can be negative (no streaming) with a small or spontaneously sealing corneal laceration.** Ask the patient to blink to wash out the fluorescein, and then examine the cornea with the cobalt blue filter on the slit lamp. A corneal abrasion will fluoresce bright green. A Wood's lamp (ultraviolet light) may also be used to look grossly (without the slit lamp) for



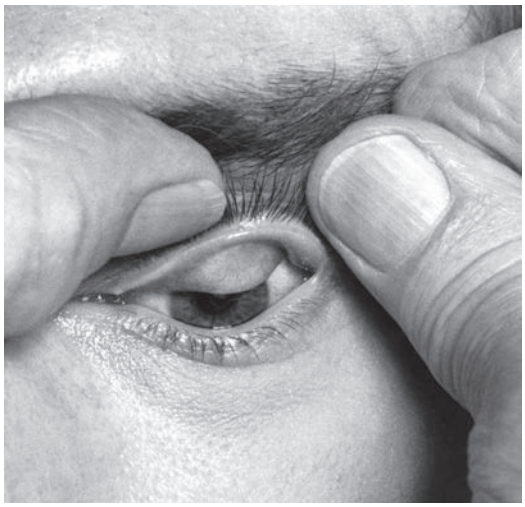


FIGURE 241-9. Single eversion of eyelid when a cotton applicator is used. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology*, 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]



FIGURE 241-11. Eyelid retractors fashioned from paper clips. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. ©2002 McGraw Hill, New York.]

corneal abrasions, but microscopic/punctate abrasions will be missed without use of a slit lamp.

Funduscopic Examination Note the size, shape, and sharpness of the borders of the optic disk, the cup-to-disk ratio, the size ratio of the arteries to veins (normal 2:3), any nicking where the arteries and veins cross, the texture and color of the retina as well as the presence of lesions (e.g., hemorrhages or exudates) of the retina or vessels (e.g., aneurysms), and the color and size of the macula. To locate lesions of the retina, note the direction (e.g., superonasal) and distance from the disk in terms of disk diameters. Opacities of the lens may obscure the view of the retina, and lens opacities appear as black spots of various shapes. Lesions in the vitreous, such as vitreous hemorrhage, will also obscure the view. Vitreous hemorrhage will have an irregular shape and may have a reddish hue.

The **direct hand-held ophthalmoscope** is used to examine the fundus. Pharmacologic dilatation will greatly enhance the view of the disk, macula, and proximal retinal vessels. Dilation is achieved by using one drop of 1% tropicamide in Caucasian patients and one drop each of 1% tropicamide and 2.5% phenylephrine in all others. An **indirect ophthalmoscope** provides an excellent three-dimensional view of the optic nerve and retina, but requires extensive practice to use and generally is not a tool for the nonophthalmologist.

The Welch Allyn Panoptic® direct ophthalmoscope allows a five times larger view of the fundus than the standard direct ophthalmoscope and provides a better view of the fundus with an undilated pupil

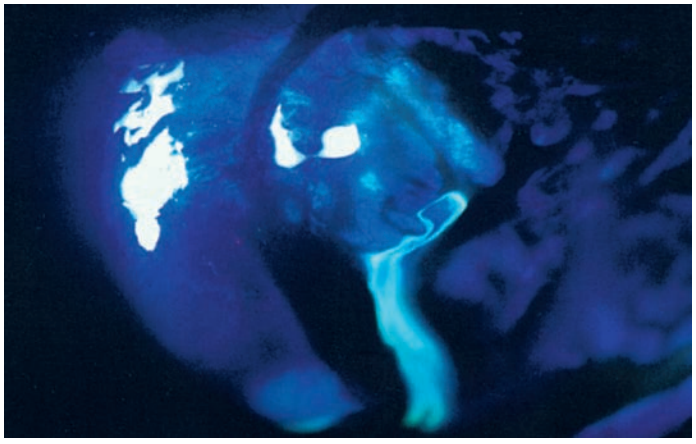


FIGURE 241-12. Positive Seidel test showing aqueous humor leaking through a full-thickness corneal wound. Aqueous humor will turn fluorescein lime green under a cobalt blue light as it oozes through the wound while being observed through the slit lamp.



FIGURE 241-13. Welch Allyn Panoptic® direct ophthalmoscope. [Copyright © Welch Allyn, Inc. All rights reserved.]

(**Figure 241-13**). It also allows for more distance between the patient and examiner, for the comfort of both. The Panoptic® device attaches to a standard Welch Allyn handle. (See Video: Panoptic Ophthalmoscope.)

Use the Panoptic® as follows:

1. Remove your glasses and the patient's glasses; seat the patient upright or with the patient's stretcher set as upright as possible. Position yourself in a direct line of vision to the patient's eyes.
2. With the scope turned off, focus on an object at least 10 ft away.
3. Set the aperture dial to small ("home" position—green line).
4. Turn on the scope and adjust to maximum brightness.
5. Ask the patient to be still and look straight ahead and tell him or her that the eyecup will touch the brow.
6. Place your hand on the patient's forehead and position the scope 6 in. away at a 15- to 20-degree angle to the temporal side.
7. Locate the red reflex and move the scope toward the patient keeping the red reflex in view.
8. Maximum view should be obtained when the eyecup is compressed by half.
9. If you have a dominant eye and prefer to use that for the examination, you may examine the opposite eye without switching your eye on the scope.
10. Make sure you wipe off the eyepiece with antiseptic/antibacterial solution after use or change eyepieces between patients.

Papilledema **Papilledema** is bilateral edema of the head of the optic nerve due to increased intracranial pressure. Any disease process that increases the intracranial pressure and inhibits vascular or axoplasmic flow in the optic nerve causes congestion and edema of the nerve head. Bilateral papilledema is a common finding in malignant hypertension, pseudotumor cerebri, intracranial tumors, and hydrocephalus. The disk margins are blurred, the cup is diminished or absent, and the nerve head is elevated with vascular congestion (**Figure 241-14**). Frequently, flame-shaped hemorrhages are seen on or adjacent to the nerve head. A distinguishing feature of papilledema is prolonged preservation of visual acuity (frequently patients are visually asymptomatic).

Intraocular Pressure The eye remains consistently "inflated" because of a delicate balance between intraocular aqueous fluid

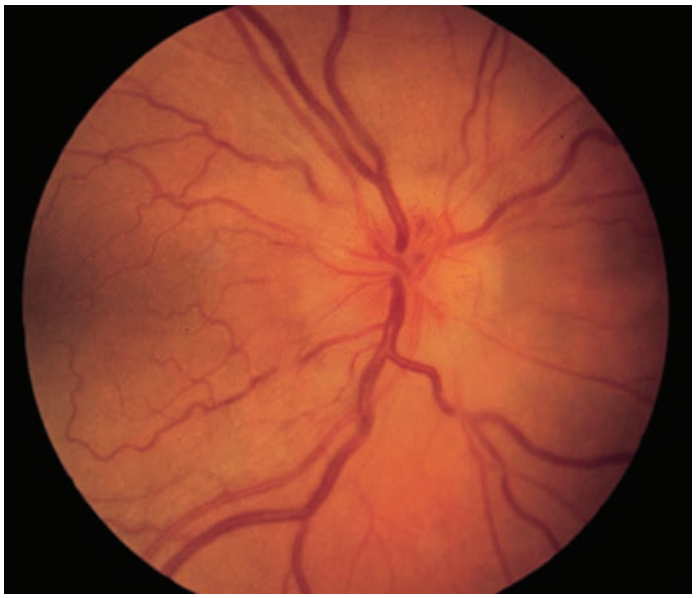


FIGURE 241-14. Optic nerve head edema. Vascular congestion, elevation of the nerve head, and blurred disk margins are characteristically seen in papilledema, papillitis, and compressive lesions of the optic nerve. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

production and outflow. Intraocular pressure can decrease due to reduced ciliary body production (some cases of iritis and uveitis) or loss of globe integrity (perforating injury). Intraocular pressure increases when intraocular fluid production exceeds outflow (glaucoma, hyphema). Measure intraocular pressure in all cases of vision loss, eye pain (suspected glaucoma), and acute or remote trauma. **Do not attempt to measure intraocular pressure if globe rupture from blunt or penetrating trauma is suspected**, as the pressure placed on the globe during pressure measurement may cause extrusion of intraocular contents. **The normal intraocular pressure is 10 to 20 mm Hg.** Digital palpation of the globe may give a rough estimation, using the examiner's eye or tip of the nose as control. Provide topical eye anesthetic when devices are used to measure pressure. To measure pressure, the lid must be open, and the patient must look straight ahead. Hold the lids open, with your fingers compressing the patient's lids against the bony rims of the orbit. Avoid placing any pressure on the globe with your fingers when holding the lids open, because this will cause a falsely high reading. Document the method used for determining intraocular pressure. In recording the pressure, refer to Table 241-1.

Schiötz Tonometer The **Schiötz tonometer** is a device using a plunger to indent the cornea. **The direct Schiötz scale reading is *not* the intraocular pressure.** Schiötz tonometry is inaccurate and not well tolerated by patients, and the instrument is difficult to sterilize, leading to potential spread of infection. The Tono-Pen® XL (Reichert, Inc., Depew, NY), Goldman® applanation tonometer, and pneumatonometer have supplanted the use of the Schiötz tonometer.

Tono-Pen® The **Tono-Pen® XL** and similar electronic devices have disposable latex covers and measure pressure by indentation of the cornea. The Tono-Pen® XL is touched to the cornea 4 to 10 times and will read out an average pressure reading (**Figure 241-15**). (See Video: Intraocular Pressure Measurement With Pen Tonometer.)

Applanation Tonometer Use of the **Goldman® applanation tonometer** requires training and practice and is a method used by optometrists and ophthalmologists. **The cone must be sterilized between patients.** The cone of the tonometer is touched to the cornea after topical anesthesia, and fluorescein is instilled into the eye (without irrigation). When looking through the slit lamp, two half circles are seen and properly aligned by adjusting the dial on the tonometer, from which the pressure is read (**Figures 241-16** and **241-17**).



FIGURE 241-15. Tono-Pen® XL (Reichert, Inc., Depew, NY). [Reproduced with permission from Rhee J: *Glaucoma: Color Atlas and Synopsis of Clinical Ophthalmology*. New York: McGraw-Hill; 2003.]

SLIT LAMP EXAMINATION

The palpebral and bulbar conjunctiva, sclerae, cornea, anterior chamber, and iris and ciliary body make up the anterior chamber, and all except the ciliary body may be examined with the slit lamp (**Figure 241-18A** and **B**). (See Video: Slit Lamp Exam.)

The **slit lamp** is a binocular microscope that provides a highly magnified three-dimensional view of ocular structures. Although there are different slit lamp manufacturers, all slit lamps have the same type of knobs and adjustments. The patient and examiner should both be seated on adjustable stools so that the examiner's and patient's eyes are at the

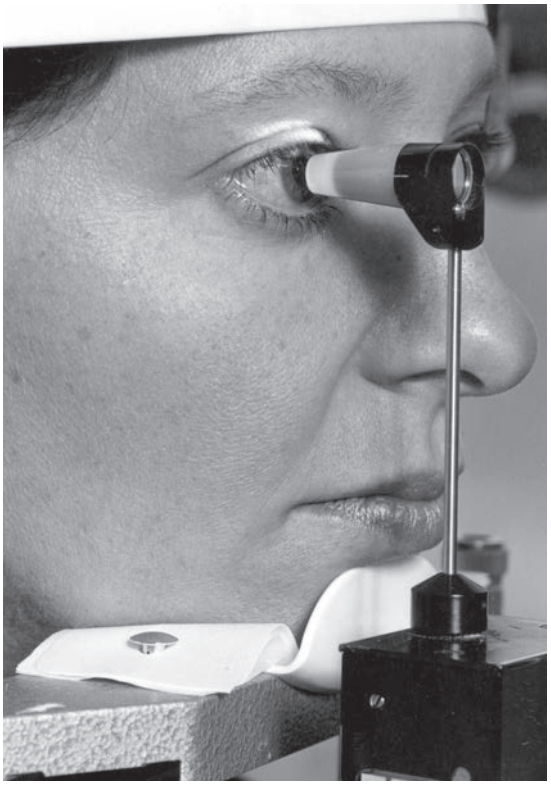


FIGURE 241-16. Goldman® applanation tonometry. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology,* 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

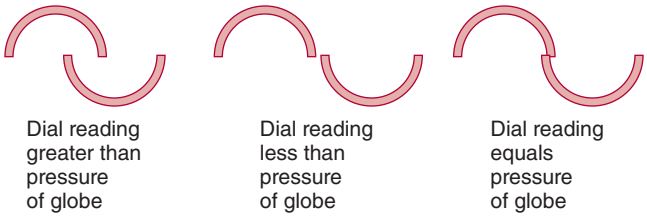
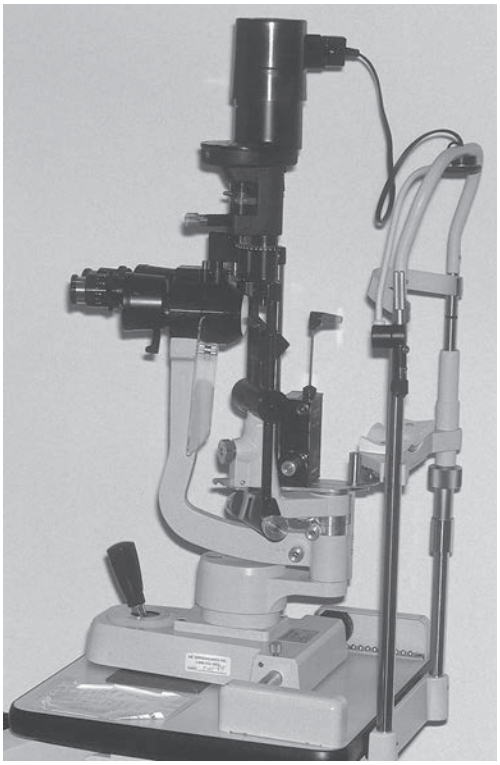


FIGURE 241-17. Appearance of fluorescein semicircles using applanation tonometry under the slit lamp. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology*, 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

same level. Cover the chin rest with tissue paper or a washcloth. Adjust the slit lamp height so the patient can lean forward and comfortably place the forehead against the upper plastic bar and the chin on the chin rest. Adjust the height of the chin rest so the patient's lateral canthus is even with the black line on the vertical bar. The oculars and light source are generally straight ahead for the general eye evaluation. Focus is adjusted by the anterior-posterior movement of the eyepiece and light source in relation to the patient. The joystick controls focus by moving the slit lamp closer to or farther away from the patient's eyes. Joystick rotation controls vertical movement of the light source and eyepieces. When one looks through the eyepieces, the focus should be close to correct if a narrow slit of light falls on the structures to be examined. Fine adjustments in focus are then made with the joystick. Adjust the vertical light beam to the full height of the cornea with a width of approximately 1 mm (Figure 241-18B).



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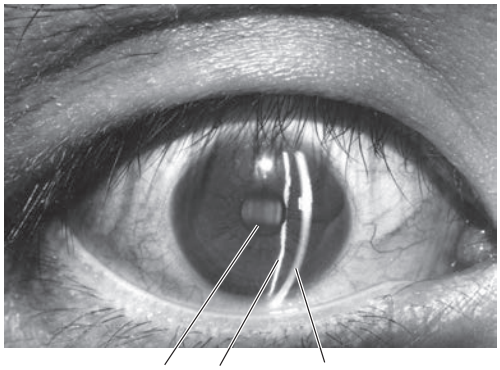


B

FIGURE 241-18. **A.** The slit lamp provides a magnified view of the eye. **B.** A thin slit can demonstrate the cornea (*C*), iris (*I*), and lens (*L*, seen directly through the pupil).

To examine the cornea, first make the light beam as thin and bright as possible (**Figure 241-19A**). Next, move the light source to a 45-degree angle relative to the body of the slit lamp (**Figure 241-19B**). By generating a thin intense light beam directed at an angle, you can view an optical cross-section of the clear structures of the eye (**Figure 241-19C to E**). Small movements of the joystick can improve visualization and also go more posteriorly into the eye. Increase magnification to 16× to visualize subtle findings.

The first structure the light beam passes through is the cornea. Inspect the corneal epithelium for abrasions, ulcers, edema, and foreign bodies (Figure 241-19C). Examine the corneal stroma (Figure 241-19D) for edema, scars, and lacerations, and examine the endothelium (Figure 241-19E) for precipitates (WBCs on the endothelium characteristic of iritis) and lacerations.

Next is the anterior chamber, which is normally empty (**Figure 241-19F**), but WBC and proteinaceous material can be evident in iritis.

Assess the depth of the anterior chamber by adjusting the angle of the light source on the slit lamp or by shining a penlight onto the iris from a lateral direction. If the iris is bowed forward, as with a shallow anterior chamber, a shadow will be cast on the medial (nasal) iris (**Figure 241-20**).

To better view the anterior chamber, move the focus inward halfway between the iris and cornea, with the pupillary aperture as a dark backdrop. This will place your focus in the center of the aqueous humor, and the light beam will illuminate WBCs and red blood cells (if present) slowly drifting up and down in the aqueous convection currents, sometimes likened to snowflakes floating through the beam from a car's headlight at night. Iritis may result in WBC layers in the anterior chamber (hypopyon) (**Figure 241-21**). Trauma to the eye may cause red blood cells in the anterior chamber (hyphema or microhyphema). **Hyphema** is layering of the red cells in the anterior chamber visible to the naked eye (**Figure 241-22**). A hyphema may occasionally be clotted (**Figure 241-23**). Flare is described as the appearance of "headlights in a fog" and represents the ability to see the course of the normally transparent light beam through the aqueous humor. **Flare** is caused by increased aqueous protein in the anterior chamber, which is common with inflammatory conditions such as iritis.

Finally, aiming posteriorly, the light beam passes to the lens (**Figure 241-19G**).

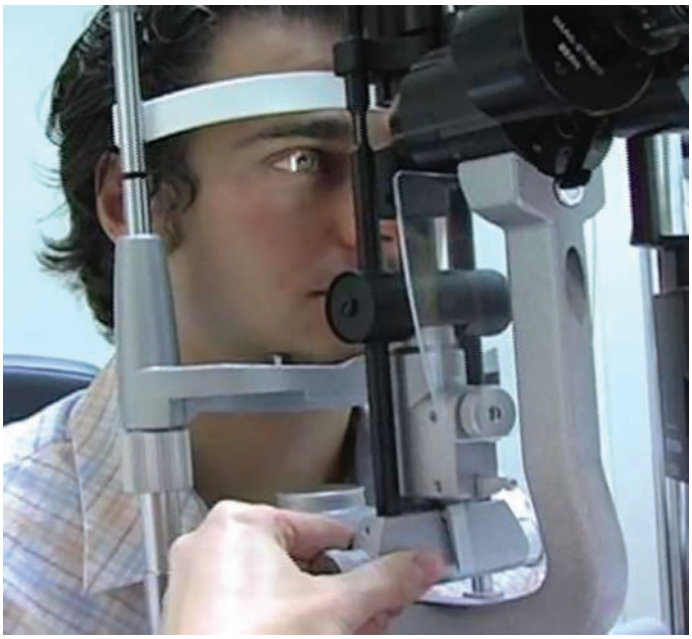
COMMON OPHTHALMIC MEDICATIONS USED IN THE ED

Topical anesthetics are needed for eye examination, intraocular pressure measurement, and corneal foreign body removal. Mydriatics and cycloplegics are needed for a more thorough eye examination. Ophthalmic antibiotics are prescribed for conjunctivitis and corneal abrasions. Antiviral medications are used for herpes simplex. Glaucoma may be treated with various combinations of topical nonselective and β_1-blockers, selective α_2-agonists, carbonic anhydrase inhibitors, cholinergic agents, and prostaglandin analogs. Allergic conjunctivitis is treated with topical nonsteroidal anti-inflammatory drugs, mast cell stabilizers, selective H_1 antagonists, or corticosteroids.

Table 241-2 lists common agents used in the ED and those that the consulting ophthalmologists may ask the emergency medicine physician to prescribe.

THE RED EYE

The differential diagnosis of the red eye is extensive. Key differentiating factors are the presence or absence of pain, itching, photophobia, systemic symptoms, discharge and injections, visual loss, and changes



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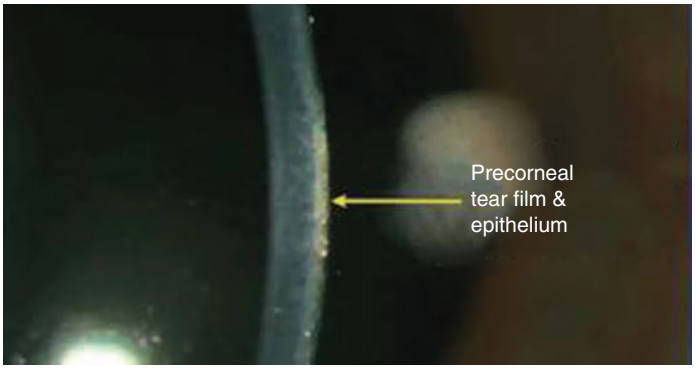

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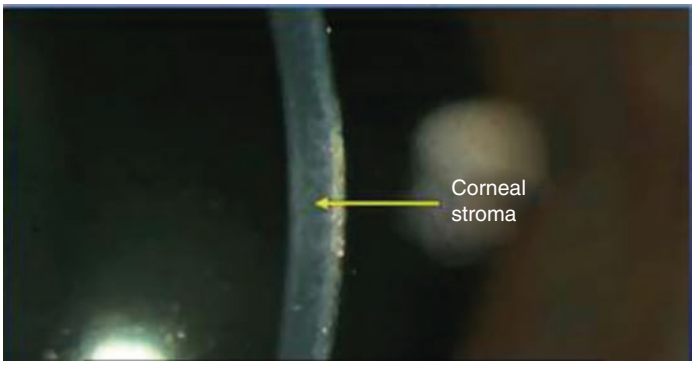

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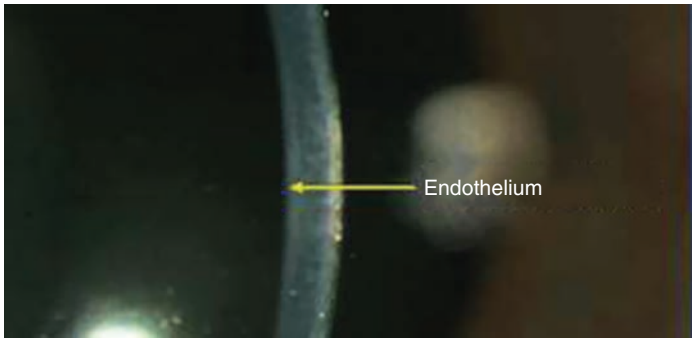

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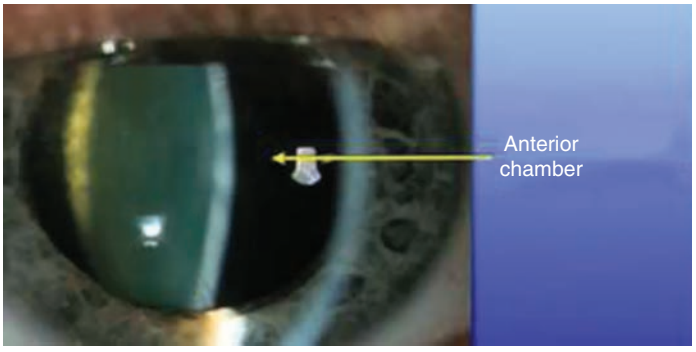

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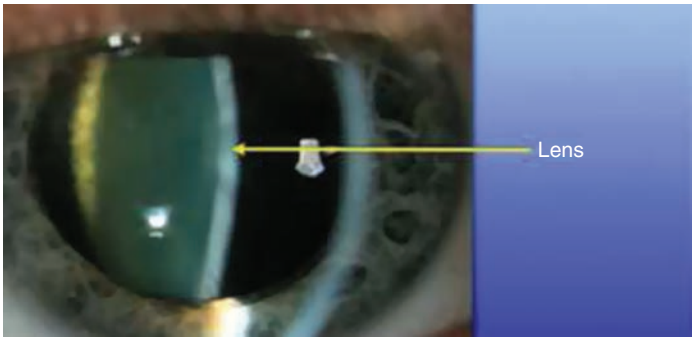

G

FIGURE 241-19. **A.** To examine the cornea, adjust the light beam to be thin and bright. **B.** Move the light source to a 45-degree angle. **C.** The first structure is the cornea. The first curve of the cornea is the tear film and corneal epithelium. **D.** Corneal stroma. **E.** Corneal endothelium. **F.** Anterior chamber. The anterior chamber is usually clear. If filled with material, it represents cells or proteinaceous material. **G.** The lens of the eye is seen posterior to the anterior chamber. As you focus on the lens of the eye, the cornea will be out of focus.

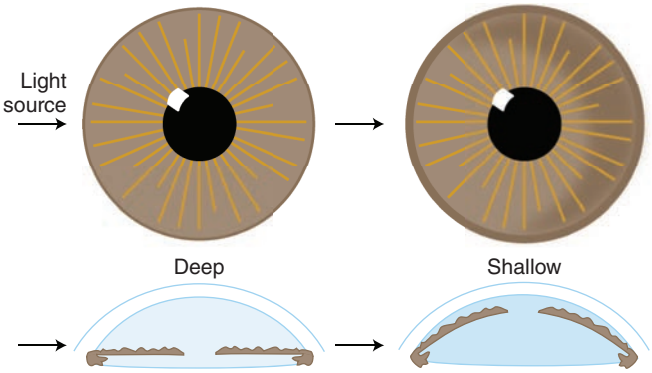

FIGURE 241-20. Estimation of depth of the anterior chamber by oblique illumination. Note the shadow cast in the shallow chamber. [Reproduced with permission from Riordan-Eva P, Whitcher J: *Vaughn & Asbury's General Ophthalmology,* 17th ed. New York: Lange Medical Books/McGraw-Hill; 2008.]

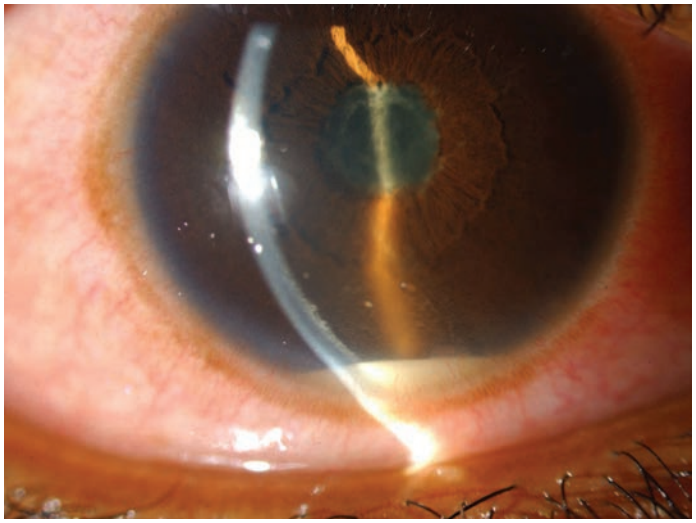

FIGURE 241-21. Hypopyon: a layering of WBCs in the inferior portion of the anterior chamber. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

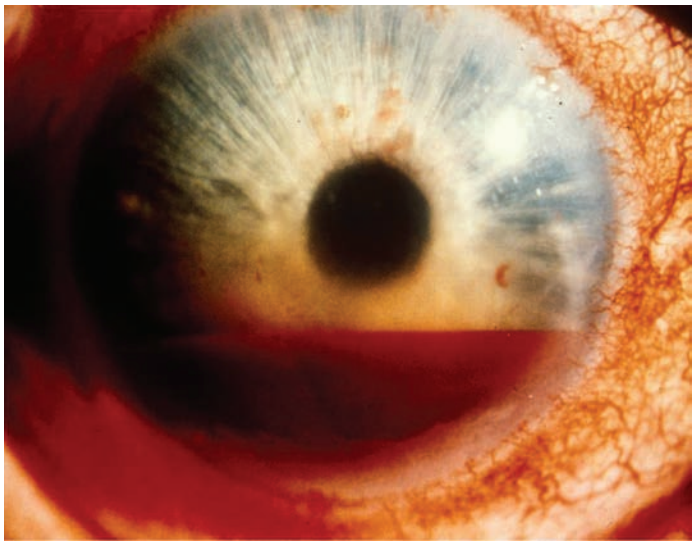

FIGURE 241-22. Hyphema secondary to blunt trauma. Note the blood filling the lower half of the anterior chamber and hazy appearance of cornea suggesting increased intraocular pressure. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

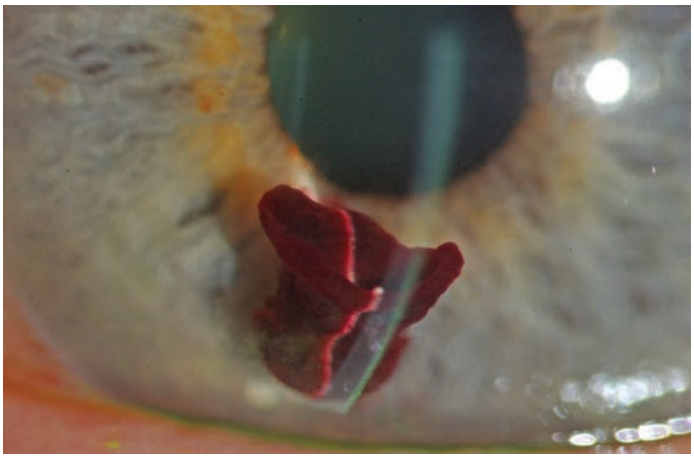

FIGURE 241-23. Hyphema appearing as a clot rather than layering out. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

in the cornea, pupils, and intraocular pressure. **Table 241-3** lists various causes of the red eye with key differentiating features. Many of these conditions are discussed more extensively in the text.

OCULAR INFECTIONS AND INFLAMMATION

PRESEPTAL (PERIORBITAL) AND POSTSEPTAL (ORBITAL) CELLULITIS

COMMON PRESENTATION

Orbital and periorbital infections exist in a spectrum of increasing severity: preseptal (periorbital) cellulitis, postseptal (orbital) cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombosis, from least to most severe. Preseptal cellulitis and postseptal cellulitis, although both of an infectious etiology and involving periocular tissues, are very different entities with different morbidities. **Preseptal cellulitis (periorbital cellulitis)** is an infection of the eyelids and periocular tissues that is anterior to the orbital septum. It is generally benign and may be treated in the outpatient setting. **Postseptal cellulitis (orbital cellulitis)** is an infection of the orbital soft tissues posterior to the orbital septum. It may be life and vision threatening and must be treated as an inpatient with IV antibiotics and occasionally surgical drainage. **Endophthalmitis** is an infection of the globe and is a completely separate entity.

The outward appearance of the patient with postseptal cellulitis may be very similar to that of the patient with preseptal cellulitis. Preseptal and postseptal cellulitis may both display excessive tearing, fever, erythema, edema, warmth, and tenderness to palpation of the lids and periorbital soft tissues.[2] Laboratory studies do not discriminate between the two conditions, and blood cultures are not helpful. **Contrast-enhanced CT scan of the orbits and sinuses differentiates the two conditions and identifies complications.**[3] A misdiagnosis can result in significant neurologic disability and death. The differential diagnosis for preseptal and postseptal cellulitis is listed in **Table 241-4**.

PRESEPTAL CELLULITIS

Preseptal cellulitis is usually associated with upper respiratory tract infections, especially paranasal sinusitis, and may result from eyelid problems such as hordeolum, chalazion, insect bites, and trauma. Preseptal cellulitis is primarily a disease of childhood, with most patients <10 years of age. The most common organisms are *Staphylococcus aureus* and *Staphylococcus epidermidis*, *Streptococcus* species, and anaerobes. Since the introduction of the *Haemophilus influenzae* type B vaccine, *H. influenzae* has become a rare cause of preseptal cellulitis in children.

TABLE 241-2 Ophthalmic Medications Used in the ED

Type	Generic Name	Trade Name	Indication	Cautions	Usual Dose
Mydriatic Sympathomimetic	2.5% phenylephrine	Mydfrin® AK Dilate®	Pupil dilation, no cycloplegia, usually adjunctive to an anticholinergic	Hypertension, glaucoma; do not use after chemical injury to the eye	One drop, onset 20–30 min, duration several hours
Mydriatic-cycloplegic Anticholinergic	Cyclopentolate	Cyclogyl®	Short-term mydriasis and cycloplegia for examination	Glaucoma; higher concentrations in children can cause agitation	0.5% in children, one drop; 1% in adults, one drop; onset 30 min, duration ≤24 h
	Tropicamide	Mydriacyl® Tropicamide Ophthalmic Solution	Short-term mydriasis and cycloplegia for examination	Glaucoma	One to two drops of 0.5% or 1% solution, onset 20 min, duration of action 6 h
	Homatropine	Isopto Homatropine®	Intermediate-term pupil dilation, cycloplegia, treatment of iritis	Glaucoma, avoid in children	One to two drops of 2% solution; onset 30 min; duration of action 2–4 d; for iritis one to two drops twice a day
Antihistamine/ decongestant	Naphazoline and pheniramine	Naphcon-A® Visine A®	Conjunctival congestion/itching	Do not use >72 h; avoid in narrow angle glaucoma; hypertension; do not use with contact lenses in place	One drop three to four times a day
Antihistamine	Olopatadine	Patanol®	Allergic conjunctivitis	Do not administer while contact lenses are present	0.1% solution, one drop twice daily, onset of action 30–60 min, duration 12 h
Topical anesthetics	Tetracaine ophthalmic solution	Pontocaine® Tetravisc®	Anesthetic for eye examination, foreign body removal	Sensitivity to ester-type anesthetics; no prolonged use; delays healing at toxic doses	0.5% solution, one to two drops; onset of action 1 min, duration 30 min
	Proparacaine ophthalmic solution	Alcaine® Ophthetic®	Anesthetic for eye examination, foreign body removal		0.5% solution, one to two drops; onset of action 20 s, duration 15 min
Antibiotics	Erythromycin ophthalmic ointment	Ilotycin® AK-Mycin®	Conjunctivitis Do not use for corneal abrasion if a contact lens wearer	Not agent of choice for contact lens wearers	$^1/_2$ in. applied to lower eyelid two to four times a day
	Ciprofloxacin	Ciloxan® Ophthalmic Solution and Ointment	Conjunctivitis, corneal abrasion if a contact lens wearer	—	Solution: one to two drops when awake every 2 h for 2 d; ointment, $^1/_2$ in. applied to lower eyelid three times a day for 2 d
	Tobramycin	Tobrex® Ophthalmic Solution and Ointment	Conjunctivitis, corneal abrasions if a contact lens wearer	One drop per time period is sufficient in most cases	0.3% solution, one to two drops every 4 h; 0.3% ointment, $^1/_2$ in. applied to lower lid two to three times/d
	Gentamicin	Garamycin® Genoptic®	Conjunctivitis, corneal abrasion if a contact lens wearer	One drop per time period is sufficient in most cases	0.3% solution, instill one to two drops every 4 h; 0.3% ointment, $^1/_2$ in. applied to lower lid two to three times/d
	Sulfacetamide sodium	Bleph-10 Ophthalmic Solution 10%®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer or if allergic to sulfa	One to two drops four times a day
	Besifloxacin	Besivance Ophthalmic Suspension®	Conjunctivitis, corneal abrasion if a contact lens wearer	—	One drop three times a day for 7 d
	Levofloxacin	Iquix Ophthalmic Solution® Quixin Ophthalmic Solution®	Conjunctivitis, corneal abrasion if a contact lens wearer	Corneal ulcer	One to two drops every 30 min to 2 h while awake and every 4–6 h at night
	Moxifloxacin hydrochloride	Moxeza Ophthalmic Solution® Vigamox Ophthalmic Solution®	Conjunctivitis, corneal abrasion if a contact lens wearer		One drop twice a day for 7 d

	Ofloxacin	Ocuflox Ophthalmic Solution®	Conjunctivitis, corneal abrasion if a contact lens wearer		Conjunctivitis: one to two drops every 2–4 h for 2 d, then one to two drops four times a day for 5 d. Corneal ulcer: one to two drops every 30 min while awake and one to two drops every 4–6 hours after retiring for 2 d, then one to two drops every hour while awake for 5–7 days, then one to two drops four times a day for 2 d or until treatment completion
	Polymyxin b sulfate, trimethoprim sulfate	Polytrim Ophthalmic Solution®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer	One drop every 3 h
	Gatifloxacin	Zymaxid Ophthalmic Solution®	Conjunctivitis, corneal abrasion if a contact lens wearer		One drop every 2 hrs while awake, up to 8 times/day for 2 days, then one drop 4 times per day for 5 days
Antivirals	Idoxuridine	Dendrid Sterile Ophthalmic Solution®	Herpes simplex keratitis		One drop every hour
	Trifluridine	Viroptic Ophthalmic Solution®	Herpes simplex keratitis		One drop every 2 h
	Ganciclovir	Zirgan Ophthalmic Gel®	Herpes simplex keratitis		One drop five times per day
Antibiotic–steroid combination	Prednisolone acetate, sulfacetamide sodium	Blephamide Ophthalmic Suspension® Brimonidine Tartrate Ophthalmic Solution®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer or if sulfa allergy	Suspension: instill two drops into conjunctival sac every 4 h during the day and at bedtime Ointment: apply ½-in. ribbon into conjunctival sac three to four times a day and two to four times a night
	Dexamethasone, neomycin sulfate, polymyxin b sulfate	Maxitrol Ophthalmic Ointment® Maxitrol Ophthalmic Suspension®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer	Ointment: ½ inch in conjunctival sac(s) up to three to four times a day Suspension: instill one to two drops four to six times a day up to every hour
	Neomycin sulfate, polymyxin b sulfate, prednisolone acetate	Poly-Pred Ophthalmic Suspension®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer	One to two drops every 3–4 h
	Dexamethasone, tobramycin	TobraDex Ophthalmic Ointment® TobraDex Ophthalmic Suspension® TobraDex ST Ophthalmic Suspension®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer	Suspension: one to two drops every 4–6 h ST: one drop every 4–6 h Ointment: ½-in. ribbon three to four times a day
	Loteprednol etabonate, tobramycin	Zylet Ophthalmic Suspension®	Conjunctivitis	Do not use for corneal abrasion if a contact lens wearer	One to two drops every 4–6 h
NSAIDs	Ketorolac	Acular Ophthalmic Solution® Acular LS Ophthalmic Solution® Acular PF Ophthalmic Solution® Acuvail Ophthalmic Solution®	Allergic conjunctivitis, corneal abrasions, UV keratitis		One drop four times a day for 3–4 d
	Bromfenac	Bromday Ophthalmic Solution®	Allergic conjunctivitis, corneal abrasions, UV keratitis		One drop every day
	Nepafenac	Nevanac Ophthalmic Suspension®	Allergic conjunctivitis, corneal abrasions, UV keratitis		One drop three times a day
	Diclofenac sodium	Voltaren Ophthalmic Solution®	Allergic conjunctivitis, corneal abrasions, UV keratitis		One drop four times a day
Mast cell stabilizers	Nedocromil sodium	Alocril Ophthalmic Solution®	Allergic conjunctivitis		One to two drops twice a day
	Pemirolast potassium	Alamast Ophthalmic Solution®	Allergic conjunctivitis		One to two drops four times a day
	Lodoxamide tromethamine	Alomide Ophthalmic Solution®	Allergic conjunctivitis		One to two drops four times a day
	Cromolyn sodium	Cromolyn Sodium Ophthalmic Solution®	Allergic conjunctivitis		One to two drops four to six times a day

(*Continued*)

TABLE 241-2 Ophthalmic Medications Used in the ED (*Continued*)

Type	Generic Name	Trade Name	Indication	Cautions	Usual Dose
Selective H_1 antagonists	Bepotastine besilate	Bepreve Ophthalmic Solution®	Allergic conjunctivitis		One drop two times a day
	Epinastine hydrochloride	Elestat Ophthalmic Solution®	Allergic conjunctivitis		One drop two times a day
	Emedastine difumarate	Emadine Ophthalmic Solution®	Allergic conjunctivitis		One drop up to four times a day
	Alcaftadine	Lastacaft Ophthalmic Solution®	Allergic conjunctivitis		One drop every day
	Azelastine hydrochloride	Optivar Ophthalmic Solution®	Allergic conjunctivitis		One drop two times a day
Combination mast cell stabilizers–H_1 antagonists	Olopatadine hydrochloride	Pataday Ophthalmic Solution® Patanol Ophthalmic Solution®	Allergic conjunctivitis		One drop two times a day
Nonselective β-blocker (may cause asthma)	Levobunolol hydrochloride	Betagan Ophthalmic Solution®	Glaucoma		0.5%: one to two drops once a day; twice a day for more severe or uncontrolled glaucoma 0.25%: one to two drops twice a day
	Timolol hemihydrate	Betimol Ophthalmic Solution®	Glaucoma		One drop 0.25% twice a day; may increase to maximum of one drop 0.5% twice a day
	Timolol maleate	Istalol Ophthalmic Solution® Timoptic Sterile Ophthalmic Solution® Timoptic-XE Sterile Ophthalmic Gel Forming Solution®	Glaucoma		One drop once a day
	Carteolol hydrochloride	Carteolol Hydrochloride Ophthalmic Solution® Ocupress Ophthalmic Solution®	Glaucoma		One drop twice a day
	Metipranolol	OptiPranolol Ophthalmic Solution®	Glaucoma		One drop two times a day
Selective β_1-blocker (safe for COPD or asthma)	Betaxolol hydrochloride	Betaxolol Hydrochloride Ophthalmic Solution® Betoptic S Ophthalmic Suspension®	Glaucoma		One to two drops twice a day
Selective α_2-agonists	Brimonidine tartrate	Alphagan P Ophthalmic Solution® Brimonidine Tartrate Ophthalmic Solution®	Glaucoma		One drop every 8 h
	Apraclonidine hydrochloride	Iopidine 0.5% Ophthalmic Solution® Iopidine Ophthalmic Solution®	Glaucoma		One to two drops three times a day
Combination α_2-agonist–nonselective β-blocker	Brimonidine tartrate, timolol maleate	Combigan Ophthalmic Solution®	Glaucoma		One drop every 12 h
Carbonic anhydrase inhibitors	Brinzolamide	Azopt Ophthalmic Suspension®	Glaucoma		One drop three times a day
	Dorzolamide hydrochloride	Trusopt Sterile Ophthalmic Solution®	Glaucoma		One drop three times a day
Combination carbonic anhydrase inhibitor–selective β-blocker	Dorzolamide hydrochloride, timolol maleate	Cosopt Sterile Ophthalmic Solution®	Glaucoma		One drop every 12 h
Cholinergic agents	Pilocarpine hydrochloride	Isopto Carpine Ophthalmic Solution®	Glaucoma; contraindicated in pupillary block glaucoma		Two drops three to four times a day

Prostaglandin analog	Bimatoprost	Lumigan Ophthalmic Solution®	Glaucoma		One drop once a day
	Travoprost	Travatan Z Ophthalmic Solution®	Glaucoma		One drop once a day
	Latanoprost	Xalatan Ophthalmic Solution®	Glaucoma		One drop once a day
	Loteprednol etabonate	Alrex Ophthalmic Suspension®	Allergic conjunctivitis, uveitis		One drop four times a day
	Difluprednate	Durezol Ophthalmic Emulsion®	Allergic conjunctivitis, uveitis		One drop four times a day
	Fluorometholone acetate	Flarex Ophthalmic Suspension® FML Forte Ophthalmic Suspension® FML Ophthalmic Ointment® FML Ophthalmic Suspension®	Allergic conjunctivitis, uveitis		One to two drops four times a day
	Loteprednol etabonate	Lotemax Ophthalmic Ointment® Lotemax Ophthalmic Suspension®	Allergic conjunctivitis, uveitis		Ointment: ½ in. four times a day Suspension: one to two drops four times a day
	Prednisolone acetate	Omnipred Ophthalmic Suspension® Pred Forte Ophthalmic Suspension® Pred Mild Ophthalmic Suspension®	Allergic conjunctivitis, uveitis		Two drops four times a day
	Rimexolone	Vexol 1% Ophthalmic Suspension®	Allergic conjunctivitis, uveitis		One to two drops every hour while awake

Note: Blue-eyed individuals are sensitive to mydriatics and cycloplegics and tend to have a longer duration of action, whereas brown-eyed individuals may require a double dose for adequate mydriasis.

Abbreviations: COPD = chronic obstructive pulmonary disease; UV = ultraviolet.

TABLE 241-3 Differential Diagnosis of the Red Eye

Diagnosis	Pain	Itching	Photophobia	Systemic Symptoms	Visual Acuity	Discharge	Injection	Cornea	Pupils	IOP
Chalazion	Mild-moderate lid	No	No	No	Normal	No	Minimal localized	Normal	Normal	Normal
Hordeolum	Mild-moderate lid	No	No	No	Normal	No	Minimal localized	Normal	Normal	Normal
Blepharitis	Mild, foreign body sensation	Yes	Yes	No	Normal	Morning crusting, tearing	Diffuse	Normal	Normal	Normal
Dacryocystitis	Mild-moderate medial canthus	No	No	Fever if severe	Normal	No	Localized	Normal	Normal	Normal
Ectropion	Irritation	No	No	No	Normal	Watery	Lid margin and diffuse	Normal	Normal	Normal
Corneal abrasion	Yes	No	No unless associated iritis (after several hours)	No	Normal unless central or with associated iritis	Watery	Diffuse	Visible abrasion	Normal or constricted with associated iritis	Normal
Ultraviolet keratitis	Severe	No	No unless associated iritis (after several hours)	No	Decreased	Watery	Diffuse	Punctate lesions	Normal or constricted with associated iritis	Normal
Superficial keratitis	Mild	No	No	No	Normal	Watery	Diffuse	Punctate lesions	Normal	Normal
Corneal ulcer	Moderate	No	No	No	No unless central or with associated iritis	Watery	Diffuse	Visible ulcer	Normal	Normal
Corneal foreign body	Moderate	No	No	No	Normal unless central	Watery	Diffuse	Visible foreign body	Normal	Normal
Chemical burn	Moderate-severe	No	No	No	Normal unless central	Watery	Diffuse—none with severe alkaline burn	Cloudy if severe	Normal	Normal
Bacterial conjunctivitis	None or irritation	No	No	No	Normal	Purulent	Diffuse bulbar and palpebral	Normal, punctate lesions if associated keratitis	Normal	Normal
Viral conjunctivitis	None or irritation, severe with EKC	No	No	Occasional URI symptoms, fever with EKC	Normal	Watery	Diffuse bulbar and palpebral	Normal, punctate lesions if associated keratitis	Normal	Normal
Allergic conjunctivitis	None	Yes	No	Sneezing, rhinorrhea	Normal	Watery	Diffuse bulbar and palpebral	Normal	Normal	Normal
Stevens-Johnson syndrome	Foreign body sensation, burning	Yes	Yes	Fever, tachycardia, hypotension, skin and mucous membranes involved	Decreased	Watery	Diffuse	Punctate lesions, corneal ulcer, neovascularization, hazy, perforation	—	—
Orbital cellulitis	Pain with eye movement	No	No	Fever	Normal, decreased late	No	Yes	Normal	Normal	Occasionally increased
Preseptal cellulitis	Mild—no pain with eye movement	No	No	Fever	Normal	No	Yes	Normal	Normal	Normal
Episcleritis	Mild	No	No	Usually none; occasional rheumatologic symptoms	Normal	Watery	Focal	Normal	Normal	Normal

(*Continued*)

TABLE 241-3 Differential Diagnosis of the Red Eye (*Continued*)

Diagnosis	Pain	Itching	Photophobia	Systemic Symptoms	Visual Acuity	Discharge	Injection	Cornea	Pupils	IOP
Scleritis	Severe, tender to palpation	No	No	Usually none; occasional rheumatologic symptoms	Decreased with advanced disease	Watery	Diffuse, occasionally violaceous color	Normal	Normal	Normal, may be increased
Subconjunctival hemorrhage	None	No	No	No	Normal	No	No	Normal	Normal	Normal
Iritis/uveitis	Yes	No	Yes	Occasional rheumatologic or GI symptoms	Decreased	Watery	Perilimbal (ciliary) flush	Normal, flare and cells in anterior chamber	Constricted, poorly reactive	Usually normal, may be low
Acute angle-closure glaucoma	Severe	No	No	Headache, nausea, vomiting	Decreased	Watery	Diffuse	Cloudy or hazy	Midpoint, poorly reactive	Increased
Endophthalmitis	Mild-moderate "ache"	No	Yes	Fever	Decreased	Purulent if present	Diffuse	Hazy, flare and cells anterior chamber, hypopyon	—	—

Abbreviations: EKC = epidemic keratoconjunctivitis; IOP = intraocular pressure; URI = upper respiratory infection.

Upper respiratory symptoms, low-grade fever, redness and swelling of the eyelid, and excessive tearing (epiphora) are signs and symptoms of preseptal cellulitis. **The eye itself is not involved, and visual acuity and pupillary reaction are maintained, and full painless ocular motility is preserved.** Exam may require lid retractors to uncover a normal globe.

CT scan of the orbit is not necessary for uncomplicated cases of preseptal cellulitis; however, when there is decreased ocular motility or other signs of orbital involvement, or when examination is unreliable, obtain a CT scan of the orbits with contrast. MRI is also an option.

The nontoxic adult patient and older child with mild preseptal cellulitis may be managed as outpatients with oral antibiotics (amoxicillin/clavulanic acid or a first-generation cephalosporin), hot packs, and close follow-up in 24 to 48 hours. Obtain ophthalmology consultation and consider admission with severe preseptal cellulitis or when orbital cellulitis cannot be ruled out (see Chapter 122, "Eye Emergencies in Infants and Children").

POSTSEPTAL OR ORBITAL CELLULITIS

Postseptal cellulitis occurs most frequently from the spread of paranasal sinusitis. The ethmoid sinus is most frequently implicated, probably due to perforation of the thin lamina papyracea. Trauma, intraorbital foreign body, spread of periorbital skin infection, seeding from bacteremia, and ocular surgery are also predisposing factors. The infection is often polymicrobial, with *S. aureus*, *Streptococcus pneumoniae*, and anaerobes being most common; however, *H. influenzae* should be considered in unimmunized young children and mucormycosis in diabetics and immunocompromised patients.[3]

TABLE 241-4 Differential Diagnosis of Preseptal and Postseptal Cellulitis

- Preseptal cellulitis
- Postseptal cellulitis
- Subperiosteal abscess
- Orbital abscess
- Cavernous sinus thrombosis
- Dacryoadenitis
- Dacryocystitis
- Hordeolum
- Bacterial and viral conjunctivitis
- Contact dermatitis
- Herpes zoster
- Herpes simplex

Orbital cellulitis presents with gradual onset of upper respiratory symptoms, including rhinitis, facial pressure, and fever. Physical exam may demonstrate pain with eye movement, limitation of extraocular muscle movement, chemosis, proptosis, abnormal pupillary response, and decreased visual acuity. Headache and fever in association with **deficits of cranial nerves III, IV, or VI suggest cavernous sinus thrombosis.**[4]

Consult ophthalmology immediately for patients with clear clinical or CT evidence of postseptal cellulitis. Postseptal cellulitis may lead to vision loss and requires an aggressive approach with hospitalization and institution of IV antibiotics (see Chapter 122, "Eye Emergencies in Infants and Children"). Antibiotics should be broad spectrum with both aerobic (including coverage for methicillin-resistant *S. aureus*) and anaerobic coverage. Choices include vancomycin plus a third-generation cephalosporin, piperacillin-tazobactam, ticarcillin-clavulanate, imipenem, or meropenem.[5] Metronidazole or clindamycin is added for anaerobic coverage.[5] Adjuvant therapy includes a topical nasal decongestant such as oxymetazoline. Consider emergent **lateral canthotomy** if the intraocular pressure is elevated or an optic neuropathy is present.[5] Patients with orbital abscess require operative drainage and debridement in addition to antibiotics. Complications include cavernous sinus thrombosis, frontal bone osteomyelitis, meningitis, subdural empyema, epidural abscess, and brain abscess that should be evident on CT or MRI scan.

LIDS

STYE (EXTERNAL HORDEOLUM)

A **stye** is an acute bacterial infection (usually *Staphylococcus*) of the follicle of an eyelash and adjacent sebaceous glands (Zeis) or sweat glands (Moll). It is located at the lash line and has the appearance of a small pustule at the margin of the eyelid (**Figure 241-24**). An **internal hordeolum** is an acute bacterial infection of the meibomian glands

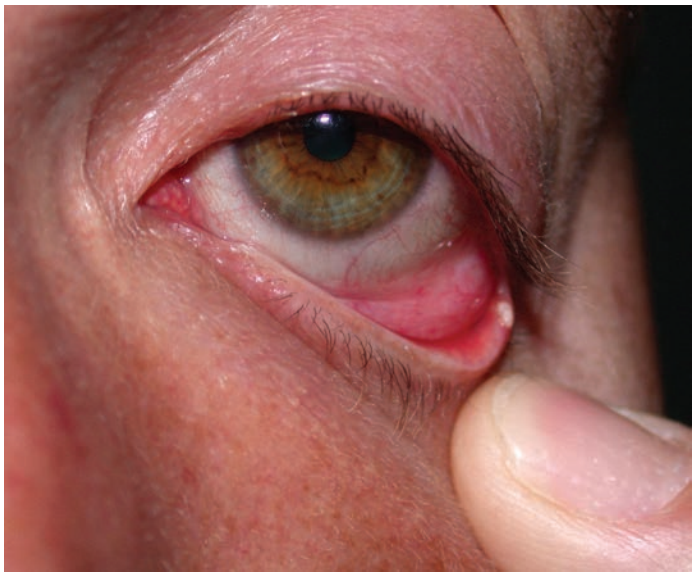

FIGURE 241-24. External hordeolum. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

associated with the eyelashes. Signs and symptoms are similar to a stye except that the pustule occurs on the inner surface of the tarsal plate. Signs and symptoms include pain, edema, and erythema of the eyelid. Warm compresses and erythromycin ophthalmic ointment twice daily for 7 to 10 days are usually sufficient treatment. Removal of the offending eyelash could be considered. Systemic antibiotics may be necessary if there is significant surrounding cellulitis. Should incision and drainage be considered, refer to an ophthalmologist.[6]

CHALAZION

A **chalazion** is an acute or chronic inflammation of the eyelid secondary to blockage of one of the meibomian or Zeis oil glands in the tarsal plate (**Figure 241-25**). The condition tends to be subacute to chronic and is associated with a (usually) painless lump that develops in the lid or at the lid margin, occasionally with mild erythema. Clinical differentiation of an acute chalazion from an internal hordeolum may be impossible, but treatment is the same. Treatment of chronic or recurrent chalazia may require injection of corticosteroids into the lesion or incision and curettage/drainage depending on the size.[6] Refer to an ophthalmologist in 1 to 2 weeks.



FIGURE 241-25. Chalazion. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

BLEPHARITIS

Blepharitis is a common cause of prolonged red eye due to inflammation of the eyelash follicles along the edge of the eyelid. The most common cause is overgrowth of *S. epidermidis*, and the inflammation is largely a reaction to the deltalike toxin produced by the bacteria. The disorder is associated with seborrheic dermatitis, atopic dermatitis, and occasionally eyelash infestation with lice or infection with *S. aureus*. Typical symptoms include conjunctival injection; crusting, swollen, pruritic eyelids; and occasional complaint of eye pain. It is most commonly treated with careful daily cleansing of the edges of the eyelids and eyelashes. In severe cases, antibiotic drops or ointment at night may be required.[6]

CONJUNCTIVITIS

Conjunctivitis is an inflammatory condition of the conjunctiva and is a common cause of the red eye. It is usually viral in etiology and is a benign self-limited condition. **The task is to sort out the occasional case of serious bacterial infection or corneal herpetic involvement that may result in vision loss without aggressive treatment.** Causes of conjunctivitis are viral, bacterial (including gonococcal and chlamydial), parasitic, or fungal infections and allergic, toxic, or chemical irritation. **Keratoconjunctivitis** is the term used to indicate corneal involvement, usually in the form of punctate ulcerations.

Bacterial Conjunctivitis Symptoms of **bacterial conjunctivitis** are painless, unilateral, or bilateral mucopurulent discharge (**Figure 241-26**), frequently causing adherence of the eyelids on awakening. The conjunctiva is injected, and the cornea is clear *without* fluorescein staining. Chemosis (edema of the conjunctiva) is common, and preauricular lymphadenopathy is usually absent, except in gonococcal infections. Typical pathogens



FIGURE 241-26. Bacterial conjunctivitis. Note the mucopurulent discharge, conjunctival injection, and lid edema in a pediatric patient with *Haemophilus influenzae* conjunctivitis. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]



FIGURE 241-27. Epidemic keratoconjunctivitis (EKC). Diffuse bulbar conjunctival injection and inferior palpebral papillae as seen in EKC. The erythema is usually much more intense than in this photo. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

are *Staphylococcus* and *Streptococcus* species. Perform fluorescein stain of the cornea (especially in infants) to avoid missing a corneal abrasion, ulcer, or herpetic dendrite. Consider culture and sensitivity of the discharge in severe cases. Cases are frequently self-limited, but antibiotic treatment shortens course of symptoms.[7] Trimethoprim–polymyxin B is very effective and avoids potential allergies to sulfa and neomycin preparations. Wearers of soft contact lenses should be treated with a fluoroquinolone (besifloxacin, gatifloxacin, levofloxacin, moxifloxacin, or ofloxacin) or aminoglycoside (tobramycin) to treat *Pseudomonas*.[8] Gentamicin is seldom used because of the high incidence of ocular irritation.

Gonococcal conjunctivitis is a cause of ophthalmia neonatorum, and **chlamydial conjunctivitis** is also a disease of the newborn (see Chapter 122, "Eye Emergencies in Infants and Children," for discussion of ophthalmia neonatorum and chlamydial conjunctivitis).

Viral Conjunctivitis The most common cause of **viral conjunctivitis** is adenovirus. **Epidemic keratoconjunctivitis** (**Figure 241-27**) is a more severe type of adenovirus infection that is highly contagious and tends to occur in epidemics. Cough, high fever, malaise, and myalgias may precede epidemic keratoconjunctivitis. Symptoms are marked eye redness, photophobia, foreign body sensation, and tearing. Physical examination findings are similar to viral conjunctivitis, except they are more severe. Several systemic viral diseases, such as measles, influenza, and mumps, may also cause conjunctival injection. Viral keratoconjunctivitis may be caused by **herpes simplex** and **herpes zoster** (see "Cornea" section later in this chapter).

An upper respiratory infection may precede viral conjunctivitis. Symptoms include a complaint of "red eye" and mild to moderate watery discharge. There is no eye pain unless there is some degree of keratitis. Generally, one eye will be involved initially, with the other eye becoming involved within days. Physical examination reveals unilateral or bilateral conjunctival injection, occasional chemosis and small subconjunctival hemorrhages, and preauricular lymphadenopathy. Slit lamp examination demonstrates follicles (small, regular, translucent bumps) on the inferior palpebral conjunctiva (Figure 241-27). Punctate fluorescein staining represents keratitis (**Figure 241-28**). Make sure to examine the cornea with fluorescein to avoid missing a herpetic dendrite.

Treatment of viral conjunctivitis consists of cool compresses; ocular decongestants such as Naphcon-A®, one drop three times daily as needed for redness and conjunctival congestion; and artificial tears five or six times a day. Viral conjunctivitis can take 1 to 3 weeks to run its course and is very contagious. Instruct the patient to wash hands frequently and use separate towels. The examiner should wear gloves to avoid self-contamination, and the slit lamp, exam table, and exam chair should be disinfected after patient contact. If, after a history and physical examination, it is still uncertain if the conjunctivitis is viral or bacterial, prescribe ocular antibiotics until the patient is reexamined by an ophthalmologist.

Allergic Conjunctivitis Allergens can cause watery discharge, redness, and itching. Physical findings may include erythematous swollen eyelids and injected and edematous conjunctiva with papillae (irregular

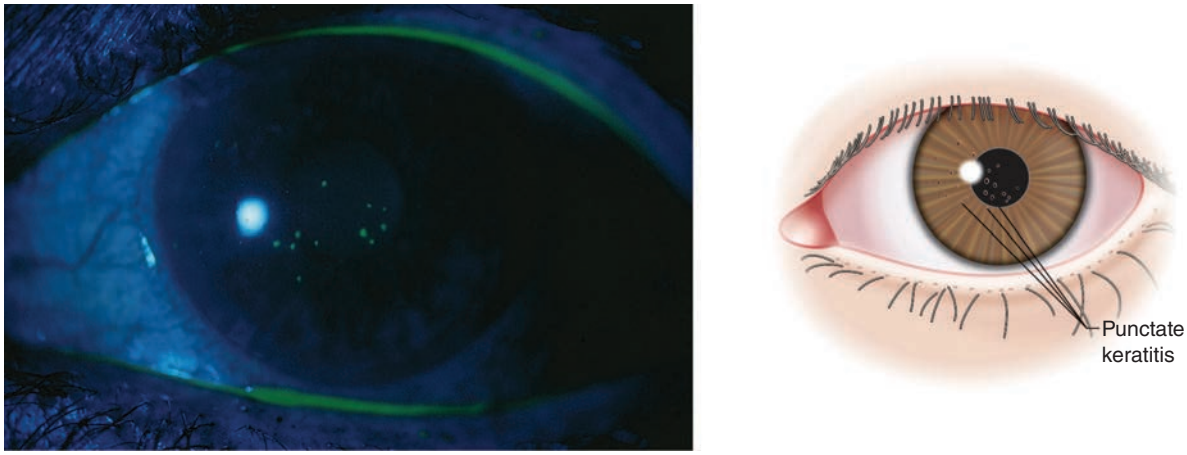

FIGURE 241-28. Fluorescein stain demonstrating punctate staining as seen with epithelial keratitis in epidemic keratoconjunctivitis. The keratitis is usually much more widespread than demonstrated here. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]



FIGURE 241-29. Prominent chemosis may be seen in allergic conjunctivitis. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

mounds of tissue with a central vascular tuft) on the inferior conjunctival fornix (**Figure 241-29**). Try to identify and eliminate the offending allergen. Treatment is cool compresses four times daily and topical drops, depending on the severity of symptoms. Mild symptoms may be treated with artificial tears alone. Moderate symptoms may require a topical antihistamine/decongestant, mast cell stabilizers, or NSAIDs. Severe symptoms may justify the use of topical steroids. However, we generally recommend against the use of ocular steroids by nonophthalmologists because occult herpetic infection is always a possibility (see following section on herpes simplex virus infection of the cornea). **Should ocular steroids be chosen as a treatment option, consult an ophthalmologist first.**

SUBCONJUNCTIVAL HEMORRHAGE

The fragile conjunctival vessels can rupture from trauma, sudden increased venous pressure related to Valsalva maneuvers (sneezing, coughing, vomiting, straining), hypertension, or spontaneously (**Figure 241-30**). The eye examination is normal other than the presence of the subconjunctival hemorrhage. Reassurance is the only treatment necessary, and the hemorrhage usually resolves within 2 weeks. For multiple recurrent episodes, coagulation studies and further investigation are warranted.

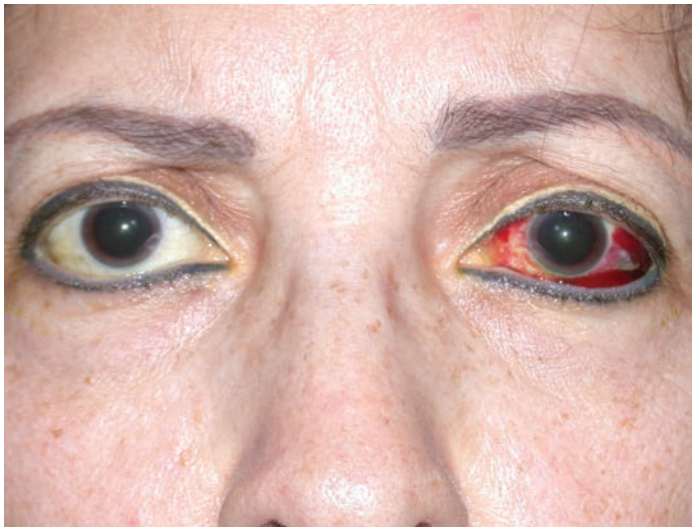

FIGURE 241-30. Spontaneous subconjunctival hemorrhage. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

CORNEA

HERPES SIMPLEX KERATOCONJUNCTIVITIS

Herpes simplex virus can affect the eyelids, conjunctiva, and cornea. The patient may give a history of oral or genital herpes infection and complain of photophobia, pain (which may be mild), eye redness, and decreased vision. The eyelid may have the typical herpetic vesicular eruptions. The infection tends to be unilateral with a palpable preauricular node. The conjunctiva can be injected, but ocular herpes simplex frequently presents with only corneal findings on physical examination. The dendrite of herpes keratitis is an epithelial defect that can be seen with fluorescein staining and classically has a linear branching pattern with terminal bulbs (**Figure 241-31**), or may be a "geographic ulcer," which is an amoeba-shaped ulceration with dendrites at the edge. **Herpetic infection may be very difficult to diagnose**, as infection may present as involvement of the cornea with a neurotrophic ulceration, which is a smooth-edged ulcer over an area of underlying stromal disease; as stromal edema and/or white infiltrates with intact epithelium and an associated mild iritis with keratitic precipitates; or as an isolated uveitis, without epithelial or stromal involvement and with an elevated intraocular pressure. Corneal sensation may be decreased and should be checked before instillation of anesthetic drops.

Herpes simplex keratitis can progress to corneal scarring and requires prompt treatment with topical antiviral agents. **An initial outbreak of herpes simplex virus involving the lids is treated with an oral acyclovir derivative such as acyclovir (Zovirax®), 500 milligrams five times daily, or famciclovir (Famvir®), 500 milligrams three times daily.[9] For conjunctival involvement, prescribe topical trifluridine (Viroptic®),[9] one drop nine times a day.** Idoxuridine (Dendrid®), one drop every 1 hour during the day and every 2 hours at night, can be substituted for those who are allergic to trifluridine. Erythromycin ophthalmic ointment can be added to prevent secondary infection. Do not prescribe topical steroids, and refer patients to an ophthalmologist in 24 to 48 hours.

HERPES ZOSTER OPHTHALMICUS

Herpes zoster ophthalmicus is shingles involving the first division (V1) of the trigeminal nerve distribution with ocular involvement. The rash usually does not cross the midline and involves only the upper eyelid, although rarely, the cheek (V2) and mandible (V3) may be affected. **Involvement of the nasociliary nerve is associated with cutaneous lesions on the tip of the nose (Hutchinson sign) and predicts a high likelihood of ocular involvement.** Symptoms that may precede the rash are pain and paresthesias in a dermatomal



FIGURE 241-31. Herpes simplex corneal dendrite in an infant seen with fluorescein staining. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

distribution; fever, headache, and malaise; and red eye, blurred vision, and eye pain/photophobia. Eye involvement may take the form of epithelial keratitis, stromal keratitis, uveitis, retinitis, and choroiditis. Optic neuritis and other cranial nerve palsies may occur, as well as elevated intraocular pressure. The cornea can have a pseudodendrite, which is a poorly staining mucous plaque with no epithelial erosion (unlike herpes simplex virus, which has a true dendrite with epithelial erosion and staining). The anterior chamber on slit lamp examination can show the cells and flare of iritis. Consider the possibility of associated immunocompromise in patients <40 years old.

Skin involvement is treated with cool compresses, and patients presenting with a rash for <1 week should be treated with oral antiviral medications for 7 to 10 days. Choices include acyclovir, 800 milligrams five times a day; famciclovir, 500 milligrams three times a day; or valacyclovir, 1000 milligrams three times a day.[10] Treat cutaneous lesions with bacitracin or erythromycin ointment to prevent secondary bacterial infection. Treat conjunctivitis with erythromycin ophthalmic ointment twice a day. Treat iritis with topical steroids such as prednisolone acetate 1%, one drop four to five times a day, but consultation with an ophthalmologist is recommended first. Consider topical cycloplegic agents (cyclopentolate 1%, one drop three times daily) for patients with significant pain. Consider admission and IV acyclovir when the orbit, optic nerve, or cranial nerves are involved, or if the patient is immunocompromised. See Chapter 250, "Skin Disorders: Face and Scalp," for additional discussion.

CORNEAL ULCER

A **corneal ulcer** is a serious infection involving multiple layers of the cornea and develops secondary to breaks in the epithelial barrier, so that infectious agents invade the underlying corneal stroma. The initial disruption of the epithelial layer can be due to desquamation, trauma, or direct microbial invasion. Exposure keratitis from incomplete lid closure secondary to **Bell's palsy** can cause corneal desiccation and sloughing of the epithelium, allowing bacteria to gain access to the underlying stroma and create an ulcer. Trauma can also breach the epithelium and inoculate the cornea. *S. pneumoniae* and *S. aureus* are common causes of corneal ulceration. Contact lens users can develop *Pseudomonas* infection (**Table 241-5**). Wearing of soft contact lenses is a very common cause of corneal ulcers, and the incidence increases dramatically in those who use extended-wear lenses and wearers who sleep with them in place. Fungi and viruses have also become a more common cause of corneal ulcer due to the widespread use of both topical and systemic immunosuppressant medications.

Collect a history of predisposing factors including the use of contact lenses, previous ocular surgery or injury, recent trauma, and presence or history of genital herpes, topical or systemic steroids, or other immunosuppressants. Redness and swelling of lids and conjunctivae, discharge from the eye, ocular pain or foreign body sensation, photophobia, and blurred vision are common complaints. Visual acuity is decreased if the ulcer is located in the central visual axis or if uveal tract inflammation is present. The eyelids and conjunctiva may be erythematous with a mucopurulent discharge. Associated iritis may cause a miotic pupil and consensual photophobia due to ciliary spasm. Examination of the cornea reveals a round or irregular ulcer with a white, hazy base extending into the underlying stroma due to WBC infiltration, or with heaped-up edges (**Figure 241-32**). Slit lamp examination reveals flare and cells from iritis and occasionally a hypopyon.

TABLE 241-5 Causative Organisms in Corneal Ulcer

Bacteria
- *Pseudomonas aeruginosa*
- *Streptococcus pneumoniae*
- *Staphylococcus* species
- *Moraxella* species

Viruses
- Herpes simplex
- Varicella zoster

Fungi
- *Candida*
- *Aspergillus*
- *Penicillium*
- *Cephalosporium (Acremonium)*

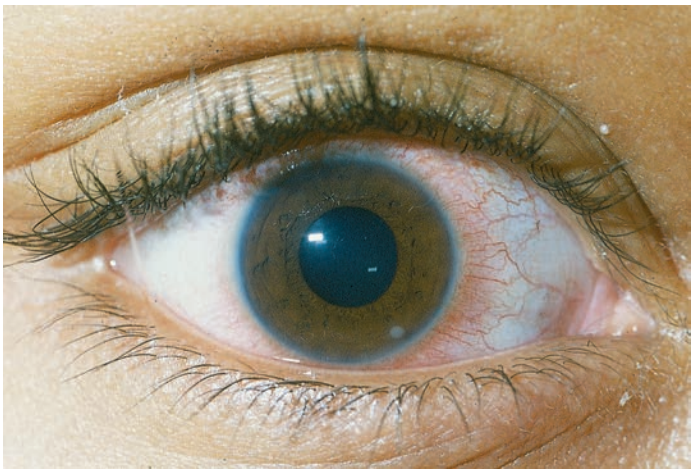

FIGURE 241-32. Corneal ulcer is seen at 5 o'clock. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

The diagnosis is clinical. The ophthalmologist typically scrapes the center of the ulcer to culture the offending organism. Table 241-5 lists the differential diagnosis of causative organisms.

Treat corneal ulcers aggressively with topical antibiotics. Emergent ophthalmologic consultation for culture of the ulcer and institution of appropriate antibiotics should be considered. Once cultures are obtained, topical antibiotics are started. A fluoroquinolone such as ciprofloxacin (Ciloxan®) or ofloxacin (Ocuflox®), one drop every hour in the affected eye, is the current recommended treatment. If the suspicion is high for a fungal infection, a topical antifungal medication (e.g., natamycin, amphotericin B, or fluconazole)[11] should be given at the direction of an ophthalmologist who may consider intrastromal injections of antifungal medication.[12]

Cycloplegic drops such as cyclopentolate 1% are often used due to pain from accompanying iritis. Topical steroids are relatively contraindicated in viral infections but may decrease the incidence of scarring and perforation. Steroid eye drops should not be initiated by the emergency physician unless advised to do so by the ophthalmologist. **Do not patch the eye because of the risk of *Pseudomonas* infection, which can cause rapid, aggressive ulceration with corneal melting and perforation.** Refer patients with corneal ulcers to an ophthalmologist to be seen within 12 to 24 hours. Complications of corneal ulcers include corneal scarring, corneal perforation, development of anterior and posterior synechiae, glaucoma, and cataracts.

ULTRAVIOLET KERATITIS (PHOTOKERATITIS)

Intense light in the ultraviolet range from any source can cause death of corneal epithelial cells. Classically described as "snow blindness," when due to reflected ultraviolet light from the sun, ultraviolet **keratitis** is also caused by unprotected exposure to arc welders ("*welder's flash*"), tanning beds, or industrial ultraviolet lighting. Ultraviolet keratitis may occur if protective glasses are not applied tightly to the face, allowing light to hit the cornea obliquely. Effects are cumulative, so multiple short exposures are the same as one long exposure. Corneal cells do not die immediately, so symptoms develop after a delay of up to 6 to 12 hours with slow onset of foreign body sensation and mild photophobia, progressing to severe pain and photophobia. Patients sometimes are awakened from sleep after midnight by pain. Physical examination may reveal blepharospasm, conjunctival injection, and prominent tearing. Topical anesthetic drops are often required to complete the eye examination. Slit lamp examination reveals diffuse punctate corneal edema, and instillation of

fluorescein reveals diffuse punctate corneal abrasion-like lesions. Treatment includes oral analgesics and topical antibiotics (erythromycin) to provide lubrication.[13] If photophobia is prominent, cycloplegics such as cyclopentolate can be used (see Table 241-2). Patching the eye does not speed healing.[14] Healing occurs in 24 to 36 hours. Follow-up with ophthalmology is recommended for moderate to severe cases.

UVEAL TRACT

UVEITIS/IRITIS

Iritis is inflammation of the anterior segment of the uveal tract (**anterior uveitis**). Systemic inflammatory diseases are the most common causes in the United States[15]; infections, such as tuberculosis, are most common in Asia (**Table 241-6**).[16] Iritis is not a true ocular emergency but does require prompt follow-up by an ophthalmologist. Irritation of the ciliary nerves and ciliary muscle spasm cause the pain of iritis. Photophobia is often marked. Keratitic precipitates are deposits of inflammatory cells on the corneal endothelium. A proteinaceous transudate from uveal vessels occurs in the anterior chamber and causes flare seen with the slit lamp. WBCs released from the uveal vessels may be seen in the anterior chamber with the slit lamp and are termed *cells* (as in "flare and cells"). Cells appear as snowflakes in a headlight beam at night.

Clinical Features and Diagnosis The patient will complain of unilateral pain, although the pain may be bilateral with systemic disease. There may be complaints of conjunctival injection, photophobia, and decreased vision. There is usually no discharge. Complaints of systemic symptoms, including arthritis, urethritis, and recurrent GI symptoms, are common when the cause is systemic inflammatory disease. Collect past medical history to include exposure to tuberculosis, history of genital herpes, or history of previous similar symptoms, and the associated diagnosis. Ask about recent trauma or exposure to welding without protective goggles.

Inspection of the eye may reveal a perilimbal flush (injection is greatest around the limbus) or diffuse conjunctival injection without mucopurulent discharge. Photophobia is usually present. **Consensual photophobia (shining light on the unaffected eye causes pain in the affected eye) is highly suggestive of iritis.** The pupil is usually miotic and poorly reactive. Visual acuity may be decreased with severe inflammation and clouding of the aqueous humor. Slit lamp examination will reveal flare and cells in the anterior chamber, culminating in a hypopyon with severe disease. Intraocular pressure may be decreased if the ciliary body is involved secondary to decreased production of aqueous humor. Fluorescein staining of the cornea may show abrasions, ulcerations, or dendritic lesions.

The diagnosis of iritis is based on the typical history and the finding of flare and cells in the anterior chamber on slit lamp examination.

Treatment The treatment of iritis depends on the underlying cause. If infection is suspected based on systemic symptoms, testing should be directed at identifying the infection, and ophthalmology should be consulted for management.[17] If an acute or chronic inflammatory condition is suspected, treatment can be directed to the eye with referral to ophthalmology. Blocking the pupillary sphincter and ciliary body with a long-acting cycloplegic agent, such as homatropine (duration 2 to 4 days) or tropicamide (duration 24 hours), will decrease pain.[17] Refer the patient to an ophthalmologist in 24 to 48 hours for topical corticosteroids and further management.[18]

TABLE 241-6 Differential Diagnosis of Iritis (Anterior Uveitis)

Systemic diseases
- Juvenile rheumatoid arthritis
- Ankylosing spondylitis
- Ulcerative colitis
- Reiter syndrome
- Behçet's syndrome
- Sarcoidosis

Infectious
- Tuberculosis
- Lyme disease
- Herpes simplex
- Toxoplasmosis
- Varicella zoster
- Syphilis
- Adenovirus

Malignancies
- Leukemia
- Lymphoma
- Malignant melanoma

Trauma/environmental
- Corneal foreign body
- Posttraumatic (blunt trauma)
- Ultraviolet keratitis

VITREOUS HUMOR

ENDOPHTHALMITIS

Endophthalmitis is inflammation (usually infectious) of the aqueous or vitreous humor that frequently leads to loss of vision. The most frequent cause is postsurgical, followed by penetrating ocular injuries and, rarely, hematogenous spread. History may include ocular surgery, hammering with steel, working with high-speed machinery such as grinders or weed whackers, or ocular trauma. Symptoms may include headache, eye pain, photophobia, vision loss, and ocular discharge. Physical examination may reveal erythema and swelling of the lids, conjunctival and scleral injection, chemosis, hypopyon, and evidence of uveitis. If suspected, immediate ophthalmologic consultation is required.[8] Treatment may include aspiration of the vitreous or pars plana vitrectomy and administration of intravitreal antibiotics and steroids, in addition to systemic antibiotics. Admission is required except for postoperative cases.

VITREOUS DETACHMENT AND HEMORRHAGE

The vitreous is avascular and attached firmly to the anterior eye at the ora serrata, posteriorly at the optic nerve head, and along the major retinal vessels. Liquefaction of the vitreous can cause detachment from the retina, with or without accompanying hemorrhage. Symptoms are sudden onset of floaters, especially with eye movement. Traction at vascular areas due to trauma or pathologic neovascularization can cause vitreous hemorrhage. The most common causes of vitreous hemorrhage are proliferative diabetic retinopathy, posterior vitreous detachment in the elderly, and ocular trauma such as shaken baby syndrome in infants. An unusual cause is subhyaloid hemorrhage associated with subarachnoid hemorrhage. **History includes sudden painless vision loss and sudden appearance of black spots, cobwebs, or generalized unilateral hazy vision.** Past medical history may include diabetes or sickle cell disease. Examination of the retina of the affected eye may be impossible due to the hemorrhage. Examination of the contralateral retina may give clues to the diagnosis. Important differential diagnoses include sickle cell disease, diabetic retinopathy, retinal detachment, central retinal vein occlusion, subarachnoid hemorrhage, and lupus erythematosus. Consult ophthalmology if the diagnosis is suspected.[19] Check the INR of patients receiving warfarin (Coumadin®) and withhold antiplatelet therapy. Ocular US can rule out retinal detachment (see later section on US).

TRAUMA TO THE EYE

CONJUNCTIVAL ABRASION, LACERATION, AND FOREIGN BODY

The conjunctiva has less innervation than the cornea, so **conjunctival abrasions** are far less symptomatic than corneal abrasions. The patient may complain of a scratchy foreign body sensation, mild pain, tearing, and, rarely, photophobia. Vision should not be affected unless there is a full-thickness conjunctival laceration with globe penetration. Physical

examination may reveal mild conjunctival injection or subconjunctival hemorrhage. A conjunctival abrasion is seen with fluorescein staining.

Conjunctival lacerations may bleed, the edges of the bulbar conjunctiva may retract with underlying sclera visible to the naked eye, and fluorescein stain may pool in the defect. Perform the Seidel test to exclude globe perforation. **The Seidel test can be negative if a full-thickness laceration is small or has spontaneously closed.** Inspect the conjunctiva for a foreign body. Conjunctival foreign bodies usually can be removed with a moistened, cotton-tipped applicator after anesthetizing the eye with a topical anesthetic. Evert the upper eyelid and inspect under the highest magnification available to avoid missing any additional foreign bodies. Frequently, small wooden particles such as sawdust will blend into the conjunctiva when moistened by the tears and be difficult to find without slit lamp magnification.

Superficial conjunctival abrasions and lacerations without any other associated ocular injury only require erythromycin ophthalmic ointment 0.5% four times a day for 2 to 3 days or no treatment if very small. Suturing of lacerations is almost never required. Any suspicion of globe laceration requires immediate ophthalmologic referral.

CORNEAL ABRASION, LACERATION, AND FOREIGN BODY

The corneal epithelium is fragile and easily damaged. It is richly innervated and therefore very painful when injury occurs. Corneal epithelium regenerates quickly, so healing time for abrasions is short, usually within 24 to 48 hours. Intact corneal epithelium is resistant to infection, but damaged epithelium is a portal of entry for bacteria, viruses, and fungi. Most abrasions not treated immediately will develop an associated inflammatory iritis.

CORNEAL ABRASION

Abrasions may be caused by contact lens wear, fingernails, makeup brushes, and foreign objects blown into eyes while driving or on windy days or that drop into the eye while working overhead (construction) or under a car (mechanics). Injury to the cornea causes intense pain that may be delayed several hours after the inciting event. Initial symptoms are a foreign body sensation, photophobia, and tearing. Ask about the work environment and the mechanism of injury if known, because corneal abrasions sustained using high-speed machinery, such as grinders, lawn mowers, or weed whackers, and hammering metal against metal are associated with corneal laceration and perforation of the globe.

Clinical Features Inspection of the eye may reveal conjunctival injection, tearing, and lid swelling. Blepharospasm may occur with severe pain, requiring a topical anesthetic to accomplish the examination and obtain the visual acuity. Relief of pain with topical anesthesia is virtually diagnostic of corneal abrasion. Photophobia may be evident when shining a light into the affected or the opposite eye. Decreased visual acuity may occur if the abrasion is in the central visual axis or if there is an associated iritis, but otherwise, vision should be normal. The corneal abrasion is often visible to the naked eye as an irregular area of light reflection off the cornea.

Diagnosis Slit lamp examination may show flare and cells from iritis if the abrasion is large and >24 hours old, but there is no corneal infiltrate. Examine the entire thickness of the cornea for full-thickness laceration. The Seidel test should be negative. The abrasion usually appears as a superficial, irregular corneal defect appearing bright green under the cobalt blue light after instillation of fluorescein (**Figure 241-33**). A series of small, fine-lined vertical corneal abrasions seen with fluorescein staining suggests the presence of a foreign body embedded in the tarsal conjunctiva of the upper lid. Multiple linear corneal abrasions or punctate keratitis also suggests a retained foreign body under the upper lid.

Some slit lamps (Haag-Streit) have a measuring dial attached to the mechanism that varies the length of the slit beam. If your slit lamp is equipped with this feature, you can vary the length of the slit beam on the cornea until it corresponds to the length or width of the abrasion. The reading on the wheel equals the length of the slit beam in millimeters. This additional feature allows you to document the dimensions of the abrasion precisely, thereby enabling subsequent examiners to evaluate the wound's healing response objectively.

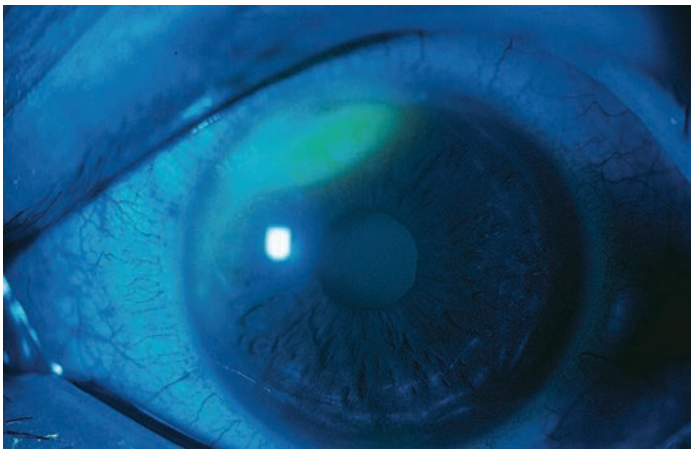

FIGURE 241-33. Corneal abrasion. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

Treatment Because the majority of corneal abrasions heal spontaneously, treatment is aimed at relieving pain and preventing infection. Topical NSAIDs such as ketorolac and diclofenac help to relieve pain, but cost more and offer little advantage over oral NSAIDs.[20,21] Topical tetracaine 1 drop hourly while awake, limited to 24 hours, has been advocated,[22] with no complications found at 24 hours in one randomized controlled trial.[23] However, pain scores were not improved compared to placebo,[23] and significant safety issues have been raised by ophthalmologists regarding misdiagnosis of more serious conditions and delayed follow-up.[24-26] The protective blink reflex is obliterated by topical tetracaine. Therefore, we cannot recommend topical tetracaine for use at home without further study. Patching the eye does not promote healing,[14] but some patients feel better with the eye patched. Loss of depth perception results from patching one eye, so patients should not drive a car. Abrasions from fingernails, vegetable matter, or a contact lens should not be patched, as they are at higher risk of infection.

Cycloplegics relax the ciliary body and relieve pain from spasm as well as decrease secondary iritis. However, two randomized controlled trials including 440 patients did not find improvement in pain scores with cycloplegics compared to placebo.[27,28] If an abrasion is large and spasm is marked, consider cyclopentolate 1%, one drop three times daily. Topical antibiotics are typically prescribed (**Table 241-7**).

Large abrasions or abrasions in the central visual axis should be checked by an ophthalmologist in 24 hours; small abrasions should be checked in 48 to 72 hours.

Eye Patch An eye patch may be recommended by ophthalmology or may be needed to prevent keratitis in a patient with Bell's palsy. Assemble supplies—two cotton oval eye pads and multiple pieces of tape pretorn to approximately 5 in. (13 cm). To properly apply an eye patch, have the patient sit with both eyes closed. Have the patient keep both eyes closed until the patch is applied and secure. Take one cotton oval eye pad, fold it in half, and hold the eye pad gently but firmly over the closed lid of the eye to be patched. Then take another eye patch, do not fold it in half, and place it over the first patch. Very deep-set eyes may require a third patch. Keep holding firmly but gently. Then tape the patch in place, applying the tape in an X fashion over the eye pad. Now have the patient open his or her eyes. If the patch is properly placed and taped, the lid under the patch will remain closed. (See Video: Eye Patch.)

TABLE 241-7 Suggested Ophthalmic Antibiotics for Corneal Abrasions

Situation	Antibiotic
Not related to contact lens wear	Erythromycin ophthalmic ointment three to four times a day
Related to contact lens wear	Ciprofloxacin, ofloxacin, or tobramycin ointment three to four times a day
Organic source	Erythromycin ointment three to four times a day

CORNEAL LACERATION

Full-thickness **corneal lacerations** can be identified by a misshapen iris, macro- or microhyphema, decrease in visual acuity, and shallow anterior chamber. The Seidel test (Figure 241-12) should be positive. **However, small corneal lacerations can close spontaneously, the Seidel test will be negative, and there may be no gross distortion of globe anatomy** (see Figure 241-47). Corneal lacerations occur in young children from a wide variety of objects—sharp sticks, fingernails, thorns, broken glass, or sharp toys.[29] Objects as diverse as bungee cords and eyelash curlers[30,31] can cause globe perforation. A history of eye irritation while working with metal fragments or high-speed machinery suggests the possibility of a corneal laceration. Pain out of proportion to physical findings, decrease in visual acuity, or other unexplained ocular symptoms may be the only symptoms or signs of a small full-thickness corneal laceration. Evaluate the entire thickness of the cornea during slit lamp examination to identify a corneal laceration.

If there is any suspicion of penetrating injury or severe blunt injury, obtain a CT of the orbit to identify changes in globe anatomy or contour or a foreign body within the globe, and consult ophthalmology. The sensitivity of CT for the detection of occult globe perforation is reported as 51% to 77%,[32] further emphasizing the need for consultation. Unrecognized corneal lacerations can quickly result in endophthalmitis or traumatic cataract. Once endophthalmitis develops, vision is at great risk.

CORNEAL FOREIGN BODIES

Corneal foreign bodies are usually superficial and benign, but penetration of a foreign body into the globe can cause loss of vision. Foreign bodies are generally small pieces of metal, wood, or plastic that become embedded in the cornea. The presence of a corneal foreign body causes an inflammatory reaction, dilating blood vessels of the conjunctiva and causing edema of the lids, conjunctiva, and cornea. When the foreign body is present for >24 hours, WBCs may migrate into the cornea and anterior chamber as a sign of iritis.

The patient will usually complain of a "foreign body" sensation during blinking. Tearing, blurred vision, and photophobia are common. Ask about details surrounding the onset of symptoms, including patient activity. If a cause is not obvious, ask about all activities in the previous 24 hours, especially activities that cause high-velocity projectiles. High-velocity globe penetration injuries include grinding, hammering metal on metal, or operation of other high-speed machinery. Visual acuity should be normal. Inspection of the eye may reveal edema of the eyelid and diffuse or focal/perilimbal conjunctival injection.

Occasionally, the foreign body may be visible with the naked eye. Evert the lid to identify and remove other foreign bodies that may be present. When a metallic foreign body is present for more than a few hours, a **rust ring** (**Figure 241-34**) develops around the metal.



FIGURE 241-34. Rust ring (*arrow*). [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]



FIGURE 241-35. Corneal foreign body. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

Foreign bodies present for >24 hours may be surrounded by a white ring representing a WBC infiltrate. Anterior chamber flare and cells and a corneal foreign body are identifiable on slit lamp examination (**Figure 241-35**). **The presence of a gross hyphema or a microhyphema evident in the anterior chamber on slit lamp examination suggests globe perforation.** If the foreign body has penetrated the cornea, the tract of the projectile *may* be seen. The Seidel test *may* be positive with penetration of the globe.

Corneal Foreign Body Removal Corneal foreign bodies should be removed carefully, with the patient and physician seated at each other's eye level, and under the best magnification available. Anesthetize the cornea with a local anesthetic such as 0.5% proparacaine. Sometimes, anesthetizing both eyes is helpful, because that can eliminate reflex blinking during attempts at foreign body removal. Irrigate with normal saline first, as a very superficial foreign body may be irrigated off the cornea. Next, try to dislodge the foreign body with a moistened cotton applicator. Efforts at removal may themselves cause corneal abrasion.

If the foreign body is tightly adherent to or embedded in the cornea, inspect the cornea using the slit lamp to assess the depth of penetration (Figure 241-19C to E). **Full-thickness corneal foreign bodies should be removed by an ophthalmologist.**

For superficial foreign bodies, a 25-gauge needle (using needle bevel up)[33] or a sterile foreign body spud (1 mm diameter) on an **Alger brush** (a low-speed, low-torque, battery-operated hand-held drill) can be used to remove the foreign body. Use slit lamp magnification to ensure safe foreign body removal. Before the removal, prepare a moistened cotton applicator and set it aside on the slit lamp table. The upper lid can be held open by an assistant or by the clinician's nondominant hand. Many slit lamps have an attached "fixation light" that can be moved in front of the unaffected eye to give the patient a steady target to concentrate on. Using either the 25-gauge needle or the Alger brush, place the tip into the slit lamp beam using the naked eye. With the tip close to the cornea, look through the slit lamp and move the tip tangentially into contact with the cornea. Using the bevel-up edge of the tip of the 25-gauge needle, hook the edge of the foreign body and dislodge it.[33] You may then lift it off the cornea using the previously moistened cotton applicator. Alternatively, using the spinning tip of the Alger brush, the foreign body may be dislodged and removed with the cotton applicator as above.

After successful foreign body removal, discharge the patient with a prescription for topical antibiotics, cycloplegics, and oral analgesics. Administer tetanus toxoid as appropriate. Provide ophthalmology follow-up the next day if the foreign body is in the central visual axis or if there is a residual rust ring. Otherwise, after complete removal of the foreign body, advise follow-up if symptoms persist at 48 hours.

Rust Ring Removal Metallic foreign bodies can create rust rings that are toxic to the corneal tissue (Figure 241-34). If a rust ring is present,

the spud or an ophthalmic burr can remove superficial rust, but rust often reaccumulates by the next day, requiring additional burring. **It is therefore not necessary to remove a rust ring in the ED if the patient can be seen by an ophthalmologist the next day.** Once the metallic foreign body is removed, the rust ring area softens overnight and can be more easily removed in the office the next day. The deeper the stromal involvement, the higher is the risk of corneal scarring, so if rust ring removal is done in the ED, perform only superficial burring. **No ED drill burring should take place if the rust ring is located in the visual axis (pupil) owing to the risk of causing visually significant scarring.** Such conditions require that an ophthalmologist remove the stromal rust in the office within 24 hours.

LID LACERATIONS

Eyelid lacerations that involve the lid margin, those within 6 to 8 mm of the medial canthus or involving the lacrimal duct or sac, those involving the inner surface of the lid, wounds associated with ptosis, and those involving the tarsal plate or levator palpebrae muscle need repair by an oculoplastic specialist. Lacerations medial to the lacrimal puncta are at high risk of canalicular involvement. Suspect involvement of the levator palpebral muscle in the presence of a horizontal laceration with ptosis or when orbital fat is seen protruding through the laceration, indicating a breach of the orbital septum.

FULL-THICKNESS LID LACERATIONS

Consider the possibility of corneal laceration and globe rupture in all full-thickness lid lacerations. Ocular injuries such as corneal abrasion, traumatic hyphema, and globe rupture are seen with lid lacerations in up to two thirds of cases. Lid lacerations require a thorough examination using a slit lamp to exclude other associated ocular injuries.

Deep lacerations to the medial one third of an eyelid potentially transect the canalicular system. Failure to repair a canalicular laceration results in chronic tearing. Instillation of fluorescein dye in the eye with subsequent appearance in the wound indicates loss of canalicular integrity. If a canalicular laceration is discovered, the patient will need to go to the operating room within 24 to 36 hours for repair and Silastic® tube stenting. Because a meticulous repair by an experienced eye surgery team is preferable, it is not unreasonable for the ophthalmologist to discharge a patient seen late in the evening or on the weekend with arrangements for surgical repair to take place within the next 36 hours. Patients discharged pending repair should be placed on oral and topical antibiotics and told to use cold compresses. Oral cephalexin, 500 milligrams two to four times daily, and topical erythromycin ophthalmic ointment four times daily are reasonable choices.

PARTIAL-THICKNESS LID LACERATIONS

Partial-thickness lid lacerations not meeting the preceding criteria can usually be repaired in the ED, with referral for ophthalmologic evaluation in 2 to 3 days. Use a soft, absorbable or nonabsorbable 6-0 or 7-0 suture. Have the suture ends closest to the cornea tucked under more distant sutures to avoid corneal irritation (**Figure 241-36**). Cut the ends of each suture 1 cm long. When the second suture is tied, take the long ends of the first suture into the loop of the knot of the second suture. This keeps the ends of the first suture secure. Do this for every successive suture. Do not incorporate the ends of the suture into the wound itself, but make sure the suture ends are kept to the side of the wound margin. Sutures are removed from the bottom.

LACERATIONS AT THE LID MARGIN

Very small lacerations (<1 mm) at the lid edge only do not need suturing and can heal spontaneously. Any laceration >1 mm at the lid edge needs repair by a specialist. Proper alignment of the lid margin during repair under magnification (loupe or microscope) is essential to preserve proper lid function and even corneal wetting with each blink. Notching of the lid can result in improper lid closure.

If there is no opportunity for the patient to see an ophthalmologist, repair should be performed as in **Figure 241-37**. Soft (gut or chromic) sutures 6-0 or smaller should be used for all repairs. One vertical mattress suture, using the meibomian gland orifices as a landmark, or two 6-0 soft sutures (one approximating the anterior and the other the posterior lamella) are used to repair the lid margin. The initial suture can be used for traction to extend the lid and facilitate the repair. The tarsus should be repaired with 6-0 absorbable suture (polyglactin) from the external side so as to approximate the wound without the need for sutures on the conjunctival side of the lid (which would abrade the cornea with each blink). Skin closure can be performed with 6-0 or smaller soft nonabsorbable suture.

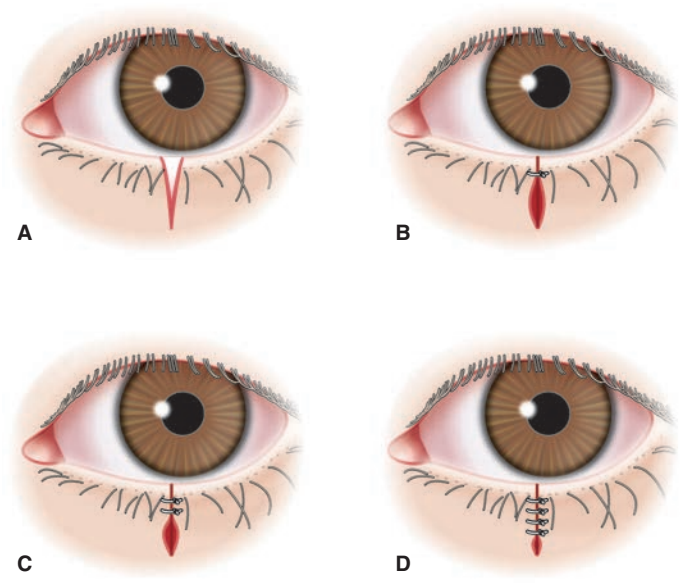

FIGURE 241-36. A through **D.** Each suture holds down the ends of the adjacent suture to prevent corneal irritation or abrasion. Note that this illustration shows a laceration at the lid margin. Lid margin lacerations >1 mm need repair by an oculoplastic specialist.

BLUNT EYE TRAUMA

CLINICAL FINDINGS AND DIAGNOSIS

The first steps are assessment of the visual acuity, anterior chamber, and integrity of the globe. The eyelids frequently swell shut, making visualization of the globe difficult. Prying the eyelids open with the fingers is difficult, usually yields an unsatisfactory view of the globe, and can raise intraocular pressure. Insertion of a paper clip bent in an appropriate shape (Figure 241-11) or an eyelid speculum (**Figure 241-38**) provides a significantly improved view of the cornea and anterior chamber. Use of an eyelid retractor allows your hands to remain free for examination of the globe using the slit lamp.

If the anterior chamber is flat, a ruptured globe is certain, so stop the examination, place a metal shield over the injured eye, and consult ophthalmology. If the globe appears intact and vision is preserved, check ocular motility. Restricted upgaze or lateral gaze suggests a **blow-out fracture** with entrapment (see later section, "Orbital Blow-Out Fractures"), and a CT scan of facial bones should be obtained. A head CT scan may be indicated to assess for associated intracranial injury. Feel the orbital rim above and below for step-off deformities. Test for cutaneous sensation along the distribution of the inferior orbital nerve (below the eye and ipsilateral side of the nose). **Perform a slit lamp examination with fluorescein staining to check for abrasions, lacerations, foreign bodies, hyphema, iritis, and lens dislocation.** Measure intraocular pressure if there are no signs of a ruptured globe. Traumatic iritis is common, causing cells and flare to be seen on slit lamp examination. The pupil can be constricted or dilated after sustaining trauma. It is important to look for pupillary irregularity because

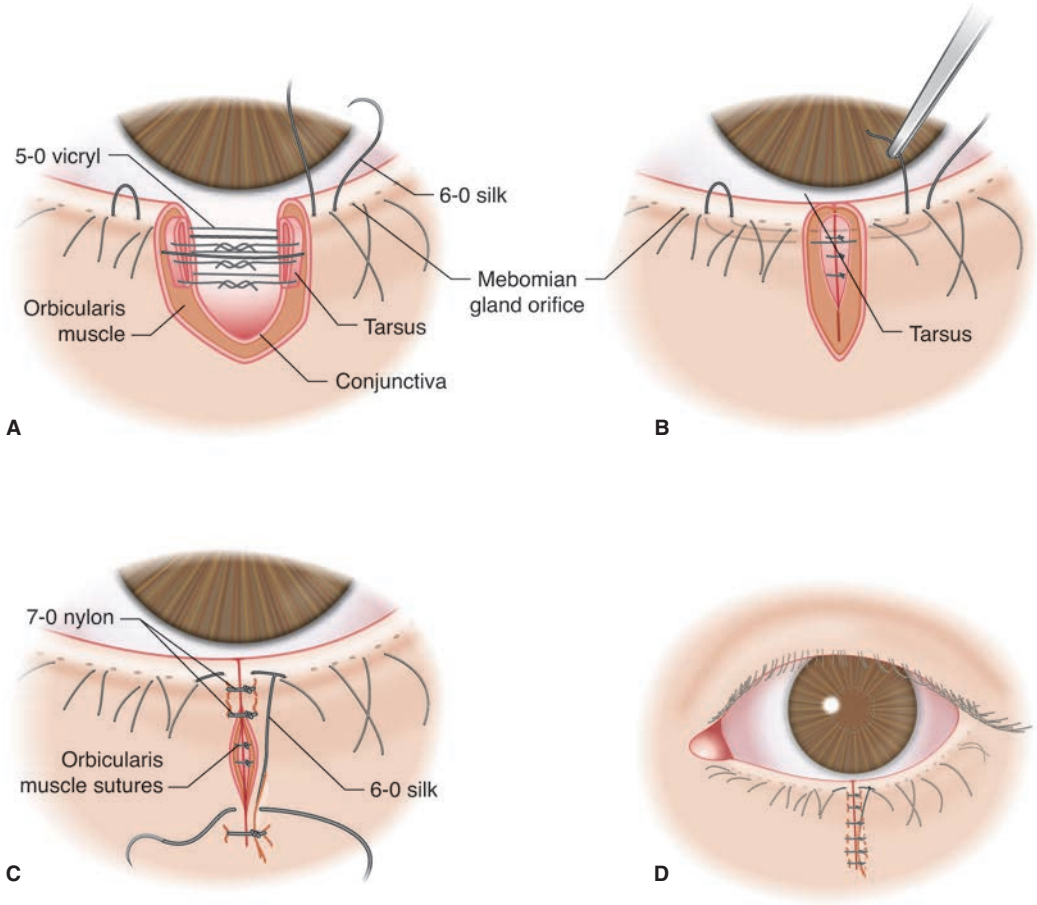

FIGURE 241-37. **A** through **D.** Full-thickness lid repair. 6-0 silk is used for lid margin. 5-0 Vicryl® is used to approximate the tarsal plate. The Vicryl® sutures should not pass through the conjunctiva on the inside of the eyelid to avoid mechanical abrasion of the cornea during blinking. 7-0 nylon is used for skin closure, and the lid margin silk suture tail can be incorporated into these sutures to avoid corneal irritation.

the pupil often will peak toward the site of a penetration or rupture. If the anterior chamber is of normal depth and not shallow, apply a mydriatic. Nonwhite, brown-eyed individuals frequently will require an additional drop of a mydriatic to achieve adequate dilation. If vision and ocular anatomy and function are preserved, outpatient follow-up by an ophthalmologist in the next 48 hours should be planned. If a ruptured globe is suspected due to loss of visual acuity, flat anterior chamber, obvious full-thickness laceration, or intraocular foreign body, do not manipulate the eye or measure intraocular pressure. Consult ophthalmology immediately.

HYPHEMA

A **hyphema** is blood or blood clots in the anterior chamber (Figures 241-22 and 241-23). Hyphemas are traumatic or spontaneous. A traumatic hyphema usually results from bleeding from a ruptured iris root vessel. Spontaneous hyphemas frequently are associated with sickle cell disease. In addition to standard ophthalmologic history, query anticoagulant or antiplatelet medication use or history of a bleeding diathesis. **A hyphema may layer out posteriorly when the patient is lying flat and may only become grossly evident when the patient is sitting upright.** The complications of hyphema include increased intraocular pressure, rebleeding, peripheral anterior synechiae, corneal staining, optic atrophy, and accommodative impairment. Patients with large hyphemas, sickle cell disease, and bleeding tendency are more likely to develop vision loss. A **microhyphema** is suspension of red blood cells in the anterior chamber without the formation of a layered blood clot. It is generally seen with a slit lamp and can progress into a hyphema. The most significant complications of microhyphema include rebleeding and intraocular pressure elevation. Patients with sickle cell disease are more likely to develop these complications. The treatment of microhyphema is somewhat controversial, but the principles of management are the same as those for the hyphema. Patients at high risk for complications include those with suspected ruptured globe, those with sickle cell disease, those taking anticoagulants, and those with a bleeding diathesis.

Hyphema Treatment Treatment consists of the prevention of rebleeding and intraocular hypertension. Elevate the patient's head to 45 degrees to promote settling of suspended red blood cells inferiorly to prevent occlusion of the trabecular meshwork. Interventions should be directed by an ophthalmologist. Treatment modalities include antifibrinolytic agents (oral and systemic aminocaproic acid, tranexamic acid, and aminomethylbenzoic acid), corticosteroids (systemic and topical), cycloplegics, miotics, and aspirin.[34] Both tranexamic acid and aminocaproic acid have been shown to decrease the rebleeding rate.[34]

Rebleeding can occur 3 to 5 days later in up to 30% of cases, sometimes causing severe elevation of intraocular pressure and necessitating surgical anterior chamber "washouts." Because of this risk, some ophthalmologists believe in admitting all patients with significant hyphemas. Generally, patients with hyphemas occupying one third or less of the anterior chamber can be followed closely as outpatients. The disposition decision should be made by the ophthalmologist after examining the patient. Topical steroids may prevent posterior synechiae and treat iridocyclitis. Close follow-up and serial examinations by an ophthalmologist are recommended in patients receiving topical ocular steroids to ensure no infection or corneal perforation occurs.

ORBITAL BLOW-OUT FRACTURES

The most frequent sites of **orbital blow-out fractures** are the inferior wall (maxillary sinus) and medial wall (ethmoid sinus through the lamina

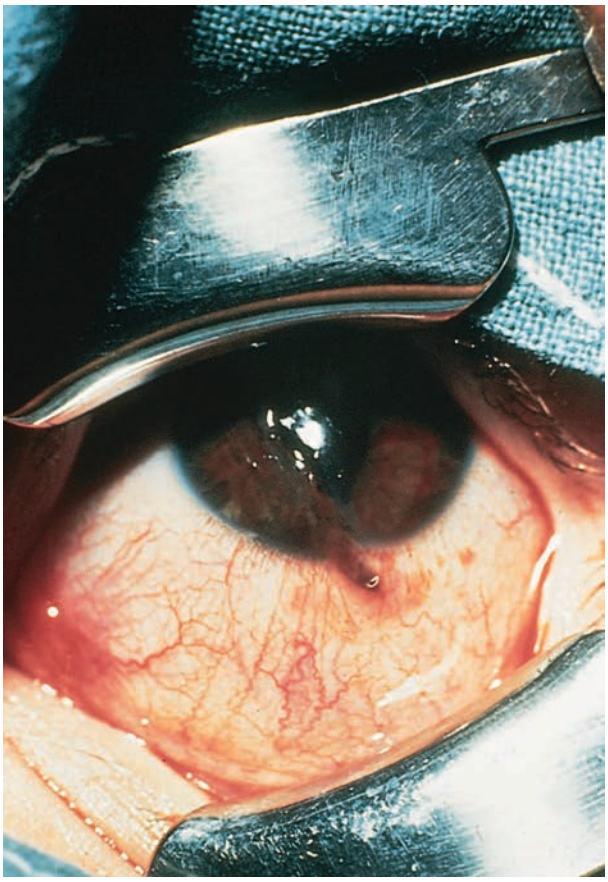

FIGURE 241-38. Commercial eyelid retractors. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

papyracea). Fractures of the medial wall can be associated with subcutaneous emphysema, sometimes exacerbated by sneezing or blowing the nose. Fractures of the inferior wall with entrapment of the inferior rectus muscle can cause restriction of upgaze and diplopia (**Figure 241-39**). Especially in children, tight entrapment of an ocular muscle or swelling putting pressure on the globe may stimulate the **oculovagal reflex** (**oculocardiac reflex**), yielding nausea, vomiting, bradycardia, and hypotension



FIGURE 241-39. Inferior wall blow-out fracture of the left eye with entrapment of the inferior rectus muscle. The patient's left eye is unable to look upward, causing diplopia on upward gaze. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

of varying degrees.[35] Orbital wall fractures are suspected on clinical examination and confirmed by CT scanning. About one third of blow-out fractures are associated with ocular trauma (abrasion, traumatic iritis, hyphema, lens dislocation/subluxation, retinal tear, or detachment); therefore, a careful eye examination in the ED is necessary. **All blow-out fractures with normal initial eye examination in the ED should be referred to an ophthalmologist for dilated examination to rule out any unidentified retinal tears or detachments.** The complete eye exam can be done as an outpatient in 24 to 48 hours if there is no need for admission or immediate surgery. The need for admission and timing of surgical repair are controversial.[35-37]

Patients demonstrating signs of oculovagal reflex and patients with CT findings demonstrating a large tissue herniation through a narrow bone fragment separation have signs of tight entrapment and should be referred immediately to ophthalmology for management.[35] All patients with entrapment as indicated by diplopia, limitation of ocular motility, CT findings, or proptosis should be discussed with ophthalmology for management.[35,36] Isolated blow-out fractures without entrapment and without eye injury do not require immediate surgery and can be referred to ophthalmology, plastic surgery, oral maxillofacial surgery, or otolaryngology (depending on the local referral patterns) for repair within the next 3 to 10 days.[37] Oral antibiotics (cephalexin, 250 to 500 milligrams PO four times daily for 10 days) are often recommended because of the presence of sinus wall fractures. Patients who develop new symptoms, such as diplopia, or who have persistent nausea and vomiting should be instructed to return to the ED for reevaluation.

RUPTURED GLOBE

Rupture of the globe is a vision-threatening emergency that may be easily missed. The patient will usually complain of eye pain but may not have a decrease in visual acuity. Rupture of the globe presenting with a large subconjunctival hemorrhage is easily recognized, but a penetrating wound of the cornea caused by a tiny piece of metal launched from a grinder may be easily overlooked and requires careful exam or imaging to detect. Periorbital ecchymosis and maxillofacial fractures, including blow-out fracture with limitation of extraocular muscle movement, should raise one's suspicion for globe rupture.

Scleral rupture may occur from blunt or penetrating trauma. Blunt trauma directly to the eyeball (for example, a blow by a fist) will cause a sudden elevation of intraocular pressure, with the globe tending to rupture at the thinnest points of the sclera, the limbus, and the insertion of the extraocular muscles. Any object that impacts the orbital rim at a high velocity and causes a seal around the orbit (tennis balls, racquetballs, etc.) will also cause a sudden peak in intraocular pressure and may result in rupture. A history of ocular surgery or previous ocular injury may predispose to globe rupture. Penetrating trauma may occur from bullets, BB pellets, knives, sticks, darts, needles, hammering, and lawn mower projectiles. **Any projectile injury has the potential for penetrating the eye.** The bony canal protects the globe from posterior and oblique injuries, but the eyelids afford little protection anteriorly. **Suspect globe penetration with any puncture or laceration of the eyelid or periorbital area,** and make sure to conduct a thorough slit lamp examination. The smaller the diameter of the offending object, the higher is the likelihood of occult injury. **Corneal abrasions occurring when hammering metal on metal; associated with the use of high-speed machinery such as lawn mowers, line trimmers (weed whackers), grinders, or drills; and sustained during explosions should always be investigated for occult globe penetration.**

Whenever globe rupture is obvious or strongly suspected, cover the eye with a metal eye shield or make a shield from a paper cup (Figures 241-40 and 241-41), and consult ophthalmology immediately without further manipulation. Elevate the head of the bed to 45 degrees. Administer broad-spectrum IV antibiotics (vancomycin plus ceftazidime, or similar coverage), and give tetanus toxoid as appropriate. Provide sedation and analgesia. Administer antiemetics to prevent increased intraocular pressure and extrusion of intraocular contents from vomiting. Avoid any topical eye solutions. Give the patient nothing by mouth, anticipating surgery.



FIGURE 241-40. Metal eye shield placed in suspected globe rupture to prevent inadvertent pressure on the eye. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

Most cases, however, will require an initial eye examination to determine the type and extent of injury before consulting ophthalmology. **If at any step of the examination globe rupture is suspected, stop the examination, place a protective shield over the eye, and consult ophthalmology. Do not measure intraocular pressure as this may result in extrusion of globe contents.**

Eye examination must be careful and gentle. If using US to evaluate for trauma, do not apply significant pressure on the globe (see later section on ocular US, including Figure 241-60). Manufactured or homemade eyelid retractors should be used to gently retract the lids to examine the eye and to avoid increasing intraocular pressure during examination.

Examination of the eye may reveal decreased visual acuity, an irregular or teardrop-shaped pupil, an afferent pupillary defect, shallow anterior chamber, hyphema, positive Seidel test, and lens dislocation (**Figure 241-42**). Presence of a large subconjunctival hemorrhage involving the entire sclera or hemorrhagic chemosis (bullous, raised subconjunctival hemorrhage) is very suspicious for rupture of the globe (**Figures 241-43** and **241-44**). Uveal prolapse through a scleral wound may appear as a brownish-black discoloration against the white sclera (**Figure 241-45**). One may occasionally visualize a corneal laceration (**Figure 241-46**) or an intraocular foreign body on slit lamp examination (**Figure 241-47**). The Seidel test may or may not be positive with a small corneal laceration. Funduscopic examination may reveal a poor view of the optic nerve and posterior pole due to vitreous hemorrhage.

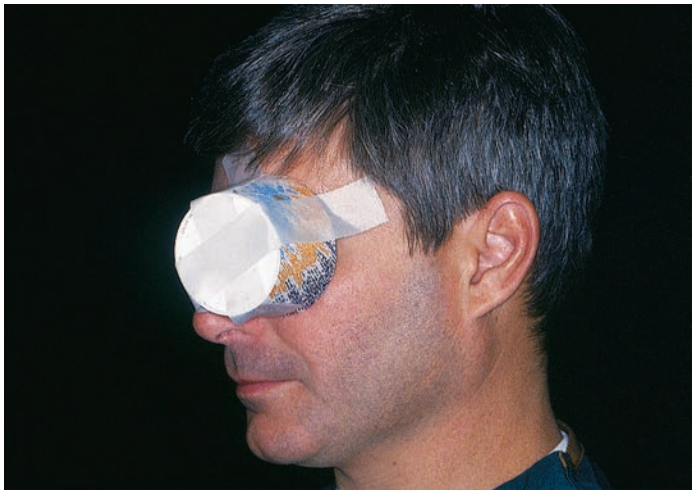

FIGURE 241-41. Protective eye shield fashioned from a paper cup. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

The diagnosis is made based on a combination of history, physical examination, and selected radiologic studies. CT scan of the eye is the preferred imaging modality to detect occult open globe rupture and associated optic nerve injury. CT scan of the orbit using 2- to 3-mm cuts in both the axial and coronal planes will also localize small intraocular foreign bodies. US and both direct and indirect ophthalmoscopy after pupillary dilatation may assist in the diagnosis and can be helpful in locating and confirming the presence of orbital and intraocular foreign bodies. See Figure 241-60 in the later ocular US section. **MRI is contraindicated if a metallic foreign body is possible**.

For patients in the ED with multiple trauma and a possible ruptured globe who require rapid-sequence intubation, there is no clear consensus on the best agent to use because quick airway stabilization takes priority. Although a depolarizing agent like succinylcholine is associated with an increase in intraocular pressure, the underlying mechanism is not clear. Pretreatment with a nondepolarizing muscle relaxant or a pretreatment dose of succinylcholine does not necessarily attenuate the increase in intracranial pressure. Use of **a nondepolarizing agent like rocuronium can mitigate increases in intraocular pressure**, but disadvantages are a longer onset and longer duration of action[38] (see Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation").

ORBITAL HEMORRHAGE: PRESEPTAL AND POSTSEPTAL

Severe blunt trauma to the orbit can occasionally cause an orbital hemorrhage. **Preseptal hemorrhage** is dramatic in appearance, but not as vision threatening as a **postseptal hemorrhage** (often called **retrobulbar hematoma**), which can cause an **orbital compartment syndrome**. A postseptal hematoma can cause an abrupt increase in intraocular pressure, resulting in decreased blood flow to the optic nerve and its blood supply and loss of vision.

Traumatic periorbital hematomas (black eyes) are common, but the extension of bleeding into the postseptal compartment is a true emergency. Differentiation of preseptal versus postseptal hematoma depends on the examination and noncontrast orbital CT findings. Clinical findings of postseptal hemorrhage are eye pain, proptosis, impaired extraocular movements, decreased vision, possibly an afferent pupillary defect, and elevated intraocular pressure. An intraocular pressure >40 mm Hg is a consideration for emergency lateral canthotomy. No matter what the intraocular pressure, if postseptal hematoma is suspected or confirmed, request emergency ophthalmology consultation. Preseptal hematomas can be observed to make sure that the hematoma is not expanding.

Lateral Canthotomy The goals of **lateral canthotomy** are to release pressure on the globe and to reduce intraocular pressure to reestablish retinal artery blood flow. To perform the procedure, place the patient in the supine position and anesthetize the lateral canthus area with 1% to 2% lidocaine with epinephrine.[39] Place a straight Kelly clamp horizontally across the lateral canthus to the lateral orbital rim for about 1 to 2 minutes to crush the tissues and minimize bleeding.[39] Remove the clamp, and with sterile scissors, make a 1- to 2-cm lateral incision in the compressed tissue at the clamp site. Then retract the lower lid to expose the lateral canthus tendon. With the scissors directed inferoposteriorly toward the lateral orbital rim, cut the inferior crus of the lateral canthus tendon. This critical incision is generally 1 to 2 cm in depth and length. If the procedure is successful, the intraocular pressure should be less than 40 mm Hg and the visual acuity should improve. If the intraocular pressure continues to remain elevated, the superior crus of the lateral canthus tendon can be cut in a similar fashion. The complications of lateral canthotomy include hemorrhage, infection, and mechanical injury. These complications generally respond to treatment better than does retinal injury from prolonged ischemia. Lateral canthotomy incisions usually heal well; repair is performed by ophthalmology.[40] (See Video: Lateral Canthotomy.)

Ocular Hemorrhage and Antithrombotic Therapy The use of anticoagulant and antiplatelet agents is very common in current clinical practice and can complicate the management of ocular hemorrhage from trauma. Spontaneous ocular hemorrhage has also been reported

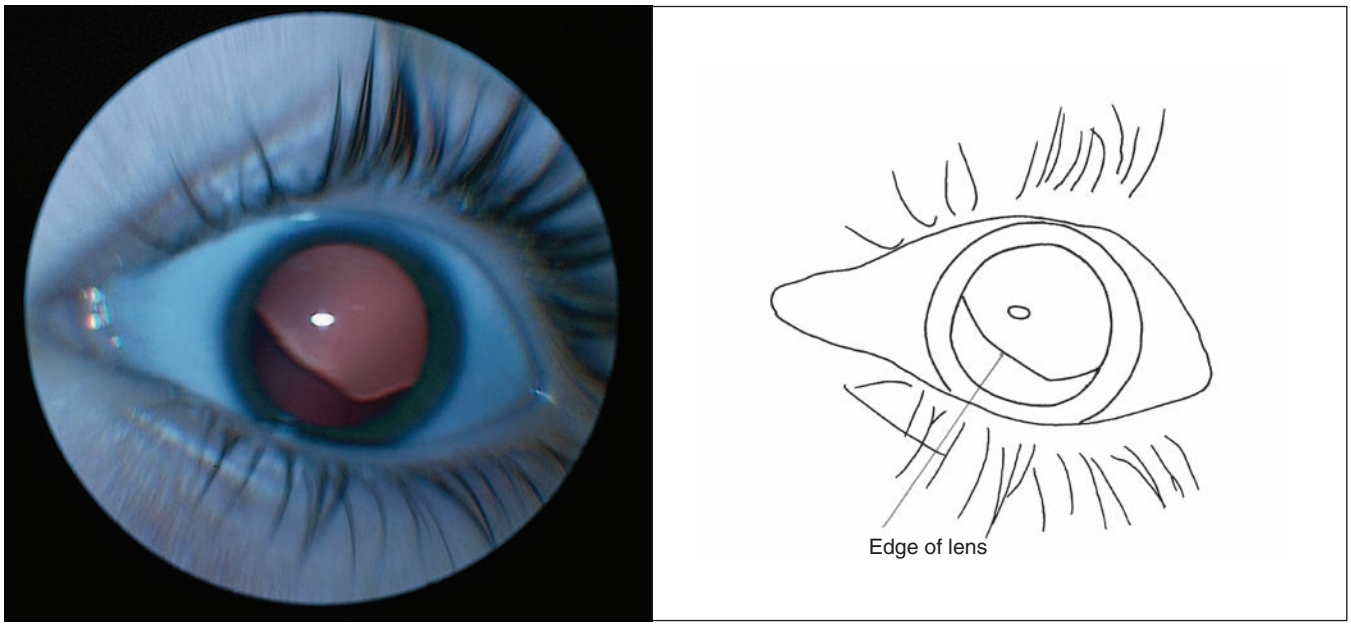

FIGURE 241-42. Lens dislocation. [Reproduced with permission from Knoop K, Stack L, Storrow A, et al: *Atlas of Emergency Medicine*, 3rd ed. © 2010 McGraw-Hill Inc.; Photo contributed by Department of Ophthalmology, Naval Medical Center, Portsmouth, VA.]

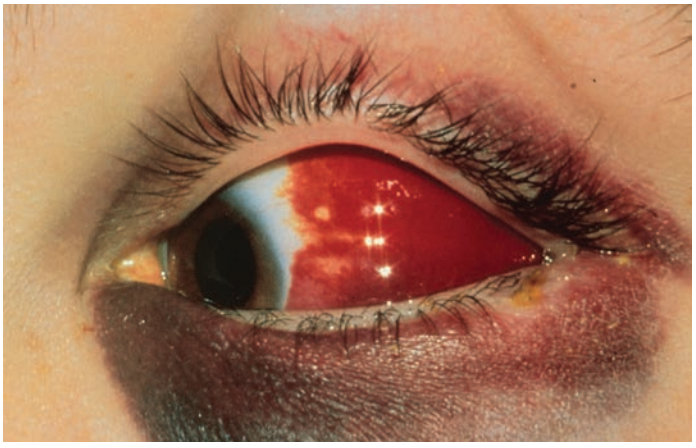

FIGURE 241-43. Large subconjunctival hemorrhage. Note that it is flat, not raised. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

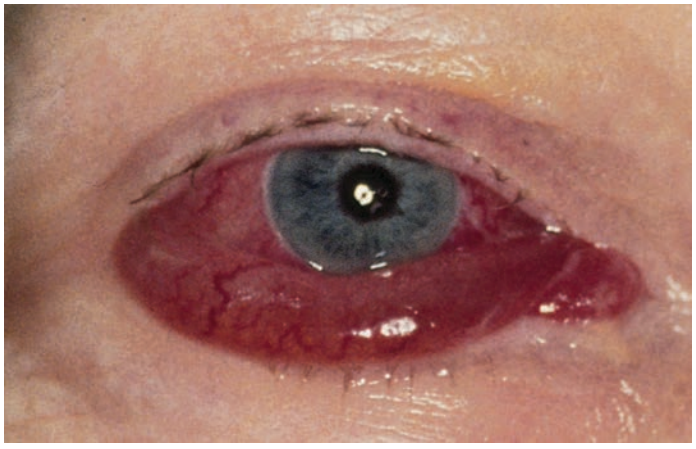

FIGURE 241-44. Bloody chemosis. Note the raised or bullous appearance. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

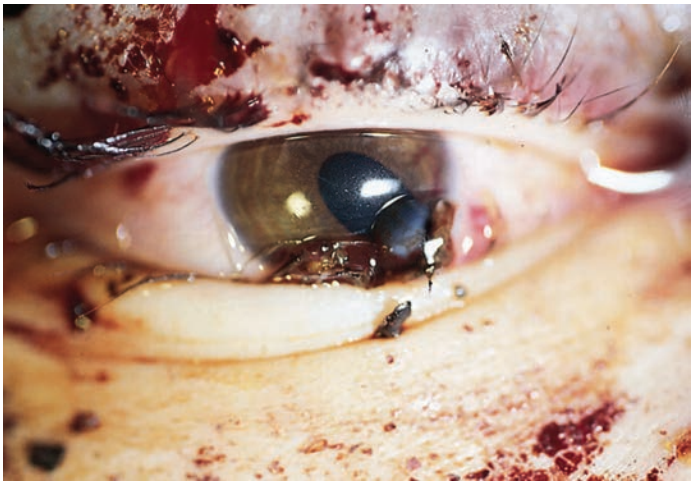

FIGURE 241-45. Uveal prolapse with globe rupture and teardrop pupil. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

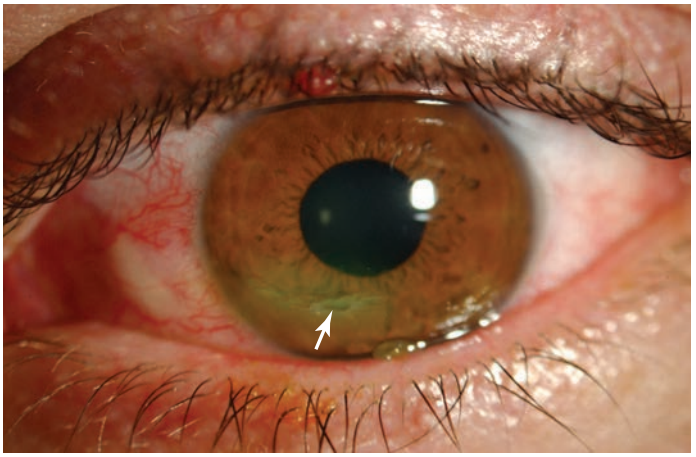

FIGURE 241-46. Corneal laceration due to hammering concrete. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

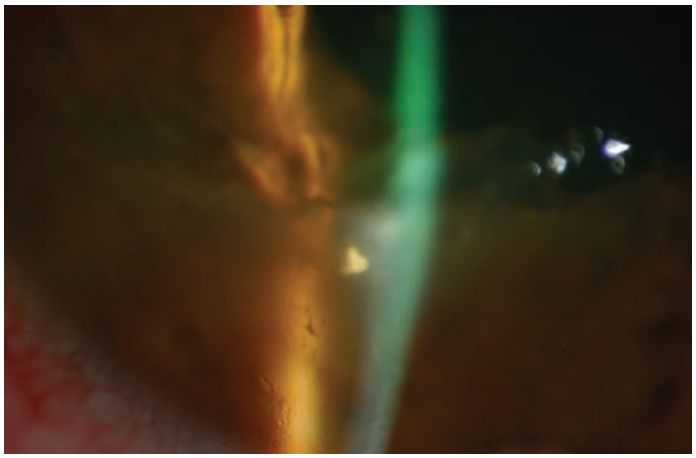

FIGURE 241-47. Intraocular foreign body associated with laceration in Figure 241-46 as seen on slit lamp examination. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

in patients taking these agents. Ocular complications in patients on oral anticoagulant therapy include subconjunctival hemorrhage, hyphema, vitreous hemorrhage, subretinal hemorrhage, and choroidal hemorrhage. A higher incidence of hemorrhagic complications has been reported in patients with macular degeneration using anticoagulants or other antithrombotic drugs. Ocular hemorrhages in patients taking warfarin can potentially be vision-threatening events, but frequently they are benign and resolve without any sequelae. See the ocular US section later in this chapter, including Figure 241-62, for US diagnosis of vitreous hemorrhage.

There are no clear guidelines to guide treatment of ocular hemorrhage in patients taking anticoagulant and antiplatelet therapy. The severity of bleeding, INR levels, and benefits of using these agents should be taken into consideration when managing these patients. Stop the anticoagulant or antiplatelet drug in patients with active bleeding. Prothrombin complex concentrate, fresh frozen plasma, and vitamin K should be considered in patients taking warfarin (see Chapter 239, "Thrombotics and Antithrombotics," for detailed discussion). Platelet transfusions might be beneficial to stop active bleeding in patients with thrombocytopenia or taking antiplatelet drugs, but efficacy differs depending on the antiplatelet agent. For example, platelet transfusions do not reverse the effects of clopidogrel.[41] Consult ophthalmology, the care provider who prescribed the anticoagulant or antiplatelet drug, and hematology for recommendations.

CHEMICAL OCULAR INJURY

Chemical burns to the eye are a true ocular emergency. Complications of chemical burns to the eye include scarring of the cornea with permanent loss of vision and loss of the eye due to corneal perforation. Irrigation of the eyes with 1 to 2 L of normal saline must be done immediately and before any examination, including testing of vision.

ALKALI AND ACID INJURIES

Alkali injuries occur more frequently than acid injuries, due to the presence of alkaline substances in household cleaning agents and in building materials. The most serious alkali injuries are associated with ammonia, found in many household cleaners, and lye, a common ingredient in drain cleaners. Lye is also a component of concrete. Alkali injuries tend to be much more serious than acid injuries because they cause a liquefaction necrosis, characterized by denaturing of proteins and saponification of fats, allowing deep penetration into tissue. Acid, on the other hand, causes coagulation necrosis, with denaturing of protein forming a coagulum that acts as a barrier to further tissue penetration.

Treatment Irrigation should begin at the scene and continue in the ED. Instill a topical anesthetic and continue irrigation for at least

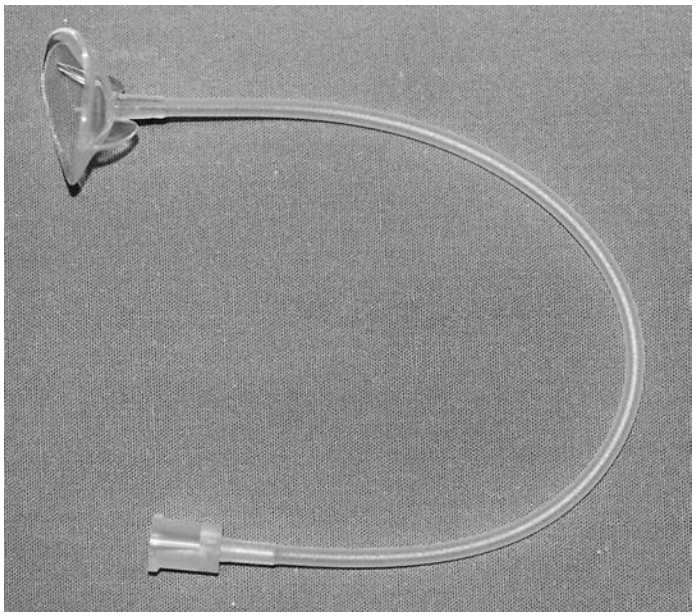

FIGURE 241-48. Eye irrigation with a Morgan Lens® (MorTan Inc., Missoula, MT). [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD. McGraw-Hill, Inc.]

30 minutes. Then check pH by touching a strip of litmus paper to the inferior conjunctival fornix. **If the pH is >7.4, continue irrigation until the pH remains neutral 30 minutes after the last irrigation.** Irrigation should be with sterile normal saline or other isotonic solution and may be instilled into the eye by hand, using bottles of eye-irrigating solution, or by a Morgan Lens® (MorTan Inc., Missoula, MT) (**Figure 241-48**) attached to a bag of an isotonic IV solution.

After irrigation and maintenance of ocular pH >7.4, perform the eye examination. Inspect the facial skin and eyelids for burns. Evert the eyelids and remove any particulate matter with a cotton applicator.

Exposure to chemical agents can cause conjunctival injection and chemosis, but severe chemical burns can cause scleral whitening, secondary to ischemia and blood vessel injury. Document visual acuity and measure intraocular pressure. Intraocular pressure may be increased if the trabecular meshwork has been damaged. Use the slit lamp to evaluate corneal injury and to detect for cells and flare in the anterior chamber. Injury to the cornea may range from punctate defects to complete loss of epithelium. The cornea may become cloudy with severe burns (**Figure 241-49**).

After irrigation, and once time permits, identify the substance. The pH is usually listed on bottles of household cleaners. The U.S.



FIGURE 241-49. Severe lye burn with corneal opacification. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

Occupational Health and Safety Administration requires the patient's workplace to maintain Material Data Safety Sheets, a list of all the physical properties, including pH, of chemicals used at the site. Data on the pH of known chemicals can also be obtained from a poison control center or from Poisindex®. Alkaline substances with pH <12 or acidic substances with pH >2 are thought not to cause serious injury, but duration of exposure can increase severity of injury. Circumstances surrounding the injury (e.g., battery explosion) should be determined to identify any other associated ocular or facial injuries.

Obtain ophthalmology consultation for all but minor burns: Any patient with corneal clouding or an epithelial defect after irrigation should receive prompt ophthalmology referral.[42]

Patients with chemosis (edema of the bulbar conjunctiva overlying the white sclera) and no corneal or anterior chamber findings should be treated after irrigation with erythromycin ointment four times daily and referred for an ophthalmologic examination in 24 to 48 hours. These patients are considered to have "**chemical conjunctivitis**."

A topical cycloplegic agent (cyclopentolate 1%, one drop) should be used three times daily for pain reduction if an epithelial defect is present.[43] Apply erythromycin ophthalmic ointment four times daily to affected eyes. Doxycycline 100 milligrams twice a day may be recommended to reduce risk of corneal melting.[43] Administer tetanus toxoid as appropriate. Consider prescribing topical corticosteroids after consultation with an ophthalmologist if recommended to control inflammation.

CYANOACRYLATE (SUPER GLUE/CRAZY GLUE)

Accidental instillation of cyanoacrylate adhesives into the eye and adnexa can cause adherence of the lids and clumps of adhesive to form on the cornea. Medicinal grade cyanoacrylates are occasionally used to seal corneal perforations and are not toxic to the cornea, so there is rarely permanent damage to the eye. The mechanical abrasive effect of hard, irregular glue aggregates rubbing against the cornea with eye movement and blinking may cause corneal abrasions. To remove crazy glue, instill generous amounts of **erythromycin ointment** onto the eye and on the surface of the eyelids to moisten, lubricate, and provide antibiotic coverage. Clumps of glue on the surface should begin to loosen. Remove only those pieces that are easily removable. Gentle traction may separate the lids. The glue will loosen and become easier to remove in a few days.

Refer to an ophthalmologist within 24 hours for complete removal.

ACUTE VISUAL REDUCTION OR LOSS

Acute visual loss is usually divided into painful and painless visual loss for diagnostic categorization. Other differentiating features include presence or absence of a relative afferent pupillary defect, the rapidity of onset, funduscopic exam, and various physical exam and historical features. The differential diagnosis of visual loss is listed in **Table 241-8**. Many of the diagnoses are discussed in further detail in the text.

TABLE 241-8 Differential Diagnosis of Visual Loss

Diagnosis	Eye Pain	Relative Afferent Pupillary Defect	Onset	Fundoscopic Exam	Other Findings
Central retinal artery occlusion	No	Yes	Sudden	Pale retina, cherry red spot	
Central retinal vein occlusion	No	+/–	Sudden	"Blood and thunder"/"ketchup" fundus	
Acute ischemic optic neuropathy	No	Yes	Gradual	Swollen pale disk	Signs of temporal arteritis
Acute angle-closure glaucoma	Yes	+/–	Sudden	Difficult to visualize the fundus due to corneal edema	Painful red eye, hazy cornea, midpoint pupil, narrow anterior chamber, firm globe
Optic neuritis	Yes	Yes	Gradual	Papilledema	Painful EOM, young female patient
Giant cell arteritis	Possible retro-orbital headache/pain	Yes	Gradual	Normal	Headache, myalgias
Cataract	No	+/–	Gradual	Often unable to visualize fundus	Opacity in the lens
Uveitis	Yes	No	Gradual	Normal	Flare and cells in anterior chamber, ciliary flush, consensual photophobia
Vitreous hemorrhage	No	+/–	Sudden	Opacity in the vitreous	Floaters, cobwebs
Amaurosis fugax	No	No	Sudden	Normal	Transient monocular vision loss
Transient ischemic attack	No	No	Sudden	Normal	Transient binocular vision loss
Cortical blindness	No	+/–	Sudden or gradual	Possible papilledema	Complete visual loss or homonymous hemianopsia, headache
Migraine headache	Possible retro-orbital headache/pain	No	Sudden	Normal	Visual scotomata, nausea, vomiting
Retinal detachment	No	+/–	Sudden	Retina may be difficult to visualize (portion of retina out of focus)	Possible localized visual field defect, "cloudy veil," "window shade"; suspect by history
Diabetic retinopathy	No	+/–	Gradual	Neovascularization, retinal hemorrhages	History of diabetes mellitus
Macular degeneration	No	+/–	Gradual	Drusen, macular pigment clumps	Spots in visual field
Cytomegalovirus retinitis	No	+/–	Sudden or gradual	"Tomato and cheese" pizza (retinal necrosis), retinal hemorrhages	History of human immunodeficiency virus or other immunosuppression
Methanol	No	No	Gradual	Normal	Headache, nausea, vomiting, history of ingestion
Functional visual loss	No	No	Sudden or gradual	Normal	Optokinetic nystagmus

Abbreviation: EOM = extraocular muscle movement.

ACUTE AND PAINFUL VISION REDUCTION OR LOSS

ACUTE ANGLE-CLOSURE GLAUCOMA (ACUTE ANGLE-CLOSURE CRISIS)

Pathophysiology Glaucoma is a group of ocular disorders characterized by increased intraocular pressure causing optic neuropathy and vision loss if left untreated. Obstruction to aqueous humor outflow is the basic underlying problem in glaucoma. In primary acute angle-closure glaucoma or crisis, the lens or the peripheral iris blocks the trabecular meshwork, obstructing the outflow of aqueous humor.[44] Angle closure occurs more easily in persons whose eyes have shallow anterior chambers where the angle between the cornea and iris is reduced. A shallow anterior chamber results in a greater area of contact between the lens and iris, impeding flow of aqueous humor from the posterior to anterior chamber. This results in a pressure differential between the posterior and anterior chamber (referred to as *pupillary block*) and causes forward bowing of the iris, further narrowing the angle (**Figure 241-50**).

An acute attack is usually precipitated by pupillary dilation. Dilation increases contact between the iris and lens as the iris becomes thicker. When the pupil is mid-dilated, relative pupillary block and peripheral laxity of the iris are maximal. This increases the degree of pupillary block, increasing pressure in the posterior chamber and causing the iris to bulge forward (iris bombe). The angle between the peripheral iris, trabecular meshwork, and cornea becomes acutely closed, resulting in a precipitous increase in intraocular pressure. Intraocular pressure eventually exceeds the capacity of the corneal pump mechanism, causing the cornea to become edematous and less transparent, thus explaining the foggy vision or halos patients complain of and the hazy appearance of the cornea on physical examination.

As people age, the lens becomes less elastic and thicker, or cataracts may develop. These events can push the iris forward into greater contact with the lens, increasing the degree of pupillary block. Hypermetropic (farsighted) eyes have a shorter anterior to posterior length, a flatter cornea, and a narrower angle, increasing the risk of acute angle-closure glaucoma.

Anything causing pupillary dilatation can trigger an acute attack. The use of topical or systemic parasympatholytic agents (mydriatics, antihistamines) or sympathomimetics (epinephrine, pseudoephedrine), dim illumination, and emotionally upsetting events have all been implicated. Precipitation of acute angle-closure glaucoma has been reported with therapeutic use, and abuse of, intranasal cocaine. Critically ill patients being treated for respiratory failure with nebulized β-sympathomimetic and anticholinergic medications (e.g., albuterol and ipratropium) may develop acute angle-closure glaucoma.[45]

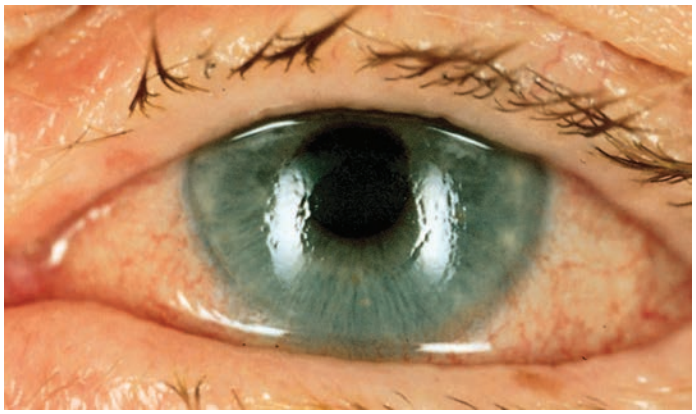

FIGURE 241-51. Acute angle-closure glaucoma. The cornea is cloudy, and there is marked conjunctival injection. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

Clinical Features Acute angle-closure glaucoma is abrupt in onset, painful, and may result in severe visual impairment if not treated quickly. Patients complain of sudden onset of severe eye pain or frontal or supraorbital headache. Associated symptoms include blurred vision, nausea, and vomiting. Rarely, acute angle-closure glaucoma may result in painless monocular vision loss. Acute angle-closure glaucoma may be misdiagnosed as migraine, temporal arteritis, subarachnoid hemorrhage, or intra-abdominal emergency.

Examination reveals a fixed, midposition pupil and a hazy (cloudy/steamy) cornea with conjunctival injection (**Figure 241-51**), most prominent at the limbus. The affected eye is rock hard. Measure the intraocular pressure to confirm the diagnosis (see earlier section, "Intraocular Pressure"), although the presence of the characteristic symptom complex—a cloudy cornea, fixed midposition pupil, and rock-hard globe—is diagnostic. Normal intraocular pressure is 10 to 20 mm Hg; ocular pressure may exceed 60 to 80 mm Hg in an acute attack.

Treatment There have been no controlled studies regarding medical treatment for acute angle-closure glaucoma. Medical treatment lowers the intraocular pressure by blocking production of aqueous humor and reducing the volume of vitreous humor (**Table 241-9**).[44,46] The initial

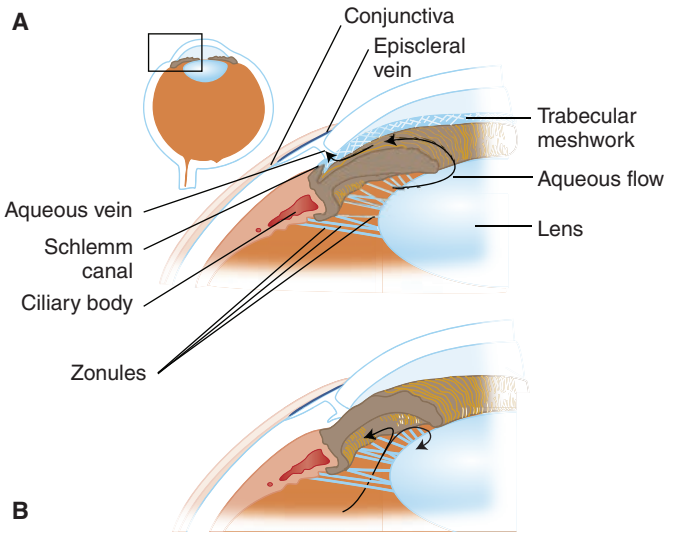

FIGURE 241-50. **A.** Normal flow of aqueous from ciliary body, through the pupil, and out through the trabecular meshwork and Schlemm canal located in the anterior chamber angle. **B.** Angle-closure glaucoma with pupillary block. Iris leaflet bows forward, blocking the chamber angle and prohibiting aqueous outflow. Meanwhile, aqueous production continues, and intraocular pressure rises.

TABLE 241-9 Treatment of Acute Angle-Closure Glaucoma (Crisis)

Agent Class	Agent, Dose, and Frequency*	Alternative Agent, Dose, and Frequency†
Initial Treatment to Reduce Intraocular Pressure and Block Production of Aqueous Humor		
Carbonic anhydrase inhibitor	Acetazolamide, 500 milligrams IV or PO, then 250 milligrams IV or PO 4 hours later, max 1000 milligrams/d	Brinzolamide 0.5%, one drop, affected eye, three times daily *Or* Dorzolamide 2%, one drop, affected eye, three times daily
Topical β-blocker	Timolol 0.5%, one drop, affected eye, two times daily	Betaxolol 0.5%, one drop affected eye, three times daily
Topical α_2-agonist	Apraclonidine 1%, one drop, affected eye, three times daily	Brimonidine 0.2%, one drop, affected eye, three times daily
Recheck IOP Hourly, Assess Need for Additional Agents		
Hyperosmotic agent	Mannitol, 15% or 20% solution, 1.5–2 grams/kg IV over 30 minutes	Glycerine, 1–2 grams/kg/dose orally, repeat every 5 hours

Abbreviation: IOP = intraocular pressure.

*Agents most commonly used, historically.

†Agents recommended by the American Academy of Ophthalmology.

treatment combines the effects of a carbonic anhydrase inhibitor (IV, PO, or topical), a topical β-blocker, and a topical α-agonist. If the intraocular pressure does not drop significantly with resolution of associated symptoms in the first hour (usually below 40 mm Hg), IV mannitol should be given if there are no contraindications. Pilocarpine is no longer recommended in the acute setting as cholinergic agents can paradoxically result in shallowing of the anterior chamber and further closure of the chamber's angle.[44,46] Begin treatment immediately, simultaneously with consulting ophthalmology. Ophthalmology, with access to a four-mirror slit lamp, may perform corneal indentation using dynamic gonioscopy to release angle closure. Pain and vomiting should be treated. Vomiting increases ocular pressure; fentanyl lowers intraocular pressure, whereas ondansetron has no effect on ocular pressure.[47,48] Definitive treatment is peripheral laser iridotomy (iridectomy). While many patients with acute angle-closure crisis are admitted to the hospital, patients who experience a stable drop in intraocular pressure with relief of associated symptoms may be discharged to definitive outpatient care at the direction of the ophthalmologist.

ACUTE VISUAL LOSS WITH OR WITHOUT PAIN

OPTIC NEURITIS

Acute optic neuritis may present without the complaint of pain, but patients frequently have mild to moderate pain with eye movement (19% to 92%).[49,50]

Visual acuity can range from mildly reduced to profound loss with no light perception. Reduction of vision occurs most commonly over days, but occasionally over hours. Visual loss is usually unilateral but can be bilateral. Color vision is affected more commonly than visual acuity, and there may be visual field deficits.

The red desaturation test is helpful in identifying optic neuropathies. This test is performed by having the patient look with one eye at a dark red object and then testing the other eye to see if the object looks the same color. The affected eye often will see the red object as pink or lighter red. An afferent pupillary defect (Figure 241-8) is commonly present. Funduscopic examination will reveal a swollen and edematous optic disk (papillitis) in approximately 30% of patients. If the head of the optic nerve is normal in appearance, the patient is said to have retrobulbar neuritis.

Optic neuritis can be idiopathic or an initial presentation of multiple sclerosis. Other causes of optic neuritis include post childhood vaccination; viral infections such as measles, mumps, chickenpox, encephalitis, herpes zoster, and mononucleosis; inflammation of structures contiguous with the optic nerve such as the meninges, orbit, and sinuses; and other infections, including syphilis, tuberculosis, *Cryptococcus*, and sarcoidosis. The differential diagnosis includes ischemic optic neuropathy (sudden onset and painless), papilledema (bilateral, painless with preserved visual acuity), hypertensive retinopathy, orbital tumor compressing the optic nerve (proptosis frequent), intracranial tumor compressing the visual pathway (seen on CT), and toxic or metabolic optic neuropathy from alcohol or various toxins such as the heavy metals or chloroquine.

Neurology and ophthalmology consultation are needed to establish a diagnosis. MRI results are important prognosticators for optic neuritis.[50]

ACUTE VISUAL LOSS WITHOUT PAIN

CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion is rare, thought to account for 1 in 10,000 ophthalmic visits.[51] The first branch off the internal carotid artery is the ophthalmic artery, which supplies the central retinal artery, which, in turn, provides the blood supply to the inner retina. If the central retinal artery becomes occluded, the inner retina will infarct and become pale, less transparent, and edematous. The macula is the thinnest portion of the retina, and the intact underlying choroidal circulation remains visible through this section of retina, creating the illusion of a "**cherry red spot**." The macular area maintains its normal color, and the surrounding ischemic retina turns pale, thus causing this classic finding on fundoscopy (**Figure 241-52**). Causes include carotid or cardiac embolus, retinal artery thrombosis, giant cell arteritis, vasculitis (lupus, polyarteritis nodosa), sickle cell disease, trauma, vasospasm (migraine), elevated intraocular pressure (glaucoma), hypercoagulable states, and low retinal blood flow (carotid stenosis or hypotension).

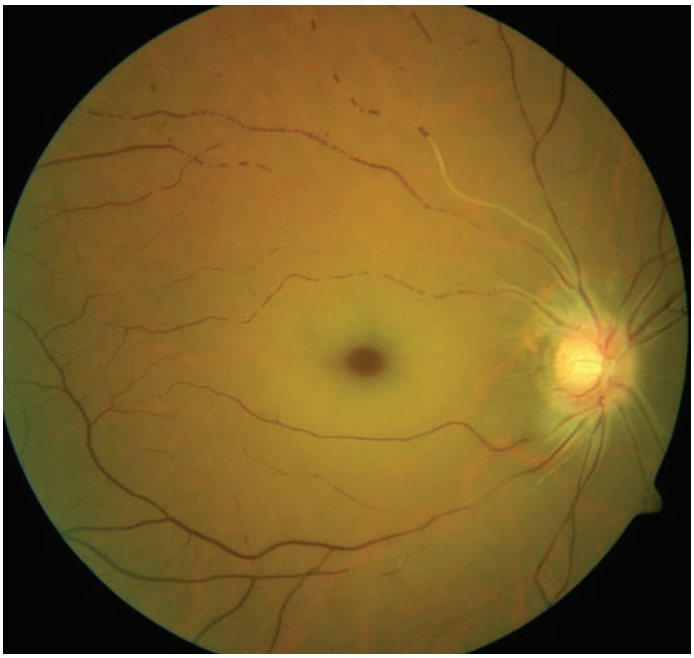

FIGURE 241-52. Central retinal artery occlusion. Note macular "cherry red spot" and retinal pallor as well as the plaques visible in the retinal vessels. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

Sudden (occurring over seconds), profound, painless, monocular loss of vision is characteristic of a central retinal artery occlusion. The event is often preceded by episodes of amaurosis fugax. Physical examination will often reveal an afferent pupillary defect in addition to the pale retina and cherry red macula. There is no evidence supporting or refuting the success of maneuvers such as digital massage or intraocular pressure–lowering drugs or breathing into a paper bag to increase partial pressure of arterial carbon dioxide.[52] Local intra-arterial tissue plasminogen activator does not appear to be effective.[53] More recent studies support IV tissue plasminogen activator within 4.5 hours of symptom onset[54-56]; however, ophthalmologists have not yet reached consensus on optimal management.[57] **Consult an ophthalmologist and neurologist immediately when suspecting acute central retinal artery occlusion, and follow institutional protocols for treatment.** Irreversible loss of visual function usually occurs after 4 hours of ischemia.

CENTRAL RETINAL VEIN OCCLUSION

Thrombosis of the central retinal vein causes retinal venous stasis, edema, and hemorrhage. Risk factors include diabetes, hypertension, cerebrovascular disease, cardiovascular disease, dyslipidemia, hypercoagulable states, vasculitis, glaucoma, and compression of the vein in thyroid disease and orbital tumors. Loss of vision is variable, ranging from vague blurring to rapid, painless, and monocular loss of vision. Funduscopic examination typically reveals optic disk edema and diffuse retinal hemorrhages in all quadrants ("blood-and-thunder fundus") (**Figure 241-53**). The contralateral optic nerve and fundus generally are normal, which helps distinguish central retinal vein occlusion from papilledema, and the diffuse retinal hemorrhages help distinguish it from optic neuritis (the peripheral retina is normal in optic neuritis). While no universally beneficial treatment exists,[58] anti–vascular endothelial growth factor and laser-induced chorioretinal anastomosis show promise.[59] Consult neurology and ophthalmology.

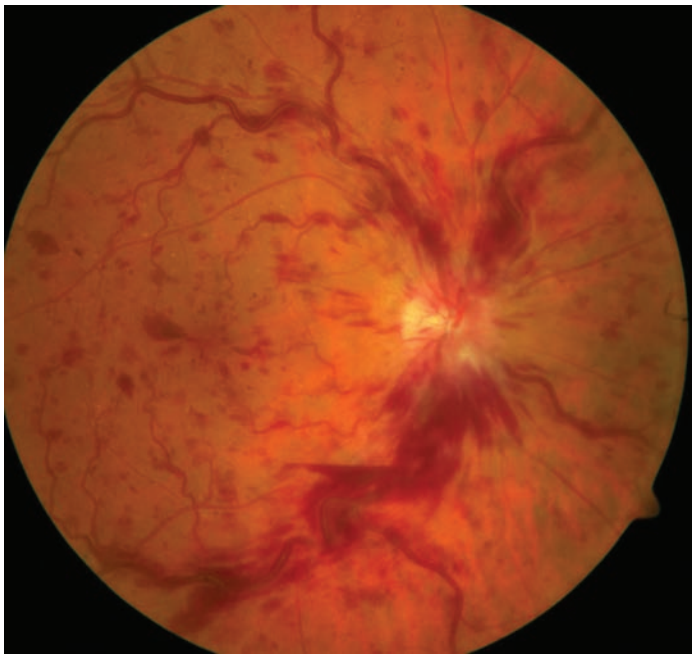

FIGURE 241-53. Central retinal vein occlusion. The disk margin is blurred, the veins are dilated and tortuous, and there is a large amount of hemorrhage typical of the "blood-and-thunder fundus." [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

RETINAL DETACHMENT/FLASHING LIGHTS AND FLOATERS

Complaints about new-onset flashing lights and/or floaters commonly cause patients to seek urgent medical attention. The first distinction to make is if the symptoms are monocular or binocular. **Binocular complaints are almost always intracranial (i.e., ophthalmic migraines), whereas monocular complaints are almost always related to the symptomatic eye.**

The posterior segment of the eye is a large cavity filled with vitreous gel. As a person ages, this gel eventually contracts centrally and separates from the posterior wall of the eye. The vitreous is very sticky and tugs on the retina before separation, stimulating the retina, which the brain perceives as light. The average age of onset is 55 years old, but it can occur as early as the 20s in severely nearsighted people. If the vitreous gel separates successfully, then floaters occur, which may persist for years until the gel liquefies enough for the floaters to sink below the visual axis. If the gel creates enough traction on the retina before separation that it tears a hole in the retina, then fluid can go through the retinal hole and start to peel the retina off like wallpaper.

Symptoms may include flashes of light, floaters, a dark veil or curtain in the field of vision, and decreased peripheral and/or central visual acuity. This is an emergent condition requiring a retina specialist to evaluate and treat the patient. **Diagnosing a retinal detachment or tear or vitreous detachment requires a dilated indirect ophthalmoscopic evaluation by an ophthalmologist within 24 hours.** Most tears occur in the peripheral retina, which is not visualized on the direct funduscopic examination. A large retinal detachment will appear as a pale billowing parachute on dilated funduscopic examination. See Figure 241-61 in the ocular US section later in this chapter for US diagnosis of retinal detachment. The US impression should be confirmed by the ophthalmologist who will manage the patient.

TEMPORAL ARTERITIS/GIANT CELL ARTERITIS

Temporal arteritis, or **giant cell arteritis**, is a systemic vasculitis involving medium-sized and large arteries. The temporal artery is the most common vessel involved. The disease causes optic neuropathy with profound visual loss and contralateral ocular involvement in days to weeks if not diagnosed and treated promptly. Patients are generally >50 years of age and frequently have a history of polymyalgia rheumatica. Symptoms may include headache, jaw claudication, myalgias, fatigue, fever, anorexia, and temporal artery tenderness. Many patients may have associated symptoms of transient ischemic attacks or stroke. The physical examination frequently will reveal an afferent pupillary defect if the optic nerve circulation is involved. An elevated sedimentation rate is usually present, with the majority of biopsy-proven cases in the range of 70 to 110 mm/h. The added presence of an elevated C-reactive protein also suggests the diagnosis. CT angiography is 71% sensitive and 85.7% specific for giant cell arteritis.[60] MRI is 94% sensitive but only 78% specific.[61] Ophthalmology should be consulted for management recommendations. Treatment consists of high-dose corticosteroids; however, the need for admission and IV steroids is controversial.[62] If the patient has no visual symptoms, typically the patient would be started on prednisone 60 milligrams once daily until follow-up with ophthalmology within 1 week. Some ophthalmologists admit all patients with any visual loss for high-dose IV methylprednisolone, 500 to 1000 milligrams per day for 3 days.[62] Steroids should not be delayed while waiting for a temporal artery biopsy to be performed; however, biopsies should be performed within 1 week of starting steroid therapy. Tocilizumab is recommended for those resistant to or unable to take corticosteroids.[61]

CRANIAL NERVE PALSIES

Bell's palsy is discussed in Chapter 172, "Acute Peripheral Neurologic Disorders."

DIABETIC/HYPERTENSIVE CRANIAL NERVE PALSIES

Chronic diabetes and hypertension eventually can create vascular compromise to the vasa nervorum of any cranial nerve. **The pupil is spared in acute diabetic cranial nerve III palsy** due to vascular compromise of the central nerve fibers primarily (the efferent pupillomotor fibers run in the periphery of the nerve and are spared) (**Figure 241-54**). Extraocular muscle testing will reveal an inhibition of ipsilateral medial gaze, upward gaze, and downward gaze as well as ptosis in an acute cranial nerve III palsy. Lateral gaze (abduction) will be preserved, and diplopia will be worse when the patient attempts to look toward the contralateral side due to the inability to adduct the eye (medial rectus dysfunction). In an acute cranial nerve VI palsy, lateral gaze will be diminished (abduction) on the ipsilateral side, and diplopia will be worse when the patient is trying to look to the affected side (lateral rectus dysfunction). Neuroimaging is needed in the ED to rule out an intracranial lesion.

If no other associated neurologic symptoms or findings are present, the blood sugar and blood pressure are under control, and neuroimaging does not suggest an alternative diagnosis, the patient can be discharged

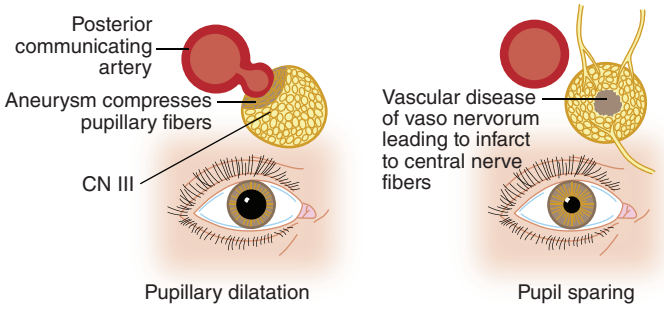

FIGURE 241-54. Posterior communicating artery aneurysm compresses the peripherally located pupillomotor fibers of cranial nerve (CN) III, causing a nerve palsy and pupillary dilatation. Diabetes and hypertension can cause microvascular compromise of the central nerve fibers, causing a nerve palsy with pupil sparing.

with ophthalmology and/or neurology follow-up. Most cases show spontaneous improvement over time.

POSTERIOR COMMUNICATING ARTERY ANEURYSM

Acute cranial nerve III palsy with ipsilateral pupillary dilatation is a posterior communicating artery aneurysm until proven otherwise. Concomitant headache is a frequent but not absolute finding. Expansion of an aneurysm of the posterior communicating artery frequently causes compression of the outer fibers of cranial nerve III. The pupillomotor fibers are located in the outer portion of cranial nerve III; therefore, the pupil becomes dilated on the affected side (Figure 241-54). Treatment is emergent blood pressure reduction if hypertensive, neuroimaging, and neurosurgical consultation.

HORNER'S SYNDROME

The physical findings of ipsilateral ptosis and miosis and anhidrosis are characteristic of Horner's syndrome (Figure 241-55). Interruption of the sympathetic nerve impulses controlling the superior tarsal muscle in the upper eyelid and the iris dilators causes these classic findings. Interruption can occur anywhere along the pathway from the brainstem to the sympathetic plexus surrounding the carotid artery (**Figure 241-56**). ED evaluation includes a chest radiograph, CT scan of the brain and cervical region, and CT angiogram or magnetic resonance angiography of the head and neck vessels for carotid dissection. Institutional protocols determine if CT angiogram or magnetic resonance angiography is preferred.

In adults, causes of Horner's syndrome include cerebrovascular accidents, tumors, internal carotid artery dissection, herpes zoster, and trauma. In children, the causes include neuroblastoma, lymphoma, and metastasis. **Neck pain and acute Horner's syndrome suggest carotid dissection and can occur spontaneously (usually >30 years old) or as a result of blunt or penetrating neck injury.** Patients presenting with Horner's syndrome will most likely need CTA or MRI imaging of the head and neck.

PSEUDOTUMOR CEREBRI (IDIOPATHIC INTRACRANIAL HYPERTENSION)

Increased intracranial pressure, papilledema, normal cerebrospinal fluid, and normal CT/MRI characterize pseudotumor cerebri. Incidence is increasing.[63] Patients complain of nausea, vomiting, headaches, and blurring of vision. **Patients can develop cranial nerve VI paresis, causing horizontal diplopia (double vision on lateral gaze).** A key component of examination is the identification of **visual field defects**. If CT/MRI is normal, perform lumbar puncture and record opening pressure; send cerebrospinal fluid for routine diagnostics. Consult ophthalmology as well as neurosurgery or neurology for the treatment plan. Initial treatment is acetazolamide, 500 milligrams PO twice daily, and outpatient visual field monitoring.

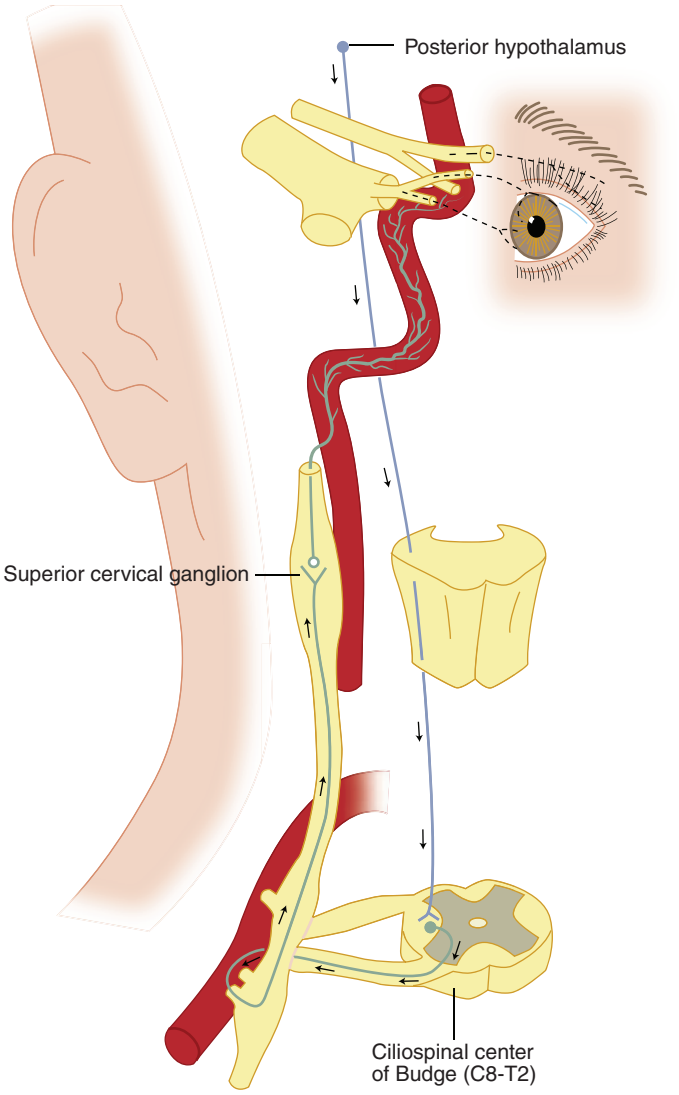

FIGURE 241-56. Sympathetic nerve pathway of the eye. An interruption anywhere along this pathway can cause Horner's syndrome.



FIGURE 241-55. Horner's syndrome. Note the ptosis and miosis of the right eye. [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine*, 2nd ed. © 2002, McGraw-Hill, New York.]

OCULAR ULTRASONOGRAPHY

Direct visualization of intraocular structures can be limited by periorbital edema, corneal abrasions, hyphema, and cataracts. The superficial location of the eye and its cystic composition make US ideal in the assessment of a variety of ocular disorders. Ocular ultrasonography can expedite the diagnosis and management of several ocular emergencies, including retinal detachment, retrobulbar hematoma, globe perforation, lens dislocation, vitreous hemorrhage, and intraocular foreign body.[64-66] The indications for ocular ultrasonography include loss of vision/decreased vision, eye pain, eye trauma, suspected intraocular foreign body, and head injury. The ability of emergency physicians to accurately diagnose ocular pathology using bedside ocular ultrasonography has been well documented in emergency medicine literature.[64,65]



FIGURE 241-57. A high-resolution linear array US transducer is being applied to the closed eyelid. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

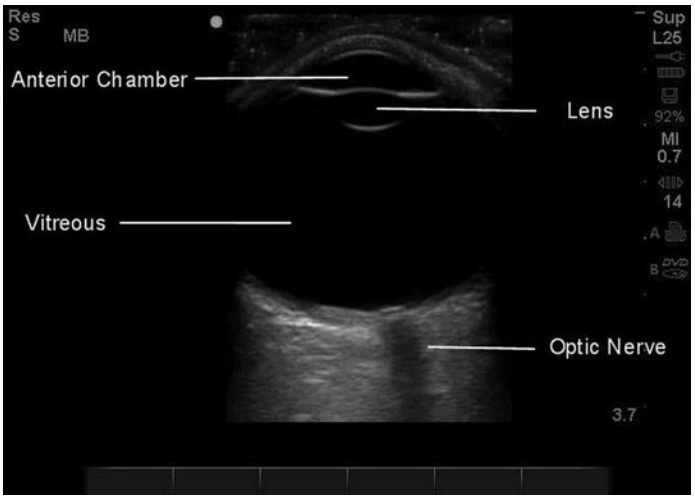

FIGURE 241-58. Normal eye in transverse view showing the anterior chamber, lens, vitreous, and optic nerve. [Courtesy of Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

SCANNING TECHNIQUE AND NORMAL ANATOMY

Use a 7.5-to 10-mHz linear array transducer and **set the unit to "Ocular" for lower energy**. Place the patient in a supine or partially upright position and have the patient keep the eyes closed (**Figure 241-57**). Apply a large amount of standard water-soluble US gel to the patient's closed eyelid so that the transducer does not touch the eyelid. US gel is not detrimental to the eye. Without applying any pressure and asking the patient to look straight ahead with the eyes closed, scan the globe in sagittal and transverse planes. Stabilize the scanning hand over the bridge of the nose or on the forehead. Scan both eyes through closed eyelids for comparison. Examine the eyes in the neutral position and during gentle eye movements from side to side and up and down to thoroughly evaluate the orbit. Dynamic examination is crucial to identify adhesions, detachments, and membranes. The probe can also be moved side to side in both scanning planes to demonstrate the full extent of the structures in the eye. Adjust the depth so that the image fills the screen. The gain also needs to be adjusted multiple times during the examination to identify subtle abnormalities and avoid artifacts. Because the eye is a fluid-filled organ, it provides a perfect acoustic window for scanning and obtaining excellent images.[67,68] (See Video: Ocular Ultrasound.)

The normal eye appears as a circular hypoechoic organ. The cornea is seen as a thin hyperechoic layer parallel to the eyelid attached to the sclera at the periphery. The iris is identified as a linear echogenic line extending from the periphery toward the lens on both sides. The anterior chamber contains anechoic fluid and is bordered by the cornea, iris, and anterior reflection of the lens. The normal lens has anterior and posterior boundary echoes with an anechoic center and is biconvex in shape. The normal vitreous chamber is filled with anechoic fluid. Vitreous is relatively echo free in a young, healthy eye. Sonographically, the normal retina cannot be differentiated from the other posterior layers such as choroid and sclera (**Figure 241-58**). The evaluation of the retrobulbar space includes optic nerve, extraocular muscles, and bony orbit. The retro-orbital fat appears very echogenic. The optic nerve is visible as a hypoechoic linear region extending away from the globe posteriorly. Minor manipulations in the angulation of the probe are necessary to visualize the optic nerve. The central retinal artery and central retinal vein can be identified using Doppler.[67,68]

OCULAR TRAUMA ULTRASONOGRAPHY

Assessment of patients with ocular trauma by US is of particular value when pain, soft tissue edema, and abnormalities like corneal edema, hyphema, or cataract make direct visualization of the posterior segment of the eye difficult. US can detect a wide variety of ocular pathologies from trauma including dislocated lens, globe disruption, vitreous hemorrhage, hyphema, retinal detachment, orbital emphysema, and retrobulbar hemorrhage. **Suspected ruptured globe is a relative contraindication to US examination, due to the risk of extruding globe contents associated with direct pressure on and around the eye.**[65]

US findings of globe rupture include distortion of the normal shape of the globe, decrease in the size of the globe, anterior chamber collapse, and vitreous hemorrhage.[64] Ocular trauma can lead to buckling of the sclera and scleral folds, which appear sonographically as irregularities in globe contour, highly reflective at their top and shadowing the orbital tissues (**Figure 241-59**). Sonographically, **lens dislocation** is seen as a highly reflective oval mass moving independently of the surrounding structures with eye movements. The dislocation is more readily visualized if it is complete or a cataract has formed. **Hyphema** can be identified on US as an echoic structure of variable echogenicity depending on the age of the bleed. Fresh hyphema will have low echogenicity and becomes more echogenic as it becomes organized. A **retrobulbar (pre- or postseptal) hematoma** is visualized as an echoluceny posterior to the globe.[69]

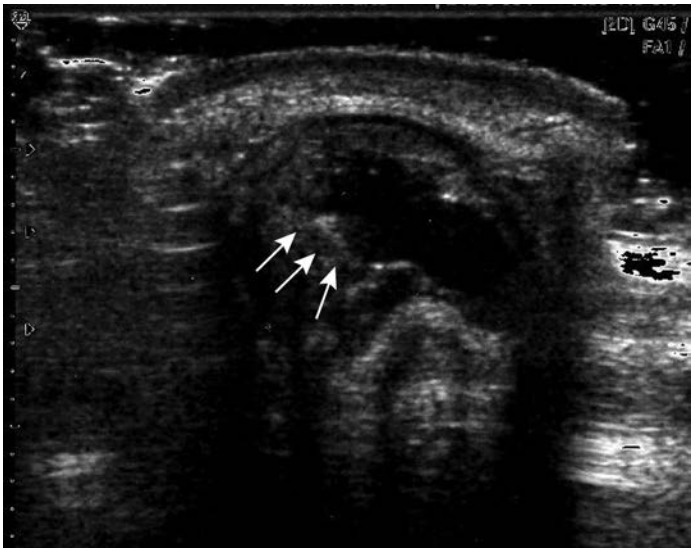

FIGURE 241-59. Extensive globe rupture from trauma. US shows abnormal, irregular shape of the eye with ocular contents displaced posteriorly (*arrows*). [Courtesy of M. Blaivas and Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

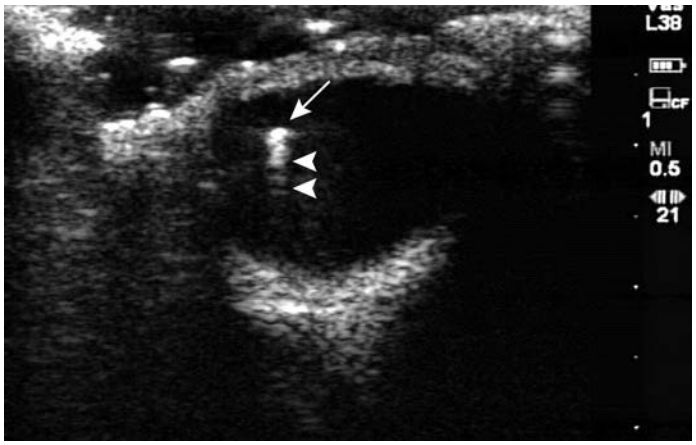

FIGURE 241-60. A hyperechoic foreign body (*arrow*) in the eye. Note the bright echogenic reverberation artifact (*arrowheads*). [Courtesy of M. Blaivas and Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]



FIGURE 241-61. Retinal detachment is seen as a hyperechoic membrane in the posterior aspect of the globe (*arrow*). [Courtesy of D. Chandwani and Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

INTRAOCULAR FOREIGN BODY ULTRASONOGRAPHY

The presence of an intraocular foreign body may not always be apparent on clinical examination. US is a useful adjunct for detecting and localizing intraocular foreign bodies, but visualization of intraocular foreign bodies depends on their intrinsic echogenicity. Metallic objects are especially visible because of their bright echogenic acoustic profile and associated shadowing or reverberation artifacts in the echolucent vitreous, whereas materials such as wood are more difficult to detect (**Figure 241-60**). Sonographic patterns of shadowing and comet tail artifacts may help distinguish different foreign body materials. The dynamic nature of the US examination is also helpful in anatomic localization, determination of the size, and analysis of the composition of the foreign body.[70-72] With penetrating ocular injuries, a track of hemorrhage may be seen outlining the route of passage of a foreign body.

RETINAL DETACHMENT ULTRASONOGRAPHY

Retinal detachment can be difficult to detect on physical examination, especially when the detachment is small. Bedside US reliably detects retinal detachment and is particularly useful when the examiner's view to the retina is obscured by periorbital edema, blood, or other opacities. For the detection of retinal detachment, ultrasonography performed by an emergency physician has a sensitivity of 97% to 100% and a specificity of 83% to 92%.[73,74]

A retinal detachment is seen as an echogenic undulating membrane in the posterior to lateral globe, protruding into vitreous (**Figure 241-61**). Even in complete retinal detachments, the typically folded surface remains bound to the ora serrata anteriorly and the optic nerve head posteriorly. Unlike choroidal detachment that does not change with ocular movements, retinal detachment moves with eye movements.[75] A shallow cuff of subretinal fluid may also be seen along with the detachment. On occasion, retinal detachments are also accompanied by vitreous hemorrhages.

VITREOUS HEMORRHAGE ULTRASONOGRAPHY

Vitreous hemorrhage can be spontaneous or associated with trauma. Vitreous hemorrhage can interfere with vision and, if it is large, can potentially cause blindness. It appears as echogenic material in the posterior chamber. The sonographic appearance of vitreous hemorrhage depends on its age and the severity of the bleed. Increasing gain is helpful for detecting acute hemorrhages because they are often minimally echogenic. Early mild hemorrhages are seen as small dots or scattered low-amplitude reflective mobile opacities in the vitreous. As the hemorrhage matures and organizes, thick mobile membranes are formed in the vitreous. Sonographically, this is seen as vitreous filled with multiple large echoes (**Figure 241-62**). Due to gravitational forces, these opacities may also layer inferiorly. Echogenic stranding and scarring of the vitreous occur as time progresses.[75-77] As vitreous hemorrhage becomes more echogenic, it can mimic the appearance of a retinal detachment. The main characteristics that can help in differentiating vitreous hemorrhage from retinal detachment are as follows: (1) Retinal detachment moves with eye movements unlike vitreous hemorrhage, which will remain horizontal; and (2) vitreous hemorrhages are frequently seen in the middle portion of the posterior chamber, and retinal detachments almost always occur at the posterior-most portion of the eye, adjacent to the optic disk and macula.[73]

OPTIC NERVE SHEATH ULTRASONOGRAPHY TO DETECT ELEVATED INTRACRANIAL PRESSURE

Optic Nerve Sheath Measurement Another novel use of bedside ocular US is the evaluation of the optic nerve sheath diameter to assess possible elevated intracranial pressure. Multiple studies have shown good correlation between intracranial pressure and sonographic optic nerve sheath diameter.[78-85] On US, a normal optic nerve sheath measures up to 5.0 mm in diameter in adults, 4.5 mm in children, and 4.0 mm in infants.[86] The linear probe is used in this assessment with the patient supine or with a 20- to 30-degree head up tilt. The measurement is

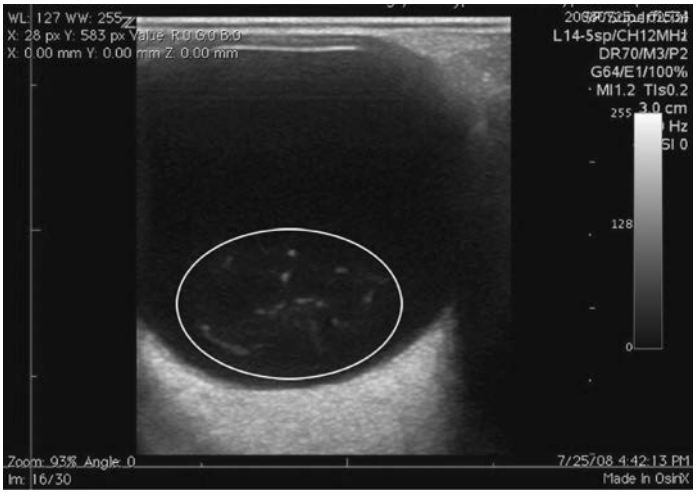

FIGURE 241-62. Bright echoes (enclosed in oval) in the posterior chamber demonstrating vitreous hemorrhage. [Courtesy of D. Chandwani and Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

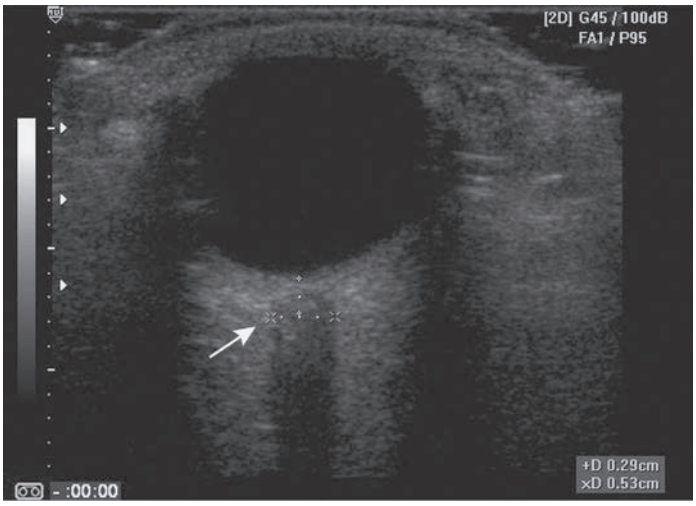

FIGURE 241-63. An optic nerve sheath measuring 5.3 mm in a patient with head injury is shown. One set of calipers measures 3 mm behind the globe, and the second measures the optic nerve sheath diameter (*arrow*). [Courtesy of M. Blaivas and Allen R. Katz, Department of Ophthalmology, University of Nebraska Medical Center.]

obtained 3 mm posterior to the globe for both eyes. A position of 3 mm behind the globe is selected because the US contrast is greatest at this point, and the measurements are more reproducible (**Figure 241-63**). Typically, three measurements are averaged. Current literature suggests that the cutoff value that provides the best accuracy for the prediction of intracranial pressure >20 mm Hg is 5.7 to 6.0 mm. Increased intracranial pressure should be suspected with values above this threshold. The sensitivity and specificity in detecting increased intracranial pressure using a cutoff value of 5.7 to 6.0 mm are in the range of 87% to 95% and 79% to 100%, respectively.[87] In addition to elevated intercranial pressure, the differential for increased optic nerve sheath diameter includes an anterior orbital mass, optic neuritis, trauma, and cavernous sinus mass.[88]

CAUTIONS WITH OCULAR ULTRASONOGRAPHY

- **If globe rupture is suspected, avoid any manipulation or pressure upon the globe or eyelid.**
- Limit the duration of ocular US examination, especially when using spectral and color Doppler, and **set the US unit for ocular imaging.** The recommended exposure limits are half those of fetal imaging.
- Various artifacts may interfere with ocular US examination. Orbital emphysema can make it difficult to visualize contents of the orbit.
- Air bubbles within the vitreous, which may appear in the setting of trauma to the globe, may resemble an intraocular foreign body.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 242

Ear Disorders

Kathleen Hosmer

This chapter discusses common nontraumatic conditions affecting the external, middle, and inner ear. Lacerations to the ear are discussed in Chapter 42, "Face and Scalp Lacerations." Ear disorders in children are discussed in Chapter 121, "Ear and Mastoid Disorders in Infants and Children."

ANATOMY

EXTERNAL EAR

The auricle, or pinna, is the visible external portion of the ear, whose trumpet shape enables it to collect air vibrations. It consists of a thin plate of elastic cartilage with a tightly adherent covering of skin. The external auditory canal is an S-shaped, skin-lined tube that extends from the auricle to the tympanic membrane (TM). The outer one third of the external auditory canal is composed of an incomplete cartilaginous tube. Its thick skin supports hair follicles plus apocrine and sebaceous glands. The inner two thirds of the canal is composed of bone covered by a thin layer of tightly adherent skin, which is easily torn by minimal trauma.

The blood supply to the external ear is derived from the posterior auricular, superficial temporal, and deep auricular arteries. Venous drainage of the external ear is into the superficial temporal and posterior auricular veins, which then drain into the external jugular vein. The posterior auricular vein frequently connects to the sigmoid sinus, providing a route for extension of infected material into the intracranial cavity.

MIDDLE EAR

The middle ear is an air-containing cavity in the petrous temporal bone. It contains the auditory ossicles, which transmit vibrations of the TM to the perilymph of the internal ear. It communicates with the nasopharynx anteriorly via the eustachian tube and with the mastoid air spaces posteriorly via the aditus ad antrum (**Figure 242-1**).

The TM is a thin, pearly gray, fibrous membrane that produces a cone-shaped light reflex anteroinferiorly when illuminated. Superiorly, the pars flaccida is the relatively slack portion of the membrane between the malleolar folds; the remainder of the membrane is tense and is called the *pars tensa*. The auditory ossicles are the malleus, incus, and stapes. Both the incus and the handle and lateral processes of the malleus are typically visible through the TM (**Figure 242-2**). Figure 242-1 shows the relationships of the facial nerve, sigmoid sinus, and internal carotid artery to the middle ear.

INNER EAR

The inner ear consists of the cochlea, which contains the auditory sensory receptors, and the vestibular labyrinth, which contains balance receptors. Cristae in the semicircular canals detect angular acceleration, and macules detect linear acceleration. Afferent nerves from the vestibular labyrinth connect to brainstem nuclei to maintain smooth movement of the eyes during head movement and to the cerebellum to control oculomotor and postural functions. Blood supply is from the vertebrobasilar system (**Figure 242-3**). The otolithic organs (utricle and saccule) lie in the vestibule. The internal auditory artery divides into the common cochlear artery and the anterior vestibular artery. The anterior

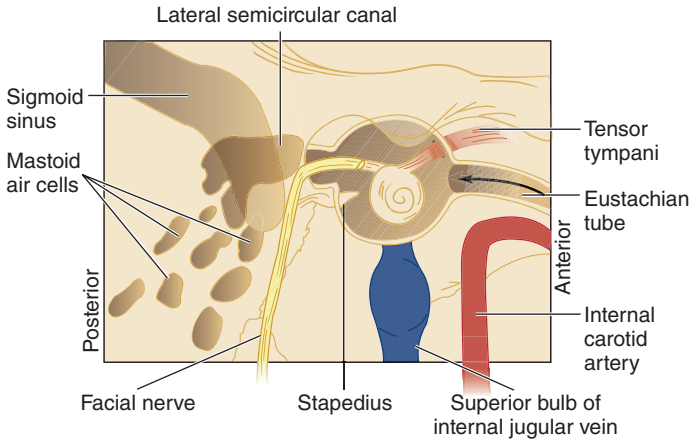

FIGURE 242-1. Sagittal section of the middle ear and related structures.

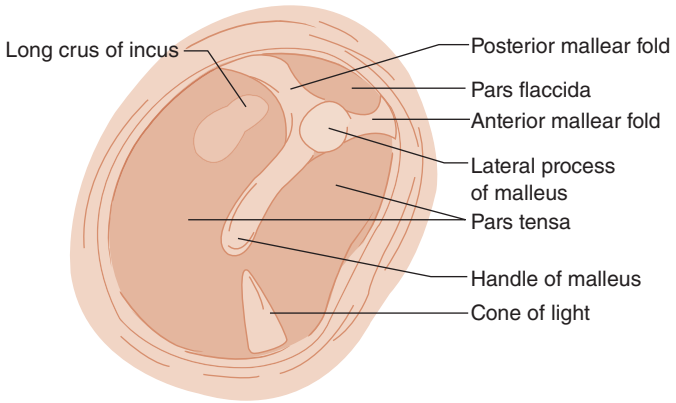

FIGURE 242-2. Right tympanic membrane as seen through the otoscope.

vestibular artery provides the blood supply to the anterior and horizontal semicircular canals but not to the cochlea. Isolated occlusion of the anterior vestibular artery may therefore cause acute vestibular syndrome without hearing loss.

OTALGIA

Primary otalgia is caused by auricular and periauricular disease, whereas referred otalgia is caused by disease originating from remote structures.[1] Referred otalgia is common because the ear and several structures of the head and neck share sensory innervation from the fifth, seventh, ninth, and tenth cranial nerves, as well as by the cervical plexus. **Table 242-1** lists common causes of primary and referred otalgia, including related neuralgias.[1]

TABLE 242-1 Causes of Otalgia

Primary	Referred
Trauma	Temporomandibular dysfunction syndrome
Infection	**Dental**
Otitis externa	Abscessed teeth/dental carries
Otitis media	Malocclusion
Mastoiditis	Bruxism
Bullous myringitis	
Pinna cellulitis	**Retro- and oropharyngeal**
Cerumen impaction	Tonsillitis
Cholesteatoma	Abscess
Neoplasms	Neoplasm
	Eustachian tube dysfunction
Foreign bodies	**Nasal cavity**
	Sinusitis
Facial neuralgias with periauricular pain	Deviated septum
Trigeminal	**Throat and neck**
Herpetic geniculate (Ramsay Hunt syndrome)	Foreign body
Great auricular neuralgia	Thyroid disease
	Neoplasm

TINNITUS

Tinnitus is the perception of sound without external stimulation. It may be constant, pulsatile, high- or low-pitched, hissing, clicking, or ringing. It is most prevalent between the ages of 40 and 70 years old.[2]

Tinnitus is divided into two types: objective and subjective. Objective tinnitus may be heard by the examiner. Subjective tinnitus is more common. Its exact origin is unknown, although it is believed to result from damage to cochlear hair cells. **Table 242-2** outlines causes of tinnitus.[2]

A number of drugs are associated with tinnitus, and some also cause hearing loss (**Table 242-3**).[2]

Accurate diagnosis usually requires referral to an otolaryngologist. Many medications have been suggested as therapies; antidepressants may help patients tolerate tinnitus but do not change the course.

SUDDEN HEARING LOSS

Sudden hearing loss occurs over 3 days or less and is divided into sensorineural (cochlea, auditory nerve, or central auditory processing) and conductive (external ear, TM, and ossicles). Conductive hearing loss is more likely due to a reversible cause, such as otitis media, serous otitis, or a cerumen impaction. Indicators of poor prognosis include more severe hearing loss on presentation and the presence of vertigo. **Table 242-4**[3] lists causes of sensorineural hearing loss.

Viral infections, most typically mumps, have long been associated with sudden hearing loss.[4] Because of the terminal branches and interosseous location of the blood supply to the inner ear, the ear is uniquely vulnerable to a variety of vascular and hematologic diseases. Sudden hearing loss may also be caused by rupture of the TMs.

The evaluation begins with a complete history and physical examination. Differentiate conductive hearing loss from sensorineural hearing loss with a tuning fork. To perform the **Weber test**, place a vibrating tuning fork on the forehead and ask the patient where it is heard. It is normal to hear it equally in both ears; if the sound lateralizes to one ear, there is conductive hearing loss in that ear, or there is sensorineural loss in the opposite ear. To perform a **Rinne test**, place the tuning fork on skin over the mastoid bone, and then move the tuning fork to the entrance of the ear canal on the same side. The sound is normally heard better through air conduction at the entrance of the ear. If the sound is heard better over the mastoid bone, there is conductive hearing

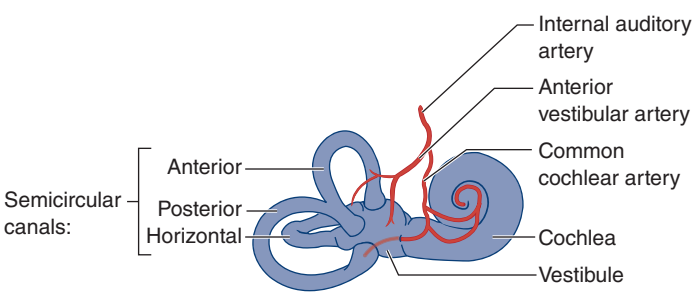

FIGURE 242-3. Schematic of the bony labyrinth containing the vestibular and auditory sensory organs.

TABLE 242-2 Common Causes of Tinnitus

Objective	Subjective
Vascular	Sensorineural hearing loss
Arteriovenous malformations	Hypertension
Arterial bruits	Conductive hearing loss
Mechanical	Head trauma
Enlarged eustachian tube	Medication side effects
Palatomyoclonus	Temporomandibular joint disorders
Stapedial muscle spasm	Depression, anxiety
	Neurologic
	Acoustic neuroma
	Multiple sclerosis
	Benign intracranial hypertension
	Ménière's disease
	Cogan's syndrome

TABLE 242-3 Ototoxic Agents Causing Tinnitus or Hearing Loss

Loop diuretics	**Chemotherapeutic agents**
Ethacrynic acid	Cisplatin
Furosemide	Carboplatin
Bumetanide	Vinblastine
Salicylates*	Vincristine
NSAIDs*	**Topical agents**
Quinine	*Solvents*
Antibiotics	Propylene glycol
Aminoglycosides*	*Antiseptics*
Erythromycin	Ethanol
Vancomycin	**Erectile Dysfunction Drugs**
Polymyxin B	Tadalafil
Neomycin	Sildenafil

*Most commonly implicated agents.

loss. Sudden conductive hearing loss may result from obstruction of the external auditory canal or from disturbances of the TM or ossicles. Evaluate all current medications for possible ototoxic agents. A history of trauma or recollection of a "popping" noise preceding the hearing loss may indicate perforation of the TM or ossicle dislocation. Coexistent tinnitus or vertigo may point to Ménière's disease.

The differential diagnosis includes both potentially reversible and potentially ominous causes (Table 242-4). If the physical examination does not identify the cause, otolaryngology consultation is necessary. Initial treatment of idiopathic sensorineural hearing loss is 60 milligrams of prednisone once daily for 7 to 14 days with follow-up arranged within 2 weeks.[5-8]

ACUTE DIFFUSE OTITIS EXTERNA

Otitis externa includes infections and inflammation of the external auditory canal and auricle. It is divided into acute diffuse and malignant types.

TABLE 242-4 Causes of Sudden Hearing Loss

Cause	Examples
Idiopathic (71%)	
Infection (12.8%)	Mumps Epstein-Barr virus Herpes simplex virus *Toxoplasma gondii* Syphilis Group A *Streptococcus* Meningitis
Otologic disease (4.7%)	Ménière's disease Skull base or otologic surgery Autoimmune disease
Trauma (4.2%)	Head Injury Acoustic trauma Barotrauma
Vascular or hematologic (2.8%)	Cardiovascular disease Neurovascular disease Hemorrhage (brain)
Neoplastic (2.3%)	Vestibular schwannoma Cerebellar angioma
Other causes (2.2%)	Pregnancy related Nonotologic surgery

PATHOPHYSIOLOGY AND MICROBIOLOGY

Predisposing factors for the development of otitis externa are trauma to the skin of the external auditory canal and elevation of the local pH. Factors include frequent contact with water from swimming or bathing in hot tubs, pools, or freshwater lakes, and living in a humid environment. Trauma is most commonly due to scratching or overzealous disimpaction of cerumen. Cerumen is an acidic mixture of sebaceous and apocrine gland secretions and desquamated epithelial cells. It forms a physical barrier that protects the skin of the external auditory canal, whereas the acidic pH has antimicrobial properties.

The most common organisms are *Pseudomonas aeruginosa*, *Staphylococcus aureus, Staphylococcus epidermidis,* and Enterobacteriaceae.[9,10] Otomycosis, or fungal otitis externa, is found in tropical climates and in the immunocompromised or after previous long-term therapy with antibiotics. Most cases are caused by *Aspergillus* or *Candida*.[11] Noninfectious causes include contact dermatitis from topical medications or resins in hearing aids, seborrhea, and psoriasis.

CLINICAL FEATURES

Otitis externa, or swimmer's ear, is characterized by pruritus, pain, and tenderness of the external ear. Physical signs include erythema and edema of the external auditory canal, which may spread to the tragus and auricle. Other signs are clear or purulent otorrhea and crusting of the external canal. As the disease progresses, the pain may become intolerable and occur with mastication or any movement of the periauricular skin. Increasing edema may eventually narrow the canal lumen and can lead to hearing impairment. In severe cases, infection may spread to the periauricular soft tissues and lymph nodes, and there may be lateral protrusion of the auricle secondary to inflammation.

TREATMENT

The treatment consists of analgesia, cleansing of the external auditory canal, acidifying agents, topical antimicrobials with or without steroids, and, in cases of edema obstructing the canal, adding an ear wick.[12,13] Cleansing may be done with gentle irrigation using hydrogen peroxide or saline or gentle suction under direct visualization.[12] Nonototoxic ototopical antibiotics are first-line therapy, particularly when the integrity of the TM is unknown or in the presence of a known TM perforation or tympanostomy tubes. Recommended topical agents are listed in **Table 242-5**.[13] Although there are few established cases of ototoxicity, there is a theoretical risk of both auditory and vestibular toxicity with the use of aminoglycosides, polymyxin, and acetic acid preparations.[12]

If cost is a factor and there are no known contraindications, acetic acid drops may be used. In this case, a suspension should be used and not a solution; theoretically, this has less chance of middle ear penetration and resultant ototoxicity.

Instill the medication into the cleansed ear with the ear facing up, with this position held for 3 minutes.

For cases unresponsive to initial treatment, cultures should be obtained. Oral antibiotics are reserved for febrile patients and those with periauricular extension.[14] Instruct patients with otitis externa to avoid predisposing factors to eliminate recurrences. Strategies include earplugs while swimming or bathing (cotton wool impregnated with

TABLE 242-5 Topical Agents for Acute Otitis Externa

Agent	Comments
Ciprofloxacin, dexamethasone	Safe with perforations
Ofloxacin	Safe with perforations
Ciprofloxacin, hydrocortisone	Not safe with perforation
2% acetic acid solution	pH 4.5–6.0 (not safe with perforation)
Acetic acid, hydrocortisone	pH 3.0 (not safe with perforation)
Neomycin/polymyxin B/hydrocortisone	Ototoxic; avoid in chronic otitis externa

petroleum jelly or commercial earplugs), brief use of a hair dryer to remove water from the ear canal, and avoiding cotton-tipped applicators or other devices to remove cerumen.

If fungal infection is suspected, topical clotrimazole 1% solution can be used, although its safety in perforated TMs has not been established.[15] Alternatively, systemic treatment with an antifungal agent such as fluconazole can be used.[16] Instruct patients to follow up with their primary physician or an otolaryngologist in 1 week to be reevaluated; they should return to the ED for sudden worsening with fever or marked swelling.

MALIGNANT OTITIS EXTERNA

Malignant otitis externa is a potentially life-threatening infection of the external auditory canal involving the pinna and soft tissues with variable extension to the skull base.

PATHOPHYSIOLOGY AND MICROBIOLOGY

Malignant otitis externa begins as a simple otitis externa that then spreads to the deeper tissues of the external auditory canal and infects cartilage, periosteum, soft tissue, and bone, with the normal anatomy of the ear serving as the conduit for the spread of infection. The majority of cases are caused by *P. aeruginosa,*[16] but methicillin-resistant *S. aureus* now accounts for 15% of cases.[17] Fungal disease occurs in diabetics and patients with immunocompromise.[18] The cerumen of diabetic patients has a higher pH than that of normal controls and represents an additional breakdown in local defense mechanisms. Small blood vessel disease of diabetics may lead to cartilaginous degeneration, further promoting the spread of infection.

CLINICAL FEATURES AND DIAGNOSIS

An individual with persistent otitis externa despite 2 to 3 weeks of topical antimicrobial therapy should be suspected of having malignant otitis externa. The typical presentation is severe otalgia (90%) and edema of the external auditory canal with otorrhea (70%).[19] Granulation tissue may be evident on the floor of the external auditory canal.

Examine both ears, inspecting both pinnas from the anterior, lateral, and posterior aspects. The infected ear will be erythematous, edematous, and more prominent than the unaffected ear. Assess nearby structures. Parotitis may be present, and trismus indicates involvement of the masseter muscle or temporomandibular joint. Cranial nerve involvement is a serious sign. The seventh cranial nerve is usually the first nerve affected by cranial extension, and the presence of dysfunction of the ninth, tenth, or eleventh cranial nerve implies even more extensive disease. Lateral or sigmoid sinus thrombosis and meningitis are more serious possible complications. Clinical diagnosis and staging are confirmed with CT or MRI of the head. Ten percent of admitted patients develop sepsis, mostly in the elderly.[20]

TREATMENT

Start ciprofloxacin 400 milligrams IV every 8 hours in adults.[16] Selected cases of early infection may be managed as outpatients with oral quinolones, 750 milligrams of ciprofloxacin two to three times daily.[16] Mild cases are likely to completely resolve with a single course of antibiotic therapy, whereas more advanced stages may require IV antibiotics and possible surgical debridement with otolaryngology. If septic, resuscitate with fluids, and start broad-spectrum antibiotics to cover methicillin-resistant *S. aureus* and *P. aeruginosa* (see Chapter 151, "Sepsis").

OTITIS MEDIA

Otitis media (OM) is primarily a disease of infancy and childhood (see Chapter 121 for management of OM in children). Although the management of OM in children and adults is similar, there are important differences in adults, highlighted in the following section, especially for the management of OM with effusion.

PATHOPHYSIOLOGY AND MICROBIOLOGY

Acute OM is much less common in adults than children, by a factor of 10 to 40 times.[21,22] The most common bacterial pathogens recovered in adults with acute OM are *Streptococcus pneumoniae*, *Haemophilus influenzae*, methicillin-sensitive *S. aureus*, and *P. aeruginosa*.[21,22,23] Only young adults have received the *H. influenzae* type b vaccine, and thus older adults remain unprotected from all *Haemophilus* strains. The predominant organisms involved in chronic OM are *S. aureus*, *P. aeruginosa*, *Aspergillus*, and less commonly, anaerobic bacteria.[24] OM with effusion is differentiated from acute OM. In adults, OM with effusion is frequently associated with significant pathology: acute or chronic sinusitis in 66% of cases, smoking-induced nasopharyngeal lymphoid hyperplasia and adult-onset adenoidal hypertrophy in 19%, and head and neck tumors in 4.8%.[25] Adult patients with OM with effusion may also have symptoms of gastroesophageal reflux.[26]

CLINICAL FEATURES AND DIAGNOSIS

Unlike children, adults with OM frequently lack the prodrome of an upper respiratory infection and may present simply with significant otalgia, with or without fever.[21,22,23] Otorrhea and hearing loss are variably present, whereas tinnitus, vertigo, and nystagmus are uncommon but possible findings. The TM may be retracted or bulging. It may be red in color, indicating inflammation, or it may be yellow or white, as a result of middle ear fluid. Pneumatic otoscopy almost uniformly demonstrates impaired mobility. **Always assess facial nerve function because of its proximity to the middle ear.**

TREATMENT

There are no treatment guidelines specifically for adults. The "wait-and-see" method recommended in children[27] has not been evaluated in adults. The preferred initial treatment is amoxicillin 1000 milligrams three times daily.[16] Alternative agents include extended-release amoxicillin-clavulanate 2000/125 milligrams twice daily, cefdinir 300 milligrams twice daily, or cefpodoxime 200 milligrams twice daily. For OM unresponsive to initial therapy after 72 hours, consider changing to amoxicillin-clavulanate, levofloxacin, or moxifloxacin. **OM with effusion** requires treatment with the same antimicrobials but for 3 weeks. Oral corticosteroids for OM with effusion provide a limited benefit in children (number needed to treat = 14),[28] but the benefit in adults is not known.

Adults with simple acute OM should receive follow-up to assess treatment efficacy and to ensure that there is no anatomic obstruction to the eustachian tube, as, for example, from occult neoplasm. Any patient who presents with complications of OM or who appears septic should have urgent consultation for diagnostic and therapeutic tympanocentesis and admission for IV antibiotics.

COMPLICATIONS OF OTITIS MEDIA

Complications of OM are intratemporal and intracranial. Perforation of the TM is a common intratemporal complication and most often occurs in the pars tensa from the increased pressure of middle ear secretions, with resultant otorrhea. Healing usually occurs in 1 week, although a chronic perforation may result. A temporary conductive hearing loss may occur secondary to fluid in the middle ear. Hearing loss should resolve as the fluid is resorbed. Acute serous labyrinthitis may occur when bacterial toxins enter the inner ear via the round window. Facial nerve paralysis is an uncommon complication but requires emergent otolaryngology consultation.

Acute Mastoiditis Acute mastoiditis results from spread of infection from the middle ear to the mastoid air cells by the aditus ad antrum. When this opening becomes blocked, the mastoid cavity becomes a closed space, and the mastoid air cells become inflamed and fill with fluid. In addition to otalgia, fever, and otorrhea (especially in patients with *Pseudomonas*), patients with mastoiditis will have postauricular erythema, swelling, and tenderness, and if it progresses, protrusion of the auricle and obliteration of the postauricular crease. Diagnosis is suspected based on the history and physical examination and confirmed

with a contrasted CT. Mastoiditis with bony involvement requires admission for IV antibiotics, tympanocentesis, and myringotomy. The most common pathogens are *S. pneumoniae*, *Streptococcus pyogenes*, and *P. aeruginosa*.[21,29] For an initial episode, treat with ceftriaxone 2 grams IV or levofloxacin 750 milligrams IV.[16] For recurrent episodes, treat with vancomycin and piperacillin/tazobactam, or imipenem.[16] Incision and drainage of subperiosteal abscess or mastoidectomy may ultimately be required.

Intracranial Complications Intracranial complications of OM are more likely with chronic than with acute OM and are, in general, decreasing with the widespread use of antibiotics in the treatment of OM. However, suppurative intracranial extension is a severe complication, and suggestive signs and symptoms should be investigated appropriately. Meningitis and brain abscess are the most common intracranial complications of OM, with an incidence of 0.42 per 100,000 per year.[30] The most prevalent causative organisms are *S. pneumoniae* and *Neisseria meningitidis*.[30] Extradural abscess and subdural empyema are also potential complications.

Lateral Sinus Thrombosis Lateral sinus thrombosis is another ominous complication of acute OM. It arises from extension of infection and inflammation in the mastoid, with eventual inflammation of the adjacent lateral or sigmoid sinus. Reactive thrombophlebitis with mural clot formation, intraluminal empyema, or perforation of the venous wall may occur.

Headache is the most common symptom, with papilledema, sixth-nerve palsy, and vertigo being less frequently present. Angiography with venous phase and MRI are more sensitive than CT in diagnosing lateral sinus thrombosis. The employed antibiotic regimen should cover *Staphylococcus*, *Streptococcus*, and upper respiratory anaerobes (*Bacteroides fragilis*) and have good penetration of the blood–brain barrier. A combination of cefepime 2 grams IV, metronidazole 500 milligrams IV, and vancomycin 1 gram IV is one regimen recommended.[16] Otolaryngology should be consulted for expected mastoidectomy.[31]

BULLOUS MYRINGITIS

Bullous myringitis is a painful condition of the ear characterized by bulla formation on the TM and deep external auditory canal. The blisters are believed to occur between the highly innervated outer epithelium and the inner fibrous layer of the TM, explaining the severe otalgia. The blisters may be blood filled, serous, or serosanguineous. Reactive middle ear effusions may accumulate. Otorrhea as a result of ruptured bullae is short lived. A reversible hearing loss is commonly associated with the condition and may be conductive, sensorineural, or mixed. This disorder is not caused by *Mycoplasma pneumoniae*, as commonly believed, but is a severe manifestation of the typical organisms that cause OM.[32] Treatment is as the same as for acute OM, discussed earlier.

EAR HEMATOMA

An auricular hematoma can develop from almost any type of trauma to the ear. As a result of the lack of subcutaneous fat on the anterior surface of the auricle, blunt force applied to this area tends to shear the perichondrium from the underlying cartilage and tear the adjoining blood vessels. Any interruption of the nourishing blood supply can result in necrosis. The resultant deformed auricle has been referred to as "cauliflower ear," which is commonly seen in boxers or wrestlers secondary to repeated head/ear trauma. The auricular hematoma itself is a painful swelling, which obscures the normal contour of the ear. The hematoma may accumulate immediately or several hours following an injury. Aspiration alone does not completely evacuate the clot and therefore leads to deformity and increased morbidity. The goal of treatment is to remove the fluid collection and maintain pressure in the area for several days to prevent reaccumulation of fluid.

Using sterile technique after local anesthesia, make a semicircular incision through the skin, and be careful not to incise the underlying perichondrium. The incision should be the minimal necessary to drain the underlying hematoma and be positioned in an area with the least chance of cosmetic deformity. This is usually accomplished by incising the skin inside the inner curvature of the helix or anthelix. The hematoma can then be removed by gentle suction or curettage. Suture the incision after hematoma removal.

There are a few ways to prevent the hematoma from recurring. Place a dental roll or a firm sterile pledget coated with antibiotic ointment over the resutured site with through-and-through sutures connected to a similar bolster on the opposite side of the ear. Apply a light nonpressure dressing and reevaluate the ear within 24 hours to ensure there has been no reaccumulation of the hematoma. A pressure dressing can also be used if you do not want to suture a dental roll though the cartilage. Simply pack the helix with petroleum jelly–impregnated gauze and then place regular gauze both in front of and behind the ear. Lastly circle the head with a compressive wrap (**Figure 242-4**). Prophylactic antibiotics can be reserved for immunocompromised patients and should cover *P. aeruginosa* and *S. aureus*, the two likely participants in posttraumatic chondritis.

EAR FOREIGN BODIES

Cerumen loops/scoops, a right-angle hook, and alligator forceps are the instruments of choice for the removal (**Figure 242-5**). Live objects should be drowned with a 2% lidocaine solution, which immediately paralyzes the offending insect and provides modest topical anesthesia. The liquid can then be suctioned out with butterfly tubing and the insect removed with gentle suction or forceps under direct visualization. Remove all insect debris from the canal.

Irrigation with room-temperature water is adequate for small particles such as hard sand or cerumen and can mobilize distally positioned objects. Irrigation should not be used unless the TM is completely visualized and free of perforation. Organic matter that can expand when moistened is also a relative contraindication to irrigation.

Inspect the ear canal after removal of the foreign body to exclude injury to the canal skin, TM, and ossicles caused by the foreign body or its extraction. Small abrasions heal spontaneously. Topical antibiotics should be considered in cases where there was more serious cutaneous damage or where the foreign body consisted of organic material or generated a local inflammatory reaction (Table 242-5).

CERUMEN IMPACTION

Symptoms of cerumen impaction are decreased hearing, a sensation of pressure or fullness in the ear, dizziness, tinnitus, or otalgia. Most of the time, cerumen loops/scoops can be used to remove impacted cerumen (Figure 242-5). In particularly difficult cases or when the canal is completely occluded, softening of the material can be accomplished using half-strength hydrogen peroxide, docusate sodium, sodium bicarbonate, mineral oil, or an over-the-counter preparation such as Debrox® (carbamide peroxide otic). Left in place for 30 minutes, such preparations soften the cerumen and facilitate its removal. If irrigation is the treatment of choice, it can usually be accomplished with an ear syringe, a flexible 18-gauge IV catheter, or a syringe attached to the tubing of a butterfly infusion catheter. Pretreatment with agents such as triethanolamine polypeptide oleate (Cereuminex®) improves success rates, but no pretreatment is superior to another.[33] Use body-temperature irrigant to minimize the development of vertigo. Insert the catheter into the cartilaginous canal (external third) and gently irrigate along the superior portion of the external auditory canal. Using this technique, the pressure of the stream is directed toward the wall of the canal and not the TM. Irrigation of the canal when the middle ear is not infected often causes a temporary redness of the TM.

The most common iatrogenic injury associated with syringing of the ear is traumatic TM perforation. Predisposing factors for perforation include previous ear surgery, a previous or current history of OM, and severe otitis externa. When in doubt, it is safer to defer irrigation/cerumen removal to an otolaryngologist. When determining if



A



C



B



D

FIGURE 242-4. Stepwise progression to build an auricular bandage to help compress a drained hematoma in the auricle of the ear. Use a petroleum jelly–impregnated gauze inside the helix of the ear (**A**) and then add dry gauze to both the back (**B**) and front (**C**) of the ear. **D.** Wrap it lightly to add slight compression to hold the perichondrium to the auricular cartilage.

a perforation has occurred, it is important to rely on symptoms (sudden hearing loss, severe otalgia, or vertigo) rather than signs, because visualization of the TM may be impaired by the irrigating fluid and debris. In case of suspected perforation, reassurance, analgesia, and otolaryngology referral in 1 week are indicated. Prophylactic antibiotics are not necessary.

TYMPANIC MEMBRANE PERFORATION

TM perforations can occur secondary to middle ear infections or as a result of barotrauma, blunt/penetrating/acoustic trauma, or, on rare occasions, lightning strikes. When it is secondary to blunt or noise trauma, the perforation almost always occurs in the pars tensa, usually



FIGURE 242-5. Different-shaped ear scoops and loops are useful to remove cerumen from an impacted ear. Miniature alligator forceps can be used to extricate foreign bodies from the external ear canal.

anteriorly or inferiorly. The pars tensa, the largest area of the TM, is only a few cell layers thick and thus is easily torn.

Symptoms are acute onset of pain and hearing loss, with or without bloody otorrhea. There may also be associated vertigo or tinnitus, but this is usually transient unless there has been injury to the inner ear or rupture of the round or oval windows. The TM should be completely visualized and the canal must be cleared of blood and debris.

Most TM perforations heal spontaneously. Patients with perforations secondary to blunt or noise trauma that are isolated injuries can be safely discharged and referred to a specialist for further evaluation and a formal audiogram as soon after the injury as possible. Patients should be instructed not to allow water to enter the canal of the ear. Topical or systemic antibiotics are not needed unless foreign material is suspected of remaining in the canal or in the middle ear. Perforations in the posterosuperior quadrant or those secondary to penetrating trauma have a greater likelihood of ossicular chain damage and should be referred to an otolaryngologist within 24 hours.

COMPLICATIONS OF COCHLEAR IMPLANTATION

Cochlear implantation functions through electronic stimulation of the auditory nerves in the cochlea in patients with bilateral moderate to severe sensorineural hearing loss. Common complications include vestibular complaints, device failure, and infection.[34] Infections include skin infection, OM, mastoiditis, and meningitis.[34-39] If infection is a concern, then a CT with IV contrast is needed to evaluate position of the implant, fluid collections, bony involvement, and subperiosteal abscess. Recurrent OM in patients with cochlear implants can result in meningitis.[34] Meningitis can occur days to years after implantation, with the greatest risk in the first 2 months.[34-42]

The most common complication is dizziness or vestibular symptoms, which occur in close to 4% of patients.[34,40,41] Facial nerve weakness is rare but can present acutely or as a delayed complication.[34] Device failure is the next most common complication and may require CT and device integrity testing.[34,43] Other rare complications include cholesteatoma, seroma, hematoma, cerebrospinal fluid leak, and TM perforation.[34]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 243

Face and Jaw Emergencies

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INTRODUCTION

This chapter will discuss facial infections and disorders involving the mandible. Bell's palsy is discussed in Chapter 172, "Acute Peripheral Neurologic Disorders." Trigeminal neuralgia is discussed in Chapter 38, "Chronic Pain." Nonfacial cellulitis and erysipelas are discussed in Chapter 152, "Soft Tissue Infections." Impetigo in children is discussed in Chapter 142, "Rashes in Infants and Children." Orbital cellulitis is discussed in Chapter 241, "Eye Emergencies."

FACIAL CELLULITIS, ERYSIPELAS, AND IMPETIGO

The differential diagnosis of facial infections is provided in **Table 243-1**.[1]

CELLULITIS

Cellulitis is a superficial soft tissue infection that lacks anatomic constraints.[2-4] Facial cellulitis is caused most commonly by *Streptococcus* species,[5] including *Streptococcus pyogenes* (group A β-hemolytic) and group G *Streptococcus*, and *Staphylococcus aureus*,[4] with an increasing predominance of methicillin-resistant *S. aureus*.[6] An important consideration for facial cellulitis is the potential for an odontogenic source of the infection in the midface. Anaerobic bacteria account for 24% to 62% of the odontogenic infections.[4,7] Methicillin-resistant *S. aureus* is the most common cause of purulent cellulitis, identified by purulent drainage, purulent bulla, or suspected abscess.[3] Methicillin-resistant *S. aureus* also is suspected when risk factors are present (see Chapter 152, "Soft Tissue Infections"). Less commonly, cellulitis may represent extension from deep space infections (see "Masticator Space Infection" section later in this chapter). Bedside US can exclude or identify facial abscess (**Figure 243-1**). CT can identify deep-seated infections incompletely imaged by US.

Treatment options organized by infection type are provided in **Table 243-2**.[3,6-12] The selection of an antibiotic for cellulitis is based on differentiation of purulent from nonpurulent forms.[3,10] Duration of therapy is incompletely studied, but recommendations range from 5 to 7 days,[3,6,7,10-12] extended to 10 to 14 days for immunocompromise or inadequate response.[3,10] Treatment failures range from 15% to 20% for β-lactams (amoxicillin-clavulanate, cephalexin, and dicloxacillin) as well as for the anti–methicillin-resistant *S. aureus* therapies[13] due to the failure to cover methicillin-resistant *S. aureus* and streptococcal species, respectively. In selected cases, traditional β-lactam therapy may be added to anti–methicillin-resistant *S. aureus* therapy, but this strategy does not improve outcome.[14] Include coverage for anaerobic bacteria when suspecting an odontogenic source (Table 243-2).[4,7,9] Incision and drainage is the most effective treatment for abscess (see Chapter 152, "Soft Tissue Infections"). Antibiotic dose recommendations are listed in **Table 243-3.**

ERYSIPELAS

Erysipelas is most common in the lower extremities (66% to 76%)[15-17] but is classically described as a disease of the face (see Figure 152-3). Erysipelas is caused by group G *S. pyogenes,* group C and group G *Streptococcus*, and *S. aureus*.[3,15] Bullous erysipelas is a more severe form of the disease and most commonly is caused by methicillin-resistant *S. aureus*.[18] Penicillin is the antibiotic treatment of choice for presumed non–methicillin-resistant *S. aureus* infections[3,17] but is chosen as empiric therapy in a minority of cases.[8,15-17] If the suspicion exists of a staphylococcal infection (i.e., bullae, trauma, or the presence of a foreign body), include coverage for methicillin-resistant *S. aureus* (Table 243-2).

IMPETIGO

Impetigo is a discrete, superficial bacterial epidermal infection characterized by amber crusts (nonbullous) or fluid-filled vesicles (bullous)

TABLE 243-1 Differential Diagnosis of Superficial Facial Infection

	Historical Features		
	Onset/Timing	Risk/Inciting Factors	Physical Findings
Infectious			
Cellulitis	Gradual	Skin breaks, foreign bodies, prostheses, immunosuppression	Diffuse erythema without clear borders, pain
Impetigo	Acute	Infants, children	Discrete vesicles or bullae; patches of crusty skin
Erysipelas	Acute	Elderly, infants and children, immune deficiency, diabetes, alcoholism, skin ulceration, impaired lymphatic drainage	Well-defined, raised area of erythema, pain
Viral exanthem	Often acute	Preceding or concurrent viral illness, fever	Variable
Parotitis	Gradual	Dehydration, diabetes, immunosuppression	Swollen angle of mandible, potentially visible sialolith
Necrotizing fasciitis	Rapid	Trauma, may be minor or not apparent	Crepitus, skin necrosis, may be subtle
Cutaneous anthrax	Gradual	Animal contact	Black eschar with surrounding erythema
Herpes zoster	Acute	Elderly, immunosuppression	Exquisitely tender erythematous or vesicular rash following a dermatome
Malignant otitis externa	Gradual	Diabetes, water exposure	Ear pain with drainage, facial swelling, tragal tenderness
Inflammatory			
Insect envenomation	Acute	Environment supporting insect life	Diffuse, red, puffy
Apical abscess with secondary buccal swelling	Gradual	Usually associated dental pain/caries	Similar to cellulitis; may have intraoral/gingival findings
Contact dermatitis	Gradual or acute	Often identifiable exposure	Variable; maculopapular, itchy rash
Immunologic			
Systemic lupus erythematosus	Gradual	Female-to-male ratio, 9:1	Erythema in classic "malar" distribution
Angioneurotic edema	Acute	Exposure to angiotensin-converting enzyme inhibitor, allergen	Lip, oral mucosal swelling, sometimes facial
Vancomycin flushing reaction	Acute	Recent exposure to vancomycin	Facial erythema, warmth

(see Figure 142-15). It is most common in children. *S. aureus* alone or in combination with *S. pyogenes* (group A β-hemolytic) is the most common cause of nonbullous impetigo.[19,20] Bullous impetigo is typically caused by *S. aureus*.[21,22] Treatment should cover streptococcal and staphylococcal species. Topical therapy is sufficient for uncomplicated patients with nonbullous lesions.[22] Mupirocin, retapamulin, or fusidic acid ointment is recommended; however, some resistance exists.[22-24] Consider oral antibiotics for extensive lesions or lesions that do not respond to topical therapy alone. There is no clear preference between macrolides, β-lactamase–resistant penicillins, and cephalosporins.[3,21] Preferred choices are penicillinase-resistant penicillins (dicloxacillin, amoxicillin-clavulanic acid) or first-generation cephalosporins (cephalexin).[3] For methicillin-resistant *S. aureus*, treat with trimethoprim-sulfamethoxazole or clindamycin[3] (Table 243-3). In endemic regions (e.g., areas of Australia), scabies infestation frequently coexists with impetigo.[25] Consider adding ivermectin, 200 micrograms/kg, single dose, in addition to antibacterial therapy for impetigo.[26]

SALIVARY GLAND INFECTIONS

There are three groups of salivary glands: the parotid, submandibular, and sublingual. The facial nerve passes through the superficial portion of the parotid gland, and the parotid (Stensen's) duct opens into the mouth opposite the upper second molar. The submandibular and sublingual glands lie below the plane of the tongue. The submandibular ducts open into the mouth at either side of the frenulum of the tongue. The multiple sublingual ducts open into the sublingual fold or directly into the submandibular duct.[27]

Signs of salivary gland infections are unilateral or bilateral facial swelling. Recurrent symptoms, dry mouth and eyes, or joint symptoms suggest etiologies such as immunologic or collagen vascular disorders. Other medical conditions, such as nutritional disorders, toxic exposures, diabetes, dehydration, medication usage (e.g., phenothiazines), pregnancy, and obesity, can result in salivary gland enlargement. On physical examination, determine the location of the swelling to identify the gland

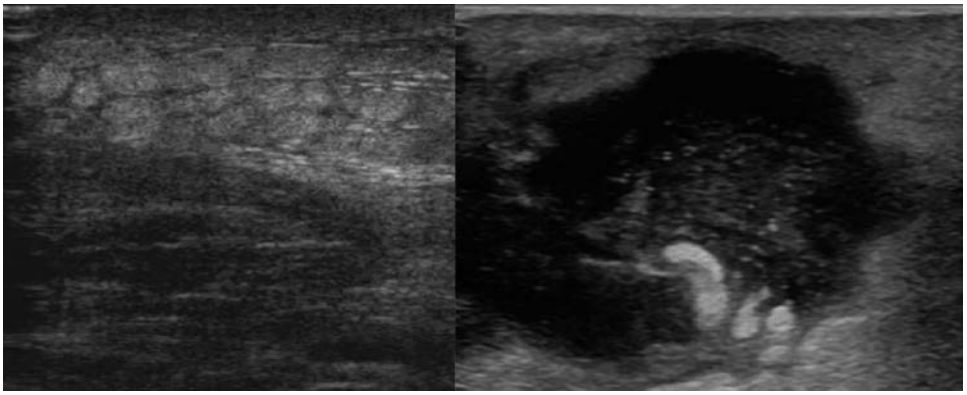


FIGURE 243-1. Cellulitis versus abscess. The image on the left shows the cobblestoned appearance of cellulitis, while the one on the right shows a heterogenous fluid collection of abscess. [Photo contributed by R. Gordon, MD.]

TABLE 243-2 Antibiotic Therapy for Facial Infections

Infection Type	Recommended Antibacterial Therapy
Nonpurulent cellulitis	Oral therapy: dicloxacillin, cephalexin, amoxicillin-clavulanate, clindamycin Parenteral therapy: nafcillin, cefazolin, clindamycin Total duration 5–7 d, extend if slow to respond or immunocompromised
Purulent cellulitis (MRSA predominate)	Oral therapy: trimethoprim-sulfamethoxazole, doxycycline, minocycline, clindamycin, linezolid Parenteral therapy: vancomycin, daptomycin, linezolid, ceftaroline Total duration 5–7 d, extend if slow to respond or immunocompromised
Facial cellulitis of odontogenic origin	Oral therapy: amoxicillin-clavulanate, clindamycin, β-lactam drug plus metronidazole Parenteral therapy: ampicillin-sulbactam, piperacillin-tazobactam, clindamycin, β-lactam drug plus metronidazole Total duration 5–7 d, extend if slow to respond or immunocompromised
Erysipelas	Oral therapy: amoxicillin or penicillin (only if MRSA is unlikely) Methicillin-sensitive *Staphylococcus aureus* suspected: amoxicillin-clavulanate, cephalexin, dicloxacillin Bullous erysipelas (or MRSA suspected): trimethoprim-sulfamethoxazole, clindamycin, doxycycline, or minocycline Parenteral therapy: vancomycin, nafcillin, clindamycin Total duration 5–7 d, extend if slow to respond or immunocompromised
Impetigo	Topical: mupirocin or retapamulin ointment alone or with oral therapy Oral therapy: dicloxacillin, amoxicillin-clavulanate, cephalexin Alternative: azithromycin MRSA suspected: clindamycin or trimethoprim-sulfamethoxazole Total duration 5–7 d, extend if slow to respond or immunocompromised
Suppurative parotitis	Oral therapy: amoxicillin-clavulanate, clindamycin, or cephalexin with metronidazole Parenteral therapy: nafcillin, or ampicillin-sulbactam; if penicillin allergic, clindamycin or the combination of cephalexin with metronidazole, or vancomycin with metronidazole Hospital acquired or nursing home patients: consider vancomycin Total duration: 10–14 d
Masticator space infection	Parenteral therapy: IV clindamycin, ampicillin-sulbactam, piperacillin-tazobactam, or the combination of ampicillin with metronidazole Oral therapy: clindamycin or amoxicillin-clavulanate Total duration: 10–14 d

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus.*

TABLE 243-3 Antibiotic Doses for Facial Infections

Antibiotic	Dosage
Oral Antibiotics	
Amoxicillin/clavulanate	875/125 milligrams twice per day
Azithromycin	500 milligrams first day, 250 milligrams 4 more days
Cephalexin	500 milligrams four times per day
Clindamycin	300 milligrams three or four times per day
Dicloxacillin	500 milligrams four times per day
Doxycycline	100 milligrams twice per day
Metronidazole	500 milligrams every 8 h
Minocycline	100 milligrams twice per day
Penicillin V	500 milligrams four times per day
Trimethoprim-sulfamethoxazole	1 double-strength tablet twice per day
Parenteral Antibiotics	
Ampicillin-sulbactam	1.5–3.0 grams every 6 h
Piperacillin-tazobactam	3.375 grams every 6 hours
Clindamycin	600 milligrams every 8 h
Ceftaroline	600 milligrams IV every 12 h (with CrCl >50 mL/min)
Cefazolin	1 gram every 8 h
Daptomycin	4 milligrams/kg IV every 24 h (with CrCl >30 mL/min)
Linezolid	600 milligrams IV every 12h
Metronidazole	1 gram loading dose, then 500 milligrams every 8 h
Nafcillin	1–2 grams every 4 h
Penicillin G	2–3 million units every 6 h
Vancomycin	15 milligrams /kg every 12 h with adjustment for renal function

Abbreviation: CrCl = creatinine clearance.

TABLE 243-4 Differential Diagnosis of Salivary Gland Swelling

	Historical Features		
Disorder	Onset	Risks/Inciting Factors	Clinical Features
Infectious			
Viral parotitis (mumps)	Gradual	Nonimmunized	Prodromal illness, unilateral tense swelling, absent warmth/erythema
Buccal cellulitis	Gradual	*Haemophilus influenzae* infection in nonimmunized	Erythematous, tender
Suppurative parotitis	Rapid	Dehydration, immunosuppression, chronic illness, recent anesthesia	Painful buccal swelling, fever, pus expression from Stensen's duct
Masseter space abscess	Gradual	Dental infection, post trauma	Trismus, posterior inferior facial swelling
Tuberculosis	Gradual	Exposure, immunosuppression	Chronic crusting plaques
Immunologic			
Sjögren's syndrome	Gradual	—	Dry mouth, eyes, sclerosis
Systemic lupus	Gradual	Female sex, Asian or African American race	No signs of infection
Sarcoidosis	Gradual	Female sex, African American race	No signs of infection
Other			
Neoplasm	Gradual	—	No erythema, warmth
Sialolithiasis	Gradual	Dehydration, chronic illness	Swelling, tenderness, no signs of infection

involved. Multiple gland involvement suggests infection. A palpable tender mass may be a sign of tumor or obstruction by a stone. The differential diagnosis of salivary gland swelling is provided in **Table 243-4**.[27,28]

VIRAL PAROTITIS (MUMPS)

Viral parotitis is an acute infection of the parotid glands, characterized by unilateral or bilateral parotid swelling. It is most often caused by the paramyxovirus and may be caused less commonly by influenza, parainfluenza, coxsackie viruses, echoviruses, lymphocytic choriomeningitis virus, and even human immunodeficiency virus.[28] It is most common in children under the age of 15 years old, but since November 2014, clusters of mumps have been reported in adult members of professional hockey teams. The virus is spread by airborne droplets, incubates in the upper respiratory tract for 2 to 3 weeks, and then spreads systemically. Vaccine protection is not 100%, and outbreaks occur in settings of close contact, such as schools, colleges, sports teams, and camps.[29]

After a period of incubation, one third of patients experience a prodrome of fever, malaise, headache, myalgias, arthralgias, and anorexia during a 3- to 5-day period of viremia.[28] The classic salivary gland

swelling then follows. Unilateral swelling is typically followed by bilateral parotid involvement. The gland is tense and painful, but erythema and warmth are notably absent. Stensen's duct may be inflamed, but no pus can be expressed.[28]

Diagnosis is clinical and treatment is supportive. Salivary gland swelling typically lasts from 1 to 5 days. The patient is contagious for 9 days after the onset of parotid swelling, and children with mumps should be excluded from school or day care for this interval.

Mumps is usually benign in children but can be severe in adults. Unilateral **orchitis** affects 20% to 30% of males (with a predisposition of ≥8 years of age), whereas **oophoritis** affects only 5% of females. Other complications of the mumps virus include mastitis, pancreatitis, aseptic meningitis, sensorineural hearing loss, myocarditis, polyarthritis, hemolytic anemia, and thrombocytopenia.[28] Immunocompetent patients with isolated viral parotitis or orchitis can be managed as outpatients. Admit patients with systemic complications.

SUPPURATIVE PAROTITIS

Suppurative parotitis is a serious bacterial infection of the parotid gland that occurs in patients with compromised salivary flow. It is caused by the retrograde migration of oral bacteria into the salivary ducts and parenchyma.[28] Predisposing factors include recent anesthesia, dehydration, prematurity or advanced age, sialolithiasis, oral neoplasms, salivary duct strictures, tracheostomy, and ductal foreign bodies.[28] Medications that cause either systemic dehydration or decreased salivary flow specifically can cause parotitis. These include diuretics, antihistamines, tricyclic antidepressants, phenothiazines, β-blockers, and barbiturates.[28] Several chronic illnesses also predispose patients to suppurative parotitis, such as human immunodeficiency virus, hepatic or renal failure, diabetes mellitus, hypothyroidism, malnutrition, Sjögren's syndrome, depression, anorexia, bulimia, hyperuricemia, and cystic fibrosis.[28]

Most cases of suppurative parotitis are caused by *S. aureus*, with *Streptococcus pneumoniae*, *S. pyogenes*, and *Haemophilus influenzae* as more infrequent pathogens.[3,28] Anaerobes such as *Bacteroides* species, peptostreptococci, and fusobacteria are common.[30,31] In the immunocompromised host, gram-negative organisms such as *Escherichia coli* and *Pseudomonas* may be seen.[30,31]

The onset of suppurative parotitis is rapid, and the skin over the parotid gland is red and tender. Pus may be expressed from the Stensen's duct. There is often fever and trismus.

Suppurative parotitis is diagnosed clinically, with evidence of purulent drainage from Stensen's duct. Cultures of Stensen's duct drainage can guide therapy in the patient not responding to first-line antibiotics.[31] Imaging is not helpful unless an abscess is suspected, in which case US or CT is diagnostic.

Because suppurative parotitis is caused by states of decreased salivary flow, treatment should optimize salivary flow. Hydrate the volume-depleted patient. Massage and apply heat to the affected gland. Stimulate salivation using sialagogues, such as lemon drops. When possible, discontinue drugs that cause dry mouth, and attempt to correct underlying medical problems.[30,31]

Treat patients with oral antibiotics if they can tolerate oral liquids and have no evidence of systemic illness. Admit for parenteral antibiotics patients who have trismus and cannot tolerate oral liquids, are immunocompromised or incapable of complying with an outpatient treatment regimen, or have not shown improvement after 48 hours of outpatient treatment.[30,31]

Antimicrobial therapy consists of agents that cover both staphylococcal and streptococcal species (Tables 243-2 and 243-3). The initial choice for oral therapy includes amoxicillin-clavulanate; in penicillin-allergic patients, use clindamycin or a combination of cephalexin with metronidazole.[3,30,31] When parenteral therapy is indicated, choices include nafcillin, ampicillin-sulbactam, or a combination of vancomycin with metronidazole. In hospitalized or nursing home patients, the possibility of methicillin-resistant *S. aureus*, for which vancomycin is appropriate,[31] must be considered. In neonates, treat with gentamicin and antistaphylococcal antibiotics combined with hydration. If there is no improvement in 24 to 48 hours, surgical drainage is required.

SIALOLITHIASIS

Sialolithiasis is the development of a calcium carbonate and calcium phosphate stone (sialolith) in a stagnant salivary duct. Salivary calculi can develop in any age group, but usually are symptomatic in men between the third and sixth decades.[28] More than 80% of stones occur in the submandibular gland, with most of the remainder in the parotid.

The symptoms of pain, swelling, and tenderness may resemble those of parotitis. It may be hard to distinguish parotitis from sialolithiasis, and the two conditions may coexist. Sialolithiasis is typically unilateral. The pain and swelling of sialolithiasis are colicky and exacerbated by meals.

The diagnosis is clinical. A stone may be palpated within the duct, and the gland is firm.[28] Intraoral radiographs are more sensitive than extraoral films in identifying salivary calculi. The calculi are radiopaque in about 70% of cases. US and thin-cut CT also will identify sialoliths but are usually obtained only if abscess is in the differential diagnosis. ED bedside US has been shown to be a useful diagnostic tool to determine number, size, and location of stones (**Figure 243-2**).[32] A conservative course of treatment should precede imaging studies. Occasionally on CT, the diagnosis of sialolithiasis is made by the typically glandular swelling and inflammatory changes (signifying ductal obstruction) without an obvious stone seen in the duct (**Figure 243-3**).

Treatment is outpatient therapy with analgesics, antibiotics if there is concurrent infection, massage, and sialagogues, such as lemon drops.[28] Palpable stones in the distal duct may be digitally "milked" from the duct. Complications of salivary duct obstruction include recurrent or persistent obstruction, strictures, infection, and gland atrophy.[28]



FIGURE 243-2. US image of sialolithiasis (the bright hemi-circular structure). [Photo contributed by R. Gordon, MD.]

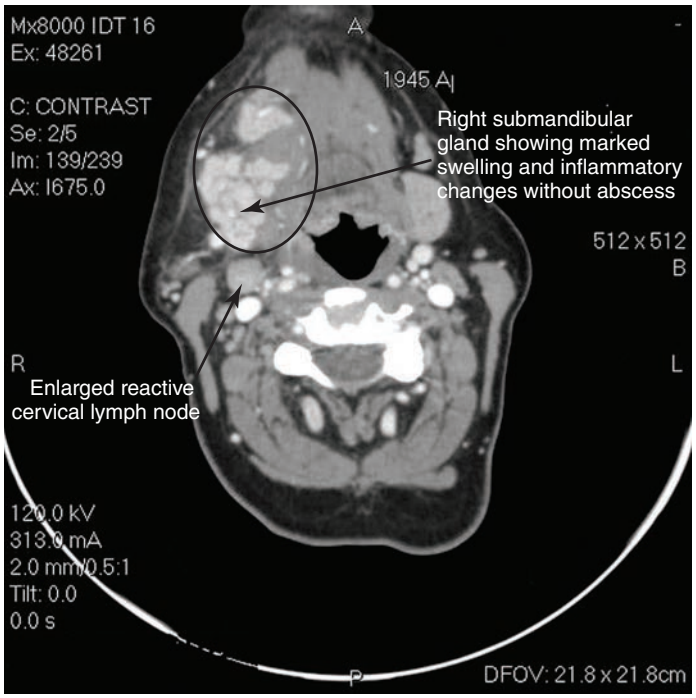


FIGURE 243-3. Marked enlargement of the right submandibular gland. This contrasted CT image shows marked enlargement of the right submandibular gland and surrounding inflammatory changes without an obvious stone or abscess formation. [Image used with permission of John Wightman, MD.]

MASTICATOR SPACE INFECTION

The masticator space consists of four potential spaces bounded by the muscles of mastication (**Figure 243-4**). These spaces include the masseteric (or submasseteric), superficial temporal, deep temporal, and pterygomandibular spaces.[33] The spaces are all contiguous. Bacteria may gain entry to the space from dental infections, trauma, surgery, or injections. Infections of the masticator space are polymicrobial and generally anaerobic, although aerobic oral streptococcal species may predominate briefly.[4,33] Typical organisms include species of *Streptococcus*, *Peptostreptococcus*, *Bacteroides*, *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Actinomyces*, *Veillonella*, and anaerobic spirochetes.[4,33]

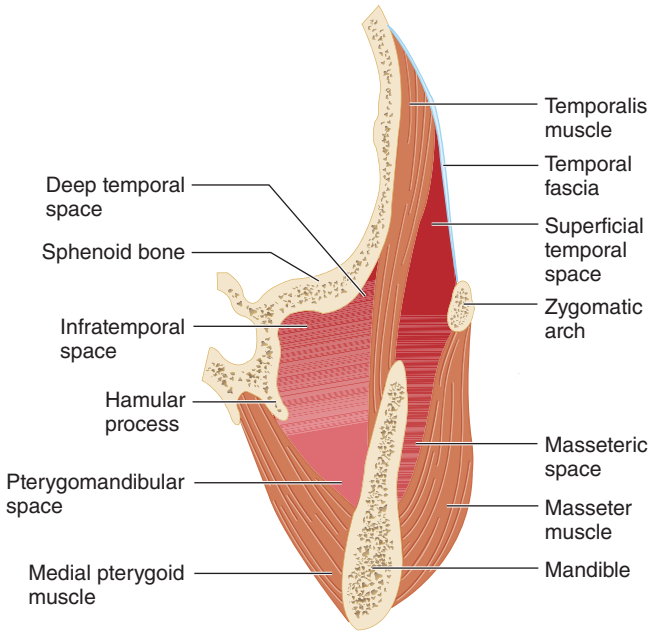


FIGURE 243-4. Masticator space.

The most frequent acute clinical findings are trismus associated with facial swelling, pain, and erythema. When infection occurs in the masseteric space, there is facial swelling posteriorly and inferiorly, with mild to moderate trismus. If the temporal space is infected, there is soft tissue swelling over the temporalis muscle and trismus. Trismus without swelling suggests pterygomandibular space abscess. In chronic infection, the patient can be afebrile but may complain of intermittent trismus.[33] Constitutional signs may include fever, malaise, dehydration, dysphagia, nausea, or vomiting. In more advanced cases, systemic signs of sepsis are present. The differential diagnosis includes other sources of lateral facial pain and swelling (Table 243-4).

Ultrasonography is helpful in differentiating abscesses from cellulitis (Figure 243-1), for the diagnosis of lymphadenitis, and to identify internal jugular thrombosis. However, contrast-enhanced CT is the preferred diagnostic tool for masseteric and related deep space infections.[33-35] CT can define the extent of the abscess and distinguish cellulitis from abscess in all spaces except the retropharyngeal.[33] MRI can be considered if infection is thought to reach the skull base.[34]

The patient's condition determines therapy. Because all the subordinate spaces of the masticator space communicate with each other and ultimately with the tissue planes that extend down the neck to the mediastinum, the extent of the infection should be defined efficiently and treatment begun promptly. Airway compromise is rare in unilateral masticator space infection. Administer antibiotics in the ED (Table 243-3), resuscitate for sepsis when present, and admit the patient. IV clindamycin is recommended, with alternatives including ampicillin-sulbactam, piperacillin-tazobactam, or the combination of penicillin with metronidazole.[4,33] Antibiotics are continued for 10 to 14 days. Consult otolaryngology for surgical intervention and management.

TEMPOROMANDIBULAR JOINT DISORDERS

The temporomandibular joint combines both a hinge and gliding action. The articular surfaces of the joint are separated by the articular disk, or meniscus, which assists in the hinge action between the mandibular condyle and the disk and in the gliding action between the disk and temporal bone.[36]

TEMPOROMANDIBULAR JOINT DYSFUNCTION

Temporomandibular joint dysfunction causes pain of the joint and its surrounding anatomic structures. Assess for temporomandibular joint injury when evaluating direct jaw trauma or acute dental injury.[37] Most studies have found no significant correlation between occlusal parameters or bruxism and signs or symptoms of temporomandibular joint disorders.[38] Over time, degenerative joint disease (osteoarthritis) may result from chronic internal derangement or occur secondary to systemic disease such as rheumatoid arthritis or systemic lupus erythematosus.[37]

The chief complaint is usually pain localized to one of the muscles of mastication or pain with chewing in one or both temporomandibular joints. The masseter muscle is the most frequently identified painful area, followed by the temporalis, sternocleidomastoid, splenius capitis, and trapezius muscles.[38] Physical findings may include limitation in the range of motion of the mandible. Palpate the muscles of mastication to find areas of sensitivity, induration, rigidity, and swelling. Palpate the condylar heads with the teeth together and then with the teeth apart. The differential diagnosis of temporomandibular joint dysfunction includes jaw trauma, including fracture and dislocation; odontogenic pain, including from abscess, caries, or trauma; otologic referred pain, including from otitis media, otitis externa, and foreign body; and temporal arteritis.

Temporomandibular joint dysfunction is diagnosed by history and physical examination. Isolated temporomandibular joint clicking without pain or other dysfunction is not diagnostically sufficient.[38] For acute trauma, the panoramic radiograph view of the mandible (panorex) identifies most fractures.[39] CT is appropriate in the assessment of potentially complex fractures, infections, and neoplastic disease. CT is often

the imaging modality of choice in the ED as panorex is typically not available.

The oral maxillofacial surgeon manages fractures and should be consulted for trismus, significant mandible displacement, and open fractures. For nontraumatic conditions, give simple analgesics, including NSAIDs.[40] Advise the patient to eat soft foods until definitive treatment is provided. The management of chronic temporomandibular dysfunction may ultimately require referral to a dentist, maxillofacial surgeon, or pain specialist.

MANDIBLE DISLOCATION

The mandible can be dislocated in an anterior, posterior, lateral, or superior direction. **Anterior dislocation is most common and occurs when the mandibular condyle is forced in front of the articular eminence.** Muscular spasm then traps the mandible in anterior dislocation, and the mandible is elevated before retraction. Spasm of the temporalis and lateral pterygoid muscles tends to prevent reduction once dislocation has occurred. Dislocations are usually bilateral but can be unilateral.[36] Posterior dislocations are rare. They follow a blow that may or may not break the condylar neck. In posterior dislocation, the mandibular condyle is thrust backward against the mastoid, and the condylar head may prolapse into the external auditory canal.[36] Lateral dislocations are often associated with mandibular fracture. With a lateral dislocation, the condylar head is forced laterally and then superiorly into the temporal space. Superior dislocations occur from a blow to the partially open mouth that forces the condylar head upward. Associated injuries include cerebral contusions, facial nerve palsy, and deafness.

Acute jaw dislocation causes severe pain, difficulty in speaking or swallowing, or malocclusion after a blow to the jaw or a seizure or, sometimes, spontaneously. There may be loose or missing teeth and areas of sensory deficit at the chin or mouth. With anterior dislocation, pain is localized anterior to the tragus. Symptoms may develop after extreme mouth opening from laughing, yawning, vomiting, taking a large bite, or trauma, or iatrogenically during dental extraction, general anesthesia, and tonsillectomy.[36] With anterior dislocations, the lower jaw is prominent appearing, and there is visible and palpable preauricular depression from the displacement of the mandibular condyle. There also will be difficulty with jaw movement. If the dislocation is unilateral, there is deviation of the jaw away from the dislocation. **When a posterior dislocation is considered, examine the external auditory canal.** Confirm that hearing is at baseline. With lateral dislocations, the condylar head is palpable in the temporal space, and there are always signs of jaw fracture (e.g., malocclusion). **Posterior, lateral, or superior dislocations result from severe trauma.** The differential diagnosis includes mandibular fracture, traumatic hemarthrosis, acute closed locking of the temporomandibular joint meniscus, and temporomandibular joint dysfunction.[36]

In the cooperative patient with a **spontaneous atraumatic anterior dislocation**, the diagnosis is clinical. In other dislocations, including any traumatic dislocation, obtain radiographs. The panoramic view (panorex) or a maxillofacial CT should be obtained for any significant trauma.

Perform reduction in the ED for closed anterior dislocations without fracture.[36] A short-acting IV muscle relaxant (e.g., midazolam) may help to decrease muscle spasm. Appropriate airway and hemodynamic monitoring should be initiated. Full procedural sedation may be required.[41] Alternatively, local anesthetic can be placed into the joint space. Using aseptic technique, place a 21-gauge needle into the preauricular depression just anterior to the tragus and inject 2 mL of 2% lidocaine[42] (**Figure 243-5**).



FIGURE 243-5. Site for injection of local anesthesia for reduction of dislocated mandible. Place a 21-gauge needle into the preauricular depression just anterior to the tragus and inject 2 mL of 2% lidocaine.

REDUCTION OF ANTERIOR TEMPOROMANDIBULAR JOINT DISLOCATION

Most publications concerning techniques of mandibular joint relocation are descriptive or case reports.[37,42,43] A single randomized controlled trial of 90 patients found that the wrist pivot method was most successful (96.7% vs. 86.7% for the conventional method and 66.7% for the extraoral method).[44] In addition, the authors found that the extraoral method was more difficult for the provider and the patient. The three methods are described in the following sections.

Conventional Method The most commonly used technique requires the patient to be firmly seated with the head against the wall or chair back, positioned so that the examiner's flexed elbow is at the level of the patient's mandible. Apply a few layers of gauze (or plastic syringes) over gloved thumbs for protection, in case the mandible snaps closed after reduction.[36]

Facing the patient, place gloved thumbs in the patient's mouth, over the occlusal surfaces of the mandibular molars, as far back as possible. Curve your fingers beneath the angle and body of the mandible. Using the thumbs, **apply pressure downward and backward (toward the patient)**. Slightly opening the jaw may help disengage the condyle from the anterior eminence (**Figure 243-6**). When the dislocation is bilateral, it may be easier to relocate one side at a time.

In an alternative version of the conventional method, with the patient recumbent and supine, stand at the head of the bed, place the thumbs on the molars, and apply downward and backward pressure (toward the stretcher) (**Figure 243-7**).[36]



FIGURE 243-6. Reduction of dislocated mandible technique in a seated patient. The thumbs are placed over the molars, and pressure is applied downward and backward.



FIGURE 243-7. Alternative mandibular reduction technique, with the examiner behind and above the reclined patient. Place the thumbs on the molars and apply downward and backward pressure (toward the stretcher).

Wrist Pivot Method The patient sits, as does the operator. The healthcare provider's thumbs are placed on the mentum, applying upward force, while the fingers apply downward force on the lower molars, forcing the body of the mandible inferiorly (**Figure 243-8**). The operator flexes the wrist, and thus the mandible rotates, and the condyle goes inferiorly, allowing the condyle to slip back into the mandibular fossa.

Extraoral Method The patient should be seated.[37] The provider stands in front of the patient. The provider places their thumb on the patient's cheek, on the mandibular ramus and coronoid process of the dislocated mandible, and applies persistent pressure posteriorly. The fingers are placed behind the angle of the mandible to stabilize the grip. At the same time on the opposite side, the provider places their fingers from the other hand on the angle of the mandible and pulls, applying anterior force.[37] Note that this maneuver causes further anterior dislocation of the ipsilateral temporomandibular joint, rotates the jaw, and facilitates contralateral temporomandibular joint reduction.

Once one side of the dislocation is reduced, the other side usually goes back spontaneously. If that does not work, repeating the same maneuver with minimal force will usually result in reduction. Another consideration is to apply posterior force on both coronoid processes at the same time if the above strategy does not work.

Postreduction Care After successful reduction, the patient should be able to close his or her mouth immediately. Postreduction radiographs usually are not needed unless the procedure was difficult or traumatic or there is significant postreduction pain. Complications from the reduction itself are unusual, but can include iatrogenic fracture or avulsion of the articular cartilage.

Dislocations that are open, superior, associated with fracture, have any nerve injury, or are irreducible by closed technique should be referred urgently to an otolaryngologist or maxillofacial surgeon.

Following successful reduction of an acute dislocation, patients may be discharged home, placed on a soft diet, and cautioned against opening their mouths >2 cm for the following 2 weeks.[36] Advise patients to support the mandible with a hand when they yawn. Nonsteroidal analgesics may help with discomfort. Elective referral to an oral maxillofacial surgeon is recommended. In severe cases, intermaxillary fixation may be required to control jaw motion during healing. Chronic dislocations may require operative intervention.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.



FIGURE 243-8. Wrist pivot method for mandibular reduction. The operator's thumbs are placed on the mentum, applying upward force, while the fingers apply downward force on the lower molars, forcing the body of the mandible inferiorly.

CHAPTER 244

Nose and Sinuses

Henderson D. McGinnis

EPISTAXIS

EPIDEMIOLOGY

Epistaxis is a common occurrence, affecting 60% of the population at some point during their lifetime.[1,2] The patients who seek medical attention are most commonly under 10 years of age and over 50 years of age.[1,2] Common causes of epistaxis include digital trauma, a deviated septum, dry air exposure (lack of humidity), rhinosinusitis, neoplasia, or chemical irritants such as inhaled corticosteroids or chronic nasal cannula oxygen use.[3] Systemic factors that increase the risk of bleeding include chronic renal insufficiency, alcoholism, hypertension, vascular malformations such as hereditary hemorrhagic telangiectasia, any kind of coagulopathy, anticoagulation use, von Willebrand's disease, and hemophilia.[3]

ANATOMY AND PATHOPHYSIOLOGY

The superior labial branch of the facial artery joins the anterior ethmoidal and terminal branch of the sphenopalatine artery to form Kiesselbach plexus on the anterior nasal septum, which is the source of 90% of nosebleeds and can usually be visualized with anterior rhinoscopy (**Figure 244-1**). The most likely source for posterior bleeds is the sphenopalatine artery, which is a terminal division of the internal maxillary artery (branch of the external carotid system). Endoscopic or open

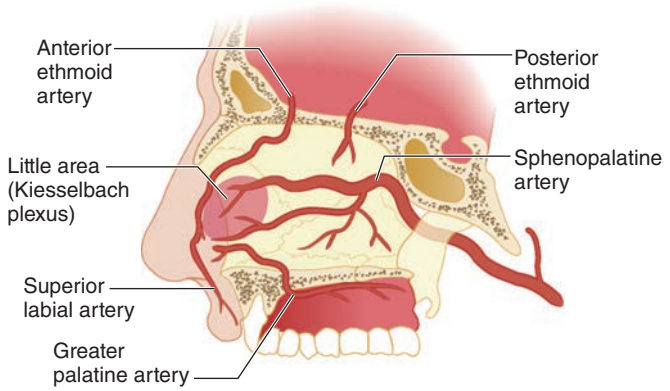


FIGURE 244-1. Arterial blood supply to the nasal cavity. The most common site of nasal hemorrhage is at Little's area of the nasal septum. The most common origin of posterior epistaxis is from the sphenopalatine artery.

surgical techniques are needed to visualize the vessel.[3,4] Sensory innervation is detailed in **Figure 244-2**.

CLINICAL FEATURES

Identify an anterior or posterior source of acute epistaxis with a directed history and physical examination. Ask about previous or recurrent epistaxis as well as duration and severity of the episode. Collect history concerning alcohol, drug, or medication use especially NSAID, anticoagulation, antiplatelet, or aspirin use. Review any history of trauma, prior head and neck procedures, and a personal and family history of coagulopathy.

The evaluation and management of the patient with epistaxis will be much easier and efficient if your department has a well-stocked and easily accessed ear, nose, and throat (ENT) procedure tray, kit, or cart so that you can examine the patient and attempt to control the bleeding. The kit should include a nasal speculum, bayonet forceps, headlamp, suction catheter, cotton pledgets, 0.05% oxymetazoline and 4% lidocaine solutions, silver nitrate swabs, and some combination of absorbable and nonabsorbable materials for anterior and posterior packing.

If there is active bleeding, wear gloves, gown, and facemask with eye shield. Assemble a focused light source, suction, and a nasal speculum. Have the patient seated and in the "sniffing" position. The sniffing position is achieved by having the patient flex and extend the head while keeping the base of the nose straight ahead. With the patient in this position, brace the speculum by resting the index finger on the tip of the nose and insert the speculum with the handle parallel to the floor. Open the blades in a cephalad-to-caudad direction to visualize the bleeding site and facilitate the performance of direct hemostatic techniques.

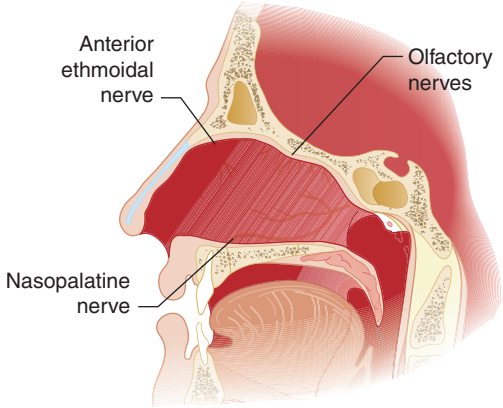


FIGURE 244-2. Sensory innervation of the external nose. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures.* © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD.]

DIAGNOSIS

Differentiating an anterior versus posterior source of bleeding is important for treatment and disposition; failure to identify the source of bleeding is associated with rebleeding and return for treatment.[5] The ability to visualize the site of bleeding depends on the adequacy of the light source and exposure afforded by the nasal speculum.[6] Generally, the diagnosis of posterior hemorrhage is only made in the ED once measures to control anterior bleeding have failed. Clinical features suggestive of a posterior source include elderly patients with either inherited or acquired coagulopathy, a significant amount of hemorrhage visible in the posterior nasopharynx, hemorrhage from bilateral nares, or epistaxis uncontrolled with either anterior rhinoscopy or an anterior pack.[7] Laboratory evaluation or other ancillary studies are not required unless management of comorbid illness requires it or the hemorrhage is poorly controlled. If drawing blood, obtain a CBC (with platelet count) to assess blood loss, a type and cross-match if you anticipate that the patient will require blood, a comprehensive metabolic panel looking for uremia or liver disfunction, and coagulation studies if patient is on warfarin or if coagulopathy is suspected.

TREATMENT

The initial management for epistaxis in the ED starts with a rapid primary survey addressing potential airway or hemodynamic compromise. You should obtain IV access in patients with severe bleeding and request cross-matched blood if there is hemodynamic instability. The need for transfusion is more common in patients with posterior epistaxis and those on anticoagulants.[8,9] Reversal of coagulopathy with blood products can be considered based on clotting studies and individual patient context. Rapid reduction of blood pressure during an episode of acute epistaxis is generally not advised.[10] In uncontrolled epistaxis requiring packing or surgical intervention, gentle reduction of persistent hypertension reduces hydrostatic pressure and thereby may aid clot formation.[10]

DIRECT NASAL PRESSURE

First, ask the patient to blow the nose to expel clots to prepare mucosa for topical vasoconstrictors. Instill a topical vasoconstrictor such as oxymetazoline or phenylephrine. The patient should lean forward in the "sniffing" position and pinch the soft nares between the thumb and the middle finger for a full 10 to 15 minutes and breathe through the mouth. If the patient is uncooperative or unable to pinch their nose, fashion a hands-free pressure device made from two tongue depressors that are taped together between halfway and two thirds of the way up the depressors. Place the device on the nose and leave it undisturbed for 10 to 15 minutes. These initial measures are often sufficient to achieve hemostasis and facilitate further examination by anterior rhinoscopy.

CHEMICAL CAUTERIZATION

If two attempts at direct pressure have failed, chemical cauterization with silver nitrate is the next appropriate step for mild bleeding. Before cautery, anesthetize the nasal mucosa using three cotton pledgets soaked in a 1:1 mixture of 0.05% oxymetazoline and 4% lidocaine solution.[3] Do not attempt chemical cautery unless the bleeding vessel is visualized. Electrical cautery should be left to the otolaryngologist due to the risk of septal perforation.

After visualizing the (anterior) bleeding site, silver nitrate sticks may be judiciously placed just proximal to the bleeding source on the anterior nasal septum. Silver nitrate requires a relatively

bloodless field, as the chemical reaction leading to precipitation of silver metal and tissue coagulation cannot proceed in the setting of active hemorrhage due to washout of substrate. You may use suction to help visualize the source of the bleeding. Once a relatively bloodless field is achieved, gently and briefly (a few seconds) apply silver nitrate directly to the bleeding site. Chemical cautery should never be attempted on both sides of the nasal septum. Subsequent attempts on the same side of the nasal septum should be separated by 4 to 6 weeks to avoid perforation.[11]

THROMBOGENIC FOAMS AND GELS AND TRANEXAMIC ACID

Thrombogenic foams and gels are a good option, and they may be considered after attempts have failed or in place of chemical cautery or insertion of nasal tampons. Gelfoam® and Surgicel® (oxidized cellulose) are effective hemostatic agents that can be placed simultaneously on visualized bleeding mucosa, and they are bioabsorbable, so removal is not needed. **FloSeal®**, another biodegradable agent, is a hemostatic gelatin matrix that is mixed in a syringe with thrombin and injected into the nasal cavity.[12] Topical use of injectable tranexamic acid is an excellent agent for nosebleed control.[2,13,14] There is no standardized approach to the application of nasal tranexamic acid. Effective options described in the literature include: 200 milligrams (100 milligrams/mL concentration) atomized into the affected nostril; cotton pledget or nasal tampon saturated with 500 milligrams of tranexamic acid and placed into the affected nostril; and 500 milligrams of tranexamic acid diluted with 5cc of NS and atomized into the affected nostril.[13,14]

ANTERIOR NASAL PACKING

Anterior nasal packing can be placed if direct pressure, vasoconstrictors, or chemical cautery are unsuccessful in controlling epistaxis and if thrombotic foams and gels are not available. A variety of nasal balloons or sponges are available, or an anterior pack created by layering ribbon gauze in the nasal cavity can be used.

ANTERIOR EPISTAXIS BALLOONS

Anterior epistaxis balloons (**Rapid Rhino®**) are easy to use and more comfortable for the patient than layered strip gauze or nasal sponges. Anterior epistaxis balloons are available in different lengths and are coated with cellulose or other materials that promote platelet aggregation. Soak the balloon with water, insert it gently along the floor of the nasal cavity, and inflate slowly with air until the bleeding stops. Read the package insert for inflation volume. Stop inflation if the patient develops discomfort. Do not inflate with saline; if a saline-filled balloon ruptures, aspiration could result. Read specific insertion instructions for each product before use. If there is a drawstring at the distal end, tape the drawstring to the face to secure the balloon in place.

PREFORMED NASAL TAMPONS OR SPONGES

Preformed nasal tampons or sponges are made of synthetic material that expands after hydration (**Figure 244-3**). These devices are commercially available in 5- and 10-cm lengths, for anterior and posterior packing, respectively. One product is **Merocel®**, a compressed dehydrated polyvinyl acetate sponge. Coat the sponge with water-soluble antibiotic ointment and insert it gently along the floor of the nasal cavity. If the tampon has not expanded within 30 seconds of placement, gently irrigate it (while in place) with 5 mL of normal saline to promote expansion. An alternative method is to cut the Merocel® pack lengthwise in two equal halves and coat each half with lubricating ointment. Insert the two halves parallel to each other and parallel with the nasal septum; irrigate each half with about 2 mL of normal saline. This method may provide better compression of septal bleeding.[15] Whichever method is used, tape the drawstring to the face (Figure 244-3) to secure the tampon in place and prevent inadvertent aspiration. Merocel®

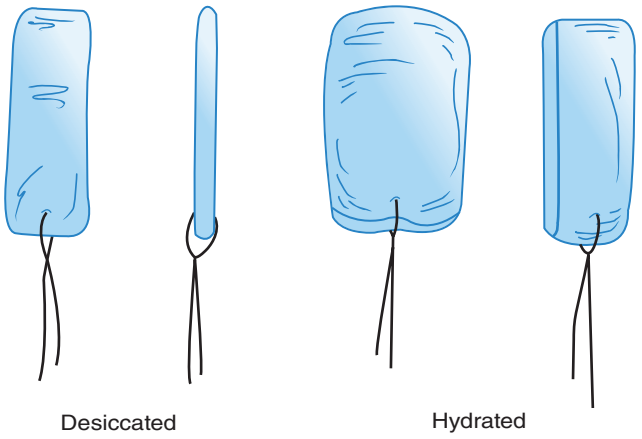


FIGURE 244-3. The Merocel® nasal sponge in its desiccated (*left*) and hydrated (*right*) forms.

nasal packs work effectively but sometimes cause more pain than balloons with removal.[16]

RIBBON GAUZE PACKING

If the preceding devices are unavailable, ribbon gauze packing can be placed to control epistaxis (**Figure 244-4**).

POSTERIOR NASAL PACKING

Failure to control hemorrhage after direct pressure, optimal use of vasoconstrictors, cautery, and anterior packing suggests (but is not diagnostic of) posterior bleeding. Bilateral anterior packing may help augment tamponade of the nasal septum. If that is not successful, the previously mentioned devices are usually available in longer lengths to provide posterior packing. If longer posterior-length packs do not work, obtain ENT consultation. Posterior packing is associated with higher complication rates, including pressure necrosis, infection, hypoxia, and cardiac dysrhythmias, especially in patients with underlying cardiopulmonary disease, and thus, posterior packing is generally applied as a temporizing measure while awaiting ENT support. A formal nasal block may be required for analgesia, as posterior packing is often quite uncomfortable for the patient, but topical anesthesia may be sufficient if applied properly. The Rapid Rhino® has both an anterior (5.5 cm) and posterior (7.5 cm) balloon that can be inflated as required to tamponade bleeding. **Figure 244-5** shows the placement of a dual balloon catheter. All posterior packing should be accompanied by an anterior pack.

If resources are limited, a satisfactory posterior pack can be achieved using a 14F Foley catheter. The procedure is as follows. Place the patient in "sniffing position," and anesthetize the nasal mucosa by placing three cotton pledgets soaked in a 1:1 mixture of 4% lidocaine solution and 0.05% oxymetazoline intranasally for 5 minutes. Consider cutting off the Foley tip beyond the balloon as the tip may stimulate the gag reflex. Lubricate the distal third of the catheter with lidocaine gel and advance the Foley catheter along the floor of the nasal cavity until the end is visualized in the posterior oropharynx. Inflate the balloon with 7 mL of air, and gently retract the catheter approximately 2 to 3 cm until it is lodged in the choanal arch of the posterior nasopharynx. Do not use saline for balloon insufflation because rupture could result in aspiration. If the balloon slides back into the nasal cavity, deflate the balloon, and advance the catheter as before. Inflate with 10 mL of air in total and retract to secure the balloon. Avoid using more than 10 mL of air to prevent risk of pressure necrosis. Secure the pack by taping the catheter to the patient's cheek.

In patients requiring posterior packing or in cases of uncontrolled anterior epistaxis, obtain early ENT intervention.[17] Approximately 10% of patients admitted for epistaxis require invasive therapy; success is

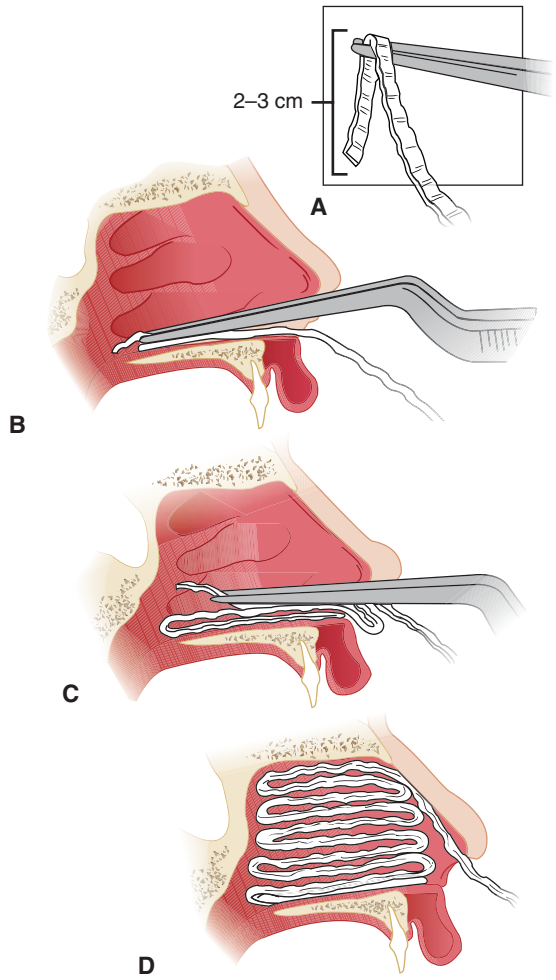


FIGURE 244-4. The key to placement of an anterior nasal pack that will control epistaxis adequately and stay in place is to lay the packing into the nasal cavity in an accordion-like manner so that part of each layer of packing lies anteriorly, preventing the gauze from falling posteriorly into the nasopharynx. **A.** The first layer of $^1/_4$-inch petrolatum-impregnated gauze strip is grasped approximately 2 to 3 cm from its end. **B.** The first layer is then placed on the floor of the nose through the nasal speculum (not pictured here). The bayonet forceps and nasal speculum are then withdrawn. **C.** The nasal speculum is reintroduced on top of the first layer of packing, and a second layer is placed in an identical manner. After several layers have been placed, it is often useful to reintroduce the bayonet forceps to push the previously placed packing down onto the floor of the nose, making it tighter and more secure. **D.** A complete anterior nasal pack can tamponade a bleeding point anywhere in the anterior nasal cavities and will stay in place until removed by the provider or patient.

similar for arterial ligation or embolization, but cost and risk of stroke are higher for patients receiving embolization.[18]

DISPOSITION AND FOLLOW-UP

If hemorrhage is controlled and hemodynamic stability is ensured over a period of observation (1 hour or more in the ED), patients with anterior epistaxis can be discharged home with primary care or ENT follow-up within 48 to 72 hours for removal of nonbiodegradable packing. Provide patients with instructions for simple techniques to control repeat hemorrhage and consider a short-term prescription of inhaled vasoconstrictors such as oxymetazoline for rebleeding. Patients on warfarin with INR levels in the desired range may continue medication.[19] Discontinue NSAIDs for 3 to 4 days. If anterior packing with either absorbable or nonabsorbable material is going to be in place for more than 48 hours, an antibiotic with staphylococcal coverage such as amoxicillin-clavulanic acid has been traditionally recommended to prevent infection with

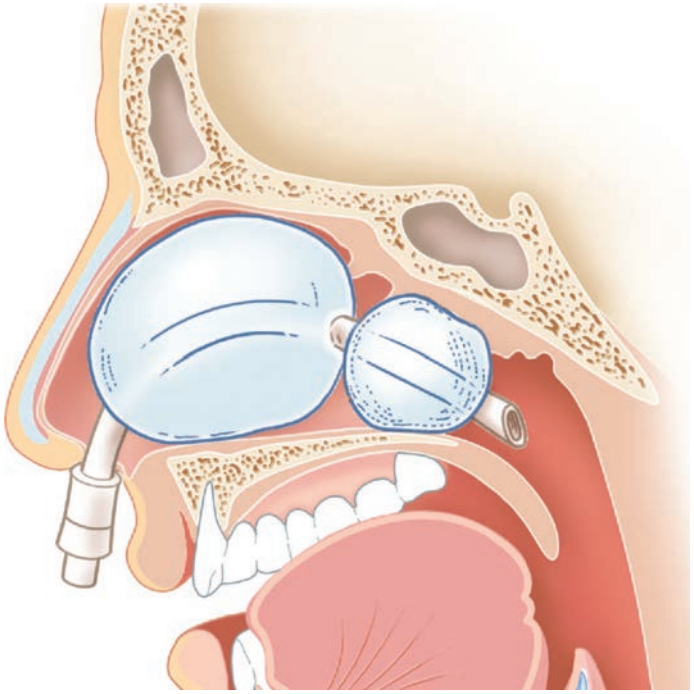


FIGURE 244-5. A dual balloon epistaxis catheter providing anterior and posterior compression. There are separate ports for inflation of the anterior and posterior balloons. The anterior port can hold 30 mL, and the posterior balloon holds 10 mL. Read package insert for proper inflation volume, as dual balloon catheters vary in size. (Reproduced with permission from Reichman EF (ed): *Reichman's Emergency Medical Procedures*, 3rd ed. New York, NY: McGraw-Hill; 2019, Figure 205-19.)

Staphylococcus aureus and possible associated toxic shock syndrome.[20] However, antibiotic benefit is not clear.[21,22] If the packing will be removed in 24 to 36 hours, prophylactic antibiotics may not be needed.[18] Consider potential drug interactions that may increase bleeding.[19] If the patient requires posterior packing, admission is strongly advised to monitor for complications.

NASAL FRACTURES AND SEPTAL HEMATOMA

ANATOMY

The nasal pyramid is formed by two rectangular-shaped bones that articulate with the frontal bone, the frontal process of the maxilla, and the perpendicular plate of the ethmoid to form a "tent-like" configuration (**Figures 244-6** and **244-7**). A large proportion of the structural

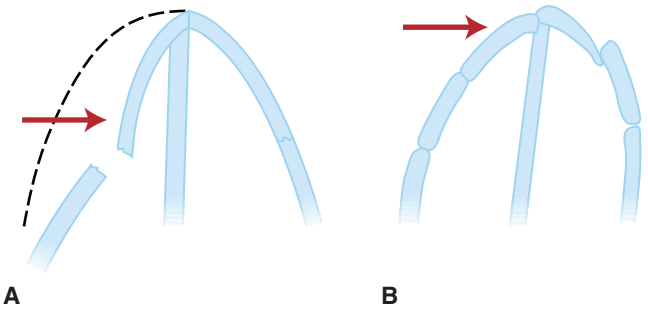


FIGURE 244-6. A and B. Lateral impact nasal injury. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD.]

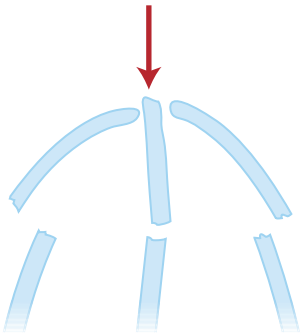


FIGURE 244-7. Frontal impact nasal injury. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD.]

integrity is maintained by a cartilaginous framework of the nasal septum, lateral processes, and medial and lateral crura of the alar cartilages (**Figure 244-8**).

CLINICAL FEATURES

Determine the mechanism of injury to evaluate the potential location of displaced bony fragments and to assess other associated pathology, especially head and neck injury. Assess the midface, zygomatic arch, orbits, sinuses, teeth, and cervical spine. Malocclusion and midface instability suggest Le Fort's fracture (see Chapter 259, "Trauma to the Face").

NASAL EXAMINATION

After a general exam, perform an examination of the nose to include an external assessment for bony crepitus, deformity, and edema (**Figure 244-9**). Periorbital ecchymosis in the absence of other findings of orbital injury is suggestive of nasal fracture. Profuse epistaxis may also suggest nasal fracture. Nasal bone mobility, which is virtually diagnostic of fracture, is appreciated by grasping the dorsum of the nose between the thumb and index finger and attempting to rock the nasal pyramid back and forth.[7] Perform anterior rhinoscopy after obtaining a relatively bloodless field with topical vasoconstrictors and evacuation of clots. Key components of the internal examination should include assessment for mucosal lacerations, septal fractures or deviation, and septal hematoma.

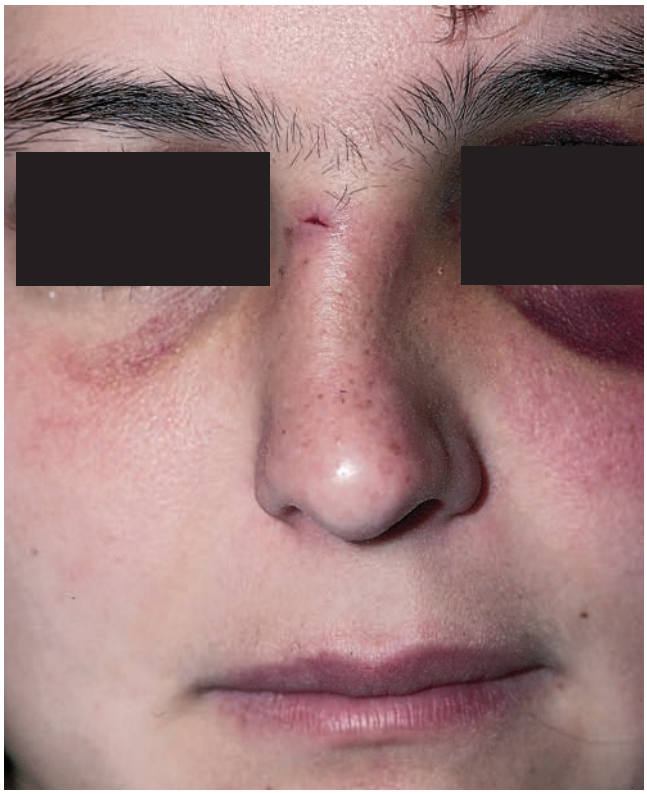


FIGURE 244-9. Nasal fracture clearly identifiable on physical examination with deformity and periorbital ecchymosis. [Photo contributed by David W. Munter. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, New York.]

DIAGNOSIS AND IMAGING

The diagnosis of nasal fracture is clinical, and radiologic confirmation of isolated nasal fracture is not required. The results of plain films rarely change management.[23,24] The indications for closed reduction are limited

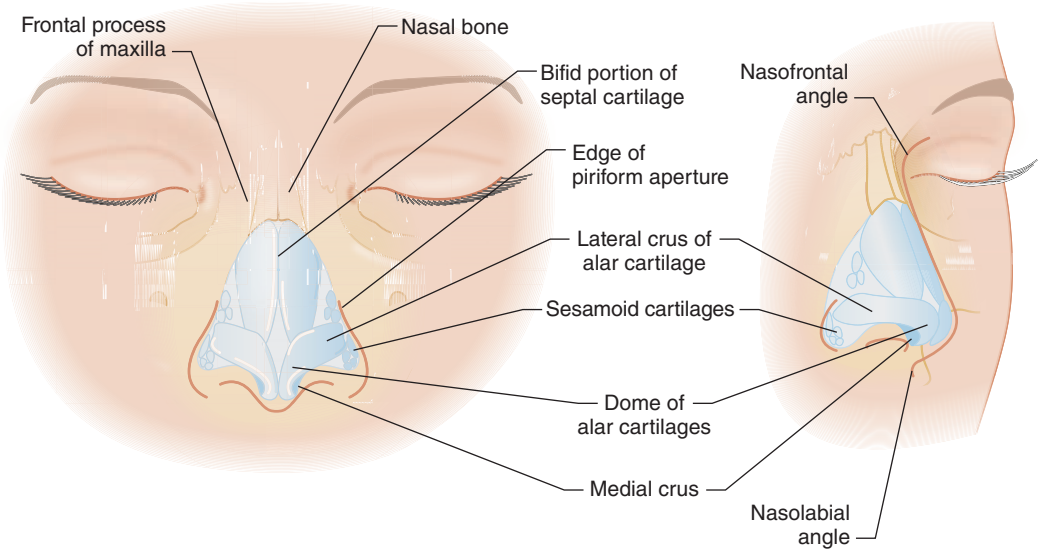


FIGURE 244-8. The nasal cartilages and the keystone area where they articulate with the nasal bones. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD.]

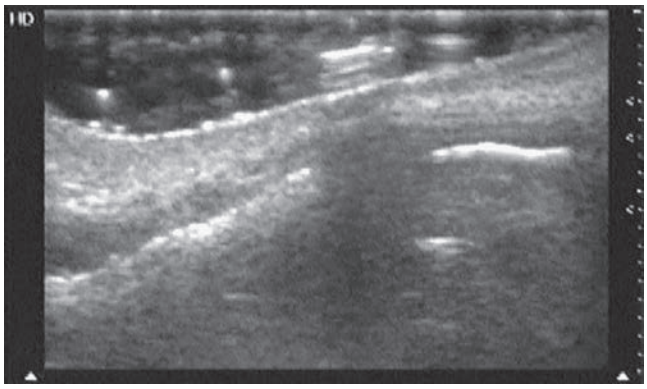


FIGURE 244-10. US still image of nasal fracture demonstrating cortical disruption. A large gap is seen between bone fragments. [Reproduced with permission from Ma OJ, Mateer JR, Blaivas M: *Emergency Ultrasound,* 2nd ed. © 2008, McGraw-Hill, New York.]

to alleviation of nasal obstruction and correcting deformity to improve cosmesis. These indications are best evaluated clinically at the bedside and usually are not emergency procedures.[23,24] Ultrasonography is an alternative to plain radiographs for the diagnosis of nasal fractures and has sensitivities and specificities similar to plain radiography[25-27] (**Figures 244-10** and **244-11**). CT scanning is not needed for isolated nasal fractures and is best reserved when there is concern for intracranial injury or other facial fractures.[25]

TREATMENT

The main priority is the exclusion of other associated traumatic injuries (see Chapter 259) and nasal septal hematoma (see later section on septal hematoma).[28] Nasal fractures with overlying lacerations should be treated similarly to other open fractures. Cerebrospinal fluid rhinorrhea is difficult to diagnose. Fluid can be sent for β-transferrin analysis. Suspicion of leaks requires further imaging and otolaryngologic or neurosurgical consultation (see Chapter 257, "Head Trauma," for more discussion).

Once serious injury is excluded, the management of uncomplicated nasal fractures is dictated by the timing of the examination in relation to the injury and ability to evaluate for significant displacement of the nasal pyramid. Early in the course, significant soft tissue swelling may obscure an adequate physical examination. If the patient presents immediately after the injury event, there may be opportunity to reduce a displaced nasal fracture before edema distorts the landmarks. Otherwise, it is prudent to recommend ENT consultation for an elective closed reduction within 6 to 10 days of the initial insult. Because of the development of fibrous connective tissue along the fracture line, failure to perform an adequate reduction within this time frame may result in an unacceptable cosmetic outcome and may ultimately require rhinoseptoplasty.[29] Most nasal fractures do not require immediate intervention and can be managed at ENT follow-up within the specified time frame of 6 to 10 days. Closed reduction is best left to the ENT specialist. Even simple nasal fractures in children deserve ENT follow-up because nasal deformity may develop during puberty when nasal growth accelerates.



FIGURE 244-11 Nasal radiograph lateral view demonstrating depressed nasal fracture with cortical disruption. [Photo contributed by Lorenz F. Lassen, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, New York.]

NASAL SEPTAL HEMATOMA

Vascular supply to the septal cartilage is provided through the perichondrium. A hematoma lifts the perichondrium, disrupting blood supply to the cartilage. If a septal hematoma is identified, incise and drain the hematoma urgently to avoid ischemic necrosis of the nasal septum (**Figures 244-12** and **244-13**). Necrosis can lead to saddle deformity and nasal obstruction, ultimately requiring rhinoseptoplasty. Because pooled, clotted blood is a nidus for infection, unidentified septal hematomas can develop into abscesses. Systemic symptoms developing after facial trauma should prompt investigation for nasal septal abscess, and any suspicion should prompt ENT referral, urgent surgical drainage, and IV antibiotics to avoid serious complications. Untreated infected hematomas not only increase risk for saddle deformity and a poor functional outcome but can also spread contiguously, leading to osteomyelitis, cavernous sinus thrombosis, meningitis, and intracranial abscesses.[30]

DRAINAGE OF NASAL SEPTAL HEMATOMA

The procedure for incision and drainage of a nasal septal hematoma is as follows:

1. Place patient in "sniffing position," and be prepared to perform adequate anterior rhinoscopy with a nasal speculum, light source, suction, irrigation, and packing materials.
2. Properly anesthetize the nasal mucosa by placing three cotton pledgets soaked in a 1:1 mixture of 4% topical lidocaine and epinephrine 1:1000 solution for 5 minutes, followed by infiltrative anesthesia if required.
3. Although sterile technique cannot be fully achieved in the nasal cavity, use sterile instruments, and keep the operative area as clean as possible with irrigation of foreign debris.
4. While obtaining adequate visualization of the hematoma with the nasal speculum, make a small horizontal incision superficially through the mucosa, making sure you do not incise the cartilaginous septum.
5. Evacuate the clot with Frazier suction or with forceps.
6. Perform bilateral anterior nasal packing with nasal tampons coated in topical antibiotic ointment to prevent reaccumulation of the clot and keep the septum midline.
7. Discharge with 24-hour ENT or ED follow-up.[31] Some recommend the use of prophylactic antibiotics for patients with packing in place, but this is not necessary if the packing will be removed in 24 to 36 hours.

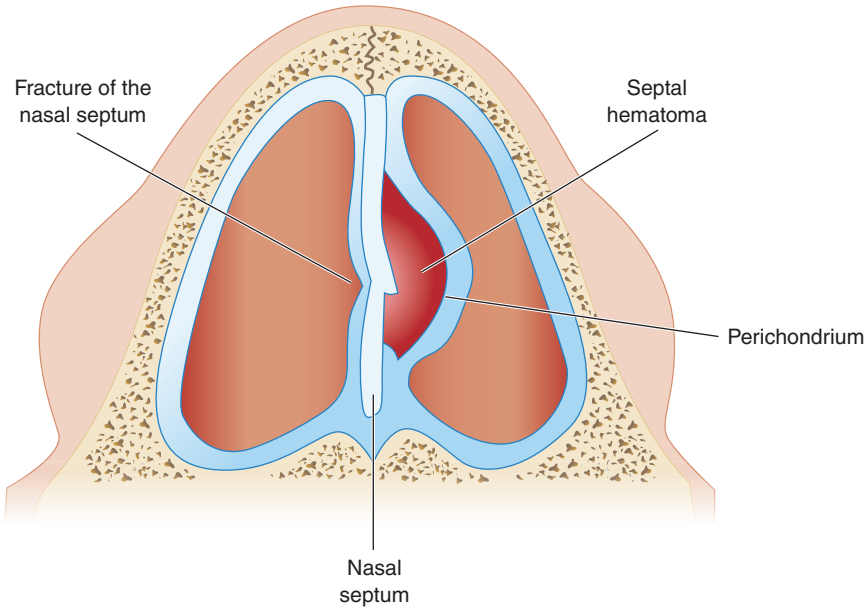


FIGURE 244-12. Graphic depiction of nasal septal hematoma. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, Eric F. Reichman, PhD, MD, and Robert R. Simon, MD.]

NASAL FOREIGN BODIES

Although nasal foreign bodies are most common in children, they should also be considered in psychiatric and intellectually disabled adults.[32,33] Morbidity of undiagnosed nasal foreign bodies includes aspiration, infection, pressure necrosis, or perforation. Consider a nasal foreign body in patients with purulent unilateral nasal discharge or recurrent unilateral epistaxis. It is important to recognize button battery impaction because it may cause liquefaction necrosis and septal perforation.[34] Plain radiography is a potential tool for foreign body identification, but many objects are not radiopaque.[35] Nasal foreign body removal is discussed in Chapter 123, "Nose and Sinus Disorders in Infants and Children."

SINUSITIS AND RHINOSINUSITIS

Sinusitis is inflammation of the mucosal lining of the paranasal sinuses. There are six nasal sinuses: two maxillary and two frontal sinuses, and a single ethmoid and frontal sinus. Rhinosinusitis is defined as an inflammation of the paranasal sinuses and the nasal cavity. The term *rhinosinusitis* is preferred because sinusitis is almost always accompanied by rhinitis.[36] Depending on the duration of the disease, rhinosinusitis is classified into acute (<4 weeks), subacute (4 to 12 weeks), or chronic (>12 weeks).[37-40]



FIGURE 244-13. Trauma patient with nasal septal hematoma in the right nares. [Photo contributed by Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, New York.]

PATHOPHYSIOLOGY

All six paranasal sinuses are coated by respiratory mucociliary epithelium, and the sinuses drain through the ostia into the nose. Any type of acute inflammation of the mucosa leads to obstruction of the ostia, accumulation of secretions within the sinuses, and reabsorption of air, resulting in negative pressure in the sinuses and clinical symptoms. Acute rhinosinusitis, like otitis media, is usually viral. *Haemophilus influenzae* and *Streptococcus pneumoniae* are the usual organisms in acute bacterial rhinosinusitis.[41] Chronic infections are usually due to anaerobes, gram-negative bacteria, *Staphylococcus aureus*, and, occasionally, fungi, especially in the immunocompromised.[39]

CLINICAL FEATURES

Acute rhinosinusitis is defined by two or more of the following symptoms: blockage or congestion of the nose, facial pain or pressure, diminished ability to smell or detect odors, and either anterior or posterior nasal discharge, for 7 days to 4 weeks.[36] Additional symptoms can include tooth pain, fever, halitosis, and sinus pressure while bending forward or changing head position.[36,38,39] The American Academy of Otolaryngology guidelines list the cardinal signs of rhinosinusitis as being purulent nasal drainage (not clear) accompanied by nasal obstruction or by facial pain, pressure, or fullness, or both.[38] On physical examination, the patient may have pain and tenderness over the sinuses with percussion. Inspect the face for swelling and redness, and inspect the nose for mucosal swelling, anatomic abnormality, and foreign bodies. Also perform a neurologic examination, and examine the ears, eyes, and teeth to evaluate for extension of disease. Subacute and chronic sinusitis persist for 4 weeks or more.

DIAGNOSIS

The diagnosis of uncomplicated **acute rhinosinusitis** is based on clinical findings[36,38,41]; most cases are viral in etiology.[38] Plain sinus radiographs or CT scans are not needed. The symptoms of acute rhinosinusitis are

similar to a common cold or viral upper respiratory infection, but symptom duration ranges from 7 days to up to 12 weeks and may present after a recent viral upper respiratory tract infection.[40]

American Academy of Otolaryngology guidelines recommend reserving the diagnosis of acute bacterial sinusitis for patients with symptoms persistent for 10 days or more.[38] Experts acknowledge that the evidence proving symptom duration alone can identify a bacterial etiology is weak.[42] However, the guideline panel considered this limitation on the diagnosis as appropriate, acknowledging the low specificity of the criteria.[38,42]

If a complication of rhinosinusitis is suspected by clinical presentation or duration of symptoms, CT scan (with contrast) is helpful to identify or rule out intracranial extension.[38] The differential diagnosis of rhinosinusitis includes migraine headache, craniofacial neoplasm, foreign body retention, and dental caries.

TREATMENT

Supportive treatment is the most common and effective treatment for acute uncomplicated rhinosinusitis. Nasal saline irrigation alone or in conjunction with other adjunctive measures, such as nasal decongestants, may decrease symptom severity.[38] Restrict the use of topical decongestants such as oxymetazoline to approximately 3 days to avoid rebound mucosal congestion or edema (rhinitis medicamentosa). Topical (intranasal spray) corticosteroids may shorten the duration of illness.[43]

In a 2014 Cochrane database systematic review analyzing the efficacy of antibiotic therapy, the authors concluded that antibiotics may provide a small treatment effect in patients with symptoms of rhinosinusitis lasting >7 days.[37] However, because 80% of patients treated with placebo also improved within 2 weeks, it is unclear whether the treatment effect is clinically significant. In general, **antibiotics should be reserved for patients with purulent nasal secretions and severe symptoms for ≥7 to 10 days.**[36-38] If antibiotics are prescribed, amoxicillin is recommended as first-line therapy for most adults,[36] at a dose of 500 milligrams PO three times per day. Patients with penicillin allergies may receive macrolide antibiotics, cephalosporins, or fluoroquinolones.[36,41] For patients who have received antibiotics within the past 4 to 6 weeks, consider a fluoroquinolone or high-dose amoxicillin-clavulanate.[37] Use caution in selection of antibiotics in patients who are on oral anticoagulation.[21] In the aforementioned Cochrane review, comparisons between different classes of antibiotics showed no significant difference.[37] Follow-up with a primary care provider is advised.

Patients with **subacute, chronic, or recurrent rhinosinusitis** should be evaluated for conditions that modify management, such as allergy, cystic fibrosis, or immunocompromise. Outpatient CT of the sinuses can evaluate for invasion of neighboring tissues and neoplasms.[37] ENT follow-up is advised.[40,44]

COMPLICATIONS

Complications of rhinosinusitis are mostly related to extension of the infection beyond usual anatomic boundaries. Meningitis, cavernous sinus thrombosis, and intracranial abscesses are rare but important complications associated with contiguous spread of sinus disease. Up to 75% of cases of orbital cellulitis, which can lead to blindness through venous congestion and ischemia of the optic nerve, are attributable to disease of the sinuses.[40] Frontal sinusitis can lead to osteomyelitis of the frontal bone with a doughy swelling of the forehead called *Pott's puffy tumor* and can also be associated with an extradural or subdural empyema. In general, patients with these deeper infections usually appear systemically ill or have focal neurologic signs and require admission and IV antibiotics.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 245

Oral and Dental Emergencies

Ronald W. Beaudreau

INTRODUCTION

Oral emergencies generally can be divided into two broad categories: (1) nontraumatic orofacial pain and (2) orofacial trauma, specifically dentoalveolar trauma. Dental pain is a common ED chief complaint, so emergency providers should be familiar with normal oral and dental anatomy to appropriately differentiate and manage dental and nondental causes of dental pain.

ORAL AND DENTAL ANATOMY

The normal adult dentition consists of 32 permanent teeth. The adult dentition has four types of teeth: 8 incisors, 4 canines, 8 premolars, and 12 molars. The primary or deciduous dentition consists of 20 teeth of three types: 8 incisors, 4 canines, and 8 molars. **Figure 245-1** shows the eruptive pattern of both the primary and permanent dentition. **Figure 245-2** illustrates the most commonly used tooth numbering system; however, description of the tooth type and location is also appropriate.

ANATOMY OF THE TEETH

A tooth consists largely of *dentin,* which surrounds the *pulp*, the tooth's neurovascular supply (**Figure 245-3**). Dentin is a homogeneous material produced by pulpal odontoblasts throughout life. Dentin is deposited as a system of microtubules filled with odontoblastic processes and extracellular fluid. The *crown*, or the visible portion of tooth, consists of a thick *enamel* layer overlying the dentin. Enamel, the hardest substance in the human body, consists largely of hydroxyapatite and is produced by ameloblasts before eruption of the tooth into the mouth. The *root* portion of the tooth extends into the alveolar bone and is covered with a thin layer of *cementum.*

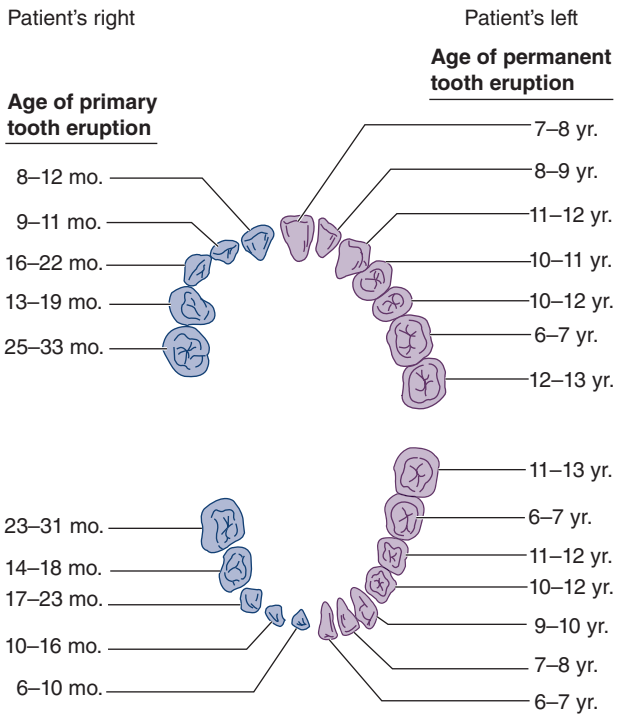


FIGURE 245-1. Normal eruptive patterns of the primary and permanent dentition. mo. = month; yr. = years.

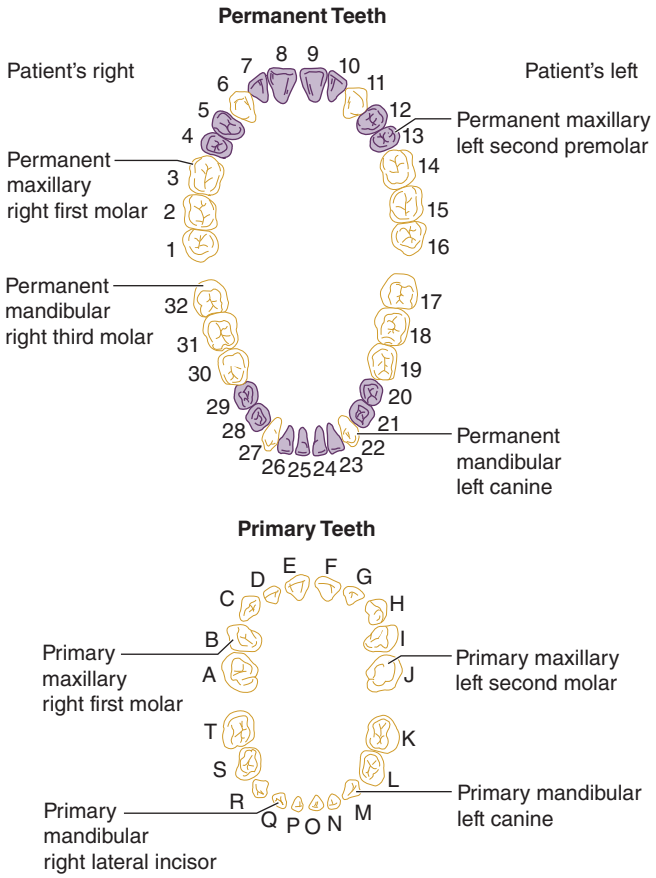


FIGURE 245-2. Tooth numbering system.

THE NORMAL PERIODONTIUM

The periodontium, or attachment apparatus, is essential for maintaining the integrity of the dentoalveolar unit. The attachment apparatus consists of a gingival component and a periodontal component. The gingival component includes the junctional epithelium, gingival tissue, and gingival fibers and primarily functions to maintain the integrity of the periodontal component. The periodontal component includes the periodontal ligament, alveolar bone, and cementum of the root of the tooth and forms most of the attachment apparatus. Disease states such as gingivitis and periodontal disease weaken and destroy the attachment apparatus, resulting in tooth mobility and tooth loss.[1]

Gingival tissue is keratinized stratified squamous epithelium. It can be divided into the free gingival margin and the attached gingiva. The free gingiva is the portion that forms the 2- to 3-mm-deep *gingival sulcus* in the disease-free state. The attached gingiva adheres firmly to the underlying alveolar bone. The nonkeratinized alveolar mucosa extends from the attached gingiva to the vestibule and floor of the mouth. The mucosal tissue of the cheeks, lips, and floor of the mouth is also composed of nonkeratinized squamous epithelium.

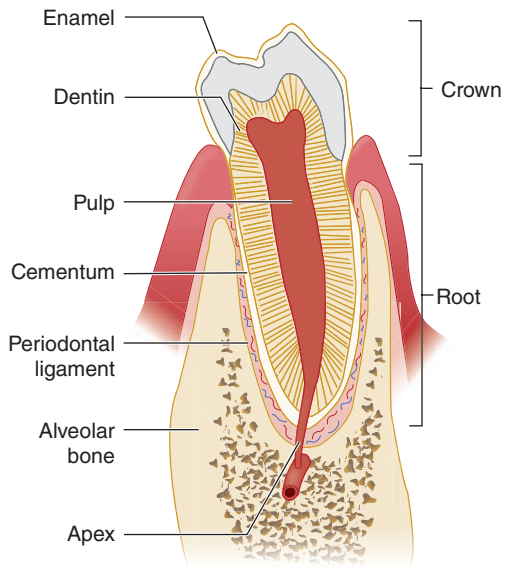


FIGURE 245-3. The dental anatomic unit and attachment apparatus.

OROFACIAL PAIN

Table 245-1 lists common causes of orofacial pain. Pain of dental origin may be diffuse in nature, presenting as a headache, sinus pain, eye pain, or jaw or neck pain, or may be localized to a single tooth. Remember to consider myocardial infarction as a cause of jaw pain.

Use a systematic approach for examination of the oral cavity. If not contraindicated, examine the patient in the sitting position with the head supported. First, evaluate the general condition of the patient, including speech, ability to swallow oral secretions, and any obvious swelling or asymmetry of the head and neck. Next, examine the oral soft tissue using a tongue depressor to expand your view, looking specifically at the inner lips, the buccal and labial mucosa, the hard and soft palate, and the tongue and floor of the mouth. Ask the patient to extend the tongue, and gently grasp it with a piece of dry gauze, further extending it to the right and to the left, to expose each base. The floor of the mouth should be palpated with a finger in the mouth and one externally under the chin to check for a mass or lesion. Examine the teeth visually, and then gently percuss the suspected teeth with a firm clean object to determine if a specific tooth is the source of pain. If the patient has experienced trauma, test each tooth for mobility and tenderness with gentle pressure and percussion. Check that all the teeth occlude as normal for the patient. Assess the degree of opening of the mouth. Palpate for potential fractures of the mandible or maxilla. Finally, evaluate the temporomandibular joint by placing your index fingers in the ears and feeling for crepitance or popping while the mandible is fully opened and closed.

PAIN OF ODONTOGENIC ORIGIN

TOOTH ERUPTION AND PERICORONITIS

Discomfort is commonly associated with the eruption of primary or deciduous teeth in infants. Gingival irritation (86.18%), irritability (68.19%), and drooling (55.72%) are commonly associated findings. Teething infants may have a mildly elevated temperature, but it is rarely high enough to be characterized as fever.[2] Eruption of permanent teeth, especially third molars, or *wisdom teeth,* may cause pain. Gingival irritation and inflammation associated with tooth eruption are common and must be distinguished from *pericoronitis.* Pericoronitis is inflammation of the *operculum*: the gingival tissue overlying the occlusal surface of an erupting tooth. Impaction of food and debris beneath the operculum results in a severe inflammatory response. Without intervention, this progressive inflammatory process will result in localized infection. Because of the close proximity of the masticator space (composed of the masseteric space, pterygomandibular space, and the superficial and deep temporalis space) to third molars, this infection can cause trismus. If the infection spreads into the connecting parapharyngeal spaces, it can be life threatening. Treatment of mild to moderate pericoronitis without associated systemic symptoms consists of appropriate oral antibiotic therapy; local irrigation of food and debris from underneath the operculum; saline mouth rinses; and analgesia with NSAIDs and opiates as appropriate. See **Table 245-2** for appropriate antibiotics for outpatient treatment of dental and oral

TABLE 245-1 Differential Diagnosis of Orofacial Pain

Nontraumatic Causes of Potential Dental Pain	
Odontogenic origin	
Tooth eruption	Cracked tooth syndrome
Pericoronitis	Periradicular periodontitis
Dental caries	Periapical abscess/facial space infection
Dentinal sensitivity/cervical erosion	Postextraction discomfort
Reversible pulpitis	Postextraction alveolar osteitis
Irreversible pulpitis	Postrestorative pain
Periodontal pathology	
Gingivitis	Periodontal abscess
Periodontal disease	Acute necrotizing gingivostomatitis
Gingival abscess	Peri-implantitis
Neurogenic/neurophysiologic syndromes	
Trigeminal neuralgia	Bell's palsy
Other cranial neuralgias	Temporomandibular disorder
Nondental infections	
Oral candidiasis	Hand-foot-and-mouth disease
Herpes simplex types 1 and 2	Sexually transmitted infections
Varicella-zoster	Herpangina
Mumps	Sinusitis
Sialadenitis	Parotitis
Malignancies	
Squamous cell carcinoma	Leukemia
Kaposi's sarcoma	Melanoma
Lymphoma	
Other etiologies	
Aphthous ulcers	Pyogenic granuloma
Traumatic ulcers	Lichen planus
Stomatitis and mucositis	Cicatricial pemphigoid
Uremia	Pemphigus vulgaris
Vitamin deficiency	Erythema multiforme
Radiation/chemotherapy related	Crohn's disease
Benign migratory glossitis	Behçet's syndrome
Orofacial Trauma	
Dental fractures	Alveolar ridge fractures
Subtle enamel cracks/infractions	Facial bone fractures
Dental crown and/or root fractures	Oral soft tissue lacerations
Dental luxations and avulsions	

TABLE 245-2 Appropriate Oral Antibiotics for Management of Dental and Oral Infections

Antibiotic	Adults Dosage	Pediatric Dosage
Amoxicillin	500 milligrams 3 times daily for 7 d	22.5 milligrams/kg 2 times daily
Augmentin	875 milligrams 2 times daily for 7 d	22.5 milligrams/kg 2 times daily
Clindamycin	300 milligrams 4 times daily for 7 d	7–10 milligrams/kg 3 times daily
Metronidazole	500 milligrams 3 times daily for 7 d	5–10 milligrams/kg 3 times daily
Doxycycline	100 milligrams 2 times daily for 7 d	2 milligrams/kg 2 times daily (not recommended <8 y old)

infections. More severe cases may require IV antibiotics and admission; see masticator space infections in Chapter 243, "Face and Jaw Emergencies," for more information. For outpatient management, referral to a general dentist or an oral and maxillofacial surgeon within 24 to 48 hours is appropriate.[3,4]

DENTAL CARIES AND PULPITIS

Dental caries is the loss of integrity of the tooth enamel from hydroxyapatite dissolution by prolonged exposure to the acidic metabolic by-products of plaque bacteria. Caries most commonly occur in areas where plaque accumulates such as pits and fissures of the occlusal surface, interproximally, and along the gingival margins. When a sufficient breach of enamel integrity occurs, and the dentin is involved, caries spread along dentinal microtubules. Direct communication between the oral environment and the vital dental pulp is established, and sensitivity to cold or sweet stimulus may result.

The pulpal inflammatory process is initially reversible, but with continued stimuli, the pulp's ability to respond and repair is compromised. *Irreversible pulpitis* can be distinguished from *reversible pulpitis* by the duration of symptoms. In reversible pulpitis, the duration of pain is short, lasting seconds, as compared with irreversible pulpitis, in which the pain may last for minutes to hours. The most common stimulus is heat or cold, although sweet or sour stimuli also can elicit pain. Irreversible pulpits may also present as spontaneous tooth pain; however, this is more commonly associated with pulpal necrosis.[3] Authors of a systematic review published in 2016 concluded that there is insufficient evidence to determine if antibiotics reduce pain when used to treat irreversible pulpitis, in the absence of obvious infection.[5] A local anesthetic block, as discussed in this chapter's section on dental local anesthesia, greatly reduces pain and should be considered for short-term pain management. NSAIDs with or without acetaminophen as an adjunct are recommended by the American Dental Association over narcotics for managing dental pain because NSAIDs offer the most favorable balance between pain reduction and potential harms.[6] The definitive treatment for irreversible pulpitis and pulpal necrosis is root canal therapy or dental extraction.

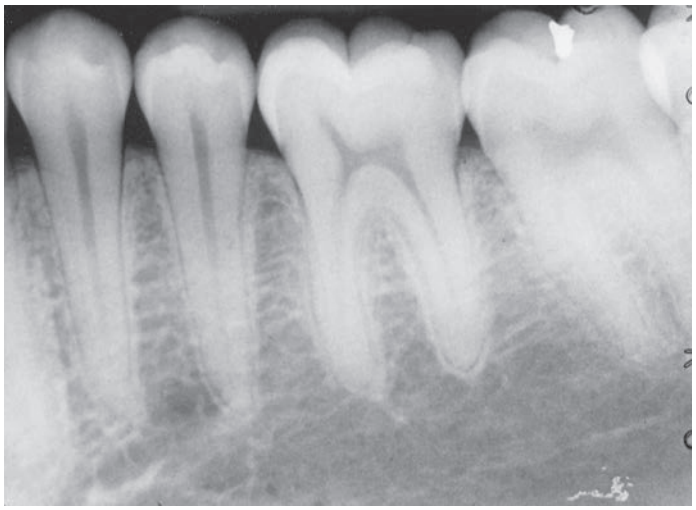
CRACKED TOOTH SYNDROME

Cracked tooth syndrome is an incomplete fracture of a tooth that may extend into the vital pulp. Molars are most commonly affected. The patient experiences sharp pain on chewing that resolves when chewing ceases. Cold and sweet stimuli may also evoke pain. NSAIDs are frequently effective at temporarily controlling pain.[3,4] The patient should avoid chewing on the affected side and see a dentist for definitive treatment.

PERIRADICULAR PERIODONTITIS

Acute *periradicular periodontitis* is the extension of pulp disease, inflammation, or necrosis into the tissues surrounding the root and apex of the tooth (deepest portion of the tooth socket). Occasionally it can be due to occlusal trauma. Periradicular lesions appear as a slight widening of the periodontal ligament space, a thinning of the lamina dura, or a radiolucent area associated with the root apex on a periapical dental radiograph. A panorex is not typically useful for periradicular periodontitis but can be important in identifying other painful osseous pathology (**Figure 245-4**).[3]

Pain on percussion of the suspected tooth with a light metal instrument, such as a handle of a dental mirror, helps to identify the offending tooth. Radiographically and clinically indistinguishable from periradicular periodontitis, a *periapical abscess* by definition contains a collection of pus. A small swelling of the gingiva with a draining fistula adjacent to the affected tooth is known as a *parulis* and can help identify the involved tooth (**Figure 245-5**). If a dental abscess erodes through the cortical bone but does not drain spontaneously, then subperiosteal extension results in intraoral or facial swelling and fluctuance that should be incised and drained. Treat dental abscesses or other periapical lesions with appropriate antibiotics[3,7] (Table 245-2). NSAIDs with



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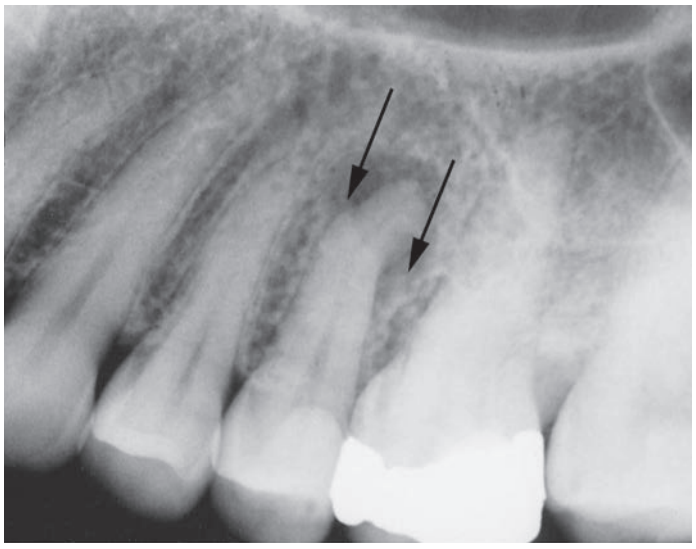


B

FIGURE 245-4. The radiographic appearance of a healthy tooth with a normal periodontal ligament space and distinct lamina dura (**A**) compared with the radiographic appearance of periapical radiolucency (*arrows*) consistent with periradicular periodontitis, a periapical abscess, or periradicular cyst (**B**). [Image used with permission of Gary M. Beaudreau.]



FIGURE 245-5. A parulis (*arrow*) superior to the maxillary molar. [Image used with permission of David E. Beaudreau.]

or without supplemental acetaminophen are preferred over opiates by the American Dental Association for pain relief.[6] Refer to a dentist for definitive treatment.

FACIAL SPACE INFECTIONS

Spread of odontogenic infections into the various facial spaces is relatively common. Buccal extension of a periapical infection of the mandibular teeth will involve the buccinator space. Maxillary labial extension of infection primarily will involve the infraorbital space. Perforation through the lingual cortical bone of mandibular molars, particularly the second and third molars, usually occurs below the mylohyoid ridge and involves the submandibular space. Lingual spread of periapical infections associated with mandibular anterior teeth will affect the lingual space. The submandibular space and lingual space communicate with each other at the posterior border of the mylohyoid muscle. Cellulitis of bilateral submandibular spaces and the lingual space is called **Ludwig's angina** and is potentially life threatening. As these spaces and the masticator space communicate directly with the parapharyngeal space, airway compromise is the immediate concern. For detailed discussion, see Chapter 243, "Face and Jaw Emergencies," and Chapter 246, "Neck and Upper Airway."

Infection of the infraorbital space may have a potentially devastating outcome if retrograde spread through the ophthalmic veins occurs and the cavernous sinus becomes involved.

POSTEXTRACTION PAIN

Immediate postoperative pain is most commonly related to the trauma of surgery. Postoperative edema, such as with extraction of third molars, peaks within the first 24 to 48 hours and is best managed with ice packs and elevation of the head of the bed to 30 degrees. NSAIDs are preferred over oral narcotics for pain.[6] Trismus, common immediately after extraction, is usually the result of postoperative inflammation. It can also be caused by direct trauma to the temporomandibular joint or the muscles of mastication during the surgical procedure or during administration of the inferior alveolar injection. Trismus peaks in the first 24 hours and usually decreases thereafter unless infection develops. Progressively worsening trismus is concerning for a postoperative infection.

POSTEXTRACTION ALVEOLAR OSTEITIS (DRY SOCKET)

Postextraction alveolar osteitis, or **dry socket**, usually occurs on the second or third postoperative day and is associated with exquisite oral pain. Total or partial displacement of the clot from the socket or fibrinolytic dissolution of the clot results in exposure of the alveolar bone and initiates a localized osteomyelitis of the exposed bone. Risk factors for developing postextraction alveolar osteitis include smoking, preexisting pericoronitis or periodontal disease, a traumatic extraction, a prior history of alveolar osteitis, and hormone replacement therapy.[8-10] The incidence of postextraction alveolar osteitis is 1% to 5% of all extractions but is considerably higher (up to 30%) among impacted third molar extractions.[9]

It is generally agreed that the goal of treatment of alveolar osteitis is pain management until healing occurs. Gentle irrigation of the socket with warmed saline or chlorhexidine 0.12% oral rinse to remove debris is recommended. Intrasocket placement of various available medicaments is controversial, and two systematic reviews concurred that there is insufficient evidence to support one method of treatment over another.[8,9] Antibiotics may be indicated if there are systemic signs of infection (Table 245-2).[10] Refer for dental follow-up.[8-10]

POSTEXTRACTION BLEEDING

Postextraction bleeding is not uncommon. Displacement of the clot may result in recurrent or continued bleeding. Generally, firm pressure applied to the extraction site is adequate to control bleeding. This is best accomplished by folding a 2 × 2–inch gauze pad and placing it over the extraction site and applying firm pressure by clenching with

the opposing teeth. Pressure must be held firmly, not a chewing action, for 20 minutes or until hemostasis is complete. If direct pressure is not successful, then apply an absorbable gelatin sponge (Gelfoam®, Pfizer Inc., New York, NY), microfibrillar collagen (Avitene®, Davol, Inc., Warwick, RI), or regenerated cellulose (Surgicel®, Ethicon, Inc., Somerville, NJ) into the socket to provide a matrix for clot formation. Pressure can also be applied with a gauze pad soaked with tranexamic acid. When using any of these agents, continue to maintain pressure for 20 to 30 minutes. Sutures can be used for holding such agents in place or to loosely close the gingiva over the socket. **Do not suture the gingiva tightly because this may cause necrosis of the gingival flap.** If the above techniques are not successful, careful injection of the soft tissue surrounding the extraction with lidocaine with epinephrine may control the bleeding. Careful cautery with silver nitrate can also be useful. If bleeding continues, then oral and maxillofacial surgical consultation is necessary.

POSTRESTORATIVE PAIN

Postrestorative pain can result from normal trauma from mechanical instrumentation of the tooth or direct exposure of the pulpal tissue during instrumentation. Pain associated primarily with mastication may be the result of improper occlusion of the new dental restoration or filling. After endodontic therapy, buildup of pressure in the pulpal chamber can cause severe pain. Provide NSAIDs or narcotic analgesia and refer to the patient's dentist. Temporary prolonged pain relief can also be obtained using 0.5% bupivacaine with epinephrine and the appropriate dental anesthetic block as discussed in the dental local anesthesia technique section of this chapter. Follow up with the dentist the next day.

ORTHODONTIC APPLIANCES

The most common emergency is a broken or bent wire that is irritating or lacerating the cheek or lip. This wire needs to be bent back away from soft tissue. This can easily be accomplished with dental instruments, or something soft such as a pencil eraser can be used to gently bend the wire. Cutting the wire is generally not indicated because it makes the end sharper. The broken portion of the wire can be removed in its entirety by removing the rubber ligatures from each orthodontic bracket, but this generally is not necessary. The patient should follow up as soon as possible with the orthodontist.

PERIODONTAL PATHOLOGY

Periodontal disease is a continuum of disease that begins with gingival inflammation and bleeding, or gingivitis, and can progress to destruction of the periodontal attachment apparatus, deepening of the normal gingival sulcus, periodontal pocket formation, bone loss, tooth mobility, and ultimately loss of teeth.[1] Besides oral hygiene, many factors including hormonal variations, medications, and systemic disease can also influence periodontal health.

Periodontal disease usually progresses painlessly but may present as swollen gingival tissue or gingival bleeding. Treatment is directed at slowing or arresting the progression of disease primarily by the removal of plaque and its by-products.[1] Antibiotics may play a role in treatment. Referral to a dentist for definitive treatment is indicated because the treatment involves extensive dental cleaning, instruction and improvement in oral hygiene, and in some cases, periodontal surgery.

GINGIVAL AND PERIODONTAL ABSCESS

A *gingival abscess* is an acutely painful swelling confined to the margin of the gingiva or interdental papilla. It usually rapidly enlarges over 24 to 48 hours, and purulent exudate can frequently be expressed from the orifice. The most common etiology is the entrapment of foreign matter such as a popcorn kernel, piece of meat, toothbrush bristle, or piece of food in the gingiva. Treatment includes identifying and removing the embedded foreign body and irrigating with normal saline. Continued home irrigation is beneficial, and symptoms resolve quickly.[1,3]

When plaque and debris are entrapped in the periodontal pocket, a *periodontal abscess* may form, resulting in severe pain. Small periodontal abscesses respond to local therapy with warm saline rinses and systemic antibiotics (Table 245-2). Larger periodontal abscesses require incision and drainage. Chlorhexidine 0.12% mouth rinses twice daily are useful in the short term.[1,3,4] Provide analgesia with NSAIDs, which are preferred over narcotics.[6]

ACUTE NECROTIZING ULCERATIVE GINGIVITIS

Acute necrotizing ulcerative gingivitis is an aggressively destructive process (**Figure 245-6**). Also known as *Vincent's disease* or *trench mouth*, it is part of a spectrum of disease ranging from localized ulceration of the gingiva to fatal noma (cancrum oris), in which localized ulceration and necrosis spread to the adjacent tissues of the cheeks, lips, and underlying facial bones.[1,3,4,11,12] The diagnostic triad includes pain, ulcerated or "punched out" interdental papillae, and gingival bleeding. Secondary signs include fetid breath, pseudomembrane formation, foul metallic taste, tooth mobility, lymphadenopathy, fever, and malaise.[1,3,11,12]

The differential diagnosis for acute necrotizing ulcerative gingivitis is quite extensive, but herpes gingivostomatitis is the most difficult to differentiate. Herpes gingivostomatitis usually has smaller vesicular eruptions, less bleeding, more systemic signs, and lack of interdental papilla involvement.[1,3,11,12]

The cause is still poorly understood. Acute necrotizing ulcerative gingivitis appears to be an opportunistic infection in a host with lowered resistance. Anaerobic bacteria such as *Treponema*, *Selenomonas*, *Fusobacterium*, and *Prevotella* invade otherwise healthy tissue, resulting in an aggressively destructive disease process.[1,3,11,12] The most important predisposing factors are human immunodeficiency virus infection and a previous episode of necrotizing gingivitis. Other contributing factors include poor oral hygiene, unusual emotional stress, poor diet and malnutrition, inadequate sleep, Caucasian descent, young age (early 20s), poor socioeconomic status, recent illness, alcohol use, and tobacco use.[1,3,11,12]

Treatment consists primarily of bacterial control. Chlorhexidine 0.12% oral rinses twice a day and professional debridement and scaling are the mainstay of treatment. Adjunctive antibiotic therapy with metronidazole (Table 245-2) is reserved for the immunocompromised or those with signs of systemic infection. Reduction in pain can be expected within 24 hours of institution of this regimen. Identification and resolution of the predisposing factors and supportive therapy with a soft diet rich in protein, vitamins, and fluids are important in establishing and maintaining a disease-free state.[1,3,11,12,]



FIGURE 245-6. Acute necrotizing ulcerative gingivitis. [Image used with permission of Philip J. Hanes.]

PERI-IMPLANTITIS

Osseointegrated dental implants have become common over the past 30 years, allowing for a dental implant to replace a tooth. Pathologic changes around an implant are all given the general term of *peri-implant disease*. Patients who present with *peri-implantitis,* a general term describing postprocedure pathologic changes, manifest similar symptoms to a periodontal abscess and require similar treatment. Gentle removal of the plaque and debris from around the implant and irrigation with normal saline or 0.12% chlorhexidine solution should be done. Give analgesia as needed and refer to a dentist for definitive care.[3,4,13]

SPECIAL CONSIDERATIONS: NEUROGENIC AND NEUROPHYSIOLOGIC SYNDROMES

See Chapter 172, "Acute Peripheral Neurologic Disorders," for management of Bell's palsy.

CRANIOFACIAL NEURALGIAS

Trigeminal neuralgia is the most common of the craniofacial neuralgias. Other significantly less common neuralgias of the craniofacial region include *glossopharyngeal neuralgia*, *vagal neuralgia*, and *superior laryngeal neuralgia* involving the respective nerve distributions. Post–herpes zoster–related neuralgia is also a cause of acute facial pain and may become chronic in nature. See Chapter 165, "Headache," for further discussion.

TEMPOROMANDIBULAR DISORDER

Temporomandibular disorder is a common cause of facial pain and headache representing a group of signs and symptoms that involve the muscles of mastication or the temporomandibular joint. See Chapter 243, "Face and Jaw Emergencies," for management.

CAVERNOUS SINUS THROMBOSIS

Cavernous sinus thrombosis may present in association with an odontogenic infection with the additional symptoms of headache with or without vomiting, or the patient may rapidly deteriorate with meningeal signs, sepsis, and coma. Contrasted CT imaging may facilitate early recognition. See Chapter 174, "Central Nervous System and Spinal Infections," for management.

SOFT TISSUE LESIONS OF THE ORAL CAVITY

RECURRENT APHTHOUS STOMATITIS

Recurrent aphthous stomatitis, or ulceration, is one of the most common oral lesions (**Figure 245-7**). Recurrent aphthous stomatitis by definition is idiopathic; therefore, other underlying causes such as trauma, vesiculobullous disease, medications, nutritional deficiencies, hematologic disorders, and fever syndromes must be considered. The etiology is multifactorial, involving physiologic interactions between the immune system and genetic and environmental factors. Aphthous ulceration involves the nonkeratinized epithelium, especially the labial and buccal mucosa, and begins as an erythematous macule that ulcerates and forms a central fibropurulent eschar. Aphthous stomatitis occurs in three forms. *Minor aphthae* usually measure <10 mm in diameter, are painful, and frequently are multiple. They usually resolve spontaneously in 10 to 14 days. *Major aphthae* have larger (>10 mm), deeper ulcers that take significantly longer to heal. The third form, called *herpetiform aphthae*, has up to 100 ulcers, each 1 to 2 mm in diameter. They tend to coalesce, creating much larger ulcers that require 10 to 14 days to heal. Treatment is primarily symptomatic. Several medications are effective in decreasing pain and increasing the rate of healing. Topical agents such as chlorhexidine 0.2% mouth rinse, anesthetic agents, and steroids applied topically or as a mouth rinse should be the first-line therapy. Commercially available bioadhesive pastes such as Orobase® (Colgate Oral Pharmaceuticals, Canton, MA), which contains both corticosteroids and anesthetic agents, are effective. In more resistant cases, systemic steroids are indicated.[14]

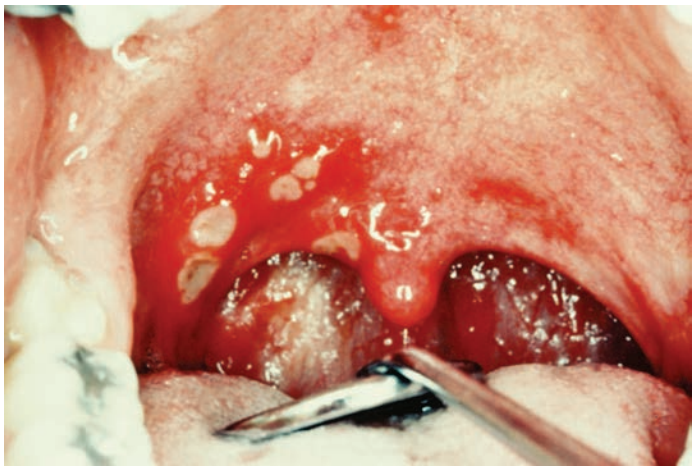


FIGURE 245-7. Aphthous stomatitis. [Image used with permission of Baldev Singh.]

HERPES ZOSTER AND OTHER INFECTIONS

Herpes zoster frequently occurs along the distribution of the trigeminal nerve (see Chapter 154, "Serious Viral Infections," for management). Isolated intraoral lesions can occur but are not common. Involvement of the ophthalmic branch of the trigeminal nerve requires urgent ophthalmologic consultation (see Chapter 241, "Eye Emergencies").[1,15]

Other common infections such herpes simplex types 1 and 2, herpangina, hand-foot-and-mouth disease, and varicella-zoster virus cause painful ulcerative lesions of the oral cavity and perioral region. These conditions are adequately discussed in Chapter 124, "Mouth and Throat Disorders in Infants and Children." Many sexually transmitted infections can affect the oral cavity. In general, the appearance of oral lesions is similar in appearance to that of their genital counterpart. Treatment of sexually transmitted diseases of the oral cavity is the same as for genital involvement.[1,15] See Chapter 153, "Sexually Transmitted Infections," for detailed discussion.

TRAUMATIC ULCERS

Traumatic ulcers are a result of direct trauma to epithelial tissue. Common sources of trauma include rough or jagged edges on teeth or restorations, ill-fitting dentures, oral hygiene mishaps, and burns to the hard or soft palate secondary to hot foods. Removal of persistent sources of trauma is essential; otherwise, treatment is palliative.

MEDICATION-RELATED SOFT TISSUE ABNORMALITIES

Gingival hyperplasia is associated with many commonly used medications (**Figure 245-8**). Three classes of drugs have been identified as causal: anticonvulsants, calcium channel blockers, and immunosuppressants. Phenytoin, nifedipine, and cyclosporine exhibit the strongest association. Concomitant use of two such medications results in accelerated gingival proliferation. Enlargement begins in the interdental papillae. Regardless of medication, the clinical and histologic characteristics of gingival hyperplasia appear to be identical. The clinical appearance of the gingival tissue depends on oral hygiene and secondary inflammation. In the absence of inflammation, gingival proliferation results in dense tissue, normal in coloration, with a smooth, stippled, or granular texture. Inflammation



FIGURE 245-8. Gingival hyperplasia (overgrowth) secondary to phenytoin (Dilantin®). [Used with permission of Philip J. Hanes.]

causes edematous changes and an erythematous coloration. Inflamed tissue bleeds readily. Histologically, an increase in collagen fibers, fibroblasts, and glycosaminoglycans is seen. Epithelial acanthosis also occurs. Although the cause of drug-related gingival hyperplasia is unclear, poor oral hygiene clearly increases its likelihood and severity. Treatment includes fastidious oral hygiene to slow the hyperplasia and gingivectomy in advanced cases.[16]

Many other medications and diseases are known to cause abnormalities of the oral mucosa or dental structures. Allergic mucositis, erythema multiforme, and fixed drug-type reactions are examples. Xerostomia and associated mucosal alterations are a side effect of many medications such as anticholinergics, antidepressants, and antihistamines. Stomatitis and mucosal ulcerations from chemotherapeutic agents are also common.[3,16]

LESIONS OF THE TONGUE

Many systemic conditions and local stimuli affect the appearance of the tongue. Various vitamin deficiencies and iron deficiency anemia cause atrophy of the filiform papillae, resulting in a smooth erythematous appearance. Occurrence of ectopic thyroid tissue on the midline posterior portion of the tongue is called a *lingual thyroid* and is a common finding. Some common conditions affecting the tongue are discussed in the following sections.

BENIGN MIGRATORY GLOSSITIS

Geographic tongue, or benign migratory glossitis, is a common benign finding on oral examination, occurring in 1% to 3% of the population. Typically, multiple areas of erythema on the tongue, caused by atrophy of the filiform papillae, are surrounded by well-demarcated zones of hyperkeratotic plaques. The lesions concentrate on the tip and dorsolateral aspect of the tongue and heal in several days, only to quickly reappear in other areas. These lesions usually are asymptomatic; however, a burning sensation or sensitivity to hot or spicy foods has been described. The cause is unknown, but an association with psoriasis, allergies, stress, diabetes, and anemia is reported. Generally, treatment is not indicated because this entity is benign. Reassurance of patients is usually sufficient. In patients in whom discomfort is a major factor, oral topical steroids such as fluocinonide gel applied several times daily may provide relief.[15]

STRAWBERRY TONGUE

Strawberry tongue is associated with erythrogenic, toxin-producing *Streptococcus pyogenes*. Clinically, the tongue has prominent red spots on a white-coated background. Microscopically, the fungiform papillae are hyperemic with a smooth, glossy surface. Treatment is with antibiotics directed at group A streptococci.

LEUKOPLAKIA AND ERYTHROPLAKIA

Leukoplakia is a white patch or plaque that cannot be scraped off and cannot be classified as any other disease. Leukoplakia is the most common oral precancer. Up to 7% of lesions exhibit dysplastic changes, with an overall risk of malignant transformation of 2% to 3% per year. The cause is unknown, but tobacco, alcohol, ultraviolet radiation, candidiasis, human papillomavirus, tertiary syphilis, and trauma have all been implicated. Lesions can occur on any intraoral mucosal site but commonly affect the buccal mucosa, tongue, and floor of the mouth. Biopsy is mandatory for all persistent leukoplakic lesions. Leukoplakic lesions of the floor of the mouth, tongue, and vermilion border are most likely associated with malignancy. Lesions demonstrating dysplastic changes warrant removal at follow-up by an oral surgeon or otolarygologist.[15,17]

Erythroplakia is defined as a red patch that similarly cannot be clinically or pathologically characterized as any other disease. Although erythroplakia is far less common than leukoplakia, it has a greater potential for dysplastic changes; refer for removal as with leukoplakia.

ORAL CANCER

Oral cancer accounts for 2% to 4% of the cancers in the United States. More than 90% of all oral malignancies are squamous cell carcinoma (**Figure 245-9**). Lymphomas, Kaposi's sarcoma, and melanoma compose most of the remainder. Extrinsic risk factors include tobacco use, especially chewing tobacco or snuff; excessive alcohol consumption; and sunlight exposure. Intrinsic factors include immunosuppression, lichen planus, chronic oral candidiasis, human papilloma virus infection, human immunodeficiency virus infection, chronic inflammation, and nutritional deficiencies and general malnutrition.[15,17]

Oral squamous cell carcinoma has four common morphologic presentations. Lesions can be exophytic, with an irregular surface; ulcerative, with irregular depressions and rolled borders; malignant leukoplakic; or erythroplakic. The most common site involved in oral cancer is the tongue, particularly the posterolateral and ventral surface, accounting for 50% of the oral cancers in the United States.[15,17] Cancer of the floor of the mouth accounts for nearly 35%. Cancer of the lips is common and usually secondary to sunlight exposure. Oral cancer is generally painless, and patients are often unaware of the presence of a mass until it is advanced. Oral cancer lesions are usually firm, may bleed from ulceration, and have a history of poor healing. There may be associated firm lymphadenopathy. Early diagnosis is the key to successful treatment of oral squamous cell carcinoma. All ulcers, erythroplakic lesions, and leukoplakic lesions of the oral cavity that do not respond to palliative treatment in 10 to 14 days warrant biopsy by otolaryngology. Treatment depends on site of involvement and stage of disease.[15]



FIGURE 245-9. Oral squamous cell carcinoma of the hard palate. [Image used with permission of H. Anthony Neal.]

DENTOALVEOLAR TRAUMA

Management of dentoalveolar trauma depends on the extent of tooth and alveolar involvement, the degree of development of the apex of the tooth, and the age of the patient. In injuries in younger patients, especially those who are <12 years of age, the pulp of anterior teeth is quite large, and dental fractures involving the pulp are common. Fortunately, in this age group, the apex of the root also is usually incompletely formed, allowing for a greater pulpal regenerative capability. As one ages, more dentin is formed. Thus, in older patients, the pulp chamber may be very small and pulpal exposure highly unlikely. Involvement of the root of the tooth compromises the attachment apparatus and makes it difficult to restore the tooth to function.

DENTAL FRACTURES

The International Association of Dental Traumatology system divides dental trauma into eight categories: enamel infraction, enamel fracture, enamel-dentin fracture, enamel-dentin-pulp fracture, crown-root fracture without pulp exposure, crown-root fracture with pulp exposure, root fracture, and alveolar bone fracture (**Figure 245-10**). The International Association of Dental Traumatology has developed guidelines to aid dentists and other healthcare professionals in the management of each these categories.[18,19]

The goal of the emergency treatment of a fractured tooth is maintaining pulpal vitality and completion of the formation of the root and apex of the tooth. The proximity of the fracture to the pulp and the length of time before treatment, as well as other associated injuries, are most important in determining outcome. Treatment is aimed at sealing the dentinal tubules and creating a barrier between the dental pulp and the oral environment. Because pulpal necrosis is a process, it can occur at any time after trauma, and serial follow-up with a dentist is recommended.[18,19]

A fracture of the crown of the tooth can involve any part of the enamel, dentin, and pulp of the tooth. *Infraction* is the least serious type of dental injury and essentially is a crack in the enamel of the tooth without loss of structure. This can be obvious or quite subtle. No emergency treatment is needed.

ENAMEL FRACTURES

Enamel fractures (Ellis class I fractures) do not extend into the dentin of the tooth (**Figure 245-11**). Generally, no emergency treatment is indicated, except to smooth sharp corners that may irritate the tongue or mucosa. If the enamel fragment is recovered and kept moist, the patient's dentist can bond it back in place. If the fragment was not recovered, soft tissue radiographs of any oral lacerations are necessary to rule out foreign bodies. Referral to a general dentist for aesthetic repair depends on the degree of cosmetic concern of the patient.[18,19]

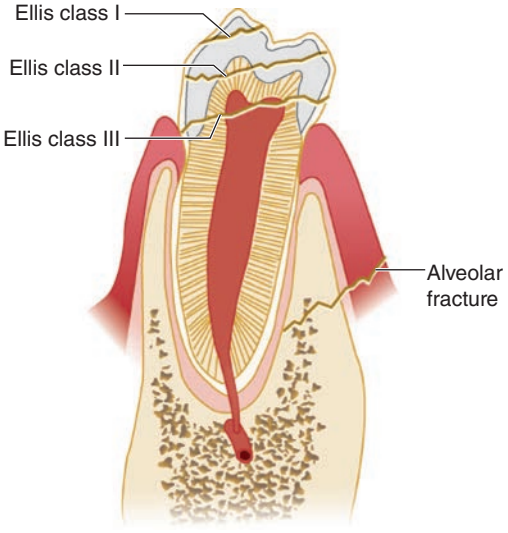


FIGURE 245-10. The International Association of Dental Traumatology classification of dental fractures.



A



B

FIGURE 245-11. International Association of Dental Traumatology classification for fractures of teeth (clinical). **A.** Enamel fracture (Ellis class I). **B.** Enamel-dentin fracture (Ellis class II) of the central incisor on the left in the photograph (notice the pink blush of the pulp through the thin layer of dentin), and an enamel-dentin-pulp fracture of the central incisor on the right in the photograph. [Image used with permission of Felicity K. Hardwick.]

ENAMEL-DENTIN FRACTURES

Enamel-dentin fractures (Ellis class II fractures) involve the dentin of the tooth and require intervention (Figure 245-11). Generally, patients experience sensitivity to hot or cold stimuli as well as air passing over the exposed surface during breathing. The enamel-dentin fracture can be identified both by the patient's symptoms and visualization of exposed dentin, which is a creamy yellow color compared with the whiter enamel. Because dentin is microtubular in structure, communication with the oral environment or desiccation from mouth breathing initiates an inflammatory response in the dental pulp. The thickness of remaining dentin determines the rate of pulpal contamination. Greater than 2 mm of remaining dentin is felt to offer some protection to the pulpal tissue. A delay in treatment of >24 to 48 hours increases the likelihood of pulpal necrosis. The ED goal is the identification of a fracture. If definitive treatment cannot be ensured in 1 to 2 days, then cover the exposed dentin to decrease likelihood of pulpal injury. This is best achieved using glass ionomer dental cement that is easily mixed according to the

manufacturer's instructions and carefully applied to the dried exposed dentin (DenTemp®, Majestic Drug Co., South Fallsburg, NY; and others). If the dentin layer is <0.5 mm and the pulp can be seen as a pink area without bleeding, then first place a thin layer of calcium hydroxide base (Dycal®, Dentsply International, York, PA) followed by glass ionomer, as described earlier, to further protect the dental pulp. Referral to a dentist for definitive treatment is important.[18,19]

ENAMEL-DENTIN-PULP FRACTURES

In *enamel-dentin-pulp* fractures (Ellis class III fractures), exposure of the pulp has occurred (Figure 245-10). On wiping the fractured surface dry with sterile gauze, blood originating from the pulp of the tooth is easily identified. After carefully controlling pulpal bleeding with sterile gauze or a cotton pellet, cover the exposed pulp with a calcium hydroxide base (Dycal®, Dentsply International, York, PA), and then cover this and the remaining exposed dentin with glass ionomer cement as in enamel-dentin fractures until urgent dental evaluation can occur. If the pulpal exposure is extremely small, placing a calcium hydroxide base and glass ionomer is adequate until dental evaluation. For all but the smallest pulpal exposures, definitive treatment is some kind of endodontic or root canal therapy. Oral analgesics should be prescribed and topical analgesics avoided.[18,19]

Crown-root fractures and *root fractures* are an uncommon consequence of dental trauma. The coronal segment of the tooth may be displaced or simply mobile. Tenderness to percussion is usual. With any dental trauma, careful attention must be paid to identifying fractures of the root, as they can be clinically obscure, and dental radiographs from several angles may be necessary to identify these fractures. This, however, is beyond the scope of most EDs. Crown-root fractures may or may not involve the pulp. Emergency treatment consists of stabilizing the coronal segment until definitive treatment can be arranged. In isolated root fractures, the pulp is always involved. Healing of stabilized root fractures has been reported; thus, current recommendations are to reposition the coronal segment to its original position, confirm that position by radiograph, if available, and then stabilize with a flexible splint as described below for luxation injuries. Dental follow-up within 24 to 48 hours is important, because splinting for a minimum of 4 weeks is required. In the ED, where oral surgical or dental consultation may not be readily available, extraction of an extremely mobile coronal segment of the tooth may be required to prevent possible aspiration.[18-20]

LUXATION INJURIES

The same forces that cause dental fractures may result in loosening of a tooth from the attachment apparatus. Careful evaluation of the teeth for tenderness, malpositioning, or mobility must be performed. There are six types of luxations: concussion, subluxation, extrusive luxation, lateral luxation, intrusive luxation, and avulsion.[18,19]

Concussion is injury to the supporting structures of a tooth with clinical tenderness to percussion but no mobility. *Subluxation* is injury resulting in mobility without clinical or radiographic evidence of dislodgement of the tooth. *Extrusive luxation* is partial or total disruption of the periodontal ligament resulting in a partial dislodgement of a tooth from the alveolar bone. *Lateral luxation* is displacement of a tooth labially (toward the lip) or lingually (toward the tongue) with concomitant fracture of the alveolar bone. *Intrusive luxation* is displacement of a tooth into its socket with associated periodontal ligament damage and alveolar bone contusion and fracture. Treatment of luxations depends on the tooth involved, the severity of injury, and the presence of associated root fracture and/or significant associated alveolar fracture.[18,19]

CONCUSSIONS

A concussive injury to a tooth is minor. The degree of tenderness to percussion determines the treatment. Stabilizing the tooth by splinting it to adjacent teeth is not indicated. Management of pain with NSAIDs, soft diet, and referral to a dentist to confirm the diagnosis and exclude more severe injury constitute the most appropriate course of action for the emergency physician.[18,19]

LUXATIONS

Subluxation represents a more significant injury than concussion and is associated with a higher incidence of subsequent pulpal necrosis. Clinically, tooth mobility and some bleeding along the gingiva may be noted. A subluxed tooth generally does not require splinting.[18,19]

An *extrusive luxation* requires repositioning the tooth to its original position and splinting to stabilize the tooth during healing. Ideally, dental radiographs should be obtained prior to repositioning the tooth to ensure that there is not a fracture of the root of the tooth, but in most EDs, this may not be possible, and repositioning and stabilizing should be attempted regardless. Repositioning the tooth may require local anesthesia. Firm, gentle pressure usually will reposition the tooth. If a clot has formed apical to the tooth, then more aggressive manipulation may be required. Splints made with flexible wire, nylon line, or bondable fiber mesh ribbon provide ideal stabilization.[18,19,21] If unavailable in the ED, a temporary splint with a noneugenol zinc oxide periodontal dressing (Coe-Pak™, GC America Inc., Alsip, IL; or ZONE Periopak®, DUX Dental, Oxnard, CA) (**Figure 245-12**) is acceptable. Avoid excess material placement, especially on the occlusal surface, because interference in occlusion will place stress on the tooth during mastication. The patient should see a dentist or oral and maxillofacial surgeon within 24 hours.

A *lateral luxation* represents a more extensive injury and is associated with fracture of the surrounding alveolar bone. Repositioning of the tooth is generally more difficult. It usually can be accomplished by manipulating the displaced tooth with the thumb and forefinger. Once the apex has been dislodged from its locked-in position labially, apically directed axial pressure will reposition the tooth. Intra-arch stabilization is necessary for a minimum of 4 weeks. Temporary splinting with a periodontal dressing is acceptable if a minimal associated alveolar fracture occurred. Otherwise, splinting by an oral and maxillofacial surgeon or general dentist in the ED is mandatory.[18,19,21]

Intrusive luxations are the most serious because significant damage to the alveolar socket and periodontal ligament occurs. Root

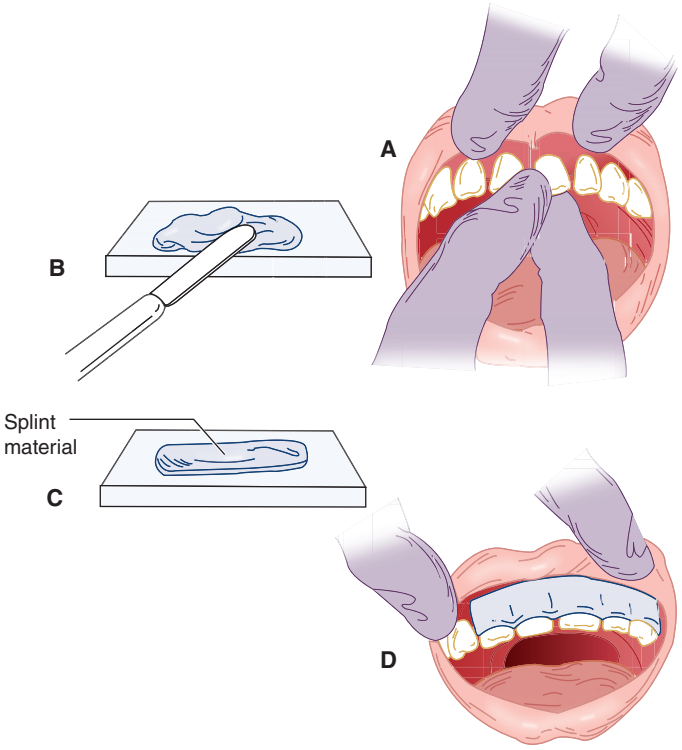


FIGURE 245-12. Temporary stabilization of a replanted or repositioned tooth. **A.** Tooth is repositioned back into its original position in the socket. **B.** Splint material is mixed thoroughly. **C.** Splint material is shaped and made ready for application. **D.** Packing is molded over repositioned tooth and two adjacent teeth to each side.

resorption is common as a result of damage to the periodontal ligament. Recommended treatment is allowing the tooth to erupt on its own or to orthodontically extrude the tooth if no eruption is noted by 3 weeks.[18,19,21]

All patients who sustain luxation injuries should be instructed to maintain a soft diet for at least 2 weeks. Meticulous oral hygiene is essential. Twice-daily rinsing with chlorhexidine 0.12% mouth rinse is helpful. Referral to a dentist for close follow-up is indicated.

AVULSIONS

Tooth Replantation and Care at the Scene **Total displacement of a tooth from its socket, or *avulsion*, is a true dental emergency.**[22,23] Replantation at the scene is the treatment of choice because the long-term prognosis for the replanted tooth is highly time dependent. Ideally, the patient or a healthcare provider at the scene should perform this procedure. Handling only the crown portion of the tooth, gently rinse the tooth for a maximum of 10 seconds with sterile normal saline or tap water to remove debris. Then replace it immediately into the socket. Anterior teeth are most commonly affected. **Figure 245-13** illustrates the morphology of the maxillary central incisor to assist replantation in the proper orientation. Early improper replantation holds a higher success rate for tooth salvage than delayed replantation resulting from waiting for arrival at the ED or for an oral and maxillofacial surgeon.[22,23]

If immediate replantation is not possible, then transport the tooth with the patient to the ED. Acceptable transport media include isotonic solutions such as Hank's balanced salt solution, organ transport media, sterile saline, milk, and saliva. Commercial preparations of Hank's balanced salt solution such as Save-A-Tooth® (Phoenix-Lazerus, Inc., Pottstown, PA) and EMT Tooth Saver™ (Smart Practice, Phoenix, AZ) are available and come with a useful transport container as part of the system.[24]

Survival of the periodontal ligament fibers that remain attached to the root of an avulsed tooth is key to successful replantation. Milk is an acceptable storage medium because of its osmolarity and essential concentration of calcium and magnesium ions, and compares favorably with Hank's balanced salt solution, which maintains periodontal ligament cell viability for up to 4 to 6 hours.[24]

Tooth Replantation in the ED In the ED, before replantation, rinse the tooth root clean of dirt and debris with sterile saline or, preferably, Hank's balanced salt solution. Do not scrub the root of the tooth, and do not disrupt existing periodontal fibers. Handle only the crown of the tooth. If an avulsed tooth with an open apex has been dry for <20 minutes, then the prognosis for reestablishing a vital pulp is good. If the tooth has been dry from 20 to 60 minutes regardless of apices, soak the tooth in a physiologic solution while preparing to replant the tooth. Physiologic solution decreases the chance of ankylosis (fixation of the tooth to the underlying bone). For an avulsed tooth that has been dry for >60 minutes, the periodontal cells are dead, and the goal is to maintain alveolar bone contour and aesthetics; however, ankylosis, root resorption, and eventual tooth loss are the expected outcome. **Table 245-3** provides specific recommendations.[22,23,25] Dentists manage avulsed immature permanent teeth (patients age 5 to 15 years) differently than avulsed mature permanent teeth, but care of avulsed teeth in the ED prioritizes rapid replacement to preserve function. If the avulsed tooth was not recovered, obtain radiographs to ensure that the tooth was not aspirated.[22-24]

Prepare the socket by carefully removing the clot and gently irrigating with sterile normal saline. Avoid socket manipulation if possible. However, any fracture of the socket wall should be carefully repositioned with an appropriate instrument. Local anesthesia is usually required. Replantation is accomplished with firm pressure. Having the patient bite on gauze until more permanent stabilization can be arranged is acceptable. Stabilization of the tooth in the ED with a flexible splint or temporary splinting such as a periodontal dressing (Figure 245-12) is necessary until follow-up with an oral and maxillofacial surgeon.[21-23]

Treatment with systemic antibiotics is controversial but still recommended because experimental studies show benefit. Doxycycline is the preferred antibiotic choice. For children <12 years old, amoxicillin is acceptable (Table 245-2). Tetanus prophylaxis is necessary if the tooth has been contaminated by soil and the tetanus status is uncertain. Post-treatment instructions for most dental trauma are essentially the same. Patient should be instructed to maintain a soft diet for 2 weeks, brush carefully with a soft toothbrush after each meal, and use chlorhexidine

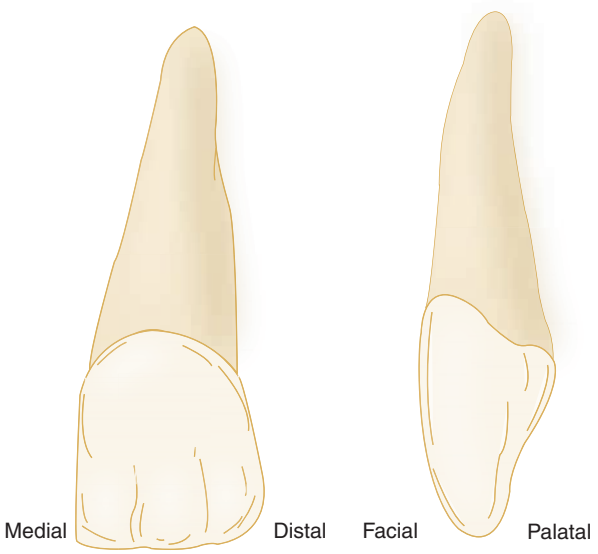


FIGURE 245-13. Illustration of a maxillary left central incisor in two views. Note that the part of the tooth facing medially comes to more of a right angle at the incisal edge (biting edge) than occurs distally. The facial portion of the tooth is more convex.

TABLE 245-3 Specific Recommendations for Replantation of Avulsed Teeth

Clinical Scenario	Treatment
Moist tooth stored in acceptable media, and/or <60 min extra oral dry time	1. Gently irrigate the tooth root clean with sterile saline. 2. Administer local anesthesia. 3. Remove coagulum from the socket with a stream of saline. 4. Examine the socket. If there is a fracture of the socket wall, reposition it with an appropriate instrument. 5. Firmly replant tooth and verify the tooth position clinically and radiographically, if possible. 6. Flexible splint for up to 2 weeks.
Extra oral dry time >60 min or other reason suggesting nonviable cells	1. Remove from tooth attached necrotic soft tissue carefully with gauze. 2. Administer local anesthesia. 3. Remove coagulum from the socket with a stream of saline. 4. Examine the socket. If there is a fracture of the socket wall, reposition it with an appropriate instrument. 5. Firmly replant tooth and verify the tooth's position clinically and radiographically, if possible. 6. Flexible splint for up to 4 weeks.

0.12% mouth rinse twice a day.[22,23,25] Follow-up should be facilitated with a dentist in 1 week.

SPECIAL CONSIDERATIONS WITH LUXATION INJURIES

SEQUELAE OF LUXATION INJURIES

Posttraumatic sequelae are variable. Pulp canal obliteration, pulpal necrosis, internal and external resorption of the root, and ankylosis may occur. The severity of luxation or avulsion is the most important determining factor in sequela occurrence. Transient apical breakdown occurs with all types of luxations, but is especially common with extrusive and lateral luxations and avulsions. Extrusive luxated teeth commonly undergo pulpal necrosis within 1.5 years of the traumatic event. Close dental follow-up is essential for early identification of these sequelae.

ALVEOLAR RIDGE FRACTURES

Significant force must occur to dislodge or fracture teeth; consequently, associated **alveolar ridge fracture** is common. Care to ensure the integrity of the maxilla and mandible is also important. Stabilization of repositioned alveolar segments and associated teeth is essential for optimal results. This is best accomplished with flexible fixation placed by a general dentist or oral surgeon. Stabilization is maintained for up to 4 weeks depending on the severity of the involvement of alveolar bone. With significant alveolar ridge fracture, segments may require intermaxillary stabilization for up to 6 weeks in order to ensure adequate healing.[22,23]

LUXATION INJURIES OF PRIMARY TEETH

Avulsion or luxation injuries of primary teeth are treated differently from those of permanent teeth. In patients age 6 to 12 years old, dentition is mixed, so it is very important to distinguish primary from permanent teeth. Avulsed primary teeth are never replanted. Most luxation injuries in children require no treatment and heal spontaneously. However, severe luxations of primary teeth generally require extraction of the tooth. Repositioning or replanting primary teeth risks injuring the underlying permanent teeth and thus is avoided. Intruded primary teeth are generally left alone to reerupt into normal position. Because of the risk of damage to the permanent dentition, unless there is occlusal interference or the risk of aspiration, a dentist should manage most complicated luxation injuries of primary teeth. Referral to a dentist for follow-up is essential to ensure optimal long-term outcome.[26,27]

SOFT TISSUE TRAUMA

ORAL CAVITY MUCOSAL LACERATIONS

Traumatic injuries to the soft tissue of the oral cavity are common and can involve any of the soft tissues of the mouth. Appropriate treatment remains an area of controversy. Generally, because of the vascularity of the oral tissue, lacerations of the mouth heal quickly. See the "Intraoral Mucosal Lacerations" section of Chapter 42, "Face and Scalp Lacerations," for management recommendations. Lacerations involving the cheek or buccal mucosa must be examined carefully for involvement of Stensen's duct, which drains the parotid salivary gland (the duct opens into the mouth opposite the upper second molar). If Stensen's duct is compromised, repair by an oral and maxillofacial surgeon or otolaryngologist is indicated. Likewise, lacerations to the floor of the mouth require careful evaluation for involvement of Wharton's duct of the submandibular salivary glands.

LIP LACERATIONS

Lip lacerations are a potential cosmetic problem, so careful closure is essential (see Chapter 42, "Face and Scalp Lacerations," for management recommendations).[28]

FRENULUM LACERATIONS

Laceration of the maxillary labial frenulum, unless unusually large, does not require repair. Because such lacerations can be very painful, scheduled NSAIDs are recommended.[6] Because of the vascularity of adjacent tissue, lacerations to the lingual frenulum of the tongue may need repair. An absorbable suture such as 4-0 chromic gut or Vicryl® is appropriate.

TONGUE LACERATIONS

Lacerations of the tongue require special consideration because bleeding and delayed swelling can compromise the airway. **Simple linear lacerations <1 cm involving the central portion of dorsal surface of the tongue and that do not gape open heal well without repair.** Except for the most extensive tongue lacerations, suturing does not necessarily improve outcome or reduce morbidity. All lacerations that bisect the tongue require repair. Partial amputations can be successfully replanted with the appropriate microsurgical techniques.[28]

Local anesthesia can be obtained by local infiltration or topically by placing 4% lidocaine-soaked gauze for 5 minutes on the laceration. Bilateral lingual nerve blocks can be used for lacerations of the anterior two thirds of the tongue that cross the midline. Repair of the tongue, especially in children, presents a special challenge, and many adjuncts such as a dental bite block or a Molt mouth prop can be helpful in keeping the mouth open. A piece of 4 × 4 gauze can be used to grasp the tongue.[28]

When laceration repair is warranted, absorbable sutures such as 4-0 chromic gut or Vicryl should be used. Sutures should be placed so as to include the muscular layer and the superficial mucosal layers of the tongue. Wound edges should be approximated and closed very loosely to allow for swelling of the tongue, which can be significant. Placing a closed hemostat between the suture and the tongue while tying can help prevent overtightening of the suture. The constant motion of the tongue quickly unties sutures in the mouth, so sutures should be tied with at least four square knots. If feasible, the sutures can also be placed so that the knots are buried into the wound. All patients should be instructed to rinse several times daily with a saline or chlorhexidine 0.12% mouth rinse.[28]

DENTAL LOCAL ANESTHESIA TECHNIQUES

Competence in dental local anesthesia is a useful skill for the emergency provider. The maxillary teeth can be anesthetized using local infiltrative or supraperiosteal techniques, which are simple to do. (See Video: Periapical Dental Block).

ANATOMY

The trigeminal nerve is the largest cranial nerve, and although it has important motor functions, it is primarily a sensory nerve (**Figure 245-14**). It divides into three main branches: the ophthalmic nerve, maxillary nerve, and mandibular nerve. The maxillary nerve provides sensory innervation to the maxilla and associated structures including the maxillary teeth and gingiva and oral mucous membranes. The third division, or mandibular nerve, is the largest of the three branches. The mandibular nerve has three main divisions. The first is the long buccal nerve that provides sensory innervation to the mucosa of cheek and buccal gingiva of the mandibular molars. The second is the lingual nerve that runs superficial to the internal pterygoid muscle and innervates the anterior two thirds of the tongue, lingual gingiva, and floor of the mouth. Finally, the largest branch is the inferior alveolar nerve, which accompanies the inferior alveolar vein and artery in a neurovascular bundle passing between the ramus of the mandible and the sphenomandibular ligament to enter the mandibular canal. It divides at the region of the premolars, with the mental nerve exiting the mental foramen to innervate the soft tissue of the lip and chin and the incisal nerve continuing within the mandibular canal to innervate the teeth and gingiva.

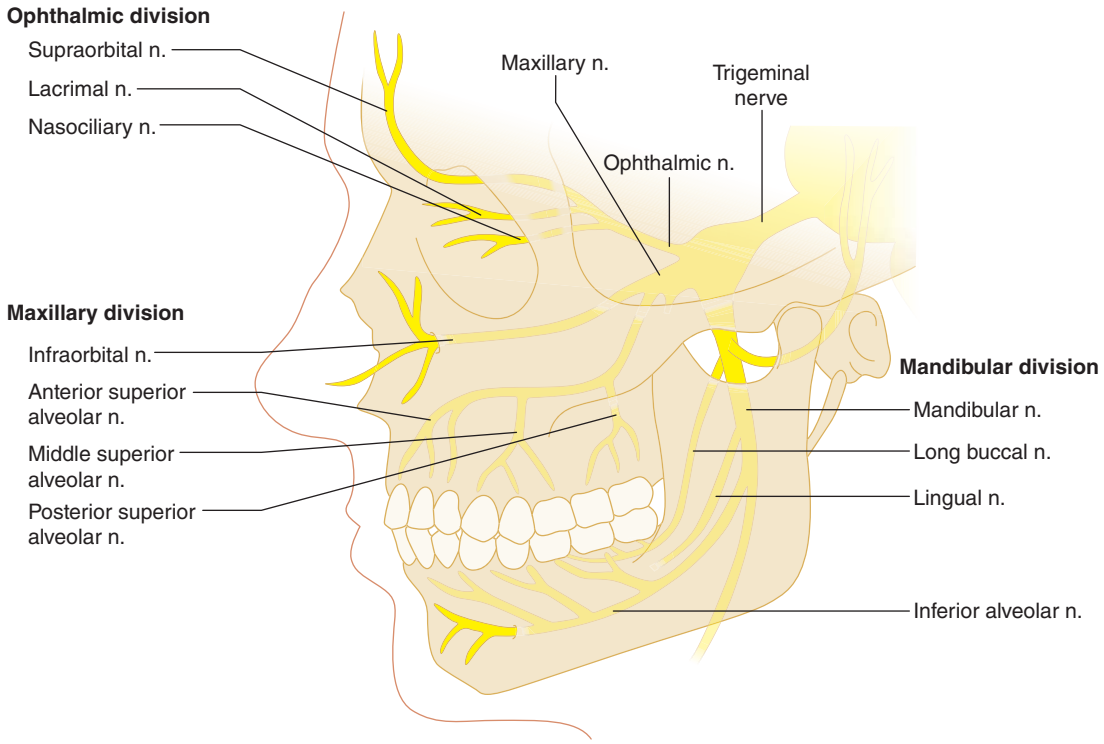


FIGURE 245-14. The trigeminal nerve and its three main divisions.

EQUIPMENT

Specialized equipment is useful when giving dental injections, especially the inferior alveolar nerve block. Equipment includes:

- A monojet aspirating dental syringe
- Dental cartridges of anesthetic solution
- Disposable 27-gauge, 32-mm needle
- Topical anesthetic, if possible

If an aspirating dental syringe is not available, any 3-mm aspirating syringe can be used. With larger syringes, the inferior alveolar nerve block is difficult because the syringe barrel interferes with the proper positioning of the needle.

Position the patient in a dental chair or stretcher in a semi-reclined position with the head firmly against the headrest. Anticipate sudden movement of the patient. An overhead light is essential because dental injections require good visibility and control at all times to ensure safety of both the patient and the physician. If available, topical anesthetic can be applied to mucosa prior to injection to lessen the discomfort. First, dry the mucosal surface with gauze; then apply the topical gel for at least 1 minute prior to proceeding.

MAXILLARY INJECTIONS

Supraperiosteal Infiltration Maxillary cortical bone is thin and porous enough to allow the diffusion of anesthetic solution to reach the apex of the root and effectively anesthetize the tooth. **Figure 245-15** illustrates the supraperiosteal infiltration technique. The upper lip or cheek, depending on which tooth you are anesthetizing, is pulled up and taut. With the bevel facing toward the bone, the needle is inserted at the height of the buccal fold adjacent to the tooth. The needle should be directed along the long axis of the tooth and inserted to the height of or slightly above the apex of the tooth. In most cases, the needle only needs to be inserted a few millimeters. Aspirate, and if negative, then slowly inject 0.5 to 1 mL of anesthetic solution. It is important to remember that the root of the canine is significantly longer than that of other teeth and that, in general, the roots of teeth are inclined in a distal direction. The goal is to deposit the anesthesia at or above the apex of the desired tooth.[29-31]

Palatal Injection Supraperiosteal infiltration of the maxillary teeth provides adequate anesthesia for pain control for a toothache, but not for procedures such as management of a dry socket or avulsed tooth. This may also require anesthesia of the palatal tissue, which can simply be accomplished by local infiltrative anesthesia. With a fine-gauge needle, puncture the palatal mucosa about halfway up the palate adjacent to the target tooth (**Figure 245-16**). Inject 0.1 mL of anesthetic solution. Blanching of the surrounding tissue is common, and this injection is usually quite uncomfortable. If a larger area of anesthesia is required, anesthesia of the anterior portion of the palate can be obtained by injecting anesthesia over the incisive foramen. The landmark is the incisive papilla. Anesthesia to the unilateral posterior portion of the palate can be obtained by injecting a small amount of anesthesia over the greater palatine foramen.[29-31]

MANDIBULAR INJECTIONS

In contrast to the maxilla where the cortex of overlying bone is relatively thin and infiltrative anesthesia is usually effective, the mandibular boney cortex is relatively thick and the inferior alveolar nerve block is usually required to gain adequate anesthesia of the mandibular molars and premolars. A mental nerve block, as described in Chapter 36, "Local and Regional Anesthesia," can provide anesthesia for the premolars, canines, and incisors, as well as soft tissue of the lip and chin, when properly administered. The bone adjacent to the canines and incisors is thinner and more amenable to infiltrative anesthesia. Also, soft tissue anesthesia of the tongue can be obtained using the basics of the inferior alveolar nerve block. Injection of the long buccal nerve may be necessary for incision and drainage of dental abscesses in the mandibular molar region, and this technique will be described. (See Video: Mental Nerve Block.)

Inferior Alveolar Nerve Block (Direct Technique) The patient should be instructed to open the mouth widely to ensure good visualization of anatomic landmarks (**Figure 245-17**). First, the physician needs to palpate the greatest depth of the anterior border of the ramus

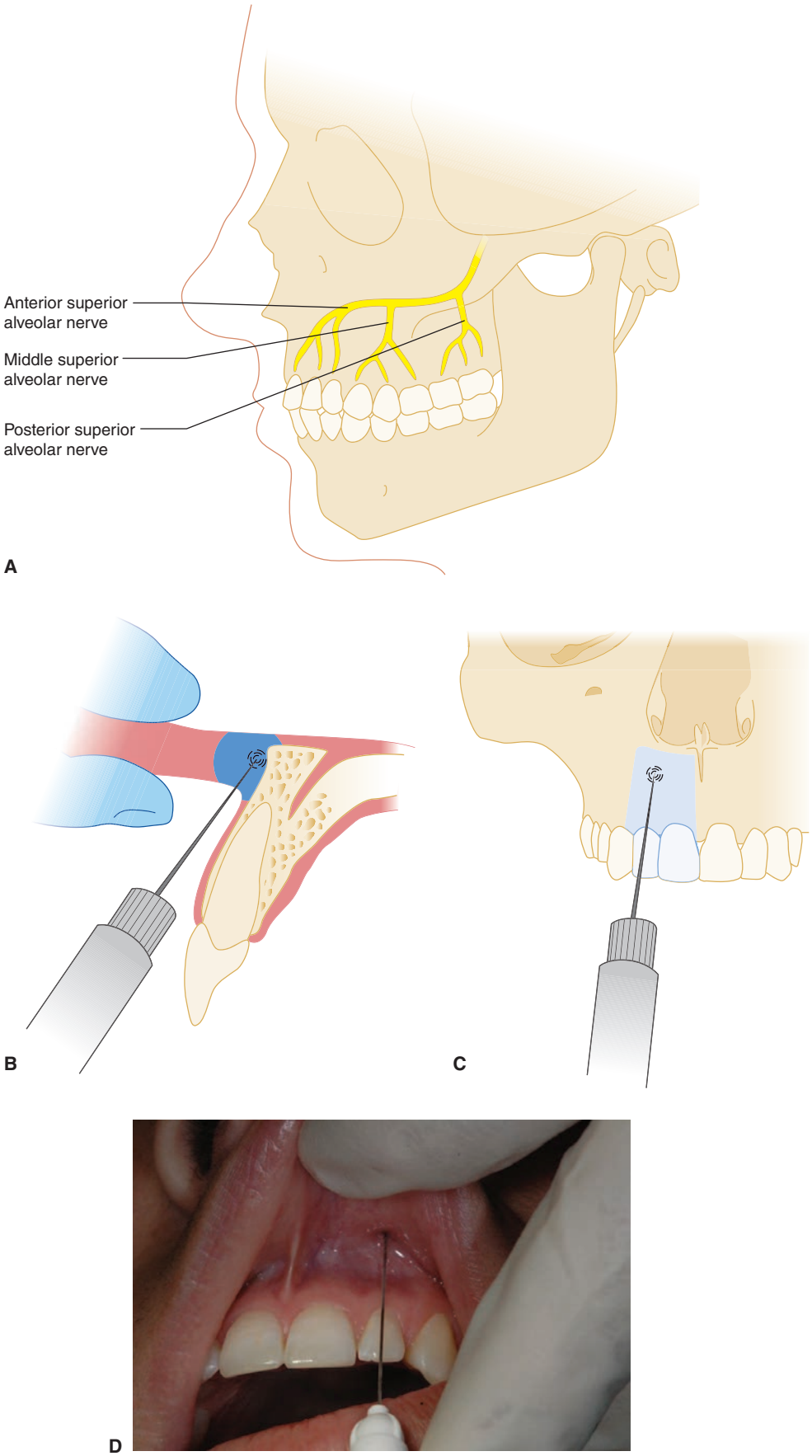


FIGURE 245-15. The supraperiosteal infiltration. **A.** The maxillary nerve and innervation of the maxillary teeth by the posterior superior alveolar nerve, the middle superior alveolar nerve, and the anterior superior alveolar nerve. **B.** With the lip or cheek pulled taut, the needle is inserted at the height of the buccal fold. Note: The two to three concentric circles of dotted lines around the needle tip indicate the area where the anesthesia is deposited. **C.** The needle is directed along the long axis of the tooth, and anesthesia is deposited just superior to the area of the root apex. **D.** Clinical photograph depicting a supraperiosteal infiltration of the maxillary lateral incisor.

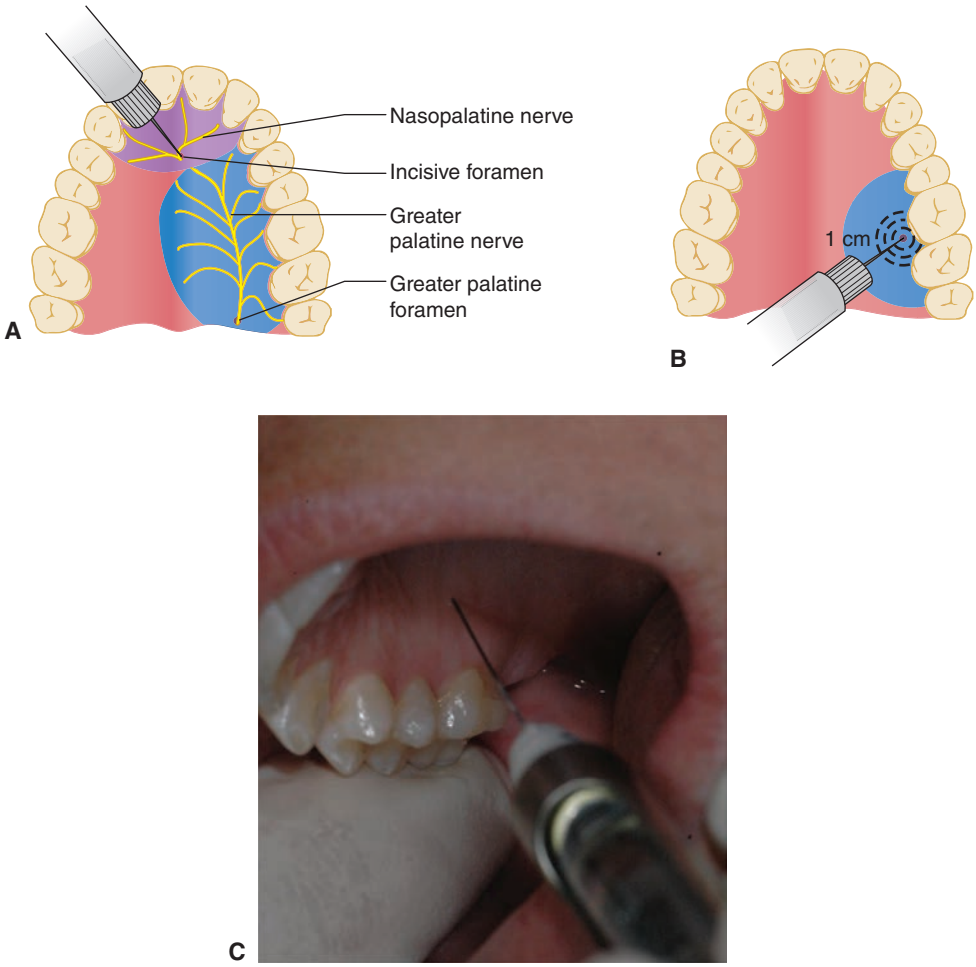


FIGURE 245-16. Palatal infiltration. **A.** The innervation to the soft tissue of the hard palate. The posterior portion of the palate is innervated by bilateral greater palatine nerves after they each exit their respective greater palatine foramens (see blue shaded area). The anterior portion of the hard palate is innervated by the nasopalatine nerve after exiting the incisive foramen. Injection over the incisive foramen (shown) will result in anesthesia to the purple shaded area. A similar injection over the area of the greater palatine foramen or the incisive foramen will provide anesthesia to its respective zone. **B.** A fine-gauge needle is inserted into the palatal tissue about 1 cm below the gingival margin, and a small amount of anesthesia is injected. Blanching of the palatal tissue surrounding the injection site is noted. This will provide anesthesia to the tissue adjacent to area injected as shown. **C.** Clinical photograph depicting a palatal infiltration.

or coronoid notch with the index finger or thumb. Then with that finger or thumb, the tissue is retracted toward the cheek, revealing the pterygotemporal depression that is between the raised ridge of mucosa (pterygomandibular raphe) medially and coronoid notch laterally. With the syringe directed from the opposite premolar area, the needle is inserted into the pterygomandibular depression at a point 1 to 1.5 cm above the occlusal plane. This is approximately at the level of index finger or thumb. The needle is then slowly advanced until bone is contacted (about 20 to 25 mm). Once bone has been contacted, the needle should be withdrawn about 1 to 2 mm and then aspirated. If no blood is aspirated, then about 1.5 mL of anesthetic solution should be slowly injected. The needle then should be withdrawn about half of the distance, and the remainder of the dental carpule injected. This will ensure the anesthesia of the lingual nerve.[29-31] With experienced operators, the direct technique has about a 20% to 25% failure rate. Most commonly, failure is due to using too low of a point of injection. This places the anesthesia below the sphenomandibular ligament, which impedes its flow toward the inferior alveolar nerve. Repositioning the syringe higher above the occlusal plane will usually result in a successful injection. (See Video: Inferior Alveolar Nerve Block.)

Lingual Nerve Block If only lingual nerve anesthesia is desired, then the above technique can be followed, except the needle need only be initially inserted about 10 mm, aspirated, and then the anesthetic agent instilled. This will provide anesthesia to the ipsilateral half of the anterior two thirds of the tongue (**Figure 245-18**).[29-31]

Long Buccal Injection If buccal soft tissue anesthesia is required, then this injection should be used. The needle is inserted into the mucosa in the buccal vestibule adjacent to the second or third mandibular molars (Figure 245-18).[29-31]

INJECTION COMPLICATIONS

The normal vasovagal symptoms, such as syncope, that can occur with any injection may occur during or after a dental injection. Flushing and elevation of the heart rate can also occur. Mild to severe allergic reactions are possible. Due to the close proximity of the inferior alveolar artery and vein and the pterygoid plexus, a potential complication of inferior alveolar nerve block is traumatic hematoma formation. These are usually self-limiting and treated with ice to the face, but can be quite uncomfortable and an aesthetic issue for more than a week. Due to the superficial nature of the lingual nerve relative to the inferior alveolar nerve, inadvertent injury to the lingual nerve with subsequent temporary or permanent paresthesia can occur. This not only can affect sensation to the anterior two thirds of the affected side but also may affect taste because taste fibers run with the lingual nerve. Postinjection trismus, due to local trauma to the muscles of mastication, can occasionally occur. Needle breakage, although uncommon, has been reported, especially with improper technique such as bending the needle prior to use or redirecting the needle while injecting. Finally, unintentional injection too posteriorly may result in injection into the parotid region and can cause temporary facial nerve palsy.[31]

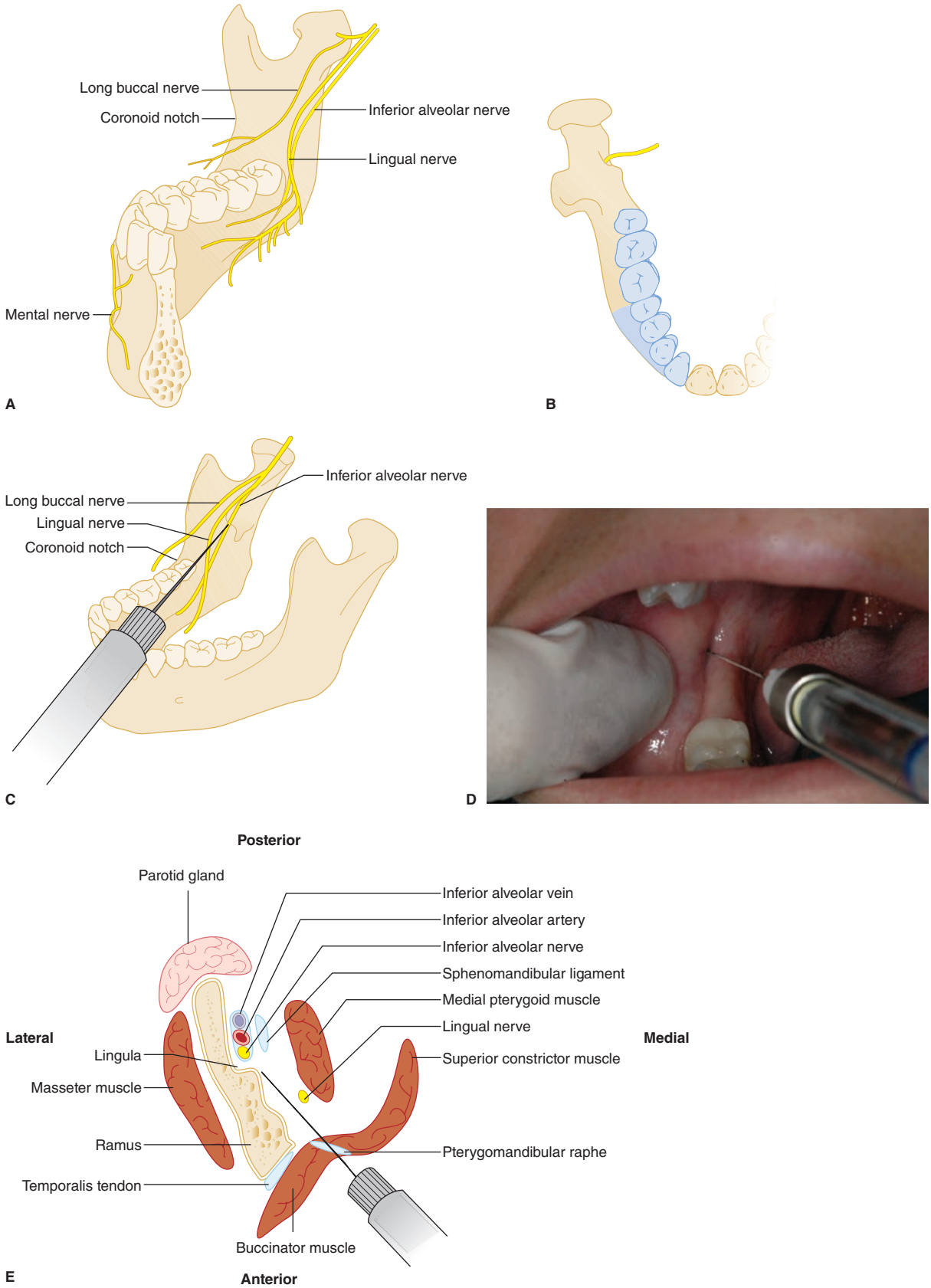


FIGURE 245-17. Inferior alveolar nerve block (direct technique). **A.** The anatomy of the inferior alveolar nerve as it enters the mandibular foramen in the pterygomandibular space. The lingual nerve lies superficial and medial to the inferior alveolar nerve. The coronoid notch is noted. **B.** The area of anesthesia obtained with a successful inferior alveolar nerve block. Usually the lingual nerve is also blocked, which provides anesthesia to the floor of the mouth, lingual gingiva, and the anterior two thirds of the tongue. **C.** The syringe should be directed from the contralateral premolar area about 1 to 1.5 cm above the mandibular plane. It is inserted about 20 to 25 mm until bone is touched in an area above the lingula. The needle should then be withdrawn 1 to 2 mm and aspirated for blood before injecting anesthesia. The sphenomandibular ligament attaches to the lingula and prevents the anesthesia from reaching the inferior alveolar nerve if the injection is too low. **D.** Clinical photograph of the direct technique. Note the point of injection in the pterygomandibular depression just lateral to the pterygomandibular raphe. **E.** A diagram of a transverse section of the pterygomandibular fossa at the level of an inferior alveolar nerve injection. Note that the needle passes through the buccinator muscle to an area just superior to the lingula.

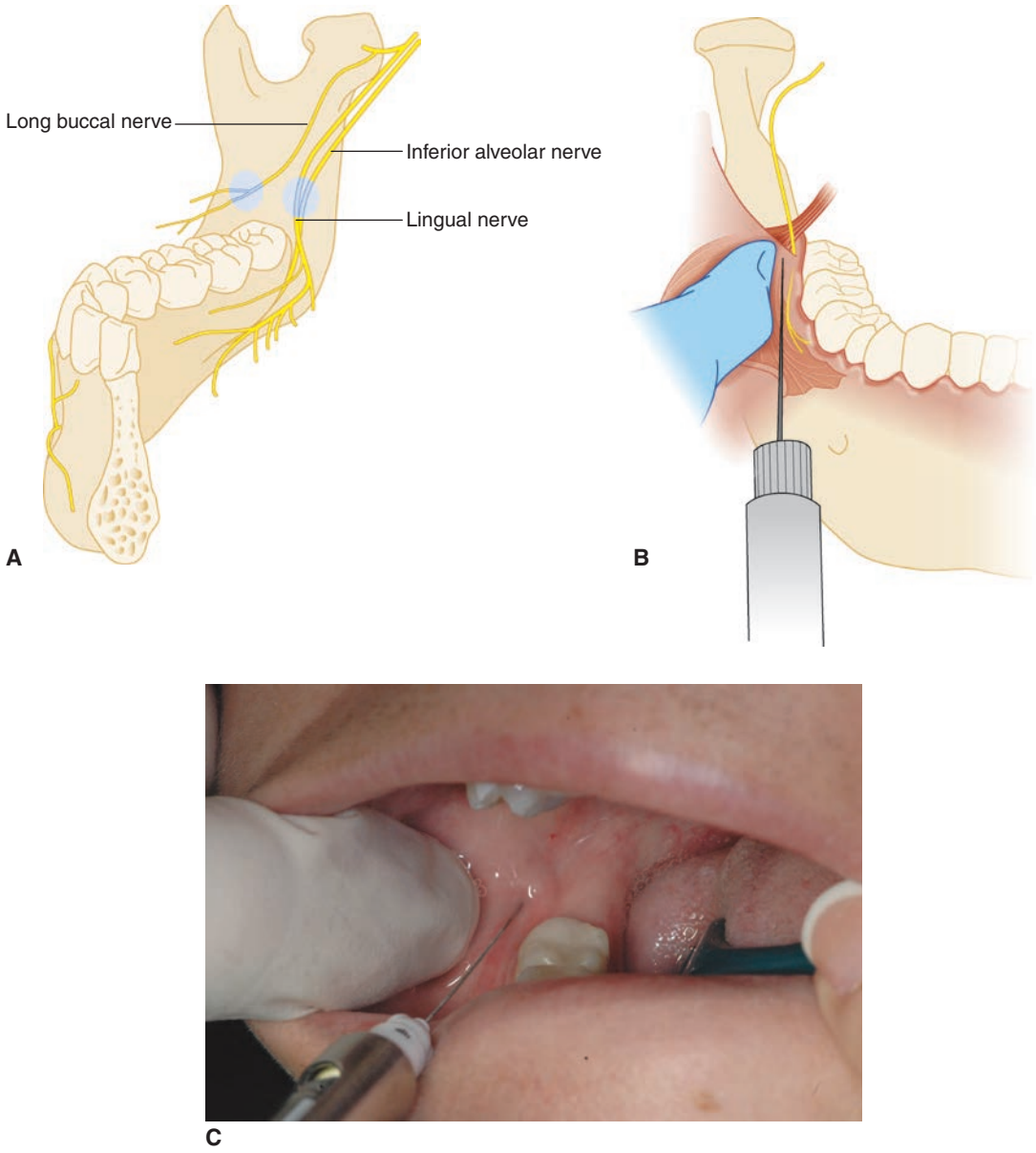


FIGURE 245-18. The lingual nerve block and the long buccal nerve block. **A.** The shaded areas represent the area in which anesthesia should be deposited for their respective blocks. The lingual nerve runs superficial and medial to the inferior alveolar nerve and can be easily anesthetized as part of the inferior alveolar nerve block. The lingual nerve block can be performed by depositing anesthesia about half the depth of the inferior alveolar nerve block. **B.** A diagrammatic representation of the long buccal nerve block. The long buccal nerve requires a separate injection of a small quantity of anesthetic just lateral to the molars in the buccal mucosa. **C.** Clinical photograph of the long buccal nerve block.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 246

Neck and Upper Airway

Nicholas D. Hartman

This chapter reviews infectious and noninfectious conditions that can obstruct the upper airway. These disorders must be recognized quickly because early airway management may be lifesaving. Neck trauma is discussed in Chapter 260, "Trauma to the Neck," and angioedema is discussed in Chapter 14, "Allergy and Anaphylaxis." Management of upper airway and neck infections in children are discussed in Chapter 124, "Mouth and Throat Disorders in Infants and Children," and Chapter 126, "Stridor and Drooling in Infants and Children."

NECK AND UPPER AIRWAY INFECTIONS

PHARYNGITIS/TONSILLITIS

Viruses account for most cases of pharyngitis or tonsillitis. Acute viral pharyngitis is most commonly caused by rhinovirus but can be caused by other viral agents (**Table 246-1**).[1]

VIRAL PHARYNGITIS

Features traditionally associated with viral pharyngitis include a vesicular or petechial pattern on the soft palate and tonsils, cough,

TABLE 246-1 Microbial Causes of Acute Pharyngitis

Pathogen	Syndrome/Disease	Estimated % of Cases*
Viral		
Rhinovirus (100 types, 1 subtype)	Common cold	15–20
Coronavirus (3+ types)	Common cold	>5
Adenovirus (types 3, 4, 7, 14, 21)	Pharyngoconjunctival fever, acute respiratory disease	6
Herpes simplex virus (type 1, 2)	Gingivitis, stomatitis, pharyngitis	4
Parainfluenza virus (types 1–4)	Common cold, croup	2
Influenza virus (types A, B)	Influenza	2
Respiratory syncytial virus	Bronchiolitis, pharyngitis	1–2
Coxsackievirus A (types 2, 4, 5, 6, 8, 10)	Herpangina	<1
Epstein-Barr virus	Infectious mononucleosis	<1
Cytomegalovirus	Infectious mononucleosis	<1
Human immunodeficiency virus type 1	Acute retroviral syndrome	<1
Bacterial		
Streptococcus pyogenes (GABHS)	Pharyngitis, tonsillitis, scarlet fever	10–23
Fusobacterium necrophorum	Pharyngitis, tonsillitis, Lemierre's syndrome	5–10
Streptococcus dysgalactiae subspecies *equisimilis* (formerly group C β-hemolytic streptococci)	Pharyngitis, tonsillitis	3–6
Neisseria gonorrhoeae	Pharyngitis	<1
Corynebacterium diphtheriae	Diphtheria	<1
Arcanobacterium haemolyticum	Pharyngitis	<1
Chlamydial		
Chlamydia pneumoniae	Pneumonia, bronchitis, pharyngitis	<1
Mycoplasmal		
Mycoplasma pneumonia	Pneumonia, bronchitis, pharyngitis	<1

Abbreviation: GABHS = group A β-hemolytic *Streptococcus*.

*Estimates of percentage of all cases of pharyngitis due to the indicated organism.

and rhinorrhea.[2] It remains difficult, however, to determine the causative agent based on clinical features alone. For example, in patients with nonstreptococcal pharyngitis (mostly viral), 16% have tonsillar exudate, 55% have cervical adenopathy, and 64% lack cough.[3] Most cases of viral pharyngitis require no specific diagnostic testing. **There are three notable exceptions where testing may be indicated: suspected influenza, infectious mononucleosis, or acute retroviral syndrome.** See Centers for Disease Control and Prevention influenza website for testing and treatment recommendations (http://www.cdc.gov/flu/). Infectious mononucleosis, influenza, herpesvirus, and cytomegalovirus infections are discussed in Chapter 154, "Serious Viral Infections." The acute retroviral syndrome of early human immunodeficiency virus infection can also mimic mononucleosis. See Chapter 155, "Human Immunodeficiency Virus Infections," for recommendations on testing and treatment. Apart from the viral causes of pharyngitis discussed earlier, viral pharyngitis should be treated symptomatically with oral hydration, antipyretics, analgesics, and rest. Patients unable to tolerate oral fluids or who become dehydrated should be given IV fluids.

BACTERIAL PHARYNGITIS

Group A β-Hemolytic *Streptococcus* (GABHS) Pharyngitis Group A β-hemolytic *Streptococcus*, the Lancefield group A species of *Streptococcus pyogenes*, is traditionally thought to be responsible for 5% to 15% of pharyngitis in adults, although recent studies reveal figures as high as 23%.[3] After an incubation period of 2 to 5 days, patients develop the sudden onset of sore throat, painful swallowing, chills, and fever. Headache, nausea, and vomiting are common. Signs and symptoms of group A β-hemolytic *Streptococcus* pharyngitis include marked swelling of the tonsils and tonsillar pillars (found in 62% of cases); tonsillar exudate (39%); and enlarged, tender cervical lymph nodes (76%).[3] A 2012 epidemiologic study in an urgent care environment, however, found that only 6% of patients with group A β-hemolytic *Streptococcus* were febrile (>101°F) and that 28% had cough.[3] Patients may have uvular edema, myalgias, and malaise but are less likely to have rhinorrhea or conjunctivitis compared to patients with viral pharyngitis.

The original Centor criteria listed four clinical indicators of group A β-hemolytic *Streptococcus* pharyngitis: (1) tonsillar exudates, (2) tender anterior cervical adenopathy, (3) absence of cough, and (4) history of fever. Increasing Centor scores have been repeatedly shown to predict higher likelihood of GAS infection.[3] The Centers for Disease Control and Prevention and Infectious Diseases Society of America recommend performing testing on patients who lack viral features.[4] **Rapid antigen diagnostic tests have an overall sensitivity of 86% and a specificity of 94% to 96%.**[5-7] The sensitivity of the test is the same in patients with and without features of viral pharyngitis.[2]

Untreated, group A β-hemolytic *Streptococcus* infection lasts 7 to 10 days. Antibiotic therapy of group A β-hemolytic *Streptococcus* improves symptoms within 24 to 48 hours of initiation of therapy and prevents suppurative complications and rheumatic fever in most patients,[8] but does not prevent glomerulonephritis.[4] **Group A β-hemolytic *Streptococcus* has never been resistant to penicillin, so penicillin remains the recommended first-line drug for group A β-hemolytic *Streptococcus*.**[9,10] Adults who test positive for group A *Streptococcus* should receive a single IM dose of benzathine penicillin G 1.2 million units, penicillin VK 500 milligrams twice daily for 10 days, or amoxicillin. A first-generation cephalosporin or clindamycin may be used for penicillin-allergic patients,[9] although resistance to these agents has been reported.[11] A single dose of PO or IM dexamethasone in immunocompetent patients with moderate to severe pharyngitis decreases time to pain relief and to complete resolution of pain, without significant increase in side effects.[12,13,14]

Other Causes of Bacterial Pharyngitis Several other bacteria can cause pharyngitis, although these infections are less common (Table 246-1). ***Streptococcus dysgalactiae* subspecies *equisimilis***, previously known as β-hemolytic groups C and G streptococci, is an important pathogen causing pharyngitis, skin infections, and more serious infections such as meningitis or toxic shock syndrome in the elderly or immunocompromised.[15] *S. dysgalactiae* subspecies *equisimilis* frequently colonizes the upper respiratory tract (60% who are culture positive are asymptomatic); thus, treatment is recommended for patients with acute symptoms.[15] These infections also appear to be clinically indistinguishable from group A *Streptococcus* infections.[16] *S. dysgalactiae* subspecies *equisimilis* pharyngitis is almost uniformly susceptible to penicillin.[15] Clindamycin and fluoroquinolones are alternatives.[15,17]

Fusobacterium necrophorum, a gram-negative anaerobe, is the causative agent in **Lemierre's syndrome**, a complication of pharyngitis causing suppurative thrombophlebitis of the internal jugular vein, with or without bacteremia and septic emboli.[18] Suspect *F. necrophorum* in adolescents or young adults, particularly smokers, with worsening symptoms and neck swelling.[18,19] *F. necrophorum* resistance to macrolides is high.[19] Evaluation for Lemierre's syndrome should include contrasted CT of the neck, broad-spectrum antibiotics (metronidazole plus ceftriaxone, or piperacillin-tazobactam), and consideration for surgical drainage.[20]

Gonococcal pharyngitis is usually associated with genital infection and is treated by the same antibiotics (see Chapter 153, "Sexually Transmitted Infections"). **Diphtheria** is caused by *Corynebacterium diphtheriae* and is rare in well-immunized populations. It is characterized by a slow onset of mild to moderate pharyngeal discomfort and low-grade fever. On physical examination, a gray membrane is seen adherent to

the tonsillar or pharyngeal surface and may extend to the uvula, soft palate, pharynx, and larynx. Treatment is with diphtheria antitoxin and metronidazole to prevent transmission to others.

Uvula edema, sometimes referred to as ***Quincke's edema***, can be associated with upper airway infections such as group A β-hemolytic *Streptococcus* pharyngitis, peritonsillar abscess, or epiglottitis. It can also be idiopathic. If it is an isolated finding and symptoms are uncomfortable to the patient, dexamethasone can be given as a single dose in the ED.

PERITONSILLAR ABSCESS

A peritonsillar abscess is a collection of purulent material between the tonsillar capsule, the superior constrictor, and palatopharyngeus muscles. Risk factors include periodontal disease, smoking, chronic tonsillitis, multiple trials of antibiotics, and previous peritonsillar abscess.[21] Peritonsillar abscess develops primarily in adolescents and young adults without seasonal variation as previously thought.[21,22] Although peritonsillar abscesses are typically polymicrobial infections, in patients 15 to 24 years of age, *F. necrophorum* has been the most common organism in many communities.[22,23]

CLINICAL FEATURES AND DIAGNOSIS

Patients with peritonsillar abscess (adolescents and adults) appear ill and present with sore throat (99%), fever (54%), malaise, odynophagia, and/or otalgia.[24] Physical signs include inferior and medial displacement of the infected tonsil(s) (46%), contralateral deflection of the swollen uvula (43%), tender cervical lymphadenopathy (41%), trismus (32%), muffled voice ("hot potato voice"), palatal edema, and dehydration[24] (**Figure 246-1**). The differential diagnosis of a peritonsillar abscess includes peritonsillar cellulitis, mononucleosis, lymphoma, herpes simplex tonsillitis, retropharyngeal abscess, neoplasm, and internal carotid artery aneurysm. In peritonsillar cellulitis, erythema and edema of the tonsillar pillar and soft palate are evident, but pus has not yet formed. Diagnosis of a peritonsillar abscess is often made by history and physical examination alone. If the diagnosis is in question, intraoral US has a sensitivity of 89% to 95% with a specificity of 79% to 100% for peritonsillar abscess.[25] CT scan with contrast is indicated if there is concern for spread beyond the peritonsillar space or lateral neck space complications.[25]

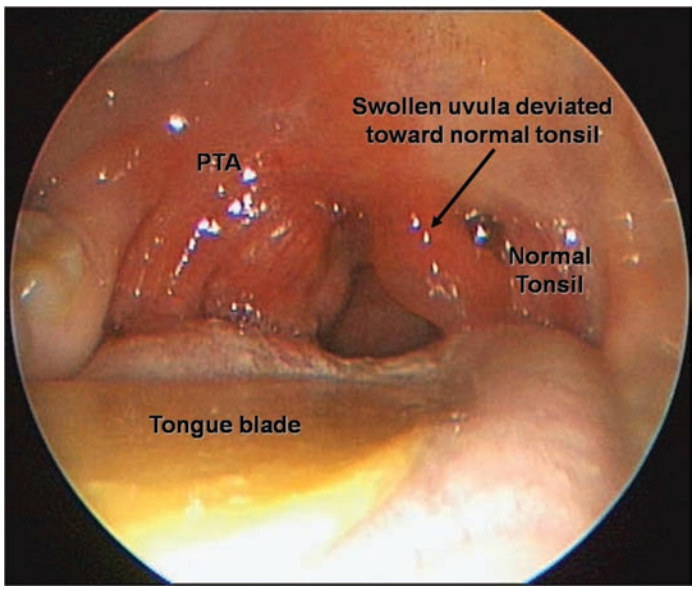


FIGURE 246-1. Right peritonsillar abscess (PTA) displacing right tonsil medially and the uvula toward the normal left tonsil. Abscess is between the right tonsil and the superior constrictor muscles.

TREATMENT

Treatment options include drainage of the abscess by needle aspiration, incision and drainage, or, rarely, immediate tonsillectomy. Choice of treatment depends on clinical symptoms, degree of patient cooperation, history of previous tonsil disease, and healthcare personnel experience. No definite difference in outcome has been found when comparing needle aspiration with incision and drainage, although some studies show less recurrence with incision and drainage.[25,26] Abscess tonsillectomy ("quinsy tonsillectomy") should only be considered when patients have strong indication for tonsillectomy, such as sleep apnea, recurrent tonsillitis, or recurrent peritonsillar abscess.[25] Approximately 90% of patients will be treated effectively after a single needle aspiration.[25,27]

Needle Aspiration Needle aspiration can be performed by an emergency provider trained in the technique. First, apply anesthetic spray or gel to the overlying mucosa. Then inject 1 to 2 mL of lidocaine with epinephrine into the mucosa of the anterior tonsillar pillar using a 25-gauge needle. **The drainage needle should penetrate no more than 1 cm because the internal carotid artery usually lies laterally and posterior to the posterior edge of the tonsil.** The plastic sheath of the needle can be cut 1 cm from its tip to serve as a guard. If the internal carotid artery lies more medial and anterior, it can usually be palpated in this area. Once adequate anesthesia is achieved, introduce an 18-gauge needle just lateral to the tonsil, approximately halfway between the base of the uvula and the maxillary alveolar ridge, until the abscess cavity is encountered and pus is aspirated. Multiple aspirations may be required to find the abscess. If not done previously, a contrast CT scan of the neck is recommended when the results of needle aspiration are negative and a parapharyngeal or retropharyngeal space process is suspected.

Pharmacotherapy and Follow-Up Initial therapy should include a 10-day course of antimicrobials effective against group A *Streptococcus* and oral anaerobes (including *F. necrophorum*).[28] Proven agents are penicillin VK plus metronidazole[25,28] or clindamycin for penicillin-allergic patients. Toxic patients or patients unable to take medicine PO should receive piperacillin-tazobactam or similar agent. Single IV use of high-dose steroid (dexamethasone, 10 milligrams) in addition to antibiotics and drainage improves severity and duration of pain.[29] Provide follow-up within 24 to 36 hours of aspiration, with instructions to return to the ED if worse. If the patient is not improving, consider repeating the aspiration, obtaining otolaryngologic consultation for incision and drainage or tonsillectomy, or obtaining a CT scan to reconsider the diagnosis.[30] Complications of a peritonsillar abscess include airway obstruction, rupture of the abscess with aspiration of contents, hemorrhage secondary to erosion of carotid sheath, retropharyngeal abscess, mediastinitis, and poststreptococcal sequelae.[28]

ADULT EPIGLOTTITIS (SUPRAGLOTTITIS)

Epiglottitis is an inflammatory condition, usually infectious, primarily of the epiglottis but often including the entire supraglottic region (also termed *supraglottitis*). It can lead to rapid airway obstruction. Prior to the introduction of a conjugate vaccine for *Haemophilus influenzae* type b in the 1980s, most cases of epiglottitis affected children age 1 to 5 years. In the postvaccine era, the dramatic decline in pediatric cases has confined the disease primarily to adults, with estimates of mean age ranging from 45 to 54 years.[31-34] Adult cases frequently result in no causative organism being identified, but *H. influenzae*, *Streptococcus* and *Staphylococcus* species, anaerobes, viruses, and fungi can be implicated.[32-34] Risk factors for mortality in patients with epiglottitis are advanced age and male sex.[35]

CLINICAL FEATURES AND DIAGNOSIS

Symptoms are typically a 1- to 2-day history of worsening sore throat, odynophagia, and dyspnea, particularly in the supine position. The clinical triad of the "three Ds" (drooling, dysphagia, and distress) is a classic but infrequent presentation. Other symptoms are fever, tachycardia, cervical adenopathy, and anterior neck tenderness with pain on



FIGURE 246-2. Acute epiglottitis. *Arrow* points to thickened epiglottis resembling a thumbprint on a soft tissue lateral radiograph.

gentle palpation of the larynx and upper trachea. Stridor is primarily inspiratory. Patients often position themselves sitting up, leaning forward, mouth open, head extended, and panting.

Diagnosis is clinical and confirmed by radiographs or transnasal fiberoptic laryngoscopy. Lateral cervical soft tissue radiographs demonstrate obliteration of the vallecula, swelling of the aryepiglottic folds, edema of the prevertebral and retropharyngeal soft tissues, and ballooning of the hypopharynx (**Figure 246-2**). The epiglottis appears enlarged and thumb-shaped, with epiglottis width >6.3 mm found to strongly suggest epiglottitis.[36] Patients who have been taking antibiotics prior to imaging are at risk for false-negative radiographic imaging.[36] Direct laryngoscopy examination can confirm the diagnosis in adults if necessary, but should be done carefully to avoid sudden, unpredictable airway obstruction. **Patients with worsening dyspnea in the supine position should *not* be sent to the CT scanner; CT of the neck is not needed to make the diagnosis.**

TREATMENT

Obtain immediate otolaryngologic consultation for suspected epiglottitis. Be prepared to establish a definitive airway. Patients should not be left unattended, and they should remain sitting up. Initial treatment consists of supplemental humidified oxygen, IV hydration, cardiac monitoring, pulse oximetry, and IV antibiotics. Humidification and hydration can help decrease the risk for sudden airway blockage. Steroids are often given to decrease airway inflammation and edema (methylprednisolone, 125 milligrams IV).

In adults, the need for intubation usually can be determined by transnasal fiberoptic examination of the supraglottis. Intubation is generally accomplished by "awake" fiberoptic intubation in the operating room, with preparations for immediate awake tracheostomy or cricothyrotomy. In cases of airway obstruction in the ED, be prepared for a very difficult intubation secondary to the swollen, distorted anatomy. In the case of intubation failure, the last resorts for preserving the airway are cricothyrotomy and needle cricothyrotomy.

Current antibiotic recommendations are second- or third-generation cephalosporins or other β-lactamase–resistant antibiotic such as piperacillin-tazobactam. Respiratory fluoroquinolones are an option for patients with severe penicillin allergies.[33]

RETROPHARYNGEAL ABSCESS

The retropharyngeal space is a potential space anterior to the prevertebral fascia that extends from the base of the skull to the tracheal bifurcation. In adults, a retropharyngeal abscess is usually due to intraoral procedures, trauma, foreign bodies such as a fishbone, immunocompromise, or extension from odontogenic infection.[37] Cultures from retropharyngeal abscesses are usually polymicrobial: group A β-hemolytic streptococci, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *H. influenzae*, and *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium* species.

CLINICAL FEATURES AND DIAGNOSIS

The most common symptoms in adults are sore throat, dysphagia, neck pain, and less commonly, stridor. In addition, patients may also have complaints of cervical lymphadenopathy, poor oral intake, muffled voice, and respiratory distress. Visible neck swelling is not common.

A lateral soft tissue radiograph of the neck taken during inspiration with moderate cervical extension can demonstrate thickening and protrusion of the retropharyngeal wall, classically with 5 to 7 cm of prevertebral widening at the second cervical vertebra.[38] However, contrast-enhanced CT scan of the neck is the test of choice for diagnosis of a retropharyngeal abscess.[39] Early CT findings may reflect reactive, nonsuppurative edema, mild fat stranding with discernible tissue planes, linear fluid, minimal mass effect, and no associated enhancement. Necrotic nodes with central low attenuation and ring enhancement reflect an abscess (**Figure 246-3**). A patient with airway distress should not be sent unobserved for CT scanning.

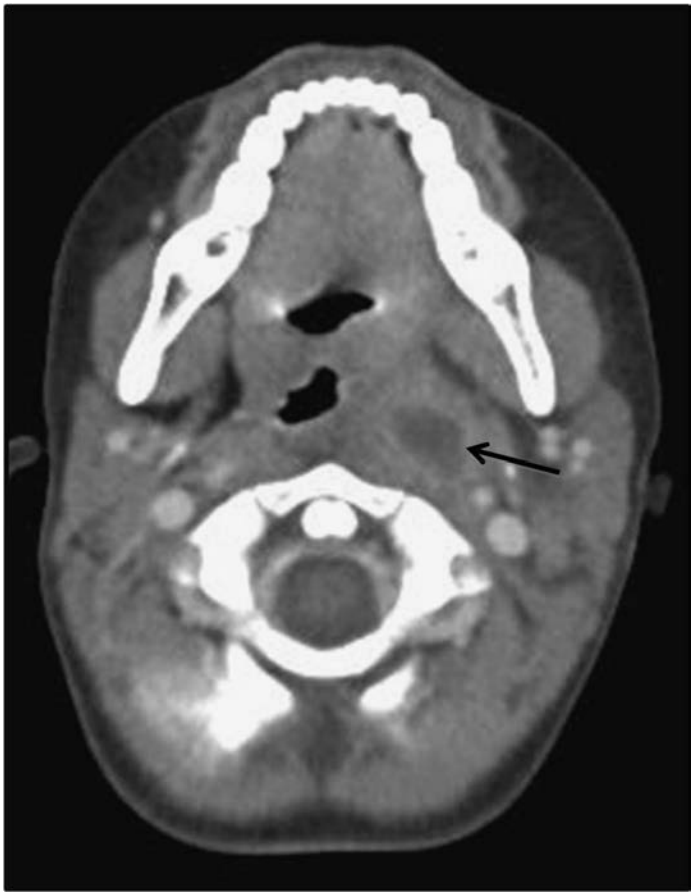


FIGURE 246-3. Contrasted CT of a left retropharyngeal abscess (*arrow*).

TREATMENT

Obtain immediate otolaryngologic consultation. Provide IV hydration and antibiotic treatment aimed at *Staphylococcus*, *Streptococcus*, and anaerobes; choices for initial therapy include clindamycin, 900 milligrams IV, plus metronidazole, 1 gram IV, or an extended-spectrum penicillin such as piperacillin-tazobactam, 3.375 grams IV, or ampicillin-sulbactam, 3 grams IV.[40] Add vancomycin if the patient is in a high-risk group.[40] Most patients will require surgical intervention. Catastrophic complications from retropharyngeal abscess include extension of the infection into the mediastinum and upper airway asphyxia from direct pressure or aspiration after sudden rupture of the abscess.

ODONTOGENIC ABSCESS

Odontogenic infections can arise from an infected tooth or after a tooth extraction. Development of the infection varies from <1 day to up to 3 weeks after the onset of tooth pain and may occur despite oral antibiotics. Odontogenic infections are polymicrobial; the most common bacteria are *Streptococcus viridians*, *Peptostreptococcus*, *Prevotella*, and staphylococci.[41] **Most deep neck infections originate from an odontogenic source, usually the mandibular teeth.** Dental abscesses may spread into the parapharyngeal and retropharyngeal spaces. Presenting features include neck mass, trismus, fever, leukocytosis, dysphagia, and dyspnea. Potential complications include necrotizing fasciitis, descending necrotizing mediastinitis, orbital infections, and hematogenous dissemination to distant organs.

CLINICAL FEATURES

See Chapter 245, "Oral and Dental Emergencies," for management of dental infections isolated to the mandible or maxilla. See Chapter 243, "Face and Jaw Emergencies," for management of deep infections of the mid-face. Infections of maxillary molars tend to involve the masticator space, which can extend into the parapharyngeal space and downward into the neck and mediastinum. Infections of anterior mandibular teeth tend to spread into the neck. Infections of anterior teeth, bicuspids, and first molars of the mandible tend to enter the sublingual space, with edema of the floor of the mouth with little extraoral swelling. Involvement of the submandibular space is typically the result of second and third mandibular molar infections.

DIAGNOSIS AND TREATMENT

Diagnosis of superficial odontogenic abscesses can be aided by US at the bedside.[42] For diagnosis of suspected deep space infections, contrast-enhanced CT scan is recommended to identify the need for surgical management. Treatment of odontogenic infections includes appropriate antibiotic therapy (aerobic and anaerobic coverage) and surgical drainage of abscesses. Penicillin VK and amoxicillin remain appropriate options for outpatient treatment; amoxicillin-clavulanate, clindamycin, cefuroxime, and levofloxacin are second-line choices.[43,44] Patients with deep neck infections require IV antibiotics. Ampicillin-sulbactam 3 grams IV, piperacillin-tazobactam 3.375 grams IV, clindamycin 900 milligrams IV, or a β-lactam drug plus metronidazole are recommended regimens.[45]

COMPLICATIONS

Ludwig's Angina Ludwig's angina is infection of the submental, sublingual, and submandibular spaces. Patients usually present with poor dental hygiene, dysphagia, and odynophagia. Clinical examination reveals trismus and edema of the entire upper neck and floor of mouth. Infection progresses rapidly and can posteriorly displace the tongue, causing airway compromise. Definitive airway management should be considered early, including awake fiberoptic intubation or awake tracheostomy.[46,47] Stridor, difficulty managing secretions, and cyanosis are late signs and require emergent airway management. Systemic antibiotics are not a substitute for definitive airway management because it may take >1 week for edema resolution with antibiotic therapy.[47]

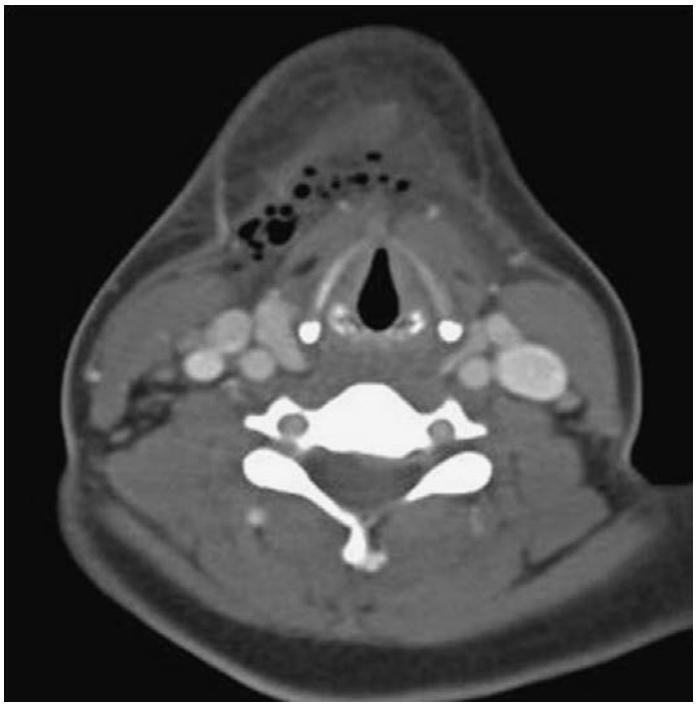


FIGURE 246-4. CT demonstrating necrotizing fasciitis with gas in the deep tissue of the anterior neck.

Necrotizing Fasciitis Patients with necrotizing infections are critically ill, with overlying skin discoloration, crepitus of the subcutaneous tissue, and systemic signs, including fever, tachycardia, hypotension, and confusion.[48,49] CT reveals subcutaneous emphysema, deep tissue gas, and pockets of suppuration (**Figure 246-4**). Aerobic and anaerobic cultures are necessary for identification of causative organisms. Therapy for necrotizing fasciitis is immediate surgery with fasciotomy with wide local debridement and broad-spectrum IV antibiotics. Mediastinal extension places the patient at risk for great vessel erosion, retroperitoneal extension, pleural abscess, pericardial effusion, and sepsis; mortality ranges from 10% to 40%.[48] Tracheostomy should be performed if airway obstruction develops. Surgery can be lifesaving, and immediate surgical consultation is required for this rapidly progressing disease.[48]

NECK AND UPPER AIRWAY MASSES

CLINICAL FEATURES

Neck masses (**Figures 246-5** and **246-6**) can result from congenital, infectious, glandular, or neoplastic disorders. Enlargement may lead to airway compromise, dehydration secondary to dysphagia and odynophagia, or secondary infection. Age of the patient and characteristics including location of the mass may aid in the diagnosis (**Tables 246-2** and **246-3**).[50] Neck masses in children are discussed in Chapter 125, "Neck Masses in Infants and Children." **In adults >40 years old, up to 80% of lateral neck masses persistent for >6 weeks are malignant**.[51]

DIAGNOSIS AND MANAGEMENT

A number of management suggestions are listed in Table 246-3. The urgency for complete diagnostic evaluation of a neck mass depends on patient acuity.[52] Patients with airway compromise or significant dysphagia and odynophagia should be evaluated by flexible



FIGURE 246-5. Right plunging ranula presenting as a painless ballotable submandibular mass.

nasopharyngolaryngoscopy **before** CT scan. CT scan will delineate the extent of the mass and likely will be required for surgical intervention. If no airway compromise or dehydration is present, the patient should follow up with primary care for outpatient imaging and further evaluation. All neck masses should have follow-up for diagnosis and treatment, particularly in light of the high risk of malignancy.

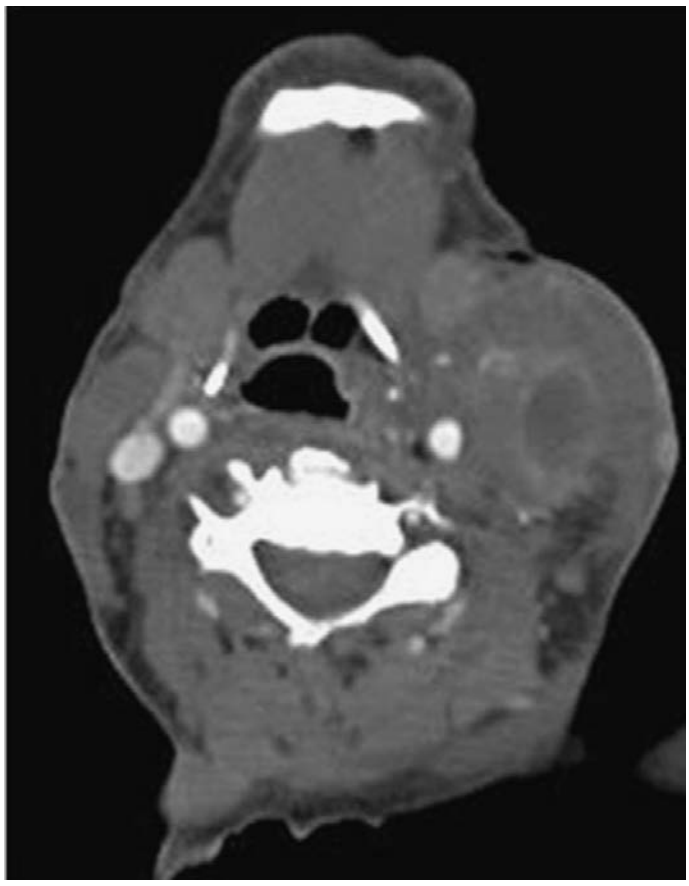


FIGURE 246-6. Hypopharyngeal squamous cell carcinoma metastatic to left cervical lymph nodes. Note the thrombosis of the left jugular vein with displacement of the airway to the right.

TABLE 246-2 Common Neck Masses in Young and Older Adults

Young Adult	Older Adult
Reactive lymphadenopathy	Metastatic aerodigestive tract carcinoma
Mononucleosis	Salivary gland infection or neoplasm
Lymphoma	Lymphoma
Branchial cleft cyst	Thyroid disorder
Thyroglossal duct cyst	Tuberculosis

A superficial neck mass or enflamed lymph node suspected of being infectious in etiology may be further investigated by ultrasound at the bedside.[30] Presence of fluid may indicate an abscess, or a cobblestone pattern may indicate surrounding cellulitis. In the absence of these findings or a history that supports a bacterial infection, antibiotics are unlikely to benefit the patient with a neck mass. Directions should be given for follow-up with primary care or otolaryngology, with return precautions for respiratory distress, dysphagia, or unexpected fever prior to the outpatient appointment.

POSTTONSILLECTOMY BLEEDING

Posttonsillectomy bleeding is a well-known complication of tonsillectomy that can, rarely, lead to death from airway obstruction or hemorrhagic shock.[53] Rate of secondary hemorrhage varies according to the method used for the procedure. Overall incidence of posttonsillectomy bleeding differs depending on age, procedure type, and location; estimates vary from <1% to 15%. Approximately half require surgical intervention for control of bleeding.[54,55]

Although bleeding can be seen within 24 hours of surgery, most significant hemorrhage occurs between postoperative days 5 and 10. There is a significantly higher incidence of bleeding in patients older than 12 years.[54] Posttonsillectomy bleeding can be fatal and requires prompt intervention with control of the airway. An otolaryngologist should be consulted early.

TREATMENT

Keep the patient NPO (nothing by mouth) and sitting upright, monitor with pulse oximetry, and maintain IV access. Obtain a CBC and coagulation studies, and type and cross-match blood. Examine the oropharynx to see if bleeding can be visualized. A grayish-white eschar is normal following a tonsillectomy. **Apply direct pressure to the bleeding tonsillar bed using a tonsillar pack or a 4×4 gauze on a long clamp, moistened with either thrombin or lidocaine and epinephrine.** To prevent loss of the pack into the airway, place a suture through the pack and tape the suture to the face. Place pressure on the lateral pharyngeal wall, avoiding midline manipulation, to decrease stimulation of the gag reflex.

Pressure alone can be adequate for control of posttonsillectomy hemorrhage until the otolaryngologist arrives. Alternatively, if a bleeding site can be visualized, bleeding may be cauterized with silver nitrate after local infiltration with 1% lidocaine with epinephrine. **Nebulized epinephrine or tranexamic acid** is one option for serious hemorrhage control. The adult dose of nebulized tranxemic acid is 1000 milligrams in 20 mL of NS; for children, 250 milligrams if < 25 kg and 500 milligrams if > 25 kg. Give IV tranexamic acid for severe uncontrolled active bleeding.[56] The dose in adults is 1000 milligrams IV, the same as for trauma-caused hemorrhage; dosage for children is not well validated. Massive bleeding is unusual, but when it occurs, intubation may be the only means of protecting the airway. This is always difficult, with oropharyngeal edema from recent surgery and blood obscuring visualization of the cords. Plans should be made for an emergent cricothyrotomy prior to attempting intubation.

Otolaryngologic consultation in the ED is always needed because patients may have a second or even third posttonsillectomy hemorrhage,[57] and surgery or endovascular embolization may be necessary for definitive control.[58]

TABLE 246-3 Physical Findings, Pathology, and Management of Neck Masses in Adults

Disorder	Physical Finding	Pathology	Management
Ranula	Sublingual area swelling	Mucus retention cyst due to ductal obstruction of the sublingual gland	Surgical excision
Laryngeal papillomas	Sessile, warty-appearing lesions on the soft palate or tonsillar pillars	Human papillomavirus type 6 or 11 infection	Surgical excision
Palatine torus	Boney smooth painless mass of the hard palate	Exostoses of the palate	No treatment needed in most cases
Mandibular torus	Boney smooth painless growth of the mandible under the tongue	Exostoses of the mandible	No treatment needed in most cases
Branchial cleft cysts	Painless, fluctuant masses close to the angle of the mandible	Incomplete obliteration of the branchial apparatus during development	Antibiotics if infected, surgical excision
Thyroglossal duct cysts	Soft, mobile, subhyoid bone midline mass	Remnant of the thyroid anlage	Antibiotics if infected, surgical excision
Lymphoma	Multiple, rubbery low-neck masses, night sweats, fever, malaise	Malignant process	Biopsy, referral to ENT and oncology
Acute retroviral syndrome	Generalized adenopathy, unprotected sex by history	Human immunodeficiency virus infection	Antiretroviral medication
Squamous cell carcinoma	Firm, possibly fixed cervical lymph node	Oral lesion metastatic to cervical node	Biopsy, referral to ENT and oncology
Parotid tumors	Nonpainful masses under or anterior to the ear	Benign or malignant process	Biopsy, referral to ENT and oncology as needed
Sialadenitis	Tender swelling in area of parotid, submandibular, or sublingual salivary gland	Salivary gland infection	Antibiotics, salivary stimulants. See Chapter 243, "Face and Jaw Emergencies"
Thyroid enlargement	Diffuse nodular thyroid enlargement or solitary nodular thyroid	Benign or malignant process	See Chapter 228, "Hypothyroidism and Myxedema Crisis," and Chapter 229, "Hyperthyroidism and Thyroid Storm"

Abbreviation: ENT = otorhinolaryngology.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 247

Complications of Airway Devices

Casey D. Bryant

TRACHEOSTOMY TUBES AND CANNULAS

A tracheostomy is an opening between cartilaginous rings in the trachea and the skin, with a tracheostomy tube placed into the stoma to facilitate ventilation. Tracheostomy is usually performed as an elective or semielective procedure and is not an emergency procedure. Most tracheostomies are performed on chronically ill patients requiring prolonged mechanical ventilation.

There are many types of tracheostomy tubes available, including those made of plastic, silicone, nylon, and metal. Tracheostomy tubes vary in diameter, total length, the length before and after the curve, and the presence or absence of a cuff (**Figure 247-1**). The size of the tracheostomy tube is usually defined by the inner diameter, ranging in adults from 5 to 10 mm and in pediatric patients from 2.5 to 6.5 mm. Most pediatric and adult tracheostomy tubes have a 15-mm standard respiratory connection that may be used with ventilator tubing or a bag-valve device.

Fenestrated tracheostomy tubes have an opening along the dorsal surface of the body of the tube. The fenestration allows the passage of air through the tracheostomy tube to the vocal cords so the patient can speak. Irritation from the fenestration may promote growth of granulation tissue, which may extend into the fenestration, leading to bleeding, obstruction, and difficulty removing the tracheostomy tube. If any difficulty is encountered removing a fenestrated tracheostomy tube, obtain surgical consultation.

Most adult tracheostomy tubes have a removable inner cannula, which allows secretions to be cleared from the lumen without removing the entire tube from the trachea. In assessing an adult tracheostomy patient, remove and examine the inner cannula for crusting or obstruction. Both disposable and reusable inner cannulas may be cleaned by using a small brush dipped in a solution of hydrogen peroxide and then rinsing the cannula with warm tap water. If the correct size of disposable inner cannula is not available, use the existing inner cannula temporarily, or change the entire tracheostomy tube. **Pediatric tracheostomy tubes never have an inner cannula because of the small inner diameter; the entire tube must be removed for cleaning.**

COMPLICATIONS OF TRACHEOSTOMIES

Complications due to the surgery are grouped according to the timing since the tracheotomy and the technique. Timing is divided into intraoperative, early, and late, with 1 week typically being used in the medical literature as the cutoff between early and late complications. Summed complication rates are 10.0% for percutaneous technique and 8.7% for

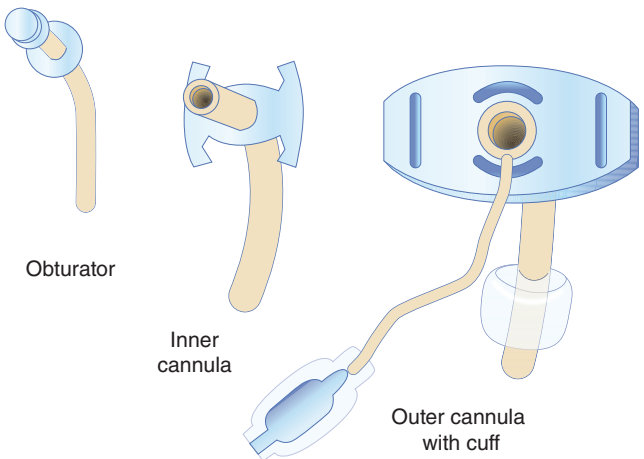


FIGURE 247-1. Common components of most tracheostomy tube sets.

open tracheostomy.[1] Bleeding, obstruction, dislodgement, and infection are all potential early complications. Late complications may include granulation, stenosis (subglottic, glottic, tracheal), persistent stoma, fistula formation (tracheocutaneous, tracheoesophageal, or tracheoinnominate), and any of the early complications listed.[1-5]

Patients with tracheostomy tubes can develop respiratory distress due to obstruction, dislodgement (decannulation), bleeding, and infection. **Figure 247-2** is a step-by-step approach to assess and treat respiratory distress. In the ED, the provider must be proficient in the following skills (as outlined in the sections that follow): replacement of an uncuffed with a cuffed tracheostomy tube for mechanical ventilation, replacement of a tracheostomy tube after accidental decannulation, correction of a tube obstruction, and control of bleeding or infection at the tracheostomy site. It is important to determine a few key elements about the tracheostomy: When and why was the procedure performed? What type of tracheostomy tube is the patient using currently? And can the patient be orally intubated if needed? **Patients who have undergone a laryngectomy or who have tumors or scarring that occlude the upper airway cannot be orally intubated.**

Tracheostomy Tube Obstruction Mucous plugging is a major cause of respiratory failure in tracheostomy patients and may occur at all levels of the respiratory system. If the tracheostomy is patent and is in the airway, leave it in place. If the tracheostomy tube is obstructed, mucous plugging is commonly the cause. Secretions may act as a ball-valve mechanism, allowing air in but restricting exhalation. Suctioning may relieve the obstruction. Preoxygenation and placement of sterile saline solution into the trachea will aid in suctioning. Prolonged use of large suction catheters without preoxygenation will cause hypoxemia. If mucous plugging of the tracheostomy tube cannot be relieved by suctioning, the inner cannula and, occasionally, the entire tracheostomy tube may need to be removed and cleaned.

Tracheostomy Dislodgement It is possible for the tracheostomy tube to become dislodged from the trachea but still be in the neck. In this case, a suction catheter cannot be passed through the tube, and on radiographs, the tracheostomy tube may be seen to extrinsically compress the trachea (**Figure 247-3**). In this circumstance, remove the entire tracheostomy tube. It may be difficult to accurately identify the actual

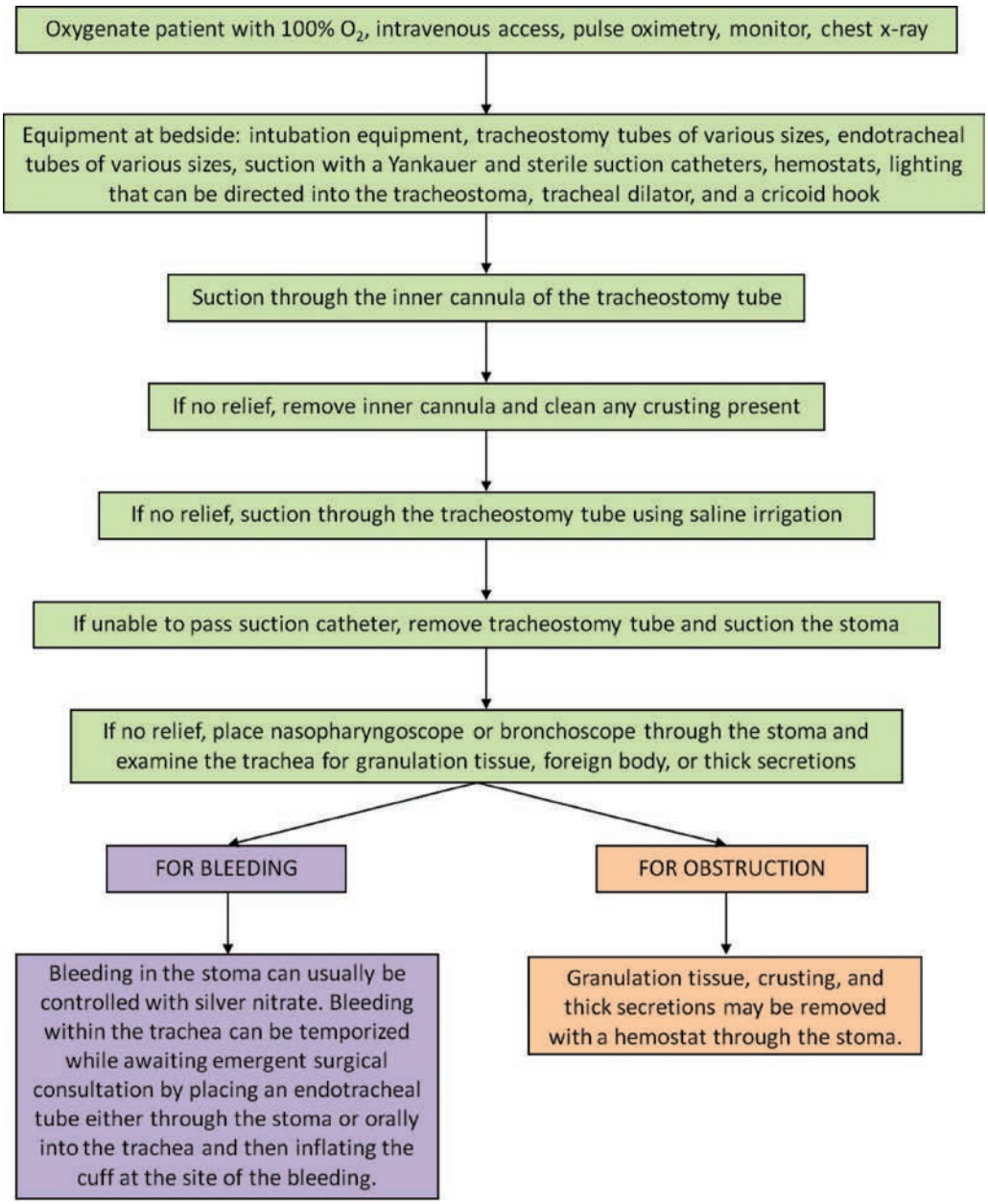
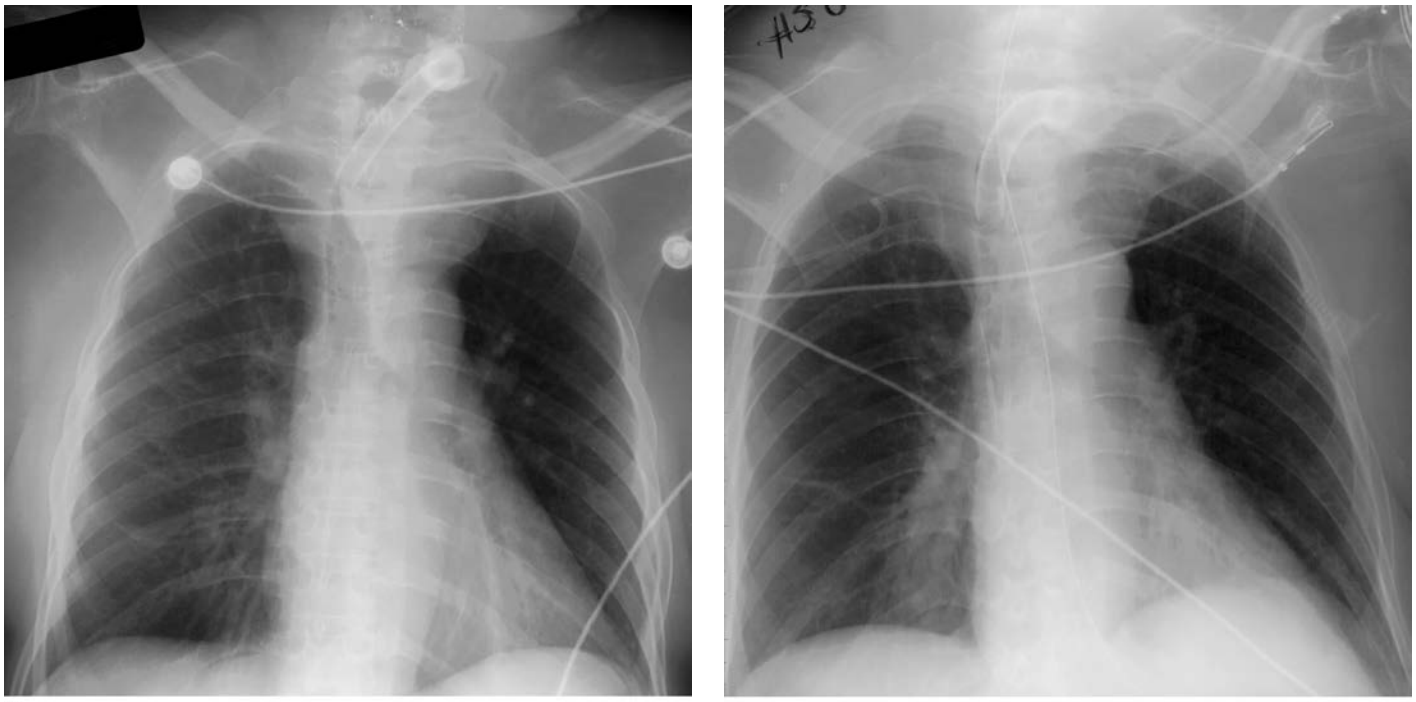


FIGURE 247-2. Steps in assessing a tracheostomy patient with respiratory distress.



A B

FIGURE 247-3. **A.** Patient with a large goiter and a No. 4 Shiley tracheostomy tube with the tip of the tube outside the trachea and compressing the tracheal wall. **B.** Same patient with a longer No. 6 Shiley tracheostomy tube with the tip of the tube correctly placed inside the trachea.

tracheal stoma when replacing the tube (see later section, "Changing a Tracheostomy Tube"). A nasopharyngoscope or flexible bronchoscope should be inserted into the visible stoma in an attempt to identify the tracheal opening. If the opening still cannot be identified, obtain surgical consultation. If the patient cannot maintain the airway, oral intubation will be necessary.

Tracheostomy Site Infection Indwelling tracheostomy tubes become contaminated with normal and/or pathogenic flora. Surgical site infection is more common in patients treated with the open technique versus the percutaneous technique.[6] This is believed to be due to a smaller incision, less tissue dissection, and less tissue exposure.[7] Stomal skin infection, tracheitis, and bronchitis can be recurring problems. Infections may be polymicrobial, and antimicrobial therapy is indicated in the setting of clinical disease. Treatment should focus on control of the source of infection with antimicrobial therapy guided by local antibiogram data and prior patient culture data, if available.[8] Dressing changes with gauze soaked in 0.25% acetic acid[9] or using silver-containing products are effective for local wound infections.[10]

Tracheostomy Site Bleeding Bleeding can occur at any time after a tracheostomy. Granulation tissue, bleeding from proximal areas such as epistaxis, erosion of the thyroid vessels or thyroid gland, the tracheal wall (frequently from suction trauma), and the innominate artery are all potential sources of hemorrhage.

Slow bleeding originating from the stoma may be controlled by packing the site with saline-soaked gauze or with a hemostatic product. If this is ineffective, remove the tube and examine the stoma and tracheal wall. Local bleeding can be controlled with silver nitrate.[10] Electrocautery should be done by a surgeon. If bleeding is brisk from a stomal site, replace the tracheostomy tube with a cuffed endotracheal tube, with the cuff below the bleeding site.

Tracheoinnominate Artery Fistula Tracheoinnominate artery fistula is a rare but life-threatening complication of tracheostomy. Cuff pressure >25 mm Hg, tracheostomy below the third tracheal ring, radiation treatment, chronic steroid use, and deformed neck or chest are all risk factors. Bleeding results from vessel erosion caused by either direct pressure of the tip of the tracheal cannula against the innominate artery or from a cuff with inappropriately high pressures due to overinflation. Most patients with a tracheoinnominate artery fistula present within the first 3 weeks after tracheostomy, with the peak incidence between the first and second week. Some patients may have a sentinel arterial bleed or hemoptysis. Bleeding may be mild or severe and should be thoroughly investigated because of the potential for sudden massive hemorrhage.[11,12] Immediate surgical consultation is required, and operative repair can be lifesaving.

If a patient presents with massive bleeding, resuscitation and operative planning should begin immediately. Hemorrhage control should first be attempted by hyperinflating the cuff. If bleeding persists, slowly withdraw the tube while exerting pressure against the anterior trachea. If these initial maneuvers do not control the bleeding, then have an assistant remove the tracheostomy tube simultaneously while the patient is being orotracheally intubated. The cuffed endotracheal should be placed distal to the source of bleeding.[11,12] **Hemorrhage control is then attempted by placing a finger into the stoma, dissecting along the trachea, and then compressing the innominate artery against the posterior manubrium.** This is known as the **Utley maneuver**.[13,14] Tamponade of the hemorrhage should be maintained during transport to the operating room.[14]

Tracheal Stenosis Tracheal stenosis may present weeks to months after decannulation and results from mucosal necrosis and subsequent scarring. Risk factors for tracheal stenosis in adults are intubation duration of more than 1 week, obesity, and having an endotracheal tube larger than 7.5 mm.[5] Signs and symptoms include dyspnea, wheezing, stridor, and the inability to clear secretions. A chest radiograph may demonstrate the narrowed tracheal airway. Medical treatment includes placing the patient in an upright position, humidified oxygen, nebulized racemic epinephrine, and steroids. If an airway needs to be established, airway adjuncts such as a bougie or fiberoptic scope may prove helpful, and a smaller tracheostomy or endotracheal tube should be considered.[15] Operative treatment involves rigid bronchoscopy with laser excision of the scar bands, and stenting or tracheal reconstruction in more severe cases.[15]

MECHANICAL VENTILATION WITH A TRACHEOSTOMY TUBE

If the patient requires mechanical ventilation, an uncuffed tracheostomy tube will result in a large air leak, and it will be difficult to ventilate the

TABLE 247-1 Equipment Needed to Change a Tracheostomy Tube

- Suction device with both a Yankauer tip and suction catheters that fit inside the tracheostomy tube
- Good lighting directed into the tracheostoma
- An appropriate-size tracheostomy tube with obturator in place
- Another tracheostomy tube one size smaller than planned
- Tracheostomy tube tie
- Cricoid hook and tracheal dilator (if physician is familiar with their use)

patient. In this case, the uncuffed tube should be exchanged for a cuffed tube.[15] If a tracheostomy tube is not readily available, an endotracheal tube may be inserted into the stoma to maintain airway security. If the stoma cannot be cannulated, the patient may be orotracheally intubated to secure the airway—unless the patient has a contraindication to attempted orotracheal intubation (see the later section, "Laryngectomy Patients").

CHANGING A TRACHEOSTOMY TUBE

The amount of difficulty encountered when changing a tracheostomy tube depends on when the procedure was performed and on patient anatomy. **If the tracheostomy is <7 days old, the tract will not be mature and manipulation may easily create a false passage within the soft tissue of the neck. In addition, a tract may easily collapse at any time in patients with obese necks or neck masses. If the situation is not emergent and the tracheostomy is <7 days old, tracheostomy tubes should be changed by a surgeon familiar with the procedure.**[16]

An uneventful tracheostomy change depends on adequate preparation and is best accomplished with an assistant. The spontaneously breathing, stable patient can easily breathe through a patent stoma without the tube in place, so there is no reason to rush through this procedure. The needed equipment is listed in **Table 247-1**.[16,17] If a cuffed tube is used, test the balloon before use and make sure the balloon is completely deflated before insertion. A cricoid hook can be used to lift and stabilize the trachea. The dilator is particularly useful if a larger tube is to be inserted, but if dilation is needed and time permits, obtain surgical consultation. Dilation may require injection of local anesthesia. Become familiar with the cricoid hook and tracheal dilator before using them. To minimize soft tissue damage, try to use an obturator whenever a tracheostomy tube is replaced. When the obturator is placed within the outer cannula, the tube presents a solid, rounded end that is less likely to damage the neck soft tissue during tube insertion (Figure 247-1). **After placement, quickly remove the obturator and place the inner cannula, because the patient cannot breathe through the tracheostomy tube when the obturator is in place.**

After gathering the necessary equipment, place the patient in the supine position and use a shoulder roll to extend the neck. Remove the old tube and gently suction and examine the stoma. In most cases, the opening in the trachea and the posterior tracheal wall can be seen. Gently direct the fresh tube with the balloon deflated into the opening, curving it downward into the trachea (**Figure 247-4**). The movement should be smooth and gentle. If resistance is met, the tube is likely caught on the cartilaginous tracheal wall. Remove the tube and reexamine the stoma, and again place the tube directly into the tracheal opening. If the tube still cannot be placed, consider placing a smaller tracheostomy tube. **However, when placing a smaller tube, one must ensure that the tube is long enough for the patient's neck.**[17] Another helpful method is to place a small suction catheter or nasogastric tube into the trachea and thread the tracheostomy tube over the catheter using a modified Seldinger technique.

Once the tube is in place, verify correct tube position by attaching an end-tidal carbon dioxide detector or by passing a suction catheter into the tube. If a suction catheter is placed, it should easily pass beyond the length of the tracheostomy tube without resistance. If there is a question about placement, pass a nasopharyngoscope or flexible bronchoscope through the tube for direct visualization of placement.

Patients with accidental decannulation who are not in distress can have the tracheostomy tube replaced as described. **If the tube has been out for several hours, the stoma may begin to close and dilation may be needed before tube insertion.** In these cases, and if the stoma is small or the tracheostomy is the patient's only airway, surgical consultation is recommended for tube replacement.[16]

LARYNGECTOMY PATIENTS

It is impossible to orally intubate patients who have had a laryngectomy. The only access to the tracheobronchial tree is through the tracheostoma in the neck. Occasionally, laryngectomy patients will have a laryngectomy tube in the stoma, similar in appearance to a tracheostomy tube. Laryngectomy patients can be distinguished from tracheostomy patients by history and physical examination and by the fact that laryngectomy patients are unable to phonate or breathe when the laryngectomy tube is occluded. **Laryngectomy patients can be emergently intubated by placing an endotracheal tube into the tracheostoma.** Do not advance the tube too far, because the adult carina may be only 4 to 6 cm from the tracheostoma.[18]

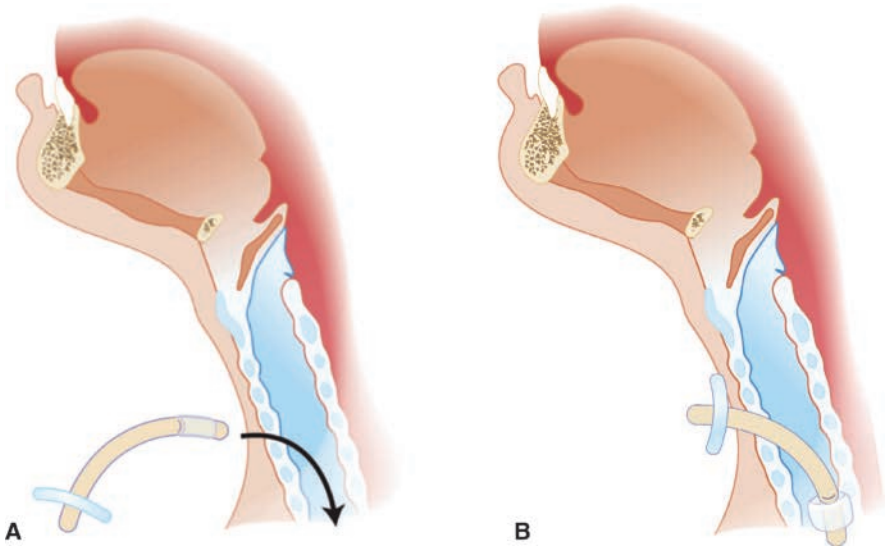


FIGURE 247-4. Insertion (**A**) and placement (**B**) of the tracheostomy tube. Cuffed tubes should be inserted with the cuff deflated.

AIRWAY STENTS

There are many different airway stent configurations and materials,[19] and a detailed discussion on all of the possible configurations is outside the scope of this chapter. In the event of any suspected complication, consultation with an expert in the type and anatomic arrangement of the airway stent is recommended.[20] It is important to note that the airway stents may be solid or hollow, may be secured within the lumen or externally, and may or may not communicate via tracheostomy.[19] Complications associated with airway stents include dislodgement, granulation tissue, mucous plugging, bleeding, and crusting.

A solid airway stent renders the patient tracheostomy dependent until the stent is removed because the solid stent blocks the airway above the level of the tracheostomy (**Figure 247-5**). In the event of respiratory failure or distress, focus should be placed on establishing an adequate airway via the tracheostomy in place (see algorithm, Figure 247-2). Although stents may be secured by a variety of methods, dislodgement is a known complication of these devices. If an airway stent becomes dislodged but the tracheostomy tube remains in position, airway security is typically not an issue. Consult the appropriate specialist for extrusion or dislodgement of a stent.

In the case of patients with hollow endoluminal stents, endotracheal intubation can be performed if needed by passing the endotracheal tube through the hollow stent from above. In this scenario and if patient stability allows, one should look for a stent card or other sources of documentation regarding the appropriate size of endotracheal tube to place. In the emergency situation, additional smaller endotracheal tubes should be available. The assistance of a specialist is certainly recommended if patient stability permits.[20]

The mainstay of treatment for symptomatic tracheal stenosis is surgical resection and anastomosis. When surgical treatment is not possible, the option exists for insertion of airway stents as a bridge to surgery, as a treatment for patients who are not surgical candidates, and in cases where there is a long segment of stenosis.[19] Dumon and Montgomery T-tube configurations are the most commonly used silicone stents. The Dumon tube also has bronchial options and is secured endoluminally via studs.[21]

The Montgomery T-tube is a modification of a tracheostomy tube and does not have an inner cannula.[22] Humidification and suctioning of the T-tube are essential to prevent mucous plugging and crusting, which are the most common complications of these devices.[21] Airway obstruction should be addressed by first suctioning both the upper and lower limbs of the T-tube (**Figure 247-6**). If suctioning both limbs of the T-tube does not relieve the obstruction, the T-tube should be removed and the trachea cannulated with an appropriately sized tracheostomy tube or an endotracheal tube. Do not try to use a bag-valve device through the T-tube because most tubes do not take a standard 15-mm connector.[22] Removal requires a strong, steady pull on the T-tube and should only be attempted if the operating surgeon is unavailable or the patient is in airway distress.

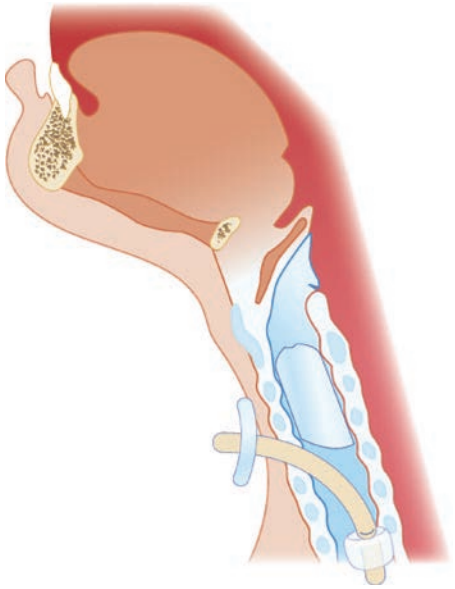


FIGURE 247-5. Relation of the tracheostomy tube to the laryngeal stent. The stent lies within the lumen of the trachea, superior to the tracheostomy tube.

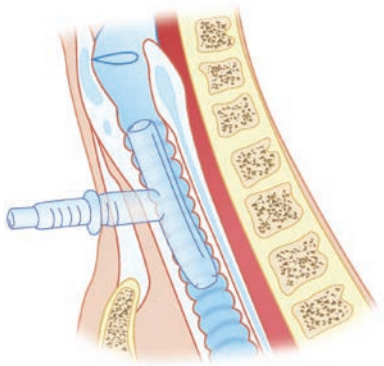


FIGURE 247-6. Suctioning is required of both the upper and lower limbs of the Montgomery T-tube. If necessary, the entire T-tube can be removed.

SPEECH DEVICES

The Passy-Muir valve is a one-way valve that fits directly over the opening of an uncuffed tracheostomy tube and allows the patient hands-free speech. When the patient inhales, the valve opens and allows air to pass into the trachea and lungs.[23] Speech is created when the patient exhales with enough force to close the Passy-Muir valve. The exhaled air is directed around the tracheostomy tube and through the vocal cords (**Figure 247-7**). Because the patient exhales around the tracheostomy tube, **a Passy-Muir valve should never be used with a cuffed tube.** If a patient with a Passy-Muir valve develops signs of airway obstruction or an inability to speak, the speaking device should be removed from the tracheostomy tube so that air can pass freely during both inhalation and

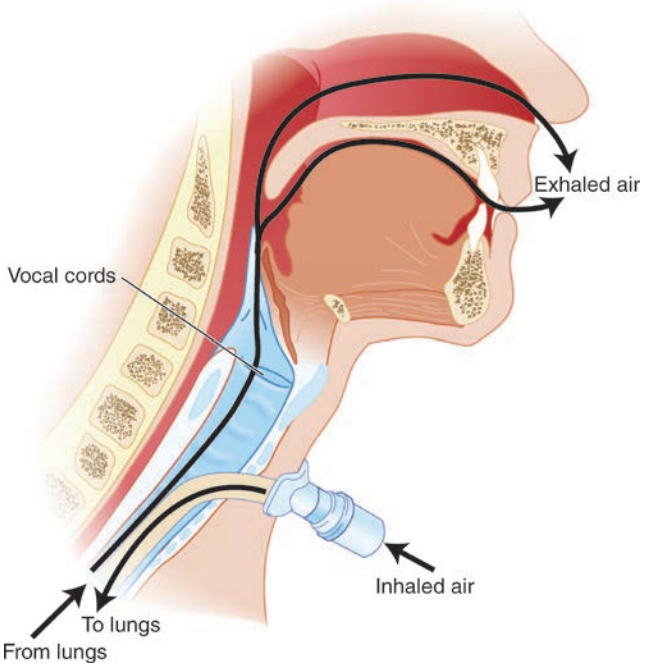


FIGURE 247-7. The Passy-Muir valve is a one-way valve that fits directly on the opening of the tracheostomy tube. Speech is created when the patient exhales as air is passed up through the vocal cords and out of the mouth.

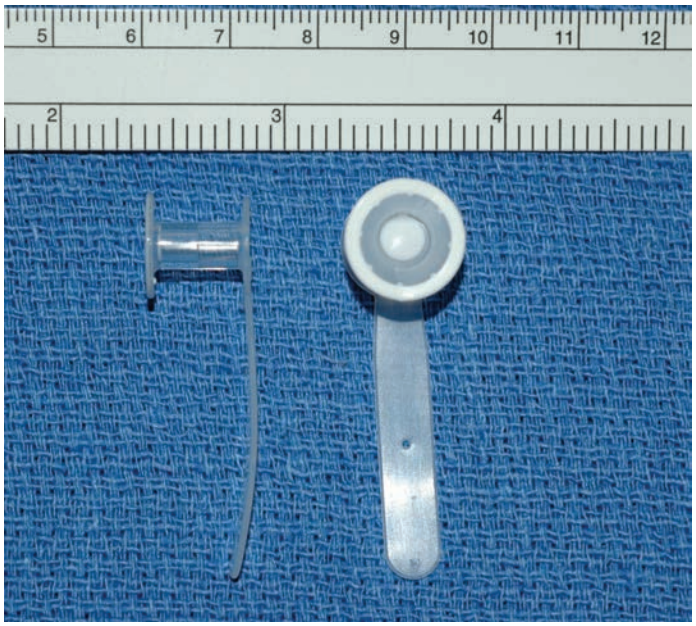


FIGURE 247-8. Tracheoesophageal prosthesis. The bobbin-shaped device is placed with the smaller flange in the esophagus and the tagged flange in the posterior tracheostoma.



FIGURE 247-9. Tracheoesophageal prosthesis in place in a laryngectomy patient. The prosthesis is in place, and the tag is usually held with tape. Finger occlusion of the tracheostoma with exhalation leads to increased airway pressure, which opens the one-way valve and allows air to enter the esophagus. This vibrates and allows the patient to speak.

exhalation. If this does not relieve symptoms, check the tracheostomy tube itself for obstruction.

A **tracheoesophageal prosthesis** allows speech in postlaryngectomy patients. This one-way valve is surgically placed between the posterior wall of the tracheal stoma and the anterior wall of the cervical esophagus. To speak, patients exhale while occluding the stoma with their thumb or finger, thus forcing the exhaled air into the esophagus. The air vibrates the esophagus (as a belch does), and the resultant tone is used to provide speech (**Figures 247-8** and **247-9**).

The most common complication associated with tracheoesophageal prosthetic valves is leakage, either around the valve or through the valve lumen. Both types of leakage may be confirmed by looking at the prosthesis while the patient drinks a colored liquid (e.g., grape juice). Leakage commonly occurs due to enlargement of the tracheoesophageal fistula.[24,25]

Leakage increases the risk of aspiration pneumonia. A temporary solution to a leaking valve begins with removal of the entire prosthesis and replacement with a larger Foley catheter into the tracheoesophageal fistula. This will prevent the tracheoesophageal fistula from closing completely as the fistula contracts in size. Leakage through a voice prosthesis is predominantly due to valve damage caused by fungal colonization or contact of a duckbill-style device against the posterior esophageal wall and is treated by replacement of the prosthesis with a temporary tube (usually a Foley catheter). Once a Foley catheter is placed and secured, the patient is unable to speak. Arrange otolaryngologist follow-up the next day. Do not inflate the balloon on the Foley catheter, as this will interfere with swallowing.

Another common complication with tracheoesophageal prostheses is valve aspiration or valve extrusion. Aspiration results in persistent cough, dyspnea with discomfort, and even respiratory distress. If there is suspicion of aspiration or if the prosthesis is dislodged, obtain a chest radiograph to visualize the radiopaque valve and consult an otolaryngologist. The tracheoesophageal puncture tract will close quickly, typically within 24 to 48 hours after the tube is dislodged. A Foley or red rubber catheter inserted into the tract will maintain its patency. **Do not attempt temporary catheter placement if the tract is <2 weeks old because a false passage may result.**

Specialty Consultation Whenever a patient presents to the ED with a complication due to an airway device, the provider should be able to troubleshoot many of the common problems. If there is concern, it is advisable to consult the appropriate specialist.

Acknowledgment: The author gratefully acknowledges John Gaillard for his contribution to this chapter in the previous edition.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 20

Dermatology

CHAPTER 248

Initial Evaluation and Management of Skin Disorders

William Rushton
William J. Brady

INTRODUCTION

Most dermatologic emergencies presenting to the ED involve skin lesions resulting from infections, irritants, and allergic etiologies, with a smaller subset related to malignancy.[1] Visual pattern recognition is the key to diagnosis. The recommended approach for the diagnosis of a skin disorder in the ED (assuming resuscitation or stabilization is not required) is to:

1. Determine the chief complaint.
2. Obtain a brief history (duration, rate of progression, and location of lesions).
3. Perform the dermatologic examination (morphology and extent of distribution).
4. Formulate the age-appropriate differential diagnosis based on lesion morphology and distribution.
5. Elicit additional concerns from the history (associated complaints, comorbidity, medications, or exposures), and include or exclude syndromes in the differential diagnosis based on this information.
6. Evaluate for systemic involvement, and consider ancillary investigations, if necessary.
7. Obtain dermatologic consultation, if necessary, and arrange for appropriate referral (primary care or dermatologic).

DIAGNOSTIC APPROACH

HISTORY

Determine the chief complaint and obtain a brief history (discomfort, duration, rate of progression, percentage of body surface involvement, and location of lesions). The secondary history should include issues relating to the lesion: morphology, evolutionary nature, rate of progression, and distribution. Associated systemic complaints and mucosal systems must be identified. Ask about exposures, immunizations, toxins, chemicals, foods, animals, insects, plants, and ill contacts. Review sexual history, if appropriate, and medical and family histories. If applicable, obtain a detailed occupational history as industrial exposure may be causative. Asking about medication use, sun exposure, travel history, or particular food ingestion also may yield helpful information. Be sure to include any other housemates or partners in your history of exposures; contact dermatitis can occur from exposure to fragrances or other products that a partner is using.[2] The patient should also be asked about the degree of discomfort of the dermatoses; a painful dermatitis is often a red flag and may not be associated with a self-limiting lesion.[3]

A detailed medication history is important, and particular attention should be paid to recently started drugs or dosage increases. Erythema multiforme, exfoliative dermatitis, photosensitivity reactions, toxic epidermal necrolysis, and vasculitis are common medication-induced drug reactions. Dermal necrosis should prompt consideration of anticoagulant use, whereas a diffuse rash in a patient on sulfa drugs, anticonvulsants, or some antimicrobials may aid the clinician in diagnosing Stevens-Johnson syndrome, drug reactions with eosinophilia and systemic symptoms, or toxic epidermal necrolysis.

EXAMINATION

The patient should be gowned and in a room with adequate lighting and appropriate privacy to allow entire skin examination. Inspect all skin and mucosal surfaces, including hair, nails, scalp, and mucous membranes. Then evaluate the specific skin lesions. A magnifying lens and a portable light are helpful aids.

Examine the skin systematically. Determine the **distribution, pattern, arrangement, morphology, extent, and evolutionary changes** of the lesions. **Distribution** is the location of the skin findings, and the **pattern** is their anatomic, functional, and physiologic arrangement. For example, a unilateral band-like arrangement of lesions on the thorax suggests varicella-zoster virus infection. Skin diseases often present with a predilection for certain body areas; the distribution of lesions will assist in narrowing the diagnostic possibilities. From the anatomic perspective, the skin surfaces that are usually considered as separate areas of distribution are generalized body; face and scalp; trunk and axillae; groin and skin folds; and hands, feet, and nails. The extremities may be further subdivided into upper versus lower, proximal versus distal, wrists versus ankles, and hands versus feet.

In a patient with diffuse erythema in whom toxic shock syndrome is suspected, identify the presence of a foreign body such as a retained tampon. Petechiae should prompt investigation for meningococcemia or Rocky Mountain spotted fever. Rashes on exposed portions of the skin should prompt inquiries about sun exposure, jewelry, topical agents, or exposures. See **Table 248-1** for a differential diagnosis of skin lesions as a function of location, including both distribution and pattern considerations.

Use the burn **rule of nines** (see Chapter 217, "Thermal Burns") to estimate the degree of skin involvement in disorders with widespread distribution. This calculation also may be used to determine the amount of topical medication required for a specific treatment course or whether an oral medication might be more appropriate. Extensive erythroderma (often >90% of body surface area) is a dermatologic emergency, particularly when accompanied by a fever. Severe erythroderma can represent underlying severe infectious dermatitis, toxic shock syndrome, cutaneous T-cell lymphoma, drug reaction, psoriasis, or seborrheic dermatitis.

Lesion arrangement refers to the symmetry and configuration. Bilateral symmetry suggests a systemic internal event or symmetric external exposure, as seen in erythema multiforme, with plaque-like lesions on the flexor surfaces of the extremities, or contact dermatitis related to a lotion application. An asymmetric arrangement supports a localized process. *Configuration* may apply to a single lesion with reference to its individual features or, alternatively, to multiple lesions and their relation to one another. For instance, internal configuration is illustrated by the relation between the central papule relative to the erythematous ring in the target lesion of erythema multiforme; on the total-body scale, configuration is demonstrated by clustering of lesions in a herpesvirus infection or by a linear arrangement as with a reaction from poison ivy or oak. Other terms used to describe the lesion configuration are listed in **Table 248-2**.

Recognition of the primary lesion is vital in establishing the diagnosis; the use of the primary lesion's **morphology** is very important regarding the generation of an appropriate differential diagnosis and ultimately the correct dermatologic diagnosis. The primary lesion is the one that has not been altered by secondary issues, including healing, complicating infection, medication application, or scratching. Examples of primary skin lesions are macules, papules, nodules, tumors, cysts, plaques, wheals, vesicles, bullae, and pustules. Careful attention should be paid

TABLE 248-1 Differential Diagnosis Relative to Lesion Distribution and Pattern

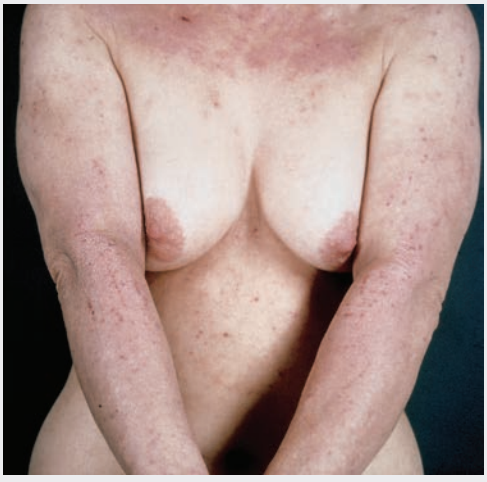
Distribution and Pattern	Differential Diagnosis
Flexor surfaces	Atopic dermatitis, candidiasis, eczema, ichthyosis
Sun exposure (face, upper thorax, distal extremities)	Sunburn, photosensitive drug eruption, photosensitive dermatitis, systemic lupus erythematosus, viral exanthem, porphyria
Distal extremities	Viral exanthem, atopic or contact dermatitis, eczema, Rocky Mountain spotted fever, gonococcemia
Front and back of chest	Pityriasis rosea, secondary syphilis, drug eruption, atopic or contact dermatitis, psoriasis
Clothing covered (thorax and distal lower extremities)	Contact dermatitis, psoriasis, folliculitis
Acneiform (face and upper thorax)	Acne, drug-induced acne, irritant dermatitides

to a nonblanching lesion. Secondary lesions have had their appearance altered due to disease evolution or various external factors, as noted earlier, and include crusts, scales, fissures, erosions, ulcerations, excoriations, atrophy, scarring, and lichenification. See **Table 248-3** for a listing and descriptions of the various morphologic descriptors of dermatologic lesions; see **Tables 248-4** and **248-5** for a differential diagnosis

TABLE 248-2 Lesion Configuration Descriptors

Descriptor	Configuration
Annular	Ring-like or pertaining to the outer edge
Arcuate	Curved or pertaining to the curve
Circinate	Circular
Confluent	Blending together
Dermatomal	Belt-like or limited to one side of the body in anatomic dermatome
Discoid	Solid, round, slightly raised, or pertaining to a disk
Discrete	Separate or individual
Grouped	Clustered
Guttate	Scattered
Gyrate	Coiled or winding
Herpetiform	Creeping
Iris	Concentric circles
Linear	In a line
Polycyclic	Overlapping circles or borders of irregular curves
Retiform	Net-like
Serpiginous	Snake-like

TABLE 248-3 Lesion Morphology

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Excoriation	Linear marks from scratching	Secondary	Flat	
Erosion	Ruptured vesicle or bulla with denuded epidermis	Secondary	Depressed	

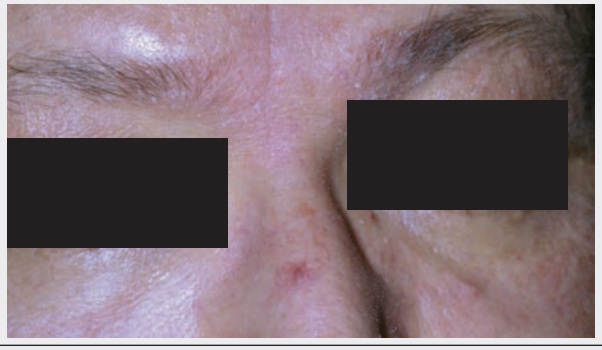
(*Continued*)

TABLE 248-3 Lesion Morphology (*Continued*)

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Fissure	Linear cracks on skin surface	Secondary	Flat	
Ulcer	Epidermal or dermal tissue loss	Secondary	Depressed	
Macule	Flat, circumscribed discoloration ≤1 cm in diameter; color varies	Primary	Flat	
Petechiae	Nonblanching purple spots <2 mm in diameter	Primary	Flat	

(*Continued*)

TABLE 248-3 Lesion Morphology (*Continued*)

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Sclerosis	Firm, indurated skin	Secondary	Flat or elevated	
Telangiectasia	Small, blanchable superficial capillaries	Primary	Flat	
Purpura	Nonblanching purple discoloration of the skin	Primary	Flat	
Abscess	Tender, erythematous, fluctuant nodule	Primary	Elevated	

(*Continued*)

TABLE 248-3 Lesion Morphology (*Continued*)

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Cyst	Sack containing liquid or semi-solid material	Primary	Elevated	
Nodule	Palpable solid lesion <1 cm in diameter	Primary	Elevated	
Tumor	Palpable solid lesion >1 cm in diameter	Primary	Elevated	 A  B

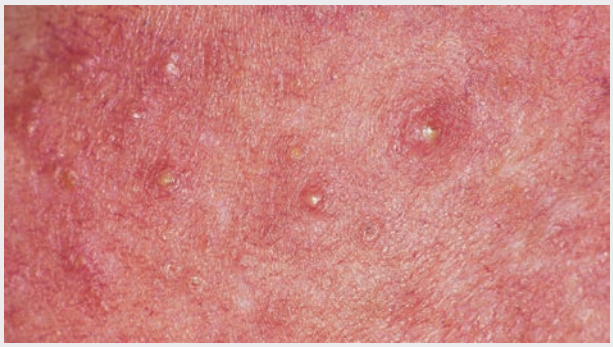
(*Continued*)

TABLE 248-3 Lesion Morphology (*Continued*)

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Scar	Sclerotic area of skin	Secondary	Flat or elevated	
Wheal	Transient, edematous papule or plaque with peripheral erythema	Primary	Flat or elevated	
Vesicle	Circumscribed, thin-walled, elevated blister <5 mm in diameter	Primary	Elevated	

(*Continued*)

TABLE 248-3 Lesion Morphology (*Continued*)

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Bulla	Circumscribed, thin-walled, elevated blister >5 mm in diameter	Primary	Elevated	
Pustule	Vesicle containing purulent fluid	Primary	Elevated	
Papule	Elevated, solid, palpable lesion <1 cm in diameter; color varies	Primary	Elevated	

(*Continued*)

TABLE 248-3 Lesion Morphology (*Continued*)

Descriptor	Morphology	Lesion Nature	Height Relative to Adjacent Skin	Image
Plaque	Flat-topped elevation formed by confluence of papules >0.5 cm in diameter	Primary	Elevated	
Comedo	Papule with an impacted pilosebaceous unit	Primary	Elevated	

Source: Images reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. © 2005, McGraw-Hill, Inc., New York; and Fleischer AB Jr, Feldman SR, McConnell CF, et al: *Emergency Dermatology: A Rapid Treatment Guide.* © 2002, McGraw-Hill, Inc., New York.

of the various skin disorders relative to primary and secondary lesion morphologies.

DIAGNOSTIC TECHNIQUES

A potassium hydroxide preparation is used in patients with suspected molluscum contagiosum and dermatophytic infections. The test is performed on loose skin scales, nail parings, subungual debris, short residual hairs, or small pearly globules (from a molluscum body). Test steps are in **Table 248-6**.

The material is then viewed under a microscope at low power, with the condenser and light at low levels. As the slide is scanned, rapidly focus up and down. True hyphae (**Figure 248-1**), seen in dermatophytic infections, are long, branching, green rods of constant width that cross the borders of epithelial cells. Molluscum bodies are oval discs with homogeneous cytoplasm (**Figure 248-2**). In hair fragments,

TABLE 248-4 Differential Diagnosis of Selected Skin Disorders Relative to Primary Lesion Morphology*

Lesion Morphology	Differential Considerations	Images
Macule	Drug eruption (fixed or photosensitive), nevus, tattoo (ink), rheumatic fever, syphilis (secondary), viral exanthema, toxic or infectious erythemas, meningococcemia (early), external trauma (ecchymosis), vitiligo, tinea versicolor, cellulitis (early)	
Papule	Acne, basal cell carcinoma, melanoma, nevus, warts, molluscum contagiosum, skin tags, atopic dermatitis, urticaria, eczema, folliculitis, insect bites, vasculitis, psoriasis, scabies, *Toxicodendron* dermatitis (poison ivy, oak, sumac), erythema multiforme, varicella (early), gonococcemia	
Plaque	Eczema, pityriasis rosea, tinea corporis and versicolor, psoriasis, seborrheic dermatitis, urticaria, syphilis (secondary), erythema multiforme	

(*Continued*)

TABLE 248-4 Differential Diagnosis of Selected Skin Disorders Relative to Primary Lesion Morphology* (*Continued*)

Lesion Morphology	Differential Considerations	Images
Nodule	Basal cell, squamous cell, or metastatic carcinoma; melanoma; erythema nodosum; furuncle; lipoma; warts	
Wheal	Urticaria, angioedema, insect bites, erythema multiforme	
Pustule	Acne, folliculitis, gonococcemia, hidradenitis suppurativa, herpetic infection (herpes simplex, herpes zoster, varicella), impetigo, psoriasis, rosacea, pyoderma gangrenosum	

(*Continued*)

TABLE 248-4 Differential Diagnosis of Selected Skin Disorders Relative to Primary Lesion Morphology* (*Continued*)

Lesion Morphology	Differential Considerations	Images
Vesicle	Herpetic infection (herpes simplex, herpes zoster, varicella), impetigo, *Toxicodendron* dermatitis (poison ivy, oak, sumac), thermal burn, friction blister, toxic epidermal necrolysis, bullous pemphigoid, pemphigus vulgaris	
Bulla	Bullous impetigo, *Toxicodendron* dermatitis (poison ivy, oak, sumac), thermal burn, friction blister, toxic epidermal necrolysis, bullous pemphigoid, pemphigus vulgaris	

*This list is not exhaustive, but it represents the more common syndromes likely to be encountered by the emergency physician.

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the organisms appear as small, round spores packed closely within the hair shaft.

Scabies and lice preparations are useful in patients with possible infestation. In scabies infestations, the rash itself may resemble other dermatologic syndromes; microscopic analysis will confirm the diagnosis. The donor site for skin specimen selection is very important. The best sites include burrows (10 mm, elongated papule with a pustule or vesicle) and papules on the fingers, wrists, and elbows (**Figure 248-3**). Within the vesicle or pustule, a small black dot is noted, which is the mite. The point of the scalpel is scraped across the lesion while holding the skin taut; the mite is then removed. A single drop of mineral oil may be applied to the blade to ensure that the scrapings adhere to the instrument. The material is then placed on the microscope slide with an additional drop of mineral oil; gentle pressure on the coverslip will flatten thick specimens. Using low power, the slide is scanned for presence of the mite, eggs, or feces. Mites are eight-legged creatures that are easily identified on thin smears; thick specimens may require additional viewing to look for the mite. Additional findings supportive of the diagnosis include eggs (smooth ovals) and feces (clusters of red-brown pellets; **Figure 248-4**). Lice are usually found on the scalp, eyelashes, and pubic areas and may be visible to the unaided eye (**Figure 248-5**).

The **Tzanck smear**, useful in blistering disorders, assists in establishing the diagnosis of a herpes infection: herpes simplex, herpes zoster, and varicella. The choice material for examination is obtained from the

TABLE 248-5 Differential Diagnosis of Selected Skin Disorders Relative to Secondary Lesion Morphology*

Lesion Morphology	Differential Considerations	Images
Scales	Psoriasis, pityriasis rosea, toxic and infectious erythemas, syphilis (secondary), dermatophytic infection (tinea), tinea versicolor, xerosis (dry skin), thermal burn (first degree)	
Crusts	Eczema, dermatophytic infection (tinea), impetigo, contact dermatitis, insect bite	
Erosions	Candidiasis, dermatophytic infection (tinea), eczema, toxic epidermal necrolysis, toxic-infectious erythemas, erythema multiforme, primary blistering disorders (bullous pemphigoid and pemphigus vulgaris), brown recluse spider envenomation	
Ulcers	Aphthous lesions, chancroid, decubitus ulcer, thermal or friction injury, subacute or chronic ischemia, malignancy, chancre (primary syphilis), primary blistering disorders (bullous pemphigoid and pemphigus vulgaris), brown recluse spider envenomation, pyoderma gangrenosum, stasis ulcer, factitial ulcer	

*This list is not exhaustive, but it represents the more common syndromes likely to be encountered by the emergency physician.

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TABLE 248-6 Potassium Hydroxide (KOH) Examination

- Collect scale with a scalpel edge, place in small heap on slide, cover with coverslip.
- Apply KOH 10%–40% solution to edge of coverslip; it will be drawn under coverslip.
- Apply heat to underside of slide (match or lighter) until bubbles appear under coverslip.
- Visualize under 10× magnification.

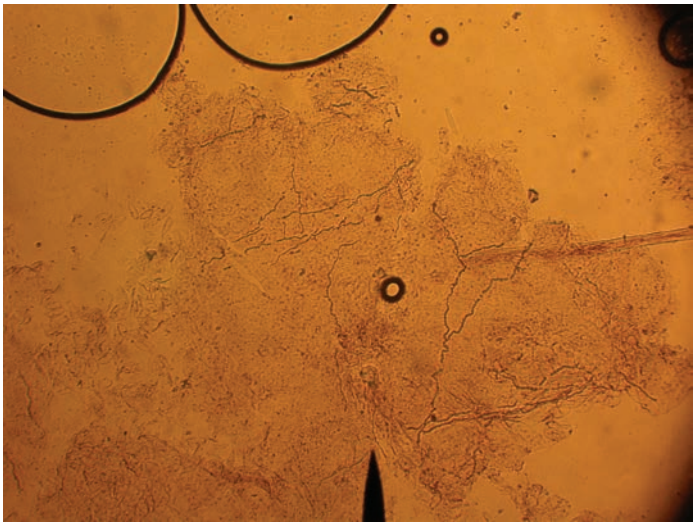

FIGURE 248-1. Hyphae in scraping from tinea pedis. [Photo contributed by University of North Carolina Department of Dermatology.]

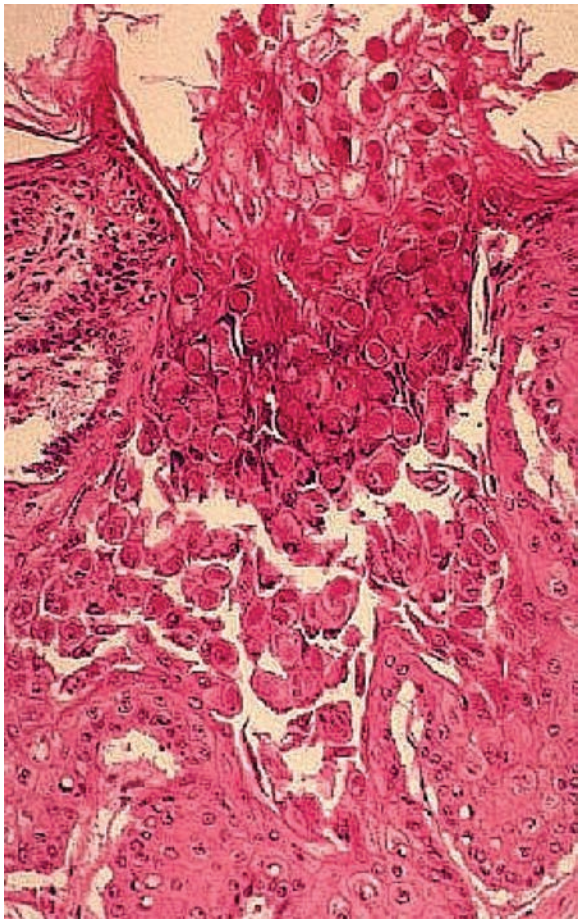

FIGURE 248-2. Molluscum bodies. [Reproduced with permission from the Centers for Disease Control and Prevention Public Health Image Library: http://phil.cdc.gov/phil/home.asp.]



FIGURE 248-3. Classic burrows of scabies. [Reproduced with permission from Fleischer AB Jr, Feldman SR, McConnell CF, et al: *Emergency Dermatology: A Rapid Treatment Guide*. © 2002, McGraw-Hill, Inc., New York.]

base of a recently unroofed lesion; purulent fluid at the base of the lesion is removed with a scalpel and placed on a microscope slide. The material is allowed to air dry and then is stained with Giemsa or Wright stain. Using low power, the slide is scanned for epithelial cells. Multinucleated giant cells (**Figure 248-6**), indicative of a herpes infection, are a syncytium of epidermal cells with multiple overlapping nuclei. The presence of the multinucleated giant cell does not distinguish between herpes simplex, herpes zoster, and varicella syndromes.

Wood's light examination is helpful in several different situations, including erythrasma (a superficial *Corynebacterium* infection of moist skin in the groin, axilla, and web spaces), fungal infections caused by *Malassezia* species or *Microsporum* species, certain pseudomonal skin infections, and porphyria cutanea tarda. Wood's light is an ultraviolet source that emits light at a wavelength of 365 nm. The following fluorescent findings are noted in these conditions: erythrasma, red or pink; tinea, green or yellow; *Pseudomonas*, yellow or green; and porphyria cutanea tarda, urine fluoresces orange or red.

Ancillary studies may also be required to assess for systemic involvement. Fever and leukocytosis may be indicative of an underlying infectious disorder or an underlying autoimmune reaction. In patients on anticonvulsants, elevated transaminases may represent underlying DRESS syndrome (drug reaction with eosinophilia and systemic symptoms).[3] Furthermore, disseminated intravascular coagulation, thrombocytopenia, and acute kidney injury may alert the astute clinician to underlying bacteremia or toxic shock syndrome.[3] Imaging may be required to rule out foreign bodies or to assess the depth of tissue involvement in conditions such as Fournier's gangrene.

ED TREATMENT

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids are the treatment of choice for some generalized conditions and are discussed in the chapters dealing with specific diagnoses. Some severe widespread dermatologic syndromes, such as erythema multiforme, toxic epidermal necrolysis, and vasculitis, are best treated with systemic steroids only after consultation with a dermatologist. Other disorders, including urticaria, angioedema, *Toxicodendron* dermatitis (rhus, poison ivy, or poison oak), and other contact or allergic

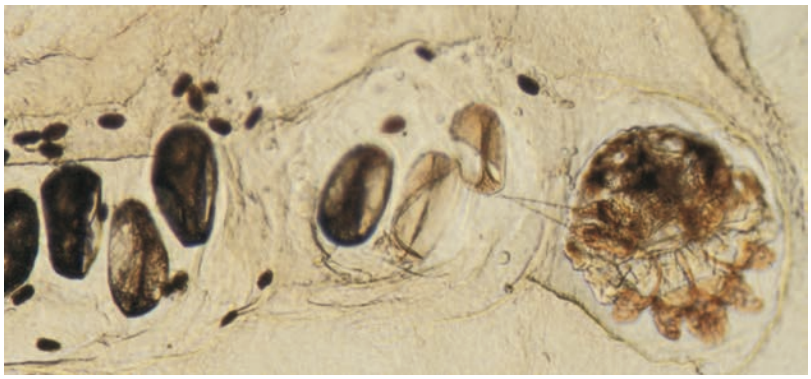

FIGURE 248-4. Microscopic view of a scabies mite with visible eggs and feces. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]



FIGURE 248-5. Adult head lice. [Reproduced with permission from the Centers for Disease Control and Prevention Public Health Image Library: http://phil.cdc.gov/phil/home.asp.]

disorders, are potential indications for systemic corticosteroids when an extensive area of skin is involved. Patients with severe disease can see significant relief with oral corticosteroids within 12 to 24 hours.[4] Patients with poison ivy or oak eruptions who require systemic steroids should be treated with oral prednisone (1 milligram/kg body weight) for 2 weeks.[5] Other contact or allergic dermatitides may benefit from an abbreviated course (4 days) of oral prednisone. Efficacy of a short course of corticosteroids in addition to antihistamines remains controversial. A 1995 randomized controlled study showed improvement within 48 hours with 20 milligrams of prednisone twice a day for a total of 5 days.[6] A more recent randomized trial, however, showed no difference with 40 milligrams of prednisone daily for 4 days.[7] Expert guidelines still recommend prednisone for refractory cases of acute urticaria, although specific doses and duration are not well defined.[8] However, oral corticosteroids are relatively contraindicated, or must be used with great care in those with diabetes, hypertension, active peptic ulcer disease, psychiatric disease, and immunodeficiency. Follow-up within 2 to 3 days with the primary care physician or a dermatologist is needed if oral corticosteroids are prescribed to patients with these comorbidities.

TOPICAL CORTICOSTEROIDS

Topical corticosteroids are powerful and useful tools in the management of dermatologic disease. Numerous agents are available for use. They differ in concentration, base components, and cost. Familiarity with a single

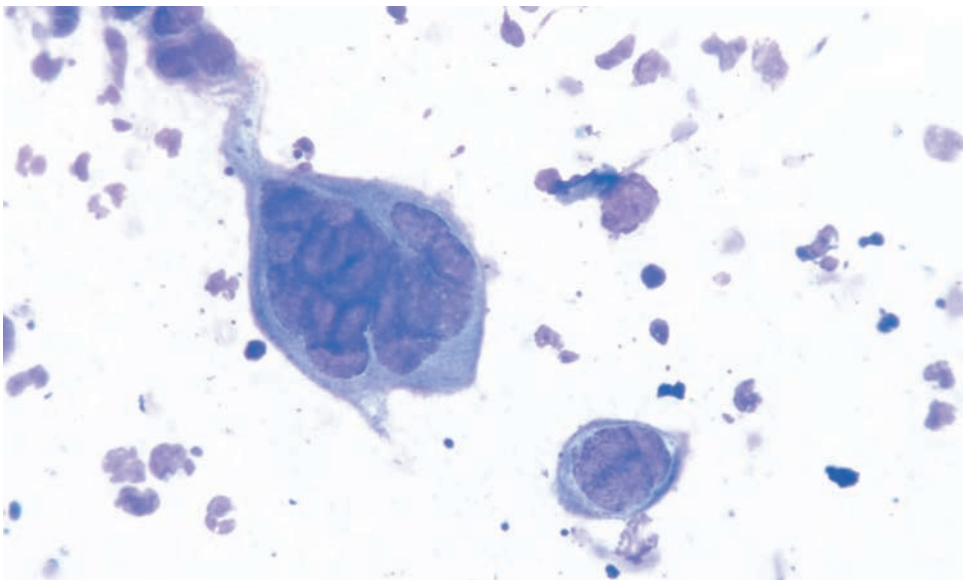

FIGURE 248-6. Tzanck smear under microscopy showing a multinucleated giant cell, indicative of a herpetic infection. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

TABLE 248-7 Examples of Topical Corticosteroid Agents by Potency Group*

U.S. Classification	British Classification	Representative Topical Agent	Formulation
1: Superpotent	1: Very Potent	Clobetasol (Temovate®, Clobex®) Halobetasol (Halonate®, Ultravate®) Betamethasone (Diprolene®)	0.05% cream or ointment
2: Potent	2: Potent	Fluocinonide (Lidex®, Vanos®) Halcinonide (Halog®) Mometasone (Elocon®)	0.05% ointment 0.1% cream 0.1% ointment
3: Upper mid-strength		Betamethasone (Diprolene®) Fluticasone (Cutivate®) Triamcinolone (Kenalog®)	0.05% lotion 0.005% ointment 0.1% ointment
4: Mid-strength		Mometasone (Elocon®)	0.1% cream, lotion
5: Lower mid-strength	3: Moderate	Betamethasone (Diprolene®) Fluocinolone (Synalar®) Fluticasone (Cutivate®)	0.1% cream 0.025% cream 0.05% cream
6: Mild		Alclometasone (Alclovate®) Desonide (Desonate®, Desocort®) Triamcinolone (Kenalog®)	0.05% cream or ointment 0.05% cream 0.025% cream
7: Least Potent	4: Mild	Hydrocortisone	1% or 2.5% cream, lotion or ointment

Note: Trade names vary. Strength classification can vary. Strength also depends upon the product itself, amount applied, and nature of skin at the application site.

*Preparations are listed by U.S. and British potency groups: Group 1 is most potent; group 7 (British 4) is least potent.

agent in each potency class is sufficient to treat any steroid-responsive skin ailment safely and effectively. Corticosteroid potency or strength (i.e., the anti-inflammatory property) is measured by the agent's ability to induce vasoconstriction. Agents' strengths are rated by vasoconstricting ability on a scale of 1 to 7; group 1 agents are the most powerful corticosteroids, and group 7 medications are the least potent (**Table 248-7**). In general, ointments are more potent than creams or lotions.

Topical Corticosteroid Strength Marked variation in potency is seen across various corticosteroids, whereas much smaller differences in strength are encountered for different concentrations of individual agents. Many corticosteroids are fluorinated. Fluorination greatly increases the potency, but also increases the risk of adverse reactions, and **fluorinated formulations should not be used in pregnancy**.

Use of the appropriate-strength topical steroid is strongly encouraged at the start of therapy. Starting with a less powerful agent is not likely to spare the patient from potential adverse effects or to produce adequate control of the disease. **Hydrocortisone**, perhaps the most frequently used topical corticosteroid in the outpatient setting, is available over the counter in strengths up to 1% and by prescription in strengths to a maximum of 2.5%. Hydrocortisone is safe and may be used on most body surfaces, including the face, genitalia, flexure creases, and intertriginous zones. It also is safe for use in infants and children. For the treatment of diseases involving the palms and soles, hydrocortisone is a poor choice, because the thickened skin does not allow adequate penetration of this relatively low-potency steroid. Corticosteroids of moderate potency, including **triamcinolone acetonide and fluocinolone acetonide**, are useful in treating severely inflamed skin and the thicker skin of the scalp, trunk, extensor surfaces, palms, and soles. These agents should not be applied to the face or genitals or used in infants because of the risk of skin atrophy. See **Table 248-8** for recommendations on the potency of corticosteroid to use in treating various dermatologic diseases. When using agents found in group 6 or 7, consultation with a dermatologist may be advised.

Different skin surfaces respond differently to topical corticosteroid therapy; this differential response relates to the absorption of the steroid into the deeper tissues. The relatively thin skin surfaces of the face respond very rapidly to the use of group 7 agents, whereas the thicker skin of the palms and soles requires a highly potent steroid. Irritations for which a low-potency agent may provide the same treatment effectiveness as a higher potency agent include those involving raw, inflamed skin (such skin absorbs medication more rapidly and readily); treatment regions with skin surfaces in frequent contact, such as intertriginous areas (the apposition of two skin surfaces produces enhanced absorption of drug, similar to the effect of an occlusive dressing); and areas of skin under tight clothing, such as the diaper area (absorption of the agent is enhanced due to the occlusive effect of the garment). In general, lower potency agents are acceptable in these situations.

Application of Topical Steroids The application of creams, ointments, gels, and lotions is relatively straightforward. The medication is applied in a thin layer and should be massaged daily into the skin, as directed. Washing the skin before corticosteroid application is unnecessary. Advise patients to follow directions closely both early and late in the treatment course. Using extra medication per dose or applying medication more frequently early in the treatment period is not desirable; likewise, reducing the frequency of application or decreasing the amount of medication as the disease process responds to therapy can cause relapse. Optimal application regimens have not been determined for topical corticosteroids in most dermatologic syndromes. The more potent agents are best applied two to three times daily for 1 to 2 weeks followed by a drug-free week; additional therapy may be required as determined by the disease and by the particular patient's response to the initial therapy. Agents from the less potent steroid groups may be applied three times daily for 2 to 4 weeks followed by a 7-day steroid-free period.

Prescribing the Correct Amount of Topical Steroid Determining the correct amount of topical steroid to prescribe is at times difficult.

TABLE 248-8 Recommended Corticosteroid Potency for Treatment of Various Dermatologic Diseases

Groups 1 and 2	Groups 3 to 5	Groups 6 and 7
Psoriasis	Atopic dermatitis	Nonspecific dermatitis of face, eyelids, and perineum
Eczema of hand (severe)	Stasis dermatitis	
Poison ivy dermatitis (severe)	Seborrheic dermatitis Tinea	
Atopic dermatitis (severe)	Scabies Nonspecific dermatitis of face (severe)	

TABLE 248-9 Determination of the Correct Amount When Prescribing Topical Steroids

- Use burn rule of nines to determine percentage of body surface area affected.
- Percentage of body surface area × 30 = grams of topical corticosteroid per application.
- Application times per day × number of days of treatment = total number of applications.
- Total grams to prescribe = [% body surface area × 30] × [times per day × number of days].

The burn rule of nines may be used to estimate the amount of topical corticosteroid to prescribe. Calculate the percentage of body surface area requiring therapy and then multiply the percentage by a correction factor of 30. This calculation provides the amount of topical corticosteroid in grams for a single application. Next, determine the number of administrations required in the treatment course. For example, a three-times-daily regimen for a duration of 10 days requires 30 applications. The number of applications is multiplied by the grams required for a single dose to yield the total amount to be prescribed (**Table 248-9**). In general, 9 grams of topical steroid cover 9% of the body surface area for 1 day with a thrice-daily application. See **Table 248-10** for a description of the amount of topical corticosteroid to be dispensed relative to the coverage area and duration of therapy.

Avoid Tachyphylaxis *Tachyphylaxis* refers to the decrease in responsiveness to a drug as a result of enzyme-mediated events. The term is used in relation to topical corticosteroids to describe the early development of tolerance to vasoconstricting ability. In general, vasoconstriction has been demonstrated to decrease progressively over time after a topical steroid has been applied. Such reductions in strength due to tolerance are encountered as soon as 4 days into the treatment course in all potency groups, but are thought to be more important for corticosteroids in groups 1 and 2. A reasonable strategy to counter the development of tachyphylaxis is the use of interrupted application schedules. An interrupted treatment course might include an initial three-times-daily application for 2 weeks, followed by 1 week without use of the drug, and then a repeat of the cycle.

ANTIHISTAMINES

Antihistamines (histamine-1 antagonists) are frequently used in clinical practice to control pruritus. These drugs include first-generation antihistamines such as diphenhydramine and hydroxyzine as well as second-generation antihistamine agents, including astemizole, cetirizine, fexofenadine, and loratadine.[9-11] Second-generation histamine-1 antihistamines, while purporting a longer duration of action, do not have the therapeutic sedation found in the first-generation class. Placebo effect and verbal cues have also been implicated in reducing pruritus.[12] True refractory cases of pruritus may require drugs treating anti–immunoglobulin E antibodies, mast cell modulators, mast cell mediator blockers, and immunomodulators; however, consultation with a dermatology expert is advised before commencement of these agents.[13]

The use of topical antihistamine preparations is discouraged, because these agents are readily absorbed and dosing is difficult to predict. See **Table 248-11** for suggested dosing, administration schedules, and routes of therapy for these antihistamines. Histamine-2 antagonists (ranitidine or famotidine) also have demonstrated some benefit in patients with a true histamine allergic-mediated event, in particular urticaria, and therefore are recommended in combination with histamine-1 antagonists in the more severe allergic reactions.

Numerous other antipruritic therapies are recommended, including Domeboro™ solution (aluminum sulfate diluted 1:10 with water) soaks and oatmeal baths.

TABLE 248-10 Amount of Corticosteroid Cream to Dispense*

Body Area	Suggested Potency	Amount to Dispense (grams)
Face	Low	45
Arm	Intermediate or low	90
Leg	Intermediate or low	180
Hand or foot	Intermediate or low	45
Forearm	Intermediate or low	45
Chest or back	Intermediate or low	180

*Based on application three times a day for 10 days of therapy.

TABLE 248-11 Antihistamines Useful in the Management of Dermatologic Disease

Medication (trade name)	Adult Dosage	Pediatric Dosage
Diphenhydramine (Benadryl®)	25–50 milligrams PO/IV/IM four times a day	5 milligrams/kg/d PO/IV/IM in four divided doses; maximum dose, 300 milligrams/d
Hydroxyzine (multiple trade names)	25–100 milligrams PO three or four times a day	2 milligrams/kg/d PO in four divided doses
Cetirizine* (Zyrtec®)	5–10 milligrams PO once a day	For children ≥6 y, 5–10 milligrams PO once a day†
Fexofenadine* (Allegra®)	60 milligrams PO twice a day	For children ≥6 y, 30 milligrams PO twice a day
Loratadine* (Claritin®)	10 milligrams PO once a day	For children ≥6 y, 10 milligrams PO once a day†
Famotidine (Pepcid®)	20 milligrams PO twice daily	0.5 milligram/kg/d in two divided doses; maximum dose, 40 milligrams/d
Ranitidine (Zantac®)	150 milligrams PO twice daily	5–10 milligrams/kg/d PO in two divided doses; maximum dose, 300 milligrams/d

*Indication limited to chronic idiopathic urticaria (see package inserts for details).

†Pediatric use is recommended only in children ≥6 years old (see package inserts for details).

ANTIMICROBIAL AGENTS

Topical antibacterial agents are used primarily as adjuncts to wound dressing and are rarely useful as primary therapy for superficial bacterial infections of the skin. The exception to this statement is topical mupirocin, which is as effective as oral antimicrobial agents in the management of impetigo. For wound dressing, the agents commonly used include polymyxin B, bacitracin, neomycin, and silver sulfadiazine. **Do not use silver sulfadiazine on the face because it will stain.** When reapplying silver sulfadiazine, thoroughly wipe off the prior medication before applying a new dose to avoid silver staining of the skin. Benefits of topical antibacterial agents include reduced adherence of bandaging material to the wound, reduced coagulum, and decreased bacterial colonization. The impact on the rate of wound healing and the prevention of wound infection is less well characterized. Another application of topical antibacterial agents is in the treatment of aphthous stomatitis, for which oral tetracycline rinses are used.

Other disorders treated with topical agents include *Candida* infections, dermatophyte infections, herpes simplex, and lice infestations and scabies. Diagnostic features and specific treatment are discussed in other chapters by the specific diagnosis.

NONANTIMICROBIAL TOPICAL AGENTS

In general, the maxim "If it's dry, wet it, and if it's wet, dry it" applies to the initial treatment of many rashes. Water, protein, and lipid losses characterize dry skin diseases. Emollient creams and lotions restore water and lipids to the epidermis, hasten the healing process, and reduce pruritus and pain. Emollients are moisturizers that reduce skin dryness and decrease skin friction and the sensation of tightness. In patients with chronic drying dermatitides, ointments are best, particularly in the winter months. In warm climates, less viscous, less oily preparations, such as a cream, are better tolerated. Open wet dressings using tap water or normal saline not only reduce discomfort due to the drying but also cleanse the skin by painlessly loosening crusts and exudates. The various

wet cutaneous syndromes involve similar protein and lipid losses due to excessive flow of transudative or exudative fluid from the diseased skin with leaching of the complex macromolecules of the epithelial cells. Drying agents retard this flow of fluid and associated biologic materials from the body, thus assisting in the curative process.

Capsaicin, a topical agent derived from chili peppers that affects the release of substance P, can desensitize local nerve fibers and has been recommended as an antipruritic agent.[14] A topical preparation of 0.025% three times a day for up to 4 weeks is well tolerated by most patients. Capsaicin is not recommended for patients under 10 years of age.[14] Topical local anesthetic treatments such as pramoxine 1% or 2.5% or the mixture of lidocaine and 2.5% cream have been reported in case series to improve pruritus; however, studies with high level of evidence are lacking, and the long-term safety profile is unknown.[15]

Topical Agent Medication Base (Vehicle) The **vehicle,** or medication base, is the substance in which the active ingredient is dispersed. The base determines the rate at which the active ingredient is absorbed through the skin. Components of some bases may cause irritation or allergy.

Creams, a mixture of oils, water, and preservative, are white and greasy in texture. Creams are the most versatile vehicle and can be applied to any body surface area. They are particularly useful in the intertriginous areas. Creams are best used for acute therapy only; chronic application may cause excessive drying. Some patients are allergic to the preservatives in creams; in these patients, consider switching to an ointment preparation of the medication.

Ointments are composed of greases such as petroleum jelly and are free of preservative. Little water is added to this vehicle. Ointments are translucent and, when applied to the skin, remain greasy. This greasy consistency lubricates particularly dry lesions. In general, ointment vehicles allow deeper tissue penetration compared with cream bases. Ointments also are occlusive, providing very thorough coverage with deep tissue penetration and allowing little movement in moisture and other material into and out of the skin. Acute exudative syndromes and intertriginous areas of the body should not be treated with topical steroids formulated using an ointment vehicle.

Gels are greaseless mixtures of propylene glycol and water and at times contain alcohol. Gels have a translucent appearance and are described as "sticky." Alcohol-containing gels are best for acute exudative lesions, such as poison ivy dermatitis, whereas alcohol-free combinations should be used for dry, scaling conditions. In denuded areas, the alcohol component may cause discomfort. Gels are sometimes preferred for the scalp, because they do not alter the hairstyle and are cosmetically tolerable.

Solutions or lotions may contain water or alcohols in addition to other agents. They are clear or milky in appearance and are most useful for the scalp and other dense hair-bearing areas because they leave no significant residue on the hair. In denuded areas, the alcohol component may cause discomfort.

Some topical steroids are available as *foams*. Clobetasol (a very potent topical steroid) is safe and effective as a foam. It is important to note that the absorption rate of clobetasol is greater for the foam vehicle formulation than for the topical solution.[16]

Topical Agent Toxicity Topical agents with certain active ingredients must be used with caution. These ingredients are often very effective, but the delivery is uncontrolled. Although the patient can control the amount and frequency of application, the actual amount of systemic absorption is not easily managed. For instance, certain agents are well absorbed through normal skin and mucous membranes, whereas other medications are absorbed only through irritated skin or mucosa. Topical formulations containing agents absorbed through irritated skin include the Lidoderm™ patch (containing lidocaine), Caladryl™ lotion (containing pramoxine, a local anesthetic), Bengay™ (containing methyl salicylate), and Icy Hot™ (containing menthol and methyl salicylate). Reports of significant toxicity, including death, have been reported with these and similar agents when excessively applied topically.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 249

Generalized Skin Disorders

William J. Brady
Amit Anil Kumar Pandit
Mark R. Sochor

INTRODUCTION

This chapter describes selected serious generalized skin disorders in adults and discusses their dermatologic diagnosis and treatment. Covered are erythema multiforme, toxic epidermal necrolysis, exfoliative erythroderma, the toxic infectious erythemas, disseminated viral infections, Rocky Mountain spotted fever, disseminated gonococcal infection, purpura fulminans, and pemphigus vulgaris. Staphylococcal scalded skin syndrome and meningococcemia are discussed in the pediatric section, in Chapter 142, "Rashes in Infants and Children." Disseminated viral infections are discussed in Chapter 154, "Serious Viral Infections" and in Chapter 142.

The disorders erythema multiforme, toxic epidermal necrolysis, exfoliative erythroderma, staphylococcal and streptococcal toxic shock syndrome, and staphylococcal scalded skin syndrome share some features in common. **Table 249-1** can help to differentiate these disorders. Management is summarized in **Table 249-2**.

ERYTHEMA MULTIFORME

Erythema multiforme is an acute inflammatory skin disease (**Figure 249-1**) that ranges from a minimal, nuisance-level event to a severe multisystem illness. It is divided into two distinct subtypes, considering the extent of involvement, presence of epidermal detachment, and the development of mucous membrane lesions. Erythema multiforme minor is a localized papular eruption of the skin, with an acral distribution and involving target lesions and/or raised, edematous papules. Erythema multiforme major is the severe form with multisystem involvement and widespread vesiculobullous lesions and erosions of the

TABLE 249-1 Comparison of Inflammatory and Infectious Generalized Skin Disorders

Disorder	Appearance	Special Features
Erythema multiforme	Erythematous macules, papules Target lesions Urticaria or vesiculobullous lesions	Cutaneous reaction to drugs or infectious agents. Stevens-Johnson syndrome is the most severe form.
Toxic epidermal necrosis	Painful, tender erythroderma Vesicles and bullae Exfoliation	Nikolsky sign present. Stevens-Johnson syndrome is most severe form. Drugs most common cause.
Exfoliative erythroderma	Nontender erythema Skin flaking and scaling Thickening of skin	Often preexisting eczema or psoriasis; can be drug induced.
Staphylococcal or streptococcal toxic shock syndrome	Staphylococcal: fine punctate erythematous lesions that become confluent; blanching erythroderma; desquamation first of trunk and face, then extremities Streptococcal: can be indistinguishable from staphylococcal toxic shock; scarlatiniform erythroderma with sheet-like desquamation of skin	Colonization or infection with *Staphylococcus aureus*; menstruation associated with tampon use; nonmenstrual associated with burns, cellulites, sinusitis, wounds, etc. Group A streptococcal cellulitis, puerperal sepsis, any group A β-hemolytic *Streptococcus* infection source.
Staphylococcal scalded skin syndrome	Scarlatiniform rash or erythema Bullae or bullous impetigo Sloughing of skin	Usually seen in neonates or children <5 y of age. Nikolsky sign present.

TABLE 249-2 Management of Serious Generalized Skin Disorders

Disorder	Treatment	Disposition/Comments
Erythema multiforme minor	• Steroid (prednisone 60–80 milligrams PO daily for 3–5 d or equivalent) • Oral antihistamine (diphenhydramine 25–50 milligrams every 4–6 h or equivalent) • Acyclovir for herpes simplex virus–related event (recurrence suppression only) • Remove trigger if identified	• Outpatient management • Primary care physician or dermatology follow-up
Erythema multiforme major (Stevens-Johnson syndrome)	• Resuscitate as needed (respiratory +/– circulatory) • Fluid and electrolyte management as needed • Steroid (as above or methylprednisolone 125 milligrams IV every 6 h or equivalent)* • Pain management as appropriate • Diphenhydramine and viscous lidocaine rinses for oral lesions • Burow's solution (5% aluminum acetate) with cool compresses for blisters • Ophthalmologist for ocular lesions • Antibiotic only for suspected or established infection (i.e., not prophylactic) • Remove trigger if identified	• Inpatient management; acute, critical care, or burn unit • Intensivist† and dermatologist consultations
Toxic epidermal necrosis	• Resuscitate as needed (respiratory +/– circulatory) • Fluid and electrolyte management as needed • Antibiotic only for suspected or established infection (i.e., not prophylactic) • Remove trigger if identified	• Inpatient management, critical care or burn unit • Intensivist† and dermatologist consultations
Pemphigus vulgaris	• Resuscitate as needed (respiratory +/– circulatory) • Fluid and electrolyte management as needed • Antibiotic only for suspected or established infection (i.e., not prophylactic) • Immunosuppressive therapy* • Plasmapheresis* • Immunoglobulin therapy*	• Inpatient management; acute, critical care, or burn unit • Intensivist† and dermatologist consultations
Exfoliative dermatitis minor	• Remove trigger if identified • Symptomatic care (oral pain and antihistamine agents as needed [PRN])	• Outpatient management • Primary care physician or dermatology follow-up
Exfoliative dermatitis major	• Resuscitate as needed (circulatory) • Correct hypothermia • Remove trigger if identified • Symptomatic care (oral pain and antihistamine agents PRN) • Steroid after dermatologist consultation (methylprednisolone 125 milligrams IV every 6 h or equivalent)*	• Inpatient management; acute, critical care, or burn unit • Intensivist† and dermatologist consultations
DRESS (drug rash with eosinophilia and systemic symptoms) syndrome	• Resuscitate as needed (respiratory +/– circulatory) • Remove trigger if identified • Symptomatic care (oral pain and antihistamine agents PRN) • Antipyretic therapy • Steroid (as above or methylprednisolone 125 milligrams IV every 6 h or equivalent)*	• Inpatient management, acute or critical care unit • Intensivist† and dermatologist consultations
Staphylococcal toxic shock syndrome	• Resuscitate as needed (respiratory +/– circulatory) • Removal of foreign body source (usually colonization only, not active infection) • Antistaphylococcal antibiotics (only reduces recurrence)	• Inpatient management, acute or critical care unit • Intensivist,† infectious disease, and dermatologist PRN
Streptococcal toxic shock syndrome	• Resuscitate as needed (respiratory +/– circulatory) • Broad-spectrum antibiotics with antistreptococcal coverage • Attention to soft tissue infection with incision/drainage, debridement, amputation, etc.	• Inpatient management, acute or critical care unit • Intensivist,† infectious disease, surgeon, and dermatologist PRN
Staphylococcal scalded skin syndrome	• Resuscitate as needed (respiratory +/– circulatory) • Fluid and electrolyte management as needed • Identification of source (colonization or active infection) • Antistaphylococcal antibiotics • Topical dressings PRN*	• Inpatient management, acute or critical care unit • Intensivist,† infectious disease, and dermatologist PRN
Meningococcemia	• Resuscitate as needed (respiratory +/– circulatory) • Parenteral antibiotics	• Critical care unit • Intensivist
Purpura fulminans	• Resuscitate as needed (respiratory +/– circulatory)	• Critical care unit • Intensivist

*Therapy guided by dermatologist.

†Intensivist involvement if patient admitted to critical care unit.



FIGURE 249-1. Erythema multiforme.

mucous membranes; specifically, erythema multiforme major includes involvement of one or more mucous membrane areas and epidermal detachment less than 10% of total body surface area. Some authorities include **Stevens-Johnson syndrome** as a severe form of erythema multiforme major, whereas others consider it a less severe form of toxic epidermal necrolysis. Perhaps the most appropriate classification approach for the emergency provider is as follows: Stevens-Johnson syndrome presents with less than 10% of the body surface area with epidermal detachment; the "overlap" presentation of Stevens-Johnson syndrome and toxic epidermal necrolysis presents with 10% to 30% epidermal detachment; and toxic epidermal necrolysis presents with greater than 30% epidermal detachment.[1] In either consideration, Stevens-Johnson syndrome is a serious dermatologic illness with significant, widespread skin involvement, more extensive epidermal detachment, and mucous membrane lesions. This taxonomic controversy has no meaning for the emergency clinician; what is important is the recognition of a significant, potentially life-threatening, multisystem dermatologic condition.

Morbidity and mortality rise with the amount of epidermal detachment.[2] The highest incidence is in young adults (age range, 20 to 40 years), and erythema multiforme occurs commonly in the spring and fall. Common precipitating factors are infection, especially with *Mycoplasma* and herpes simplex virus; drugs, especially antibiotics and anticonvulsants; and malignancies. However, the cause is often unknown.[3] Most likely, erythema multiforme is the result of a hypersensitivity reaction, with immunoglobulin and complement components demonstrated in the cutaneous microvasculature on immunofluorescent studies of skin biopsy specimens, circulating immune complexes found in the serum, and mononuclear cell infiltrate noted on histologic examination.[3,4]

Symptoms include malaise, fever, myalgias, and arthralgias. Diffuse pruritus or a generalized burning sensation can occur before the skin lesions develop. The morphologic configuration of the lesions is variable, hence the descriptor *multiforme*. Maculopapular (**Figure 249-2**) and target, or iris (**Figure 249-3**), lesions are the most characteristic. Erythematous papules appear symmetrically on the dorsum of the hands and feet and on the extensor surfaces of the extremities. The maculopapule evolves into the classic target lesion during the next 24 to 48 hours. As the maculopapule enlarges, the central area becomes cyanotic, occasionally accompanied by central purpura or a vesicle. Urticarial plaques also may occur with or without the iris lesion in a similar distribution. Vesiculobullous lesions, which may be pruritic and painful, develop within preexisting maculopapules or plaques, usually on the extensor surface of the arms and legs and less frequently on the trunk. Vesiculobullous lesions are found most often on mucosal surfaces, including the mouth, eyes, vagina, urethra, and anus; they may also be seen on the



FIGURE 249-2. Maculopapular erythema multiforme.

trunk. Ocular involvement rarely occurs in erythema multiforme minor, whereas ophthalmologic lesions are seen in almost 70% of patients with Stevens-Johnson syndrome.[5] The various lesions (**Table 249-3**) develop in successive crops during a 2- to 4-week period and heal over 5 to 7 days. The **differential diagnosis of erythema multiforme** includes herpetic (herpes simplex virus and varicella-zoster virus) infection, vasculitis, toxic epidermal necrolysis, various primary blistering disorders (pemphigus and pemphigoid), urticaria, Kawasaki's disease, and the toxic and infectious erythemas.

Recurrence may be noted on repeat exposure to the etiologic agent, a special concern in cases associated with herpes simplex virus infection or medication use.[6] **The rate of erythema multiforme recurrence is very**



FIGURE 249-3. Target, or iris, lesions of erythema multiforme. [Photograph used with permission of Kenneth Greer, MD, University of Virginia Dermatology.]

TABLE 249-3 Erythema Multiforme and Toxic Epidermal Necrolysis

Lesions of Erythema Multiforme	Lesions of Toxic Epidermal Necrolysis
Erythematous maculopapules	Warm, tender erythroderma
Iris or target lesions	Vesicles and bullae
Urticaria	Exfoliation
Mucous membranes involved	Mucous membranes involved

high in children with herpes simplex virus infection. For example, 75% of children with a history of herpes simplex virus–related erythema multiforme developed erythema multiforme recurrence after herpes simplex virus reactivation.[6] Fluid and electrolyte disorders and secondary infection from cutaneous sites are the most frequent complications.

Treatment is provided in Table 249-2. Systemic steroids are commonly used for localized disease and provide symptomatic relief, but are of unproven benefit in influencing the duration and outcome of erythema multiforme.[7] Many authorities recommend a short, intensive steroid course of prednisone, 60 to 80 milligrams PO once a day, particularly in drug-related cases, with abrupt cessation in 3 to 5 days if no favorable response is noted. Unfortunately, burst steroid therapy does not reduce the chance of development or significance of existing ocular lesions. Provide symptomatic relief of stomatitis and blisters. Do not swallow oral viscous lidocaine because it causes neurotoxicity. Consult ophthalmology for ocular involvement. Acyclovir may reduce recurrence of herpes simplex virus infection and therefore lessen the potential for another bout of erythema multiforme; prolonged prophylactic acyclovir therapy may reduce the chance of recurrent erythema multiforme related to herpes simplex virus.[6]

TOXIC EPIDERMAL NECROLYSIS

Toxic epidermal necrolysis (**Figure 249-4**) is an explosive dermatosis characterized by tender erythema, bullae formation, mucous membrane lesions, and subsequent exfoliation. Patients are systemically ill. Many authorities consider Stevens-Johnson syndrome to be a less severe form of toxic epidermal necrolysis, whereas others consider Stevens-Johnson syndrome to be a more severe form of erythema multiforme major; in either case, Stevens-Johnson syndrome and toxic epidermal necrolysis are severe dermatologic illnesses, whether they are distinct entities or two forms of the same syndrome.[4]

Toxic epidermal necrolysis is found in all age groups without predilection for either sex. The syndrome has multiple causes, with medications being the most common cause.[3,4,8] Sulfa and penicillin antibiotics, anticonvulsants, and oxicam NSAIDs are the most frequent drug triggers for toxic epidermal necrolysis.[9,10] Other causes include malignancy and human immunodeficiency virus infection.[8,11,12] In many cases, a cause is not found. The pathogenesis is poorly understood and may be partly immunologic and partly genetic.[8]

Symptoms include a 1- to 2-week prodrome of malaise, anorexia, arthralgias, fever, or symptoms of upper respiratory tract infection. Skin tenderness, pruritus, tingling, or burning may be found at this time. Skin signs (Table 249-3) begin with a warm erythema, initially involving only the eyes, nose, mouth, and genitalia, but later becoming generalized. The erythematous areas become tender and confluent within hours. Flaccid, ill-defined bullae then appear within the areas of erythema. Lateral pressure with a finger on normal skin adjacent to a bullous lesion dislodges the epidermis, producing denuded dermis and demonstrating **Nikolsky sign**. Nikolsky sign is slippage of the epidermis from the dermis when slight rubbing pressure is applied to the skin. The bullae form along the cleavage plane between the epidermis and the dermis. The epidermis is then shed in large sheets, which leaves raw, denuded areas of exposed dermis. The average time until onset after exposure to the inciting agent is 2 weeks. Cutaneous extension follows an unpredictable time course, ranging from 24 hours to 15 days, with some severe cases demonstrating rapid, extensive involvement within 24 hours.

Perilabial blistering and erosive lesions are disfiguring and often impair adequate oral intake, contributing to hypovolemia. Ocular complications include purulent conjunctivitis, painful erosions, and potential blindness. Anogenital lesions are common. Additional mucous membrane involvement includes the GI, urinary, and respiratory tracts. The two major complications and leading causes of death in toxic epidermal necrolysis are infection and hypovolemia with electrolyte disorders. A broad range of pathogens is usually found, with staphylococcal and pseudomonal species predominating. The mortality rate is as high as 30%.[8] The clinical characteristics associated with poor prognosis include advanced age, extensive disease, idiopathic nature, use of multiple medications, steroid therapy, azotemia, hyperglycemia, leukopenia, and thrombocytopenia.[9] The differential diagnosis of toxic epidermal necrolysis is presented in Table 249-1 and also includes primary blistering disorders (pemphigus and pemphigoid) and Kawasaki's disease in children.

Treatment is presented in Table 249-2**.** Toxic epidermal necrolysis requires hospitalization in an intensive care or burn unit.[9] Immediate concerns center on the airway, because sloughing of airway and respiratory epithelium can occur. Hypovolemia and electrolyte abnormalities should be corrected. Prompt, aggressive antibiotic administration is necessary in suspected or documented infection; initial prophylactic antibiotics are not recommended by most. Solicit the advice of the burn center regarding any topical dressings that are applied before transfer.



FIGURE 249-4. Toxic epidermal necrolysis.

TABLE 249-4 Characteristics of Pemphigus Vulgaris Lesions

- Large, flaccid bullae
- Nikolsky sign present
- Skin ulcerations
- Exfoliation
- Mucous membrane involvement

PEMPHIGUS VULGARIS

Pemphigus vulgaris is a generalized, mucocutaneous, autoimmune, blistering eruption with a grave prognosis characterized by intraepidermal acantholytic blistering (**Table 249-4**). The primary lesions of pemphigus vulgaris are vesicles or bullae (**Figure 249-5**) that vary in diameter from <1 cm to several centimeters. They commonly first affect the head, trunk, and mucous membranes. The blisters are usually clear and tense, originating from normal skin or atop an erythematous or urticarial plaque. Within 2 to 3 days, the bullae become turbid and flaccid. Rupture soon follows, producing painful, denuded areas. These erosions are slow to heal and prone to secondary infection. The Nikolsky sign is present in pemphigus vulgaris. Mucous membranes are affected in most patients, and in some, the mucous membranes are the primary sites of involvement. Blisters on mucous membranes are more transitory than blisters on the skin in that they are more vulnerable to rupture; this is particularly true in the mouth, where ragged ulcerative lesions readily develop after inadvertent biting of the tissues.

Bullous pemphigoid, another mucocutaneous blistering disorder, can present in similar fashion to pemphigus vulgaris with the following significant differences found in the bullous pemphigoid: older average age at onset, larger blister size, lower rate of mucous membrane involvement, and overall "less toxicity" with better outcome.

Limited oral intake and accelerated protein, fluid, and electrolyte losses through the involved skin can rapidly lead to hypovolemia and electrolyte disturbances. Treatment is provided in Table 249-2.

EXFOLIATIVE DERMATITIS

Exfoliative dermatitis is a condition in which most or all of the skin surface is involved with a scaly erythematous dermatitis. It is a cutaneous reaction in response to a drug or a chemical agent or to an underlying systemic or cutaneous disease. Most patients are over 40 years of age. The cause is unknown.

Exfoliative dermatitis can have an abrupt onset, particularly when related to a drug,[13,14] contact allergen, or malignancy; exacerbations related to an underlying cutaneous disorder usually evolve more slowly. Exfoliative dermatitis tends to be a chronic condition, with a mean duration of 5 years, when related to a chronic illness; the course is often shorter after suppression of the underlying dermatosis, discontinuation of causative drugs, or avoidance of allergen. Idiopathic and chronic disease–related exfoliative dermatitis can continue for ≥20 years; death is rare.



FIGURE 249-5. Scattered bullous lesions intermixed with erosions and painful inflammatory plaques in a patient with pemphigus vulgaris.



FIGURE 249-6. Exfoliative dermatitis demonstrated by generalized, warm erythema accompanied by scaling or flaking.

Generalized erythema and warmth are noted, but skin tenderness is usually lacking. Erythema is accompanied by scaling or flaking, and the patient often complains of pruritus and skin tightness (**Figure 249-6**). The process generally begins on the face and upper trunk with progression to other skin surfaces. The patient usually has a low-grade fever. Excessive heat loss and hypothermia can complicate exfoliative dermatitis. Widespread cutaneous vasodilation may result in high-output congestive heart failure. The disruption of the epidermis results in increased transepidermal water loss, and continued exfoliation can result in significant protein loss and negative nitrogen balance. Chronic inflammatory exfoliation produces many changes, such as dystrophic nails, thinning scalp and body hair, and patchy or diffuse pigmentation changes.

The differential diagnosis is found in Table 249-1, and treatment is provided in Table 249-2. Patients generally require admission. Correct hypothermia and hypovolemia. Obtain dermatology consultation before giving systemic corticosteroids.

DRESS (DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS) SYNDROME

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug reaction that usually develops within 8 weeks of initiation of drug therapy. Aromatic anticonvulsants (such as phenytoin and phenobarbital), allopurinol, and sulfa medications are the most common culprits; however, other causes include NSAIDs, antiretroviral medications, angiotensin-converting enzyme inhibitors, calcium channel blockers, and other antibiotics.[13-16]

It is believed that there is a genetic predisposition if exposed to the appropriate medication.[15] Because of the potential genetic risk, DRESS syndrome risks and implications should be discussed with the family members of any patient in whom it is diagnosed.

DRESS syndrome is defined by fever, rash, and internal organ involvement, with the liver, kidneys, and hematologic system being most commonly affected.[15] Rash and fever are typically the first signs of the syndrome, and they may have associated lymphadenopathy (**Figure 249-7**). The rash itself can take multiple forms, ranging from an erythematous scaly rash similar to that of exfoliative dermatitis, to a blistering/bullous rash similar to that of Stevens-Johnson syndrome, with varying degrees of severity. Abnormal laboratory findings include eosinophilia, which occurs in about 30% of DRESS syndrome patients,[17] and hepatic and renal dysfunction. Because of the variety of clinical presentations, early diagnosis of DRESS syndrome is difficult and requires a high level of clinical suspicion. The current treatment



FIGURE 249-7. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome caused by phenytoin.



FIGURE 249-8. Early findings of meningococcemia with petechiae evolving into pruritic lesions. [Photograph used with permission of Kenneth Greer, MD, University of Virginia Dermatology.]

(Table 249-2) involves immediate stoppage of the suspected culprit medication, administration of systemic steroids in severe cases (those with evidence of hepatitis, pneumonitis, or extensive exfoliative dermatitis), supportive care including antipyretic and antipruritic medications, and hospital admission.[17,18]

PURPURIC DISORDERS

MENINGOCOCCEMIA

Meningococcemia is a potentially fatal infectious illness caused by the gram-negative diplococcus *Neisseria meningitidis*. Meningococcal disease presents across a wide clinical spectrum in the acute and chronic forms. The acute entities include pharyngitis, meningitis, and bacteremia. Meningococci are present in mucosal samples from approximately 5% to 10% of the general population (the carrier state).[19,20] In high-risk populations, such as military recruits, the organism may be found in almost half of people without evidence of active disease.[21]

The illness usually strikes patients <20 years of age, with the vast majority of cases occurring in children and infants <5 years old. A rash is frequently noted on presentation and is an invaluable clue to the correct diagnosis early in the disease course. The dermatologic manifestations include petechiae, urticaria, hemorrhagic vesicles, macules, and/or maculopapules (**Figure 249-8**). The classic petechial lesions are found on the extremities and trunk but also are noted on the palms, soles, head, and mucous membranes. The petechiae evolve into palpable purpura with gray necrotic centers, a pathognomic finding for meningococcal infection. The skin findings result from the organism's invasion and destruction of the endothelium. Histopathologic analysis shows an infectious vasculitis. For further discussion, see Chapters 142, "Rashes in Infants and Children," and 120, "Meningitis in Infants and Children."

PURPURA FULMINANS

Purpura fulminans is a rare vascular disorder characterized by fever, shock, multiorgan failure, and the rapid development of hemorrhagic skin necrosis. It is associated with dermal vascular thrombosis, vascular collapse, and disseminated intravascular **coagulation**. Purpura fulminans can result from hereditary or acquired protein C deficiency, activated protein C resistance, or protein S deficiency. It may also result from any condition that causes disseminated intravascular coagulation.

Purpura fulminans presents with the dermatologic triad of widespread ecchymoses, hemorrhagic bullae (**Figure 249-9**), and epidermal necrosis. Cyanosis with initial ecchymoses and ultimate necrosis of the tip of the nose, ears, and genitalia frequently occur; in general, distal



A



B

FIGURE 249-9. Purpura fulminans (**A**) with early skin necrosis and (**B**) later with hemorrhagic bullae. [Photographs used with permission of Kenneth Greer, MD, University of Virginia Dermatology.]

tissue areas with end circulation are affected. Large confluent ecchymoses can develop, often on the extremities, from distal to proximal, and on the perineum, buttocks, and abdomen. The extremities are often involved symmetrically. Treatment is directed at the underlying cause.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 250

Skin Disorders: Face and Scalp

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INTRODUCTION

This chapter discusses common infections and inflammations affecting the face and scalp; allergic dermatitis involving the face (including poison ivy); and photosensitivity reactions. Erysipelas and facial cellulitis are discussed in Chapter 152, "Soft Tissue Infections," and impetigo and bullous impetigo are discussed in Chapter 142, "Rashes in Infants and Children."

FACE

SEBORRHEIC DERMATITIS

Seborrheic dermatitis has both infantile and adult forms. The infantile form is called "cradle cap" and peaks in the first 3 months of life (see Chapter 142, "Rashes in Infants and Children" for further discussion of infantile seborrheic dermatitis). Adult seborrheic dermatitis presents as white to yellow greasy scaling of the scalp (i.e., dandruff), eyebrows, nasolabial folds, ears, and postauricular skin associated with mild erythema and variable pruritus (**Figure 250-1**). Occasionally, the lesions may extend onto the upper central chest and intertriginous areas. Adults with acquired immunodeficiency syndrome and Parkinson's disease are predisposed to severe disease. The typical distribution of seborrheic dermatitis is in areas with high concentrations of sebaceous glands. *Malassezia* yeasts residing on the skin may contribute to inflammation.[1] This factor may explain why seborrheic dermatitis responds to both antifungal and anti-inflammatory agents. In adults, the condition is chronic and recurrent but without any systemic symptoms.



FIGURE 250-1. Adult seborrheic dermatosis. Erythema and scaling on face and facial skin folds. [Reproduced with permission from Wolff K, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York, McGraw Hill, Inc.; 2005:51.]

Treat adults with an antidandruff shampoo containing zinc pyrithione, selenium sulfide 2.5%, salicylic acid, or tar. Ketoconazole can also be used and is available over the counter as 1% shampoo and by prescription at 2% for shampoo and cream. Lather the shampoo into the scalp and leave on briefly before rinsing. For severe cases, a topical corticosteroid such as fluocinonide solution may be applied to the scalp daily. For the face, *low-potency* topical corticosteroids applied twice per day may be used (**Table 250-1**). **The use of higher potency topical corticosteroids on the face for more than a few days can lead to the development of perioral dermatitis or steroid rosacea and should be avoided.** Treatment continues until the dermatitis is cleared. Re-treat recurrences as needed.

TINEA BARBAE AND SYCOSIS BARBAE

Tinea barbae is a dermatophyte infection involving the beard area of the face and neck and occurs in postpubertal males. The cause is usually the genus *Trichophyton*. Predisposing factors to tinea barbae include use of topical steroids, contact with infected pets, and diabetes mellitus.[2] **Sycosis barbae** is a deep folliculitis within the beard area with perifollicular inflammation. The causative agent is usually *Staphylococcus aureus*.

In tinea barbae, severe inflammatory plaques and follicular pustules occur in the beard area (**Figure 250-2**). Kerion-like lesions can develop as well as abscesses and sinus tracts. Hairs are usually loosened or broken off.

In sycosis barbae, discrete pustules, usually involving *S. aureus*, with perifollicular inflammation are evident (**Figure 250-3**). Unlike tinea barbae, the hairs are usually not loosened or broken off.

The diagnosis is clinical, but tinea barbae sometimes can resemble acne vulgaris or bacterial folliculitis. A potassium hydroxide preparation or fungal culture can be done to confirm the diagnosis. Permanent alopecia and scarring can result if left untreated.

Treatment of tinea barbae requires oral antifungals. Microsize griseofulvin, 500 milligrams PO daily, or ultramicrosize griseofulvin, 375 milligrams PO daily, for 6 weeks can be used. **Terbinafine 250 milligrams PO daily for 2 to 4 weeks can also be used; both griseofulvin and terbinafine should be avoided in patients with known hepatic dysfunction** (Table 250-1). Supportive care includes shaving or depilating the hair and warm compresses to remove the crust.

For sycosis barbae, initial treatment with warm compresses and mupirocin ointment may be sufficient. If lesions are chronic, treatment usually requires systemic antibiotics with adequate *S. aureus* coverage (Table 250-1).

HERPES ZOSTER INFECTION

Herpes zoster or "shingles" is a cutaneous manifestation of reactivation of varicella-zoster virus from its latent state in neural ganglia following primary infection. For discussion of other manifestations of varicella-zoster virus infection, see Chapter 154, "Serious Viral Infections."

Pain or dysesthesia typically precedes cutaneous findings of herpes zoster by 3 to 5 days. Erythematous papules progress to clusters of vesicles and pustules on an erythematous base in a dermatomal distribution (**Figure 250-4**). Vesicles crust over in about 1 week. While zoster typically involves the thoracic and lumbar dermatomes, presence of lesions within the ophthalmic branch (V1) of the trigeminal nerve and especially on the tip of the nose is concerning for herpes zoster ophthalmicus, which requires emergent ophthalmology evaluation. **Ramsay Hunt syndrome** results from reactivation of varicella-zoster virus in the geniculate ganglion and presents with ear pain, vesicles in

TABLE 250-1 Clinical Features and Treatment of Seborrheic Dermatitis of the Face, Tinea Barbae, Sycosis Barbae

Condition	Clinical Features	Treatment	Comments
Seborrheic dermatitis	White to yellow scale involving scalp, eyebrows, nasolabial folds, and chest with variable erythema and pruritus	OTC antidandruff shampoo Ketoconazole 2% shampoo Ketoconazole 2% cream Desonide 0.05% or hydrocortisone 2.5%	Leave shampoos on for 3–5 minutes before rinsing
Tinea barbae	Scaly erythematous plaques, follicular pustules, or erythematous boggy plaques in beard distribution; associated with loosened/broken hairs	Griseofulvin, microsize 500 milligrams PO daily for 6 weeks Griseofulvin, ultramicrosize 375 milligrams PO daily for 6 weeks Terbinafine 250 milligrams daily for 2–4 weeks	Avoid griseofulvin and terbinafine in patients with known hepatic disease; reasonable to obtain baseline liver function tests when prescribing
Sycosis barbae	Follicular pustules and perifollicular erythema in beard distribution	Warm compresses Mupirocin 2% ointment Oral antistaphylococcal antibiotics	

Abbreviation: OTC = over the counter.



FIGURE 250-2. Tinea barbae. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 250-3. Sycosis barbae. [Photo contributed by University of North Carolina Department of Dermatology.]

the external auditory canal, facial nerve paralysis, and vestibulocochlear dysfunction.[3]

The key to diagnosis is the unilateral distribution and pronounced pain in the area of involvement. Diagnosis can be confirmed by polymerase chain reaction analysis of swabs taken from the base of an intact vesicle. Tzanck smear can also demonstrate multinucleated giant cells, but unlike polymerase chain reaction, it cannot differentiate between varicella-zoster virus, herpes simplex virus 1, or herpes simplex virus 2 infection.

Treatment is most effective if it is initiated within the first 72 hours of symptoms and decreases healing time, new lesion formation, and the risk of postherpetic neuralgia. Treatment options in an immunocompetent patient include oral acyclovir or valacyclovir (**Table 250-2**). In immunocompromised patients, intravenous acyclovir is necessary. Local care can be provided with aluminum acetate compresses three times daily followed by antibiotic ointment to prevent secondary bacterial infection. Assess and treat associated pain, which may be severe. Vaccination against zoster reduces the incidence and severity of illness as well as risk of postherpetic neuralgia and is indicated for adults over the age of 50.[4]

Patients with herpes zoster are contagious to nonvaccinated individuals without natural immunity, and isolation is needed for patients suspected of the disease at triage. Patients should be instructed to cover all open areas when visiting the physician at follow-up.

HERPES SIMPLEX VIRUS INFECTIONS

Herpes simplex virus type 1 most commonly occurs on the face. Primary infection occurs during childhood or adolescence and is typically asymptomatic but occasionally presents with painful orofacial vesicular lesions associated with systemic symptoms. Recurrences tend to be milder and occur primarily on the lips, nose, and oral cavity.

The typical lesions of herpes simplex virus are painful, grouped vesicles on an erythematous base (**Figure 250-5**). The characteristic primary eruption is a gingivostomatitis with herpetic lesions on the lips and in the oral cavity that may persist for weeks accompanied by fever and malaise. Recurrences may be induced by ultraviolet light, fever, stress, or local trauma and typically present as herpes labialis ("fever blisters" or "cold sores"). Individuals often experience a prodrome of localized tingling or burning several hours before the onset of the eruption. The herpetic lesion usually occurs along the lip margin and completely heals within 10 days.

In patients with underlying atopic dermatitis, a severe form of herpesvirus infection can occur called *eczema herpeticum* in which herpes simplex virus or varicella-zoster virus can infect active atopic dermatitis lesions (see Chapter 142, "Rashes in Infants and Children").

Treatment for primary herpes simplex virus gingivostomatitis works best when given within the first 24 hours (Table 250-2).[5] Treatment can continue for up to 10 days if lesions have not crusted.

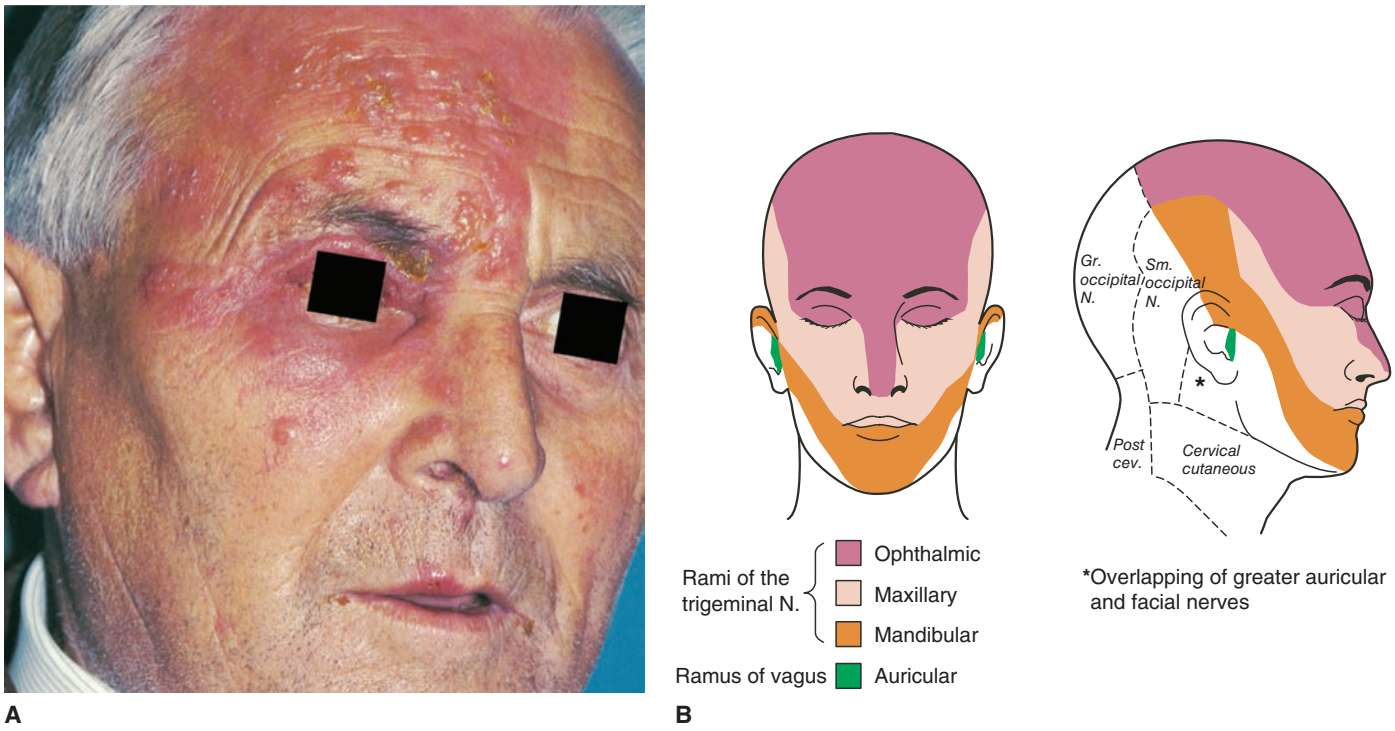


FIGURE 250-4. **A.** Herpes zoster in trigeminal nerve distribution. Note the lesion on the tip of the nose, which suggests nasociliary branch involvement. **B.** Dermatomes of the head and neck. Cev = cervical; gr = greater; N = nerve, Sm = smaller [**A.** Reproduced with permission from Fleischer A Jr, Feldman S, McConnell C, et al: *Emergency Dermatology: A Rapid Treatment Guide*. New York: McGraw-Hill, Inc.; 2002, p. 157. **B.** Reproduced with permission from Wolff K, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, Inc.; 2005.]

Immunocompromised patients with severe involvement require hospitalization for IV acyclovir. Suppressive treatment with acyclovir or valacyclovir can decrease outbreaks of herpes labialis.[5] Patients with recurrent disease should be instructed to avoid triggers, especially the sun, by using sunscreen and a lip balm with ultraviolet light protection.



FIGURE 250-5. Herpetic gingivostomatitis. [Photo contributed by University of North Carolina Department of Dermatology.]

SCALP

DISSECTING CELLULITIS OF THE SCALP

Dissecting cellulitis of the scalp is an intense inflammatory and scarring disease of the scalp and neck, driven by follicular occlusion and often complicated by secondary bacterial infection. It occurs most commonly in young men of African descent and consists of boggy tender nodules in multiple areas of the scalp and the neck (**Figure 250-6**). Osteomyelitis of the skull has been reported as a sequela.[6] The nodules suppurate and develop interconnecting, draining sinus tracts. Hair loss develops over these nodules, and permanent scarring, alopecia, and keloids can occur. **ED therapy** includes antibacterial washes, such as chlorhexidine, which

TABLE 250-2 Clinical Features and Treatment of Herpes Zoster and Herpes Simplex

Condition	Clinical Features	Treatment Options	Comments
Herpes zoster	Vesicles and pustules on erythematous base in dermatomal distribution; associated pain, pruritus, dysesthesia	Acyclovir: 800 milligrams PO 5 times a day for 7 d Valacyclovir: 1000 milligrams PO 3 times a day for 7 d	Treatment should be initiated within the first 72 h after symptom onset, if possible
Herpes simplex, initial episode	Asymptomatic infection *or* painful vesicles and ulcers with surrounding erythema on mucosa associated with fevers, malaise, lymphadenopathy	Acyclovir: 400 milligrams PO 3 times a day for 7–10 d *or* 200 milligrams PO 5 times a day for 7–10 d Valacyclovir: 1000 milligrams PO twice a day for 7–10 d	Can extend treatment of acyclovir or valacyclovir if not healed after 10 d
Herpes simplex, recurrence	Recurrent painful vesicles at or near site of primary infection preceded by prodrome of pruritus or dysesthesia	Acyclovir: 400 milligrams PO 5 times a day for 5 d *or* 800 milligrams PO twice a day for 5 d Valacyclovir: 2000 milligrams PO twice a day for 1 d	Avoid triggers: ultraviolet exposure, trauma, stress, illness; may require referral to dermatology for suppression of frequent flares



FIGURE 250-6. Dissecting cellulitis of the scalp. [Photo contributed by University of North Carolina Department of Dermatology.]

is available without prescription, and oral antibiotics such as doxycycline and minocycline (**Table 250-3**). Incision and drainage of individual suppurative nodules does not treat the underlying condition but may provide symptomatic relief. Refer to a dermatologist for continued management. Dapsone, intralesional corticosteroids, and prednisone have variable efficacy in treating this challenging condition. Isotretinoin, surgical excision, laser treatment, and tumor necrosis factor-α blockers have also been used successfully.[7]

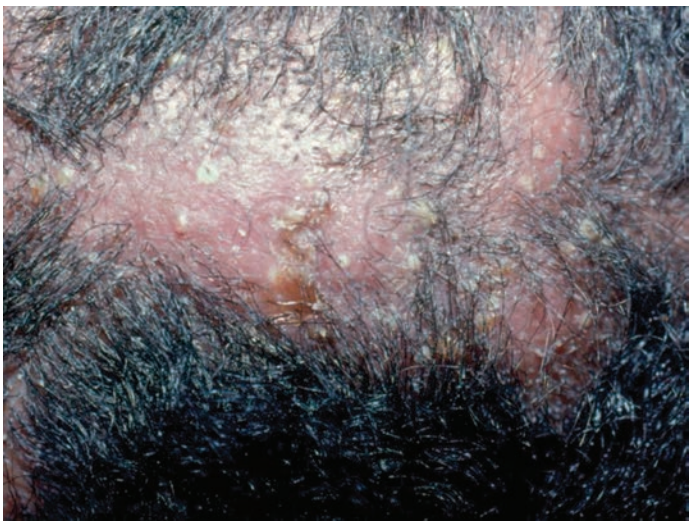
TINEA CAPITIS

Tinea capitis is a dermatophyte infection of the scalp. Causative agents are usually from the genus *Trichophyton*. The fungi invade the hair shaft and stratum corneum of the skin.

Clinically, there are nonscarring patches of alopecia with broken hairs and scale at the periphery. Occasionally, there is intense inflammation, with a boggy, tender, indurated plaque with superficial pustules and overlying alopecia (**Figure 250-7**). This reaction, referred to as a *kerion*, may result in permanent scarring and alopecia. Cervical and/or occipital lymphadenopathy may be present. In some cases of tinea capitis, especially after initiation of oral antifungal therapy, patients will mount an immune response to the dermatophyte, called an id reaction, at distant sites. This id reaction appears as widespread, symmetric, pruritic, monomorphic, eczematous papules and responds to topical



A



B

FIGURE 250-7. **A.** Tinea capitis with Wood's light fluorescence. **B.** Kerion. [Photo contributed by University of North Carolina Department of Dermatology.]

TABLE 250-3 Clinical Features and Treatment of Pediculosis Capitis, Tinea Capitis, and Dissecting Cellulitis of Scalp

Condition	Clinical Features	Treatment	Comments
Dissecting cellulitis of scalp	Tender, suppurative nodules and sinus tracts associated with scarring and alopecia	Over-the-counter antibacterial wash, doxycycline or minocycline 100 milligrams PO twice a day; incision and drainage for painful, fluctuant nodules	Due to chronic condition, referral to dermatology recommended
Tinea capitis	Scalp pruritus, broken hairs, alopecia, and lymphadenopathy	Griseofulvin, microsized 20–25 milligrams/kg/d PO (<1 gram/d) for 8 wk *or* Griseofulvin, ultramicrosized 15–20 milligrams/kg/d PO (<750 milligrams/d) for 8 wk *or* Terbinafine 125–250 milligrams/d PO for 6 wk	May be associated with id reaction or kerion formation; treatment duration may be extended based on response
Pediculosis capitis (head lice)	Scalp pruritus (especially behind ears), presence of adult lice and/or nits along hair shaft	Permethrin cream, pyrethrin lotion, ivermectin lotion, or malathion cream; repeat treatment in 7–10 d	Machine wash and dry recently used clothing and bed linens

TABLE 250-4 Fluorescence From Wood's Lamp

- Nits
- Lice
- *Microsporum*
- *Malassezia*

steroids. Development of an id reaction does not require discontinuation of antifungal therapy.

Diagnosis is mainly clinical. Wood's lamp examination (**Table 250-4**) is not helpful because **more than 90% of cases of tinea capitis are due to *Trichophyton* species, which do not fluoresce**.

If necessary, diagnosis can be confirmed by a positive potassium hydroxide preparation or positive fungal culture. Scraping only the scalp rarely gives a positive potassium hydroxide examination because *Trichophyton* species invade the hair shaft. If fungal culture is necessary to establish or confirm the diagnosis, it usually takes 3 to 4 weeks for the culture to grow. A positive culture will help to exclude other conditions such as atopic dermatitis or seborrheic dermatitis.

Topical treatment alone is not effective for tinea capitis. **The current first-line therapy is oral griseofulvin or terbinafine.** Higher doses of griseofulvin are needed to treat *Trichophyton* species, which represent the most common cause of tinea capitis. Ultramicrosize griseofulvin or liquid microsize griseofulvin for those who cannot swallow pills is an effective treatment (Table 250-3). Treat for a minimum of 8 weeks, and then reevaluate to determine whether therapy should be continued. Alternatively, treatment with weight-based terbinafine dosing can be used. To decrease contagiousness and scale, patients should also wash hair with antifungal shampoo (ketoconazole 2% or selenium sulfide 2.5%) three times per week for the first 2 weeks of therapy.

Other family members, especially children, and other close contacts, such as classmates at school or day care, should be evaluated. Other affected members should be treated simultaneously to prevent reinfection. If *Microsporum* is diagnosed by culture, pets (cats and dogs) should be examined by a veterinarian. Follow-up with a primary care provider or dermatologist is crucial, because persistent infection may manifest only as scale and go unrecognized by caregivers.

HEAD LICE (PEDICULOSIS CAPITIS)

Head lice, or pediculosis capitis, is a common worldwide infestation that usually occurs in children age 3 to 11 years, but can occur at any age. It is caused by the head louse, *Pediculus capitis*, which is approximately 2 to 3 mm in size. Lice need a blood meal every 4 to 6 hours and live for 30 days while laying numerous eggs. Adult lice cannot survive more than 24 hours without a blood meal. The eggs are cemented to the hair by a proteinaceous matrix (**Figure 250-8**). Transmission occurs by head-to-head contact and by brushes and combs.

Head lice are limited to the scalp, behind the ears, and on the back of the neck. Intense pruritus is a feature. Diagnosis is made by identification of nits and/or adult lice in the scalp hair. Nits are oval, gray-white egg capsules. If all nits are located >7 mm from the scalp surface, active infestation is unlikely. **Nits and lice fluoresce with a Wood's lamp** (Table 250-4).

Topical application of permethrin cream (1% or 5%) is the first-line treatment. Apply to the hair, leave on overnight, and rinse off in the morning (Table 250-3). Alternatively, pyrethrin cream or ivermectin lotion can be applied for 10 minutes and then rinsed off. Malathion 0.5% cream is another alternative and is applied to the scalp overnight, but malathion is flammable and should not be used in children less than 6 years old.

Application of thick moisturizing creams to hair followed by drying with a blow dryer has also been used for resistant cases. Repeat treatment in 7 to 10 days is recommended for the above therapeutic options. Children with head lice do not need to be removed from school, because "no-nit" policies have been shown to be excessive.[8]



FIGURE 250-8. Head lice. [Photo contributed by the Department of Dermatology, University of North Carolina.]

POISON IVY/OAK, OTHER ALLERGIC CONTACT DERMATITIS, AND PHOTOSENSITIVITY

Two types of contact allergies are likely to result on the face. The first is the result of an aerosolized allergen. The second is due to direct physical contact that is most prominent on the sensitive parts of the face.

POISON IVY AND POISON OAK/SUMAC

About 70% of individuals are sensitized to poison ivy, oak, or sumac. Involvement of the face can be through aerosolization or direct contact with the plant.

Exposure to aerosolized poison ivy or oak presents as erythema and scale with or without vesiculation (**Figure 250-9**). The involvement is diffuse, with upper and lower eyelids affected. Aerosolization can occur if plants are burned or from activities that can cause the toxic urushiols to become airborne, such as using a weed wacker or lawnmower in a poison ivy patch. Direct contact from plants or contaminated clothing results in the typical linear lesions with vesicle and bullae formation.

Treatment is prednisone, 0.5 milligram/kg/d for 2 to 3 weeks. Washing with water, alcohol, or Tecnu® can help remove the urushiol.

OTHER ALLERGIC CONTACT DERMATITIS

Examples of common direct contactants affecting the face include nickel, nail polishes, toothpaste, preservatives in makeup, contact lens solutions, eyeglasses, and hair care products. Chemical-splash injuries are a common cause of facial irritant contact dermatitis. A thorough history is



FIGURE 250-9. Poison ivy. [Photo contributed by University of North Carolina Department of Dermatology.]

necessary to uncover the offending agent. Referral to a dermatologist may be necessary if the history is unrevealing. This distribution is in contrast with photosensitive eruptions in which non–sun-exposed areas, such as the upper eyelids and the upper lip, are spared (see Figure 250-10). Direct allergic contact dermatitis tends to be most prominent on the most sensitive skin, such as the eyelids.

Medical treatment is of little value if the offending agent is not removed from the patient's environment. Depending on the severity, topical or oral corticosteroids and oral antihistamines are used. Aluminum acetate (Burow's solution, available commercially as Domeboro®) compresses can be beneficial as well. Short duration (3 to 5 days) of medium- to high-potency topical corticosteroids can be used on the face (**Table 250-5**). Often, extensive and severe periocular involvement



FIGURE 250-10. Photosensitivity reaction. [Photo contributed by University of North Carolina Department of Dermatology.]

requires oral prednisone. See Chapter 253, "Skin Disorders: Extremities" for further discussion of treatment of poison ivy, oak, or sumac.

PHOTOSENSITIVITY

Photosensitivity is suspected when exposure to ultraviolet light either exacerbates or directly causes certain conditions. Examples of the former include lupus erythematosus, dermatomyositis, porphyria cutanea tarda, dermatitis of niacin deficiency (pellagra), and recurrences of herpes simplex virus. Examples of the latter include exogenous photosensitivity disorders and the sunburn reaction (see Chapter 217, "Thermal Burns").

Exogenous photosensitivity disorders result from topical application or ingestion of agents that increase the sensitivity of skin to ultraviolet light. Photosensitivity disorders may be phototoxic or photoallergic. Phototoxic reactions occur quickly and appear similar to a sunburn and are thought to be due to direct damage to keratinocytes by UV radiation. Photoallergic reactions occur later and exhibit eczema-like changes in the skin with vesiculation (**Figure 250-10**). Photoallergic reactions are a form of delayed-type hypersensitivity reaction to an allergen formed in the skin after exposure to ultraviolet radiation.

TABLE 250-5 Clinical Features and Treatment of Poison Ivy or Oak, Allergic Contact Dermatitis, and Photosensitivity

Condition	Clinical Features	Treatment	Comments
Poison ivy/oak	Pruritic, linear, erythematous, edematous plaques with vesicles and excoriations	Oral antihistamines Clobetasol 0.05%, fluocinonide 0.05%, or other high-potency topical steroids Prednisone 0.5 milligram/kg/d for 2 to 3 wk	Severe cases may require oral prednisone
Direct contact allergens	Pruritic, scaly, erythematous papules and plaques with or without vesicles in distribution suggestive of exposure	Identification and avoidance of allergen Mid- to high-potency topical steroids such as triamcinolone 0.1% or fluocinonide 0.05%	Severe cases may require oral prednisone
Photosensitivity	Sunburn-like erythema (phototoxic) or pruritic erythematous papules and plaques with or without vesicles (photoallergic) in sun-exposed distribution	Photoprotection Identification and avoidance of photosensitizer	See Table 250-6 for list of common photosensitizing medications

TABLE 250-6 Medications Commonly Causing Photosensitivity Eruptions

Phototoxic	Photoallergic
Chlorpromazine	NSAIDs
Furosemide	Griseofulvin
Tetracyclines (demeclocycline > doxycycline)	Sulfonamides
Thiazides	Para-aminobenzoic acid and most sunscreens
Psoralen	Promethazine
Coal tar	Psoralen
Amiodarone	Sulfonylureas (glipizide, glyburide)
Isotretinoin	Fragrances
Fluoroquinolones	Dapsone

Topical photosensitizers usually result in a cutaneous eruption at the sites of application. Subsequent ultraviolet light exposure is necessary for the eruption to occur. Phytophotodermatitis refers to a topical phototoxic dermatitis due to plants, most commonly caused by a group of chemicals called furocoumarins that are found in lime juice, fragrances, figs, celery, and parsnips. **Table 250-6** lists several ingested substances that can result in a photosensitivity eruption.

History and distribution of the eruption can assist in photosensitivity disorders. Often a linear or spray pattern suggests that an externally applied substance is the culprit. Because photosensitizing medications are ingested and distributed throughout the body, the eruption can involve all sun-exposed areas. The characteristic distribution of a photosensitivity eruption is the face, posterior neck, dorsal hands, and extensor arms. Certain areas, including the creases of the eyelids, upper lip, submental anterior neck, and postauricular neck, are spared.

Photopatch testing performed by a dermatologist or allergist may be helpful in identifying the photosensitizing agent. If the diagnosis is unclear, other photosensitivity disorders, such as lupus erythematosus, dermatomyositis, and polymorphous light eruption, should be excluded.

The most important part of treatment of sunburn and photosensitivity is prevention. Sun avoidance, liberal use of sunscreen (ultraviolet A and B protection with sun protection factor of at least 30) with frequent reapplications, and use of sun-protective clothing are recommended.

In cases of photosensitivity, discontinue the causative agent. Initial management includes topical corticosteroids, and management similar to a sunburn reaction. The patient should avoid the sun until the eruption has cleared completely.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 251

Skin Disorders: Trunk

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Dean S. Morrell
Diana B. McShane

INTRODUCTION

There are many conditions that can have truncal involvement. This section focuses on some common eruptions that frequently affect the trunk: papulosquamous disorders; urticarial and morbilliform disorders; blistering disorders; and miscellaneous disorders. Urticaria and angioedema are discussed in **Chapter 14, "Allergy and Anaphylaxis."** Although the truncal location of an eruption can be a helpful clue for diagnosis, the clinical appearance of the lesions and overall assessment of the patient are needed to make the correct diagnosis.

PAPULOSQUAMOUS DISORDERS

Scaling conditions include psoriasis, seborrheic dermatitis, tinea corporis, pityriasis ("tinea") versicolor, eczema/atopic dermatitis, lichen planus, secondary syphilis, and scabies. **Table 251-1** lists common features distinguishing these eruptions, and **Table 251-2** summarizes common treatments.

PSORIASIS

Psoriasis is discussed in detail in **Chapter 253, "Skin Disorders: Extremities."** Flares of psoriasis can be idiopathic or related to other factors including infection, stress, alcohol ingestion, and medications. The following medications can be related to an exacerbation: steroid withdrawal, lithium, β-blockers, interferon, and antimalarials.[1] The differential diagnosis is listed in Table 251-1.

Diagnosis is clinical. Psoriasis is characterized by well-demarcated erythematous papules and plaques with a silvery white scale (**Figure 251-1**). Removal of the scale typically reveals minute bleeding points referred to as **Auspitz sign**. Chronic plaque psoriasis is the most common variety, and localization to the sacrum, gluteal cleft, or umbilicus can occur. In the skin folds, psoriasis often lacks the characteristic silvery scale and is present only as well-demarcated, red- to salmon-colored plaques. Involvement of the scalp and nails is not uncommon. Lesions of psoriasis tend to be symmetric with a predilection for the extensor surfaces. Localized physical trauma can cause new lesions to form (**Koebner phenomenon**—scratching causes new lesions to form in linear distribution of the scratch). Small, scattered discrete lesions, like water droplets, represent a distinctive form of psoriasis called **guttate psoriasis** (**Figure 251-2**). This can be seen on the trunk as an abrupt eruption following an infection, such as streptococcal pharyngitis, and can also be associated with human immunodeficiency virus. Generalized pustular psoriasis (**Figure 251-3**) should be included in the differential diagnosis of the acutely ill patient with generalized pustules.

First-line topical treatment for localized plaques includes topical steroids (Table 251-2). Ointment-based products penetrate best into thick plaques. High-potency steroids, such as clobetasol ointment or cream, can be used on the trunk (avoid use in axillae). Prolonged use may result in atrophy, steroid acne, pyoderma, or rebound with abrupt discontinuation. Follow-up with a dermatologist is critical for continued management. **Do not prescribe systemic steroids due to the great risk of rebound or induction of pustular psoriasis.**

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a chronic inflammatory disease with a predilection for areas of increased sebaceous gland activity. Incidence increases with age and in specific disease states.[2] Erythema with a greasy yellowish scale is seen in the sebum-producing areas, such as the scalp, eyebrows, ears, beard, midchest, and groin (**Figure 251-4**). The lesions are often well marginated and symmetric. Weeping, crusting, and pruritus may occur, especially in the body folds and ears. Severe involvement may occur in patients with Parkinson's disease, trisomy 21, human immunodeficiency virus, or acquired immunodeficiency disease. In an otherwise healthy-appearing patient with severe or new-onset seborrheic dermatitis, consider human immunodeficiency virus testing.

The presternal area, axillae, and groin are common sites for truncal involvement. The axillary involvement typically starts in the apices, similar to a contact dermatitis to deodorants, whereas clothing dermatitis involves the periphery but spares the axillary vault. The inframammary regions and umbilicus may also be involved. **Treatment** is aimed at controlling disease (Table 251-2). Mild cases may respond to over-the-counter shampoos containing ketoconazole 1%, selenium sulfide, zinc pyrithione, or salicylic acid. These can be lathered into any affected area on the scalp or body. Prescription-strength ketoconazole 2% shampoo

TABLE 251-1 Comparison Features of Common Papulosquamous Eruptions

Condition	Distinguishing Clinical Features	Location	Special Signs	Comments
Psoriasis	Erythematous, well-marginated papules and plaques with silvery scale	Trunk, extensor surfaces, scalp	Auspitz sign, Koebner phenomenon, nail pitting	Hereditary predilection; onset in early 20s
Seborrheic dermatitis	Greasy, yellow scales	Mid chest, suprapubic, scalp, facial creases	Can overlap with psoriasis, "sebopsoriasis"	Debilitated, elderly, or infants (cradle cap)
Pityriasis rosea	Oval scaly macules with collarettes of scale following skin tension lines	Trunk, in Christmas tree pattern	Herald patch 1–2 wk before general eruption	Spring and fall, age 15–40 y old; viral exanthem, herpes 6 and 7
Tinea corporis	Sharply demarcated, erythematous, scaly annular plaques; may coalesce into gyrate patterns	Trunk, legs, arm, neck	May need KOH/culture to diagnose; septate branching hyphae on KOH	All ages; from pets, soil, or autoinoculation from hands/feet; incubation days or months
Pityriasis (tinea) versicolor	Versicolored—red, salmon, light brown, dark brown, hypopigmented; well-demarcated scaly patches	Central upper chest and back	"Spaghetti and meatballs" on KOH; nonseptate pseudohyphae and yeast cells	Young adults, summer, hot humid environments
Atopic dermatitis	Erythematous scaly macules/patches; chronic with lichenification	Flexures > trunk	Spares the nose	Pruritic "itch that rashes"; atopic individuals
Contact dermatitis	Ill-defined vesicles forming plaques with scale; chronic lesions lichenified	Varies based on site of exposure; dorsal hands, face commonly affected	Burning > itching in irritant contact (vs. allergic contact)	Common allergens: nickel, poison ivy, fragrances Common irritants: soap, wet work/frequent hand washing, production work materials
Lichen planus	5 Ps: purple, pruritic, polygonal, planar papules	Any skin, mucous membranes, hair follicles	Wickham striae, Koebner phenomenon	Age 20–60 y old
Secondary syphilis	At 2–10 wk, macular erythema on trunk, abdomen, inner extremities; followed by papular or papulosquamous lesions	Palms, soles, trunk	Serology	Great masquerader—can take any form; can be confused with pityriasis rosea
Scabies	Pruritic papules and burrows with crusting	Finger webs, wrists, axillae, areolae, umbilicus, abdomen, waistband, genitals	Scrapings show mites, feces, eggs	Can be chronic "7-year itch"; intensely pruritic, especially at night

Abbreviation: KOH = potassium hydroxide.

TABLE 251-2 Treatment of Common Papulosquamous Disorders

Condition	Method	Agent(s)	Dosage	Comments
Psoriasis	Topical	Clobetasol 0.05% cream or ointment Triamcinolone 0.1% cream or ointment	Twice a day	Use clobetasol for thick plaques and triamcinolone for thinner plaques. **Avoid systemic steroids!**
Seborrheic dermatitis	Topical	**Scalp and body:** Ketoconazole 2% shampoo OTC selenium sulfide shampoo (Selsun Blue®) or zinc pyrithione shampoo (Head & Shoulders®) **Face:** Ketoconazole 2% cream Hydrocortisone 2.5% cream	**Scalp and body:** Apply to scalp twice a week. Let sit 3–5 min before rinsing. **Face:** Twice a day until improved	May need to use low-potency topical steroid for chest involvement until improved.
Pityriasis rosea	Topical	Triamcinolone 0.1% cream Hydrocortisone 2.5% cream	Twice a day	
	Oral	Antihistamines		
Tinea corporis	Topical	Terbinafine cream (Lamisil®) (OTC) Butenafine cream (Lotrimin Ultra®) (OTC) Ciclopirox cream (Rx)	Twice a day, extend ≥3 cm beyond edges; treat ≥4 wk and until 1 wk after clearing	
	Oral	Terbinafine Fluconazole	250 milligrams PO daily for 2 wk 200 milligrams PO weekly for 4 wk	**Oral:** Check detailed references for adverse effects, contraindications, drug interactions, and pediatric dosing. Therapy duration for tinea capitis and tinea unguium/onychomycosis differs from treatment duration for tinea corporis.

(*Continued*)

TABLE 251-2 Treatment of Common Papulosquamous Disorders (*Continued*)

Condition	Method	Agent(s)	Dosage	Comments
Pityriasis (tinea) versicolor	Topical	Ketoconazole 2% shampoo	Apply and let sit 3–5 min as a body wash daily for 7 d	Treatment is successful with cessation of scaling. Pigment alterations may take several months to resolve.
		Ketoconazole 2% cream Miconazole 2% cream Econazole 1% cream	Twice a day for 2–4 wk	
	Oral	Fluconazole	200 milligrams weekly for 2 wk	
		Itraconazole	200 milligrams daily for 5 d	
Atopic dermatitis	Topical	**High-potency corticosteroids:** Clobetasol 0.5% Halobetasol 0.5% **Mid-potency steroids:** Triamcinolone 0.1% **Low-potency steroids:** Hydrocortisone 2.5%	Twice a day	These options are available in ointment and cream formulations.
	Oral	**Antihistamines**		
		Fexofenadine	180 milligrams every morning	Encourage scheduled dosing during flares.
		Zyrtec	10 milligrams every evening	
Contact dermatitis	Topical	Same as for atopic dermatitis	Same as for atopic dermatitis	
	Oral	Prednisone	40–60 milligrams PO every morning tapered over 3 wk Children: 1–2 milligrams/kg PO (up to 40 milligrams) tapered over 3 wk	For severe contact dermatitis.
		Antihistamines Same as for atopic dermatitis	Same as for atopic dermatitis	
Lichen planus	Topical (cutaneous)	Triamcinolone 0.1% ointment Fluocinonide 0.05% ointment	Twice a day	
	Topical (mucous membranes)	Fluocinonide 0.05% gel	Four times daily	
		Lidocaine 2% jelly	Three times a day	
Secondary syphilis	Intramuscular	Benzathine penicillin G	Single dose of 2.4 million units IM Doxycycline 100 milligrams PO every 12 h for 2 wk	Doxycycline for use in penicillin-allergic patients.
Scabies	Topical	Permethrin 5% cream	One application at bedtime to entire body from neck down. Wash off in 8–12 h. Repeat in 7 d.	Permethrin is acceptable in infants older than 2 months. Patient and all household members/close contacts must be treated concurrently. Wash linens and recently worn clothes in hot water, dry on high heat.
	Oral	Ivermectin	200 micrograms/kg PO once. Repeat in 7 d.	

Abbreviation: OTC = over the counter.

can be used several times weekly, or ketoconazole cream for the face can be used twice daily. Hydrocortisone 1% cream or lotion, or 2.5% cream or lotion for more difficult cases, can be used twice daily in combination with antifungals until improvement is seen.

PITYRIASIS ROSEA

Pityriasis rosea is a viral exanthema associated with herpesvirus 6 and 7. It may be a reactivation of the latent herpesvirus that triggers a viremia and subsequent eruption.[3] Typically, it affects those between 15 and 40 years old, most often in spring and fall. Pityriasis rosea often begins with a "herald" patch, which is a single, fine scaling, erythematous to salmon-colored discrete oval patch 2 to 5 cm in size (**Figure 251-5**). In 1 to 2 weeks, a generalized eruption occurs on the trunk and proximal arms, with a characteristic "Christmas tree" pattern of macules and plaques, with the long axis of the lesions oriented along skin tension lines (**Figure 251-6**). A collarette of scale with the open edge of scale on the inside of the lesion is a helpful diagnostic finding. Rarely, the face, palms, soles, or oral cavity can be involved. Pruritus can be moderate to severe. Mild constitutional symptoms may also occur at the onset of the eruption. Spontaneous resolution occurs within 4 to 16 weeks. Relapses or recurrences are uncommon.

Table 251-1 lists the major differential diagnoses. In addition, several medications can cause a pityriasis-like eruption, including captopril, barbiturates, lisinopril, ketotifen, arsenicals, interferon, imatinib mesylate, gold, and clonidine. Guttate psoriasis can mimic pityriasis rosea but does not have the characteristic collarette of scale. **Syphilis** is another key item on the differential, particularly with palm and sole involvement, and a rapid plasma reagin should be considered if the diagnosis is at all in question.

Treatment is symptomatic (Table 251-2). Oral antihistamines and topical steroid creams (triamcinolone 0.1% cream) with emollients (petroleum jelly–based preparations) can help the pruritus. Ultraviolet B phototherapy from a dermatologist or natural sunlight may speed the resolution of the lesions. Improvement with high-dose acyclovir has been reported.[4] Macrolides are not indicated.[5,6]



FIGURE 251-1. Psoriasis. Large, well-marginated scaling plaques. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-2. Guttate psoriasis. Note discrete erythematous scaly papules resembling raindrops on the trunk. [Photo contributed by University of North Carolina Department of Dermatology.]

TINEA CORPORIS

All superficial dermatophyte infections of the trunk, neck, arms, and legs are referred to as *tinea corporis*. Specific names are used for eruptions involving the groin (tinea cruris), feet (tinea pedis), hands (tinea manuum), face (tinea faciei), and scalp (tinea capitis); see associated chapters in this section for more detailed information about these specific locations. All ages can be affected, and lesions can spread by autoinoculation from other parts of the body. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the most common organisms that can spread from involvement of the feet. Occupational or recreational exposure (gyms, locker rooms) occurs from contaminated clothing, furniture, and/or equipment. Exposure to animals or contaminated soil may also cause tinea corporis. Pets may harbor *Trichophyton verrucosum* or *Microsporum canis*, whereas *T. mentagrophytes* from Southeast Asian bamboo rats can cause a very inflamed and highly contagious widespread eruption. The incubation period is variable and may be days or months after exposure.[7] The eruption may be chronic with mild pruritus as the only symptom. Tinea corporis is characterized by one or more sharply demarcated, mildly erythematous, annular scaling plaques (**Figure 251-7**). Central clearing gives the name "**ringworm**." The advancing scaling border is a characteristic finding, and the border is an excellent area to demonstrate long branching hyphae with a potassium hydroxide preparation (see Figure 248-1). Abrupt onset of widespread tinea may be associated with acquired immunodeficiency syndrome or other immunosuppressive disorders, or use of topical steroids. Occlusion, shaving, or topical steroid use may result in a deep, purulent, boggy folliculitis. The differential diagnosis is provided in Table 251-1.

Treatment of localized lesions is with topical antifungal preparations (Table 251-2). Apply twice a day and **extend the application to at least 3 cm beyond the advancing margin**. Treat for at least 4 weeks and continue for 1 week after resolution. If tinea pedis or unguium is also present, apply the antifungal to the feet and nails. Widespread tinea corporis or involvement of hair follicles warrants oral therapy (Table 251-2).[7] Oral agents may be expensive and can have interactions and contraindications in specific patient populations. Refer to a drug reference manual

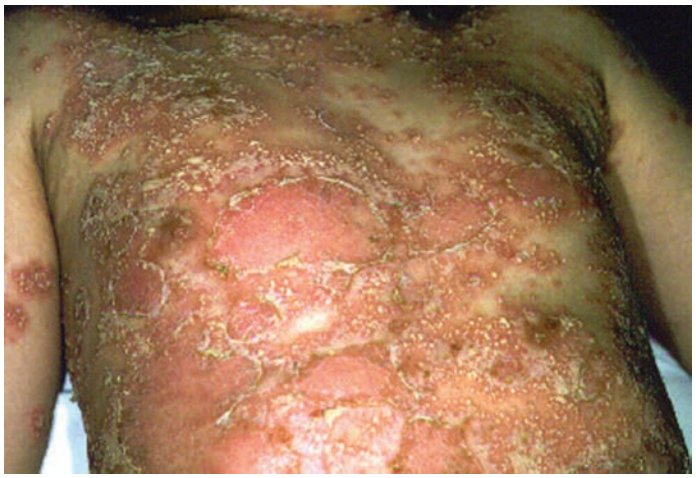


FIGURE 251-3. Pustular psoriasis. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-4. Seborrheic dermatitis. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

for specific details. Baseline or concurrent liver enzyme levels when prescribing **terbinafine** are optional. Drug-induced liver injury is reported to be between 1 in 50,000 and 1 in 120,000 prescriptions, and 1% of patients develop a transient asymptomatic elevation of liver enzymes.[8] Safety profiles of both terbinafine and **fluconazole** in children are similar to those in adults.[8,9] Provide scheduled follow-up with a dermatologist or primary physician to assess treatment response.

"TINEA" PITYRIASIS VERSICOLOR

Pityriasis versicolor is caused by the overgrowth of the yeasts *Malassezia furfur* (previously *Pityrosporum ovale*) and *Malassezia globosa*. *Malassezia* species are part of the normal cutaneous flora and reside in keratin of skin and hair follicles. They require oil to grow, so the disease is more prevalent in young adults when sebaceous gland activity is highest. Predisposing factors include high temperature/humidity, oily skin, and steroid treatment.



FIGURE 251-5. Herald patch in pityriasis rosea (*arrow*). [Courtesy of the Centers for Disease Control and Prevention.]



FIGURE 251-6. Pityriasis rosea. Fine scaly plaques along skin tension lines. [Photo contributed by University of North Carolina Department of Dermatology.]

Asymptomatic, hypo- or hyperpigmented, often coalescing scaly macules are seen on the trunk or proximal extremities. The central upper chest and back are the most common areas of involvement (**Figure 251-8**). Facial lesions may be present in infants and the immunocompromised. The "versicolor" refers to the varying shades of erythema and pigmentation. In untanned individuals, the lesions may be salmon or light brown. On darkly pigmented skin, the lesions may be hypopigmented. The fine scale is best appreciated by gently abrading the lesions with a glass slide or blade. The condition may be present for months or years and is usually asymptomatic, although pruritus can occur. Patients usually present due to cosmetic concerns regarding the inconsistent pigmentation.

The hyperpigmented, scaling pink macules of pityriasis versicolor may appear similar to those found in tinea corporis, psoriasis, pityriasis rosea, seborrheic dermatitis, or nummular eczema. Hypopigmented lesions should be differentiated from pityriasis alba, leprosy, or postinflammatory conditions. A potassium hydroxide preparation obtained by gently scraping the surface of the lesion and examining under the microscope (Table 248-6) will reveal the characteristic short chopped hyphae and yeast forms termed "spaghetti and meatballs" (**Figure 251-9**) characteristic of *Malassezia* infection.

Treat with ketoconazole 2% shampoo, applied daily for a week, washing off after 3 to 5 minutes, or consider twice-daily treatment with azole



FIGURE 251-7. Tinea corporis. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-8. Tinea versicolor. Hypopigmented macules with fine scale. [Photo contributed by University of North Carolina Department of Dermatology.]

antifungal creams, such as clotrimazole (Table 251-2). Widespread involvement usually makes these less cost effective and more difficult to apply. Extensive or refractory pityriasis versicolor can be treated with oral fluconazole or itraconazole (Table 251-2).[7,10]

Discoloration may take months to resolve after treatment and is not a sign of treatment failure. Relapses are frequent, and instructions on prophylactic regimens should be given to include once-weekly selenium sulfide 2.5% or ketoconazole 2% shampoo.

ECZEMA/ATOPIC DERMATITIS/CONTACT DERMATITIS

The terms *eczema* and *atopic dermatitis* are often used interchangeably and have a variety of presentations. This section focuses on truncal involvement. In chronic eczema, the hallmark is the "itch that rashes," in which an itch–scratch cycle perpetuates the condition. Itching is common and often worse at night and is aggravated by heat and sweat. Atopic individuals have a personal or family history of asthma, allergic rhinitis, nasal polyps, or "sensitive" skin. The acute stage demonstrates erythematous plaques that may be edematous and with miniature vesicles, whereas subacute lesions have more scale. The chronic stage presents with thickened (lichenified)

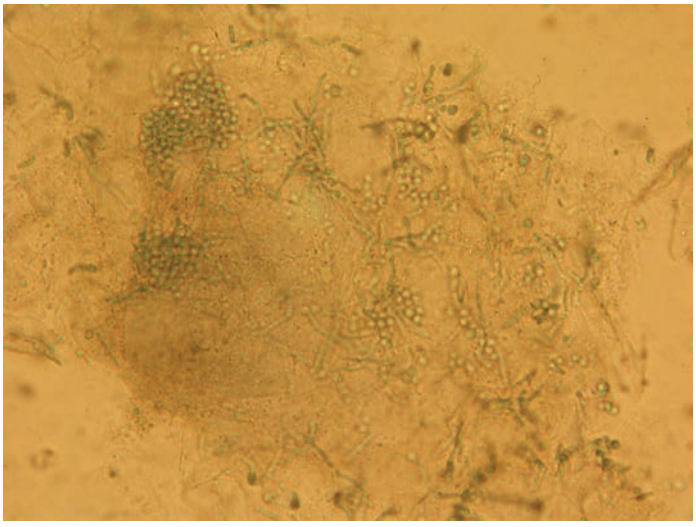


FIGURE 251-9. Tinea versicolor. Potassium hydroxide preparation with pseudohyphae, showing "spaghetti and meatballs" pattern. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-10. Atopic dermatitis. Lichenification, excoriations, and ill-defined scaling erythema. [Photo contributed by University of North Carolina Department of Dermatology.]

skin showing accentuation of the normal skin markings caused by chronic rubbing (**Figure 251-10**). Scratching causes excoriations.

Chronic contact dermatitis may be misdiagnosed as eczema or atopic dermatitis (Table 251-1) or may actually be a factor in the flare of eczema. See **Chapter 253, "Skin Disorders: Extremities,"** for further discussion. The acute stage is typically limited to the area of contact with well-marginated erythema and edema. Papules and vesicles may be present, and bullae may occur in severe reactions with secondary crusting and erosions. Linear (such as from poison ivy) or geographic lesions (such as nickel allergy; **Figure 251-11**) are typical. Pruritus can be severe. Subacute lesions have mild erythema, dry scale, and fine papules. Chronic eruptions will be lichenified with accentuation of the skin markings and show postinflammatory pigmentary changes. The subacute and chronic stages are frequently confused with endogenous eczema. The distribution is initially confined to the site of exposure but later can spread to sites beyond.

Treatment is directed at disease control (Table 251-2).[11] Avoid harsh soaps and other irritants or contactants. Moisturize within 2 minutes of bathing with plain petroleum jelly, Aquaphor®, or Eucerin® cream. Use topical steroids, such as 2.5% hydrocortisone ointment, for mild disease or intertriginous sites; medium-potency preparations, such as triamcinolone 0.1%, for moderate involvement; or higher potency steroids, such as clobetasol, for more severe eruptions. Ointments are the most effective vehicle, but creams are also effective if patients prefer not to use ointments. Severe contact reactions may require an oral prednisone taper over 3 weeks. The usual dose in a child is prednisone, 1 to 2 milligrams/kg PO, up to 40 milligrams/d. Adults respond well to a tapering dose of prednisone, starting at 40 to 60 milligrams/d PO each morning. Oral antihistamines, such as diphenhydramine or hydroxyzine, can control nighttime pruritus and scratching. Staphylococcal or streptococcal superinfections typically present with crusting and exudates. Prescribe cephalexin or dicloxacillin



FIGURE 251-11. Allergic contact dermatitis. Erythematous scaly papules and lichenified plaques on the lower abdomen (contact with belt buckles). [Photo contributed by University of North Carolina Department of Dermatology.]

because antibiotic resistance is common with erythromycin. Obtaining cultures prior to initiating antibiotics may be useful.

Treat for community-acquired methicillin-resistant *Staphylococcus aureus* based on cultures or local patterns of bacterial resistance.

LICHEN PLANUS

Lichen planus may affect the skin, mucous membranes, and hair follicles. It is idiopathic in most cases, although cell-mediated immunity and human leukocyte antigen genetic susceptibility probably play a role. Age of onset is usually between 20 and 60 years old, and there is a 1% to 2% familial incidence.[12]

The hallmark of lichen planus is the constellation of the "5 Ps": purple, polygonal, pruritic, planar papules. The onset may be abrupt or over several weeks. The course is variable and may last months to years. Spontaneous resolution may occur, but recurrences are also common. The violaceous flat-topped papules may be discrete or generalized (**Figure 251-12**). Common sites of involvement include the lumbar region, flexor wrists, pretibia, scalp, and penis. **Koebner phenomenon**, caused by scratching, may result in a linear array of papules. In pigmented skin, a deep brown hyperpigmentation may occur. **Wickham striae** are fine white lacy reticulate lines that adhere to the papules and are pathognomonic for this condition (**Figure 251-13**). Mucous membrane involvement occurs in approximately half of those with the disease, and oral involvement only is common. The posterior buccal mucosa is most commonly affected; however, gingiva, tongue, and lips may also be involved. Painful erosions may be present and carry a 2% to 3% lifetime risk of squamous cell carcinoma in these areas. Approximately 70% of



FIGURE 251-12. Lichen planus. Violaceous, flat-topped polygonal papules on the back. [Photo contributed by University of North Carolina Department of Dermatology.]

patients with mucosal vulvovaginal lichen planus also have oral involvement, so it is important to ask about genital symptoms.[12]

There are many other variants of lichen planus, with the most common being hypertrophic, which presents with thick, hyperkeratotic plaques on the shins. Annular lichen planus is more common in men and typically involves the axillae, penis, or groin. This variant presents with asymptomatic ringed lesions approximately 1 cm in diameter.



FIGURE 251-13. Lichen planus. Wickham striae, lace-like striations. [Photo contributed by University of North Carolina Department of Dermatology.]

Follicular involvement of the scalp can result in a scarring alopecia. Nail changes can result in destruction of the nail fold and nail bed, with longitudinal splintering (pterygia).

Other papulosquamous diseases are included in the differential diagnosis of lichen planus (Table 251-1). The oral mucosal involvement and Wickham striae are helpful in distinguishing lichen planus from psoriasis. Chronic discoid lupus and fungal infections may have similar cutaneous findings.

Lichenoid drug eruptions can be identical to lichen planus, except they tend to be more generalized and photodistributed and there is a history of drug ingestion. The latent period can be months to years, with an average of 12 months, and it may take years to resolve after withdrawal of the offending agent. Common medications are listed in Table 251-4. Chronic graft-versus-host disease, dermatomyositis, and malignant lymphomas may also have lichenoid eruptions.

Treatment is with topical or intralesional steroids. Mid- to high-potency preparations, such as triamcinolone 0.1% ointment or fluocinonide 0.05% ointment twice a day, are helpful, although treatment does not cure the disease. Intralesional triamcinolone, 3 milligrams/mL, can be used for very symptomatic cutaneous or mucous membrane lesions. Fluocinonide or clobetasol 0.05% gel four times a day can be used in the mouth. Oral analgesics, such as lidocaine jelly 2%, can be applied to the erosions three times a day before meals. Severe erosions or oral involvement may require PO prednisone, 40 to 60 milligrams every morning for 1 to 2 weeks. If oral or other mucosal erosions are present, prompt follow-up with a dermatologist is crucial for further management and monitoring. Other systemic treatments include cyclosporine, retinoids, azathioprine, methotrexate, and mycophenolate mofetil.

SECONDARY SYPHILIS

Although the lesions are transient and often clinically unimpressive, the inclusion of secondary syphilis in the differential diagnosis of papulosquamous conditions in the ED is important. Primary syphilis is discussed in Chapter 153, "Sexually Transmitted Infections."

Secondary syphilis exhibits skin manifestations in most patients and consists of early and later manifestations. The **early eruption** appears 2 to 10 weeks after the appearance of the primary chancre and is an evanescent macular rash lasting only a few hours or days. The macular erythema commonly appears on the sides of the trunk, midabdomen, and inner extremities. The discrete round macules are of varying shades from light pink to rose or even brownish red. They may be faint and difficult to appreciate on darkly pigmented skin. This phase of the disease is often asymptomatic, although associated symptoms can include pruritus, fever, sore throat, fatigue, headache, meningismus, and shotty, firm, nontender lymphadenopathy of the posterior cervical, axillary, and epitrochlear regions. The macular eruption resolves spontaneously and may leave postinflammatory hyperpigmentation.[13]

Later eruptions of secondary syphilis may present in a variety of forms, hence the name the *great imitator*. This phase typically lasts 2 to 6 weeks and resolves spontaneously. There is usually no itching. Multiple recurrences over a period of 1 year can occur before infection enters the latent stage. The later eruptions of secondary syphilis are often papular lesions 2 to 5 mm in size, may be generalized, and are reddish to copper in color. The papules may be subtle or deeply infiltrated and firm. The surface may be smooth and shiny or have a thick, adherent scale (**Figure 251-14** and Figures 153-6 and 153-7). Palmar-plantar involvement is a helpful finding and is characterized by tender copper-colored discrete macules with a collarette of scale. Postinflammatory hyperpigmentation can be prominent and persist for weeks to months. Psoriasiform, follicular, lichenoid, or acneiform lesions can occur. Patients with human immunodeficiency virus may have atypical presentations, including very large infiltrated, scaling, and crusted plaques. Annular lesions may occur, most frequently around the mouth, and may mimic sarcoidosis. Patchy nonscarring "moth eaten" alopecia may be present. Split papules at the corners of the mouth, asymptomatic white plaques on mucous membranes, and condyloma lata in the genitals are highly infectious stigmata.

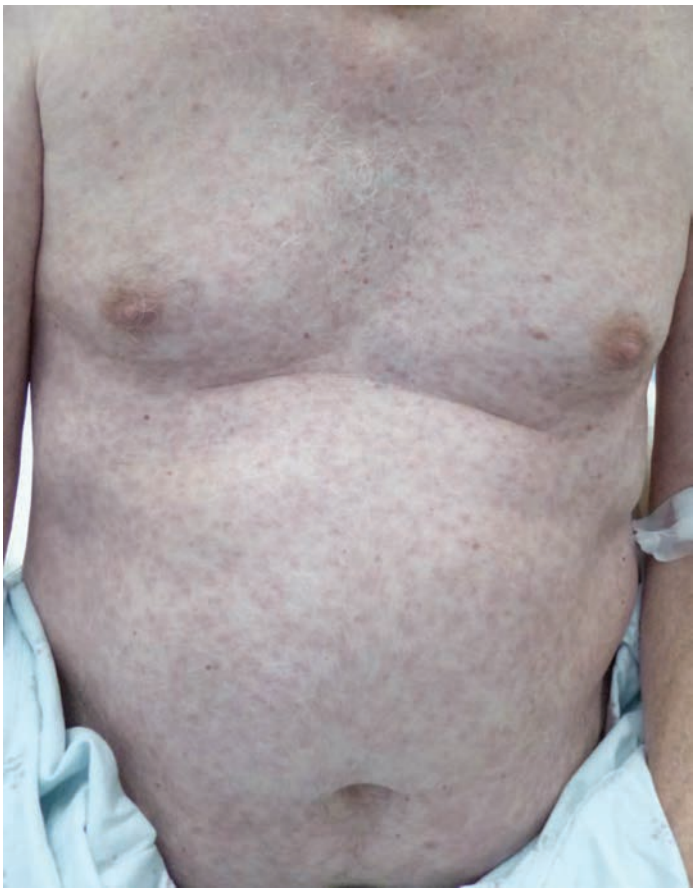


FIGURE 251-14. Secondary syphilis. Papulosquamous eruption. [Photo contributed by University of North Carolina Department of Dermatology.]

In secondary syphilis, the nontreponemal serologic tests are strongly reactive. Exceptions include the prozone phenomenon, in which a false-negative result occurs with high antibody titers, and rarely, in patients with acquired immunodeficiency syndrome, seronegative syphilis may occur. Histologic stains of affected tissues can be performed to confirm the diagnosis in seronegative patients.

The various cutaneous manifestations of syphilis may resemble many other cutaneous diseases (Table 251-1). **Pityriasis rosea** is the most common condition to consider and can have very similar cutaneous findings. However, the lesions of syphilis tend to be more circular and randomly arranged on the trunk, whereas pityriasis rosea has the oval "Christmas tree" distributed pattern. Pityriasis rosea also lacks palmoplantar and mucous membrane lesions and lymphadenopathy.

Treatment is benzathine penicillin G (Table 251-2). Doxycycline, 100 milligrams PO twice a day for 2 weeks, can be used in penicillin-allergic patients. Further discussion is provided in **Chapter 153, "Sexually Transmitted Infections."**

SCABIES

Scabies is infestation by the *Sarcoptes scabiei* mite and **should be considered in any patient with complaints of severe generalized pruritus**. The mite burrows and multiplies within the upper layer of the skin, and itching results from an immunologic response to the mites or their feces. In classic scabies, there are only 6 to 10 live mites present on the skin. In immunocompromised patients, there may be more than 1 million mites present.

Scabies is usually spread by skin-to-skin contact and can occur in any age group. **The mite can also remain alive for >48 hours on inanimate objects, such as clothing and linens.** The eruption can vary, ranging from minimal findings to extensive secondary excoriations and eczematous lesions. Hypersensitivity to the mite occurs before the development of symptoms. The initial exposure may not produce symptoms for several weeks. Reinfestation may produce pruritus within 1 to 3 days.



A B

FIGURE 251-15. **A** and **B.** Scabies. Erythematous scaling papules with excoriation. [Photos contributed by University of North Carolina Department of Dermatology.]

Previous sensitization, inadequate treatment, and the host's immune status can alter the appearance of the condition. Chronic, undiagnosed scabies is referred to as *the 7-year itch*.

Intense pruritus is common, especially at night, although immunosuppressed patients may be asymptomatic. Common sites of involvement include the finger webs, wrists, axillae, areolae, umbilicus, lower abdomen, waistband, and genitals (**Figure 251-15, A and B**). Women frequently complain of nipple itching, whereas men most frequently note the penile or scrotal pruritic lesions. Pruritic papules, secondary excoriations, and burrows (especially of finger or toe webs) are the classic findings. Secondary infection with crusting may occur. The head and neck are typically spared, although they may be involved in infants and the immunocompromised. Red-brown papules and nodules may occur on the penis and scrotum.

Crusted scabies occurs in immunosuppressed or debilitated patients. The lesions can be generalized and include the face and scalp, with marked crusting and heavy scaling. Pressure-bearing sites, such as the buttocks, elbows, and feet, are common areas of hyperkeratotic lesions. The tips of the fingers can be swollen, crusted, and have a psoriasiform scaling under the nails. See Chapter 252 and Figure 252-4 for more discussion of crusted scabies.

Atypical lesions can be seen in infants with involvement of the face and scalp, as well as vesicles or pustules on the palms and soles. An autosensitization-type reaction ("id") can occur with widespread urticarial papules predominantly on the trunk and proximal extremities. Other pruritic disorders, including eczema, atopic dermatitis, contact dermatitis, urticarias, dermatitis herpetiformis, pediculosis infestation, lichen planus, and metabolic disorders such as uremia or hypo- or hyperparathyroidism, should be considered in the evaluation. The presence of pruritus in other family members or close contacts is a helpful clue to scabies. A #15 blade can be gently scraped across a typical burrow and placed on a slide with mineral oil for microscopic confirmation. Diagnosis is made by the presence of the mite, feces, or ova (**Figure 251-16**).

Treat with **permethrin 5% cream** applied overnight to the patient and all family members and close contacts (Table 251-2). Apply permethrin from the neck down, covering all areas of the body, including under the nails, in the umbilicus, around the nipples, and the genitals. Treat the face and scalp in affected infants and young children. Wash off in 8 to 12 hours. A second application administered 1 week after the first is recommended. **Lindane® is no longer recommended** because of potential neurotoxicity and resistance.[14]

Ivermectin, 200 micrograms/kg PO single dose, is a very effective therapy for common and crusted scabies. Once-a-week dosage for two treatments is recommended. Three or more treatments may be required in the heavily infested or immunocompromised patient. This is also a convenient treatment for institutions or large groups.

Equally important in the treatment is the decontamination of the clothing, bed linens, and towels by hot water washing and machine drying. Items that cannot be washed should be sealed in plastic bags for 10 days. Itching may last for several weeks after treatment and is a sensitivity reaction to the remaining dead mites and mite products in the skin. Cortisone creams, such as triamcinolone 0.1%, or oral antihistamines can be given for the pruritus.

MORBILLIFORM/URTICARIAL ERUPTIONS

This section discusses the common morbilliform and urticarial eruptions: urticaria, pruritic urticarial papules and plaques of pregnancy, erythema migrans, and drug eruptions. See **Table 251-3** for a summary of clinical presentations and treatments.

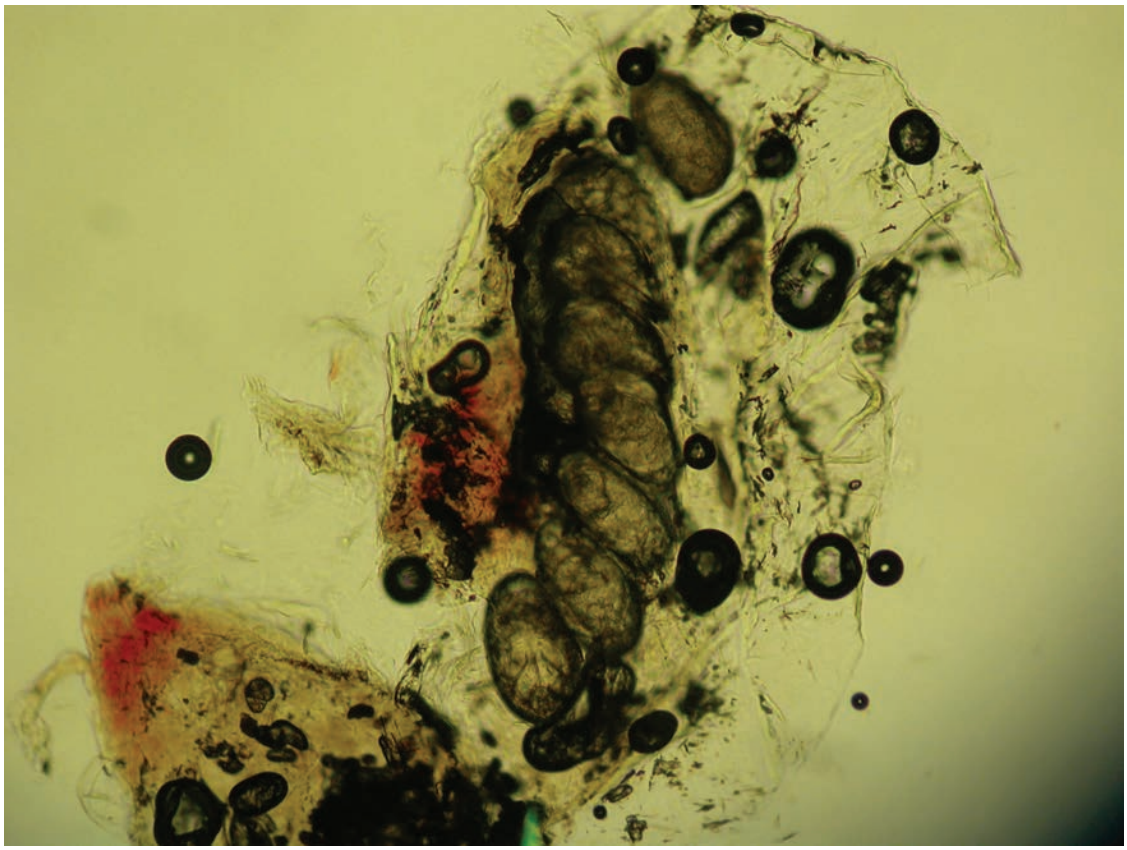


FIGURE 251-16. Scabies eggs and feces. [Photo contributed by University of North Carolina Department of Dermatology.]

URTICARIA AND ANGIOEDEMA

Urticaria is a vascular leak in the superficial dermis of the skin characterized by transient pruritic wheals and welts. **Angioedema** is the presence of larger edematous areas that involve the deeper dermis and the subcutaneous tissue. Both of these conditions may be acute or chronic, and the individual lesions come and go within 24 hours. The acute course is <6 weeks, whereas chronic urticaria/angioedema can last several years.

Acute urticaria can be immunoglobulin E–mediated or triggered by penicillins, sulfa drugs, minocycline, food allergies, stings or bites, and infections. An unusual allergy characterized by acute urticaria or anaphylaxis is allergy to meat (beef, lamb, pork), resulting from immunoglobulin E–mediated **allergy to galactose-α-1,3 galactose**.[15] It is thought that sensitization is mediated by a Lone Star tick bite (often not recognized), which introduces the oligosaccharide galactose-α-1,3 galactose into the bitten person, resulting in immunoglobulin E antibody production. About 4 hours after eating meat, urticaria or anaphylaxis develops. Treatment is the same as for urticaria or anaphylaxis of any cause, and control is maintained by avoidance of eating any meat. Duration of allergy is unknown. Galactose-α-1,3 galactose allergy is reported in the middle United States and the north, central, and southern Atlantic states where the Lone Star tick is prevalent. Nonimmunologic causes of urticaria, angioedema, and anaphylaxis include NSAIDs and radiocontrast material.

Angioedema occurring in the absence of urticarial wheals can occur in hereditary and nonhereditary forms. C1 esterase inhibitor deficiency is a hereditary cause of recurrent angioedema without wheals. Nonhereditary, non–immunologic-mediated triggers include NSAIDs, angiotensin-converting enzyme inhibitors, radiocontrast material, penicillins, and monoclonal antibodies. **In the case of angiotensin-converting enzyme inhibitors, an angioedema reaction can occur more than a year after**

TABLE 251-3 Clinical Features and Treatment of Common Morbilliform/Urticarial Eruptions

Condition	Clinical Features	Treatment	Comments
Urticaria/angioedema	Urticaria: transient pruritic edematous wheals Angioedema: deeper, poorly defined edematous plaques	Epinephrine (if associated with anaphylaxis) First-generation antihistamines (diphenhydramine, hydroxyzine) Second-generation antihistamines (cetirizine, loratadine) Prednisone 1 milligram/kg/d up to 60 milligrams PO daily	See Chapter 14 and Table 14-4 for details
Polymorphic eruption of pregnancy (formerly pruritic urticarial papules and plaques of pregnancy)	Pruritic erythematous papules often in abdominal striae, progress to plaques	Triamcinolone 0.1% cream twice a day Diphenhydramine, loratadine, or cetirizine	Do not use fluorinated steroids in pregnancy
Erythema migrans	Expanding, annular, erythematous patch; may have concentric rings of erythema	Doxycycline 100 milligrams twice a day for 3 wk	Refer to Chapter 161, "Zoonotic Infections" for more details

starting the medication and is a reason for discontinuation of the medication.[16,17]

Chronic urticaria consists of recurring lesions for longer than 6 weeks. Intolerance to NSAIDs, benzoates, contrast dye, and opiates is common, but the cause is often unknown. Physical stimuli such as cold, pressure, and extreme exercise may produce urticarial reactions.[17] Ask about reactions occurring 4 to 6 hours after eating meat (see above discussion).

Pruritic edematous papules coalescing into plaques can affect any area of the skin. The urticarial wheals are white, pink, or erythematous nonscaling lesions that range in size from <1 cm to >10 cm. The pattern can be annular, serpiginous, or confluent (**Figure 251-17, A and B**).



A



B

FIGURE 251-17. **A** and **B.** Urticaria. Characteristic wheals. [Photos contributed by University of North Carolina Department of Dermatology.]

Lesions wax and wane over 24 hours. Angioedema consists of deeper, less well-demarcated edematous plaques and can be associated with bronchospasm and hypotension. The diagnosis is clinical. **Atypical erythema multiforme** can resemble urticaria, but the lesions of erythema multiforme are not pruritic or transient. Contact urticaria can develop from specific allergies (latex) or chemicals.

Treatment, summarized in Table 251-3, includes various antihistamines and systemic corticosteroids. H_1 blockers have been a mainstay of treatment. Long-acting, nonsedating (second-generation) antihistamines such as fexofenadine (Allegra®, 180 milligrams/d), loratadine (Claritin®, 20 milligrams/d), or cetirizine (Zyrtec®, 10 to 20 milligrams/d) can lessen new lesions and control pruritus. The short-acting (first-generation) H_1 blockers diphenhydramine and hydroxyzine are helpful for breakthrough and nighttime pruritus. H_2-blocking agents such as ranitidine can be used in chronic urticaria along with H_1-blocking agents, but not as a monotherapy. Doxepin (10 to 25 milligrams), which has H_2-blocking effects, can be used at night, but it is also sedating.

Prednisone may be required for angioedema and widespread urticaria. The dose is 40 to 60 milligrams daily for 5 to 7 days. However, a double-blind randomized ED clinical trial of 100 adults with acute urticaria of up to 24 hours in duration reported no clinical improvement with the addition of prednisone to an H_1 antihistamine, levocetirizine.[18] Reassure patients that acute urticaria nearly always resolves within several weeks. Refer refractory cases to a dermatologist or allergist. Please see Chapter 14 "Allergy and Anaphylaxis", Table 14-6 for more details on urticaria and angioedema.

POLYMORPHIC ERUPTION OF PREGNANCY

Polymorphic eruption of pregnancy (formerly called pruritic urticarial papules and plaques of pregnancy) is an idiopathic, intensely pruritic eruption that usually begins in the third trimester of pregnancy. Primiparous women and women with multiple-gestation pregnancies are most often affected, but it rarely recurs in subsequent pregnancies.[19] It does not affect fetal or maternal outcomes.

Intensely pruritic, erythematous, 1- to 2-mm papules begin in the abdominal striae and quickly spread into plaques over several days. The abdomen, buttocks, proximal thighs, and, in some cases, arms can be involved (**Figure 251-18, A and B**). The face, mucous membranes, palms, and soles are spared. Urticarial plaques can be polycyclic or figurate and can sometimes have discrete tiny vesicles present. Most cases resolve within 10 days of delivery.

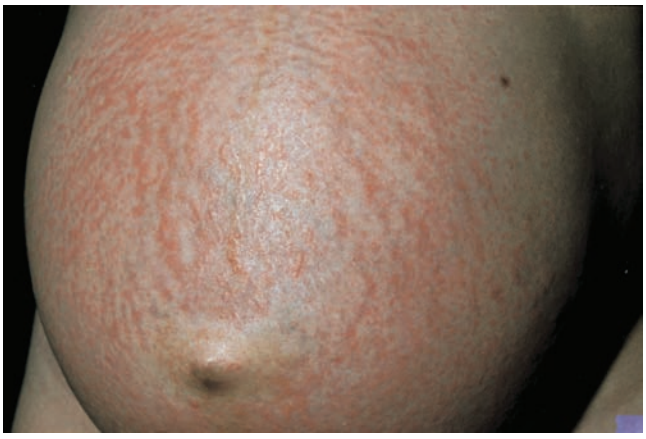
Conditions to consider in the differential diagnosis include drug reactions, erythema multiforme, cholestasis of pregnancy, atopic dermatitis, and the rare autoimmune condition pemphigoid gestationis.[19]

Treatment is symptomatic. Frequent moisturization with over-the-counter creams and lotions, as well as mild- to moderate-potency topical steroids, can be useful. Oral antihistamines may also be helpful.[19] For severe symptoms, patients may require a short course of PO prednisone, 20 to 40 milligrams/d, for relief of the symptoms.

ERYTHEMA MIGRANS

Lyme borreliosis is caused by spirochetes in the genus *Borrelia*, and the Ixodidae tick is the vector. It is a complex multisystem disease and can present with cutaneous findings of erythema migrans in localized stage 1 disease (**Figure 251-19**). Stage 2 is disseminated infection involving multiple organ systems and can have numerous skin lesions. Stage 3 is persistent infection that can develop months to years later with lesions of acrodermatitis chronica atrophicans. For detailed discussion, see Chapter 161, "Zoonotic Infections."

Early **Lyme disease** begins with a red macule or papule at the site of the tick bite. Disease transmission is more likely if the tick was attached for >36 hours.[20] Slow expansion of nonscaling erythema occurs over 3 to 32 days after the bite. It may become annular with central clearing around the bite site. Varying shades of red in concentric rings may be seen, and less commonly, the central portion may be indurated, blistering, or necrotic. There is usually no pain or itching. Patients may develop 2 to 100 multiple smaller lesions, sparing the palms and soles; this reflects disseminated infection. Most lesions fade within 1 month,



A



B

FIGURE 251-18. **A** and **B.** Polymorphic eruption of pregnancy (formerly called pruritic urticarial papules and plaques of pregnancy). Urticarial papules accentuated in the striae. [Reproduced with permission from Fleischer AB Jr, Feldman SR, McConnell CF, et al: *Emergency Dermatology: A Rapid Treatment Guide.* © 2002, McGraw-Hill, Inc., New York.]



FIGURE 251-19. Erythema migrans. Well-defined erythematous plaque. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

but recurrences can occur over the following months.[20] Other cutaneous findings include diffuse urticaria, malar rash, or conjunctivitis. Mild flu-like symptoms of malaise, fever, headaches, arthralgias, GI symptoms, and lymphadenopathy may be present.

Early Lyme disease diagnosis is clinical, due to poor test standardization and variable results of testing methods.[20,21] Approximately 50% of biopsies may demonstrate spirochetes if obtained from the center of the lesion.[20] Culture and polymerase chain reaction testing are specific but are neither sensitive nor widely available. Serologic testing is variable. Immunoglobulin M and G titers can be measured, with immunoglobulin M peaking between the third and sixth weeks of infection and immunoglobulin G developing over months. Enzyme-linked immunosorbent assay testing should be followed by Western blot testing if the results are equivocal or positive.[20] The lesions of erythema migrans can resemble urticaria, cellulitis, insect bites, dermatophytoses, granuloma annulare, early morphea, erythema multiforme, or even annular subacute cutaneous lupus.

Avoid exposure by applying tick repellents containing *N,N*-diethyl-*m*-toluamide (DEET) to clothing and exposed skin. Check the skin after possible exposure and promptly remove ticks.[20,21] Antibiotic prophylaxis for a tick bite is recommended if the tick was engorged at time of removal; if treatment can be given within 72 hours of the time the tick was removed; if the *Ixodes* tick was identified in a hyperendemic region; and in pregnant or immunocompromised patients. In nonpregnant patients, a single dose of doxycycline, 200 milligrams, after a known tick bite (with above risk factors) is recommended.[20,21] Further information regarding treatment of tickborne diseases is found in **Chapter 161, "Zoonotic Infections."** Most recommend at least 3 weeks of therapy for erythema migrans.

DRUG REACTIONS

Adverse cutaneous drug eruptions (**Table 251-4**) are a potential complication of nearly all medications. They can be immunologically mediated or nonimmunologic. Nonimmunologic reactions can be due to enzyme deficiencies, cumulative ingestion, photosensitivity, or topical irritants. Risk factors may include age, gender, dose, and the type of medication.

Cutaneous drug eruptions can mimic almost any other skin disease. Most reactions occur within 1 to 3 weeks of exposure, but hypersensitivity reactions may take longer to develop, so obtain a careful drug history when evaluating any type of rash.[22] Patients may have taken the drug in the past without any problems.

The most common presentation is the **morbilliform exanthem** (**Figure 251-20**). Diffuse, symmetric, pruritic, erythematous macules and papules appear first on the trunk and then spread to the extremities. The initial eruption is usually within 7 to 14 days of exposure, usually resolves within 2 weeks after discontinuation, and resembles a viral exanthem. **Pruritus is common with a drug eruption but often absent with a viral exanthem.** Common offending agents are the semisynthetic penicillins, trimethoprim-sulfamethoxazole, and anticonvulsants. Ampicillin or amoxicillin given to patients with Epstein-Barr virus infection and sulfonamides administered to patients with human immunodeficiency virus have a high incidence of exanthems.

Frequent offenders causing **urticaria or angioedema** are aspirin, NSAIDs, opiates, and iodinated contrast material. The eruptions usually occur within 36 hours of initial exposure or within minutes of rechallenge. Few to hundreds of lesions can be present, pruritus is prominent, and respiratory symptoms and serum sickness–like symptoms (fever, arthralgias, lymphadenopathy, and myalgias) can occur.[17]

Photosensitivity eruptions are characterized by confluent erythema, macules, papules, or even vesicles in sun-exposed areas such as the chest, neck, face, and arms[22] (Table 251-3). Photosensitivity can be divided into photoallergic and phototoxic reactions based on the mechanism. When prescribing drugs with a propensity for photosensitivity, advise patients to use skin protection and proper clothing to avoid sun exposure.

Pigmentation from drug ingestion can be striking in appearance. It may be related to postinflammatory changes, increased melanin

TABLE 251-4 Drug Reactions and Common Causative Agents

Type of Reaction	Common Drugs	Comments
Morbilliform exanthem	Penicillins/cephalosporins, sulfonamides, minocycline, anticonvulsants	Usually <14 d of exposure, resolves within 2 wk; trunk first, then extremities
Urticaria or angioedema	Aspirin, NSAIDs, opiates, iodinated contrast material	Usually <36 h since exposure, or within minutes of exposure
Photosensitivity eruption	**Toxic:** tetracyclines, NSAIDs, fluoroquinolones, amiodarone, psoralens, phenothiazides **Allergic:** thiazides, sulfonamides, antimalarials, quinidine, quinine, tricyclic antidepressants, NSAIDs	Sun-exposed areas; exaggerated sunburn responses
Lupus erythematosus–like	Procainamide, phenytoin, minocycline, hydralazine, penicillamine	Photodistributed eruption
Acneiform eruption	β-Lactam antibiotics, steroids, contraceptives, phenytoin, halogens, lithium, phenobarbital, haloperidol, ethambutol, isoniazid	No comedones; monomorphic papules and pustules on back, shoulders, and chest; within 5 d of exposure
Pigmentation	Zidovudine, heavy metals, phenytoin, oral contraceptives, minocycline, amiodarone, clofazimine, antimalarials	Chronic drug ingestion
Fixed drug eruption	Tetracyclines, sulfas, NSAIDs, barbiturates, phenolphthalein	Reexposure causes recurrence in same location
Vesiculobullous eruption	Penicillamine, captopril, sulfas, thiols	Hard to distinguish from bullous disorder
Lichenoid eruption	ACE inhibitors (captopril enalapril), β-blockers (labetalol, propranolol), methyldopa, antimalarials, quinidine, TNF inhibitors (etanercept, infliximab), hydrochlorothiazide, gold and other metals, penicillamine, NSAIDs	May occur months after exposure, oral lesions, slow resolution up to 2 y
Anticoagulant necrosis	Coumadin®, heparin	Onset in 3–5 d, well-demarcated painful area of fatty tissue
Acute generalized exanthematous pustulosis	β-Lactam antibiotics, macrolide antibiotics, calcium channel blockers (especially diltiazem), and antimalarials	Onset <4 days after start of medication. Pustules start on face/intertriginous areas then rapidly generalize. Resolve in 1–2 wk, followed by desquamation.

Abbreviations: ACE = angiotensin-converting enzyme; TNF = tumor necrosis factor.

production, or actual deposition of the drug or metabolites in the skin. Zidovudine is associated with both nail and generalized hyperpigmentation. Heavy metals, phenytoin, or oral contraceptives may cause pigmentation. Minocycline or amiodarone may give a gray-blue coloration. Clofazimine can cause a diffuse red hue and also blue-gray discoloration, especially in leprosy lesions. Antimalarials may produce gray or yellow discoloration.

Fixed drug eruptions (**Figure 251-21**) occur as solitary or occasionally multiple, discrete, round to oval erythematous patches that eventually turn dusky red or violaceous. Although the trunk may be involved, most cases occur in the oral mucosa or genitals. Lesions may become edematous, forming vesicles or bullae, and then erode. Reexposure to



FIGURE 251-20. Drug eruption. [Photo contributed by University of North Carolina Department of Dermatology.]

the causative drug results in recurrence of lesions in the identical location of the primary eruption within hours.

Anticoagulant necrosis may occur within 3 to 5 days of initiation of warfarin or heparin. It typically begins with a single painful area, followed by erythema that rapidly turns blue-black with subsequent necrosis of the skin. The lesion is very well demarcated. Common sites of involvement are regions of high subcutaneous fat distribution, including the buttocks, thighs, or breasts. Risk factors include high doses, obesity, female gender, and deficiency of protein C or S or antithrombin III.

Some drugs produce **vesiculobullous eruptions** that can be difficult to distinguish from pemphigus or bullous pemphigoid. Penicillamine, captopril, sulfa-based, and thiol drugs can cause a blistering eruption. A pseudoporphyria-like reaction with tense small blisters and vesicles



FIGURE 251-21. Fixed drug eruption. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-22. Acute generalized exanthematous pustulosis. [Photo contributed by University of North Carolina Department of Dermatology.]

on the extensor arms and dorsal hands is associated with furosemide, NSAIDs, tetracycline, and penicillamine exposure.

Acute generalized exanthematous pustulosis occurs within a few days (<4) of drug exposure. Patients develop fever and a generalized eruption of small, sterile pustules on a background of widespread erythema and edema (**Figure 251-22**). Pustules often start on the face, axillae, and/or groin before generalizing within a few hours (**Figure 251-23**). Rapid onset and lack of psoriatic nail changes help distinguish acute generalized exanthematous pustulosis from pustular psoriasis.[23] Although edema of hands and face can be associated with acute generalized exanthematous pustulosis, rapid onset and widespread distribution of pustules distinguishes acute generalized exanthematous pustulosis from drug rash with eosinophilia and systemic symptoms (see below).[23] Drugs most commonly implicated in acute generalized exanthematous pustulosis include β-lactam antibiotics, macrolides, calcium channel blockers, and antimalarials. **Treatment** involves discontinuing the offending drug, antipyretics, and topical corticosteroids.

Drug reaction with eosinophilia and systemic symptoms, drug-induced hypersensitivity syndrome, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis are most commonly caused by the aromatic amines, phenytoin, carbamazepine, and phenobarbital, as well as sulfonamides. These reactions are discussed in **Chapter 249, "Generalized Skin Disorders."**



FIGURE 251-23. Acute generalized exanthematous pustulosis. [Photo contributed by University of North Carolina Department of Dermatology.]

For diagnosis, exclude exanthems triggered by infections, and then obtain a thorough history of exposure to prescription and over-the-counter agents. The pattern of the eruption and the likelihood of particular agents associated with the clinical findings can be found in drug reference manuals.

Treatment is discontinuation of the suspected agent. When the patient is on multiple medications, simplify drugs and discontinue unnecessary agents. Rechallenge, even at reduced dosages, may produce rapid recurrence of the reaction. Oral antihistamines can be helpful for pruritus. Severe symptoms may require topical or oral steroids. Patients may be referred for skin testing in evaluation of type 1 immunoglobulin E–mediated reactions, such as penicillin, anesthetics, or vaccines. Radioallergosorbent tests for immediate reactions and lymphocytotoxicity assays can also be performed to identify anticonvulsant or sulfonamide hypersensitivity reactions.

BLISTERING DISEASES

Blistering diseases can be divided into vesicular, bullous, and pustular. A small blister <1 cm is termed a *vesicle*. Primary vesicular diseases that may affect the trunk include herpes infection (both simplex and varicella), insect bites, and allergic contact dermatitis. Larger blisters, >1 cm, are called *bullae* and may actually begin as vesicles. The most common bullous disease to affect the trunk is bullous pemphigoid. Severe allergic contact dermatitis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and bullous impetigo may also present with bullae. Blood-filled, or hemorrhagic, bullous diseases include necrotizing fasciitis, vasculitis, *Vibrio vulnificus* infection, and bite reactions to brown recluse spiders or rattlesnakes. Cloudy, whitish fluid within a blister is termed a *pustule*. Any blistering condition can become pustular as the lesion ages or becomes secondarily infected. Life-threatening blistering conditions are discussed in **Chapter 249**. **Varicella** is discussed in **Chapter 142, "Rashes in Infants and Children."**

HERPES ZOSTER

After primary exposure to varicella, the virus remains latent in the sensory dorsal root ganglia until it later reactivates and spreads down the sensory nerve to the skin.[24] Reactivation of the latent varicella virus produces the unilateral, painful, localized, vesicular eruption of herpes zoster. It primarily affects one dermatome, although overlap to adjacent dermatomes can be seen. Herpes zoster is more common in the elderly and immunosuppressed.

More than half of cases affect the thoracic nerves, 20% affect the cranial or trigeminal region, 15% affect the lumbar region, and 5% affect the sacral region.[24] Pain (can be severe), tingling, pruritus, or burning sensations may precede the eruption by several days or weeks.

The initial lesions are erythematous papules coalescing into plaques within a dermatome, followed by vesicles or bullae within 24 to 48 hours (**Figure 251-24**). Single lesions in varying stages resemble varicella. Lesions may become pustular, hemorrhagic, or necrotic over the following days. New lesions may develop for up to 1 week, and crusting of the lesions occurs within 7 to 10 days.

Herpes zoster can be difficult to clinically distinguish from herpes simplex. Herpes simplex more commonly involves the perioral, lumbosacral, or external genital areas, and a history of recurrent lesions with typical prodromal symptoms is helpful. Other diseases to include in the differential diagnosis of the dermatomal eruption are allergic contact reactions, erysipelas, and impetigo.

Diagnosis is clinical. A Tzanck test (Figure 248-6) can be performed, which is also positive in varicella. Definitive diagnosis can be made by polymerase chain reaction studies or viral cultures on the vesicle fluid or biopsy specimen.

Treatment is with oral acyclovir, valacyclovir, or famciclovir. Dose adjustment is required for patients with renal impairment. Combined



FIGURE 251-24. Herpes zoster. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-25. Bullous pemphigoid. [Photo contributed by University of North Carolina Department of Dermatology.]

treatment with gabapentin and acyclovir at the time of outbreak may be more effective at reducing postherpetic neuralgia than antivirals alone.[25] In severe cases, such as ophthalmic zoster or disseminated disease, IV acyclovir should be given at a dose of 10 milligrams/kg three times a day. Topical antiviral therapy or antibiotics are not useful in the treatment of zoster. Application of moist dressings (Burow's solution or petroleum jelly) may be soothing. Rest and NSAIDs are recommended. Evaluate and treat associated pain, which may be severe. Herpes zoster is contagious several days before the lesions appear and until all the lesions have crusted over. Exposure may result in varicella infection in those without previous infection or in immunocompromised individuals. Refer to Chapter 154 for more details.

BULLOUS PEMPHIGOID

Bullous pemphigoid is the most common autoimmune blistering disease in the elderly. It mostly affects individuals between 60 and 80 years old and has equal incidence in males and females. Bullous pemphigoid is generally self-limited and typically resolves over 5 to 6 years. Relapses occur in 10% to 15% of patients.

Autoantibodies to the basal keratinocyte hemidesmosomal antigens cause blisters at the basement membrane zone between the epidermis and dermis. Circulating basement membrane zone immunoglobulin G antibodies can be detected in most patients, and blood eosinophilia is present in about half of patients.

Bullous pemphigoid often begins with pruritic urticarial plaques and papules. These are not transient like urticaria. Bullae evolve over weeks to months. The bullae are tense and firm-topped, appearing on normal or erythematous skin (**Figure 251-25**). They do not extend when lateral pressure is applied. Sites of predilection include the axillae, abdomen, inner thighs, flexural forearms, and lower legs. The eruption may be localized or generalized. Bullae eventually rupture, leaving a thin blister roof overlaying the lesion, crusts, and erosions.

Bullous pemphigoid can be confused with urticaria or urticarial reactions in the early phase. Dermatologic consultation, with histopathology and immunofluorescence studies, is required for diagnosis and treatment.

Treatment is typically provided by a dermatologist. High-potency topical steroid (clobetasol) ointment can be used for localized disease. The mainstay of treatment for extensive disease is oral prednisone, l.0 to 1.5 milligrams/kg/d. This dose can be gradually tapered when the disease is in remission. Systemic dapsone, azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate are useful steroid-sparing agents.

INSECT BITES

Bites can produce an inflammatory or allergic reaction. Sensitive individuals can develop an intensely pruritic papule, vesicle, or bulla within hours to days after the bite. The lesions can last for days to weeks. Patients are often unaware of exposure. Systemic symptoms may occur in some individuals, ranging from mild to severe, including anaphylactoid reactions. Spiders, centipedes, millipedes, shellfish, fleas, mosquitoes, and fire ants are responsible for most bites.

Each type of bite can cause a different type of reaction, and individuals will differ in their local response. Transient red macules may occur at the site of the bite. Urticarial papules and vesicles can form, and secondary excoriations are frequent (**Figure 251-26**). A central punctum may be noted at the site of the bite. Large bullae may occur, particularly in patients with chronic lymphocytic leukemia. Necrosis can develop and may be associated with systemic symptoms, including fever, headache, malaise, and arthralgias. **Flea bites** most commonly occur on the lower extremities, although children are more likely to have generalized bites. Mosquito bites occur on any exposed areas. **Bedbugs** will bite in linear groups ("**breakfast, lunch, dinner**") on sites exposed during sleep. **Fire ants** produce a brisk inflammatory reaction that forms a sterile pustule and can be quite painful. Other causes of blistering reactions include the **blister beetle**, which contains the chemical cantharidin and, when crushed, can produce vesicles and blisters on exposed areas. The **caterpillar** family can cause an immunoglobulin E–mediated allergic contact dermatitis. Clinical features and treatment of bites with envenomation are discussed in **Chapter 211, "Bites and Stings."**

Treat bites with NSAIDs to relieve pain and reduce the local reaction. Remove any stingers. Deflea animals and the house. Topical corticosteroids can be used, such as fluocinonide 0.05% or clobetasol 0.05% cream or ointment. Severe reactions may require a short course of oral steroids: prednisone, 40 to 60 milligrams once a day (adults) or 1 to 2 milligrams/kg once a day (children) each morning for 3 to 5 days. Antihistamines can help control pruritus. Provide an EpiPen® to any patient who has had a severe bite reaction.

BOTFLY BITE

One unusual bite is that of the botfly or furuncular myiasis, caused by *Dermatobia hominis*. The condition is endemic to Mexico and Central America. Botfly larvae are deposited onto the surface of a mosquito or fly. When an individual is bitten, the botfly larva painlessly penetrates the skin. Bites most commonly affect the trunk, followed by the head, legs, and arms—any exposed skin areas. The initial lesion is usually felt to be a generic "insect bite." In 3 to 4 weeks, the lesion evolves into a furuncle



FIGURE 251-26. Bug bites. [Photo contributed by University of North Carolina Department of Dermatology.]

with a central pore, which clinically appears as an infected bite, inflamed cyst, or cellulitis. There may be a sensation of movement within the furuncle. Diagnosis is typically made when the furuncle is drained and the larva is seen. Completely extract the larva or infection or a foreign body reaction will develop. There are no systemic complications, and no specific prevention exists, other than the application of insect repellents.

SELECTED COMMON MISCELLANEOUS DISORDERS OF THE TRUNK

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a common viral infection of the epidermis occurring in children, atopics, sexually active adults, and immunosuppressed individuals (especially patients with human immunodeficiency virus). It is caused by poxvirus variants molluscum contagiosum viruses 1 to 4, with the most common being molluscum contagiosum virus 1 in children and molluscum contagiosum virus 2 in human immunodeficiency virus infections. Transmission is by direct skin-to-skin contact and via fomites.

There can be a single skin-colored, pearly, umbilicated papule (1 to 2 mm) or multiple, scattered papules or nodules and plaques (5 to 10 mm) (**Figure 251-27**). Autoinoculation is evident by the clustering of lesions in areas of rub or friction, some with a linear array from scratching. The lesions may become crusted, inflamed, or pustular if irritated. An inflammatory reaction may precede the spontaneous resolution of the lesions. In children, the lesions may range in number from a few to >100. The face, trunk, and extremities are commonly affected. Generalized involvement may occur in atopic dermatitis. In sexually active adults, there are 20 or fewer lesions on the lower abdomen, thighs, and genital



FIGURE 251-27. Molluscum contagiosum. Centrally umbilicated papules. [Photo contributed by University of North Carolina Department of Dermatology.]

region. Other sexually transmitted diseases may coexist. In immunosuppressed patients, hundreds of lesions may be present, and involvement of the face, with lesions being spread by shaving, is common. In human immunodeficiency virus, this occurs when CD4 counts are less than 100 cells/mm^3. Giant molluscum lesions, involvement of the oral and genital mucosa, and facial disfigurement may occur (CD4 <50 cells/mm^3).

Diagnosis is clinical. If necessary, a Giemsa stain of the expressed keratotic core demonstrates intracytoplasmic inclusion bodies ("molluscum bodies") (Figure 248-2). In the immunocompromised, if diagnosis is unclear, obtain a biopsy to exclude fungal infection.

Most patients require no **treatment** because spontaneous resolution of molluscum occurs within 6 months to 4 years. Avoid shaving the affected area. For bothersome cases, application of topical cantharidin (blister beetle fluid) will produce good resolution of lesions, although multiple treatments may be necessary.[26] Curettage, cryotherapy, or electrodesiccation can also be done. In individuals infected with human immunodeficiency virus, treatment of the underlying human immunodeficiency virus infection may lead to resolution.

MILIARIA

Miliaria occurs due to obstruction of eccrine sweat glands and can be associated with pruritus. It can occur at any age but is more common in children.[27] **Miliaria rubra** is the most common form and presents with small punctate vesicles overlying erythematous macules or papules.[27] **Miliaria crystallina** is characterized by small, clear vesicles without underlying erythema. When ruptured with a needle, miliaria will drain clear sweat.[27] This condition is self-limited and improves with a cool environment and avoidance of sweat duct occlusion.

FOLLICULITIS

Superficial folliculitis is a common inflammatory disorder of hair follicles that presents with multiple erythematous, follicularly based, scattered papules and pustules (**Figure 251-28**). It is sometimes associated with pruritus or pain.[27] Areas of involvement include the trunk, buttocks, extremities, neck, and scalp. Treatment of common folliculitis can include over-the-counter topical benzoyl peroxide washes and topical clindamycin. Oral doxycycline can be used for widespread involvement.[28]

"Hot tub folliculitis" (**Figure 251-29**) is due to *Pseudomonas aeruginosa* and occurs within 1 to 2 days of hot tub use. Pruritus is a common symptom. It is self-limited in otherwise healthy patients, but antibacterial soaps can be used as treatment. In immunosuppressed patients, treatment with ciprofloxacin, 500 milligrams twice a day for 7 to 14 days, is recommended.[28]



FIGURE 251-28. Folliculitis. [Photo contributed by University of North Carolina Department of Dermatology.]

KAPOSI'S SARCOMA

Kaposi's sarcoma is a vascular neoplasia characterized by endothelial cell proliferation with multisystem involvement. Human herpesvirus 8 has been identified in all variants of the lesions, although it is not known how this virus induces the proliferation of the microvasculature. Individuals infected with human immunodeficiency virus are at high risk for Kaposi's sarcoma. The use of highly active antiretroviral therapy has reduced the incidence by 10-fold. The clinical presentation of Kaposi's sarcoma is different from the classic form seen in elderly males of eastern European heritage. Patients with human immunodeficiency virus can present with widespread, numerous lesions. The lesions may be erythematous or violaceous macules that can progress to tumors or nodules. The lesions on the trunk may be arranged parallel to the skin tension lines and can occur in areas of trauma (**Figure 251-30**). Erosions, ulceration, crusting, and hyperkeratosis may be secondary changes seen. The trunk is an area of predilection, as are the hard palate, penis, and lower extremities.

Classical or European Kaposi's sarcoma occurs in elderly males of Mediterranean or Ashkenazi Jewish heritage. This variant predominantly arises on the lower extremities and can be associated with edema. It can also affect the lymph nodes and abdominal viscera.

Treatment depends on the extent and severity of the disease and underlying cause. Referral to infectious disease and hematology/oncology specialists is necessary in most cases.



FIGURE 251-29. Hot tub folliculitis. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 251-30. Kaposi's sarcoma. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 252

Skin Disorders: Groin and Skinfolds

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INTRODUCTION

The skinfolds of the body include the groin, intergluteal cleft, axilla, inframammary, and pannus regions. Although many skin diseases can affect the skinfolds to some degree, this chapter focuses on the most common skinfold eruptions (**Table 252-1**). Sexually transmitted infections are discussed in Chapter 153, "Sexually Transmitted Infections". Molluscum contagiosum is discussed in Chapter 251, "Skin Disorders: Trunk".

The skinfolds have unique characteristics that set them apart from other regions of the body. For one, these areas are almost continuously occluded. As a result, scale does not develop; maceration and fissuring develop instead. This situation alters the appearance of papulosquamous diseases and inflammatory processes. The occlusion also allows for the development of a warm, moist environment favorable to the growth of fungi, yeast, and bacteria.

An important point for treatment of intertriginous diseases is avoiding combination corticosteroid and antifungal products. Although processes in the groin folds can be confusing and complicated by secondary change, using combination products may further cloud the clinical picture. If improvement is seen after application of combined products, it is difficult to determine which medication prompted the change. Finally, the corticosteroid component of combined medications is too strong to be used in the occluded intertriginous skin and may

TABLE 252-1 Clinical Features and Treatment of Common Disorders of Groin and Skinfolds

Condition	Clinical Features	Treatment	Comments
Tinea cruris	Symmetric, annular, erythematous, scaly plaques	Topical antifungals for 1–6 wk	Permanent cure is rare, patients require periodic re-treatment
Candidiasis	Well-demarcated erythema and maceration with satellite pustules involving the skinfolds	Topical antifungals; oral fluconazole if recalcitrant and/or recent oral antibiotics	Predisposing factors including obesity and endocrine disease such as diabetes or Cushing's syndrome
Scabies	Widespread, highly pruritic, erythematous papules; other common locations: intergluteal cleft, digital web spaces, axilla, waistband Look closely for burrows: fine, thread-like lines with a terminal black speck	Permethrin cream (safe in pediatric patients older than 2 months) and containment Machine wash and machine dry any clothing, linens, or towels that were worn in 3 days prior to treatment Consider oral ivermectin for immunocompromised patients or refractory cases	A negative scabies prep does not rule out this diagnosis; immunocompetent hosts typically harbor less than 20 mites
Pediculosis pubis	Erythematous macules or papules ± wheals and inguinal lymphadenopathy Look closely for lice and nits	Permethrin cream and containment Machine wash and machine dry any clothing, linens, or towels that were worn in 3 days prior to treatment Treat all sexual partners; notify all sexual partners within the past 3 months	Approximately 30% of those found to have pediculosis pubis also have concomitant infection with another sexually transmitted infection
Seborrheic dermatitis	Erythematous plaques with loose greasy scale	Antifungal shampoos or creams ± low-potency topical corticosteroid creams (hydrocortisone, desonide)	There is no cure, and the condition is expected to wax and wane
Intertrigo	Erythema/erosions of opposing skin surfaces	Conservative measures aimed at eliminating friction, moisture Barrier creams such as Desitin®	Diagnosis of exclusion; consider streptococcal infection, *Candida*, irritant dermatitis May require antifungal treatment as it is often superinfected with *Candida* Avoid combination antifungal–topical steroid creams as these often contain mid-potency steroids that are too strong for use in intertriginous areas
Hidradenitis suppurativa	Firm, tender nodules and abscesses often with extensive scarring and sinus tract formation; often also found in axilla, inframammary folds, and under the panus	For acute flares: intralesional triamcinolone injections or oral antibiotics (doxycycline or combination therapy with clindamycin and rifampin)	Because this is a chronic disease with many social and psychological implications, refer to dermatology and plastic surgery for long-term management

produce irreversible striae with long-term use. Chronic use of potent topical corticosteroids should be followed by a dermatologist.[1,2]

TINEA CRURIS

Tinea cruris is a fungal infection of the groin commonly called *jock itch*. It is very common in males, uncommon in females, and exceedingly rare in children. Tinea cruris results from invasion of the stratum corneum by the dermatophyte types of fungi (see Table 253-4). It is transmitted via direct contact (person to person or animal [usually kittens or puppies] to person) or fomites.

Lesions are characterized by symmetric erythema with a peripheral annular slightly scaly edge (**Figure 252-1**). The groin is typically involved, and the process may extend onto the inner thighs and even the buttocks. The penis and scrotum are typically spared, a distinguishing feature of tinea cruris because most other eruptions will affect the scrotum. Frequently, tinea pedis is also present, and the infection may spread from the feet to the groin when putting on clothes.

Scraping the leading edge and performing a potassium hydroxide examination will demonstrate branching hyphae, unless the patient has recently applied topical antifungal preparations.

Treatment is with antifungal creams, such as clotrimazole, ketoconazole, or econazole, twice a day (**Table 252-2**). Start with clotrimazole because it is low cost and available without a prescription. Econazole also has antibacterial properties and is preferred if maceration is present. Keep the affected area as cool and dry as possible, and recommend loose-fitting clothing. Use an antifungal powder daily to prevent recurrences. Recommend follow-up with a primary care provider or dermatologist if the eruption has not resolved in 4 to 6 weeks.

CUTANEOUS CANDIDIASIS

Candidal infections of the skin favor moist, occluded areas of the body. Superficial *Candida* infections are commonly seen in the diaper area of infants, vulva and groin of women, glans penis (balanitis) of



FIGURE 252-1. Tinea cruris. Note raised, sharp-edged margins. [Photo contributed by University of North Carolina Department of Dermatology.]

TABLE 252-2 Commonly Used Topical Antifungal Preparations

Generic	Trade	Formulations	Status
Clotrimazole	Lotrimin®	1% cream or solution	OTC
	Mycelex®	1% solution	OTC
Ketoconazole	Nizoral®; Xolegel® gel; Kuric gel®	2% cream, shampoo, gel	Prescription
Econazole	Spectazole	1% cream	Prescription
Miconazole	Zeasorb AF®	2% cream or powder	OTC

Abbreviation: OTC = over the counter (no prescription required in United States).

uncircumcised males, and inframammary and pannus folds of obese patients. Antibiotic therapy, systemic corticosteroid therapy, urinary or fecal incontinence, immunocompromised states, poorly controlled diabetes mellitus, and obesity are predisposing factors. Women with vulvar or inner thigh involvement will often have vaginal candidiasis as well. Frequently, *Candida* infection may complicate other inflammatory intertriginous disorders.

The typical presentation is erythema and maceration with peripheral small erythematous papules or satellite pustules (**Figure 252-2**). **The rim of satellite pustules helps to distinguish *Candida* infection from other eruptions of the skinfolds.**

A potassium hydroxide preparation of the pustules or of the leading edge scale may demonstrate short hyphae and spores, but these may be difficult to find. If *Candida* is suspected and the diagnosis is in question, obtain a skin swab for fungal culture.

Treat with a topical antifungal cream, such as clotrimazole, ketoconazole, or econazole. Keep the affected area dry and cool. Clothing should be loose and lightweight. Astringent solutions (such as aluminum acetate [Burow's solution]) aid in drying weepy inflammatory eruptions. Once the infection is controlled, recommend daily application of drying powders. Patients with vulvar candidiasis should be evaluated and treated for *Candida* vaginitis (see Chapter 102, "Vulvovaginitis"). Patients with *Candida* balanitis often have a female sexual partner with *Candida* vaginitis, so evaluate and treat partners as well. In infants or adults with urinary or fecal incontinence, change diapers frequently. Zinc oxide paste applied over the antifungal agent provides a protective barrier to the irritation of urine and feces.



FIGURE 252-2. Cutaneous candidiasis with satellite papules and pustules. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

SCABIES

Infestation of the skin by *Sarcoptes scabiei*, or scabies mite, produces an intensely pruritic eruption. Symptoms manifest approximately 30 days following exposure to the organisms as a result of the host immune response to the mites and their excrement. History may elicit an encounter with another person, or with a new environment, about 4 to 6 weeks before the symptoms appear. Scabies infestation is a major problem in immigrants and asylum seekers, where both prevention and treatment are initiated to control the disease.[3] Individuals with crusted scabies have very large numbers of mites and are quite contagious. Transmission can occur from brief skin or fomite contact.

The main presenting feature is intense, intractable pruritus, most notable at night. In adults, the typical findings are slightly longitudinal erythematous or brown papules, predominantly on the lateral feet, wrists, ankles, and interdigital spaces of the fingers and toes. Involvement may be evident within the axillae, groin, and extensor extremities (**Figure 252-3**). The head and neck are characteristically spared. A variant, **crusted or Norwegian scabies,** can develop in the immunocompromised, those with dementia, or those who are institutionalized (**Figure 253-4**). Crusted scabies consists of thick, crusted, confluent plaques on the hands, feet, and scalp, with or without a generalized distribution. Pruritus is not a common feature of crusted scabies.

To visualize the organisms by light microscopy, scrape a burrow with a scalpel blade, transfer to a glass slide, and cover with a drop of mineral oil and a coverslip (see Figure 251-15). Sensitivity of this test is limited, and a negative result does not rule out the diagnosis.

Treat with 5% permethrin cream (pregnancy category B), apply from the neck down, leave on for 12 hours, and then bathe with soap and water. Repeat treatment in 1 week. Treat all resident family members and household and intimate contacts.

Do not prescribe lindane to children or pregnant women secondary to neurotoxicity.

Oral ivermectin is an alternative to permethrin cream, but it may have a slightly lower cure rate.[2] It is given as a single oral dose, 150 micrograms/kg. Oral ivermectin can be used as an adjunct to permethrin for



FIGURE 252-3. Scabetic papules and burrows. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]



FIGURE 252-4. Norwegian or crusted scabies. [Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *The Atlas of Emergency Medicine*, 4th ed. McGraw-Hill Education, Inc., New York, 2016. Fig. 20.35, p. 709. (Photo Contributor: Larry Mellick, MD).]

refractory cases or in the setting of an immunocompromised or uncooperative patient. **Do not prescribe ivermectin to pregnant and lactating women or to children weighing less than 15 kg.**

Supportive care involves use of oral antihistamines and topical corticosteroids after use of the appropriate scabicidal agent. Symptoms gradually resolve over 1 to 2 weeks, although pruritus can sometimes persist for several weeks. Return of new lesions after initial improvement signifies incomplete treatment or reinfestation.

PEDICULOSIS PUBIS

Pediculosis pubis is infestation of the groin with *Phthirus pubis*. Rarely, the eyebrows, eyelashes, chest, or axillary hair may also be involved.

Close examination of the hair-bearing areas reveals multiple, small, flesh-colored or slightly reddish organisms grasping the hairs close to the skin surface (**Figure 252-5**). In severe infestations, small bluish-gray macules may be noted, called *maculae caeruleae*. Secondary infection and excoriations may also be present. Diagnosis of pediculosis pubis in children should prompt evaluation for sexual abuse.

Treatment **is the same as for scabies**. Topical treatments should be applied liberally to all affected hair-bearing areas, including the perirectal hairs.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is one of the most common skin disorders. It most notably affects the scalp ("dandruff") and creases of the face and ears; however, other skinfolds, such as the intergluteal cleft, groin, axilla, inframammary folds, and umbilicus, can be affected (see Chapters 250, "Skin Disorders: Face and Scalp" and 251, "Skin Disorders: Trunk"). It is a chronic condition that typically reappears after stopping treatment.

Seborrheic dermatitis of the scalp and skinfolds of the face presents as erythema with a greasy yellow scale (see Figure 250-1). When seborrheic dermatitis affects other skinfolds, erythema and maceration are evident.



FIGURE 252-5. *Arrow* points to louse on the skin. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

Diagnosis is clinical. By itself, groin or other skinfold involvement is hard to differentiate from cutaneous candidiasis, inverse psoriasis, allergic contact dermatitis, or streptococcal infection.

Treatment is symptomatic. Shampoos containing zinc pyrithione, selenium sulfide, salicylic acid, or tar preparations are used. Ketoconazole shampoo can be effective and is available by prescription (2%) or over the counter (1%). Hydrocortisone 1% cream can be used in mild cases, whereas hydrocortisone 2.5% cream or desonide cream or lotion may be required initially in more severe cases. Avoid long-term regular use of corticosteroids on facial or intertriginous skin, which may result in irreversible skin thinning and striae formation.

INTERTRIGO

Intertrigo is an irritant dermatitis of the skinfolds resulting from moisture, heat, friction, and irritating substances like urine and feces. Intertrigo presents as erythema, maceration, and fissures in the occluded area of skinfolds, especially the groin and inframammary folds (**Figure 252-6**). **Satellite papules and pustules are absent**, and the affected areas are



FIGURE 252-6. Intertrigo with possible streptococcal superinfection. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

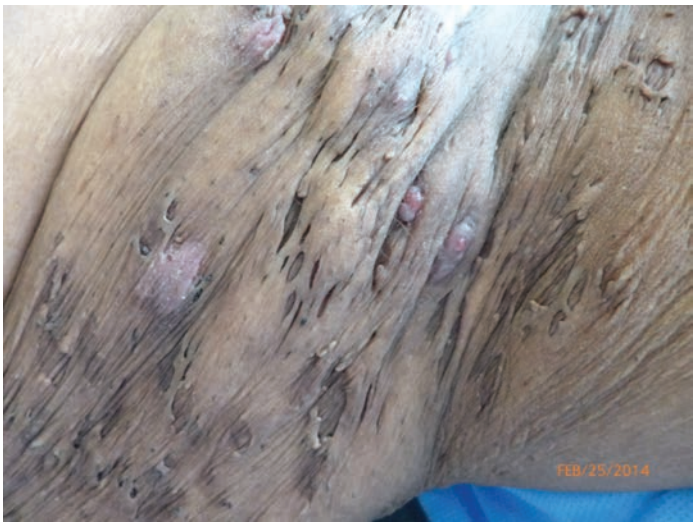

FIGURE 252-7. Hidradenitis suppurativa involving the buttock region. [Photo contributed by University of North Carolina Department of Dermatology.]

pruritic and may burn. **Streptococcal superinfection** should be considered if there is marked erythema and tenderness, especially in the extremes of age and the immunocompromised.

Intertrigo is a diagnosis of exclusion (Table 252-1). Bacterial infection, especially with *Streptococcus*, is common. Differentiating cutaneous candidiasis from inflammatory intertrigo can be difficult. A diagnosis of cutaneous candidiasis is supported by the presence of satellite pustules and a positive potassium hydroxide examination. However, a negative potassium hydroxide examination does not exclude the diagnosis because yeast is difficult to obtain and visualize. Obtain fungal culture when diagnosis is uncertain.

Clinically, irritant dermatitis cannot always be distinguished from allergic contact dermatitis. Ask about possible contact allergens or irritants such as neomycin-containing ointments, anesthetic creams, diphenhydramine cream, deodorants, feminine hygiene sprays, or other lotions, solutions, or home remedies.

Treat by keeping the affected areas dry and cool. Avoid potential irritants. Zinc oxide paste provides an excellent barrier to urine and fecal material. **Apply aluminum acetate (Burow's solution)** compresses for moist, weepy intertrigo. **Treat secondary bacterial infection** with oral antibiotics with staphylococcal and streptococcal coverage. Topical antiyeast preparations, such as ketoconazole, may be helpful. If significant inflammation is present, a short course of 1% hydrocortisone cream or lotion may be helpful.

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa is an inflammatory condition typically affecting the apocrine gland–bearing areas of the skin with recurrent, painful, draining nodules. The inciting event is follicular occlusion, prompting rupture of the follicular contents and resulting in intense inflammation.[4]

Axillary and inguinal skin demonstrates varying numbers of inflammatory nodules, many of which may form connecting tracts, with resultant drainage onto the skin surface (**Figure 252-7**). Lesions may heal with characteristic icepick scarring. Diagnosis is clinical. **Treatment** is clindamycin 1% lotion twice daily and use of antibacterial soaps, such as chlorhexidine, once to twice weekly. Incision and drainage may increase scarring. Refer to a plastic surgeon or dermatologist. Further systemic treatments, such as acitretin, finasteride, oral antibiotics, or prednisone, is best coordinated by a dermatologist.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 253

Skin Disorders: Extremities

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INTRODUCTION

This chapter focuses on common disorders of the hands, feet, and extremities.

EXTREMITY ULCERS

VENOUS STASIS DERMATITIS AND VENOUS LEG ULCERS

The vast majority of leg ulcers are venous stasis ulcers resulting from chronic venous insufficiency.[1] Chronic venous insufficiency is usually caused by episodes of phlebitis or varicose veins, both of which damage venous valves. This results in poor venous return from the lower extremities, leading to increased hydrostatic pressure and lower extremity edema and stasis dermatitis.

Dependent edema, erythema, and orange-brown hyperpigmentation characterize early stasis dermatitis. The medial distal legs and the pretibial leg are the areas most frequently affected. More chronic and severe cases may have bright weepy erythema and even ulceration (**Figure 253-1**). Pruritus is common. Cellulitis and lymphangitis may complicate stasis dermatitis. The presence of honey-colored crust and pustules suggests secondary bacterial infection.

Stasis ulcers often begin within areas of stasis dermatitis. The bilateral malleoli and the medial aspect of the calf are the most common sites of involvement. Diagnosis is clinical, and secondary infection is common. **Table 253-1** lists the differential diagnosis of leg ulcers. Certain disorders, such as arterial ulcerations, pyoderma gangrenosum, and polyarteritis nodosa, require immediate attention. If peripheral pulses are diminished or absent, obtain vascular blood flow studies to exclude arterial ulcers. If the patient reports a rapidly developing ulcer that began as a pustule or erythematous nodule and has violaceous overhanging borders, suspect pyoderma gangrenosum. If the diagnosis is in question, consult with a dermatologist.

Treatment of venous stasis dermatitis and ulcers begins with leg elevation and the use of support stockings. Treat weeping eruptions with an astringent compress. A low- to mid-potency topical steroid, such as fluocinolone acetonide 0.025% or hydrocortisone 2.5% ointment,



FIGURE 253-1. Venous stasis. [Photo contributed by University of North Carolina Department of Dermatology.]

TABLE 253-1 Clinical Features and Treatment of Common Extremity Ulcers

Condition	Clinical Features	Treatment	Comments
Venous stasis	Dependent erythema, edema and orange-brown hyperpigmentation	Compression stockings Leg elevation Low- to mid-potency topical steroid	Medial distal leg and pretibial leg
Pyoderma gangrenosum	Superficial pustule/nodule that grows into a large, painful ulcer on lower extremity; purulent base with irregular, gun metal gray borders	Treat underlying disease, if present Topical steroid Intralesional steroid Systemic steroid Immunosuppressive/cytotoxic agents for recalcitrant disease	Often associated with systemic disease: inflammatory bowel disease, rheumatoid arthritis, and myeloproliferative disorders
Diabetic/neuropathic ulcers	Asymptomatic ulcer often occurring with diabetic neuropathy; "punched out" appearing with a thick rim of peripheral callous	Redistribution of pressure off the wound Creation of moist wound environment Debridement of nonhealing tissue PO antibiotics for simple soft tissue infection IV antibiotics for cellulitis and/or osteomyelitis	Plantar surface underlying first and fifth metatarsal heads, great toe, and heel; may complain of burning, numbness, pruritus or paresthesia from associated neuropathy
Buruli ulcers	Erythematous nodule that progresses to a painless ulcer with deep white and yellow necrotic base with undermined edges surrounded by edema	Surgical excision is the treatment of choice Streptomycin and rifampin for 8 wk but antimicrobial therapy often ineffective	Forms approximately 8 wk after inoculation; most common sites: face and extremities
Cutaneous leishmaniasis	Many varieties of cutaneous infection; painless ulcer occurs often on unclothed skin	Most lesions heal spontaneously over several months	Endemic in North Africa, Mediterranean, Middle East, India, Central Asia, and Central/South America

should be applied twice a day until erythema, scale, and pruritus resolve. Oral antihistamines, such as diphenhydramine or hydroxyzine, are useful for pruritus and for nighttime sedation. Treat secondary bacterial infection with cephalexin, dicloxacillin, or ciprofloxacin for 7 to 10 days. **Do not use topical neomycin, antihistamine creams, and anesthetic creams because they may complicate the condition with allergic contact dermatitis.** Cellulitis or lymphangitis may require hospitalization for IV antibiotics. Otherwise, arrange follow-up with a chronic wound care team.[1]

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is a recurrent cutaneous, necrotizing, and noninfective ulceration of the skin. Most cases are associated with underlying disease, such as inflammatory bowel disease, rheumatoid arthritis, and myeloproliferative disorders.[2]

The classic lesion begins as a superficial pustule or erythematous nodule that expands into a large painful ulcer on the lower extremity with a purulent base and irregular, undermined borders and gun metal gray hue (**Figure 253-2**). A history of multiple surgical debridements with sterile cultures should suggest a potential diagnosis of pyoderma gangrenosum.



FIGURE 253-2. Pyoderma gangrenosum. [Reproduced with permission from Wolff KL, Johnson RA, Saavedra AP, Roh EK: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 8th ed. © 2017, McGraw-Hill, Inc., New York. Fig 7-2.]

The diagnosis is clinical and one of exclusion. Search for associated conditions, such as inflammatory bowel disease and myeloproliferative disorders. The onset of new skin lesions or ulcers at previous sites of trauma can also be helpful in identifying pyoderma gangrenosum.[3]

Treatment of the underlying disorder and corticosteroids, either topical, intralesional, or combined local and systemic, are the standard therapy for pyoderma gangrenosum. Resistant disease may require adjunctive systemic therapy with immunosuppressive or cytotoxic agents.

DIABETIC AND NEUROPATHIC ULCERS

Most patients with diabetic foot ulcers have coexistent diabetic neuropathy.[4] Other causes of neuropathic leg ulcers are much rarer and include leprosy, tabes dorsalis, medications, and spinal cord lesions. In most patients with foot ulcers, one will note a triad of neuropathy, deformity, and trauma. Neuropathy leads to atrophy of the intrinsic muscles of the foot, collapse of the arch, and loss of stability of the metatarsal-phalangeal joints. The musculoskeletal alterations result in abnormal pressure points and greater friction on the foot during ambulation. Lack of sensation allows for repeat injury. The most common source of trauma is inappropriate footwear.[5]

Classic locations for neuropathic ulcers are the plantar surface underlying the first and fifth metatarsal heads, great toe, and heel. Ulcers are usually asymptomatic and "punched out" with a thick rim of surrounding callous (**Figure 253-3**). However, patients may complain of burning, numbness, itching, or paresthesias. The architecture of the foot is also altered, with flexed toes and prominent metatarsal heads secondary to neuropathy of the intrinsic muscles of the foot. Hypo- or anhidrosis from autonomic impairment may lead to dryness and fissuring of the surrounding skin. The diagnosis is clinical.

A diabetic foot infection is diagnosed clinically when there are systemic signs of infection, purulence, or multiple signs of local inflammation (redness, warmth, pain, tenderness, or edema).[6] Osteomyelitis is suggested by the ability to probe bone with a blunt, sterile, stainless-steel probe and should be confirmed with imaging.

Treatment includes offloading or redistributing the pressure off the wound, maintenance of a moist wound environment, debridement of



FIGURE 253-3. Diabetic foot and diabetic neuropathy. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

nonhealing tissue, and treatment of infection. Soft tissue infections can be treated for 7 to 14 days in an outpatient setting with oral cephalosporin, clindamycin, amoxicillin/clavulanate, or fluoroquinolones.[6]

More severe ulcers or those with associated cellulitis or osteomyelitis require admission and treatment with IV antibiotics for 4 to 6 weeks, such as cefotetan, ampicillin/sulbactam, or clindamycin and a fluoroquinolone. Vancomycin should be given if methicillin-resistant *Staphylococcus aureus* is suspected. Further discussion is provided in Chapter 224, "Type 2 Diabetes Mellitus"; Table 224-2 lists the characteristics of diabetic foot ulcers.

BURULI ULCERS

Buruli ulcer is a new emerging disease and the third most common chronic mycobacterial infection in humans after tuberculosis and leprosy.[7] Buruli ulcers are rapidly growing ulcers caused by the acid-fast bacillus, *Mycobacterium ulcerans*. It is usually confined to the tropical areas, with the highest rate in sub-Saharan Africa, but reports have come from subtropical and nontropical nations, including Australia, China, and Japan.[8]

M. ulcerans is an environmental saprophyte that is present on lush vegetation in swampy areas.[9] It infects humans after abrasions come into contact with contaminated soil, water, or vegetation.[9] *M. ulcerans* produces mycolactone, a cytotoxic lipid and necrotizing immunosuppressive polypeptide toxin that induces both apoptotic and necrotic changes in fibroblasts, lipid cells, macrophages, and keratinocytes.[10] Buruli ulcers are painless, and it is thought that mycolactone damages the peripheral nerves.[11]

The Buruli ulcer begins as an erythematous nodule approximately 8 weeks after inoculation that eventually ulcerates. The lesions develop on exposed parts of the body, especially on the extremities and face. The resulting painless ulcer has a deep white or yellow necrotic base and undermined edges, as well as edematous surroundings (**Figure 253-4**). Regional lymphadenopathy and systemic symptoms are minimal to absent. Without treatment, ulcers may spontaneously heal within 6 to 9 months, or they may spread rapidly, causing extensive deformity.

Smears from the base of the ulcer or biopsy specimens should be cultured and examined for acid-fast bacilli. Visible growth by culture requires 6 to 8 weeks, and its success rate is low. Polymerase chain reaction performed on a fresh biopsy is the best method for early diagnosis. The World Health Organization recommends rifampin and streptomycin dual therapy for 8 weeks, local wound care, and physical therapy.[12] Another regimen used in Australia is rifampin plus clarithromycin, ciprofloxacin, or moxifloxacin for 12 weeks.[12] If antimycobacterial treatment is ineffective, surgical debridement with skin grafting is the next choice.[12] New skin lesions may develop during antimicrobial therapy, and this is known as "paradoxical reactions," which are thought to be an exaggerated immune response to mycobacterial antigens.[12]

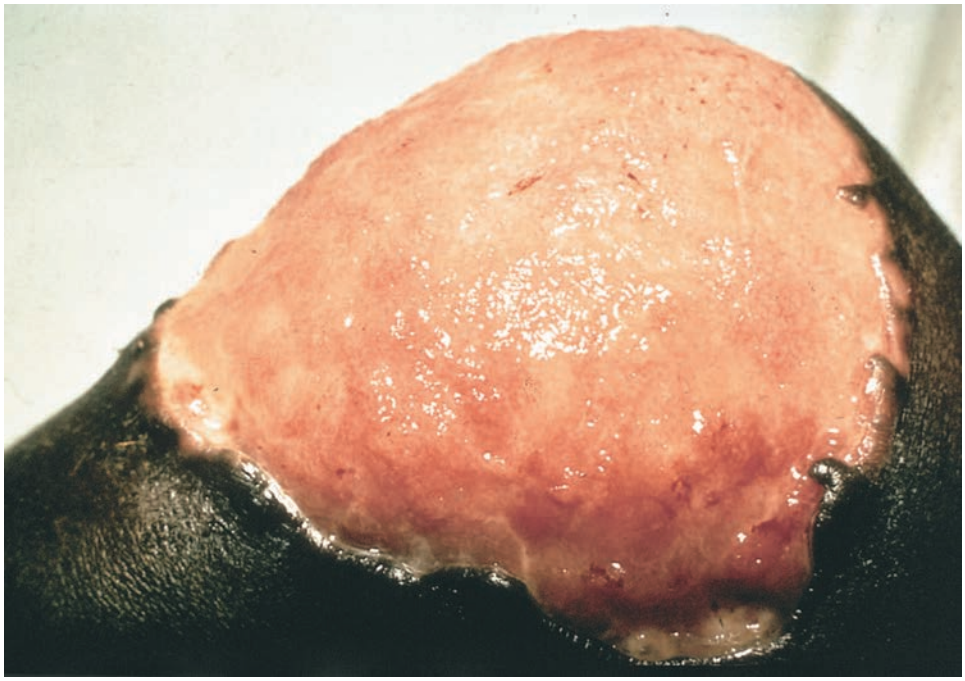

FIGURE 253-4. Buruli ulcer. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis is transmitted by the bite of the sand fly, which is infected by protozoan parasites of the genus *Leishmania*. In tropical and subtropical regions, leishmaniasis is one of the most common and serious infectious diseases. It is endemic in North Africa, the Mediterranean, the Middle East, India, Central Asia, and Central and South America. Reactivation of latent leishmaniasis can occur in immunosuppressed, human immunodeficiency virus, malnourished, or organ transplant patients.[13] There are many varieties of cutaneous leishmaniasis. The typical cutaneous ulcer usually occurs on unclothed skin, is painless, varies in size from 0.5 to 3.0 cm in diameter, and is covered with an exudative crust (**Figure 253-5**). Diagnosis is clinical but can be confirmed with culture, biopsy, or polymerase chain reaction test. Most lesions heal spontaneously over several months; however, for severe disease, treatment failures and resistance to antimonials, amphotericin B, and miltefosine are increasing worldwide.[14,15]



FIGURE 253-5. Cutaneous leishmaniasis. [Reproduced with permission from Walter Reed Army Institute of Research.]

HANDS, LEGS, AND FEET

HAND AND FOOT DERMATITIS

Hand and foot dermatitis simply means inflammation of the skin of the hands and/or feet and consists of nonspecific and more specific disorders (**Tables 253-2** and **253-3**). The most common causes are contact dermatitis (allergic and irritant), dyshidrosis, and atopic dermatitis. Most contact dermatitis is caused by irritants as opposed to allergens. Atopic dermatitis affects up to 20% of children, usually before 5 years of age, but only 2% to 3% of adults.[16]

IRRITANT AND ALLERGIC CONTACT DERMATITIS

Common irritants include soaps, detergents, friction, frequent hand washing, and cold, dry air, resulting in erythema, scaling, and fissuring, particularly of the dorsal hands. Strong irritants, such as an acid

TABLE 253-2 Clinical Features and Treatment of Common Conditions Involving Extremities

Condition	Clinical Features	Treatment	Comments
Irritant/allergic contact dermatitis	Irritant dermatitis: erythema, scaling, and fissuring Allergic contact dermatitis: erythema with papules, vesicle and/or bullae; significant clinical overlap can occur depending on acuity/chronicity	Removal of offending agent High-potency topical corticosteroids (ointments preferred)	Avoid antihistamine, antibiotic, anti-itch creams as they can cause secondary allergy
Poison ivy/oak (a specific allergic contact dermatitis)	Linear streaks of erythematous papules, vesicles, and/or bullae; lesions develop 48–72 h or more after exposure, and minute amounts of urushiol can cause eruption	Remove contaminated clothing, wash with soap and water; for severe cases, oral prednisone starting at 60 milligrams for 5–7 d and then taper over 2–3 wk (shorter courses result in relapse)	For milder cases, oral antihistamines and topical steroids. aluminum subacetate compresses; for acute exposure, an over-the-counter skin cleanser Tecnu® is a popular remedy.
Dyshidrosis	Deep-seated pruritic vesicles on lateral aspects and volar surfaces of palms and soles; vesicles may form pustules or desquamate over time	Aluminum acetate compresses High-potency topical corticosteroids Hydroxyzine	In chronic cases, erythema and scale may become more prominent
Atopic dermatitis	Erythematous, pruritic scaly patches on dorsal surfaces, palms, and soles; common areas: antecubital, popliteal fossa, posterior neck, wrists, ankles	Aluminum acetate compresses High-potency topical corticosteroids Hydroxyzine No systemic steroids due to relapse	Chronic atopic dermatitis will have hyperpigmentation, lichenification, and fissuring
Psoriasis	Plaque type: discrete plaques of erythema, scales, and fissures on extremities Pustular type: erythema, sterile pustules with minimal scale on palms and soles	High-/ultrahigh-potency topical corticosteroids White petrolatum-based emollients No systemic steroids (rebound, induction of pustular psoriasis)	Common sites: elbows, knees, scalp, lower back, gluteal cleft, umbilicus, nails Nail involvement can give clues to diagnosis: onycholysis, nails pits, and yellow discoloration of nails
Erythema nodosum	Tender, warm, ill-defined erythematous nodules	Leg elevation NSAIDs	Pretibial area of lower extremities Extensor aspect of arms and torso (less often)
Dermatitis herpetiformis	Pruritic vesicles, papules, and urticarial plaques on extensor surfaces of extremities, back, and buttocks	Oral dapsone Gluten-free diet	Cutaneous manifestation of gluten insensitivity
Cutaneous larva migrans	Erythematous and serpiginous tracts on the skin (migration of hookworm larvae); often complain of pruritus	Single oral dose of albendazole or ivermectin	Occurs after walking barefoot in environments contaminated by animal feces in tropical, subtropical climates
Lichen simplex chronicus	Intensely pruritic, well-demarcated, lichenified plaque; minimal scale	High-potency topical corticosteroids Oral antihistamines for itch	Ankles, shins, dorsal feet, and hands

TABLE 253-3 Clinical Features and Treatment of Common Conditions of the Feet

Condition	Clinical Features	Treatment	Comments
Corns and calluses	Corns: firm, dome-shaped papules with translucent central core on dorsal, lateral, and interdigital toes Calluses: thickened plaque at areas of repetitive trauma	Paring Keratolytics (salicylic acid) Proper footwear	Both are most commonly located on the feet
Tinea pedis	Interdigital type: most common, maceration, scale in the web spaces between toes; ulceration can be seen in severe cases, can be superinfected with bacteria, yeast Hyperkeratotic type: chronic, dry scales on palms and soles; can see "moccasin distribution" involving lateral and medial aspects of feet; nails may be involved (onychomycosis) Bullous type: acute, painful, erythematous, and pruritic vesicular eruption on palms or soles; toenails, web spaces spared	Interdigital/hyperkeratotic types: topical antifungals Bullous type: oral antifungal agent Onychomycosis: oral antifungal agent Keep hands and feet including web spaces as dry as possible	Predisposing factors: hot, humid weather, excessive sweating, and occlusive footwear Disease is chronic and recurrences are common
Plantar warts	Thickened papules and plaques on sole of foot, often over pressure points Can see "black dots" or thrombosed capillaries with paring	Salicylic acid Cryotherapy Electrodessication	Most spontaneously regress within 1–2 y
Acral nevi	Symmetric, well-circumscribed, often small, 5- to 6-mm, uniformly pigmented macules or papules with only slight elevation; can often see linear striations on the surface; depending on skin type, range from brown to black in color	No treatment needed	These are benign growths
Acral lentiginous melanoma	Volar surface of palms or soles; can appear as growing "stain" during radial growth phase Subungual type: thumb or great toe, grows in the nail bed; can see nodules, ulceration, nail deformity, nail shedding	Excisional biopsy for diagnosis by dermatology Treatment may include surgical excision, immunotherapy depending on staging	

or alkali, cause immediate burning, followed by erythema, vesiculation, and bullae formation.

Causes of allergic contact dermatitis include nickel, chromate, rubber components of gloves and shoes, dyes in leather and socks, and dichromates used in tanning leather. Distribution is the most helpful clue to aid in diagnosis. When the hands or feet are involved in allergic contact dermatitis, the eruption tends to be present on the dorsal surfaces, sparing the palms, soles, and web spaces. The thick stratum corneum of the palms and soles prevents penetration of potential allergens. Sharp demarcation lines of footwear indicate a reaction to a component of the patient's shoes. Treatment is the removal of offending agents. Antihistamine, anesthetic, antibiotic, and anti-itch creams should be stopped because they may cause a second allergy. Lubricate with petroleum jelly or thick ointments with a petroleum base frequently and liberally.

For acute eruptions with vesiculation, use **aluminum acetate**, two to three times per day. Mix one aluminum acetate powder packet or tablet with 1 pint of water, and then apply with a towel or gauze to the affected area for 5 to 10 minutes. Use a high-potency topical corticosteroid, such as clobetasol ointment, twice a day, after the compress. Hydroxyzine, 25 to 50 milligrams up to four times a day, can relieve itching.

In severe acute cases with debilitating eruptions, oral glucocorticoids are indicated. Treat chronic eruptions with high-potency topical corticosteroids two to three times a day, but do not give oral glucocorticoids in chronic cases and atopic dermatitis. Ointments are preferred because they help with lubrication and medication delivery.

POISON IVY/OAK

Poison ivy or oak is a type of allergic contact dermatitis to urushiol. The rash can result from direct contact of any part of the plant, contact with tools or clothes, or inhalation if the plant is burned. Rash develops 2 days or more after exposure. Exposures involving the face or neck are most serious (see Chapter 250, "Skin Disorders: Face and Scalp"). Exposure results in erythema with papules, vesicles, and/or bullae. Pruritus is intense, resulting in excoriations. Distribution with linear streaks is common with **poison ivy or oak** (**Figure 253-6**). See Table 253-2 for treatment. Involvement of palms and soles is uncommon due to thickness of skin in those areas. For severe exposures, give oral prednisone, starting at 60 milligrams/d, for at least 5 days and then slowly tapering over a total of 2 to 3 weeks. Shorter courses of prednisone result in relapse.



FIGURE 253-6. Vesicular lesions produced after contact with poison ivy. [Reproduced with permission from Wolff KL, Johnson RA, Saavedra AP, Roh EK: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 8th ed. © 2017, McGraw-Hill, Inc., New York. Fig 2-8.]



FIGURE 253-7. Dyshidrosis. Clear, tapioca-like lesions with secondary encrustation. [Photo contributed by University of North Carolina Department of Dermatology.]

DYSHIDROSIS

Dyshidrosis initially begins as very small, deep-seated, pruritic vesicles on the lateral aspects and the volar surfaces of the palms and soles (**Figure 253-7**). The dorsal surface of the distal phalanges may also become involved. There is no erythema. Over time, the vesicles may form pustules or desquamate to leave small collarettes of scales. In chronic cases, erythema and scales become more prominent and may be difficult to distinguish from other forms of hand and foot dermatitis. See Table 253-2 for treatment.

ATOPIC DERMATITIS

Atopic dermatitis is part of the "atopic triad" consisting of dermatitis, asthma, and allergic rhinitis.[17] Atopic dermatitis of the hands and feet often presents as erythematous, pruritic, scaly patches with prominent involvement of the dorsal surfaces as well as the palms and soles. Chronic atopic dermatitis will also have hyperpigmentation, lichenification, and fissuring. Often, other areas of the body are involved. Common areas of involvement include the antecubital and popliteal fossae, posterior neck, and wrists and ankles (**Figure 253-8**).

The diagnosis is clinical. See Table 253-2 for treatment. Do not give oral corticosteroids for atopic dermatitis. Differentiating contact dermatitis (allergic and irritant) from dyshidrosis and atopic dermatitis can be extremely difficult. More than one disorder may be present at a time, such as atopic dermatitis complicated by irritant dermatitis. Always consider a fungal infection (see later section, "Tinea Pedis and Tinea Manuum"), and a potassium hydroxide preparation can exclude this possibility. A biopsy cannot differentiate between the different types of dermatitis. See **Table 253-4** for definitions of terms in superficial cutaneous fungal infections and **Table 253-5** for causes of superficial cutaneous fungal infections. Dermatologic consultation is often necessary for specific diagnosis.



FIGURE 253-8. Atopic dermatitis with lichenification. [Photo contributed by University of North Carolina Department of Dermatology.]

TABLE 253-4 Definitions of Terms for Superficial Cutaneous Fungal Infections

- Dermatophytes: a group of fungi that infect nonviable keratinized cutaneous structures such as stratum corneum, nails, and hair. They most commonly include *Trichophyton* species, *Microsporum* species, and *Epidermophyton* species.
- Dermatophytosis: an infection caused by dermatophytes
- Tinea: a term used for specific clinical manifestations of dermatophyte or dermatophyte-like infections, with the addition of a term that usually indicates the anatomic area affected (tinea pedis, tinea manuum, etc.)
- *Malassezia* species: a yeast causing tinea versicolor or pityriasis versicolor

PSORIASIS

Psoriasis vulgaris or plaque-type psoriasis may involve only the palms and soles but often extends to other areas, especially the elbows, knees, scalp, umbilicus, and gluteal cleft (see Chapter 251 for more discussion). If pustules are present, the disorder is called *pustular psoriasis*. Peak ages of onset are between 20 and 30 years old and between 50 and 60 years old.

Psoriasis is characterized by discrete plaques of erythema, scales, and fissures on the extremities (**Figure 253-9**). Extensive disease may extend over the entire palms, soles, and dorsal surfaces of the hands or feet (**Figure 253-10**). Onycholysis (separation of the nail plate from the nail bed), nail pits, and yellow discoloration of the nails help support the diagnosis of psoriasis (**Figure 253-11**).

In pustular psoriasis, the pustules are in various stages of evolution from small pustules to larger confluent "lakes of pus" to crusts to rings of scale (**Figure 253-12**). Pustules are most commonly seen bilaterally on the instep of the foot and the thenar and hypothenar eminences of the hands.

Complete examination of the skin focusing on the sites commonly affected by psoriasis, including the elbows, knees, scalp, lower back, gluteal cleft, umbilicus, and nails, may reveal other areas of involvement to aid in diagnosing psoriasis. If no other psoriatic plaques are noted, differentiation from hand and foot dermatitis can be difficult (**Table 253-6**). A biopsy may be helpful in this instance. A potassium hydroxide examination should be performed to exclude a dermatophyte infection. Bacterial and viral cultures should be obtained when disease is pustular and localized to one area. See Table 253-2 for treatment. Do not prescribe oral corticosteroids because of the risk of rebound or induction of pustular psoriasis. The disease is chronic and slow to respond to treatment. Arrange follow-up with a dermatologist.

ERYTHEMA NODOSUM

Erythema nodosum is an inflammatory eruption of the subcutaneous fat. It has many possible causes (**Table 253-7**) and is idiopathic in nearly half of cases. All age groups can be affected.

Tender, warm, ill-defined erythematous nodules characterize erythema nodosum (**Figure 253-13**). Nodules are most commonly seen on the pretibial area of the lower extremities, although the extensor aspects of the arms and torso can occasionally be involved. Ulceration is not a feature and suggests another diagnosis. Nodules can persist for weeks.

TABLE 253-5 Causes of Superficial Cutaneous Fungal Infections

- Dermatophytes
- *Trichophyton* species (cause most superficial cutaneous fungal infections)
- *Microsporum* species
- *Epidermophyton* species
- *Candida*
- *Malassezia* species



FIGURE 253-9. Psoriasis vulgaris. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 253-10. Psoriasis vulgaris of the plantar foot. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 253-11. Psoriasis nails. [Photo contributed by University of North Carolina Department of Dermatology.]

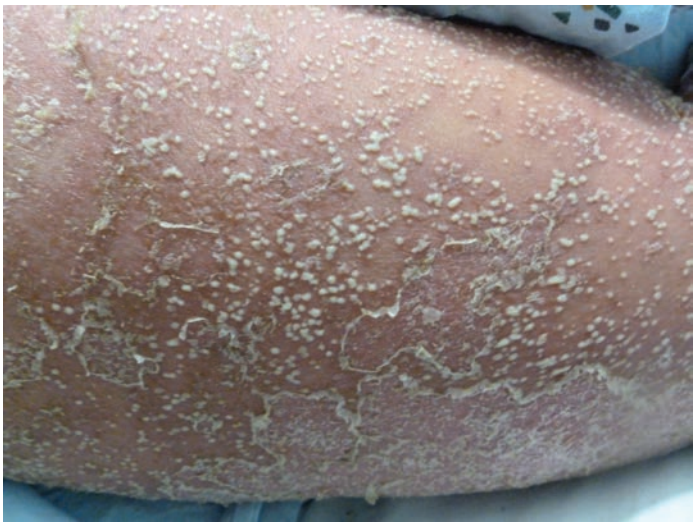

FIGURE 253-12. Pustular psoriasis. [Photo contributed by University of North Carolina Department of Dermatology.]

The diagnosis is clinical and should include evaluation for possible causes (Table 253-7). Treatment is symptomatic, with leg elevation and NSAIDs. Treat the underlying cause. Refer refractory or unclear cases to a dermatologist.

HERPETIC WHITLOW

Herpetic whitlow is a herpes simplex viral infection, due either to HSV-1 or -2, located on the distal finger or hand. Typical transmission is skin-to-skin, typically through a break in the skin, from individuals who shed the virus but do not have lesions (**Figure 253-14**). Lesions are painful grouped vesicles on an erythematous base. Lesions may become confluent. Misdiagnosis is common. Paronychia is a localized bacterial infection under the nail bed. Treatment of herpetic whitlow is 1 week of valacyclovir, 1 gram orally twice a day. Lesions heal over 2 to 3 weeks.

MALIGNANT MELANOMA

Melanoma is a melanocytic tumor that most often originates in the skin and is most often caused by exposure to ultraviolet light. Involvement can also occur on oral, conjunctival, and vaginal surfaces, including the uveal tract of the eyes and leptomeninges. Clinical presentation includes brown to black tumors, attributed to melanin deposition (**Figure 253-15**), whereas some are flesh colored to pink-red and termed *amelanotic*.[18,19] One type of aggressive melanoma that occurs on hairless skin, such as under the nails and on palms or soles, and is more common in dark-skinned individuals is called *acral lentiginous melanoma*. This is the type of melanoma that led to Bob Marley's death at age 36. He noted a small spot under his nail that was thought to be from a trivial toe stub. Thus, any new or unusual spot on the body or extremities is worthy of dermatologic referral for definitive diagnosis.

TABLE 253-6 Differential Diagnosis of Psoriasis

- Psoriasis vulgaris
- Hand and foot dermatitis
- Lichen simplex chronicus
- Reiter's syndrome
- Pustular psoriasis
- Tinea pedis and tinea manuum
- *Staphylococcus aureus* infection
- Herpes simplex infection
- Dyshidrosis

TABLE 253-7 Causes of Erythema Nodosum

Infectious	Pharmacologic
Fungal	Sulfonamides
Blastomycosis	Oral contraceptive pills
Coccidioidomycosis	Penicillin
Histoplasmosis	Bromides
Dermatophyte	Vaccines
Bacterial	Sarcoidosis
Streptococcal infections	Inflammatory bowel disease
Campylobacter	Pregnancy
Yersinia species	Behçet's syndrome
Tuberculosis	Leukemia and lymphoma
Leprosy	Idiopathic
Parasitic	
Leishmaniasis	
Toxoplasmosis	
Viral	
Herpes simplex	
Infectious mononucleosis	



FIGURE 253-14. Herpetic whitlow, grouped vesicles on an erythematous base, with clear discharge. Figure courtesy of Department of Dermatology, University of North Carolina. [Photo contributed by University of North Carolina Department of Dermatology.]

LICHEN SIMPLEX CHRONICUS, CORNS, AND CALLUSES

Lichen simplex chronicus, corns, and calluses are all thickenings of the upper layer of the skin (stratum corneum) in response to chronic friction and scratching. Most commonly, the ankles, lower extremities, neck, scrotum, and vulva are involved. When friction occurs in the presence of pruritus, a plaque of lichen simplex chronicus is formed. When friction in the absence of pruritus is distributed over a large area, a callus is formed. When the same frictional forces occur over a localized area of the foot, a corn is formed. Calluses and corns are most commonly located on the feet.

Calluses and corns present as thickened plaques at areas of repetitive trauma. Corns form firm, dome-shaped papules with translucent central cores on the dorsal, lateral, and interdigital toes (**Figure 253-16**).

Diagnosis is clinical (**Table 253-8**). A potassium hydroxide examination can be helpful to rule out a dermatophyte infection. If the diagnosis is uncertain, refer for a skin biopsy. Paring of warts reveals punctuate thrombosed capillaries, which are not found in calluses or corns.

Paring and keratolytics, such as salicylic acid, are first-line treatments for corns and calluses, as well as proper footwear and medical management.[20] For further treatment, refer to a podiatrist or dermatologist.



FIGURE 253-13. Erythema nodosum nodules on the legs. [Reproduced with permission from Wolff KL, Johnson RA, Saavedra AP, Roh EK: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 8th ed. © 2017, McGraw-Hill, Inc., New York. Fig 7-9.]

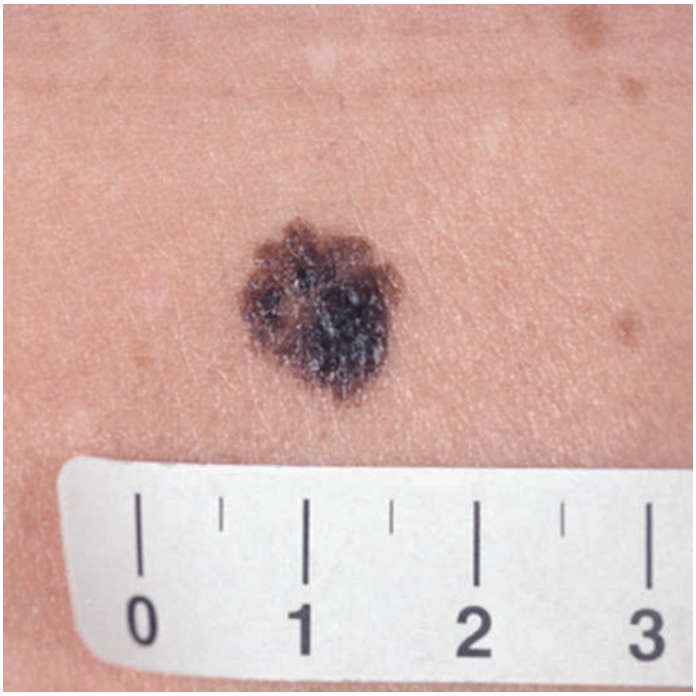

FIGURE 253-15. Malignant melanoma. [Reproduced with permission from Wolff KL, Johnson RA, Saavedra AP, Roh EK: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 8th ed. © 2017, McGraw-Hill, Inc., New York. Fig 12-3.]



FIGURE 253-16. Corn. Painful, hyperkeratotic lesion. [Photo contributed by University of North Carolina Department of Dermatology.]

Lichen simplex chronicus presents as one or several intensely pruritic, well-demarcated plaques, with lichenification as a result of chronic scratching and rubbing (**Figure 253-17**). Erythema, hyperpigmentation, and excoriations are also present. Scale is minimal. The ankles, shins, dorsal feet, and hands may be affected.

Interrupting the scratch–itch cycle is the most important aspect of treatment for lichen simplex chronicus. High-potency topical corticosteroids such as fluocinonide or clobetasol ointment should be applied to the plaque two to three times a day. Oral antihistamines help for pruritus.

TABLE 253-8 Differential Diagnosis of Lichen Simplex Chronicus, Corns, and Calluses

- Lichen simplex chronicus
- Dermatophyte infection
- Nummular eczema
- Psoriasis
- Squamous cell carcinoma
- Corns and calluses
- Plantar wart
- Arsenical keratosis
- Squamous cell carcinoma
- Palmoplantar keratoderma
- Punctuate palmoplantar keratoses
- Punctuate porokeratosis
- Poroma (benign hair follicle tumor)



FIGURE 253-17. Lichen simplex chronicus. [Photo contributed by University of North Carolina Department of Dermatology.]

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is a cutaneous manifestation of **gluten sensitivity**. It is most common in individuals of northern European descent.[21] Often, there is familial involvement, and there is almost universal association with HLA-DQ2 or HLA-DQ8, located on chromosome 6, with close relatives being affected by either dermatitis herpetiformis or celiac disease.[22]

Granular deposits of immunoglobulin A are found at the dermal–epidermal junction of all patients with dermatitis herpetiformis. These deposits are believed to attract neutrophils, which induce vesicle formation. The presence of immunoglobulin A antibodies to tissue transglutaminase is also highly sensitive and specific for the disorder.[23]

Extremely pruritic vesicles, papules, or urticarial plaques are symmetrically distributed on extensor surfaces of the extremities, back, and buttocks (**Figure 253-18**). Chronic scratching may result in excoriations and lichenification in these locations. Approximately 20% of patients will have clinical evidence of malabsorption.[24] The diagnosis is supported by clinical, biopsy, and laboratory findings (**Table 253-9**). Diagnosis and treatment require dermatology referral.



FIGURE 253-18. Dermatitis herpetiformis. Papules and vesicles are grouped together, not in a dermatomal distribution, and are symmetrically distributed on extensor areas of elbows and knees. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. © 2005, McGraw-Hill, Inc., New York.]

TABLE 253-9 Differential Diagnosis of Dermatitis Herpetiformis

- Erythema multiforme
- Bullous lupus erythematosus
- Linear immunoglobulin A bullous dermatosis
- Bullous pemphigoid
- Atopic dermatitis (eczema)
- Papular urticaria
- Chronic prurigo
- Scabies

Treatment for dermatitis herpetiformis includes oral dapsone and a gluten-free diet. Oral dapsone relieves pruritus within 72 hours of beginning therapy. Systemic steroids are ineffective.

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans is a cutaneous eruption caused by the migration of **hookworm larvae** within the epidermis. The disease is most commonly found in tropical and subtropical climates where people walk barefoot in environments contaminated with animal feces.

Erythematous and serpiginous tracks are formed as the larva migrates within the skin (**Figure 253-19**). The patient will often complain of pruritus. A CBC may demonstrate peripheral eosinophilia; patients are otherwise well. Diagnosis is clinical. A single oral dose of **albendazole** or **ivermectin** is usually effective.[25]

PLANTAR WARTS

Plantar warts are a common infection of children caused by the human papillomavirus. They may be acquired through direct contact with infected individuals or indirectly through contaminated surfaces. Most warts will spontaneously regress within 1 to 2 years.

Plantar warts occur on the sole of the foot, especially over pressure points, as thickened papules and plaques that disrupt normal skin lines (**Figure 253-20**). Black dots, representing thrombosed capillaries, will often cover the surface or become evident upon superficial paring. Diagnosis is clinical (**Table 253-10**). Initial treatment is topical salicylic acid. Cryotherapy and electrodesiccation are other options.



FIGURE 253-19. Cutaneous larva migrans with elevated serpiginous tracks caused by migration of the larva under the skin. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 253-20. Plantar warts. Painless papules with red-black dots of thrombosed capillaries. [Photo contributed by University of North Carolina Department of Dermatology.]

TINEA PEDIS AND TINEA MANUUM

Tinea pedis, or athlete's foot, is a fungal infection of the feet, and tinea manuum involves the hand. Tinea manuum is often unilateral and associated with tinea pedis. Often, if one hand is involved, both feet are involved as well. It is unclear why the other hand is spared in this "two-foot, one-hand" type of fungal infection. Tinea pedis is very common and usually begins in early adulthood. It is rare in children. Predisposing factors include hot, humid weather, excessive sweating, and occlusive footwear. *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* are the most common organisms involved. *T. mentagrophytes* is most likely to cause inflammatory bullous tinea pedis. Infections are transmitted from person to person or from animal to person via fomites or direct contact.

TABLE 253-10 Differential Diagnosis of Plantar Warts

- Callus
- Corn
- Epithelioma cuniculatum
- Squamous cell carcinoma
- Arsenic keratoses
- Palmoplantar keratoderma
- Punctuate palmoplantar keratoses
- Punctuate porokeratosis
- Verrucous carcinoma
- Benign hair follicle tumor (poroma)



FIGURE 253-21. Interdigital tinea pedis. [Photo contributed by University of North Carolina Department of Dermatology.]



FIGURE 253-23. Bullous tinea pedis. [Photo contributed by University of North Carolina Department of Dermatology.]

There are three main clinical types: interdigital, hyperkeratotic (scaling), and bullous. Interdigital tinea pedis is the most common and is characterized by maceration and scale in the web spaces between the toes. Ulceration may even be present in severe cases that have a secondary infection with bacteria or yeast (**Figure 253-21**).

Hyperkeratotic, chronic, dry scales involve palms and soles, with little, if any, inflammation. When involving the medial and lateral aspects of the feet, it is called "moccasin" tinea (**Figure 253-22**). Nails may be affected.

Bullous tinea consists of an acute, painful, erythematous and pruritic vesicular eruption on the palms or soles (**Figure 253-23**). Toenails and web spaces are usually not involved.

Diagnosis is based on clinical examination and identification of fungal elements on a potassium hydroxide preparation or with fungal culture. If the clinical examination is highly suspicious for a fungal infection, empiric therapy is reasonable. If the diagnosis is uncertain, obtain scrapings for fungal cultures before beginning therapy because culture results (whether positive or negative) can help the follow-up physician choose the most appropriate therapy.

Although a potassium hydroxide examination appears to be a simple test, it is often difficult for clinicians to perform and interpret (see Table 248-6). Scraping of scale can also be sent to the laboratory for potassium hydroxide examination and fungal culture. Hyphae appear as light-green, thin strands that cross over cells and have branches (see Figure 248-1).



FIGURE 253-22. Moccasin-type tinea pedis. [Reproduced with permission from Fleischer AB Jr, Feldman SR, McConnell CF, et al: *Emergency Dermatology: A Rapid Treatment Guide*. © 2002, McGraw-Hill, Inc., New York.]

Treat interdigital and hyperkeratotic (nonbullous) tinea with topical antifungals, such as clotrimazole, miconazole, ketoconazole, or econazole cream. Apply to affected areas twice a day and continue for 1 week after clearing. Although econazole cream is expensive, it is preferred for interdigital tinea pedis because it has antibacterial properties to treat secondary bacterial (often *Corynebacterium*) infection. Topical **terbinafine cream** is a nonprescription alternative and is applied once a day. Topical agents do not treat nail infections. For treatment of onychomycosis, an oral agent such as itraconazole, fluconazole, or terbinafine is needed, but this treatment is best managed by the primary care physician or dermatologist.

Bullous tinea pedis often does not respond to topical treatment. For mild cases, a topical agent can be tried initially. In more severe cases, oral antifungal treatment is necessary. Itraconazole, 200 milligrams PO each day for 14 days, or terbinafine, 250 milligrams PO each day for 14 days, is effective. Review the potential drug interactions and the uncommon, but serious, side effects before prescribing these medications. Baseline liver function studies are optional when prescribing terbinafine.

Hands and feet should be kept as dry as possible. After bathing, web spaces should be thoroughly dried. Socks should be changed any time they become wet with sweat. If the eruption is not clear in 4 to 6 weeks, dermatology referral is needed. The disease is chronic, and recurrences are common.

VASCULAR CUTANEOUS CONDITIONS

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever is a potentially fatal multisystem illness caused by *Rickettsia rickettsii*. Symptoms begin 2 to 14 days after an infected tick bite. The organism disseminates through the bloodstream and invades the vascular endothelium, causing a necrotizing vasculitis. Fever, headache, and myalgias develop about 1 week after exposure. The rash in classic Rocky Mountain spotted fever is evident 2 to 5 days after the onset of fever and other symptoms. In most patients, some type of rash develops during the illness, but about 10% never develop a rash.[26]

The rash first appears on the wrists and ankles and rapidly spreads to the palms and soles (**Figure 253-24, A and B**). As the rash moves centrally, the proximal extremities, trunk, and face become involved. The skin lesions at the onset are described as discrete macules or



A



B

FIGURE 253-24. **A.** Petechiae on the ankles of a patient with Rocky Mountain spotted fever. **B.** Petechiae involving hand, wrist, and forearm. [From the Centers for Disease Control and Prevention; National Center for Emerging and Zoonotic Infectious Diseases; Division of Vector-Borne Diseases: Rocky Mountain Spotted Fever. www.cdc.gov/rmsf/symptoms/. Updated September 5, 2013.]

maculopapules that blanch with pressure. The initial lesions evolve into petechiae over 2 to 4 days, fade slowly over 2 to 3 weeks, and heal occasionally with hyperpigmentation. Rarely, the petechiae may coalesce into ecchymotic areas with eventual gangrene of the distal extremities, nose, ear lobes, scrotum, and vulva—purpura fulminans. Treatment for adults is doxycycline, 100 milligrams PO twice a day; for children under 45 kg, treatment is doxycycline, 2.2 milligrams/kg twice a day. For further discussion of the treatment of this and other tickborne diseases, see Chapter 161, "Zoonotic Infections."

PURPURA

Purpura is visible hemorrhage into the skin or mucous membranes. Small, flat lesions are petechiae, and large, flat lesions are ecchymoses. Palpable purpura has a physically palpable elevation. Diverse abnormalities of coagulation and blood vessel function lead to hemorrhage into the skin. These include abnormalities of platelet number or function, procoagulant defects, poor dermal support of vessels, increased pressure within vessels, trauma, vascular inflammation, and vascular occlusion.

The cutaneous and systemic causes of purpura are broad. Nevertheless, some broad generalizations can be made. Large ecchymoses generally signify coagulation defects or trauma and may be associated with signs of external or internal bleeding. Petechiae are often associated with thrombocytopenia and bleeding in other locations. Palpable purpura and persistent, localized purpura suggest **vasculitis** (**Figure 253-25**). Because vasculitis can affect any organ system, a complete history and physical examination and a detailed laboratory investigation are required.



FIGURE 253-25. Purpura from cutaneous vasculitis. [Photo contributed by University of North Carolina Department of Dermatology.]

Major coagulation defects and platelet disorders can be diagnosed through coagulation studies. Cutaneous vasculitis is diagnosed by skin biopsy. Systemic vasculitis is diagnosed by laboratory investigation. Treatment and disposition are based on the underlying diagnosis. For additional discussion, see Chapter 142, "Rashes in Infants and Children" and Chapter 249, "Generalized Skin Disorders."

PYOGENIC GRANULOMA

A pyogenic granuloma is a benign proliferation of immature capillaries occurring at the site of minor skin trauma. The name is a misnomer because it is neither an infection nor a granuloma. It most commonly occurs in children, young adults, and pregnant women. In pregnant women, it is called *granuloma gravidarum*. A pyogenic granuloma initially presents as a bright red, shiny papule with a surrounding thin collarette of hyperkeratosis (**Figure 253-26**). It may be ulcerated and tends to bleed profusely with minor injury. Later, the lesion reepithelializes and becomes a dull red to purple color. Although lesions can occur anywhere on the body, the extremities, especially hands, are the most common sites of involvement. If the lesion is bleeding profusely, obtain hemostasis with



FIGURE 253-26. Pyogenic granuloma. Solitary vascular nodule that develops after minor trauma. [Photo contributed by University of North Carolina Department of Dermatology.]

TABLE 253-11 Differential Diagnosis for Pyogenic Granuloma

- Amelanotic melanoma
- Squamous cell carcinoma
- Bacillary angiomatosis
- Cutaneous metastasis
- Kaposi's sarcoma

pressure or suturing. Refer for a biopsy of the lesion to exclude other disorders, especially an amelanotic melanoma (**Table 253-11**). Lesions do not resolve without specific treatment by excision, laser therapy, or electrodesiccation.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 21

Trauma

CHAPTER 254

Trauma in Adults

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INTRODUCTION AND EPIDEMIOLOGY

Traumatic injury accounts for more than 40 million ED visits in the United States each year,[1] and worldwide, about 6 million people die each year as a result of injuries. By 2030, road traffic crashes are predicted to become the fifth leading cause of death worldwide.[2] In the United States, firearm, suffocation, and drowning/submersion have the highest case fatality rates.[2] Trauma remains the leading cause of death among children and adults under the age of 46 years, accounting for nearly half of all deaths in these age groups.[3] In all countries, the incidence of death from injury increases more than threefold with increasing poverty. For the 90% of patients who survive the initial trauma, the burden of ongoing morbidity from traumatic brain injury, loss of limb function, and ongoing pain is even more significant.

The major causes of death following trauma are head injury, chest injury, and major vascular injury. Trauma care should be organized according to the concepts of rapid assessment, triage, resuscitation, diagnosis, and therapeutic intervention.[4] Worldwide, there are few countries or regions that have comprehensive systems of trauma care, from roadside to rehabilitation, and that incorporate effective injury prevention strategies.

TRAUMA SYSTEMS AND TIMELY TRIAGE

A systematic approach is required to reduce the morbidity and mortality that occur after traumatic injury (**Figure 254-1**).

Recognizing the need to establish a system to triage injured patients rapidly to the most appropriate setting and to promote collaboration among emergency medicine, trauma surgery, and trauma care subspecialists, the U.S. Congress passed the Trauma Care Systems Planning and Development Act of 1990.[5] This act provided for the development of a model trauma care system plan to serve as a reference document for each state in creating its own system. Each state must determine the appropriate facility for treatment of various types of injuries. Trauma centers are certified based on the institution's commitment of personnel and resources to maintain a condition of readiness for the treatment of critically injured patients. Some states rely on a verification process offered by the American College of Surgeons for the designation of certain hospitals as trauma centers.[4] In a well-run trauma center, the critically injured patient undergoes a multidisciplinary evaluation, and diagnostic and therapeutic interventions are performed with smooth transitions between the ED, diagnostic radiology suite, operating room, and postoperative intensive care setting. **Table 254-1** details the requirements for designation as a Level 1 trauma center.

A well-functioning trauma system defines trauma centers with specific triage criteria, so that patients can be initially transported by EMS to these centers or transferred to trauma centers from other hospitals after stabilization (**Table 254-2**). In accordance with the principles of advanced trauma life support, injured patients are assessed and treated based on three concepts:

1. Treat the greatest threat to life first.
2. The lack of definitive diagnosis should never impede the application of an indicated treatment.
3. A detailed history is not essential to begin the evaluation of a patient with acute injuries.[6]

PRIMARY SURVEY

Prior to the patient's arrival at the hospital, EMS providers should inform the receiving ED about the mechanism of trauma, suspected injuries, vital signs, clinical symptoms, examination findings, and treatments provided. In preparation for the patient's arrival, ED staff should assign tasks to team members, prepare resuscitation and procedural equipment, and ensure the presence of surgical consultants and other care team members. For patients transported to EDs that are not trauma centers, consider immediately whether transfer to a trauma center is appropriate and what resuscitation or stabilization can or should be performed prior to transfer.

A focused history obtained from the patient, family members, witnesses, or prehospital providers may provide important information regarding circumstances of the injury (e.g., single-vehicle crash, fall from height, environmental exposure, smoke inhalation), ingestion of intoxicants, preexisting medical conditions (e.g., diabetes, depression, cardiac disease, pregnancy), and medication use (e.g., steroids, β-blockers, anticoagulants) that may suggest certain patterns of injury or the physiologic response to injury.

ED care of the trauma patient begins with an initial assessment for potentially serious injuries. A primary survey is undertaken quickly to identify and treat immediately life-threatening conditions, with simultaneous resuscitation and treatment. Specific injuries that should be immediately identified and addressed during the primary survey include airway obstruction, tension pneumothorax, massive internal or external hemorrhage, open pneumothorax, flail chest, and cardiac tamponade. After assessing the patient's airway, breathing, and circulation, perform a more thorough head-to-toe examination (the **secondary survey**) (**Table 254-3**). Follow the secondary survey with appropriate diagnostic testing, further therapeutic interventions, and disposition. When derangements are identified in any of the systems assessed in the primary survey, undertake treatment immediately.

AIRWAY MANAGEMENT WITH CERVICAL SPINE CONTROL

Determine airway patency by inspecting for foreign bodies or maxillofacial fractures that may result in airway obstruction. Perform a jaw thrust maneuver (simultaneously with in-line stabilization of the head and neck) and insert an oral or nasal airway as part of the first response to a patient with inadequate respiratory effort. Insertion of an oral airway may be difficult in patients with an active gag reflex. Avoid nasal airway insertion in patients with suspected basilar skull fractures. **Whenever possible, use a two-person spinal stabilization technique in which one provider devotes undivided attention to maintaining in-line immobilization and preventing excessive movement of the cervical spine while the other manages the airway.** If the patient vomits, logroll the patient and provide pharyngeal suction to prevent aspiration. Perform endotracheal intubation in comatose patients (Glasgow Coma Scale score between 3 and 8) to protect the airway and to prevent

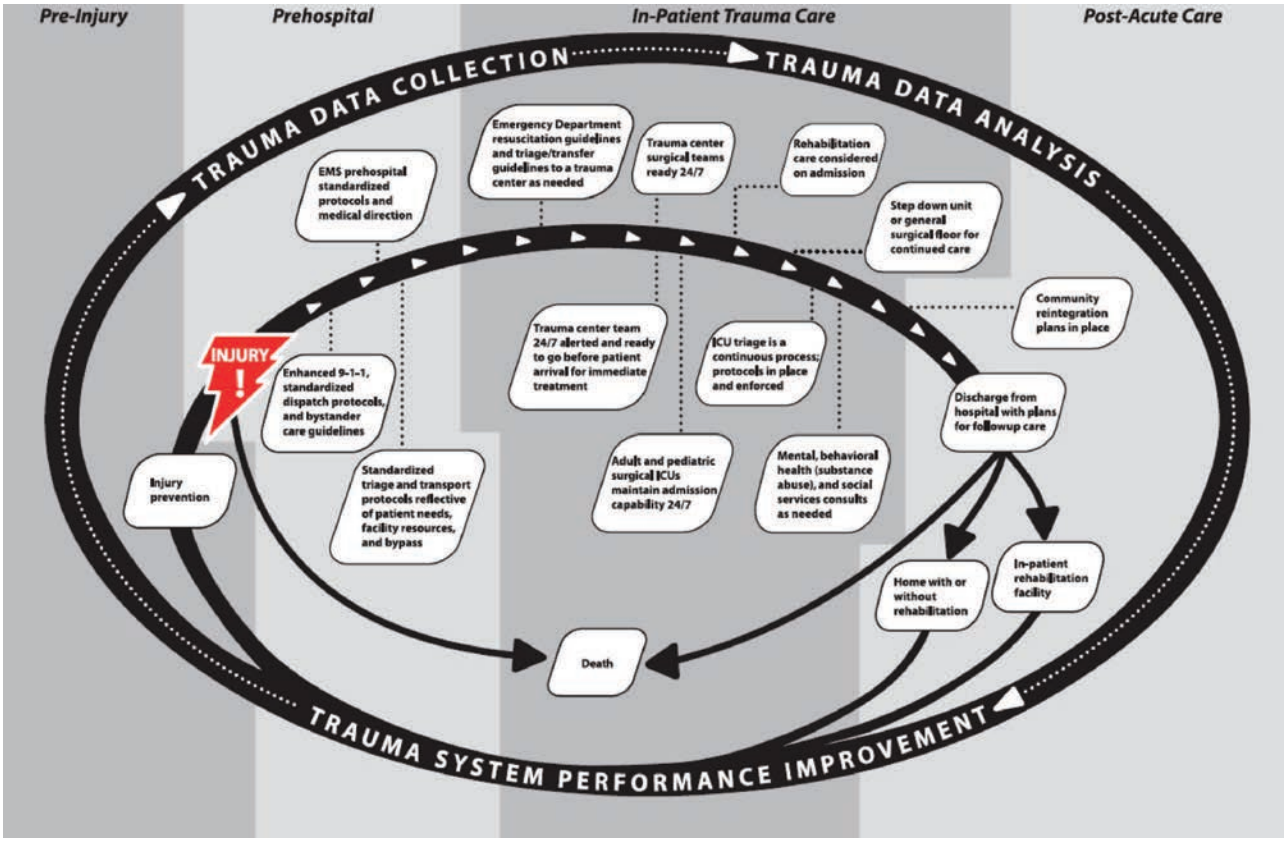

FIGURE 254-1. Phases of a preplanned trauma care continuum. ICU = intensive care unit. [Reproduced from U.S. Department of Health and Human Services, Health Resources and Services Administration. Model Trauma System Planning and Evaluation. Rockville, MD: U.S. Department of Health and Human Services; 2006. Available at: https://www.facs.org/quality-programs/trauma/vrc/resources. Accessed February 12, 2018.]

secondary brain injury from hypoxemia. Agitated trauma patients with head injury, hypoxia, or drug- or alcohol-induced delirium may be at risk for self-injury. Trauma patients are frequently difficult to intubate due to the need for neck immobilization, the presence of blood or vomitus, or upper airway injury. Video laryngoscopy devices are beneficial because they aid in vocal cord visualization while minimizing cervical spine manipulation. **Use a rapid-sequence intubation technique for intubation** (see Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation"). If anatomy or severe maxillofacial injury precludes endotracheal intubation, cricothyroidotomy may be needed.

Clearance of the cervical spine from serious injury involves careful clinical assessment, with or without radiologic imaging. Not all patients require cervical spine radiographs. The **National Emergency X-Radiography Utilization Study (NEXUS) criteria** (**Table 254-4**)[7] and the **Canadian Cervical Spine Rule** (**Table 254-5**)[8] are useful only in awake and alert patients and are not a substitute for good clinical judgment. Patients meeting NEXUS or Canadian criteria for low risk of cervical spine injury should undergo full examination of the cervical spine, including active range-of-motion testing in all directions along with a thorough neurologic examination.

If the patient is obtunded, assume a cervical spine injury until proven otherwise. Even when plain radiographs or CT images show normal findings, it is possible for a patient to have unstable ligamentous injuries. Therefore, maintain spinal immobilization during the resuscitation. Imaging of the spine should not delay urgent operative procedures because imaging results will not change the immediate management. CT of the cervical spine is the preferred initial imaging modality. For full

TABLE 254-1 Essential Characteristics of Level 1 Trauma Centers

- Meet the admission volume requirements (at least 1200 trauma patients yearly or have 240 admissions with an Injury Severity Score of >15)
- Maintain a surgically directed critical care service
- Participate in the training of residents and be a leader in education and outreach activities
- Conduct trauma research

TABLE 254-2 Triage and Trauma System Entry Criteria

Physiologic abnormalities
- Systolic blood pressure <90 mm Hg
- Glasgow Coma Scale score <14
- Inadequate airway or need for immediate intubation

Injury pattern
- Penetrating wound to head, neck, or torso
- Gunshot wound to extremities proximal to elbow or knee
- Extremity with neurovascular compromise
- Amputation proximal to wrist or ankle
- CNS injury or paralysis
- Flail chest
- Suspected pelvic fracture

Mechanism of injury
- MVC with intrusion into passenger compartment >12 in
- MVC with major vehicular deformity >20 in
- Ejection from vehicle
- MVC with entrapment or prolonged extrication of >20 min
- Fall of >20 feet
- MVC with fatality in same passenger compartment
- Auto–pedestrian or auto–bicycle collision at >5 mph
- Motorcycle crash >20 mph

Abbreviation: MVC = motor vehicle crash.

TABLE 254-3 Primary and Secondary Survey in Trauma Resuscitation

PRIMARY SURVEY (RAPID IDENTIFICATION AND MANAGEMENT OF IMMEDIATELY LIFE-THREATENING INJURIES)

A. Airway and cervical spine

- Assess, clear, and protect airway: jaw thrust/chin lift, suctioning.
- Perform endotracheal intubation with in-line stabilization for patient with depressed level of consciousness or inability to protect airway.
- Create surgical airway if there is significant bleeding or obstruction or laryngoscopy cannot be performed.

B. Breathing

- Ventilate with 100% oxygen; monitor oxygen saturation.
- Auscultate for breath sounds.
- Inspect thorax and neck for deviated trachea, open chest wounds, abnormal chest wall motion, and crepitus at neck or chest.
- Consider immediate needle thoracostomy for suspected tension pneumothorax.
- Consider tube thoracostomy for suspected hemopneumothorax.

C. Circulation

- Assess for blood volume status: skin color, capillary refill, radial/femoral/carotid pulse, and blood pressure.
- Place two large-bore peripheral IV catheters.
- Begin rapid infusion of warm crystalloid solution, if indicated.
- Apply direct pressure to sites of brisk external bleeding.
- Consider central venous or interosseous access if peripheral sites are unavailable.
- Consider pericardiocentesis for suspected pericardial tamponade.
- Consider left lateral decubitus position in late-trimester pregnancy.

D. Disability

- Perform screening neurologic and mental status examination, assessing:
  - Pupil size and reactivity
  - Limb strength and movement, grip strength
  - Orientation, Glasgow Coma Scale score
- Consider measurement of capillary blood glucose level in patients with altered mental status.

E. Exposure

- Completely disrobe the patient, and inspect for burns and toxic exposures.
- Logroll patient, maintaining neutral position and in-line neck stabilization, to inspect and palpate thoracic spine, flank, back, and buttocks.

SECONDARY SURVEY (HEAD-TO-TOE EXAMINATION FOR RAPID IDENTIFICATION AND CONTROL OF INJURIES OR POTENTIAL INSTABILITY)

- Identify and control scalp wound bleeding with direct pressure, sutures, or surgical clips.
- Identify facial instability and potential for airway instability.
- Identify hemotympanum.
- Identify epistaxis or septal hematoma; consider tamponade or airway control if bleeding is profuse.
- Identify avulsed teeth or jaw instability.
- Evaluate for abdominal distention and tenderness.
- Identify penetrating chest, back, flank, or abdominal injuries.
- Assess for pelvic stability; consider pelvic wrap or sling.
- Inspect perineum for laceration or hematoma.
- Inspect urethral meatus for blood.
- Consider rectal examination for sphincter tone and gross blood.
- Assess peripheral pulses for vascular compromise.
- Identify extremity deformities, and immobilize open and closed fractures and dislocations.

discussion of cervical spine imaging and management in trauma, see Chapter 258, "Spine Trauma."

BREATHING

Once the airway is controlled, inspect, auscultate, and palpate the thorax and neck to detect abnormalities such as a deviated trachea (tension pneumothorax); crepitus (pneumothorax); paradoxical movement of a chest wall segment (flail chest); sucking chest wound; fractured sternum; and absence of breath sounds on either side of the chest (simple or tension pneumothorax, massive hemothorax, or right mainstem intubation). Any of these findings warrants immediate intervention, including needle thoracostomy for tension pneumothorax (see the section "Needle Decompression" in Chapter 68, "Pneumothorax"); insertion of large-bore chest tubes (36F) to relieve hemopneumothorax (see Chapter 261, "Pulmonary Trauma"); and application of an occlusive dressing to a sucking chest wound. For asymmetric or absent breath sounds in the intubated patient, partially withdraw the endotracheal tube from the right mainstem bronchus or reintubate. If no breath sounds are heard, and if massive hemothorax or vascular injury is suspected (initial chest tube output of >1500 mL, or >200 mL/h), a thoracotomy or video-assisted thoracic surgery is indicated to identify and control the source of bleeding.

TABLE 254-4 NEXUS (National Emergency X-Radiography Utilization Study) Criteria for Omitting Cervical Spinal Imaging*

- No posterior midline cervical spine tenderness
- No evidence of intoxication
- Alert mental status
- No focal neurologic deficits
- No painful distracting injuries

*Failure to meet any one criterion indicates need for cervical spine imaging.

CIRCULATION AND HEMORRHAGE CONTROL

Assessment of the patient's overall hemodynamic status is critical. This assessment includes evaluation of level of consciousness, skin color, and presence and magnitude of peripheral pulses. Note the heart rate and pulse pressure (systolic minus diastolic blood pressure), particularly in young, previously healthy trauma patients, as these may be early clues to impending hemodynamic compromise.

As part of the primary survey in the prehospital and hospital settings, identify and control external hemorrhage. Apply direct pressure, a compression bandage, or a hemostatic dressing to control active external bleeding. QuikClot Combat Gauze® is a kaolin-impregnated rayon and polyester hemostatic dressing that is safe and effective for arterial or venous bleeding.[4,9] For exsanguinating extremity injury, apply a tourniquet (**Fig. 254-2**). Prehospital and battlefield use of tourniquets is common. With aggressive tourniquet use, death rates from isolated limb exsanguination in Iraq decreased to 2% compared to 9% in the Vietnam War.[10] In civilian trauma, the need for tourniquet application is less common but lifesaving in some cases.

CIRCULATION

Any hypotensive trauma patient is at risk for development of hemorrhagic shock, a common cause of postinjury death. One system is commonly used for classifying the degree of hemorrhage (**Table 254-6**),

TABLE 254-5 Canadian Cervical Spine Rule

Any high-risk factor that mandates radiography? (Age >64 y or dangerous mechanism or paresthesias in extremities) **No**	**If Yes, radiography indicated**
Any low-risk factor that allows safe assessment of range of motion? (Simple rear-end collision or sitting position in the ED or ambulatory at any time or delayed onset of neck pain or absence of midline cervical spine tenderness) **Yes**	**If No, radiography indicated**
Able to rotate neck actively? (45 degrees left and right) **Yes**	**If No, radiography indicated**
No radiography indicated if all criteria are met	

REBOA: Resuscitative Endovascular Balloon Occlusion of the Aorta

BACKGROUND

Exsanguinating hemorrhage is a leading cause of preventable death following trauma. The U.S. military has improved survival from exsanguinating extremity injuries by means of field tourniquet application, but noncompressible torso hemorrhage remains a difficult problem. Historically, definitive control of noncompressible torso hemorrhage has been attempted through the field application of specially designed tourniquets, as well as emergent thoracotomy. Thoracotomy and laparotomy for definitive hemorrhage control require rapid transport to surgical care. One tool for alternative hemorrhage control is resuscitative endovascular balloon occlusion of the aorta (REBOA), which was originally described during the Korean War and has been re-popularized during the recent wars in Iraq and Afghanistan. REBOA involves insertion and inflation of an endovascular balloon into the proximal aorta via the common femoral artery. Balloon inflation is a temporizing maneuver until definitive hemostasis by vascular interventional procedures or open surgical control.

INDICATIONS

REBOA is primarily used in the United States for trauma or intraoperative exsanguination. It has been used internationally for a wider range of indications and for many years. Other indications reported in the literature include massive exsanguination from postpartum hemorrhage, upper GI bleeding, pelvic surgery, and ruptured aortic aneurysm. Although many protocols exist, experts generally agree that exsanguinating hemorrhage originating from a source below the diaphragm, which is unresponsive or transiently responsive to resuscitation, could benefit from REBOA.[1] In addition, REBOA can be considered for acute traumatic cardiac arrest due to presumed life-threatening hemorrhage below the diaphragm. The balloon catheter can be inflated into one of two general "zones" of the descending aorta. Inflation of the balloon at **zone 1** is for control of hemorrhage originating from below the diaphragm to above the renal arteries **(Figure 1).** If the source of hemorrhage is below the level of the renal arteries, including severe pelvic, groin, or proximal lower extremity hemorrhage, the balloon may be inflated within **zone 3. Zone 2** extends from the diaphragm to the lowest renal artery and is generally avoided due to the presence of the visceral arteries.

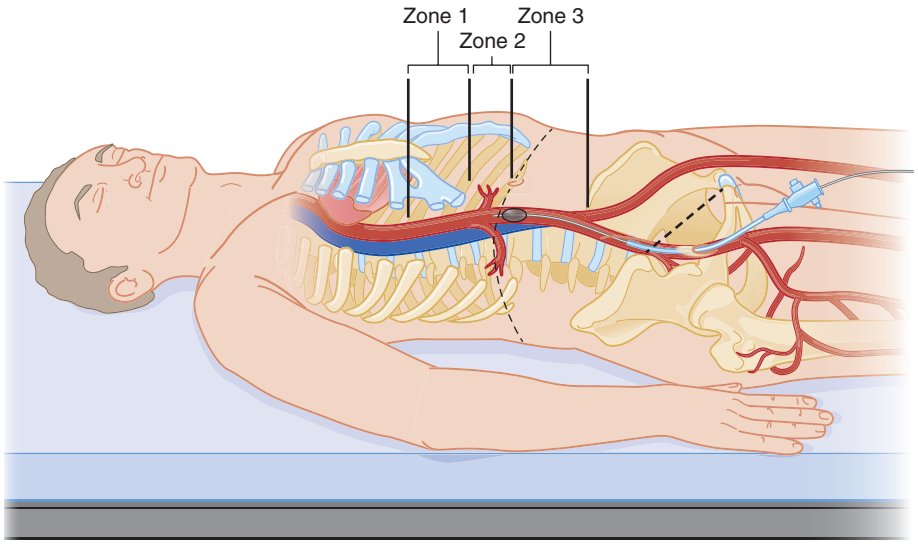

FIGURE 1. Anatomic zones for REBOA placement. Avoid inflation in Zone 2.

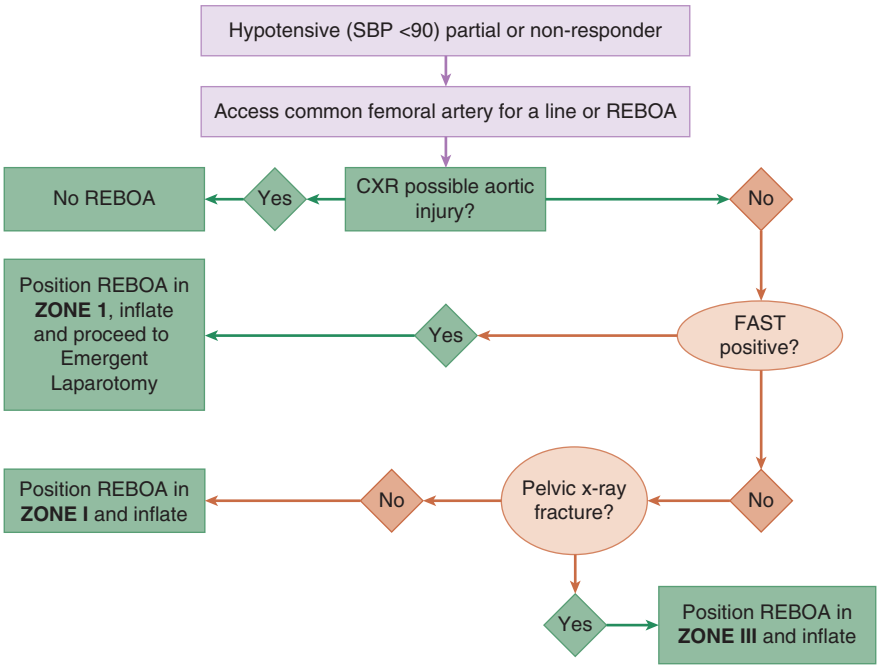

FIGURE 2. Suggested REBOA algorithm.

REBOA: Resuscitative Endovascular Balloon Occlusion of the Aorta (Cont.)

PROCEDURE (See Video: REBOA: Resuscitative Endovascular Balloon Occlusion of the Aorta)

A general description of the procedure was originally described by Stannard and colleagues[2] as a five-step procedure including arterial access, balloon selection and positioning, balloon inflation, balloon deflation, and sheath removal. With the development of purpose-designed REBOA catheters through smaller introducer sheaths, the procedure requires fewer steps with more rapid insertion and inflation compared to previous technology adapted from vascular surgery.

Training typically consists of a course discussing the risks, benefits, and application of the technique, coupled with simulation, animal model, or cadaver model training.[3,4]

Procedural steps include obtaining vascular access in the common femoral artery 1 cm below the inguinal ligament by either US-guided percutaneous or open exposure access. Many experts recommend open access in cardiac arrest. Insert the catheter sheath using the Seldinger technique. Measure the balloon for insertion length, which can be obtained by using either external landmarks, using the xiphoid for zone 1 and umbilicus for zone 3, or standardized length measurements, which place the balloon correctly for a large portion of the population. Then insert the balloon to the measured length and inflate with sterile fluid with or without radiopaque contrast. Imaging may be obtained after catheter insertion and balloon inflation to confirm placement within the aorta, but some experts feel this is not necessary. After inflation, assess patient response and send the patient for definitive hemorrhage control as soon as possible.

The prime consideration for the emergency provider is the most rapid disposition of the patient possible from the ED to definitive hemorrhage control in the operating room or by interventional radiology.[3] Field application is possible in the military or in systems with robust prehospital resources as long as there is very rapid transport for definitive hemorrhage control. The effects of prolonged aortic occlusion with REBOA, including partial or intermittent REBOA for mitigation of distal ischemia, are poorly studied.

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although it has not been validated and there is wide variability in individual patient response to hypovolemia. Hemorrhage and shock are on a continuum, and some patients can compensate for significant blood loss better than others. Hemorrhage of up to 30% of total blood volume may be associated with only mild tachycardia and a decrease in pulse pressure, but may quickly progress to profound hypoperfusion and decompensated shock if not recognized early. Be aware that medications, such as β-blockers, can mask early hemodynamic indicators of shock.

Establish two large-bore IV lines (18 gauge or larger), infuse lactated Ringer's, and obtain blood samples or specimens for laboratory studies, particularly blood type and screen. In patients who are unstable or in whom upper extremity peripheral veins are not easily cannulated, establish central venous access via the subclavian, internal jugular, or femoral vein. Avoid placement of a central venous line distal to a potential venous injury. Placement of an IO catheter is a second-line option (after peripheral IV attempt) because it is quick and easy and can accommodate infusion of large volumes. Most medications including blood products can be administered IO. Use a pressure bag to maximize flow rates. A balanced crystalloid, such as lactated Ringer's, is the fluid of choice for initial resuscitation. There is some advantage of lactated Ringer's over normal saline when large volumes are given in order to avoid hyperchloremic acidosis, although this is unlikely to be significant for most patients during initial resuscitation.

Reassess hypotensive patients without an obvious indication for surgery after rapid infusion of 2 L of crystalloid solution. If there is no marked improvement, then transfuse type O blood (O-negative for females of childbearing age). **Aggressive volume resuscitation is not a substitute for definitive hemorrhage control.**

Patients requiring massive transfusions generally require urgent surgical intervention to control hemorrhage. A well-defined source of bleeding may be evident on external examination, assessment of chest tube output, extended FAST examination (**Figure 254-3**), or conventional or CT imaging of the chest or abdomen. There may also be considerable blood loss from blunt trauma to the pelvis and limbs without a discrete source. Immobilize open pelvic fractures in a pelvic wrap or sling and reduce and immobilize limb fractures to tamponade bleeding from fractured bone ends.

Major trauma patients may develop a bleeding diathesis almost from the time of injury, which results in defective clotting and platelet function. Data from both military and civilian experience reveal that patients receiving >10 units of packed red blood cells showed decreased mortality when they simultaneously receive fresh frozen plasma in a ratio of packed red blood cells to fresh frozen plasma of 1:1 rather than 1:4 (26% vs. 87.5% mortality, respectively).[13] There is general consensus that there should be a higher ratio of fresh frozen plasma and platelets to packed red cells up to 1:1:1 ratio in massive transfusion protocols.[14]



FIGURE 254-2. C.A.T.® tourniquet. [Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Maa, D.M. Yealy, G.D. Meckler, D.M. Cline: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 8th ed. www.accessmedicine.com. (Copyright © McGraw-Hill Education. All rights reserved.)]

TABLE 254-6 Classification of Hemorrhage Based on Estimated Blood Loss at Initial Presentation

	Class I	Class II	Class III	Class IV
Blood loss (mL)*	Up to 750	750–1500	1500–2000	>2000
Blood loss (% blood volume)	Up to 15	15–30	30–40	40
Pulse rate (beats/min)	<100	100–120	120–140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased

*Assumes a 70-kg patient with a preinjury circulating blood volume of 5 L.

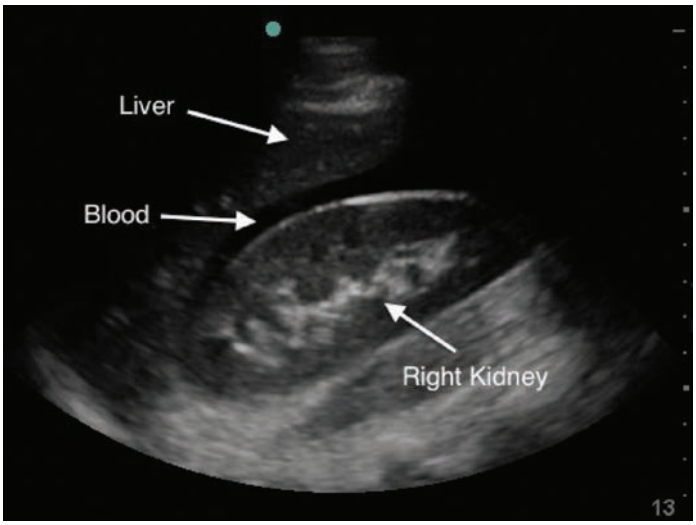

FIGURE 254-3. Positive extended FAST exam with blood identified in Morison's pouch. [Photo contributed by Barry Knapp, MD.]

Both acidosis and hypothermia contribute to the coagulopathy and should be corrected as quickly as possible.

An emerging tool in the management of noncompressible torso hemorrhage is resuscitative endovascular balloon occlusion of the aorta (REBOA). **REBOA** is potentially indicated for traumatic life-threatening hemorrhage below the diaphragm in patients in hemorrhagic shock who are unresponsive to resuscitation. Depending on the location of hemorrhage, an inflatable balloon catheter is inserted in the femoral artery and advanced to the distal thoracic aorta or distal abdominal aorta. REBOA should be considered as a bridging therapy to definitive surgery. The technique should not delay definitive surgery and is suitable for only a limited number of patients. It is important to note that no current, high-grade evidence clearly demonstrates REBOA improves outcomes or survival compared to standard treatment of severe hemorrhage.[11,12] Complications of REBOA include arterial disruption, hematoma, thromboemboli, dissection, and extremity ischemia.

TRANEXAMIC ACID (TXA)

Tranexamic acid is an antifibrinolytic agent that reduces blood loss after surgery and may reduce blood loss after traumatic injury. It prevents cleavage of plasmin and degradation of fibrin. It is on the World Health Organization list of essential medications affecting coagulation.[15] Studies involving >20,000 patients reported a risk reduction of death from bleeding of 10% to 15%. There was no reported difference in risk of death from myocardial infarction, vascular occlusion, stroke, pulmonary embolism, mutiorgan failure, or head injury.[16] Criticism of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) study was that the patient populations studied were heterogeneous in terms of injury and were in low- to middle-income countries with basic and very limited resources for major trauma management.[17,18] Nevertheless, the evidence to date indicates that tranexamic acid may reduce mortality without significant adverse side effects when given as early as possible after injury, with administration within 1 hour of injury reported to decrease the relative risk of death from bleeding by 32% and within 1 to 3 hours by 21%.[19] Administration of tranexamic acid more than 3 hours after injury is less effective and potentially harmful.[16] Tranexamic acid must be given before transfer/arrival to a trauma center in order to meet the time requirement of early administration.[17] The dose is 1 gram of tranexamic acid IV bolus over 10 minutes, followed by 1 gram IV over 8 hours.

DISABILITY

Once airway, breathing, and circulation have been addressed and stabilized, perform a focused neurologic evaluation to assess level of consciousness, pupillary size and reactivity, and motor function. Consider alternative causes of altered sensorium, including measurement of capillary blood glucose level and intoxicants. Despite the concomitant use of drugs and alcohol in many trauma patients, do not simply attribute altered mental status to intoxication. Assess the Glasgow Coma Scale (GCS) (**Table 254-7**). The GCS is an instrument widely used for assessment of consciousness at the site of injury, in EDs, and in hospitals, and it helps monitor progress or deterioration during treatment. The GCS consists of the following three components: eye (scored 1 to 4), verbal (scored 1 to 5), and motor (scored 1 to 6). Scores on each of these components are added to obtain the total Glasgow Coma Scale (tGCS) score.[20] Assume that a patient with a history of head trauma associated with altered mental status (tGCS <15) has a significant intracranial injury until proven otherwise. **Because a persistent tGCS score of ≤8 generally suggests a poorer prognosis than scores >8, secure a definitive airway to protect against aspiration or asphyxia.** The **tGCS scale assessment can be insensitive in patients with normal or near-normal tGCS score, and a score of 15 does not exclude the presence of traumatic brain injury.** Because the tGCS is often difficult to record for trauma patients, some systems have begun using only the motor component of the GCS (mGCS) to triage patients. An mGCS score <6, "patient does not follow commands," is almost as accurate as the tGCS in predicting traumatic injury outcome.[21,22] Sensitivity, specificity, and accuracy of GCS score ≤13 versus mGCS score <6 are very similar (69.8% vs. 67.3% for sensitivity; 88.1% vs. 90.1% for specificity; and 87.1% vs. 88.8% for accuracy, respectively).[21,22]

Direct efforts toward resuscitating brain-injured patients in order to maintain normal cerebral perfusion. Monitor serum glucose levels and maintain euglycemia. Mild hyperventilation may reduce intracranial pressure, although at the expense of cerebral vasoconstriction and hypoperfusion. Avoid hyperventilation during the first 24 hours after injury when cerebral blood flow is often critically reduced. **Prophylactic hyperventilation (partial pressure of arterial carbon dioxide of 25 mm Hg or less) is not recommended.**[23]

EXPOSURE

No primary survey is complete without completely disrobing the patient and examining carefully for occult bruising, lacerations, impaled foreign bodies, and open fractures. After completing the primary survey, logroll the patient, with one team member assigned to maintain in-line cervical stabilization. **Palpate the spinous processes of the thoracic and lumbar spine for tenderness or deformity, and then carefully logroll the patient back to a neutral position.** Routine rectal examination is not performed, but it is useful in pelvic injury to identify gross rectal bleeding or loss of rectal tone in patients with suspected spinal injury. Examine the perineum for bruising, laceration, or bleeding. Cover the patient with warm blankets to prevent heat loss. Some have advocated the use of hypothermia in cases of severe brain injury. However, as of this writing, there is no conclusive evidence in favor of this therapy. Potential therapeutic benefits must be weighed against the coagulopathy, increased bleeding, and reduced myocardial function that hypothermia can cause.

TABLE 254-7 Glasgow Coma Scale (GCS) with Motor Glasgow Coma Scale

GCS Score	6	5	4	3	2	1
Best motor response	Obey command	Localize the pain	Withdrawal to pain	Flexion to pain	Extension to pain	None
Verbal response		Oriented	Confused	Inappropriate word	Incomprehensible sound	None
Eye opening			Spontaneous	To verbal	To pain	None

SPECIFIC INJURIES OF IMPORTANCE

Place special emphasis on identifying the injuries described in the following sections during the primary survey, because they can be rapidly fatal if not recognized and treated.

SEVERE HEAD AND SPINAL TRAUMA

Rapidly assess neurologic status in patients with suspected traumatic brain injury. **To quickly identify patients with intracranial injuries who may benefit from operative treatment, defer any procedures that do not correct a specific problem discovered during the primary survey until after the head CT is performed.** In patients requiring intubation, provide in-line immobilization when the cervical collar is removed during intubation, and then reapply after intubation. Obtain a chest radiograph or US to assess endotracheal tube placement and exclude pneumothorax.

TENSION PNEUMOTHORAX, OPEN PNEUMOTHORAX, AND MASSIVE HEMOTHORAX

Tension pneumothorax, open pneumothorax, and massive hemothorax all should be readily apparent during the primary survey. If tension pneumothorax is clinically suspected, immediately perform tube thoracostomy. If equipment is not immediately available, needle thoracostomy can be a temporizing measure. Delays in diagnosis and treatment (including awaiting confirmatory chest radiograph) can result in complete hemodynamic collapse. In equivocal cases, US can confirm the presence of pneumothorax and prompt emergent intervention. Perform tube thoracostomy in a timely manner in patients with a significant pneumo- or hemothorax, as determined by US, chest radiograph, or CT (see Chapter 261).

PENETRATING ABDOMINAL TRAUMA

Abdominal tenderness or distention on palpation, coupled with hypotension, indicates the emergent need for exploratory laparotomy in a patient who has sustained a penetrating abdominal injury; this should prompt immediate transport to the operating room if unstable. Early operative intervention in patients experiencing penetrating trauma who are in shock results in better outcomes. Placement of nasogastric, urinary, and IV catheters may proceed in the ED only if they do not delay definitive operative intervention. Otherwise, these procedures should take place in the operating room as the patient is being prepared for general anesthesia. In the setting of a penetrating gunshot wound to the abdomen, CT is not indicated if the patient requires emergent exploratory laparotomy.

IMPALED OBJECTS

Objects deeply impaled in the chest and abdomen should be left in place and the patient emergently transported to the operating room for surgical removal under direct visualization to ensure vascular control and hemostasis. The impaled object may be cut or shortened outside the skin to facilitate transport.[24]

TRAUMATIC CARDIAC ARREST

Unless obvious signs of death are present in the field, providers in most emergency medical systems continue to transport patients without pulse or respiration to a hospital once cardiopulmonary resuscitation has been initiated. For patients in traumatic arrest upon arrival to the ED, a critical decision must be made regarding the appropriate level of intervention and, specifically, the use of emergent thoracotomy. One study analyzing 862 patients undergoing ED thoracotomy at a regional trauma center showed that the proportion of neurologically intact survivors was 3.9%. The best outcomes were in patients with stab wounds to the chest. Further analysis revealed that the survival rate was 23% among thoracic stab wound victims who showed breathing or pulse in the field and 38% among those who were moribund, but had some indication of respiration or pulse on arrival to the ED. Therefore, **the strongest recommendation for performing ED thoracotomy can be made for patients with penetrating chest trauma with witnessed signs of life during transport to or in the ED and at least cardiac electrical activity upon arrival.**[25-27] There were no survivors among patients with blunt trauma and no respiration or pulse in the field. ED thoracotomy for this group is not indicated (including in the presence of myocardial electrical activity).[6]

Any recommendation for the termination or escalation of resuscitative efforts (penetrating or blunt) should be based on an immediate search for readily reversible causes. US can identify some of these causes including cardiac tamponade, pneumothorax, massive hemoperitoneum, and the presence or absence of ongoing cardiac activity. One suggested algorithm for this decision making is outlined in **Figure 254-4**.[28]

SECONDARY SURVEY

The secondary survey is a rapid but thorough head-to-toe examination for injuries (Table 254-3). Do not start the secondary survey until basic functions have been corrected in conjunction with the primary survey (airway, breathing, circulation, disability, exposure) and resuscitation has been initiated. The secondary survey can help set priorities for ongoing evaluation and management. Frequent reassessment of the patient's blood pressure, pulse rate, and response to interventions should continue during this period.

Scalp lacerations can bleed profusely. Bleeding can be controlled with plastic Raney clips (see Chapter 42, "Face and Scalp Lacerations") or staples that grasp the full thickness of the scalp. Inspect the tympanic membranes for hemotympanum and repeat the pupil examination. Repeat the examination of the neck and thorax for any changes. When there is facial trauma or evidence of basilar skull fracture, insert the gastric tube through the mouth rather than the nose.

Inspect the urinary meatus, scrotum, and perineum for the presence of blood, hematoma, or laceration. Perform a rectal examination, noting sphincter tone, gross blood, and prostatic bogginess or displacement. The rectal examination is no longer routinely performed in alert patients without evidence of pelvic or spinal injury. If the prostate is normal and there is no blood at the urethral meatus, a urinary catheter can be placed in the bladder. **If meatal blood is present or the prostate is displaced, which suggests a urethral injury, perform retrograde urethrography before inserting a Foley catheter.** If there is vaginal bleeding, perform a manual and speculum examination to identify a possible vaginal laceration in the presence of a pelvic fracture. Evaluate the extremities for fracture and soft tissue injury, with attention to peripheral pulses. Perform a more thorough neurologic examination, carefully checking motor and sensory function.

Certain conditions are typically not evident during the secondary survey unless specifically sought. Injuries to the esophagus, diaphragm, and small bowel often remain undiagnosed, even with diligent examination, and further imaging and hospital observation for delayed presentation may be required. The most frequently missed conditions are orthopedic. Careful consideration of orthopedic extremity injuries is essential in patients with multisystem trauma. A tertiary survey has been recommended in patients with multisystem trauma within the first 24 hours to lessen the risk of missed injury.[29]

IMAGING AND LABORATORY TESTING

For patients who are not rapidly transported to the operating room or CT suite after the initial assessment, standard radiographic imaging may include cervical spine, chest, and pelvic radiographs. The chest and pelvic radiographs image regions outside the peritoneal cavity that can accommodate volumes of blood sufficient to produce hypotension and shock. In patients with gunshot wounds to the torso, a chest radiograph is required, with or without abdominal films, depending on the site of injury.

The **extended FAST** examination is a rapid and effective screening tool for the identification of major intraperitoneal bleeding, pericardial tamponade, pneumothorax, and hemothorax as the source of hypotension or shock.[30] It should be performed to identify causes of shock immediately after the primary survey. Perform a CT scan with IV

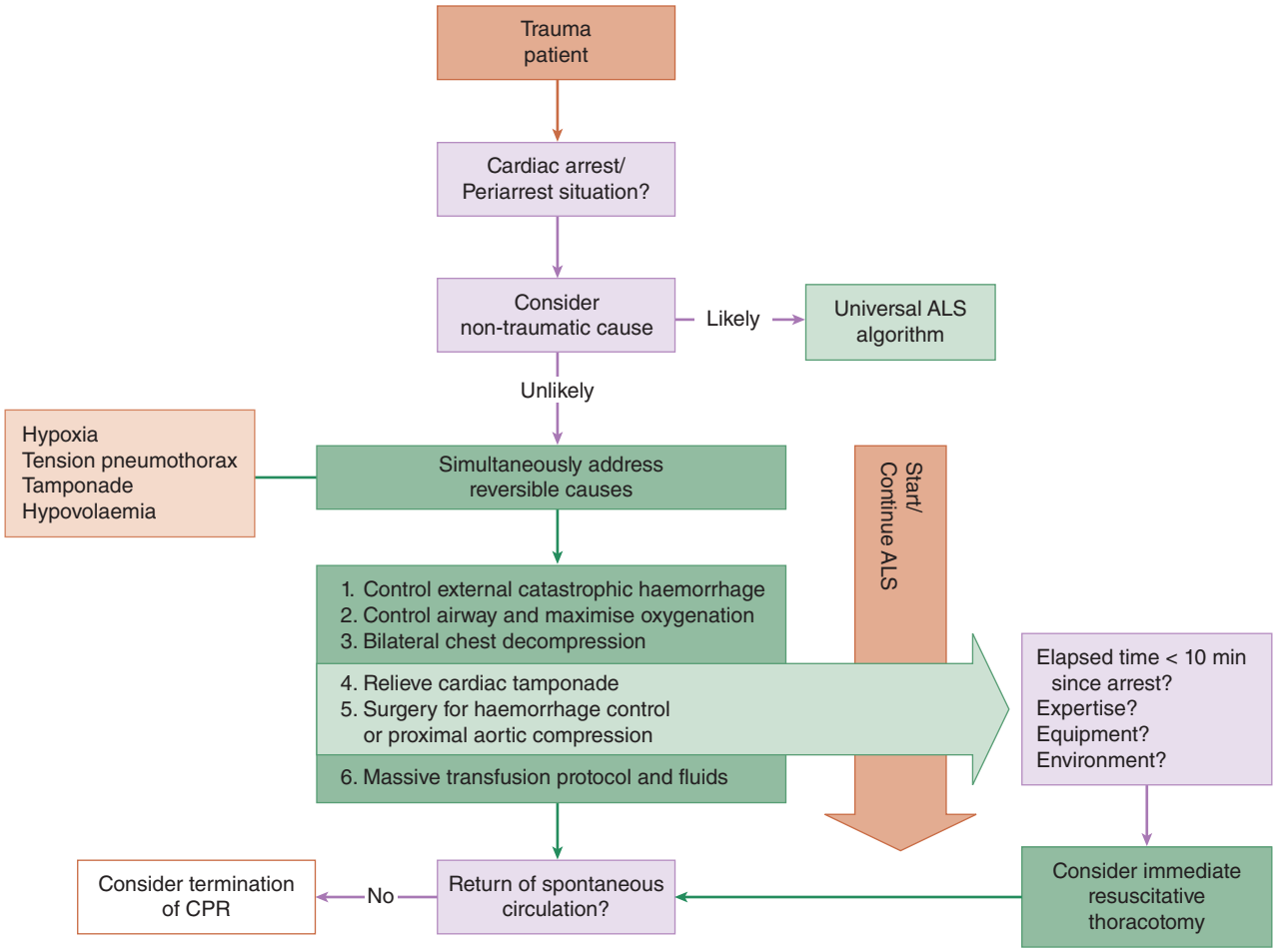

FIGURE 254-4. Decision-making algorithm. ALS = advanced life support. [Reproduced with permission from Truhlar AJ, Deakin, CD, Soae J, et al: European Resuscitation Council Guidelines for Resuscitation 2015. Section 4. Cardiac arrest in special circumstances. *Resuscitation* 95: 148-201, 2015. Copyright Elsevier.]

contrast for definitive imaging of the chest and abdomen-pelvis. Obtain appropriate extremity radiographs to exclude fractures as directed by the physical examination findings.

In obtunded patients or those with multisystem trauma, consider imaging of the **entire spine** if the mechanism of injury warrants it. Contrast imaging of the vertebral and carotid arteries can identify blunt carotid and vertebral artery injury, especially in patients with head, cervical spine, and chest injuries.[31] See Table 260-7 for risk factors. In patients undergoing head CT, most EDs perform cervical spine CT at the same time. If chest and abdominal CTs are performed, CT images of the thoracic and lumbar spines can be reconstructed.

In the setting of significant trauma, a liberal approach to the use of CT scanning has been recommended by some, as it can be done quickly and has the potential to detect injuries not clinically apparent.[32] The benefits of this "pan scan" approach need to be balanced by the undesirable consequences of increased ionizing radiation exposure. Studies have questioned this "pan scan" approach. The REACT-2 (Randomized Study of Early Assessment by CT 2) trial found no significant difference in in-hospital mortality in patients with severe trauma who underwent immediate total-body CT scanning compared with the standard workup with conventional imaging and selective CT scanning.[33]

Routine laboratory studies often include blood type and screen, hemoglobin level, urine dipstick testing for blood, and ethanol level. In women of childbearing age, always perform a pregnancy test. The use of bedside viscoelastic hemostatic tests such as rotational thromboelastometry and thromboelastogram are not routine but show promising results in some centers in directing massive transfusion protocols. Check capillary blood glucose level in patients with altered mental status or a history of diabetes mellitus. In patients older than 55 years, consider obtaining an ECG and measuring levels of markers for cardiac ischemia, such as troponin I.

DISPOSITION AND FOLLOW-UP

Expeditiously transport patients with hemodynamic instability and ongoing bleeding to the operating room or transfer the patient to another facility with appropriate surgical or critical care resources. Complete a rapid but thorough primary and secondary survey prior to transfer. In most urban Level 1 trauma centers, the trauma surgeon will have been present for the primary and secondary surveys. In rural hospitals that transfer the most severely injured trauma patients, the resuscitating physician should relate all the physical findings discovered during the primary and secondary surveys to the physician receiving the patient. Laboratory results, imaging studies, and the chronologic record of the patient's blood pressure, pulse, fluids infused, urine output, gastric output, and neurologic findings should accompany the patient. Personnel capable of performing ongoing resuscitation of the patient should accompany a patient transported to another facility.

Serial examinations are essential for patients without clear indications for surgery identified on initial assessment. Patients may be admitted to the hospital or an ED observation unit. Blunt abdominal injuries such as those involving the pancreas and bowel may not be readily apparent on initial CT. These injuries may become clinically apparent upon serial examinations. In addition, consider admission or observation for patients with closed head trauma who have normal levels of consciousness and require repeat neurologic examinations as well as patients at risk for delayed pneumothorax or pulmonary contusion that require repeat chest radiography.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 255

Trauma in the Elderly

Ross J. Fleischman
O. John Ma

INTRODUCTION AND EPIDEMIOLOGY

The elderly have worse outcomes following trauma because of physiologic changes that occur with aging. They are more susceptible to serious injury from low-energy mechanisms, less able to compensate from the stress of injury, and more likely to suffer complications during treatment and recovery. Emergency physicians should have a higher suspicion for injury and lower threshold for diagnostic testing and admission than in younger patients.

While studies most commonly define geriatric trauma by an age of 65 or older, some have shown mortality to increase by as young as 45 years of age.[1] The U.S. Census Bureau projects that those ≥65 years old will increase from 15% of the population in 2014 to 21% by 2030.[2] These older patients consume trauma resources at a greater rate than younger patients.[3]

PATHOPHYSIOLOGY

The difficulty in describing the elderly population derives from the discrepancy between chronologic and physiologic age. Chronologic age is the actual number of years the individual has lived, whereas physiologic age describes the functional capacity of the patient's organ systems. Studies have shown a clear association between age and mortality. Comorbid diseases have been shown to be associated with increased mortality after minor and moderate injuries in all age groups.[4]

The physiologic changes of aging complicate recovery from injury and make assessment of injury more difficult. With age, myocytes are lost and replaced by collagen. Contractility and compliance decrease for any given preload.[5] An 80-year-old person will have approximately 50% of the cardiac output of a 20-year-old, even without significant coronary artery disease. Maximal heart rate and cardiac output decrease with age. Aging myocardium has a decreased chronotropic response to catecholamines and is dependent on preload (intravascular volume). Hypovolemia can easily result in shock. Deterioration of the cardiac conduction system leads to atrial fibrillation and bundle branch blocks. Medications, especially digoxin, β-blockers, and calcium channel blockers, impair the tachycardic response to catecholamines, both impairing the body's inability to compensate for hemorrhage and making heart rate an unreliable predictor of hypovolemia.

Chest wall compliance, respiratory muscle strength, and the capacity for oxygen exchange all decrease with age. The response to hypoxia may decline by 50% and that to hypercarbia by 40%, such that the patient may not appear to be in respiratory distress despite impending respiratory failure.[6] Because of weakened respiratory muscles and degenerative changes in the chest wall, maximum inspiratory and expiratory force may be decreased by up to 50% compared with younger patients. Age-related reductions in vital capacity, functional residual capacity, and forced expiratory volume can limit older patients' ability to compensate for chest injuries.

Renal function declines with age and predisposes patients to dehydration, requiring medication dose adjustments and making them susceptible to acute kidney injury.

This state of decreased physiologic reserve and resistance to stressors, now formally referred to as "frailty," is being increasingly recognized. Instruments for assessing frailty go beyond counting medical comorbidities and may include assessments of mobility, activity level, cognition, and independence with activities of daily living. In one study, a validated frailty scoring system outperformed age, vital signs, and injury severity score in predicting adverse outcomes.[7]

COMMON MECHANISMS OF INJURY

Falls Falls are the most common cause of fatal and nonfatal injury in people ≥65 years of age.[8,9] One third of older adults fall annually, with the rate increasing with age. Hip fractures are the most common fracture in elders hospitalized for injury, but the overall incidence of nonhip, nonspine fractures in women >55 years old is five times greater than hip fractures.[10,11] There are age-related changes in postural stability, balance, motor strength, coordination, and reaction time that make the elderly more prone to falling. Other causes of falls in the elderly are listed in **Table 255-1**. Bathroom falls are concerning because hard surfaces can result in head and spinal injuries, and slippery surfaces can cause falls. Falls on stairs involve higher energy and potential for injury than those on flat ground. Falls in which an individual is unable to get help for a prolonged period should prompt investigation for rhabdomyolysis and dehydration with a check of the creatine kinase and electrolytes.

Motor Vehicle Crashes Motor vehicle crashes are the second most common cause of injury in the elderly and are the leading cause of death, with a case fatality rate twice that of those under 65 years.[2] The elderly make up 17% of U.S. traffic fatalities.[12]

Pedestrian–Motor Vehicle Collisions The elderly are second only to children as victims of pedestrian–motor vehicle collisions. Those ≥65 years old account for 19% of pedestrian–automobile fatalities in the United States. Pedestrian–motor vehicle collisions are one of the most lethal mechanisms of injury in this age group, with a 53% case fatality rate.

Burns Burns are the second leading cause of traumatic death in the home in older adults.[13] There is a direct relationship between age and burn mortality, as evidenced by the traditionally taught mortality-predicting **Baux score.**[14]

Elder Abuse Maintain a high suspicion for intentional injuries and injuries caused by neglect. Warning signs include poor hygiene, untreated decubitus ulcers, injuries not explained by the reported mechanism, and subacute injuries in various stages of healing.

CLINICAL FEATURES

HISTORY

Treat injured elders as both trauma and medical patients. Ask the patient, family, and prehospital care providers about the exact events leading up to the injury. Avoid skipping the review of systems, past medical history, and medications list. **Investigating the cause of a fall may uncover serious underlying medical causes or prevent future trauma.**

TABLE 255-1 Common Causes of Falls in the Elderly

Associated with syncope/loss of consciousness
- Dysrhythmias
- Seizures
- Acute coronary syndrome
- Hypoglycemia
- Pulmonary embolism

Associated with near-syncope, positional change, vasodilation (e.g., hot water)
- Antihypertensive medications (especially β-blockers, calcium channel blockers)
- Dehydration, diuretic medications
- Hemorrhage (GI bleed, abdominal aortic aneurysm)
- Hot bath or shower
- Sepsis
- Anemia

Nonsyncopal, "mechanical" causes
- Deconditioning
- Decreased visual acuity
- Unsafe home conditions (e.g., poor lighting, loose rugs)
- Alcohol
- Sedating medications (narcotics, benzodiazepines, antihistamines, sleep aids)
- Neurologic disease (cerebrovascular attack, Parkinson's disease)

PRIMARY SURVEY

Avoid feeling reassured by "normal" vital signs. A tachycardic response to pain, hypovolemia, or anxiety may be absent in the elderly trauma patient. Medications such as β-blockers may mask tachycardia and hinder evaluation. One study demonstrated that eight of 15 geriatric blunt trauma patients initially considered to be hemodynamically "stable" had cardiac outputs <3.5 L/min, and none had an adequate response to volume loading. Of seven patients with normal cardiac outputs, five had inadequate oxygen delivery.[15] Another study reported that 39% of patients with a systolic blood pressure >90 mm Hg and heart rate <120 beats/min had occult hypoperfusion, defined by lactate >2.2 or base deficit less than –2.[16] The elderly also have blunted responses to hypoxia, hypercarbia, and acidosis, which can mask the signs of respiratory failure.

Blood pressures are also misleading in the elderly patient. Because the incidence of underlying hypertension approaches 90%, use a higher cutoff for hypotension than in younger patients. **In blunt trauma patients ≥65 years old, there is an association between hypotension and mortality starting with systolic blood pressures <110 mm Hg and heart rates >90 beats/min.** Therefore, it is reasonable to use these more conservative cutoffs as markers of abnormal vital signs.[17] A decrease in blood pressure of 30 mm Hg below a known baseline or a falling trend is also a marker of instability.

Be highly concerned about the elderly patient with abnormal vital signs. One study found that patients with a respiratory rate <10 breaths/min had 100% mortality.[18] Likewise, a systolic blood pressure <90 mm Hg in the blunt trauma patient has been associated with a mortality between 82% and 100%.[19]

Anatomic variations may complicate airway management. These include the presence of dentures (which may occlude the airway and make laryngoscopy more difficult), cervical arthritis (which adds danger to extending the neck), or temporomandibular joint arthritis (which may limit mouth opening).

SECONDARY SURVEY

A thorough secondary survey is essential to uncover less serious injuries. **Patients with no apparent life-threatening injuries can have potentially fatal injuries if there is some degree of limited physiologic reserve.** Seemingly stable geriatric trauma patients can deteriorate rapidly and without warning. Undertake a medication review early in the patient's evaluation, paying particular attention to medications that affect heart rate, blood pressure, and coagulation.

DIAGNOSIS

HEAD INJURY

Head injuries in the elderly cause almost 142,000 U.S. ED visits resulting in discharge, 82,000 survivable hospitalizations, and 14,000 deaths annually.[20] Age is an independent predictor for morbidity and mortality in patients with moderate or severe head trauma. When evaluating the patient's mental status, it would be a grave error to assume that alterations in mental status are due solely to dementia.

Elders are less prone to develop **epidural hematomas** than the general population because of the denser fibrous bond between the dura mater and the inner table of the skull. There is, however, a higher incidence of **subdural** and **intraparenchymal hematomas** in the elderly than in younger patients. As the brain mass decreases with age, there is greater stretching and tension of the bridging veins that pass from the brain to the dural sinuses. Bridging veins are more susceptible to traumatic tears. Diagnosis of intracranial bleeding may be delayed because brain atrophy increases intracranial free space, allowing blood to accumulate without initial signs or symptoms.

One study of blunt head trauma patients taking warfarin who were experiencing no or minimal symptoms found a rate of injury on head CT that changed disposition in 7%.[21] Therefore, **immediate noncontrast head CT is recommended for patients who take warfarin or clopidogrel and have a minor head injury mechanism, even if asymptomatic.**[22] Check the INR, because the degree of anticoagulation correlates with the risk of adverse outcomes.[23] The limited data on dabigatran suggest a risk similar to warfarin, so have a similarly low threshold for CT scan of patients on direct-acting oral anticoagulants.[24,25] There is insufficient evidence to delineate the risk conferred by aspirin or low-molecular-weight heparins.[26,27]

CERVICAL SPINAL INJURIES

The incidence of cervical spine injury is about twice as great in elders as in a younger cohort of blunt trauma patients. Odontoid fractures are particularly common in geriatric patients, accounting for 20% of geriatric cervical spine fractures, as compared with 5% of nongeriatric fractures.[28] Preexisting cervical spine pathology, such as osteoarthritis, bulging discs, and osteoporosis, may predispose elderly patients to spinal cord injuries. With hyperextension injuries, elderly patients may develop a **central cord syndrome**, which causes motor deficits in the upper extremities more often than the lower extremities, variable sensory loss, and bladder dysfunction. The **Canadian Cervical Spine Rule**, but not the **National Emergency X-Radiography Utilization Study** criteria, excludes patients age ≥65 years from being considered low risk for cervical spine injury.[29,30] Thus, liberal imaging of the cervical spine in geriatric trauma patients is warranted. **CT scan is the preferred initial modality for assessing the geriatric cervical spine because of the higher pretest probability of injury and the difficulties in interpreting plain radiographs in a patient with age-related degeneration.** Many fractures in one section of the spine are accompanied by fractures in another section, **so identification of one fracture should prompt imaging of the entire spinal column.**[31]

THORACOLUMBAR SPINAL INJURIES

Thoracic and lumbar spine fractures account for almost half of all osteoporotic fractures.[32] They are most common at the thoracolumbar junction (T12-L1) and midthoracic areas (T7-T8).[33] Anterior wedge compression fractures are the most common. Because of the low sensitivity of plain films for identifying thoracolumbar fractures in trauma patients, CT scan is the first-line imaging modality for adult patients.[34] This is even more significant in elders, in whom osteoporosis and degenerative changes make plain radiographs more difficult to interpret. See Chapter 258, "Spine Trauma," for more information on specific fracture types and management.

CHEST TRAUMA

The elderly are more susceptible to chest injuries from blunt trauma and have a decreased ability to compensate for these injuries. Rib fractures in the elderly often lead to morbidity, pneumonia, and death. The adjusted odds of death in the elderly with rib fractures are about five times that of a younger cohort.[35] Rates of pneumonia and mortality in patients ≥65 years old are twice that of younger patients, with most studies showing a correlation between the number of rib fractures and the risk of death.[36,37] Because of the complications associated with rib fractures in elders, a CT may be necessary to assess the extent of injuries that might not be seen on plain radiographs.

ABDOMINAL TRAUMA

The abdominal examination in elderly patients is unreliable. The FAST examination is an ideal imaging study to detect large volumes of free intraperitoneal fluid. Even with an initially benign physical examination, maintain a high suspicion for intra-abdominal injuries in patients with associated pelvic and lower rib cage fractures. As in younger patients, many solid organ injuries can be managed nonoperatively. Rates of successful nonoperative management of splenic injuries in elderly patients range from 62% to 85%.[38] Therefore, CT with contrast is a crucial diagnostic test for evaluating the extent of injury and ongoing hemorrhage. The risk of acute kidney injury following injury increases with age, hypovolemia, diuretic and nephrotoxic medications, diabetes, and preexisting renal disease; however, recent studies have questioned the strength of the association between low and iso-osmolar contrast given at the doses used for CT and acute kidney injury (contrast-induced

nephropathy).[39] **The risk can be reduced by volume expansion with isotonic crystalloids.** Oral *N*-acetylcysteine does not appear to prevent contrast-induced nephropathy in patients undergoing coronary angiography.[40] Other strategies, including sodium bicarbonate, ascorbic acid, and low versus iso-osmolar contrast, have had mixed results in studies.[41-45]

ORTHOPEDIC INJURIES

Pelvic Fractures While pelvic fractures in the young are generally caused by high-energy mechanisms, the elderly, especially women, frequently suffer pelvic fractures from low-energy falls to the ground from a standing or seated position. Pubic ramus fractures are the most common injuries, and lateral compression is the most common mechanism.[46]

CT of the pelvis should be ordered in stable patients with pelvic tenderness after an injury if plain radiographs are negative.[47,48] Plain radiography is especially insensitive for posterior fractures involving the sacrum and iliac wings, so tenderness of the posterior pelvis especially suggests the need for cross-sectional imaging.[49] Plain radiography may be omitted in stable patients who will be going promptly to CT.[50] Even CT may be only 77% sensitive for pelvic fractures in the elderly, particularly with nondisplaced posterior fractures in osteoporotic bone. Therefore, consider MRI for patients with pelvic pain or pain on weight bearing with negative CT imaging.[51]

Studies have been contradictory on whether age is an important predictor of the need for angiographic assessment for bleeding in pelvic fractures.[52] One study found that 94% of patients 60 years of age and older taken to angiography required embolization, which is significantly higher than the rate of 52% in younger patients.[53] Therefore, these authors advocate liberal use of angiography in elderly patients with significant pelvic fractures, even in the absence of hemodynamic instability or need for transfusion. Other studies did not demonstrate an association between age and the need for angioembolization.[54,55]

Hip Fractures Hip fracture is the single most common injury diagnosis that leads to hospitalization in the elderly. Hip fractures are a significant cause of mortality, with about 25% of elderly patients dying within a year of injury.[56] The vast majority of hip fractures are caused by falls to the ground. The age-adjusted incidence of hip fractures in women is approximately twice that of men. Hip fractures in men occur at older ages than in women. Femoral neck (intracapsular) and intertrochanteric fractures are about equally common, with subtrochanteric fractures comprising the remaining 5% to 10%.[57] Bleeding from closed pelvic and long-bone fractures can cause hypovolemia in elderly patients.

Obtain anteroposterior radiographs of the pelvis, as well as dedicated anteroposterior and lateral radiographs of the affected hip. Because plain radiographs are only 90% sensitive for hip fractures and delay in operative repair is associated with an increase in morbidity and mortality, **normal plain radiographs should be followed by more definitive imaging in patients in whom suspicion of hip fracture persists.**[58] MRI has higher sensitivity than CT for detecting hip fractures, with one study finding that 17% of hip fractures that were occult on plain radiographs were seen by MRI but not CT.[59] The sensitivity of CT is lower in patients with risk factors for osteoporosis (older age, female sex, chronic steroid use, alcoholism, inactivity, poor calcium intake, endocrine disorders) and a lower-energy mechanism of injury (ground-level falls), in which fractures are less likely to be displaced.[58] If MRI is difficult to obtain, CT may yield a diagnosis, but should be followed by MRI if nondiagnostic. Consider admitting patients with hip fractures to a multidisciplinary team of geriatricians, orthopedists, and rehabilitation specialists.

Upper Extremity Injuries Distal radius fractures (**Colles' fractures**) are the most common fractures in women up to age 75, with a lifetime risk of about 15%.[60,61] Such fractures are often caused by a fall onto an outstretched hand and are associated with low bone mineral density or osteoporosis. Assess median nerve function before and after reduction, as a deficit will require immediate orthopedic consultation for possible nerve decompression. Unstable or displaced fractures require closed reduction with a hematoma block for anesthesia. A systematic review of unstable distal radius fractures in the elderly reported that functional outcomes were similar with nonoperative and operative management, even though nonoperative management was associated with a less satisfactory radiographic appearance.[62] So while elderly patients with active lifestyles and good functional statuses may benefit from surgical treatment, many others will do as well with conservative treatment.

Fractures of the proximal humerus and humeral shaft are also common after falls from standing. Carefully assess for axillary nerve injury by checking sensation at the area of deltoid muscle insertion and deltoid muscle engagement with shoulder abduction. Note that the initial 18 degrees of shoulder abduction are generated by the supraspinatus muscle, so movement in this range may still be possible with an axillary nerve injury.

LABORATORY TESTING

Elderly trauma patients should receive more intensive laboratory evaluation than younger patients. This may be helpful to identify comorbid diseases (e.g., creatinine for renal dysfunction) or acute causes of syncope (e.g., troponin for myocardial infarction) or to uncover occult physiologic insults (e.g., lactate, INR, and base deficit). As discussed earlier, vital signs are an unreliable marker of shock in the elderly. **Base deficit and lactate levels are useful initial indicators of shock, and serial measurements can guide resuscitation progress.** Elevated lactate levels correlate with systemic hypoperfusion, intensive care unit and hospital length of stay, and mortality.[63,64] A "normal" or mild base deficit of –3 to –5 correlates with 24% mortality, a moderate base deficit of –6 to –9 correlates with 60% mortality, and a severe base deficit of ≤–10 correlates with 80% mortality.[65] Check creatine kinase levels to assess for rhabdomyolysis in patients who have fallen and been unable to receive assistance for a prolonged period.

TREATMENT

OUT-OF-HOSPITAL CONSIDERATIONS

EMS providers should recognize that seemingly minor trauma mechanisms, such as ground-level falls and low-speed motor vehicle crashes, may result in significant injury. For these reasons, the threshold for scene triage or transfer to a trauma center should be lower for elderly patients than for younger patients.[66]

Rates of prehospital undertriage are higher in older than in younger patients, with significant associated mortality.[67,68] For the reasons discussed earlier, traditional triage criteria of physiology (e.g., heart rate and blood pressure), anatomic injury, and mechanism are unreliable in elderly patients. Therefore, the 2011 U.S. Centers for Disease Control and Prevention National Expert Panel on Field Triage recommended a lower threshold for triage of injured elderly patients, giving three key recommendations: **"Risk of injury/death increases after age 55 years. Systolic blood pressure < 110 mm Hg might represent shock after age 65 years. Low impact mechanisms (e.g. ground level falls) might result in severe injury."**[69] While the guidelines emphasize that anticoagulated patients are at "high risk for rapid deterioration," they stop short of making anticoagulation a criterion for triage to a trauma center. Although the Advanced Trauma Life Support guidelines also stop short of making age ≥55 years a mandatory criterion, they recommend transporting patients to a trauma center or hospital capable of evaluation of injuries and considering consulting medical control.[70]

The elderly can rapidly develop tissue damage leading to decubitus ulcers. Consider padded backboards or vacuum splints for prolonged transports. Patients with cervical kyphosis may need firm padding placed behind the head when in spinal immobilization in order to prevent forcing the spine into an abnormal position.

BLEEDING AND HEAD INJURY

The volume of intracranial blood and hematoma expansion are the most important determinants of morbidity and mortality in head injury.[71] Rapidly reverse anticoagulation in patients taking warfarin or dabigatran with intracranial bleeding on CT scan. Despite a lack of definitive evidence, it is recommended to reverse other direct thrombin inhibitors and heparin. While studies on the effectiveness of platelet transfusion

and desmopressin in patients with intracranial hemorrhage taking aspirin or clopidogrel have been mixed, one guideline recommends desmopressin, but would reserve platelet transfusion only for patients undergoing a neurosurgical procedure.[72]

Admit patients with bleeding on head CT to an intensive care unit. The disposition of patients taking warfarin but with a normal initial CT scan is challenging because such patients have a reported rate of delayed intracranial hemorrhage between 1% and 8%.[73,74] Admission for a repeat head CT at 24 hours will catch most, but not all, delayed hemorrhages. Discharge after an initial negative head CT is also reasonable in patients with lower INRs and caregivers to watch them closely at home.

RIB FRACTURES AND RESPIRATORY FAILURE

Maintain a low threshold for admitting elderly patients with rib fractures for a period of observation until good pain control and pulmonary toilet are ensured. More severe thoracic injuries, such as hemopneumothorax, pulmonary contusion, flail chest, and cardiac contusion, can quickly lead to decompensation in the elderly, especially those with baseline respiratory insufficiency. Pain control after chest wall trauma is vital to encourage ventilation in order to reduce atelectasis and the risk of infection. Pain control is challenging because the elderly may have decreased tolerance for opioid analgesics, which can have profound respiratory (hypoventilation), hemodynamic (hypotension), and CNS effects (imbalance and delirium).

Continuous pulse oximetry and capnometry are helpful to assess oxygenation and ventilation. Serial arterial blood gas analysis may provide early insight into respiratory function and reserve. Consider prompt tracheal intubation and use of mechanical ventilation in patients with more severe injuries, respiratory rates >40 breaths/min, or when the partial pressure of arterial oxygen is <60 mm Hg or the pressure of arterial carbon dioxide is >50 mm Hg.

SHOCK

Multiple studies have shown that occult hypoperfusion is frequently present even with normal vital signs.[16,17] The optimal approach to optimizing hemodynamics is unknown. A general strategy is to perform the initial imaging necessary to identify life-threatening injuries (e.g., chest radiograph, CT of the head, spine, chest, abdomen, and pelvis) and then transport to the intensive care unit, after which nonessential imaging and interventions (e.g., extremity radiographs and suturing) can be performed.

Resuscitate the elderly trauma patient with small volumes of isotonic crystalloid (normal saline or lactated Ringer's), watching for a response, to avoid underresuscitation or volume overload. Strong consideration should be made for early red blood cell transfusion, which may enhance oxygen delivery and minimize tissue ischemia. Depending on the type of injury and severity of blood loss, consider switching to blood transfusion after 1 to 2 L of crystalloid resuscitation. Routine use of pulmonary artery catheters is no longer recommended.[75]

ENVIRONMENTAL AND IATROGENIC INJURY

The decreased lean muscle mass and impaired peripheral circulation associated with aging make the elderly patient more susceptible to pressure sores and hypothermia. Patients with prolonged extrications or transport in cool climates may be hypothermic. Expose the patient as needed for a thorough examination, but keep the patient covered as much as possible to maintain body heat. Hypothermia not explained by environmental factors may be a sign of sepsis or endocrine abnormalities. Logroll patients onto a padded surface as soon as possible.

DISPOSITION AND FOLLOW-UP

Have a low threshold for admitting geriatric trauma patients. Admit elderly patients with polytrauma, significant chest wall injuries, abnormal vital signs, or evidence of overt or occult hypoperfusion to the intensive care unit.

Even in patients without the need for inpatient treatment or observation, consider whether the patient is immediately ready to return home with a trial of ambulation and discussion of their home situation. In patients whose preinjury mobility was already tenuous, pain, decreased mobility, and medications may make a return to home dangerous. While opioid analgesics may be necessary, they may also cause delirium, decrease balance, and impair ambulation. Observation for establishment of a safe and effective pain regimen, consultation with physical therapy, and assurance of a safe home environment may be advisable to prevent a secondary injury.

OUTCOME

The ultimate goal is to return the elderly trauma patient to the preinjury state of function. Immediately after discharge, about half of survivors return home, and half go to skilled nursing or rehabilitation facilities.[76] The general consensus is that elderly trauma patients benefit from preferential triage to trauma centers and from aggressive and thoughtful resuscitation. In light of investigations showing that elderly patients often return to preexisting health status after trauma, **aggressive resuscitation efforts for geriatric trauma patients are warranted in keeping with their preexpressed end-of-life care preferences.**

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 256

Trauma in Pregnancy

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INTRODUCTION AND EPIDEMIOLOGY

Trauma is the leading cause of non–obstetric-related morbidity and mortality in pregnant women.[1,2] Seven percent of all pregnant women will experience a traumatic injury, of whom 0.4% will require admission.[3] Blunt trauma is more common than penetrating trauma. Motor vehicle crashes, falls, and assaults compose the major causes of blunt trauma during pregnancy.[2,4]

Motor vehicle crashes account for 50% of pregnancy-related trauma, and placental abruption can occur even with low-speed deceleration crashes.[3,5] The best predictors of fetal loss or other adverse outcomes are crash severity and lack or improper use of seat belts.[6] **Pregnant women should be advised to use both seat belts and air bags.**[7] For proper fit, the lap belt should be worn under the gravid uterus (i.e., across both anterior superior iliac spines and the pubic symphysis) with the shoulder harness positioned snugly between the breasts and off to the side of the uterus.[7] Combined with proper body positioning (i.e., mother seated 10 inches from the dash and steering column) and seat belt placement, the benefits of air bags appear to outweigh the risks.[7,8]

Falls occur most frequently during the second and third trimesters. This risk is likely due to weight gain affecting balance and coordination. Twenty-seven percent of women fall at least once during pregnancy; the vast majority occur indoors and/or on stairs.[9]

One in three women are raped, physical assaulted, and/or stalked by an intimate partner in their lifetime.[10] Studies have shown that 3% to 9% of pregnant woman are abused during their pregnancy.[11,12] Consider intimate partner violence in all cases of trauma and use screening tools.[10,13] Provide social services consultation or referral if there is concern for the mother's safety.[1]

Trauma during pregnancy is associated with several complications, including preterm labor, premature rupture of membranes, placental abruption, fetal maternal hemorrhage, uterine rupture, cesarean section, and pregnancy loss. Placental abruption is second only to maternal death as the most common cause of fetal death. Placental abruption may also lead to the introduction of placental products

into the maternal circulation, stimulating disseminated intravascular coagulation or amniotic fluid embolism. Even minor maternal injuries have been associated with placental abruption and sudden fetal demise.[5]

A fetus is considered viable at 22 to 24 weeks of gestation or a weight of 500 grams. Achieving successful outcomes for both mother and fetus requires a collaborative effort by the prehospital, ED, trauma, obstetrics, and neonatology (neonatal intensive care unit) teams. The emergency physician should be well-versed in the care of the pregnant patient as this will enhance her care in the setting of trauma. **Fetal survival is dependent on maternal survival. Therefore, resuscitation of the mother always takes priority**.

ANATOMIC AND PHYSIOLOGIC CHANGES OF PREGNANCY

See **Chapter 25 "Resuscitation in Pregnancy,"** and **Table 25-1** for detailed discussion of the important physiologic changes in pregnancy that affect resuscitation. Key points are presented below.

Maternal blood volume expands at approximately week 10 of gestation and peaks at week 28 with a 45% increase from baseline. Cardiac output increases by 30% to 50%. The relative hypervolemic state can mask clinically significant injuries. **A pregnant woman may lose 30% to 35% of her circulating blood volume before manifesting clinical signs of shock.** Uterine blood flow increases significantly during pregnancy. Uterine injury can result in severe maternal hemorrhage.

The uterine fundus remains relatively protected in the pelvis until about week 12 of gestation when it reaches the level of the pubic symphysis. **Direct fetal injury** during the first trimester is relatively rare in blunt abdominal trauma as the fetus is protected by the bony pelvis. However, if the maternal pelvis is fractured or the trauma occurs later in pregnancy when the fetal head is engaged, fetal injury may occur and typically involves the skull and brain. After week 12 of gestation, the uterus becomes an intra-abdominal organ. **By week 20, the uterus has reached the umbilicus and continues to grows approximately 1 cm beyond the umbilicus per each additional week of gestation**. During direct abdominal trauma or deceleration injury, intrauterine pressure increases. While the relatively elastic uterus deforms, as with even a mild deceleration injury, the relatively inelastic placenta can shear from the uterine wall, causing placental abruption. Additionally, as an intra-abdominal organ, the uterus is at risk for rupture during blunt abdominal trauma.

Mothers at ≥20 weeks of gestation are at risk of **supine hypotension syndrome**, in which venous return and cardiac output are decreased by compression of the maternal inferior vena cava by the gravid uterus while the mother is lying in the supine position.

During pregnancy, the diaphragm elevates by as much as 4 cm, so adjust the anatomic landmarks for thoracostomy tube insertion by one to two ribs spaces cranially. Physiologic changes affect the ability to compensate for respiratory compromise. Anticipate difficult intubation due to upper airway hyperemia and friability.

Gastric emptying time is delayed, increasing the risk for aspiration. The small bowel is moved upward in the abdomen by the enlarging uterus, which increases the chance of complex bowel injuries in penetrating trauma of the upper abdomen. The bladder moves anteriorly into the abdomen in the third trimester, becoming more vulnerable to injury. The gravid uterus passively stretches the abdominal wall and peritoneum as it enlarges, which may lead to diminished sensitivity to irritation from intraperitoneal blood.

PRINCIPLES OF RESUSCITATION

The algorithm for trauma resuscitation of the pregnant patient is the same as the nonpregnant patient with a few special considerations. Although there are two patients, priority is given to the mother as **maternal resuscitation is the best fetal resuscitation. Fetal survival is dependent on early and aggressive maternal resuscitation. Never withhold critical maternal interventions or diagnostic procedures out of concern for potential adverse fetal consequences.**

Develop a major trauma protocol for pregnant patients that includes the ED, trauma service, and OB teams. For minor direct or indirect abdominal trauma (e.g., low-speed motor vehicle accident, ground-level fall, or minor assault), a simpler protocol involving the ED and obstetric teams is sufficient. The simpler protocol should include cardiotocodynamometry and fetal heart rate monitoring as soon as possible after ED arrival.

PREHOSPITAL CARE

Prehospital providers should ask about the possibility of pregnancy when evaluating women of childbearing age. When possible, a known pregnant woman at >20 weeks of gestation should be triaged to a hospital with trauma, obstetric, and neonatal capabilities.[14] Women at >20 weeks of gestation who require spinal immobilization should be placed in a semi-left lateral decubitus position to prevent inferior vena cava compression by the gravid uterus. This positioning is accomplished by placing a wedge or rolled blanket under the right side of the spine board and tilting the entire patient approximately 30 degrees to the left (see Figure 25-2).

MATERNAL AND FETAL ASSESSMENT AND TREATMENT

PRIMARY SURVEY

Prioritize the primary survey of the mother. Manage the maternal airway and ensure adequate ventilation. Administer supplemental oxygen to maintain a pulse oximetry >95% because compensation for hypoxia is limited in pregnancy. Similarly, consider early endotracheal intubation when indicated by the nature or severity of injuries. Maintain cervical spine immobilization as indicated. Establish large-bore peripheral IV access above the diaphragm. Avoid placing IV lines in the femoral region or lower extremity because of uterine inferior vena cava compression and the possibility of injured pelvic veins. Keep the patient in the semi-left lateral decubitus position or use a second provider to continually manually displace the gravid uterus. Identify and control sources of hemorrhage since hypovolemia exacerbates fetal hypoperfusion. **Increase the crystalloid infusion volume by 50% to account for the patient's additional plasma volume.** Do not administer vasopressors until volume and blood are replaced to minimize risk of uteroplacental hypoperfusion. Perform a brief neurologic assessment. Expose the patient and provide warm fluids and blankets.

An in-depth fetal assessment should not occur during the airway, breathing, circulation, disability, and exposure phase of trauma evaluation. However, assess **fetal heart tones** and **uterine size** by ultrasonography if maternal resuscitation allows.

ADJUNCTS TO THE PRIMARY SURVEY

Place the mother on continuous telemetry and pulse oximetry monitoring. Perform frequent blood pressure checks. Place a nasogastric tube early; delayed stomach emptying and diminished lower esophageal sphincter tone increase the risk of aspiration of gastric contents.

Obtain a portable single view anteroposterior chest and pelvis radiographs as indicated by the nature of the injury. Perform an **extended FAST** to identify intra-abdominal or thoracic injury. The sensitivity and specificity of abdominal US for the detection of intraperitoneal fluid are similar in pregnant and nonpregnant patients.[15]

SECONDARY SURVEY

After completing the primary survey and performing resuscitative steps, proceed with the secondary assessment. Obtain pertinent medical, surgical, obstetrical, and social histories. Perform a head-to-toe examination of the patient. **Perform a thorough abdominal examination: assess for ecchymosis, abdominal and uterine tenderness, and fundal height.**

The loss of a palpable uterine contour or palpation of fetal parts is suggestive of **uterine rupture**. Uterine rupture accounts for <1% of all injuries and is more likely to occur during the late second and third trimesters and when there is direct and forceful impact on the uterus.[4] The fetal mortality rate is high.

The classic clinical presentation for **placental abruption** includes abdominal pain, abdominal and uterine tenderness, painful vaginal

bleeding, and tetanic uterine contractions, but severe placental abruption can occur without such signs. A sterile pelvic examination can identify injuries of the lower genital tract, vaginal bleeding, and rupture of amniotic membranes. To assess for amniotic membrane rupture, test vaginal fluid with pH paper. **Fluid in the vagina with a pH of 7 is suggestive of amniotic fluid; a pH of 5 is consistent with vaginal secretions.** Evidence of **ferning** on microscopic evaluation of dried vaginal fluid suggests membrane rupture and an amniotic fluid leak (see Figure 100-3).

CARDIOTOCOGRAPHIC MONITORING AND OBSTETRICAL US

For pregnant women at ≥20 weeks of gestation, begin cardiotocographic and fetal heart rate monitoring in the ED as soon as maternal resuscitation allows. The protocol for pregnant trauma patients should include the mobilization of an obstetrical nurse or obstetrician to the ED to begin monitoring. Even minor blunt abdominal trauma or deceleration injury can result in placental abruption and fetal distress.[5] Observe for uterine contractions and assess fetal heart rate patterns (see Figure 101-1). Uterine irritability may be precipitated by abdominal trauma; preterm labor occurs in 25% of trauma cases after 22 to 24 weeks of gestation.[16] Decelerations, tachycardia, and bradycardia are signs of fetal distress. **The most sensitive clinical finding for placental abruption after trauma is uterine irritability, which is defined as more than three uterine contractions per hour.**[5] Fetal distress and demise can occur quickly and abruptly, so vigilant monitoring is necessary. Tocolytic agents are generally not recommended for use in pregnant trauma patients, unless recommended by an obstetrician. Tocolytic agents have numerous adverse effects, including fetal and maternal tachycardia, which may complicate trauma evaluation.

For pregnant patients at >20 weeks of gestation, obtain an obstetric US to assess fetal size and gestational age, cardiac activity heart rate, and fetal activity. A normal fetal heart rate is between 120 and 160 beats/min. If fetal cardiac activity is absent, then direct the remainder of treatment efforts solely at maternal resuscitation. US may show evidence of placental abruption (**Figure 256-1**). **However, the sensitivity for placental abruption is only about 25%,** although specificity is >90%.[17] US has many limitations: uterine rupture or fetal-placental injuries can be undetected; fetal distress is not monitored; and sensitivity for placental abruption is low.[5,17]

IMAGING

Attempt to minimize fetal exposure to ionizing radiation; however, do *not* withhold imaging that is necessary to appropriately manage the mother. The risk of injury to the fetus from radiation is much lower than the risk of a missed or delayed diagnosis of maternal injury.[18,19] See Chapter 99 and Tables 99-8 and 99-9 for detailed discussion of the teratogenic effects and radiation doses.

One potential benefit of obtaining an abdominopelvic CT scan is the ability to detect placental abruption, with a reported sensitivity of 86% and specificity of 98% for abruption.[20] Fetal radiation exposure can be decreased by shielding the maternal abdomen and pelvis, performing modified studies, and using dose-reducing techniques. IV iodinated contrast is safe both in pregnancy and breastfeeding; oral contrast material is safe as well.[21,22] IV gadolinium for MRI should not be given during pregnancy, but gadolinium is considered safe during breastfeeding.[21-23]

LABORATORY TESTING

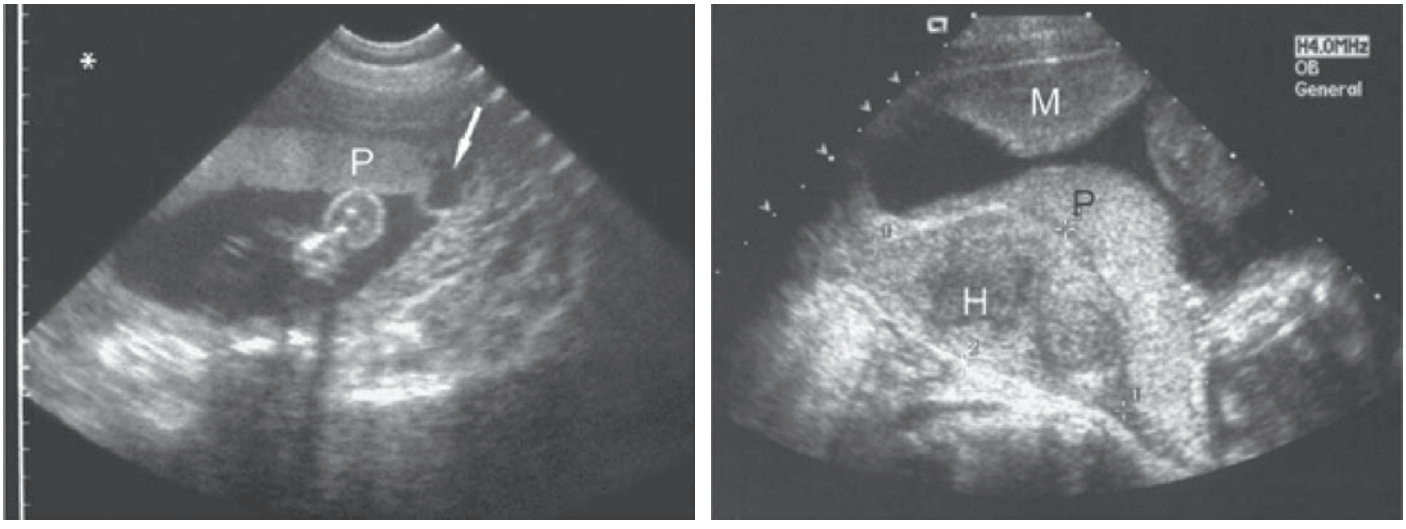
Perform a qualitative urine pregnancy test on all female trauma patients of childbearing age. Obtain a CBC, comprehensive metabolic panel, type and screen (or type and cross [if indicated]), coagulation profile including fibrinogen to assess for disseminated intravascular coagulation, and additional laboratory studies as clinically indicated.

If available, perform a Kleihauer-Betke analysis on pregnant women who are >12 weeks of gestation.[3] Fetal maternal hemorrhage occurs when fetal red blood cells enter into the maternal circulation, which is assumed in the setting of maternal trauma. **The Kleihauer-Betke test provides a quantitative determination of the presence of fetal hemoglobin in maternal blood.** Acid elution is applied to an aliquot of maternal blood, and then both maternal and fetal red blood cells are counted under the microscope. The percentage of fetal red blood cells is used to determine the amount of fetal-maternal hemorrhage.

THERAPEUTIC INTERVENTIONS

Administer Rho(D) immunoglobulin to all Rh-negative pregnant women with abdominal trauma. If as little as 0.1 μL of Rh-positive fetal blood enters an Rh-negative mother's circulation, the mother can develop Rh antibodies, endangering the current pregnancy and subsequent pregnancies.[24] Rho(D) immunoglobulin is given to the Rh-negative pregnant mother to prevent antibody formation that could occur if her fetus is Rh positive.

The dose depends on the gestational age: 50 micrograms IM for gestation ≤12 weeks and 300 micrograms IM in the second and third trimester. Total fetal blood volume at 12 weeks of gestation is approximately 4.2 μL. A 50-microgram dose of immunoglobulin is effective for up to 5 μL of fetomaternal hemorrhage. A 300-microgram dose protects for up



A B

FIGURE 256-1. **A.** Placental abruption. Transabdominal long-axis scan shows an anterior placenta with a contained marginal abruption (*arrow*). [Image used with permission of L. Sens and L. Green, Gulfcoast Ultrasound.] **B.** Placental abruption. Transabdominal scan, sagittal plane, demonstrating retroplacental hematoma (H) in an 18-week pregnancy. The placenta (P) is located on the posterior wall. A myometrial contraction (M) of the anterior wall is evident.

to 30 μL of fetomaternal hemorrhage. **The Kleihauer-Betke test is used to determine if doses >300 micrograms are indicated.** The immunoglobulin should be given within 72 hours.

Provide tetanus prophylaxis if indicated. Tetanus antibody crosses the placenta, so it can also reduce the incidence of neonatal tetanus.

There are no studies on the administration of tranexamic acid for massive hemorrhage from trauma in pregnancy, **although it is used to reduce bleeding and transfusion requirements during cesarean section and for postpartum hemorrhage.**

The indications for **emergent laparotomy** in the management of pregnant trauma patients are the same as for nonpregnant patients. Do not withhold surgery out of concern for fetal compromise. The obstetric team may wish to accompany the surgeon to the operating room or, at a minimum, remain in hospital on standby should an emergency cesarean section be needed.

RESUSCITATIVE HYSTEROTOMY/PERIMORTEM CESAREAN DELIVERY

Emergent delivery of a viable fetus (>24 weeks of gestational age) by ED vertical cesarean section should be considered within 4 minutes of maternal cardiac arrest. See Chapter 101, "Emergency Delivery" for discussion of emergency cesarean section. The term *perimortem cesarean delivery* has been replaced by *resuscitative hysterotomy* to emphasize that fetal delivery may also be beneficial to the mother. The procedure is the same, however. With delivery of the fetus, the aortocaval pressure is relieved, improving cardiac output and the ability to perform maternal cardiopulmonary resuscitation, which may lead to return of spontaneous maternal circulation.

DISPOSITION AND FOLLOW-UP

The disposition of the pregnant trauma patient depends on the nature and severity of presenting injuries and the gestational age of the pregnancy. If transfer is needed for definitive care, then the patient should be stabilized to the extent possible with provisions for an appropriate level of care during transport. Adhere to transfer policies and comply with federal regulations.

Four to 6 hours of external cardiotocographic monitoring is indicated for all pregnant trauma patients >20 weeks of gestation, even if the mother has been deemed safe for discharge by the trauma service.[3] Emergency physicians should be familiar with cardiotocographic rhythms and patterns of decelerations that suggest fetal distress (e.g., fetal tachycardia, lack of beat-to-beat or long-term variability, or presence of late decelerations) (see Figure 101-1 for examples of fetal heart rate variability). Monitoring is not indicated for the nonviable fetus as any obstetrical intervention would be futile.

If any signs of fetal distress develop, admission for a minimum of 24 hours is warranted.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 257

Head Trauma

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Lisa H. Merck

INTRODUCTION AND EPIDEMIOLOGY

Traumatic brain injury (TBI) is defined as brain function impairment that results from external force.[1] Clinical manifestations represent a broad constellation of symptoms from brief confusion to coma, severe disability, and/or death. The underlying pathology ranges from temporary shifts in cellular ionic concentrations to permanent structural damage.

TABLE 257-1 Factors That Affect Cerebral Blood Flow

- MAP = DBP + [(SBP – DBP)/3]
- CPP = MAP – ICP

Abbreviations: CPP = cerebral perfusion pressure; DBP = diastolic blood pressure; ICP = intracranial pressure; MAP = mean arterial pressure; SBP = systolic blood pressure.

TBI is classified as mild, moderate, and severe based on the Glasgow Coma Scale (GCS) score. Over 80% of TBI is defined as **mild** (GCS 14 to 15) (**mTBI**) and is often called "concussion."[2] The label of mild, however, is a misnomer. mTBI may lead to significant, debilitating short- and long-term sequelae. **Moderate** TBI (GCS 9 to 13) accounts for approximately 10% of head injuries. Mortality rates for patients with isolated moderate TBI are <20%, but long-term disability can be higher. Overall, 40% of patients with moderate TBI have an abnormal finding on CT scan, and 8% will require neurosurgical intervention. In **severe** TBI (GCS 3 to 8), mortality rate approaches 40%, with most deaths occurring in the first 48 hours after injury. Fewer than 10% of patients with severe TBI experience good recovery.[2,3]

The prevalence of TBI is twice as high in males as in females. Distribution of age at injury is trimodal, with peaks at 0 to 4 years, 15 to 24 years, and >75 years of age. Mortality rate increases with age at time of injury.[4-6] Motor vehicle collisions are the primary cause of blunt head injury in young adults and children, and falls are more common in the elderly.[2] TBI has been called a "signature injury" of modern-day warfare.[7]

PATHOPHYSIOLOGY

CEREBRAL BLOOD FLOW

Autoregulation, cerebral perfusion pressure (CPP), mean arterial pressure (MAP), and intracranial pressure (ICP) are interrelated factors that affect cerebral blood flow (**Table 257-1**). Under normal circumstances, **autoregulation** regulates local cerebral blood flow to maintain equilibrium between oxygen delivery and metabolism.[8] Other systemic factors, such as hypertension, hypocarbia, and alkalosis, can affect cerebral blood flow by causing vasoconstriction.

Under normal situations, autoregulation can adjust to accommodate CPPs from 50 to 150 mm Hg in order to maintain local cellular oxygen demands and regional cerebral blood flow. In brain injury, autoregulation is often impaired, so even modest drops in blood pressure can decrease brain perfusion and result in cellular hypoxia. A CPP <60 mm Hg is considered the lower limit of autoregulation in humans, below which local control of cerebral blood flow cannot be adjusted to maintain flow adequate for function.[9] Traumatic hypotension leads to ischemia within low-flow regions of the injured brain, so aggressive fluid resuscitation may be required to prevent hypotension and secondary brain injury. In the absence of an ICP monitor, it is important to maintain a MAP of ≥**80 mm Hg** because **low blood** pressure in the setting of elevated ICP will result in a low CPP and brain injury.

The cranium is an enclosed space with a fixed volume. Any changes to the volume of the intracranial contents (e.g., bleeding) affect the ICP, and an increase in ICP can decrease the CPP. ICP is determined by the volume of the three intracranial compartments: the brain parenchyma (<1300 mL in the adult), cerebrospinal fluid (100 to 150 mL), and intravascular blood (100 to 150 mL). When one compartment expands, there is a compensatory reduction in the volume of another, and/or the baseline ICP will increase (**Figure 257-1**). Elevations in ICP are life threatening and may lead to a phenomenon known as the **Cushing reflex** (hypertension, bradycardia, and respiratory irregularity).[10] Hypertension is an attempt to maintain cerebral perfusion. Normal values for ICP vary with age (**Table 257-2**).

PRIMARY BRAIN INJURIES

The initial insult associated with moderate and severe TBI imparts mechanical forces that produce high levels of direct damage and strain to the brain parenchyma. The **primary injuries** include contusions

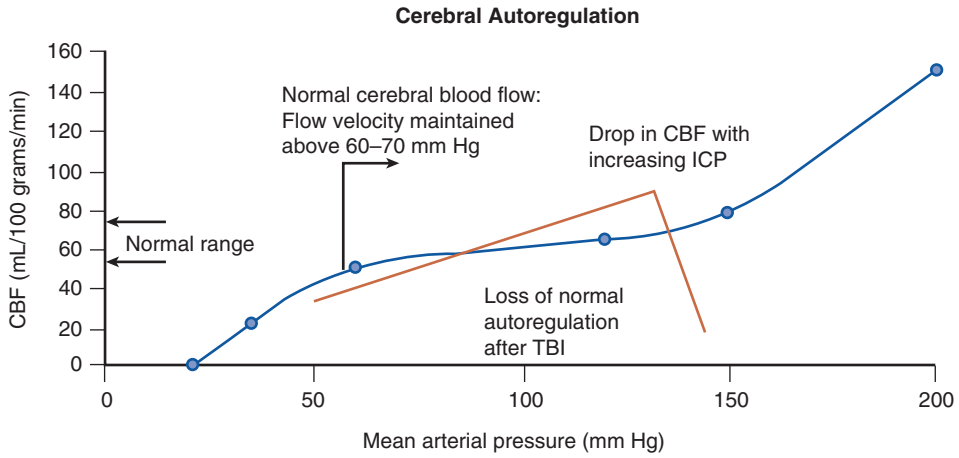


FIGURE 257-1. Pressure–volume relationship in brain injury. Normal cerebral blood flow (CBF) autoregulation curve and the abnormal curve with traumatic brain injury (TBI). Normal autoregulatory control (*blue line*) maintains a relatively constant CBF over a broad range of mean arterial pressure (MAP).[9] Loss of autoregulation results in a more linear relationship between CBF and MAP. Elevated intracranial pressure (ICP) can dramatically decrease CBF when autoregulation is impaired (*inflection point of red line*). Increases in ICP may result in a net loss in CBF.

(bruises to brain parenchyma), hematomas (subdural, epidural, intraparenchymal, intraventricular, and subarachnoid), diffuse axonal injury (stress or damage to axons), direct cellular damage (neurons, axons, and other supportive cells), loss of the blood–brain barrier, disruption of the neurochemical homeostasis, and loss of the electrochemical function.

SECONDARY BRAIN INJURIES

A wave of secondary damage is unleashed by the impact that results in a series of deleterious cellular and subcellular events (also known as the **secondary neurotoxic cascade**).[11,12] The secondary neurotoxic cascade causes ongoing damage to the brain and ultimately results in a poorer neurologic outcome than might have occurred based on the original mechanism.

The secondary neurotoxic cascade should not be confused with the term **secondary insults**, a term used in the clinical literature to describe conditions or circumstances (e.g., hypotension, hypoxemia, hyperglycemia) that accelerate neurotoxic damage and worsen long-term outcome.[13-24] Mediation of secondary insults reduces morbidity and mortality and is discussed in the treatment section.

The **secondary neurotoxic cascade** is a massive release of neurotransmitters, such as glutamate, into the presynaptic space, with activation of *N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, and other receptors.[11] Ionic shifts activate cytoplasmic and nuclear enzymes, induce mitochondrial damage, and lead to cell death and necrosis.[11,25,26] Proinflammatory cytokines and other enzymes are released in an attempt to clean and repair the damage. Secondary injury, however, is indiscriminate and produces extensive neuronal loss. Additionally, many survivable cells undergo apoptosis, or programmed cell death, during secondary injury.[27] Apoptosis has been reported to occur longer than a year after injury.[27,28]

BRAIN EDEMA

Brain edema results from two distinct processes and can be fatal in TBI.[29] Cellular swelling, or **cytotoxic edema**, results from large ionic shifts and the loss of cellular membrane integrity from mitochondrial damage (loss of adenosine triphosphate, ion pump productivity, and increased free radical production). **Extracellular edema** results from direct damage to, or the breakdown of, the blood–brain barrier, ionic shifts, and alteration of water exchange mechanisms (e.g., aquaporins).[30,31] As intracellular and extracellular water content rises, the brain swells and the ICP increases, leading to direct compressive tissue damage, vascular compression-induced ischemia, brain parenchyma herniation, and brain death.

TABLE 257-2 Intracranial Pressure by Age Group

Age Group	Intracranial Pressure (mm Hg)
Adults	<10–15
Young children	3–7
Infants	1.5–6.0

BRAIN HERNIATION

There are four major brain herniation syndromes: uncal transtentorial, central transtentorial, cerebellotonsillar, and upward posterior fossa. The most common is uncal herniation, which occurs when the uncus of the temporal lobe is displaced inferiorly through the medial edge of the tentorium. This is usually caused by an expanding lesion in the temporal lobe or lateral middle fossa. **Uncal transtentorial herniation leads to compression of parasympathetic fibers running with the third cranial (oculomotor) nerve, causing an ipsilateral fixed and dilated pupil due to unopposed sympathetic tone. Further herniation compresses the pyramidal tract, which results in contralateral motor paralysis.** In some cases, the pupillary changes can be contralateral, whereas the motor changes are ipsilateral.

Central transtentorial herniation is less common and occurs with midline lesions, such as lesions of the frontal or occipital lobes, or vertex. **The most prominent symptoms are bilateral pinpoint pupils, bilateral Babinski's signs, and increased muscle tone.** Fixed midpoint pupils follow along with prolonged hyperventilation and decorticate posturing.

Cerebellotonsillar herniation occurs when the cerebellar tonsils herniate through the foramen magnum. **This may lead to pinpoint pupils, flaccid paralysis, and sudden death.** Upward transtentorial herniation results from a posterior fossa lesion and leads to a conjugate downward gaze with absence of vertical eye movements and pinpoint pupils.

CLINICAL FEATURES

The results of history, examination, and diagnostic imaging will allow the distinction into two categories of injury: moderate-severe brain injury and mild brain injury. Treatment and disposition are quite different in the two categories and are detailed later in this chapter.

HISTORY

Obtain an accurate history from the patient, witnesses, and EMS crew members to gain important insight into the mechanism of injury and overall severity of TBI (e.g., height of fall, impact surface condition, damage sustained to vehicle, air bag deployment, seat belt use, history of ejection from the vehicle, or report of fatalities at the scene). Premorbid medical history, medications (especially anticoagulants), drug use, and/or

alcohol intoxication are also important in the assessment and treatment of acute TBI. **Initial clinical findings and physical exam as reported by EMS are an essential component of triaging and managing TBI.** The presence of a focal neurologic deficit, seizures, emesis, or depressed level of consciousness increases concern for underlying brain injury.

THE GLASGOW COMA SCALE

TBI severity is classified using the GCS (Table 257-3). The scale is composed of three components: eye opening (1 to 4 points), verbal response (1 to 5 points), and motor response (1 to 6 points) (Table 257-3). The sum of these components defines the TBI severity classification into **severe** (GCS score of 3 to 8), **moderate** (GCS score of 9 to 13), and **mild** (GCS score of 14 or 15). The motor score independently correlates with outcome, almost as well as the full score.[32]

The GCS is an objective measurement of clinical status, correlates with outcome, is a reliable tool for interobserver measurements, and is effective for measuring patient recovery or response to treatment over time. However, the scale has several limitations. It measures behavioral responses, not the underlying pathophysiology. Patients with similar GCS scores may have dramatically different underlying structural injuries and require different clinical interventions (**Figure 257-2**). It is not as useful for defining severity at one point in time; rather, it is intended to gauge disease progression over time. Serial GCS exams provide a broader picture of neurologic recovery and/or worsening. ED documentation and EMS documentation of best GCS after resuscitation are important for prognostication. The GCS may be confounded by drugs; alcohol; medications; paralytics; or ocular, spinal, or peripheral extremity injuries. The GCS is designed for moderate and severe TBI and lacks the granularity necessary to assess mTBI.

The motor GCS (**simplified GCS**) consists of three motor variables (**Table 257-4**). The motor GCS has been validated in multiple large studies.[33-35] Scores <2 predict the need for ED intubation, clinically significant brain injuries, and the need for neurosurgical intervention, with similar accuracy to the full GCS.

TABLE 257-3 Glasgow Coma Scale for All Age Groups

	4 y to Adult	Child <4 y	Infant
Eye opening			
4	Spontaneous	Spontaneous	Spontaneous
3	To speech	To speech	To speech
2	To pain	To pain	To pain
1	No response	No response	No response
Verbal response			
5	Alert and oriented	Oriented, social, speaks, interacts	Coos, babbles
4	Disoriented conversation	Confused speech, disoriented, consolable, aware	Irritable cry
3	Speaking but nonsensical	Inappropriate words, inconsolable, unaware	Cries to pain
2	Moans or unintelligible sounds	Incomprehensible, agitated, restless, unaware	Moans to pain
1	No response	No response	No response
Motor response			
6	Follows commands	Normal, spontaneous movements	Normal, spontaneous movements
5	Localizes pain	Localizes pain	Withdraws to touch
4	Moves or withdraws to pain	Withdraws to pain	Withdraws to pain
3	Decorticate flexion	Decorticate flexion	Decorticate flexion
2	Decerebrate extension	Decerebrate extension	Decerebrate extension
1	No response	No response	No response
Total score range: 3–15			

Note: In intubated patients, the Glasgow Coma Scale verbal component is scored as a 1, and the total score is marked with a "T" (or tube) denoting intubation (e.g., 8T).

PHYSICAL EXAMINATION

Follow Advanced Trauma Life Support principles to perform the trauma-focused examination, with simultaneous lifesaving procedures as needed. Protect the cervical spine during evaluation, treatment, and imaging.

Obtain the GCS. Classify the injury as **severe (GCS score of 3 to 8), moderate (GCS score of 9 to 13), or mild (GCS score of 14 or 15). If emergency intubation is necessary, obtain a preintubation GCS and record the patient's best score.**

Determine **pupillary response**. In an unresponsive patient, a single fixed and dilated pupil may indicate an intracranial hematoma with uncal herniation that requires rapid surgical decompression. **Bilateral fixed and dilated pupils** suggest increased ICP with poor brain perfusion, bilateral uncal herniation, drug effect (e.g., atropine), or severe hypoxia. Bilateral pinpoint pupils suggest either opiate exposure or a central pontine lesion.

Altered **motor function** can indicate brain, spinal cord, or peripheral nerve injuries. Assess movement in a coma patient by observing the patient's reaction to noxious stimuli, such as pressure to a nail bed. Assessment of symmetry, as well as gradation of motor strength is important initially and upon serial neurologic exams. **Decorticate posturing** (upper extremity flexion and lower extremity extension) indicates severe intracranial injury above the level of the midbrain. **Decerebrate posturing** (arm extension and internal rotation with wrist and finger flexion and internal rotation and extension of the lower extremities) indicates a more caudal injury. For completely unresponsive patients, respiratory pattern and eye movements can provide information regarding brainstem function. Pupillary reflex, corneal reflex, cough, and gag reflexes will offer information on the patient's brainstem function. Do not assess oculovestibular (cold caloric) and oculocephalic (doll's eyes) responses in a patient under cervical spine precautions.

IMAGING

Individually assess each patient's mechanism of injury, history, comorbidities, and signs and symptoms when determining the need for CT imaging of the head and cervical spine.

Head CT is exquisitely sensitive to the presence of blood and guides ED management. Do not delay head CT; expanding hemorrhagic lesions need emergency neurosurgical intervention. Therefore, **if the patient is uncooperative or combative, endotracheal intubation and sedation are often the best options to enable rapid CT imaging.** Other means to control agitated patients with TBI include midazolam (1 to 2 milligrams IV) and propofol (20 milligrams every 10 seconds to desired effect).

Several decision rules have been developed to minimize unnecessary head CT imaging.[36-40] The guidelines strive to identify patients with surgical emergencies. These studies do not specifically address the relationship between minor CT findings (**Figure 257-3**)[41] (which may place the patient at risk for the development of seizures), the duration of postconcussive symptoms, and progressive changes on CT during the course of a patient's evaluation. Adults with mTBI and a GCS score of 14 or 15 will have an intracranial lesion on CT up to 15% of the time; <1% will require neurosurgical intervention.[36]

The prevalence of **cervical fractures** in comatose TBI patients is approximately 8%, and an estimated 4% of injuries are missed on the initial assessment of the trauma patient.[36] Cervical imaging is a vital component in the care of the brain-injured patient. Perform CT imaging of the cervical spine in patients with altered mental status and who were injured by a mechanism that increases the risk of cervical spine injury. CT is superior to plain radiography in patients with altered mental status and can be performed at the same time as the head CT.

The **NEXUS (National Emergency X-Radiography Utilization Study)** and **Canadian Cervical Spine Rules** are discussed in detail in Chapter 258, "Spine Trauma."

MRI can detect subtle lesions missed by CT imaging and can better define the extent of contusions. However, MRI cannot be performed if the patient is unstable, and is not always available.

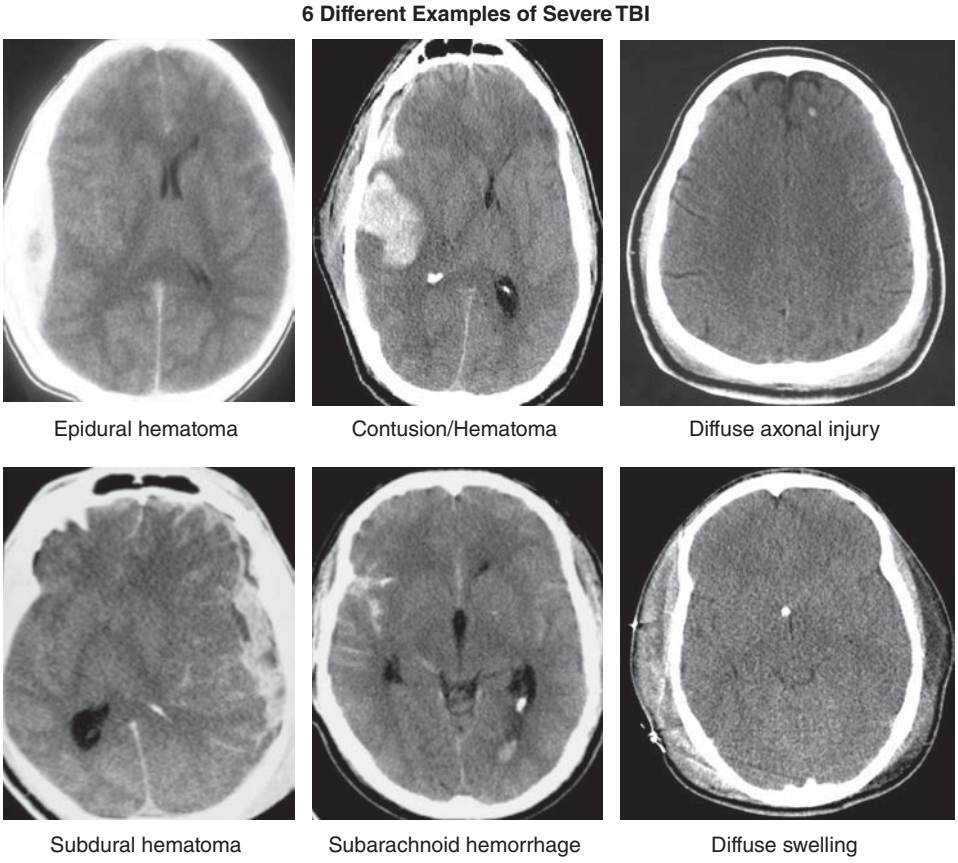


FIGURE 257-2. Each of these CT images shows a distinct trauma-induced pathophysiologic abnormality, yet all patients had a Glasgow Coma Scale score of 4. TBI = traumatic brain injury. [Image used with permission of Alisa Green, MD, University of California, San Francisco.]

TABLE 257-4 Simplified/Motor Glasgow Coma Scale

Criteria	Value
Obeys commands	+2
Localizes pain	+1
Withdraws to pain or worse	0

DECISION RULES FOR HEAD CT IMAGING IN ADULTS

Decision rules can guide clinical practice, but each patient must be assessed individually, and none of the rules described here address short- or long-term nonoperative sequelae of TBI. See Chapter 110, "Pediatric Trauma," for a discussion of the role of head CT imaging in children with minor head injury.

The two most commonly used evidence-based clinical decision rules for head CT in adults are the **New Orleans Criteria**[42] and the **Canadian CT Head Rule (Table 257-5)**.[36] Both rules have been validated and are

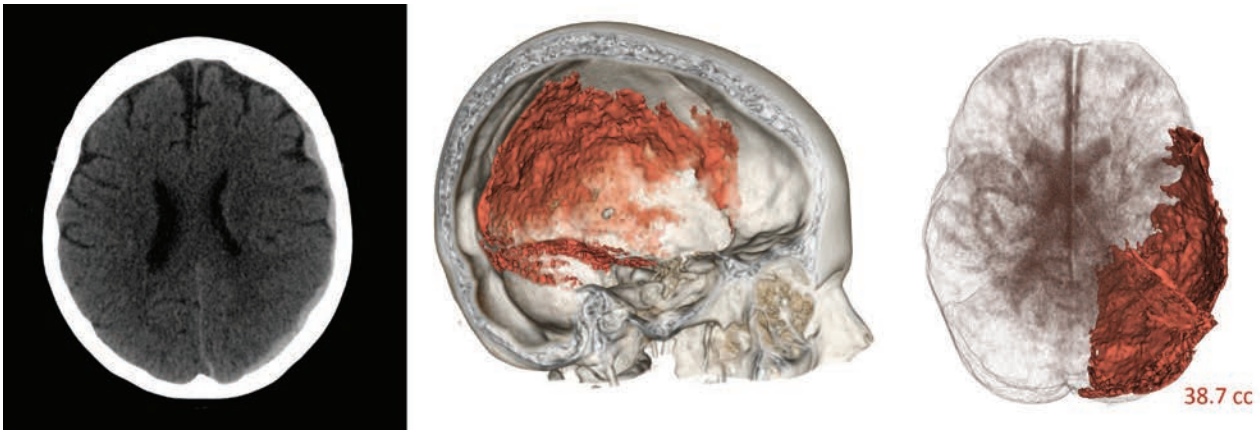


FIGURE 257-3. Sample comparison between images used for standard ABC/2 (**A**) and three-dimensional image analysis (**B and C**) methods in quantification of subdural hematoma. ABC/2 is a method for estimating the volume of intracerebral hemorrhage derived from multiplanar CT measurements.[41] [Images contributed by Derek Merck, PhD, and Scott Collins, RT, (R) (CT), Rhode Island Hospital, Brown University.]

TABLE 257-5 New Orleans Criteria and Canadian CT Head Rule Clinical Decision Rules

New Orleans Criteria—GCS 15*	Canadian CT Head Rule—GCS 13–15*
Headache	GCS <15 at 2 h
Vomiting	Suspected open or depressed skull fracture
Age >60 y	Age ≥65 y
Intoxication	>1 episode of vomiting
Persistent antegrade amnesia	Retrograde amnesia >30 min
Evidence of trauma above the clavicles	Dangerous mechanism (fall >3 ft or struck as pedestrian or fall >5 stairs)
Seizure	Any sign of basal skull fracture
Identification of patients who have an intracranial lesion on CT	
100% sensitive, 5% specific	83% sensitive, 38% specific
Identification of patients who will need neurosurgical intervention	
100% sensitive, 5% specific	100% sensitive, 37% specific

Abbreviation: GCS = Glasgow Coma Scale.

*Presence of any one finding indicates need for CT scan.

TABLE 257-6 Odds Ratio (OR) for Head CT and Clinical Features

	Smits et al[38]	Ibanez et al[39]	Fabbri et al[40]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Glasgow Coma Scale score of 14	2 (1–3)	7 (4–14)	19 (14–26)
Neurologic deficits	2 (1–3)	7 (2–25)	19 (13–28)
Signs of basilar skull fracture	14 (8–22)	11 (6–23)	10 (6–16)
Loss of consciousness	2 (1–3)	7 (4–11)	2 (2–3)
Posttraumatic amnesia	1.7 (1–2)	3 (2–5)	8 (6–12)
Headache	1.4 (1–2)	3 (2–6)*	—
Vomiting	3 (2–4)	4 (2–7)	5 (3–8)
Posttraumatic seizure	3 (1–10)	2 (0.25–17)	3 (2–5)
Intoxication	1 (0.6–2)	1 (0.3–3)	—
Antithrombotics	2 (1–4)	4 (3–7)	8 (3–9)
Age >65 y	—	2 (1–3)	2 (1–3)
Dangerous mechanism of injury	2 (1–4)	—	3 (2–4)

Abbreviation: CI = confidence interval.

*For severe headache.

100% sensitive in detecting patients who will need neurosurgical intervention, but they have limited specificity (5% vs. 37%, respectively). The Canadian CT Head Rule is less sensitive (83%) if intracranial lesion is the defined end point. *The studies used to validate these rules included loss of consciousness and/or amnesia as inclusion criteria and technically are not valid for patients who do not have these features.* **Most minor brain injury events do not result in loss of consciousness, and loss of consciousness is not the best predictor of intracranial pathology.** Do not apply these rules to patients taking anticoagulants or antiplatelet agents or to children, because these variables were not included in the validation studies.

The National Institute for Clinical Excellence and the Neurotraumatology Committee of the World Federation of Neurosurgical Societies have evaluated clinical signs and symptoms associated with TBI in adults and adolescents and adults, respectively.[38,40] The resultant decision rules for head CT have been applied to large data sets and shown to be relatively sensitive (National Institute for Clinical Excellence: 94% for neurosurgical lesions, 82% for intracranial lesions; Neurotraumatology Committee: 100% for neurosurgical lesions and intracranial injuries). One study evaluated 1101 patients with mTBI who had GCS scores of 14 or 15; approximately 2% of these patients without loss of consciousness had intracranial lesions and 0.6% required surgery (rates similar to patients with loss of consciousness).

One of the most important findings from these studies is the relative significance of certain elements of the history and physical examination. For example, nausea and vomiting after concussion has an odds ratio comparable to that of loss of consciousness for a positive CT finding (**Table 257-6**). Importantly, the predictive value of individual clinical signs and symptoms differs between adults and children (see Chapter 111, "Minor Head Injury and Concussion in Children"). A combination of rules helps identify patients *at risk* and determine the possible need for a head CT (Tables 257-5 and 257-6).

PREHOSPITAL TREATMENT

Early appropriate management can have a profound impact on the patient's final outcome. For patients with moderate to severe head injury, provide stabilization and rapid transport to a facility with experience in the management of brain injury. The most important prehospital interventions are airway and blood pressure management.[43] If the patient needs prehospital intubation, avoid hyperventilation (which causes cerebral vasoconstriction and can negatively affect outcome), and use **capnometry** to keep P_{CO_2} at 35 to 45 mm Hg. Treat hypotension aggressively. If transport times are short, do not give mannitol or hypertonic saline for presumptive elevated ICP. Guidelines for prehospital care are available at http://www.braintrauma.org.

ED TREATMENT

The primary goals of treatment are to maintain cerebral perfusion and oxygenation by optimizing intravascular volume and ventilation; prevent secondary injury by correcting hypoxia, hypercapnia, hyperglycemia, hyperthermia, anemia, or hypoperfusion; recognize and treat elevated ICP; arrange for neurosurgical intervention to evacuate intracranial mass lesions; and treat other life-threatening injuries.[13,20]

Systolic blood pressure of <90 mm Hg and hypoxemia (Pa_{O_2} <60 mm Hg) are associated with a 150% increased risk in mortality.[44]

Observe for the **signs/symptoms of elevated ICP**: change in mental status, pupillary irregularities, focal neurologic deficits, decerebrate or decorticate posturing, or CT pathology. Some CT signs of intracranial hypertension are loss of symmetry, attenuation of the visibility of sulci and gyri, compressed lateral ventricles, and poor gray/white matter distinction. Papilledema is a sign of increased ICP; however, it may not be evident early in the patient's course. **Sedation and analgesia** may decrease baseline ICP and prevent transient rises in ICP attributed to agitation, coughing, or gagging from the endotracheal tube. Control seizure activity, which also is associated with transient increases in ICP.

Treat hypotension, hypoxemia, hypercarbia, and hyperglycemia. A single occurrence of hypotension and hypoxia after brain injury is associated with a 150% increase in mortality.[45] TBI is progressive, so appropriate early management will have a greater impact on outcome than treatments initiated after neuronal cell death and the development of secondary injury, such as cerebral edema. Jointly develop and apply goal-directed protocols with emergency medicine, trauma, neurosurgery, and intensive care teams. An example of early goal-directed therapy is provided in **Table 257-7**.

Airway and Breathing Treat any condition that compromises ventilation (e.g., altered mental status, facial/neck trauma, pneumothorax). **Patients with severe injury (GCS score of ≤8) require intubation.** Use short-acting induction agents that have limited effect on blood pressure or ICP (**Table 257-8**). Avoid nasotracheal intubation if facial trauma or basilar skull fracture is evident or suspected. Monitor blood pressure throughout the procedure. Preinduction agents such as low-dose succinylcholine, vecuronium, pancuronium, and lidocaine do not improve outcome, but can be used as adjuncts if they do not delay airway control.[46] Ketamine is not advocated by the Brain Trauma Foundation or American College of Surgeons and can cause adverse reactions such as agitation in patients after trauma. The authors do not recommend ketamine as a preintubation agent. Maintain inline cervical spine stabilization during intubation.

Maintain oxygenation and use capnometry to control P_{CO_2} and avoid hyperventilation. Prolonged (>6 hours) hypocapnia causes cerebral

TABLE 257-7 Checklist for ED Treatment of Brain Injury

	Treatment	Comments
Cervical spine	Spinal precautions	
Airway	Maintain airway, intubate for GCS <8 or as needed	
Oxygenation and ventilation	Oxygen saturation >90%; Pco_2 35–45 mm Hg	No prophylactic hyperventilation
BP	Systolic BP >90 mm Hg, MAP 80 mm Hg; give NS, blood products, or transfuse as needed	No permissive hypotension; pressors may be required if fluids not sufficient
Exam and GCS	GCS before paralytics if possible; treat life-threatening injuries and active bleeding	Serial GCS is helpful in identifying change; keep goal of "brain resuscitation" as top priority
Stat head CT and cervical spine CT	Identify mass lesions and signs of increased ICP	Protect cervical spine until cleared
Repeat exam	Check GCS for changes and for signs of impending herniation/deterioration	Change of >2 points should prompt further workup
Check glucose	Treat hypoglycemia *and* hyperglycemia	Hyperglycemia is bad for the brain
Control temperature	Maintain between 36°C and 38.3°C	Aggressive cooling: Tylenol™, cooling blanket, etc.
Seizure prophylaxis	Give antiepileptic drug if GCS ≤10, acute seizure with injury, or abnormal head CT scan	Phenytoin (Dilantin™)/fosphenytoin/levetiracetam
Identify and treat elevated ICP, herniation	Keep head of the bed at 30 degrees; ensure good BP, ventilation, and temperature control; give mannitol 1 gram/kg IV bolus; urgent NS consult	Consider adding hypertonic saline (3% NaCl 250 mL/30 min) for refractory elevations in ICP; monitor BP and electrolytes
Neurosurgery referral/transfer for advanced care	ICP monitoring, ventriculostomy for ICP management, aggressive tiered approach to management, emergency surgery	ICP monitoring and CSF diversion in GCS ≤8

Abbreviations: BP = blood pressure; CSF = cerebrospinal fluid; GCS = Glasgow Coma Scale; ICP = intracranial pressure; MAP = mean arterial pressure; NS = normal saline.

vasoconstriction and worsens cerebral ischemia. **Keep oxygen saturation >90%, Pao_2 >60 mm Hg, and Pco_2 at 35 to 45 mm Hg.**

Circulation Traumatic hypotension leads to ischemia within low-flow regions of the injured brain. Ischemia amplifies the neurotoxic cascade and increases cerebral edema. Provide aggressive fluid resuscitation to prevent hypotension and secondary brain injury. Normal saline is recommended for volume resuscitation. **Maintain systolic blood pressure at ≥100 mm Hg for patients 50 to 69 years old or at ≥110 mm Hg for patients 15 to 49 years old or >70 years old.**[23,24,47,48] A blood pressure within "normal" range may be inadequate to maintain adequate flow and CPP if ICP is increased. **Permissive hypotension worsens outcome in patients with brain injury.**

Isolated head injury rarely produces hypotension, except as a preterminal event. Hypovolemic shock may be seen with polytrauma, massive blood loss from scalp lacerations, or in small children from subgaleal hematoma. If fluid and blood resuscitation is not effective, use vasopressors to preserve cerebral perfusion. Transfusion has been associated with improved outcomes in TBI, and studies have associated anemia, defined as a hemoglobin <8 grams/dL, with worsening outcome after brain injury.[19,49,50]

Pain and increased ICP can cause hypertension. Treat pain, and assess for impending herniation (*Cushing reflex*). For management, see discussion within this chapter under "Increased Intracranial Pressure Management" section.

Patient Positioning Raising the head of the bed may improve cerebral blood flow by lowering ICP. However, the interaction between ICP, MAP, and tissue oxygenation is complex and highly variable. Response to position change depends on many factors such as degree of intact autoregulation, brain compliance, and individual patient variability. There is still uncertainty as to whether this procedure is beneficial, but in the setting of suspected elevated ICP, it is currently recommended as a simple maneuver to improve cerebral blood flow. One must ensure that the patient's blood pressure is maintained above the minimum recommended level (MAP 80 mm Hg), because elevation of 30 degrees can drop the mean pressure within the brain by up to 10 to 15 mm Hg and improve CPP. (Remember CPP = MAP — ICP, so lowering the ICP improves CPP, but lowering MAP in the setting of hypotension could be counterproductive and lower CPP.) Elevating the head of the bed to 30 degrees can be safely accomplished even when the spine has not been cleared, as long as the cervical spine is stabilized within a collar (reverse Trendelenburg).[51]

TABLE 257-8 Intubation Agents in Brain Injury

Agent	Comments
Induction agent	
Etomidate, 0.3 milligram/kg IV	May be neuroprotective; may lower intracranial pressure; adrenal suppression unlikely with single use
Propofol 1–3 milligrams/kg IV	Rapid onset and offset; antiseizure properties; can cause hypotension if inadequate fluid resuscitation
Paralytics	
Succinylcholine 1–1.5 milligrams/kg IV	Short acting; avoid in burns, extensive muscle injury, etc.
Rocuronium, 0.6–1.0 milligram/kg IV	Short acting, safe in hyperkalemia

Glucose Control Hyperglycemia in the setting of neurologic injury (both stroke and TBI) is associated with worse outcome. Tight hyperglycemic control is recommended in patients with moderate to severe TBI. Insulin drips may be required to achieve adequate control (glucose 100 to 180 milligrams/dL or 5.55 to 9.99 mmol/L).[52]

Temperature Control Elevated temperature is associated with an increased metabolic demand and excessive glutamate release. Elevated temperature elevates ICP and worsens outcome in many neurologic critical care conditions including TBI. Treat fever with the goal of normothermia. The evidence for hypothermia in TBI is not sufficient to recommend its use.[53]

Seizure Treatment and Prophylaxis Seizures after head injury can change the neurologic examination, alter oxygen delivery and cerebral blood flow, and increase ICP. Prolonged seizures can worsen secondary injury. Treat acute seizures with midazolam or lorazepam, and if seizures continue, treat as for status epilepticus.[53] In consultation with the neurosurgeon, administer prophylactic phenytoin/phosphenytoin if the GCS is ≤10, if the patient has an abnormal head CT scan, or if the patient has had an acute seizure after the injury. The dose is 18 milligrams/kg IV at 25 milligrams/min. Prophylactic anticonvulsants reduce the occurrence of posttraumatic seizures within the first week. Phenytoin/phosphenytoin is the agent most studied. Levetiracetam can be used, but there are fewer data supporting its use. Steroids have no role in the treatment of TBI.[54]

Cerebral Herniation Develop a team approach to ICP management between emergency medicine, neurosurgery, intensive care unit, and trauma teams.

Use patient history and physical examination to identify signs and symptoms of impending herniation. Indicators of rising ICP include

severe headache, visual changes, numbness, focal weakness, nausea, vomiting, seizure, change in mental status, lethargy, hypertension, coma, bradycardia, and agonal respirations. Signs of impending transtentorial herniation include unilateral or bilateral pupillary dilation, hemiparesis, motor posturing, and/or progressive neurologic deterioration.

Measure neurologic deterioration by comparing sequential GCS scores. In a patient with a rapidly deteriorating GCS, if time permits, obtain a repeat head CT to identify an expanding intracranial hematoma.

Mannitol and/or hypertonic saline can lower ICP. Mannitol is an osmotic agent that can reduce ICP and improve cerebral blood flow, CPP, and brain metabolism. Mannitol is also a free radical scavenger. It generally has an effect within 30 minutes. Mannitol expands plasma volume and can improve oxygen-carrying capacity. Administer mannitol by repetitive bolus (0.25 to 1 gram/kg) and not by constant infusion. Because no dose-dependent effect is seen with mannitol, some clinicians advocate beginning at the lower range of the suggested dose. Mannitol results in a net intravascular volume loss because of its diuretic effect. Monitor the patient's input and output. Osmotic diuresis is *relatively contraindicated* in hemorrhage and hypotension. However, in the setting of acute herniation, mannitol has been demonstrated to effectively reduce life-threatening elevations of ICP.

Hypertonic saline may be used as an alternative to mannitol in the patient who is not adequately fluid resuscitated or hypotensive. The Brain Trauma Foundation indicates that at this time, data support the primary use of mannitol for the acute treatment of ICP. Most EDs have 3% sodium chloride available; the dose for adults is 250 mL over 30 minutes. Intensive care units may stock 23.4% sodium chloride solution; the dose for adults is 30 mL over 30 minutes. Monitor serum osmolality and serum sodium.

Mannitol and hypertonic saline may be given serially and in conjunction with one another.

ADVANCED TREATMENT OF BRAIN INJURY

Advanced treatment of brain injury requires invasive and close monitoring (**Table 257-9**).

Cerebral Perfusion Pressure Management **If the GCS is ≤8, arrange for placement of an intracranial bolt or extraventricular drain with monitoring capabilities as soon as possible to monitor ICP and to direct treatment.** The Brain Trauma Foundation recommends a target CPP of between 60 and 70 mm Hg in order to improve survival and outcomes. Increasing CPP >70 mm Hg may result in injury to other organs (e.g., acute respiratory distress syndrome from lung tissue trauma), and further research is needed in this area.

Consider ICP monitoring for patients with a normal admission brain CT scan if two or more of the following criteria are met: age over 40 years, unilateral or bilateral motor posturing, and systolic blood pressure <90 mm Hg. In addition, provide ICP monitoring in patients undergoing emergency surgery (e.g., orthopedic repair). Management of CPP is essential intraoperatively, where the patient with elevated ICP may experience large shifts in central volume status due to surgical blood loss.

Increased Intracranial Pressure Management An ICP of >20 mm Hg increases morbidity and mortality. Early consultation with neurosurgery for direct ICP monitoring, cerebrospinal fluid diversion, or surgical intervention is highly recommended in moderate and severe TBI. In certain circumstances, an ICP monitor will be placed in the ED by neurosurgery to help guide medical management, as well as for direct cerebrospinal fluid diversion to lower ICP.[13,18,21,24]

TABLE 257-9 Goal-Directed Therapy of Brain Injury

Goal-Directed Therapy—Suggested Targets		
Pulse oximetry ≥90%	CPP ≥60 mm Hg	Physiologic sodium 135–140 mEq/L
SBP ≥90 mm Hg	ICP <20 mm Hg	INR ≤1.4
MAP ≥80 mm Hg	$PbtO_2$ ≥15 mm Hg	Platelets ≥75 × 10^3/mm^3
$Paco_2$ 35–45 mm Hg	pH 7.35–7.45	Hemoglobin ≥8 grams/dL
Temperature 36.0°C–38.3°C	Glucose 80–180 milligrams/dL	

Abbreviations: CPP = cerebral perfusion pressure; ICP = intracranial pressure; INR = International Normalized Ratio; MAP = mean arterial pressure; $PbtO_2$ = brain tissue oxygen tension monitoring; SBP = systolic blood pressure.

SPECIFIC HEAD INJURIES

SCALP LACERATIONS

Scalp lacerations can lead to massive blood loss, so control bleeding as rapidly as possible. If direct pressure is not effective, locally infiltrate lidocaine with epinephrine and clamp or ligate bleeding vessels. Before closure, carefully examine wounds to identify foreign bodies, underlying fractures, and galeal lacerations. Large galeal disruptions should be repaired. For discussion of repair of scalp lacerations, see Chapter 42, "Face and Scalp Lacerations."

SKULL FRACTURES

Patients who have or are suspected of having a skull fracture require a head CT scan. Skull fractures are usually categorized by location (basilar vs. skull convexity), pattern (linear, depressed, or comminuted), and whether they are open or closed (**Figures 257-4** and **257-5**). A linear skull fracture with an overlying laceration is an open fracture. Explore wounds gently to avoid driving bone fragments into the brain.

Fractures that cross the middle meningeal artery, a major venous sinus, or linear occipital fractures have high intracerebral complication rates. Patients with skull fractures that are open or depressed, involve a sinus, or are associated with pneumocephalus should be given antibiotics (vancomycin, 1 gram IV, and ceftriaxone, 2 grams IV). A skull fracture that is depressed by more than the thickness of the skull usually requires operative repair.

BASILAR SKULL FRACTURE AND CEREBROSPINAL FLUID LEAKS

The presence of a basilar skull fracture is a significant risk factor for intracranial injury. The most common basilar skull fracture involves the petrous portion of the temporal bone, the external auditory canal, and the tympanic membrane. It is associated with dural tearing, which often leads to otorrhea or rhinorrhea. Basilar skull fractures may occur anywhere along the skull base, from the cribriform plate through the occipital condyles. Do not place a nasogastric tube through the nares if

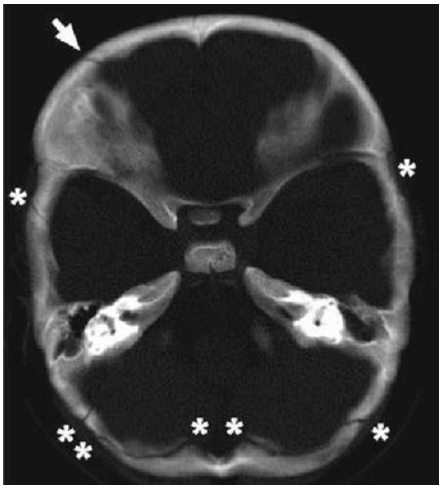


FIGURE 257-4. Linear fracture seen on CT. *Arrow* indicates skull fracture; *asterisks* indicate normal cranial suture lines. [Image used with permission of Joseph Piatt, Jr., MD, Division of Neurosurgery, A. I. duPont Hospital for Children, Wilmington, Delaware; Departments of Neurological Surgery and Pediatrics, Thomas Jefferson University, Philadelphia, Pennsylvania.]

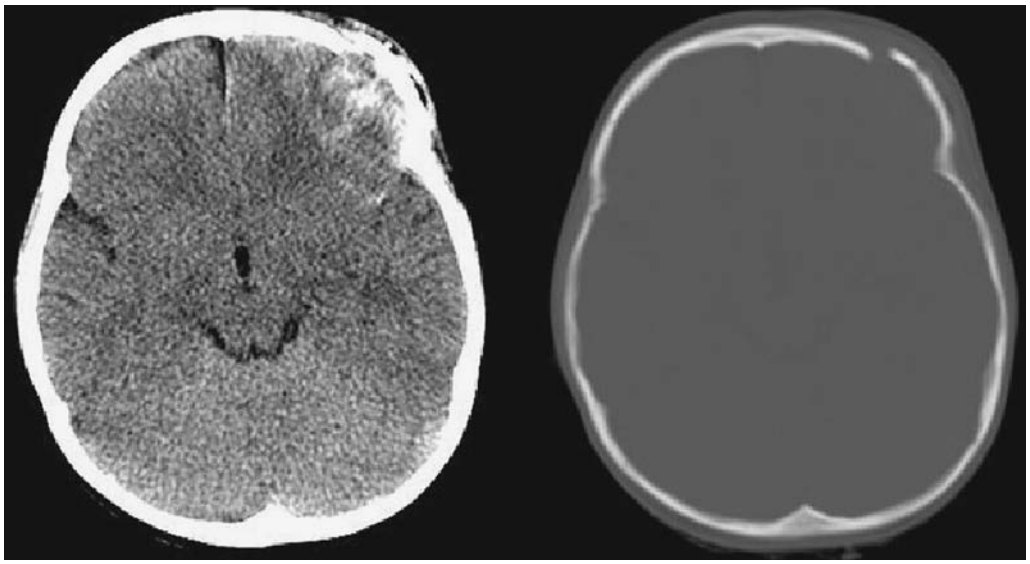


FIGURE 257-5. Open skull fracture with underlying cerebral contusion. This injury was sustained from a fall of two stories. [Image used with permission of Joseph Piatt, Jr., MD, Division of Neurosurgery, A. I. duPont Hospital for Children, Wilmington, Delaware; Departments of Neurological Surgery and Pediatrics, Thomas Jefferson University, Philadelphia, Pennsylvania.]

cribriform plate fracture is suspected; this can lead to direct intracranial injury. **Signs and symptoms associated with basilar skull fractures include cerebrospinal fluid leak, mastoid ecchymosis (Battle sign), periorbital ecchymoses (raccoon eyes), hemotympanum, vertigo, decreased hearing or deafness, and seventh nerve palsy.** Periorbital and mastoid ecchymoses develop gradually over hours after an injury and are often absent in the ED. Cerebrospinal fluid leaks (otorrhea or rhinorrhea) are difficult to diagnose; however, the patient often complains of discharge of clear fluid from the nose or ears. Fluid may be collected and sent for analysis (identification of β-transferrin). The β_2-transferrin isoform of transferrin is found only in cerebrospinal fluid, and not in blood, mucus, or tears.

Patients with acute cerebrospinal fluid leaks are at risk for meningitis. Antibiotic prophylaxis is often recommended to reduce the incidence of infection.[55] Administration of antibiotics should be done in consultation with the neurosurgeon who will be following the patient. If prophylactic antibiotics are instituted, the drugs selected should have broad coverage with good penetration into the meninges, such as ceftriaxone, 2 grams IV, and vancomycin, 1 gram IV. Elevate the head of the patient's bed to 30 degrees. A lumbar drain is often placed by the neurosurgical team. Cerebrospinal fluid leaks may require repair by a neurosurgeon or otolaryngologist.

CEREBRAL CONTUSION AND INTRACEREBRAL HEMORRHAGE

Contusions most commonly occur in the subfrontal cortex, in the frontal and temporal lobes, and, occasionally, in the occipital lobes (**Figure 257-6**). They are often associated with subarachnoid hemorrhage. Contusions may occur at the site of the blunt trauma or on the opposite side of the brain, known as a *contrecoup* injury.

Intracerebral hemorrhage can occur days after significant blunt trauma, often at the site of resolving contusions. This complication is more common in patients with coagulopathy. CT scan findings immediately after injury may be normal. Obtain serial CTs if any change in mental status occurs in a patient with coagulopathy until the clot is stable.

SUBARACHNOID HEMORRHAGE

Traumatic subarachnoid hemorrhage results from the disruption of the parenchyma and subarachnoid vessels and presents with blood in the cerebrospinal fluid (**Figure 257-7**). Patients with isolated traumatic subarachnoid hemorrhage may present with headache, photophobia, and meningeal signs. **Traumatic subarachnoid hemorrhage is the most common CT abnormality in patients with moderate to severe TBI.** Patients with early development of traumatic subarachnoid hemorrhage have a threefold higher mortality risk than those without traumatic subarachnoid hemorrhage (42% vs. 14%, respectively).[56] Some traumatic subarachnoid hemorrhages can be missed on early CT scans. Generally, CT scans performed 6 to 8 hours after injury are sensitive for detecting traumatic subarachnoid hemorrhage.

EPIDURAL HEMATOMA

An epidural hematoma results when blood collects in the potential space between the skull and the dura mater (**Figure 257-8**). The anatomic relationships of the branches of the middle meningeal artery



FIGURE 257-6. CT scan demonstrating delayed intraparenchymal hemorrhages from a traumatic contusion. [Image used with permission of Jack Fountain, Jr., MD, Emory University and Grady Memorial Hospital.]



FIGURE 257-7. CT scan demonstrating subarachnoid hemorrhage. *Arrow 1* indicates prepontine cisternal blood, and *arrow 2* identifies blood in the ambient cistern. [Image used with permission of Jack Fountain, Jr., MD, Emory University and Grady Memorial Hospital.]

and the sequelae of fracture and laceration of the artery are shown in Figure 257-2.

Blunt trauma to the temporal or temporoparietal area with an associated skull fracture and middle meningeal arterial disruption is the primary mechanism of injury. Occasionally, trauma to the parieto-occipital region or the posterior fossa causes tears of the venous sinuses with epidural hematomas.

The classic history of an epidural hematoma involves a significant blunt head trauma with loss of consciousness or altered sensorium, followed by a lucid period and subsequent rapid neurologic demise. This clinical presentation occurs in a minority of cases. Traumatic blows to the thin temporal bone over the lateral aspect of the head carry the highest risk (e.g., baseball or pool stick injury). The diagnosis of an epidural hematoma is based on CT scan and physical examination findings. The CT appearance of an epidural hematoma is a biconvex (football-shaped) mass, typically found in the temporal region.

The high-pressure arterial bleeding of an epidural hematoma can lead to herniation within hours after an injury. Early recognition and evacuation reduce morbidity and mortality. Underlying injury of the brain parenchyma is often absent; full recovery may be expected if the hematoma is evacuated prior to herniation or the development of neurologic deficits.

SUBDURAL HEMATOMA

Subdural hematoma is caused by sudden acceleration-deceleration of brain parenchyma with subsequent tearing of the bridging dural veins. This results in hematoma formation between the dura mater and the arachnoid (**Figures 257-9** and **257-10**). Subdural hematoma tends to collect more slowly than epidural hematoma because of its venous origin. However, subdural hematoma is often associated with concurrent brain injury and underlying parenchymal damage. **Brains with extensive atrophy, such as in the elderly or in chronic alcoholics, are more susceptible to the development of acute subdural hematoma.** Even seemingly benign falls from standing position can result in subdural bleeding in the elderly. Children <2 years old are also at increased risk of subdural hematoma.

Traditionally, subdural hematomas have been classified as acute, subacute, or chronic depending on the length of time from onset and occurrence of active hemorrhage. Acute symptoms usually develop within 14 days of the injury. After 2 weeks, the term *chronic subdural hematoma* is used. There is no specific clinical syndrome associated with a subdural hematoma. Acute cases usually present immediately after severe trauma, and often the patient is unconscious. In the elderly or in alcoholics, chronic subdural hematomas may result in vague complaints or mental status changes. Often, there is no recall of injury. On CT scan, acute subdural hematomas are hyperdense (white), crescent-shaped lesions that cross suture lines. Subacute subdural hematomas are isodense and are more difficult to identify. CT scanning with IV contrast or MRI can assist in identifying a subacute subdural hematoma. A chronic subdural hematoma appears hypodense (dark) because the iron in the blood has been metabolized.

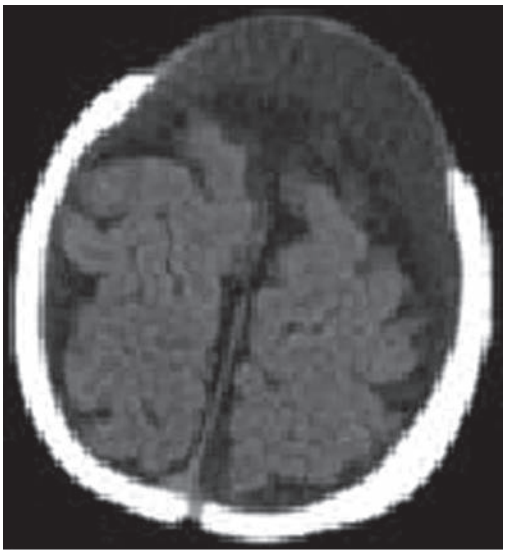
The definitive treatment depends on the type, size, effect on underlying brain parenchyma, and the associated brain injury. Mortality and the need for surgical repair are greater for acute and subacute subdural hematomas. Chronic subdural hematomas can sometimes be managed without surgery depending on the severity of the symptoms. **Table 257-10** compares intracranial injuries.



FIGURE 257-8. Epidural hematoma. Note the convex shape and focal location. [Image used with permission of Jack Fountain, Jr., MD, Emory University and Grady Memorial Hospital.]



FIGURE 257-9. Small subdural hematoma in the right frontotemporal region in an adult. [Image used with permission of Jack Fountain, Jr., MD, Emory University and Grady Memorial Hospital.]



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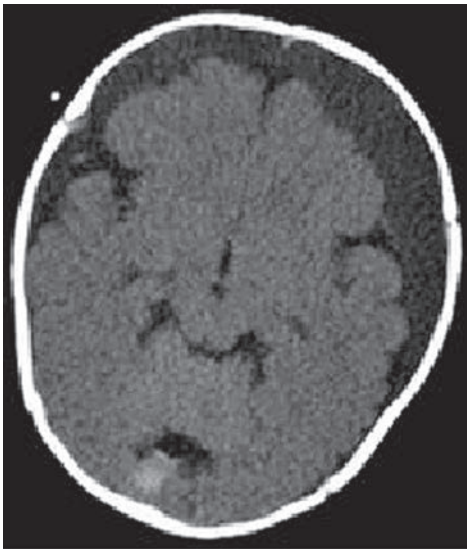


B

FIGURE 257-10. **A.** Bifrontal chronic subdural hematoma extending through the anterior fontanelle in a 1-month-old child. **B.** Second image in the same child showing bifrontal chronic subdural hematoma, as well as small, acute intraparenchymal hemorrhage in the posterior fossa.

DIFFUSE AXONAL INJURY

Diffuse axonal injury is the disruption of axonal fibers in the white matter and brainstem. Shearing forces on the neurons generated by sudden deceleration cause diffuse axonal injury. The condition is seen after blunt trauma, such as from a motor vehicle crash. In infants, shaken baby syndrome is a well-described cause.[57]

In severe diffuse axonal injury, edema can develop rapidly. The underlying injury can result in devastating and often irreversible neurologic deficits. A CT scan of a patient with diffuse axonal injury may appear normal, but classic CT findings include punctuate hemorrhagic injury along the gray-white junction of the cerebral cortex and within the deep structures of the brain (**Figures 257-11** and **257-12**). Treatment options are very limited, but an attempt should be made to prevent secondary damage by reducing cerebral edema and limiting pathologic increases in ICP.

PENETRATING INJURY

Depending on the velocity, a bullet that passes through the brain can create a cavity three to four times larger than its diameter. Direct penetration of the bullet through the brain substance and the transfer of kinetic energy cause the majority of the destruction (**Figure 257-13**). The GCS can be used to predict the prognosis for nonintoxicated patients with a gunshot wound to the brain. Patients with a GCS score of >8 and reactive pupils have a 25% mortality risk, whereas mortality approaches 100% in those with a GCS score of <5. Intubate patients with a penetrating gunshot wound to the brain and treat with prophylactic antibiotics, such as vancomycin, 1 gram IV, and ceftriaxone, 2 grams IV.

Stab wounds have very low energy and impart only direct damage to the area contacted by the penetrating object. Patients with penetrating injury require admission, broad-spectrum antibiotics, and operative intervention. **Leave impaled objects in place until controlled surgical removal is facilitated.**

MILD TRAUMATIC BRAIN INJURY

Mild traumatic brain injury (mTBI) and *concussion* are terms used interchangeably in this chapter. While some clinicians believe concussion to be a subset of mTBI, we do not make the distinction here. It is important that patients with an mTBI be identified in the ED, as it may be the patient's only interaction with a healthcare entity and only chance for appropriate diagnosis and management. mTBI, an impairment in brain function without overt hemorrhage or other gross lesions, is caused by an external force, and results in a GCS score of 14 or 15 (see Chapter 110, "Pediatric Trauma," and Table 257-3).[1] The diagnosis is made by a history of any alteration in consciousness or disturbance in brain function occurring at the time or shortly after the inciting mechanical force

TABLE 257-10 Comparison of Intracranial Injuries

	Type of Patient	Anatomic Location	CT Findings	Common Cause	Classic Symptoms
Epidural	Young, rare in the elderly and those age <2 y	Potential space between skull and dura mater	Biconvex, football-shaped hematoma	Skull fracture with tear of the middle meningeal artery	Immediate LOC with a "lucid" period prior to deterioration (only occurs in about 20%)
Subdural	More risk in the elderly and alcoholic patients	Space between dura mater and arachnoid	Crescent- or sickle-shaped hematoma	Acceleration-deceleration with tearing of the bridging veins	Acute: rapid LOC, lucid period possible Chronic: altered mental state and behavior with gradual decrease in consciousness
Subarachnoid	Any age group after blunt trauma	Subarachnoid	Blood in the basilar cisterns and hemispheric sulci and fissures	Acceleration-deceleration with tearing of the subarachnoid vessels	Mild, moderate, or severe traumatic brain injury with meningeal signs and symptoms
Contusion/intracerebral hematoma	Any age group after blunt trauma	Usually anterior temporal or posterior frontal lobe	May be normal initially with delayed bleed	Severe or penetrating trauma; shaken baby syndrome	Symptoms range from normal to LOC

Abbreviation: LOC = loss of consciousness.

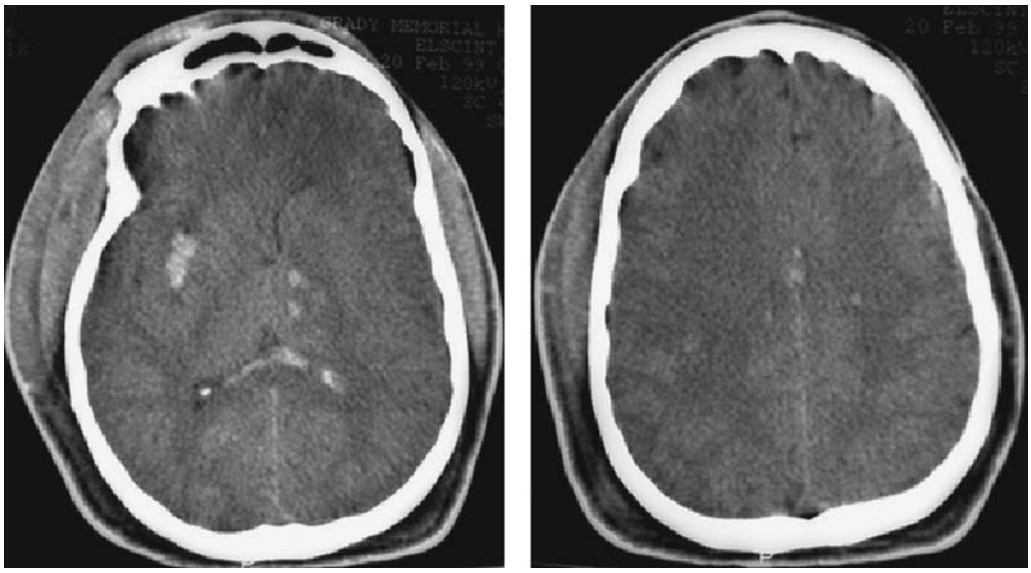


FIGURE 257-11. Diffuse axonal injury with intraventricular blood. [Image used with permission of Jack Fountain, Jr., MD, Emory University and Grady Memorial Hospital.]

(acceleration-deceleration or blunt force). Alteration in consciousness includes the individual's account of "getting his/her bell rung," "seeing stars," or being dazed or confused as a result of the force. The presence of amnesia further supports the diagnosis and is often associated with more significant injury.

Signs and symptoms such as vomiting, headache, loss of consciousness, focal neurologic deficit, age >65 years, coagulopathy, and/or dangerous mechanism of injury are factors that increase risk of serious injury (see Tables 257-5, 257-6, and 257-7).[39,40,55] The presence of alcohol, distracting injuries, and other barriers to obtaining a clear history of the event confound the signs and symptoms of mTBI.

PATHOPHYSIOLOGY

mTBI represents a spectrum of pathophysiology. In its mildest form, mTBI causes an ionic shift that leads to a momentary disruption in function. Symptom recovery is rapid, and the concussive injury results in no obvious structural damage. More "severe" forms of mTBI lead to long-term and/or permanent structural damage. Mild insults may mediate gene regulation that cause fundamental changes to the brain (e.g., the upregulation of ion channels along axons). A single traumatic event has been shown to increase ion channel density. An increase in the density of ion channels leaves the brain vulnerable to overactivation. Repeated exposure to trauma during this vulnerable period greatly increases neuronal toxicity and cell death.

In addition to ion channel upregulation, large shifts in ion concentrations may lead to mitochondrial dysfunction and depletion of intracellular energy stores.[26,58-60] The state creates a metabolic "mismatch" during which neuronal dysfunction persists until recovery occurs. This pathway is a recognized pattern of injury in moderate/severe TBI but is thought to also play a role in mTBI.

Metabolic insults, electrochemical imbalances (calcium influx and sodium and potassium shifts), and mitochondrial dysfunction also result in damage to axonal transport systems. Structural abnormalities are not always identified on MRI or CT. However, histopathology shows



FIGURE 257-12. Diffuse axonal injury with loss of the gray matter–white matter interface. [Image used with permission of Daniel Curry, MD, PhD, Texas Children's Hospital and Baylor College of Medicine.]

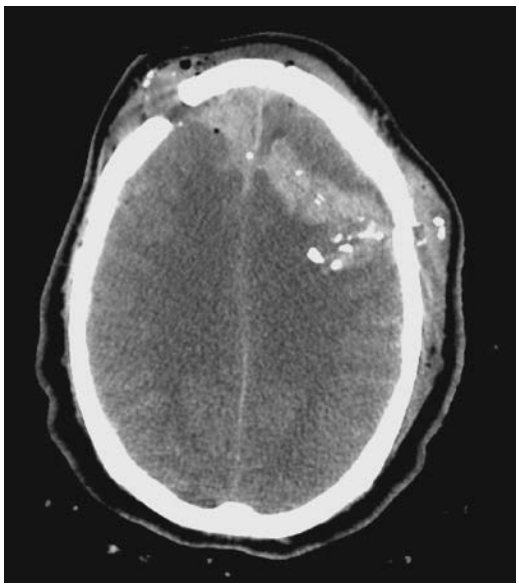


FIGURE 257-13. Gunshot wound traversing through frontal lobes bilaterally; note bone fragments. [Image used with permission of Thomas Egglin, MD, Director of Emergency Radiology and an Associate Professor of Diagnostic Imaging at the Warren Alpert Medical School of Brown University, Providence, RI.]

microscopic injury. Indeed, evidence of damage on diffusion tensor imaging has been demonstrated in high school athletes after a single football season, even without clinical signs or symptoms of a concussion.[61,62] Chronic traumatic encephalopathy[63] is hypothesized to occur as a result of repeated exposure to TBI in sports.[64-66]

Repetitive concussions can result in long-term cognitive deficits and structural damage to the brain.[67-70] In extreme cases, when a second concussion occurs prior to recovery from the first, rapid onset of cerebral edema and death can occur, particularly in athletes prematurely returning to play (**second impact syndrome**).[71]

DIAGNOSIS

HISTORY

The signs and symptoms of concussion can be subtle and easily overlooked, especially in patients with polytrauma in the setting of a busy ED. A systematic approach is necessary to ensure at-risk patients are identified. **The physical examination findings in isolated mTBI are often normal, and by definition, head CT scans are normal.** Currently, there are no objective tests that can confirm the diagnosis of concussion. The diagnosis is clinical and based on symptoms and neurologic functional impairments associated with a mechanical force.

A two-question screen can help alert clinicians to the need for further evaluation: (1) Did the patient sustain a blunt force mechanism and/or whiplash-type acceleration-deceleration event? *and* (2) Did the event cause any neurologic alteration in mental state (e.g., dazed, confused, loss of consciousness)? Some mTBIs may be missed by this screen, such as those with delayed onset, those that occur in the setting of polytrauma, or those that present primarily as isolated symptoms and are not initially associated with trauma. Even if a clinician is confident of an mTBI diagnosis, it is important to complete a thorough history and exam because it informs management and helps predict the patient's recovery trajectory.

The fundamental mTBI-focused evaluation includes the following five components: (1) event history and immediate postevent symptoms; (2) mechanism; (3) key premorbid cofactors (concussion, migraine/headache, and depression history; bleeding disorders; or anticoagulant medication); (4) current symptom checklist; and (5) concussion-specific neurologic exam.

Obtain the history of the event from the patient and a witness if possible. Symptoms may have completely resolved by the time the patient presents to the ED, and lack of current symptoms does not preclude the diagnosis. Mechanism of injury informs the level of suspicion and may instruct modifiable risk behaviors or guide management and discharge instructions, such as in the setting of sports-induced injury. When available, the patient's medical history may provide information that needs further evaluation, such as imaging if the patient is on anticoagulants, or predict poorer recovery (history of depression, headaches, attention-deficit/hyperactivity disorder, or prior mTBI).

Symptoms are best assessed using a symptom checklist (ideally embedded in an electronic medical record). The most commonly used are those listed in the Sport Concussion Assessment Tool 5 or the Post-concussion Symptom Index (see http://bjsm.bmj.com/content/bjsports/early/2017/04/26/bjsports-2017-097506SCAT5.full.pdf).[72] Symptoms are sensitive but nonspecific (**Table 257-11**). The greater number of symptoms reported, the longer duration of symptoms, and the greater severity of symptoms all correlate with length of recovery. Treatment of acute symptoms may shorten a patient's course.

TABLE 257-11 Signs and Symptoms of Mild Traumatic Brain Injury

Cognitive Symptoms	Physical Signs and Symptoms	Behavioral Changes
Attention difficulties	Headaches	Irritability
Concentration problems	Dizziness	Depression
Amnesia and perseveration	Insomnia	Anxiety
Short-term and long-term memory problems	Fatigue Uneven gait	Sleep disturbances Emotional lability
Orientation problems	Nausea, vomiting	Loss of initiative
Altered processing speed	Blurred vision	Loneliness and helplessness
Altered reaction time Calculation difficulties and problems with executive function	Seizures	Problems related to job, relationship, home, or school management

Note: At 3 months after injury, <30% are symptomatic; at 1 year, 15% are symptomatic.

PHYSICAL EXAMINATION

Ominous findings include an abnormal GCS, racoon's eyes, Battle's sign, hemotympanum, cerebrospinal fluid rhinorrhea, and an abnormal pupil exam.

The **focused mTBI exam** has the following five elements: (1) awareness and alertness; (2) brief cognitive assessment; (3) cervical spine assessment; (4) oculomotor exam; and (5) balance exam.

1. Alertness is grossly measured by the GCS. A patient with a GCS of <15 may not be able to cooperate with the remainder of the mTBI exam and should raise serious concerns for intracranial pathology.
2. A comprehensive cognitive exam is impractical in the ED setting, but a brief exam exploring short-term memory, encoding, or working memory should be performed. In adults, serial 7's counted backward from 100 (down to 65) is sufficient. Inability to complete or more than four errors is abnormal.
3. Evaluate the cervical spine in all trauma patients with suspected head injury and prior to neck movement or ambulation. If injury is clinically suspected, order a noncontrast CT scan.
4. The vestibular ocular motor system is highly complex and involves sensory integration among multiple neuronal pathways that are vulnerable to shear forces. The **Vestibular Ocular Motor Screening Exam** is relatively sensitive and specific for mTBI and can be rapidly performed in the ED. The Vestibular Ocular Motor Screening Exam includes five components: near-point convergence, near-point accommodation, smooth pursuits, saccades, and vestibulo-ocular reflex. Published instructions are available.[73] When scoring the Vestibular Ocular Motor Screening Exam, symptom exacerbation is as important as an abnormal functional finding.
5. Balance is an important sensory integration task using visual, vestibular, and proprioception input from cortical networks that is frequently disturbed after an mTBI. Balance is initially tested in the standing position with the examiner nearby for safety. A formal Romberg's test with feet together and eyes open and then closed (falling to one side >30 degrees, moving feet to adjust balance, or lifting hands off hips is abnormal) may illicit gross balance abnormalities. Gait assessment can also be used to interrogate balance. Normal gait should not result in swaying, wide-based gait, or slow staggered steps. The patient should be able to turn around rapidly without imbalance as well. For more intense testing, such as might be needed in an athlete, tandem gait can be tested.

BIOMARKERS

Serum markers specific to neurologic injury may improve future diagnosis and management.[74,75] Two protein biomarkers, glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1), were recently cleared by the U.S. Food and Drug Administration for risk-stratifying significant intracranial hemorrhage and distinguishing the need for CT in patients with presenting GCS scores of 9 to 15. UCH-L1 was found to be most sensitive (100% sensitive and 39% specific if <40 pg/mL) at 6 hours after injury. UCH-LI, GFAP, and S100B had similar areas under the curve in the primary study, with GFAP and S100B having lower specificity. Rapid laboratory testing for these proteins is not yet widely available, and how to deploy the tests is still in question (e.g., what time frame after injury is optimal for testing to maintain high sensitivity). S100B is also not currently approved by the U.S. Food and Drug Administration for mTBI. Note that the studies validating these biomarkers (and the U.S. Food and Drug Administration clearance) are specific to ruling out significant intracranial hemorrhage on CT and are not diagnostic of mTBI.[76-79]

NEUROIMAGING AND ELECTROENCEPHALOGRAM

CT remains the imaging tool of choice for TBI because it is sensitive to intracranial blood and provides the clinician with the needed information regarding surgical intervention. In mTBI, CT imaging is normal. MRI is more sensitive for contusion and other subtle findings, but provides no additional actionable data to the ED clinician.

Several studies have shown the utility of using portable electroencephalogram with proprietary algorithms to determine the need for CT imaging. The devices provide a risk profile (negative, positive, equivocal) for the possibility of intracranial blood and structural abnormalities that would be visible on CT. BrainScope® is one device that is U.S. Food and Drug Administration cleared for such purpose and is being adopted in some EDs.[80]

TREATMENT AND DISPOSITION

mTBI is a treatable disease. Not dissimilar to the treatment of a fracture, the primary intervention is rest ("splinting the brain"). Although the duration of rest remains controversial, emerging evidence shows that physical and neurologic rest past the acute 48-hour period shortens the duration of symptoms.

ED treatment objectives are to identify patients who have intracranial lesions requiring neurosurgical intervention; to admit patients whose condition might deteriorate over time; to provide some prognostication based on the evaluation (e.g., patients with history of depression, prior concussions, multiple symptoms, abnormal Vestibular Ocular Motor Screening Exam or balance test, or who are at risk for prolonged course); to treat symptoms; to provide injury prevention messaging (especially for athletes); and for those discharged, to provide instructions for cognitive and physical rest and provide follow-up for reassessment before return to normal activities.

When the patient is safe for discharge, one of the most important "interventions" is to provide thorough concussion discharge instructions. The Centers for Disease Control and Prevention has developed excellent discharge instructions that include a letter to school/work to help inform stakeholders of the possible need for accommodations. Physical and neurologic rest is needed until symptoms abate. Discharge the patient to the care of a responsible individual and provide instructions to both the patient and that individual. Patients with mTBI may not comprehend or remember detailed discharge instructions. Have the patient return to the ED for worsening symptoms, headaches, altered mental status, nausea, or vomiting. Refer patients for further evaluation and follow-up care. Patients at an increased risk for reinjury, such as athletes, should undergo a formal graduated return-to-activity program (**Table 257-12**).

RETURN TO ACTIVITY

Symptoms reflect underlying metabolic dysfunction and are currently the only reliable guide to brain health.[59,81] Return to play or work decisions are based on symptoms and a graduated evaluation program.

Assessments incorporate serial symptom checklists, neuropsychological tests (memory and reaction time assessment), and a balance evaluation (see Table 257-12).[81,82] **Because this type of assessment is not practical in the ED setting, emergency physicians should not provide definitive return-to-activity directions.**

TABLE 257-12 Return-to-Activity Program

Sports Related	Non–Sports Related
No activity (rest until symptom free)	No activity (rest until symptom free)
Light aerobic exercise	Light aerobic exercise
Sport-specific training (noncontact)	Moderate aerobic exercise
Noncontact drills	Return to normal activities
Full-contact drills	
Game play	

Note: Patient must remain asymptomatic for 24 hours between each step. Development of symptoms at any level requires return to the previous symptom-free level.

SPECIAL CONSIDERATIONS

POSTCONCUSSIVE SYNDROME

Patients often report a series of physical, emotional, and cognitive symptoms in the days and weeks after mTBI. The estimated prevalence of postconcussive syndrome varies widely, with about 20% to 40% of patients reporting symptoms at 3 months and about 15% at 1 year.[83,84] The most commonly reported postconcussion symptoms are headache, dizziness, decreased concentration, memory problems, sleep disturbances, irritability, fatigue, visual disturbances, judgment problems, depression, and anxiety.[85] When a cluster of symptoms becomes chronic after mTBI, they are often called **persistent postconcussive symptoms** or **postconcussion syndrome**. Clinical findings at the time of the injury do not reliably predict the development of postconcussive syndrome. Postconcussive syndrome symptoms can overlap those of posttraumatic stress disorder. Neuropsychological testing and use of a symptom checklist are the cornerstones of diagnosis and management. Treatment is symptomatic. Refer patients to a neuropsychologist or mTBI clinic.

RECURRENT CONCUSSIONS

Three or more concussions pose a risk for long-term sequelae, especially in adolescents and young children.[67,68,86] Almost all cases of **second impact syndrome** have occurred in young athletes. **Chronic traumatic encephalopathy**,[63] characterized by early onset of memory loss and depression, is a concern in athletes who compete in collision sports. Pathologically large deposits of tau protein are seen in the brains of deceased chronic traumatic encephalopathy patients.[66] Tau protein deposits have been discovered even in youth football players who died from other causes.

SECOND IMPACT SYNDROME

Second impact syndrome is a rare disorder that results in rapid cerebral edema and high mortality (60% to 80%).[71] The pathophysiology and the predictors are not well understood. It is hypothesized that occurrence of a second impact before the brain has reset or recovered from a first mTBI causes a loss of autoregulation and ion imbalance and leads to rapid cerebral edema. This explanation fits well with the concept of enhanced vulnerability due to metabolic disturbances, energy-demand mismatch, and ion channel upregulation after a concussion.[87,88]

ANTICOAGULATION

Anticoagulants and antiplatelet agents increase the risk of intracranial hemorrhage after injury, especially in the elderly.[16]

Intracranial hemorrhage in patients taking warfarin and who have an elevated INR is associated with a high mortality rate (89%).[89] In general, patients with head trauma, who are taking anticoagulants or antiplatelet agents, should undergo emergent head CT. The odds ratio for the risk of intracranial lesions after mild head injury in patients taking any antiplatelet therapy is 2.6.[90] Clopidogrel use seems to be a potent risk factor.[91] The effect of low-dose aspirin (162 mg or less taken daily) on post–head injury bleeding has not been determined. Patients with intracranial hemorrhage need immediate anticoagulant reversal. Patients taking warfarin who have an elevated INR are optimally treated with plasma or four-factor concentrate. See Chapter 239, "Thrombotics and Antithrombotics," and Chapter 166, "Spontaneous Subarachnoid and Intracerebral Hemorrhage," for in-depth discussion.

A negative initial CT finding in an asymptomatic TBI patient receiving anticoagulation or antiplatelet therapy is reassuring, but delayed hemorrhage may occur and is not easily predicted.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 258

Spine Trauma

Steven Go

INTRODUCTION AND EPIDEMIOLOGY

Trauma to the spine can cause a vertebral column injury, a spinal cord injury, or both. A few studies have tried to estimate the annual incidence of specific types of vertebral column injuries in the general population with results ranging from 15 to 65 cases per 100,000,[1,2] but no current figures are available for the U.S. population. In contrast, the estimated annual incidence of spinal cord injury in the United States is 54 cases per million or 17,500 new cases per year, with 81% male victims, a mean age of 42 years, and a 63% non-Hispanic white predominance.[3] Since 2010, the leading causes of spinal cord injury are vehicular (38%), falls (31%), and violence (13%). Lifetime costs for spinal cord injury victims vary according to age at time of injury, severity of injury, and socioeconomic status; however, estimates range in millions of dollars per patient.[3]

FUNCTIONAL ANATOMY

VERTEBRAL COLUMN

The vertebral column is composed of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 4 (usually fused) coccygeal. The axial vertebrae (C1 and C2) are anatomically unique in that they are designed for rotary motion. The odontoid (dens) of the axis (C2) is held against the atlas (C1) by the strong transverse ligament. The remaining vertebrae share some common anatomic features (**Figure 258-1**). A typical subaxial vertebra is composed of an anterior body and a posterior vertebral arch. The vertebral arch is comprised of two pedicles, two laminae, and seven processes (one spinous, two transverse, and four articular). These articulations enable the spine to engage in flexion, extension, lateral flexion, rotation, or circumduction (combination of all movements). The orientation of these articular facet joints changes at different levels of the spine and accounts for variations in motion of specific regions of the vertebral column. Due to its inherent flexibility, the cervical spine is overall the most commonly injured region of the spinal column, with most injuries occurring at the C2 level and from C5 to C7.[4] The second most common region of injury is in the thoracolumbar transition zone (T11 to L2). However, these population tendencies can be influenced by mechanism of injury. For example, in one study,[5] cervical spine fractures were more common in traffic collisions, whereas falls more commonly resulted in lumbar fractures. Even the type of motor vehicle collision can skew injury patterns, as motorcycle drivers tend to have cervical spine injuries much more commonly than other types of motor vehicle collision victims.[6]

A series of ligaments serves to maintain alignment of the spinal column. The anterior and posterior longitudinal ligaments run along the vertebral bodies. Surrounding the vertebral arch are the ligamentum flavum and the supraspinous, interspinous, intertransverse, and capsular ligaments. Between adjacent vertebral bodies are the intervertebral disks, consisting of a peripheral annulus fibrosus and a central nucleus pulposus. The intervertebral disks act as shock absorbers to distribute axial load. When compressive forces exceed the absorptive capacity of the disk, the annulus fibrosus ruptures. This allows the nucleus pulposus to protrude into the vertebral canal, and this may result in spinal nerve or spinal cord compression.

SPINAL CORD

The spinal cord is a cylindrical structure that begins at the foramen magnum, where it is continuous with the medulla oblongata of the brain and extends down the spinal canal to the first and second lumbar vertebrae. The spinal cord gives rise to 31 pairs of spinal nerves: 8 cervical, 12 thoracic,

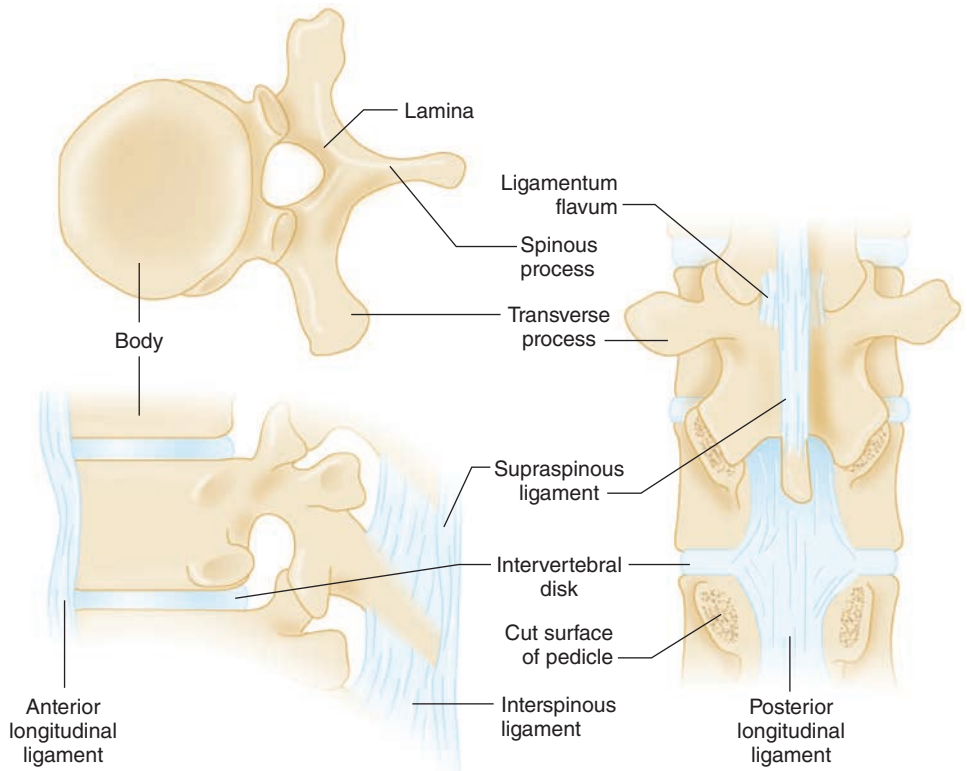


FIGURE 258-1. Vertebral anatomy. Each vertebra consists of a vertebral body and posterior element. Vertebrae are stabilized by an anterior longitudinal ligament, posterior ligament, and interspinous ligament.

5 lumbar, 5 sacral, and 1 coccygeal. Each spinal nerve emerges through the intervertebral foramen corresponding to the appropriate spinal cord level. The lower nerve roots form an array of nerves called the *cauda equina* ("horse's tail").

PATHOPHYSIOLOGY

SPINAL COLUMN INJURIES

Given their multiple axes of motion, the bony vertebrae can be injured via several mechanisms and present with a number of different injury patterns (**Table 258-1**).[7-12]

The variable anatomic qualities of the regions of the spinal column cause characteristic injury patterns in each region. The **cervical spine (C1-C7)** is particularly vulnerable to injury because it is the most exposed, flexible, and mobile portion of the spinal column. The **cervicothoracic junction (C7-T1)** is one of the **transitional zones** of the spinal column, which are locations where the vertebral morphology changes. This designation is important because transitional zones sustain the greatest amount of stress during motion and are most vulnerable to injury. In contrast to the cervical spine, the **thoracic spine (T1-T10)** is a rigid segment, with its stiffness enhanced by articulation with the rib cage. Therefore, not only is injury to the thoracic spine less common than in other regions, but this also means that the presence of a thoracic vertebral injury indicates the patient was subjected to severe traumatic forces and is at high risk for intrathoracic injuries. Moreover, the spinal canal in the thoracic region is also narrower than in other regions. This increases the risk of cord injury, which is often complete when it occurs. The **thoracolumbar junction (T11-L2)** is a transitional zone between the highly fixed thoracic and relatively mobile lumbar spine. In addition to this change in bone anatomy, the thoracolumbar junction serves as the level of transition from the end of the spinal cord (about L1) to the nerve roots of the cauda equina. Relative to the thoracic spine, the width of the spinal canal in the thoracolumbar region is greater. Therefore, despite a large number of vertebral injuries at the thoracolumbar junction, most do not have neurologic deficits, or, if present, they are partial or incomplete. Relative to the thoracic and thoracolumbar regions, the **lower lumbar spine (L3-L5)** is more mobile. Because of the width of the spinal canal in the lumbar region and the ending of the spinal cord at the L1 level, isolated fractures of the lower lumbar spine rarely injure the spinal cord or result in neurologic injury. The **sacrum** and **coccyx** form the lower portion of the spinal column. The vertebral foramina of the sacrum together form the sacral canal that contains the nerve roots of the lumbar, sacral, and coccygeal spinal nerves and the filum terminale. The coccyx, which articulates with the sacrum, consists of four vertebrae fused together. When neurologic injuries occur, they are usually complete cauda equina lesions or isolated nerve root deficits. **Sacral fractures that involve the central sacral canal can produce bowel or bladder dysfunction.**

FRACTURE STABILITY

Much has been written about determining whether or not a particular injury is "stable." Spinal stability is defined as the ability of the spine to limit patterns of displacement under physiologic loads so as not to damage or irritate the spinal cord or nerve roots. Several paradigms have been created, including the Denis column system, which splits the spinal column into anterior, middle, and posterior elements.[13] A spine injury is considered unstable if at least two columns of a particular region are involved. Although this schema and other instability scoring systems have been published,[14-17] determining spinal stability after an acute injury in the ED is particularly difficult. This is because these injuries often occur in the setting of polytrauma, altered mental status, and severe pain, which may result in suboptimal initial imaging. In addition, many EDs lack quick access to emergent MRI to evaluate the spinal ligaments. Therefore, **assume any spine fracture is unstable, and maintain appropriate precautions until expert consultation can be obtained from a spine surgeon**.

SPINAL CORD INJURIES

Damage to the spinal cord is the result of two types of injury. First is the **primary injury** from mechanical forces that directly traumatize the spinal cord and vasculature. This insult sets into motion a series of vascular and chemical processes that lead to **secondary injury**.[18] The initial phase is characterized by hemorrhage into the cord and formation of edema at the injured site and surrounding region. Local spinal cord ischemia ensues secondary to vasospasm and thrombosis of the small arterioles within the gray and white matter. Extension of edema may further compromise blood flow and increase ischemia. A later tissue degeneration phase begins within hours of injury. This is associated with neural membrane dysfunction, driven by a pathologic excitation of sodium ion channels, an influx of calcium ions, and the release of glutamine.[19] Cell death ensues from a combination of mechanisms including electrolyte imbalances, cell edema, and the formation and release of oxidative substances.[19]

SPINAL CORD LESIONS

The severity of spinal cord injury determines the prognosis for recovery of function, so it is important to distinguish between complete and incomplete spinal cord injuries. The American Spinal Injury Association defines a **complete neurologic lesion as the absence of sensory and motor function below the level of injury**. This includes loss of function to the level of the lowest sacral segment. In contrast, **a lesion is incomplete if sensory, motor, or both functions are partially present below the neurologic level of injury**. This may consist only of sacral sensation at the anal mucocutaneous junction or voluntary contraction of the external anal sphincter upon digital examination. Complete lesions have a minimal chance of functional motor recovery. Patients with incomplete lesions are expected to have at least some degree of recovery. The differentiation between complete and incomplete spinal cord damage may be complicated by the presence of **spinal shock**. Patients in spinal shock lose all reflex activities below the area of injury, and lesions cannot be deemed truly complete until spinal shock has resolved.

A number of descending and ascending tracts have been identified in the spinal cord (**Figure 258-2**). The three most important of these in terms of neuroanatomic localization of cord lesions are the **corticospinal tracts**, **spinothalamic tracts**, and **dorsal (posterior) columns**.

The **corticospinal tract** is a descending motor pathway. Its fibers originate from the cerebral cortex through the internal capsule and the middle of the crus cerebri. The tract then breaks up into bundles in the pons and finally collects into a discrete bundle, forming the pyramid of the medulla. In the lower medulla, approximately 90% of the fibers cross to the side opposite that of their origin and descend through the spinal cord as the lateral corticospinal tract. These fibers synapse on lower motor neurons in the spinal cord. The 10% of corticospinal fibers that do not cross in the medulla descend in the anterior funiculus of the cervical and upper thoracic cord levels as the ventral corticospinal tract. **Damage to the corticospinal tract neurons (upper motor neurons) in the spinal cord results in ipsilateral clinical findings such as muscle weakness, spasticity, increased deep tendon reflexes, and a Babinski's sign**.

The two major ascending pathways that transmit sensory information are the spinothalamic tracts and the dorsal columns. The **spinothalamic tracts** transmit pain and temperature sensation. As the axons of the first neurons enter the spinal cord, most ascend one or two levels before entering the dorsal gray matter of the spinal cord, where they synapse with the second neuron of the spinothalamic tract. The second neuron immediately crosses the midline in the anterior commissure of the spinal cord and ascends in the anterolateral funiculus as the lateral spinothalamic tract. **Therefore, when the spinothalamic tract is damaged, the patient experiences loss of pain and temperature sensation in the contralateral half of the body.** The (pain and temperature) sensory loss begins one or two segments below the level of the damage.

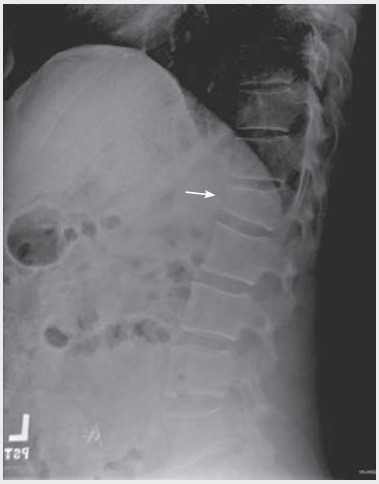
The **dorsal columns** transmit vibration and proprioceptive information. Neurons enter the spinal cord proximal to pain and temperature

TABLE 258-1 Major Spinal Column Injuries

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
Flexion	Anterior subluxation (hyperflexion sprain) (usually stable, but depends on the integrity of posterior ligaments)	Cervical	 [Photo contributors: Mark Silverberg, MD/Steven Pulitzer, MD. (Reproduced with permission from Shah BR, Lucchesi M, Amodio J (Eds): *Atlas of Pediatric Emergency Medicine*, 2ed, © 2013, McGraw-Hill Education, New York, NY. Figure 20-57.]	Anterior subluxation produces ligamentous failure and may have no associated fractures. Plain films can be normal. However, significant ligamentous injury can display anterior soft tissue swelling, a widening of the spinous processes at the level of injury ("fanning"), posterior widening of the intervertebral space, and cervical disk space alignment ≥11 degrees between adjacent spaces.
	Atlantoaxial dislocation (unstable)	Cervical	 [Used with permission of Jake Block, MD.]	Transverse ligament **rupture** without an associated fracture can occur in older patients from a direct blow to the occiput. Radiographic diagnosis relies on measuring the *predental space*, which is the space between the posterior aspect of the anterior arch of C1 and the anterior border of the odontoid. A predental space of >3 mm on a lateral radiograph (2 mm for CT images) implies damage to the transverse ligament; >5 mm implies rupture of the transverse ligament.
	Bilateral interfacetal dislocation (unstable)	Cervical		Bilateral interfacetal dislocation (*locked facets*) occurs when the articular masses of one vertebra dislocate anteriorly and superiorly from the articular surfaces of the adjacent vertebra below. Disruption of all ligamentous structures occurs. On radiographs, the vertebral body is dislocated anteriorly ≥50% of its width. These injuries usually present with neurologic deficits due to compromise of the intervertebral foramen, unless the dislocation is only partial (*perched facets*).

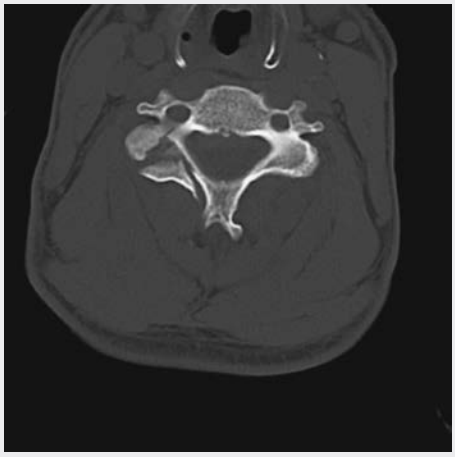
(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
	Simple wedge (compression) fracture (usually stable)	Cervical; TL	 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (Eds): The Atlas of Emergency Radiology. McGraw-Hill, Inc., 2013. Fig. 11-22 Part A.]	Most common thoracic fracture (52%).[5] A vertebral wedge fracture typically involves a fracture of the superior end plate of the vertebral body while sparing the inferior end plate. An isolated simple wedge fracture is stable, but the presence of significant posterior ligamentous disruption can make the injury unstable. A simple wedge fracture is differentiated from a burst fracture by the absence of a vertical fracture of the vertebral body and lack of bulging of the posterior vertebral border.
	Spinous process avulsion fracture (stable)	Cervical	 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (Eds): The Atlas of Emergency Radiology. McGraw-Hill, Inc., 2013. Fig. 11-10 Part A.]	This is a spinous process avulsion most commonly seen in the lower cervical and upper thoracic spine. When a single avulsion is present in this region, it is often called a "clay-shoveler" fracture. It is thought to be caused by strong muscle contractions pulling on the bone via the ligamentous complex. In isolation, it is generally not associated with neurologic compromise.
	Flexion teardrop fracture (highly unstable)	Cervical	 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (Eds): The Atlas of Emergency Radiology. McGraw-Hill, Inc., 2013. Fig. 11-1.]	Extreme hyperflexion causes complete disruption of the spinal ligaments at the level of injury. The "teardrop" is the anteroinferior portion of the vertebral body that is separated and displaced from the vertebral body by the anterior spinal ligament. "Fanning" of the spinous processes may be present, with or without fracture. A sagittal fracture through the vertebral body may be seen on CT. Anterior spinal cord syndrome is associated with this injury

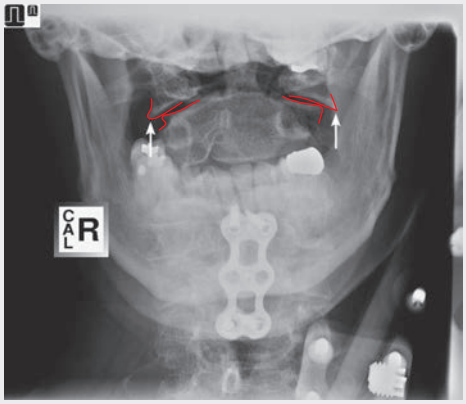
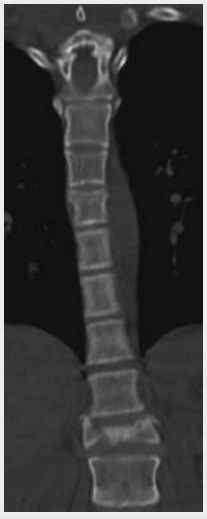
(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
Flexion-rotation	Unilateral facet dislocation (stable unless associated with an articular mass fracture)	Cervical	 [Reproduced with permission from Simon RR, Sherman Scott C (eds): *Emergency Orthopedics*, 6th ed. McGraw-Hill, Inc., 2011. Fig 9-21B.]	A unilateral facet dislocation occurs when the articular mass and inferior facet on one side of the vertebra are anteriorly dislocated. On a lateral radiograph, the involved vertebral body will be displaced <50% of its width. On the anterior view, the spinous process at the level of the rotation will be pointing toward the side that is dislocated.
	Fracture of lateral mass (can be unstable)	Cervical	 Comminuted fracture of the lateral mass of C4 extending into the right lamina.	Typically presents with severe neck pain and sometimes radicular symptoms. May be associated with Brown-Séquard syndrome or vertebral artery injury; therefore, some experts feel that magnetic resonance angiography should be done in all patients with this lesion.[6] A *pillar fracture* is a type of lateral mass fracture that consists of an isolated vertical or oblique fracture through the lateral mass. The adjacent lamina and pedicle remain intact. The fractured articular mass is displaced posteriorly and may be visible as a double outline on the lateral radiograph.
Flexion-distraction	Anterior compression with associated transverse fracture through vertebral body (unstable)	TL	 *Arrow* points to splaying of the posterior elements. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig 11-27C.]	These injuries are associated with seatbelt injuries, especially when lap belts alone are used. Radiographic findings include posterior vertebral wall fracture, increased height of the posterior vertebra, and "fanning" of the spinous processes. The **Chance fracture** variant presents with minor anterior vertebral compression and significant distraction of the middle and posterior ligamentous structure. It often occurs from T11 to L2 (TL transition zone). These injuries are often misdiagnosed as an anterior compression fracture. They may require CT to visualize and are often associated with intra-abdominal injuries.

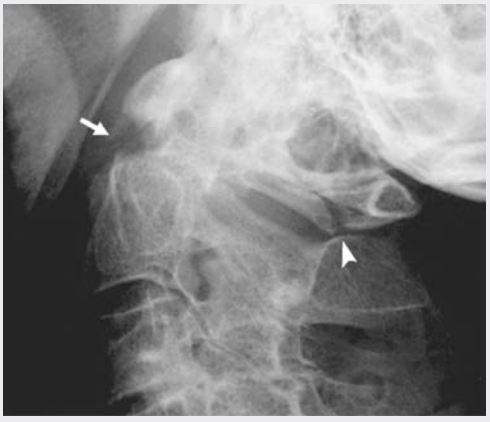
(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
Vertical compression	Jefferson burst fracture of atlas (potentially unstable)	Cervical	 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig 11-13.]	Vertical compression forces the occipital condyles downward and produces a burst fracture by driving the lateral masses of C1 apart. This is best seen as outward displacement of the lateral masses on the open-mouth odontoid radiograph or on CT. If displacement of both lateral masses (measured as offset from the superior corner of the C2 vertebral body on each side) is >7 mm when added together, rupture of the transverse ligament is likely, and the spine is unstable.
	Burst fracture (unstable)	Cervical; TL	 	A burst fracture occurs when a vertebra is crushed by an axial load, causing fragments to displace in all directions. The lateral radiograph may show an obvious fracture of the end plates, but sometimes all that is seen is a bowing or disruption of the posterior cortex of the affected vertebra. The anterior radiographic view may show a vertical fracture through the vertebral body and widening of the interpedicular distance. The burst fracture is usually obvious on CT. The spinal cord may be injured if a retropulsed fragment enters the spinal canal.

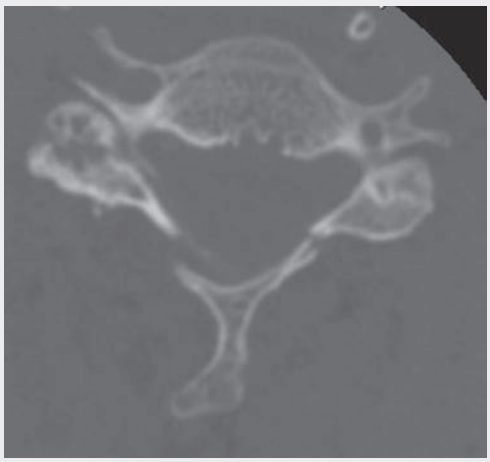
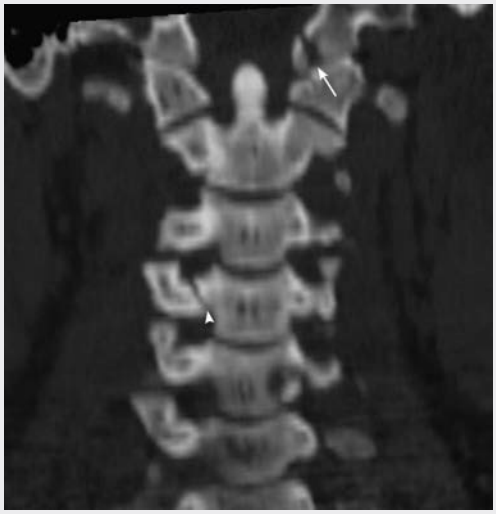
(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
Extension	Hyperextension dislocation (unstable)	Cervical	 [Reproduced with permission from Schwartz DT (ed): *Emergency Radiology: Case Studies*. McGraw-Hill, Inc., 2008. Sect V: Cervical Spine Radiology; Fig 6.]	Extreme hyperextension can cause a complete tear of the anterior longitudinal ligament and intervertebral disk, with disruption of the posterior ligamentous complex. On the lateral radiographic view, the vertebrae may appear normal if the dislocation spontaneously reduces or if the injury is masked by a cervical immobilization collar. **Prevertebral soft tissue swelling may be the only radiographic finding present**. Anterior disk space widening or fracture of the anteroinferior end plate of the vertebral body may occur. Patients usually present with a central cord syndrome.
	Hyperextension teardrop fracture or extension corner avulsion fracture (unstable in extension)	Cervical		Hyperextension may cause the anterior longitudinal ligament to avulse a fragment off the anteroinferior corner of the vertebral body. The height of the avulsed fragment usually exceeds its width. This fracture is more common in older patients with osteoporosis.
	Fracture of posterior arch of atlas (stable)	Cervical	 Fracture of posterior arch of C1. [Reproduced with permission from Galli, et al: *Emergency Orthopedics: The Spine*. New York, NY: McGraw-Hill, 1989.]	Fracture occurs from wedging of the posterior arch between the occipital bone and the C2 vertebra. A CT is indicated to rule out an associated Jefferson fracture or a dens fracture.

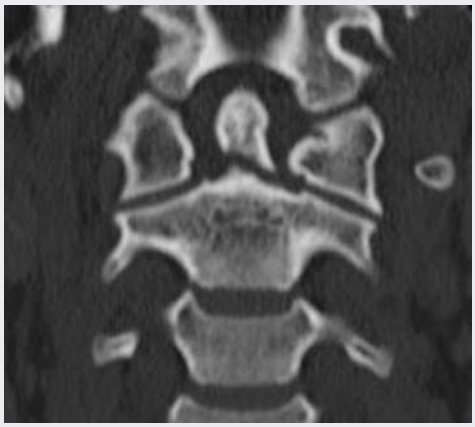
(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
	Laminar fracture (usually stable)	Cervical	 [Reproduced with permission from Simon RR and Sherman SC (EDS). *Emergency Orthopedics*, 6 ed. McGraw-Hill, Inc., 2011. Fig. 9-26B.]	Laminar fractures may be associated with spinous process fractures. They may not be evident on plain radiographs and usually require CT for diagnosis.
	Traumatic spondylolisthesis (hangman's fracture) (unstable)	Cervical		The hangman's fracture is a fracture of both pedicles of C2, with the anterior displacement of C2 on C3. This was associated with the neck hyperextension from judicial hangings, where the noose knot is placed under the subject's chin and snaps the head backward. Suicidal hangings do not usually cause extreme hyperextension and are not associated with the hangman's fracture. Because the spinal canal at the level of C2 is large, a hangman's fracture does not cause neurologic injury.
Injuries caused by a combination of mechanisms or poorly understood mechanisms	Occipital condyle fractures (usually stable)	Cervical	 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig. 11-11B.]	Occipital condyle fractures are rarely visible on plain radiographs and usually require CT imaging for detection. Presentation is rather variable due to proximity of multiple neurovascular structures.[7] Neurologic impairment is common and usually involves lower cranial nerve deficits and/or limb weakness.

(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
	Atlanto-occipital dissociation (AOD) (highly unstable)	Cervical	 [Photo contributors: Konstantinos Agoritsas, MD/Steven Pulitzer, MD. Reproduced with permission from Shah BR, Lucchesi M, Amodio J (eds): *Atlas of Pediatric Emergency Medicine*, 2nd ed. © 2013, McGraw-Hill Education, New York, NY. Fig 20-52.]	Secondary to high-energy impact. Historically, strongly associated with mortality[8]; however, modern patients may survive due to better prehospital care/transport. The classic presentation is paralysis of upper extremities with lack of lower extremity paralysis or weakness (cruciate paralysis).[9] However, presentation can be variable with a common presentation being lower cranial nerve deficits. CT may be required for detection. In radiographs in the normal patient, the distance between the basion and the superior cortex of the dens (basion-dental interval [BDI]) should be ≤10 mm in adults (≤8.5 mm on CT). In addition, the distance from the basion to the posterior border of the body of C2 (basion-atlantal interval [BAI]) should be ≤12 mm anterior displacement or ≤4 mm posterior displacement on a lateral radiograph. If there are abnormalities in both the BDI and BAI, this strongly suggests the existence of AOD.[10]
	Odontoid (dens) fractures (type II and III are unstable)	Cervical	 Type 1 odontoid fracture. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig 11-18.]  Type 2 odontoid fracture. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig. 11-19C.]	Frequently involves other injuries to the cervical spine and multisystem trauma. Conscious patients will usually describe immediate and severe high cervical pain with muscle spasm. The pain may radiate to the occiput. Neurologic injury is present in 18% to 25% of cases with odontoid fractures, ranging from minimal sensory or motor loss to quadriplegia. Odontoid fractures are classified according to the level of injury. CT can miss odontoid fractures if the fracture line is aligned with the cut of the CT (*en face*).

(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
			 Type 3 odontoid fracture. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig 11-20C.]	
	Translational fracture-dislocation (unstable)	TL	 T10-T11 fracture-dislocation.	This is a high-energy disruption of all three columns of spine and is readily apparent both on radiographs and CT. Patients commonly present with severe neurologic findings. These fractures are most often unstable; however, in the absence of destabilizing rib cage fractures, lesions above T7 can be stable.

(*Continued*)

TABLE 258-1 Major Spinal Column Injuries (*Continued*)

Mechanism of Injury	Injury	Spinal Column Regions Typically Affected	Image	Notes
Sacrum and coccyx fractures	Sacral fracture		 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig. 8-16A.]	Usually associated with pelvic fracture(s). Transverse fractures through the body can injure the cauda equina. Longitudinal fractures can cause radiculopathies. Central sacral fracture can present with bowel/bladder incontinence.
	Coccyx fracture		 [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig 8-24.]	Coccygeal injuries are usually associated with a direct fall onto the buttocks, with resultant coccyx pain exacerbated by sitting or straining. Localized tenderness can be elicited with coccyx palpation during a rectal exam, but this is not required for diagnosis. Imaging is not needed to diagnose coccygeal fractures. Treatment is symptomatic with analgesics and use of a rubber doughnut pillow.

Abbreviations: C1 = first cervical vertebra; C2 = second cervical vertebra; C3 = third cervical vertebra; C5 = fifth cervical vertebra; C7 = seventh cervical vertebra; T1 = first thoracic vertebra; T7 = seventh thoracic vertebra; T12 = 12th thoracic vertebra; TL = thoracolumbar.

neurons. They differ from pain and temperature neurons in that they do not immediately synapse in the spinal cord. Instead, these axons enter the ipsilateral dorsal column and do not synapse until they reach the gracile or cuneate nuclei of the medulla. From these nuclei, fibers cross the midline and ascend in the medial lemniscus to the thalamus. **Injury to one side of the dorsal columns will result in ipsilateral loss of vibration and position sense**. The sensory loss begins at the level of the lesion. Light touch is transmitted through both the spinothalamic tracts and the dorsal columns. Therefore, **light touch is not completely lost unless there is damage to both the spinothalamic tracts and the dorsal columns.**

Each spinal nerve is named for its adjacent vertebral body (**Figure 258-3**). In the cervical region, there is an additional pair of spinal nerve roots compared to the number of vertebral bodies. The first seven spinal nerves are named for the first seven cervical vertebrae, each exiting through the intervertebral foramen above its corresponding vertebral body. The spinal nerve exiting below C7, however, is referred to as the C8 spinal nerve, although no eighth cervical vertebra exists. All subsequent nerve roots, beginning with T1, exit below the vertebral body for which they are named.

During fetal development, the downward growth of the vertebral column is greater than that of the spinal cord. Because the adult spinal cord ends as the conus medullaris at the level of the lower border of the first lumbar vertebra, the lumbar and sacral nerve roots must continue inferiorly below the termination of the spinal cord to exit from their respective intervertebral foramina. These nerve roots form the **cauda equina**. A potential consequence of this arrangement is that injury to

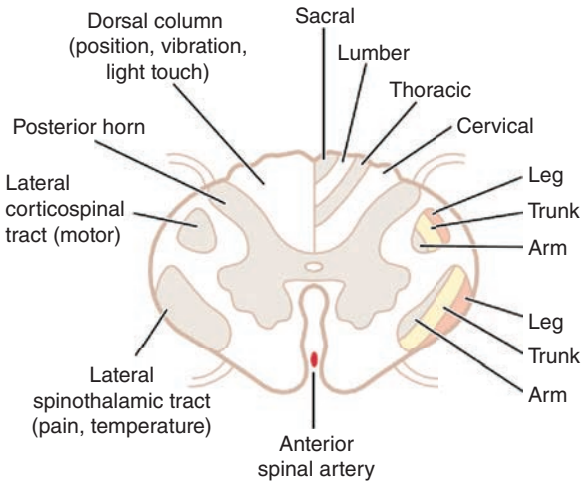


FIGURE 258-2. The anatomy of a cross section of cervical spinal cord. [Reproduced with permission from Simon RR, Sherman SC (eds): *Emergency Orthopedics*, 6th ed. McGraw-Hill, Inc., 2011. Fig 9-5.]

a single lower vertebra can involve multiple nerve roots in the cauda equina. For example, an injury at the L3 vertebra can involve the L3 nerve root as well as the lower nerve roots that are progressing to a level caudal to the L3 vertebra.

PREHOSPITAL CARE

The prehospital treatment of patients with spinal injury involves recognition of patients at risk, appropriate immobilization, and triage to an appropriate facility (see Chapter 1, "Emergency Medical Services" and Chapter 2, "Prehospital Equipment"). Presume that patients with an appropriate traumatic mechanism who have complaints of neck or back pain, tenderness on prehospital exam, neurologic complaints, significant injury above the clavicles, or altered sensorium that precludes accurate evaluation of the spine to have a spinal cord injury, and take appropriate spinal precautions. Transport of these patients to a center that is capable of rapid diagnostics and therapeutics is important to optimize outcome following spinal injury.

Prehospital care for spinal injuries traditionally involves immobilization of the entire spine at the scene with a rigid cervical collar (or similar devices) plus a long backboard. However, there is little evidence that cervical collars and/or long spine boards reduce neurologic injury, spinal instability, or mortality.[20,21] In fact, cervical collars and long backboards can induce complications such as pressure sores,[22,23] patient discomfort,[24] and respiratory compromise.[25] In light of these data, some experts have recommended transporting the patient on a gurney with a scoop stretcher[26] or other soft, padded devices[27] to avoid the rigid spine board. In addition, based on data suggesting extrication cervical collars are associated with pressure ulcers,[28] indentation marks, pain, and increased intracranial pressure,[29] some authors have proposed early replacement of the extrication cervical collar,[30] or even abandoning the routine use of cervical collars.[31] The most recent position statement by

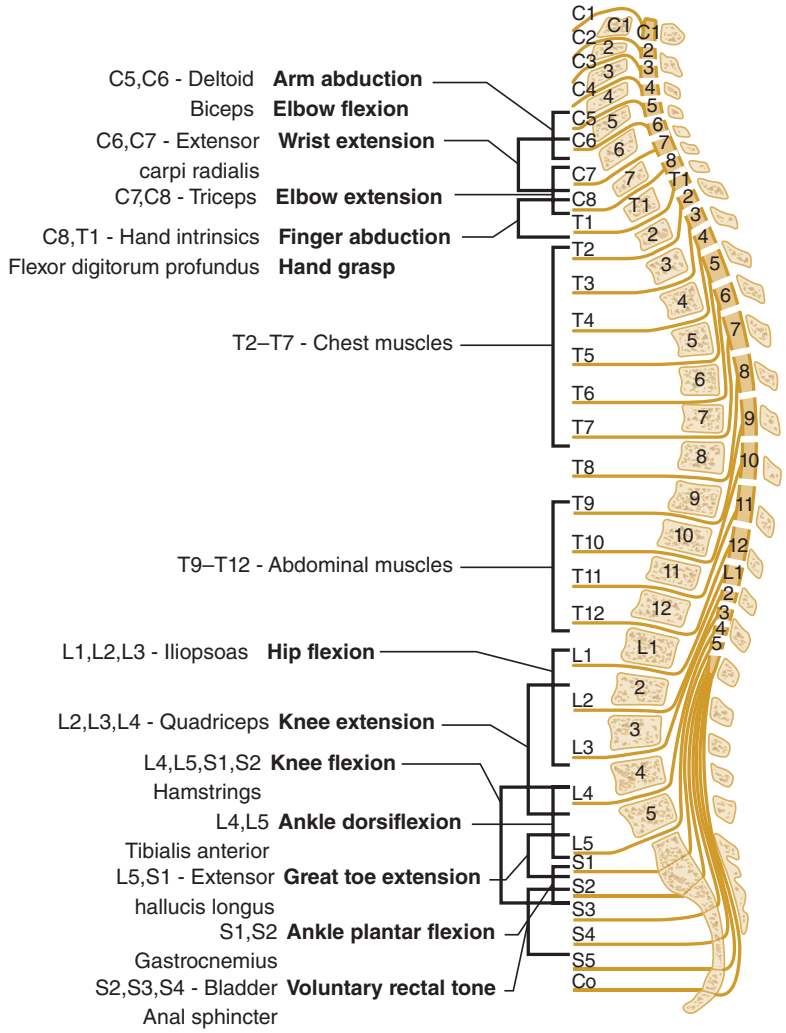


FIGURE 258-3. Spinal cord level. The spinal cord level of injury can be delineated by physical examination, including a detailed neurologic examination.

the National Association of EMS Physicians and the American College of Surgeons Committee on Trauma suggested utilization of backboards should be "judicious" and used in such a way that "benefits outweigh the risks"; however, they continued to recommend the use of rigid cervical collars.[32] A consensus document by the Faculty of Pre-hospital Care went further, stating that the long board should only be used as an extrication device and not during transport.[33] Furthermore, they strongly argued for "selective immobilization" based on clinical factors (e.g., level of consciousness) and that manual in-line stabilization may be more appropriate than cervical collars in the setting of airway compromise, increased intracranial pressure, or patient combativeness and in children.[33] However, some authors have concluded that these position statements do not go far enough given that there is little evidence to show benefit compared with ample data that demonstrate harm.[34] Thus, this area remains controversial, with all sides calling for more randomized controlled data to settle these issues. In contrast, expert consensus is that **spinal immobilization is NOT recommended for fully conscious, neurologically intact patients with isolated *penetrating* neck injury** because collars can delay resuscitation and obscure neck injuries.[32,33]

INITIAL ED STABILIZATION

AIRWAY

ED evaluation of the patient with potential spinal injury should not differ substantially from that of any patient with multiple injuries, with the first priority being the airway. **The higher the level of spinal injury, the more likely is the need for early airway intervention.** For example, unstable spine lesions above C3 can cause immediate respiratory arrest, and lesions affecting C3-C5 can affect the phrenic nerve and diaphragm function. For this reason, some experts recommend that **any patient with an injury at C5 or above should have the airway secured by endotracheal intubation**. Delayed respiratory compromise can occur if spinal cord edema from more caudal lesions progresses rostrally to cause phrenic nerve paralysis. Many patients can initially support ventilatory function using intercostal muscles or abdominal breathing, but they eventually tire and subsequently develop respiratory failure. Therefore, be vigilant for respiratory compromise in patients with high cervical injuries. If safety allows, perform a brief focused neurologic assessment before sedation and intubation. Given the unclear benefit of cervical collars, **do not hesitate to substitute manual in-line stabilization if the collar is compromising the airway**.

Maintain manual in-line spinal stabilization while intubating, because human cadaver studies demonstrate less cervical motion and better glottis visualization with in-line stabilization than with cervical collars in place,[35] and movement of an unstable cervical spine may produce or worsen spinal cord injury. Videolaryngoscopes improve visualization in cervical immobilized patients and may reduce failed intubations,[36,37] but manual in-line stabilization is still recommended to minimize cervical motion.[38]

HYPOTENSION

Hypotension in patients with spinal cord injuries may be due to neurogenic shock, blood loss, cardiac injury, tension pneumothorax, or other injuries. Although hypotension and relative bradycardia are classic signs of neurogenic shock, bradycardia can also be associated with intraperitoneal bleeding or prior medication with calcium channel blockers or β-blockers. In one study,[39] 74% of hypotensive patients with penetrating spinal cord injury had major blood loss causing hypotension. Therefore, presume **blood loss as the cause of hypotension in spinal injury patients until proven otherwise.** Hypotension is initially treated with IV crystalloid or blood as appropriate. (See Chapter 254, "Trauma in Adults.")

SPINE PRECAUTIONS IN THE ED

Long spine boards are associated with pressure sores, so remove them as soon as possible if the patient arrives with them. Logrolling is the traditional method for board removal. In cadaver studies, logrolling has been shown to generate significantly more spine motion at injured vertebrae than alternative maneuver and transfer techniques[40]; however, there is a paucity of published data demonstrating negative clinical outcomes from logrolling.[41] Nevertheless, some experts recommend the "6+ lift and slide maneuver" because it produces less spine motion than logrolling.[42] The 6+ maneuver consists first of unstrapping the patient from the board. Next, one person maintains in-line stabilization at the head, while six others positioned at the chest, pelvis, and lower extremity levels lift the patient as a unit 10 to 20 cm above the board. Another person slides the board out from under the patient, and the patient is then lowered to the bed, maintaining spinal alignment. Disadvantages are the need for many staff members to perform this maneuver and inability to visualize the patient's back.[43]

Hard cervical collars are associated with patient discomfort and pressure sores of the neck.[44] Therefore, promptly clear the cervical spine if possible (see "Clinical Decision Rules in Cervical Spine Imaging" and "Cervical Spine Imaging" below). Do not overtighten the cervical collar on head-injured patients, because jugular venous compression can raise intracranial pressure,[29,45] although Stifneck® and Miami J® collars may be better than other rigid collars in this regard.[46] Avoid physically fighting with an agitated patient in a forcible attempt to place a cervical collar, as overly aggressive attempts to restrain a patient may possibly cause or exacerbate a cervical injury.

CLINICAL FEATURES

HISTORY

If the patient is able to give a history, focus on key historical points as they pertain to spine injury. Specifically, seek the presence or absence of the historical elements included in imaging decision rules (see Tables 258 4-7[47–50]). Obtain an accurate history regarding the mechanism of injury. Evaluate for symptoms of midline spine pain, painful distracting injury, paresthesias, loss of function, change in mental status (including loss of consciousness), or other neurologic symptoms (especially priapism or urinary or fecal incontinence). **Pay particular attention to any symptoms indicating present or impending respiratory compromise, including dyspnea, palpitations, abdominal breathing, and anxiety, which may indicate a high cervical spine injury**.

PHYSICAL EXAMINATION

Once the patient is stabilized and other life-threatening injuries have been excluded or treated, perform a detailed neurologic assessment. An appropriately detailed initial neurologic examination is important to allow for comparison later should the patient deteriorate. Assess the patient's mental status and note any clinical evidence of intoxication. Focus the physical examination on delineating the level of the spinal cord injury (Figure 258-3). Document the presence or absence of midline neck or back tenderness. Test motor function for muscle groups (**Table 258-2**). Determine the level of sensory loss (**Figure 258-4**), and investigate proprioception or vibratory function to examine posterior column function. Test for "saddle anesthesia," which is a sensory deficit in the region of the buttocks, perineum, and inner aspect of the thighs. Test deep tendon reflexes along with **anogenital reflexes because "sacral sparing" with preservation of anogenital reflexes denotes an incomplete spinal cord level, even if the patient has complete sensory and motor loss.** To test the bulbocavernosus reflex, squeeze the penis to determine whether the anal sphincter simultaneously contracts. Document anal sphincter tone and sensation around the anus. An "anal

TABLE 258-2 Motor Grading System

Grade	Movement
0	No active contraction
1	Trace visible or palpable contraction
2	Movement with gravity eliminated
3	Movement against gravity
4	Movement against gravity plus resistance
5	Normal power

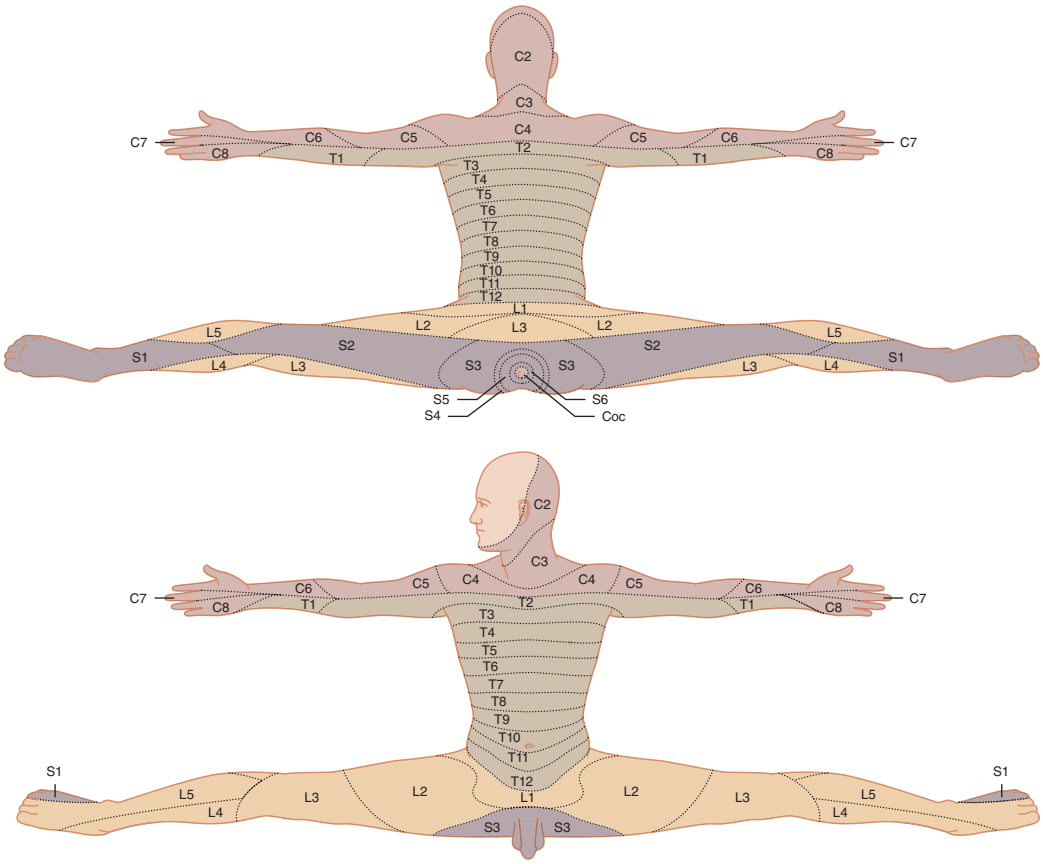


FIGURE 258-4. Dermatomes for sensory examination.

wink reflex" (contraction of the anal musculature when the perianal region is stimulated with a pin) indicates some sacral sparing. Test the cremasteric reflex by stroking the medial thigh with a blunt instrument. If the scrotum rises, some spinal cord integrity exists. Conversely, priapism implies a complete spinal cord injury. In 2015, the American Spinal Injury Association published a revised version of the International Standards for Neurological Classification of Spinal Cord Injury.[51] This scoring system is used by spine surgeons to document their initial examination and has prognostic value[52]; however, the scale is rather lengthy and is not practical for ED initial assessment.

INCOMPLETE SPINAL CORD SYNDROMES

There are three major incomplete spinal cord syndromes identified by predictable physical examination findings, although overlap in findings may occur (**Table 258-3**).

ANTERIOR CORD SYNDROME

The anterior cord syndrome results from damage to the corticospinal and spinothalamic pathways, with preservation of posterior column function. **This is manifested by loss of motor function and pain and temperature sensation distal to the lesion. Only vibration, position, and tactile sensation are preserved.** This syndrome may occur following direct injury to the anterior spinal cord. Flexion of the cervical spine may result in cord contusion or bone injury with secondary cord injury. Alternatively, thrombosis of the anterior spinal artery can cause ischemic injury to the anterior cord. Anterior cord injury can also be produced by an extrinsic mass that is amenable to surgical decompression. The overall prognosis for recovery of function is poor.

CENTRAL CORD SYNDROME

The central cord syndrome is usually seen in older patients with preexisting cervical spondylosis who sustain a hyperextension injury. As named, this injury preferentially involves the central portion of the cord more than the peripheral. The centrally located fibers of the corticospinal and spinothalamic tracts are affected. The neural tracts providing function to the upper extremities are most medial in position compared with the thoracic, lower extremity, and sacral fibers that have a more lateral distribution. Clinically, **patients with a central cord syndrome present with decreased strength and, to a lesser degree, decreased pain and temperature sensation, more in the upper than the lower extremities**. Vibration and position sensation are usually preserved.

TABLE 258-3 Three Major Incomplete Spinal Cord Syndromes

Syndrome	Mechanisms	Symptoms	General Prognosis*
Anterior cord	Direct anterior cord compression Flexion of cervical spine	Complete paralysis below the lesion with loss of pain and temperature sensation	Poor
	Thrombosis of anterior spinal artery	Preservation of proprioception and vibratory function	
Central cord	Hyperextension injuries Disruption of blood flow to the spinal cord Cervical spinal stenosis	Quadriparesis—greater in the upper extremities than the lower extremities. Some loss of pain and temperature sensation, also greater in the upper extremities	Good
Brown-Séquard	Transverse hemisection of the spinal cord Unilateral cord compression	Ipsilateral spastic paresis, loss of proprioception and vibratory sensation, and contralateral loss of pain and temperature sensation	Good

*Outcome improves when the effects of secondary injury are prevented or reversed.

Spastic paraparesis or spastic quadriparesis can also be seen. The majority will have bowel and bladder control, although this may be impaired in the more severe cases.

BROWN-SÉQUARD SYNDROME

The Brown-Séquard syndrome results from hemisection of the cord. It is manifested by **ipsilateral loss of motor function, proprioception, and vibratory sensation, and contralateral loss of pain and temperature sensation**. The most common cause of this syndrome is penetrating injury.[53,54] It can also be caused by lateral cord compression secondary to disk protrusion, hematomas, spine fractures, infections, spinal cord infarctions, multiple sclerosis, or tumors.

CAUDA EQUINA SYNDROME

Cauda equina syndrome is not a true spinal cord syndrome because the cauda equina is composed entirely of lumbar, sacral, and coccygeal nerve roots; therefore, injuries to this region produce peripheral nerve injuries. **Symptoms and signs may include bowel and/or bladder dysfunction, decreased anal sphincter tone, "saddle anesthesia" (sensory deficit over the perineum, buttocks, and inner thighs), variable motor and sensory loss in the lower extremities, decreased lower extremity reflexes, and sciatica.** Bowel or bladder incontinence is not a universal finding. **Anal sphincter tone can be spared**,[55] and the accuracy of a digital rectal exam to detect decreased anal sphincter tone has been questioned.[56] In addition, if the patient presents acutely, the patient's **bladder may not yet be full enough to cause overflow urinary incontinence**. Careful history and physical examination, including identification of saddle anesthesia,[57] are helpful to suggest the diagnosis, **but no one symptom or sign has 100% predictive value for this entity**.[58,59] Therefore, perform an emergent MRI of the lumbosacral spinal cord if clinical suspicion warrants. See the section "Epidural Compression Syndrome" in Chapter 279, "Neck and Back Pain," for further discussion of cauda equina syndrome.

NEUROGENIC SHOCK

Neurogenic shock is a type of distributive shock that can occur with CNS or spinal cord injury that probably occurs in less than 20% of spinal cord–injured patients.[60,61] Loss of peripheral sympathetic innervation results in extreme vasodilatation secondary to loss of sympathetic arterial tone. This causes blood pooling in the distal circulation with resultant hypotension. If the T1 through T4 cord levels are compromised, loss of sympathetic innervation to the heart leaves unopposed vagal parasympathetic cardiac innervation. This results in bradycardia or an absence of reflex tachycardia. In general, **patients with neurogenic shock are warm, peripherally vasodilated, and hypotensive with a relative bradycardia**. Patients tend to tolerate hypotension relatively well, because peripheral oxygen delivery is presumably normal. Loss of sympathetic tone and subsequent inability to redirect blood from the periphery to the core may cause excessive heat loss and hypothermia.

The diagnosis of neurogenic shock is one of exclusion. Certain clues, such as bradycardia and warm, dry skin, may be evident, but **hypotension in the trauma patient can never be presumed to be caused by neurogenic shock until other possible sources of hypotension are excluded**.[39]

SPINAL SHOCK

Spinal shock is **not** neurogenic shock; the two terms have very different meanings and are not interchangeable. **Spinal shock is the temporary loss or depression of spinal reflex activity that occurs below a complete or incomplete spinal cord injury.** The typical presentation involves flaccidity, loss of reflexes, and loss of voluntary movement.[62] The lower the level of the spinal cord injury, the more likely it is that all distal reflexes will be absent. Loss of neurologic function that occurs with spinal shock can cause an incomplete spinal cord injury to mimic a complete cord injury. Therefore, cord lesions cannot be called complete until spinal shock has resolved. The delayed plantar and bulbocavernosus reflexes are among the first to return as spinal shock resolves.[63] The duration of spinal shock is variable; it generally lasts for days to weeks but can persist for up to 6 months.[64]

DIAGNOSIS

Although spinal column and spinal cord injuries can sometimes be diagnosed clinically, diagnostic imaging is necessary to confirm the diagnosis and direct definitive care. However, judicious use of imaging is desirable to avoid unnecessary costs and ionizing radiation exposure to patients. Therefore, the challenge is identifying the appropriate patients to image and selecting the appropriate imaging modality.

CLINICAL DECISION RULES IN CERVICAL SPINE IMAGING

In some cases, it is obvious who needs cervical spine imaging. For example, patients with head or neck trauma who are not fully alert (Glasgow Coma Scale score of <15) should undergo imaging of their cervical spine because the frequency of cervical spine injury in association with traumatic brain injury ranges from 1.7% to 8%.[65] However, in less obvious cases, the decision to perform imaging is not quite so clear cut.

An unstructured clinical exam is **not** adequately sensitive for the detection of cervical spine injuries,[66] so guidelines can assist clinical judgment in deciding whom to image. In alert, stable, adult trauma patients who have no neurologic deficits (i.e., low-risk trauma patients), two major clinical decision rules have been defined to avoid unnecessary radiography.

The first decision rule was derived by the **National Emergency X-Radiography Utilization Study (NEXUS)**, which determined that plain cervical spine **imaging can be safely avoided in patients who have all five clinical criteria** (**Table 258-4**) (See Video: NEXUS Criteria).[47] In the study population of 34,069 patients, the NEXUS criteria were 99.6% sensitive (95% confidence interval [CI], 98.6% to 100%) for detecting prospectively defined clinically significant cervical spine injuries, but only 12.9% specific (95% CI, 12.8% to 13.0%), with a negative predictive value of 99.9% (95% CI, 99.8% to 100%).

The original NEXUS trial excluded patients >60 years old, but a post hoc analysis of the NEXUS data set showed the criteria to be 100% sensitive (95% CI, 97.1% to 100%) and 14.7% specific (95% CI, 14.6% to 14.7%) for clinically significant injuries in 2943 patients ≥65 years of age.[67] In a retrospective Australian trial (n = 4035) that investigated NEXUS's performance in patients ≥65 years of age, NEXUS was 94.8% sensitive (95.5% on a one-way sensitivity analysis) for cervical spine injuries detected on a 64-slice multidetector CT.[68] However, this trial contained several sources of potential bias (i.e., single center, undocumented NEXUS data in 14.1% of those with cervical spine fractures). This study also did not clarify whether the fractures detected on CT were clinically significant or if any intervention was required. Two previous prospective studies have also challenged the use of NEXUS in elders,[69,70] but significant selection biases hamper external validity. Other studies[71,72] have suggested using modified NEXUS criteria (more specific definitions of "normal alertness" and "painful distracting injuries") in elders in an attempt to improve performance characteristics. However, these studies sacrifice a strength of the original NEXUS study: the definitions in the original study **were based on the individual clinician's judgment**, yet the decision rule performed well in the NEXUS cohort

TABLE 258-4 NEXUS Criteria[47]

- Absence of midline cervical tenderness
- Absence of focal neurologic deficit
- Normal level of alertness and consciousness*
- No evidence of intoxication
- Absence of painful distracting injury†

*For example: Glasgow Coma Scale score <15; disorientation to person, place, time, or events; inability to remember three objects at 5 minutes; delayed or inappropriate response to external stimuli.

†"a clinically apparent, painful injury that might distract . . . [the patient] . . . from the pain of a cervical-spine injury."

TABLE 258-5 Canadian Cervical Spine Rule for Radiography: Cervical Spine Imaging Unnecessary in Patients Meeting These Three Criteria[48]

Assessment	Definitions
Assessment #1: There are no high-risk factors that mandate radiography.	High-risk factors include: Age 65 years or older; A dangerous mechanism of injury*; The presence of paresthesias in the extremities
Assessment #2: There are low-risk factors that allow a safe assessment of range of motion.	Low-risk factors include: Simple rear-end motor vehicle crashes; Patient able to sit up in the ED; Patient ambulatory at any time; Delayed onset of neck pain; Absence of midline cervical tenderness
Assessment #3: The patient is able to actively rotate his/her neck (regardless of pain).	Can rotate neck 45 degrees to the left and to the right

*Defined as fall from a height of >3 feet; an axial loading injury; high-speed motor vehicle crash, rollover, or ejection; motorized recreational vehicle or bicycle collision.

of 34,000 patients[47,73] and in the subgroup of elders in this cohort.[67] Therefore, more prospective, externally validated data are needed to determine the best way to use NEXUS in the elderly.

The **Canadian Cervical Spine Rule for Radiography (CCR)** was developed for alert, stable trauma patients to reduce practice variation and inefficiency in the ED use of plain cervical spine radiography.[48] The Canadian rule consists of three assessments, which are asked **in sequential order** (**Table 258-5**).[48] To proceed to the next assessment, the answer to the previous assessment must be "Yes." If the answer to any assessments is "No," then imaging is immediately performed. In the original study sample of 8924 patients, the CCR was 100% sensitive (95% CI, 98% to 100%) and 42.5% specific (95% CI, 40% to 44%) for identifying patients with "clinically important" cervical spine injuries.[48] The CCR has also been validated in both larger hospital-based studies[74] and prehospital studies.[75] However, the CCR has been criticized for its complexity relative to NEXUS,[76,77] although this may now be less of an issue with the availability of CCR calculators that can be accessed on a smartphone.[78]

There is one published direct prospective comparison of NEXUS and CCR (n = 8283) that reported that CCR was more accurate for detecting cervical spine injury compared to NEXUS, with superior sensitivity (99% vs. 91%), specificity (45% vs. 37%), positive likelihood ratio (1.81 vs. 1.44), and negative likelihood ratio (0.01 vs. 0.25).[79] However, some have questioned the methodology of this comparison as being biased in favor of CCR.[80,81] A meta-analysis of 15 studies (79,526 patients) concluded that the CCR appeared to have better diagnostic accuracy than NEXUS[82]; however, the quality of methods of the included studies was termed "modest," and further, more rigorous studies were suggested to be done. In both rules, the more subjective parts ("absence of painful distracting injury" and "no evidence of intoxication" for NEXUS; "dangerous mechanism of injury" and assessment of range of motion for CCR) are the most common misinterpretation of the rules, which obviously affects their performance.[82]

Both NEXUS and CCR were developed in an era prior to the routine use of CT as a primary tool to evaluate the cervical spine in blunt trauma patients. Consequently, studies have been done to compare both decision rules using CT scan as the gold standard. In a 2011 study of 2606 blunt trauma patients, NEXUS was found to only be 82.8% sensitive and 45.7% specific for spine injury. Of the 26 missed injuries, 19 patients required further intervention, including two who went to the operating room and one who needed a halo.[83] The same group compared CCR to CT scan (3201 blunt trauma patients), finding excellent sensitivity of 100% but only 60% specificity.[84] Nevertheless, the use of NEXUS has been recommended in several national guidelines and trauma societies.[85,86]

In summary, many experts feel that **because both NEXUS and CCR have been widely validated and have demonstrated adequate sensitivity, either rule may be used to determine which low-risk patients should undergo cervical spine imaging**.[82]

CERVICAL SPINE IMAGING

Plain Radiography In the past, cervical spine radiography was the gold standard for the initial evaluation to detect a cervical spine fracture; however, it has largely been replaced by CT in EDs with access to that modality (see below). Plain radiography for the identification of bony cervical injury includes three views of the cervical spine: lateral, anterior-posterior, and odontoid. A single lateral cervical spine film will identify only about 90% of injuries to bone and ligaments.[31] The anterior-posterior and open-mouth odontoid views will identify many of the remaining abnormalities. **It is important to image all seven cervical vertebrae, along with the superior border of the first thoracic vertebra**, given the propensity for injuries at the cervical-thoracic junction. Therefore, a "swimmer's view" may be necessary to visualize this junction clearly, but this often requires an assistant to pull down the shoulders during the radiograph. The main advantages of plain radiography are that it can be quickly done at the bedside and exposes the patient to only small amounts of ionizing radiation. The main disadvantage of plain radiography is that it misses injuries when compared with CT[87] and is especially poor for imaging C1 and C2. In addition, visualization of the entire cervical spine by plain films is often problematic in obese, elderly, or extremely muscular patients, especially with a cervical collar in place.

Cervical Spine CT CT is the initial imaging modality of choice to evaluate the traumatized cervical spine. **Multidetector CT is more sensitive and specific than plain radiography for evaluating the cervical spine in trauma patients and can be performed quickly.**[88,89] CT can be used to visualize the entire cervical spine and is particularly useful at the craniocervical and cervicothoracic regions, where the sensitivity of plain films is most limited. In addition, a 3-year retrospective review found that plain radiography did not add any clinically useful information to a cervical spine CT.[90] Furthermore, cost analyses have shown CT to be cost-effective to screen for cervical spine injuries in moderate- to high-risk trauma patients.[91,92] Accordingly, the American Association of Neurological Surgery and the Congress of Neurological Surgeons,[86] the Eastern Association for the Surgery of Trauma (EAST),[85] and the National Institute for Health and Care Excellence (NICE)[93] all recommend CT as the primary initial diagnostic tool for suspected cervical spine injury. In addition, if plain radiography is chosen as the primary imaging modality, a CT should be ordered if the initial plain radiograph is inadequate or if an injury is detected or still suspected after the initial radiography. Despite this general consensus, some have opined that plain radiography may be preferable to CT for patients who are at "low to moderate risk"[87]; however, there are no controlled studies that have defined "moderate risk" and no published data to suggest it is acceptable to miss injuries that would have been detected on CT scanning.

Cervical Spine MRI MRI is the imaging modality of choice if a ligamentous or spinal cord injury is strongly suspected because MRI has excellent sensitivity for soft tissue and spinal cord injuries.[94,95] However, there are practical limitations on its use for emergent presentations, including the requirement for the patient to be stable, availability, cost, and patient tolerance for the procedure. A prospective, multicenter, observational study (n = 10,276) found that CT was 98.5% sensitive (negative predictive value 99.97%) for ruling out clinically significant spinal column injuries in patients who failed the NEXUS criteria.[96] The three patients (0.03%) who had clinically significant injuries missed by CT all had focal neurologic symptoms (which were consistent with central cord syndrome in all three cases, and the diagnoses were subsequently confirmed on MRI). These results are largely consistent with previous smaller studies. Therefore, MRI is appropriately used for symptomatic patients with a negative CT who have persistent neurologic deficits that could be attributed to a spinal lesion and for patients with a positive CT in order to evaluate the spinal cord.

Imaging for Cervical Ligamentous Injury In patients with pure ligamentous injuries, the ligaments are disrupted, but the spine spontaneously reduces to a normal position. The resulting instability risks subsequent neurologic injury if the spine moves. Signs and symptoms

include persistent neck pain/midline tenderness, extremity paresthesias, or focal neurologic findings despite normal plain radiographs and/or CT.

Although flexion and extension radiographs have been traditionally used to try to detect ligamentous instability, numerous studies have demonstrated their lack of sensitivity and inefficiency (30% to 80% of flexion and extension radiographs are inadequate), and they provide no further information beyond a CT.[97-101] Therefore, flexion and extension radiographs should not be ordered when more advanced imaging is available.

MRI is the test of choice for these patients and should be obtained if available. If MRI is not available and the patient's **only** symptom is neck pain, there is a paucity of published data to direct next steps, and local expert opinion may vary.[96] Therefore, in these patients, consult a spine surgeon to help make the decision between spine immobilization until MRI is available versus emergent transfer for MRI.

Imaging for Suspected Carotid/Vertebral Dissection Cervical spine fractures and head injury are risk factors for carotid or vertebral artery dissection. Many patients are initially asymptomatic and diagnosis can be delayed for days until neurologic symptoms become evident. See Chapter 260, "Neck Injuries", and Table 260-7 for further discussion.

CLINICAL DECISION RULES IN THORACIC AND LUMBAR SPINE IMAGING

It has been well-established in the literature that clinical examination is insufficiently sensitive to rule out thoracolumbar injuries. A prospective observational study (n = 884) found that a clinical examination was only 48.2% sensitive for thoracolumbar spine fractures (78.6% sensitive for clinically significant fractures), with 52% of thoracolumbar spine fractures having a negative clinical examination.[102] A prospective study of patients with distracting injuries (n = 950) found the clinical examination was only 75% and 89% sensitive for all thoracolumbar fractures and clinically significant fractures, respectively.[103] Since the clinical exams in both of these studies were standardized and structured, it seems more likely than not that these sensitivities would be even lower in actual practice with unstructured exams. However, in contrast to the cervical spine, there are no commonly accepted, prospectively validated clinical decision rules as to which patients require imaging. This led the Eastern Association for the Surgery of Trauma to release general guidelines based on expert opinion (**Table 258-6**).[49] A prospective, multicenter study (n = 3065) derived a decision rule that was 98.9% sensitive (negative predictive value 99.6%) for clinically significant injuries and 100% sensitive (negative predictive value 100%) for those requiring surgery (**Table 258-7**).[50] To date, a prospective validation of this rule has yet to be published; however, in light of these data, it seems reasonable to be aggressive in seeking thoracolumbar injuries and to not rely solely on clinical examination to defer imaging.

TABLE 258-6 Eastern Association for the Surgery of Trauma Guidelines for Thoracic and Lumbar Imaging after Trauma[49]

Level I (convincingly justifiable based on scientific evidence)	When imaging is deemed necessary, CT scans with axial collimation should be used to screen for and diagnose injury, because CT scans are superior to plain films in identifying thoracolumbar spine fractures.
Level II (reasonably justifiable based on scientific evidence and expert opinion)	Patients with back pain, thoracolumbar spine tenderness on examination, neurologic deficits referable to the thoracolumbar spine, altered mental status, intoxication, distracting injuries, or known or suspected high-energy mechanisms should be screened for thoracolumbar spine injury with CT scan. In blunt trauma patients with a known or suspected injury to the cervical spine, or any other region of the spine, thorough evaluation of the entire spine by CT scan should be strongly considered due to a high incidence of spinal injury at multiple levels within this population. Patients without complaints of thoracolumbar spine pain who have normal mental status, as well as normal neurologic and physical examinations, may be excluded from thoracolumbar spine injury by clinical examination alone, without radiographic imaging, provided that there is no suspicion of high-energy mechanism or intoxication with alcohol or drugs.
Level III (supported by available data, but scientific evidence lacking)	MRI should be considered in consultation with the spine service for CT findings suggestive of neurologic involvement and of gross neurologic deficits.

Abbreviation: CT = multidetector CT.

TABLE 258-7 American Association for the Surgery of Trauma Thoracolumbar Multicenter Study Group (AAST TL-Spine) Clinical Decision Rule for Thoracic and Lumbar Imaging After Blunt Trauma*[50]

Imaging of the thoracic and lumbar spine is indicated in a multisystem blunt trauma patient when *any* of the following criteria are met:

- Patient is ≥60 years old *or*
- Patient is *not* alert and evaluable† *or*
- Patient has pain, tenderness to palpation, deformity, or neurologic deficit *or*
- Mechanism of injury was "high risk" (fall [not including ground-level fall or fall from ≤5 steps], crush injury, motor vehicle collision with rollover or ejection, unenclosed vehicle crash, or automobile versus pedestrian)

*Rule may not be applied to patients who are <15 years old, have preexisting paraplegia/tetraplegia, have a concurrent cervical spine injury causing neurologic deficit, or who present >24 hours after injury.

†Evaluable = Glasgow Coma Scale score of 15, nonclinically intoxicated, and without painful, distracting injury.

THORACIC AND LUMBAR SPINE IMAGING

As with the cervical spine, **CT is more sensitive for injuries than plain radiography in screening for thoracolumbar injuries in patients with significant trauma** (97.2% and 33.3%, respectively, for unstable fractures),[104] and plain radiography does not add any important diagnostic information when CT is used.[105] CT can reveal the anatomy of an osseous injury, grade the extent of spinal canal impingement by bone fragments, and assess the stability of an injury. Rather than obtaining dedicated CT images, the thoracic and abdominal CT scans typically obtained to evaluate the multiple trauma patient can be used to reconstruct images of the thoracic and lumbar spine, thereby sparing the patient additional ionizing radiation exposure while detecting spinal column injuries not seen on the unreconstructed scans alone.[106] As in the case of cervical spine injuries, if an associated spinal cord or nerve root injury is suspected, MRI is the imaging study of choice.

It is less clear how to screen for thoracolumbar injuries in patients who have less severe mechanisms of injuries. Although it has been well established that CT is more sensitive for thoracolumbar injuries in severely injured patients,[49] there has been no prospective controlled comparison between plain radiography and CT in more mildly injured patients. Nevertheless, CT should still be considered the standard screening modality for thoracolumbar injuries.[49]

Imaging for Thoracolumbar Spinal Cord and Ligamentous Injuries As with cervical imaging, **MRI is the diagnostic test of choice for describing the anatomy of ligamentous or neural tissue injury** in the thoracolumbar region. MRI is indicated in patients with neurologic findings with no clear explanation after plain films and/or CT scanning. If the patient is stable and MRI is unavailable, transfer to a facility with MRI capabilities is appropriate.

CONCURRENT IMAGING OF THE ENTIRE SPINE

The determination of a spinal column injury at one level should prompt imaging of the entire remainder of the spine with CT because approximately 20% of patients with a spine fracture in one segment will have a noncontiguous second fracture at another segment.[107-109]

SPINE IMAGING IN OBTUNDED PATIENTS

While experts recommend that all obtunded patients with significant blunt trauma should have their entire spine imaged, consensus does not

yet exist on what imaging is necessary to clear the spine in obtunded patients. Specifically, **it remains controversial whether a negative CT of the spine is adequate or if a subsequent MRI needs to be done**.[96,110] The literature on this topic consists largely of small, retrospective, single-center studies. Consequently, in 2015, two systematic reviews of the literature could only "probably"[111] and "conditionally"[112] conclude that a "high-quality" CT scan could be used to clear the cervical spine in obtunded patients. However, a more recent prospective multicenter trial (n = 10,276) found an extremely high sensitivity of CT for cervical spine injuries (98.5%), yet three patients had central cord syndrome that would have been missed by CT alone.[96] Therefore, given the absence of definitive data at this time, maintain spinal precautions in the obtunded trauma patient in the ED, and defer any subsequent spine clearance to local expert consultants.

TREATMENT AND DISPOSITION OF SPINAL COLUMN INJURIES

The goals of treatment are to prevent secondary injury, alleviate cord compression, and establish spinal stability. Maintain spinal immobilization and keep movement to a minimum. **Obtain emergent consultation with a spine surgeon (neurosurgeon or orthopedic surgeon depending on the particular facility) on all spinal column fractures or ligamentous injuries, regardless of neurologic compromise**.

CERVICAL SPINE FRACTURES

The majority of cervical spinal fractures will require admission for definitive treatment or for the care of associated injuries. Until transfer of care to a surgeon, spine precautions should be maintained, associated injuries stabilized, and the patient carefully monitored for respiratory or neurologic deterioration.

THORACIC AND LUMBAR SPINE FRACTURES

Thoracolumbar fractures are also high risk for associated spinal cord or other traumatic injuries, such as aortic, intrathoracic, or intra-abdominal visceral injuries.[113] Although many of these injuries will require admission, there are two types of thoracolumbar fractures that may be amenable to outpatient therapy.

Compression fractures, also known as "wedge" or "anterior" compression fractures, have been reported to compose approximately 33.6%[113] to 52%[10] of thoracolumbar fractures. These fractures occur as a result of a hyperflexion during an axial load that crushes the anterior portion of the vertebra. If the percentage of loss of vertebral height is <40%, the patient may be a candidate for outpatient therapy, and this should be discussed on a case-by-case basis by the spine surgeon. However, if the loss of vertebral height is ≥50% or if the angle between the damaged vertebra and the rest of the spinal column is >25% to 30%, the compression fracture is generally considered unstable.

In addition, make certain that an apparent compression fracture seen on plain radiographs is not a **burst fracture**, which is a compression-type fracture that involves the posterior half of the vertebrae and is reported to be 39.5% of thoracolumbar fractures.[113] Burst fractures may result in retropulsed fragments that can impinge on the spinal canal and cause neurologic injury. In two studies, the incidence of misdiagnosis of burst fractures on plain radiographs ranged from 20% to 23%.[114,115] Another fracture that is sometimes misdiagnosed as a wedge compression fracture on plain radiograph is the **Chance fracture**. This fracture occurs via a flexion-distraction mechanism and involves minor anterior vertebral compression and significant distraction of the middle and posterior ligamentous structures. Typical radiographic findings reveal a transverse fracture lucency in the vertebral body, an increased height of the posterior vertebral body, fracture of the posterior wall of the vertebral body, and posterior opening of the disk space. Finally, minor to moderate trauma can cause **pathologic fractures** secondary to preexisting neoplastic, infectious, or osteoporotic processes in the spine. Because the above-mentioned fractures can be easily misdiagnosed with plain radiography alone, **further evaluate compression fractures of the thoracolumbar spine on plain radiographs with CT**.[116]

If, after a thorough evaluation, a stable wedge compression fracture with no neurologic compromise is diagnosed, the patient may be treated as an outpatient with analgesia, heat, massage, rest, and appropriate follow-up for consideration of physical therapy.

SACRUM AND COCCYX FRACTURES

Injuries of the sacral spine and nerve roots are very unusual. When they occur, they are frequently associated with fractures of the pelvis. In general, transverse fractures through the body are most significant in that they cause injury to part or all of the cauda equina. Longitudinal fractures may cause radiculopathy. **Sacral fractures that involve the central sacral canal can produce bowel or bladder dysfunction**. For these reasons, obtain emergent consultation for sacral fractures.

One notable exception to the need for emergent consultation is an **isolated coccyx fracture**. Coccygeal injuries are usually associated with a direct fall onto the buttocks, with resultant coccyx pain exacerbated by sitting or straining. Imaging is not needed to diagnose coccygeal fractures. Treatment is symptomatic with analgesics and use of a rubber doughnut pillow.

SPECIAL CONSIDERATIONS

CORTICOSTEROIDS

High-dose methylprednisolone remains a controversial treatment in acute blunt spinal cord injury and should not be given routinely. The major neuroprotective mechanism by which high-dose methylprednisolone is believed to work is in its inhibition of free radical–induced lipid peroxidation. Other proposed beneficial actions include its ability to increase levels of spinal cord blood flow, increase extracellular calcium, and prevent loss of potassium from injured cord tissue. Methylprednisolone is advocated in preference to other steroids because it crosses cell membranes more rapidly and completely.

In the 1990s, the National Acute Spinal Cord Injury Study (NASCIS) group published three prospective, double-blind studies to evaluate the efficacy of methylprednisolone in blunt spinal cord injury: NASCIS I, II, and III.[117-119] NASCIS I compared high-dose methylprednisolone and a lower-dose methylprednisolone regimen (n = 330). NASCIS I showed no evidence in recovery of function between the groups. NASCIS II compared a higher dose of methylprednisolone (**Table 258-8**), naloxone, and placebo (n = 427). This trial was also negative, but based on post hoc subgroup analysis, NASCIS II showed modest improvements in motor function when steroids were administered within 8 hours of injury. NASCIS III compared high-dose methylprednisolone for 24 hours, high-dose methylprednisolone for 48 hours, and tirilazad mesylate for 24 hours (n = 499). NASCIS III was also a negative trial, but post hoc analysis found that patients who received the 48-hour methylprednisolone regimen within 3 to 8 hours of their injury showed motor improvement. In all three trials, patients who received high-dose methylprednisolone and longer duration protocols were more likely to develop complications such as severe sepsis, severe pneumonia, wound infection and delayed healing, pulmonary embolism and deep vein thrombosis, GI bleeding, and death. In 2012, a Cochrane systematic review (written by the lead author of the NASCIS trials) essentially confirmed the conclusions of NASCIS II and III that there was a small but statistically significant benefit to high-dose methylprednisolone when administered within 8 hours of injury, but these patients were also more

TABLE 258-8 The National Acute Spinal Cord Injury Study II High-Dose Methylprednisolone Protocol

Indications	Blunt trauma Neurologic deficit referable to the spinal cord Treatment must be started within 8 h of injury
Treatment	Methylprednisolone, 30 milligrams/kg IV bolus over 15 min Followed by a 45-min pause Methylprednisolone, 5.4 milligrams/kg/h IV is then infused for 23 h

likely to develop complications.[120] This systematic review also recommended that more randomized trials be done urgently.

However, the results of the NASCIS clinical trials have been criticized as not providing sufficient clinical evidence to support the use of steroids in acute spinal cord injury. Examples of bias cited include the use of post hoc subgroup analysis, the artificiality of the 3- and 8-hour time limits, and a difference in the severity of injury in particular treatment groups. Reassessment of the original trials and subsequent studies by other authors have questioned the validity of the NASCIS trials and the effectiveness of high-dose steroid therapy in these patients.[121-123] Consequently, the 2013 updated guidelines for the management of acute spinal cord injuries endorsed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons stated that "there is no consistent or compelling medical evidence of any class to justify the administration of methylprednisolone for acute spinal cord injury," and that "methylprednisolone should not be routinely used in the treatment of patients with acute spinal cord injury."[124] Moreover, the U.S. Food and Drug Administration has not approved corticosteroids for acute spinal cord injury.[125] In 2016, a more rigorous systematic review and meta-analysis (four randomized controlled trials and 17 observational studies) concluded that high-dose methylprednisolone "is not associated with an increase in long-term motor score recovery" and "may be associated with increased gastrointestinal bleeding"; however, because confidence in effect estimates is limited, "strong recommendations are not warranted."[126] Despite these data, it has been reported that an upcoming AOSpine guideline will recommend that 24 hours of high-dose methylprednisolone may be considered as a treatment *option* within 8 hours of blunt injury in the absence of medical contraindications.[127]

Therefore, given the continued controversy over its use, **the option to start corticosteroids should only be made in conjunction with the surgeon who will ultimately be caring for the patient and *not* given routinely**.

It is important to realize that the NASCIS trial protocol was evaluated only in patients with **blunt** spinal cord injury, while penetrating injuries were excluded from these studies. In fact, **high-dose methylprednisolone therapy has not been found to be efficacious in penetrating spinal cord injury**.[128] In addition, because corticosteroids worsen outcomes in brain-injured patients, they should be avoided in this population as well.[129]

CARDIOVASCULAR COMPLICATIONS

If neurogenic shock is present, initiate an infusion of IV crystalloid to correct this relative hypovolemia. However, the aggressive use of fluids in neurogenic shock should be performed with careful monitoring, because there is danger of excessive fluid replacement, resulting in heart failure and pulmonary edema. **If prudent use of IV fluids is not adequate to maintain organ perfusion, positive inotropic pressor agents *may* be beneficial adjuncts to improve cardiac output and raise perfusion pressure.** In terms of target systolic blood pressure and mean arterial pressure, the evidence in the literature is limited, with mixed results, but it has been recommended that systolic blood pressure should be kept greater than 90 mm Hg, with the mean arterial pressure kept at 85 to 90 mm Hg.[130] There is no definitive evidence that any particular vasopressor is superior to another for this indication.[131] It should be noted that the potential benefits of this strategy should **not** be generalized to patients with penetrating spinal cord injuries.[132]

However, two studies in 2015 reach opposite conclusions in terms of the efficacy of striving to reach this mean arterial pressure target.[133,134] Furthermore, in a trial involving central cord syndrome patients, administration of vasopressors to reach these mean arterial pressure goals was associated with cardiovascular complications in over three fourths of patients.[135] Currently, the Mean Arterial Blood Pressure Treatment for Acute Spinal Cord Injury trial[136] is an ongoing prospective, randomized, double-blind noninferiority trial that is comparing the current target of mean arterial pressure ≥85 mm Hg to a mean arterial pressure ≥65 mm Hg. Therefore, given the unsettled state of the literature on this topic, a dogmatic adherence to these mean arterial pressure guidelines is not desirable. Rather, a case-by-case approach may be more reasonable.[137]

Bradycardia, when present, usually occurs within the first few hours or days after spinal cord injury because of a predominance of vagal tone to the heart. In cases of hemodynamically significant bradycardia, atropine may be needed. Rare occurrences of atrioventricular conduction block with significant bradycardia require a pacemaker.

PENETRATING INJURY

Penetrating injuries to the neck are discussed in Chapter 260, "Trauma to the Neck." For spinal gunshot wounds with a transabdominal or transintestinal trajectory, administer prophylactic broad-spectrum IV antibiotics in the ED. **Corticosteroids are contraindicated in patients with any type of penetrating spinal injuries,**[128] and emergent consultation with a spine surgeon is indicated.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 259

Trauma to the Face

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INTRODUCTION AND EPIDEMIOLOGY

Assaults, motor vehicle crashes, falls, sports, and gunshot wounds account for the majority of facial fractures (in descending order of incidence), with motor vehicle crashes and gunshot wounds resulting in a higher severity of injury.[1] The lack of a seat belt or air bag increases the risk of facial fractures and panfacial fracture.[2] The most common fractures are to the nasal bone, followed by orbital floor, zygomaticomaxillary, maxillary sinuses, and mandibular ramus.[1] Mechanisms and injury patterns vary with geography. In the urban setting, penetrating trauma and assaults result in midface and zygomatic fractures. In the rural setting, motor vehicle crashes and recreational injuries result in fractures of the mandible and nose. Males are more frequently affected than females, but domestic violence and elder and child abuse must always be considered in any patient presenting with facial trauma. The majority of abused women and children will have injuries to the head, face, and neck.[3,4]

PATHOPHYSIOLOGY

The facial skeleton is designed to create effective mastication. Vertical and horizontal buttresses are formed by bony arches joined at suture lines. Stronger vertical buttresses are formed by the zygomaticomaxillary buttress laterally and the frontal process of the maxilla medially. Weaker horizontal buttresses are formed by the superior orbital rims, orbital floor, and hard palate. The orbit itself is comprised of seven different bones, with the inferior and medial walls being particularly fragile. Therefore, frontal, lateral, and oblique forces often result in facial fractures.

The identification of facial injury and the restoration of normal appearance, sight, mastication, smell, and sensation are all essential tasks,[5] but the principal focus should be on protecting the patient's airway during the primary survey and the other initial considerations described in **Table 259-1**.

Up to 44% of patients with severe maxillofacial trauma require endotracheal intubation due to mechanical disruption or massive hemorrhage into the airway.[6] The incidence of associated injury to the brain,

TABLE 259-1 Initial Considerations in Facial Trauma

Primary survey
- Airway—endotracheal intubation for mechanical disruption or severe hemorrhage.
- Circulation—early packing of nasal and oral cavity. Apply direct pressure to external wounds. Avoid blind clamping.
- Evaluate and manage emergent life-threatening conditions before facial injuries.

Secondary survey
- Early meticulous facial and ocular examinations.

History
- Mechanism predicts severity of facial and associated brain, cervical spine, and pulmonary injury.
- Screen for abuse, especially in women, children, and elders.

orbit, cervical spine, and lungs is directly related to the mechanism of injury and severity of facial fractures.[6-8] Evaluate facial injuries as part of the secondary survey only after managing life-threatening injuries. Because up to 6% of patients with maxillofacial trauma will develop vision loss, a detailed eye examination is essential, especially in patients with high-energy mechanisms, orbital fractures, significant head injury, and abnormal pupillary findings.[8,9]

CLINICAL FEATURES

The mechanism of injury helps estimate the extent of injury. Exact details of motor vehicle crashes and assaults are often incomplete due to associated traumatic brain injury, intoxication, or other factors. Always address the possibility of abuse. When reported mechanisms do not match the injury, ask patients, especially women and the elderly, about interpersonal violence. Contact pediatricians and local child protective services when considering child abuse. It is better to report all suspected abuse than allow violence to continue and escalate. Obtain history of allergies, medications (especially cardiovascular and antithrombotic agents), comorbidities, tetanus immunization status, and time of last meal from the trauma patient or other available sources.

The secondary survey begins with three screening questions to help localize injuries while simultaneously examining the patient from the upper to the lower face. Important clinical findings in facial trauma are presented in **Table 259-2**.

(1) How is your vision? Any patient with visual complaints or evidence of periorbital injury requires a thorough eye examination. (2) Is your face numb? Ask this question while checking for anesthesia of the forehead, lower eyelid, cheek and upper lip, or chin, suggesting injury to the supraorbital, infraorbital, or mental nerves. (3) Do your teeth fit together normally? Malocclusion typically occurs in patients with mandibular or maxillary fractures. Pain and tenderness near the ear indicate mandibular condyle injury. With zygomaticomaxillary complex fractures, patients often report pain over the cheek and trismus from masseter spasm or mechanical impingement of either the temporalis muscle or coronoid process of the mandible.

Inspect the face from the front, sides, feet, and above to detect subtle asymmetry in facial structure from zygomatic, orbital, and Le Fort injuries (**Figures 259-1 to 259-3**). Palpate the entire orbital rim for tenderness and step-off deformities, which suggest fracture, and for crepitus, which suggests sinus involvement.

Examine the eyes before significant swelling occurs, or use lid retractors to better inspect the globe. Begin with corrected visual acuity using a wall, pocket, or phone app Snellen eye chart, name tag, or finger counting. In patients with loss of visual acuity, note light perception and color perception. **Loss of vision implies injury to the optic nerve or globe.** Subconjunctival hemorrhage and bloody chemosis occur with orbital fractures.

Assess extraocular motion and pupils. **Binocular double vision suggests entrapment of the extraocular muscles, whereas monocular double vision suggests lens dislocation.** Limitation on upward gaze occurs with fractures of the inferior and medial orbital wall from entrapment or injury to the inferior rectus, inferior oblique, or oculomotor

TABLE 259-2 Important Clinical Issues in Facial Trauma

History
- How is your vision?
- Do any parts of your face feel numb?
- Does your bite feel normal?

Inspection
- Lateral view for dish face with Le Fort III fractures.
- Frontal view for donkey face with Le Fort II or III fractures.
- Bird's eye view for exophthalmos with retrobulbar hematoma.
- Worm's view for enophthalmos with blow-out fractures or flattening of malar prominence with zygomatic arch fractures.
- Raccoon eyes (bilateral orbital ecchymosis) and Battle's sign (mastoid ecchymosis) typically develop over several hours, suggesting basilar skull fracture.

Palpation
- Palpating the entire face will detect the majority of fractures.
- Intraoral palpation of the zygomatic arch, palpating lateral to posterior maxillary molars to distinguish bony from soft tissue injury.
- Assess for Le Fort fractures by gently rocking the hard palate with one hand while stabilizing the forehead with the other.

Eye
- Examine early before swelling of lids, or use retractors. Document visual acuity. Systematically examine the eye from front to back. Specifically, check the pupil for teardrop sign pointing to globe rupture; hyphema; and swinging flashlight test for afferent papillary defect.
- Fat through wound indicates orbital septal perforation.
- Check intraocular pressure for evidence of orbital compartment syndrome only in absence of globe injury.

Nose
- Crepitus over any facial sinus suggests sinus fracture.
- Nasal septal hematoma appears as blue, boggy swelling on nasal septum.
- Cerebrospinal fluid leak.

Ears
- Auricular hematoma.
- Hemotympanum.
- Cerebrospinal fluid leak.

Oral
- Jaw deviation due to mandible dislocation or condyle fracture. Malocclusion occurs in mandible, zygomatic, and Le Fort fractures.
- Missing or injured tooth.
- Lacerations and mucosal ecchymosis suggest mandible fracture.
- Place finger in external ear while the patient gently opens and closes jaw to detect condyle fractures.
- Tongue blade test: Patient without fracture can bite down on a tongue blade enough to break blade twisted by examiner.



FIGURE 259-1. Zygomatic arch fracture. Note flattening of the right malar eminence on bird's eye. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]



FIGURE 259-2. Traumatic exophthalmos. Note significant right exophthalmos on bird's eye view due to retrobulbar hematoma. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]

nerve (**Figure 259-4**). Examine the pupils for shape, position, symmetry, and reactivity. Teardrop-shaped pupil indicates globe injury. Note the distance between the medial canthi; normal is the width of the patient's globe. **Telecanthus, widening of this distance with normal interpupillary distance, occurs with naso-orbito-ethmoid injuries.** Widening of the interpupillary distance, or hypertelorism, results from a "blow-out" injury to the orbits, often resulting in blindness.

Check the swinging flashlight test for evidence of an afferent papillary defect (Marcus Gunn pupil) (see Chapter 241, "Eye Emergencies"). With normal function, the swinging light results in brief dilation during movement followed by constriction when the light is directly over the eye. With injury to the optic nerve or retina, the affected pupil will not constrict until the light is again moved to the unaffected eye. The test is sensitive but not specific for optic nerve injury, because an afferent papillary defect may result from pathology anywhere along the visual pathway.

Finish the physical examination of the eye by completing funduscopic, slit-lamp, and fluorescein examinations, as well as checking intraocular pressures when indicated. Flashes of light and floaters may be reported in patients with retinal detachments and vitreous hemorrhage. Foreign-body sensation and photophobia suggest corneal abrasions. Check for hyphema after having the patient sit upright for several minutes. In patients without evidence of globe rupture, check intraocular pressure in patients with significant exophthalmos, afferent nerve defects, or other evidence of retrobulbar hematoma.

Check carefully for globe injury with any penetrating injury to the periorbital area. Consult ophthalmology for suspected hyphema or vitreous hemorrhage. Fat herniating through the wound suggests an injury



FIGURE 259-4. Orbital blow-out fracture causes limitation of upward gaze due to entrapment of inferior rectus.

through the orbital septum. Through-and-through injuries, tarsal plate injuries, and injuries to the medial quadrant involving the lacrimal duct require repair by an ophthalmologist.

Begin the examination of the nose by checking for deformity from multiple angles while asking the patient about prior nose injury. Check for tenderness, crepitus, septal hematoma, and cerebrospinal fluid rhinorrhea. A septal hematoma appears as a blue, boggy, and tender area of swelling along the nasal septum (**Figure 259-5**). Incision and



FIGURE 259-3. Le Fort III fracture has a classic dish face deformity on lateral view. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]



FIGURE 259-5. Septal hematoma presenting as a grapelike mass on left nasal septum. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]

evacuation are required to prevent destruction of cartilage resulting in a saddle nose deformity. Ensure that simple nasal fractures are not associated with complex naso-orbito-ethmoid injuries. Perform the bimanual nasal palpation test with tenderness over the medial canthus. Begin by anesthetizing the nose. Then insert a cotton tip applicator inside the nose along the lateral nasal wall to the area behind the medial orbital wall and canthus. Palpate the area of the medial canthus externally with the opposite hand to check for movement from fracture of the medial wall of the orbit. Obtain a CT scan for suspected injury to the medial canthus or when telecanthus is present. Isolated nasal fractures and septal hematoma evacuation are reviewed in Chapter 244, "Nose and Sinuses."

Classic tests for cerebrospinal fluid rhinorrhea are not accurate in distinguishing cerebrospinal fluid from serous nasal discharge in the presence of nasal bleeding. The double ring or halo sign occurs when clear cerebrospinal fluid diffuses past blood when dropped on a paper towel, but is not sensitive or specific for cerebrospinal fluid leak. Trauma-related serous nasal discharge will also diffuse past blood. The glucose test is likewise not reliable. Nasal discharge does not contain glucose, whereas cerebrospinal fluid does. Bleeding may create a false-positive glucose test. Assays of **serum beta-2 transferrin** from the drainage are highly sensitive and specific for cerebrospinal fluid leakage.[10]

Begin the inspection of the ear by checking the mastoid process for Battle's sign (suggesting a basilar skull fracture) and the ear for auricular hematoma. Incision and drainage are required to prevent destruction of cartilage resulting in a cauliflower deformity. Traumatic injury to the ear, including auricular hematoma evacuation, is reviewed in Chapter 242, "Ear Disorders." Check the external auditory canal for lacerations, cerebrospinal fluid leak (temporal bone or middle cranial fossa injury), and hematotympanum (a purple and often bulging tympanic membrane). Insert a finger into the external auditory canal and ask the patient to gently open and close the mouth to check for a mandibular condyle fracture.

Inspect the jaw for deviation resulting from a fracture or dislocation. Malocclusion occurs in mandibular fractures, Le Fort fractures, and zygomatic fractures. Check the mouth carefully for missing or subluxed teeth, fractures of the alveolar ridge, sublingual hematoma, or breaks in the oral mucosa (**Figure 259-6**). Be sure to inspect the tongue for lacerations that may result in significant swelling later on. The tongue blade test has been reported to be 96% sensitive in identifying clinically significant mandibular fracture injuries in facial trauma patients.[11-13] The patient without a mandible fracture bites down forcefully enough on a tongue blade to allow the physician to snap the tongue blade with a twisting motion. Patients who open the mouth and cannot break the blade require further imaging. The tongue blade test is best used in conjunction with other clinical findings because test sensitivity may be as low as 85%.[13]



FIGURE 259-6. Open mandible fracture with a fracture line through gingiva into oral cavity. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]

DIAGNOSIS

IMAGING

Noncontrast CT is the imaging modality of choice. Plain radiographs remain helpful when CT is not available or to exclude injury in the low-risk patient. Recommendations for imaging based on level of injury and clinical findings are summarized in **Table 259-3**.

Subtle fractures of the frontal bone require head CT with bone windows for optimal evaluation. Because fracture of the frontal bones requires a significant force, head CT is also required to evaluate for associated traumatic brain injury. With involvement of the supraorbital ridge, include a facial CT with axial and coronal sections to better define often complex orbital fracture anatomy.

The Waters' view safely replaces the multiple views in traditional facial series for midfacial fractures.[14,15] One study suggested that at least two views be obtained due to recalculated sensitivities as low as 87% and the lack of comparison of the Waters' view to CT.[16] Not included in this analysis was a study of 730 patients demonstrating a sensitivity of 100% for Waters' view read by emergency physicians versus facial series read by specialists.[17]

Head CT has been reported to be 90% sensitive in excluding injury found on facial CT. **An additional Waters' view is unnecessary with a low clinical suspicion for facial fracture in patients undergoing a head CT for suspected traumatic brain injury.**[18] Using this strategy avoids additional radiation from unnecessary Waters' view or facial CT and prevents additional trips to CT after cervical spine clearance required for facial CT coronal positioning.

Facial CT with coronal and axial sections is the imaging study of choice for patients with an abnormal Waters' view or as the initial study with significant clinical findings.[17] Multiplanar computer reconstructions increase the effectiveness of visualization of fractures, especially in the case of fractures in the inferior orbital wall.[19]

Head and cervical spine CT scans are recommended in addition to facial CT in patients with high-energy mechanisms or significant clinical findings.

Panorex (Dental Panoramic X-Ray) remains the imaging study of choice for mandible fractures. However, mandible CT is 92% to 100% sensitive for detecting injury compared with 70% to 86% for Panorex in adults and children and has become the "gold standard" for diagnosing mandible fractures.[20,21] Mandible CT is easier to interpret with less interphysician variability compared with Panorex.[22] Mandible CT scans may miss fractures of the dental root.[20] Panorex is not often available in the ED, requires an upright patient, and may miss mandibular condyle fractures. Mandible CT is recommended in patients requiring head CT to evaluate for traumatic brain injury or when a Panorex is not available.

TABLE 259-3 Recommendations for Imaging Based on Level of Injury and Clinical Findings

Level	Low Suspicion	Significant Clinical Findings	Additional Considerations
Frontal bone	Head CT	Head CT (skull windows)	Facial CT with orbital involvement. Cervical spine CT with significant clinical findings.
Midface	Waters' view	Face CT with coronal and axial sections; head CT as strong force causes midface fractures	Coronal face sections require cervical spine clearance for positioning. Computer-generated, three-dimensional reconstructions with complex injuries. Head CT can replace Waters' view.
Mandible	Panorex (orthopantomogram)	Mandible CT	Facial CT detects mandible fractures.

The traditional mandible series (including posterior-anterior, Towne's view, and lateral oblique view) remains an option when Panorex and CT are not available.

TREATMENT

AIRWAY MANAGEMENT

During the primary survey of facial trauma patients, aggressively protect the airway from hemorrhage and mechanical obstruction. Significant hemorrhage into the airway can result from mandible and midfacial fractures. Loss of mechanical support resulting in airway obstruction can occur with bilateral posterior mandible fractures. Significant edema of the soft palate may result from midfacial injuries. Furthermore, the patient is often unable to maintain the damaged airway due to concomitant traumatic brain injury, intoxication, or other life-threatening injuries.

Reposition the airway as needed with a jaw thrust or head tilt and chin lift after cervical spine clearance. Grasp an obstructing tongue with gauze, a towel clip, or suture, to pull anteriorly and out of the airway with mandible fractures. Remove avulsed teeth and foreign bodies. Use nasal trumpets very carefully to avoid worsening of the injury or intracranial placement in severe midfacial injuries. Bag-mask ventilation often requires a two-person technique because of loss of normal facial bony structures and the need to suction the airway secondary to significant hemorrhage. When the cervical spine has been clinically cleared, allow the alert patient without significant associated injury to remain in an upright position of comfort, with suction in hand, to better handle bleeding and secretions.

Each patient's unique clinical presentation and the physician's experience dictate the best method for establishing a definitive airway. Rapid-sequence intubation is the preferred method of airway management in trauma. The presence of mandible fractures occasionally makes intubation easier than expected. However, always plan for the difficult airway in patients with facial trauma. **To prevent the "can't intubate/can't oxygenate" failed airway, do not administer paralytics unless a patient can be bagged effectively or alternative airway devices or plans are in place.**

Awake intubation with sedation and local airway anesthesia may allow the emergency physician to quickly determine how difficult orotracheal intubation will be while preserving airway reflexes.[23] Etomidate and ketamine both provide sedation with preservation of respiratory drive. When oral endotracheal intubation appears more straightforward than expected on direct laryngoscopy, the endotracheal tube may be placed or paralytics administered followed by orotracheal intubation. When endotracheal intubation appears more difficult or impossible, primary cricothyrotomy or alternative airway management techniques may be performed (see Chapter 22, "Basic Cardiopulmonary Resuscitation," Chapter 108, "Resuscitation of Neonates," and Chapter 109, "Resuscitation of Children").

The best approach to the difficult trauma airway involves planning ahead by having equipment ready for oral endotracheal intubation as well as the neck prepared and a cricothyrotomy kit ready. A laryngeal mask airway device may be a temporizing measure, but does not protect the airway from aspiration of stomach contents and may not be possible with injuries involving the pharynx. Fiberoptic devices are an excellent option in the rare case when time, a lack of significant hemorrhage, and an experienced operator are present. Avoid nasal intubation to prevent worsening of injury, hemorrhage, or intracranial placement.[8]

HEMORRHAGE

Significant hemorrhage with severe midfacial or mandible injury can obstruct the airway and make attempts at intubation difficult. The blood supply to the face originates primarily from the sphenopalatine and greater palatine branches of the external carotid artery. Extensive anastomoses occur in the nasal cavity with the anterior and posterior ethmoidal branches of the internal carotid artery. Control posterior nasal epistaxis early with nasal tampon, dual balloon device, or traditional Foley catheter placement with anterior layered gauze packing. Be careful to avoid intracranial placement of nasal packing in severe midfacial fractures. After intubation, oral packing may be needed in a patient with significant mid- and lower-facial bleeding. Reduction of significantly displaced nasal fractures and Le Fort injuries may be needed (although rarely) to stop arterial bleeding. Life-threatening hemorrhage can occur in up to 10% of patients with midface fractures.[24] With significant persistent bleeding, immediate operative intervention is required for ligation of injured vessels or better reduction of fractures. Arterial embolization may also be effective in controlling bleeding from branches of the external carotid artery, but is associated with a small risk of stroke and other complications.[25] To date, there are no reports describing the use of tranexamic acid for control of massive bleeding from facial injury in the ED.

SPECIFIC FACIAL FRACTURES

FRONTAL BONE FRACTURES

Frontal bone fractures are uncommon injuries resulting from high-energy mechanisms such as unrestrained motor vehicle crashes or assaults with blunt objects. The significant amount of force needed to fracture the thick frontal bone likewise increases the immediate risk of traumatic brain injury, additional facial fractures, and cervical spine injury. Concomitant craniofacial injuries are present in 56% to 87% of patients with frontal sinus fractures.[26] Severe frontal fractures may extend to the temporal bones and require a hearing and facial nerve function evaluation. Otorrhea in this setting is a cerebrospinal fluid leak until proven otherwise.[27] Ocular injuries can occur in up to 25% of patients with frontal bone fractures. The most common finding is an afferent pupillary defect, occurring in about 10% of patients.[28]

Lacerations typically overlie frontal sinus fractures. Careful exploration is needed to identify all fractures. Crepitus is frequently palpable with any sinus fracture. In cases of suspected fracture, obtain a head CT to evaluate the anterior and posterior tables as well as the underlying intracranial structures (**Figures 259-7** and **259-8**).

Because the dura is adherent to the posterior table, operative repair of through-and-through frontal sinus fractures is necessary to prevent pneumocephalus, cerebrospinal fluid leak, and infection. Consider rhinorrhea in any patient with a frontal bone fracture to be a cerebrospinal fluid leak until proven otherwise.[27] Mucopyoceles, collections of pus that develop as a result of nasal ducts blocked by fracture, and cranial empyema can result. Oral antibiotics, such as first-generation cephalosporins or amoxicillin clavulanate, are recommended with any sinus fracture. The patient with an isolated anterior table fracture may be discharged with nasal and oral decongestants and appropriate follow-up with a facial surgeon (otolaryngologist, plastic surgeon, or ophthalmology). Admit patients with depressed fractures for IV antibiotics and operative repair.



FIGURE 259-7. Forehead laceration overlying a frontal sinus fracture. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, New York.]

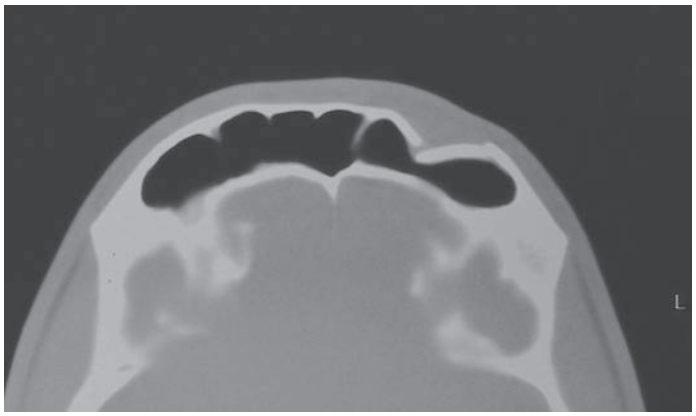


FIGURE 259-8. Frontal sinus fracture from patient in Figure 259-7. CT demonstrating fracture of the anterior table of the frontal sinus. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]

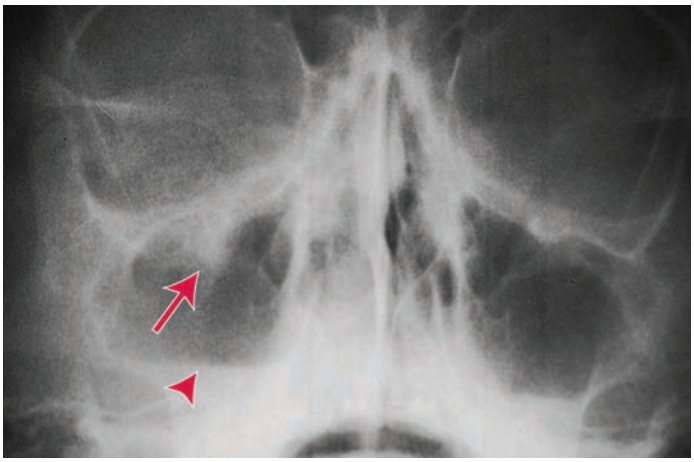


FIGURE 259-10. Blow-out fracture. Waters' view with teardrop sign (*arrow*) and fluid in right maxillary sinus (*arrowhead*). [Reproduced with permission from Knoop K, Stack L, Storrow A: *Atlas of Emergency Medicine,* 2nd ed. © 2002, McGraw-Hill, New York.]

ORBITAL FRACTURES

The orbit is traditionally thought of as a four-walled structure. It is made up of the frontal bone superiorly, the zygoma and sphenoid bones laterally, the zygoma and maxilla inferiorly, and the thin-walled lamina papyracea of the ethmoid bone medially. There are two categories of orbital fractures: pure, blow-out fractures and unpure, orbital fractures. The pure orbital blow-out fracture involves only the orbital walls and occurs when an object of small diameter strikes the globe without causing an orbital ridge or rim fracture. Force transmitted through the fluid-filled globe results in a fracture of the weaker inferior or medial orbital walls. Adipose tissue, the inferior rectus, or the inferior oblique can then herniate and become entrapped within the maxillary or ethmoid sinus (**Figure 259-9**). Lateral, inferior, and superior orbital ridge fractures typically occur with other facial fractures. See Chapter 241, "Eye Emergencies," for further discussion of orbital fractures and ocular injuries. **Significant force applied to the nasal bridge can result in naso-orbito-ethmoid fractures that are often accompanied by injury to the lacrimal duct, dural tears, and traumatic brain injury.**

Several key physical examination findings suggest orbital fracture. Enophthalmos occurs with herniation of globe contents before significant edema. Carefully palpate the entire orbital rim to detect any step-off deformity or crepitus. Infraorbital anesthesia often occurs with fracture of the orbital floor. Diplopia on upward gaze occurs with entrapment of the inferior rectus, inferior oblique, or orbital fat, or from injury of muscles or the oculomotor nerve. Naso-orbito-ethmoid fractures result in pain on eye movement, traumatic telecanthus, epiphora (tears spilling over the lower lid), and cerebrospinal fluid leak.[29]

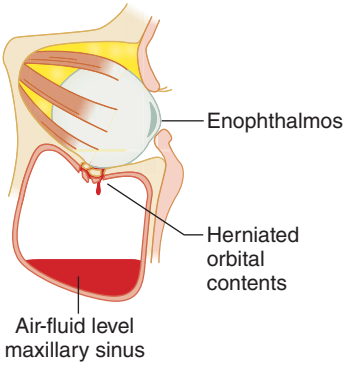


FIGURE 259-9. Blow-out fracture findings, including fluid in the maxillary sinus, herniated fat or muscle, and delayed enophthalmos, occur with orbital floor fracture. [Reproduced with permission from Scaletta TA, Schaider JJ: *Emergency Management of Trauma,* 2nd ed. © 2001, McGraw-Hill, Inc., New York.]

Radiographic findings consistent with orbital fracture are seen in **Figure 259-10**. Additional findings include air-fluid levels or opacification of the maxillary sinus. Obtain a facial or orbital CT with axial and coronal sections to plan surgical management in patients with positive findings on a Waters' view or as the initial study in patients with significant clinical findings (**Figure 259-11**).

The patient with an isolated orbital fracture requires treatment with oral amoxicillin-clavulanate to treat sinus pathogens, decongestants, and

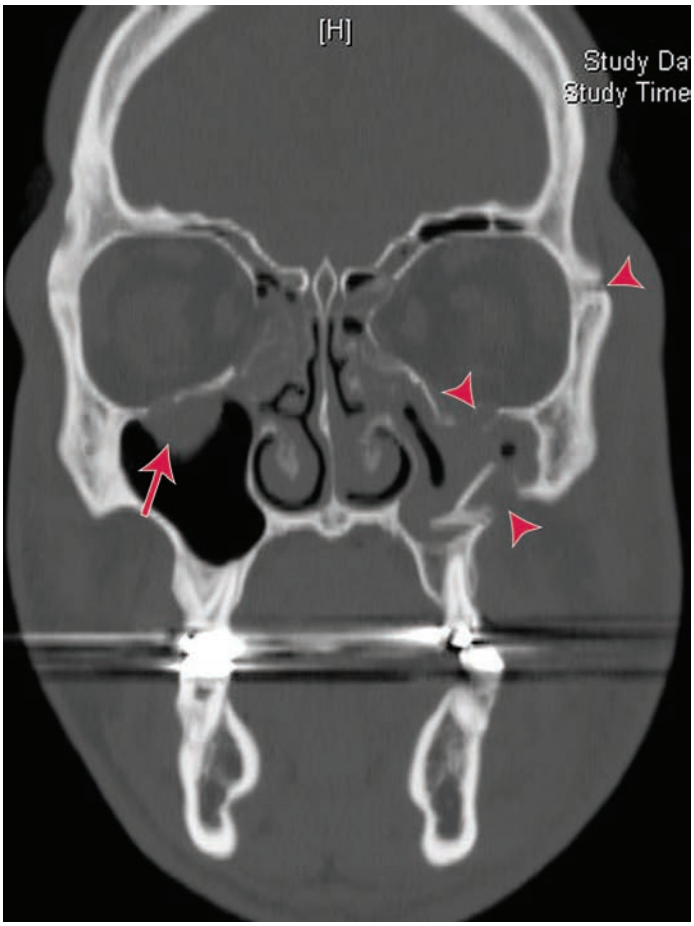


FIGURE 259-11. Left zygomatic maxillary complex and right blow-out fractures. Disruption of zygomatic frontal suture and maxillary sinus on left (*arrowheads*) with herniation of orbital contents into maxillary sinus on the right (*arrow*) on face CT coronal section.



FIGURE 259-12. Retrobulbar hematoma. CT of patient in Figure 259-2 demonstrates right retrobulbar hematoma. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine, 3rd ed.* © 2010, McGraw-Hill, New York.]

instructions to avoid nose blowing until the defect has been repaired. Specialty consultation before discharge is important because controversy continues regarding the best time and indications for operative repair. Repair may be delayed 1 to 2 weeks in adults, whereas children require a shorter time for follow-up and repair. Naso-orbito-ethmoid fractures require admission for specialty consultation with facial surgery and neurosurgery.

Emergent ophthalmology consultation is required for associated ocular injury. **Retrobulbar hematoma or malignant orbital emphysema may create an ocular compartment syndrome, resulting in an acute ischemic optic neuropathy (Figure 259-12).** Physical examination findings include exophthalmos, decreasing visual acuity, and increased intraocular pressure. Emergency lateral canthotomy reduces ocular pressure and ischemia. Orbital fissure syndrome results from a fracture of the orbit involving the superior orbital fissure with injury to the oculomotor and ophthalmic divisions of the trigeminal nerve. Physical examination findings include paralysis of extraocular motions, ptosis, and periorbital anesthesia. Orbital apex syndrome occurs when the optic nerve is also involved, resulting in the preceding physical examination findings and diminished visual acuity.

ZYGOMA FRACTURES

The prominent location of the zygoma results in frequent fractures. Zygomatic arch fractures occur when an anterior and lateral force is applied typically from a fist or blunt object. **The less common zygomaticomaxillary (or "tripod") fracture results classically from a high-energy deceleration injury with disruption of the zygomaticofrontal suture, zygomaticotemporal junction, and infraorbital rim (Figures 259-13).** Because the zygoma forms the inferior and lateral walls of the orbit and superior and lateral roof of the maxillary sinus, zygomaticomaxillary fractures are considered orbital and sinus fractures.

On physical examination, flattening of the malar eminence will be noted in the absence of often significant swelling (Figure 259-1). The eye may appear to tilt as the lateral canthus is pulled inferiorly, often with a large lateral subconjunctival hemorrhage. Trismus results from masseter spasm or mechanical impingement of either the temporalis muscle or coronoid process of the mandible. Place a finger adjacent to the maxillary molars and palpate the posterior surface of the arch for tenderness or loss of the space compared to the uninjured side. Diplopia, infraorbital anesthesia, and crepitus occur with significant orbital and sinus involvement. Facial CT is needed to define the extent of the injury.

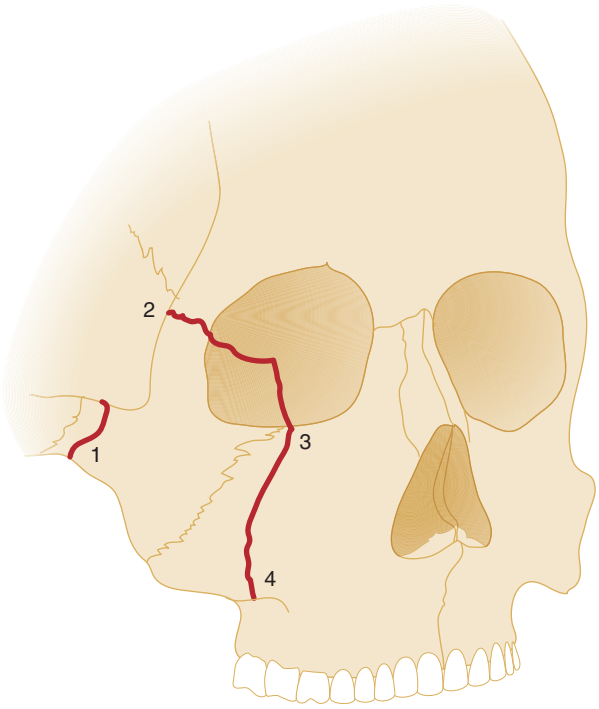


FIGURE 259-13. Tripod fracture locations. Zygomatic arch fracture (*1*), lateral orbital rim fracture (*2*), inferior orbital rim fracture (*3*), and lateral wall of maxillary sinus fracture (*4*). [Reproduced with permission from Schwartz DT: *Emergency Radiology: Case Studies.* © 2008, McGraw-Hill, New York.]

Patients with isolated temporal arch fractures can be discharged with appropriate medications and follow-up. Patients with zygomaticomaxillary fractures with any loss of vision or significant displacement require admission for IV antibiotics and operative repair.

MIDFACIAL FRACTURES

Midfacial fractures can be caused by motor vehicle crashes, sports, assault, and falls due to seizures or intoxication or in the elderly. The incidence of midfacial fractures in motor vehicle crashes has declined significantly due to improvements in vehicle restraint systems.[30] Fractures of the maxilla require a significant force such as an unrestrained motor vehicle crash patient whose face strikes the dashboard or the severely battered patient.

Le Fort injuries often present dramatically, with significant hemorrhage, early swelling, bilateral orbital ecchymosis, and cerebrospinal fluid leaks in Le Fort II and III injuries. Each pattern results in a unique movement of the midface while gently rocking the hard palate with one hand and stabilizing the forehead with the other hand (**Figure 259-14**). **Le Fort I** is a transverse fracture separating the body of the maxilla from the pterygoid plate and nasal septum. Only the hard palate and teeth move, similar to a loose upper denture. **Le Fort II** is a pyramidal fracture through the central maxilla and hard palate. Movement of the hard palate and nose occurs, but not the eyes. **Le Fort III** is craniofacial dysjunction when the entire face is separated from the skull from fractures of the frontozygomatic suture line, across the orbit and through the base of the nose and ethmoids. The entire face shifts with the globes held in place only by the optic nerve. A **Le Fort IV** fracture includes characteristics of the Le Fort III and also involves the frontal bone. CT scan of the face with coronal and axial slices with three-dimensional reconstructions best defines these complex injuries.

Patients with Le Fort injuries often present with significant hemorrhage, requiring airway protection and nasal packing. Oral packing is often required for control of fractures involving the hard palate. Le Fort injuries require admission for management of significant associated injuries, IV antibiotics, and surgical repair.

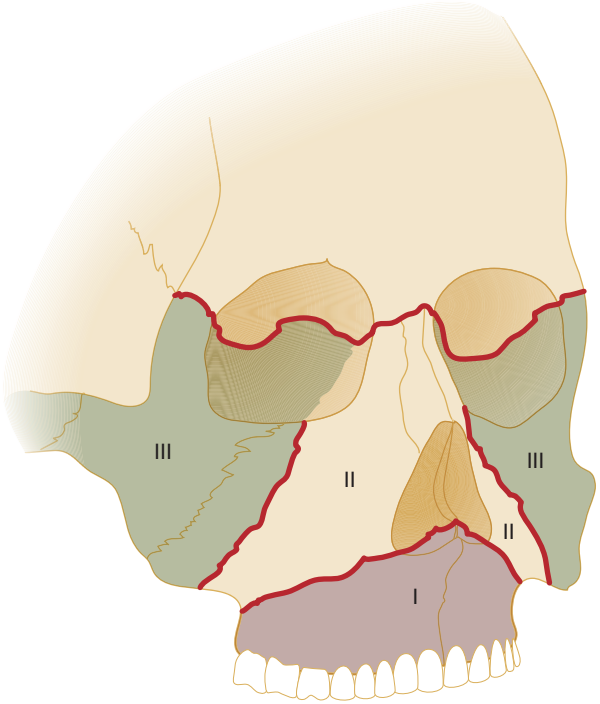


FIGURE 259-14. Le Fort injury patterns. Illustration of the fracture lines of Le Fort I (alveolar), Le Fort II (zygomatic maxillary complex), and Le Fort III (craniofacial dysjunction) fractures. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]

MANDIBLE FRACTURES

Mandible fractures are the second most common facial fracture after nasal fractures. Assaults, motor vehicle crashes, and falls are the most commonly reported mechanisms.[31] One large trauma center reported 36% of fractures in the region of the angle, followed by 21% in body, and 17% in the parasymphyseal region.[32] Always look for multiple mandibular fractures with one injury at the site of impact and a second subtle injury on the opposite side of the ring. In fact, a mandibular fracture should be considered bilateral until proven otherwise. Comminuted mandible fractures could result in upper airway obstruction due to the tongue being unsupported anteriorly. Presume an open fracture until a thorough intraoral examination determines otherwise. Fractures are classified as either favorable or unfavorable, depending on whether the musculature reduces or opens the fracture.

Patients with mandible fractures usually complain of malocclusion with pain worsened by attempted movement. On inspection, the mandible may appear widened or displaced to one side. Patients may present with trismus due to pain and swelling. Palpation reveals loss of the smooth counters of the mandible, tenderness, and anesthesia in the distribution of the proximal inferior alveolar or distal mental nerve. **A careful intraoral examination is important to exclude small breaks in the mucosa seen with open fractures, sublingual hematoma or ecchymosis, and dental or alveolar ridge fractures and to identify missing teeth.** Examine the ears for evidence of tympanic membrane perforation, hematotympanum, or evidence of condyle displacement. Place a finger into the external auditory canal and ask the patient to open and close the mouth to palpate for injury to the condyle.

Panorex remains the initial imaging study in patients with a low clinical suspicion of injury (**Figure 259-15**). Order mandible or face CT with coronal and axial sections in patients suspected of having condyle fractures, complex fractures, or multiple facial fractures. A chest radiograph is necessary in the unconscious patient with missing teeth to exclude aspiration of the missing teeth.

In the patient with a stable airway, placement of a Barton's bandage, an ace wrap over the top of the head and underneath the mandible, will stabilize the fracture and help relieve pain. Administer pain control and antibiotics, such as penicillin G 2 to 4 million units IV (or clindamycin, 600 to 900 milligrams, in penicillin-allergic patients), for open fractures. Although studies question the utility of antibiotics, given the overwhelming number of potentially virulent oral anaerobes contaminating open mandible fractures, antibiotics remain a logical therapeutic agent.[33,34] Patients with closed fractures may be given urgent outpatient follow-up. Open fractures require admission for operative repair.

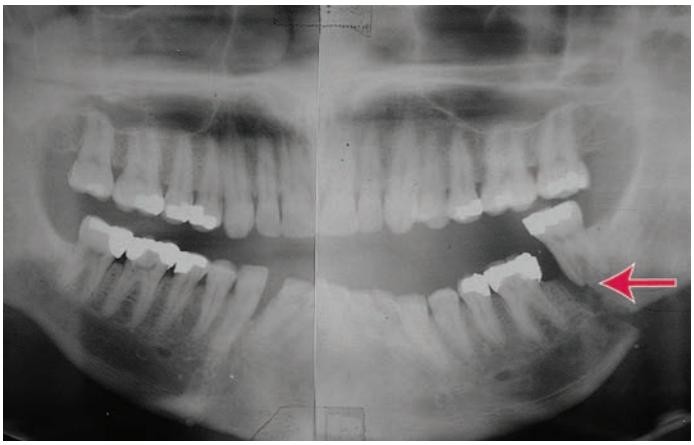


FIGURE 259-15. Mandible fracture. Panoramic view demonstrating an unfavorable mandibular fracture with obvious misalignment (*arrow*) due to the distracting forces of the masseter muscle. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, New York.]

PEDIATRIC CONSIDERATIONS

Facial fractures in the pediatric population are typically due to falls, bicycle accidents, pedestrian accidents, and transport accidents. The nasal bones and mandible are most commonly fractured.[35] Several unique considerations must be made in the initial management of the pediatric patient with facial trauma. Cricothyrotomy is contraindicated in patients <8 years old because the cricothyroid membrane is not developed until age 8 and should be avoided in those between 9 and 12 years of age. In children with severe midfacial injury in whom oral endotracheal intubation is not possible, laryngeal mask airway placement or needle cricothyrotomy serves as a temporizing measure pending emergency tracheostomy. Facial trauma in children should always prompt the consideration of child abuse.

Skull development predisposes children to certain facial and associated injuries while making others less likely. The child's high center of gravity, relatively poor balance, explorative nature, and prominent forehead make the child more susceptible to frontal bone impact and underlying brain injury. Cervical spine injury in children occurs at higher levels and more often without bony radiographic injury (spinal cord injury without radiologic abnormality). The maxillary sinuses do not begin developing until age 6 years old, which reduces the incidence of midfacial fractures compared with adults.

The pliable pediatric orbital floor is more likely to bend and crack, forming a small "trapdoor" through which muscle and fat become entrapped and potentially ischemic.[36] Pediatric mandible fractures are more likely to be incomplete fractures and more irregular secondary to the underlying developing teeth.[37] Rapid bone remodeling in children with callus formation begins within 1 week and makes delayed reduction difficult. Children with mandible fractures require prompt diagnosis and 1- to 2-day referral to a pediatric facial surgeon to prevent long-term problems with asymmetrical facial growth, cosmetic deformities, and difficulty with mastication.[38]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 260

Trauma to the Neck

Ashley S. Bean

INTRODUCTION

The human neck contains numerous vital structures. Both blunt and penetrating injuries can damage structures from many organ systems. The challenge is to treat immediate, life-threatening complications of neck injury, such as airway compromise and hemorrhage, while recognizing subtle signs of serious pathology.

ANATOMY

The neck is anatomically defined by triangles, zones, and fascial planes. Each sternocleidomastoid muscle separates the neck into two descriptive triangles, anterior and posterior (**Figure 260-1**). The posterior triangle is bordered by the anterior surface of the trapezius, posterior surface of the sternocleidomastoid muscle, and the middle third of the clavicle. The anterior triangle is formed by the borders of the sternocleidomastoid muscle, inferior mandible, and midline of the neck. Most vital structures are contained within the anterior triangle.

The anterior triangle is further subdivided into three horizontal zones (**Figure 260-2**), which have historically determined whether a patient undergoes mandatory surgical exploration or further diagnostic evaluation. Using this classification system, the index of suspicion for injury to a particular structure is dictated by the zone (**Table 260-1**). **Classically, zone II injuries undergo surgical exploration; zone I and III wounds undergo further evaluation.** This zone-based approach assumes a direct correlation between the site of the external wound and damage to deep structures; however, the trajectory of the penetrating object can be difficult to determine clinically, and nearly half traverse multiple zones.[1,21–23]

Finally, the neck is divided into fascial planes (**Figure 260-3**). The platysma is a thin muscle that stretches from the facial muscles to the thorax, demarcating superficial from deep wounds. **Wounds that do not penetrate the platysma are not life threatening.** The platysma muscle is enclosed within superficial fascia anteriorly and deep fascia posteriorly. The deep fascia is comprised of the investing, pretracheal, and prevertebral fascia and the carotid sheath.[3] These fascial layers compartmentalize neck structures and, thus, can prevent exsanguination by confining hematomas. Conversely, increased pressure from expanding hematoma or edema can compromise the airway. Further, the layers can serve as a conduit for infection tracking from the neck into the mediastinum.

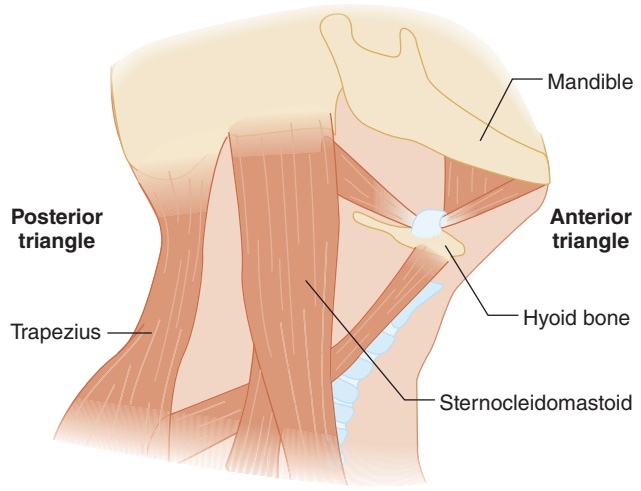


FIGURE 260-1. Triangles of the neck.

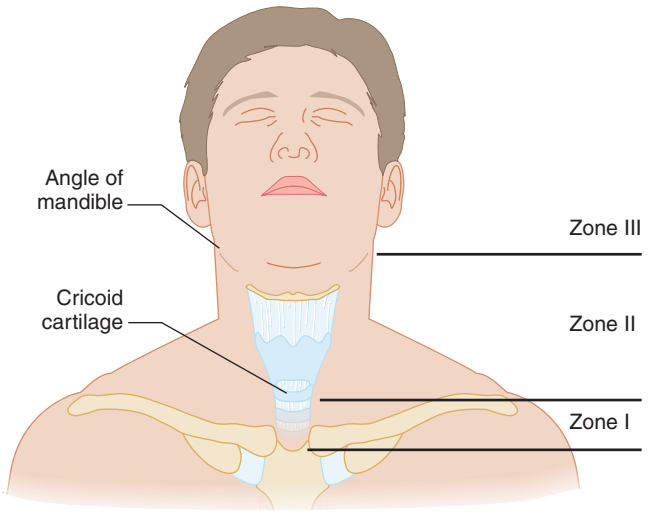


FIGURE 260-2. Zones of the neck.

INITIAL MANAGEMENT OF NECK INJURIES

The initial management of neck trauma follows the Advanced Trauma Life Support Guidelines with the systematic Airway, Breathing, Circulation, and Disability approach. Perform a primary survey to identify and treat immediate life-threatening injuries, followed by a secondary survey to discover further injuries.

AIRWAY

Many patients with neck trauma have signs and symptoms of airway compromise.[4] Patients with shock, airway obstruction, impending airway collapse, or altered mental status require immediate airway control (**Table 260-2**). Promptly intubate any patient at risk for airway compromise (**Table 260-3**) as airway anatomic distortion can progress rapidly. **Assume a difficult airway in a patient with neck trauma.** Keep all your adjuncts to intubation, as well as a secondary means of securing the airway, readily available.

Rapid-sequence orotracheal intubation, the preferred modality for securing the airway in patients with neck trauma, is successful in 98%

TABLE 260-1 Anatomic Zone and Structures of the Anterior Neck

Neck Zone	Anatomic Boundaries	Structures
Zone 1	Clavicles to the cricoid cartilage	Proximal carotid vertebral arteries Major thoracic vessels Superior mediastinum Lungs Esophagus Trachea Thoracic duct Spinal cord
Zone 2	Cricoid cartilage to the angle of the mandible	Carotid and vertebral arteries Jugular veins Esophagus Trachea Larynx Spinal cord
Zone 3	Angle of the mandible and the base of the skull	Distal carotid and vertebral arteries Pharynx Spinal cord

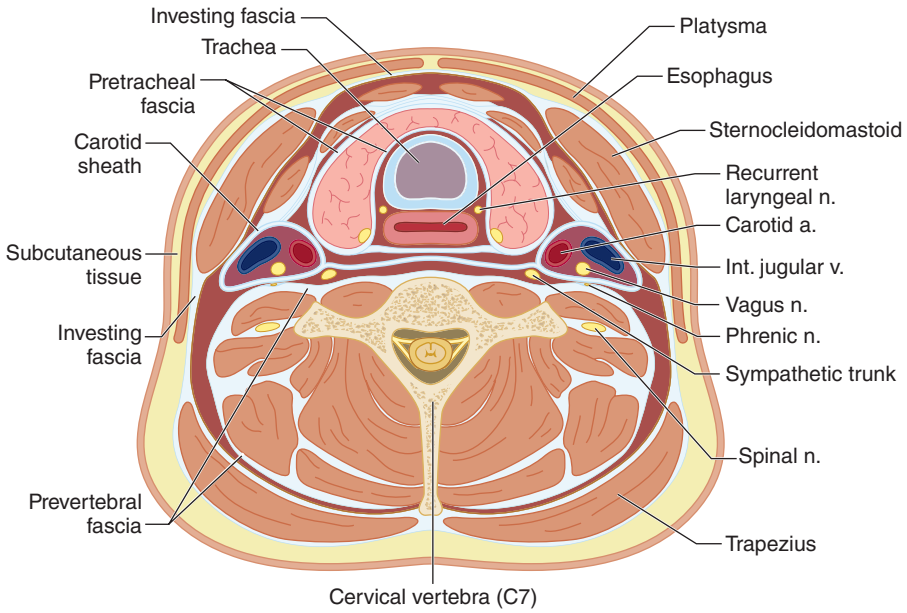


FIGURE 260-3. Fascial layers of the neck. a. = artery; Int. = internal; n. = nerve; v. = vein.

of patients, and may decrease the risk of hematoma expansion due to bucking or coughing.[5] Cricoid pressure and positive-pressure ventilation prior to intubation may worsen airway injuries.[6] When bag-mask ventilation is contraindicated or proves difficult due to airway distortion or physical characteristics, perform an awake, orotracheal intubation using a sedative or local anesthetic without a paralytic. Anticipate difficulty with bag-mask ventilation in patients with facial hair precluding a seal; unstable midfacial fractures; airway obstruction from blood, vomitus, or expanding hematoma; subcutaneous emphysema; or an open laryngeal injury that allows external passage of air.

Video laryngoscope–guided intubation[7] and endotracheal intubation over a fiberoptic bronchoscope are useful techniques to secure the airway.[8] Video laryngoscopes with an endotracheal tube channel cause less manipulation of the pharynx and may be preferred in patients with neck trauma. Additionally, the video laryngoscope may be used to guide a fiberoptic bronchoscope by allowing visualization of the relation of the larynx to the bronchoscope tip.[9]

The laryngeal mask airway is a bridging device but is contraindicated in patients with significant airway distortion. Even if effective, the laryngeal mask airway is only a temporary method for ventilating trauma patients, not a definitive airway.

A surgical cricothyrotomy, or needle cricothyrotomy if the patient is younger than 12 years of age, is generally the last step in the failed airway management. Patients with neck trauma are at increased risked for requiring a surgical cricothyrotomy due to disruption of the laryngotracheal anatomy.[6] In patients with extensive airway injuries, consider a surgical airway as the preferred primary modality.[5] Although there are no absolute contraindications to cricothyrotomy, relative contraindications include suspected or known tracheal transection, fractured larynx, or laryngotracheal disruption with retraction of the distal segment into the mediastinum. Tracheal transection can occur in patients with a "clothesline injury." In such patients, pharmacologic paralysis may cause loss of muscle tone with disruption of the proximal and distal tracheal segments. However, failure of intubation is an absolute indication for cricothyrotomy or surgical tracheostomy.[5] If the patient has an open laryngeal disruption, you can perform direct intubation through the wound into the distal segment.

BREATHING

Pneumothorax and hemothorax are present in up to 20% of patients with penetrating neck trauma. Auscultate for the presence or absence of breath sounds during the primary survey. Suspect tension pneumothorax in patients with unilateral breath sounds, hypotension, and respiratory distress, and treat with needle decompression and/or placement of a thoracostomy tube. Needle decompression at the fourth or fifth intercostal space in the anterior axillary line is more likely to successfully penetrate the chest wall.[10,11] Provide continuous pulse oximetry monitoring and supplemental oxygen.

CIRCULATION

Exsanguination is the proximate cause of death in most penetrating neck injury victims.[4] Massive bleeding from trauma kills more rapidly than an unstable airway. Control hemorrhage by applying direct pressure to bleeding wounds. Be careful not to simultaneously occlude both carotid arteries or obstruct the patient's airway. Do not blindly clamp vessels in the ED because this practice can lead to cerebral ischemia or nerve injury. If life-threatening hemorrhage is not controlled by simple

TABLE 260-2 Clinical Factors Indicating Need for Aggressive Airway Management

- Stridor
- Acute respiratory distress
- Airway obstruction from blood or secretions
- Expanding neck hematoma
- Profound shock
- Extensive subcutaneous emphysema
- Alteration in mental status
- Tracheal shift

TABLE 260-3 Relative Indications for Airway Management

- Progressive neck swelling
- Voice changes
- Progressive symptoms
- Massive subcutaneous emphysema of the neck
- Tracheal shift
- Alteration in mental status
- Expanding neck hematoma
- Need to transfer symptomatic patient
- Symptomatic patient with anticipated prolonged time away from ED

pressure, you can insert a Foley catheter into the wound tract and inflate the balloon until bleeding stops or you encounter resistance.[12] Tactical medicine experience suggests that topical hemostatic static agents may improve the survival of patients with bleeding not controlled by pressure. Hemostatic dressings combined with direct pressure appear to decrease blood loss and increase patient survival.[13] Hemostatic dressings applied to bleeding wounds during civilian prehospital transport demonstrated a 95% success rate of achieving hemostasis; half of the injuries treated with hemostatic dressing were head and neck wounds.[14] Additionally, hemostatic dressings may benefit patients with uncontrolled bleeding who need transfer to another hospital for definitive care. Patients with uncontrolled hemorrhage despite these attempts require immediate surgery.[15] If subclavian vessels are involved, uncontrolled hemorrhage in zone I injuries may require emergent thoracotomy.

DISABILITY

Unstable cervical spine injury is uncommon in awake, neurologically intact patients with an **isolated penetrating neck injury**.[16] Vertebral fractures and spinal cord injury are exceedingly rare in patients with isolated stab wounds to the neck.[17] Therefore, cervical collar placement may be detrimental by obscuring the injury and increasing the difficulty of hemorrhage control and intubation.[13] Cervical collars should not be maintained at the expense of monitoring the injury or lifesaving procedures.

Spinal cord damage is more likely from gunshot wounds, and cord damage is sustained at the time of injury. Deficits should be evident at time of presentation unless the patient has an altered sensorium. Place a cervical collar on patients with a neurologic deficit or altered mental status precluding exam, after checking the neck to identify any penetrating injuries, vascular thrills or bruits, or bleeding or hematoma.[18]

However, patients with blunt neck trauma frequently have cervical spine fractures, so maintain cervical spine immobilization in such injuries.[19]

INITIAL RADIOLOGIC EVALUATION

Although conventional radiographs of the chest and neck may suggest a variety of pathologies in the patient with neck trauma (**Table 260-4**), most patients with penetrating or blunt neck trauma will require advanced imaging in the form of multidetector CT angiography (MDCTA), MRI, or magnetic resonance angiography. Obtain a chest radiograph to evaluate for pneumothorax and hemothorax in patients with neck trauma because there is a high incidence of these thoracic complications. In addition, pneumothorax and hemothorax can be detected rapidly by bedside ultrasound. Do not delay transfer of patients between hospitals or to the operating room to obtain conventional radiographs of the neck.

TABLE 260-4 Pathologic Findings on Conventional Radiographs

Chest radiograph
- Pneumothorax
- Hemothorax
- Mediastinal air
- Widened mediastinum
- Subcutaneous emphysema
- Foreign body or bullet fragments
- Pulmonary edema
- Aspiration pneumonia

Soft tissue neck radiograph
- Prevertebral air
- Foreign body or bullet fragments
- Tracheal narrowing or deviation
- Subcutaneous or retropharyngeal emphysema

Cervical spine radiograph (anteroposterior, lateral, and odontoid)
- Vertebral fracture
- Hyoid bone fracture

TABLE 260-5 Signs and Symptoms of Neck Injury

Hard	Soft
Vascular injury	
Shock unresponsive to initial fluid therapy	Hypotension in field
Active arterial bleeding	History of arterial bleeding
Pulse deficit	Nonpulsatile or nonexpanding hematoma
Pulsatile or expanding hematoma	Proximity wounds
Thrill or bruit	
Laryngotracheal injury	
Stridor	Hoarseness
Hemoptysis	Neck tenderness
Dysphonia	Subcutaneous emphysema
Air or bubbling in wound	Cervical ecchymosis or hematoma
Airway obstruction	Tracheal deviation or cartilaginous step-off
	Laryngeal edema or hematoma
	Restricted vocal cord mobility
Pharyngoesophageal injury	
	Odynophagia
	Subcutaneous emphysema
	Dysphagia
	Hematemesis
	Blood in the mouth
	Saliva draining from wound
	Severe neck tenderness
	Prevertebral air
	Transmidline trajectory

DIAGNOSIS AND TREATMENT

Any wound deep to the platysma raises concern for damage to the vital structures of the neck. Simple diagnostic maneuvers add valuable information to the physical exam. Instruct awake and cooperative patients to cough (to check for hemoptysis), to swallow saliva (to assess for dysphagia from esophageal injury), and to speak (to evaluate for laryngeal fracture). **In patients with penetrating neck trauma, a careful, structured physical exam is more than 95% sensitive for detecting clinically significant vascular and aerodigestive injuries.**[16] The physical exam is most accurate for identifying arterial injuries; conversely, esophageal and venous injuries may be missed. Assess the patient for "hard" and "soft" signs of injury (**Table 260-5**).[8] **Nine out of 10 patients with hard signs will have an injury requiring repair and should be rapidly transferred to the operating room or angiography suite.** If your institution does not have the requisite surgical or diagnostic capabilities readily available, transfer to an appropriate hospital. Presence of soft signs increases suspicion of structural damage and indicates the need for additional diagnostic evaluation; however, only a minority of patients with soft signs will have a clinically significant injury.[8]

PENETRATING NECK INJURY

Although penetrating neck wounds account for only 1% of traumatic injuries, the mortality rate is as high as 10%.[4] Gunshot wounds and stab wounds are the predominant mechanisms of injury, whereas flying debris and sharp object impalement are less frequent causes.[4,20] Patients often have significant concurrent wounds to the head, chest, or abdomen.[4]

Gunshot wounds are more likely than stab wounds to cause vascular and aerodigestive system damage. Transcervical gunshot wounds have at least a 70% chance of substantial associated injuries. **Vascular injuries are the most common cervical injury and the leading cause of death from penetrating neck trauma.** The remainder of associated neck injuries are split among spinal cord, aerodigestive tract, and peripheral nerve injuries.[8]

There is no debate regarding the treatment of unstable patients with clear evidence of vascular or aerodigestive injury—this group of patients should undergo invasive intervention.[1,4] Controversy arises in two areas concerning the management of stable patients:

1. Should all zone II injuries undergo mandatory exploration?
2. Should all zone I and III injuries undergo a specific, extensive battery of diagnostic testing?

GENERAL TREATMENT OPTIONS

MANDATORY OPERATIVE EXPLORATION

Historically, all zone II injuries were surgically explored. This aggressive practice began during World War II as a response to a high incidence of missed injuries and mortality, but selective management is generally recommended today to minimize unnecessary surgery. Zone II is the most commonly injured area and is easily accessed surgically. Exposure and vascular control are more difficult for zone I and III injures, so most patients with zone I and III injuries undergo angiography and endoscopy to determine the need for operative intervention.

SELECTIVE MANAGEMENT

The movement toward selective management rather than mandatory exploration began in response to the high rate of negative neck explorations. Furthermore, advocates of a more conservative methodology cite the sensitivity of physical exam in detecting clinically significant injuries. Contrarians maintain concerns about missed lethal injuries when relying solely on the clinical exam. Less invasive, selective protocols, which mandate rapidly obtained angiography, esophagography, and panendoscopy, have radically decreased nontherapeutic neck operations without increasing morbidity and mortality; however, the yield of angiography and endoscopic studies in asymptomatic patients is exceedingly low.[4,8]

NO-ZONE TARGETED DIAGNOSTIC WORKUP

A new iteration in selective management has evolved with the addition of information gleaned from MDCTA to the diagnostic process. MDCTA now permits fast, reliable information about injuries in all neck zones. Furthermore, physical examination plus MDCTA is up to 100% sensitive and 97.5% specific for detecting significant vascular or aerodigestive injury. Perhaps more importantly, the negative predictive value for arterial injury is 98% to 100%. Unlike angiography, MDCTA also allows assessment of the aerodigestive tracts and the cervical spine.[3]

In addition to defining specific injuries, MDCTA can determine if the wound track approximates important structures. Wounds with a trajectory not concerning for injury do not need further invasive (angiographic or endoscopic) workup. Conversely, trajectories in close proximity to vital structures should prompt a targeted diagnostic workup. Disadvantages of MDCTA include exposure to ionizing radiation, use of iodinated IV contrast, and image artifacts due to motion or metallic foreign bodies.[21] Less than 2% of MDCTAs are nondiagnostic due to artifact.[22]

One concern is that undergoing post-MDCTA angiography poses unnecessary contrast nephropathy risk for patients suffering penetrating neck injuries. However, several studies suggest that the incidence of postcontrast nephropathy is much lower than formerly believed.[23-26]

A penetrating neck trauma protocol (**Figure 260-4**) that combines a structured physical exam and MDCTA dramatically reduces formal neck explorations.[1,27] In this scheme, the zone of injury has little impact on the management of the patient because the neck is considered to be a single unit. Per this protocol (see Figure 260-4), symptomatic patients with hard signs of neck injury undergo emergent operative or angiographic intervention. Symptomatic patients with only soft signs of injury are at intermediate risk and should undergo MDCTA. Further diagnostic testing can be guided by MDCTA findings. Symptomatic patients with an indeterminate MDCTA artifact should undergo traditional testing.[1,28]

Asymptomatic patients are at low risk for injury. A study of 99 asymptomatic patients (80% underwent MDCTA) demonstrated no clinically significant injuries. No patient is this group underwent further diagnostic testing.[29] Specific concern for digestive tract injuries can be addressed via esophagoscopy or esophagram; potential laryngotracheal injuries can be evaluated with endoscopy. Trauma centers with a high volume of penetrating neck injuries may opt to observe patients with serial physical exams in lieu of advanced diagnostic testing.[29]

PENETRATING VASCULAR INJURIES

Vascular injuries are present in up to 40% of patients with penetrating neck trauma and are the most commonly associated cervical injury in this population. Arterial injuries, which predominantly involve the carotid artery, account for 45% of penetrating neck vascular trauma and are the most frequent cause of death.[4,8] The morbidity and mortality of vascular injuries are related both to exsanguination and neurologic complications.[3] For instance, **carotid artery injury** leads to stroke in 15% of patients and death in up to 22%. **Venous injuries** are discovered in up to 20% of patients with penetrating neck wounds. Signs of venous injury are often subtle and difficult to identify by physical exam; however, most asymptomatic venous injuries do not require repair.

The overwhelming majority of patients with hard signs of vascular injury (Table 260-5) will require operative intervention. In contrast, while up to one quarter of patients with soft signs of vascular injury will have a vascular abnormality identified at angiography, only 3% of these patients will require vascular repair.[8]

DIAGNOSIS AND TREATMENT

Several imaging modalities are useful during the evaluation of vascular neck trauma (**Table 260-6**). Although angiography remains the gold standard for investigating penetrating neck vascular injuries, **MDCTA is now the first-line imaging modality**.[3] Angiography continues to be useful, however, in specific circumstances. MDCTA findings that are inconclusive or incongruent with the patient's clinical exam should be refined by angiography.[30] In addition, stable patients with injuries suitable for endovascular repair may undergo definitive angiographic intervention.[3]

Disadvantages of **angiography** include its inability to provide a comprehensive evaluation of nonvascular neck structures, limited availability, and mobilization of additional personnel.[2] Potential complications include contrast-induced nephropathy, puncture site hematoma, thrombosis, embolism, vascular spasm, ischemia, and arterial dissection.

The advent of CT angiography and improvements in multidetector CT technology have revolutionized the diagnosis and treatment of penetrating neck injuries. MDCTA images the vascular, aerodigestive, and osseous structures of the neck. Furthermore, MDCTA is sensitive for the detection of injury, can be rapidly performed, and is noninvasive, accurate, and widely available.[2]

Color flow Doppler US is highly sensitive for detecting clinically important vascular injuries. Advantages of US include its portability, noninvasive nature, lack of ionizing radiation, and relatively decreased capital expense. Disadvantages include the inability to scan through subcutaneous emphysema, hematoma, marked operator variability, and limited availability. Additionally, US cannot penetrate bone and is thus unable to image intrathoracic or intracranial vessels.[2] Finally, it cannot evaluate the aerodigestive structures of the neck.[2]

MRI or MRI angiography in patients with metallic projectiles is contraindicated due to concern for ferromagnetic material.[3] Furthermore, the role of MRI in the diagnosis of aerodigestive injuries has not been evaluated. Thus, MRI cannot be used to comprehensively evaluate neck structures.[2] MRI may play a select role in the evaluation of nonprojectile penetrating trauma that involves the cervical spine.[31]

Treatment of vascular injuries depends on the vessel involved and accessibility of the lesion. Options vary from observation to surgical repair to angiographic embolization or stenting. Patients with carotid artery injuries that are asymptomatic, low-velocity injuries, or small intimal tears or pseudoaneurysms may not need repair if they have intact distal circulation and reliable surgical follow-up.

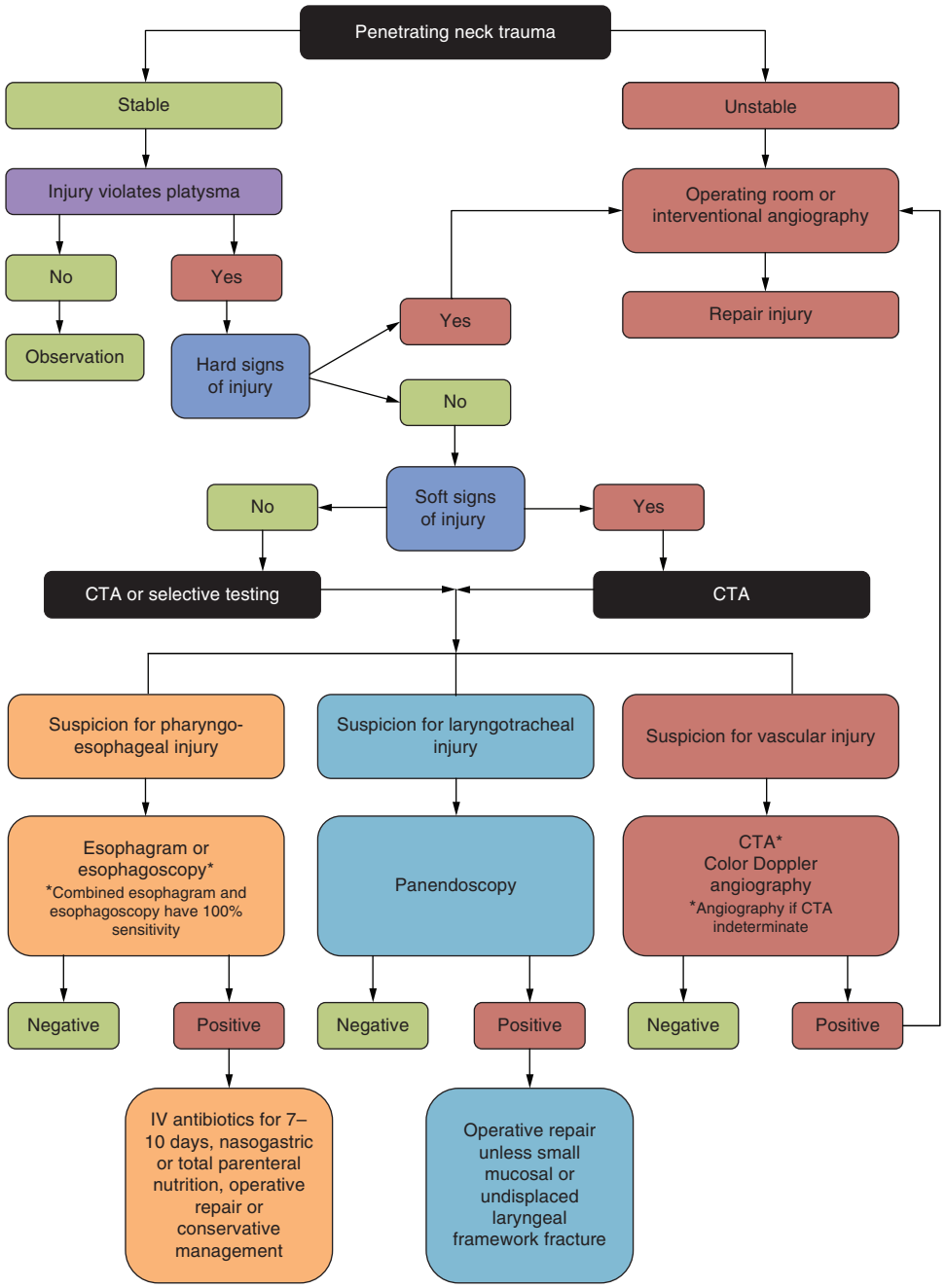


FIGURE 260-4. Penetrating neck trauma protocol. CTA = CT angiography.

BLUNT NECK INJURY

Blunt neck trauma composes only 5% of traumatic injuries to the neck. Road traffic accidents are the most common cause of blunt neck trauma. Other causes of blunt neck injury include assault, pedestrians struck by vehicles, falls, and hanging.[32] While vascular injury occurs in approximately 1% of patients with blunt neck trauma, cervical aerodigestive injuries are rare. As with penetrating neck trauma, patients with blunt neck injury frequently have significant associated injuries. In contrast, airway occlusion rather than hemorrhage is the most rapidly fatal injury.

BLUNT CAROTID AND VERTEBRAL DISSECTION

The mortality rate of symptomatic blunt cerebral vascular injury approaches 60%.[31] However, most patients with blunt cerebral vascular injury are initially asymptomatic and do not develop neurologic symptoms for hours to days.[32] Fortunately, angiographic screening of certain asymptomatic patients for blunt cerebral vascular injury can increase the likelihood of diagnosis 10-fold.[31] Moreover, early identification and treatment of blunt cerebral vascular injury significantly reduce the rate of stroke and death.[32] Numerous screening criteria can be used to increase blunt cerebral vascular injury detection in asymptomatic patients (**Table 260-7**).[17,33,34] Unfortunately, if using traditional screening criteria, 20% of blunt cerebral vascular injuries occur without any established risk factor. To capture all injuries using injury pattern modeling, an estimated 96% of trauma patients would need to be screened[35]; however, a proposed expanded Denver screening protocol is purported to reduce the number of missed blunt cerebral vascular injuries to 5%.[36]

The mechanism of injury for blunt cerebral vascular injury is cervical hyperextension and rotation or hyperextension during rapid deceleration, which can result in intimal dissections, thromboses, pseudoaneurysms, fistulas, and transections.[33] Intimal tears expose subendothelial collagen that acts as a substrate for platelet aggregation. The subsequent

TABLE 260-6 Vascular Evaluation of Penetrating Neck Trauma

Imaging Modality	Advantages	Disadvantages
Catheter angiography	Gold standard Both diagnostic and therapeutic Access to zone I and III injuries where surgical repair is difficult	Invasive Expensive Labor intensive Requires skilled operators
Helical CT angiography	Readily available Fast Minimally invasive Visualization of missile trajectory High-resolution images of vascular, aerodigestive, and bone structures with single study	Only diagnostic, not therapeutic Requires IV contrast Image quality affected by technique of contrast injection Metallic streak artifact may obscure findings Limited evaluation of low zone I and high zone III injuries May miss small intimal flaps, pseudoaneurysms, and arteriovenous fistulas
Duplex ultrasonography	Noninvasive Inexpensive No contrast medium	Highly operator dependent Limited view of zones I and III Obscured by subcutaneous emphysema and hematomas May miss small lesions

thrombus can embolize, cause stenosis, or create critical vessel occlusions. Furthermore, tears can provide a pathway for dissection.

DIAGNOSIS AND TREATMENT

Digital subtraction angiography is the gold standard for the diagnosis of blunt cerebral vascular injury. Rapid diagnosis and treatment are crucial. Due to the lack of digital subtraction angiography availability and potential complications associated with this procedure, many institutions use MDCTA as the initial screening modality. While MDCTA has a negative predictive value approaching 100% for subsequent stroke, it has a false-positive rate of approximately 45%. To avoid unnecessary anticoagulation, a reasonable approach is to use MDCTA as a screening exam followed by digital subtraction angiography to confirm true positives. Continue anticoagulation until digital subtraction angiography results confirm the need for further therapy.[37]

US has a low sensitivity for blunt cerebral vascular injury and should not be used as a screening test.

MRI has a variable sensitivity (50% to 100%) and specificity (29% to 100%) as compared to digital subtraction angiography for detection of blunt cerebral vascular injury. Therefore, do not use MRI as the sole screening study for blunt cerebral vascular injury unless the patient has an absolute contraindication to iodinated contrast.[38]

Patients with untreated or undiagnosed blunt cerebral vascular injury have up to a 60% risk for stroke with rates increasing with injury grade severity.[39] Antithrombotic agents (aspirin, clopidogrel, or heparin) and operative or interventional angiographic repair are blunt cerebral vascular injury treatment options. Antithrombotic agents dramatically reduce mortality and morbidity after blunt cerebral vascular injury[40] and are safe even if the patient has a traumatic brain injury, solid organ injury, spinal cord injury, or concomitant neurologic hemorrhage.[41,42] No differences in outcomes of blunt cerebral vascular injury patients treated with anticoagulant versus antiplatelet therapy have been demonstrated.[43,44] Specific therapy is determined by a grading scale (**Table 260-8**).

TABLE 260-7 Screening Criteria for Blunt Cerebral Vascular Injury

Signs and symptoms

- Arterial hemorrhage from nose, neck, or mouth
- Cervical bruit in patients <50 y old
- Expanding cervical hematoma
- Focal neurologic deficit: transient ischemic attack, hemiparesis, vertebrobasilar symptoms, Horner's syndrome
- Stroke on secondary CT
- Neurologic deficit unexplained by head CT

Risk factors for blunt cerebral vascular injury

- High-energy transfer mechanism and one of the following:
  - Facial fractures: Le Fort II or III fracture, mandible fracture, frontal skull fracture, orbital fracture
  - Cervical spine fracture patterns: subluxation, fractures extending into the transverse foramen, fracture at any level
  - Any basilar skull fracture or occipital condyle fracture
  - Petrous bone fracture
  - Diffuse axonal injury with Glasgow Coma Scale score ≤8
  - Concurrent traumatic brain and thoracic injuries
  - Neck hanging with anoxic brain injury
  - Clothesline type injury or seat belt injury with significant swelling, pain, or altered mental status
  - Scalp degloving
  - Thoracic vascular injuries
  - Blunt cardiac rupture
  - Upper rib fractures

TABLE 260-8 Blunt Carotid and Vertebral Artery Injury Grading Scale

Grade	Description	Treatment
Grade I	Luminal irregularity or dissection with <25% luminal narrowing	Antithrombotic agent
Grade II	Dissection or intramural hematoma with ≥25% luminal narrowing, intraluminal thrombus, or raised intimal flap	Antithrombotic agent or surgical repair if accessible
Grade III	Pseudoaneurysm	Antithrombotic agent or surgical repair if accessible
Grade IV	Occlusion	Antithrombotic agent or surgical repair if accessible
Grade V	Transection with free extravasation	Surgical repair if accessible Balloon occlusion or embolization

UPPER AIRWAY AND ESOPHAGEAL INJURIES FROM BLUNT AND PENETRATING TRAUMA

LARYNGOTRACHEAL INJURIES

Penetrating neck trauma causes laryngotracheal injury in 2% to 5% of penetrating trauma patients and has a 2% to 15% mortality rate.[1,8] **Significant laryngotracheal injuries should be detected by physical exam.** Patients with hard signs of laryngotracheal injuries (Table 260-5) need urgent airway control and operative intervention. Soft signs of laryngotracheal injury (Table 260-5) are present in approximately 18% of patients with penetrating neck injury, but only 15% of these patients will have a laryngotracheal injury diagnosed.[8]

Blunt laryngotracheal injuries occur in less than 0.5% of blunt trauma patients. The majority of blunt laryngotracheal trauma is caused by car collisions. Such injuries are rare because the larynx is protected by the mandible and supported by muscles that deflect most external forces.[45] **Patients with laryngotracheal injuries due to blunt trauma may have a quiescent phase with progressively increasing subclinical airway edema or hematoma that can result in delayed airway obstruction.**

TABLE 260-9 Laryngeal Injury Grading Scale

Grade I	Minor endolaryngeal hematoma without detectable fracture
Grade II	Edema, hematoma, minor mucosal disruption without exposed cartilage, nondisplaced fractures
Grade III	Massive edema, mucosal disruption, exposed cartilage, vocal fold immobility, displaced fracture
Grade IV	Grade III with two or more fracture lines or massive trauma to laryngeal mucosa
Grade V	Complete laryngotracheal separation

DIAGNOSIS AND TREATMENT

Evaluate patients with a history of significant anterior neck trauma or signs and symptoms of a laryngotracheal injury[45,46] with flexible fiberoptic laryngoscopy to define airway patency and the extent of intraluminal injury. CT imaging is critical in patients with suspected laryngotracheal injury without airway compromise and can impart information that influences management.[47] Treatment of laryngotracheal injuries is based on the classification system developed by Schaefer and Brown (**Table 260-9**). Patients with grade I and II injuries can be managed medically; grade III, IV, and V injuries typically require operative intervention.

PHARYNGOESOPHAGEAL INJURIES

Up to 9% of patients with **penetrating neck trauma** have pharyngoesophageal injuries. Whereas laryngotracheal injuries are usually apparent, **pharyngoesophageal injuries typically have more subtle signs, resulting in diagnostic delays**. In fact, there are no hard signs of pharyngoesophageal injury. Deaths from esophageal injury are usually due to mediastinitis and sepsis. Soft signs and symptoms (Table 260-5) that portend injury may be present and signal the need for further evaluation. Also suspect this injury if the trajectory of the bullet visualized by CT is in close proximity to the pharynx or esophagus.[3] Finally, in patients receiving conventional soft tissue neck radiographs, prevertebral air is suggestive of a pharyngoesophageal injury.

Pharyngoesophageal injuries are exceedingly rare in patients with blunt neck trauma. Between 1970 and 2003, 11 cases of cervical digestive tract injury due to blunt forces were reported. **Suspect esophageal injury in patients with a history of a sudden acceleration or deceleration event in which the neck was extended.** In this scenario, injuries occur as the esophagus is forced against the spine. However, the low incidence of injuries coupled with their subtle clinical presentation can lead to a delay in diagnosis, leading to morbidity and mortality. In patients with blunt trauma, the signs and symptoms of pharyngoesophageal injury are much more likely to result from laryngotracheal pathology.

DIAGNOSIS AND TREATMENT

Patients with hard signs of vascular or laryngotracheal injuries should undergo intraoperative endoscopy if a pharyngoesophageal injury is identified or suspected during exploration. Symptomatic patients who do not meet criteria for neck exploration can be evaluated by either direct esophagoscopy or swallowing studies.[4] Esophagoscopy is more sensitive for detecting esophageal injuries with the added benefit of quantifying the size and extent of the injury. It can be performed intraoperatively and on unstable or intubated patients. The combination of these two studies achieves 100% sensitivity for detecting these injuries.

Patients who are asymptomatic can be evaluated for digestive tract injuries with multidetector CT. Patients without evidence of injury by multidetector CT should either be observed or, if a high suspicion for injury exists, undergo direct esophagoscopy or swallowing studies using a water-soluble agent.[4]

Treat pharyngoesophageal injuries with IV antibiotics. Small pharyngeal perforations may be managed medically, whereas pharyngeal perforations larger than 2 cm and esophageal perforations require surgical repair.

STRANGULATION

Strangulation is one form of blunt neck trauma. Mechanisms include hanging, postural strangulation, ligature strangulation, and manual strangulation.[48] Accidental, homicidal, and suicidal strangulations are frequent causes of death. In fact, 10% of violent deaths in the United States are due to strangulation,[18] and hanging is the second most common means of suicide death in the United States.[49] Accidental strangulation is more frequent in children, but also occurs in adults whose clothing or hair becomes entangled in machinery or who participate in the paraphilia of erotic asphyxiation. In all forms of strangulation, death is ultimately due to cerebral anoxia and ischemia; obstruction of cerebral venous return rather than acute airway compromise is postulated to be the most common pathophysiologic mechanism of death.

CLINICAL FEATURES

Although airway compromise is envisioned by most people to be the cause of strangulation deaths, **the major pathologic mechanism is neck vessel occlusion rather than airway obstruction**. There are numerous case reports of people with functioning tracheostomies committing suicide by hanging or strangulation. Only limited pressure is needed for venous compression. If both external and internal jugular veins are simultaneously occluded, cerebral vascular congestion, edema, and unconsciousness result. Next, loss of muscle tone allows arterial compression with subsequent cerebral anoxia. Airway obstruction and carotid body reflex–mediated cardiac dysrhythmia are minor mechanisms of death in strangled patients.

In addition to cerebral anoxia, strangulation injuries include laryngotracheal fractures, cervical spine fractures, pharyngeal lacerations, and carotid artery injuries. Although hyoid bone fractures are classically associated with strangulation, they are found in a minority of these patients—even those with fatal injuries. Furthermore, except for judicial hangings, cervical spine and cord injuries are not frequently seen in patients who survive strangling. Carotid artery dissection is a rare complication, but should be suspected in a patient with a lateralizing neurologic exam or bruising or tenderness over the carotid artery. Moreover, consider unreported strangulation in young patients with acute neurologic deficits or a spontaneous carotid artery dissection.

Physical signs of strangulation include petechiae and neck contusions; however, half of victims have no visible signs of neck trauma, and two thirds are asymptomatic.[18] In fact, patients with extensive laryngeal injury may have few external signs. In those who are symptomatic, the most common complaints are neck pain, voice changes, swallowing difficulty, and breathing problems. Any of these symptoms can signal impending airway compromise and should be investigated.

Patients presenting in cardiac arrest have a dismal prognosis. Conversely, recovery of patients with neurologic symptoms is unpredictable. Patients with severe neurologic symptoms, such as a Glasgow Coma Score of 3, may recover without sequelae, whereas patients with normal initial exams may progressively deteriorate.[49] Most in-hospital, poststrangulation deaths occur due to laryngeal or pulmonary edema or cerebral anoxia.

Perhaps the most difficult task in caring for strangled patients is evaluating the "walking and talking" victim who lacks physical signs of strangulation. Victims may be under the influence of alcohol or drugs or be hyperventilating. Physicians may be tempted to ascribe symptoms to anxiety and to discount the patient's story.[18] Furthermore, there is a subset of seemingly asymptomatic patients who die after developing delayed cerebral or pulmonary edema.

DIAGNOSIS

The evaluation of patients with suspected strangulation is multifaceted and may involve radiologic imaging or endoscopy. Although pulmonary edema, aspiration pneumonia, larynx or hyoid bone fractures, or tracheal deviation caused by edema or hematoma may be visible on chest radiography, CT and MRI can provide more detailed information of

soft tissue neck structures. Radiologically demonstrated intramuscular hemorrhage or edema, swelling of the platysma, subcutaneous bleeding, and hemorrhagic lymph nodes are indicative of strangulation injury.[18] To exclude carotid dissection, carotid artery imaging should be performed on patients with neurologic deficits discordant with brain CT findings.[18] Finally, patients with symptoms of laryngeal tracheal injury such as dyspnea, dysphonia, aphonia, or odynophagia should undergo laryngobronchoscopy, which may reveal petechiae, edema, or vocal cord paralysis.[18]

TREATMENT AND DISPOSITION

Patient with hard signs of strangulation injury (**Table 260-10**) should undergo further diagnostic testing. Admit patients with abnormal radiologic or endoscopic imaging to the appropriate service and level of care. Observe symptomatic patients with normal imaging. Barring psychosocial issues, asymptomatic patients may not need further evaluation and may be discharged if friends or family are available for patient monitoring. Emphasize strict return precautions as well as education about possible delayed respiratory and neurologic dysfunction.[50]

Unconscious patients and those with progressive symptoms such as odynophagia, hoarseness, neurologic changes, or dyspnea require aggressive airway management. Patients with pulmonary edema may benefit from positive end-expiratory pressure ventilation. Furthermore, patients may develop cerebral edema, requiring strategies to reduce intracranial pressure or seizure prophylaxis.[49]

Addressing the numerous psychosocial issues that are typically present in strangled victims is a critical element of their overall coordinated treatment plan. Victims of domestic violence may need social services. Only 5% of strangled domestic violence victims seek medical attention within 2 days of the strangulation. Such patients are at high risk for subsequent harm and death from the same abuser.[18] Survivors are also at risk for posttraumatic stress disorder. Patients who have attempted suicide require psychiatric evaluation. Hangings are often one component of a complex suicide attempt. When suicide is suspected, evaluate patients for other methods of self-harm such as wrist lacerations, self-stabbing, gunshot wounds, or ingestions.[49]

TABLE 260-10 Hard Signs of Strangulation Injury

Head, Eyes, Ears, Nose, and Throat
• Visual disturbances
• Conjunctival or facial petechial hemorrhages
• Swollen tongue or oropharynx
• Foreign body (blood, vomit, tissue) in oropharynx
• Facial edema, lacerations, abrasions, ecchymosis
• Neck abrasions, edema, lacerations, or ligature marks
• Tenderness to palpation over larynx
• Hoarseness or stridor
• Subcutaneous edema or crepitus
Cardiovascular
• Cyanosis or hypoxia
• Arrhythmias
• Respiratory distress
• Crackles or wheezes
• Cough
Neurologic
• Altered mental status
• Seizures
• Stroke-like symptoms
• Incontinence

Source: Data from https://www.ncbi.nlm.nih.gov/books/NBK459192/ (Dunn RJ, Smock W: Strangulation injuries. 2017.) Accessed July 23, 2018.

SPECIAL CONSIDERATIONS

CHILDREN

Children with blunt or penetrating trauma are susceptible to the same mechanisms and injuries as adults. Additional mechanisms of injury seen in childhood include child abuse, playground trauma, and handlebar injuries during bike falls.

The initial management and indications for emergent intervention for children with penetrating neck trauma mirror those of adults. Children are at higher risk for complications from angiography, endoscopy, and ionizing radiation. Thus, the need for an extensive workup in the asymptomatic child must be critically evaluated.

Children have the same incidence of injury and ischemic sequelae of blunt cerebral vascular injury. The 40% rate of ischemic symptom development in untreated children with blunt cerebral vascular injury is reduced to nearly zero when treatment is initiated during the quiescent phase.[51]

Children have certain anatomic characteristics that protect them from laryngeal injury. In addition to being more flexible, the larynx is located in a higher, more protected position. Conversely, there are features that predispose children to developing symptomatic airway edema. During childhood, the diameter of the larynx is smaller and its mucosa is more loosely attached, allowing edema and hematomas to progress. Therefore, children are more likely to present with respiratory distress.

As with adults, pharyngoesophageal injuries are rare and often have a subtle, delayed presentation. Maintain a high index of suspicion for these injuries.

ANTICOAGULATED OR MASSIVELY BLEEDING PATIENTS

Correct coagulopathy in patients with neck trauma who are taking anticoagulants. See Table 166-5 for suggested protocols for anticoagulant reversal. The exception to this recommendation is for patients with blunt cerebral vascular trauma, because the majority of these injuries are treated with antithrombotic agents.

Finally, resuscitate massively bleeding patients with blood products in ratios as outlined by a **massive transfusion protocol**.[52] Also, consider administering tranexamic acid to bleeding trauma patients. The **CRASH-2 trial** demonstrated that this antifibrinolytic significantly reduces deaths from traumatic bleeding when given within 3 hours of the inciting injury.[53]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 261

Pulmonary Trauma

Yvonne L. Wang
David Jones

INTRODUCTION AND EPIDEMIOLOGY

Blunt thoracic trauma produces damage by direct injury, compression, and forces of acceleration or deceleration, whereas penetrating thoracic trauma causes direct injury along the path of a stab wound or projectile. Injuries most often involve the lungs and, less frequently, the heart and great vessels. Regardless of mechanism, stabilization and treatment of these patients follow a similar pathway. In general, patients with penetrating injuries who survive to reach the hospital have better outcomes than those who have sustained blunt injuries.

Blunt chest trauma from blast injuries is discussed in Chapter 7, "Bomb, Blast, and Crush Injuries." Presume penetrating chest injuries in the "cardiac box" (see Figure 262-1), an area bounded by the sternal notch, xiphoid process, and nipples, to involve the heart or great vessels until proven otherwise.

Blunt thoracic injuries account for up to one fourth of all deaths, and chest wall trauma is a component of 10% of trauma admissions.[1,2] Penetrating injuries that violate the pleura typically result in pneumothorax, with an accompanying hemothorax in most cases. In polytrauma patients, thoracic trauma is the third leading cause of death after abdominal trauma and head trauma.[3] The mechanism of injury and severity of tissue damage predict the clinical course and outcome.[2,4]

ANATOMY

The thorax is bordered superiorly by the clavicles and inferiorly by the diaphragm. There are 12 paired sets of ribs projecting forward from the thoracic vertebrae, with the upper 10 ending in a cartilaginous joint with the sternum and the bottom 2 "floating" freely. The muscular diaphragm has muscle fibers inserting into ribs 6 to 12 and posteriorly into the T12, L1, and L2 vertebrae. The thoracic cavity is created by a pleural membrane covering the inner thoracic cavity (the parietal pleura) and folding back over the lungs and other intrathoracic structures (the visceral pleura). The lungs have three lobes on the right and two lobes on the left. The mediastinum in the center of the thoracic cavity between the lungs contains the heart and its associated blood vessels, the trachea, the phrenic and cardiac nerves, the esophagus, and the thoracic duct. The trachea descends from the larynx and branches into several tiers of bronchi before ending in alveoli where gases are exchanged in the lung (**Figure 261-1**).

PATHOPHYSIOLOGY

Chest trauma can disrupt the respiratory mechanism, which can have an immediate negative impact on resuscitation and patient outcomes. Bleeding or free air in any portion of the thoracic cavity can limit lung excursion as well as lung volumes. Injury to the chest wall can decrease chest recoil, restricting the ability to generate the negative intrathoracic pressure needed for ventilation and gas exchange. Similarly, disruption of the diaphragm can inhibit the patient's ability to initiate a breath. Injury to the trachea and bronchi prevent air flow, thereby creating areas of both dead space and physiologic shunting that can impede effective oxygenation and ventilation. Injury to the lung itself can result in disrupted gas exchange due to tissue-level injury and create a ball-valve system resulting in a pneumothorax. As more gas becomes trapped in the extrapulmonary space, intrathoracic pressure increases, which limits venous return and disrupts respiratory mechanics.

CLINICAL APPROACH

HISTORY

The most frequent symptoms of thoracic trauma are chest pain and shortness of breath. Pain is most often localized to the involved area of the chest wall, but is sometimes referred to the abdomen, neck, shoulder, back, or arms. Dyspnea and tachypnea are nonspecific findings and may also be caused by blood loss, pain from other injuries, or anxiety.

PHYSICAL EXAMINATION

Rapidly perform the physical examination during the primary and secondary surveys to detect life-threatening injuries.

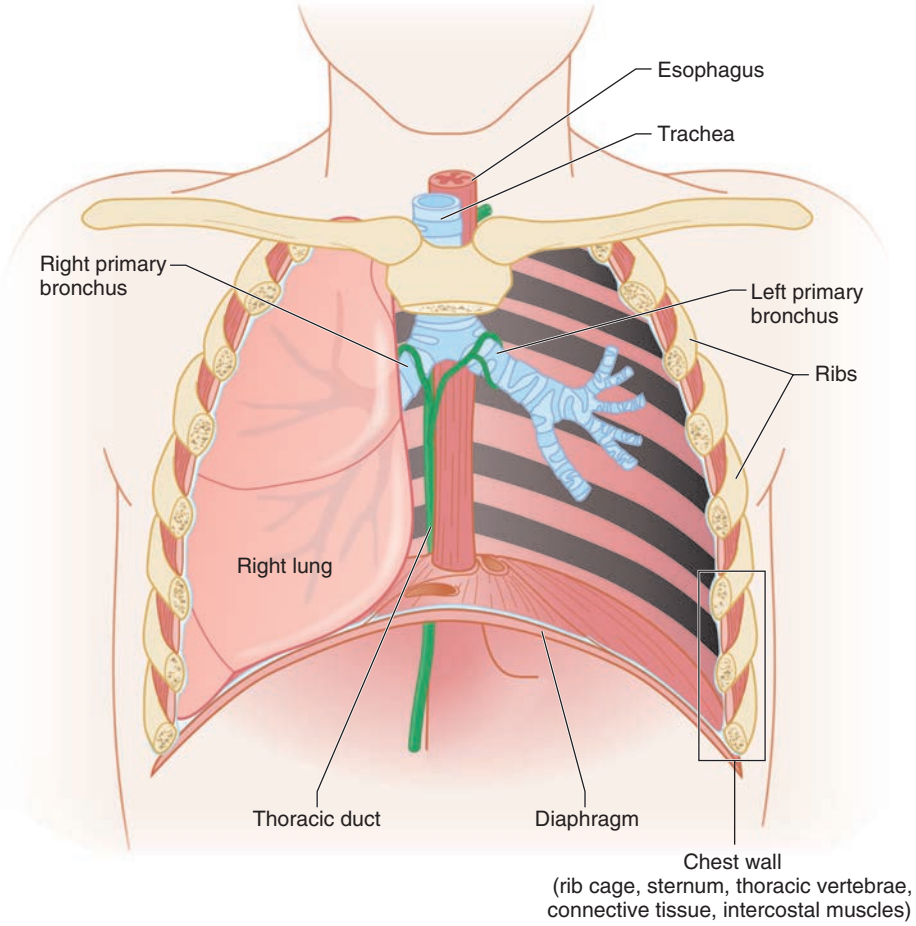


FIGURE 261-1. Anatomy of the thorax.

Inspect the chest wall for contusions, abrasions, and other signs of trauma, including a "seat belt sign" that can indicate deceleration and potential vascular injury. Examine the chest for signs of paradoxical segments or flail chest, intrathoracic bleeding, and open chest wounds. The patient must be making a reasonable ventilatory effort to demonstrate these injuries.

Distended neck veins may indicate the presence of cardiac tamponade, tension pneumothorax, or air embolism; however, in the setting of hypovolemia, this sign may be absent. If the face and neck are cyanotic or swollen, then suspect severe injury to the superior mediastinum with occlusion or compression of the superior vena cava. Subcutaneous emphysema from a torn bronchus or laceration of the lung can also cause severe swelling of the neck and face.

A scaphoid abdomen may indicate a diaphragmatic injury with herniation of abdominal contents into the chest. Excessive abdominal movement during breathing may indicate chest wall damage that might not otherwise be apparent.

Breath sounds are most readily heard in the axillae. Unilaterally decreased breath sounds may indicate the presence of hemothorax or pneumothorax. If the patient has an endotracheal tube in place, assess for possible mainstem bronchus intubation (the usual depth should be no more than three times the inner diameter of the endotracheal tube—23 cm in adult males and 21 cm in adult females) before performing tube thoracostomy in these patients. Persistent decreased breath sounds on one side may also be due to a bronchial foreign body or ruptured bronchus. The presence of bowel sounds in the thorax usually indicates a diaphragmatic injury.

Palpate the neck to determine whether the trachea is midline or displaced. Palpation of the chest wall may reveal areas of localized tenderness or crepitus due to fractured ribs or subcutaneous emphysema. Localized and consistent tenderness over ribs should be attributed to rib fractures, even in the absence of findings on conventional chest radiography. Severe localized tenderness, crepitus, or a mobile segment of the sternum may be the only objective evidence of a sternal fracture. Palpation of the chest with the patient coughing or straining may detect flail, an abnormal motion of an unstable portion of the chest wall, better than visual inspection.

The sensitivity and specificity of most physical examination findings are not high enough to exclude common thoracic injuries. The sensitivity of auscultation for the detection of a traumatic hemopneumothorax is only 50%.[5] Subcutaneous emphysema of the chest, however, has a specificity of 98% for underlying overt or occult pneumothorax. Consider patient symptoms, vital signs, and physical examination findings together to detect significant injuries in stable chest trauma patients and to guide further investigation with imaging. Obtain a chest radiograph. Perform an extended FAST examination as an adjunct to the secondary survey because it can rapidly diagnose both pneumo- and hemothorax with excellent sensitivity and specificity.

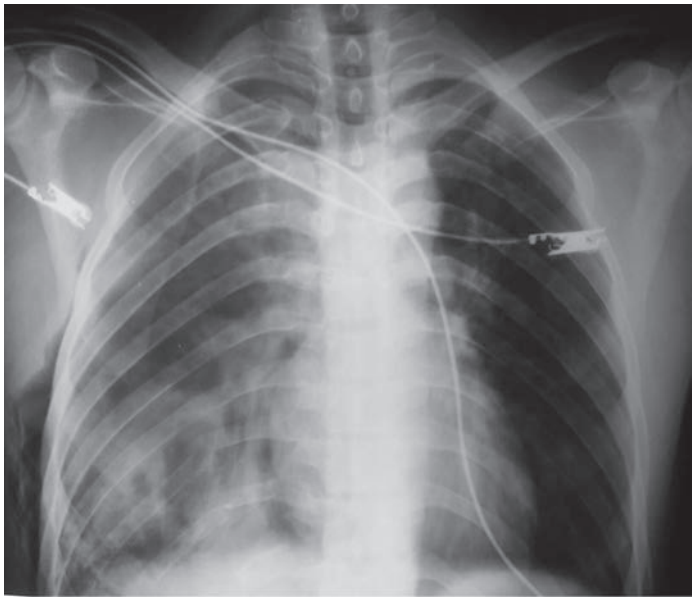
SPECIFIC PULMONARY INJURIES

PULMONARY CONTUSION

Pulmonary contusions, defined as direct injury to the lung resulting in both hemorrhage and edema in the absence of a pulmonary laceration, are a source of severe morbidity and mortality following penetrating and blunt trauma. CT has shown this entity to be much more prevalent than previously recognized.[6] The most common cause of pulmonary contusions is a compression-decompression injury to the chest, such as seen in high-speed motor vehicle crashes.

There are two stages in the pathophysiology of pulmonary contusions. First, there is direct injury to lung parenchyma. Second, resuscitative measures, particularly IV crystalloid fluid administration directed at restoring intravascular volume loss due to hemorrhage, can precipitate cardiopulmonary decompensation. Fluid resuscitation in the setting of unilateral pulmonary contusion can cause extravasation of fluid into the contralateral (uninjured) lung. Increased capillary hydrostatic pressures result in leakage of blood and fluid into the interstitium and alveoli. Unfortunately, the process is self-perpetuating; as each proximate segment of lung sees the full force of right heart activity, it becomes functionally congested and contused, and the process continues to the next uninjured segment of lung. This process results in increased intrapulmonary shunting and resistance to airflow, decreased lung elasticity, and increased work of breathing, leading to hypoxia, hypercarbia, and respiratory acidosis. Cardiopulmonary decompensation may quickly ensue.

Chest pain, tachypnea, chest wall contusions, and hypoxia suggest underlying pulmonary contusion. Physical examination may reveal decreased or coarse breath sounds over the affected lung field. Chest radiograph and CT may show patchy, ground-glass opacities in mild or moderate contusion and widespread consolidation in severe contusion.[7] Contusions are found in nonsegmental areas of the lung and across pleural fissures. Radiographic findings of pulmonary contusion may mimic those associated with aspiration pneumonia and fat embolism, but these entities are typically not seen for 12 to 24 hours and usually have a segmental distribution. **Areas of lung opacification on chest imaging within 6 hours of blunt trauma are usually considered diagnostic of pulmonary contusion (Figure 261-2).** CT is more sensitive for the detection of pulmonary contusions than plain radiographs, with as many as 70% of pulmonary contusions not visible on the initial radiograph.[6] In addition to the high diagnostic rate of CT scan for pulmonary contusion, it may also be possible to anticipate complications such as acute



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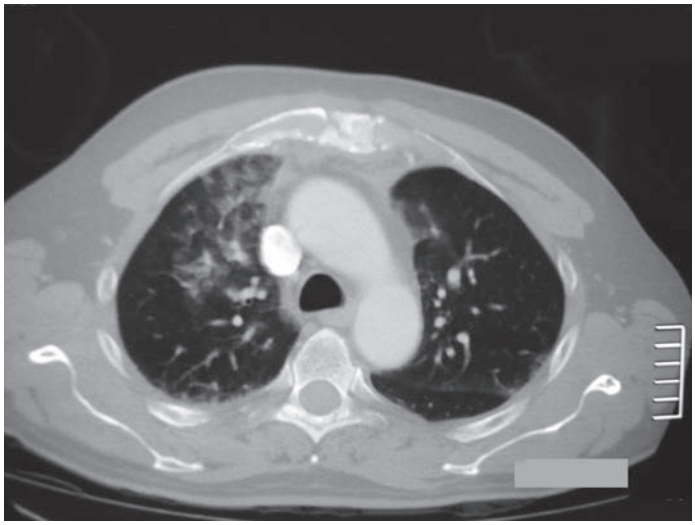

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FIGURE 261-2. Pulmonary contusion. **A.** Chest radiograph shows pulmonary contusion from blunt chest trauma, along with ninth and tenth rib fractures. **B.** CT shows pulmonary contusions on the anterior part of the right lung and a sternal fracture with mediastinal hematoma.

TABLE 261-1 Eastern Association for the Surgery of Trauma Practice Management Guideline for Pulmonary Contusion—Flail Chest

Level 1 recommendations (convincingly justifiable based on the available scientific information alone)	None.
Level 2 recommendations (reasonably justifiable by available scientific evidence and strongly supported by expert opinion)	Unnecessary fluid administration should be meticulously avoided; a pulmonary artery catheter may be useful to avoid fluid overload. Obligatory mechanical ventilation should be avoided. The use of optimal analgesia and aggressive chest physiotherapy should be applied to minimize the likelihood of respiratory failure and ensuing ventilatory support. Patients with pulmonary contusion requiring mechanical ventilation should be weaned from the ventilator at the earliest possible time. Positive end-expiratory pressure/continuous positive airway pressures should be included in the ventilatory regimen. Steroids should not be used in the therapy of pulmonary contusion.
Level 3 recommendations (supported by available data but adequate scientific evidence is lacking)	A trial of mask continuous positive airway pressure should be considered in alert, compliant patients with marginal respiratory status. Independent lung ventilation may be considered in severe unilateral pulmonary contusion. Diuretics may be used in the setting of hydrostatic fluid overload as evidenced by elevated pulmonary capillary wedge pressures in hemodynamically stable patients or in the setting of known concurrent congestive heart failure. Surgical repair may be considered in severe unilateral flail chest or in patients requiring mechanical ventilation when thoracotomy is otherwise required.

lung injury (also known as *acute respiratory distress syndrome* or *noncardiogenic pulmonary edema*), depending on the extent of the pulmonary contusion. Patients who have a contusion >20% of lung volume have up to an 80% risk of developing acute lung injury.[8]

Treatment primarily involves maintenance of adequate ventilation and pain control. Epidural analgesia is the preferred method of pain control; however, consider intercostal nerve blocks and paravertebral analgesia when an epidural is contraindicated.[9] The volume of contused lung influences the need for mechanical ventilation. Patients with less than one fourth of total lung volume involvement (about one lobe) usually do not require such support. If ventilatory assistance is required, avoid overinflation of normal alveoli. Patients with extensive pulmonary contusion may be candidates for high-frequency oscillatory ventilation, a technique that can improve oxygenation, although it may not improve survival.[10] Guidelines for the management of pulmonary contusion and flail chest are listed in **Table 261-1**.[9]

Patients with severe unilateral lung injury who are not responding to conventional mechanical ventilation may benefit from synchronous independent lung ventilation provided through a double-lumen endobronchial catheter. This technique helps prevent overinflation of the normal lung and underinflation of the damaged, poorly compliant lung.

HEMOTHORAX

Bleeding from direct lung injury is the most common cause of hemothorax. The compressing effect of the blood within the pleural space, high concentration of lung thromboplastin, and low pulmonary arterial pressure help limit bleeding as a result of torn lung parenchyma. Bleeding into the hemithorax may arise from mediastinal, diaphragmatic, pulmonary, pleural, or chest wall injuries. Bleeding of venous origin usually tamponades without intervention. Damage to intercostal or internal mammary arteries or pulmonary vessels causes more severe bleeding and almost always requires invasive management.

If the hemothorax is judged large enough to drain (>200 to 300 mL), tube thoracostomy remains the standard of care. Large clots in the pleural space can act as a local anticoagulant by releasing fibrinolysins from their surface. Bleeding from multiple small intrathoracic vessels often stops fairly rapidly after the hemothorax is completely evacuated. (See Video: Chest Tube Insertion.)

Fluid collections >200 to 300 mL can usually be seen on upright or decubitus chest radiographs. However, if the patient is supine, >1000 mL of blood may be missed due to posterior layering of blood, producing only diffuse haziness on that side (**Figure 261-3**). POCUS may be used

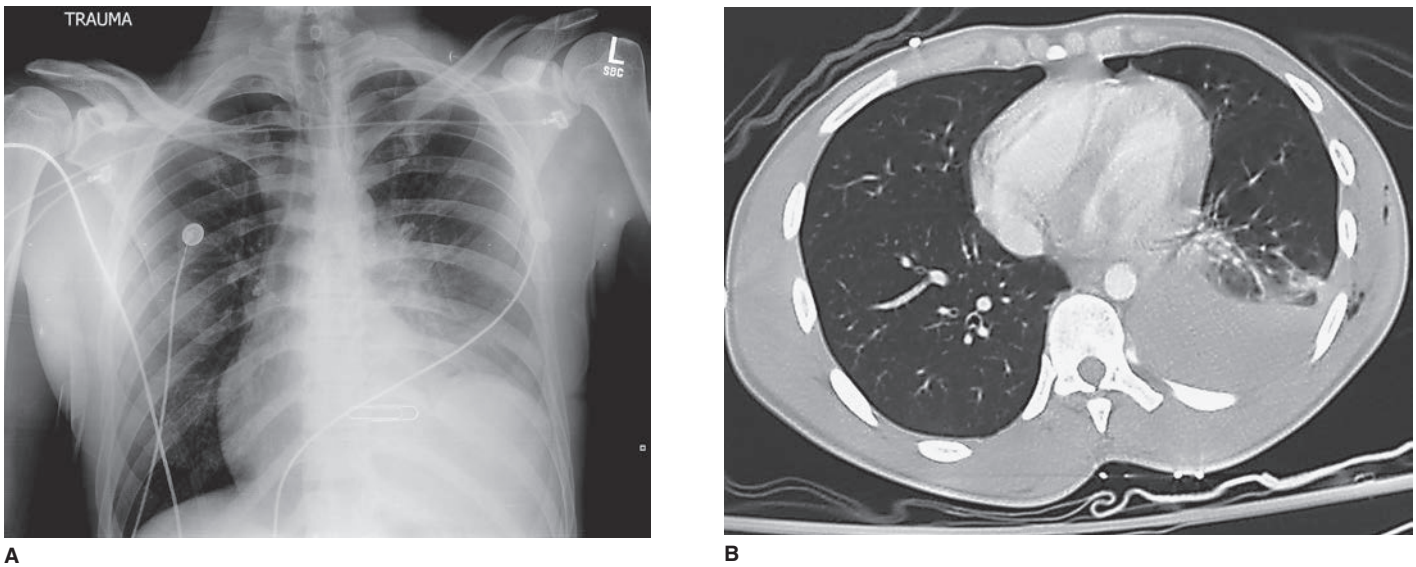

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FIGURE 261-3. Hemothorax. **A.** Anteroposterior view of the chest in patient with penetrating knife injury to the posterior left thorax. The site of injury is marked by a paper clip. Hazy opacity on the left, with associated volume loss in the left lung, is indicative of posteriorly layering hemothorax and atelectatic change. **B.** CT image in the same patient showing large hemothorax layering dependently in the supine patient. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. McGraw-Hill, Inc., 2013. Fig 4.23 & 4.24.]

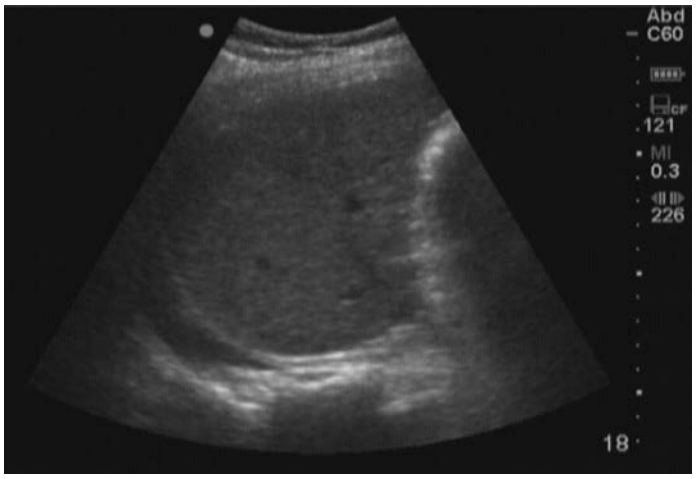


FIGURE 261-4. Hemothorax. US can evaluate for pleural fluid, which usually represents hemothorax. Pleural fluid (hemothorax) can be seen superior to the diaphragm.

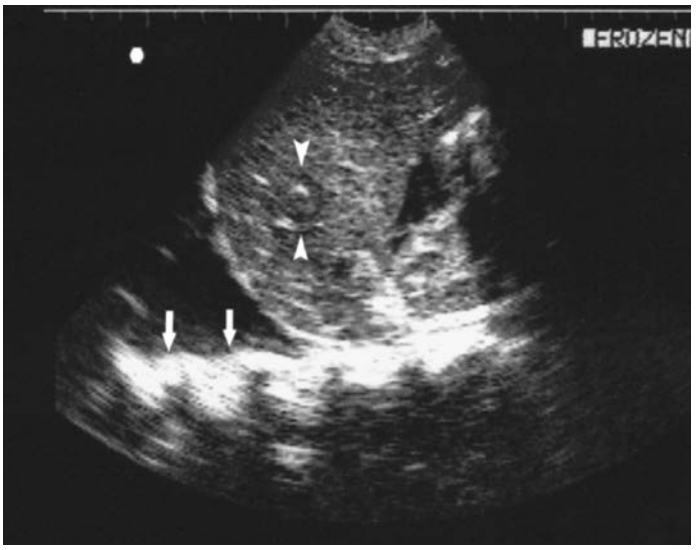


FIGURE 261-5. Free pleural fluid. The right diaphragm appears as a bright hyperechoic structure along the border of the liver. Free pleural fluid can be identified as an anechoic stripe superior to the diaphragm. The pleural fluid allows visualization of the posterior chest wall (*arrows*) that cannot be visualized when the air-filled lung is normally present. The patient also has a circular defect in the liver (*arrowheads*) from a bullet wound and there is fluid in Morison's pouch. [Reproduced with permission from Ma OJ, Mateer JR (eds): *Ma and Mateer's Emergency Ultrasound*, 3rd ed. © 2014, McGraw-Hill, Inc., New York. Fig 5-20.]

in the critically ill patient to detect hemothorax (**Figure 261-4**), showing a fluid density between visceral and parietal pleura normally occupied by lung tissue. **CT has the highest sensitivity and specificity for detecting hemothorax.**

INDICATIONS FOR OPERATIVE INTERVENTION

Most patients with intrathoracic bleeding can be treated adequately by IV administration of fluids and evacuation of the hemothorax with a chest tube. Fewer than 5% of patients will require operative management. **Consider surgical exploration in the following circumstances: >1500 mL of blood is evacuated immediately after tube thoracostomy, chest tube drainage of blood at 150 to 200 mL/h for 2 to 4 hours, or persistent blood transfusion is required to maintain hemodynamic stability.**

MASSIVE HEMOTHORAX

Common causes of massive hemothorax include injury to the lung parenchyma, intercostal arteries, or internal mammary arteries. Each hemithorax can hold 40% of a patient's circulating blood volume. A massive hemothorax is defined in the adult as a volume of at least 1500 mL. Massive hemothorax is life threatening by three mechanisms. First, acute hypovolemia does not allow for sufficient preload to sustain left ventricular function and adequate cardiac output. Second, the collapsed lung results in hypoxia by creating alveolar hypoventilation, ventilation–perfusion mismatch, and anatomic shunting. Third, the hydrostatic pressure of the hemothorax compresses the vena cava and the pulmonary parenchyma, further impairing preload and raising pulmonary vascular resistance, respectively. Although the clinical signs and symptoms of hemothorax in the chest trauma patient can vary, suggestive findings include decreased or absent breath sounds and no chest movement with respiratory effort.

The diagnosis is made by plain chest radiography when complete opacification of a hemithorax is observed. POCUS may reveal a large fluid collection between the chest wall and lung (**Figure 261-5**). Lung collapse, due to intubation of the contralateral mainstem bronchus, can mimic the appearance of hemothorax on chest radiograph; always verify proper endotracheal tube placement. For symptomatic hemothoraces or hemothorax with greater than 500 mL of blood, treatment is tube thoracostomy and replacement of blood products as clinically indicated. For patients with hemothorax who are hemodynamically stable, early video-assisted thoracic surgery is beneficial.[11]

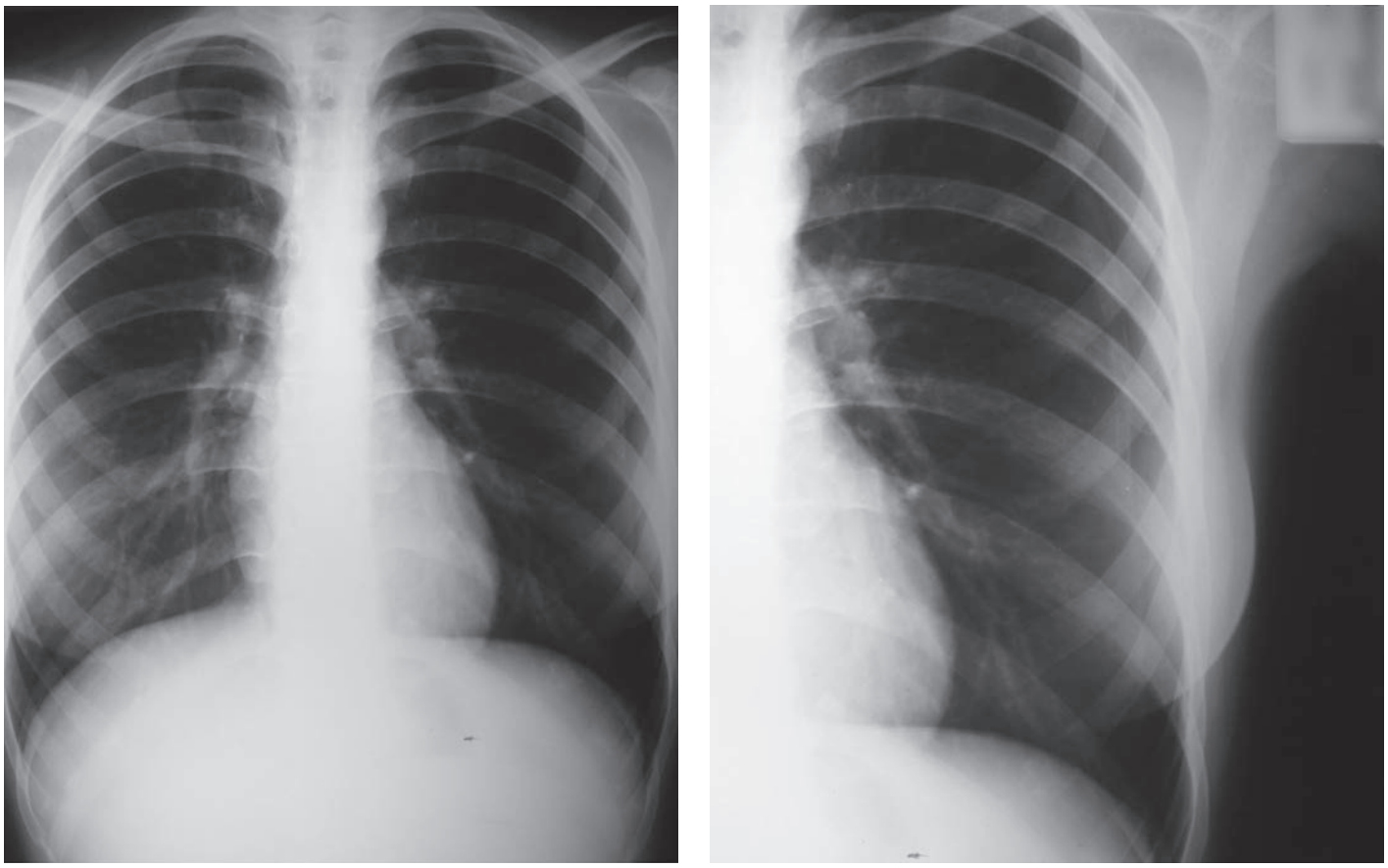
PNEUMOTHORAX

To establish the diagnosis of a pneumothorax with upright plain chest radiography, identify a thin white pleural line usually seen best in the upper lateral aspect of the affected hemithorax in the upright patient (**Figure 261-6**). If the radiograph is obtained with the patient supine, small pneumothoraces may not be apparent as air migrates to the anterior chest, resulting in loss of the interface between the parietal pleura and the air-filled pleural space. POCUS can diagnose a pneumothorax. Sonographic imaging of a *normal* lung with the high-frequency linear probe at the anterior superior aspect of the chest will reveal "ants marching in a line" or the "lung sliding sign," a result of the movement of the pleural layers during the ventilatory phase. This movement is absent in the presence of pneumothorax. Occasionally, the "lung point" or "transition point," where normal lung sliding transitions to absent lung sliding in a patient with a pneumothorax, can also be seen. Lung point is 100% specific but less sensitive for pneumothorax, whereas the absence of lung sliding is more sensitive but not 100% specific; patients with large pulmonary contusions or incorrect endotracheal tube placement may not demonstrate normal lung sliding.

Pneumothorax is found in approximately 20% of patients with significant chest trauma.[10] Traumatic pneumothorax can be open, closed, or occult. In an individual without preexisting cardiopulmonary disease, an isolated pneumothorax usually does not cause severe symptoms unless it occupies >40% of the hemithorax. Occult pneumothoraces may complicate the management of patients who are emergently taken to the operating room because intubation and positive-pressure ventilation may convert a small occult pneumothorax into a tension pneumothorax.

A pressure differential across the pulmonary pleura results in airflow down the gradient. Therefore, positive pulmonary pressure or negative intrapleural pressure during inspiration increases the tendency for air or blood to leak into the pleural cavity through any wound in the lung or chest wall. Any collection of air or blood within the pleural cavity may reduce vital capacity, increase intrathoracic pressure, and decrease minute ventilation and venous return to the heart. Additional air may be forced into the pleural cavity during expiration in patients with outflow obstruction, such as in chronic obstructive lung disease or airway occlusion, thus increasing the likelihood of tension pneumothorax.

Maintain a high suspicion for occult pneumothoraces in patients with more subtle injuries. **Although chest radiography remains the most common diagnostic tool for detecting pneumothorax in the ED (Figure 261-7), it will miss between 17% and 80% of pneumothoraces for upright and supine chest radiographs, respectively.** POCUS is more sensitive than a supine radiograph and is rapid and accurate for detecting pneumothorax.[12-14] Occult pneumothoraces are detected by CT (**Figure 261-8**).[10] Importantly, with the exception of patients who



A B

FIGURE 261-6. Pneumothorax. **A.** The pleural line is seen in the left hemithorax, but lateral to the pleura, there is increased lucency (air density) and an absence of lung markings. These findings should prompt concern for a pneumothorax. **B.** Enlarged area of the same image to further illustrate the increased lucency and absent lung markings lateral to the pleural line.

may require intubation and positive-pressure ventilation (which may convert a small occult pneumothorax into a tension pneumothorax), the detection of occult pneumothoraces using chest CT has minimal clinical significance and does not improve outcome.[15,16]

If pneumothorax is suspected despite normal initial chest radiography, obtaining serial films or performing POCUS or CT may be helpful. **Pneumothorax after a stab wound may be delayed for up to 6 hours.** Consequently, repeat chest imaging in 4 to 6 hours is indicated in these patients or at any time when symptoms worsen. Patients with initially asymptomatic stab wounds to the chest have a reported 12% incidence of



FIGURE 261-7. Pneumothorax. This right-sided pneumothorax can be diagnosed by the absence of lung markings and increased (air density) lucency lateral to the pleural line.



FIGURE 261-8. Pneumothorax. Pneumothorax of the right hemithorax, with small bilateral posterior pulmonary contusions.

TABLE 261-2 Causes for Failure of Complete Lung Expansion or Evacuation of a Pneumothorax

- Improper connections or leaks in the external tubing or water-seal collection apparatus
- Improper positioning of the chest tube
- Occlusion of bronchi or bronchioles by secretions or foreign body
- Tear of one of the large bronchi
- Large tear of the lung parenchyma

delayed hemothorax or pneumothorax that requires tube thoracostomy.[17] A common practice is to observe patients with asymptomatic thoracic stab wounds, repeat the chest radiograph in 4 to 6 hours, and discharge the patient if no delayed pneumothorax is seen in the absence of other concerns.

If the patient cannot be observed closely, requires intubation and mechanical ventilation, or will be transported by air or over a long distance, insert a chest tube or small pleural (pigtail) catheter. Small pneumothoraces (<1.0 cm wide, confined to the upper third of the chest) that are unchanged on two chest radiographs taken 4 to 6 hours apart in an otherwise healthy individual can usually be treated by observation alone.

Occult pneumothoraces (small pneumothoraces not apparent on conventional chest imaging but seen on a CT scan of the chest or abdomen) usually do not require chest tube drainage unless the patient requires mechanical ventilation. Avoid unnecessary tube thoracostomy because there is a 22% risk of major insertional, positional, or infective complications.[18]

In general, small- or moderate-sized pneumothoraces, once treated, do not cause significant problems unless there is a continuing air leak or preexisting cardiopulmonary disease. Even a small air leak usually will not result in serious complications, provided the lung is completely expanded. However, the incidences of empyema and bronchopleural fistula are greatly increased in pneumothoraces with continued air leak persisting for >24 to 48 hours.

If the lung does not completely expand or the pneumothorax does not evacuate, then investigate potential causes (**Table 261-2**). If a pneumothorax persists or there is a large air leak, perform emergency bronchoscopy to examine and clear the bronchi or to identify and repair any damage to the tracheobronchial tree. Continued large air leakage or failure of the lung to adequately expand, despite these measures, is an indication for early thoracotomy.

TENSION PNEUMOTHORAX

Diagnose and treat tension pneumothorax clinically, before the chest radiograph is obtained. Although the classic presentation includes distended neck veins, hypotension or evidence of hypoperfusion, diminished or absent breath sounds on the affected side, and tracheal deviation to the contralateral side (**Figure 261-9**), one or more of these elements may be absent in the presence of hypovolemia. Patients requiring assisted ventilation with a tension pneumothorax are more likely to be hypoxic, be hypotensive, and experience cardiac arrest than those who are breathing spontaneously.[19] **Perform immediate needle decompression, usually in the fourth intercostal space at the anterior axillary line, followed by chest tube insertion.**[11]

OPEN PNEUMOTHORAX

Open pneumothorax is a communication between the pleural space and surrounding atmospheric pressure. This is sometimes referred to as a "sucking chest wound," but also may be due to small rents in the parietal pleura or small air passages without an obvious penetrating injury. Respiratory distress is due to lung collapse and subsequent inability to ventilate the affected lung. Air entry and breath sounds are often diminished on the affected side, and chest wall motion can be impaired. The initial therapeutic maneuver to treat a sucking chest wound is to cover the wound with a three-sided dressing such that air can exit but not enter the chest. Avoid complete occlusion, as this may convert the injury into a tension pneumothorax. Do not insert a chest tube through the trauma wound, as it is likely to follow the missile or knife tract into the lung or diaphragm.

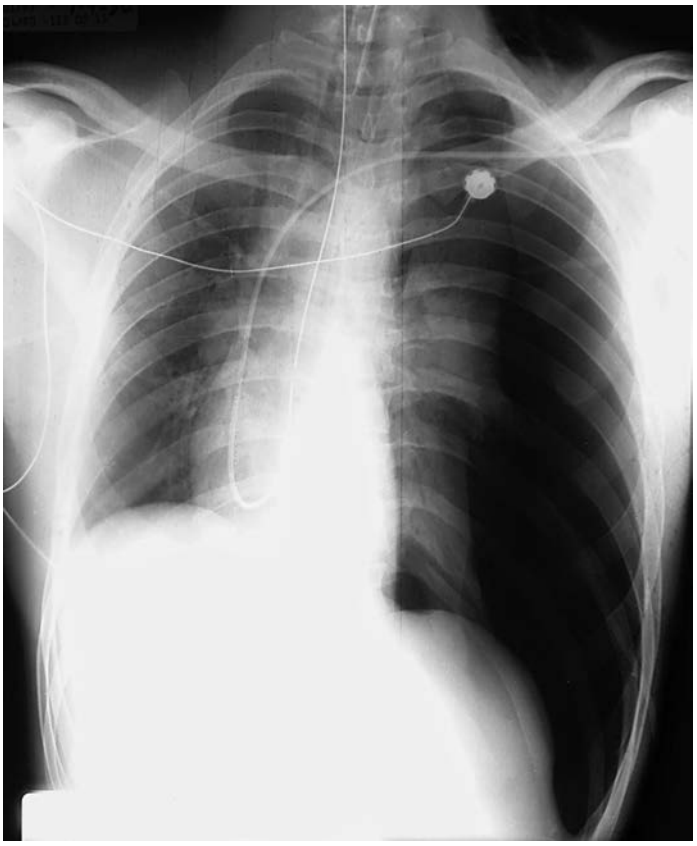


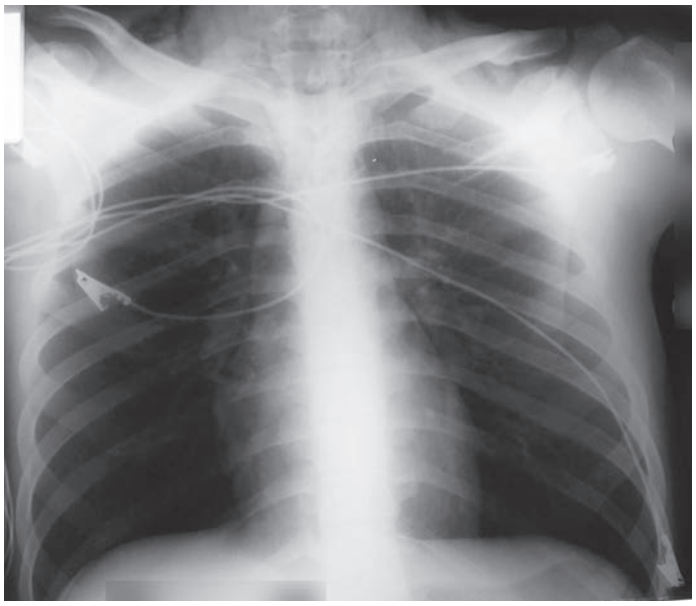
FIGURE 261-9. Tension pneumothorax. Supine chest radiograph of a tension pneumothorax. Note the deviation of the trachea and shifting of the mediastinal contents to the right. Tension pneumothorax should clinically be diagnosed prior to chest radiograph. [Reproduced with permission from Schwartz DT (ed): *Emergency Radiology, Case Studies*. © 2008 McGraw-Hill Inc., Fig I-9-10.]

PNEUMOMEDIASTINUM

Subcutaneous emphysema in the neck or the presence of a crunching sound (Hamman's sign) over the heart during systole suggests the presence of a pneumomediastinum. This diagnosis can usually be made on chest radiography (**Figure 261-10A**) and is readily apparent on CT of the chest (**Figure 261-10B**). Pneumomediastinum in blunt chest trauma is most commonly the result of alveolar rupture, followed by dissection along the bronchoalveolar sheath and subsequent spread of air to the mediastinum, a process known as the *Macklin effect*. Traumatic pneumomediastinum may be asymptomatic or can cause mild to moderate chest pain, voice change, cough, or stridor. **Pneumomediastinum alone does not require further diagnostic testing or intervention unless the patient is symptomatic,** in which case a search for other serious injuries to the larynx, trachea, major bronchi, pharynx, or esophagus is essential.

PULMONARY HEMATOMA

Pulmonary hematomas are parenchymal tears filled with blood. Although these generally resolve spontaneously over a few weeks, they sometimes can become infected and progress to lung abscesses. Infection is more likely in patients on a ventilator, who require prolonged chest tube drainage, or who are postthoracotomy.



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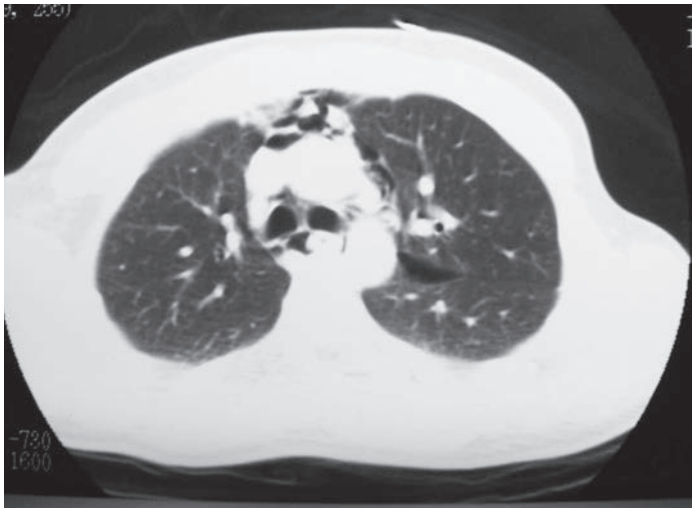


B

FIGURE 261-10. Pneumomediastinum. **A.** Blunt trauma to the chest while playing basketball. Patient had sudden onset of chest pain and shortness of breath. Subcutaneous emphysema was evident in the neck. Chest radiograph reveals mediastinal and subcutaneous air. **B.** In this same patient, a CT scan shows pneumomediastinum.

PULMONARY LACERATION WITH HEMOPNEUMOTHORAX

Hemorrhage from pulmonary lacerations is most commonly seen in the setting of displaced rib fractures due to direct trauma from the exposed ends of bone. Hemorrhage may also be due to the effect of shear forces on preexisting pleural adhesions during rapid deceleration injuries or from penetrating chest injuries.

ASPIRATION

Aspiration of gastric contents is common after severe trauma, especially if the patient was unconscious at any time. Radiographic changes may be delayed for up to 24 hours and can include consolidation virtually anywhere in the lungs, with the most common sites being the right middle and lower lung fields. This is the result of a chemical pneumonitis as lung parenchyma is exposed to gastric contents. Frequent suctioning is indicated, as well as continual assessment of the need for endotracheal intubation if the patient is at further risk for aspiration. **There is no evidence to support the use of prophylactic antibiotics to prevent pulmonary infection after gastric aspiration.**

Aspirated opaque foreign bodies in the tracheobronchial tree may be diagnosed on plain radiographs, but even teeth can be easily missed due to size, relative lucency, and the presence of overlying bone and soft tissue densities. Once recognized, prepare for urgent bronchoscopy to remove tracheal or bronchial foreign bodies.

Expiratory chest radiographs may help diagnose foreign bodies that act as a one-way valve, causing air trapping and hyperinflation on the affected side. Undiagnosed bronchial foreign bodies lead to recurrent or difficult-to-treat pulmonary infections, sometimes taking months to discover. Persistent or recurrent cough, atelectasis, and pneumonia after trauma are indications for bronchoscopy.

TRACHEOBRONCHIAL INJURY

INTRABRONCHIAL BLEEDING

Intrabronchial bleeding can lead to severe hypoxemia and rapid death. Hemorrhage into dependent alveoli hinders gas exchange in a mechanism similar to drowning. It is important to identify the involved lung and to keep the other lung as free of blood as possible. Bronchoscopy is often necessary to identify injury and control bleeding. Intubation with frequent tracheal suction may be effective. If the hemorrhage is severe, a double-lumen endotracheal tube can be used as a temporizing measure to confine the bleeding to one lung. If a double-lumen endotracheal tube is not available, a standard tube may be inserted over a flexible bronchoscope into the unaffected lung, or an endotracheal tube can be purposely passed into the right mainstem bronchus as a diagnostic measure and the patient placed with the affected lung in the dependent position.

LOWER (INTRATHORACIC) TRACHEA AND MAJOR BRONCHI

Injuries to the major bronchi occur primarily due to rapid deceleration injuries, which cause shear forces to mobile distal bronchi relative to more fixed proximal structures. Forced expiration against a closed glottis and compressive forces on the pulmonary tree against the vertebral column may also cause injury to these structures. **Most tracheobronchial injuries occur within 2 cm of the carina or at the origin of lobar bronchi.**

The most common presenting signs and symptoms are dyspnea, hemoptysis, subcutaneous emphysema, Hamman's sign, and sternal tenderness. A large pneumothorax, pneumomediastinum, or deep cervical emphysema may also suggest tracheobronchial injury. On careful inspection, the endotracheal tube balloon may have a spherical rather than oval appearance on chest radiographs. Approximately 10% of patients present with very mild symptoms or are completely asymptomatic. When tracheobronchial injuries are suspected, bronchoscopy is the gold standard for diagnosis, and operative repair can prevent significant complications.[20]

The air leak due to bronchopleural fistula following tube thoracostomy is continuous and massive. High-frequency oscillation is the ventilator modality of choice to maintain gas exchange and expand the alveoli in the face of the massive gas leak.

All lacerations of the bronchi involving more than one third of the circumference should be operatively repaired. Untreated tracheal tears may result in severe mediastinitis or can lead to severe bronchial stenosis with atelectasis and repeated pulmonary infections.

Intrathoracic tracheal transection is usually associated with two or more major injuries and is almost invariably fatal. Patients who survive a tracheal transection generally sustain an injury in the cervical trachea and have no other associated injuries. Concurrent esophageal injuries occur in almost 25% of penetrating tracheobronchial injuries and can be missed unless esophagoscopy or contrast studies are also performed.

CERVICAL TRACHEAL INJURIES

Blunt injuries to the upper (cervical) trachea are usually found at the junction of the trachea and cricoid cartilage. This most frequently occurs when the anterior neck strikes the steering wheel or dashboard in an automobile accident. However, hyperextension of the neck can also cause tracheal lacerations, fractures, and even laryngotracheal separation. **Evidence of direct trauma to the neck, including contusions and subcutaneous emphysema, vocal cord paralysis, aphonia, and pneumothorax, should raise suspicion for this injury as well as accompanying nerve, vascular, esophageal, and spinal injuries.**[21,22] Laryngotracheal separation may not be suspected until attempts to pass the endotracheal tube past the cricoid cartilage are unsuccessful. Treatment and diagnosis are discussed in Chapter 260, "Trauma to the Neck."

DIAPHRAGMATIC INJURY

Diaphragmatic injuries are caused most frequently by penetrating trauma, particularly gunshot wounds of the lower chest or upper abdomen. Diaphragmatic rupture due to blunt trauma is much less common and occurs in <5% of patients hospitalized with chest trauma. If there is a fracture of the pelvis, the incidence of diaphragmatic hernia increases.

More diaphragmatic injuries following blunt trauma are diagnosed on the left hemidiaphragm.[23] This left-sided predominance is likely due to the protective effect of the liver on the right hemidiaphragm and the possible increased weakness of the left posterolateral diaphragm.

The initial signs and symptoms of diaphragmatic hernia are often masked by other injuries and have a delayed presentation unless the defect is large. Over time, the abdominal viscera can gradually migrate into the chest through even small diaphragmatic tears; patients may present years after the initial injury with a traumatic diaphragmatic hernia. The intrathoracic bowel may become obstructed or ischemic due to torsion or strangulation or cause severe compression of the adjacent lung, a phenomenon referred to as *tension enterothorax*.

If a penetrating wound of the abdomen is associated with intrathoracic injury or foreign body, it should be assumed that the injury traversed the diaphragm. Chest radiographs may display injury to the diaphragm in only approximately 25% of such patients.[24] With blunt trauma, any abnormality of the diaphragm or lower lung fields on chest images should arouse suspicion of a diaphragmatic tear (**Figure 261-11**).

Techniques for diagnosing diaphragmatic injuries include (1) orogastric tube placement with evaluation to see if the tube curves up from the abdomen into the chest; (2) upper GI series looking for displacement of viscera into the chest; (3) CT of the chest and abdomen with contrast (**Figure 261-12**); (4) laparoscopy; and (5) thoracotomy or laparotomy. Laparoscopy is the favored approach for diagnosis of isolated traumatic diaphragmatic injury. Laparoscopy or traditional laparotomy is necessary to repair the diaphragm, and thoracotomy may be necessary for associated chest injury, resuscitation, delayed repair of the diaphragm, or management of thoracic complications.

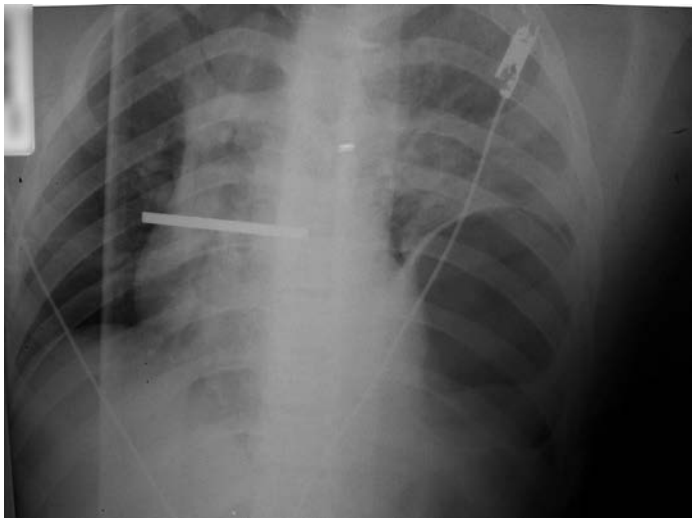


FIGURE 261-11. Diaphragmatic injury. Patient with diminished breath sounds of the left hemithorax after blunt thoracoabdominal injury. Chest radiograph shows left diaphragmatic injury.



FIGURE 261-12. Diaphragmatic injury. Right diaphragmatic injury on CT.

ESOPHAGEAL AND THORACIC DUCT INJURIES

ESOPHAGEAL INJURIES

Injuries to the thoracic esophagus may occur through direct penetrating trauma and, less often, via blunt trauma. Mortality is high as a result of associated injuries to other organs in the chest. Lacerations of the esophagus occur iatrogenically as a result of endoscopic biopsy or dilatation of a narrowed or obstructed esophagus. Swallowed foreign bodies can also traumatize the esophagus.

Overall, esophageal injuries are rare after blunt thoracic trauma. In one large retrospective review of patients with incidental pneumomediastinum found on chest radiograph or CT scan, there was poor positive predictive value for either tracheobronchial or esophageal injury. Of over 9000 patients with pneumomediastinum, only a single case of esophageal injury was diagnosed.[25]

If traumatic esophageal injury is suspected but there is no indication for immediate operative exploration, obtain CT angiography of the neck.[26]

Despite the diagnostic and therapeutic advances, esophageal injuries are associated with significant morbidity and mortality, particularly if there is a delay in recognition and definitive management. For full discussion, see Chapter 260, "Trauma to the Neck."

THORACIC DUCT INJURIES

Suspect thoracic duct injuries in patients with penetrating trauma near the left proximal subclavian vein. Although the diagnosis is rarely made in the ED, the development of a chylothorax, accumulation of lymphatic fluid in the pleural space, is associated with metabolic, nutritional, and immunologic derangements, and has a mortality rate of 50%. Traumatic chylothorax should be considered in trauma patients, as early surgical intervention and thoracic duct embolization have demonstrated improved success in treating this rare injury.[27]

INJURIES TO THE CHEST WALL

BLEEDING AND TISSUE LOSS

Probing of a penetrating chest wound to determine its depth or direction is not recommended and may not give an accurate picture of the depth of penetration. Such wounds, especially if there is continued bleeding, are better managed by local exploration in the operating room.

Injuries caused by high-powered rifles or close-range shotgun blasts may cause large tissue defects of the chest wall. In such patients, intubation and mechanical ventilation are required until the defect is definitively closed.

SUBCUTANEOUS EMPHYSEMA

Subcutaneous emphysema usually develops because air from lung parenchyma or the tracheobronchial tree gains access to the chest wall through an opening in the parietal pleura. The air may also reach the chest wall from an interstitial lung injury by dissecting back along the bronchi into the hilum and mediastinum and then into the extrapleural spaces. Extensive subcutaneous emphysema may also suggest an injury to the pharynx, larynx, or esophagus.

Presume patients with subcutaneous emphysema have an underlying pneumothorax, even if it is not visible on the chest radiograph. POCUS is more sensitive than chest radiograph for the detection of pneumothorax. If the patient requires intubation and subsequent positive-pressure ventilation, insert a chest tube on the involved side. If subcutaneous emphysema is severe, suspect a major bronchial injury and investigate further with bronchoscopy.

RIB FRACTURES

Rib fractures are the most common bony injuries in chest trauma and are diagnosed in approximately 50% of patients admitted to the hospital following chest trauma.[10] Rib fractures are painful injuries, heal slowly, and are closely associated with mortality and morbidity.[28] Rib fractures can be markers of potential internal injury; the principal diagnostic goal with clinically suspected rib fractures is the detection of significant associated complications, such as hemopneumothorax, pulmonary contusion, intra-abdominal injury, or major vascular injury. In the patient with severe chest trauma or significantly displaced rib fractures or in the presence of other injuries, perform serial chest imaging to evaluate for developing pneumothoraces or other injuries.

Assume the presence of rib fractures in any patient with localized pain and tenderness over one or more ribs after chest trauma. Up to 50% of rib fractures (especially those involving the anterior and lateral portions of the first five ribs) are not apparent on conventional radiography, particularly in the first few days after injury.[29] Furthermore, injuries to the cartilaginous portions of the ribs may never be appreciated on plain radiographs. US is a promising diagnostic tool for evaluating rib fractures and even for cartilaginous injury.[30]

The pain of rib fractures can greatly interfere with ventilation, leading to splinting and atelectasis. Rib fractures can also prolong the time for weaning from ventilator support. Do not immobilize the chest wall with tape or binders. Adequate analgesia is critical to maintain normal respiratory function during the healing process.[31] A combination of opioids, benzodiazepines, topical lidocaine patch, and NSAIDs provides the most effective analgesia for mild to moderate chest wall pain.

An intercostal nerve block or serratus anterior plane block with a long-acting agent such as bupivacaine will relieve severe pain associated with muscle spasm and ventilation for up to 12 hours. For patients admitted to the hospital, epidural analgesia or intrapleural catheters for administration of local anesthetics also relieve chest wall pain.[32] Epidural analgesia for blunt chest trauma may be a better choice than IV opioid analgesia.[33]

With the exception of direct local trauma, **it takes great force to fracture the first and second ribs,** given their short length, relative immobility, and protection by other structures in the upper chest. Such fractures can be associated with significant injuries to underlying organs such as blunt myocardial injury, bronchial tears, or a major vascular injury, with 15% to 30% associated with poor outcome, usually from head injury or rupture of a major vessel.

In patients with multiple fractured ribs of the middle (ribs 5 to 8) and lower segments (ribs 9 to 12), unexplained hypotension may be the result of intra-abdominal bleeding from the liver or spleen.[34] Consider imaging of the abdomen by CT or US in any patient with middle or lower rib fractures. Patients with multiple fractured ribs will often have difficulty coughing or adequately clearing secretions and should be considered for 24- to 48-hour observation unit admission, especially the elderly or those with preexisting pulmonary disease.

FLAIL CHEST

Segmental fractures of three or more adjacent ribs anteriorly or laterally often result in an unstable chest wall physiology known as *flail chest*. This injury is characterized by a paradoxical inward movement of the involved chest wall segment during spontaneous inspiration and outward movement during expiration. Although paradoxical motion can greatly increase the work of breathing, the primary cause of the hypoxemia is contusion to the underlying lung. These patients may fatigue rapidly as a vicious cycle of decreasing ventilation, increased work of breathing, and hypoxemia may develop, resulting ultimately in sudden respiratory arrest.

Patients with mild to moderate flail chest and, importantly, little or no underlying pulmonary contusion or associated injury can often be managed without a ventilator. Adequate, multimodal pain relief by analgesics or nerve blocks allowing good ventilation and pulmonary toilet are important adjuncts when managing these patients.[35] **Indications for early ventilatory support include shock, severe head injury, comorbid pulmonary disease, fracture of eight or more ribs, other associated injuries, age >65 years, or arterial partial pressure of oxygen (Po_2) <80 mm Hg despite supplemental oxygen.** Increased age and global injury severity as measured by the Injury Severity Score are poor prognostic signs in flail chest.[36,37] Early intubation and ventilatory assistance in patients with flail chest reduce mortality compared with delaying intubation until the onset of respiratory failure.

There is mounting evidence for the benefit of surgical fixation of rib fractures causing flail chest.[38-42] The aim of fixation is to reduce the need for ventilatory assistance, decrease complications (pneumonia and tracheostomy), and shorten hospital and intensive care unit length of stay; however, improved pain relief and ventilatory support may achieve a similar goal.[43,44] The Eastern Association for the Surgery of Trauma recommends consideration of surgical fixation in flail chest patients requiring mechanical ventilation when thoracotomy is undertaken to manage other injuries (Table 261-1).[9]

STERNUM FRACTURE

Tenderness over the sternum may indicate sternal fracture. Sternal fractures usually occur at the body.[45] Lateral chest radiography can detect a fracture (**Figure 261-13**), but diagnosis is usually made by CT (**Figure 261-14**).[8] US is more sensitive and specific than chest radiographs for sternal fractures.[46,47]

Sternal fractures have historically been considered a marker of serious life-threatening injury, particularly cardiovascular injury. However, patients with isolated sternal fractures and otherwise negative workup (including chest CT, echocardiogram, cardiac US, and cardiac enzymes at the time of presentation and 6 hours afterward) can safely be discharged home.[48-51] Current experience with sternal fractures as a result of motor vehicle crashes notes a 1.5% incidence of cardiac dysrhythmias requiring treatment and a mortality rate of <1%.[52] Such data suggest that sternal fractures are not an indicator of significant blunt myocardial injury. Patients with sternal fractures presenting with normal vital signs and an initial normal ECG should have a repeat ECG in 6 hours and, if unchanged, require no further workup for cardiac injury.[53,54]

SYSTEMIC AIR EMBOLISM

Systemic air embolism is an acute complication of severe chest trauma and presents with disastrous circulatory and cerebral complications. Patients with penetrating chest wounds who require positive-pressure ventilation



FIGURE 261-13. Sternal fracture. Lateral chest radiograph reveals a sternal body fracture after blunt chest injury.

are at risk for developing air embolus. High ventilatory pressures, especially >50 cm H_2O, may force air from an injured bronchus into an adjacent injured vessel. Air embolus may lead to severe dysrhythmias or CNS deficits. Patients presenting with hemoptysis in the setting of penetrating chest trauma are at particular risk for this serious complication.

If systemic air embolism is suspected or diagnosed, place the patient in a flat supine position with 100% oxygen applied, which may decrease air bubble size by displacing nitrogen and promoting resorption of the embolus. **There is no evidence to support the theoretical benefit of the Trendelenburg (head down) position in arterial air embolism.**

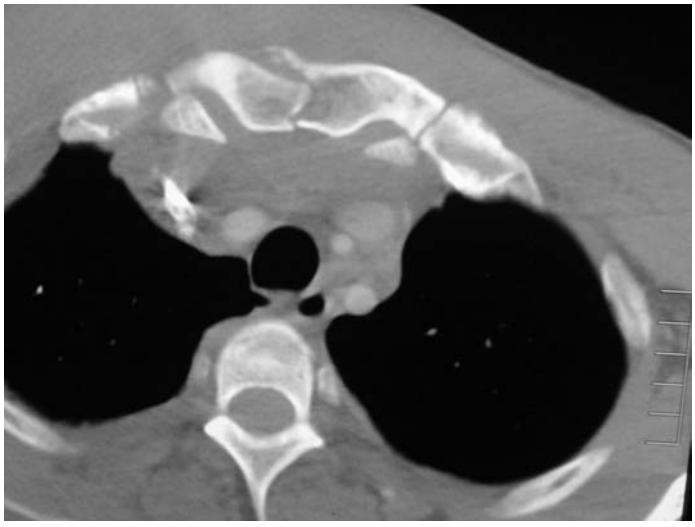


FIGURE 261-14. Sternal fracture. Patient presents with seat belt sign on the chest wall and tenderness over the sternum. CT shows vertical fracture of sternum and mediastinal hematoma under the fracture.

Hyperbaric oxygen therapy, if available, helps to decrease size and increase resorption of air bubbles. Airway management of patients at risk for systemic air embolism should include maneuvers that can selectively ventilate each lung. In unilateral lung injury, isolating and ventilating the uninjured lung can, in theory, be used to prevent systemic air embolism. In the event of circulatory collapse, treatment begins with cardiopulmonary resuscitation protocols and an immediate thoracotomy to clamp the injured area of lung. This is followed by air aspiration from the heart and ascending aorta.[55,56] Open cardiac massage with clamping of the ascending aorta may help push air through the coronary arteries. Initiate cardiopulmonary bypass promptly, if available.

BLAST INJURIES

Blast injuries can result in a variety of thoracic injuries through multiple mechanisms. An explosive blast can damage the chest through primary, secondary, tertiary, and quaternary blast injury patterns. The primary blast injury is due to barotrauma from rapidly increasing then decreasing atmospheric pressure, resulting in compression and shearing injuries in gas-filled structures such as the lung, ears, and bowels. Secondary blast injuries are blunt or penetrating injuries due to materials thrown from the explosive casing. Tertiary injuries are injuries sustained as a result of being thrown from the blast site or due to structural collapse. Quaternary injuries are burns, inhalational injuries, and radiation that can occur as a result of the explosion and combustible materials. Suspect occult and ongoing injuries.[57] (See Chapter 7, "Bomb, Blast, and Crush Injuries.")

DIAGNOSIS

CHEST RADIOGRAPH

Plain chest radiographs are helpful to screen for abnormal mediastinal contours, hemothorax, pneumothorax, pulmonary contusions, diaphragmatic injury, and osseous trauma. Mark penetrating surface wounds before imaging. Most chest radiographs are initially taken in the supine position at the bedside due to concern for occult spinal cord injuries and to facilitate resuscitation. **Chest radiographs frequently underestimate the severity and extent of chest trauma and may fail to detect an injury.** Up to 50% of blunt chest trauma patients with normal initial chest radiography have multiple injuries on CT; however, some of these occult injuries do not change management or outcome.[6,7,15,16,58] Chest radiograph is obtained to identify findings such as pneumothorax, hemothorax, aortic or great vessel injury, multiple rib fractures, sternal fracture, diaphragmatic rupture, and pulmonary contusions or lacerations. The National Emergency X-Radiography Utilization Study (NEXUS) Chest Rules were developed in a manner similar to NEXUS Cervical Spine Imaging rules to identify patients with blunt chest trauma with very low risk of thoracic injury. The rules were developed and validated in a convenience sample of 9905 patients >14 years old. If all of the NEXUS Chest Rules criteria were absent, chest imaging (plain radiography or CT) could be omitted (**Table 261-3**). Patients in this cohort were not evaluated with bedside US, and decision for plain chest radiography or chest CT was left to the discretion of the caring physician. Sensitivity and specificity were 98.8% and 13.3%, respectively, for thoracic injury.

TABLE 261-3 National Emergency X-Radiography Utilization Study Rules for Chest Radiography

Blunt trauma in patients >14 y old in whom chest imaging is considered to exclude intrathoracic injury	Presence of 1 or more criteria: cannot exclude intrathoracic injury and obtain chest imaging: Age >60 y old Rapid deceleration: fall >20 ft (>6 m); motor vehicle crash >40 mph (>64 km/h) Chest pain Intoxication Abnormal alertness or abnormal mental status Distracting painful injury Tenderness to chest wall palpation

Only about half of the study group underwent CT, limiting any conclusions about plain radiography versus CT in patients with blunt chest trauma. However, in the majority of patients who have suffered minor trauma, only a single posteroanterior chest radiograph is required; dedicated rib radiographs rarely provide additional information that would alter clinical management.[59,60]

US

POCUS can quickly diagnose pneumothorax, hemothorax, and pericardial tamponade as part of the extended FAST examination. In trained hands, US has greater sensitivity and equal specificity for detecting hemothorax in patients with chest trauma compared with chest radiography.[61] Likewise, the sensitivity of US for detecting pneumothorax approaches 92%, with near 100% specificity (as compared with 50% to 80% sensitivity and 90% specificity for chest radiographs)[12]; thus, US appears to have greater "diagnostic performance" than clinical exam and chest radiograph together.[13,62] **US in the ED can detect occult pneumothorax as accurately as CT.**[63] In addition, US has also been found helpful for describing small, medium, or large pneumothoraces with good agreement with CT (**Figure 261-15**).[14] (See Videos: Lung Ultrasound and FAST.)

CT

CT can detect major and occult injuries and identify the need for additional interventions, but may demonstrate incidental findings that require follow-up and do not change acute care.[16] CT is more sensitive for detecting pulmonary contusion and hemothorax than plain radiography.[6] For penetrating lung injury, if the clinical condition allows, CT is performed to identify the extent of injury and involvement of the heart or great vessels. CT adds little to the evaluation of low-risk patients (fall from standing or sitting) with normal physical examinations.[64]

OTHER DIAGNOSTIC STUDIES

Thoracic trauma often requires a contrast esophagogram to diagnose esophageal injury. **Water-soluble contrast is preferred over barium-containing contrast in patients with high suspicion for esophageal rupture.** Barium swallow imaging has fewer false positives, but may cause mediastinitis if there is leakage of contrast out of the esophagus.

In selected cases, such as in penetrating wounds of the chest or lower neck, bronchoscopy or esophagoscopy may be indicated to exclude an injury to the aerodigestive tract. Such studies may be deferred until the patient is resuscitated and hemodynamically stable.

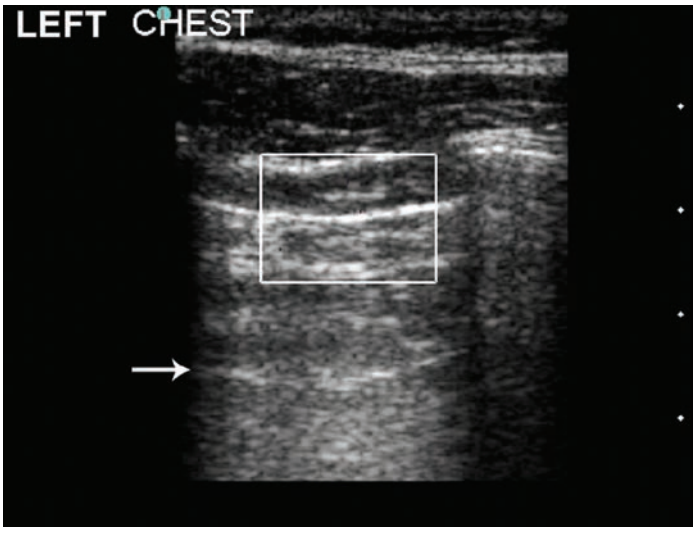


FIGURE 261-15. Pneumothorax (7.5–10 MHz). Power Doppler is activated and the gain adjusted correctly by comparison with the normal right hemithorax. The patient's left hemithorax showed a negative pleural sliding sign, no comet tail artifacts, and no power Doppler signal at the pleural interface. The specificity for pneumothorax is improved when an A-line is also visible (*arrow*). [Reproduced with permission from Ma OJ, Mateer JR, Reardon RF, Joing S (eds): *Emergency Ultrasound,* 3rd ed. McGraw-Hill, Inc., 2014. Fig 5-26, p. 82.]

GENERAL TREATMENT

INITIAL RESUSCITATION

Perform initial resuscitation and airway management according to established principles (see Chapter 254, "Trauma in Adults"). If the patient is making little or no respiratory effort, consider CNS dysfunction due to head trauma, intoxication, or spinal cord injury. In patients with respiratory effort but with little or no air movement, suspect upper airway obstruction. Absent or abnormal breath sounds may indicate flail chest, hemopneumothorax, diaphragmatic injury, or parenchymal lung damage. Although each of these has unique therapies, respiratory distress that is not immediately relieved by specific intervention should prompt intubation and ventilation. Suspect, diagnose, and treat specific life-threatening pulmonary injuries during the primary survey. These include tension pneumothorax, massive hemothorax, and open pneumothorax.

VENTILATORY SUPPORT

The management of chest trauma patients with respiratory instability is challenging. Hypoxia and hypoventilation are two preventable causes of mortality; therefore, **maintaining adequate oxygenation and ventilation in the acute chest trauma patient is essential**. Early goals while the lungs are still compliant should include pulmonary recruitment, normocapnea, and reversal of associated metabolic acidosis. However, if acute respiratory distress syndrome develops and the lung compliance decreases, or after the patient is out of the acute resuscitative phase, initiate a lung protective strategy to decrease barotrauma.[65] See Chapter 29A, "Tracheal Intubation" and Chapter 29B, "Mechanical Ventilation," for detailed discussion of ventilation parameters. Monitor all trauma patients by continuous noninvasive pulse oximetry to ensure adequate oxygen saturation. In patients with severe chest trauma or respiratory compromise, an arterial blood gas is helpful to monitor metabolic status and adequate oxygenation and ventilation. Metabolic acidosis with insufficient respiratory compensation is an indication for ventilatory support. Ventilatory support is indicated in chest trauma patients who continue to exhibit impaired ventilation despite measures to relieve chest wall pain and evacuate hemopneumothorax (**Table 261-4**). Early use of noninvasive ventilation in patients with chest trauma and normal mentation, but no respiratory distress, may prevent progression of disease and decrease the need for intubation and intensive care.[66]

NEEDLE DECOMPRESSION

The most traditional approach to needle decompression is to introduce a 14-gauge IV needle and catheter into the pleural space in the midclavicular line just above the rib at the second intercostal space (**Figure 261-16**). An anterior midclavicular approach is important because this avoids the internal mammary vessels that are located approximately 3 cm lateral to the sternal border and avoids mediastinal vessels.[67-69] A standard needle

TABLE 261-4 Considerations for Early Ventilatory Assistance After Thoracic Trauma

- Altered mental status
- Hypovolemic shock
- Multiple injuries
- Multiple blood transfusions
- Elderly patient
- Preexisting pulmonary disease
- Respiratory rate >30–35 breaths/min
- Vital capacity <10–15 mL/kg
- Negative inspiratory force <25–30 cm H_2O

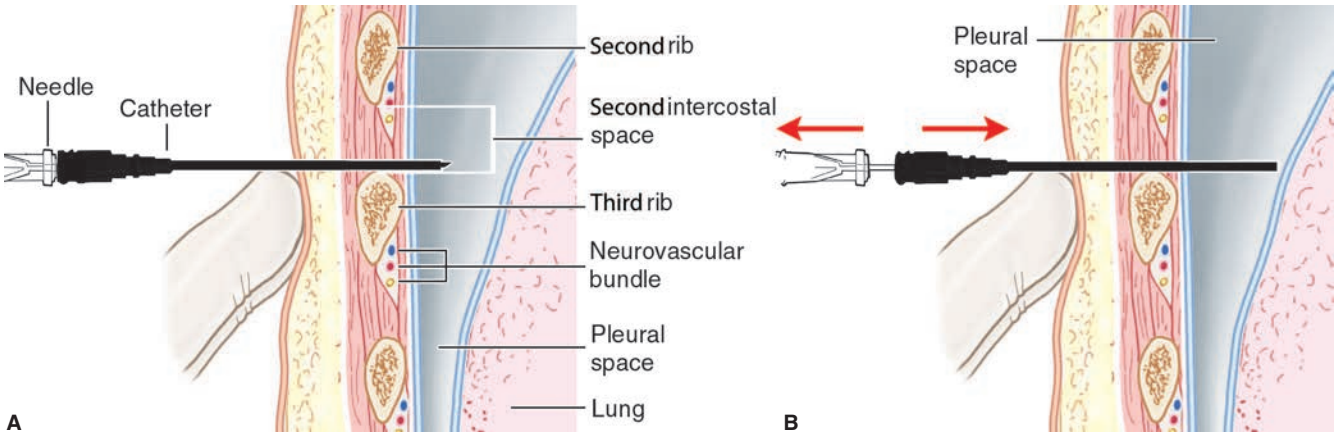


FIGURE 261-16. Decompression of a tension pneumothorax with a catheter-over-the-needle. **A.** The catheter-over-the-needle is inserted through the second intercostal space and into the pleural cavity. **B.** The catheter is advanced while the needle is removed. [Reproduced with permission from Reichman EF (ed): *Emergency Medicine Procedures*, 2nd ed. © 2013. McGraw-Hill Education, New York, NY. Fig 38-2A&B.]

and catheter, however, may not be long enough for decompression, as the mean chest wall thickness in the United States is 4.5 cm.[68] **A site that is being more commonly used is the fourth to fifth intercostal space at the anterior axillary line, which is the shortest distance from the skin to the pleura.**[69] A rush of air exiting the pleural space may be audible and is diagnostic of a pneumothorax. Needle depression converts the tension pneumothorax into an open pneumothorax; needle decompression is a temporizing measure and should be followed promptly with tube thoracostomy. If the patient's hemodynamics fail to improve following decompression, consider other causes of hypoperfusion, such as pericardial tamponade.

TUBE THORACOSTOMY

Evacuate large hemothoraces or hemopneumothoraces as rapidly as possible to decrease their negative effects on ventilation and perfusion. Double-check clinical and radiographic findings to ensure placement of the chest tube is on the correct side of the patient. Historically, a 24F or 28F (8.0 or 9.3 mm) chest tube was recommended for a simple pneumothorax and a >32F (>10.7 mm) chest tube for a suspected hemothorax. Multiple studies suggest there are no differences in efficacy of drainage, complication rate, pain, or need for additional procedures when using small or large chest tubes.[70,71] (See Video: Chest Tube Insertion.)

Perform tube thoracostomy for treatment of traumatic pneumothorax or hemothorax in the anterior axillary line at the level of the nipple in men or inframammary crease in women (corresponding to the fifth intercostal space) just behind the lateral edge of the pectoralis major.

Make an oblique skin incision at least 1 to 2 cm **below** the interspace through which the tube will be placed. Insert a large clamp through the skin incision and into the muscles in the next higher intercostal space, just **above** the rib, thus avoiding the neurovascular bundle (**Figure 261-17**). The resulting oblique tunnel through the subcutaneous tissue and intercostal muscles usually closes promptly after the chest tube is removed, thereby reducing the chances of recurrent pneumothorax.

Once the clamp is pushed through the internal intercostal fascia, open it to enlarge the hole to at least 2.0 cm. Insert a finger along the top of the clamp through the hole to verify the position within the thorax and to verify that the lung is not adhering to the chest wall (**Figure 261-18**).

Advance the tube at least until the last side hole is 2.5 to 5.0 cm (1 to 2 inches) inside the chest wall. For a pneumothorax, direct the tube toward the apex, away from the hilum and mediastinum. For a hemothorax, direct the tube posteriorly and laterally. However, do not reposition any tube position that functions effectively unless indicated by abnormal or suboptimal placement identified on the chest radiograph. In general, do not clamp the chest tube. Any continuing air leakage can rapidly collapse the lung or cause a tension pneumothorax. Importantly, loss of vital signs and clinical deterioration after chest tube placement may indicate exsanguinating injury and loss of the protective vascular tamponade effect as the hemothorax is evacuated. In this circumstance, clamp the chest tube and transport the patient directly to the operating room for an emergency thoracotomy.

Classically, the open end of the tube was attached to a combination fluid-collection water-seal suction device, with 20 to 30 cm H_2O of suction. Recent studies have called into question the need for suction as opposed to a water seal without suction in patients with uncomplicated traumatic pneumothoraces and hemothoraces.[72] If a significant hemothorax is known to be present or if a large amount of blood starts to drain immediately, consider collecting the blood in a heparinized autotransfusion device so that it can be returned to the patient.

Check the intrathoracic position of the chest tube and of its last hole and the amount of air or fluid remaining in the pleural cavity with a portable chest radiograph as soon as possible after the tube is inserted. Serial chest auscultation, chest radiographs, and careful recording of the volume of blood loss and the amount of air leakage are important guides to the functioning of chest tubes. If a chest tube becomes blocked

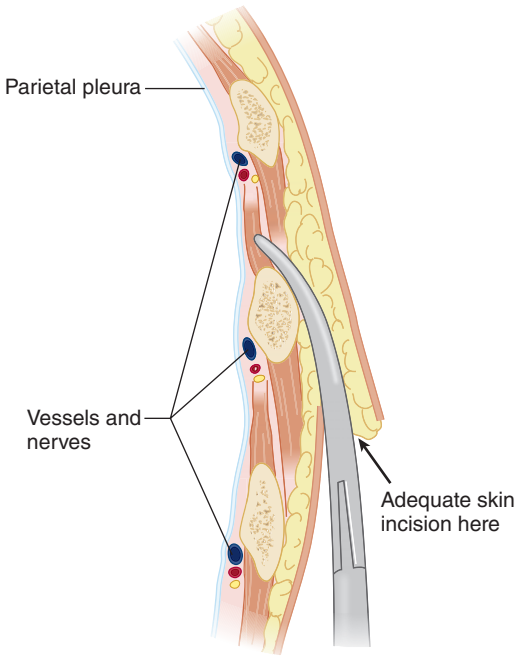


FIGURE 261-17. Chest tube insertion. The clamp is inserted through the incision and is tunneled up to the next intercostal space.

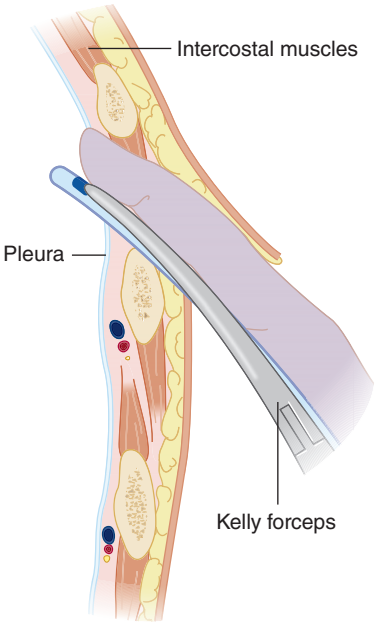


FIGURE 261-18. Chest tube insertion. Using the finger as a guide, place the tip of the clamp into the pleural cavity just above the rib to avoid intercostal vessels and nerves.

and a significant pneumothorax or hemothorax is still present, replace the tube or place a second chest tube on the affected side. Irrigating an occluded chest tube or passing a Fogarty catheter through it in an effort to reestablish its patency is not advised.

Leave chest tubes in place on suction for at least 24 hours after all air leaks have stopped (if placed for a simple pneumothorax) or until drainage is serous and <200 mL/24 h (if placed for hemothorax).[73] However, in intubated patients, maintain chest tubes throughout mechanical ventilation to prevent sudden development of a new pneumothorax.

The use of prophylactic broad-spectrum antibiotics in patients who require tube thoracostomy for a traumatic hemothorax or pneumothorax remains controversial.[74-76] Whether or not antibiotics are given, adhere to protocols for the placement, maintenance, and early removal of chest tubes to decrease the risk of infection.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 262

Cardiac Trauma

Brit Long
Alex Koyfman

BLUNT AND PENETRATING CARDIAC TRAUMA AND GREAT VESSEL INJURY

INTRODUCTION

Detection of cardiac injuries is critical for patient survival in trauma. Penetrating cardiothoracic injury causes one quarter to one third of deaths immediately following trauma, and the majority of these fatalities involve either cardiac or great vessel injury.[1,2] Penetrating cardiac injury results when a foreign object enters the body, piercing the pericardium or heart, and cardiac injury may account for close to 10% of deaths from gunshot wounds.[2,3] Invasive cardiac procedures or therapies may cause iatrogenic trauma to the pericardium and myocardium. Even noncardiac procedures like central lines placed into the internal jugular vein can lead to penetration of the pericardium, heart, and great vessels.[4] The incidence of blunt cardiac injury has been reported to range anywhere from 8% to 71%.[5,6] Blunt cardiac injury results from physical forces acting externally on the body, and up to 20% of all motor vehicle collision deaths are due to blunt cardiac injury.[2,3]

Suspect the diagnosis of cardiac or great vessel injury in a patient with chest, lower neck, epigastric, or precordial injury. Closely observe for evidence of hemodynamic instability, loss of circulating blood volume, electrocardiographic changes, cardiac tamponade, and hemothorax.[2,6]

EPIDEMIOLOGY

Most penetrating injuries occur from guns and knives, with a shift toward gunshot wounds becoming more common than knife wounds.[2,7-9] The injury usually involves only the free cardiac wall, but other structures can be injured, such as cardiac valves, chordae tendineae, papillary muscles, atrial or ventricular septum, coronary arteries, and conduction system (**Table 262-1**).[2,10] Rates of involvement of cardiac structures due to penetrating injuries to the right ventricle, left ventricle, right atrium, and left atrium are approximately 40%, 35%, 20%, and 5%, respectively.[11,12] Mortality approximates 40% for penetrating cardiac injury.[7]

Types of blunt cardiac injury can be sustained from any of the mechanisms listed in **Table 262-2**.[13] Rapid deceleration is the most common mechanism responsible for most blunt cardiac injury followed by a direct blow to the precordium. Blunt cardiac injury results in a range of conditions from clinically silent transient dysrhythmias to cardiac wall rupture.[6]

The most common reported blunt injury is "myocardial or cardiac contusion." These terms describing blunt cardiac injury are nonspecific and have been used to report a wide range of injuries. Further, there is not a clear definition or a gold standard for testing, which makes the diagnosis and treatment difficult. The term *blunt cardiac injury* has

TABLE 262-1 Injuries From Penetrating Wounds of the Heart

Pericardial damage
- Laceration or perforation
  - Hemopericardium with or without cardiac tamponade
  - Serofibrinous or suppurative pericarditis
  - Pneumopericardium
  - Constrictive pericarditis

Myocardial damage
- Laceration
- Penetration or perforation
- Retained foreign body
- Structural defects
  - Aneurysm formation
  - Septal defects
  - Aorticocardiac fistula

Valvular injury
- Leaflet or cusp injury
- Papillary muscle or chordae tendineae laceration

Coronary artery injury
- Laceration or thrombosis with or without myocardial infarction
- Arteriovenous fistula
- Aneurysm

Embolism
- Foreign body
- Thrombus (septic or sterile)

Infective endocarditis

Rhythm or conduction disturbance

TABLE 262-2 Mechanisms for Blunt Cardiac Injury

- Direct precordial impact
- Crush injury from compression between the sternum and spine
- Abrupt pressure fluctuations in the chest and abdomen
- Shearing from rapid deceleration or torsion causing a tear in the heart at a point of fixation (right atrium and vena cava)
- Injury from rib fracture fragments
- Hydraulic effect resulting in cardiac rupture
- Blast injury

replaced the terms *cardiac contusion* and *myocardial contusion*. Blunt cardiac injury can encompass cardiac dysfunction (diminished contractility in the absence of dysrhythmia or hemorrhage), dysrhythmias, specific injuries (septal rupture, valvular injuries, myocardial infarction), and cardiac rupture, the most devastating blunt cardiac injury.[5,6,14,15]

Most patients who present with thoracic great vessel injury have sustained penetrating trauma and have a dire prognosis; most die before they reach medical care.[16-18] Aortic injuries from blunt trauma are usually due to motor vehicle crashes. Over 90% of patients who sustain this injury die at the scene; of the remaining 10% who survive, 50% die within 24 hours and 90% die within 4 months.[17] The mortality for untreated patients is 1% per hour for the initial 48 hours.[18]

ANATOMY AND PATHOPHYSIOLOGY

Cardiac and great vessel anatomy relates to the specific injury patterns found in penetrating and blunt injury. **The anatomic "cardiac box" (Figure 262-1) is the area of the chest bound by the sternal notch superiorly, the xiphoid process inferiorly, and the nipples laterally.** A high likelihood for cardiac injury is present for injuries in the corresponding lateral and posterior areas of the thorax. This results in a three-dimensional cardiac box that should be considered in penetrating injury.[2,19] Most stab wounds injuring the heart enter through this area. Gunshot wounds, however, may enter at regions well outside this area, so any penetrating injuries involving the thoracoabdominal region, back region, or any potential of transmediastinal trajectory place the heart at risk for injury. Pericardial injury can result in acute tamponade. The right ventricle is at greatest risk due to its large anterior exposure on the chest wall. The right and left atria are less frequently involved due to their smaller surface area. Blunt cardiac injury most often involves the right heart due to the anterior location of the right atrium and ventricle within the mediastinum. Injury often involves more than one chamber in over half of the reported cases.[2,20]

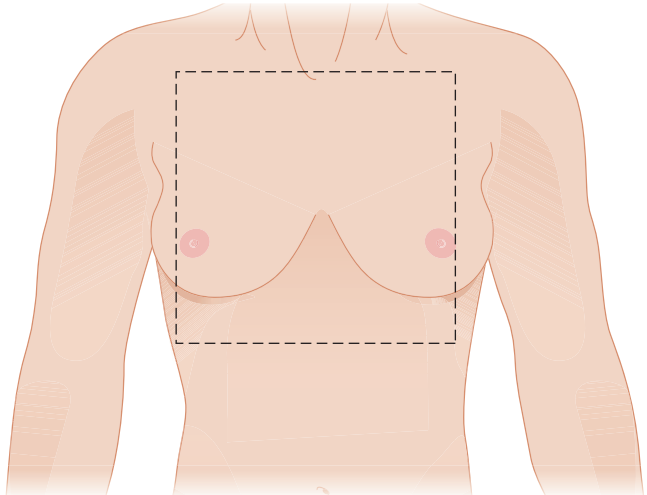


FIGURE 262-1. The cardiac box: chest area with potential for cardiac injury.

The thoracic great vessels consist of the aorta and its brachiocephalic trunk and its branches; the left subclavian, left common carotid, and pulmonary arteries and veins; the superior and intrathoracic venae cavae; and the innominate and azygos veins. Injuries to these vessels occur in both penetrating and blunt trauma. The large blood volume flowing through these vessels leads to exsanguinating hemorrhage as the primary acute manifestation of trauma. Even if not immediately ruptured, injury to these vessels can produce aneurysm and pseudoaneurysm through fistula formation, which in turn can lead to massive hemorrhage.[2,21]

PATHOPHYSIOLOGY

The pathophysiology is determined by the type and location of injury. With regard to penetrating trauma, knives tend to involve a single cardiac chamber, producing a single slit-like defect that is often more amenable to medical and surgical therapy than gunshot wounds, with survival for right ventricle injuries at nearly 60%.[22] Gunshot wounds, however, can cause a spectrum of injury from multiple-chamber perforation to gaping defects depending on the caliber and velocity of the missile. Patients with stab wounds to the heart are 17 times more likely to survive than those with gunshot wounds.[23] Atrial injuries are less common and generally less severe, whereas multichamber injuries are associated with higher mortality.[7,23-25]

The pathologic changes seen in blunt cardiac injury typically include subendocardial hemorrhage and a much larger area of focal myocardial edema, interstitial hemorrhage, and myocytolysis with infiltrates of polymorphonuclear leukocytes. Additional myocardial injury may occur if there are concomitant intimal tears or compression from adjacent hemorrhage or edema. Myocardial injury may also be due to redistribution of coronary blood flow. Minor myocardial marker elevation or ECG abnormalities and dyskinesia or dysrhythmias typically resolve over time, usually within the first 24 hours.[6,13] Blunt cardiac injury can lead to death from complex dysrhythmias, acute heart failure, cardiac-free wall rupture, or laceration of a coronary artery that causes extracardiac hemorrhage. Most of these lethal mechanisms result in death at the scene of the injury.[26-28] Less severe injuries to the ventricular wall may lead to delayed necrosis and clinically manifest as delayed rupture days after admission. If a low-pressure chamber or coronary vein is injured, patients may survive until presentation to the hospital.[2,29]

Blunt cardiac injury can also result in rupture of an atrial or ventricular septum, resulting in shunting of blood and presentation similar to heart failure.[30] Similarly, blunt cardiac injury can result in regurgitation of blood from a high-pressure chamber or artery into a lower-pressure chamber, such as with an acute valve dysfunction or papillary muscle injury.[30,31] Valvular injury tends to worsen over time. The degeneration of the valve's function appears to depend on its location. High-pressure valves like the aorta and mitral valves tend to manifest symptoms immediately or within the first few weeks, whereas injury to lower-pressure valves like the pulmonic and tricuspid can be asymptomatic for years.[6,13] Coronary arteries can have occlusion, dissection, or spasm that can manifest as immediate or delayed injury patterns. Coronary artery injury presents most often in a myocardial infarction pattern.[33]

CLINICAL APPROACH

Nonspecific signs and concomitant injuries will affect clinical presentation. Such other clinical findings in the trauma patient may make it difficult to determine whether symptoms stem from cardiac or other injuries. Specific signs of cardiac injury (e.g., distended neck veins or specific murmurs) may not be present if the patient is hypotensive from other injuries. Symptoms of cardiac injury may occur in a delayed fashion coincident with fluid resuscitation.[2,6]

HISTORY

For penetrating injury, mechanism, initial hospital signs, injuries, and treatments are valuable if obtainable from prehospital providers. In unstable patients with penetrating trauma, history may not be obtainable from the patient. The most common symptom of blunt cardiac trauma is chest pain. All different qualities of chest pain occur, ranging

from pleuritic to pressure-like. Even the classic crushing retrosternal pain of myocardial ischemia can occur if coronary arteries are involved. Patients with injuries on the chest wall such as rib fractures, sternal fractures, or clavicular fractures may have underlying cardiac injury. Be cautious about attributing symptoms only to those of the superficial chest wall, because pericardial and myocardial structures may be damaged as well. Patients may have shortness of breath due to overlying chest and pulmonary injury or due to myocardial dysfunction from cardiac tamponade or heart failure. Other nonspecific symptoms such as lightheadedness and palpitations are also common.[13,15] Clinical findings vary widely depending on the structures injured, the extent of the injuries, concomitant injuries, and the patient's body habitus and mental status.

PHYSICAL EXAMINATION

Close observation of heart rate and blood pressure and their associated trends is important. In patients with chest trauma, initial vital signs are not reliable, as patients can decompensate quickly. Often, the presence of unexplained tachycardia may be the only finding of cardiac injury. Listening to breath sounds and heart sounds may assist in diagnosing cardiac injury. Identification of all injuries and retained foreign bodies is imperative, with complete visualization of the torso, including back and axilla. Clear lungs with muffled heart sounds may be indicative of cardiac tamponade, but this finding is quite rare and difficult to detect in a noisy ED. Coarse crackles in the lungs, extra heart sounds, and elevated jugular venous pressure may be present if myocardial dysfunction leads to heart failure. Physical examination may also reveal a "seat belt sign," chest wall deformity, or subcutaneous emphysema, although the absence of these findings does not exclude injury.[2,6,34] Repeat examination and vigilance are needed, as these patients may rapidly decompensate.

PENETRATING CARDIAC TRAUMA

PENETRATING CARDIAC TRAUMA

The two conditions that can occur after penetrating cardiac injury are exsanguinating hemorrhage and cardiac tamponade. Pericardial defects that are large or remain open may present with hemothorax and clinical signs of blood loss that may progress to rapid exsanguination and death. If the pericardial wound seals itself, which is common with the linear defect in a stab wound, the result is intrapericardial hemorrhage that may progress to cardiac tamponade.[2] The location of the wound will also determine the rate of accumulation. Right ventricular wounds tend to seal themselves more readily than right atrial wounds due to the thicker, more muscular walls of the ventricle. Atrial injuries may have subtle or no clinical findings initially; however, rapid clinical deterioration can occur. Injury to the coronary arteries is manifested by tamponade or myocardial ischemia.[2,6]

CARDIAC TAMPONADE

Cardiac tamponade, characterized by the accumulation of pericardial fluid under pressure, can be found in up to 2% of penetrating trauma to the thoracoabdominal region and very rarely in blunt trauma. Up to 80% of myocardial stab wounds may develop cardiac tamponade. Gunshot wounds leave defects in the pericardium that are larger and more irregular than stab wounds. Gunshot wounds are therefore less likely to develop tamponade because it is more difficult for the pericardium to seal the defect.[35,36]

Blood in the pericardial cavity may be defibrinated by the lytic activity normally present in the pericardium, resulting in a hematoma that may inhibit normal myocardial function. Intrapericardial blood accumulation eventually causes elevated intrapericardial pressure, which leads to decreasing right and left ventricular filling. Catecholamines are released in this state as a compensatory mechanism that results in tachycardia and further elevated right-sided filling pressures. Once the distensibility limits from intrapericardial fluid are reached by the pericardium, the myocardial septum shifts toward the left side, which further reduces left ventricular filling and subsequent cardiac output. This downward spiral eventually produces irreversible shock and death. Even small amounts of blood (65 to 100 mL) can lead to an acute rise in intrapericardial pressure. Hypovolemic shock from other injuries may partially or completely compensate for the elevated right-sided pressures, resulting in normal or even low central venous pressures.[2,6]

Cardiac tamponade is identified by the FAST exam. Without point-of-care US, cardiac tamponade can be deceptively difficult to diagnose as the body compensates for the hemodynamic effects by various mechanisms. The reduced cardiac output is offset by the increase in heart rate and increase in systemic vascular resistance. Often, the only clinical finding of pericardial tamponade is sinus tachycardia. Hypotension may be a sign of ominous decompensation and emergent need for surgical intervention if due to pericardial tamponade or systemic hypovolemia from other injuries. The classic finding of Beck's triad of muffled heart sounds, hypotension, and distended neck veins is present in less than 10% of cases.[2,3,6] Pulsus paradoxus, a substantial fall in systolic blood pressure during inspiration, and Kussmaul's sign, an increase in jugular venous distention on inspiration, are not reliable signs and may only be found with moderate to severe tamponade.[36] A more reproducible sign of cardiac tamponade is a narrowing of the pulse pressure, which along with elevation of the central venous pressure, is cardiac tamponade until proven otherwise. The narrowed pulse pressure is not sensitive, and its absence should never be used to exclude tamponade. Usually the jugular venous pressure is elevated and may be associated with venous distention of the neck veins, forehead, and even scalp. (See Video: FAST.)

INTRACARDIAC MISSILES

The heart may have a retained missile from a direct injury or as a result of venous migration from another injury. These missiles, or the thrombus that may form as a result, may embolize into systemic or pulmonary arteries.[1] Many patients with a retained cardiac missile are hemodynamically stable. The patients may do well with prolonged observation and no operative intervention.[37] The treatment for missiles is highly variable, depending on missile size, shape, and location. Missiles that cause any hemodynamic instability or symptoms should be removed. A left ventricular missile that is free or partially exposed should be removed to prevent systemic embolization.[37] Right-sided missiles may be removed or left alone because embolization to the pulmonary vascular bed usually has minimal consequences.[38] Most intramyocardial and intrapericardial bullets and pellets are generally well tolerated and left in place. Embolized missiles need immediate removal because of the downstream ischemic effects of arterial occlusion. If a missile is embedded or adjacent to a coronary artery, it should be removed because of the potential for erosion and bleeding, which may lead to myocardial infarction and pericardial tamponade. Long-term effects of a retained missile may include bacterial endocarditis, thrombosis, embolization, and cardiac neurosis (many patients feel that they need any missile removed at all cost).[37]

IATROGENIC CARDIAC INJURY

Diagnostic and therapeutic percutaneous procedures may lead to many cardiovascular complications. Vascular (including extra- and intracardiac), valvular, and myocardial injuries are well-recognized complications of procedures such as central line placement, thoracentesis, chest tube placement, pericardiocentesis, percutaneous coronary catheterization, valvuloplasty, and electrophysiologic lab procedures.[39]

TREATMENT OF PENETRATING CARDIAC TRAUMA

The utility of pericardiocentesis for cardiac tamponade identified on FAST exam in cardiac trauma is controversial, though it may act as a temporizing measure. Perform ED thoracotomy in unstable patients with cardiac tamponade who may not survive transfer to an operating room.

PERICARDIOCENTESIS

Pericardiocentesis is a prelude to formal thoracotomy if there are inevitable delays to definitive surgery (i.e., transport to trauma center). Use of US guidance of the needle increases accuracy and is a class I American College of Cardiology/American Heart Association recommendation for critically injured patients. Detailed discussion is provided in Chapter 34, "Pericardiocentesis." (See Video: Pericardiocentesis.)

ED RESUSCITATIVE THORACOTOMY

Patients in extremis but with electrical cardiac activity should be rapidly transported to the ED. Resuscitative ED thoracotomy can be lifesaving in carefully selected patients. The decision to perform an ED thoracotomy or alternately determine that resuscitation is futile must be made in short order under highly stressful circumstances.

Candidates for ED thoracotomy include penetrating chest trauma patients who are hemodynamically unstable and those who demonstrated signs of life (palpable pulse, a blood pressure, pupil reactivity, any purposeful movement, organized cardiac rhythm, or any respiratory effort) either in the field or ED but subsequently lost these signs of life. Resuscitative ED thoracotomy is likely to be futile in patients under the following clinical scenarios: (1) no pulse or blood pressure in the field; (2) asystole is the presenting rhythm and there is no pericardial tamponade; (3) prolonged pulselessness (>15 minutes) at any time; (4) other massive, nonsurvivable injuries; or (5) blunt traumatic cardiac arrest.[40,41]

Exposure to the heart is accomplished by a left anterolateral thoracotomy. No matter where the penetrating injury occurs, use the left-sided approach initially. This approach allows for quick access to the pericardium and heart and exposure for aortic cross-clamping if necessary. Identify the left fourth or fifth intercostal space, which corresponds to an intercostal space below the male nipple or at the inframammary fold in a woman. Make the incision in a single stroke through all layers down through the intercostal musculature from sternum to posterior axillary line. Use Mayo scissors to cut the remaining intercostal muscles. Insert a Finochietto retractor with the crank positioned near the bed. Open the retractor to allow exposure of the left thorax. Remove blood and inspect for brisk bleeding. Control intrathoracic hemorrhage with direct pressure, the application of appropriate pulmonary or vascular clamps, and direct suture ligation. Gently push the lung out of the field to expose the pericardium. To minimize the left lung obscuring the field, a right mainstem bronchus intubation may be performed.

A distended, discolored, and often tense pericardial sac confirms cardiac injury. Perform a pericardiotomy by making a long incision from the apex of the heart to the root of the aorta just anterior to the phrenic nerve. Remove any blood and clot from the pericardial sac. Patients who do not have blood in the pericardium and do not exhibit cardiac activity may be declared dead at this point. If there is evidence of blood in the pericardium or cardiac activity, then expose the heart for inspection. After extruding the heart through the incision in the pericardium, identify the cardiac wound. One of several techniques may be used to control hemorrhage (**Figure 262-2**). Simple digital occlusion on top of the wound is the first maneuver to attempt initial hemostasis. Never insert a finger

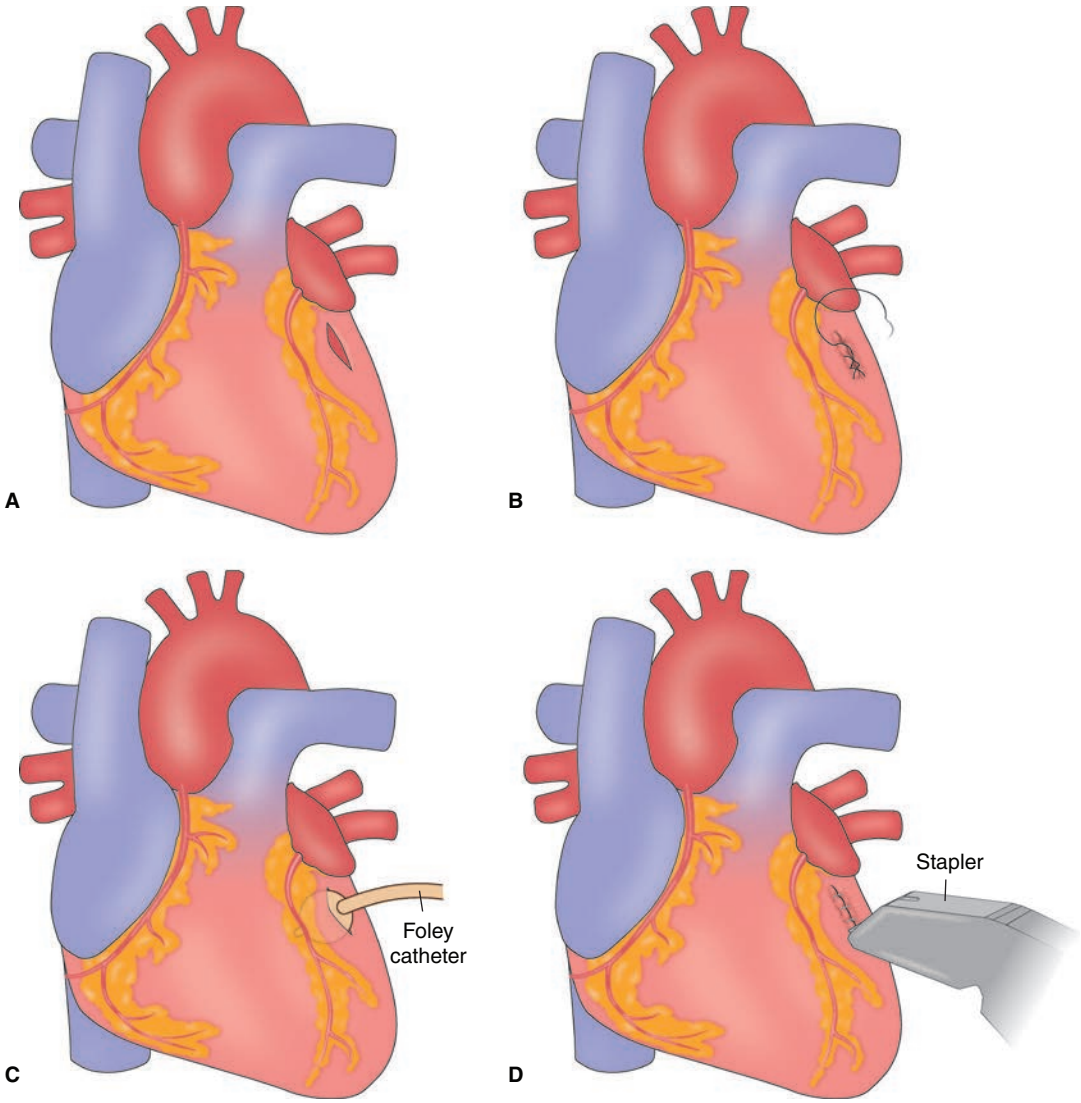


FIGURE 262-2. Temporary techniques to control bleeding of myocardial laceration. Emergency center management of injury to the epicardium. **A.** Stab wound to the left ventricle. **B.** Initially managed with either a continuous 4-0 polypropylene suture or interrupted sutures tied beneath the surgeon's finger. **C.** Injuries that are more complex and cannot be managed in the ED can be temporized using a Foley catheter for ventricular injuries and either a Foley catheter and/or partial occluding clamp for atrial injuries. **D.** Because of concerns about surgeon needle stick during cardiorrhaphy on the beating heart, hemostasis can initially be achieved with the skin stapler. Care must be observed in avoiding ligation of coronary arteries.

into the wound because this may extend the defect. The defect can then be stapled with regular skin staplers, which is a quick and easy method of temporary cardiac repair. Suturing of wounds is often technically difficult due to the dynamic nature of the myocardium, the slippery edges, the ease with which the sutures pull through the myocardium, inadequate lighting, and bloody field. Putting a Foley catheter into the defect and blowing up the balloon can fill a large circular defect. Gentle traction on the catheter will allow the balloon to seal the defect. A purse string suture can then be placed around the Foley catheter so that when the catheter is removed, tightening of the suture will seal the defect. Myocardial defects can be sutured with horizontal mattress sutures, but use pledgets to reinforce the repair and prevent cutting through the heart tissue.

Cross-clamp the aorta and then perform internal cardiac massage in the absence of coordinated cardiac function. Whatever type of repair is attempted, be careful and **do not ligate major coronary vessels**. If there is no evidence of injury to the left side or there is a high index of suspicion of right-sided injury, the ED thoracotomy incision can be extended to the right side. This is done by extending the incision across the sternum ("clam shelling") in the same manner as the primary left-sided incision to gain access to the right side of the chest and allow for better exposure of the right ventricle and atrium. Patients with suspected intra-abdominal hemorrhage should have the descending aorta cross-clamped.

After resuscitative ED thoracotomy, if vital signs are regained, transfer the patient to the operating room for definitive repair. The survival rate for patients who make it to the operating room is 70% to 80% for stab wounds and 30% to 40% for gunshot wounds.[40,41]

A second approach for ED thoracotomy, which is perhaps faster with greater exposure, is to perform bilateral finger thoracostomies and then connect these incisions anteriorly, completing a clamshell.[42-44]

ADJUNCTIVE MEASURES: TRANEXAMIC ACID

Antibrinolytic agents have demonstrated utility in preventing death due to hemorrhage in severe trauma. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 and Military Application of Tranexamic Acid (TXA) in Trauma Emergency Resuscitation trials are landmark studies demonstrating improved outcomes with TXA when given within 3 hours of traumatic injury.[45-47] Administer TXA 1 gram IV to patients with penetrating cardiac or great vessel injury if within 3 hours of injury. There is no study directly evaluating TXA in cardiac trauma or great vessel injury patients; however, a 2012 meta-analysis of patients undergoing surgery, the majority cardiac, found reduced death and need for transfusion in patients receiving TXA.[47] TXA can provide a potential benefit in these severely injured patients with little risk for adverse event from the medication.

BLUNT CARDIAC TRAUMA

COMMOTIO CORDIS

Commotio cordis, meaning "disturbance of the heart" in Latin, is sudden death as a result of blunt trauma to the chest wall. It often results from an innocent-appearing chest wall blow. It is the second most common cause of death in youth athletics following hypertrophic obstructive cardiomyopathy. Usually victims are young athletes who are struck in the chest by hard projectiles that are used in the particular sport. Sports using small dense projectiles like baseball, hockey, and lacrosse have the highest incidence of commotio cordis. The hardness of the impact object, location of impact, and velocity of the object affect the risk of development of ventricular fibrillation. Commotio cordis blows are generally low impact, most of which are insufficient to cause any significant structural damage to the ribs, sternum, or heart. Commotio cordis is a primary electrical event resulting in the induction of ventricular fibrillation; it is a result of a blow that occurs 10 to 30 milliseconds before the peak of the T wave, a time of vulnerability to ventricular fibrillation.[6,48] Autopsy findings typically show normal cardiac anatomy with no evidence of injury. The overall survival rate is less than 15%, but due to increasing prevalence of automated external defibrillators being placed in sporting venues, survival rates may improve.[48]

TABLE 262-3 Associated Injuries With Blunt Cardiac Trauma[3]

Associated Injuries	Incidence of Finding in Patients With Blunt Cardiac Injury
Thoracic injury	
Chest pain	18%–92%
Rib fracture	18%–69%
Aortic or great vessel injury	20%–40%
Hemothorax	7%–64%
Pulmonary contusion	6%–58%
Pneumothorax	7%–40%
Flail chest	4%–38%
Sternal fracture	0%–60%
Head injury	20%–73%
Extremity injury	20%–66%
Abdominal solid organ injury	5%–43%
Spinal injury	10%–20%

Source: With permission from Schultz JM, Trunkey DD. Blunt cardiac injury. *Crit Care Clin*. 2004;20(1):57-70. Copyright Elsevier.

CARDIAC DYSFUNCTION

The exact incidence of cardiac dysfunction (decreased contractility) in blunt cardiac injury is unknown. Further, the cause of dysfunction may be difficult to determine in the hypotensive, multiply injured trauma patient. Patients almost universally present with chest pain. The pain usually results from associated thoracic trauma (**Table 262-3**). Associated blunt injury to the lung can lead to a rise in pulmonary vascular resistance, which can result in a reduction in preload of the left ventricle. This, coupled with the reduced cardiac output of the involved right ventricle, can lead to hypotension.[15,49] The damaged myocardial tissue may be a focus for both atrial and ventricular dysrhythmias, which may further produce decreased contractility and hemodynamic deterioration.

Monitor for dysrhythmias. Persistent tachycardia, new bundle branch block, supraventricular tachycardia, atrial and ventricular fibrillation, and minor dysrhythmias (occasional premature ventricular contraction) can occur after blunt injury.

INJURY TO THE PERICARDIUM

Direct impact or increased intra-abdominal pressure can cause pericardial tears. The tears usually occur on the left side of the pericardium parallel to the phrenic nerve. Herniation can occur through the defect leading to cardiac dysfunction and dysrhythmias. Tears in the pericardium often are missed and may have little clinical impact. Physical examination (pericardial rub), point-of-care US, or CT findings (pneumopericardium, displacement of the heart, abnormal bowel gas in chest or around heart, or evidence of intra-abdominal contents inside pericardium) may lead to the diagnosis. Pericardial laceration may cause herniation and strangulation of the myocardium if not diagnosed and corrected surgically.[2,49] Patients with detectable pericardial rents are usually taken to the operating room for repair unless the tear is too large so that closure would lead to tension on the pericardium and potentially produce myocardial dysfunction.[2]

INJURY TO CARDIAC VALVES, PAPILLARY MUSCLES, CHORDAE TENDINEAE, AND SEPTUM

Injury to cardiac valves occurs in approximately 10% of blunt cardiac injury.[6] Isolated valvular injuries appear to be rare. The aortic valve is most often involved, followed by the mitral and tricuspid valves. Injury to the aortic valve can cause severe regurgitation with development of pulmonary edema. Presentation may vary from new murmur to acute valvular insufficiency with right- or left-sided cardiac failure. A widened pulse pressure can be seen with acute aortic valvular injuries. Septal

injuries are also rare with variable presentations, ranging from insignificant tears to frank rupture. They may occur in isolation or with valvular injury. The muscular portion of the septum can rupture several days after blunt trauma. Suspect patients with new-onset murmurs of having valvular, septal, or papillary muscle pathology. Any patients with clinical or echocardiographic evidence of injury require emergent surgical consultation. Treatment for septal and valvular injury is generally surgical, and timing depends on the presenting signs and acuity. Acute heart failure resulting from elevated pulmonary pressure due to structural injury warrants rapid surgical intervention, whereas small septal injuries with minimal clinical effects can be treated conservatively because many eventually close spontaneously.[2,6,15,50]

INJURY TO CORONARY VESSELS/MYOCARDIAL INFARCTION

Although blunt cardiac injury rarely leads to injury of the coronary vessels, arteriovenous fistula, coronary artery dissection, and coronary thromboses have been reported.[51,52] The most common artery involved is the left anterior descending artery. Coronary artery injury presents in the same fashion as atherosclerotic heart disease, has similar treatment by percutaneous coronary intervention with stenting, and has a more favorable prognosis. Because of the possibility of other injuries, extreme caution must be taken in using anticoagulation therapy due to bleeding complications.[51,52] Fibrinolytic therapy is contraindicated.

CARDIAC RUPTURE

The most severe form of blunt cardiac injury is cardiac rupture. Most patients with cardiac rupture die at the scene of the trauma. The right-sided portion of the heart is much more prone to rupture due to its more anterior location, as are the thin-walled atria compared with the thicker-walled, stronger ventricles. In patients who survive to ED arrival, the physical examination may reveal a "splashing mill wheel" sounding murmur ("bruit de Moulin"), but this finding is rare. ECG may show conduction defects or, if herniation has occurred, axis deviation. A skilled sonographer can rapidly reveal the diagnosis, and immediate thoracotomy is required for survival.[2,6,28]

PERICARDIAL INFLAMMATION SYNDROME

The cause of pericardial inflammation may be a delayed hypersensitivity reaction to the presence of damaged myocardium in the pericardial cavity. Consider this syndrome in individuals who develop chest pain, fever, and pleural or pericardial effusions 2 to 4 weeks after cardiac trauma (or surgery). Patients may also have friction rubs, arthralgia, and pulmonary infiltrates. The ECG will often show ST-T wave changes consistent with pericarditis. Treatment is primarily symptomatic. NSAIDs and rest can often reduce symptoms dramatically within 12 to 24 hours, and glucocorticoids are occasionally required. Rarely, drainage of pleural or pericardial fluid may be required to relieve symptoms or to exclude other problems.

TREATMENT OF BLUNT CARDIAC INJURY

Treat hypotension with boluses of crystalloid or blood products to optimize intravascular blood volume, which will also optimize preload. Trauma patients often have multiple injuries, especially in blunt injury, so the most common reason for hypotension is due to hypovolemia requiring blood products, not myocardial dysfunction.

The management of blunt cardiac injury (myocardial or cardiac contusion) is otherwise not standardized. Surgical intervention is rarely required, although pericardial fluid discovered on FAST may require operative intervention for subxiphoid pericardial window.[2] The only universally accepted practice pattern is to observe patients with hemodynamic and continuous cardiac monitoring.[15] It is generally agreed that low-risk patients (minor injuries, no dysrhythmias, and normal ECG) usually will not develop complications so that further workup is not warranted. A patient with normal troponin and ECG is at low risk for blunt cardiac injury. Evaluate moderate- to high-risk patients (evidence of associated injuries, dysrhythmias, elevated cardiac biomarkers, abnormal ECG) with echocardiogram. Admit patients for cardiac monitoring with minor ECG abnormalities (premature ventricular or atrial contractions), no significant concomitant injuries, and normal hemodynamics.[53,54] Telemetry monitoring criteria do not exist, but monitoring for 24 hours is reasonable for minor abnormalities.[2,6,13,14]

Subsequent management depends on complications. After ruling out hypovolemia as the source of hypotension, vasopressor and inotropic support may be required to maintain cardiac output and blood pressure. Dysrhythmias that result in hemodynamic instability or are ventricular in origin are treated according to advanced cardiac life support algorithms. Dysrhythmias and myocardial dysfunction from blunt injury typically resolve in 24 hours.[49] Patients in cardiogenic shock require evaluation for structural injury. Patients with cardiac rupture, valvular injury, papillary muscle or chordae tendineae rupture, or coronary thromboses or dissection require emergent surgery or percutaneous coronary intervention depending on specific injury. Stabilizing therapies can be performed based on the specific injury.[2] Mitral valve injuries with regurgitation may need afterload reduction, as well as inotropic therapy. Aortic valvular injuries typically require emergent surgery.[2]

GREAT VESSEL INJURY

BLUNT INJURY

Blunt trauma injury to the great vessels involves high-speed deceleration. Usually the chest strikes the steering wheel, which subsequently transmits the force across the mediastinum. There may also be vascular compression of the vessels between the sternum and vertebral bodies and subsequent marked increases in intraluminal pressure.[18] Consider blunt aortic injury when the mechanism involves sudden deceleration such as a fall over 10 ft (3 m) or a motor vehicle crash at speeds greater than 30 mph (50 km/h).[2,6]

The proximal descending aorta is most commonly injured in blunt trauma because of the fixation of the vessels between the left subclavian artery and the ligamentum arteriosum.[2,6] The aorta is mobile and continues to move forward as the tethered portions decelerate with the remainder of the chest, leading to shearing forces that produce aortic injury. The diagnosis of ascending aortic injury is rarely made since very few patients survive long enough to diagnosis and repair. Ascending aortic injuries are frequently associated with cardiac rupture or severe myocardial contusion, and the aortic tears are often multiple. Usually large amounts of energy are required to injure the ascending aorta. The distal descending aorta is also a less frequently injured structure. Patients may present with paraplegia, mesenteric ischemia, anuria, or lower extremity ischemia. The more distal the injury, the better is the anticipated outcome, provided the patient does not exsanguinate prior to repair.

Although the subclavian artery is occasionally avulsed at its origin because of sudden deceleration, direct trauma to the distal artery with intimal damage and occlusion associated with fractures of the first rib or clavicle is more likely. Shoulder restraints that are loose may be a major factor in causing this injury. Injuries to the innominate artery are second in frequency only to rupture of the aorta at the isthmus. This injury is difficult to diagnose because less than half of patients have any physical findings at all and those who do have some diminution of the right radial or brachial pulse, a systolic murmur, or distal ischemia (rarely).

The pulmonic veins and the venae cavae attach to the atria and can serve as a nidus for injury with shearing forces. Venous thoracic great vessel injury is extremely rare, and most are fatal. Suspicion of inferior vena caval injury should occur with major hepatic injury, and both the superior and inferior venae cavae should be considered a source if there is cardiac tamponade or arterial bleeding that cannot be identified.

The aorta is primarily involved in about 85% of cases, but branch vessels are involved in 15% of documented vascular injuries.[21] The branch injuries are potentially fatal so their identification is of the utmost importance as well. Concurrent vascular injuries should be identified because the definitive surgical approach may change depending on where the injuries occur.[55]

PENETRATING INJURY

The pathophysiology of penetrating trauma to the great vessels is straightforward: either there is direct vessel injury or the kinetic energy damages the vessels by propagation through the tissues. Patients with penetrating injuries rarely survive to reach the hospital. Iatrogenic injuries from central line placement and other invasive thoracic procedures can lead to great vessel injury.

Bullets entering large systemic veins or the right heart can embolize to the lungs, whereas bullets entering the pulmonary veins or left heart can embolize to major systemic arteries. Some of these embolized foreign bodies do not cause symptoms or signs and can be located only after taking multiple radiographs. Suspect embolization if the missile appears distant from the anticipated trajectory. The other explanation for missiles off trajectory is gravity: low-velocity bullets that violate the pleural space but are not trapped in lung parenchyma often fall to the lowest place in the hemithorax, namely the posterior costophrenic recess.

CLINICAL FEATURES

Blunt trauma involving motor vehicle crashes can injure the aorta with side-impact collisions just as often as head-on collisions. Any blunt trauma from significant force (falls from a significant height, blast injuries, high-speed motor vehicle crash, crush injuries, pedestrian versus automobile injuries) can lead to blunt aortic injury.

Half the patients with blunt thoracic vascular injury present without external physical signs of injury. Although the physical examination findings of great vessel injury can be minimal to nonexistent, several important clues should be investigated. Hypotension, hypertension in the upper extremity and hypotension in the lower extremity, unequal blood pressures in the extremities, external evidence of major chest trauma (seatbelt or steering wheel contusion on the chest), thoracic outlet expanding hematoma, interscapular murmurs or bruits, palpable fractures of the sternum and ribs, or flail chest should increase suspicion of great vessel injury.[2,6]

Proximity of a missile trajectory to the brachiocephalic vessels, even without any physical findings of vascular injury, is an indication for pursuing a diagnosis of vascular injury. Close inspection of a penetrating wound should look for evidence, by inspection only, of retained implement or foreign body. Under no circumstances should the wound be deeply probed to determine depth or trajectory. Perform a complete neurologic examination due to involvement of the spinal arteries from the initial trauma.

DIAGNOSIS

ELECTROCARDIOGRAM

Patients with penetrating and blunt chest trauma require monitoring and immediate IV access. For blunt chest trauma, place the patient on a cardiac monitor, and obtain an ECG. The negative predictive value for cardiac injury in a patient with a normal ECG approaches 90%, but using the ECG alone does not exclude cardiac injury.[15,56-58] A clinically significant cardiac event can occur over the first 24 hours following injury.[34] The ECG is more sensitive for left ventricular injury and is poorly sensitive for the more common right-sided injuries. The most common dysrhythmia includes sinus tachycardia, followed by atrial fibrillation.[6] Nondiagnostic findings on ECG, such as sinus tachycardia and nonspecific ST-T wave changes, do not help diagnose blunt cardiac injury. A small subset of blunt cardiac injury patients may have symptoms and ECG findings consistent with myocardial infarction. In such patients, consider coronary artery disease or acute coronary artery dissection, which may manifest with thrombosis of a cardiac artery and typically develops 5 to 7 days after injury (**Table 262-4**).[17,59]

In patients in whom concern for blunt cardiac injury exists but in whom the ECG is normal, monitor for 4 to 6 hours with repeat examinations, ECGs, and cardiac monitoring. ECG can be utilized in combination with troponin to evaluate for blunt cardiac injury. If there are no new signs or symptoms and no abnormalities occur during this time period, patients can be safely discharged in absence of any other injuries.[6,13] If the ECG is abnormal but there is no hemodynamic instability, admit the patient to a monitored setting, with serial ECGs to monitor for disease progression.[6,13,15]

TABLE 262-4 Electrocardiographic Findings in Cardiac Injury[36]

Nonspecific abnormalities
• Pericarditis-like ST-segment elevation
• Prolonged QT syndrome
Myocardial injury
• New Q wave
• ST-T segment elevation or depression
Conduction disorders
• Right bundle branch block
• Fascicular block
• Atrioventricular nodal conduction disorders (first-, second-, and third-degree atrioventricular block)
Dysrhythmias
• Sinus tachycardia (most common)
• Atrial and ventricular extrasystoles
• Atrial fibrillation
• Ventricular tachycardia
• Ventricular fibrillation
• Sinus bradycardia
• Atrial tachycardia

Source: Reproduced with permission from Sybrandy KC, Cramer MJ, Burgersdijk C. Diagnosing cardiac contusion: old wisdom and new insights. *Heart*. 2003;89(5):485-489.

CARDIAC BIOMARKERS

Although cardiac markers can be used to assist in the diagnosis of myocardial trauma, the utility of cardiac biomarkers in the setting of blunt cardiac injury remains unclear.[6,60] The Eastern Association for the Surgery of Trauma guideline provides a Level 3 recommendation stating troponin I should be utilized for patients with blunt cardiac injury. The guideline provides a Level 2 recommendation that normal troponin and ECG rule out blunt cardiac injury.[69] Creatine kinase has limited reliability in the trauma patient because it is elevated in cases of severe skeletal muscle, liver, diaphragm, or intestinal injury; the creatine kinase-MB fraction will therefore be elevated as well. Creatine kinase-MB fraction elevation has been shown to occur in this situation in the absence of clinical evidence of cardiac injury. The isolated elevation of creatine kinase-MB, with no other associated injury, is not predictive of complications and mortality.[2,6,61] Thus, obtaining creatine kinase-MB is of no value.

Cardiac troponins, specifically troponin I and troponin T, are very specific to myocardial injury and can detect very small amounts of myocardial necrosis. Neither cardiac troponin I nor cardiac troponin T is released with skeletal muscle injury. Elevation of troponins occurs in all myocardial trauma, including both blunt and penetrating trauma, surgery, ablation, pacing, defibrillator shocks, cardioversion, and interventional cardiac procedures. The sensitivity and specificity of troponins for blunt cardiac injury vary from 12% to 23% and 97% to 100%, respectively.[58,62] Also, injuries remote from the chest from multisystem trauma and the presence of preexisting disease may result in dysrhythmia and elevated biomarkers, making their presence even less specific.[63]

Troponins in conjunction with a presenting ECG may increase the effectiveness of risk stratification.[6] Patients with a normal ECG and normal serial measurements of serial cardiac troponin I had no significant blunt cardiac injury–related complications in one study.[64] The sensitivity of an abnormal ECG and elevated cardiac troponin I for clinically significant blunt cardiac injury (cardiogenic shock, dysrhythmias requiring intervention, or structural cardiac abnormalities related to trauma) was 100%, with a positive predictive value of 62%.[62] Troponin T may also be used with similar sensitivity and specificity.[57,65] Clinically significant blunt cardiac injury can occur without elevation of troponins, but there

is usually an abnormality of the ECG. Monitor any serum troponin elevation and follow serially. Increased troponin levels at admission or within 6 hours of arrival have correlated with increasing risk of dysrhythmia and decreased ejection fraction.[66] Troponin elevations have been associated with ventricular dysrhythmias and left ventricular dysfunction.[67]

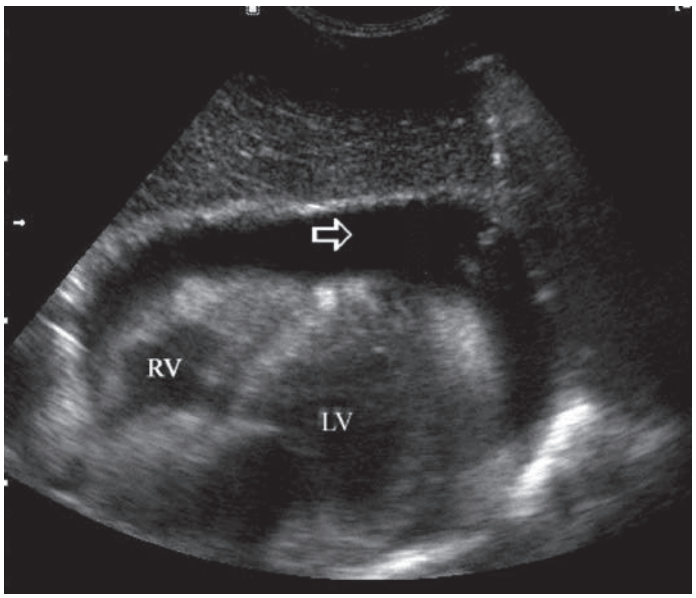
Ultimately, the use of cardiac biomarkers may not affect the management of blunt trauma patients with hemodynamic instability, signs of severe injury, or an abnormal ECG. Such patients generally undergo echocardiography and are admitted regardless of biomarker elevation.

In rare blunt trauma patients with ECG findings of myocardial infarction, obtain cardiac biomarkers and immediately consult cardiology and cardiac surgery.[5,6]

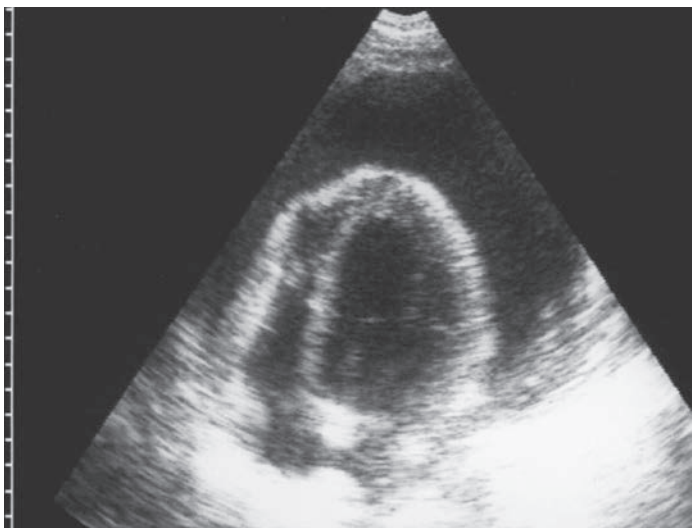
ECHOCARDIOGRAPHY

The FAST examination includes a cardiac window using either the subxiphoid (**Figure 262-3**) or parasternal long-axis approach and is useful in penetrating and blunt trauma. This allows detection of free pericardial fluid and can give an estimation of general cardiac function. Point-of-care US has been shown to have a sensitivity of 100% and a specificity of 99% for detecting pericardial effusion.[68]

Point-of-care US is an invaluable tool for blunt trauma patients with unexplained, persistent shock out of proportion to apparent injuries and in any patients with signs consistent with blunt cardiac injury. Echocardiography provides information about global cardiac function, individual chamber function and wall motion, valvular function, and ejection fraction. It can also assist in alternative diagnoses for conditions such as aortic disruption/dissection, pericardial effusion, pleural effusion, and intracardiac thrombus.[68,69] Transesophageal echocardiography has been shown to be up to three times more sensitive in diagnosing blunt cardiac injury than transthoracic echocardiography.[70] Transthoracic echocardiography and transesophageal echocardiography, however, are not helpful in identifying patients at risk for developing blunt cardiac injury–related complications.[13] Obtain comprehensive echocardiography for patients demonstrating elevated cardiac markers, dysrhythmias, or myocardial dysfunction.[71]



A



B

FIGURE 262-3. A. Traumatic pericardial effusion. Large pericardial effusion (*arrow*) after stab wound to chest visualized by subxiphoid approach of a FAST scan. The effusion can be seen outside the right ventricular (RV) and left ventricular (LV) walls. **B.** Large effusion (apical view). [Image contributed by James Mateer, MD.]

CHEST RADIOGRAPH

Many findings on the initial chest radiograph may be indicative of cardiac and great vessel injury (**Tables 262-5** and **262-6**), but many of these findings are insensitive and nonspecific.

Widening of the mediastinum on chest radiograph (**Figure 262-4**) has classically been considered as being a very sensitive finding for detection of major vascular injury. Definitions of a widened mediastinum have included a measured width greater than 8 cm or a clinician gestalt of mediastinal widening and mediastinum to chest width ratio of >0.38. Trauma patients have <20% probability of major thoracic vascular injury with the absence of this finding on chest radiograph.[72] However, a normal mediastinum on chest radiograph does not rule out aortic injury. Therefore, the investigation of great vessel injury should occur if mechanism of injury, physician gestalt, physical examination findings, or radiographic indicators are consistent with injury. One sensitive radiographic sign for traumatic aortic injury is deviation of the esophagus more than 1 cm to the right of the spinous process at T4.[73]

TABLE 262-5 Radiographic Findings Suggestive of a Great Vessel Injury

Fractures
• Sternum
• Scapula
• Multiple ribs
• Clavicle in multisystem-injured patients
• First rib
Mediastinal Clues
• Obliteration of the aortic knob contour
• Widening of the mediastinum
• Depression of the left mainstem bronchus >140 degrees from trachea
• Loss of paravertebral pleural stripe
• Calcium layering at aortic knob
• Abnormal general appearance of mediastinum
• Deviation of nasogastric tube to the right at T4
• Lateral displacement of the trachea
Lateral Chest Radiograph
• Anterior displacement of the trachea
• Loss of the aortic/pulmonary window
Other Findings
• Apical pleural hematoma (cap)
• Massive left hemothorax
• Obvious diaphragmatic injury

Source: Reproduced with permission from Mattox KL, Moore EE, Feliciano DV: *Trauma*, 7th ed. New York, NY: McGraw-Hill; 2013. Table 26-5.

TABLE 262-6 Reliability of Selected Clinical and Radiographic Criteria in the Detection of Traumatic Rupture of the Aorta*†

Chest Radiograph Finding	Correlation With TAI (*P* value)	Sensitivity	Specificity	Accuracy
Widened mediastinum (<65 years old)	.001	0.95	0.82	0.84
Widened mediastinum (all ages)	.001	0.80	0.82	0.82
Murmur	.002	0.32	0.93	0.84
Pneumothorax/ pulmonary contusion	.07	0.22	0.67	0.51
Hemothorax	.21	0.25	0.88	0.81
First/second rib fracture	.39	0.36	0.73	0.68

Abbreviations: FN = false negative; FP = false positive; TAI = traumatic aortic injury; TN = true negative; TP = true positive.

*All other clinical and radiographic criteria were less useful in detecting TAI.

†Sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); accuracy = (TP + TN)/All tests.

Source: Table 259-6 from Tintinalli, et al: *Emergency Medicine: A Comprehensive Study Guide*, 6th ed. © 2002, McGraw-Hill, New York.

CT ANGIOGRAPHY

CT angiography is the diagnostic modality of choice for both penetrating and blunt trauma of the thorax. Because CT is widely used in the evaluation of multisystem trauma, incorporating CT imaging for vascular injury can be easily done. Newer-generation multidetector scanners are very sensitive and specific for injury to the great vessels.[2] Three-dimensional reconstructions of high-resolution data sets produce extremely accurate representations of the vascular anatomy and may be the only diagnostic imaging studies required by vascular surgeons. Multidetector CT scanners can detect pericardial rupture and effusion, and ECG-gated CT scan can identify structural cardiac injuries.[74,75] Although CT does require the patient to leave an intensive monitoring area, the information it provides can lead to treatment avenues vital for patient survival. Full-body scans are relatively rapid, with image acquisition occurring in less than 5 minutes. In comparison to classical angiography, CT angiography is faster and less expensive and eliminates complications related to vessel catheterization. Most institutions use multidetector CT scanners with CT angiography as the screening study of choice for aortic injury. Thin-slice multidetector CT with rapid scanning and contrast-bolus timing has shown great promise in detecting and localizing a variety of nonaortic vascular injuries, including active bleeding that can lead to early surgical or angiographic intervention to control blood loss.[55] Major CT angiography findings for blunt trauma can be seen in **Table 262-7**.

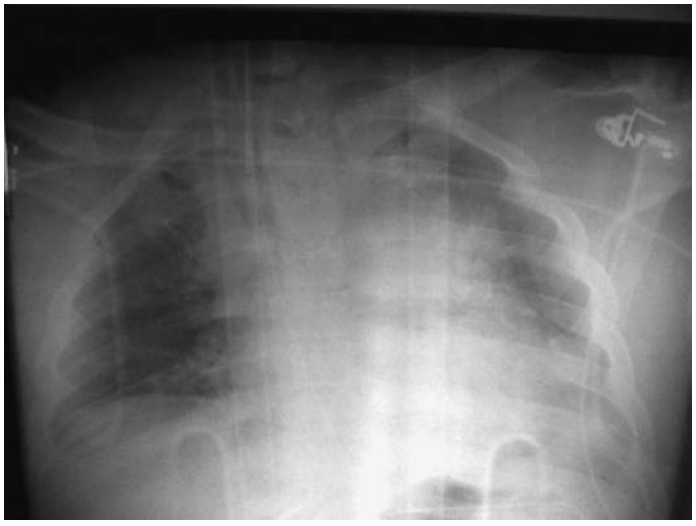


FIGURE 262-4. Portable chest radiograph of a patient with blunt thoracic trauma: chest radiograph shows widened mediastinum, obliteration of the aortic knob contour, and loss of visualization of the left hemidiaphragm, which are consistent with aortic injury.

TABLE 262-7 CT Signs of Traumatic Aortic Injury[65]

Common Signs
- Aortic pseudoaneurysm
- Periaortic hemorrhage
- Displacement of the trachea and esophagus to the right by hematoma, an irregular shape to the aortic lumen
- Intimal flaps projecting into the lumen

Uncommon Signs
- Luminal clot at sites of intimal disruption
- Sudden change in caliber of the aorta without intervening branch vessels (coarctation)
- A small aortic caliber in the lower chest and abdomen
- Peridiaphragmatic hemorrhage (from proximal intraluminal thrombus)

Rare Signs
- Transection of the aorta
- Active bleeding from the aorta into the mediastinum

Source: Reproduced with permission from Mirvis SE. Thoracic vascular injury. *Radiol Clin North Am*. 2006;44(2):181-197. Copyright Elsevier.

The major role of CT in penetrating trauma is determination of the presence or absence of mediastinal involvement along or near the course of the penetrating object (**Figure 262-5**). This can lead to direct finding of injury to major mediastinal structures. Aortic or major arterial injuries can be detected and appear as irregular vascular contours, luminal narrowing or irregularity, pseudoaneurysms, dissections, and acute bleeding. CT angiography is also helpful in penetrating injury to the thoracic great vessels.[55] In some cases, the vessel lumen may appear completely normal on CT due to the external forces to the vessel. Damage surrounding the vessel, usually in the form of perivascular hemorrhage, is present. Following the tract of the missile on CT should also help in determining the likelihood of direct vascular involvement.[2,55]

OTHER IMAGING MODALITIES

MRI and magnetic resonance angiography provide similar detailed information. However, MRI and magnetic resonance angiography require lengthy study times, have limited emergent availability at most institutions, and require the transport of a potentially unstable patient away from a monitored environment. These limitations make MRI and magnetic resonance angiography impractical for most trauma patients presenting to the ED.[2]

Transesophageal echocardiography remains a very attractive diagnostic option because of its advantages of speed, portability, immediate availability of results, and low cost. With recent advances in echocardiographic instrumentation and technology, it has evolved as a promising imaging technique that can provide comprehensive information on the location and extent of aortic injury. Transesophageal echocardiography allows diagnosis of limited intimal lesions frequently missed by other conventional methods and permits rapid diagnosis of complete rupture at the bedside of hemodynamically unstable patients. One study demonstrated that despite significant blurring of the aortic outline in 20% of cases and intraluminal artifacts being observed in 36% of cases, the accurate diagnosis of traumatic aortic injury was made.[32] Transesophageal echocardiography is contraindicated in patients with potential airway problems or suspected cervical spinal injuries.

Aortography remains a viable imaging option for determining the location of aortic injury, which is paramount in operative management (**Figure 262-6**). Angiography is more time consuming to perform, invasive, and not as readily available as CT on an acute basis. It is more expensive than CT as a screening study. Angiography is useful when CT results are indeterminate and may be required by surgeons for planning and guiding operative repair. Angiography may be used to pursue injury in the aorta or branch vessels in penetrating injuries that have only proximity to these vessels. Caution should be exercised with "negative"

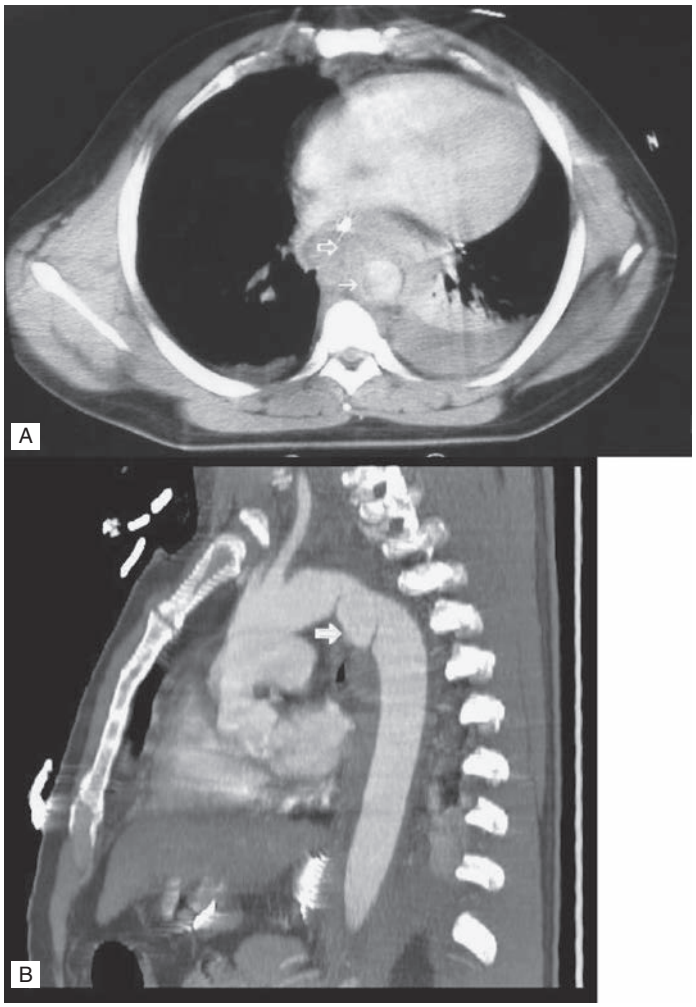


FIGURE 262-5. CT scan of traumatic aortic injury. **A.** Axial CT scan showing mediastinal hematoma (*open arrow*) and irregularity and thrombus in the aorta (*closed arrow*). **B.** Sagittal CT scan of same patient with pseudoaneurysm (*arrow*) from tear in aorta distal to left subclavian artery.

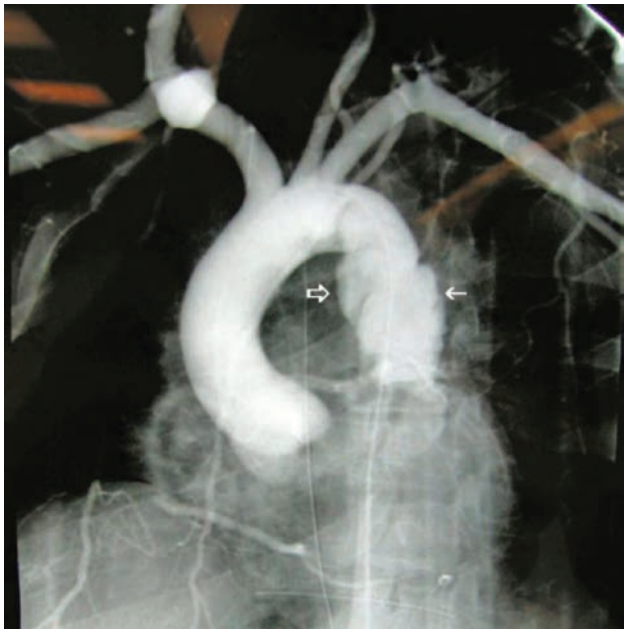


FIGURE 262-6. Angiogram of the same patient in Figure 262-5 showing pseudoaneurysm (*open arrow*) and irregular lumen (*closed arrow*) of injured aorta.

results because a clot or an intimal flap may close the luminal defect. The overall complication rate of angiography has remained at about 25%, but rates for serious complications, such as amputation and death, remain low at 0.1% and 0.3%, respectively.[76]

TREATMENT OF GREAT VESSEL INJURY

Consult a trauma or vascular surgeon at the time of initial suspicion of great vessel injury or immediately upon diagnosis. Transport patients with great vessel injury who exhibit hemodynamic instability, profound hemorrhage from chest tubes, and radiographic evidence of a rapidly expanding mediastinal hematoma immediately to the operating room.

Immediate surgical repair may not be possible in all patients. Patients with instability from other injuries, such as from intra-abdominal injuries or severe closed head injuries, may require a delayed repair due to the severity of these other life-threatening issues. Some elderly patients may have comorbidities that require medical management prior to surgery. Pharmacologic control of blood pressure and heart rate is extremely important when delayed or nonoperative management is contemplated.[2,77] Avoid large swings in blood pressure that may increase vessel-shearing forces in patients who are hemodynamically stable. Administer β-adrenergic blocking agents, sedatives, analgesics, and vasodilators as needed to keep the patient's heart rate and systolic blood pressure at appropriate levels. Use autotransfusion devices in cases of large bleeding vessels if available.

Traumatic aortic injuries can be partial thickness (as in the classic intimal flap of aortic dissection) or full thickness with containment by surrounding structures. These histopathologic entities mandate a similar therapeutic approach as aortic dissection. Decreasing the slope of the dP/dT (change in pressure over the change in time) will decrease wall tension and shearing forces. This may lead to permissive hypotension and bradycardia as a treatment and temporizing measure in aortic disruption. **Maintain systolic blood pressure in the 100 to 120 mm Hg range with a heart rate around 60 beats/min.** This will decrease the shearing forces on the internal lumen. Patients should not perform any maneuver, like a Valsalva, that will increase intrathoracic pressure. Titrating a short-acting β-blocker, such as esmolol, can decrease the heart rate. Once the heart rate is controlled, an arterial vasodilator, such as a calcium channel blocker or sodium nitroprusside, can be added to help control the blood pressure. A vasodilating calcium channel blocker such as nicardipine or clevidipine is recommended over sodium nitroprusside. Do not use sodium nitroprusside alone due to the reactive tachycardia associated with its administration.[2,6]

Acknowledgments: The authors thank Christopher Ross and Theresa Schwab for their contributions to this chapter in the prior edition.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 263

Abdominal Trauma

Anthony A. Ferroggiaro
O. John Ma

INTRODUCTION

Abdominal trauma accounts for 15% to 20% of all trauma deaths.[1] Although the liver is the most frequently injured abdominal organ, the spleen is the most frequently injured intra-abdominal organ from sports accidents.[2] Death may occur as a consequence of massive hemorrhage and generally results in early demise soon after the injury. Patients who survive the initial traumatic insult are at risk for infection and sepsis.

PATHOPHYSIOLOGY

BLUNT ABDOMINAL TRAUMA

In blunt trauma, all abdominal structures are at risk, and ultimately the biomechanics of the traumatic force determine which organs are affected. Compressive, shearing or stretching, and acceleration/deceleration forces impact the abdominal cavity and structures leading to abdominal wall, solid organ, or hollow viscous injuries. Abdominal organs may be relatively mobile or fixed. Injury is common in transition areas between these structures, such as the ligament of Treitz, where mesenteric or small bowel injuries may occur.

The most common mechanism for blunt abdominal trauma is a motor vehicle collision.[1] Falls, **second in frequency as causes of blunt trauma,** produce injury due to the fall distance, the impact surface, and the manner of surface impact. Both solid and hollow organ rupture can occur with retroperitoneal injury and hemorrhage resulting when the force is transmitted along the axial skeleton.[3] Pedestrians struck by vehicles or motorcyclists and bicyclists who crash generally have no protection to their abdomen and are at high risk for intra-abdominal injuries.

PENETRATING ABDOMINAL TRAUMA

Stab and gunshot wounds produce injury as the foreign object passes through tissue. With gunshot wounds, there may be additional injury from the transmitted energy of the blast. Furthermore, gunshot wounds create secondary missiles such as fragmented bone that may increase the traumatic burden.

The length, trajectory, and fragmentation of the penetrating object will not necessarily be known during the evaluation. **Therefore, assume any penetrating injury to the chest, pelvis, flank, or back to have penetrated the abdominal cavity until proven otherwise.**

CLINICAL FEATURES

Clinical signs may be obvious (such as evisceration) or occult. Factors making the diagnosis of an abdominal injury challenging include concomitant injuries (particularly significant head injuries), referred pain, intoxication with alcohol or other toxicologic substances, or language barriers. Young, healthy patients may be able to compensate for intra-abdominal hemorrhage before clinical signs become overt. Elderly patients may be on anticoagulation medications or on medications limiting physiologic response, such as antihypertensives (beta-blockers or calcium channel blockers).

PHYSICAL EXAMINATION

Inspect the abdomen for external signs of trauma (e.g., abrasions, lacerations, contusions, seatbelt marks). A normal-appearing abdomen does not exclude serious intra-abdominal injury. Following inspection, palpate the abdomen in all quadrants, making note of general or regional tenderness and signs of acute abdomen (rigidity, rebound, guarding). Regardless of imaging, document serial exams for patients who remain in the ED for several hours.

A traumatic abdominal process may progress over hours, and new symptoms and signs may indicate the development of a surgical process. Reliance on physical exam alone, particularly with a worrisome mechanism of injury, may result in an unacceptably high misdiagnosis rate or delay in treatment. As many as 45% of blunt trauma patients thought to have a benign abdomen on initial physical exam are later found to have a significant intra-abdominal injury.[4]

ABDOMINAL WALL INJURIES

Contusions of the abdominal wall musculature may result either from a direct blow or indirectly via a sudden muscular contraction. Symptoms include pain and possibly soft tissue swelling or a hematoma. Abdominal wall injuries may mimic or implicate more extensive intra-abdominal injury. Imaging may be indicated to "rule out" intra-abdominal injury.

SOLID ORGAN INJURIES

Signs and symptoms of a solid organ injury are generally due to pain and blood loss. Exclusive reliance on the Advanced Trauma Life Support shock classification may lead to underrecognition of progressive instability.[5] In general, early intra-abdominal hemorrhage may result in minimal change in vital signs. As blood loss continues, heart and respiratory rate increase and urinary output drops. Patients may also become anxious and confused. Hypotension may not occur until the circulating blood volume significantly decreases.

Hepatic and splenic injuries are at high risk for hemorrhage in both penetrating and blunt abdominal trauma. **Any blunt abdominal trauma patient with diffuse peritonitis or who is hemodynamically unstable should be taken urgently for laparotomy.**[6,7] Hepatic and splenic injuries are graded; low grades indicate less severe injury. CT imaging has improved the definition of injuries, and combined with the development of interventional radiology and catheter-based vascular management, many patients with hepatic or splenic injuries are managed nonoperatively. Surgical consultation is required in any solid organ injury; transfer to a level 1 trauma center reduces mortality.[8] Delayed rupture can occur in splenic and hepatic injuries, and at times, pain with solid organ injury may be referred to the shoulder/scapular region.

HOLLOW VISCUS AND MESENTERIC INJURIES

In blunt abdominal trauma, the incidence of blunt bowel and mesenteric injuries is infrequent (1% to 12%).[9,10] Hollow viscus injuries produce symptoms from the combination of blood loss and peritoneal contamination by GI contents. Hemorrhage from a mesenteric injury may be minimal and not be obvious on physical exam. Chemical irritation of the peritoneum from gastric acid contents may produce immediate pain, although bacterial contamination of the abdominal cavity may result in delayed signs and symptoms. Delays in diagnosis and operative management are associated with an increase in mortality.[10]

RETROPERITONEAL INJURIES

The retroperitoneal structures discussed in this chapter include the pancreas (excluding the tail) and duodenum. See Chapter 265, "Genitourinary Trauma" for a discussion of kidney, ureter, and bladder injuries.

Pancreatic injuries infrequently occur (4%) with abdominal trauma, yet are associated with significant morbidity and mortality.[11] Pancreatic trauma often occurs from rapid deceleration, such as unrestrained drivers who hit the steering column or bicyclists who fall against a handlebar, and these patients are at risk for pancreatic injuries.

Similarly, **duodenal injuries** may be relatively asymptomatic and go undiagnosed. As the duodenal hematoma expands, signs and symptoms of obstruction may develop (abdominal pain, distention, and vomiting). Duodenal rupture generally occurs following high-velocity deceleration. The ruptured contents may be contained within the retroperitoneum and missed with studies that investigate the peritoneum exclusively. Fever and leukocytosis herald the development of an abscess or sepsis.

DIAPHRAGMATIC INJURIES

Diaphragmatic injuries are uncommon (0.8% to 5% of patients with thoracoabdominal injury). Diaphragmatic injury diagnosis is often delayed in blunt trauma due to concomitant severe injuries and may be incidentally identified during operative treatment for hemodynamic instability.[12] CT imaging has variable sensitivity and specificity (ranging to a low of 60% and 70%, respectively). Delayed diagnosis may lead to herniation or strangulation of abdominal contents through the diaphragmatic defect, with mortality rates up to 50%.

DIAGNOSIS

Although multiple diagnostic modalities exist to detect intra-abdominal injuries, no study is fail-proof. Therefore, a combination of careful physical exam, attention to the mechanisms and circumstances of injury, and judicious selection of diagnostic studies is used for diagnosis.

TABLE 263-1 Abdominal Injuries That Need Expanded Evaluation

- Presence of abdominal pain, tenderness, distention, or external signs of trauma
- Mechanism of injury with a high likelihood of causing an abdominal injury
- Suspicious lower chest, back, or pelvic injury
- Inability to tolerate a delayed diagnosis (e.g., patients who are elderly, on anticoagulants, or have liver cirrhosis/portal hypertension)
- Presence of distracting injuries
- Altered consciousness/sensorium (e.g., CNS injury, intoxicating substances)

Hemodynamic instability may limit the immediate use of some diagnostic testing (CT). The FAST examination has become integral to early resuscitation and the diagnostic algorithms of abdominal trauma patients.

Indications to consider an expanded abdominal trauma evaluation are listed in **Table 263-1**. Often these evaluations include laboratory testing, imaging, further resuscitation, and reevaluation. Trauma service consultation may be invaluable.

ULTRASONOGRAPHY

The FAST examination is a widely accepted primary diagnostic study. The underlying premise of the FAST exam is that many clinically significant injuries will be associated with free intraperitoneal fluid (**Figure 263-1**). **The greatest benefit of FAST is the rapid identification of free intraperitoneal fluid in the hypotensive patient with blunt abdominal trauma.**

The FAST examination is accurate, rapid, noninvasive, repeatable, and portable, and involves no nephrotoxic contrast material or ionizing radiation. Massive hemoperitoneum is quickly detected with a single view of Morison's pouch. FAST also evaluates for free pericardial or pleural fluid and for pneumothorax.

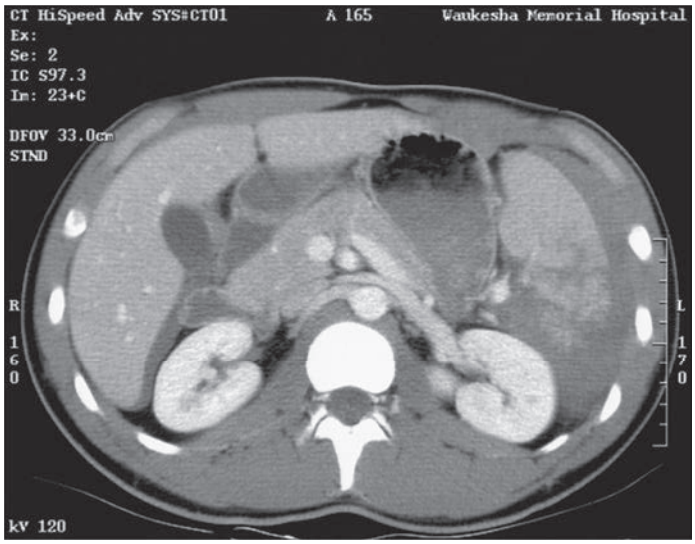
The main disadvantage of US compared to CT is the inability to identify the exact source of free intraperitoneal fluid. Other potential disadvantages of the FAST examination are the operator-dependent nature of the examination, the difficulty in interpreting the images in patients who are obese or have subcutaneous air or excessive bowel gas, and the difficulty in distinguishing intraperitoneal hemorrhage from ascites. Also, the FAST examination cannot evaluate the retroperitoneum as well as CT. Therefore, US and CT are complementary rather than competing technologies when time and stability permit, and the potential benefits of CT outweigh the risks.

Beyond diagnosis, US can be a clinically helpful tool for trauma resuscitation. US may guide the placement of central venous catheters, suprapubic catheters, and large-bore peripheral lines. The inferior vena cava diameter of trauma patients, as measured on initial CT imaging, is a marker of intravascular volume and a predictor of mortality,[13,14] although the reliability of inferior vena cava diameter measurement is still debated.[15,16]

Because the FAST examination can reliably detect small amounts of free intraperitoneal fluid and can estimate the rate of hemorrhage through serial examinations, US has replaced diagnostic peritoneal lavage (DPL) for blunt abdominal trauma in the majority of North American trauma centers. A positive DPL in isolation is no longer an absolute indication for exploratory laparotomy; the amount of hemorrhage and the hemodynamic status of the patient are important factors for determining further management steps.

COMPUTED TOMOGRAPHY

Abdominopelvic CT with IV contrast is the noninvasive gold standard study for the evaluation of abdominal injury (unless the patient has allergy to iodinated contrast). The addition of PO contrast can result in aspiration and is too time-consuming to be practical in trauma management. The major advantage of IV contrast CT over other diagnostic modalities is that the precise location(s) of specific injury can be identified (Figure 263-1). CT can quantify and differentiate the amount and type of free fluid in the abdomen. CT can also evaluate for



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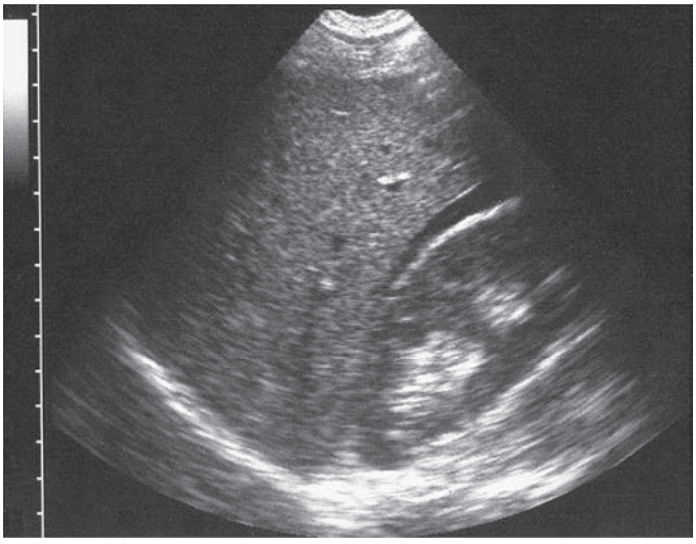

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FIGURE 263-1. Hemoperitoneum. The abdominal IV contrast CT. **A.** A fractured spleen with surrounding hematoma is demonstrated, but a small stripe of fluid is also present above the right kidney in Morison's pouch. **B.** A right intercostal oblique US view from the same patient reveals a thin stripe of fluid in Morison's pouch. [Reproduced with permission from Ma OJ, Mateer JR, eds: *Ma and Mateer's Emergency Ultrasound,* 3rd ed. © 2014, McGraw-Hill, Inc. New York.]

retroperitoneal injuries; it is the ideal study for assessment of the duodenum, pancreas, and vascular and renal systems. The use of multiphasic CT (arterial, portal, and equilibrium phases) accurately identifies life-threatening mesenteric hemorrhage and transmural bowel injuries.[9] CT evidence of a flat inferior vena cava suggests hypovolemia.

With a focus on patient safety, source EDs should transmit completed imaging with patient transfer to avoid repeat CT imaging whenever possible. Outcomes and time to definitive care are not significantly improved when imaging is repeated at the accepting trauma center.[17]

DIAGNOSTIC PERITONEAL LAVAGE

Despite the reproducibility and prospectively validated sensitivity of DPL to diagnose intraperitoneal injury, the advent and acceptance of other diagnostic modalities have significantly reduced the frequency of DPL.[18] DPL can be performed using a closed (**Figure 263-2**) or open technique. However, the open DPL technique requires advanced training and expertise. Some advocate the use of DPL in the hemodynamically

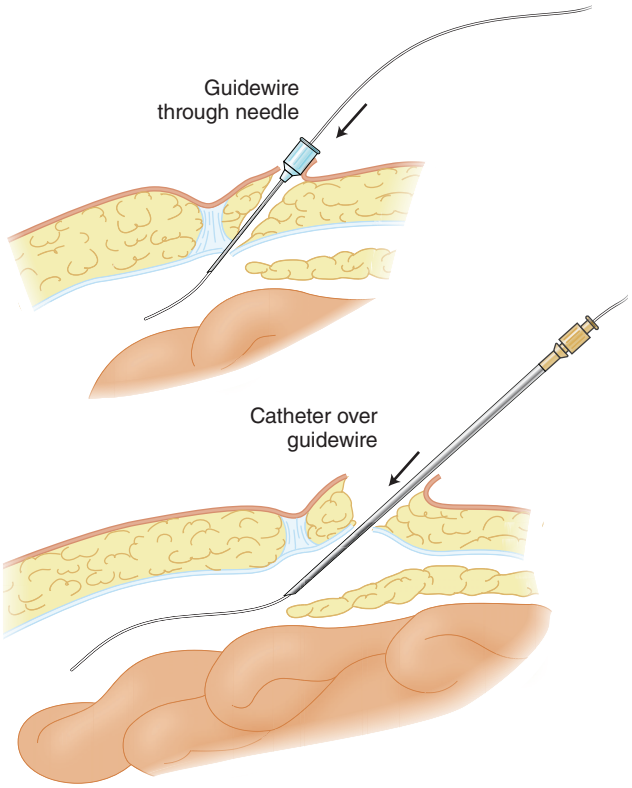


FIGURE 263-2. Closed diagnostic peritoneal lavage. Drain the urinary bladder. Infiltrate the area just below the umbilicus with lidocaine and epinephrine. Insert the needle two fingerbreadths below the umbilicus. Aspirate directly with a syringe attached to the needle, or insert a guidewire into the abdomen and place the peritoneal lavage catheter over the guidewire. Instill 1 L of normal saline through the catheter, and then aspirate.

unstable patient with concern for intra-abdominal injury when the FAST exam is negative or unavailable.[18]

DIAGNOSIS IN PENETRATING TRAUMA

The same diagnostic tools are available for evaluation of intraperitoneal injury in the patient with penetrating trauma (CT, US, and DPL). Mandatory exploration for patients sustaining a stab wound to the abdomen has yielded unacceptably high rates of nontherapeutic laparotomy,[19] yet physical exam alone can miss important intra-abdominal injuries. **The emergency physician or consultant surgeon may locally explore anterior abdominal stab wounds** (**Figure 263-3**) to assess for violation of the peritoneum.[20] Patients with transabdominal gunshot wounds almost always have intra-abdominal injuries. In the hemodynamically stable patient with penetrating trauma, CT can help guide the surgeon for operative versus nonoperative management.[21]

TREATMENT

LAPAROTOMY

Laparotomy remains the gold standard therapy for significant intra-abdominal injuries. It is definitive, rarely misses an injury, and allows for complete evaluation of the abdomen and retroperitoneum. **Table 263-2** describes generally accepted indications for exploratory laparotomy. **All patients with persistent hypotension, abdominal wall disruption (peritoneal violation), or peritonitis need surgical exploration.** In addition, the presence of extraluminal, intra-abdominal, or retroperitoneal air on plain radiograph or CT should prompt surgical exploration. Early surgical involvement in decision making and resuscitation may be valuable in blunt abdominal trauma patients; in smaller medical centers or community hospitals, transfer to a trauma center may best serve such patients.

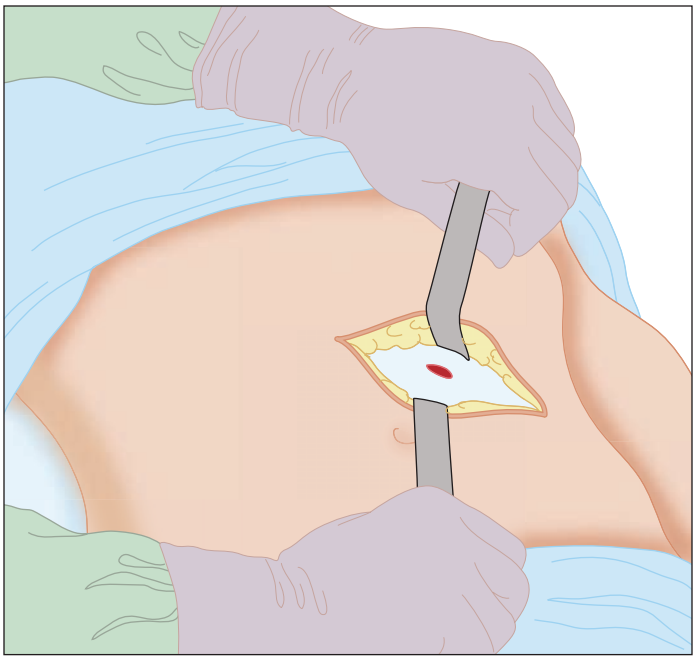


FIGURE 263-3. Local abdominal wound exploration for anterior abdominal stab wounds. This is a surgical procedure requiring expertise, proper instrumentation, and lights. Use only for anterior abdominal stab wounds. Widen the stab wound and explore down to the level of the fascia to determine if the anterior fascia and/or posterior fascia have been violated.

NONOPERATIVE MANAGEMENT OF BLUNT TRAUMA

Nonoperative management of trauma patients has been greatly advanced by the evolution of CT. CT can make the diagnosis of solid organ injury along with ruling out other injuries requiring surgery. Solid visceral injuries are graded according to their severity.

Both the Eastern Association for the Surgery of Trauma and the Western Trauma Association have published guidance on nonoperative management of blunt abdominal trauma. Nonoperative management is now the treatment of choice in hemodynamically stable blunt hepatic and splenic injured patients "irrespective of the grade of injury, patient age, or the presence of associated injuries."

Several technologic advances have increased the sophistication of nonoperative therapy. The increased resolution of helical CT can identify intraparenchymal vascular injuries (i.e., pseudoaneurysms or arteriovenous fistulae) and active extravasation of contrast, further defining

TABLE 263-2 Indications for Laparotomy

	Blunt	Penetrating
Absolute	Anterior abdominal injury with hypotension	Injury to abdomen, back, and flank with hypotension
	Abdominal wall disruption	Abdominal tenderness
	Peritonitis	GI evisceration
	Free air under diaphragm on chest radiograph	High suspicion for transabdominal trajectory after gunshot wound
	Positive FAST or DPL in hemodynamically unstable patient	CT-diagnosed injury requiring surgery
	CT-diagnosed injury requiring surgery	
Relative	Positive FAST or DPL in hemodynamically stable patient	Positive local wound exploration after stab wound
	Solid visceral injury in stable patient	
	Hemoperitoneum on CT without clear source	

Abbreviations: DPL = diagnostic peritoneal lavage; FAST = focused assessment with sonography for trauma.

operative and nonoperative options. In patients in whom vascular injury is diagnosed, percutaneous transcatheter embolization with either stainless steel coils or Gelfoam® pledgets can reliably arrest hemorrhage and is advancing as a nonoperative modality within trauma centers. Also using intravascular techniques, resuscitative endovascular balloon occlusion of the aorta may be employed at level 1 trauma centers and represents an intravascular "clamping" of the aorta with unresponsive shock due to intra-abdominal hemorrhage.

Medication-induced coagulopathy is a management challenge in abdominal trauma patients. Patients on warfarin or on non–vitamin K oral anticoagulants are at higher risk for hemorrhage. For patients on warfarin or factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), reverse anticoagulation with prothrombin complex concentrate is available for all situations of life-threatening hemorrhage or hemodynamic instability.[22] For dabigatran, infusing the antidote idarucizumab is recommended.

Consider tranexamic acid in all patients with traumatic abdominal hemorrhage.[23] Based on the CRASH-2 trial, the risk of death was most reduced with tranexamic acid administration within 1 hour and in those with the most severe hemorrhagic shock, whereas treatment beyond 3 hours implicated an increased risk of death.[24] Physicians managing abdominal trauma should have tranexamic acid available within the ED.

DISPOSITION AND FOLLOW-UP

Patients with significant intra-abdominal injury need admission to the surgical or trauma service for definitive surgical intervention or observation. Given the high rate of concomitant injuries, even patients who suffer minor abdominal injury may need hospitalization to manage other injuries. In patients in whom ED discharge is considered, discuss appropriate follow-up and careful instructions for return to the ED. Patients who develop fever, vomiting, increased pain, or symptoms suggestive of blood loss (e.g., dizziness, weakness, fatigue) should return promptly for reevaluation. Admission for observation may be the best option in some patients.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 264

Trauma to the Flank and Buttocks

Amy M. Stubbs

INTRODUCTION

Penetrating trauma to the flank or buttocks may result in a number of serious retroperitoneal, intraperitoneal, or vascular injuries, many of which require operative repair. Further complicating the evaluation, the signs and symptoms may be subtle or delayed in retroperitoneal, diaphragmatic, bowel, or rectal injuries. The decision to pursue an operative versus conservative course is informed by the emergency evaluation and imaging.

PENETRATING FLANK TRAUMA

ANATOMY AND PATHOPHYSIOLOGY

The flank is defined as the region between the anterior and posterior axillary lines, bordered superiorly by the sixth ribs and inferiorly by the iliac crests, containing retroperitoneal organs, soft tissue, ribs, and spine.[1] Although a penetrating wound to the flank can produce intraperitoneal injury with the associated findings of peritonitis or hemoperitoneum, it is possible that a penetrating flank injury could injure only the retroperitoneal organs or musculoskeletal tissue, which can be difficult to ascertain from exam alone. The thoracic cavity, spine, intra-abdominal, and retroperitoneal organs are all at risk for injury from a penetrating flank wound depending on the depth, trajectory, velocity, and construct of the projectile. Bullet or missile wounds, especially high-velocity wounds, may cause damage from direct trauma, kinetic energy, or cavitation.[2] Stab injuries are low velocity and cause injury through direct tissue damage.[3]

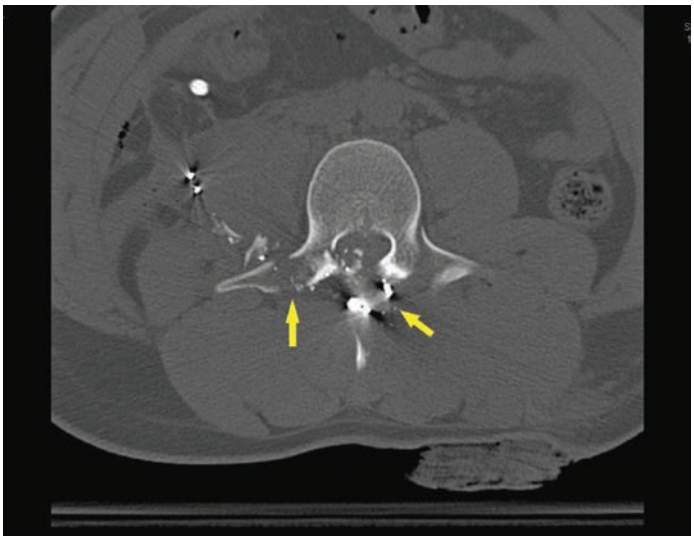


FIGURE 264-1. Bone windows of abdominopelvic CT after a gunshot wound to the flank. Comminuted fracture of L3 with retained bullet fragments and hematoma in spinal canal are visible (*arrows*). The patient was paraplegic and also had a perinephric hematoma. [Photo contributed by Truman Medical Center-Hospital Hill, Kansas City, MO.]

CLINICAL APPROACH

Perform a primary survey using the Advanced Trauma Life Support protocol. Obtain information about the mechanism of injury, how much time has passed since the event, and the nature of the weapon. For gunshot wounds, attempt to ascertain the type of gun, number of wounds, and patient distance from the weapon. Examining the location of wounds may assist in estimating the bullet path and structures at risk for injury; however, trajectory estimates can be unreliable as bullets can fragment or ricochet.[4,5] For stab wounds, attempt to determine the size and trajectory of the weapon as well as the depth of penetration. Examine for abdominal tenderness and peritoneal signs that may indicate intraperitoneal injury along with signs of injury to the GI or GU tracts, such as gross blood on rectal exam, at the urethral meatus, or in the urine. Spinal tenderness or neurologic deficits mandate further evaluation of the spine (**Figure 264-1**). Wounds near the costal margin or superior flank should raise concern for possible thoracic or diaphragmatic injury.

DIAGNOSIS

Patients with penetrating flank trauma who do not require emergent laparotomy need further evaluation to establish the extent of injury and to determine if the projectile has violated the peritoneum. Evaluation of flank trauma represents challenges related to its anatomic position and potential for retroperitoneal injury with late manifestations. Sparse data exist on isolated penetrating flank trauma; most of the recommendations for management come from studies of both flank and back trauma or flank and abdominal trauma.[6] Several diagnostic modalities exist to further evaluate penetrating flank trauma, each with some degree of limitation in its ability to exclude injury. **Table 264-1** lists the diagnostic

TABLE 264-1 Diagnostic Modalities for Evaluation of Flank Trauma

Modality	Advantages	Disadvantages
CT	Sensitive and specific for injury of peritoneal and retroperitoneal organs Useful for ascertaining injury path	Can miss diaphragmatic injury or colon injuries Oral/rectal contrast, time consuming
Ultrasound	Rapid, portable, noninvasive Sensitive and specific for hemopericardium and intraperitoneal fluid	Not sensitive for retroperitoneal or hollow viscous injuries Insufficient to rule out specific organ injury
Diagnostic peritoneal lavage	Sensitive for intraperitoneal injury	Invasive, high false-positive rate Unable to detect diaphragmatic or retroperitoneal injuries
Local wound exploration	Sensitive for peritoneal violation in abdominal trauma when technically adequate	Limited utility in flank/back due to no discernable fascial planes[3] Can lead to nontherapeutic laparotomy
Laparoscopy	Highly sensitive and specific for peritoneal and diaphragmatic injury[6] Can avoid unnecessary laparotomy	Invasive Not as sensitive for retroperitoneal injury

modalities available as well as their advantages and disadvantages (see also Chapter 263, "Abdominal Trauma"). No single method is currently considered sufficient to rule out significant injuries and a combination of modalities, along with observation, is recommended.[6-9] Blind probing of the wound(s) with swabs or digits is not recommended.

LABORATORY TESTING AND IMAGING

Initial laboratory testing and imaging often follow institutional protocols. At minimum, obtain a hemoglobin/hematocrit, type and screen, urinalysis, urine pregnancy test (if applicable), and chest radiograph. Radiographs of the abdomen or pelvis are of minimal use unless attempting to determine trajectory.[3]

CT is the imaging modality of choice in hemodynamically stable patients with penetrating flank trauma.[3,6,10] Historically, double contrast (PO and IV) or triple contrast (PO, IV, and PR) has been recommended. However, some evidence demonstrates that single contrast (IV) with modern multirow detector CT is sufficient to detect significant injuries (**Figures 264-2** and **264-3**).[11,12] The choice of imaging is dependent on trauma and radiology protocols at the specific facility, as well as consideration of the drawbacks of PO/PR contrast administration. CT angiography is used in many medical centers now for suspected vascular injury. Free intraperitoneal fluid or air suggests peritoneal perforation. Bowel wall thickening with adjacent hematoma or contrast extravasation from the bowel suggests bowel injury. Delayed images of the GU tract are useful to detect urinary extravasation. The presence of a wound track near either the diaphragm or bowel mandates inspection for injury to either of those organs.[6]

TREATMENT AND DISPOSITION

Evaluate and resuscitate patients with penetrating trauma to the flank according to standard protocols (see Chapter 254, "Trauma in Adults"). Obtain emergent surgical consultation. Administer broad-spectrum IV antibiotics, such as a carbapenem, to cover for gram-negative aerobic and anaerobic organisms for suspected intraperitoneal injury.[13] **Exploratory laparotomy is indicated for patients who are hemodynamically unstable or who exhibit peritoneal signs after sustaining a penetrating wound to the flank.** Resuscitative endovascular balloon occlusion of the aorta, if available, may also be considered as an option for signs of shock or hemorrhage.[3]

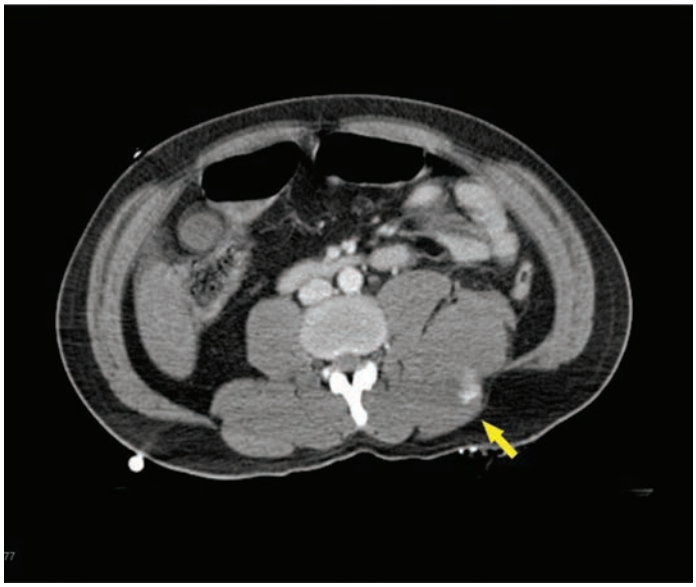


FIGURE 264-2. Abdominopelvic CT with IV contrast after stab wound to left flank. Contrast extravasation is seen in the left paraspinous muscles with an adjacent retroperitoneal hematoma. [Photo contributed by Truman Medical Center-Hospital Hill, Kansas City, MO.]

Selective nonoperative management, which combines serial exams and other diagnostic modalities, is appropriate for patients with stab wounds to the flank who are hemodynamically stable and have no abdominal tenderness. Traditionally, all patients with a gunshot wound to the flank underwent exploratory laparotomy; however, studies have demonstrated that selective nonoperative management is safe for specific patients with tangential injuries and no signs of instability or peritonitis. Benefits of this approach are decreased length of stay and lower rates of nontherapeutic laparotomies.[14-16] Appropriate patient selection, trauma center experience, and surgical staff availability are all key aspects to successful outcomes with selective nonoperative management.[6,8,9,14,15,17]

Patients with penetrating trauma to the flank who are managed nonoperatively typically require admission to the hospital for observation and serial abdominal exams, which have been shown to be highly

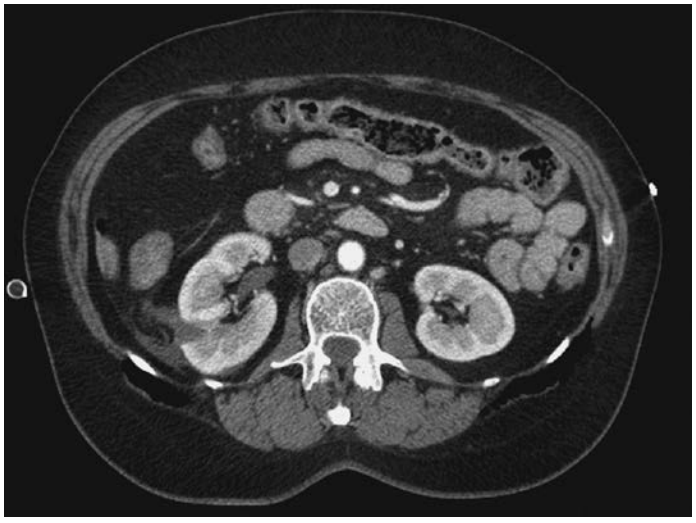


FIGURE 264-3. Abdominal CT with IV contrast demonstrating a renal laceration from a stab wound. [Reproduced with permission from Block J, Jordanov MI, Stack LB, Thurman RJ (eds): *The Atlas of Emergency Radiology*. New York: McGraw-Hill, Inc.; 2013, Fig. 6-21.]

sensitive for significant abdominal injury.[6,9] The ability to obtain a reliable exam is essential; factors such as examiner experience, body habitus, and patient mental status should be considered.

PENETRATING BUTTOCK TRAUMA

ANATOMY AND PATHOPHYSIOLOGY

The gluteal region extends from the iliac crest to the gluteal fold and is bordered by the greater trochanters. The gluteal region is divided into an upper zone and a lower zone by a line drawn at the level of the trochanters. Depending on trajectory, any pelvic or intra-abdominal structure is susceptible to injury following a penetrating injury to the buttocks; however, gunshot wounds most commonly cause injury to the small bowel, colon, and rectum. Stab wounds more frequently cause injuries to the rectum or vasculature, with the superior gluteal artery being injured most commonly.[18-21]

Most of the major pelvic vasculature and organs reside in the upper zone; therefore, penetrating wounds in the upper zone have a higher risk of major injury compared to wounds in the lower zone, which contains the lower bladder, prostate, vagina, urethra, external genitalia, and the distal rectum.[21] An important component of the history is information regarding the weapon used and the patient's position at the time of injury, as this can help determine the trajectory of the bullet or knife.

DIAGNOSIS AND TREATMENT

As discussed above, exploratory laparotomy and broad-spectrum antibiotics are indicated for patients with hemodynamic instability or peritoneal signs. The evaluation of penetrating buttock wounds focuses on identification of potential injury to the lower GI and GU tract, as well as to pelvic vasculature. Perform a rectal examination to identify gross blood and perform stool guaiac testing, although a negative guaiac test does not rule out rectal injury. Evaluate for the presence of hematuria. Assess the peripheral pulses in the lower extremities for decreased pulses or pallor as evidence of a more proximal injury. Assess the ankle-brachial index if there is concern for vascular injury. Perform a thorough neurologic examination of the lower extremities, searching for any signs of injury to the sciatic or femoral nerves.[21]

Patients with penetrating buttock injury who do not meet criteria for emergent laparotomy may be candidates for selective nonoperative management using a combination of serial exams and adjunctive modalities, including the FAST exam, CT or CT angiography, sigmoidoscopy, and cystourethrogram. Upper zone gluteal stab wounds can undergo local wound exploration to evaluate for muscle violation. Patients without muscle violation can be observed with serial exams, whereas those with muscle violation require CT and sigmoidoscopy, plus cystography for hematuria.

A similar conservative approach is appropriate for lower zone gluteal stab wounds and gluteal gunshot wounds. Order a CT scan, preferably with triple contrast, to evaluate for injury in the stable patient. Obtain a cystourethrogram, either as a separate study or in conjunction with contrasted CT, if there is blood on urinalysis or the wound is close to the GU tract.[18,21,22]

In most cases, sufficient diagnostic workup may be obtained with CT (**Figure 264-4**), but sigmoidoscopy under anesthesia is advised if there is any concern about injury to the rectum based on exam findings, wound location, or imaging. If the CT demonstrates a pelvic hematoma, angiography or venography may be indicated to document a significant vascular injury. In many centers, CT angiography has replaced these techniques, but endovascular intervention may be required for extensive pelvic bleeding.[21]

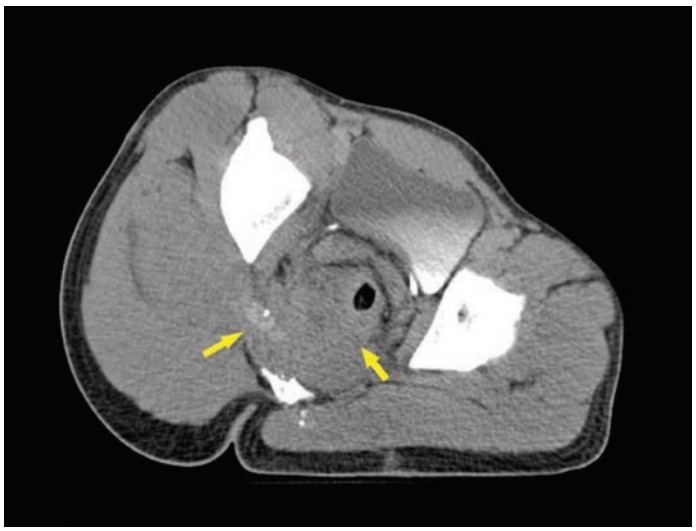


FIGURE 264-4. Pelvic CT with IV contrast in patient with gunshot wound to buttocks. Bullet fragments are visible in the soft tissue as well as in the presacral region. Hematoma is causing anterior displacement of the rectum (*arrows*). [Photo contributed by Truman Medical Center-Hospital Hill, Kansas City, MO.]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 265

Genitourinary Trauma

Regina C. Mysliwiec

INTRODUCTION

Falls, assaults, motor vehicle crashes, and sports injuries are the most common mechanisms for blunt GU injuries, whereas gunshot wounds and stab wounds are the most common causes for penetrating injuries.[1] Seatbelt use and air bag deployment have increasingly been associated with decreased rates of nephrectomy in renal trauma patients.[2] Epidemiologic data are different for civilian populations when compared to military personnel, whose exposure to explosive devices increases the risk of external genitalia trauma.[3] GU organs are injured in approximately 5% of traumas.[4] Isolated GU injuries are uncommon due to their relatively protected anatomical position. Significant damage is usually associated with other injuries. Due to lack of periadipose tissue and relatively large kidneys, children are anatomically more susceptible to GU injury than the general population.[5] Appropriate management will minimize or prevent complications such as renal function impairment, urinary incontinence, and sexual dysfunction.

CLINICAL FEATURES

HISTORY

Obtain a detailed history to determine the time and mechanism of injury and the magnitude of forces involved. In motor vehicle crashes, seat location, use of restraints, vehicle speed, and crash details provide information about forces applied to the victim. Sudden deceleration can cause major vascular disruption and parenchymal damage to the kidneys and bladder, even in the absence of symptoms and physical findings.

Determine patient symptomatology whenever possible. An inability to urinate may be due to an empty bladder or inability to void because of pain, but can also result from bladder perforation, urethral injury, or spinal cord injury. Presence of preexisting genitorenal dysfunction may

predispose to worse outcomes and should prompt consideration of more extensive workup.[6]

PHYSICAL EXAMINATION

Inspect the perineum during the secondary survey. Blood on the underwear or pants is an important finding and may suggest genital trauma. Inspect the folds of the buttocks for ecchymoses, abrasions, or lacerations, which may be related to an open pelvic fracture. Do not deeply probe perineal injuries because probing could disrupt a clot.

Rectal examination identifies sphincter tone, position of the prostate gland, and presence of blood. If the prostate is "missing" or riding high or feels boggy, assume disruption of the membranous urethra until proven otherwise. In males, examine the scrotum for ecchymoses, laceration, and testicular disruption. Palpate and inspect the penis for ecchymoses, deformity, and blood at the meatus. In females, examine the vaginal introitus for lacerations and hematomas, which can accompany pelvic fracture. Perform a speculum examination when vaginal bleeding or hematoma is present to exclude vaginal laceration. Complications of missed vaginal injuries include infection, fistula formation, and hemorrhage.

KIDNEY INJURIES

DIAGNOSIS

Renal injury is present in up to 10% of patients with abdominal trauma.[4,5] Because of the protected position of the kidneys, most injuries are associated with other intra-abdominal injuries.[5] Flank contusions or ecchymosis, palpable mass, lower rib fractures, and penetrating wounds in the flank mandate consideration of renal injury. Renal injuries consist of lacerations, avulsions, and hematomas to the kidney itself and renal pelvis. Renal vascular injuries (avulsion, laceration, occlusion) are uncommon but must be considered in the specific diagnosis of kidney injury.[7]

URINALYSIS

Although urinalysis is a commonly ordered laboratory study for suspected renal injury, **there is no direct relationship between the presence, absence, or degree of microscopic hematuria and the severity of injury**.[6,8-11] Microscopic and dipstick urinalysis are equally reliable for detecting the presence of hemoglobinuria.[6,12] In blunt trauma, there is some evidence suggesting that gross hematuria has predictive value for more severe renal injury.[11,12] In addition, patients with a systolic blood pressure of <90 mm Hg and microscopic hematuria have a higher likelihood of significant injury.[9] Children with <50 red blood cells per high-powered field have a low likelihood of significant renal injury.[10,12]

IMAGING

The main objectives of imaging are to (1) accurately stage the renal injury, (2) recognize preexisting pathology of the injured kidney, (3) document the function of the opposite kidney, and (4) identify associated injuries to other organs.[5] Imaging guidelines are listed in **Table 265-1**. An IV contrast-enhanced CT scan of the abdomen and pelvis is the imaging "gold standard" for the stable patient with suspected renal injury.[4,6,9,11,13,14] Contrast-enhanced CT detects contusion, lacerations, hematomas, and perfusion abnormalities (**Figure 265-1**). Early contrast extravasation is consistent with ongoing hemorrhage. However, urinary extravasation cannot be detected until the contrast-enhanced urine is excreted into the collecting system, which usually can take up to 10 minutes. Therefore, a delayed scan of the kidney, ureter, and bladder is recommended to exclude urinary extravasation from any source. If the kidney is normal and there is no abnormal fluid collection in the perinephric, retroperitoneal, or peripelvic areas, then the delayed scan can be omitted.

The FAST examination is useful for identifying free intraperitoneal fluid, but does not specifically evaluate renal injury and does not identify renal vascular injury.[13,14] Renal angiography can identify vascular injuries. Embolization of appropriate injuries can then be accomplished. Embolization can also be used to treat delayed traumatic arteriovenous fistulas.

TABLE 265-1 Imaging for Genitourinary Trauma

Injury	Imaging	Comments
Multisystem trauma or suspected renal parenchymal or vascular injury	Abdominal-pelvic IV contrast CT scan	Include pelvis to view entire GU tract Delayed films needed to identify urinary extravasation
Any visceral injury resulting in free intraperitoneal fluid	FAST	Identifies free fluid, but does not specify type of visceral injury and does not identify renal vascular injury
Renal artery injury	Renal angiography	Details vascular injuries
Ureteral injury	Abdominal-pelvic IV contrast CT scan	Delayed films needed to identify extravasation; obtain IV pyelogram or retrograde pyelogram if still suspicious with negative CT
Bladder injury	Retrograde cystogram	Can use plain radiographs or CT scan
Urethral injury	Retrograde urethrogram	Discuss sequencing with radiologist, because if performed prior to abdominal-pelvic contrast CT scan, can interfere with diagnosis
Scrotal/testicular injury	Color Doppler US	Contrast-enhanced US or MRI if suspicion is high and initial US is negative

GRADING OF RENAL INJURY

Grading of the renal injury is based on the American Association for the Surgery of Trauma organ injury scale (**Table 265-2**).[15] This grading system correlates with the need for operative repair and nephrectomy. In a study of 2467 patients with renal trauma, 86.5% were grade I, 3.5% grade II, 4.8% grade III, 4.0% grade IV, and 1.1% grade V. The rate of nephrectomy ranged from 0% for grades I and II to 82% for grade V.[16] Decreased kidney function is also directly correlated with renal injury grade.[17]

TREATMENT OF RENAL INJURIES

Absolute indications for renal exploration and intervention include life-threatening hemorrhage due to a renal injury; expanding, pulsatile, or

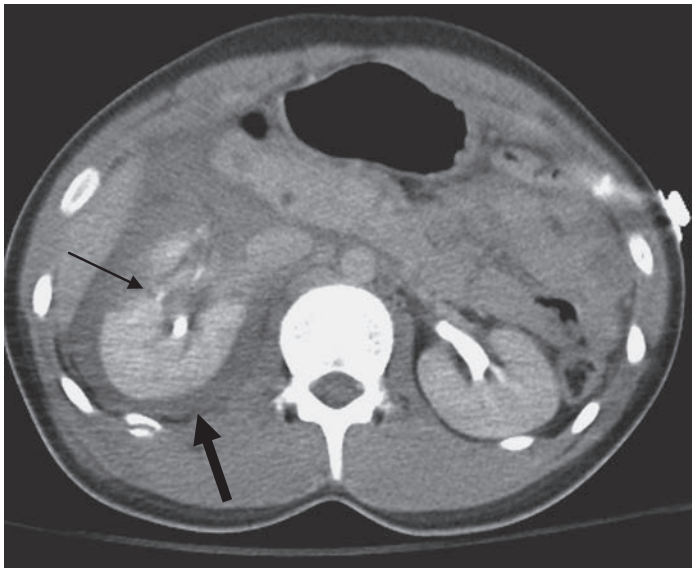


FIGURE 265-1. Renal laceration. *Narrow arrow* = renal laceration. *Thick arrow* = perinephric hematoma. [Image used with permission of Matthew C. Gratton, MD.]

TABLE 265-2 Renal Injury Scale

Grade	Description
I	Hematuria with normal anatomic studies (contusion) or subcapsular, nonexpanding hematoma; no laceration
II	Perirenal, nonexpanding hematoma or <1 cm renal cortex laceration with no urinary extravasation
III	>1 cm renal cortex laceration with no collecting system involvement or urinary extravasation
IV	Laceration through cortex and medulla and into collecting system or segmental renal artery or vein injury with hematoma
V	Shattered kidney or vascular injury to renal pedicle or avulsed kidney

noncontained retroperitoneal hematoma (thought to be from a renal avulsion injury); and a renal avulsion injury (grade V vascular injury) demonstrated on imaging studies.[4,6,12,18-20] High injury grade, high injury severity score, large blood transfusion requirement, and hemodynamic instability are predictive of the need for nephrectomy. Urinary extravasation alone is not an indication for exploration because it resolves spontaneously in the majority of cases. Extravasation from a renal pelvis or ureteral injury, however, does require repair.

Most authorities agree that grade I, II, and III renal injuries can be handled nonoperatively. Selected grade IV and V parenchymal injuries may be managed nonoperatively, although many of these patients have other indications for operative intervention.

If the trauma patient is hemodynamically stable and there is suspicion for renal injury with or without gross hematuria or if the patient has a penetrating injury, then CT imaging is indicated. If the CT scan reveals a renal pelvis, vascular, or ureteral injury, then surgical consultation is indicated.

Renal Vascular Injury Renal vascular injury identified on CT scanning requires emergent surgical consultation in order to arrange treatment to minimize the time of renal ischemia.[7]

COMPLICATIONS

Complications that may result from renal trauma include delayed bleeding, urinary extravasation, urinoma, perinephric abscess, and hypertension and failure of the affected kidney. Delayed bleeding can occur up to a month after injury and is most commonly due to an arteriovenous fistula that has developed after a deep parenchymal laceration. Arteriovenous fistula occurs in up to 25% of cases of grade III or IV injuries that are managed conservatively.[12,21] Most can be managed with angiographic embolization, but renorrhaphy or nephrectomy may be necessary.[6,21,22] A urinoma may develop from a few weeks to many years after injury and may have no symptoms or may cause a feeling of abdominal discomfort, mass, or low-grade fever. Treatment is usually percutaneous drainage or ureteral stenting. A perinephric abscess can present similarly and can also be treated with percutaneous drainage. Hypertension may occur due to renal artery injury, devascularized tissue, renal parenchymal compression by clot, or by arteriovenous malformation, and may occur from days to many years after injury. Nephrectomy is the most common treatment, but medical management may be indicated.

DISPOSITION AND FOLLOW-UP

Most patients with significant renal injury are admitted on the basis of associated injuries. For patients with isolated renal trauma, few data support specific recommendations for disposition and follow-up.

Patients with isolated renal trauma and a grade I injury can be separated into two groups after urology consultation. Those with a renal contusion (microscopic hematuria with normal imaging) can be discharged home, as mentioned earlier. Patients with a subcapsular hematoma can be admitted for a short observation stay followed by a hematocrit and clinical reevaluation. Patients with gross hematuria usually need admission and require bed rest until the gross hematuria clears. Admit patients with grade II or higher injury to the hospital under the care of a trauma surgeon, general surgeon, or urologist as appropriate for the practice setting.



FIGURE 265-2. Ureteral injury. *Narrow single arrow* = contrast material that has leaked from a transected ureter. *Thick arrow* = multiple metallic foreign bodies with artifact (shotgun pellets).

URETERAL INJURIES

DIAGNOSIS

Isolated ureteral injury is rare in trauma patients because the ureter is well protected in the retroperitoneum. Approximately 80% of ureteral injuries occur from intraoperative, iatrogenic damage. Of the 20% of injuries due to external trauma, almost 90% occur as a result of penetrating trauma (81% gunshot wounds, 9% stab wounds) and 10% occur due to blunt trauma. Because there are no history or physical examination findings that are specific for ureteral injuries, these injuries can be easily missed.[5,14,23] Approximately 70% of patients with ureteral injuries have either gross or microscopic hematuria. The absence of hematuria does not exclude ureteral injury.[4,6,24]

In the stable patient with suspicion of ureteral injury, obtain a CT of the abdomen and pelvis with IV contrast with a delayed phase. Extravasation of contrast along the course of the ureter is diagnostic for ureteral injury (**Figure 265-2**).[6,14,23] If the CT is nondiagnostic and there remains a high index of suspicion for this injury, the next step is IV pyelography or retrograde pyelography.

TREATMENT AND DISPOSITION

Treatment of ureteral injuries is operative. Partial tears can be stented, and simple lacerations can be primarily repaired over a stent. More complex injuries can be reconstructed using a variety of techniques. Complications include urinary leakage, urinoma, periureteral abscess, peritonitis, ureteral stricture, and urinary fistula. All cases require urology consultation and admission for operative management.

BLADDER INJURIES

DIAGNOSIS

Bladder injury occurs in fewer than 2% of blunt abdominal trauma cases, and more severe injuries are often associated with pelvic fractures.[4,25-27] Suspect bladder injury in alcohol-intoxicated patients (bladder often distended) who are in a motor vehicle crash (potentially high-energy transfer resulting in pelvic fracture).[20] Lower abdominal pain and tenderness and gross hematuria are commonly associated findings. Lower



FIGURE 265-3. Bladder rupture. Retrograde cystogram demonstrates an intraperitoneal rupture of the bladder.

abdominal bruising, abdominal swelling from urinary ascites, perineal or scrotal edema from urinary extravasation, and inability to void are also common findings on examination of patients with bladder injury. Bladder injury also occurs secondary to penetrating trauma to the abdomen, rectum, and buttocks.

Gross hematuria is present in most significant bladder injuries. Gross hematuria in the setting of pelvic fracture requires investigation of the bladder with a retrograde cystogram.[4,11,24,27] The presence of microscopic hematuria associated with a pelvic ring fracture can indicate a bladder injury, but the exact degree of microscopic hematuria warranting cystogram in this setting is undetermined and depends on clinical judgment.

A retrograde cystogram is the "gold standard" imaging study for the diagnosis of bladder rupture. This study can be performed with plain radiographs or with CT (**Figure 265-3**).[4,14,27] The bladder must be filled in a retrograde fashion (through an indwelling bladder catheter) by gravity feed with enough contrast material (at least 350 mL) to distend the bladder. Obtain a postvoid film. The diagnosis is made when contrast material is seen spilling out of the bladder into the peritoneal cavity (intraperitoneal rupture) or into the retroperitoneal area surrounding the bladder (extraperitoneal rupture). A contrast-enhanced CT with passive bladder filling, even with a clamped catheter, is not sensitive enough to exclude bladder rupture. Sonographic diagnosis of bladder rupture is not accurate.

TREATMENT AND DISPOSITION

Extraperitoneal ruptures of the bladder are most common (55%), followed by intraperitoneal (38%) and combined intra-/extraperitoneal ruptures (5% to 8%).[19,20,25] Intraperitoneal ruptures always require surgical exploration and repair.[4,19] Extraperitoneal ruptures can usually be managed with bladder catheter drainage alone. **Table 265-3** lists conditions when operative repair may be needed for extraperitoneal rupture.[4]

Missed intraperitoneal rupture can lead to urinary ascites, local abscess, peritonitis, or sepsis.[28] If bladder neck injuries or rectal or vaginal injuries are missed, then incontinence or fistula may result. Associated injury to the sacral nerve roots or pelvic nerves can damage innervation of the bladder, resulting in a neurogenic bladder or impotence. Simple ruptures are less likely to produce complications, but may occasionally be associated with persistent bladder diverticulum, decreased bladder volume, or urinary tract infection.

Because bladder rupture is frequently associated with other injuries, admitting the patient for either operative intervention or catheter drainage under the care of a trauma surgeon, general surgeon, or urologist is the general rule.

TABLE 265-3 Operative Repair May Be Needed for Extraperitoneal Rupture of the Bladder

- Urinary catheter does not allow appropriate drainage
- Associated rectal or vaginal injury
- Associated bladder neck injury
- Open fixation of a pelvic fracture (to avoid contamination of the hardware)
- Pelvic fracture with bone spicules in bladder lumen

URETHRAL INJURIES

DIAGNOSIS

Timely diagnosis and effective treatment of urethral injury are paramount to limiting long-term adverse outcomes, including impotence, stricture, urinary retention, or incontinence. Urethral injuries are less common in women primarily due to differences in urethral length (4 cm in women vs. 20 cm in men).[29] Urethral injuries are classified anatomically as either anterior or posterior, an important distinction because comorbid injuries and treatment may vary.

POSTERIOR URETHRAL INJURIES

The posterior urethra consists of prostatic and membranous portions. Because the posterior urethra is relatively well insulated by bony and soft tissues, injuries here are generally the result of major blunt-force trauma from deceleration mechanisms such as motor vehicle collisions or falls from heights.[30] Such mechanisms lead to shearing forces applied to the prostatic-membranous urethral junction. Posterior urethral injuries may occur in about 4% to 6% of patients with pelvic fractures.[27]

ANTERIOR URETHRAL INJURIES

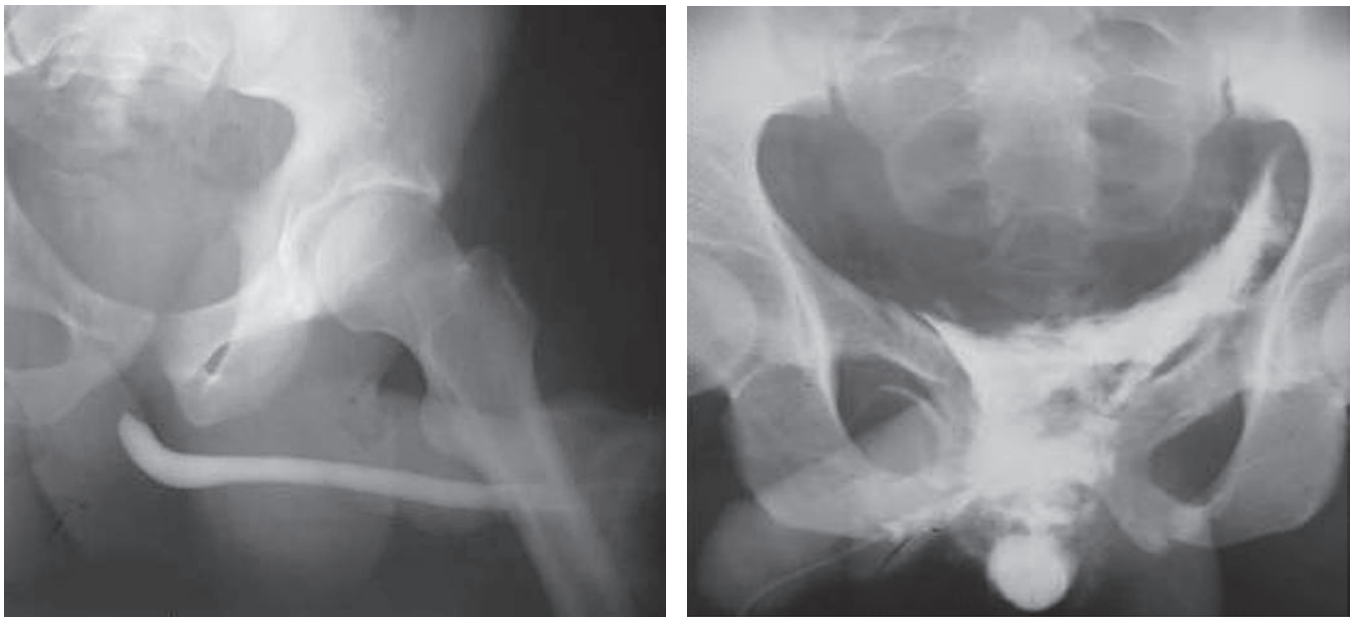
The anterior urethra is divided into the relatively fixed bulbar segment and the penile segment. Anterior urethral injuries are generally the result of direct perineal trauma, either blunt or penetrating. Straddle injury is the classic mechanism, although strikes or kicks to the perineum may lead to the same injury. The bulbar rather than penile segment is typically affected.[4] Anterior urethral trauma can also occur as a result of penile fracture. Penetrating trauma to the urethra usually occurs to the penile urethra. Evaluate for female urethral injuries in association with extensive pelvic fractures.[29] Trauma to the anterior urethra may be missed initially, and patients may present years later with urethral stricture.

CLINICAL FEATURES

Suspect urethral injury from common mechanisms (straddle or penetrating perineal injuries), comorbid injuries (5% to 10% of pelvic fractures),[27] or iatrogenic complications (traumatic catheterization). Symptoms may include hematuria, dysuria, or inability to void. Rectal and perineal examination may demonstrate a perineal hematoma or high-riding prostate. Posterior urethral injury is suggested by the triad of urinary retention, blood at the meatus, and a high-riding prostate.[11] Intuitively, hematuria should be a helpful clue; however, this is neither specific nor sensitive enough to be used alone to diagnose or exclude a urethral injury.[4,11,31] Difficulty passing a Foley catheter raises concern for a urethral injury; insertion should never be a forceful process. Female urethral injuries may present with vaginal bleeding, but should also be considered in patients with pelvic ring disruption, sacral spine injuries, or multiple pelvic fractures who present without bleeding.[26] In women, no consensus exists on the best modality to detect urethral injury because cystography or urethrography may not be adequate.[29]

DIAGNOSIS

If there are signs of possible urethral injury, such as high-riding prostate, meatal blood, perineal ecchymosis, scrotal hematoma, pelvic fracture, or gross hematuria, any resistance to gentle passage of a Foley catheter



A B

FIGURE 265-4. **A.** Normal retrograde urethrogram. **B.** Extravasation of contrast.

should indicate the need for consideration of suprapubic catheterization for bladder drainage and retrograde urethrogram for diagnosis of urethral injury.[32]

Perform retrograde urethrogram by gently injecting 20 to 30 mL of contrast into the urethra and obtaining a radiograph. Extravasation identifies the existence and location of the urethral tear. In partial anterior urethral lacerations, the retrograde urethrogram reveals contrast extravasation at the site of injury and contrast material outlining the urethra proximal to the site of injury (**Figure 265-4**). In complete anterior urethral lacerations, the retrograde urethrogram reveals contrast extravasation at the site of injury without contrast proximal to the site of injury. Extravasation of contrast along fascial planes of the perineum is another indication of urethral disruption. **Performing a retrograde urethrogram before completing a CT of the abdomen and pelvis to evaluate for other life-threatening injuries can interfere with CT diagnosis and embolization treatment of pelvic arterial extravasation from pelvic fractures, so discuss the sequencing of studies with the trauma surgeon, urologist, or radiologist.**[33] If a Foley catheter has already been successfully inserted, and then a urethral injury is considered, keep the Foley catheter in place. Using a 16-gauge angiocatheter, inject contrast material at the meatus, around the urinary catheter, and then obtain radiographs in the standard fashion.[34] In males, the location and displacement of anterior pelvic fractures, if present, can predict the risk of urethral injury. For every millimeter of symphysis pubis diastasis or inferomedial pubic bone fracture displacement, the risk of urethral injury increases by 10%.[27]

TREATMENT AND DISPOSITION

Patients with urethral trauma often have multiple injuries, some of which take precedence over the urethra trauma. Prioritize treatment(s) according to standard Advanced Trauma Life Support guidelines. The treatment for male patients with posterior urethral injury secondary to pelvic fracture has generally been immediate placement of a suprapubic catheter (for bladder drainage) with delayed surgical repair (often weeks later). Suprapubic catheter placement allows for urinary drainage without urethral manipulation or disruption of a pelvic hematoma.

Most penetrating injuries to the anterior urethra require surgical exploration and repair. It is more difficult to perform urethrography in women due to the relatively short urethra; urethroscopy may be more helpful. Concomitant bladder injury needs to be excluded with CT cystography. Because urethral injury is frequently associated with other injuries, admit the patient for either operative intervention or catheter drainage under the care of a trauma surgeon, general surgeon, or urologist.

INJURIES TO THE EXTERNAL GENITALIA

CLINICAL FEATURES

Penile fracture, with or without urethral injury, occurs when the corpus cavernosum ruptures after being forcibly bent, usually during sexual intercourse. A cracking sound may be heard, followed by penile pain, rapid swelling, discoloration, and visible deformity ("eggplant deformity").[35] Amputations are usually self-inflicted or result from clothing trapped by heavy machinery. Self-inflicted trauma to the penis can also result from vacuum cleaner injuries, which cause extensive injury to the glans penis and urethra, and strangulation from constricting penile rings used to enhance erections. Penetrating injuries are less common and may also involve the urethra.

Injuries to the scrotum may occur from blunt or penetrating trauma, burns, and avulsions. More than half of all testicular trauma is a result of sporting activity.[5] Impingement of the testicles against the symphysis pubis is the primary cause of blunt testicular injuries. Resultant injury to the testicle ranges from contusion to rupture. In both conditions, the tunica vaginalis fills with blood, forming a hematocele. If the tunica albuginea is disrupted, a rupture has occurred.

Symptoms after a direct scrotal blow are usually scrotal pain and swelling. Other signs may include scrotal discoloration and a tender, firm scrotal mass that fails to transilluminate, which indicates a hematocele. An empty hemiscrotum suggests testicular dislocation. Many patients will be exquisitely tender, potentially limiting a thorough exam. Furthermore, the external signs of trauma may not correlate well with the degree of testicular injury; thus, there should be a low threshold for diagnostic imaging.[20]

DIAGNOSIS

Color Doppler US is the diagnostic modality of choice in the evaluation of scrotal/testicular trauma.[14] Although there is no advantage initially, contrast-enhanced US and testicular MRI may be useful adjuncts if the Doppler US results are inconclusive and clinical suspicion remains high for testicular injury.[36,37] CT plays an important role in the evaluation of concomitant abdominopelvic injuries. Penile injuries often result in urethral injuries; thus, consider retrograde urethrogram in this scenario. While the diagnosis of penile fracture is largely clinical, US may detect

corpus cavernosum hematomas and can be an adjunct to both diagnosis and operative management.[35]

TREATMENT

Most closed testicular contusions are managed conservatively with opiate analgesics, ice, elevation, scrotal support, and appropriate urologic follow-up. Testicular rupture requires immediate drainage and repair. Any patient with penetrating scrotal trauma should undergo immediate scrotal exploration.[38,39] Obtain emergent urologic consultation for all confirmed or suspected penile fractures. With immediate surgical intervention, erectile function may be spared.[35]

Loss of penile skin by avulsion injury or burns is managed by split-thickness skin grafts after the denuded penis is clean and sterile. Do not reapply avulsed skin, because avulsed skin invariably becomes necrotic and infected and must be subsequently removed. Penile amputations require repair by microsurgical reimplantation if the amputated segment is deemed viable by the urologist.

Strangulation injuries can usually be managed simply by removing the constricting agent. Zipper injury to the penis is caused when the penile skin is trapped in the trouser zipper. Mineral oil and lidocaine infiltration are useful in freeing the penile skin from the zipper. Otherwise, wire-cutting or bone-cutting pliers are used to divide the median bar (or diamond) of the zipper, which causes the zipper to fall apart, freeing the penile skin. Contusions of the perineum or penis are treated conservatively with cold packs, rest, and elevation. Insert a Foley catheter if the patient is unable to void.

SPECIAL POPULATIONS

ELDERLY

As men age, they experience anatomic changes, including laxity of scrotal tissue, atrophy of the perineal muscles, and loss of collagen tissue. Changes in women are secondary to declining secretion of estrogen after menopause and include atrophy of the cervix and uterus, atrophy of the walls of the vaginal canal, decrease in vaginal length and width, and decrease in vaginal lubrication. These changes predispose the elderly to complex injuries of the external genitalia even with a minor mechanism of injury. Compared to younger trauma patients, trauma to the GU system in the elderly patient tends to be more common from blunt mechanisms and tends to result in higher rates of bladder and urethral injuries.[40]

The presence of a **penile prosthesis** can transform a minimal blunt trauma genital injury into a complicated surgical issue for the patient.[41] Extrusion and rupture of penile prostheses predispose patients to infection and complications of wound healing. This becomes a special concern in diabetic patients who are more likely to have prostheses. Obtain urologic consultation for any patient who has sustained trauma to the genitalia with a prosthesis in place (see Chapter 95, "Complications of Urologic Procedures and Devices").

PREGNANT WOMEN

With pregnancy, women experience physiologic changes that predispose them to more severe injury in both blunt and penetrating trauma to the genitalia. During pregnancy, venous outflow from the perineal area is slowed because of the pressure on the vena cava from the enlarging uterus. Slowed blood flow to the area can cause edema of the vulva. The increased level of progesterone during pregnancy also contributes to fluid retention and edema of the genitalia. Engorgement of the perineum predisposes pregnant patients to increased risk of hemorrhage from penetrating trauma to this anatomic region.

CHILDREN

Roughly 33% of males worldwide are circumcised.[42] The aim of circumcision is to excise sufficient foreskin (both penile shaft and inner preputial epithelium) to leave the glans uncovered. Complications of circumcision are more common in older children. Early complications of circumcision include bleeding, infection, pain, and inadequate skin removal.[42] Direct pressure alone is adequate to stop bleeding in most scenarios, although in some instances, the application of pressure alone is insufficient to control local hemorrhage and other methods of hemostasis must be employed. Circumferential dressings may cause urinary retention and even necrosis of the distal penis if blood flow is compromised.

Genital trauma in children should prompt consideration of sexual abuse.[43] The clinical evaluation of prepubescent females with blunt urogenital trauma may underestimate the severity of injuries when compared with examination under anesthesia. Consider consultation for examination under anesthesia for accurate diagnosis and to minimize psychological sequelae of examination. In boys, nonsexual trauma to the external genitalia most commonly occurs between ages 6 and 12 years. Bicycle accidents, kicks, and falls are the typical mechanisms, and scrotal and penile lacerations or testicular contusions are the most common injuries.[44]

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 266

Trauma to the Extremities

James Heilman

INTRODUCTION AND EPIDEMIOLOGY

Trauma to an extremity with associated vascular injury has a 5% rate of mortality, 5% rate of primary limb amputation, and 17% rate of delayed limb amputation.[1] Penetrating trauma with early shock from proximal arterial hemorrhage is more likely to lead to mortality. Blunt distal extremity trauma with associated distal vascular injury is more commonly involved in early limb loss and amputations. Risk factors for delayed amputation include major soft tissue injury, compartment syndrome, ischemia of more than 6 hours, and associated fracture.[2] Injuries involving the lower extremities are more common than injuries involving the upper extremities. The two most commonly injured blood vessels are the femoral and popliteal vessels.[3]

Advances in diagnostic imaging[4] and surgical management have dramatically reduced the rate of limb loss and disability due to limb ischemia.[5] The extent of injury to extremity nerves, bones, and soft tissues now determines if the limb can be surgically salvaged. Identifying and detecting which injuries require surgical evaluation and/or imaging are essential skills for emergency physicians.

PATHOPHYSIOLOGY

Gunshot and knife wounds are the two most common causes of penetrating trauma. Stab wounds have a more predictable pattern of injury, making them more straightforward to manage. Gunshot injuries are more difficult to evaluate due to the extent of tissue damage and wider range of patterns of injury. More sophisticated vascular surgical repair techniques of arterial injuries,[6] advances made during military conflicts, improved imaging, and other factors have led to a decreased rate of limb amputations and limb disability associated with penetrating trauma.[7]

CLINICAL FEATURES

Perform the primary trauma survey, immediate resuscitation, and secondary survey before focusing on injuries to the extremities. Apply direct pressure, pressure dressings, or a tourniquet to any actively bleeding extremity (see Chapter 254, "Trauma in Adults"). Do not get distracted or deviate from the initial trauma management because associated injuries to other areas of the body are common with penetrating injuries. After identifying an injury during the secondary survey,

TABLE 266-1 Clinical Manifestations of Extremity Vascular Trauma

Hard signs
- Absent or diminished distal pulses
- Obvious arterial bleeding
- Large expanding or pulsatile hematoma
- Audible bruit
- Palpable thrill
- Distal ischemia (pain, pallor, paralysis, paresthesias, coolness)

Soft signs
- Small, stable hematoma
- Injury to anatomically related nerve
- Unexplained hypotension
- History of hemorrhage
- Proximity of injury to major vascular structures
- Complex fracture

thoroughly evaluate the affected extremity for vascular integrity, nerve function, skeletal injury, and soft tissue injury. The rapid evaluation of extremities for associated arterial injury is critically important for the management of these injuries. Note any hard or soft signs of vascular injury (**Table 266-1**). Use a Doppler flow device to detect a pulse if distal pulses cannot be palpated.

Thoroughly evaluate nerve, tendon, and muscle function during the physical exam (**Table 266-2**). Pain on palpation or movement of bony structures or obvious deformities suggests an underlying fracture. Note any intra-articular hematomas or other signs of joint injury. Measure soft tissue lacerations and other associated injuries with a tape measure. Accurately describe injuries to consultants because measurement of the injury may change management in some situations.[8]

ANKLE-BRACHIAL INDEX

In the absence of hard signs, determine the ankle-brachial index for any injured extremity along with the nonaffected extremity for comparison (See Video: Ankle-Brachial Index). An ankle-brachial index reading of <0.9 is considered abnormal and is concerning for associated arterial injury. The ankle-brachial index reliably detects occlusive arterial injury with accuracy as high as 95%, but the true sensitivity and specificity have varied in clinical studies.[9,10] Use caution in relying on a normal ankle-brachial index to rule out arterial injury. It does not detect nonocclusive arterial injuries such as intimal flaps, focal narrowings, small pseudoaneurysms, and arteriovenous fistulas in up to 10% of cases.[11]

TABLE 266-2 Clinical Examination of the Nerves of the Extremities

Nerve	Test of Motor Function	Test for Sensation
Axillary (C5-C6)	Arm abduction Arm internal, external rotation	Lateral aspect of shoulder
Musculocutaneous (C5-C6)	Forearm flexion	Lateral forearm
Radial (C5-C8)	Forearm, wrist, and finger extension	Dorsoradial hand, thumb
Median (C6-T1)	Wrist flexion, finger adduction	Volar aspect of thumb and index finger
Ulnar (C7-T1)	Finger abduction	Volar aspect of little finger
Femoral (L1-L4)	Knee extension	
Obturator (L2-L4)	Hip adduction	
Superior gluteal (L4-S1)	Hip abduction	
Sciatic (L4-S3)	Knee flexion	
Deep peroneal (L4-S1)	Ankle and great toe dorsiflexion	
Superficial peroneal (L5-S1)	Foot eversion	
Tibial (L5-S2)	Ankle plantar flexion	
Posterior tibial (L5-S2)	Great toe plantar flexion	
Spinal L4		Medial calf
Spinal L5		Dorsal foot
Spinal S1		Lateral plantar foot

DIAGNOSIS

Diagnosis of associated injuries depends on a complete history and physical exam of the involved extremity. If any hard signs of vascular injury are present, then consult vascular surgery immediately. If there are any soft signs of vascular injury and/or if the ankle-brachial index is <0.9, then order imaging tests to evaluate for associated vascular injuries, or transfer to an institution with vascular care capability (**Figure 266-1**).

The differential diagnosis for injuries associated with penetrating trauma to the extremities includes arterial or venous injury, nerve damage, tendon lacerations, fractures, soft tissue injury, degloving injuries, damage to joint capsule, bullet embolization of artery, or vein and compartment syndrome.[12]

LABORATORY TESTING

No specific laboratory testing is indicated for isolated penetrating extremity injuries; in certain cases, type and screening, baseline renal function, and a CBC may be indicated. If the patient has soft signs of vascular injury or an ankle-brachial index <0.9, then obtain a creatinine to determine renal function in patients with risk for preexisting renal disease. Underlying renal insufficiency creates potential for contrast-induced nephropathy when performing CT angiography. See Chapter 88, "Acute Kidney Injury," for discussion of radiocontrast-induced nephropathy.

IMAGING

Plain Radiographs Obtain anteroposterior and lateral radiographs of extremities with suspected fracture, joint injury, or retained bullet or other foreign body fragments. Oblique views may add value if there is clinical suspicion of retained foreign body. Obtain radiographs of the joint above and below the site of injury. Evidence of air in the joint or an intra-articular fracture on the radiograph demonstrates that joint involvement has occurred.

There are four types of fracture patterns associated with low-energy gunshots[13] (**Figure 266-2**). The drill-hole wound track pattern appears in lower-density cancellous bone and is most common in the distal femur, pelvis, and proximal humerus. Unicortical fractures appear in the metaphyses of long bones. Comminuted fractures occur most frequently in diaphyseal bone; multiple bone fragments are common. The fourth type of fracture is the distal spiral fracture, and this occurs most commonly in the femur.

For shotgun or blast injuries, obtain radiographs of the extremity and joint distal to the injury in order to detect any pellets that have embedded into the bone or soft tissues or entered into a joint capsule (**Figure 266-3**).

CT Angiography CT angiography is the primary diagnostic study for the evaluation of vascular injuries to the extremities.[2] CT angiography is noninvasive, provides higher resolution images, and is less expensive when compared to catheter angiography. It provides three-dimensional reconstruction with minimal artifact. CT angiography also assists in the evaluation of extravascular injuries such as fractures, foreign objects, or joint involvement.[14] Studies comparing CT angiography to catheter angiography have demonstrated that the CT angiography sensitivity and specificity rates for identifying clinically significant arterial injuries are equivalent to those with conventional catheter angiography.[15-18] Limitations of CT angiography include scatter artifact interference caused by bullets, poor visualization of

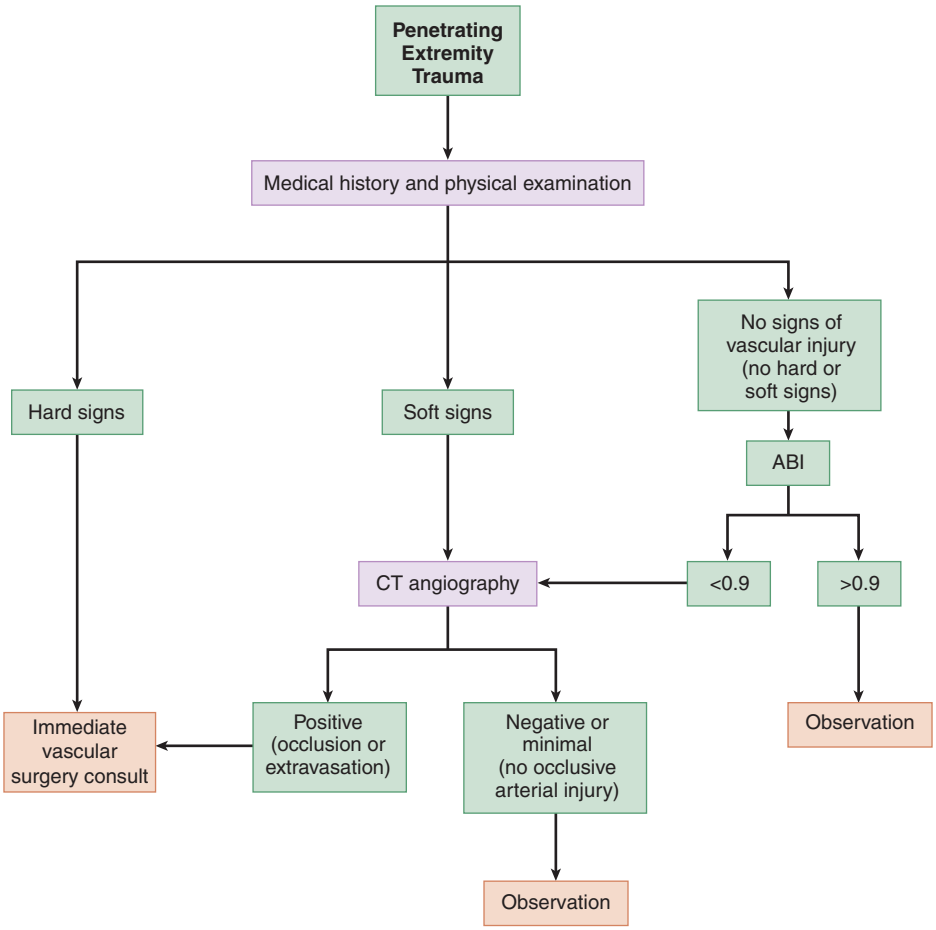

FIGURE 266-1. Algorithm for penetrating extremity trauma. ABI = ankle-brachial index.

tibial vessels, and the inability to perform any therapeutic interventions during the study.

Ultrasonography Historically, the sensitivity of color flow duplex ultrasonography has ranged from 50% to 100% for evaluating vascular injuries.[19] However, the 2-Point Fast Doppler (2PFD) protocol appears promising to identify vascular injury.[20] The presence of normal triphasic arterial flow in both the dorsalis pedis artery and posterior tibial artery had a sensitivity and specificity of 100% in ruling out arterial lesions in lower-limb penetrating trauma. Further studies are needed to determine generalizability of these results.[10]

TREATMENT

CONTROL OF BLEEDING

Patients with venous trauma can bleed profusely. Control bleeding with direct pressure, pressure dressing, or a tourniquet.[21] Avoid clamping vessels in an attempt to control bleeding, as this risks nerve damage. Nerves are bundled with vascular structures and can be easily damaged by blind clamping or ligation during the initial trauma resuscitation.

ARTERIAL INJURY

Penetrating injuries to the extremities that involve any associated arterial injury are critically important to recognize early. Figure 266-1 outlines the approach to these injuries.

FRACTURES AND JOINT INJURIES

Penetrating trauma can cause joint sepsis and destruction, rapid chondrolysis, and loss of anatomic contours. These can lead to serious long-term consequences, including posttraumatic degenerative arthritis and partial or total loss of flexibility. Treat bone fractures from penetrating trauma as open fractures. Surgically debride the injury and admit the patient for IV antibiotics. Synovial joint fluid is an organic acid that causes lead bullets to become soluble in the joint, which can lead to systemic lead toxicity.[22] If a patient has an obvious bony or joint capsule injury, obtain consultation to evaluate the injury.

WOUND MANAGEMENT

Careful wound management is critical to prevent infection after penetrating injuries. The most important component of wound management is irrigation. Copiously irrigate with saline or tap water (500 to 1000 mL) at high pressures (15 to 20 pounds per square inch). Antiseptic solution does not decrease infection rate and may actually be harmful.[23]

Heavily contaminated wounds may require more fluid and/or more pressure. If the wound is older than 3 to 4 hours, gently scrub the wound. Despite the importance of irrigation and wound management, there are many other factors that play a role in infection risk and proper healing, including bacterial inoculum, tissue devitalization, blood supply, time to presentation and treatment, presence of foreign bodies, and host immune status.

WOUND CLOSURE

The decision to close associated open wounds depends on the time that has elapsed since the injury and the degree of contamination. If there is minimal contamination and the wound is well irrigated, it can be closed. It is important to arrange close follow-up in 24 to 48 hours in order to check for developing wound infection. Extremity wounds with retained foreign bodies, major tissue destruction, or contamination should be closed after a delay of 72 to 96 hours. Do not routinely administer antibiotics

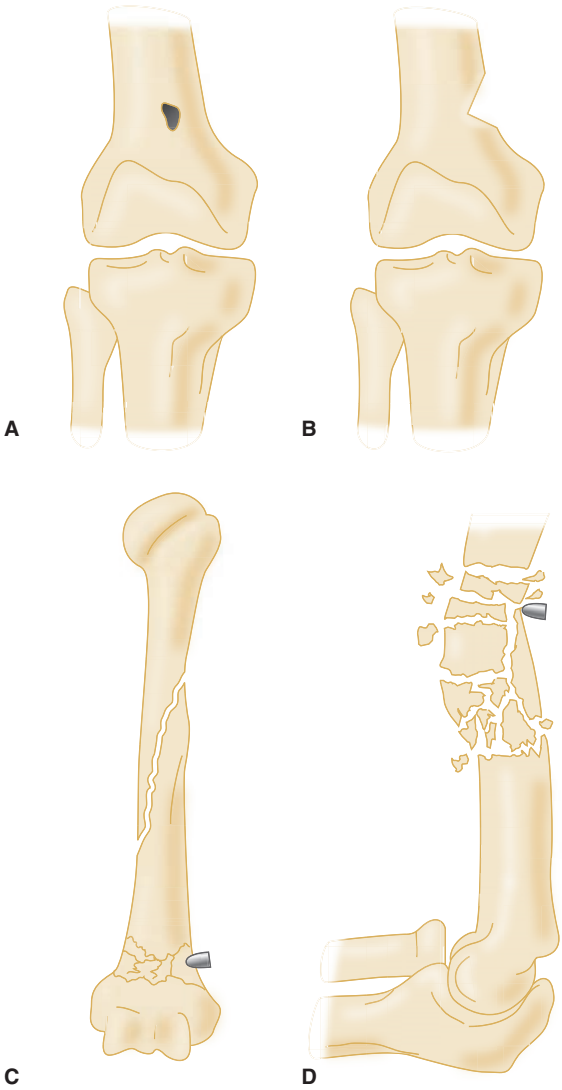

FIGURE 266-2. Fracture patterns created by bullets: drill-hole (**A**), unicortical (**B**), distant spiral (**C**), comminuted (**D**).

for uncomplicated extremity gunshot and knife wounds because there is an approximately 2% rate of infection in these injuries.[24] However, antibiotics may be beneficial for treating hand injuries, joint or bony involvement, immunocompromised patients, and wounds with significant contamination.[25]

SOFT TISSUE FOREIGN BODIES

Plain radiographs will detect glass, metal, bone, or gravel. Wood and other organic material may be missed on plain films, and US is better at identifying these objects. CT scanning is the best modality for identifying both radiolucent and opaque foreign bodies. Several factors impact whether the foreign body should be removed. The benefit of exploring the wound and removing the substance must be weighed against the associated damage to surrounding tissues and the increased risk of infection. Organic material is more reactive and has a higher rate of infection than metal or glass. A bullet generally should not be removed unless the bullet has potential to migrate into surrounding vital structures or if it is in the joint capsule.

DISPOSITION, FOLLOW-UP, AND DISEASE COMPLICATIONS

Hard signs of arterial injury require immediate surgical consultation, and such patients will need further imaging, surgery, and hospital admission.

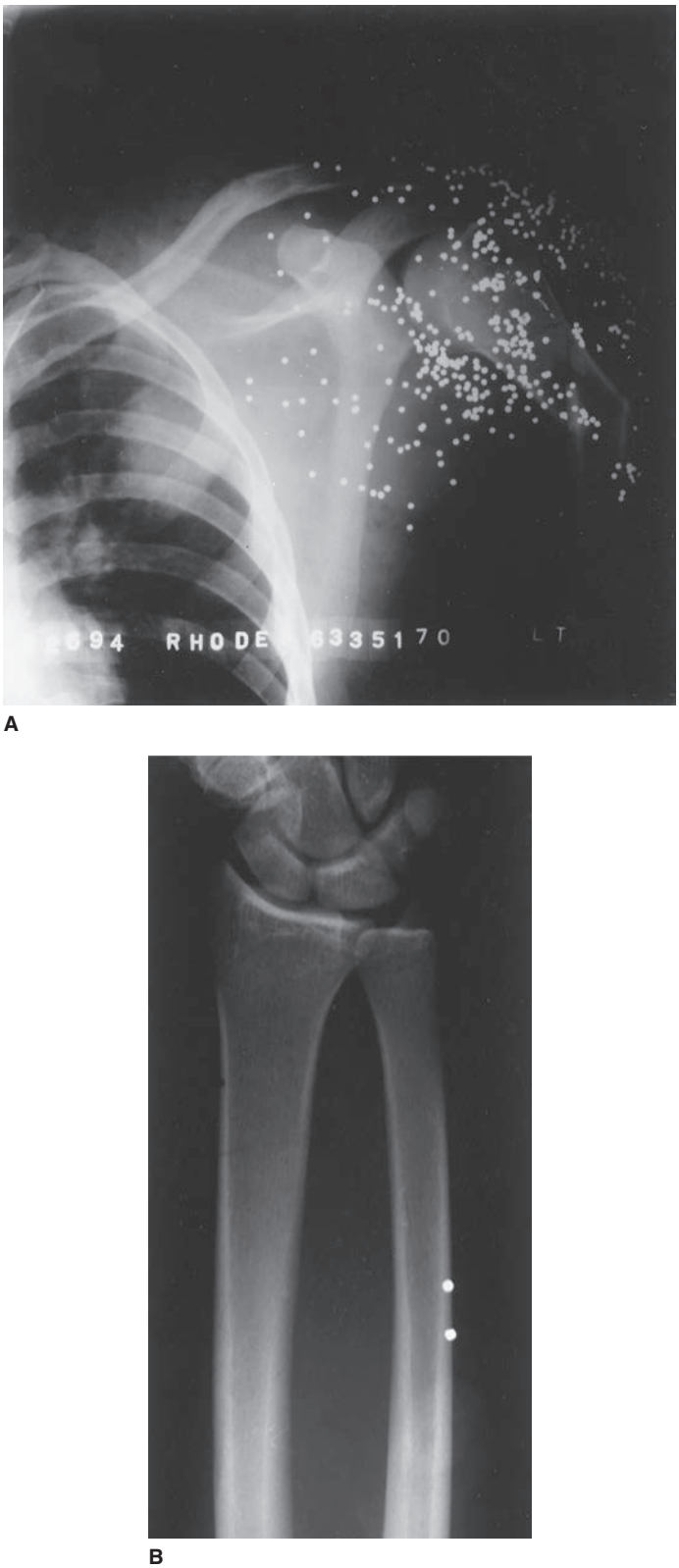

FIGURE 266-3. **A.** Gunshot wound to the shoulder and axilla. **B.** Embedded pellet of shotgun in the distal ulna, illustrating the importance of obtaining images of the extremity distal to such injuries.

All other patients with penetrating extremity trauma should undergo a period of observation with associated serial examinations to detect any delayed or missed injuries. There is no consensus on the required observation time required, but a minimum of 24 hours is reasonable.[17]

Wound healing may be complicated by infections, missed nerve injuries, tendon or joint injuries, delayed vascular injury, and compartment syndrome. Discuss return precautions with patients before discharge. State these precautions as clearly as possible. Recommend that patients return to the ED for increasing pain, numbness, weakness, redness, or pus drainage from the wound site. Ensuring follow-up with the appropriate surgical service, a primary care provider, or the ED is essential, especially in uninsured patients or patients transported long distances from home, as well as for other high-risk populations.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 22

Orthopedics

CHAPTER 267

Initial Evaluation and Management of Orthopedic Injuries

Ryanne J. Mayersak

INTRODUCTION

Musculoskeletal trauma involves injury to one or more of the following structures:

Bone: A unit of the skeleton composed of the hardest variety of connective tissue. Bones give shape and support to the body. In addition to surrounding and protecting vital organs, they serve as points of attachment for the muscles of the limbs, making movement possible.

Joint: The area where two or more bones articulate with one another. Joints are usually classified in terms of the amount of motion permitted at the articulation. Most joints of the extremities are synovial joints, which allow the greatest amount of motion.

Ligament: A bundle of connective tissue forming part of the fibrous capsule surrounding a joint and attached to it. Every joint of the extremities is reinforced by two or more ligaments, whose purpose is to stabilize the joint by confining its movements to specific planes and preventing movement beyond physiologic limits.

Tendon: The fibrous structure connecting a voluntary muscle to bone, cartilage, or ligaments. Tendons enable muscles to effect motion in the joint or body area to which they are attached.

Orthopedic injuries to these structures include the following:

Fracture: A disruption of bone tissue. Fractures may be caused by (1) an application of force exceeding the strength of the bone, (2) repetitive stress, or (3) an invasive process that undermines the bone's integrity.

Dislocation: Complete disruption of a joint, such that the articular surfaces of the bones that comprise the joint are no longer in contact with one another.

Subluxation: Partial disruption of a joint, in which some degree of contact between the articular surfaces remains.

Fracture-dislocation or fracture-subluxation: Disruption of a joint combined with fracture of at least one of the bones involved in the articulation.

Diastasis: A separation of the interosseous membrane connecting two syndesmotic joints as seen between the radius and ulna and tibia and fibula.

Strain: A tearing injury to muscle fibers resulting from excessive tension or overuse. Strains can be further subdivided in first, second, and third based on their level of pain and functional ability.

Sprain: A tearing injury to one or more ligaments of a joint, which occurs when the joint is forced beyond the limits of its normal planes of motion. These injuries can be further classified into first-, second-, and third-degree sprains depending on their extent.

PATHOPHYSIOLOGY OF FRACTURES

Properly assessing and treating bony injuries in the ED requires an understanding of the physiologic processes by which fractures are created and by which they heal. Practical knowledge of fracture pathophysiology may provide the index of suspicion needed to diagnose an injury that might otherwise be missed. It also may help prevent or minimize complications and sometimes may form the basis for advising the patient regarding the outlook for recovery of function.

TYPES OF FRACTURES

Although fractures are sometimes classified in terms of the mechanism that created them, they also may be described in terms of the physiology involved.

"Common" Fractures Most fractures are the result of significant trauma to healthy bone. The bony cortex may be disrupted by a variety of forces, including a direct blow, axial loading, angular (bending) forces, torque (twisting stress), or a combination of these.

Pathologic Fractures Fractures that result from relatively minor trauma to diseased or otherwise abnormal bone are termed pathologic fractures. In such cases, a preexisting process has weakened the bone and rendered it susceptible to fracture by forces that, under normal circumstances, would not disrupt the cortex. Common examples of such injuries are fractures through metastatic lesions, fractures through benign bone cysts, and vertebral compression fractures in patients with advanced osteoporosis. Numerous other disease processes, such as osteogenesis imperfecta, Paget's disease, and osteomalacia, may render an individual susceptible to pathologic fracture. Because these injuries often are not associated with a history of significant trauma, subtle pathologic fractures may go undetected unless there is a clinical index of suspicion.

Stress Fractures Bone may undergo a "fatigue" fracture by being subjected to low-intensity trauma or repetitive forces before the bone and its supporting tissues have had adequate time to accommodate to such forces. Stress fractures often involve the lower extremity, are common in athletes such as runners or dancers, and occur in deconditioned individuals who begin new exercise programs. An example is a metatarsal shaft fracture in unconditioned foot soldiers ("**march fracture**"). Radiographs often are negative early in the clinical course of stress fractures. The initial diagnosis may be presumptive, based solely on the history and findings of point tenderness or localized swelling. Days or weeks may pass before the fracture line or new bone formation becomes visible radiographically. Triple-phase nuclear bone scans, although not often obtained in the ED setting, are more sensitive than radiographs in early detection. Consider other conditions, such as muscle strain, bursitis, exertional compartment syndrome, and nerve entrapment, in the differential, and further imaging with follow-up radiographs, CT, or MRI may be necessary.[1]

Salter (Epiphyseal Plate) Fractures Fractures involving the physis, the cartilaginous epiphyseal plate near the ends of the long bones of growing children, were originally classified by Salter and Harris[2] and are commonly called *Salter fractures*. New bony material needed for the elongation of bones during growth is provided by specialized cells within the physis. When growth is completed, the physis transforms from cartilage into bone, ultimately fusing with the bone surrounding it, and disappearing as a distinct entity. By definition, Salter fractures cannot occur in fully grown adults.

Damage to the epiphyseal plate during a child's growth may destroy part or all of its ability to produce new bone substance, resulting in aborted or deformed growth of the limb. The potential for growth disturbance from an epiphyseal plate injury is related to the number of years the child has yet to grow (the older the child, the less time remains for deformity to develop) and to the pattern of the fracture line through the epiphyseal area. Classification of Salter fractures and their clinical

implications are discussed in the section "Describing Radiographs" later in this chapter.

Pediatric fractures also differ from adult fractures (aside from the aforementioned growth plate) because pediatric bone tends to be more porous and malleable, allowing for incomplete fractures. Such examples include a greenstick fracture, which results in the bowing of the affected bone, and a torus fracture, which can cause "buckling" of the bone cortex. These findings may be subtle on radiographs.

FRACTURE HEALING

An understanding of the short- and long-term aspects of bone healing helps decision making regarding fracture reduction, treatment modality, and the prognosis for regaining function or being left with residual deformity. Fracture healing consists of three phases: inflammatory, reparative, and remodeling, each of which blends into the next, with some degree of overlap between them.[3] When a fracture occurs, the microvessels crossing the fracture line are severed, depriving the damaged bone ends of their blood supply. As a result, the bone ends gradually necrose, triggering a classic inflammatory response in which neutrophils, macrophages, and lymphocytes migrate to the area. The proteins and peptides (collectively termed *cytokines*) released by these cells promote revascularization.[4] This early phase is brief, but creates the tissue environment for the most predominant aspect of fracture healing, the reparative phase.

Granulation tissue soon begins to infiltrate the area.[5] Within the granulation tissue are specialized cells capable of forming collagen, cartilage, and bone—the ingredients of callus. Callus gradually surrounds the fractured ends and stabilizes them, becoming more densely mineralized with time.

Meanwhile, the necrotic edges of the fragments are removed by osteoclasts, cells whose function is to resorb bone. That is why some "hairline" fractures do not appear on a radiograph until days after injury. Invisible initially, the diagnostic fracture line appears only after necrotic bone has been resorbed from the area.

The final phase of bone healing, the remodeling phase, is the longest, sometimes lasting years. Remodeling is the tendency of bone gradually to regain its original shape and contour. During this phase, superfluous portions of callus are resorbed, and new bone is laid down along the natural lines of stress. These layers, easily visible on radiographs of normal bone, are the bony trabeculae. The formation of trabecular bone is a physiologically efficient process providing maximum strength relative to the amount of bone material used.

The anticipated degree of remodeling after a fracture is related to a number of factors. Predictors of satisfactory remodeling include youth, proximity of the fracture to the end of the bone (but not involving the epiphyseal plate), the amount of angulation, and the extent to which the direction of angulation coincides with the plane of natural joint motion.

Clinical decisions regarding the aggressiveness of fracture reduction are directly linked to knowledge of bone-healing physiology. Some angulation near the end of a long bone, for example, may be more acceptable than the same amount of angulation near the midshaft. In the wrist, dorsal or volar angulation has a better prognosis than does ulnar or radial angulation because the natural plane of wrist motion is dorsal to volar. Mild angulation in a 2-year-old child may be left to remodel on its own, whereas the same amount of angulation in an adult may require correction.

Strain is an important concept in optimal fracture healing. Excessive or insufficient strain can affect the fracture-healing process and disrupt the normal biological and mechanical signals for repair. Multiple terms are used to describe fracture healing. Union refers to the complete healing of a fracture. Malunion refers to a healing fracture with some residual deformity. Delayed union refers to prolonged healing time, usually longer than 6 months. Nonunion refers to failed fracture healing usually caused secondary to poor vascular supply and stabilization.[6]

ORTHOPEDIC EMERGENCIES

OPEN FRACTURE

An open fracture is a fracture associated with overlying soft tissue injury, creating communication between the fracture site and the skin. Although this term may convey the image of grossly exposed bone, the term is equally applicable to any puncture wound extending to the depth of an underlying fracture. Such puncture wounds may be created by external forces or may occur from within, when a sharp bone fragment transiently protrudes through the skin before receding back beneath the surface.

TABLE 267-1 Gustilo-Anderson Open Fracture Classification System

Grade I	Low energy injury with an open wound <1 cm in length and no evidence of contamination
Grade II	Moderate injury with comminution of the fracture and a 1- to 10-cm wound with some contamination
Grade IIIA	High-energy fracture pattern with a wound >10 cm and gross contamination
Grade IIIB	High-energy fracture with a >10 cm contaminated wound with exposed bone
Grade IIIC	Similar to grade IIIB with vascular involvement

A potential major complication of open fracture is osteomyelitis. Once established, osteomyelitis may result in months or years of pain, disability, medical therapy, surgical procedures, and, in some cases, amputation. Although osteomyelitis may sometimes be unavoidable, it is less likely when treatment is prompt and meticulous.

Open fractures are usually classified by their severity, based on the extent of overlying tissue disruption, lack of bone coverage, kinetic energy of the injuring force, and evidence or likelihood of significant contamination. A classification system (**Table 267-1**) is useful when communicating with an orthopedic consultant regarding these types of injuries.[6] Irrespective of these factors, promptly treat any open fracture.

Skin blisters can be seen with fractures and appear to be related to the severe swelling that can occur. Fracture blisters may appear as early as 6 hours after the injury and can be clear or hemorrhagic. Hemorrhagic blisters have a worse prognosis because that indicates a detachment between the epidermal and dermal layers. These blisters tend to occur over bony prominences, and early reduction and stabilization can help decrease their occurrence. These blisters have been associated with increased infection rate and wound dehiscence. Treatment is controversial, but most experts recommend keeping the blisters intact, covering them with an antibiotic ointment or silver sulfadiazine dressing, and applying elevation and compression to control swelling.[7]

SUBLUXATION AND DISLOCATION

Subluxation is a condition in which the articular surfaces of a joint are nonconcentric to any degree. Dislocation is the most extreme form of subluxation. A joint is dislocated when the articular surfaces of the bones that normally meet at the joint are completely out of contact with one another. The urgency of reducing a dislocation is based on several factors. One is the potential for neurologic or circulatory compromise. The neurovascular bundle passing close to the affected joint may become "kinked" around the dislocation. This may result in neurologic or vascular deficit that might be temporary if the deformity is reduced promptly but irreversible if treatment is delayed. Another consideration is that the longer a joint has been dislocated, the more difficult it may be to reduce and the less stable the reduction is likely to be. This is probably due, at least in part, to edema, muscle spasm, and other tissue changes that increase over time.

Dislocation of the hip also carries the potential for avascular necrosis of the femoral head. The necrosis occurs because much of the blood supply to the femoral head is delivered through vessels that emerge from the acetabulum. When the joint is dislocated, circulation to the femoral head is disrupted. At some point, the vascular insult becomes irreversible, and bony necrosis results. Although aseptic necrosis may occur despite the clinician's best efforts, its likelihood increases with the delay until reduction.

NEUROVASCULAR INJURY

Any injury associated with neurologic or vascular compromise should be addressed as soon as possible. The longer such a deficit goes untreated, the longer it is likely to persist and the greater the possibility

that it will be irreversible. In some cases, reducing a deformity by means of longitudinal traction is all that is necessary to restore circulation or nerve function.

PREHOSPITAL CARE

PRELIMINARY SPLINTING

Effective splinting of an injured extremity is important for several reasons: (1) it reduces pain; (2) it reduces damage to nerves and vessels by preventing them from being compressed between the fracture fragments or being stretched by angulation at the fracture site; (3) it reduces the chance of inadvertently converting a closed fracture to an open one should a sharp bone fragment poke its way through the skin; and (4) it reduces the pain associated with patient transport by minimizing motion of the fracture fragments.

PREHOSPITAL SPLINTING DEVICES

Many splinting modalities are available to EMS personnel. These may range from sophisticated devices, such as vacuum splints containing small beads that conform to the extremity when air is removed, to simpler techniques such as cardboard or pillow splints, or padded IV boards.

Sling and Swath For injuries of the wrist or forearm, consider using a sling to supplement the splint, because optimal immobilization includes the joint above and the joint below the fracture, and a sling helps keep the elbow at rest.

For suspected injuries to the shoulder, humerus, or elbow, a sling-and-swathe arrangement works well. This method involves applying a sling, then binding the affected arm to the thorax with a gauze wrap. An exception to this principle is immobilization of patients with suspected anterior dislocation of the shoulder. Many patients with this injury have difficulty adducting the forearm, and forcibly binding it to the thorax may be painful. A simple sling is adequate in such cases. Injuries to the ankle may be immobilized in a pillow or well-padded cardboard splint. If a fracture of the tibial shaft or knee is suspected, the device should extend well above the knee to immobilize the joint above and the joint below the fracture.

Splints Some injuries warrant special splints, such as a winch-mechanism traction apparatus for femoral shaft fractures. Although such a device does not immobilize the hip (the joint above the fracture), the traction component makes this unnecessary. If a traction device is not available, then both the hip and knee should be immobilized. One method of accomplishing this is to bind the legs together and then bind the patient to a backboard from ankles to thorax with folded sheets or towels beneath the lower legs (but not the feet) to ease pressure on the heels.

Other types of splints exist, but their use is controversial. Inflatable plastic splints, for example, may be used for injuries to the ankle or wrist but sometimes are used inappropriately for fracture of the humerus or femur. Because these devices normally do not extend sufficiently proximally, they provide inadequate immobilization for such injuries. Also, overinflating the device may impair circulation. **If the inflatable splint cannot be dented by moderate thumb pressure, it is probably overinflated.** Inflatable splints should not be applied over clothing, because wrinkles in the clothing may cause pressure sores in swollen and vulnerable tissue.

Also controversial are nonmalleable aluminum splints, because they are based on the "one size fits all" principle, which some clinicians interpret as "this size fits none." Malleable aluminum splints are preferable, as they can be made to conform more closely to the contour of the extremity, even accommodating some degree of deformity. If used, aluminum splints of either type should be well padded, because their hard surface may cause pressure sores. Like any splint, they should immobilize the joint above and the joint below the fracture when used for long-bone injuries. For example, an above-knee splint is indicated for suspected fracture of the tibial shaft. Aluminum splints should be removed promptly once a fracture is diagnosed or ruled out. If a fracture is confirmed, replace the splint with an alternative immobilization dressing before the patient leaves the ED, because aluminum splints may cause pressure sores even when padded.

Pelvic Binding An outdated device is military antishock trousers, which historically were applied during ambulance transport for patients in shock with already diagnosed pelvic ring fracture, or for patients with a clinically apparent femoral fracture when a traction device is not at hand, as the device immobilizes the joints above and below the fracture. Military antishock trousers were cumbersome to apply, prolonging scene time; they possibly contributed to compartment syndrome, fluid and electrolyte imbalance, pressure ulcers, and circulatory impairment.[8,9] A variety of current methods may be used by EMS to stabilize an injured pelvis. Advanced Trauma Life Support recommends circumferential application of a pelvic sheet wrap. Other commercial devices that may be available to use are the SAM® PelvicSling, T-POD®, and PelvicBinder®.[10,11]

REDUCING DEFORMITY IN THE FIELD

Many EMS programs do not recommend prehospital reduction of deformity for an injured extremity, as injudicious manipulation may convert a pure dislocation to a fracture-dislocation. Even if a fracture had already existed, there would be no way to prove it was not caused by the manipulation. One circumstance in which prehospital reduction of obvious fracture to the shaft of a long bone may be justified is a nonpalpable distal pulse. In the absence of a common standard, the indications for reduction of deformity by prehospital personnel remain at the discretion of the supervising EMS program.

CLINICAL FEATURES

The importance of a careful history and physical examination cannot be overstated. Orthopedic diagnosis is sometimes thought of as being as simple as taking a radiograph of the painful area. Although imaging is an important adjunct, it is not the ultimate diagnostic resource. **The pain of a fracture or a dislocation may be referred to another area.** For example, patients with disruption of the sternoclavicular joint or fracture of the humeral shaft may complain only of shoulder pain. If the radiograph is based solely on where the patient reports discomfort, then the injured part might not be included on the film. **Imaging decisions should be based not only on the chief complaint but also on systematic palpation, observation of subtle deformity or significant point tenderness, and mechanism of injury.**

Some fractures or dislocations may be demonstrated only by special radiographic views, which are not part of the standard series for that body part. Such views will never be ordered unless the clinician has already formulated a presumptive diagnosis based on the history and physical findings.

Some injuries might not be radiographically apparent on the first day, regardless of what views are taken. Common examples are fracture of the scaphoid, nondisplaced fracture of the radial head, and stress fracture of a metatarsal. The classic radiographic signs accompanying these injuries, such as the fat pad sign of the elbow, are not always conveniently present, but mechanism, history, and findings suggesting the injuries often are. CT or MRI may allow early diagnosis of fractures that are not radiographically evident. However, such tests are not always available or feasible on the day of injury. In such cases, the diagnosis of fracture may be purely clinical until 7 to 10 days after trauma, when enough bony resorption has occurred at the fracture site to reveal a lucency on plain radiographs.

HISTORY

The value of the history in cases of orthopedic trauma is often underestimated. Knowing the precise mechanism of injury may be the key to diagnosing some fractures or dislocations. For example, a history of shoulder injury combined with the complaint of dysphagia may be the only clue to the existence of posterior sternoclavicular dislocation. This entity, which causes pressure on mediastinal structures, often can be demonstrated only by CT and may result in severe complications if treatment is delayed. **Table 267-2** provides other examples of mechanisms that may lead the clinician to suspect, or presumptively treat for, specific injuries. This is by no means a definitive or exhaustive list. Some of the mechanisms described may produce injuries other than those

TABLE 267-2 Mechanisms Associated With Particular Orthopedic Injuries

Mechanism	Possible Injury
Bilateral compression of the shoulders	Anterior or posterior sternoclavicular dislocation
Direct blow to the medial clavicle	Posterior sternoclavicular dislocation
Fall, landing on the apex of the shoulder	Acromioclavicular separation
Direct blow to the anterior shoulder, fall on the outstretched arm, seizure or electroconvulsive muscular activity	Posterior dislocation of the shoulder
Sudden traction force to a toddler's arm	Subluxed radial head (sometimes misdiagnosed as brachial plexus injury because of pseudoparalysis of the arm)
Fall, landing on the outstretched arm or with the elbow beneath the body	Fracture of the radial head (may be occult on initial radiograph)
Forced dorsiflexion of the wrist	Fracture of the scaphoid, lunate dislocation, perilunar dislocation, Colles' fracture
Striking the knee against the dashboard in a high-speed collision	Posterior dislocation of the hip
Landing flat on the feet from a height	Calcaneus fracture; tibial plateau fracture; acetabular fracture; vertebral compression fracture, usually lumbar
Ankle inversion force	Fracture of any of the three malleoli, fracture of the base of the fifth metatarsal
Rotatory ankle force	Fracture of any of the three malleoli, disruption of the anterior tibiofibular ligament with proximal fibular fracture (Maisonneuve's injury)
Inversion or medial or lateral stress to the forefoot; axial load on the metatarsal heads with the ankle plantarflexed	Midfoot dislocation (Lisfranc's injury)

mentioned. Conversely, the injuries may be produced by mechanisms in addition to those listed.

Some musculoskeletal injuries or conditions may not necessarily be associated with a history of direct trauma. Occult fracture of the hip in an osteoporotic individual, occult stress fracture of a metatarsal in someone who has recently done an unusual amount of walking, and slipped capital femoral epiphysis in a preteenager or young adolescent are examples of injuries in which symptoms may be gradual and insidious in onset, unrelated to an isolated traumatic event. **Exquisite tenderness to palpation or pain on weight bearing or passive range of motion suggests the possibility of an occult or easily missed fracture.** Depending on the index of suspicion, further studies, such as a bone scan or MRI, may be indicated to exclude significant pathologic conditions before the patient is allowed to resume weight bearing.

History taking should not necessarily be limited to orthopedic issues. Depending on the situation, a general medical history should be obtained because it may have implications for further workup, the potential for complications, or ultimate prognosis for recovery of function. Relevant issues may include a history of cancer, heart disease or neurologic disease, taking anticoagulant medication, falling due to syncope or transient hemiparesis, or an unsteady baseline gait that cannot withstand further impairment.

PHYSICAL EXAMINATION

Essential components of the examination for musculoskeletal trauma are (1) inspection for wounds, swelling, discoloration, or deformity; (2) assessment of active and passive range of motion of the joints proximal and distal to the injury; (3) palpation for tenderness or deformity; and (4) assessment of neurovascular status.

Inspection and Range of Motion Gross deformity along the shaft of a long bone is pathognomonic for fracture. Deformity at a joint, loss of range of motion, and severe pain at rest suggest the presence of a dislocation or fracture near the joint. An exception is posterior dislocation of the shoulder, which, although intensely painful, might not be accompanied by obvious deformity, although the humeral head may be palpable posteriorly.

Palpation When gross deformity is not present, presumptive diagnosis strongly depends on findings noted on palpation. Palpation may disclose areas of bony step-off and the precise location of point tenderness.

The palpation examination should be done systematically and consistently from one patient to the next. The area palpated should extend well beyond the location of pain described by the patient, as the pain may be referred. For example, when an injured patient complains of shoulder pain, palpation should begin at the sternoclavicular joint, then proceed along the clavicle onto the acromioclavicular joint, then onto the humeral head and along the entire humeral shaft. In addition, the scapula should be palpated for tenderness, and the posterior aspect of the shoulder should be palpated for any unnatural prominence or fullness that might suggest posterior dislocation of the humeral head. Injury to any of these areas may be reported by the patient as "pain in the shoulder." Only a meticulous palpation examination may protect the clinician from being misled by referred pain and missing a crucial diagnosis.

Neurovascular Assessment When injury involves an extremity, as opposed to the vertebral column, sensorimotor testing should be performed on the basis of peripheral nerve function, rather than nerve root and dermatomal distribution (**Figure 267-1**). In the upper extremity, the

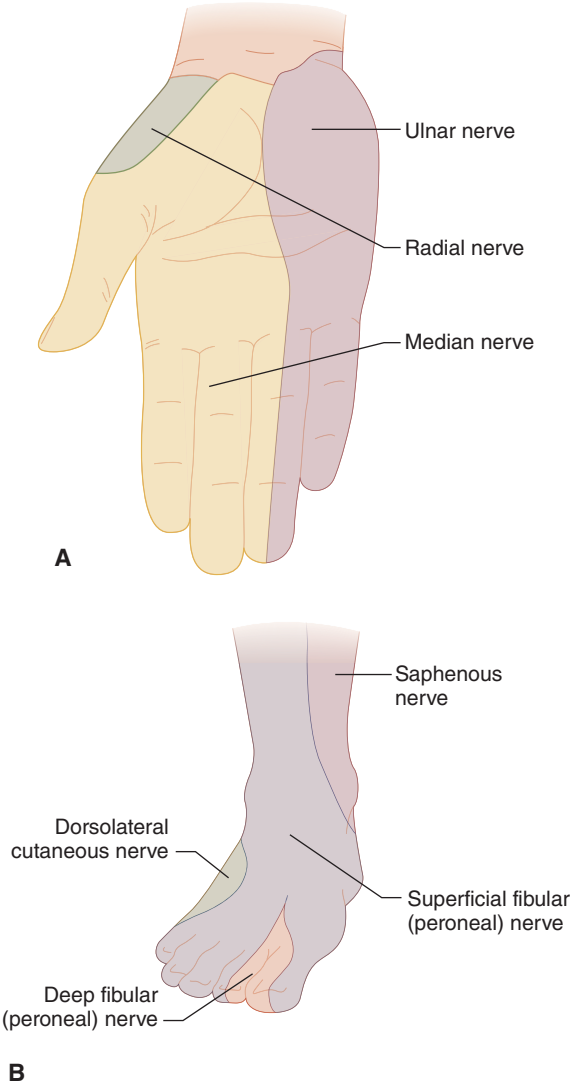

FIGURE 267-1. **A.** Peripheral sensory nerve distribution of the hand. **B.** Peripheral sensory nerve distribution of the foot.

radial, median, and ulnar nerves should be tested. When the shoulder is anteriorly dislocated, two additional nerves, the axillary (supplying sensation to the lateral aspect of the shoulder) and the musculocutaneous (supplying sensation to the extensor aspect of the forearm), also should be checked. In the lower extremity, examination of the saphenous (sensory only), peroneal, and tibial nerves should be performed. Neurologic deficit is important to document early, particularly before the patient has undergone any significant manipulation or reduction maneuvers.

Assess vascular status early. **The sooner circulatory compromise is identified and addressed, the better the chance of avoiding tissue ischemia or necrosis.** Injuries such as dislocation of the knee (tibiofemoral joint), fracture-dislocation of the ankle, and displaced supracondylar fracture of the elbow in children may be associated with vascular disruption, with resulting circulatory impairment.

DIAGNOSIS

IMAGING

The joints above and below a fracture should generally be imaged because injury at the proximal or distal joint may coexist with long-bone fractures. Injuries that may require special views or advanced imaging modalities in order to be visualized include acromioclavicular separation, fracture of the scaphoid, posterior shoulder dislocation, and sternoclavicular dislocation. Plain radiographs are still the mainstay for fracture diagnosis. They can also be helpful in detecting foreign bodies, air, or gas. It is important that the physician be familiar with routine views as well as specialized views such as the Judet's view of the acetabulum, the sunrise view of the patella, or stress views of the foot and ankle. Remember that at least two perpendicular views are necessary when evaluating long bones. If the degree of injury suspicion is high, then request more views or consider other imaging modalities for further evaluation.[6]

The use of bedside US has been reported for pediatric clavicle and forearm fractures and long-bone fractures. However, US for these purposes is operator dependent and has not replaced traditional diagnostic imaging.[12-15] US has become a common bedside diagnostic aid in the ED, and its role in orthopedic complaints continues to evolve. Soft tissue and musculoskeletal US is now recognized as one of the core emergency applications. This modality is noninvasive, quick, and allows for comparison of the affected side to an unaffected side. Common US applications in the ED include tendon evaluation, joint effusion evaluation, muscle evaluation, foreign body identification, and procedural guidance. US can be used in conjunction with plain radiographs and has even shown benefit in diagnosing injuries missed on plain radiographs, such as rib or scaphoid fractures.[16,17]

Children who have sustained trauma at or near a joint may need comparison studies of the opposite extremity to differentiate fracture lines from normal epiphyseal plates or ossifying growth centers. This is particularly true of the pediatric elbow, which typically exhibits six ossification centers sequentially as the child grows.

Although the clinician may be tempted to base diagnostic and treatment decisions on the radiologist's report, this is not advisable for at least two reasons. First, **a negative radiologic report does not exclude significant injury.** Fracture of the radial head, scaphoid, or metatarsal shaft, for example, may be undetectable on radiographs initially, even when special views are taken. Second, the terminology used by radiologists to describe malposition of fracture fragments or disrupted joints often differs from the terminology used by orthopedists. Because the emergency physician may confer with an orthopedist regarding the initial management of a patient, and because this interaction commonly involves describing the radiographic appearance of an injury, it is important that the two physicians "speak the same language." CT may be used to confirm fractures in some cases and helps to better define displacement, alignment, and fragmentation of the fracture, which may assist the orthopedist with operative planning.

DESCRIBING RADIOGRAPHS

As more hospitals convert from film-based to digital imaging, orthopedic consultants are increasingly likely to be able to examine a patient's imaging studies by remote access. In the absence of such technology, proper management of the patient may depend on the emergency physician's ability to convey the radiographic appearance of the injury to the consultant. In such cases, the narrative often will influence the orthopedist's decision regarding the need for hospital admission and whether surgical versus nonsurgical management is warranted. In essence, the emergency physician should be able to transmit a virtual copy of the radiograph by means of verbal description.

There are a number of ways to characterize the appearance of fractures. The method presented below is intended to be the most practical from the standpoint of communicating with an orthopedic consultant.

Open Versus Closed Although not a radiologic finding per se, whether a bony injury is open or closed is an important consideration and should be conveyed to the orthopedist at the outset. The implications of open fracture are of such significance that this factor alone may determine the patient's immediate care or ultimate disposition.

Location of the Fracture **Typical reference points used by orthopedists to describe the location of a fracture along the shaft of a long bone are the midshaft, the junction of the proximal and middle thirds, and the junction of the middle and distal thirds.** Any fracture more proximal or distal than these locations may be described in terms of its distance, in centimeters, from the bone end.

When a fracture extends into the adjacent joint, it is termed intra-articular. Intra-articular fractures have special significance because disruption of the joint surface may warrant surgery to restore the joint's contour and prevent subsequent traumatic arthritis. This feature of a fracture line, if present, constitutes important information.

Anatomic bony reference points should be cited when applicable. A fracture just above the condyles of the distal humerus or femur, for example, is termed a supracondylar fracture. A fracture running from the greater to the lesser trochanter of the proximal femur is an intertrochanteric hip fracture, whereas a fracture just below the trochanters is subtrochanteric, a fracture just above them is said to involve the femoral neck, and a higher fracture just below the femoral head is referred to as subcapital. The area at or proximal to the coronoid process of the ulna is the olecranon and should be referred to as such, rather than simply the "proximal ulna." Other bony landmarks include the radial head at the elbow, radial styloid at the wrist, and the greater tuberosity of the humeral head. Numerous additional examples exist.

Orientation of the Fracture Line The most common orientations of fracture lines are illustrated in **Figure 267-2**. Torus and greenstick fractures occur almost exclusively in young children, whose bones are more pliable than those of adults. Note the segmental fracture, which is commonly described incorrectly as a comminuted fracture. To an orthopedist, the term *comminuted* implies splintering or shattering. A single, large, free-floating segment of bone between two well-defined fracture lines is a segmental fracture.

Displacement and Separation The term *displacement* may be used in either of two ways. In the broadest sense, it pertains to any deviation from anatomic position or alignment. Used more precisely, displacement refers to the extent to which fracture fragments are nonconcentric or offset from each other. The magnitude of displacement may be expressed in terms of direct measurement (e.g., 4-mm displacement) or in terms of the percentage of the width of the bone (e.g., 50% displacement, complete displacement). The direction of displacement is based on the position of the distal fragment relative to the proximal fragment.

Displacement should not be confused with separation, which is the distance two fragments have been pulled apart. **Figure 267-3** illustrates principles of displacement and separation.

Shortening Shortening, expressed in millimeters or centimeters, is the amount by which a bone's length has been reduced. Shortening may occur by impaction (telescoping of the fragments into one another) or by the overlap of two completely displaced fragments (**Figure 267-4**). The latter is referred to by some orthopedists as *overriding*. Because a radiograph affords no depth perception, a fracture that appears impacted on one view needs to be visualized at an angle 90 degrees from the first to differentiate it from a fracture whose ends are completely displaced and overriding. Depending on the location of the fracture and the age of the patient, shortening may have long-range functional implications and may have to be corrected by closed manipulation or by surgery.

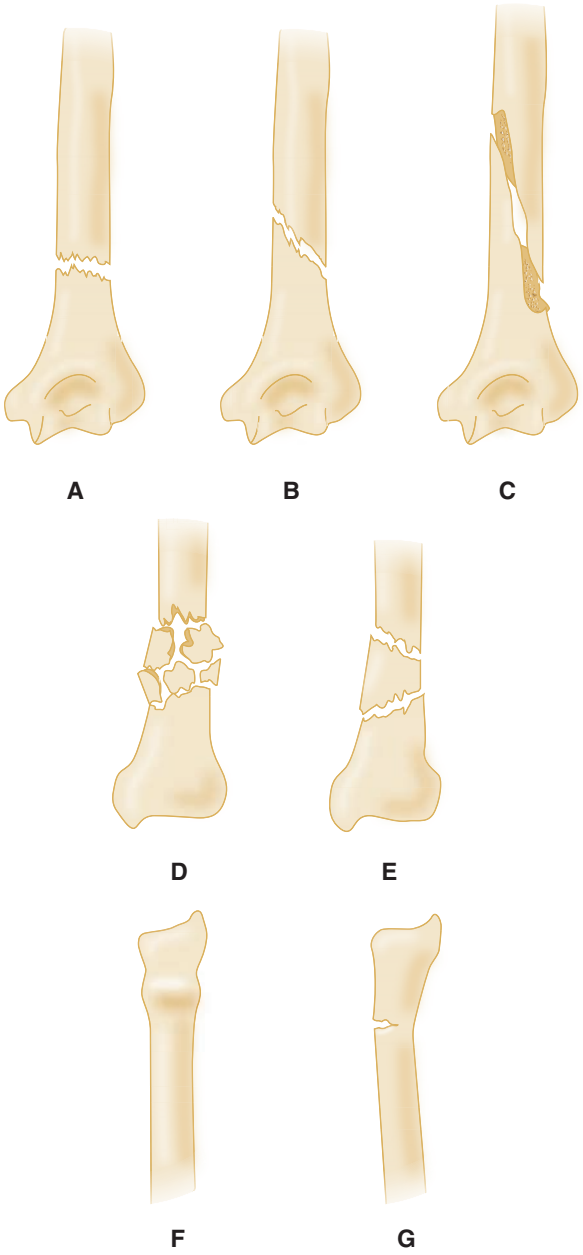

FIGURE 267-2. Fracture line orientation. **A.** Transverse. **B.** Oblique. **C.** Spiral. **D.** Comminuted. **E.** Segmental. **F.** Torus. **G.** Greenstick.

Angulation Angulation is described in terms of two parameters: degree and direction (**Figure 267-5**). Quantifying the angulation is relatively simple. One need only estimate the amount of "unbending" (expressed in degrees) that would be needed to make the fragments parallel.

Conveying the direction of angulation may be more difficult because the terminology is less consistent among clinicians. In general, when a fracture is near the midshaft of a long bone, the direction of angulation is the direction of the apex of the angle formed by the two fragments. Figures 267-5A and 267-5B illustrate 30 degrees of dorsal angulation. When a fracture is near the end of a bone, however, angulation is described in terms of the direction the terminal fragment is deviated. Thus Figure 267-5C also shows 30 degrees of dorsal angulation, even though the apex of the angle formed by the fragments is pointing in the opposite direction from that in the preceding figures. **If there is a possibility of ambiguity in the description, specifying the *direction of deviation of the distal fragment* usually can resolve it.**

Depending on the anatomic area involved, direction of angulation may be expressed as anterior or posterior, lateral or medial, radial or ulnar, or dorsal or volar.

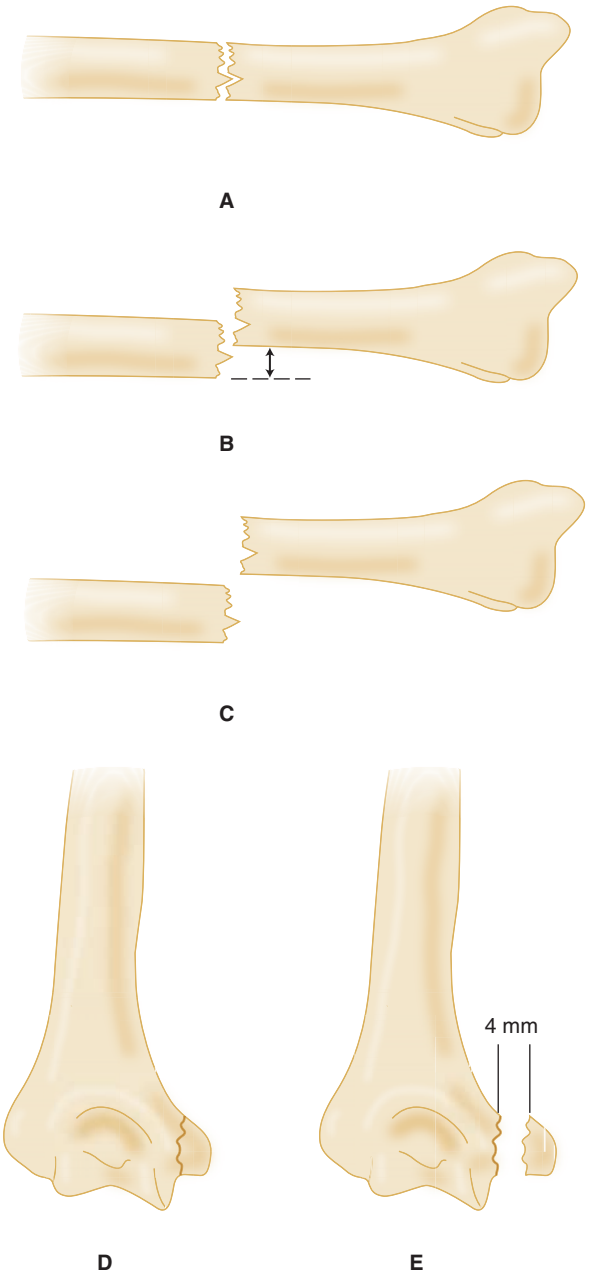

FIGURE 267-3. Fracture displacement and separation. **A.** No displacement, slight separation. **B.** Fifty percent dorsal displacement. **C.** Complete dorsal displacement. **D.** Nondisplaced, no separation. **E.** A 4-mm separation.

Rotational Deformity Rotational deformity—that is, the extent to which the distal fracture fragment is twisted on its own axis relative to the proximal fragment—is generally not apparent on radiographs. This element of fracture description depends on physical examination. Its detection is particularly important in the phalanges of the fingers, where, if rotational deformity goes unrecognized and uncorrected, the injured finger will permanently be malaligned when the hand is closed.

Fracture Combined With Dislocation or Subluxation Injuries near a joint may involve dislocation or subluxation combined with a proximate fracture. An example is fracture of one or more ankle malleoli, together with partial or complete displacement of the talus from beneath the tibia. These are significant injuries, often requiring surgical intervention. If, in describing the injury, the clinician emphasizes the fracture component but expresses the dislocation or subluxation as mere "displacement," then the full severity may not be appreciated by the orthopedist. Such injuries should be described as fracture-dislocations or fracture-subluxations.

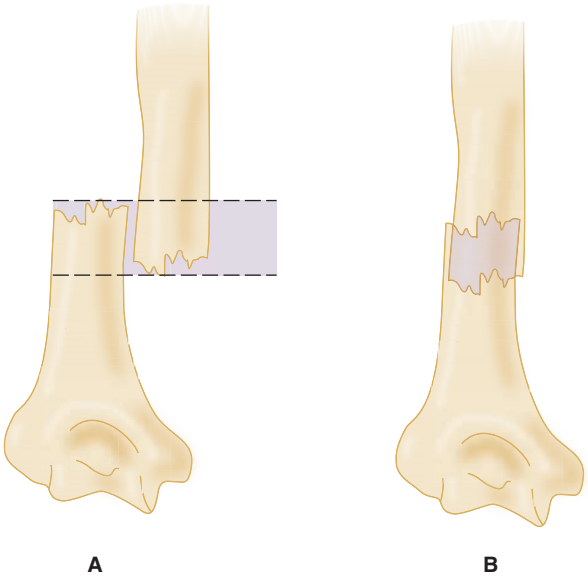

FIGURE 267-4. Shortening at fracture site. **A.** Complete displacement with overriding. **B.** Impaction. In both cases, the width of the shaded area represents the amount of shortening.

Salter-Harris Fractures Salter and Harris classified fractures involving the epiphyseal plate at the end of the long bone of a growing child into five types based on the pattern of the fracture line. Because the type generally correlates with the potential for future growth disturbance (and, consequently, with the aggressiveness of the treatment warranted), the ability to identify the fracture type based on its radiographic appearance is important.

Perhaps the easiest way to remember the Salter-Harris classification system is to think of these injuries not in terms of where the fracture line runs, but in terms of what has been *broken off*. Figure 267-6 illustrates the anatomy involved. **Table 267-3** lists the five types of Salter-Harris fractures, which are illustrated in **Figure 267-7**. The potential for growth disturbance is least for type I and increases with the classification number, with the worst prognosis being associated with type V injuries.

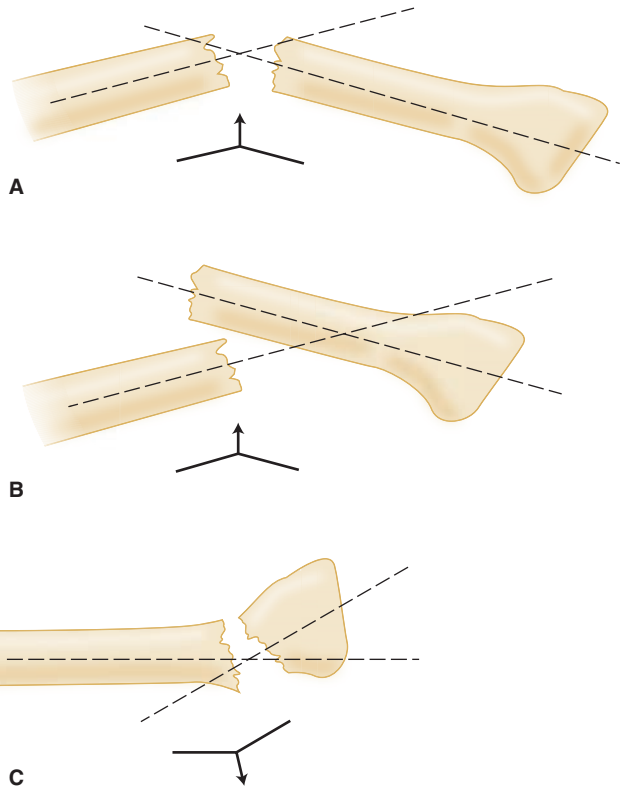

FIGURE 267-5. Fracture angulation. All figures depict 30-degree dorsal angulation. **A, B.** Direction is based on the apex of the angle drawn below the figures. **C.** Direction is based on the direction of the terminal fragment.

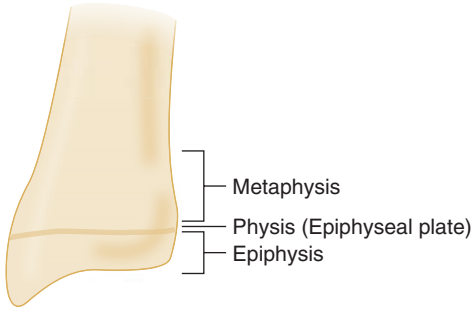

FIGURE 267-6. Epiphyseal anatomy in the growing child.

Type I and type V Salter fractures may be radiographically undetectable. Type I injuries usually involve no transverse displacement and little or no separation of the epiphysis from the rest of the bone. Also, the lucent fracture line is not visible within the equally lucent epiphyseal plate. Diagnosis of acute Salter type I fractures is usually presumptive, based on the presence of swelling and tenderness in the region of the physis.

Type V injuries may be evident only retrospectively, when growth disturbance first begins to appear. At the time of initial presentation, however, a history of a significant axial loading force, coupled with significant tenderness in the area of the epiphyseal plate, should suggest the possibility of a type V injury. Such injuries should be immobilized and referred for orthopedic follow-up.

TREATMENT

CONTROL PAIN AND SWELLING

Initiate measures to reduce swelling early. Severe swelling not only intensifies the pain of injury but also may delay the application of a definitive immobilization dressing and may make the skin more susceptible to skin blisters and pressure sores. Although sometimes regarded as trivial modalities, the application of cold and elevation are often quite effective in keeping swelling to a minimum or at least halting its progression. Jewelry, watches, or rings that may cause compression or constriction as an extremity swells should be removed immediately and prior to imaging.

Administer analgesics as necessary. Underuse of analgesics after orthopedic injuries has been a well-documented occurrence in the ED. If the patient is relatively comfortable at rest, medication may not be required. **Even opiate analgesics may have minimal effect on the pain of movement or manipulation unless combined with other CNS-acting agents.** Consider alternative pain control methods, such as local injection, hematoma blocks, and regional blocks, which have been shown to provide adequate analgesia and help to reduce patient discomfort and need for procedural sedation and recovery time.[18-20]

WITHHOLD ORAL INTAKE

Any patient who might be a candidate for prompt surgical fixation, manipulation, or any other procedure under general anesthesia or procedural sedation should not be allowed to eat or drink from the moment

TABLE 267-3 Description of Salter-Harris Fractures

Salter Type	What Is Broken Off
I	The entire epiphysis
II	The entire epiphysis *along with* a portion of the metaphysis
III	A portion of the epiphysis
IV	A portion of the epiphysis *along with* a portion of the metaphysis
V	Compression injury of the epiphyseal plate (nothing is "broken off")

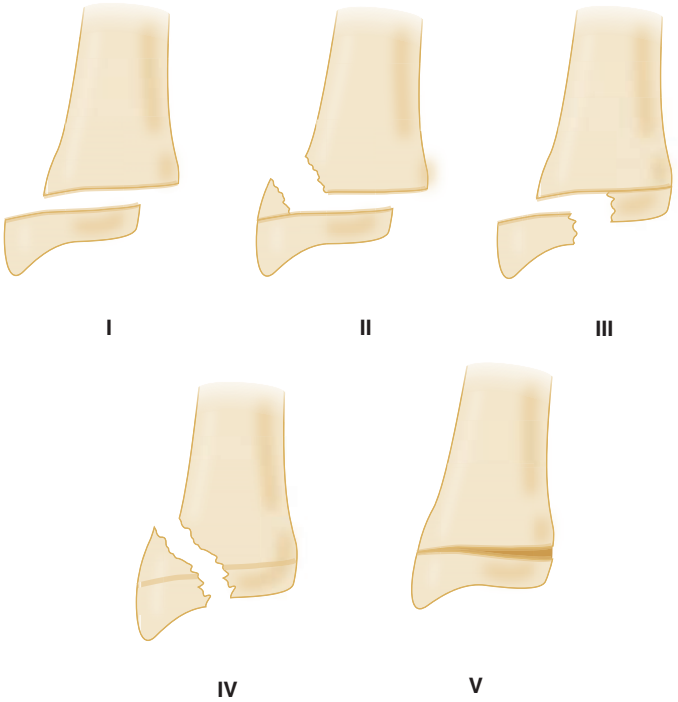

FIGURE 267-7. Epiphyseal plate fractures based on the classification of Salter and Harris.

of arrival until the need for, and timing of, such a procedure has been ascertained.

REDUCE FRACTURE DEFORMITY

The long-term purpose of reducing significant deformity associated with fractures is restoration of normal appearance and function of the extremity. However, there are also short-term benefits to reducing deformity early: (1) alleviating pain, (2) relieving the tension on nerves or vessels that may be stretched as they pass along the deformity, (3) eliminating or significantly minimizing the possibility of inadvertently converting a closed fracture to an open one when the skin is tented by a sharp bony fragment, and (4) restoring circulation to a pulseless distal extremity.

After the patient has been appropriately sedated, deformity at or near the midshaft of a long bone is usually reduced with gradual, steady, longitudinal traction. Any rotational deformity should be corrected only after the angular component has been addressed and should be performed while traction is maintained.

The nearer a deformity is to a joint, the more difficult it may be to correct and the more specialized the reduction maneuver may have to be. **When deformity is associated with circulatory deficit, a true emergency exists, and the anticipated delay until reduction should be considered.**

REDUCE DISLOCATIONS

The techniques used to reduce specific dislocations are discussed in subsequent chapters. In general, prereduction radiographs are advisable when there has been significant trauma, unless time is crucial because circulation is threatened. Radiographs are needed because dislocations and fracture-dislocations may have a similar appearance on physical examination, but the techniques used to treat them may be very different.

Of course, there are circumstances in which the potential benefits of a prereduction radiograph may be outweighed by the associated expenditure of time and money. For example, a prereduction radiograph may be omitted in a patient with a history of multiple recurrent dislocations of the shoulder who presents with history, signs, and symptoms typical of another recurrence in the absence of significant trauma.

After a reduction maneuver, postreduction radiographs are valuable for confirming the success of the procedure, as well as for providing documentation in the event that the joint redislocates after the patient is discharged from the ED.

INITIAL MANAGEMENT OF OPEN FRACTURES

Open fractures warrant prompt and meticulous attention. The most important elements in the treatment of open fractures, aside from tetanus prophylaxis that applies generally to any wound, are irrigation, debridement, and antibiotics as soon as is practical.[21]

Early administration of antibiotics can prevent or reduce the clinical consequences of bacterial contamination in open fractures.[22,23] Consequently, initiate antibiotic therapy promptly in the ED. There is no standard antibiotic regimen. An accepted approach, but by no means the only regimen in use, is a first-generation cephalosporin, with the addition of an aminoglycoside when the wound is >10 cm with severe soft tissue injury and loss of bone coverage.[24,25] Some studies advocate the use of ciprofloxacin as an alternative to a cephalosporin.[26] When there is significant contamination by plants or soil, consider the addition of penicillin (or metronidazole, clindamycin, or vancomycin for penicillin-allergic patients) for anaerobic coverage. Aerobic and anaerobic wound cultures may be obtained before antibiotics are administered, although the value of pretreatment cultures for open fractures is controversial.[27]

To lower the infection rate, not only antibiotics but also generous irrigation and adequate debridement are necessary to reduce bacterial contamination and colonization.[28] The purposes of debridement and irrigation are (1) to expose the wound in order to allow better identification of the limits of injury and facilitate inspection for foreign material; (2) to identify and remove clots, debris, and nonviable tissue; and (3) to reduce bacterial contamination and make the wound more resistant to the effects of any residual contamination. (See Chapter 40, "Wound Preparation," for complete discussion of wound irrigation.)

Debridement and irrigation of minor wounds overlying a fracture sometimes may be performed in the ED. When tissue damage is moderate or severe, debridement and irrigation are typically performed in the operating room.

ORTHOPEDIC CONSULTATION IN THE ED

In many cases, such as fracture of the hip, the need for hospital admission and/or orthopedic consultation in the ED is obvious. In some situations, however, differences of opinion may exist regarding whether the patient needs to be seen by an orthopedist in the ED or whether the patient may be treated in preliminary fashion and referred for definitive orthopedic management. Even patients with injuries that ultimately may require surgical repair, such as an unstable ankle fracture, sometimes may be immobilized and discharged with a referral for prompt orthopedic follow-up.

COMPARTMENT SYNDROME

In cases of known or suspected compartment syndrome, obtain prompt orthopedic consultation. Emergency surgical intervention may be required to try to avert permanent tissue damage and muscle contracture. The physiology and potentially catastrophic consequences of compartment syndrome are described in the section "Complications" later in this chapter and in Chapter 278, "Compartment Syndromes."

IRREDUCIBLE DISLOCATION

The emergency physician sometimes may be unable to reduce a dislocation, even with the aid of a nerve block or procedural sedation. Although technique is certainly a factor, there may be other reasons closed reduction cannot be accomplished, such as the interposition of soft tissues within the joint or the presence of an associated fracture. Orthopedic consultation should be sought in such cases. Timely reduction, which sometimes can be achieved only surgically, may help minimize the complications (and shorten the duration of pain) resulting from a dislocated joint.

CIRCULATORY COMPROMISE

Circulatory deficit due to musculoskeletal injury warrants prompt orthopedic consultation. Even if circulation has been restored by the emergency physician through the correction of deformity, the orthopedist may wish to investigate the integrity of the involved vessels and should at least be contacted to discuss the case.

OPEN FRACTURE

Some open fractures need to be treated aggressively in the operating room. Other types, such as those involving the phalanges, often may be irrigated in the ED and referred for follow-up. If there is any question, a discussion with the orthopedist may result in a mutually agreeable plan of care.

INJURIES REQUIRING SURGICAL INTERVENTION

Whereas some musculoskeletal injuries require operative intervention as soon as possible, others may be treated on a delayed basis. In many cases, orthopedists differ in their preferred approach to the timing of surgery. Orthopedic consultation, at least by telephone, is indicated in cases of musculoskeletal injury that the emergency physician believes may require operative fixation or repair. The orthopedist may then exercise the option to admit the patient or to see the patient in timely follow-up and schedule any necessary surgery at that time.

SPLINTING MATERIALS AND TECHNIQUES

Immobilization is indicated not only for fractures but also for dislocated joints that have been reduced. When a joint becomes dislocated, the ligaments that had provided its stability are disrupted, and the joint is susceptible to redislocation until healing has occurred.

The materials most commonly used for orthopedic immobilization are plaster of Paris (calcium sulfate) and fiberglass fabric combined with a polyurethane resin. Fiberglass has the advantages of being lightweight, fast setting, and resistant to damage by moisture. However, it is not as malleable as plaster, so it might not conform as well to the contour of the limb. This may be an issue when the purpose of the dressing is not only to provide immobilization but also to maintain the position of the fragments once a displaced fracture has been reduced.

Whether plaster or fiberglass is used for immobilization depends on a number of factors, including the emergency physician's preference, the philosophy of the orthopedic community, the needs of the patient, and the hospital's resources.

PRINCIPLES OF SPLINTING

The chemical reactions that cause plaster or fiberglass to set are initiated by contact with water. The higher the water temperature, the faster the materials harden. However, these reactions are exothermic, meaning they liberate heat. The faster the setting process, the more heat is generated. Therefore, the temperature to which the skin ultimately is exposed will be the additive result of the water temperature and the heat released by the chemical reaction. For this reason, severe burns may occur when plaster or fiberglass has been immersed in mildly hot water, even though the temperature of the water itself would not be sufficient to cause such burns. Although there is no universally prescribed ideal water temperature, a safe practice is to make the water room temperature. If steam is visible, the water is certainly too hot.

To avoid irritation and to minimize the potential for pressure sores, plaster or fiberglass dressings should include several layers of padding over the skin. When non-prepadded longitudinal plaster splints are used, cast padding has to be applied separately. The padding does not necessarily have to be circumferential. Several layers of longitudinal padding will effectively protect the skin as long as they exceed the width and length of the splinting material. The best way to ensure this is to fashion the dry splint first, then measure the padding over it. Longitudinal splints may be fashioned from fixed-length plaster strips, from plaster rolls normally used to create circumferential casts, or from prepadded material with plaster or fiberglass enclosed. The splint should be long enough to provide the leverage needed to immobilize the injured joint. To immobilize the elbow, for example, a splint should begin distal to the wrist and extend high up the lateral arm, almost to the level of the humeral neck. To immobilize the ankle effectively, a splint should extend from beneath the metatarsal heads to the proximal calf. If the fracture is along the midportion of a distal extremity (i.e., the forearm or the lower leg) rather than at a joint, the splint should be long enough to immobilize the joint above and the joint below the fracture.

NON-PREPADDED PLASTER

When a splint is fashioned from plaster rolls, determine the length of the splint by measuring out a single layer along the extremity according to the principles described previously. Then, on a flat surface, unroll the plaster back and forth over itself to make a multilayered splint. If fixed-length plaster strips are used instead of rolls, the only way their length can be customized is to shorten them, so an adequate length should be selected at the outset and trimmed as necessary. In either case, the splint should be at least 12 layers thick for an adult. Even more layers should be used for children, who typically remain as active as possible and have little regard for protecting the dressing.

When the dry splint has been prepared, measure out several layers of padding over it, making the padding longer and wider than the plaster. After setting the padding aside, grip each end of the splint and immerse it in water, keeping it submerged until bubbling stops (indicating that water has been fully absorbed into the interstices of the material). Then withdraw the splint and remove the excess water by sliding the compressed thumb and index finger along the length of the plaster on each edge. (Use a stripping motion, rather than crumpling or wringing out the dressing, or much of the plaster may be lost.)

The next step, frequently overlooked, is to lay the splint on a flat surface and massage the layers into one another so that they fuse together. This creates a strong dressing that is solid on cross-section. A splint whose separate layers are still visible on cross-section is much weaker.

The padding should now be laid on the plaster and the dressing applied to the extremity, with the padded surface against the skin. When two plaster segments are used, as for a thumb spica or a posterior ankle mold with an additional transverse "sugar-tong" component, no padding should be interposed between the segments. Rather, they should be molded into each other where they overlap. An assistant can hold the splint against the extremity while it is wrapped in place with gauze bandage. The assistant should use the palms, rather than the fingertips, when holding the splint in place. Hardened finger dents may cause irritation or even pressure sores. When a compressive effect is desired, an elastic bandage may be wrapped over the gauze. (If an elastic bandage is wrapped directly onto plaster without an interposed layer of gauze, it will set into the plaster and may lose most of its compressive function.)

While the plaster is setting, the affected joint may need to be held in a particular position. Again, use the palms, rather than the fingers, for reasons already described. Once the setting process is well under way, the position of a joint should not be changed, or the dressing may crack and become functionally useless. If the joint has gradually migrated from the desired position, the clinician must decide to accept the current position or remove the dressing and start over. There is no need to feel hesitant about the latter course. Patients generally appreciate a desire for perfection by their clinician.

PREPADDED MATERIAL

Some plaster or fiberglass splinting products are manufactured with the immobilization material already enclosed in padding, either as strips of predetermined length or as rolls from which splints may be cut to the desired length. Precut strips come packaged in airtight foil. When a roll is used, the cut end is sealed with a tight clip to protect the exposed material. (Even when not immersed in water, fiberglass may set within 10 to 15 minutes, simply from exposure to moisture in the air.)

Prepadded material is fast and convenient to use because the layers are already in place and the padding need not be applied separately. However, the potential disadvantages are that the thickness of the dressing cannot be customized, and the material does not lend itself to

TABLE 267-4 Immobilization Devices and Uses

Immobilization Technique	Clinical Application
Shoulder immobilizer	Clavicle fracture Acromioclavicular separation Shoulder dislocation (postreduction) Humeral neck fracture
Sling	A variety of upper extremity injuries, in conjunction with other immobilization techniques; may be used alone for nondisplaced or clinically suspected fracture of the radial head
Long-arm gutter	Elbow fracture other than nondisplaced radial head fracture Reduced elbow dislocation
Sugar-tong	Wrist or forearm fracture
Short-arm gutter	Metacarpal or proximal phalanx fracture (ulnar gutter for fourth or fifth ray; radial gutter for second [index] or third [middle] ray)
Thumb spica	Scaphoid fracture (proven or suspected) Thumb metacarpal or proximal thumb phalanx fracture
Knee immobilizer	Fracture or reduced subluxation of patella Knee dislocation, postreduction (temporary) Tibial plateau fracture Knee ligament injury Suspected meniscal tear (provided the knee can be fully extended)
Posterior ankle mold (consider above-the-knee extension and/or adjunctive use of ankle sugar-tong for unstable ankle injuries)	Ankle dislocation or fracture-dislocation Unstable ankle fracture (high distal fibular fracture or medial and/or posterior malleolar fracture) Widened medial mortise (indicates disruption of stabilizing medial structures) Metatarsal fracture (alternative immobilization dressings may be used)
Ankle stirrup	Simple ankle sprain Stable lateral malleolus fracture (below the superior border of the talus) without other ankle involvement (no medial swelling or tenderness, posterior malleolus intact)
Hard-soled shoe	Toe fracture Some metatarsal fractures (see the section "Hard-Soled Shoe" later in this chapter)
Short-leg walking boot	Some toe or foot contusions or fractures where weight bearing is allowed[29]

applying two overlapping segments, because they cannot be molded into each other to create a sturdy dressing. If these issues are not a consideration, then prepadded material is a reasonable choice.

TYPES OF IMMOBILIZATION DRESSINGS

The more common immobilization dressings used in the ED are discussed next and are summarized in **Table 267-4**.[29]

Shoulder Immobilizer This is a removable Velcro®-fastened device that keeps the arm in "sling position" but allows less mobility than a sling (**Figure 267-8**). A wide band wraps around the thorax. Two cuffs are attached to the thoracic piece: one on the lateral side, which grasps the upper arm, keeping the shoulder adducted, and one anteriorly, which holds the wrist to the chest, keeping the shoulder internally rotated. This dressing is suitable for fractures about the shoulder girdle, including clavicle and well-positioned humeral neck fractures, and for reduced shoulder dislocations.

A shoulder immobilizer is also commonly used for acromioclavicular separations, although from a mechanical standpoint, the ideal dressing for this injury is one that exerts upward pressure on the elbow and downward pressure on the clavicle to bring the clavicle and acromion back into alignment. Commercial versions of such dressings exist, but they are cumbersome to apply and uncomfortable to wear, leading to noncompliance. A shoulder immobilizer (or sling and swathe) is an acceptable alternative dressing.

Arm Sling Although it does not provide rigid immobilization, a sling (**Figure 267-9**) may be used as an adjunct to other splinting techniques for a variety of upper extremity injuries to enhance comfort, reduce motion, and provide some degree of support and elevation to the upper extremity. In some cases, as for nondisplaced fracture of the radial head, it may be used alone, without the need for supplementary immobilization.

Clavicle Strap (Figure-of-Eight Bandage) The figure-of-eight clavicle strap is mentioned only as a historical note. This dressing had long been considered the appropriate immobilization method for fracture of the clavicle, but in fact it is fairly ineffective at maintaining alignment of the fracture fragments and produces no difference in clinical outcome compared with a simple sling.[30] In addition, the clavicle strap may be awkward to apply, may require frequent readjustment, may cause problems related to pressure on the brachial plexus, and is often uncomfortable for the patient. A shoulder immobilizer or sling is a much better choice.



FIGURE 267-8. Shoulder immobilizer.



FIGURE 267-9. Arm sling.

Long-Arm Gutter Splint A long-arm gutter splint immobilizes the elbow (**Figure 267-10**). The upper extremity is placed in "sling position" (elbow flexed about 90 degrees and palm facing the abdomen). The splint begins on the ulnar surface of the hand at the metacarpal heads and extends along the ulnar surface of the forearm, past the elbow, to a spot high on the lateral surface of the upper arm just opposite and below the axillary crease. It should be supplemented with a sling.

The most common error associated with fashioning this dressing is insufficient length. If the splint is not carried far enough above the elbow, it will not exert enough leverage to prevent motion of that joint.

The long-arm gutter is useful for injuries about the elbow, including displaced radial head fracture, supracondylar humeral fracture, and reduced dislocation of the elbow.

Sugar-Tong Splint The sugar-tong is a splint that prevents motion of the wrist and elbow, including pronation-supination (**Figure 267-11**). The upper extremity is placed in "sling position," as described in the preceding section "Long-Arm Gutter Splint." The splint begins on the extensor aspect of the hand at the level of the metacarpal heads and runs along the extensor aspect of the forearm, around the elbow and humeral condyles, onto the flexor aspect of the forearm, and ultimately to the palmar aspect of the hand, ending at the level of the metacarpal heads. It is wrapped in place with gauze and often topped off with an elastic compression bandage. It should be supplemented with a sling.

Proper length of the sugar-tong dressing is important. Too short a splint will fail to immobilize the wrist. If the dressing is too long, it will impair motion of the metacarpophalangeal joints, leaving them stiff and making the fingers more susceptible to swelling due to immobility.



FIGURE 267-11. Sugar-tong splint.

The sugar-tong splint is appropriate for fractures about the wrist or distal forearm. Some orthopedists use it as a definitive dressing after reduction of wrist fractures.

Cock-Up Wrist Splint (to Be Avoided) A cock-up splint extends from the distal forearm to the proximal portion of the hand and maintains the wrist in a dorsiflexed position. **It should not be used for fractures of the wrist or carpals** because injuries to those areas usually are caused by forceful dorsiflexion, and a cock-up splint reproduces the position of injury, imposing considerable pain in the process. Generally, fractures about the wrist are immobilized in neutral position. Colles' fractures may sometimes be immobilized in palmar flexion after reduction.

Cock-up splints may be useful in some situations not related to trauma, such as to immobilize the wrist for tendinitis or to support it in the case of wrist drop due to radial nerve palsy. In such instances, passive dorsiflexion of the wrist is indicated to preserve grip strength.

Short-Arm Gutter Splint A short-arm gutter splint immobilizes the wrist and the ulnar or radial half of the hand (**Figure 267-12**). The ulnar



FIGURE 267-10. Long-arm gutter splint.



FIGURE 267-12. Short-arm ulnar gutter splint.

gutter, for example, extends along the ulnar surface of the hand and forearm, beginning just proximal to the tip of the fifth finger and ending high on the forearm. It should be wide enough to encompass the fourth and fifth rays (phalanges and metacarpals) on the extensor and flexor aspects of the hand. The splint is wrapped in place so that the fourth and fifth fingers are bound together, with a thin layer of padding between them to prevent maceration of the skin. The metacarpophalangeal joints and interphalangeal joints are positioned in gentle flexion. The dressing may be supplemented with a sling.

The short-arm ulnar gutter is useful for fracture of the proximal phalanx of the ring or little finger or for fracture of the fourth or fifth metacarpal (including the common "boxer's fracture"). The counterpart of this splint, the short-arm radial gutter, is designed in similar fashion but extends along the radial surface of the hand and forearm and is used for comparable injuries of the index or middle rays. It can be fashioned with a hole that allows the thumb to pass through, or by splitting the distal end so the two halves can be run along the extensor and volar aspects of the index and middle rays while the thumb remains free.

Thumb Spica Splint A thumb spica immobilizes the wrist and the thumb (**Figure 267-13**). The term *spica* applies to any dressing that encompasses a main trunk plus one or more of its branches—in this case, the forearm plus the thumb. It is used for fracture of the scaphoid or for fracture of the thumb metacarpal or proximal phalanx.

A thumb spica may be fashioned from one wide splint that runs along the thumb and radial aspect of the wrist and forearm, but an even more effective dressing can be made from two separate non-prepadded plaster splints. The wrist piece runs along the extensor aspect of the hand and forearm, beginning at the metacarpal heads and ending just short of the antecubital crease. The narrower thumb piece, approximately 2 inches wide, extends from the tip of the thumb, along the outer aspect of the thumb metacarpal, and onto the extensor aspect of the forearm, well overlapping the first splint. Along their area of contact, the two splints are molded into each other, with no padding between them, to form a sturdy dressing. The plaster is wrapped in place with gauze, and a compression wrap may be added at the clinician's discretion. The dressing may be supplemented with a sling.

This technique is not suitable for prepadded splints with plaster or fiberglass already enclosed, as the two pieces cannot be molded into one another, which compromises the structural integrity of the dressing. When prepadded material is used, a single wide splint encompassing the thumb must suffice.

While the dressing is setting, optimal position may be achieved by keeping the wrist in neutral position and having the patient oppose the tips of the thumb and index finger in the form of an "OK" sign. This preserves thumb-to-index pinch function, so as to minimize the patient's incapacitation. The neutral position of the wrist also avoids reproducing the position of injury in the case of scaphoid fracture, which is typically caused by forced dorsiflexion.

Knee Immobilizer The knee immobilizer is a removable circumferential device that extends from the thigh to just above the ankle (**Figure 267-14**).



FIGURE 267-13. Thumb spica splint.



FIGURE 267-14. Knee immobilizer.

The splint contains longitudinal struts that, in some cases, may be repositioned as needed, and is secured with Velcro® straps.

A knee immobilizer maintains the knee in extension, the position of maximum stability. The device is useful for a variety of injuries, including fracture of the lateral or medial tibial plateau, fracture of the patella, meniscal injuries (provided the knee is not locked in partial flexion), and ligamentous strains or tears.

Use of an immobilizer for more than a few days in the elderly or for more than a week or two in young patients may result in painful stiffness of the knee joint. For that reason, orthopedic follow-up should occur within approximately 7 days. If immobilization is indicated beyond that point, the orthopedist may replace the original device with a cast brace or other orthosis that allows controlled and progressive range of motion.

Motion and Strength Exercises for the Knee Joint stiffness and instability due to quadriceps weakness may occur rapidly when the knee is immobilized. **Patients wearing an immobilizer should be encouraged to remove the device periodically and perform the following exercises:**

1. Passive flexion: While sitting on a flat surface, grasp the ends of a towel draped beneath the sole of the foot and pull upward, creating as much knee flexion as possible without undue pain.
2. "Gravity-assisted" flexion: While sitting on the edge of a bed or chair, support the knee in extension, with the well foot beneath the ankle of the injured extremity, then gradually lower the supporting foot so the injured knee "drops" into flexion. When tolerance is reached, bring the knee back into extension.
3. Quadriceps strengthening: While lying supine with a pillow beneath the knee, actively bring the knee to full extension in a straight leg raise, then relax.

Each of these exercises should be performed as multiple repetitions several times a day.

Posterior Ankle Mold The posterior ankle mold is used to immobilize the ankle (**Figure 267-15**). It begins beneath the metatarsal heads, runs along the plantar aspect of the foot, and continues up the back of the lower leg, ending at high calf. The splint is used for fractures or severe



FIGURE 267-15. Posterior ankle mold.

sprains of the ankle. Support may be supplemented by a transverse sugar-tong component running down the lateral side of the lower leg, beneath the heel, and up the medial side. Where the two components overlap, they are molded together. (Non-prepadded plaster should be used in this situation.) The transverse component helps minimize inversion and eversion of the ankle. Even more stability is provided by continuing the posterior splint past the back of the knee to the high posterior thigh, using wider splinting material for this area. With the knee slightly flexed, rotational motion at the ankle also will be prevented.

While the dressing is setting, the ankle should be maintained in a position as close as possible to neutral dorsiflexion—that is, at 90 degrees to the leg. This may facilitate regaining range of motion after the dressing is removed. Because most patients with ankle injuries tend to keep the ankle plantar flexed, the clinician usually will have to counteract this by exerting gentle pressure with a palm beneath the metatarsal heads. An exception to the 90-degree principle is immobilization for rupture of the Achilles tendon. Patients with this injury should be immobilized in plantar flexion to reduce tension on the tendon.

Ankle Stirrup The ankle stirrup (**Figures 267-16A** and **B**), used for ankle sprains and minor lateral malleolus fractures, is easy to apply and is less cumbersome for the patient than a posterior ankle mold. The ankle stirrup is essentially an air-padded "sugar-tong" splint held in place by Velcro® straps. Unlike the posterior mold, this device is intended for use in conjunction with weight bearing. It limits inversion more effectively than taping but allows normal plantarflexion and dorsiflexion. This feature and the graduated compressive effect of the air-filled bladders may result in less swelling and edema, less joint stiffness, and a faster return to comfortable ambulation than is typically observed after rigid immobilization.[31]

The stirrup may be removed for purposes of bathing or when not bearing weight. If the patient does remove the splint temporarily, a common error when reapplying it is failing to unwrap the straps completely—specifically, to leave the straps attached posteriorly, so that the splint is "hinged like a book" along its posterior aspect. This may result in the foot persistently slipping forward and out of the splint. The clinician may wish to instruct the patient that the proper way to reapply the splint is to unwrap the straps all the way around, so that the sides fall apart bilaterally, with the heel pad acting as the "hinge" on the plantar aspect (**Figure 267-17**). The foot may then be positioned on the lower pad, and the sides reapplied to the medial and lateral aspects of the ankle and lower leg. The final step is to rewrap the straps around the dressing.



A



B

FIGURE 267-16. A and B. Ankle stirrup.



FIGURE 267-17. Technique for applying ankle stirrup.

Motion and Strength Exercises for the Ankle Exercises to restore range of motion, stability, and balance should be started as soon as possible after an ankle injury.

1. Active dorsiflexion and plantarflexion: When performed supine with the foot well elevated, this exercise may also enhance lymphatic drainage, thereby reducing swelling.
2. Passive dorsiflexion: One method for performing this exercise is to stand with the palms braced against the wall, then to bend the knee toward the wall while keeping the heel flat on the floor.
3. Eversion, dorsiflexion, and plantarflexion against resistance: This exercise may be accomplished by manually applying a counterforce with a stretchable elastic cord (commercially available). Standing on the toes is another means of resistive plantarflexion.

Each of these exercises should be performed as multiple repetitions several times a day.

Hard-Soled Shoe A hard-soled shoe is a removable "sandal" with wraparound sides usually secured with Velcro® and a flat, nonflexible sole (**Figures 267-18A** and **267-18B**). This device is intended to allow weight bearing by patients with toe fractures or certain types of metatarsal fractures. The firm sole prevents the toes from bending and provides support for the forefoot. Although immobilization dressings may be warranted for some metatarsal fractures, the hard-soled shoe is an accepted treatment modality for fracture of the second, third, fourth, or proximal fifth metatarsal.[32,33]

Pneumatic Walking Brace The pneumatic walking brace is a device that provides firm support about the foot, ankle, and lower leg. It is available in high-top or short-top varieties. The high-top walker (**Figure 267-18C**), which extends almost to the knee, is suitable for injuries such as moderate to severe ankle sprains or for stable fractures of the foot or ankle. Short-top walkers extend just above the ankle joint and may be used for phalangeal or stable metatarsal fractures.

The term *pneumatic* refers to the fact that the inner lining of the brace is inflatable. Although nonpneumatic models are available, the pneumatic component has at least two advantages. It provides added compression, which helps reduce swelling and pain, and allows the walker to conform more closely to the contour of the extremity, which enhances immobilization.



A



B



C

FIGURE 267-18. **A and B.** Hard-soled shoe. **C.** Pneumatic walking brace.

ADJUNCTS TO AMBULATION

CRUTCHES

Crutches should be used by patients who can bear little or no weight on an injured lower extremity. There are two types of crutches in common

use, the underarm or axillary crutch, or the forearm crutch. Axillary crutches are typically provided for short-term use. Ideal axillary crutch height is one hand width below the axilla. The grip bar should be adjusted to a height at which the elbows are mildly flexed while supporting the body weight. The patient should be instructed to bear the pressure of the pads against the sides of the thorax rather than in the axillae, or brachial plexus injury (crutch palsy) might result.

Any of several crutch gaits may be prescribed. The most common is the three-point gait, in which the patient keeps the injured extremity off the ground, advances both crutches simultaneously, then brings the well leg to a point between the crutches ("swing-to" gait) or just past them ("swing-through" gait). Alternatively, the patient may use a two-point gait, in which one crutch and the opposite extremity are advanced together followed by the other crutch and extremity, or a four-point gait, in which one crutch is advanced, then the opposite extremity, then the other crutch, then the remaining extremity. The two- and four-point gaits are slower in forward progression than the three-point gait but require less arm and wrist strength. They should be used only for patients who are able to bear some weight on the injured extremity. To ascend stairs, the patient advances the well extremity up to the next step, followed by the crutches and the injured extremity. To descend stairs, the crutches are lowered first.

WALKERS AND CANES

Most elderly or infirm patients do not have the strength needed to use crutches safely. For them, a walker or a cane is more suitable. Unfortunately, these devices are more appropriate for partial weight-bearing than for non–weight-bearing conditions. Elderly patients who can bear no weight at all on an injured extremity may require initial bedrest or use of a wheelchair and subsequent rehabilitation.

The technique for using a walker is essentially intuitive, with the patient simply lifting it and placing it a short distance ahead and then advancing toward it. In contrast, the technique for using a cane tends to be counterintuitive. Many patients instinctively hold a cane on the same side as the injured extremity. In fact, when the cane is held in the hand on the well side, less strength is required to maintain balance, resulting in a less awkward gait. The patient should be instructed to advance the cane (held on the well side) and the injured extremity simultaneously, and then advance the noninjured extremity to meet them.

DISCHARGE INSTRUCTIONS

Elevation of the injured part usually helps minimize pain and swelling. Elevation must be above the level of the heart to be effective. Patients with an injured lower extremity often sit at home or at work with the foot resting on a stool or chair, thinking they are complying with instructions. The patient should understand that the benefits of elevating a lower extremity can be achieved only in a recumbent or near-recumbent position, with the leg supported higher than the rest of the body.

Patients discharged in a lower extremity plaster dressing should be cautioned not to rest the heel on the floor or any other hard surface during the first day, as plaster takes about 24 hours to fully set. During this time, prolonged pressure on the heel might create an indentation that could cause significant discomfort or even a pressure sore. This is not a consideration with fiberglass, which sets almost immediately.

If an upper extremity sugar-tong dressing has been applied, the patient should be instructed to work the fingers (wiggle or wave) as much as possible to minimize stiffness and swelling. The sugar-tong splint should extend to, but not beyond, the metacarpal heads, so as to allow full flexion of the metacarpophalangeal joints.

Patients should be advised to monitor the fingers or toes for excessive swelling, decreased sensation, or cyanosis and to be alert for a significant increase in pain. Any of these signs or symptoms warrants a return to the ED or prompt evaluation by the follow-up physician.

When crutches, a cane, or a walker is supplied, instruction for use should be provided, and the patient's ability to navigate with such aids should be verified.

TABLE 267-5 Vascular Loss Related to Injury Site

Fracture Location	Expected Blood Loss
Radius and ulna	150–250 mL
Humerus	250 mL
Tibia and fibula	500 mL
Femur	1000 mL
Pelvis	1500–3000 mL

COMPLICATIONS

Complications associated with musculoskeletal injury may be early or delayed and may occur minutes, days, weeks, or even months later.

HEMORRHAGE

The skeleton has a rich vascular supply so a fracture can have the potential for large blood loss, shock, and even exsanguination causing death. Pelvic fractures can cause large vascular compromise from an inability to obtain adequate tamponade. In the adult population, blood loss can vary from 100 mL to 3 L depending on the injury location (**Table 267-5**). Ongoing hemorrhage, as associated with pelvic fractures, can also lead to disseminated intravascular coagulation.

NEUROLOGIC DEFICIT

Neurologic injury resulting from long-bone fracture or joint dislocation is usually due to traction or pressure on a peripheral nerve or a nerve plexus. Such complications usually manifest themselves early. Recovery may take hours, days, or weeks. Sometimes, the injury is irreversible. Neurapraxia is a simple contusion of the nerve, and normal function is usually expected to return in weeks to months. Axonotmesis is a severe crush injury to the nerve that may also heal, but over time. Neurotmesis is a severed nerve and requires surgical repair. Certain nerve injuries accompany particular fractures (**Table 267-6**). Perform a thorough examination, including sensory and motor function. If there is neurotmesis, all functions will be absent. Consider two-point discrimination as part of the sensory exam when examining digital nerves; 4 to 6 mm is normal at the fingertips. Prompt reduction of the deformity often may prevent, eliminate, or mitigate the effects of neurologic involvement, but it is not a guarantee against permanent deficit.

VASCULAR INJURY

Peripheral vessels that run close to a joint sometimes may be compressed or disrupted when the joint becomes dislocated, as, for example, with dislocation of the ankle or knee (tibiofemoral joint). Loss of peripheral pulses or poor to absent capillary refill calls for expeditious reduction of deformity. Even after reduction, evidence of significant vascular injury may be delayed. When pulses are present but the injury mechanism suggests the possibility of vascular injury, then perform arteriography. Patients who experience tibiofemoral dislocation, for example, often undergo routine postreduction angiography to verify the integrity and patency of the popliteal vessels, regardless of whether a circulatory

TABLE 267-6 Orthopedic Injuries and Their Potential Associated Nerve Injury

Elbow injury	Median or ulnar nerve
Shoulder dislocation	Axillary, musculocutaneous
Sacral fracture	Cauda equina
Acetabulum fracture	Sciatic
Hip dislocation	Femoral nerve
Femoral shaft fracture	Peroneal nerve
Knee dislocation	Tibial or peroneal nerve
Lateral tibia plateau fracture	Peroneal nerve

deficit has been observed clinically. Late complications of undiagnosed vascular injuries include thrombosis, arteriovenous fistulas, aneurysm, false aneurysm, and tissue ischemia with limb dysfunction.

COMPARTMENT SYNDROME

After a fracture or a direct blow to an extremity, there may be extravasation of blood, swelling of muscle tissues, and impairment of venous flow within one or more fascial compartments. The resulting increase in pressure within the limb may lead to circulatory compromise, neurologic damage, and muscle necrosis, known collectively as *compartment syndrome*. This is a surgical emergency, and early recognition is crucial. Pain with passive stretching, active contraction against resistance, or direct pressure over the compartment is cause for alarm and suggests need for immediate surgical intervention. The most common site is the anterior compartment of the lower leg, and tissue ischemia begins when compartment pressures exceed 30 mm Hg. Compartment syndrome is discussed further in Chapter 278, "Compartment Syndromes."

DELAYED AND LATE COMPLICATIONS

Patients who have sustained a fracture (usually long bone) may be at risk for pulmonary fat embolus, usually originating from the marrow of a large bone, such as the femur. If fat embolism occurs, it is typically within the first few days after injury, rather than the first hours. This event may have a variable effect on pulmonary function, ranging from mild distress to severe or even fatal respiratory failure. An episode can be characterized by the following symptoms: dyspnea, tachypnea, pulmonary edema, confusion, or a petechial rash. Treatment is generally supportive.

The most delayed complications of fracture include nonunion, malunion (healing with deformity), joint stiffness, traumatic arthritis, reflex dystrophy, avascular necrosis of bone (scaphoid, capitate, and femoral head are particularly prone), and, in the case of open fracture, osteomyelitis.

IMMOBILIZATION COMPLICATIONS

Fracture treatment can often result in prolonged periods of immobilization, which can present further medical problems, especially in the geriatric population. Complications can include infection, deep vein thrombosis, pulmonary embolism, muscle atrophy, and even psychiatric disorders requiring further medical care and possible hospitalization. Avoiding unnecessary immobilization and encouraging early ambulation should be major goals of optimal orthopedic care.

DISPOSITION AND FOLLOW-UP

There is no universally prescribed follow-up interval for specific injuries. Orthopedists differ in their opinions regarding how soon patients should be seen. In general, patients with unreduced fractures or injuries that may require surgical intervention should be seen within a few days.

Sometimes the situation may be discussed with the follow-up physician and an appointment arranged while the patient is still in the ED. Alternatively, the emergency physician may instruct the patient to contact the follow-up physician or clinic as soon as possible. If the name of the injury is written on the discharge instruction sheet, the patient can convey it at the time of the call. This information may help the follow-up physician decide when the patient should be seen.

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 268

Injuries to the Hand and Digits

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ANATOMY

The hand consists of 27 bones: 14 phalangeal bones, 5 metacarpal bones, and 8 carpal bones arranged in five rays of metacarpals and phalanges having its base at the carpometacarpal (CMC) articulation (**Figure 268-1**).

The carpal bones are made up of two rows, each with four bones. The bones are concave volarly and are bridged by the flexor retinaculum. This forms the carpal tunnel through which the median nerve and the nine long flexor tendons of the fingers pass (flexor pollicis longus [FPL]; flexor digitorum profundus [FDP] from the index, middle, ring, and small fingers; and flexor digitorum superficialis [FDS] from the index, middle, ring, and small fingers) (**Figure 268-2**).

The index and middle finger CMC articulations have relatively little mobility, whereas the thumb, ring, and small finger CMC articulations have greater mobility at the CMC joint, which allows grasping and adaptive movements of the hand. More metacarpal deformity can be accepted due to the greater mobility of the CMC joints.

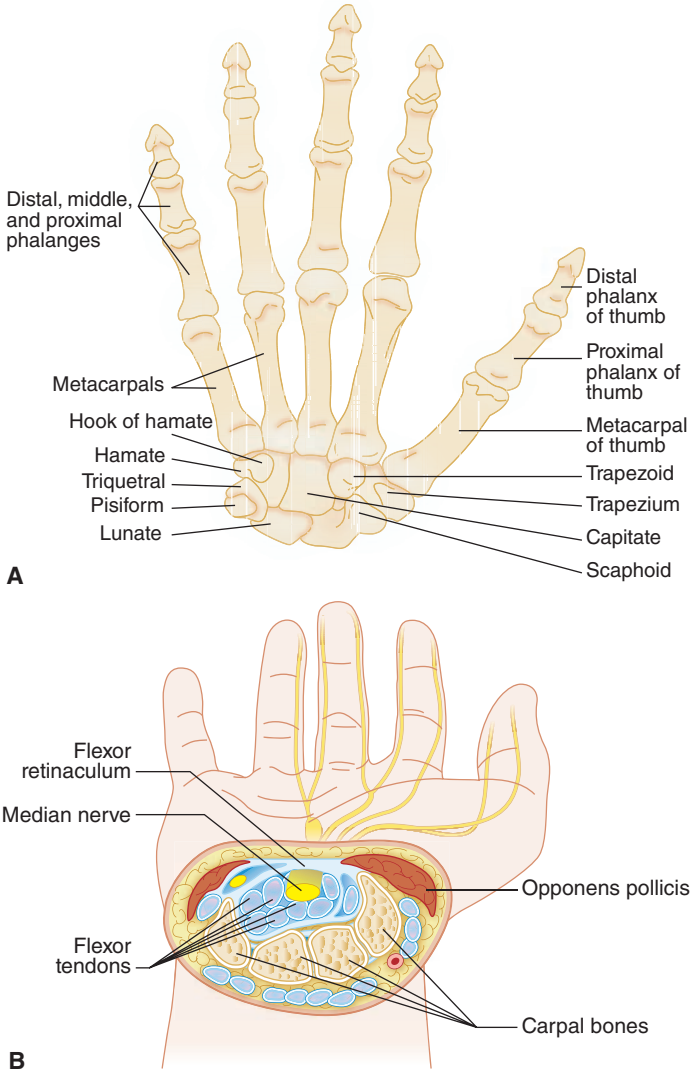


FIGURE 268-1. **A.** Bones of the hand and wrist. **B.** Carpal tunnel.

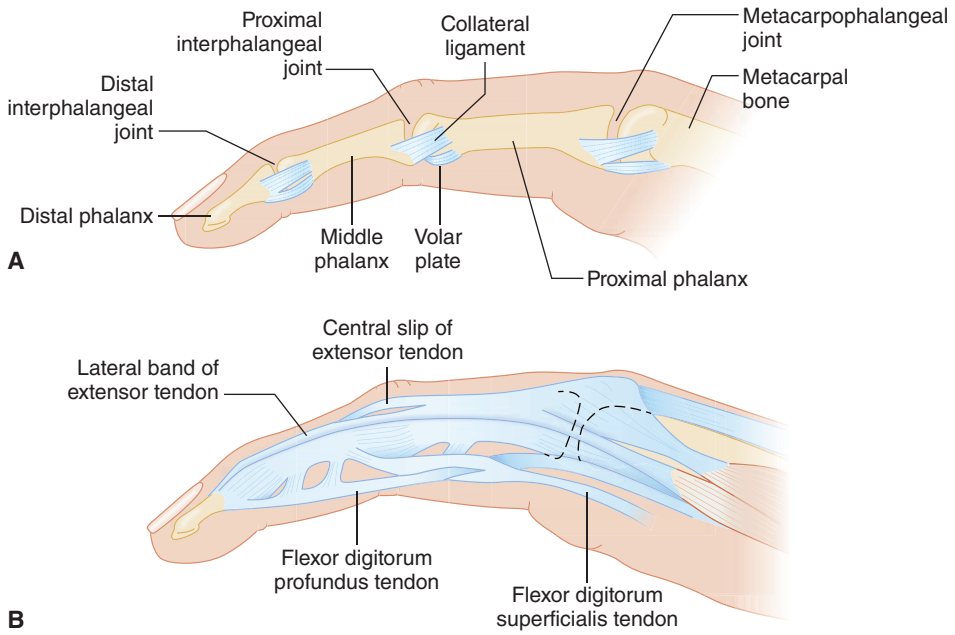


FIGURE 268-2. Joints, ligaments, and tendons of the digits.

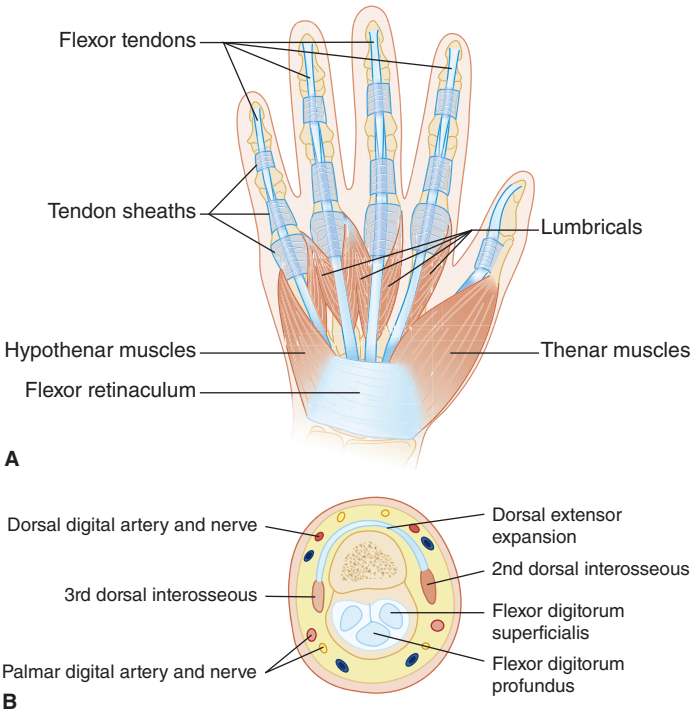
Multiple soft tissue structures support the bones and joints of the hand: capsules and ligaments provide stability, whereas muscles/tendons of the hand and forearm generate mobility **(Figures** 268-2, **268-3,** and **268-4)**. The collateral ligaments of the metacarpophalangeal (MCP) joints are tightest in flexion in the index through small fingers (to allow stability in grasp), while the collateral ligaments of the MCP thumb are tight in flexion and extension (which also provide stability for the thumb in all positions) (Figure 268-3). The collateral ligaments of the interphalangeal (IP) joints are also tight throughout the entire range of motion.

INTRINSIC HAND MUSCLES

The intrinsic muscles of the hand are those that have both their origins and insertions within the hand. They consist of the thenar and hypothenar muscles, the adductor pollicis, the interossei, and the lumbricals (**Figures** 268-3, 268-4, and **268-5**).

The **thenar muscles** (from superficial to deep: abductor pollicis brevis, opponens pollicis, and flexor pollicis brevis) originate in the flexor retinaculum and carpal bones and insert on the radial base of the thumb proximal phalanx and the radial aspect of the first metacarpal. The motor branch of the median nerve innervates all three muscles except for the deep head of the flexor pollicis brevis, which is innervated by the ulnar nerve. The adductor pollicis is innervated by the ulnar nerve and originates from the capitate and second and third metacarpals and inserts on the ulnar base of the thumb proximal phalanx.

The **hypothenar muscles** include, from superficial to deep, the abductor digiti minimi, the flexor digiti minimi, and the opponens digiti minimi. These muscles, innervated by the ulnar nerve, originate in the



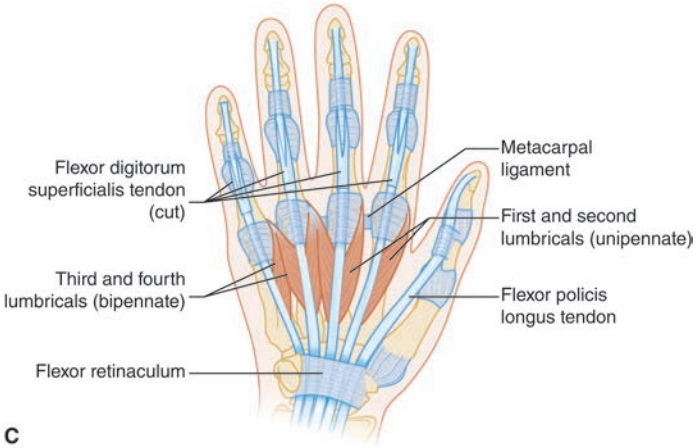


FIGURE 268-3. **A.** Palmar (volar) view of the hand showing the relationship of the some of the intrisic muscles, and flexor tendons and sheaths. **B.** Cross-sectional view of digit at the middle phalanx. **C.** Lumbricals.

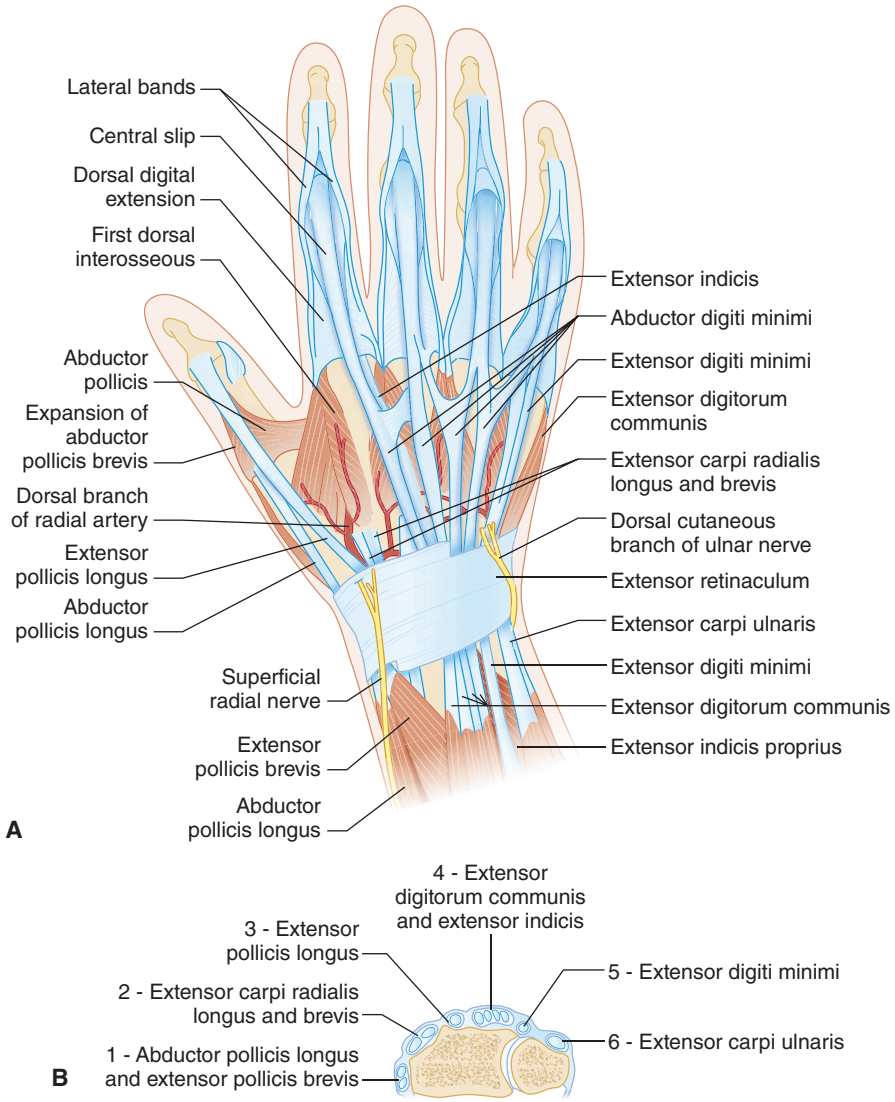


FIGURE 268-4. **A.** Dorsal view of the hand showing the extensor tendons and retinaculum, and intrinsic musculature. **B.** Cross-sectional view with the six extensor compartments.

flexor retinaculum and carpal bones and insert at the ulnar base of the small finger proximal phalanx and the ulnar aspect of the fifth metacarpal.

There are seven **interosseous muscles**, all innervated by the ulnar nerve (Figure 268-5). The three palmar and four dorsal interossei lie between the metacarpal bones and originate from them. The palmar interosseous muscle and the palmar portion of the dorsal interosseous muscle have an insertion into the extensor hood. The palmar interosseous muscle adducts the index, ring, and small finger to the midline, which is designated as the middle finger. The dorsal portion of the dorsal interosseous muscle has a tendinous insertion into the base of the proximal phalanx. The dorsal interosseous muscles abduct the fingers away from the midline.

The **lumbrical muscles** (Figure 268-3) do not attach to bone. They arise from the FDP tendons in the palm, course radially near the MCP joints, and attach to tendons or expansions, reinforcing the interosseous lateral band on the radial side of the digit. The median nerve innervates the radial two lumbricals, and the ulnar nerve innervates the ulnar two. The lumbricals flex the MCP joint and extend the IP joints of the index to the small fingers. Lumbrical muscles also play a critical role coordinating the flexor and extensor systems of the digits.

EXTENSOR AND FLEXOR TENDONS

The **extensor tendons** course over the dorsal side of the forearm, wrist, and hand (Figure 268-4). Nine extensor tendons pass under the extensor retinaculum and separate into six compartments. In the dorsum of the hand, the extensors digitorum communis are connected by juncturae (**Figure 268-6**). **Based on this anatomy, finger extension may still be possible with a complete tendon laceration that is proximal to the juncture.** In the finger, the extensor mechanism divides into a central slip that attaches to the middle phalanx and into two lateral bands that join with the tendons of the lumbrical and interosseous muscles, which then attach to the dorsal base of the distal phalanx as the terminal tendon. The central band extends the PIP, while the lateral bands extend the DIP.[1,2]

The **flexor tendons** (flexor carpi radialis, flexor carpi ulnaris, and palmaris longus) course over the volar side of the forearm, wrist, and hand and primarily flex the wrist. The remaining nine tendons (four FDP, four FDS, and the FPL) pass through the carpal tunnel (Figure 268-1). The FPL goes to the base of the distal phalanx of the thumb. The other four digits have two tendons each (Figure 268-2). The FDS inserts into the volar, proximal half of the middle phalanx and flexes all the joints it crosses, including the proximal interphalangeal (PIP) joint and MCP joints. The FDP runs deep to the FDS until the level of the MCP joint, at which point it bifurcates. The FDP inserts at the volar base of the distal phalanx and acts primarily to flex the distal interphalangeal (DIP) joint as well as all the PIP and MCP joints. Unlike the extensor tendons, the flexor tendons are enclosed in synovial sheaths, making them prone to deep space infections.

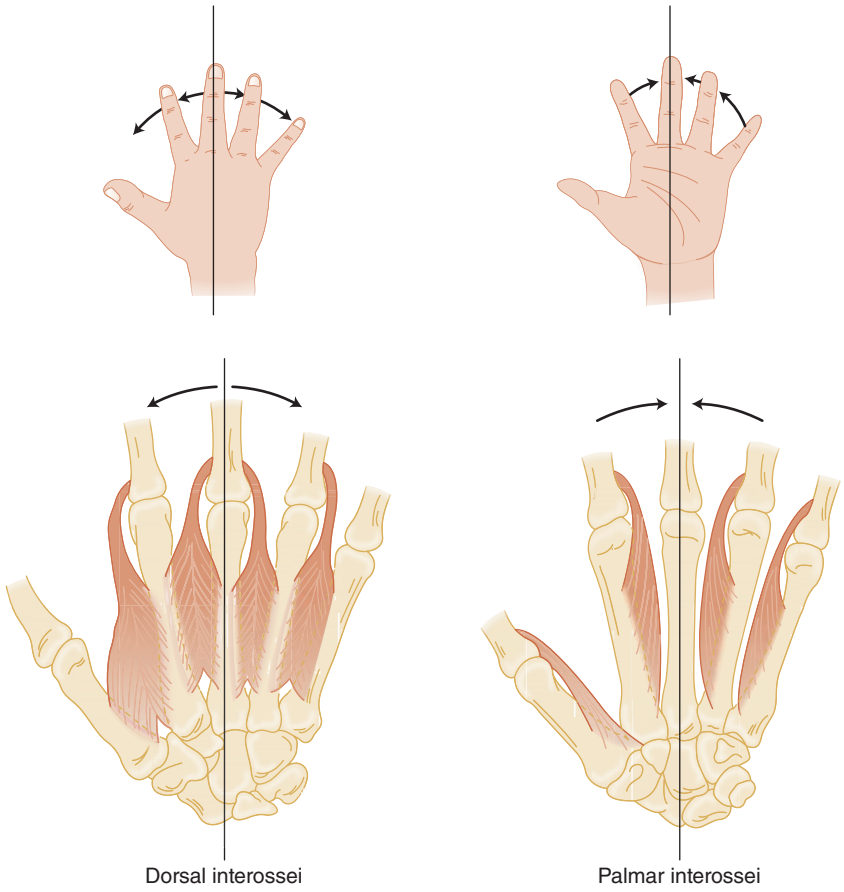


FIGURE 268-5. Origins, insertions, and actions of the palmar and dorsal interossei.

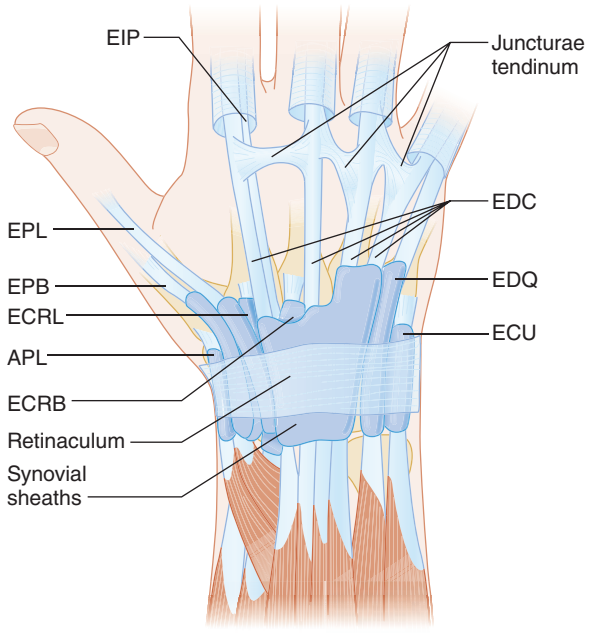


FIGURE 268-6. Dorsal view of the hand showing juncturae tendinum. APL = abductor pollicis longus; ECRB = extensor carpi radialis brevis; ECRL = extensor carpi radialis longus; ECU = extensor carpi ulnaris; EDC = extensor digitorum communis; EDQ = extensor digitorum quinti; EPB = extensor pollicis brevis; EPL = extensor pollicis longus; EIP = extensor indicis proprius.

VASCULAR SUPPLY

The hand and digits are perfused by the radial and ulnar arteries. The radial artery forms the deep palmar arch, whereas the ulnar artery forms the superficial palmar arch. The common digital arteries (in the second, third, and fourth web spaces) arise from the superficial palmar arch (**Figure 268-7**) and provide blood supply to the fingers. The blood supply to the thumb arises from the princeps pollicis, which is the radial artery as it turns into the palm. The radialis indicis, which is on the radial side of the index finger, arises from the radial artery or the princeps pollicis.

NERVE SUPPLY

The radial, ulnar, and median nerves innervate the hand (**Figure 268-8**). In the hand, the median and ulnar nerves have mixed motor and sensory function. The superficial radial nerve (C5-T1) provides sensation to the dorsal radial aspect of the hand. The radial nerve extends the fingers and wrist, supinates the hand, and innervates the posterior interosseous nerve. The ulnar nerve (C7-T1) supplies sensory function to the small finger and the ulnar volar half of the ring finger and motor function to the hypothenar muscles, ulnar two lumbricals, interossei, adductor pollicis, and deep head of the flexor pollicis brevis. The median nerve (C5-T1) supplies sensory function to the thumb, index, middle, and radial volar half of the ring fingers and motor function to the abductor pollicis brevis, opponens pollicis brevis, superficial head of flexor pollicis brevis, two radial-side lumbricals, and thenar muscles. The recurrent median nerve innervates the OAFT muscles (opponens, abductors, flexors of thumb, and thenar eminence) and is pure motor. As the digital nerves course across the palm, they are superficial structures and thus easily injured. Digital nerve sensation and two-point

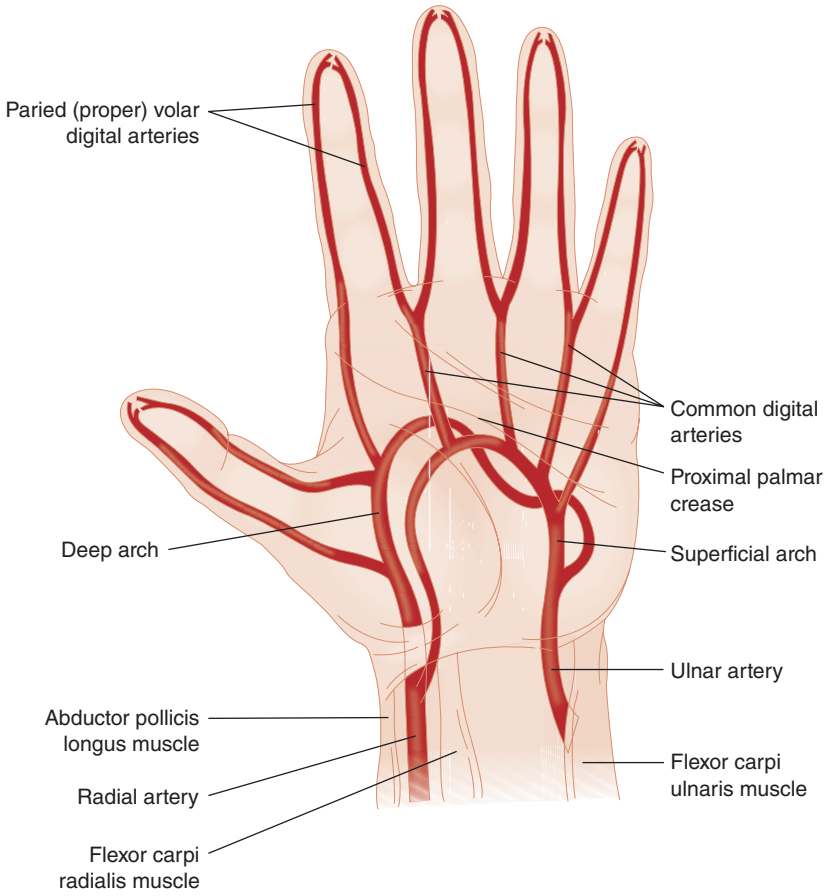


FIGURE 268-7. The dual blood supply to the hands and digits.

discrimination should be routinely assessed when evaluating lacerations of the palm (Figure 268-8). **Normal two-point discrimination is 5 mm.** Sensation is best tested at the tip of the fifth digit (little finger) for the ulnar nerve, the tip of the second digit (index finger) for the median nerve, and at the dorsal side of the first web space (superficial radial nerve). Consult a hand specialist if the extent of injury is uncertain. In the digits, the digital nerves divide into volar and dorsal branches. Knowing the location of these nerves is important to properly perform a digital block (Figure 268-3, cross-sectional view) (See Video: Digital Nerve Block).

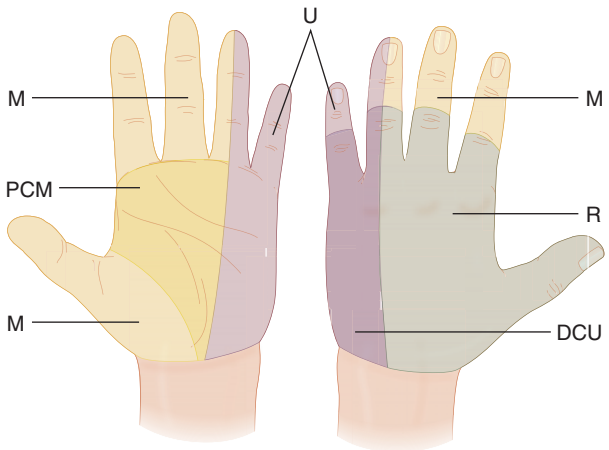


FIGURE 268-8. The cutaneous nerve supply in the hand. DCU = dorsal cutaneous branch of ulnar nerve; M = median nerve; PCM = palmar cutaneous branch of median nerve; R = superficial radial nerve; U = ulnar nerve.

CLINICAL FEATURES

A striking hand injury must not delay the identification and treatment of other potentially life-threatening injuries. After hemorrhage control, assessment involves a detailed history, general hand examination, testing of nerves and tendons, anesthesia, and direct wound inspection (See Video: Hand Exam). **Remove rings from the injured hand/digits** (See Video: Ring Removal). Compare with the uninjured hand, especially to identify partial motor or sensory deficits.

HISTORY

The history should include the time and cause of injury as well as the position of the hand at the time of injury. Ask about the possibility of associated crush, burn, injection, or chemical exposure. When applicable, determine the type and amount of chemical to which the patient was exposed. Document the patient's occupation, avocations, prior hand injuries, and hand dominance to determine the functional impact of the injury. Obtain past medical history including baseline functional status, immunosuppression (diabetes, vascular disease, asplenia), rheumatologic disease, bleeding history, medications, allergies, and smoking, as these factors all affect healing.[1,2]

PHYSICAL EXAMINATION

Detail the extent of injury by examining and documenting the vascularity, skin integrity, posture of the fingers, and presence of deformity or active bleeding. **Table 268-1** provides key elements of the history and physical examination. Ask the patient to demonstrate the hand position at the time of injury. Evaluate injuries with skin violation in a bloodless field. **Injuries with the digits in flexion may result in retraction of the cut end of the tendon when the digit is examined in extension.** Check bilateral grip strength. Compare general appearance, motor, sensory,

TABLE 268-1 Hand Physical Examination

Examination	Finding
General inspection	Swelling, discoloration, open wound, deformity, penetrating injury, bleeding Puncture wound consistent with fight bite Boutonnière deformity, Jersey finger, mallet finger Rotation deformity of the digits
Range of motion (passive and active)	Digits 2–5 MCP, PIP, DIP Thumb MCP and IP
Palpation	Point tenderness Crepitus Anatomical snuffbox tenderness due to scaphoid fracture
Tendon (extensor and flexor)	FDS and FDP tendon function in all digits Extensor tendon function
Ligamentous stability	Valgus/varus stress of PIP, DIP, MCP Joint laxity 30-degree with radial stress of thumb MCP joint
Vascular	Evidence of bleeding, with control of pulsatile bleeding Capillary refill and skin color compared to other extremity, or Doppler assessment
Nerve function	Median: Thumb opposition/abduction, light touch/two-point discrimination at distal second digit Ulnar: Thumb adduction, Froment sign, light touch/two-point discrimination at distal fifth digit Radial: Extension of all digits and wrist, light touch/two-point discrimination at dorsal thumb CMC joint

Abbreviations: CMC = carpometacarpal; DIP = distal interphalangeal; FDP = flexor digitorum profundus; FDS = flexor digitorum superficialis; IP = interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

and tendon function of both hands to assess baseline function. Test range of motion and strength against resistance. Have the patient make a clenched fist to observe the orientation and rotation of the middle and distal phalanxes. All phalanges should be oriented parallel to each other with the nails positioned in the same plane and be pointing toward the scaphoid when the fist is clenched. Circulation is assessed by regional pulses and capillary refill.[1] Doppler assessment can also help assess digital artery flow.

NERVE TESTING

To test the **median nerve**, have the patient flex the IP joint of the thumb against resistance, which tests FPL function. Alternatively, hold the index or middle finger PIP and MCP joints in extension and have the patient flex the DIP joint, which tests FDP function of the index and middle fingers. **The "OK" sign** will reveal the ability to flex the IP joint of the thumb and the DIP joint of the index finger. To test the motor branch of the median nerve, position the thumb in palmar abduction with the palm up. Have the patient resist a force directing the thumb toward the palm, and assess the motor power while palpating the belly of the abductor pollicis brevis muscle to ensure it is contracting. Abnormal function of the median nerve can result in weakness of thumb opposition and anterior interosseous function. Note that a laceration at the level of the wrist or distal forearm may demonstrate intact FDP function of the index and middle fingers and FPL function to the thumb, because these muscles have been innervated at the proximal forearm. A median nerve injury at the level of the wrist or distal forearm can only be determined by examining two-point discrimination in the three and a half radial digits or motor branch integrity to the thenar muscles.

To assess ulnar nerve integrity, have the patient spread the fingers apart (finger abduction) and assess motor power by resisting a force pushing the index and small fingers to midline. Alternatively, have the patient cross the fingers. To test thumb adduction (**the ulnar nerve innervates the adductor pollicis muscles**), have the patient hold a piece of paper with the volar pulp of the thumb against the radial side of the PIP joint of the index finger. If the patient can maintain the key pinch of the paper against resistance, then the adductor pollicis is relatively strong. Froment's sign occurs with weak adductor pollicis function and ulnar nerve pathology, displayed when the patient cannot hold the paper and uses the FPL and flexes the IP joint to compensate. All these reviewed maneuvers for the ulnar nerve test intrinsic muscles so that an ulnar nerve injury at the level of the wrist would be revealed by these test maneuvers.

To test the **radial nerve**, have the patient hyperextend the finger MCP joints against resistance, which will test the extensor digitorum communis tendons. One way to test this is to have the patient put the palm on a table, with fingers flat and hyperextended, and then lift each digit straight up and extend up from the table while keeping the palm flat. Finger resistance can also be checked in this extended, upright position. During this maneuver, it is important to keep the finger MCP joints in hyperextension because the interossei extend the IP joints of the fingers (but flex the MCP joints), and failure to keep the digit in full extension can mislead the examiner into believing the radial nerve is intact. The interossei cannot hyperextend the finger MCP joints. By extending the thumb against resistance, the extensor pollicis longus integrity is confirmed. If a patient has a posterior interosseous nerve (which innervates the majority of the extensor muscles) palsy, the patient will be unable to hyperextend his or her fingers, but may be able to extend the wrist in a radial direction because the extensor radialis longus and extensor radialis brevis are innervated by the radial nerve proper before the posterior interosseous nerve branches.

Sensation is determined by two-point discrimination. **Normal two-point discrimination is 5 mm at the volar fingertips. Older patients may have 6 mm of two-point discrimination.** Compare both injured and contralateral fingers to establish a reasonable baseline, because patients may have preexisting compressive neuropathies such as carpal and cubital tunnel syndrome or previous nerve injuries. Examine the radial and ulnar sides of each finger to determine which digital nerve is injured. Hand specialists recommend repeating two-point discrimination testing two to four times on each side of the digit, because patients can guess sensation correctly by chance. At least 80% accuracy is considered acceptable. Less than 80% or indeterminate accuracy suggests the possibility of digital nerve injury. **A sensory deficit also implies a potential digital artery laceration because of the close proximity of the two.**

TESTING OF TENDONS

Assess full range of motion of each tendon against resistance and compare with the uninjured side. It is important to test resistance because **up to 90% of a tendon can be lacerated with preservation of range of motion without resistance.** In addition, the juncturae tendinum contributes to digital extension, so patients with lacerations to the extensor digitorum communis may be able to extend the digit but may not have the same motor power. **Pain along the course of the tendon during resistance testing suggests a partial laceration even if strength appears adequate. US of the digits in a waterbath,** using a linear high frequency transducer, provides high-resolution images of small-digit structures and can identify tendon lacerations, foreign bodies, and fluid or blood collections (See Video: Waterbath for Finger Exam). US waterbath testing also causes minimal patient discomfort.

Test FDP function by checking flexion of the DIP joint against resistance while holding the PIP and MCP joints in extension. Test the FDS by having the patient flex the PIP joint against resistance while the remaining fingers are held in full extension. When the rest of the fingers are in extension, the FDP of the tested finger cannot fire and the FDS function is isolated. If the test is not performed this way, PIP joint flexion may be due to the FDP because this tendon also traverses the PIP joint, whereas the FDS does not.

To determine whether the central slip is intact, perform the **Elson's test**. Hold the PIP joint of the affected finger in flexion (therefore tightening the central slip and loosening the lateral bands) and ask the patient to extend the finger at the PIP. The examiner should resist

extension; if the DIP is loose, then Elson's test is negative, meaning the central slip is intact and the extension force is being transmitted to the central slip. If the DIP is rigid and the PIP does not extend, Elson's test is positive, meaning the central slip is not intact and the extension force is being transmitted through the lateral bands to the terminal tendon to the DIP joint. The contralateral finger should be examined. Sometimes the patient can overpower the examiner and should be asked to decrease the extension force on the finger. Lastly, if the patient resists PIP flexion due to pain, a digital block can be placed and the test repeated.

ANESTHESIA AND DIRECT WOUND EXAMINATION

Anesthesia and direct wound inspection are necessary because partial tendon lacerations or intra-articular injuries are not always readily apparent. Perform the initial motor and sensory exam before anesthesia (**Figure 268-9**). **If pain limits the motor exam, a digital block can be performed and then motor function reassessed.** A bloodless field can be facilitated by milking the digit proximally and then applying a local tourniquet or Penrose drain around the base of the digit. The tourniquet should not be stretched to more than 150% of its length and can be held in place with a hemostat. The digit can be milked by wrapping another Penrose drain circumferentially around the entire digit, going from distal to proximal, or by reconfiguring a 4 × 4-inch gauze dressing into a narrow band and wrapping that circumferentially around the entire digit. Only moderate compression should be used to avoid compression injury to the digit. **Do not leave the tourniquet in place for >20 minutes.** If repair may require greater time, intermittent tourniquet release is recommended. Irrigate contaminated wounds copiously with normal saline, and administer antibiotics. Cephalosporins are often the first choice, but tailor antibiotic selection to the particular contaminant. Administer tetanus toxoid as needed.

TABLE 268-2 Immediate Hand Surgery Consultation Guidelines

- Vascular injury with signs of tissue ischemia or poorly controlled hemorrhage
- Irreducible dislocations
- Grossly contaminated wounds
- Severe crush injury
- Open fracture
- Compartment syndrome
- High-pressure injection injury
- Hand/finger amputation

IMAGING, CONSULTATION, AND DISPOSITION

Radiologic evaluation should include at a minimum posteroanterior, lateral, and oblique projections of the hand. Similar projections are used for the digits, except that the radiographic beam is centered over the affected digit(s), so that true posteroanterior and lateral views should be obtained of the affected digit. Evaluate all radiographs for adequacy of view, bony alignment, and individual bone morphology. CT displays greater sensitivity and specificity for fracture than radiograph, although it is usually not required in the emergency setting and can be obtained as an outpatient. It is recommended if intra-articular fracture is suspected but not found on radiograph.[1,2] US is useful to identify fractures, with sensitivity and specificity over 90%, as well as assess reduction of fractures.[3-6] Waterbath US testing may also be used to assess tendon function and presence of rupture. Several studies suggest high sensitivity and specificity for tendon injury, although nerve injury is not assessable with US.[7,8] Actual or suspected injuries of tendons and nerves should be referred to a hand specialist. Whether consultation is provided in the ED or in follow-up (1 to 3 days) depends on local resources. Injuries requiring immediate and delayed follow-up by a hand surgeon are listed in **Tables 268-2** and **268-3**, respectively.

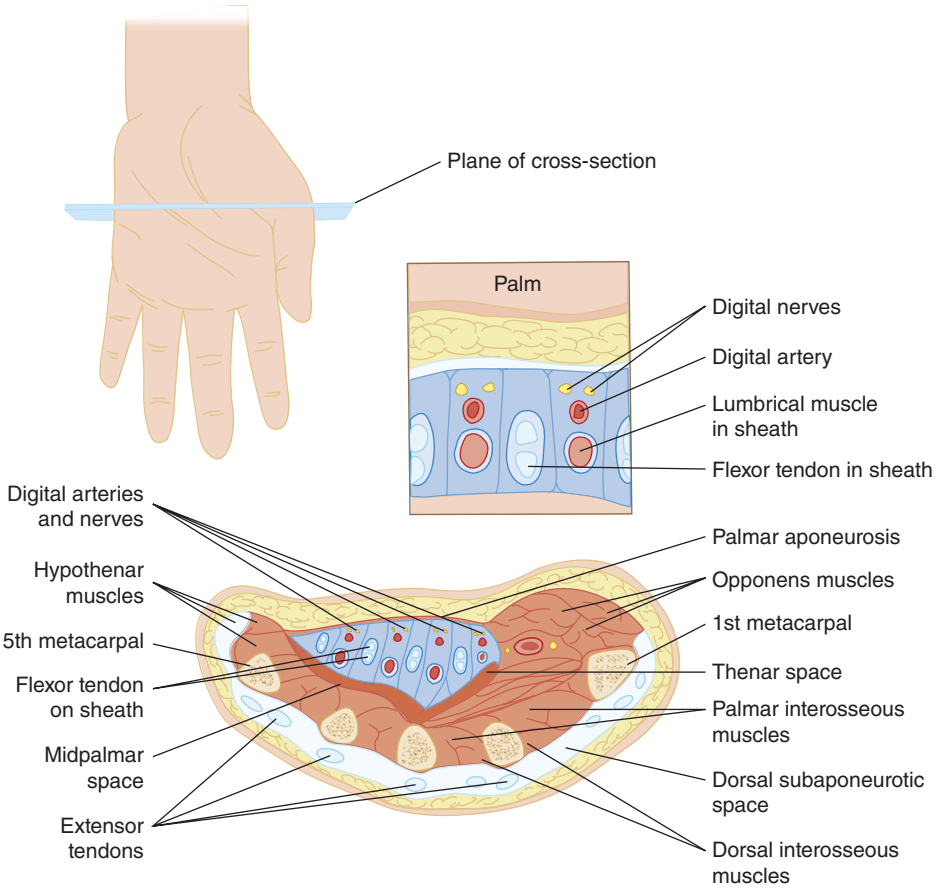


FIGURE 268-9. Relationship of nerves, arteries, tendons, and muscles at the level of the metacarpals.

TABLE 268-3 Delayed Hand Surgery Consultation Guidelines

- Extensor/flexor tendon laceration (if not repaired in ED)
- Flexor digitorum profundus rupture (closed) (Jersey finger) or extensor digitorum rupture (mallet finger)
- Nerve injury
- Closed fractures
- Dislocations
- Ligamentous injuries with instability

Table 268-4 provides guidelines for immobilization and follow-up for specific hand injuries referred for delayed hand surgery evaluation. Often, the skin can be closed and the hand splinted in the position of function. The wound can be extended and explored at follow-up, with definitive repair performed by the hand specialist. **Most hand specialists prefer to do definitive repair of the acute injuries as soon as possible so patients should be informed to seek evaluation immediately and *not* in 2 weeks, as is often instructed.** Also, some diagnoses may be missed in the acute stage when patients are in pain and a thorough exam is difficult. Thus, early referral to a hand specialist verifies the diagnosis and can detect other injuries. Although most injuries involving <20% of the tendon are not surgically repaired, hand specialist follow-up and rehabilitation are still necessary to accurately determine the extent of injury, minimize scarring and tendon contraction, and minimize neuroma formation.

Primary closure can be completed in the ED for hand lacerations, although contraindications include infected wounds, wounds requiring hand surgery repair, and high infection risk (immunocompromise, bites, puncture wounds, crush injury, open fracture, gross contamination). Patients with dirty wounds and those at risk for infection undergoing primary closure should receive antibiotics.[1,2] For patients with hand or digit lacerations that are sutured in the ED, and when there is no suspicion of neurovascular or tendon injury, follow-up evaluation and suture removal in the ED should always include repeat hand examination to make sure that significant injuries have not been missed.

TABLE 268-4 Immobilization for Common Hand Injuries

Injury	Splint
Ligamentous injuries	
Thumb MCP ulnar collateral ligament rupture	
Partial tears	Thumb spica, IP free to flex
Complete or equivocal	Thumb spica (presurgical repair) (See Video: Thumb Spica Splint)
Tendon injuries	
Mallet finger	Dorsal splint, full extension at DIP
Flexor tendon laceration	Dorsal splint, 30-degree wrist flex, 70-degree MCP flexion, 30- to 45-degree PIP flexion (presurgical repair)
Dislocations	
DIP joint	Dorsal splint, full extension
PIP joint	
Stable/postreduction	Dorsal splint, 30-degree PIP flexion
Unstable/postreduction	Dorsal splint, 30-degree PIP flexion
MCP joint	Buddy taping
Carpometacarpal joint	Dorsal-volar splint
Thumb IP joint	Dorsal splint, full extension
Thumb MCP joint	Thumb spica
Fractures	
Distal phalanx	Volar or hairpin splint not immobilizing PIP
Middle/proximal phalanx	
Stable/nondisplaced	Buddy taping/dynamic splinting
Unstable/displaced	Radial/ulnar gutter, 90-degree MCP flexion, <15- to 20-degree PIP flexion, <5- to 10-degree DIP flexion
Thumb proximal phalanx	Thumb spica
Metacarpal	
Index, middle	Radial gutter, 20-degree wrist flexion, 90-degree MCP flexion, PIP left mobile (See Video: Radial Gutter Splint)
Ring, small	Ulnar gutter, 20-degree wrist flexion, 90-degree MCP flexion, PIP left mobile (See Video: Ulnar Gutter Splint)
Thumb metacarpal	
Extra-articular	Thumb spica
Intra-articular	Thumb spica for initial immobilization (presurgical repair)

Abbreviations: DIP = distal interphalangeal; IP = interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

Note: Hairpin splint: metal-backed splint with foam padding; dynamic splint: spring-loaded splint that allows some motion at unaffected joints while protecting the injured joint, usually available from a hand surgeon or occupational therapist.

FLEXOR TENDON INJURIES

The most common cause of flexor tendon injury is laceration. Flexor tendon lacerations can be subtle. A hand surgeon should repair all flexor tendon lacerations, and injuries should be referred to a hand surgeon for evaluation within 7 days of injury.[2] Temporary stabilization and loose closure may be performed in the ED, but should occur within 12 hours. Definitive treatment can occur up to 4 weeks after the injury, but as soon as possible is best. In general, flexor tendon lacerations of <25% do not need to be repaired, but it is difficult to make this assessment in the ED. A distal-to-proximal five-zone (I to V) classification system for flexor tendon injuries has been developed based on location, treatment considerations, and prognosis (**Figure 268-10**).[9]

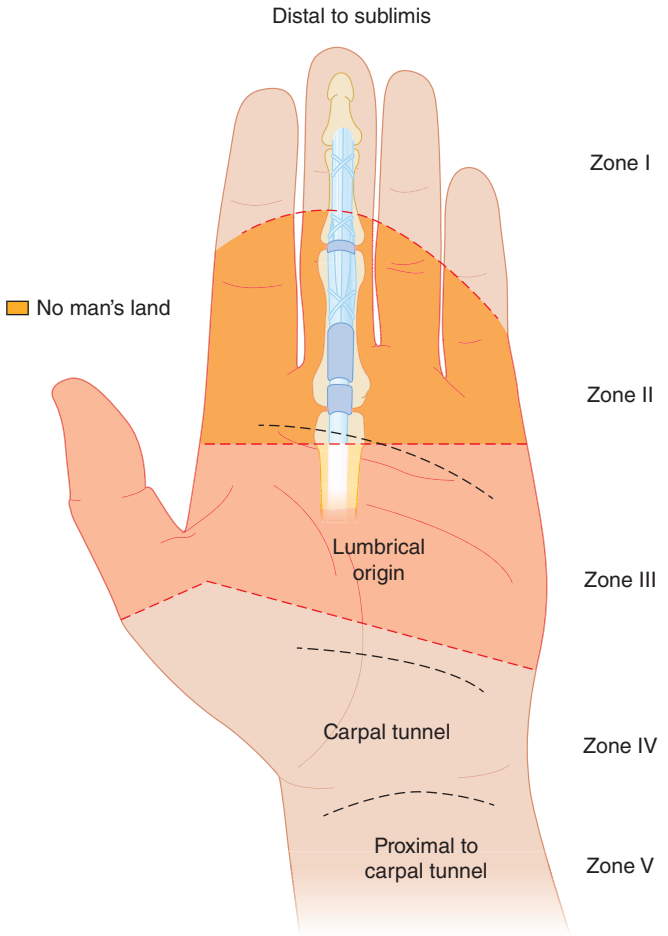


FIGURE 268-10. Flexor tendon zones and no man's land.

FLEXOR ZONE I

Zone I is distal to the insertion of the FDS so that injuries involve the FDP alone. Patients with such injuries lose flexion at the DIP joint. Jersey finger results from hyperextension of the DIP during active flexion, causing avulsion of the flexor digitorum profundus tendon. This most commonly occurs in the dominant fourth digit, or ring finger, due to its anatomic weakness and increased protrusion while grasping. Flexion is preserved at the PIP and MCP, but not DIP. DIP swelling and volar DIP tenderness are common.[10,11] Surgical referral is recommended.[10-12]

FLEXOR ZONE II

Zone II involves the portion of the digital canal occupied by both FDS and FDP tendons (Figure 268-10). This zone is known as **no man's land** because injury in this zone has historically resulted in poor outcomes. This is due to the narrow fibro-osseous tunnel that consists of the metacarpals/phalanges. Lacerations in this zone are common, and partial lacerations are more common than complete injuries.

FLEXOR ZONE III

Zone III extends from the distal edge of the carpal tunnel to the proximal edge of the flexor tendon pulley system. The lumbrical muscles originate from the FDP tendons in this region. Outcomes are generally favorable.

FLEXOR ZONE IV

Zone IV is at the level of the carpal tunnel. The area must be explored carefully because many vital structures traverse this region. Isolated injuries are the exception.

FLEXOR ZONE V

Zone V involves injuries to tendons proximal to the carpal tunnel. Injuries here tend to be severe and often involve multiple tendons as well as the median or ulnar nerve (i.e., "spaghetti wrist"). Examine and test all major structures.

EXTENSOR TENDON INJURIES

The extensor tendons are the most common site of tendon injuries because of the superficial nature of the tendons on the dorsum of the hand. A separate zone classification system (I to VIII) for extensor tendon injuries has been developed for assessing injury patterns, repair techniques, and rehabilitation[13] (**Figure 268-11**). There is growing opinion that extensor tendon injuries should now be repaired operatively as well, although ED repair has often been the standard of care. In general, extensor tendon lacerations <25% do not need repair. Discuss injuries with associated fracture, gross contamination, neurovascular injury, thumb involvement, and specific patient populations (rheumatologic conditions, professional athletes/musicians, etc.) with a hand surgeon for definitive care. If repair in the ED is elected, 4-0 or 5-0 nonabsorbable braided suture with tapered needle is recommended.[14,15]

EXTENSOR ZONE I

Zone I involves the area over the distal phalanx and DIP joint. Injury can occur from blunt or sharp trauma. Complete laceration or rupture of the tendon at this level will result in the inability to extend the DIP joint. This injury, called a **mallet finger** (**Figure 268-12**), occurs due to forced flexion of the DIP while the joint is in extension. It is the most common tendon injury in athletes. This injury has been classified as type I if there is tendon-only rupture, type II if there is a small avulsion fracture, and type III if >25% of the articular surface is involved. Type I can be treated with the DIP joint immobilized in continuous full extension for 6 to 8 weeks. For the best outcome, **no** flexion of the DIP joint is permitted for the duration of splinting. Thus, instruct patients to not take off the splint. If they do remove the splint to clean the finger

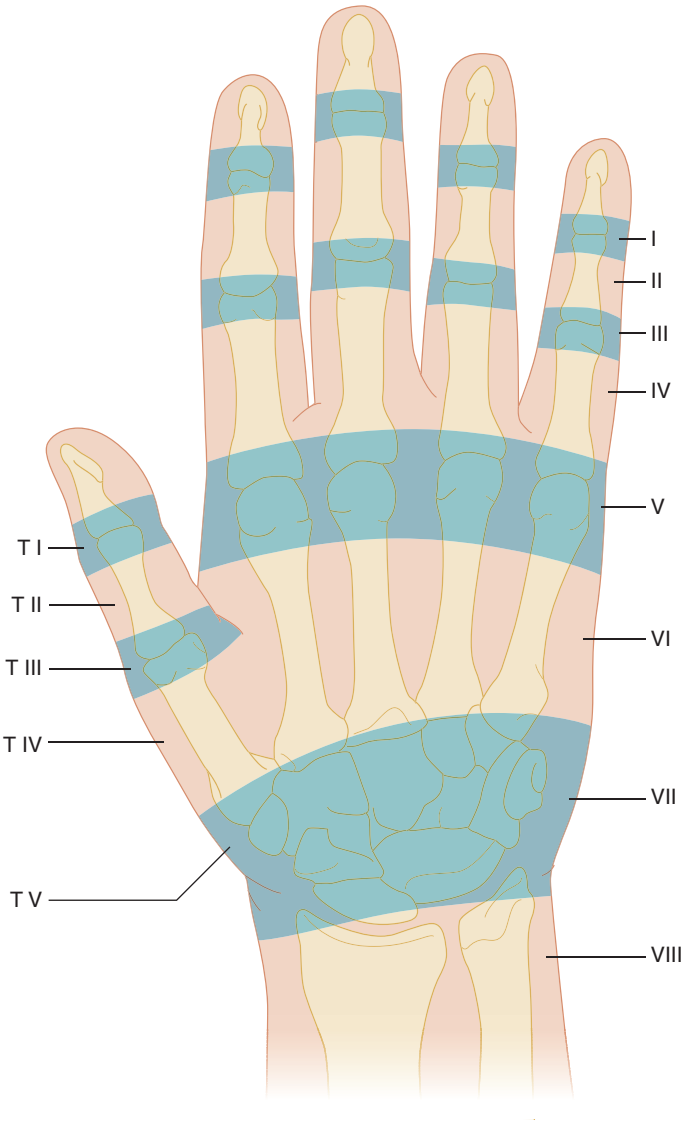


FIGURE 268-11. Extensor tendon zones of the hand. T = thumb.

and the splint, the DIP should be held in extension. The DIP **cannot** be allowed to fall into flexion. Splints for the mallet finger can be a Stax or aluminofoam splint as long as the splint holds the DIP in full extension (**Figure 268-13**).

Type II injuries can be treated the same way if on the radiograph the splinted finger in extension shows congruency with the rest of the noninjured articular surface of the distal phalanx on the distal articular surface of the middle phalanx. Other indications for surgery include an open injury and >30% to 50% articular fracture involvement. Chronic untreated mallet finger may result in a **swan neck deformity** (**Figure 268-14**). This occurs when the lateral bands are displaced dorsally, resulting in increased extension forces on the PIP joint.

EXTENSOR ZONE II

Zone II involves the area over the middle phalanx. Injuries are usually a result of laceration. Injuries to this area are treated similarly to zone I injuries.

EXTENSOR ZONE III

Zone III involves the area over the PIP joint. The central tendon is the most commonly injured structure. Complete disruption of the central tendon may result in the volar displacement of the lateral bands, causing

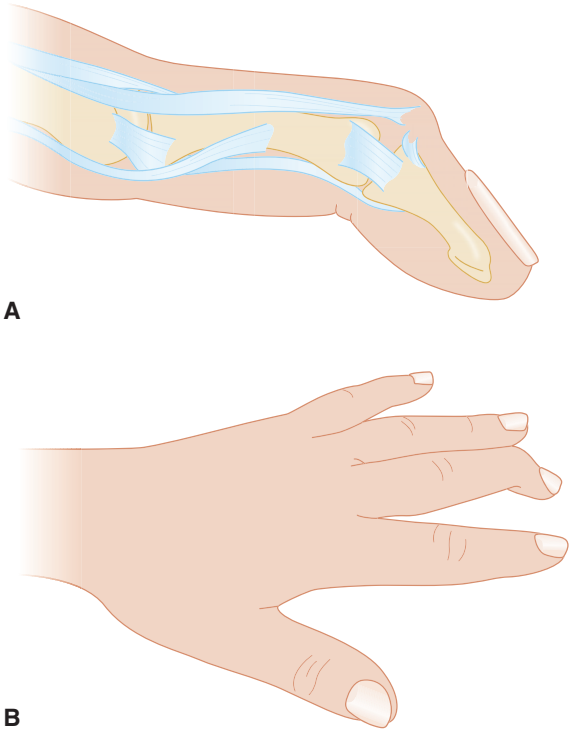


FIGURE 268-12. **A.** Mallet finger. **B.** Clinical appearance.

them to be flexors, along with the unopposed FDP. Additionally, the extensor hood retracts, causing extension of the DIP joint, resulting in the **Boutonnière deformity** (**Figure 268-15**). Controversy exists regarding whether treatment of zone III injuries should be conservative or operative. Closed injuries are initially treated with the PIP joint

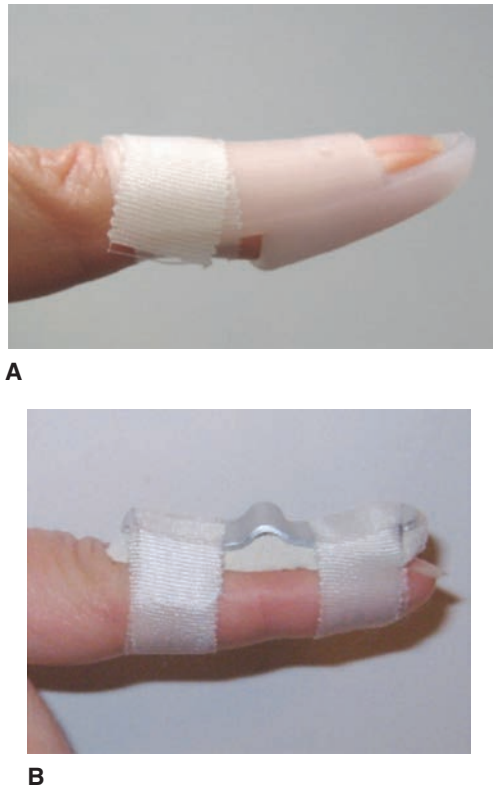


FIGURE 268-13. **A and B.** Splinting for mallet finger.

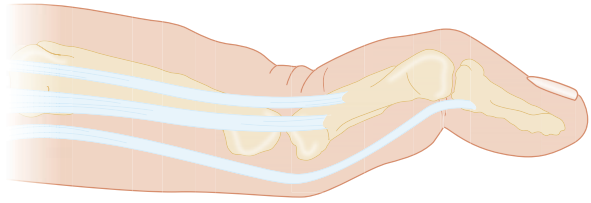


FIGURE 268-14. Swan neck deformity.

immobilized in continuous extension for 5 to 6 weeks and should be followed closely by a hand specialist.

EXTENSOR ZONE IV

Zone IV involves the area over the proximal phalanx. These injuries have clinical findings similar to zone III injuries. These injuries are often less likely to have long-term morbidity because the joint is not involved and the tendon at this level is broad and flat.

EXTENSOR ZONE V

Zone V involves the area over the MCP joint. Open injuries to this area should be considered human bites until proven otherwise, although patients may provide a history incongruent with injury. Obtain radiographs to evaluate for retained foreign body and fracture. Wounds from human bites should have delayed repair following hospital admission for a course of broad-spectrum IV antibiotics. This injury may require operative washout. Clean, nonbite wounds can be repaired primarily using mattress sutures to reapproximate tendon edges.

EXTENSOR ZONE VI

Zone VI involves the area over the dorsum of the hand. Because the tendons in this area are so superficial, even minor-appearing lacerations may be associated with one or more tendon injuries. If the laceration is proximal to the juncturae tendineae, the patient may be able to extend the involved MCP joint, because extensor forces are transmitted to the juncturae from adjacent extensor tendons. Injuries to zones VI, VII, and VIII typically require advanced suture techniques.[16]

EXTENSOR ZONE VII

Zone VII involves the area over the wrist. Repair can be difficult because of the presence of the extensor retinaculum. This thick, fibrous structure

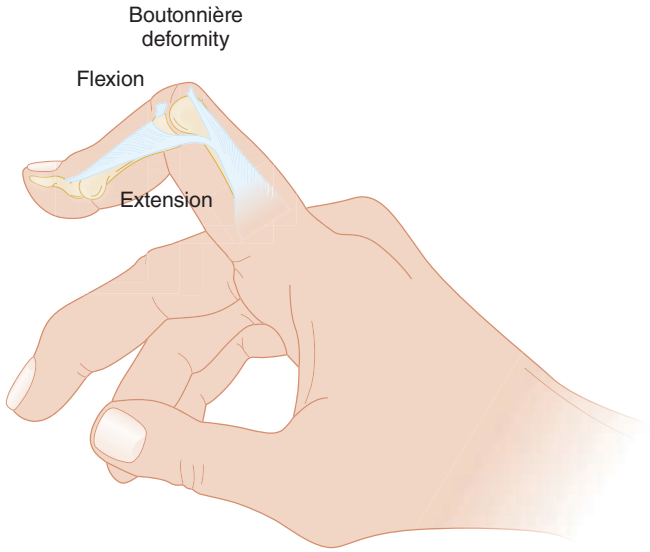


FIGURE 268-15. Boutonnière deformity.

on the dorsum of the wrist contains 12 extensor tendons and six synovial-lined retinacular compartments. Due to the anatomic complexity of this region, operative repair is needed.

EXTENSOR ZONE VIII

Zone VIII involves the area of the distal forearm. Injuries to this area require a thorough exploration to identify all injured structures. The tendons frequently retract into the forearm and must be retrieved and repaired. After repairs in zones V through VII, splinting should occur with the wrist in 15-degree extension, the MCP joint in 15-degree flexion, and the IP joint in 15-degree flexion in the involved and adjacent digits.

LIGAMENTOUS INJURIES AND DISLOCATIONS

Soft tissue injuries to the hand are extremely common. Accurate diagnosis and treatment are important to avoid complications such as joint luxation, loss of motion, chronic pain, and deformity.

DISTAL INTERPHALANGEAL JOINT

Dislocations of the DIP joint are uncommon because of the firm attachments of the skin and subcutaneous tissue to the underlying bone by osteocutaneous fibers. Additional stability is provided by the flexor and extensor tendons. When dislocations do occur, they are usually dorsal. Longitudinal traction and hyperextension followed by direct dorsal pressure to the base of the distal phalanx usually accomplish reduction. Attempts at reduction should be made after a digital nerve block or other means of anesthesia has been performed. **Irreducible cases may be due to the entrapment of an avulsion fracture, the profundus tendon, or volar plate.**

PROXIMAL INTERPHALANGEAL JOINT

Dislocations of the PIP joint are common hand injuries. The mechanism is usually due to axial load and hyperextension. Dorsal dislocation occurs when the volar plate ruptures. Lateral dislocations occur when one of the collateral ligaments ruptures with at least a partial avulsion of the volar plate from the middle phalanx. The digit is usually ulnarly deviated because the radial collateral ligament is six times more likely than the ulnar collateral ligament to rupture. Volar dislocations are rare but may be associated with central slip rupture. Dorsal dislocations are reduced in the same manner as dorsal DIP joint dislocations. Active motion and strength should be tested following reduction. If testing is normal, splint the joint at 30 degrees of flexion for 3 weeks. **If the joint is irreducible or there is evidence of complete ligamentous disruption, operative repair is required.** Untreated PIP dislocation with volar plate tear can result in swan neck deformity. For volar dislocation, the PIP should be splinted in extension after reduction.

METACARPOPHALANGEAL JOINT

Dislocations of the MCP joint are usually due to hyperextension forces that rupture the volar plate, causing dorsal dislocation. Subluxation is more common than dislocation. In subluxation, the joint appears to be hyperextended 60 to 90 degrees, and the articular surfaces are still in contact. Reduction for this injury does not involve hyperextension because it might convert a subluxation into a complete dislocation. **Reduction is performed by flexing the wrist to relax the flexor tendon and then applying pressure over the dorsum of the proximal phalanx in a distal and volar direction.** After reduction, splint the MCP joint in flexion. Multipart dislocations appear less deformed because of the number of disrupted structures. Because the volar plate is interposed in the MCP joint space, closed reduction is usually not possible. Volar dislocations are rare and usually require operative reduction.

CARPOMETACARPAL JOINT

Dislocations of the CMC joint are uncommon because the joint is supported by strong dorsal, volar, and interosseous ligaments and is reinforced by the broad insertions of the wrist flexors and extensors. The cause is usually a result of high-speed mechanisms such as motor vehicle crashes, falls, crushes, or clenched fist trauma. If a dislocation occurs, it is usually dorsally oriented and associated with fracture(s). **Reduction of dorsal CMC joint dislocations can be attempted after regional anesthesia is administered. Traction and flexion with simultaneous longitudinal pressure on the metacarpal base should reestablish normal anatomic alignment.** Early referral after reduction is needed to determine if further fixation is needed. Volar CMC joint dislocations are exceedingly rare and should be referred to a hand specialist.

THUMB INTERPHALANGEAL JOINT

Dislocations of the thumb IP joint are rare but, if present, are usually open. The mechanism is typically hyperextension with rupture of the volar plate. Reduction is similar to that of the IP joints of the other digits. After reduction, the joint should be immobilized in 15 to 20 degrees of flexion for 3 weeks.

THUMB METACARPOPHALANGEAL JOINT

Dislocations of the MCP joint of the thumb are usually dorsal and result from a hyperextension force causing rupture of the volar plate. The dislocation may be simple or complex. Reduction, after radial nerve block, is accomplished with pressure directed distally on the base of the proximal phalanx with the metacarpal flexed and abducted.

THUMB METACARPOPHALANGEAL (ULNAR) COLLATERAL LIGAMENT RUPTURE

Rupture of the ulnar collateral ligament (**gamekeeper's thumb**, **skier's thumb**) occurs when the mechanism causes radial deviation (abduction) of the MCP joint. This injury is more commonly due to chronic laxity of the MCP, rather than acute tear. The tear usually occurs at the insertion into the proximal phalanx. Often significant injury to the dorsal capsule and volar plate occurs. A Stener lesion refers to interposition of the adductor aponeurosis/adductor pollicis muscle between the ulnar collateral ligament and MCP, which requires surgery. **Hand surgery referral within 7 days is recommended for all patients with suspected complete tears of the ulnar collateral ligament of the thumb**, signs of which are pain, ecchymosis of the thumb MCP, and weakness of pinch. The diagnosis is made with stress testing of the ulnar collateral ligament. The examiner tests the thumb MCP joint, both in full extension and 30-degree flexion, by stabilizing the metacarpal with one hand while applying lateral (radial) stress on the proximal phalanx with the other. **More than 30 to 35 degrees of radial angulation or 10 to 15 degrees more than the contralateral thumb indicates complete rupture and requires surgical consultation.** Partial tears are treated with splinting. If patients are discharged from the ED, a thumb spica splint should be applied and urgent orthopedic follow-up arranged. Repair is best accomplished within 1 week. **Radial collateral ligament rupture** is not as common, and the mechanism is forced adduction. This injury can lead to avulsion fracture and chronic instability. Examination with the same parameters applied in the ulnar direction is used to make the diagnosis of a complete radial collateral ligament rupture.

THUMB CARPOMETACARPAL JOINT

Isolated thumb CMC joint dislocation is rare compared with the more common Bennett's fracture dislocation (see below). These are easy to reduce but unstable after reduction. After reduction, a thumb spica splint should be applied. These injuries should have a surgical referral for a decision on operative repair.

FRACTURES OF THE PHALANX AND METACARPALS

DISTAL PHALANX

Fractures of the distal phalanx usually result from crush or shearing forces. The fractures can be classified as tuft, shaft, or intra-articular. Tuft fractures are the most common distal phalanx fracture and can be associated with nail bed lacerations. Fractures at the base may be associated with flexor or extensor tendon involvement. Generally, fractures of the distal phalanx are treated as soft tissue injuries with protective splinting. Subungual hematoma with an intact nail plate should be drained if it covers more than 50% of the nail bed. If the nail plate is damaged, it may need to be removed with repair of the nail bed including placement of a protective covering, suturing the covering in place, and splinting. Prophylactic antibiotics offer no benefit to low-risk open tuft fractures.[17]

PROXIMAL AND MIDDLE PHALANX

The proximal phalanx has no tendinous attachments, so fractures frequently result in apex volar angulation from the forces of the extensor and interosseous muscles. Greater than 25 degrees of angulation can cause loss of flexion and extension.[18] For the middle phalanx, the FDS tendon inserts on the proximal volar half and the extensor tendon inserts at the proximal base. Therefore, fractures at the base of the middle phalanx demonstrate apex dorsal angulation, and fractures at the neck result in apex volar angulation. A direct blow mechanism usually causes a transverse or comminuted fracture, whereas a twisting mechanism will more often result in a spiral fracture. Most often, such fractures are stable and nondisplaced and can be treated with early protected motion by buddy taping. Unstable fractures amenable to closed reduction can be splinted from the MCP to the DIP joint with the MCP joint in 70 degrees of flexion and the IP joints in extension. Midshaft transverse fractures, spiral fractures, and intra-articular fractures often require internal fixation.

METACARPAL (SECOND TO FIFTH) FRACTURES

The second and third metacarpals are relatively immobile, and fractures require anatomic reduction. Metacarpal fractures account for 30% of hand fractures.[19] The ring and fifth metacarpals have 15- to 20-degree anteroposterior motion, which allows for some compensation for malunion. Metacarpal fractures are categorized as head, neck, shaft, or base fractures.[20] The presence of a metacarpal fracture should prompt close evaluation of the associated CMC joint, because CMC joint dislocation often accompanies these fractures and is often missed at the initial presentation.[21]

METACARPAL HEAD FRACTURES

Fractures of the metacarpal head are usually caused by a direct blow, crush, or missile. These fractures are distal to the insertion of the collateral ligaments and are often comminuted with significant joint disruption. If a laceration is present, a human bite must be considered. Treatment consists of ice, elevation, and immobilization with referral to a hand surgeon.

METACARPAL NECK FRACTURES

Fractures of the metacarpal neck are usually caused by a direct impaction force. A fracture of the fifth metacarpal neck is often referred to as a **boxer's fracture**. Imbalance of extrinsic and intrinsic musculature from metacarpal neck fracture can result in pseudoclaw deformity. These fractures are usually unstable with volar angulation. **Angulation of ≤20 to 30 degrees in the fourth and ≤40 degrees in the fifth metacarpal will not result in functional impairment. If greater angulation in these metacarpals occurs, reduction should be attempted.**[22] To perform the reduction, flex the wrist and the MCP joint. Apply slight force to the volar aspect of the affected metacarpal while distracting the phalanx away from the palm. Following splinting, patients may have residual cosmetic deformity (decreased prominence of the metacarpal head), but in most cases regain full function. The amount of angulation at the time of injury does not correlate with resultant cosmetic defects.[23] **With second and third metacarpal fractures, angulation of <15 degrees is acceptable.**[22] However, rotational deformity is not acceptable.[22] Splint metacarpal neck fractures with the wrist in 20-degree extension and the MCP joint flexed at 70 degrees. Extend the splint to cover the DIP. Obtain radiographs after splinting, with neurovascular reassessment. Fractures of the second or third metacarpal that are significantly displaced or angulated require anatomic reduction and surgical fixation.

METACARPAL SHAFT FRACTURES

A direct blow usually results in fractures in the metacarpal shaft region. Rotational deformity and shortening are more likely in shaft fractures than in neck fractures. Minimally or nondisplaced injuries without significant angulation, rotation, or shortening can be immobilized. Typically no angulation is acceptable for the second and third metacarpals, while 20 degrees and 30 degrees are acceptable for the fourth and fifth digits, respectively.[22] If manipulative reduction is necessary, operative fixation is usually indicated.

METACARPAL BASE FRACTURES

Fractures at the base of the metacarpal are usually caused by a direct blow or axial force and often associated with carpal bone fractures. CMC joint subluxation or dislocation should be suspected with these injuries. Given the overlap of the bones and joints on the lateral radiograph, a CT scan may be needed to definitively rule out joint subluxation or dislocation. Fractures at the base of the fourth and fifth metacarpals can result in paralysis of the motor branch of the ulnar nerve, although this is rare.[24] Management is controversial, and orthopedic consultation is recommended, as many patients require operative intervention.[22]

THUMB METACARPAL FRACTURES

Because of the mobility of the thumb metacarpal, shaft fractures are uncommon. Fractures usually involve the base.

Extra-Articular Fractures Extra-articular fractures are caused by a direct blow or impaction mechanism. The mobility of the CMC joint can allow for 30-degree angular deformity. Angulation greater than this requires reduction and a thumb spica splint for 4 weeks. Spiral fractures often require fixation.

Intra-Articular Fractures: Bennett's Fracture and Rolando's Fracture Intra-articular fractures are caused by impaction from striking a fixed object.

Bennett's fracture is an intra-articular fracture with associated subluxation or dislocation at the CMC joint. The ulnar portion of the metacarpal usually remains in place ("constant fragment"). The distal portion usually subluxes radially and dorsally from the pull of the abductor pollicis longus and the adductor pollicis. Treatment is application of a thumb spica splint and orthopedic referral.

Rolando's fracture is an intra-articular comminuted fracture at the base of the metacarpal. The mechanism of injury is similar to Bennett's fracture but less common. Treatment includes a thumb spica splint and orthopedic consultation.

SPECIAL CONSIDERATIONS

COMPARTMENT SYNDROME OF THE HAND

Crush injury of the hand, with or without associated fracture, may result in compartment syndrome. Iatrogenic causes of compartment syndrome of the hand include extravasation of IV fluids or contrast media or arterial punctures.[25,26] The involved compartments of the hand include the thenar, hypothenar, adductor pollicis, three palmar, and four interossei muscles (see Figure 278-3). Edema of tissues or hemorrhage within any of these compartments may lead to elevated pressures that result in tissue necrosis and subsequent loss of hand function due to contracture.[13] Classic signs and symptoms of compartment syndrome typically include

pain and paresthesias early, with paralysis and pulselessness occurring later in the course of the ischemic injury. **Hand compartment syndromes, however, may not be associated with paresthesias, and the extremely subtle motor deficits and difficulty in assessing response to passive stretch make the diagnosis more elusive than other anatomic sites.** Pain, the most consistent clinical sign, is often described as deep, constant, poorly localized, and disproportionate to clinical findings. Physical examination findings suggestive of hand compartment syndrome include extreme swelling, the intrinsic minus position at rest (MCP joint extended with PIP joint slightly flexed), pain with passive stretch of the involved compartment muscles (interosseous: performed with MCP joint extended and PIP joint fully flexed with slight radial and ulnar deviation; thenar, hypothenar: performed by extension of MCP joint), and tense swelling of the affected compartment. Compartment pressure measurement is difficult and inexact in the relatively small compartments of the hand. The diagnosis is typically made on a clinical basis, not on actual compartment pressures.[27,28] Compartment pressure assessment is operator dependent and technically difficult, and false-negative readings can occur.[2]

In the setting of severe crush injury with signs and symptoms suggestive of compartment syndrome, immediately consult with a hand specialist to determine if emergency fasciotomy is indicated.

HIGH-PRESSURE INJECTION INJURY

The injection of certain substances under high pressures (often 2000 to 10,000 psi) into the soft tissues of the hand may initially appear benign but is actually a true orthopedic emergency. The operator of the high-pressure device typically attempts to test or clean the nozzle with the nondominant hand and inadvertently injects the substance. The initial dissipation of kinetic energy through the soft tissues of the hand and the subsequent chemical inflammation produce tissue edema and ischemia. The most commonly injected substances include grease, paint, hydraulic fluid, diesel fuel, paint thinner, and water. Paint, especially oil-based paint, triggers an intense inflammatory response that contributes to significant ischemic injury.[29,30] The benign appearance of the small injection site in the immediate postinjection period is misleading, and historical information must dictate treatment and disposition decisions. With time, the digit becomes edematous, pale, and severely tender to palpation, suggesting ischemic injury. Pressure to areas surrounding the wound may express the injected substance. Plain radiographs of the injected hand and forearm provide valuable information, as radiopaque substances, such as lead-based paints or grease, or subcutaneous emphysema may delineate the extent of the injection. **Definitive treatment of high-pressure injection injuries is early surgical decompression and debridement of injected areas.[29]** Obtain immediate hand surgery consultation, immobilize and elevate the affected hand, administer tetanus prophylaxis and broad-spectrum antibiotics, and provide adequate analgesia.[29–31] Amputation rates following injection injury are as high as 30%,[32] highlighting the need for rapid identification and proper treatment of the injury.

BURNS

Major burn victims commonly experience burn injuries to the hand (50%).[33] Once the patient is stabilized, burns require cleansing with cool water at 10°C to 25°C. Ice water or water cooled to 1°C to 8°C is not recommended, as this may result in further tissue damage.[34] Remove nonviable loose tissue. Blister management is controversial and should be discussed with a burn surgeon, especially for partial thickness and full thickness burns.[35-38] Topical antibiotics are recommended, followed by covering wounds with sterile dressing. Place the hand in the anatomic position when covered. Early burn specialist consultation is recommended for partial and full-thickness burns.

Acknowledgments: The authors thank Moira Davenport and Peter Tang, who served as authors on the eighth edition of this chapter.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 269

Wrist Injuries

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Alex Koyfman

INTRODUCTION AND EPIDEMIOLOGY

The wrist is the area from the distal radius and ulna to the carpometacarpal joints. Wrist injuries are common, accounting for 2.5% of ED visits annually, and up to 25% of all sports injuries include the hand or wrist.[1-3] Clinical diagnosis is often difficult, and even subtle injuries may lead to significant impairment if not properly diagnosed and treated. Management options vary from conservative to surgical, so an understanding of the functional anatomy, mechanisms of injury, and clinical evaluation is needed for proper diagnosis and treatment.

ANATOMY

The wrist is a complex unit with articulations among the eight carpal bones and the distal radius and ulna that allows for flexion, extension, and radial/ulnar deviation.[4,5] Not only does it consist of the carpal bones, radius, and ulna, but it also contains distal radioulnar joint, triangular fibrocartilage complex (TFCC), and thumb radial and ulnar collateral ligaments. The wrist has dual blood supply, although most carpal bones do not. The radial nerve provides dorsal sensation and wrist/finger extension, the median nerve volar sensation to the first three digits and wrist/finger flexion, and the ulnar nerve sensation to the palm and last two digits and hypothenar and fourth/fifth digit lumbrical movement.[4,5]

DISTAL RADIUS AND ULNA

The distal radius is the only forearm bone that articulates directly with the carpal bones (scaphoid and lunate). The distal radius has three articular surfaces: radiocarpal, distal radioulnar, and the triangular fibrocartilage complex. The radiocarpal surface is concave and tilted in two planes. It has an ulnar inclination, or tilt, of 15 to 25 degrees in the frontal plane, and a volar tilt of 10 to 15 degrees in the sagittal plane (**Figure 269-1**).[4,5] The ulna is separated from the carpal bones by the triangular fibrocartilage complex, the main stabilizer of the distal radioulnar joint, on its distal end.

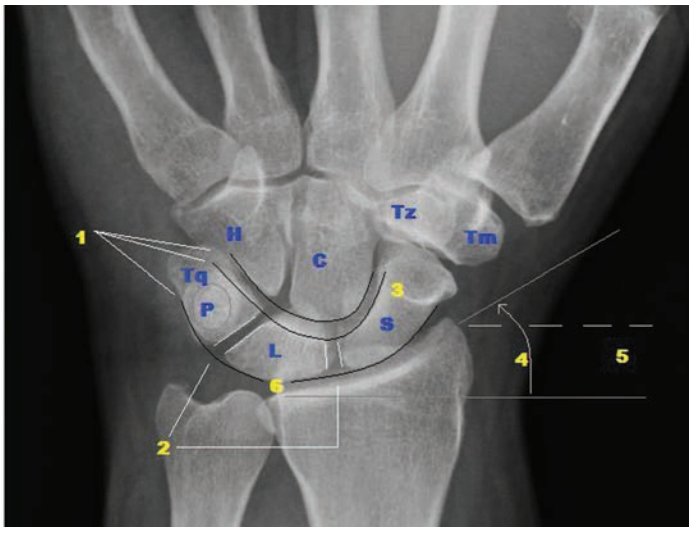


FIGURE 269-1. Wrist. Normal posteroanterior (PA) view. 1. The carpal bones are arranged in two rows forming three smooth arcs (Gilula lines). 2. The carpal bones are separated by a uniform 1- to 2-mm space. 3. The scaphoid (S) is elongated. 4. The radius has an ulnar inclination of 13 to 30 degrees. 5. The radial styloid projects 8 to 18 mm. 6. Half the lunate articulates with the radius, with equal length over the ulna (neutral ulnar variance). C = capitate; H = hamate; L = lunate; P = pisiform; Tm = trapezium; Tq = triquetrum; Tz = trapezoid.

The triangular fibrocartilage complex forms a smooth, continuous, ulnarly directed extension of the distal radial surface, and supports the lunate and triquetrum on the distal ulna. The distal radius has a concave sigmoid notch at its ulnar aspect that articulates with the curvature of the ulnar head, which permits wrist rotation during pronation/supination of the forearm.[6] The distal radioulnar joint is also supported by dorsal and volar radioulnar ligaments that merge with the triangular fibrocartilage complex.[7]

CARPAL BONES

Eight carpal bones are arranged in two rows. The distal carpal row (trapezium, trapezoid, capitate, and hamate) is joined tightly together and to the adjoining metacarpals. The distal row is quite stable and moves with the metacarpals as a unit in a relatively stable arch. The proximal carpal row (scaphoid, lunate, triquetrum, and pisiform) is also arranged in an arch between the distal radius and the distal carpal row, functioning as a mobile link, or "intercalated segment," and is potentially unstable by virtue of this position. The scaphoid is critical to wrist stability, acting as a stabilizing strut and linking the proximal and distal carpal rows at the radial aspect of the wrist. This position explains the scaphoid's greater propensity for injury.

Forearm muscles that insert onto the bases of the metacarpals produce wrist motion. Except for the pisiform, a sesamoid bone of the flexor carpi ulnaris, there are no direct tendon insertions on the carpal bones.[8] The carpal bones move passively in response to hand position. Often, the radiocarpal joint is referred to as the *wrist joint*. However, wrist motion is divided almost equally between the radiocarpal and midcarpal joints.[9] This is best understood by viewing carpal movement from the sagittal view. During flexion and extension of the wrist, each row moves in the same direction with similar degrees of angulation.

The carpal bones are stabilized to one another by intrinsic ligaments and to the bones of the forearm by extrinsic ligaments. The key extrinsic ligaments are arranged in three arcades, two of which are volar and one dorsal. The two volar ligaments are arranged in two inverted V-shaped arches and are thought to play a major role in stabilizing the wrist. The apex of one arch inserts on the lunate supporting the proximal carpal row, whereas the other arch reaches to the distal carpal row, inserting on the capitate. The area between these two palmar arches is inherently weak and is known as the *space of Poirier* (**Figure 269-2**).[4,5] This space lies at the junction of the capitate and lunate and widens upon dorsiflexion of the wrist. Forceful dorsiflexion may tear the capsule here and produce a lunate or perilunate dislocation. The single dorsal arcade has its origins on the rim and styloid of the radius on one side and distal ulna/triangular fibrocartilage complex on the other. This ligament is less important for wrist stability, acting as a sling across the dorsum of the wrist.[4,9]

The space of Poirier on the volar aspect of the wrist is the site of disruption in perilunate and lunate dislocations. The intrinsic ligaments are largely responsible for holding the carpal bones together as a kinematic unit in their respective carpal rows, and these ligaments of the mobile proximal carpal row have high propensity for injury. The intrinsic ligaments of the proximal carpal row are named after the respective carpal bones they connect: the scapholunate and triquetrolunate. The palmar flexed posture of the scaphoid produces a flexion torque on the lunate that is counterbalanced by an extension torque from the triquetrum. This delicate balance is lost if either ligament is disrupted, producing a dorsal or volar tilt of the proximal carpal row and carpal instability.[4]

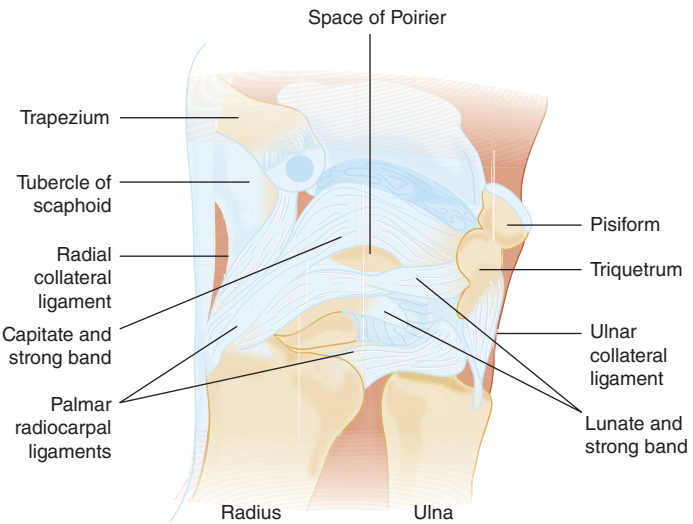


FIGURE 269-2. Ligaments of the wrist.

PATHOPHYSIOLOGY

It is helpful to understand the mechanism of injury when assessing wrist injuries. Most injuries are caused by a fall creating an axial load on an outstretched arm and dorsiflexed wrist and hand. Impact on the thenar eminence is likely to injure the scaphoid and its supporting ligaments. An impact on the hypothenar eminence is likely to cause injury to the triquetrum, pisiform, and their supporting ligaments. Age affects the maturity of the bones and predisposes patients to certain types of injury.[10] **Children are likely to sustain injuries to the immature, weaker epiphyseal plate or metaphysis of the radius, sparing the still cartilaginous carpal bones.**[4] Young adults, particularly those with active lifestyles, are likely to be injured with greater force and disrupt either the scaphoid, proximal row intrinsic ligaments, or distal radial metaphysis.[4] **In the elderly, especially with underlying osteoporosis, the weak point is the brittle distal radial metaphysis, resulting in a Colles' fracture, often with intra-articular involvement.**[11] The elderly possess the highest rate of injury to the carpal bones, primarily due to falls.

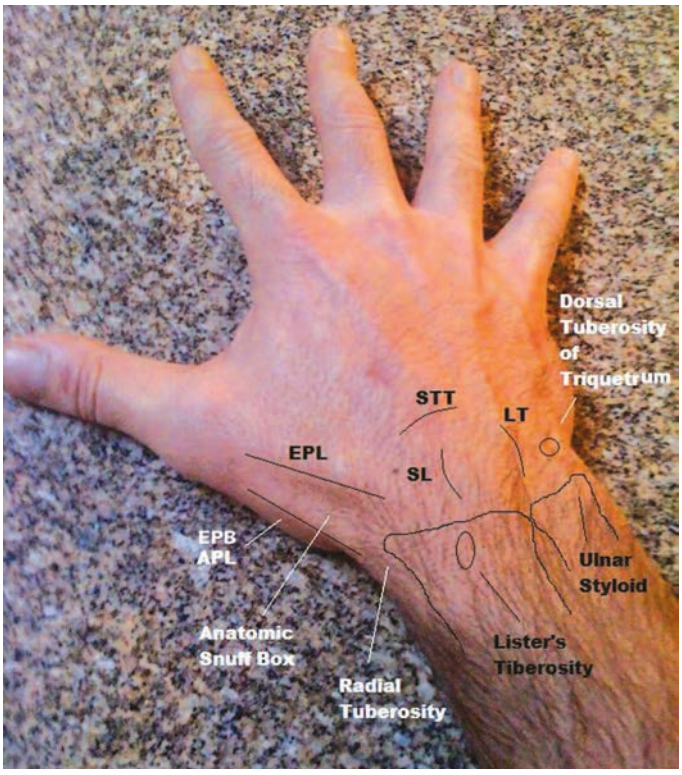
CLINICAL FEATURES

Begin assessment by **looking at both wrists** to assess for symmetry and range of motion in dorsiflexion, palmar flexion, and radioulnar deviation, in addition to obvious deformities and soft tissue swelling. Pinpoint areas of tenderness and correlate them to anatomic landmarks of the wrist to determine which structure may be injured and the best way to evaluate it radiographically (**Figure 269-3**).

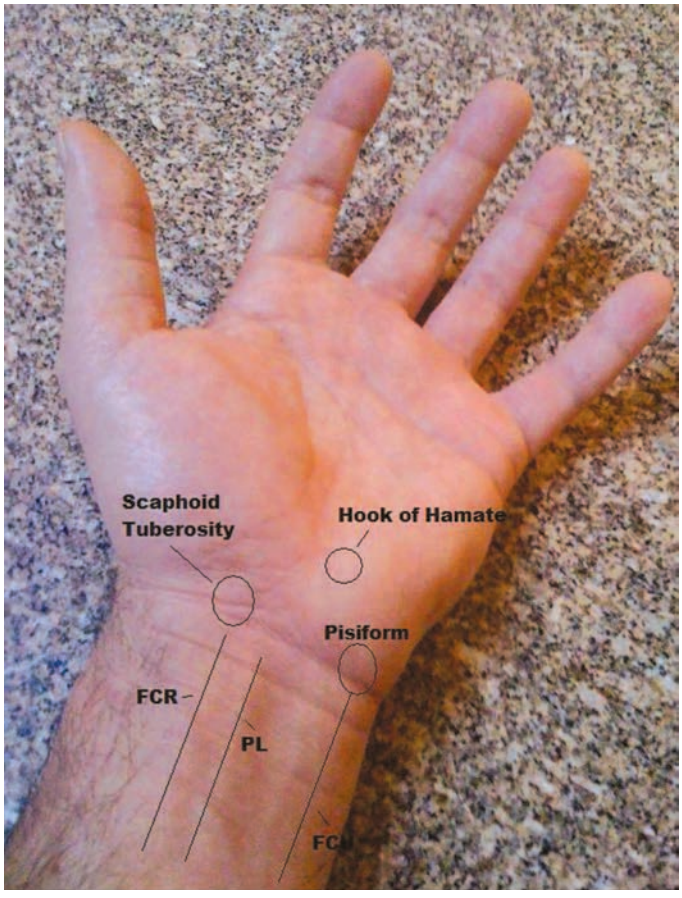
The most noteworthy landmark on the dorsum of the wrist is the anatomic snuffbox. **The anatomic snuffbox is a triangle formed by the bony radial styloid at its proximal base, the extensor pollicis brevis tendon at its radial aspect, and the extensor pollicis longus tendon at its ulnar aspect. Palpate the scaphoid within this triangle, as well as the scaphoid tubercle.**[12] Tenderness in this area may suggest a scaphoid fracture.[12] The extensor pollicis longus tendon wraps around a bony prominence of the distal radius, known as **Lister's tubercle**. The area immediately distal to this point marks the location of the scapholunate joint. Tenderness in this area suggests scapholunate ligamentous injury or lunate fracture.[13] The **scaphoid shift test** can further assess scapholunate ligament injury. To perform the scaphoid shift test, place the wrist in ulnar deviation and apply pressure with your thumb over the scaphoid tuberosity. Then move the wrist from ulnar to radial deviation; in the event of ligament injury, a palpable "clunk" will be felt.[4,13]

Immediately ulnar to the scapholunate joint is a palpable indentation in the center of the wrist. This is the location of the lunate and capitate, which are palpable as they rise out of this space during wrist flexion.[13] Wrist flexion allows lunate palpation distal to the radius in line with the third phalanx, ulnar to the scaphoid.[4] Tenderness here may indicate lunate or triquetrolunate joint injury. The ulnar styloid is the bony prominence on the ulnar aspect of the wrist. The triquetrum and triangular fibrocartilage complex are located just distal to this prominence. The triquetrum can be palpated on the volar distal wrist (distal to the ulna and pisiform) in line with the fifth phalanx.[4] Tenderness over the ulnar styloid may indicate ulnar styloid or triangular fibrocartilage complex injury. The **ulnocarpal stress test** can further evaluate the triangular fibrocartilage complex; apply a compression load to the wrist in ulnar deviation.[10] Pain or clicking may indicate triangular fibrocartilage complex injury.

Pain with pronation and supination of the forearm may indicate distal radioulnar joint injury. The **piano key sign**, which is the ulnar head springing back when depressed while supporting the forearm in pronation, suggests distal radioulnar joint injury.[13]



A



B

FIGURE 269-3. Surface anatomy of the wrist. **A.** Dorsal aspect. **B.** Palmar aspect. APL = abductor pollicis longus; EPB = extensor pollicis brevis; EPL = extensor pollicis longus; FCR = flexor carpi radialis; FCU = flexor carpi ulnaris; LT = lunotriquetral joint; PL = palmaris longus; SL = scapholunate joint; STT = scaphotrapeziotrapezoid joint.

The crease on the volar aspect of the wrist marks the location of the proximal carpal row (Figure 269-3). The scaphotrapezial joint is palpable at the base of the thenar eminence. The pisiform is the palpable bony prominence at the base of the hypothenar eminence. The hook of the hamate is palpable in the soft tissue 1 to 2 cm distal and radial to the pisiform in the hypothenar eminence.[14] Tenderness in these areas may require further evaluation than standard radiographic views.[15]

IMAGING

Clinical examination determines which radiographic views will best support a diagnosis. Standard views of the wrist include posteroanterior, lateral, and oblique views. These views are adequate in most cases, but other projections may be necessary for specific injuries.[15,16]

The key to interpreting the radiograph is to first ensure proper hand positioning, then identify specific features on each projection. On a properly positioned posteroanterior view, the distal radius and ulna should not overlap at their distal articulation, and the axis of the third metacarpal should parallel that of the radius. In addition to looking for disruption of the bony cortex, key elements on the posteroanterior view are illustrated in Figure 269-1.

On the posteroanterior view, three smooth arcs (Gilula lines) outline the articular surfaces at the radiocarpal and midcarpal joints. Two of these arcs are formed by the proximal and distal surfaces of the scaphoid, lunate, and triquetrum. The first arc includes the proximal scaphoid, whereas the second arc includes the distal scaphoid. The third arc is formed by the proximal articular surface of the capitate and hamate in the midcarpal joint. Any distortion of these lines implies a fracture, dislocation, or subluxation at the site.[4,15,16]

The carpal bones fit together much like a jigsaw puzzle, with the pieces separated by a uniform 1- to 2-mm space. This space is increased or obliterated with ligament disruption, carpal instability patterns, or fracture/dislocations. This occurs most often around the lunate at the scapholunate and capitolunate joints.

The **scaphoid** has an elongated shape in its normal, palmarly flexed position. Fractures or ligament disruption may cause further palmar rotation, causing the scaphoid to appear shortened on the posteroanterior view. Injuries to the scaphoid also may obscure the **scaphoid fat stripe**, a linear or triangular radiolucent collection of fat distal to the radial styloid and parallel to the radial border of the scaphoid.

Unfortunately, incorrect positioning can produce overlap patterns that can be misinterpreted as pathologic. For example, radial deviation of the wrist causes normal physiologic rotation of the proximal carpal row, obliterating the capitolunate space. At the same time, the scaphoid that should appear elongated on the posteroanterior view appears shorter as it rotates palmarly and can be confused with a rotary subluxation of the scaphoid.

The **radial styloid** should project 8 to 18 mm beyond the distal radioulnar joint and create an ulnar inclination of 13 to 30 degrees on the posteroanterior view. Distal radius fractures can alter these measurements. At the distal radioulnar joint, the ulna and adjacent portion of the radius should be of equal length, forming a smooth articular surface, and the distal radius generally should articulate with at least half the lunate. The extrinsic ligaments along with the triangular fibrocartilage complex prevent ulnar translocation (migration of the carpal bones down the ulnar tilt of the radiocarpal surface).[17] The lunate would have less contact and support from the radius if ulnar translocation were present. A shorter ulna (negative ulnar variance) provides less support to the lunate and increases potential shear stress to the lunate, predisposing the lunate to injury.[18]

A properly positioned lateral radiograph is important for determining carpal alignment and degree of fracture angulation.[15] The radius and ulna should completely overlap one another, and the radial styloid should be centered over the distal radial articular surface. The key elements are illustrated in **Figure 269-4A**.

The axis of the radius, lunate, and capitate is collinear on the lateral view. If the articular surfaces of these bones were highlighted, they would appear as three consecutive C's. This provides a simple radiographic assessment of wrist dislocation. Measurement of the capitolunate and scapholunate angles is a more precise assessment of carpal alignment. The axis of the capitate, lunate, and scaphoid runs through the center of their proximal and distal articular surfaces. The axis of the lunate and

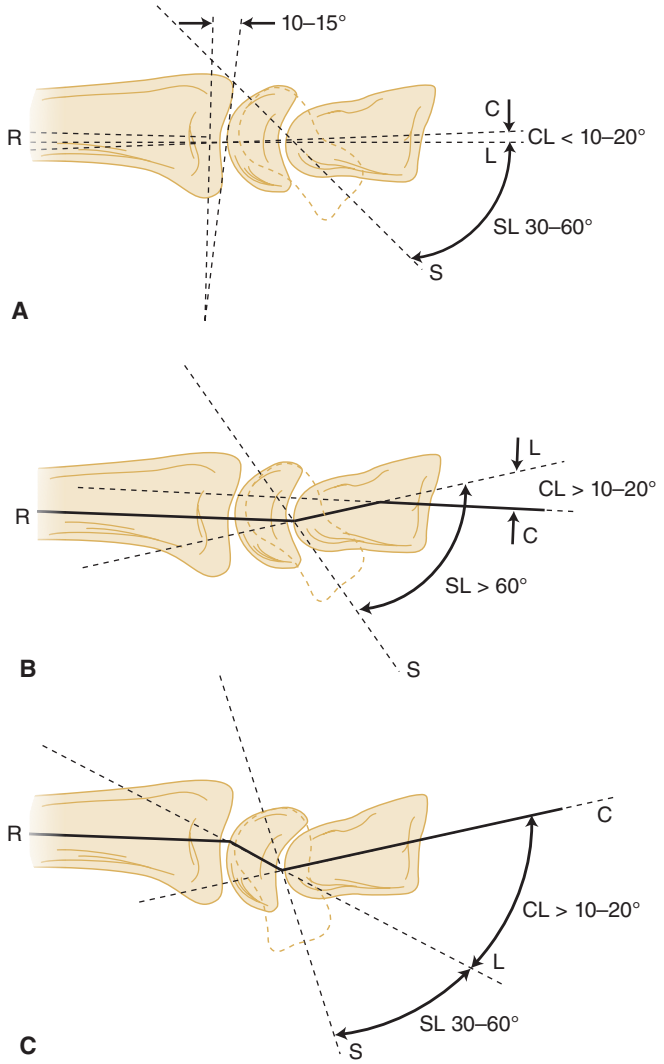


FIGURE 269-4. **A.** Normal wrist. Axis of the radius (R), lunate (L), and capitate (C) are collinear (three C's sign). The capitolunate (CL) angle is <10 to 20 degrees. The scapholunate (SL) angle is between 30 and 60 degrees. The radial volar tilt is 10 to 15 degrees. **B.** Dorsal intercalated segment instability. The lunate tilts dorsal and slides palmar, increasing the capitolunate angle. The scaphoid (S) tilts more palmar and increases the scapholunate angle. The axes of the radius, lunate, and capitate take on a zigzag pattern (yellow line). **C.** Volar intercalated segment instability. The lunate tilts palmar and the capitolunate angle increases, but the scapholunate angle is maintained. The zigzag pattern is in the opposite direction.

capitate should nearly overlap and form an angle that is <10 to 20 degrees. **The scaphoid is normally palmar-flexed on the lateral view; its axis should form an angle between 30 and 60 degrees with the lunate.** Deviation from either of these angles suggests ligament disruption and carpal instability patterns (**Figure 269-4B** and **C**).[19]

Fracture of the distal radius is the most common fracture in the wrist.[17] Although a displaced fracture is the obvious deformity, the **alteration of the normal volar tilt of 10 to 15 degrees of the distal radial articular surface has greater long-term consequences for wrist function**, resulting in carpal misalignment and, subsequently, the instability patterns mentioned above.[18]

Other radiographic views profile specific areas of the wrist. Oblique views are performed in either partial pronation or supination and project the scaphotrapezial joint or pisiform away from overlapping adjacent carpal bones. The scaphoid view is a cone-down posteroanterior view of the scaphoid in ulnar deviation. This position extends the normal flexed posture of the scaphoid so that the bone is projected lengthwise. This view may assist in detecting subtle fractures and is used whenever scaphoid injury is suspected.[16] The carpal tunnel view is a tangential view through the carpal tunnel and is helpful in visualizing the pisiform and hook of the hamate. Motion studies are dynamic views in flexion, extension, and radial and ulnar deviation. These views examine carpal movement relative to one another and stress the intercarpal ligaments for laxity, characterized by widening of the intercarpal space.[20] Likewise, the grip compression or fist view is a stress view in the posteroanterior projection of the tightly clenched fist. The capitate is pushed into the proximal carpal row and forces the carpal bones apart if intrinsic ligaments are disrupted. CT is useful for defining fractures and dislocations, whereas MRI is useful for evaluation for both bony and soft tissue abnormalities such as occult fractures, avascular necrosis, and triangular fibrocartilage complex abnormality.[20] **Table 269-1** presents a summary of standard and supplemental wrist radiographs and the injuries they enhance.

TABLE 269-1 Wrist Radiography

View	Injuries to Identify
Posteroanterior	Distal radius/ulna fractures, carpal bone fractures, ligamentous disruptions
Lateral	Radius/ulna fractures, lunate/perilunate dislocation, dorsal intercalated segment instability, volar intercalated segment instability
Scaphoid	Scaphoid fracture, scapholunate dissociation
Carpal tunnel	Pisiform and hamate fractures
Motion studies	Scapholunate or triquetrolunate instability
Grip compression	Scapholunate or triquetrolunate instability
CT	All fractures and dislocations
MRI	Occult fracture, avascular necrosis, soft tissue abnormality

LIGAMENTOUS INJURIES

The lunate is located in the middle of the wrist, so it is not surprising that the majority of ligamentous injuries are centered on the **lunate**. Injuries usually result from forceful dorsiflexion of the wrist, most often from a fall on an outstretched hand. The various injuries occur sequentially depending on the degree of force and range from isolated tears to perilunate and lunate dislocations.[21,22] Although infrequent, they account for 7% of carpal injuries.[23] Four distinct stages are present: scapholunate, perilunate, perilunate and triquetrum, and lunate dislocation.[23,24]

SCAPHOLUNATE LIGAMENT INSTABILITY

The scapholunate ligament is the intrinsic ligament that binds the scaphoid and lunate. Because the scaphoid bridges the proximal and distal carpal rows, the **scapholunate ligament has a marked propensity for injury and is the most commonly injured ligament of the wrist**. Injury most often is from a fall on an outstretched hand with impact on the thenar eminence.[21] Patients complain of pain and swelling on the radial side of the wrist and often a "clicking" sensation with wrist movement. Examination reveals localized tenderness on the dorsum of the wrist in the area immediately distal to Lister's tubercle. Ballottement of the scaphoid may also produce pain in this area.[19]

This injury is often referred to by the various radiographic appearances it may take. There are three different radiographic signs that may occur separately or in combination with one another (**Figure 269-5A**). **Scapholunate dissociation is a widening of the scapholunate joint space of >3 mm on the posteroanterior view or >8 mm on the ulnar/deviation/clenched fist view.** If it is not apparent on routine views, a grip compression view or motion study may be necessary to demonstrate the abnormal gap (**Figure 269-5B**).[4,22] These maneuvers are particularly helpful in identifying an incomplete tear of the ligament. Rotary subluxation of the scaphoid is another radiographic finding that often accompanies scapholunate dissociation. A torn scapholunate ligament can cause the scaphoid to tilt more palmar and increase the scapholunate angle to >60 degrees on the lateral view. On the posteroanterior view, the scaphoid tilts toward the observer so that it appears shorter as it is viewed more on its end. This causes the circular cortex of the bone to become more prominent and appear as a ring, known as the "cortical ring sign" (Figure 269-5A).



A



B



C

FIGURE 269-5. **A.** Scapholunate dissociation and rotary subluxation of the scaphoid. The scaphoid and lunate are separated by a gap of >3 mm (*black arrow*), and the scaphoid appears shorter from rotation with a dense ring, the "cortical ring sign" (*white arrow*). **B.** Grip compression view showing enhancement of scapholunate dissociation (*arrow*). **C.** Dorsal intercalated segment instability. Lateral view exhibiting dorsal intercalated instability with scapholunate dissociation. (See Figure 269-4.)

A third radiographic abnormality is a carpal instability pattern known as **dorsal intercalated segment instability** (Figure 269-4B). The normal flexed posture of the scaphoid produces a flexion torque on the lunate that is counterbalanced by an extension torque from the triquetrum. When the scapholunate ligament is torn, this balance is disrupted. The lunate tilts dorsal from the unopposed extension torque from the triquetrum, whereas the scaphoid tilts more palmar (rotary subluxation of the scaphoid) because it has lost support from the lunate. The dorsal tilt of the lunate also causes a slight flexion tilt of the capitate. In the lateral view, the normal collinear arrangement of the axes of the capitate, lunate, and radius is replaced by a characteristic zigzag pattern. Both the scapholunate and capitolunate angles are increased. The concept of the proximal carpal row being the middle link or "intercalated segment" in this system, combined with the lunate's pathologic dorsal tilt and zigzag pattern (**Figure 269-5C**), is how this abnormality came to be named dorsal intercalated segment instability.

Refer to an orthopedist or hand surgeon. **ED treatment is with a radial gutter splint or short arm volar posterior mold.** Orthopedic referral is necessary because these injuries require either closed reduction with percutaneous pinning or open reduction and internal repair of the ligament.[21] Dorsal intercalated segment instability and subsequent early, severe degenerative arthritis can occur if left untreated.[18] Failure to identify this injury may result in scapholunate advanced collapse and altered wrist biomechanics.[25,26]

TRIQUETROLUNATE LIGAMENT INSTABILITY

The triquetrolunate ligament binds the triquetrum and lunate on the ulnar aspect of the wrist. Injury to this ligament is the ulnar equivalent of the scapholunate ligament injury. Triquetrolunate ligament injury occurs much less often than scapholunate ligament injury, is more stable, and can be confused with other causes of ulnar-sided wrist pain such as triangular fibrocartilage complex injury or distal radioulnar joint abnormality.[18,19] This injury most often results from falls on the outstretched, dorsiflexed hand with impact on the hypothenar eminence. There will be localized tenderness on the ulnar aspect of the wrist just distal to the ulna. Ballottement of the triquetrum may produce a painful clicking sensation.[4]

Subtle injuries may have a normal radiographic appearance.[18] Complete disruption of the triquetrolunate ligament removes the ability of the triquetrum to counterbalance the flexion torque from the palmar-flexed scaphoid. The lunate then tilts palmar, and the capitate extends slightly in response. A zigzag pattern in the opposite direction of the scapholunate injury is produced. The capitolunate angle is increased >10 to 20 degrees; however, the scapholunate angle is unaffected because the scapholunate ligament is still intact. The lateral radiograph may reveal the "volar intercalated segment instability" pattern (Figure 269-4C and **Figure 269-6**). The posteroanterior view may reveal a widening of the triquetrolunate joint space and obliteration of the capitolunate joint space and the normal smooth arcs typically seen because of the volar tilt of the lunate.

Refer to an orthopedist or hand surgeon. **ED treatment is an ulnar gutter splint or short arm posterior mold** and referral to an orthopedist. Immobilization in a cast for 6 to 8 weeks, followed by a protective splint, is sufficient in most cases. Open reduction and internal fixation are generally reserved for chronic injuries.[18] Unrecognized injuries can cause early degenerative arthritis, weakened grip, ulnar neuropathy, and chronic wrist pain.[27,28]

PERILUNATE AND LUNATE DISLOCATIONS

Perilunate and lunate dislocations represent the final stages of midcarpal ligament disruption and are thought to account for 10% of all carpal injuries.[29] These injuries are the result of forceful dorsiflexion and impact on the outstretched hand, but usually with great force, such as a fall from height, impact from a motor vehicle collision, or a sporting event.[30] These injuries are often associated with other injuries, including scaphoid fractures (61% to 65%) and other upper extremity injuries (11%).[4,31] Polytrauma involving other systems is present in 26% of these patients.[31]

Perilunate dislocation is the posterior dislocation of carpal bones while the lunate maintains its position with respect to the distal radius. This is a very rare dislocation. **Lunate dislocation** produces posterior dislocation of carpal bones with the concavity of the lunate facing anteriorly.

The injury can begin on either side of the lunate, but typically begins on the radial aspect, with either a tear of the scapholunate ligament or a fracture of the scaphoid. Injury progresses around the lunate in a semicircular fashion, tearing the volar ligament arcade at the radiocapitate ligament. Remember that the extrinsic ligaments form two strong volar arcades with an inherently weak area between them that widens with dorsiflexion of the wrist (Figure 269-2). The **space of Poirier** lies at the

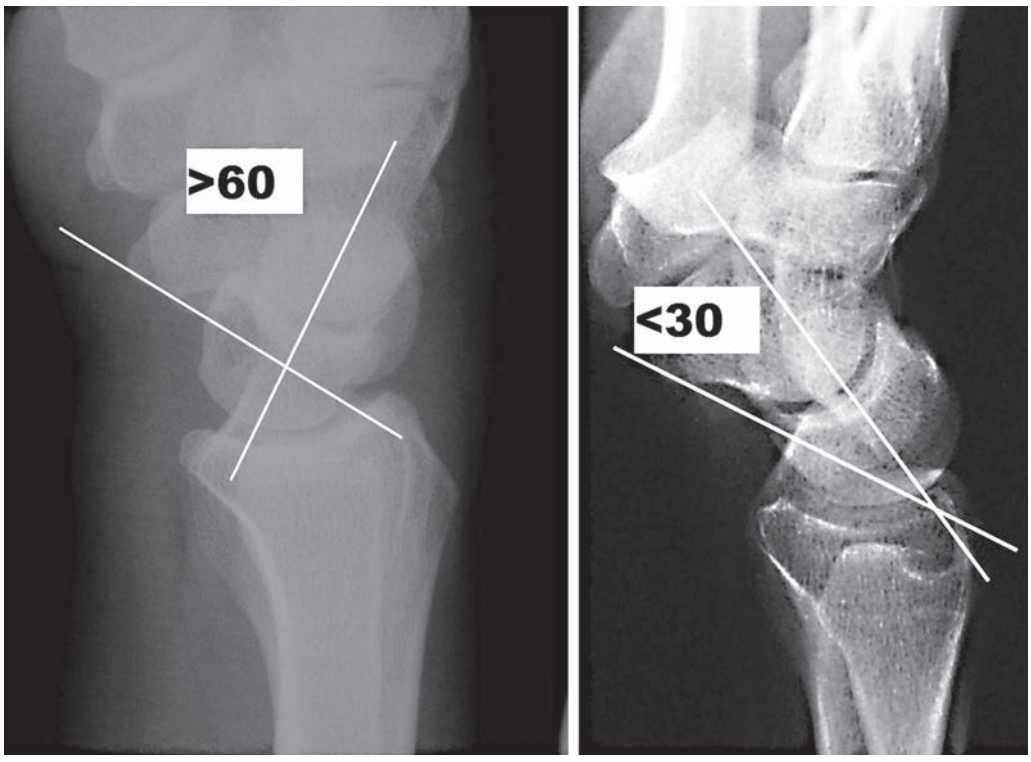


FIGURE 269-6. **A.** Volar intercalated instability. Note widened capitolunate angle. **B.** Dorsal intercalated instability.

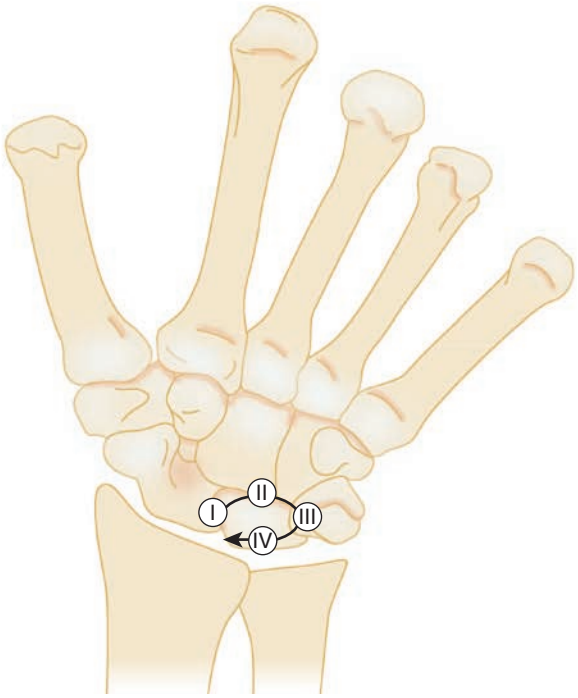


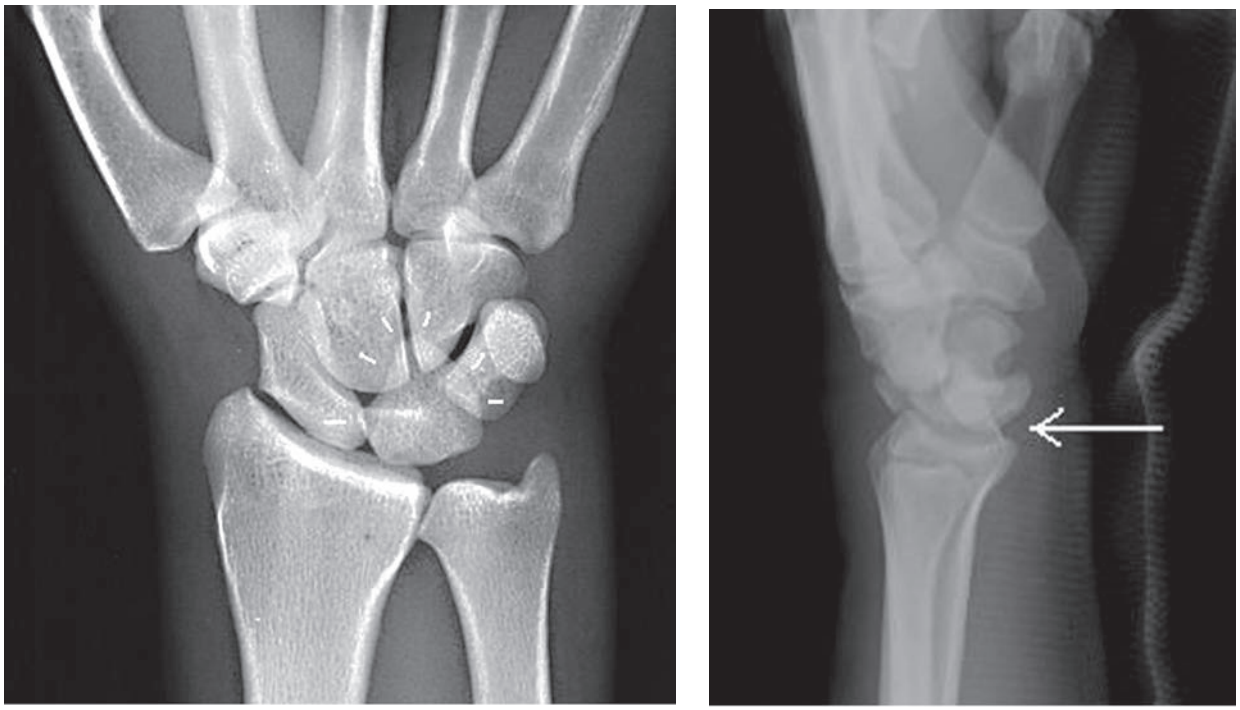
FIGURE 269-7. Four stages of perilunate instability. The first stage (I) is disruption of the scapholunate articulation (scapholunate dissociation). The second (II) and third (III) stages are separation of the capitolunate and triquetrolunate joints (perilunate dislocation). The fourth (IV) stage is a lunate dislocation.

junction of the lunate and capitate. This space opens further as heavy loading disrupts the lunotriquetral ligament. Besides ligament disruption, any number of carpal bones may fracture along an arc around the lunate (**Figure 269-7**). If sufficient force is applied, the ligaments and carpal bones around the lunate are stripped away. The capitate is displaced dorsal to the lunate, producing a **perilunate dislocation**. If the capitate rebounds with sufficient force, it can push the lunate off the radius and into the palm, creating a **lunate dislocation**. These injuries are all part of a continuous spectrum of ligament disruption (Figure 269-7).[32]

On clinical examination, there is generalized swelling, pain, and tenderness of the wrist. However, a gross deformity, typical of many joint dislocations, is often absent. Radiographic interpretation is the key to diagnosis. **The perilunate dislocation is best appreciated on the lateral view. The linear arrangement of the three C's sign is disrupted with the capitate, represented by the third C, displaced dorsal to the lunate. The lunate retains its contact with the radius.** The scapholunate and capitolunate angles are increased. On the posteroanterior view, the three smooth arcs are disrupted, and the capitolunate joint space is obliterated as the bones overlap one another. The scapholunate and triquetrolunate joint space may either be increased because of torn ligaments or obliterated by rotation of the fractured carpal fragments. The scaphoid will appear shortened from rotary subluxation or fracture (**Figure 269-8**). A perilunate dislocation may also overshadow any associated carpal bone fracture. The scaphoid and capitate are most often involved, so carefully inspect these bones for fractures. Such fractures are designated by adding the prefix "trans-" to the carpal bone name (e.g., transscaphoid perilunate dislocation) (**Figure 269-9**).

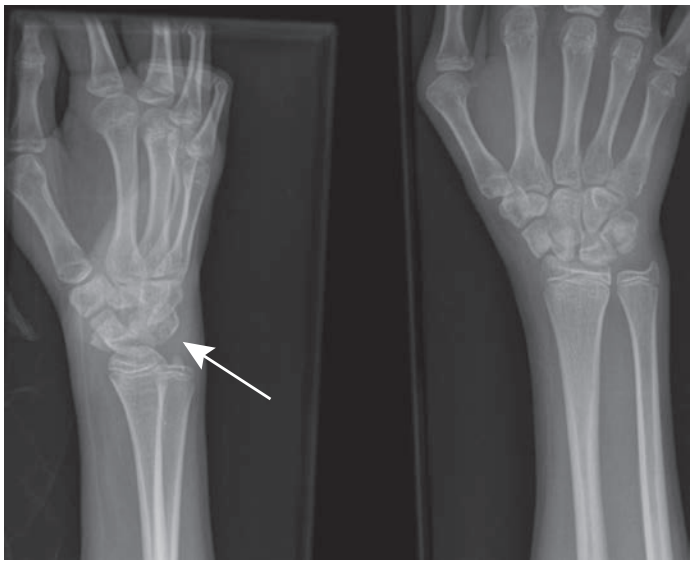
A lunate dislocation has many similar and several distinct radiographic features when compared with a perilunate dislocation. On the posteroanterior view, the lunate has a triangular shape ("piece-of-pie" sign) that is suggestive of lunate dislocation (**Figure 269-10A**). On the lateral view, it also disrupts the three C's sign. **The lunate (represented by the middle C) is pushed off the radius into the palm. This has been called the "spilled teacup" sign because it resembles a cup spilling in the direction of the palm (Figure 269-10B).** The capitate may rebound back and even rest on the radius. The signs of ligament disruption and the associated carpal bone fractures described with perilunate injuries may also be present.

Perilunate or lunate dislocations require emergency orthopedic/hand consultation.[32] Treatment is determined by the extent of the injury. Closed reduction and long arm splint immobilization are appropriate for reducible dislocations, although closed reductions are often



A B

FIGURE 269-8. Perilunate dislocation. **A.** Posteroanterior view shows obliteration of the three smooth arcs as bones overlap one another (*white hash marks*). **B.** Lateral view shows capitate dorsal to lunate, disrupting the "three C's" (*arrow*).



A



B

FIGURE 269-9. A and B. Transscaphoid perilunate dislocation. [Photos contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

unsuccessful.[30,31] Open, unstable, and irreducible dislocations require open reduction and internal fixation, with repair of the ligaments and fractures. Some orthopedists operate on all perilunate and lunate dislocations.[18] **The complications include development of carpal instability patterns that lead to early degenerative arthritis, delayed union, malunion, nonunion, avascular necrosis, and occasionally, median nerve compression from the volar dislocation of the lunate into the carpal tunnel.[30]**



A



B

FIGURE 269-10. Lunate dislocation. **A.** Posteroanterior view demonstrates pathognomonic triangular shape of the lunate (piece-of-pie sign; *circle*). **B.** Lateral view exhibits the lunate tilting into the palm (spilled teacup sign; *circle*) and the capitate positioned dorsal to the lunate (*arrow*).

CARPAL BONE FRACTURES

Carpal bone fractures are the most commonly missed wrist injuries. A careful examination is critical to recognize carpal bone fractures. The carpal fractures are listed in **Table 269-2** in descending order of occurrence.

SCAPHOID FRACTURE

The scaphoid is the most common carpal bone fractured, with non-scaphoid fractures accounting for the other 13% to 38% of carpal bone fractures.[4,33] Scaphoid injuries result from a fall on either an outstretched dorsiflexed hand or from an axial load directed along the thumb's metacarpal. There is pain along the radial aspect of the wrist and localized tenderness in the anatomic snuffbox.[34,35] Examination of the wrist in ulnar deviation exposes more of the scaphoid to direct palpation within the anatomic snuffbox. Snuffbox tenderness demonstrates a sensitivity and specificity for scaphoid fracture of 90% and 40%, respectively, whereas tubercle tenderness demonstrates a sensitivity and specificity of 87% and 57%, respectively. Eliciting pain in this area when the patient resists supination or pronation of the hand (sensitivity 79% and specificity 58%) or pain with axial pressure directed along the thumb's metacarpal also suggests injury. Pain at the snuffbox with thumb–index finger pinch possesses a sensitivity of 73% and specificity of 75%.[34,35] One study examined the combination of several findings for diagnosis of scaphoid fracture including anatomic snuffbox tenderness, scaphoid tubercle tenderness, tenderness with longitudinal compression of thumb on scaphoid, and pain with active thumb movement. The first three maneuvers demonstrated an individual sensitivity of 100%, whereas the fourth had a sensitivity of 69%.[34] Specificities included 9%, 30%, 48%, and 66%, respectively, and if the first three maneuvers were combined, specificity increased to 75%.[34]

Radiographic evaluation includes both standard and scaphoid views for cortical disruption (**Figure 269-11**). The scaphoid view profiles the bone lengthwise and may assist in detecting subtle fractures. Distortion of a soft tissue fat stripe adjacent to the radial aspect of the scaphoid is suggestive of injury. Two thirds of the fractures occur at the waist or middle third of the bone, 16% to 28% in the proximal third, and 10% in the distal third.[4] CT possesses a sensitivity of 89% to 100% and specificity of 85% to 100%. MRI demonstrates a sensitivity of 98% to 100% and specificity up to 100%.[36,37] A scaphoid fracture may also have an associated injury in 12% of cases.[4] Associated injuries may include the radius, neighboring carpal bones, a carpal instability pattern, or a dislocation. In patients with initial negative plain films, yet in whom a high index of suspicion remains for fracture, MRI is considered the gold standard for definitive diagnosis.[38]

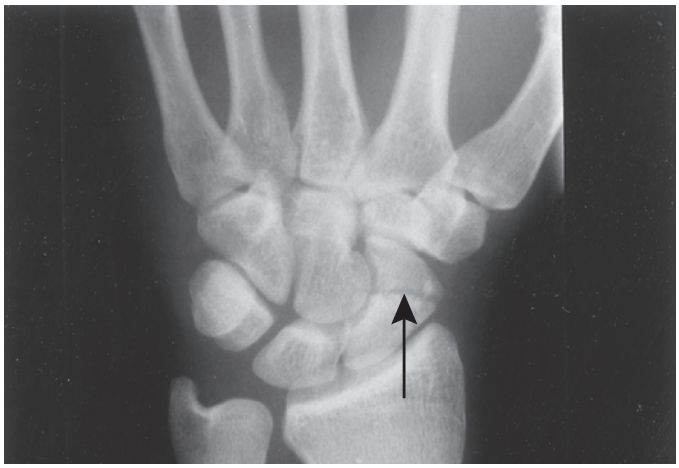


FIGURE 269-11. Scaphoid fracture in the middle third or waist (*arrow*).

A scaphoid fracture can develop avascular necrosis of the proximal fracture segment that can lead to disabling arthritis.[39] Because the vascular supply to the scaphoid enters the distal portion of the bone through small branches off the radial artery and palmar and superficial arteries, a fracture can easily disrupt the blood supply to the proximal segment. The more proximal, oblique, or displaced a fracture, the greater is the risk of developing avascular necrosis (up to 80% of proximal fractures result in necrosis).[4,39,40] A scaphoid fracture is considered unstable if it is oblique, if there is as little as 1 mm of displacement, if

TABLE 269-2 Summary of Carpal Bone Fractures and ED Management

Carpal Bone	Mechanism of Injury	Examination	Initial ED Management
Scaphoid	Fall on outstretched hand or axial load on thumb metacarpal	Snuffbox tenderness; pain with radial deviation and flexion; scaphoid tubercle tenderness; pain with resisted supination/pronation; pain with active thumb movement	If diagnosed, long arm thumb spica splint in dorsiflexion with radial deviation If continued pain but no definitive radiograph findings, short arm thumb spica splint, in dorsiflexion with radial deviation
Triquetrum	Avulsion fracture—twisting of hand against resistance or hyperextension and ulnar deviation Body fracture—direct trauma	Tenderness at the dorsum of the wrist, distal to the ulnar styloid; axial compression along the third metacarpal may cause pain	Short arm sugar-tong splint
Lunate	Fall on outstretched hand or trauma to the wrist in hyperextension and ulnar deviation	Tenderness at shallow indentation of the mid-dorsum of the wrist, ulnar and distal to Lister's tubercle	Short arm thumb spica splint
Trapezium	Direct blow to thumb; force to wrist while dorsiflexed and radially deviated	Painful thumb movement and weak pinch strength Snuffbox tenderness	Short arm thumb spica splint
Pisiform	Fall or trauma directed on the hypothenar eminence	Tender pisiform, prominent at the base of the hypothenar eminence; decreased grip strength; ulnar/median nerve paresthesias may occur	Short arm volar splint in 30 degrees of flexion and ulnar deviation
Hamate	Interrupted swing of a golf club, bat, or racquet; repeated microtrauma or acute fall	Tenderness at the hook of the hamate, just distal and radial to the pisiform; positive hook of hamate test	Short arm volar wrist splint with fourth and fifth metacarpal joints in flexion
Capitate	Forceful dorsiflexion of the hand with radial impact; direct blow to the dorsum of the wrist; force applied to the second to fourth metacarpals; flexion force to the wrist	Tenderness and swelling over the capitate just proximal to the third metacarpal	Short arm volar wrist splint
Trapezoid	Axial load onto the index metacarpal; second metacarpal palmar hyperflexion	Tenderness over the radial aspect of the base of the index metacarpal	Short arm thumb spica splint

there is rotation or comminution, or if a carpal instability pattern is present. Two thirds of the scaphoid's surface is articular. This only adds to the scaphoid's problems because articular fractures are more difficult to heal. Thus, the main complications of improperly healed scaphoid fractures are avascular necrosis, delayed union, nonunion, malunion, and subsequent early degenerative arthritis.

Up to 16% of initial radiographs fail to detect a fracture, so initial treatment should be directed by clinical suspicion.[34,36] Immobilize scaphoid fractures in a long arm thumb spica splint with hand surgery consultation. If fracture is suspected despite negative radiograph, apply a short arm thumb spica splint, with repeat imaging in 7 to 10 days.[4,39,40] Several studies have evaluated immediate CT or MRI for definitive diagnosis versus prolonged immobilization on costs (including patient lost income and productivity), suggesting earlier advanced imaging is more cost effective.[40-42]

TRIQUETRUM FRACTURE

Triquetrum fractures are the second most common carpal bone injury, accounting for up to 20% of carpal fractures, and occur as a fracture through the dorsal cortex, palmar cortex, or body.[33,43] Avulsion fractures are produced when a twisting motion of the hand is suddenly resisted or a hyperextension shear stress pushes the hamate or ulnar styloid against the triquetrum. This may occur with a fall on an outstretched hand with hyperextension and ulnar deviation.[4,33] Fractures of the body occur from direct trauma and are found in association with perilunate and lunate dislocations (part of the arc fractures). Localized tenderness is found over the dorsum of the wrist in the area immediately distal to the ulnar styloid. **The dorsal avulsion fracture is best seen on the lateral radiograph or an oblique view in partial pronation.** The fracture appears as a tiny flake of bone on the dorsum of the triquetrum best seen on lateral view (**Figure 269-12**). Triquetrum body fractures are usually nondisplaced because numerous ligaments encase the bone; these are best seen on the posteroanterior view. Nonunion is possible, but avascular necrosis has not been reported.

Refer triquetrum fractures to an orthopedist or hand surgeon. Patients with a dorsal avulsion fracture have an excellent prognosis for full recovery. Symptomatic patients are treated with a wrist splint for 1 to 2 weeks. Asymptomatic or minimally symptomatic patients may be treated with early range of motion. Stable body fractures are treated in a cast for 6 weeks. Unstable body fractures (>1 mm displacement) and those associated with perilunate/lunate dislocations may require internal fixation.[33,44] Palmar cortical fractures are treated surgically.[33]

LUNATE FRACTURE

Lunate fractures tend to occur with other carpal injuries. Isolated lunate injuries are rare, as 70% of the lunate rests on the radius and 30% articulates with the TFCC.[4,33] The mechanism of injury is commonly the result of a fall on the outstretched hand or trauma to the wrist in hyperextension and ulnar deviation.[33] The lunate is present in the shallow indentation on the mid-dorsum of the wrist. The lunate is easily palpable as it rises out of the floor of this indentation when the wrist is in a flexed position. Examination reveals tenderness at this point. Axial compression applied along the third metacarpal ray may also elicit pain in this area and is suggestive of injury. **The lunate's blood supply enters through the distal end of the bone. A fracture subjects the lunate to risk for avascular necrosis of the proximal portion.[4,24]**

The lunate is seated in the middle of the wrist, so overlap with other carpal bones may make it difficult to identify an injury on a plain radiograph. On the lateral radiograph, the lunate, capitate, and distal radius should lie in the same vertical plane.

Refer suspected or actual lunate fractures to an orthopedist or hand surgeon. Clinical suspicion dictates the acute treatment. A short arm thumb spica splint should be applied when the diagnosis is unclear. MRI and CT may be used to identify occult fractures. The major complication is avascular necrosis (Kienböck's disease), leading to lunate collapse, osteoarthritis, chronic pain, and decreased grip strength.[4]

TRAPEZIUM FRACTURE

The trapezium is a saddle-shaped bone that articulates with the thumb metacarpal. Injuries are produced by a direct blow to the thumb or from a dorsiflexion and radial deviation force. Fractures occur either at the trapezial ridge or body and are often intra-articular. Vertical fractures occur and are analogous to a Bennett's fracture (an intra-articular proximal thumb metacarpal fracture) (**Figure 269-13**). Examination reveals painful thumb movement and a weak pinch. There is tenderness at the apex of the anatomic snuffbox and at the base of the thenar eminence. This injury is best profiled on a 20-degree pronated oblique view. The major complication is nonunion.

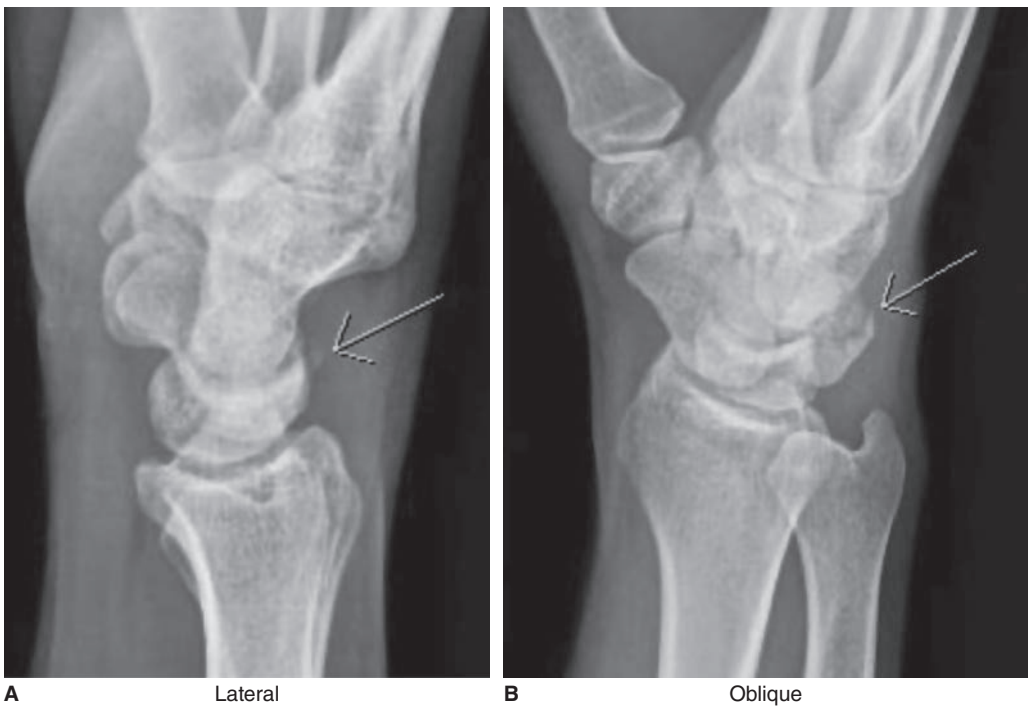


FIGURE 269-12. A and B. Triquetrum fracture seen at tip of *arrow*. [Photos contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]



FIGURE 269-13. Trapezium fracture seen at tip of *arrow*. [Photo contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

Refer to an orthopedist or hand surgeon. Initial ED stabilization of nondisplaced fractures is a short arm thumb spica splint. **Displaced fractures >1 mm or diastases >2 mm require surgery.**[45] Missed diagnosis or inadequate management can result in permanent pinch and grip strength impairment.[4]

PISIFORM FRACTURE

The pisiform is a sesamoid bone within the flexor carpi ulnaris tendon. It is positioned immediately volar to the triquetrum and is the palpable bony prominence at the base of the hypothenar eminence. Injuries usually result from a fall or trauma directed on the hypothenar eminence. There will be localized tenderness on the pisiform itself, as well as decreased grip strength and ulnar/median nerve paresthesias.[46,47] If the wrist is flexed, the pisiform can be grasped and palpated between the examiner's fingers. This should elicit pain. The pisiform and hook of the hamate form the bony walls of **Guyon's canal** that contains the ulnar nerve and artery; therefore, it is important to exclude injury to them.[46] Radiographs in partial supination, or the carpal tunnel view, are optimal because they remove the overlap with the triquetrum that is present on standard views (**Figure 269-14**).[47] The pisiform is the last carpal bone to ossify, and it is usually complete by age 12 years old. Before the age of 12, multiple ossification centers in the pisiform may be confused with a fracture. The ossification centers differ in that they will have smoother margins and lack the perfect jigsaw-puzzle fit seen with fracture fragments. After age 12, any radiographic line is suggestive of fracture.

Refer to an orthopedist or hand surgeon. ED treatment is either a compression dressing or a splint in 30 degrees of flexion with ulnar deviation that relaxes the tension from the flexor carpi ulnaris. Pisiform fractures have an excellent prognosis. Complications include diminished grip strength and ulnar nerve palsy.[46]



FIGURE 269-14. Pisiform fracture. [Photo contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

HAMATE FRACTURE

Hamate fractures may involve the body of the hamate, the hook of the hamate, or any of its articular surfaces. Body fractures are rare and are generally associated with fracture dislocations of the fourth or fifth metacarpals (**Figure 269-15**). Most hamate fractures involve the hamate hook, which is a small bony prominence on its volar aspect. The classic mechanism is an interrupted swing with a golf club, bat, or racquet. The handle impacts against the hypothenar eminence and compresses the bone. Others include repeated microtrauma or fall. Localized tenderness over the hook of the hamate is found by palpating the soft tissue of the hypothenar eminence, distal and radial to the pisiform. Other findings suggesting fracture include the hook of hamate pull test, in which the hand is held in ulnar deviation as the patient flexes the distal interphalangeal joints of the fourth and fifth digits, which causes pain. **Standard and carpal tunnel views are necessary to visualize the fracture,** although sensitivity is 71%.[33,47] **Occult fractures may be identified by bone scan or CT** (sensitivity approaches 100%).[4,33] Physical examination should assess for injury to **Guyon's canal** (**Figure 269-16**), which houses the ulnar nerve and artery.

Refer to an orthopedist or hand surgeon. In the ED, treat hamate hook fractures with a compression dressing or ulnar gutter splint. Nonunion is common, and excision of the bone may be necessary. Nondisplaced body fractures are treated by splint immobilization. Displaced body fractures or those with injury to Guyon's canal are surgically treated. Complications include ulnar and/or median nerve neuropathy, as well as decreased grip strength.

CAPITATE FRACTURE

The capitate is the largest carpal bone. It is an elongated bone with a large proximal head that articulates with the lunate. The midportion



FIGURE 269-15. Hamate fracture (*arrow*) is best seen on posteroanterior (PA) view. [Photo contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

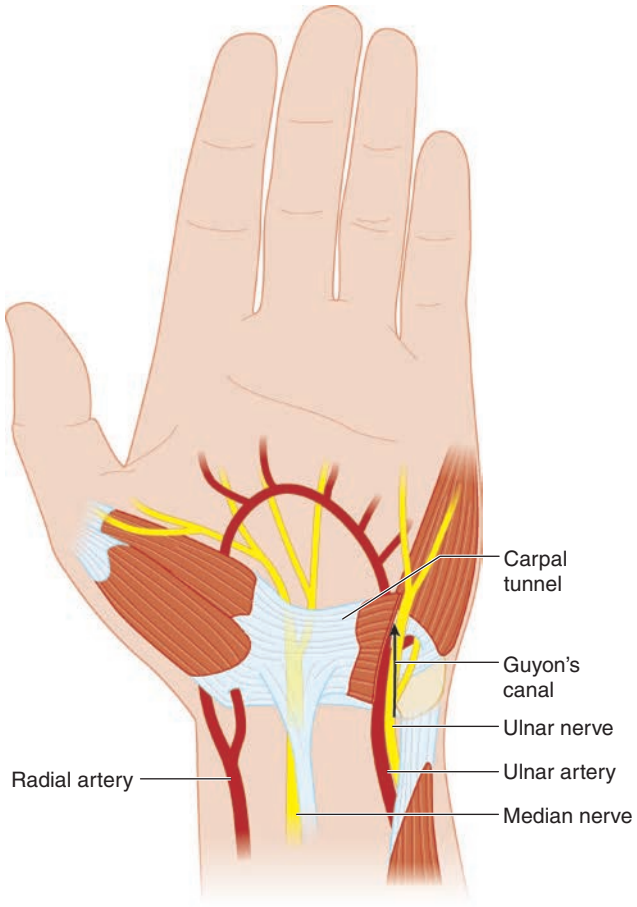


FIGURE 269-16. Guyon's canal.

of the bone is the neck, and the distal end, or body, articulates with the third metacarpal. Capitate fractures most often occur in the neck and usually occur in conjunction with a scaphoid fracture (**Figure 269-17**). The association of scaphoid and capitate fractures is called the **scaphocapitate syndrome**. Isolated capitate fractures are rare.[48] Capitate fractures result from forceful dorsiflexion of the hand with impact on the radial side, direct blow to the dorsum of the wrist, force applied to the second to fourth metacarpals, or flexion force to the wrist. The scaphoid fractures first, and then the neck of the capitate fractures. The fracture can continue around the lunate, creating other so-called arc fractures, eventually resulting in perilunate or lunate dislocation. The capitate's blood supply enters through the distal end. Thus, capitate fractures also share the same potential avascular necrosis of the proximal fracture segment as the lunate and scaphoid.

Physical examination reveals diffuse swelling and tenderness over the capitate, just proximal to the third metacarpal. Radiographs include posteroanterior radial and ulnar deviation views. Capitate neck fractures are best seen on the lateral radiograph. If radiograph is negative, then CT or MRI may be needed. The head of the capitate should be carefully identified because it can rotate as much as 180 degrees. A capitate fracture is often overlooked because of the accompanying scaphoid fracture or perilunate/lunate dislocation that overshadows it. Complications include avascular necrosis, delayed union, nonunion, and malunion.

ED treatment of undisplaced, isolated capitate fractures is splint immobilization (short arm thumb spica) and early orthopedic/hand surgeon referral.[33] Most capitate fractures, however, are displaced or associated with the scaphocapitate syndrome and require surgical treatment.[49]

TRAPEZOID FRACTURE

Trapezoid fracture is extremely rare. The injury results from an axial load onto the index metacarpal or second metacarpal palmar hyperflexion.[4,33] There will be tenderness on the radial aspect that is augmented by applying pressure along the index metacarpal ray. Fractures are difficult to visualize on standard radiographs, and CT or MRI may be necessary. ED treatment is with a thumb spica splint.[33]

DISTAL RADIUS AND ULNA FRACTURES

Fractures of the distal metaphysis of the radius and ulna are among the most common injuries affecting the wrist, with an annual incidence of 640,000 in the United States.[50] Women older than age 50 years possess a 15% lifetime risk of a distal ulna and/or radius fracture, and distal radius fracture is the most common pediatric fracture (<16 years).[51] Among the factors that influence the type and amount of displacement of the fracture are the point and direction of impact, the degree of force, and the patient's age (**Table 269-3**). Importantly, close to 50% of distal radius fractures involve the intra-articular surface.[52]

In general, the thinner cortices of the elderly make them more likely to sustain extra-articular fractures, whereas younger adults often sustain more complicated intra-articular fractures.

COLLES' FRACTURE

Colles' fracture results most often from a fall on the outstretched, extended hand. This mechanism produces a distal radial metaphysis fracture that is dorsally angulated and displaced proximally and dorsally (**Figure 269-18**). Compression forces on the dorsal side often produce dorsal comminution of bone. The fracture line may also comminute and extend into the radioulnar or radiocarpal joint ("die-punch" fracture). A fracture of the ulnar styloid is often present and may be suggestive of injury to the triangular fibrocartilage complex.

The wrist has the characteristic dorsiflexion, or "dinner fork," deformity. Patients may complain of palmar paresthesias from pressure on the median nerve. Posteroanterior radiographs reveal a distal metaphyseal fracture of the radius that often appears shortened from the angulation or comminution. **The lateral view provides the best view of the dorsal angulation and comminution. In general, unstable fractures have >20 degrees of angulation, intra-articular**

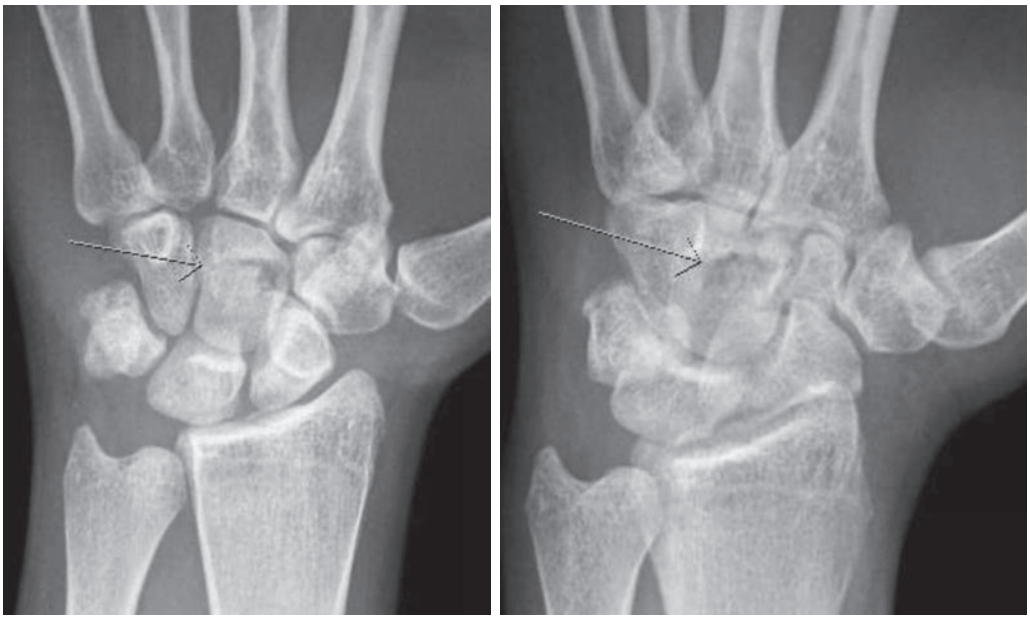


FIGURE 269-17. A and B. Capitate fracture (*arrow*) is seen best on posteroanterior (PA) view. [Photos contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

involvement, marked comminution, or more than a centimeter of shortening. These injuries are more likely to develop loss of reduction, distal radioulnar joint instability, radiocarpal instability patterns, and subsequent arthritis. If the fracture has significant intra-articular extension, or comminution or if distal radioulnar joint instability is suspected, CT may provide important additional information for diagnosis and treatment.[52,53]

Stable fractures may be treated with a compression dressing and splint until they can be evaluated by an orthopedic surgeon within 7 to 10 days; otherwise, closed reduction is performed. After adequate local anesthesia (see Chapter 36, "Local and Regional Anesthesia"), provide traction with finger traps while the fracture fragment is pushed distal and palmar and the patient's forearm is held firmly (**Figure 269-19**). Finger traps relax the deforming forces from spasm, may perform the reduction alone, and hold the reduction in place during splinting. The goal is to restore the volar tilt, radial inclination, and proper length to the radius. This is particularly important in younger patients. The volar tilt ideally should be restored to its normal position, but a minimum of neutral or zero degrees of angulation is acceptable. Periosteal entrapment entails folding of the periosteum into the fracture site, preventing reduction to the anatomic position, and disrupting periosteal blood supply. This is corrected by re-creating the mechanism of injury and then reversing the mechanism under traction, unfolding the periosteum, and releasing it from the fracture site.

Most Colles' fractures can be treated with closed reduction and application of a sugar-tong splint. If a short arm cast is applied, it should be bivalved to allow for edema. Immobilization for 4 to 6 weeks is required. Fractures that are unstable, severely comminuted, or intra-articular may require surgery. **All open and neurovascularly compromised fractures require prompt evaluation by an orthopedic surgeon.**

A wide range of complications occur in 6% to 80% of cases; complications are more common with open fracture.[54,55] The most common complication is immediate or delayed carpal tunnel syndrome, due to primary nerve damage or secondarily from tissue swelling.[56] Fractures of the distal ulnar styloid occur in 60% of radius fractures, and ulnar styloid fractures may also occur but are typically reduced during reduction of the distal radius.[4,57] Complications include malunion, median nerve injuries (17%), triangular fibrocartilage complex injuries, radioulnar and radiocarpal instability, and arthritis. These complications may result in a weak, stiff, and painful wrist. Factors associated with long-term disability or instability include dorsal angulation ≥20 degrees and ≥5 mm of radial shortening.[51] Other complications are often iatrogenic. Splinting in extreme flexion can result in median nerve damage. A closed fracture may convert to an open fracture due to thin skin.[54]

TABLE 269-3 Radiographic Appearance of Distal Radius Fractures

Colles' fracture
• Dorsal angulation of the plane of the distal radius
• Distal radius fragment is displaced proximally and dorsally
• Radial displacement of the carpus
• Ulnar styloid may be fractured
Smith's fracture
• Volar angulation of the plane of the distal radius
• Distal radius fragment is displaced proximally and volarly
• Radial displacement of the carpus
• The fracture line extends obliquely from the dorsal surface to the volar surface 1–2 cm proximal to the articular surface
Barton's fracture
• Volar and proximal displacement of a large fragment of radial articular surface
• Volar displacement of the carpus
• Radial styloid may be fractured

SMITH'S FRACTURE

Smith's fracture, or **reverse Colles' fracture**, is a volar angulated fracture of the distal radius. This may result from a fall or direct blow on the dorsum of the hand and wrist, or from a fall on the outstretched hand in flexed position or in supination that then shifts into a pronated position. The hand is displaced palmarly and produces a "garden-spade deformity" on physical examination. The posteroanterior radiograph looks much like the Colles' fracture, with a distal metaphyseal radius fracture that may be shortened and comminuted. **The lateral radiograph shows the volar angulated and displaced fracture (Figure 269-20).**[4,50,51]

The treatment objectives and complications are much like those seen with the Colles' fracture. In this case, however, the angulation is volar rather than dorsal, and during reduction, pressure is applied in the opposite direction. Urgent orthopedic follow-up is recommended due to higher incidence of instability.



FIGURE 269-18. Colles' fracture. **A.** Anteroposterior view. **B.** Lateral view. [Photos contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

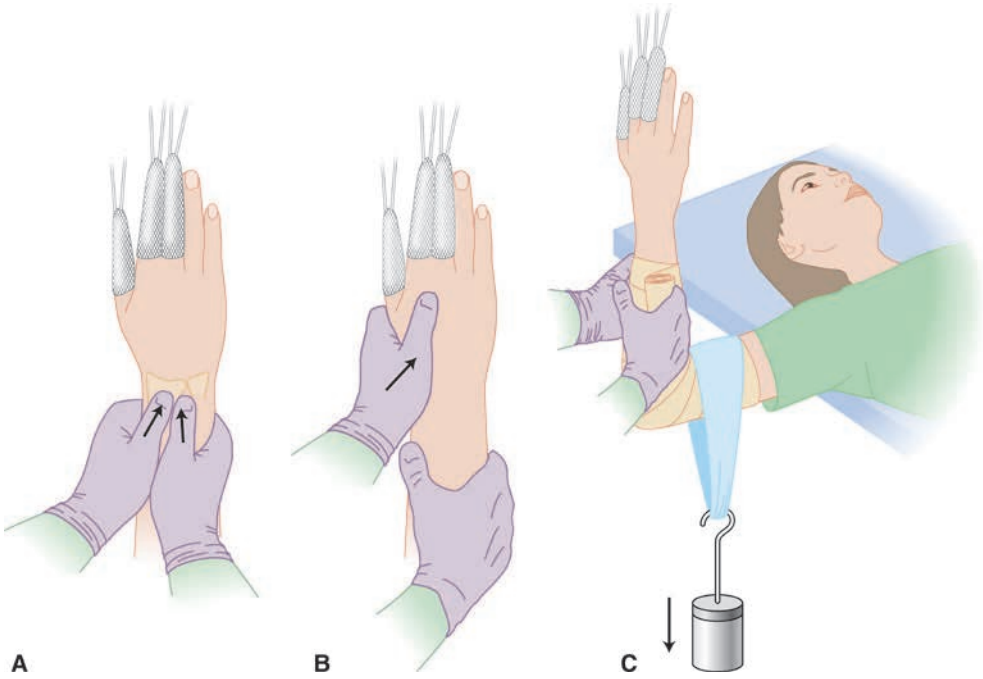


FIGURE 269-19. **A and B.** *Arrows* demonstrate application of force for proper reduction of Colles' fracture. **C.** Figure demonstrates proper patient position with the use of finger traps. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, McGraw-Hill, New York.]



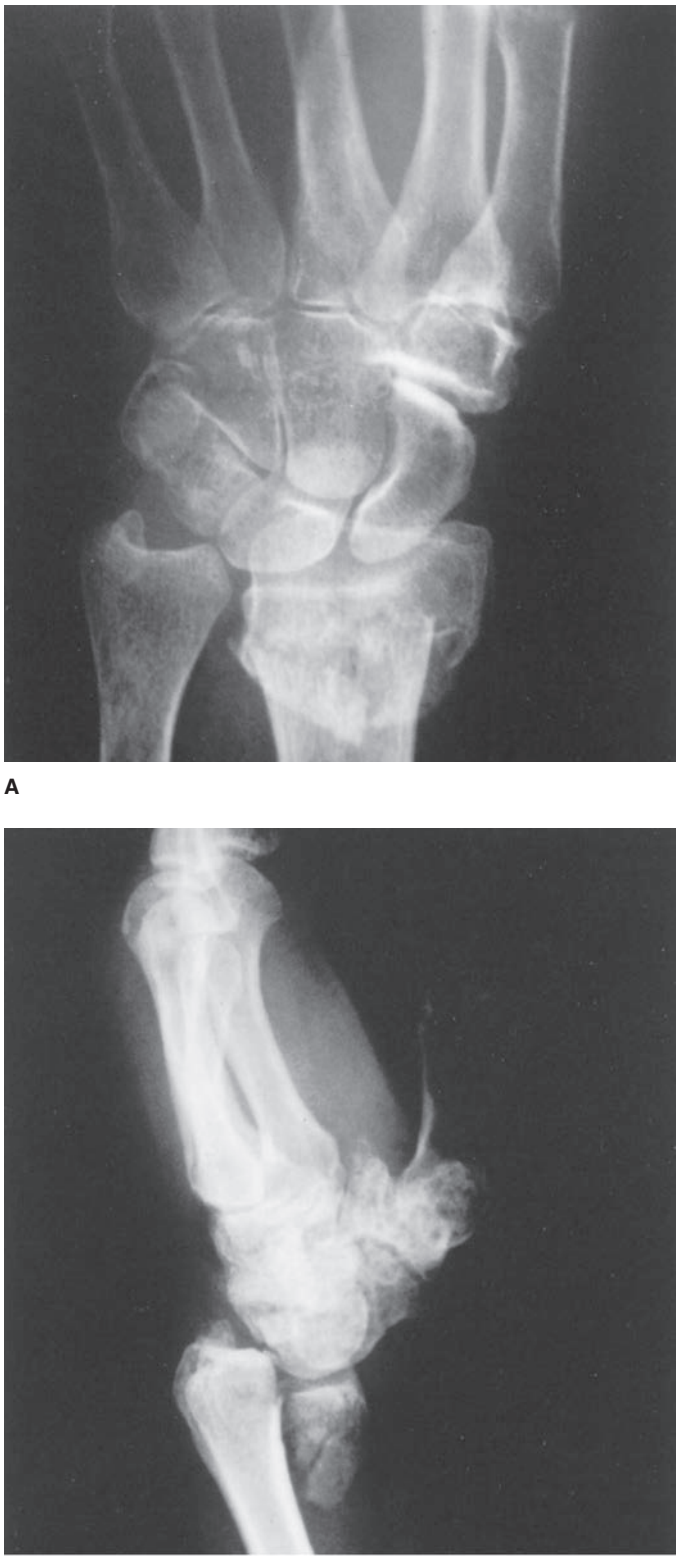
FIGURE 269-20. Smith's fracture.

BARTON'S FRACTURE

Barton's fractures are dorsal or volar rim fractures of the distal radius. The dorsal rim fractures result from a dorsiflexion and pronation force, whereas the less common volar rim fracture is produced by a fall on the outstretched hand in supination. These injuries are often fracture-dislocations or subluxations, because the carpus is frequently displaced in the direction of the fracture. Accompanying ligamentous injuries create radiocarpal instability. This instability is not fully appreciated in the acute setting, but may lead to various secondary carpal instability patterns and premature degenerative arthritis.

The posteroanterior radiograph often shows a comminuted fracture of the distal radial metaphysis. The lateral view reveals an intra-articular fracture of the volar or dorsal rim of the radius, which may be accompanied by carpal subluxation in the same direction (**Figure 269-21**).

Minimally displaced fractures can be treated acutely in a sugar-tong splint until evaluation by an orthopedist. **Unstable fractures involving >50% of the radial articular surface or those with accompanying carpal subluxation require open reduction and internal fixation. Emergent orthopedic consultation is recommended.**



A

B

FIGURE 269-21. Volar Barton's fracture. **A.** Posteroanterior view. **B.** Lateral view.

RADIAL STYLOID FRACTURE

A force directed along the radial aspect of the hand can produce a transverse or oblique fracture that extends from the scaphoid fossa to the metaphysis of the radius (**Figure 269-22**). Primary mechanisms of injury include direct blow to the dorsal surface of the wrist, fall on an outstretched hand with avulsion of the radial styloid, and fall on an outstretched hand with wrist extension and abduction.[4] **Radial styloid fracture** is often accompanied by a dislocation of the lunate. It is best seen on the posteroanterior radiograph as a thin, lucent line beneath the radial styloid. Because the major carpal ligaments along the radial aspect of the wrist insert on the radial styloid, displacement of this fracture can produce carpal instability. This instability is aided by the extracarpal ligaments (i.e., wrist/finger flexors and extensors causing further displacement of the styloid). Displaced fractures often require

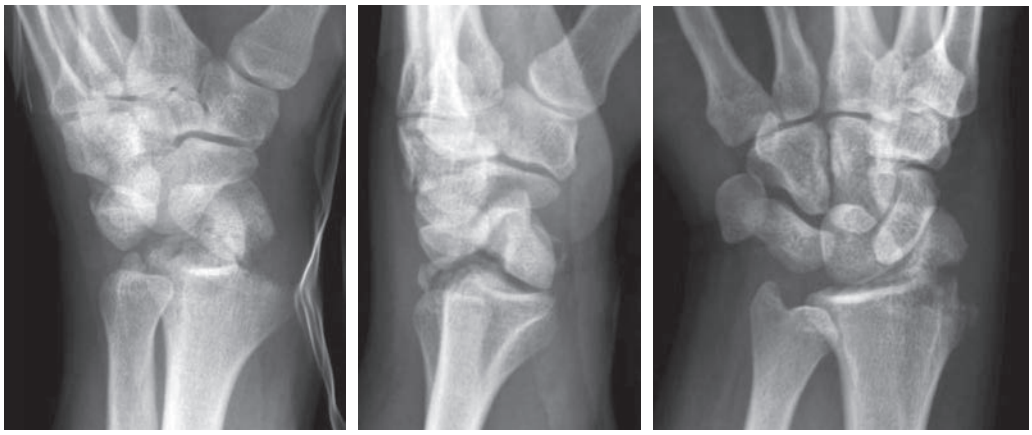


FIGURE 269-22. Radial styloid fracture with lunate dislocation. PA = posteroanterior. [Photos contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University, Portland, OR.]

open reduction and internal fixation. Displacement of as little as 3 mm is often associated with accompanying scapholunate dissociation. Failure to recognize intercarpal ligament tears adds to the potential for subsequent posttraumatic arthritis. Refer to an orthopedist. In the ED, place a short arm splint positioning the wrist in mild flexion and ulnar deviation.

ULNAR STYLOID FRACTURE

A forced radial deviation, dorsiflexion, or rotatory stress can fracture the **ulnar styloid**. The ulnar styloid fracture may be isolated or may accompany other injuries, such as a Colles' fracture. Clinically, avulsion fractures are rarely significant, with the major consideration being the associated radial soft tissue and bony injuries. Displaced ulnar base fractures can be intra-articular and be associated with tears of the triangular fibrocartilage complex, which is the main stabilizer of the distal radioulnar joint. Patients complain of a painful clicking or locking sensation in the wrist. If the distal radioulnar joint is stable, ulnar styloid fractures are treated acutely in an ulnar gutter splint in slight ulnar deviation and neutral positioning of the wrist. If there is any question about stability, these patients should be referred acutely for surgical evaluation. Arthrograms or MRI imaging may be necessary to delineate the full extent of injury.

DISTAL RADIOULNAR JOINT DISRUPTION

Distal radioulnar joint disruption is associated with several conditions including ulnar styloid and distal ulna fractures, triangular fibrocartilage complex tear, ulnar impaction syndrome, Essex-Lopresti injury, and Galeazzi's fracture.[4] The primary stabilizers of the distal radioulnar joint include the volar and dorsal radioulnar ligaments and triangular fibrocartilage complex. Disruption of the triangular fibrocartilage complex of the distal radioulnar joint is generally seen with intra-articular or distal radial shaft fractures (**Galeazzi's fracture-dislocation**)[58] or with fractures of both bones of the forearm. Injury to the triangular fibrocartilage complex of the distal radioulnar joint is found in up to 84% of distal radius fractures.[4,53] These more apparent injuries often overshadow distal radioulnar joint disruption and, unfortunately, may remain unrecognized until subsequent pain and diminished wrist movement are appreciated.

Isolated radioulnar joint dislocations are uncommon and are often unrecognized acutely, although these may occur in isolation in the setting of distal ulnar dislocation.[4,53] Dorsal dislocation of the ulna results most often from falls on the wrist in hyperpronation and is associated with pain with supination on examination. The rare volar dislocation results from forced hypersupination of the wrist and is associated with pronation on examination. Patients with disruption of the distal radioulnar joint present with pain at the distal radioulnar joint, weak grip, and restricted range of motion, especially pronation and supination. The ulnar head is often prominent but may be subtle and easily overlooked. A positive fovea sign has a sensitivity of 95% and specificity of 87% for triangular fibrocartilage complex instability, which is comprised of tenderness in the soft area between the ulnar styloid and flexor carpi ulnaris tendon. Signs of distal radioulnar joint instability include ulnar styloid fracture involving the base with ≥2 mm displacement, radius sigmoid notch fracture, wide distal radioulnar joint displacement, shortened radius, or failure to reduce distal radioulnar joint dislocation.[4,53]

The posteroanterior radiograph reveals narrowing and overlap of the distal radioulnar joint. **The lateral radiograph demonstrates either volar or dorsal displacement of the ulna, which is normally centered and overlapping the radius.** Because slight oblique positioning of the wrist can produce a misleading appearance of ulnar displacement, make sure to obtain a properly positioned lateral view. A true lateral view should have superimposition of the four ulnar metacarpals, superimposition of the proximal pole of the scaphoid with the lunate and triquetrum, and the radial styloid centered over its distal articular surface. CT scanning may be necessary to establish the diagnosis if plain films are inconclusive.

Immobilizing the wrist in supination reduces dorsal dislocations, whereas volar dislocations are placed in pronation. Patients with acute distal radioulnar joint disruption are referred acutely for orthopedic follow-up. These injuries have a high recurrence rate and may require reconstructive surgery, particularly if there is a delay in diagnosis.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 270

Elbow and Forearm Injuries

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ANATOMY

Articulations of the distal humerus and proximal ulna and radius form the elbow joint (**Figure 270-1**).

The distal humerus is comprised of the medial and lateral condyles. The articulating surfaces of the medial and lateral condyles are the trochlea and the capitellum, respectively. Medially, the trochlea articulates with the olecranon of the ulna to form a uniaxial hinge joint.

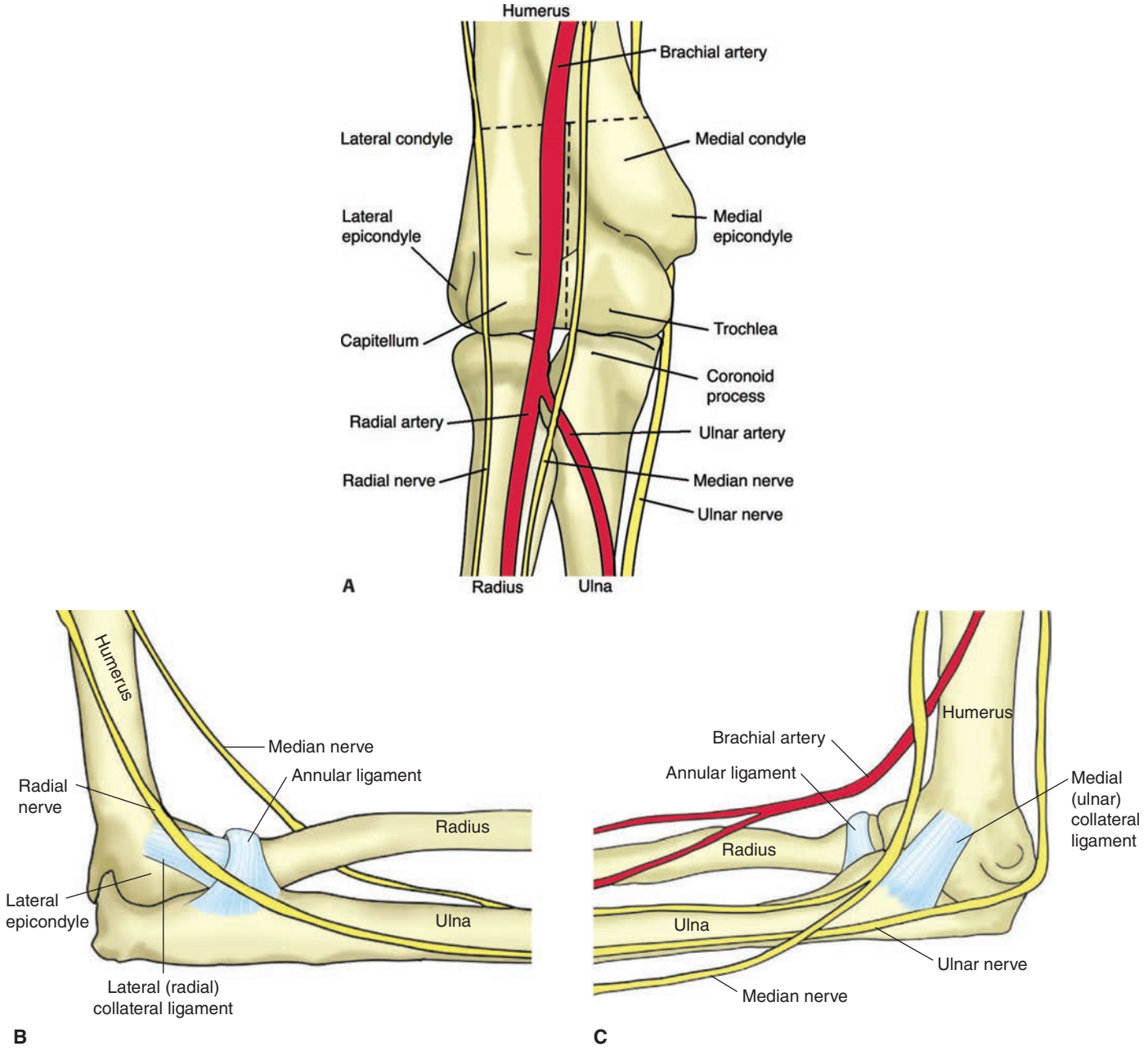

FIGURE 270-1. Elbow anatomy. **A.** Anterior view. **B.** Lateral view. **C.** Medial view.

Laterally, the capitellum abuts the radial head to form a pivot joint. The medial and lateral epicondyles are nonarticulating surfaces where the forearm, wrist, and digit flexors and pronators (medial), and extensor and supinator (lateral) muscles originate.

The radius and ulna articulate at their ends to form the proximal and distal radioulnar joints and are joined along their entire length by a fibrous interosseous membrane. The ulna is a fairly straight bone, whereas the radius has an important outward bowing. During supination and pronation, the radius rotates around the relatively fixed ulna. Because these bones have such a close relationship, injury to one will frequently impact the other.

Several neurovascular structures lie in proximity to the distal humerus, and evaluation of their function is essential. These include the brachial artery and the radial, median, and ulnar nerves (**Table 270-1**).

The neuroanatomy is best understood by appreciating the neural control of wrist and finger movements (**Figure 270-2**). The radial nerve travels over the lateral epicondyle into the forearm before splitting into a deep branch that pierces through the supinator muscle and a superficial branch that lies adjacent to the radial artery. The proximal portion of the radial nerve controls the more proximal function of wrist extension, the deep branch (posterior interosseous nerve) controls the more distal function of finger and thumb extension, and the superficial branch is purely sensory, providing sensation over the dorsal aspect of the hand from the thumb to the radial half of the ring finger. Thus, an isolated

TABLE 270-1 Sensory and Motor Function Testing of the Radial, Median, and Ulnar Nerves

	Radial	Median	Ulnar
Sensory function (test with 2-point discrimination)	Dorsum of the thumb and index web space	Tip of the index finger	Tip of the little finger
Motor function (test against resistance)	Extend wrist and fingers ("Rock" and "Paper" motions)	"OK" sign with thumb and index finger; abduct thumb ("thumbs up" motion)	Abduct index finger ("Scissors" motion)

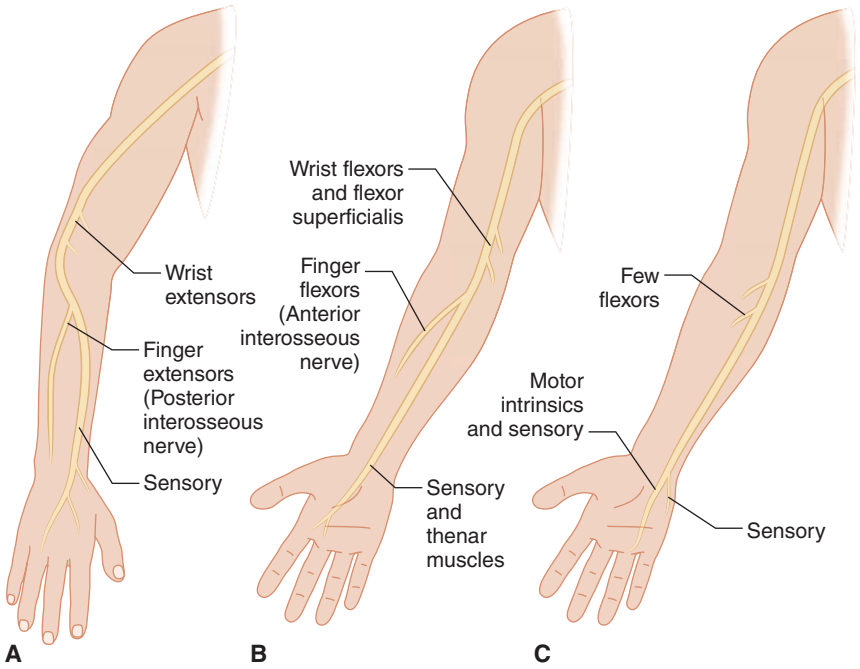

FIGURE 270-2. Neural innervation of the forearm, wrist, hand, and digits. **A.** Radial nerve innervation. **B.** Median nerve innervation. **C.** Ulnar nerve innervation.

injury to the posterior interosseous branch affects finger extension but spares wrist extension and sensation to the dorsum of the hand. This can be seen in a compression neuropathy to the posterior interosseous nerve at the level of the supinator muscle.

The proximal portion of the median nerve controls the muscles of wrist flexion and the superficial finger flexors before it gives off the anterior interosseous nerve, which controls the radial half of the deep finger flexors and thumb flexion at the interphalangeal joint. The remaining portion of the median nerve provides sensation to the volar surface of the hand from the thumb to the radial half of the ring finger, including the dorsal tips of the thumb, index, and middle fingers. A separate motor branch (recurrent branch of the median nerve) controls the thenar muscles for thumb opposition and abduction.

The ulnar nerve innervates the forearm muscles and the intrinsic muscles of the hand while providing sensation to the little finger and the ulnar half of the ring finger. Proximal to the elbow, the ulnar nerve courses under a ligamentous band called the arcade of Struthers before entering the cubital tunnel posterior to the medial epicondyle. These are two sites where the nerve can become entrapped, leading to ulnar neuropathy syndromes. The ulnar nerve is palpable as a cord in the cubital tunnel and is vulnerable to injury with trauma over this area.

The biceps brachii muscle has two proximal heads and two distal attachments (**Figure 270-3**). The proximal long head originates proximal to the shoulder capsule, and the proximal short head originates at the coracoid process. The distal attachments are to the radial tuberosity by the distal biceps tendon and the forearm by the bicipital aponeurosis. The biceps muscle is innervated by the musculocutaneous nerve (C5 and C6) and functions primarily to supinate and assist in flexion of the forearm.

The brachialis muscle lies deep to the biceps muscle. It is innervated by both the musculocutaneous and radial nerves (C5, C6, C7, and C8) and is the primary flexor of the forearm.

The triceps muscle has three proximal heads (**Figure 270-4**): a long head originating from the scapula, a lateral head, and a medial head. The triceps inserts at the olecranon via the triceps tendon. The triceps muscle is innervated by the radial nerve (C6, C7, and C8) and is the sole extensor of the forearm.

The intrinsic forearm muscles include the brachioradialis, pronator teres, pronator quadratus, anconeus, and supinator (**Figure 270-5**). The motor functions of these muscles are summarized in **Table 270-2**.

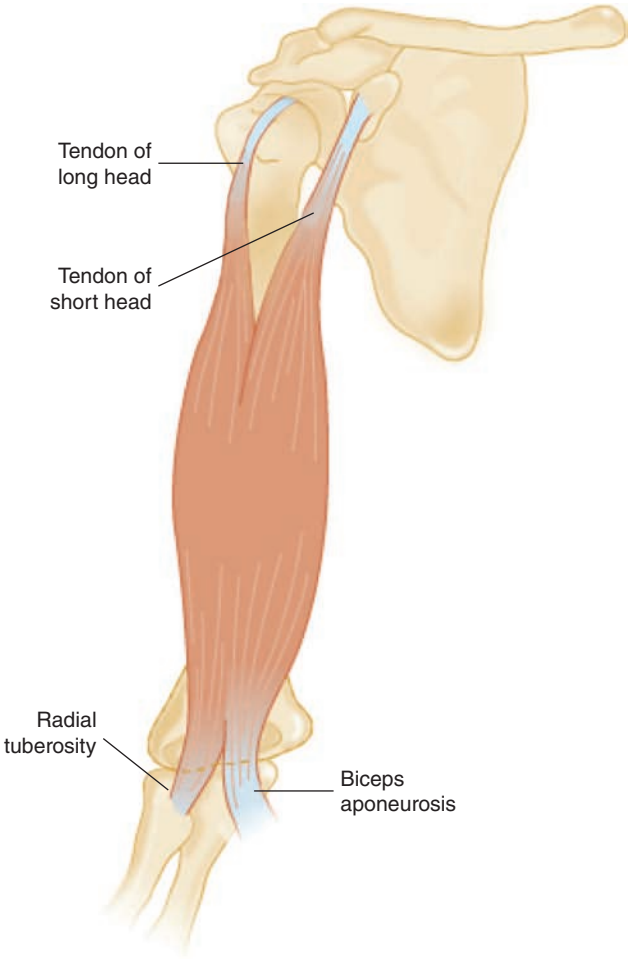

FIGURE 270-3. Biceps muscle anatomy.

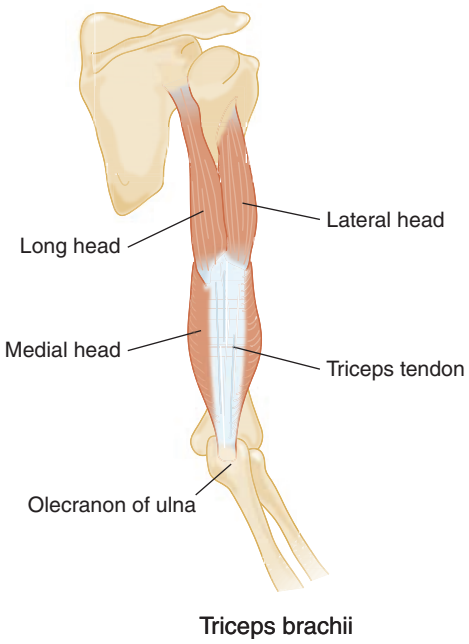

FIGURE 270-4. Triceps muscle anatomy.

CLINICAL FEATURES

HISTORY

A thorough history is essential for determining the correct diagnosis in a patient with elbow or forearm pain. Onset of symptoms, mechanism of injury, exact location of pain, and associated symptoms such as numbness, weakness, or distal wrist and hand complaints are important elements to obtain. Most acute traumatic injuries to the elbow and forearm occur due to either a fall onto an outstretched hand or a direct blow. Chronic overuse injuries should correlate with preceding activity involving a repetitive motion. A history of arthritides may point to a systemic disorder such as lupus, rheumatoid arthritis, or gout.

TABLE 270-2 Motor Functions of the Intrinsic Forearm Muscles

Muscle	Function
Brachioradialis	Assists with forearm flexion
Pronator teres	Assists with forearm pronation and flexion
Pronator quadratus	Primary forearm pronation
Anconeus	Trivial forearm extension
Supinator	Primary forearm supination

PHYSICAL EXAMINATION

Inspect the elbow and forearm for gross deformity, soft tissue swelling such as bursitis, or open wounds. Assess range of motion of the elbow in flexion, extension, pronation, and supination. Inability to fully extend the elbow is correlated with the presence of a fracture.[1] Conversely, full range of motion in all four planes has high negative predictive value for fracture.[2]

Radial, median, and ulnar nerve function can be conducted by isolated nerve testing. Test motor function against resistance. Assess sensory function using two-point discrimination. **Test radial nerve motor function by having the patient extend both the wrist and fingers against resistance** (Table 270-1). Assess sensation over the dorsum of the thumb index web space. Evaluate the median nerve through its distal branches—the anterior interosseous nerve and the recurrent branch of the median nerve. **Assess anterior interosseous nerve function by having the**

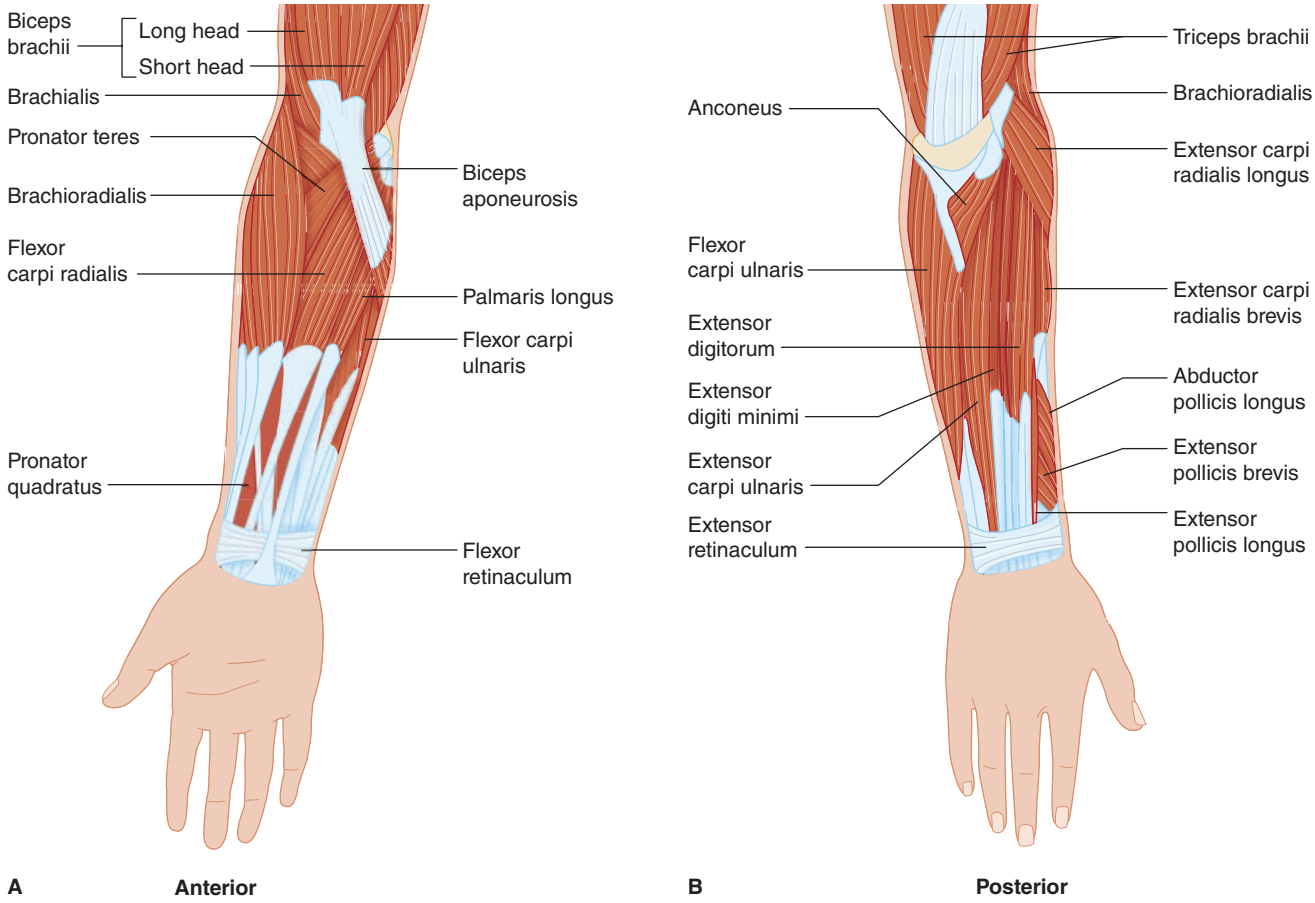

FIGURE 270-5. Intrinsic forearm muscles. **A.** Anterior forearm. **B.** Posterior forearm.

patient make a circle, or "OK" sign, with the thumb and index finger. Abduction of the thumb through a "thumbs up" sign against resistance (recurrent branch of the median nerve) and sensory testing over the tip of the index finger complete the evaluation of the median nerve. **Test ulnar nerve function by having the patient spread the fingers apart against resistance**; sensation is tested over the tip of the fifth digit. A simple and thorough way to assess radial, median, and ulnar nerve motor function, particularly in children, is to have the patient perform the motions of the game Rock, Paper, Scissors, followed by the OK sign.[3] This routine includes the movements of wrist extension (proximal radial nerve), finger extension (posterior interosseous nerve branch of radial nerve), finger abduction (ulnar nerve), and thumb and finger flexion (anterior interosseous nerve branch of the median nerve) described above.

DIAGNOSIS

IMAGING

Initial imaging studies should include anteroposterior and lateral views of the elbow, and anteroposterior, lateral, and oblique views of the humerus and forearm. If a distal forearm injury is present, obtain anteroposterior, lateral, and oblique views of the wrist instead of the humerus. Clinical decision rules to guide imaging decisions for the elbow, similar to published ankle and knee imaging rules, have to date produced conflicting data and are not helpful.[1,4,5]

On lateral films of the elbow, a line drawn straight through the center of the radial shaft (radiocapitellar line) should bisect the radial head and capitellum (**Figure 270-6A**). Loss of this relationship should raise suspicion for an occult radius fracture or dislocation. A line drawn straight along the anterior border of the humerus (anterior humeral line) should transect the posterior two thirds of the capitellum (**Figure 270-6B**). Abnormal extension of the line through the anterior one third of the capitellum suggests a distal humerus (in adults) or supracondylar fracture (in children). A small anterior fat pad may be a normal finding. **Large anterior and any posterior fat pads are always abnormal** and indicate the presence of a joint effusion (**Figure 270-7**).

Obtain CT imaging to evaluate for fracture when plain radiographs are normal in the setting of concerning physical exam findings.[6] CT also assists in characterizing certain elbow fractures, particularly coronoid and comminuted intra-articular fractures. MRI is useful in the evaluation of soft tissue injuries but has a limited role in the acute setting. US can demonstrate effusions, fractures, postreduction fracture alignment, and tendon injury.[7-10] Several studies have demonstrated sensitivities and specificities of over 90% for the diagnosis of forearm and elbow fractures using point-of-care US.[11,12] While it cannot completely replace plain radiography due to variations in operator skill, point-of-care US can be a powerful diagnostic adjunct in the evaluation of elbow and forearm injuries.

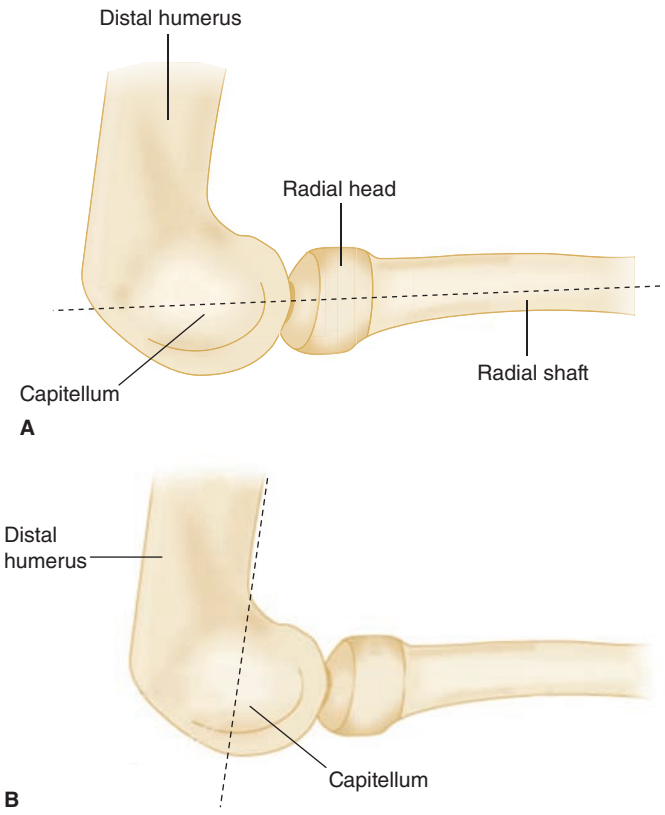

FIGURE 270-6. **A.** Radiocapitellar line. **B.** Anterior humeral line.



FIGURE 270-7. Anterior and posterior fat pad signs.

TREATMENT

Consult an orthopedic surgeon immediately for open fractures, irreducible dislocations, injuries resulting in a grossly unstable elbow joint, nerve injury, or vascular injury with signs of ischemia or uncontrolled hemorrhage. All other injuries may be referred for follow-up within 1 to 2 days for operative planning or up to a week for nonoperative treatment. **Table 270-3** outlines guidelines for ED immobilization and appropriate orthopedic consult time frames for the conditions discussed in this chapter.

SOFT TISSUE INJURIES

BICEPS TENDON RUPTURE

Most biceps injuries are proximal, and nearly all of these involve the proximal long head. Injuries usually manifest as tendinopathies from repetitive microtrauma and overuse. The classic mechanism leading to tendon rupture is a sudden or prolonged contraction against resistance in middle-aged and older individuals with a history of chronic biceps tendinopathy. A snap or pop is usually described, and pain is present in the anterior shoulder. Examination of the anterior shoulder will reveal swelling, tenderness, and often crepitus over the bicipital groove. Ecchymosis may extend the entire length of the biceps. **Flexion of the elbow will elicit pain and may produce a midarm "ball," which represents the distally retracted biceps muscle.** Comparing arms for symmetry

TABLE 270-3 Immobilization and Follow-Up Guidelines

Injury	Splint	Referral
Soft tissue injuries		
Biceps tendon rupture	Sling immobilization	1 wk
Triceps tendon rupture	Sling immobilization	1 wk
Lateral/medial epicondylitis	Rigid wrist brace, forearm counterforce brace	2–4 wk PRN
Elbow dislocation		
Stable/postreduction	Long arm posterior splint, elbow slightly less than 90 degrees, forearm neutral	1–2 d
Unstable/postreduction	Long arm posterior splint (presurgical stabilization)	Immediate
Irreducible	Long arm posterior splint (presurgical stabilization)	Immediate
Elbow fractures		
Distal humerus nondisplaced	Long arm posterior splint, forearm neutral	1 wk
Supracondylar	Long arm posterior splint (presurgical stabilization)	<24 h
Intercondylar	Long arm posterior splint, forearm neutral	1–2 d
Lateral condyle/epicondyle		
Nondisplaced	Long arm posterior splint, forearm in supination	1–2 d
Displaced	Long arm posterior splint (presurgical stabilization)	Immediate
Medial condyle/epicondyle		
Nondisplaced	Long arm posterior splint, forearm in pronation	1–2 d
Displaced	Long arm posterior splint (presurgical stabilization)	Immediate
Articular surface	Long arm posterior splint, forearm neutral	1–2 d
Coronoid		
Nondisplaced or minimally displaced	Long arm posterior splint, elbow past 90 degrees, forearm in supination	1–2 d
Markedly displaced or unstable	Long arm posterior splint (presurgical stabilization)	Immediate
Olecranon	Long arm posterior splint, forearm neutral	<24 h
Radial head		
Nondisplaced	Sling immobilization with early range of motion	1 wk
Displaced or range of motion block	Long arm posterior splint, forearm neutral	<24 h
Forearm fractures		
Both bones		
Pediatric		
Greenstick	Long arm posterior splint	1 wk
Displaced	Long arm posterior splint	Immediate
Adult		
Nondisplaced	Sugar-tong splint	1 wk
Displaced	Long arm posterior splint (presurgical stabilization)	<24 h
Isolated ulna shaft	Long arm posterior splint, forearm neutral *or* sugar-tong splint if stable and nondisplaced	1 wk
Proximal two thirds of radius		
Nondisplaced	Long arm posterior splint, forearm neutral	1 wk
Displaced	Long arm posterior splint, forearm neutral	1–2 d
Monteggia's	Long arm posterior splint (presurgical stabilization)	Immediate
Galeazzi's	Long arm posterior splint (presurgical stabilization)	Immediate

helps. Loss of flexion strength is minimal, due to the preserved functions of the brachialis and supinator. Avulsion fractures occasionally occur, so radiographs of the shoulder should be obtained.

ED treatment includes sling, ice, analgesics, and referral to an orthopedic surgeon for definitive care.

Distal biceps injuries are less common than proximal injuries.[13] Complete distal tendon ruptures are most common in middle-aged men and usually involve the dominant extremity. Partial tears are seen in men and women. Mechanism of injury is typically a sudden eccentric (extension) load applied to a flexed elbow. Pain is felt in the antecubital fossa, with swelling, ecchymosis, and tenderness to palpation noted on examination. A palpable defect in the antecubital fossa and a midarm "ball" may be present. Strength loss, especially supination, is more notable than with proximal ruptures. The **biceps squeeze test**, similar to the Thompson test for assessing Achilles tendon rupture, can detect biceps rupture.[14] With the patient seated and the forearm at 60 to 80 degrees of flexion, place one hand on the muscle belly of the biceps and the other hand on the myotendinous junction, and squeeze with both hands. The squeeze should result in forearm supination. Lack of supination is considered a positive test, indicating rupture of the distal biceps tendon. To perform the **hook test**,[15] flex the patient's elbow to 90 degrees. During active supination, if the biceps tendon is intact, the examiner can "hook" the index finger under a cord-like structure in the antecubital fossa. Obtain elbow radiographs to search for an associated avulsion fracture. Although most complete distal ruptures are diagnosed clinically, US can aid in confirming the diagnosis of partial tears.[16,17]

ED treatment includes sling, ice, analgesics, and referral to an orthopedic surgeon for definitive care. Although distal biceps ruptures were historically treated with surgery, management can be either surgical or conservative, depending on the patient.[18]

TRICEPS TENDON RUPTURE

Injury to the triceps is rare and almost always occurs distally.[19] Ruptures result from either a fall on an outstretched hand causing a forceful flexion of an extended elbow or a direct blow to the olecranon. Pain is felt in the posterior elbow. Examination of the elbow reveals posterior swelling and tenderness, just proximal to the olecranon. A sulcus with a more proximal mass, representing the retracted triceps muscle, may be palpable. With partial tears, some degree of function remains; however, **with complete ruptures, the ability to extend the elbow is lost**. A modified Thompson test can be used to evaluate triceps function. The upper extremity is positioned such that the arm is supported and the forearm is hanging in a relaxed position with 90 degrees of flexion. Squeezing the triceps muscle should produce extension of the forearm, unless a complete rupture is present. Radiographs of the elbow are needed because avulsion fractures of the olecranon are common. Point-of-care US can aid in diagnosis, especially of partial tears.[20,21]

ED treatment includes sling, ice, analgesics, and referral to an orthopedic surgeon for definitive care. Complete ruptures require surgical repair, whereas most partial tears can be treated conservatively with immobilization.

LATERAL EPICONDYLITIS

Lateral epicondylitis, or "tennis elbow," is an overuse syndrome affecting the wrist and digit extensors and the forearm supinators. The diagnosis is made clinically by tenderness over the lateral epicondyle and pain with resisted wrist extension, digit extension, and forearm supination. Treatment is usually conservative, with rest, friction massage, anti-inflammatory medications, immobilization with a rigid wrist brace to limit wrist extension or a counterforce forearm brace, and physical therapy. Refer to an orthopedic surgeon or sports medicine specialist for follow-up care.[22-24]

MEDIAL EPICONDYLITIS

The less common counterpart to lateral epicondylitis is medial epicondylitis ("golfer's elbow"). As with lateral epicondylitis, the diagnosis is made clinically. Tenderness over the medial epicondyle and pain with resisted wrist flexion and forearm pronation are expected, as these are the muscle groups affected. In addition, patients may develop an ulnar neuropathy, given the proximity of the ulnar nerve to the medial epicondyle. Ulnar neuropathy requires orthopedic follow-up. Treatment is similar to that of lateral epicondylitis, with rest, anti-inflammatory medications, bracing, and physical therapy.

ELBOW DISLOCATION

The elbow is one of the more stable joints. The muscular attachments, lateral collateral ligament, and medial ulnar collateral ligament augment its inherent stability in the flexion-extension plane. Dislocations of the elbow rank third in large-joint dislocations, after glenohumeral and patellofemoral dislocations. The mechanism of injury is usually a fall on an outstretched hand. **Approximately 90% of all elbow dislocations are posterolateral.**[25] Fractures of the coronoid process, radial head, medial epicondyle, and olecranon can complicate the treatment of elbow dislocations. The "terrible triad" injury consists of an elbow dislocation coupled with fractures of the radial head and coronoid. This injury creates an unstable joint and requires emergent orthopedic consultation.

Clinically, the patient presents with the elbow in 45 degrees of flexion. The olecranon is prominent posteriorly, and the deformity resembles a displaced supracondylar fracture. If the patient is seen immediately after the injury, the bony landmarks can be identified. Later, however, the swelling may be quite severe, with no possibility of evaluating the injury topographically. **The priority is to assess the neurovascular status of the brachial artery, ulnar nerve, and median nerve, as these structures may become entrapped.** Perform neurovascular examination before and after manipulation. Neurologic complications most frequently involve the ulnar nerve and occur in up to 20% of elbow dislocations. Brachial artery injuries are estimated to occur in 5% to 13% of elbow dislocations.[26] Absence of a radial pulse before reduction, an open dislocation, and systemic injuries (such as those of the head, chest, and abdomen) are findings associated with arterial injury.[27,28] If vascular injury is suspected, then angiography may be required to assess the extent of injury and need for repair.



FIGURE 270-8. Posterior elbow dislocation.

On the lateral radiograph, both the ulna and radius are displaced posteriorly (**Figure 270-8**). In the anteroposterior view, there may be lateral or medial displacement, with the ulna and radius in their normal relationship to each other. Assess for associated fractures, particularly of the coronoid process and radial head.

Due to the amount of force that is necessary to reduce a dislocated elbow, success often depends on IV analgesia or procedural sedation. Intra-articular lidocaine is also helpful for closed reduction of dislocated elbows. Regardless of the type of analgesia used, ensure appropriate patient comfort prior to attempting closed reduction.

Closed reduction can be accomplished by several methods. In the first two-person reduction technique, position the forearm supine. While an assistant applies a stabilizing countertraction force on the upper arm, use one hand to apply a longitudinal traction on the wrist and forearm (**Figure 270-9**). With the other hand, manipulate the elbow to correct any medial or lateral displacement. Then apply slow and steady downward pressure to the proximal forearm with the other hand to help disengage the coronoid process from the olecranon fossa. Continue distal traction and flex the elbow. In the second two-person technique, the patient is prone with the arm abducted and the elbow slightly flexed. The patient may also be supine with the arm adducted across the torso and the elbow slightly flexed (**Figure 270-10**). Have an assistant apply longitudinal traction on the wrist and forearm. Then, grasp the elbow, positioning both thumbs on the olecranon, and apply firm pressure against the olecranon to push it up and over the trochlea and back into anatomic position. Apply countertraction with the fingers against the distal humerus. A preliminary report described a single-person reduction technique with the patient in a seated position (**Figure 270-11**). Place an elbow in the patient's antecubital fossa, then grasp the patient's hand or wrist. Flex the patient's forearm while leveraging a force into the antecubital fossa to bring the olecranon back into anatomic position. As this is a preliminary report of the technique, success and complication rates are not known with certainty. The last technique is a modification of the Stimson hanging technique used in shoulder reductions (**Figure 270-12**). Place the patient prone with the elbow flexed over the edge of the stretcher. Support the humerus proximal to the elbow with a folded blanket or pillow. Suspend 5-lb weights from the wrist. The patient's elbow should reduce over a period of several minutes. Gentle manipulation may be applied to the olecranon to aid reduction.

With reduction, a palpable "clunk" is felt as the olecranon is seated back in the trochlea. Move the elbow through its full range of motion to assess stability. Obtain postreduction films to determine reduction and identify fractures not previously identified. Inability to maintain

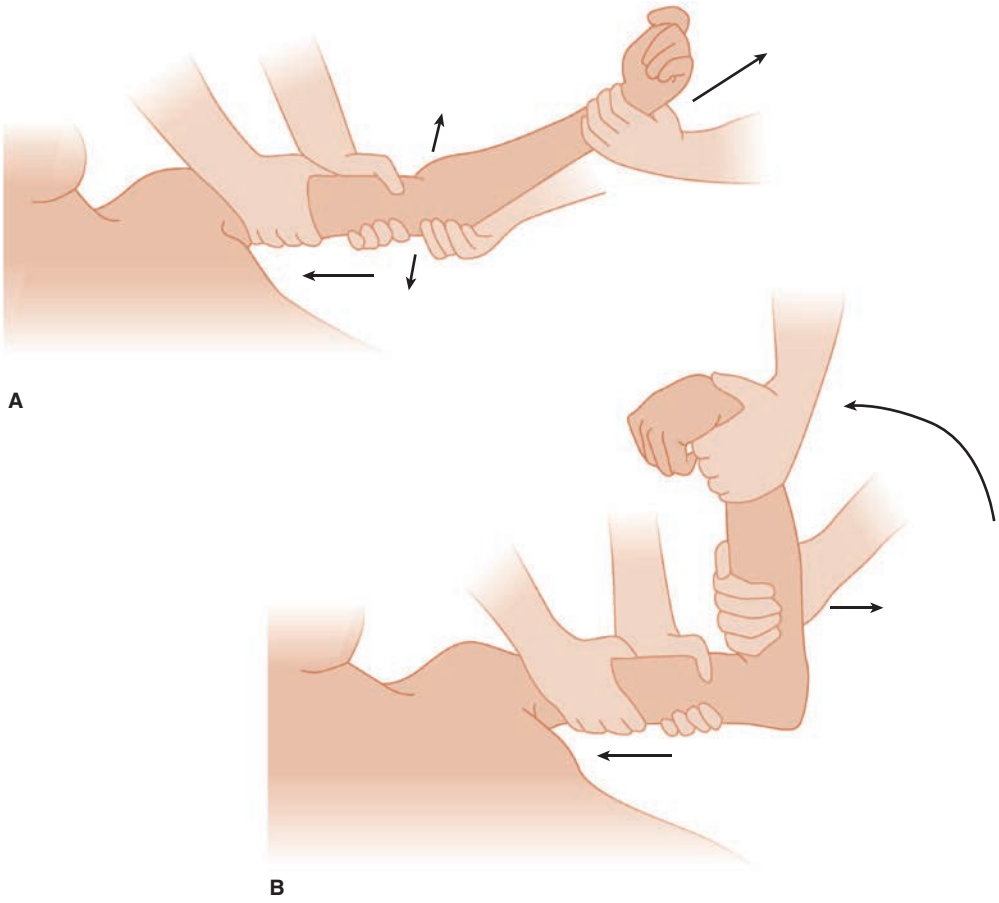

FIGURE 270-9. Traction and flexion reduction method. **A.** Side-to-side manipulation is used to correct medial or lateral displacement. **B.** The elbow is then flexed while maintaining longitudinal traction.

reduction necessitates emergency orthopedic consultation. If the joint is stable and good neurovascular status has been confirmed, splint with a long arm posterior splint with the forearm and wrist both in neutral position and the elbow at slightly less than 90 degrees of flexion. Arrange orthopedic follow-up in 1 to 2 days.[29,30]

Obtain emergency orthopedic consultation for irreducible dislocations, neurovascular compromise, postreduction instability, associated fractures, and open dislocations.

FRACTURES ABOUT THE ELBOW

Elbow fractures can be divided into those of the distal humerus, proximal ulna, and proximal radius. The distal humerus includes the condylar structures and the articular surface (trochlea and capitellum). The proximal ulna includes the coronoid process and olecranon, and the proximal radius is essentially the radial head.

Radiographs of fractures about the elbow may reveal abnormal fat pads (Figure 270-7). **A traumatic hemarthrosis displaces fat from the olecranon fossa posteriorly (posterior fat pad), and the anterior fat pad may become prominent ("sail sign").** However, abnormal fat pads may also be seen with nontraumatic joint effusions. Furthermore, they may be absent in severe trauma that disrupts the joint capsule and allows intra-articular fluid extravasation. In some nondisplaced fractures, the fracture line may not be seen, with the fat pad sign being the only evidence of injury. Treatment is initiated as though a fracture were identified, with splint immobilization and orthopedic consultation.

DISTAL HUMERUS FRACTURES

Routine ED care of nondisplaced distal humerus fractures with normal neurovascular function includes immobilization, ice, elevation, analgesics, and orthopedic referral. Displaced fractures or those with neurovascular compromise require immediate orthopedic consultation. See Chapter 271, "Shoulder and Humerus Injuries," for a detailed discussion of shoulder and humerus injuries.

SUPRACONDYLAR FRACTURES

Supracondylar fractures are the most common fracture about the elbow in children between 5 and 10 years of age, but can occur in adults, especially from high-velocity injuries. Fractures can be either extension type (>95%), which are displaced posteriorly, or flexion type (<5%), which are displaced anteriorly. Treatment varies widely between nonoperative management to emergent surgical management. In 2014, the American Academy of Orthopedic Surgeons developed recommendations on the management of supracondylar fractures based on various clinical scenarios called the Appropriate Use Criteria for the Management of Pediatric Supracondylar Humerus Fractures.[31] Due to the complexity of these guidelines, the authors recommend emergency orthopedics consultation. However, a more conservative approach with urgent, rather than emergent, fixation has become more common. Treatment largely depends on the degree of displacement of the distal fragment and any concurrent neurovascular or soft tissue injury.

EXTENSION-TYPE SUPRACONDYLAR FRACTURES

Injuries most often occur with a fall on an outstretched hand with the elbow in full extension. Examination reveals significant edema and tenderness at the elbow, a prominent olecranon, and a depression proximal to the elbow. The appearance may be easily mistaken for a posterior elbow dislocation. Nondisplaced fractures may be subtle and diagnosed only by the presence of a posterior fat pad, anterior "sail sign," or disruption to the normal path of the anterior humeral line. Initially treat with

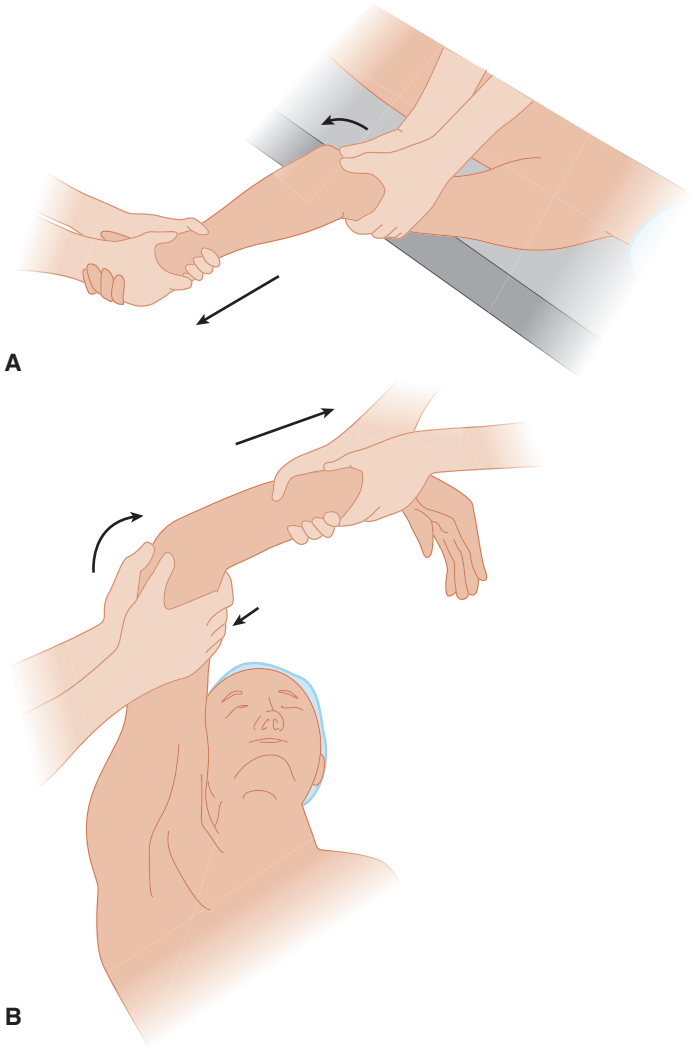

FIGURE 270-10. Olecranon manipulation reduction method with the patient positioned (**A**) prone or (**B**) supine.

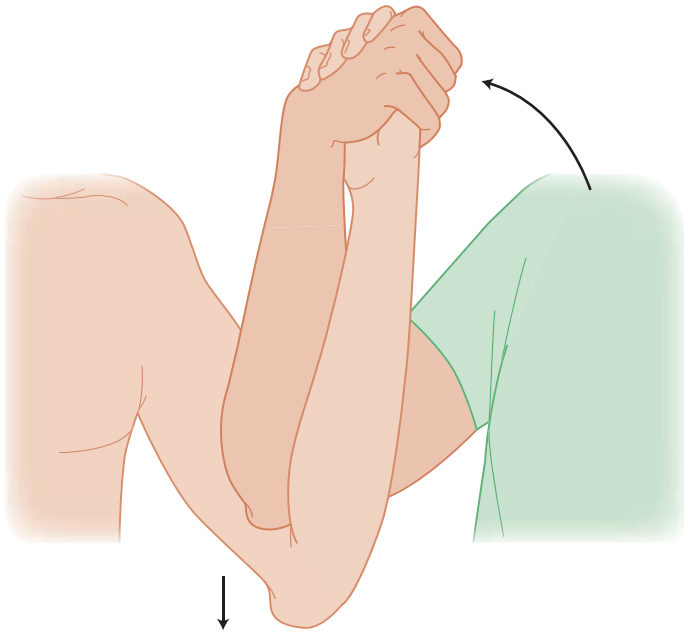

FIGURE 270-11. Single-person reduction method.

immobilization using a long arm posterior splint, keeping the elbow at 90 degrees of flexion and the forearm in neutral rotation, followed by outpatient referral for casting. The presence of >20 degrees of angulation necessitates orthopedic consultation for reduction under anesthesia and possible pin fixation.[32] In displaced fractures, the distal fragment will be displaced proximally and posteriorly. More severely displaced fractures may show medial or lateral displacement or rotation along the axis of the humerus (**Figure 270-13**). **Displaced fractures must be reduced and require orthopedic consultation.** Historically, these fractures were treated with immediate reduction and pinning. However, there is now a trend toward delayed reduction and fixation up to 24 hours after injury without evidence of complication, thus lessening the need for emergent orthopedic intervention.[31,33-36] Indications for emergent consultation are vascular insufficiency or decreased perfusion, nerve injury, open fracture, or an irreducible fracture. Admit patients with displaced fractures or significant soft tissue swelling for observation of neurovascular function.

FLEXION-TYPE SUPRACONDYLAR FRACTURES

Flexion-type fractures are rare. The mechanism of injury is a direct anterior force against a flexed elbow, resulting in anterior displacement of the distal fragment. Because the mechanism is direct force, these fractures are often open. Management of flexion-type fractures is identical to that for extension-type fractures, with the same criteria for determining emergent versus urgent orthopedic consult. Flexion-type injuries are more likely to require open reduction and pinning, particularly if an associated ulnar nerve injury is present.[37]

COMPLICATIONS OF SUPRACONDYLAR FRACTURES

There are numerous potential complications of supracondylar fractures (**Table 270-4**). Neurologic complications—resulting from traction, direct trauma, or nerve ischemia—have an incidence of 10% to 20%.[38] Ulnar nerve injuries are uncommon, with the highest incidence reported iatrogenically from pin placement. Posteromedial displacement may involve the radial nerve, and posterolateral displacement can affect the median nerve. **There is a high incidence of anterior interosseous nerve injuries with supracondylar fractures**. The mechanism of injury is usually traction or contusion. Complete transection is rare, and entrapment within the fracture occurs only occasionally. **Because there is no sensory component to the anterior interosseous nerve, the injury can only be identified through motor testing by making the "OK" sign.**[39]

Always suspect acute neurovascular injuries in patients with supracondylar fractures. Absence of a radial pulse is an indicator of brachial artery injury, even if the hand appears warm, pink, and well perfused.[40] Injury can be due to a partial or complete transection, an intimal tear and thrombosis, or entrapment within the fracture fragment of the brachial artery. Suspected or actual neurovascular injury requires emergency orthopedic consultation.[41,42]

The most serious complication is a compartment syndrome of the forearm, also known as Volkmann's ischemic contracture. This classically occurs following a displaced supracondylar fracture. Postischemic swelling increases pressure within the enclosed osteofascial forearm compartment and reduces capillary blood perfusion below the level necessary for tissue viability. If unrelieved, the result is muscle and nerve necrosis and eventual replacement by fibrotic tissue, producing a contracture. **Refusal to open the hand, pain with passive extension of the fingers, and forearm pain out of proportion to exam findings are signs of impending Volkmann's ischemia.** Extremities with signs of ischemia require emergency orthopedic consultation.

INTERCONDYLAR FRACTURES

Intercondylar fractures, in which the condylar fragments are separated, are much more common in adults than in children. Assume any distal humerus fracture in an adult to be intercondylar rather than supracondylar. The mechanism of injury is a force directed against the posterior elbow. This drives the olecranon against the humeral articular surface,

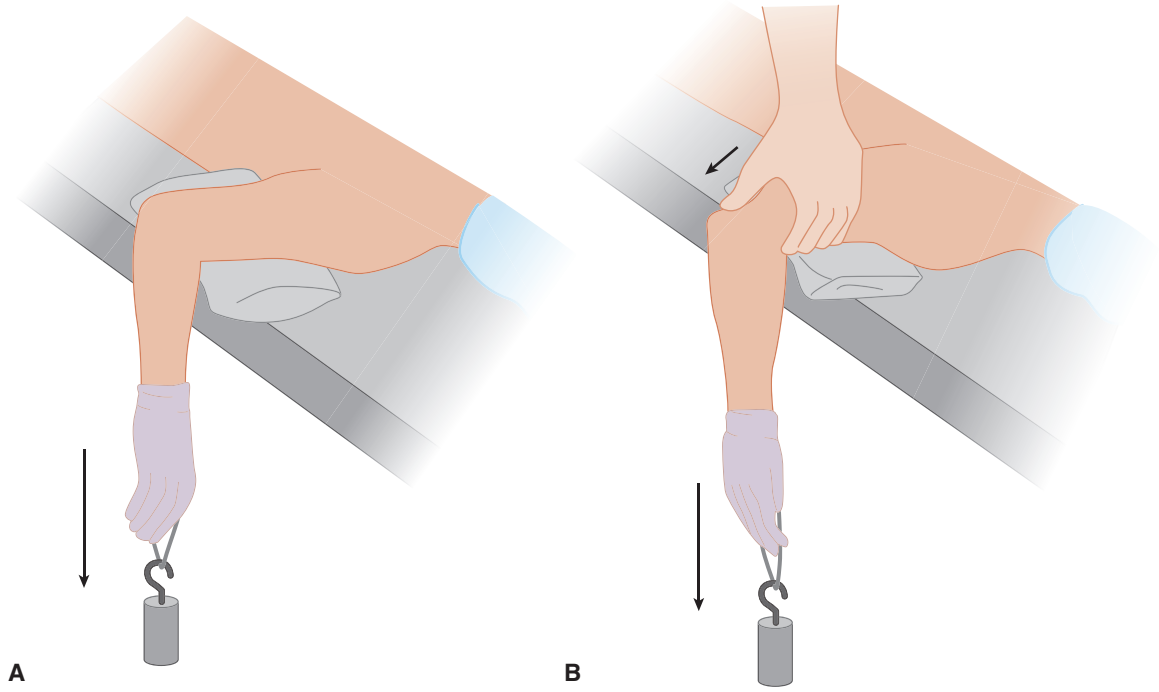

FIGURE 270-12. **A.** Hanging arm reduction method. **B.** Gentle manipulation can be applied to the olecranon if necessary.

separating the condyles and producing the fracture. Carefully search for a fracture line separating the condyles from each other and from the humerus. All intercondylar fractures involve the articular surface. CT imaging is useful for identifying comminuted fractures and for planning operative therapy for displaced fractures. Treatment is dependent on the amount of displacement of the fracture fragments.

Nondisplaced intercondylar fractures are stable and can be treated initially with immobilization in a long arm posterior splint with the elbow flexed at 90 degrees and the forearm in neutral position. Obtain orthopedic consultation for treatment of displaced, rotated, or comminuted fractures or severe edema.[43]

EPICONDYLE FRACTURES

Lateral epicondyle fractures are uncommon, because the anatomic position of the condyle reduces its exposure to direct blows. When they do occur, lateral epicondyle fractures are usually avulsion fractures. These can be treated with immobilization in a long arm posterior splint, with the elbow flexed to 90 degrees and the forearm in supination, and orthopedic referral.

Isolated medial epicondyle fractures are considered extra-articular injuries and usually occur in children and adolescents. Mechanisms include a posterior elbow dislocation, repeated valgus stress such as throwing a baseball (Little League elbow), or a direct blow. If there is an associated tear of the medial (ulnar) collateral ligament, the epicondyle itself may become entrapped in the joint space. Patients present with pain over the medial elbow that is exacerbated by supination of the forearm and flexion of the forearm, wrist, and digits. Edema and tenderness are noted in the same area. Carefully test neurovascular function. Obtain standard radiographs with special attention to any intra-articular fragment. Comparison views of the unaffected contralateral elbow may be helpful for diagnosis.

Treat stable, nondisplaced or minimally displaced fractures from a low-energy mechanism nonoperatively, with early range of motion. ED treatment consists of long arm posterior splint immobilization, with the forearm in flexion and pronation, and orthopedic referral. High-energy injuries, open fractures, unstable joints, significant fragment displacement, an intra-articular fragment, and ulnar neuropathy are indications for emergency orthopedic consultation.[44-46] Because surgical treatment should be determined on an individual basis, orthopedic consultation is recommended for all epicondyle fractures.



FIGURE 270-13. Extension-type, displaced supracondylar fracture.

CONDYLE FRACTURES

Lateral condyle fractures occur in children and are more common than their medial counterpart.[47] They result from either a direct blow to the lateral elbow or from a fall on an outstretched hand. Patients complain of pain in the lateral elbow, and swelling is noted in the same area.

TABLE 270-4 Complications of Supracondylar Fractures

Early complications	**Neurologic** Radial nerve injury Median nerve injury (anterior interosseous branch) Ulnar nerve injury (iatrogenic) **Vascular** Brachial artery injury Volkmann's ischemic contracture (compartment syndrome of the forearm)
Late complications	Nonunion Malunion Myositis ossificans Loss of motion

Medial condyle fractures are uncommon and are mostly limited to children. Mechanism of injury is from either a fall on an outstretched hand or excessive valgus stress. Medial pain and swelling are the prominent findings. The injury is often confused with the more common medial epicondyle fracture for two reasons. First, the mechanism and examination findings are similar. Second, because the trochlea ossification center does not appear until age 9 to 10 years old, it is often missed on radiographs.

ED care of nondisplaced condyle fractures with normal neurovascular function includes long arm posterior splint immobilization, ice, elevation, analgesics, and orthopedic referral. Follow-up imaging every 2 weeks is recommended due to the risk of late displacement, which is treated with surgical fixation. Displaced fractures or those with neurovascular compromise require immediate orthopedic consultation.

ARTICULAR SURFACE FRACTURES

TROCHLEA AND CAPITELLUM FRACTURES

Isolated trochlea fractures are rare and are often associated with other elbow injuries, such as posterior elbow dislocations. Physical findings usually include swelling, tenderness, and limited movement of the elbow joint. Radiographic findings can be subtle, and CT or MRI may be required for diagnosis.

Isolated capitellum fractures are also rare. They are usually associated with radial head fractures. Pain is present over the lateral elbow, and examination reveals lateral swelling, tenderness, and limitation of flexion and extension. If pain and tenderness are present medially, then suspect injury to the medial (ulnar) collateral ligament. Radiographic findings may be subtle and are best seen on a lateral view. The capitellum has no tendinous or ligamentous attachments, so many fractures are nondisplaced. A radial head–capitellum view can be helpful in addition to standard anteroposterior and lateral views. CT imaging is useful for diagnosis.

ED treatment of articular surface fractures includes long arm posterior splint immobilization and orthopedic consultation. Complications are common and include limited flexion and extension, elbow joint instability, avascular necrosis, nonunion, and arthritis.

PROXIMAL ULNA FRACTURES

Nearly all proximal ulna fractures are considered intra-articular, except for proximal olecranon chip fractures.

CORONOID FRACTURES

Coronoid fractures are usually associated with posterior elbow dislocations as the trochlea impacts the coronoid. Rarely, a coronoid fracture can occur as an isolated injury secondary to elbow hyperextension.[48] There is pain, swelling, and tenderness over the antecubital fossa. Radiographic visualization is best with lateral and oblique films. CT is often needed to make the diagnosis.

ED treatment should include long arm posterior splint immobilization with the elbow in flexion and the forearm in supination, ice, elevation, analgesics, and referral to an orthopedic surgeon within 24 hours. Due to the critical role the coronoid plays in elbow stability, early orthopedic referral is indicated even for isolated, nondisplaced fractures.[49] Displaced fractures or those with joint instability require open reduction and internal fixation and frequently have poor outcomes.

OLECRANON FRACTURES

Olecranon fractures represent up to 10% of upper extremity fractures.[50] The mechanism is usually direct trauma or by a fall with forced hyperextension of the elbow. Associated injuries are common, including open fractures, dislocations, other fractures (especially of the radial head), and ulnar nerve injury. Pain is present over the posterior elbow, and examination reveals swelling, tenderness, and occasionally crepitus. Because the triceps muscle inserts at the olecranon, elbow extension can be compromised. It is important to test extension against resistance, as the patient may falsely appear to have intact extension function by using gravity to draw the forearm down. Ulnar nerve injury is common; therefore, a careful neurologic examination is required. Lateral radiographs offer the best view of the olecranon. In adolescents, the epiphysis ossifies by 11 years of age and fuses by 16 years of age, so comparison films and the appearance of an abnormal fat pad can aid in the diagnosis. ED treatment includes long arm posterior splint immobilization with the elbow in flexion and forearm neutral, ice, elevation, analgesics, and referral to an orthopedist within 24 hours. Stable, nondisplaced fractures with intact extensor function can be treated conservatively with immobilization. Nonoperative treatment may also be considered for elderly patients who are poor candidates for surgery. All other olecranon fractures require surgical repair.[51]

RADIAL HEAD FRACTURES

Radial head fractures are the most common fractures of the elbow. They result from a fall on an outstretched hand, causing the radial head to drive into the capitellum. Associated injuries are common and may include capitellum, olecranon, and coronoid fractures, medial collateral ligament injury, medial epicondyle avulsion fracture, and elbow dislocation. A specific associated injury, the *Essex-Lopresti lesion*, occurs when there is disruption of the triangular fibrocartilage complex of the wrist and the interosseous membrane between the radius and ulna, causing dissociation of the distal radioulnar joint. This is analogous to a Maisonneuve injury in the lower extremity. Do not miss this injury. Failure to recognize this injury can result in proximal migration of the radius, so obtain emergency orthopedic consultation.

Radial head fractures cause pain in the lateral elbow, especially with pronation and supination of the forearm. On examination, there may be swelling laterally and tenderness with palpation of the radial head. Pronating and supinating the forearm with the elbow flexed allows the examiner to palpate the radial head. On standard elbow radiographs, radial head fractures may be subtle (**Figure 270-14**). Radiographic



FIGURE 270-14. Subtle radial head fracture and anterior fat pad sign (*arrow*).

clues include the presence of an abnormal fat pad or abnormal displacement of the radiocapitellar line away from the center of the capitellum (Figure 270-7). This is especially helpful in children whose epiphysis has not fused. Additional images, including obliques and a radial head–capitellum view, may be helpful.

Nondisplaced fractures can be treated conservatively with immobilization and early range of motion exercises to avoid the development of a stiff joint. ED treatment consists of sling immobilization, ice, elevation, analgesics, and referral to an orthopedic surgeon or sports medicine specialist within 1 week. Consider aspiration of the joint hematoma in the ED to improve pain and facilitate early mobilization.[52] For displaced fractures or those with restricted range of motion, surgical repair is generally indicated, and orthopedic referral should be made within 24 hours. Complications of radial head fracture include chronic pain and restricted range of motion at the elbow.

FOREARM FRACTURES

In adults, solitary fractures of the forearm are uncommon due to the close relationship of the radius and ulna. The fibrous interconnection between the radius and ulna transmits force above and below the injury. As a result, fractures usually occur at two or more sites or involve ligamentous injury or joint dislocation. Because distant structures are commonly injured, examine joints above and below the involved bones both clinically and radiologically. Be suspicious for associated injuries if there is significant angulation of the fracture.

FRACTURES OF BOTH RADIUS AND ULNA

A large amount of force is necessary to fracture both the radius and the ulna. This occurs most often from vehicular trauma, falls from a height, or a direct blow. Force magnitude determines the injury type. Moderate forces produce transverse or mildly oblique fractures. High-impact forces produce comminuted and segmental fractures (often displaced).

Nondisplaced fractures of both bones are exceedingly rare, because the force necessary to produce the injury is also sufficient to displace the bones. Examination of the forearm reveals swelling, deformity, and tenderness. Carefully assess the neurovascular status. Nerve injuries can occur with severe open fractures, but are uncommon with closed injuries. Because of the excellent collateral circulation of the forearm, vascular compromise is generally not a major concern if either the radial or ulnar circulation is intact.

The fractures are clearly visible on radiographs. Note the degree of angulation, displacement, and shortening. Changes in rotational alignment may be subtle. Assessing the orientation of bony prominences on the radius and ulna can help determine rotational alignment. On the anteroposterior view, the radial styloid and radial (bicipital) tuberosity normally point in opposite directions, whereas the ulnar styloid and coronoid process do so on the lateral view. A change in this arrangement suggests rotation malalignment. Because these bones are oblong rather than circular in their cross-sectional appearance, a sudden change in the bone's width at the fracture site is another clue to a rotational deformity. Obtain radiographs of the wrist and elbow because of the likelihood of an associated dislocation or articular fracture.

Treatment depends on the type of fracture. Torus or greenstick fractures with minimal angulation in children can be treated with immobilization in a long arm splint. Angulation >15 degrees warrants referral for closed reduction. In younger children, treat displaced fractures with closed reduction and cast immobilization due to the continued remodeling that occurs after fracture healing. Perform closed reduction urgently in the ED to ensure appropriate alignment. Traditionally, closed reduction is performed by an orthopedic consultant, but reductions performed by emergency physicians for nonoverlapping fractures have also been show shown to have good outcomes.[53] Surgical intervention is indicated if acceptable reduction cannot be achieved through closed reduction and casting.[54] Nondisplaced fractures in adults can be immobilized with a long arm splint and referred for urgent follow-up. All other fractures in adults require orthopedic consultation, ideally within 24 to 48 hours.

Complications include reduced ability to supinate and pronate, osteomyelitis, nonunion, malunion, neurovascular injury, and compartment syndrome. **Recognizing the development of a compartment syndrome is particularly important to prevent Volkmann's ischemic contractures of the forearm.** Direct measurements of elevated compartment pressures confirm the diagnosis. Emergent orthopedic consultation for fasciotomy is required.

ULNA FRACTURES

ISOLATED ULNA FRACTURE (NIGHTSTICK FRACTURE)

Isolated fractures of the ulna most often result from a direct blow to the forearm. A fracture resulting from the natural response to raise the forearm in defense of a strike is referred to as a *nightstick fracture*. Nondisplaced fractures are immobilized in a sugar-tong splint and closely followed for subsequent displacement.

Fractures with >50% displacement, with >10% angulation, or that involve the proximal third of the ulna are considered unstable.[55] Obtain orthopedic consultation for unstable fractures. Assess for any concomitant radius fracture or dislocation.

MONTEGGIA'S FRACTURE-DISLOCATION

Fracture of the proximal third of the ulna with a radial head dislocation is referred to as *Monteggia's fracture-dislocation* (**Figure 270-15**). The associated radial head dislocation may be easily missed.[56] **Missing the radial head dislocation can lead to chronic pain, limited range of motion, and, possibly, radial head excision as treatment.** Monteggia's fracture-dislocations occur following a fall onto an outstretched hand or a direct blow. Clinically, there is considerable pain and swelling at the elbow. The radial head may be palpable in an anterolateral or posterolateral location. The forearm may appear shortened and angulated. The ulnar fracture is clearly visible on radiographs and may overshadow the less obvious radial head dislocation. An abnormal



A B

FIGURE 270-15. Monteggia's fracture-dislocation. The angulation of the comminuted fracture of the proximal ulna points in the direction of the radial head dislocation.

radiocapitellar line may aid in the diagnosis. Additionally, the apex of the ulna fracture points in the direction of the radial head dislocation to provide another radiographic clue.

Obtain consultation with an orthopedic surgeon. Monteggia's fracture-dislocations are generally treated with open reduction and internal fixation of the ulna fracture and closed reduction of the radial head dislocation. Complications include nonunion, recurrent dislocation, chronic pain, infection, and paralysis of the posterior interosseous nerve, the deep branch of the radial nerve that controls finger extension.

RADIUS FRACTURES

FRACTURES OF THE PROXIMAL TWO THIRDS OF THE RADIUS

Radius fractures can be divided into those in the proximal two thirds and those in the distal one third of the bone. Excluding radial head fractures, isolated fractures of the proximal two thirds of the radius are uncommon because the radius is relatively well protected from direct blows by the ulna and surrounding forearm musculature. Fractures of the proximal two thirds of the radius are often displaced by both the force of the injury and the action of the forearm supinators and pronators on the radius. Typically, supination of the proximal segment and pronation of the distal segment are seen, although a fracture located beyond these muscle groups may have minimal deformity. Displaced fractures require emergent orthopedic consultation. Nondisplaced fractures are treated with cast immobilization. Compartment syndrome is rare with these fractures. Most complications involve malunion or nonunion because of inadequate or lost reduction.

GALEAZZI'S FRACTURE-DISLOCATION

Fracture of the distal third of the radial shaft accompanied by a dislocation of the distal radioulnar joint is known as *Galeazzi's fracture-dislocation* (**Figure 270-16**). This injury results from falls on the outstretched hand in forced pronation or from a direct blow. Galeazzi's fracture-dislocation is also referred to as *Piedmont fracture, reverse Monteggia's fracture,* or *fracture of necessity*, reflecting the need for surgical intervention.[57] There is localized tenderness and swelling over the distal radius and wrist. The radius fracture usually results in dorsal lateral angulation. The distal radioulnar joint injury can be subtle. Radiographs may show only a slightly increased distal radioulnar joint space on the anteroposterior view. On the lateral view, the ulna is displaced dorsally. Obtain immediate orthopedic consultation in the ED. Complications include infection, nonunion, and malunion. If the radius heals with a rotational deformity, there may be pain at the distal radioulnar joint with extreme pronation and supination.



A B

FIGURE 270-16. Galeazzi's fracture-dislocation.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 271

Shoulder and Humerus Injuries

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STERNOCLAVICULAR SPRAINS AND DISLOCATIONS

ANATOMY

The sternoclavicular joint contains an intra-articular fibrocartilaginous disc and has the least amount of bony stability of any major joint because less than half of the medial end of the clavicle articulates with the upper sternum. However, the joint is remarkably stable, due to the strong surrounding ligaments. As a result, most injuries are simple sprains, while dislocations and fractures are uncommon.[1-4]

The medial clavicular epiphysis is the last epiphysis of the body to appear radiographically (age 18 years old) and the last to close (age 22 to 25 years old). Because of this, an apparent sternoclavicular joint dislocation in children and young adults is typically a Salter-Harris type I or II fracture, with either anterior or posterior displacement of the clavicular metaphysis that requires orthopedic consultation and follow-up for optimal healing and remodeling.[1,5]

CLINICAL FEATURES AND DIAGNOSIS

The major symptom of dislocation is severe pain, exacerbated by arm motion and lying supine. A **posterior dislocation** results from a direct blow or from an indirect force to the shoulder, causing the shoulder to roll forward at the time of impact. The shoulder may appear shortened and rolled forward. In posterior dislocations, the medial clavicle end is less visible and often not palpable, and the patient may have signs and symptoms of impingement of the superior mediastinal contents, such as stridor, dysphagia, and shortness of breath (**Figure 271-1**).[3,4] An **anterior dislocation** may result from a similar indirect force if the shoulder is rolled backward at the moment of impact. On examination, anterior dislocations have a prominent medial clavicle end that is visible and palpable anterior to the sternum, although swelling and tenderness may impede diagnosis.

Minor trauma may result in a sprain to the sternoclavicular joint with only pain and swelling localized to the joint. Sprains of the sternoclavicular joint are treated with ice, sling, and analgesics. In a nontrauma

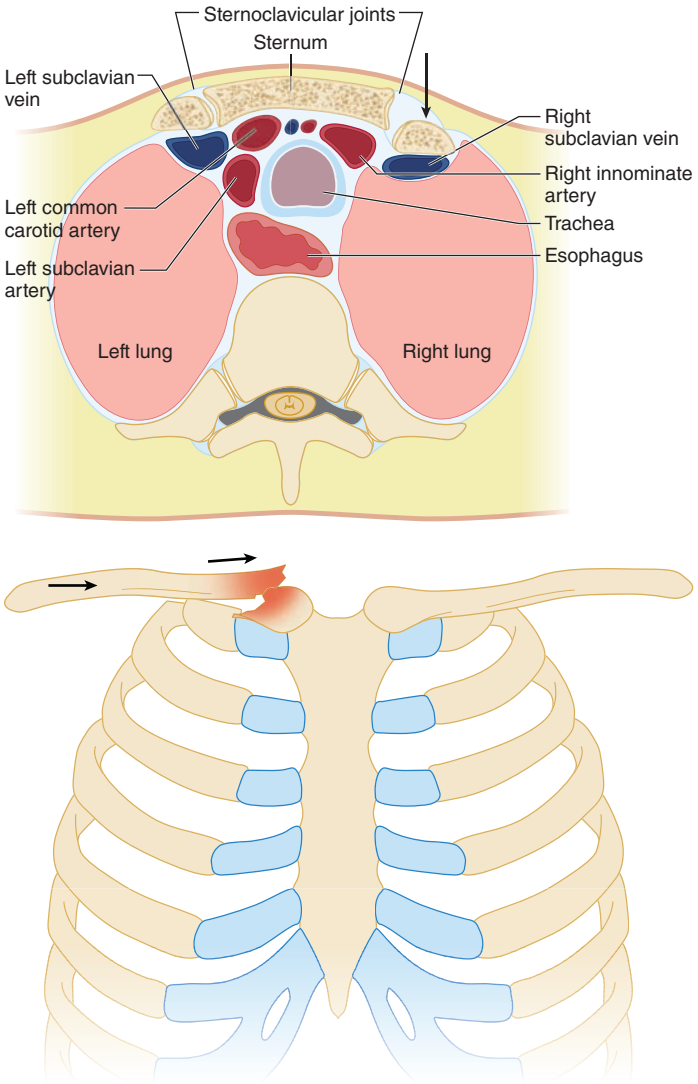


FIGURE 271-1. Posterior sternoclavicular joint dislocation impinging on the mediastinal structures.

patient, pain at the sternoclavicular joint should raise suspicion for septic arthritis, especially in injection drug users. US can detect effusion and aid in joint aspiration.

Routine radiographs have a low sensitivity for the detection of dislocation, but an immediate chest radiograph is needed to exclude a pneumothorax, pneumomediastinum, and hemopneumothorax. Special views and comparison with the other clavicle may be helpful.[1] CT is the imaging procedure of choice (**Figure 271-2**) and is recommended in any posterior dislocation with concern for injury to the mediastinal structures. IV contrast may be administered to further delineate injury. Point-of-care US can identify sternoclavicular joint effusions and may been used to rapidly diagnose posterior sternoclavicular dislocation in the ED.[6,7]

TREATMENT OF ANTERIOR STERNOCLAVICULAR DISLOCATIONS

Patients with uncomplicated anterior dislocations may be discharged without an attempted reduction, because this injury has little or no impact on function. Clavicular splinting, ice, analgesics, sling, and orthopedic referral are required.

For closed reduction, which can be performed within 10 days of the injury, the patient is placed supine with a towel roll or similar between the scapulae. The arm is abducted to 90 degrees, longitudinal traction is

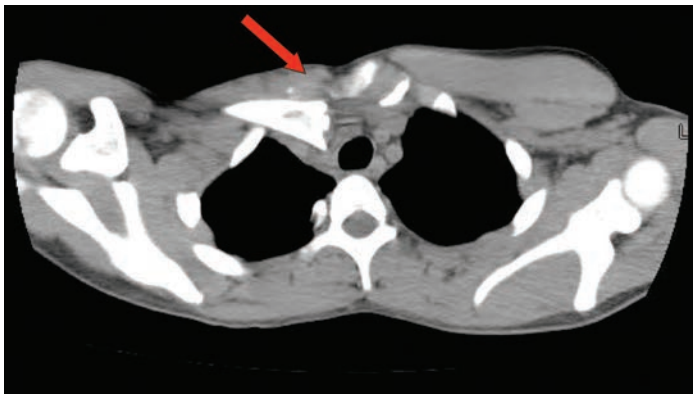


FIGURE 271-2. CT scan of right posterior sternoclavicular dislocation. *Arrow* indicates disrupted sternoclavicular joint with posterior displacement of clavicle and compression of adjacent lung.

applied with slight extension by moving the arm toward the ground, and pressure is placed over the medial end of the clavicle.[8] Even with reduction, the joint is usually unstable and redislocates (50%) when pressure is released. Refer to an orthopedist.[9]

TREATMENT OF POSTERIOR STERNOCLAVICULAR DISLOCATIONS

Posterior dislocations may be associated with life-threatening injuries to adjacent structures, including pneumothorax or compression or laceration of surrounding great vessels, trachea, or esophagus.[1,2] Orthopedic consultation is necessary for closed or open reduction. Open reduction should be performed in the operating room with trauma or vascular surgery available.[1,3,8,10]

CLAVICLE FRACTURES

ANATOMY

The clavicle provides support and mobility for upper extremity tasks by functioning as a strut that connects the shoulder girdle to the trunk. It articulates with the sternum proximally and the acromion distally. In addition, the clavicle protects the adjacent lung, brachial plexus, and subclavian and brachial blood vessels. The clavicle is S-shaped, and the midportion of the clavicle is the thinnest, having no accompanying ligamentous or muscular attachments. Fracture results from a direct blow to the shoulder, buckling the clavicle.

CLINICAL FEATURES AND DIAGNOSIS

Clinical signs are swelling, deformity, and tenderness overlying the clavicle. The arm is slumped inward and downward, and range of motion is limited. The fracture can often be palpated, and crepitus may be present.

Most clavicle fractures can be diagnosed on standard shoulder and clavicle radiographs. Occasionally, routine clavicle radiographs may miss some fractures, particularly at either end of the bone, due to overlap of surrounding structures. If a fracture is clinically suspected but not initially diagnosed with standard radiographs, a 45-degree cephalad tilt view may be used for further assessment. Definitive diagnosis may require CT.

Obtain emergent orthopedic consultation for open fractures, fractures with neurovascular injuries, and fractures with persistent skin tenting.

TREATMENT OF MIDDLE THIRD CLAVICLE FRACTURES

Fractures of the middle third of the clavicle are most common. Although midclavicular fractures are often managed nonoperatively, operative fixation may result in improved functional outcome and a lower rate

TABLE 271-1 Middle Clavicle Fracture Nonunion Risk Factors

- Initial shortening >2 cm
- Comminuted fracture
- Displaced fracture >100%
- Significant trauma
- Female
- Elderly

of malunion and nonunion.[11-13] Some fractures (**Table 271-1**), including severely comminuted or displaced fractures, benefit from referral and possible operative intervention.[14,15] Additional considerations for orthopedic referral include athletes, professional impact, and cosmetic concerns. Referral to an orthopedist within a few days of injury should be considered in the above instances. In cases where the patient does not want surgery or is a poor surgical candidate, conservative treatment is an appropriate strategy. Initial treatment of midclavicle fractures includes immobilization with either a sling or figure-of-eight brace. The length of immobilization is typically 4 to 8 weeks, until the fracture is no longer painful. Initial primary care or orthopedic follow-up should be in 1 to 2 weeks after injury in conservative treatment. The patient may use the arm as pain permits, but should avoid repeat injury from direct contact. Encourage daily range of motion of the elbow immediately and of the shoulder as soon as pain allows (3 to 5 days).

TREATMENT OF DISTAL CLAVICLE FRACTURES

Distal clavicle fractures are divided into three subtypes.[16] In type I fractures, the fracture is distal to the coracoclavicular ligaments, with the ligaments remaining intact. Type II fractures are broken into two categories. In type IIa, the fracture is medial to the coracoclavicular ligaments, although the ligaments remain intact. This results in an upward displacement of the proximal aspect of the clavicle. In a type IIb distal clavicle fracture, the fracture is between the coracoacromial ligaments with the conoid ligament torn and the trapezoid ligament intact, or lateral to the coracoacromial ligaments with both ligaments disrupted (**Figure 271-3**). Type II distal clavicle fractures may require operative intervention to avoid nonunion.[17] Type III fractures are intra-articular fractures through the acromioclavicular (AC) joint. Type I and III fractures can be managed conservatively with sling immobilization and primary care follow-up in 1 to 2 weeks.[18]

TREATMENT OF PROXIMAL THIRD CLAVICLE FRACTURES

Proximal third clavicle fractures are often high-mechanism injuries and can be associated with intrathoracic trauma. CT can diagnose the fracture and identify additional injuries. Emergent referral is required when posteriorly displaced fragments compromise mediastinal structures. Refer all other proximal third fractures to orthopedics within 1 to 2 weeks. Initial management includes sling immobilization.

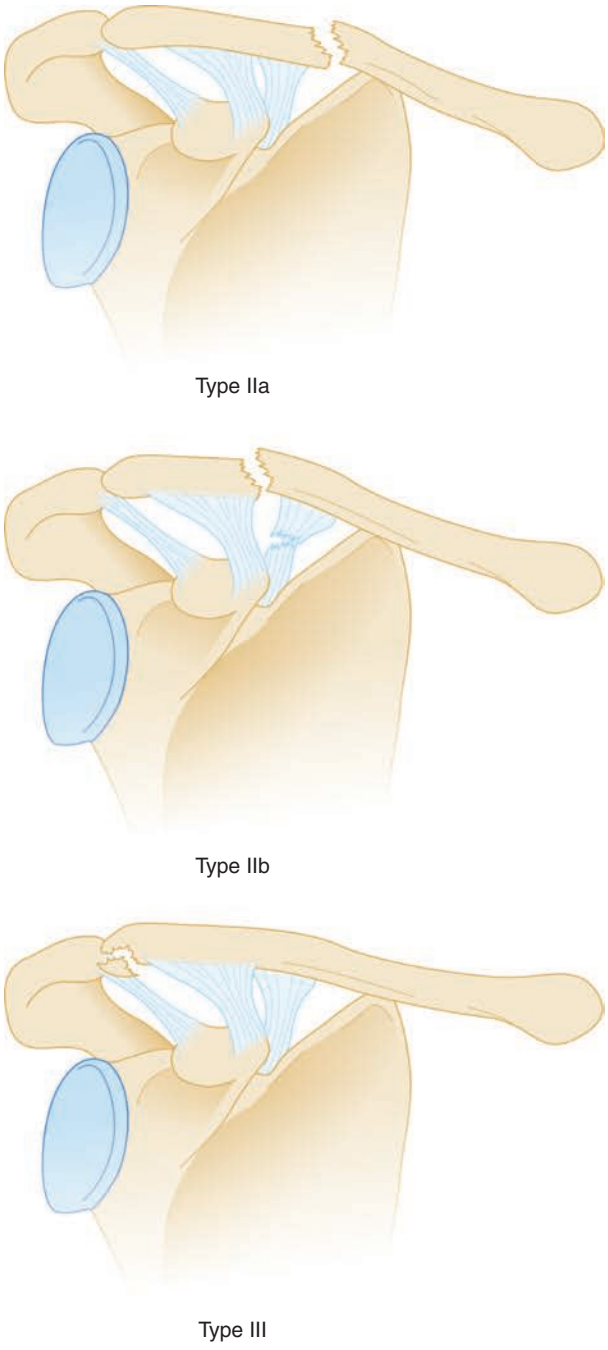


FIGURE 271-3. Classification of distal clavicular fractures.

SCAPULA FRACTURES

ANATOMY

The scapula is a triangularly shaped, flat bone that links the axial skeleton to the upper extremity and stabilizes motion of the arm. It serves as the site of origin of the rotator cuff and muscles about the shoulder. The mechanism of injury usually is from high-energy trauma to the shoulder area or from a fall on an outstretched hand. Scapular fractures are classified by their anatomic location (**Figure 271-4**),[19,20] with fractures of the body (**Figure 271-5**) and glenoid neck being most common.

CLINICAL FEATURES AND DIAGNOSIS

Patients with isolated scapular fractures typically present with localized tenderness over the scapula and the arm held in adduction. Arm movement exacerbates pain. Due to the high energy typically required to fracture this protected bone, there is a high association of injuries to the ipsilateral lung, thoracic cage, and shoulder girdle, with fractures of the ribs being most common. Carefully determine the mechanism of injury to assist in diagnosis and raise suspicion for concurrent injuries. Assess the spine and pelvis because scapular injuries often occur with high-impact trauma.[19-21] The indirect axial load transmitted by a fall on an outstretched arm may result in a scapular neck fracture or glenoid fracture through shoulder impaction or dislocation.

Overlying structures may obscure a scapular fracture on a single trauma anteroposterior chest radiograph. A dedicated scapular series, including anteroposterior, lateral, and axillary scapular views, will identify most fractures and will guide the need for a CT scan.[20] Scapular fractures are often associated with other significant injuries, and hence, diagnosis may be delayed or initially missed entirely. CT scan of the chest can identify both scapular and associated pathology, and a dedicated CT of the scapula can also be obtained.

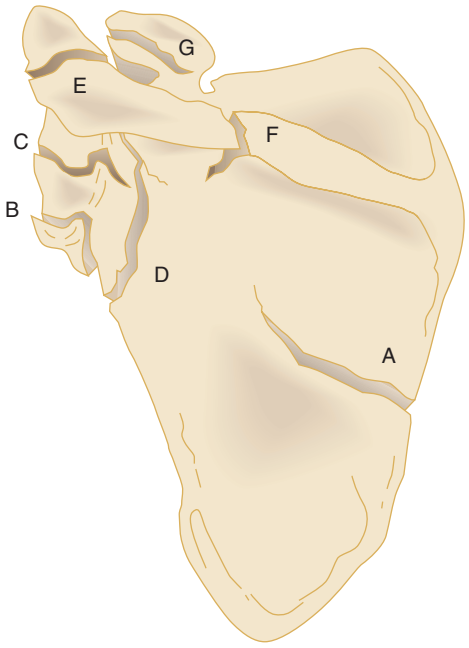


FIGURE 271-4. Sites of scapular fractures. **A.** Body. **B.** Glenoid rim. **C.** Intra-articular glenoid. **D.** Neck. **E.** Acromion. **F.** Spine. **G.** Coracoid.

TREATMENT OF SCAPULAR FRACTURES

Most scapular fractures are treated nonsurgically, with sling, ice, analgesics, and early range-of-motion exercises. Surgery may be necessary for significant or displaced articular fractures of the glenoid, angulated glenoid neck fractures, acromial fractures associated with a rotator cuff tear, and some coracoid fractures.[19,22] Disability is more likely to be associated with fractures of the glenoid, acromion, or coracoid. Isolated scapular fractures should be referred to an orthopedic surgeon.



FIGURE 271-5. Scapular Y view demonstrating scapular body fracture. [Photo used with permission of Alexander Ebinger, MD.]

TREATMENT OF SCAPULOTHORACIC DISSOCIATION

Traumatic dislocation of the scapula from the thoracic wall results from severe massive traction force applied to the ipsilateral upper extremity and shoulder girdle. Associated disruption of the subclavian or axillary arteries and brachial plexus makes proper identification and treatment critical.[23,24]

Chest radiograph demonstrates significant lateral displacement of the scapula.[23,24] Associated radiographic abnormalities include distracted clavicle fracture, AC separation, and sternoclavicular dislocation. Perform a CT scan to identify intrathoracic injuries.

ACROMIOCLAVICULAR JOINT INJURIES

ANATOMY

The AC joint is a diarthrodial joint that, together with the sternoclavicular joint, connects the upper extremity to the axial skeleton (**Figure 271-6**).

Support of the AC joint is through the AC and coracoclavicular ligaments and the attachment of the trapezius and deltoid muscles. Surrounding the AC joint is a thin capsule, which is reinforced by the AC ligaments. The AC ligaments provide horizontal stability to the joint. The strong coracoclavicular ligaments consist of two parts, the more lateral trapezoid and the medial conoid, and attach the distal inferior clavicle to the coracoid process of the scapula. The coracoclavicular ligament is the major suspensory ligament of the upper extremity and provides vertical stability to the AC joint.

AC joint injuries range from mild sprain to complete disruption of the ligaments that link the scapula and clavicle. The mechanism of injury is usually direct trauma to the joint from a fall with the arm adducted. The result is that the scapula and shoulder girdle are driven inferiorly while the clavicle remains in its normal position. An indirect mechanism is a fall on the outstretched hand with transmission of force to the AC joint.

CLINICAL FEATURES AND DIAGNOSIS

The diagnosis of an AC joint injury is clinical. The mechanism of injury, along with tenderness and deformity at the AC joint, especially when compared with the contralateral AC joint, is confirmatory. Range of

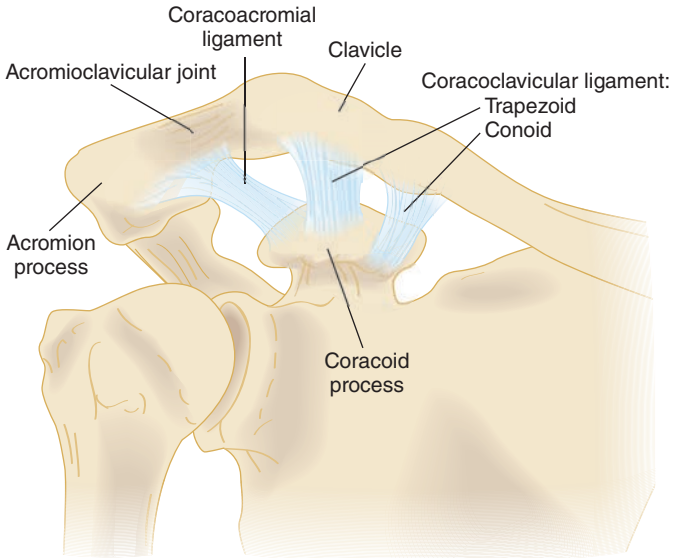


FIGURE 271-6. Anatomy of the acromioclavicular joint.

motion may be limited, depending on the severity of injury. Cross-arm abduction testing is often painful.

Radiographs are useful for identifying other fractures and determining the severity of injury. Specifically order AC radiographs because they require only one third to one half of the penetration of standard shoulder films. Shoulder radiographs may overpenetrate the AC joint, and small fractures can be missed. Although standard AC radiographs are generally sufficient, an axillary view is required to identify posterior clavicular dislocation (type IV). Stress radiographs may be ordered but are no longer routinely obtained.[25,26]

TREATMENT OF ACROMIOCLAVICULAR JOINT INJURIES

Obtain emergency orthopedic consultation for open fractures, fractures with neurovascular injuries, and fractures with persistent skin tenting. **Table 271-2** describes specific AC joint injuries. Treatment of **type I and II injuries** consists of rest, ice, analgesics, and immobilization, followed by early range-of-motion exercises (7 to 14 days).[27] A simple sling is the most convenient and effective initial treatment. Prognosis for type I and II injuries is excellent, with only a small percentage of patients developing late symptoms requiring excision of the distal clavicle.

Treatment of **type III injuries** varies, with most orthopedists recommending a trial of conservative treatment with sling immobilization.[28-30] Surgical strategies have yielded good results in selected patients, with the specific management being operator dependent. Treatment decisions are based on such factors as age, occupation, and activity level. **Types IV, V, and VI are severe injuries**, and most experts recommend surgical repair. Because other injuries are associated with these more severe forms of AC joint injuries (especially type VI), a careful clinical and radiographic examination must be performed.[28,29]

GLENOHUMERAL JOINT DISLOCATION

ANATOMY

The glenohumeral joint is a ball-and-socket joint, with the articulation between the glenoid fossa of the scapula and the articular surface of the humeral head. The socket of the shoulder is shallow. The glenoid labrum deepens the socket and helps provide joint stability. The capsule and tendinous attachments about the joint also provide stability. Anterior dislocations of the glenohumeral joint are the most common; posterior dislocations account for <1%. Other dislocations include inferior (luxatio erecta) and superior (very rare).

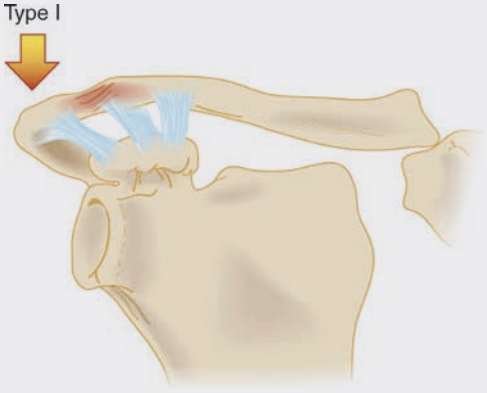
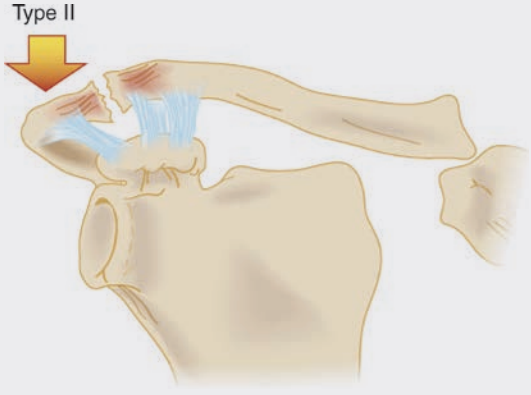
CLINICAL FEATURES AND DIAGNOSIS

The combination of abduction, extension, and external rotation with sufficient force will cause an anterior dislocation. There are multiple types of anterior glenohumeral dislocations (**Figure 271-7**). These include subcoracoid, which is the most common; subglenoid; subclavicular; and the very rare intrathoracic dislocation.

In an anterior dislocation, the associated arm is usually in slight abduction and external rotation. The shoulder is "squared off," lacking the normal rounded contour. The patient resists adduction and internal rotation and often cannot touch the contralateral shoulder with the hand of the affected extremity. The humeral head can often be palpated anteriorly. Perform a careful neurovascular examination. The axillary nerve is most commonly injured. This nerve may be tested by pinprick sensation over the skin of the deltoid muscle.

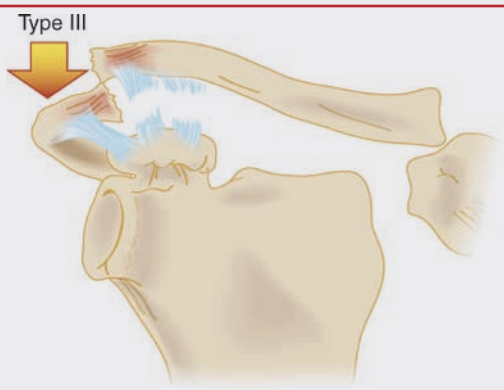
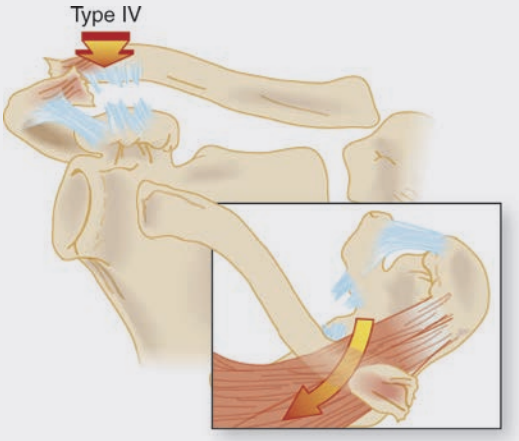
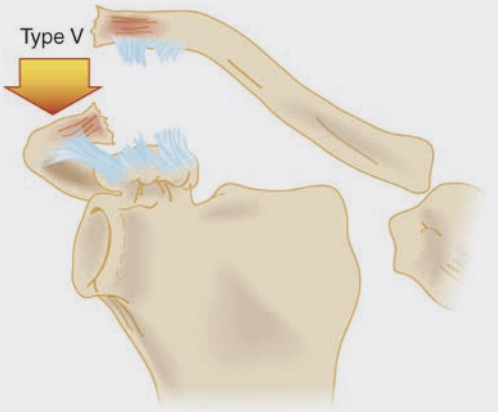
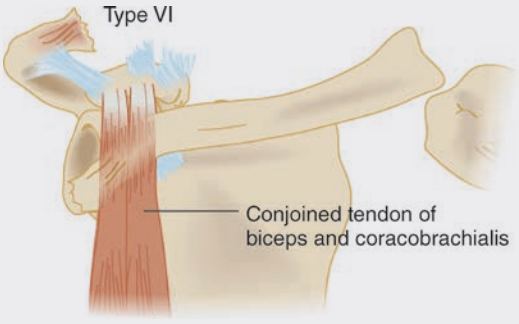
Prereduction radiographs are advisable when there has been significant trauma, unless time is crucial because circulation is threatened.[31] Radiographs are needed because dislocations and fracture-dislocations may have a similar appearance on physical examination, but the techniques used to treat them may be very different.

TABLE 271-2 Classification and Physical Findings in Acromioclavicular Joint Injuries

Type	Injury	Mechanism	Radiograph/Exam
I	Sprained acromioclavicular ligaments		Radiograph: Normal Exam: Tenderness over acromioclavicular joint
II	Acromioclavicular ligaments ruptured; coracoclavicular ligaments sprained		Radiograph: Slight widening of acromioclavicular joint; clavicle elevated 25%–50% above acromion; may be slight widening of the coracoclavicular interspace Exam: Tenderness and mild step-off deformity of acromioclavicular joint

(*Continued*)

TABLE 271-2 Classification and Physical Findings in Acromioclavicular Joint Injuries (*Continued*)

Type	Injury	Mechanism	Radiograph/Exam
III	Acromioclavicular ligaments ruptured; coracoclavicular ligaments ruptured; deltoid and trapezius muscles detached		Clavicle elevated 100% above acromion; coracoclavicular interspace widened 25%–100% Exam: Distal end of clavicle prominent; shoulder droops
IV	Rupture of all supporting structures; clavicle displaced posteriorly in or through the trapezius		Radiograph: May appear similar to type II and III; axillary radiograph required to visualize posterior dislocation Exam: Possible posterior displacement of clavicle
V	Rupture of all supporting structures (more severe form of type III injury)		Radiograph: Acromioclavicular joint dislocated; generally 200%–300% disparity of coracoclavicular interspace compared to normal shoulder Exam: More pain; gross deformity of clavicle
VI	Acromioclavicular ligaments disrupted; coracoclavicular ligaments may be disrupted; deltoid and trapezius muscles disrupted		Radiograph: Acromioclavicular joint dislocated; clavicle displaced inferiorly Exam: Severe swelling; multiple associated injuries

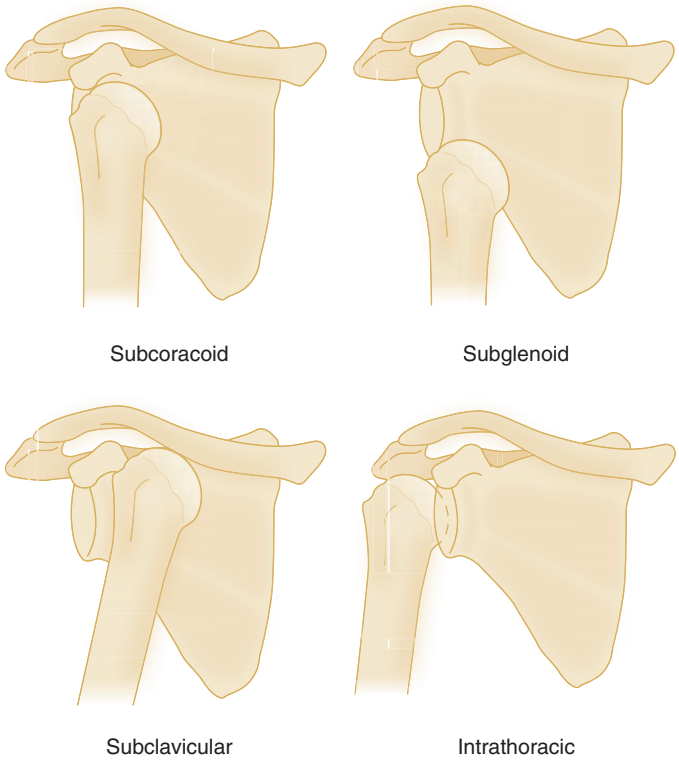


FIGURE 271-7. Types of anterior shoulder dislocations.

Obtain anteroposterior and either axillary or scapular lateral or ("Y") radiographs before attempting reduction in patients with first-time dislocation or if a fracture is suspected to confirm the anatomic type of dislocation and identify any associated fractures. Although the anteroposterior radiograph will reveal the dislocation, the axillary or scapular Y radiograph will indicate whether the dislocation is anterior or posterior.[31,32]

Postreduction radiographs are valuable for confirming the success of joint reduction, as well as for providing documentation, in the event the joint redislocates after the patient is discharged from the ED.

There is an expenditure of time, money, and radiation associated with pre- and postreduction films; however, there is currently no validated clinician decision rule that allows safe elimination of prereduction films after injury.[33] In clinical practice, films are sometimes omitted in patients with a history of multiple recurrent dislocations of the shoulder who present with history, signs, and symptoms typical of another recurrence in the absence of significant trauma.[32,33]

GENERAL TREATMENT OF ANTERIOR GLENOHUMERAL DISLOCATIONS

Shoulder dislocations or subluxations combined with proximal humerus fractures generally require orthopedic consultation and may need operative repair. Through the third decade, fracture-dislocations occurred less than 1% of the time. The incidence of shoulder dislocation with associated proximal humerus fracture increases with age and rises with each decade of life.[34]

In most patients, shoulder dislocation produces a significant amount of pain and muscle spasm. It is essential to provide appropriate analgesia. The use of procedural sedation is common, but any reduction technique may be attempted without medication when performed slowly and atraumatically.[35,36] Muscle relaxation and pain management should be tailored to the individual patient and may include NSAIDs, opiates, or benzodiazepines, intra-articular lidocaine injection, or procedural sedation. Although one can significantly reduce pain with IV medications, the most effective way to relieve pain is to rapidly reduce the dislocation.[31]

Intra-articular injection of 10 to 20 mL of 1% lidocaine reduces the pain associated with reduction and can complement procedural sedation.[31,37,38] After sterile skin preparation, introduce the needle at the hollow created by the displaced humeral head, just inferior to the acromion. US can facilitate intra-articular injection. Perform neurovascular examination before and after reduction.

COMPLICATIONS OF GLENOHUMERAL DISLOCATION

Complications associated with anterior glenohumeral dislocations include recurrence, rotator cuff tears, humeral head bony defects (Hill-Sachs deformity), glenoid labral defects (Bankart lesions), and rarely, neurovascular injuries.[39] The most common complication is recurrent dislocation, and children and young adults may have a recurrence rate of more than 90%.[39,40] Early surgical repair may decrease the recurrence rate, so patients with first-time shoulder dislocations should be referred for orthopedic evaluation.[41-43]

The rotator cuff weakens with advancing age, and in older patients, anterior dislocation is usually associated with rotator cuff tears. Rotator cuff tears can be difficult to identify on ED examination after reduction but can be suspected with weakness upon external rotation.[39] Any patient with pain persisting for greater than 2 weeks should follow up with orthopedics. For further discussion, see Chapter 280, "Shoulder Pain."

Bony injuries are common and include fractures of the humeral head (Hill-Sachs lesions) and glenoid (bony Bankart lesion) (**Figures 271-8** and **271-9**) and tears of the anterior glenoid labrum (soft Bankart lesion) and greater tuberosity. Such fractures are often evident only on postreduction films,[32] and there is no specific ED treatment other than follow-up with orthopedics.

Vascular injuries are rare, but when they occur, they tend to involve the axillary artery in elderly patients. Clinical findings of vascular injury include absent radial pulse, axillary hematoma, bruising of the lateral chest wall, and an axillary bruit.

Nerve injuries, which occur in 10% to 25% of acute dislocations, are the result of traction neurapraxia. Most involve the axillary nerve, resulting in loss of sensation over the skin of the upper arm. This injury



FIGURE 271-8. Bankart lesion. CT of right shoulder showing a frontal view with fracture tear of the anterior-inferior glenoid bony cavity (Bankart lesion). [Photo used with permission of Erik Magnus Berntsen, MD, PhD, Department of Radiology, St. Olavs University Hospital, Trondheim, Norway.]

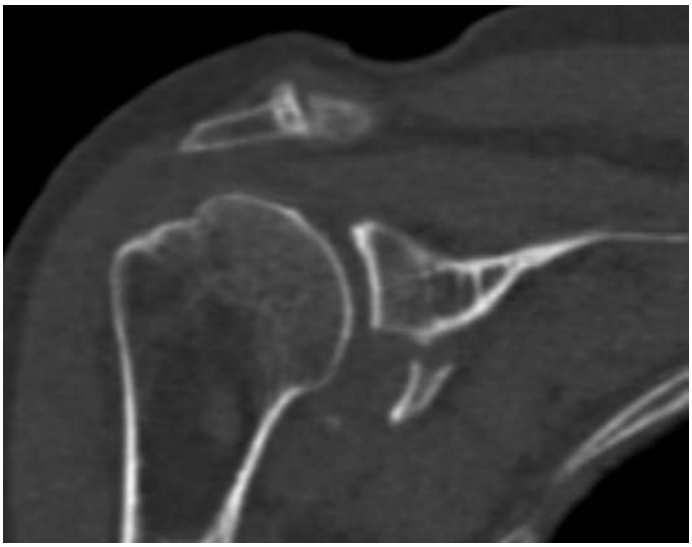


FIGURE 271-9. Bankart lesion and Hill-Sachs fracture. CT of right shoulder, oblique coronal view, demonstrating both the bony Bankart lesion and the Hill-Sachs fracture of the humeral head. [Photo used with permission of Erik Magnus Berntsen, MD, PhD, Department of Radiology, St. Olavs University Hospital, Trondheim, Norway.]

is temporary and resolves spontaneously. The motor portion of the axillary nerve supplies the teres minor and the deltoid, and injury can result in weakness of shoulder abduction and external rotation. Other nerves that may be injured are the radial, ulnar, median, musculocutaneous, and brachial plexus.[39]

DISPOSITION

After reduction, place the arm in a shoulder immobilizer or sling that maintains the shoulder in adduction and internal rotation (**Figure 271-10**). Provide instructions for orthopedic follow-up in 1 week for uncomplicated dislocations and within 1 to 2 days for dislocations complicated by bony or soft tissue injury.[44]

REDUCTION TECHNIQUES

The three main categories of reduction techniques are traction, leverage, and scapular manipulation[31,45-50] (See Video: Anterior Shoulder Dislocation Reduction: Traction Techniques). Success rates are between 70% and 96% regardless of technique. It is best to be comfortable with two or three techniques in case of a failed first attempt. Considerations in selection of a technique include ease of performance, effectiveness, requirement for sedation, number of assistants, and duration. The most common techniques are described below.



FIGURE 271-10. Arm sling.

TRACTION-COUNTERTRACTION TECHNIQUE (MODIFIED HIPPOCRATIC)

A modification of the Hippocratic method uses traction-countertraction (**Figure 271-11**). The patient is supine with the arm abducted and elbow flexed at 90 degrees. A sheet is tied and placed across the thorax of the patient and then around the waist of the assistant. Another sheet is tied and placed around the forearm of the patient at the elbow and the waist of the physician. Gradually apply traction to the proximal forearm as the assistant provides countertraction. Gentle internal and external rotation or outward pressure on the proximal humerus may aid reduction.

STIMSON TECHNIQUE

Place the patient prone with the dislocated extremity hanging over the side of the stretcher and a 10-lb weight attached to the wrist. Inject intra-articular lidocaine. Complete muscle relaxation is required. Reduction



FIGURE 271-11. Modified Hippocratic technique.



FIGURE 271-12. Scapular manipulation technique.

occurs in 20 to 30 minutes. Although the time to reduction can be a drawback, this technique is safe, effective, and easy to learn.

SCAPULAR MANIPULATION TECHNIQUE

The patient is positioned with weights in the same manner as the Stimson technique (**Figure 271-12**). After adequate sedation, the physician pushes the tip of the scapula medially using the thumbs, while stabilizing the superior aspect with the cephalad hand. This technique reports a 96% success rate.[49]

EXTERNAL ROTATION TECHNIQUE (KOCHER'S TECHNIQUE)

Place the patient supine with the affected arm adducted to the patient's side. With the elbow at 90 degrees of flexion, slowly externally rotate the arm (**Figure 271-13**). No longitudinal traction is applied. Perform the movement slowly to allow time for spasm and pain to resolve. Reduction is usually complete before reaching the coronal plane and is often not noted either by the patient or physician. If needed, the elbow may be brought anteriorly and internally rotated to the opposite shoulder.[51]

MILCH TECHNIQUE

The maneuvers for the Milch technique are external rotation, arm abduction to 180 degrees with simultaneous pressure on the humeral head, and in-line longitudinal traction with continued pressure on the humeral head (**Figure 271-14**).

CUNNINGHAM TECHNIQUE

The Cunningham technique is based on the combination of humerus and scapular positioning and specific massage of a spasming biceps muscle (**Figure 271-15**) (See Video: Anterior Shoulder Reduction: Cunningham Technique). Seat the patient comfortably, as upright as possible, with shoulders relaxed. Supporting the affected arm, slowly and gently move the humerus into full adduction with the elbow in flexion. Have the hand of the affected extremity resting against the physician's shoulder. Gently massage the trapezius and deltoids, which helps to relax the patient. Then, gently massage the biceps at the mid-humeral level. Ask the patient to elevate and shrug or retract the shoulders (attempting to touch the scapulae together) and continue the biceps massage. The goal is to wait for the patient to relax fully and have the humeral head slip back into place.[46]

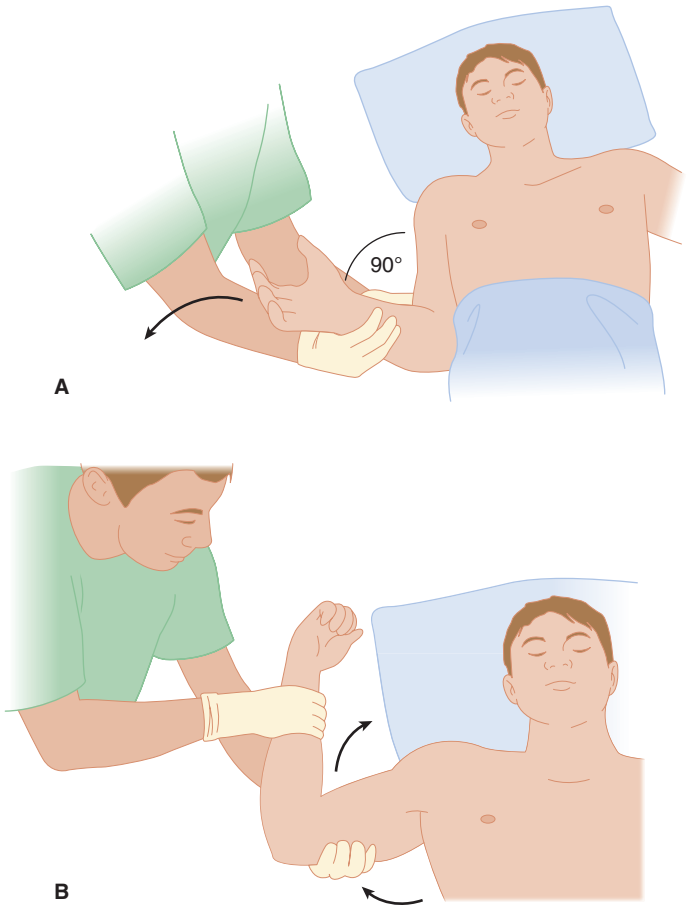


FIGURE 271-13. A and B. External rotation (Kocher's) technique. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics, The Extremities*, 5th ed. © 2007, McGraw-Hill Inc., New York.]

FARES TECHNIQUE

The FARES (FAst, REliable, and Safe) method, which was first described in 2009, is a modified Milch technique[50] (**Figure 271-16**) (See Video: Anterior Shoulder Dislocation: Fares Technique). The FARES method may be the alternative of choice, with a success rate of almost 90% without the use of any sedation, anesthesia, or analgesia.[45] Place the patient in a supine position and hold the patient's wrist with gentle traction in a neutral position. Gently move the limb anteriorly and posteriorly in small oscillating movements on the outstretched arm and start abducting the limb slowly while continuing to apply traction. Once the limb is abducted 90 degrees, the limb is externally rotated. Continue to slowly abduct the limb past this position. Reduction is usually achieved once the limb is abducted to 120 degrees. Successful reduction of acute posterior shoulder dislocations without general anesthesia has been achieved using the FARES method.[44]

POSTERIOR GLENOHUMERAL DISLOCATIONS

Posterior dislocation may occur with the humeral head in the subacromial, subglenoid, or subspinous position, but most often, it occurs with the humeral head posterior to the glenoid and inferior to the acromion (**Figure 271-17**). The subglenoid and subspinous positions are rare. The usual mechanism is an indirect force that produces forceful internal rotation and adduction or a direct blow to the anterior shoulder. On examination, there is a prominence of the posterior shoulder and anterior flattening of the normal shoulder contour on the affected side, especially when compared to the nonaffected side. The patient will be unable to externally rotate or abduct the affected arm. (See Video: Posterior Shoulder Dislocation Reduction.)

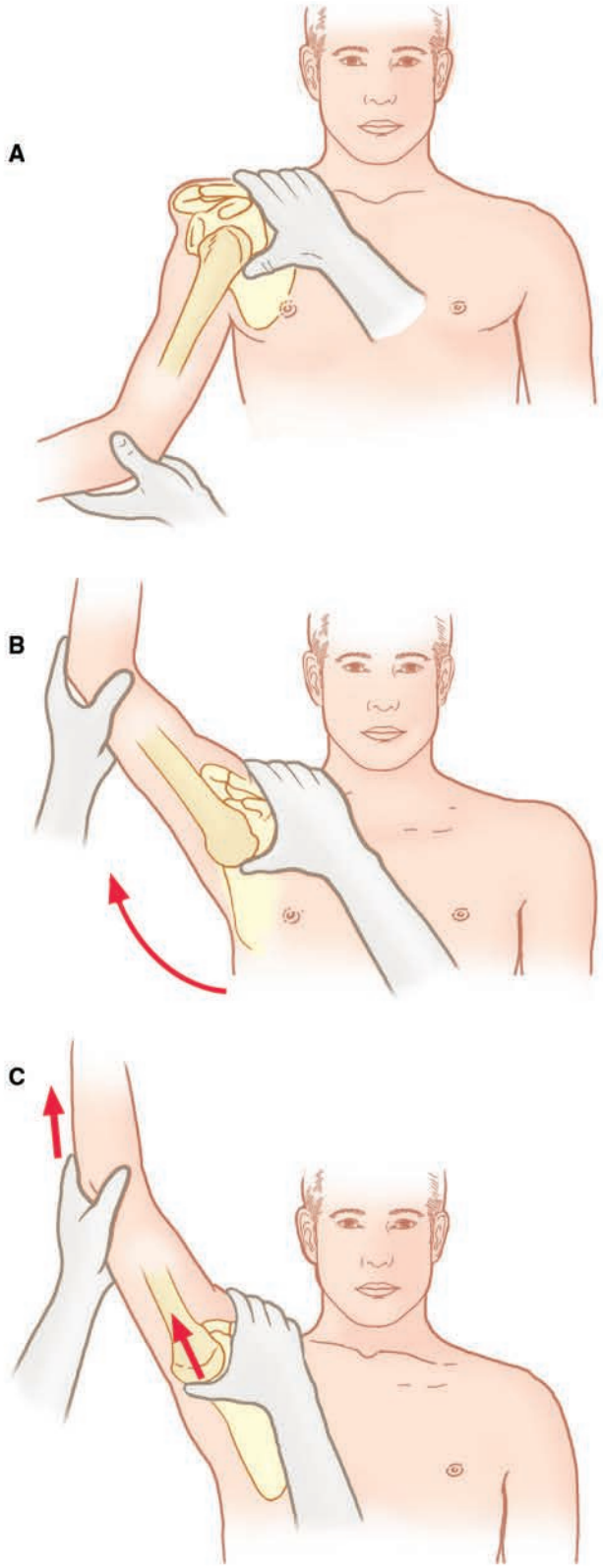


FIGURE 271-14. Milch technique. [Reproduced with permission from Reichman EF: *Emergency Medicine Procedures*, 2nd ed. Chapter 81. Shoulder Joint Dislocation Reduction. McGraw-Hill, Inc., 2013. Figure 81-7A-C.]

The scapular Y radiograph is diagnostic (**Figure 271-18**). An axillary view can also demonstrate a posterior dislocation (**Figure 271-19**).

Reduction of a posterior dislocation is performed with the patient supine. Apply traction to the adducted arm in the long axis of the humerus. Have an assistant gently push the humeral head anteriorly into the glenoid fossa.[52] Fractures of the posterior glenoid rim, humeral head (reversed Hill-Sachs deformity), humeral shaft, or lesser tuberosity are common complications. Neurovascular and rotator cuff tears are less common than in anterior dislocations. Obtain postreduction radiographs to confirm successful reduction. Immobilize the shoulder with an arm sling, with follow-up with an orthopedist.

INFERIOR DISLOCATIONS (LUXATIO ERECTA)

Inferior dislocation is associated with significant soft tissue trauma or fracture. The mechanism of injury is a hyperabduction force, which levers the neck of the humerus against the acromion. As the force continues, the inferior capsule tears, and the humeral head is forced out inferiorly. The patient presents with the humerus fully abducted, the elbow flexed, and the patient's hand on or behind the head. The humeral head can be palpated on the lateral chest wall.

Reduction consists of traction in an upward and outward direction in line with the humerus (**Figure 271-20**). Have the assistant apply countertraction. Reduction is signaled by a "clunk." The arm is then brought to the patient's side and immobilized in a shoulder immobilizer.

Complications include severe soft tissue injuries and fractures of the proximal humerus. The rotator cuff, which usually becomes detached, requires orthopedic follow-up. Neurovascular compression injuries are usually found but almost always resolve after reduction. When the humeral head is buttonholed through the inferior capsule, the dislocation is irreducible, and operative reduction is required. (See Video: Luxatio Erecta Dislocation Reduction.)

PROXIMAL HUMERUS FRACTURES

ANATOMY

The proximal humerus is composed of the articular segment and anatomic neck, the greater and lesser tuberosities, and the proximal shaft (**Figure 271-21**). The supraspinatus, infraspinatus, and teres minor insert on the greater tuberosity, whereas the subscapularis inserts on the lesser tuberosity. The biceps tendon passes through the bicipital groove. The anterior and posterior humeral circumflex arteries branch off the axillary artery and course around the surgical neck.

CLINICAL FEATURES AND DIAGNOSIS

Patients with fractures typically present with pain, swelling, and tenderness about the shoulder. Range of motion is often significantly limited, and the arm is held in adduction. Crepitus and ecchymosis may be present. Carefully perform the neurovascular examination. The most commonly injured nerve is the axillary nerve, and sensation overlying the deltoid muscle should be tested. The second most commonly injured nerve is the suprascapular nerve, which innervates the supraspinatus and infraspinatus.[53] Range of motion may be limited, but assessment of shoulder abduction should be performed. Vascular injuries may occur with even trivial trauma in atherosclerotic elderly patients. The most common vascular injury is to the axillary artery and may be suggested by weak distal pulses compared to the uninjured side, paresthesias, pallor, pulselessness, or an expanding hematoma. Neurovascular injuries can occur in nondisplaced and displaced fractures but are much higher (>50%) in displaced fractures.

Radiographs consisting of anteroposterior, lateral shoulder, and axillary views will diagnose most proximal humerus fractures and evaluate for accompanying glenohumeral dislocation.

SPECIFIC PROXIMAL HUMERUS INJURIES

The most common fractures of the proximal humerus include the surgical neck and greater tuberosity. To guide treatment, the **Neer system** classifies fracture displacement into "parts." The proximal humerus is divided into four segments based on epiphyseal lines where fractures primarily occur: the articular surface of the humeral head; the greater tuberosity; the lesser tuberosity; and the shaft of the humerus (**Figure 271-22**). The

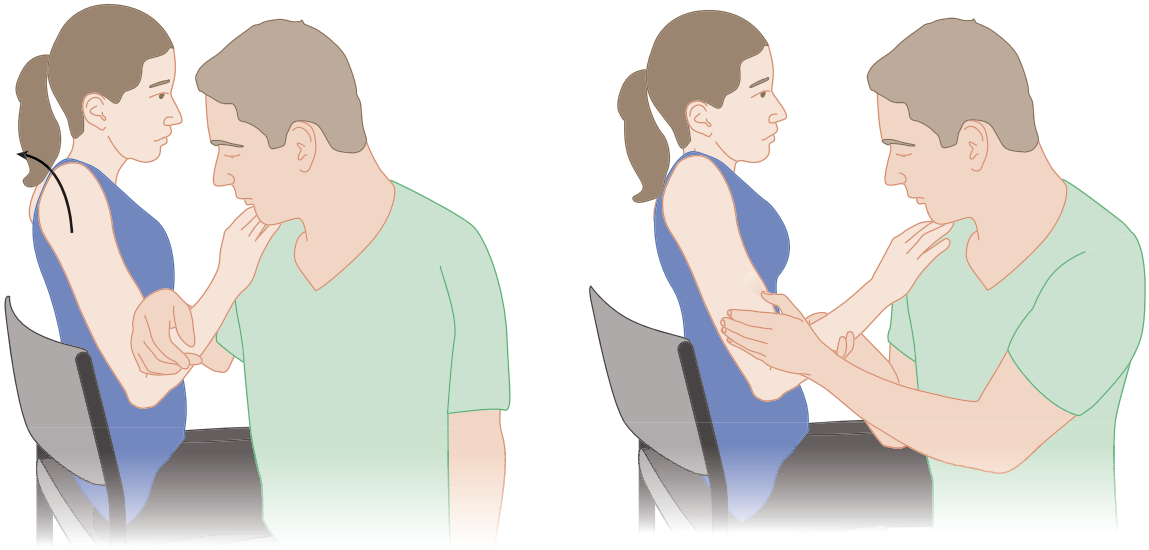


FIGURE 271-15. Cunningham technique.

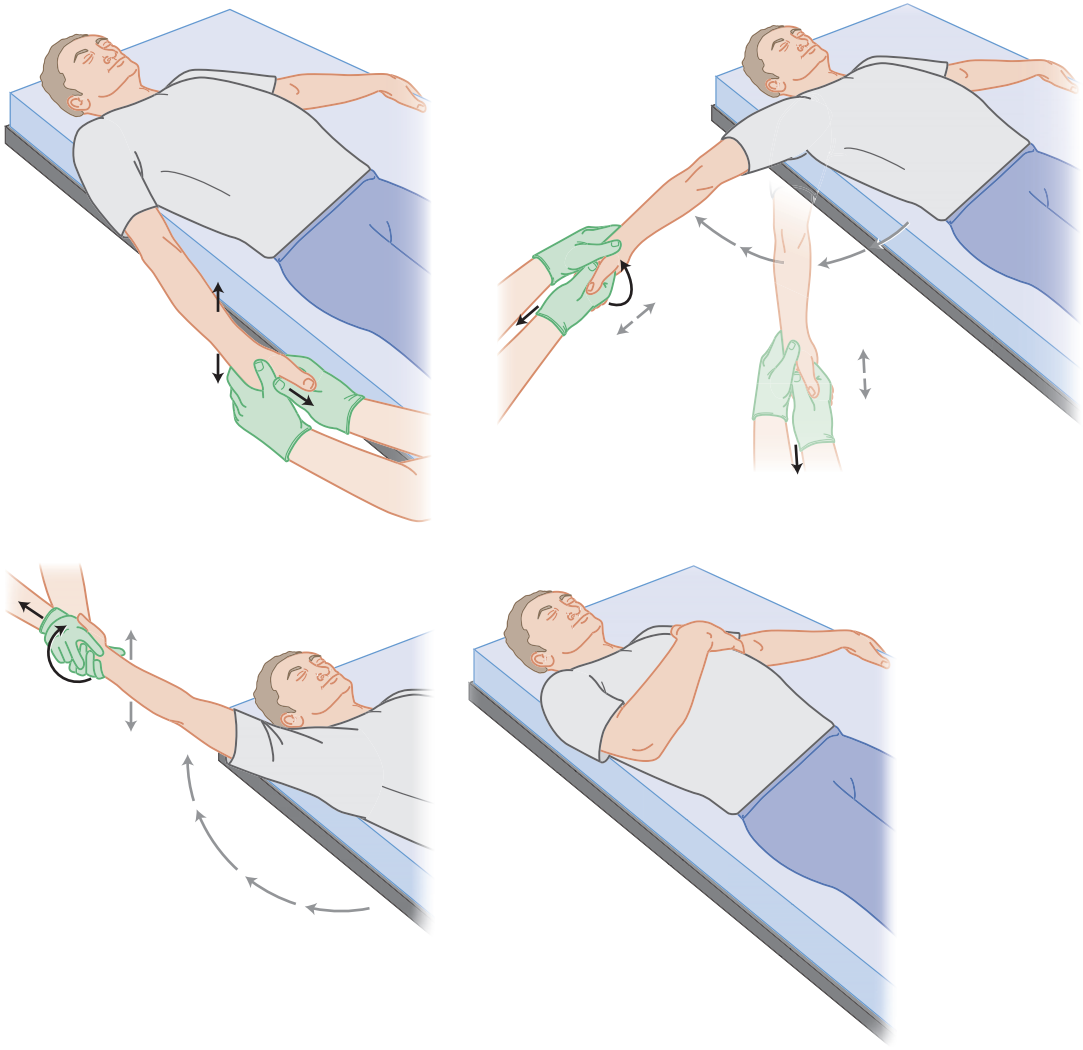


FIGURE 271-16. FARES (FAst, REliable, and Safe) technique.

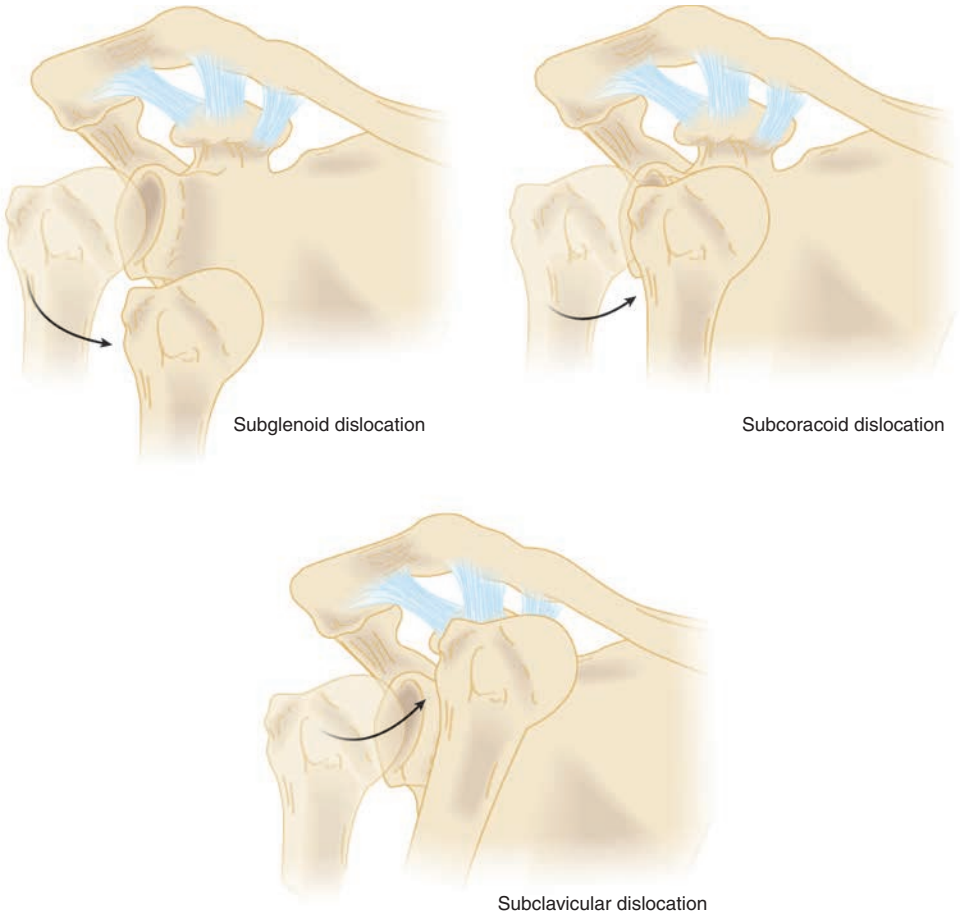


FIGURE 271-17. Posterior shoulder dislocations.

displacement of a fracture fragment from the proximal humerus is called a "part." Parts are therefore not based on the number of fracture lines or segments. Rather, a "one-part" fracture is one in which the fragment is not displaced at all, is displaced <1 cm, or is not angulated >45 degrees. There can be multiple fragments, but if none of the fragments is displaced >1 cm or is angulated >45 degrees, the proximal humerus fracture is termed a "one-part" fracture. Approximately 50% of all proximal humerus fractures are one-part fractures.[54,55] Treatment of a one-part proximal humerus fracture generally consists of immobilization (such as sling and swathe),



FIGURE 271-18. Scapular Y view of posterior dislocation, with the humeral head posterior. [Photo used with permission of Alexander Ebinger, MD.]

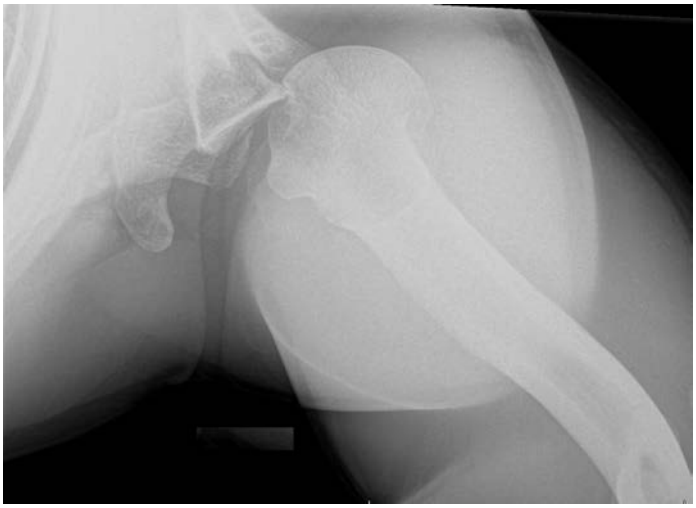


FIGURE 271-19. Axillary view of posterior dislocation. [Photo used with permission of Alexander Ebinger, MD.]

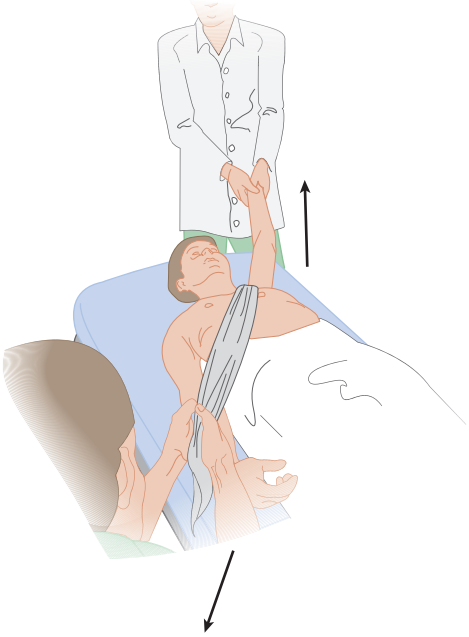


FIGURE 271-20. Reduction of luxatio erecta.

ice, analgesics, and orthopedic referral. Early mobilization is important to avoid subsequent adhesive capsulitis and can be started when pain allows. The prognosis is generally good. All other proximal humerus fractures and fracture-dislocations require orthopedic consultation in the ED because they are more frequently associated with complications and are often difficult to manage. Closed reduction, operative treatment, or a combination of the two may be necessary.[56-58]

Any fracture involving the anatomic neck or the articular surface may result in compromise of the blood supply to the articular segment of the humeral head. If ischemic necrosis of the articular segment occurs, insertion of a humeral head prosthesis may be required. Significantly angulated surgical neck fractures are a risk for neurovascular damage (axillary neurovascular structures as well as the brachial plexus) and should be immobilized and radiographed in the position of presentation.

Significant displacement of a greater tuberosity fracture implies a concomitant rotator cuff tear, with surgical repair often necessary for the active patient. Fracture of the lesser tuberosity should alert the examiner to a potential posterior shoulder dislocation.

Pediatric humerus fractures are discussed in Chapter 141, "Pediatric Orthopedic Emergencies."

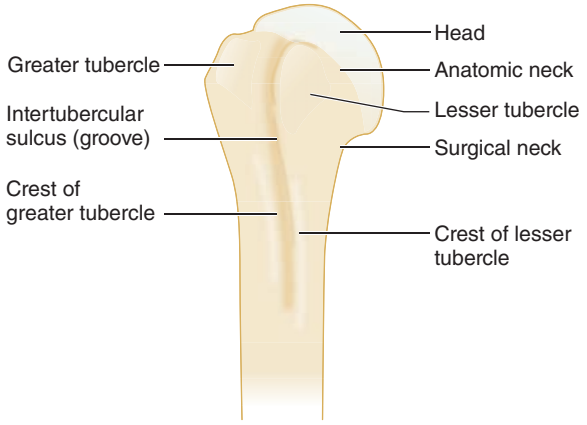


FIGURE 271-21. Proximal humerus. [Reproduced with permission from Pansky B: *Review of Gross Anatomy*, 6th ed. New York: McGraw Hill, 1995.]

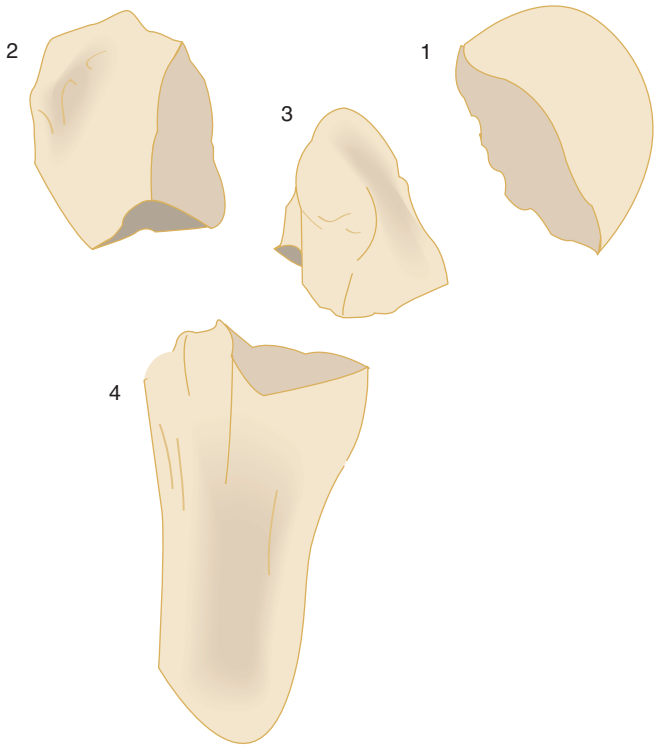


FIGURE 271-22. The four segments of the humerus according to the Neer classification: 1, articular surface of the humeral head; 2, greater tubercle; 3, lesser tubercle; 4, diaphysis or shaft of humerus. A one-part fracture is defined as a fracture fragment displaced by <1 cm or <45 degrees; two-, three-, and four-part fractures have more displacement and angulation.

HUMERAL SHAFT FRACTURES

ANATOMY

The humerus serves as the attachment site for the rotator cuff muscles, deltoid, pectoralis major, and coracobrachialis. Additionally, it is the site of origin of the biceps, triceps, and brachioradialis. The radial nerve courses along the spiral groove on the posterior aspect of the humerus.

Fractures of the humeral shaft occur in a bimodal age distribution, with peaks in the third and seventh decades of life, representing active young men and osteoporotic elderly women, respectively. Humeral shaft fractures may be caused by a direct blow that produces a bending force resulting in a transverse fracture. They may also be caused by an indirect mechanism, such as a fall on an outstretched hand that produces a torsion force, resulting in a spiral fracture. A combination of bending and torsion forces results in an oblique fracture, sometimes with comminution, producing the "butterfly" fragment. The humerus is also a common site of pathologic fractures, especially from metastatic breast cancer. Fractures in young children should raise suspicion of abuse.[59]

CLINICAL FEATURES AND DIAGNOSIS

Clinical examination reveals localized tenderness, swelling, pain, and abnormal mobility or crepitus on palpation. Displaced fractures are associated with shortening of the upper extremity. Attention must be given to the initial neurovascular status. Complications may include injury to the brachial artery and vein, or the radial, ulnar, or median nerves. A radial nerve injury, which is the most common, may be manifested by weak wrist extension, wrist drop, or altered sensation at the dorsal thumb index web space. Fractures of the distal third are particularly prone to entrapment of the radial nerve, either as a result of the initial injury or after closed reduction. Neurovascular injuries require emergency orthopedic consultation.[60]

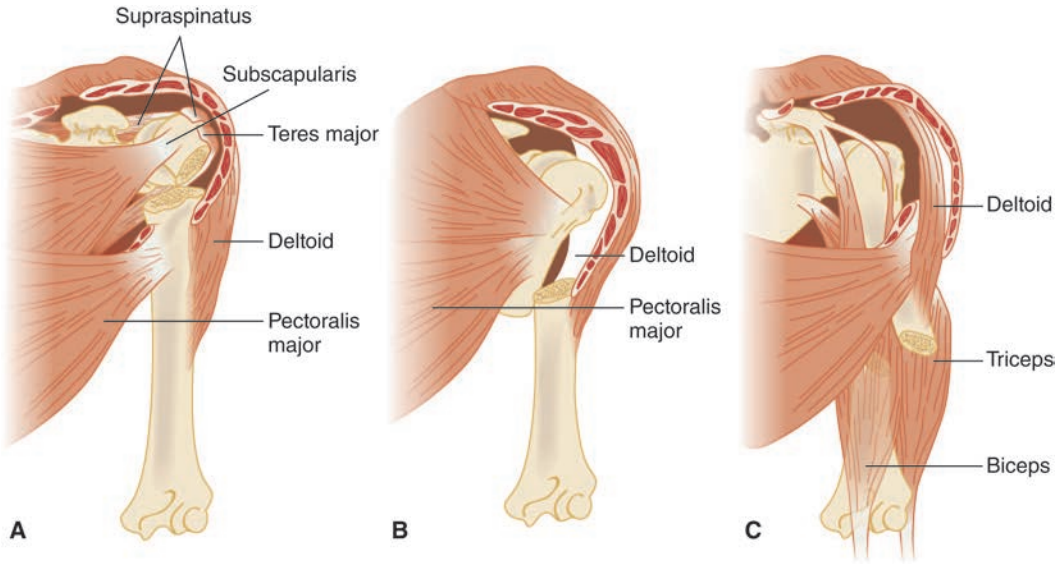


FIGURE 271-23. Humeral fractures anterior view. The actions of the muscles inserting on the humeral shaft determine fracture angulation and displacement. **A.** Angulation of fragments with fracture line distal to rotator cuff insertion. **B.** Angulation of fragments with fracture line distal to pectoralis major insertion. **C.** Angulation of fragments with fracture line distal to deltoid insertion.

Radiographs should include two views of the humerus. Images of the shoulder and elbow should be obtained if additional injuries cannot be excluded.

FRACTURES OF THE MIDDLE THIRD OF THE HUMERUS

The most common site of fracture is the middle third of the humerus. Displacement of fracture fragments is the result of the insertions and actions of the various muscles (deltoid, biceps, triceps, supraspinatus, and pectoralis major) that act on the upper arm (**Figure 271-23**). Most closed fractures of the shaft of the humerus are managed nonoperatively, although treatment options vary and there has been an increase in operative fixation.[61,62] A 2012 Cochrane Review did not find any evidence to suggest outcome differences from surgical versus nonsurgical management.[63] Fractures with less than 20 degrees of angulation in the sagittal plane and less than 30 degrees of varus or valgus angulation and that are shortened less than 2 to 3 cm often can be managed nonoperatively.[64] The treatment of uncomplicated fractures includes immobilization, ice, analgesia, and referral. Closed treatment options include the coaptation splint (sugar-tong), hanging cast, and functional bracing. A simple sling and swathe are adequate for the emergency management of most such patients.

DISTAL HUMERUS FRACTURES

Distal humerus fractures require emergency orthopedic consultation. These fractures are complex given the anatomical relationship of the bony and neurovascular structures. Clinical examination should include evaluation of the radial, median, ulnar, and anterior and posterior interosseous nerves. See Chapter 270, "Elbow and Forearm Injuries," for a discussion of supracondylar fractures.

BRACHIAL PLEXUS INJURIES

ANATOMY

The brachial plexus (**Figure 271-24**) and its peripheral nerve branches are infraclavicular and lay anteromedial to the glenohumeral joint. Anatomically, the brachial plexus stems from the C4-T1 cervical roots and ultimately from the lateral, posterior, and medial cords. At the lateral border of the pectoralis minor, these cords ultimately form the five major peripheral nerves of the arm (musculocutaneous nerve, axillary nerve, radial nerve, median nerve, and ulnar nerve).[65] Traumatic brachial plexus lesions are the most common form of plexus injuries and can occur from penetrating, compression, or closed traction injuries. Injuries can be divided into supraclavicular (roots and trunks) or infraclavicular (cords and terminal nerves) injuries.

CLINICAL FEATURES AND DIAGNOSIS

High-speed motor vehicle or motorcycle crashes result in traction injuries as nerves are stretched longitudinally, with simultaneous traction of the arm and opposite distraction of the head.[65,66] Penetrating trauma and surgical interventions can also lead to a disruption of the nerves. The initial identification of brachial plexus injuries is often overshadowed by the presence of other severe injuries to, for example, the head, chest, and vasculature. In addition to neurologic impairment, neuropathic pain in the arm is frequently present. Significant swelling and soft tissue injury to the neck and shoulder girdle suggest traumatic forces sufficient to injure the brachial plexus. The accumulation of cerebrospinal fluid from avulsed spinal roots may cause swelling in the posterior triangle. Horner's syndrome (ipsilateral ptosis, miosis, and anhidrosis of the face) may be present due to adjacent ganglion damage. However, brachial plexus injury may not be clinically apparent until a responsive patient can indicate the extent of motor and sensory deficits, days to weeks after initial stabilization and treatment. Arm pain that is constant and burning in character is common. The pain is usually worst in the distal parts of the arm and hand, typically in a nondermatomal distribution.

Upper limb and shoulder girdle motor and sensory deficits define the extent of damage to the brachial plexus. Adduction and internal rotation of the shoulder indicate weakness of the deltoid and infraspinatus muscles (C5), whereas elbow extension is due to weakness of the biceps (C6), and flexion of the digits and wrists is due to weakness of the extensors (C7). The sensory distributions of the cervical roots and the peripheral nerves are shown in **Figure 271-25**.

MRI and CT myelography are common radiographic imaging procedures. Electromyographic and nerve conduction velocity studies may aid in diagnosis, and surgical exploration of the area may be necessary. The delineation of pre- and postganglionic injury may not be possible until Wallerian degeneration is completed 2 weeks after injury. Treatment and prognosis will depend on the location and extent of nerve damage.

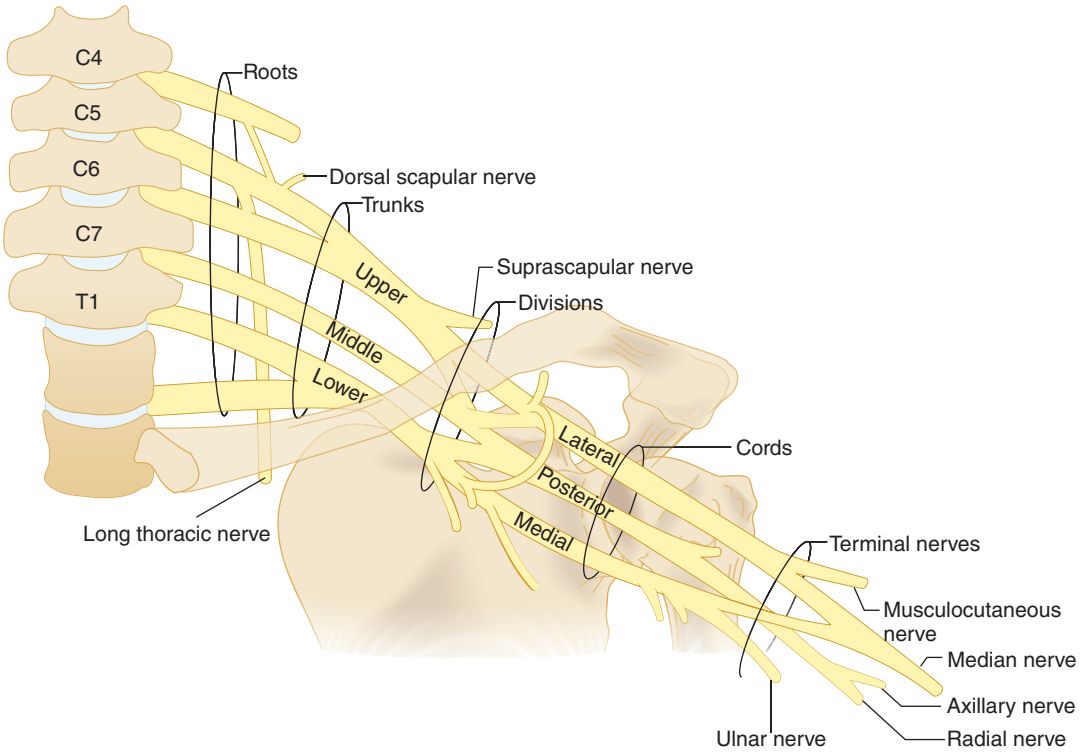


FIGURE 271-24. Brachial plexus.

COMPLICATIONS OF TOTAL SHOULDER ARTHROPLASTY

Total shoulder arthroplasty is an increasingly common method of surgical management of glenohumeral arthritis and degenerative shoulder conditions. Overall, surgical outcomes are excellent. Similar to many surgical conditions, complications may arise after this procedure. Prosthetic loosening, infection, periprosthetic fracture, glenohumeral instability, and soft tissue dysfunction are the most commonly encountered postoperative complications.

Perform a thorough neurovascular exam of the affected extremity. Neurologic injuries occur in 1% to 4.3% of shoulder arthroplasty cases, with the axillary nerve most commonly affected.[67] There are also reports of injury to the brachial plexus and radial nerve.

Obtain radiographs in patients with shoulder pain in the setting of shoulder arthroplasty. Radiographs can be useful for detecting periprosthetic fractures as well as prosthetic dislocation. Infection is the most concerning of the possible complications, although the incidence of infection is only between 0% and 4%.[67] The diagnosis of infection can be challenging. Most infections develop in patients with underlying immunocompromise, including diabetes, rheumatoid arthritis,

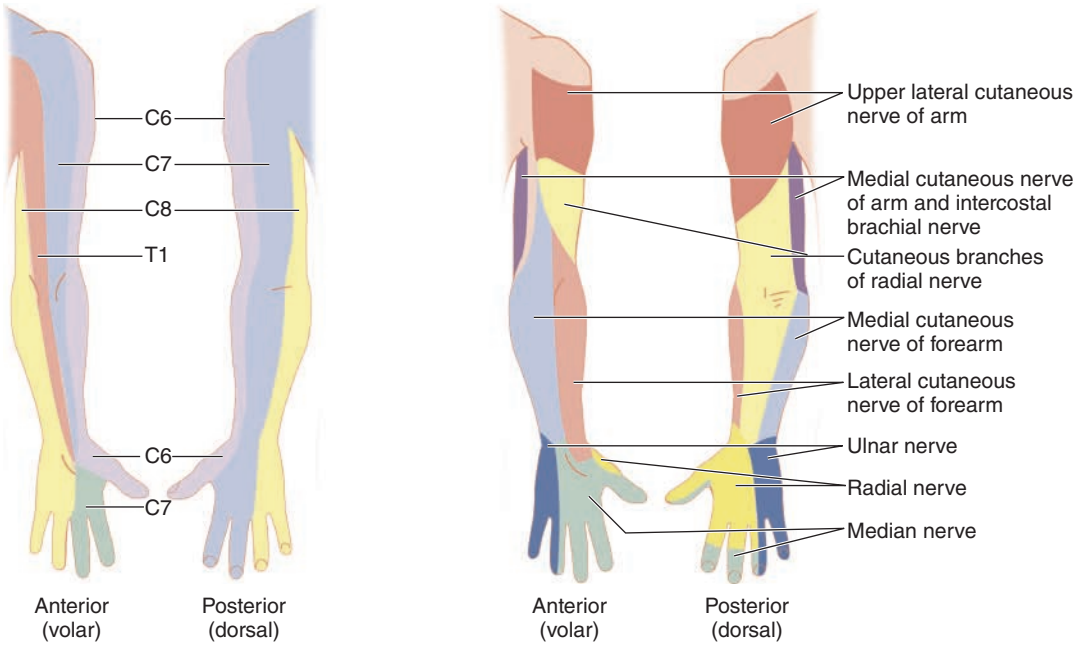


FIGURE 271-25. Sensory distribution of the brachial plexus.

lupus, and other prior joint infections.[67,68] Postoperative infections can be acute (0 to 3 months), subacute (3 months to 1 year), or late (after 1 year). One study of 2512 patients reported that of the 26 infected replacements, the mean time to infection development was 3.5 years.[69] The typical presentation of infection is nonspecific shoulder pain. The workup for infection includes blood work including WBC count, erythrocyte sedimentation rate, and C-reactive protein. Unfortunately, one cannot completely rely on the laboratory markers to be elevated. In one study, the average WBC count of infected shoulders was 11.98/mm^3, with an erythrocyte sedimentation rate of 75 mm/h.[68] Other studies have shown an average WBC of 7.4/mm^3, erythrocyte sedimentation rate of 47 mm/h, and C-reactive protein elevation in only 25% of infected cases.[69,70]

Fractures, dislocations, neurovascular compromise, joint instability, and suspected infection require orthopedic consultation in the ED.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

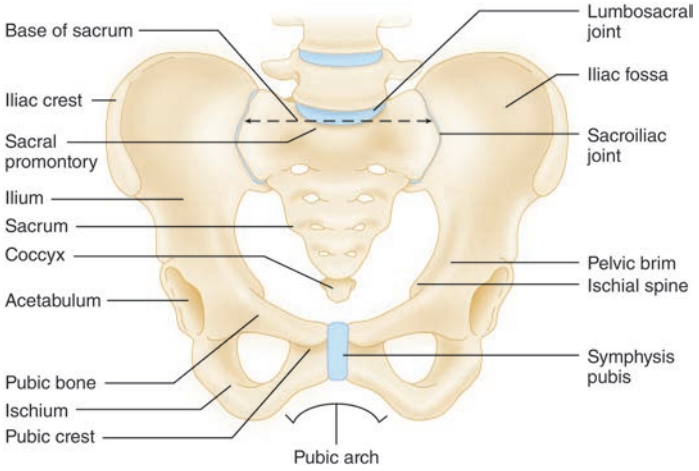


FIGURE 272-1. Bones and joints of the pelvis.

CHAPTER 272

Pelvis Injuries

Ciara J. Barclay-Buchanan
Melissa A. Barton

EPIDEMIOLOGY

Pelvic fractures are most commonly the result of a motor vehicle or motorcycle collision, automobile versus pedestrian collision, fall from a significant height, or a crush injury. Isolated pubic rami fractures can occur in the elderly following a low-energy mechanism of injury, such as falling off of a chair, due to underlying fragility and osteopenia.[1] The in-hospital mortality rate from all pelvic fractures is approximately 8% and approaches 20% with complex pelvic fractures.[2] Higher mortality rates are found in older patients, men, African Americans, and those living in the northeastern United States.[2] The mortality rate is 30% in patients who present in shock.[3] Pelvic ring fractures have been found to be an independent risk factor for death.[4]

ANATOMY AND BIOMECHANICS

The major functions of the bony pelvis are protection of the visceral organs, mechanical support, and hematopoiesis. The bony pelvis consists of the sacrum, coccyx, and bilateral innominate bones: the ischium, ilium, and pubis. Collectively, they provide pelvic stability that is further supported by the strong posterior sacroiliac, sacrotuberous, and sacrospinous ligaments (**Figures 272-1** and **272-2**). A small amount of pelvic stability is also provided by the pubic symphysis.

Five joints that allow some movement of the bony ring are incorporated into the pelvic structure. The lumbosacral, sacroiliac, and sacrococcygeal joints, as well as the symphysis pubis, allow limited movement. The acetabulum, a ball-and-socket joint, is divided into three portions: (1) the iliac portion, or superior dome, is the chief weight-bearing surface; (2) the inner wall, which consists of the pubis, is thin and easily fractured; and (3) the posterior acetabulum, which is derived from the thick ischium. **Generally, a single break in the ring results in a stable injury without significant risk of displacement, and two breaks in the ring result in an unstable injury.**

The pelvis is extremely vascular. The iliac artery and venous trunks pass near the sacroiliac joints bilaterally. The nerve supply through the pelvis is derived from the lumbar and sacral plexuses. Injury to the pelvis may produce deficits at any level from the nerve root to small peripheral branches (**Figure 272-3**). The lower urinary tract is contained in the pelvis (**Figure 272-4**). In the adult, the bladder lies behind the symphysis and pubic bones, and the peritoneum covers the dome and base posteriorly. The location of the bladder and the degree of peritoneal reflection are determined by urine volume. Portions of the lower GI tract are housed in the pelvis including a portion of the descending colon, as well as the sigmoid colon, rectum, and anus. In women, the uterus and vagina are also located within the bony pelvis. The location of these organs places them at risk following a traumatic pelvic injury.

CLINICAL FEATURES

HISTORY

Determining the mechanism of injury is important when assessing a trauma patient. Consider the possibility of a pelvic fracture in every patient with serious blunt trauma (e.g., fall from a height, pedestrian struck by a motor vehicle, crush injury, ejection from a vehicle, motorcycle or all-terrain vehicle collision). Ask the patient about location of pain, last urination or defecation, present bladder sensation, and last solid and fluid intake. In addition, determine the time of the last menses or the presence of pregnancy. Obtain a brief past medical history, current medications, and allergies.

PHYSICAL EXAMINATION

In patients who are awake and alert, a careful physical examination is sensitive (93% in one study) for the diagnosis of a pelvic fracture.[5] Signs and symptoms of bony pelvic injury vary from localized pain and tenderness and inability to bear weight to pelvic instability and severe shock. Unexplained hypotension may be the only sign of a major pelvic disruption.

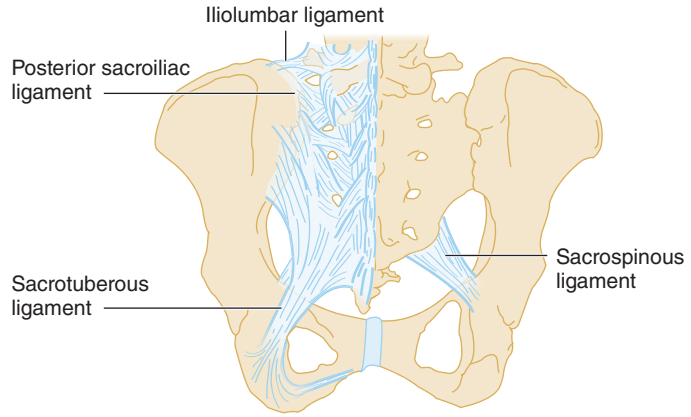


FIGURE 272-2. Pelvic ligaments.

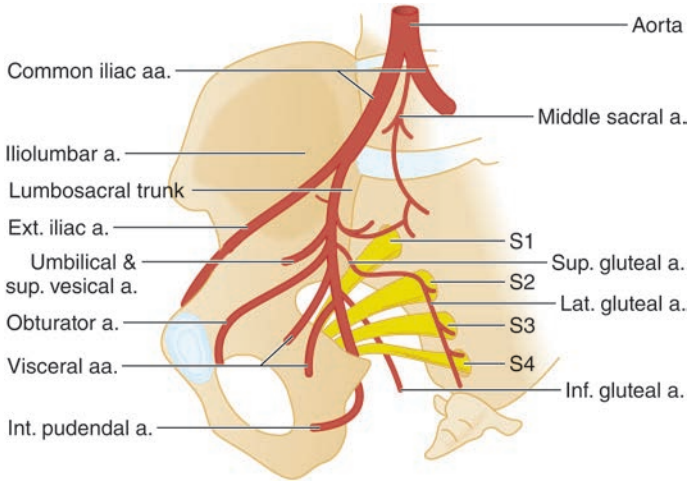


FIGURE 272-3. Arterial and nerve supply of the pelvis. a. = artery; aa. = arteries; Ext. = exterior; Inf. = inferior; Int. = interior; Lat. = lateral; Sup. = superior. [Reproduced with permission from Pansky B: *Review of Gross Anatomy*, 6th ed. Copyright © 1995, McGraw-Hill, New York.]

Serious Injury For a patient with a serious or high-energy mechanism of injury, examine for abdominal tenderness, perineal and pelvic ecchymoses, lacerations, and deformities. Scrotal hematoma (Destot's sign) indicates a pelvic fracture. Leg length discrepancy or rotational deformity of the lower extremity without an obvious femur fracture or dislocation suggests a pelvic fracture. Evidence of blood at the urethral meatus suggests a urethral injury.

Perform a **FAST** examination as an adjunct to the physical examination during the primary trauma survey in any unstable patient or when the mechanism of injury could suggest a pelvic fracture. Fluid in the peritoneum can suggest solid organ injury, but fluid in the pelvis can also lead the clinician to suspect a pelvic fracture prior to radiographic confirmation.

Assess for pelvic instability on every trauma patient, which could include visual inspection in patients with obvious pelvic fractures, pelvic rim compression, or radiologic survey. Gentle downward and medial manual compression of the pelvis over the iliac wings should be performed only **once** during the trauma survey. Repeated manipulation of the pelvic ring on a patient with a suspected pelvic fracture can increase the severity of injury, resulting in greater blood loss. **Do not perform compressive pelvic maneuvers in a patient with shock or an obvious pelvic fracture. Movement of an unstable fracture can worsen the injury and lead to further blood loss.**

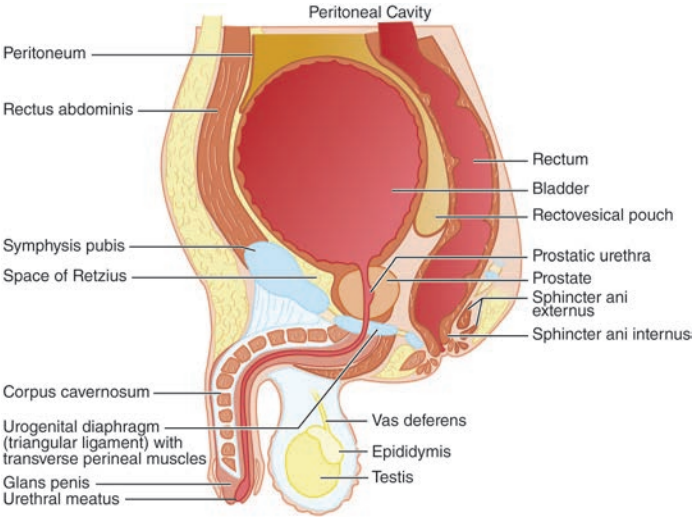


FIGURE 272-4. Sagittal section of the male pelvis showing the relationships of the full bladder.

Rectal examination may detect superior or posterior displacement of the prostate, rectal injury, an abnormal bony prominence, large hematoma, or tenderness along the suspected fracture line. Proctoscopic or bimanual pelvic examinations may be required to assess for mucosal tears indicating an open fracture. Such injuries increase the risk of infection at the fracture site and resultant sepsis.[6] Decreased anal sphincter tone may suggest neurologic injury. Carefully evaluate lower extremity pulses and sensation. Assume an associated intra-abdominal, retroperitoneal, gynecologic, and urologic injury until proven otherwise.

Stable Patient and Low Mechanism of Injury In stable patients or those with a low-energy mechanism of injury (e.g., an elderly patient who falls from a seated position), examine the entire spine and the abdomen. Palpate for tenderness along the pelvic bony structures, including the iliac crests, pubic rami, sacrum, and coccyx. Compress the pelvis, lateral to medial, through the iliac crests, as well as through the greater trochanters. In addition, compress the pelvic ring from anterior to posterior through the symphysis pubis and iliac crests. Evaluate lower extremity pulses, motor function, and sensation.

IMAGING

The initial stabilization of the patient takes priority over imaging. If not already done, perform a FAST exam to identify intraperitoneal bleeding.

If there is no tenderness to palpation in an otherwise stable, alert patient, a standard anteroposterior pelvis radiograph is not indicated. In patients with a suspected hip fracture, a standard anteroposterior pelvic radiograph is often used to evaluate for bony injury. However, routine pelvic radiographs are not needed in **stable** patients who will otherwise undergo an emergent CT scan of the abdomen and pelvis unless there is suspicion for a hip fracture or dislocation.[7-12]

Indications for an anteroposterior pelvis radiograph include hemodynamic instability, pelvic tenderness, or other physical examination findings that are concerning for pelvic fracture, hip fracture, or hip dislocation. With an **unstable** blunt trauma patient, a pelvic radiograph should be obtained for early identification, stabilization, and rapid mobilization of resources for emergent angiography.

CT is the gold standard for evaluating bony and ligamentous pelvic injury. **CT is more sensitive than plain radiographs for the detection of pelvic fracture. Compared with CT, pelvic radiographs have a sensitivity of ≤85% for identifying pelvic fractures in blunt trauma patients.**[1] CT is also superior to radiography in evaluating pelvic ring instability.[9-11,13] Therefore, a CT scan should be ordered when a pelvic fracture is suspected despite negative pelvic radiographs. Additionally, if a pelvic fracture is identified on plain films, a CT should be ordered to evaluate for additional fractures or instability. Contrast-enhanced CT can assess for associated ligamentous injury, contrast extravasation, pelvic hematoma, and retroperitoneal bleeding. Contrast extravasation on CT scan is 80% to 90% sensitive for the identification of arterial bleeding.[14]

The approach to pelvic imaging varies at the extremes of age. Up to half of elderly patients with a low-energy mechanism and pubic ramus fracture may have an associated posterior pelvic ring disruption demonstrated on CT scan.[15] Sacral fractures are often missed on plain radiographs due to degenerative bony changes (i.e., osteoporosis) and overlying bowel gas.[16] This often overlooked finding may contribute to the fact that one third of elderly patients with isolated rami fractures do not return to their previous independent living or fail conservative treatment for pain management.[15] Pain on sacral palpation is suggestive of a posterior ring disruption and indicates the need for a CT scan. Most children with a low-energy mechanism and normal examination do not usually require imaging because pelvic fractures are rare in the pediatric population. Avulsion-type iliac wing fractures from sports injuries are reportedly the most common pelvic injuries in children.[17] Clinical scenarios associated with pelvic fracture in children include a high-risk mechanism (e.g., motor vehicle collision with ejection or rollover; automobile versus pedestrian or bicycle) combined with either a Glasgow Coma Scale score <14 or pelvic tenderness, and also medically complex children, such as those with preexisting bone disease or developmental delay.[17,18]

PELVIC FRACTURE PATTERNS

Pelvic fractures include breaks in the pelvic ring, fractures of a single bone without a break in the pelvic ring, and acetabular fractures.

The most clinically useful classification, the Young-Burgess Pelvis Fracture Classification System, is presented in a simplified version in **Table 272-1**. This system differentiates fracture patterns based on mechanism of injury and direction of causative force. The incidence of complications (e.g., urogenital and vascular) is correlated with the fracture pattern, making identification of the type more clinically significant and useful.

There are three main types of pelvic fracture patterns: lateral compression, anterior-posterior compression (open-book), and vertical shear. The different injury types may be suggested by history, but may often be differentiated radiographically. The pattern of a pubic rami fracture is a clue to the mechanism and direction of force. In general, horizontal fractures suggest lateral compression injury, whereas vertical fractures suggest a vertical shear force. Open-book fractures point to an anteroposterior injury. Based on the recognition of the fracture pattern, one can then predict the likelihood of severe hemorrhage or urogenital injury (see Table 272-1).

LATERAL COMPRESSION FRACTURE

Lateral compression fractures are the most common, accounting for 60% to 70% of pelvic fractures with an overall mortality rate of 8%.[19] Motor vehicle collisions, in which a car is broadsided or a pedestrian is struck from the side, are possible mechanisms that could result in a lateral compression fracture. At a minimum, a pubic ramus will be fractured. If the pelvis is further compressed, the sacroiliac joint is crushed, leading to disruption of the posterior ligaments, fracture of the sacrum, and rotation of the contralateral hemipelvis (**Figure 272-5**).

ANTERIOR-POSTERIOR COMPRESSION OR OPEN-BOOK FRACTURE

Anterior-posterior compression injuries, or open-book fractures, account for about 25% of severe injuries. A head-on motor vehicle crash is the classic example. The force is delivered in an anteroposterior direction (arrow in **Figure 272-6**), "opening" the pelvis, splaying the pubic symphysis, and rupturing the sacral ligaments. Finally, total disruption of the sacroiliac joint will occur because of the wide "opening" of the pelvis. All supporting ligament groups, including the posterior sacroiliac ligaments, can be disrupted.

VERTICAL SHEAR FRACTURE

The least common are **vertical shear fractures,** which typically result from a fall or jump from a height, and account for approximately 5% of pelvic fractures. With this injury, the force vector is delivered in a vertical plane (**Figure 272-7**). Fractures of the pubic rami are usually seen anteriorly, whereas fractures of the sacrum, sacroiliac joint, or iliac wing are usually seen posteriorly. Any of the pelvic ligaments may be disrupted.

Combinations of injury patterns make up the other 20% to 25% of injuries.

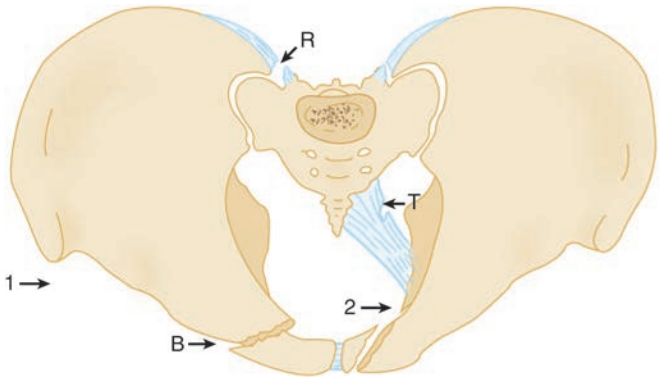


FIGURE 272-5. Lateral compression fracture (*arrows 1 and 2*) with rupture of posterior sacroiliac ligaments (R), sacrospinous/sacrotuberous complex (T), and rupture of pubic ramus (B).

AVULSION AND SINGLE-BONE PELVIC FRACTURES

Isolated, closed avulsion fractures and single-bone, closed pelvic fractures are more common than pelvic ring disruption. It is important to know which of these fractures require further diagnostic testing, orthopedic consultation, or admission.

Isolated fractures of the anterior superior iliac spine, anterior inferior iliac spine, ischial tuberosity, pubic ramus, body of the ischium, iliac wing, sacrum, or coccyx typically do not disrupt the pelvic ring and, as a result, typically do not require surgical repair (**Figure 272-8** and **Table 272-2**). Most of these fractures require only analgesia, crutches, bed rest or non–weight-bearing status, and orthopedic follow-up on an outpatient basis.

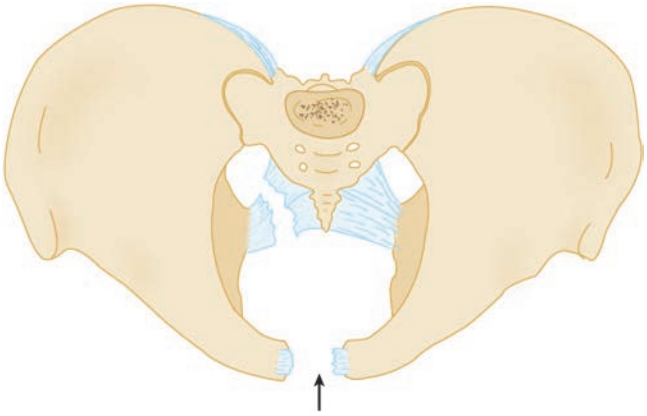


FIGURE 272-6. Open-book fracture, with opening of the anterior pelvis (*arrow*) and rupture of the sacral ligaments.

TABLE 272-1 Abbreviated Young-Burgess Pelvis Fracture Classification System and Potential Incidence of Complications

Category	Characteristics	Severe Hemorrhage (%)	Bladder Rupture (%)	Urethral Injury (%)
Lateral compression (LC)	Transverse pubic rami fracture ipsilateral or contralateral to posterior injury	60	20	20
Anterior-posterior (AP) ("open-book")	Symphyseal diastasis or longitudinal rami fractures			
	Injury to *secondary structures varies based on severity of AP pelvic fracture*			
	Minimal widening of sacroiliac (SI) joint with intact posterior ligaments	1	8	12
	Complete SI joint widening with disruption of posterior ligaments	53	14	36
Vertical shear (VS)	Separation of symphysis or SI joint with vertical displacement anteriorly or posteriorly, occasionally through iliac wing or sacrum	75	15	25
Mixed patterns	Combination of other injury patterns LC and VS patterns are most common	58	16	21

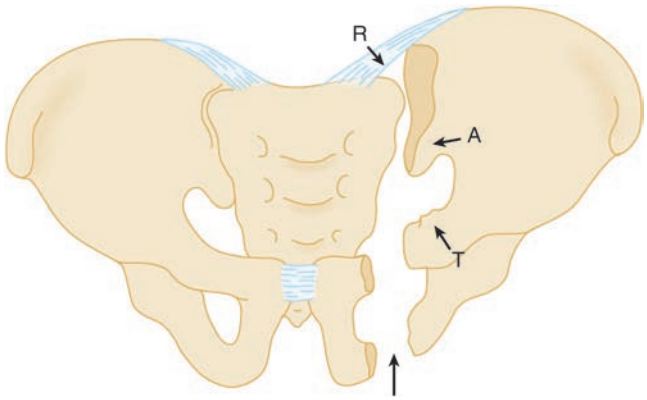


FIGURE 272-7. Vertical shear fracture. Injury vector is delivered in a vertical plane (*arrow*). There is injury to the posterior (R) and anterior (A) sacroiliac ligaments and sacrospinous/sacrotuberous (T) ligaments.

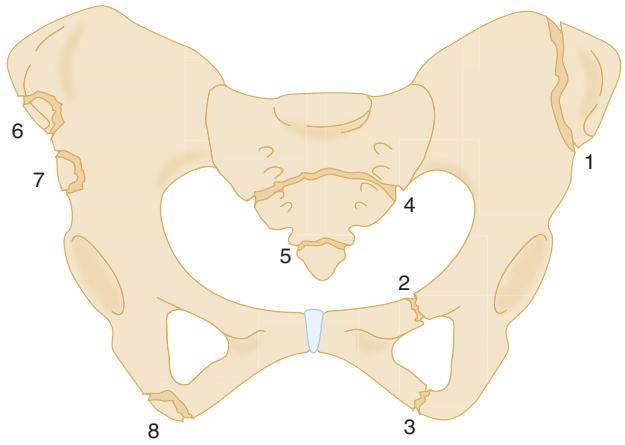


FIGURE 272-8. Avulsion fractures of the pelvis. (1) Iliac wing fracture (Duverney fracture). (2) Superior pubic ramus fracture. (3) Inferior pubic ramus fracture. (4) Transverse sacral fracture. (5) Coccyx fracture. (6) Anterior superior iliac spine avulsion. (7) Anterior inferior iliac spine avulsion. (8) Ischial tuberosity avulsion.

Simple fractures in the elderly may not be as benign as at first glance. If indicated by physical exam or mechanism of injury, obtain a CT scan of the pelvis with bone windows to detect occult posterior pelvic ring disruption that will alter management (**Figures 272-9** and **272-10**).[15] Although isolated pelvic ramus fractures are frequently due to low-impact trauma (e.g., fall from standing) in the elderly, isolated pelvic fractures still result in increased rates of hospital admission, morbidity, need for living assistance after hospital discharge, and overall mortality at 1 year.[20]

Pay special attention to isolated fractures of either the sacrum or iliac wing due to the tremendous amount of force required to produce this type of fracture. If there is concern for associated injuries, a more extensive evaluation is mandated with admission for observation.

ACETABULAR FRACTURES

Acetabular fractures are usually secondary to motor vehicle collisions. The fracture force is either transmitted laterally through the hip or posteriorly through the femur as with a knee-versus-dashboard mechanism. Acetabular fractures are commonly associated with other injuries, including pelvic, femur, hip, and knee injuries (**Figure 272-11A**). However, these fractures may be subtle and, as a result, necessitate careful inspection via radiography (**Figure 272-11B**). If an acetabular fracture is suspected, it can be evaluated with an anteroposterior film,

TABLE 272-2 Avulsion and Single Bone Fractures

Fracture	Description/Mechanism of Injury	Clinical Findings/ Associated Injuries	Treatment	Disposition and Follow-Up
Iliac wing (Duverney) fracture	Direct trauma, usually lateral to medial	Swelling, tenderness over iliac wing; abdominal pain; ileus; acetabular fractures Serious injury infrequent	Analgesics, non–weight bearing until hip abductors pain-free, usually nonoperative	Discharge with orthopedic follow-up in 1–2 wk Admit for open fracture or concerning abdominal examination
Single pubic rami or ischium fracture	Fall or direct trauma in elderly; exercise-induced stress fracture in young adult; or in pregnant women	Local pain and tenderness; may have inability to ambulate	Analgesics, crutches, weight bearing as tolerated	Discharge with PCP or orthopedic follow-up in 1–2 wk Admit for intractable pain or mobility concerns (elderly)
Ischium body fracture	External trauma or fall in sitting position Least common pelvic fracture	Local pain and tenderness; pain with hamstring movement	Analgesics, bed rest, donut-ring cushion, crutches	Discharge with orthopedic follow-up in 1–2 wk
Sacral fracture	Transverse: direct anteroposterior trauma Upper transverse: fall in flexed position	Pain on rectal examination; vertical fractures may transect the pelvic ring; sacral root injury with upper transverse fractures	Analgesics, bed rest, surgery may be needed for displaced fractures or neurologic injury	Discharge with orthopedic follow-up in 1–2 wk Orthopedic consultation for displaced fracture or neurologic deficit
Coccyx fracture	Fall in sitting position More common in women	Pain, tenderness over coccyx region; pain on compression during rectal examination	Analgesics, bed rest, stool softeners, sitz baths, donut-ring cushion; surgical excision of fracture fragment if chronic pain	Discharge with PCP or orthopedic follow-up in 2–3 wk
Anterior-superior iliac spine fracture	Forceful sartorius muscle contraction (e.g., adolescent sprinter)	Pain with hip flexion and abduction	Analgesics, bed rest for 3–4 wk with hip flexed and abducted, crutches	Discharge with orthopedic follow-up in 1–2 wk
Anterior-inferior iliac spine fracture	Forceful rectus femoris muscle contraction (e.g., adolescent soccer player)	Pain in groin; pain with hip flexion	Analgesics, bed rest for 3–4 wk with hip flexed, crutches	Discharge with orthopedic follow-up in 1–2 wk
Ischial tuberosity fracture	Forceful contraction of hamstrings	Pain with sitting or flexing the thigh	Analgesics, bed rest for 3–4 wk in extension, external rotation, crutches	Discharge with orthopedic follow-up in 1–2 wk

Abbreviation: PCP = primary care physician.

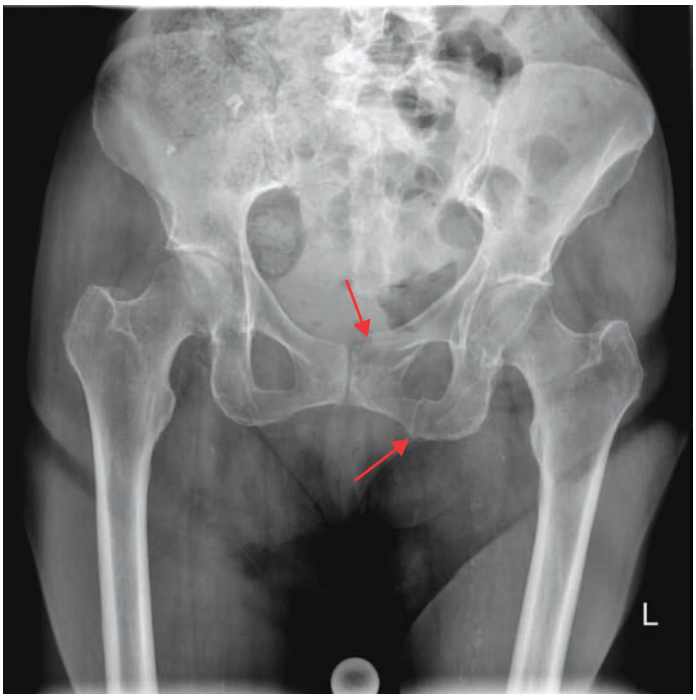


FIGURE 272-9. Fracture of superior ramus (*top arrow*) as the result of fall from standing. Healed fracture of the inferior ramus is noted as well (*bottom arrow*). [Photo used with permission of Patrick Studer, MD.]

a 45-degree iliac oblique view, and a 45-degree obturator oblique view—together known as *Judet views*. **CT is more sensitive than radiography in detecting acetabular injury.**[21] CT provides more detailed information about the displacement of fracture fragments, degree of comminution, and other information that is useful in preoperative planning.

Patients with acetabular fractures require hospital admission and orthopedic consultation, as well as evaluation for associated visceral, neurovascular, and other orthopedic injuries. Sciatic nerve injury is a common complication.

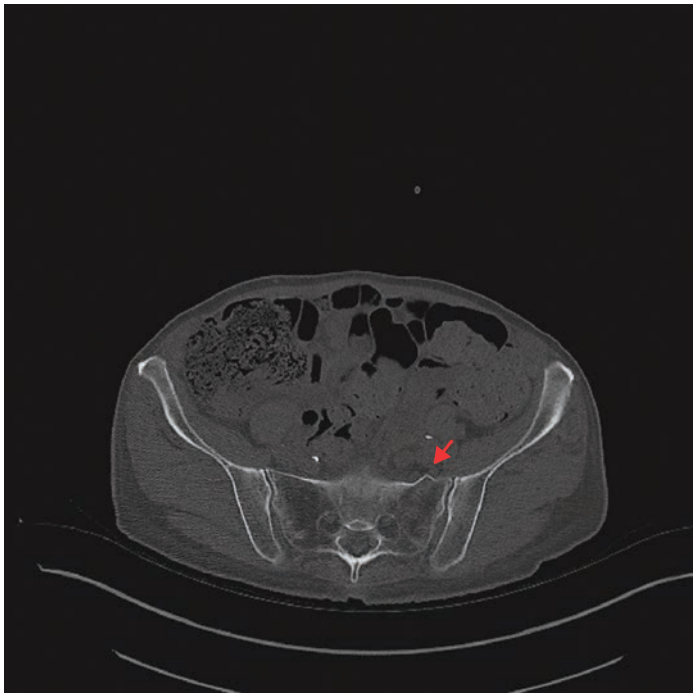
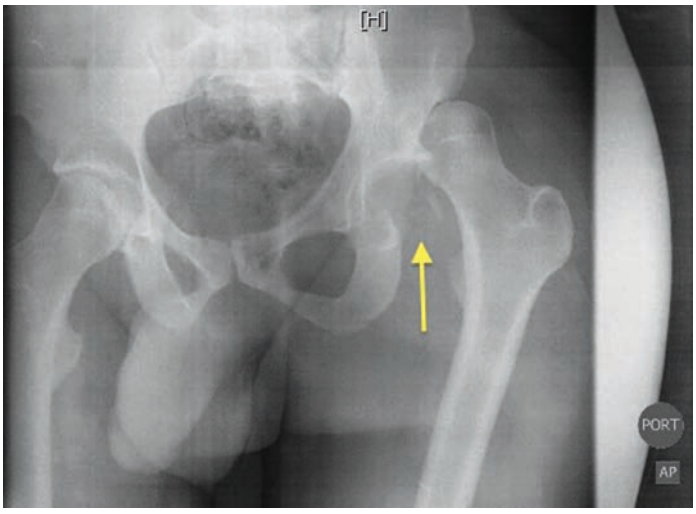


FIGURE 272-10. Same patient with fracture of left lateral sacral body discovered on CT scan. [Photo used with permission of Patrick Studer, MD.]



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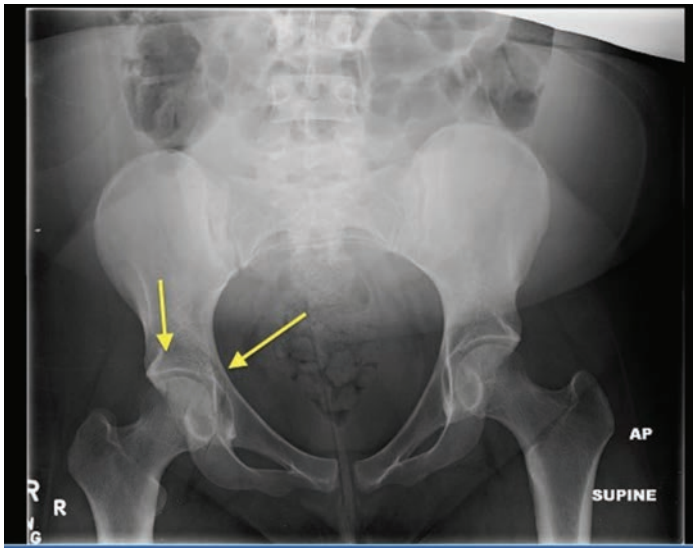

B

FIGURE 272-11. **A.** Left posterior hip dislocation with avulsed fracture fragments of the posterior acetabular rim. **B.** Multiple curvilinear lucencies demonstrating nondisplaced fractures (*arrows*) of the right acetabulum and right ischium. Pubic symphysis is also slightly widened.

TREATMENT

It is important to prevent movement of fracture segments, particularly in the hemodynamically unstable patient. The pelvis can be temporarily yet quickly stabilized with a bed sheet or other pelvic binding device to reduce pelvic volume and stabilize fracture ends.[22-24] The simplest technique is the application of either a folded bed sheet secured with towel clips or a commercially manufactured binder that is tightly wrapped around the pelvis at the level of the greater trochanters. A pelvic binder can decrease the volume of the pelvis and, in turn, help diminish blood loss for both open-book and vertical shear fractures. Lateral compression pelvic fractures do not benefit from the application of a pelvic binder because they are already rotated internally; in fact, these patients may be harmed from further lateral compression.[25]

Provide appropriate resuscitation with crystalloid, blood, and blood products. **Retroperitoneal bleeding may complicate pelvic fractures. Up to 4 L of blood can be lost in the pelvis before vascular pressure is**

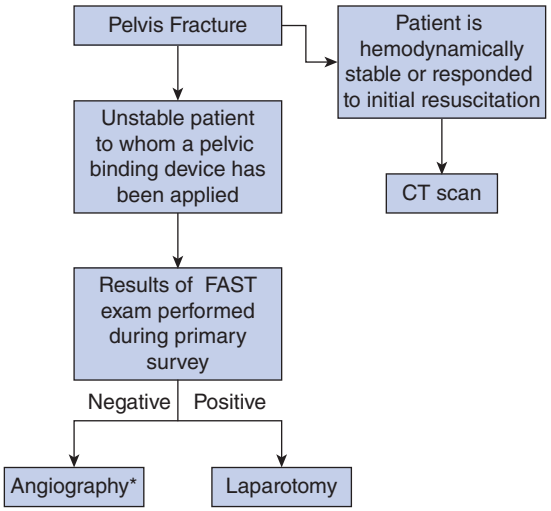

FIGURE 272-12. Suggested algorithm for pelvic fracture treatment. OR = operating room.

overcome and tamponade occurs. Most bleeding is due to the low-pressure venous injury, rather than from arterial vessels, or results from broken, mobile bone edges. Predictors for the need of either a transfusion or a therapeutic intervention (tranexamic acid) due to hemorrhage include: (1) initial hematocrit <30%, (2) presence of pelvic hematoma on CT scan, or (3) systolic blood pressure <90 mm Hg on arrival.[26] Presence of any of these factors mandates intensive care admission.[26] Moreover, a recent prospective study showed that a base deficit <6 mmol/L or a worsening base deficit >2 mmol/L while in the ED significantly correlated with the need for either angiography or laparotomy.[27]

FAST, CT, AND PELVIC FRACTURE

In hemodynamically unstable trauma patients with pelvic fractures, carefully evaluate for other sources of blood loss. Patients who have sustained a pelvic fracture from a significant mechanism of injury should undergo a thoraco-abdomino-pelvic CT scan even if the FAST exam is negative. In the presence of pelvic fracture and serious blunt trauma mechanism, patients with a negative FAST exam are still very likely to have concomitant visceral injury.[28]

If the FAST exam reveals free intraperitoneal fluid (**Figure 272-12**), then CT scan is also needed to determine the next treatment step. The FAST false-positive rate for intraperitoneal hemorrhage in patients with pelvic ring disruption can be up to 30%.[29,30] Distortion of the anatomy from fractures, retroperitoneal bleeding, urine from a ruptured bladder, or pelvic hematoma may mimic free intraperitoneal fluid. The sensitivity and specificity of FAST exam for free peritoneal blood in major pelvic injury appear to be related to the severity of the pelvic fracture.[29,30]

One study reported the overall sensitivity and specificity of the FAST exam to detect free peritoneal fluid in major pelvic injury to be 81% and 87%, respectively.[30] The fluid was blood in 76% and urine in 19%.[30] Moderate to large free fluid as evidenced by fluid noted in two or more regions of the FAST exam is reported to be associated with the need for hemorrhage control, either by laparotomy or angiography.[31]

HEMORRHAGE CONTROL: ANGIOGRAPHY, EMBOLIZATION, EXTERNAL FIXATION, PREPERITONEAL PACKING, AND RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA

The need for hemorrhage control can be predicted based on the fracture pattern and whether blood products were given during resuscitation.[3] If a patient with a pelvic fracture is hemodynamically unstable and other sources of bleeding (e.g., splenic or liver laceration) have been excluded through CT scan or laparotomy, treatment options include angiography with embolization, with or without external fixation of the pelvic fracture. Angiographic embolization is effective at controlling arterial bleeding. External fixation is thought to be effective at controlling venous bleeding.[32,33] Both may be needed to control hemorrhage.

Shock and death are generally due to arterial rather than venous bleeding.[14,34,35] Arterial bleeding can occur in all types of pelvic fractures yet does so in only 10% to 15% of cases.[32] The arteries involved are typically branches of the internal iliac system, with the superior gluteal artery and the obturator artery being the most common (see Figure 272-3). Hemorrhage from pelvic fractures refractory to resuscitation is more likely arterial than venous in origin. Angiography and embolization can control arterial hemorrhage in most patients.[32-34] **Consider angiography early in a hemodynamically unstable patient with a pelvic fracture, after other sources of bleeding have been excluded.**

Contrast extravasation on CT is considered by many to be an indication for angiography to evaluate for an arterial source of bleeding that may be amenable to embolization.[14,33,36] Some protocols advocate angiography based on hemodynamic status, the need for ongoing blood transfusion, or in patients who meet certain blood transfusion criteria.[14,32] No intervention is needed for nearly half of all patients who demonstrate a pelvic blush on CT scan without clinical signs of ongoing bleeding.[37] The need for arterial embolization has a positive predictive value of 39% for death in open pelvis fractures, as noted in one recent study.[6]

Preperitoneal packing, in which surgically placed packs tamponade the potential space available for ongoing blood loss, can be performed quickly to control bleeding in a hemodynamically unstable patient.[38] Consider this treatment option for an unstable patient when angiography is not readily available, when a laparotomy is needed prior to angiography, or if the patient is in extremis and needs quick stabilization prior to angiography.[26,38]

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a newer technique that can be used to temporarily limit aortic inflow to the pelvis, limit arterial bleeding, and preserve cerebral and myocardial perfusion.[39]

The definitive treatment of pelvic fractures occurs once the patient has been stabilized and after other associated injuries have been addressed. All pelvic fractures require orthopedic consultation, even in the most stable of patients, and admission when warranted. Elderly patients with simple pubic ramus fractures typically require admission for pain control, observation for complications, and physical therapy for ambulation. The exact treatment is guided by fracture location and pelvic stability. Fractures that disrupt the pelvic ring often need open reduction and internal fixation. Early operative fixation has been associated with better long-term function outcomes.[40] The admitting service will vary between hospitals and depends on multiple factors including the presence of a trauma surgery service, volume of orthopedic cases, comorbidities of the patient, and absence of other significant injuries.[41]

COMPLICATIONS OF PELVIC FRACTURES

Acute complications and associated injuries of pelvic fractures include urogynecologic injury, rectal injury, ruptured diaphragm, and nerve root injury. Pelvic fractures can also have long-term effects, including chronic pain, sexual dysfunction, and persistent functional disability.

UROGYNECOLOGIC INJURY

If a urethral injury is suspected clinically, perform retrograde urethrography before Foley catheter placement. Urinary tract injuries are discussed in greater detail in Chapter 265, "Genitourinary Trauma." Gynecologic injuries are uncommon with pelvic trauma. Vaginal laceration can occur with anterior pelvic fractures. Perform a bimanual pelvic examination on women with pelvic fractures. If blood is detected, a speculum examination is needed to identify vaginal hematoma, laceration, or urethral bleeding.

RECTAL INJURY

Rectal injuries are uncommon and are usually associated with urinary injuries and ischial fractures. Diagnosis is by careful rectal examination or proctoscopy, during which gross blood is found in the rectum. Treatment includes early diverting colostomy with washout of the distal colon and presacral space drainage. Administer antibiotics that cover gram-negative organisms as soon as the injury is discovered.

NERVE ROOT INJURY

Nerve root or peripheral nerve injuries can occur because of traction, pressure from hemorrhage, callus or fibrous tissue, and impingement laceration by bone fragments. The onset of symptoms and signs may be delayed, but deficits usually follow a nerve root pattern. Lumbar nerve root injuries are associated with sacroiliac joint dislocation or fracture and longitudinal displacement of the fracture.[42] Sacral root injuries are associated with transverse fractures of S1 and S2 as can be seen secondary to trauma from an intentional suicide attempt by jumping from a height.[42]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

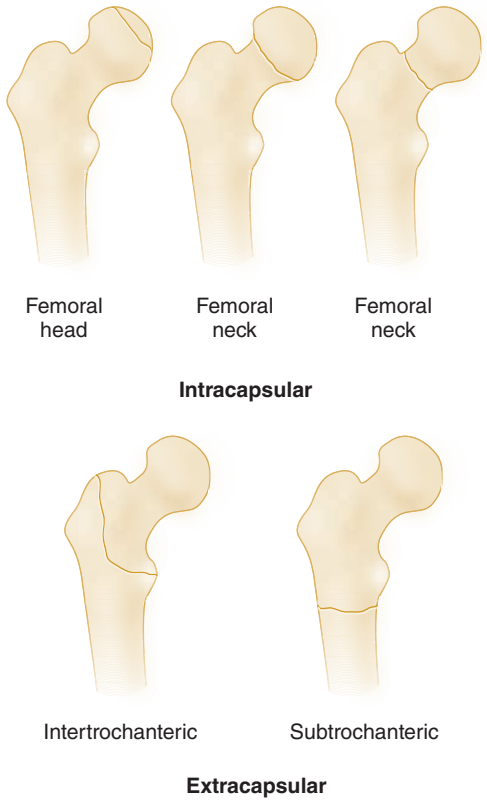

FIGURE 273-1. Fractures of the proximal femur are traditionally classified as intracapsular and extracapsular.

CHAPTER 273

Hip and Femur Injuries

Chris Courtney

INTRODUCTION AND EPIDEMIOLOGY

Over 350,000 hip fractures occur annually, costing nearly $6 billion. Hip fractures are a life-changing injury. Forty percent of patients fail to regain preinjury ambulation status at 6 months and fail to return to independent living at 1 year, and nearly 25% of those suffering from this injury die within 12 months. Morbidity and mortality result from prolonged immobilization. Compromised preinjury ambulation status and dependent living are predictors of poor functional outcome and long-term mortality.[1,2]

Hip dislocations are associated with devastating complications. Disruption of vascular supply can result in avascular necrosis and is estimated to occur in up to 25% of hip dislocations. This life-changing complication nearly always mandates total hip arthroplasty (THA).[3]

Femur fractures are most often associated with trauma and occur across a much broader demographic. These high-energy fractures can result in life-threatening blood loss.[4]

ANATOMY AND PATHOPHYSIOLOGY

Hip fractures are defined by their anatomic location (**Figures 273-1** and **273-2** and **Table 273-1**) and classified as **intracapsular** (femoral head and neck) or **extracapsular** (trochanteric, intertrochanteric, and subtrochanteric). Treatment will vary considerably with fracture type (**Table 273-2**).

The extracapsular bone between the greater and lesser trochanter defines the intertrochanteric region. The greater trochanter is the insertion for the gluteal hip abductors. The lesser trochanter is the insertion for the iliopsoas, which is the strongest hip flexor. Fractures extending from the greater to lesser trochanter are considered **intertrochanteric hip fractures**.

Fractures in the region 5 cm below the lesser trochanter are **subtrochanteric hip fractures**. The femoral shaft describes the diaphysis, beginning 5 cm below the lesser trochanter and extending to but not including the femoral condyles.

Most hip dislocations are posterior due to the more common anterior-posterior mechanisms of injury and the relatively weaker posterior joint capsule. Blood is supplied to the femoral head from the medial and lateral femoral circumflex arteries forming a ring with branching arteries that extend into the joint capsule. The foveal artery, a branch of the obturator artery, contributes blood to the femoral head through the teres ligament connecting the hip and the acetabulum. Dislocation always results in rupture of this ligament and its artery. Patients with circulation dependent on this foveal branch will almost inevitably develop avascular necrosis.

Femoral neck fractures often disrupt the primary circulation from the circumflex femoral arteries. This explains why femoral neck fractures with minimal or no displacement may be amenable to reduction and internal fixation while grossly displaced fractures are more likely to require a partial or THA. Avascular necrosis occurs in 15% to 35% of patients with hip fractures when capsular vessels are disrupted.[5] Intertrochanteric and subtrochanteric fractures are unlikely to result in vascular compromise.

CLINICAL FEATURES

HISTORY

Any fall in an elderly patient should raise suspicion for hip fracture. Altered patients "found down" should be considered high risk for occult fractures. Motor vehicle collisions and high-energy mechanisms should raise suspicion for hip dislocation or femoral shaft fracture. Chronic kidney disease and prolonged steroid use increase the risk of avascular necrosis, and pathologic fractures should be considered in patients with known or suspected malignancy.

Complaints can vary. Patients with a hip fracture or dislocation may complain of knee pain or groin pain. Patients with altered sensorium may have no complaints, and demented patients may even ambulate on occult hip fractures.

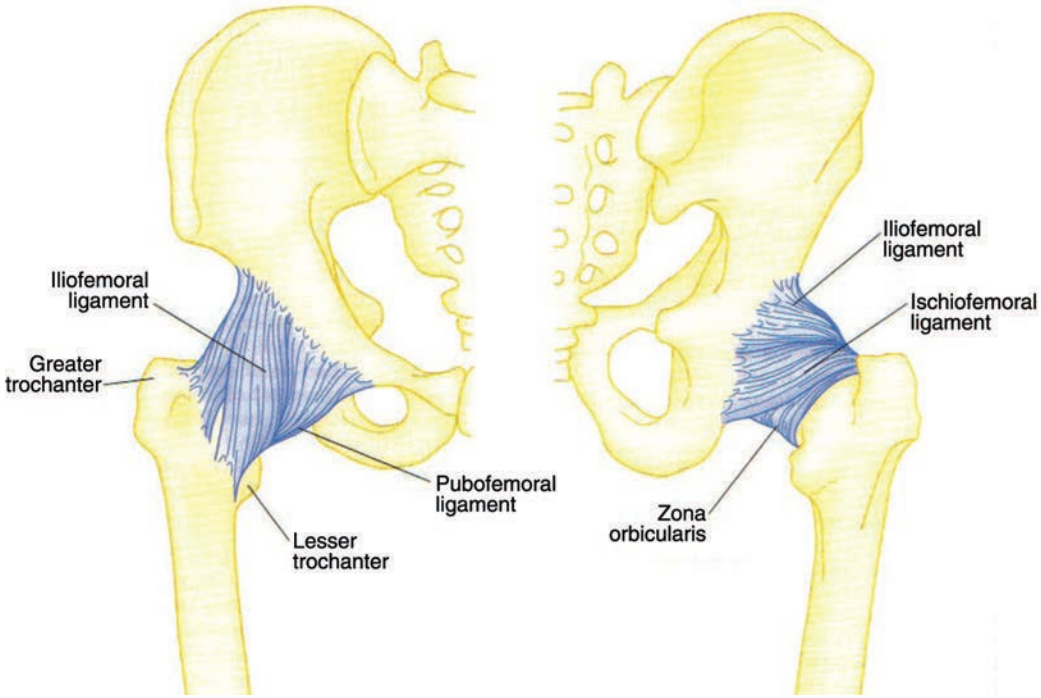

FIGURE 273-2. Hip and joint capsule.

TABLE 273-1 Proximal Femur Fractures: Demographics and Clinical Features

Fracture	Incidence/Demographics	Mechanism	Clinical Findings	Concomitant Injuries
Femoral head	Isolated fracture rare; seen in 6%–16% of hip dislocations	Usually result of high-energy trauma; dashboard to flexed knee most common	Limb shortened and externally rotated (anterior dislocation); shortened, flexed, and internally rotated (posterior dislocation)	Closed head injury; intrathoracic and/or intra-abdominal injuries; pelvic fracture, knee injuries
Femoral neck	Common in older patients with osteoporosis; rarely seen in younger patients	Low-impact falls or torsion in elderly; high-energy trauma or stress fractures in young	Ranges from pain with weight bearing to inability to ambulate; limb may be shortened and externally rotated	Ipsilateral femoral shaft fracture
Greater trochanteric	Uncommon; older patients or adolescents	Direct trauma (older patients); avulsion due to contraction of gluteus medius (young patients)	Ambulatory; pain with palpation or abduction	—
Lesser trochanteric	Uncommon; adolescents (85%) > adults	Avulsion due to forceful contraction of iliopsoas (adolescents); avulsion of pathologic bone (older adults)	Usually ambulatory; pain with flexion or rotation	—
Intertrochanteric	Common in older patients with osteoporosis; rare in younger patients	Falls; high-energy trauma	Severe pain; swelling; limb shortened and externally rotated	Anemia from blood loss into thigh; concomitant traumatic injuries
Subtrochanteric	Similar to intertrochanteric; 15% of hip fractures	Falls; high-energy trauma; may also be pathologic	Severe pain; ecchymosis; limb shortened, abducted, and externally rotated	Vascular injuries, anemia/hypovolemic shock from fracture itself or other traumatic injuries

TABLE 273-2 Proximal Femur Fractures: Treatment Issues

Fracture	ED Management	Disposition and Follow-Up	Complications
Femoral head	Immediate orthopedic consultation; emergent closed reduction of dislocation; ORIF if closed reduction is unsuccessful	Admission to orthopedic or trauma service	AVN; posttraumatic arthritis; sciatic nerve injury; heterotopic ossification
Femoral neck	Orthopedic consultation; ranges from nonoperative to total hip arthroplasty	Admission to orthopedic service	AVN; infection; DVT and/or pulmonary embolus
Greater trochanteric	Analgesics; protected weight bearing	Orthopedic follow-up 1–2 wk; possible ORIF if displacement >1 cm	Nonunion rare
Lesser trochanteric	Analgesics; weight bearing as tolerated; evaluate for possible pathologic fracture	Orthopedic or PCP follow-up in 1–2 wk; admit or urgent follow-up for pathologic fracture	Nonunion rare
Intertrochanteric	Orthopedic consultation	Admit for eventual ORIF; may need preoperative testing and clearance by PCP or hospitalist	DVT and/or pulmonary embolism; infection
Subtrochanteric	Orthopedic consultation; consider Hare® or Sager® splint	Admit for ORIF	DVT and/or pulmonary embolism; infection; malunion (shortened limb); nonunion

Abbreviations: AVN = avascular necrosis; DVT = deep venous thrombosis; ORIF = open reduction and internal fixation; PCP = primary care physician.

PHYSICAL EXAMINATION

After primary survey, evaluate for deformities, shortening, rotation, lacerations, bruising, or instability of the limb. Identify focal bony tenderness or crepitance. Axial load is extremely sensitive in identifying occult hip fractures. If no significant deformities are noted then perform range of motion of the hips. Identification of a hip or pelvic injury in trauma should raise suspicion for intra-abdominal or urologic injuries. Perform a rectal exam if concern exists for concurrent spinal or pelvic injuries. Complete a neurovascular exam of the motor and sensory function of the perineum and lower extremities along with vascular exams at the groin, popliteal fossa, and ankle. If concern exists for vascular injury, CT angiography may be indicated with concurrent evaluation of associated bony trauma.

DIAGNOSIS

IMAGING

Consider radiographic evaluation of the pelvis and hips in all unconscious patients who have sustained trauma or have fallen. Hip radiographs should include anterior and lateral views along with a complete anteroposterior view of the pelvis. Conventional radiographs are estimated to be 90% to 98% sensitive for hip fractures.[6]

When femoral shaft fracture is suspected, images of the femur should include an anteroposterior view along with a lateral view. **Radiographs should include a joint above and below the suspected injury.**

HIP FRACTURES

FEMORAL HEAD FRACTURES

Isolated femoral head fractures are uncommon and typically associated with dislocations (Table 273-1). Metastatic or pathologic lesions in the femoral head increase the risk for sustaining this rare injury. Reduction is extremely challenging and usually requires operative intervention. Consult orthopedic surgery prior to reduction, but avoid delays as these injuries are at risk for avascular necrosis. If orthopedic surgery is not readily available, at least one ED attempt at reduction is recommended. CT may be required to characterize the position of the retained fragment. Treatment may or may not involve internal fixation (Table 273-2). Prognosis is related to the severity of the initial trauma, associated injuries, delay in reduction, and repetitive unsuccessful reduction attempts.[7]

FEMORAL NECK FRACTURES

Femoral neck fractures are one of the most common orthopedic injuries seen in the ED. These injuries typically occur in older adults and occur more frequently in women. Falls are the most common mechanism (90%), but stress or traumatic femoral neck fractures may be seen in younger patients.[8] Consider the possibility of pathologic fractures in all pediatric hip fractures, with unicameral bone cyst the most likely lesion.[9] Consider underlying malignancy in all ages with an unusually low-energy mechanism.[10,11]

The symptoms seen with femoral neck fractures range from mild pain in the groin or inner thigh, to severe pain with subtle movement. Patients with nondisplaced fractures may be somewhat ambulatory. Those with displaced fractures are typically unable to bear weight. Displaced fractures typically result in shortening and external rotation of the affected extremity (**Figure 273-3**).

Obtain an anteroposterior view of the pelvis and a lateral view of the hip. Any altered or demented patient with a fall should undergo a thorough examination with low threshold to obtain radiographs. Any patient with a change in ambulatory status should undergo radiographic evaluation of the hip. The femur and knee should be imaged in altered or demented patients or those unable to clearly localize their pain.

Displaced fractures are obvious on the anteroposterior view, but a lateral view may be helpful in identifying subtle fractures. Approximately 6% to 9% of patients with a femoral neck fracture will have an ipsilateral femoral shaft fracture.[12] These concurrent injuries occur in high-energy



FIGURE 273-3. Shortened, abducted, externally rotated limb (*arrow*) seen in femoral neck fracture. [Image used with permission of Dr. Allan Mishra, http://www.emedx.com.]

trauma patients. In this setting, consider obtaining femur and knee radiographs. **The most reliable radiographic finding in identifying femoral neck fractures is disruption of the bony cortex or disruption of the trabecular lines** (**Figures 273-4** and **273-5**). Shenton line and neck shaft angle have been proven unreliable and to yield significant interuser variability even among radiologists. They are rarely used by orthopedists and are unreliable methods for identifying fracture. They are also highly dependent on radiographic angle and technique.

There are multiple classification systems for femoral neck fractures, but it is most useful to describe them as displaced or nondisplaced. Because femoral neck fractures are intracapsular, displaced fractures often disrupt blood supply, resulting in avascular necrosis. Displaced femoral neck fractures are more likely to undergo partial hip arthroplasty (bipolar arthroplasty). This procedure involves replacing the hip component without relining the acetabular component. It also allows patients to ambulate immediately following surgery, which is crucial in avoiding complications associated with immobilization. Internal screw fixation is performed in younger, more active patients and preserves the native femoral head but does not allow early weight bearing.

Once a fracture is identified, maintain the extremity in a position of comfort. Additional external immobilization is unnecessary. **Skeletal traction is contraindicated for femoral neck fractures because it may result in avascular necrosis.** "Bucks" boot traction is no longer



FIGURE 273-4. Radiograph of femoral neck fracture. The disruption of the bone is most visible when following the superior surface of the femoral neck. Also notice the shortening and impaction of the femoral neck.

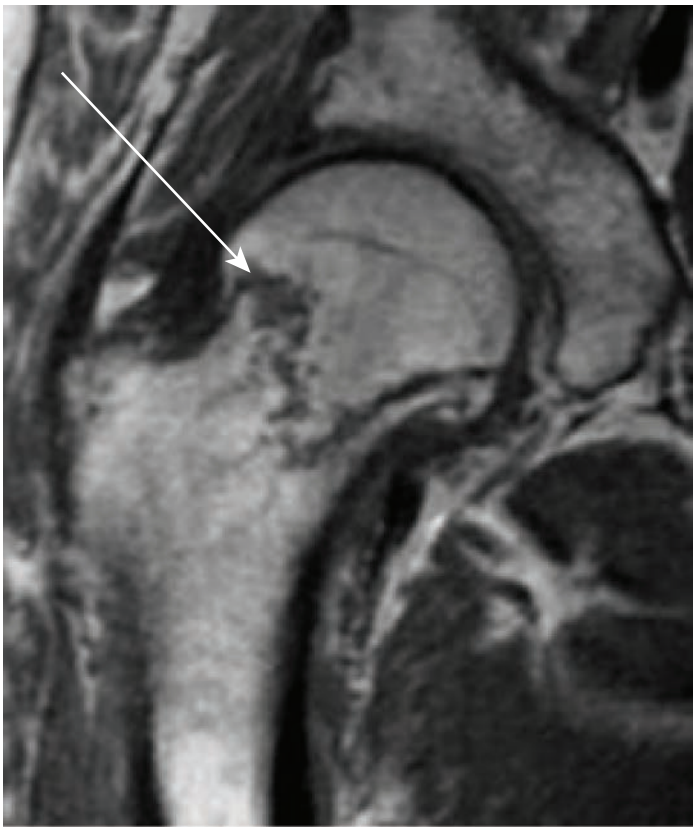

FIGURE 273-5. MRI demonstrating right hip fracture in a patient with a plain radiograph of the right hip that did not reveal the fracture. [Photo contributed by Brooke Beckett, MD, Department of Radiology, Oregon Health & Science University.]

consistently used during admission, although some orthopedists may continue this dated practice. It is not necessary in the ED.

All patients with hip fractures hoping to return to ambulation will require surgery. For both displaced and nondisplaced fractures, surgical fixation results in decreased morbidity and mortality when compared with nonoperative management.[13,14] Decisions regarding the timing and type of operative intervention depend on the patient's physiologic age, activity level, and fracture severity.[15] Nonoperative treatment is rarely considered and only appropriate in nonambulatory patients with reasonable pain control. A decision to forgo operative intervention for a hip fracture should be considered an end-of-life decision. Nonambulatory, hospice, or palliative care patients may still undergo operative intervention for pain control. This includes patients with pathologic fractures from diffuse metastatic disease.

The complications of femoral neck fractures are significant (Table 273-2). Discuss expected management with the patient and family, **emphasizing the importance of early ambulation and physical therapy**. Consider efforts to facilitate early operative intervention. Mortality significantly increases after a 24-hour delay.[16] Facilitating preoperative clearance can impact clinical outcome. This can include ordering preoperative diagnostics or early communication with consultants. A multidisciplinary team, including social services for home safety evaluation, and early involvement of the patient's primary care physician or a hospitalist can improve outcomes.[13]

ISOLATED TROCHANTERIC FRACTURES

Greater trochanteric fractures are usually avulsions at the insertion of the gluteus medius. In younger patients (7 to 17 years of age), this is a true epiphyseal separation. In adults, the cause is usually direct trauma.

Lesser trochanteric fractures are avulsions secondary to forceful contraction of the iliopsoas. They are commonly seen in children and young adult athletes, particularly gymnasts and dancers. Lesser trochanter fractures in older patients with minimal trauma should raise concern for pathologic fracture.[17] Standard anteroposterior and lateral views are recommended. CT of the pelvis may be helpful if a fracture is strongly suspected but difficult to visualize. In most instances, the treatment is nonoperative. Crutch ambulation with touch–toe weight bearing is recommended until orthopedic follow-up in 3 to 5 days. Full recovery is expected in patients with healthy bone. Operative fixation may be indicated in cases where there is significant displacement of a large fracture fragment.

INTERTROCHANTERIC FRACTURES

Intertrochanteric fractures are defined as extracapsular fractures occurring in a line between the greater and lesser trochanters. They generally occur in the elderly and are more common in women. The mechanism of injury is usually a fall. Patients typically have pain and deformity on examination. Fractures are usually seen on standard anteroposterior and lateral views. Intertrochanteric fractures are classified based on the number of fracture lines and the amount of displacement.[18] When fractures extend perpendicular to the intertrochanteric line, they are referred to as reverse obliquity intertrochanteric fractures. Perform the same assessment with intertrochanteric fractures as with femoral neck fractures. Traction of any form is contraindicated.[19,20]

Intertrochanteric hip fractures require a unique operative technique. The femoral head is preserved, and a sliding "dynamic" screw is used to cross the fracture site and hold fixation into the femoral head.

The complications and prognosis are related to associated injuries, prior disease, and immobilization. **Blood loss can be significant, and some patients will require crystalloid or blood transfusion.**[21] Infection and pulmonary embolism are significant complications. Avascular necrosis and nonunion are uncommon.

SUBTROCHANTERIC FRACTURES

Subtrochanteric fractures are defined as fractures anywhere 5 cm below the lesser trochanter. They are seen in older patients who fall, younger patients with major trauma, and patients with bony metastases. Symptoms include localized pain, deformity, swelling, and crepitance. Significant blood loss may occur. Obtain standard anteroposterior and lateral views of the hip along with radiographs of the pelvis, femur, and knee. ED treatment consists of pain control, immobilization, and orthopedic consultation. As with femoral shaft fractures, Hare® (Dynamed, Westbury, Tasmania) or Sager® (Minto Research and Development, Inc., Redding, CA) splints are commonly employed in the prehospital setting. Traction splinting may ease pain and provide some fracture reduction (See Video: Hare Traction Splint).[20] Operative reduction with internal fixation or intramedullary nailing is almost universally indicated.

OCCULT HIP FRACTURES

Any patient unable to ambulate or experiencing severe pain with ambulation and who has negative radiographs should undergo CT or MRI. Stress, incomplete, or nondisplaced fractures may not be evident on plain radiographs for days or weeks after injury. MRI is the preferred imaging study and nearly 100% sensitive in identifying occult fractures (Figure 273-5). When MRI is unavailable, CT is a reasonable but less sensitive alternative. In recent years, a rapid-sequence MRI protocol dedicated to rapid ED evaluation of occult hip fractures has been developed and validated. The rapid hip protocol MRI involves only two sequences (large field of view T1 and inversion recovery/fat saturation T2) and takes only 7 to 8 minutes. All nonspecialist radiologists can accurately assess it at the time of acquisition. MRI offers the added benefit of identifying metabolic or pathologic lesions.[22] Imaging should include the pelvis and extend to the lesser trochanter. Any change in ambulatory status should raise suspicion for occult fracture. If MRI is unavailable, fracture should be presumed in all patients unable to weight bear even in the setting of a normal CT.[22-27]

FEMORAL SHAFT FRACTURES

Fractures of the femoral diaphysis or "femoral shaft" most often occur in young patients with high-energy trauma. Associated traumatic injuries are common. The mechanism of injury varies from direct trauma resulting in transverse fractures to axial load, which typically results in oblique

fractures often with a free-floating triangular "butterfly" fragment. A rotational mechanism may contribute to a spiral pattern and may also cause ligamentous injury at the knee. Pathologic fractures are typically the result of bone metastases. Pathologic fractures in young patients can be benign lesions or malignant primary bone tumors. Unicameral bone cysts are among the most common cause of pathologic femur fractures in pediatric patients.[28]

Femoral shaft fractures are generally evident in the prehospital setting because of the shortening, deformity, and associated swelling. Initiate traction in the field to minimize pain, prevent further fracture comminution, and minimize blood loss. **Traction splints are contraindicated in cases of open fracture or in suspected nerve, knee, or vascular injury**. For the latter, splint placement without traction is indicated.

Neurovascular examination with focus on the sciatic nerve is always indicated. The fracture is typically evident on standard anteroposterior and lateral views of the femur, but radiographic evaluation should include the joints above and below the injury (pelvis, hips, knees). Open femur fractures require broad-spectrum antibiotics and copious irrigation. Cover the open wound or exposed bone in saline-soaked gauze. Open femur fractures require operative washout and debridement.

Blood loss can be life threatening. It is estimated that the average blood loss in femur fractures can be as high as 1200 mL. It is possible to exsanguinate from a femur fracture, and the threshold to transfuse should be low.

Intramedullary nailing is the preferred treatment for most femoral shaft fractures. Severely contaminated open fractures, patients with concomitant injuries, or highly comminuted fractures may require external fixation and delayed operative fixation.[29]

HIP DISLOCATION

Dislocations of native hips result from high-energy trauma, and up to 95% of patients have other associated injuries.[30] Motor vehicle collisions are the most common mechanism. **Posterior dislocations of native hips account for >90% of all dislocations.** The remaining 10% are anterior-superior or anterior-inferior.[31] Dislocations of prosthetic hips occur with minimal trauma.

Native hip dislocations are orthopedic emergencies and should be reduced as quickly as possible and no more than 6 hours after the injury. Risk of avascular necrosis increases from <10% to nearly 25% when delay extends from 10 hours to 15 hours. If closed reduction under procedural sedation fails or is not an option, open or closed reduction under general anesthesia is required. Anterior hip dislocations mandate reduction in the operating room. Open reduction by an orthopedic surgeon is indicated for irreducible fractures, unsatisfactory reductions, and complex fracture dislocations.[31]

POSTERIOR HIP DISLOCATION AND REDUCTION MANEUVERS

Posterior hip dislocations (**Figure 273-6**) result from a posterior force applied to a flexed knee, most commonly a dashboard injury. These injuries are associated with acetabular, femoral neck, and femoral shaft fractures. Ligamentous injury to the knee is also common. On examination, the extremity is shortened, adducted, and internally rotated, which differentiates the injury from femoral neck fractures that are typically externally rotated. A careful neurovascular examination to identify associated sciatic nerve or vascular injury is essential.

Anteroposterior and lateral radiographs of the pelvis and hip identify posterior dislocations (**Figure 273-7**). When identified, perform additional evaluation of acetabulum and femur with CT. **Complications of posterior dislocation include sciatic nerve injury in approximately 10% of patients. The risk of avascular necrosis of the femoral head increases in direct proportion to delay in reduction.**

Multiple techniques have been described for closed reduction of posterior hip dislocations (**Figures 273-8** to **273-11**); it is advisable for the emergency physician to be proficient with more than one technique. **Nearly all techniques require in-line traction while flexing the hip to 90 degrees and adducting the hip.**

The **Allis maneuver** is the most commonly performed technique. In-line traction is performed with simultaneous hip flexion and internal



FIGURE 273-6. Posterior dislocation of the hip. **A.** Schematic representation. **B.** The clinical appearance of a posterior dislocation of the right hip.



FIGURE 273-7. Radiograph of posterior hip dislocation. There is also a concomitant acetabular fracture visible.

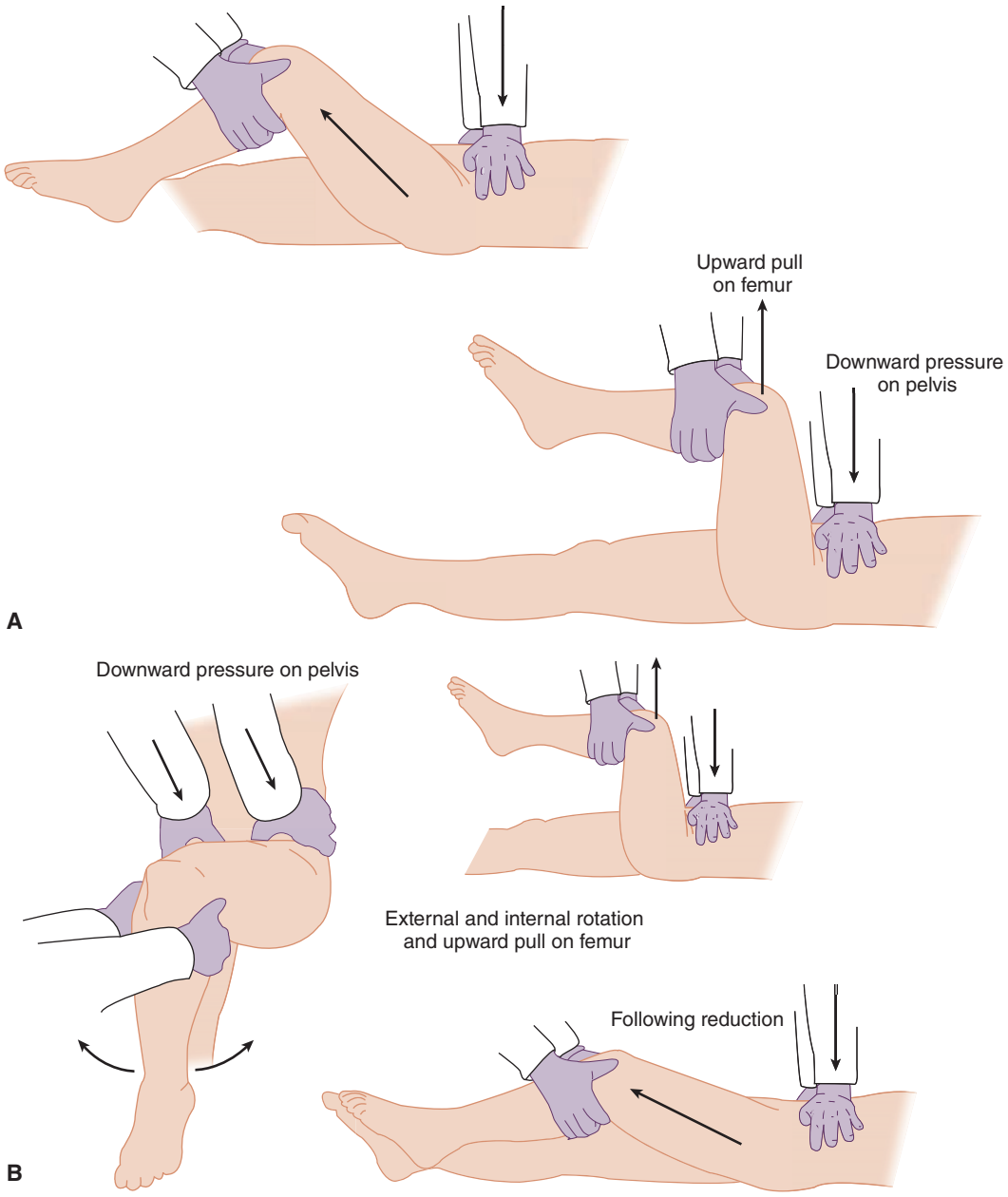

FIGURE 273-8. **A** and **B.** Allis maneuver for reduction of posterior hip dislocation.

rotation (Figure 273-8). While flexing both the patient's knee and hip to 90 degrees, apply in-line traction upward toward the ceiling and slightly toward the contralateral side, resulting in the desired flexion and adduction necessary for reduction. While under traction, perform gentle internal rotation if necessary. Aggressive or forced rotation can result in spiral fracture of the femur. An assistant should apply downward pressure to the anterior superior iliac spines. Stabilizing the pelvis is essential. Direct pressure can also be applied to the dislocated femoral head on the posterolateral aspect of the buttocks. The femoral head can often be palpated and pressure can be applied in line with the direction of traction.

With the **Bigelow maneuver**, the patient is supine with the affected hip and knee flexed 90 degrees (Figure 273-9). Secure the patient's knee with your flexed elbow, and grasp the patient's foot with the opposite hand. Have an assistant apply downward pressure to the anterior superior iliac spines. Now, using your flexed elbow, lift upward at the patient's knee to apply traction to the femur. Gently externally rotate and extend the hip while applying traction to the femur at the patient's knee. Another variation is represented in Figure 273-10.

Another method is the **Captain Morgan technique**, in which the physician's knee is used as a fulcrum (Figure 273-11) (See Video: Posterior Hip Dislocation Reduction).[32]

In all reduction maneuvers, be gentle, not forceful, when applying any rotation. The posteriorly dislocated hip is locked in internal rotation. While gentle external rotation may assist in rotation, torsion with only minimal force can easily result in a spiral femoral shaft fracture in osteoporotic bone. After reduction, gently range the hip and recheck neurovascular status. Confirm reduction with postreduction imaging. Immobilization to prevent recurrent dislocation is required. Because flexion and adduction cause posterior dislocations, the opposite, extension and abduction, protect against it. This can be achieved with a triangular "abduction pillow" (**Figure 273-12**). A knee immobilizer prevents extreme extension at the hip while limiting internal rotation and is a reasonable substitute. Because dislocation of a native hip typically results from extreme trauma, most patients will require admission.

If several attempts at reduction are unsuccessful, emergency orthopedic consultation is required. Difficulties with reduction may be due to

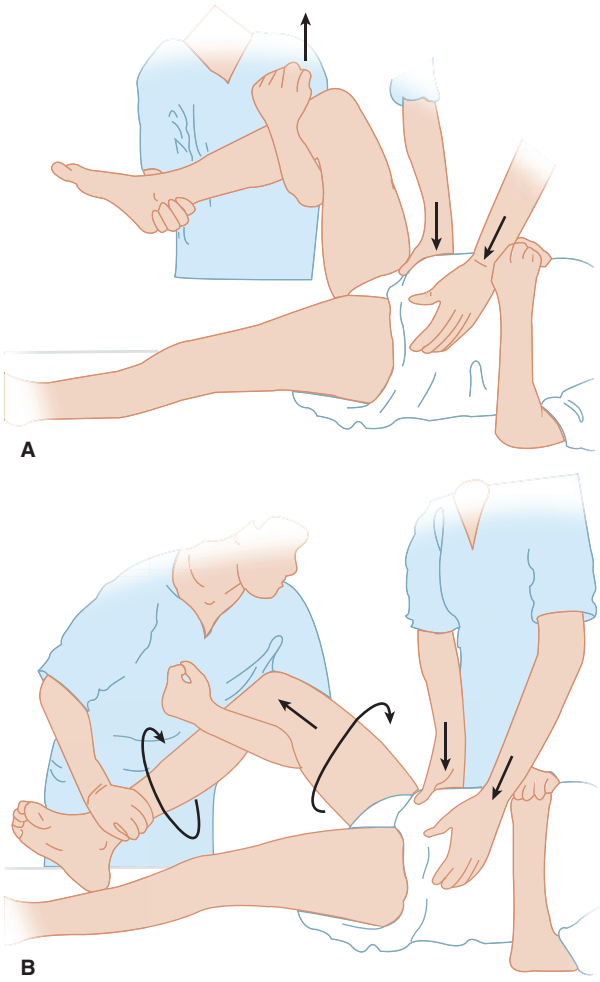

FIGURE 273-9. The Bigelow maneuver for reduction of posterior hip dislocation. **A.** The physician applies upward traction on the femur while an assistant stabilizes the pelvis. **B.** The hip is externally rotated and extended while the femur is distracted. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, McGraw-Hill, New York.]

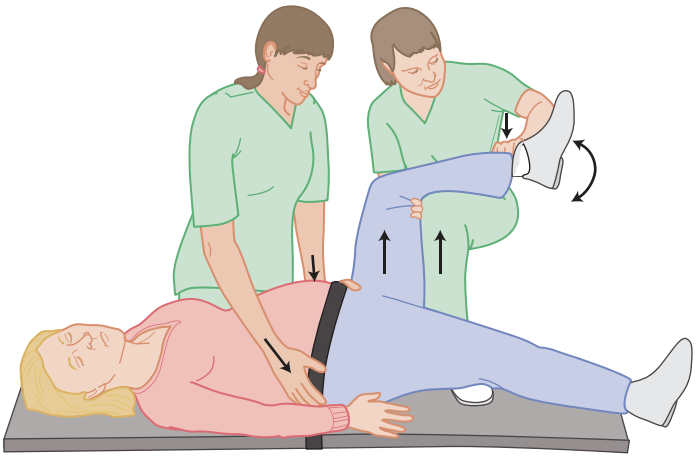

FIGURE 273-11. The Captain Morgan technique for reduction of posterior hip dislocation. (*1*) Stabilize the patient's pelvis by placing the patient on a backboard in the supine position and strapping the pelvis to the board, or have an assistant stabilize the pelvis on the stretcher by placing both hands on the patient's iliac crests and using pressure to keep the pelvis stable. (*2*) To reduce the dislocation, place your foot on the stretcher or board with your knee posterior to the patient's knee. (*3*) With the patient's knee in flexion, gently pull downward at the patient's ankle while applying an upward force to the patient's hip by lifting your heel by stepping on your toes and contracting your calf. Gently rotate the patient's hip while applying the upward traction behind the patient's knee.

occult fracture or incarcerated soft tissue. A postreduction CT is recommended to identify associated acetabular or femoral head fractures that were not evident on plain radiographs.[31]

ANTERIOR HIP DISLOCATION

Anterior hip dislocations are rare and result from forced abduction that causes the femoral head to be levered out through an anterior capsular tear (**Figure 273-13, A and B**). Anterior dislocations can be superior

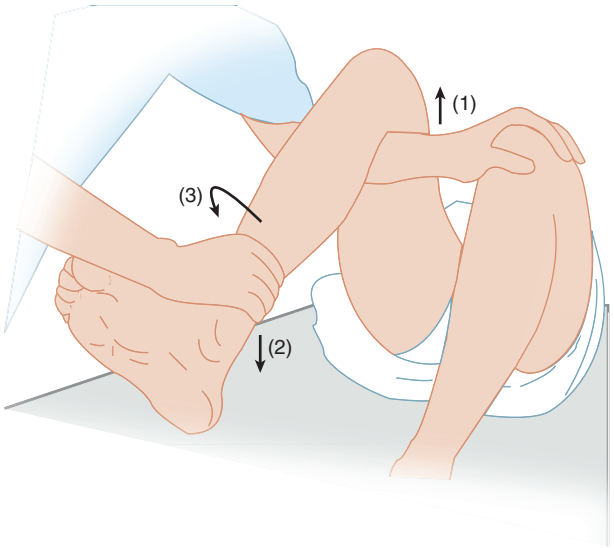

FIGURE 273-10. (*1*) Flex the patient's knee 90 degrees and place your flexed elbow under the patient's knee while placing your hand on the other knee to stabilize the pelvis. (*2, 3*) With the other hand, externally rotate the leg. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures*. © 2004, McGraw-Hill, New York.]



FIGURE 273-12. Abduction pillow.

(pelvic) or inferior (obturator) depending on the degree of hip flexion at the time of injury. The affected extremity is in abduction and external rotation (the opposite position of most posterior dislocations). The clinical appearance of superior versus inferior dislocations is dramatically different (**Figure 273-13, C and D**). Neurovascular compromise is an unusual complication. However, a thorough exam is warranted to detect injury to the femoral artery or nerve.

An anteroposterior view of the pelvis can easily demonstrate the femoral head to be anterior to the acetabulum. A lateral view illustrates the anterior dislocation more clearly, although it may be difficult to

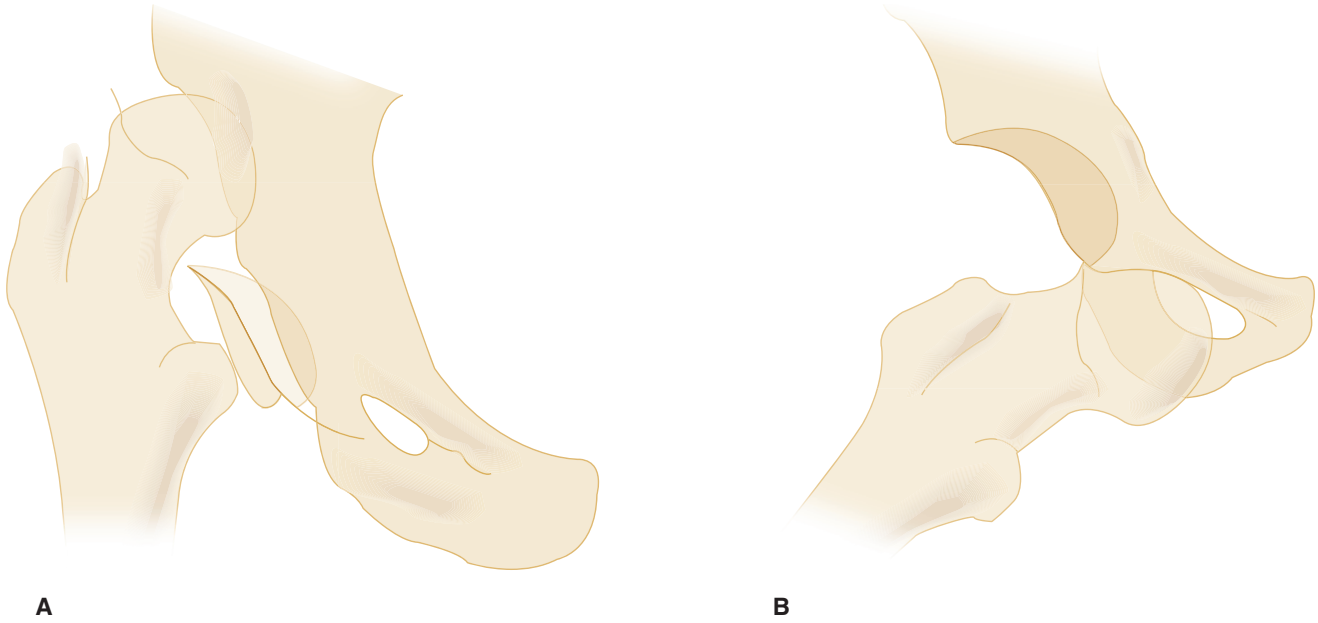



FIGURE 273-13. Anterior hip dislocation. **A.** Anterior superior dislocation of the hip. **B.** Inferior dislocation. **C.** Clinical appearance of a superior-type anterior dislocation of the hip. **D.** Clinical appearance of an inferior-type dislocation of the hip.

obtain secondary to patient discomfort. Anterior hip dislocations usually require reduction in the operating room.

DISLOCATIONS OF PROSTHETIC HIPS

Prosthetic hips dislocate relatively easily and represent an overwhelming majority of hip dislocations seen by the emergency physician. Up to 10% of prosthetic hips dislocate, the majority in the first few months after surgery.[33] Total hip arthroplasties dislocate in the direction of the surgical approach taken. Because most hip arthroplasties are performed through a posterior approach, posterior dislocations are by far the most common. Dislocations through an anterior approach will also present to the ED, and recognizing that these require an entirely different reduction approach is critical.

Posterior dislocations result from flexion, adduction, and internal rotation. This is common when going from a low-seated position to a standing position. Getting out of a booth, bending over to clip toenails, and standing up from the toilet are common mechanisms. Anterior dislocations occur from hyperextension of the hip, which is more awkward and less common in normal activities of daily living. This is one of the reasons some orthopedists advocate the anterior approach. Avascular necrosis of the femoral head is not a complication since there is no blood flow to the prosthetic joint. For this reason, reduction is not particularly time sensitive, although sciatic nerve injury or damage to the prosthesis may occur.

Most posterior dislocations of prosthetic hips can be reduced using procedural sedation in the ED with the techniques described previously for posterior reductions of native hips. Anterior dislocations of total hip arthroplasties can often be reduced with simple gradual longitudinal traction on the dislocated leg while an assistant stabilizes the pelvis. This technique is known as the Allis leg extension method.

A common cause for difficulty in reducing a dislocated total hip arthroplasty is the use of a "constrained cup." These acetabular components are often placed during revisions for chronic instability in patients prone to dislocations. The constrained cup has a locking ring that is intended to prevent the femoral cup from dislocating. When they do dislocate, they are essentially impossible to reduce using closed methods. **Because of the variability of implants and approaches, an attempt to contact the surgeon who performed the arthroplasty should be made prior to any reduction attempts.**

A review of 410 prosthetic hip dislocations reported that emergency physicians were successful at 79% of reductions in the ED, and orthopedists were successful at 71% of reductions in the ED—with no difference between emergency physicians and orthopedists in the proportion of successfully relocated hips in the ED and no difference in complications. The ED length of stay for ED-reduced prosthetic hip dislocations was about one third shorter than that for orthopedist-reduced dislocations. This study did not describe the types of prostheses reduced.[34]

SPECIAL CONSIDERATIONS

PAIN CONTROL

Patients with orthopedic injuries require early analgesia in the ED.[35] Any patient with suspected fracture should immediately receive pain medications. Consider a femoral nerve block as a nonopiate option (See Video: Femoral Nerve Block).

SPECIAL POPULATIONS

ATHLETES

Stress fractures of the femoral neck are a common cause of hip pain in athletes, particularly runners and football players. The onset of pain is often insidious and may mimic other conditions such as bursitis or muscle strain. Patients reporting persistent pain in the groin, medial thigh, or knee or having pain with ambulation should undergo MRI.[36] If imaging is not readily available, then the patient should be made non–weight bearing and told to avoid all athletic activities until orthopedic evaluation can be obtained (optimally in the next 48 hours).[37] Dislocation has also been described in professional athletes with a high rate of avascular necrosis.

ELDERLY PATIENTS

The majority of hip and femur injuries occur in the elderly. Consider elder abuse or self-neglect in patients with suspicious injuries. See Chapter 295, "Abuse of the Elderly and Impaired," for a detailed discussion of elder abuse.

Many older patients perceive these diagnoses as an end-of-life event. Emphasize that immobility and nonoperative management result in the majority of complications. Communication with family about potential loss of independence can allow for anticipatory planning. Appropriate early communication can alleviate patients' fears and facilitate compliance with physical therapy and rehabilitation, maximizing the potential for return to a preinjury quality of life.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 274

Knee Injuries

Rachel Bengtzen

ANATOMY

The knee consists of two joints, the tibiofemoral joint and the patellofemoral joint. Within the tibiofemoral joint, the distal femur (comprised of the medial and lateral femoral condyles) articulates with the proximal tibia (comprised of the medial and lateral tibial condyles) (**Figure 274-1**).

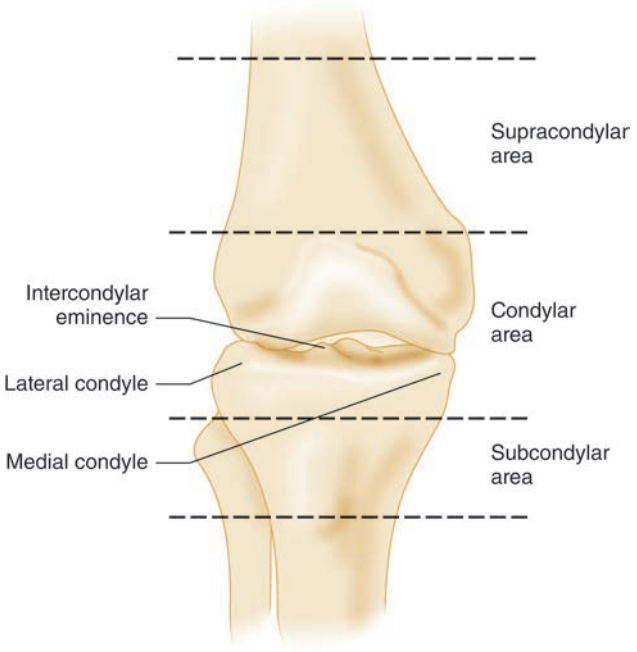

FIGURE 274-1. The supracondylar and condylar areas of the femur, and the medial and subcondylar areas of the tibia.

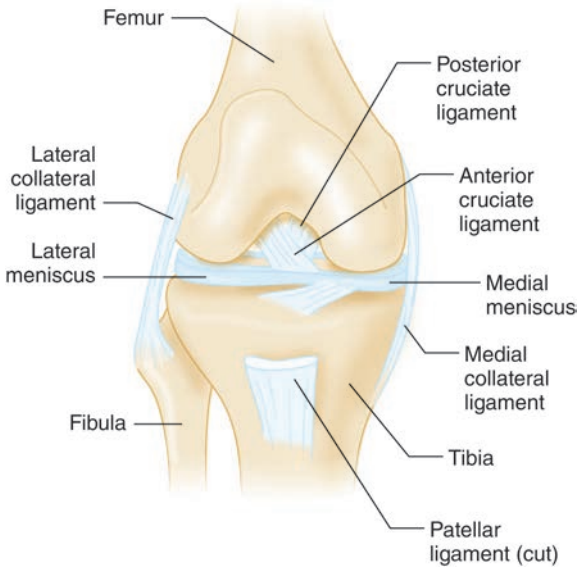

FIGURE 274-2. Ligaments of the right knee joint. The articular capsule and the patella have been removed.

The medial and lateral menisci are situated between the articular surfaces, and the menisci provide cushion, lubrication, and resistance to articular wear (**Figure 274-2**). In the patellofemoral joint, the patella articulates with the distal femur along the anterior depression called the patellofemoral groove during flexion and extension of the knee. The patella is stabilized by the patellar tendon and medial retinaculum.

There are four ligaments in the knee: the anterior cruciate ligament, the posterior cruciate ligament, and the medial and lateral collateral ligaments (Figure 274-2). These ligaments provide strength and stability to the knee. The posterior aspect of the knee, the popliteal fossa, contains the popliteal artery and vein, the common peroneal nerve, and the tibial nerve (**Figure 274-3**).

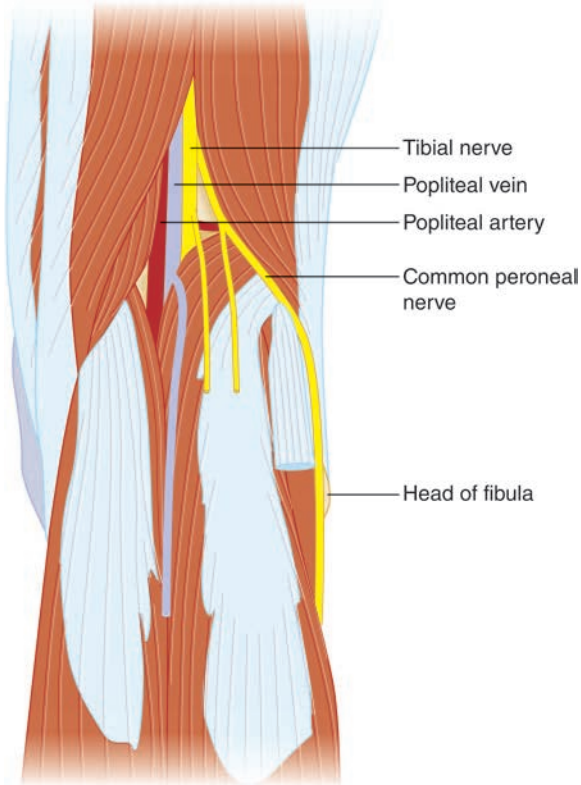

FIGURE 274-3. Posterior knee: popliteal fossa anatomy.

CLINICAL FEATURES

Determine the mechanism of knee injury and review all prior orthopedic injuries or surgical procedures. Compare contralateral noninjured or normal joint with the injured joint, especially during ligament stress testing.

The first examination is usually the easiest to perform and may be the most valid, as a patient's anticipatory pain or an effusion limiting the examination may not have yet developed.

Assess gait (if possible) and the ability to perform a straight leg raise (evaluates the extensor complex). Evaluate the knee for ecchymoses, swelling (extra-articular fluid), effusion (intra-articular fluid), masses, patella location and size, muscle mass, erythema, and evidence of local trauma. With the patient supine, determine whether leg lengths are equal or unequal. Ask the patient to demonstrate the best possible active range of motion. Assess distal neurovascular function. Palpate the nontender areas first and work toward the tender area to minimize patient apprehension. Include palpation of the patella, patellar facets, proximal fibula, and femoral and tibial condyles for pain and crepitus. Make note of joint effusion, tenderness, increased temperature, strength, sensation, and location of pulses.

Examine the patella for size, shape, and location with the knee in flexion. Assess patellar mobility with the knee in extension for lateral and medial movement without apprehension. Palpate the popliteal space for masses, swelling, and pulses. With the knee in flexion, palpate both the medial and lateral joint lines and the medial and lateral collateral ligaments, because tenderness at those locations suggests the possibility of a meniscal or ligamentous injury, respectively. The final phase of the examination of the knee is stress testing (see "Ligamentous and Meniscal Injuries" below) (See Video: The Knee Exam). The patient must be relaxed and made as comfortable as possible. Testing is often easier if the patient sits up with the leg hanging over the side of the bed and with the bed supporting the posterior thigh. Examine the uninjured, presumably normal, opposite knee first to determine the patient's normal laxity. Meniscus stress testing can include the McMurray test where the patient is supine with knee flexed to 90 degrees, and the examiner medially rotates the tibia and extends the knee stressing the lateral meniscus, and then repeats this laterally rotating the tibia and extending the knee again, stressing the medial meniscus. A positive test may elicit joint line pain or a painful click.

NEUROVASCULAR INJURIES

Popliteal artery injury can occur from fractures about the knee, especially femoral condyle fractures or displaced tibial plateau fractures, and from ligamentous injuries such as isolated posterior cruciate ligament injuries, multiple ligamentous injuries, or knee dislocation.[1-3] Popliteal artery circulation must be restored within 8 hours to avoid amputation, because collateral circulation is insufficient to maintain blood flow to the leg. Measure distal pulses on ED admission and after any manipulation, and compare pulses to those in the noninjured leg. A diminished pulse raises concern for vascular injury and should not be interpreted as vascular spasm. It is important to remember that vascular injury can be present even in the presence of normal pulses. Ancillary studies include measurement of ankle-brachial index and duplex US (reported to be 95% sensitive and 99% specific for arterial injury, but can miss small intimal tears).[1,3] Patients with normal pulses and an ankle-brachial index ≥0.9 can be observed (See Video: Ankle-Brachial Index). Vascular compromise is suspected in patients with abnormal palpable and Doppler pulses and/or ankle-brachial index <0.9 and warrants further vascular imaging and consultation. Vascular surgery consultation can aid in determining the need for CT angiogram versus on-table angiography and can help monitor for the development of compartment syndrome, venous injury, and arterial thrombosis.[3]

Peroneal nerve injuries (stretch or, less often, transection) can result from severe ligamentous knee injuries or knee dislocations. Nearly half of fibular head fractures or avulsions are associated with peroneal nerve injury. The deep peroneal nerve provides sensation to the first dorsal web space of the toes and allows dorsiflexion of the foot and extension of the toes. Injury results in foot drop and gait difficulty. Prognosis is variable, depending on the severity of injury.[3]

TABLE 274-1 Ottawa Knee Rules: Radiograph if One Criterion Is Met

- Patient age >55 y (rules have been validated for children 2–16 y of age)
- Tenderness at the head of the fibula
- Isolated tenderness of the patella
- Inability to flex knee to 90 degrees
- Inability to transfer weight for four steps both immediately after the injury and in the ED

DIAGNOSIS

IMAGING

The **Ottawa Knee Rules** (**Table 274-1**) (See Video: Ottawa Knee Rules) are sensitive in identifying a clinically significant fracture, and their use reduces ED waiting times and costs. The **Pittsburgh Knee Rules** (**Figure 274-4**) are similar and may have greater specificity.[4-7] Subsequent studies found barriers to implementation by physicians due to patient concerns or because specialists expect knee imaging.[5] It is reasonable to order radiographs on multisystem trauma patients with knee pain, especially those unable to undergo gait testing.

According to the most recent meta-analysis available, the Ottawa Knee Rules are valid for children >5 years old.[8] For further discussion of pediatric knee injuries, see Chapter 141, "Pediatric Orthopedic Emergencies."

Anteroposterior and lateral radiographs are typically obtained if radiographs are needed.[9] Fat-fluid levels (lipohemarthrosis; **Figure 274-5**) suggest intra-articular fracture and may be identified on a lateral view of the knee.[10] Consider weight-bearing radiographs when tolerated, which allows for a functional assessment. Additional radiograph views can be very useful. Oblique views are particularly helpful for detecting subtle tibial plateau fractures (internal oblique view is best for visualizing the lateral plateau, and external oblique view is best for visualizing the medial plateau).[9] A tunnel or intercondylar view provides a clear image of the intercondylar region and is particularly useful in identifying tibial spine fractures. A sunrise (skyline, axial, or tangential) view is most useful in detecting nondisplaced vertical or marginal fractures of the patella, which may be missed with the conventional views. The sunrise view is indicated if patellar subluxation or fracture is suspected. CT may be necessary to fully delineate the extent of tibial plateau fractures. MRI is also helpful in this regard and has the added benefit of being able to assess soft tissue (i.e., ligamentous and meniscal) injury.[9]

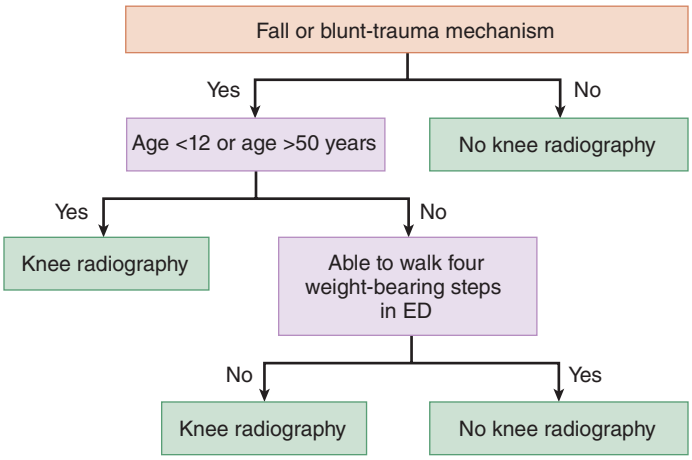

FIGURE 274-4. Pittsburgh Knee Rules for radiography. [Reproduced with permission from Seaberg DC, Yealy DM, Lukens T, et al: Multicenter comparison of two clinical decision rules for the use of radiography in acute, high-risk knee injuries. *Ann Emerg Med*. 1998;Jul;32(1):8-13. Copyright Elsevier.]

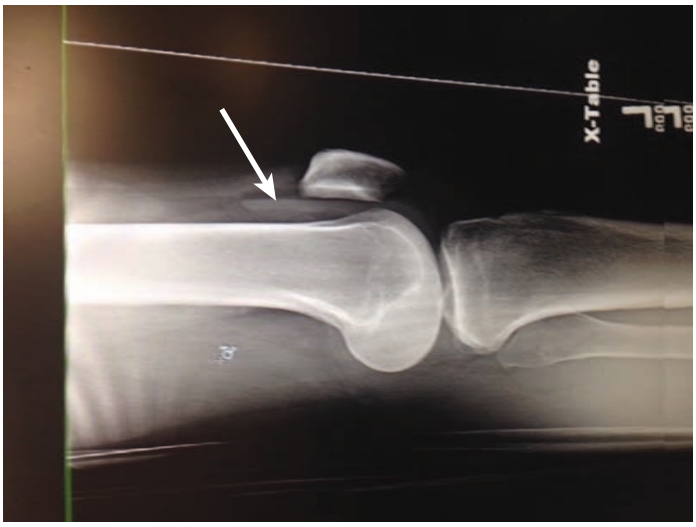

FIGURE 274-5. Lipohemarthrosis. Arrow points to lipid/blood interface.

SPECIFIC INJURIES

PATELLA FRACTURES

Table 274-2 reviews the mechanisms of injury and treatment of patellar fractures.[11-14] Patellar fractures may be transverse, comminuted, or of the avulsion type when the quadriceps or patellar tendon pulls off a small portion of the patella (**Figure 274-6**).

Transverse fractures of the patella are most common, followed by stellate and comminuted fractures. Patients with nondisplaced fractures may be ambulatory. On examination, there is focal patellar tenderness, swelling, and effusion. Check the integrity of the extensor mechanism of the knee by having the patient perform a straight-leg raise against gravity. Nonoperative management is indicated for fractures with an intact extensor mechanism and <2 mm of step-off and <3 mm of fracture displacement.[11,15] Transverse fractures are more likely to be displaced and to be associated with a disrupted extensor mechanism. Differential diagnosis of patellar fractures radiographically includes bipartite patella. This condition involves the superior lateral corner of the patella, is typically bilateral, and is differentiated from fracture by the smooth cortical margins.

FEMORAL CONDYLE FRACTURES

Fractures of the femoral condyles account for 6% of femur fractures and include supracondylar, intercondylar, condylar, and distal femoral epiphyseal fractures (Figure 274-1). Table 274-2 reviews the mechanisms of injury and treatment for femoral condyle fractures. Examination reveals pain, swelling, deformity, rotation, shortening, and an inability to ambulate. Although neurovascular injuries are uncommon, the potential for popliteal artery injury exists, so the status of distal sensation and pulses must be checked. Test the space between the first and second toes, innervated by the deep peroneal nerve, for sensation. In addition, search for associated injuries, including ipsilateral hip dislocation or fractures and damage to the quadriceps apparatus. The overall outcome of these injuries is fair. Complications include deep venous thrombosis, fat embolus syndrome, delayed union or malunion, and the subsequent development of osteoarthritis.[12,16]

TIBIAL SPINE AND TUBEROSITY FRACTURES

Isolated injuries of the tibial spine are uncommon; however, they usually result in cruciate ligament insufficiency. Table 274-2 reviews the mechanism of injury and treatment for tibial spine and tuberosity fractures. Fracture of the anterior tibial spine is about 10-fold more common than

TABLE 274-2 Mechanisms of Knee Injury and Treatment

Fracture	Mechanism	Treatment
Patella	Direct blow (i.e., fall, motor vehicle crash) or forceful contraction of quadriceps muscle	Nondisplaced fracture with intact extensor mechanism: knee immobilizer, rest, ice, analgesia. Follow-up for serial radiographs. Displaced >3 mm, articular incongruity >2 mm, or with disruption of extensor mechanism: above treatment plus early referral for ORIF.[11] Severely comminuted fracture: surgical debridement of small fragments and suturing of quadriceps and patellar tendons. Open fracture: irrigation and antistaphylococcal antibiotics in the ED; debridement and irrigation in the operating room.
Femoral condyles	Fall with axial load with valgus/varus/rotational forces, or a blow to the distal femur	Incomplete or nondisplaced fractures in any age group or stable impacted fractures in the elderly: long leg splinting and orthopedic referral. Displaced fractures or fractures with any degree of joint incongruity: splinting and orthopedic consult for ORIF.[12]
Tibial spines and tuberosity	Force directed against flexed proximal tibia in an anterior or posterior direction (i.e., motor vehicle crash, sporting injury)	Incomplete or nondisplaced fractures: immobilization in full extension (knee immobilizer) and orthopedic referral in 2–7 d. Complete or displaced fracture: early orthopedic referral, often requires ORIF.[13]
Tibial tuberosity	Sudden force to flexed knee with quadriceps contracted	Incomplete or small avulsion fracture: immobilization. Complete avulsion: ORIF.[11]
Tibial plateau	Valgus or varus forces combined with axial load that drives the femoral condyle into the tibia (i.e., fall, leg hit by car bumper)[14]	Nondisplaced, lateral fracture: knee immobilizer with non–weight bearing and orthopedic referral in 2–7 d. Depression of articular surface: early orthopedic consult for ORIF.[14]

Abbreviation: ORIF = open reduction internal fixation.

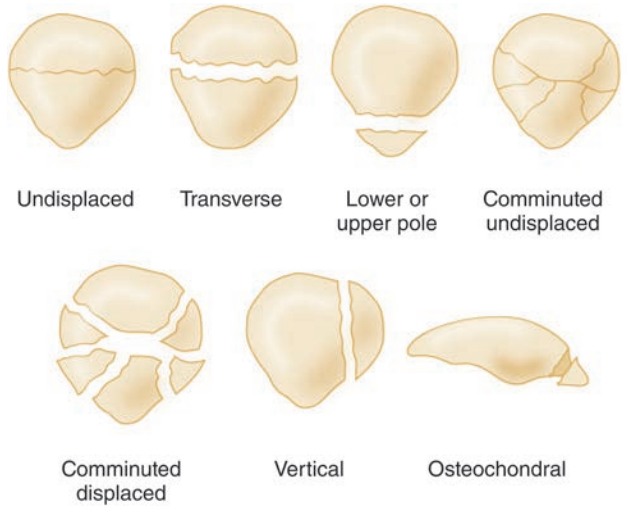

FIGURE 274-6. Classification of patellar fractures.

fracture of the posterior spine. Examination shows a painful, swollen knee secondary to hemarthrosis, inability to extend fully, and a positive finding on the Lachman test (see "Ligamentous and Meniscal Injuries" below).[13] The quadriceps mechanism inserts on the tibial tubercle. A sudden force to the flexed knee with the quadriceps muscle contracted may result in a complete or incomplete avulsion of the tibial tubercle. The fracture line may extend into the joint. Examination reveals pain and tenderness over the proximal anterior tibia with pain on passive or active extension.

TIBIAL PLATEAU FRACTURES

Fractures of the tibial plateau are seen more commonly in the older population and can be very difficult to detect.[17] Table 274-2 reviews the mechanism of injury and treatment for tibial plateau fractures. Both medial and lateral plateaus may be fractured simultaneously, although the lateral plateau is more often fractured.[14] Direct trauma to the lateral aspect of the knee may account for the preponderance of lateral tibial plateau fractures. The patient may experience painful swelling of the knee and limitation of motion. Radiographs may demonstrate a fracture, but often show only a lipohemarthrosis on the lateral view. Consider adding an anteroposterior view in the plane of the plateau (10 to 15 degrees caudal) or oblique views to help assess for displacement. If the patient cannot tolerate the additional views or there are negative radiographs but the patient cannot bear weight, consider obtaining a CT scan.[9] Soft tissue injuries associated with tibial plateau fractures may influence outcomes. Anterior cruciate ligament and medial collateral ligament injuries are associated with lateral plateau fractures, whereas posterior cruciate and lateral collateral ligament injuries occur with medial plateau fractures. A Segond's fracture (see below) is pathognomonic for an anterior cruciate ligament injury, and it is important recognize and treat the ligament injury, rather than just the plateau fracture.[14] Potential complications of tibial plateau fractures include popliteal artery injury with high-energy displaced fractures, the development of deep venous thrombosis, and osteoarthritis.

LIGAMENTOUS AND MENISCAL INJURIES

The knee joint depends on ligaments and muscles for support (Figure 274-2). It is frequently subjected to injuries from traumatic forces, including hyperextension, valgus and varus stresses, and anteroposterior displacement. By far the most common forces are valgus, which produce injuries to the medial side of the knee. Injuries to the lateral side of the knee are produced by varus stresses. Such forces may result in a strain or rupture of the medial or lateral collateral ligaments, the anterior or posterior cruciate ligaments, or the capsular structures, or a tear in the medial or lateral menisci. Functional instability of the knee can be determined by stress testing, which may demonstrate abnormal laxity. Functional stress testing assessment must be considered in the context of the composite history and complete physical exam as sensitivity and specificity of individual tests remain poor.[18-20]

MEDIAL COLLATERAL LIGAMENT AND LATERAL COLLATERAL LIGAMENT INJURIES

The medial stabilizers of the knee are tested by applying a valgus stress (**Figure 274-7**) to the knee at 0 degrees and in approximately 30 degrees of flexion to determine the integrity of the medial capsular and ligamentous structures. The medial collateral ligament supplies the majority of restraint to valgus deformities of the knee in all stages of flexion. A varus force is then applied to the lateral aspect of the knee to ascertain the integrity of the lateral structures. The lateral collateral ligament, analogous to the medial collateral ligament, is the major restraint to varus laxity on the knee at all positions of flexion. Injuries to these ligaments can include a strain, partial tear, or complete rupture. If there is no demonstrated laxity but the valgus or varus test reproduces pain, a grade 1 strain has likely occurred. If there is a laxity demonstrated without a firm end point compared with the other knee, this is concerning

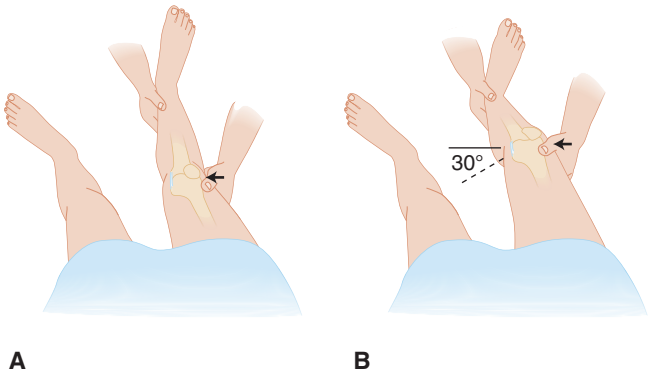

FIGURE 274-7. Valgus stress in full extension (**A**) and in 30 degrees of flexion (**B**).

for a complete tear of the medial or lateral collateral ligament. If there is laxity with the varus or valgus test performed with 30 degrees of flexion, similar maneuvers should be applied with the leg in full extension, if possible. Laxity to valgus stress while in full extension indicates a significant lesion involving the entire medial collateral ligament complex and/or in association with a cruciate ligament and posterior capsule tear.[19,21] Laxity to varus stress in full extension likewise indicates a significant injury that may involve the posterolateral corner of the knee as well as the cruciate ligaments. Peroneal nerve injuries may also occur in lateral injuries. Although these tests may aid in the diagnosis of medial collateral ligament and lateral collateral ligament injuries, there are no adequate published reports to allow comment on their sensitivity and specificity.[18,19]

ANTERIOR CRUCIATE LIGAMENT INJURIES

The mechanism of injury to the anterior cruciate ligament is usually noncontact—a deceleration, hyperextension, or marked internal rotation of the tibia on the femur resulting in an injury to this ligament. Injury is often associated with a "pop," swelling that develops within hours, and a sense of instability. The pop is considered pathognomonic for anterior cruciate ligament injury.[19] The history of this mechanism of injury combined with the presence of a traumatic effusion is very suggestive of an anterior cruciate ligament disruption.

The diagnosis of an anterior cruciate ligament injury is made using the **Lachman test** (**Figure 274-8**), the anterior drawer sign (**Figure 274-9**), and the pivot shift (**Figure 274-10**). The Lachman test is the most sensitive and specific test (81% for both).[19,22] For this test, the examiner places the knee in 30 degrees of flexion and stabilizes the femur above the knee with his or her nondominant hand. The dominant hand is placed grasping the lower leg at the level of the tibial tubercle, and the examiner introduces an anterior force, attempting to displace the tibia anteriorly on the femur. If a displacement compared with the opposite

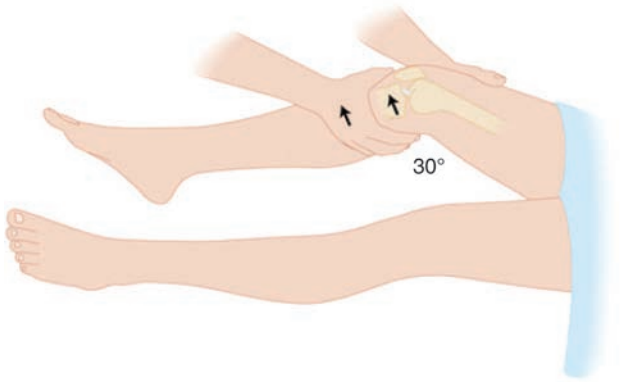

FIGURE 274-8. Lachman test, performed with the knee flexed between 15 and 30 degrees. One hand stabilizes the thigh, while the other moves the tibia anteriorly.

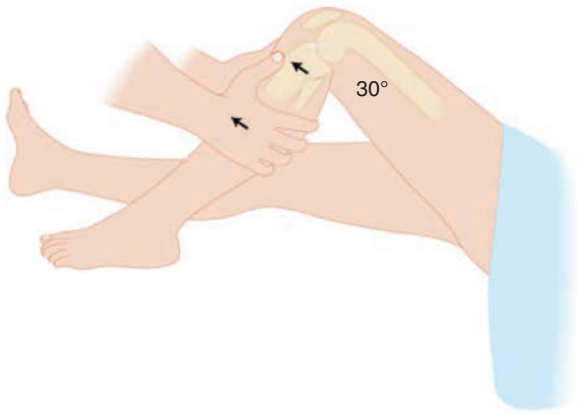

FIGURE 274-9. Anterior drawer test, performed with 45-degree flexion at the hip and a 90-degree flexion at the knee. Try to displace the tibia from the femur in an anterior direction.

knee is found, or if there is a soft end point, then a tear in the anterior cruciate ligament has occurred.

The **anterior drawer test** is only approximately 38% sensitive and 81% specific.[19,22] This maneuver is performed with a 45-degree flexion at the hip and a 90-degree flexion at the knee. Then, an attempt is made to displace the tibia from the femur in an anterior direction. A displacement of >6 mm compared with the normal, opposite knee indicates an injury to the anterior cruciate ligament. False-negative findings may be associated with this maneuver. False-positive results may occur when there is a posterior cruciate ligament tear as the tibia will start out in a more posterior position, thus allowing for a perceived increase in translation when moved anteriorly. Although the Lachman test is more sensitive than the anterior drawer test and is able to identify partial tears in the anterior cruciate ligament, it can be difficult to perform on patients with large legs.

The **pivot shift** (Figure 274-10) is the third maneuver by which the examiner can determine the integrity of the anterior cruciate ligament. The pivot shift may be painful to the patient and is often most easily tested under anesthesia in the operating room. The pivot shift test without anesthesia was found to be only 28% sensitive but 81% specific.[19,22,23] With the patient supine and relaxed, lift the heel of the foot to approximately 45 degrees of hip flexion with the knee fully extended. The opposite hand grasps the knee with the thumb behind the fibular head. Then internally rotate the ankle and knee, apply a valgus force to the knee, and flex the knee. If an anterior subluxation of the tibia is

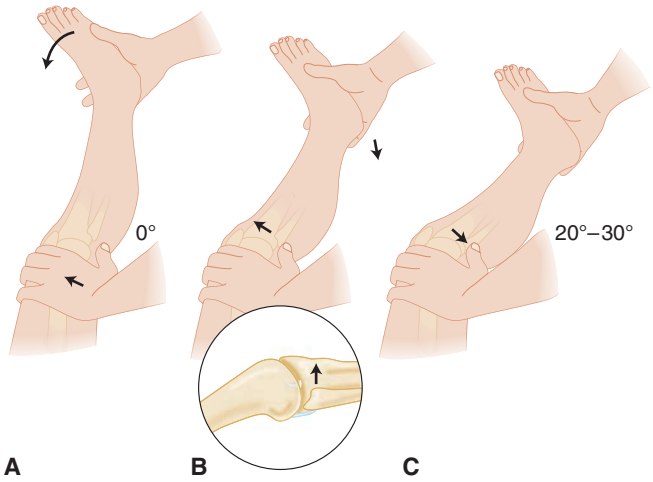

FIGURE 274-10. A-C. The pivot shift is done with the knee in full extension with application of valgus and internal rotation stress. The clunk of reduction is felt in the first 20 to 30 degrees of flexion.

present, a sudden visible, audible, and palpable reduction of the subluxation occurs at about 20 to 30 degrees of flexion. This indicates a deficit in the anterior cruciate ligament, which is required to stabilize the knee in this position. Other tests are described in the literature to determine the integrity of the anterior cruciate ligament, including the jerk test and dynamic extension testing.

POSTERIOR CRUCIATE LIGAMENT INJURIES

The posterior cruciate ligament can be injured in isolation or in combination with other ligamentous structures of the knee. In contrast to anterior cruciate ligament injuries, isolated posterior cruciate ligament injuries are much less common. The posterior cruciate ligament provides initial resistance to posterior translation at all angles of flexion of the knee. The mechanism of injury then is usually an anterior-to-posterior force applied to the tibia or lower leg. Nearly all posterior cruciate ligament injuries diagnosed in the ED are seen in association with other ligamentous injuries. A deficit of this ligament is identified by the posterior drawer test (**Figure 274-11**) and the sag sign. The posterior drawer test is performed with the knee and hip in flexion as described for the anterior drawer test. The physician applies a posterior force to the tibial tubercle. If there is displacement posteriorly, then the examiner can diagnose an injury to this ligament. One might also notice a sag sign, where there is a posterior sag or drop back of the tibial tubercle because of loss of integrity of the posterior cruciate ligament when observing the knee with 45-degree flexion at the hip and 90-degree flexion at the knee. Results of this test can be misleading, however, if there is a straight anterior instability resulting in a subluxation of the knee forward. This abnormal position gives the false impression of too much posterior play when the posterior drawer test is performed, because the knee is reduced to its normal anatomic alignment from the forwardly subluxed position. Although the posterior drawer test has only a 55% sensitivity, the composite history and physical examination findings are much more accurate in the diagnosis of posterior cruciate ligament injuries.[18,19,24]

Combined ligamentous laxity of the knee is often seen, especially in acute athletic injuries. Combined anteromedial and anterolateral laxity occurs most frequently, but virtually any combination of medial and lateral laxity of the knee can occur.

POSTEROLATERAL INJURY

One knee injury that is especially difficult to detect is injury to the posterolateral structures. Posterolateral instability usually involves a tear of the popliteus–arcuate complex, which may occur in combination with lateral ligament injury and possible anterior cruciate ligament or posterior cruciate ligament injury. Isolated injuries to the popliteus–arcuate complex are rare. Isolated posterolateral instability is demonstrated by testing at 0 to 30 degrees of flexion for maximal posterior translation and at 90 degrees of flexion for maximal external rotation compared with that of the normal opposite knee. Further testing to determine the integrity of the lateral collateral ligament and anterior or posterior cruciate ligaments must be done as well.

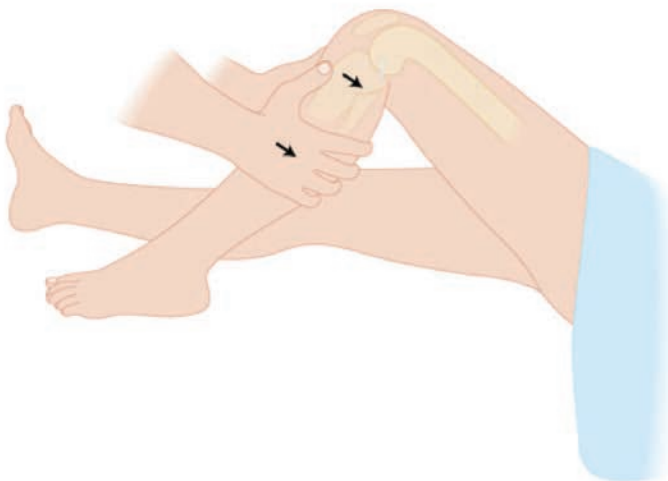

FIGURE 274-11. Posterior drawer test.

HEMARTHROSIS OR EFFUSION

The presence of a hemarthrosis can suggest an underlying ligamentous injury to the knee (most commonly the anterior cruciate ligament), fracture, meniscus tear, osteoarthritis flare, or loose body. Serious ligament injuries, however, may present with minimal pain and no hemarthrosis because of complete disruption of the ligamentous and capsular fibers, which allows leakage of the blood into the soft tissue spaces. Hemarthrosis can also be caused by osteochondral fractures or fractures that extend into the joint line, or peripheral meniscal tears. Traumatic hemarthroses usually occur within minutes to hours of injury, in contrast to chronic effusions of the knee due to synovial inflammation, which occur 1 to 2 days after strenuous use of the joint.

With ligamentous injuries, plain radiographs are typically normal or reveal only an effusion. An avulsion fracture at the site of attachment of the lateral capsular ligament on the lateral tibial condyle (Segond's fracture)[25] is a marker for anterior cruciate ligament rupture.[5,14] Cortical avulsion of the medial tibial plateau (very uncommon) is associated with tears of the posterior cruciate ligament and medial meniscus.[25] Continued refinements in MRI have enabled this imaging method to produce high-quality images of the ligamentous and meniscal structures of the knee, which results in an accuracy rate of close to 90% to 95% in identifying meniscal and cruciate ligament disruption.[26] Such an MRI examination, however, is typically ordered by the patient's primary care provider, sports medicine physician, or orthopedist in follow-up.

TREATMENT OF SPECIFIC INJURIES

LIGAMENTOUS INJURIES

Injuries involving a single ligament with a minor strain can be managed with a simple neoprene hinged brace (available over the counter), ice packs, elevation, NSAIDs, and ambulation as soon as is comfortable for the patient.[27] Contractures are more common in the elderly and can occur after only a few days of immobilization. Although there is no universally accepted regimen for range-of-motion exercise, one procedure is first to apply ice to relieve pain and then to perform 10 to 20 knee flexion-extensions (no weights should be added) three or four times a day. Refer patients to an orthopedic surgeon, sports medicine physician, or primary care provider within the next few days to a week for follow-up examination.

Complete rupture of an isolated ligament can initially be treated conservatively in the same fashion, with straight leg quadriceps strengthening, range-of-motion exercises, and functional bracing (knee immobilizer or t-scope hinged brace if available) included as a part of the follow-up care. When knee immobilizers are placed, instruct the patient to perform daily range-of-motion exercises to avoid contracture and maintain mobility and reassess need within about 1 week as an outpatient. Professional athletes with single-ligament ruptures or patients with more than one torn ligament need urgent orthopedic consultation so that definitive surgical management can be planned.

Arthrocentesis may be of therapeutic benefit in patients with large, tense effusions of the knee; however, good evidence of its efficacy has not been reported (See Video: Knee Arthrocentesis).[28] Furthermore, recurrence of the effusion following aspiration is common. Arthrocentesis may be of assistance diagnostically if the effusion is not clearly due to trauma. The presence of blood and glistening fat globules is pathognomonic of lipohemarthrosis, which indicates intra-articular knee fracture. Aspiration is also used to assess for a septic joint. In instance of clinical suspicion of an effusion, but a drip tap, point-of-care ultrasound can be used to confirm the needle is within hypoechoic intra-articular fluid, rather than

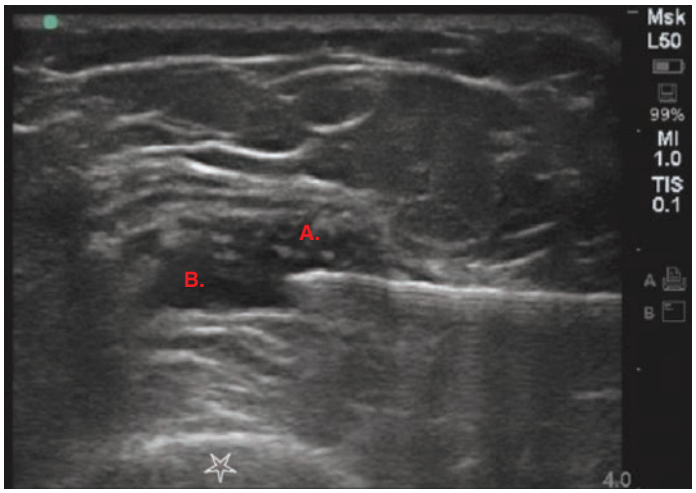

FIGURE 274-12. Linear probe short axis view proximal to patella, with needle tip (*A*) within hypoechoic knee effusion (*B*). *Star* depicts the femur.

performing repeated needle placement attempts (**Figure 274-12**). The major complication of arthrocentesis is inducing septic arthritis.

MENISCAL INJURIES

Meniscal injuries of the knee occur by themselves or in combination with ligamentous injuries. For example, anterior cruciate ligament injuries are commonly associated with meniscal injuries. Cutting, squatting, or twisting maneuvers may cause injury to the meniscus. The medial meniscus is approximately twice as likely as the lateral meniscus to be injured. Many of the tears involve the peripheral posterior aspect of the meniscus. Many maneuvers have been described in the literature to determine whether a meniscus has been injured. However, most maneuvers have an unacceptable sensitivity and specificity (e.g., joint line tenderness has a sensitivity of 70% and specificity of 15% in the ED population).[18] Although the diagnosis of a meniscal tear is difficult to make in certain patients, the combination of a suggestive history and physical findings on examination should lead one to consider the diagnosis. Ask if the patient experiences painful locking of the knee joint on either flexion or extension and if this limits further activity. This sign clearly points to the diagnosis of a torn meniscus. Other signs of a meniscal tear include effusions that occur after activity; a sensation of popping, clicking, or snapping; a feeling of instability in the joint, especially with activity; and tenderness in the anterior joint space after excessive activity.

At physical examination, attempt to identify atrophy of the quadriceps muscle as a result of disuse and joint-line tenderness. Various maneuvers, such as the McMurray test, have been described but yield positive results only about 50% of the time.[18,19,29] If a tentative diagnosis of a meniscal tear is considered, refer to an orthopedic surgeon or the patient's primary care provider and instruct partial weight bearing, as tolerated. Definitive diagnosis can be made by MRI or arthroscopy, with the latter also allowing for definitive surgical treatment (usually partial meniscectomy or meniscal repair).

LOCKED KNEE

The "locked knee" describes when a knee cannot actively or passively fully extend. A patient who presents to the ED with a locked knee can experience a great deal of pain along with loss of mobility. The most common cause of an acutely locked knee is a torn meniscus. The differential diagnosis also includes anterior cruciate ligament rupture, patella dislocation, loose bodies, or foreign body. Historically the treatment includes one attempt at closed reduction under procedural sedation. After procedural sedation is initiated, one can attempt to unlock the knee. Position the patient with the leg hanging over the edge of the table and the knee in 90 degrees of flexion. After a period of relaxation, apply longitudinal traction to the knee, along with internal and external rotation, in an attempt to unlock the joint. If this maneuver is unsuccessful, orthopedic consultation for operative arthroscopy is indicated. If the unlocking is successful, referral to an orthopedist for MRI and/or arthroscopy is appropriate.[30]

KNEE DISLOCATION

Knee dislocation (**Figure 274-13**) primarily occurs in younger male populations. It is a result of tremendous ligamentous disruption due to either high-velocity mechanisms (motor vehicle crashes, fall from height) or low-velocity mechanisms (martial arts, walking, or trampoline falls); dislocations can also occur spontaneously in morbidly obese patients.[1,3,31] An anterior dislocation is most common, occurring about 40% of the time, with posterior dislocations (33%), lateral dislocations (18%), medial dislocations (4%), and rotary dislocations also occurring.[2,31] Due to severe ligamentous damage, spontaneous reduction occurs in up to 50% of knee dislocations.[2,3] Therefore, **a severely injured knee that is unstable in multiple directions raises suspicion of a spontaneously reduced knee dislocation.** Maintaining awareness of the possibility of this injury is important because of the high incidence of associated complications, including popliteal artery injury and peroneal nerve injury (mostly with posterolateral dislocations), in addition to ligamentous and meniscal injury.

Timely reduction of the dislocated knee is essential. Apply longitudinal traction to the affected knee. Document neurovascular status of the extremity before and after reduction. **Splint the lower extremity with the knee at 20 degrees of flexion after dislocation reduction,** in a manner that allows for serial vascular examinations. Reimage after splint application. Hospitalization is required along with emergent orthopedic

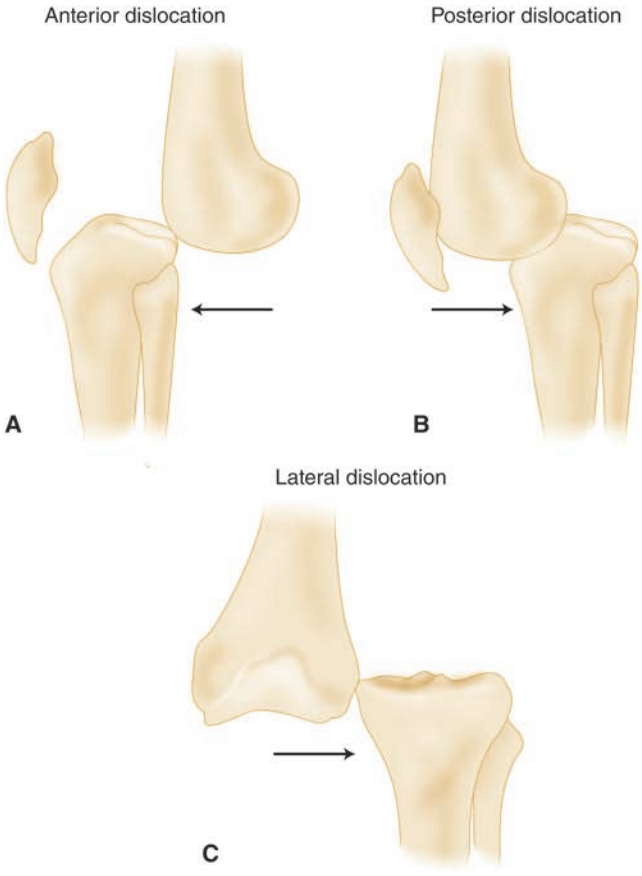

FIGURE 274-13. Types of knee dislocation: anterior (**A**), posterior (**B**), and lateral (**C**).

and vascular surgery consultation. If the patient is neurovascularly intact and vascular and/or orthopedic surgery consultation is unavailable, then transfer the patient prior to reduction to the nearest hospital with those clinical services. Timely reduction can occur at that time.

Historically, arteriography was recommended for all patients with confirmed knee dislocations since there is a high incidence of popliteal artery injury (up to one third of patients) and poor outcomes associated with delays in vascular reconstruction.[1,32] Current recommendations include serial neurovascular exams and performing ankle-brachial index (see Chapter 61, "Arterial Occlusion") (See Video: Ankle-Brachial Index). Patients with distal pulses present before and after reduction and an ankle-brachial index ≥0.9 can be observed with serial neurovascular checks over 24 hours. The orthopedist may want a CT angiogram prior to ligamentous reconstruction. **For patients in whom distal pulses are asymmetric, the ankle-brachial index is <0.9, or there is any other clinical concern of vascular injury (including ischemia, hemorrhage, or an expanding hematoma), proceed with CT angiogram or angiography.** Patients with absent pulses before reduction with a return of a pulse after reduction need measurement of an ankle-brachial index and emergent vascular surgery consultation. Patients with an open knee dislocation, absent distal pulses after reduction, or any other signs of vascular injury, as above, need emergent vascular surgery consultation for surgical exploration and possible angiography in the operating room.[3,31]

PATELLAR DISLOCATION

Dislocation of the patella usually occurs from a twisting injury to the extended knee. The patella is displaced most commonly laterally over the lateral condyle, which results in pain and deformity of the knee (**Figure 274-14**). Tearing of the medial knee joint capsule often occurs.



FIGURE 274-14. Lateral dislocation of the right patella. [Photo contributed by Rob Hendrickson, MD, and Michael Martinez, MD.]

Reduction is accomplished with adequate analgesia then by flexing the hip, gently extending the knee, and guiding the patella back into place. This results in immediate relief of pain; however, caution patients that they will have residual soreness from the medial patellofemoral retinacular tissue injury. Obtain radiographs of the patella and knee to exclude a fracture, and place a knee immobilizer after reduction and provide crutches. Give instructions for partial weight bearing and straight leg raises to strengthen the quadriceps. Arrange follow-up with an orthopedist within 1 week. Recurrent lateral dislocation of the patella occurs in approximately 15% of patients, and superior, horizontal, and intercondylar dislocations require referral to an orthopedic surgeon for possible surgical intervention.[5]

In the case of irreducible patellar dislocation, surgical correction is needed. Clues that a patient may have an irreducible patellar dislocation include older age, preexisting patellofemoral arthritis, flexion of <45 degrees, anterolateral (rather than pure lateral) patellar position, and internal rotation of the patellar axis.[33]

QUADRICEPS OR PATELLAR TENDON RUPTURE

Rupture of the quadriceps or patellar tendons can occur from forceful contraction of the quadriceps muscle or falling on a flexed knee. Quadriceps tendon rupture is most frequent in those >40 years of age. Patellar tendon rupture occurs most commonly in individuals <40 years of age. A history of tendinitis or past oral or injected steroid use can increase risk of rupture.[11] Quadriceps or patellar tendon rupture disrupts the extensor mechanism of the knee. There is severe pain and diffuse swelling, and the patient is unable to do a straight leg raise, actively extend the knee, or maintain a passively extended knee against gravity in both types of tendon rupture. Depending on the tendon ruptured, a defect may be palpable proximal or distal to the patella. **Figure 274-15** shows a quadriceps tendon rupture. A high-riding patella (patella alta) may be seen on a lateral radiograph of the knee in the setting of a patellar tendon rupture (**Figure 274-16**). Bedside point-of-care ultrasound using a high-frequency linear transducer can be used to visualize and diagnose a quadriceps or patella tendon rupture (**Figure 274-17**). The treatment of a complete tear is surgical repair of the involved tendon. Orthopedic consultation in the ED is indicated. Incomplete tears with an intact extensor mechanism can be treated with immobilization and close follow-up.[11]

PATELLAR TENDINITIS

Also known as jumper's knee, patellar tendinitis is primarily seen in runners, high jumpers, and basketball and volleyball players. Pain is located at the patellar tendon and is worsened when going from sitting



FIGURE 274-15. Quadriceps tendon rupture. Note the defect above the patella and prominence of the proximal edge of the patella. [Photo contributed by the Department of Emergency Medicine, Feinberg School of Medicine, Northwestern University.]



FIGURE 274-16. Patella alta.

to standing, jumping, or running up hills. Evaluate the extensor mechanism to rule out tendon rupture. Point tenderness can be found at the distal aspect of the patella or proximal part of the patellar tendon. Treatment consists of NSAIDs, eccentric quadriceps-strengthening exercises, and activity modification. Steroid injections predispose to tendon rupture and thus should be avoided.

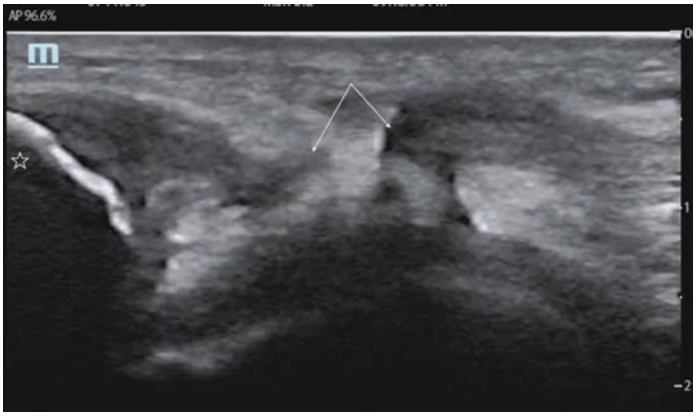

FIGURE 274-17. Patella tendon rupture on ultrasound (high-frequency linear probe). Tendon remnant ends located at *arrows*. *Star* denotes patella. [Photo contributed of Dr. Craig Rudy and Dr. Bryson Hicks.]

POSTARTHROSCOPY PROBLEMS

Patients may present to the ED following arthroscopy because of pain and swelling. Effusions are common after arthroscopy, but joint infection is very uncommon. Perform diagnostic arthrocentesis if joint infection is suspected. Arthrocentesis and then injection of bupivacaine may be helpful therapeutically for large, tense effusions.

POSTARTHROPLASTY PROBLEMS

Over 1 million total hip and knee joint arthroplasties are performed annually in the United States. Approximately 9.3% of patients who undergo elective total knee replacements visit the ED at least once within 90 days after discharge; readmission rates are around 5%. Leading causes for ED visits include pain, injuries, dislocation, deep vein thrombosis, cardiopulmonary events, physiologic decompensation, and infection (surgical site or elsewhere).[34-36] Assess with radiographs (anteroposterior, lateral, and axial patella views). If infection is suspected, obtain laboratory testing for erythrocyte sedimentation rate, C-reactive protein, and synovial fluid evaluation. Gram stain has low sensitivity and specificity; a leukocyte count >2500/mm^3 and >60% polymorphonuclear leukocytes have a higher sensitivity and specificity for infection.[37] Dislocation of total knee arthroplasty is rare. When it occurs, complications are as above with native knee dislocations, with particular risk of associated neurovascular injury. Data are limited, but risk factors appear to be obesity, female sex, and presence of other neuromuscular problems. Total knee arthroplasty dislocations are managed initially with closed reduction, although there is a high rate of redislocation without subsequent operative repair.[38]

PENETRATING KNEE INJURY AND JOINT FOREIGN BODIES

The history should elicit information to re-create the position of the knee when the penetrating injury occurred. Many occupational injuries occur with the knee flexed, and failure to appreciate the trajectory of injury with the knee flexed can lead to misdiagnosis and failure to anticipate joint penetration. Management of lacerations in proximity to joint spaces is discussed in Chapter 44, "Thigh, Leg, and Foot Lacerations."

If a wound is periarticular, assess the integrity of the joint capsule, as joint involvement can lead to developing septic arthritis. One study found that open knee joint injuries had a mean periarticular wound size of approximately 4 cm and an infection rate ranging from 0% to 11.8%. CT scans can be useful if they detect intra-articular air; however, other diagnostic modalities such as the saline load test may be used initially. Perform the saline load test by injecting sterile saline into the joint where a penetrating injury is suspected, and assess for extravasation of the saline from the periarticular wound. Failure of extravasation is a negative saline load test. The traditional injection volume of the knee had been 60 mL; however, data suggest that load volumes of 155 and 194 mL help achieve a sensitivity of 95%. There was no added benefit of using methylene blue.[39]

Radiopaque foreign bodies (i.e., metal, glass) can be visualized on conventional radiographs. In general, foreign bodies in the knee joint need to be removed. A bullet in the joint can injure the cartilage and cruciate ligaments, and lead poisoning can occur. Antibiotics to cover streptococci and staphylococci are generally indicated for both penetrating knee wounds and foreign bodies. Administer tetanus prophylaxis as indicated.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 275

Leg Injuries

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ANATOMY

BONE

The tibia provides primary support for weight bearing. The tibia has a thick cortex, and significant force is required to fracture it. Proximally, the tibia splays out to form the medial and lateral plateaus that articulate with the femoral condyles. The lateral plateau is higher and smaller than the medial and is more susceptible to fracture. The distal tibia articulates with the fibula laterally and the talus inferiorly. A dense interosseous membrane connects the tibia and fibula. The distal tibial articulation is supported by the ankle syndesmosis, a series of ligaments inferior to the interosseous membrane. The fibula has a small diameter and lies lateral and posterior to the tibia. It bears little weight but is more easily fractured than the tibia.

COMPARTMENTS

The lower leg is divided into four compartments, each coursing parallel to the tibia (**Figure 275-1**). The compartments are enclosed by nonexpandable bones and connective tissue that limit the compartment size and prevent compartment expansion if its volume increases. Each compartment contains muscles and nerves that may sustain permanent damage with elevated tissue compartment pressure (**Table 275-1**). (See also Chapter 278, "Compartment Syndromes.")

A cross-section at the midcalf level shows the anterior compartment enclosed by the tibia, interosseous membrane, and anterior crural septum (Table 275-1 and Figure 275-1). Muscles in the anterior compartment group dorsiflex the foot and ankle. The deep peroneal nerve courses within the anterior compartment and exits to provide sensation to the dorsal web space between the first and second toes.

The lateral compartment is bordered by the anterior crural septum, the fibula, and the posterior crural septum. Its muscles plantarflex and evert the foot. The superficial peroneal nerve in this compartment provides sensation to the dorsum of the foot. The superficial posterior compartment contains muscles that flex the knee and the tibiotalar joints. Its sural nerve provides sensation for the lateral aspect of the foot and the distal calf. The muscles of the deep posterior compartment plantarflex the foot and toes and invert the foot. The posterior tibial nerve that exits this compartment provides sensation to the sole of the foot.

CLINICAL FEATURES

The history may give clues about the mechanism of injury and atraumatic soft tissue injuries. Evaluate the nerves by checking sensation in the web space, lateral heel, and sole of the foot. Plantarflex and dorsiflex the foot, and evert the foot to test motor function. Evaluate the extent of soft tissue injury visually and by palpating the compartmental muscle groups. It is often the extent of soft tissue injury, rather than the fracture itself, that determines the outcome. Palpate the knee, and the tibia and fibula along their entire lengths. Palpate the popliteal, dorsal pedal, and posterior tibial pulses. An absent or decreased pulse may indicate the need for urgent fracture reduction and further vascular evaluation.

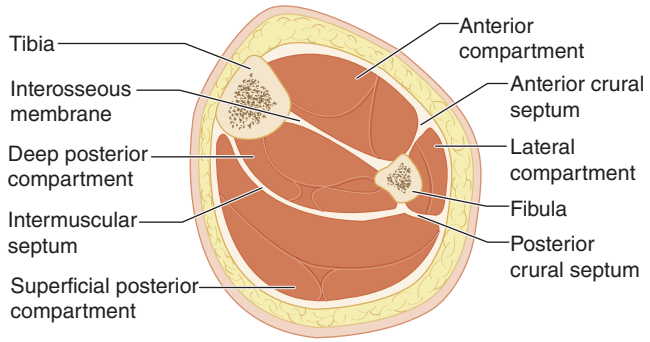


FIGURE 275-1. Lower leg anatomy.

TABLE 275-1 Lower Leg Anatomy

	Compartments			
	Anterior	Lateral	Superficial Posterior	Deep Posterior
Muscles	Dorsiflex foot and ankle	Plantarflex and evert foot	Flex knee and ankle	Plantarflex toes, inversion of foot
Nerve	Deep peroneal	Superficial peroneal	Sural	Posterior tibial
Sensation	First dorsal web space	Dorsum of foot	Lateral aspect of foot and distal calf	Sole of foot
Artery	Anterior tibial	—	—	Posterior tibial

DIAGNOSIS

Anteroposterior and lateral radiographs of the leg that include the knee and ankle are sufficient to evaluate bony injuries. If ankle or knee injuries are suspected, then further imaging is needed. If a tibial shaft fracture is suspected, splint the leg with a radiolucent device to control pain and prevent further soft tissue damage before obtaining films. Check pulses, movement, and sensation before and after splinting the leg.

TREATMENT

Cleanse wounds and debride loose tissue and foreign material. Administer tetanus immunization as indicated. Splint fractures before obtaining radiographs; this will prevent further damage to soft tissue caused by movement of bone fragments. Irrigate open wounds and administer parenteral antibiotics (such as cefazolin, 1 gram IV) for open fractures. If compartment syndrome is suspected, measure compartment pressure (see Chapter 278, "Compartment Syndromes"). Treatment of compartment syndrome is fasciotomy of the involved compartment.

COMPLICATIONS

Wounds that are not adequately cleansed and debrided are prone to infection. Patients with compartment syndromes may develop permanent disability if elevated tissue pressures are not suspected or diagnosed in a timely fashion. Fractures that are not adequately aligned or immobilized heal poorly or not at all.

SPECIFIC INJURIES

TIBIAL SHAFT FRACTURES

The tibia is the most commonly fractured long bone. Fractures often result in open injuries because of the minimal amount of subcutaneous tissue between the tibia and the skin. The fracture pattern seen on radiographs will give a clue to the force that caused the injury. Transverse shaft fractures typically result from a direct blow to the bone. Spiral fractures are the result of rotational forces. A comminuted fracture suggests the mechanism had a very high-energy impact. A force powerful enough to shatter the dense cortex of the tibial shaft will often be transmitted through the interosseous membrane to the fibula, fracturing that bone as well.

A major determinant of treatment type and expected outcome is the amount of energy that caused the fracture. High-energy injuries can be predicted somewhat by the history (i.e., low-energy boot-top ski

TABLE 275-2 Gustilo Classification of Open Tibia Shaft Fractures

	Gustilo Grade				
	I	II	IIIA	IIIB	IIIC
Energy	Low	Moderate	High	High	High
Wound size	<1 cm	>1 cm	Often large zone of injury	Often large zone of injury	Often large zone of injury
Soft tissue damage	None	None	Extensive	Extensive	Extensive
Contamination	Clean	Moderate	Extensive	Extensive	Extensive
Fracture pattern	Simple fracture pattern with minimal comminution	Moderate comminution	Severe comminution or segmental fractures	Severe comminution or segmental fractures	Severe comminution or segmental fractures
Periosteal stripping	No	No	Yes	Yes	Yes
Skin coverage	Local coverage	Local coverage	Local coverage	Requires replacement of exposed bone with a free flap for coverage	Local coverage
Neurovascular injury	Normal	Normal	Normal	Normal	Exposed fracture with arterial damage that requires repair

injury vs. high-energy motorcycle collision). The amount of energy involved can also be revealed by the fracture pattern on the radiograph. Low-energy accidents often result in transverse or oblique fracture lines, whereas a high-energy accident may cause a comminuted fracture. On physical exam, the amount of damage to the skin and soft tissue is important.

Table 275-2 reviews the pattern of injury found in open fractures of the tibia.[1]

This system is used to optimize management. A type I open fracture describes a break in the skin that is less than 1 cm in length. A type II open fracture has a laceration that is 1 to 10 cm in length without extensive soft tissue damage, flaps, or avulsions. The fracture pattern here shows simple transverse fractures or short oblique fractures with minimal comminution.

Type III injuries are further subdivided into three subtypes. Type IIIA involves segmental fractures or severely comminuted fracture fragments. Type IIIB injuries demonstrate extensive soft tissue loss with periosteal stripping and bony exposure. A type IIIC injury has extensive fracture with major arterial injury requiring repair.

The initial management of tibial fractures involves administration of analgesics. Promptly splint the leg with radiolucent material to avoid further soft tissue injury from the movement of the bony fragments. Assess for possible compartment syndrome. Some closed injuries may be treated simply by casting if reduction is able to achieve adequate alignment. Parameters for acceptable reduction include 50% or more of cortical contact, <10 to 15 degrees of angulation on the lateral film, <10 degrees of angulation on the anteroposterior film, and <5 degrees of rotational deformity.[2] Injuries with significant edema and spiral fractures often require surgical fixation. An intact fibula may make obtaining or maintaining reduction of the tibial fracture more difficult.

A *long leg splint* from high above the knee with the knee at 5 degrees of flexion and the foot in slight plantarflexion can be applied. **Tight-fitting splints or casts may increase the risk of compartment syndrome.** Injuries amenable to casting often heal in 4 to 5 months.

Patients who can be discharged home after splinting include those who suffered low-energy injuries, have their pain well controlled, and are not at risk of compartment syndrome.

The patient with an open tibial fracture requires orthopedic consultation. Injuries with type I soft tissue damage may be cleaned in the operating room and medullary nails inserted to maintain reduction. Those with more extensive injuries may require external fixation or medullary nailing after debridement in the operating room.

REDUCTION OF CLOSED TIBIAL SHAFT FRACTURES

With many tibial shaft fractures, the break extends through the entire cortex of the bone, but the periosteum is intact on one side of the fracture. Use of this sturdy periosteal tether can aid in reduction of the fracture. One method of immobilization of long bone fractures incorporates the presence of this intact periosteal hinge and the use of three points of pressure on the shaft of the bone. One focus of pressure is at the site of the fracture, with the pressure being applied from the side opposite the intact periosteum (**Figure 275-2**). Two additional sites of pressure are applied, one at the proximal tibia and the other at the distal end of the tibia. These two forces are applied from the opposite direction of the pressure at the fracture site. This three-point immobilization technique does not always succeed in maintaining the reduction. If the fracture site is near the proximal or distal ends of the tibial shaft, it may be difficult to mold a splint or cast that can effectively transmit the forces needed. Obesity may make molding difficult. If there is a significant amount of swelling already present, or if edema is anticipated in the next several days, then a cast should not be placed as it may result in elevated pressures in the soft tissue and subsequent compartment syndrome. In these settings, splints should be used with elastic bandages that are able to accommodate the increased swelling. A cast can later be placed in the office of the orthopedist.

There are several fractures that may require operative treatment. Open fractures that have concomitant soft tissue damage and swelling can be difficult to adequately control in a cast. In addition, continued care of the soft tissue injury may require multiple cast or splint changes.

A second indication for surgical intervention is an inability to obtain or maintain adequate reduction with a closed technique. Many orthopedists use the following parameters as a guide for adequate reduction: (1) >50% abutment of the fractured complex; (2) angulation of <5 degrees on the anteroposterior film; and (3) <5 degrees of rotation of the distal tibia in comparison to the proximal fragment.

The presence of an intact fibula may be an indication for operative fixation. When the fibula is intact, it often leads to bowing of the tibia into a varus or valgus position.

PILON FRACTURES

Pilon is a French word for pestle, a tool used to grind substance in a mortar. In the lower leg, an axial force on the foot can drive the talus into the articular surface of the tibia, grinding or crushing the distal tibia. This injury is also called a *tibial plafond fracture* (**Figure 275-3**).

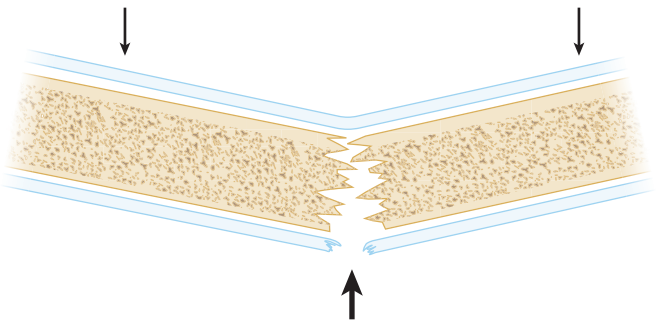


FIGURE 275-2. Periosteal hinge.



FIGURE 275-3. Plafond fracture. Tibial plafond fracture (pilon fracture) due to an axial compression force. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities*, 5th ed. © The McGraw-Hill Companies. All rights reserved. Part III: Lower Extremities, Chapter 17 Ankle, Fractures, Axial Compression, Imaging, Figure 17-24.]

The amount of energy involved in the accident often predicts the type of injury and is important in planning treatment. A high-energy mechanism (motor vehicle crash) often results in significant soft tissue damage with extensive fragmentation of the bone. By contrast, low-energy injuries (skiing) have minimal surrounding soft tissue damage and less comminution of the bone. Radiographs may show at least one fracture plane that extends proximally from the articular surface of the ankle. There are often several fracture planes present. Obtain a CT scan while the leg is in a splint or cast. The scan will help determine the direction of the fracture planes, reveal the amount of articular surface displacement that exists, and aid in the development of a treatment plan. **Pilon fractures may be accompanied by compartment syndrome or by vertebral body fractures, particularly a fracture of the first lumbar vertebrae (L1).**[3]

The goal of treatment is reduction of the fracture fragment and optimal alignment of the articular surfaces. The extent of soft tissue damage may determine when surgical repair occurs. In the setting of significant soft tissue damage, an external fixation device may temporarily be used to allow this tissue time to heal before definitive surgery.

PROXIMAL FIBULA FRACTURE (MAISONNEUVE FRACTURE)

Maisonneuve fracture results from an external rotation force applied to the foot. This creates a plane of injury that starts at the medial ankle as either a deltoid ligament rupture or a medial malleolus injury. The injury is then directed upward and laterally, tearing the interosseous membrane that tethers the distal tibia to the fibula. The third component of this injury is a fracture of the proximal fibula. The word *proximal* is relative; the fibula may be fractured at its head or as far down as 6 cm above the ankle joint (a Weber C ankle fracture).

The surgical treatment for this injury is to reduce and stabilize the fractured medial malleolus and to secure the fibula to the distal tibia, allowing the ruptured interosseous membrane to heal.

MIDSHAFT FIBULA FRACTURES

The shaft of the fibula is most often fractured by a force that has also fractured the tibia; in these cases, treatment is directed by the tibial injury. A direct blow to the fibula can result in an isolated injury to this bone. The patient typically presents with pain or tenderness over the fracture site. With the tibia intact, the patient is often able to bear weight and should be treated with a short leg cast and crutches. Patients with less intense pain may be immobilized with a knee immobilizer (proximal fibula) or elastic wrap (distal fibula) and directed to bear weight as tolerated.

STRESS FRACTURE

Stress fracture occurs when there is increased muscle activity on bones that are not able to tolerate the additional forces. Extrinsic causes may include a recent increase in activity, running over hard surfaces, or excessive wear on the athlete's shoes. Adolescent female athletes with eating disorders and military recruits are at high risk for stress fractures. As our population ages, the elderly are taking up activities that may result in stress fractures. The prototypical patient is the Caucasian woman with demineralized bone. Stress fractures are twice as common in women compared with men. About half of stress fractures in athletes occur in the tibia. Less common sites are the tarsals and fibula. Stress fractures may be bilateral. In adolescents, the site is often the proximal third of the tibia. Runners typically sustain fractures at the junction of the middle and distal third of the tibia. The distal fibula is another common site.

The history typically involves a change in the patient's training pattern. In an early stage of stress fracture, the patient notices activity-induced pain that is relieved by rest. This can progress to constant pain. On examination, there is pain on palpation over the fracture site, and there may be edema. The pain may be intensified by load bearing on the affected bone.

The radiographs of the site are often normal on initial presentation. They may reveal the fracture, which can have the appearance of sclerosed areas oriented linearly. Radiographs obtained 10 to 15 days later may show periosteal elevation or demineralization at the fracture line. Plain films that are initially normal do not exclude the diagnosis. More sensitive tests for stress fracture are the bone scan and MRI. Although these studies are typically ordered at follow-up and not in the ED setting, they can demonstrate the severity of the change and can be used to predict time to recovery.[4]

Treatment of a suspected stress fracture includes discontinuation of the activity. A cast can be applied if significant pain continues. It is not unusual to have pain lasting up to a year despite treatment.

ACHILLES TENDON RUPTURE

The Achilles tendon is the largest and strongest tendon in the human body. The gastrocnemius and soleus muscles of the calf have tendinous complexes that coalesce to the Achilles tendon that extends about 15 cm to where it inserts on the calcaneus. **Its vascular supply is the weakest in the area 2 to 6 cm above the calcaneus, and this is the area that is most frequently ruptured.** A typical patient is a 30- to 50-year-old man who participates in strenuous activities on an occasional basis ("weekend warrior"). **Risk factors for rupture include older age, prior fluoroquinolone use, and prior steroid injection.** The injury often occurs when eccentric force is suddenly applied to a dorsiflexed foot. The patient suffers sudden severe pain and is unable to run, stand on toes, or climb stairs. The most notable finding on examination is a palpable gap in the Achilles tendon 2 to 6 cm proximal to the calcaneus. The calf may be swollen. The patient will be unable to stand on toes. The Thompson test (see Figure 276-8 in Chapter 276, "Ankle Injuries") will help demonstrate the tendon rupture. The patient lies prone with the knee bent at 90 degrees. The examiner squeezes the calf: an intact Achilles tendon will transmit this force to the foot, resulting in its plantarflexion. **If the Achilles tendon is ruptured, the foot will not plantarflex when the calf**

is squeezed. The diagnosis of Achilles tendon rupture can be made without radiographs. When the diagnosis is not clear, perform a bedside US or obtain an MRI of the Achilles tendon. The reliability of US is largely dependent on the operator's skill. Initial care for Achilles tendon rupture involves immobilization from just below the knee to the metatarsals with the ankle in some plantarflexion. Crutches are necessary for non–weight-bearing status. Ice and analgesics are also used.

Refer patients with Achilles tendon rupture to an orthopedist or sports medicine specialist. Subsequent therapy involves either surgical repair of the ruptured tendon or immobilization and gradual physical therapy to regain range of motion. Immobilization is typically needed for 2 to 3 months.

MEDIAL GASTROCNEMIUS MUSCLE STRAIN

The medial gastrocnemius originates from the medial femoral condyle, crosses the knee, and joins the lateral gastrocnemius. The tendon complex of this muscle merges with that of the soleus muscle to form the Achilles tendon, which inserts on the calcaneus to act in plantarflexion of the foot. Injury to the medial gastrocnemius muscle usually occurs when a person forcefully plantarflexes the foot while the knee is extended, occurring when the gastrocnemius is at its maximal length. The typical patient is 40 to 60 years old and an intermittently active athlete. A sharp pain is suddenly felt in the calf as if a stick had struck the person. An audible "pop" may be heard. The pain is severe enough to cause an immediate cessation of the activity, as plantarflexion of the ankle is too painful.

On examination, there may be asymmetric calf swelling and tenderness of the calf. The Achilles tendon is intact. The patient's pain can be elicited by passive dorsiflexion of the ankle. Differential diagnosis can include deep vein thrombosis, ruptured Baker's cyst, and compartment syndrome. Radiographs are not necessary for making the diagnosis. Nonurgent MRI can be obtained to confirm the diagnosis. Treatment includes immobilization with the foot maximally plantarflexed. Rest, ice, and elevation may decrease swelling.

SHIN SPLINTS (EXERTIONAL COMPARTMENT SYNDROME)

Shin splints is a complex syndrome characterized by aching, squeezing, or cramping in the anterior compartment of the leg. If pain does not resolve with rest or is out of proportion to examination, consider acute compartment syndrome. See Chapter 278 for further discussion.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 276

Ankle Injuries

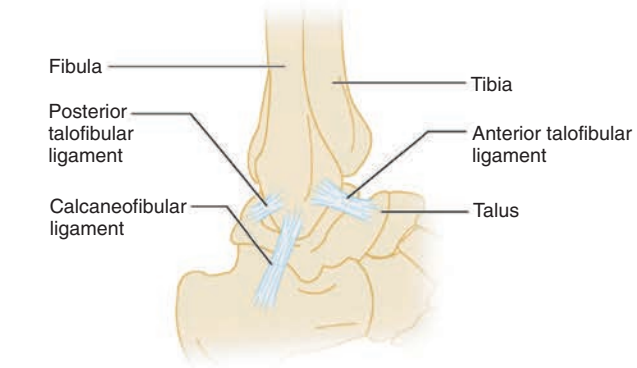
Talib Omer
Margarita Santiago-Martinez

INTRODUCTION AND EPIDEMIOLOGY

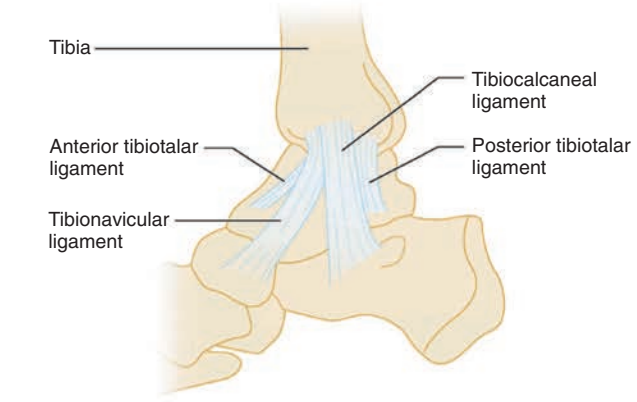
Given the mobility of the ankle joint and our bipedal existence, ankle injuries are a common complaint. They represent about 4% of all visits to the ED.[1] Previous ankle sprain and participation in contact sports are risk factors for ankle injuries.[2,3]

ANATOMY

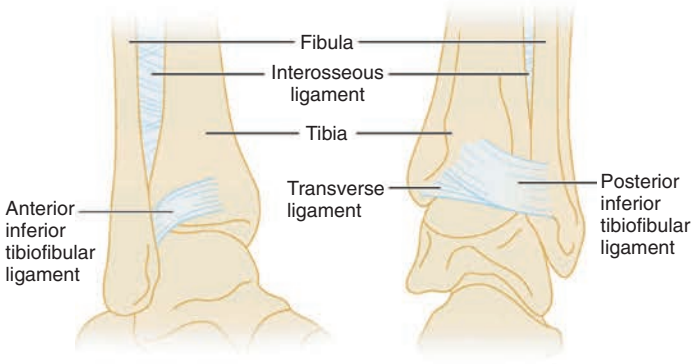
The proximal part of the ankle mortise is composed of the distal fibula and tibia that fits on top of the talus. These bones are wider anteriorly than posteriorly. Joint stability is provided by medial and lateral malleoli extending on either side of the talus. The **medial deltoid ligament**, **lateral ligament complex**, and **syndesmosis** are the three distinct groups of ligaments that stabilize the ankle[4] (**Figure 276-1**). The deltoid ligament is the strongest of these ligaments and is a thick, triangular band of tissue originating from the medial malleolus. The lateral ligament complex consists of the lateral malleolus that attaches to the anterior and posterior aspects of the talus and calcaneus by the anterior talofibular, posterior talofibular, and calcaneofibular ligaments, respectively. This ligament complex, weaker than the deltoid and prone to inversion injuries, is commonly injured and represents 85% of all ankle sprains.[5] The



A Lateral view



B Medial view



C Anterior and posterior view

FIGURE 276-1. Ligaments of the ankle joint. **A.** The three lateral ligaments: the anterior and posterior talofibular ligaments and the calcaneofibular ligament. **B.** The four bands of the deltoid ligament: the anterior and posterior tibiotalar, the tibiocalcaneal, and the tibionavicular. **C.** Anterior and posterior view of the ankle syndesmosis. The ligaments of the syndesmosis are the anterior inferior tibiofibular ligament, the posterior inferior tibiofibular ligament, the transverse ligament, and the interosseous ligament, which connects the entire length of the tibia and fibula.

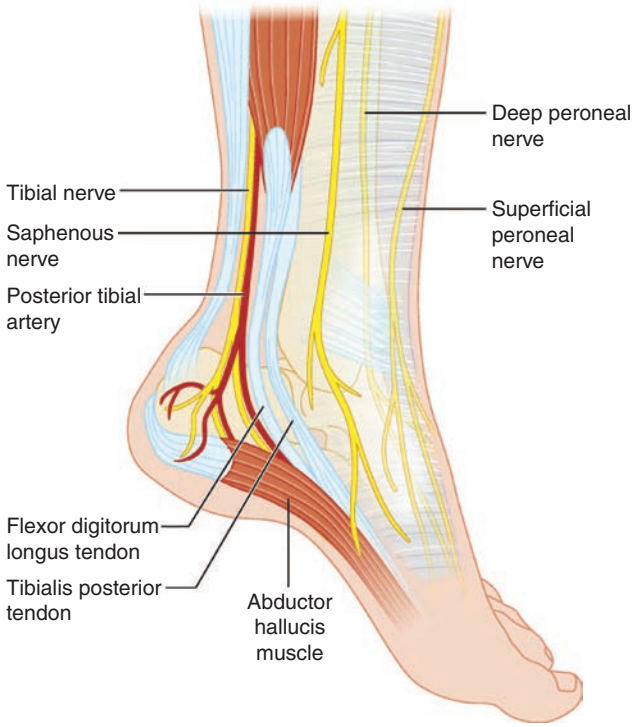


FIGURE 276-2. Neurovascular anatomy of ankle.

syndesmosis, which holds the tibia and fibula together, yet allows the fibula to rotate, is a group of four distinct ligaments attaching the distal tibia to the fibula just above the talus (Figure 276-1). While the fibula has no direct contact to the weight-bearing portion of the talus, the syndesmosis transmits about 16% of the axial load to the fibula.[6]

The ankle is considered a hinged joint, but ligamentous attachments allow for some rotation and translation within the mortise of the talar dome.[6] Branches of the sciatic nerve, the superficial peroneal, deep peroneal, peroneal, and tibial, innervate the four muscle groups of the ankle joint with branches of the popliteal artery serving as the blood supply (**Figure 276-2**). The tibialis anterior, extensor digitorum longus, and extensor hallucis longus muscles run over the anterior aspect of the joint and are responsible for dorsiflexion. Inversion is accomplished by the tibialis posterior, flexor digitorum longus, and flexor hallucis longus. The peroneus longus and brevis muscles, sharing a common synovial sheath held in place by a groove on the posterior aspect of the lateral malleolus and superior retinaculum, run laterally to evert and plantarflex the joint. Plantarflexion is primarily accomplished by the gastrocnemius and soleus muscles.

CLINICAL FEATURES

HISTORY

Understanding the mechanism and timing of the injury is important. Document these details along with any previous bony or soft tissue injuries. Patients with signs of neurovascular compromise, including coldness and numbness of the foot, a rapid onset of swelling, extreme pain, and complicating conditions such as diabetes, require urgent evaluation.[2] A normal-appearing ankle does not preclude the need for further inquiry. Due to the significant swelling that typically presents after acute injuries, examining the ankle is challenging but can be helped by elevation of the injured extremity and ice applied at triage. Peroneal spasms may mask any instability in the joint.[6]

PHYSICAL EXAMINATION

Place the patient on a stretcher to perform a thorough evaluation. A systematic approach to the examination decreases the chance of missed

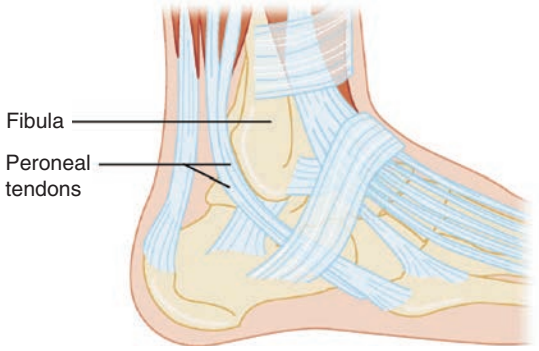


FIGURE 276-3. Peroneal tendon of the foot, lateral view.

injuries. Starting with the skin and soft tissues, note any ecchymosis, abrasions, or swelling. Note the position, swelling, and skin integrity of the joint as well as any areas of tenderness or crepitus. Joints above and below the ankle need to be examined for any concomitant injuries. Suspect a **Maisonneuve fracture** (or fibulotibialis ligament tear) if there is tenderness of the fibular head or proximal fibular shaft. Palpate the area of obvious injury last. Test the functionality of the joint with both active and passive plantarflexion, dorsiflexion, and full range-of-motion exercises. **Peroneal tendon injuries** can occur from forced dorsiflexion, which presents as weakness on eversion (**Figure 276-3**).[4] Check stability in external rotation, varus, and valgus. Palpate the posterior aspects of the lateral and medial malleoli, starting proximally to the joint and working distally. If there is a concern for isolated fibular fractures, check for evidence of injury to the syndesmosis or deltoid ligament.[6]

Functional testing of the joint can reveal significant injuries. A positive anterior drawer test (**Figure 276-4**) is indicative of a torn anterior talofibular ligament. To perform the test, have the patient sit with the ankle in 10 to 15 degrees of plantar flexion, cup the heel in one hand, and provide countertraction to the tibia with the other hand while attempting to draw the heel forward. Increased subluxation of 2 mm or more compared to the uninjured side or visible dimpling of the anterior skin of the affected ankle indicates a significant anterior talofibular ligament injury.[4] A positive anterior drawer test, swelling, and a hematoma are signs of a grade III sprain. **Syndesmosis injuries** can be deceiving because the patient describes ankle pain, but there is typically little ankle edema or ecchymosis. The **crossed-leg test** (compressing the fibula toward the tibia just above the midpoint of the calf[7]) can detect a syndesmosis injury and is indicated if pressure to the medial aspect of the knee elicits pain in the syndesmosis (**Figure 276-5**). The **squeeze test** is performed by squeezing the calf just above the ankle joint. Pain indicates syndesmosis injury. Calcaneofibular ligament instability can be detected with the **inversion stress test** or **talar tilt**.[4] If the examination is uncomfortable for the patient, consider a hematoma block, sedation, or both to perform a more thorough examination.

Examine areas in close proximity to the ankle as well. What may be described as an ankle injury may end up being an injury to the Achilles tendon or foot and cannot be excluded by ankle radiographic imaging.

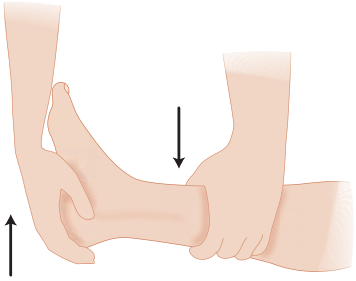


FIGURE 276-4. Technique for performing the anterior drawer stress test of the ankle. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics, The Extremities*, 5th ed. © 2007, McGraw-Hill Inc., New York.]

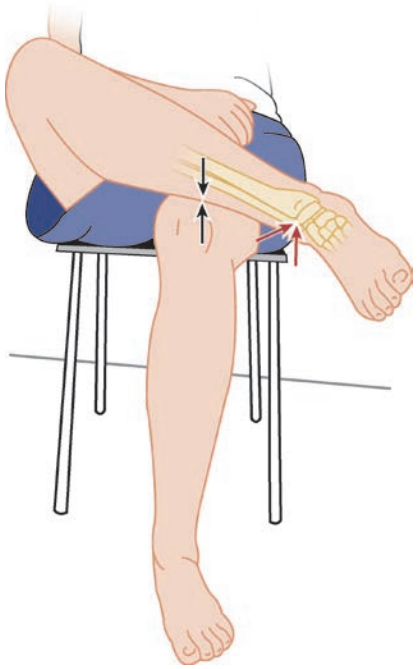


FIGURE 276-5. The crossed-leg test. The affected leg is crossed over the opposite leg as demonstrated. If pain results at the arrow sites when pressure is applied to the medial side of the affected knee, the test is positive and indicates syndesmosis injury. [Copyright © 2010 by the American Orthopaedic Foot and Ankle Society, Inc., originally published in *Foot & Ankle International* in Kiter E, Bozkurt M: The crossed-leg test for examination of ankle syndemosis injuries. *Foot Ankle Int* 2: 187, 2005, and reproduced here with permission.]

Assess the integrity of the **Achilles tendon**. Fluoroquinolones and corticosteroids increase the risk of such an Achilles tendon injury.[8] Palpate the hindfoot and midfoot over the calcaneus, tarsals, and base of the fifth metatarsal to check for areas of tenderness that may require further investigation.

Perform a neurovascular examination. Check dorsalis pedis and posterior tibial pulses and document digital capillary refill. Inability to dorsiflex the toes suggests a tibial nerve injury. Inability to plantarflex the great toe is suspicious for peroneal nerve injury.

If there are any significantly displaced fractures or dislocations, immobilize the joint in a neutral position with a well-padded splint to reduce further soft tissue injury. Follow this with elevation and application of ice to reduce edema. Emergently reduce any displaced fractures or dislocations with neurovascular compromise (see later treatment section under "Dislocations").

DIAGNOSIS

IMAGING

The Ottawa Ankle Rules for Ankle and Midfoot Injuries[9-13] are easily applied by physicians and other healthcare providers[14] and can rule out ankle fractures without the need for radiography with high accuracy.[15] The rules are summarized in **Figure 276-6**. (See Video: Ottawa Ankle Rules).

They were originally developed for patients older than age 18 years who were able to cooperate, were not intoxicated, and had no distracting injuries or decreased sensation. See Chapter 141, "Pediatric Orthopedic Emergencies" for detailed discussion of the rules in children.[16,17] Assuming the patient does not have any bony tenderness, assess the ability to bear weight by having the patient take four steps, resulting in two transfers to and from the injured ankle. The initial studies demonstrated an approximately 30% reduction for the need of ankle radiographs.[12]

The standard ankle trauma series consists of three views: anteroposterior, 15-degree internal oblique, and lateral views. See **Figure 276-7** for normal anatomy. About 95% of all ankle fractures can be detected with any two of these views.[6]

When there is an abnormal motion of the talus within the mortis, there is stress on the malleoli and ligaments, which causes the injury. Fractures above the talus and those that cause disruption of both sides of the joint have the potential to create an unstable injury. Instability of the joint is usually diagnosed based on plain radiographs because pain and swelling make it difficult to determine true stability of an acutely injured ankle. If radiographs are normal but there is concern about stability, weight-bearing ankle films can be helpful. Point-of-care ultrasound can detect Achilles tendon injuries[18] and ankle fractures.[19]

CT and MRI may play a role in better delineating pathology. Ideal imaging for a CT includes both axial and direct coronal images with sagittal reformations. To obtain these images, keep the ankle between neutral and 20 degrees of plantarflexion when possible, similar to that for plain radiographs. CT can be used for operative planning by orthopedic surgeons and to evaluate comminuted fractures and complex bony injuries like pilon fractures and malunions. MRI can help define soft tissue, muscle, ligamentous, and tendon injuries and is used more in the outpatient setting for subacute and chronic pain presentations.[20]

TENDON INJURIES

CLINICAL FEATURES

A **peroneal tendon** subluxation and dislocation occurs when there is a sudden hyperdorsiflexion of the foot in a position of eversion, as in skiing. The superior retinaculum, which holds the peroneal tendons in place, is torn from the posterolateral malleolus. This leads to a small avulsion fracture in more severe injuries with a dislocation or anterior subluxation of the peroneal tendon over the tip of the fibula. Consider this injury when there is ecchymosis or tenderness over the posterior

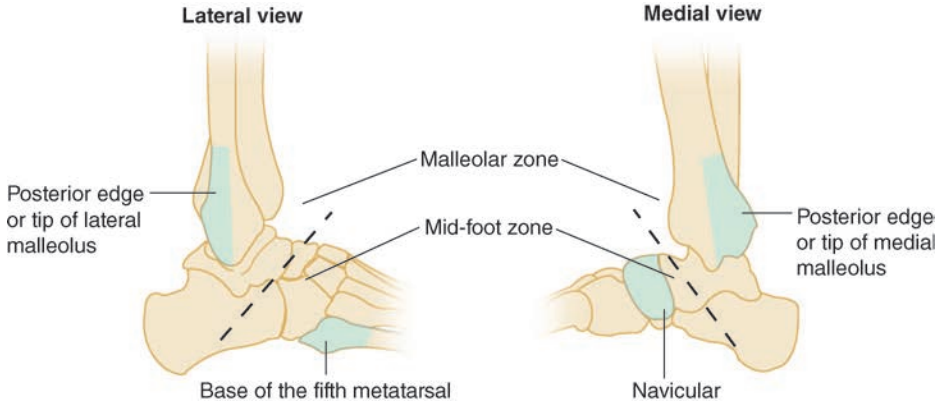


FIGURE 276-6. Ottawa Ankle Rules for Ankle and Midfoot Injuries. Ankle radiographs are required only if there is any pain in the malleolar zone or midfoot zone along with bony tenderness in any of these four locations or the inability to bear weight both immediately and in the ED.



FIGURE 276-7. Normal ankle radiograph. **A.** Anteroposterior view. **B.** Lateral view. **C.** Oblique view. [Image used with permission of Robert DeMayo, MD.]



FIGURE 276-8. Thompson test. There is no plantarflexion with squeezing the calf of the affected leg, or less plantarflexion compared with the normal leg. [Adapted with permission from Stone CK, Humphries RL. *Current Diagnosis and Treatment Emergency Medicine*, 7th ed. Copyright @ The McGraw Hill Companies, 2011. Figure 28-20.]

edge of the lateral malleolus and no tenderness over the talofibular ligament.

Achilles tendon ruptures occur with sudden plantarflexion of the foot. A complete tendon rupture will become apparent with palpation of a defect over the Achilles tendon and is identified by the Thompson test (**Figure 276-8**). Perform the **Thompson test** if there is tenderness or a defect. Place the patient prone on the stretcher and squeeze the calf on the affected side. Loss of plantarflexion indicates a complete Achilles tendon rupture. Ultrasound can also identify Achilles tendon ruptures (**Figure 276-9**).

TREATMENT

The treatment for both types of tendon rupture is often operative repair, especially for those who wish to return to full activity.

LIGAMENT INJURIES

CLINICAL FEATURES

The most common type of ankle sprain is one to the **lateral ankle**. Typically, these are minor and are due to an inversion injury when the ankle is plantarflexed. Sprains are categorized into three grades. Grade I involves no tearing of the ligaments with minimal functional loss, pain, swelling, and ecchymosis. Weight bearing is tolerable. Grade II sprains occur with a partial tear and result in some loss of functional ability. These tend to be more painful, with swelling, ecchymosis, and difficulty bearing weight. Grade III sprains result from a complete tear, with significant functional loss, pain, swelling, bruising, and almost a universal inability to bear weight.[21] However, joint stability is the primary determinant of a treatment plan for a sprain.

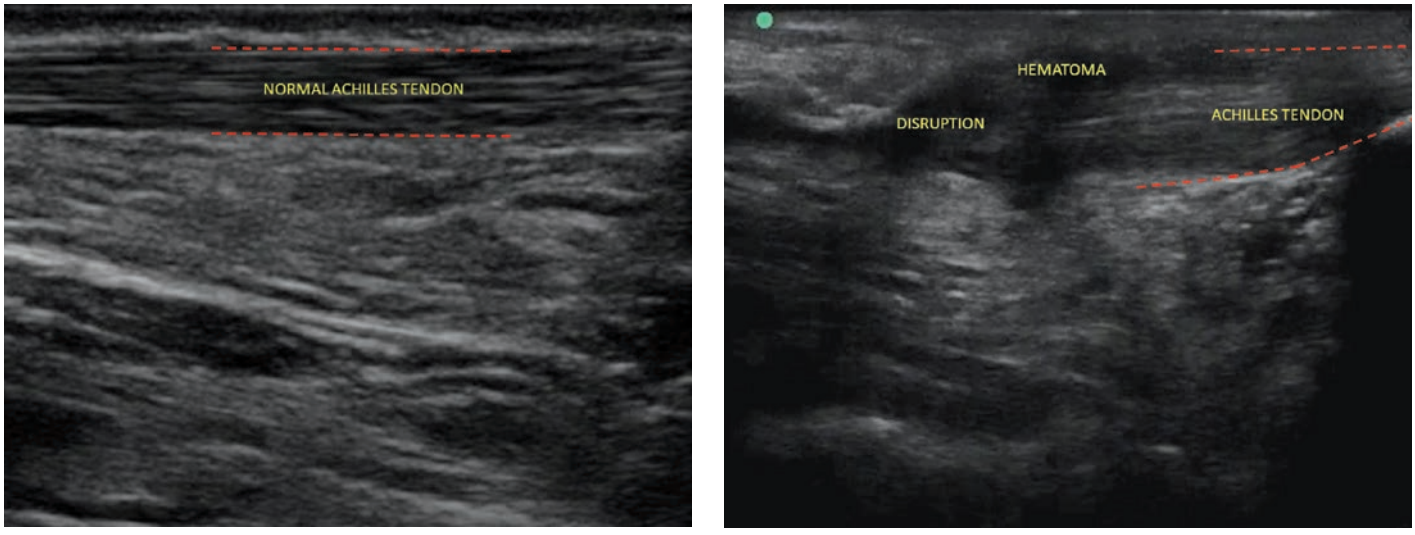
An isolated sprain of the medial deltoid ligament is rare. **Medial deltoid ligament** tears are usually associated with a fibular fracture or tear of the tibial-fibular syndesmosis from an eversion injury. If there is significant medial malleolus tenderness and swelling, suspect a Maisonneuve fracture of the proximal fibula and fibular shaft. Negative radiographs should suggest syndesmosis tears.

Injuries to the tibiofibular syndesmotic complex are associated with hyperdorsiflexion injuries when the talus moves superiorly and separates the tibia and fibula. This leads to a partial or complete tear of the syndesmosis with complaints of pain just above the talus.

If there is concern for an unstable ligamentous injury, weight-bearing views of the ankle can help diagnosis—an unstable ligamentous injury may demonstrate talar shift.

TREATMENT

The immediate goals are to decrease pain and swelling and protect ligaments from further injury. The **PRICE protocol** (protection, rest, ice, compression, elevation) involves elevating the ankle and protecting it with a compressive device along with applying ice and resting up to 72 hours to allow the ligaments to heal.[3] There is controversy as to whether or not early immobilization versus functional treatment results in the best outcomes. There is a trend toward favoring early functional treatment over immobilization.[22] Patients returned to mobility anywhere between 4.6 and 7.1 days sooner with functional treatment when compared with immobilization.[23] Functional treatment usually consists of three phases: (1) PRICE protocol within the first 24 hours of injury; (2) motion and strength exercises to begin within 48 to 72 hours; and (3) endurance training, focused toward specific sports when applicable, and training to improve balance after the second phase begins.[3]



A B

FIGURE 276-9. Point-of-care ultrasound of Achilles tendon. **A.** Unaffected side. **B.** Ruptured Achilles tendon. [Used with permission of Talib Omer, MD, and Division of Emergency Ultrasound at LAC+USC Medical Center.]

In patients with a lateral ligament sprain, a stable joint, and the ability to bear weight, treatment consists of analgesics, an elastic bandage or ankle brace, and no sports engagement, with follow-up in a week if no improvement. There is consensus among reviews that bracing is effective at preventing a recurrence of an ankle sprain.[24] For patients who are unable to bear weight but have a stable joint, provide an ankle brace and crutches and have them follow up with either their primary care provider or orthopedic surgeon within 1 week for repeat evaluation. Given the trend for early immobilization, functional braces, such as semirigid (e.g., Aircast®) and soft, lace-up braces, are commonly used. There is no consensus as to which leads to a more favorable outcome,[25] although early rehabilitation of low-grade ankle sprains results in a good outcome.[26] Another option is an inflatable cast boot (also called a walking fracture boot or Aircast boot) that molds to the foot with inflatable air bladders. This device can also be used for stable ankle fractures.

Treat medial ligament sprains with PRICE and early referral to an orthopedic surgeon given the risk for undetected underlying fractures. Consider early orthopedic referral for **syndesmotic complex sprains** given the expected prolonged recovery time.

Refer patients with an unstable joint to an orthopedic surgeon after placement of a posterior splint for stabilization. Establish contact with the orthopedic surgeon early because the timing of treatment and follow-up is ultimately at his or her discretion.

There is no consensus as to whether surgery versus conservative treatment results in more favorable outcomes. Cryotherapy with ice will help decrease pain and limit swelling and should be applied directly to the ankle or splint but not left on for >20 minutes at a time. Therapeutic ultrasonography is not helpful.[2]

DISLOCATIONS

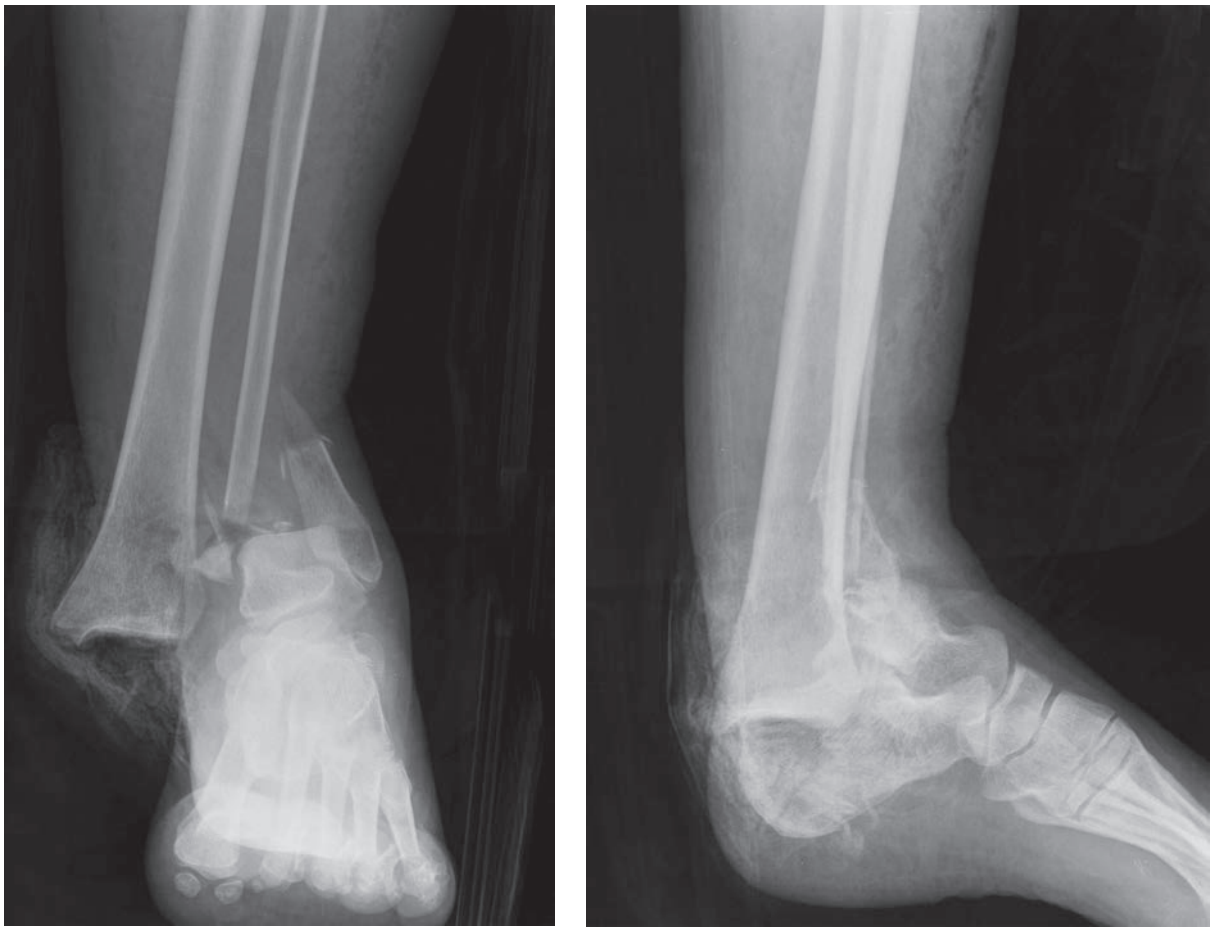
CLINICAL FEATURES

Most ankle dislocations are associated with a fracture and can occur in one of four planes. Posterior dislocations are the most common and occur with a backward force on the plantarflexed foot, usually resulting in rupture of the tibiofibular ligaments or a lateral malleolus fracture. The less common anterior dislocation results from a force on the dorsiflexed foot with an associated anterior tibial fracture. A lateral dislocation results in ligamentous disruption and fracture of one or both malleoli (**Figure 276-10**). An axial compression force can drive the talus upward with an associated fracture of the talar dome and disruption of the syndesmosis.

TREATMENT

There is a significant concern for neurovascular compromise. Check carefully for an open fracture in these instances. If the patient has intact pulses, dislocations associated with fractures should be reduced by an orthopedic surgeon. If vascular compromise is present, as evidenced by a dusky foot or absent pulses, or there is tenting of the skin, an immediate reduction by the emergency physician is warranted without any prereduction radiographs.

First provide appropriate sedation and analgesia before attempts at reduction. Grasp the heel and foot with both hands, and gently apply traction and rotation opposite to the direction of the mechanism of injury. Confirm pulses and distal perfusion, and then apply a splint and elevate the foot while waiting for orthopedic evaluation. Confirm and document distal perfusion again after splint application. Any dislocations that cannot be reduced using closed techniques will require open reduction.



A B

FIGURE 276-10. Open fracture with dislocation. **A.** Anteroposterior view. **B.** Lateral view. [Image used with permission of Robert DeMayo, MD.]

MUSCULAR INJURIES

CLINICAL FEATURES

Strains are injuries to muscle or tendons not usually associated with a specific injury but due to repetitive stress and overuse. Common muscles and tendons involved include the extensor digitorum longus, extensor hallucis longus, peroneus brevis and longus, and anterior tibial tendon (**Figure 276-11**). Strains can be due to athletics or poorly fitting footwear. Contusions are usually caused by direct trauma from a projectile like a baseball or hockey puck. Fractures associated with contusions are rare and usually involve only the bony cortex.

TREATMENT

For overuse injuries, analgesics, especially NSAIDs, will help, along with rest and cessation of the activities that are causing the strain. Targeted exercises may help in the recovery as well. Contusions are treated symptomatically with analgesia and ice.

FRACTURES

CLINICAL FEATURES

Radiographically, ankle fractures are described as unimalleolar, bimalleolar (**Figure 276-12**), and trimalleolar (**Figure 276-13**). A bimalleolar fracture is fracture of the lateral and medial malleoli; trimalleolar fracture additionally involves the posterior malleolus.

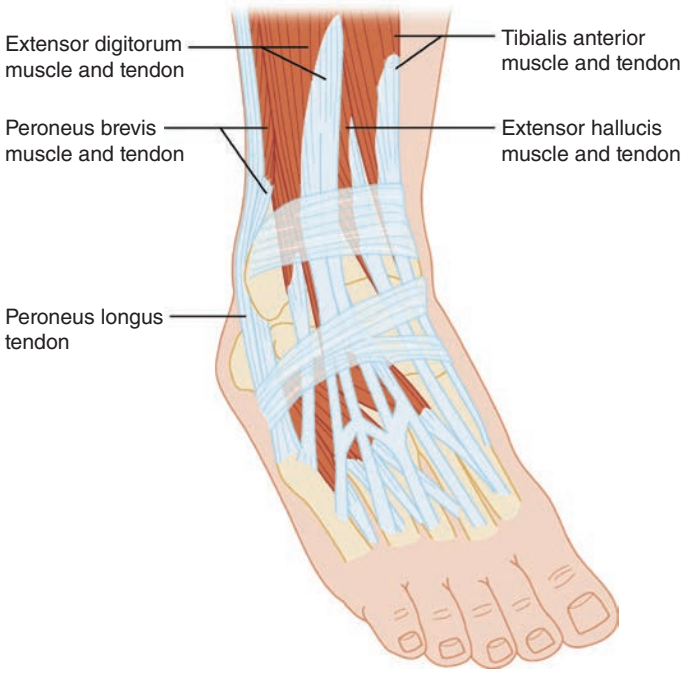
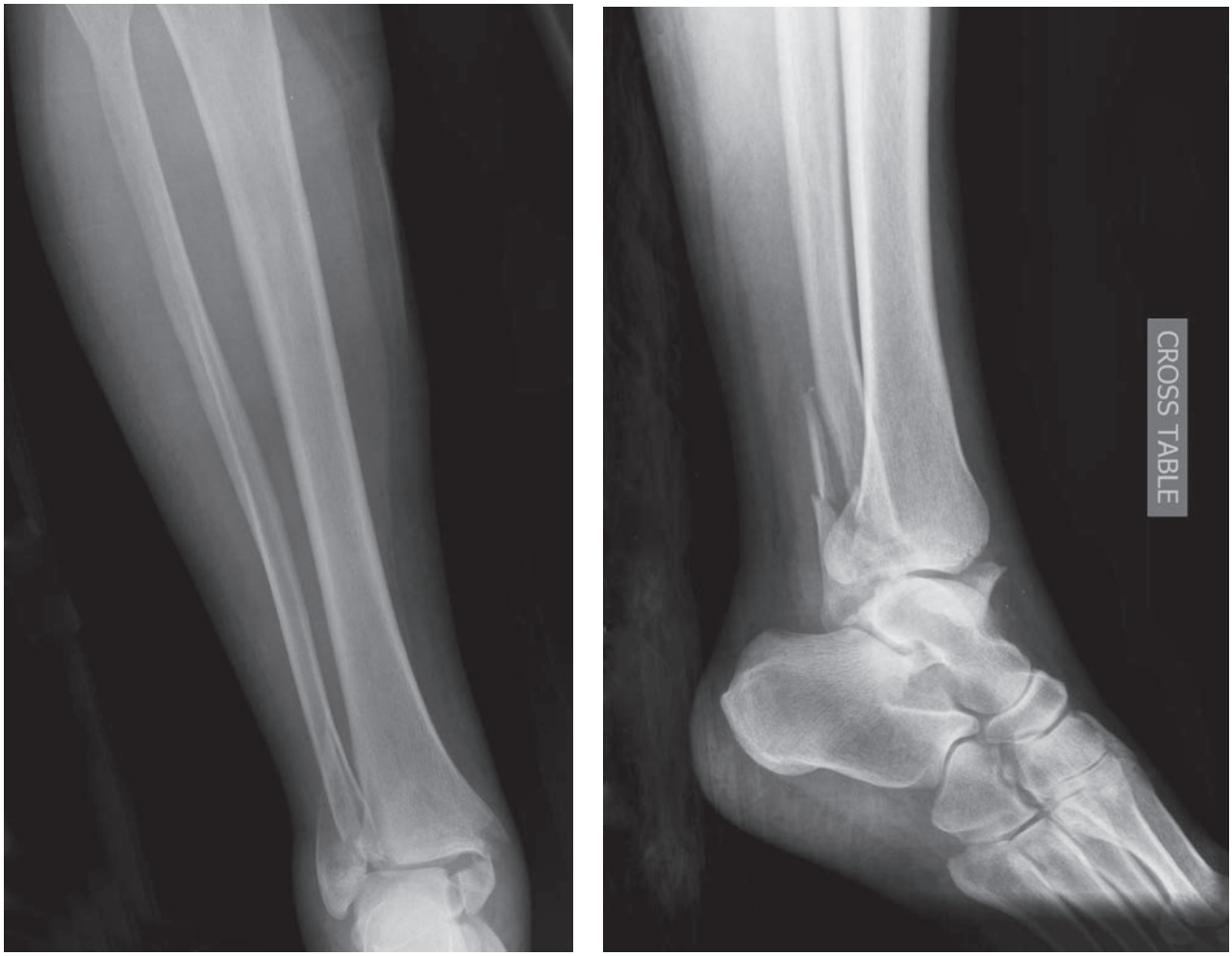


FIGURE 276-11. Muscles of the ankle.



A B

FIGURE 276-12. Bimalleolar fracture. **A.** Anteroposterior view. **B.** Lateral view. [Image used with permission of Robert DeMayo, MD.]



A B

FIGURE 276-13. Trimalleolar fracture. **A.** Anteroposterior view. **B.** Lateral view. [Image used with permission of Robert DeMayo, MD.]

The ankle consists of a ring of bone and ligaments around the talus. The ring is composed of the tibia, tibiofibular ligament, fibula, lateral and medial ankle ligaments, and calcaneus.[27] A single ring disruption is typically a stable injury. Injuries involving two or more components of the ring are unstable injuries and usually need surgical fixation.

The Danis-Weber and Lauge-Hansen schemes are used by orthopedic surgeons to classify ankle fractures and help determine surgical repair. The Danis-Weber system classifies fracture patterns based on the level of the fracture of the fibula.[4] The Lauge-Hansen system classifies fractures based on the position of the foot at the time of injury.[28]

Critical aspects of the examination for ankle fractures are summarized in **Table 276-1**.

TREATMENT

The goal is to restore the anatomic relationship of the ankle, maintain reduction during the healing, and mobilize the ankle early. Treat small fibular avulsion fractures as stable ankle sprains (see earlier section, "Ligament Injuries") if they are minimally displaced (<3 mm in diameter) and there is no sign of medial ligament injury.

Most other ankle fractures require immobilization by either cast alone or surgical repair and casting.[29,30] Severe comminuted fractures are at risk for compartment syndrome, fat emboli, and poor healing. Urgent orthopedic consultation in the ED is necessary. Until definitive fracture treatment can be provided, apply a posterior splint and stirrup and keep the patient non–weight bearing (see Chapter 267, "Initial Evaluation and Management of Orthopedic Injuries"). Provide analgesics, and remind the patient to elevate the leg and apply ice. **Table 276-2** provides guidelines for orthopedic consultation and follow-up.

TABLE 276-1 Associated and Occult Injuries of the Ankle

Injury	Clinical Suspicion	Confirmatory Test
Maisonneuve fracture	Examine proximal fibula and shaft, tenderness to palpation; proximal fracture and syndesmosis tear indicate unstable fracture[9]	Fibula radiograph
Peroneal tendon dislocation	Palpable anterior tendon dislocation or subluxation	Clinical examination
Usually identified in follow-up of ankle sprains		
Osteochondral injuries	Diffuse ankle swelling, passive plantarflexion	Ankle mortise view/CT
Syndesmosis tear	Significant ankle pain, positive squeeze test	Widened mortise with weight bearing
Anterior calcaneal process fracture	Tenderness more inferoanterior than a typical ankle sprain	Lateral ankle radiograph/CT
Lateral talar process fracture	Tenderness just distal to the tip of fibula	Ankle mortise view/CT
Os trigonum	Tenderness anterior to Achilles tendon	Lateral ankle radiograph

TABLE 276-2 Timing of Consultation

Immediate Consultation in ED	Deferred Consultation*	Within 1 Week
All open fractures	Stable unimalleolar fractures	Potentially unstable sprains
All fracture dislocations	Unstable ligamentous injuries	
All dislocations	Acute peroneal dislocations	
All trimalleolar fractures†		
All bimalleolar fractures†		
Unstable unimalleolar fractures†		
Maisonneuve fractures†		

*Implies that communication is established at time of diagnosis and specific time of consultation has been set.

†Consultation can be delayed in the ED in fractures without neurovascular compromise and appropriate splinting.

OPEN FRACTURES

The most important prognostic factor in open ankle fractures is the amount of energy involved in the injury and amount of soft tissue damage involved. Open fractures require rapid surgical management that involves aggressive debridement of nonviable tissue and either internal or external fixation.[31] Administer empiric antibiotics, which decrease infection by 59%.[32] The most commonly used antibiotic is IV cefazolin, but consider adding an aminoglycoside for contaminated wounds. Use clindamycin in patients with a penicillin allergy. Update the tetanus status of the patient as needed.

While waiting for the orthopedic surgeon, irrigate the wound with several liters of normal saline, then apply sterile gauze soaked in saline over the open wound, and secure it in place with a gauze roll. Do not use iodine solutions, as they are caustic to tissues. Splint the injury to stabilize it while obtaining radiographs and coordinating orthopedic care.

DISPOSITION AND FOLLOW-UP

To date, there is no established standard of care regarding the time of orthopedic consultation and follow-up. Whether an orthopedic surgeon sees the patient in the ED depends on the specialist resources available. Table 276-2 can serve as a general guideline for local practice standards and resources. Most severe fractures require orthopedic consultation in the ED.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 277

Foot Injuries

Talib Omer
Margarita Santiago-Martinez

INTRODUCTION

Foot injuries are a common presentation in the ED and are frequently missed.[1–3] These injuries typically occur in work, athletic, and traffic environments.[4,5] Foot injuries can be associated with substantial medical and economic costs.[6,7] Sport-related foot and ankle injuries require care so the athlete can return to the demands of the sport as quickly as possible.[3] Motor vehicle crash patients with a foot or ankle injury typically have a higher injury severity score than those without such injuries.[8] The majority of foot injuries involve fractures of the metatarsals.[9]

ANATOMY

The foot is divided into three sections: the hindfoot, the midfoot, and the forefoot. The **Chopart joint** separates the hindfoot from the midfoot. The **Lisfranc joint** divides the midfoot and the forefoot. The hindfoot is composed of the talus and the calcaneus. The midfoot encompasses the medial, middle, and lateral cuneiforms; the navicular; and the cuboid. The tarsus refers to the bones of the hind and midfoot. The forefoot includes the metatarsals and the proximal, middle, and distal phalanges (**Figure 277-1**). Ligaments and muscles enable foot movements of eversion, inversion, adduction, and abduction.

Vascular supply of the foot originates from branches of the popliteal artery: the anterior tibial artery, with its branch the dorsalis pedis supplying the dorsal aspect of the foot; and the posterior tibial and peroneal arteries supplying the sole (**Figure 277-2**).

The sural, saphenous, peroneal, and lateral plantar nerves innervate the foot for both motor and sensory function and originate in branches from the sciatic and femoral nerves.

CLINICAL FEATURES

HISTORY

Ask about the mechanism of injury and direction of force. Obtain key information, including ability to bear weight after the injury, prior injury or surgery to the area, and any other potential injuries. Because it requires great force to fracture the foot, other injuries can coexist, and foot pain can distract from other serious injuries, or conversely, other injuries can distract from foot pain, leading to a high miss rate of foot fractures in polytrauma patients.[5]

PHYSICAL EXAMINATION

The foot examination does not necessarily begin with the foot, but with the entire lower extremity on the affected side. Examine the hip, knee, and ankle. Evaluate neurovascular integrity. Vascular compromise of the foot is identified with diminished pulses, a cool extremity, and mottled skin. Once the general examination is completed and the focused foot examination begins, start with the general appearance of the foot and compare it with the uninjured side. Look for obvious closed or open deformities. Ask the patient to identify painful areas, although pain is often poorly localized. Palpate the foot for abnormal findings or tenderness. Pay particular attention to the base of the fifth metatarsal and the dorsal aspect of the base of the second metatarsal. Range the joint both passively and actively through all typical motions of the foot. Evaluate gait when possible.

HINDFOOT INJURIES

CALCANEUS INJURIES

CLINICAL FEATURES

The calcaneus is the most commonly fractured tarsal bone.[10] Fractures in the hindfoot typically require a large force, like an axial load to the heel, to occur. Because of this force, associated injuries are common.

Calcaneal fractures are subdivided into intra-articular and extra-articular fractures, with intra-articular fractures being the more common of the two. A displaced intra-articular fracture is common and poses its own challenges for long-term care. Some surgeons advocate for open reduction and internal fixation; others prefer nonoperative closed reduction; and still others prefer primary arthrodesis, with all management strategies having mixed results.[11,12]

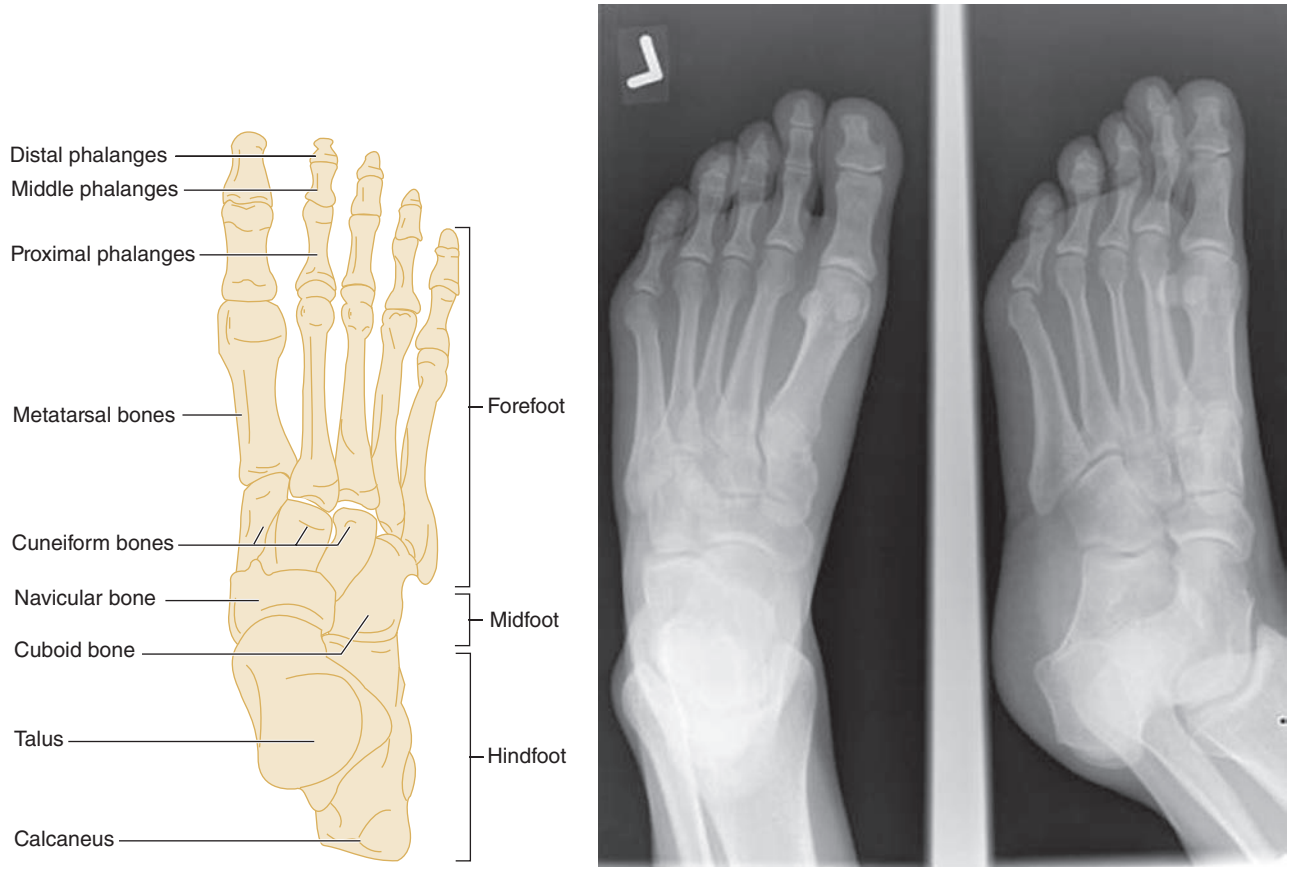


FIGURE 277-1. **A.** Diagram of normal bony anatomy of the foot. **B.** Radiograph of normal bony alignment of the foot. [Panel B image used with permission of Robert DeMayo, MD.]

DIAGNOSIS

Plain radiographs, specifically the lateral view, are needed for fracture diagnosis. The Boehler angle is measured using the lateral view and represents the intersection of two lines: (1) the line drawn from the highest part of the anterior process of the calcaneus and the highest point of the posterior articular surface of this bone, and (2) the line between the highest point of the posterior articular surface of the calcaneus and the most superior part of the calcaneal tuberosity. The normal angle measures between 25 and 40 degrees. When the angle is <25 degrees, suspect a fracture (**Figure 277-3**). Because this angle varies widely between individuals, a comparison view is helpful if the diagnosis is in question. Although plain radiographs are helpful when the fracture is visible, a CT can provide detail and help clarify the management plan.

TREATMENT AND FOLLOW-UP

For intra-articular fractures, obtain orthopedic consultation to determine the management plan. For nondisplaced fractures, treat an intra-articular fracture with immobilization, a well-padded posterior splint, strict

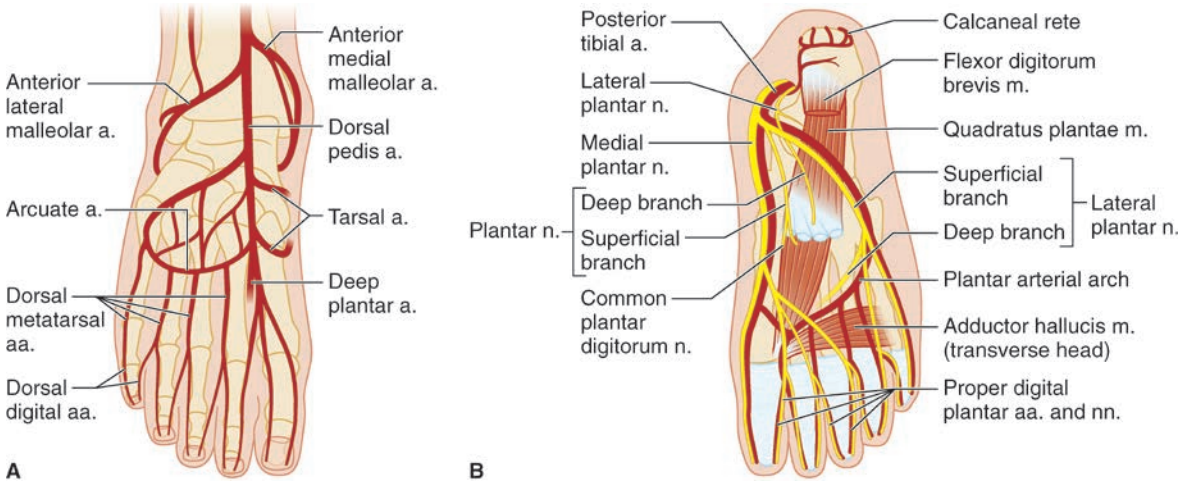


FIGURE 277-2. **A.** Arteries of the dorsum of the foot. **B.** Vessels, muscles, and nerves of the sole of the foot and nerves of the sole of the foot. a. = artery; aa. = arteries; n., nn. = nerves; m. = muscles.



A



B

FIGURE 277-3. **A.** Calcaneal fracture with abnormal Boehler angle. **B.** Normal radiograph with normal Boehler angle. [Image used with permission of Robert DeMayo, MD.]

elevation, non–weight-bearing status, and appropriate analgesia. Elevate the leg above the heart to minimize edema and the risk of compartment syndrome (see the Chapter 278, "Compartment Syndromes"). Displaced fractures may require surgical repair. Care for an extra-articular fracture is elevation, immobilization, analgesia, and orthopedic follow-up. Some of these will require outpatient surgical intervention, with less invasive, percutaneous approaches being adopted in more recent years.[13]

TALUS INJURIES

CLINICAL FEATURES

Fractures of the talus usually require a significant mechanism such as extreme dorsiflexion or a fall from a great height. "Major" talus fractures are those involving the head, neck, or body of the talus (**Figure 277-4**) and can result in avascular necrosis. "Minor" talus fractures are those that do not cross the central part of the talus (**Figure 277-5**). A lateral process talar fracture is sometimes called "snowboarder's ankle" and is commonly mistaken for a lateral ankle sprain.

DIAGNOSIS, TREATMENT, AND FOLLOW-UP

Diagnosis begins with plain radiography, but CT provides better visualization of the talus. Minor talus fractures can be treated on an outpatient basis with a posterior splint, non–weight-bearing status, analgesia, and orthopedic referral. Major talar fractures ideally require orthopedic consultation in the ED.

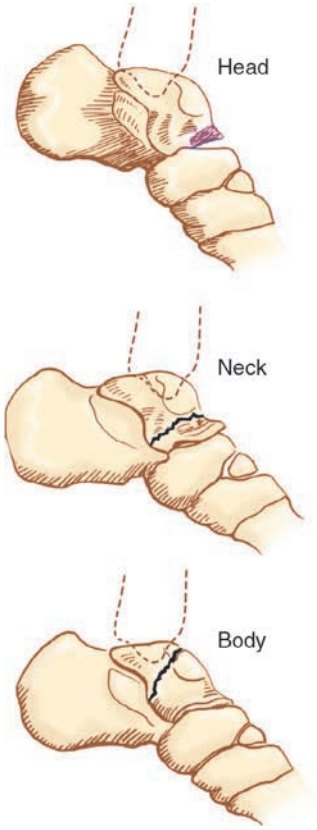


FIGURE 277-4. Major talus fractures. [Reproduced with permission from Simon RR, Sherman SC (eds): *Emergency Orthopedics*, 6th ed. New York: McGraw-Hill; 2011; Fig. 23-13, p. 525.]

Dislocations of the talus, when the tibiotalar joint remains intact, are subtalar dislocations, also known as peritalar dislocations.[14] The talocalcaneal and talonavicular joints are disrupted by a rotational-inversion force. Dislocations are rare but are orthopedic emergencies. Immediate orthopedic consultation and reduction are necessary to prevent neurovascular compromise to the foot.

MIDFOOT INJURIES

LISFRANC INJURIES

CLINICAL FEATURES

The midfoot is divided into two columns; the medial column contains the navicular, cuneiforms, and first three tarsometatarsal joints, and the

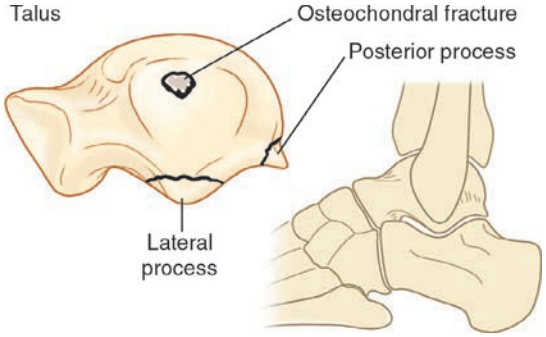


FIGURE 277-5. Minor talus fractures. [Reproduced with permission from Simon RR, Sherman SC (eds): *Emergency Orthopedics*, 6th ed. New York: McGraw-Hill; 2011; Fig. 23-14, p. 527.]

lateral column contains the cuboid and fourth and fifth tarsometatarsal joints (Figure 277-1). The midfoot is a vital bridge between the hindfoot and the forefoot. Injuries to the midfoot have the potential to dramatically affect an individual's daily function, including the ability to stand and walk. Untreated midfoot injuries in diabetics can lead to the development of **Charcot's foot** (collapse of the midfoot arch) and lifelong complications with ambulating.[15]

The cornerstone of mechanism, diagnosis, and treatment of Lisfranc injuries lies in the anatomy of the second metatarsal and the Lisfranc ligament, which runs between the lateral base of the medial cuneiform and the medial base of the second metatarsal. Lisfranc injuries range from sprains to fracture-dislocations, with concurrent fractures of the hindfoot and forefoot being relatively common, especially fractures of the second metatarsal. The usual mechanism of injury for sprains is a low-velocity indirect force, whereas plantarflexion with an axial load (e.g., strenuous jumping over an obstacle) is seen in more significant injuries. Sports injuries (specifically football) and motor vehicle crashes are common causes of these injuries.[10,16–18]

DIAGNOSIS

The Ottawa Ankle Rules (see Figure 276-6) can safely be applied to help exclude midfoot injuries with high accuracy, both in the adult and pediatric populations.[19,20] If no bony tenderness is present at the base of the fifth metatarsal or at the navicular, and the patient is able to bear weight immediately after injury, and while in the ED, no radiograph is required. However, significant pain elicited by torsion of the midfoot or pain on passive dorsiflexion or plantarflexion of the foot may specifically raise suspicion for a Lisfranc injury. When indicated, radiographic studies should include at minimum bilateral weight-bearing anteroposterior (when tolerable), lateral, and 30-degree oblique views of the foot. Bony displacement of 1 mm or greater between the bases of the first and second metatarsals is considered unstable. CT imaging is recommended when radiographic imaging is equivocal because it provides better delineation of bony structures and diagnoses occult fractures or subluxations that can be missed on plain radiographs (**Figure 277-6**).[21]

Lisfranc injuries have multiple classification systems. The Nunley classification groups low-energy ligamentous injuries by diastasis and preservation or loss of arch height: type I are nondisplaced, type II involve diastasis between the first and second metatarsal heads, and type III involve diastasis with loss of arch height.[16] (See Video: Ottawa Ankle Rules)

TREATMENT AND FOLLOW-UP

Treatment of a nondisplaced injury (<1 mm between the bases of the first and second metatarsals) is with a non–weight-bearing splint, rest, ice, and elevation. Orthopedic reevaluation is usually scheduled within 2 weeks when repeat imaging will likely be obtained, and a cast will likely remain on for an additional 4 weeks. At 6 weeks, gradual progressive weight bearing can be attempted.

Fracture displacement, associated dislocation, or evidence of compartment syndrome requires emergent intervention and orthopedic consultation.[10] Whether the reduction is open or closed depends on the degree of the injury and is determined by the orthopedic consultant. Surgical options are variable and range from open reduction and internal fixation to primary arthrodesis.[22]

NAVICULAR INJURIES

Navicular fractures are typically caused by a direct blow or axial loading. Avulsion injuries can also occur with a pulling or rotational force. On physical examination, tenderness and ecchymosis are found about the navicular. Imaging includes bilateral weight-bearing anteroposterior, lateral, and oblique radiographs. CT is best for evaluating the talonavicular joint surfaces. The goals of treatment are maintenance of anatomy and restoration of articular congruity. Nondisplaced fractures should be treated in a non–weight-bearing short leg cast for 6 to 8 weeks, with orthopedic reevaluation in approximately 2 weeks. Orthopedic



A



B

FIGURE 277-6. **A.** Radiograph of Lisfranc injury. **B.** CT of Lisfranc injury. Note the metatarsal bones are fractured (*arrow*) and displaced from the tarsus. [Image used with permission of Robert DeMayo, MD.]

consultation in the ED is usually required for displaced and, therefore, unstable fractures to determine the management plan. Given that the central part of the navicular bone is avascular, complications include avascular necrosis, nonunion, and instability, all of which can lead to a flatfoot deformity.[23,24]

CUBOID INJURIES

The cuboid articulates with the calcaneus and the fourth and fifth metatarsals. Plantarflexion and abduction is the most common mechanism of injury. Imaging includes bilateral weight-bearing anteroposterior, lateral, and oblique radiographs. CT may be helpful. Nondisplaced fractures are treated with a short leg cast and initial non–weight-bearing status. Comminuted injuries are treated with surgery. Complications include foot instability and joint arthrosis.

CUNEIFORM INJURIES

The cuneiforms all articulate with the navicular. Isolated cuneiform injuries are very rare, but especially with a high-energy mechanism of injury, cuneiform fractures can coexist with other fractures of the foot. Imaging studies are the same as for the other bones of the midfoot. Treatment depends on which bone is injured: medial cuneiform injuries are typically treated with surgery, whereas closed reduction usually suffices for the middle and lateral cuneiform bones.

FOREFOOT INJURIES

Forefoot injuries cover a broad range, from those requiring minimal intervention to those requiring operative repair. Fractures range from the minimally displaced to open, comminuted fractures.

FIFTH METATARSAL INJURIES

CLINICAL FEATURES

Fractures of the proximal fifth metatarsal occur in three forms and can be identified using the joint between the proximal fourth and fifth metatarsal as a guide: (1) tuberosity or styloid fractures, which are proximal to the joint; (2) Jones fractures, which are also known as metaphyseal-diaphyseal junction fractures; and (3) diaphyseal stress fractures.

DIAGNOSIS

Plain radiographs are usually adequate. CT scans should be considered for more detailed imaging in the high-performance athlete[25] (**Figure 277-7**).

TREATMENT AND FOLLOW-UP

Patients with nondisplaced Jones fractures should be non–weight bearing in a cast for 6 to 8 weeks. Complications of a Jones fracture treated nonoperatively include bony nonunion, which may later require intramedullary screw fixation. Some orthopedic surgeons are advocating for early surgical correction, especially in athletes, so posterior splinting and outpatient referral to an orthopedic surgeon are appropriate initial treatment.[26,27] Nondisplaced avulsion fractures of the tuberosity, also known as a pseudo-Jones fracture, can be treated with a walking cast and pain control with weight bearing as tolerated.

METATARSAL INJURIES

Proximal fractures of the first through fourth metatarsals are typically caused by a crush injury or direct blow. **Take care to exclude an associated Lisfranc injury**. An isolated proximal metatarsal fracture can be treated with a posterior splint and non–weight-bearing status. Orthopedic follow-up within 2 to 3 days is needed for the likely placement of a more definitive cast.



A



B

FIGURE 277-7. **A.** Anteroposterior radiograph of Jones fracture (*arrow*). **B.** Lateral radiographs of Jones fracture (*arrow*). [Image used with permission of Robert DeMayo, MD.]

Nondisplaced isolated fractures of the shaft of a metatarsal, usually caused by an acute direct blow or twisting force, can typically be seen on oblique or lateral foot films. These can typically be treated with a posterior splint or orthopedic shoe or walking boot (see Chapter 267, "Initial Evaluation and Management of Orthopedic Injuries"). Repeat imaging can be performed 1 week after injury and then again at 6 weeks. Fractures with displacement of 3 to 4 mm or angulation >10 degrees usually require surgical reduction[28] (**Figure 277-8**).



A



B

FIGURE 277-8. **A.** Anteroposterior radiograph of multiple metatarsal shaft fractures. **B.** Lateral radiograph of multiple metatarsal shaft fractures. [Image used with permission of Robert DeMayo, MD.]

STRESS INJURIES

Chronic direct forces cause stress fractures. Stress fractures typically occur in the setting of increasing activity or chronic overuse and are sometimes called "march fractures." Stress fractures are rarely visible on plain radiographs; MRI can be used when pain is persistent. A clinical diagnosis typically suffices. Cessation of the causative activity usually results in good outcomes for recovery.[26]

METATARSOPHALANGEAL INJURIES

Metatarsophalangeal joint injuries are caused by multiple mechanisms and occur in various forms, including sprains, subluxations, and dislocations. **Turf toe** is a form of a sprain that results when there is acute or chronic hyperdorsiflexion of the first metatarsophalangeal joint while the foot remains in plantarflexion. History usually yields the diagnosis. When radiographs are obtained, a capsular avulsion, the hallmark of this injury, is seen. On physical examination, passive ranging results in a pathologically increased range of motion. Treatment is rest, ice, and elevation. Upon returning to sports, a reinforced shoe can be helpful and protective from further injury.[29]

Dislocations of the metatarsophalangeal joint, usually dorsal, can also occur. A high-energy mechanism is the usual cause, and this injury often accompanies other foot injuries. Treatment ranges from closed reduction to operative repair, depending on the severity of injury.

PHALANGE INJURIES

Fractures of the phalanges are the most common fractures of the forefoot, with a stubbing mechanism of the hallucal proximal phalanx being the most common injury.[29] Radiographs are obtained if there is extensive injury or suspicion of foreign body or open fracture or if the great toe is injured. Radiographs are not necessarily obtained for the distal phalanges of the other toes if the only injury is a closed isolated injury of the distal phalanx. Crush mechanisms can lead to distal phalanx fractures. Treatment is with buddy taping to the adjacent toe or application of tape about the forefoot for greater stability (taking care to avoid undue pressure from the tape) and a hard-soled shoe.

For general guidance regarding the care of patients with acute bony foot injuries, see **Table 277-1**.

TENDON INJURIES

Lacerations to the foot may result in injury to the **extensor hallucis longus tendon**, with inability to dorsiflex the great toe, or **tibialis anterior tendon**, with loss of dorsiflexion of the foot. Consult with the orthopedist. Treatment is primary repair if the tendon edges are opposable; otherwise, tendon reconstruction is necessary.[30]

Lacerations of the **flexor hallucis longus** are typically repaired. Lacerations to the **flexor tendons of the other toes** are generally left unrepaired, as there is little if any functional impact.

Dislocation of the **posterior tibial tendon** is uncommon and is often misdiagnosed as ankle sprain. Mechanism of injury is forced dorsiflexion of the foot and ankle eversion when the posterior tibial tendon is contracted, as may occur in snowboarding or ice skating.[31] Treatment is surgical repair.

Achilles tendon injuries are discussed in Chapter 275, "Leg Injuries," Chapter 276, "Ankle Injuries," and Chapter 285, "Soft Tissue Problems of the Foot." Repair of lacerations of the foot is discussed in Chapter 44, "Thigh, Leg, and Foot Lacerations."

Acknowledgments: The authors would like to thank Drs. Esther Choo and Robert DeMayo for many of the radiographic images.

TABLE 277-1 Summary of Emergent Care of Bony Foot Injuries

Fracture or Injury Type	ED Imaging	ED Care*	Orthopedic Referral (immediate: within 24 h; early: within 2 wk)	Home Care/Weight-Bearing Status	Advice on Long-Term Care and Management	Special Considerations
Calcaneal, intra- and extra-articular	Plain films, Boehler angle; CT for subtle findings	Posterior splint	Intra-articular: immediate; extra-articular: early	NWBS; RICE	Possible surgery	
Talus fracture	CT	Posterior splint	Major: immediate; minor: early	NWBS; RICE	Possible surgery	Risk of avascular necrosis
Lisfranc	CT	Splint	Displaced: orthopedic consult in ED; nondisplaced: early	NWBS; RICE	Possible surgery	Risk of compartment syndrome; arthritis. Plain radiographs have low sensitivity
Navicular fracture	Plain films or CT	Splint	Nondisplaced: early; displaced: immediate	NWBS; RICE	Possible surgery	Risk of avascular necrosis; nonunion
Cuboid fracture	Plain films or CT	Splint	Early	NWBS; RICE	Comminuted: possible surgery	
Cuneiform fracture	Plain films or CT	Splint	Early	NWBS; RICE	Medial: possible surgery	
Jones	Plain films; CT for athletes	Splint	Early	NWBS; RICE	Athletes: possible surgery	
Metatarsal fracture	Plain films	Posterior splint	Within a week for a cast	NWBS; RICE	Surgery not likely	
Stress fracture	Clinical			Cessation of causative activity		Plain radiographs usually negative initially
Phalange fracture	Plain films	Buddy taping		Hard-soled shoe and weight bearing as tolerated		
Open fractures of any kind	Consider antibiotics, Td	Pain control	Orthopedic consult in ED			

*All patients with fractures should receive adequate analgesia, and splints should be well padded.

Abbreviations: NWBS = non–weight-bearing status; ortho = orthopedist; RICE = rest, ice, compression, elevation; Td = tetanus booster.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 278

Compartment Syndrome

Maxwell A. Beck
Paul Haller

INTRODUCTION

Compartment syndrome occurs when increased pressure within a limited space compromises the circulation and function of the muscles and nerves within that space. It was first described in 1881 by Richard Van Volkmann, a German physician who noted that paralysis and contractures were the late sequelae of an interruption of the blood supply to the muscles in the forearm.

A high degree of clinical suspicion, coupled with timely surgery, can be used to save function of the muscles and nerves that are at risk of permanent damage from elevated compartment pressures.

ANATOMY

The borders of a confined space are often made up of bone or tissue that offers minimal capacity to stretch. Any increase in volume within that compartment results in an elevated intracompartmental pressure. In the lower extremity, the most common site is at the level of the tibia and fibula, where 40% of compartment syndromes occur. The lower leg has four compartments: anterior, lateral, superficial posterior, and deep posterior (**Figure 278-1**). (Also see Figure 275-1 in Chapter 275, "Leg Injuries.")

The upper leg has three compartments: anterior, posterior, and medial. Due to the larger size of these compartments and their interconnectivity, they are less predisposed to elevated tissue pressures. The foot and buttock region of the leg also have a lower incidence of compartment syndrome.

In the upper extremity, the forearm has three compartments: flexor, extensor, and mobile wad (**Figure 278-2**). These are the high-risk areas in the arm. The hand (**Figure 278-3**) and upper arm (**Figure 278-4**) are less likely to develop a compartment syndrome.

The size of the compartment increases through youth into early adulthood. It then remains the same size through the subsequent years. The amount of muscle mass in a compartment also increases in size until the early 20s, but after age 35 years, it begins to diminish. Thus, after age 35 years, a patient is less likely to develop compartment syndrome.[1]

PATHOPHYSIOLOGY

Tissue perfusion is created by a gradient between the arterial pressure (diastolic in particular) and the venous capillary pressure. Ischemia may occur when the tissue pressure within a compartment exceeds the venous capillary pressure. The normal pressure within a compartment is <10 mm Hg. Pressures up to 20 mm Hg can be tolerated without damage. Cell death results from prolonged exposure to elevated pressures. The exact duration and elevation at which a pressure becomes dangerous remain unclear. Some tissues are more resistant to ischemic damage. Bone is relatively immune; muscle tissue is rather sensitive to ischemia, and nerves can also be easily damaged. Muscles can tolerate ischemic events that last longer than 4 hours. Greater than 12 hours of ischemia clearly leads to cell death and long-term contracture of an extremity. Nerve cells can tolerate periods

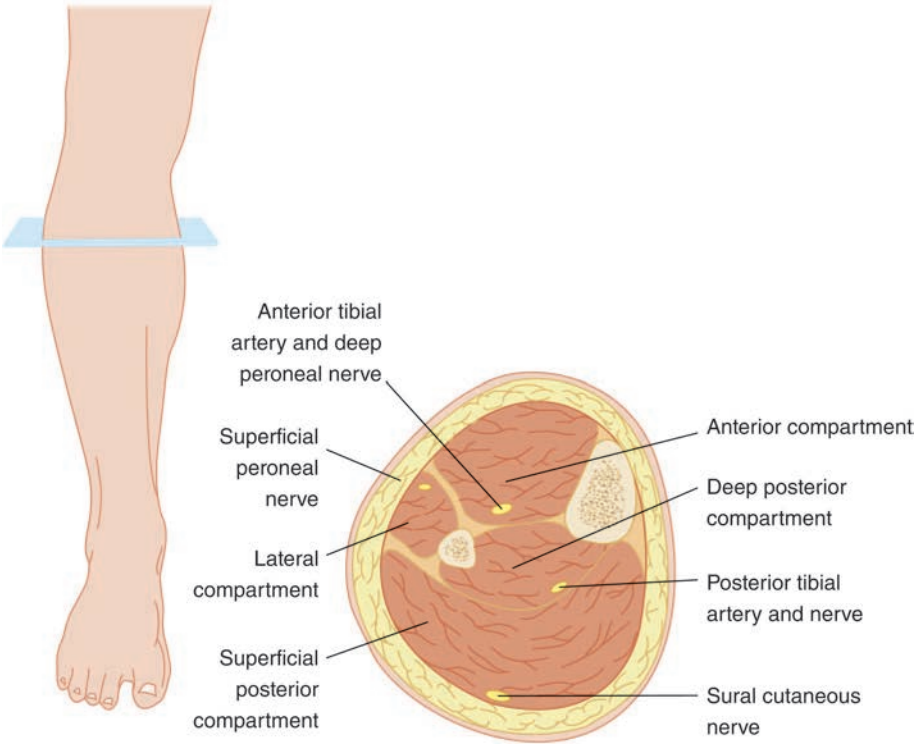


FIGURE 278-1. The four compartments of the lower leg.

of ischemia less than 4 hours in duration. With nerves, ischemic insults longer than 8 hours often result in neuropathy (**Table 278-1**).

CLINICAL FEATURES

HISTORY

Compartment syndrome may occur with or without known trauma. For example, patients with hemophilia or rhabdomyolysis can develop compartment syndrome without direct trauma, and crush injury or tibial fracture can result in compartment syndrome to the affected extremity. In the setting of trauma, symptoms usually develop within a few hours of the injury. The awake patient may initially complain of severe pain in the affected compartment, often refractory to opioids. The pain is due to elevated tissue pressures within a compartment. Thus, the pain worsens when the muscle groups within that compartment are passively or actively stretched. Young age has been shown to be the strongest predictor of developing acute compartment syndrome.[1]

PHYSICAL EXAMINATION

The aggravation of pain by passive or active stretching of muscles in the compartment in question is the most sensitive (and often the only) clinical finding before the onset of ischemic dysfunction.

When nerve conduction is affected, the patient will note numbness or dysesthesia in the sensory distribution of the nerve traversing that compartment; motor nerve function may also be affected. Because tissue pressures do not become higher than arterial pressures, the distal pulse in the extremity will remain normal, and there will not be a change in

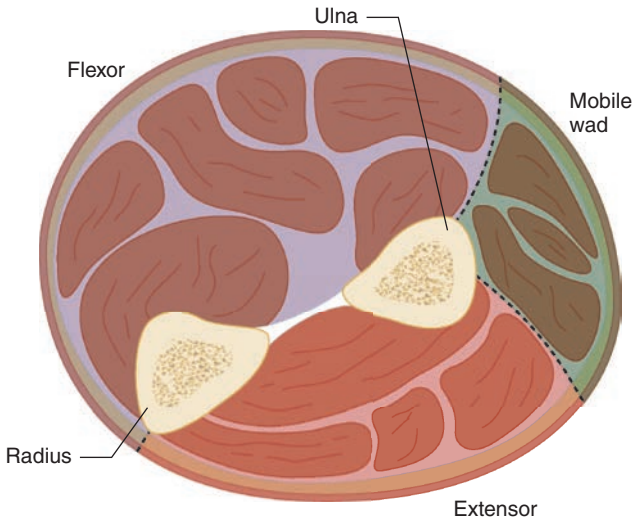


FIGURE 278-2. Forearm compartments.

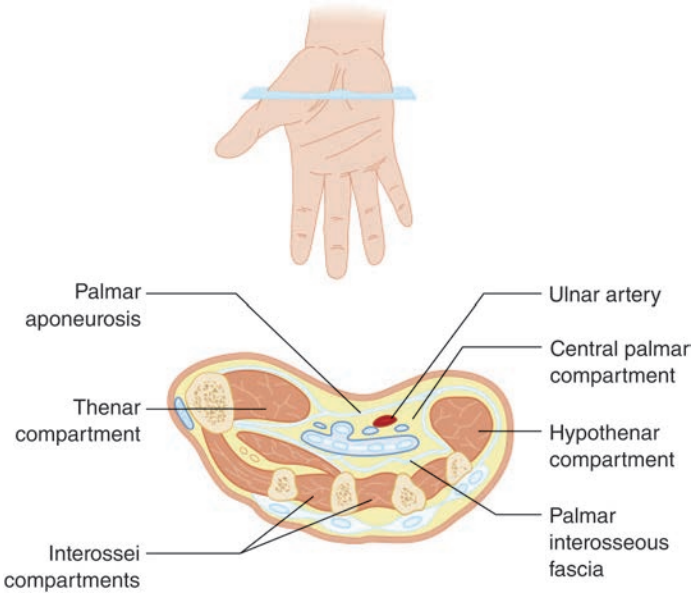


FIGURE 278-3. Hand compartments: transverse section through the right hand.

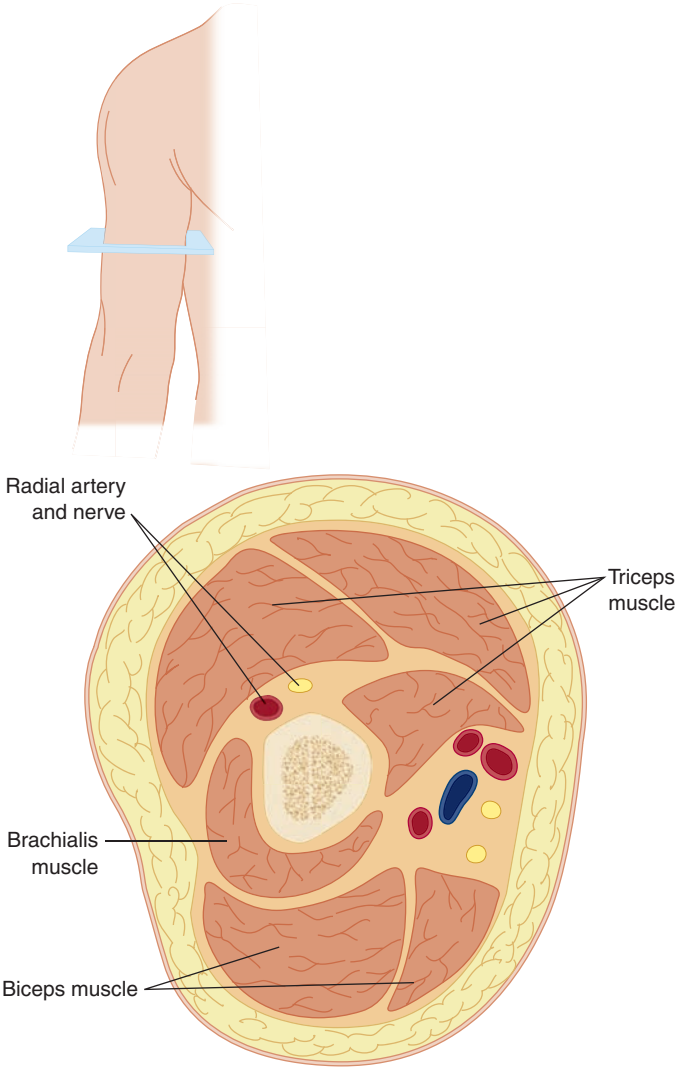


FIGURE 278-4. The biceps brachialis (anterior) and triceps (posterior) compartments of the right arm.

the color or warmth of the extremity. Squeezing or palpation of the muscle groups in the compartments will exacerbate pain. Firmness or fullness in the affected compartment is often detected.

DIAGNOSIS

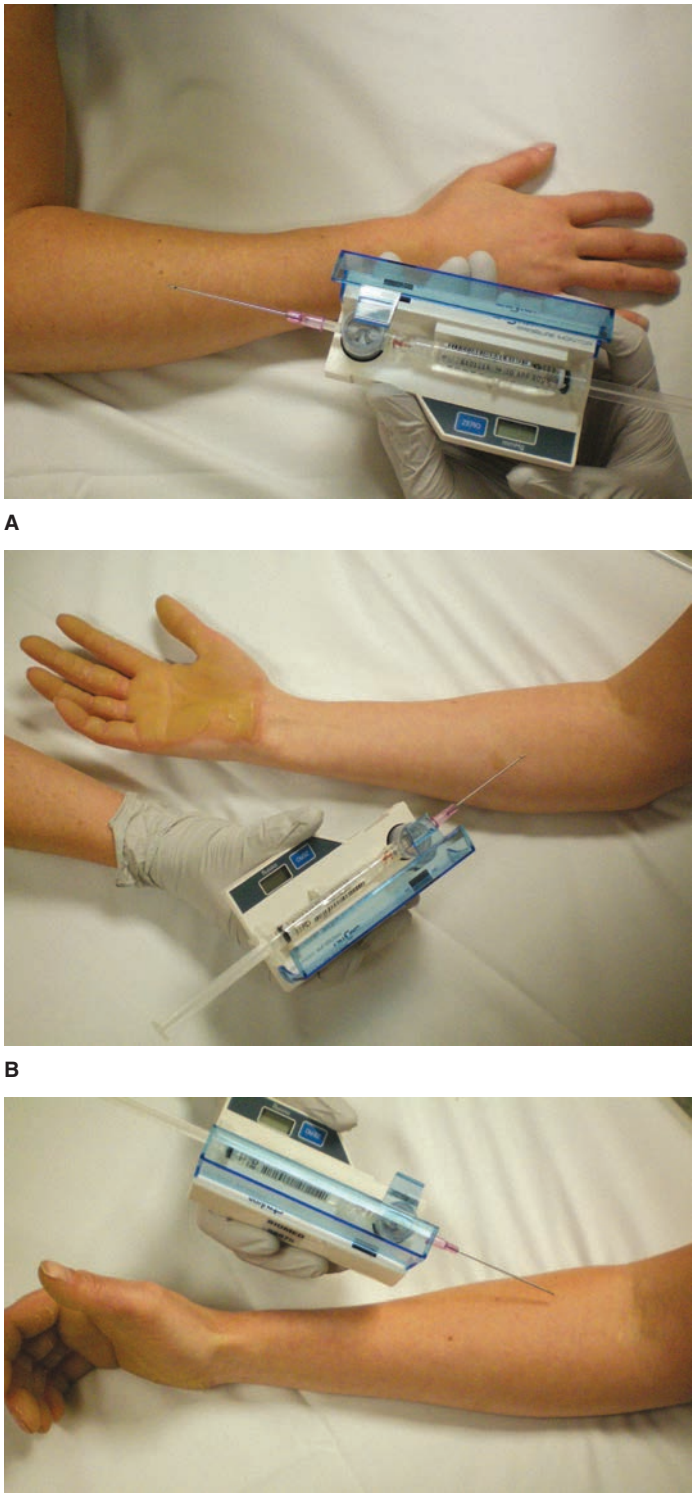
In the appropriate clinical setting, exam findings alone may be sufficient to make the diagnosis and propel the patient in a timely fashion to the operating room for surgical treatment. At times, direct measurement of the tissue pressures in the compartment should be performed to help calculate the delta pressure, confirm the diagnosis, and determine patient disposition.

COMPARTMENT PRESSURE MEASUREMENT

Several commercial devices are available for measuring intracompartmental pressures. A Stryker Kit® is one such system. The kit consists of a saline-filled syringe, a manometer, and a needle with a side port. Connect the manometer between the syringe and the needle. Insert the needle into the compartment. Inject a few drops of saline to ensure that there are no air pockets and that the needle is not inserted into a tendon. The gauge gives the pressure reading in mm Hg. Check pressures twice in each compartment. Also check adjacent compartment pressures. Because pressures are highest near the injured area, obtain the measurements within 5 cm of a fracture site. Figure 278-1 demonstrates appropriate sites for pressure measurements in the lower leg, whereas **Figure 278-5** shows sites for

TABLE 278-1 Tissue Survival of Ischemia

Muscle		Nerve	
3–4 h	Reversible change	2 h	Loss of nerve conduction
6 h	Variable damage	4 h	Neurapraxia
8 h	Irreversible damage	8 h	Irreversible damage



A

B

C

FIGURE 278-5. **A.** Forearm extensor compartment. **B.** Forearm flexor compartments. **C.** Mobile wad compartment.

the forearm. The hands and feet have many compartments within them, all too numerous and small to easily measure. If compartment syndrome is suspected in these sites, some specialists opt for surgical intervention without documentation of elevated pressures.

The precise intracompartment pressure that should mandate surgical decompression remains unclear. Two different pressure measurements are often used. Using only intracompartmental pressures as a guide, it is clear that pressures <30 mm Hg require no intervention, whereas pressure readings >45 mm Hg require decompression. An alternative approach is to measure the difference between the diastolic blood pressure and the intracompartmental pressure. This may be particularly useful in the hypotensive patient. A diastolic pressure that is 30 to 40 mm Hg higher than the compartment pressure may be managed conservatively. A difference between the diastolic pressure and intracompartmental pressure <30 mm Hg does not allow adequate perfusion and should be managed with fasciotomy.

In cases where compartment syndrome is less obvious, such as in patients who are obtunded, continuous measurement of compartment pressures can be helpful. One study determined that continuous intracompartmental pressure monitoring had an estimated sensitivity and specificity of 94% and 98%, respectively.[2] The anterior compartment is usually chosen for monitoring, as it has the highest pressures at any given time. Continuous measurement of compartment pressures in a clinically obvious compartment syndrome is not necessary.

LABORATORY TESTING

Laboratory testing is of no benefit in the setting of compartment syndrome. At times, the serum creatine phosphokinase may be elevated, as may myoglobin levels. Urinalysis may reveal myoglobinuria. Hemophiliacs or patients with clotting disorders need assay of coagulation parameters and factor levels.

TREATMENT

The initial medical management of these patients includes prioritizing the primary survey. Immediately remove restrictive casts or dressings, which alone can markedly reduce tissue pressures. Place the affected limbs at the level of the heart; elevation higher than the heart increases the arteriovenous pressure gradient.

Hemophiliacs should have replacement of factor levels (see Chapter 235, "Hemophilias and von Willebrand's Disease"), and patients on anticoagulants should have reversal or factor replacement (see Chapter 239, "Thrombotics and Antithrombotics").

Surgical fasciotomy reduces intracompartmental pressure. Long incisions are necessary to release pressure in the affected compartment and simultaneously incise adjacent compartments. Tissue edema within the compartment will typically cause the muscle to bulge from the incision sites. The wounds should be initially left open with a second-look procedure for debridement and possible closure scheduled within 48 to 72 hours after the initial intervention. Ideally, definitive wound closure is obtained within 7 to 10 days, which may require skin grafting.

A contraindication to fasciotomy is a missed timely diagnosis of compartment syndrome. Tissue pressures that have been elevated for 24 to 48 hours may have already caused permanent dysfunction, and opening the compartments at this time may be futile.

DISEASE COMPLICATIONS

When fasciotomy is performed in a timely fashion, it can prevent death of the muscle within that compartment and the nerves that travel through it. When delayed, permanent neuropathy and muscle death may occur. Functional impairment is unlikely when compartment syndrome is diagnosed and treated within 6 hours of onset. Delays in diagnosis and treatment carry not only functional implications but also medicolegal ones. In a retrospective review of malpractice claims involving compartment syndrome, increasing time from the first onset of symptoms to fasciotomy was associated with increased indemnity payments.[3]

DISPOSITION AND FOLLOW-UP

Admit all patients with compartment syndrome for surgical management or to an appropriate inpatient unit for serial observation and reexamination. For patients with equivocal findings who are discharged, stress the importance of close outpatient follow-up and immediate return to the ED for worsening pain, paresthesias, or motor dysfunction.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

SECTION 23

Musculoskeletal Disorders

CHAPTER 279

Neck and Back Pain

David Della-Giustina
Jeffrey Dubin

Ankylosing spondylitis is discussed in Chapter 282, "Systemic Rheumatic Diseases."

EPIDEMIOLOGY

Patients presenting with low back pain account for 3% of all ED visits in the United States.[1] Nearly one third of ED back pain patients receive radiographs, and 10% undergo CT or MRI imaging.[2] Analysis of the 2010 Global Burden of Disease study reveals a point prevalence of 5% for low back pain and 9% for neck pain. Back pain is the number one cause of disability in the United States; neck pain is number four.[3,4]

RISK FACTORS FOR SERIOUS CAUSES OF NECK AND BACK PAIN

There are many causes of neck and back pain, including trauma and biomechanical injuries, degeneration, inflammation (arthritides), infection (e.g., diskitis, meningitis, and epidural abscess), infiltration (e.g., metastatic cancer and spinal cord tumors), and compression (e.g., epidural hematoma and abscess). In many cases of atraumatic neck and back pain, no specific cause can be identified. However, due to the high volume of ED patients with neck and back pain, clinicians can develop an indifference to this complaint and potentially overlook serious causes. Take care to perform a systematic evaluation based on risk factors in the history and physical examination, and let findings guide diagnostic testing and management (**Table 279-1**). Consider spinal anatomy while focusing on the presence or absence of neurologic signs to identify pathologic causes and prevent complications.

Radiculopathy and myelopathy are identified through pattern recognition of the motor and dermatome innervations and their associated spinal level (see Figure 164-1 and Tables 164-1 and 164-2 in Chapter 164, "Neurologic Examination").

CLINICAL FEATURES OF NECK PAIN

It is helpful to classify patients with neck pain into two groups: those with uncomplicated neck pain arising mainly from the joints, associated ligaments, and muscles of the neck, and those with neck pain and *radiculopathy* (signs and symptoms attributable to a single nerve root) and/or *myelopathy* (signs or symptoms due to a spinal cord lesion, stenosis, or compression).

HISTORY IN PATIENTS WITH NECK PAIN

Ask about the onset, duration, and location of the neck pain; recent or remote trauma; associated symptoms; stiffness; deformity; neurologic complaints (e.g., weakness, changes in sensation, gait, or vision); constitutional symptoms such as fever, anorexia, and weight loss; and comorbid conditions such as arthritis, cancer, and infections. See Table 279-1 for clues to serious pathology. Rheumatoid arthritis, ankylosing spondylitis, and psoriatic spondyloarthropathy may involve the C1–C2 joint, damage the transverse ligament, and erode the odontoid process, yielding instability of the atlantoaxial joint. Subluxation may occur spontaneously or following a trivial injury. Morning stiffness may signify arthritis. Identify precipitating and palliative factors, maneuvers, or activities. Inquire about prior episodes of neck pain, past diagnostic studies, and treatment. Determine the character of pain and its distribution. Patients with radiculopathy often complain of sharp, burning, intense pain that radiates to the trapezius, periscapular area, or down the arm. Weakness or paresthesias may develop weeks after pain onset. Patients with myelopathy may have neck pain that progresses insidiously and may complain of clumsy hands, gait disturbances, and sexual or bladder dysfunction. **Table 279-2** summarizes important differences in symptoms between uncomplicated mechanical neck pain and neck pain associated with radiculopathy or myelopathy.

PHYSICAL EXAMINATION IN PATIENTS WITH NECK PAIN

Begin with a general assessment of the patient, noting evidence of weight loss, pallor, adenopathy, and abnormalities of posture, movement, and facial expression.[5] Pain may cause splinting of the head on the shoulders during position change. Assess active and passive movement, including rotation (chin to shoulder), lateral flexion (ear to shoulder), and flexion-extension (chin down, then up). Most mechanical causes of neck pain result in asymmetric lesions and asymmetrically limited or painful movements, whereas inflammatory or neoplastic disorders are typically more widespread, with pain and movement restriction being more symmetric.[5] When localized ipsilateral neck pain is felt toward the side of head movement, suspect facet (zygapophyseal) joint irritability. Examine for **Spurling's sign** (Table 279-2). The **abduction relief sign**, performed by having the patient place the hand of the affected upper extremity on the top of his or her head to obtain relief, may indicate soft disk protrusion causing radicular pain. When neck pain occurs on the side away from head movement, suspect a ligamentous or muscular source.

Palpate the posterior cervical triangle, the supraclavicular fossa, carotid sheaths, and the anterior neck. C5–C6 root lesions often elicit tenderness over the brachial plexus at Erb's point, 2 to 3 cm above the clavicle, midway up the posterior border of the sternocleidomastoid muscle in the posterior triangle of the neck. A C8–T1 root lesion may cause tenderness over the ulnar nerve at the elbow.

Pathology in the lymph nodes, salivary glands, or thyroid gland may cause neck pain. A bruit over the subclavian arteries may be associated with thoracic outlet or vascular steal syndrome. Examine the temporal artery for tenderness, because temporal arteritis may be the cause of neck and shoulder pain (see also Chapter 165, "Headache").

Sensory symptoms of pain or dysesthesias are difficult to evaluate, particularly when motor signs are absent, which is often the case in cervical spinal radiculopathies. The discrete separation of the motor and sensory roots at the cervical neural foramina can explain motor sparing despite severe sensory symptoms. For example, C7 root irritability without motor weakness can present as aching at the medial to middle scapular border; aching in the myotome distribution to the chest, axilla, or triceps; or numbness or tingling in the middle finger.

Early detection of cervical spinal myelopathies requires a complete neurologic examination. Hyperreflexia, a positive Babinski's sign, clonus, gait disturbance, sexual or bladder dysfunction, lower extremity weakness, impaired fine hand movement, and upper and lower extremity spasticity may signal myelopathy. Examine for **Lhermitte's sign** (Table 279-2), which is indicative of possible cord compression. **Hoffman's sign** indicates an upper motor neuron lesion. With the patient's hand and wrist supported at rest, the clinician holds the middle finger at the midpoint of the middle phalange, then flicks the tip of the middle finger downward, causing a quick forced flexion at the distal interphalangeal joint. A positive (abnormal) response is flexion of the thumb and index finger in a pinching motion.

TABLE 279-1 Risk Factors for Serious Causes of Neck and Back Pain

Risk Factors	Concern
Historical Risk Factors	
Pain >6 wk	Tumor, infection
Age <18, >50 y	Congenital anomaly, tumor, infection
Major trauma	Fracture
Minor trauma in elderly or rheumatologic disease	Fracture
History of cancer	Tumor
Fever and rigors	Infection
Weight loss	Tumor, chronic infection
Injection drug use	Infection
Immunocompromised	Infection
Night pain	Tumor, infection
Unremitting pain, even when supine	Tumor, infection
Incontinence	Epidural compression
Saddle anesthesia	Epidural compression
Severe/progressive neurologic deficit	Epidural compression
Anticoagulants and coagulopathy	Epidural compression
Physical Risk Factors	
Fever	Infection
Patient writhing in pain	Infection, vascular cause
Unexpected anal sphincter laxity	Epidural compression
Perianal/perineal sensory loss	Epidural compression
Major motor weakness/gait disturbance	Nerve root or epidural compression
Positive straight leg raise test	Herniated disk

Table 279-3 summarizes the sensory, motor, and reflex findings in cervical radiculopathy. This information should be used to determine the level of motor and sensory involvement and to compare findings in the affected and unaffected sides. Bilateral or multilevel involvement usually implies serious pathology.

TABLE 279-2 Differentiating Cervical Radiculopathy From Uncomplicated Musculoskeletal Neck Pain

Factors Favoring Cervical Radiculopathy or Myelopathy*	Factors Favoring Uncomplicated Musculoskeletal Neck Pain*
Pain from the neck radiates down the arm in dermatome pattern.	Tenderness of involved muscles; examiner may find a focal point of tenderness.
Sensory changes along dermatome distribution.	Atrophy or thinning of shoulder muscles (may occur after rotator cuff injury).
Pushing down on top of head, with neck in extension (chin up) and head leaning toward symptomatic side elicits pain, typically toward or down the arm (positive **Spurling's sign**); 90% specific, 45% sensitive.	Pain increases with shoulder abduction on the side of neck pain (increased pain could derive from rotator cuff–related pain; radicular pain may decrease with this maneuver).
Pain may worsen with Valsalva, which increases intrathecal pressure.	Repetitive movement of arm or shoulder at work or play; may be new activity.
Flex neck forward until chin meets chest or pain stops movement. An electric shock sensation radiating down spine into both arms is a positive result (**Lhermitte's sign**). Occasionally, paresthesias occur.	History of recent injury or recent event of awkward position (e.g., neck or head position during sleep in an unfamiliar setting) or awkward standing posture to accommodate a special situation.
Depressed reflexes or, uncommonly, increased reflexes (see also Table 279-3).	Pain is accompanied by "stiffness" of involved muscle group.

*Patient in either pain category is not expected to have all, or majority, of listed signs.

TABLE 279-3 Signs and Symptoms of Cervical Radiculopathy

Disk Space	Cervical Root	Pain Complaint	Sensory Abnormality	Motor Weakness	Altered Reflex
C1–C2	C2	Neck, scalp	Scalp		
C4–C5	C5	Neck, shoulder, upper arm	Shoulder	Infraspinatus, deltoid, biceps	Reduced biceps reflex
C5–C6	C6	Neck, shoulder, upper medial, scapular area, proximal forearm, thumb, index finger	Thumb and index finger, lateral forearm	Deltoid, biceps, pronator teres, wrist extensors	Reduced biceps and brachioradialis reflex
C6–C7	C7	Neck, posterior arm, dorsum proximal forearm, chest, medial third of scapula, middle finger	Middle finger, forearm	Triceps, pronator teres	Reduced triceps reflex
C7–T1	C8	Neck, posterior arm, ulnar side of forearm, medial inferior scapular border, medial hand, ring, and little fingers	Ring and little fingers	Triceps, flexor carpi ulnaris, hand intrinsics	Reduced triceps reflex

DIAGNOSIS OF NECK PAIN

Laboratory testing is rarely helpful, unless considering infection. See the "Epidural Compression Syndrome," "Transverse Myelitis," and "Spinal Infection" sections later in this chapter, as well as Chapter 174, "Central Nervous System and Spinal Infections."

The need for **imaging studies** depends on the clinical condition suspected and the duration of neck pain. Acute (days to weeks), uncomplicated, nonradicular, nonmyelopathic, atraumatic neck pain typically requires no imaging because the cause is likely benign and the treatment is conservative.[5] Obtain three-view cervical spine films in patients with chronic (weeks to months) neck pain with or without a history of trauma, those with neck pain and a prior history of malignancy or remote neck surgery,[5] and those with neck pain and preexisting spinal disorders such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic spondyloarthropathy. Flexion-extension films may be useful if instability is suspected, especially in patients with rheumatoid arthritis or other inflammatory arthritides.[6] Patients with normal radiographs, patients with radiographic evidence of degenerative changes without neck instability, or patients with radiographic evidence of previous trauma *and* no neurologic signs or symptoms require no further imaging.[5] **MRI is indicated for patients with chronic neck pain with new neurologic signs or symptoms regardless of the plain radiographic findings.**[5] MRI is also indicated when plain radiographs reveal bone or disk margin destruction, if there is cervical instability, and (with IV contrast) if epidural abscess or malignancy is suspected.[5] CT myelography is recommended when contraindications to MRI exist.

DIFFERENTIAL DIAGNOSES OF NECK PAIN

Mechanical Neck Disorders Mechanical neck disorders are also called hyperextension strain, acceleration-deceleration injury, hyperextension-hyperflexion injury, neck strain, neck sprain, and whiplash. The most common precipitating events are motor vehicle collisions, falls, sports injuries, and work-related injuries (see Chapter 258, "Spine Trauma" for discussion of acute injury). Strain injury, caused by an awkward position during sleep or prolonged abnormal head-neck positions during work or recreation, is another cause.

Cervical Disk Herniations Cervical disk herniations occur as the nucleus pulposus protrudes through the posterior annulus fibrosis, producing an acute radiculopathy or, occasionally, a myelopathy. Protrusions are usually confined by the posterior longitudinal ligament but can occasionally extrude through this ligament as free fragments. Direct posterior ruptures, although infrequent, can produce progressive myelopathy, whereas the more common posterolateral herniations can cause acute cervical radiculopathy. The levels of most frequent involvement are C5–C6 (C6 root) and C6–C7 (C7 root).

The symptoms of an acute cervical disk prolapse include neck pain, headache, pain distributed to the shoulder and along the medial scapular border, dermatome pain, and dysesthesia in the spinal root distribution to the shoulder and arm. Motor signs include fasciculations, atrophy and weakness in the dermatome distribution of the spinal root, loss of deep tendon reflexes, and, with cervical myelopathy, lower extremity hyperreflexia, Babinski's sign, and in rare cases, loss of sphincter control. Cervical hyperextension and lateral flexion to the symptomatic side (Spurling's sign; Table 279-2) may replicate the symptoms, as can a Valsalva maneuver, whereas manual cervical distraction in flexion alleviates them. A thorough physical examination, including strength, sensory, and reflex testing, may delineate the level of root involvement (Table 279-3). MRI is necessary for diagnosis.

Cervical Spondylosis and Stenosis Cervical spondylosis (or *degenerative disk disease* or osteoarthritis) is a progressive, degenerative condition resulting in a loss of cervical flexibility, neck pain, occipital neuralgia, radicular pain, or occasionally progressive myelopathy. There is progressive degeneration of the disks, ligaments, facet joints (zygapophyseal joints), and uncovertebral joints (joints of Luschka). From a radiographic standpoint, cervical spondylosis may be diagnosed if any one of three findings is present: osteophytes, disk space narrowing, or facet disease. However, there is a high prevalence of cervical spondylosis in asymptomatic individuals. Do not assume painful syndromes are due to findings on imaging. Degenerative disk disease predisposes a patient to progressive osteoarthrosis of the cervical spine, joint instability, and incongruous joint motion during neck movement. Spondylosis most commonly occurs at the C5–C6 and C6–C7 levels.

Osteophytic spurs can encroach posteriorly on the spinal canal, producing cervical myelopathy; laterally on the intervertebral foramen, producing cervical radiculopathy; and anteriorly on the esophagus, producing dysphagia. Spurious osteophytes may also produce Horner's syndrome, vertebrobasilar symptoms, severe radicular symptoms without associated neck pain, painless upper extremity myotome weakness, and chest pain mimicking angina. Neurologic findings (radiculopathy or myelopathy) may be gradual in onset unless there is a history of recent trauma.

Cancer of the Cervical Spine Consider metastatic cancer in the differential diagnosis of chronic neck pain, especially unremitting night pain. Lung, breast, and prostate cancers, lymphoma, and multiple myeloma may involve the cervical spine. Although most cases of epidural cord compression occur in the thoracic spine, involvement of the cervical spine and multiple levels is not unusual. Myelopathy, which is commonly caused by disk or degenerative disease, is rarely caused by metastatic tumors. Plain films have inadequate sensitivity (10% to 17% false-negative rate)[5] in detecting spinal metastases, but may reveal destruction of the vertebral bodies, lytic lesions of the pedicles, and pathologic compression fractures. MRI is the standard for the detection of spinal epidural metastatic disease and cord compression. Cancer patients with radiographic evidence of bone or disk margin destruction should undergo MRI.[5]

Cervical Myofascial Pain Syndrome Myofascial pain syndrome is a cause of chronic neck pain and is often confused with radiculopathy. Myofascial pain symptoms may present or exacerbate acutely, especially after trauma. Psychological distress and specific personality traits are risk factors. Typically, patients complain of pain in the neck, scapula, and shoulder with or without nondermatomal radiation into the upper extremity. Tender spots, "trigger points," may be evident on palpation of the head, neck, shoulder, and scapular region. Neurologic examination is normal. See Chapter 38, "Chronic Pain," for management.

Other Conditions Epidural abscess, osteomyelitis, and transverse myelitis are infectious and inflammatory causes of neck pain (see related sections later in this chapter). Cervical spinal epidural hematoma often presents as neck pain followed by symptoms and signs of cord compression (see later section on epidural compression syndrome) and should be considered in the patient taking anticoagulants or in the patient with a bleeding diathesis. Pain from ischemic heart disease may radiate into the neck and shoulder. Peripheral nerve involvement, such as carpal tunnel syndrome, may present as a C6–C7 sensory radiculopathy, whereas multiple sclerosis, amyotrophic lateral sclerosis, subacute combined degeneration, and syrinx are in the differential of myelopathy.

TREATMENT AND DISPOSITION OF PATIENTS WITH NECK PAIN

Treatment issues can be divided into three categories: neck pain, neck and arm pain consistent with radiculopathy, and myelopathy. There is little evidence-based science to support many of the commonly recommended conservative treatment modalities (e.g., physiotherapy, acupuncture, electrotherapy, manipulation, traction, thermotherapy, medicinal and injection therapies, exercises).[7-11] A European guideline for the management of acute neck pain summarized the available evidence.[12] Individual patients may indeed benefit from one or more of these therapies.

TREATMENT OF UNCOMPLICATED NECK PAIN

Most cases of neck pain without clear underlying pathology will improve with minimal intervention. The patient should be advised to "act as usual" and avoid activities that produce pain. Initial medications may include NSAIDs, muscle relaxants, and for significant pain, a short course of oral opioids; no NSAID, muscle relaxant, or opioid is clearly superior to another in its class.[8,12] Encourage patients to follow up with their primary physician to assess the need for physical or manual therapies or additional medications.

Patients with acute neck pain following an acceleration-deceleration (whiplash) injury may benefit from a similar pharmacologic regimen. Treatment with a semi-rigid collar provided no measurable benefit.[13] A soft collar reduces range of motion of the neck less than 20% and provides no measurable reduction of pain or shortening of recovery time.[14] Spinal manipulation therapy or home exercises after two 60-minute physical therapy sessions may each be more effective than medication therapy for short- and long-term pain relief.[15]

Therapy for neck pain from myofascial pain syndrome should address both muscular tension and psychobehavioral issues. See Chapter 38, "Chronic Pain," for further discussion, including recommendations for alternative therapies.

TREATMENT OF CERVICAL RADICULOPATHY

In the absence of myelopathy, first-line treatment is conservative activity modification to prevent symptom exacerbation or injury and oral medications. Immobilization with a soft or hard cervical collar is controversial without clear evidence for or against its use. Encourage follow-up with a primary physician for possible referral to a spine specialist, an electrodiagnostic evaluation, and additional rehabilitation interventions. Oral medications may include NSAIDs, opioid analgesics, and muscle relaxants. A 7- to 10-day course of oral steroids (e.g., methylprednisolone or prednisone) is commonly prescribed for acute radiculopathy, but steroid efficacy has not been demonstrated.[16] Epidural steroid injections may be effective for chronic cervical radiculopathy when other treatments have failed.[12] If the symptoms and signs of acute cervical root compression fail to respond to conservative treatment, or if they recur, and if imaging demonstrates concordant findings, surgery may be recommended.[12] Indications for hospital admission include progressive upper extremity weakness, especially in the C7 distribution; acute or progressive symptoms or signs of myelopathy; and finally, in a small subset of patients, intractable radicular pain unresponsive to treatment.

TREATMENT OF CERVICAL MYELOPATHY

Treatment decisions for patients with symptoms and signs of cord compression should be made in conjunction with specialists. Cervical spondylotic myelopathy causes the greatest degree of impairment and disability in the continuum of spondylosis. In addition, myelopathy is the most common cause of spastic paraparesis in patients older than 55 years of age, thus paralleling the time course of spondylosis. The patient with myelopathy should be referred to a spine surgeon to discuss the possibility of decompressive surgery. Additional therapeutic considerations (e.g., steroids and radiation in spinal epidural metastases) will depend on the time course of symptoms and signs and etiology, but should be addressed in conjunction with a spine surgeon.[12]

CLINICAL FEATURES OF THORACIC AND LUMBAR PAIN SYNDROMES

Back pain is categorized based on the duration of symptoms: acute back pain lasts <6 weeks, subacute pain lasts between 6 and 12 weeks, and chronic pain continues beyond 12 weeks.[17] Pain lasting >6 weeks is an indicator of more serious disease, since most episodes of nonspecific back pain (80% to 90%) resolve within 6 weeks. Risk factors for serious causes of back and neck pain are listed in Table 279-1; specific historical factors that help to identify benign versus serious causes of back pain are listed in the following sections.

HISTORICAL RISK FACTORS IN BACK PAIN

Patient Age Back pain secondary to tumor or infection is more common in patients <18 years old and >50 years old than in the 18- to 50-year-old age group. Patients <18 years old also have a higher incidence of congenital and bony abnormalities such as spondylolysis, spondylolisthesis, and Scheuermann's kyphosis. Patients >50 years old are also more prone to fractures (age >65 years is more specific for fracture), spinal stenosis, and intra-abdominal processes such as an abdominal aortic aneurysm.

Pain Location and Radiation Pain that originates from muscular, ligamentous, vertebral, or disk disease without nerve involvement is located primarily in the back, possibly with radiation into the buttocks or thighs. *Sciatica*, radicular back pain in the distribution of a lumbar or sacral nerve root, is often accompanied by sensory or motor deficits.[17] Sciatica occurs in only 1% of patients with back pain and is associated with disk herniation or nerve root impingement below the L3 nerve root. Ninety-five percent of herniated disks occur at the L4–L5 or the L5–S1 lumbar disk spaces, impinging on the L5 or S1 nerve roots, respectively.[17,18]

Occult or Minor Trauma In the elderly, minor trauma, such as falling from standing or from sitting in a chair, may cause fracture due to associated osteoporosis. Risk factors for osteoporosis increase the incidence of compression fractures (i.e., female sex, steroid use, alcoholism).

Systemic Complaints Systemic symptoms such as fever, chills, night sweats, malaise, and an undesired weight loss suggest infection, systemic rheumatologic disease, or malignancy. These symptoms are more concerning for infection if the patient has any of the following risk factors: recent bacterial infection (including urinary tract infection, pneumonia, and especially skin abscesses), recent GU or GI procedure, immunocompromised status, injection drug use, alcoholism, renal failure, or diabetes.[19-21] The most significant predictors of spinal infection in decreasing order are fever (or rigors), antimicrobial therapy use in the past 30 days, significant spinal pain, injection drug use, advanced age, and diabetes.[22]

A rupturing abdominal aortic aneurysm is the most immediately life-threatening extraspinal cause of back pain. Other potential causes of pain referred to the back include pancreatitis, a posterior lower lobe pneumonia, nephrolithiasis, and renal infarct.

Pain Features A dull, aching pain that generally worsens with movement but improves with rest and lying still is the typical description of benign back pain. Symptoms suggestive of tumor and infection include pain that occurs at night and often awakens the patient from sleep or that is unrelenting despite appropriate use of analgesics and rest.[17,23] Pain worsened by coughing, Valsalva maneuver, or sitting and that is relieved by lying in the supine position suggests herniation. Spinal stenosis is associated with bilateral sciatic pain that is worsened by activities such as walking, prolonged standing, and back extension and is relieved by rest and forward flexion. In the authors' experience, night pain and unrelenting pain are worrisome symptoms that should be specifically queried as part of the history, because these symptoms are risk factors for serious disease and such queries are often omitted in history taking.

Neurologic Deficit by History Neurologic complaints such as paresthesias, numbness, weakness, and gait disturbances must be further addressed in the history and delineated in the physical examination to determine whether the symptoms involve single or multiple nerve roots. Bowel or bladder incontinence is a serious symptom that raises concern for an epidural compression syndrome, such as spinal cord compression, cauda equina syndrome, or conus medullaris syndrome. If a patient has back pain and has a history of urinary incontinence (acute or chronic) but an otherwise completely normal history and evaluation, measure the postvoid residual volume with bedside US or by catheterization if US findings are in doubt. A large postvoid residual volume (e.g., >100 mL) indicates overflow incontinence, which, when combined with the presence of low back pain, suggests neurologic compromise and an epidural compression syndrome.[17,24]

Past Medical History History of cancer is a risk factor because back pain is the initial symptom in the majority of those with spinal metastases.[24] Malignant neoplasm is the most common systemic disease affecting the spine. Most patients with this diagnosis are >50 years old. In 20% of patients presenting with spinal cord compression, the primary malignancy has yet to be diagnosed.[25] Thus, symptoms such as unremitting pain, night pain, and weight loss require further diagnostic testing.

PHYSICAL EXAMINATION RISK FACTORS IN BACK PAIN

Although fever is a marker of infection, sensitivity for infection is low, varying from 27% for tuberculous osteomyelitis to 50% for pyogenic osteomyelitis, 60% to 70% for pyogenic diskitis, and 66% to 83% for spinal epidural abscess.[19,23] In patients with severe or excessive pain, consider acute spinal infection or abdominal aortic aneurysm. Examine the abdomen, listen for bruits, and palpate for masses, tenderness, and an enlarged aorta.

Examine the back for signs of erythema, warmth, skin abscesses, furuncles, and purulent drainage, which suggest an underlying spinal infection. Contusion and swelling suggest trauma. Palpate the back from cervical spine to sacrum, and percuss the vertebral bodies. Consider fracture or bacterial infection if there is point tenderness to vertebral percussion. Perform **straight leg raise testing**. With the patient lying supine, lift each leg separately to approximately 70 degrees in an attempt to produce radicular pain. A positive straight leg raise test causes a radicular pain radiating below the knee of the affected leg. This pain is worsened by ankle dorsiflexion and improved with ankle plantar flexion or decreasing leg elevation. Reproduction of the patient's back pain or pain in the gluteal or hamstring area when the leg is raised is **not** a positive result. The straight leg raise test can be easily replicated with the patient in the seated position with similar leg extension and foot dorsiflexion (**Figure 279-1**). Straight leg raise testing is a screening examination for a herniated disk. One third of those with positive straight leg raising test and a negative sitting knee extension test have an MRI-proven herniated disk.[26] **A positive straight leg raise test is 68% to 80% sensitive for a L4–L5 or L5–S1 herniated disk.**[26] Radicular pain down the affected leg when lifting the asymptomatic leg is called a positive **crossed straight leg raise test**. A positive result is highly specific but insensitive for nerve root compression by a herniated disk.

Neurologic Examination for Back Pain The neurologic examination is directed to detecting deficits in each of the specific spinal nerve roots. Sensation may be tested by using light touch initially, followed more formally by pinprick, temperature, proprioception, and vibration testing

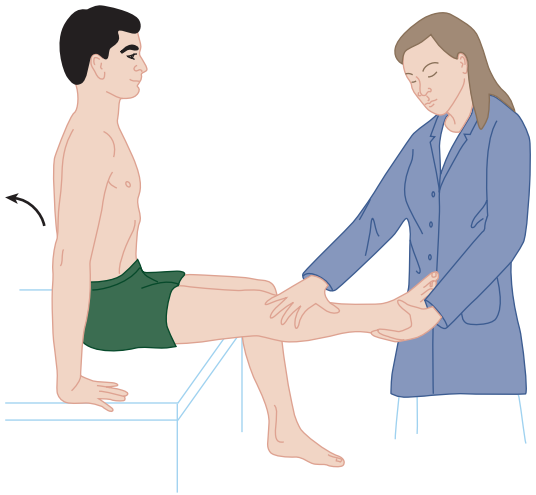


FIGURE 279-1. Sitting knee extension test. With the patient sitting on a table and both hip and knees flexed at 90 degrees, slowly extend the knee as if evaluating the patella or bottom of the foot. This maneuver stretches nerve roots as much as a moderate degree of supine straight leg raising.

if there are any questions regarding diminished sensation. Next assess strength, with a focus on those muscle groups innervated by individual nerve roots (**Figure 279-2**). Individually test the ankle dorsiflexors (L4), extensor hallucis longus (great toe dorsiflexion) (L5), and ankle plantar flexors (S1/S2). Finally, evaluate the patellar (L3–L4), Achilles (S1), and Babinski's reflexes. There is no easily obtainable reflex for the L5 nerve root.

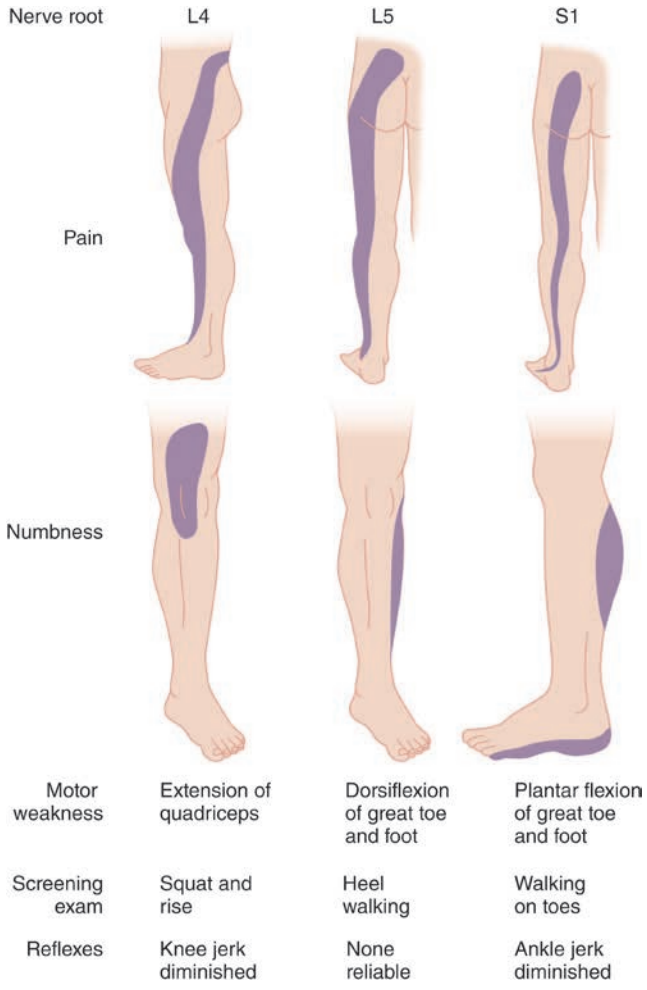


FIGURE 279-2. Testing for lumbar nerve root compromise.

It is not necessary to perform a digital rectal examination on all patients with back pain. However, perform rectal examination in patients with neurologic complaints or findings on physical examination and those with risk factors for serious disease. Evaluate rectal sphincter tone and perianal sensation and the presence of prostatic and rectal masses. Poor rectal tone in association with back pain and saddle anesthesia indicates an epidural compression syndrome.

DIAGNOSIS OF BACK PAIN SYNDROMES

For most patients, no testing is required. However, laboratory testing is indicated in the ED if there is concern for infection, tumor, or rheumatologic causes of the back pain. Order a CBC, erythrocyte sedimentation rate, and urinalysis. With infection, the WBC count may be normal or elevated. However, the erythrocyte sedimentation rate is typically elevated (>20 mm/h), even in immunocompromised patients, with a sensitivity of 90% to 98% for spine infection.[19,23,27] The erythrocyte sedimentation rate will also be elevated in patients with a rheumatologic or neoplastic disease of the spine.[17,19] The C-reactive protein will also be elevated with acute spinal infection.[17,19,23] Obtain a urinalysis to identify urinary tract infection or renal disease causing pain referred to the back.

IMAGING

Plain Spinal Radiographs Plain radiographs can be considered when one suspects fracture, tumor, or long-standing osteomyelitis, but sensitivity is only 83% for tumor and very poor for infection. Anteroposterior and lateral views are sufficient. The coned-down L5–S1 and oblique views rarely add clinically useful information while more than doubling gonadal radiation exposure and cost.

CT Scanning CT imaging is most useful for evaluating vertebral fractures, the facet joints, and the posterior elements of the spine. It shows good detail of the vertebral bodies, but has poor resolution of the spinal canal and spinal cord in comparison with MRI. CT may be useful if MRI is unavailable or unsuitable, but CT myelography is the best substitute for conditions such as epidural abscess or cord compression when MRI is unavailable.

MRI MRI provides the best resolution for lesions in the vertebral bodies, spinal canal, and spinal cord, and for disk disease. MRI is the standard study in cases of suspected spinal infection, neoplasm, and epidural compression syndromes. MRI is also used to determine progression of neoplastic processes of the spine and disk disease and for continued back pain for 6 to 8 weeks. In cases of suspected infection, tumor, or epidural compression, contrast enhancement with gadolinium should be used.[28,29]

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF BACK PAIN SYNDROMES

ACUTE NONSPECIFIC BACK PAIN

Nonspecific back pain is a symptom complex that has countless names, including back strain/sprain, mechanical back pain, and lumbago. However, because strain and/or sprain have no histopathologic findings, a more accurate term to use is *idiopathic or nonspecific back pain*. Nonspecific back pain is the authors' choice of term, especially because most patients will never be given a more precise diagnosis.

Diagnosis is clinical. The pain is mild to moderate and is aggravated with movement and relieved with rest. Although the typical mechanism is usually minor exertion or lifting, the patient may not recall any remarkable etiology. There are no risk factors for serious disease on the history and physical examination, or if any risk factors are present, the diagnostic evaluation is normal.

General Management Treatment focuses on restriction of activity, analgesia, manipulation, and other physical modalities. Monitor symptoms for 4 to 6 weeks before embarking on further diagnostics. In 80%

to 90% of patients, symptoms will resolve on their own within this time period.[17] Watchful waiting avoids wasting time and money and eliminates exposure to unnecessary radiation. This course of action should be discussed with patients because they may expect diagnostic testing.

Patients who resume their normal activities to the furthest extent tolerable recover more rapidly than those on 2 or 7 days of bed rest or those who perform back-mobilizing exercises.[30] Thus, patients should continue daily activities using pain as the limiting factor.[17] Withhold exercise programs until the acute painful episode has resolved or improved significantly.

NSAIDs Medication should primarily be NSAIDs.[31-33] Previously, acetaminophen was recommended; however, recent research shows no benefit.[31,34,35] Most NSAIDs are equally efficacious for back pain.[36] However, there are significant differences in the side effect profiles and toxicity. Ibuprofen was reported to be the least toxic of the 12 NSAIDs studied, with regard to upper GI bleeding.[37] However, a population study did not find a difference in bleeding rates between NSAIDs.[38] Because there is a linear relationship between dose and toxicity, the lowest dose possible should be used in patients at risk. In patients at risk for GI bleeding, the addition of a proton pump inhibitor or misoprostol can reduce the risk.[31,32]

We recommend ibuprofen, 400 to 800 milligrams three times daily, or naproxen, 250 to 500 milligrams twice daily. If there is a concern for GI bleeding, then add a proton pump inhibitor such as omeprazole, 20 milligrams once daily.

Opioid Analgesics Opioid analgesics should only be offered to patients with moderate to severe pain with a limited (3-day) duration.[17,31,33,35] Guidelines do not recommend opioids as first-line treatment for acute back pain.[31,33,35,39]

Muscle Relaxants Muscle relaxants are useful for treating back pain.[31,33] Muscle relaxants, such as methocarbamol, 1000 to 1500 milligrams four times a day, provide some benefit.[31,33] Benzodiazepines, while providing benefit similar to other muscle relaxants, have greater side effects and potential for addiction and therefore are not recommended by guidelines.[31,33] There does not appear to be any additional pain relief or synergistic benefit when muscle relaxants and NSAIDs are used in combination.[31,33,40,41] Corticosteroids taken systemically or injected locally or into the epidural space have no role in the treatment of nonspecific back pain.[31,33,42]

Manipulative Therapy Manipulative therapy, while not generally an ED treatment, is one of the more controversial treatment options for back pain. Clinical outcome of manipulation is no better than standard medical therapy according to a Cochrane review,[43] but in other reviews, it was considered helpful.[33,44,45]

Other Treatments The application of heat or ice may provide temporary symptomatic relief in some patients, with evidence favoring heat.[31] Other physical modalities include traction, diathermy, cutaneous laser treatment, exercise, US treatment, and transcutaneous electrical nerve stimulation; none of these has any proven efficacy in the treatment of acute low back symptoms.

CHRONIC NONSPECIFIC BACK PAIN

There is a higher concern for serious disease in patients with ongoing or intermittent symptoms for a time period of months to years. The best approach is to review the previous evaluations for completeness and to be sure that abnormalities were not overlooked. If the evaluation has been incomplete, then consider completing it in the ED at that visit, or facilitate referral for an outpatient evaluation, with urgency guided by the severity of symptoms. If the evaluation has been thorough but negative, then treat as described for nonspecific back pain. Opioid analgesics should not be prescribed for chronic back pain from the ED. Pharmacologic therapies shown to be effective and recommended for chronic back pain by guidelines include NSAIDs and the serotonin-norepinephrine reuptake inhibitor duloxetine, 30 milligrams once daily.[31,33] Both gabapentin and pregabalin are commonly used for chronic back pain, but neither has been shown to be effective,[46] both have significant sedation effects, and the potential for abuse has been raised.[47] In contrast to the lack of proven benefit for acute back pain, exercise therapy, yoga, tai chi, and multidisciplinary management (at follow-up) have been shown to provide a small to moderate benefit in patients with chronic back pain.[31,33]

LOW BACK PAIN WITH SCIATICA

Although sciatica affects only a very small proportion of all patients with back pain, it is present in the vast majority of patients with a symptomatic herniated disk. Although disk herniation is the most common cause of sciatica, anything that compresses or impinges on the spinal nerve roots, cauda equina, or spinal cord can cause sciatica. Other important etiologies to consider include intraspinal tumor or infection, foraminal stenosis, extraspinal plexus compression, piriformis syndrome (see Chapter 281, "Hip and Knee Pain"), and lumbar canal stenosis (spinal stenosis). Studies find little benefit for most therapy, including NSAIDs, corticosteroids, antidepressants, anticonvulsants, muscle relaxants, or opioids.[48,49] A small study found benefit from gabapentin.[50]

DISK HERNIATION

Diagnosis The diagnosis is suspected clinically and confirmed with nonurgent MRI (urgent MRI only in the setting of suspected epidural compression). Patients who present with sciatica due to a herniated disk generally complain more about the radicular symptoms than about back pain. Because the vast majority of disk herniations occur at the L4–L5 (L5 nerve root) or L5–S1 (S1 nerve root) level, the radicular pain extends below the knee in the dermatomal distribution of that nerve root. A small proportion of patients (often the elderly) have disk herniation at the L2–L3 (L3 nerve root) and L3–L4 (L4 nerve root) levels. The physical examination generally demonstrates localization of pain and a neurologic deficit in a unilateral single nerve root, usually L5 or S1, and frequently includes a positive result on straight leg raise testing.

If the patient has no risk factors in the history and physical examination for serious disease other than sciatica, treat conservatively and do not perform any diagnostic tests in the ED.[17] If the patient has a demonstrable neurologic deficit, consider obtaining plain radiographs to look for other possible causes for symptoms such as tumor, fracture, spondylolisthesis, and infection. Guidelines recommend imaging (MRI preferred) in patients with severe or progressive neurologic deficits and those with serious underlying conditions suspected based on history or physical examination.[17,18] If the symptoms have not progressed rapidly or the symptoms are not severe, the MRI can be ordered routinely or urgently rather than emergently.[18]

Treatment Management is similar as for nonspecific back pain. Routine daily activity is as good as 2 weeks of bed rest in terms of intensity of pain, distress associated with symptoms, and functional status.[18,30] Recommendations for analgesics include primarily NSAIDs and limited opioids for more severe pain.[18,48] NSAIDs are less effective in treating the symptoms of a herniated disk than they are in treating nonspecific back pain.[51] There is insufficient evidence to recommend the use of muscle relaxants and antiepileptic drugs.[18,48-50]

Corticosteroid therapy for herniated disk has limited benefit. Specifically, epidural corticosteroid injection provides a minor reduction in leg pain and sensory deficits in comparison with placebo. However, the improvement in symptoms is not associated with any significant functional benefit, and it does not reduce the need for surgery.[18,48] Although epidural steroid injection is not an ED procedure, it offers an alternative for the moderately to severely symptomatic patient in follow-up. Although oral steroids are used widely, they have no lasting measurable benefit in patients with sciatica.[48]

Spinal manipulative therapy has had varying results. At this time, reviews show that it results in a small decrease in pain up to 12 weeks.[18,44]

Most patients with a herniated disk may be treated and monitored by their primary care physician without specialist referral. Patients generally improve with nonsurgical therapy, with over half recovering in 6 weeks. Most spine surgeons agree that surgery is appropriate only when all three of the following criteria are met: definitive evidence of herniation on imaging study; corresponding clinical picture and neurologic

deficit; and conservative treatment for 4 to 6 weeks that fails to produce improvement.

Emergency decompressive surgery is required only in patients with acute epidural compression syndromes. Patients who underwent surgery had improved function and fewer symptoms at 1 and 2 years postoperatively, compared with those treated conservatively; however, by 4 and 10 years postoperatively, both groups had comparable results.[18,52-54] This is an important point to discuss with your patients to give them reassurance about your treatment plan.

SPINAL STENOSIS

Spinal stenosis is a narrowing of any part of the lumbar spine, including the spinal canal, nerve root canal, and intervertebral foramina, which may occur at single or multiple spinal levels. Degenerative disease causes narrowing and compression of vascular and neural structures. It is a cause of chronic back pain, with or without associated sciatica. The symptoms, which usually begin in the sixth decade, include low back pain that is aggravated by prolonged standing and spinal extension and is relieved by rest and forward flexion. Typically, symptomatic patients present with low back and lower extremity pain while walking that is symptomatically similar to vascular claudication. This symptom is termed *neurogenic claudication* or *pseudoclaudication* to distinguish it from vascular claudication. **Neurogenic claudication is relieved with rest and forward flexing of the spine and worsened by extending the spine**.[54] Physical examination findings are often absent. The diagnosis is made principally by history with confirmation by CT scan or MRI. Symptomatic treatment is the same as for chronic back pain with primary care follow-up.

EPIDURAL COMPRESSION SYNDROME

Epidural compression syndrome is a collective term encompassing **spinal cord compression**, **cauda equina syndrome**, and **conus medullaris syndrome**.

Although the diagnosis of a complete epidural compression is obvious, the challenge is to make the diagnosis in patients with early signs and symptoms. The initial differential diagnosis is broad and includes most conditions that cause weakness, sensory changes, or autonomic dysfunction of the lower extremities. The history and physical examination should narrow the differential diagnosis to a compressive lesion of the spinal cord or cauda equina.

Possible causes of nontraumatic epidural compression include spinal canal hemorrhage with hematoma, tumors of the spine or epidural space, spinal canal infections including spinal epidural abscess, and massive midline disk herniation. Transverse myelitis is a noncompressive condition that may present clinically like a compressive lesion of the spinal cord.

Clinical Features The history usually includes back pain with associated neurologic deficits. Specifically, it may include perianal sensory loss, fecal incontinence or urinary incontinence with or without retention, and sciatica in one or both legs. The duration of symptoms does not differentiate these syndromes from benign causes of back pain. In one small study, **urinary retention of >500 mL alone or in combination with two of the following characteristics—bilateral sciatica, subjective urinary retention, or rectal incontinence symptoms—is the most important predictor of MRI-confirmed cauda compressions**.[55] In addition, a history of malignancy and a rapid progression of neurologic symptoms, especially bilateral symptoms, increase the likelihood of compression.

The physical examination findings vary depending on the level of compression and the amount and area of the spinal cord or cauda equina that is compressed. **The most common finding in cauda equina syndrome is urinary retention with or without overflow incontinence**, with a sensitivity of 90% and a specificity of about 95%.[55] Other common findings for epidural compression include weakness or stiffness in the lower extremities, paresthesias or sensory deficits, gait difficulty, and abnormal results on straight leg raise testing. The most common sensory deficit occurs over the buttocks, posterosuperior thighs, and perineal regions and is commonly called *saddle anesthesia*. Anal sphincter tone is decreased in 60% to 80% of cases.

Diagnosis and Management **When one clinically suspects epidural compression, especially due to tumor, treat the patient with dexamethasone, 10 milligrams IV, before obtaining any confirmatory tests.**[29,56] **After the patient has received dexamethasone, obtain an emergent MRI with gadolinium of the spine.** If investigating the possibility of epidural compression due to neoplasm, obtain an MRI of the **entire spine** because 10% of patients with vertebral metastases have additional silent epidural metastases that would be missed by a localized imaging study.[29,57] The presence of tumors remote from the symptomatic site may change patient management. In addition, the neurologic examination may falsely localize the spinal lesion(s) and limited regional MRI may not detect the lesion. If one suspects a pure cauda equina syndrome from a herniated disk, then it is reasonable to obtain an MRI localized to the lumbosacral spine.

The functional clinical outcome for epidural compression from tumor depends on patient symptoms at presentation. Patients who cannot walk before treatment rarely walk again. Those who are too weak to walk without assistance but who are not paraplegic have a 50% chance of walking again. Those who are able to walk when treatment begins are likely to remain ambulatory.[57] Of those patients who require a catheter for urinary retention before treatment, 82% will continue to require the urinary catheter after treatment. The presence of cord compression is an indication for urgent consultation with a spine surgeon for decompression and/or radiation therapy for a tumor mass, determined by MRI findings.[29,58]

TRANSVERSE MYELITIS

Transverse myelitis is an inflammatory disorder that involves a complete transverse section of the spinal cord. It usually presents with neck or back pain in association with neurologic complaints and findings on physical examination, depending on the level of the spinal cord that is involved. The typical clinical syndrome involves bilateral motor, sensory, and autonomic disturbances that may progress over a period of days to weeks. Fecal and urinary retention and incontinence are common.[59,60] Transverse myelitis may result from viral infection, after vaccination, or as part of a systemic disease such as systemic lupus erythematosus, cancer, or, more commonly, multiple sclerosis.[61] The most important issue regarding transverse myelitis is recognition of the potential for a compressive lesion of the spinal cord and managing the patient as outlined under epidural compression syndromes.[59,60] The MRI may demonstrate lesions of the spinal cord, but MRI findings may lag the clinical presentation, especially early in the disease process.[59] In those situations where the patient has definite neurologic findings that are consistent with epidural compression but has a normal MRI, transverse myelitis is one of the primary working diagnoses. In such cases, consult a neurologist for admission and consider performing a lumbar puncture to assist in the diagnosis. The spinal fluid most commonly demonstrates lymphocytosis and elevated protein.[59] Treatment includes corticosteroids and plasma exchange at the direction of a neurologist.[59,60] Disability is common despite treatment.[62]

SPINAL INFECTION

Spinal infections, such as *vertebral osteomyelitis, diskitis,* and *spinal epidural abscess*, are uncommon but serious causes of back pain. Unfortunately, these infections are commonly missed on first assessment.[23,27] Risk factors for infection include the following: immunocompromised states (diabetes, human immunodeficiency virus infection, and organ transplant recipients), alcoholism, recent invasive procedures, spinal implants and devices, injection drug use, and skin abscesses.[19,23,27,29] See Chapter 174, "Central Nervous System and Spinal Infections for further discussion."

Vertebral Osteomyelitis Patients with **vertebral osteomyelitis** usually have had prolonged symptoms, and in many cases, pain has been present for >3 months.[23,63] On physical examination, about half have fever and vertebral body tenderness to percussion.[23,63] The WBC may be normal, but the erythrocyte sedimentation rate and C-reactive protein are almost always elevated, although this is nonspecific.[19,23,29,63] Blood cultures are positive in approximately 40% of cases of vertebral osteomyelitis and should be routinely drawn as part of the management. In osteomyelitis, plain radiographs are normal until the bone demineralizes, which can take from 2 to 8 weeks. **The most common radiographic abnormalities with vertebral osteomyelitis are bony destruction, irregularity of**

vertebral end plates, and disk space narrowing.[23] See the section on osteomyelitis in Chapter 281 for further discussion.

Diskitis In patients with diskitis, >90% present with a complaint of unremitting back or neck pain, which awakens them at night and is relieved by neither rest nor analgesics.[23] Fever is present in 60% to 70% of patients, whereas the percentage of patients with neurologic deficits is highly variable, from 10% to 50%.[23] Elevation in the erythrocyte sedimentation rate occurs in >90% of patients, whereas elevated WBC count occurs in less than half of patients.[23]

Spinal Epidural Abscess The classic triad of symptoms suggesting spinal epidural abscess is severe back pain, fever, and neurologic deficits, but the triad occurs in only 8% to 13% of patients.[27] Spinal epidural abscess is commonly found in association with vertebral osteomyelitis and diskitis in 62% and 38% of cases, respectively.[27,64] Risk factors for epidural abscess include injection drug use, immunocompromise, alcohol abuse, recent spine procedure, distant site of infection, diabetes, indwelling catheter, recent spine fracture, chronic renal failure, and cancer.[19,27] Erythrocyte sedimentation rate is elevated (>20 mm/h) in >95% of patients,[19,24,29,64] and the C-reactive protein is elevated in >90% of patients.[29] For all suspected spinal infections, contrast-enhanced MRI is the gold standard imaging study. For detailed discussion, see Chapter 174, "Central Nervous System and Spinal Infections."

Treatment of Spinal Infections Evaluation of all spinal infections should occur initially with a spine surgeon. To better understand the approach that your surgeon may direct, we outline the general management of the various spinal infections. Epidural abscess requires antibiotics and emergent evaluation by a spine surgeon with surgical evacuation being a primary consideration. The treatment for diskitis is long-term antibiotics, with surgery reserved for those with spinal cord compression or biomechanical instability. The treatment for vertebral osteomyelitis is primarily medical, consisting of 6 weeks of IV antibiotics followed by a 4- to 8-week course of oral antibiotics. Empiric antibiotic therapy should be directed against methicillin-resistant *Staphylococcus aureus*. Parenteral piperacillin-tazobactam, 3.375 grams IV, and vancomycin, 1 gram IV, or similar agents with broad-spectrum coverage can be given until culture results are available.[20,21,29]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 280

Shoulder Pain

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ANATOMY

The shoulder is designed for mobility in all directional planes, but stability is less than other joints. To meet the many demands placed on it, the shoulder uses three bones, four joints, and a specialized set of soft tissues consisting of muscles, tendons, ligaments, and bursae. Common causes of nontraumatic shoulder pain are subacromial impingement syndrome, rotator cuff tears, acromioclavicular joint disease, adhesive capsulitis, and referred pain.

BONES AND JOINTS

The humerus, clavicle, and scapula are the bones of the shoulder complex. The scapula consists of the body plus three bony extensions: the glenoid, the coracoid, and the acromion. The four joints of the shoulder are the glenohumeral, acromioclavicular, sternoclavicular, and scapulothoracic. The glenohumeral joint is a ball-and-socket joint and is the central axis of shoulder motion. The glenohumeral joint is the most mobile and least stable joint in the body. Stability is derived from three components. The first is the glenoid labrum, which is a fibrous ring of tissue encircling the glenoid cavity. The glenoid labrum increases the surface contact area of the humeral head within the relatively shallow glenoid fossa. The second component consists of three glenohumeral ligaments, which aid stability by reinforcing the joint capsule. Finally, four specialized muscles, known as the rotator cuff, encompass the glenohumeral joint and provide stability during motion.

The sternoclavicular and acromioclavicular joints together contribute to glenohumeral motion, but their primary function is to suspend and stabilize the shoulder girdle. Rotation at the acromioclavicular joint and elevation at the sternoclavicular joint allow complete arm elevation. The scapulothoracic joint represents the articulation of the scapula on the posterior wall of the thorax. Scapular motion is essential for overall shoulder motion: every degree of scapulothoracic motion allows 2 degrees of glenohumeral motion.

SHOULDER MUSCLES

The deltoid, which drapes the shoulder complex and forms its contour, acts as a powerful and independent elevator of the arm. Along with the pectoralis, the deltoid is the primary source of movement of the upper extremity.

The rotator cuff consists of four muscles: supraspinatus, infraspinatus, teres minor, and subscapularis (**Figures 280-1** and **280-2**). All originate on the scapula, traverse the glenohumeral joint, and insert on the proximal humerus. The rotator cuff muscles also contribute to the power of the upper extremity, providing 30% to 50% of the power in abduction and 90% in external rotation.

The supraspinatus muscle originates on the posterior and superior aspect of the scapula and passes beneath the acromion, inserting onto the great tuberosity of the humeral head. It initiates arm elevation and abducts the shoulder. It also balances the power of the deltoid, keeping the humerus centered in the glenoid during deltoid contraction. The infraspinatus originates on the posterior scapula just inferior to the scapular spine. It inserts on the posterior aspect of the greater tuberosity and acts primarily as an external rotator of the arm (Figure 280-1). The teres minor originates on the lateral border of the scapula just inferior to the infraspinatus and inserts on the posterior aspect of the humerus. It works with the infraspinatus to provide external rotation (Figure 280-1). The subscapularis is the only rotator cuff muscle that arises from the anterior aspect of the scapula. It attaches to the lesser tuberosity of the humeral head and provides internal rotation of the arm (Figure 280-2).

The long head of the biceps tendon, although not part of the rotator cuff, assists in rotator cuff function. The long head of the biceps tendon

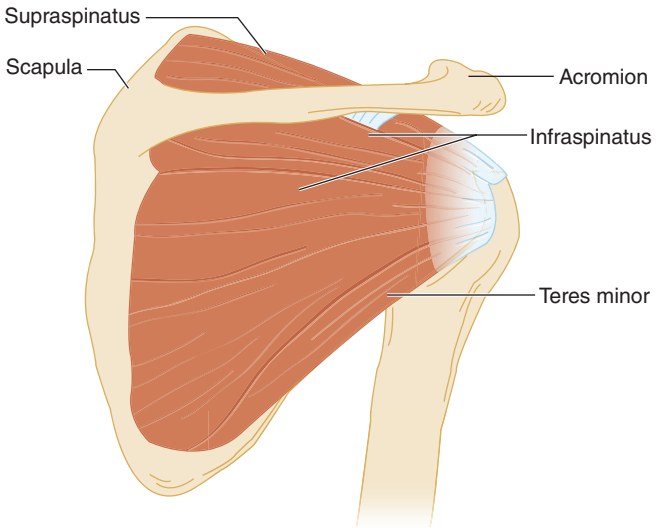


FIGURE 280-1. Posterior view of the shoulder illustrating rotator cuff muscles.

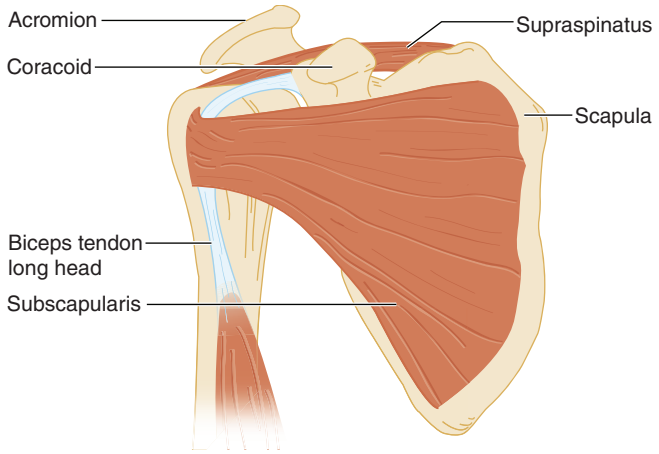


FIGURE 280-2. Anterior view of the shoulder illustrating the supraspinatus muscle and the long head of the biceps.

courses superiorly in the bicipital groove of the humerus between the greater and lesser tuberosities, passes between the subscapularis and supraspinatus tendons, and penetrates the glenohumeral joint to insert on the labrum (Figure 280-2). During arm elevation, the tendon of the long head of the biceps depresses the humeral head, helping it remain centered in the glenoid.

BURSAE

The bursae facilitate frictionless motion between the components of the shoulder. Although there are eight bursae in the shoulder complex, only the extra-articular subacromial bursa is clinically significant. Its roof adheres to the undersurface of the deltoid, and its floor to the underlying rotator cuff. The bursa is lubricated by synovial fluid and surrounded by a layer of peribursal fat.

CORACOACROMIAL ARCH

The coracoacromial arch is formed by the coracoid posteriorly, by the acromion anteriorly, and by the coracoacromial ligament that forms the anterior roof of the arch (**Figure 280-3**). The humeral head provides the floor of the arch. This arch defines the space within which the tendons of the rotator cuff, the tendon of the long head of the biceps, and the subacromial bursa must function.

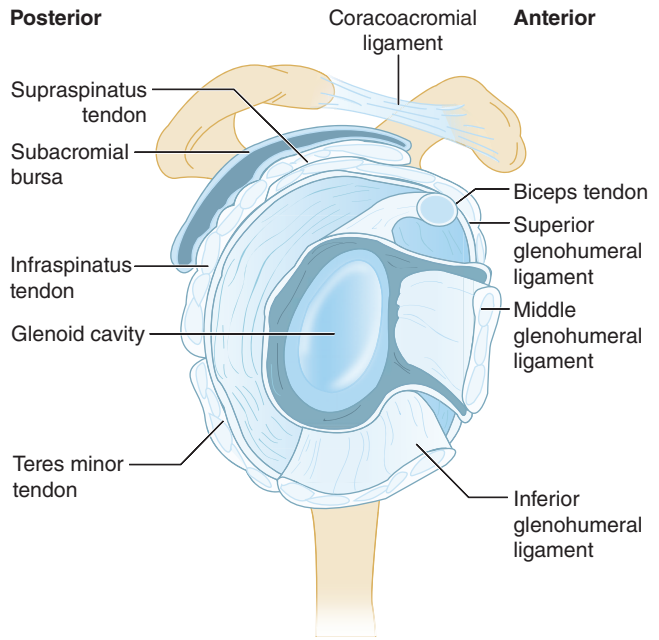


FIGURE 280-3. Lateral view of the shoulder illustrating the coracoacromial arch with the rotator cuff and subacromial bursa.

SUBACROMIAL IMPINGEMENT SYNDROME

PATHOPHYSIOLOGY

Repetitive overhead use of the arm or movement of the shoulder above the horizontal causes encroachment on the subacromial space by the humeral head (**Figure 280-4**).[1-3] Repetitive subacromial encroachment or "impingement" produces pathologic changes of the bursa, rotator cuff, and biceps tendon that result in a loss of the normal gliding mechanism between the rotator cuff and related soft tissues within the coracoacromial arch. Subacromial impingement syndrome is the encompassing term including the conditions of subacromial bursitis, rotator cuff tendinitis, supraspinatus tendinitis, and painful arc syndrome.[1-4]

Subacromial impingement syndrome represents a progressive three-stage pattern of clinical findings due to repetitive impingement of the subacromial space rather than inflammation or injury of a specific structure.[3,4] In stage 1, reversible edema and hemorrhage about the rotator cuff occur. Although possible at any age, it is classically seen in young athletes <25 years old who have excessive overhead use of the shoulder. During this stage, patients complain of a dull ache over the anterolateral shoulder that is aggravated by activity and improved by rest. The clinical course at this point is typically reversible.

Repeated mechanical trauma from the impingement can progress to stage 2, where tendinitis of the rotator cuff creates fibrosis and thickening of the tendons of the rotator cuff and bursa. This stage is typically seen in patients between the ages of 25 and 40, and the prolonged duration (weeks to months) or recurrence of symptoms is useful in making this diagnosis. During this stage, patients complain of a recurrent or chronic aching pain with daily activities, pain with vigorous activity, and night pain (caused by irritation triggered by a relaxed supporting muscle tone).

Continued overuse can lead to stage 3 with rotator cuff tears, rupture of the long head of the biceps, and subacromial spurs. Patients at this stage have progressive symptoms and disability, and they often require surgical decompression of the subacromial space.

CLINICAL FEATURES

The primary symptom of subacromial impingement syndrome is pain, developing insidiously over a period of weeks to months. The pain is located over the anterior to lateral shoulder and frequently radiates to the lateral mid-humerus, but not below the elbow.[1,5] Patients usually complain of pain at night that is deep and aching and interferes with sleep. This pain occurs especially when the patient lies on that shoulder or sleeps with his or her arms overhead. The pain may be exacerbated

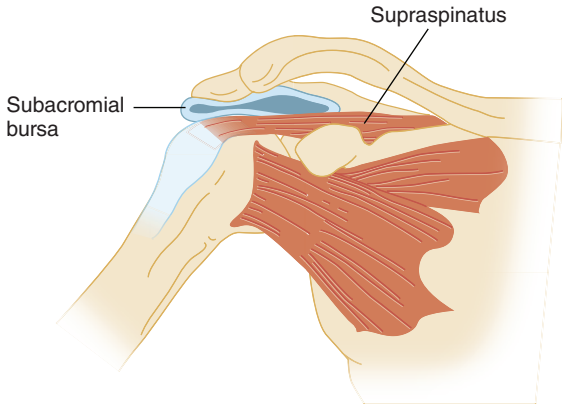


FIGURE 280-4. Impingement of the subacromial bursa and rotator cuff.



FIGURE 280-5. The "empty can" position, which isolates the supraspinatus tendon. Pain or weakness against resistance in this position suggests injury to the supraspinatus muscle.



FIGURE 280-6. Hawkins impingement test. The examiner positions the patient's shoulder at 90 degrees of abduction and 90 degrees of elbow flexion. The examiner then rotates the shoulder internally and brings the patient's arm across the front of the patient.

by activities that require overhead arm use, such as brushing the hair or reaching into a cupboard. Patients also note weakness and stiffness of the shoulder that is usually secondary to pain.[1,5] Once the shoulder pain has resolved, any weakness should trigger a search for a rotator cuff tear or cervical radiculopathy.

Disuse atrophy of the shoulder musculature occurs when impingement or tendinitis symptoms are chronic (stages 2 and 3). Palpation of the rotator cuff insertion at the lateral aspect of the proximal humerus usually produces tenderness. During range-of-motion maneuvers, fibrosis and scarring within the tendon can cause crepitus, but the patient should have a normal and full active and passive range of motion.[5] Pain with an active arc of abduction, especially between 60 and 100 degrees, is consistent with rotator cuff pathology.[1] A sensation of catching also may be present if scar tissue is trapped beneath the acromion. Rotator cuff strength testing usually reveals mild to moderate weakness secondary to pain. The pain is usually present when resistance is applied.

The individual muscles of the rotator cuff should be isolated and tested individually, looking for pain or weakness; to isolate the supraspinatus, abduct the arm to 90 degrees and forward flex it 30 degrees with the thumb pointed down in the "empty can" position (**Figure 280-5**). Either symptom against resistance (continued abduction) in this position suggests inflammation or injury to the supraspinatus muscle, which is the most likely muscle to be involved in the subacromial impingement syndrome.[2]

To isolate the infraspinatus and the teres minor, externally rotate the shoulder with the patient's arm against the body and the elbow bent to 90 degrees and the forearm in neutral position. Stabilize the elbow against the patient's waist and instruct the patient to rotate the arm outward.

To isolate the subscapularis, have the patient place the hand behind the back and attempt to push the examiner's hand away by moving the dorsum of the hand away from the back (lift-off test).

Specific maneuvers on physical examination test for signs of impingement by compressing the rotator cuff and bursa between the humeral head and coracoacromial arch. In the classic impingement maneuver of Neer, the examiner prevents scapular rotation with one hand while raising the patient's straightened arm smoothly in full forward flexion to overhead. A positive sign is pain in the arc between 70 and 120 degrees. A second test, the Hawkins impingement test (**Figure 280-6**), requires the examiner to position the patient's arm (shoulder) in 90 degrees of abduction and 90 degrees of elbow flexion. Rotation of the arm inwardly across the front of the patient with internal rotation of the shoulder compresses the cuff and bursa between the humeral head and coracoacromial ligament. The Neer and Hawkins tests are 75% to 89% and 91% to 92% sensitive, respectively, but specificity is much lower at 30% to 40% and 25% to 44%, respectively.[6]

DIAGNOSIS

The diagnosis is based on a history of chronic shoulder pain with a full range of motion, with possible weakness of the rotator cuff muscles and positive responses to provocative maneuvers. Radiography is used to identify other causes such as fracture or degenerative joint changes. Early nonspecific radiographic signs of rotator cuff syndromes include sclerosis and subchondral cyst formation of the greater tuberosity of the humerus or sclerosis or spur formation on the anterior edge of the acromion.[7] US can be used to rule out tendon rupture or assess for bursitis.[5]

TREATMENT

The goals of treatment of subacromial impingement syndrome are to reduce pain and inflammation and to prevent progression of the process.[5] Therapy starts with a conservative treatment program[5] that should include the following:

- *Relative rest and activity modification.* Advise the patient to avoid the aggravating activity and minimize all overhead activities. Although brief periods of support with a sling may help, **avoid complete immobilization and prescribe range-of-motion exercises** (see later discussion) three to four times daily to minimize the chance of developing adhesive capsulitis.
- *Anti-inflammatories and analgesics.* NSAIDs for 7 to 21 days are key, with short-term (3 days) opioid analgesics added if needed for severe pain. Acetaminophen may aid in lesser pain syndromes.
- *Cryotherapy.* Apply ice to the affected shoulder for 10 to 15 minutes three to four times daily for analgesic effects and potential reduction of inflammation and edema. This is a cornerstone of treatment and should be used liberally.
- *Range-of-motion exercises.* Two simple exercises can help the patient maintain glenohumeral motion. Pendulum swings are done with the patient slightly bent at the waist with the arm hanging freely in front of the body. The arms should be swung in gentle arcs of motion in both a clockwise and counterclockwise direction to the level of pain tolerance for 5 to 10 minutes three to four times daily. The size of the

arcs should increase daily as symptoms allow. Also, the patient should stand sideways an arm's length from a wall and walk the fingers up the wall to the level of pain tolerance, repeating the exercise three to four times daily.

- *Stretching and strengthening.* Stretching and strengthening exercises are best carried out under the supervision of a physical therapist.
- *Corticosteroid injections.* Although local corticosteroid injections into the subacromial space relieve pain, adverse effects include muscular atrophy, weakness, and further tissue degeneration. Injection directly into the tendon can lead to necrosis and rupture. Injection is not an emergency procedure and is best left to the primary care physician or orthopedist.
- *Follow-up.* Ensure reassessment within 7 to 14 days with an orthopedist and/or a rehabilitation expert for consideration of additional therapies.[5]

ROTATOR CUFF TEARS

PATHOPHYSIOLOGY

Patients with rotator cuff tears present with shoulder pain after acute traumatic injury, chronic injury, or an acute extension of a chronic subacromial impingement syndrome (stage 3), the most common cause in patients over age 40.[8] In younger patients, rotator cuff tears are seen in laborers and athletes who participate in sports that require overhead activities like tennis, swimming, and baseball.[8] In general, healthy rotator cuff tendons are resistant to acute injury, with acute rotator cuff tears accounting for only a small minority of all rotator cuff tears. These acute tears usually occur as a result of trauma, such as forced or extreme hyperabduction or hyperextension from falling on an outstretched arm, lifting a heavy object, or catching a heavy object as it falls. Glenohumeral dislocation is a common cause of acute rotator cuff tear, with the frequency of rotator cuff tear after an anterior dislocation ranging from 7% to 32%, with more occurring with advancing age.[8] In patients >40 years of age with a first-time dislocation or in those with weakness >3 weeks after an acute dislocation, think of a rotator cuff tear.[8]

Rotator cuff tears are categorized by the acuteness of the injury and as full- or partial-thickness injuries; however, the differentiation is difficult to identify on the clinical evaluation. Partial-thickness tears are twice as common as full-thickness tears and most commonly occur on the inferior aspect of the tendon. The type and extent of the tear have significant implications for the ultimate treatment and prognosis. The supraspinatus, due to its location within the coracoacromial arch, is the most commonly affected tendon of the rotator cuff.

CLINICAL FEATURES

The clinical features of a chronic rotator cuff tear differ from those of an acute tear. Only about half of patients with chronic rotator cuff tears can recall specific trauma or an event associated with the onset of pain, often seemingly insignificant in description. Patients more commonly report a history of gradual and progressive pain; while initially described as worse at night, the pain eventually becomes persistent. The pain may be diffuse, but is commonly localized to the lateral aspect of the upper arm. Often, initial therapy with rest, anti-inflammatory agents, and glucocorticoid injections helps. If the rotator cuff weakens, the frequency, intensity, and duration of the symptoms increase and are less responsive to the usual treatments. Shoulder dysfunction progressively worsens and interferes with work, recreation, and normal daily activities. Arm elevation, external rotation, and lifting of even light objects worsen the symptoms.

With acute injuries, such as those due to falling or catching a heavy object, the patient may report a "tearing" sensation in the shoulder followed by severe pain and inability to raise the arm. An acute rotator cuff tear produces immediate profound pain and disability, with asymmetry often present due to local swelling. Active motion is limited, with inability to abduct or externally rotate the arm against even minimal resistance. On examination, disuse atrophy is often present in patients with chronic rotator cuff tears. Palpation may produce discomfort at the lateral aspect of the upper arm or in the subacromial region. Most patients with rotator cuff tears have weakness and pain on abduction, elevation, and, most commonly, external rotation. The result of the drop arm test is positive if the patient is unable to hold or lower a fully extended arm at 90 degrees of shoulder abduction without dropping it. Crepitus and pain are usually present on range-of-motion testing.

DIAGNOSIS

It may be very difficult to distinguish a full-thickness tear from a partial-thickness tear or a rotator cuff injury from impingement syndrome. The diagnosis is primarily clinical based on a finding of rotator cuff weakness on examination in a patient with a history of chronic shoulder pain or acute shoulder pain after significant trauma. In patients with an acute injury, it may be difficult to diagnose the tear due to excessive pain from the injury. In these cases, assume a preliminary diagnosis of acute rotator cuff tear and treat conservatively, with appropriate follow-up in 1 week.

Routine shoulder radiographs occasionally give additional diagnostic information. The most specific radiographic sign for large rotator cuff tears is a narrowing of the acromiohumeral space (<7 mm).[7] No radiographic findings are diagnostic of an acute rotator cuff tear, and the diagnosis should rely on clinical findings. MRI, US, and arthrography are the most sensitive modalities for detecting rotator cuff tears, although all tend to underestimate the extent of the tear.[7]

TREATMENT

The basic goals of emergency care for suspected rotator cuff injuries are the same as with impingement (see previous discussion), with analgesia, support, and prevention of further dysfunction and disability. An arm sling can provide support and comfort until the acute symptoms subside. Avoid prolonged immobilization and prescribe range-of-motion exercises three to four times daily to minimize the development of adhesive capsulitis.

Any evidence or suspicion of neurovascular compromise requires immediate orthopedic consultation. Refer all patients with an acute rotator cuff tear (with or without a history of chronic symptoms) and those with significant disability to an orthopedist for follow-up within 1 week. Complete rotator cuff tears usually require surgical repair, and functional results are better if repair is carried out early, before retraction, fibrosis, tendon degeneration, and muscular atrophy have occurred. Partial-thickness or chronic tears may respond to conservative measures.

CALCIFIC TENDINITIS

PATHOPHYSIOLOGY

Calcific tendinitis is a self-limiting disorder characterized by calcium crystal deposition within one or more tendons of the rotator cuff. In time, the calcium undergoes painful spontaneous resorption with subsequent healing of the tendon. The condition most commonly afflicts patients aged 30 to 50 years, and this process is rarely seen in patients >70 years of age. Females are more commonly affected than males, and calcification is often present bilaterally. Primary tendon degeneration as a result of chronic repetitive microtrauma, age, and tissue hypoxia is the proposed cause of this disorder, although a clear etiology remains elusive. Calcific tendonitis most commonly affects the supraspinatus tendon, with calcium deposition usually occurring near its origin on the humerus. However, any of the rotator cuff tendons or the long head of the biceps may be affected.

CLINICAL FEATURES

Three stages represent the process of calcific tendonitis.[9] Because calcification occurs over a period of time, patients are generally asymptomatic or have mild pain at rest or at night in the initial precalcific stage. Pain

with abduction or a "catching" sensation may be present on movement. Calcium deposits accumulate during the calcific stage. During the third portion of the calcific stage, the resorptive phase, incapacitating pain can occur from vascular proliferation, formation of granulation tissue, and calcium crystal extravasation into the subacromial bursa. Symptoms typically last 1 to 2 weeks. After the initially painful resorptive phase, patients can have variable levels of pain and shoulder dysfunction that may last for several months (postcalcific period).

Symptomatic patients experience sudden onset of shoulder pain, usually at rest. Movement of the shoulder further exacerbates the pain. The pain is often worse at night and interferes with sleep. During an acute attack with intense pain, the patient may hold the arm adducted and often is reluctant to move it. A point of maximum tenderness may be palpated over the proximal humerus near the tendinous insertion of the rotator cuff. Both active and passive range of motion of the glenohumeral joint may be limited to varying degrees; document range of flexion, extension, abduction, and internal and external rotation. Crepitus may be present and muscle atrophy may develop.

DIAGNOSIS

Obtain shoulder radiographs for patients with suspected calcific tendinitis to localize deposits and seek any signs of possible impingement.[10] During the initial formative phase, calcium deposits are usually dense and well defined if visualized. In patients who are experiencing intense pain in the resorptive phase, calcium deposits may appear hazy with poorly defined borders. The presence of visible calcifications is not necessarily specific for this disorder. US is unlikely to be helpful during the resorptive phase because the poorly defined calcifications produce little or no acoustic shadowing.[9]

TREATMENT

Treatment is similar to that for impingement syndrome, and nonoperative management is successful in 90% of cases.[10] During an acute attack, NSAIDs, analgesics, and ice help to calm the intense pain. The shoulder may be rested using a sling for brief periods, but avoid prolonged immobilization. Instruct patients to rest the shoulder in abduction on the back of a chair as often as is tolerable. At night, instruct patients to sleep with a pillow beneath the axilla in order to prevent restriction of motion. Local application of heat may be recommended once acute symptoms have diminished. Emphasize and encourage gentle and progressive range-of-motion exercises. Consider physical therapy for patients with more chronic cases who have significantly limited range of motion of the shoulder.

Multiple treatment modalities including subacromial corticosteroid injection, oral steroids, platelet-rich plasma therapy, transcutaneous electrical nerve stimulation, and therapeutic US are used, but no strong supporting evidence exists for their use.[10] Emerging evidence exists for US-guided needle lavage; a comparison of US-guided needle lavage with corticosteroid injection to corticosteroid injection alone showed modestly favorable clinical and radiographic results for the US group at 1 year.[11] This modality also results in an estimated 55% reduction in pain at 1 year.[12] This procedure is not available at many centers.

DISPOSITION AND FOLLOW-UP

Calcific tendinitis is a self-limited process in the vast majority of cases. For patients with new presentation of this disease, arrange follow-up with a primary care doctor within a week. For the 10% of patients in whom nonoperative methods are unsuccessful, arthroscopic or open surgery may be indicated.[10] Refer patients who have progression of symptoms, constant pain interfering with daily activities, or absence of improvement after conservative therapy.[13] Adhesive capsulitis is the most common complication of calcific tendinitis and results in more chronic symptoms.

ADHESIVE CAPSULITIS

PATHOPHYSIOLOGY

Adhesive capsulitis, commonly referred to as frozen shoulder syndrome, begins as painful inflammation of the glenohumeral joint, followed by eventual fibrosis of the joint capsule and restriction of shoulder motion, especially external rotation. Primary or idiopathic adhesive capsulitis is associated with a wide variety of unrelated conditions, including diabetes; thyroid disease; postmenopausal; pulmonary neoplasm; and autoimmune disorders. Secondary adhesive capsulitis produces similar findings, but results from a known cause, such as prolonged immobilization after trauma, surgery, stroke, or a primary inflammatory condition of the shoulder such as impingement syndrome or bicipital tendinitis. The condition is typically unilateral and resolves with conservative therapy in most patients within 1 to 2 years, although some are left with residual pain or stiffness.

Four stages of this disorder exist, although patients do not necessarily follow these stages in a linear fashion. Stage 1, within the first 2 to 3 months, presents with acute synovial inflammation with limitation of shoulder movement due to pain. Decreased shoulder motion, from capsular thickening and scarring, and chronic pain characterize stage 2 (freezing stage) around months 3 to 9. Stage 3 (frozen stage), months 9 to 15, is characterized by less pain but a more fibrotic thick capsule and increased limitation in range of motion. Progressive improvement in the range of motion of the shoulder, usually after 15 months, distinguishes stage 4 (thawing stage), along with significant improvement in pain.[14]

DIAGNOSIS

Limited active and passive range of motion are the hallmarks of adhesive capsulitis. Pain is typically diffuse and aching, poorly localized, accompanied by stiffness, and often extends down the upper arm. The pain is frequently worse at night and at rest, especially in earlier stages. Disuse may lead to muscle atrophy. Impingement testing is difficult due to the restriction of motion. Occasionally, posterior glenohumeral dislocation leads to additional restricted motion of the shoulder; exam and imaging can help detect this condition. US may demonstrate increased vascular flow, thickening of rotator cuff structures, and bulging of the supraspinatus tendon. MRI or magnetic resonance angiography (through follow-up) findings approach 70% sensitivity and 95% specificity for the condition.[14]

TREATMENT

Treatment is geared toward reducing pain and restoring motion and function. Avoid shoulder immobilization; if a sling is used in patients in early stage 1 who have severe pain, limit it to daytime to prevent increased loss of motion due to further capsular restriction. Although physical therapy is difficult in the early, more painful stages of disease, it is crucial, along with NSAIDs, analgesics, and ice. Intra-articular steroid injection is a potential option during follow-up to improve pain and function in the short term; the long-term efficacy is unclear.

Refer patients to an orthopedist if ongoing symptoms persist despite adequate therapy (usually after >6 months) or when the diagnosis is unsure. Closed manipulation under general anesthesia, arthroscopic capsular release, and open capsular release are surgical options.

DISORDERS OF THE BICEPS TENDON

PATHOPHYSIOLOGY

Disorders of the proximal aspect of the long head of the biceps tendon include tendinopathy, subluxation or dislocation, and partial or complete tears; these occur from inflammation, instability, or trauma.[15] The long head of the biceps tendon originates from the superior labrum and the supraglenoid tubercle on the scapula. As it exits the glenohumeral

joint, it courses through the bicipital groove and travels anterior and superior to the humeral head.[15] Approximately 50% of the long head of the biceps tendon originates from the superior labrum. Due to this anatomic association, tears of the superior labrum, known as SLAP (superior labrum anterior to posterior) lesions, are frequently found in conjunction with long head of the biceps tendon pathology. Injuries of one or the other structure may be difficult to distinguish, both clinically and operatively. Biceps tendon pathology is also commonly associated with adjacent pathologies including rotator cuff dysfunction, adhesive capsulitis, glenohumeral joint arthritis, and supraspinatus tendinosis. (See Chapter 271, "Shoulder and Humerus Injuries," for the approach to traumatic ruptures of the distal bicipital tendon.)

CLINICAL FEATURES

Bicipital tendinopathy may be due to inflammation (tendinitis) or collagen tears in or around the tendon (tendinosis) and may be acute or chronic. Tendinitis and tendinosis are difficult to distinguish clinically. Bicipital tendinopathy triggers intense pain localized to the anterior aspect of the shoulder. Repetitive overhead arm motion may result in an acute SLAP lesion, particularly in athletes, or chronic inflammation. Pain at rest, night pain, and pain on rotation are common. Subluxation of the biceps tendon from the bicipital groove is painful and occurs medially or laterally, while complete dislocation is seen only medially and is associated with a subscapularis tear. Posterolateral instability is associated with a supraspinatus tear. Concurrent injury to the biceps reflection pulley is necessary for tendon dislocation in either direction.[15]

Partial or complete rupture is almost always proximal and is due to micro-tears and other age-related degenerative changes in this area of the tendon. In younger patients, mild trauma may cause complete rupture of the biceps tendon, which is heralded by an audible snap or pop followed by severe pain and deformity.

DIAGNOSIS

Palpation of the tendon within the bicipital groove reproduces the intense pain. However, even the apparently simple maneuver of palpating the long head of the biceps tendon is notoriously inaccurate; its identification may be assisted by US. Forearm supination, one of the main actions of the long head of the biceps, also reproduces pain, especially when resistance is applied. In assessing for instability, resisted forearm supination may cause palpable subluxation or a painful popping sensation as the tendon undergoes subluxation; these findings are classic but not common.

Because biceps tendon pathology is frequently associated with pathology of adjacent structures, clinical testing is often inconclusive and inaccurate.[15] Many provocative tests to confirm the presence of pathology of the long head of the biceps or superior labrum have been described in the literature. Speed's test identifies tear or tendinitis of the long head of the biceps; flex the shoulder to 90 degrees with the patient's arm (elbow) fully extended and supinated. Provide downward resistance against shoulder flexion. Pain localized to the bicipital groove indicates a positive test. The Speed's test appears to have a sensitivity of 60% to 87% and a specificity of 80% for tear of the long head of the biceps, with a positive likelihood ratio of 2.77.[16] The uppercut test results in the most favorable positive likelihood ratio (3.38) for diagnosis of biceps tendinopathy, with a sensitivity of 73% and specificity of 78%. The uppercut test combined with US results in 97% sensitivity and up to 100% specificity.[17] The uppercut test is performed with the shoulder held in a neutral position, elbow flexed to 90 degrees, and the forearm supinated, as the patient forms a fist. The patient is instructed to simulate a boxing "uppercut" punch resisted by the examiner who places a hand over the patient's fist. Pain or a painful pop over the anterior portion of the involved shoulder indicates a positive test.

SLAP lesions (superior labral tear from anterior to posterior) are complex, and physical examination alone is usually insufficient to diagnose a SLAP lesion. The test most likely to indicate a SLAP lesion is the active compression test. To perform the test, have the standing patient flex his or her shoulder to 90 degrees, and then adduct 10 to 15 degrees medially and internally rotate so the thumb points to the floor, with elbow extended. The examiner applies a uniform downward force to the arm. This is repeated in full supination. A positive response is indicated by eliciting pain on the first maneuver, which is significantly diminished or absent on the second maneuver; the test is 60% to 100% sensitive and 85% to 98% specific.[16]

The classic finding of biceps tendon rupture is described as a "Popeye" deformity caused by distal contraction of the muscle belly. Supination is weak on muscle testing, but elbow flexion remains strong because of the presence of other intact elbow flexors (short head of the biceps and brachialis muscles).

Plain radiographs are generally unhelpful in diagnosing biceps tendon or SLAP lesions. MRI is also poor in diagnosing biceps tendon and SLAP lesions; magnetic resonance arthrography is preferable. In the hands of skilled operators, US reliably detects biceps tendon dislocation and complete tears. US currently appears to have sensitivity similar to MRI (50%) in detecting partial biceps tendon tears. Arthroscopy is considered the gold standard, although studies have demonstrated poor inter-rater reliability of arthroscopic diagnosis.[18]

TREATMENT

Manage tendinitis and subluxation with brief use of a sling as needed for support and comfort, aided by analgesics, anti-inflammatory agents, application of ice several times daily, and elevation to reduce swelling. Prescribe early mobilization with stretching exercises and follow-up within 7 to 14 days with a primary care provider.

Although not commonly administered by emergency physicians, intra-articular injections of local anesthetic and steroid can improve symptoms. Intra-articular injections can relieve bicipital symptoms but may be ineffective if adhesions or synovitis prevent dispersal into the bicipital groove. Direct injection into the bicipital groove with US guidance may be an option for specialists if previous intra-articular injections have not worked.[18] Bicipital tendinitis usually resolves with conservative therapy.

Reserve orthopedic consultation for those with tendinopathy associated with instability, partial rupture, or high-grade SLAP lesion, or those failing to respond to a conservative treatment regimen. Surgical options include debridement, tenotomy, or tenodesis.[18] Bicipital tendon rupture often requires surgical repair; refer to an orthopedic surgeon for evaluation within 24 to 48 hours. Patients with suspected SLAP lesions or other mechanical proximal biceps injuries generally require arthroscopic or other surgical intervention when symptomatic.

OSTEOARTHRITIS

Because the glenohumeral joint is non–weight bearing, primary osteoarthritis is rare. When it does occur, presentation is like that of degenerative disease in other joints: the patient experiences gradual and progressive onset of pain that is worse with motion and better with rest. This usually occurs concurrently with degenerative disease of the acromioclavicular joint. Secondary osteoarthritis is more common and is usually associated with a previous fracture, recurrent dislocations, or an underlying rheumatologic, metabolic, or endocrine disorder. ED care of both primary and secondary arthritis relies on analgesics, anti-inflammatory agents, and gentle exercises to preserve range of motion.

OTHER CAUSES OF SHOULDER PAIN

Although disorders of the rotator cuff and other intrinsic structures of the shoulder are the most common cause of shoulder pain, extrinsic conditions outside the shoulder complex can refer pain to the shoulder. The differential diagnosis includes disorders of the cervical spine, brachial plexus injuries, axillary artery thrombosis, suprascapular nerve injury, thoracic outlet syndrome, Pancoast's tumor, and miscellaneous thoracoabdominal disorders.

The neck is the most common source of pain referred to the shoulder. Degenerative disease of the cervical spine, degenerative disk disease, and herniated nucleus pulposus can all refer pain to the shoulder. A patient with a C5–C6 herniated disk may present with pain very similar to that due to rotator cuff disease. Careful and thorough examination of the cervical spine and a complete neurovascular examination should be included in the evaluation of any patient with shoulder pain. (See Chapter 279, "Neck and Back Pain.")

Brachial plexus injury can cause pain referred to the shoulder and can produce weakness and atrophy in the muscles of the shoulder within weeks of injury. Radiographic evaluation of the cervical spine should be included in the ED evaluation of patients with suspected brachial plexus injury or involvement. **Brachial plexus neuritis** is uncommon but can be very painful. Its etiology is unknown, although inflammatory, postimmunization, and viral origins have been proposed. Inflammation of the brachial plexus can lead to weakness and atrophy of the muscles of the shoulder complex within weeks following the onset of pain.[19] Brachial plexus neuritis is usually self-limiting and treated with pain medication. Referral to a neurologist should be arranged if this disorder is suspected.

Compression of the suprascapular nerve can cause shoulder pain. This nerve originates from the brachial plexus distal C5–C6 nerve roots and courses posteriorly to the suprascapular notch. It can become entrapped beneath the transverse ligament at the level of the suprascapular notch. Traction injuries from explosive movements can also injure the nerve. On examination, active external rotation typically reveals infraspinatus atrophy and associated weakness. The initial treatment is conservative. Electromyography and nerve conduction velocity studies will reveal the extent and location of nerve injury. Surgery for decompression is considered if conservative measures fail.

The most serious vascular injury that can cause shoulder pain is **acute thrombosis of the axillary artery**. Repetitive mechanical trauma or explosive stress from lifting heavy objects can compress and contuse the intimal lining of the axillary artery, predisposing the artery to thrombosis. Consult vascular surgery.

Compression of the brachial plexus and blood vessels proximal to the shoulder, the **thoracic outlet syndrome**, can cause shoulder pain.[20-22] It is more common in women; the female-to-male ratio is 60:40.[22] The condition most commonly involves the medial trunk of the brachial plexus, and symptoms usually include pain that radiates through the shoulder to the medial forearm and occasionally to the small and ring fingers. Patients also complain of numbness and tingling of the fingers and a weak grip. Patients can commonly identify motions that reproduce the symptoms. A minority of patients will have plain film evidence of a prior clavicular fracture with malunion or the presence of a cervical rib band that compresses the brachial plexus. Conservative measures include activity modification, education, postural exercises, NSAIDs, and physical therapy. CT angiography identifies arterial lesions.[22] US identifies upper extremity venous thrombosis.[21] Imaging in the ED should be based on severity of symptoms, such as evidence of distal ischemia, or signs of upper extremity deep vein thrombosis. In stable patients, referral to the primary care provider is important to initiate a thorough evaluation to differentiate between neurogenic, arterial, and venous thoracic outlet syndrome.[20-22]

Pancoast's tumor may compress the brachial plexus against the chest wall and cause shoulder pain. The patient may experience local or radicular shoulder pain or a sense of fullness in the supraclavicular fossa. CT imaging with contrast is often required for initial diagnosis. Finally, life-threatening disorders should be considered. Myocardial ischemia and infarction, pneumonia, pulmonary embolism, or any disorder that irritates the diaphragm can also cause referred shoulder pain. Abdominal disorders that can cause shoulder pain include biliary tract disease, splenic injury or inflammation, perforated viscus, and ruptured ectopic pregnancy.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 281

Hip and Knee Pain

Kelly P. O'Keefe

INTRODUCTION AND EPIDEMIOLOGY

Every practicing emergency physician over their career will see hundreds of patients with complaints of hip or knee pain that are unrelated to major trauma or an acute fracture. Discomfort and limitations to normal use in these areas are typically related to the minor trauma that occurs on a repetitive basis from performing routine daily functions or exercising. Athletes of all varieties are especially prone to these maladies, where strenuous activity transmits forces that are equivalent to three to five times the body weight directly to these joints. Conversely, the problem of obesity similarly contributes to joint and supporting structural stress and pain.

However, be alert to the various catastrophic processes that can mimic more mundane etiologies, including ruptured abdominal aortic aneurysm, epidural abscess, and septic joint (among others). Pay close attention to historical points, specific risk factors, abnormal vital signs, and physical findings to avoid making a life- or limb-threatening misdiagnosis.

PATHOPHYSIOLOGY AND ANATOMY

The **hip** is a ball-and-socket joint (enarthrosis), allowing motion in all directions. The hip is similar to the shoulder in this capacity but is much more stable and relatively resistant to dislocation. The bones of the joint (femoral head, pelvic acetabulum) are strongly reinforced with a fibrocartilaginous labrum, a joint capsule, overlying ligaments, and numerous muscles.

The **knee** is the largest synovial joint in the body and is relatively complicated in structure, comprising two distinct articulating groups: the tibiofemoral and patellofemoral joints. The patella floats above the main joint, attaching to the femur superiorly by the quadriceps tendon and inserting into the tibia inferiorly by the patellar ligament. The knee is stabilized internally by the anterior and posterior cruciate ligaments, and externally by the medial and lateral collateral ligaments. In addition, distal to the main joint, the fibular head attaches by ligaments to the proximal lateral tibia. The medial and lateral menisci are interposed between, and protect, the femoral and tibial condyles. Numerous muscles, tendons, bursa, and additional ligaments add to the complexity of the joint and serve as potential sources for pain and dysfunction (**Figures 281-1** and **281-2**).

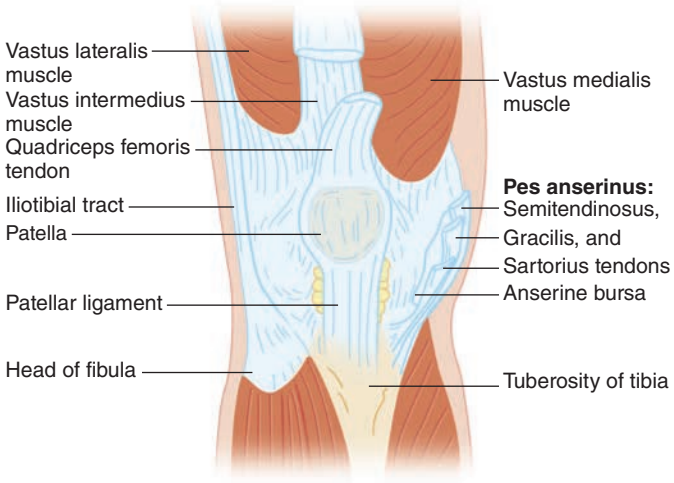


FIGURE 281-1. Anterior view of the knee. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

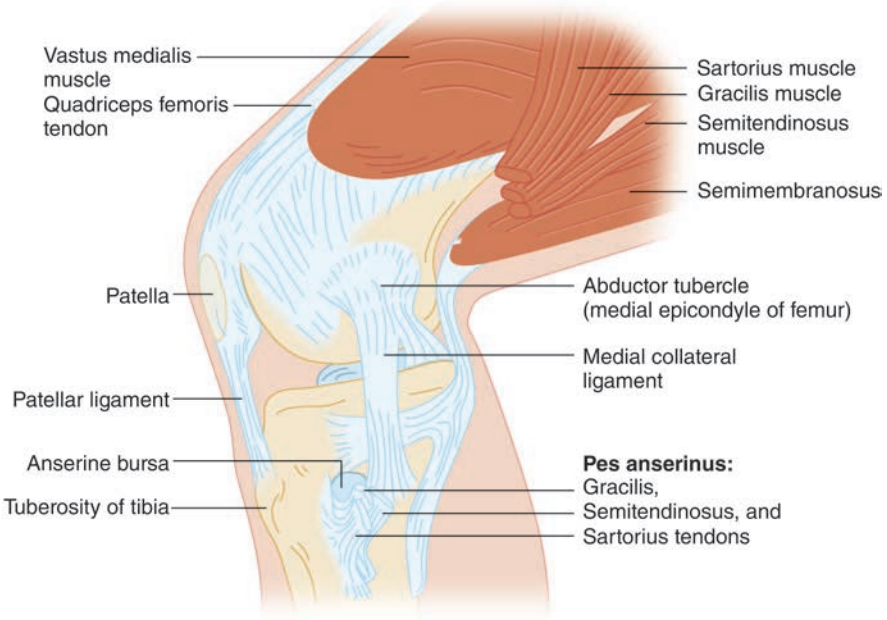


FIGURE 281-2. Medial view of the knee. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

NERVES OF THE UPPER LEG AND REFERRED PAIN

The femoral and sciatic nerves are the major nerves within the thigh (**Figure 281-3**). The femoral nerve is the largest branch of the lumbar plexus, and the sciatic is the longest nerve in the body, traveling posteriorly and supplying sensation to the hip joint through its articular branches. The femoral and obturator nerves also innervate the hip. The femoral nerve divides into anterior and posterior branches, with the posterior becoming the saphenous nerve and providing sensation to the lower leg. The anterior nerve supplies sensation to the anterior medial thigh by the medial and intermediate cutaneous nerves. The two major branches of the sciatic, the peroneal and tibial nerves, course through the posterior fossa of the knee, along with the popliteal artery and vein.

Pain in the area of the knee is not commonly referred to other sites and is usually due to local pathology. However, referred pain from hip pathology is commonly felt in the buttocks, thigh, or groin; may extend to the knee; and may even travel to the foot. Pain felt in the hip and surrounding locations may be referred from pressure on the proximal nerve roots as they exit the lumbar and sacral spine. **In the patient with appropriate risk factors, consider expansion or rupture of an abdominal aortic aneurysm as the cause of hip pain that is not otherwise explained by the history or physical examination, especially when there are no preexisting joint issues.** Bedside US may exclude this life-threatening diagnosis. Other extra-articular sources of hip pain include intra-abdominal or pelvic tumors; diverticular, epidural, or psoas abscess; and the generally less worrisome diagnoses of herpes zoster or herniated lumbar disc.

DIAGNOSIS OF KNEE AND HIP DISEASES AND SYNDROMES

The majority of knee and hip problems can be diagnosed or excluded with a focused history and physical examination (**Table 281-1**).

IMAGING

A suspected diagnosis obtained via history and physical examination is confirmed or ruled out by imaging. For most soft tissue injuries or overuse syndromes, radiographs are not particularly useful unless a history of significant trauma or cancer exists. More sophisticated imaging is typically not needed for evaluation in the ED, but may be indicated

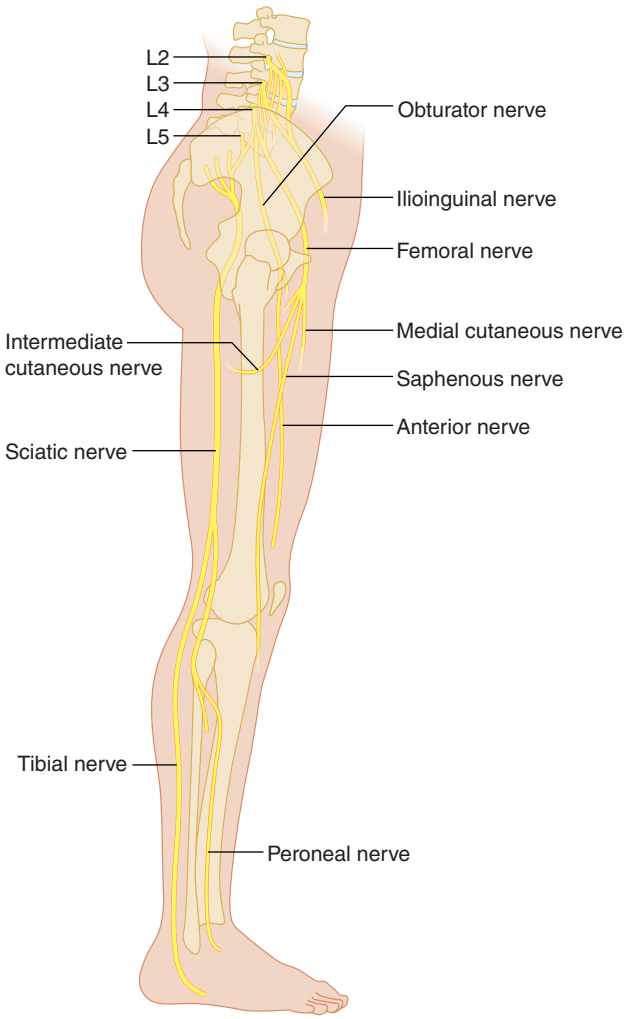


FIGURE 281-3. Nerves that innervate the thigh.

TABLE 281-1 Suggested Clues for the Differential Diagnosis of Hip and Knee Pain

- Determine the location of the pain to narrow down the potential diagnosis.
- Determine the activities that bring on the pain.
- Complaints that the joint "gives out" or "buckles" generally are due to pain and reflex muscle inhibition rather than an acute neurologic emergency. This complaint may also represent patellar subluxation or ligamentous injury and joint instability.
- Poor conditioning or quadriceps weakness generally causes anterior knee pain of the patellofemoral syndrome; therapy should address this weakness.
- Locking of the knee suggests a meniscal injury, which may be chronic.
- A popping sensation or sound at the onset of pain suggests a ligamentous injury.
- A recurrent knee effusion after activity suggests a meniscal injury.
- Pain at the joint line of the knee (palpable indentation between distal femur and proximal tibia) suggests a meniscal injury.

at follow-up or for selected ED patients on an individual basis. US can identify intra-articular or bursal effusions and soft tissue swelling and can localize muscle or tendon injuries.[1-5] Normal comparison US views from the unaffected leg can be helpful. US is very useful for the evaluation of popliteal cysts and arterial structures and will exclude deep venous thrombosis as a cause of pain and swelling.

Plain films are used in the evaluation of bony abnormalities such as severe arthritic changes and spurring, calcification derangements, and other inflammatory processes late in their courses. CT scan provides superior detail of osseous structures, will identify intra-articular loose bodies, and visualizes the early changes of osteonecrosis. Abnormalities of the labrum and joint capsule may also be seen. MRI precisely defines the anatomy of both the hip and knee and provides great detail for soft tissue and bony abnormalities. Although infrequently ordered from the ED, bone scans may be useful for the assessment of a variety of infectious and inflammatory processes, including avascular necrosis. Ultimately, arthroscopy of the knee and hip allows direct visualization of intra-articular lesions and simultaneous treatment.

SPECIFIC SYNDROMES AND DISEASES BY LOCATION

See **Table 281-2** for a summary of the most important conditions.

PSOAS ABSCESS

The psoas muscle is susceptible to the hematogenous spread of infection from distant sites because of its rich blood supply and proximity to overlying retroperitoneal lymphatic channels.[6] *Staphylococcus aureus* is the most common pathogen (80%); other less frequent pathogens include *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Haemophilus aphrophilus*, *Proteus mirabilis*, and enteric pathogens.[6] *Mycobacterium tuberculosis* is a common pathogen in immune-compromised hosts and in non-Western countries.[6]

Symptoms include hip or flank pain (43%), abdominal pain (14%), fever (41%), and limp (22%).[6] Presentation may be insidious. Other symptoms include nausea, weight loss, and malaise. To provoke pain, instruct the patient to perform forceful contraction of the psoas. Place your hand just proximal to the patient's ipsilateral knee, and have the patient raise his or her thigh against your hand. The overall sensitivity of contrasted CT imaging for the diagnosis is over 90%, but is reduced to only 33% if symptoms have been present for less than 6 days.[7] Treatment includes antibiotics to cover *S. aureus* and enteric pathogens and drainage. Consult surgery for percutaneous (most commonly) or open drainage.[6,7]

REGIONAL NERVE ENTRAPMENT SYNDROMES

Lateral Femoral Cutaneous Nerve Entrapment/Meralgia Paresthesia (Anterolateral Thigh Pain) *Meralgia paresthetica*, or compressive inflammation of the lateral femoral cutaneous nerve, is the best known of the lower extremity nerve entrapment syndromes. The nerve enters the thigh under the inguinal ligament near the anterior superior iliac spine and is subject to a variety of minor, recurring traumatic events. Nerve irritation can be triggered by tight clothing belts, heavy tool belts, car seat belts, or corsets; pregnancy; certain sitting positions (i.e., riding a lawnmower); focal trauma, including surgical interventions such as appendectomy or hysterectomy; and obesity. It has been reported in women with muscular thighs performing activities that require repetitive flexion/extension of the leg, such as cheerleading, and in runners. Symptoms include pain to the hip area, thigh, or groin along the distribution of the nerve (proximal anterior lateral aspect of the leg; **Figure 281-4**), burning or tingling paresthesias, and hypersensitivity to light touch. Pain may be worsened or reproduced during physical examination by tapping over the area of the anterior superior iliac spine. Those affected should limit the exacerbating activity and

TABLE 281-2 Selected Syndromes by Location

Diagnosis Category	Diagnosis	Pain Location
Nerve entrapment	Meralgia paresthetica	Anterolateral thigh pain or paresthesias
	Obturator nerve entrapment	Groin and inner thigh pain
	Ilioinguinal nerve entrapment	Groin pain
	Piriformis syndrome (sciatic nerve compression by piriformis muscle)	Buttocks and hamstrings pain
Hip bursitis	Trochanteric bursitis	Hip pain when lying on side or with hip abduction and adduction
	Ischiogluteal bursitis	Ischial pain
	Iliopectineal and iliopsoas bursitis	Anterior pelvis and groin, hip extension
Knee bursitis	Pes anserine bursitis	Anterior medial knee pain
	Prepatellar bursitis	Pain anterior to patella
Hip overuse syndromes	External snapping hip syndrome (coxa saltans)	Posterior lateral hip pain
	Fascia lata syndrome	Lateral thigh pain
Knee overuse syndromes	Patellofemoral syndrome (runner's knee)	Anterior knee pain, worse with prolonged knee flexion
	Medial plica syndrome	Anterior medial knee pain, knee snapping during repeated flexion/extension
	Iliotibial band syndrome or snapping knee syndrome	Pain over lateral epicondyles, or snapping when iliotibial band passes over femoral condyle
	Popliteus tendinitis	Posterior lateral knee pain, worse on downhill exercise
	Patellar tendinitis (jumper's knee)	Inferior patellar or proximal patellar tendon pain
	Quadriceps tendinitis	Proximal patellar pain
	Popliteal (Baker) cyst	Posterior knee pain

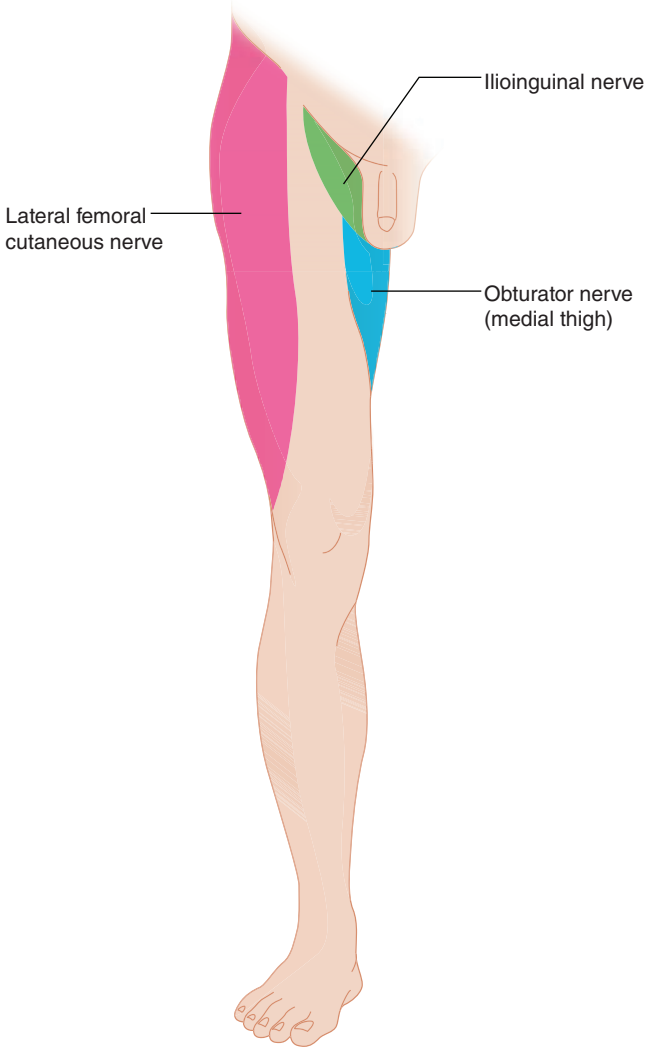


FIGURE 281-4. Local innervation and locations of pain for specific thigh and groin nerves.

eliminate the source of the irritation. NSAIDs, local injections, weight loss, and (rarely) surgical excision of the nerve are other treatment options.[8,9]

Obturator Nerve Entrapment (Medial Thigh/Groin Pain) Obturator nerve entrapment is typically a sequela of pelvic fractures or abdominal/pelvic surgery. Obturator nerve inflammation is generally sensed in the groin and down the inner thigh (Figure 281-4) and aggravated by movement of the hip. Exercise-induced medial thigh pain may be the predominant symptom. The nerve is entrapped in athletes due to the presence of a fascial band at the distal obturator canal or may be compressed due to pelvic hematomas or other masses. Surgery may be required for pain relief. Imaging studies are of limited value, but needle electromyography reveals the characteristic findings of chronic denervation. Local injection of lidocaine into the area of the nerve relieves the pain and associated reactive weakness and may make the diagnosis; however, the nerve block is both difficult to perform and rarely done in the ED.[10]

Ilioinguinal Nerve Entrapment (Groin Pain) The ilioinguinal nerve arises from the lumbar plexus and passes through the psoas muscle, the transversus abdominis muscle adjacent to the anterior superior iliac spine, and the abdominal oblique muscles into the inguinal canal to innervate the groin and scrotum or labrum. Entrapment occurs due to hypertrophy of the abdominal wall musculature or pregnancy. Hyperextension of the hip produces pain and hypoesthesia in the distribution of the nerve, yielding groin pain.[11]

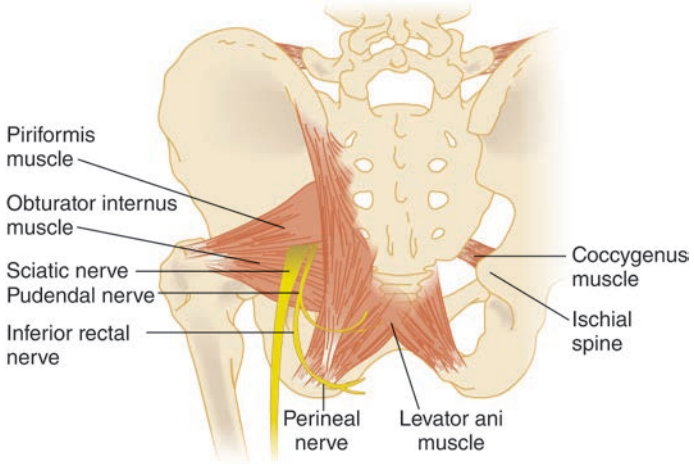


FIGURE 281-5. Proximity of the piriformis muscle and the sciatic nerve. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

Piriformis Syndrome (Buttock/Posterior Thigh Pain) Compression of the sciatic nerve generally produces pain in the distal extremity, but irritation of the sciatic nerve from the piriformis muscle, referred to as the piriformis syndrome, causes pain in the area of the buttocks and hamstring muscles that is worsened by sitting, climbing stairs, or squatting (**Figure 281-5**). The clinician may palpate a tender mass over the piriformis muscle and elicit pain in the region of the sacroiliac joint or gluteal musculature. Hip flexion and passive internal rotation will exacerbate the symptoms. Imaging is useful only to rule out other conditions. Treatment is conservative.

BURSAL SYNDROMES OF THE HIP AREA

Bursae are self-contained flat sacs, lined with synovium, that reduce friction between tissues moving over each other in a repetitive fashion, such as ligaments, tendons, and bone. New bursae may form at any area that is subject to repeat irritation. Causes of bursal pain include inflammation (with repetitive minor trauma; rheumatologic disorders, such as psoriatic arthritis, rheumatoid arthritis, or ankylosing spondylitis; and crystalline disease, such as gout or pseudogout) and infection. Certain bursae are more prone than others to these insults, and these produce symptoms in specific locations that the practitioner should recognize.

Inflammation may be difficult to distinguish from infection, because both share common symptoms and signs, with a significant overlap in diagnostic cell counts when bursal fluid is aspirated. A positive Gram stain or bacterial culture is definitive for septic bursitis, but infection may be present in the absence of these findings. Occasionally, with trauma or prolonged inflammation, a bursa may develop direct communication with a joint. Arthrocentesis is required when a septic joint is suspected. The development of a draining sinus tract favors septic bursitis (see Chapter 284, "Joints and Bursae").

Trochanteric Bursitis (Posterolateral Hip Pain) The trochanteric bursae lie between the gluteus maximus and the posterolateral greater trochanter, with deep and superficial components (**Figure 281-6**). Female runners with a broad pelvis are prone to inflammation in this location. Pain in this location is also commonly seen in older patients and can be a complication of rheumatoid arthritis. Pain is elicited when lying on the affected side, with direct pressure, or with motion such as walking or stair climbing. Activities where the hip is abducted aggravate the deep bursa, while the superficial component is irritated with adduction. Pain is revealed by palpation over the greater trochanter and resisted abduction or adduction of the hip.[12,13]

Bursitis from abnormal calcification is uncommon but may affect the trochanteric bursa. Calcific bursitis is identified on plain radiographs or CT as a poorly marginated line that is clearly separated from the femoral

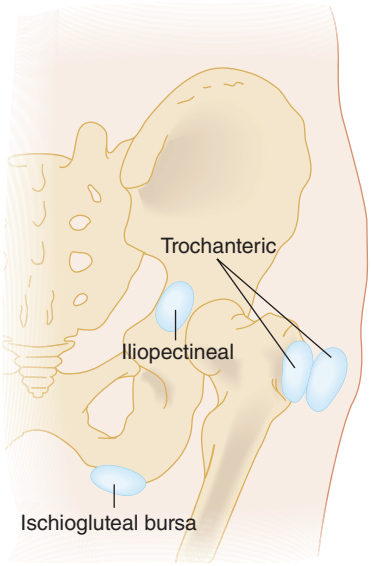


FIGURE 281-6. Selected bursae of the hip and pelvis. Proximity of the piriformis muscle and the sciatic nerve. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

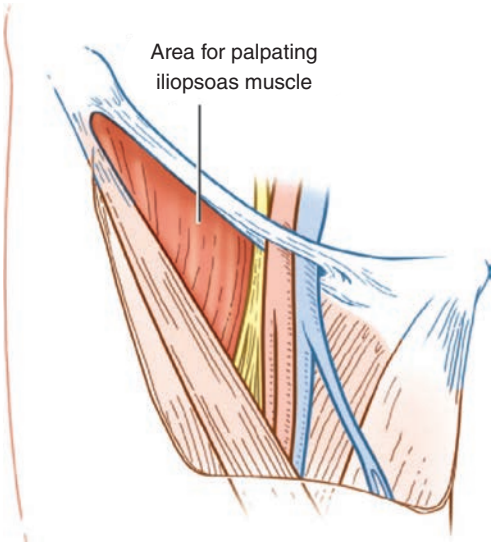


FIGURE 281-7. Iliopsoas bursitis. Area for palpating the iliopsoas muscle and bursa. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 7th ed. © 2014, McGraw-Hill, Inc., New York. Figure 18-21.]

cortex. Calcification may also form around tendons. Trochanteric bursitis is overdiagnosed.[14] Alternative causes of the "greater trochanteric pain syndrome" include external coxa saltans (snapping hip syndrome), abductor tendinopathy (involving one or more of the three gluteal muscles or the tensor fascia lata), and tendon tears.[15] Patients who do not respond to typical measures should be referred for further evaluation, as treatment may include surgical options.[14,15] Sonography may assist in making a more precise diagnosis.[16-19]

Gluteus medius tears are often misdiagnosed as trochanteric bursitis and are sometimes called the **rotator cuff injury of the hip**. The gluteus medius inserts onto the greater trochanter, and is important for leg abduction and stabilization of the hip during the stance phase of gait. Acute tears may cause a "pop" in the hip. Symptoms include pain on weight bearing, difficulty climbing stairs, and limping. Back, buttock, and leg pain develop with chronicity, and common misdiagnoses for chronic pain include spinal stenosis, lumbar radiculopathy, or osteoarthritis. On exam, there is tenderness over the trochanter. Hip rotation movements are normal but may cause buttock pain. Pain is reproduced with the patient lying on the side with hip extended and leg abducted. US or MRI can identify a gluteus medius tear. Treatment is physical therapy or endoscopic surgical repair.[20,21]

Ischial or Ischiogluteal Bursitis (Posterior/Gluteal Pain) More common in sedentary individuals, ischiogluteal bursitis presents with pain over the ischial prominence (Figure 281-5). "Weaver's bottom" is a nickname for the inflammatory version of this bursitis, which is particularly exacerbated by sitting on a hard surface for long periods. The bursa lies in close proximity to the sciatic nerve and the posterior femoral cutaneous nerve, predisposing to concomitant inflammation of these nerves and subsequent characteristic radicular pain.

Iliopectineal Bursitis (Anterior Hip, Pelvis/Groin Pain) The iliopectineal bursa is interposed between the hip joint and the iliopsoas muscle (Figure 281-6). Pain is located over the anterior pelvis and the groin on the affected side. The patient may reflexively assume a position of hip flexion and external rotation to aid in relief. On examination, extend the hip and palpate the area overlying the joint capsule to reproduce pain.[22]

Iliopsoas Bursitis (Groin Pain) The iliopsoas bursa lubricates movement of the iliopsoas tendon over the lesser trochanter and is the largest bursa in the hip region. The patient complains of pain on extension of the hip, which is reduced by hip flexion. There may be tenderness over the middle third of the inguinal ligament in the area of the femoral pulse (**Figure 281-7**). This process may be confused with iliopsoas tendinitis, hernias, femoral aneurysms, adenopathy, or psoas abscess.[23]

BURSAL SYNDROMES OF THE KNEE

Pes Anserine Bursitis (Anterior Medial Knee Pain) The pes anserine (from the Latin for three-toed foot of the goose) bursa lies deep to the three tendons that insert on the medial aspect of the tibia below the knee joint—the gracilis, sartorius, and semitendinosus—and above the medial collateral ligament and medial femoral condyle (**Figure 281-8**). Pes anserine bursitis is common in obese women with osteoarthritis of the knee, in runners, and with other various overuse syndromes. The patient complains of anterior medial pain below the joint line, and focal swelling may be noted over the bursa, with increased tenderness to palpation. The symptoms are sometimes confused with the pain from a medial meniscal tear or a medial collateral ligament injury.[22]

Prepatellar Bursitis (Pain Anterior to the Patella) Also known as *housemaid's knee*, *nun's knee*, or *carpet-layer's knee*, this bursa is commonly inflamed through repetitive kneeling on hard surfaces. Pain is frequently mild, with a restricted range of motion from the swelling, presenting as an effusion over the lower pole of the patella. This swelling

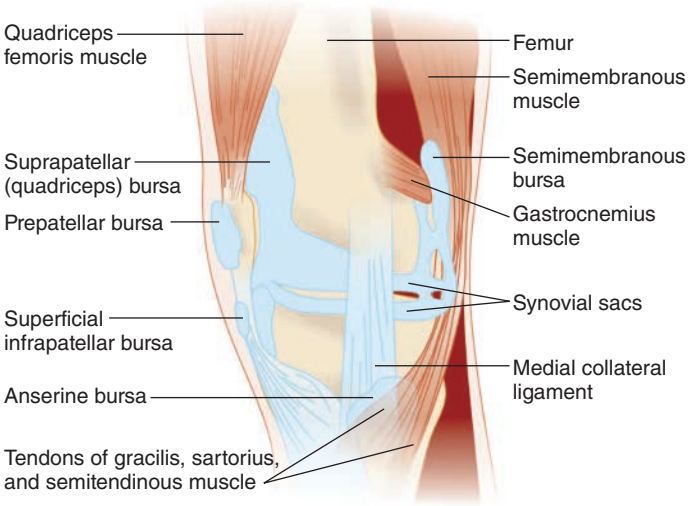


FIGURE 281-8. Medial view of the right knee, showing local bursa. [Reproduced with permission from Reichman EF, Simon RR: *Emergency Medicine Procedures.* © 2004, McGraw-Hill, Inc., New York.]

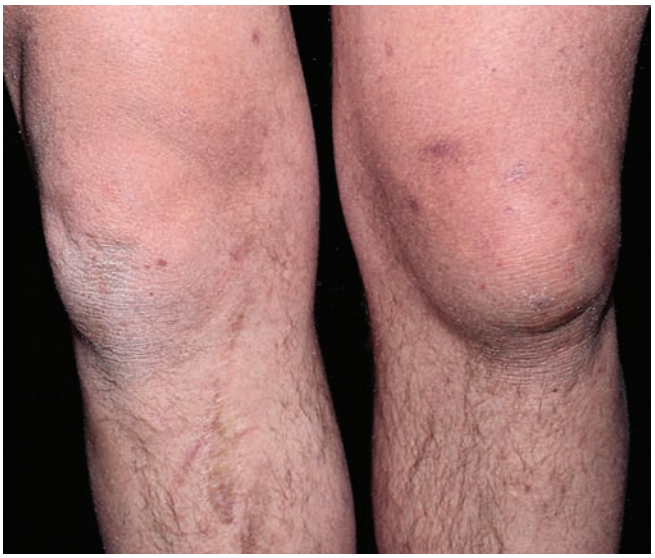


FIGURE 281-9. Prepatellar bursitis. Photograph reveals local bursal swelling of the left knee. [Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine,* 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

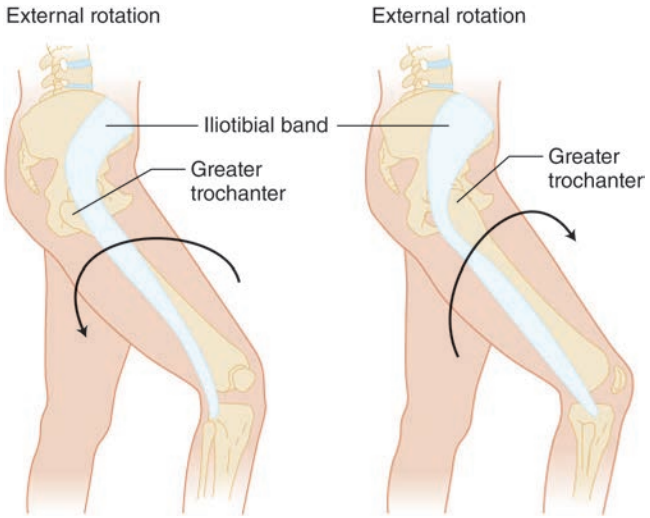


FIGURE 281-10. External snapping hip syndrome. In the snapping hip syndrome, the iliotibial band courses over the greater trochanter. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

may be so significant that one must differentiate it from a joint effusion (**Figure 281-9**). The area is tender to palpation, and bursal margins are often palpable. The prepatellar bursa is also one of the more common sites for septic bursitis, especially in children (see Chapter 284, "Joints and Bursae").[25,26]

Other Knee Bursae The superficial infrapatellar bursa lies between the tibial tubercle and the overlying skin (Figure 281-8). The deep infrapatellar bursa is situated between the patellar tendon and the tibia. Neither bursa is commonly inflamed or infected. Consider infection when symptoms resemble septic arthritis or osteomyelitis of the proximal tibia, with swelling and loss of full extension of the knee.[27]

The tibial collateral ligament bursa lies between the ligament and the knee capsule. Calcification may occur here, and point tenderness accompanies fibrositis of the ligament. Consider this diagnosis in the patient with medial joint line pain, especially when there is no history of knee instability. Pellegrini-Stieda disease refers to the ossification of the proximal portion of the medial collateral ligament. This results from injury and presents as a palpable, tender mass. The fibular collateral ligament has a surrounding bursa; when inflamed, it produces lateral knee pain that is increased with varus strain.

TREATMENT OF BURSITIS

Treatment is aimed at the suspected cause. For inflammatory conditions, NSAIDs, rest, heat, and time are the basis of conservative treatment. Steroids may occasionally be required, but steroid injections into the more readily accessible bursa are indicated only when it is clear that no infection exists. **Do not inject steroids into tendons, because this may weaken the tendon and lead to rupture.**

For bursal pain with an unclear cause, concomitant treatment for inflammation (rest, NSAIDs) and infection (antibiotics, most commonly for *S. aureus* and *Streptococcus* species) may be reasonable while awaiting culture results. See Chapter 284, "Joints and Bursae," for recommendations concerning bursal aspiration and diagnosis. Serial aspiration and surgical drainage or removal of the afflicted bursa are indicated for refractory, chronic conditions. If infection is suspected in an immunosuppressed patient (consider atypical organisms such as mycobacterial or fungal species) or if any patient presents with toxicity, admit for IV antibiotics and consultation with orthopedic surgery.

When fibrosis or synovial thickening leads to the development of painful nodules, surgical excision of the bursa is indicated. Inflammation of the bursa and the surrounding ligaments and tendons frequently coexists and is difficult to separate clinically.

HIP MYOFASCIAL SYNDROMES/OVERUSE SYNDROMES

The diagnosis of these syndromes is clinical. Overuse syndromes are simply the result of repetitive stresses and microtrauma outpacing the body's ability to heal.

External Snapping Hip Syndrome (Posterior Lateral Hip Pain) Also known as *coxa saltans*, a snapping sound is heard and popping sensation felt as the iliotibial band (an extension of the fascia lata) slips over the greater trochanter (**Figure 281-10**). In athletes, the syndrome is usually associated with painful inflammation of the band and the involved bursa. The iliotibial band courses from the iliac crest, sacrum, and ischium to the lateral condyles and fibular head, separating the vastus lateralis from the posterior thigh muscles (the hamstrings, consisting of the semitendinosus, semimembranosus, and biceps femoris). The patient will be able to voluntarily cause the snap with hip flexion and extension. Young women are predisposed to this syndrome, which occurs with activities such as dancing or stair climbing. Occasionally, the snap may be due to an intra-articular loose body. MRI may identify intra-articular causes or demonstrate inflammation of the local bursa, the iliotibial band, or the gluteal musculature. Dynamic sonography is also an aid for the diagnosis of extra-articular causes.[28,29]

Fascia Lata Syndrome (Lateral Thigh Pain) The fascia lata syndrome is a potential cause of pain in the lateral thigh region and is associated with pain to palpation and trigger points. Unilateral enlargement of the tensor fascia lata may occur with overuse or as a protective mechanism in injury. Athletes develop pain in the anterior groin and point tenderness over the anterior iliac crest. US is a useful aid to confirm the diagnosis.

KNEE MYOFASCIAL SYNDROMES/OVERUSE SYNDROMES

The diagnosis of these syndromes is clinical.

Patellofemoral Syndrome/Runner's Knee (Anterior Knee Pain) This syndrome is a major cause of anterior knee pain, with three typical causes: focal trauma (least common), overuse, and abnormal patellar tracking as it glides and rotates in the patellar groove. A major contributor to abnormal patellar tracking is weakness of the quadriceps muscle. The syndrome is more common in females due to the presence of an abnormal Q angle (>20 degrees), resulting from a broader pelvis. The Q angle is measured at the junction of a line drawn from the anterior superior iliac spine to the central patella and a second line drawn from the central patella to the tibial tubercle (**Figure 281-11**). A normal angle

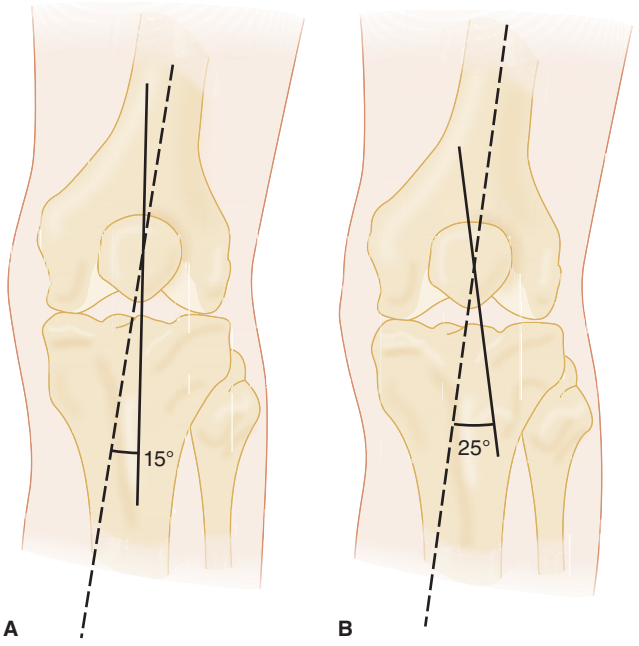


FIGURE 281-11. Measuring the Q angle. **A.** The normal Q angle is approximately 15 degrees. **B.** A Q angle of >20 degrees is considered to be abnormal. Patellar malalignment is determined clinically by measuring the Q angle. The Q angle is formed by a line drawn from the midpoint of the patella through the midpoint of the femoral shaft and a second line drawn from the midpoint of the patella through the tibial tuberosity. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

is approximately 15 degrees. An increased Q angle increases the risk for patellar subluxation. Because of this relationship, females have a 50% to 100% greater incidence of knee injuries compared with males in both athletes and nonathletes.[30]

The symptoms of anterior knee pain are gradual in onset, nonradiating, and typically unilateral. Pain is exacerbated by prolonged flexion of the knee, such as sitting in on-air flights or at the movie theater. Pain frequently occurs with activities of daily living, such as walking, and especially with stair climbing.

The presence of crepitus to palpation at the patellofemoral joint suggests degenerative changes but may be normal. The patellar grind test is accomplished by direct anterior to posterior pressure on the patella or the quadriceps tendon while asking the patient to contract the quadriceps muscles. A positive test evokes sudden patellar pain and relaxation of the muscle. The opposite test involves lifting the patella away from the knee joint while passively bending and straightening the knee. If this relieves pain, the patellofemoral joint is likely the source. Radiographic studies are of limited value but may detect arthritis.

Treatment involves the usual conservative measures, with an emphasis on physical therapy and strengthening. Brace support of the knee will also help correct the patellofemoral mechanism.[31]

Inflammatory pain to the knee may last for months to a few years following surgery or trauma and is based on a genetic predisposition to arthrofibrosis from these insults. Arthroscopy may cause the release of calcium pyrophosphate from tissue, resulting in a severe synovitis.

Chondromalacia Patellae (Anterior Knee Pain) *Chondromalacia patellae* refers to a softening of the cartilage on the posterior surface of the patella, most commonly occurring with the patellofemoral syndrome (**Figure 281-12**). This diagnosis is made by direct arthroscopic visualization of a ragged appearance of the affected cartilage.[24]

Medial Plica Syndrome (Anterior Medial Knee Pain) The plica syndrome is uncommon and is difficult to distinguish from other causes of patellofemoral pain. Plicae are abnormal, redundant folds in the connective tissue of the knee, persisting from embryologic septa that initially divide the knee into compartments, normally disappearing as the fetus

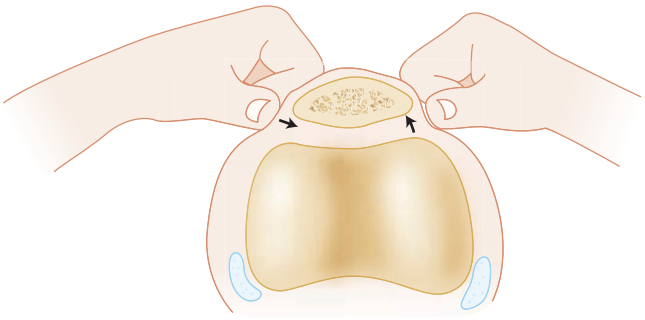


FIGURE 281-12. Patellar tenderness in chondromalacia. Palpation of the undersurface of the patella will elicit tenderness in chondromalacia of the patella. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

matures. Plicae become symptomatic for unclear reasons. Recurring synovitis may result in a palpable, inelastic band that interferes with normal knee movement and pain. This band-like structure is best palpated parallel to the medial border of the patella and produces pain in the area of the medial femoral condyle that radiates anteriorly. Pain may be brought on with activity or may occur at rest. Patients may also report a snapping sensation as the plica moves over the femoral condyle with repeated flexion and extension. Arthroscopy or MRI findings confirm the diagnosis. Treatment is conservative, with strengthening and stretching exercises; some patients require arthroscopic resection of the band.[32]

Iliotibial Band Syndrome (Lateral Knee Pain) Iliotibial band syndrome is most common in distance runners or cyclists. The iliotibial band inserts onto the lateral femoral and tibial condyles (**Figure 281-13**). The thickened fascia serves as a ligament and stabilizes the joint in extension. With overuse, the bursa underlying the band becomes irritated. Pain is

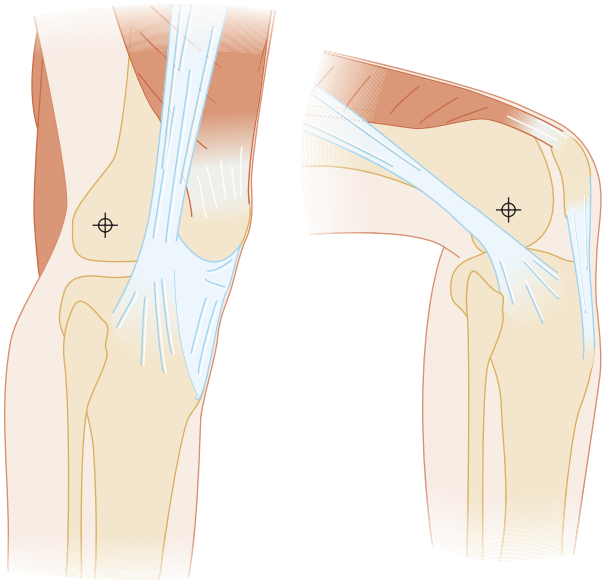


FIGURE 281-13. Iliotibial band site. **A.** The iliotibial band lies anterior to the lateral femoral epicondyle when the knee is in extension and passes posterior to it with flexion. **B.** The coursing back and forth over this bony prominence is the cause of a symptom complex referred to as the *iliotibial band syndrome*. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

reproduced consistently after reaching a certain mileage during running or other physical exertion, and examination reveals localized tenderness to palpation over the lateral epicondyles. Treatment involves rest, decreasing the training distance, changing shoes to reduce stress on the structures, stretching exercises, and steroid injections locally.

Popliteus Tendinitis (Posterior Lateral Knee Pain) The small popliteus muscle passes under the lateral head of the gastrocnemius and inserts into the posterior tibia. It assists with internal rotation of the tibia, withdraws the meniscus during flexion to prevent impingement, and stabilizes the knee, preventing forward displacement. A bursa separates the tendon from the underlying structures in the area of the lateral femoral condyle. Overuse syndromes of the popliteus tendon and irritation of the bursa are associated with excessive use of the quadriceps muscle. Pain is localized over the posterior lateral aspect of the knee and is worsened by running downhill. Point tenderness may be appreciated over the insertion on the proximal posterior tibia or along the lateral joint line (palpable "soft" area between the lateral proportions of the "hard" femur and tibia). The Webb test assists in making the diagnosis: internally rotate the leg in the supine patient, flex the knee at 90 degrees, and ask the patient to force external rotation while the examiner provides resistance. A positive test produces pain with the maneuver. Treatment is rest and eventual quadriceps rehabilitation, aided by ice and NSAIDs.[33]

Patellar Tendinitis/Jumper's Knee (Anterior Inferior Knee Pain) The patella tendon is subject to significant wear, with microtears and complete ruptures occurring in athletes and nonathletes alike (**Figure 281-14**). Any activity that involves jumping can result in focal pain, typically at the inferior pole of the patella or proximal portion of the tendon. Other activities that may exacerbate pain include running (especially uphill), squatting, cutting maneuvers, standing from a sitting position, or even simple walking. Symptoms may improve with activity early in the course or may progress to the point of significant discomfort at rest. Treatment involves rest, NSAIDs, and cryotherapy. Steroid injections are contraindicated. Complete immobilization is not recommended, because this will reduce collagen production and stimulation of healing by load bearing. Most recently, US-guided intratendinous injection of platelet-rich plasma has been suggested to allow rapid healing in the patellar tendon and other major tendons. However, insufficient evidence exists to support this modality definitively.[34,35] Further diagnosis and management of complete patellar tendon rupture are discussed in Chapter 274, "Knee Injuries."

Infrapatellar Fat Pad Syndrome (Anterior Inferior Knee Pain) The infrapatellar fat pad location is suggested by its name: it fills the anterior part of the knee joint and is held in place by the patellar tendon, the retinaculum on both sides, and the infrapatellar synovial plica inferiorly. Due to its close anatomic relationship, the fat pad commonly becomes inflamed with patellar tendinitis.

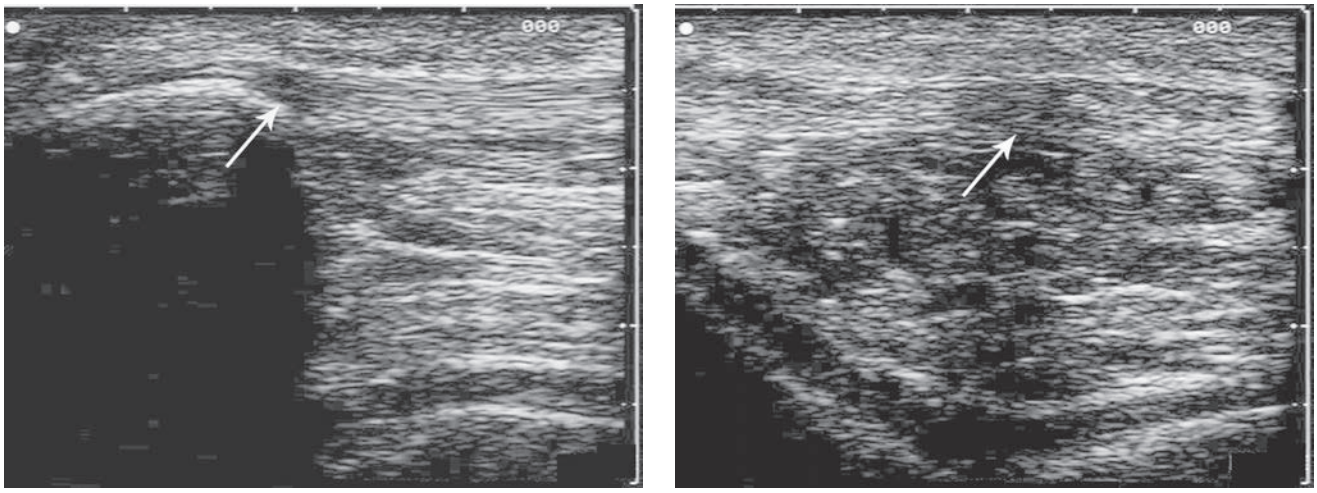
Quadriceps Tendinitis (Anterior Superior Knee Pain) The quadriceps muscles and tendon are subject to significant forces in athletes, resulting in microtears and inflammatory changes, localized predominantly at the insertion of the tendon into the proximal pole of the patella. Chronic recurrent injury or acute explosive trauma can result in complete tear of the tendon. Tendinitis is more likely to occur on a rigid playing surface and with increased frequency of training. Diagnosis and management of complete quadriceps tendon rupture are discussed in Chapter 274.

Semimembranosus Tendinitis (Posteromedial Knee Pain) Pain is elicited just distal to the joint line, where the tendon is easily palpated in most patients. In younger patients, the pain is associated with athletics and overuse. In older patients, it is seen secondary to degenerative changes of the knee joint, especially within the medial compartment. MRI will confirm the diagnosis if conservative therapy fails.

Snapping Knee Syndrome (Knee Pain) Snapping syndrome of the knee, similar to the same process in the hip, is a result of the iliotibial band passing over the lateral femoral condyle. The same effect may also result from the semitendinosus muscle passing over the medial condyle with the initiation of flexion and termination of extension of the knee. The snapping sensation and sound may be accompanied by pain in the location of the involved tendon. A third cause is the popliteal tendon snapping over the incisura poplitea extensoria on the lateral femoral condyle. Other causes of a snapping knee include intra-articular ganglion cysts, intra-articular loose bodies, and degenerative joint disease.[36,37]

POPLITEAL (BAKER) CYST (POSTEROINFERIOR KNEE PAIN)

A popliteal (Baker) cyst develops posteriorly and inferiorly to the knee as a distention of a local bursa, with several potential contributors existing in the areas of the hamstring tendons, the collateral ligaments of the knee, the condyles, and the heads of the gastrocnemius (**Figure 281-15**). The cyst frequently communicates with the knee (especially in adults), and associated intra-articular pathology is common. The cyst may



A B

FIGURE 281-14. Patellar tendon defect. **A.** Long-axis sonogram of the proximal patellar ligament showing a hypoechoic tendon defect near the origin of the patellar tendon (*arrow*). The remainder of the tendon appears fibrillar and echogenic. A heel–toe insonating technique confirmed that a hypoechoic defect was present and that a tendinopathy ("jumper's knee") was present. **B.** Short-axis sonogram of the same patellar ligament. The ligament is seen as a somewhat echogenic horizontal structure approximately 5 mm beneath the skin surface and approximately 4 mm in width. In the central portion of the tendon, there is a focal area of hypoechogenicity that persists with careful imaging (*arrow*). This is the classic location and appearance of a "jumper's knee" or tendinopathy of the proximal patellar tendon. [Reproduced with permission from Ma OJ, Mateer JR, Blaivas M: *Emergency Ultrasound,* 2nd ed. © 2008, McGraw-Hill, Inc., New York.]

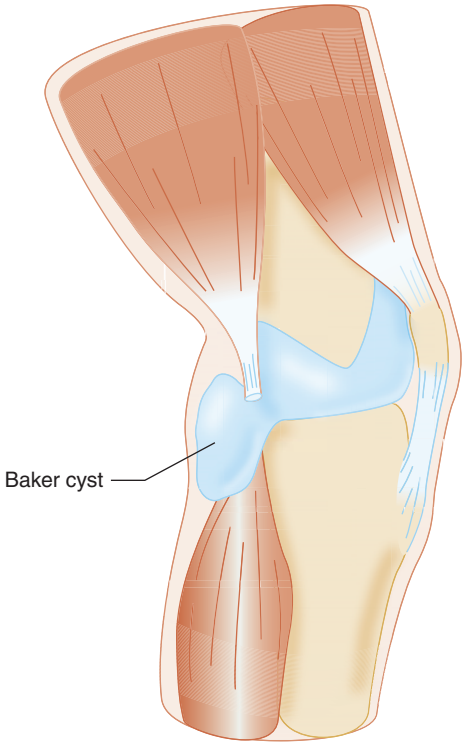


FIGURE 281-15. A Baker cyst (an extension of the semimembranosus bursa). [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

develop as a herniation of the synovial membrane through the posterior joint capsule. Giant synovial cysts of the calf may develop in patients with rheumatoid arthritis and will also communicate with the knee. Popliteal venous thrombosis can be confused with the pain and swelling produced by these posterior cysts or may exist concomitantly.[38] Other potential diagnoses include aneurysms, vascular tumors, fibrosarcoma, lipoma, and other tumors.

US is useful and readily available for cyst evaluation and for the identification of other conditions (**Figure 281-16**). Arthrography or MRI is suggested for complete evaluation. Excision may eventually be required for symptom relief.[39]

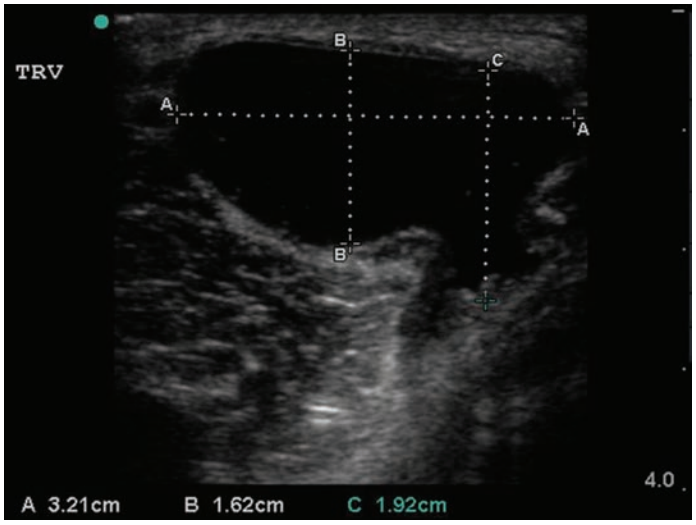


FIGURE 281-16. US of a Baker cyst. Transverse US view of Baker cyst, measuring approximately 3 cm by 2 cm.

PIGMENTED VILLONODULAR SYNOVITIS

Pigmented villonodular synovitis is a proliferative disorder, also referred to as *giant cell tumor of the tendon sheath*. The articular form can be present in many joints, including the hip and knee. The synovium and synovial fluid may appear red or brown, hence the name. Radiographs show specific findings, with erosions and cysts on both sides of the articular surface, usually with normal joint space and bone density. Typically, only one joint is involved. Chronic discomfort may be present, or the radiographic findings may be incidental for the asymptomatic joint.[40]

MRI and arthroscopy are required for definitive diagnosis.

GENERALIZED ARTHROPATHY OR TENDINOPATHY RELATED TO MEDICATIONS

An important source of generalized joint pain and swelling, as well as debilitating tendinopathy/tendinitis, including frank tendon rupture, is the use of specific medications and drugs.[41] In particular, the fluoroquinolone antibiotics are well described as causing these problems. In 2008, the U.S. Food and Drug Administration issued a black box warning to this effect for the quinolones. This issue occurs with enough frequency that providers should consider alternatives to the use of these antibiotics when possible.[42] Other agents that are associated with tendinopathy include corticosteroids, oral contraceptives, and the recreational drugs marijuana and cocaine.

BONE/ARTICULAR DERANGEMENTS (DIFFUSE/VARIED JOINT PAIN)

Septic arthritis, viral arthritis, the arthritis of Lyme disease, osteoarthritis, and the other arthritides such as rheumatoid arthritis, crystalline arthritis, and seronegative spondyloarthropathy are covered in Chapter 282, "Systemic Rheumatic Diseases."

Osteonecrosis Other terms used to describe osteonecrosis include ***avascular necrosis, aseptic necrosis***, and ***ischemic necrosis***. Osteonecrosis is the result of bone infarction caused by a lack of blood supply. Osteonecrosis may occur as an idiopathic or primary disorder, secondary to a variety of systemic conditions, or following trauma (**Table 281-3**). The trauma may be major and obvious or occult and due to repetitive injury. Major trauma leads to sudden disruption of the blood supply, as commonly occurs following dislocation or fracture in the area of the joint. When the hip is involved, pain may be present anywhere in the region of the joint, the buttocks, thigh, or even the

TABLE 281-3 Conditions Associated With Avascular Necrosis (Osteonecrosis) of the Femoral Head

Traumatic
• Femoral neck fracture
• Hip dislocation
• Occult or minor trauma
Nontraumatic
• Sickle cell disease
• Collagen vascular diseases
• Alcohol abuse
• Renal transplant
• Systemic lupus erythematosus
• Dysbarism
• Chronic pancreatitis
• Exogenous steroid administration
• Cushing's disease
• Caisson disease
• Gaucher's disease
• Renal osteodystrophy
Idiopathic



FIGURE 281-17. Avascular necrosis, bilateral hips (stage IV). [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]



FIGURE 281-19. CT scan of the posterior ankle. Calcaneal osteomyelitis is seen after percutaneous fixation of a closed fracture with a large pin. Thermal necrosis of bone from drilling resulted in a ring sequestrum around the path of the pin, best shown on this CT scan. This sequestrum needed to be removed in order to control the infection. [Reproduced with permission from Slaven EM, Stone SC, Lopez FA: *Infectious Diseases: Emergency Department Diagnosis & Management.* © 2007, McGraw-Hill, Inc., New York.]

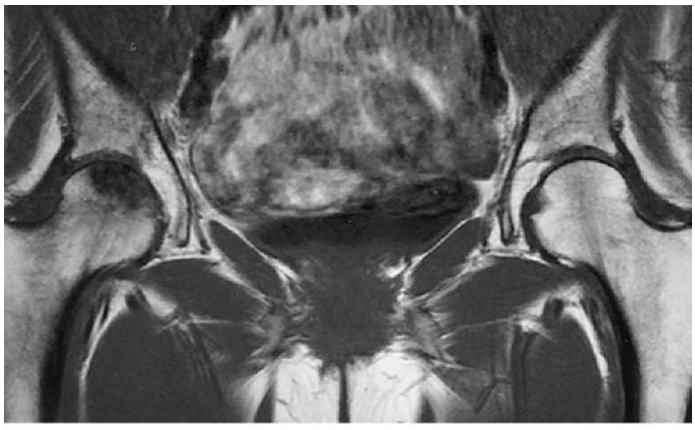
knee. Plain radiographs are helpful in establishing the diagnosis, with findings ranging from mottled densities and lucencies to severe collapse of the femoral head (**Figure 281-17**). With the knee, the weight-bearing medial femoral condyle is more commonly affected. Early in the disease process, CT or MRI will be more helpful in establishing the diagnosis (**Figure 281-18**). Joint replacement may be required.

Osteomyelitis Osteomyelitis is an infection of the bone by bacteria or fungus, resulting in bony changes and destruction (**Figure 281-19**). It develops by spread of infection from contiguous structures (~80%) or by hematogenous spread (~20%). Hematogenous spread is more common to the long bones in children and to the spine in adults. Spinal epidural abscess is an important differential diagnosis to consider (see Chapter 279, "Neck and Back Pain"). Risk factors for osteomyelitis are listed in **Table 281-4**. Pain at the site is a universal complaint and may be accompanied by warmth, swelling, and erythema. Radiographs are normal early in the course, but later will show bone demineralization, periosteal elevation, and lytic lesions. MRI is the preferred imaging modality, with approximately 95% sensitivity, but bone biopsy confirms the diagnosis with certainty. The urgency to make the diagnosis depends on the clinical situation. Osteomyelitis in diabetics is more common with skin ulcerations >2 cm, a positive probe-to-bone test (sterile instrument reaches periosteum when probed into wound), an erythrocyte sedimentation rate >70 mm/h, or an abnormal radiograph. *S. aureus* is the most common causative agent overall. Other infectious agents and recommended therapies are listed in Table 281-4.[43]

Blood cultures may identify the causative agent. When a blood culture is negative, bone biopsy is necessary to guide long-term antibiotic



A



B

FIGURE 281-18. Osteonecrosis of femoral head: MRI versus plain films. A 45-year-old woman receiving high-dose glucocorticoids developed right hip pain. **A.** Conventional radiographs demonstrated only mild sclerosis of the right femoral head. **B.** T1-weighted MRI demonstrated low-density signal in the right femoral head, diagnostic of osteonecrosis. [Reproduced with permission from Fauci AS, Kasper DL, Braunwald E, et al: *Harrison's Principles of Internal Medicine,* 17th ed. © 2008, McGraw-Hill, Inc., New York.]

TABLE 281-4 Risk Factors, Likely Infecting Organism, and Recommended Initial Empiric Antibiotic Therapy for Osteomyelitis

Risk Factor	Likely Infecting Organism	Recommended Initial Empiric Antibiotic Therapy*
Elderly, hematogenous spread	*Staphylococcus aureus*, including MRSA, gram-negative bacteria	Vancomycin *plus* piperacillin-tazobactam, or imipenem
Sickle cell disease	*Salmonella,* gram-negative bacteria (*S. aureus* becoming more common)	Ciprofloxacin; add vancomycin if *S. aureus* suspected
Diabetes mellitus, or vascular insufficiency	Polymicrobial: *S. aureus, Streptococcus agalactiae,* and *Streptococcus pyogenes* plus coliforms and anaerobes	Vancomycin *plus* piperacillin-tazobactam, or imipenem
Injection drug user	*S. aureus,* including MRSA, and *Pseudomonas*	Vancomycin *plus* piperacillin-tazobactam, or ceftazidime
Developing nations	*Mycobacterium tuberculosis*	See Chapter 67, "Tuberculosis"
Newborn	*S. aureus* including MRSA, gram-negative bacteria, group B *Streptococcus*	Vancomycin *plus* ceftazidime
Children	*S. aureus* including MRSA	Vancomycin *plus* ceftazidime
Postoperative with or without retained orthopedic hardware	*S. aureus* and coagulase-negative staphylococci	Vancomycin
Human bite	Streptococci or anaerobic bacteria	Piperacillin-tazobactam or imipenem
Animal bite	*Pasteurella multocida, Eikenella corrodens*	Cefuroxime if known *P. multocida,* piperacillin-tazobactam or imipenem

Abbreviation: MRSA = methicillin-resistant *Staphylococcus aureus.*

*All patients require bone biopsy and debridement of infected/dead bone.



FIGURE 281-20. Osteochondritis dissecans (*arrow*) is shown at the lateral portion of the medial femoral condyle. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

therapy. In acutely ill patients, begin presumptive treatment based on the clinical findings, with high-dose, broad-spectrum, parenteral antibiotics ensuring coverage for *S. aureus*. The most recent Cochrane systematic review (2013) could not identify the optimal empiric antibiotic agent from randomized controlled trials in the literature.[43] Therefore, empiric therapy is based on the suspected organism(s) from risk factors, as listed in Table 281-4.

Osteochondritis Dissecans (Knee Pain) In osteochondritis dissecans, a portion of the joint surface cartilage separates from the underlying bone. It is rare, but seen most often in adolescents, and is of unclear origin. Occult trauma likely plays a role. The lateral portion of the medial femoral condyle is predominantly involved, with unilateral occurrence. The patient experiences pain and swelling. Plain radiographs may reveal a thin rim of calcium separated from the underlying bone (**Figure 281-20**), with MRI showing much greater detail.[44] Arthroscopic repair of the lesion or removal of associated loose bodies is required if conservative therapy fails.[45]

Synovial Osteochondromatosis (Hip or Knee Pain) Synovial osteochondromatosis is characterized by idiopathic, nodular synovial membrane proliferation and subsequent calcification of the affected tissue. Eventually, multiple fragments of this growth (as large as 2 cm) break off and occupy the joint space or the area of the bursa and tendon sheaths. With time, degenerative changes and joint deterioration with secondary osteoarthritis occur. The disease is more common in males between the ages of 20 and 50 years old. Patients complain of chronic symptoms, with pain and joint swelling. There is a limitation in range of motion, and the joint may lock. The large joints are commonly involved. Radiographs will show the calcification and the intra-articular bodies and later the changes of osteoarthritis. Surgical excision of the proliferating synovium and removal of the ossified bodies from the joint space are required.[46]

Transient Osteoporosis of the Hip (Hip Pain) Transient osteoporosis of the hip occurs in middle-aged men and in pregnant women in the third trimester. The disease is uncommon, idiopathic, and characterized by sudden onset of hip pain, with the findings of osteoporosis on plain films. The disease spontaneously resolves within 6 to 12 months. Symptoms may abate before the associated radiographic findings have resolved. Take precautions against hip fracture while the disease remains active.[47,48]

Paget's Disease Osteitis deformans, or Paget's disease, is a chronic disorder resulting in enlarged, deformed bones from overactive breakdown and reformation. Paget's disease affects the hip joint in 50% of patients. The disease is familial and is suggested by an elevated serum alkaline phosphate level. Patients complain of pain, and radiographs reveal joint space narrowing with minimal hypertrophic changes (**Figure 281-21**). Treatment is symptomatic, and medications that slow the rate of bone turnover (calcitonin, alendronate, others) may be helpful to control the disease systemically. Surgery is required for complications of the disease, such as fracture and severe arthritis.[49,50]

Osteitis Pubis (Midline Pelvis and Groin Pain With Radiation to Hips) Osteitis pubis should be considered as a possible diagnosis in athletes with pain in the region of the pubis. It also occurs following pregnancy and after bladder and prostate surgery. In athletes, it is an inflammatory process related to overuse of the adductors and gracilis muscles. Bony changes with periostitis occur at the sites of the origins of the involved muscles. The disease is seen in runners, soccer players, weightlifters, fencers, and football players. Symptoms start off gradually and progress to severe pain with any movement of the legs. Rolling over in bed may be next to impossible due to excruciating pain, and there is a characteristic "duck waddling gait." The symptoms may resolve completely over a period of months with rest and NSAID use. Rarely, arthrodesis of the pubic symphysis and local debridement are required.

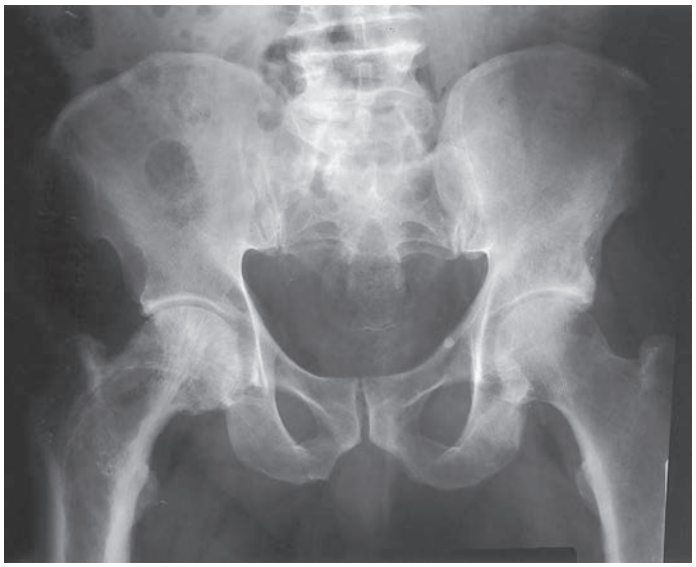


FIGURE 281-21. Radiograph of a 73-year-old man with Paget's disease of the right proximal femur. Note the coarsening of the trabecular pattern with marked cortical thickening and narrowing of the joint space consistent with osteoarthritis secondary to pagetic deformity of the right femur. [Reproduced with permission from Fauci AS, Kasper DL, Braunwald E, et al: *Harrison's Principles of Internal Medicine,* 17th ed. © 2008, McGraw-Hill, Inc., New York.]

Radiographs show symmetric bone reabsorption medially, widening of the pubic symphysis, and sclerosis along the pubic rami. These changes may take several weeks to develop. MRI more clearly details the changes, and bone scans show evidence of the inflammatory process.[51-53]

Diseases of Abnormal Calcification Myositis ossificans, or heterotrophic calcification, is the deposition of bone at a site where bone does not normally occur. The process is related to direct trauma, with the thigh and hip muscles frequently involved. Bleeding follows direct trauma to the muscle, and calcium deposits form inside the hematoma. A firm, palpable, painful mass will develop within 2 weeks and may persist for up to 1 year. Plain radiographs reveal an irregularly shaped mass around the joint or in the fascial planes (**Figure 281-22**). The



FIGURE 281-22. Myositis ossificans. This radiograph shows extraskeletal ossification of the medial proximal right thigh (immediately inferior to the head of the femur), approximately 3 weeks after a severe contusion to that area. [Reproduced with permission from Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities,* 5th ed. © 2007, McGraw-Hill, Inc., New York.]

TABLE 281-5 Treatment Caveats

- Do not inject steroids in areas where infection is a concern, or where they may accidentally be injected into tendon sheaths and contribute to tendon rupture.
- Use caution in the examination of the immunocompromised patient, because signs of infection may be subtle or altered.
- Injuries in athletes should be referred to a sports medicine specialist to optimize therapy and decrease time to return to maximum activity levels.

appearance may be confused with a primary neoplasm, such as osteosarcoma or periosteal osteogenic sarcoma. Range of motion in the muscle or joint is limited due to pain or physical presence of the mass. Radicular pain from nerve irritation may also be present. Operative removal of the deposition may be required.

Calcifying peritendinitis and bursitis are also traumatic in origin but are relatively uncommon. The trochanteric bursa of the hip is frequently affected. Radiographs reveal a thin, poorly marginated white line that is separated from the cortex of the hip.[54]

CORE TREATMENT

Treatment for the majority of inflammatory and overuse syndromes consists of NSAIDs, rest, heat, and time as the basis of conservative treatment (**Table 281-5**). "Rest" does not require full immobilization, which can lead to muscle atrophy and delayed return to normal function. Full knee immobilization, which is commonly prescribed from the ED, should therefore be used sparingly in most of these conditions. Appropriate rest is followed by gradual resumption of activities, physical therapy, and strengthening activities where appropriate. Steroids may occasionally be required, and steroid injections into the more readily accessible bursa are useful when it is clear that no infection exists but can be detrimental when infection is present. It is critical to avoid steroid injections into tendons, because steroids may weaken the tendon and lead to rupture. Athletes are best served by referral to a sports medicine specialist or an orthopedist. Advanced therapies such as stem cell or platelet-rich plasma injections continue to develop for a variety of conditions.[55-60]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 282

Systemic Rheumatic Diseases

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Andrew C. Seymore
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INTRODUCTION

Systemic rheumatic diseases are chronic, inflammatory autoimmune disorders, such as osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis (scleroderma). ED patients with systemic rheumatic diseases have complex clinical and pharmacologic histories and multi–organ system pathology. Many extra-articular manifestations of rheumatic diseases can result in serious morbidity or mortality if not recognized and properly managed.[1,2] This chapter discusses rheumatologic emergencies from an organ system perspective. It will review both rheumatologic emergencies as well as care for the rheumatologic patient in the ED. **Table 282-1** categorizes emergencies associated with systemic rheumatic diseases. Although the chapter should be

TABLE 282-1 Categories of Emergencies in Patients With Systemic Rheumatic Diseases

Category	Clinical Manifestations
Disease exacerbation	Flare-up of preexisting systemic rheumatic disease
Complication	Known complication of an acute systemic rheumatic disease (i.e., pulmonary hemorrhage, pericarditis, respiratory, or renal impairment)
Infection	Infection complicated by immunosuppressive therapy
Comorbidity exacerbation	Worsening or onset of a serious illness that is not a direct manifestation of the systemic rheumatic disease
Adverse drug reaction	Reaction to a systemic rheumatic disease drug treatment

reviewed in its entirety, high-yield clinical pearls can be found at the end of the chapter in Table 282-8.

CLINICAL FEATURES AND DIAGNOSIS

Table 282-2 lists typical clinical manifestations and complications specific to rheumatic diseases. The clinical descriptors may allow suspicion for a systemic rheumatic disease in a previously undiagnosed patient; however, the diagnosis cannot be confirmed during an ED visit. The diagnostic criteria and testing sequence, which are usually completed in the outpatient setting, are beyond the scope of this chapter. The need to admit a patient with a known or suspected systemic rheumatic illness depends on the severity of the patient's presentation. In systemic rheumatic diseases, infection is the leading cause for intensive care unit admission followed by rheumatic disease flare.[3] The intensive care unit admission may be the site of initial diagnosis in 20% of those with systemic rheumatic disease. Rheumatoid arthritis is the most common rheumatic disease seen in intensive care unit patients (also the most common rheumatic disease), followed in decreasing frequency by systemic lupus erythematosus and systemic sclerosis.

AIRWAY EMERGENCIES

Critical airway obstruction may develop at the level of the larynx, subglottic region, or trachea.

CRICOARYTENOID JOINT ARTHRITIS

In patients with rheumatoid arthritis and relapsing polychondritis, arthritis or edema of the cricoarytenoid joints can lead to acute upper airway obstruction.[1,4] In addition, secondary infections such as bacterial epiglottitis or tracheitis can quickly compromise the airway. Signs and symptoms of cricoarytenoid arthritis are throat pain, tenderness over cartilaginous structures (aggravated by swallowing or speaking), foreign body sensation or fullness in the throat, voice changes or hoarseness, and in more severe cases, dyspnea, cough, or stridor.[1] Pain from cricoarytenoid arthritis is sometimes referred to the ear or to the neck.

CT and fiberoptic laryngoscopy can evaluate the cricoarytenoid joint. Initial treatment consists of systemic high-dose corticosteroids and racemic epinephrine inhalation, although tracheostomy may be required.[1,5]

TRACHEOMALACIA

Relapsing polychondritis can cause inflammation, destruction, and collapse of tracheobronchial cartilage, resulting in airway obstruction. Regions of segmental collapse due to tracheomalacia or refractory stenosis may be resected or treated with stents. The use of noninvasive

TABLE 282-2 Common Features and Complications of Systemic Rheumatic Diseases

Disorder	Common and Characteristic Clinical Features	Complications
Antiphospholipid syndrome	Multiple and recurrent venous and arterial thromboses, recurrent early abortions. Secondary form is associated with systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and Sjögren's syndrome. Thrombophlebitis and deep vein thrombosis, thrombocytopenia, hemolytic anemia, microangiopathic hemolytic anemia, livedo reticularis, stroke, transient ischemic attack, eye vascular complications. Coronary, renal, mesenteric, and cerebral vascular occlusion.	ARDS, pulmonary embolism, ischemic complications of vascular occlusion, severe anemia, vision loss, catastrophic antiphospholipid syndrome.
Ankylosing spondylitis	Chronic inflammatory disease of the axial skeleton, with progressive stiffness of the spine. Young adults (peak at 20 and 30 years old). Back pain (improves with exercise, morning stiffness lasting >1 hour); buttock, hip, or shoulder pain; systemic complaints (fever, malaise, fatigue, weight loss, myalgias); uveitis and restrictive pulmonary failure due to costovertebral rigidity; ILD; fracture of the ankylosed spine; asymptomatic ileal and colonic mucosal ulcerations. Secondary amyloidosis.	Acute spinal cord or nerve compression, subluxation of the atlantoaxial joint, spine fracture from minimal or no trauma, aortic regurgitation.
Adult Still's disease	Inflammatory disorder (similar to systemic-onset juvenile rheumatoid arthritis). Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), arthritis, evanescent (salmon-colored) rash, pharyngitis, lymphadenopathy, splenomegaly, anemia, thrombocytopenia. Pericarditis, myocarditis, pleurisy.	ARDS, arrhythmias, heart failure, fulminant hepatic failure, red cell aplasia, disseminated intravascular coagulation, microangiopathic hemolytic anemia.
Behçet's disease	Chronic, relapsing, inflammatory disease. Systemic vasculitis involving arteries and veins of all sizes (carotid, pulmonary, aortic, and inferior extremity vessels are most commonly involved, with aneurysm, dissection, rupture, or thrombosis). Systemic complaints (fever, malaise, fatigue, weight loss, myalgia); recurrent painful skin and mucosal lesions (oral and genital ulcerations); asymmetric, nondeforming arthritis of the medium and large joints; thrombophlebitis and deep vein thrombosis; ocular complications. Neuropsychiatric manifestations. Pericarditis, myocarditis.	Hypopyon, retinal vasculitis, optic neuritis, eye vascular complication. Dural sinus thrombosis, aseptic meningitis, and encephalitis. Arrhythmias. Superior and inferior vena cava syndrome. Abdominal aorta or pulmonary artery emergencies. Bowel perforation.
Eosinophilic granulomatosis with polyangiitis (formally, Churg-Strauss syndrome)	Vasculitis with a multisystemic involvement. Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), myalgia, allergic rhinitis, nasal obstruction, recurrent sinusitis, asthma, and peripheral blood eosinophilia. Systemic hypertension, pericarditis, abdominal pain, peripheral symmetric neuropathy; skin lesions and rash.	Heart failure, acute myocardial infarction, acute and constrictive pericarditis, mononeuritis multiplex, transverse myelitis.
Dermatomyositis/polymyositis	Idiopathic inflammatory myopathies. Symmetric proximal muscle weakness, myalgia, and muscle tenderness. Elevated serum creatine kinase. Systemic complaints (fever, malaise, fatigue, weight loss), Raynaud phenomenon, nonerosive inflammatory polyarthritis, esophageal dysfunction, ILD, aspiration lung infections.	ARDS. Respiratory failure and arrest due to diaphragmatic or chest wall muscle weakness, alveolar hemorrhage, and ILD. Heart failure, arrhythmias, and conduction disturbances.

(*Continued*)

TABLE 282-2 Common Features and Complications of Systemic Rheumatic Diseases (*Continued*)

Disorder	Common and Characteristic Clinical Features	Complications
Giant cell arteritis (temporal arteritis)	Chronic vasculitis of large-sized vessels. Elderly (mean age at diagnosis, 70 y old). Associated with polymyalgia rheumatica in 40% of cases. Localized headache of new onset, tenderness of the temporal artery, and biopsy revealing a necrotizing arteritis. Temporal artery may be normal on clinical examination. Systemic complaints, jaw claudication, eye complaints, and visual loss. Aortic regurgitation and aortic arch syndrome. Neurologic complications due to carotid and vertebrobasilar vasculitis.	Ischemic optic neuropathy, eye vessel occlusion. Aortitis (especially the thoracic tract) and aortic emergencies. Stroke.
Henoch-Schönlein purpura	Systemic vasculitis associated with immunoglobulin A deposition, generally in children. Frequently, acute presentation follows an upper respiratory infection. Palpable purpura (in patients with neither thrombocytopenia nor coagulopathy), arthritis/arthralgia, abdominal pain, and renal impairment (adult), ILD.	Respiratory failure and alveolar hemorrhage. GI hemorrhage, bowel ischemia or perforation, acute pancreatitis, intussusception (children). Acute scrotum.
Microscopic polyangiitis	Small-vessel systemic vasculitis, characterized by rapidly progressive glomerulonephritis and pulmonary involvement. Lung complications differentiate microscopic polyangiitis from polyarteritis nodosa. Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), arthralgias, skin lesions, hemoptysis, abdominal pain, renal impairment, systemic hypertension.	Rapidly progressive glomerulonephritis, severe lung hemorrhage, GI bleeding.
Polyarteritis nodosa	Systemic necrotizing vasculitis of the medium-sized muscular arteries. Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), arthralgias, skin lesions, abdominal pain, renal impairment, systemic hypertension, peripheral mononeuropathy typically with both motor and sensory deficits, eye complications, leukocytosis, and normochromic anemia.	Acute scrotum, ischemic and hemorrhagic stroke, ACS, heart failure, peripheral artery ischemia, mesenteric ischemia and bowel perforation, GI bleeding, acute pancreatitis, malignant hypertension.
Relapsing polychondritis	Immune-mediated condition. Ears (violaceous and erythematous auricula), nose (saddle nose deformity), and other cartilaginous structures inflammation (respiratory tract). Sternoclavicular, costochondral, and manubriosternal arthritis; upper airway involvement; aortic or mitral valvular regurgitation; pericarditis; renal impairment; peripheral neuropathies; ocular complications.	Airway obstruction. Acute renal failure, aortitis and aortic emergencies, heart block, ACS, scleritis, peripheral ulcerative keratitis.
Rheumatoid arthritis	Chronic, systemic, inflammatory disorder. Symmetric and potentially destructive arthritis. Systemic symptoms (fever, malaise, fatigue, weight loss, myalgia), skin lesions, splenomegaly. Cervical spine involvement, pleuritis, ILD, pericarditis, myocarditis, and aortitis. Cricoarytenoid arthritis with potential for airway obstruction, ocular involvement. Peripheral artery disease, Sjögren's syndrome, vasculitis. Anemia, leukopenia, thrombocytosis, and Felty's syndrome. Increased risk of lymphoproliferative diseases, particularly non-Hodgkin's lymphoma.	Airway obstruction, obliterative bronchiolitis, acute respiratory failure. Acute coronary syndrome, heart failure, thoracic aorta dissection, arrhythmias and conduction disturbances, subluxation of the atlantoaxial joints, bowel ischemia and perforation. Septic arthritis. Scleritis.
Systemic lupus erythematosus	Systemic autoimmune disease, characterized by relapses and remissions and affecting virtually every organ. Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), symmetric and polyarticular inflammatory arthritis (small joints of the hands, wrists, and knees), butterfly rash, oral and/or nasal ulcers, Raynaud's phenomenon. Neuropsychiatric manifestations, pleurisy, ILD, and pulmonary hypertension. Libman-Sacks endocarditis, pericarditis, myocarditis, endocarditis. Renal impairment (nephritis), leukopenia, mild anemia, and thrombocytopenia. Antiphospholipid syndrome. Ocular complications.	Airway obstruction, ARDS, respiratory failure and arrest, alveolar hemorrhage, ACS, cardiac tamponade, heart failure, arrhythmias, pulmonary embolism, stroke, acute renal failure, Guillain-Barré–like syndrome, transverse myelitis, seizures. Bowel ischemia and perforation, GI bleeding, acute pancreatitis. Hemolytic anemia, thrombotic microangiopathic hemolytic anemia.
Sjögren's syndrome	Autoimmune disease. May be primary; secondary form is mostly associated with rheumatoid arthritis, systemic lupus erythematosus. Xerophthalmia and xerostomia, systemic symptoms, arthralgia, skin lesions, Raynaud's phenomenon. ILD, pulmonary hypertension, pericarditis, neuropsychiatric manifestations, peripheral neuropathy, hepatic abnormalities, renal impairment, increased risk of non-Hodgkin's lymphoma.	Hypokalemic respiratory arrest. Heart block, pulmonary embolism, ischemic stroke, transverse myelitis, optic neuritis, renal tubular acidosis, acute pancreatitis.
Systemic sclerosis (scleroderma)	Inappropriate and excessive accumulation of collagen and matrix in a variety of tissue; widespread vascular lesions with endothelial dysfunction, vascular spasm, thickening of the vascular wall and narrowing of the vascular lumen. Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), skin lesions (fingers, hands, and face), carpal tunnel syndrome, Raynaud's phenomenon. ILD, renal impairment, GI dysmotility, gastroesophageal reflux (aspiration pneumonitis), chronic esophagitis, and stricture formation. Vascular ectasia in the stomach ("watermelon stomach").	Scleroderma renal crisis. Respiratory failure, ARDS, aspiration pneumonitis, pulmonary hypertension, alveolar hemorrhage, heart failure, arrhythmias, and conduction disturbances. Ischemia and gangrene of the digits.
Takayasu's arteritis	Chronic vasculitis, young women, predominantly Asians. Systemic complaints (fever, malaise, fatigue, weight loss, myalgia), arthralgias, skin lesions, abdominal pain, and diarrhea. Aorta and its primary branches, and pulmonary artery involvement. Neurologic manifestations, syncope, subclavian steal syndrome, extremity ischemia. Renovascular hypertension. Normochromic normocytic anemia.	ACS, bowel ischemia and perforation, GI bleeding, stroke.
Granulomatosis with polyangiitis (Wegener's)	Multiple organ system vasculitis and necrotizing granulomas. Upper and lower respiratory tract manifestations—nose, oral cavity, upper trachea, external and middle ear, and orbit inflammations. Constitutional symptoms, arthralgias, glomerulonephritis, and small-vessel vasculitis (scleritis and episcleritis, palpable purpura or cutaneous nodules, peripheral neuropathy, deafness). Systemic hypertension. Pericarditis, myocarditis. Renal impairment. Anemia, leukocytosis, and thrombocytosis.	Airway obstruction, subglottic stenosis, diffuse alveolar hemorrhage. ACS, arrhythmias. Rapidly progressive glomerulonephritis.

Abbreviations: ACS = acute coronary syndrome; ARDS = adult respiratory distress syndrome; ILD = interstitial lung disease.

positive-pressure ventilation may help to prevent airway collapse. Cartilaginous destruction results in a small glottis, so when intubation is required, use a smaller endotracheal tube than normal.

INTUBATION IN PATIENTS WITH SYSTEMIC RHEUMATIC DISEASES

Endotracheal intubation is considered "difficult" in patients with systemic rheumatic diseases because of airway-related aspects of the disease.[1,5] Anticipate the need for adjunctive airway techniques, consider video laryngoscopy or fiberoptic intubation, and prepare to perform surgical cricothyrotomy. When the airway is patent but intubation is anticipated, and the patient can be safely transferred, it may be preferable to go to the operating room for a "double setup," with preparation for a formal tracheostomy if oral intubation is unsuccessful.

Many rheumatic diseases can complicate the mechanics of intubation including rheumatoid arthritis, ankylosing spondylitis, and scleroderma. Patients with rheumatoid arthritis and ankylosing spondylitis can develop temporomandibular joint dysfunction with reduced mouth opening. Skin tightening from scleroderma can significantly decrease oral aperture.

In both rheumatoid arthritis and ankylosing spondylitis, flexion and hyperextension can exacerbate atlantoaxial instability and C1-C2 subluxation and increase the risk of fracture.[1] Atlantoaxial instability and C1-C2 subluxation are prevalent in long-standing, seropositive rheumatoid arthritis (especially if poorly controlled) and should be taken into account with intubation. Patients with cervical ankylosis are at high risk for cervical fractures (even after minor trauma).

Subglottic stenosis or acute upper airway obstruction with an inability to clear tracheobronchial secretions may be observed in and even be a presenting sign of granulomatosis with polyangiitis (Wegener's). Subglottic stenosis often requires surgical intervention.

PULMONARY EMERGENCIES

Lung involvement, due to the underlying disease itself or secondary to infection, is a frequent cause of major morbidity and death, particularly in systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, vasculitis, and polymyositis/dermatomyositis.[1,2,5] Pulmonary complications of systemic rheumatic disease manifest primarily as interstitial lung disease and vascular disease.[5,6] Due to chronic lung injury, interstitial pulmonary fibrosis, or pulmonary hypertension, even mild infections in patients with systemic rheumatic disease can lead to respiratory failure.[5-7] Respiratory arrest has been reported in systemic lupus erythematosus and dermatomyositis/polymyositis patients due to phrenic nerve involvement, in rheumatoid arthritis patients due to cervicomedullary compression associated with rheumatoid atlantoaxial dislocation, and in Sjögren's syndrome patients due to hypokalemic paralysis secondary to distal renal tubular acidosis.

Symptoms can develop due to chronic manifestations of the underlying disease (e.g., interstitial lung disease), or new symptoms can develop due to an acute complication such as pneumonia or alveolar hemorrhage. Several complications outside the pulmonary parenchyma cause respiratory symptoms such as involvement of the joints of the thoracic cage (in ankylosing spondylitis), pleural effusion, respiratory muscle inflammatory disease (polymyositis/dermatomyositis), cardiac involvement, and anemia.[5,6] Of note, respiratory muscles can be involved in myositis, and if there is concern, serial measurements of negative inspiratory force can provide information about impending respiratory decline.[5] Pulmonary embolism risk is higher in systemic rheumatologic diseases.[8,9] Lastly, immunosuppressive therapies themselves can cause pulmonary complications (e.g., methotrexate can cause pulmonary fibrosis) as well increase the risk of both typical and atypical infections.[6,10]

ALVEOLAR HEMORRHAGE

Alveolar hemorrhage requiring hospital admission has a hospital mortality rate of 25%.[11] It is a complication of systemic lupus erythematosus, antiphospholipid syndrome, systemic vasculitis (granulomatosis with polyangiitis [Wegener's], microscopic polyangiitis, others), Behçet's disease, and very rarely, systemic sclerosis. Early recognition and aggressive management are critical for improved outcome.[11] Delay in treatment, age >60 years old, end-stage renal failure, and cardiovascular comorbidity worsen prognosis.[11] Patients with alveolar hemorrhage complain of acute shortness of breath, fever, and cough. Symptom onset is usually abrupt, with a progression to respiratory failure requiring mechanical ventilation.

The classical triad of hemoptysis, pulmonary infiltrates on chest radiograph, and rapid decrease in hemoglobin level supports the diagnosis, but the triad is frequently not present.[12,13] Most commonly, alveolar hemorrhage is mistakenly diagnosed as "atypical" pneumonia. Thus, a diagnosis of atypical pneumonia should raise the consideration of alveolar hemorrhage, especially if a new anemia is present.[12] If symptoms are accompanied by high fever, it is difficult to distinguish between alveolar hemorrhage and infectious pneumonia. The distinction is of utmost importance, because the therapeutic options are exactly the opposite (immunosuppressant vs. antibiotics). Emergent bronchoscopy with bronchoalveolar lavage can confirm the diagnosis but is done after admission. Treatment is directed to the underlying condition and includes high-dose glucocorticoids (up to 1 gram of methylprednisolone daily) and cyclophosphamide.[14,15] Local vessel embolization and plasmapheresis are used, but benefit is less clear.[15]

INTERSTITIAL LUNG DISEASE

Interstitial lung disease is characterized by infiltration of the pulmonary interstitium by inflammatory cells and matrix, leading to fibrosis, pulmonary hypertension, and respiratory insufficiency. Rheumatoid arthritis, systemic sclerosis, and polymyositis/dermatomyositis are commonly associated with interstitial lung disease.[5,16] Interstitial lung disease may be asymptomatic, may produce slowly progressive symptoms (cough and dyspnea), or, rarely, can cause acute respiratory failure. Treatment in the ED is ventilatory support, with oxygen, noninvasive ventilation, and intubation as needed.[16] Immunomodulators, such as rituximab, are given at the discretion of the rheumatology consultant.[17]

PULMONARY HYPERTENSION

Pulmonary arterial hypertension can be a complication of any rheumatic disease with associated pulmonary fibrosis and interstitial lung disease but is most common in systemic sclerosis and systemic lupus erythematosus.[7] Acute or chronic pulmonary embolism may also lead to pulmonary arterial hypertension. Clinical symptoms reported by patients with pulmonary arterial hypertension range from cough or mild shortness of breath to severe dyspnea, cardiac arrhythmias, chest pain, and right ventricular failure. Management includes optimization of fluid volume and treatment of right heart failure.[18] For further discussion, see Chapter 58, "Pulmonary Hypertension."

CARDIOVASCULAR EMERGENCIES

Cardiac disease develops through several pathophysiologic mechanisms, accounting for different manifestations such as inflammation, fibrosis, infiltration, vasculitis, thromboembolism, and accelerated coronary atherosclerosis.[19] **Table 282-3** provides a review of cardiac disorders in patients with systemic rheumatic diseases.[20-24]

ACUTE CORONARY SYNDROMES

Many systemic rheumatic diseases promote accelerated coronary atherosclerosis and have an increased rate of cardiovascular morbidity and mortality.[19-23] The relative risk is most pronounced in systemic lupus erythematosus and rheumatoid arthritis.[20,21] The risk of myocardial infarction in young, premenopausal women with lupus is between 2- and 10-fold compared with women without lupus and is a major cause of mortality, especially in younger patients.[20] Surprisingly, traditional risk factors do not fully explain the rates of cardiovascular disease in these patient populations.[22] It is hypothesized to be driven by the underlying disease, proinflammatory state, and potentially the medications used to treat the disease (e.g., glucocorticoids).

The risk of cardiovascular disease in inflammatory systemic rheumatic diseases equals that of type 2 diabetes, so clinically, it is useful

TABLE 282-3 Cardiovascular Emergencies in Patients with Systemic Rheumatic Diseases

	ACS, AMI	Acute Pericarditis	Aortic Emergencies	Aortic Valve Regurgitation	Arrhythmias, Heart Blocks	Aneurysm	Budd-Chiari Syndrome	Cardiac Tamponade	DVT and PE	Endocarditis	Heart Failure	Malignant Hypertension	Myocarditis	Peripheral Artery Ischemia	Pulmonary Artery Injury	Subclavian Steal Syndrome	Sudden Cardiac Death	Superior Vena Cava Syndrome
Ankylosing spondylitis				X														
Adult Still's disease					X						X		X					
Antiphospholipid antibody syndrome	X			X			X		X	X		X			X			X
Behçet's disease	X	X	X		X	X	X		X	X			X	X	X			X
Churg-Strauss syndrome	X	X						X			X							
Dermatomyositis/polymyositis					X			X			X		X					
Giant cell (temporal) arteritis			X	X		X												
Granulomatosis with polyangiitis (Wegener's)		X			X					X			X					
Polyarteritis nodosa	X					X					X	X		X				
Rheumatoid arthritis	X	X	X		X			X			X		X	X			X	
Systemic lupus erythematosus	X	X			X		X	X	X	X			X		X		X	
Sjögren's syndrome		X			X													
Systemic sclerosis		X			X			X	X		X	X	X				X	
Takayasu's arteritis	X		X	X		X						X		X	X	X		

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; DVT = deep vein thrombosis; PE = pulmonary embolism.

to consider systemic rheumatic disease a "risk factor" for coronary atherosclerosis.[25] Consequently, consider acute coronary syndrome in younger patients without traditional cardiovascular risk factors who have rheumatic diseases, particularly systemic lupus erythematosus and rheumatoid arthritis. Medical management of acute coronary syndrome is the same as in the normal population.

ACUTE HEART FAILURE

Acute heart failure may develop as a consequence of a myocardial disease (ischemia, cardiomyopathy, myocarditis, fibrosis), pericardial disease (tamponade or constrictive), valvular diseases (acute regurgitation), and/or conduction or rhythm disturbance.[19,20,24] Acute management of decompensated heart failure does not differ from the normal population, except when a flare of the underlying disease is responsible. In systemic sclerosis, diastolic dysfunction, malignant hypertension during a scleroderma renal crisis, and decompensated pulmonary hypertension are important causes of acute heart failure.

CARDIAC ARRHYTHMIAS

Rhythm and conduction disturbances are common, especially in rheumatoid arthritis, systemic sclerosis, sarcoidosis, systemic lupus erythematosus, and polymyositis/dermatomyositis. The pathophysiologic basis for these disorders is complex, involving reentry pathways, fibrosis, altered automaticity, conduction system injury, primary and/or secondary myocardial injury, and side effects of treatment. Population studies demonstrate a 40% higher risk for atrial fibrillation in patients with rheumatoid arthritis.[24,26] Arrhythmias and sudden cardiac death in systemic rheumatic disease have a higher incidence compared with the normal population.[24,26] Ventricular arrhythmias are a risk for sudden cardiac death, especially in patients with systemic sclerosis.[24]

MALIGNANT HYPERTENSION

Systemic hypertension may be a clinical manifestation of renal injuries or an adverse effect of disease treatment. Severe malignant hypertension is a complication of systemic sclerosis (usually observed during a "renal crisis"), but it can be also observed in catastrophic antiphospholipid syndrome, polyarteritis nodosa, and a few other rheumatic diseases.

VASCULAR AND VALVULAR DISEASE

Valvular heart disease is an extra-articular manifestation of spondyloarthropathies, particularly ankylosing spondylitis. Fibrotic changes of the aortic valve cusps lead to valvular insufficiency of the aortic and/or mitral valves. Arterial lesions can be aneurysmal (frequently complicated by fatal rupture) or, less commonly, occlusive. Aortitis may lead to aortic aneurysms in patients with giant cell arteritis (temporal arteritis), Takayasu's arteritis, and Behçet's disease, and aneurysms may rupture or dissect. In giant cell arteritis, great vessel involvement due to arteritis can result in aortic valve incompetence and aortic aneurysm as a late complication of the disease.

Takayasu's arteritis involves the larger vessels, which can include pulmonary artery inflammation (resulting in hemoptysis, aneurysm, thrombosis, hemorrhage, and pulmonary infarction), as well as arterial narrowing and/or aortitis, which can produce neurologic symptoms or syncope related to the subclavian steal syndrome. Because Takayasu's arteritis is found in predominantly young women, these would be uncommon symptoms or manifestations as compared to their healthy peers.

Libman-Sack's endocarditis (sterile verrucous lesions) can produce valvular abnormalities seen in both antiphospholipid antibody syndrome and systemic lupus erythematosus.[27] Valvular lesions are often asymptomatic, although emboli can produce systemic symptoms (stroke, renal infarction). In both diseases, valvular destruction with resultant regurgitation are possible, with mitral valve involvement most common. Additionally, valves with underlying pathology are often fertile areas for infective endocarditis to settle.

THROMBOEMBOLISM

Superficial thrombophlebitis and deep vein thrombosis are common in Behçet's disease. Thrombosis is related to vascular inflammation and more commonly venous than arterial.[28] After the veins of the lower extremities, other affected veins are the inferior and superior vena cava and hepatic veins (Budd-Chiari). Immunosuppression is

the mainstay of treatment of thromboembolism in Behçet's disease,[29] with much controversy over whether ongoing anticoagulation is indicated.[30,31] Acute cases should be treated at diagnosis with methylprednisolone 1 gram.[29,32] When considering an anticoagulant, consider potential for active bleeding and discuss with a rheumatology consultant prior to initiation.

Thromboembolic disease may also be observed as a complication of systemic lupus erythematosus and the antiphospholipid syndrome; for treatment recommendations, see later discussion. Vessel thrombosis can be venous and/or arterial, affect any vessel, and be recurrent and bilateral. Peripheral gangrene, acute coronary syndrome, renal artery thrombosis, sagittal sinus thrombosis, transient ischemic attack, and Budd-Chiari syndrome due to hepatic vein thrombosis are possible examples of thromboembolism from rheumatic disease.

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

This uncommon vaso-occlusive process leads to multiorgan failure and is often associated with systemic lupus erythematosus, but it may be observed in other systemic rheumatic diseases.[33,34] Multiple simultaneous venous and/or arterial occlusive thromboses with resultant multiorgan failure develop suddenly and progress rapidly over days. In half of the cases, a precipitating factor may be identified (e.g., infection, surgery, trauma, exogenous estrogen exposure). The kidney is the primary organ involved (acute kidney injury), followed by the lungs (adult respiratory distress syndrome, embolism), CNS (stroke, seizures, venous occlusion), heart (acute myocardial infarction and heart failure), and skin (necrosis). *Livedo reticularis* (lacelike purplish discoloration of the lower extremities) and thrombocytopenia are important diagnostic findings (a decrease in platelet count is observed in 60% of cases), and occasionally, laboratory features of disseminated intravascular coagulation may be present. This dramatic clinical scenario is frequently fatal, with a reported mortality rate approaching 50% despite therapy. Initial treatment is heparin and high-dose glucocorticoids (methylprednisolone 1 gram) along with treatment of the underlying triggering condition.[35] Unfractionated heparin followed by transition to warfarin is the recommended anticoagulant regimen of choice because of the anti-inflammatory properties of unfractionated heparin and the safety and efficacy demonstrated in this population.[33] Other modalities of treatment to consider include plasma exchange, cytotoxic therapy, and IV immunoglobulins.[33]

NEUROLOGIC EMERGENCIES

Neurologic disease can result from accelerated atherosclerosis, direct involvement by the primary disease, vasculitis, arterial aneurysm, rupture or dissection, embolism, or infection.[36] Libman-Sacks valvular endocarditis of lupus can result in embolism of valve vegetations. Vasculitis of the cerebral vessels, with vessel rupture or occlusion, may lead to ischemic or hemorrhagic stroke. IV tissue plasminogen activator and thrombectomy have been successfully used to treat ischemic stroke in patients with lupus.[36-40] However, patients with CNS vasculitis should be considered at higher risk for post–tissue plasminogen activator hemorrhage.[41,42] Although less common, giant cell arteritis can affect the extracranial vasculature, causing transient ischemic attacks, especially involving the vertebrobasilar circulation, with signs and symptoms of vertigo, hearing loss, gait disturbance, and other focal neurologic deficits involving the brainstem.

Neurologic disease can also manifest as a consequence of therapy for systemic rheumatic diseases.[43] Tumor necrosis factor-α inhibitors increase the risk for herpes zoster outbreaks, especially multidermatomal and zoster ophthalmicus.[43] Lupus and rheumatoid arthritis are independent risk factors for herpes zoster outbreaks.[44]

SPINAL CORD COMPRESSION AND SPINAL FRACTURES

Degenerative disease of the cervical spine may result in acute spinal cord compression, gait abnormalities, paresthesias, or obstructive hydrocephalus in patients with rheumatoid arthritis and ankylosing spondylitis. Rigidity and osteoporosis of the spine in ankylosing spondylitis increase the risk for fracture and spinal cord injury. Occult fracture of the ankylosed spine may occur, even in the absence of trauma, and may result in acute radiculopathy, paralysis, or death from complications.[45] The most common symptom is severe and progressive pain. CT and/or MRI are recommended for evaluation.[45]

INSTABILITY OF THE CERVICAL SPINE

The atlantoaxial joint is a preferred target of rheumatoid arthritis and less commonly, ankylosing spondylitis. Instability of the cervical spine and spontaneous atlantoaxial subluxation can result in acute cervical myelopathy, even after minor trauma. The signs and symptoms that raise suspicion for an unstable cervical spine are severe neck pain with occipital radiation and paresthesias involving the upper extremities.[1] Instability may produce vertigo or other signs of vertebral insufficiency.

Atlantoaxial instability can be clinically silent, so avoid neck flexion and extension (especially during intubation) in the patient with rheumatoid arthritis as well as ankylosing spondylitis. After even mild trauma or if neurologic symptoms as described earlier develop, keep the cervical spine stabilized. CT of the cervical spine will detect fracture, but MRI is needed to assess spinal cord integrity. Neurosurgical (or orthopedic spine specialist) consultation is needed for management.

TRANSVERSE MYELITIS

Transverse myelitis is a rare, devastating acute inflammatory process affecting a focal area of the spinal cord that may lead to rapid onset of irreversible paraplegia. It is clinically manifested with acute or subacute progressive symptoms and signs of neurologic dysfunction of the spinal cord. The clinical picture may be insidious at the beginning, with weakness, back or limb pain, urinary retention, and autonomic and sensory deficits.[46] Transverse myelitis occurs more commonly in patients with Sjögren's syndrome,[47] eosinophilic granulomatosis with polyangiitis, and also systemic lupus erythematosus, in whom acute transverse myelitis may be the initial manifestation.[48] Management includes high-dose corticosteroids and immunosuppressive agents at the direction of the rheumatology and/or neurology consultants.

The clinical picture of transverse myelitis may also be caused by vasculitis, arterial thrombosis, embolism, or artery dissection. An anterior spinal artery syndrome may be observed in other rheumatic diseases and is caused by blood supply impairment secondary to dissection of the aorta, vasculitis, or embolism involving the anterior spinal artery. The clinical picture is indistinguishable from transverse myelitis.

OCULAR EMERGENCIES

The eye is a sensitive barometer for onset or flare of rheumatic diseases.[49] Ocular pain or discomfort, vision disturbances, red eye, tearing, photophobia, diplopia, or reduced visual acuity should lead to careful evaluation (**Table 282-4**). Optic neuritis and keratitis are complications of systemic rheumatic diseases and are discussed in Chapter 241, "Eye Emergencies."

Sudden and permanent blindness is also a concern in temporal or giant cell arteritis, a systemic disease that may lead to vasculitis and ischemia and that affects middle-aged to elderly individuals. The patient may report amaurosis fugax and complain of new headache, tender scalp, visual disturbance, or jaw claudication. Frequently, vision loss is the presenting feature of giant cell arteritis. To prevent permanent vision loss, high-dose steroids are administered based on the clinical diagnosis, even before biopsy of the temporal artery (see Chapter 241).

RENAL EMERGENCIES

The kidney is frequently involved in systemic rheumatic disease and is a major factor leading to morbidity and mortality. A decline in renal function should prompt careful observation and follow-up in any rheumatic disease patient. Kidney impairment may be related to the rheumatic disease itself, the results of therapy, or both. Acute nephritic syndrome, renal thrombotic events, and renal artery lesions are other possible causes of acute renal failure. In polyarteritis nodosa, rupture of arterial aneurysms can cause a perirenal hematoma.

Scleroderma renal crisis is a true rheumatic emergency because it is associated with high mortality and requires prompt involvement of rheumatology and nephrology. Scleroderma renal crisis typically develops early in the course of systemic sclerosis, with 75% of cases occurring

TABLE 282-4 Ocular Emergencies in Patients With Systemic Rheumatic Diseases

		Ankylosing Spondylitis	Behçet's Disease	Churg-Strauss Syndrome	Giant Cell (Temporal) Arteritis	Polyarteritis Nodosa	Rheumatoid Arthritis	Relapsing Polychondritis	Systemic Lupus Erythematosus	Sjögren's Syndrome	Granulomatosis With Polyangiitis
Ocular	Episcleritis						x	x			x
	Ischemic eye complications		x	x	x						x
	Scleritis			x			x	x	x		x
	Optic neuritis		x						x	x	
	Peripheral ulcerative keratitis			x		x	x	x	x		x
	Retinal vasculitis		x								x
	Scleromalacia perforans						x				
	Uveitis	x	x					x	x		x

during the first 4 years after the onset of disease.[50] The prior use of glucocorticoids has also been implicated in precipitating scleroderma renal crisis. It is more common with patients with diffuse systemic sclerosis and presents with abrupt and rapid deterioration in renal function along with hypertensive encephalopathy. Microangiopathic anemia frequently accompanies the other features.

The mainstay of therapy in scleroderma renal crisis is effective and prompt blood pressure control with angiotensin-converting enzyme inhibitors.[51] Start captopril, 6.25 to 12.5 milligrams PO three times daily, and increase as tolerated.[51] Enalaprilat can be used if PO therapy is not possible. Second-line choice is a calcium channel blocker.[51] Dialysis is required in 50% of patients initially, but more than half will recover renal function.[51]

Distal renal tubular acidosis occurs in patients with primary Sjögren's syndrome. This condition is characterized by hyperchloremic metabolic acidosis with low bicarbonate levels and hypokalemia. Consider hypokalemia as a cause of progressive weakness in patients with Sjögren's syndrome. Hypokalemia is corrected with standard treatment (see Chapter 17, "Fluids and Electrolytes").

GI EMERGENCIES

GI emergencies are outlined in **Table 282-5**. GI complications include ischemia (primarily due to vasculitis), infarction, perforation, vascular rupture, infection (e.g., cholecystitis, diverticulitis), and hemorrhage.

TABLE 282-5 GI and Other Emergencies in Patients With Systemic Rheumatic Diseases

		Adult Still's Disease	Antiphospholipid Syndrome	Behçet's Disease	Churg-Strauss Syndrome	Henoch-Schönlein Purpura	Microscopic Polyangiitis	Polyarteritis Nodosa	Rheumatoid Arthritis	Systemic Lupus Erythematosus	Sjögren's Syndrome	Systemic Sclerosis	Takayasu's Arteritis	Granulomatosis With Polyangiitis
GI	Acute pancreatitis				x	x		x		x	x			
	Bowel perforation		x	x	x	x		x		x				x
	Esophageal necrosis with perforation		x											
	GI bleeding		x		x	x	x	x		x			x	
	Mesenteric vasculitis and ischemia		x		x	x		x	x	x			x	x
	Severe hepatic failure	x												
Other emergencies	Acute scrotum					x		x						
	Adrenal insufficiency		x											
	Disseminated intravascular coagulation	x	x											
	Hemolytic anemia		x							x				
	Microangiopathic hemolytic anemia	x	x							x		x		
	Pure red cell aplasia	x							x					
	Thrombotic thrombocytopenic purpura	x								x				

Vasculitis is the most common GI manifestation and may affect any size vessel. Bowel ischemia can be the result of the same pathophysiologic process that leads to acute coronary syndrome, embolic phenomenon, or mesenteric artery vasculitis. The patient may complain of symptoms consistent with "intestinal angina" prior to bowel infarction. Due to chronic or recurrent ischemia, the bowel may develop wall edema, strictures, and stenosis. These changes may account for colicky abdominal pain, diverticular disease, intestinal obstruction, or episodes of paralytic ileus. Lupus mesenteric vasculitis is one of the most serious complications of systemic lupus erythematosus, with mortality of 13%.[52] Leukopenia, hypoalbuminemia, and elevated serum amylase are associated with poor outcome. Acute pancreatitis can be a result of several systemic rheumatic diseases or a result of many of the therapies (notably azathioprine).

INFECTIOUS EMERGENCIES

Rheumatic diseases predispose to infection in several ways, including immunocompromise at baseline and medications that induce immunosuppression (see "Adverse Drug Reactions" section later in this chapter for infections associated with specific immunosuppressant drugs used to manage systemic rheumatic diseases). Differentiating flares of systemic rheumatic diseases, such as rheumatoid arthritis or systemic lupus erythematosus, is difficult.[53] Using an elevated procalcitonin level of 0.5 nanogram/mL is 90% specific for sepsis in patients with autoimmune diseases but is only 68% to 75% sensitive for acute infection.[54,55] For acutely ill patients, empiric antibiotics are indicated until infection can be excluded. In general, isolated organisms do not differ from the normal population, although certain rheumatic diseases may leave patients more susceptible to atypical infections. For example, patients with systemic lupus erythematosus are more likely to have infections from encapsulated bacteria (e.g., *Salmonella*), although typical infections are still more common. Regardless, the differential for infectious causes should always remain broad because both the underling disease itself as well as chronic immunosuppressive therapy may predispose patients with systemic rheumatic disease to opportunistic infections (e.g., *Candida*, *Pneumocystis jirovecii*, *Legionella*, *Mycobacterium tuberculosis*).

While symptoms of septic arthritis may mimic flares of the underlying rheumatic disease, care must be taken to rule out infection with aspiration of the involved joint if indicated. The risk of septic arthritis is increased in any joint with preexisting arthritis. Thus, patients with joint-destructive disease such as rheumatoid arthritis are at high risk of developing septic arthritis, which is often amplified by the immunosuppressive medications used to treat their disease. The prevalence of septic arthritis is doubled in patients with rheumatoid arthritis who are treated with glucocorticoids or tumor necrosis factor-α blockers.[56,57] The physical findings of severe pain and limited range of motion may be absent in cases of septic arthritis in patients with systemic rheumatic disease.[58] Patients suspected of having septic arthritis should have arthrocentesis prior to initiation of antibiotic therapy. It is important to remember that the presence of a crystalline arthropathy (e.g., gout) does not exclude the possibility of concurrent septic arthritis. If the clinical suspicion for septic arthritis is high, it is prudent to start antibiotics after aspiration, consult orthopedics, and admit the patient while awaiting cultures. See Chapter 284, "Joints and Bursae," for further discussion of diagnosis and treatment.

OTHER EMERGENCIES

Several hematologic complications and other emergencies are encountered in patients with rheumatic diseases (Table 282-5).

Anemia, thrombocytopenia, leukopenia, and coagulation abnormalities are some of the important hematologic emergencies. Severe hemolytic anemia may develop in systemic lupus erythematosus (autoimmune) and in systemic sclerosis during renal crisis (microangiopathic). Thrombocytopenia may be present in systemic lupus erythematosus and also observed in antiphospholipid syndrome patients; it may present as thrombotic thrombocytopenic purpura. A low WBC count may occur as a part of underlying disease or secondary to immunosuppressive regimens. Pancytopenia may be observed when the rheumatic disease itself affects all the cellular lines in acute hemophagocytic syndrome and in medullar suppression secondary to cytotoxic drugs. In autoimmune hematologic emergencies, transfusion of blood product may carry some risk of transfusion reaction.

Patients with steroid-dependent rheumatic diseases are at risk for acute adrenal insufficiency either from unexpected stressors (illness, surgery) or from abrupt cessation of prescribed steroid medication.

Orchitis is one of the most characteristic manifestations of polyarteritis nodosa, and scrotal involvement may be found in boys with Henoch-Schönlein purpura. Clinical findings include pain, tenderness, and swelling of the involved testicle and/or scrotum. The presentation may mimic testicular torsion. Ultrasonography confirms the correct diagnosis.

RAYNAUD'S PHENOMENON

Raynaud's phenomenon, digital ulcers, and rash are some examples of skin manifestations. While often benign in nature, Raynaud's phenomenon can rarely have disastrous consequences including gangrene and loss of digits.[59] These serious complications are rarely seen in primary Raynaud's phenomenon and are most frequently seen in patients with systemic sclerosis. Failure of the Raynaud's phenomenon to resolve, either manifested as consistently blue fingers or ulcerations, is an emergency.[59] Warming techniques (both core and peripheral) should be initiated immediately, but with insufficient response, oral calcium channel blockers and topical nitroglycerin paste applied to the webbed spaces can help to save tissue.[59,60] Depending on the severity, admission to the hospital may be indicated for more aggressive intervention (e.g., IV prostacyclin, surgical sympathectomy) and pain control.[60]

ADVERSE DRUG REACTIONS

Table 282-6 lists the more common clinical manifestations of adverse reactions associated with drugs used to manage systemic rheumatic diseases. When patients with systemic rheumatic diseases develop new alarming and unexplained symptoms, a drug reference guide or similar resource should be consulted for a listing of rare adverse drug reactions.

IMMUNOSUPPRESSION

IMMUNOSUPPRESSION CAUSED BY DRUGS USED TO MANAGE SYSTEMIC RHEUMATIC DISEASES

Immunosuppressants and disease-modifying antirheumatic drugs are used to treat multiple types of systemic rheumatologic diseases with the aim to induce or maintain remission, to reduce exacerbations or relapse, and/or to allow tapering of glucocorticoids. These drugs have a variety of actions that are not completely understood but that modify critical pathways in the inflammatory process. They may cause immunosuppression primarily or as a side effect and lead to secondary diseases, infections, and reactivation of latent diseases or malignancies (**Table 282-7**).[61-68]

Risk factors for infection during immunosuppression include the drug, dose, duration of use, concomitant use of immunomodulators, the nature of the disease process, the functional status of the patient, healthcare facility exposure, and older age.[69] For the treatment of systemic rheumatic disease, immunosuppressive therapies are often used in combination especially with glucocorticoids, enhancing the risk of infection.

In particular, glucocorticoid therapies are associated with a dose-dependent increase in risk of infection.[70] The immunosuppressive properties of glucocorticoids are thought to be from the impact on both the innate and acquired immune system, which occurs through a variety of inhibitory mechanisms. Immediate effects on the innate immune system include decreased phagocyte migration, eosinophil apoptosis, decreased macrophage production and function, decreased degranulation of mast cells, decreased inflammatory cytokine production, and decreased pro-inflammatory mediators. Neutrophils are affected by decreased ability to bind to and exit the endothelium, increased release from bone marrow, and decreased apoptosis resulting in increased overall leukocytosis but decreased effectiveness.

Acquired immunity is also affected by a decrease in dendritic cells, rapid depletion of T cells, increased apoptosis of CD4 and CD8 cells,

TABLE 282-6 Common Clinical Manifestations of Adverse Reactions to Drugs Used to Manage Systemic Rheumatic Diseases

	Abdominal Pain	Acute/Hemorrhagic Cystitis	Adrenal Insufficiency	Alopecia	Anaphylaxis	Anemia	COPD Exacerbation	Dermatologic Manifestations	Diarrhea	Diverticulitis	Fatigue/Malaise	GI Bleed	Hepatic Enzyme Elevation	Immunosuppression/Infection	Injection Site Reaction	Leukopenia	Nausea and Vomiting	Ophthalmic Impairment	Psychiatric Symptoms	Pulmonary Fibrosis	Renal Impairment	Stomatitis/Oral Ulcers	Thrombocytopenia
Abatacept	X				X		X	X						X	X		X						
TNF-α inhibitors*						X							X	X	X								
Apremilast	X							X	X		X			X			X		X				
Azathioprine						X			X				X	X		X	X						X
Belimumab					X			X	X					X	X	X	X		X				
Cyclophosphamide		X							X					X		X	X						X
Glucocorticoid			X									X		X					X				
Hydroxychloroquine				X													X	X					
Interluekin-1 inhibitors (anakinra, canakinumab)									X					X	X		X						
Leflunomide	X			X		X		X	X				X	X		X	X						
Methotrexate				X		X			X		X	X	X	X		X	X			X		X	
Mycophenolate	X					X		X	X				X	X		X	X				X		X
NSAID												X	X				X				X		
Rituximab	X					X		X	X					X		X	X						X
Sulfasalazine	X					X		X					X	X		X	X						X
Secukinumab					X				X					X	X		X						
Tocilizumab	X				X	X		X	X	X		X		X	X	X							X
Tofacitinib	X					X			X	X	X		X	X		X							
Ustekinumab									X					X			X						

Abbreviations: COPD = chronic obstructive pulmonary disease; TNF = tumor necrosis factor.

*Adalimumab, etanercept golimumab, infliximab, certolizumab pegol.

TABLE 282-7 Drugs Used to Treat Rheumatic Diseases and Common Infections Associated With Their Respective Use

Drug	Common Infections Associated With Agent
Abatacept	Pneumonia, URI, pharyngitis, UTI.
TNF-α inhibitors*	URI, sinusitis, pharyngitis. Reactivation of TB.
Apremilast	URI, bronchitis, pharyngitis, influenza.
Azathioprine	Reactivation of latent viruses, bacteremia, interstitial pneumonia. Lower rates of infection in RA patients compared to transplant.
Belimumab	Viral gastroenteritis, UTI, influenza, bronchitis, URI, sinusitis.
Cyclophosphamide	Reactivation of latent viruses, sepsis (*Salmonella, Staphylococcus, Meningococcus*), URI, pneumonia, opportunistic infections.
Glucocorticoid	High rate of infection with both typical and atypical pathogens.
Hydroxychloroquine	Overall infection is low.
Interluekin-1 inhibitors (anakinra, canakinumab)	Nasopharyngitis, cellulitis, URI.
Leflunomide	URI, bronchitis, pharyngitis, skin abscess.
Methotrexate	Viral infections, CMV, EBV, reactivation of latent viruses.
Mycophenolate	Viral infections, CMV, HSV, VZV. Candidiasis, URI.
NSAID	None
Rituximab	Pneumonia, cerebral toxoplasmosis. Reactivation of latent viruses. Progressive multifocal leukoencephalopathy due to JC virus reactivation.
Sulfasalazine	Overall serious infection risk is low but increased in the setting of neutropenia.
Secukinumab	Nasopharyngitis. URI. Herpes virus infection, staphylococcal infection.
Tocilizumab	Pharyngitis, rhinitis, conjunctivitis, diverticulitis.
Tofacitinib	URI, nasopharyngitis, diverticulitis.
Ustekinumab	Nasopharyngitis, URI, sinusitis. Vaginal mycosis and candidiasis.

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus; JC = John Cunningham; RA = rheumatoid arthritis; TB = tuberculosis; TNF = tumor necrosis factor; URI = upper respiratory infection; UTI = urinary tract infection; VZV = varicella-zoster virus.

*Adalimumab, etanercept golimumab, infliximab, certolizumab pegol.

TABLE 282-8 Critical Actions for the Care of Rheumatologic Disease Patients in the ED

Rheumatoid arthritis	• Increased risk of ACS in absence of traditional risk factors; treat as ACS equivalent • Atlantoaxial subluxation; avoid neck extension with intubation
Lupus	• Increased risk of ACS in absence of traditional risk factors; treat as ACS equivalent; consider ACS in young lupus patient with chest pain
Scleroderma	• Avoid steroids because they may precipitate renal crisis • Scleroderma renal crisis (renal failure, hypertension, MAHA) is an emergency; prompt treatment with ACE inhibitors is mandatory
Ankylosing spondylitis	• Spinal fractures may occur with minimal to no trauma; plain radiographs frequently miss fractures; consider CT/MRI if clinical suspicion high
Raynaud's phenomenon	• If refractory or ischemia present, topical nitroglycerin paste can be applied to webbed spaces of fingers to help save tissue
Septic arthritis	• Concurrent crystalline disease does not rule out a concurrent septic arthritis; await cultures • A negative Gram stain is insufficient to rule out septic arthritis
Giant cell arteritis	• Consider in new-onset headache, jaw claudication, scalp tenderness, or visions changes • If clinical concern high, start high-dose steroids (prednisone 1 milligram/kg) prior to obtaining biopsy for confirmation

Abbreviations: ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; MAHA = microangiopathic hemolysis.

B-cell reduction (although to a lesser extent than T cells), and in chronic use, a decrease in immunoglobulin G and immunoglobulin A.

CRITICAL ACTIONS FOR SYSTEMIC RHEUMATIC DISEASE PATIENTS

Important actions and facts about the care of patients with systemic rheumatic disease are listed in **Table 282-8**.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 283

Nontraumatic Disorders of the Hand

Carl A. Germann

HAND INFECTIONS

PATHOPHYSIOLOGY

The most common pathogens causing hand infection are *Staphylococcus aureus, Streptococcus* species, and gram-negative species.[1] Most routine infections involve a single gram-positive organism, whereas infections from IV drug use or mouth flora are usually polymicrobial. In most U.S. cities, community-associated methicillin-resistant *S. aureus* is the most common pathogen cultured from patients with skin and soft tissue infections in EDs,[2] including 47% to 78% of hand infections.[3-8]

Injection drug users typically present with abscesses or deep space infections secondary to *S. aureus* and gram-negative organisms.[9] These infections are most commonly caused by direct introduction, but hematogenous spread from bacterial endocarditis is a possibility (see Chapter 296, "Injection Drug Users").

Paronychia and felons are caused by minor trauma, chewing fingernails, or exposing minor injuries to saliva. Most of these infections are polymicrobial, including *S. aureus* (most common) and anaerobic bacteria.[8,9]

Infections caused by animal bites reflect the oral flora of the involved species. Bites introduce a broad range of bacteria, including gram-positive, anaerobic, and gram-negative organisms. Common pathogens include streptococci, staphylococci, *Haemophilus*, *Eikenella*, *Fusobacterium*, peptostreptococci, *Prevotella*, and *Porphyromonas* species.[10] Cat and dog bites harbor *Pasteurella multocida*, which typically produces an aggressive, rapidly spreading cellulitis that becomes suppurative. Hand infections are also discussed in Chapter 46, "Puncture Wounds and Bites."

Patients with diabetes or acquired immunodeficiency syndrome have common bacterial infection or develop atypical infections, including those caused by *Mycobacterium* or *Candida albicans*. Those who are immunocompromised or asplenic are at risk for rapid progression and require prompt source control and antibiotics.

PRINCIPLES OF EVALUATION AND MANAGEMENT

Hand infections are most commonly introduced by an injury to the dermis. The infection initially may remain superficial and broader, termed *cellulitis*, or may be localized, as seen in a paronychia or felon. Left untreated, infections may spread along anatomic planes or to adjacent compartments in the hand. Deeper injuries may directly seed underlying structures, creating rapidly spreading infections such as those seen with closed fist injuries or cat bites.

Obtain a directed history to delineate a likely cause of the infection. The physical examination should note the anatomic limits of the infection. Look for skin, subcutaneous tissue, tendon, joint, or bone involvement. If deep structures of the hand are involved, emergently consult a hand specialist because treatment likely will involve inpatient care and operative drainage.

With the exception of superficial cellulitis, hand infections are managed using basic principles. **First**, incise and drain any abscess. Superficial and discrete infections, such as paronychia and felons, can be drained in the ED. Deep infections are better treated in the operating room by a hand surgeon. **Second**, immobilize and elevate the extremity. This will rest the hand, reduce inflammation, avoid secondary injury, and limit extension of the infection. Immobilize by applying a bulky hand dressing and splinting the hand in a position of function: the wrist at 15 to 30 degrees of extension, the metacarpophalangeal joints at 50 to 90 degrees of flexion, and the interphalangeal joints at 5 to 15 degrees of flexion (**Figure 283-1**). Elevate the hand on pillows or suspended using stockinette. **Third**, use broad-spectrum antibiotics initially targeting possible common and serious bacteria, altering only based on response and culture results (**Table 283-1**). Empiric treatment for these infections should be based on local antibiotic resistance patterns. **Fourth**, if the patient is not admitted to the hospital, ensure reexamination within 48 hours.

CELLULITIS

Cellulitis is the most superficial of hand infections and is treated with oral antibiotics absent widespread involvement or systemic signs. Microbes most commonly breach the cutaneous surface through cracked skin, local trauma, or surgery. Diagnosis is made by documenting erythema, warmth, and edema in the affected portion of the hand without any involvement of deeper structures in the hand. Specifically, range of motion of the digits, hand, or wrist should not be painful, and palpation of the deeper structures of the hand should not produce any tenderness.

The most common offending organisms are *S. aureus* **(predominantly methicillin-resistant)**[1-8] and *Streptococcus pyogenes.* Initial treatment is

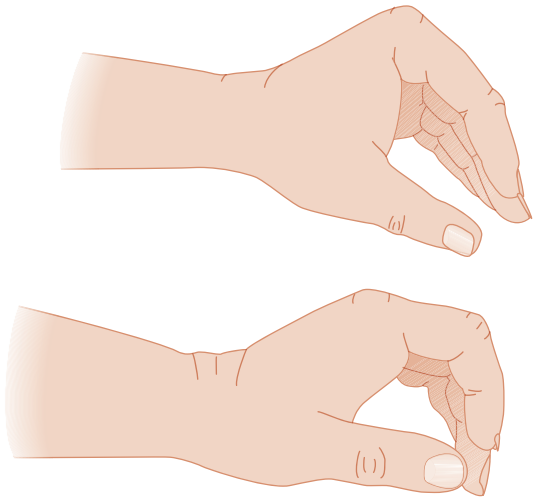


FIGURE 283-1. Positioning the hand during immobilization. Top position is used when splints are applied in fractures or severe sprains. Bottom position is the position of function used when applying a soft bulky dressing.

listed in Table 283-1. Cases of cellulitis without systemic signs of infection and a low suspicion for methicillin-resistant *S. aureus* should receive an antimicrobial agent that is active against streptococci.[11] For patients with cellulitis associated with purulent drainage, penetrating trauma, evidence of methicillin-resistant *S. aureus* infection elsewhere, nasal colonization with methicillin-resistant *S. aureus*, injection drug use, or systemic inflammatory response syndrome, antimicrobial treatment effective against methicillin-resistant *S. aureus* and streptococci is recommended.[11] Empiric monotherapy with trimethoprim-sulfamethoxazole or doxycycline is not recommended given the limited published efficacy data and concerns about effectiveness against streptococci.[10,11] Given the increasing rates of methicillin-resistant *S. aureus* and difficulty distinguishing among the types of *S. aureus* cellulitis, routine empiric treatment of methicillin-resistant *S. aureus* may be considered. In addition, the choice of antibiotic should be based on cultures (if available) and local resistance patterns. Consider empiric broad-spectrum antibiotics such as vancomycin and piperacillin-tazobactam (Table 283-1) and admission for the immunocompromised, those with clinical toxicity, and those with rapidly spreading infections. Hospitalization is recommended if there is concern for a deeper or necrotizing infection, for patients with poor adherence to therapy, for infection in a severely immunocompromised patient, or if outpatient treatment is failing.

For all cases of cellulitis, immobilize the hand in a position of function, and make sure the patient keeps the hand elevated as much as possible. Remove digit rings and give tetanus prophylaxis as needed. For those discharged, arrange reexamination within 48 hours.

FLEXOR TENOSYNOVITIS

Infectious flexor tenosynovitis is a surgical emergency. Failure to accurately diagnose and manage flexor tenosynovitis may result in adhesions, tendon vascular compromise and necrosis, or extension into

TABLE 283-1 Initial Antibiotic Coverage for Common Hand Infections

Infection	Initial Antimicrobial Agent(s)	Likely Organisms	Comments
Cellulitis	*MSSA coverage*: Cephalexin, 500 milligrams PO four times per day for 7–10 d,* *or* dicloxacillin, 500 milligrams PO four times daily for 7–10 d, *or* clindamycin 300–450 milligrams PO four times daily for 7–10 d *MRSA coverage*†: Clindamycin, 300–450 milligrams PO four times daily for 7–10 d, *or* doxycycline, 100 milligrams PO twice a day for 7–10 d, *or* minocycline, 100 milligrams PO twice a day for 7–10 d, *or* TMP-SMX double strength, 1–2 tablets twice per day PO for 7–10 d *For severe cellulitis*‡: Vancomycin, 1 gram IV every 12 h, *or* linezolid, 600 milligrams IV every 12 h	*Staphylococcus aureus* (MRSA) *Streptococcus pyogenes*	Clindamycin is an option, but increasing MRSA resistance to clindamycin has been reported. Consider local resistance patterns. Consider vancomycin for injection drug abusers.
Felon/paronychia	TMP-SMX double strength, 1–2 tablets twice per day PO for 7–10 d* *Plus/minus* cephalexin, 500 milligrams PO four times per day for 7–10 d,* *or* dicloxacillin, 500 milligrams PO four times daily for 7–10 d* *Consider* addition of clindamycin or amoxicillin-clavulanate to TMP-SMX (rather than cephalexin) if anaerobic bacteria are suspected	*S. aureus* (MRSA), *S. pyogenes*, anaerobes, polymicrobial	Antibiotics indicated for infections with associated localized cellulitis; otherwise, drainage alone may be sufficient. Culture recommended by hand surgeons.[4-7]
Flexor tenosynovitis	Ampicillin-sulbactam, 1.5–3 grams IV every 6 h, *or* cefoxitin, 2 grams IV every 8 h, *or* piperacillin-tazobactam, 3.375 grams IV every 6 h *Plus:* Vancomycin, 1 gram IV every 12 h, if MRSA is prevalent in community	*S. aureus,* streptococci, anaerobes, gram negatives	Parenteral antibiotics are indicated; consider ceftriaxone for suspected *Neisseria gonorrhoeae*.
Deep space infection	Ampicillin-sulbactam, 1.5–3 grams IV every 6 h, *or* cefoxitin, 2 grams IV every 8 h, *or* piperacillin-tazobactam, 3.375 grams IV every 6 h *Plus:* Vancomycin, 1 gram IV every 12 h, if MRSA is prevalent in community	*S. aureus,* streptococci, anaerobes, gram negatives	Inpatient management.
Animal bites (including human)	If no visible signs of infection: amoxicillin/clavulanate, 875/125 milligrams PO twice daily for 5 d For active signs of infection: ampicillin-sulbactam, 1.5–3 grams IV every 6 h, *or* cefoxitin, 2 grams IV every 8 h, *or* piperacillin-tazobactam, 3.375 grams every 6 h For penicillin allergy, use clindamycin plus moxifloxacin or TMP-SMX and metronidazole	*S. aureus,* streptococci, *Eikenella corrodens* (human), *Pasteurella multocida* (cat), anaerobes, and gram-negative bacteria	All animal bite wounds should receive prophylactic oral antibiotics.
Herpetic whitlow	Acyclovir, 400 milligrams PO three times daily for 10 d	Herpes simplex	No surgical drainage is indicated.

Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; TMP-SMX = trimethoprim-sulfamethoxazole.

*Although many sources recommend 7 to 10 days of therapy, the Infectious Diseases Society of America recommends 5 days of therapy if symptoms resolve and to continue therapy if symptoms persist.

†For patients whose cellulitis is associated with purulent drainage, penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or systemic inflammatory response syndrome, vancomycin or another antimicrobial active against both MRSA and streptococci is recommended.

‡Severe infection: failed oral antibiotic treatment, systemic signs (sepsis), immunocompromised, or clinical signs of deeper infection.

TABLE 283-2 Kanavel's Four Cardinal Signs of Flexor Tenosynovitis	
Percussion tenderness	Tenderness over the entire length of the flexor tendon sheath
Uniform swelling	Symmetric finger swelling along the length of the tendon sheath
Intense pain	Intense pain with passive extension
Flexion posture	Flexed posture of the involved digit at rest to minimize pain

adjoining deep spaces. This can lead to loss of function of the digit and eventually loss of function of the entire hand. The diagnosis is supported by the presence of the classic clinical signs described by Kanavel[1]; however, the absence of Kanavel's signs does not exclude the diagnosis of flexor tenosynovitis (**Table 283-2**).

The infection usually is associated with penetrating trauma of the affected area 2 to 5 days prior to presentation, although the patient may be unaware of injury. *Staphylococcus* is the most common bacterium isolated; however, infections often harbor anaerobes or are polymicrobial. Suspect disseminated *Neisseria gonorrhoeae* in a patient with a recent history consistent with a sexually transmitted infection (see Chapter 153, "Sexually Transmitted Infections").

Initiate treatment with parenteral antibiotics because the infection can spread rapidly through deep fascial spaces (Table 283-1). The use of vancomycin is recommended because of the high prevalence of methicillin-resistant *S. aureus* in most communities. Send any spontaneous exudate for Gram stain and culture with sensitivities. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.

Immobilize and elevate the hand, and consult the hand surgeon in the ED. If the infection is identified early in its course, nonoperative therapy with parenteral antibiotics, immobilization, elevation, and reevaluation is a common path.

DEEP SPACE INFECTIONS

Deep space infections arise from penetrating inoculation, contiguous spread, and rarely, hematogenous seeding.[1] *S. aureus* and *Streptococcus* species are the most common organisms isolated.[1]

Compartments where infection may propagate and migrate include the thenar space, midpalmar space, radial bursa (sheath for the flexor pollicis longus), and ulna bursa (common flexor sheath); see Figure 268-9 in Chapter 268, "Injuries to the Hand and Digits."

The volar aspect of the hand is covered by the tough and fixed tissues. The veins and lymphatics course through the softer tissues on the dorsum of the hand. Therefore, the dorsum of the hand often swells whenever there is an inflammatory or infectious process. For this reason, a deep space infection initially may be misdiagnosed as a cellulitis over the dorsum of the hand. An ideal **examination includes palpation of the volar surface of the hand to elicit tenderness, induration, or fluctuance.** Range of motion of the digits often produces marked pain for patients with deep space infection. Point-of-care US can assist in differentiating simple cellulitis from deep space infections.[12,13]

Occasionally, infections will arise in the web space. These "collar button" abscesses present with pain and swelling of the web space causing separation of the affected digits. Examination reveals induration or fluctuance in the dorsal and/or volar web space, along with erythema, warmth, and tenderness.

Give parenteral antibiotics (Table 283-1) and analgesia, and immobilize and elevate the hand. Operative draining is often needed, requiring emergent hand surgeon consultation.

INFECTIONS FROM CLOSED FIST INJURIES

Human bite injuries to the hand may occur due to accidental trauma or purposeful biting, but are often the result of striking another individual's teeth with a clenched fist (**Figure 283-2**). These injuries, termed "fight bite infections," usually occur over the dorsal aspects of the third, fourth, and fifth metacarpophalangeal joints. Although these injuries may at first appear innocuous, morbidity can result from late presentation or inadequate initial management.



FIGURE 283-2. Clenched fist injury. The lacerations in this photograph were sustained from teeth during a fight. Note the subtle black ink stamp across the proximal metacarpals, possibly revealing a clue about the wound's etiology. [Photo contributor: Lawrence B. Stack, MD. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *The Atlas of Emergency Medicine*, 3rd ed. New York, NY: McGraw-Hill, Inc.; 2010, Fig 11-30.]

Because of the force and the penetrating nature of the human incisor, closed fist infections tend to occur in multiple planes and spread rapidly to adjacent compartments. Skin, extensor tendons, joint space, bone, and surrounding deep spaces often are involved because the inoculum may traverse all these structures.

On examination, document the extent of the infection. Plain radiographs will detect fractures or foreign material including tooth fragments. The most common organisms reflect the natural flora of the mouth and include *Streptococcus* species, *S. aureus, Eikenella corrodens, Fusobacterium, Peptostreptococcus,* and *Candida* species; polymicrobial sources are common. Early antimicrobial therapy against both aerobic and anaerobic bacteria is recommended for patients with animal bites to the hand (Table 283-1). If you suspect any deep space, palmar space, joint, or tendon infection, give broad-spectrum antibiotics and consult a hand surgeon for open debridement and irrigation in the operating room. Closing animal bite wounds of the hand may be associated with a high infection rate. Treat all infections with hand elevation and splinting in the position of function.

PARONYCHIA

Paronychia is an infection of the lateral nail fold or perionychium, occasionally extending to the cuticle or eponychium. It is usually caused by minor trauma such as nail-biting, manicures, or embedded lateral nails ("hangnails"). The infection often starts as a small area of induration that progresses to eponychial swelling, tenderness, erythema, and drainage. Most cases of paronychia contain both aerobic and anaerobic bacteria, with *S. aureus* and *Streptococcus* species the most common aerobic bacteria cultured. Chronic paronychia (>6 weeks) can occur, particularly in patients who are immunocompromised, and may include usual pathogens or atypical bacteria and fungi such as with *C. albicans*.[14]

Absent fluctuance, treat the paronychia with warm soaks, elevation, and antibiotics (Table 283-1). Suppuration leads to either fluctuance or identifiable pus requiring drainage. Recommendations for drainage include the use of a digital nerve block and avoidance of incision across the eponychial fold to prevent nail deformity (**Figure 283-3**). Minor infections can be treated with elevation of the perionychium or eponychium with a flat probe to encourage drainage. If drainage is

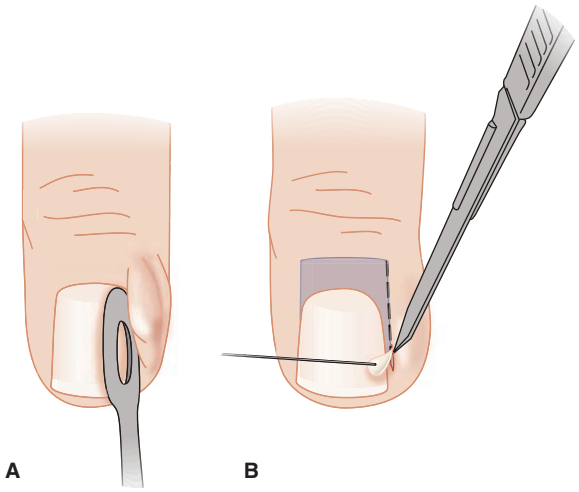


FIGURE 283-3. Paronychia. **A.** The eponychial fold is elevated using a flat probe or a #11 blade to allow the wound to drain. **B.** Alternatively, for more extensive infections, a #11 blade may be used to incise the area of greatest fluctuance directly into the eponychium. The wound may then be gently probed with a small clamp to ensure drainage.

successful, use warm soaks for days after care. In general, only nonviable tissue can be incised without provoking pain.

More extensive infections that do not communicate directly with the nail fold require digital block and incision directly into the area of greatest fluctuance. Severe infections with pus beneath the nail require removal of a portion of the lateral or proximal nail to ensure adequate drainage. Rarely, a free-floating nail will be encountered on a bed of pus, necessitating removal of the entire nail.

Following incision and drainage, keep the hand elevated and immobilized. Warm soaks may be initiated to keep the wound open and clean. Routine antibiotics are not needed unless cellulitis, immunocompromise, or vascular insufficiency exists; when used, a 7-day course is common or until resolution of the infection.[15] In complicated or drained cases, reassess the wound within 48 hours. Chronic paronychia (>6 weeks) should be treated with topical corticosteroids and topical antifungal agents, by avoiding wet environments, and with referral to dermatology.[1] (See Video: Paronychia Incision and Drainage.)

FELON

A felon is a subcutaneous pyogenic infection of the pulp space of the distal finger or thumb.[1] The septa of the finger pad produce multiple individual compartments and confine the infection under pressure. This results in a red, tense, and markedly painful distal pulp space. Infection typically begins with minor trauma, often a puncture wound, to the dermis overlying the finger pad. The infection can start and spread between septae, forming multiple compartmentalized abscesses. Left untreated, the infection may spread to the flexor tendon sheath, causing flexor tenosynovitis, or to the underlying periosteum, resulting in osteomyelitis.

S. aureus is the most common organism (primarily methicillin-resistant *S. aureus*),[3] but *Streptococcus* species, anaerobes, and gram-negative organisms are frequent. If possible, obtain a Gram stain and culture because these infections may be difficult to eradicate and chronic infections may be caused by atypical organisms. If osteomyelitis occurs, identification of the offending organism guides long-term antibiotic therapy.

Drain the infection if the finger pad is swollen and tense or if there is any palpable fluctuance.[1] A digital block using a long-acting anesthetic is ideal for comfort (see Chapter 36, "Local and Regional Anesthesia"). A unilateral longitudinal approach spares the sensate volar pad and achieves adequate drainage (**Figure 283-4A**). Do not incise the distal end of the finger pad because this can cause instability and loss of sensation to the fingertip. Dissect the septa using a small clamp to ensure complete drainage. A small wick encourages continued drainage.

If the felon is pointing toward the volar fat pad, an option is a longitudinal volar approach, depicted in **Figure 283-4B**. Avoid extending the incision to the flexor crease of the distal interphalangeal joint. **More extensive incisions such as the "fishmouth," "hockey stick," and through-and-through incisions are not indicated** because these can alter sensation to the fingertip or compromise pulp vascularity.

Following drainage, irrigate the wound and place a dry, sterile dressing; ask the patient to keep the extremity elevated. Reevaluate the wound within 48 hours, and use warm soaks to keep the wound clean and promote continued drainage.

Most felons have associated cellulitis that should be treated with oral antibiotics (Table 283-1). Refer chronic felons or felons not responding to the previously discussed treatments to a hand specialist for more definitive management and long-term follow-up. (See Video: Felon Incision and Drainage.)

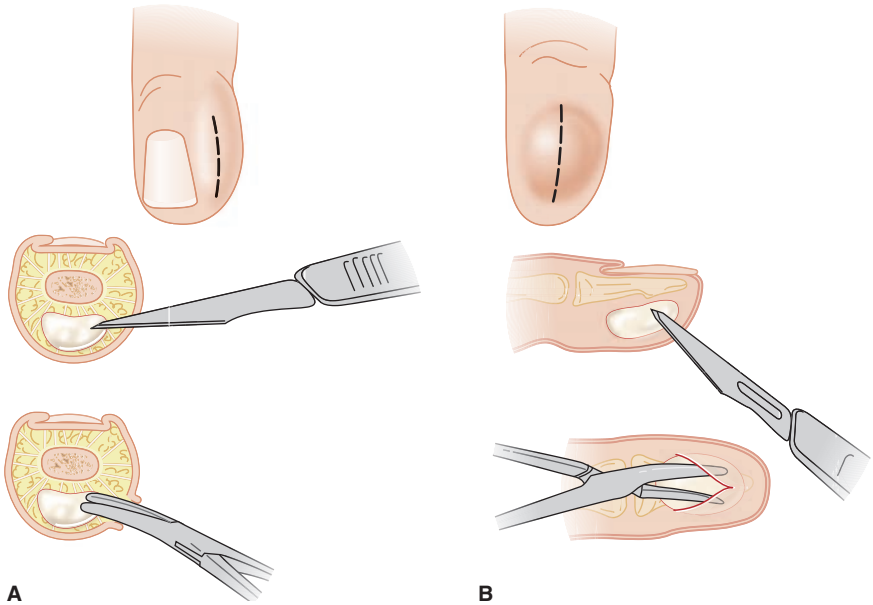


FIGURE 283-4. Felon. **A.** The unilateral longitudinal approach is the most frequently used method for draining felons. This approach minimizes interference with sensate areas of the finger pad. **B.** If the felon is pointing toward the volar surface of the finger pad, the longitudinal volar approach may be used.



FIGURE 283-5. Herpetic whitlow. Note the cluster of vesicles on an erythematous base located at the distal finger. Tzanck smear is positive. [Photo contributor: Lawrence B. Stack, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ (eds): *Atlas of Emergency Medicine,* 3rd ed. New York, NY: McGraw-Hill, Inc.; 2010.]

HERPETIC WHITLOW

Herpetic whitlow is a viral infection of the distal finger caused by the herpes simplex virus, usually from contact with oral herpetic infections. Herpetic whitlow in children tends to be associated with gingivostomatitis and herpes simplex virus type 1, whereas adults most commonly harbor herpes simplex virus type 2. Healthcare workers, often nurses and respiratory and dental technicians, are at increased risk of this infection given their exposure to orotracheal secretions.

The patient develops a burning, pruritic sensation similar to all herpes simplex infections. On examination, the lesion is erythematous and tender, with vesicular bullae (**Figure 283-5**). The infection occurs 2 to 14 days after contact, usually maturing in 14 days.[16] The finger may be indurated, but is not tense, as is seen in a felon. **Do not mistake herpetic whitlow for a felon because incision and drainage may result in a secondary bacterial infection and prolonged failure to heal.** If there is any question concerning the diagnosis of herpetic whitlow, a vesicle may be unroofed, and the drainage fluid may be used for a Tzanck smear or direct antibody testing to confirm the diagnosis.

Treatment consists of immobilization, elevation, and pain medication. Treat with antiviral agents such as acyclovir or valacyclovir for 1 week to abort recurrent infections and decrease the course of protracted cases[16] (Table 283-1). The finger should be kept in a clean dressing to prevent autoinoculation or spread of the herpes infection to other individuals.

NONINFECTIOUS INFLAMMATORY STATES OF THE HAND

Noninfectious inflammatory states of the hand often present as an acute exacerbation of symptoms related to recent overuse. Inflammatory states of joints and tendons are painful and difficult to distinguish from acute septic arthritis or suppurative tenosynovitis. If the diagnosis is in doubt, treat for infection, and consult a hand specialist.

If an inflammatory state is diagnosed, treat with rest, immobilization, elevation, and anti-inflammatory agents.

TENDINITIS AND TENOSYNOVITIS

Inflammatory tendinitis may involve the flexor or extensor tendons of the hand. Most often, the patient is able to recount a history of repetitive motion directly affecting the inflamed tendon. Palpation of the tendon produces tenderness. Active or passive movement of the tendon produces significant pain.

Treatment is splinting in the position of function with elevation of the affected area and prescribing NSAIDs, with referral for care from the primary care physician or a hand surgeon. Remind patients to return to the ED for worsening pain, increased swelling, or any signs of infection, including fever and erythema.

TRIGGER FINGER

Tenosynovitis can develop in the flexor sheaths of the fingers and thumb as a result of repetitive use. The ring finger and thumb are most frequently affected.[17] Scarring or inflammation may cause the tendon to become nodular, which results in friction and catching between the tendon and its sheath, usually in the vicinity of the A1 pulley at the volar crease at the base of each digit. The A1 pulley is the proximal portion of the tendon sheath. This is referred to as *stenosing tenosynovitis* or *trigger finger*. The patient experiences binding of the tendon, usually as the finger extends, relieved by a painful "snap" as the tendon nodule clears the first annular pulley. Occasionally, this condition may progress to the point that the finger locks, usually in flexion. Conservative treatment includes rest, anti-inflammatory medications, and immobilization (buddy tape or finger split) to reduce inflammation and swelling of the flexor tendon sheath. Early stages of trigger finger have been treated successfully with corticosteroid injection into the tendon sheath.[18,19] If conservative treatment and steroid injection fail, surgical release of the A1 pulley is often curative.[20]

DE QUERVAIN'S STENOSING TENOSYNOVITIS

De Quervain's tenosynovitis involves the extensor pollicis brevis and abductor pollicis tendons and occurs in patients who have experienced excessive use of the thumb or wrist. This condition is often associated with pregnancy, the postpartum period, and activities involving repeated radioulnar deviation such as hammering, cross-country skiing, or lifting a child.[21]

The patient presents with pain along the radial aspect of the wrist that may radiate to the thumb or extend into the forearm. The diagnosis of De Quervain's tenosynovitis is supported by a history of pain in this location along with a painful range of motion of the thumb and local tenderness over the distal portion of the radial styloid. Further confirmation of the diagnosis may be provided by a positive Finkelstein test (**Figure 283-6**), in which the patient grasps the thumb in the palm of the hand and the examiner ulnar deviates the thumb and hand. This stretches the tendons over the radial styloid and produces sharp pain along the involved tendons.

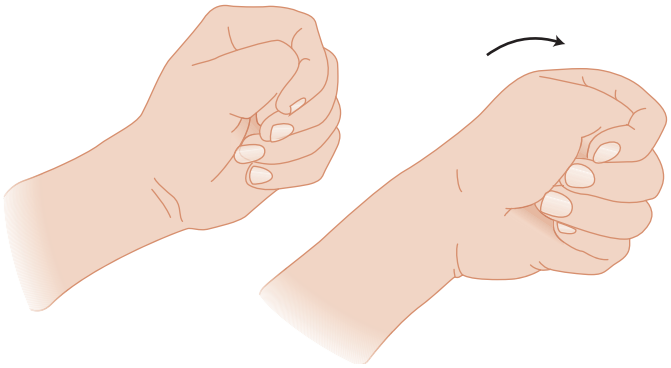


FIGURE 283-6. The Finkelstein test. The thumb is cupped in the closed fist, and ulnar deviation reproduces pain along the extensor pollicis and abductor pollicis.

Immobilize the thumb and wrist with a thumb spica splint or similar device. Instruct the patient to remove the splint briefly each day and perform range-of-motion exercises to prevent joint stiffness. In addition, start an anti-inflammatory medication for 10 to 14 days. Recurrence of this condition is common, particularly when related to occupational stress. Persistent cases may benefit from local corticosteroid injection or surgical decompression by a hand specialist.[22]

CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome is a peripheral mononeuropathy involving entrapment of the median nerve in the carpal canal or tunnel, which is covered by the tense transverse carpal ligament. Whenever a condition causes swelling in the carpal tunnel, the median nerve is compressed, causing paresthesias extending into the index and long fingers, the radial aspect of the ring finger, and along the palmar aspect of the thumb. Pain may also radiate proximally into the forearm or shoulder. The patient often complains of awakening at night with burning pain and tingling in the hand or numbness when driving a car or maintaining the wrist in prolonged flexion.

Carpal tunnel syndrome may develop from traumatic, hematologic, rheumatologic, anatomic, and infectious causes. A common scenario is overuse, in which the patient recounts a history of repeated flexion and extension of the wrist. In addition, edematous conditions such as pregnancy and congestive heart failure may acutely exacerbate symptoms in patients with a predisposition for carpal tunnel syndrome. The final common pathway consists of a space-occupying lesion that increases intracanal pressures. As the pressure increases, perfusion of the epineurium decreases, causing ischemia and nerve conduction block.

Pain or paresthesia in the median nerve distribution suggests carpal tunnel syndrome and may be confirmed by electrodiagnostic testing. The median nerve sensory distribution is illustrated in Chapter 36, "Local and Regional Anesthesia," Figures 36-5 and 36-6. Two-point discrimination in this distribution is described as one of the most useful physical examination maneuvers for diagnosing carpal tunnel syndrome.[23] In addition, Tinel's sign supports the diagnosis and involves tapping the volar aspect of the wrist over the median nerve. A positive sign produces paresthesias that extend into the index and long finger. Phalen's sign is more sensitive and specific and involves flexing the wrist maximally and holding it in this position for at least 1 minute.[23] A positive test occurs when the patient complains of tingling and numbness along the median nerve distribution. Both tests are subject to false-positive and false-negative results.

The presence of median nerve motor deficit requires emergency hand consultation. Otherwise, initial treatment is a volar splint to maintain the wrist in neutral position coupled with anti-inflammatory medications for 10 to 14 days. Refer those with persistent symptoms to a hand surgeon for surgical decompression. Most patients have complete resolution of their symptoms following surgical decompression, with around 5% requiring revision.[24]

DUPUYTREN'S CONTRACTURE

Dupuytren's contracture is a relatively common yet poorly understood disorder characterized by fibroplastic changes of the subcutaneous tissues of the palm and volar aspect of the fingers. The fourth and fifth fingers are affected earliest. The condition is found most commonly in men of northern European descent. Dupuytren's contracture is seen in those with tobacco use, alcoholism, diabetes mellitus, and repetitive handling or overuse.[25]

This progressive fibrosis eventually may lead to tethering and joint contracture (**Figure 283-7**). Firm longitudinal thickening and nodularity of the superficial tissues over the distal tendon sheath of the palm are usually readily appreciated as the scarring process advances. The diagnosis is made by identifying a nodule in the palm, usually at the distal palmar crease of the ring or small finger, which is held in the classic flexion contracture. Refer to a hand specialist for surgical excision options.[26,27]



FIGURE 283-7. Dupuytren's contracture. This chronic problem is seen at the most common site: the ring finger. [Photo contributor: Alan B. Storrow, MD. Reproduced with permission from Knoop KJ, Stack LB, Storrow AB, Thurman RJ (eds): *The Atlas of Emergency Medicine*, 3rd ed. New York, NY: McGraw-Hill, Inc.; 2010, Fig. 12-36.]



FIGURE 283-8. A dorsal ganglion cyst. [Reproduced with permission from Simon RR, Sherman SC (eds): *Simon's Emergency Orthopedics*, 7th ed. New York, NY: McGraw-Hill, Inc.; 2014.]

GANGLION CYSTS

A ganglion or synovial cyst is a cystic collection of synovial fluid within a joint or tendon sheath (**Figure 283-8**). It is common, often following an injury or repetitive microtrauma. Ganglion cysts arise from a herniation of synovial tissue from a joint capsule or tendon sheath. The patient presents with a tender cystic swelling over or near a tendon sheath. Common locations are the dorsal and volar wrist, flexor surface of the metacarpophalangeal joint, or the base of the nail. Involvement of the thumb may appear as generalized thumb pain, pain with movement, and edema. Treatment is pain control and anti-inflammatory medications. About one third of cysts resolve spontaneously, with referral to a hand surgeon for those with persistent or recurrent pain or cosmetic deformity. Treatment options include observation, cyst aspiration, or surgical excision. Surgical excision offers significantly lower chance of recurrence compared with aspiration.[28]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 284

Joints and Bursae

John H. Burton
Timothy J. Fortuna

INTRODUCTION

Many mechanisms provoke acute joint symptoms: degradation and degeneration of articular cartilage (osteoarthritis), deposition of immune complexes or immune system–related phenomena (rheumatoid arthritis, rheumatic fever, and possibly, a component of gonococcal arthritis), crystal-induced inflammation (gout and pseudogout), seronegative spondyloarthropathies (ankylosing spondylitis [see Chapter 282, "Systemic Rheumatic Diseases"] and reactive arthritis [postinfectious with HLA-B27 susceptibility]), and bacterial or viral invasion (gonococcal and nongonococcal septic arthritis, including Lyme arthritis). These processes impact joint capsules and surfaces, resulting in a cascade of reactive and inflammatory events. This chapter reviews the common causes and treatments of acute nontraumatic joint pain. Joint injuries are discussed in Section 22, "Orthopedics," and disorders due to repetitive use syndromes are discussed throughout Section 23, "Musculoskeletal Disorders," by anatomic site.

CLINICAL APPROACH TO ACUTE JOINT PAIN

Septic arthritis is the most important consideration in the evaluation of a swollen, warm, and painful joint. *Septic arthritis* is invasion of a joint by an infectious agent with organism proliferation and associated inflammation; bacterial arthritis is a subset of septic arthritis. Urgent treatment may prevent both joint destruction and mortality (6% to 11% with treatment).[1-3] Septic arthritis is a clinical diagnosis supported by diagnostic tests.[1,4] **No single diagnostic parameter is sufficiently sensitive to screen patients for septic arthritis including synovial WBC counts.**[5]

CLINICAL FEATURES AND RISK FACTORS

Risk factors (**Table 284-1**),[5,6] the number of joints involved (**Table 284-2**), and the migratory pattern, if one exists, aid in the differential diagnosis. Approximately 85% of patients with nongonococcal septic arthritis present with a single joint infected; *Staphylococcus aureus* and *Streptococcus pneumoniae* are more likely to infect two or more joints simultaneously.[7-10] Septic arthritis involving more than one joint can occur in rheumatoid arthritis (50%), immunocompromise, gout, diabetes, and/or renal disease; the morality rate is significantly higher in patients with polyarticular septic arthritis (11% vs. 30%).[7,9] Recent joint surgery and cellulitis overlying a prosthetic hip or knee are the only findings on history or physical examination that significantly alter (both increase) the probability of nongonococcal septic arthritis.[5] Joint disorders associated with migratory pattern include gonococcal arthritis, acute rheumatic fever, Lyme disease, and viral arthritis.

TABLE 284-1 Risk Factors for Nongonococcal and Gonococcal Septic Arthritis

Nongonococcal	Gonococcal
Injection drug use*	HIV infection*
Diabetes mellitus*	Injection drug use*
Rheumatoid arthritis*	Pregnancy
Prosthetic joint, knee,* or hip*	Menses
Immunosuppression, HIV*	Systemic lupus erythematosus
Age: >80 y old*	Complement deficiency
Skin ulceration and/or infection*	
Hemophilia	
Hypogammaglobulinemia	
Malignancy	
Hemodialysis	
Liver disease	
Alcoholism	
Steroid therapy	

Abbreviation: HIV = human immunodeficiency virus.

*Risk factors supported by epidemiologic study.

TABLE 284-2 Differential Diagnosis of Arthritis by Number of Affected Joints

Number of Joints	Differential Considerations for Typical Presentations
1 = Monoarthritis	85% of nongonococcal septic arthritis*
	Crystal-induced (gout, pseudogout)
	Gonococcal septic arthritis
	Trauma-induced arthritis
	Osteoarthritis (acute)
	Lyme disease
	Avascular necrosis
	Tumor
2–3 = Oligoarthritis†	15% of nongonococcal septic arthritis, more common with *Staphylococcus aureus* and *Streptococcus pneumoniae*
	Lyme disease
	Reactive arthritis (Reiter's syndrome)
	Gonococcal arthritis
	Rheumatic fever
>3 = Polyarthritis†	Rheumatoid arthritis
	Systemic lupus erythematosus
	Viral arthritis
	Osteoarthritis (chronic)
	Serum sickness
	Serum sickness–like reactions

*Involvement of more than one joint does not rule out septic arthritis.

†The distinction between oligoarthritis and polyarthritis varies in the literature with a cut point of either three or four joints.

SYNOVIAL FLUID ANALYSIS

When septic arthritis is suspected, aspirate joint fluid, and obtain analysis and culture of the aspirate to direct treatment.[1,4] **Table 284-3** provides diagnostic guidance based on synovial fluid results in the context of different patient characteristics.[1,3-14]

Analyze joint fluid for Gram stain, leukocyte count with differential, and a wet preparation for crystals.[6,8] Glucose, protein, and lactate dehydrogenase levels do not direct treatment decisions.[6] An elevated synovial lactate level or novel biomarker presepsin suggests septic arthritis.[5,15] Culture for gonococci and anaerobes, in addition to typical gram-positive and gram-negative organisms.[1,4,6]

SERUM LABORATORY STUDIES

Serum erythrocyte sedimentation rate and C-reactive protein levels are commonly elevated in several acute inflammatory and reactive arthritides (gonococcal and nongonococcal septic arthritis, crystal-induced, spondyloarthropathies, and rheumatoid and Lyme arthritis) but are not helpful for establishing a specific diagnosis in adults. However, erythrocyte sedimentation rate and C-reactive protein are recommended by the British Society of Rheumatology[4] and the American Academy of Orthopedic Surgeons as an aid to monitor response to therapy. These guidelines include erythrocyte sedimentation rate and C-reactive protein as part of their minor criteria for the diagnosis of acute periprosthetic joint infection (Table 284-3).[13] The American Academy of Orthopedic Surgeons also recommends that an elevation of either erythrocyte sedimentation rate or C-reactive protein be used as a criterion to aspirate a painful prosthetic joint with increased warmth.[13] The sensitivity of the serum WBC count in adults for the diagnosis of nongonococcal bacterial septic arthritis is approximately 60%.[5] Blood cultures should

TABLE 284-3 Septic Arthritis: Joint Aspiration Results in Different Patient Groups*

Key Factor	Patient Status	Joint Aspiration	Diagnostic Considerations/Management
Positive Gram stain	Acute joint pain and swelling	Gram stain positive for bacteria	Initiate empiric IV antibiotics, admit to the hospital, monitor culture and patient course (positive Gram stain is found in <50% of patients with septic arthritis).
Classic synovial WBC count	Acute joint pain and swelling	>50,000 WBC/mm^3 or >90% PMNs	Synovial fluid with >50,000 WBC/mm^3 is 56% sensitive and 90% specific for septic arthritis. Initiate empiric IV antibiotics and hospital admission.
Increased sensitivity of lower synovial WBC counts	Acute joint pain and swelling in a patient with risk factors for septic arthritis or systemic signs of infection	>25,000 WBC/mm^3 or >90% PMNs	Synovial fluid with >25,000 WBC/mm^3 is 73% sensitive and 77% specific for septic arthritis. Consider empiric IV antibiotics and admission to the hospital for monitoring of patient course and cultures.
Acute gout with coexisting septic arthritis	Acute joint pain and swelling; patient with acute gout or history of gout with systemic signs of infection	Crystals, >2000 WBC/mm^3, or >90% PMNs	Crystal-induced arthritis may coexist with septic arthritis in up to 27% of cases; cell counts are <6000 WBC/mm^3 in 10% of infected joints; more than one joint is involved in 10%–45%. Look for infected tophi. Consider empiric IV antibiotics and admission to the hospital pending cultures.
Prosthetic joint	Acute pain and swelling in patient with prosthetic joint	>10,000 WBC/mm^3, >90% PMNs	Consult operating orthopedic surgeon before aspiration if possible. AAOS definition for acute periprosthetic infection is 3 of the following: (1) CRP elevated above 100 milligrams/L *and* ESR elevated above local norm, (2) synovial WBC >10,000/mm^3, (3) synovial PMNs >90%, (4) positive culture, and (5) positive histologic analysis of periprosthetic tissue.
Immunocompromise	Joint swelling in an immunocompromised patient or systemic signs of infection in a patient with immunocompromise	>200 WBC/mm^3, >25% PMNs	Immunocompromised patients sustain septic arthritis with diminished immune response; cell counts and percent PMNs are frequently lower than in immunocompetent patients with similar infections. Consider empiric IV antibiotics and admission to the hospital for monitoring of patient course and cultures.
Gonococcal arthritis	Monoarticular or polyarticular joint pain in a patient with history of unprotected sex (primarily in young patients)	10,000–80,000 WBC/mm^3	Positive culture in <50% of infected joints; collect urogenital cultures plus pharynx and rectum cultures as determined by history. Consider empiric IV antibiotics and admission to the hospital for monitoring of patient course and cultures.
Rheumatoid arthritis with coexisting septic arthritis	Joint pain and/or swelling in a patient with rheumatoid arthritis	2000–120,000 WBC/mm^3	Severe pain and limited range of motion may be absent in patients on immunosuppression. Look for infected rheumatoid nodules or ulcerated foot calluses; source in 76% of cases. Consider empiric IV antibiotics and admission to the hospital for monitoring of patient course and cultures.
Lyme disease	Acute joint pain in a patient living in a Lyme disease–endemic area or with a history of rash or tick bite	200–300,000 WBC/mm^3	Consider empiric antibiotics and close follow-up to monitor culture and patient course; admit if clinical picture is indistinguishable from septic arthritis. Arthralgia appears months after initial symptoms. Joint effusion (moderate to large) may be out of proportion to the patient's pain (mild to moderate). Knee is the most common affected joint.
Post trauma	Joint trauma several days prior, initial swelling, now increasing pain	0–2000 WBC/mm^3, <25% PMNs, 0–500 RBC/mm^3	Posttraumatic effusions may become infected in patients with skin infections or bacteremia. Aspiration of the joint reduces pain for approximately 1 week, but has no effect on long-term disability.
Dry tap	Patient with acute joint pain and suspected swelling, with or without other symptoms or signs to suggest septic arthritis	No fluid aspirated	Major causes of dry tap are mistaken physical diagnosis of effusion; blockage of the needle by plica, fat, or debris; or synovial fluid with high viscosity or true lipoma arborescens (benign replacement of subsynovial tissue by fat cells). Use US to determine true effusion and direct needle to largest collection of fluid.
Normal synovial cell counts	Patient with sufficient joint pain and swelling to warrant arthrocentesis, no comorbidities, absent signs and symptoms of sepsis	<200 WBC/mm^3, <25% PMNs	Normal WBC cell counts and differential percentages make the diagnosis of septic arthritis unlikely in a patient without comorbidities or objective signs of infection. A mechanism should be in place for timely follow-up of culture results if they turn positive.

Abbreviations: AAOS = American Academy of Orthopedic Surgeons; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PMNs = polymorphonuclear leukocytes; RBC = red blood cell.

*All patients who received joint aspiration for suspected septic arthritis should have cultures of synovial fluid, blood, and any nonjoint source clinically suspected of infection (e.g., skin, urine).

be obtained before antibiotic therapy for presumptive or possible septic arthritis. However, the sensitivity for identifying the causative organism in adults and children with nongonococcal bacterial septic arthritis is 23% to 36%.[5] Elevated procalcitonin levels provide 90% specificity to help rule in the diagnosis of septic arthritis but are only 67% sensitive in screening for the diagnosis.[5,16]

Laboratory studies can aid in the diagnosis at follow-up. Possible studies include Lyme titer, rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, HLA-B27 tissue typing, lupus anticoagulant, and repeat synovial fluid analysis.

IMAGING

Bedside US is a useful tool to identify joint effusion and aids successful joint aspiration.[17,18] Obtain radiographs of an inflamed joint if trauma, tumor, avascular necrosis, and osteomyelitis are diagnostic considerations. MRI is not recommended for directing assessment of septic arthritis but may be helpful for difficult diagnostic cases. MRI is more sensitive to identify joint effusion than specific for the diagnosis of septic arthritis.[19] Radioisotope scanning is not usually required for ED diagnosis but can be useful to detect osteomyelitis, occult fracture, avascular necrosis, or tumor.

ARTHROCENTESIS

Prepare the site to avoid bacterial contamination. The skin overlying the affected joint should be free of cellulitis or impetigo to avoid contamination of the joint space during arthrocentesis. Orthopedics should be consulted before aspiration of a prosthetic joint for direction in diagnostic workup and interpretation of results.[13] Other relative contraindications to joint aspiration are coagulopathy in high-risk patients such as suspected hemarthrosis in hemophiliac patients before

factor replacement.[20] Routine preprocedure laboratory screening for coagulopathy prior to arthrocentesis is not necessary. Anticoagulation should not be viewed as an absolute contraindication to arthrocentesis. Arthrocentesis is typically a safe procedure in the anticoagulated patient, including those on direct oral anticoagulants.[21]

Cleanse a large area overlying and adjacent to the affected joint with povidone-iodine solution. After air drying, clean the skin with an alcohol wipe to remove the povidone-iodine solution from the skin surface. Removal of the overlying povidone-iodine prevents the introduction of the povidone-iodine antiseptic into the joint, which can result in chemical irritation or sterilization of the aspiration sample. Next place sterile drapes over the site and maintain sterile technique throughout the procedure.

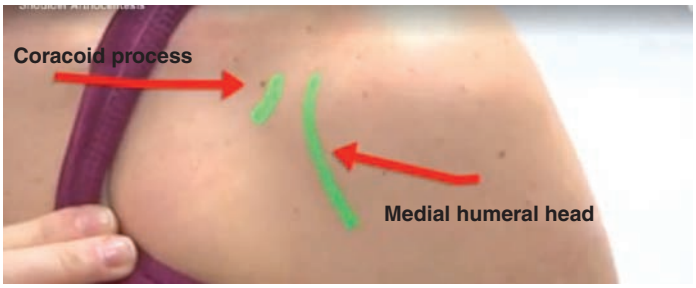
Anesthetize the skin and soft tissues overlying the joint with a 25- to 30-gauge needle. Avoid intra-articular injection of anesthetic because the anesthetic can inhibit bacterial growth and may result in a spuriously negative culture in an early septic joint.

Use a large-bore needle (18 or 19 gauge) for aspiration of fluid from large joints. Use smaller-bore needles for small joints (no smaller than 22 gauge). Choose a syringe large enough to accommodate the anticipated volume of fluid within the joint space. Remove as much synovial fluid as possible to obtain a good diagnostic sample and to relieve pain from joint capsule distention. Promptly send aspirated fluid to the laboratory for culture, Gram stain, leukocyte count with differential, and crystal analysis. US should be used in the event of a dry tap to visualize the largest collection of fluid (see Table 284-3).

SHOULDER JOINT ASPIRATION

US can facilitate shoulder aspiration. The anterior or posterior approach can be used.

Anterior Approach Have the patient sit upright, facing you, and externally rotate the humerus. Insert the needle just lateral to the coracoid process, between the coracoid process and the humeral head (**Figure 284-1A**). Direct the needle posteriorly. If it is difficult to locate the coracoid process, the posterior approach to the glenohumeral joint may be easier.



A



B

FIGURE 284-1. Shoulder arthrocentesis. **A.** Anterior approach. **B.** Posterior approach. The skin overlying the lateral margin of the acromion is outlined in green.

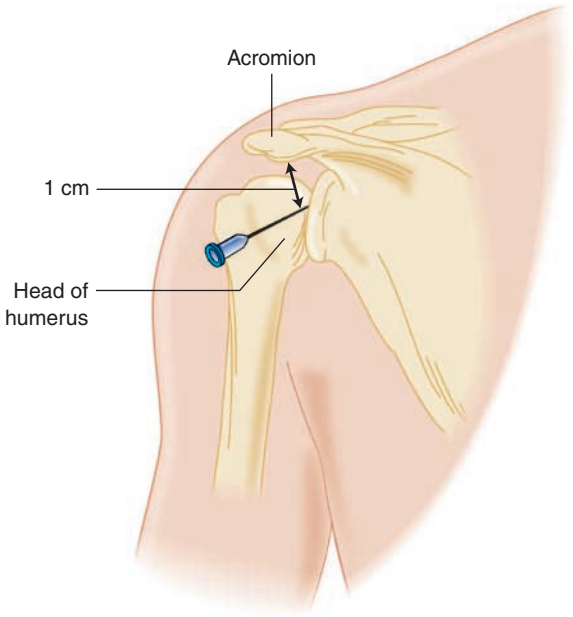


FIGURE 284-2. Shoulder arthrocentesis, posterior approach.

Posterior Approach Sit the patient upright with the back facing you. Palpate the spine of the scapula to its lateral limit: the acromion. Identify the posterolateral corner of the acromion. Use a 1.5-inch needle. The point for needle insertion is 1 cm inferior and 1 cm medial to the posterolateral corner of the acromion (**Figures 284-1B** and **284-2**). Direct the needle anterior and medial toward the presumed position of the coracoid process. The glenohumeral joint is located at a depth of approximately 1.0 to 1.5 inches. (See Video: Shoulder Arthrocentesis.)

ELBOW JOINT ASPIRATION

Use a lateral or posterior approach to the elbow joint. Do not use a medial approach to avoid neurovascular structures. Place the elbow in 90-degree flexion, resting on a table, with the hand prone to widen the joint space. Locate the radial head, lateral epicondyle of the distal humerus, and the lateral aspect of the olecranon tip. These three landmarks form the anconeus triangle. The center of this triangle is the site for needle entry into the skin. Using the tip of the gloved index finger of the nondominant hand, palpate a sulcus just proximal to the radial head. The sulcus is the needle entry point. Direct the needle medial and perpendicular to the radius toward the distal end of the antecubital fossa (**Figure 284-3**). (See Video: Elbow Arthrocentesis.)



FIGURE 284-3. Arthrocentesis of the elbow.

WRIST JOINT ASPIRATION

Landmarks for wrist arthrocentesis are palpable with the wrist in a neutral position. The landmarks are the radial tubercle of the distal radius, the anatomic snuffbox, the extensor pollicis longus tendon, and the common extensor tendon of the index finger (**Figure 284-4**). Insert the needle perpendicular to the skin, ulnar to the radial tubercle and the anatomic snuffbox, between the extensor pollicis longus (just ulnar to the extensor pollicis longus) and the common extensor tendons. (See Video: Wrist Arthrocentesis.)

HIP JOINT ASPIRATION

Hip arthrocentesis may be performed by an anterior or medial approach. If local practice dictates open surgical assessment and drainage, an orthopedic consultant will often perform this procedure. US-guided arthrocentesis by an emergency physician or radiologist is also acceptable if local practices and training are in place to support this approach (**Figure 284-5**). Controversy exists regarding the utility of US or MRI as a screening test before open surgical evaluation.[18,22] Immediate consultation with an orthopedic surgeon is therefore desirable when a diagnosis of septic hip arthritis is considered.

KNEE JOINT ASPIRATION

The knee joint can be entered either medial or lateral to the patella. With the patient supine, fully extend the knee and make sure the quadriceps muscle is relaxed. Identify the midpoint of the patella. The insertion point of the needle is located approximately 1 cm inferior to the patellar edge, either lateral (**Figure 284-6**) or medial (**Figure 284-7**) to the middle of the patella. Direct the needle posterior to the patella and horizontally toward the joint space. Compression or "milking" applied to both sides (proximal and distal) of the joint space by an assistant who is using sterile technique may facilitate aspiration of small amounts of fluid. In patients with obese or large knees, it may be necessary to use

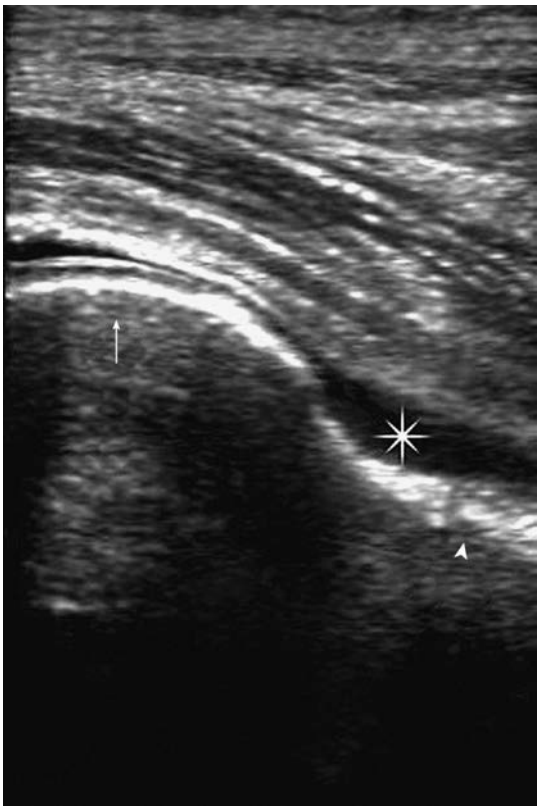


FIGURE 284-5. US image of a hip effusion. The hypoechoic effusion (*asterisk*) is located in the anterior synovial recess between the echogenic cortices of the femoral neck (*arrowhead*) and the femoral head (*arrow*). [Reproduced with permission from Reichman EF (ed): *Emergency Medicine Procedures*, 3rd ed. Figure 97-18. Copyright © 2019, McGraw-Hill Education, Inc. All rights reserved.]

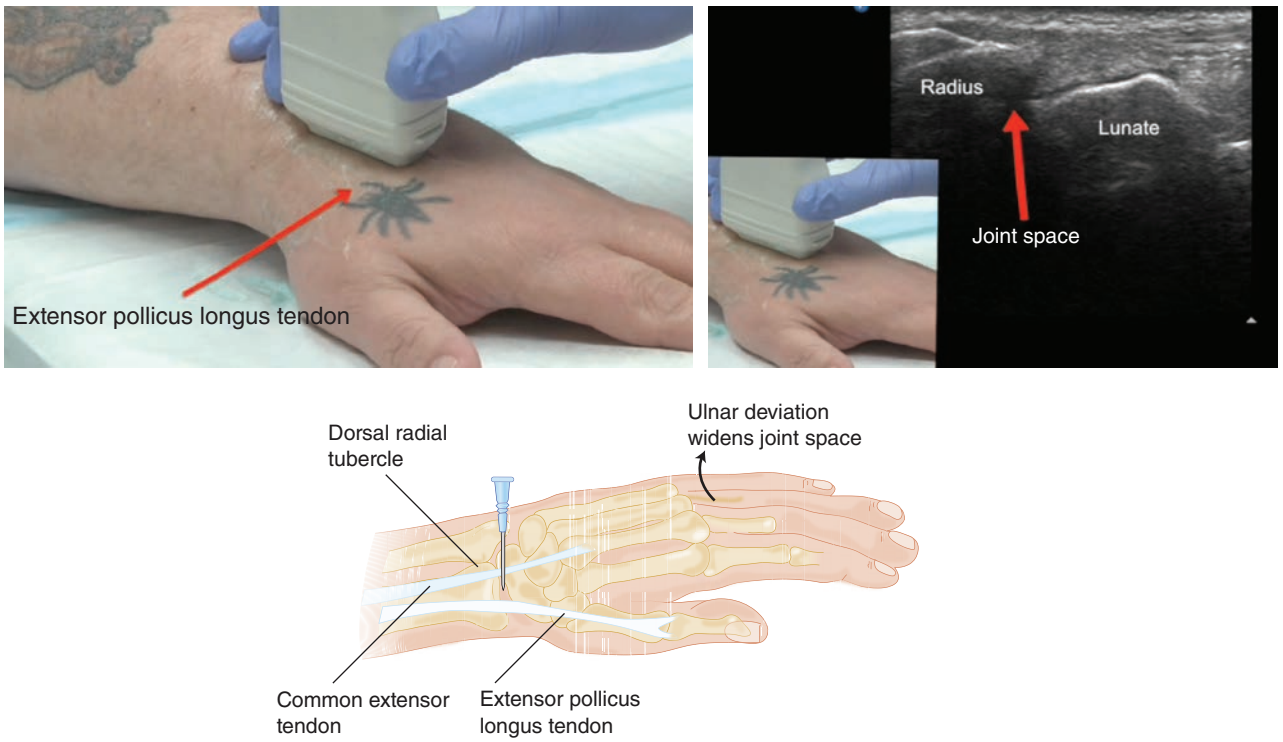
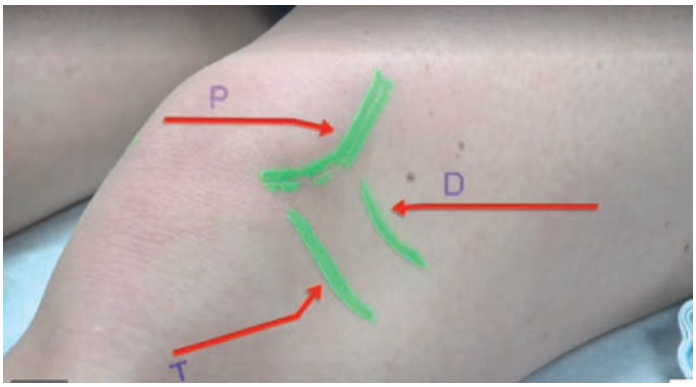


FIGURE 284-4. Arthrocentesis of the wrist. [Images used with permission of Sandra Werner.]



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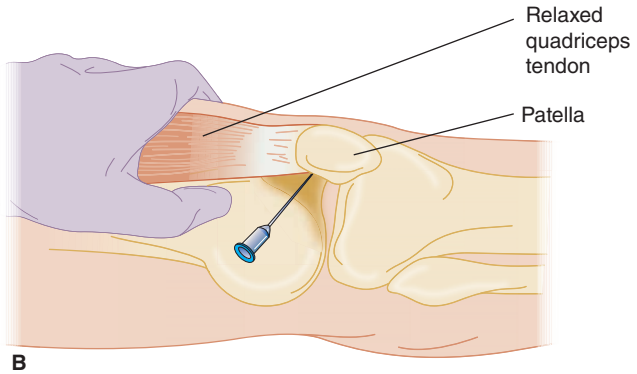


B

FIGURE 284-6. **A.** Landmarks for knee arthrocentesis. D = distal femur; P = patella; T = tibia. **B.** Arthrocentesis of the knee, lateral approach.

a needle longer than 1.5 inches to enter the joint space. **Figure 284-8** demonstrates the use of US to visualize a knee joint effusion. (See Video: Knee Arthrocentesis.)

ANKLE JOINT ASPIRATION

Ankle arthrocentesis may be performed at either the tibiotalar joint (medial approach) (**Figure 284-9**) or the subtalar joint (lateral approach) (**Figure 284-10**). The medial approach is generally preferred. (See Video: Ankle Arthrocentesis.)

Medial (Tibiotalar) Approach Have the patient supine with the foot initially perpendicular to the leg. This position facilitates the location of a sulcus lateral to the medial malleolus and medial to the

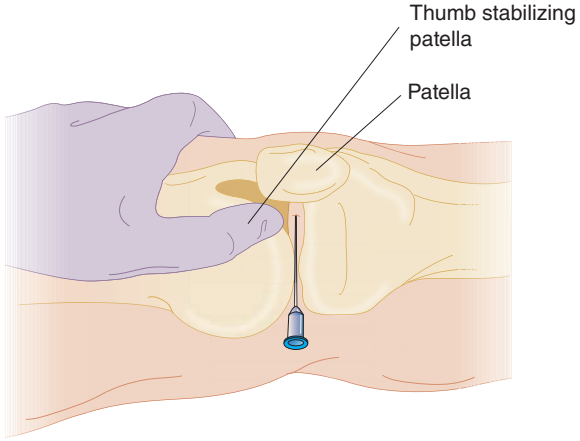
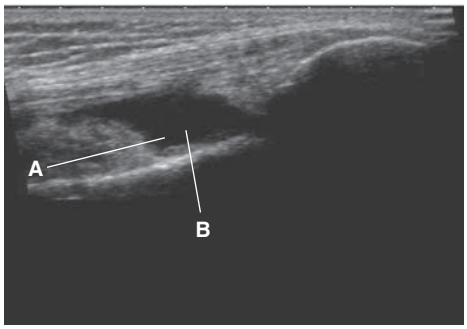
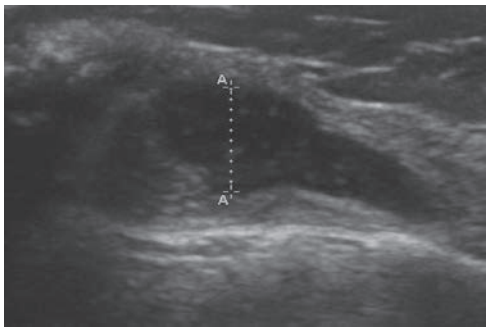


FIGURE 284-7. Arthrocentesis of the knee, medial approach.



A



B

FIGURE 284-8. Bedside US of the knee in long axis (**A**) and short axis (**B**) demonstrating joint effusion.

tibialis anterior and extensor hallucis longus tendons (Figure 284-9 and **Figure 284-11A and B**). Then plantar flex the foot with the needle entering the skin overlying the sulcus. Angle the needle slightly cephalad as it passes between the medial malleolus and the tibialis anterior tendon.

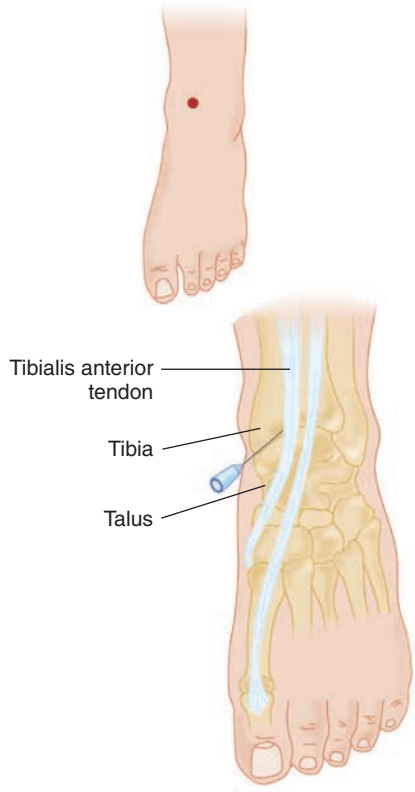


FIGURE 284-9. Arthrocentesis of the ankle, medial approach.

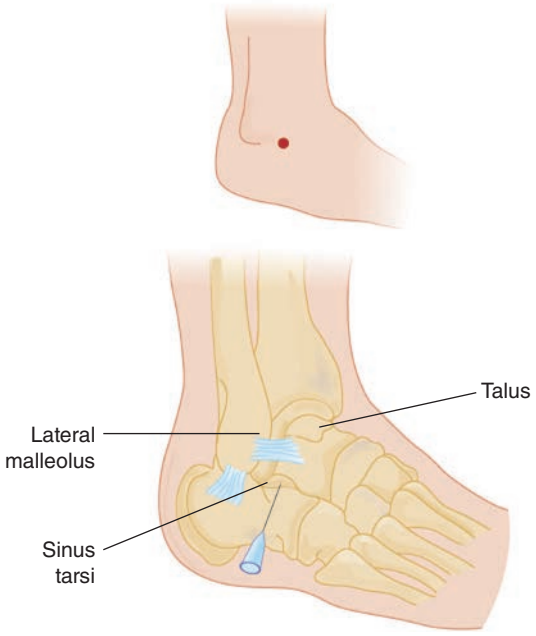


FIGURE 284-10. Arthrocentesis of the ankle, lateral approach.

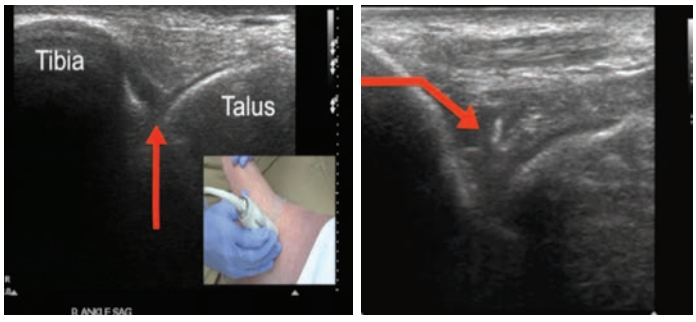
Lateral (Subtalar) Approach Keep the patient's foot perpendicular to the leg. Enter the subtalar joint just below the tip of the lateral malleolus (Figure 284-10). Direct the needle medially toward the joint space.

SEPTIC ARTHRITIS

An acutely hot, swollen, and tender joint (or joints) with restriction of movement is bacterial nongonococcal septic arthritis until proven otherwise.[1] Clinical features, risk factors, and treatment differ for bacterial, nongonococcal septic arthritis, and gonococcal arthritis (Tables 284-1 through 284-3). For management of septic arthritis in infants and children, see Chapter 141, "Pediatric Orthopedic Emergencies." In young adults, sexual activity increases the prevalence of gonococcal arthritis and reactive arthritis (formerly known as Reiter's syndrome) associated with chlamydial urethritis.

BACTERIAL NONGONOCOCCAL SEPTIC ARTHRITIS

Clinical Features and Diagnosis Although no clinical pattern is diagnostic of bacterial nongonococcal septic arthritis, certain general observations are helpful. Joint pain (85%), a history of joint swelling (78%), and fever (57%) are the only findings that occur in >50% of patients with bacterial nongonococcal septic arthritis.[6]



A B

FIGURE 284-11. **A.** US-guided approach to medial ankle arthrocentesis. *Arrow* points to the ankle effusion. **B.** *Arrow* points to needle in the tibiotalar joint, medial approach with transducer in the sagittal plane. [Images used with permission of Sandra Werner.]

The involved joint can become exquisitely painful over a few hours. The patient may splint the affected joint to relieve pain with movement. Joint effusion may be small or large. Resistance to passive and active movement and limitation of full joint movement are notable findings but are common with gout without infection and may be absent in immunosuppressed patients. Although joint aspiration and analysis are essential to the diagnosis, the sensitivity of any one finding for the diagnosis of nongonococcal septic arthritis is only moderate. For example, the sensitivity of joint fluid WBC to make the diagnosis of nongonococcal septic arthritis using the commonly quoted cutoff of 50,000 cells/mm^3 is only 56%.[5] The sensitivity of erythrocyte sedimentation rate for nongonococcal septic arthritis using a cutoff of 30 mm/h ranges between 76% and 96%,[5] but this test is nonspecific.

Treatment **If a septic arthritis diagnosis cannot be reliably excluded after clinical evaluation, including arthrocentesis, admit the patient** for parenteral antibiotics and pain control until synovial fluid culture results are available. Antibiotic coverage is directed at staphylococcal and streptococcal species including methicillin-resistant *S. aureus*. Vancomycin plus a broad-spectrum cephalosporin or carbapenem is the preferred therapy (**Table 284-4**).[1,23] Patients found to have septic arthritis caused by methicillin-resistant *S. aureus* are often significantly older; have more comorbidities, including end-stage renal disease; have increased erythrocyte sedimentation rates and C-reactive protein levels; and have nosocomial infections. Methicillin-sensitive *S. aureus* septic arthritis patients are more likely to be IV drug users.[24]

Consult orthopedic surgery for possible joint irrigation in the operating room and further management if the joint aspiration is positive for infection. Consultation with infectious disease may be required to determine ideal antibiotic choice in select patients.[4]

GONOCOCCAL SEPTIC ARTHRITIS

Clinical Features and Diagnosis Gonococcal arthritis is the most common cause of septic arthritis in young sexually active adults.[25,26] Joint infection will typically have a prodromal phase in which migratory arthritis and tenosynovitis predominate before pain and swelling settle on one or more septic joints. Vesiculopustular lesions, especially on the fingers, may be found (see Figure 153-3A in Chapter 153, "Sexually Transmitted Infections").

TABLE 284-4 Commonly Encountered Organisms in Septic Arthritis in Adolescents and Adults

Patient/Condition	Expected Organisms	Antibiotic Considerations
Young healthy adults, or patients with risk factors for *Neisseria gonorrhoeae*	*Staphylococcus, N. gonorrhoeae, Streptococcus*, gram-negative bacteria	Vancomycin, 15 milligrams/kg IV load, if Gram stain reveals gram-positive organisms in clusters. Ceftriaxone, 1 gram IV, or imipenem, 500 milligrams IV, should be used/added if either gram-negative organisms are present or no organisms are present on Gram stain and *N. gonorrhoeae* is suspected (also culture urethra, cervix, or anal canal as indicated).
Adults with comorbid disease (rheumatoid arthritis, human immunodeficiency virus, cancer) or injection drug users	*Staphylococcus*, gram-negative bacilli	Vancomycin, 15 milligrams/kg IV load, plus cefepime, 2 grams IV, or imipenem, 500 milligrams IV. Meropenem, 1 gram IV, may be used as an alternative agent.
Sickle cell patients	*Salmonella* (increasingly *Staphylococcus*)	Vancomycin, 15 milligrams/kg IV load, plus ciprofloxacin, 400 milligrams IV. Imipenem, 500 milligrams IV, may be used as an alternative agent.

Synovial fluid cultures are often negative in gonococcal arthritis, with only 25% to 50% of cases yielding positive identification of the organism.[6] Cultures of the posterior pharynx, urethra, cervix, and rectum (as directed by history of sexual contact) before antibiotic treatment increase the culture yield.[25,27] Cases of gonococcal arthritis suspected clinically should be treated despite negative initial results while waiting for all culture results to return.

Treatment Treatment for gonococcal arthritis follows the same general principles as treatment for nongonococcal septic arthritis (see Table 284-4 for details). However, gonococcal arthritis does not yield joint destruction with the frequency of nongonococcal arthritis, and therefore, surgical intervention is rarely needed.[27,28] Daily joint aspiration is routinely done until there is clinical improvement.[25,27,28] *Neisseria gonorrhoeae*, in the setting of arthritis, remains sensitive to third-generation cephalosporin ceftriaxone, 1 gram IV every 24 hours,[25,27,28] (see Chapter 153, "Sexually Transmitted Infections").

CRYSTAL-INDUCED SYNOVITIS (GOUT AND PSEUDOGOUT)

Crystal-induced synovitis is primarily an illness of middle-aged and elderly adults. Uric acid (monosodium urate monohydrate crystals, gout) and calcium pyrophosphate (calcium pyrophosphate deposition, or pseudogout) are the two most common crystalline agents, with gout representing the most common form of inflammatory joint disease in men >40 years old.[29,30] The classic description of gout is monoarthritis involving the great toe or knee joint in a man >40 years old.[29,31] Gout is less common in women during their reproductive years, but may occur in association with periods of increased insulin resistance such as gestational diabetes.[32]

CLINICAL FEATURES

Joint pain develops over hours. Gout results from precipitation of uric acid crystals in the joint, and pseudogout results from calcium pyrophosphate crystals. Crystalline involvement of joints has a predilection for the foot and knee. Although the first metatarsophalangeal joint is a classic focus for acute gout, no joint is the exclusive site of involvement for either gout or pseudogout. (See Video: Joint Arthrocentesis.)

DIAGNOSIS

The diagnosis of a crystal-induced synovitis is by joint aspiration and identification of crystals through a polarizing microscope. Uric acid crystals (gout) appear needle shaped and blue when the source of light is perpendicular to the crystal (negative birefringence). Calcium pyrophosphate (pseudogout) is yellow in this alignment (positive birefringence), with a rhomboid shape. Crystals are located within phagocytes from aspirates of synovial fluid, or within inflamed tissues adjacent to the affected joint.

Radiography and CT are not useful in the routine diagnosis of gout but can be used to rule out other reasons for an erythematous, painful, swollen, and tender joint. Imaging can be useful to identify fractures, osteomyelitis, gaseous gangrene, or retained foreign bodies. Typical US findings in gout are the double-contour sign, tophi, and the snowstorm sign.[33] US in the hands of an experienced user can be more sensitive than radiography in identifying bony erosions.[34]

Serum uric acid levels are not generally useful for diagnosis, as up to 30% of patients will have normal uric acid levels during an acute gout attack.[29,31] There is no elevation of serum uric acid, calcium, or phosphate in pseudogout. The joint aspirate WBC count can be elevated with gout and pseudogout.[29-31,35] However, the presence of crystals, the absence of bacteria on Gram stain or culture, and frequently, the dramatic response to NSAIDs clarify the diagnosis. When the diagnosis of a septic joint cannot be excluded, hospital admission until cultures and/or clinical response clarify the diagnosis is the safest course of action.[1,4,31,35]

TREATMENT

When the diagnosis of gout or pseudogout is established, treatment is an NSAID for 5 to 7 days. First-line treatment is indomethacin (or naproxen).[29,30] **Do not give NSAIDs to patients with renal insufficiency.** For patients with normal renal function, the initial dose of indomethacin is 50 milligrams up to three times a day or naproxen 250 to 500 milligram twice daily. Therapy is continued for 3 to 7 days as needed. Substantial pain relief typically occurs within 2 hours of NSAID administration.[29,30] **Colchicine** is an alternative agent to treat acute gout and pseudogout in patients with normal renal and hepatic function.[31,35] Oral colchicine for an acute gout attack is typically administered at a dose of 1.2 milligrams, followed by another dose of 0.6 milligram in 1 hour. After 12 hours, 0.6 milligram can be given once or twice daily until symptoms resolve.[33] IV administration of colchicine can be associated with serious side effects, such as bone marrow suppression, neuropathy, myopathy, and death.[29] For patients with renal insufficiency, narcotic analgesics may be needed for pain relief because NSAIDs and colchicine are generally avoided. **Prednisone** is a first-line treatment option but must be used with caution in patients with diabetes, congestive heart failure, or hypertension.[33] The use of prednisone compared to indomethacin has similar clinical effectiveness.[36] A proton pump inhibitor may be added to NSAID therapy if there is concern for gastritis.[35]

Discharge is typical unless pain is not controlled or if septic arthritis is a consideration. Once acute symptoms have resolved, long-term control may be achieved with reduction or elimination of gout-inducing agents (diuretics, aspirin, or cyclosporine) and treatment with urate-lowering therapy, such as allopurinol or probenecid. There is no effective prophylaxis for pseudogout.

VIRAL ARTHRITIS

The most common causes of viral arthritis in the United States are parvovirus B19, rubella, and hepatitis B. **Table 284-5** lists these viruses along with incidence, clinical findings, typical duration, and other significant features.

TABLE 284-5 Common Causes of Viral Arthritis

Virus	Prevalence of Arthritis	Findings	Duration	Additional Features
Parvovirus B19	Children 10% Adults 50%–70%	Polyarticular Symmetric	2–8 wk or chronic	Causes erythema infectiosum in children, rarely causes aplastic crisis
Rubella	Adults 50%	Polyarticular	5–7 d	Relapse
Epstein-Barr virus	1%–5%	Poly- or monoarticular	1–12 wk	Autoantibodies
Hepatitis B	10%–25%	Migratory	1–3 wk	Vasculitis
Hepatitis C	10%	Polyarticular	Chronic	Vasculitis
HIV	10%–50%	Mono- or oligoarticular	Chronic	Viral load >10,000 copies of HIV RNA, CD4 count <350 cells
Alphaviruses*	>50%	Oligoarticular	1–4 wk	More common in Asia, Africa; fever, myalgias

Abbreviation: HIV = human immunodeficiency virus.

*Alphaviruses include Sindbis virus, Mayaro virus, Ross River virus, Semliki Forest virus, O'nyong-nyong virus, chikungunya virus, and Barmah Forest virus.

LYME DISEASE

The arthritic manifestations of Lyme disease occur weeks, months, or years after primary, stage I infection. Symptoms include monoarticular or oligoarticular asymmetric joint involvement. Large joints are most often affected, particularly the knee.[37] A migratory pattern of oligoarthritis may be noted in addition to brief attacks of bursitis and tendonitis.

The diagnosis of Lyme arthritis is initially suspected in patients residing in, or with a recent visit to, an endemic area. A history of tick bite or erythema chronicum migrans rash (see Figure 251-19, erythema migrans, in Chapter 251, "Skin Disorders: Trunk") is helpful but often absent. Arthrocentesis yields an inflammatory synovial fluid, usually with negative cultures. Given the difficulty of making a definitive diagnosis in many patients, treatment of suspected Lyme arthritis is often initiated on the grounds of high clinical suspicion. Treatment is administered for 4 weeks, with a number of antibiotics recognized as effective, including doxycycline, 100 milligrams PO twice daily; amoxicillin, 500 milligrams three times daily; or cefuroxime, 500 milligrams twice daily.[23,37] For detailed discussion of the diagnosis and treatment of Lyme disease, including the involvement of other body sites, see Chapter 161, "Zoonotic Infections."

HEMARTHROSIS

TRAUMATIC HEMARTHROSIS

Traumatic hemarthrosis has a high association with ligamentous injury or an intra-articular fracture. Effusions following trauma may range from small minor effusions to large painful fluid collections that impede range of motion. Aspiration of very large traumatic effusions will provide temporary pain relief and increase range of motion, but has no effect on long-term outcome.[14] Treatment of traumatic hemarthrosis consists of immobilization, ice, and elevation of the affected joint. In the absence of a fracture or significantly unstable joint requiring immediate orthopedic evaluation, follow-up is needed for possible ligamentous and articular injuries.

SPONTANEOUS HEMARTHROSIS

Spontaneous hemarthrosis usually indicates underlying systemic illness and should prompt consideration for primary or secondary coagulopathies. Hemophiliacs should receive specific clotting factor replacement for hemarthrosis (see Chapter 235, "Hemophilias and von Willebrand's Disease"). Joint aspiration for acute hemarthrosis in hemophilia is controversial but recommended by some for a large hemarthrosis that can be aspirated during the first 12 hours of symptoms. **Joint aspiration should only be performed after factor replacement.**[20] Follow-up and/or consultation should be provided with hematology and orthopedics.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is typically a progressive disease, with polyarticular involvement of symmetric joints and sparing of the distal interphalangeal joints. Women are affected more commonly than men. Patients describe stiffness of the joints occurring after prolonged periods of inactivity (morning stiffness). A "boggy," slightly edematous synovium may be palpated. Arthrocentesis of synovial fluid is typically noted for an inflammatory profile. For further discussion of systemic clinical features of rheumatoid arthritis, see Chapter 282, "Systemic Rheumatic Diseases."

Salicylates or other NSAIDs are the cornerstone of treatment for an acute exacerbation. Corticosteroids may be used for brief periods, with long-term therapy using agents such as methotrexate, leflunomide, sulfasalazine, and other nonbiologic and biologic disease-modifying antirheumatic drugs.[38] Consider septic arthritis in patients with an acute episode of arthritis who are also receiving immunosuppressive agents.

OSTEOARTHRITIS

Osteoarthritis is distinguished from rheumatoid arthritis by a lack of constitutional symptoms and/or multisystem involvement. Destruction of joints in osteoarthritis may involve the distal interphalangeal joints, with less dramatic symmetric, polyarticular exacerbations. Although osteoarthritis is a chronic, polyarticular disease, patients may present with an acute monoarthritis exacerbation, typically of the knee. Effusions are small and difficult to aspirate. If fluid is aspirated, it is noninflammatory.

Radiographs demonstrate characteristic joint space narrowing due to destruction of articular cartilage. Treatment is joint rest and NSAIDs or acetaminophen in the setting of GI complications.[39] Systemic corticosteroids are not indicated. Ongoing long-term management may include intra-articular corticosteroid injections by a primary care physician or orthopedist.

REACTIVE ARTHRITIS

Reactive arthritis (formerly known as *Reiter's syndrome*) is a seronegative spondyloarthropathy characterized by an acute, asymmetric oligoarthritis occurring 2 to 6 weeks after an infectious illness.[40-42] **The classic triad of Reiter's syndrome is arthritis, urethritis, and conjunctivitis. A history of all three components is not necessary for diagnosis.** *Chlamydia* or *Ureaplasma* are common inciting infectious agents (postvenereal reactive arthritis). Enteric infections may precipitate a reactive arthritis (postdysentery reactive arthritis). Implicated agents of postdysentery reactive arthritis are *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter*, and possible agents include *Escherichia coli* and *Clostridium difficile*.[40,41] Conjunctivitis occurs in one third of postvenereal and >50% of postdysentery forms of reactive arthritis.[41]

Joint involvement in reactive arthritis typically involves the lower extremities, including the feet. Back and buttock pain may occur. A diffuse swelling of an entire digit (sausage digit) may be found as well but is not specific to reactive arthritis.[41,42] Synovial fluid aspirates demonstrate an inflammatory profile. Treatment has traditionally been supportive, with emphasis on pain control with NSAID therapy.[40,41] Antibiotics were previously thought to be of no benefit, but now long-term combination antibiotic therapy is being used for *Chlamydia*-induced reactive arthritis, using rifampin 300 milligrams daily combined with either doxycycline 100 milligrams twice daily or azithromycin 500 milligrams daily.[40,42] Arthroscopic synovectomy may also provide benefit.[43] Suspected cases should be referred to rheumatology for confirmation of diagnosis and management.

BURSITIS

NONSEPTIC BURSITIS

Bursitis is an inflammatory process involving one of the >150 bursae in the body, but most commonly the bursa overlying the elbow or the knee (see also Chapter 281, "Hip and Knee Pain").[44] Bursitis can be caused by repetitive trauma or can be associated with gout, pseudogout, or rheumatoid arthritis. Repetitive activities that can precipitate bursitis are identified by the typical names given: "carpet layer's or housemaid's knee" (prepatellar bursitis) or "student's elbow" (olecranon bursitis). The affected bursa is easily palpated but is not tender and not erythematous. Bursal enlargement is usually chronic or progressive but not acute. If bursitis is acute, consider septic bursitis (see following section, "Septic Bursitis"). In nonseptic bursitis, there is no limitation of, or pain upon, joint movement. The skin over the bursa may be thickened and calloused, indicating chronic repetitive trauma or pressure. Treatment is NSAIDs and elimination of activities that produce symptoms. Aspiration and drainage of bursal fluid are

TABLE 284-6 Characteristics of Bursal Fluid in Patients With Septic and Nonseptic Olecranon and Prepatellar Bursitis

	Septic	Traumatic and Idiopathic	Crystal Induced
Appearance	Purulent or serosanguineous	Straw colored, serosanguineous, or bloody	Straw colored to bloody
Leukocytes/mm^3	Range, 350–392,000; mean, 54,3300 ± 34,197; >3000 is considered diagnostic	Range, 0–11,700; mean, 2475 ± 1988	Range, 1000–6000; mean, 2900
Differential count	>50% polymorphonuclear cells is considered diagnostic	Predominantly mononuclear	Highly variable
Ratio of bursal fluid to serum glucose	<50% in 90% of cases (diagnostic)	>50%, 70%–80% in 98% of cases	Unknown
Gram stain	Positive in 70% (diagnostic)	Negative	Negative
Crystals present	No*	No	Yes
Culture results	Positive (diagnostic)	Negative	Negative

*The presence of crystals does not rule out infection.

controversial (if infection is not suspected), because bursal fluid often reaccumulates after aspiration.

SEPTIC BURSITIS

Unlike septic arthritis, septic bursitis is more likely secondary to bacterial spread from a skin lesion or local cellulitis to an injured or inflamed bursa. Therefore, cultures more closely reflect skin flora.[44] Septic bursitis is characterized by acute pain, tenderness, erythema of the affected bursa, and overlying warmth when compared with the unaffected side.[44,45] The most common sites for septic bursitis are the prepatellar bursa (50% to 53%) and the olecranon bursa (40% to 45%).[45-47]

Fever occurs in <50% of patients with septic bursitis.[45] Pain can occasionally be mild (10%) but is usually moderate or severe.[46] Associated cellulitis of the surrounding skin may be evident.

Most authors recommend the aspiration of bursal fluid if septic bursitis is considered.[44,46] Bursal aspiration can be diagnostic and therapeutic. Bursal fluid demonstrates characteristic findings in infection (**Table 284-6**).[44] Culture is the definitive test for presence or absence of infection. Diagnosis is presumed by one of the following criteria based on bursal fluid results: positive Gram stain, >3000 WBC/mm^3, >50% polymorphonuclear cells, glucose <31 milligrams/dL, or bursal to serum glucose ratio of <50%.[44]

S. aureus accounts for the majority of infections, but *Staphylococcus epidermidis* and *Streptococcus* species are also encountered.[44-46] Septic bursitis generally responds well to oral antibiotics, with emphasis on coverage of *Staphylococcus* and *Streptococcus* species. With the increasing prevalence of methicillin-resistant *S. aureus,* adjust antibiotic choice according to local sensitivities. Conditions that require hospital admission for incision and debridement and IV antibiotics include sepsis, extensive purulent bursitis, extensive surrounding cellulitis, suspected joint involvement, immunocompromise, or failure to respond to a course of oral antibiotics.[44] See specific treatment recommendations later in this chapter.

OLECRANON BURSITIS

The olecranon bursa overlies the olecranon process on the extensor surface of the elbow. The bursa is tense and edematous. Pain elicited with range of motion at the elbow is minor until the motion tightens and compresses the distended overlying bursa. Gouty tophi on the extensor surface of the elbow may be palpable or visible if the cause of bursitis is crystal-induced bursitis. If bursal fluid is aspirated, uric acid crystals are evident on microscopy.

To aspirate the olecranon bursa, prepare the bursal skin and use antiseptic technique. The patient's arm can be extended to allow for maximal bursal distention. Use a lateral approach to the affected bursa. Remove as much fluid as possible, and send the aspirate to the laboratory for analysis for WBC, Gram stain, crystals, glucose, and culture.

Treatment depends on patient condition; if sepsis is generalized, the patient should be treated with vancomycin, 15 milligrams/kg, plus piperacillin/tazobactam, 4.5 grams IV, or meropenem, 500 to 1000 milligrams IV. Most patients have localized infection only and can be treated as outpatients with a 14-day course of oral antibiotics.[44-46] Common antibiotics chosen include clindamycin, 300 milligrams three times per day for 10 days, or dicloxacillin, 500 milligrams four times per day.[46] Trimethoprim-sulfamethoxazole is an alternative.[45] Steroids are not indicated in the ED because infection cannot be definitively excluded by negative culture results. Admission is indicated for clinical toxicity, extensive surrounding cellulitis, failure of outpatient treatment, or immunocompromise.[46] Some patients benefit from surgical excision of the bursa sac.[47,48]

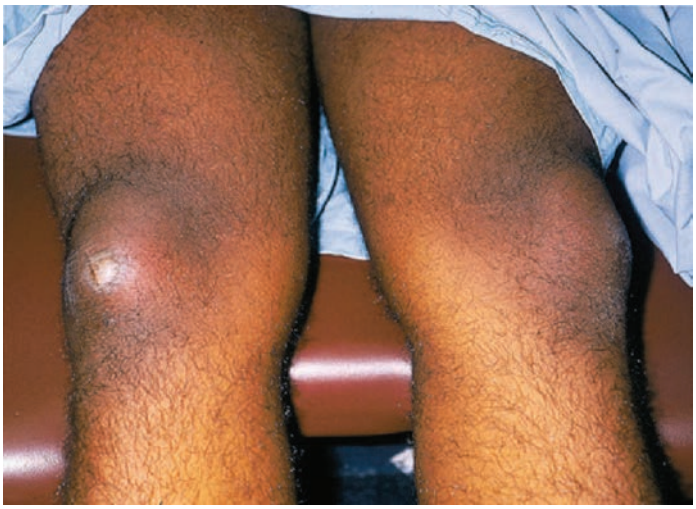


FIGURE 284-12. Septic prepatellar bursitis. This patient presented with obvious purulence of his right prepatellar bursal sac. Aspiration confirmed septic bursitis. [Courtesy of Alan B. Storrow, MD. Reproduced with permission from Knoop K, Stack L, Storrow A, Thurman RJ: *Atlas of Emergency Medicine*, 3rd ed. © 2010, McGraw-Hill, Inc., New York.]

PREPATELLAR BURSITIS

Bursitis may affect any of the four bursae surrounding the extensor aspect of the knee (see Figure 281-8). A history of overuse or repetitive trauma to the prepatellar area is typical.[44] The noninfected or aseptic bursa is enlarged and taut but nontender and not warm. There is full range of motion of the knee. If septic patellar bursitis is a consideration (**Figure 284-12**), aspirate the prepatellar bursa to obtain fluid for analysis. Prepare the skin overlying the bursa and use aseptic technique. Use either a lateral or medial approach. Fluid analysis and treatment are the same as for septic olecranon bursitis (see earlier section, "Olecranon Bursitis").

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 285

Soft Tissue Problems of the Foot

Mitchell C. Sokolosky

INTRODUCTION

This chapter discusses the common foot disorders that are likely to present to the ED. Patients with chronic or complicated foot problems generally should be referred to a dermatologist, orthopedist, general surgeon, or podiatrist, depending on the disease and local resources. Melanoma, tinea pedis, diabetic foot ulcers, onychomycosis, corns, and warts are discussed in Chapter 253, "Skin Disorders: Extremities." Diabetic ulcers are discussed in Chapter 224, "Type 2 Diabetes Mellitus." Puncture wounds of the foot are discussed in Chapter 46, "Puncture Wounds and Bites." Lower extremity osteomyelitis is discussed in Chapter 281, "Hip and Knee Pain."

INGROWN TOENAIL

Normal nail function requires maintenance of a small space between the nail and the lateral nail folds. Ingrown toenails occur when irritation of the tissue surrounding the nail causes overgrowth, obliterating the space.[1-3] Causes include improper nail trimming, using sharp tools to clean the nail gutters, tight footwear, rotated digits, and bony deformities.[1,3] Curvature of the nail plate is another predisposing factor.[3] Symptoms are characterized by inflammation, swelling, or infection of the medial or lateral aspect of the toenail. The great toe is the most commonly affected. In patients with underlying diabetes or arterial insufficiency, cellulitis, ulceration, and necrosis may lead to gangrene if treatment is delayed.

TREATMENT OF INGROWN TOENAILS

If infection or significant granulation is absent at the time of presentation, acceptable treatment is daily elevation of the nail with placement of a wisp of cotton or dental floss between the nail plate and the skin.[4] Daily foot soaks and avoidance of pressure on the nail help.[4] Another option, if no infection is present, is to remove a small spicule of the nail (**Figure 285-1**).[3] (See Video: Ingrown Toenail Removal.)

A digital nerve block is placed (see Chapter 36, "Local and Regional Anesthesia"). Cleanse the area and prepare the skin for an antiseptic procedure. Trim an oblique portion of the affected nail about one to two thirds of the way back to the posterior nail fold. The nail groove should then be debrided and a nonadherent dressing placed.[1,2]

If granulation or infection is present, a larger partial removal of the nail plate is indicated (**Figure 285-2**). Preprocedure antibiotics are not needed unless the patient is systemically ill.[5] First, perform a digital nerve block and prepare the area for antiseptic technique. Longitudinally, cut the entire affected area base to tip, cutting about one fourth of the nail plate, including the portion of the nail beneath the cuticle.

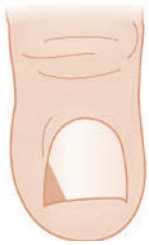


FIGURE 285-1. Partial toenail removal. This method is used for small nail fold swellings without infection. After antiseptic skin preparation and digital nerve block, an oblique portion of the affected nail is trimmed about one to two thirds of the way back to the posterior nail fold. Use scissors to cut the nail; use forceps to grasp and remove the nail fragment.

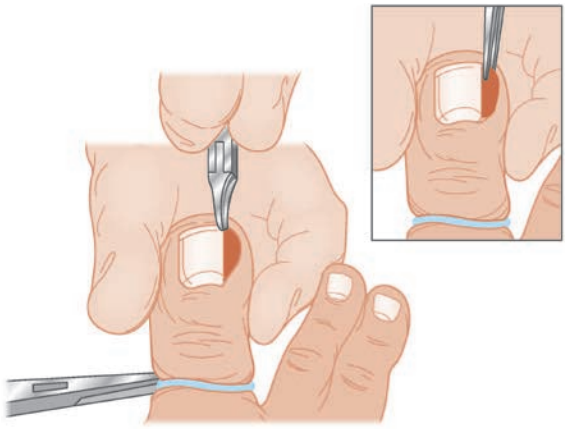


FIGURE 285-2. Partial toenail removal (infection present). This method is used for onychocryptosis in the setting of significant granulation tissue or infection. See "Treatment of Ingrown Toenails" for a description of the procedure.

Cutting the nail is made easier by first sliding mosquito forceps or small scissors between the nail and nail bed on the affected side, freeing the nail from the bed below. Rotate the forceps, turning up the portion of the nail on the affected side. A nail splitter is the optimal instrument for cutting the nail; however, sturdy scissors are a reasonable alternative. Then grasp the affected cut portion of the nail with a hemostat and, using a rocking motion, remove it from the nail groove. Then debride the nail groove.[1] Once the procedure is completed, place a nonadherent gauze or antibiotic ointment on the wound and a bulky dressing over that, covering the toe. Check the toe in 24 to 48 hours.[1,3] Although not mandatory, phenol is often used for chemical matricectomy to reduce growth of granulation tissue. If used, massage the involved nail matrix vigorously with a cotton-tipped swab dipped in an aqueous solution of phenol 88%, with a rotation directed toward the lateral nail fold, for 1 minute. Irrigate the nail matrix using isopropyl alcohol to neutralize completely the phenol solution.[3] Do not expose normal skin or tissues to the phenol solution. Postprocedure antibiotics are not needed unless cellulitis is proximal to the toe.[2]

For recurrent ingrown toenails, refer to a podiatrist for permanent nail ablation, which may require a combination of surgical excision plus chemical matricectomy (phenol ablation).[3]

OTHER NAIL LESIONS

Other common toenail afflictions include paronychia (see Chapter 283, "Nontraumatic Disorders of the Hand") and subungual hematoma (see Chapter 43, "Arm, Forearm, and Hand Lacerations"), which are treated similarly to when they occur in the fingers. Hyperkeratotic toenails can be a problem in the elderly. These may become so severe as to affect gait and cause ulcerations and infections. Refer such patients to podiatry for repeated trimming or nail plate removal.

BURSITIS INVOLVING FEET

Calcaneal bursitis causes posterior heel pain that is similar to Achilles tendinopathy; however, the pain and local tenderness are located at the posterior heel at the Achilles tendon insertion point.[6-8] In contrast, Achilles tendinopathy causes symptoms 2 to 6 cm superior to the posterior calcaneus. Pathologic bursae can be divided into noninflammatory, inflammatory, suppurative, and calcified. Noninflammatory bursae are usually pressure induced and are found over bony prominences. Inflammatory bursitis is commonly due to gout or rheumatoid arthritis. Suppurative bursitis is due to bacterial invasion of the bursae (primarily staphylococcal species), usually from adjacent wounds. Acute bursitis can lead to the formation of a hygroma or calcified bursae. Diagnosis can be aided by the use of US and MRI[6,8] but is not indicated for evaluation in the ED. Treatment of the bursitis depends on its cause. For nonseptic bursitis, symptoms usually resolve with simple measures

including heel lifts, comfortable footwear, rest, ice, and NSAIDs.[9] Management of septic bursitis is discussed in Chapter 284, "Joints and Bursae." Diagnosis of these lesions is dependent on analysis of bursal fluid, which can be obtained by large-bore needle aspiration.[6]

PLANTAR FASCIITIS

Plantar fasciitis, inflammation of the plantar aponeurosis, is the most common cause of heel pain.[10-12] Peak age incidence is usually between 40 and 60 years old, but it has a younger peak in runners.[13,14] Plantar fasciitis is common among ballet dancers and those performing aerobics. The plantar fascia anchors the plantar skin to the bone and provides support to the foot during gait. The cause is usually overuse. Other causes of heel pain include abnormal joint mechanics, tightness of the Achilles tendon, shoes with poor cushioning, abnormal foot position and anatomy, and obesity.[6,10] In the younger patient, autoimmune and rheumatic diseases can be considered.

The symptom of plantar fasciitis is pain on the plantar surface of the foot that is worse when initiating walking. Examination usually reveals a point of deep tenderness at the anterior medial aspect of the calcaneus, the point of attachment of the plantar fascia. Pain and tenderness tend to be increased upon dorsiflexion of the toes. Diagnosis is clinical. Radiographic studies are not indicated unless other causes are being considered. The presence of heel spurs is of no diagnostic value because many patients without plantar fasciitis have this finding on imaging. For resistant cases, US and MRI may aid in diagnosis but are not indicated for evaluation in the ED.[6]

Plantar fasciitis is generally a self-limited disease. Eighty percent of cases resolve spontaneously within 12 months. Initial treatment consists of rest, ice, NSAIDs, heel and arch support shoe inserts, taping or strapping of the foot, and dorsiflexion night splints (molded ankle-foot orthotics that hold the plantar fascia and Achilles tendon stretched).[10] Plantar-specific stretch exercises are the most beneficial treatment in the acute phase: with the ankle dorsiflexed, the patient uses one hand to dorsiflex the toes and, with the other hand, palpates the plantar surface of the foot, confirming tension.[15] Patients should be taught Achilles tendon stretching exercises and be told to avoid the use of flat shoes and barefoot walking.[10] In severe cases, a short-leg walking boot may be useful to unload and rest the plantar fascia. Corticosteroid injections provide short-term benefit, up to 1 month,[15] but are associated with plantar fascia rupture[10] and are best left to the orthopedist.[10,11] Refer patients to a podiatrist, orthopedist, or primary care physician for follow-up care.[10,11]

NERVE ENTRAPMENT SYNDROMES

TARSAL TUNNEL SYNDROME

Tarsal tunnel syndrome is an uncommon source of foot pain and numbness in runners due to compression of the posterior tibial nerve as it courses behind the medial malleolus.[16,17] The cause is usually from prior injury (scar tissue, bone or cartilage fragments, or bony spurs) and overpronation during running.[16,17] Overpronation (inward rotation) makes the nerve more vulnerable both to direct trauma from stretch and to indirect trauma from inflammation of the surrounding structures, resulting in compression.[16,17] Other causes include activities requiring restrictive footwear (ski boots, skates), edema from pregnancy, ganglion cysts, and tumors, but frequently, no inciting event is known.[18]

Symptoms include numbness or burning pain of the sole and may be limited to the heel, mimicking plantar fasciitis. Distal calf pain may be due to retrograde radiation (Valleix phenomenon). Weakness is uncommon. Pain is often worse with running, at night, and after standing, and often leads to the desire to remove the shoes. **Tinel sign** is positive with percussion inferior to the medial malleolus yielding pain radiating to the medial or lateral plantar surface of the foot.[16] Simultaneous dorsiflexion and eversion of the ankle exacerbates symptoms. Diagnosis is aided by nerve conduction studies or MRI,[16,17] but these are not routinely ordered from the ED.

The differential diagnosis includes plantar fasciitis and, if limited to the heel, Achilles tendinitis. Plantar fasciitis will cause point tenderness over the plantar heel, and pain is worse upon morning standing.

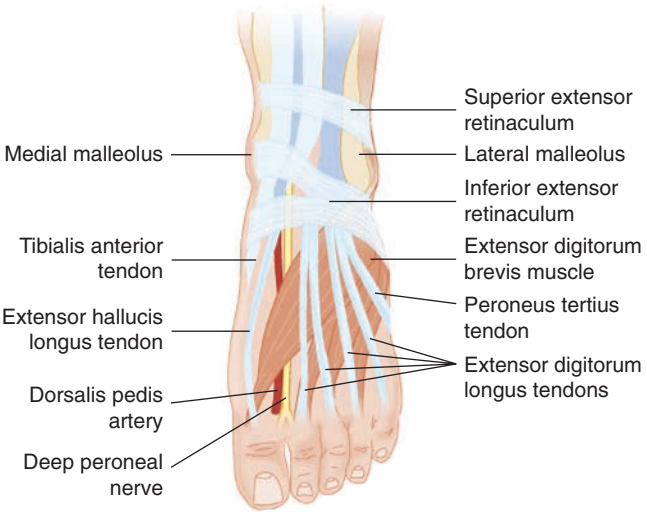


FIGURE 285-3. Tendons of the foot, anterior view, including deep peroneal nerve.

Tarsal tunnel syndrome causes greater medial heel and arch pain due to involvement of the abductor hallucis muscle. Tarsal tunnel pain worsens with ambulation throughout the day. In addition, tarsal tunnel syndrome may produce distal calf pain, whereas plantar fasciitis does not. Initial treatment includes avoidance of the exacerbating activities, NSAIDs, shoe modification, anti–neuropathic pain medications if NSAIDs are not helpful, and occasionally orthotics. If there is no improvement or symptoms recur after a few weeks, then orthopedic evaluation is recommended.[16,17]

DEEP PERONEAL NERVE ENTRAPMENT

Deep peroneal nerve entrapment occurs most commonly at the location where the nerve courses under the inferior extensor retinaculum[19] (**Figure 285-3**). Recurrent ankle sprains, soft tissue masses, trauma (both acute and repetitive),[20] chronic biomechanical misalignment, edema, and tight-fitting footwear (ski boots) are the most common causes. Symptoms are dorsal and medial foot pain and sensory hypoesthesia at the first toe web space. There may be loss of the ability to hyperextend the toes due to wasting of the extensor hallucis brevis and extensor digitorum brevis muscles. Pain and tenderness can be elicited on palpation of the peroneal nerve at the site of entrapment and by plantar flexion with inversion of the foot. Pain is exacerbated by activity and relieved by rest. Nighttime pain is common. Treatment is the same as for tarsal tunnel syndrome.[21]

GANGLIONS OF THE FOOT

A ganglion is a common benign synovial cyst. Ganglions are 1.5 to 2.5 cm in diameter and are often attached to a joint capsule or tendon sheath. Although ganglions typically occur in the wrist or hand, they may also occur in the foot. Ganglions typically arise in the anterolateral aspect of the ankle but can occur in many areas of the foot. The cause is unknown. Ganglions may appear suddenly or gradually, may enlarge and diminish in size, and may be painful or asymptomatic. On examination, a ganglion is a firm, cystic lesion. Diagnosis is usually made clinically, although outpatient US or MRI may exclude other causes when serious pathology is suspected. Phenol cauterization by an orthopedist may lead to the complete resolution of ganglions in some cases,[22] with surgical excision required for persistence.[23,24]

TENDON LESIONS OF THE FOOT

TENOSYNOVITIS AND TENDINITIS

Tenosynovitis and tendinitis may occur in the foot, usually due to overuse. Patients present with pain over the involved tendon (Figure 285-3).

The flexor hallucis longus, posterior tibialis, and Achilles tendon are most commonly involved.[25] Once infection has been clinically ruled out, treatment consists of rest, ice, and oral NSAIDs.[25]

Flexor hallucis longus tenosynovitis classically affects ballet dancers but can also be seen in runners and nonathletes. Presentation is similar to plantar fasciitis and tarsal tunnel syndrome. Posteromedial ankle pain, medial arch pain, and a positive Tinel sign (see earlier description in "Tarsal Tunnel Syndrome") are seen. Conservative management (rest, mobilization, orthotic shoe implant, NSAIDs) is usually successful. Surgery is reserved for refractory cases.

TENDON LACERATIONS

Tendon lacerations can result from penetrating injuries to the dorsal or plantar aspect of the foot. Tendon repairs in the foot are complex, and orthopedic consultation is needed for repair.[25]

The foot should be casted in dorsiflexion after the repair of extensor tendons and in equinus after repair of flexor tendons.

TENDON RUPTURES

Spontaneous rupture of the Achilles tendon is common. Rupture of the anterior tibialis and posterior tibialis tendons may also occur.[25] Age and chronic corticosteroid and fluoroquinolone use are risk factors for spontaneous rupture. Diagnosis is usually clinical but is aided by US or MRI studies in difficult cases.

Achilles tendon rupture occurs when a sudden shear stress, such as sudden pivoting on a foot or rapid acceleration, is applied to an already weakened or degenerative tendon. Many patients report immediate sharp pain, and some hear an audible "pop." The peak age for rupture is 30 to 40 years, and rupture is four to five times more common in men than women.[26] Over 80% of ruptures occur during recreational sports ("weekend warrior"). Patients often present with pain, a palpable defect in the area of the tendon, and inability to stand on tiptoes. A minority of patients with complete tendon ruptures are able to ambulate and may be misdiagnosed as having an ankle sprain. Squeezing the calf of the prone patient whose knee is flexed at 90 degrees will normally cause the foot to plantar flex (calf squeeze or Thompson test). The absence of plantar flexion indicates a positive test indicative of rupture. Initial ED treatment consists of ice, analgesics, immobilization of the ankle or foot in plantar flexion, crutches, and referral to an orthopedic surgeon for management and physical rehabilitation. Definitive treatment is generally surgical in younger patients and conservative (casting in equinus or plantar flexion) in older patients[25,27]; however, rehabilitation may be the most important determinant of outcome.[28] For further discussion, see Chapter 276, "Ankle Injuries," and Figure 276-8 (Thompson test) in Chapter 276.

Ruptures of the **anterior tibialis tendon** are rare. Ruptures usually occur after the fourth decade and are not excessively painful. Patients present with varying degrees of foot drop and a palpable defect distal to the ankle joint in the area of the tendon. In most cases, disability is minimal, and surgery is not necessary.[25]

Spontaneous ruptures of the **posterior tibialis tendon** also occur after the fourth decade. Two thirds of these cases occur in women. The presentation is usually chronic and insidious. Patients notice a gradual flattening of their arch, with modest discomfort and swelling over the medial ankle. Examination reveals absence of the tendon's normal prominence and weakness on inversion of the foot. Patients find it impossible to stand on tiptoes. Treatment may be conservative or surgical, depending on the duration of the tear and activity of the patient.[12]

Flexor hallucis longus rupture presents as a loss of plantar flexion of the great toe. The need for surgery will depend on the patient's occupation and lifestyle.[25]

Disruption of the **peroneal retinaculum** can occur as a result of direct trauma during dorsiflexion of the foot. Besides pain localized to the peroneal tendon behind the lateral malleolus, the patient complains of a clicking when walking as the tendon subluxes. Peroneal tendon injuries may lead to lateral ankle instability. Treatment is generally surgical repair.[25]

PLANTAR INTERDIGITAL NEUROMA (MORTON'S NEUROMA)

Neuromas may form in a plantar digital nerve, usually proximal to its bifurcation. Neuromas may occur in any of the digital nerves but are most common in the third interspace. The cause is thought to be local irritation of the nerve due to entrapment, usually from tight-fitting shoes. Women between the ages of 25 and 50 years old are the most commonly affected group. Patients present with pain located in the area of the metatarsal head. The pain is described as burning, cramping, or aching. Pain is worsened by ambulation and resolved by rest and removal of shoes. The pain may radiate to the affected toes, and patients may note numbness in the toes. Pain is usually easily reproduced upon palpation of the area, and at times, a mass is felt. Diagnosis is usually made clinically, but nerve conduction studies, electromyograms, US, and MRI may be helpful at times. Conservative treatment consists of wearing wide shoes with good metatarsal head supports and metatarsal head off-loading inserts.[29] Local glucocorticoid injections can sometimes be curative. Surgical removal may be necessary for refractory symptoms.[30]

COMPARTMENT SYNDROMES OF THE FOOT

The foot has up to nine compartments. Compartment syndrome occurs when an elevation of tissue pressure within one of these nonyielding fascial compartments impedes vascular flow. The cause of compartment syndrome is a high-energy injury (crush injury)[31] associated with multiple fractures. Compartment syndromes have been reported in association with foot and ankle fractures (especially calcaneal and Lisfranc's fracture/dislocation), burns, contusions, bleeding disorders, postischemic swelling after arterial injury or thrombosis, venous obstruction, snakebites, exercise, and prolonged pressure to the affected area (e.g., cast immobilization, prolonged abnormal positioning).[32] Pain out of proportion to injury is one of the early findings. Additional symptoms include pain that is worsened on active or passive movement, paresthesias, and neurovascular deficits. An absent pulse and complete anesthesia are late findings and may be difficult to assess due to underlying swelling. The only reliable objective method to diagnose compartment syndrome is by obtaining compartment pressures using an intracompartmental pressure monitoring system (Stryker STIC Device [Stryker, Kalamazoo, MI] or similar equipment). A difference between diastolic blood pressure and intracompartmental pressure of <30 mm Hg is an indication for fasciotomy.[33] Once the diagnosis is made, fasciotomy should be performed emergently. In the ED, elevate the extremity to the level of the heart pending fasciotomy. The sequelae of compartment syndrome range from transient neurologic compromise to complete myoneural necrosis, fibrosis, and ischemic contractures. The prognosis of compartment syndrome is directly related to the time delay in diagnosis and treatment (see Chapter 278, "Compartment Syndromes").[33]

Chronic exertional compartment syndrome is due to overuse.[34] Symptoms occur with exertion and are relieved by rest. Patients should be instructed to avoid overexertion and be referred for further investigation and treatment.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

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CHAPTER 286

Mental Health Disorders: ED Evaluation and Disposition

Veronica Tucci
Nidal Moukaddam

INTRODUCTION AND EPIDEMIOLOGY

This chapter is designed to provide the emergency provider with a general approach to the psychiatric emergency patient, identify potential pitfalls, and provide strategies for successfully managing this difficult patient population.

Psychiatric and behavioral emergencies have become a staple in every ED around the world. The busy emergency provider must successfully navigate encounters with patients who can exhibit a wide range of psychosocial pathology including substance use disorders, anxiety and agitation, depression and suicidal ideation, psychoses, neurocognitive disorders, and personality disorders, all of which can present with medical, psychiatric, or a combination of complaints.

Globally, according to the World Health Organization, one in four people suffer from mental illness or neurologic disorders, with depression as the number one cause of disability worldwide.[1] The National Institute of Mental Health in the United States estimates that 1 in 5 Americans suffers from a mental, behavioral, or emotional disorder and 1 in 25 suffer from a severe mental illness.[2] The Centers for Disease Control and Prevention announced a 24% increase in the rate of suicide in the United States from 1999 to 2014.[3]

Psychiatric patients have a higher incidence of medical conditions[4-6] and a greater risk of injury[7] than those without mental health or behavioral disorders. Fifty to 90% have at least one chronic medical condition and have a shortened life expectancy by anywhere from 8 to 30 years.[8] Sixty percent of this shortened life expectancy is estimated to be due to physical illness. Moreover, the National Alliance on Mental Health reports that 26% of homeless people in the United States who live in shelters have a serious mental illness, and 24% of state prisoners had a "recent history of a mental condition."[9] This is of particular concern in urban, busy EDs and has special relevance for high ED users, discussed below.

GOALS OF CLINICAL EVALUATION

Anywhere from 7% to 10% of patients admitted to psychiatric wards have an organic condition that should have been identified, with higher figures often cited for patients at the extremes of life.[10,11] Examples of missed life-threatening organic pathology include meningitis; sepsis; delirium; toxicologic processes including acetaminophen toxicity; neuroleptic malignant syndrome; metabolic abnormalities including hepatic encephalopathy, myxedema coma, or DKA; and traumatic conditions including epidural or subdural hematomas.[12,13] The distinction between functional and organic causes is crucial because organic issues may be reversible with prompt intervention and failure to identify such pathology can have devastating outcomes. The evaluative process for identifying primary or comorbid medical conditions is often referred to as *medical clearance*.

Little disagreement exists over the evaluation of patients with no known psychiatric history who present with altered mental status or new-onset psychosis. Such patients are presumed to have an underlying medical disorder or an "organic" cause until proven otherwise. Clinical evaluation is needed to identify any medical or surgical emergencies. Assuming a psychiatric condition for first-time episodes is ill advised because a psychiatric condition is a diagnosis of exclusion. Evaluation should include appropriate reassessment and observation periods which, realistically, may not be entirely completed in the ED.

Controversy, however, arises on how in depth the ED evaluation needs to be for a patient with a known psychiatric history (with or without chronic medical problems) and who is presenting with a psychiatric or behavioral complaint. Because of missed organic pathology in patients admitted to psychiatric wards over the past 50 years, emergency providers have been tasked with completing a medical evaluation of patients with psychiatric or behavioral complaints. This initial medical evaluation may be the only one that the patient will receive and, by design, is meant to ensure that potentially serious medical problems will not be left unaddressed and untreated. This thorough evaluation is more commonly referred to as *medical clearance*. As of this writing, there is still no interdisciplinary consensus on the necessary historical and physical examination elements, ancillary testing, and treatment that constitute an acceptable clearance process or medical stability examination. The lack of consensus is rooted in the fact that the term itself is ambiguous and means different things to different providers.[14-16] Regardless of the lack of interdisciplinary consensus, the medical clearance or medical stability assessment is critical in evaluation and treatment of patients with psychiatric and behavioral emergencies.

Two common situations are as follows: (1) Patients with chronic medical conditions can be viewed as stable as long as such conditions are not responsible for the patient's psychiatric or behavioral issues or are incidental complaints. (2) Patients can be viewed as stable for psychiatric evaluation as long as medical illness has been treated and the patient's condition has stabilized (e.g., diabetes, hypertension). For all patients, a thoroughly documented medical decision-making process, including specific ED treatment, further recommendations, and suggestions for follow-up, can facilitate placement in an inpatient facility.[17]

ED MEDICAL STABILITY OR CLEARANCE EVALUATION

The end goal of the medical clearance or stability examination is to distinguish between an organic or psychiatric condition. Comorbid medical diseases may be causing or exacerbating psychiatric symptoms in 34% to 50% of patients who present with psychiatric emergencies.[10,18,19] The journey of the patient with mental health complaint is summarized in **Figure 286-1.**

ED ARRIVAL AND TRIAGE

Paramedics or police typically provide advance notice to the ED regarding patients with serious mental health issues or severe agitation, so preparations can be made for the patient's arrival. For patients who threaten harm to others or who have altered mental status or severe agitation, hospital security and ED nursing and medical staff can be prepared to search the patient for weapons, secure an appropriate ED room, and provide verbal de-escalation, restraints, or medication as needed.

Place the patient in a room where there are no objects, liquids, or devices that can be used to harm the patient or others. Undress the patient and provide a hospital gown. If the patient has not already been screened for weapons, make sure it is done as soon as possible.

Many EDs have systems in place to flag patients at risk of eloping or those who cannot be released until assessment is complete. Terms such



FIGURE 286-1. Elements of ED evaluation.

as *protective custody* or *precautionary hold* are sometimes used. Different color gowns, special area assignments, and special flagging of the chart are some means for identifying high-risk patients that are widespread.

For other more stable patients, triage is accomplished in the usual manner as for medical patients, to identify high-risk versus lower-risk patients or situations. High-risk situations include suicidal or homicidal ideation, psychotic or violent behaviors, and risk for elopement. The Emergency Severity Index, the Canadian Triage Acuity Scale, the Manchester Triage System, the Australasian Triage Scale, and the South African Triage Scale are the most widely used ED triage systems worldwide.

HISTORY

Obtain a detailed description of recent symptoms from the patient. Explore the severity of symptoms including any changes in behavior identified by the patient himself or herself or an alternative storyteller, any provoking and palliative features, similar previous occurrences, and the timing and duration of symptoms.

Patients with psychiatric or behavioral issues may not be cooperative or may offer tangential responses. Patients may provide diagnostic terms for their disorder that are technically inaccurate. It is best to ask the patient to describe symptoms rather than ask about a diagnosis. Ask openly about substance use disorders.

Try to obtain collateral information from as many ancillary sources as possible. Additional sources can provide a baseline for the patient's symptoms and confirm the story, especially if the patient's mental capacity is impaired or not known or if the patient is uncooperative. Chart reviews can provide additional collateral. **Table 286-1** lists historical features more likely to be characteristic of an organic pathology for psychiatric complaints.

In one study, investigators found that 63% of patients with new psychiatric symptoms had significant medical pathology, 42% of which could be diagnosed from a proper history alone.[25] Identify current infections and consider delirium when faced with an acutely psychotic or agitated patient.[26] See Chapter 288, "Mental Health Disorders of the Elderly," and Chapter 287, "Acute Agitation," for further discussion of delirium, dementia, and agitation. Patients reporting any of the historical features noted in Table 286-1 should receive further focused testing.

REVIEW OF SYSTEMS

The review of systems can be accomplished in a more structured manner than the rest of the interview and sometimes can help redirect the patient. Unfortunately, many avoid asking detailed questions on the review of systems because of concerns that the patient will endorse everything asked. Specific targeted yes or no questions in this part of the encounter can help hone the differential diagnosis. Focus on elements of the review of systems most likely to point to organic problems (e.g., recent fevers, productive cough, rashes, headaches, trauma).

PHYSICAL EXAMINATION

The cornerstone of the medical stability assessment is the physical examination. Where the history and review of systems may prove troubling to decipher, the physical exam is more objective and can lead to an underlying medical disorder as the root or exacerbating cause of symptoms.

First, obtain a full set of vital signs and address any abnormalities. Obtain vital signs in the agitated or hostile patient as soon as feasible, and recheck before discharge. One study from 2008 noted a failure to document a complete set of vital signs in up to 50% of patients.[27]

Perform a head to toe examination. For psychiatric patients, like most medical patients in the ED, the patient's complaints and known medical

TABLE 286-1 Historical Features Suggestive of Medical Causes for the Psychiatric Presentation[20-24]

- No previous psychiatric history
- Recently hospitalized or with symptoms suggestive of possible infections
- Recent medication changes
- Sudden changes in behavior
- Visual hallucinations
- Extremes of life; age >40 y or <12 y
- New-onset seizure
- Recent memory loss
- History of substance abuse

TABLE 286-2 Physical Examination Features Suggestive of Organic Causes of Psychiatric Complaints

- Abnormal vital signs
- Fluctuating level of consciousness/alertness (e.g., clouded sensorium)
- Significantly decreased level of consciousness (Glasgow Coma Scale score <8)
- Focal neurologic findings (e.g., new-onset seizures, inability to walk unassisted)
- Ophthalmologic abnormalities (e.g., rotary nystagmus)
- Evidence of trauma (e.g., raccoon eyes, Battle's sign, septal hematoma, abrasions, lacerations)
- Abnormal dermatologic manifestations (e.g., rashes, purpura, jaundice, uremic frost, cool, mottled extremities)
- Abnormal mental examination or Quick Confusion Scale
- Presence of visual hallucinations

comorbidities dictate the order of the exam and the amount of attention given to each element. Patients with limited histories or who have self-inflicted injuries (especially adolescents) should receive a comprehensive physical examination in a manner akin to a standardized trauma assessment.[28,29] **Table 286-2** summarizes physical examination features that may help the emergency physician differentiate organic from primary psychiatric disease.

Many inpatient psychiatrists expect the ED physical examination to include a mental status examination.[13,30] Common mental status examinations include the Mini-Mental Status Examination, the Brief Mental Status Examination, and Quick Confusion Scale. These tools generally focus on seven major areas: affect, attention, language, orientation, memory, visual-spatial ability, and conceptualization.[13] In the case of uncooperative or violent patients, a significant portion of the examination can be done by observing from the doorway.[31]

LABORATORY AND ANCILLARY TESTING

Medical history, physical examination, review of systems, and tests for orientation have relatively high yield for detecting active medical problems, and routine laboratory testing is typically low yield. In general, testing is best left to the discretion of the emergency provider, with individualized assessments being the best guide to optimal evaluation.[32] Most inpatient psychiatric facilities will still require extensive ancillary testing as part of the clearance process or otherwise will list specific test abnormalities as part of their exclusionary criteria in determining the patient's suitability for admission. Most psychiatric facilities lack laboratories and imaging suites on their premises and do not have access to immediate turnarounds. Therefore, in the interest of patient safety, they often require substantial testing as either part of the medical clearance process or as specific exclusionary criteria.

REASSESSMENT AND ANTICIPATION OF DECOMPENSATION

Like the ECG or a FAST examination, the initial assessment is a snapshot in time. Reassess patients and document the reassessments for the following reasons: (1) patients can decompensate in the in-hospitable ED environment; (2) withdrawal or overdose symptoms may develop (indeed, one study asserted that one third of cases of severe intoxication were missed and that 12.5% of patients with withdrawal or delirium tremens and 12.5% of patients with a medication overdose had not been identified on initial assessment)[33]; (3) a coexisting medical disorder will require attention (e.g., a diabetic requiring insulin or a patient with hypertension requiring twice-daily dosing of home medications); and (4) a coexisting medical disorder may reveal itself.

SPECIAL CONSIDERATIONS

DEFICIENCIES IN THE INITIAL ASSESSMENT

Although most impending medical disasters can be uncovered with a thorough history, review of systems, and physical examination including attention to abnormal vital signs, studies over the past 40 years have demonstrated poor quality assessments performed on patients presenting with psychiatric symptoms in the ED (**Table 286-3**).

TABLE 286-3 Medical Clearance Assessment Deficiencies

- Obtaining an incomplete or inaccurate history
- Failing to seek out collateral sources (e.g., family, EMS, police)
- Failing to acknowledge and address abnormal vital signs
- Failing to recognize immediate life and limb threats (e.g., respiratory failure due to narcotic overdose)
- Performing a cursory or incomplete physical examination
- Failure to develop and refine a differential diagnosis for the patient's symptoms
- Anchoring on psychiatric diagnoses
- Failing to reassess the patient
- Applying a "kitchen sink" mentality in ordering laboratory and radiographic tests

One group of investigators found that over one third of medical clearance assessments lacked a history.[33] Another found that 8% of patients had no documented exam,[34] and even when present, many did not include critical components. For example, complete sets of vital signs were often not documented, and even when abnormal, they were not reassessed or noted. Mental examinations (depending on whether they are defined as mini-mental or orientation status) are frequently missing, with statistics as high as 56%. Neurologic examinations were similarly neglected, with one study noting absence of cranial nerve testing in 50%, motor exam testing in 72% of cases, sensory exam testing in 88% of cases, and gait testing in 75% of cases.[35]

INTERVIEWING TECHNIQUES

Table 286-4 summarizes interviewing basics. Time constraints are common in the ED, and the time to conduct a detailed interview is often lacking. The recommended approach to the patient with mental health complaints focuses on safety first, followed by establishing and maintaining a therapeutic rapport.

VIOLENT RESTRAINTS

In some cases, no matter how well trained the ED staff is in de-escalation techniques, physical restraints will need to be applied rapidly and safely to protect the patient from self-harm and/or the staff from harm. The term sometimes used is *violent restraints*.

Application of violent restraints is ideally accomplished by a team of five staff members with one team leader and one person for each limb. Shows of force with multiple team members poised to act can at times be sufficient in themselves to subdue the patient without actually applying the restraints. As with all elements of care, the patient and any family members present should be provided with clear, ongoing explanations of the procedure and reasons for it. Place the patient on a bed or stretcher, and secure all four limbs with leather restraints (soft restraints are more commonly used in nonviolent settings). Be careful to avoid injury to the patient and personnel assisting in the process. Elevate the patient's head,

TABLE 286-4 Interview Techniques in the ED

Safety

- Know where the exits are before you talk to the patient; stand close to exit
- Leave enough distance to avoid being physically hurt
- Wear a badge clip that cannot be used to choke you

Cooperation/rapport

- Always introduce yourself clearly
- Establish eye contact; smile if possible
- Reuse terms the patient uses to describe their condition before asking for clarification; this makes the patient feel heard
- Start with open-ended questions because they are best to establish therapeutic rapport
- Transition to close-ended questions if open-ended questions are not productive
- Last resort: Yes or no and multiple-choice questions

if possible, to minimize risk of aspiration. Once the patient is restrained, offer medications, and if refused, administer medications involuntarily.

Emergency providers must familiarize themselves with hospital policies and laws regarding the frequency of reassessment and the elements that they must document in their face-to-face assessment (e.g., vital signs; airway, breathing, and circulation; range of motion; skin integrity; turning the patient as needed; attending to toileting and any other hygiene needs). The first face-to-face assessment is generally completed in the first hour after application. Computerized or written orders can specify the time limit for the restraint and protocols for removal. Many hospitals require a new order to maintain physical restraints at regular intervals for violent patients with restraints. Once the patient is calm and cooperative, the nursing or security staff under the direction of the emergency provider may remove the restraints. It is usually best to remove the restraints in a stepwise fashion, one at a time, while carefully monitoring the patient to ensure continued compliance and cooperation.

ASSESSING THE DEGREE OF AGITATION

Some patients may require medications either before or after the application of restraints. Pharmacologic treatment of violent or agitated patients is discussed in detail in Chapter 287, "Acute Agitation." The Sedation Assessment Tool score is one method of grading behavior and assessing medication options.[12] Treatment options can be selected based on behavior (**Table 286-5**).

HIGH ED USERS

High users are a group of patients who present to the ED at much higher rates than expected for their conditions or severity of illness. Pejoratively dubbed *frequent flyers,* and often accused of malingering, these individuals are some of the most challenging to deal with in the ED. High users typically consist of a mix of individuals with chronic conditions, a background of trauma, broken families/poor social support, and severe psychosocial stressors (e.g., homelessness).[36-38] They tend to elicit strong, often negative feelings in providers (discussed below).

TABLE 286-5 Sedation Assessment Tool and Treatment Suggestions*

Sedation Assessment Tool Score	Description	Treatment
3+	Combative, violent, out of control with continual loud outbursts	Physical restraint Lorazepam 1–2 milligrams IM AND Haloperidol 5–10 milligrams IM OR Olanzapine (Zyprexa®) 5–10 milligrams IM OR Droperidol 2 milligrams IM
2+	Very anxious and agitated with loud outbursts	As above, or if will take PO, lorazepam 1–2 milligrams PO and haloperidol 5–10 milligrams PO OR Olanzapine orally disintegrating tablets (ODT) 5 milligrams
1+	Anxious and restless with normal to talkative speech	If will take PO, lorazepam 1–2 milligrams PO and haloperidol 5–10 milligrams PO OR Olanzapine ODT 5 milligrams or 5 milligrams IM
0	Awake and calm, cooperative with normal speech	Not applicable

*Data from Calver LA, Stokes B, Isbister GK: Sedation Assessment tool to score acute behavioral disturbance in the emergency department. *Emerg Med Australas* 23: 732, 2011. [PMID: 22151672]

Families and communities are unable to take care of mentally ill individuals[39] and ensure the necessary safety nets, and the ED becomes the go-to for crises and decompensations. "Bedless" psychiatry, embedded in outpatient and emergency care, has shown so many challenges that many have called for a return of long-term care,[40,41] and although psychiatric asylums are not the answers, they did fulfill a stabilizing function for a very difficult and fragile population.

The advent of deinstitutionalization for psychiatric patients in the 1960s resulted in a dearth of inpatient psychiatric beds and outpatient and community outreach services, more hospital admissions, shorter hospital stays, and significant gaps in care. Many patients who would have previously been housed in long-term state hospitals or facilities were left with nowhere to live and nowhere to go to receive the kind of care to which they had become accustomed. Indeed, from 1970 to 2006, inpatient psychiatric beds decreased from an estimated 400,000 beds to less than 50,000.[42,43] The authors of the report "No Room at the Inn: Trends and Consequences of Closing Public Psychiatric Hospitals, 2005-2010"[43] found that the number of state psychiatric beds continued to dwindle by another 14% from 2005 to 2010, effectively decimating the number of public psychiatric beds available to treat both chronic and acutely decompensated psychiatric patients.[44] In 2016, Becker Hospital Review reported that the number of needed inpatient psychiatric beds in the United States is, at minimum, 123,300, and the number of beds actually available is 37,679.[45] With less than 30% of the needed inpatient beds available, demand for care for mental illness continues to reach new heights and is simply outstripping supply. Substance use disorders/addiction, depression, anxiety, and psychoses in the general population have exploded, with more ED visits for disadvantaged populations.[46]

Consequently, the ED is the last beacon of hope and is a safety net for the community's most vulnerable, with an estimated one in eight ED visits now involving mental and substance abuse disorders, according to the U.S. Agency for Healthcare Research and Quality.[47,48]

There is no denying that high users sometimes derive emotional benefit from the ED visits,[49-51] and there are (sadly not infrequent) anecdotal reports of patients who call their previous inpatient units on a regular basis to update on their progress. However, some strategies can help deal more effectively with this group.

Factors to consider in managing high users include the following. First, most of the individuals in this category have unresolved symptoms and low treatment adherence,[52] as well as urgent social needs. Thus, social interventions such as supported housing may help more than purely medical interventions; providing housing reduces medical visits and ED-seeking behavior.[53,54] Second, many of these patients have trouble navigating the health system and are often ignored or lack primary care resources. Programs that address these factors can reduce ED recidivism.[36,55,56]

Third, chronic substance abuse and mental illness, alone or in conjunction, often have profound impacts on cognition. High ED users often present with an undisclosed or unexplored history of head trauma,[57] as victimization rates are elevated in both substance use disorders and mental illness.[58,59] The natural corollary of this is a decreased ability to recall and comprehend instructions given in the ED. Simplifying instructions and making sure the patient understood the explanation are crucial. Provide a limited, singular-focused plan, without multiple steps or complicated follow-up provisions. Simple planning applies to verbal, written, or even E-health/mobile-based interventions.[60]

Beyond the social needs, however, high users often have unmet medical needs. To get to the point of providing proper medical care, the emergency provider must deal with the patient's attitudes and behavioral difficulties. The difficult patient is a staple of every ED and every clinical practice. Intense patients can provoke negative feelings in providers.

Unconscious biases influence health decisions, cloud clinical judgment, and can lead to discrepancies and disparities in health care.[61-64] Negative bias is an unconscious, automatic reaction to a patient's pre-existing attributes such as gender, race, obesity status, ED recidivism, socioeconomic status, or sexual orientation. Negative bias can alter care, even with the provider's best intentions.

Dealing with difficult patients can be improved by adherence to existing protocols to the extent possible. Discussion of difficult cases with colleagues and the ED team can be helpful to develop effective strategies and to decrease provider isolation and burnout.

INVOLUNTARY PATIENTS

To consider an involuntary admission, the patient must be suffering from a severe mental disorder and must need treatment on an inpatient basis, and compulsory/involuntary treatment must be necessary in the interest of the patient's health or safety or the protection of other persons. A crucial element that is often missed is that there must be a prospect of recovery if the patient is treated involuntarily. Thus, patients with intellectual disabilities, autism spectrum disorders, or substance use disorders may not qualify for involuntary admission no matter how dramatic their presentation.

The core criteria that dictate involuntary transport to the ED are typically divided into three categories: harm to self; harm to others; and continuing deterioration without treatment.

Harm to self, planned suicide, active suicidal attempt, or reason to believe the patient may harm himself or herself imminently if discharged is the first category. Although many interviewers evaluate this by asking the question "Do you feel you want to hurt yourself?" the assessment of self-harm risk is much more complex, so that suicidal ideations are usually linked to a specialized psychiatric consultation.

The second category of involuntary commitment is **harm to others** or *risk* of harm to others. Frank homicidal ideations are actually fairly rare, but irritability and impulsivity are dangerous when unbridled, especially when combined with substance use, access to weapons, or personal crises that compound the situation, such as recent breakups, divorces, custody battles, and perceived need for revenge.

Lastly, the third category that may allow involuntary detention of a patient in the ED is **continued deterioration** to the extent where self-care and self-preservation are doubtful. Such cases will lack open statement of self-harm but may include catatonia, self-starvation, eating disorders, or severe psychosis with distortion of reality. This group of patients will typically lack capacity to make full medical decisions for themselves. **Table 286-6** illustrates the differences between capacity and competency. An involuntary commitment assumes (in most states) the patient lacks capacity to consent to an admission or emergency medications but is not linked to any competency determination, the latter being a legal term and decided on by the court.

The rules for involuntary commitment vary by state, both in scope and in the assignment of responsibility for who should fill out the court documents. Commonalities shared by all states (and countries) are based on the principles from European Convention for the Protection of Human Rights and Fundamental Freedoms (1950), the Principles for the Protection of Persons with Mental Illness (or MI Principles, 1991), The Declaration of Hawaii (1983), and Ten Basic Principles for Mental Health Law published by the World Health Organization. Two sources of information are usually required for involuntary commitment, such as an affidavit filled by the police or physician and another filled by a family member or social worker. Psychiatric consultation is recommended for involuntary commitment situations.

EXCLUSIONARY CRITERIA FOR PSYCHIATRIC ADMISSION

Once it is determined that the patient requires psychiatric admission and medical clearance/stabilization has been accomplished, various processes are used to find an inpatient psychiatric facility bed. In some cases, an on-site social worker will help identify local inpatient facilities for consideration. In other cases, a unit secretary will fax over the forms and facilitate the doctor-to-doctor calls to secure the patient a bed. The rules governing this process are very complex and, at times, elusory. Exclusionary criteria add yet another layer of complexity and add to the patient's overall length of stay in the ED and can trigger the problem of ED boarding.

A protracted discussion is beyond the scope of this chapter. However, facilities can deny patients for a myriad of reasons ranging from preexisting medical conditions (i.e., pregnancy or intellectual delay), to inability to manage the patient's medical comorbidities (i.e., patients requiring peritoneal dialysis), to requiring specific laboratory or ancillary testing irrespective of clinical need, to facility issues (i.e., requiring patients in the same room to be of the same gender). ED staff should familiarize themselves with the exclusionary criteria of local inpatient facilities. Failure to do so will lead to increased lengths of stay and further strain the ED staff and the patient.[65]

TABLE 286-6 Capacity Versus Competency

Capacity
• The ability to make a decision about a specific health matter at a discrete point in time.
• The concept includes the ability to understand risks and benefits of the suggested intervention, medication, or procedure; the repercussions of declining it; and alternative choices.
Competency
• Legal term decided by court and extends to financial, health, and personal matters. It is not a dynamic concept like capacity. Absence of competence usually implies the presence of a legal guardian, either an individual or a court-appointed entity. The concept is not to be confused with power of attorney.

DISPOSITION

The evaluation of the patient presenting with mental health complaints in the ED is a challenging process, because the complaints can indicate a medical issue, mental issue, or both. By following a rigorous process for evaluation and testing selection and seeking psychiatric consultation when needed, the emergency provider can untangle the case fairly reliably.

There are three types of disposition for patients with mental health complaints. The first and simplest is a discharge. Problems may arise in terms of destination of discharge for individuals with housing insecurity and inability to buy prescribed medications. Providers should be familiar with local pharmacy and supermarket generic/cheaper lists and discount programs and apps to help selected patients offset costs. The second potential disposition is an admission, whether psychiatric or medical. Bed availability is the main issue in this scenario, with inpatient facility shortages even for patients with insurance coverage. The extent of this problem has made headlines nationally. The third possibility is described differently across facilities and can be viewed as a reassessment or a brief observation period. This option may be the most useful for individuals who present with substance intoxication or crises expected to resolve in a period of time that is below the typical admission duration, but places pressure of increased length of stay and potential jurisdiction and liability issues on ED staff.

Lastly, cooperation between psychiatry and emergency medicine follows the same principles for any successful collaboration. We invite open communication and an effort to avoid stigma to enhance and optimize care for individuals with mental illness, one of the most vulnerable populations we are responsible for as a medical community.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 287

Acute Agitation

Michael Wilson

INTRODUCTION AND EPIDEMIOLOGY

Patient agitation is frequently encountered in the ED. Although exact numbers are difficult to determine, it is likely that as many as 1.7 million episodes of acute agitation are treated annually in U.S. EDs, with countless more in the prehospital setting.[1-4]

Over the past several years, modern expert consensus both inside and outside the field of emergency medicine has called for improved

treatment of agitated patients who need emergent treatment.[3,5-8] Broadly, the following best practices have been recommended for optimum care:

- Approach the agitated patient with safety in mind. This safety planning should start even before agitated patients arrive.
- Attempt verbal de-escalation in all patients.
- If agitation persists or worsens, employ a "show of concern."
- Treat underlying medical problems first.
- Restraints should be used sparingly and only to protect the staff or patient from harm.
- Target medication to the most likely cause of agitation and use oral medicines when possible.
- Use second-generation antipsychotics as first-line agents in most situations not involving alcohol intoxication.

The underlying goal of treatment with every acutely agitated patient is to treat agitation in order to allow performance of a thorough medical evaluation as soon as it safe to do so.[9-11]

GENERAL THERAPEUTIC APPROACH

Agitation has been defined by many experts as a "temporary disruption of the typical physician-patient collaboration which has unintended consequences for the staff or other patients."[9] This broad definition encompasses more than the typical aggressive or violent patient, because by the time patients are agitated to the point of violence, treatment options are usually limited to restraints and forced medication.

It is important to treat acute agitation early, because nursing staff caring for the patient may be the most vulnerable to untreated agitation. A survey by the Emergency Nurses Association in 2011 indicated that 54.5% of emergency medicine nurses had been physically or verbally abused in the past 7 days.[12] The National Emergency Department Safety Study surveyed staff at 65 U.S. EDs and found that at least 25% of ED staff felt safe at work "sometimes," "rarely," or "never."[13] In another study conducted at a medium-size university teaching hospital, university police had to respond an average of twice daily to violent incidents.[14]

An agitation scale may be helpful, as this provides a uniform way to communicate the level of agitation to other staff.[15] There are currently nearly two dozen potential scales that have been used to rate agitation, but unfortunately, as of yet there has been no head-to-head research that has established the superiority of any of these scales.[16] One scale that has been studied in an Australian ED as part of an ongoing sedation protocol is the Sedation Assessment Tool (**Table 287-1**).[17]

In the single study assessing the Sedation Assessment Tool scoring system, patients who could not be calmed by verbal de-escalation or oral medication were administered medication at values of +2 or +3.[17]

SAFETY FIRST

There are few reliable predictors of when agitated patients will become aggressive or violent, although community studies and risk stratification tools have indicated that historical factors, such as which patients have been violent in the past, are reasonable predictors of which patients will become violent again.[18,19] "Safety first" starts with the planning for, and recognition of, agitation. Although agitated patients may not always become aggressive, patients who are aggressive should only be approached by hospital security or police. If not immediately available, maintaining a safe distance and attempting verbal de-escalation should occur until security resources arrive. Agitated patients should have a prepared place in a separate room away from potential weapons and sharp objects, and there should be an easy way of notifying security if the need arises. Rooms should ideally have more than one exit, and external stimuli such as loud noises should be minimized.[20]

TABLE 287-1 Sedation Assessment Tool Scoring System

Score	Responsiveness	Speech
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious/restless	Normal/talkative
0	Awake and calm/cooperative	Normal
−1	Asleep but rouses if name called	Slurring or prominent slowing
−2	Responds to physical stimulation	Few recognizable words
−3	No response to stimulation	Nil

SHOW OF CONCERN

Patients who require ongoing verbal de-escalation or who refuse medication may benefit from a show of concern.[7] In this scenario, patients are approached with security agents and staff standing in a visible location outside the patient's room. Oral medication is typically offered at this point, with the decision to use IM medication only if the patient continues to escalate and/or refuse medication. In the ED, this is typically done while awaiting medication or security at the bedside.

PHARMACOLOGY

FIRST-GENERATION ANTIPSYCHOTICS

The decision to administer IM or IV medication involuntarily requires a determination that the patient is not willing or capable of controlling behavior and that the patient is at risk of harm to self or others.[21]

The presumed etiology of agitation will most likely guide the best choice of medication (**Figure 287-1**). Haloperidol and lorazepam are perhaps the most common combination used in U.S. EDs.[22,23] Haloperidol, first approved by the U.S. Food and Drug Administration in 1967, is a butyrophenone with primary activity at the dopamine 2 receptor.[5] Haloperidol, like all antipsychotics, carries a black box warning about the risks of use for dementia-related psychosis. In addition, this medication lengthens QT intervals, is associated with motor-related side effects, and is likely not appropriate for use as a single agent.[24] IV use is off-label.

There is no strong evidence that haloperidol alone is more efficacious than lorazepam in terms of number of people asleep or repeat injections and no strong evidence that the adverse effects of haloperidol are offset by concomitant use of lorazepam.[24,25] Concomitant use of promethazine is an acceptable alternative to lorazepam and is recommended by the United Kingdom National Institute for Health and Care Excellence.[26] Although addition of promethazine has better support from randomized trials, a recent Cochrane review[24] found no evidence in one trial that there was any difference in acute dystonias by 12 hours after injection. Given both this and concerns over excessive sedation with the combination, an American expert consensus panel has recommended second-generation antipsychotics instead of this combination (see below).[5]

Another medication in the butyrophenone class, droperidol, has often been used in the ED despite a Food and Drug Administration black box warning.[22,27-30] Both haloperidol and droperidol are thought to have minimal interactions with other medications, although droperidol has been implicated in respiratory depression in alcohol-intoxicated patients.[31] Droperidol may have a lower risk of movement-related side effects than haloperidol.[32] When administering first-generation antipsychotics, identify and treat electrolyte disturbances, especially if using the IV route. Select an alternative agent if possible and provide continuous cardiac monitoring when administering the agent to patients receiving other QT_c-prolonging medications.

KETAMINE

Another potential medication for agitation treatment is ketamine, an *N*-methyl-D-aspartate antagonist that has long been used in the ED for procedural sedation.[33] The use of ketamine has been proposed as a treatment both for patients with excited delirium syndrome, a syndrome in which patients are at high risk of death if not emergently treated,[34,35] and for patients who have proven refractory to other antipsychotics.[36] However, the routine use of ketamine for severely

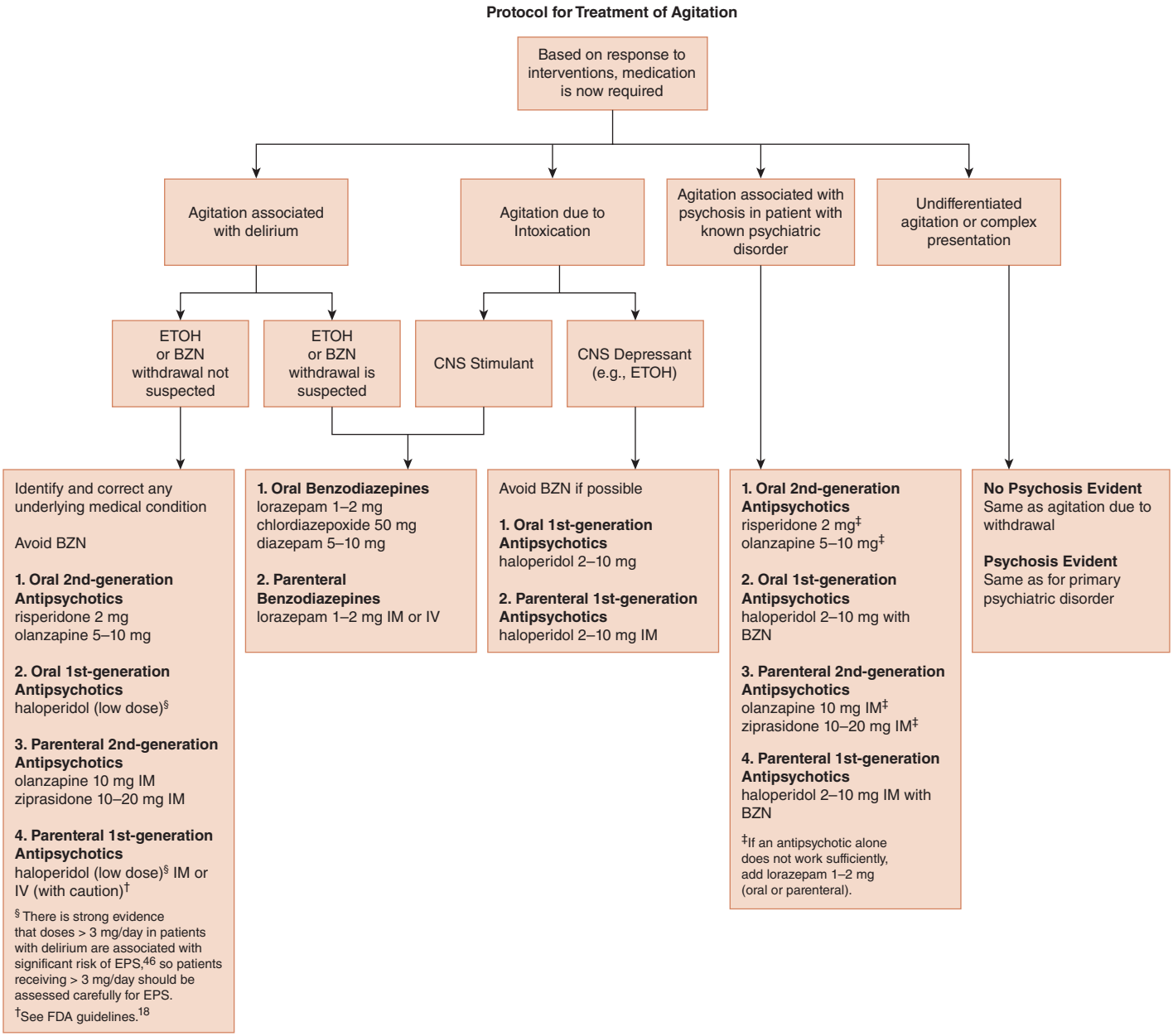

FIGURE 287-1. A suggested algorithm for the treatment of acute agitation. BZN = benzodiazepine; EPS = extrapyramidal side effects; ETOH = alcohol; FDA = U.S. Food and Drug Administration. Low-dose haloperidol is considered <3.0 milligrams/d. [Reproduced with permission from Wilson MP, Pepper D, Currier GW, et al: The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project Beta Psychopharmacology Workgroup. *West J Emerg Med* 13: 26–34, 2012.]

agitated patients is not well studied,[37] and most importantly, dose regimens have not been validated. Some suggest a dose of 4 to 5 milligrams/kg IM or 1 to 2 milligrams IV.[38-41] In the prehospital setting, use of ketamine for severely agitated patients may result in increased adverse airway events requiring intubation upon arrival in the ED.[38-41] Cole et al[38] reported that 39% of patients who received 5 milligrams/kg IM required ED intubation. Severe hypersalivation was another reported complication. Although ketamine administered in the ED setting may be generally well tolerated with few vital sign abnormalities, other potential drawbacks include the inability of the patient to participate in their own care or provide history, the fact that ketamine is not a specific treatment for agitation, and the need for frequent redosing.[42] In addition, there is some evidence from one small trial that the use of ketamine may worsen psychosis.[43] A recent clinical policy from the American College of Emergency Physicians stated that ketamine may be a "reasonable option" in the treatment of agitated patients, although it noted that there are no methodologically rigorous trials that support its use.[37]

SECOND-GENERATION ANTIPSYCHOTICS

Given the side effects of first-generation antipsychotics, second-generation antipsychotics have been recommended by multiple expert panels as better first-line agents in patients who are not intoxicated with alcohol,[5,7] although their efficacy may be similar to first-generation antipsychotics in reducing agitation.[8] Certain second-generation antipsychotics may also be as effective as benzodiazepines. In a recent prospective nonrandomized study, for instance, 10 milligrams IM olanzapine achieved equally rapid sedation as 5 milligrams IM midazolam.[44] Current guidelines also recommend that medication be administered at a dose that promotes calming but not sleep, as sleeping patients cannot generally be evaluated by physicians and nursing staff for disposition.[3,45]

Second-generation antipsychotics antagonize dopamine 2 receptors to a lesser degree than first-generation antipsychotics and have a relatively higher affinity for other receptor types such as serotonin.[46] Although second-generation antipsychotics such as olanzapine have a risk of side effects that is comparable to the use of haloperidol plus

TABLE 287-2 Treatment of Agitation: Comparison of Agents

Drug	PO or IM Dose	Half-Life	Comments on IV Dosing
Risperidone (Risperdal®)	1–6 milligrams/d, divided daily or twice a day	20 h	N/A
Olanzapine (Zyprexa®)	10 milligrams × 1, may repeat 2 h after 1st dose, then 4 h after 2nd dose to max 30 milligrams Consider lower doses or oral route in elderly or alcohol-intoxicated patients.	21–54 h	Some studies have shown that IV olanzapine is efficacious, although it has a greater risk of airway adverse effects; it is not FDA approved for this route. IV route may not offer additional advantages over PO or IM route.
Ziprasidone (Geodon®)	20 milligrams × 1 (may repeat every 4 h to maximum dose of 40 milligrams); alternatively, may administer 10 milligrams every 2 h	7 h	Not studied
Haloperidol (Haldol®)	0.5–10 milligrams every 1–4 h (use lowest effective dose; do not exceed 100 milligrams/d)	21–24 h	FDA black box warning for IV use

Abbreviations: FDA = U.S. Food and Drug Administration; N/A = not applicable.

promethazine, use of second-generation antipsychotics does not cause as much somnolence.[47] One expert consensus panel on the treatment of agitation recommended that medications be selected to target the presumed etiology of the agitation and that second-generation antipsychotics were almost always first-line treatment for agitation of psychiatric origin (Figure 287-1 and **Table 287-2**).

OTHER TREATMENTS

VERBAL DE-ESCALATION

A variety of other approaches have been recommended for the treatment of agitated patients. Perhaps the most common recommendation is the use of verbal de-escalation or "talking down" the patient.[48] Use of verbal de-escalation is standard in many psychiatric settings[49] and may even be useful in patients with dementia.[50]

The goal of verbal de-escalation is to help the patient regain control. Clinicians should use the 10 principles in **Table 287-3** to optimize the chances for successful verbal de-escalation.[2,49]

Verbal de-escalation likely does not need to be provided for long periods of time and may allow PO medication over IM injections.[44] In some clinical trials of agitation, a high proportion of patients have been ineligible for medication treatment after successful verbal calming.[51]

RESTRAINTS

The decision to restrain has philosophical and legal implications.[21,52,53] If possible, restraint should be placed by police, security officers, or similarly trained individuals. According to guidelines published by the American College of Emergency Physicians, restraint should be performed in the least restrictive manner possible (e.g., never face down) and only after verbal de-escalation is attempted.[54] Although clinicians often assume that a restrained patient is safer for staff than an unrestrained patient, this may not be true, as most of the injuries to both patients and staff occur during restraint episodes.[55,56] In addition, there are many disadvantages of restraint; it may consume a disproportionate share of ED resources, result in increased lengths of stay in the ED, and be associated with poorer outpatient follow-up.[57-59] In one study on ED lengths of stay, Weiss and colleagues[59] found that restrained patients remain 4.2 hours longer on average in the ED than other psychiatric patients.

TABLE 287-3 Principles of Verbal De-escalation

- Respect personal space
- Do not be provocative
- Establish verbal contact
- Be concise
- Identify wants and feelings
- Listen closely to what the patient is saying
- Agree or agree to disagree
- Lay down the law and set clear limits
- Offer choices and optimism
- Debrief the patient and staff

Source: Reproduced with permission from Richmond JS, Berlin JS, Fishkind AB, et al: Verbal De-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup. *West J Emerg Med* 13: 17–25, 2012.

SPECIAL POPULATIONS

Pregnant women, elderly patients, and children represent specific subgroups in whom nonpharmacologic approaches are generally preferred over antipsychotics or benzodiazepines,[60-63] even though acute short-term use of these agents has occasionally been suggested in the ED literature.[64] Extra attempts should be made to use nonpharmacologic treatments such as verbal de-escalation, which may work even in patients with dementia.[50,65] If medications must be used as a final resort, second-generation agents are preferred over first-generation agents.[66-68] In elderly patients with delirium, the safest approach is to treat the underlying cause that is producing both the delirium and agitation.[5,69,70] If medications are needed, second-generation agents and low-dose haloperidol (<3.0 milligrams/d) do not seem to worsen delirium.[67,71] Avoid benzodiazepines and antihistamines. For further discussion, see Chapter 149, "Behavioral Disorders in Children," and Chapter 288, "Mental Health Disorders of the Elderly."

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 288

Mental Health Disorders of the Elderly

Christina L. Shenvi

INTRODUCTION

The proportion of ED visits by older adults is expected to continue its rapid increase over the coming decades.[1] As a result, we can expect to see many patients who present for, or present with, mental health disorders. In 2013, the American Psychiatric Association released the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[2] in which they introduced the terms *mild* and *major neurocognitive disorder*, the latter of which was previously called dementia. We will continue to use the term *dementia* to represent major neurocognitive disorder in this chapter. Delirium, dementia, and depression affect many older

TABLE 288-1 Features of Delirium, Dementia, and Psychiatric Disorder

Characteristic	Delirium	Dementia	Psychiatric Disorder
Onset	Over days	Insidious	Varies
Course over 24 h	Fluctuating	Stable	Varies
Consciousness	Reduced or hyperalert	Alert	Alert or distracted
Attention	Disordered	Normal	May be disordered
Cognition	Disordered	Impaired	Rarely impaired
Orientation	Impaired	Often impaired	May be impaired
Hallucinations	Visual and/or auditory	Often absent	May be present
Delusions	Transient, poorly organized	Usually absent	Sustained
Movements	Asterixis, tremor may be present	Often absent	Varies

adults, and the differentiation of these disorders can be challenging because they are interrelated. Patients with dementia are more likely to develop delirium,[3] and patients who experience delirium are more likely to develop dementia later in life.[4-7]

It can also be difficult to diagnose depression in patients with dementia, as both disorders can demonstrate similar symptoms such as apathy and behavioral changes.[8] Also, depression in late life has been associated with an increased risk of developing dementia, further demonstrating that dementia, delirium, and depression are interconnected, increase the risk of each other, and are all associated with an increased risk of mortality and morbidity.[9-15] **Table 288-1** provides distinguishing features of delirium, dementia, and psychiatric disorders. Chapter 168, "Altered Mental Status and Coma," and Chapter 286, "Mental Health Disorders: ED Evaluation and Disposition," also discuss the distinctions between delirium, minor neurocognitive disorder, and psychiatric disorders.

Finally, the management of acute delirium, psychosis, or behavioral disturbances in older adults in the ED can be difficult. Medications such as benzodiazepines and antipsychotics, which are frequently used in younger agitated patients, may have significant side effects in older patients, such as prolonged sedation, or paradoxical agitation with benzodiazepines. Medications for acute agitation should be selected carefully and typically at lower doses than for younger patients, and should only be used after nonpharmacologic modifications and interventions have been exhausted.

DELIRIUM

Delirium is an acute change in cognition that fluctuates rapidly over time and is often reversible. Delirium is frequently the first sign of an underlying acute medical illness. Patients demonstrate altered levels of consciousness, inattention, disorganized thinking, and altered perception. There are three main types of delirium: hypoactive, hyperactive, and mixed.[16] By far, the most common types are hypoactive and mixed delirium, which also have the highest potential to be missed.[17-23] Hypoactive delirium has been called "quiet delirium" because patients have decreased psychomotor activity and can appear somnolent. If hypoactive delirium is confused for depression, the underlying medical disorder causing the delirium can be missed.[24-26] Hyperactive delirium, in contrast, is characterized by increased psychomotor activity. Patients with hyperactive delirium are often agitated, anxious, and sometimes combative. Mixed type can present with a combination of both hyperactive and hypoactive states that fluctuate over time.

Delirium is present in 7% to 10% of older patients presenting to the ED.[17,27,28] Environmental risk factors for delirium include functional dependence, living in a nursing home, and hearing impairment.[17,29] Delirium in the ED is an independent predictor of 6-month mortality. Delirium is associated with a longer hospital length of stay, more in-hospital complications, higher likelihood of discharge to long-term care facilities, and lasting cognitive deficits.[30-37] Even though delirium is a common disorder in the elderly, the diagnosis may be missed by providers in 57% to 83% of cases.[27,38–41] If delirium is missed in the ED, it is likely to be missed on the inpatient services as well.[17]

CLINICAL FEATURES

The differential diagnosis of delirium includes minor neurocognitive disorder, depression, or another underlying psychiatric disorder. Such conditions can also be comorbidities of each other. However, it is important to first assess for delirium and then consider the possibility of the other disorders. If delirium is suspected, the history and physical should be thorough to help determine the underlying cause.

History It is important when taking the history to find out the patient's baseline mental status and level of functioning, and the time course of changes. This may require calling the patient's family members or their facility to obtain collateral information. Patients with delirium may not be able to provide a clear history, or may confabulate. Ask a reliable source about past medical history and recent illness. Obtain an accurate medication list, and ask about over-the-counter medications, particularly medications with anticholinergic properties, or any new medications.[42] Ask about substance abuse to assess the likelihood of intoxication or withdrawal. Any past psychiatric history requires close investigation of prior diagnoses, hospitalizations, and medications. Determine the patient's ability to make informed medical decisions, and determine whether another individual has legal power of attorney for medical decision making.

When attempting to differentiate delirium from minor neurocognitive disorder, consider several key factors. An acute change in mental status is more consistent with delirium than with minor neurocognitive disorder, and a fluctuating course over time is also more likely due to delirium.[43] Altered level of consciousness, inattention, and disorganized thinking are all more common in delirium than in minor neurocognitive disorder.[43] However, delirium is more likely to occur in patients who have underlying minor neurocognitive disorder, so features of both may be present.

Physical Examination The physical examination should be thorough. Vital signs must be complete, including oxygen saturation and temperature. Baseline blood pressures are usually higher than in younger age groups, with a wider pulse pressure. Older patients may not be able to mount a tachycardic response to physiologic stress either due to effects of medications such as β-blockers, or because of physiologic limitations. Older patients have lower basal temperatures, with means of 97.3 to 97.8°F depending on the time of the day, so the threshold for a fever is lower.[44] Look for evidence of trauma, as patients may not recall falling or injuring themselves. Examine the entire body, making sure to look at the patient's back and heels for evidence of decubitus ulcers. Check between the toes for infections such as tinea or cellulitis. Perform a complete neurologic exam, looking for focal findings, abnormal posturing, or difficulty with gait, coordination, or vision. A normal physical examination does not exclude the diagnosis of delirium.

Mental Status Examination Mental status examination is performed to identify delirium and to differentiate it from other conditions.[27,35,38–41,45,46] The examination consists of an assessment of six mental-behavioral components (**Table 288-2**).

Two of the most common screening tests used to detect delirium are the **Confusion Assessment Method** for general use and the **Confusion Assessment Method–Intensive Care Unit** for intubated patients who

TABLE 288-2 Mental Status Examination

Appearance, behavior, and attitude
- Is dress appropriate?
- Is motor behavior at rest appropriate?
- Is the speech pattern normal?

Disorders of thought
- Are the thoughts logical and realistic?
- Are false beliefs or delusions present?
- Are suicidal or homicidal thoughts present?

Disorders of perception
- Are hallucinations present?

Mood and affect
- What is the prevailing mood?
- Is the emotional content appropriate for the setting?

Insight and judgment
- Does the patient understand the circumstances surrounding the visit?

Sensorium and intelligence
- Is the level of consciousness normal?
- Is cognition or intellectual functioning impaired?

are not heavily sedated.[47,48] **Figure 288-1** outlines the components of the Confusion Assessment Method. Inattention is characterized by an easily distracted patient who has difficulty keeping track of the conversation. Disorganized thought processes are rambling, unclear, or illogical. An altered level of consciousness is lethargy, lack of responsiveness, or coma—essentially anything other than alert. The diagnosis of delirium requires features 1 and 2 and either 3 or 4. See **Table 288-3** for further details about using the Confusion Assessment Method and the Confusion Assessment Method–Intensive Care Unit.[47,48]

There are also standardized questions that can be used to formalize the Confusion Assessment Method assessment. One such method is the 3D-Confusion Assessment Method, which is a 3-minute structured assessment developed and validated for Confusion Assessment Method–defined delirium, with tasks or questions to test for each of the Confusion Assessment Method criteria.[49,50]

Laboratory Testing and Imaging Laboratory testing and imaging are obtained to identify the underlying causes of delirium (**Table 288-4**) and to direct treatment.[46]

In geriatric patients, infections, such as urinary tract infections and pneumonia, are associated with nearly 50% of delirium cases,[51] and medications account for another 40%.[52-54]

Laboratory Testing for Delirium **Check point-of-care glucose as soon as possible after the patient arrives in the ED.** Other laboratory testing should be directed by the patient's symptoms and presentation. However, often a broad range of tests may be needed to determine the underlying cause of the delirium. Obtain a CBC and basic metabolic studies and liver function tests. A urinalysis is necessary because urinary tract infections are a frequent cause of delirium. However, the results of the urinalysis should be considered within the clinical context of new symptoms such as fever, dysuria, or new incontinence. It is also important to know that asymptomatic bacteriuria is very common in older adults, with rates of 5% for men and 6% to 10% for women who are community dwelling, and as high as 15% to 35% for men and 25% to 50% for women who are institutionalized.[55] Incidental pyuria is also common, especially in those with chronic incontinence. Obtain cardiac markers and consider a blood gas analysis, especially in patients with chronic lung disease, because hypercarbia can cause delirium.[42] Urine or serum toxicologic studies, a troponin level, and thyroid-stimulating hormone level[56] may be in order. Lumbar puncture may be necessary (after CT scan) if there is suspicion for meningitis or encephalitis or if the patient has had a new-onset seizure.[44] Further studies may be needed depending on the results of history, examination, and basic tests.

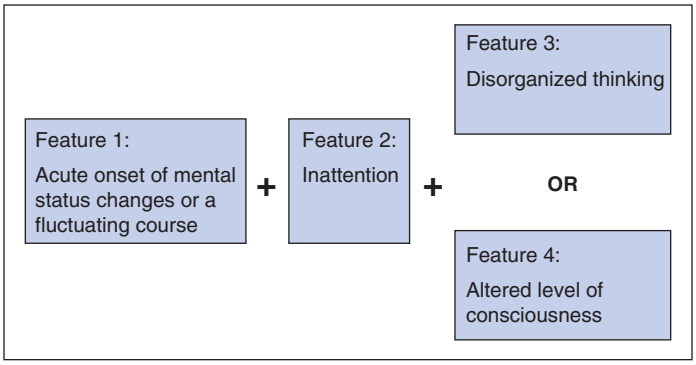

FIGURE 288-1. Confusion Assessment Method (CAM). To make a diagnosis of delirium, the patient must have features 1 and 2 and either 3 or 4.

Imaging/Ancillary Tests ECG and chest radiograph are essential.[57] Head CT scan is advised for patients with signs of, or a history of, trauma, focal neurologic deficits, impaired level of consciousness, or an otherwise unrevealing evaluation.[58,59]

TREATMENT

Prevention Patients can develop delirium or their delirium can worsen while they are in the ED both because of their underlying disease process and because of the unfamiliarity and chaotic nature of the environment. In high-risk patients, such as the very old or those with a history of minor neurocognitive disorder, avoid medications that could be deliriogenic, such as anticholinergics or antihistamines, unless necessary. Titrate pain medications carefully to treat pain but avoid sedation. In addition, try to ensure the patient has access to fluids, hearing aids, and glasses whenever possible. Allow family or caregivers to stay at the bedside, provide frequent reorientation about surroundings and course of care, and make sure there is access to a bathroom.[60] The Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients study identified six risk factors for the development of delirium and targeted each risk factor with specific interventions carried out by a multidisciplinary team. The risk factors included cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration.[60] Precipitating factors in the development of delirium in the hospital include the use of physical restraints, malnutrition, use of a bladder catheter, more than three medications added, and any iatrogenic event.[61] Preventing and minimizing these factors are especially important when long ED stays are unavoidable.

Medical Treatment Treatment should be directed toward the underlying cause of delirium. Withhold or remove medications that may be responsible for the delirium. Treat infection, provide IV fluids for dehydration, correct hypoglycemia and other metabolic derangements, and treat pain.

Agitation If the patient is agitated, begin with a nonpharmacologic approach by addressing patient needs (such as using the restroom and, if possible, allowing the patient to eat or drink), providing comfortable surroundings, and having the family close by.[60,62] Avoid bladder catheters unless unavoidable. If these basic interventions and the preventive measures above are not successful, consider medication (**Figure 288-2**). **We recommend the avoidance of benzodiazepines in the elderly if at all possible, unless alcohol withdrawal is the cause of delirium.**[63] Benzodiazepines can cause paradoxical disinhibition and increased agitation in the elderly. If a benzodiazepine is used, consider a short-acting agent such as **lorazepam** to minimize prolonged benzodiazepine effects. **Avoid antihistamines**, because this drug class has strong anticholinergic effects and can induce or worsen delirium in the elderly. Physical restraints should be an absolute last resort when patient or staff safety is in jeopardy. When it comes to psychiatric medications for acutely agitated older patients, the adage "start low and go slow" is particularly apt.

DISPOSITION AND FOLLOW-UP

The vast majority of patients with delirium should be hospitalized. Criteria for possible discharge include the following: the source of delirium

TABLE 288-3 Confusion Assessment Method and Confusion Assessment Method (CAM)–Intensive Care Unit*

	Confusion Assessment Method	Confusion Assessment Method–Intensive Care Unit Version
Feature 1. Acute Onset or Fluctuating Course	Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase or decrease in severity? Sources: Family or nurse	Is there evidence of an acute change in mental status from the baseline? Did the (abnormal) behavior fluctuate during the past 24 h, that is, tend to come and go or increase and decrease in severity? Sources of information: Serial Glasgow Coma Scale or sedation score ratings over 24 h, as well as readily available input from the patient's bedside critical care nurse or family
Feature 2. Inattention	Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?	Did the patient have difficulty focusing attention? Is there a reduced ability to maintain and shift attention? Sources of information: Attention screening examinations by using either picture recognition or Vigilance A random letter test. Neither of these tests requires verbal response, and thus they are ideally suited for mechanically ventilated patients.
Feature 3. Disorganized Thinking	Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?	Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject? Was the patient able to follow questions and commands throughout the assessment? "Are you having any unclear thinking?" "Hold up this many fingers." (Examiner holds two fingers in front of the patient) "Now, do the same thing with the other hand." (Not repeating the number of fingers)
Feature 4. Altered Level of Consciousness	Is the patient's mental status anything other than alert, for example, vigilant, lethargic, stuporous, or comatose?	Any level of consciousness other than "alert." Alert—normal, spontaneously fully aware of environment and interacts appropriately Vigilant—hyperalert Lethargic—drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor—difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly Coma—unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult or impossible even with maximal prodding

*To diagnose delirium, the patient must have features 1 and 2 and *either* 3 or 4.

TABLE 288-4 DELIRIUM: Mnemonic for Reversible Causes of Delirium

Drugs	Any new additions, increased dosages, or interactions Consider over-the-counter drugs and alcohol Consider high-risk drugs*
Electrolyte disturbances	Dehydration, sodium imbalance, thyroid abnormalities
Lack of drugs	Withdrawals from chronically used sedatives, including alcohol and sleeping pills Poorly controlled pain (lack of analgesia)
Infection	Especially urinary and respiratory tract infections
Reduced sensory input	Poor vision, poor hearing
Intracranial	Infection, hemorrhage, stroke, tumor Rare; consider only if new focal neurologic findings, suggestive history, or diagnostic evaluation otherwise negative
Urinary, fecal	Urinary retention: "cystocerebral syndrome" Fecal impaction
Myocardial, pulmonary	Myocardial infarction, arrhythmia, exacerbation of heart failure, exacerbation of chronic obstructive pulmonary disease, hypoxia

*High-risk drugs: anticholinergics, anticonvulsants, antidepressants, antihistamines, antiparkinsonian agents, antipsychotics, barbiturates, benzodiazepines, H_2-blocking agents, zolpidem, opioid analgesics.

Reproduced with permission from Marcantonio ER: Delirium. In: Pacala JT, Sullivan GM, eds. *Geriatrics Review Syllabus: A Core Curriculum in Geriatric Medicine*, 7th ed. New York, NY: American Geriatrics Society; 2010:297.

has been identified and treated; the patient has returned to baseline function and mentation in the ED; the patient can be cared for after discharge by a capable individual or a responsible facility; and the patient has access to follow-up in 24 hours or has the ability to return immediately to the ED if the condition deteriorates. Patients with unrecognized delirium who are discharged home are less able to understand discharge instructions and less likely to seek further treatment, underscoring the importance of screening for delirium in geriatric patients.[64]

DEMENTIA (MAJOR NEUROCOGNITIVE DISORDER)

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* published in 2013, dementia was retermed *major neurocognitive disorder*, and the criteria for diagnosis were modified.[2] The diagnosis now requires significant decline in cognitive function in one or more of the following cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition. The diagnosis cannot be made in the setting of delirium, and deficits should be severe enough that they interfere with the ability to live independently and perform all activities of daily living or independent activities of daily living. In addition, the cognitive deficits should not be attributable to other mental disorders such as major depressive disorder or schizophrenia.

The most common type of dementia (major cognitive disorder) is Alzheimer's disease, which affects approximately 5 million people in the United States.[65] Alzheimer's disease is reported in 6% to 8% of those over 65 years old and in ≥30% of those over 85 years old.[66] Some other common types are vascular dementia, Lewy body dementia, frontotemporal dementia, dementia associated with Parkinson's disease, and mixed dementia.

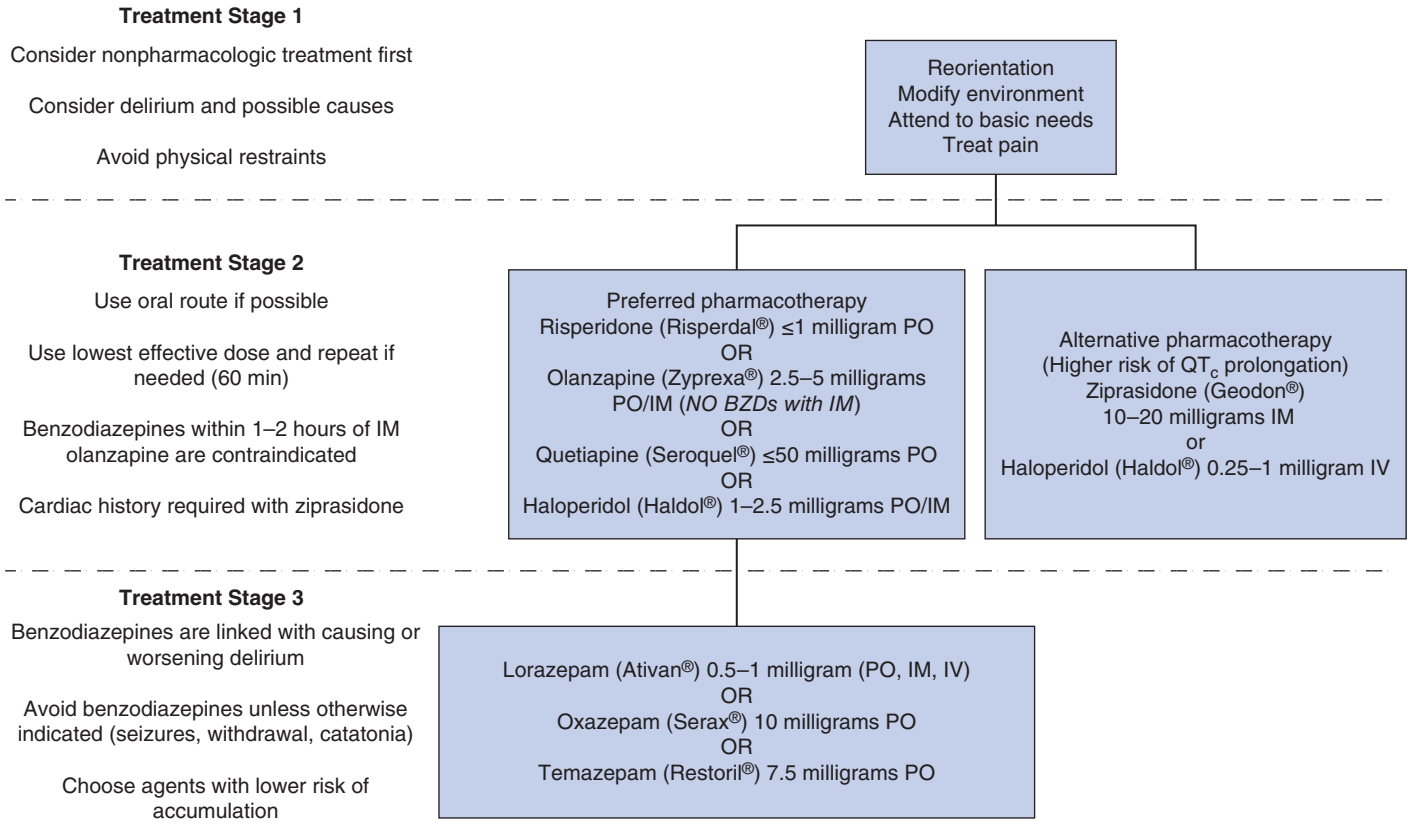

FIGURE 288-2. Acute agitation in the elderly: dosing considerations. BZDs = benzodiazepines.

PATHOPHYSIOLOGY

Alzheimer's disease has a gradual onset and primarily affects memory. The disease can also result in personality changes and visual-spatial problems.[65] Vascular dementia characteristically has a sudden or stepwise onset, and symptoms typically correlate with the affected area of brain ischemia.[65] Lewy body dementia has a gradual onset of memory deficits, and patients will also frequently have hallucinations and parkinsonian-like features.[65] **Patients with Lewy body dementia do very poorly when given typical antipsychotics, so avoid them in these patients.**[67,68] Patients with Lewy body dementia also frequently resemble patients with delirium. They can have a rapid decline, fluctuating course, and perceptual disturbances.[43] Frontotemporal dementia often presents in patients less than 60 years old and is associated with disinhibition, apathy, language difficulties, and atrophy in the frontal and temporal lobes.[65]

CLINICAL FEATURES

The main long-term pharmacologic therapy for patients with dementia is cholinesterase inhibitors such as donepezil. The side effects of these medications may prompt an ED visit and include GI upset, anorexia, urinary incontinence, bradycardia, dizziness, and abdominal cramps.[64]

Behavioral disturbances are frequently encountered in patients with dementia and are common reasons for ED presentation, especially when caregivers are feeling overwhelmed. The first steps are to screen for delirium and to identify the presence of a comorbid medical disorder (see earlier discussion and Tables 288-1, 288-3, and 288-4, and Figure 288-1). Subsequent management strategies for agitation are listed in Figure 288-2.

Mental Status Examination Perform a mental status exam on all geriatric patients because patients with dementia can often appear intact if a formal evaluation is not performed. In the ED, short screening tests such as the **Mini-Cog**, which takes 3 minutes to complete, can be used efficiently. The Mini-Cog (**Figure 288-3**) combines a three-word recall with a **clock drawing test**.[69] Ask patients to remember three words (e.g., apple, table, penny). Then ask them to immediately repeat the words and remember them. Three minutes later, ask for the three words again. If patients can recall all three words, they do not need to complete the clock drawing test and do not have signs of cognitive impairment. If patients are not able to recall *any* of the words, they may have cognitive impairment, and the clock drawing test is not needed. If patients recall one or two words, they will need to perform the clock drawing test. Ask the patient to draw a specific time, indicating hour and minute. The test is graded as either normal (negative for cognitive impairment) or abnormal (positive for cognitive impairment).[69] Alternatively, while waiting the 3 minutes to test the patient's recall, ask the patient to draw the clock, as valuable information can be obtained from that exercise alone.

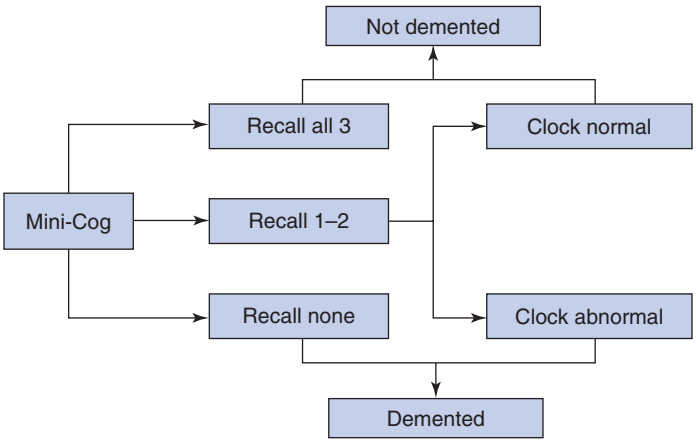

FIGURE 288-3. Mini-Cog Screening Test. Scoring is as follows: 1 point for each word recalled and clock drawing test is rated as either normal or abnormal. If the patient scores a 0 in word recall or can recall one or two words but has an abnormal clock drawing test, this is consistent with cognitive impairment.

MENTAL HEALTH DISORDERS

As the population of older adults continues to increase, so will the number of geriatric patients with mental health disorders. One estimate predicts that the number of geriatric patients with mental illness will increase by 275% from 4 million in 1970 to 15 million in 2030.[70] The most common mental health disorders in older adults are major depression and alcohol use disorders.[71] Significant research remains to be done in the field of geriatric psychiatry. The next sections will give a short overview of what is currently known regarding several mental health disorders found in older patients including depression, bipolar disorder, schizophrenia, and eating disorders.

DEPRESSION AND SUICIDE

Although the prevalence of major depressive disorder among community-dwelling older adults is low (1.4% to 4.4%), the proportion of patients with symptoms of depression below the threshold of major depressive disorder can be quite high, around 8% to 16%.[8,72,73] Older patients with overt or subclinical depression can both benefit from treatment.[74]

Depression in the geriatric population is associated with chronic medical illness, disability, increased use of health services, and poor health outcomes.[8,74,75] Risk factors associated with development of depression in older adults include lack of social support, living alone, being unmarried, cognitive impairment, bereavement, and lower socioeconomic status.[8,75]

Depression presents differently in older adults compared to younger age groups. Older adults with depression frequently report loss of appetite and sexual interest, rather than crying spells, sadness, or feelings of failure.[8] They are more likely to be irritable and withdrawn than sad.[76] Older patients may also present with somatic or cognitive complaints when they are actually suffering from depression, which can make the diagnosis difficult.[8] Caregivers and patients themselves may attribute depressive symptoms to normal aging, again making the diagnosis difficult.[8] Comorbid anxiety is common with depression, and generalized anxiety disorder is frequently seen in the elderly population, with a reported lifetime prevalence of 15% in older adults.[77]

There are several screening tests for depression currently available to practitioners. Many are lengthy and would be difficult to use in the ED setting. The Patient Health Questionnaire-2 and Patient Health Questionnaire-9 are two- and nine-item self-administered questionnaires that have been developed to screen for depression based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria.[78] The Patient Health Questionnaire-9 assesses nine features of depression: anhedonia, depressed mood, trouble sleeping, feeling tired, change in appetite, guilt or worthlessness, trouble concentrating, feeling slowed down or restless, and suicidal thoughts. The Patient Health Questionnaire-2 has two questions addressing anhedonia and low mood, and has sensitivity and specificity of 83% and 90%, respectively.[78] See **Table 288-5** for the Patient Health Questionnaire-2.[79] Both questionnaires can easily be located and are comparable to longer scales used to screen for depression with more evidence supporting the use of the Patient Health Questionnaire-9.[80] Several sources recommend starting with the Patient Health Questionnaire-2 and, if positive, then administering the Patient Health Questionnaire-9.

Treatment for depression combines both nonpharmacologic and pharmacologic interventions.[8] It is unlikely that new medications will be started in the ED for depression in geriatric patients, but recognizing depressive symptoms and ensuring that the patient has appropriate follow-up are important. Review antidepressant doses, side effects, and drug interactions, as ED visits may be precipitated by symptoms from side effects or interactions. Selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors are some of the most frequently prescribed and effective antidepressants, but they can be associated with serotonin syndrome.[8]

Screening for **suicide** is vital in the assessment of geriatric patients with depression.[81] People over 65 years old have the highest rates of completed suicide of any age group.[82]

Older adults may give fewer warning signs of suicidal intent, and they are more successful in attempting suicide.[83] **Depression is the largest risk factor for suicide. Other risk factors include perceived poor health status, poor sleep quality, alcohol abuse, absence of a confidant, physical illness, functional decline, and presence of a firearm.**[81]

TABLE 288-5 Patient Health Questionnaire-2

- Scores range from 0 to 6. A score of 3 or greater indicates the need for further screening.
- Over the past 2 weeks, how often have you been bothered by any of the following problems?
- Feeling down, depressed, or hopeless?
  - 0 = Not at all
  - 1 = Several days
  - 2 = More than half the days
  - 3 = Nearly every day
- Have you often been bothered by little interest or pleasure in doing things?
  - 0 = Not at all
  - 1 = Several days
  - 2 = More than half the days
  - 3 = Nearly every day

SUBSTANCE ABUSE

Substance abuse is relatively common in the geriatric population and may increase with the aging baby-boomer cohort.[84] The number of older adults who will need substance abuse treatment is expected to increase from 1.7 million in 2000–2001 to 4.4 million in 2020.[84] Although the vast majority of substance abuse in the elderly is related to alcohol and prescription medications, there are reports of increased illicit drug use as well, highlighting the need to ask all patients about drug use.[85]

Alcohol abuse in older adults is the most prevalent substance use problem. In a cross-sectional study of 12,000 older adult primary care patients, 15% of patients were felt to be at risk for, or were affected by, high-risk drinking.[86] Other community surveys estimate the prevalence of high-risk drinking to be between 1% and 15%.[87–89] Physiologic changes from advancing age decrease alcohol tolerance, increasing the risk of complications.[90] Current guidelines consider high-risk drinking in older adults to be either more than one standard drink per day or more than three drinks on an occasion.[90] Alcohol-related problems, such as falls, confusion, and malnutrition, may be misattributed to normal aging, and thus alcohol misuse may be missed.[90] If you identify high-risk drinking, refer the patient to an inpatient or outpatient treatment facility. Also, if the plan is to admit a patient with known alcohol or substance abuse, notify the admitting physician so withdrawal symptoms can be monitored.

BIPOLAR DISORDER

Research regarding bipolar disorder in older adults is limited. The prevalence of bipolar disease in older adults is approximately 0.08% to 0.5%.[91] Older adults who present with new-onset mania therefore require a complete medical evaluation before a new diagnosis of bipolar disorder is made. While the overall prevalence is very low, one study found that 17% of patients over 60 years old presenting to a psychiatric ED carried a diagnosis of bipolar disorder.[92] There are some differences between younger and older patients with bipolar disorder. Older patients are more likely to be female. Late-onset bipolar disorder (onset between age 30 and 50 years) is associated with fewer genetic associations and more neurologic illnesses.[93] The frequency of psychotic features is essentially the same in young and old patients with bipolar disorder.[93]

Patients may present to the ED both for symptoms of bipolar disorder and from adverse effects of the treatments. One of the most common medications used for bipolar disorder is the mood stabilizer lithium.[94,95] Older patients can benefit from lithium even at lower serum levels than younger patients. The renal clearance of lithium decreases with age, increasing the elimination half-life and predisposing to lithium toxicity.[96] Side effects of lithium include tremor, muscle twitches, GI symptoms, and CNS effects such as sedation.[96] Many common medications interact with lithium, including thiazide diuretics, NSAIDs, and

angiotensin-converting enzyme inhibitors, which can increase serum lithium concentrations and the risk of toxicity.[96] **Older adults taking lithium can display signs of toxicity even if the level is within the therapeutic window.[96]** See Chapter 181, "Lithium," for further details of toxicity and treatment. Three anticonvulsants have also been approved to treat bipolar disorder: valproate, carbamazepine, and lamotrigine. The literature regarding their use in older adults is sparse.[91]

PSYCHOSIS AND SCHIZOPHRENIA

Several disorders, such as schizophrenia, psychosis associated with dementias, and more acute processes such as delirium, can present with symptoms of psychosis (hallucinations and delusions) in geriatric patients.

The prevalence of schizophrenia in older adults is around 0.1% to 0.5%.[97-99] The majority of patients with schizophrenia develop the disease in the second or third decade of life (considered early-onset schizophrenia), meaning that most geriatric patients with schizophrenia have had the disorder since they were much younger.[100] There are two other groups of patients with schizophrenia: late-onset schizophrenia (over 40 years old) and very-late-onset schizophrenia-like psychosis (over 60 years old).[100] Individuals with late-onset schizophrenia have many of the same symptoms as patients with early-onset schizophrenia, but late-onset patients have fewer problems with learning, abstraction, and flexibility.[101] The diagnosis of very-late-onset schizophrenia and primary psychotic disorders is rare.[100] Very-late-onset patients tend to have fewer negative symptoms, greater risk of tardive dyskinesia, and evidence of a neurodegenerative process rather than a neurodevelopmental process.[100]

Schizophrenia in geriatric patients involves a complex interplay of the psychiatric, medical, and social factors. Nonadherence to medical therapy is common.[102] Mortality secondary to cardiovascular disease is more than twice as common compared with the general population, likely due to high rates of smoking, diabetes mellitus, hypertension, and obesity in schizophrenic patients. Older patients with schizophrenia often have a more sedentary lifestyle and a worse diet.[102] Atypical antipsychotics used for treatment increase the risk of metabolic syndrome and weight gain, which in turn increase the risk of cardiovascular diseases.[103] The use of typical antipsychotics is limited because of the higher risk of tardive dyskinesia.[104] The cumulative annual incidence of tardive dyskinesia in patients over 45 years old treated with low-dose typical antipsychotics is about 26%, which is five to six times greater than in younger patients.[104] Antipsychotic medications should be carefully selected and doses titrated upward slowly with close monitoring for side effects. Older patients with schizophrenia can also benefit from adjunctive psychosocial interventions. For example, Functional Adaptation Skills Training, a group therapy targeting everyday life skills, improves the functional capabilities of older patients with schizophrenia.[105-107]

EATING DISORDERS

There is little information regarding eating disorders such as anorexia nervosa and bulimia nervosa in older adults. A study of women over 50 years old found that about 13% reported some form of current eating disorder symptoms. Binge eating and purging in the absence of binge eating were the most common symptoms.[108] Approximately 71% of women in the study were trying to lose weight.[108] Another review identified 48 cases of eating disorders in adults over 50 years old. In this article, 88% were female and 60% were over 65 years old. The most frequent diagnosis was anorexia nervosa (81% of cases).[109] Of the 48 cases, 79% had the onset of eating disorders later in life.[109] Importantly, this study identified a strong connection between eating disorders and other psychiatric conditions (60% of cases), with major depression being the most important. Eating disorders were often preceded by a stressful event such as widowhood, bereavement, or marriage difficulties.[109] Of the 48 patients reviewed, 21% of the patients died from complications of their eating disorder.[109]

Diagnosis is difficult and is made by excluding any physical or medical cause of unexplained weight loss. Eating disorders in older patients are treated similarly to those in any other age group, with a combination of cognitive-behavioral treatment and pharmacotherapy.[109]

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 289

Mood and Anxiety Disorders

Tracy M. DeSelm

INTRODUCTION

Mood disorders, which include depressive disorders and bipolar disorders, are the most common mental health complaints presenting to the ED, accounting for about half of mental health–related visits, behind anxiety and substance use disorders (about 25% each).[1] Trends for ED visits for depressive disorders, bipolar disorders, and suicide ideation are sharply increasing.[2-5] The prevalence of depression and bipolar disorders in the ED patient population is twice that of the general population.[6] This chapter discusses the depressive disorders, bipolar disorders, and anxiety disorders. Substance use disorders are discussed in detail in Chapter 292.

DEPRESSIVE DISORDERS

Depressive disorders appear to affect women twice as often as men. Adolescents,[7] the elderly (especially nursing home patients),[8] and people living below the poverty level[9] appear to be particularly vulnerable populations for depression. Increased rates of depressive disorders are seen with chronic illnesses, including CNS diseases,[10,11] cardiovascular disorders,[12] cancer,[13] and chronic obstructive pulmonary disease.[14]

PATHOPHYSIOLOGY

The pathophysiology of depressive disorders includes genetic, biological, and psychosocial factors. A genetic predisposition heightens susceptibility.[15,16] Malfunctioning monoamine neurotransmitters (especially serotonin, norepinephrine, and dopamine)[17-19] are implicated and may explain the effectiveness of some current medical therapies. Abnormal γ-aminobutyric acid and glutamate levels in various areas of the brain have been noted.[20] Abnormal neurocircuitry that links the prefrontal cortex to the amygdala, ventral striatum and pallidum, medial thalamus, hypothalamus, and the periaqueductal gray areas has been shown in mood disorders.[21] Early childhood stress may alter corticotropin-releasing hormone cells in the hypothalamus to heighten future stress responses.[22,23]

A large number of medical disorders, medications, and substances of abuse may cause depressive symptoms (**Table 289-1**). A thorough

TABLE 289-1 Differential Diagnosis of Depression

- Neurologic: CNS infection, CNS tumor, cerebrovascular accident, Alzheimer's disease, traumatic brain injury, multiple sclerosis, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus
- Endocrine/metabolic: hypothyroidism, hyperthyroidism, Addison's disease, Cushing's disease, hyperparathyroidism, hypoglycemia, porphyria, severe anemia
- Infectious: meningitis, encephalitis, Lyme disease, human immunodeficiency virus, encephalopathy, Epstein-Barr virus, tertiary syphilis
- Inflammatory: systemic lupus erythematosus
- Medication side effects: steroids, neurologic or psychiatric medications (especially withdrawal from), β-blockers, calcium channel blockers, hormone therapies, chemotherapy drugs
- Substances of abuse: withdrawal from cocaine and amphetamines, alcohol, opiates
- Other psychiatric disorders: bipolar, posttraumatic stress disorder, substance abuse, anxiety disorder

TABLE 289-2 Diagnostic Criteria for Major Depressive Disorder*

- Depressed mood
- Anhedonia (decreased interest or pleasure)
- Significant weight loss or gain
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Difficulty with concentration or indecisiveness
- Suicidal ideation, with or without a plan

*The patient needs to have five or more of the symptoms for 2 weeks; one symptom has to be depressed mood or anhedonia. Symptoms cannot be due to substance abuse or a medical condition. Symptoms must be significant enough to impair normal functioning.

Source: Data from *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA: American Psychiatric Association; 2013.

TABLE 289-3 Suicide Prevention Resource Center Decision Support Tool[36]*

Transition question: *Confirm suicidal ideation.* Have you had recent thoughts of killing yourself? Is there other evidence of suicidal thought, such as reports from family or friends? This confirms that suicide risk exists and one should move forward to questions 1 to 6.

A "yes" response to any question below indicates the need for emergency psychiatric consultation.

1. *Thoughts of carrying out a plan.* Have you been thinking about how you might kill yourself?
2. *Suicide intent.* Do you have intention of killing yourself?
3. *Past suicide attempt.* Have you ever tried in the past?
4. *Significant mental health conditions.* Have you had treatment for mental health problems?
5. *Substance use disorder.* Do you have a history of alcohol or substance abuse? Have you used drugs or medication for nonmedical reasons in the past month?
6. *Irritability/agitation/aggression.* Have you been feeling anxious or agitated? Having conflicts or getting into fights? Is there direct evidence of irritability, agitation, or aggression?

Source: Suicide Prevention Resource Center. (2015). Caring for adult patients with suicide risk: A consensus guide for emergency departments. Waltham, MA: Education Development Center, Inc. www.sprc.org/ed-guide.

history, examination, and appropriate laboratory studies will help differentiate the disorders. Strongly consider medical causes of the depressive symptoms in patients with new-onset symptoms of depression, in the elderly, and in those with complex medical problems.

CLINICAL FEATURES OF DEPRESSION

The most common type of depressive disorder is major depressive disorder. Clinical features are listed in **Table 289-2**. Depressive disorders are often unrecognized in the ED, as the investigation of somatic complaints usually takes priority during patient evaluation.[24,25] Vague complaints and repeat ED visits,[26] especially in patients with nonspecific abdominal pain,[27] suggest the need for additional questioning regarding symptoms of depression. The two simple questions in the Patient Health Questionnaire-2 have been validated as a screening tool for depressive disorders in the primary care setting[28] but may also be useful in the ED:

1. During the past month, have you been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you been bothered by little interest or pleasure in doing things?

Other screening tools used in the primary care setting include the SAD PERSONS scale,[29-31] Patient Health Questionnaire-9 Self-Assessment Tool,[32] the Geriatric Depression Scale,[33] and the Beck Depression Inventory for Primary Care.[34]

DETERMINATION OF SUICIDE RISK

The most important part of the evaluation of depression is the assessment of suicide risk. Use straightforward, nonjudgmental questions regarding the patient's suicide or homicidal thoughts or intent, and seek corroborative information from family members, friends, law enforcement, EMS, and outside providers. If the patient is at potential risk for harm to self or others, perform a thorough search for weapons, medicines, and potentially harmful items; place the patient in a safe environment with monitoring; and consider initiating a precautionary, safety, or involuntary hold. Complete the appropriate history taking (including potential access to guns) with outside source verification, physical examination to include a mental status evaluation, and laboratory studies. Detailed evaluation of patients with mental health disorders is provided in Chapter 286, "Mental Health Disorders: ED Evaluation and Disposition." Alcohol and drug abuse are important suicide risk comorbidities.[35] Patients cannot be adequately evaluated for depression or suicidal intent until they are no longer intoxicated. This does not necessarily mean an alcohol level of 0, but rather a return to normal or baseline cognition.

A guide for the evaluation of suicide risk and disposition determination in ED patients is provided by the Suicide Prevention Resource Center[36] and begins with the Decision Support Tool (**Table 289-3**).

If the patient answers yes to any of the questions in Table 289-3, then an emergency psychiatric consultation is warranted. If all answers are "no," then a brief intervention is suggested to include follow-up resources. The Emergency Department Safety Assessment and Follow-Up Evaluation study demonstrated that a brief intervention in the ED, including resources and a follow-up phone call for at-risk patients who are being discharged, showed an absolute reduction in suicide attempt risk by 5%.[37]

TREATMENT OF DEPRESSIVE DISORDERS

Antidepressants are usually prescribed by primary care physicians or psychiatrists for depression, neurogenic pain, or smoking cessation. The side effect profiles, potential serious adverse effects, and toxicities of common antidepressants are reviewed in **Table 289-4** and in the Toxicology section of this text. Antidepressant therapy is typically not initiated in the ED, although resumption of a well-tolerated, recently stopped medication may be considered. Antidepressants take about 2 to 3 weeks to have clinical effects and may initially place a patient at increased risk of suicide. Ideally, ED antidepressant prescriptions should be discussed with the follow-up practitioner and should include an arranged visit within a week. Antidepressants may pose fetal risk, so the risks and benefits during pregnancy and lactation must be weighed carefully under the guidance of a psychiatrist and obstetrician. The major categories of antidepressants in use today are the **selective serotonin reuptake inhibitors** (SSRIs), **serotonin-norepinephrine reuptake inhibitors** (SNRIs), and **atypical antidepressants** (Table 289-4). **Heterocyclic antidepressants** and **monoamine oxidase inhibitors** are used infrequently due to adverse effects and drug–drug interactions.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

The mainstays of current antidepressant therapy are the SSRIs and SNRIs, which increase the amount of intrasynaptic serotonin or serotonin and norepinephrine, respectively. A significant advantage of SSRIs and SNRIs over other classes of antidepressants is their high therapeutic index and favorable side effect profile. Common side effects for the **SSRIs** include nausea and vomiting, drowsiness, headache, changes in sleep patterns, sexual dysfunction, cognitive dysfunction, and precipitation of mania in bipolar patients. SSRIs may initially increase suicidal ideation, and the U.S. Food and Drug Administration currently requires that all antidepressants carry a black box warning that antidepressants may increase suicide risk in patients <25 years old. **When SSRIs are**

TABLE 289-4 Commonly Used Antidepressants in the United States

Agent (Generic/Brand Names)	Mechanism of Action	Common Adverse Effects of Class	Starting Dose	Comments
Selective serotonin reuptake inhibitors (SSRIs)	Block presynaptic serotonin uptake	N/V, drowsiness, HA, dizziness, insomnia, agitation, mania, paresthesias, sexual/cognitive dysfunction, weight gain		Insufficient clinical studies to determine safety in pregnancy
Citalopram/Celexa®			10–20 milligrams once a day	Lower doses if anxiety prominent
Fluoxetine/Prozac®			10–20 milligrams once a day	First line for children/adolescents
Fluvoxamine/Luvox®			50 milligrams at night	More sedating, shorter half-life
Paroxetine/Paxil®			10–20 milligrams once a day	More anticholinergic, more sedating, more withdrawal symptoms
Sertraline/Zoloft®			25–50 milligrams once a day	Okay in breastfeeding patients
Escitalopram/Lexapro®			5–10 milligrams once a day	Okay in breastfeeding patients
Serotonin norepinephrine reuptake inhibitors (SNRIs)	Blocks presynaptic serotonin and norepinephrine uptake	Same as for SSRIs, except less sexual dysfunction, elevated BP, urinary hesitancy/retention		Insufficient clinical studies to determine safety in pregnancy
Duloxetine/Cymbalta®			30 milligrams once a day	More withdrawal symptoms; may increase anxiety
Venlafaxine/Effexor®			37.5–50 milligrams once a day	More withdrawal symptoms
Desvenlafaxine/Pristiq®			50 milligrams once a day	Synthetic active metabolite of venlafaxine
Atypicals				
Bupropion/Wellbutrin®, Zyban Bupropion/Wellbutrin® sustained release Bupropion/Wellbutrin® extended release	Dopamine and norepinephrine reuptake inhibitor	Seizures, dry mouth, nausea, agitation and irritability, aggressive behavior, insomnia, HA	50–75 milligrams 3 times a day 150 milligrams once a day, increase to twice a day after 3 days	When used with linezolid can precipitate serotonin syndrome Seizures associated with doses >450 milligrams; contraindicated if underlying seizure disorders or risk factors for seizure; history of anorexia or bulimia; abrupt discontinuation of alcohol, benzodiazepines, or antiepileptic drugs; less sexual dysfunction, less weight gain, used for smoking cessation
Mirtazapine/Remeron®	DA and NE reuptake inhibitor Increases release of NE, serotonin by antagonizing inhibitor receptors	Dry mouth, nausea, restlessness, insomnia, HA, pharyngitis, constipation, dizziness, somnolence, weight gain, malaise	15 milligrams once a day	More weight gain, more sedation, good choice for oncology patients with failure to thrive
Trazodone/Desyrel®	Serotonin antagonist and reuptake inhibitor; antagonist at histamine and α-adrenergic receptors	Marked sedation, priapism, orthostatic hypotension, ventricular dysrhythmias in patients with known cardiac disease	50 milligrams once a day	Also used in insomnia, prominent sedation
Heterocyclics	Blockage of presynaptic reuptake of NE, serotonin	Cardiotoxic: prolonged QT_c/AV block Anticholinergic: sedation, dry mouth, tachycardia, constipation		
Amitriptyline/Elavil®			25 milligrams once a day	Also used for chronic/neurogenic pain control, low therapeutic index
Nortriptyline/Pamelor®			25 milligrams at night	Metabolite of amitriptyline, although less sedating

Abbreviations: AV = atrioventricular; BP = blood pressure; DA = dopamine; HA = headache; NE = norepinephrine; N/V = nausea and vomiting.

abruptly stopped or rapidly decreased in dosage, a withdrawal syndrome may occur, characterized by flulike symptoms, including nausea, vomiting, fatigue, myalgias, vertigo, headache, insomnia, and paresthesias. Although these symptoms are not life threatening, they may be very uncomfortable for the patient.

SNRIs are very similar to SSRIs in side effect profile, although they may cause elevated blood pressure and result in less sexual dysfunction. Withdrawal may also occur several days after discontinuation or rapid decrease in dosage of an SNRI.

Serotonin Syndrome **Serotonin syndrome**, a potentially life-threatening adverse drug reaction, may occur in patients taking SSRIs (or any other antidepressant) when used in combination with another agent that has serotonergic activity such as monoamine oxidase inhibitors, opiates (including **tramadol**), CNS stimulants (including cocaine, ecstasy), serotonin agonists, St. John's wort, lithium, dextromethorphan, risperidone, olanzapine, ondansetron, and metoclopramide. The syndrome is manifested by neuromuscular hyperactivity (tremor, myoclonus, hyperreflexia/clonus, seizures), altered mental status (restlessness, agitation, excitement, confusion), autonomic hyperactivity (tachycardia, tachypnea, fever, diaphoresis), and GI irritability (nausea, vomiting, diarrhea). Treatment consists of discontinuing the affecting agents, administering benzodiazepines, and supportive care.

ATYPICAL ANTIDEPRESSANTS

Atypical antidepressants include **bupropion, mirtazapine, and trazodone**. Bupropion, a dopamine reuptake inhibitor, is also used for smoking cessation. It typically causes less weight gain and less sexual

dysfunction than other antidepressants. Trazodone is a serotonin antagonist and reuptake inhibitor that is more sedating than other antidepressants with less anticholinergic effects and is commonly used as a sleep aid. Mirtazapine is related to the heterocyclic antidepressants, tends to cause weight gain, and has a more rapid onset of action of about 1 week. As with the other antidepressants, these medications may cause withdrawal when abruptly stopped.

Although not approved by the U.S. Food and Drug Administration, ketamine is being studied for treatment-refractory depression, as its onset of action is much faster than current therapies.[38] Ketamine's long-term efficacy and side effect profile need further investigation.[39]

HETEROCYCLIC ANTIDEPRESSANTS

Heterocyclic antidepressants, once commonly used for depression, are prescribed less often now due to low therapeutic index, many possible side effects at prescribed doses, and dangerous overdose potential. The side effects are mainly anticholinergic related and cardiotoxic, including prolonged QT_c interval and atrioventricular block. One agent in this category, **amitriptyline**, is commonly prescribed for chronic or neurogenic pain.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors are rarely used first line in treating depression because of potentially lethal drug–drug and dietary interactions. Monoamine oxidase inhibitors block oxidative deamination of tyramine and may precipitate a sometimes fatal hypertensive crisis when certain drugs **(sympathomimetic amines, levodopa, narcotics, and heterocyclic antidepressants)** or **tyramine-containing foods or beverages** (aged cheese, beer, and wine) are co-ingested.

DISPOSITION

The disposition of the depressed patient is based on the assessment of harm to self or others, the ability to care for one's self, level of supportive environment at home, and complicating medical or substance abuse problems. Any combination of the above may require psychiatric consultation for admission evaluation. Patients who may safely go home need specific, timely follow-up plans with a primary care provider, psychiatrist, or other appropriate counselor. "No-harm" contracts between ED providers and patients are not recommended. Two helpful websites for both practitioners and patients are www.samhsa.gov (Substance Abuse and Mental Health Services Administration) and www.sprc.org (Suicide Prevention Resource Center). An ED-specific guide regarding safe patient disposition is found at www.sprc.org/edguide.

SPECIAL CONSIDERATIONS

Mood disorders in the elderly are discussed in Chapter 288, "Mental Health Disorders of the Elderly," and mood disorders in children are discussed in Chapter 149, "Behavioral Disorders in Children."

POSTPARTUM DEPRESSION

Postpartum depression affects 10% to 15% of women within 1 year of delivery,[40] but typically occurs within the first month. In one urban pediatric ED, one third of postpartum patients screened positive for depression.[41] Symptoms are extreme fatigue, ambivalent feelings about caring for the newborn, guilt about those feelings, and the other classic major depressive disorder symptoms. Low energy is in excess of the normal fatigue felt by most postpartum women. Risk factors for postpartum depression are prior depression, young age, low socioeconomic status, and partner abuse.[42] Recognition in the ED is important to identify and mitigate infant vulnerability.

CROSS-CULTURAL ISSUES

Surveys of depressive disorders show a wide range of prevalence across diverse cultures, although it is unclear how much of this difference is due to each culture's definition and expressions of depressive disorders. Non-Western cultures may emphasize somatic symptoms of depression, whereas in Western cultures, it may be more acceptable to express psychological complaints. Avoid stereotyping, but acknowledge the possibility of cultural influence in symptom description.

BIPOLAR DISORDERS

Bipolar disorders, previously called manic-depressive disorder, are the other major type of mood disorder and are characterized by mania, typically cycling with periods of depression. The depressive periods tend to last longer than the manic periods. Mania can be diagnosed if there is a distinct period of elevated, expansive, or irritable mood for at least 1 week.[43] This behavior must be associated with three of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas or racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, or involvement in high-risk activities (often sexual or financial in nature). These symptoms must cause marked impairment in usual functioning and must not be attributable to medical disease or substance abuse.[43] Mania may exist with or without psychotic features. Bipolar disorder is divided into several subtypes including bipolar I (mania, with or without major depressive episodes), bipolar II (intermittent hypomania with depressive episodes), and cyclothymic (recurrent dysthymic and hypomania episodes). A "mixed" state is one in which the patient meets the criteria for a manic episode plus depressive disorder symptoms for at least 1 week. Bipolar disorders affect men and women equally and have no race/ethnicity predilection.

PATHOPHYSIOLOGY

The pathogenesis of bipolar disorder is likely multifactorial. There is a strong genetic component, with about 50% of all bipolar patients having a parent with a mood disorder.[44] The concordance rate is 40% in monozygotic twins compared with 6% in dizygotic twins.[45] Areas of the brain involved in normal emotional responses, ventral prefrontal networks and limbic regions, demonstrate decreased connectivity on functional MRIs in bipolar patients.[45] Environmental factors, such as negative life events, increase the likelihood of developing bipolar disorder in predisposed persons.[46]

CLINICAL FEATURES

The manic patient may seem "fun," energetic, and expansive, but beware; the patient may quickly become irritable or even hostile if plans are antagonized by providers or family members. Manic patients may experience grandiose or delusional ideas and loss of cognitive abilities, with little insight. The initial evaluation of the manic patient is similar to that of patients with other psychiatric disorders and is discussed in Chapter 286. Consider nonpsychiatric causes of agitation, such as thyroid disease, acute toxic ingestions (cocaine, stimulants), and drug withdrawal (antidepressants, alcohol, benzodiazepines). Consider other psychiatric diseases, such as schizophrenia and attention deficit disorder, as features may mimic the manic phase of bipolar disorder. Patients exhibiting mania should be questioned about a previous history of depressive disorder, because most bipolar disorder patients are initially diagnosed with depressive disorder.

TREATMENT OF BIPOLAR DISORDER

Treatment for bipolar disorder is complex, often requires more than one medication, and thus should not be initiated by the emergency physician, except for treatment of acute agitation (see Chapter 287, "Acute Agitation") or to restart lithium or an anticonvulsant medication that has been recently stopped. Medications to treat the acutely manic patient include "**mood stabilizers**," such as **lithium, valproic acid, or carbamazepine**, with or without the addition of an antipsychotic (such as **haloperidol) or a benzodiazepine** (**Table 289-5**). The same mood stabilizers may also be used for maintenance therapy. Lithium and valproic

TABLE 289-5 Medications Used for Bipolar Disorder

Generic Name	Brand Name	Mechanism of Action	Side Effects (BLACK BOX WARNING IN CAPS)	Usual Starting Dose	Comments
Lithium carbonate	Eskalith®, Lithonate®, Lithotabs®	? increase NE function ? increase serotonin function	TOXICITY closely related to serum lithium levels: diarrhea, vomiting, tremor, mild ataxia, drowsiness or muscular weakness. Initially: nausea, dry mouth, excessive thirst, tremors, polyuria, peripheral edema, cognitive impairment Long-term: polyuria, diabetes insipidus, goiter, hypothyroidism, rashes, leukocytosis	300 milligrams 2 or 3 times a day	Effective for both acute and maintenance therapy Narrow therapeutic window; toxicity common; symptoms may be delayed up to 48 h in acute overdose Avoid giving with NSAIDs, ACE inhibitors, or diuretics to avoid toxicity. Dose is lower in elderly and patients with renal dysfunction
Valproic acid	Depakene®, Depakote® (12 h), Depakote Sprinkles® (12 h), Depacon® (IV)	Antiepileptic; enhances transmission of GABA	HEPATOTOXICITY, FETAL RISK, PANCREATITIS, weight gain, nausea, vomiting, hair loss, bruising, tremor, thrombocytopenia	250 milligrams 2 or 3 times a day	Effective for both acute and maintenance therapy Can monitor drug levels Monitor liver and platelet function May be used alone to treat BD, or in combination with antipsychotic or lithium
Carbamazepine	Tegretol®	Antiepileptic; stabilizes sodium channels, potentiates GABA receptors	AGRANULOCYTOSIS, STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS, nausea, vomiting, hyponatremia, rash, leukopenia	100–200 milligrams 1 or 2 times a day	Effective for acute or maintenance therapy Can monitor drug levels Monitor LFTs May be better in rapid cycling disorder Do not use with antipsychotics Many drug interactions with similarly liver-metabolized medications OCP failure
Lamotrigine	Lamictal®	Antiepileptic; sodium channel blockade	STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS—rare complications but potentially fatal; nausea, vomiting, fatigue, dizziness	25 milligrams once a day (unless on other antiepileptic medication)	Used with more severe depressive symptoms Dose adjustment required with other antiepileptic Progestin-only OCP failure Requires slower dose titration when used with valproic acid
Olanzapine	Zyprexa®	Antipsychotic; muscarinic; dopamine and serotonin antagonist	INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS, sedation, constipation, dry mouth, glucose intolerance, orthostatic hypotension, hyperlipidemia	2.5–5.0 milligrams 1 or 2 times a day	May be used in combination with lithium or valproic acid Injection cannot be given within 1 h of injectable benzodiazepine
Quetiapine	Seroquel®	Antipsychotic; dopamine, serotonin, and adrenergic antagonist	INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS, SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS, headache, dry mouth, weight gain, sedation, dizziness, orthostatic hypotension	25–50 milligrams 1 or 2 times a day	May be used in combination with lithium or valproic acid
Risperidone	Risperdal®	Antipsychotic; serotonin and dopamine antagonist	INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS, extrapyramidal side effects, prolactin elevation, sedation, dyspepsia, nausea, weight gain	0.25–1 milligram 1 or 2 times a day	May be used with lithium or valproic acid Use lower doses in elderly due to orthostasis risk
Aripiprazole	Abilify®	Antipsychotic; partial agonist of dopamine/serotonin receptors; antagonist of other serotonin receptors	INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS, SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS, headache, nausea, vomiting, extrapyramidal symptoms, especially akathisia	2–10 milligrams once a day	May be used with lithium or valproic acid
Ziprasidone	Geodon®	Antipsychotic; serotonin and dopamine antagonist; adrenergic antagonist; agonist at other serotonin receptors	INCREASED RISK OF DEATH IN DEMENTIA-RELATED PSYCHOSIS; rash, weight gain, constipation, nausea, tremor, extrapyramidal side effects, sedation, vision changes	40 milligrams twice a day	May be used with lithium or valproic acid
Lurasidone	Latuda®	Antipsychotic; serotonin and dopamine antagonist; adrenergic antagonist; agonist at other serotonin receptors	INCREASED RISK OF DEATH IN DEMENTIA-RELATED PSYCHOSIS, nausea, vomiting, extrapyramidal side effects, sedation, anxiety	20 milligrams once a day	

Abbreviations: ACE = angiotensin-converting enzyme; BD = bipolar disorder; GABA = γ-aminobutyric acid; LFTs = liver function tests; NE = norepinephrine; OCP = oral contraceptive pill.

acid may be combined with an atypical antipsychotic medication for bipolar maintenance therapy. Lithium has a narrow therapeutic index and requires frequent monitoring. Patients taking lithium must avoid dehydration to prevent toxic levels from accumulating. The efficacy of antidepressant use in bipolar disorder is unclear because of the possible risk of precipitating mania.[47]

DISPOSITION

Disposition of the bipolar disorder patient is similar to that of the depressive disorder patient, including careful assessment of suicide risk. Lack of insight to the loss of cognitive abilities and delusional ideas may put the patient at significant risk for self-harm, though not explicitly expressed.

Bipolar disorder patients who are exhibiting psychotic features or are at risk for harm to self or others need psychiatrist evaluation for admission.

ANXIETY DISORDERS

Anxiety is the most common mental health disorder overall, although second behind mood disorder in ED presentation,[1] accounting for approximately 1% of all ED visits. ED patients with anxiety are more likely to be women, nonelderly, and non-Hispanic whites.[48] Patients with anxiety disorders seek medical care about twice as often as non-anxiety patients and are high users of the ED.[49,50] This is partly due to the fact that anxiety disorders, especially panic disorder, may mimic life-threatening conditions, such as acute coronary syndrome. Anxiety disorders are often associated with mood disorders,[51] alcohol abuse,[52] personality disorders,[53] and other anxiety disorders.[51] **Anxiety disorders are characterized by excessive fear or worry about real or imagined events.** Fears often adversely impact both physical and psychological health.

PATHOPHYSIOLOGY

The pathophysiology of anxiety disorder is multifactorial. Dysregulation of γ-aminobutyric acid inhibitory neurotransmission and increased excitatory neurotransmitters, specifically serotonin, have been implicated and may explain the utility of SSRIs and benzodiazepines to treat anxiety disorder. Hyperactivity in the limbic regions, especially the amygdala, and the inability of executive cortex areas to modulate the limbic response to stimuli may contribute.[54] There appears to be a genetic role, especially in panic disorder,[44] although it does not seem to be as strong a predictor as in other psychological illnesses. Exposure to stressful events, especially in childhood, is a risk factor for development of anxiety disorder.[55] A specific stressful event precedes the development of posttraumatic stress disorder.

CLINICAL FEATURES

Anxiety disorders are a heterogeneous group, although they share many common somatic and cognitive symptoms (**Table 289-6**), with timing, severity, and associated beliefs separating the different types. Generalized anxiety disorder, panic disorder, and posttraumatic stress disorder are discussed here.

GENERALIZED ANXIETY DISORDER

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, defines patients with generalized anxiety disorder as having chronic excessive anxiety and worry about real or imagined events, occurring more days than not, for at least 6 months.[43] The symptoms cause significant impairment in daily functioning and are generally recognized by the patient as excessive and inappropriate. The anxiety and worry are associated with three or more of the following symptoms: restlessness or being keyed up or on edge, irritability, muscle tension, being easily fatigued, difficulty concentrating or "mind going blank," and sleep disturbance. Patients with generalized anxiety disorder may have interspersed, more intense panic attacks.[56]

TABLE 289-6 Symptoms of Anxiety Disorders

Physical Symptoms	Cognitive Symptoms
Palpitations, pounding heart, tachycardia	Fear of losing control or "going crazy"
Sweating	Derealization (feeling of unreality) or depersonalization (feeling detached from oneself)
Trembling or shaking	Inability to concentrate
Feeling of choking	Obsessions and compulsions
Chest pain or discomfort	Feeling generally ill at ease
Nausea or abdominal distress	Fear of dying
Feeling dizzy, unsteady, lightheaded, or faint	
Paresthesias	
Chills or hot flashes	
Difficulty sleeping	
Increased muscle aches or soreness	

PANIC DISORDER

Panic disorder ("panic attack") is a common, often chronic illness characterized by recurrent, spontaneous panic attacks. **Panic attacks are short-lived episodes of anxiety or intense fear accompanied by a range of somatic symptoms** (commonly cardiac, GI, or neurologic), usually peaking within 10 minutes and but that may last up to an hour. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, criteria for panic disorder also stipulate that the panic attack must be followed by 1 month of persistent concern about having additional attacks, worry about the implications of the attack or its consequences, or a significant change in behavior related to the attacks. It cannot be better accounted for by another psychiatric or medical disorder.[43] Panic disorder may occur with or without agoraphobia (irrational fear of crowded spaces); panic disorder with agoraphobia may be severely disabling both socially and occupationally. Because of the often debilitating symptoms, panic disorder patients are high users of the ED. In one Canadian study, 25% of patients presenting to the ED with chest pain were ultimately diagnosed with panic disorder.[57] Underrecognition of anxiety disorders, which are treatable, continues the cycle of overutilization of medical resources. Panic disorder may have an association with several medical disorders, including asthma,[58] hypertension,[59] interstitial cystitis,[60] migraine headaches,[61] and cardiovascular disease.[62] The long-held association between mitral valve prolapse is less clear.[63]

POSTTRAUMATIC STRESS DISORDER/ACUTE STRESS DISORDER

Posttraumatic stress disorder (PTSD) patients have all experienced or witnessed an intense traumatic event, such as rape, combat, natural disaster, child abuse, chronic exposure to an extreme stressor, or motor vehicle crash. The prevalence of PTSD within the first several months after a motor vehicle crash is 25% to 40%, and in 15% of patients, PTSD will persist.[64] Elderly patients are at higher risk, with 21% having significant PTSD at 6 months.[65]

Diagnostic criteria state that the patient has to be exposed to the stressor and that the response involved intense fear, hopelessness, or horror.[43] This is followed by "intrusive recollection," which would include one or more of the following: recurrent distressing dreams of the event, acting or feeling as if the event were recurring ("flashbacks"), and intense psychological distress with or without physiologic reactivity upon exposure to internal or external cues that symbolize the traumatic event. There may also be avoidance of stimuli associated with the trauma and a numbing of general responsiveness. Hyperarousal demonstrated by hypervigilance or exaggerated startle may occur. The symptoms have to be present for at least a month and cause significant impairment in functioning and cannot be better explained by another psychiatric or medical cause.[43] **Acute stress disorder** is diagnosed when the same symptoms of PTSD last between 2 days and 1 month. Feinberg and colleagues found a direct correlation between development of PTSD after a motor vehicle crash and persistent moderate to severe axial pain.[66] At discharge of

TABLE 289-7 Pharmacotherapy for Anxiety Disorder

	Class of Drug	Drug and Dosage	FDA Approved for Which Anxiety Disorder
Acute medication treatment	Benzodiazepines	Lorazepam (Ativan®), 0.5–1.0 milligram 3 times a day	All
		Clonazepam (Klonopin®), 0.5–1.0 milligram twice a day	All
		Alprazolam (Xanax®), 0.25–1.0 milligram 3–4 times a day	All
		Diazepam (Valium®) 2–10 milligrams 2–4 times a day	All
Ongoing medication treatment	Selective serotonin reuptake inhibitor	Sertraline (Zoloft®), 50–200 milligrams daily (initial dose, 25 milligrams)	PD, PTSD, SAD, OCD
		Paroxetine (Paxil®), 40–70 milligrams daily (initial dose, 10–20 milligrams)	GAD, PD, PTSD, SAD, OCD
		Escitalopram (Lexapro®), 10–20 milligrams daily (initial dose 5–10 milligrams)	GAD
		Fluoxetine (Prozac®) 20–60 milligrams daily (initial dose 10 milligrams)	PD, OCD
	Serotonin-norepinephrine reuptake inhibitor	Venlafaxine (Effexor®), 75–300 milligrams daily (initial dose, 37.5 milligrams) (Venlafaxine XR preferred in anxiety)	GAD, PD, SAD
		Duloxetine (Cymbalta®) 20–120 milligrams daily (initial dose, 20 milligrams)	GAD

Abbreviations: FDA = U.S. Food and Drug Administration; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder.

initial visit for a motor vehicle crash, or during return visits to the ED after serious trauma, patients should be questioned about persistent pain, coping strategies, general well-being, and follow-up plan to possibly avert development of acute stress disorder, PTSD, or chronic pain.

DIAGNOSIS

Initially, assess patients who present with anxiety for life-threatening medical conditions, such as myocardial infarction, pulmonary embolus, hypoglycemia, hypoxia, tachyarrhythmias, thyroid storm, and cerebrovascular accident. Also ask about suicidal and homicidal ideation, as there is a 10-fold greater suicide risk among patients with anxiety disorders compared with the general population,[67] and even greater risk when the patient also has both an anxiety disorder and a mood disorder.[68] Try to identify current stressful situations that may have precipitated symptoms. Anxiety symptoms may also be caused by certain medications or substances of abuse, including corticosteroids, neuroleptics, bronchodilators, decongestants, caffeine, nicotine, cocaine, and amphetamines. Withdrawal from benzodiazepines, opiates, SSRIs/SNRIs, and alcohol may cause agitation and anxiety. One useful screening question for panic attacks is: "Have you experienced brief periods for seconds or minutes of an overwhelming panic or terror that was accompanied by racing heart, shortness of breath, or dizziness?"[69] Take care to identify victims of domestic violence, sexual abuse, or assault, because such past or present experiences can provoke panic attacks.

TREATMENT OF ANXIETY DISORDERS

Psychological treatment with cognitive-behavioral therapy and pharmacologic therapy with antidepressants for long-term treatment have both been shown to be effective for anxiety disorders and may be more effective when used in combination.[70,71] Benzodiazepines for short-term use and low-dose β-blockers to mitigate physical symptoms may also be helpful.

Benzodiazepine pharmacotherapy in the ED may be considered (**Table 289-7**) for acute panic attack, especially for patients who need rapid control of debilitating symptoms. The limitation of benzodiazepines for anything but very short-term use is their potential for abuse and dependence. Use with caution in patients with a respiratory disorder or history of substance abuse or dependence. The use of benzodiazepines is discouraged in the elderly because of concerns for falling, cognitive slowing, paradoxical agitation, and drug interactions due to polypharmacy.

SSRIs and SNRIs are effective treatments for anxiety disorders and ideally administered in conjunction with a primary care or psychiatric practitioner with a follow-up plan in place. Starting doses may be lower than used when treating depression and may take longer to be effective.

Cognitive-behavioral therapy is not usually arranged in the ED, although one study in patients who presented to the ED with noncardiac chest pain (thought to be panic disorder) demonstrated a decrease in panic disorder symptoms with a single session of cognitive-behavioral therapy within 2 weeks of discharge.[72] This may have return ED visit implications.

DISPOSITION

Once a diagnosis of anxiety disorder is considered, the next step is to educate patients and provide reassurance that they are not dying or "going crazy." Emphasize that this is an illness that can be treated effectively with cognitive-behavioral therapy and antidepressants. Choice of treatment is based on an individual assessment of risks, benefits, efficacy, availability, acuity, and patient preference. Although cognitive-behavioral therapy is not practiced in the ED, education regarding it is worthwhile. Therapy consists of patient education about the disorder, symptom and thought records, and learning anxiety management skills (e.g., breathing retraining) with the guidance of a trained therapist.

After exclusion of a life-threatening medical condition, the need for admission or emergent psychiatric consultation is rare, except in patients expressing suicidal or homicidal ideation, or other psychiatric or medical comorbidities that prohibit the patient from self-care. Medication changes or initiation of antidepressants should be done in conjunction with the primary care provider or psychiatrist.

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 290

Psychoses

Adam Z. Tobias

INTRODUCTION AND EPIDEMIOLOGY

Psychosis has been defined as a "fundamental derangement of the mind characterized by defective or lost contact with reality."[1] The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition,[2] defines psychotic disorders as those that include abnormalities in one or more of five domains: hallucinations, delusions, disorganized or abnormal

motor behavior, disorganized thinking, and negative symptoms. The hallmark of these psychoses, schizophrenia, has a worldwide prevalence of 0.5% to 1%[3] and affects approximately 2.4 million adults in the United States.[4] Schizophrenia is considered one of the leading causes of chronic incapacity.[5-7]

The assessment of the psychotic patient presenting to the ED can be challenging, because patients may be agitated, combative, uncooperative, or unable to provide any history. The goals of evaluation are multiple. First, minimize any potential harm to the patient and ensure the safety of the ED staff and other patients. In the case of an aggressive or violent patient, this may require the use of verbal de-escalation techniques, physical restraints, or chemical sedation. Second, assess for any coexisting or confounding medical or traumatic conditions. Emergency care providers are gatekeepers to the psychiatric world, because once the patient is funneled into the psychiatric treatment realm, organic conditions may become more difficult to identify and treat. Psychiatric conditions contribute to increased mortality from comorbid medical conditions as compared to the general population.[8] In fact, patients with schizophrenia have a life expectancy of approximately 20 years less than that of the general population.[9] Finally, aim to optimize the treatment of the patient's underlying psychiatric illness, either by connection with the appropriate inpatient or outpatient resources or by contacting their psychiatrist.

PATHOPHYSIOLOGY

Both environmental and genetic factors contribute to the schizophrenia spectrum of disorders.[10,11] The disorders have been linked to a spectrum of risk alleles, with overlap between the alleles associated with schizophrenia and those associated with other disorders such as autism and bipolar disorder.[12] It is thought that dopamine acts as the common final pathway of a wide variety of predisposing factors, either environmental, genetic, or both, that lead to the disease. Other neurotransmitters, such as glutamate and adenosine, may also collaborate with dopamine to give rise to the entire picture of schizophrenia.[13,14]

CLINICAL FEATURES

HISTORY

Features of psychoses include hallucinations, delusions, disorganized thinking, and negative symptoms.

A **hallucination** is an "apparent, often strong subjective perception of an external object or event when no such stimulus or situation is present."[2] Although hallucinations may occur in any sensory modality, they are most commonly *auditory* in schizophrenia and other psychotic disorders. Typically these are experienced as voices distinct from the individual's own thoughts. Not all hallucinations are considered to be pathologic; they may be a normal part of certain religious and cultural experiences.

A **delusion** is "a false belief or wrong judgment, sometimes associated with hallucinations, held with conviction despite evidence to the contrary."[15] Delusions may be classified based on various themes, including *grandiose* (i.e., "when an individual believes that he or she has exceptional abilities, wealth, or fame"), *persecutory*, *erotomanic* (i.e., "when an individual believes falsely that another person is in love with him or her"), and *referential* or *ideas of reference* (i.e., "belief that certain gestures, comments, environmental cues, and so forth are directed at oneself"). Delusions are considered bizarre if they are clearly implausible. In the ED, a nonbizarre delusion may be difficult to distinguish from a strongly held idea.[2]

Typically, **disorganized thinking** is inferred from a patient's speech. Commonly encountered patterns may include *derailment or loose associations*, wherein the individual switches from one topic to another; *tangentiality*, wherein answers to questions may be unrelated or loosely related; and *word salad*, wherein the individual's speech becomes so disorganized that it becomes nearly incomprehensible.[2]

Negative symptoms associated with psychotic disorders include *avolition* (decreased motivation), *diminished emotional expression*, *anhedonia* (decreased ability to experience pleasure), *asociality* (decreased interest in social interaction), and *alogia* (decreased speech). Patients with negative symptoms often present with flat affect. These symptoms can be the most chronically impairing features of psychoses.

PHYSICAL EXAMINATION

Aside from grossly disorganized or abnormal motor behavior (discussed below), there are no specific physical findings associated with the psychotic disorders. The goal of physical examination is the exclusion of coexisting medical or traumatic conditions. For agitated patients, be particularly vigilant to assess for any self-inflicted injuries, environmental injuries such as frostbite, or injuries occurring as a result of combative behavior or the restraint process.

Grossly disorganized or abnormal motor behavior may take on various forms, although it is likely most familiar to emergency practitioners as unpredictable agitation. Catatonia is a "marked decrease in reactivity to the environment." Catatonic features may range from *negativism*, which is a resistance to instructions, to maintenance of a rigid or inappropriate posture, to complete lack of motor or verbal response. Catatonic behavior may occur in association with a variety of psychiatric and medical conditions.[2]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Psychotic symptoms may be caused by numerous medical conditions and often occur in conjunction with delirium. Consider medical causes before attributing psychosis to a primary psychiatric illness. Some of the many potential causes include infections such as encephalitis, meningitis, or sepsis; CNS conditions such as stroke, seizure, Parkinson's disease,[16] or brain tumor; and metabolic derangements such as hypoglycemia or hepatic encephalopathy. Additionally, various medications and illicit substances may give rise to psychotic symptoms (**Table 290-1**).[17-20]

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, delineates specific diagnostic criteria for the schizophrenia spectrum and other psychotic disorders (see discussion below). However, such granular distinctions are typically not necessary or relevant for emergency assessment and treatment. Rather than making a specific psychiatric diagnosis, the ED provider's focus should be on emergency treatment and stabilization, identification of comorbid conditions, and appropriate disposition. Diagnostic testing is directed by the history and physical examination. Routine extensive laboratory testing for otherwise stable, cooperative, and previously diagnosed psychiatric patients is of low yield and need not be performed in most cases. Similarly, urine toxicologic screening rarely affects ED management and need not be routinely obtained.[21]

Many psychotic patients presenting to the ED have been previously diagnosed with a psychiatric condition. In such cases, determine whether there has been an acute change from the patient's baseline and whether the current presentation is confounded by another condition that requires medical treatment. In cases where the patient is unable to aid with providing history, use other resources, including past medical records, medication lists, family members, and case workers.

For patients with new-onset psychosis, the ED is a common point of first contact with the healthcare system.[22] The provider must then

TABLE 290-1 Common Medications and Drugs of Abuse Causing Psychosis

Medications	Drugs of Abuse
Corticosteroids	Ethanol*
Fluoroquinolones	Cocaine
Atropine and other anticholinergics	Amphetamines and other stimulants (including "bath salts")
Dextromethorphan	LSD and other hallucinogens
Benzodiazepines*	Marijuana
	Phencyclidine (PCP)
	MDMA (ecstasy)

*Psychosis is more commonly seen in benzodiazepine withdrawal but can occur with ethanol intoxication or withdrawal.

determine whether the patient's psychosis is the by-product of an acute medical condition, a reaction to a medication or illicit substance, or truly the new onset of a primary psychiatric illness. Newly symptomatic patients often warrant a more extensive medical evaluation than those with known underlying psychotic disorders.

DISPOSITION AND FOLLOW-UP

Patients with a chronic psychotic illness may present anywhere along a spectrum ranging from high functioning to completely disabled. Guide disposition decisions by considerations of patient safety and optimization of treatment. Patients thought to be violent, at risk of self-harm, or unable to care for themselves typically require emergent psychiatric evaluation and possibly inpatient psychiatric care. Patients with new-onset psychosis (not thought to be due to a medical cause) or those with worsening of underlying psychotic symptoms should have psychiatric consultation in the ED, if available, or be transferred to a psychiatric facility. Patients with known psychoses under apparent good control may be referred for outpatient management. Ideally, such referrals should be made in consultation with the patient's treating psychiatric provider.

Finally, patients with psychosis secondary to a medical condition or those with comorbid illness should be managed accordingly. Give special consideration to a patient's functional level and ability to manage the medical condition as an outpatient. For example, a schizophrenic patient with an infection that might otherwise be treated with oral antibiotics at home might benefit from hospitalization if there is doubt about the patient's ability to comply with treatment and follow-up instructions.

PHARMACOTHERAPY

Antipsychotic (neuroleptic) medications are typically used in the treatment of schizophrenia and the other psychoses. The exact mechanism of action of the antipsychotics is not known. The majority of antipsychotics block the D_2 dopamine receptors and 5-HT_{2A} serotonin receptors in the brain to a varying degree. Antipsychotics are classified as first-generation (typical) or second-generation (atypical) antipsychotics.

The typical antipsychotic medications are often categorized as being of low, medium, or high potency. The "potency" of these drugs does not refer to effectiveness, but rather to the degree of dopamine blockade. High-potency drugs have higher D_2 dopamine receptor blockade and lower serotonergic and muscarinic binding affinity. In general, **low-potency medications** tend to be more sedating and are more often associated with hypotension, dizziness, and anticholinergic symptoms. **High-potency medications** are generally less sedating, but are more frequently associated with extrapyramidal effects such as tremors, rigidity, muscle spasms, and akathisia.[13] **Table 290-2** reviews the common typical antipsychotics.

The U.S. Food and Drug Administration (FDA) has placed black box warnings on a number of the typical antipsychotics, due to concerns about possible cardiac dysrhythmias associated with their use. In particular, several of these medications have been associated with QT_c prolongation and the FDA recommends evaluation of the QT_c interval prior to their use. In clinical situations in which rapid treatment of agitation is necessary, a priori determination of the QT_c interval is impractical and usually impossible. If ECG data are available from the ED visit, these should be reviewed for evidence of QT_c prolongation. Similarly, if prior ECG data are available, incorporate them into clinical decision making. Haloperidol remains a popular and effective agent for rapid tranquilization, although newer agents such as olanzapine may be safer and equally effective.[23,24] Unfortunately, QT_c prolongation does not directly correlate with the clinical risk of dysrhythmias or the development of the malignant arrhythmia torsades de pointes. The black box warnings have led to apprehension in the use of highly effective medications.

The atypical antipsychotics (**Table 290-3**) are generally newer medications that more specifically target the dopamine receptors or inhibit the reuptake of serotonin. Early studies showed that they had increased efficacy in the treatment of the negative symptoms of psychosis, although more recent data have found this effect to be comparable to that of the typical antipsychotics.[25] Based on this improved receptor specificity, adverse effects such as sedation, extrapyramidal effects, QT_c prolongation, and tardive dyskinesia are generally reduced but are not completely eliminated. The incidence of hypotension does not appear to have been significantly altered. The FDA has placed a black box warning on both typical and atypical psychotics for their off-label use in managing agitation and psychosis in elderly patients with dementia, due to increased rates of cerebrovascular accidents, cardiovascular events, and mortality associated with chronic use.[26,27]

TABLE 290-2 Typical Antipsychotics

Generic Name	Brand Name	Relative Potency	U.S. Food and Drug Administration Warnings
Phenothiazines			
Chlorpromazine	Thorazine®	Low	
Mesoridazine	Serentil®	Intermediate	QT_c prolongation
Thioridazine	Mellaril®	Intermediate	QT_c prolongation
Perphenazine	Trilafon®	Intermediate	
Trifluoperazine	Stelazine®	High	
Fluphenazine	Prolixin®	High	
Thioxanthenes			
Loxapine	Loxitane®	Intermediate	
Thiothixene	Navane®	High	
Dihydroindolones			
Molindone	Moban®	Intermediate	
Butyrophenones			
Haloperidol	Haldol®	High	QT_c prolongation and torsades de pointes
Droperidol	Inapsine®	High	QT_c prolongation and torsades de pointes

ADVERSE EFFECTS

The following side effects are more commonly associated with the typical antipsychotics, but may also occur with medications in the atypical class: acute dystonia, akathisia, parkinsonism, anticholinergic effects, cardiovascular effects, and neuroleptic malignant syndrome.

Acute Dystonia Acute dystonias are probably the most common side effect of antipsychotic medications seen in the ED and are more common in younger patients and those who have never taken antipsychotic drugs before.[13] Muscle spasms of the neck, face, and back are the most common dystonias, but oculogyric crisis and even laryngospasm may also occur. Treatment with either benztropine, 1 to 2 milligrams IV or IM, or diphenhydramine, 25 to 50 milligrams IV, rapidly corrects the dystonia. For persistent reactions, both medications may be used, and benzodiazepines may be added for treatment failures or given prophylactically. Dystonias often recur despite dosage reduction or discontinuation of the offending antipsychotic.

Akathisia (Motor Restlessness) Akathisia, a sensation of motor restlessness with a subjective desire to move, can begin several days to several weeks after initiation of antipsychotic treatment. Management can be difficult. If possible, decrease the dosage of the antipsychotic after psychiatric consultation. The best treatment is probably administration of benzodiazepines or β-blockers such as propranolol.

Antiparkinsonian or anticholinergic drugs such as benztropine, 1 milligram PO twice daily, may also afford some relief, although these may lead to anticholinergic side effects if not subsequently tapered off. In refractory cases, the antipsychotic may need to be changed to an atypical agent.

Antipsychotic-Induced Parkinson's Syndrome A complete Parkinson's syndrome, including bradykinesia, resting tremor, cogwheel rigidity, shuffling gait, masked facies, and drooling, can occur. The elderly are at greatest risk, with development in the first month after initiation of the antipsychotic agent.[13] Often only one or two features

TABLE 290-3 Atypical Antipsychotics

Drug	U.S. Food and Drug Administration–Approved Indications	Warnings and Common Side Effects (BLACK BOX WARNINGS IN CAPS)
Clozapine (Clozaril®)	Treatment-resistant schizophrenia Reduction in the risk of recurrent suicidal behavior in schizophrenic or schizoaffective disorders	Sedation, dizziness, hypotension, tachycardia, salivation, weight gain, hyperthermia. AGRANULOCYTOSIS, SEIZURES, MYOCARDITIS, OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS
Olanzapine (Zyprexa®)	Schizophrenia Bipolar disorder Agitation associated with schizophrenia and bipolar I mania	CVAE, sedation, postural hypotension, hyperglycemia, weight gain, dizziness
Quetiapine (Seroquel®)	Bipolar mania Schizophrenia	NMS, hyperglycemia, sedation, hypotension, headache, weight gain CATARACT FORMATION
Risperidone (Risperdal®)	Schizophrenia Bipolar mania	Extrapyramidal effects, hyperglycemia, hypotension, hyperprolactinemia, weight gain
Ziprasidone (Geodon®)	Schizophrenia Bipolar mania Acute agitation in schizophrenic patients	Sedation, rash, dizziness, hypotension, hyperglycemia, extrapyramidal effects QT PROLONGATION AND RISK OF SUDDEN DEATH
Aripiprazole (Abilify®)	Schizophrenia Bipolar disorder	NMS, CVAE, hyperglycemia, seizure, hypotension, headache, akathisia
Asenapine (Saphris, Sycrest®)	Schizophrenia Bipolar mania	Blood dyscrasias, cerebrovascular effects, dyslipidemia, extrapyramidal symptoms, NMS, hyperglycemia, QT_c prolongation, orthostatic hypotension, increased mortality with chronic use in dementia patients
Iloperidone (Fanapt®)	Schizophrenia	
Paliperidone (Invega, Sustenna®)	Schizophrenia Schizoaffective disorder	

Abbreviations: CVAE = cerebrovascular adverse event; NMS = neuroleptic malignant syndrome.

of the syndrome are obvious. Antipsychotic dosage reduction and/or anticholinergic medication is usually effective.

Anticholinergic Effects Anticholinergic effects range from mild sedation to delirium. Peripheral manifestations may include dry mouth and skin, blurred vision, urinary retention, constipation, paralytic ileus, cardiac dysrhythmias, and exacerbation of angle-closure glaucoma. The central anticholinergic syndrome is characterized by dilated pupils, dysarthria, and an agitated delirium. Treatment is discontinuation of the antipsychotic and supportive measures.

Cardiovascular Effects Cardiovascular side effects, such as orthostatic hypotension and tachycardia, are commonly encountered. These effects are likely related to anticholinergic and adrenergic blockade and occur at therapeutic dosages. Typically, hypotension can be managed with IV fluids. In severe cases, vasopressor support may be required. Additional effects caused by blockade of sodium, calcium, and potassium channels in the central nervous and cardiac systems are less well delineated. However, effects on specific potassium channels in the myocardium have been linked to the drug-induced prolongation of the QT_c interval associated with several of the antipsychotics.[28,29] It is this mechanism of action by which the antipsychotics are believed to induce torsades de pointes.

TABLE 290-4 The Schizophrenia Spectrum of Disorders

- Schizophrenia
- Brief psychotic disorder
- Substance/medication-induced psychotic disorder
- Schizotypal personality disorder
- Unspecified catatonia
- Unspecified schizophrenia spectrum and other psychotic disorder
- Catatonia associated with another mental disorder
- Delusional disorder
- Schizoaffective disorder
- Schizophreniform disorder
- Psychotic disorder due to another medical condition
- Catatonic disorder due to another medical condition
- Other specified schizophrenia spectrum and other psychotic disorder

Neuroleptic Malignant Syndrome Neuroleptic malignant syndrome is an uncommon idiosyncratic reaction to neuroleptic drugs manifested by rigidity, fever, autonomic instability (tachycardia, diaphoresis, and blood pressure abnormalities), and a confusional state. Although high-potency antipsychotics may be more likely to cause the disorder, all antipsychotics are potential offenders. Neuroleptic malignant syndrome is a medical emergency and has a mortality rate as high as 20%. Management includes immediate discontinuation of the antipsychotic medication, hydration, and supportive treatment in an intensive care setting. Anticholinergic medications are not helpful and may worsen the condition by further impairing centrally mediated temperature regulation. Medications such as dantrolene sodium or bromocriptine are sometimes used to relieve the rigidity.

SCHIZOPHRENIA SPECTRUM OF DISORDERS

The schizophrenia spectrum of disorders is listed in **Table 290-4**. Some of the more commonly encountered conditions are discussed in detail below.

Schizophrenia is the most common form of psychosis. It typically involves a wide range of impairments in functioning and may affect all areas of a patient's life, including occupational and social aspects. It usually begins to manifest between the late teens and the mid-30s. Its course is characterized by acute episodes and periods of partial or full remission. It is diagnosed more in men than in women, and the incidence varies significantly based on age, gender, socioeconomic, racial, and geographic factors, with a higher incidence among migrants, urban populations, and ethnic minorities.[30-32] Patients with schizophrenia have high rates of medical comorbidity and concomitant substance abuse.[33,34]

Signs of the disturbance must be present for at least 6 months for a formal diagnosis, and symptoms cannot be attributable to another medical condition or the effects of a substance. Diagnostic criteria are listed in **Table 290-5**.

Delusional disorder is diagnosed in the absence of schizophrenia and involves the presence of one or more delusions for at least 1 month.[35]

TABLE 290-5 Diagnostic Criteria for Schizophrenia[2]

Criterion A*	Other Selected Criteria
Hallucinations	Disturbance present for at least 6 months
Disorganized speech	Significant deficiencies in major areas of function (work, self-care, interpersonal relations)
Delusions	Depression, bipolar disorder, schizoaffective disorder ruled out
Negative symptoms	Not attributable to another medical condition or substance
Grossly disorganized or catatonic behavior	

*Must have two or more criteria and at least one must be delusions or disorganized speech.

The central theme of the *somatic type,* and a potential trigger for an ED visit, is a preoccupation with health and organ function. For example, individuals may be convinced that they have an infestation of insects on their skin or that a part of their body is not functioning.[2]

Schizoaffective disorder is about one third as prevalent as schizophrenia.[36] It is characterized by Criterion A of schizophrenia (see Table 290-5) occurring concurrently with a major mood episode (major depressive or manic). Patients with schizophrenia and schizoaffective disorder have a 5% lifetime risk of suicide, with higher risk in patients with depressive symptoms.[37]

Catatonia may occur in the context of various conditions. Medical conditions associated with catatonia include encephalitis, head trauma, hepatic encephalopathy, and neoplasms. The acute presentation of catatonia often includes stupor, and therefore, patients often have their first clinical contact in the ED. **It is therefore important to recognize that catatonia is frequently associated with an organic cause.**[38]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 291

Eating Disorders

Gemma C.L. Bornick

INTRODUCTION AND EPIDEMIOLOGY

Eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating disorder, are psychological conditions characterized by a pathologic relationship with food that adversely affects psychosocial functioning. Eating disorders can be challenging in the ED because physical manifestations may be subtle and historical features may not be elicited unless a disorder is suspected from medical complications. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* refines the diagnostic criteria of eating disorders from the previous edition (**Table 291-1**).[1]

There are two subtypes of anorexia nervosa: restrictive and binge/purge, with crossover between the two.[2] Restrictive patients minimize their food intake, whereas those with bingeing/purging make up for unacceptable food intake with diuretics, laxatives, enemas, or vomiting. There are also two subtypes of bulimia: purging and nonpurging. Those who purge do so by the above methods; those classified as nonpurging use other compensatory methods such as fasting or excessive exercise. Up to 50% of anorexia patients develop bulimia.[3] Binge eating disorder is characterized by habitual, recurrent binge consumption episodes that cause significant distress. This is distinct from simple episodic overeating and must be both independent of anorexia or bulimia and free of compensatory mechanisms. The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, also defines avoidant/restrictive food intake disorder, pica, and rumination disorder, which are not addressed here.

Anorexia nervosa has an estimated lifetime prevalence of 0.9% in women and 0.3% in men, and median age of onset is 18 years old.[4,5] **Bulimia nervosa** has an estimated lifetime prevalence of 1.5% in women and 0.5% in men, and median age at onset is also 18 years old.[5] **Binge eating disorder** is more common in older individuals and males than both anorexia and bulimia, with a lifetime prevalence of 3.5% in women and 2.0% in men.[4,5]

PATHOPHYSIOLOGY

There is evidence that eating disorders run in families, possibly due to both genetic influences and similar underlying temperaments and behaviors.[6,7] For example, genetic locus (rs4622308) on chromosome 12 is associated with anorexia nervosa.[8] MRI studies detect differences in brain behavior and structure, and some implicate brain regions involved in reward processing.[9-12]

CLINICAL FEATURES

HISTORY

Patients with eating disorders often present to the ED with vague signs and symptoms such as weakness, fatigue, pallor, dizziness, syncope, confusion, bloating, edema, or persistent nausea.[13] Complaints may otherwise be due to medical complications, such as chest pain and hematemesis caused by a Mallory-Weiss tear from purging; palpitations from dysrhythmias; dysmenorrhea from disruption of the hypothalamic-pituitary axis; or fractures from osteoporosis. Depression, anxiety, substance abuse, self-injurious behavior, or suicidality may coexist.[14,15] **Therefore, if an eating disorder is suspected, consider screening for depression and suicidality.**

If clinical suspicion is raised for an eating disorder based on complaint cluster, physical examination, or family report, explore a more focused history. Important data points to elicit include eating and dieting behavior; desire for weight loss; typical daily dietary intake; presence of calorie counting; compensatory exercise behavior; guilt patterns following eating; menstruation pattern; and use of over-the-counter dietary supplements or laxative agents. Certain sensitive history points may be difficult to elicit in the ED, such as early childhood GI issues or picky eating or obesity, self-esteem issues, societal thinness pressures, teasing, propensity toward perfectionism, or sexual abuse. Certain physical activities raise risk for eating disorders, such as gymnastics, ballet and other dance, wrestling, swimming, and cross-country running.[16-18] Because eating disorders are characterized by denial of symptoms and behaviors, take a nonjudgmental approach to encourage trust and truthful disclosure.[14]

PHYSICAL EXAMINATION

Patients with **anorexia** are typically easily identifiable based on a very thin body habitus. Other signs include hypotension (resting or orthostatic), bradycardia or tachydysrhythmia, heart murmur and S_2 "click" of mitral valve prolapse, or hypothermia. Patients may also exhibit signs of vitamin deficiencies such as brittle, flaking, or ridged nails (nonspecific malnutrition); stomatitis or cheilitis (B vitamin deficiency); or perifollicular petechiae (scurvy). They may also develop fine, long hair on the arms and face, acral cyanosis (impaired thermoregulation), and/or pretibial edema secondary to malnutrition.[14] Nonsuicidal self-injury is also common, and stigmata of cutting, picking, burning, or bruising may be present.[19]

Patients with **bulimia or binge eating disorder** can be difficult to detect in the ED because they tend to be normal weight or overweight. **Consider eating disorder diagnoses in the presence of other physical indicators, even in normal weight or overweight patients.** Self-induced vomiting can cause painless hypertrophy of the parotid glands (sialadenosis), dental erosion, and trauma or callus formation to the dorsal hands (**Russell's sign**),[20] as well as pharyngeal erythema or abrasions, gingivitis, facial petechiae or subconjunctival hemorrhage, and halitosis. Laxative abuse may cause peripheral edema, anal fissures, hemorrhoids, perianal dermatitis, and rectal bleeding. Patients with binge eating disorder will likely have no abnormalities apparent on physical examination.

DISEASE COMPLICATIONS

Eating disorders can be life threatening. Death by suicide is six and four times more common in patients with anorexia and bulimia, respectively, than in the general population.[21] Medical complications are typically more severe in anorexia than in bulimia or binge eating. Complications of anorexia are generally directly due to malnutrition[22] and can account for a large proportion of deaths.[23] Bulimia medical complications are usually related to method and frequency of purging and are often the result of chemical derangements or structural damage to the GI tract.[24] Patients with binge eating disorder describe significantly

TABLE 291-1 *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, Criteria for Eating Disorders

Anorexia Nervosa	Bulimia Nervosa	Binge Eating Disorder
Restriction of caloric intake relative to requirements, leading to a lower than expected body weight in the context of age, sex, development, and physical health (<85% predicted)	Recurrent episodes of binge eating characterized by both: • Eating in a discrete time period an amount of food that is larger than most people would eat in the same period under the same circumstance • A feeling of lack of control over eating during an episode	Recurrent episodes of binge eating characterized by both: • Eating in a discrete time period an amount of food that is larger than most people would eat in the same period of time under the same circumstance • A feeling of lack of control over eating during an episode
Fear of weight gain or becoming fat, despite lower than predicted body weight	Recurrent, inappropriate compensatory behaviors to prevent weight gain including self-induced emesis; abuse of laxatives, diuretics, or other medications; caloric restriction; or excessive exercise	The episodes are associated with three of the following: • Eating much more quickly than normal • Eating until feeling uncomfortably full or overfull • Eating large amounts of food even when not feeling hungry • Eating alone because of embarrassment about how much one is eating • Feeling disgusted, depressed, or guilty afterward
Derangement in the way the patient's body weight or appearance is experienced, undue effects of body weight on self-evaluation, or denial of the dangerousness of the current low body weight	Bingeing and purging at least 1 time a week for 3 weeks	The patient exhibits marked distress regarding binge eating.
	Self-evaluation is unduly influenced by body weight and appearance	The binge eating occurs at least 1 time a week for 3 months.
	The disturbance does not occur exclusively during episodes of anorexia	The binge eating is not associated with inappropriate compensatory behavior and does not occur exclusively during the course of anorexia, bulimia, or avoidant/restrictive food intake disorder.

Source: Data from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5th ed. Washington, DC: American Psychiatric Association; 2013.

more somatic symptoms than the general population, but true medical complications are rare.[25]

Cardiopulmonary Complications Among the most deadly of the eating disorder complications in anorexia are structural and functional changes to the cardiovascular system.[26] Malnutrition causes decreased cardiac muscle mass and increased vagal tone. This leads to decreased contractility and cardiac output and, therefore, results in hypotension, bradycardia, and orthostasis. Relative decreases in cardiac muscle mass can lead to the development of mitral valve prolapse.[27] Rarely, patients with anorexia nervosa can develop myocardial fibrosis[28] or pericardial effusion, which in a few cases has led to cardiac tamponade requiring pericardiocentesis.[29] Syrup of ipecac, used as an emetogenic, is directly cardiotoxic and can cause an irreversible cardiomyopathy. Prolongation of the QT interval on ECG has been described, but this is rare in the absence of electrolyte disturbance or congenital long QT syndrome and should prompt evaluation for these conditions.[22] Increased QT dispersion (difference between maximum and minimum QT intervals seen in each lead of a single ECG) indicates heterogeneous ventricular depolarization and is a marker for increased arrhythmic risk.[30] QT derangements as a result of eating disorders are reversed by adequate refeeding. QT resolution is associated with normalization of heart rate, heart rate variability, and exercise tolerance[31] and, therefore, has been used as a marker to guide rehabilitation.[32] Most other cardiac sequelae are also reversible with appropriate weight gain, but there is increased risk of cardiac complications during the first week of refeeding after severe nutrient depletion.[31,33] Cardiac complications are only rarely seen in patients with bulimia nervosa or binge eating disorder.[24,34]

Pulmonary Complications Anorexia can lead to weakness of respiratory muscles, decreased pulmonary and aerobic capacity,[35,36] and aspiration due to pharyngeal muscle weakness. Aspiration pneumonitis and subsequent pneumonia can occur as a result of pharyngeal muscle weakness and from chronic purging.[37] There are case reports of pneumothorax and pneumomediastinum.[38] Patients with bulimia and binge eating disorder are often smokers and may have pulmonary complications related to smoking.[39]

GI Complications Patients with anorexia are at increased risk of constipation, gastroparesis, acute gastric dilatation, gastroesophageal reflux, and acute pancreatitis.[14,40,41] Gastroesophageal reflux and laryngopharyngeal reflux commonly occur in patients with bulimia or purging-type anorexia and may result in hoarseness or dysphagia.[14,42] Forceful vomiting can result in Mallory-Weiss tears or, rarely, Boerhaave syndrome.[34] Chronic stimulant laxative abuse can lead to development of ileus, rectal prolapse, melanosis coli, or the cathartic colon syndrome.[43-45]

Nutritional Complications The proportion of eating disorder patients with vitamin deficiencies is difficult to determine because many take supplements. Decreased bone mineral density and skeletal fragility are common but are not associated with decreased vitamin D levels.[46] Iron and vitamin B_{12} deficiencies can lead to anemia in severely food-restrictive patients but are uncommon. Skin erythema and pruritus with sun exposure, glossitis, epidermal desquamation, and diarrhea should raise suspicion of pellagra.[47] Confusion, confabulation, ataxia, ophthalmoplegia, and/or nystagmus suggest Wernicke-Korsakoff encephalopathy. Other vitamin deficiencies reported in association with eating disorders include wet beriberi and scurvy, although these are extremely rare.[48,49] Poor nutritional state can result in hypoplastic or aplastic bone marrow[50] and resultant cytopenias.[51]

Renal and Electrolyte Complications Electrolyte derangements and other lab abnormalities are more common in purging-type eating disorders. Patients with restrictive-type anorexia may not demonstrate any laboratory abnormalities. Frequent vomiting can result in metabolic alkalosis, hyponatremia, and hypochloremia. Laxative and diuretic abuse and vomiting can lead to potassium and magnesium depletion. Hyponatremia may also develop in patients who abuse diuretics. Signs of starvation ketosis may be evident. In patients with very severe anorexia, hypoglycemia and hypophosphatemia can develop.[14,22,52,53]

Refeeding following prolonged nutrient depletion can also cause electrolyte abnormalities, most commonly hypokalemia, hypophosphatemia, and hypomagnesemia, due to redistribution of electrolytes from the extracellular to the intracellular space triggered by insulin release and from depletion of phosphorus during protein synthesis. This can lead to arrhythmias, congestive heart failure, pericardial effusions, and cardiac arrest.[33]

Endocrine Complications Profound food restriction affects the hypothalamic-pituitary axis. Low levels of gonadotropins, loss of the normal pulsatile waves of luteinizing hormone, and estrogen deficiency lead to hypothalamic amenorrhea.[54] Anorexia is also associated with the **"euthyroid sick syndrome"** in which thyroid-stimulating hormone is normal or slightly low, T_3 is low, and sometimes T_4 levels are also decreased. Thyroid deficiencies likely contribute to the bradycardia, orthostasis, and hypothermia in anorexia. High cortisol levels and low levels of insulin-like growth factor 1 (somatomedin C), T_3, estradiol, and testosterone contribute to loss of bone mass.[55] Refeeding and recovery from illness do not fully return bone mass to normal levels, and patients with anorexia remain at an increased risk of fracture for many years following initial diagnosis.[56] The endocrine effects of bulimia and binge eating disorder are less well studied. Bulimia is associated with both

TABLE 291-2 SCOFF Questionnaire

- Do you make yourself sick because you feel uncomfortably full?
- Do you worry you have lost control over how much you eat?
- Have you recently lost more than 1 stone (14 lb) in a 3-month period?
- Do you believe yourself to be fat when others say you are too thin?
- Would you say that food dominates your life?

Note: A score of 2 or more indicates a probable eating disorder with a sensitivity of 84.6% and a specificity of 89.6%.

Source: Reproduced with permission from Morgan JF, Reid F, Lacey JH: The SCOFF questionnaire: a new screening tool for eating disorders. *West J Med* 2000;172(3):164-165.

type 1 and type 2 diabetes mellitus. There is some evidence to support an increased risk of dyslipidemia, glucose dysregulation, and diabetes in binge eating disorder.[25,57] Repeated vomiting can lead to metabolic alkalosis, hypokalemia, and increased aldosterone secretion—a cluster described as pseudo-Bartter syndrome.[58]

DIAGNOSIS

Diagnostic criteria are outlined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, but screening tools are more practical for presumptive diagnosis in the ED. The **SCOFF Questionnaire** (**Table 291-2**) is useful for screening for anorexia and bulimia in a brief encounter and can be remembered by its acronym: Sick, Control, One stone, Fat, Food.[59] Other screening tools, such as the Eating Disorder Diagnostic Scale or the Eating Attitudes Test, are more extensive and are more useful in a primary care setting.[60,61] The Questionnaire on Eating and Weight Patterns–Revised is specific for binge eating disorder.[62]

It is very important to search for, diagnose, and treat organic pathology as part of the assessment of a patient with a potential eating disorder (**Table 291-3**).

LABORATORY TESTING

Initial testing should include an ECG and a full chemistry panel including magnesium, calcium, and phosphorus; CBC; urinalysis; pregnancy test; hepatic function panel; serum albumin; lipase and amylase; and thyroid-stimulating hormone.[63]

TABLE 291-3 Differential Diagnosis of New-Onset Eating Disorders

Endocrine	Adrenal insufficiency
	Hyperthyroidism
	Diabetes
GI	Hepatitis
	Pancreatitis
	Celiac disease
	Inflammatory bowel disease
	Superior mesenteric artery syndrome
Infectious disease	Mononucleosis
	Human immunodeficiency virus
	Tuberculosis
Cancer	Nervous system malignancy
	Ovarian malignancy
	Intra-abdominal malignancy
Pregnancy	Hyperemesis gravidarum
Psychiatric	Substance abuse
	Major depressive disorder
	Bipolar disorder
	Schizophrenia
Inborn error of metabolism	Mitochondrial disorders
	Enzyme deficiency

TABLE 291-4 Society of Adolescent Medicine Criteria for Hospital Admission

Anorexia Nervosa	Bulimia Nervosa
Body weight <75% of ideal for age, sex, and height	Potassium <3.2 mmol/L
Daytime heart rate <50 beats/min or nighttime heart rate <45 beats/min	Chloride <88 mmol/L
Body fat <10% of body weight	Esophageal trauma and hematemesis
Dehydration	Vomiting unresponsive to antiemetics
Cardiac arrhythmia including QT prolongation	Dehydration
Temperature <96°F	Cardiac arrhythmia including QT prolongation
Orthostasis and syncope	Temperature <96°F
Acute psychiatric emergencies such as hallucinations or suicidality	Orthostasis and syncope
Systolic blood pressure <90 mm Hg	Acute psychiatric emergencies such as hallucinations or suicidality
Ongoing weight loss despite outpatient treatment	Ongoing purging despite outpatient treatment

IMAGING

Obtain imaging only to rule out an underlying organic cause of presenting symptoms or to exclude medical complications. Nonspecific radiographic findings in patients with anorexia may include decreased muscle mass, paucity of subcutaneous fat, mild small bowel dilatation,[63] and osteoporosis.[65] There are no specific radiographic findings diagnostic of binge eating disorder or bulimia, but a swallowed toothbrush or similar item suggests purging by induced vomiting.[66]

TREATMENT AND DISPOSITION

The ED treatment of eating disorders is limited to stabilization of urgent medical complications, followed by hospital admission or outpatient referral to a mental health specialist. **Tables 291-4** and **291-5** list guidelines for hospital admission.[63,67] Most medical complications of anorexia nervosa can be treated in an outpatient setting if the patient's weight is >70% of ideal body weight or body mass index is >15 kg/m^2.[52]

TABLE 291-5 American Psychiatric Association Criteria for Hospital Admission

Medical status	Adults: heart rate <40 beats/min, blood pressure <90/60 mm Hg, glucose <60 milligrams/dL (<3.3 mmol/L), potassium <3 mEq/L, temperature <97.0°F, end-organ compromise requiring acute treatment, poorly controlled diabetes Children: heart rate near 40 beats/min, orthostasis, blood pressure <80/50 mm Hg, hypokalemia, hypophosphatemia, hypomagnesemia
Suicidality	Specific plan with high lethality or intent
Weight	Generally <85% of ideal body weight or acute weight change with food refusal
Motivation to recover	Very poor motivation; patient preoccupied with intrusive repetitive thoughts and/or uncooperative with treatment
Comorbid disorders	Any existing psychiatric disorder requiring hospitalization
Structure required	Needs supervision to ensure caloric intake, prevention of exercise, or prevention of purging behaviors
Environmental	Severe family conflict or absence of family, absence of appropriate outpatient resources in patient's geographic region

Long-term treatment of all eating disorders requires a multidisciplinary approach, including psychotherapy, dietary interventions, and pharmacotherapy in certain cases.[63] If pharmacotherapy is indicated, it should be initiated by a psychiatrist or primary care provider.

SPECIAL POPULATIONS

PREGNANT WOMEN

Pregnancy can be a stressful time for a woman with an eating disorder, particularly with respect to maintaining adequate weight gain. There are conflicting data on whether the presence of eating disorders increases the risk of complications. The broadest study of its kind revealed that the majority of patients with anorexia and bulimia have normal pregnancies and healthy babies with, however, an increased risk of birth by cesarean section and an increased risk of postpartum depression. These differences remained between groups who had active symptoms and those with history of an eating disorder who were asymptomatic during pregnancy.[68]

MEN

Do not neglect the possibility of eating disorders in men. Men may account for between 10% and 25% of cases of anorexia and bulimia,[69] and binge eating is more prevalent in men than both anorexia and bulimia. The exact proportion of men with eating disorders is unknown because men are less likely to be diagnosed. Eating disorders in males are typically characterized by the drive to add muscle bulk and lean mass and are often associated with antecedent obesity, athletic performance concerns, bullying, and occasionally (but not always) sexual abuse. Men with eating disorders are more likely to abuse steroids and growth hormones, particularly when muscle dysmorphia is present.[70]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 292

Substance Use Disorders

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INTRODUCTION AND EPIDEMIOLOGY

In EDs around the world, on every shift, patients present for medical conditions related to the consequences of unhealthy drinking or drug use. The World Health Organization reported in 2012 that 5.9% of all global deaths (3.3 million people) were attributed to the consumption of alcohol.[1] From 2006 to 2014, ED alcohol-related visits increased in the United States from 827,100 to 1.46 million.[2,3] In 2015, an estimated 29.5 million people, or 0.6% of the global adult population, qualified for a drug use disorder, yet fewer than 16% were afforded treatment. The majority of worldwide illicit drug–related deaths (190,000) were attributed to opioids. In 2016, the United States accounted for more than 25% of these deaths.[4] U.S. ED drug-related visits doubled from 2005 to 2014,[5] fueled by increased supply and misuse of prescription opioids; social and economic determinants; and the low cost and easy availability of heroin, synthetic fentanyl, and analogs.[6] Between July 2016 and September 2017, U.S. opioid overdose ED visits among those aged 11 years old and older increased 29.7% overall, with significant increases across all demographics examined.[7] It is noteworthy that "available data suggest that nonmedical prescription-opioid use is neither necessary nor sufficient for the initiation of heroin use and that other factors are contributing to the increase in the rate of heroin use and related mortality."[8]

TABLE 292-1 Nonstigmatizing Substance Use Disorder Language

Avoid These Terms	Use These Instead
Addict, user, drug abuser, junkie	Person with opioid use disorder or person with opioid addiction, patient
Addicted baby	Baby born with neonatal abstinence syndrome
Opioid abuse or opioid dependence	Opioid use disorder
Problem	Disease
Habit	Drug addiction
Clean or dirty urine test	Negative or positive urine drug test
Opioid substitution or replacement therapy	Opioid agonist treatment
Relapse	Return to use
Treatment failure	Treatment attempt
Being clean	Being in remission or recovery

Source: Data adapted from www.thenationalcouncil.org/consulting-best-practices/national-council-shareables. Accessed June 27, 2018.

The scope of substance use disorders (SUDs) includes unhealthy use of alcohol, use of illicit drugs, and nonmedical use of prescription drugs. Severe SUDs resemble asthma, diabetes, hypertension, and other chronic diseases in that they have genetic components and patients have problems with adherence to medication, loss to follow-up, exacerbations, repeat visits to the ED, and hospital admissions.[9] Nevertheless, only a small fraction of those needing alcohol or drug treatment actually receive indicated therapy, compared with a much higher fraction of patients with chronic medical conditions.[10] This understanding of addiction as a chronic, relapsing medical condition requires us to shift our focus toward providing linkage to ongoing integrated treatment and community support services as an addition to acute care.[11] The gap in SUD treatment also reflects the impact of social stigma on disparities in availability, accessibility, and affordability of services. Language is powerful, especially when talking about substance use because stigma perpetuates negative perceptions, discourages use of treatment services, and contributes to further substance use. Words do matter and the language used to discuss addiction is important to decrease stigma (**Table 292-1**).[12-14]

UNHEALTHY ALCOHOL USE

The term *unhealthy alcohol use* describes a spectrum of alcohol consumption ranging from "risky" or hazardous use (no consequences experienced), to harmful use (experience of consequences), to what was previously called *alcohol dependence* but is now termed mild, moderate, or severe *alcohol use disorders* in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition classification.[15] The National Institute on Alcohol Abuse and Alcoholism defines low-risk drinking as follows: for men, no more than 14 drinks per week and no more than four drinks over a 2-hour occasion. Women of all ages and men >65 years old are advised to drink no more than seven drinks per week and no more than three drinks over a 2-hour occasion, because of gender and age differences in volume distribution and concentrations of alcohol dehydrogenase in the liver. Binge drinking (drinking too much too fast) is alcohol consumption that results in a blood alcohol level over the U.S. legal limit of 0.08 gram/dL, which for the average male is the result of more than four drinks in 2 hours and for the average female is more than three drinks in 2 hours. Nearly 32 million adults engage in extreme binge drinking, described as consuming two or more times these thresholds.[16] Abstinence is advised for pregnant women and underage drinkers, and a lower limit or abstinence is advised for patients with chronic conditions exacerbated by alcohol or who are taking medications with an alcohol interaction.[17]

Those who begin drinking before age 15 have a fourfold increased risk of developing dependence than those who begin drinking later.[18] Early onset also predicts adverse health status.[1] Underage drinking and drug use have a profound impact on the developing nervous system,

Alcohol Screening in the ED (Revised and approved by the American College of Emergency Physicians [ACEP] Board of Directors April 2011. Reaffirmed January 2017.)

"ACEP believes alcohol abuse is a significant public health problem. Further, ACEP believes emergency medical professionals are positioned and qualified to mitigate the consequences of alcohol abuse through screening programs, brief intervention, and referral to treatment. ACEP encourages wide availability of resources necessary to address the needs of patients with alcohol-related problems and those at risk for them."

FIGURE 292-1. American College of Emergency Physicians policy on alcohol screening in the ED.

so early intervention is needed to mitigate life-altering consequences.[19] Gaps between women and men are narrowing for prevalence, frequency, and intensity of drinking; early-onset drinking; and driving under the influence.[16,20] Women who drink are more likely to experience medical complications of alcohol use including liver injury and cirrhosis, some cancers, cognitive dysfunction, and cardiovascular complications such as stroke, hypertension, and cardiomyopathy.[21-24] National survey data demonstrate an upward trend in drinking among U.S. adults aged 60 and older, particularly among women who were found to have increased rates of binge drinking.[25] The ED is an important site for alcohol screening **(Figure 292-1).**

SUBSTANCE USE DISORDERS

The *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition, groups *substance abuse* and *dependence* into categories from mild to severe SUD.[26] The diagnosis of SUD requires two or more of the following 11 criteria: (1) tolerance; (2) withdrawal; (3) recurrent use in greater quantities or for a greater duration than intended; (4) failed attempts to cut back or quit substance use; (5) spending a great deal of time obtaining, using, or recovering from the substance; (6) persistent or recurrent use despite physical and or psychological consequences; (7) giving up important activities in order to use; (8) failure to fulfill responsibilities in work, school, and/or home because of recurrent use; (9) recurrent use resulting in physically hazardous behavior, such as driving under the influence; (10) persistent use despite social or interpersonal problems; and (11) craving alcohol or other drugs. Severity is based on the number of criteria met: two or three of the criteria constitute mild SUD, four to five constitute moderate SUD, and six or more constitute severe SUD.[26] More than 20 million Americans aged 12 and older[27] and 110 million people worldwide[28] meet criteria for an SUD.

SCREENING, BRIEF INTERVENTION, AND REFERRAL TO TREATMENT

Screening, brief intervention, and referral to treatment techniques were established in 2003 by the U.S. Substance Abuse and Mental Health Services Administration to address the gap in preventive services for unhealthy alcohol and drug use, to stem the progression to addiction by early intervention, and to address the treatment gap by promoting help seeking and facilitating access to addiction treatment and recovery support services. Screening, brief intervention, and referral to treatment have been associated with short-term benefits and reduction in cost and ED utilization.[29-43]

SCREENING FOR UNHEALTHY DRINKING AND DRUG USE

Brief standardized screening questions have a higher sensitivity for identifying heavy and dependent drinkers and illicit drug–using patients than noting the smell of alcohol on breath, patient self-report, or profiling based on demographics or presenting complaint. Brief screening instruments are easy to administer and may help match an individual to the most appropriate treatment resource. Validated brief screening questions useful for ED providers include the National Institute on Alcohol Abuse and Alcoholism Quantity/Frequency Questions[17] and the Single Screening Questions for Alcohol[44] and Drug Use (**Table 292-2**).[45] Questions can be integrated into the triage electronic medical record.[46] Screening for heavy smoking is also important since there is an association between heavy smoking and multiple drug use.[15] An alternative approach is to implement the National Institute on Drug Abuse–Modified Alcohol, Smoking and Substance Involvement Screening Test instrument into ED practice if additional ED support personnel are available (e.g., health promotion advocate, alcohol and drug counselors, recovery coaches, trained medical workers, behavioral health or social workers).[33,47-49] The National Institute on Drug Abuse–Modified Alcohol, Smoking and Substance Involvement Screening Test instrument was developed to guide clinicians through a series of questions to identify risky substance use in their adult patients. Final scores of 4 to 26 on the instrument stratify risk and encourage clinicians to advise, assess, and assist patients with follow-up to primary care; a score of greater than 26 indicates the need for referrals to SUD specialty treatment.

As part of the social history, emergency care providers can integrate questions that reflect their concern for the patient's overall health and safety. SUD screening questions could be embedded among other preventive health issues to reduce stigma and patient resistance and encourage veracity and trust. Questions asked in a nonjudgmental, matter-of-fact fashion are well accepted by patients.[50]

Patients who are above the "low-risk" drinking guidelines could benefit from a brief intervention and primary care referral to motivate reducing consumption. For moderate to severe alcohol use, provide referral to a specialized treatment center.

THE BRIEF NEGOTIATED INTERVIEW FOR SUBSTANCE USE INTERVENTION

The *brief negotiated interview*[29,30,36,37,51,52] has four key elements: establish rapport, provide feedback, enhance motivation, and negotiate a plan of action. The first principle of promoting health behavior change is that the argument for change needs to come from the patient, not the healthcare provider. Begin a respectful, nonjudgmental conversation by recognizing the patient as the decision maker and asking the patient's permission to talk about alcohol or drug use and health concerns. An important opportunity for early intervention may occur during an ED visit for acute medical care or a social or criminal justice crisis.[53] The entire interaction often can be accomplished in 5 to 7 minutes,[51] and the conversation can take place at any point in care, such as at discharge or while suturing or casting or performing an incision and drainage of an abscess.

The brief negotiated interview algorithm incorporates key elements of motivational interviewing: open-ended questions, affirmations, reflective listening, and summaries (**Figure 292-2**). (See Videos: Brief Negotiated Interview and Active Referral to Treatment.)

TABLE 292-2 Single Screening Questions

"Would it be okay with you if I ask you some very personal questions that I ask all my patients to improve the care I give? You do not have to answer them if you are uncomfortable."

- Single Screening Question for Alcohol: "Do you drink beer, wine, liquor, or distilled spirits? How many times in the past year have you had 5 or more (for men)/4 or more (for women) drinks in a day?"[6,44] Clarify that a standard drink is 1.5 oz of spirits, 6 oz of wine, and 12 oz of beer.[6]
- Single Screening Question for Drug Use: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" You can add something like ". . . for instance, for the experience or feeling it gives you?"[45]

BNI Steps	Dialogue/Procedures
1. Raise subject	Hello, I am _____. Would you mind taking a few minutes to talk with me about your alcohol use? <<PAUSE and LISTEN>>
2. Provide feedback	
• Review screen	From what I understand you are drinking [insert screening data]… We know that drinking above certain levels can cause problems, such as [insert facts]…I am concerned about your drinking.
• Make connection	What connection (if any) do you see between your drinking and this ED visit?
	If pt sees connection: reiterate what pt has said
	If pt does not see connection: make one using facts
• Show NIAAA guidelines and norms	These are what we consider the upper limits of low risk drinking for your age and sex. By low risk we mean that you would be less likely to experience illness or injury if you stayed within these guidelines.
3. Enhance motivation	
• Readiness to change	[Show readiness ruler] On a scale from 1–10, how ready are you to change any aspect of your drinking?
• Develop discrepancy	*If patient says:*
	≥2 ask Why did you choose that number and not a lower one?
• Explore pros and cons	*<2 or resistance ask pros and cons*
	Help me to understand what you enjoy about drinking? <<PAUSE AND LISTEN>>
	Now tell me what you enjoy less about drinking. <<PAUSE AND LISTEN>>
• Use reflective listening	On the one hand you said, <<RESTATE PROS>>
	On the other hand you said, <<RESTATE CONS>>
	So tell me, where does this leave you?
4. Negotiate and advise	
• Negotiate goal	What's the next step?
• Give advice	What do you think you can do to stay within the safe drinking guidelines? If you can stay within these limits you will be less likely to experience [further] illness or injury related to alcohol use.
• Summarize	This is what I've heard you say…Here is a drinking agreement I would like you to fill out, reinforcing your new drinking goals. This is really an agreement between you and yourself.
	Provide drinking agreement [pt keeps 1 copy]
• Provide handouts and suggest PC f/u	Suggest Primary Care f/u to discuss drinking level/pattern
• Thank patient	Thank patient for his/her time

FIGURE 292-2. Screening, brief intervention, and referral to treatment algorithm as taught in the standardized ED curriculum. BNI = brief negotiated interview; f/u = follow-up; NIAAA = National Institute on Alcohol Abuse and Alcoholism; PC = primary care; pt = patient. [Reproduced with permission from D'Onofrio G, Pantalon MV, Degutis LC, Fiellin DA, O'connor PG: Development and implementation of an emergency practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. *Acad Emerg Med* 12: 249, 2005. Copyright John Wiley & Sons.]

Establish Rapport *Establish rapport and ask the patient's permission to discuss his or her use of alcohol and drugs.* Establish an atmosphere of trust through respect. The patient is not the problem (a stigmatizing approach) but is a person who has a problem. Instead of "What's wrong with our patient?", an alternative approach based on compassionate curiosity would lead the clinician to inquire, "What's happening with our patient?"

Provide Feedback Elicit the patient's thoughts on low-risk or safe alcohol and drug use. Provide information by reviewing current drinking and drug use and guidelines. Express concern that by drinking in excess of safe limits, the patient is at risk for injury or illness. Elicit/solicit the reaction to the guidelines. Ask patients to make a connection between alcohol and/or drug use and quality of life; possible negative consequences related to health, family, legal system, and employment; and, if applicable, the current ED visit or injury. If appropriate, discuss physical dependence, withdrawal, and the cycle of behaviors to obtain more alcohol and/or drugs.

Enhance Motivation *Assess readiness to change on a readiness ruler.* Ask patients to mark on a drawing of a ruler, with a scale of 1 to 10, how ready they are to change, cut back, or quit their alcohol and/or drug use. If they say 5, give affirmation and say that "You are 50% on the way," and ask, "Tell me why you didn't mark a 2 or 3 or a lesser number?" Here is when we try to elicit change talk or reasons and motivation for change. Repeat what the patient has shared with you and follow up with, "It sounds like you have some important reasons to change, so what small steps can you take to stay healthy and safe?" If the patient shows resistance to the readiness ruler or the score is <2, then *explore the pros and cons of current use. A discussion of the pros and cons* promotes self-questioning and draws attention to the patient's own reasons for tipping the scale toward change. Use open-ended questions such as, "Help me to understand (or see it through your eyes) what you like and dislike about your use of alcohol?" Explore the importance to the patient of the issues that emerge. *Use reflective listening* to summarize what you think the patient said to verify your interpretation, for example: "On the one hand, you like the taste and how it helps you to loosen up and forget your problems, and it

is something to do when you're bored. On the other hand, you said you don't like how you feel the next day and that wrecking your car in a crash and ending up in the ED is no fun. You also told me you are spending a lot of money on drinking and are concerned about not meeting some responsibilities. So then, in the balance, where does that leave you?"

Negotiate and Advise Negotiate an action plan. Explore with patients what life might be like if they made these changes. What would be the benefits of change, and what would be the challenges? Add the steps they would need to take to address challenges and explore and support confidence in ability to make a change. *Offer a menu of options and resources* to assist with the change plan, including, if appropriate, referrals to primary care providers and SUD treatment. *Document the plan.* Ask the patient to state in her or his own words the agreed-on steps and document them on a piece of paper or discharge instructions as a reminder of goals (a prescription for change). Reflect back to the patient and reinforce reasons for, and steps toward, change. End the conversation by thanking the patient for being honest and spending time talking with you.

Afterward, take a minute for self-assessment using the FLOAT mnemonic: To what degree did you provide *f*eedback? Did you *l*isten carefully? Did you ask *o*pen-ended questions? Did you offer *a*ffirmations and *a*lternatives? Did the patient have enough *t*ime to talk, or did you do the majority of talking? Did you negotiate a concrete action plan?

REFERRAL TO TREATMENT

Factors that often accompany unhealthy alcohol and drug use, such as psychiatric illness, trauma, homelessness, low level of health literacy, lack of insurance coverage or ability to pay for medications, criminal justice involvement, absence of family support, and limited availability of treatment and recovery support services, make patient management and disposition challenging.

Effective linkage to SUD treatment can be facilitated by training ED staff in screening, brief intervention, and referral to treatment. Develop an ED collaborative team with staff such as behavioral health and social workers, care managers, psychologists, nurse specialists, peer alcohol and drug counselors, volunteers from Alcoholics Anonymous or Narcotics Anonymous, health promotion advocates, or recovery coaches to enhance the efforts of existing staff and motivate and assist patients with identifying and accessing treatment options.[33,47-49,52]

Build and maintain a referral and resource service network.[33,47,52] Current practice in most EDs is to provide patients and family members with a list of detoxification or treatment resources in the community. The Center for Substance Abuse Treatment at the U.S. Department of Health and Human Services has an online resource locator (http://dasis3.samhsa.gov). The resource list and referral networks ideally would include a continuum of specialized treatment facilities for patients with co-occurring medical, traumatic, and psychiatric illnesses; inpatient and outpatient detoxification, acupuncture, and medication for addiction treatment such as methadone maintenance programs, buprenorphine, and oral and IM naltrexone for opioid and alcohol addiction; outpatient individual and group counseling; intensive outpatient or partial hospitalization; sober housing and residential treatment communities; Alcoholics Anonymous and Narcotics Anonymous meetings; and programs focused on the needs of women, culture-specific programs, and programs designed for gay, lesbian, and transgender clients.

If patients are not ready to enter specialized treatment or attend Alcoholics Anonymous or Narcotics Anonymous, then try to provide information and negotiate a safety plan such as the identification of a designated driver or use of a taxicab when drinking heavily or avoiding drinking while taking medications. The injection drug user who is not ready to accept a treatment referral may accept testing for human immunodeficiency virus or hepatitis C virus, condoms, a referral to a syringe exchange program, or other harm reduction strategies. The patient with opioid use disorder, heroin or fentanyl use, or a recent opioid overdose would benefit from overdose education, provision of naloxone through direct distribution or prescription, and a safe discharge plan that includes engaging the patient's social support network and linkage to addiction treatment. Opioid agonist therapy, also known as medication-assisted treatment, with buprenorphine or methadone is vital to reduce mortality among patients with opioid use disorder.[54]

THE MEDICAL EVALUATION

EDs often function as sources for the medical evaluation before patient transfer to a substance or psychiatric treatment facility. There is considerable variability in the levels of medical care provided in such facilities, ranging from facilities that manage an array of chronic health problems to those with minimal nursing support only for very stable patients. Medical evaluation means that the patient does not have a medical emergency or acute medical condition requiring hospitalization or preventing addiction treatment. Patients with mild or moderate uncomplicated alcohol withdrawal that responds well to initial ED treatment (i.e., those with no trauma or major medical comorbidities, with no suicidal or homicidal ideation or a seizure disorder) can be managed successfully in a detoxification unit.

The criteria for placement in a detoxification unit are very similar to those for safe discharge and include the following: patients are stable (in the short term rather than long term) and ambulatory, can take oral medications, and are not suicidal or likely to seize. Patients on medications (including buprenorphine) should bring them to the treatment facility or be given prescriptions or provided with several doses. Stable patients with dual diagnoses who are not suicidal or acutely psychotic can be medically cleared for transfer, as long as they have a supply of current psychiatric and nonpsychiatric medications and can be expected to take their medications correctly and reliably. Because detoxification from opioids can place patients at high risk for opioid overdose once discharged because of loss of tolerance, opioid overdose education and provision of take-home naloxone are critically important.

PHARMACOLOGIC MANAGEMENT FOR ALCOHOL, OPIOID, AND SEDATIVE USE DISORDERS

A large body of evidence supports the efficacy of pharmacologic interventions for the treatment of alcohol, opioid, and sedative use disorders. Management of alcohol, opioid, and sedative intoxication; overdose; and withdrawal syndromes is covered in chapters dedicated to each substance. Pharmacologic management of individuals with moderate to severe alcohol, opioid, and sedative use disorders is discussed here. Many of these treatments will not be typically initiated in the ED, but knowledge of their existence and effectiveness is important for the ED provider to understand both when caring for patients who are prescribed these medications and in providing referrals for medical management to patients with SUDs.

ALCOHOL USE DISORDER MANAGEMENT

Medications for the treatment of alcohol use disorder include alcohol antagonist agents, such as disulfiram (Antabuse®), and medications that directly reduce alcohol consumption, including acamprosate (Campral®), oral naltrexone, and long-acting injectable naltrexone (Vivitrol®). **Disulfiram** is an oral medication that irreversibly binds to and inhibits alcohol dehydrogenase, causing the unpleasant disulfiram-ethanol reaction, which can include nausea, vomiting, diaphoresis, flushing, and tachycardia, the avoidance of which serves as a deterrent for the consumption of alcohol.[54,55] **Acamprosate**, an amino acid derivative that increases γ-aminobutyric acid transmission, was previously found to be effective in reducing return to alcohol use in a number of U.S. and European studies, but did not show efficacy in a large multicenter trial.[56] In the Combined Pharmacotherapies and Behavioral Interventions study, a large prospective multisite study investigating the effect of combinations of medications and behavioral therapies on alcohol use disorder, acamprosate showed no significant effect on drinking versus placebo, either by itself or with any combination of naltrexone, cognitive behavior therapy, or both.[57]

Naltrexone, an opioid receptor antagonist with no intrinsic agonist activity, is hypothesized to lead to reduce alcohol consumption by indirectly affecting the dopaminergic reward pathway through effects on the μ opioid receptor.[55] Early studies reported that oral naltrexone, in conjunction with behavioral intervention, led to lower reports of craving, fewer drinks and drinking days, and fewer relapses; more recent systematic reviews report that naltrexone is effective at reducing return

to heavy drinking and the amount of alcohol consumed.[56,58] A long-acting IM naltrexone injection was approved by the U.S. Food and Drug Administration in 2006 and can decrease heavy drinking days while avoiding the challenges of taking a daily medication.[59] Importantly, these medications are not mutually exclusive to each other, as multiple studies have shown improved outcomes in patients taking a combination of medications for alcohol use disorder, as well as medications augmented with behavioral or psychosocial interventions.[56,57]

OPIOID USE DISORDER MANAGEMENT

A substantial body of literature supports medications for addiction treatment or medication-assisted treatment for moderate or severe opioid use disorders, and such treatment is recognized by the Centers for Disease Control and Prevention, National Institute of Drug Abuse, and World Health Organization.[60-63] Collectively, methadone and buprenorphine are referred to as opioid agonist treatments and have been associated with a variety of improved outcomes including reduced craving, decreased opioid use, decreased crime, decreased nonfatal overdose, decreased mortality, cost-effectiveness, and improved social functioning.[61,62,64-66]

Methadone Methadone is a long-acting oral medication with full opioid agonist properties at the μ receptor. Methadone can be prescribed by physicians for the treatment of pain, but the prescription of methadone for treatment of addiction is limited by the Federal Narcotics Act to inpatient units or outpatient facilities licensed by the U.S. Drug Enforcement Administration. Several large-scale studies have shown a relationship between outcomes and methadone dose, with improved outcomes including less opioid and cocaine use at doses above 60 milligrams.[61,67] Methadone has been associated with QT prolongation on the ECG.[68]

Buprenorphine Buprenorphine is a partial opioid agonist and a weak antagonist. It has a high affinity for μ receptors, displacing other opioids from the receptor and causing acute withdrawal in patients who have recently used opioids. The antagonist effects of buprenorphine block respiratory depression and provide a good margin of safety to treat withdrawal or to provide opioid substitution therapy. The U.S. Food and Drug Administration approved two sublingual formulations of buprenorphine in 2002 for the treatment of opioid dependence. The preferred preparation is a combination of buprenorphine combined with naloxone in a ratio of 4:1, as a sublingual tablet or film (brand name Suboxone® or Zubsolv®) to prevent diversion and overdoses.[56,69] The naloxone component is rapidly bioavailable if the medication is tampered with and will precipitate withdrawal symptoms in opioid users. Non–naloxone-containing films are traditionally reserved for pregnant patients or settings with directly observed medication ingestion. Overdoses can be managed with naloxone. Advise patients about the risks of concurrent benzodiazepine use, including respiratory depression and overdose of prescribed and illicit sedatives with all opioids, including methadone and buprenorphine.

The *Drug Addiction Treatment Act of 2000* established office-based opioid treatment in an effort to integrate treatment options into comprehensive clinical care practice and reduce stigmatization of medication-assisted treatment. The prescription of methadone for treatment of addiction is limited by the Federal Narcotics Act to inpatient units or outpatient facilities licensed by the U.S. Drug Enforcement Administration, and buprenorphine is limited to certified clinicians in office- or clinic-based practices. However, there is a **"3-day rule" (Title 21, Code of Federal Regulations, Part 1306.07b)** that allows a practitioner who is not separately registered as a narcotic treatment program or certified as a "waivered Drug Addiction Treatment Act of 2000" physician to administer (but not prescribe) narcotic drugs to a patient to relieve acute withdrawal symptoms while arranging for referral to treatment (http://www.buprenorphine.samhsa.gov/faq.html). Only 1 day's supply may be administered or given to a patient, and this may be done for 72 hours only, which cannot be extended. The intent of Title 21, Code of Federal Regulations, Part 1306.07b is to provide flexibility in emergency situations and is especially relevant to emergency physicians. This offers patients options for relief of withdrawal symptoms to bridge the patient for follow-up to either a specialized treatment program or an office-based physician program in the community.

A study of 329 ED patients found that patients with moderate or severe opioid use disorder randomized to receive a brief intervention with initiation of buprenorphine in the ED with primary care follow-up were significantly more likely to be engaged in formal treatment for opioid use disorder at 30 days (78%; 95% confidence interval [CI], 70% to 85%), compared with referral alone (37%; 95% CI, 28% to 47%) and brief intervention with a facilitated, direct referral (45%; 95% CI, 36% to 54%; $P < .001$).[70] The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1 to 5.7) to 0.9 days (95% CI, 0.5 to 1.3) versus a reduction from 5.4 days (95% CI, 5.1 to 5.7) to 2.3 days (95% CI, 1.7 to 3.0) in the referral group and from 5.6 days (95% CI, 5.3 to 5.9) to 2.4 days (95% CI, 1.8 to 3.0) in the brief intervention group ($P < .001$ for both time and intervention effects; $P = .02$ for the interaction effect).[70]

This important study from 2015, combined with the rapid increase in opioid-associated fatalities, laid the foundation for EDs to help bridge the treatment gap for patients with opioid use disorder by collaborating with local treatment providers to develop pathways for rapid linkage to care.

The starting dose for treatment of opioid withdrawal is sublingual buprenorphine/naloxone, 4 to 8 milligrams of buprenorphine/2 milligrams of naloxone, given to patients who meet criteria for moderate or severe opioid use disorder and show signs of opioid withdrawal according to the **Clinical Opiate Withdrawal Scale** (**Figure 292-3**).[56,71] If the patient does not yet exhibit symptoms of at least a score of 7 on the Clinical Opiate Withdrawal Scale, a physician with a Drug Addiction Treatment Act of 2000 waiver can prescribe a short course of buprenorphine and discharge with instructions and with close follow-up in place (**Figure 292-4**). In the case of naloxone administration after an overdose, patients will likely not meet criteria for opioid withdrawal during the length of an ED stay after the naloxone wears off. Thus, if they wish to start buprenorphine, they will be discharged with a prescription for unobserved induction with close follow-up.

Naltrexone Naltrexone is a long-acting μ receptor antagonist that reduces relapse or return to opioid use in patients by blockading any positive reinforcement from taking opioids.[71] Naltrexone is best suited to patients with opioid use disorder who are highly motivated to avoid opioids, as it provides modest relief from craving, or who were recently released from a controlled environment such as incarceration or an abstinence program. **Naltrexone requires at least a 7-day period without opioid exposure to avoid the complication of precipitated withdrawal.** Recent studies comparing it with opioid agonist treatment such as buprenorphine highlight the fact that patients may refuse treatment, and evaluation of effectiveness has been complicated by poor study and treatment retention.[55,56]

Benzodiazepines The chronic use of sedatives, particularly benzodiazepines, is a common comorbidity with other substance use disorders. The emergency provider often encounters patients with signs and symptoms of withdrawal, when prescriptions are not filled after hospitalizations or surgeries. Symptoms of withdrawal may develop up to 7 to 10 days after stopping chronic benzodiazepine use, and patients may develop withdrawal seizures. The clinical picture resembles alcohol withdrawal with symptoms of hypertension, tachycardia and tachypnea, tremulousness, anxiety, agoraphobia, insomnia, altered mental status, delirium, and hallucinations. Medical management for the treatment of benzodiazepine withdrawal is complicated by risk of withdrawal seizures. Most evidence supports a prolonged benzodiazepine taper over 4 to 12 weeks.[57] A 2006 Cochrane review found support for a gradual benzodiazepines taper, although it did not find significant differences between patients being tapered on long- versus short-acting benzodiazepines, and no additional benefit was found to support the adjunct use of additional medications such as propranolol or hydroxyzine.[58] A meta-analysis of 29 studies evaluating strategies for the discontinuation of benzodiazepines found that both minimal interventions and systematic discontinuation of benzodiazepines were more effective than treatment as usual and concluded that there is adequate support of the stepped care model, in which minimal intervention is followed by systematic discontinuation.[57] Preliminary evidence for the use of carbamazepine exists, but large, controlled trials have not been reported.[59] Benzodiazepines should be continued in collaboration with the primary care provider or mental health provider, and the patient should be referred to an

APPENDIX 1
Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *Over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *Over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *Observation of outstreched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal
This version may be copied and used clinically.

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FIGURE 292-3. Clinical Opiate Withdrawal Scale. [Reproduced with permission from Wesson DR, Ling W: The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 35: 253, 2003. Copyright Taylor & Francis Ltd.]

addiction medicine specialist as needed. If benzodiazepines are necessary for continued treatment of debilitating psychiatric illness, patients should have a psychiatry consult or evaluation as these medications are frequently inappropriately prescribed or overprescribed.

REDUCTION OF HARM FROM OPIOID USE DISORDER

Many ED patients with opioid use disorder will not be ready to enter treatment at the time of the ED visit, but we still have an opportunity to help them progress in their readiness to seek treatment, prevent individual and societal harms associated with drug use, and prevent future overdose deaths. Syringe access[72,73] and supervised consumption facilities have demonstrated lower human immunodeficiency virus and hepatitis C virus transmission rates, fewer injection drug risk behaviors, decreased overdose incidents, and more rapid entry into detox programs.[74-76] **Naloxone**, a competitive opioid receptor antagonist, has been distributed for bystander opioid overdose reversal since 1996 at community naloxone distribution programs.[77] Community naloxone distribution programs have demonstrated that lay people and injection drug users can reliably administer naloxone.[78-82] Population studies have noted that naloxone distribution is associated with decreased community overdose deaths[83] and decreased deaths among people released from prison,[84] is cost-effective when provided to heroin users,[85] and reduces opioid-related ED visits when co-prescribed with opioids for chronic pain by a primary care provider.[86] Given the increasing incidence of opioid overdose, some cities and states have started storing publicly accessible naloxone with automated external defibrillator devices, in designated NaloxBoxes, and at public schools.[87]

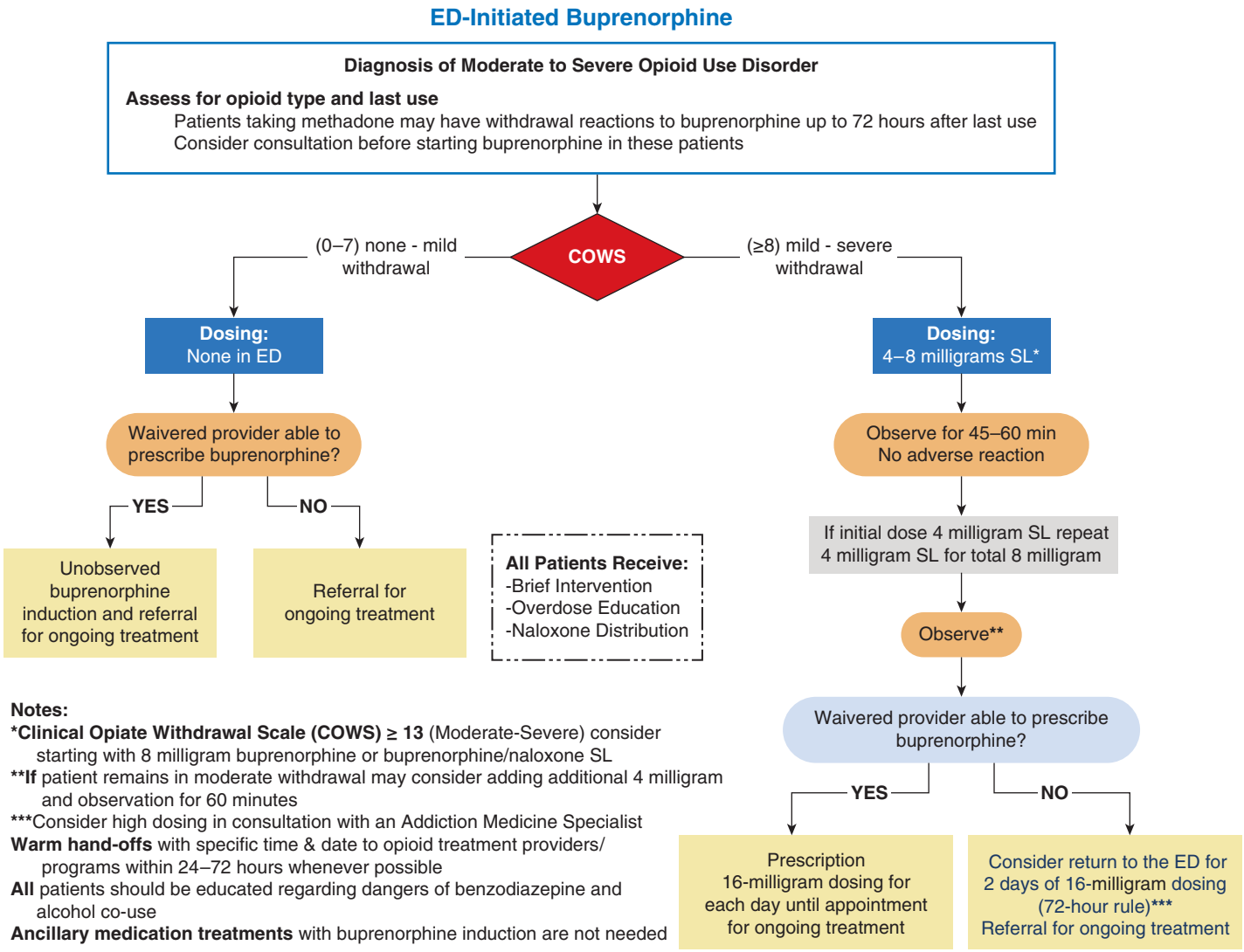

FIGURE 292-4. ED-initiated buprenorphine. SL = sublingual. [Adapted from study protocol D'Onofrio G, O'Connor PG, Pantalon MV, et al: Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence. *JAMA* 313: 1636, 2015. The study was supported by grant 5RO1DA025991 from National Institute on Drug Abuse. https/www.drugabuse.gov/ed-buprenorphine]

In addition to referring patients to addiction treatment, community syringe access, and naloxone distribution programs, in 2009 EDs started providing take-home naloxone to patients at high risk of opioid overdose to prevent opioid overdose death.[88-91] Naloxone can be either prescribed for pickup at a pharmacy or given to patients in a preassembled "kit" that includes administration instructions, a mouth barrier for CPR, and two doses of naloxone. Provision of naloxone at the time of the ED visit decreases access barriers and ensures that the patient and/or their family member has received the medication.

Naloxone can be given IM or intranasally. IM naloxone can be prescribed as two single-dose vials, 0.4 milligram/mL with a 3-mL syringe and 1-inch 23-guage needle (**Table 292-3**). This is the cheapest formulation, but it requires drawing up the medication into a syringe prior to administration. Another IM formulation, Evzio®, is a U.S. Food and Drug Administration–approved prefilled autoinjector. It has a single dose of naloxone 2 milligrams/0.4 mL (prior formulation had 0.4-milligram dose) and comes in packs of two. It is easy to use but more expensive and requires prior insurance authorization, limiting its utility in the ED setting.

Narcan® is a U.S. Food and Drug Administration–approved intranasal form of naloxone that contains 4 milligrams of naloxone and requires no assembly. It is very easy to use but more expensive than generic formulations. Generic intranasal naloxone is prescribed as two prefilled Luer-Lock needless syringes containing 2 milligrams/2 mL to be dispensed with a mucosal atomizing device. This formulation requires assembly before use.

TABLE 292-3 Naloxone Formulations Characteristics and Prescriptions

	Generic Intramuscular	Evzio® Auto-Injector	Generic Intranasal	Narcan® Nasal Spray
Dose	0.4 milligram/mL	2 milligrams/0.4 mL	1 milligram/mL	4 milligrams/0.1 mL
Titratable dose	X		X	
Assembly required	X		X	
Cost	$	$$$	$$	$$
Prescription and quantity	Two single-use 1-mL vials PLUS two 3-mL syringes with 23- to 25-gauge 1- to 1.5-inch IM needles; two refills	One two-pack of two 2 milligram/0.4 mL prefilled autoinjector devices; two refills	Two 2-mL Luer-Jet® Luer-Lock needleless syringes plus two mucosal atomizer devices (MAD-300); two refills	One two-pack of two 4 mg/0.1 mL intranasal devices; two refills

Primary considerations when considering distributing naloxone include state regulatory barriers, which can limit direct to patient naloxone distribution and third-party prescribing; cost; and patient education. Naloxone is covered by most insurance plans. Any trained staff member can provide overdose prevention, response, and naloxone administration education. Patient education is best done in person in combination with facilitation of treatment referral; however, it can also be done with video.[88]

SAFE PRESCRIBING OF OPIOID PAIN RELIEVERS

Emergency providers commonly treat painful conditions.[92] Opioids are frequently prescribed for patients with pain, with a multicenter study showing that 17% of discharged patients received an opioid prescription.[93] With heightened awareness of the risks associated with opioids, that percentage is decreasing, but it is likely that opioids will always continue to have a role for certain ED patients with pain. ED prescribing is not a significant contributor to the overall number of opioid prescriptions written annually in the United States, providing only about 4% to 5% of the total number of opioid prescriptions and about 2% when converted to morphine equivalents.[94,95] However, providers must be aware that short-term ED prescriptions can have long-term consequences: One study showed that 12% of opioid-naive patients given an ED opioid prescription had recurrent use,[96] and another concluded that about one third of patients with opioid use disorder who were first exposed to opioids by a legitimate prescription obtained that prescription from the ED.[97] Standardization of treatment is key: There is currently wide variation in rates of opioid prescribing among physicians practicing within the same ED, and higher-intensity opioid prescribers within an individual department are more likely to have patients who are on opioids long term.[98] Furthermore, the longer the duration of an initial opioid prescription, the more likely it is the patient will develop long-term use,[99] leading to the following recommendation by the Centers for Disease Control and Prevention: **"When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed."**[100] Therefore, a framework for safe prescribing of opioids from the ED is essential to incorporate into practice and consists of the following four pillars.

1. *Determine if an opioid is indicated.* There is mounting evidence that outcomes for acutely painful conditions are the same whether or not an opioid is used. For example, for patients with acute arm or leg sprain pain, the combination of ibuprofen and acetaminophen results in the same level of pain reduction at 2 hours as do combinations of acetaminophen with oxycodone, hydrocodone, or codeine.[101] Likewise, patients with nonradicular back pain who were given naproxen had similar functional outcomes at 1 week whether or not they also took oxycodone/acetaminophen or cyclobenzaprine.[102] Given these similar outcomes, it would be prudent to use nonopioid pain relievers (e.g., acetaminophen, ibuprofen, topical lidocaine) and avoid the exposure altogether. A formal "alternatives to opioids" program can be created, which encourages use of nonopioid pain medications, triggerpoint injections, nitrous oxide, and ultrasound-guided nerve blocks to avoid opioids when possible.
2. *Screen patients for opioid misuse risk factors.* If the decision is made to prescribe an opioid, determine whether the patient is at higher risk for future opioid misuse. Several screening tools have been produced for this purpose, including the Screener and Opioid Assessment for Patients with Pain–Revised and the Opioid Risk Tool.[103,104] It is important to note that these tools were derived and validated in non-ED settings, and recently, the Centers for Disease Control and Prevention declared that the tools have insufficient accuracy for classification of patients as at low or high risk for abuse or misuse.[105] It is therefore prudent to use caution for *all* patients when prescribing opioids, although be particularly careful when patients have high-risk features that are detected by these tools, such as concomitant psychiatric illness and/or previous personal or family history of drug or alcohol abuse.
3. *Utilize a prescription drug monitoring program.* Nearly all states have implemented prescription drug monitoring programs that track the prescribing and dispensing of controlled substances at the pharmacy level.[106] When first implemented, states with prescription drug monitoring programs appeared to have lower rates of substance abuse treatment admission and lower rates of increase in abuse/misuse compared to states that did not have them.[107] Prescription drug monitoring program data can change prescribing behavior because providers do not have adequate sensitivity or positive predictive value in detecting certain aberrant drug-related behaviors (e.g., "doctor shopping") without the aid of this tool.[108] Although they should be used prior to every opioid prescription, there are limitations to these databases, particularly that they do not detect medications that are diverted or purchased illegally, which are the main sources of non–medically used opioid pain relievers.[109,110] Use prescription drug monitoring program data along with history, physical examination, and clinical impression. Do not use prescription drug monitoring program data as a reason to withhold adequate and necessary analgesia. Several factors from prescription drug monitoring program data may suggest concerning substance abuse risk (**Table 292-4**).
4. *Educate about safe opioid use.* Every patient who receives an opioid prescription should be provided with specific education about safe use and the risks of the medication. This education should include the following: (1) use recommended nonopioid pain relievers (e.g., acetaminophen and ibuprofen, if not contraindicated) first and understand that the opioid is an adjunct that should be used only to make the pain tolerable but not remove the pain entirely; (2) immediately stop use of the opioid medication once the pain is tolerable with nonopioid medications; (3) safely store the medication away from others in the household who may be at increased risk of nonmedical use, such as adolescents; and (4) dispose of any unused medication promptly and properly, which can now be done at most pharmacies and police stations.[111]

TABLE 292-4 Identifying Substance Abuse Risk

When assessing a prescription drug monitoring program (PDMP) profile, it is important to look at the following factors:

- From how many providers did the patient receive prescriptions?
  — Patients who used 4 or more prescribers or 4 or more pharmacies in 6 months may have risk of death from overdose.[59,60]
- Is the patient taking both opioids and benzodiazepines?
  — Patients who use combinations of medications may be at increased risk for overdose.[61]
- How many morphine milligram equivalents of opioids is the patient taking per day?
  — Patients who take 50 to 100 morphine milligram equivalents per day are at greater risk of overdose death.[62-64]
- Is the patient taking long-acting/extended-release (LA/ER) opioids?
  — Patients taking LA/ER may be at increased risk for overdose.[65]
- How often did the patient fill another prescription before the previous one was scheduled to finish?
  — Early refills indicate nonmedical use or noncompliance with treatment plan.[65]
- Is the patient taking buprenorphine?
  — Patients taking buprenorphine are likely under the care of a pain specialist who should be contacted prior to prescribing a scheduled medication.
- Is the patient taking psychiatric medications, such as methylphenidate?
  — Psychiatric comorbidities are associated with increased risk of overdose.
- If reported by the PDMP, how often did the patient self-pay?
  — Patients may pay out of pocket for a prescription without involving an insurer to avoid detection of nonmedical use.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 293

Female and Male Sexual Assault

Lisa A. Moreno-Walton

INTRODUCTION AND EPIDEMIOLOGY

Sexual assault is a crime of violence, intended to dominate and humiliate the victim through the use of intimidation and fear.[1] In many parts of the world, sexual assault is a tool for oppression, a weapon of war, and an act of genocide. Psychological trauma is a universal consequence of rape and sexual assault, but the absence of physical injury does not indicate that an assault did not take place. Sexual assault remains a major public health problem throughout the world, with case rates of police-recorded incidents as high as 92.9 per 100,000 in Botswana to a first-time record of 0.0 in Liechtenstein in 2010.[2] In the United States, the incidence of rape decreased from 1.6 cases per 1000 people in 2015 to 1.1 cases per 1000 in 2016[3]; however, nearly one in five American women (18.3%) report being raped at some time during their lives.[4]

Although males are less commonly victimized, studies estimate that between 0.6% and 22.2% of males have experienced sexual assaults.[5-7] According to the National Electronic Injury Surveillance System, sexual assaults accounted for >150,000 ED visits in 2001 in the United States.[8] However, many sexual assault survivors do not report the assault to police or seek medical care.[9] The Department of Justice estimates that only 34.8% of sexual assaults are ever reported.[10] Women are likely to seek treatment earlier for more severe assaults and injuries, and they are more likely to delay seeking assistance if assaulted by a known perpetrator.[9]

In most cases of rape in the United States, a single assailant is involved, and most often, the perpetrator is known to the victim.[11] Twenty-six percent of assailants are current or former partners, 38% are friends or acquaintances, and only 26% are strangers.[10] Force or coercion is used in most assaults, but a weapon is reported in only 11% of cases.[4]

About half of female[12] and male[13] assault survivors have genital or rectal trauma on examination, and about two thirds have some evidence of bruising elsewhere.[12] Injuries are more often found in female patients <20 years old or >49 years old, those who have experienced anal assault, and those who present within 24 hours of assault. Survivors age 12 to 17 years are more likely to have anogenital injuries than those age 18 to 49 years.[14]

HEALTHCARE RESPONSIBILITIES

Care of the sexual assault victim is complex and can be time consuming. Responsibilities include obtaining the medical and forensic history; performing and documenting results of the medical examination; collecting forensic evidence and ensuring that material follows the proper chain of custody; treating potential sexually transmitted infections; treating other acute medical problems and injuries; assessing pregnancy risk and providing treatment options; providing referral for crisis intervention and medical follow-up; coordinating care with sexual assault advocates; and testifying in court if needed.[15] Although some hospitals provide **sexual assault nurse examiners** (see next paragraph) to aid in medical and forensic evaluation, in many institutions, emergency physicians will be expected to provide most of the care for sexual assault victims.

Sexual assault nurse examiners (SANEs) provide expert assistance for sexual assault evaluation. SANEs are certified by examination through the Commission for Forensic Nursing Certification. Requirements before examination include an unrestricted registered nurse license, 2 years of nursing experience, 40 hours of coursework, and competency in supervised sexual assault examination.[16] Physicians, physician assistants, and nurses can also complete a separate course of training and receive certification as **sexual assault forensic examiners (SAFEs)**. The Department of Justice established national training standards for SAFEs in 2006.[17] Individuals, most often physicians and physician assistants, who complete the proscribed training and pass a standardized exam receive certification as a SAFE. There is little difference between SANE and SAFE training, but only registered nurses are eligible to train as SANEs, and the Commission for Forensic Nursing maintains authority over the certification of SANEs.

Because SAFEs and SANEs are specially trained to perform the precise and sensitive history, physical and forensic examination, and to preserve evidence in a chain of custody, many U.S. hospitals have designated these individuals as part of **sexual assault response teams (SARTs)**. Local EMS personnel can transport survivors of sexual assault to SARTs as a matter of protocol.

CULTURAL DIFFERENCES AND MINORITIES

Appropriate cultural competency skills often set the tone for the first steps toward healing. Some cultures consider rape a punishment or a consequence of aberrant sexual behavior.[18] Societies characterized by gender-based power disparities are often less likely to define sexual coercion and threats of violence as rape. Women from such cultures often present for care with other chief complaints or will give inconsistent histories if they feel they are culpable or could have offered more resistance.[19] In countries with a history of slavery, indentured servitude, human property laws, and rigid caste or class systems, policies, traditions, and biases affect the treatment and adjudication of sexual assault. Survivors may be reluctant to report victimization if they fear a biased criminal justice system, do not think police will help, or anticipate being blamed by their family or community.[11,20,21]

Fear of deportation may impact the decision of illegal aliens regarding evidence collection, police reporting, and testifying in court. Before encouraging patients to make a police report, learn your state's laws about illegal aliens who are crime victims.

Women of color face more challenges than white women in obtaining assistance after rape. Services for victims of diverse backgrounds are limited, and minority victims are often reluctant to contact rape crisis centers.[11] For black women survivors of sexual assault, poverty is a positive predictor of increased lifelong risk of depression and posttraumatic stress disorder.[11,22,23] Sexual minorities also suffer disproportionately. In September 2018, the Centers for Disease Control and Prevention published its National Intimate Partner and Sexual Violence Survey,[24] documenting that 46% of bisexual women have been raped, in contrast to 17% of heterosexual women and 13% of lesbians. Although most large cities have good referral services and resources for providers, smaller communities may not have support services for minority and ethnically diverse patients. **The Substance Abuse and Mental Health Services Administration National Council for Trauma-Informed Care** provides excellent resources for institutions, providers, and patients,[25] especially for referrals for continuing care.

THE SEXUAL ASSAULT EVALUATION

TRIAGE

Triage sexual assault patients as a high priority, in accordance with Department of Justice recommendations.[15] Notify the SAFE or SANE on call, and place the patient in a private room, ideally one reserved for

the care of sexual assault victims. If a SAFE or SANE examiner is not in-house or if the hospital does not have a SART program, the triage nurse should notify the emergency physician of the patient's presence in the department. Make sure the patient does not undress or change into a hospital gown, as all clothing must be properly removed and stored for forensic evaluation. Tell the patient not to wash, drink, or rinse the mouth. Provide appropriate medical care whether or not patients agree to evidence collection, police reporting, or assisting with criminal prosecution.

HISTORY

Begin the interview with introductions, express regret about the assault, and provide reassurance that medical and psychological needs will be addressed. Maintain a professional, caring attitude. A patient's response is affected by the physician's attitude. A physician's shock or outrage may increase the patient's concern about physical injuries or cause the patient to feel marginalized. Questions perceived as critical or judgmental result in feelings of guilt and shame and interfere with the survivor's ability to provide a thorough history. Calm reassurance will facilitate the history, examination, and collection of evidence.

Ask open-ended questions about sexual history. For some women, sexual assault is the first sexual encounter, and for some lesbian patients, it may be the first sexual encounter with a male.

Obtain a thorough past medical history and general assault description, and ask the patient about injuries. In some instances, the triage nurse will have obtained the past medical history. In EDs with SANE services, a detailed assault history, to help guide the evidentiary examination, will be obtained by the SANE. If there are no SANE services, but a sexual assault advocate, police representative, or social worker is available, have those individuals in the room during the history taking so that the patient does not have to repeat information.

Details to gather about the assault and medical history are listed in **Tables 293-1 and 293-2**. Most authorities caution that the chances of finding forensic evidence >72 hours after the assault are slim, so **a forensic examination is not necessary if >72 hours have elapsed since the assault, unless the specific state allows evidence collection up to 96 hours after the assault**. Verify the policy in your state well in advance of the need to know.

TABLE 293-1 Assault History

Who?
- Did the assault survivor know the assailant?
- Was it a single assailant or multiple assailants?
- Can the survivor recall any identifying features of the assailant (height, build, age, race, tattoos, scars, birthmarks, etc.)? (Document in the medical records.)

What happened?
- Was the patient physically assaulted?
- With what (e.g., gun, bat, or fist) and to what part of the body?
- Was there actual or attempted vaginal, anal, or oral penetration?
- Did ejaculation occur? If so, where?
- Was a foreign object used?
- Was a condom used?
- Has alcohol been recently ingested? (Alcohol affects ED treatment with metronidazole or tinidazole.)
- Has the victim been sexually assaulted before?
- Does the victim have suicidal or homicidal ideation?

When?
- When did the assault occur?
- (Emergency contraception is most effective when started within 72 h of the assault.)

Where?
- Where did the assault occur?
- (Corroborating evidence may be found based on the location of the assault.)

Suspicion of drug-facilitated rape?
- Was there a period of amnesia?
- Is there a history of being out drinking and then suddenly feeling very intoxicated?
- Is there a history of waking up naked or with genital soreness?

Douche, shower, or change of clothing?
- Did the patient douche, shower, or change clothing after the assault? (Performing any of these activities prior to seeking medical attention may decrease the probability of sperm or acid phosphatase recovery, as well as recovery of other bits of trace evidence.)

CONSENT FOR FORENSIC EXAMINATION

Have the patient sign the consent form for the forensic examination, collection of evidence, photography, and transfer of evidence to law enforcement authorities. Most hospitals have a prepackaged rape kit with equipment and directions. However, check with the police if you are unsure about the utility of your hospital's kit, because some police departments may require use of a specific kit for their precincts. Hospitals will usually allow the storage of a rape kit for a specified period of time while the patient decides whether or not she wishes to make a police report. In such a case, encourage the patient to consent to the forensic exam. **Not every part of the forensic evidence kit needs to be used every time. Tailor the collection of evidence to the specifics of the assault.**

If >72 hours (or 96 hours, according to your hospital's policy) have elapsed or the patient does not want an evidentiary examination, still perform a full history and physical examination, provide pregnancy and sexually transmitted disease prophylaxis, and refer for follow-up medical care and rape crisis counseling.

PHYSICAL EXAMINATION

General Examination Record general information such as vital signs and mental status. After clothing is properly removed and stored, perform a head-to-toe inspection, and look for injuries. Focus on defensive injury areas such as the extremities, and carefully check potential areas of injury such as the oral cavity, the neck (for strangulation signs), and the breasts, thighs, and buttocks. Describe all injuries, and record all areas of tenderness, even if there is no outward sign of injury. Injuries, predominantly bruises, are often located on limbs (32%), face (23%), and torso (7%), with most assault survivors sustaining light (44%) or moderate (18%) injuries.[26] Other nongenital injuries include abrasions (40%), lacerations (4%), and bites and burns (1%).[12]

FORENSIC EXAMINATION

The forensic examination includes collection of head and pubic hair and buccal swabs for DNA comparison, photographs of injuries, and vaginal and perineal examination, often with colposcopy. Tell the patient what the examiner is doing at each stage of the process. Tell the patient she can take a break at any point during the examination. (See Video: Sexual Assault.)

Assemble all of the needed equipment for forensic examination. Throughout the examination, keep the patient's body covered as much as possible. Have several pairs of gloves available for different parts of the examination—change gloves between the physical and the genital exam, and again between the genital and the anal exam. A detailed list of equipment and a demonstration of the examination and evidence collection are available. Take photographs of abrasions, bruises, contusions,

TABLE 293-2 Medical History

- Last menstrual period? Birth control method?
- Last consensual intercourse?
- If the patient has had consensual intercourse within the past 3 to 4 days, it may confuse laboratory analysis for sperm and acid phosphatase and genetic typing.
- Allergies, medication history, and possible pregnancy?
- Medical comorbidities
- Mental health issues or substance use disorder history

lacerations, bite marks, burns, areas of erythema, hematomas, incisions, petechiae, and swelling. Document location, position of patient, and position of injury, using a clock face reference. Traditionally, when the patient is in lithotomy position, the pubic bone is at 12 o'clock, the left hip is at 3 o'clock, and the right hip is at 9 o'clock. Begin the photographic series with a photograph of the patient's face and end with a photograph of the patient's hospital wrist band. If photography is not available, describe signs of trauma and areas of tenderness in detail using a body map.

Begin the genital exam with combing of the pubic hair and extraction of hair samples. Patients can pluck their own hair, but make sure that the hair root is included. Examine the genital and rectal areas for injuries and signs of trauma. Note any vaginal discharge, vaginal abrasions, cervical abrasions, and cervical lacerations. In some institutions, a topical application of **toluidine blue dye** is used to highlight microtrauma. Toluidine is a dye with affinity for DNA and RNA.[27] When placed on an area where the topical nonnuclear layer has been removed (as by abrading by injury), toluidine dye will be taken up by underlying cellular tissue. It is typically mixed for use by the hospital pharmacy. Toluidine is applied to the external vulva, especially the posterior fourchette, but not onto mucous membranes. If toluidine dye is used, do not perform a speculum examination until after the toluidine dye examination is completed, because the speculum examination itself may induce small abrasions that can be confused with injuries from the assault.[28] After examination, remove excess dye with a water-soluble lubricant. If the solution is not used soon after it is mixed, cover the bottle with aluminum foil, store at 4°C (39.2°F), and bring to room temperature before use.[29] An alternative to bottles of toluidine blue dye is the commercially available **Forensic Blue Swabs®**.

Colposcopy detects injuries not visible to the naked eye.[13] In one study, only 34% of genital lesions were seen with the naked eye, 49% were seen with a colposcopy, and 52% were seen with toluidine blue dye.[28] If the colposcope is used to photograph injuries, document magnification. If the patient reports anal penetration, examine the anus and rectum for abrasions or lacerations.

Finally, darken the room and scan the entire body surface with a **Wood's lamp** to detect traces of semen. Swab areas where the perpetrator made any oral contact, and swab areas that illuminate with the Wood's lamp. Dry and label all swabs and add to the rape kit.

After all evidence is collected, make sure to maintain chain of custody. Do not leave the kit unattended. Each party that releases and accepts the evidence kit must sign, date, and time the chain-of-evidence form. If the police are not present to receive the evidence, store the kit in a locked cabinet specifically designated for this purpose. Many rape kits contain elements that require refrigeration. In this case, when police are not available to accept the kit, store the entire kit in a locked refrigerator only used to store rape kits.

LABORATORY TESTING

Obtain ancillary tests as clinically indicated. If there is high suspicion of **drug-facilitated rape**, a urine sample can be sent to a laboratory for toxicologic testing. Drugs that are typically thought of as "date rape" drugs, such as ketamine, flunitrazepam (Rohypnol), and γ-hydroxybutyric acid, are not detected on routine ED toxicology screening tests, and special "send out" tests must be ordered. Rohypnol can be detected in the urine for up to 72 hours, and γ-hydroxybutyric acid can be detected for 12 hours. Results, however, are not available for days.[30] Most SANEs typically send these tests when indicated and assume responsibility for checking the results. In some hospitals with SART programs, consent forms give the right to the prosecuting attorney in the Special Victims Unit to receive the results. If these "send out" tests are ordered by the ED physician, develop a protocol for checking results and documenting results in the patient's record. Guidance for appropriate ordering can be obtained from womenshealth.gov or by calling 800-994-9662.

Obtain a urine or serum pregnancy test before giving emergency contraception. Testing for gonorrhea, chlamydia, and bacterial vaginosis is not necessary, because treatment is provided at the ED encounter. However, **do test for syphilis, hepatitis B and C, and human immunodeficiency virus (HIV)**. Obtain serum chemistry, liver function studies, and CBC for patients who will receive HIV postexposure prophylaxis.[31] Follow baseline HIV testing with repeat testing at 6 weeks and 3 and 6 months.

TREATMENT

Follow standard care protocols and also individually assess the needs of the survivor.[32,33] Treat physical injuries and provide immediate crisis intervention if needed. Offer emergency contraception, sexually transmitted disease prophylaxis, tetanus and hepatitis B vaccination if needed, and prophylaxis against HIV infection (**Table 293-3**).[31]

SEXUALLY TRANSMITTED INFECTION PROPHYLAXIS

The prevalence of sexually transmitted infections in an adolescent urban population varies as follows by causative organism: *Neisseria gonorrhoeae*, 0.0% to 26.3%; *Chlamydia trachomatis*, 3.9% to 17%; *Treponema pallidum*, 0.0% to 5.6%; *Trichomonas vaginalis*, 0.0% to 19.0%; and human papillomavirus, 0.6% to 2.3%.[34] The regimens currently recommended by the Centers for Disease Control and Prevention are provided in **Table 293-4**.

EMERGENCY CONTRACEPTION

Obtain a pregnancy test on all women unless there is a history of hysterectomy. Offer pregnancy prevention to those who are not pregnant and of childbearing age.[35-40] The probability of a single act of intercourse *within the fertile window* is about 25%.[41] Also prescribe an antiemetic for nausea and vomiting.[39,40] Offer meclizine 50 milligrams, metoclopramide 10 milligrams, or ondansetron 4 milligrams.[40] **Four emergency contraceptive regimens are listed in Table 293-5.**[42] A fifth method of emergency contraception is the insertion of a copper intrauterine device, but this method is not commonly used after sexual assault or in the ED, there is little information on its effectiveness for emergency use,[43] and availability is limited. Provide emergency contraception as soon as possible following exposure; best results are within 3 days, and effectiveness is lower within 4 to 5 days.[44,45] Pregnancy after emergency contraception is 3.6 times more likely for obese women than for women with a normal body mass index. Failure of emergency contraception

TABLE 293-3 Centers for Disease Control and Prevention Guidelines for Postassault Prophylaxis

- If assailant status unknown and survivor not previously vaccinated, give postexposure hepatitis B vaccination without HBIG, and inform survivor that subsequent doses must be given at 1–2 and 4–6 mo after first dose.[31]
- If the assailant is known to be HBsAg positive, unvaccinated survivors should receive hepatitis B vaccine and HBIG at the time of initial examination.
- For survivors previously vaccinated but who have not had postvaccination testing, give a single hepatitis B vaccine booster.
- HPV vaccination is recommended for female survivors age 9–26 y and male survivors age 9–21 y at the time of initial examination. Inform survivor that subsequent doses must be given at 1–2 mo and 6 mo after the first dose.[16]
- Empiric antibiotics for chlamydia, gonorrhea, and trichomoniasis (see Table 293-4).
- Tetanus prophylaxis if needed.
- Offer emergency contraception if the assault could result in pregnancy.[31]
- Baseline testing for syphilis, hepatitis C, and HIV.
- Obtain serum chemistries and liver function studies if HIV postexposure prophylaxis given.
- Provide first follow-up at 1 week.

Abbreviations: HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; HPV = human papillomavirus.

Source: https://www.cdc.gov/std/tg2015/sexual-assault.htm cdc.gov (Centers for Disease Control and Preventions: 2015 Sexually Transmitted Diseases Treatment Guidelines.) Accessed November 18, 2018.

TABLE 293-4 Centers for Disease Control and Prevention Recommended Regimens for Infection Prophylaxis

- Ceftriaxone, 250 milligrams IM, single dose

Plus

- Azithromycin, 1 gram PO, single dose

Plus

- Metronidazole,* 2 grams PO, single dose

Or

- Tinidazole *2 grams PO, single dose

*If alcohol has been recently ingested or emergency contraception is provided, metronidazole or tinidazole tablets can be given to the patient in the ED to take at home.

Source: https://www.cdc.gov/std/tg2015/sexual-assault.htm cdc.gov (Centers for Disease Control and Preventions: 2015 Sexually Transmitted Diseases Treatment Guidelines.) Accessed November 18, 2018.

is more likely to occur with levonorgestrel than with ulipristal acetate; however, in all women, regardless of body mass index, the most significant factor predicting failure is the cycle day of intercourse.[46]

Breastfeeding is not contraindicated following emergency contraception. Advise women that emergency contraception does not protect against HIV infection, other sexually transmitted infections, or subsequent unprotected intercourse. Recommend follow-up with a healthcare provider for all women and especially those with abnormal bleeding after cessation of emergency contraception.[40] Advise women who use emergency contraception to follow up with a regular provider to begin use of ongoing contraception in the form of oral contraception pills or copper intrauterine device to ensure successful prevention of pregnancy from subsequent unprotected intercourse.[45,46]

HIV POSTEXPOSURE PROPHYLAXIS

Viral load in the assailant is the most significant factor determining infectivity.[48] HIV seroconversion has occurred in persons whose only known risk factor was sexual assault or sexual abuse.[49] HIV transmission risk increases when bleeding occurs with vaginal, anal, or oral penetration; if viral load in the ejaculate is high; and if genital lesions are present in the assailant or the survivor.[31] Assistance in determining the advisability for postexposure prophylaxis can be obtained by calling the toll-free National HIV/AIDS Postexposure Hotline at 1-888-448-4911 (available 9 am to 8 pm Eastern time Monday through Friday, and 11 am to 8 pm Eastern time on weekends and holidays) or by accessing their website at http://nccc.ucsf.edu/clinician-consultation/pep-post-exposure-prophylaxis/. There is also a Clinicians' Warmline (1-899-933-3413) open 9 am to 8 pm Monday through Friday where clinicians may obtain answers to questions about caring for these patients. The Centers for Disease Control and Prevention recommendations for postexposure assessment of adolescents and adults are listed in **Table 293-6**.

If postexposure prophylaxis is administered, follow the standard protocol recommended by your hospital's infectious disease specialists. When prescribing HIV postexposure prophylaxis, ask about sulfa allergy. Truvada® includes tenofovir, which has a sulfa moiety.

TABLE 293-5 Emergency Contraception

Drug	Dose	Comments
Levonorgestrel (Plan B®)	1.5 milligrams once *or* 0.75 milligram at 1 and 12 h	Prescribe antiemetics; less nausea than combined estrogen-progestin; available without prescription; 11–24/1000 estimated pregnancy risk
Combined estrogen-progestin[47] (Yuzpe®)	100 micrograms ethinyl estradiol *plus* 0.50 milligram levonorgestrel, at 1 and 12 h	Prescribe antiemetics; 29/1000 estimated pregnancy risk
Mifepristone	25–50 milligrams PO as a single dose	Menstrual delay most common side effect; 1–10/1000 estimated pregnancy risk
Ulipristal acetate (Ella®/Fibristal®)	30 milligrams PO as a single dose	Prescribe antiemetics; possibly fewer pregnancies than with levonorgestrel

Source: Data adapted from Shen J, Chey Y, Showell E, et al: Interventions for emergency contraception. *Cochrane Database Syst Rev* 8: CD001324, 2017. [PMID: 28766313]

TABLE 293-6 Recommendations for Postexposure Assessment of Human Immunodeficiency Virus (HIV) Infection Risk for Adolescent and Adult Survivors Within 72 Hours of Sexual Assault

- Assess risk for HIV infection in the assailant.
- Evaluate characteristics of the assault event that might increase risk for HIV transmission.

Because recommendations vary with time and between institutions, consult with a specialist in HIV treatment for specific postexposure prophylaxis (PEP).

- If the survivor appears to be at risk for HIV transmission from the assault, discuss antiretroviral prophylaxis, including toxicity and lack of proven benefit.
- If the survivor chooses to start antiretroviral PEP, provide enough medication to last until the next return visit. Reevaluate the survivor 3–7 d after initial assessment and assess tolerance of medications.
- If PEP is started, perform CBC and serum chemistry panel at baseline. Do not delay PEP while awaiting laboratory results.
- Perform HIV antibody test at original assessment; repeat at 6 wk, 3 mo, and 6 mo. Repeat serologic assessment for syphilis can also be repeated at these times.[31]

Source: https://www.cdc.gov/std/tg2015/sexual-assault.htm cdc.gov (Centers for Disease Control and Preventions: 2015 Sexually Transmitted Diseases Treatment Guidelines.) Accessed November 18, 2018.

DISPOSITION AND FOLLOW-UP

Excellent care for survivors of sexual assault requires the coordination of clinical medicine with forensic science, law enforcement, and survivor advocacy. Once injuries are assessed and managed, offer counseling. This can be done by a dedicated rape counselor or trained social worker. If injuries are not severe, a rape counselor may be present prior to the physician's assessment. Gaps in service and patient care have largely involved lack of treatment of sexually transmitted infections and lack of availability of pregnancy-related services.[50]

For patients with underlying mental health or substance use disorders, recommend or arrange follow-up with their specific providers within a week. Sexual assault victims are more likely to have substance use disorders and previous mental health admissions, may be at risk for depression and even suicide, and have a strong need for mental health support.[51] However, even those without such underlying disorders should be encouraged to receive mental health support, because posttraumatic stress disorder symptoms and depression are common.[43]

Prior to discharge, make sure that the patient has a safe place to go, a safe way to get there, and a plan for addressing absence from home or work. This conversation should include a discussion of if, to whom, and how she will reveal her assault for the present time. Cultural competency of the caregivers is essential throughout the delivery of healthcare services to survivors of sexual assault, but it is critical at this juncture. If the team is not familiar with the cultural attitudes and practices surrounding sexual assault in the survivor's religious, ethnic, or social group, ask the patient how his or her family, religious community, or social network may respond.

Prior to discharge, provide the opportunity for bathing and oral care. Because clothing has been sequestered as part of the evidence kit, hospitals should provide fresh, packaged underwear and outerwear for the patient. Sweat suits are customarily provided at most SART hospitals. This is an appropriate time to raise the issue of returning to the home environment, since the patient will return in clothing that is not customary dress. Provide a headscarf for women who customarily wear head coverings in public.

Arrange follow-up appointments according to Centers for Disease Control and Prevention recommendations. Patients receiving postexposure prophylaxis should be seen within 1 week following initial assessment, and all patients should be seen in 1 to 2 weeks.[31] This ensures the effectiveness of pregnancy prophylaxis and sexually transmitted infection treatment.

Male sexual assault survivors should follow up with a urologist or proctologist. Special populations, such as children, should be referred to a pediatrician or a pediatric abuse clinic.

SPECIAL POPULATIONS

ADOLESCENTS AND CHILDREN

Consider sexual abuse in children if no definitive explanation for nonsexual transmission of a sexually transmitted infection can be identified.[31] For extensive discussion, see Chapter 150, "Child Abuse and Neglect." The most experienced examiner available should examine children to minimize pain or further trauma.

ELDERLY PATIENTS

Most elder assaults take place at the patient's home, and most assaults are by an unknown assailant.[52] In the case of an elderly assault survivor, the forensic interview and examination present unique challenges. The patient not only may resist the pelvic examination because of injury or pain, but the pelvic area may be difficult to visualize because of hip contractures or vaginal atrophy. It is also difficult to explain the examination to a patient with dementia or cognitive impairment. Further challenges include obtaining an accurate and reliable history of the details of the assault, the injuries sustained, and regions of pain or discomfort.[52,53] Special adjustments may be needed for the interview and sexual assault examination.[52,53]

TRANSGENDER AND LESBIAN PATIENTS

Until recently, information about sexual assault of lesbian and transgendered women has mostly relied on data from informal surveys[54] and anecdotal evidence. These data indicate that 47% of transgender women report being raped at least once in their life.[55] The Centers for Disease Control and Prevention's 2018 report, National Intimate Partner and Sexual Violence Survey,[24] used more rigorous research methods and presents significant data about the lesbian, gay, bisexual, transgender, and queer community and sexual assault. **FORGE** (www.forge-forward.org) is a Wisconsin-based group for the support of the transgender population. The group has a website with printable handouts for lesbian and transgendered patients who are sexual assault survivors, survivor first-person narratives, and resource links for both patients and providers.

MEN

Male sexual assault is less common than sexual assault of women.[56] Assaults on males generally result in more severe injuries,[57,58] with 40% to 60% of males sustaining anogenital injuries,[58,59] and assaults on men are likely to involve multiple assailants.[60] At least a third of males who are sexually assaulted have a history of psychiatric or cognitive disability.[59] One major factor that complicates the care of male survivors is the fact that physiologically, the stimulation of anal penetration can lead to involuntary erection and sometimes to ejaculation. Furthermore, many assailants manually stimulate their victims to cause ejaculation. Numerous cases of male sexual assault have been determined to be consensual by judges and defense attorneys who fail to understand the involuntary nature of this physiologic response.[60] The survivors themselves can be confused and distressed by this response and may hesitate to offer this information. Use a short, simple explanation of the physiology using lay language to assist in history taking.

Hospitals have male rape kits available, and the same guidelines should be followed for history, physical exam, collection of forensic evidence, and maintaining chain of custody as have already been described. SANEs and SAFEs are all trained in the sexual assault forensic examination of males. Resources for counseling may be more difficult to find for the male survivor, especially in small communities. The **Rape, Abuse & Incest National Network** does have special resources for men. Its victim hotline can be reached at 1-800-656-HOPE, and its website can be accessed at www.rainn.org.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 294

Intimate Partner Violence and Abuse

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INTRODUCTION AND EPIDEMIOLOGY

Intimate partner violence includes physical violence, sexual violence, threats of physical or sexual violence, stalking, progressive social isolation, and psychological aggression perpetrated by someone who is, was, or wishes to be involved in an intimate or dating relationship with an adult or adolescent individual. These actions are aimed at establishing control by one partner over the other.[1-3]

Intimate partner violence and abuse is the preferred alternative for previously used terms such as *spousal abuse*, *wife battering*, and *domestic violence*. This term more accurately reflects the fact that this type of abuse occurs not only in adult heterosexual married relationships but also in relationships between cohabiting, separated, gay and lesbian, bisexual, and transgender individuals as well as in adolescent dating relationships.[3]

Intimate partner violence and abuse occurs in every racial, ethnic, cultural, geographic, and religious group, and it affects individuals of all socioeconomic and educational backgrounds worldwide. Men are affected, but the overwhelming burden of victimization from intimate partner violence is borne by women.[1,4] Intimate partner violence occurs in both opposite sex and same sex relationships.[3] Risk factors for intimate partner violence and abuse include female sex, age between 18 and 24 years, low income level of the household, black or multiracial race/ethnicity, bisexual sexual orientation, and relationship status of separated rather than divorced or married.[1] Presence of weapons in the home and threats of murder are associated with increased risk of homicide.

Effects extend to family members, friends, coworkers, other witnesses, and the community at large.[1] In families in which *either* child maltreatment or spousal abuse is identified, it is likely that both forms of abuse exist.[5] Children exposed to violence in the home have higher rates of behavioral difficulties; mental and health problems including depression, anxiety, abusive behaviors, and drug abuse; and eating, sleeping, and pain problems.[5] Frequent exposure to violence in the home may normalize violence for children, resulting in higher rates of victimization and perpetration later in life.[1,5]

Providers should ask about a history of intimate partner violence or abuse during healthcare encounters. Failure to recognize and intervene in situations of intimate partner violence may have serious consequences for the survivor and family. Such consequences may include continued violence, physical and behavioral health problems, and injury or even death.[1,6,7]

CLINICAL FEATURES

Intimate partner violence is often cyclical in nature. The cycle begins with a period of tension building, which may include arguing, blaming, or controlling behaviors or jealousy. The next phase is escalation

TABLE 294-1 Health Consequences of Intimate Partner Violence

Adults	Adolescents	Children
Injuries	Same as for adults	Low birth weight
Alcohol and substance abuse	*plus*	Prematurity and associated complications
Sexually transmitted infections	Victimization as an adult	Failure to thrive
Human immunodeficiency virus infection	Fertility problems	Parental neglect syndrome
Pelvic inflammatory disease	Poor school performance and school dropout	Speech disorders
Urinary tract infections	Unwanted pregnancy and associated complications of pregnancy, frequent pregnancies	Bedwetting
Vaginal bleeding	Obesity	Headaches
Unintended pregnancy	Behavioral disorders	Cognitive functioning problems—lower verbal and quantitative skills
Headaches	Involvement with the legal system and courts	Psychological and emotional problems—aggression, hostility, withdrawal, acting out
Chronic pelvic pain	Risky sexual behaviors	Child abuse
Back pain	Prostitution	
Eating disorders	Alcohol and drug use	
GI disorders		
Depression		
Anxiety disorders		
Difficulty sleeping		
Posttraumatic stress disorder		
Substance abuse		
Homelessness		
Social isolation		
Suicide		
Death		

TABLE 294-2 Signs Suggestive of Intimate Partner Violence

Findings	Comments
Injuries characteristic of violence	Fingernail scratches, broken fingernails, bite marks, dental injuries, black eyes, broken bones, cigarette burns, bruises suggesting strangulation or restraint, and rope burns or ligature marks may be seen.
Injuries suggesting a defensive posture	Forearm bruises or fractures may be sustained when individuals try to fend off blows to the face or chest.
Injuries during pregnancy	Up to 45% of women report abuse or assault during pregnancy.[10] Preterm labor, placental abruption, direct fetal injury, and stillbirth can occur.
Central pattern of injury	Injuries to the head, neck, face, and thorax, abdominal and genital injuries.
Extent or type of injury inconsistent with the patient's explanation	Multiple injuries at different anatomic sites inconsistent with the described mechanism of injury. The most common explanation of injury is a "fall." Embarrassment, evasiveness, or lack of concern with the injuries may be noted.
Multiple injuries in various stages of healing	These may be reported as "accidents" or "clumsiness."
Delay between the time of injury and the presentation for treatment	Victims may wait several days before seeking medical care for injuries. Victims may seek care for minor or resolving injuries.
Visits for vague or minor complaints without evidence of physiologic abnormality	Frequent ED visits for a variety of injuries or illnesses, including chronic pelvic pain and other chronic pain syndromes.
Suicide attempts	Women who attempt or commit suicide often have a history of intimate partner violence.[10]

and may include verbal threats, physical and sexual abuse, or assault. Weapons may be used at this point. Sometimes there may be a "honeymoon" phase in which the perpetrator may apologize or make excuses for inappropriate behavior. Over time, the abusive behavior tends to increase in severity, and the intervals between abusive episodes become shorter.

There are no "usual" features to help identify a victim of intimate partner violence. Health-related consequences of violence or abuse often lead to an ED visit (**Table 294-1**).[2,8,9] Signs suggestive of intimate partner violence and abuse are summarized in **Table 294-2**.[1,8]

Signs of abuse may be suspected by behavior of the partner. The abusive partner may be defensive, hostile, and aggressive, and might demonstrate controlling or overly solicitous behavior toward the patient.[9] The patient may appear frightened of the partner or refuse to answer questions and instead defer all responses to the partner. In situations raising concern, and if the patient agrees, hospital security can prevent the alleged perpetrator from visiting the patient in the ED and hospital.

SCREENING AND ASSESSMENT

Many experts, including the U.S. Preventive Services Task Force and the American College of Emergency Physicians, recommend routine screening for intimate partner violence for all adolescent and adult women who present to the ED and for mothers of children brought to the ED. Futures Without Violence has published national screening consensus guidelines.[9] Because of the known adverse long-term impacts of intimate personal violence on health, when time permits, consider screening for lifetime exposure.

A protocol should be implemented that addresses identification of, and screening for, intimate partner violence; training of ED personnel; confidential interviewing; and appropriate interventions, including validation and referral.[2,9,11]

Multicultural and multilingual information about intimate partner violence and effects on abused individuals and family members should be made available to the public and employees. This may consist of posters and/or brochures in areas of the hospital such as public areas, examination rooms, and restrooms. Community resources that provide services to victims should be a part of the shared information.

Screening should be conducted by providers educated about the dynamics of intimate partner violence. Provide a safe and private environment for the interview. Take into account cultural differences and expectations. If language interpreters are required, use individuals who have no connection to the patient. Document screening results, safety assessment, and any interventions, including referrals and required reporting. Screening guidelines for adolescent and adult patients are summarized in **Table 294-3**.[9] Sample verbal screening questions are listed in **Table 294-4**.[9] The U.S. Preventive Services Task Force has published a review of a variety screening tools.[2]

When conducting screening and assessment, be nonjudgmental, sensitive, and direct. Let the patient know that you take the situation seriously. Assure victims of confidentiality. Communicate an understanding of the complexity of the situation and the difficulties of achieving a "quick fix." Reassure the victim that no one deserves abuse and victims are not at fault. It is the abuser whose behavior is unacceptable. Avoid pressuring, respect patient decisions, and work together to determine an appropriate course of action.[12] **Ask abused individuals if they have suicidal or homicidal ideation. Such ideation, particularly if accompanied by a concrete plan of action, should trigger immediate consultation with a mental health provider.**

RISK ASSESSMENT AND DISPOSITION

Ensuring the safety of the abused individual and children is the foremost goal. The most dangerous periods for abused individuals are during the time of abuse disclosure and during attempts to leave the relationship. **Indicators of a high-risk and potentially lethal situation**

TABLE 294-3 Summary of National Consensus Guidelines for Screening for Intimate Partner Violence and Abuse in the ED[9]

Screening	Assessment	Intervention	Documentation	Referral and Follow-Up
Routinely screen at every visit. Screen for current abuse, and if time allows, screen for history of abuse. Screen privately (one on one) or with nonrelated trained interpreter. Ask: What happened? When did it happen? Where did it happen? Who did this? Respect patient decision to disclose or not. Discuss any required reporting. Include screening questions on intake forms.	Assess immediate safety. Assess health impact of abuse. Assess pattern of abuse. Assess for danger and potential lethality. If the danger assessment findings are positive, assess potential for suicide and homicide.	Listen carefully and provide support. "I'm concerned for your health and safety." "You are not alone." "Help is available." "It is not your fault." "You don't deserve it." "What happened to you can affect your health." Provide information and materials. "What can I do for you?" Provide a safety plan. Offer services, including an advocate, social worker, police, shelter, etc.	Legible, fluent; maintain confidentiality of records Abuse history: Subjective information: Patient's own words Objective information: Detailed description of patient's appearance, behavioral indicators, injuries, and health complaints Use of forensic evidence kits where appropriate Results of physical examination Use of body maps Photographs (with patient's consent) Radiologic, laboratory findings, collection of forensic evidence: clothes, debris, etc. Any materials and referrals offered Results of health and safety assessments	Refer to primary care physician, mental health provider, social worker, or intimate partner abuse advocate. Obtain permission to notify provider. Know current phone numbers for: Abuse and assault prevention programs Legal services Children's programs Mental health services Law enforcement Substance abuse programs Transportation Local clergy or other community organizations

include escalation in the frequency or severity of violence; the threat or actual use of weapons; obsession with the abused individuals; hostage taking; stalking; strangulation; and homicide or suicide threats or attempts and evidence of violent behavior outside the home. Another risk factor for serious injury or death is **substance abuse by the perpetrator**, which can increase violent behaviors.[1,8]

If lethality risk is high, consult with experts before ED discharge.[9] Hospital admission of the abused individual or children is an option in high-risk situations in which there is no other way to ensure safety. Use of a 24-hour safe room, a location established by some hospitals and communities to provide a safe place for the patient to stay while arrangements for safe disposition of the patient and family members are made, is another option. Use of an alias name on admission and screening of incoming phone calls may also be of benefit.

Some individuals feel safer remaining in the violent relationship than leaving without adequate planning for a safe departure.[9] Placing the patient in a shelter or having the attacker arrested may not be congruent with the individual's goals. Ultimately, the abused individual must decide if it is safe to return home. By providing information about intimate violence, risks, and options, the ED provider can help the patient decide what is best. The patient's decision making may be very complex, because depression, lack of self-esteem, lack of support, social isolation, financial dependence on the perpetrator, and fear make it difficult to leave the relationship.

Refer individuals to intimate violence experts, such as trained hospital social workers or community-based advocates, who can help the victim assess the situation, understand options, plan for safety, and arrange safe shelter. Community advocates are typically on call or available by telephone. If the patient can be safely discharged from the ED and personal contact with an advocate cannot be made before discharge, give the patient up-to-date information about available services in the community. **Intimate personal violence advocates should not be asked to call the patient directly unless the patient agrees, because calls to the home could jeopardize the patient's safety.**

Resources for healthcare providers to assist in preparing their practices for optimal response to victims of intimate personal violence are available from a number of organizations (**Table 294-5**). **Table 294-6** lists hotlines for patients.

TABLE 294-4 Sample of Intimate Partner Violence Screening Questions*

The healthcare worker should explain the following in his or her own words:

- We are concerned about your health and safety, so we ask all patients the same questions about violence at home and personal life.
- Violence is very common, and we want to improve our response to individuals and families experiencing violence.

The healthcare worker may ask the following questions of ALL patients:

- Are you ever afraid of your partner?
- In the last year, has your partner hit, kicked, punched, or otherwise hurt you?
- In the last year, has your partner put you down, humiliated you, or tried to control what you can do?
- In the last year, has your partner threatened to hurt you?

If intimate partner violence has been identified in any of the above questions, ask if the individual would like assistance today. Be prepared to offer resources, assess for safety, and discuss a safety plan with the individual.

*Additional screening tools are available.[2,9]

ED RECORD DOCUMENTATION

Voluntary descriptions of intimate personal violence should be quoted and described in the patient's own words. Do not use the word *alleged* because it implies that the person recording the incident does not believe the complaint.[9] A complaint of "sexual assault" is no more alleged than is a complaint of "ear pain" or a "sore throat."

Record past and current abuse, with details of date, time, location, witnesses, and specific injury. Describe the patient's health complaints, injuries, appearance, and demeanor. Annotated body maps and photographs can supplement written notes.

TABLE 294-5 Resources for Healthcare Providers

Futures Without Violence (formerly Family Violence Prevention Fund)	http://www.futureswithoutviolence.org
National Domestic Violence Hotline	http://www.thehotline.org/ 800-799-SAFE (7233)
National Coalition Against Domestic Violence	http://www.ncadv.org

TABLE 294-6 Hotlines for Patients	
National Domestic Violence Hotline: 24 h; links caller to help in her (or his) area—emergency shelter, domestic violence shelters, legal advocacy and assistance programs, social services	800-799-SAFE (7233) 800-787-3224 (TTY)
Rape, Abuse, and Incest National Network: 24 h; automatically transfers caller to nearest rape crisis center anywhere in the nation	800-656-HOPE (4673) http://www.rainn.org

Obtain relevant forensic evidence, and follow the appropriate chain of custody of evidence. If sexual assault has occurred, document ED testing and treatment; arrange for a sexual assault nurse examiner exam, if locally available. See Chapter 293, "Female and Male Sexual Assault," for detailed discussion.

Record safety assessment and planning. A safety assessment form or referral notes from an expert are helpful adjuncts.

LEGAL CONSIDERATIONS

Most states in the United States have laws that require healthcare providers to report specified injuries, wounds, or crimes. Intimate personal violence is a crime in all 50 states.[13] Four states have exceptions to mandatory reporting for injuries related to domestic violence. The specifics of the reporting requirements vary from state to state, and the adequacy of response by the police to reporting varies by jurisdiction. Inadequate or inappropriate response to the reports (e.g., informing the perpetrator of the report without providing for the safety of the abused individual) can increase the risk of harm to the abused. Inform the victim if there is an obligation to make a police report and explain possible ramifications.

SPECIAL POPULATIONS

PREGNANCY

Prevalence of intimate partner violence during pregnancy ranges from 6% to 22%.[4,8] Women who report intimate partner violence and abuse during pregnancy are at increased risk of postnatal abuse. Women assaulted during pregnancy are three times more likely to be admitted to the hospital than nonpregnant women.[8]

IMMIGRANT POPULATIONS

Overall, prevalence of intimate partner violence is lower in people born outside of the United States. However, certain immigrant populations have rates far higher than U.S. natives.[1,14] Moreover, the burden of intimate partner violence can be much higher in these populations as victims may be socially and linguistically isolated and perpetrators can use threats of deportation to restrain victims from seeking help.[14] The federal Violence Against Women Act establishes protection that may protect undocumented persons from deportation if they have been a victim of crime, including intimate partner violence.

LGBTQ PERSONS

Intimate partner violence occurs in same sex relationships at rates generally similar to opposite sex relationships. Bisexual women and men, however, report substantially higher rates of intimate partner physical violence overall.[1] Transgender women and gender nonconforming persons also experience intimate partner violence at higher rates. Lesbian, gay, bisexual, transgender, and queer persons may not report to police or seek advocacy services for fear of discrimination.[3]

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REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 295

Abuse of the Elderly and Impaired

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INTRODUCTION

Elder abuse is an act or omission resulting in harm to the health or welfare of an elderly person. Three key groups have published definitions of elder abuse.[1-3] Although the incidence of elder neglect and abuse is unknown and widely felt to be underreported, the rate of different types of abuse among the elderly has been estimated to be in the mid-single digits up to 10% of persons age >65 years,[4] or between 500,000 and 1 million U.S. adults.[5,6] One meta-analysis identified the pooled prevalence of elder abuse overall in geographically diverse countries to be 15.7%.[7] Alternatively, a clinician seeing between 20 and 40 adults over age 60 per day could encounter more than one victim of elder mistreatment on a daily basis.[8] **Table 295-1** summarizes the categories of elder abuse.

CLINICAL FEATURES

PHYSICAL ABUSE

Physical abuse is the most easily recognized form of elder abuse. It is defined as the use of physical force that might result in bodily injury, physical pain, or impairment. Pushing, slapping, burning, striking with objects, and improper use of restraint are all examples of physical abuse. Chemical restraint (such as intentional overmedication or administration of tranquilizers) is a more subtle form. Regardless of mechanism, physical abuse is carried out with the intention of causing suffering, pain, or other physical impairment to the abused person.

CAREGIVER NEGLECT

Elder neglect is the most common form of elder maltreatment, accounting for more than half of all elder maltreatment cases reported to adult protective services agencies annually.[9] Elder neglect is defined as the failure of a caregiver to meet basic needs for a person or to provide goods and services necessary to prevent physical harm or emotional

TABLE 295-1 Categories of Elder Abuse	
Categories of Abuse	Example
Physical abuse	Pushing, slapping, burning, striking with objects, improper use of restraint (physical or chemical)
Caregiver neglect	Deprivation of food, clothing, hygiene, medical care, shelter, or supervision
Sexual abuse	Unwanted touching, indecent exposure, unwanted innuendo, rape
Financial or material exploitation	Forcible transfer of property or other assets, including changing elderly person's will
Emotional or psychological abuse	Verbal threats (such as threats of violence, institutionalization, or deprivation), humiliation, intimidation, harassment, social neglect, and isolation
Abandonment	Desertion of an elder in the home or a hospital, nursing facility, shopping mall, or other public location by a caregiver or caretaker
Self-neglect	Failure or unwillingness to provide adequate food, clothing, shelter, medical care, hygiene, or social stimulation to self in individuals with diminished capacity to perform essential self-care tasks

Source: Reproduced from U.S. Department of Health and Human Services, Administration on Aging and Administration for Children and Families: *The National Elder Abuse Incidence Study*. Washington, DC: National Center on Elder Abuse, 1998.

discomfort.[10,11] Examples of neglect include deprivation of food, clothing, hygiene, medical care, shelter, or supervision that a prudent person would consider essential for the well-being of another.[10,11]

Elder neglect is both underrecognized and potentially lethal. It likely accounts for the majority of cases of unreported abuse.[12] It is also an independent risk factor for mortality, even taking into account that the deaths themselves may not be immediately ascribed to injury.[9] Elder neglect may be difficult to diagnose. Although some cases may be obvious (such as in a patient with multiple deep pressure ulcers), neglect is often more subtle and difficult to detect.

SEXUAL ABUSE

Sexual abuse is broadly defined as nonconsensual sexual contact of any kind with an elderly person. The spectrum of sexual abuse ranges from unwanted touching, indecent exposure, or unwanted innuendo, to rape itself. Although sexual abuse is underreported across all age groups, in the elderly, sexual abuse is even less likely to be reported. Fear of retaliation and shame on the part of patients, as well as stereotyping of older patients as asexual or not sexually desirable by clinicians, police, and others, may be factors in underrecognition and underreporting of sexual abuse.[13]

FINANCIAL OR MATERIAL EXPLOITATION

Financial abuse is estimated to be the second most common form of elder abuse, accounting for approximately 20% to 30% of abuse cases.[14] Financial or material exploitation is the illegal or improper use of an elder's funds, property, or assets.[15] It occurs when family members, caregivers, or friends take control of the elder person's resources. Coercion or outright theft may occur, with or without the awareness of the elder person experiencing abuse. An elderly person may unwittingly sign over access to savings accounts and other assets when he or she is in an incapacitated state. Social Security checks or pensions may be used by caregivers for personal gain. Theft may be blatant or coerced, with forcible transfer of property, including changing of the elder's will. Anticonstitutional abuse is a term coined to describe violation of constitutionally guaranteed human rights, such as theft of identity papers, coercion, or false pretense resulting in the surrender of rights.[16] Abuse may result in a decrease in the standard of living and an inability to pay bills, purchase food, or obtain medications.

EMOTIONAL OR PSYCHOLOGICAL ABUSE

Emotional or psychological abuse is defined as the infliction of anguish, emotional pain, or distress. Examples of psychological and emotional abuse include verbal threats (such as threats of violence, institutionalization, or deprivation), humiliation, intimidation, and harassment. Social neglect and isolation are also forms of abuse. Psychological and emotional abuse can contribute to the development and worsening of mental health problems such as depression, which is common in many older victims.[15]

ABANDONMENT

Abandonment constitutes the desertion of an elderly person by an individual who is that person's custodian or who has assumed responsibility for providing care to the elder. Desertion of an elder in the home, hospital, nursing facility, shopping mall, or other public location may occur.

SELF-NEGLECT

Self-neglect includes those behaviors of an elderly person that threaten his or her own safety. Such behaviors include failure or unwillingness to provide adequate food, clothing, shelter, medical care, hygiene, or social stimulation for oneself. It is the result of an adult's inability, due to diminished capacity, to perform essential self-care tasks. By definition, this applies to one who understands the consequences of his or her choices and makes a conscious decision to engage in acts that threaten his or her own health or safety.[17] Patients who have cognitive impairment or who are living in poverty are at greater risk of self-neglect and may have increased mortality.[9]

TABLE 295-2 Risk Factors for the Occurrence of Elder Abuse

Risk Factors for Elders	Risk Factors for Perpetrators
Cognitive impairment	History of mental illness
Physical dependency	History of substance abuse
Lack of social support	Excessive dependence on elder for financial support
Alcohol abuse	History of violence within or outside the family
History of domestic violence	Unemployed
Female gender	History of financial difficulties
Developmental disability	
Difficult behavior (such as aggression or verbal outbursts)	
Special medical or psychiatric needs	
Limited experience managing finances	
Institutionalization	

DIAGNOSIS

RISK FACTORS

An awareness of risk factors is important for the recognition of potential victims of elder abuse or neglect. Risk factors can be divided into two categories: factors associated with the elders and factors associated with the perpetrators (**Table 295-2**).[10,17-21]

Patient characteristics associated with a higher risk for elder mistreatment are cognitive impairment, physical dependency, lack of social support, alcohol abuse, female sex, and a history of domestic violence.[18] In addition, developmental disabilities, special medical or psychiatric needs, and difficult behavior (such as aggression or verbal outbursts) also increase the risk for abuse. Individuals with limited experience in managing finances are at increased risk for financial or material exploitation. Although elder abuse is more common in residential than institutional settings, institutionalization is also recognized as a risk factor for neglect and abuse.[10,20]

Three characteristics of perpetrators have been identified as risk factors: a history of mental illness and/or substance abuse, excessive dependence on the elder for financial support, and a history of violence within or outside of the family.[21] Abusers are most often the primary caregiver. Adult children tend to be more inclined to abuse than are spouses, and males engage in abuse more often than females.[17] Caregivers may be well intentioned but simply overwhelmed by the amount of care required. They may themselves be impaired by mental or physical problems that serve as barriers to the provision of adequate care.

HISTORY

The approach to the patient interview is important. Potential sufferers of abuse should be interviewed in private. The presence of caregivers, family, or friends may cause the patient to feel intimidated or embarrassed, which limits the amount and accuracy of information obtained. Try to put the patient at ease by making the assessment seem like a routine part of the evaluation.[15] Separately interview individuals accompanying the patient. Screening tools are available to aid in the detection of elder abuse.[22-24] The use of lengthier tools is not feasible in a busy ED, but the American Medical Association has proposed a list of nine screening questions that may be more practical to implement (**Table 295-3**). An affirmative answer to any of the questions in this screening tool raises concern and mandates further exploration.

During the interview, be prepared to recognize behavioral signs and symptoms that suggest elder abuse. These include depression, fear, withdrawal, confusion, anxiety, low self-esteem, and helplessness. Other history-related indicators that suggest abuse or neglect include a pattern of "physician shopping," unexplained injuries inconsistent with medical findings, and recurrent visits for similar injuries. Additional history taking should explore risk factors for abuse as outlined earlier in "Risk Factors."

TABLE 295-3 Screening Questions for Elder Abuse

- Has anyone ever touched you without your consent?
- Has anyone ever made you do things you didn't want to do?
- Has anyone taken anything that was yours without asking?
- Has anyone ever hurt you?
- Has anyone ever scolded or threatened you?
- Have you ever signed any documents you didn't understand?
- Are you afraid of anyone at home?
- Are you alone a lot?
- Has anyone ever failed to help you take care of yourself when you needed help?

Information can be obtained by the physician prior to conducting the private interview or by other members of the healthcare team, such as nurses, who are likely to have more frequent interaction with the patient and caregivers. Observing the interaction between the accompanying individuals can yield valuable clues (**Table 295-4**).

PHYSICAL EXAMINATION

Physical examination findings range from subtle and nondiagnostic to highly suspicious. Abuse is often detected when examination findings prompt further history taking with results suggesting elder mistreatment. Psychological abuse and financial abuse are especially hard to diagnose in the ED setting because physical examination findings are uncommon. Nonetheless, it is important to perform a detailed evaluation, including obtaining adequate exposure of the body to evaluate for trauma and pressure ulcers. Common physical findings in sufferers of elder abuse are bruising or trauma, poor general appearance and hygiene, malnutrition, and dehydration.[23]

Although not the most common form of elder abuse, physical abuse is the most easily recognized. Evidence of injury to normally protected areas of the body is highly suspicious for physical abuse.[18] Examples include contusions or lacerations on the inner arms or inner thighs and injury to the mastoid area. It is important to expose these areas when examining the patient to avoid missing significant findings. Contusions on the palms, soles of the feet, and buttocks also raise concern for elder abuse.[18] Multiple injuries in various stages of healing can suggest abuse but may also be seen in patients with recurrent falls. Taking a thorough history is especially important in differentiating these two causes. Although older patients may sustain burns through accidental injury (such as coming too close to an open flame while cooking), unusual burns or multiple burns in various stages of healing should also raise concern. Traumatic alopecia is highly suspicious, although not necessarily diagnostic (because it may be seen in patients with some psychiatric conditions). Rope or restraint marks on wrists or ankles[17] occur when elders are inappropriately restrained. Midshaft ulnar fractures (nightstick fractures) can occur from attempts to shield blows by raising the forearm. Fractures of the head, spine, and trunk may be more indicative of abuse, although these can occur by other mechanisms. More recently, the radiologic literature has investigated specific findings that may be suggestive of elder abuse, although so far these are not considered pathognomonic; examples include upper, posterior, or multiple rib fractures; multiple subdural hematomas; small bowel hematomas; and injuries inconsistent with reported mechanism. Spiral fractures of long bones and fractures with rotational components also raise suspicion of abuse.[25,26]

TABLE 295-4 Clues During the Medical Interview That May Suggest Elder Abuse

- The patient appears fearful of his or her companion.
- There are conflicting accounts of an injury or illness from the patient and caregiver.
- The caregiver displays an attitude of indifference or anger toward the patient.
- The caregiver is overly concerned with the costs of treatment needed by the patient.
- The caregiver denies the patient the chance to interact privately with the physician.
- The caregiver appears overly concerned and attentive.

Findings resulting from caregiver neglect or self-neglect are less specific. Perhaps the most identifiable finding is that of multiple or deep pressure ulcers. Ulcers that are uncared for (such as open ulcers lacking appropriate dressings or packing) or those not in lumbar or sacral areas raise suspicion even further. Incapacitated patients should be turned as part of the examination to evaluate for skin breakdown. Poor personal hygiene, inappropriate or soiled clothing, dehydration, malnutrition, contractures, fecal impaction, and excoriations suggest neglect.[11]

Sexually transmitted diseases or findings of genital trauma, especially in an incapacitated patient, raise concern for sexual abuse. Patients may complain of genital or anal pain, itching, bruising, or bleeding. Torn or stained underwear, with unexplained difficulty walking or sitting, may be present. Oral trauma can also be a manifestation of sexual abuse.

Depression, anxiety, and fear can be manifestations of psychological abuse, although they are nondiagnostic. Observation of interactions with caregivers and companions can provide further important clues to this type of abuse.

Although elder abuse is widely underrecognized and underreported, remember that underlying medical disorders are often associated with findings that could otherwise be identified with abuse. Advanced neurologic disorders such as multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease may lead to immobilization and severe disability. Individuals with such conditions are at risk for pressure ulcers, pneumonia, or venous thromboembolism, even with adequate care.[17]

TREATMENT, DISPOSITION, AND FOLLOW-UP

Treatment of elder abuse in the ED involves three key components:

- Addressing associated medical and psychological needs
- Ensuring patient safety
- Complying with local reporting requirements (https://ncea.acl.gov/)

Medical problems, including injuries, should be stabilized and treated and may be best managed through hospital admission. In addition to physical injury, metabolic derangements may be present. Patients with dehydration or malnutrition can have a variety of electrolyte abnormalities and may also have coexisting renal failure. Elders left in the same position for an extended period of time may be at risk for rhabdomyolysis. Additional problems may exist due to failure to administer usual medications at home. These issues should all be addressed during the ED visit, including the ability to conduct activities of daily living, such as meal preparation, housework, bathing, dressing oneself, toileting, and managing finances.

Psychological problems brought on by abuse, as well as preexisting psychiatric conditions and substance abuse, should also be addressed. The severity of the problem and planned disposition can affect the extent to which treatment is completed in the ED. For patients requiring hospitalization, concerns and findings should be communicated to the admitting service and documented in the medical record. For patients who are discharged to home, arrangements should be made for appropriate follow-up. Follow-up must be arranged for the patient's medical and psychiatric needs, and arrangements must also be made for monitoring and assessment of home safety and assessment of caregiver stress or substance abuse. A variety of resources are available to assist with these issues (**Table 295-5**). Social work consultation can be helpful in finding local resources.

Patients in immediate danger should be hospitalized, transferred to the care of a friend or reliable family member, or placed in an emergency shelter. Suspected abuse should be reported to the appropriate state agency (https://ncea.acl.gov/) or local adult protective services agency in order to ensure a follow-up investigation and a thorough long-term assessment. Adult protective services is the federal program that receives mandatory reports of suspected abuse, typically leading to a home visit and further investigation. Although all 50 states have adult protective services and long-term care ombudsman programs, reporting is not mandated by law in every state. Elderly who live in the community are protected in all states by adult protective services agencies. Elders in institutional settings are protected in all states by long-term care ombudsman programs. Violations specific to nursing home

TABLE 295-5 Resources for Elder Abuse

Who to Contact	Services Provided
Clinical Justice Services Public Policy Institute American Association of Retired Persons 601 E St., NW Washington, DC 20049 202-434-2222	Provides self-instruction training program, pamphlets, and brochures on elder abuse prevention.
National Adult Protective Services Association (NAPSA) PO Box 96503 PMB 74669 Washington, DC 20090 202-370-6292 http://www.napsa-now.org/	Provides a variety of resources for elder abuse, both nationally and by state and county.
National Center on Elder Abuse c/o University of Southern California Keck School of Medicine Department of Family Medicine and Geriatrics 1000 South Fremont Avenue, Unit 22, Building A-6 Alhambra, CA 91803 855-500-3537 http://ncea.acl.gov/	One of the main information sites for elder abuse; provides a variety of resources, both nationally and by state.
National Organization for Victim Assistance 510 King St., Suite 424 Alexandria, VA 22314 800-TRY-NOVA or 703-535-6682 http://www.trynova.org	Provides referrals, resources in every state.
National Coalition Against Domestic Violence One Broadway, Suite B210 Denver, CO 80203 303-839-1852 http://www.ncadv.org	Provides training and education on domestic violence, publications, and programs.
National Domestic Violence Hotline Toll free: 800-799-SAFE TTY: 800-787-3224 (for hearing impaired) http://www.thehotline.org/	Provides intervention; cannot take reports; confidential; available 24 h via phone. Live chat service available via website 19 h/day.
National Long-Term Care Ombudsman Resource Center http://www.ltcombudsman.org	Provides information on support, technical assistance as well as information on local long-term care ombudsman resources by state.
National Council on Aging 251 18th Street South, Suite 500 Arlington, VA 22202 571-527-3900 http://www.ncoa.org	Addresses many aging issues through various programs.
Commission on Law and Aging American Bar Association 321 North Clark Street Chicago, IL 60654 312-988-5000 http://www.abanet.org/aging	Provides information on laws pertinent to elders; has contact information by state and other law-related services for legal assistance providers; provides mandatory reporting requirements for each state. Makes available Domestic Violence and Sexual Assault in Later Life, a resource packet of information and materials accessible online.
National Center on Elder Abuse 1201 15th Street, NW, Suite 350 Washington, DC 20005 202-898-2586 Email: ncea@nasua.org https://www.elderabusecenter.org/	One of the main information sites for elder abuse; provides a variety of resources, both nationally and by state. Also provides link to Training Library for Adult Protective Services and Elder Abuse.
Family Caregiver Alliance 235 Montgomery Street, Suite 950 San Francisco, CA 94104 415-434-3388 or 800-445-8106 http://www.caregiver.org	Lead agency in CareJourney, a program designed to provide Internet services to caregivers of adults with cognitive impairments.
AARP 601 E St., NW Washington, DC 20049 888-OUR-AARP http://www.aarp.org	Leading organization representing people over age 50. Provides publications on caregiving issues, financial planning, durable power of attorney, trusts, and insurance.
Other resources: Administration on Aging 330 Independence Ave., SW Washington, DC 29201 202-245-0641 https://www.acl.gov/about-acl/administration-aging	
National Committee for the Prevention of Elder Abuse 1730 Rhode Island Ave., NW, Suite 1200 Washington, DC 20036 202-464-9481 http://www.preventelderabuse.org	
National Committee for the Prevention of Elder Abuse c/o Institute on Aging 119 Belmont St. Worcester, MA 01605 508-793-6166	
Elder Care Locator U.S. Administration on Aging 800-677-1116 https://eldercare.acl.gov/Public/Index.aspx	Nationwide service connecting older Americans and caregivers with local support resources.

residents might include the following: failure to respond to calls for help, unattended symptoms, injury of unknown origin or falls, physical abuse, poor staff attitudes related to respect or dignity, inappropriate medications or dosages, stolen or lost property, or abuse by other residents. Much long-term facility abuse occurs between residents; many facilities have younger psychiatric patients who are more mobile and aggressive than the older debilitated residents.[27] Become familiar with requirements pertaining to your own practice area (https://ncea.acl.gov/).

TABLE 295-6 American College of Emergency Physicians Policy on Domestic Family Violence[31]

- Emergency personnel assess patients for intimate partner violence, child and elder maltreatment, and neglect.
- Emergency physicians are familiar with signs and symptoms of intimate partner violence, child and elder maltreatment, and neglect.
- Emergency medical services, medical schools, and emergency medicine residency curricula should include education and training in recognition, assessment, and interventions in intimate partner violence, child and elder maltreatment, and neglect.
- Hospitals and EDs encourage clinical and epidemiologic research regarding the incidence and prevalence of family violence as well as best practice approaches to detection, assessment, and intervention for victims of family violence.
- Hospitals and EDs are encouraged to participate in collaborative interdisciplinary approaches for the recognition, assessment, and intervention of victims of family violence. These approaches include the development of policies, protocols, and relationships with outside agencies that oversee the management and investigation of family violence.
- Hospitals and EDs should maintain appropriate education regarding state legal requirements for reporting intimate partner violence and child and elder maltreatment.

In cases of unintentional neglect, education of the caregiver may be the only intervention necessary. Other support options include home health aide visits, respite services, day programs, accessible transportation, support groups, adult day care, and church activities or pastoral visitations.[20,28] When mistreatment results because the caregiver is overburdened, interventions to decrease stress and anxiety may be welcomed by all parties. Spouses are most likely to be primary caregivers; most of these are women. Lack of sleep and inadequate exercise and nutrition are commonly expressed by caregivers, perhaps leading to anger and risk of abuse. Services for caregivers may be publicly funded or community based with support groups. Some programs provide home-delivered meals, respite care, counseling, and assistance with advance directives and estate planning.[29]

If available, medical case management teams can provide consultation and support by assisting in the multidisciplinary evaluation of suspected abuse cases and developing treatment plans. Team members generally are composed of a physician, nurses, and social workers.[30] Teams may make house calls, arrange physical and occupational therapy, and provide for nutritional improvement and management of disease states. Legal intervention teams can also be used to address financial management, probate and guardianships, and other legal and housing issues. Civil courts can issue protective orders, create guardianships, and issue emergency removal orders. Recommendations for ED management of cases of elder abuse and neglect are provided in **Table 295-6**.[31]

SPECIAL CONSIDERATIONS

BARRIERS TO THE DETECTION OF ELDER ABUSE

Sufferers of elder abuse often have low self-esteem and may blame themselves for the abuse. They may not want to admit vulnerabilities and feel disgraced for having raised a child who would betray them.[28,32]

Elder abuse victims may also be unwilling to press charges against a family member. Abused older adults are frequently unaware of available resources.[32] In addition, they may harbor a fear of being removed from the home or placed in a long-term care facility, of implicating family members, or of experiencing further abuse in retaliation for having divulged information. They may worry about not being believed. Victims may be unable to articulate their circumstances due to cognitive impairment. Abusers may control access to others and prevent encounters with outsiders to ensure that secrecy is maintained. There may also be differing perceptions as to what constitutes abuse based on cultural background.[33]

Physicians may fail to report abuse for a variety of reasons. They may not be familiar with reporting laws or adequately understand reporting mechanisms.[5] They may fear offending patients or their family members. Time constraints in the ED can also be a barrier to recognition and reporting. There are no published studies of physical markers of mistreatment to distinguish preventable injury from intentional, inflicted, or avoidable trauma.[34] In addition, some physicians may have the misperception that the law requires them to obtain the patient's permission before reporting suspected abuse.[35] Hospitals may also lack protocols for identifying or addressing elder abuse. It has been noted that screening for elder abuse and neglect has not been recommended by the U.S. Preventive Services Task Force for some of the aforementioned reasons.[4]

ABUSE IN LONG-TERM CARE FACILITIES

Approximately 1.4 million Americans lived in nursing homes on any given day in 2012.[36] Elder abuse in nursing homes is well documented. In one study, 36% of nurses and nursing aides working in long-term care facilities reported witnessing at least one act of physical abuse in the previous year.[37] A study of 2400 deaths in Arkansas nursing homes found 50 cases of suspected abuse or neglect, which indicates that forensic studies need to play a larger role in the investigation of unexplained deaths of older adults in long-term care facilities.[38] Abuse in institutional settings manifests in similar ways to abuse in residential settings: theft of money or personal property, unsanitary conditions, poor personal hygiene, sexual assault, physical abuse or unexplained injury, bed sores, physical or chemical restraint, and malnutrition and dehydration. Perpetrators appear to be evenly divided between residents of the facility and staff members involved in the direct care of the victim.[36] Nursing homes participating in Medicare and Medicaid programs must comply with certain quality-of-care requirements.[39] Suspicion of abuse or neglect among patients in nursing homes should be reported to the state nursing home ombudsman program (http://www.ltcombudsman.org) or to an adult protective services agency.

LEGAL CONSIDERATIONS

Circumstances may occur in which hospital admission is advised, but the patient refuses. If the patient is competent, his or her wishes must be honored, even if those wishes do not appear to be in the patient's best self-interest. Decisional capacity by the patient depends on his or her ability to understand all of the relevant information in order to make a choice, to communicate that choice, and to appreciate the current situation and treatment options. Therefore, it is especially important to interview the patient alone and to explain in detail the concerns of the healthcare provider. The physician should also attempt to explore reasons for the patient's reluctance to stay.

Patients who refuse admission but who lack decision-making capacity should not be discharged back to an unsafe environment. Contact with an adult protective services agency should be initiated. ED social workers can help locate contact information for the local adult protective services agency. If the agency determines that the victim of abuse lacks decision-making capacity, an emergency court order for protective services may be necessary.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 296

Injection Drug Users

Suzanne M. Shepherd

INTRODUCTION AND EPIDEMIOLOGY

In 2015, multiple groups estimated that a quarter of a million people, approximately 5% of the adult population, used illicit drugs of any variety at least once; the expected use likely causes between 12 million and 28 million years of "healthy life" lost due to premature disability and death.[1] In 2015, the United States had approximately one quarter of reported drug-related deaths worldwide, with more than double the death rate seen in 1999. Globally, drug-related deaths produced more mortality than road traffic accidents or violence. Opioids remain the most harmful type of drug of abuse, with a higher risk of fatal and nonfatal overdose and risk of acquiring infection. Of people who inject illicit drugs worldwide, about 1.6 million are infected with human immunodeficiency virus (HIV) and 6.1 million are infected with hepatitis C.

RISK BEHAVIORS OF INJECTION DRUG USERS

The practice of injection and the lifestyle and culture of injection drug users place such individuals at risk for a wide variety of infectious and noninfectious medical complications. In addition to carrying an increased risk of infection with HIV, hepatitis B and C, Kaposi's sarcoma-associated herpes virus, tetanus, tuberculosis, and sexually transmitted diseases, the injection drug user also has an increased risk of trauma and intimate partner violence.[2,3] It is important to vaccinate injection drug users against hepatitis B virus, human papillomavirus, and, when it becomes available, HIV.[4] The Centers for Disease Control and Prevention recommends routine HIV screening in EDs and that consent for testing should be "opt-out."[5]

An association between childhood emotional, physical, and sexual abuse or trauma and IV drug abuse also highlights the importance of trauma-informed interventions for injection drug users and the importance of early screening and treatment for drug abuse in those who have undergone childhood trauma.[6] The high incidence of migration, incarceration, homelessness, nutritional deficiencies, coincident smoking and alcohol use, and mental illness further compromises the health of this group.

PATHOPHYSIOLOGY

Injection drug use increases the risk for immunomodulating infections, such as HIV infection and hepatitis, and may induce immune dysregulation. Exaggerated and atypical lymphocytosis, diminished lymphocyte responsiveness to mitogenic stimulation and depressed chemotaxis, hypergammaglobulinemia, increased opsonin production, decreased T-cell and natural killer cell activity, high levels of circulating immune complexes, and reticuloendothelial abnormalities can be evident with ongoing drug injection. False-positive results on nontreponemal syphilis serologic tests, positive results on Coombs tests, low measured antibody response to vaccination, and thrombotic thrombocytopenic purpura are possible in this population.[7] The immunomodulatory effects of injection drug use may also contribute to the progression of HIV infection, as HIV-infected patients who inject drugs are found to be less likely to suppress HIV-1 RNA than those who do not.[8] Given their immune dysfunction, suspect infection in all febrile patients with ongoing drug injection even if the temperature elevation is modest or WBC counts and erythrocyte sedimentation rates are normal or near normal.

CLINICAL FEATURES

Be aware of the drugs used in local ED catchment areas, the constantly evolving street names (e.g., "H," "skag," "tar," "bud light"), and adulterants used to cut the drugs. Ask about drug type(s) and amount, preparation of materials for injection (e.g., crushing capsules in the mouth, licking needles, blowing on injection sites or blowing out clots in needles, or using saliva, lemon juice, or tap or toilet water for drug reconstitution), reuse of needles, needle sharing and HIV/hepatitis status of drug-sharing partner(s), use of antibiotics, antiretroviral and hepatitis C therapy, and coincident medical and mental illness.

Complications of injection drug use may be obvious, such as a painful, erythematous, fluctuant abscess. However, more subtle and vague symptoms such as weakness, anorexia, myalgias, weight loss, night sweats, and fever are common and may be the only signs of serious underlying disease (**Table 296-1**). In addition, approximately 1 in 30 female injection drug users seeking care has alloantibody in pregnancy, possibly due to needle sharing, that can accompany early pregnancy loss and poor obstetric care.[9]

FEVER

Fever is associated with infection in most patients. Noninfectious causes of fever include acute toxic reactions to substances of abuse, reactions to injected adulterants, and withdrawal syndromes. Cocaine and amphetamines can cause acute fever. Patients with "**cotton fever**" develop a flulike syndrome within hours after injection with drug suspensions filtered through cotton balls. Findings may include tachypnea, tachycardia, abdominal pain, and inflammatory retinal nodules. Chest radiographs typically are normal but may demonstrate inflammatory pulmonary granulomata. Symptoms spontaneously resolve within 24 hours.[10] Patients withdrawing from barbiturates or heroin also may appear acutely ill, presenting with chest and abdominal pain, diaphoresis, tachycardia, and fever.

Because no reliable markers are available to exclude serious illness in the febrile injection drug user, common practice samples blood for culture to detect bacteremia or endocarditis when no clear other source exists (e.g., pneumonia, urine infection, cellulitis, or abscess) while admitting such patients for observation pending results. In clinically well patients for whom follow-up can be ensured, outpatient management is reasonable after appropriate culture specimens are obtained.

Explore socioeconomic issues such as the injection drug user's ability to purchase medications and access to outpatient follow-up; the latter may impact disposition plans.

Deliver nonjudgmental instruction on measures to reduce the risk of recurrent harm and offer drug rehabilitation (even as an outpatient referral) in all cases. If available, counsel about local needle exchange centers or supervised drug injection centers, which can save lives, prevent disease transmission, and improve health in this population.

TABLE 296-1 Evaluation of Injection Drug Users in the ED

Presenting Symptom	Potential Findings	Possible Diagnoses	Ancillary Tests
Fever alone	Shortness of breath, cough	Pneumonia	Chest radiography; blood cultures; ESR CRP; echocardiography
	Heart murmur	Endocarditis	CXR; blood cultures; ESR; CRP; TTE or TEE
	Needle and track marks	Occult bacteremia	Blood cultures; CXR; possible Doppler US to evaluate abscess, septic thrombophlebitis
	Hypoxemia		CXR; possible ECHO
	Dysuria		UA
Fever with nausea and vomiting, rigors, abdominal pain	Diaphoresis	Drug withdrawal	Complete blood cell count; blood cultures; hepatitis serologic testing; liver panel; UA
	Recent injection	"Cotton fever"	
	Jaundice or icterus	Hepatitis	CBC; LFTS; INR; consider hepatitis serology
Fever with dyspnea and cough	Rales and rhonchi	Bacterial pneumonia	Chest radiography; blood cultures; chest CT
	Purulent sputum	Atypical pneumonia	
	Hypoxemia	Tuberculosis	Also sputum cx & gram stain and AFB stain
		Pneumonia due to opportunistic organisms	
		Septic pulmonary emboli	
Fever with weakness, weight loss, anorexia, night sweats, diarrhea	Cachexia	HIV infection; tuberculosis	HIV serologic testing; blood cultures; chest radiography; sputum staining for acid-fast bacillus; sputum culture; hepatitis serologic testing
	Oral thrush	HIV infection	
		Hepatitis B and C	
Fever with back pain	Heart murmur	Osteomyelitis	Blood cultures; ESR; CRP; bone radiography; CT or MRI; urinalysis
	Focal neurologic signs	Epidural abscess	
	Flank tenderness	Endocarditis	
		Renal abscess	
Dyspnea and cough	Expiratory wheezes	Hypersensitivity reaction	Chest radiography; spirometry; echocardiography; blood cultures
	Rales and rhonchi	Noncardiogenic pulmonary edema	CXR; ECHO
	Fever	Pneumonia	
	Pleuritic chest pain	Septic pulmonary emboli	Blood cultures, ECHO
		Talc reaction	
Painful limb	Localized erythema	Cellulitis	Wound specimen cultures; soft tissue radiography; CT; blood cultures
	Tenderness	Abscess	
	Localized bruit	Pseudoaneurysm	Doppler ultrasound
	Muscle pain and swelling	Myositis	ESR, CK, aldolase
	Fever	Fasciitis	
		Retained foreign body	X-ray or CT
Altered mental status	Obtundation	Drug overdose or intoxication	CT; drug screen; lumbar puncture; blood cultures
	Focal neurologic signs	Drug withdrawal	
	Meningismus	Central nervous system lesion	
	Seizure	Meningitis	
		Tetanus	
Eye pain and vision loss	Periorbital vesicles	Herpes zoster	Viral and fungal cultures; serology for HSV/syphilis; slit lamp exam; funduscopy; ophthalmology consult
	Subconjunctival lesions	Kaposi sarcoma	
	Keratitis	Keratoconjunctivitis sicca	
	Iridocyclitis	Herpes simplex	
	Retinitis	Cytomegalovirus infection	
	Poorly reactive pupil	Varicella zoster	
	Vitreous exudates	Toxoplasmosis	
		Syphilis	
		Fungal infection	

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus.

DYSPNEA

A wide range of infectious and noninfectious entities may produce dyspnea and cough in patients with ongoing drug injection. Pneumonia in injection drug users is typically community acquired (see Chapter 155, "Human Immunodeficiency Virus Infections"). However, dyspnea may arise from aspiration during intoxication, tuberculosis, opportunistic infections, presence of foreign body, and septic pulmonary emboli complicating right-sided endocarditis. Place all febrile injection drug users who present with dyspnea, cough, or abnormal findings on chest radiograph in respiratory isolation until tuberculosis is excluded or an alternative diagnosis is found.

Noninfectious causes of dyspnea include noncardiogenic pulmonary edema, pneumo- or hemothorax, toxic reaction to injected substances, hypersensitivity reaction, foreign body granulomatosis, and exacerbation of reactive airway disease. Pneumothorax and hemothorax are seen most commonly in association with the practice of "pocket shooting," in which drug users inject into the supraclavicular fossa to access the subclavian, jugular, or brachiocephalic vein. "Talc lung" is a syndrome of progressive respiratory distress and diffuse interstitial infiltrates caused by the injection of the talc adulterant. Hypersensitivity reactions, associated with both heroin and cocaine injection, present with cough and wheezing and typically respond to inhaled β-agonist therapy. Noncardiogenic pulmonary edema is associated with both heroin and cocaine use, and patients display dyspnea, exhibit a low pulse oximetry reading, or have a radiograph revealing diffuse alveolar infiltrates. Treatment is supportive. Finally, septic, air, or needle fragment emboli to the lungs can produce dyspnea.

ALTERED MENTAL STATUS AND NEUROLOGIC ABNORMALITIES

Drug intoxication or withdrawal, stroke syndromes, hypoxia, delayed leukoencephalopathy, infectious diseases, mycotic aneurysms, and secondary trauma from either loss of consciousness and fall or drug-related violence may all produce altered mental status or other neurologic impairment in injection drug users. CNS infections may result from contiguous spread of overlying soft tissue infection, embolic complications of distant infections (e.g., endocarditis), or extension of local infections (e.g., vertebral osteomyelitis). Nervous system infections that commonly occur in this population include epidural abscess, bacterial and fungal meningitis, and brain abscess. Meningococcus, pneumococcus, and *Staphylococcus aureus* bacteremia from endocarditis are common causes of bacterial meningitis. Both tetanus and botulism exist more often in patients who inject drugs and may present with cranial nerve involvement, altered mental status, and progressive symmetric paralysis. Infections caused by opportunistic organisms, such as *Toxoplasma*, are common in patients with coincident HIV infection who have low CD4 counts (especially <100/mm^3). Stroke syndromes may occur secondary to low-flow states during heroin intoxication; hypertensive hemorrhage from amphetamines, phencyclidine, or cocaine; and embolized vegetations associated with infectious endocarditis. Delayed leukoencephalopathies, both hypoxic and nonhypoxic, have been reported in injection drug users but are rare.

BACK PAIN

Back pain may result from an epidural abscess, vertebral osteomyelitis, spondylodiscitis, or trauma; often the WBC count, sedimentation rate, or C-reactive protein are elevated in these conditions but not universally. Mycobacterial infections usually involve the ribs and vertebral column (Pott's disease). These infections may be indolent and present only with pain or may demonstrate night sweats, fevers, and weight loss. In patients with coincident HIV infection, opportunistic infections may present with a more indolent course, and the only symptom may be local pain. Nontraumatic focal back pain in febrile or nonfebrile injection drug users requires imaging studies, usually MRI, to evaluate for possible infection. In patients with chronic back pain, failure to inquire about a history of IV drug use or ignoring features that suggest infection (e.g., pain that does not resolve when the patient lies down, severe nighttime pain, or failure of pain to improve with conservative therapy) can lead to missed diagnosis of a cord-compromising infections.[11]

SPECIFIC INFECTIONS IN INJECTION DRUG USERS

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

HIV infection and management are discussed in Chapter 155. All-cause mortality is three times higher among HIV-positive injection drug users than those who do not inject, with the largest portion attributable to acquired immunodeficiency syndrome–related deaths.[12,13] Evidence supports the effectiveness of HIV prevention programs including needle exchange, education on condom usage, and agonist maintenance treatment,[14] and more recently the use of preexposure prophylaxis.[15]

INFECTIVE ENDOCARDITIS

The incidence of endocarditis in injection drug users is estimated to be 40 times that in the general population.[16] For injection drug users presenting with fever, the risk of endocarditis increases to one in eight, and for injection drug users from an inner-city population who are later found to be bacteremic, the risk increases to 40%.[16] Endocarditis in injection drug users is typically right sided (57% to 86% of cases); 55% to 94% of cases involve the tricuspid valve, 20% to 40% involve the mitral and aortic valves, and 5% to 14% involve both sides of the heart[17,18] (see Chapter 156, "Endocarditis").[16] Hospitalizations for endocarditis are increasing in the setting of the current opioid epidemic.[19,20] Chapter 156 covers endocarditis management in detail.

Presenting signs and symptoms in injection drug users with endocarditis include fever, murmur (up to 65%), cough, pleuritic chest pain, and hemoptysis. Right-sided heart murmurs that vary with respiration are typically pathologic and more specific for the diagnosis.[16] Multiple opacities on chest radiograph, consistent with septic pulmonary emboli, are common in patients with right-sided endocarditis (**Figures 296-1** and **296-2**).[14] Other findings include pyuria (22%) and hematuria (35%) due to glomerulonephritis from immune complex deposition, embolic renal infarction, and perinephric abscess.[17,21] Systemic embolization is found in approximately 22% to 50% of cases, and embolic infections may precede the finding of endocarditis in 25% to 60% of cases.[17,22,23]

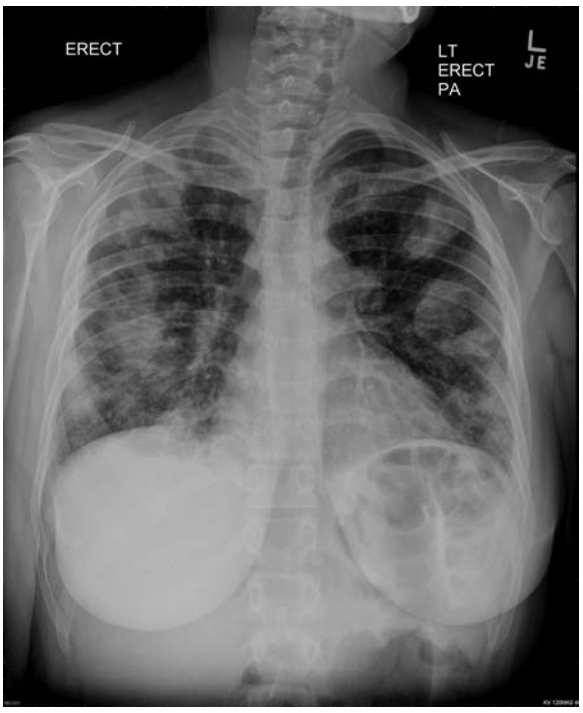

FIGURE 296-1. Chest radiograph showing septic emboli. Multiple opacities are seen in this chest radiograph of an injection drug–using female patient who was found to have bacterial endocarditis.

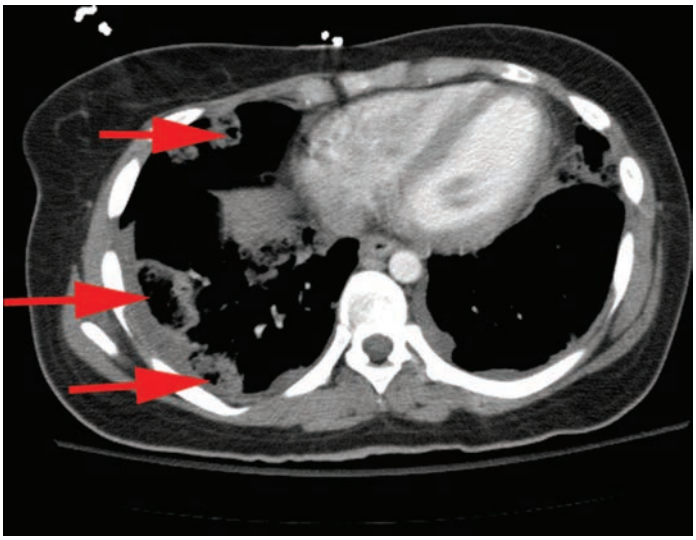

FIGURE 296-2. CT image showing multiple peripheral cavitary lesions consistent with septic pulmonary emboli.

Diagnosis of infective endocarditis generally requires isolation of microbes in a blood culture and/or demonstration of typical lesions on echocardiography. The classic findings of embolic phenomena, including Janeway lesions and Roth spots, are usually not observed unless the infection is advanced and occur in less than 15% of cases.[21] Osler's nodules are usually not seen with right-sided endocarditis. Obtain at least three sets of blood cultures from separate sites, with at least an hour's wait between collection of the first and last set, before the initiation of antibiotic therapy.

Determine empiric antibiotic therapy based on the stability of the patient and the ability to wait for initial blood culture results. Direct initial treatment against *S. aureus* (methicillin-specific or methicillin-resistant *S. aureus*) and *Streptococcus* and *Enterococcus* species, with consideration of local sensitivities and pathogens. If the injection drug user engages in needle licking or uses saliva to reconstitute the drug, antibiotic selection must cover oral (streptococcal and anaerobic) and skin flora.

PULMONARY INFECTIONS

Community-acquired pneumonia caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* remains the most common pulmonary infection in injection drug users. Patients are also at high risk for infection due to *S. aureus*, including methicillin-resistant *S. aureus*; *Klebsiella pneumoniae* infection; aspiration pneumonia; tuberculosis; and, in HIV-positive patients, opportunistic infections caused by *Pneumocystis jiroveci*, cytomegalovirus, and atypical mycobacteria. Suspect aspiration pneumonia in those with a history of depressed level of consciousness and/or radiographic infiltrate in the posterior or basal lung segments.

The risk of tuberculosis, including drug-resistant tuberculosis and extrapulmonary tuberculosis (see earlier discussion of Pott's disease), is higher in injection drug users, accompanied by delays in diagnosis and poor adherence to treatment regimens. The tuberculin skin test may be negative. Coincident HIV infection is one of the major risks for the high incidence of tuberculosis.[1] Tuberculosis management is discussed in detail in Chapter 67, "Tuberculosis."

Patients are usually admitted to the hospital with respiratory isolation until tuberculosis is excluded.[17] In patients without risk for *Pseudomonas* infection, an IV quinolone and IV ceftriaxone or cefotaxime are reasonable empiric coverage until culture results return. In those at risk for *Pseudomonas* infection (structural lung disease, malnutrition, current or recent corticosteroid use or antibiotic use), consider an IV antipseudomonal β-lactamase agent (cefepime, imipenem, meropenem, or piperacillin/tazobactam) and an IV antipseudomonal fluoroquinolone or, alternatively, an antipseudomonal β-lactamase agent, IV aminoglycoside, and fluoroquinolone.[24] Injection drug users are also at increased risk for influenza due to injection practices and living conditions, so encourage yearly influenza vaccination.[4]

SKIN AND SOFT TISSUE INFECTIONS

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Skin and soft tissue infections are common among injection drug users and include cellulitis, skin ulcers, subcutaneous abscesses, septic phlebitis, necrotizing fasciitis, Fournier's gangrene, gas gangrene, and pyomyositis. Most are caused by the user's own flora, with *S. aureus* and streptococcal species common pathogens. Because these infections are often self-treated and reporting is not required, the prevalence is difficult to determine.

Injection techniques and eventual loss of easily accessible veins predispose injection drug users to soft tissue trauma and ischemia. The drugs themselves and the adulterants irritate, sclerose, and necrose the skin. Desomorphine (street name Krokodil) typically contains large amounts of toxic components such as iodine and phosphorus and can cause serious damage to skin, blood vessels, bone, and muscles. Limb amputation may be necessary, which has given this drug the nickname "the flesh-eating drug."[25]

CLINICAL FEATURES AND DIAGNOSIS

Cutaneous infection presents with fever, pain, localized erythema, and edema. Inspect painful areas for fluctuance, crepitus, and lymphangitis suggestive of deeper infection or abscess. Cellulitis and abscesses are typically caused by *S. aureus, Streptococcus*, or community-acquired methicillin-resistant *S. aureus*.[26] Abscess cultures may also demonstrate polymicrobial growth, with aerobic gram-negative rods, anaerobic cocci, and bacilli. Increased rates of *Clostridium botulinum* infection exist in injection drug users who engage in skin popping, particularly those using Mexican black tar heroin.

Tetanus is another potential complication of injection drug use, and mortality from tetanus is high in older, unvaccinated patients.[4] Other skin concerns include retained portions of broken needles, which act as a nidus for infection or migrate into adjacent vessels and, in addition, pose an increased risk to the examining healthcare provider. These may be identified by radiograph prior to exploration.

Infections overlying venipuncture sites may produce septic thrombophlebitis and infected pseudoaneurysms. Femoral vein injection ("groin hit") may start development of local gangrene as well as rapidly progressive and fatal Fournier's gangrene. Injection into the jugular vein ("pocket shot") may lead to cutaneous abscess formation involving the carotid triangle and produce airway obstruction, vocal cord paralysis, and laryngeal edema.

Imaging For nonpulsatile areas of induration, bedside US can define an underlying abscess. Image any pulsatile masses with Doppler US prior to incision and drainage. Angiography may identify vasospasm, thrombosis, emboli, or mycotic aneurysms. Plain radiographs are not routinely needed, unless suspecting air in the soft tissues or radiopaque foreign bodies. CT or MRI can delineate the involvement of other structures and the extent of deep abscesses, especially in complex areas such as the neck or groin.

TREATMENT AND DISPOSITION

Incise and drain all uncomplicated small abscesses, large furuncles, and carbuncles. Treat injection drug users with superficial cellulitis without evidence of systemic involvement with oral antibiotics to cover streptococci and methicillin-resistant *S. aureus* (see Chapter 152, "Soft Tissue Infections," Table 152-2).[27]

Febrile or toxic-appearing patients or those not responding to outpatient treatment require hospital admission. If hand, deep tissue, or muscle involvement is detected or suspected clinically, consult for possible exploration or debridement.

For admitted febrile or toxic-appearing patients, obtain blood and wound specimens for culture and start broad-spectrum IV antibiotic therapy. Base antibiotic coverage on community microbial prevalence and host factors. Appropriate choices include a penicillinase-resistant synthetic penicillin or vancomycin plus an antipseudomonal aminoglycoside, antipseudomonal penicillin, or cephalosporin (see Chapter 152, "Soft Tissue Infections"). Update tetanus immunization.[4]

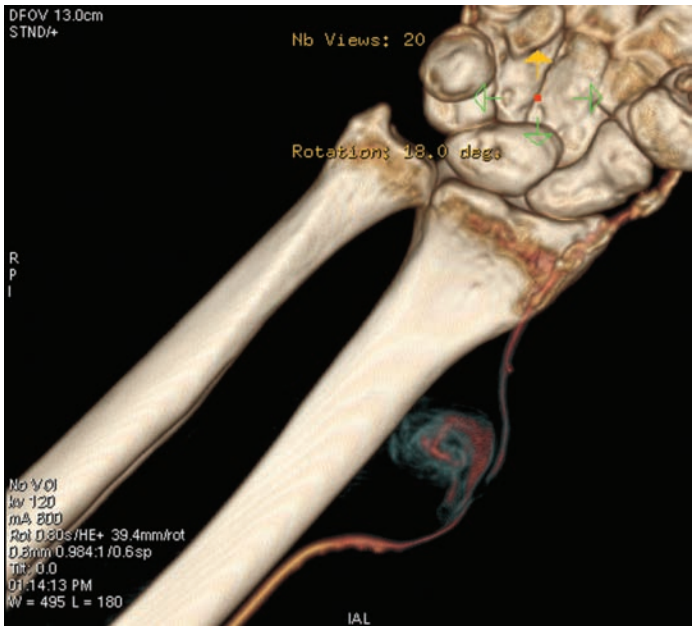

FIGURE 296-3. Volume-rendering CT of the wrist showing a radial artery pseudoaneurysm in the inferior portion of the image. The pseudoaneurysm has displaced the radial artery away from the bony radius.

VASCULAR INFECTIONS

Vascular infections associated with injection drug use include inadvertent arterial injection with resultant vasospasm or thrombosis, septic thrombophlebitis, venous and arterial pseudoaneurysms, and infected hematomas. Arterial injection causes pain, edema, and patchy mottling of the affected limb due to ischemia. Tissue necrosis and gangrene are the consequence of persistent focal ischemia.[28] When suspecting limb ischemia, promptly consult a vascular surgeon to determine whether anticoagulation, surgical intervention, or intra-arterial thrombolysis is best. Limb edema and ischemia can progress to compartment syndrome or may be complicated by rhabdomyolysis.[29]

Intra-arterial drug injection can result in an infected arterial pseudoaneurysm (**Figure 296-3**).[28] Venous pseudoaneurysms are relatively rare and are usually secondary to septic phlebitis. Signs and symptoms are fever and a painful mass. Complications include life-threatening hemorrhage, sepsis, chronic claudication, chronic skin and soft tissue infections, posttraumatic ulcers, and limb loss.[30,31] A pseudoaneurysm is similar in gross appearance to an abscess; the presence of pulsations and a bruit suggest this diagnosis. Because of the disastrous hemorrhagic consequences of attempted incision and drainage, all painful masses, particularly in the groin, should be first imaged with duplex US or contrast CT.

Treatment is antibiotic therapy guided by recommendations for endocarditis (see Chapter 156, "Endocarditis"). Surgical options include ligation and resection of the infected pseudoaneurysm with or without selective revascularization.

BONE AND JOINT INFECTIONS

Bone and joint infections occur either through contiguous spread from an overlying skin or soft tissue infection or through hematogenous spread from a distant site. Infecting microorganisms in injection drug users include *S. aureus* and other streptococci, or they may be unusual, such as *Candida* and gram-negative organisms.

OSTEOMYELITIS

In injection drug users, osteomyelitis is more frequent in the axial skeleton than in the extremities. Injection drug use–related osteomyelitis involves the vertebral column in approximately 50% of cases, particularly the lumbar segments, followed by the sternoclavicular joint in approximately 18% of cases, the sacroiliac joints, and the extremities, especially the hip and knee joints, in 17% of cases. Vertebral osteomyelitis usually presents with localized pain and tenderness to palpation over the involved bone, and a soft tissue mass may be palpable. Osteomyelitis coexists with spinal epidural abscess in approximately 80% of cases.[32] Symptoms may be present for days in the case of bacterial infections or weeks in the case of fungal or mycobacterial infections. The presence of fever, leukocytosis, and an elevated erythrocyte sedimentation rate and C-reactive protein level is helpful, but their absence does not exclude these infections.

Culture any drainage from a contiguous abscess. Biopsy or needle aspiration of joint spaces and bony infections may be necessary, especially in the case of infection with unusual or fastidious organisms, such as *Mycobacterium*, *Candida*, or *Eikenella*. *Eikenella corrodens* osteomyelitis may occur in injection drug users who lick their needles prior to injection.

Fungal infections are rare but increasing in spinal infections related to immunosuppression and IV drug use. *Candida* species infection occurs in as many as 20% of patients with injection drug use–related osteomyelitis. Candidal infections are probably hematogenous in origin and have been reported from the use of contaminated reconstituted lemon juice to mix drugs before injection. An initial flulike syndrome lasting 3 to 4 days is followed by the appearance of metastatic lesions involving the skin, eye (chorioretinitis and endophthalmitis), and then bones and joints several days to weeks later. Rarely, *Aspergillus* species may cause osteomyelitis of the sternum in injection drug users.

MRI is currently the imaging modality of choice at many facilities because it delineates both the longitudinal and paraspinous extension of an abscess and can determine the exact site of infection. CT may reveal disk space narrowing and bony lysis suggesting osteomyelitis, but it is neither as sensitive nor as specific as MRI.[32] Patients with osteomyelitis warrant admission, and unless the patient appears septic, the patient has focal neurologic complaints, or coincident endocarditis is a concern, antibiotic therapy should be withheld until culture results are obtained.

Early consultation with the orthopedist or neurosurgeon guides the timing of antimicrobial coverage, because blood culture results may be insufficient, and a CT-guided needle biopsy for epidural abscess or a bone sample culture for osteomyelitis is often required.[26] Base antimicrobial choice on culture results. Therapy is typically required for 4 to 6 weeks. Unstable injection drug users who are suspected of having osteomyelitis should receive vancomycin to cover *S. aureus* and ceftazidime to cover *Pseudomonas* (see Chapter 281, "Hip and Knee Pain," Table 281-4).

SEPTIC ARTHRITIS

Septic arthritis in injection drug users usually involves the knee or hip (see Chapter 284, "Joints and Bursae"). Sternoclavicular septic arthritis strongly suggests injection drug use.[33] Patients often report recent trauma to the area, but causality is unclear. Consider gonococcal arthritis and tenosynovitis as causes of joint or ligamentous pain.

The initial symptoms are pain, localized tenderness, and swelling at the sites. The erythrocyte sedimentation rate is usually elevated, and fever and leukocytosis may be present. Most plain radiographs are normal; however, joint space widening, articular surface erosion, and surrounding soft tissue infection may be noted. CT or MRI may detect early infection. See Table 284-3 for discussion of findings of synovial fluid analysis. Treatment includes immobilization; empiric antibiotic therapy providing wide-spectrum coverage, including coverage for methicillin-resistant *S. aureus*; physical therapy; therapeutic arthrocentesis/washout; and occasional open drainage.

HEPATIC DISEASE

Injection drug users can develop liver disease from both parenterally and sexually transmitted hepatitis A, B, C, D, E, and non–A through G. In injection drug users, hepatitis B virus seroprevalence ranges from 25% to 55%. Worldwide hepatitis C virus infection is hyperendemic and rising, with a steady infection and death frequency over the past decade.[1] In 2007, injection drug use was cited as a risk factor for 15% of new cases of hepatitis B virus and nearly half (48%) of new hepatitis C virus cases in the United States.[34] Currently, the United States is experiencing an increase in HCV incidence attributed to injection drug use, and

hepatitis C is associated with more deaths in the United States than combined deaths from 60 other infectious diseases.[35]

For evaluation of a clinical syndrome suggestive of acute hepatitis (e.g., weakness, nausea, fever, abdominal pain, or jaundice), obtain laboratory tests that include serum transaminase levels, bilirubin level, alkaline phosphatase level, prothrombin time, and serologic testing. Many patients can receive an outpatient care plan. Admission criteria include inability to tolerate oral intake, toxicity, and significantly prolonged prothrombin time. Counsel patients about sexual transmission and needle exposure, and encourage informing all sexual and needle-sharing partners and household contacts of their exposure. Long-term sequelae of infection include chronic active hepatitis, decompensated cirrhosis, and primary liver cancer.

Unfortunately, drug treatment programs often lack adequate funding to offer optimal hepatitis B and C prevention, diagnosis, and care. Current hepatitis B virus vaccination rates among injection drug users remain low at 30%. The short- and long-term benefit and cost of antiviral treatment for hepatitis C for both the individual patient who continues to intravenously inject drugs (increasing reexposure or reinfection) and any partners are unclear.[36] Both partners are key in appropriately framed therapeutic discussions.[37]

OPHTHALMOLOGIC INFECTIONS

Ophthalmologic infections in injection drug users are usually the result of hematogenous seeding from a primary source of infection or from opportunistic infections associated with HIV disease. Bacterial endophthalmitis often presents acutely, with pain, redness, lid swelling, and decrease in visual acuity. Inflammation is usually present in both the anterior and posterior chambers. White-centered, flame-shaped embolic hemorrhages (Roth spots), cotton-wool exudates, and macular holes may be present. *S. aureus* is the most commonly isolated organism, followed by *Streptococcus* species. Treatment involves subconjunctival, intravitreal, and systemic antibiotic therapy. Surgical intervention, such as vitrectomy, may be needed.[38]

Fungal organisms, often *Candida* or *Aspergillosis*, but sometimes rarer organisms such as *Torulopsis*, *Helminthosporium*, and *Penicillium* species, are causes of endophthalmitis among injection drug users, notably from Mexican black tar heroin injection. In injection drug users coinfected with HIV, cytomegalovirus infection, toxoplasmosis retinitis, and choroidal *Cryptococcus* and *Mycobacterium avium-intracellulare* complex infections must also be considered. Symptoms include blurred vision, pain, poorly reactive pupil, and decreased visual acuity and can progress over days to weeks. White cotton-like lesions are seen on the choroid retina, with vitreous haziness. Uveitis, papillitis, and vitreitis also have been reported. Microbiologic diagnosis is made from the results of blood and vitreous culture. Treatment includes amphotericin B, amphotericin lipid complex, and fluconazole, with or without intravitreous antifungal therapy and early vitrectomy.[39,40]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 297

The Transplant Patient

Brit Long
Alex Koyfman

INTRODUCTION

Organ transplantation is growing in frequency, with the first successful kidney transplant in the early 1950s.[1,2] As of the beginning of 2013, there were 76,047 active candidates waiting for solid-organ transplants in the United States, with the kidney transplant waitlist being the largest at 57,903 candidates.[3] The kidney is the most commonly transplanted organ (58%), followed by liver (21%), heart (8%), lung (5%), pancreas (5%), and, less commonly, combined organ transplants and intestine transplants. Annually, there are approximately 18,000 hematopoietic stem cell transplants in the United States, with about one third of these transplants being allogenic transplants and two thirds being autologous transplants.[4] The recent opioid epidemic has produced several challenges for the transplant-awaiting population. The increase in opioid-related deaths has led to an increase in the number of available organs; however, the risk of infection from opioid-related donor organs is slightly higher than from non–opioid substance user donors. The U.S. Public Health Service states that organs obtained from opioid abusers are at slightly increased risk of infection, although recent data suggest these organs can be safely used for transplant. Potential recipients also may suffer from addiction, which is associated with worse outcomes with transplantation.[5]

Most transplant patients require lifelong immunosuppression. Transplant patients can develop a number of acute to life-threatening emergencies, including (1) transplant-related infection, (2) medication side effects, (3) rejection, (4) graft-versus-host disease, and (5) postoperative complications or complications of altered physiology secondary to the transplanted organ. Transplant patients may also have common medical problems that require unique management. Adverse outcomes often are directly proportional to increasing age of the recipient and the donor organ.[6] Patients with transplanted organs may present significant challenges due to anatomic and physiologic variations, immunosuppression, complications from transplantation, and comorbidities.[2,6-8]

The most common acute disorders prompting ED visits are infection (39%), followed by noninfectious GI/GU pathology (15%), dehydration (15%), electrolyte disturbances (10%), cardiopulmonary pathology (10%) or injury (8%), and rejection (6%).[9-12] Acute graft-versus-host disease is an important complication, especially in those with hematopoietic stem cell transplantation.[13] Coronary artery disease, sudden cardiac death, and heart failure are the result of premature cardiovascular disease in solid-organ recipients, due to underlying comorbidities and metabolic effects of immunosuppression.[14] Preoperative and regular postoperative cardiovascular assessment identifies risk factors and enables treatment to mitigate risks.[15]

GENERAL APPROACH TO EVALUATION

HISTORY AND COMORBIDITIES

Key historical elements for the management of transplant patients are listed in **Table 297-1**.

PHYSICAL EXAMINATION

Direct the physical examination to the chief complaint, present illness, and evidence of complications of the transplant or immunosuppressive medications (**Table 297-2**).[9-13,16,17]

DIFFERENTIAL DIAGNOSIS

Consider complications of immunosuppressive medication, infection, solid-organ rejection, and graft-versus-host disease (**Tables 297-3** and **297-4**). Chronic immunosuppressant medications, including corticosteroids, cause a wide range of physical changes evident on physical examination. Medication changes should be made by, or in consultation with, the patient's transplant team. Outpatient or inpatient management depends on the severity of illness; the need for ongoing immunosuppression often requires admission when symptoms interrupt maintenance of medication.

Solid-organ rejection and graft-versus-host disease are immune-medicated inflammatory reactions that may present with fever, signs and symptoms, and laboratory and radiographic findings that resemble

TABLE 297-1 Key Historical Elements Specific to Transplant Patients

Historical Item	Significance
Recent temperature increase or decrease from baseline	Potential clue to onset of infection or rejection.
Changes from baseline function	Decreased urine may signify rejection in renal transplant patients or acute dehydration. Decreased exercise tolerance may signify rejection in heart transplant patients. Change in skin color (jaundice specifically) may signify rejection in liver transplant patients or graft-versus-host disease.
Date of transplant surgery	The date from transplant helps to predict typical infections and types of posttransplant complications (i.e., graft-versus-host disease).
Graft source for solid-organ transplant, special features of graft if any, prior infections; donor living related vs. cadaveric	These details predict the potential for certain infections and rejection.
Graft source for hematopoietic stem cell transplant: autologous, degree of match, related donor	These details predict potential graft-versus-host disease.
Rejection history	May predict current rejection if similar presentation and difficulty in controlling a current episode of rejection.
Recent changes in dosages of antirejection and other medications	Although a planned part of transplant management, rejection is very common when immunosuppression doses are reduced.
Chronic infections (CMV, Epstein-Barr virus, hepatitis B and C, other viruses)	History of chronic infections increases the chances that current presentation is an exacerbation.
Recent exposure to infections (chickenpox, CMV, tuberculosis)	Increases the chance of current infection.
Recent history of compliance with immunosuppressive medications	Noncompliance increases chance of rejection.
Recent travel, exposure to persons arriving from countries with endemic infections, exposure to potential foodborne illness or insect vectors	Exposure may predict unusual infections not commonly considered.
Complete list of all medications, including over-the-counter medication	Complex drug interactions are common causes of symptoms in transplant patients and must be evaluated.
Baseline: blood pressure, body weight, serum creatinine (for renal transplants), and expected levels of immunosuppressive medication	Changes in these parameters may predict rejection or acute illness.

Abbreviation: CMV = cytomegalovirus.

TABLE 297-2 Physical Examination in Transplant Patients

Examination	Comments
Volume status	Check static vital signs, orthostatic blood pressures, and pulse. Use US to assess inferior vena cava diameter as a measure of intravascular volume status.
Head, ears, eyes, nose, and throat	Periorbital edema (glomerulonephritis), retina (CMV or toxoplasmic chorioretinitis, *Listeria* endophthalmitis), sinuses (*Staphylococcus aureus*, mucormycosis, and invasive fungal disease), mouth (*Candida*, HSV), neck (meningismus, retropharyngeal abscess), lymphadenopathy (CMV, EBV, hepatitis, posttransplant lymphoproliferative disorder).
Lungs	Pneumonia is a common source of infections in transplant patients. *Streptococcus pneumoniae* and other community-acquired agents are still common sources, but opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, *Aspergillus*, tuberculosis, coccidioidomycosis, and viral pneumonias, should be suspected. Noninfectious pulmonary infiltrates may also cause dyspnea.
Heart	Pericardial friction rubs as a complication of uremia and a wide range of viral infections. New heart murmur can represent infection.
Abdomen	Peritonitis without a defined source is one of the most common sites for infection in transplant patients. Right upper quadrant tenderness associated with hepatitis B and C, CMV, and EBV. Varicella-zoster virus causes pancreatitis. If left in place, peritoneal dialysis catheters can be sources of infection.
Flank and suprapubic area	The urinary tract was the most common site of infection identified.
Graft	Renal graft usually placed in abdominal flap; inspect (look for signs of wound infection), palpate (graft tenderness and swelling are often seen in acute rejection, outflow obstruction, and pyelonephritis), and auscultate (bruits suggest renal artery stenosis and AV malformation or AV fistula). Deep tenderness over liver graft could indicate abscess.
Rectal	Perirectal abscess is a common, yet often overlooked, source of infection in transplant patients.
Extremities	Access sites for hemodialysis can be sources of infection. Peripheral edema in the transplant patient can represent a number of different etiologies: recurrent versus de novo glomerulonephritis, renal graft failure, liver graft failure, cirrhosis, nephrotic syndrome (from native kidneys), renal vein thrombosis, malnutrition, hypoalbuminemia, and heart failure.
Skin	Rashes are commonly seen in graft-versus-host disease, viral syndromes (hepatitis B and EBV), cellulitis from indwelling catheter sites, nocardial cutaneous lesions, and drug reactions.
Mental status/ neurologic examination	Cyclosporine/tacrolimus neurotoxicity, steroid psychosis, HSV encephalitis, *Listeria* meningitis/encephalitis, and cryptococcal meningitis.

Abbreviations: AV = arteriovenous; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus.

infection (see later discussions). Infection and rejection (or an exacerbation of graft-versus-host disease) can occur simultaneously, and treatment should be started for both. When suspecting acute rejection or acute graft-versus-host disease, consult the transplant team about treatment. Typically, high-dose corticosteroids are given, but the steroid, the dose, and the duration of therapy should be confirmed.

POSTTRANSPLANT INFECTIONS

Infections account for a large number of deaths in transplant patients, with many infections undiagnosed until autopsy. Patients are at increased risk of infection, with an incidence of infection within the first year after transplant of 25% to 80%.[7,18-21] Although immunosuppressive regimens can reduce the risk of rejection, they can also increase risk of infection. The level of immunosuppression depends on current regimen, underlying diseases, presence of necrotic fluid/fluid collection, presence of an indwelling device, metabolic disease, and concomitant viral infection. The time from transplant also affects risk of infection and type of infection.[20-25] Viral and bacterial illnesses may occur concurrently. Febrile episodes in the early phase after allogenic stem cell transplantation are likely related to infections secondary to neutropenia. Immunosuppression-induced blunting of the inflammatory response may mask the classic signs, symptoms, and laboratory markers of infection if the patient presents early in the course of the illness. Later in the course of infection, patients may present with more advanced ominous signs such as seizure, obtundation, coma, and cardiac arrest. Solid-organ transplant recipients have risk of bacteremia, often in the setting of urinary tract infection.[10,12,19,21,26,27]

CLINICAL FEATURES

The most common reason for an ED visit by a transplant recipient is fever.[9-12] Fever may be masked by immunosuppressive agents and

TABLE 297-3 Adverse Reactions to Immunosuppressant Medications

Body System	Adverse Effects
Constitutional	Fever, rigors, malaise, dizziness, anorexia
Ophthalmologic	Blurred vision, conjunctivitis, cataracts, papilledema, blindness
Mouth/ears	Gingival hyperplasia, stomatitis, hearing loss, tinnitus
Respiratory	Cough, dyspnea, interstitial lung disease, pneumonitis, pleural effusion, noncardiogenic pulmonary edema
Cardiovascular	Hypertension, tachycardia, bradycardia, cardiomyopathy, congestive heart failure, hypotension, syncope
GI	Nausea, vomiting, diarrhea, epigastric pain, esophagitis, gastritis, hiccups, constipation, hepatotoxicity, ascites, pancreatitis, colonic necrosis, bleeding
Musculoskeletal	Myopathy, osteoporosis, tendon rupture
Hematologic	Neutropenia, lymphopenia, anemia, thrombocytopenia, bleeding, thrombosis
Renal	Nephrotoxicity, oliguria, dysuria, renal failure
Neurologic	Headache, vertigo, paresthesias, tremors, convulsions, agitation, neuropathy, confusion, generalized weakness, leukoencephalopathy, encephalopathy, cerebral edema
Skin	Alopecia, hirsutism, thickening, thinning, necrosis, edema
Metabolic	Electrolyte disturbances (sodium, potassium, calcium, magnesium, phosphorus), fluid retention, hypercholesterolemia, hyperlipidemia, hyperglycemia, hypoglycemia
Endocrine	Adrenal suppression
Immunogenic	Susceptibility to infection, acute allergic reactions, anaphylaxis

other factors, such as steroids, uremia, and hyperglycemia, and may be absent in half of those with infection.[10] Fever may be due to factors other than infection, such as drug effects, hypersensitivity reaction, rejection, or malignancy. Even a low-grade fever in a transplant patient should prompt an aggressive workup. Although in the setting of infection transplant patients demonstrate temperatures lower than those of nontransplant patients,[10-12,28] those with transplant still demonstrate a physiologic response to infection (temperature of 37.9°C vs. 38.2°C for transplant vs. nontransplant patients, respectively). Specifically, patients on regimens including mycophenolate mofetil and azathioprine demonstrate decreased temperatures.[28-30]

Signs and symptoms of infection depend on the type of infection and can, in part, be predicted by the time frame since the transplant (**Table 297-5**).[7] The specific site of infection also depends on the transplanted organ. Combining all posttransplant period groups, urinary tract infections (43%) and pneumonia (23%) are likely to be the most common infections.[16] In contrast, a study of 238 ED presentations of febrile pediatric heart transplant patients found pneumonia in 24%, bacteremia in 3%, cellulitis in 2%, and urinary tract infection in 1%; the majority had a negative workup.[17]

TABLE 297-4 Physical Examination Clues to Complications of Medications and Graft-Versus-Host Disease

Concern	Signs and Symptoms
Edema and other swelling	Assess symmetry, pain, color, temperature, and active range of motion. Suspect infection, orthopedic conditions, deep vein thrombosis (due to immobility).
Skin breakdown	The back, pressure points, heels, elbows, and leg ulcers (due to corticosteroid-induced weakness).
Joint range of motion	Shoulders, elbows, fingers, wrists, and knees (may be limited due to steroid-induced weakness or sclerodermatous skin changes).
Thoracic constriction	Relatively noncompliant edema like swelling on the chest wall. If present, ask about associated dyspnea on exertion.
Abdominal constriction	Firm skin. History of bloating, gas, constipation, diarrhea, nonspecific pains.
Sclerodermatous skin	Sclerodermatous skin changes can affect joint mobility and GI and respiratory function. Note the firmness of edema and skin, especially on the thorax and around joints. A firm, soft leather consistency of swelling, tougher than cardiogenic pitting edema, can be a serious problem. Assess for recent-onset dyspnea on exertion.
Dehydration	Increased thirst, loss of appetite, chills, fatigue, weakness, skin flushing, dark or decreased volume of urine, dry mouth, tachycardia, weight loss.
Electrolyte disturbance	Signs and symptoms of dehydration above, hypotension, headache, bradycardia or tachycardia, irregular heartbeat, tremor, muscle weakness, increased urination, constipation, altered tendon reflexes, mood changes, abdominal pain, weight loss, muscle cramping.

DIAGNOSIS AND TREATMENT

The evaluation should include routine testing as well as additional tests based on complaint, history, and physical examination (**Table 297-6**).[31]

Leukopenia can represent acute bacterial infection,[10] and leukopenia with an increase in atypical lymphocytes is commonly seen with viral infections, especially cytomegalovirus. Pulmonary infections that are encountered frequently include *Pneumocystis jiroveci*, *Nocardia*, *Legionella pneumophila*, and *Aspergillus*; these require special stains and studies for accurate diagnosis.

Treatment recommendations should be determined by careful analysis of each individual patient for potential atypical infections requiring specific coverage. Resuscitation with intravenous fluids and broad-spectrum antimicrobials is recommended in patients with sepsis or septic shock. Empiric antimicrobial therapy for transplant patients is outlined in **Table 297-7**.[32-34] Empiric treatment prior to confirmatory studies should first involve antibacterial agents and then, especially if there is concern for meningitis or encephalitis, antiviral agents such as acyclovir. Discuss treatment of suspected fungal infections or atypical infections with the transplant team. The emergency provider should discuss the case with the patient's transplant physician, and consultation with infectious disease specialist may improve outcomes and reduce mortality.[2,7,18,19,35]

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease is a major cause of morbidity and mortality, affecting approximately 50% of allogeneic hematopoietic stem cell transplantation patients, and is caused by donated T cells attacking antigens on host cells,[36] but it also occurs after small bowel or liver transplantation, as well as transfusion of unirradiated blood products in high-risk groups.[37] Hyperacute graft-versus-host disease is an unusual and severe form of acute graft-versus-host disease. Onset occurs in the first week after hematopoietic stem cell transplantation and is characterized by fever, generalized erythroderma, severe hepatitis, fluid retention, widespread inflammation, and shock.[38-41]

Acute graft-versus-host disease is classified as appearance of the disease up to 100 days after transplant. A well-appearing hematopoietic stem cell transplantation recipient with a nonspecific **rash** (most common symptom) or **diarrhea** (second most common symptom) should be suspected of having new-onset or an exacerbation of graft-versus-host disease.[38] The most widely used graft-versus-host prophylaxis includes a combination of a calcineurin inhibitor (e.g., cyclosporine, tacrolimus) with methotrexate.[38] In patients who recover from acute graft-versus-host disease, later long-term complications from chronic graft-versus-host disease are common.

Chronic graft-versus-host disease is a late complication characterized by immune dysregulation (>100 days after transplantation) and is a distinct clinical syndrome from the acute form.[42] It results in severe morbidity, with complications affecting skin (sclerodermatous contractures), muscles (myopathy), bone (osteoporosis), eyes (keratoconjunctivitis sicca), nerves (peripheral neuropathy), and the cardiopulmonary system (physical deconditioning), resembling autoimmune disorders. Risk factors include older age, CMV seropositivity, and a male who received a

TABLE 297-5 Infections Stratified by Post-transplant Period

Period After Transplant/Conditions	Infection	Comments
<1 mo: resistant organisms	MRSA Vancomycin-resistant *Enterococcus faecalis* *Candida* species (including non-*albicans*)	Opportunistic infections are generally absent during this period as full effect of immunosuppression not complete. MRSA important in HSCT patients.
<1 mo: complications of surgery and hospitalization	Aspiration Catheter infection Wound infection Anastomotic leaks and ischemia *Clostridium difficile* colitis	*C. difficile* common during this period. Early graft injuries may abscess. Unexplained early signs of infection such as hepatitis, encephalitis, pneumonitis, or rash may be donor derived.
<1 mo: colonization of transplanted organ or HSCT neutropenia	*Aspergillus* *Pseudomonas* *Klebsiella* *Legionella*	Microbiologic analysis of aspirates or biopsy from surgery essential for therapeutic decisions.
<1 mo: HSCT-specific infections	Additional bacterial pathogens: *Streptococcus viridans* and enterococci Viral infections include respiratory syncytial virus and HSV	Neutropenia and mucocutaneous injury increase risk for HSCT patients. Lungs, bloodstream, and GI tract most commonly affected sites.
1–6 mo: in patients with *Pneumocystis jiroveci* pneumonia and antiviral (CMV, HBV) prophylaxis	Polyomavirus BK infection, nephropathy *C. difficile* colitis HCV infection Adenovirus infection, influenza *Cryptococcus neoformans* infection *Mycobacterium tuberculosis* infection Anastomotic complications	Activation of latent infections, relapse, residual, and opportunistic infections occur during this period. Viral pathogens and allograft rejection cause the majority of febrile episodes during this period. Polyomavirus BK, adenovirus infections, and recurrent HCV are becoming more common.
1–6 mo: in patients without prophylaxis	*Pneumocystis* Infection with herpesviruses (HSV, varicella-zoster virus, CMV, Epstein-Barr virus) HBV infection Infection with *Listeria, Nocardia, Toxoplasma, Strongyloides, Leishmania, Trypanosoma cruzi*	Discontinuation of prophylaxis at the end of this period may prompt active infection, especially CMV. Graft-versus-host disease and mucocutaneous injury increase risk for HSCT patients.
>6 mo: general	Community-acquired pneumonia and urinary tract infections Infection with *Aspergillus*, atypical molds, *Mucor* species Infection with *Nocardia, Rhodococcus* species	Community-acquired organisms dominate during this period. Transplant recipients have a persistently increased risk of infection due to community-acquired pathogens.
>6 mo: late viral infections	CMV infection (colitis and retinitis) Hepatitis (HBV, HCV) HSV encephalitis Community-acquired viral infections (severe acute respiratory syndrome, West Nile) JC polyomavirus infection (progressive multifocal leukoencephalopathy) Skin cancer, lymphoma (PTLD)	In some patients, chronic viral infections may cause allograft injury (e.g., cirrhosis from HCV infection in liver transplant recipients, bronchiolitis obliterans in lung transplant recipients, accelerated vasculopathy in heart transplant recipients with CMV infection) or a malignant condition such as PTLD or skin or anogenital cancers.

Abbreviations: CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; HSCT = hematopoietic stem cell transplant; HSV = herpes simplex virus; MRSA = methicillin-resistant *Staphylococcus aureus*; PTLD = posttransplantation lymphoproliferative disorder.

stem cell transplant from a multiparous woman.[43] Management is similar to the acute form with prolonged immunosuppression.[44]

ACUTE GRAFT-VERSUS-HOST DISEASE

The disease is typically characterized by involvement of three different systems: skin (rash), gastrointestinal, and liver (jaundice, hepatitis). Consider graft-versus-host disease in any patient with a rash. Rash is often misattributed as a drug reaction.[45] The typical rash is maculopapular, frequently demonstrating a brownish hue and slight scaling (**Figure 297-1**). The rash can be pruritic and painful. The distribution varies greatly but often affects palms and soles initially, and later progresses to cheek, ears, neck, trunk, chest, and upper back. In the more severe forms, erythroderma or bullae develop.[13] Mucositis has been reported to occur in 35% to 70% of patients.

Diarrhea, GI bleeding, or hepatic dysfunction can occur. Diarrhea, with or without upper GI symptoms such as anorexia, nausea, and emesis, is common and may appear green, mucoid, and watery. Symptoms include painful cramping, ileus, and, sometimes, life-threatening hemorrhage from the colon. Hepatic involvement is characterized by increase in liver function studies. GI hemorrhage in the early posttransplant period may be a result of coagulation abnormalities, especially thrombocytopenia. The differential diagnosis of GI bleeding in this setting includes all the usual causes of GI bleeding in addition to bleeding due to acute graft-versus-host disease–related damage to colonic tissues and infection (viral, fungal, or bacterial).[36,46] Diagnosis requires endoscopy.

Treatment is directed by the transplant team, typically PO prednisone or IV methylprednisolone, at 1 to 2 milligrams/kg daily, and possibly adjustment of other immunosuppressant doses.[13] Patients may require resuscitation with balanced crystalloids, blood product resuscitation

TABLE 297-6 Diagnostic Tests to Consider in the Evaluation of Infections in the Transplant Patient

Test	Comments
CBC	Leukocytosis or left shift of the WBC count may be blunted by immunosuppressive agents.
Renal function tests: BUN, creatinine	Essential in the evaluation of renal transplant patients; may help determine dosing of antibiotics in all transplant patients.
Liver function tests	May show mild transaminase elevations with cytomegalovirus and Epstein-Barr virus infections and much higher elevations with hepatotropic viruses such as hepatitis B and C viruses. May be elevated in *Legionella* infections.
C-reactive protein	Significant elevations more likely in infections versus noninfectious infiltrates.
Procalcitonin level	Significant elevations more likely in infections versus noninfectious infiltrates.
CT of the brain	Focal infections in the brain are much more common in this population, but CT should be used only as clinically indicated.
Cyclosporine or tacrolimus level or other levels of immunosuppressants	These levels may be deliberately low depending on the desired level of immunosuppression. Bioavailability may be variable.
Cultures of mouth, sputum, urine, blood, stool, vascular access, and wound sites	Collect as indicated by history and physical. Urine *Legionella* antigen should be considered before treatment of patients with pneumonia with GI complaints. Bacterial and fungal cultures of blood and urine should be obtained on all patients.
Cerebrospinal fluid cultures and antigen tests	Collect as indicated by history and physical.
Serology: cytomegalovirus, Epstein-Barr virus, hepatitis, toxoplasmosis, cryptococcosis	Because viral and fungal cultures are not very sensitive, clinicians should rely on their acumen to order organism-specific antigen assays and antibody titers. When contemplating viral or parasitic infections, these tests should be obtained to allow identification of bacterial, fungal, and viral pathogens. May be useful in patients with diffuse lymphadenopathy.
Chest radiograph	Infiltrates on chest radiograph may reflect infectious or noninfectious complications of hematopoietic stem cell transplant or organ transplant. Obtain in posttransplant fever to evaluate for source.
CT of the chest	Patients with evidence of pulmonary infiltrates on chest radiograph or high-resolution CT, but without productive sputum, may ultimately require bronchoscopy with bronchoalveolar lavage and transbronchial biopsy for definitive diagnosis.
CT or US to include the graft	These scans can be used to identify likely abscess formation or possible anastomotic leaks.
Tests after admission	Beyond the scope of this chapter, but may include biopsy of the transplanted organ, bronchoalveolar lavage on bronchoscopy, and focused imaging of suspected sites of infection.
Creatine kinase	May have increased levels in infections with certain organisms, such as *Legionella*.
Urinalysis	As dictated by history and examination. Recommended in patients with renal transplant.
Lactate	Evaluate for severity of illness (sepsis and septic shock).
Biopsy	Typical standard diagnosis requires biopsy of graft, which is not obtainable in ED but should be discussed with admitting physician.

(leukocyte-depleted and irradiated red blood cells), electrolyte replacement, and broad-spectrum antibiotics.[47]

Disposition and interval for follow-up are also determined by the transplant team. Survival approaches 50% at 1 year with intensive corticosteroid therapy, with 50% developing chronic disease.[41,44,45]

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE

Most living cells that are in transfused blood survive for no more than a few days or weeks. However, in some patients, transfused cells engraft, expand, and circulate. When immunocompetent T lymphocytes engraft in an immune-suppressed patient, transfusion-associated graft-versus-host disease may occur and is almost always fatal.[48,49] It is possible to avoid transfusion-associated graft-versus-host disease by irradiating blood products before transfusion. **Patients with immunocompromise or other risk factors (Table 297-8) should receive irradiated blood products.**

POSTTRANSPLANTATION LYMPHOPROLIFERATIVE DISORDER

Posttransplantation lymphoproliferative disorders consist of lymphomas occurring after organ transplantation, particularly solid-organ and allogeneic hematopoietic stem cell transplants. Posttransplantation lymphoproliferative disorders are associated with poor outcomes and are not uncommon, accounting for up to 21% of all cancers in patients receiving solid-organ transplants.[50,51] The incidence is increasing due to older age of transplant donors and recipients, increasing number of transplants, new immunosuppressive agents, newer types of stem cell transplantation, greater awareness of the disease, and improved diagnosis.[52] Primary risk factors depend on the organ transplanted (kidney transplant has the lowest risk). Specific T-cell depletion procedures display higher risk of posttransplantation lymphoproliferative disorders in the setting of haploidentical allogeneic hematopoietic stem cell transplantation, as does the specific immunosuppressive regimen used. Age greater than 50 years and Epstein-Barr virus seronegative status before transplantation elevate the risk of posttransplantation lymphoproliferative disorders.[52-55] The incidence of posttransplantation lymphoproliferative disorders follows a bimodal curve, with an initial spike during the first and second year and a second spike 5 to 15 years after transplantation. The presentation varies, ranging from asymptomatic to fulminant organ failure or tumor lysis syndrome. Posttransplantation lymphoproliferative disorders display a high incidence of extranodal involvement often involving the GI tract (up to 30% of cases), solid allografts (15%), and the CNS (5% to 20%).[51,56,57] Diagnosis typically includes histopathologic examination based on six subclasses. However, this is not available in the ED. Treatment varies but typically involves reduction of immunosuppression, surgical extirpation, local radiation, rituximab, chemotherapy, cellular immunotherapy, and/or stem cell transplantation.[57]

TRANSPLANTATION MEDICATION EFFECTS

Transplant patients are typically on extensive medication regimens including immunosuppression. In the 1980s, this consisted of corticosteroids and azathioprine, but current regimens are more extensive, with many options dependent on the patient, specific organ transplant, and time from transplant (**Table 297-9**).[2]

TRANSPLANTATION REJECTION

A feared complication other than infection includes graft rejection, as many do not fully recover from an episode of rejection. Immunosuppressive regimens have reduced the risk of rejection, although this is balanced with the risk of infection. Several phases of rejection are present including hyperacute (minutes to hours after transplant due to preexisting antibodies), acute (within the first 6 months due to acute cellular rejection or humoral rejection), and chronic (months to years after transplant due to antibody and cell-mediated rejection). Presentations of rejection are demonstrated in **Table 297-10**.[2]

TABLE 297-7 Empiric Antimicrobial Therapy

Condition	Antimicrobial Agent	Comments*
All patients	Discuss agent(s) with transplant team.	The transplant team caring for the patient should always be consulted as soon as possible; however, in certain life-threatening situations, empiric broad-coverage therapy may be indicated immediately.
Suspected infection site based on history and physical examination	Site-specific agents are preferable if predicted by initial findings, balanced by known pathogens as listed in Table 297-5.	The urgency for treatment should be based on the patient's presenting condition; bacterial infections are the most aggressive organisms requiring coverage, but some fungal infections may yield sepsis. In general, broad coverage for any suspected site infection is recommended initially pending cultures and further workup to define noninfectious causes of fever.
Neutropenia in the absence of symptoms suggesting site-specific infection	Third-generation cephalosporin such as ceftazidime or a carbapenem plus coverage for MRSA below.	Multiple alternative agents used, including an aminopenicillin plus a β-lactam inhibitor such as piperacillin-tazobactam or cefepime. Monotherapy has fewer complications, but concern for MRSA remains high. Addition of antiviral and antifungal agents should be at the discretion of the transplant team.
Suspected MRSA	Vancomycin	In the majority of patients, MRSA infection should be seriously considered as a potential cause of infection, pending cultures. Linezolid is an alternative antibiotic.
Parasitic infections	Trimethoprim-sulfamethoxazole after discussion with transplant team	Consider *Toxoplasma gondii, Pneumocystis jiroveci.*
Viral infections	Ganciclovir or valganciclovir for CMV, acyclovir for herpes simplex and varicella-zoster	Consider treatment for CMV pneumonia, CMV chorioretinitis, CNS or disseminated herpes simplex or varicella-zoster.
Fungal infections	Discuss with transplant team; agent depends on site and severity of illness	Consider *Aspergillus, Candida albicans, Cryptococcus neoformans.*

Abbreviations: CMV = cytomegalovirus; MRSA = methicillin-resistant *Staphylococcus aureus*.

*Standard doses apply but may be altered by transplant team recommendations.

SPECIFIC TYPES OF TRANSPLANTATION

RENAL TRANSPLANTATION

Renal transplantation is the preferred treatment for end-stage renal disease. Kidneys obtained from deceased or living donors are most commonly placed in the recipient's pelvis, with the ureters anastomosed to the bladder.[3,6,8,58] Vascular complications that occur following renal transplantation include renal artery stenosis, allograft infarction, arteriovenous fistulas, pseudoaneurysm, graft hematoma, and renal artery or vein thrombosis. Nonvascular complications include ureteral obstruction, urine leak, periallograft fluid collections (hematomas, lymphoceles, and abscesses), neoplasms, GI complications, and post-transplant lymphoproliferative disease.[8] The major causes of renal transplant loss are death from vascular, malignant, or infectious disease, and loss of the allograft from chronic renal dysfunction associated with the development of graft fibrosis and glomerulosclerosis. Medication changes and use of an imaging contrast agent that may affect renal function (including gadolinium-based contrast agents) should be discussed with the patient's transplant team.[2]



FIGURE 297-1. Rash of acute cutaneous graft-versus-host disease. The maculopapular lesions have acquired a brownish hue, and there is slight scaling. [Reproduced with permission from Wolff KL, Johnson R, Suurmond R: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. © 2009, McGraw-Hill, Inc., New York.]

DIAGNOSTIC TESTING

Table 297-6 lists recommendations on diagnostic testing in transplant patients, including renal transplant patients. The serum creatinine level is the most valuable prognostic marker of graft function at all times after transplantation and should be obtained whenever renal failure or infection is suspected, which is often elevated in the setting of transplant infection or rejection.[59] The urinalysis provides important clues to acute changes in graft viability. Red blood cell casts and proteinuria are commonly seen in recurrent or de novo glomerulonephritis. The presence of WBCs, bacteria, and nitrites is helpful in diagnosing urinary tract infections, which is one of the most common complications with renal transplant.[60,61] However, pyuria may present with rejection.[2,60,61]

TABLE 297-8 Significant Risk Factors for the Development of Transfusion-Associated Graft-Versus-Host Disease

- Congenital and acquired immunodeficiency syndromes
- History of bone marrow (stem cell) transplantation, whether allogeneic or autologous
- Transfusions from blood relatives ("directed donation")
- Transfusions with fresh whole blood
- Premature infants receiving any sort of transfusion
- Human leukocyte antigen–matched platelet transfusions
- Hodgkin's disease, even when in remission
- Leukemia not in remission
- Patients treated with purine analogues; the effects of fludarabine and cladribine (2-CdA) persist for a year

TABLE 297-9 Transplantation Medications

Medication	Mechanism	Adverse Effect
Cyclosporine (Sandimmune®, generic)	Calcineurin inhibitor; decreases T lymphocyte activity and IL-2 function	Acute/chronic nephrotoxicity, electrolyte derangements (hyperkalemia, hypomagnesemia), gout, hemolytic-uremic syndrome, gingival hyperplasia, hirsutism, hypertension, hyperlipidemia
Tacrolimus (Prograf®)	Calcineurin inhibitor; inhibits T lymphocyte activity and IL-2 function	Similar to cyclosporine Neurotoxicity (headache, tremor, paresthesias, seizures), hair loss instead of hirsutism, less hypertension/hyperlipidemia
Azathioprine (Imuran®)	Blocks nucleotide production for immune cell replication	Bone marrow suppression, macrocytosis, anemia, hepatotoxicity, pancreatitis
Mycophenolate mofetil (CellCept®)	Cytostatic effect on B and T cells; decreases proliferation by inhibiting nucleotide synthesis	Abdominal pain, decreased oral intake, nausea/vomiting, diarrhea, anemia, leukopenia, thrombocytopenia
Corticosteroids	Impairs phagocyte function Attenuates production of proinflammatory mediator Decreases T-cell activity Decreases cell signal transduction	Weight gain, cataracts, acne, skin thinning, bruising, osteoporosis, GI bleeding, hyperglycemia, hyperlipidemia, psychologic effects, cushingoid appearance
Sirolimus (Rapamune®)	Blocks mTOR receptor and immune cell signal transduction, reducing B- and T-cell activity	Thrombocytopenia, leukopenia/anemia (less common), diarrhea, mucosal irritation, buccal ulceration, interstitial pneumonitis, hyperlipidemia
Polyclonal antibodies (antithymocyte γ-globulin)	Antilymphocyte antibody Used for immunosuppression when nephrotoxic agent is held Used for treatment of corticosteroid resistant rejection	Fever, serum sickness, anaphylaxis, anemia, thrombocytopenia
Monoclonal antibodies (OKT3, IL-2 receptor antibody)	Antilymphocyte antibody Used for prophylaxis against rejection in early period Used for immunosuppression when nephrotoxic agent is held Used for treatment of corticosteroid resistant rejection	OKT3: During first 3 days of therapy, may have headache, aseptic meningitis, encephalopathy, seizures, nausea, vomiting, diarrhea, pulmonary edema, nephrotoxicity IL-2 receptor antibodies have rare adverse effects such as anaphylaxis

Abbreviations: IL-2 = interleukin-2; mTOR = mammalian target of rapamycin.

Proteinuria may signal rejection, drug toxicity, glomerular disease, or other graft nephropathy, although proteinuria from a remaining native kidney should also be considered. Obtain cyclosporine or tacrolimus blood levels for all patients on these medications. Contact the patient's transplant team regarding abnormal drug levels, because low drug levels are sometimes deliberately used to reduce side effects.

IMAGING

US is the best test to detect urinary obstruction. Renal graft US can also be useful in patients suspected of having pyelonephritis, vascular abnormalities (stenosis, thrombosis, pseudoaneurysm, hematoma, and arteriovenous fistula), perinephric abscess, urine leak, wound infection, or an episode of rejection.

TABLE 297-10 Presentations of Transplant Rejection

Transplant Organ	Symptoms/Signs	Management
Renal	Many asymptomatic Symptoms: • Hypertension • Fever, malaise, oliguria, graft pain, and tenderness over site • Worsening renal function with decreased urine output and rising serum creatinine	Acute rise in serum creatinine; electrolyte abnormalities. US may demonstrate increased graft size, loss of corticomedullary junction, prominent hypoechoic pyramids. Renal Doppler studies may demonstrate elevated vascular resistance indices. Biopsy needed during admission.
Liver	Fever, malaise, abdominal pain, hepatosplenomegaly, ascites	Laboratory abnormalities: elevated liver function tests and bilirubin. US of graft and vasculature may find focal lesion or vascular abnormality. Biopsy needed during admission.
Cardiac	Dyspnea at rest/exertion, orthopnea, palpitations, near-syncope/syncope, peripheral edema, or GI symptoms with right heart involvement Chest pain is absent due to denervation during surgery Dysrhythmias common	Cardiac troponin and B-type natriuretic peptide often elevated. ECG may demonstrate T-wave/ST-segment changes. Echocardiogram with systolic/diastolic dysfunction. Chest radiograph may demonstrate findings of congestive heart failure. Biopsy needed during admission.
Lung	Shortness of breath and cough most common Lung examination variable: clear lung fields, crackles, or decreased breath sounds May demonstrate stridor or wheezes May present with respiratory distress or failure	Eosinophilia suggestive on CBC with differential. Normal chest radiograph is not reliable to rule out disease. Chest CT often required. Pulmonary function testing not helpful in differentiating infection and rejection. Effusion requires thoracentesis. Bronchoscopy and biopsy needed during admission.

CT angiography may be used to diagnose vascular complication such as hematoma, artery stenosis, and vascular thrombosis.[62-64]

MRI can be helpful in evaluating hematomas and other fluid collections, vascular abnormalities, and small infarcts caused by medication-induced vasculitis. Magnetic resonance angiography has the advantage of requiring either no contrast material or a gadolinium chelate that is less nephrotoxic than other agents.[2] However, gadolinium-based contrast agents can cause acute renal failure in up to 3.5% of patients with underlying chronic renal insufficiency.[65] Therefore, the patient's transplant team should be consulted before using gadolinium-based contrast agents.

GRAFT DYSFUNCTION AND FAILURE

Chronic renal dysfunction precedes the majority of graft failures. Acute renal failure in transplant patients is defined as a 20% rise from baseline serum creatinine levels, as opposed to a 50% rise in other patients with acute renal failure. Consider the conditions described in **Table 297-11** when evaluating possible graft dysfunction or even a small increase in serum creatinine.[66,67]

TABLE 297-11 Differential Diagnosis of Renal Allograft Dysfunction

Differential Disorder	Comments
Mechanical Complications of surgery Ureteral obstruction Urine leak: urinoma, ascites, or abscess	Presents with decreased urine output. At US, a urine leak (i.e., urinoma) appears as a well-defined, anechoic fluid collection with no septations that increases in size rapidly. Requires consultation with urology and transplant physician. Obstruction typically requires Foley catheter placement, followed by stent placement.
Lymphocele	Results from perivascular lymphatic vessel leakage, which forms a collection of lymphatic fluid in up to 15% of patients within the first 3 months of transplant.
Vascular Renal artery stenosis or thrombosis (12%) Renal vein thrombosis Renal artery and renal vein thromboses are uncommon; they usually occur in the first month after transplant. Peritransplant hematoma	The transplanted kidney is usually placed extraperitoneally in the right iliac fossa. End-to-side anastomosis to the external iliac vasculature provides circulation. Color duplex imaging of the renal artery and vein is helpful in assessing renal vascular stenosis or thrombosis. CT angiography can be utilized as well. Treatment often includes thrombolysis for vascular stenosis/thrombosis and surgery for peritransplant hematoma.
Glomerulonephritis	
Infection Urinary tract infection Interstitial nephritis from polyoma BK virus, cytomegalovirus, herpes viruses 1 and 2, and adenovirus	Urinary tract infections are the most common source of bacteremia in renal transplant recipients, and infectious diseases are the second leading cause of death in this population. See "Posttransplant Infections" section. At least two antibiotics should be used for treatment of urinary tract infection.
Rejection Hyperacute Acute Late (recurrent acute) Chronic cellular Chronic humoral	Most common presentation of rejection in renal transplant patients is hypertension and falling urine output, but rejection may be asymptomatic. Fever, pain, malaise, oliguria, and site tenderness may occur. Comparison of creatinine at the time of presentation to prior levels is critical, as creatinine elevation is common. Fever may be a presentation of rejection.
Recurrent pyelonephritis/vesicoureteral reflux	Common problem threatening graft and patient survival
Nephrotoxic agents Aminoglycosides, fluoroquinolones, cidofovir, foscarnet, sulfonamides, calcineurin inhibitors (cyclosporin A and tacrolimus), NSAIDs, gadolinium-based and some other contrast agents, herbal preparations	Drug serum levels do not correlate well with the degree of renal damage. NSAIDs are contraindicated in this group. Avoid contrast agents if possible.
Noncompliance with Medications Management of risk factors such as diabetes and hypertension	Diabetes often follows transplantation; marked exacerbations in hypertension are frequently associated with graft failure.
Chronic allograft nephropathy	Common cause of graft dysfunction

LIVER TRANSPLANTATION

The most common reasons for ED visits are fever and abdominal pain.[11] Hepatosplenomegaly, ascites, and malaise may also occur, specifically with rejection.[2] Complications include bleeding, rejection, and infection, as well as biliary, vascular, and wound complications. Bacterial infection may accompany acute rejection.[68] Specific complications of liver transplantation are listed in **Table 297-12**. Obtain a CBC with platelet count and differential; serum chemistries, including electrolytes, BUN, creatinine, basic coagulation studies, liver function tests, amylase, and lipase levels; and cultures of blood, urine, bile, and ascites. Radiographic testing as indicated may include chest radiograph and abdominal US with Doppler flow studies. US with Doppler can identify fluid collections, thrombosis of the hepatic artery or portal vein, and dilatation of the biliary tree (although the absence of biliary dilatation does not exclude obstruction or other posttransplantation pathology).[69-73] With partial obstruction, the intrahepatic ductal system often does not appear to be dilated appreciably by US. With complete obstruction, duct dilation is usually seen. CT with contrast may be required for diagnosis of vascular complication or biliary stricture.[2,69,70] Patients often require cholangiography for complete evaluation. Patients with choledochocholedochostomy may be best evaluated by endoscopic retrograde cholangiopancreatography because it permits both a radiographic diagnosis and the potential for nonoperative intervention. Patients with a Roux-en-Y hepaticojejunostomy or those who cannot have endoscopic retrograde cholangiopancreatography must undergo percutaneous cholangiography.[72-75] Early, broad-spectrum prophylactic antibiotics should be administered before any biliary tract manipulation. Discuss treatment and disposition with the transplant team.

LUNG TRANSPLANTATION

Lung transplantation involves three anastomoses: airway (the most vulnerable to complication, 2% to 33%), pulmonary arterial, and pulmonary vein to the left atrium.[3,6,76-78] Fever, cough, and increasing dyspnea are common reasons for ED visits in lung transplant patients. Important clinical features to note are the respiratory rate, pulse oximetry measurement, and physical findings of cyanosis, diaphoresis, use of accessory muscles, signs of congestive heart failure, and adequacy of peripheral perfusion. Obtain a chest radiograph and arterial blood gas analysis when adequacy of ventilation is in question. Give β_2-agonists and anticholinergics as indicated. Signs of infection often overlap with the signs and symptoms of rejection, and the management of infection is quite different from that of rejection. A drop in the forced expiratory volume in 1 second of >10% warrants clinical investigation, but pulmonary function testing cannot distinguish between acute rejection, infection, and nonimmunologic causes of respiratory dysfunction such as airway stenosis.[79] Therefore, bronchoscopy is required for specific diagnosis. Lung transplant patients can deteriorate very quickly in the absence of the proper therapy. Thus, it is common practice to cover both infection and rejection until additional histopathologic and culture results are obtained.[80]

TABLE 297-12 Complications of Liver Transplantation

Complication	Comments
Bleeding complications	GI bleeding should be managed in the usual fashion but may signal graft dysfunction.
Biliary complications Bile leak Biliary stricture (anastomotic and nonanastomotic) Biloma	Bile leaks present early, and biliary strictures present late (>2 mo from transplant). In both cases, cholestatic liver enzymes are elevated, typically with right upper quadrant pain (more pronounced with bile leak). Jaundice and fever may also be present. US with Doppler of hepatic vessels displays sensitivity of 38%–66%. If US is negative, cholangiogram may be needed, with patients often requiring endoscopic retrograde cholangiography (ERC). Strictures come in two forms, with anastomotic strictures occurring within the first year after surgery. Imaging includes CT, US, and MRI, with treatment including ERC and stent placement. Bile leaks occur in up to 25% of patients, with ERC needed for diagnosis and treatment (stent). Bilomas can be diagnosed with US and managed with drainage and antibiotics.
Hepatic artery complications Hepatic artery thrombosis Hepatic vein thrombosis Portal vein complications Pseudoaneurysm	Vascular complications affect the hepatic artery or portal vein most commonly. CT with contrast (if renal function adequate) or US is helpful in the evaluation of these conditions. CT with IV contrast has greater sensitivity for arterial stenosis, but US displays a sensitivity up to 90% for venous thrombosis. Mortality reaches 80% for portal vein thrombosis if not diagnosed. For thrombosis, thrombolysis may be required. Pseudoaneurysms are typically treated with transcatheter embolization.
Rejection	Early alkaline phosphatase and bilirubin levels rise, followed by a rise in aspartate aminotransferase and alanine aminotransferase. US may reveal focal lesion or vascular abnormality. Biopsy is needed during admission.
Neurologic complications	Causes include hemorrhage, cerebrovascular infarct, cerebral abscess, hypertensive encephalopathy, osmotic demyelination syndrome, and sinus thrombosis. MRI is best for evaluation.
Malignancy	Increased risk for squamous cell carcinoma, lymphomas, and posttransplant lymphoproliferative disorder.

COMPLICATIONS OF LUNG TRANSPLANTATION

Complications occur most frequently in the first year, but can occur at any time starting from the first few weeks after transplant and can continue throughout the lifetime of the patient (**Table 297-13**).[80,81] Airway complications often occur with dyspnea, wheezing, or stridor or postobstructive pneumonia. A variety of mechanisms of airway obstruction may occur, such as bronchial stenosis, tracheobronchomalacia, hyperplastic granulation tissue, and bronchial necrosis. Diagnosis typically includes chest CT and bronchoscopy.[76-78,82-84] Vascular complications (stenosis, kinking, and thrombus formation) are not as frequent but have poor outcomes and can present with hypoxemia, dyspnea, hypotension, and edema.[85-87] US may reveal right-sided cardiac dysfunction with vascular complications, although definitive diagnosis includes CT angiography. Phrenic nerve dysfunction is more common in heart-lung transplant (40% of cases) as compared to lung-only transplant (3% to 9%).[88-91] Indications for hospital admission are listed in **Table 297-14**.

Acute rejection is common and may occur three to six times in the first postoperative year. After the first year, the frequency of acute rejection decreases, but it can occur for several years after transplant. Signs of rejection include cough, chest tightness, increase or decrease in temperature from baseline of >0.28°C (0.5°F), hypoxemia, decline in forced expiratory volume in 1 second (10% or more), and infiltrates on the chest radiograph, although the chest radiograph may be normal. Lung auscultation is often variable, with examination revealing clear lung fields, crackles, or decreased breath sounds.[92-95] Patients may present in respiratory distress or failure. Eosinophilia may be present with rejection. Radiographic abnormalities are less common >6 weeks after transplant, and an acute rejection episode actually may be "radiographically silent" after this. Discuss treatment with the transplant team. If the maintenance immunosuppressant regimen has been tapered, it can be very helpful to return to pretaper dosages. In addition, high-dose corticosteroids are often used to treat acute rejection. The usual dosing regimen is 15 milligrams/kg of IV methylprednisolone each day for 3 consecutive days. After the corticosteroid bolus, if the maintenance prednisone had been tapered, increasing the prednisone to 1 milligram/kg/d and tapering over the next 10 days may be helpful.[79,95,96] Clinical response to treatment is gauged by improvements in oxygenation, spirometry, and radiographic appearance and typically occurs within 24 to 48 hours after treatment is initiated. Failure to improve should suggest infection as an alternative diagnosis. After clinical improvement, the maintenance dose of prednisone is increased, with a slow taper back to baseline.

Pulmonary infections from bacteria, fungi, or viruses are the most common causes of morbidity and mortality in lung transplant

TABLE 297-13 Time Course of Lung Transplant Complications

Days After Transplant	Complications Most Commonly Seen in Each Time Period
0–3 d	Hemorrhage from technical/mechanical problems Reperfusion injury Dysrhythmia
3 d–1 mo	Infection: bacterial, *Mycoplasma*, community respiratory viruses Rejection Anastomotic failure Pulmonary embolism Muscle weakness Dysrhythmia
Starting at 1 mo	Rejection Obliterative bronchiolitis Infection Bacterial, fungal, community respiratory viral (can occur at any later time) *Mycoplasma* 0–4 mo Mycobacteria after 4 mo
Other	Cytomegalovirus infection and *Pneumocystis jiroveci* pneumonia may occur any time, but are more common when prophylaxis is not being given, especially when such treatment has been recently discontinued.

TABLE 297-14 Indications for Hospital Admission for Lung Transplant Patients

Pretransplant patients

- Respiratory failure
- Infiltrate
- Systemic infection
- Decompensated congestive heart failure or pulmonary edema
- Pneumothorax

Posttransplant patients

- Respiratory failure
- Acute rejection
- Rapidly progressive airflow limitation (forced expiratory volume in 1 second decreases >10% over 48 h)
- Infiltrate
- Systemic infection
- Febrile neutropenia
- Pneumothorax

patients[97,98] (Tables 297-5 and 297-13). Lung transplant patients are at risk for pneumonia because of colonization of the recipient's airway in the setting of transplantation for bronchiectasis and cystic fibrosis and at risk of aspiration in the presence of gastroesophageal reflux disease.[81] Antibiotic selection is best left to the lung transplant specialist.

CARDIAC TRANSPLANTATION

Cardiac transplantation has been applied successfully to patients of all ages, from newborns through persons in their late 60s. Heart transplantation is indicated for patients with end-stage heart failure not remediable by standard medical or surgical therapy. Many in the latter group will have undergone previous coronary artery bypass or valve surgery or been bridged on mechanical assist devices. The leading causes of death in those age 60 to 69 years are graft failure and infection.[99]

The success of a heart transplantation operation depends on the ability of the denervated heart to support the normal circulation. The lack of sympathetic and parasympathetic innervation does, however, induce an altered physiologic state. The denervated heart has a normal sinus rhythm with a heart rate between 90 and 100 beats/min. Denervation results in the absence of the initial centrally mediated tachycardia in response to stress or exercise, but the heart remains responsive to circulating catecholamines. Thus, the cardiac response to stress or exertion is blunted. With proper conditioning, patients are able to resume normal activity levels, including vigorous exercise, following transplantation.[100-103]

The donor heart is implanted with its own sinus node intact to preserve normal atrioventricular conduction. The technique of cardiac transplantation also results in preservation of the recipient's sinus node at the superior cavoatrial junction, and the two sinus nodes remain electrically isolated from each other. Thus, ECGs frequently will have two distinct P waves (**Figure 297-2**). The sinus node of the donor heart is easily identified by its constant 1:1 relationship to the QRS complex, whereas the native P wave marches through the donor heart rhythm independently. The presence of the two separate P waves may lead to confusion about the patient's rhythm, mistakenly interpreting sinus rhythm as second-degree heart block. The ECGs may also be interpreted erroneously as showing atrial fibrillation, atrial flutter, or frequent premature atrial complexes. Some patients may have evidence of "cardiomegaly" related to the transplantation of a heart from a donor who was larger than the recipient (**Figure 297-3**). Clinical evaluation is based on the reason for the ED visit. Patients may present with a variety of symptoms in the setting of rejection including dyspnea, orthopnea, syncope, and edema, but chest pain is typically absent due to denervation during surgery.[92] Chest radiograph, ECG, and further evaluation are based on complications of cardiac transplantation (**Table 297-15**) and underlying patient comorbidities, especially in elderly transplant recipients. Cardiac biomarkers are typically elevated in rejection, with findings consistent with heart failure on echocardiogram and chest radiograph.[2]

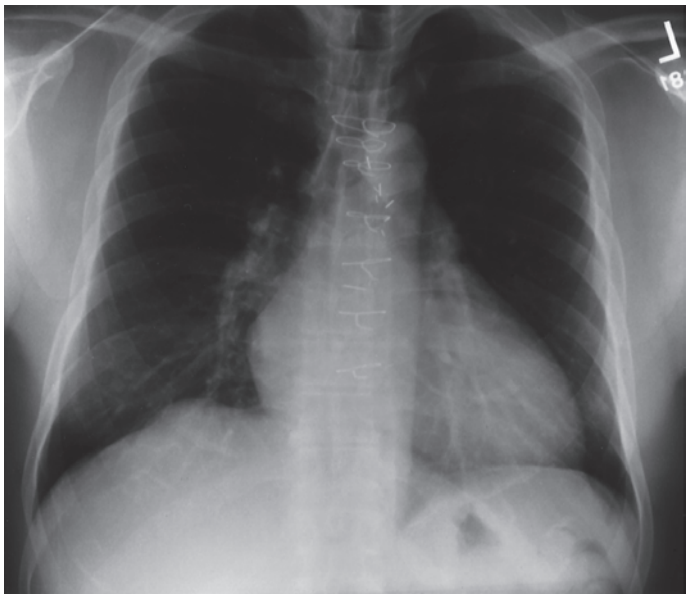

FIGURE 297-3. Chest radiograph of healthy post–heart transplant patient with typical postoperative changes, including "cardiomegaly" due to transplantation of a heart from a donor who was larger than the recipient.

CORNEAL TRANSPLANTATION

Corneal transplantation (penetrating keratoplasty) is the most common form of human solid-tissue transplantation and is a key element in vision restoration. Unlike other tissue and organ transplants, corneal allotransplantation usually does not require systemic or permanent

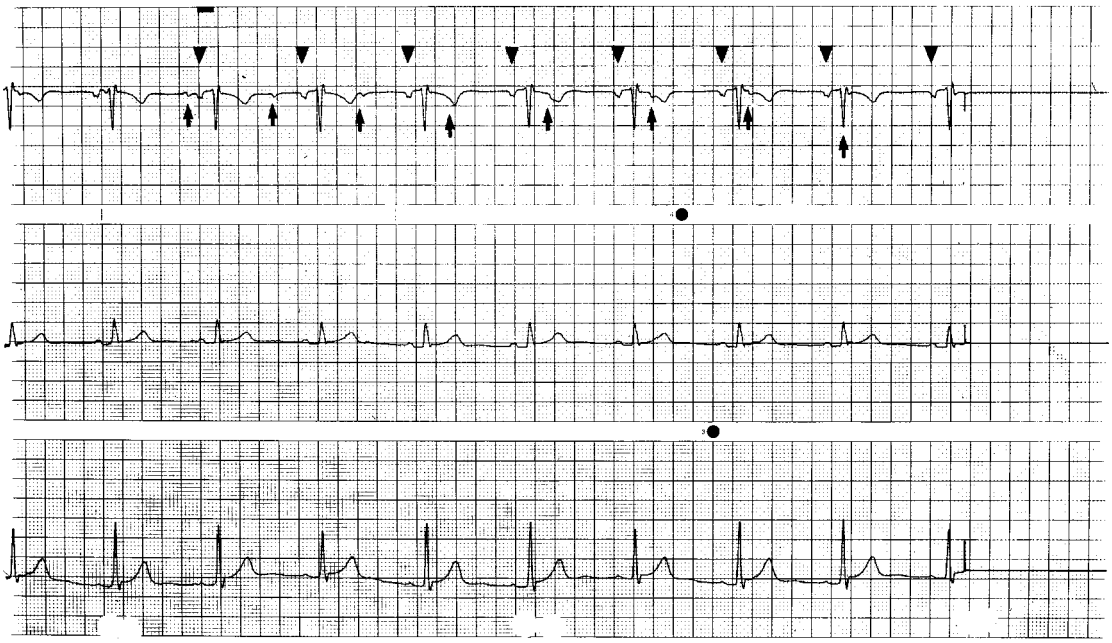

FIGURE 297-2. ECG in a heart transplant patient. ECG demonstrates donor and recipient P waves (*arrowhead* = donor P wave; *arrow* = recipient P wave).

TABLE 297-15 Complications After Cardiac Transplant

Complication	Comments
Altered physiology	See text in "Cardiac Transplantation" section.
Dysrhythmias	Dysrhythmias after transplantation are frequently due to rejection. Treat the unstable patient presenting in extremis with 1 gram of methylprednisolone IV; delay rejection therapy in the stable patient for consult with the transplant team and biopsy. Atropine and vagal maneuvers have no effect due to denervation. Adenosine should be provided at half the normal dose in supraventricular tachycardia.
Sinus node dysfunction	Pacemaker usually required.
Pulmonary complications Pneumonia Thromboembolic disease Exercise-induced hypoxemia Pneumothorax Interstitial fibrosis	Diagnosis may require CT or more invasive diagnostic procedures.
Cardiac ischemia	Patients do not experience pain due to denervation; symptoms typically occur with complications such as congestive heart failure.
Rejection	Presents a variety of ways: dyspnea, syncope, orthopnea, palpitations, edema. Cardiac biomarkers typically elevated. Often presents with dysrhythmias and findings of heart failure. Treat the patient presenting in extremis; withhold treatment for biopsy if possible.
Infection	See section "Posttransplant Infections."
Congestive heart failure	Echocardiography can help to determine etiology and therefore ideal treatment.
Ischemic stroke and intracranial hemorrhage	Increased risk after heart transplant.
Complications specific to ventricular assist devices	Increased risk of infection and thromboembolism.
Cardiac allographic vasculopathy	Beyond 1 y after transplant, one of the major causes of graft failure due to rapid atherosclerosis. Pediatric heart transplant recipients are at risk for graft coronary artery disease and ischemia. May occur with no symptoms or fulminant heart failure. Diagnosis includes angiography. May require retransplantation.

immunosuppression. Reasons for graft failure include corneal graft rejection (30.9%), corneal endothelial cell failure (21.0%), glaucoma (8.5%), and other causes (26.2%).[104,105] **Ophthalmology consultation is required for any change in visual acuity or other ocular signs or symptoms in a patient with a corneal transplant.**

Corneal graft rejection is a specific process in which a graft that has been clear suddenly develops graft edema with anterior segment inflammatory signs. Rejection can occur at any time starting at 10 days after transplant. The inflammatory process starts at the graft margin nearest to the most proximal blood vessels and then moves toward the center to involve the entire graft.[104] Signs and symptoms include eye pain, photophobia, corneal or scleral injection, and decreased visual acuity. Examination may reveal unilateral anterior chamber reaction with keratic precipitate or corneal edema in a previously clear graft. Late graft failure can present with gradual onset of graft edema with no associated inflammation or keratic precipitates. Treatment includes topical or systemic steroids, cycloplegics, and immunosuppressive drugs such as local and systemic cyclosporine A and tacrolimus.

Wound dehiscence can occur early or late after corneal transplantation as a result of infection or after eye trauma. Trauma may be unrecognized or be a result of events such as motor vehicle airbag deployment or a fall with the patient's glasses impacting the eye. There may be globe rupture, slight separation of part of the suture line, or just broken sutures.

Viral,[104] bacterial,[106] or fungal[107] infection can threaten the transplanted cornea. In patients with a history of herpetic keratitis, consider recurrence and examine with fluorescein for characteristic corneal staining and signs of anterior chamber inflammation.[104] Ophthalmology consultation is needed for diagnosis and treatment.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 298

The Patient With Morbid Obesity

Joanne Williams

INTRODUCTION AND EPIDEMIOLOGY

Since 1980, worldwide obesity has more than doubled. In 2008, more than 1.4 billion adults, age 20 and older, were overweight. Of these, over 200 million men and nearly 300 million women were obese. Sixty-five percent of the world population resides in countries where overweight and obesity kill more people than underweight. In 2010, more than 40 million children under the age of 5 were overweight.[1]

In children, an age- and sex-specific percentile for body mass index (BMI) determines weight status rather than the BMI categories used for adults, because children's body composition varies as they age and varies between boys and girls.

The Centers for Disease Control and Prevention uses a BMI threshold of above the 85th percentile to define overweight and above the 95th percentile to define obese, compared to children of the same age and sex.[2] The World Health Organization defines overweight as a BMI ≥25 kg/m^2, whereas obesity is defined as a BMI ≥30 kg/m^2.[1]

Care for bariatric surgery patients is discussed in Chapter 87, "Complications of General Surgical Procedures."

PATHOPHYSIOLOGY

Obesity is an independent risk factor for acute coronary syndrome, especially in those <40 years old.[3,4] Atypical symptoms may pose a problem with acute coronary syndrome diagnosis.[5,6] Approximately 11% of cases of congestive heart failure are attributable to obesity alone.[7] The physical deconditioning of obesity manifests with orthopnea, dyspnea, and lower extremity swelling mimicking acute congestive heart failure. Plain chest radiograph findings of congestive heart failure may be obscured by redundant overlying soft tissue and hypoventilation artifact. Brain natriuretic peptide levels are lower in the obese patient than in the nonobese.[8,9] Cardiomyopathy may affect up to 10% of patients with a BMI >40 kg/m^2.[10] Obesity is a risk factor for venous thromboembolism[11] and its recurrence once anticoagulation therapy is withdrawn.[12]

The increased prevalence of type 2 diabetes is closely linked to the upsurge in obesity. Excess weight accounts for 90% of type 2 diabetes.[13] Obesity is strongly associated with insulin resistance in normoglycemic persons and in individuals with type 2 diabetes.[14]

The accumulation of fat impairs the function of ventilation in obese children and adults.[15-17] Reductions in forced expiratory volume in 1 second, forced vital capacity,[15,16] total lung capacity, functional residual capacity, and expiratory reserve volume are associated with increasing BMI.[18]

Obesity is a well-recognized risk factor for obstructive sleep apnea. Forty percent of people who are obese have obstructive sleep apnea, and approximately 70% of people with obstructive sleep apnea are obese.[19]

Increased fat deposition in the pharyngeal area along with reduced operating lung volumes associated with obesity reduce upper airway

TABLE 298-1 Diagnostic Criteria for Obesity Hypoventilation Syndrome

- Body mass index 30 kg/m^2
- Daytime $Paco_2$ >45 mm Hg
- Associated sleep-related breathing disorder (obstructive sleep apnea–hypopnea syndrome or sleep hypoventilation or both)
- Absence of other known causes of hypoventilation

Abbreviation: $Paco_2$ = partial pressure of arterial carbon dioxide.

caliber, modifying airway configuration, which in turn increases upper airway collapsibility. Thus, airways are predisposed to repetitive closure during sleep.[20] Daytime sleepiness increases and may be associated with accidental trauma.[19]

Cor pulmonale and hypercapnic respiratory failure are common. Obesity hypoventilation syndrome (**Table 298-1**) was first described over 50 years ago.[21,22] The most common symptoms are (1) respiratory failure, (2) severe hypoxemia, (3) hypercapnia, and (4) pulmonary hypertension.[22-24]

ESTIMATING PATIENT WEIGHT

The Broselow tape inaccurately predicts actual weight in one third of children.[25] The significance of this inaccuracy has not been studied in depth. A weight-estimation formula based on mid-arm circumference is reliable for use in school-age children and may be an alternative to the Broselow tape.[26] The formula is as follows: weight (kg) = (mid-arm circumference [cm] – 10) × 3. When compared to the Argal, Advanced Pediatric Life Support, and Best Guess formulas, Krieser et al[27] found that parental estimation of weight was more accurate.[27]

The concern for equipment weight capacity in the adult patient with obesity is an important determination for imaging. Scales in most EDs have a maximum weight capacity of 150 kg. Mechanized beds that weigh patients are not common in the ED but are a consideration for equipment. Patients with obesity tend to significantly underestimate their own weight. A variety of formulas are available to estimate weight in adults who are obese using height and waist, hip, and arm circumference. The formula developed by Crandall et al[28] seems to require the least amount of time and patient manipulation. Two distinct formulas for nonpregnant females and males have been developed as follows:

Nonpregnant females: Weight (kg) = 64.6 + 2.15 (arm circumference in cm) + 0.54 (height in cm)

Males: Weight (kg) = 93.2 + 3.29 (arm circumference in cm) + 0.43 (height in cm)

SPHYGMOMANOMETRY

Improper blood pressure cuff width and circumference will artificially elevate pressure readings. The standard adult blood pressure cuff is too short for patients with an arm circumference of 32 cm or larger. Patients who are overweight or obese will require cuffs larger in size.

The American Heart Association recommends the following cuff widths when evaluating blood pressure in patients who are obese: (1) for arm circumferences ranging from 35 to 44 cm, a bladder measuring 16 cm in width is needed; (2) for circumferences from 45 to 52 cm, the bladder width should be 20 cm; and (3) in patients with short upper arm length, a 16-cm-wide cuff should be used.[29,30]

MEDICATION DOSING

Little evidence-based literature is available for appropriate dosing in obesity, and nearly none is available in the obese child. Fortunately, many drugs used in resuscitation are not lipophilic, and lean body mass is a reasonable dosing guide. Altered physiology is characterized by an increased clearance of hydrophilic drugs, a larger volume of distribution for lipophilic drugs, and a decrease in lean body mass and tissue water content, as compared to their lean counterparts.[31] Altered mechanics can predispose the morbidly obese to systemic toxicity due to either overdosing or lack of efficacy from underdosing.[32,33]

TABLE 298-2 Dosing of Select Drugs

Dosing	Drugs
Ideal body weight	Penicillins, cephalosporins, linezolid, corticosteroids, H_2-blockers, digoxin, β-blockers, atracurium, vecuronium, fentanyl*, midazolam*, lorazepam*, phenytoin, propofol
Total body weight	Succinylcholine, rocuronium, unfractionated heparin, enoxaparin, vancomycin
Dosing weight	Aminoglycosides, fluoroquinolones

*Initial dose based on total body weight.

A weight-based medication schedule uses ideal body weight, total body weight, or dosing weight to avoid systemic side effects and lack of clinical efficacy by underdosing. Ideal body weight according to the Devine formula[34] is as follows:

Ideal body weight (male) = 50.0 kg + 2.3 kg (each inch >5 feet)

Ideal body weight (female) = 45.5 kg + 2.3 kg (each inch >5 feet)

Dosing weight is an adjusted body weight of overweight or obese patients and is used only for drugs for which there are recommendations specifying that the actual body weight should be adjusted to use in the dose calculation.

Dosing weight = Ideal body weight + [0.4 × (Actual – Ideal body weight)]

Exception: If actual < ideal body weight, then the dosing weight = actual

Table 298-2 divides select drugs into ideal body weight, total body weight, and dosing weight dosing.[35] **Fentanyl and the benzodiazepines are lipophilic and have a prolonged half-life in obese patients.** With these drugs, the initial dose based on total body weight may be needed, but subsequent doses should be based on ideal body weight.[36] It is best to check with a pharmacist for specific dosage regimens.

VASCULAR ACCESS

Vascular access is problematic. Patients who are critically ill and morbidly obese patients require fluid administration often guided by central venous pressure and urine output.[37] Central venous pressure placement is extremely challenging even for the most skilled physician. In the obese patient, the distance from skin to vessel is much farther than normal, anatomic landmarks are obscured (**Figure 298-1A and B**), and the angle of approach may be too steep to allow cannulation even after reaching the vessel. There is no clear consensus as to the preferable site and approach to central venous catheterization. In general, there is an increased incidence of infection and deep venous thrombosis when using the femoral approach.[38] If this proves to be the only option, then use this site.

The internal jugular vein can be accessed with equal success to the subclavian approach in patients who are obese. The success rate might be increased with the head maintained in the neutral position, thereby reducing the risk of overlap of the internal jugular vein over the carotid artery.[39]

A US-guided 15-cm catheter can be used to cannulate the brachial or basilic vein.[40] Another approach is the use of a pediatric central venous catheter placed into the basilic vein. The pediatric central venous catheter is 8 cm (3.15 in.) in length, is a double-lumen catheter, and has 18- and 20-gauge lumens.[41] Longer catheters can also be considered to guard against inadvertent dislodgement.

IMAGING

Attenuation severely limits the image quality of plain radiographs (**Figure 298-2**). Increasing exposure time can improve the image but at the expense of increased radiation. Motion artifact increases with increased exposure time. Multiple cassettes may be required if the patient is too large for a single 14 × 17–inch film. Patients may be able to stand for plain radiography if too large for the tables.[42]

CT and MRI scanners have both patient weight and girth limits, consider patient shoulder and pelvis girth. Newer CT scanners can



A



B

FIGURE 298-1. **A and B.** Difficulties in landmark identification.

accommodate up to 660 lb. If the patient outweighs equipment capacity, consider transferring the patient to an institution with a larger-capacity scanner, or veterinary schools may be an option. Most standard MRIs have a maximum shoulder-to-shoulder width of 52 inches (137 cm) and weight limits of 300 to 350 lb (136 to 159 kg), although open MRI scanners can sometimes be an option for large body diameters.

Diagnostic peritoneal lavage has been suggested as an option in the patient with obesity and blunt abdominal trauma who is too large for imaging equipment[43]; however, many surgeons are no longer accustomed to making decisions based on results, and in the morbidly obese patient, diagnostic peritoneal lavage is difficult to perform.

PROCEDURAL SEDATION

Give procedural sedation drugs and pain medications cautiously. Select doses at the lower end of the range, and titrate to effect. Local and regional anesthesia might be considered for complicated or prolonged procedures.[44]

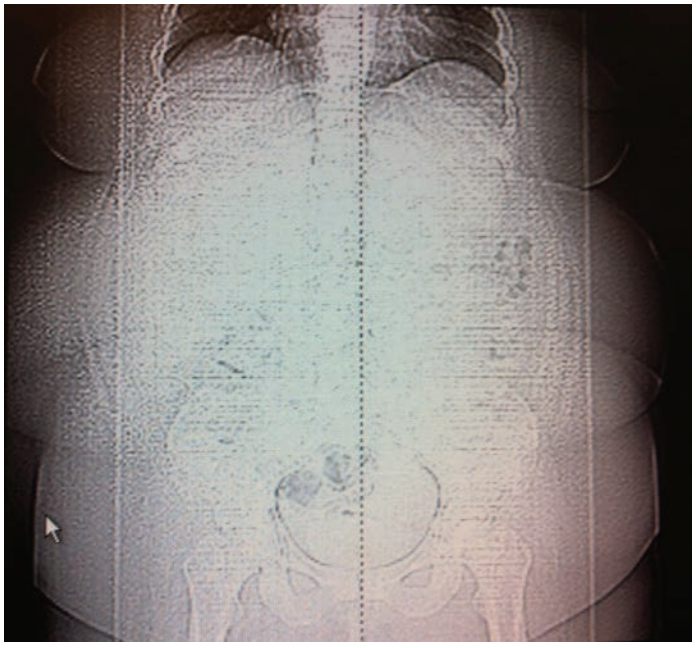

FIGURE 298-2. Attenuation can blur findings on plain radiographic films.

AIRWAY MANAGEMENT

Difficulty with mask ventilation, rapid oxygen desaturation, and altered pharmacokinetics can make airway management challenging.[45] Impedance to airway management is caused by excess fatty tissue externally on the breast, neck, thoracic wall, and abdomen and internally in the mouth, pharynx, and abdomen. First-attempt success is significantly less in obese patients.[45]

Patients who are obese have increased intra-abdominal pressure and increased incidence of hiatal hernia and gastroesophageal reflux disease. These characteristics render patients more prone to aspiration during airway management.[45,46]

Patients who are obese will desaturate more rapidly after preoxygenation than their lean counterparts. When no cervical spine injury is suspected, desaturation may be partially prevented by keeping the patient in a 25-degree head-up position during preoxygenation.[47]

Two-person bag-valve mask with a two-handed bilateral jaw thrust is recommended in patients who are morbidly obese. If tolerated, an oral airway may be used to prevent the tongue from occluding the airway. The early use of noninvasive positive-pressure ventilation may abate the need for endotracheal intubation. High expiratory positive pressures may be needed.

Obesity is not a contraindication for rapid-sequence intubation. Advance preparation is critical, and assessment for a potential difficult airway is of utmost importance.[48]

The "sniffing" position results in suboptimal positioning for laryngoscopy in patients who are obese, and this may also confound results and falsely worsen graded views.[49] The "ramping" position (**Figure 298-3A**) offers improved intubation conditions in patients who are morbidly obese compared to the "sniffing" position (**Figure 298-3B**). This position is achieved by placing multiple folded blankets under the upper body, head, and neck until the external auditory meatus and the sternal notch are horizontally aligned.[50] Another option is elevating the patient's head and thorax with the intubation physician standing on a stool behind the patient and essentially intubating with the patient semi-upright (see Chapter 29A, "Tracheal Intubation", Figure 29A-3).

First give consideration to awake intubation, given that patients who are obese may be difficult to mask ventilate and rapid oxygen desaturation may occur after the ablation of spontaneous ventilation, especially in patients with a BMI greater than 40 kg/m^2.[51-53] The awake intubation may be performed either by the nasotracheal or orotracheal routes.

The relative benefits and risks of the awake intubation approach must be weighed against the merits of rapid-sequence intubation, which reduces risk of aspiration, improves intubating conditions, and results in easier insertion of advanced and rescue airway devices. During rapid-sequence intubation, the chance for first-pass success can be optimized



A



B

FIGURE 298-3. The ramping position **(A)** is more effective for intubation than the sniffing position **(B)** in patients with morbid obesity.

by video laryngoscopy. The intubating laryngeal mask airway is effective in obesity and should be readily available because surgical access to the airway may be difficult. The bougie is a good rescue device.[54]

Percutaneous and open surgical access to the airway may be difficult when landmarks are obscured by excess soft tissue and a short neck in the "cannot intubate, cannot ventilate" scenario.[55] Obesity and a short neck are associated with difficult transtracheal needle ventilation and retrograde tracheal intubation.[56,57] However, in the elective surgical airway management setting, cricothyroidotomy is technically feasible even in patients with difficult neck anatomy caused by obesity.[58]

Until the proper size tracheostomy tube is located, a 6-mm-inner-diameter endotracheal tube passed through a cricothyroidotomy incision may serve as a temporizing measure.[59] There is limited literature concerning the success rates of surgical airways in patients in the emergency setting. Even in an ideal setting, cricothyroidotomy requires more than 100 seconds to achieve ventilation,[57] and most clinicians rarely perform the procedure.[60]

With respect to ventilator management, calculate initial tidal volume using ideal body weight and begin with volumes of 6 to 8 mL/kg of ideal body weight. See Chapter 29B, "Mechanical Ventilation," for detailed discussion of mechanical ventilation.[61,62]

TRAUMA

Victims of motor vehicle accidents who are obese (BMI >31 kg/m^2) have significantly more rib fractures, pelvic fractures, pulmonary contusions, and extremity fractures and fewer head and liver injuries.[63] Even with seatbelt and airbag use, risk of death for morbidly obese patients was 1.52 times greater than that in nonmorbidly obese patients.[64]

Mildly overweight patients, not the morbidly obese, are less prone to intra-abdominal injury because of the protective effect of the abdominal fat, known as the "cushion effect."[65]

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 299

The Transgender Patient

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INTRODUCTION

A transgender person is someone whose gender identity differs from their sex assigned at birth. Sex is an assignment of "male" or "female" based on birth assessment of genitalia. An intersex assignment can also be made at birth based on ambiguous genitalia. Unlike sex, gender identity is self-identified, not assigned, and may or may not be congruent with sex. Thus, transgender persons include those who were assigned as being of male sex at birth but who identify as female and those who were assigned as being of female sex at birth but who identify as male. Further, some individuals identify outside the male–female binary, including those who identify as both, neither, or in between, and may identify with terms such as *gender nonbinary*, *gender nonconforming*, or *gender fluid*.[1] Approximately 0.5% of people in the United States identify as transgender.[2] Not all transgender patients desire physical alignment.

Transgender identity is not classified as a mental disorder.[3] Transgender patients should have access to respectful, nondiscriminatory, and affordable medical care. According to the 2015 National Transgender Discrimination Survey, 28% of the transgender respondents reported postponing necessary medical care due to prior negative experiences. In addition, 19% of those surveyed reported being *denied* care because they were transgender.[4] More than 50% of transgender persons reported that they had to teach their healthcare provider about the health care that they needed.[5] Transgender individuals may abstain from seeking medical care in an office-based setting due to fear of mistreatment and only seek episodic care in free clinics and EDs.[4,6] Thus, it is of great importance that emergency providers become aware of the special healthcare needs of the transgender patient.

The World Professional Association for Transgender Health is a nonprofit organization that works for high-quality and evidence-based care for transgender and gender nonconforming individuals. The World Professional Association for Transgender Health provides an online resource for identifying culturally competent caregivers based on geographic location (state).[7]

Table 299-1 contains a summary of current important terminology and definitions. Terminology is evolving and may change over time.

CLINICAL ENVIRONMENT

Reducing barriers and creating a positive environment for health care for the transgender patient in the ED begins at triage and continues throughout ED care.[9] Use respectful and sensitive communication and documentation, including the use of correct terminology and pronouns.[10] Provide privacy. If family or friends accompany the patient to the ED, ask the patient about any limits to conversation when others are present. Transgender-identified minors are at high risk for being forced to leave the home when family members become knowledgeable about the gender identity.[4,11]

TABLE 299-1 Terminology and Definitions

Sex	An assignment of "male" or "female" based on birth assessment of genitalia. "Sex" is identified as male or female on legal documents such as birth certificates, passports, and driver's licenses, although some states are beginning to offer additional options (e.g., "other" or "X") on legal documentation.[8]
Gender or gender identity	A person's inner feeling related to being male, female, both, something else, or neither. It is self-identified, and although it is initially identified as the same as the birth sex, it can be changed as a person ages. Thus, gender does not always align with sex.
Gender expression	The external expression of how one affirms their gender. Gender expression is manifested through a person's dress, mannerisms, hairstyle, speech pattern, or other behaviors. All of these components of gender result in an external identification of one's being masculine and/or feminine. Gender expression may not always align with gender identity, as persons can identify as a feminine male or a masculine female.
Transgender	An individual who identifies their gender as different from their sex assigned at birth. A transgender male was assigned female sex at birth but identifies as male gender. A transgender female was assigned male sex at birth and identifies as female gender.
Gender nonconforming/gender nonbinary/gender fluid	An individual whose gender identity falls outside the male–female gender binary (identifying as both male and female, neither, or something else). In this chapter, the term *transgender* includes persons identifying along the nonbinary spectrum as well.
Transmasculine	A person with a female sex assigned at birth who identifies as masculine on the gender spectrum.
Transfeminine	A person with a male sex assigned at birth who identifies as feminine on the gender spectrum.
Cisgender	A person whose gender identity is congruent with their sex assigned at birth. A cisgender person is also referred to as non-transgender.
Sexual orientation	This term describes the sexual attraction for others that an individual possesses. It is self-identified and identified by gender, not sex. A transgender male who is attracted to other males may identify as a gay man. A transgender female who is attracted to males may identify as a straight female.
Transition	The process of affirming or aligning one's body with their gender. The process can include medical, legal, or social changes that are made during this process.
Gender dysphoria	A state of distress. In the context of transgender care and gender identity, dysphoria describes the anxiety, trauma, or unease felt by a transgender person in situations when there is discordance between their gender and sex assigned at birth.
Gender affirmation	A term used to describe actions, medications, surgeries, or feelings that are used by a transgender person to express their gender and/or align their body with their gender.
Chosen name	The name a person uses when referring to themselves. May not be the same as their legal name. The name that should always be used when referring to a patient both directly and indirectly *and included in handoffs*.
Legal name	This name is used on legal documentation and often is the name assigned at birth. The legal name is also called the "dead name" when the name is no longer used by the patient.
Pronouns	Pronouns have historically been defined based on gender expression. Pronouns are a core part of a person's identity and should not be presumed. Pronouns include masculine (he/him/his), feminine (she/her/hers), and gender neutral (they/them/theirs).

THE PATIENT GREETING

The first priority is to ensure that the patient is being addressed in the desired manner. Use the patient's chosen name and be consistent in communication, documentation, and healthcare provider handoffs (including to allied healthcare professionals, trainees, financial counseling, volunteer staff, etc.). Ways to ask about names and preferred pronouns[12] include the following:

1. "Hello, my name is Dr. Lastname. What name do you go by? It is a pleasure to meet you [insert chosen name]. What pronouns do you use?"
2. "Hello, I'm here to see [insert legal name]. What name would you like me to call you? What pronoun do you want me to use?"
3. "Hello [insert chosen name], my name is Dr. Lastname. My pronouns are she, her, and hers. What pronouns do you use?"

PATIENT HISTORY AND EXAMINATION: SPECIAL CONSIDERATIONS

Contextualizing why questions are being asked can help the patient understand and help them prepare for difficult questions. Asking if there is a preferred, more gender-neutral terminology for body parts or processes (e.g., saying "monthly bleed" instead of "menses") can help a patient feel more comfortable (**Table 299-2**). Next, it is important to ask about gender-affirming hormones and surgeries, not only for a complete history but also so that this information can be considered in the context of a chief complaint. For example, it is important to know if a transfeminine person has a neovagina if they are presenting with pelvic pain. Ask about past surgery, especially gender-affirming surgery, and hormone use and route. Not all transgender persons follow the same path with regard to hormones and surgeries or gender expression. Although a transgender male may experience amenorrhea shortly after the initiation of masculinizing hormone therapy, testosterone does not provide a form of birth control.[13] Determine sexual activity and pregnancy risk.

It is not necessary to visualize or examine the anatomic changes that accompany gender-affirming therapy and surgery, unless clinically applicable.[4] Address the chief complaint and describe the body exposure that will be required. Respect the patient's preferences. If refusal puts the patient at risk, explain the risks in a compassionate manner.

TABLE 299-2 Medical Named Body Part With Possible Alternative Name*

Medical Term	Alternative Name
Penis	External genitalia, phallus
Testes	External genitalia
Breasts	Chest tissue
Vagina	Front hole, internal genitalia

*Defer to patient preference.

MANIFESTATIONS OF GENDER-AFFIRMING TREATMENTS

This section discusses hormone therapy, medical illnesses that may be affected by hormone therapy, transgender-affirming surgery, and the complications of transgender-affirming surgery.

HORMONES

Because everyone's transitional journey is unique, not every patient will use hormones, and the utilization of hormones does not make a patient more or less transgender than someone else. Some people will desire to use hormones but will lack access. These individuals may, in turn, use alternative resources for nonprescription hormones. Complications of hormone therapy are listed in **Table 299-3**.

TABLE 299-3 Gender-Affirming Hormone Therapy–Related Complications

Feminizing Hormone Therapy
- Hypercoagulability
  - Venous thromboembolism
- Electrolyte imbalances
  - Hyperkalemia (with spironolactone use)
- Prolactinoma
- Increased risk of cardiovascular disease[15]

Masculinizing Hormone Therapy
- Erythrocytosis

GONADOTROPIN BLOCKERS

Gonadotropin analogues (also termed *gonadotropin-releasing hormone analogues* or *puberty blockers*) are commonly used. Suppression of puberty allows a youth the opportunity to further explore gender identity without acquiring unwanted secondary sex characteristics from natal pubertal hormones. Puberty blockers can be initiated once a child reaches the pubertal stage of Tanner stage II.

Because the puberty blockers work to occupy the receptors in the pituitary, initially there is an increase in gonadotropin production followed by suppression. This increase is termed the *flare* and happens roughly 10 days after initiation. Some patients may experience hot flashes or fatigue if puberty blockers are initiated further along in puberty due to exposure to natal gonadal steroids followed by suppression.[14]

Youth on puberty blockers alone should be treated like any prepubertal youth. They normally will not have progression of secondary sex characteristics, and laboratory values will show gonadotropin and sex hormone levels in the prepubertal range.[14]

MASCULINIZING HORMONES

The goal with masculinizing hormones is to suppress estradiol levels and to achieve male range total testosterone levels (320 to 1000 nanograms/dL). **Testosterone** at this level suppresses menses; increases libido; increases clitoral size; deepens the voice; produces male-pattern fat, muscle, and hair distribution; and increases energy. Side effects of testosterone include erythrocytosis (hematocrit >50%), which can increase risk for cerebrovascular disease and thrombosis; vaginal dryness; and changes in lipid profile (via decreasing circulating levels of high-density lipoprotein). Transaminase elevation can result from testosterone therapy. Cigarette smoking and morbid obesity increase the risk of venous thromboembolism (VTE).[1,14]

Transmasculine persons who have been prescribed testosterone continue to have risks for estrogen-sensitive pathology. Guidelines recommend including any estrogen-sensitive pathology, such as uterine, ovarian, or breast malignancies, in the diagnosis as appropriate (**Table 299-4**).

Testosterone does not provide any form of birth control. Screen for pregnancy if the patient has a uterus and ovaries, regardless of testosterone use. If a patient is found to be pregnant, stop testosterone pending pregnancy planning.

Some patients will present with pelvic bleeding while on testosterone. Testosterone causes vaginal atrophy, which can be a source of bleeding. Evaluate for infection, pregnancy, and uterine pathology.[1] Progestins can stabilize the uterine lining in patients with persistent uterine bleeding while on testosterone.

TABLE 299-4 Breast Tissue Cancer Risk

- Transfeminine patients: proliferative tissue
- Transmasculine patients: residual tissue

Note: Guidelines recommend that transmasculine patients continue breast cancer screening guidelines for cis females and that transfeminine patients begin breast cancer screening guidelines for cis females after 5 years on estrogen therapy or at age 50.[1]

FEMINIZING HORMONES

Feminizing hormones come in two forms because of the potency of testosterone: estrogens and antiandrogens. **17-β-Estradiol** is the form of estrogen used for feminization because it is the most bioidentical and the least thrombogenic of estrogen preparations. It comes in oral, transdermal, and intramuscular injectable forms. The goal of estrogen use is to suppress testosterone (to <55 nanograms/dL) and promote increased estradiol levels. Antiandrogens can be used as adjuvant therapies and include spironolactone (which inhibits testosterone secretion and androgen binding to receptors), finasteride (which inhibits the conversion of testosterone to dihydrotestosterone) and gonadotropin-releasing hormone analogues (which suppress gonadal steroid production). Feminizing hormone regimens cause breast growth, reduce body hair growth, redistribute fat and muscle, and soften skin. They have no effect on vocal cords or bone structure.

Side effects of feminizing hormones in general include decreased libido and reduced testicular volume and sperm production. Less frequent and less firm erections can also occur (mostly in those on spironolactone).

Estradiol side effects include breast tenderness, nausea and vomiting, dry skin, brittle nails, headaches, and increased appetite and weight gain. Estradiol also increases the risk of thromboembolic disease due to increased production of coagulation factors. Patients with signs or symptoms concerning for thromboembolism should be considered at risk and should be evaluated for venous thromboembolism.[16,17] Estradiol can cause prolactinomas in transfeminine persons. If a transfeminine patient taking estradiol presents with concerns for a pituitary space-occupying lesion or new-onset vision changes, especially any compromise of vision in one lateral field or in both lateral fields, or headaches, consider prolactinoma in the differential.[14] Estrogen can increase the incidence of hypertension, gallstones, and hypertriglyceridemia.[14]

Spironolactone is a diuretic and is the most commonly used antiandrogen in the adult transfeminine population. Side effects include hyperkalemia, increased urine output, and hypotension. GI upset can also occur.

Transgender patients may restrict fluid intake due to unsafe restroom conditions during the day. For those who are taking spironolactone, this is dangerous and can result in dehydration. Patients on spironolactone should have potassium and renal function checked as clinically indicated. Those who present with dehydration are also at increased risk of hyperkalemia.[14]

NON–MEDICALLY PRESCRIBED HORMONES

Testosterone and estradiol can be acquired through nonmedical sources. Shared oral medication and third party–acquired injectable testosterone are common. With injectable testosterone use, there is an increased risk for human immunodeficiency virus and hepatitis due to shared needles. Also common is the use of birth control pills in place of prescribed estrogen.[18]

GENDER-AFFIRMING SURGERIES AND THEIR COMPLICATIONS

Gender-affirming surgeries include procedures that are performed for non–gender-affirming reasons as well (e.g., breast implants, mastectomies, and hysterectomies), and the complications do not differ greatly. However, there are surgeries specific to gender affirmation with which many healthcare providers have limited or no experience. Gender-affirming surgeries and their complications are listed in **Table 299-5**.[1,19-27]

GENITAL FEMINIZING PROCEDURES

Complete expulsion of a vaginal skin graft is a possible occurrence (usually in the first postoperative week). This represents a failure of the procedure and requires consultation with a surgeon for repair.[1,22] Depending on the type of neovagina created, masses and precancerous lesions can appear inside the vaginal canal. If used to create the neovagina, colonic tissue poses risk for inflammatory bowel disease, colitis,

TABLE 299-5 Complications of Gender-Affirming Surgeries

- Facial feminization surgery: Bleeding, wound infection, hematoma, swelling, pain
- Facial masculinization surgery: Bleeding, wound infection, hematoma, swelling, pain
- Transfeminine breast surgery: Prolonged swelling, surgical site wound infection, wound dehiscence, hematoma, pain, movement or rotation of implants, neuropathy around nipples
- Transmasculine chest surgery: Bleeding, surgical site wound infection, wound dehiscence, hematoma, pain, swelling, neuropathy around nipples
- Transfeminine genital surgery: After surgery—bleeding, hematoma, surgical wound dehiscence, urinary retention; long term—granulation of the tissue with dilation, stenosis of vagina, webbing of vagina or complete expulsion of graft, vaginal drainage and odor, rectovaginal fistula, urethra-vaginal fistula, urinary tract infection
- Transmasculine genital surgery: After surgery—bleeding, hematoma, catheter infection; long term—urethrocutaneous fistula, urethral stricture, implant erosion, expulsion or rupture

or adenocarcinoma. Penile inverted tissue can develop skin lesions such as melanoma or psoriasis.[23] Frequent discharge can be common after a vaginoplasty as dilation postoperatively will cause repeated trauma to granulation tissue. Discharge will diminish over time. Silver nitrate can be applied to any bleeding granulation tissue in the interim.[1]

GENITAL MASCULINIZING PROCEDURES

Early in the postoperative course, patients go home with urinary catheters, which can obstruct or kink. Care should be taken with evaluation because the neourethra is still healing. Should a patient present further along with dysuria, evaluation should include a urine culture because white and red blood cells are present in urine sample after a normal reconstruction and are not necessarily evidence of a pathologic condition. Negative cultures in the setting of dysuria may indicate a stricture. Urethral strictures may happen up to 6 to 12 months after surgery. Patients may present with dysuria, reduced stream, and inability to pass a catheter on exam. Cystourethrography can be useful in identifying postoperative urethral complications.[1,26] If the patient underwent a vaginectomy as a component of genital surgery, rectal injury is a possible complication. Another complication is the development of a fistula, which may communicate with the skin of the neophalus, scrotum, or perineal suture sites.[25] For patients who have erectile implants, erosion through the skin of the phallus is a possible complication.[1]

MENTAL HEALTH

Transgender persons disproportionately experience societal discrimination, mistreatment, harassment, and prejudice in everyday life. **Table 299-6** provides a list of mental health disorders and social issues.[28,29]

Do not assume that mental health issues are always related to the gender experience of the patient.[28] At a minimum, depression, anxiety, and mood disorders occur as frequently in transgender patients as in the general population. Treatment of these mental health disorders follows typical treatment plans. However, be vigilant for mental health complaints that may be a result of the patient's gender experience. Gender-related depression and anxiety with resultant suicidal ideation are prevalent in the transgender community.[29] Also common are mental health issues related to drug and alcohol addiction, homelessness, and traumatic experiences such as physical assault, sexual assault, and abuse.[1]

TABLE 299-6 Mental, Social, and Health Issues in Transgender Persons

Compared to the cis population, transgender persons have increased prevalence of:

- Human immunodeficiency virus infection
- Substance abuse (drug and alcohol)
- Mental health disorders (depression, suicide, anxiety disorder)
- Physical assault (domestic violence, sexual assault, physical assault)
- Homelessness
- Sexually transmitted diseases

Emergency treatment of mental health issues in the transgender patient should follow the practices outlined in Section 24, "Psychosocial Disorders." The transgender patient should be referred to a mental healthcare provider who specializes in transgender care.[30-32] In addition, because of the high rate and impact of societal stressors associated with being transgender, social services should be considered when patients need housing, food, and safety.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 300

Palliative Care

Justin K. Brooten

INTRODUCTION

The goal of palliative care is to relieve the suffering of patients with serious illness. Regardless of the patient's prognosis, relief of suffering should be a primary goal for both emergency medicine and palliative care.[1] **Palliative care** is defined by specialty advocates as the physical, spiritual, and psychosocial care given by multiple disciplines to patients and their families who are living with life-threatening illness.[2] Although these principles are applicable to all stages of a patient's illness, a palliative care consultation from the ED is generally considered in the context of previously predicted end-of-life care. **Hospice care**, a branch of palliative care, is a comprehensive program of palliative treatment that is appropriate when patients with chronic, progressive, and eventually fatal illness are determined to have a life expectancy of 6 months or less. Palliative care is patient centered rather than disease centered. It strives to ensure that the patient or his or her (formal or informal) representatives have chosen realistic goals of care after the patient's diagnosis, prognosis, and therapeutic options have been considered. This discussion and decision making should take place during a meeting that includes the patient's healthcare team, surrogate decision maker(s), and those loved ones who are privileged to receive confidential information.

Palliative care is guided by the axiom that distressing symptoms should be treated. It thus provides expert assessment and treatment of symptoms, including pain, dyspnea, and vomiting. Pain is the most common reason for seeking care in the ED, accounting for 58% to 78% of visits in the United States.[3-5] Unfortunately, only 60% of patients reporting pain receive pain medications.[6] Dyspnea is the seventh most common chief complaint and vomiting the ninth most common chief complaint of patients presenting to the ED.[7]

Palliative care also trains healthcare professionals to compassionately communicate diagnosis, prognosis, and treatment alternatives and guide the formulation of a therapeutic plan. Palliative care clinicians work to coordinate caregivers and interventions for the patient and family, to make care more effective, and to lessen the stress and obstacles for achieving satisfactory outcomes. Standards for compassionate care spelled out by the Institute of Medicine[8] and numerous professional societies require that distressing symptoms be alleviated concurrently with all treatments directed toward the pathology of the medical disorder. The patient or surrogate must play a key role in decisions regarding care.

The first American Board of Medical Specialties board exam, administered in 2008, qualified the first emergency medicine physicians for practice of the subspecialty of hospice and palliative medicine.[9]

In 2014, the American College of Emergency Physicians reaffirmed its 2008 policy statement: **Ethical Issues and End-of-Life Care** (**Table 300-1**).[10] In 2011, the Center to Advance Palliative Care (the primary advocate for palliative care in the United States) released its **Improving**

TABLE 300-1 The American College of Emergency Physicians Board of Directors: Ethical Issues at the End of Life

The American College of Emergency Physicians believes that:

- Emergency physicians play an important role in providing care at the end of life (EOL).
- Helping patients and their families achieve greater control over the dying process will improve EOL care.
- Advance care planning can help patients formulate and express individual wishes for EOL care and communicate those wishes to their healthcare providers by means of advance directives (including state-approved advance directives, do not attempt resuscitation orders, living wills, and durable powers of attorney for health care).

To enhance EOL care in the ED, the American College of Emergency Physicians believes that emergency physicians should:

- Respect the dying patient's needs for care, comfort, and compassion.
- Communicate promptly and appropriately with patients and their families about EOL care choices, avoiding medical jargon.
- Elicit the patient's goals for care before initiating treatment, recognizing that EOL care includes a broad range of therapeutic and palliative options.
- Respect the wishes of dying patients including those expressed in advance directives. Assist surrogates to make EOL care choices for patients who lack decision-making capacity, based on the patient's own preferences, values, and goals.
- Encourage the presence of family and friends at the patient's bedside near the end of life, if desired by the patient.
- Protect the privacy of patients and families near the end of life.
- Promote liaisons with individuals and organizations in order to help patients and families honor EOL cultural and religious traditions.

Palliative Care in Emergency Medicine project. This project informs and enables EDs to develop thoughtful, creative, and streamlined programs to integrate palliative care into the day-to-day operation of the ED.[11]

By implementing principles of palliative care (**Table 300-2**), emergency physicians will become better skilled at assessing patients' preferences and health status to determine whether initiating aggressive therapy is both concordant with the patients' or surrogates' preferences and potentially beneficial. Patients already receiving a palliative care approach will be able to have their existing care plan continued in a coordinated fashion when presenting to the ED for worsening symptoms, although they would be more optimally managed as outpatients.[12]

TABLE 300-2 Description of Palliative Care in Emergency Medicine

- **Who:** Patients with serious, potentially life-threatening illness and their families.
- **What:** Relief of symptoms from potentially curable conditions in the presence of chronic devastating disease when standard treatment impedes the patient's remaining quality of life, to incurable conditions such as stage IV heart failure, metastatic lung cancer, or advanced dementia.
- **When:** After a life span–limiting prognosis has been defined or when requested by patients and their families to enhance the patient's quality of life. Late-stage palliative care for incurable illnesses with a prognosis estimated of 6 mo or less is provided in the United States under the hospice benefit of Medicare.
- **Where:** In the ED and every other setting in which the patient receives care, or wishes to receive care, such as at home.
- **Why:** Because the relief of suffering is the primary goal of medicine, and there are few places with greater patient suffering than in the ED.
- **How:** The patient and/or family decide the goals of care after a realistic discussion based on diagnosis, prognosis, and effectiveness of potential therapies. An interdisciplinary team consisting of at least the doctor and nurse provides care measures, such as symptom relief, and initiates the coordination of care needed to reach the patient's goals. Most commonly, this occurs in consultation with a palliative care service, unless the emergency physician is trained in palliative care.
- **Who Decides:** The patient, provided he or she retains decision-making capacity, or the surrogate decision maker, the legally appointed Durable Power of Attorney for Healthcare or closest family relative who speaks for the patient.

EPIDEMIOLOGY

In 2016 in the United States, the proportion of medical decedents who received hospice prior to death ranged from 23% in Puerto Rico to 58% in Utah.[13] Although hospice was initially designed for cancer patients, 72.8% of patients enrolled in hospice in 2016 had a noncancer diagnosis.[13] Eighteen percent of hospice patients' death diagnosis is dementia.[13]

In 2002, there were 12.7 million people aged >65 years in the United States.[14] In 2030, there will be >72 million elderly people. The **Hospitalized Elderly Longitudinal Project** study found that the very elderly (>80 years) are most likely to want and to consider comfort care as the best option when facing serious chronic illness.[15] The surge in growth in the aging population will increase the demand for quality palliative care.

Approximately 30% of healthcare costs occur in the last 6 months of life. Data from the Health and Retirement Study showed that 51% of patients over age 50 visit the ED during their last month of life, 77% of those are admitted to the hospital, and 68% of those admitted die during their hospital stay.[16] A meta-analysis found that the use of hospice saved as much as 40% of healthcare costs during the last month of life and 17% over the last 6 months of life.[17] A subsequent study found that hospice care reduced Medicare costs during the last year of life by an average of $2309 per hospice user.[18] Admitting eligible patients to hospice is one promising route for addressing the quality/cost chasm.[19]

Currently, only 4% to 7% of hospitalized patients are referred to palliative care or hospice directly from the ED.[20-22] The average time in the hospital before transfer to a palliative care bed is 5 to 9 days.[21,22]

IDENTIFYING PATIENTS FOR PALLIATIVE CARE

In 2011, the Center to Advance Palliative Care released its Improving Palliative Care in Emergency Medicine program, a program that provides a thoughtful approach to palliative care practice in the ED, formulated for and by emergency clinicians. The program covers all aspects of palliative care in the ED.[11] Emergency physicians have enthusiastically received the Improving Palliative Care in Emergency Medicine program,[11] despite expressing concerns about the challenges facing them when discussing palliative or hospice care with patients such as interruption of workflow, lack of long-term relationships with patients, and lack of training to facilitate interactions.[23]

Patients whose long-term care needs are complex and require skilled nursing care for transfusions, tracheostomy care, or infusions of antibiotics or inotropes are likely in need of palliative care, especially if the disease is progressive. In one study, 54% of patients transported to the ED from a long-term care facility as a level 1 triage priority were dead in 30 days.[24]

FUNCTIONAL DECLINE

Functional decline is the loss of the ability to care for oneself. This ranges from the loss of complex abilities, like driving, shopping, and managing finances, to basic activities like ambulating to the bathroom and getting safely out of bed. The loss of activities of daily living is the cardinal feature of decline, especially if accompanied by unintentional weight loss, and it indicates the need for increased care assistance and suggests a short life expectancy.

PROGNOSIS

Space in this textbook does not allow for a comprehensive discussion of formulating a prognosis and how to share it with patients and families. There are several key diagnoses and prognostic findings that are extraordinarily helpful to understand. Patients with chronic, progressive, life-threatening diagnoses will almost always benefit from palliative care. Those with extensive disease, be it metastatic cancer, organ failure, or neurologic deterioration (with anorexia/cachexia and decreased self-care), are frequently on a dying trajectory.[25] Examples of diagnoses of patients who may benefit from palliative care are listed in **Table 300-3**. A predictive instrument known as the **Palliative Prognostic Score** correlates with prognosis.[26] Elements of the Palliative Prognostic Score include ability to ambulate, provide self-care, and maintain oral intake and level of consciousness. A bed-bound patient completely dependent

TABLE 300-3 Common Diagnoses and Key Findings of Patients Who May Benefit From Palliative Care

Diagnosis	Key Findings
Solid organ neoplasm	Widespread metastasis unresponsive to treatment
End-stage heart failure	Significant symptoms at rest despite therapy
End-stage COPD	Significant symptoms at rest despite therapy
Advanced dementia	Impaired mobility and inability to communicate health needs
Degenerative neurologic disease	Inability to complete ADLs or communicate health needs
End-stage AIDS	Multiple opportunistic infections and/or AIDS dementia
End-stage renal disease	Patient no longer willing or able to undergo dialysis
End-stage liver disease	Repeated episodes of hepatic encephalopathy, bleeding, or symptomatic ascites resistant to medical therapy
End-stage rheumatologic disease	Inability to complete ADLs without significant discomfort
Multisystem trauma	Nonsurvivable injury
Burn	When age plus percent burn exceeds or nears 140
Multiorgan failure	When two or more key body systems fail
Any chronic, progressive, debilitating disease	Whenever symptom burden exceeds resources and the ability of the patient and/or family to cope with medical condition

Abbreviations: ADLs = activities of daily living; AIDS = acquired immunodeficiency syndrome; COPD = chronic obstructive pulmonary disease.

TABLE 300-4 Key Communication Phrases[28]

Determining Patient Decision-Making Capacity

- Will you describe your current condition?
- Tell me about the treatment options we have just discussed.
- Explain to me why you feel that way.

Quality of Life

- What symptoms bother you the most? What concerns you the most?

Prognosis

- Has anyone talked to you about what to expect?
- Do you have any sense of how much time is left? Is this something you would like to talk about?

Talking With Surrogate Decision Makers

- These decisions are very hard; if [the patient] was sitting with us today, what do you think [he/she] would say?
- Can you tell me why you feel that way?
- It is not a question of whether we care for [your loved one], but we will care for them.
- Then we will do everything possible to keep [your loved one] comfortable, but we won't be providing ineffective and burdensome therapies such as CPR or intubation.

Discussing Palliative Care or Hospice Referral

- To meet the goals we've discussed, I've asked the palliative care team to visit with you; they are experts in treating the symptoms you are experiencing. They can help your family deal with the changes brought on by your illness.

Breaking Bad News—Death Pronouncement

- I wish there is more we could have done; I'm very sorry for your loss. This has to be really difficult for you. Is there anyone I can call to be with you now?

for all care with reduced oral intake and a diminished level of consciousness has a Palliative Prognostic Score of 10% and a 1-week median expected survival.[26]

DISCUSSING PROGNOSIS AND SETTING THE PLAN OF CARE

DETERMINING PATIENT DECISIONAL CAPACITY AND IDENTIFYING SURROGATE DECISION MAKERS

The ED team should immediately identify the decision makers when a debilitated patient arrives in crisis to the ED. **A patient with decisional capacity is one who has the mental ability to grasp and retain information about his or her condition, weigh risks and benefits, and demonstrate these abilities by verbalizing a medical decision**[27] (see Chapter 303, "Legal Issues in Emergency Medicine," for a more detailed discussion of patient capacity). **Table 300-4** lists phrases to aid meaningful communication with patients and families.[28] If the patient lacks decisional capacity, then the patient's advance directive should be accessed and the named surrogate decision maker should be contacted as soon as possible. If none of these resources are available, then the closest family member(s) should be consulted regarding the plan of care. If no one is available to speak for the patient, then the treating physician should act in the patient's best interest. This may include an order to "do not resuscitate" the patient if it is clear that aggressive therapy would not be beneficial.

FAMILY MEETING

Once the physician has determined the patient's decision-making capacity, chronic health status, a clinical diagnosis for the current visit, and a general understanding of the patient's care preference, the doctor and team are prepared to have an abbreviated family meeting with the decision maker(s) to discuss the approach to care. The physician must be clear in his or her own mind whether there is any available therapy that will restore the patient's health; have access to the advice of consultants, specialists, and the patient's primary care physician; and be prepared to issue honest, compassionate, and helpful recommendations based on his or her own assessment.

Realistic Prognosis and Values Discussion A productive approach to start such meetings is to ask the surrogate decision maker what he or she understands about the patient's past health and current condition (Table 300-4). After patiently listening, the physician should share his or her insight into the patient's condition and prognosis while monitoring the family's reaction to determine whether the ED team and the family are in agreement. An example of a physician's opinion in a particular case follows: "Your mother's advanced medical condition cannot be cured, and her illness has made her defenseless against the bacteria in her own body. Treating her again and providing another round of intensive care will not bring her health or immune system back to normal, but may only prolong her suffering."

The next step is to ask the surrogate decision makers whether they know about the patient's values and preference for care, for example, how their mother would wish to be treated in the current circumstances. If the answer to that is unknown, ask how the surrogate decision makers would wish to be treated if they were in the same condition.

Separate Desired Outcome From Likely Outcome Carefully explore discrepancies in the perception of what might be gained from aggressive therapy in patients who are less likely to benefit from such care. Delivering realistic information about the likely outcome and the expectation of poor quality of life significantly impacts subsequent decisions for code status or scope of treatment in a patient with an underlying progressive terminal condition.[29] Patients or surrogates who are aware of poor prognosis and low likelihood of survival from CPR often choose against aggressive therapy or resuscitation.[30,31] Patients and surrogates may decide to forgo aggressive care if a small potential for survival from an acute event would likely result in a loss of significant function or would necessitate constant skilled nursing care for the foreseeable future.[32] Painting a clear picture in lay terms of what the future may hold if various avenues of care are chosen may be a much more effective means of conveying the gravity of choice between various options.[33]

Cultural Differences Cultural differences should be taken into account when discussing treatment options with patients and families, including religious preferences. African Americans are more likely to select aggressive treatment options and less likely to select hospice care than non-Hispanic whites.[34] Reasons cited for end-of-life preferences among African Americans facing these decisions include historical mistrust toward the healthcare system and the importance of spirituality.[34]

CODE STATUS

Do not resuscitate is part of **advance healthcare directives**. Do not resuscitate status or other limitations of resuscitation should evolve directly from harmonious decisions reached at the family meeting. Do not resuscitate orders and advance directives are discussed in Chapter 301, "Death Notification and Advance Directives."

CONSULTATION OPPORTUNITIES

Palliative care consultation services are likely available at your hospital and should be used just as you would any specialist consultation. ED consultation can provide assistance when conducting a family meeting or when access to an inpatient hospice or palliative care unit is needed. When symptom relief, medical decision making, or disposition and coordination of care are beyond your expertise or available time, a consult is appropriate. Notify the patient's attending physician of the consultation if time allows.[35]

TREATMENT AND SYMPTOM MANAGEMENT

The most common targets of symptom management are pain control, dyspnea, nausea/vomiting, constipation, and agitation.

PAIN CONTROL

Acute and chronic pain are addressed elsewhere in detail (Chapters 35 and 38, respectively). The biggest obstacle to aggressive pain management with opiates has been the fear of respiratory depression. Opioid dosing is reviewed in Chapter 35, "Acute Pain Management," and is an essential skill in the practice of emergency medicine. It is also important to understand the progression of side effects from opioids, because these will serve as warnings to reduce the dose or delay the next dose of opioids. Respiratory depression is not a sudden occurrence, but instead is part of a progression that starts with sedation, somnolence, and then respiratory depression.[36] The safety of patient-controlled analgesic devices is predicated on this concept. A patient can be safely dosed and redosed until the pain is palliated, as long as level of consciousness is monitored. IV opiates reach maximum therapeutic levels and have peak effects or side effects at 6 to 10 minutes. **Therefore, IV pain medications can be safely redosed every 15 minutes until relief is reached if potential adverse effects are monitored.**

DYSPNEA

While identifying the cause of dyspnea and treating the underlying pathology may bring definitive relief, treatment should also be offered to palliate the symptoms. Although opioids have traditionally been withheld due to concerns about respiratory depression, opioids are beneficial in treating the agitation and anxiety provoked by dyspnea.[37] When treating breathlessness/dyspnea in an opioid-naive patient, start with morphine at a dose of 0.05 milligram/kg IV, and monitor for sedation and hypoventilation. This is half of the starting dose of morphine when it is used to treat pain. Use a goal of maintaining a respiratory rate of at least 10 to 12 breaths/min.

NAUSEA AND VOMITING

Understanding the underlying cause of nausea can help identify the class of antiemetic drugs most likely to be therapeutic. Chemotherapy-induced nausea often responds to high doses of serotonin 5-hydroxytryptamine-3 antagonists such as ondansetron. Corticosteroids such as dexamethasone also may improve nausea from chemotherapy. Steroids can also improve symptoms caused by increased intracranial pressure and bowel obstruction from cancer. Dopamine antagonists such as haloperidol or droperidol are used for refractory nausea in the palliative care setting. Metoclopramide is excellent for the symptoms of diabetic gastroparesis or compression of the stomach due to tumor or ascites.

CONSTIPATION

Constipation is a commonly seen side effect in patients on opiates for pain control. Patients prescribed opiates need a concurrent bowel regimen, such as an osmotic agent (i.e., polyethylene glycol) or stimulant laxatives. A digital rectal exam is also important to rule out a suspected fecal impaction. When evaluating a patient for constipation, an abdominal radiograph can help to evaluate the amount of stool and lower the index of suspicion for bowel obstruction.

AGITATION

Patients with terminal illness may become agitated, with or without delirium. The causes of this agitation are multifactorial, including pain, effects of the terminal illness, anxiety, terminal restlessness, breathlessness, and mental anguish. The indicated class of medications varies depending on the situation but includes antipsychotics such as haloperidol, anxiolytics such as midazolam, and opiates such as morphine. There is no evidence that these palliative interventions hasten death.[38]

DISPOSITION AND COORDINATION OF CARE

Although the majority of patients consulted to palliative care services from the ED will be admitted to the hospital, outpatient treatment is always an option, depending on the resources available and the patient's needs.

HOSPICE REFERRALS

Patients who qualify for the hospice benefit should be aware of these outstanding programs of care for the physically declining patient. Inpatient hospice units, where patients can be directly admitted, provide a good option for care and rapid ED disposition if available at your hospital.[39] Not all families are eager to hear the word "hospice," but such a recommendation should be phrased in a way that sends a message about your concern for the patient and his or her health status. Exploring any prior experience a patient or family may have had with hospice care and determining their primary goals and explaining how those goals might align with hospice can be an effective way to introduce a potential transition in care.

Patients are eligible for hospice care by Medicare regulations if they wish to take a palliative approach to their condition and if they have a prognosis that, in the judgment of two physicians, is likely ≤6 months, given the usual and natural course of the illness. Hospice referrals can be made from the ED for patients with qualifying debilitating illnesses, such as dementia with sepsis or stage IV cancer with poor performance status. Referrals also can be made for patients with clearly expressed prior wishes for comfort care should they sustain a catastrophic acute illness, such as those with an intracerebral bleed, infarcted bowel, devastating neurotrauma, or renal failure in the presence of advanced heart failure, leading to multiorgan failure.

SPECIAL TOPICS

IMMINENT DEATH

It is common in the ED to receive a patient whose death is likely imminent. Such a patient has entered the process of multiorgan failure due to a disease such as sepsis, vascular crisis, uremia, or metastatic cancer. Vital signs indicate a patient in extremis; breathing may be irregular with pauses; a Foley catheter finds an empty bladder or only a small amount of concentrated urine. The assessment that a patient's death is imminent should be communicated to family members and the primary care physician. Agreement should be sought to offer comfort measures only. Intermittent or infused opiates plus intermittent or infused midazolam should be initiated and titrated to patient comfort. Delirium therapy can be directed to underlying cause (pain, fever) or, if not known or reversible, treated with 0.5- to 5-milligram doses of IV haloperidol. A total dose of 5 milligrams can produce a calming effect on a patient and, by extension, his or her family. Especially in patients who are having respiratory symptoms, opiates should be considered even though they may induce hypoventilation. Explain to a patient's family that the goal of opiate therapy is not intended to artificially hasten death but to ensure comfort. There is firm ethical support for providing medication expressly with a goal of comfort even if there is potential for an unintentional double effect.[40,41]

OPIOID DOSING AND ROTATION

In the opioid-naive (hydrocodone, oxycodone, morphine, hydromorphone, and methadone) patient, a 2-milligram dose of IV morphine or a 0.5- to 1-milligram dose of hydromorphone is a reasonable starting dose. This should be administered every 15 minutes until the pain is relieved by approximately 50%. Dose stacking will produce additional, cumulative effects when the doses have all been distributed to the μ-receptors. In the opioid-tolerant patient, the average 4-hourly dose of opioids already prescribed should be doubled for severe pain and increased by 50% for moderate pain (pain scale score of 4 to 6).[41] Smaller doses are required in elderly patients, those with a low body mass index, patients with unstable vital signs, or those with baseline severe cardiorespiratory compromise (e.g., chronic obstructive pulmonary disease) because such patients are at risk for hypoventilation.

CARE OF THE PREVIOUSLY DESIGNATED HOSPICE PATIENT IN THE ED

Occasionally, hospice patients may be directed to the ED. The three most common scenarios are (1) a hospice patient with an acute symptom crisis; (2) a hospice patient who has a health concern unrelated to the hospice diagnosis; or (3) a patient who has previously revoked and signed out of hospice and presents to the ED.

A patient enrolled in hospice may be hospitalized under the care of hospice (general inpatient hospice) if there is an acute symptom crisis related to the hospice diagnosis. An inpatient setting can allow for more aggressive treatment of symptoms such as a pain crisis, new-onset dyspnea, or other concerning symptoms. A patient may also be sent to the ED for a new medical issue unrelated to the hospice diagnosis. For example, a patient admitted to hospice for refractory heart failure may fall and fracture a bone. The fracture is unrelated to the hospice issue.

A patient may revoke hospice care at any time for any reason and may present to the ED for aggressive treatment rather than a palliative approach. Occasionally, a patient or family may panic and call 911 when there is a change in the patient's health status. The ED physician should care for the patient as appropriate. It can be very helpful to contact the patient's hospice agency. Someone should be available 24 hours a day and may be very useful in helping to clarify the patient's goals and disposition.

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The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 301

Death Notification and Advance Directives

Lindsay M. Weaver
Cherri D. Hobgood

DEATH NOTIFICATION

Death notification is perhaps the most difficult, emotionally laden physician communication. In most situations, the notification of death occurs during the first meeting of the emergency physician with the deceased patient's family. The notification often comes after extensive resuscitation efforts, creating an upheaval of emotion for the physician and ED staff and leaving the team emotionally and physically exhausted.[1,2]

For survivors, death notification is a life-altering event. The language used during the communication, the venue, and the characteristics of the individual delivering the news create indelible memories for the family.[3]

EFFECTS ON SURVIVORS

Because death that occurs in the ED is frequently sudden, unexpected, and often violent, survivors can develop complicated bereavement and/or posttraumatic stress disorder.[4-7] Death notifications that provide limited or incorrect information about the death or occur in chaotic settings with limited support may exacerbate the grief reaction.[6] When properly performed, death notifications may mitigate substantial negative effects on surviving family members.[8] A well-delivered death notification can reduce the incidence of posttraumatic stress disorder in the families of patients who died suddenly, particularly notifications involving the loss of a spouse or the death of a child.[9]

WHAT REACTIONS TO EXPECT

Responses to loss vary greatly. Families often describe themselves as numb immediately after learning of the loss. They have difficulty processing information and making decisions. Following the initial shock, the family may experience denial, anger, and/or guilt.[10] Denial is most typically expressed as incredulity and is thought to be a defensive mechanism. Your role is to understand this condition and allow time and, if needed, to provide additional information to confirm death. Seeing the body of the deceased may help the family to accept the truth. Anger is not unusual. Be prepared to react in a supportive manner rather than responding with anger or becoming defensive. These are typically expressions of grief and misplaced guilt.

The survivors' culture is an important predictor of the types of emotional responses that may be exhibited. These may range from no expression of emotion to wailing and hysterical collapse. Allow these expressions and remain calm and respectful. If you want to touch the grieving individual, the shoulder is the most suitable location.

EFFECTS ON PHYSICIANS

Physicians find death notification physically and emotionally difficult, with evidence of increased heart rate, heart rate variability, and cortisol levels immediately after the event.[11-14] Common emotional reactions in emergency physicians faced with the task of death notification are sadness (60%) and disappointment (38%), resulting in insomnia in 37%.[14] The cause of death, the patient's age, the presence of family, and the similarity to self are the most common reasons cited by emergency physicians for powerful impact of a recent death notification experience.[14,15] Other factors that may also increase the stress level for the physician include racial and ethnic differences between the physician and the family, lack of a clear family leader, a nontraditional family (e.g., broken or blended), and situations in which the physician is personally emotional or cannot control his or her own reaction.[16]

Skillful death notification is a priority in emergency medicine practice.[2,3] Protocols to enhance communication skills for delivering bad news in the ED improve satisfaction of survivors.[17] The use of successful methods to communicate effectively with families may also mitigate physician burnout and reduce stress on ED staff.[18] Understanding and using compassionate methods of information exchange are critical to success. Providers must learn to recognize emotions, even when they are indirectly expressed, and allow these to be aired and displayed without judgment.[19]

GRIEV_ING©: A METHOD FOR DELIVERY OF DEATH NOTIFICATION

The **GRIEV_ING©** mnemonic is a method for delivering concise and accurate death notification. This mnemonic provides physicians with an organized, sequenced approach to deliver the news of death (**Table 301-1**).[20] The structured organization of communication elements provides a coherent sequence of information to the family that is easy for providers to remember and ensures complete information transfer to the family. (See Video: Grieving: Announcing a Death in the Emergency Department.)

TABLE 301-1	The GRIEV_ING Mnemonic	
G	Gather	Assemble the family in a calm, considerate place for the discussion. Gather as many family members as time allows. This mitigates the need for multiple episodes of information delivery. This step may be done by ED support staff.
R	Resources	Ask for any additional support available to aid the family (e.g., hospital chaplain services, family ministers, additional family and friends [especially if the survivor is alone], and, if needed, an interpreter).
I	Identify	Upon entering the room with the family: Identify yourself. Identify the deceased patient by name. Identify the family's state of knowledge. Are they aware of the situation, or will news of the death be unexpected?
E	Educate	In a concise manner, educate the family about the events that have transpired since the patient entered care. EMS should be included in this description. Fire a "warning shot" by stating that you bring "very bad news." Tell them the current state of their loved one.
V	Verify	Confirm the news of death. State emphatically that their family member is dead. *Be clear!* Use the words dead or died. Express your sincere condolences.
_	Space	Stop talking. Allow the news to settle and give them time to process the information.
I	Inquire	After a brief interval, ask if they have any questions. Then take the time to answer all of them.
N	Nuts and bolts	Provide additional information on: Organ donation Funeral service that will collect the body The deceased's personal belongings Be sure to offer the family the opportunity to view the body.
G	Give	Give the family your card and contact information. Offer to answer any questions that they may have later. Return their call if contacted. Express condolences.

Modified with permission from Hobgood C, Harward D, Newton K, Davis W: The educational intervention "GRIEV_ING" improves the death notification skills of residents. *Acad Emerg Med* 12: 296, 2005. Copyright John Wiley & Sons.

G (GATHER)

As early as possible during the resuscitation, instruct ED staff, nursing, social work, or chaplain services to "gather" the family. Place the group in a quiet, private environment with few distractions. Assist the family with outreach to other family members or friends. **Gathering** allows the physician to deliver the information a single time, ensuring that everyone hears the same information. This also allows the family to support each other during this most difficult time.

R (RESOURCES)

Ask if there are any needs, and work to collect any needed items. Ask about desires for a chaplain, minister, or priest who may provide support for the family. Obtain interpreter services if needed.

I (IDENTIFY)

Confirm that the deceased individual is properly identified. As the physician and staff join the family, they must clearly identify themselves and their role in the resuscitation. Clarify and confirm that the family is associated with the deceased individual by saying the patient's full name, for example, *"Are you the family of Ellen Smith?"* Ask the family members to state their relation to the patient. Identify the next of kin. All discussion moving forward is between you and the next of kin. Face that person directly and ask permission to discuss the events of the day in the presence of the extended family and those gathered in the room.

Ask for a brief statement of the state of knowledge of the family regarding the patient's status. This final step is important because it allows you to begin your story at the point their knowledge ends. Depending on the prior state of knowledge, the family will process information differently and at different rates.

If possible, before you begin your discussion, ask the family to take a seat. You and your team should sit as well. Having the family sit reduces the risk of falling and sustaining injury during the notification. Position yourself across from the next of kin, preferably at eye level, and address the majority of the dialogue to that person. This posture creates open communication and allows you to assess understanding as you deliver the information.

E (EDUCATE)

From this point forward, your role is to educate. Your description of the event should begin at the conclusion of the family's knowledge of events. The narrative should be a focused summary of the scene, including any EMS response and the events in the ED. Communicate with nontechnical, nonmedical words; be thoughtful with your language and listen and watch for incomprehension. **Throughout your summary, on multiple occasions, provide the family with "warning shots," such as "this is difficult news" or "the information that I am relating is bad news."** These "warning shots" are a communication strategy intended to adjust the family toward the idea that they are about to learn something difficult and portend the disclosure of death. Carefully observe the family's reactions and those of the next of kin. If it appears that they do not understand the severity of events, reemphasize the finality of the news. Once the family appears to be following your story with clarity, then you must disclose the death.

V (VERIFY)

Continuing your dialogue seamlessly, you will "verify" the death. You should unequivocally state that their family member has died. You must decisively affirm this fact clearly and say the words *death*, *died*, or *dead*. Provide your condolences on their loss. This may include language such as, "I am sorry for your loss" or "I can see how difficult it is for you to learn of the death of your [mother, brother, sister, friend, etc.]." Without knowing the religious convictions of the patient and everyone present, it is inappropriate to say "they are in a better place" or that the events "were God's will."

_(SPACE)

Now **stop talking.** Give the family some room to comprehend what you have just said. Even families who were anticipating the death will need a moment to register the information and compose themselves. Once you have allowed an adequate period of time to pass, you may move into the last three steps of notification.

I (INQUIRE)

The next phase, "inquire," is a very natural progression of the dialogue. Ask the family, "Are there any questions for me?" or "How can I help you?" In most cases, if the preceding steps have gone well and there has been complete information transfer, then there will be no major questions. The family may ask if there was pain or suffering. This is a difficult question to answer. Maintaining your credibility is important, and you can never state with full certainty that the patient did not suffer. If you did everything possible to mitigate pain and suffering while the patient was in the ED, you can reassure the family with this fact.

N (NUTS AND BOLTS)

The "nuts and bolts" are the necessary practical things that require attention. The physician has several key tasks at this stage. Inform the family

that they will need to complete documents before they leave the hospital. You should also ask the family's wishes regarding autopsy. You should also offer the family the chance to view the body after it is appropriately prepped. This preparation includes removal of blood and secretions, closing the eyes, and covering the body except for the hands and face. It is fine to remove tubes and catheters as long as it is not a medical examiner's case. If the patient is disfigured, cover the wound as best as possible with towels or bandages. You should warn the family that there is trauma or if tubes must be left in place and that these sights may result in a lasting memory of their loved one. In all situations, it is best to have the family members seated.

G (GIVE)

The concluding step in the notification process is "give." During this period, you give the family your name and, if possible, your business card. Inform them that, if they call, you may not be immediately available but that you will contact them after you receive the message. If they reach out to you, be sure to return the call. Typically, calls are made to provide additional clarity or to express thanks. Express your condolences and then close the encounter.

SPECIAL SITUATIONS

LONG-DISTANCE NOTIFICATION

Occasionally, death notification must be made to survivors over the telephone. The GRIEV_ING protocol steps are still appropriate. Ask the survivor to "gather" other family members to join on the phone. If the survivor is alone, ask the survivor to get "resources," such as friends, relatives, or personal clergy, and call you back. At that time, proceed with the rest of the steps of in-person notification. After notification, the survivors may wish to come to the hospital to attend to the "nuts and bolts." Recommend that they do not drive alone and assure them someone will be available to answer all of their questions.

AUTOPSY AND MEDICAL EXAMINER CASES

The Joint Commission requires that physicians ask families if an autopsy is desired. Autopsies are voluntary and serve to clarify premortem diagnoses or aid in the diagnosis of new diseases. Autopsies do not prevent an open-casket funeral. If there are religious concerns, a chaplain can help. Local and institutional policies regarding autopsy billing and payment vary; however, if the family will be charged for the autopsy, they should be informed.

Depending on state laws, certain deaths must be referred to the medical examiner or coroner for investigation and/or autopsy. Medical examiners may choose to investigate deaths due to trauma, homicide, suicide, or medical procedures; death from a disease that is a public threat; death of a person in custody or incarcerated; pediatric and sudden infant death syndrome deaths; and deaths that are unexpected and unexplained. An autopsy may or may not be performed in these cases, but the family is not allowed to refuse investigation or autopsy by the medical examiner if that is necessary. Families are still permitted to view the body, but they are discouraged from removing mementos or disturbing the body until after the medical examiner investigation. **Do not remove resuscitative lines and tubes in a medical examiner case.** Designation of the death as a medical examiner case does not prevent organ donation, but the consent of the medical examiner is required before organ procurement.

ORGAN DONATION

Currently >110,000 patients are on the national transplant list.[21] The Joint Commission requires physicians to contact an organ-procuring agency for all deaths in the ED. The role of the ED physician is to notify the family of the grave prognosis or death of the patient and remain supportive and available to the family.

Traditionally, the family consent process has been the largest single obstacle to obtaining organ donation. The best predictor of consent is the family's initial reaction to the request for donation. Currently, all 50 U.S. states have first-person consent and registry laws associated with the Department of Motor Vehicles.[22] These laws increase families' satisfaction and likelihood of consent for organ donation.[23] Trained organ procurement specialists should manage conflicts with the family disagreeing with the deceased's stated wishes. They are trained in this type of conflict resolution and are aware of each state's laws. Physicians can provide information while allowing the coordinator to initiate and lead the conversation about organ donation.

WITNESSED RESUSCITATION

Emergency physicians should consider developing programs to educate staff and develop procedures to routinely invite family members to observe resuscitation in the ED.[24-26] Family-witnessed resuscitation gives family members closure and comprehension of the patient's situation and grave condition.[24] Emergency medicine providers may be concerned about the family interfering with resuscitation efforts, patient confidentiality, increased litigation, distraction from resuscitation efforts, wrongly prolonging the code, and increased stress for the family and staff members.[24] However, many of these concerns have been found to be unwarranted. In one study, family members who witnessed CPR had fewer symptoms of posttraumatic stress disorder and less complicated grief 1 year after the death.[27] However, family members should be screened for appropriateness to attend the resuscitation and escorted out if safety becomes a concern.[28] A staff member should prepare the family members for what they may see during the resuscitation and then remain with them to offer support, answer questions, and explain procedures.[24]

PEDIATRIC DEATH

Recognizing that the death of a child in the ED is uniquely different from other ED deaths, the American College of Emergency Physicians and the American Academy of Pediatrics addressed challenges by developing a set of principles.[28] They recommend ED physicians provide "personal, compassionate, and individualized" support through a "family-centered and team-oriented approach."[28] The family-centered approach begins with allowing the family to be with the child during the resuscitation. After the child's death, the family should be encouraged to stay with the child. The healthcare team should respect families' "social, religious, and cultural diversity."[28] Many pediatric deaths are medical examiner cases. Therefore, tubes and lines may need to be kept in place, which may affect what the family can do. The team-oriented approach provides appropriate resources, including organizations and individuals that may assist families, and a coordinated response to the child's death.[28] In more than one third of pediatric deaths, an autopsy provides information of undiagnosed findings and complications.[28] The ED physician should notify the child's pediatrician concerning the circumstances of the child's death so that the pediatrician can follow up with the child's family and siblings.[29]

ADVANCE HEALTHCARE DIRECTIVES, PHYSICIAN ORDERS FOR LIFE-SUSTAINING TREATMENT, AND WITHDRAWAL OF LIFE-SUSTAINING TREATMENT

Advance healthcare directives (AHD) are legal documents that assist in communicating to healthcare providers a patient's healthcare preferences when a patient is incapacitated and cannot speak for him- or herself.[30] There are many forms of AHDs, including, but not limited to, out-of-hospital do not resuscitate (DNR) orders, living wills, designation of a healthcare durable power of attorney or healthcare representative, and the Physician Order for Life-Sustaining Treatment (POLST) form. Unfortunately, only 29% to 33% of American adults have an AHD.[31,32] The traditional DNR form facilitates the patient's or healthcare proxy's refusal of CPR should the patient sustain a cardiac or respiratory arrest. However, DNR forms generally do not outline

TABLE 301-2 PREDICT Score

PREDICT Feature Points*	
Referral to palliative care team for a noncancer diagnosis	12
Current residence in nursing home	3
Department of intensive care unit admission with multiorgan failure	10
Current diagnosis of cancer	10
Two or more medical admissions in the past year	3
Age at ED visit 55–65 y	1
Age at ED visit 66–75 y	2
Age at ED visit ≥76 y	3

*Score of >13 predicts mortality at 1 year with 95% specificity.

the patient's treatment wishes for a life-threatening condition.[31] The inadequacy of DNR forms led to the development of POLST forms, including other states' iterations (e.g., Medical Orders for Life-Sustaining Treatment, Physician Orders for Scope of Treatment). The POLST form is meant to translate a patient's end-of-life wishes into actionable physician orders. Forms may include directives concerning the patient's code status; desire for further medical interventions including hospital transport, intubation, IV fluids, and comfort measures; desire for antibiotics; and desire for artificial nutrition. Forms are transportable (authority transferred from the patient's living situation to the ED) and may be brought into the ED from extended-care facilities, from patients' homes, and with EMS.[33] These directives should be honored in the ED. It is important to become aware of what form of the POLST is available in the state in which you work as well as the rules and regulations regarding who may complete the form and how it may be used.

AHDs can assist emergency medicine providers with facilitating discussion about goals of care. However, physicians may wonder when it is appropriate to begin these discussions in the acute setting of the ED. Clinical prediction tools, such as PREDICT, can assist providers in recognizing patients who would benefit from advance care planning and or a palliative care consult.[34] PREDICT assesses a patient's risk of mortality at 1 year with a reported 95.3% specificity for a cutoff score >13[34] (**Table 301-2**). Recognizing the likelihood of someone having <1 year to live can assist providers in knowing when it may be appropriate to discuss AHDs such as the POLST form, initiate goals of care discussion, and consult palliative medicine.

WITHDRAWAL OF LIFE-SUSTAINING TREATMENT

At times, it is appropriate to move from aggressive life-sustaining treatment to comfort measures for patients who are facing imminent death in the ED. This conversation may be initiated by the physician, the patient, the healthcare proxy when patients cannot speak for themselves, and/or by available AHDs such as the POLST form. The patient and/or healthcare proxy should agree that continued aggressive therapies are futile and discuss possible symptoms and outcomes. The physician should explain that medicine would be given to treat symptoms and alleviate suffering. Family should be made aware that patients might display restlessness, dyspnea, or air hunger. Encourage the family to stay and care for the patient and to notify a nurse or physician for concerning symptoms.

When possible, move the patient to a room that is quiet, private, and secluded from high-traffic areas; has low lighting; and is of sufficient size to accommodate chairs for the family. Offer to call the chaplain. Turn off or silence all alarms in the room, and remove any unnecessary equipment from the patient, such as cardiac leads, blood pressure cuffs, cardiac pads, and oxygen saturation monitors. Comfort treatment is further discussed in Chapter 300, "Palliative Care."

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 302

Military Medicine

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INTRODUCTION

The principles of military medical care are applicable to care in civilian mass casualties, in remote settings, for tactical medicine, and in bioterrorism incidents.

Advanced trauma life support approaches are well applied in a hospital setting, but in combat, how do you function without ancillary staff? What do you do without ready access to a surgical team? How will you manage in the dirt, at night, while engaged with enemy forces? Chapter 7, "Bomb, Blast, and Crush Injuries," Chapter 8, "Chemical Disasters," and Chapter 9, "Bioterrorism," discuss many conditions relevant to the combat situation. **Table 302-1** lists the roles of medical care for combat casualties.

EQUIPMENT

Combat casualty treatment requires a properly supplied aid bag. Mission analysis, phases of care, and potential worst-case scenarios guide needed equipment. Pack the aid bag with attention to weight and volume; overpacking creates challenges locating supplies. Supplies with multiple purposes reduce weight and volume. Bundling simplifies tasks (i.e., bundle hemostatic dressings with other wound packing material and compression bandages).

Tables 302-2 and **302-3** provide example packing lists. Building multiple, mission-specific bags or packaging extra bundled items assists with modification of bags and resupply. Every soldier is outfitted with an individual first aid kit (**Table 302-4**). Train on your personal equipment, maintain it, and pack smartly to ensure easy access to critical items.

TACTICAL COMBAT CASUALTY CARE

Tactical combat casualty care (TCCC) is a standardized, prehospital combat trauma guideline designed to address preventable causes of death. TCCC has three phases of care: care under fire, tactical field care, and tactical casualty evacuation.

PHASE 1: CARE UNDER FIRE

The medical actions taken under enemy fire are extremely limited: apply tourniquet for massive exsanguination, protect the casualty, and move him or her to safety. The urge to tend to a casualty must be tempered

TABLE 302-1 Military Roles of Medical Care

- Role 1: self/buddy aid, nonmedical unit–level combat lifesaver, medic or corpsman aid up to battalion aid station; special operations forces medical elements (SOFME)
- Role 2: brigade or division level, medical companies/battalions, support battalions, forward surgical teams, PRBCs, limited x-ray and lab capability, damage control care for evacuation to next role
- Role 3: corps level, combat support hospitals, in-theater military treatment facility (MTF), comprehensive stabilizing care for evacuation out of theater
- Role 4: definitive care, ultimate treatment capability, full rehabilitative care, tertiary care MTF, typically located in continental United States or comparable out-of-theater safe havens

Abbreviation: PRBCs = packed red blood cells.

TABLE 302-2 Trauma Aid Bag Suggested Packing List

Tourniquets	**Optional Advanced Airway List**
Hemostatic gauze	Oropharyngeal airway
Gauze or packed gauze	Laryngoscope with blade
Trauma dressing(s) 4 or 6 inch	Endotracheal tube
Cricothyroidotomy kit*	Stylet and/or gum elastic bougie
Nasopharyngeal airway(s) with lubricant	Syringe 10 mL or 10-mL saline flush
Supraglottic airway	Endotracheal tube–securing device or tape
Suction device	Colorimetric carbon dioxide detection device or esophageal detection device
14- or 10-gauge, 3.5-inch decompression needle(s)	Digital capnography monitor
Chest seal(s)	**Optional Items – Mission Dependent†**
Bag-valve mask	Minor wound kit (suture, needle driver, etc.)
Finger pulse oximetry	Chest tube kit
IV starter kit(s) with saline lock	Thermometer
Intraosseous device (peripheral and/or sternal)	Traction splint
Sodium chloride flush(es) (10 or 5 mL)	Cervical collar, adjustable
IV administration tubing (10 gtt)	Otoscope/ophthalmoscope
IV fluid for blood administration priming and carrier fluid	IV fluids (i.e., volume replacement for burns, dehydration)
Pressure infuser device	Red/green/blue/yellow glow sticks for marking and mass casualty events
Sharps container	Litter
Abdominal dressing	Blood pressure cuff with stethoscope (may not be useful in noisy environments)
Junctional hemorrhage device (consider one that also works as pelvic splint)	Electronic monitors (minimum with noninvasive blood pressure and pulse oximetry)
Cravat or elastic bandage(s)	Ventilator
Splint(s), malleable	**Basic Medication List**
Tape, silk 2 inches	Hard plastic case
Exam gloves	Combat wound medication pack (acetaminophen, meloxicam, moxifloxacin)
Trauma shears	Syringes (1, 3, and 10 mL)
Casualty cards	18-gauge filter and 21-gauge needles
Permanent marker	Alcohol pads
Hypothermia management	Tranexamic acid
Scalpel #10 blade	Ketamine
Large skin stapler	Fentanyl oral transmucosal lozenge
Chlorhexidine and/or betadine swab(s)	Narcotic analgesia (hydromorphone, morphine, or fentanyl)
Eye shield(s)	Midazolam
Headlamp with colored filter	Naloxone
Sick call items	Ondansetron orally disintegrating tablet/IV
Blood Transfusion	Lidocaine 1%
Blood cooler/transport container	Ertapenem
Blood tubing with filter	Epinephrine (vial or autoinjector)
Blood product(s)	Benadryl
Normal saline	Tetracaine, ophthalmic

*"Kits" are packaged together as a functional unit in a resealable plastic bag or vacuum sealed with quick-open tabs.

†Optional items may need to be in additional bags and located on evacuation platforms or secured locations.

by situational awareness: return fire, and secure the site before tending to casualties.

TOURNIQUET APPLICATION

A tourniquet is the first-line intervention for massive hemorrhage in a combat setting. If applied before the onset of shock, survival is improved from 17% to 94%.[1,2] A wide tourniquet (at least 1.5 inches wide) causes less soft tissue damage and is more comfortable for the patient. To control hemorrhage from a large vessel, a tourniquet must have a windlass to gain a mechanical advantage when tightening. Tourniquets without a windlass cannot attain sufficient force to stop arterial bleeding. In combat, we use a tourniquet that can be applied with one hand for self-treatment.[3]

Place the tourniquet about 2 inches proximal to the wound.[4] Tighten to greater than arterial pressure, because tightening that exceeds venous but not arterial pressure may increase bleeding. Apply the tourniquet until the distal pulse disappears. If no distal pulse is present on initial evaluation, apply the tourniquet with a force estimated to be greater than the systemic blood pressure. If placement of a single tourniquet does not control bleeding, place a second tourniquet immediately adjacent and proximal to the first. See "Tourniquets," in Chapter 254, "Trauma in Adults." See Figures 254-1, 254-2, and 254-3 for images and detailed application instructions of TCCC-recommended tourniquets.

TABLE 302-3 Items to Be Carried on Medical Provider

- Light-emitting diode headlamp with colored filter
- Tourniquet(s) (immediately available and reachable by both hands)
- Trauma dressings (4 inch) or elastic bandages
- Hemostatic gauze
- Gauze
- Cricothyroidotomy kit
- Nasopharyngeal airway(s) with lubricant
- 14- or 10-gauage, 3.5-inch decompression needle(s)
- Chest seal(s)
- Finger pulse oximeter
- Combat pill pack(s)
- Analgesic medication (fentanyl oral transmucosal lozenge preferred)
- Trauma shears or rescue knife
- Examination gloves heavy duty
- Casualty cards
- Permanent marker
- Nine-line medical evacuation card

POSTTOURNIQUET CARE

The safe time limit for tourniquet application has not been determined. Tourniquets are routinely left in place for up to 2 hours in the operating room, and this is the basis for the recommendation to remove a tourniquet within 2 hours, situation permitting.[5] At 6 hours with a tourniquet in place, it is probably best not to remove it; at this point, the release of potassium, lactate, myoglobin, and other toxins from a severely acidotic limb into the circulation would likely cause more systemic harm than benefit. There are, however, several cases of limb salvage with tourniquet times greater than 6 hours.[6]

TABLE 302-4 Individual First Aid Kit Packing List

- Tourniquet (reachable by both hands)
- Trauma dressing
- Hemostatic gauze
- Gauze
- Nasopharyngeal airway with lubricant
- 14- or 10-gauge, 3.5-inch decompression needle
- Chest seal
- Trauma shears or rescue knife
- Examination gloves, heavy duty
- Combat wound medication pack
- Casualty card
- Permanent marker

A tourniquet is a temporizing measure. The next step is to convert the tourniquet to an effective pressure dressing, using direct pressure and a basic gauze roll and elastic wraps and/or hemostatic agents, if required. A knee or hand can apply additional pressure to the bleeding site or proximal pressure point. Once an effective pressure dressing is applied, release but **DO NOT REMOVE** the tourniquet. If bleeding recurs, retighten the tourniquet to control bleeding.

PHASE 2: TACTICAL FIELD CARE—THE PRIMARY SURVEY

This phase begins once the patient and provider are no longer under effective enemy fire. Tactical security, similar to "scene safe" in civilian EMS training, must be maintained at all times.[7] Conduct a complete primary survey and perform lifesaving interventions.

Combat medicine deviates from the universally accepted *a*irway, *b*reathing, and *c*irculation algorithm. Massive hemorrhage is the most common correctable cause of death on the battlefield and is the top clinical priority in battlefield trauma care.[7] Airway compromise accounts for relatively few combat deaths, and respiratory difficulties typically progress over time. This is the reason that TCCC recommends the modified primary survey algorithm of **MARCH**:

Massive hemorrhage

Airway

Respiratory

Circulation

Hypothermia prevention/**h**ead injury

After hemorrhage control, the algorithm mirrors the airway, breathing, and circulation algorithm, with the additional consideration of a closed head injury and hypothermia prevention as primary survey responsibilities. Level of consciousness and pulse strength are used as indicators of peripheral perfusion in injured soldiers. If the soldier's peripheral pulse is weak or absent, if the level of consciousness is altered, or if the solder is not verbally responsive, then immediate intervention is needed before moving down the algorithm.

MASSIVE HEMORRHAGE

Topical Hemostatic Agents If the wound is not amenable to tourniquet use and a pressure dressing is inadequate, use a hemostatic agent. The TCCC Committee recommends the following agents: Combat Gauze® (zeolite impregnated gauze), Celox Gauze® and ChitoGauze® (both chitosan-impregnated gauze), and XSTAT® (chitosan-impregnated sponge).[8]

To apply any of these gauze-like hemostatic agents, prepare the wound by evacuating excess blood, taking care to preserve any clot that may have formed around the damaged vasculature; pack the hemostatic gauze/sponge directly over the site of the most active bleeding; repack or adjust the gauze for optimum placement; and use additional hemostatic agent as required. With the exception of XSTAT®, hold direct pressure for a minimum of 3 minutes, then reassess for bleeding and repack as needed. Secure the hemostatic agent in place with a pressure dressing. Do not remove XSTAT® in the field. If bleeding continues, pack directly over it.

Junctional Hemorrhage Junctional hemorrhage (from the "junctional" anatomic area between the limbs and intracavitary areas of the abdomen or thorax) is difficult to control. Hemorrhage in the axilla and groin is not amenable to tourniquet application and hemostatic agents.[9] Specialized junctional tourniquets may be beneficial in certain cases. Presently, these include the Abdominal Aortic Tourniquet,[10] the Combat Ready Clamp®,[11] the Junctional Emergency Tourniquet Tool,[12] and the SAM Junctional Tourniquet®.[13] Each product has specific directions for application.

A potential tool in the management of abdominal and junctional hemorrhage that fails to respond to other measures is resuscitative endovascular balloon occlusion of the aorta (REBOA). See Chapter 254 for a discussion of REBOA. REBOA has been performed successfully in combat >20 times by U.S. Air Force surgical teams,[14] but is currently not considered a first-line treatment for out-of-hospital junctional hemorrhage.[15] The use of prehospital REBOA is still largely unexplored and thus requires extensively careful selection before implementation.[16]

Systemic Hemorrhage Control: Tranexamic Acid Tranexamic acid decreases mortality in trauma.[17] It is recommended for use in all casualties that require significant fluid or blood products, both children and adults. Tranexamic acid is most effective when given within 1 hour of injury and must be given within the first 3 hours. The dose is 1 gram of tranexamic acid in 100 mL of normal saline, infused over 10 min.[18]

AIRWAY

Airway intervention during the primary survey is similar for both combat and civilian casualties. Less than 1% of combat trauma requires lifesaving airway intervention in the prehospital setting.[19,20]

If there are no spontaneous respirations after opening the airway, the casualty is triaged to the expectant category (expected to die) in a mass casualty (MASCAL) situation (defined as more casualties than resources available); if the situation and resources allow, perform advanced airway techniques including cricothyrotomy,[21] supraglottic airway intubation,[22] and mechanical ventilation. If space is limited, cricothyrotomy equipment is the most important. In austere conditions with minimal sedatives and analgesics, prolonged evacuation times spanning hours to days, and delayed medical logistical resupply, the threshold for performing a cricothyrotomy should be low. It is critical to confirm placement and firmly secure the airway.

RESPIRATORY/BREATHING

Tension Pneumothorax The nearly universal use of body armor in present combat operations provides critical protection to the chest and upper abdomen, as evident in the 5% to 7% thoracic wound rate, the lowest in U.S. military conflicts.[23]

In a tactical setting, the threshold to perform a needle decompression is very low, as most casualties with penetrating chest trauma in respiratory distress will have some degree of hemo- or pneumothorax and possible tension pneumothorax. Use the largest and longest catheters available. The TCCC minimum standard is the 14-gauge, 3-inch-long needle.[24] However, there are 10- and 12-gauge catheters available in 3-inch lengths that are highly recommended over the standard because they are less likely to kink when penetrating a muscular chest or occlude with patient movement. Two locations are recommended: (1) the second intercostal space, midclavicular line; or (2) the anterior axillary line at the fourth to fifth intercostal space (see Chapter 68, "Pneumothorax," for further discussion).[25]

Penetrating Chest Trauma Penetrating chest trauma with open pneumothorax or sucking chest wounds is common with large injuries to the chest wall. The updated TCCC standard is to use a valved/vented chest seal as the first choice. Unvented chest seals require continuous reassessment for possible accumulating tension pneumothorax and need for needle decompression.[26] Most casualties encountered in a combat setting are bloody and sweaty; applying a chest dressing that actually adheres to the chest requires skill and proper preparation of the skin. Wipe the skin as dry as possible. Consider using tincture of benzoin or Mastisol® to facilitate dressing adherence if it is available and you have the luxury of time.

Chest Tubes The lifesaving intervention for a chest injury in the setting of tactical field care is needle decompression; a chest tube is not immediately required. Needle decompression can be as effective as a chest tube in a patient for up to 4 hours if the patient is not subjected to much movement.[27] Needle decompression can be repeated as needed.

CIRCULATION

The TCCC mainstays of circulation management are the appropriate use of low-volume resuscitation (also known as **permissive hypotension** or **hypotensive resuscitation**) and the preferred resuscitation fluids. The first step is vascular access.

IV Access Vascular access is the lifeline for severe combat casualties. Smaller-bore IVs (primarily 18-gauge catheters) are preferred in a

tactical environment to provide fluid resuscitation. If blood products are available, which is atypical at this phase of field care, then a larger-gauge catheter is indicated.

It is critical to firmly secure the catheter in the combat setting. Use a clear adhesive bandage first; then wrap enough tape to ensure that the catheter will hold in place if you were to throw the IV bag. There are also commercially available IV catheters with Velcro® wraps that work very well.

IO Access An IO line is the alternative to IV access. Nearly universal use of body armor in the modern tactical environment protects the sternum, so this site is ideal for IO access. Provide secure fixation to prevent dislodgement during patient movement. Some devices may require a removal instrument, which you should secure to the patient; without this removal instrument, the IO must be surgically removed at the next level of care.

Permissive Hypotension/Low-Volume Resuscitation Following the landmark 1994 Ben Taub study documenting increased survival,[28] permissive hypotension is the TCCC standard for managing penetrating wounds of the abdomen, thorax, junctional areas where specific tourniquets have failed, or any **noncompressible hemorrhage**. The goal is to preserve survival of casualties by maintaining a delicate balance between a blood pressure high enough to provide adequate tissue perfusion but low enough to avoid clot "blow-out" and clotting factor dilution. **Current recommendations are to maintain a mean arterial pressure of 60 mm Hg or a systolic blood pressure of approximately 80 to 90 mm Hg.**[29,30] A blood pressure of 80 to 90 mm Hg is clinically noted by a normal level of consciousness and a weakly palpable radial pulse.[31] The exception is the multiple trauma casualty with head injury; maintain a systolic blood pressure between 90 and 95 mm Hg to preserve cerebral blood flow.[32,33]

Resuscitation Fluid The prehospital resuscitation fluid of choice for combat trauma has changed over the past 10 years of U.S. military conflict. The goals of the TCCC Committee in recommending the appropriate resuscitation fluid are the following:

1. Enhance the body's ability to form clots with platelets, plasma, and red blood cells at sites of active bleeding.
2. Minimize adverse effects (edema and dilution of clotting factors) resulting from iatrogenic resuscitation injury.
3. Restore adequate intravascular volume and organ perfusion prior to definitive surgical hemorrhage control.
4. Optimize oxygen-carrying capacity as much as possible.

The current resuscitation fluid recommendations for severe hypovolemic shock are as follows, in order of preference: (1) fresh whole blood; (2) blood components in a 1:1:1 ratio of packed red blood cells (PRBCs):plasma:platelets; (3) blood components in a 1:1 ratio of PRBCs:plasma; (4) plasma (freeze-dried plasma or fresh frozen plasma appropriately reconstituted); (5) PRBCs; (6) Hextend®; and (7) lactated Ringer's or multiple electrolyte injection, type 1.

Whole-Blood and Blood Component Infusions In the combat setting, prehospital blood transfusion is carried out under specifically approved theater protocols by specially trained and certified providers and medics. For example, several special operations units can give European-produced freeze-dried plasma under an approved protocol.

Fresh whole blood is the TCCC primary resuscitation fluid of choice because it has all the required blood components in their natural state and provides a survival advantage to casualties with severe trauma and shock.[34,35] In a battlefield environment, whole blood is often obtained from fellow soldiers known as "walking blood banks" or special operations forces tactical universal donors. During Operation Iraqi Freedom, 13% of blood transfusions used fresh whole blood.[33]

All potential donors should be screened for pathogen risk, although perceived risk is often outweighed by potential benefit; additionally, all recipients and donors have blood samples sent to the Armed Forces Blood Program for retrospective analysis. The collection kits for fresh whole-blood transfusions are readily available through military medical supply channels. Over the past several years of combat, special operations medical teams have employed cold-stored low-titer type O whole blood. This product is collected and produced at military blood-banking facilities and shipped to locations in Iraq and Afghanistan. Cold-stored low-titer type O whole blood typically has a shelf-life of only 24 days, limiting its utility on a large scale compared with standard PRBCs, which typically have a 42-day shelf-life.

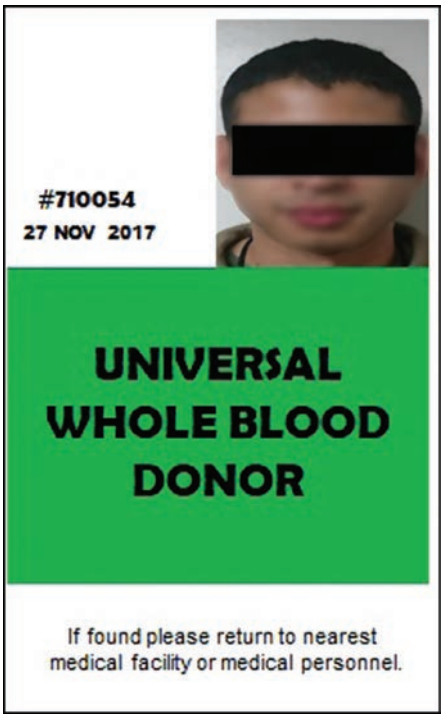

FIGURE 302-1. Universal donor card example, with low-titer O-positive blood.

In response to blood supplies that may not meet the wartime requirements due to collection, transport, storage, and distribution issues, some entire theaters have embraced "walking blood bank" or "tactical donor" programs. In 2018, United States Forces Korea instituted a tactical donor program that prescreens both low-titer type O universal whole blood donor personnel and type-specific donors (**Figures 302-1** and **302-2**).

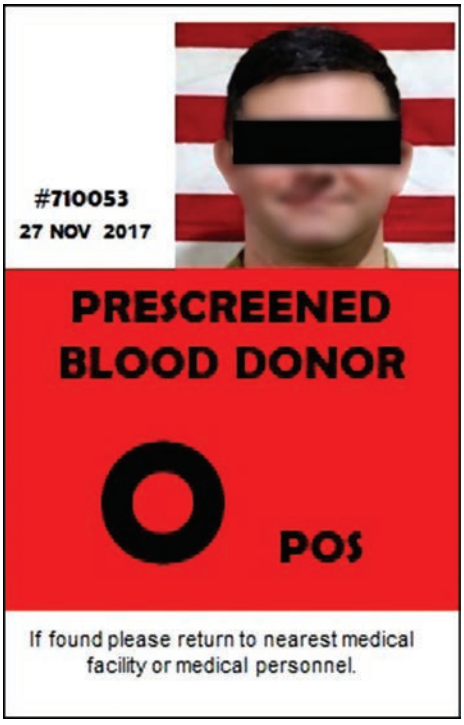

FIGURE 302-2. Type-specific donor card example.

Using operationally secure identification cards, each prescreened individual can act as a blood donor once every 56 days for a full year from the date of testing, dramatically reducing time from injury to resuscitation with fresh warm whole blood, as well as reducing the cost for one unit of reconstituted 1:1:1 therapy from approximately $650 to $150 for the prescreened donor testing and special operations forces blood collection kit combined. Providers can use these individuals within a fixed treatment facility or at the point of injury during combat conditions without specialized blood storage or testing equipment.[36]

If fresh whole blood is not available, the next preferred choice is plasma, PRBCs, and platelets in a 1:1:1 ratio.[37,38] A unit of plasma is given first, followed by the PRBCs, and then platelets. In addition to PRBCs, the military fields frozen red blood cells to augment current supplies of liquid-packed red blood cells, although the thawing process (deglycerization) creates a rate-limiting step during active hostilities.

The next preferred choice is PRBCs and plasma in a 1:1 ratio if platelets are not available.[39,40] Plasma is again given first, followed by PRBCs. Advances in warm platelet storage will hopefully increase the availability of platelets in the near future.

If availability of blood products is limited, you may have to choose between PRBCs and plasma alone. Debate exists as to whether PRBCs or plasma alone is best, so product availability is more likely to drive this decision. Although availability of plasma is somewhat limited, some special operations combat medics can now carry freeze-dried plasma, as well as PRBCs. The freeze-dried plasma concentrate currently carried by U.S. medics is produced in France and available for use by the North Atlantic Treaty Organization.[41] All patients who receive blood or blood products in the field or who the provider expects may require blood products should receive 1 gram of IV tranexamic acid if it can be administered within 3 hours of wounding.[17]

Colloids and Crystalloids If no blood products are available, **Hextend®** (hetastarch, synthetic colloid, in lactated Ringer's solution) is recommended.[42] It is compatible with tranexamic acid.[43] Colloid has a clear advantage from a weight/volume perspective in the prehospital environment, where the medic must carry the fluid on his back. Hetastarch 500 mL provides intravascular volume expansion of 600 to 800 mL. Hextend® is potentially protective against multisystem trauma–induced acute respiratory distress syndrome, induces a favorable acid-base balance, and results in less severe coagulopathy.[44] Indiscriminate colloid use can have coagulopathic and immunologic effects, but these adverse effects typically do not occur with colloid administrations of <1500 mL.[45,46]

If fluid resuscitation requires >1500 mL of colloid, lactated Ringer's solution is given next. Initial use of colloids to replenish intravascular volume during resuscitation must be balanced at some point with an appropriate volume of crystalloid to avoid extensive intracellular dehydration. Start with a 500-mL bolus, and repeat the bolus in 30 minutes if there is no clinical response, using pulse strength and level of consciousness to guide the volume infused. Maintain a systolic blood pressure of 80 to 90 mm Hg, but in head injury, a systolic blood pressure between 90 and 100 mm Hg may be required to ensure sufficient cerebral perfusion pressure.

One liter of infused lactated Ringer's results in only 200 to 250 mL of intravascular volume expansion; normal saline is not recommended for resuscitation due to the hyperchloremic acidosis it produces.[47] Additionally, aggressive resuscitation with saline-based resuscitation strategies is associated with a number of adverse effects, including increased bleeding, acute respiratory distress syndrome, multiorgan failure, acute coronary syndrome, and increased mortality.[48-50]

Other Resuscitation Solutions Hypertonic saline has some benefits in the intensive care setting.[51-53] Hypertonic saline 3% is the first-line adjunct therapy in the Joint Trauma System Neurosurgery and Severe Head Injury Clinical Practice Guidline.[54] Additional options include mannitol or 23.4% saline.[55] When commercial hypertonic saline is not available, providers can add 50 mL of 23.4% saline to 500 mL of 0.9% saline to achieve a 2.98% saline solution to simplify dosing options. Hypertonic saline may be administered through both IV and IO access.

Hemoglobin-based oxygen-carrying solutions are promising, but none are presently approved by the U.S. Food and Drug Administration or available on the commercial market.[56,57]

Oral Hydration In the combat setting, there are often limited IV fluids available and long waiting times for evacuation or surgical intervention. In the patient with a normal level of consciousness, the risk of aspiration is very low and outweighed by the benefit of maintaining adequate hydration and patient comfort if evacuation is delayed. As such, oral fluid hydration is acceptable for combat casualties in many situations, even if surgery is anticipated at the next level of care. The only contraindication is active vomiting or an altered level of consciousness that increases risk of aspiration. Time to surgery is not an issue in oral provision of clear liquids to combat casualties.[58]

HYPOTHERMIA AND HEAD INJURY

Under TCCC, we prevent hypothermia by wrapping the patient in a multilayer insulating wrap with a vapor barrier liner. Closed head injury is one of the final considerations in this modified algorithm. If a casualty has an altered level of consciousness, it is either because of inadequate cerebral perfusion or cerebral injury. If hypovolemic shock has been ruled out or treated and the mechanism is consistent with closed head injury, we treat for head injury. Have the patient recline with the head elevated at 30 degrees. Give oxygen to maintain an oxygen saturation of at least 90%. Maintain a systolic blood pressure of at least 90 mm Hg.[31] Consider adjunct therapy such as hypertonic saline or mannitol and minimize interventions that may cause constriction of venous return in the neck such as cervical collars and endotracheal tube tie systems.

SECONDARY SURVEY

Expose the casualty as much as the tactical situation will allow. Be prepared to preserve body heat to avoid hypothermia. Stabilize fractures and treat less severe wounds. **Continually reassess the casualty.** Attend to the casualties who require intervention, but remember to reassess everyone. This can be as quick as asking a quick question to assess airway, hemodynamic status, and level of consciousness, or quickly palpating a radial pulse to determine rate and strength; obtain blood pressure if possible. The character of the peripheral pulse and the Glasgow Coma Scale are reliable severity indicators.[59] Recheck dressings or bandages for continued bleeding.

PAIN CONTROL

Pain control is crucial for facilitating transport and patient comfort. Under TCCC, there are three primary pharmacologic modes of pain control. For lesser injuries with normal mental status, use a combat wound medication pack.[7] This contains two 500-milligram acetaminophen tablets and a meloxicam tablet. This combination is effective for moderate pain control, does not affect mental status, and is administered orally. Because meloxicam has a favorable side effect profile and no effect on platelet function, it is the TCCC NSAID of choice.[7]

FENTANYL AND KETAMINE

For more severe pain, we recommended either **oral transmucosal fentanyl citrate lozenge**, informally known as the fentanyl "lollipop," or **ketamine**. Oral transmucosal fentanyl citrate provides rapid-onset, long-lasting pain relief for severe pain without the need for an IV. When placed into the buccal fold and slowly sucked on, 25% of the fentanyl is absorbed sublingually, with onset in 15 minutes. The remainder that is swallowed enters the GI tract and loses about 50% of its bioavailability through first-pass effect, but the remaining 50% is slowly absorbed, providing more extended pain relief for the next 4 to 6 hours.[60] An 800-microgram fentanyl lozenge is the recommended starting dose. Rapidly chewing and swallowing the lozenge will decrease the total amount of fentanyl received, because less is absorbed sublingually and more is subject to first-pass effect. To avoid swallowing, the recommended technique is to tape the lozenge to the patient's finger, which will deter swallowing and prevent overdosing should the patient become somnolent (as the lozenge attached to the hand will fall from the mouth). If pain control is not achieved in 15 minutes, a second 800-microgram lozenge can be placed in the other cheek. Fentanyl can also be given intranasally with the use of a nasal atomizer.[61] If an IV is available, then IV fentanyl or IV ketamine can be used and titrated to effect.

Ketamine at subdissociative doses is an effective pain control agent. It can be given IM, IV, IO, or intranasally via nasal atomizer or syringe with rapid onset and good efficacy. The initial dose is 50 milligrams IM or intranasally repeated every 30 minutes and titrated to effect, or 20 milligrams IV/IO by slow push repeated every 20 minutes and titrated to effect. For treatment of associated nausea, the TCCC Committee now recommends **ondansetron** oral dissolving tablets every 6 hours as needed.

ANTIBIOTICS

All war wounds are dirty and contaminated. Early antibiotic use with such wounds may decrease subsequent infection.[62] For those able to tolerate PO administration, a single 400-milligram dose of oral moxifloxacin, found in the combat wound medication pack,[7] is recommended. For casualties with hypotension or an altered level of consciousness, administer ertapenem, 1 gram IV.

SPECIFIC INJURIES

BURN CARE: UNDERSTANDING THE ENVIRONMENT

Resuscitation decisions for burns in an austere environment are influenced by the availability of medical supplies and the time from definitive care. Underresuscitation may result in shock and progression into the lethal triad (hypothermia, acidosis, and coagulopathy). Overresuscitation may result in fluid overload and respiratory collapse with little to no equipment available to handle an airway emergency.

When optimal resources are available, the Joint Trauma System Clinical Practice Guidelines recommend using fluid resuscitation software (Burn Navigator) to determine fluid resuscitation rates.[63] The device makes isotonic fluid rate of administration recommendations based on the patient's urine output to keep the patient's resuscitation in the ideal range. This device is not recommended for electrical burn injuries that have caused rhabdomyolysis.[63]

If fluid resuscitation devices are not available, a simplified rule of 10s is used for burn management, which is clinically effective and easy to implement in a prehospital environment.[64] For burns >20% total body surface area, first estimate the total body surface area burned to the nearest 10%. Then, **for adults weighing 40 to 80 kg, give IV fluid as follows: 10 mL × % total body surface area burn per hour. For every 10 kg of patient weight above 80 kg, add another 100 mL of fluid per hour** (resuscitation for hemorrhagic shock takes precedence over resuscitation for burn shock).

For example, for a 90-kg patient with 40% total body surface area burns, the following would be given: 40% × 10 mL = 400 mL, plus 100 mL for 10 kg above the 40 to 80 kg range, giving a total of 500 mL of IV fluid per hour. Once the patient is at a higher level of care, the fluid rate can be adjusted based on clinical status and urinary output.

BLAST INJURIES

Injuries from explosions are exceedingly common in combat and frequently cause overpressurization injuries. **Tympanic membrane perforations** and hypopharyngeal petechiae are common findings in blast casualties and are easily missed without a thorough exam. After the 2013 Boston Marathon bombings, only 15 of 127 patients evaluated on the day of the bombing (11.8%) were diagnosed with tympanic membrane injuries.[65] More than 100 patients who were hospitalized after the event were prospectively followed, and 90% were found to have sustained tympanic membrane injuries.[66] There are many factors that contribute to a pattern of injury, such as body orientation relative to the blast and confined versus open space, so be wary of relying on a particular clinical finding to triage casualties.[67] If anything, the most reliable sign may be respiratory distress immediately after the blast. Casualties with clinically significant lung injury typically manifest as respiratory failure within minutes of the blast.[67,68] See Chapter 7, "Bomb, Blast, and Crush Injuries," for detailed discussion. All casualties should be screened for traumatic brain injury.

CERVICAL SPINE INJURY

The vast majority of penetrating injuries in the combat setting do not require cervical spine immobilization, unless there is direct injury to the neck with associated neurologic deficit.[69] Cervical spine immobilization for penetrating injury in a combat casualty is not recommended because it will impede the ability to manage the more immediate concerns of a penetrating neck injury. Blunt head trauma should be treated with cervical spine immobilization, situation permitting, as practiced in the civilian sector.[70]

ABDOMINAL TRAUMA

Although body armor does provide some protection to the upper abdomen, the lower abdomen is still relatively vulnerable. There is a groin attachment for the issued body armor that provides some protection to the lower abdomen and groin, but it is composed of flexible Kevlar® to allow freedom of movement, rather than the more durable rigid Kevlar® plate that is used to protect the chest and back. Use of this additional piece of equipment has become more prevalent among combat troops.

With a significant large-vessel (aorta, inferior vena cava, iliac vessels), liver, or splenic injury, there is not much a combat physician can do to save a casualty. In this situation, stabilize the casualty as best as possible, start an IV, administer antibiotics, and transport to a higher level of care with surgical capability immediately. For management of difficult-to-control, noncompressible massive hemorrhage, see the section on massive hemorrhage control and REBOA.

If there is a bowel evisceration, replacing the contents will minimize insensible fluid and heat loss and allow for easier casualty movement. First remove any significant particulate matter or dirt; then attempt to replace the bowel contents intra-abdominally (this might not be possible if there is significant bowel edema and/or a small abdominal defect); cover exposed bowel and the abdominal defect with a moist dressing; cover with plastic wrap or other fluid-impervious dressing to minimize insensible fluid loss; start an IV and administer IV fluids as needed; and administer IV antibiotics in preparation for evacuation.

PELVIC TRAUMA

The standard torso body armor does not provide any protection to the pelvis. The groin attachment protects the genital region and some of the perineum, but the inguinal regions are left largely unprotected. The femoral vessels are vulnerable to penetrating injury, often resulting in life-threatening hemorrhage.

A tourniquet or pressure dressing to a proximal femoral artery or vein injury may be ineffective. For this type of injury, use of a hemostatic agent is imperative. Direct pressure should be applied to gain immediate control of the bleeding. Vessel clamping should only be attempted if an effective tourniquet or pressure dressing cannot be applied, a hemostatic dressing is not available, there is no device to control junctional hemorrhage, and there is no ability for immediate evacuation.

Pelvic fractures can result in significant hemorrhage that is difficult to control. Determination of a pelvic fracture, if not obvious, should be done from symptoms of pain and a clinical suspicion. The practice of "springing" or doing a "pelvic rock" is no longer recommended because this technique is likely more harmful than beneficial.[71] Past recommendations of improvised pelvic splinting with a sheet to produce needed compression for hemorrhage control can be used (if no other more effective options are available), but such splinting is inferior to more recent commercially manufactured pelvic splints and binders.[71]

EXTREMITY AMPUTATION

About 7% of wounded soldiers in Operation Iraqi Freedom and Operation Enduring Freedom had a major extremity amputation, and 50% of soldiers killed in action or who died of wounds had major amputations.[72] Field treatment of an amputation is focused primarily on hemorrhage control and preserving as much tissue as possible. Often the vessels of the limb have retracted proximally from the initial force of the amputation, making it particularly difficult to identify and control hemorrhage. It may appear that hemostasis has been achieved with little effort; however, effective hemorrhage control may be necessary in the form of a hemostatic agent, pressure dressing, or tourniquet

because delayed bleeding often occurs as the damaged vessels relax and dilate shortly after the patient appears stable. Constant reevaluation of the patient is essential. A partial amputation where the limb is still attached by substantial tissue or bone should be treated the same as an open fracture with hemorrhage control, wound debridement and irrigation, antibiotic administration, and splinting in an attempt to salvage the limb.

MASS CASUALTY TRIAGE

Mass casualty, or MASCAL, events are generally defined as medical contingencies in which the number and needs of the casualties exceed available resources (personnel and supplies). MASCAL events are time-constrained, complex operational problems that require the understanding and calculation of multiple risk variables to accomplish the goal of doing the most good for the greatest number of people.[73] In addition to medical considerations, risk variables may include mission objectives, ongoing kinetic activity and threats, availability of casualty evacuation platforms, time and distance to other treatment facilities, environmental conditions, nonmedical manpower, and communications.[74] It is critical to have a rehearsed and validated PACE (Primary, Alternate, Contingency, Emergency) MASCAL response plan.[74] After security considerations, the first step in any MASCAL response will involve the consolidation and triage of casualties.

The triage process is ongoing and dynamic and should occur at and through each level of care. Optimal triage is a key component of managing a MASCAL (**Table 302-5** provides one example of a simple triage algorithm) that requires a system of command and control, the funneling of casualties through a single designated triage point, a triage algorithm, and a designated triage officer. Medical providers familiar with triage algorithms, triage-specific training, and more relevant clinical experience achieve better accuracy in the triage process.[75,76] Multiple triage algorithms exist. Validation of algorithms is difficult, and no standardized criteria exist to assess algorithm efficacy.[76,77] However, evidence suggests that the SALT algorithm (**Figure 302-3**) best balances sensitivity and specificity.[76]

THREE-TIER PRIORITIZATION

SALT stands for sort, assess, lifesaving interventions, and treatment/transport, which are the key activities that must be accomplished during the triage process. SALT begins with a global sorting of casualties, prioritizing them into three tiers for individual assessment. The triage physician directs casualties to walk to a designated area "if they need help." Those who follow the command to walk are the last priority for individual assessment, because they demonstrate an intact airway, breathing, circulation, and mental status and are therefore the least likely to have a life-threatening condition. The remaining casualties should then be asked to wave or be observed for purposeful movement. Those who remain still and do not move, as well as those with obvious life-threatening injuries, such as massive external hemorrhage, are assessed first. Those who wave are individually assessed next, followed by the ones who previously walked to a designated area. Although this initial sorting is not perfect, it is an attempt to organize numerous casualties.

INDIVIDUAL CASUALTY ASSESSMENT

The second step of SALT is to perform individual assessments and apply lifesaving interventions, such as controlling massive external hemorrhage or opening an airway. Lifesaving interventions must meet all of the following criteria: can be provided quickly; can greatly improve a casualty's likelihood of survival; does not require the physician to stay with the casualty; are within the physician's scope of practice; and require only immediately available equipment. After appropriate interventions are performed, casualties are prioritized for treatment and assigned to one of the following triage categories: **immediate, delayed, minimal, and expectant** (includes the dead for the purpose of military triage), known in the military by the acronym **DIME**.

TABLE 302-5 Mass Casualty Triage Algorithm

AIRWAY: *Is the casualty moving air?*
Yes—assess breathing
No—open airway, moving air now?
Yes—assess breathing
No—EXPECTANT
BREATHING: *Respiratory rate >30 breaths/min?*
Yes—IMMEDIATE, address cause
No—assess circulation
CIRCULATION: *Radial pulse weak/absent or heart rate >140 beats/min?*
Yes—IMMEDIATE, address cause
No—assess mental status
MENTAL STATUS: *Responds to simple commands?*
Yes—NOT an IMMEDIATE
No—IMMEDIATE, address cause

Colored triage tags or chemical light markers can mark casualties based on triage category. Colored triage tags typically are red for immediate, yellow for delayed, green for minimal, and black for expectant or deceased. If chemical light sticks are employed, red is typically used for immediate, green/yellow for delayed, and blue for expectant. Avoid using green and yellow chemical lights for different triage categories to mirror the markings on the triage tags, because it may be difficult to distinguish the two colors during night operations.

The **field triage score** is another easy, rapidly applicable method to identify casualties who are more seriously injured and expected to have a higher mortality. The field triage score is based on two variables: character of the radial pulse and the motor component of the Glasgow Coma Scale (GCS-M), namely the ability to follow commands. A weak or absent radial pulse, which correlates with a systolic blood pressure of ≤90 to 100 mm Hg, is assigned a score of 0, whereas normal pulse character (systolic blood pressure >90 to 100 mm Hg) is assigned a score of 1. Similarly, an abnormal GCS-M (<6) is assigned a score of 0, whereas the ability to follow simple commands (GCS-M of 6) receives a score of 1. A casualty can therefore receive an aggregate field triage score of 2, 1, or 0. A retrospective review of 4988 casualties in Iraq and Afghanistan from 2002 to 2008 demonstrated that those with a field triage score of 2 had a mortality of only 0.1% (5 of 4366), whereas those with a field triage score of 1 and 0 had a mortality of 10.8% (33 of 540) and 41.4% (34 of 82), respectively.[78]

Triage categories are not the same as evacuation categories. Triage identifies the severity of a casualty's injuries and determines a treatment priority based on the likelihood of survival, whereas evacuation is based on the urgency of transport to definitive care and the likelihood of deterioration over time. Triage is an ongoing, dynamic process, and triage categories may change if an intervention stabilizes a casualty or if a casualty deteriorates clinically. For example, a delayed casualty with second-degree burns over 30% of his body may change to the immediate triage level if unrecognized inhalational injury leads to airway swelling and compromise.

CPR

Battlefield resuscitation of victims of blast or penetrating trauma who have no pulse, respiratory effort, or other signs of life will not be successful and should not be attempted because CPR on combat casualties has failed to show any benefit.[79,80] Therefore, **CPR on the battlefield is not currently recommended**. Even in the civilian setting, very few trauma arrest patients survive when prehospital CPR is performed.[81,82] In a tactical situation, CPR should be considered only as a last effort if the situation permits and appropriate resources are available and in the case of nontraumatic disorders such as hypothermia, near-drowning, and electrocution. Casualties with torso trauma or polytrauma, who are pulseless and apneic, should receive bilateral needle decompression of the chest to ensure they do not have a tension pneumothorax prior to discontinuation of care.

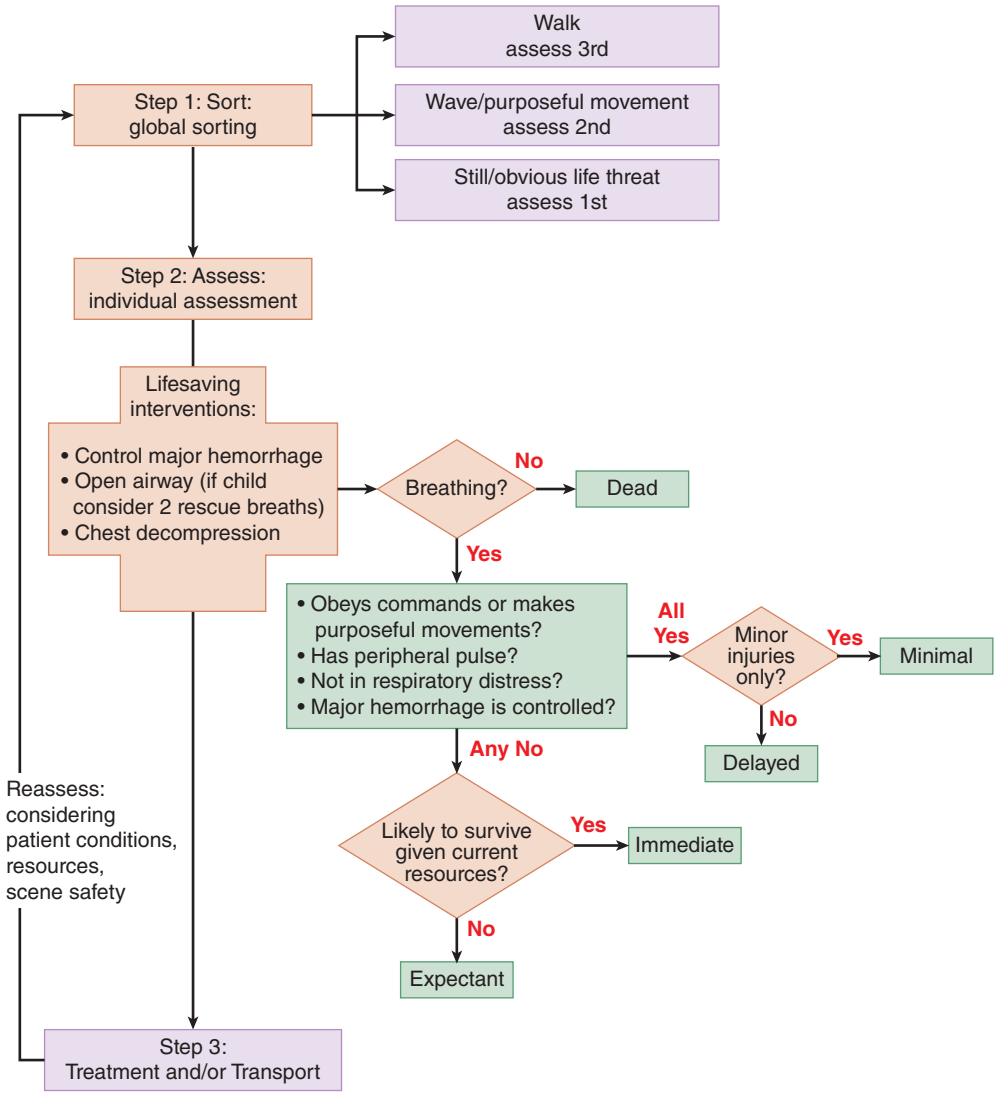

FIGURE 302-3. SALT (sort, assess, lifesaving interventions, treatment/transport) triage algorithm.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.

CHAPTER 303

Legal Issues in Emergency Medicine

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INFORMED CONSENT

Informed consent is a requirement for providers to educate patients with the capacity enough to make medical decisions (or their surrogates) about proposed treatments and alternatives, to gain agreement or refusal, and to document that decision.[1,2] Informed consent fosters the twin concepts of patient well-being and autonomy. The American College of Emergency Physicians Code of Ethics[3] recognizes the obligations, stating: Emergency physicians "serve the best interest of their patients by treating or preventing disease or injury and by informing patients about their condition." It also states that: "Adult patients with decision-making capacity have a right to accept or refuse recommended health care, and physicians have a concomitant duty to respect their choices. This right is grounded in the moral principle of respect for patient autonomy and is expressed in the legal doctrine of informed consent."[3]

ELEMENTS OF INFORMED CONSENT

Most patients arriving at an ED agree to and sign a general consent for treatment. This consent covers history taking, standard examinations, and basic procedures such as venipuncture and blood analysis. General consent forms do not provide consent for more detailed, risky, or invasive testing or treatments.

Informed consent requires two elements: The patient must possess decision-making capacity, and the patient can make a voluntary choice free of undue influence. Informed consent begins with the delivery of information to the patient by the provider, using an understandable format. The patient must then reach a decision and authorize the procedure or treatment. Each part of the process is separate, albeit linked.

Patient Capacity Decision-making capacity (hereafter called "capacity") is the ability of the patient to make informed medical decisions; it is the provider's task to determine patient capacity.[4] The definition of capacity varies among jurisdictions, but in general describes an individual's ability to make a decision based on his or her values and comprehension of the likely consequences of that decision.[5-7] The American College of Physicians *Ethics Manual* describes decision-making capacity as "the ability to receive and express information and to make a choice

TABLE 303-1 Factors for Emergency Providers to Consider When Determining Capacity

- Presence of conditions impairing mental function
- Presence of basic mental functioning (awareness, orientation, memory, attention)
- The patient understands specific treatment-related information
- Appreciation of the significance of the information for the patient's situation
- Patient's ability to reason about treatment alternatives in light of values and goals
- Complexity of the decision-making task
- Risks of the patient's decision
- Patient's ability to describe, and consistency in reporting, the basis of their decision

consonant with that information and one's values."[5] Competence, which is *not* the same as capacity, is a legal term indicating a ruling *by a court* that a person is able to manage his or her own affairs.[8]

Capacity requires the ability to receive information; to process and understand information; to deliberate about a decision; and to make, articulate, and defend choices. Generally, the physician assesses the patient abilities by taking a history from an alert patient absent barriers to communication. If needed, remove any barriers to communication due to language through translation, ideally by an impartial, in-person, medically trained translator.

Patients with altered mental status may not possess ability to receive or process information and thus lack capacity.[9,10] However, not all conditions that affect cognition or speech reception/use *remove* capacity (e.g., stroke, psychiatric illness, or dementia should not lead to a presumption of incapacity). Assess whether the disorder affects the patient's cognitive abilities.[6] Another potential trap is assuming that disagreement with a physician's plan indicates a lack of capacity; if the patient can defend the decision based on his or her values and beliefs, disagreement does not mean lack of capacity.[10] A patient's decision-making capacity may change over time based on changes in medical condition; for example, those recovering from intoxication, hypoglycemia, or hypoxia regain capacity.

Capacity also depends on the complexity of the decision and consequences of accepting or declining the intervention. For example, a patient may have capacity to make a minor decision but not a major decision at a given point in time.[11,12] The more important the decision, the more important is the assessment.[5,12,13] If a patient has capacity to make a given decision, a provider should respect and follow his or her wishes.

Factors useful to assess capacity are in **Tables 303-1**[1] and **303-2**.[13]

Free Choice Informed consent must be voluntary and free of coercion. The choice must avoid manipulation or threats by providers, family, or other outside influences, and be free of emotional or physical coercion.[3]

Information Necessary for Patient Decision Making The physician must provide the patient with the appropriate information needed to make a reasoned informed decision. Generally, the provider performing the intervention or creating a care path or plan obtains consent. A delegate such as a resident or nurse practitioner may obtain consent, but the supervisor is responsible to ensure that consent was informed.[14] The required information for decision making is the diagnosis; the nature and purpose of treatment; risks and consequences of treatment; alternatives and their risks and benefits; and prognosis if treatment is or is not accepted.[14]

There are two standards that address disclosure for informed consent.[14] One requires providers to give the patient all the information a *reasonable person* (not defined) would need to make the same decision under similar circumstances.[15] The alternate is the less-stringent *professional standard* for informed consent, which requires disclosure to be the same as any reasonably prudent, similarly trained physician would provide in a similar circumstance.[14,16] Emergency providers benefit from giving more, not less, information to the patient.

Discussion and Decision Give the patient the opportunity to ask questions while considering the decision. If needed, make the patient aware of ED time constraints that impact a decision, but do not use time to coerce a decision. Shared decision making may be used when appropriate to the situation.[17] A patient who is unable or unwilling to express a preference for a particular course of action may be presumed to lack capacity.[18]

TABLE 303-2 Common Errors in the Assessment of Capacity

- Assuming that if the patient lacks capacity for one type of decision, he or she lacks capacity for all decisions
- Assuming that legal competence is the same as medical decision-making capacity
- Presuming that capacity is constant over time
- Assuming that a blood alcohol level is related to competence
- Presuming that psychiatric disorders preclude adequate capacity
- Failing to ensure the patient has relevant and consistent information before making a decision
- Assuming that capacity should only be considered for refusal of treatment
- Failure to recognize that the capacity to make decisions varies with the risks and benefits inherent in the decision

DOCUMENTATION OF CONSENT

When obtaining informed consent, the **process** is important.[19] Some states have specific requirements regarding written consent.[14] Where specific requirements regarding written consent are not present, oral consent is acceptable, although written documentation signed by the patient aids the provider if consent challenges arise later.[14] At a minimum, the chart or consent form should reflect who obtained consent; the provider(s) authorized to perform the treatment; that information on risks, benefits, and alternatives was disclosed; and that the patient had the opportunity to ask questions.[14,15,20,21] Ideally, the chart will contain both a signed consent form and a documented recap of the consent process.[22]

EXCEPTIONS TO INFORMED CONSENT

There are several exceptions to the right to informed consent in specific healthcare situations. These exceptions include emergencies; therapeutic privilege; public health imperatives, such as the treatment of certain diseases; patient waiver of consent; and, rarely, emergency research.[14,23] Of these, emergencies and public health imperatives are applicable to clinicians working daily in the ED.

Providers should render needed emergency treatment when consent cannot be obtained or capacity ascertained in a timely fashion due to the nature of the illness. Implied consent is the basis of this exception, positing that a reasonable person would give consent to emergency or lifesaving treatment.[14,24] If treatment can be delayed without harm, obtain consent first. Should the initial care aid and conditions permit consenting, do the latter before further treatment.

Public Health Imperatives Public health imperatives are situations where the larger good may limit individual patient autonomy. Patients with high-risk communicable diseases,[25] such as severe acute respiratory syndrome and tuberculosis, or patients with mental illness who pose an immediate danger to themselves or others are examples where the public harm outweighs individual autonomy. When patients meet criteria for health department–mandated treatment and quarantine yet do not give consent, consult hospital infectious disease staff, legal staff, and local health officials.

WHEN INFORMED CONSENT CANNOT BE OBTAINED

If a patient lacks capacity to give informed consent for a condition where no exception exists, or once an emergently ill patient is stabilized and further nonemergent decisions need to be made, identify a surrogate decision maker or an existing directive when possible.[3,10] Advance directives or healthcare powers of attorney provide guidance or specify a decision maker (see Chapter 301, "Death Notification and Advance Directives"). In the absence of a power of attorney, state law determines the patient's decision maker. A typical decision-making progression is as follows (in order): spouse, adult children, parents, adult siblings, and the nearest relative not previously described.[26]

Surrogates help providers determine what the patient would want in a particular situation and should not substitute their values for the patient's. In the absence of a directive or surrogate, proceed with your judgment of the patient's best interest in mind and involve hospital counsel to begin a guardianship process if the lack of capacity is likely to be of significant duration.[11]

INFORMED REFUSAL

Patients may refuse part of a treatment plan, refuse any or all care, or wish to leave before the completion of the planned evaluation. In these situations, ensure there are no miscommunications or misunderstandings at the root of the refusal.[11] Often, when issues are clarified, an agreement is possible that defuses the situation. Some solutions are simple, but aid an open, noncontentious discussion by, for example, giving a blanket, calling the patient's personal physician, or relieving pain.[11,27] If needed, develop an alternative to the original plan that does not enhance risk, or at least minimizes any added risk (with that being clearly shared); do not fall prey to the even greater risk setting of believing, "If my top plan is refused, I cannot offer *any* care." For instance, a patient may not want a certain procedure but would be willing to accept admission for further evaluation.[11]

ED DEPARTURE AGAINST MEDICAL ADVICE AND ED ELOPEMENT

Approximately 1.1 million patients left hospital EDs against medical advice in 2014, representing 1% of patients,[28] often with poorer outcomes than the general ED population.[29,30] Characteristics of patients who leave against medical advice include lack of insurance, male sex, younger age, alcohol or drug dependency, psychiatric illness, and low income.[29,30] Patients often have serious complaints such as chest pain, abdominal pain, or trauma. Patients give many reasons for their desire to leave, including outside obligations such as family or pets; the wish for treatment at another hospital; concerns for cost of treatment; fear of recommended treatment; a desire for tobacco, drugs, or alcohol; narcotic requests; or improvement in the condition that prompted the ED visit.[31-33]

Start by assessing the patient's capacity, with special attention to barriers limiting capacity. Alcohol use and psychiatric diagnoses are not always *absolute* barriers to discharge against medical advice, except for suicidal and homicidal patients; if allowing departure against medical advice with these conditions, document the patient's behavior and features of intact capacity. Educate the patient about the risks associated with refusing to complete evaluation and/or treatment. Discuss the patient's reasons for leaving, as these present opportunities for negotiation and convincing the patient to continue care.[10] Use plain language and avoid medical terms, sharing the real medical and other risks of leaving before completing care. While it is key to invest effort to assess understanding and to convince the patient to remain, do not use any threats.[34] Statements such as, "Insurance will not pay for this visit if you leave against medical advice" are inaccurate and may damage the patient–provider relationship; in addition, they often discourage the patient from returning, adding to risk.[35,36]

Documentation of an against-medical-advice disposition ideally contains the following[27,37]:

- Clear description of capacity (with examples)
- Discussion of the risks reviewed including diagnoses considered
- Notation of the treatments, procedures, and courses of actions that were refused
- Statement of alternative treatments or courses of action that were offered
- Description of efforts to involve family, friends, or clergy in the decision
- Explanation of any potentially problematic entries in the chart such as nursing notes or abnormal laboratory values—for example, if the patient has an elevated serum alcohol level, document capacity evaluation
- A signature by the patient on the against-medical-advice form, and if patient refused to sign, documentation of the refusal
- Details of the treatment and follow-up recommended and provided
- Notation that the patient was advised that he or she is welcome to return at any time

While the most important part of documenting an against-medical-advice discharge is the discussion with the patient addressing the items listed earlier, having the patient sign an actual against-medical-advice form may help provide further liability protection in three ways: "1) it may terminate the providers legal duty to treat a patient; 2) creation of the affirmative defense of 'assumption of risk'; and 3) the creation of a record of evidence of the patient's refusal of care."[38]

When a patient leaves against medical advice, provide reasonable treatment appropriate for the medical condition and concordant with the patient's wishes.[34] For example, provide antibiotics for infection, aspirin for chest pain, or stabilization for fractures. Instruct the patient on signs and symptoms to prompt a return visit to the ED should the patient change his or her mind.[10,27]

It is also important to document situations when a patient leaves after treatment has begun but without informing ED staff, commonly called *elopement*. Attempt to locate the patient within the facility and then check logical destinations. Often a phone call to the patient's home, cell phone, or emergency contact can provide an opportunity to encourage the patient to return to the ED. Document communication attempts and their outcome.

ISSUES IN THE ED CARE OF MINORS

A minor is generally considered to be anyone less than 18 years of age, and parental consent is usually required for the nonemergency treatment of minors. In some circumstances, older children may be able to make many medical decisions independent of their parents.[39] Exceptions to parental consent for minors include emergencies, the treatment of certain diseases and conditions that are in the best interest of the minor or society, minors emancipated under law, and circumstances in which the best interests of the child are not being addressed by parents. State laws regarding minor care vary widely; providers caring for minors should review local regulations and call on legal counsel as needed.

TREATMENT OF MINORS IN EMERGENCIES

Minors often present to the ED without a parent or legal guardian, alone or in the care of an alternate caretaker such as a grandparent, school teacher, babysitter, camp counselor, or social worker. In the United States, under the Emergency Medical Treatment and Active Labor Act (EMTALA), EDs must evaluate *all* patients presenting with a medical condition and stabilize any emergency condition absent any requirement for consent.[40,41] Providers have latitude in defining an emergency medical condition, especially if there is a delay in obtaining consent. Try to find parents or legal guardians and document efforts while emergency care is being provided. Once stabilizing any emergency condition, the need for appropriate parental informed consent applies.

When an adult family member, such as a grandparent or adult sibling, brings the minor to the ED and grants consent, give care but continue efforts to contact the parent or guardian. In the case of preplanned parental absence, not all U.S. states require a signed note from the parent authorizing treatment. In some U.S. states, laws authorize relatives to consent to medical treatment for minors under their care. However, if the treatment proposed carries a substantial risk and is not emergent, contact the parents or guardian before proceeding. Providers may obtain parental consent by telephone and should document the details in the record (who gave consent, when, and for what).

EMANCIPATED MINORS

Minors who have become independent from the care and control of their parent or guardian are considered emancipated and may provide consent as adults. The definition of emancipation varies, and some states do not have specific emancipation statutes.[42] Common situations in which minors may be considered emancipated include minors who

are married, enlisted in the U.S. armed services, pregnant or parents themselves, declared emancipated by a court, or self-supporting and not living at home.

Mature Minor Exception If a minor is sufficiently mature to understand the nature and consequences of a proposed medical treatment, the minor should be able to consent to or refuse treatment without parental involvement. The mature minor exception is accepted under common law and in some states under specific legislation. Requirements for the mature minor exception are as follows: the child should generally be at least 14 or 15 years old; the treatment should be beneficial, not elective, and of low risk; and the minor must meet the requirements of informed consent. Given the subjectiveness of this standard, consider each individual case before treating a minor under the mature minor doctrine.[43] If a minor is capable of providing informed consent for a given issue, then he or she is equally capable of refusing that same treatment.

Sexually Transmitted Diseases Exception All states allow minors to access testing and treatment for sexually transmitted diseases without parental consent. In most states, the minor must be at least 12 years old, but some areas have a higher age requirement.[44,45] In some states, testing and/or treatment for human immunodeficiency virus may not be included in the exception.

Prenatal and Pregnancy Care Exemption Many states allow minors to consent to prenatal care and pregnancy-related care. In states lacking such statutes, minors are often provided prenatal care under the mature minor doctrine, particularly if the state allows minors to consent to other reproductive services.[44,45] Thirty states have laws allowing a minor to consent to treatment for their own child.[46]

Alcohol or Substance Abuse and Mental Health Treatment Exemption Nearly all states allow minors to access treatment for alcohol or substance abuse. Most states have specific laws regarding access of mental health services, and of those that do, the range of services that can be accessed without parental involvement varies.[47]

Sexual or Physical Abuse Treatment Exemption The evaluation and treatment of sexual or physical abuse without parental consent is generally permitted. In many instances, these patients may be treated under the emergency exemption, because minors who have suffered physical or sexual abuse require prompt treatment. However, if the parents are not the alleged perpetrators, seek parental involvement early.

PRACTICAL IMPLICATIONS OF TREATING MINORS UNDER STATUTORY EXCEPTIONS OR AS MATURE MINORS

The minor consenting to the treatment is generally responsible for the cost of treatment. Once a minor is treated under one of these statutes, the minor should be afforded the same confidentiality as an adult. In some states, certain exceptions exist if the provider feels that it is in the minor's best interest to have the parent notified. The Health Information Portability and Accountability Act of 1996 (HIPAA) Privacy Rule generally defers to state law or other applicable laws that expressly address a parent's ability to obtain health information about a minor including when a parent agrees to a confidential relationship between the physician and the minor.[48] The hospital bill may pose a potential risk for breach of confidentiality if sent to a parent or parent insurer.

Assent and Refusal by the Older Minor Providers should seek the assent and cooperation of older or "mature" minors even when parents are granting permission for treatment. If the proposed treatment is nonemergent and the older minor refuses to give assent, respect the minor's decision initially and seek legal input to assess the best option.

WHEN THE MINOR'S INTERESTS ARE NOT BEING PROTECTED

In almost all cases, parents make decisions they believe to be in their child's best interests. However, situations arise when the physician wishes to override or delay the decision making of the parent. For example, if the parent is intoxicated or lacks capacity to give informed consent or refuse care for a minor child, do not accept that consent or refusal. If parents disagree with a treatment plan based on religious or moral reasons, the court or child protective agencies may intervene if the disputed intervention is lifesaving. The American Academy of Pediatrics recommends giving care to children who need medical care to prevent substantial harm or suffering, seeking legal aid to help adjudicate, especially if religious opposition exists.[49]

PRIVACY, CONFIDENTIALITY, AND REPORTING

The ideas of privacy and confidentiality are important elements of ethics, religion, and law because they affirm the dignity and value of the individual.[50] The Hippocratic Oath reads, "All that may come to my knowledge in the exercise of my profession. . . . I will keep secret and will never reveal." The American College of Emergency Physicians Code of Ethics states that emergency physicians should "Respect patient privacy and disclose confidential information only with consent of the patient or when required by an overriding duty such as the duty to protect others or to obey the law."[51] All states and the federal government have laws that govern privacy and confidentiality, including mandatory or voluntary reporting requirements that may override considerations of individual patient privacy and confidentiality.

BARRIERS TO PRIVACY AND CONFIDENTIALITY IN THE ED

ED barriers to privacy and confidentiality include physical design; operational issues; the presence of visitors, students, and other individuals; and video technology.

Design and operational issues that impact privacy and confidentiality include the triage area, frequent movement of patients between beds, open ED areas for documentation and work, and patient placement for close observation to minimize risk from falls or self-harm.[50,52] In addition, ED crowding and boarding lead to the use of nontraditional bed spaces such as hallways, which reduce the ability of staff to provide optimum privacy to patients.[53] ED staff should be vigilant when conducting interviews, teaching, or communicating to maximize patient privacy and confidentiality.

Students of various disciplines, law enforcement, and visitors should respect patient privacy and confidentiality.[54,55] Requests from patients to exclude healthcare students from observation or care are usually honored, with some exceptions.[50,54] Obtain verbal consent from patients for the presence of students who do not participate in care, and accept refusals.

Ask patients for permission to discuss personal information in front of any visitor, including family. Visitors should generally be allowed (as space permits) with consent from the patient.[50] Disclosure of certain diseases, such as human immunodeficiency virus infection, to a third party requires a written consent.[56] Providers should always consider the nature and gravity of the information being related to a patient and try to give serious or very personal results in private, even if previously given permission to discuss in front of a visitor.

Patients brought to the ED in the custody of law enforcement officials pose unique challenges. The biggest issue is balancing the safety of staff and patient(s) with the privacy and confidentiality rights of the individual. The American College of Emergency Physicians recommends providing unbiased, attentive, and complete care to these patients and communicating instructions appropriate to the medical condition to correctional or law enforcement staff while maximizing patient privacy.[57] Law enforcement officials may engage in the collection of evidence and interviewing in the ED. Except where required by law, allow patients the option of whether or not to speak with law enforcement; patient information releases that are not expressly required by law require consent.[55]

Photography and video for evidence collection, quality assurance, and documentation are generally acceptable and governed by clear policy, but patients should give consent except where not required under the law.[58] Photography and filming for educational and publication purposes always require patient consent. Images recorded for nonmedical or educational purposes without consent (especially with cell phones) are generally prohibited.[59,60] Obtain any necessary permissions from hospital administration and learn and follow all applicable policies and state laws surrounding filming and photography of patients in all circumstances. Cell phones, tablets, and laptop computers with

identifiable patient information must be physically secured and with viewing/use protection, and images should never be sent via unencrypted email.

THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT AND PROTECTED HEALTH INFORMATION

Definitions HIPAA protects the healthcare privacy and confidentiality of individuals. This legislation required standards for the security, exchange, and integrity of electronic health information, and set rules for basic national privacy standards and fair information practices for health care.

The U.S. Department of Health and Human Services produced the "Standards for Privacy of Individually Identifiable Health Information," also called the *Privacy Rule*, in 2000. The rule has been amended several times with a major revision in January of 2013, referred to as the *Omnibus Final Rule*.[61] Covered entities include "health plans, health care clearinghouses, and health care providers (broadly defined to include anyone who furnishes, bills, or is paid for health care in the normal course of business) and business associates of these entities, who transmit health information in electronic form when dealing with an individual's health information."[62] Only those parts of the privacy rule most applicable to emergency providers will be covered here.

Under HIPAA, key health information (often referred to as *protected health information* [PHI]) is "any information, including genetic information, whether oral or recorded in any form or medium that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual."[62] HIPAA applies when PHI is transmitted or maintained by a covered entity. The rule also discusses individually identifiable health information, including demographic data such as name, Social Security number, date of birth, and other identifiers that "identify the individual or for which there is a reasonable basis to believe can be used to identify the individual."[62]

Disclosure of Protected Health Information PHI should be shared with the clear understanding that only the minimum amount of information required to accomplish the purpose of the disclosure will be released. These "minimum" necessary standards do not apply to information that is given to patients directly, used for treatment, or required by law.[63] Covered entities should have procedures, including limitations on access to electronic medical records, to ensure that users know and obtain only that information necessary to their job or business purpose.

HIPAA allows covered entities to use PHI without authorization for purposes of treatment, payment, and operations. Treatment is the provision, management, and coordination of health care and related services, including consultations and referrals.[64] The payment exclusion allows a healthcare provider to use PHI to obtain payment or be reimbursed for the care provided to an individual.[64] Operations include a number of activities, including quality improvement, employee evaluation and credentialing, auditing programs, and business activity such as planning, development, management, and administration.[64] An exception to this rule is that psychotherapy notes often require written consent for their use outside treatment, certain legal matters, and the protection of the public from a serious threat.[65]

HIPAA allows providers to disclose information without consent in emergency or dangerous situations if in the patient's best interests, although this is often limited by more restrictive state law.[66-68] There are 12 national priorities, as shown in **Table 303-3**,[69,70] in addition to treatment, payment, and operations usage, for which covered entities can disclose PHI without authorization. These allowable disclosures have specific conditions or limitations to balance the privacy of the individual and the public interest for the information.[69]

Under the privacy rule, the risk of every possible incidental use or disclosure of PHI does not have to be eliminated[69]; the covered entity should have reasonable safeguards (as defined in the rule) and applied the minimum necessary standards. If achieving these conditions, any accidental event is likely to not be judged a violation of the rule.[71]

TABLE 303-3 The 12 National Priorities for Which Protected Health Information May Be Disclosed or Used Without Written Authorization

- As required by law (statute, regulation, or court order)
- For public health reporting (e.g., vital statistics, disease, adverse event reporting)
- For reporting abuse, neglect, or domestic violence
- For health oversight activities (e.g., inspections, audits)
- For judicial and administrative proceedings
- For law enforcement purposes (e.g., criminal investigations) under certain circumstances
- For disclosures about deceased persons to medical examiners, coroners, and funeral directors
- For organ, eye, and tissue donation purposes
- For some types of research (e.g., in cases where an institutional review board has waived the authorization requirement)
- To avert a serious threat to the health or safety of the public
- For specialized government functions, such as military missions or correctional activities
- For workers' compensation claims

Patient Rights to Protected Health Information The HIPAA regulations also require that a notice of privacy practices be given to all patients, informing them of their rights regarding their health information.[72] Patients are asked to sign these documents and receive a copy of the notice.

These rights to PHI include access to records in the patient's preferred format, request for amendments, request for additional restrictions, notice of PHI use, and an accounting of disclosures made from their PHI.[73-76] In general, most of these functions are handled by support or records staff, but requests to amend records must be addressed by the provider promptly (60 days). If the provider denies a request to amend a record, the patient has the right to place a written statement in the medical record disagreeing with the denial.[73]

Law Enforcement Rights to Protected Health Information HIPAA allows the limited release of PHI for certain law enforcement purposes. Release is permitted to respond to a judicially issued warrant, subpoena, court order, or grand jury subpoena. Release is allowed to assist law enforcement in identifying or locating a suspect, fugitive, material witness, or missing person by releasing only the following information: "name and address, date and place of birth, Social Security number, ABO blood type and Rh factor, type of injury, date and time of treatment, date and time of death, if applicable, and a description of distinguishing physical characteristics, including height, weight, gender, race, hair and eye color, presence or absence of facial hair (beard or moustache), scars, and tattoos."[77] Providers may notify authorities of a person's death if a possible criminal activity was the cause of the death. With patient consent, PHI may be released in response to law enforcement requests for information about a victim or suspected victim of crime. When a patient is a victim of a crime and unable to consent, the provider may release information to law enforcement if they believe the release is in the patient's best interests and that the information is not intended to be used against the patient by law enforcement.[62]

Impact of Protected Health Information on Emergency Physicians HIPAA allows for open discussions with primary providers, consultants, and other persons involved in the care of an individual. Primary providers can discuss or share information and records for a patient with other providers engaged in care without first obtaining the patient's consent. Providers are cautioned about releasing additional information over the phone unless they can reasonably confirm the identity of the caller and have the patient's permission to release additional health information.

Do not access records for which you are not the treating provider, unless such information is needed for operations, for law enforcement, or for another legitimate reason. Document the reason for access to any chart where you are not the treating provider. Failure to comply with these regulations can lead to significant monetary and even criminal penalties for providers. See **Table 303-4** for HIPAA do's and don'ts.

TABLE 303-4 Health Insurance Portability and Accountability Act (HIPAA) Do's and Don'ts

HIPAA Do's

- Talk openly with patient's primary physician.
- Discuss protected health information with consultants and other members of the patient's healthcare team.
- Use protected health information for reimbursement and operational issues.
- Release records to the patient or an authorized representative.*
- Discuss patient protected health information with family or friends if the patient is in an emergency situation, unable to consent, and the information would be beneficial to the patient.

HIPPA Don'ts

- Discuss patients or protected health information in public or unsecured areas.
- Leave computers with access to protected health information logged on and unattended.
- Discuss protected health information in front of others without permission.
- Speak loudly when discussing protected health information, particularly in public areas.
- Look at records for which you have no legitimate purpose as a provider.

*May require the patient to sign an authorization form.

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Need to Report Protected Health Information **Privacy and confidentiality are not absolute rights.** Ethicists, courts, and legislators recognize the rights of the individual are overridden by the needs of the public in select settings. In many cases, this takes the form of permitted or mandatory reporting of certain diseases, pathogens, forms of abuse, and other medical conditions or situations.

Abuse All states require the reporting of suspected child abuse or neglect and generally give providers legal protection if reports are made in good faith.[52] Most states have similar reporting requirements for elder abuse. Some of these laws only pertain to those elderly patients who are incapacitated or in care facilities, whereas other states include all persons above a certain age.[78] Mandatory reporting laws for domestic partner violence exist in some states.[79-82] Regardless of the reporting mandate, it is best for the provider to discuss potential abuse cases with the affected patient.[80,82]

Injury by Deadly Weapon or due to a Criminal Act Most states mandate the reporting of injuries from deadly weapons, including stab and gunshot wounds.[80,81] Several states also require reporting of injuries that occur as a result of a criminal act, but do not require reporting of so-called "victimless" crimes such as drug abuse.[52]

Driving Impairment Many patients have medical conditions that may impair their ability to safely operate motor vehicles; a wide variety of conditions may meet this concern, such as seizure disorders, dementia, vision impairment, Parkinson's disease, and other degenerative conditions, and certain medications may also impair abilities to safely operate a vehicle.[83] A majority of states provide physicians with immunity when reporting impaired drivers, and many require specific conditions be reported (commonly epilepsy, but others may exist). In other states, immunity is not provided, and providers could be found liable for damages resulting from reporting or nonreporting.[80] The American Academy of Neurology supports optional reporting of medically impaired or potentially impaired drivers.[83] Despite the requirements, many physician do not report these conditions; one study found very low reporting rates in compliance with a state law requiring physicians to report all patients with lapses of consciousness.[84] In addition, some states require that providers report drivers who are in accidents while intoxicated.[80]

Infectious Disease Reporting The U.S. federal government requires the reporting of contagious diseases for surveillance purposes.[50] The annual lists of diseases and conditions under national surveillance are on the Centers for Disease Control and Prevention website.[85] Other pathogens, such as methicillin-resistant *Staphylococcus aureus*, may be reportable to other databases or to state health departments. The diseases under surveillance change over time, so frequent reeducation is important.

Reporting of Medical Errors Several states and organizations have mandatory and voluntary reporting systems in an attempt to improve healthcare processes and reduce patient morbidity and mortality due to hospital errors and adverse events.[86] Providers should comply with these systems to improve overall care.

Reporting of Breaches and Penalties Under HIPAA Under HIPAA, any disclosure, access, or use of PHI in a manner not permitted under the law is a breach.[87] If a breach is found, required notification includes to the party whose information was compromised, the secretary of the Department of Health and Human Services, and (in the case of large breaches) the public at large.[88-90] Penalties for violation of HIPAA range from $100 per violation if the covered entity was unaware of the violation and should not reasonably have been aware, to $1.5 million per violation if the breach was due to willful neglect and not adequately addressed in the required time frame.[88] Federal law also provides for criminal penalties of up to 10 years in jail and $250,000 in fines for HIPAA violations.[91] Providers should promptly discuss any breach potential with their hospital privacy officer or any potential HIPAA violation with hospital legal counsel to optimally manage the event and follow-up.

EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT

Enacted initially in 1985, EMTALA imposes obligations on hospitals operating EDs. These include the provision of a *medical screening exam* performed by *qualified medical personnel* to look for an *emergency medical condition* (EMC) for all patients who *come to the ED seeking care* for a medical condition. If an EMC is found, the patient must be stabilized within the capability of the hospital or transferred if necessary to complete stabilization.

"Comes to the ED" Under EMTALA a "dedicated emergency department" is "any department or facility of the hospital, regardless of whether it is located on or off the main hospital campus that" (1) is licensed by the state as an emergency room or ED; (2) is held out to the public as providing unscheduled care for EMCs on an urgent basis; or (3) provides one-third of its outpatient visits for the treatment of EMCs on an urgent, unscheduled basis.[92] Hospital-owned urgent care centers may meet this definition.

Hospitals must provide a screening examination to any patient who comes to the "dedicated ED" (hereafter "ED") and requests, or has a request made by another, for evaluation or treatment of a medical condition. If a prudent layperson observer would believe the person needed evaluation or treatment for a medical condition, the obligation under EMTALA starts.[92] Note that the language says for a "medical condition," not an "emergency medical condition." Other hospital locations, such as labor and delivery, psychiatric intake areas, and urgent care areas, which meet the above definition, are subject to EMTALA obligations.[93] An infant born alive is an individual under the law and EMTALA obligations apply, including when the infant was born in the ED.[40]

Emergency Medical Condition An EMC is a "medical condition manifesting itself by acute symptoms of sufficient severity (including severe pain, psychiatric disturbances and/or symptoms of substance abuse) such that the absence of immediate medical attention could reasonably be expected to result in: 1) Placing the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) in serious jeopardy; 2) Serious impairment to bodily functions; or 3) Serious dysfunction of any bodily organ or part; or with respect to a pregnant woman who is having contractions: 1) That there is inadequate time to effect a safe transfer to another hospital before delivery; or 2) That transfer may pose a threat to the health or safety of the woman or the unborn child."[92] For pregnant women with contractions, an EMC exists if there is insufficient time to transfer the patient before delivery or the transfer may pose a risk to mother or child.[92]

If it is determined that no EMCs exists, then EMTALA no longer applies to that patient. It is good practice to note the time of that decision. The courts have generally ruled that the physician must be aware an EMC exists before he or she is liable under EMTALA.[93] The EMTALA obligation does not suggest that *any* particular symptom, including severe pain,

is in and of itself an EMC, only that the presence of such symptoms mandates a screening to determine if the patient has an EMC.[94]

Medical Screening Examination A medical screening examination is the process required to reach, with reasonable clinical confidence and based on the patient's presenting signs and symptoms, the point at which it can be determined whether an EMC does or does not exist.[40] This may involve a brief history and physical examination or a more complex process involving ancillary studies, consultants, and procedures.[40]

The initial screening must be the same for every patient presenting with similar symptoms or complaints to be EMTALA compliant.[93] This is true even in cases of misdiagnosis. Case law notes that misdiagnosis and the adequacy of screening are issues of negligence and are better addressed under state malpractice statutes. **Nurse triage alone does not meet the hospital obligation to provide a medical screening examination.**[93]

EMTALA dictates that a hospital may not *delay* the screening examination and stabilizing treatment to assess method of payment or insurance status.[95] Hospitals may follow reasonable registration procedures, including inquiring about insurance, provided that it does not delay the medical screening examination or discourage patients from remaining for evaluation.[95,96] Ideally, defer requests for any payments or authorizations until after the screening examination and any indicated stabilization to avoid triggering this concern.[93] Providers may contact another caring physician for information regarding the patient's history, treatment, and evaluation (but not to obtain prior authorization).[97] Policies by payors that attempt to restrict the number of ED visits or consults a patient may have, that deny payment based on ED visit diagnosis codes, or that attempt to require insurer input into admission or transfer decisions do not change the EMTALA obligations of hospitals or physicians.[96]

Qualified Medical Personnel The statute states that, "The examination must be conducted by an individual(s) who is determined qualified by hospital bylaws or rules and regulations."[98] These individuals must be recognized by the hospital governing body as qualified to perform this type of examination.[98] Although the regulations do not specify what type of provider (e.g., registered nurse, medical doctor, physician's assistant) should perform the medical screening examination, the qualifications of the provider may be retrospectively reviewed and found inadequate.[93]

Stabilized To have a duty to stabilize, the treating providers must be aware of the presence of an EMC. Under EMTALA, stabilize means to provide "treatment as necessary to assure, within reasonable medical probability, that no material deterioration of the condition is likely to result from or occur during the transfer of an individual from a facility or that . . . the woman has delivered the child and placenta."[92] **Stabilization does *not* require that the underlying medical condition be resolved.** For example, a patient with difficulty breathing and a history of asthma may be stable once provided with medication and oxygen, even though the underlying condition of asthma is still present.[99]

The decision regarding whether or not the patient is stable rests with the qualified medical provider treating the patient.[100,101] This decision is subjective, not defined otherwise, and in an investigation, the burden of proof for stability rests with the transferring hospital.

After stabilization, EMTALA no longer applies, and patients may be discharged or admitted for further care. Once a patient is admitted, the hospital EMTALA duty is met.[102]

Transfers in accordance with local protocols, including for trauma, acute myocardial infarction, or stroke, generally meet the stabilization requirement if the transferring hospital stabilizes within its means first.[40] If a hospital is unable to stabilize the patient, then transfer to a higher level of care is appropriate, with efforts made to stabilize before transfer documented in the patient chart.[40]

The U.S. Supreme Court has ruled that the hospital or physician does not need to have an improper motive for a transfer to be successfully sued for failure to stabilize under EMTALA.[103]

Stable for Discharge According to EMTALA, "An individual is considered stable and ready for discharge when, within reasonable clinical confidence, it is determined that the individual has reached the point where his/her continued care, including diagnostic work-up and/or treatment, could be reasonably performed as an outpatient or later as an inpatient, provided the individual is given a plan for appropriate follow-up care as part of the discharge instructions. The EMC that caused the individual to present to the dedicated ED must be resolved, but the underlying medical condition may persist. Hospitals are expected within reason to assist/provide discharged individuals the necessary information to secure the necessary follow-up care to prevent relapse or worsening of the medical condition upon release from the hospital."[99]

The availability of follow-up and content of discharge instructions may be reviewed and could a trigger an investigation. One area where this is problematic is follow-up for uninsured patients if the emergency physician knew or should know that follow-up was or is unlikely to occur (e.g., if a patient is referred for needed follow-up care, such as fracture reduction, and is subsequently refused care). If there is any question about the patient's ability to obtain the needed intervention, ask the specialist to see the patient in the ED.[100] All discharge instructions should educate patients to return to the ED if they have any problem accessing follow-up care as recommended.

Psychiatric Patients EMTALA states, "Psychiatric patients are considered stable when they are protected and prevented from injuring or harming him/herself or others. The administration of chemical or physical restraints for purposes of transferring an individual from one facility to another may stabilize a psychiatric patient for a period of time and remove the immediate EMC, but the underlying medical condition may persist, and if not treated for longevity the patient may experience exacerbation of the EMC. Practitioners should use great care when determining if the medical condition is in fact stable after administering chemical or physical restraints."[99] In 2017, a single hospital settled the largest-ever EMTALA case for nearly $1.3 million over violations stemming from the practice of boarding psychiatric patients in the ED, often for many days. The settlement noted the failure of the hospital to have the patients evaluated by a psychiatrist and the failure of the organization to admit these patients to open beds in their own psychiatric unit rather than waiting for open beds at the state facility.[104-107] Psychiatric patients remain one of the greatest challenges under EMTALA due to the difficulty of determining stability and the lack of available psychiatric resources in most communities, and all organizations should review their policies and practices considering this settlement.

Transfers Under EMTALA, transfer is "the movement (including discharge) of an individual outside a hospital's facilities at the direction of any person" representing the hospital, regardless of that person's employment status with the hospital.[92]

Hospitals can transfer patients if they do not possess either the capability or capacity to care for the patient. Capability includes the availability of technology, specialists with the needed skills to care for a patient, and equipment or supplies required by the patient's condition. Capacity looks at numbers and availability of qualified staff, beds, and equipment and what the hospital "customarily does to accommodate patients in excess of its occupancy limits."[92] If a hospital routinely opens extra beds to accommodate patients, they must do so if necessary to avoid the transfer of a patient for whom they could otherwise provide care.

Hospitals may not transfer a patient who has not been stabilized unless an appropriate transfer is performed and either (1) the patient requests the transfer and the request is documented in writing, including the patient's awareness of the risks and benefits of the transfer; or (2) a physician documents that the medical benefits of transfer to a hospital with greater resources reasonably outweigh the increased risk to the patient, pregnant woman, or unborn child.[108] An "appropriate transfer" is defined in the EMTALA regulations. The following four elements are required for an appropriate transfer.[108]

1. The transferring hospital stabilized the patient (or the unborn child) to the best of its ability, minimizing the risks of the transfer to the patient or, in the case of a woman in labor, her unborn child.
2. The receiving (accepting) hospital has the capability and capacity to care for the patient and agrees to accept the individual and provide appropriate medical treatment.

3. The transferring facility sends all pertinent medical records, including test and study results, treatment provided, and the written consent for the transfer. Information not available at the time of transfer must be sent as soon as possible. If the transfer is necessary due to the failure of an on-call physician to appear, that physician's name and address must be provided to the accepting hospital.
4. The transfer must be performed through qualified personnel and transportation as determined by the transferring physician. The accepting facility may not condition its acceptance on the use of a specific transport service or method.[101,109]

If a hospital attempts to transfer a patient to meet its EMTALA obligation and the patient, or person acting on the patient's behalf, refuses the transfer, the first hospital's EMTALA obligation is met. The hospital should attempt to obtain written informed refusal with a discussion of the risks and benefits of the refusal of transfer and describe both the facts of the transfer that was proposed and the stated reasons for refusal.[110] A patient "stable for transfer" does not mean that the patient is stable under EMTALA, and therefore, any EMTALA obligation does not automatically end with the decision to transfer a patient.[96] Hospitals may not penalize a provider who refuses to authorize the transfer of a patient with an unstabilized EMC or take negative action against any employee who reports a violation of EMTALA.[108]

Duties of Receiving Hospitals A U.S. hospital with specialized capabilities or facilities such as (but not limited to) burn units, trauma units, designated disease treatment centers, or regional referral centers may not refuse to accept a transfer from a referring hospital when the patient in question requires the specialized capabilities *and* the receiving hospital has the capacity to treat the patient.[111,112] The failure of centers with specialized capabilities to appropriately accept patients requiring their services is sometimes called "reverse dumping" and applies even if the receiving hospital does not have its own dedicated ED.[111]

Due to the risk of a citation, some authors suggest that all transfers be accepted by hospitals with specialized capabilities without inquiry into the patient's insurance status.[100] Should the accepting hospital find that the transfer was not appropriate or improperly motivated, it is its duty to report the transferring hospital for a potential violation of EMTALA.[100,113] Delays in accepting a patient in transfer who has an unstabilized EMC to receive or confirm financial information may be an EMTALA violation by the receiving hospital.[114] **Failure to report an EMTALA violation is a violation.**

On-Call Responsibilities Hospitals must maintain an on-call list of physicians "who are on the hospital's medical staff or who have privileges at the hospital, or who are on the staff or have privileges at another hospital participating in a formal community call plan in accordance with the resources available to the hospital."[115] The call list must specifically name an individual physician with accurate contact information, not solely the name of a group or specialty.[116] The stipulation that the hospital provide these services "in accordance with the resources available to the hospital" leaves considerable leeway for hospitals to decide what services to offer. Physicians who are formally on call must assist when requested to determine if an EMC exists, to help stabilize patients, and to accept appropriate transfers. They must do this in a reasonable amount of time (not specified by EMTALA, but best set by each site).[40]

Although regulations allow for physicians to be on call at multiple hospitals and to perform elective surgery while on call, a clear plan must exist to provide adequate care in these situations.[117] The emergency physician determines if the on-call provider needs to appear in person to the ED to see a patient. In general, EMTALA does not allow patients to be sent to private physician offices for examination or stabilization, except where the office is part of the hospital-owned facility and on the hospital campus.

Hospitals that allow physicians to selectively take call only for their own established patients who present to the ED must ensure the availability of adequate on-call services to all ED patients requiring similar care.[116] If the on-call doctor will not come after substantial, well-documented efforts, including engaging hospital administration and legal service when available, from the emergency provider, a site may transfer the patient to receive necessary care. The emergency provider must inform the accepting hospital that that is why the patient is being sent and provide them with the on-call doctor's name and address (failure to do so is an EMTALA violation).

The widespread adoption of communications technology makes consults by a variety of electronic methods increasingly common. There is no restriction to the use of any means of communication with consultants.[116]

Table 303-5 outlines some EMTALA do's and don'ts.

TABLE 303-5 EMTALA Do's and Don'ts

EMTALA Do's

- Treat all patients in the same way.
- Provide a medical screening examination appropriate to the patient's complaints.
- Appropriately transfer patients you cannot stabilize.
- Accept transfers who require specialized services your hospital offers, as long as the specialized services have the capacity for care.
- Involve on-call specialists when needed to diagnose or stabilize an EMC.
- Educate ED, hospital staff, and faculty on the EMTALA rules.
- See patients quickly and efficiently.
- Document the completion of the MSE and if an EMC was identified or not during the visit.

EMTALA Don'ts

- Substitute triage for an MSE.
- Discourage or coerce patients away from receiving their screening exams and stabilization.
- Allow yourself to be convinced that a specialist does not need to come to the ED.
- Fail to stabilize within your capabilities.
- Delay the MSE for preauthorization or registration.
- Fail to follow your own rules, policies, and procedures.

Abbreviations: EMC = emergency medical condition; EMTALA = Emergency Medical Treatment and Active Labor Act; MSE = medical screening exam.

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ENFORCEMENT OF EMTALA

The U.S. Department of Health and Human Services enforces EMTALA. A complaint initiates an investigation of a hospital for an EMTALA violation and may start from a patient, hospital, hospital employee, or anyone who thinks care has been denied someone inappropriately. Hospitals may not penalize employees who report violations.[108] An EMTALA violation does not imply medical malpractice.

Punishments under EMTALA can be severe and may include a hospital's exclusion from participating in Medicare and Medicaid, in addition to substantial fines. Providers found to violate EMTALA can also be fined; the maximum fine per violation is now over $100,000 and is not covered by malpractice insurance, and/or the provider may be excluded from federal programs, making them nearly unemployable.[106,118-120] Between 2002 and 2015, 75% of EMTALA settled violations involved failure to screen, 42% involved failure to stabilize, and 16% involved insurance or financial status gaps (some cases had more than one omission).[121]

Physicians, particularly on-call physicians, are often unaware of their obligations under EMTALA,[122] requiring hospitals to have initial and ongoing educational programs.[102]

SPECIAL ISSUES AND CONCERNS UNDER EMTALA

Situations Where EMTALA Does Not Apply or Ceases to Apply Once a patient is admitted, in good faith, as an inpatient to the hospital for further care, EMTALA ceases to apply. However, EMTALA still applies to patients in the ED and patients on observation status, such as patients in an ED chest pain unit or in observation status within the main hospital even if they are on a unit that also contains patients on inpatient status.[93,101,123] Inpatients who subsequently develop an EMC are not covered by EMTALA, even if they are physically moved back to the ED. EMTALA does not apply to outpatients who have already begun a scheduled appointment. EMTALA may not apply during a declared

national emergency or pursuant to a state emergency or pandemic preparedness plan following the issuance of a waiver under law.[124]

Ambulance "Parking" Prolonged delays in moving patients from EMS care to hospital care, referred to as "parking," may be considered a violation.[109] This does not mean that every ambulance patient must instantly be taken from the care of EMS, particularly in instances where the hospital may lack capacity or capability to immediately care for the patient; the key is reasonableness, often determined in hindsight.[109]

Patient-Initiated Transfers Any transfer not for medical reasons is a patient-requested transfer. The chart should reflect the patient's reason for wanting the transfer, and the transfer should be to an appropriate facility.

Use of the ED for Nonemergency Services If a request is made by or for a patient presenting for treatment of a medical condition but the "nature of the request makes it clear that the medical condition is *not* of an emergency nature, the hospital is required only to perform such screening as would be appropriate for anyone presenting in a similar manner to determine" if an EMC exists.[125]

Withdrawal of Request for Screening Patients who fail to start or complete the screening and treatment process fall into one of three categories: patients who arrive at the ED and leave before their medical screening examination (often classified as left without being seen or left before exam); patients who leave or "elope" without informing staff at any point during the evaluation[126]; and patients who refuse recommended treatment or admission and leave "against medical advice."

In each scenario, the hospital must make a clear, documented effort to find a missing patient using the usual tools available.[127] Describe in the medical record the services offered (examination and treatment) and refused, and try to get written refusal on a document that outlines the risks and benefits. A hospital could violate EMTALA if waits are so long that patients leave without being seen, particularly if the hospital does not attempt to determine and document why individuals left and reiterate to them that the hospital is prepared to provide medical screening if they stay.[127]

State Law Some states impose additional duties or requirements on emergency physicians and hospitals. Follow these laws unless they directly conflict with the federal EMTALA rule, in which case the federal statute takes precedence.

Requests for Testing Patients may present to the ED for testing, such as radiographs or blood work, due to their misunderstanding or under the order of their personal physician. Because these patients are not requesting examination or treatment of a medical condition, EMTALA does not apply. Note in the record that a medical screening examination was not requested (signed by the patient), and record any interactions with the ordering physician. Patients who independently present for testing (e.g., pregnancy) should receive a medical screening examination before testing, and if they formally refuse the screening examination, refer them elsewhere for the requested testing *and* document the refusal.[93]

If a patient comes with law enforcement, do an MSE (prudent layperson) and any other requested care.

Screen Away Programs Such programs aim to comply with EMTALA by performing medical screening examinations and then either sending away those patients found not to have an EMC or requesting payment before treatment. Physicians and hospitals should consider the legal risk and ethical and moral implications of such programs, particularly in those cases where alternative sources of care are not provided.[128, 129]

Private Patients in the ED In some EDs, it is common for staff physicians to send their patients to the ED, with plans to meet the patient. Although this is acceptable, these patients should be evaluated in the standard manner including an MSE and stabilized while waiting for the private physician if she or he is not available immediately.

"The Guarantee" Some hospitals promise a patient will be triaged or seen by a doctor within a specific amount of time. These guarantees may be used as declared standards during an EMTALA investigation.

Pain and EMTALA Although EMTALA indicates that pain may be a symptom suggestive of an EMC, it only requires that the patient with pain receive a medical screening exam consistent with the presenting complaints. Once a patient has been identified as not having an EMC, providers can make clinical determinations about the appropriateness of opioids and other medications. The Centers for Medicare and Medicaid Services clarified that the posting of signage that discusses restrictions on ED prescribing or use of opioids may discourage patients from receiving their medical screening exam and could be in violation of EMTALA.[130,131] Providers and staff should also not discuss with patients the results of state pharmacy database queries prior to the completion of the medical screening exam to prevent patients from feeling coerced not to complete their exam.[131] The best course in dealing with patients with painful complaints is to provide a medical screening exam and, once an EMC is determined not to exist, to treat the patient based on the clinical scenario, risk for pharmaceutical abuse, and applicable state law.[130]

RISK MANAGEMENT

The ED presents a unique setting in health care where numerous factors interact to create the potential for error.[132,133] These errors can create adverse outcomes for patients and increased medical-legal risks for ED providers. Risk management identifies and mitigates factors that may be a source of error.

Certain presenting complaints and conditions are associated with poor outcomes leading to legal action (**Table 303-6**).[132-136]

The error types most commonly reported in emergency medicine include diagnostic error or delay, treatment error or delay, improper performance of procedure or treatment, misinterpretation of tests, failure to supervise or monitor a case, and a failure or delay to consult or refer.[132,134] Diagnostic error, which includes failure to diagnose, delay in diagnosis, and wrong diagnosis, is consistently the most frequent and costly in terms of malpractice claims paid, both in emergency medicine and across all specialties.[132,133,136-138] Diagnostic error is judgment that is "missed, wrong, or delayed."[139] These lead to permanent injury or death in almost half of filed ED malpractice cases related to diagnostic error.[133,136,138]

One study evaluated the sources of these diagnostic errors in the ED,[135] finding that cognitive errors in judgment, knowledge, and vigilance or memory contributed to 96% of claims with identified errors. Communication errors, particularly as they relate to patient handoffs, were involved in 35% of diagnostic errors. System errors, including issues with supervision, workload, and fatigue, occurred in 37% of

TABLE 303-6 Complaints and Diagnoses Associated With High Risk of Diagnostic Error

- Chest pain/missed acute myocardial infarction (AMI)*
- Wounds (retained foreign body, nerve or tendon damage, poor healing)
- Fractures (vertebral, forearm, leg)
- Symptom involving the abdomen and pelvis (including appendicitis and abdominal aneurysm)
- Pediatric fever
- Meningitis
- CNS bleed
- Stroke
- Embolism
- Trauma related
- Spinal cord injuries
- Ectopic pregnancy
- Spinal cord abscess
- Headache/subarachnoid hemorrhage
- Aortic dissection
- Torsion—testicular or ovarian

*Missed AMI is the most frequently alleged missed diagnosis.

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TABLE 303-7 Provider Interpersonal Behaviors That Can Reduce Risk

- Introduce yourself to the patient and family.
- Dress neatly and professionally.
- Address patients respectfully.
- Sit down at the bedside.
- Discuss with patients their expectations of care.
- Speak in clear, simple language, avoiding medical terms.
- Provide emotional support and show empathy.
- Meet each signed-out patient.
- Personally provide discharge instructions and answer questions prior to patient departure.

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cases; these errors were more prevalent where students or residents were involved. Patient-related factors were involved in an additional 34% of cases. Of note, two thirds of the errors involved cases in which more than one provider participated in the care, further underscoring the importance of communication-related factors.

REDUCING RISK

Improving patient safety and reducing risk in emergency medicine require a broad focus involving multiple disciplines and addressing numerous issues including medication administration; electronic health records; ED staffing, flow, and culture; interruptions; and available equipment and resources.[132,133,140] Although these systemic changes are often beyond the ability of the individual physician to influence, there are a number of steps each physician can take to reduce the risk of error and of being named in a malpractice suit.

Establish a good patient and family interaction (**Table 303-7**).[141] This relationship is key to facilitating good communications and reducing risk. Introductions are simple and important; start with telling each patient your name and your place on the healthcare team (e.g., attending or supervising doctor, resident physician, student). Engage any family or friends when appropriate and permitted by the patient. Ensure that the patient and others understand the diagnosis and discharge instructions, particularly those related to follow-up, treatment, and when to return to the ED. The physician should provide the opportunity for patients and caregivers to ask questions prior to discharge to ensure comprehension.

Providers can modify other practice behaviors that may perpetuate or lead to error and risk. Patient handoffs are an area of risk; these cannot be eliminated, but try to lessen these or avoid using rushed patient handoffs to reduce the risk associated with shift change and multiple providers on the care team. Providers may fail to consider all the diagnostic possibilities in a transferred or signed-out patient because they receive the patient with a preexisting plan and diagnosis. It is a good practice for new providers to meet each patient signed out to them and to evaluate them at least once before discharge.[142]

Errors around procedures were the second highest category of error in one ED study.[132] Provide adequate supervision of residents and students performing procedures, provide informed consent for every procedure when possible, and follow established best practices and guidelines.

Another opportunity to reduce risk lies in reducing interruptions. Although common in the ED, defer interruptions when possible to allow accurate completion of the current task.[140] Avoid criticizing the care provided by other providers, and never make guarantees about patient outcomes.

SPECIFIC HIGH-RISK DIAGNOSES AND TREATMENTS

Certain diagnoses have a higher risk of poorer outcome, error, or a malpractice filing, noted in Table 303-6. Be aware of these diagnoses and their atypical presentations and consider the possibility of a high-risk problem in every patient.

The optimal treatment of many diseases is unclear, and a single ideal care path or set of ideal care paths is not always defined. Providers should have careful and well-documented discussions about what treatments are or are not being given and why.

NEWBORNS LEFT AT THE ED

All U.S. states, the District of Columbia, and Puerto Rico have laws allowing a mother or others to leave a newborn at a "safe haven" to reduce the numbers of deaths and abandonments in unsafe places.[143] These laws vary with respect to who may leave the infant, how long after birth the child may be left, whom the child may be entrusted to, and the amount of legal protection and anonymity due the person leaving the child.[143] In most states, a healthcare provider or emergency services provider is authorized to accept the child.[143] Providers should be aware of the laws in their state, and every ED should have a policy to deal with this situation.

DUTY TO THIRD PARTIES

The *Tarasoff* ruling set the precedent that a physician owes a duty to a foreseeable third party when the physician is aware of a reasonable risk to that individual.[144] Over the years, courts have extended that duty to include an obligation to warn or protect others against a variety of dangers, including communicable diseases, impaired drivers, employment physicals, and medication or treatment reactions.[145,146] Physicians have varying obligations and protections under state laws for reporting patients and warning potential victims or authorities when third parties may be at risk.[146-150]

TELEPHONE ADVICE

Calls for telephone advice should be routed to an established "advice line" operated by the hospital, an insurer, or other entity. By dispensing telephone medical advice, a physician may enter a binding physician–patient relationship.[151] Teach the ED staff a standard response to unsolicited phone calls from the general public: they should state that they are not allowed to give advice over the phone and should encourage the patient to seek evaluation as they best judge including coming to the ED for evaluation.[152]

EXTENSION OF CARE OUTSIDE OF THE ED ENCOUNTER

Emergency providers can be exposed to liability extending outside of the ED. Two common sources of this risk are the writing of inpatient orders and responding to emergencies elsewhere in the hospital.[153] Emergency physician orders that cover any part of the inpatient stay create ambiguity about when the transfer of care to the inpatient provider takes place. The American College of Emergency Physicians recommends that the emergency physician not be compelled to write orders extending outside of the ED. In those cases where the emergency physician initiates hospital orders, the medical staff policies ideally provide for timely orders for and evaluation of admitted patients by the inpatient staff and require that the time the transfer of care occurred be clearly documented.[154]

In some hospitals, the emergency physician is expected to address a variety of medical issues on the inpatient floors.[153] Hospitals are responsible for the treatment of inpatients; using ED providers to treat inpatients threatens their ability to meet their ED requirements. In cases in which no other option is available, consider bringing these acutely changed inpatients to the ED for evaluation and treatment.[155]

NEGLIGENCE STANDARDS

Physicians are expected to exercise reasonable care and practice within the accepted standard of care, the latter defined by medical opinion and science. A failure is *negligent* and often the foundation in a medical malpractice lawsuit. Efforts to protect the healthcare safety net provided by EDs and specialists treating ED patients led some states to enact a more rigorous standard of negligence for emergency care. This higher standard is often referred to as *gross negligence*. Gross negligence has various definitions across jurisdictions that include "conduct so reckless as to demonstrate a substantial lack of concern for whether an injury results" and a "failure to exercise slight care or diligence."[156,157] The term

TABLE 303-8 Other Legal Issues of Concern to Emergency Providers

- Peer review
- Business arrangements (anti-kickback Stark laws)
- Credentialing
- Recommendation writing
- Emergency situations arising outside of the hospital
- Compliance
- Medical malpractice
- Translation services for patients
- Acting as an expert witness
- Signing death certificates

reckless is sometimes used to describe a standard of negligence and often is equivalent to gross negligence.[156] A third standard, *willful or wanton misconduct*, is often found in "Good Samaritan" laws.[156] Willful or wanton misconduct is behavior "where someone knew that an injury was likely to result from an action and, despite this knowledge, acted with a conscious disregard for the safety of another person."[156] The willful and wanton standard requires the provider to know that what he or she was doing was almost certain to lead to injury.[156]

OTHER LEGAL ISSUES OF CONCERN

Other areas of ED practice with legal implications are listed in **Table 303-8**. The legal risk varies across states.

DISCLAIMER

This chapter does not address state-specific issues or replace the advice of the hospital attorney in a given situation. The information provided in this chapter is not intended to be legal advice. Laws and regulations are always changing, and this chapter does not replace a timely consultation with an attorney specialized in healthcare issues.

REFERENCES

The complete reference list is available online at www.TintinalliEM.com.



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